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A. Stephen K. Hashmi

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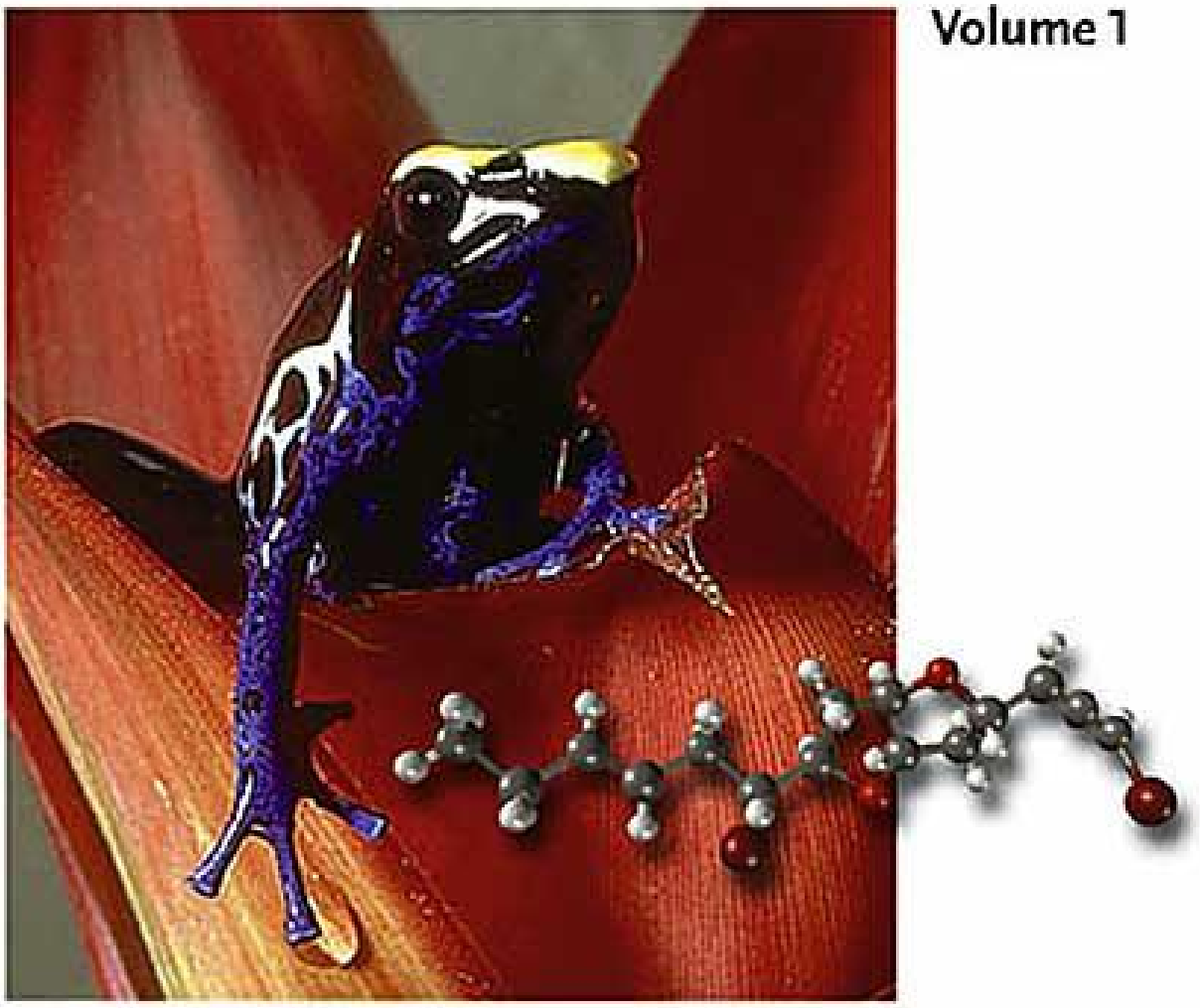
Modern Allene Chemistry

Volume 1



Modern Allene Chemistry

Edited by
Norbert Krause and A. Stephen K. Hashmi

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Volume 1

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Norbert Krause and A. Stephen K. Hashmi

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Editors

Professor Dr. Norbert Krause
University of Dortmund
Organic Chemistry II
Otto-Hahn-Strasse 6
44227 Dortmund
Germany

Professor Dr. A. Stephen K. Hashmi
University of Stuttgart
Department of Organic Chemistry
Pfaffenwaldring 55
70569 Stuttgart
Germany

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Preface

Chemists have always been fascinated by the cumulated diene system of allenes with its extraordinary properties, such as the axial chirality of the elongated tetrahedron and a higher reactivity than non-cumulated C-C double bonds. Over the past 20 years allenes have become increasingly popular among chemists, and even occupied fields where their use was previously difficult due to selectivity problems – transition metal-catalyzed reactions, for example. At the end of 2000, Stephen Hashmi published a highlight on such new and selective transition metal-catalyzed reactions of allenes. Subsequently, Henning Hopf turned our attention to the fact that – following a series of books on allenes (including such well known volumes as Müller's Houben-Weyl issue on allenes, Patai's issue on allenes, Brandsma's wonderful laboratory manual and Landor's "Chemistry of Allenes") – the last monograph on the topic, Schuster/Coppola "Allenes in Organic Synthesis", appeared back in 1984 and now, after 20 years, it might be time for a new one.

A closer survey revealed that in the period elapsed since 1984 an average of 400 publications on allenes have appeared each year, amounting to close to 8000 in total. This made it obvious that one mortal author could not cover the whole field alone. As a consequence, Norbert Krause, both a renowned expert in allene chemistry and experienced in editing books, was commissioned as an additional editor. The crucial part then was to identify those fields of allene chemistry displaying the new and significant developments since 1984. We decided to divide the project into four parts, "Synthesis of Allenes", "Special Classes of Allenes", "Reactions of Allenes", and "Applications".

Twenty chapters cover such new and exciting developments as metal-catalyzed synthesis of allenes, strained cyclic allenes, the numerous applications of different metallated allenes in organic synthesis, as well as the many addition and rearrangement reactions of allenes and allene units in natural products like the remarkable enyne-allenes.

For these chapters an international team of 16 authors, all experts in their respective fields of allene chemistry, was put together and did an extraordinary job in compiling this two-volume handbook. We are very grateful for their effort, as well as for the organizational skills of Dr. Bettina Bems and Dr. Gudrun Walter from Wiley-VCH. Special thanks go also to Kerstin Hammerschmidt-Assmann for editing the over 1600 chemical drawings of this monograph.

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From the chapters of this book it is evident that the allene group is more versatile than ever before and that the developments in new reactions are still proceeding at a high rate, such that we are not witnessing the decreasing slide after a peak of scientific interest, but rather a continuous development.

We are confident that this book will be both a very useful source for scientists teaching chemistry and an inspiration for all those involved in chemical research.

Dortmund and Stuttgart,
September 2004

Norbert Krause
A. Stephen K. Hashmi

Modern Allene Chemistry

Volume 2

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List of Contributors

Jan-Erling Bäckvall
Stockholm University
Department of Organic Chemistry
Arrhenius Laboratory
10691 Stockholm
Sweden

Klaus Banert
Chemnitz University of Technology
Institute of Chemistry
Strasse der Nationen 62
09111 Chemnitz
Germany

Kay M. Brummond
University of Pittsburgh
219 Parkman Avenue
Pittsburgh, PA 15260
USA

Hongfeng Chen
University of Pittsburgh
219 Parkman Avenue
Pittsburgh, PA 15260
USA

Manfred Christl
Bayerische Julius-Maximilians-
Universität Würzburg
Am Hubland
97074 Würzburg
Germany

Melissa L. Grachen
Department of Chemistry
12 Oxford Street
Cambridge, MA 02138
USA

Benjamin Gung
Miami University
Department of Chemistry and
Biochemistry
Oxford, OH 45056
USA

Jens Hartung
Fachbereich der Chemie der
Technischen Universität Kaiserslautern
Erwin-Schrödinger-Strasse 54
67663 Kaiserslautern
Germany

A. Stephen K. Hashmi
University of Stuttgart
Institute of Organic Chemistry
Pfaffenwaldring 55
70569 Stuttgart
Germany

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Tamio Hayashi
Kyoto University
Department of Chemistry,
Graduate School of Science
Sakyo
Kyoto 606–8502
Japan

Anja Hoffmann-Röder
Laboratorium für Organische Chemie
ETH Zürich
Hönggerberg
8093 Zürich
Switzerland

Henning Hopf
University of Braunschweig
Institute of Organic Chemistry
Hagenring 30
38106 Braunschweig
Germany

Attila Horváth
Stockholm University
Department of Organic Chemistry
Arrhenius Laboratory
10691 Stockholm
Sweden

Thomas Kopf
Fachbereich der Chemie der
Technischen Universität Kaiserslautern
Erwin-Schrödinger-Strasse 54
67663 Kaiserslautern
Germany

Norbert Krause
University of Dortmund
Organic Chemistry II
Otto-Hahn-Strasse 6
44227 Dortmund
Germany

Jens Lehmann
Chemnitz University of Technology
Institute of Chemistry
Strasse der Nationen 62
09111 Chemnitz
Germany

Shengming Ma
Zhejiang University
Laboratory of Molecular Recognition
and Synthesis
Department of Chemistry
Hangzhou
Zhejiang 310027, P.R. China
and
State Key Laboratory of Organometallic
Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
354 Fenglin Lu
Shanghai 200032, P.R. China

Tadakatsu Mandai
Kurashiki University of Science
and the Arts
College of Life Science
2640 Nishinoura, Tsurajima
Kurashiki 712–8505
Japan

James A. Marshall
University of Virginia
Department of Chemistry
PO Box 400319
Charlottesville VA 22904
USA

Takanori Matsuda
Kyoto University
Department of Synthetic Chemistry
and Biological Chemistry
Yoshida
Kyoto 606–8501
Japan

Masahiro Murakami
Kyoto University
Department of Synthetic Chemistry
and Biological Chemistry
Yoshida
Kyoto 606–8501
Japan

Yasuo Nagaoka
Kansai University
Faculty of Engineering
Suita
Osaka 564–8680
Japan

Masamichi Ogasawara
Hokkaido University
Catalysis Research Center
Kita-ku
Sapporo 001–0021
Japan

Hiroaki Ohno
Osaka University
Graduate School of Pharmaceutical
Sciences
1–6 Yamadaoka
Suita
Osaka 565–0871
Japan

Hans-Ulrich Reissig
Freie Universität Berlin
Institut für Chemie
Takustrasse 3
14195 Berlin
Germany

Marcus A. Tius
University of Hawaii
Department of Chemistry
2545 The Mall
Honolulu, HI 96822
USA

Kiyoshi Tomioka
Kyoto University
Graduate School of Pharmaceutical
Sciences
Yoshida, Sakyo-ku
Kyoto 606–8501
Japan

Kung K. Wang
C. Eugene Bennett
West Virginia University
Department of Chemistry
Morgantown
WV 26506–6405
USA

Reinhold Zimmer
Freie Universität Berlin
Institut für Chemie
Takustrasse 3
14195 Berlin
Germany

I
Synthesis of Allenes

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1
Synthesis of Allenes by Isomerization Reactions

A. Stephen K. Hashmi

1.1
Introduction

Isomerization reactions are associated with a change in either the connectivity (the constitution) of the molecule or the steric arrangement of atoms or groups in the molecule. However, no change of the empirical formula is involved. Thus in isomerization reactions leading to allenes, the 1,2-diene substructure that is characteristic of this class of compounds has to be formed by one of the following reactions (Scheme 1.1):

(a) *Migration* of a non-cumulated π-bond into cumulation with a second π-bond. The non-cumulated π-bonds can either be an alkyne (Reaction A) or a conjugated or isolated diene (Reaction B). If in Reaction A the group X = H this is a prototropic *rearrangement*; another possibility would be a sigmatropic rearrangement in which X typically is a two- or three-atomic unsaturated moiety. These two cases are the most important isomerization reactions leading to allenes. Another priciple that would also fall into this category would be the rearrangement of one allene to another.

(b) Transformation of a ring (a double bond equivalent) to a π-bond by a kind of intramolecular *elimination* process (Reaction C) or an electrocyclic ring opening (Reaction D).

(c) Another option would be the *addition* of an intramolecular nucleophile to a conjugated, alkyne-containing system such as a 1,3-enyne (Reaction E) or a higher cumulene (Reaction F).

(d) A *substitution* would only fall into the category of isomerization if it is entirely intramolecular; both the attacking and the leaving group would need to remain part of the molecule. This would mean that the formation of the new bond needs to be a ring closure and the bond cleavage would be a ring opening (Reaction G).

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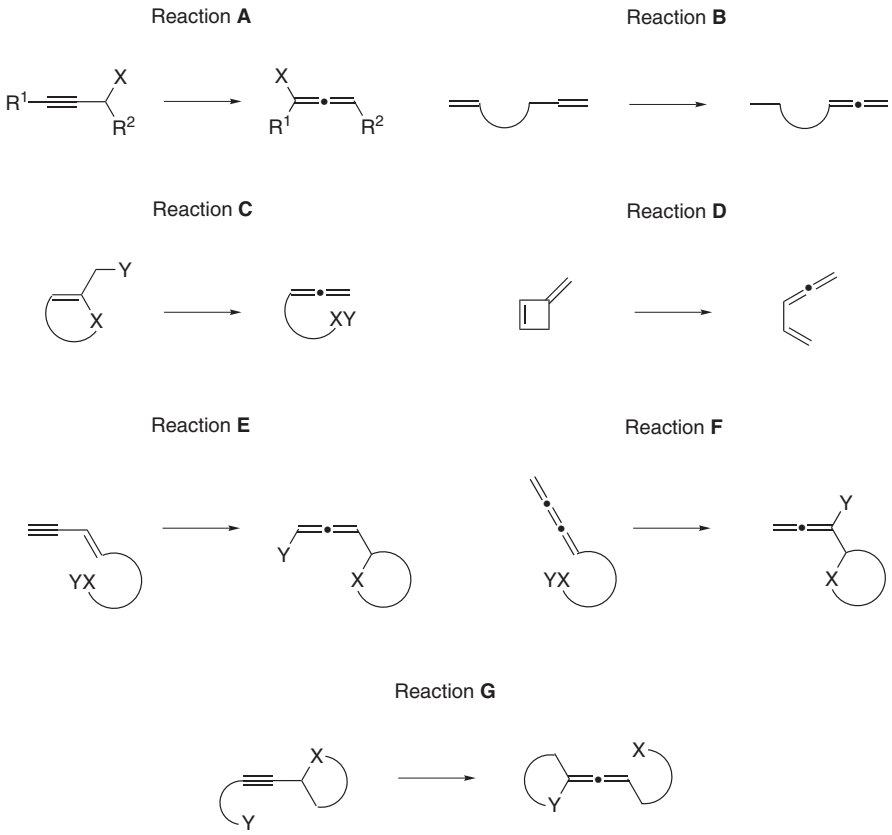


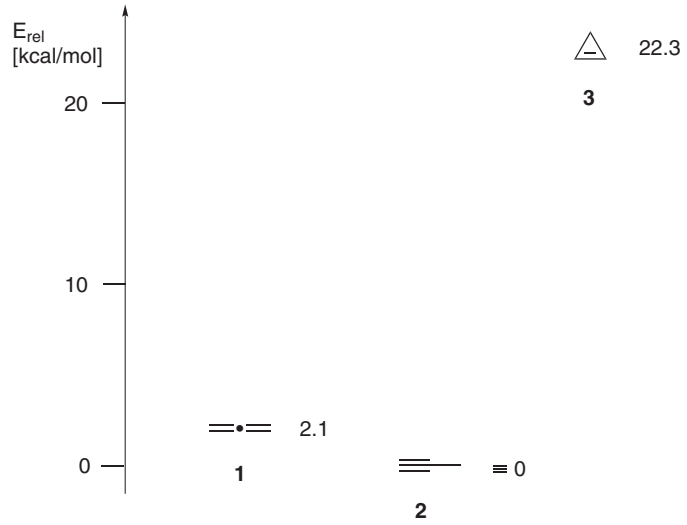
Scheme 1.1 Different conceivable Reactions A–G forming allenes by isomerization reactions.

This chapter will cover only reactions in which the isomerization to the allene starts from a stable molecule and *not* from a reactive intermediate generated in situ by reactions which are not isomerizations, such as the Doering–Moore–Skattebol reaction or free carbenes. Metallotropic rearrangements also will not be covered; many of these reactions can be found in Chapter 9. Furthermore, the allene should be the final product of the reaction and not only a transient species leading to other products (see, for example, Chapters 6 and 20).

The last review in this field was published in 1980 [1]; this chapter will focus on the new developments and applications in the past two decades, but also cite important key papers from previous work.

The isomers of the simplest allene, 1,2-propadiene **1**, are propyne **2** and cyclopropene **3** (Scheme 1.2). Their isomerization engergies have been measured and calculated [2–4]. Compound **2** is clearly the most stable isomer, **1** lies 2.1 kJ higher and **3** about 22.3 kJ. Hence in principle, if reversible, thermodynamics of an equilibrium should favor the alkyne. However, several factors can influence this in two ways, i.e. a change of the relative thermodynamic stability, for example by substituents, or a

reaction under kinetic control, for example stoichiometric deprotonation followed by kinetic protonation. For a long time different thermodynamic stability was only deduced from the ratio of the products isolated, and apart from obvious cases, where for example the relief of strain led to a clear preference in the equilibrium, a clear explanation was not possible. It was only recently that by thorough calculations the influence of the substituents on the allene was investigated [5]; for example in the synthetically important allenyl ethers and allenylamines which are thermodynamically more stable than their propargylic counterparts! The substituents are most important for the synthetic chemist because they define both the starting material and the class of allenes and thus the reactivity of the latter (see, for example, Chapters 7 and 8). Therefore, this chapter is not only ordered by the *reaction types* but these are also subdivided by the *substituents on the allenic product*.



Scheme 1.2 Isomers of the smallest allene C_3H_4 and their relative energies.

Most of the reactions are either catalytic in a reagent that initiates the isomerization, for example a base, or initiated by heating or irradiation, for example in sigmatropic rearrangements and electrocyclic ring openings. Only a small number of the reactions need a stoichiometric amount of a reagent; a typical example would be stoichiometric deprotonation with an organolithium reagent and a subsequent protonation.

As we shall see, in most of the examples smaller building blocks are synthesized by such isomerizations. The high reactivity of the allene is then utilized in further synthetic steps. However, there are also numerous reactions where complex molecules in later stages of a synthesis are synthesized by isomerizations.

1.2
Prototropic Rearrangements and Related Reactions of Alkynes

This is, as the numerous references will show, probably the most important method for the synthesis of allenes by isomerizations (Reaction A in Scheme 1.1). Examples following a different mechanism but overall delivering analogous products will also be covered in this section.

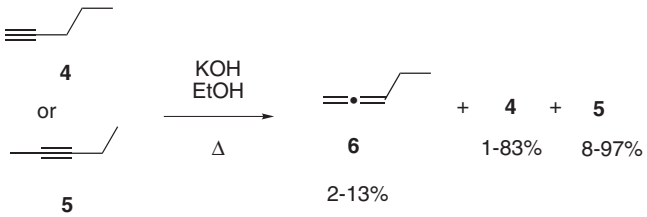
1.2.1
Hydrogen Atoms or Alkyl Groups as Substituents

In these reactions, usually an equilibrium mixture, favoring the internal alkyne, is observed. Thus it is difficult to obtain preparatively useful yields of allenes.

For the thermal isomerization of **2** to **1** [6] on the basis of kinetic data, it was suggested that at least 50% of **1** is formed via cyclopropene **3** as an intermediate [7] rather than a direct 1,3-H-shift as proposed before [8, 9]. Later theoretical calculations provided further support for that suggestion [10]. A number of other publications, some of them with basic catalysts such as sodium hydroxide, deal with this reaction [11–17]. Furthermore, **2** can be isomerized to **1** by a stoichiometric reacion with $[RuHCl(CO)(PPh_3)_3]$ and subsequent treatment with NaS_2CNMe_2 [18]. The 1,1-bisdeuterated **2** has also been investigated [19].

The next homologues are 1- and 2-butyne, where similar isomerizations have been observed [20]; a recent report describes the reaction on a basic, alkali metal-exchanged zeolite [21]. As an unexpected product, an allene was obtained in reactions with hydrogen and a samarium catalyst [16, 22].

With pentynes **4** or **5**, a similar reaction was possible with potassium hydroxide at 175 °C; here, depending on the reaction time and the temperature, between 2 and 13% of 1,2-pentadiene **6** could be obtained along with the pentynes (Scheme 1.3) [23].

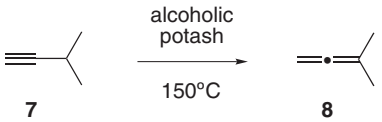


Scheme 1.3

Of further significance is the fact that *no* 1,3-pentadiene is formed! This behavior is similar to that of the butynes, where also no 1,3-butadiene was observed. Furthermore, this is in complete accordance with the proposed mechanism of the potassium 3-aminopropylamide-mediated isomerization of internal alkynes to terminal alkynes by repetitive alkyne–allene–alkyne isomerizations [24].

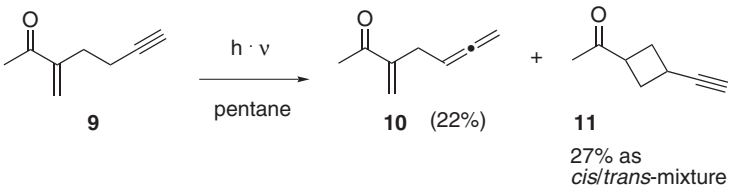
One of the papers initiating this field deals with a pentyne isomer, as early as 1888 Faworski [25] reported the isomerization of 3-methylbutyne **7** to **8** (Scheme 1.4)

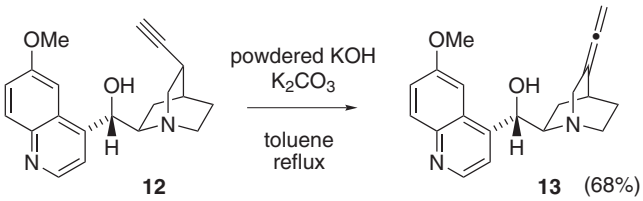
[26]. Similar reactions were conducted with ethynylcyclohexane [27, 28] and a terpene-derived alkyne [29].



Scheme 1.4

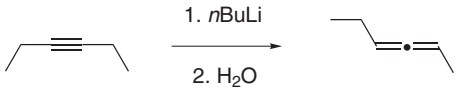
The thermal isomerization of higher terminal alkynes also delivered some allene, from 1-hexyne and 1-heptyne, for example, some 1,2-diene was formed [30]. With an α,β-unsaturated unit in the alkyne **9**, a photochemical isomerization to **10** was successful but delivered only a low yield and **11** as a significant side-product [31]. These reactions tolerate different functional groups; alcohols, ethers or, as in **12**, tertiary amines and nitriles have been used (Scheme 1.5) [32, 33].



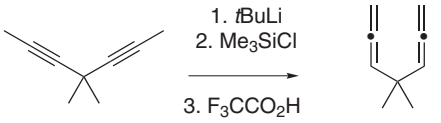


Scheme 1.5

Under basic conditions, obviously only one isomerization step takes place and thus a terminal alkyne will deliver 1,2-dienes selectively. With internal alkynes, on the other hand, selectivity can only be achieved when the alkyne is either symmetrical as in **14** [34] (Scheme 1.6) or has a tertiary center on one side as in **16** [35, 36] (Scheme 1.7). So, unlike potassium 3-aminopropylamide in 1,3-diaminopropane, where the π-bonds can migrate over a long distance by a sequence of deprotonations and reprotonations, here the stoichiometric deprotonation delivers one specific anion which is then reprotonated (in **16** after transmetalation).

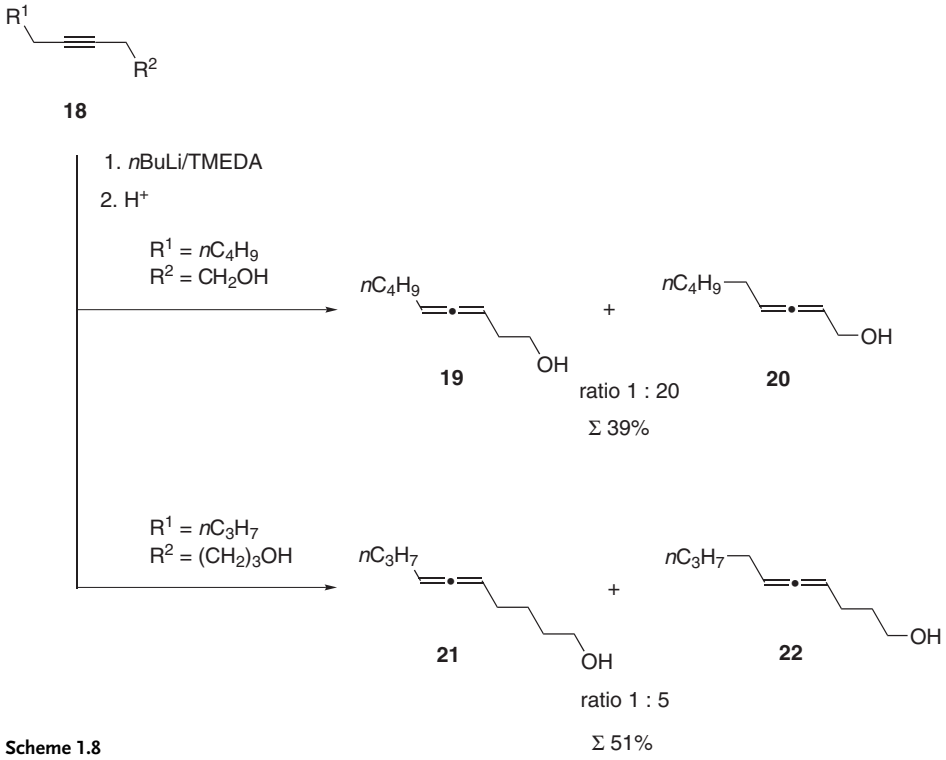


Scheme 1.6



Scheme 1.7 **16** **17** (> 27%)

On the other hand, unsymmetrical internal alkynes usually lead to two different constitutional isomers. In compounds of type **18**, selectivity in favor of **20** rather than **19** is observed (1:20) owing to the hydroxyl groups which might direct the deprotonation by directing the base to the closer propargylic methylene protons (Scheme 1.8) [37]. This chelate-like behavior, of course, becomes less significant as the tether increases; for **21** and **22** the yield is better but the selectivity is reduced to only 1:5.

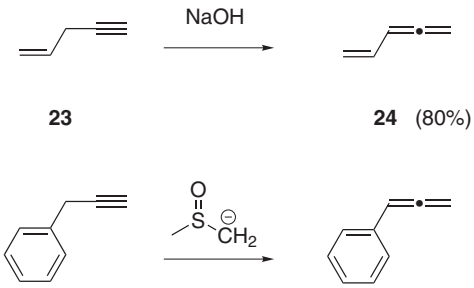


Scheme 1.8

1.2.2
Alkenyl or Aryl Groups as Substituents

The preparatively useful examples in this section can be divided into three categories.

(a) The migrating π-bond moves into conjugation with the neighboring alkene or arene. Most of these reactions follow this scheme. Here the starting material is an alkyne separated by one sp^3 center from the alkene or arene; the prototypes of these reactions leading to **24** [38, 39] and to **26** [40] have been described (Scheme 1.9).

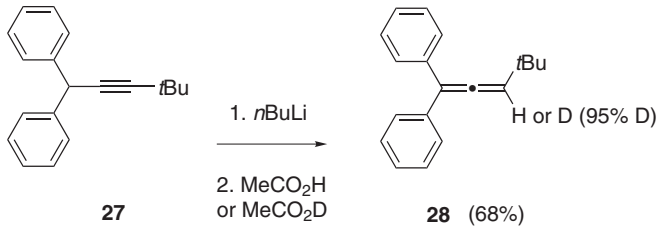


23 **24** (80%)

25 **26** (67%)

Scheme 1.9

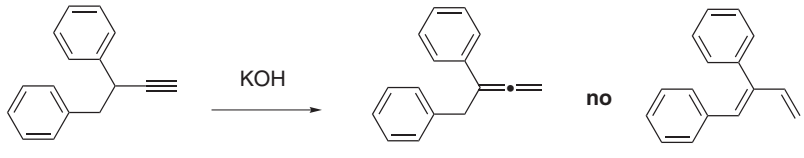
The above references, along with a number of others [41, 42], describe some more examples of substituted substrates. Even with a 1,1-diphenyl substrate **27**, a stoichiometric metalation followed by protonolyis (or deuterolyis) is necessary to obtain a good yield [43] (Scheme 1.10).



27 **28** (68%)

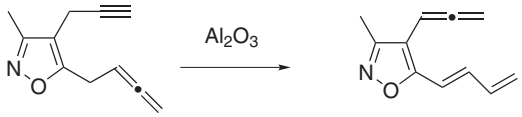
Scheme 1.10

It is notable that with substrates such as **29** still only **30** but no 1,3-diene **31**, which would bring the two aromatic rings into conjugation, is formed [44, 45] (Scheme 1.11).



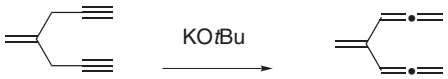
Scheme 1.11

Such a behavior cannot always be guaranteed; the heterocycle **32** with a terminal alkyne *and* an allene isomerizes both fuctional groups, the benzylic alkyne to an allene and the benzylic allene to a 1,3-diene, both now in conjugation with the heteroarene [46] (Scheme 1.12).



Scheme 1.12 **32** **33** (94%)

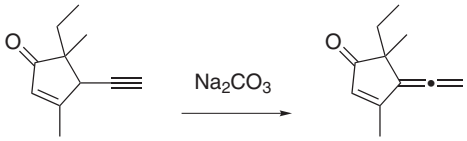
In some examples, two alkynes isomerized, leading to cross-conjugated systems such as **35** [47, 48] (Scheme 1.13).



Scheme 1.13 **34** **35** (88%)

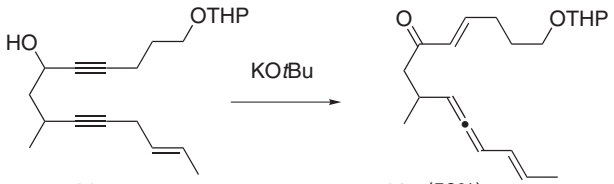
The isomerizations have also proven to be very useful in the synthesis of a series of 1,3-diarylallenes [49–55], even tolerating other functional groups such as aryl chlorides, aryl bromides [56–58] and vinyl bromides [59]. Mixed systems with an alkene on one side and an arene on the other could also be prepared [41, 60], as well as products with two olefinic substituents [61] or bisallenes [62–64].

Other functional groups tolerated in these isomerizations are ethers [65], alcohols [38, 66–69], propargylic trifluoromethyl groups [70], conjugated enones such as **36** [71] and esters [72] (Scheme 1.14).



Scheme 1.14 **36** **37** (100%)

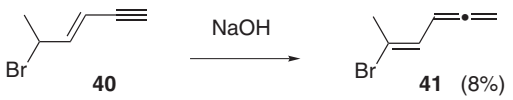
Still, occasionally the other fuctional groups react as well, for example in **38** under basic conditions the propargylic alcohol isomerizes to the α,β-unsaturated ketone [73] (Scheme 1.15), whereas in a closely related substrate from the synthesis of a subunit of compactin an allylic alcohol remains unchanged [74].



Scheme 1.15 **38** **39** (50%)

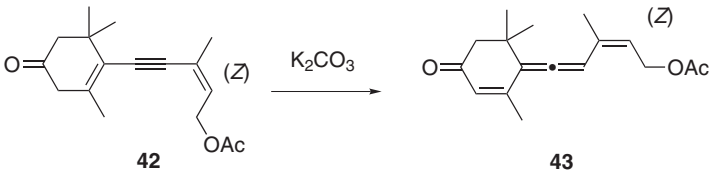
Substrate **38** also nicely displays the selectivity accompanying the neighboring alkenes or arenes: whereas with two alkyl chains on an alkyne two products would be formed, here a selective isomerization to the conjugated allene is observed.

(b) The migrating π-bond is already in conjugation to an alkene and *both* are shifted by one carbon atom during the isomerization. This 'vinylogous' case is best explained by the reaction of **40** to **41**, where – albeit in low yield due to elimination processes – even an allylic bromide delivers a vinyl bromide [75] (Scheme 1.16).



Scheme 1.16 **40** **41** (8%) (+ other products)

Similarly, the isomerization can be performed with an allylic ether [65, 76] and ketones such as **42** (with preservation of the double bond geometry!) [77] have also been reported to undergo these isomerizations (Scheme 1.17).

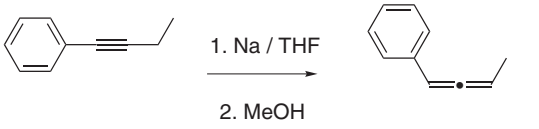


Scheme 1.17 **42** **43** (*E*) gives only (*E*)

Related steps, leading to unusual cross-conjugated systems, were discussed for the isomerization (*E*)-enediynes [78].

(c) The migrating π-bond is in conjugation with the neighboring alkene or arene and moves away. As one can imagine, this is much more difficult to achieve and therefore only a handfull of examples are found in the literature, usually providing the allene only as a side-product even in reactions with a stoichiometric amount of reagent. In the hydrocarbon series [79], **44** was reported to undergo this mode of

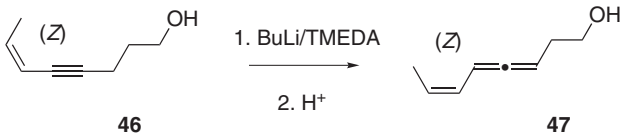
isomerization, along with a reduction, when treated with sodium or potassium [80] (Scheme 1.18).



44 **45** (up to 20%)

Scheme 1.18

Substrates with carbamate-protected [81, 82] and even free hydroxyl groups [69] reacted similarly in a deprotonation–reprotonation sequence, the latter even with retention of the *Z*-configuration of an alkene such as **46** (Scheme 1.19). The analogous (*E*)-alkene also delivers only *E*-product.



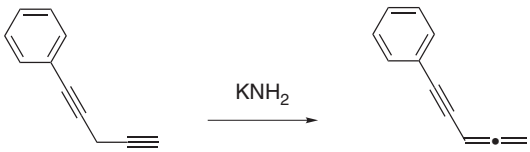
46 **47**

Scheme 1.19

An unusual approach is the isomerization of a methyl-substituted 1,2,3-butatriene to a vinylallene by stoichiometric deprotonation with *n*BuLi–TMEDA and reprotonation [83]. With an ether substituent on the butatriene a similar reaction is possible with KO*t*Bu in DMSO [84], while a phenyl-substituted butatriene reacted spontaneously in $CHCl_3$ [85].

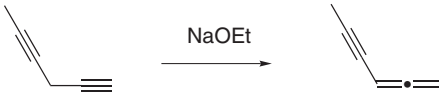
1.2.3
Alkinyl Groups as Substituents

This is a rare case; all the substrates have a skipped diyne structure, automatically raising the question of which triple bond will isomerize. In the case of the phenyl-substituted **48** it is the terminal alkyne, delivering the larger conjugated system in **49** [86] (Scheme 1.20).



Scheme 1.20 **48** **49**

Other examples reported with a terminal and an internal alkyne as in **50**, which do not like **49** have an additional possibility for conjugation, show that then the terminal alkyne isomerizes [62, 87, 88] (Scheme 1.21).



Scheme 1.21 **50** **51** (74%)

Comparable selectivities have been published for the intramolecular competition of an ester- and an alkyl-substituted alkyne [89] or a silyl- and an alkyl-substituted alkyne [90].

When the diyne is already conjugated as in 1,3-pentadiene **52**, with 4 equivalents of *n*BuLi–TMEDA, an isomerization can also be achieved [91] (Scheme 1.22). The selectivity of this process is low; starting material and 1,4-pentadiyne are also found.

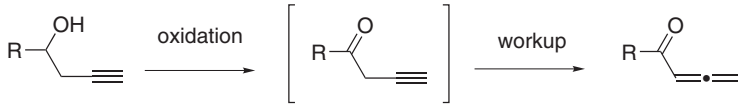
Scheme 1.22 **52** **53** (20%)

1.2.4
Carbonyl Groups as Substituents

This is a group of substrates which, along with sulfoxides, sulfones, phosphonates and related acceptors (see Sections 1.2.8 and 1.2.10), gives the most predictable results. Mild bases can be applied and this has found numerous applications in organic synthesis.

Most of the substrates for these isomerizations have a tetrahedral carbon with at least one hydrogen substituent between the carbonyl group and the alkyne. Due to the comparable high acidity of this C–H bond neighboring the carbonyl group, already a weak base such as a carbonate, a tertiary amine or aluminum oxide can deprotonate this position and a subsequent protonation at the other end of the propargyl/allenyl anion delivers the allene.

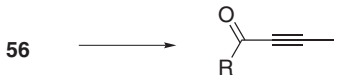
Ketones and aldehydes possess the highest α-acidity, many examples being known. In fact, it is usually very difficult to keep a terminal propargyl ketone from isomerizing to the allenyl ketone. Thus the oxidation of a homopropargylic alcohol **54**, a typical precursor, in most of these cases directly delivers the allenyl ketones **56** rather than the propargyl ketones **55** in high yields [92–109] (Scheme 1.23).



54 **55** **56**

Scheme 1.23

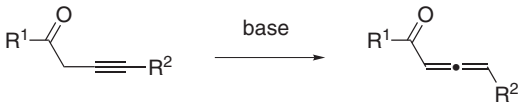
In these isomerizations, a base is not necessarily needed; for example, NMR investigation proved that oxidation under slightly acidic conditions initially indeed delivers **55**, which is stable for more than 1 week. During subsequent silica gel chromatography, which separates the acid from **55**, even with hexane–ethyl acetate on silica gel complete isomerization to **56** takes place [110]. Subsequently, more such isomerizations on silica gel were reported [111]. Studies with partially deuterated substrates prove that only the C–H bonds next to the ketone are broken during the reaction, the other propargylic C–H bonds remaining intact [112]. If the group R in **56** is strongly electron-withdrawing, even on silica gel a further isomerization to the alkynyl ketone **57** can be observed as a side reaction [110] (Scheme 1.24).



Scheme 1.24 **57**

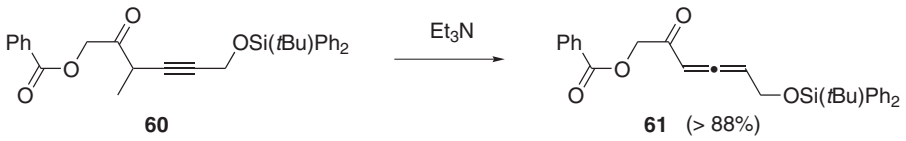
Only a distillative work-up from an acidic oxidation reaction, for example, delivers **55**, which then has to be isomerized by base to obtain **56** [113]. Similar precautions for the synthesis of **55** have been reported recently for a chromium-catalyzed oxidation [114]; here again the key is to avoid a base and even a chromatographic work-up, as already demonstrated for chromium-free Dess–Martin oxidations [110].

The whole situation changes slightly when the substrate contains a disubstituted alkyne **58** (Scheme 1.25). Then often no or only an incomplete or very slow isomerization is observed without a base. For example, a methyl substitution of the alkyne slows the reaction about 300-fold compared with the terminal alkyne [115]. However, with the base again high yields of the isomerization product **59** are obtained [116–121]. A substituent α to the carbonyl group seems to have a similar effect [122].



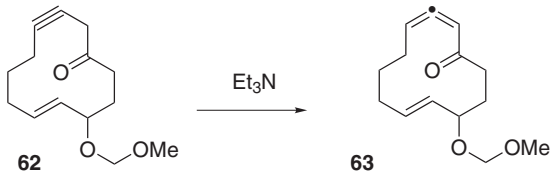
Scheme 1.25 **58** **59**

Among the most impressive applications are the reactions of the silyl- and acyl-protected diol **60** [123] (Scheme 1.26) and the 12-membered macrocyclic *E*-configured allylic ether **62** [124] (Scheme 1.27).



60 **61** (> 88%)

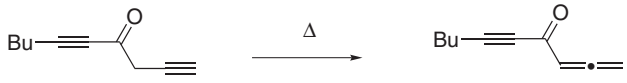
Scheme 1.26



62 63 (100%)

Scheme 1.27

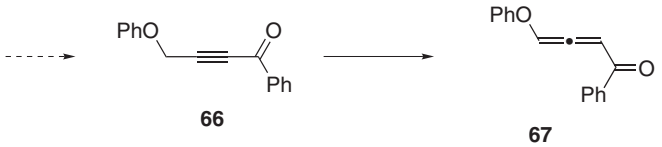
The last question still open addresses the alkynyl ketones. The reaction of **64** shows an example with a potential intramolecular competition and here it is possible to isomerize the propargyl substitutent on the ketone quantitatively without changing the 1-hexynyl substituent on the other side [125] (Scheme 1.28). From the publication it is not clear whether the isomerization is really a thermal reaction or occurs during the workup of the thermolysis reaction, for example by chromatography (compare the discussion above [110]).



64 **65** (100%)

Scheme 1.28

When alkynyl ketones are synthesized, occasionally an in situ isomerization to the allene was reported, for example in the propargylic ether **66** [126] (Scheme 1.29).

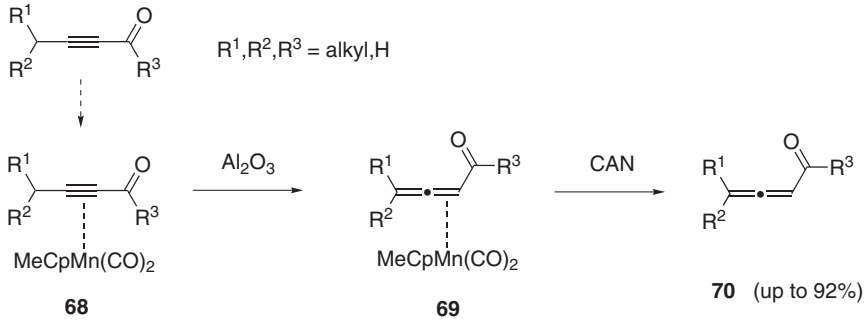


66 67

Scheme 1.29

The latter mode of reaction has even been reported to proceed in presence of silver(I) ions [127], which is not easy to understand in the context of Marshall's silver-catalyzed cycloisomerization of allenyl ketones (see Chapter 15).

An interesting sequence, again overall an isomerization, is the stoichiometric formation of the manganese complexes **68**, which, on basic alumina, isomerize to the allenyl complexes **69**; from the latter the allenes **70** can be liberated with cerium(IV) ammonium nitrate (CAN) in good yields [128] (Scheme 1.30).

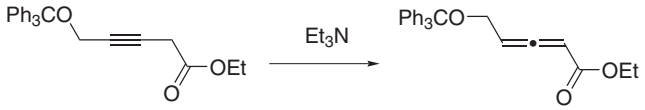


Scheme 1.30

A unique photochemical rearrangement in which an *o*-alkynylphenol is isomerized to an allenyl ketone has also been reported [129].

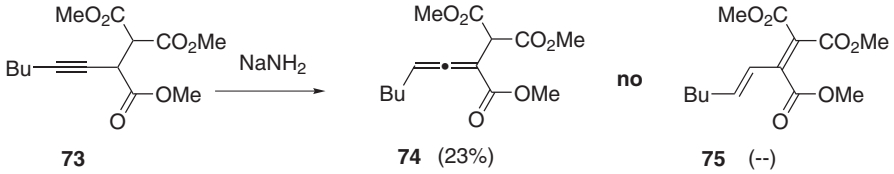
The second large class of allenes with carbonyl groups as substituents is derivatives of carboxylic acids. Overall, the same principles as with the aldehydes and ketones apply, but not as many examples are known, which might originate in part from the lower acidity of the α-hydrogen atoms of the carbonyl group compared with aldehydes and ketones.

Still, with ester groups, triethylamine is sufficient to catalyze the isomerization, as shown with the trityl-protected example **71** [130] (Scheme 1.31).



Scheme 1.31

Numerous related reactions have been published, some of them using aqueous potassium carbonate [131–135]. Again 1,3-dienes are not formed; **73** provides – apart from starting material – only **74** and no **75** [136] (Scheme 1.32).

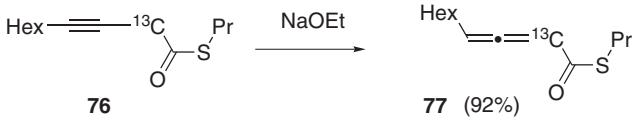


Scheme 1.32

Silyl esters have also been transformed successfully [137]; another example reports the *O*-acylation of serine with a β-alkynyl carboxylic acid anhydride accompanied by an in situ isomerization of the alkyne to the allene [138].

A number of references cover similar syntheses of allenes with carboxylic acids [131, 139–142] and amides [143] instead of carboxylic esters as electron-withdrawing

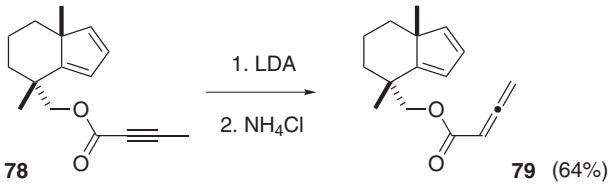
groups. A further significant example is the ^{13}C-labeled thioester **77** synthesized by isomerization for an investigation of the inactivation of β-hydroxydecanoyl thioester dehydrase [144] (Scheme 1.33). Even enyzme-catalzed isomerizations have been reported; with a hog liver isomerase, β-alkynyl thioesters deliver the corresponding allenes [144, 145].



76 **77** (92%)

Scheme 1.33

Again, the isomerization of an α-alkynyl ester to an allene requires stronger bases, in most known cases sodium amide in liquid ammonia or other strong bases [128, 147–149]. One further example is the step **78** → **79** from one of the efforts to synthesize myltaylenol [150] (Scheme 1.34).

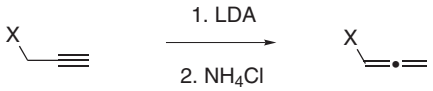


78 **79** (64%)

Scheme 1.34

1.2.5
Halogens as Substituents

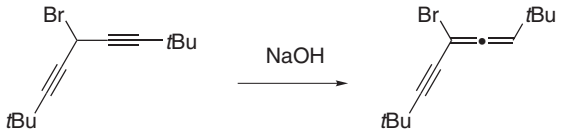
The isomerization of the smallest alkynes **80** with halogens in a propargylic position has been described for chlorine [151, 152], bromine [153] and iodine [154] (Scheme 1.35), but often might proceed by an S_N2'-type substitution rather than a prototropic rearrangement [155–159]. On the other hand, transformations such as **82** → **83** [160] or **84** → **85** [161] are clearly prototropic (Scheme 1.36). This is also true for propargylic halides such as **86** with its additional ester group assisting the prototropic isomerization [162, 163] (Scheme 1.37).



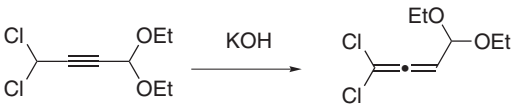
80 **81**

X = Cl,Br,I

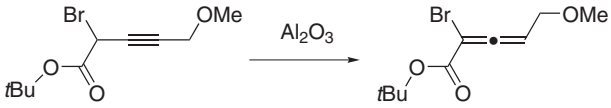
Scheme 1.35



82 **83** (65%)



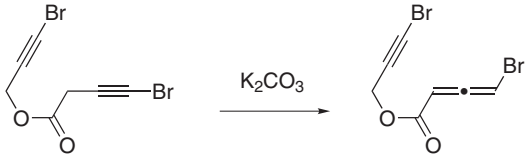
Scheme 1.36 **84** **85** (67%)



86 **87** (92%)

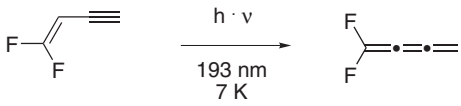
Scheme 1.37

An entirely different situation is found in alkynyl halides. Here only examples in which the rearrangement is supported by carbonyl groups [106, 164] or electron-withdrawing pentafluorophenyl groups [165] are known. As one example, the selective reaction of the alkynyl bromide next to the carbonyl group, in the presence of a second alkynyl bromide with a propargylic C–O sigma bond, is shown (**88** → **89**) [164] (Scheme 1.38).



Scheme 1.38 **88** **89**

A unique reaction is the photochemical rearrangement of **90** to the 1,1-difluorobutatriene **91** in an argon matrix at 7 K [166] (Scheme 1.39).



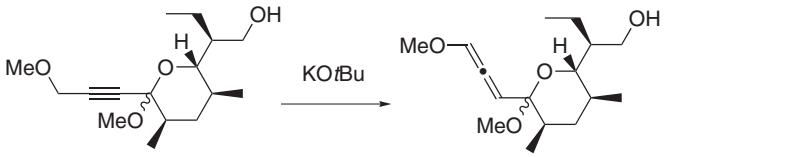
Scheme 1.39 **90** **91**

1.2.6
Oxygen as the Substituent

These allenes are very important for organic synthesis and their use is discussed in Chapter 8. For their synthesis usually a strong base is needed, typically KO*t*Bu. There are many examples; most of them cover the isomerization of a propargylic ether to the corresponding allenyl ether.

The significance of this reaction is reflected by the isomerization of the smallest representative, propargyl methyl ether, with a number of references from 1968 up to 2000 [167–175].

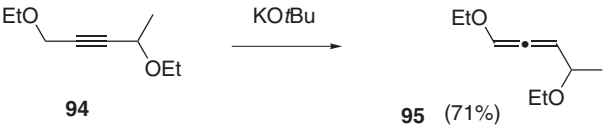
Further, a large number of examples with simple alkyl substituents [168, 171, 176–184], cyclic alkanes [185], aryl substituents [177, 186–192], olefinic substituents [78, 177, 193–196], deuterated compounds [172], thioether groups [171], ester groups [197], orthoesters [198, 199], acetals [168, 182, 200–204], silyl-protected alcohols [198, 205–211], aldehydes [212], different heterocycles [213–217], alkyl halides [218, 219] and aryl halides [192, 220–223] have been reported. A representative example is the reaction of **92**, possessing a free hydroxyl group, an acetal and a propargylic ether, to **93** [224] (Scheme 1.40).



92 **93** (49% after four more steps)

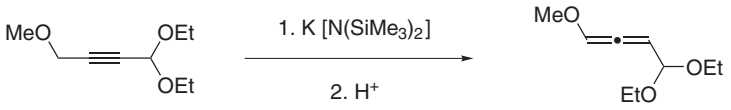
Scheme 1.40

The intramolecular competition of two propargylic alkoxy groups, one on each side of the alkyne, is interesting. In a series of substrates related to **94** [180], always the 1,2-disubstituted allene **95** (Scheme 1.41) and not a 1,1,3-trisubstituted allene is formed (see also [225, 226]). The opposite regioselectivity was described in one publication (deprotonation with *t*BuLi, then protonation), but the allenes described there proved to be labile and quickly converted to other products [227].



Scheme 1.41 **94** **95** (71%)

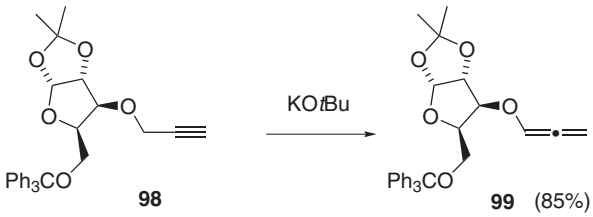
Related competitions between a propargylic ether on one side and a propargylic acetal on the other always delivered the product of an isomerization in the direction of the ether. Compound **96** with stoichiometric amounts of potassium hexamethyldisilazide serves as a recent example [228] (Scheme 1.42); other references describe the same reactivity [229–231].



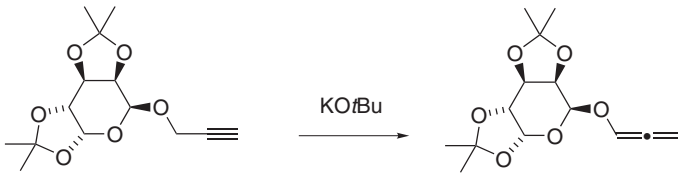
96 **97** (88%)

Scheme 1.42

The competition between a propargylic ether and a teriary propargylic amine provided an allenyl ether rather than an allenylamine [182]. The reaction was also successful with propargyl allyl ethers [232]. An additional ester group in the propargylic position is tolerated [233], and consequently the reaction also works with esters of propargylic alcohols [234–236]. In the past 4 years, several derivatives of carbohydrates were converted successfully [217, 237–241]; two examples are the isomerizations of enantiomerically pure **98** [242] and **100** [217, 243] (Scheme 1.43).



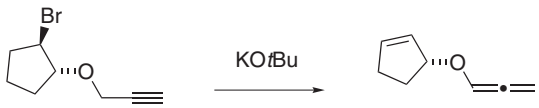
98 **99** (85%)



100 **101** (84%)

Scheme 1.43

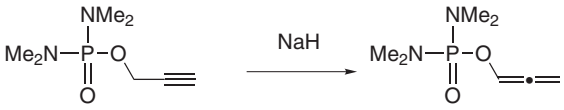
Due to the basic conditions, the reaction can be accompanied by an elimination, and then it is only locally (at the propargylic ether) an isomerization; see **102** [195] (Scheme 1.44) as one of several examples [218, 244, 245].



Scheme 1.44 **102** **103** (87%)

The combination of a silyl-migration from carbon to oxygen and a prototropic isomerization leads to allenyl silyl ethers [246].

A last and unusual substrate in this section is a propargyl ester of a phosphorus acid diamide **104** [247] (Scheme 1.45).

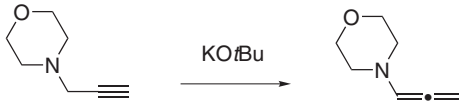


Scheme 1.45 **104** **105** (70%)

1.2.7
Nitrogen as the Substituent

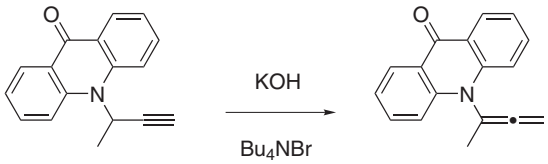
The basic principles of the previous section (oxygen substituent) can be transferred to nitrogen as the substituent. Here most of the examples use either potassium *tert*-butylate or a stoichiometric deprotonation with *n*-butyllithium followed by protonation with methanol.

A number of alkyl-substituted propargylic amines have been isomerized in that way [186, 191, 248–251], occasionally also providing alkynylamines as side-products. Compound **106** shows a recent example of a selective isomerization [252] (Scheme 1.46).



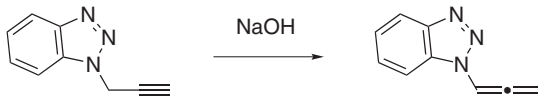
Scheme 1.46 **106** **107** (39%)

Arylamines with a propargyl group react under the same conditions [191, 253–256]; in the case of the vinylogous amide **108**, potassium hydroxide and a phase-transfer catalyst are sufficient [257] (Scheme 1.47).



Scheme 1.47 **108** **109** (65%)

In heteroaromatic compounds such as **110** [258] (Scheme 1.48), the nitrogen atom can be part of the aromatic ring [252, 259–262]. The most significant examples are found in the area of nucleobases and related heterocyclic compounds [263–271]; in **112**, for example, an alcohol group is competing with the propargylic nucleobase, and this alcohol group is probably responsible for the low yield as an isomerization



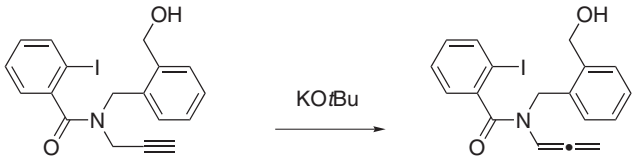
Scheme 1.48 **110** **111** (60%)

112 **113** (40%)

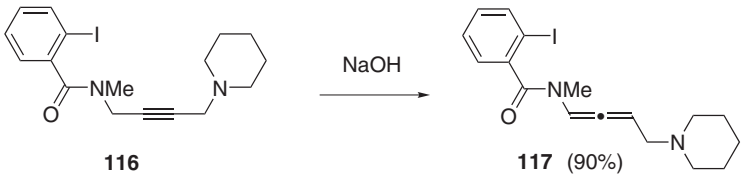
Scheme 1.49

in this direction will ultimately lead to an enone and products derived from it under the nucleophilic conditions [272, 273] (Scheme 1.49).

Amides and carbaminates are a further class of substrates [255, 274–278]. Compound **114** shows a substrate with an unprotected hydroxyl group and an aryl iodide [279] (Scheme 1.50), **116** an aryl iodide and the competition of an amide with an amine, yielding a 2.5:1 mixture of amide isomers favoring the (*Z*)-amide configuration depicted in **117** [280] (Scheme 1.51).



Scheme 1.50 **114** **115**

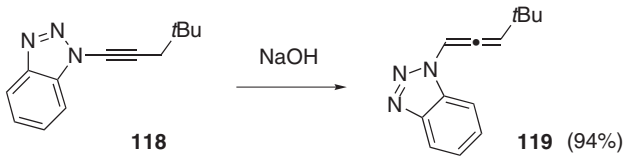


116 **117** (90%)

Scheme 1.51

Propargylated tosylamides also isomerize efficiently [221, 281]. On the other hand, rare examples are propargylated hydrazines [251], *N*-propargylated imines [282], isonitriles (must be *N*-propargylated) [283], ammonium salts [284] and azides [285].

Finally, an 'inverse' reaction, the isomerization of an alkynylbenzotriazole **118** to the corresponding allenyl compound **119**, has also been described [286] (Scheme 1.52).



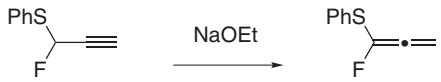
118 **119** (94%)

Scheme 1.52

1.2.8 Sulfur as the Substituent

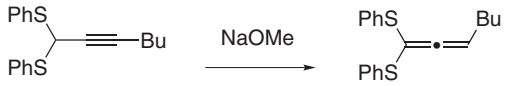
As far as propargyl thioethers are concerned, the substrates in this section follow all the principles discussed for propargyl ethers and propargylamines in the two preceding sections. For alkyl propargyl thioethers typical bases used are sodium amide in liquid ammonia, alcoholate or alkali metal hydroxide [178, 186–189, 191, 287–291], and again some derivatives of carbohydrates have been used successfully [292, 293]. If an ester group is also present in the molecule, the reaction can be accompanied by a hydrolysis to the carboxylate [294].

Among the aryl propargyl thioethers [187, 188, 191, 295–300], the fluorinated **120** is worth mentioning [301, 302] (Scheme 1.53). A few heteroaryl propargyl thioethers have also been investigated [213, 303–305].



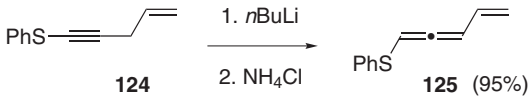
Scheme 1.53 **120** **121** (70%)

As known from the 'Umpolung' reactions, dithioacetals can be deprotonated efficiently; among others [230, 306], a recent application is **122** [307] (Scheme 1.54). Even basic aluminum oxide can catalyze these isomerizations. One older example reports the isomerization of an *S*-propargyl phosphanesulfide to the allene [308].



Scheme 1.54 **122** **123** (95%)

The 'inverse' isomerization mode, providing allenyl thioethers from alkynyl thioethers, is also known [309, 310]; for example, **124** is first deprotonated with *n*-butyllithium and then protonated with ammonium chloride [311] (Scheme 1.55).

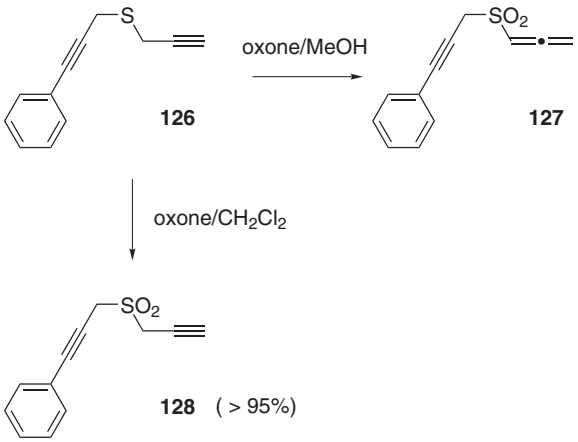


124 **125** (95%)

Scheme 1.55

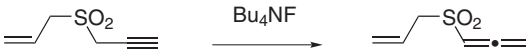
With selenium only a handfull of reactions has been published, involving both propargyl selenoethers [187, 188] and alkynyl selenoethers [312].

The reactions of the corresponding propargyl sulfoxides and sulfones now resemble the chemistry of the other acceptor-substituted derivatives such as ketones and aldehydes (see Section 1.2.4). Compared with the thioethers, here much milder bases are sufficient; apart from aluminum oxide, often triethylamine or potassium carbonate are used. Sometimes even a spontaneous isomerization takes place. The selective isomerization of one triple bond in the presence of a second triple bond in **126** [313] (Scheme 1.56) or an allyl sulfone in **129** [314] (Scheme 1.57) are just two examples out of a whole series [178, 304, 313, 315–331]. When, on the other hand, the in situ oxidation of **126** was carried out in an aprotic solvent, no isomerization at all was observed.



126 **127** **128** (> 95%)

Scheme 1.56

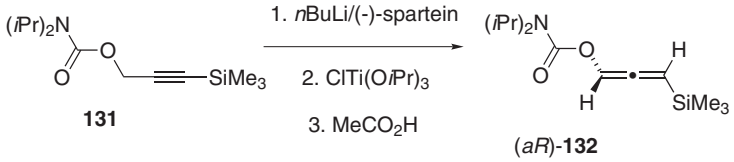


129 **130** (65%)

Scheme 1.57

1.2.9
Silyl and Stannyl Substituents

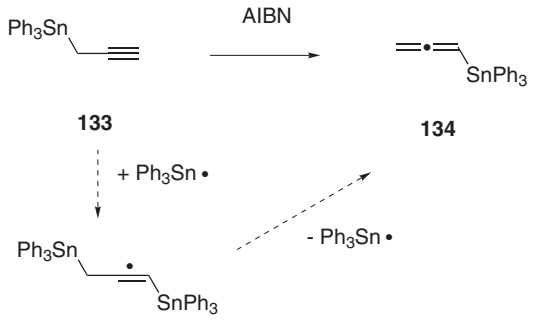
The synthesis of such compounds by prototopic rearrangement is rare; most examples use a stoichiometric deprotonation followed by reprotonation. All reactions use alkynylsilanes as substrates; there the α-effect might still influence the vinylog position, and strong bases such as *n*BuLi or LDA are needed [332–335]. Often the allene is only a side product from a reaction where an alkynyl silane is deprotonated and subjected to other electrophiles [336]. Wherease in earlier examples of a metalation with *n*BuLi, a subsequent transmetalation to zinc and a final protonolyis only traces of allene could be observed [337], the reaction of a related substrate **131** with *n*BuLi, a transmetalation to titanium and a final protonolysis delivered the allenylsilane **132** [338, 339] (Scheme 1.58). The use of sparteine as a ligand in the synthesis of **132** led to an *ee* of 88% in favor of (*aR*)-**132**.



Scheme 1.58

Deuteration studies with a silylbutatriene with KO*t*Bu in *t*BuOD provided evidence for a selective α-deprotonation [340].

For stannanes, there exists one example of a rearrangement (**133** → **134**) which at first sight resembles a prototropic rearrangement, but is in fact a radical chain reaction [341] (Scheme 1.59).



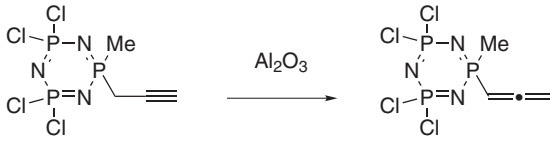
Scheme 1.59

Most of the allenes with silyl or stannyl substituents are prepared by the routes discussed in Chapter 9.

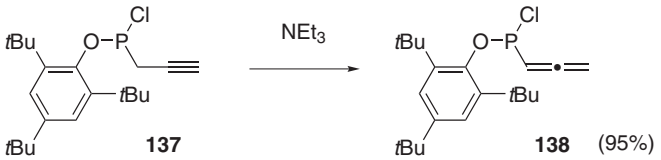
1.2.10
Phosphorus as the Substituent

The field of allenes bearing phosphorus is dominated by sigmatropic rearrangements (see Section 1.3.1). Nevertheless, some examples of prototropic rearrangements are known.

For propargyl phosphorus compounds, examples with cyclotriphosphazenes **135** [342] (Scheme 1.60), phosphinates **137** [343] (Scheme 1.61) and phosphonates **139** [344] (Scheme 1.62) have been published.



Scheme 1.60 **135** **136**

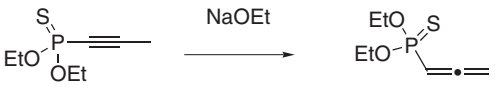


137 **138** (95%)

Scheme 1.61

Scheme 1.62 **139** **140** (40%)

The alkynyl thiophosphonate **141** allowed an isomerization with sodium ethoxide [345] (Scheme 1.63).



Scheme 1.63 **141** **142** (35%)

If one considers a TMS group to be equivalent to a proton, a recent paper describes the formation of a phosphanyl-substituted allene by a keto–enol tautomerization-like silyl migration [346].

1.2.11
Allenes from Prototropic Isomerizations of Alkynes as Reactive Intermediates

As mentioned in the Introduction, this chapter focuses on reactions that deliver allenes as the product. The principles discussed in Sections 1.2.1–1.2.9, of course, also allow the synthesis of allenes as reactive intermediates, which due to other functional groups that are present, undergo further reactions in situ. The most important examples here are base-catalyzed isomerizations to furans [347, 348] ring transfer reactions of propargylic ethers or amines [216, 349–371] and enyneallene cyclization reactions starting from propargylic sulfones [372–375] and related substrates [376, 377]. Details are discussed, for example, in Chapters 16 and 20.

1.3
Sigmatropic Rearrangements

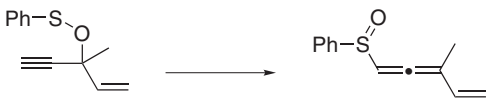
After the prototropic isomerizations, these rearrangements are the second most important synthetic methodology. In the concerted reactions a highly selective central to axial chirality transfer is possible, but this has already been exploited before the timeframe covered by this review and has been summarized [378].

1.3.1
[2,3] Sigmatropic Rearrangements

1.3.1.1 With Sulfur

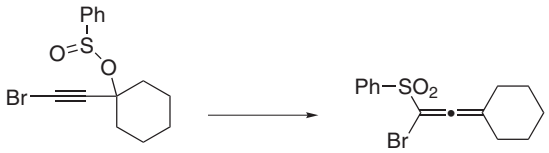
Two different types of substrates are used here, propargyl sulfenates and propargyl sulfinates. In both cases often the propargylic esters are prepared and then converted to the allenes in situ.

An example involving propargyl sulfenates is the reaction of **143** leading to the vinylallene **144** [379] (Scheme 1.64); related conversions have been reported [380] and often the propargyl sulfenates are prepared in situ and isomerize at low temperatures [381–424].



Scheme 1.64 **143** **144**

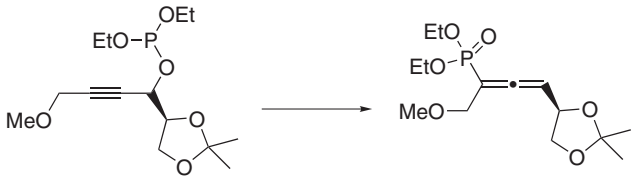
The corresponding propargyl sulfinates behave similarly. Compound **145** [425] (Scheme 1.65), demonstrating the principle with an interesting alkynyl bromide as the substrate, is just one of numerous examples [322, 380, 403, 423, 426–443].



Scheme 1.65 **145** **146** (71%)

1.3.1.2 With Phosphorus

Propargyl phosphites and derivatives thereof, in addition to phosphinates, are feasible substrates for this conversion. Here also a reaction is already observed at low temperatures. The chiral **147** delivers a mixture of diastereomers in about a 1:1 ratio [444] (Scheme 1.66).



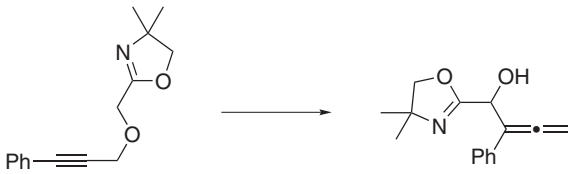
147 **148** (85%)

Scheme 1.66

Other examples cover phosphites [380, 403, 425, 445–477] and phosphinates [375, 392, 396, 423, 425, 462, 464, 471, 478–500], which have become very important in, for example, the field of enyneallenes (Chapter 20).

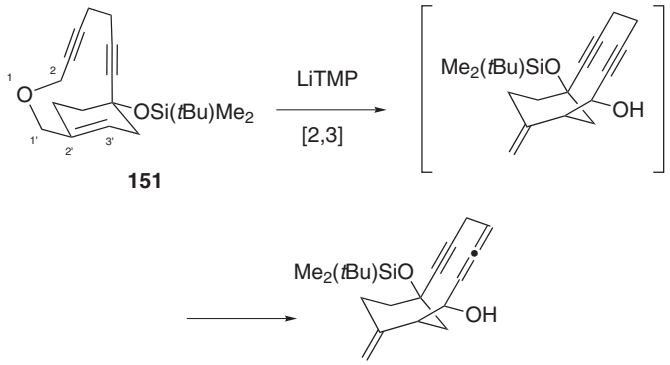
1.3.1.3 [2,3]-Wittig Rearrangement

A few isomerizations cover the Wittig rearrangement [501, 502]. Usually, anion-stabilizing groups, for example an imidate such as **149**, are used [503] (Scheme 1.67).



Scheme 1.67 **149** **150** (55%)

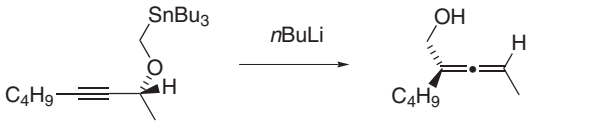
Another recent example is the formation of **152** [504] (Scheme 1.68). However, the allene unit was formed by a base-catalyzed isomerization *after* the [2,3]-Wittig rearrangement of **151**. Only one diastereomer was detected; the configuration of the allenic unit in **152** was not determined.



151 **152** (67%)

Scheme 1.68

In this context, albeit not real isomerizations, the [2,3]-Wittig rearrangements induced by a tin–lithium exchange must also be mentioned. Starting from enantiomerically pure propargylic alcohols, high *ee* values for the axial chiral allenes could be observed as shown for **153** (Scheme 1.69) [505, 506].



153 **154** (71%, 93% *ee*)

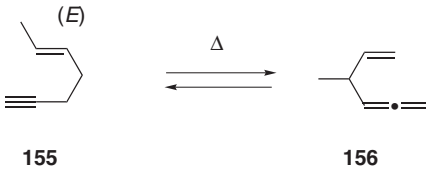
Scheme 1.69

1.3.2 [3,3]-Sigmatropic Rearrangements

This second class of sigmatropic rearrangements can again be subdivided; here we find several classical named reactions that, again with propargylic substrates, lead to allenic products.

1.3.2.1 Cope Rearrangement

There exist early examples of this transformation [507, 508], but due to the symmetric structure of the alkene part, only isotope labeling, etc., allowed the exclusion of a prototropic rearrangement. Furthermore, due to the high reaction temperatures of 340 °C and above, several different products are formed. A low-temperature version (77 K) of this reaction via the radical cation has been reported [509]. The chirality transfer has been studied and a detailed mechanistic investigation has been conducted [510]; typical experiments in that context were the reactions of substrates such as **155** and **157** (Scheme 1.70).



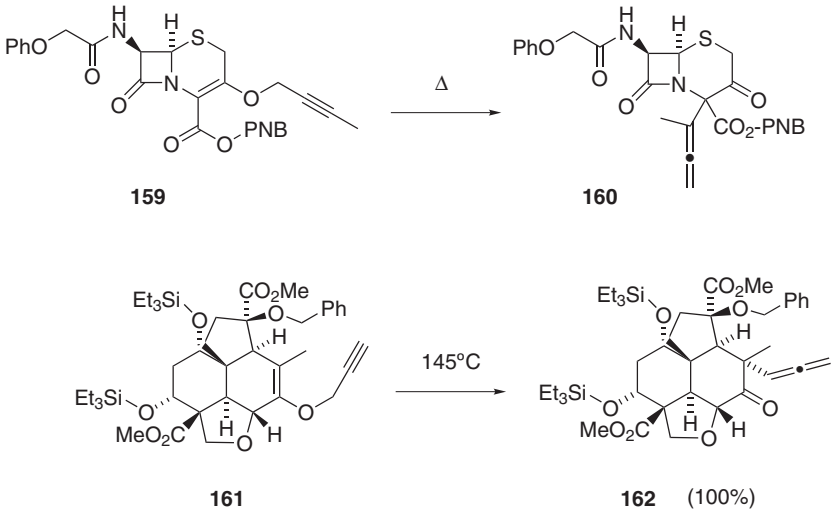
(*R*,*E*)-**157** (*R*,*E*)-**158**

Scheme 1.70

Thermodynamic and kinetic data for Cope rearrangements leading to allenes have been measured [511]. For preparatively useful yields the equilibrium can be shifted to the allene, for example by the classical use of allylic alcohols leading to carbonyl compounds [512].

1.3.2.2 **Claisen Rearrangement**

The Claisen rearrangement of propargyl vinyl ethers directly delivers the allene; no equilibrium is observed. This reaction was also successful with complex substrates; in order to show this, of numerous examples [375, 513–536], the compounds **159** [537] and **161** [538] are depicted (Scheme 1.71).

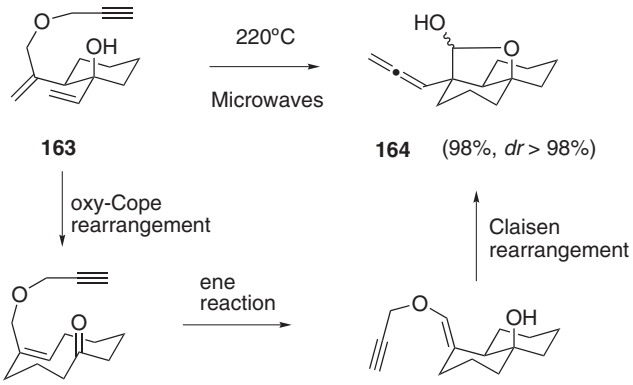


159 **160**

161 **162** (100%)

Scheme 1.71

A remarkable example is the combination of three pericyclic reactions for the synthesis of decalin frameworks with quaternary centers by a tandem oxy-Cope–ene–Claisen reaction shown in **163** [539] (Scheme 1.72).



Scheme 1.72

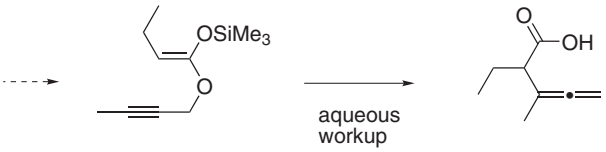
In many of the reactions the allenes are only intermediates in such tandem sequences [540–542] or the starting materials generated in situ [543–545].

Thio- [546] and even iodonio-Claisen rearrangements are known [547].

In arylpropargylamines with two *ortho*- and a *para*-substituent, by protonation a charge-induced sequence of a [3,3]-sigmatropic aza-Claisen rearrangement (with inversion of the propargyl system to the allene) and a subsequent [1,2]-shift (without inversion of the allene) can be observed [548]. 1-Propargyloxy-λ^5-phosphorin derivatives undergo comparable isomerizations; the thermodynamic driving force is the formation of the phosphane oxide [549]. However, the reaction probably does not follow a concerted mechanism, otherwise after the equivalent of a *para*-Claisen-rearrangement not an allene but an alkyne should be generated from the propargyl reactant.

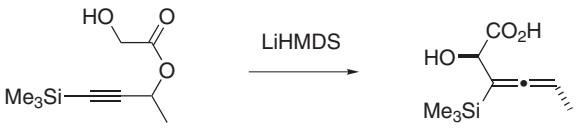
1.3.2.3 **Keteneacetals, Esterenolates and Orthoesters**

Reactions proceeding via propargyl keteneacetals such as **165** [550] (Scheme 1.73) also generate allenes by isomerization reactions.



Scheme 1.73 **165** **166** (53%)

Often these intermediates are generated in situ from orthoesters and propargylic alcohols [551] or propargyl esters such as **167** (Scheme 1.74) [552].



167 **168** (88%)

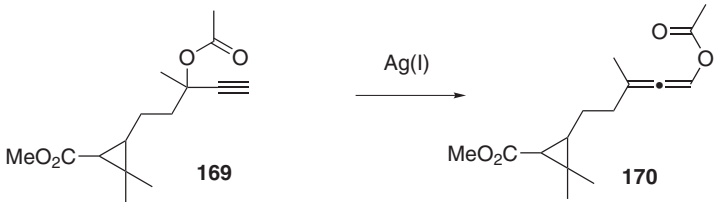
dr 95 : 5 in favor of the depicted diastereomer

Scheme 1.74

Other examples are based on the classical one-pot procedure starting from an orthoester, a catalytic amount of acid and a propargylic alcohol [553–558]. Esterenolates react similarly [559, 560].

1.3.2.4 **Esters**

The [3,3]-sigmatropic rearrangement of propargyl esters [234, 561] is usually an equilibrium reaction; for example steric repulsion can help to deliver mainly the allene [562] and faster reaction kinetics are observed with silver(I) and copper(I) catalysts [562–571] (see cyclopropane **169** in Scheme 1.75) [572], and recently also rhodium(I) catalysts [573].

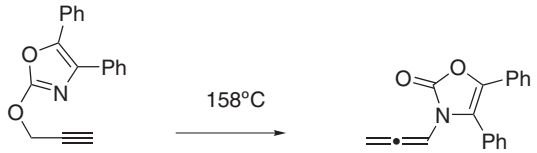


169 **170**

Scheme 1.75

1.3.2.5 **Acetimidates**

In analogy with the propargyl esters, propargyl acetimidates can be used, and then the equilibrium clearly lies on the side of the allene [574, 575]. Often the acetimidate is a substructure of a heterocycle such as **171** (Scheme 1.76) [576] or related compounds [577, 578].

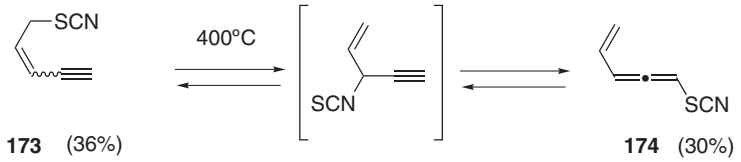


Scheme 1.76 **171** **172** (90%)

A thioimidate substructure was reported to react analogously with good yields [579].

1.3.2.6 Other Substrates

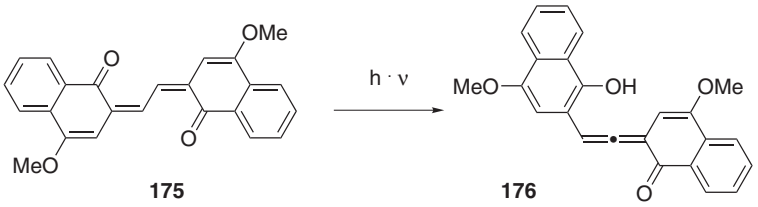
Several other propargylic substrates have successfully undergone [3,3]-sigmatropic rearrangements. Examples are thiocyanates to isothiocyanates [580], the opposite conversion [581] and the equilibrium between such species as exemplified by **173** (Scheme 1.77) [582], cyanates to isocyanates [582] and the formation of isoselenocyanates [583] and azides [584].



Scheme 1.77

1.4 Rearrangements of Other Systems with at Least Two π-Bonds

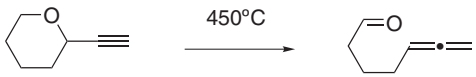
These reactions would fall into the category Reaction B in Scheme 1.1. Thermodynamically such an isomerization should be strongly disfavored and indeed the only example seems to be the conversion of **175** to **176** under photochemical conditions [129] (Scheme 1.78). There a significant amount of energy is put into the system and the aromatization also helps.



Scheme 1.78

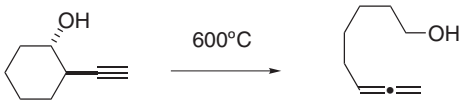
1.5 Retro-ene Reactions

While there seem to exist only a few examples for Reaction C in Scheme 1.1 [585], which mostly are photochemical [586–595], these retro-ene reactions can be considered as the purely intramolecular case of a substitution described in Reaction G. The thermolysis of **177** delivers **178** by such a retro-ene reaction [596] (Scheme 1.79).



Scheme 1.79 **177** **178**

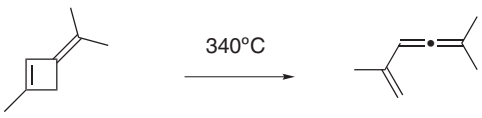
A C–C bond cleavage instead of C–O bond cleavage in the examples above was reported for the vacuum pyrolysis of **179** [597] (Scheme 1.80).



Scheme 1.80 **179** **180** (71%)

1.6 Electrocyclic Ring Openings

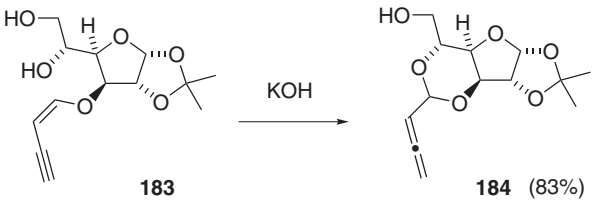
This is Reaction D in Scheme 1.1. The reaction gives preparatively useful yields of **182** from the substituted **181** [598] (Scheme 1.81). On the other hand, a vinylallene often is only a transient species [599]. Further references cover the inverse reaction, the ring closure of the unsubstituted vinylallene [600] and the equilibrium of related substrates [601–605].



Scheme 1.81 **181** **182** (55%)

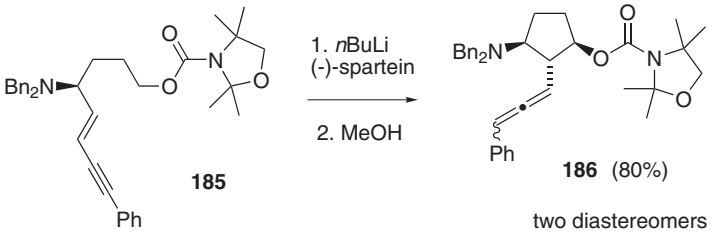
1.7 Intramolecular Conjugate Additions

Some examples of Reaction E in Scheme 1.1 are known. A 1,3-enyne, **183**, will deliver the allene **184** [606] (Scheme 1.82). A related reaction of **185** was also successful [607] (Scheme 1.83).



183 **184** (83%)

Scheme 1.82



185 **186** (80%)

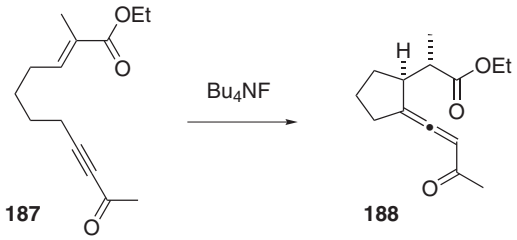
two diastereomers
dr 70 : 30

Scheme 1.83

It seems that there exist no examples of Reaction F in Scheme 1.1.

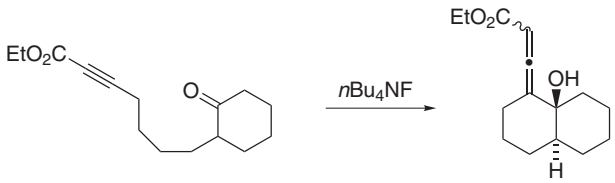
1.8
Complex Reactions and Rearrangements

A combination of a deprotonation with an intramolecular Michael addition/isomerization is found in the conversion of **187** to **188** [608] (Scheme 1.84). The analogous intramolecular addition to a carbonyl group leads to **190** [609] (Scheme 1.85).



187 **188**

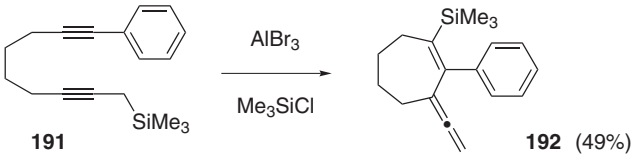
Scheme 1.84



189 **190** (87%)

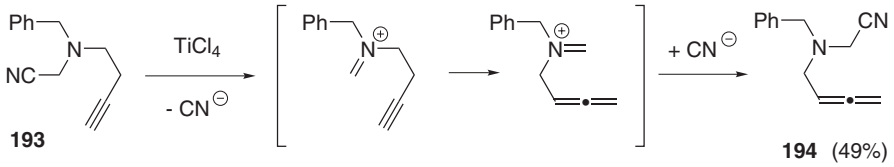
Scheme 1.85

The migration of a silyl group in **191** instead of a proton is possible with $HfCl_4$ or $AlBr_3$ as a catalyst [610] (Scheme 1.86).



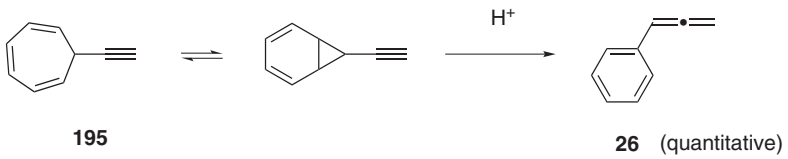
Scheme 1.86

The combination of a $TiCl_4$-catalyzed formation of an iminium salt from **193**, a subsequent [3,3]-sigmatropic rearrangement followed by a return of the cyanaide provided **194** (Scheme 1.87) [611].



Scheme 1.87

Ethynylcycloheptatriene **195** when treated with acid isomerizes to phenylallene **26** [612] (Scheme 1.88).



Scheme 1.88

1.9 Conclusion

Isomerization reactions are an excellent method for the synthesis of allenes. Depending on the method, numerous functional groups are tolerated, hence these reactions match the demands of modern synthesis. In the other chapters of this book we will encounter these reactions again, embedded in a wider chemical context. Not the preparation of the allene but its use in organic synthesis and the benefits of its high reactivity will then be the major focus.

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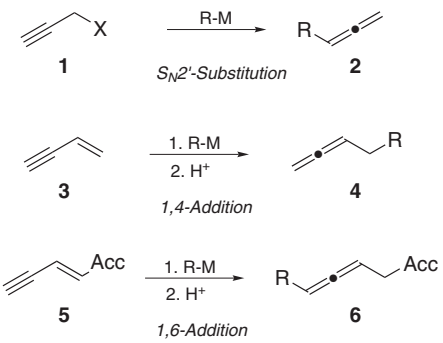
2
Metal-Mediated Synthesis of Allenes

Anja Hoffmann-Röder and Norbert Krause

2.1
Introduction

The use of organometallic reagents for the synthesis of allenes is highly developed and several fundamentally different methods, which are covered in separate chapters throughout this book, are now well established. Isomerization reactions to generate allenes involving organometallic bases are covered in Chapter 1, and the transition metal-catalyzed synthesis of allenes is discussed in Chapter 3. The well-known Doering–Moore–Skattebøl method is described inter alia in Chapters 5 and 6 and finally, the preparation of allenes from allenyl- or propargylmetal reagents can be found in Chapter 9. In contrast, the present chapter deals with the use of *stoichiometric amounts* of *non-allenic* organometallic reagents for the generation of allenic target molecules starting from unsaturated electrophiles. A number of these transformations can be carried out in either a catalytic or stoichiometric fashion using the same type of organometallic reagent; in these cases the reader will be referred to the corresponding section of Chapter 3.

The fundamental reaction types suitable for metal-mediated syntheses of allenes (Scheme 2.1) comprise S_N2' nucleophilic substitution reactions of propargylic elec-



Scheme 2.1 Important reaction types in the metal-mediated synthesis of allenes. X = leaving group; Acc = acceptor substituent.

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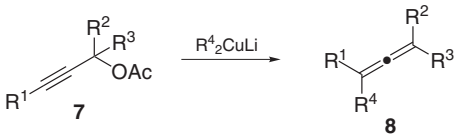
trophiles **1**, as well as 1,4-additions to (unfunctionalized) enynes **3** and 1,6-addition reactions to acceptor-substituted enynes **5**.

In these transformations, organocopper compounds are often the reagents of choice, although recently other metals such as aluminum, titanium, samarium and indium have also proven to be highly useful. Since earlier contributions to this field have already been summarized extensively [1], we shall concentrate on more recent contributions published after 1980. Rather than trying to be comprehendsive, representative examples with references to the most important reaction types will be given.

2.2 Copper-Mediated Synthesis of Allenes

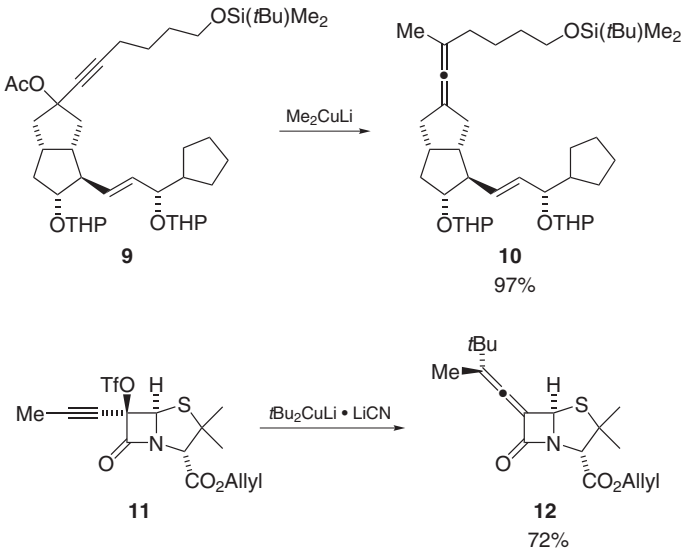
2.2.1 Substitution Reactions

The first examples of allene syntheses using copper-mediated S_N2' substitution processes are documented for the reaction of propargylic acetates **7** with lithium dialkylcuprates, which led to the formation of allenes **8** with moderate to good chemical yields (Scheme 2.2) [2].



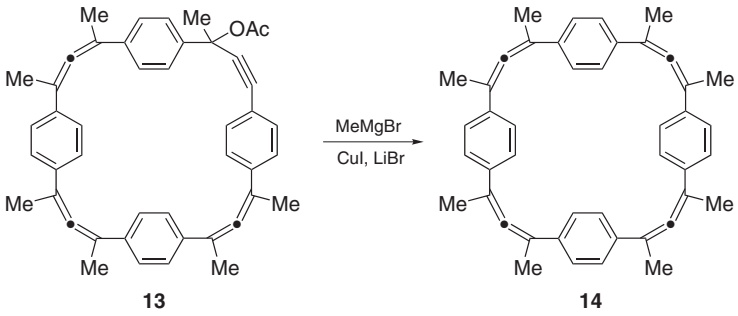
Scheme 2.2 Allene synthesis via S_N2' substitution of propargylic acetates **7** with cuprates.

Since its discovery by Rona and Crabbé in 1968 [2], this method has developed into one of the most versatile and popular protocols for the synthesis of allenes [1, 3]. One reason for its popularity is the fact that many combinations of organocopper reagents and leaving groups result in clean conversions of the propargylic electrophiles to the desired allenes, which are often isolated in high chemical yield. Thus, in addition to acetates, benzoates and carbonates [2–4], propargylic sulfonates [5], ethers and acetals [6], halides [7], oxiranes [8] and even aziridines [8a, 9] have been successfully employed as substrates. With regard to the reagent, simple lithium diorganocuprates have been complemented inter alia by magnesium cuprates of different composition [10], and also by functionalized cuprates derived from the corresponding Grignard and organozinc reagents [11]. In addition to numerous applications in natural product synthesis summarized in Chapters 18 and 19, this strategy has likewise been highly relevant for the generation of pharmacologically active target molecules. For example, the methylated carbacyclin derivative **10** [4a] (cf. Section 18.3.2) and the 6-alkylidenepenam **12** [12], and also related 7-alkylidenecephalosporins [13], were efficiently formed by cuprate-mediated S_N2' substitution reaction of the corresponding propargylic derivatives **9** and **11** (Scheme 2.3).



Scheme 2.3 Formation of pharmacologically active target molecules by S_N2' substitution of propargylic electrophiles with organocuprates. THP = tetrahydropyranyl; Tf = trifluoromethanesulfonyl.

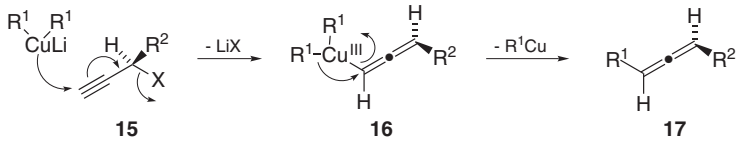
In the area of allenic non-natural product chemistry, the synthesis of the [3$_4$]allenophane **14** (Scheme 2.4) is particularly noteworthy, with all four of its allenic bridges being formed through subsequent S_N2' substitution reactions of propargylic acetates with a methyl magnesium cuprate [14] (see Section 2.5 for an alternative synthesis of macrocyclic allenes).



Scheme 2.4 Final step of the synthesis of the [3$_4$]allenophane **14**.

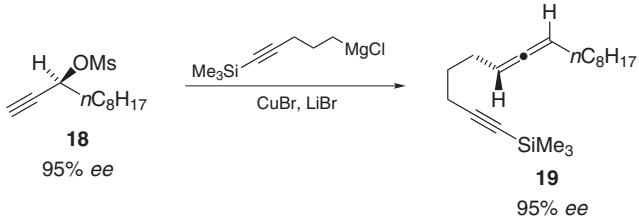
Furthermore, the copper-mediated S_N2' substitution reaction is not restricted to carbon–carbon bond formation, as can be seen form the synthesis of silylallenes [15], stannylallenes [16] and bromoallenes [17] using propargylic electrophiles and the corresponding heterocuprates. The resulting allenes are often used as intermediates in target-oriented synthesis, e.g. in cyclization and reduction reactions [15–17].

In particular, the S_N2' substitution of propargylic acetates with $LiCuBr_2$ has proven to be valuable for the synthesis of naturally occurring bromoallenes, as demonstrated in the work of Crimmins and others (cf. Section 18.2.3) [18]. Many of these applications take advantage of the fact that the copper-promoted S_N2' substitution of propargylic electrophiles (in particular sulfonates) often proceeds with high *anti*-stereoselectivity (cf. formation of allene **12**, Scheme 2.3) [1, 3, 19]. This efficient center-to-axis chirality transfer is rationalized by an interaction of a copper-centered d-orbital with σ and π^* orbitals of the substrate (for details, see Chapter 4). This leads to the formation of a σ-copper(III) species **16**, which finally undergoes a reductive elimination of an alkylcopper compound to furnish the *anti*-substitution product **17** (Scheme 2.5). Unfortunately, theoretical calculations, which have been highly useful for the mechanistic understanding of other copper-mediated transformations [20], have not yet been carried out for the S_N2' substitution of propargylic electrophiles.



Scheme 2.5 Mechanistic model for the *anti*-stereoselective S_N2' substitution of propargylic electrophiles.

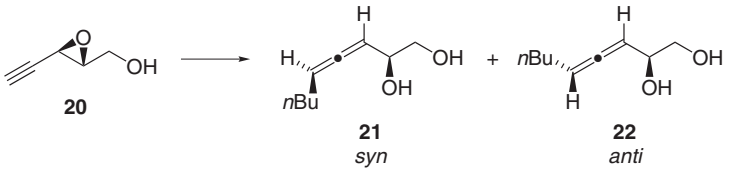
Due to its reliability, the S_N2' substitution is often used in applications which require the highly enantioselective formation of the allene; for example, Brummond et al. [19g] prepared the yneallene **19** (a starting material for intramolecular allenic Pauson–Khand cycloadditions) through the *anti*-selective S_N2' substitution of the chiral propargylic mesylate **18** with a suitable magnesium cuprate (Scheme 2.6).



Scheme 2.6 *Anti*-stereoselective S_N2' substitution of propargylic mesylate **18**.

For several reasons, propargyl oxiranes belong to the most interesting propargylic electrophiles among the many different kinds which can be employed in these transformations. Thus, the α-hydroxyallenes formed in the S_N2' substitution reaction contain not just one, but two functionalities which are highly useful for further synthetic manipulations; furthermore, due to the availability of enantiomerically pure or enriched oxiranes [21] by Katsuki–Sharpless [22], Jacobsen [23] or Shi epoxidation [24], the corresponding α-hydroxyallenes can also be obtained easily in stereochemically defined form. Finally, a particular deep insight into details of the reactions mechanism has been gained for this class of compounds [8, 25]. For exam-

ple, Alexakis and co-workers revealed a strong halogen effect on the stereoselectivity (*anti* versus *syn*) of the copper-catalyzed S_N2' substitution of propargyl oxiranes (and other ethers) with Grignard reagents, which was explained in terms of a competing addition–elimination mechanism (cf. Sections 3.2.1.3 and 4.2.1) [6, 8h–j]. *Syn*-selective S_N2' substitutions of propargyl oxiranes can also be achieved with Grignard reagents under iron catalysis [26] and with aluminum hydrides (cf. Section 2.4). Likewise, deviations from the preferred *anti*-selectivity can occur in the corresponding transformations with stoichiometric amounts of organocopper reagents, but for different reasons. Thus, in the first systematic study of the S_N2' substitution of a chiral propargyl epoxide **20** with organocuprates, Oehlschlager and Czyzewska [8e] found in 1983 that *syn*–*anti* mixtures are formed in the absence of any additives. If, however, the reaction was carried out in the presence of dimethyl sulfide, high *anti*-stereoselectivities were obtained with both lithium and magnesium cuprates (Scheme 2.7).



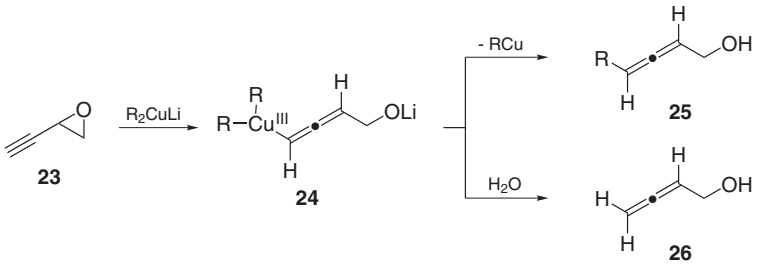
nBu$_2$CuLi:	60 : 40
nBu$_2$CuLi • Me$_2$S:	6 : 94
nBu$_2$CuMgBr • Me$_2$S:	1 : 99

Scheme 2.7 Influence of dimethyl sulfide on the S_N2' substitution of propargyl oxirane **20**.

The reduced selectivity in the reaction with the pure cuprate is probably due to a racemization of the allene entity by the cuprate itself or by other reactive copper species present in the reaction mixture. Such racemizations of allenes have frequently been observed in copper-promoted substitution reactions of propargylic electrophiles [3a, 3b, 6b, 27, 28] and probably occur via single-electron transfer (SET) steps even at rather low temperatures. For example, if a 98:2 mixture of allenes **22** and **21** is treated with lithium di-*n*-butylcuprate in diethyl ether for 2 h, the *anti*/*syn* ratio decreases to 93:7 at –60 °C and to 73:27 at –20 °C. [8e]. In contrast, the thermal isomerization of allenes requires substantially higher activation barriers in the range 35–47 kcal mol^{-1} [29], explaining the fact that chiral allenes do not racemize thermally at room temperature. The tendency of organometallic reagents to racemize allenes is not restricted to organocopper compounds and can also be used to deracemize allenes (e.g. by employing chiral europium complexes [30]).

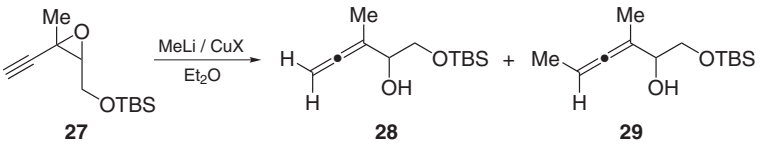
The effectiveness of dimethyl sulfide as an additive for the selective formation of *anti*-product **22** from propargyl epoxide **20** may be due to the formation of 'stabilized' copper species, which are less prone to undergo electron transfer processes. In this respect, other soft ligands which bind strongly to copper, in particular phosphines and phosphites [8h–j, 25, 28], have been used even more frequently. These additives also serve to suppress the formation of a common side product, i.e. an allene containing a hydrogen atom instead of the carbon substituent which should

have been delivered by the cuprate. The occurrence of such reduction products is also in accordance with the generally accepted mechanistic model (cf. Scheme 2.5) in which the copper(III) intermediate **24** resulting from the epoxide **23** may be sufficiently stable to 'survive' until work-up of the reaction mixture [or undergo reductive elimination of R–R to give an allenic copper(I) compound], so that protonation leads to the reduction product **26** in addition to the desired substitution product **25** (Scheme 2.8) [25].



Scheme 2.8 Mechanistic model for the formation of the reduction product **26** from propargyl oxirane **23** and lithium cuprates.

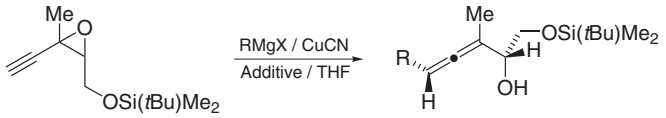
The beneficial effect of added phosphine on the chemo- and stereoselectivity of the S_N2' substitution of propargyl oxiranes is demonstrated in the reaction of substrate **27** with lithium dimethylcyanocuprate in diethyl ether (Scheme 2.9). In the absence of the phosphine ligand, reduction of the substrate prevailed and attempts to shift the product ratio in favor of **29** by addition of methyl iodide (which should alkylate the presumable intermediate **24** [8k]) had almost no effect. In contrast, the desired substitution product **29** was formed with good chemo- and *anti*-stereoselectivity when tri-*n*-butylphosphine was present in the reaction mixture [25, 31]. Interestingly, this effect is strongly solvent dependent, since a complex product mixture was formed when THF was used instead of diethyl ether. With sulfur-containing copper sources such as copper bromide–dimethyl sulfide complex or copper 2-thiophenecarboxylate, however, addition of the phosphine caused the opposite effect, i.e. exclusive formation of the reduced allene **28**. Hence the course and outcome of the S_N2' substitution show a rather complex dependence on the reaction partners and conditions, which needs to be further elucidated.



CuX = CuCN:	80 : 20
CuCN / nBu$_3$P:	4 : 96 (*anti:syn* = 85 : 15)
CuBr • SMe$_2$:	68 : 32
CuBr • SMe$_2$ / nBu$_3$P:	> 99 : < 1

Scheme 2.9 Influence of copper salt and additives on the S_N2' substitution of propargyl oxirane **27** with lithium cuprates. TBS = Si(*t*Bu)Me$_2$.

Whereas the S_N2' substitution of propargyl epoxides of type **27** with lithium diorganocuprates proved to be rather capricious, the corresponding transformations with magnesium cuprates [32] proceed in a more predictable manner. Thus, treatment of the epoxide **27** in THF with cuprates formed from 2 equiv. of a Grignard reagent and 1 equiv. of CuCN in the presence of 1 equiv. of tri-*n*-butylphosphine or triethyl phosphite consistently led to the exclusive formation of the desired S_N2' substitution products **30** with good chemical yields and high *anti*-diastereoselectivity [25, 31] (Scheme 2.10).

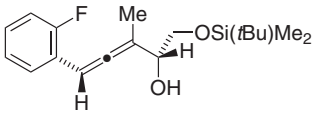


27 **30**

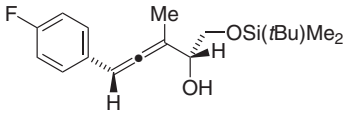
MeMgBr / nBu$_3$P:	71% (*ds* = 94 : 6)
*t*BuMgCl / (EtO)$_3$P:	82% (*ds* > 95 : 5)
*n*HexMgBr / (EtO)$_3$P:	95% (*ds* > 95 : 5)
*i*PrMgCl / (EtO)$_3$P:	76% (*ds* > 95 : 5)
PhMgBr / nBu$_3$P:	84% (*ds* = 95 : 5)

Scheme 2.10 S_N2' substitution of propargyl oxirane **27** with magnesium cuprates.

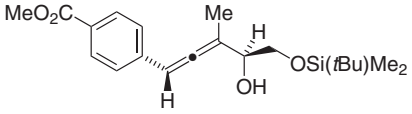
Most gratifyingly, these conditions are also applicable to functionalized magnesium reagents [33], as demonstrated by the formation of α-hydroxyallenes **31**–**34** from *cis*- or *trans*-**27** and the corresponding magnesium cuprates bearing substituted aryl groups (Scheme 2.11) [31].



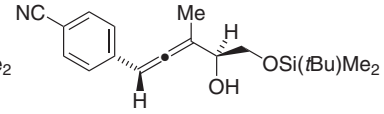
31
99% (*ds* = 85 : 15)



32
63% (*ds* = 90 : 10)



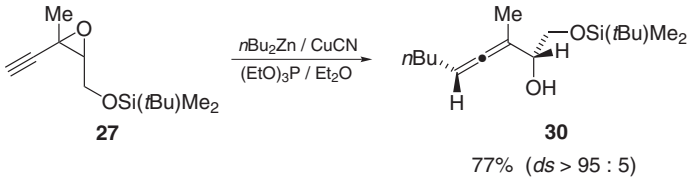
33
85% (*ds* = 85 : 15)



34
62% (*ds* = 90 : 10)

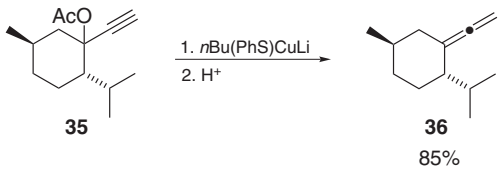
Scheme 2.11 α-Hydroxyallenes obtained by S_N2' substitution of propargyl oxirane **27** with functionalized magnesium cuprates.

The related zinc cuprates formed from diorganozinc reagents and copper(I) cyanide also undergo smooth S_N2' substitution reactions with propargyl oxiranes in the presence of phosphines or phosphites (Scheme 2.12). These transformations can also be performed with catalytic amounts of the copper salt since no direct reaction between the organozinc reagent and the substrate interferes [31, 34], and therefore should also be applicable to functionalized organozinc compounds.



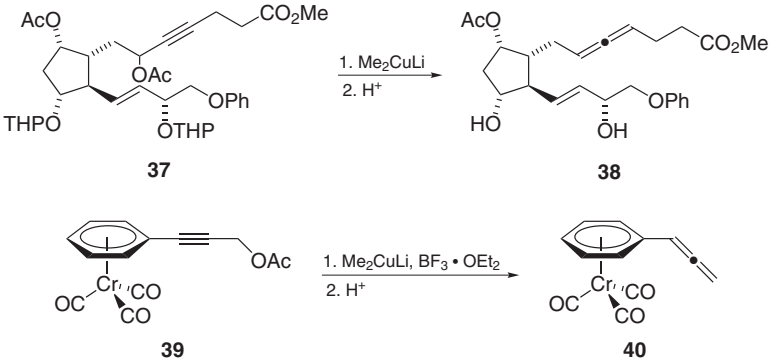
Scheme 2.12 S_N2' substitution of propargyl oxirane **27** with a zinc cuprate.

The occurrence of reduction products in S_N2' substitution reactions of propargylic electrophiles with organocuprates is not limited to oxiranes [35, 36] and can even be controlled in such a way that the reduced allenes are formed (almost) exclusively (see above). For example, treatment of tertiary propargyl acetates (e.g., **35**) with lithium *n*-butyl(phenylthio)cuprate furnished terminal allenes (e.g., **36**) in high yields [36] (Scheme 2.13). Presumably, the presence of the phenylthio group bound to copper again leads to a relative stabilization of the intermediate copper species (cf. Schemes 2.8 and 2.9) through its electron-donating ability.



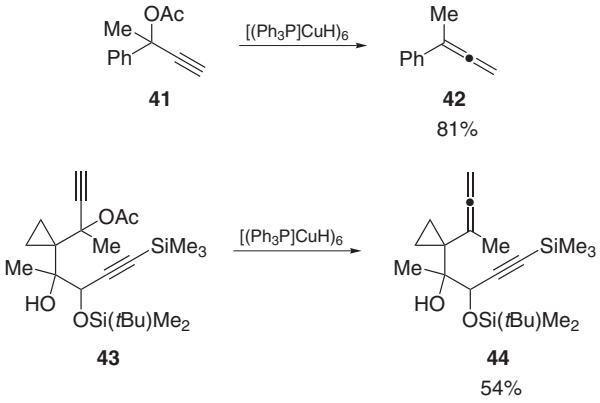
Scheme 2.13 Reduction of propargyl acetate **35** to allene **36**.

Interestingly, even treatment of certain substrates with simple lithium dimethylcuprate induced a selective reduction of the propargylic electrophile to an allene (Scheme 2.14). Thus, the precursor **38** of the allenic prostaglandin analogue enprostil (cf. Section 18.3.2) was obtained after reaction of propargyl acetate **37** with Me_2CuLi and hydrolytic work-up [37]. A similar procedure was applied by Müller et al. to the synthesis of the chromotricarbonyl-complexed phenylallene **40** starting from precursor **39** [38]. In the latter case, however, addition of boron trifluoride etherate improved the yield of **40** from 37 to 74%.



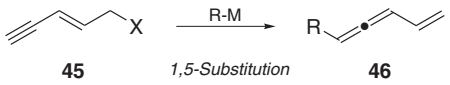
Scheme 2.14 Synthesis of allenes **38** and **40** by reduction of propargyl acetates with lithium dimethylcuprate. THP = tetrahydropyranyl.

Another, albeit less frequently employed, option for a copper-mediated reduction of propargylic electrophiles to allenes relies upon the use of a copper hydride, e.g. Stryker's reagent $[(Ph_3P)CuH]_6$. Whereas substrates without a leaving group lead to a reduction of the triple to a *cis* double bond, propargyl acetate **41** furnished allene **42** in good yield (Scheme 2.15) [39]. The method was applied by Brummond and Lu [40] to the synthesis of the structurally complex precursor **44** for the potent antitumor agent (±)-hydroxymethylacylfulvalene.



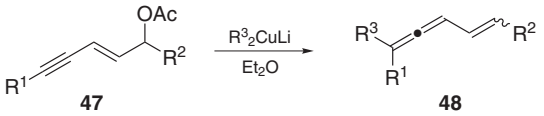
Scheme 2.15 Reduction of propargyl acetates to terminal allenes with Stryker's reagent.

Introduction of a double bond between the triple bond and the leaving group leads to enyne electrophiles **45**, which would give access to vinylallenes **46** if the attack of the nucleophile takes place at the triple bond in an S_N2'' (1,5) substitution reaction (Scheme 2.16). In addition to the regioselectivity, two types of stereoselectivity also have to be considered in this transformation, i.e. the configuration of the olefinic double bond of the vinylallene and the (relative or absolute) configuration of the allenic chirality axis.



Scheme 2.16 S_N2'' (1,5) substitution of enyne electrophiles.

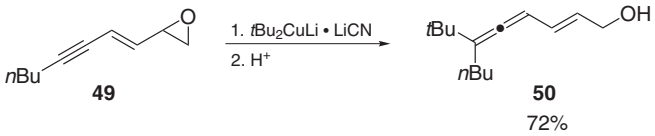
The 1,5-substitution of 1-chloro-2-en-4-ynes with Grignard reagents has been described by Dulcere and co-workers [41] but lacks generality with regard to the nucleophile (see Section 2.3). In contrast, the regioselective reaction of enyne acetates **47** with various lithium cuprates proceeds smoothly in diethyl ether, furnishing exclusively vinylallenes **48** with variable substituent patterns (Scheme 2.17) [42].



$R^1 = R^2 = Me$, $R^3 = n$Bu:	90% ($E : Z = 67 : 33$)
$R^1 = R^2 = Me$, $R^3 = t$Bu:	93% ($E : Z = 25 : 75$)
$R^1 = Me_3Si$, $R^2 = Me$, $R^3 = t$Bu:	96% ($E : Z = 40 : 60$)
$R^1 = n$Bu, $R^2 = t$Bu, $R^3 = Me$:	92% ($E : Z > 99 : 1$)

Scheme 2.17 1,5-Substitution of enyne acetates **47**.

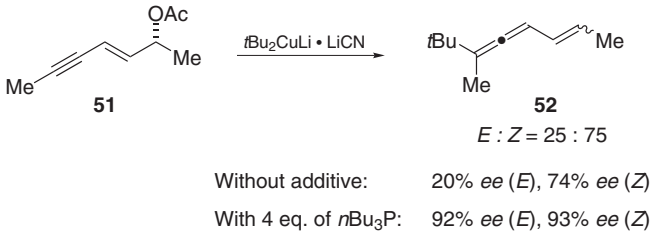
Although the resulting vinylallenes **48** were usually obtained as mixtures of the *E* and *Z* isomers, complete stereoselection with regard to the vinylic double bond was achieved in some cases. In addition to enyne acetates, the corresponding oxiranes (e.g. **49**) also participate in the 1,5-substitution (Scheme 2.18) and are transformed into synthetically interesting hydroxy-substituted vinylallenes (e.g. **50**) [42]. Moreover, these transformations can also be conducted under copper catalysis by simultaneous addition of the organolithium compound and the substrate to catalytic amounts of the cuprate (see Section 3.2.3).



Scheme 2.18 1,5-Substitution of enyne oxirane **49**.

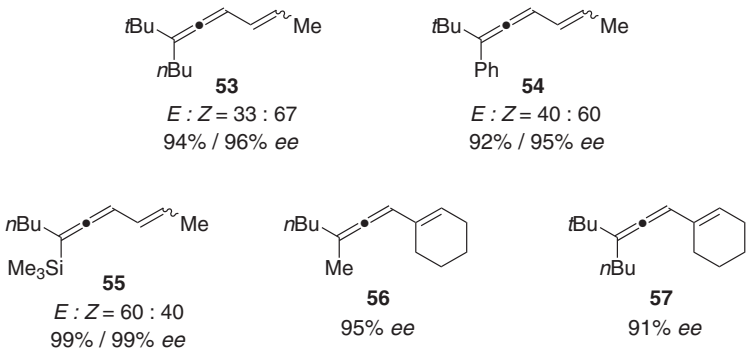
Initial attempts to perform the 1,5-substitution enantioselectively with chiral enyne acetates proceeded disappointingly. For example, treatment of the enantiomerically pure substrate **51** with the cyano-Gilman cuprate tBu$_2$CuLi·LiCN at –90 °C provided vinylallene **52** as a 1:3 mixture of *E* and *Z* isomers with 20 and 74% *ee*, respectively (Scheme 2.19) [28]. As previously described for the corresponding S_N2' substitution of propargylic electrophiles, this unsatisfactory stereoselection may be attributed to a racemization of the allene by the cuprate or other organome-

tallic species present in the reaction mixture. Fortunately, the use of phosphines or phosphites as additive served again to improve the enantioselectivity up to a preparatively useful level (92/93% *ee* in the case of **52**) [28].



Scheme 2.19 Enantioselective 1,5-substitution of chiral enyne acetate **51**.

Due to the distance between the stereogenic center and the place of the nucleophilic attack, the enantioselective 1,5-substitution of chiral enyne acetates constitutes one of the rare cases of *remote stereocontrol* in organocopper chemistry. Moreover, the method is not limited to substrate **51**, but can also be applied to the synthesis of enantiomerically enriched or pure vinylallenes **53–57** with variable substituent patterns (Scheme 2.20) [28].

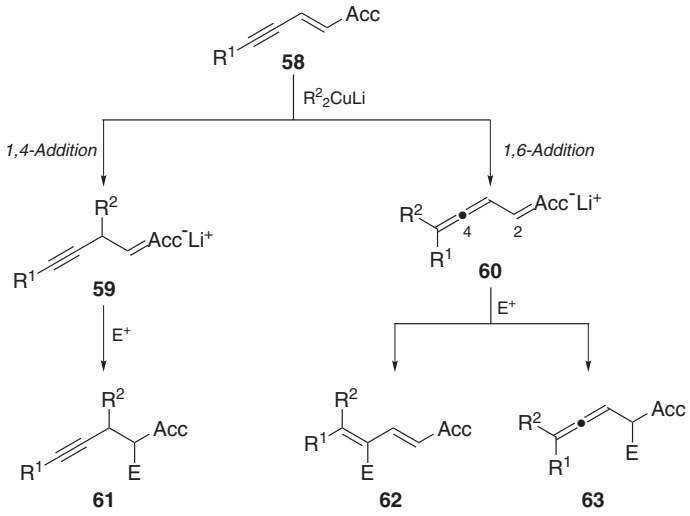


Scheme 2.20 Enantiomerically enriched or pure vinylallenes formed by 1,5-substitution of chiral enyne acetates in the presence of tri-*n*-butylphosphine (**53–56**) or triethyl phosphite (**57**).

2.2.2
Addition Reactions

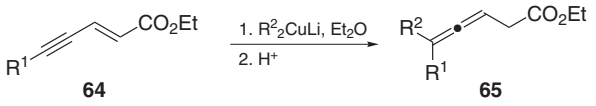
As for the substitution reactions summarized in the previous chapter, organocopper compounds are also the reagents of choice for the synthesis of allenes by (conjugate) addition reactions [43]. The preferred substrates for this transformation are conjugated enynes **58** with an activating acceptor substituent at the double bond whereas the regioisomeric enynes with the acceptor group at the triple bond react with cuprates under 1,4-addition leading to conjugated dienes [44]. However, the outcome of

the reaction depends strongly on the regioselectivity of both the nucleophilic attack of the copper reagent (1,4- or 1,6-addition) and the electrophilic trapping of the enolate thus formed (Scheme 2.21). As the allenyl enolate **60** formed by 1,6-addition can furnish either a conjugated diene **62** or an allene **63** on reaction with a soft electrophile and hence offers the possibility to create axial chirality, this transformation is of special interest from both preparative and mechanistic points of view. Fortunately, the regio- and stereoselectivity of both steps can be controlled by the choice of the reactants, in particular by 'fine-tuning' of the organocopper reagent and the electrophile.



Scheme 2.21 Regioselectivity in conjugate addition reactions to acceptor-substituted enynes **58**.

The first copper-mediated addition reactions to enynes bearing an acceptor group at the triple bond were reported by Hulce and co-workers [45], who found that 3-alkynyl-2-cycloalkenones react with cuprates regioselectively in a 1,6-addition. However, the allenyl enolates thereby formed were protonated at C-4 to provide conjugated dienes of type **62**. In contrast, 2-en-4-ynoates **64**, which also react with the Gilman cuprate $Me_2CuLi \cdot LiI$ or cyano-Gilman reagents $R_2CuLi \cdot LiCN$ ($R \neq Me$) in diethyl ether in a 1,6-fashion, provided β-allenic esters **65** with variable substituents by regioselective protonation of the allenyl enolate (with dilute sulfuric acid) at C-2 (Scheme 2.22) [46–48]. Gratifyingly, this 1,6-addition reaction can also be carried out with catalytic amounts of the cuprate [43a] or a copper arenethiolate [49] by simultaneous addition of the substrate and the organolithium reagent to the copper source (see Section 3.3.2).

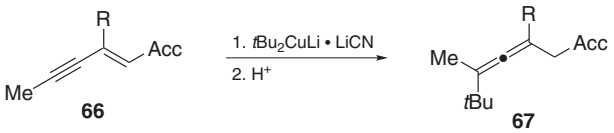


64 **65**

R^1 = Ph, R^2 = Me:	79%
R^1 = Ph, R^2 = *t*Bu:	81%
R^1 = *n*Bu, R^2 = Ph:	62%
R^1 = Me_3Si, R^2 = Me:	57%

Scheme 2.22 Synthesis of β-allenic esters **65** by 1,6-cuprate addition to 2-en-4-ynoates **64** and regioselective enolate protonation.

The nature of the acceptor substituent hardly affects the regioselectivity of the cuprate addition to acceptor-substituted enynes. Hence enynes **66** comprising thioester, lactone, dioxanone and also keto, sulfonyl, sulfinyl, cyano and oxazolidino groups reacted in a 1,6-manner furnishing functionalized allenes **67** [48] (Scheme 2.23). By contrast, 1-nitro-l-en-3-ynes were attacked at the C–C double bond with the formation of the corresponding 1,4-adducts. The differences in reactivity can be described qualitatively by the following reactivity scale: acceptor (Acc) = NO_2 > COR, CO_2R, COSR > CN, SO_3R, oxazolidino > SO_2R > SOR >> $CONR_2$. In order to achieve acceptable chemical yields with the less reactive Michael acceptors, e.g. sulfones and sulfoxides, it is often necessary to use more reactive organocopper reagents (e.g. Me_3CuLi_2 instead of Me_2CuLi) or to activate the substrate by Lewis acid catalysis. Here, mild Lewis acids such as Me_3Sil or Me_3SiOTf proved to be effective [48]. Unfortunately, enyne amides completely failed to form 1,6-adducts even under these conditions.

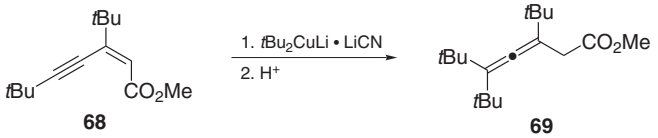


66 **67**

Acc = CN, R = Me:	79%
Acc = SO_2Ph, R = H:	91%
Acc = SO_3Et, R = H:	49%

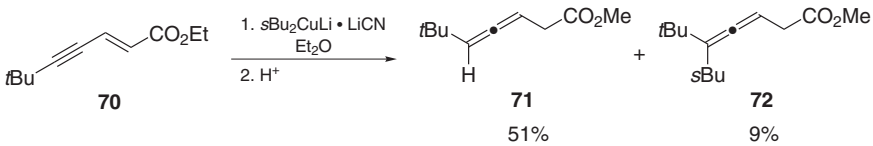
Scheme 2.23 1,6-Cuprate addition to different acceptor-substituted enynes **66**.

Remarkably, the regioselectivity of the cuprate addition to acceptor-substituted enynes is also insensitive to the steric properties of the substrate. Thus, enynes with *tert*-butyl substituents at the triple bond (e.g. **68**) underwent 1,6-additions even when the cuprate was also sterically demanding (Scheme 2.24) [47]. The method is therefore highly suitable for the preparation of sterically encumbered allenes of type **69**.



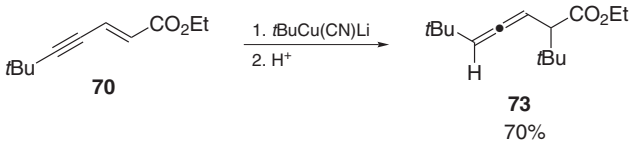
Scheme 2.24 Synthesis of sterically encumbered allenes by 1,6-cuprate addition.

Unlike the substrate, the type of organocuprate used for the addition to acceptor-substituted enynes has a pronounced influence on the regiochemical course. Whereas the Gilman cuprate $Me_2CuLi \cdot LiI$ or cyano-Gilman reagents $R_2CuLi \cdot LiCN$ ($R \neq Me$) readily underwent a 1,6-addition, the Yamamoto reagent $RCu \cdot BF_3$ and organocopper compounds RCu activated by Me_3SiI furnished 1,4-adducts [43a]. Interestingly, the use of lithium di-*sec*-butylcyanocuprate in diethyl ether predominantly led to the formation of reduced allenes as the major product (Scheme 2.25). For example, treatment of 2-en-4-ynoate **70** with this reagent gave the 1,6-reduction product **71** with 51% yield, accompanied by 9% of the 1,6-adduct **72** [50]. Similarly to the corresponding reduction of propargylic electrophiles with organocopper reagents (see; Schemes 2.8 and 2.9), the formation of allene **71** may be attributed to the hydrolysis of a fairly stable copper intermediate. In accordance with this assumption, two deuterium atoms were introduced into positions 2 and 5 of the allene when a deuterated proton source was used during work-up. In contrast, the 1,6-addition products of type **72** were the major products if THF instead of diethyl ether was used as the solvent.



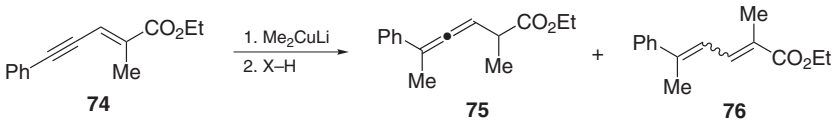
Scheme 2.25 1,6-Reduction of enynoate **70** with $sBu_2CuLi \cdot LiCN$.

Lower order cyanocuprates RCu(CN)Li displayed again a different behavior: although they usually do not react with acceptor-substituted enynes, the cyanocuprate *t*BuCu(CN)Li nevertheless underwent anti-Michael additions to 2-en-4-ynoates (e.g. **70**) and nitriles affording allenes of type **73** (Scheme 2.26) [51]. Unfortunately, an adequate interpretation of the abnormal behavior of this particular cuprate is still lacking.



Scheme 2.26 Anti-Michael addition of the cyanocuprate *t*BuCu(CN)Li to enynoate **70**.

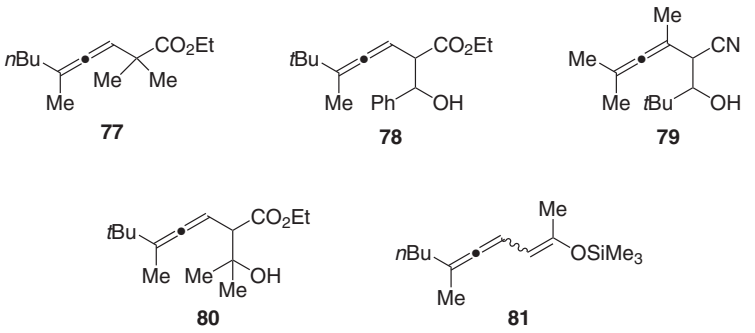
As already mentioned at the beginning of this section, allenes can only be obtained by 1,6-addition to acceptor-substituted enynes **58** if the intermediate allenyl enolate **60** reacts regioselectively with an electrophile at C-2 (or at the enolate oxygen atom to give an allenyl enol ether; see Scheme 2.21). Interestingly, the regioselectivity of the simplest trapping reaction, the protonation, depends on the steric and electronic properties of both the substrate and the proton source. Whereas the allenyl enolates obtained from 3-alkynyl-2-cycloalkenones provided conjugated dienones by protonation at C-4 (possibly via allenyl enols) [45], the corresponding ester enolates were usually found to be protonated at C-2 (Scheme 2.22), in particular when sterically demanding groups at C-5 blocked the attack of a proton source at C-4 (Scheme 2.24) [43, 46–48]. In the presence of a substituent at C-2 of the enolate (cf. substrate **74**), however, mixtures of both allenes and conjugated dienes were formed for steric reasons (Scheme 2.27). Fortunately, this problem can be solved by using weak organic acids as proton source; in particular, pivalic acid at low temperature gave rise to the exclusive formation of the desired allenes of type **75** [46].



X–H = 2N H_2SO_4, 25°C:	50 : 50
AcOH, 25°C:	64 : 36
*t*BuCO_2H, 25°C:	82 : 18
*t*BuCO_2H, -80°C:	> 99 : < 1

Scheme 2.27 Regioselectivity of the protonation of the allenyl enolate obtained by 1,6-cuprate addition to enynoate **74**.

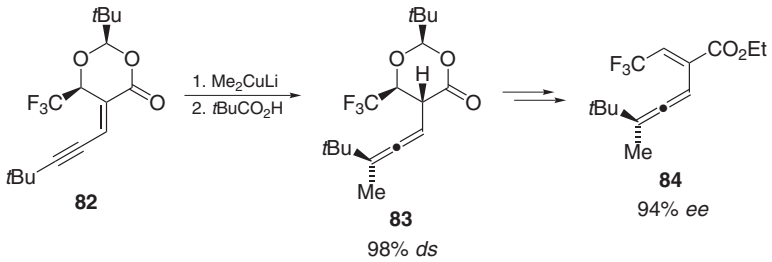
In contrast to protonation, the regioselectivity of the reaction of other electrophiles with allenyl enolates derived from acceptor-substituted enynes is independent of the steric and electronic properties of the reaction partners [43, 48, 52]. As expected according to the HSAB principle, hard electrophiles such as silyl halides and triflates reacted at the enolate oxygen atom to form allenyl enol ethers, whereas soft electrophiles such as carbonyl compounds attacked at C-2 (see Scheme 2.28 for a selection of allenes obtained by this method). Only allyl and propargyl halides reacted at C-4 of the allenyl enolate to give substituted conjugated dienes. Again, cyclic allenyl enolates obtained through 1,6-cuprate addition to 3-alkynyl-2-cycloalkenones showed a deviating behavior: treatment with iodomethane provided product mixtures derived from attack of the electrophile at C-2 and C-4, whereas the reaction with aldehydes and silyl halides took place at C-4 exclusively [53].



Scheme 2.28 Functionalized allenes obtained by 1,6-cuprate addition to acceptor-substituted enynes and regioselective enolate trapping with methyl triflate (**77**), aldehydes (**78**, **79**), ketones (**80**) and silyl halides (**81**).

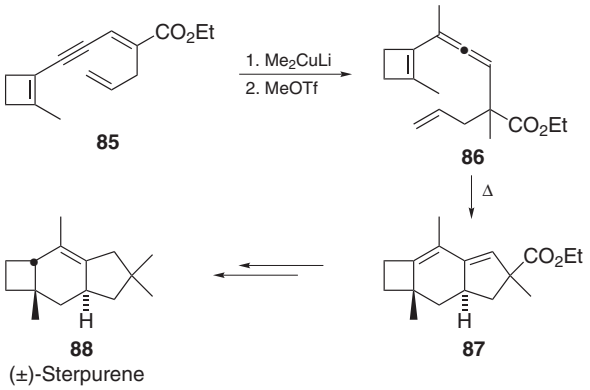
In order to control the configuration of the chirality axis of the resulting allenes, the 1,6-addition has to proceed diastereo- or enantioselectively. Among many different chiral substrates examined, chiral 5-alkynylidene-1,3-dioxan-4-ones of type **82** have proven to be particularly useful for diastereoselective 1,6-additions since these Michael acceptors adopt a very rigid conformation. Due to the equatorial position of the *tert*-butyl group, the trifluoromethyl residue shields the top face of the enyne moiety, exposing the underside of the molecule to be preferably attacked by the nucleophile (Scheme 2.29) [54] Therefore, reaction with lithium dimethylcuprate and pivalic acid gave the allene **83** with a diastereoselectivity of 98%, and the stereochemical information generated in this step remained intact during the subsequent conversion into the chiral vinylallene **84**. In contrast, all attempts to establish an enantioselective 1,6-addition by treatment of acceptor-substituted enynes with various chirally modified organocopper reagents failed owing to the low reactivity of the latter towards the Michael acceptors. Interestingly, this problem was recently solved by Hayashi et al. [55], who employed aryltitanates as nucleophiles in rhodium-catalyzed enantioselective 1,6-addition reactions to 2-en-4-ynones (see Section 2.4 for details).

As was the case for allene synthesis by copper-promoted S_N2' substitution reactions, the corresponding 1,6-addition to acceptor-substituted enynes has found sev-



Scheme 2.29 Diastereoselective 1,6-cuprate addition to chiral 5-alkynylidene-1,3-dioxan-4-one **82**.

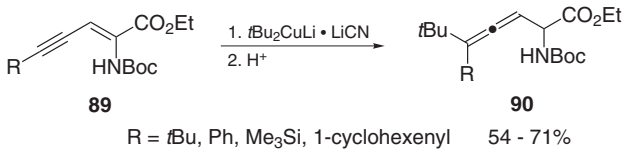
eral preparative applications [43]. In natural product synthesis, the method has been used to generate the insect pheromone methyl 2,4,5-tetradecatrienoate (cf. Section 18.2.1), and also the precursor **86** of the fungal metabolite (±)-sterpurene (**88**) and oxygenated metabolites thereof (Scheme 2.30) [56]. In the latter case, the reaction sequence started with the 1,6-addition of lithium dimethylcuprate to enynoate **85** and subsequent regioselective enolate trapping with methyl triflate. The vinylallene **86** thus formed underwent an intramolecular [4 + 2]-cycloaddition to the tricyclic product **87**, which finally was converted into the target molecule **88**.



Scheme 2.30 Synthesis of the fungal metabolite (±)-sterpurene (**88**).

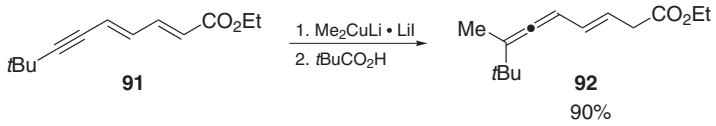
The Diels–Alder reaction outlined above is a typical example of the utilization of axially chiral allenes, accessible through 1,6-addition or other methods, to generate selectively new stereogenic centers. This transfer of chirality is also possible via intermolecular Diels–Alder reactions of vinylallenes [57], aldol reactions of allenyl enolates [19f] and Ireland–Claisen rearrangements of silyl allenylketene acetals [58]. Furthermore, it has been utilized recently in the diastereoselective oxidation of titanium allenyl enolates (formed by deprotonation of β-allenecarboxylates of type **65** and transmetalation with titanocene dichloride) with dimethyl dioxirane (DMDO) [25, 59] and in subsequent acid- or gold-catalyzed cycloisomerization reactions of α-hydroxyallenes into 2,5-dihydrofurans (cf. Chapter 15) [25, 59, 60].

α-Allenic α-amino acids represent another type of heteroatom-substituted allenes which are of interest as irreversible, mechanism-based inhibitors of vitamin B_6-dependent decarboxylases. They are accessible via chelate-controlled Claisen rearrangement of zinc ester enolates (see Section 2.3) or by 1,6-cuprate addition to 2-amino-substituted enynes **89** (Scheme 2.31) [25]. Due to the low reactivity of these Michael acceptors, however, the reaction succeeded only with the most reactive cuprate, i.e. the *tert*-butyl cyano-Gilman reagent $t\mathrm{Bu_2CuLi \cdot LiCN}$. Nevertheless, the addition products **90** were obtained with good chemical yields and selective deprotection of either the ester or amino functionality under acidic conditions provided the desired target molecules.



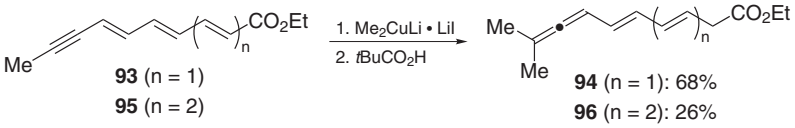
Scheme 2.31 Synthesis of α-allenic α-amino acid derivatives **90** by 1,6-cuprate addition. Boc = *tert*-butoxycarbonyl.

In view of the high value of the 1,6-cuprate addition to acceptor-substituted enynes for the synthesis of functionalized allenes, it was considered of interest to explore whether extended Michael acceptors with further C–C double bonds between acceptor group and triple bond can also be utilized for the formation of extended unsaturated allenic systems. Of course, the number of possible regioisomeric products rises with increasing length of the Michael acceptor. For example, the 2,4-dien-6-ynoate **91** can be attacked by an organocopper reagent at C-3, C-5 or C-7 and the last possibility leads to a vinylogous allenyl enolate having four reactive positions for the subsequent trapping reaction (enolate oxygen, C-2, C-4, C-6). Therefore, the high regioselectivity found for the reaction of **91** with lithium dimethylcuprate is striking: the cuprate attacked the triple bond exclusively and protonation with pivalic acid occurred selectively at C-2 of the enolate, giving rise to the formation of vinylallene **92** (a 1,8-addition product) as the only isolable regioisomer with 90% yield (Scheme 2.32) [57].



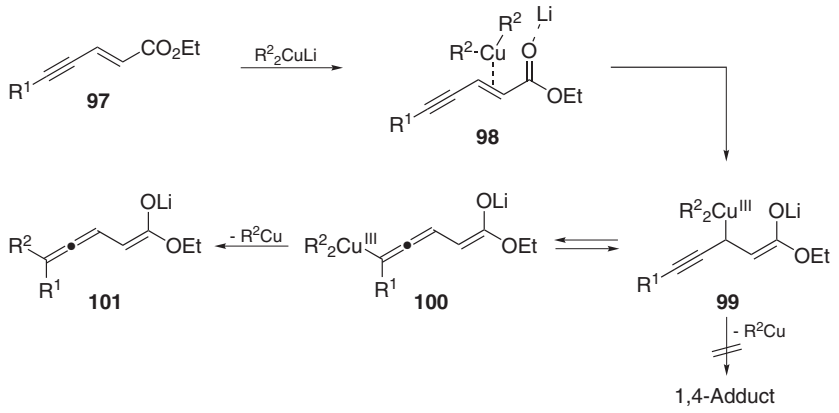
Scheme 2.32 1,8-Addition of lithium dimethylcuprate to dienynoate **91**.

Analogously, the trienynoate **92** reacted in a 1,10-addition to give the 3,5,7,8-tetraenoate **93** and the even higher unsaturated allene **95** was obtained from the Michael acceptor **94** containing four double bonds between the triple bond and the acceptor substituent (Scheme 2.33). In the latter case, however, the yield was only 26%; this is presumably due to the reduced thermal stability of the starting material and/or the addition product (the 1,12-adduct **95** was the only isolable reaction product, apart from polymeric compounds) [57].



Scheme 2.33 Synthesis of highly unsaturated allenes by 1,10- and 1,12-cuprate addition.

A mechanistic model for the 1,6-cuprate addition to acceptor-substituted enynes has been developed on the basis of NMR spectroscopic investigations [61], isotope effects [62] and kinetic measurements [63]. Thorough ^{13}C NMR spectroscopic studies have revealed that these addition reactions proceed via π-complexes **98**, which are characterized by an interaction between the π-system of the C–C double bond and the nucleophilic copper atom (a soft–soft interaction in terms of the HSAB principle), and a second interaction between the hard lithium ion of the cuprate and the hard carbonyl oxygen atom (Scheme 2.34) [61]. In particular, the use of ^{13}C-labeled substrates has shed light on the structure of the metal-containing part of these π-complexes, indicating, for example, that the cuprate does not interact with the triple bond of the enyne [61b, 61c]. Recently, ^{13}C kinetic isotope effects have been determined which prove that the bond formation between C-5 of the acceptor-substituted enyne and the cuprate occurs in the rate-determining step [62]. Moreover, by means of kinetic measurements with a variety of different substrates, even activation parameters for these transformations have been determined [63]. All these experimental results are in accordance with a model that comprises the formation of the σ-copper(III) species **99**, which should be in equilibrium with the allenic copper(III) intermediate **100**. Both intermediates can undergo reductive elimination of an alkylcopper compound to produce the 1,4- and 1,6-adduct, respectively. The experimentally observed exclusive formation of the 1,6-addition product, however, may indicate that the allenic copper species **100** undergoes a much faster reductive elimination than the intermediate **99**.



Scheme 2.34 Mechanistic model for the 1,6-addition of organocuprates to acceptor-substituted enynes.

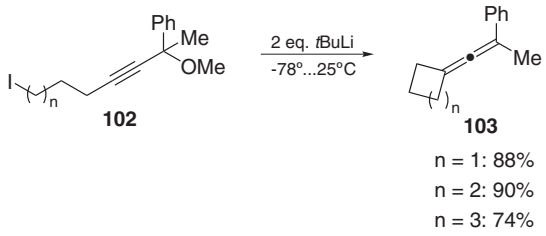
Similar models explain the 1,8-, 1,10- and 1,12-addition reactions to the extended Michael acceptors **91**, **93** and **95**, respectively (Schemes 2.32 and 2.33). Again, these transformations start with the formation of a cuprate π-complex at the double bond neighbouring the acceptor group [61a]. Subsequently, an equilibrating mixture of σ-copper(III) intermediates is presumably formed and the regioselectivity of the reaction may then be governed by the different relative rates of the reductive elimination step of these intermediates. Consequently, the exclusive formation of allenic prod-

ucts would be attributable to a comparatively fast reductive elimination of the corresponding allenic σ-copper(III) species.

2.3 Lithium-, Magnesium- and Zinc-Mediated Synthesis of Allenes

As is evident from numerous examples in this and other chapters of this book, organolithium, magnesium and zinc reagents are indispensable in allene synthesis, where they act either as precursors for other organometallic reagents (e.g. cuprates; see above) or as nucleophiles in (transition) metal-catalyzed transformations (e.g. in palladium- or copper-catalyzed substitution reactions; see Chapter 3). However, there is also a significant number of methods for the generation of allenes available that rely on the direct use of these 'basic' nucleophiles in addition or substitution reactions without the participation of other metals. It should be noted, however, that nowadays these transformations are rarely applied, presumably owing to their limited generality and functional group compatibility.

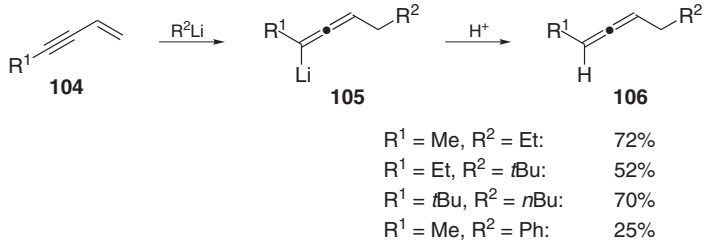
One of the very few examples of an S_N2' substitution reaction of propargylic electrophiles with organolithium reagents was reported by Bailey and Aspris [64] (Scheme 2.35). Iodine–lithium exchange of propargyl ethers **102** at low temperature led to the corresponding alkyllithium compounds, which cyclized to furnish exocyclic allenes of type **103** on warming to room temperature. Four-, five- and six-membered rings were efficiently formed by *exo*-dig ring closure, whereas a substrate comprising a five-carbon tether furnished the corresponding seven-membered ring product with only 9% yield.



102 **103**

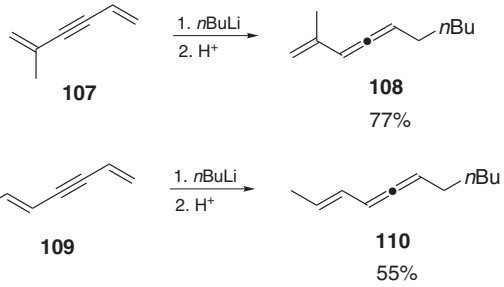
Scheme 2.35 Formation of exocyclic allenes **103** by intra-molecular S_N2' substitution of organolithium compounds.

Moreover, organolithium compounds are the reagents of choice for the synthesis of allenes by 1,4-addition to conjugated enynes (cf. Scheme 2.1). In a comprehensive series of papers in the 1960s, a Russian group has reported various aspects of this chemistry [65–69]. It was found that aliphatic, aromatic and heteroaromatic lithium reagents (and also lithium phosphides [66]) react with enynes **104** regioselectively at the double bond terminus, leading to allenic lithium species **105** [67], which were then regioselectively protonated to provide allenes **106** (Scheme 2.36) [65]. However, this 1,4-addition reaction competes with the anionic oligomerization/polymerization of the enyne precursor, so that the chemical yields of the allenes are sometimes only moderate.



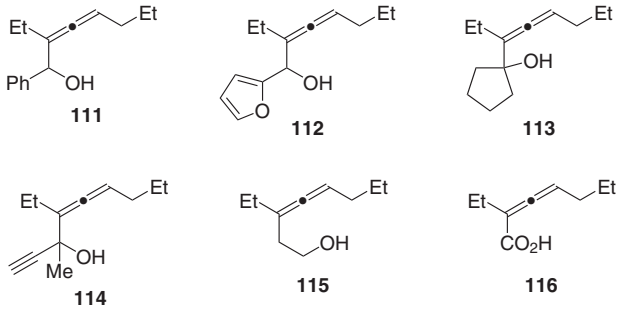
Scheme 2.36 1,4-Addition of organolithium reagents to enynes **104**.

Unsymmetrical dienynes react regioselectively with organolithium compounds at the less substituted double bond (Scheme 2.37). Thus, addition of *n*-butyllithium to 2-methylhexa-1,5-dien-3-yne (**107**) led after hydrolysis to vinylallene **108**, whereas the corresponding carbolithiation of the linear isomer **109** furnished product **110** with 55% yield [68].



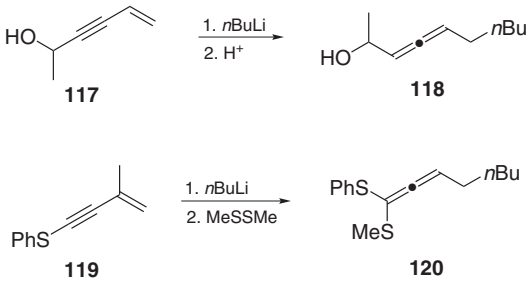
Scheme 2.37 1,4-Addition of *n*-butyllithium to dienynes **107** and **109**.

Besides protonation, a variety of other electrophiles have been employed for the trapping of allenyllithium intermediates **105**, e.g. aldehydes and ketones, oxiranes and carbon dioxide [69]. Scheme 2.38 shows a selection of functionalized allenes obtained by this method.



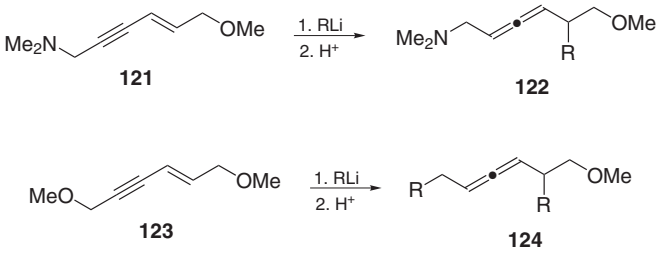
Scheme 2.38 Functionalized allenes formed by 1,4-addition of organolithium reagents to enynes and electrophilic trapping with aldehydes (**111**, **112**), ketones (**113**, **114**), ethylene oxide (**115**) and carbon dioxide (**116**).

Enynes with oxygen or nitrogen substituents at the double bond react in an analogous manner [70]. With the regioisomeric 4-en-2-yn-1-ols (e.g. **117**) as substrates, however, the hydroxy group might direct the attack of the organolithium reagent towards the triple bond. In contrast to this expectation, the usual 1,4-addition reaction under C–C bond formation at the olefinic terminus prevailed again, so that α-hydroxyallenes **118** emerged as products (Scheme 2.39) [71]. Accordingly, carbolithiation of 1-thio-3-en-1-ynes of type **119** opened up an access to allenic dithioacetals (e.g. **120**) and related products [72].



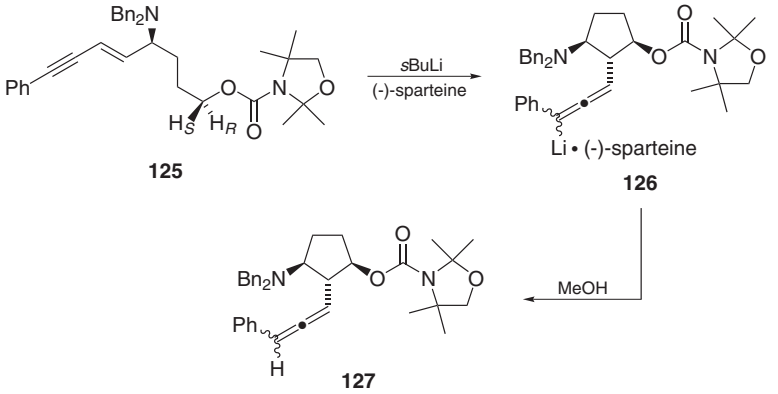
Scheme 2.39 1,4-Addition of organolithium reagents to heterosubstituted enynes.

Miginiac and co-workers [73] examined the reaction of organolithium, Grignard and organozinc reagents with conjugated enynes bearing various oxygen and nitrogen substituents at both termini (e.g. **121**). Usually, 1,4-addition with attack of the nucleophile at the C–C double bond was observed again (Scheme 2.40). In the case of the bis-ether **123** and similar substrates, however, two carbon groups from the nucleophile were incorporated into the product owing to a 1,4-addition accompanied by a substitution reaction of the propargylic methoxy group.



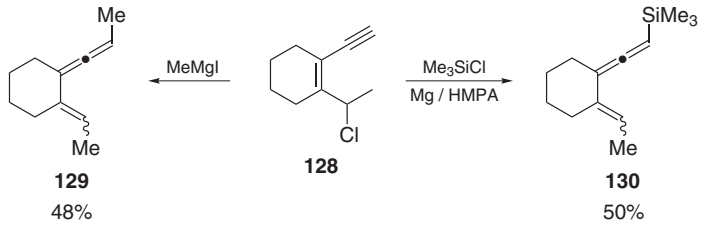
Scheme 2.40 1,4-Addition of organometallic reagents to bis-heterosubstituted enynes.

A more recent application of this chemistry was reported by Oestreich and Hoppe [74] and involved the enantioselective deprotonation of the enyne carbamate ester **125** with *sec*-butyllithium in the presence of (–)-sparteine (Scheme 2.41). Removal of the pro-*S* hydrogen atom led to the corresponding organolithium intermediate, which then underwent a highly enantioselective intramolecular 1,4-addition to the enyne. Protonation of the resulting allenyllithium species **126** provided a 70:30 mixture of the two diastereomeric allenes **127**.



Scheme 2.41 Enantioselective intramolecular 1,4-addition of enyne carbamate ester **125**. Bn = benzyl.

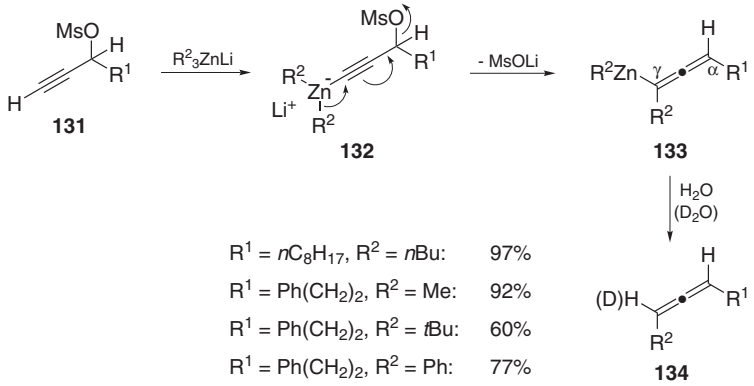
Apart from some examples of the 1,4-addition reaction of Grignard reagents to conjugated enynes [73], such nucleophiles have only found application in allene synthesis (without the aid of additional metals) with regard to 1,5-substitution reactions of 1-chloro-2-en-4-ynes (e.g. **128**) [41]. By treatment of these electrophiles with methylmagnesium iodide, Dulcere and co-workers obtained vinylallenes of type **129** (Scheme 2.42). However, the method is not as general as the copper-mediated 1,5-substitution of enyne acetates (cf. Section 2.2.1), since other Grignard reagents completely failed to form the desired vinylallenes. The only notable exception is the generation of silylallenes (e.g. **130**) from chloroenynes and trimethylsilylmagnesium chloride (or trimethylsilyllithium) [41d].



Scheme 2.42 1,5-Substitution of chloroenyne **128** with Grignard reagents.

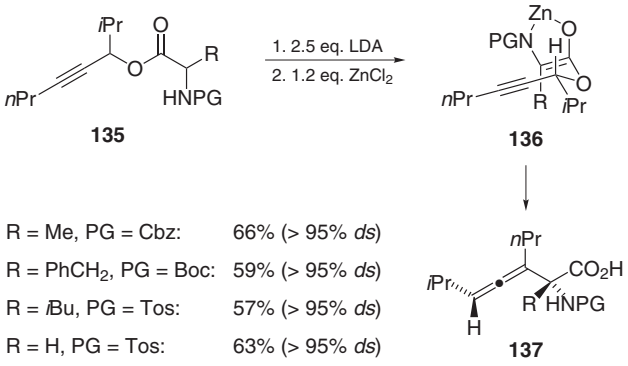
The use of organozinc nucleophiles in allene synthesis is equally limited. Harada and co-workers [75] reported the formation of allenes **134** by treatment of propargyl mesylates **131** (or the corresponding chlorides) with lithium triorganozincates (or silylzincates) and subsequent hydrolysis (Scheme 2.43). The reaction probably proceeded via deprotonation of the alkyne and transfer of a carbon group from the zinc acetylide **132** to the triple bond, affording the allenylzinc species **133**. The presence of the latter intermediate was corroborated by incorporation of deuterium in the γ-position when D_2O was used for quenching. However, all of the other electrophiles examined, such as halogens, silyl halides and carbonyl compounds, reacted

preferably in the α-position of the allenylzinc intermediate **133**, thereby furnishing functionalized alkynes.



Scheme 2.43 Formation of allenes from propargyl mesylates and lithium triorganozincates.

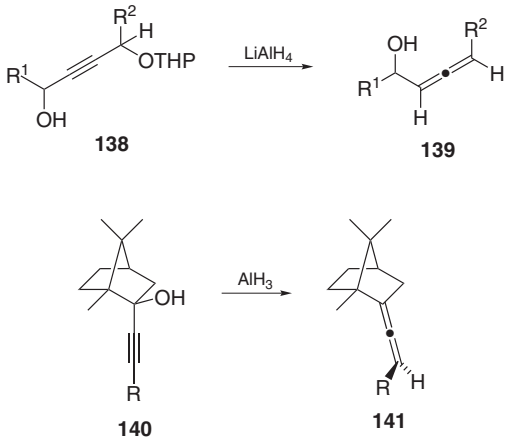
A second approach using organozinc compounds for the synthesis of allenes relies on the chelate-controlled Claisen rearrangement of zinc ester enolates. Kazmaier and Görbitz [76] have demonstrated that this route opens up an access to α-allenic α-amino acids, which are of interest as irreversible, mechanism-based inhibitors of vitamin B_6-dependent decarboxylases (cf. Sections 2.2.2 and 18.3.3). Thus, the zinc enolates **136** of propargylic esters **135** (which are readily accessible by deprotonation of the latter with LDA and transmetalation with zinc chloride) underwent a highly *syn*-stereoselective rearrangement to the allenic amino acid derivatives **137** on warming to room temperature (Scheme 2.44). Remarkably, both the chemical yield and the diastereoselectivity were found to be almost independent of the substitution pattern and the amino protecting group used.



Scheme 2.44 Chelate-controlled Claisen rearrangement of zinc ester enolates **136**. Cbz = benzyloxycarbonyl; Boc = *tert*-butoxycarbonyl.

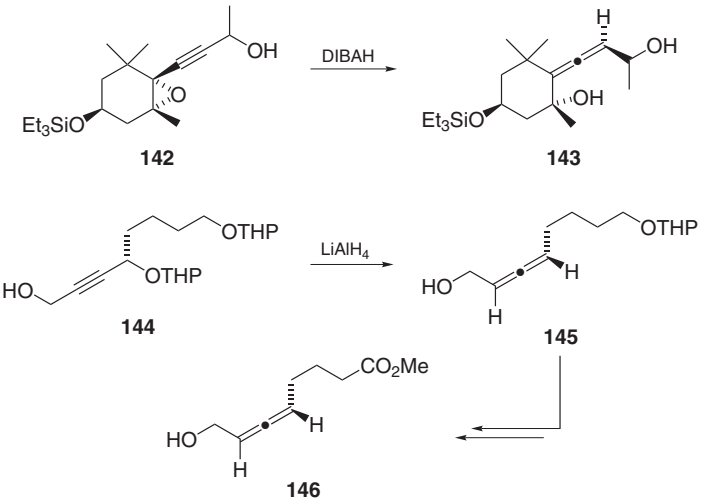
2.4
Aluminum- and Indium-Mediated Synthesis of Allenes

The application of aluminum reagents in allene synthesis comprises mainly the formation of C–H bonds with aluminum hydrides, in addition to the use of aluminum-based Lewis acids for C–C bond formation processes. Various propargylic electrophiles such as alcohols, ethers, halides and oxiranes can be reduced to the corresponding allenes with the aid of lithium aluminum hydride, diisobutylaluminum hydride (DIBAH) and other aluminum hydrides [1]. Depending on the substrate structure and the reducing agent, the transformation takes place with either *syn*- or with *anti*-stereoselectivity. More recent applications of the numerous examples of this chemistry include the synthesis of α-hydroxyallenes **139** from the mono-THP ethers of bispropargylic alcohols [77] and the highly *anti*-stereoselective formation of various camphor-based allenes **141** via reduction of propargylic alcohols **140** with AlH_3 (Scheme 2.45) [78]. In the latter case, the alane not only served as the nucleophile but also permitted the removal of the hydroxy group as an aluminum oxide.



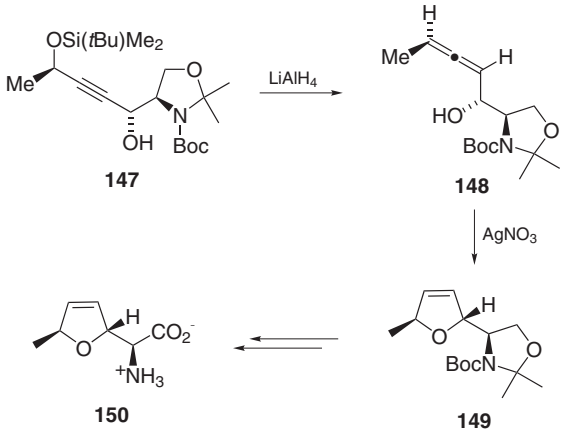
Scheme 2.45 Reduction of propargylic electrophiles with aluminum hydrides. THP = tetrahydropyranyl.

Due to its reliability, this method has frequently been applied in natural product synthesis. Thus, reduction of propargyl oxiranes of type **142** with diisobutylaluminum hydride (DIBAH) allowed the formation of many allenic carotinoids and terpenoids, including the famous grasshopper ketone [79] (Scheme 2.46; see Section 18.2.2 for details). Moreover, as a result of a precoordination of the aluminum hydride to the epoxide oxygen atom, these reductions took place with high *syn*-diastereoselectivity. In a similar fashion, reduction of the propargylic THP ether **144** with $LiAlH_4$ again proceeded *syn*-selectively, furnishing allenic alcohol **145**, a main precursor in the synthesis of the antifungal natural product methyl (*R*)-8-hydroxyocta-5,6-dienoate (**146**) [80].



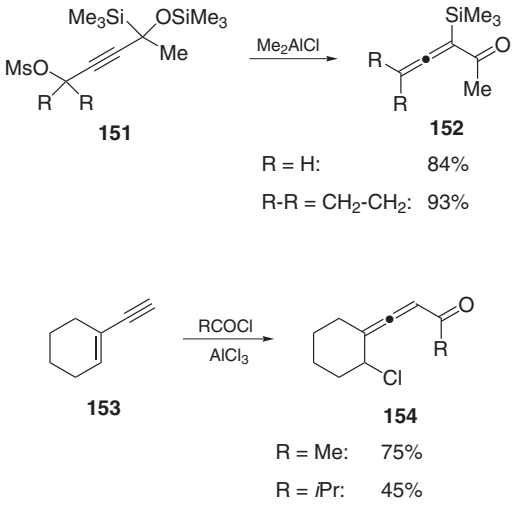
Scheme 2.46 Synthesis of natural products by reduction of propargylic electrophiles with aluminum hydrides. DIBAH = diisobutylaluminum hydride; THP = tetrahydropyranyl.

A further example of the reductive allene formation in the synthesis of a non-allenic natural product was reported recently by VanBrunt and Standaert (Scheme 2.47) [81]. Treatment of the propargylic silyl ether **147** with $LiAlH_4$ led to the *syn*-stereoselective formation of the hydroxyallene **148**, albeit with unsatisfactory chemical yield (25–50%). The latter was then transformed into the antibiotic amino acid furanomycin (**150**) by silver-mediated cycloisomerization to dihydrofuran **149** and elaboration of the side-chain.



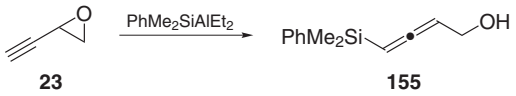
Scheme 2.47 Synthesis of the amino acid furanomycin (**150**) by reduction of propargylic silyl ether **147**.

With regard to the use of aluminum-based Lewis acids for the synthesis of allenes, several examples of such transformations have been documented in recent years. Thus, the propargyl mesylates **151** were found to undergo a silyl migration to generate α-trimethylsilylallenones **152** on treatment with dimethylaluminum chloride (Scheme 2.48) [82], whereas allenic ketones **154** were obtained through acylation of conjugated enynes **153** with acid chlorides in the presence of $AlCl_3$ [83]. Although these allenic products were contaminated with variable amounts of the isomeric conjugated dienones, reasonably high chemical yields were achieved in several cases.



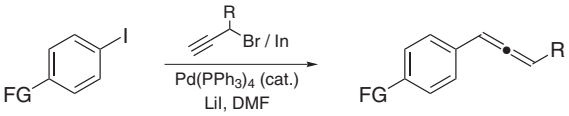
Scheme 2.48 Synthesis of allenic ketones with the aid of aluminum-based Lewis acids.

An aluminum-mediated C–Si bond formation for the generation of allenes has been described by Trost and Tour [84]. Treatment of propargyl oxirane **23** with the silylaluminum reagent $PhMe_2SiAlEt_2$ led to a selective transfer of the silyl group to the electrophile, thereby furnishing the silylated α-hydroxyallene **155** in 89% yield (Scheme 2.49). It seems reasonable to assume again that the aluminum reagent served not only as the nucleophile, but also as a Lewis acid to activate the oxirane for the subsequent S_N2' substitution reaction.



Scheme 2.49 S_N2' substitution of propargyl oxirane **23** with a silylaluminum reagent.

A highly promising application of indium in the synthesis of (functionalized) allenes has recently been reported by Lee and co-workers [85]. The palladium-catalyzed coupling reaction of allenylindium reagents (prepared in situ from propargyl bromides and indium) with various unsaturated halides (e.g. **156**) provided arylallenes of type **157** with high chemical yields (Scheme 2.50). Due to its mildness, the reaction is compatible with various functional groups present in the coupling partner and it is not limited to aromatic and heteroaromatic halides, but proceeds equally well with alkenyl halides, iodoalkynes and even an imidoyl bromide.

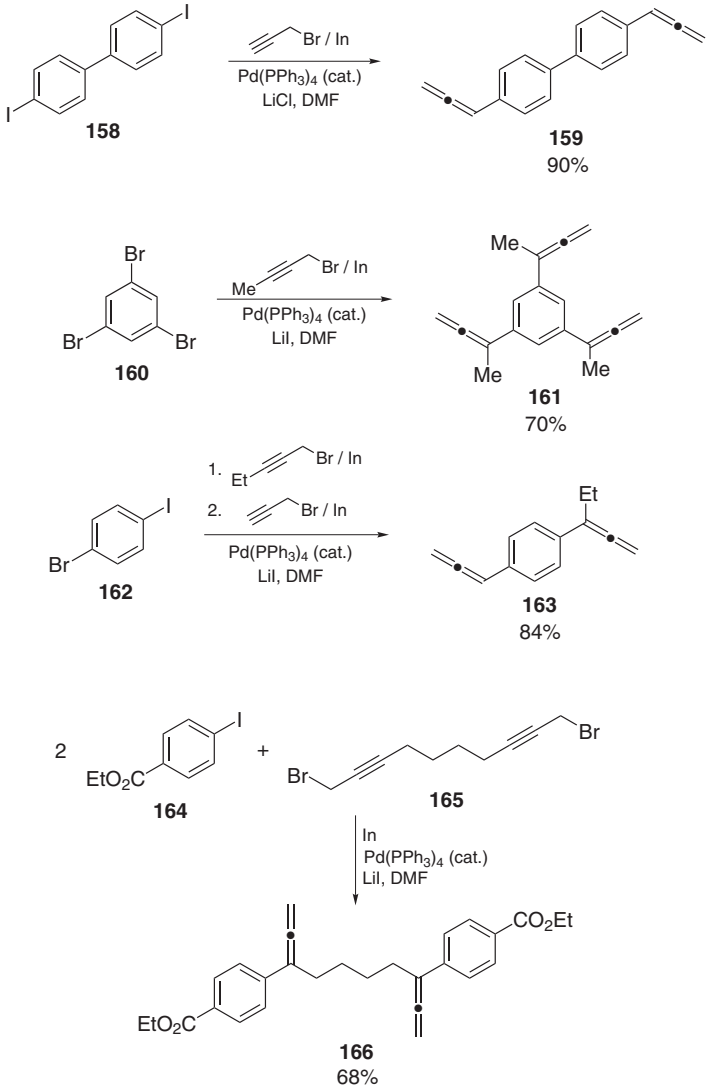


156 **157**

R = Me, FG = NO_2: 90%
R = H, FG = COMe: 87%
R = H, FG = MeO: 91%
R = Ph, FG = *n*Bu: 90%

Scheme 2.50 Palladium-catalyzed coupling of allenylindium reagents with aryl iodides.

Furthermore, this protocol can be employed for the highly efficient introduction of two (**159**) and even three allene entities (**161**) into an aromatic 'workbench' (Scheme 2.51). Thus, by starting with two different halides, e.g. **162** (or with identical halides in different positions of a heteroaromatic substrate), two diverse allenic groups can be introduced by sequential coupling reactions. Furthermore, a structurally different bisallene **166** was also assembled via a twofold coupling of the bispropargyl bromide **165** with the functionalized aryl iodide **164** [85].

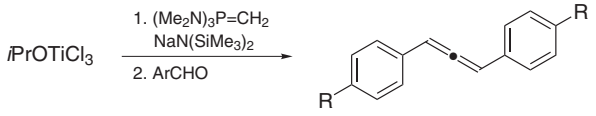


Scheme 2.51 Synthesis of bis- and trisallenes by palladium-catalyzed coupling of allenylindium reagents with aryl halides.

2.5
Titanium- and Samarium-Mediated Synthesis of Allenes

The use of organotitanium compounds in the synthesis of allenes involves mainly Wittig-type olefination reactions of carbonyl compounds [86] with titanium ylides. The formation of allenes according to the scheme $C_1 + C_1 + C_1$ was described by

Finn and co-workers [87], who treated aromatic aldehydes with a mixed titanium–phosphorus ylide formed from *i*PrOTiCl$_3$, (Me$_2$N)$_3$P=CH$_2$ and an excess of sodium hexamethyldisilazide as base (Scheme 2.52). Symmetrical allenes **167** were thereby obtained with moderate to good yield.

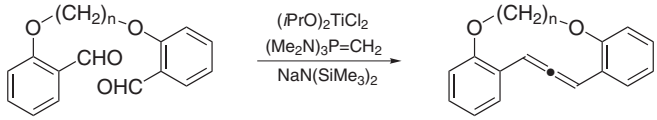


167

R = Me:	56%
R = MeO:	52%
R = Me$_2$N:	32%

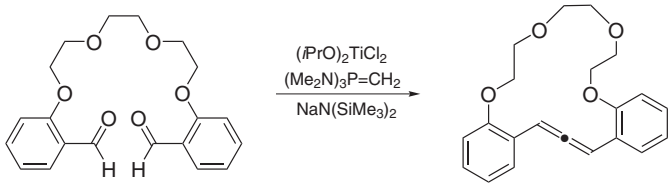
Scheme 2.52 Titanium-mediated synthesis of symmetrical allenes **167**.

This route was also employed for the synthesis of macrocyclic allenes **169** via intramolecular coupling of aromatic dialdehydes **168** [88]. Depending on the ring size, chemical yields of up to 90% of the desired products were achieved (Scheme 2.53). Furthermore, the introduction of additional oxygen atoms into the tether did not diminish the efficiency of the protocol and therefore allowed an access to allenic crown ethers of type **171**.



168 **169**

n = 2:	45%
n = 4:	80%
n = 6:	90%
n = 8:	87%
n = 10:	40%

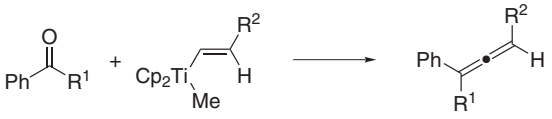


170 **171**

67%

Scheme 2.53 Titanium-mediated synthesis of macrocyclic allenes.

The alternative building scheme $C_2 + C_1$ was used by Petasis and Hu [89], who reacted various aldehydes and ketones with alkenyltitanocene derivatives **172** to obtain the corresponding allenes **173** in high chemical yields (Scheme 2.54). The reaction probably proceeds via titanocene vinylidene complexes, which can also be trapped with alkynes and isocyanides to afford allenylketene imines [90].

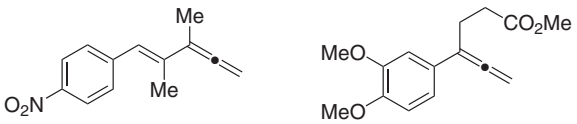


172 **173**

R^1 = Me, R^2 = H:	89%
R^1 = Ph, R^2 = H:	86%
R^1 = Me, R^2 = Me:	88%
R^1 = Ph, R^2 = Me:	80%

Scheme 2.54 Synthesis of allenes with titanocene vinylidene complexes.

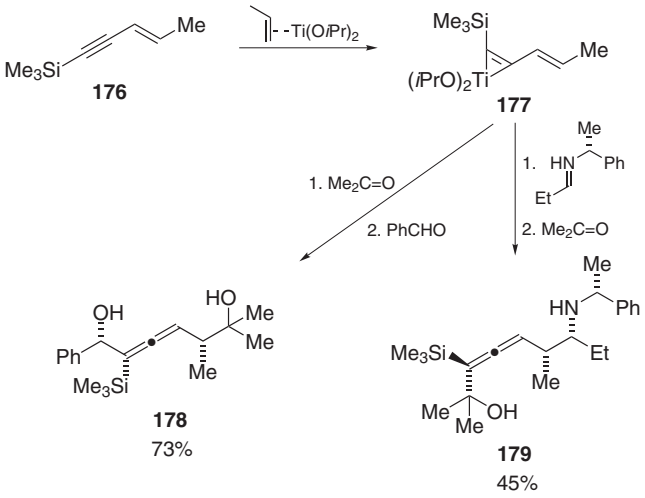
The latter method can also be applied to aliphatic or α,β-unsaturated ketones, to diketones and to aromatic or acetylenic aldehydes. Furthermore, it tolerates a variety of functional groups present in the substrate, as demonstrated by the efficient formation of allenes **174** and **175**, which bear an additional nitro and ester group, respectively (Scheme 2.55) [89].



174 **175**

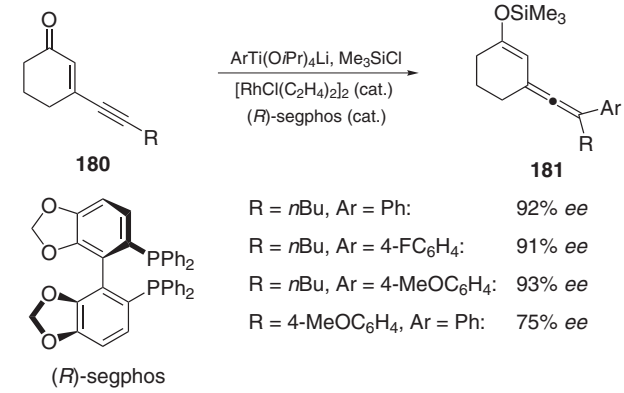
Scheme 2.55 Functionalized allenes formed from ketones and titanocene vinylidene complexes.

Conjugated enynes represent further useful substrates for the titanium-mediated synthesis of allenes. Hamada et al. [91] prepared titanium alkoxide complexes of type **177** from enynes (e.g. **176**) and (η^2-propene)Ti(O*i*Pr)$_2$ and converted these into densely functionalized allenes (e.g. **178**, **179**) by sequential trapping with two electrophiles. In addition to protonating agents, aldehydes, ketones and imines can also be used for this purpose, thereby allowing the highly regio- and diastereoselective formation of two further stereogenic centers besides the allenic chirality axis (Scheme 2.56).



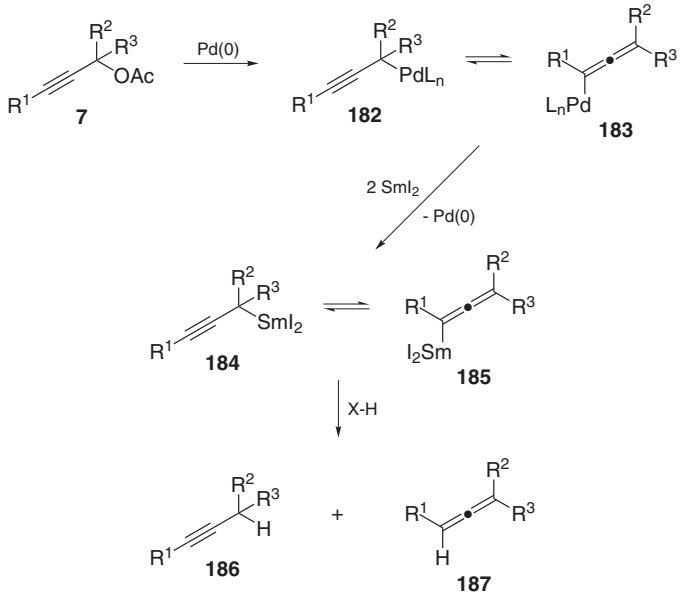
Scheme 2.56 Synthesis of functionalized allenes by electrophilic trapping of the enyne–titanium alkoxide complex **177**.

A different approach towards titanium-mediated allene synthesis was used by Hayashi et al. [55], who recently reported rhodium-catalyzed enantioselective 1,6-addition reactions of aryltitanate reagents to 3-alkynyl-2-cycloalkenones **180** (Scheme 2.57). In the presence of chlorotrimethylsilane and (*R*)-segphos as chiral ligand, allenic silyl enol ethers **181** were obtained with good to excellent enantioselectivities and these can be converted further into allenic enol esters or triflates. In contrast to the corresponding copper-mediated 1,6-addition reactions (Section 2.2.2), these transformations probably proceed via alkenylrhodium species (formed by insertion of the C–C triple bond into a rhodium–aryl bond) and subsequent isomerization towards the thermodynamically more stable oxa-π-allylrhodium intermediates [55].



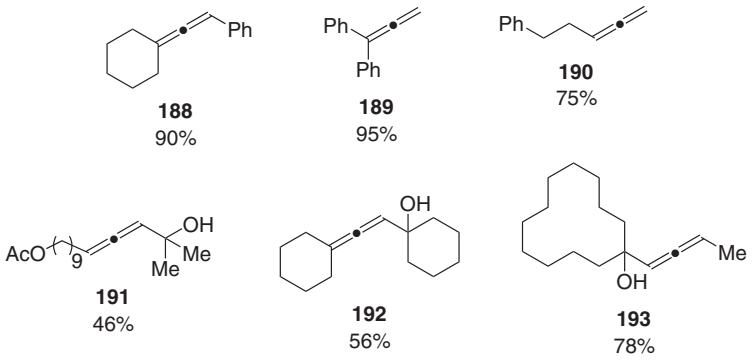
Scheme 2.57 Rhodium-catalyzed enantioselective 1,6-addition of aryltitanium reagents to 3-alkynyl-2-cycloalkenones **180** (*ee* values refer to the corresponding allenic enol pivalates).

The use of samarium reagents for the synthesis of allenes was pioneered by Tabuchi et al. [92], who employed samarium diiodide in the palladium-catalyzed reduction of propargyl acetates **7**. The reaction probably takes place via oxidative addition of Pd(0) to the propargyl acetate, resulting in an allenic palladium(II) intermediate **183**, which is in equilibrium with the corresponding propargylic palladium species **182** (Scheme 2.58). Subsequent transfer of two electrons from SmI_2 leads to the release of Pd(0) into the catalytic cycle and formation of an allenic samarium(III) species **185** (which again exists in an equilibrium with the corresponding propargylic samarium intermediate **184**). Protonation of the latter affords either an allene **187** or an alkyne **186**.



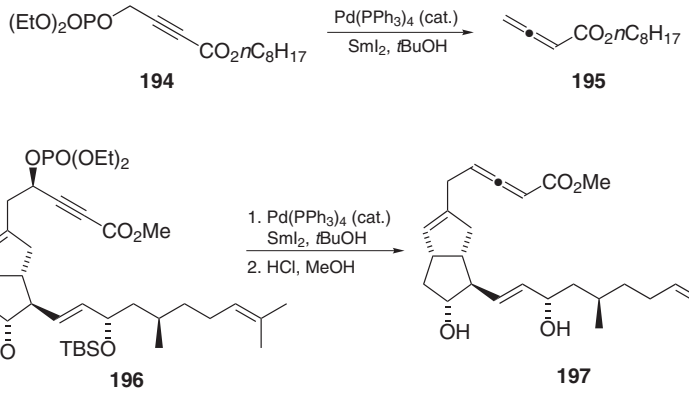
Scheme 2.58 Palladium-catalyzed reduction of propargylic acetates with samarium diiodide.

The regioselectivity of the protonation was found to depend on both the substrate structure and the protonating agent. Thus, whereas tertiary acetates furnished allenes with high selectivity, the less pronounced tendency of secondary acetates to give allenes was improved by using bulky protonating agents such as *tert*-butanol [92]. Only primary acetates afforded alkynes as the major product, regardless of the proton source. A selection of allenes obtained by this method is shown in Scheme 2.59. Furthermore, the intermediate samarium species **184**/**185** can also be trapped with carbonyl compounds [93]. Again, the C–C bond formation took place at the sterically less hindered site, so that allenic alcohols were obtained from secondary and tertiary acetates whereas primary acetates provided mainly the isomeric acetylenic products.



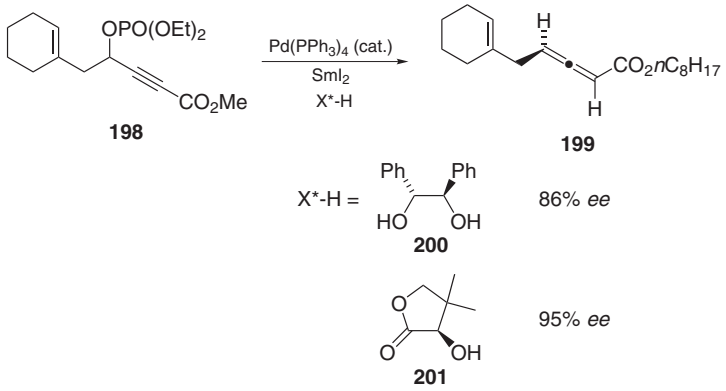
Scheme 2.59 Allenes obtained from samarium intermediates **184**/**185** by protonation (**188**–**190**) or trapping with ketones (**191**–**193**).

Mikami and Yoshida extended the scope of this method considerably by using propargyl phosphates and chiral proton sources [94]. The propargylic phosphates thereby have been found to be advantageous owing to their high reactivity towards palladium and the extremely low nucleophilicity of the phosphate group [95]. In some cases, it was even possible to obtain allenes from primary substrates, e.g. ester **194** (Scheme 2.60) [96]. A notable application of this transformation is the synthesis of the allenic isocarbacyclin derivative **197** from its precursor **196** [97].



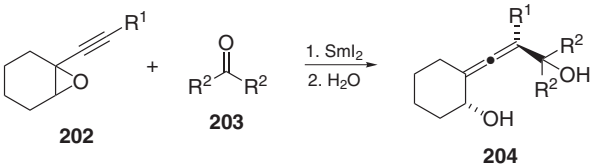
Scheme 2.60 Palladium-catalyzed reduction of propargylic phosphates with SmI_2. TBS = Si(*t*Bu)Me_2.

By employing chiral proton sources for the protonation of the intermediate samarium species **184**/**185**, highly enantioenriched allenes were accessible in some cases [98]. Thus, in the reaction of propargylic phosphate **198**, (*R*,*R*)-1,2-diphenyl-1,2-ethandiol (**200**) and (*R*)-pantolactone (**201**) were found to give the highest selectivities, affording allene **199** with up to 95% *ee* (Scheme 2.61).



Scheme 2.61 Enantioselective allene synthesis with chiral protonating agents.

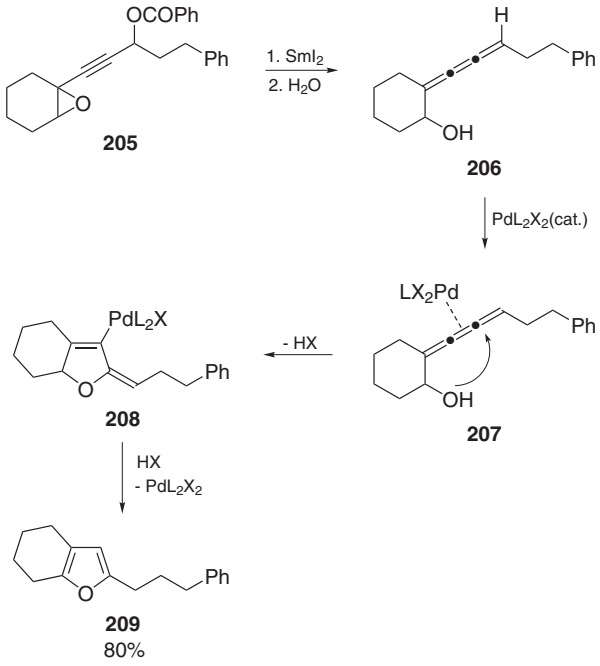
Moreover, propargyl oxiranes **202** were found to react with samarium diiodide and ketones to form α,α'-dihydroxyallenes **203** with moderate to high *anti*-diastereoselectivities (Scheme 2.62). Aurrecoechea and co-workers [99] reported this reductive coupling to proceed smoothly in the absence of a palladium catalyst, i.e. a direct electron transfer from the samarium(II) to the substrate has to take place in order to generate an allenyl/propargyl samarium intermediate of type **184**/**185**, which is then regioselectively trapped by the electrophile.



R^1 = H, R^2 = Me: 81% (85% *ds*)
R^1 = H, R^2-R^2 = $(CH_2)_5$: 74% (83% *ds*)
R^1 = Me, R^2-R^2 = $(CH_2)_5$: 77% (> 99% *ds*)
R^1 = Ph, R^2-R^2 = $(CH_2)_5$: 38% (69% *ds*)

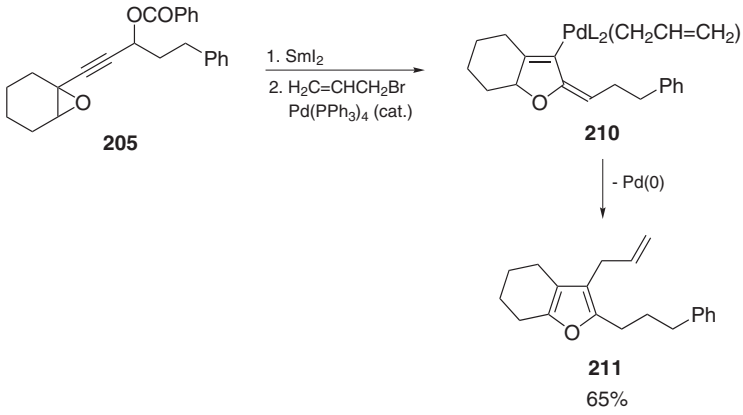
Scheme 2.62 Samarium-mediated reductive coupling of propargyl oxiranes with ketones.

The analogous treatment of oxiranes bearing an additional leaving group at a second propargylic position (e.g. **205**) afforded rather unstable butatrienes of type **206** through an SmI_2-promoted reduction–elimination sequence (Scheme 2.63) [100]. Although some of these cumulenes had been isolated, they were usually cycloisomerized in situ to trisubstituted furans (e.g. **209**) in the presence of a palladium(II) catalyst and acetic acid as the proton source. Presumably, these heterocyclic products are formed through activation of a butatriene double bond (**207**), followed by ring closure to σ-palladium intermediate **208**, which upon protonation and tautomerization releases the palladium into the catalytic cycle.



Scheme 2.63 Samarium-mediated synthesis of trisubstituted furan **209** via butatriene **206**. L= PPh_3; X = OAc.

Interestingly, if the cyclization was carried out in the presence of an aryl or allyl halide and a palladium(0) catalyst, an additional C–C coupling step via presumed intermediate **210** led to the formation of tetrasubstituted furans of type **211** (Scheme 2.64) [101].



Scheme 2.64 Samarium-mediated synthesis of tetrasubstituted furan **211** (L= PPh_3).

2.6 Conclusion

Over the years, organometallic reagents have become indispensable tools in allene synthesis. In many cases, protocols involving stoichiometric amounts of organometallic compounds are superior to similar catalytic procedures (if they exist at all) in terms of efficiency, selectivity and reliability. Whereas copper is still the metal of choice for the generation of allenes by C–C bond-forming addition and substitution reactions of multiply unsaturated substrates, it is now nicely supplemented by several other metals (e.g. titanium, indium) and future development of the latter appears to be particularly promising. In the field of C–H bond formation, aluminum and samarium have proven to be prolific, whereas titanium-mediated olefination methods allow the efficient formation of allenes from smaller fragments. A crucial feature of many of these transformations is the fact that they take place with high levels of regio- and steroselectivity, making them very attractive for target-oriented synthesis.

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3
Transition Metal-Catalyzed Synthesis of Allenes

Masamichi Ogasawara and Tamio Hayashi

3.1
Introduction

This chapter will cover reactions in which allenyl C=C=C skeletons are constructed using transition metal catalysts. Thus, functionalization or derivatization of compounds having cumulated C=C=C moieties will not be covered in this chapter. In addition, reactions using 'stoichiometric' transition metal reagents (see Chapter 2) will be excluded from the discussion.

There are three practical approaches to the construction of the C=C=C moiety. The first one is substitution reactions of propargyl compounds, conjugated 1,3-dienes or other related substrates. The degree of unsaturation in the main frameworks of the reactants remains unchanged between the starting substrates and the final allenic products; however, the C=C=C moieties can be introduced into the products with proper redistribution of the carbon–carbon π-bondings. The second category is addition reactions to substrates in which the degree of unsaturation is more than two. Conjugate additions of appropriate reagents to conjugated enynes or related substrates give substituted allenes. The third is elimination reactions from olefinic substrates. A few other examples which are outside these categories will be mentioned in Section 3.5. Transition metal-catalyzed preparation of 1,2,3-butatrienes, which have three cumulated C=C double bonds in a molecule, are also discussed in this chapter.

3.2
Formation of Allenes by Substitution Reactions

3.2.1
S_N2'-Substitution of Propargyl Compounds

Propargylic substitution reaction is one of the most important routes to allenic compounds [1, 2]. As shown in Scheme 3.1, replacement of a leaving group at the propargylic position with an incoming nucleophile via an S_N2' pathway rearranges the C≡C–C skeleton into a C=C=C moiety to give a propadienyl species. With certain

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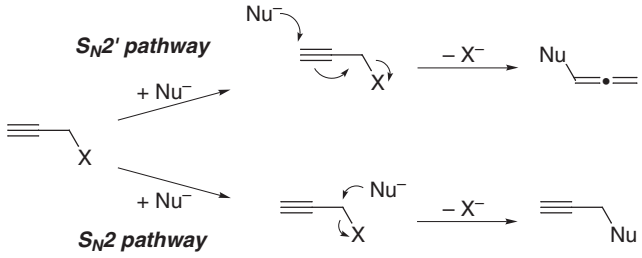
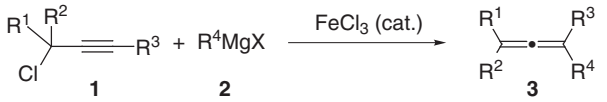
nucleophiles, such as $LiAlH_4$ and organocuprates, the reaction proceeds without assistance from transition metal catalysts giving an allenic product. In many cases, however, direct substitution of the propargylic substrate by way of an S_N2 pathway, which results in the formation of an acetylenic product, may compete with the S_N2' displacement. In many transition metal-catalyzed propargylic substitutions, high levels of regioselectivity (S_N2 vs S_N2') have been achieved. Indeed, most reported examples of metal-catalyzed allene preparations can be classified into this type of transformation. Palladium is the most commonly used transition metal for the reactions and there are some reports with copper, nickel or other metal catalysts.



Scheme 3.1

3.2.1.1 Early Reports

Most probably a paper published in 1976 by Pasto et al. is the first report on the transition metal-catalyzed reaction of organometallic nucleophiles with propargylic electrophiles to give allenes [3]. The reaction of an alkylmagnesium halide with a substituted propargyl chloride in the absence of a transition metal catalyst afforded a mixture of allenic (via an S_N2' pathway), propargylic (via an S_N2 pathway) and some other isomers [4]. On the other hand, both terminal and internal propargyl chlorides **1** react with primary or secondary Grignard reagents **2** in the presence of 5×10^{-5} M $FeCl_3$ to produce the corresponding allenes **3** in excellent yield (Scheme 3.2) [3]. Other transition metal species, such as $CoBr_2$, $NiBr_2$, CuCl and $Fe(acac)_3$, were also found to be capable of accelerating the formation of the allenes [5].

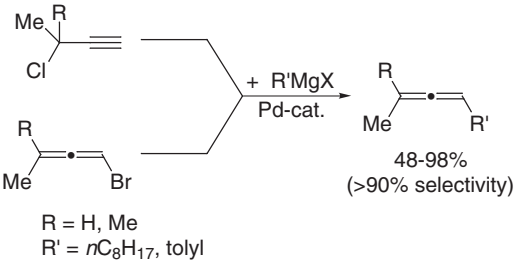


1	2	3 (yield/%)
$R^1 = R^2 = Me$, $R^3 = H$	$R^4 = n$Bu	80
$R^1 = Me$, $R^2 = R^3 = H$	$R^4 = n$Bu	90
$R^1 = R^2 = R^3 = Me$	$R^4 = n$Bu	87
$R^1 = R^2 = R^3 = Me$	$R^4 = i$Pr	88
$R^1 = R^2 = -(CH_2)_5-$, $R^3 = H$	$R^4 = Me$	84
$R^1 = R^2 = -(CH_2)_5-$, $R^3 = Me$	$R^4 = n$Bu	70-80

Scheme 3.2

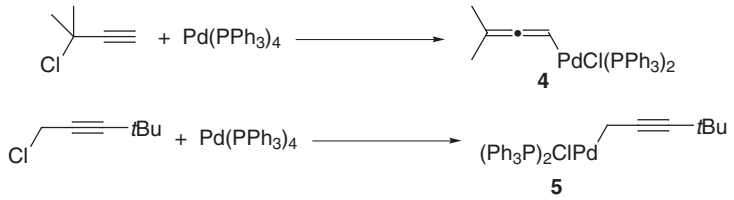
3.2.1.2 Palladium-Catalyzed Reactions

Following the reports by Pasto and co-workers [3–5], Jeffery-Luong and Linstrumelle described the analogous selective formation of allenic species using a Pd catalyst (10 mol%), which was generated from $PdCl_2$, PPh_3 and DIBAL [6]. They employed both propargyl and allenyl halides as substrates and the allenic products were obtained with >90% selectivity from either of them (Scheme 3.3).



Scheme 3.3

Since then, many useful palladium-catalyzed transformations of propargyl compounds have been reported and there are several review articles on this topic [7–14]. In most of the Pd-catalyzed formations of allenes from propargyl electrophiles, (σ-allenyl)palladium(II) complexes are assumed to be intermediates. Indeed, it was found that oxidative addition of substituted propargyl halides to $Pd(PPh_3)_4$ gave the (σ-allenyl)palladium complex **4** and the (σ-propargyl)palladium complex **5**, depending on the steric characteristics of the propargyl halides [15, 16]. The formation of **4** is preferred in most cases; however, **5** is formed when there is a bulky substituents at the C-3 position of the propargyl halide (Scheme 3.4).



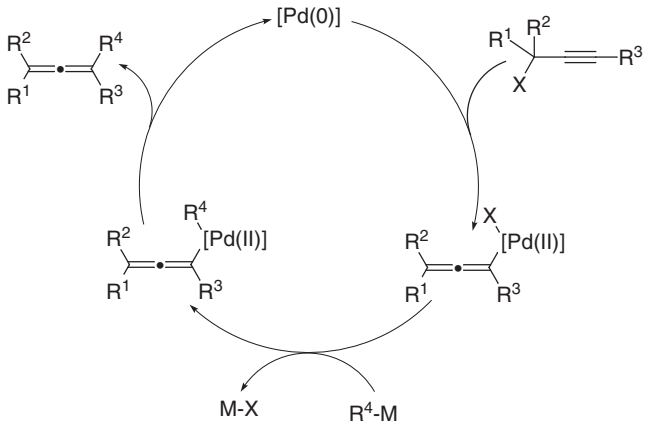
Scheme 3.4

On the other hand, several isolable (η^3-allenyl)palladium complexes have been prepared recently [17–21] and their role in catalytic reactions has been discussed [22–26].

In the following sections, the palladium-catalyzed conversion of the propargyl electrophiles into allenes will be briefly summarized with some representative examples and some recent reports. Although selectivity between the allenic and the propargylic products has been one of the central topics in Pd-catalyzed reactions of the propargyl electrophiles, reactions giving allenes as main products will be considered. For more comprehensive reviews on these topics, previous publications should be consulted [7–14].

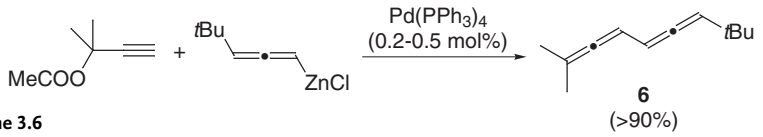
Palladium-Catalyzed Coupling Reactions of Propargyl Electrophiles with Hard Carbon Nucleophiles

In a (σ-allenyl)palladium(II) species, which can be generated from a propargyl electrophile and a Pd(0) species as shown in Scheme 3.4, the allenyl ligand binds to the palladium center with an sp^2-carbon. The (σ-allenyl)palladium(II) species has some similarity with an alkenylpalladium complex. As expected from this, the (σ-allenyl)-palladium(II) species reacts with a hard carbon nucleophile, such as organomagnesium, -zinc or -boron reagents, via transmetallation followed by reductive elimination to give a substituted allene (Scheme 3.5). The reactions are somewhat similar to Pd-catalyzed cross-coupling reactions, but the propargyl substrates rearrange into allenyl moieties in the oxidative addition step. The S_N2' substitution reactions with Grignard reagents reported by Jeffery-Luong and Linstrumelle [6] probably proceed via this catalytic cycle.



Scheme 3.5

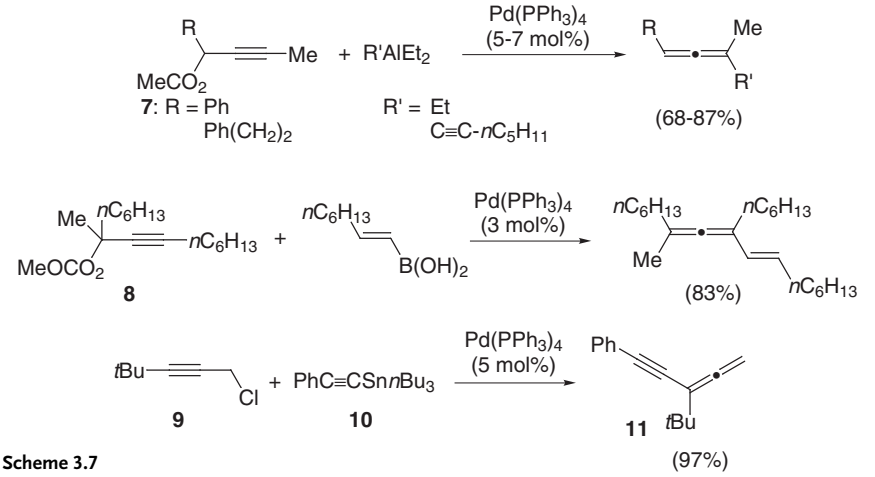
Vermeer and co-workers found that the use of organozinc compounds in place of Grignard reagents for the Pd-catalyzed reaction of propargyl electrophiles showed better regioselectivity in giving allenic products (>99%) with higher yields (~90%) even with lower catalyst loadings (0.2–0.5 mol%) [27–29]. As propargyl electrophiles, propargyl acetates were also used for the Pd-catalyzed reaction with organozinc reagents [27–30]. Application of the reaction for the preparation of a bisallene, **6**, is shown in Scheme 3.6.



Scheme 3.6

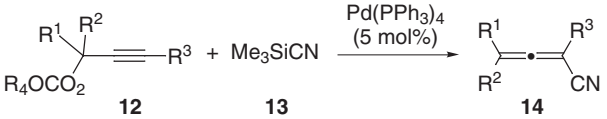
Other hard carbon nucleophiles, such as organoaluminium [31] or organoboron [32, 33] reagents, are also applicable to the Pd-catalyzed S_N2' substitution of pro-

pargylic electrophiles (Scheme 3.7). Note that the reactions of organoboron compounds with methyl propargyl carbonate **8** took place under neutral conditions (i.e. without additional base), because methoxide was generated in situ from **8** by successive oxidative addition to Pd(0) and decarboxylation. Whereas tetraallylstannane was inert to the palladium-catalyzed reaction with propargyl acetates **7** [31], reaction of the propargyl chloride **9** with the alkynylstannane **10** afforded the alkynylallene **11** [24].



Scheme 3.7

Cyanoallenes **14** were obtained in moderate to good yields by the reactions of trimethylsilyl cyanide **13** and propargyl carbonates **12** in the presence of 5 mol% $Pd(PPh_3)_4$ (Scheme 3.8) [34].

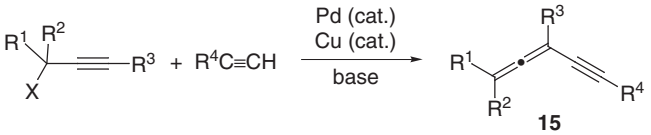


R^1	R^2	R_3	R^4	14 (%)
Me	Me	nC_6H_{13}	Me	91
Me	Me	nC_6H_{13}	Et	88
Me	Me	$Me_2CH(CH_2)_2$	Et	86
Me	Et	nC_4H_9	Et	86
Me	Et	nC_6H_{13}	Me	91
Me	Me_2CHCH_2	HC≡C	Et	57
H	Me	nC_6H_{13}	Et	49
H	H	nC_6H_{13}	Et	35

Scheme 3.8

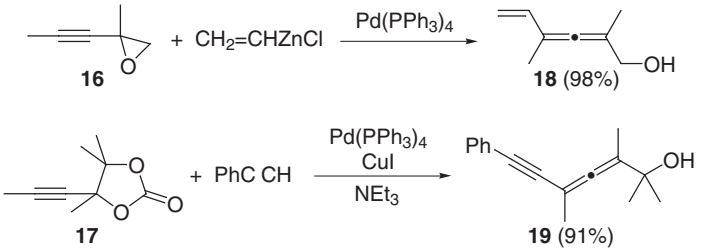
Pd-catalyzed cross-coupling reactions of the in situ-generated (σ-allenyl)palladium (II) intermediates with terminal alkynes were also realized in the presence of a catalytic amount of CuI [35–38]. The reactions are similar to the well-known Sonoga-

shira coupling. Thus, the propargyl electrophiles are converted into conjugated allenylalkynes **15** (Scheme 3.9). As the leaving groups X in the propargyl electrophiles, carbonates [36, 37], acetates [38], tosylates [38] and halides [35, 38] can be used.



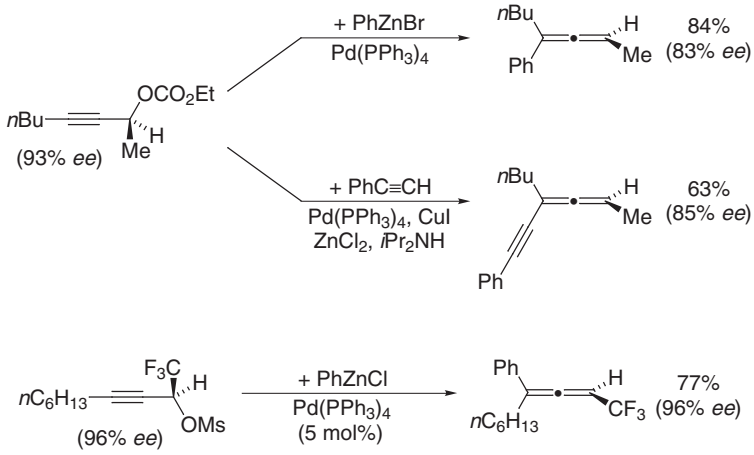
Scheme 3.9

The use of 2-(1-alkynyl)oxiranes **16** [39] or cyclic alkynyl carbonates **17** [40] for the palladium-catalyzed reaction afforded allenylmethyl alcohols **18** and **19**, as shown in the representative examples in Scheme 3.10.



Scheme 3.10

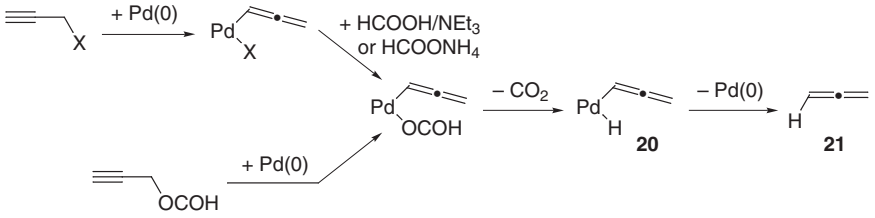
A propargyl substrate having a substituent at the propargyl position is centrally chiral and an allenic product from the S_N2' substitution reaction will be axially chiral. Chirality transfer in the S_N2' reaction, accordingly, may be achieved starting from an enantiomerically enriched propargyl electrophile [29]. The reactions in Scheme 3.11 are some recent examples of the center to axis chirality transfer by Pd-catalyzed S_N2' reactions [41, 42].



Scheme 3.11

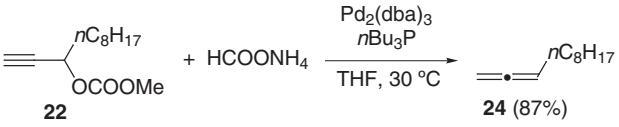
Palladium-Catalyzed Reduction of Propargyl Electrophiles

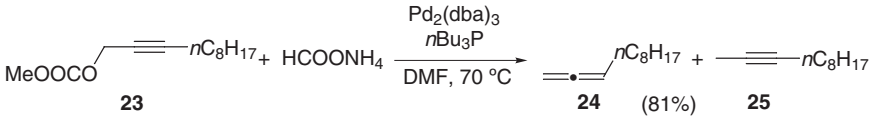
In the presence of an appropriate hydride source, palladium-catalyzed 1,3-reduction of a propargyl electrophile takes place to give the corresponding allene. The key intermediate of this catalytic reduction is a (σ-allenyl)hydridopalladium(II) species **20**, and reductive elimination from **20** gives the hydridoallene **21**. Ammonium salts of formic acid were found to be excellent hydride sources for this transformation. After transmetallation of the formate anion to a Pd-center, decarboxylation leads to a Pd–H species **20**. Another convenient route to hydridoallenes is palladium-catalyzed self-degradation of propargyl formates. Oxidative addition of the propargyl formate to a Pd(0) species gives an intermediate (σ-allenyl)palladium formate, which is identical with the intermediate from the reaction of a formic acid salt (Scheme 3.12).



Scheme 3.12

Hydridoallene formation using ammonium formate was achieved most satisfactorily from primary and secondary propargyl carbonates with a terminal alkyne moiety [43, 44]. Using $Pd_2(dba)_3$ and nBu$_3$P in THF at 30 °C, the terminal allene **24** was obtained with excellent selectivity starting from the secondary propargyl carbonate **22** (Scheme 3.13). The reaction temperature is important for the selective preparation of the allene: at higher temperature (65 °C) an over-reduction product, nC$_8$H$_{17}$CH$_2$CH=CH$_2$, was also formed even with one equivalent of HCOONH$_4$. An isomeric internal alkyne **23** was less reactive than **22** and the reduction proceeded at 70 °C, but the product was a mixture of the allene **24** and the alkyne **25** (Scheme 3.13).

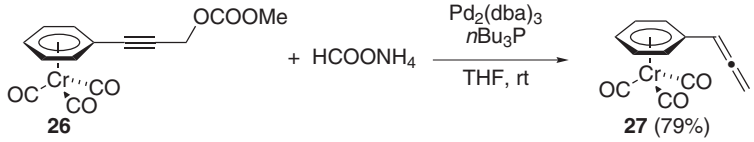




Scheme 3.13

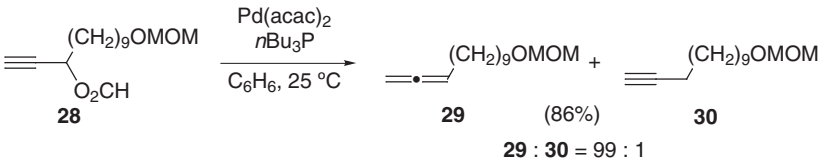
24 : **25** = 5 : 1

An interesting application of the Pd-catalyzed reduction was reported for the preparation of the chromiumtricarbonyl complexed phenylallene **27** (Scheme 3.14), which was obtained from the internal alkyne **26** with good regioselectivity [45].



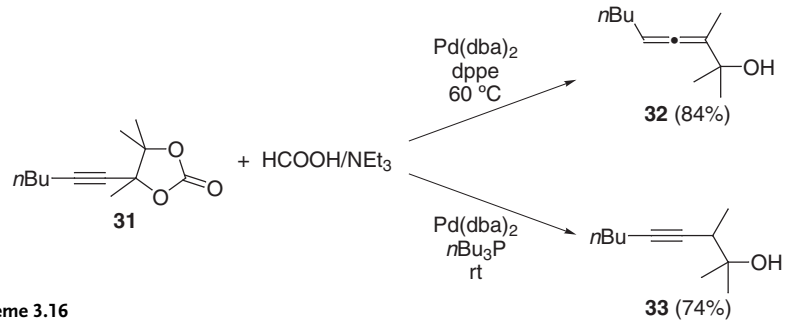
Scheme 3.14

Using terminal propargylic formates, allenes were prepared much more cleanly by Pd-catalyzed intramolecular reduction [46, 47]. The reduction process can be seen as a kind of decomposition reaction and therefore no additional reductant (ammonium formate) is required. In the Pd-catalyzed self-reduction of **28**, the terminal allene **29** was formed in 86% yield with 99% selectivity and only a trace amount of alkyne **30** was detected (Scheme 3.15).



Scheme 3.15

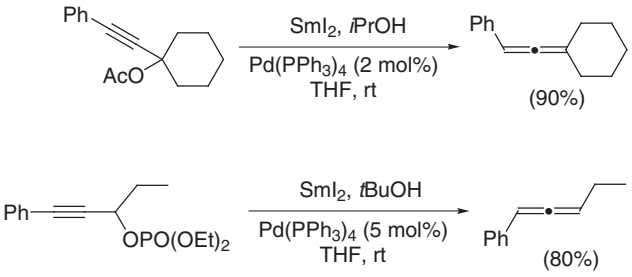
Reduction of the cyclic alkynyl carbonate **31** afforded two different products depending on the phosphine ligands on the palladium catalyst [48]. Whereas $Pd(dba)_2$/dppe gave the allenic product **32**, the homopropargyl alcohol **33** was obtained with nBu$_3$P (Scheme 3.16).



Scheme 3.16

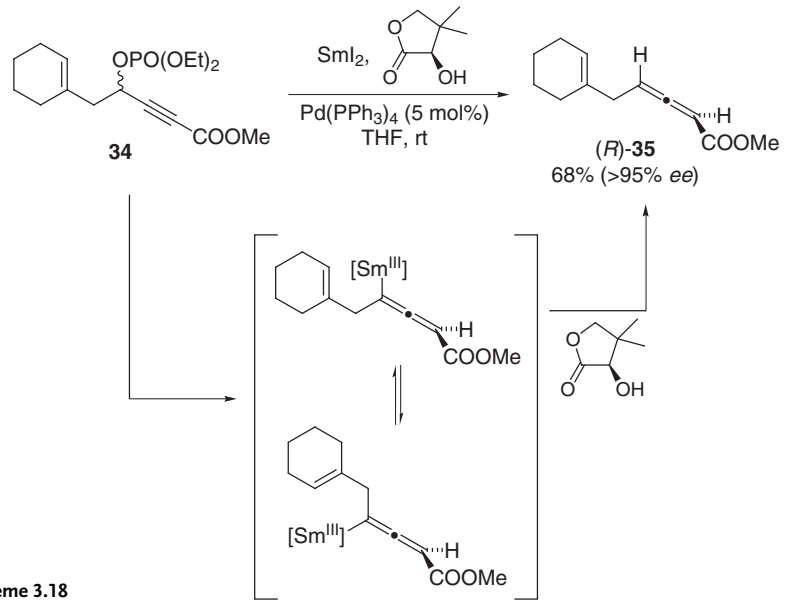
Reductions of propargyl bromides, mesylates and phosphates using $LiAlH_4$, $NaBH_4$ and $LiBHEt_3$ as reductants were reported; however, the selectivity towards allenic products was generally low [49, 50].

Palladium-catalyzed reduction of propargyl acetates is possible with SmI_2 in the presence of a proton source (Scheme 3.17) [51]. The allene/alkyne selectivity is greatly influenced by the choice of the proton source. Propargyl phosphates were also converted into hydridoallenes by Pd-catalyzed reduction with SmI_2 [52].



Scheme 3.17

The allenyl carboxylate **35** was obtained in an enantiomerically enriched form by the palladium-catalyzed reduction of the racemic phosphate **34** using a chiral proton source [53]. The two enantiomers of the (allenyl)samarium(III) intermediate are in rapid equilibrium and thus dynamic kinetic resolution was achieved for the asymmetric preparation of (*R*)-**35** (Scheme 3.18).

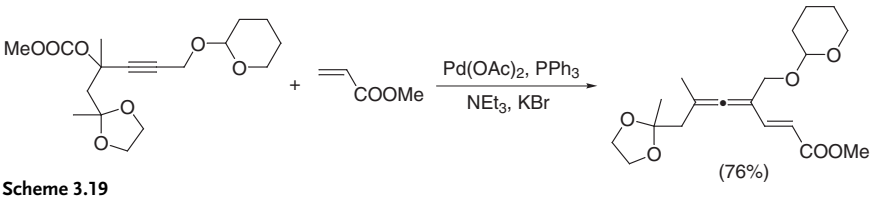


Scheme 3.18

Insertion of Olefins into Allenylpalladium Species

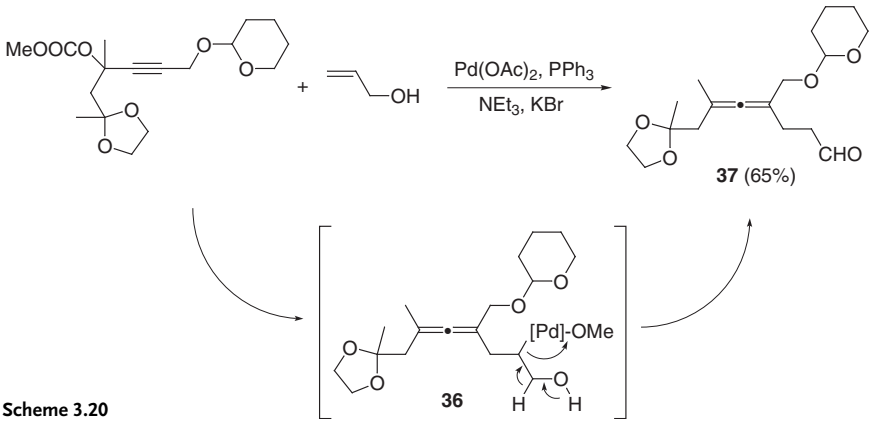
As shown in the previous sections, a (σ-allenyl)palladium species, which is formed from a propargyl electrophile and a Pd(0) catalyst, reacts with a hard carbon nucleophile in a manner analogous to the Pd-catalyzed cross-coupling reaction to give a substituted allene. The results indicate that the reactivity of the (σ-allenyl)palladium species is similar to that of an alkenylpalladium intermediate. Indeed, it was found that the (σ-allenyl)palladium species reacted with olefins to give vinylallenes, a reaction process that is similar to that of the Heck reaction of alkenyl halides [54].

In 1991, Mandai et al. reported that the palladium-catalyzed reaction of propargyl carbonates with olefins proceeded smoothly in DMF at 70 °C in the presence of triethylamine and potassium bromide to give vinylallenes in good yields [54]. The active palladium catalyst was generated in situ from $Pd(OAc)_2$ and PPh_3. A typical example is shown in Scheme 3.19.



Scheme 3.19

Using allyl alcohol as an olefinic reagent, the allenyl aldehyde **37** was formed by the elimination of a β-hydrogen atom which is adjacent to the –OH group in the intermediate **36** (Scheme 3.20) [54].

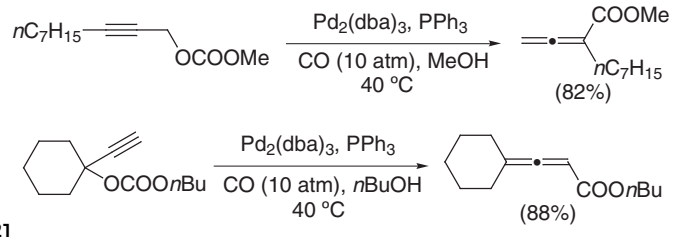


Scheme 3.20

Carbonylation of Allenylpalladium Species

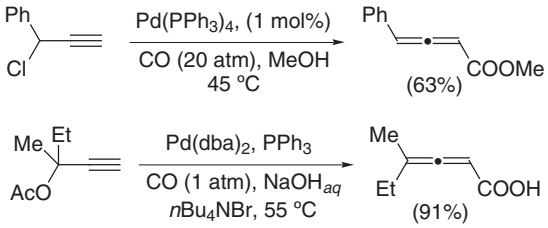
The Pd-catalyzed reaction of propargyl electrophiles with carbon monoxide is a convenient route to allenyl carboxylic acid derivatives. In 1986, Tsuji et al. reported the Pd-catalyzed decarboxylation–carbonylation of propargyl carbonates under a CO at-

mosphere [55]. Carbon monoxide was introduced at the γ-position of the propargyl group and 2,3-dienyl carboxylates were obtained in alcoholic solvents in good yield. Under more severe conditions, the allenic products undergo further palladium-catalyzed carbonylation or other transformations, however, under properly controlled reaction conditions (including the choice of suitable propargylic substrates), the 2,3-dienyl carboxylates were obtained in excellent yields (Scheme 3.21).



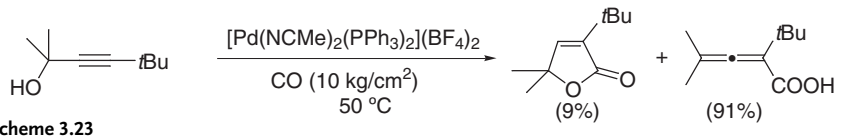
Scheme 3.21

Propargyl halides [56] and propargyl acetates [57] have also been employed for Pd-catalyzed carbonylation (Scheme 3.22). From the latter substrates, allenylcarboxylic acids were obtained under phase-transfer conditions (with nBu$_4$NBr in aqueous NaOH and 4-methyl-2-pentanone) [56].



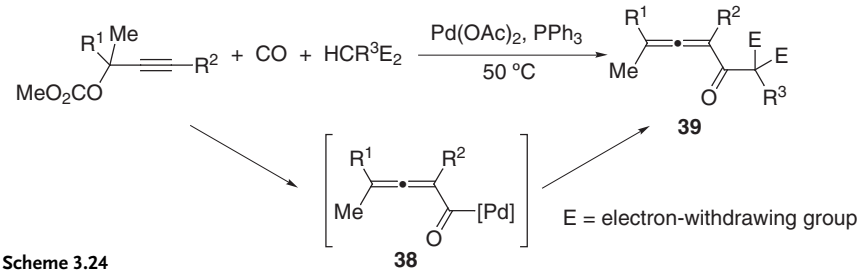
Scheme 3.22

Tertiary propargylic alcohols reacted with carbon monoxide in the presence of a cationic palladium(II) complex, [Pd(NCMe)$_2$(PPh$_3$)$_2$](BF$_4$)$_2$, to afford mixtures of 2(5*H*)-furanones and 2,3-dienoic acids (Scheme 3.23). Control experiments demonstrated that the latter products were converted into the former quantitatively with a trace amount of acid [58].



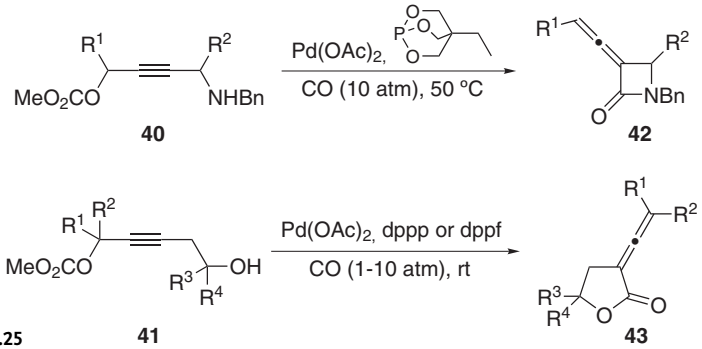
Scheme 3.23

When the Pd-catalyzed carbonylation of a propargyl carbonate was performed in the presence of an activated methylene or methine pronucleophile, the acylpalladium intermediate **38** was trapped by the pronucleophile to give **39** (Scheme 3.24) [59].



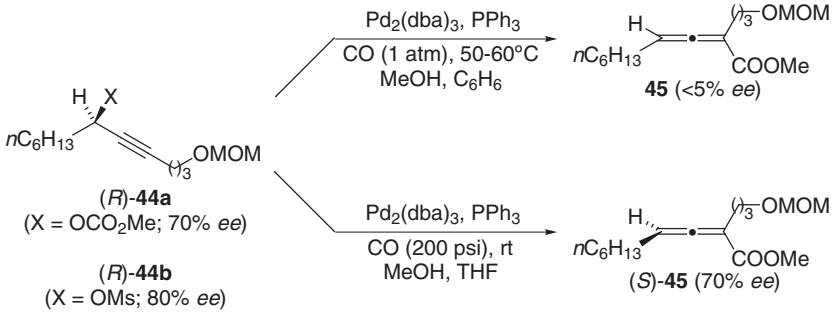
Scheme 3.24

The palladium-catalyzed carbonylation of 4-amino-2-alkynyl carbonates **40** or 5-hydroxy-2-alkynyl carbonates **41** afforded α-vinylidene-β-lactams **42** [60] or α-vinylidene-γ-lactones **43** [61] in good yields (Scheme 3.25). The initially formed (allenylcarbonyl)palladium(II) intermediates were trapped by the intramolecular amino- or hydroxy-nucleophiles to give **42** or **43**.



Scheme 3.25

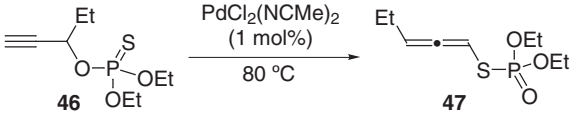
Chirality transfer from the centrally chiral propargyl electrophile **44** to the axially chiral allene **45** was reported for Pd-catalyzed carbonylation [62]. Under reaction conditions analogous to those in the previous report [with X = OCO_2Me (**44a**); 50–60 °C; 1 atm CO] [55], the allene **45** with <5% *ee* was obtained from (*R*)-**44a** of 70% *ee*. The low level of chirality transfer was ascribed to Ph_3P-catalyzed racemization of **45** at elevated temperatures. Changing the leaving group to mesylate [X = OSO_2Me (**44b**)] and increasing the CO pressure (200 psi) enabled the reaction to be run at room temperature. Under these improved conditions, (*S*)-**45** (70% *ee*) was obtained in 85% yield from (*R*)-**44b** (80% *ee*). The chirality transfer efficiency of the reaction was 88% (Scheme 3.26).



Scheme 3.26

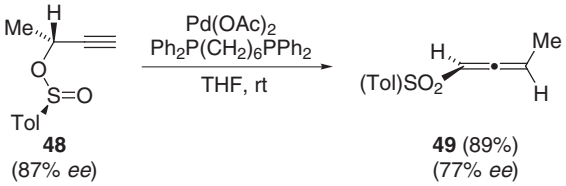
Other Palladium-Catalyzed Syntheses of Allenes from Propargyl Electrophiles

The [3,3]-sigmatropic type rearrangement of propargyl thionophosphates **46** was catalyzed by $PdCl_2(NCMe)_2$ [63]. The rearrangement reaction took place stereospecifically and the allenyl thiolophosphates **47** were obtained in good yields (Scheme 3.27).



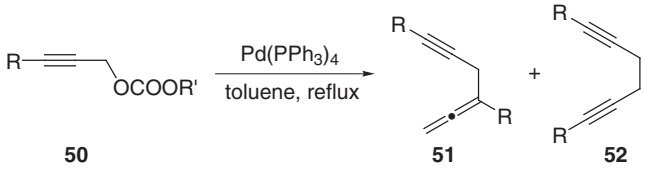
Scheme 3.27

The propargyl sulfinates **48**, which have chirality on both the α-carbon of the propargyl group and the sulfur atom of the sulfinate, were rearranged into axially chiral allenyl sulfones **49** by the Pd-catalyzed reaction [64]. The reactions proceeded with high stereospecificity and the central chirality in the propargyl sulfinates was transferred to the axial chirality in the allenyl sulfones. The sufinate (*Ss,R*)-**48** of 87% *ee* was converted to the allenyl sulfone (*R*)-**49** of 77% *ee* by the reaction, for which the chirality transfer efficiency was 89% (Scheme 3.28).



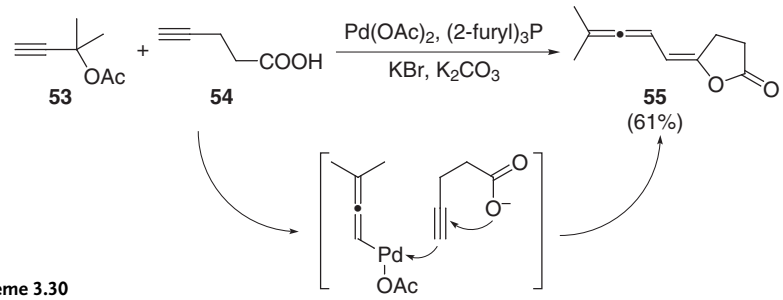
Scheme 3.28

In the presence of $Pd(PPh_3)_4$, reductive homocoupling of 3-silylpropargyl carbonate **50** proceeded to give a mixture of allenenyne **51** and diyne **52** [65]. The highest allene selectivity (**51**:**52** = 95:5) was achieved for the reaction of **50** with R = Si*i*Pr$_3$ and R′ = Et (Scheme 3.29).



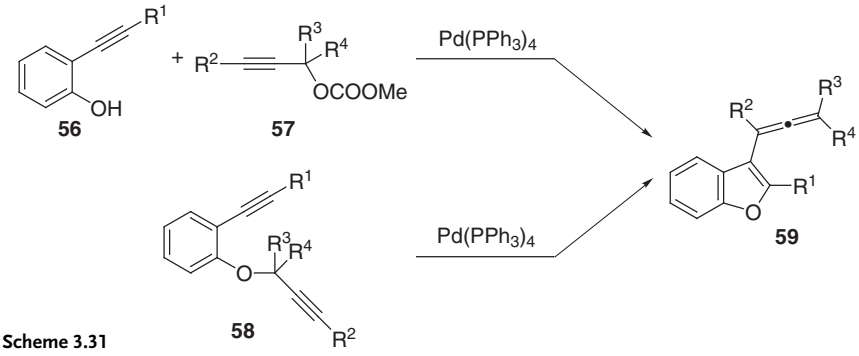
Scheme 3.29 For R = Si*i*Pr$_3$, R' = Et; Yield: 85%, **51**:**52** = 95:5

The Pd-catalyzed coupling reaction of the propargyl acetate **53** and 4-pentynoic acid (**54**) in the presence of potassium bromide produced the unsaturated *exo*-enol lactone **55** [66]. The reaction proceeded via oxypalladation of the triple bond of **54** with an allenylpalladium intermediate, which was formed from Pd(0) and **53** and the carboxylate as shown in Scheme 3.30.



Scheme 3.30

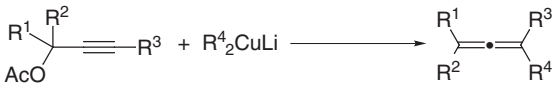
Two groups independently demonstrated that the strategy for the preparation of **55** could be used for the synthesis of 2-substituted-3-allenylbenzo[*b*]furans **59** (Scheme 3.31). The synthesis of **59** was achieved by intermolecular cyclization between alkynylphenols **56** and propargyl carbonates **57** [67] or by intramolecular rearrangement of (2-alkynylphenyl)propargyl ethers **58** [67, 68].



Scheme 3.31

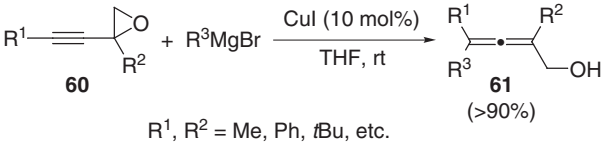
3.2.1.3 Copper-Catalyzed Reactions

One of the most popular methods for the synthesis of allenes is the S_N2' reaction of propargylic derivatives with organocopper reagents [1, 2]. Most probably a study published in 1968–69 by Rona and Crabbé represents the first example of the Cu(I)-mediated S_N2' reaction of propargylic electrophiles giving allenic products (Scheme 3.32) [69, 70]. Since then, many researchers have used modified organocopper reagents with stoichiometric or catalytic amounts of Cu(I) salt.



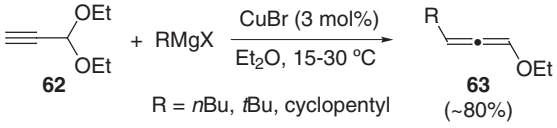
Scheme 3.32

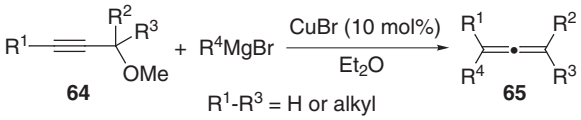
In 1974, Vermeer et al. described formation of allenic alcohols **61** by the reaction of alkynyl epoxides **60** with Grignard reagents in the presence of 10 mol% of CuI (Scheme 3.33) [71]. In the absence of CuI, a complicated mixture of products was obtained. Furthermore, the Cu-catalyzed reactions exhibited higher yields and higher selectivity than analogous reactions of alkynyl epoxides with lithium dialkylcuprates [72]. This method was applied to a reaction of allylmagnesium bromide with an alkynyl epoxide [73].



Scheme 3.33

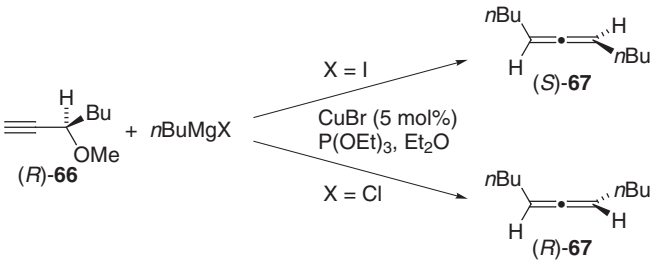
Two examples of a Cu(I)-catalyzed S_N2' replacement of propargylic –OR groups with Grignard reagents appeared in 1976 (Scheme 3.34). Propiolaldehyde diethyl acetal (**62**) reacts with Grignard reagents in the presence of CuBr (3 mol%) to give allenyl ethers **63** [74, 75]. The CuBr-catalyzed reaction of propargyl methyl ethers **64** afforded the allenic hydrocarbons **65** [76].





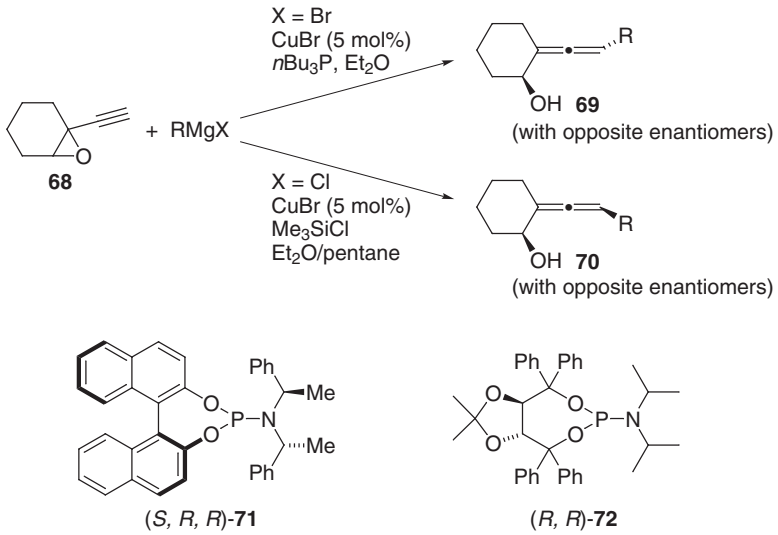
Scheme 3.34

Alexakis and co-workers also investigated the stereochemistry of the reaction. They applied enantiomerically enriched propargyl ether (*R*)-**66** to the CuBr-catalyzed reactions with BuMgX in the presence of $P(OEt)_3$ [77, 78]. The S_N2' reaction proceeded through an *anti* overall process with the Grignard reagent *n*BuMgI to form (*S*)-**67**, whereas a *syn* overall process was dominant with *n*BuMgCl giving (*R*)-**67** (Scheme 3.35). The additive $P(OEt)_3$ prevents Cu-catalyzed racemization of the allene **67**. Prior to Alexakis and co-workers' report, Olsson and Claesson had described analogous chirality transfer from chiral propargyl electrophiles to axially chiral allenes [79]. Due to inappropriate reaction conditions, however, the axially chiral allenes showed very low enantiopurity (~16% *ee*).



Scheme 3.35

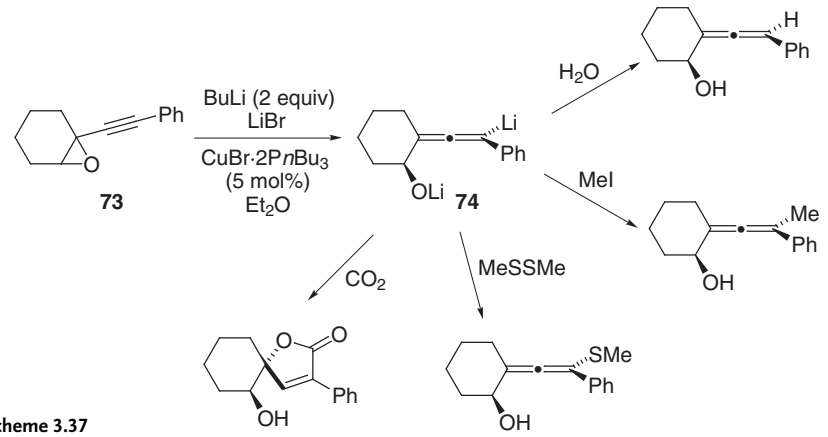
With the proper choice of reaction conditions, diastereoselective synthesis of α-allenic alcohols **69** and **70** from propargylic epoxide **68** was achieved [80, 81]. With RMgBr and 5 mol% of $CuBr/2P(n)Bu_3$, '*anti*' allenic alcohols **69** are obtained with up to 100% diastereoselectivity. On the other hand, '*syn*' allenic alcohols **70** can be prepared with 88–96% diastereoselectivity with RMgCl, Me_3SiCl and 5 mol% CuBr (Scheme 3.36).



Scheme 3.36

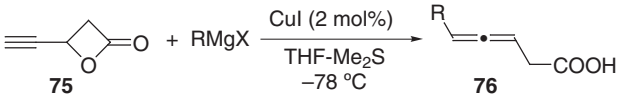
The allenic alcohols **69** and **70** were also prepared in optically active form by Cu(II)-catalyzed kinetic resolution of **68** [82]. The racemic **68** reacted with Et_2Zn in toluene in the presence of $Cu(OTf)_2$ (1.5 mol%) and (*S*,*R*,*R*)-**71** (3 mol%) to give **69** of 36% *ee* (at 50 ± 5% conversion; absolute configuration not determined) with >97% diastereoselectivity. Using $Cu(OTf)_2$ (1.5 mol%) and (*R*,*R*)-**72** (3 mol%), **70** of 36% *ee* (at 50 ± 5% conversion; absolute configuration not determined) was obtained with >95% diastereoselectivity

The alkynyl epoxide **73** undergoes a copper-catalyzed reductive metallation by *n*BuLi [81, 83]. The resultant allenyllithium compound **74** is a versatile intermediate and reacts with various electrophiles (Scheme 3.37).



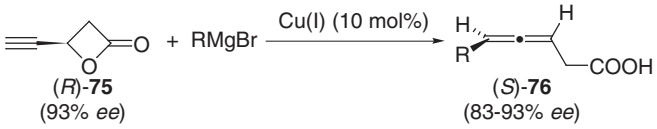
Scheme 3.37

3-Ethynyl-β-propiolactone (**75**) reacts regioselectively with Grignard reagents in the presence of the CuI catalyst to afford 3,4-alkadienoic acids **76** in high yields (Scheme 3.38) [84].



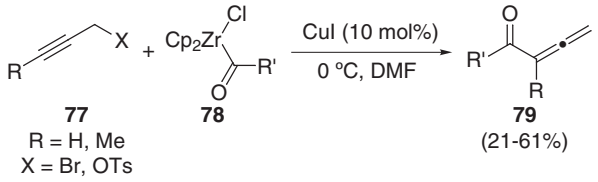
Scheme 3.38

Efficient chirality transfer was reported for the reactions of enantiomerically enriched **75** with Grignard reagents [85]. Using 10 mol% of CuBr or CuCN · 2LiBr, the axially chiral allenes **76** are obtained from the centrally chiral **75** with nearly complete chirality transfer (Scheme 3.39).



Scheme 3.39

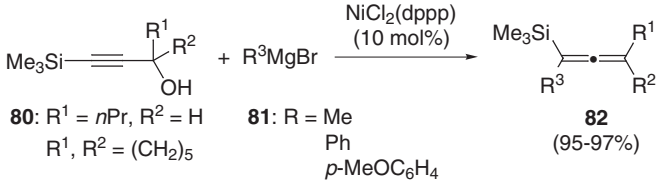
Acylzirconocene chlorides **78**, which are easily available through the hydrozirconation of alkenes or alkynes with $Cp_2Zr(H)Cl$ and subsequent CO insertion, can be used as acyl anion equivalents; Cu(I)-catalyzed reactions with propargyl compounds **77** afford allenyl ketones **79** (Scheme 3.40) [86]. The use of an excess of **77** (2 equiv. to **78**) is important for the selective preparation of **79**, which prevents an undesirable side reaction of the allenic products **79** with **78**.



Scheme 3.40

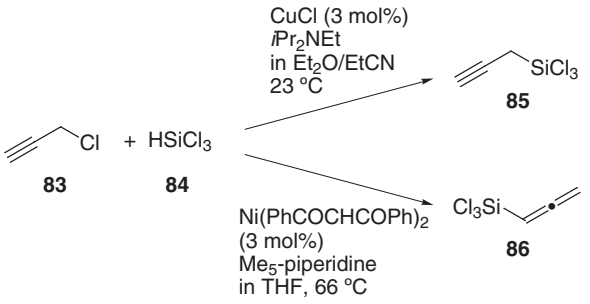
3.2.1.4 Reactions Catalyzed by Transition Metals other than Palladium and Copper

A nickel-catalyzed reaction of silylpropargyl alcohols **80** and Grignard reagents **81** was reported in 1985 [87]. The reaction proceeded in the presence of $NiCl_2$(dppp) (10 mol%) and the silylallenes **82** were obtained in excellent yields (Scheme 3.41).



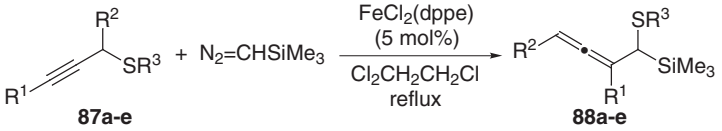
Scheme 3.41

The reaction of propargyl chloride **83** and trichlorosilane **84** showed two different regioselectivities depending on the choice of transition metal catalysts [88]. Whereas the S_N2 substitution proceeded to give the propargylsilane **85** with 94% selectivity using a CuCl catalyst, the silylallene **86** was obtained via an S_N2' pathway with >97% selectivity with 3 mol% of $Ni(PhCOCHCOPh)_2$ (Scheme 3.42).



Scheme 3.42

An example of an iron-catalyzed C–C bond formation reaction was reported in 2001 [89]. Treatment of propargyl sulfides **87** with trimethylsilyldiazomethane in the presence of 5 mol% $FeCl_2$(dppb) gave substituted homoallenylsilanes **88** in good to moderate yields (Scheme 3.43). The silanes **88d** and **88e**, which bear two centers of chirality, were obtained as 1:1 mixtures of diastereomers. Slight diastereoselectivity (2:1) was seen for the formation **88f**, which is an axially chiral allene with a sterogenic center.

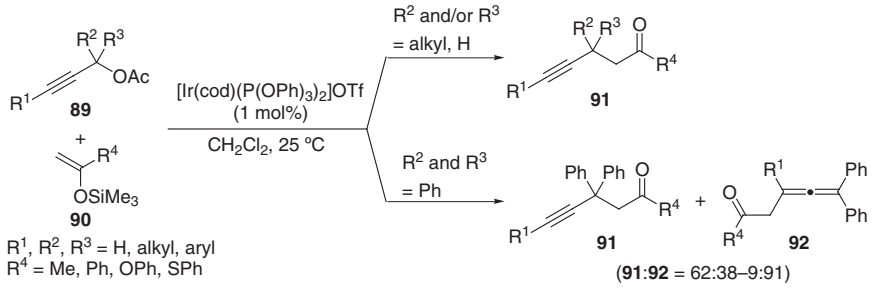


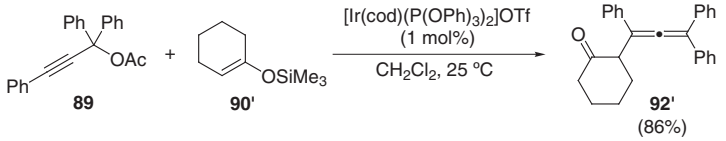
87a-e **88a-e**

	yield of **88**
a: $R^1 = R^2 = H$, $R^3 = p$-$MeOC_6H_4$	73%
b: R^1 = Me, $R^2 = H$, $R^3 = p$-$MeOC_6H_4CH_2$	76%
c: R^1 = Me, $R^2 = H$, $R^3 = p$-$MeOC_6H_4$	78%
d: R^1 = CH(OAc)Ph, $R^2 = H$, $R^3 = p$-$MeOC_6H_4CH_2$	73%
e: R^1 = CH(OAc)Ph, $R^2 = H$, R^3 = 2,5-MeC_6H_3	90%
f: $R^1 = H$, R^2 = Me, $R^3 = p$-$MeOC_6H_4CH_2$	48%

Scheme 3.43

Iridium-catalyzed substitution of propargyl acetates **89** with silyl enol ethers **90** gave S_N2 and/or S_N2' products depending on the substituents at the propargylic position in **89** [90]. For the substrates in which both or either of R^1/R^2 are alkyl or H, the S_N2-substituion products **91** were the main products and no or traces of the allenic species **92** were detected. On the other hand, with **89**, having two phenyl groups at the propargylic position, the S_N2' reaction became more dominant and the allenic products **92** were detected together with **91**. The allenic product **92′** was obtained in 86% yield as the sole product in the reaction of **89** ($R^1 = R^2 = R^3$ = Ph) and **90′** (Scheme 3.44).

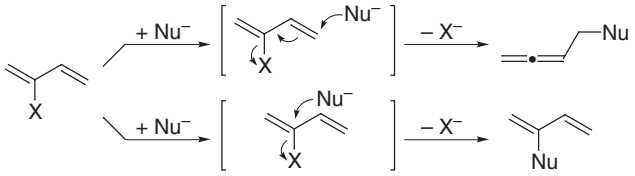




Scheme 3.44

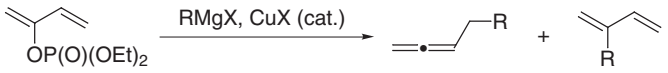
3.2.2
S_N2' Substitution of 2-Halo-1,3-Butadienes and Related Compounds

The S_N2' substitution of a 1,3-butadiene derivative having an appropriate leaving group in the 2-position affords a substituted allene. During the S_N2' reaction, the double bond between the 3- and 4-positions rearranges to the adjacent position to form a C=C=C moiety (Scheme 3.45). Direct substitution of the leaving group via an S_N2 pathway often competes with the S_N2' substitution and gives an undesirable conjugated diene. Control of the two reaction paths is the key to the selective preparation of allenes.



Scheme 3.45

An early example of this class of substitution reactions appeared in 1983 [91]. Claeson et al. reported the reaction of 1,3-alkadien-2-yl phosphates with Grignard reagents in the presence of a catalytic amount of a Cu(I) salt (Scheme 3.46). The reaction of the parent butadienyl phosphate **93** with a Grignard reagent gave a mixture of S_N2' and S_N2 substitution products (**94** and **95**). The selectivity of the reaction was dependent on several factors such as counter anions of the Cu(I) catalyst, Grignard reagents, reaction solvents and amount of the copper salt. In any case, concurrent formation of the conjugated diene could not be completely suppressed and selective preparation of the allenic products was not achieved.

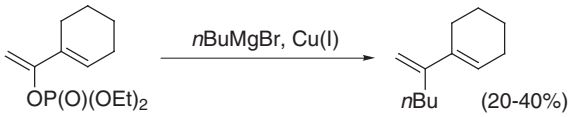


93 **94** **95**

R = $PhCH_2$	CuI (10%)	72%	12%
Octyl	$CuBr{\cdot}Me_2S$ (50%)	21%	6%
Cyclohexyl	CuI (20%)	23%	7%

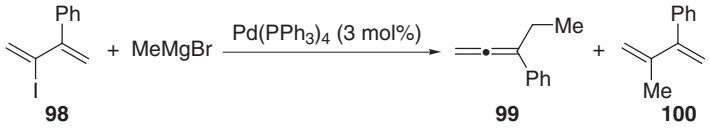
Scheme 3.46

When the same reaction was performed with a phosphate **96** and *n*BuMgBr in the presence of a copper salt, a conjugated diene **97** was obtained exclusively and no allenic product was detected (Scheme 3.47) [91].



Scheme 3.47 **96** **97**

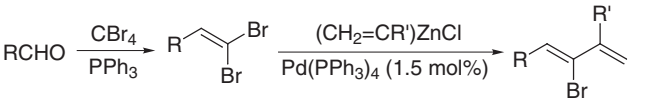
A single example of allene formation was reported for a reaction of 2-iodo-3-phenyl-1,3-butadiene (**98**) with MeMgBr (Scheme 3.48). The reaction, however, proceeded with poor selectivity and the terminal allene **99** was obtained in 36% yield together with 36% of a conjugated diene **100** [92].



98 **99** **100**

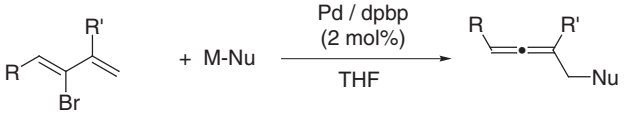
Scheme 3.48 36% 36%

A general and highly selective preparation of a variety of functionalized allenes was achieved by Ogasawara et al. in 2000 [93]. The substrates of the reaction, 2-bromo-1,3-butadiene derivatives **101**, are easily obtained from aldehydes via Wittig dibromoolefination followed by a palladium-catalyzed regioselective cross-coupling reaction with alkenylzinc reagents (Scheme 3.49).



Scheme 3.49 **101** (63-90%)

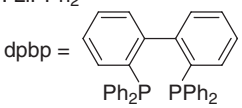
Treatment of **101** with a variety of soft nucleophiles **102** in the presence of 2 mol% of a Pd–dpbp catalyst gave the corresponding allenes **103** in excellent yield (Scheme 3.50). The choice of dpbp as a supporting ligand was important for the high catalytic activity of the palladium species. With more common phosphines, such as $Ph_2P(CH_2)_nPPh_2$ (n= 2–4) or PPh_3, the catalytic activity of the palladium species was much lower, although the allenes were obtained as sole organic products [93].



101a-i **102m-r** **103** (62-96%)

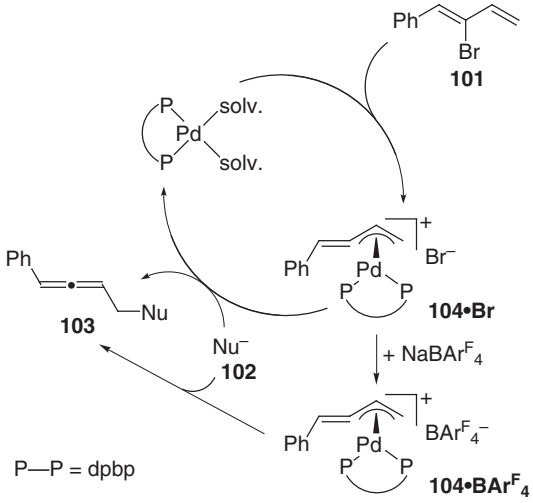
101a: R = Ph, R' = H
101b: R = $PhCH_2$, R' = H
101c: R = (*E*)-PhCH=CH, R' = H
101d: R = *i*Pr, R' = H
101e: R = nC_7H_{15}, R' = H
101f: R = Ph, R' = Me
101g: R = R' = Ph
101h: R = H, R' = Ph
101i: R = Ph, R' = H

102m: $Na[CMe(COOMe)_2]$
102n: $Na[CH(COOMe)_2]$
102o: Na[CMe(COMe)(COOEt)]
102p: $K[CMe(COMe)_2]$
102q: NaOPh
102r: $KN(Boc)_2$
102s: $LiPPh_2$



Scheme 3.50

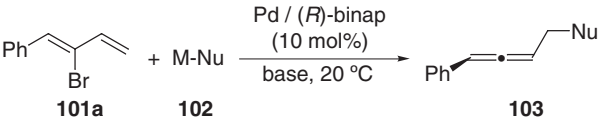
The reaction mechanism of the allene-forming reaction was clarified as shown in Scheme 3.51. The key intermediate of the catalytic cycle, the (benzylidene-π-allyl)-palladium complex **104·Br**, was isolated as the $BAr^F{}_4^-$ salt [$Ar^F = C_6H_3$-3,5-$(CF_3)_2$] **104·BAr$^F_4$**. A stoichiometric reaction of **104·BAr$^F_4$** with **102** gave the corresponding allene **103** in good yield. An analogous (alkylidene-π-allyl)palladium species was suggested as an intermediate for Pd-catalyzed fuctionalization of (allenylmethyl)esters [94, 95].



Scheme 3.51

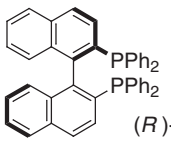
The palladium-catalyzed allene preparation method was extended to an asymmetric counterpart using a Pd/(*R*)-binap species as a chiral catalyst and axially chiral allenes **103** were obtained with good eantioselectivity [96]. It was found that the pres-

ence of dba (dibenzalacetone) as a co-catalyst was important for high enantioselectivity of the reaction. Under optimized reaction conditions, the highest enantioselectivity of 89% *ee* was achieved for the reaction of **101a** with Cs[C(NHAc)(COOEt)$_2$] (**102t**) (Scheme 3.52).



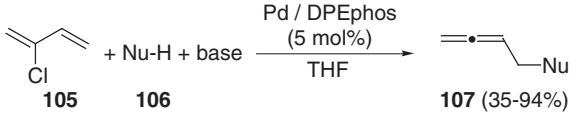
101a **102** **103**

M-Nu: Na[CMe(COOMe)$_2$] (**102m**) without dba 11% *ee*
with dba 68% *ee*
M-Nu: Cs[C(NHAc)(COOEt)$_2$] (**102t**) with dba 89% *ee*



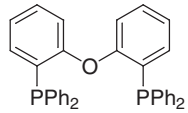
Scheme 3.52

Chloroprene (2-chloro-1,3-butadiene: **105**), which is a mass-produced, inexpensive industrial material, is an excellent precursor to a variety of terminal allenes **107** [97]. The palladium-catalyzed reaction of **105** with pronucleophiles **106** in the presence of an appropriate base gave the terminal allenes **107** in good yields (Scheme 3.53). The palladium species generated from $Pd_2(dba)_3 \cdot CHCl_3$ and DPEphos was a good catalyst for these reactions of chloroprene. In contrast, (*Z*)-1-Phenyl-2-chloro-1,3-butadiene, which is isostructural with the bromo-substrate **101**, was nearly inert under these conditions. There is no substituent at the vicinal *cis*-position to the chloride in **105**, which allows oxidative addition of the C–Cl bond in **105** to the Pd(0) species.



105 **106** **107** (35-94%)

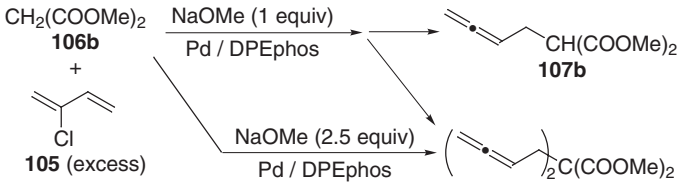
106a: Nu = CMe(COOMe)$_2$
106b: Nu = CH(COOMe)$_2$
106c: Nu = C(CH$_2$CH=CH$_2$)(COOMe)$_2$
106d: Nu = CMe(COMe)(COOEt)
106e: Nu = N(boc)$_2$
106f : Nu = CH(NHCOO*t*Bu)(COO*t*Bu)



DPEphos

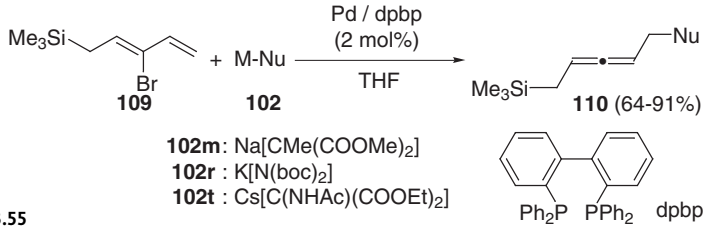
Scheme 3.53

When a mixture of **106b** and an equimolar amount of base (NaOMe) was used as a nucleophile, the product was obtained as a mixture of monoallene **107b** (57%) and bisallene **108** (13% based on **106b**). Because the sodium salt of the initially formed **107b** is more reactive than that of **106b**, the monoallene **107b** could not be prepared selectively under the conditions employed. Alternatively, the bisallene **108** was obtained as a sole allenic product in 67% yield using 2.5 equiv. (with respect to **106b**) of NaOMe (Scheme 3.54) [97].



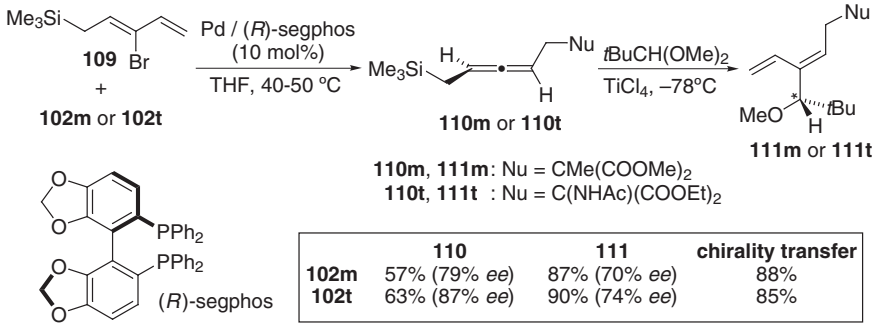
Scheme 3.54

The Pd-catalyzed reaction was applied to the synthesis of (allenylmethyl)silane derivatives [98]. A series of 4-substituted-1-trimethylsilyl-2,3-butadienes **110** were prepared in 64–91% yields from easily accessible (3-bromopenta-2,4-dienyl)trimethylsilane **109** and soft nucleophiles **102** in the presence of 2 mol% of a Pd catalyst generated in situ from $[PdCl(\pi\text{-allyl})_2]_2$ and dpbp (Scheme 3.55).



Scheme 3.55

The axially chiral (allenylmethyl)silanes **110** were also prepared in optically active form using chiral Pd catalysts [98]. For the asymmetric synthesis of **110**, a Pd/(*R*)-segphos system was much better in terms of enantioselectivity than the Pd/(*R*)-binap catalyst. Under the optimized conditions, **110m** and **110t** were obtained in 79% *ee* (57% yield) and 87% *ee* (63% yield), respectively (Scheme 3.56). The enantiomerically enriched (allenylmethyl)silanes **110** served for Lewis acid-promoted S_E' reaction with *t*BuCH(OMe)$_2$ to give conjugated dienes **111** with a newly formed chiral carbon center (Scheme 3.56). During the S_E' reaction, the allenic axial chirality was transferred to the carbon central chirality with up to 88% transfer efficiency.



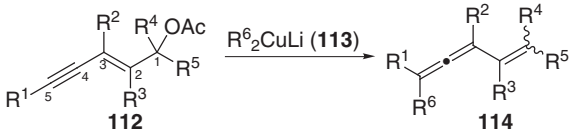
	110	111	chirality transfer
102m	57% (79% *ee*)	87% (70% *ee*)	88%
102t	63% (87% *ee*)	90% (74% *ee*)	85%

Scheme 3.56

3.2.3

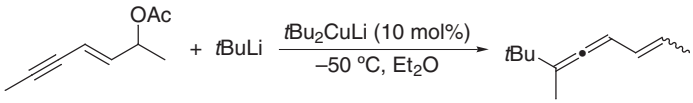
S_N2' Substitution of Pent-2-en-4-ynyl Acetates

It was demonstrated that reactions of pent-2-en-4-ynyl acetates **112** with organocuprates **113** proceeded in an S_N2'' fashion (1,5-substitution) to give the corresponding vinylallene derivatives **114** in good yield [99]. The nucleophilic attack of **113** took place at the triple bond (at the 5-position) in **112** highly regioselectively, the allenic products **114** usually being obtained as mixtures of *E*- and *Z*-isomers (Scheme 3.57).



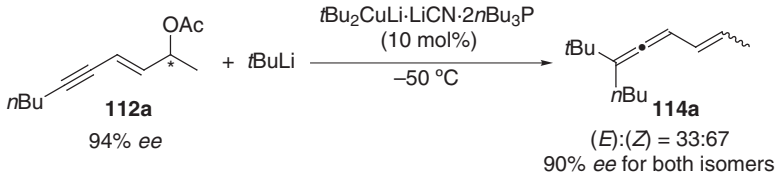
Scheme 3.57

The S_N2'' substitution could be performed in the presence of a catalytic amount of a copper(I) salt [99]. The simultaneous addition of the substrate **112a** and *t*BuLi to 10 mol% $t\mathrm{Bu_2CuLi \cdot LiI}$ in diethyl ether at –50 °C gave the vinylallene **114a** in 90% yield as a 1:2 mixture of *E*- and *Z*-isomers (Scheme 3.58).



Scheme 3.58

Chirality transfer from the centrally chiral substrate **112** to the axially chiral product **114** was also realized in the Cu-catalyzed S_N2'' reaction [100]. Slow addition of the enantiomerically enriched acetate **112b** (94% *ee*; 1 equiv.), which was obtained by lipase-catalyzed kinetic resolution of the racemic acetate and subsequent acylation of the alcohol and *t*BuLi (1 equiv.) to $t\mathrm{Bu_2CuLi \cdot LiCN \cdot 2}n\mathrm{Bu_3P}$ (10 mol%) at –50 °C gave vinylallene **114b** as a 33:67 *E*/*Z* mixture in 80% yield with 90% *ee* for both isomers (the absolute configuration of **114a** was not determined) (Scheme 3.59). The presence of $n\mathrm{Bu_3P}$ was important for high degree of chirality transfer: the enantiopurity of the allenic products was decreased without $n\mathrm{Bu_3P}$ due to probable racemization of the axially chiral allenes **114** [100].

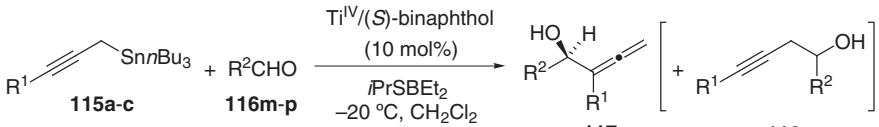


Scheme 3.59

3.2.4

S_E2' Substitution of Propargyl–Metal Species

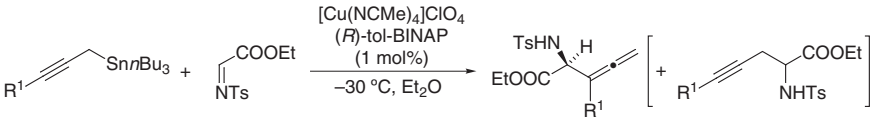
A titanium species prepared from $Ti(OiPr)_4$ and (*S*)-binaphthol (2 equiv. with respect to Ti) is an excellent catalyst for enantioselective S_E2' substitution of propargylstannanes **115** with aldehydes **116** (see Chapter 9) [101]. In the presence of 10 mol% of the Ti catalyst and $iPrSBEt_2$ (1.2 equiv. with respect to **115**), the reactions of **115** and **116** proceeded smoothly and (allenylmethyl)alcohols **117** were obtained in good yields with excellent enantioselectivity (Scheme 3.60). The highest enantioselectivity (97% *ee*) was achieved for the reaction of **115b** and **116p**. The regioselectivity of the electrophilic attack was fairly high and no or trace amounts of isomeric propargylic carbinols **118** (<3%) were formed.



115a: R^1 = Me **116m**: R^2 = $PhCH_2CH_2$
115b: R^1 = Et **116n**: R^2 = nC_6H_{13}
115c: R^1 = Pr **116o**: R^2 = Me_2CHCH_2
116p: R^2 = Ph

Scheme 3.60

Similarly, reactions of **115** with the α-imino ester **119** gave corresponding allenylamino acid esters **120** as the main products [102]. The S_E2' reactions were catalyzed by a copper species (1 mol%), which was generated from $[Cu(NCMe)_4]ClO_4$ and (*R*)-tol-BINAP, and showed good enantio- and regioselectivity (Scheme 3.61).

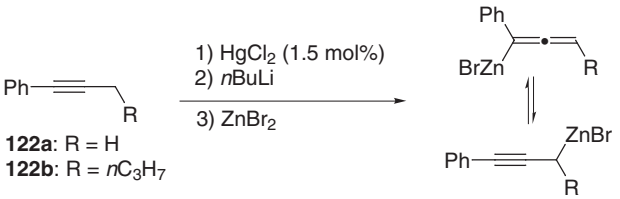


115 **119** **120** **121**

	yield (%)		% *ee* (of **6**)
115a: R^1 = Me	95	**120a**: **121a** = 95 : 5	61
115d: R^1 = Ph	25	**120d**: **121d** = 91 : 9	97
115e: R^1 = $SiMe_3$	93	**120e**: **121e** = >97 : <3	93

Scheme 3.61

The organozinc reagents **123**, which were generated from 1-phenyl-1-alkyne **122** with *n*BuLi in the presence of 1.5 mol% of $HgCl_2$ followed by addition of 1.5 equiv. of $ZnBr_2$, exists as a tautomeric mixture of an allenylzinc and a propargylzinc species (Scheme 3.62) [103].

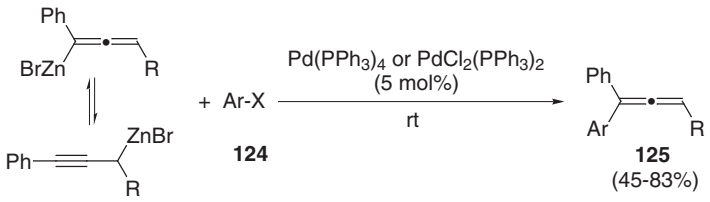


122a: R = H
122b: R = nC_3H_7

123a: R = H
123b: R = nC_3H_7

Scheme 3.62

Palladium-catalyzed cross-coupling reactions of **123** with aryl halides **124** proceeded via the allenylzinc isomers and afforded 1,1-diarylallenes **125** exclusively (Scheme 3.63).



124

125
(45-83%)

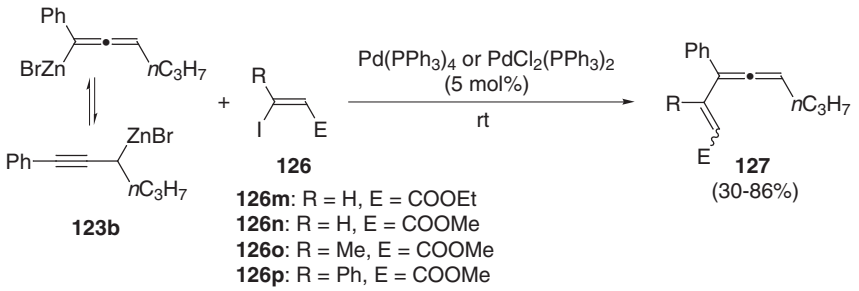
123a: R = H
123b: R = nC_3H_7

124: PhI, 4-MeC_6H_4I,
4-$MeOC_6H_4I$,
4-$O_2NC_6H_4Br$,
1-iodonaphthalene

Scheme 3.63

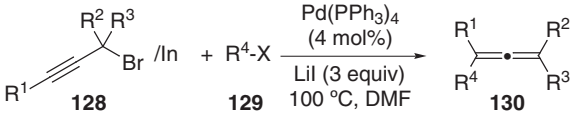
Likewise, the palladium-catalyzed coupling of the allenyl/propargylzinc bromide **123b** with alkenyl iodides **126** gave alkenylallenes **127** with good selectivity (Scheme 3.64). In the Pd-catalyzed coupling reactions with **126m** and **126n**, the olefinic moi-

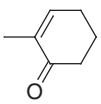
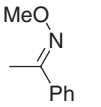
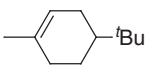
ety isomerized to give (*E*)-**127**, whereas the reactions of **123b** with **126o** and **126p** gave the corresponding (*Z*)-**127** with retention of the stereochemistry. The zinc reagent **123a** reacted with **126** via the propargylzinc species to give 1-en-4-ynes under the identical conditions [104, 105].



Scheme 3.64

Organoindium reagents, which are generated in situ from metallic indium and propargyl bromides **128**, were demonstrated to be effective cross-coupling partners in palladium-catalyzed reactions with a variety of organic electrophiles **129** to produce substituted allenes **130** in excellent yields [106]. The reactions proceeded with complete regioselectivity to give the allenes **130** and no propargyl products were detected (Scheme 3.65). The organoindium reagents were inert to a variety of functionalities, such as nitro, hydroxy and carbonyl groups, and therefore electrophiles with susceptible functional groups could be used for the reactions.



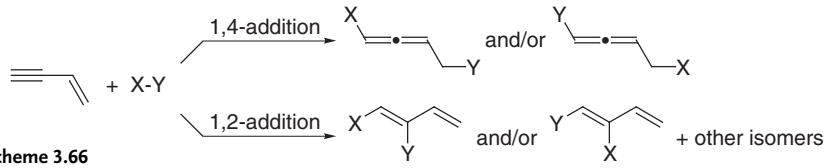
R^1	R^2	R^3	R^4		X	130 (%)
H	H	H	1-naphthyl		I	98
Ph	Me	H	Ph		I	80
$THPOCH_2$	H	H	4-O_2N-C_6H_4	**a** = 	I	91
H	H	Me	4-O_2N-C_6H_4		I	90
H	H	H	4-Ac-C_6H_4		I	87
H	H	H	3-HO-C_6H_4		I	90
H	H	H	4-MeO-C_6H_4		I	91
H	H	Ph	4-*n*Bu-C_6H_4		I	90
Et	H	H	4-Cl-C_6H_4		I	96
Me	H	H	5-pyrimidyl	**b** = 	Br	92
Me	H	H	CH_2=CPh-		Br	91
Me	H	H	**a**		I	90
H	H	H	**b**		Br	86
Me	H	H	PhC≡C-	**c** = 	I	91
H	H	H	**c**		OTf	90

Scheme 3.65

3.3
Formation of Allenes by Addition Reactions

3.3.1
1,4-Addition to Conjugated Enynes and Related Reactions

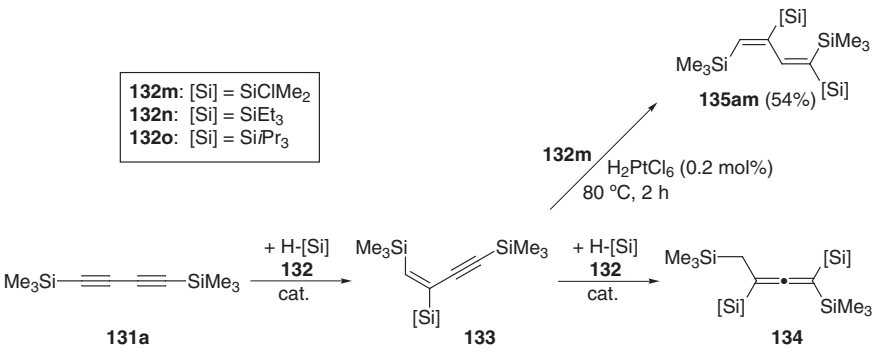
The 1,4-addition of an appropriate reagent, such as a hydrosilane or a hydroborane, to a conjugated enyne produces an allenic derivative. Occasionally, 1,2-addition to the alkynyl moiety of the substrate competes as an undesirable side reaction to give a conjugated diene (Scheme 3.66). Suppression of the latter reaction path is required for the selective preparation of the allenic products.



Scheme 3.66

3.3.1.1 **Double Hydrosilylation to 1,3-Butadiynes**

In 1985, Hiyama and co-workers reported the hydrosilylation of 1,4-bis(trimethylsilyl)-1,3-butadiyne (**131a**) [107, 108]. In the presence of transition metal catalysts, double hydrosilylation proceeded in a stepwise manner and tetrasilylallenes (**134**) were obtained with a proper choice of the catalyst and hydrosilane (Scheme 3.67).

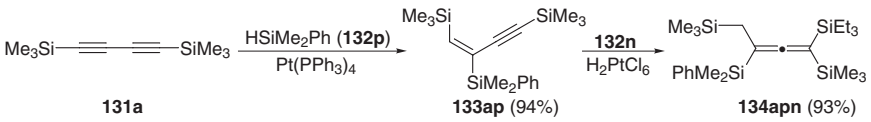


cat.	H-[Si]	Conditions	133 + 134 (% yield)
H_2PtCl_6 (0.2 mol%)	**132n**	80 °C, 0.5 h	0 + 100 (**134an**)
H_2PtCl_6 (0.2 mol%)	**132o**	90 °C, 8 h	92 (**133ao**) + 0
$RhCl(PPh_3)_3$ (0.5 mol%)	**132n**	90 °C, 5h	0 + 83 (**134an**)

Scheme 3.67

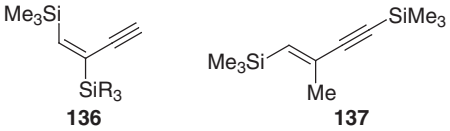
The first step of the reaction was a regio- and cis-selective hydrosilylation of **131a** to give an enyne **133**, then the second hydrosilylation of **133** via a 1,4-addition pathway formed the allenic product **134**. Hexachloroplatinic acid (H_2PtCl_6) was found to be an excellent catalyst for the hydrosilylation of **131a**. Although the conjugated diene **135am** was formed as a sole product via two successive 1,2-additions when $HSiClMe_2$ (**132m**) was used, the allene **134an** was obtained exclusively in quantitative yield with $HSiEt_3$ (**132n**). With the more bulky hydrosilane **132o**, the second reaction was slow and a single hydrosilylation product **133ao** was isolated in 92% yield. Wilkinson's catalyst, $RhCl(PPh_3)_3$, was less reactive than H_2PtCl_6; prolonged reaction times and higher temperatures were required for the reaction of **131a** with **132n** and the allene **134an** was obtained in 83% yield.

$Pt(PPh_3)_4$, $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ were much less efficient than H_2PtCl_6 and $RhCl(PPh_3)_3$. With these less reactive catalysts, the enyne **133** could be selectively prepared. Subsequent hydrosilylation of **133** also afforded the allene **134**. In this stepwise route, two different silyl groups could be introduced into the allenic product. A typical example is illustrated in Scheme 3.68.

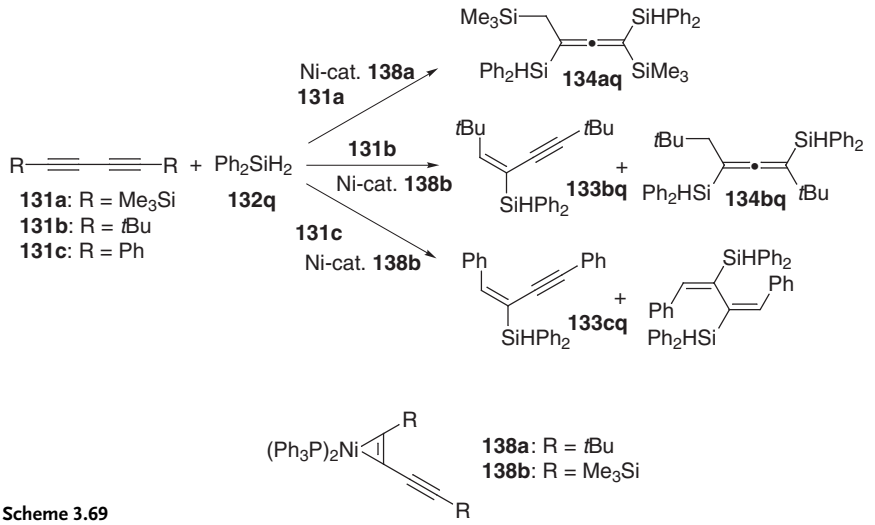


Scheme 3.68

For the selective 1,4-hydrosilylation to **133** giving the allenic product **134**, the presence and orientation of the two $-SiMe_3$ groups at the 1- and 4-positions in **133** play important roles. Reaction of the hydrosilanes with the closely related conjugated enynes **136** and **137** in the presence of the Pt or Rh catalyst proceeded in a 1,2-addition manner to produce conjugated dienes instead of allenes [108].

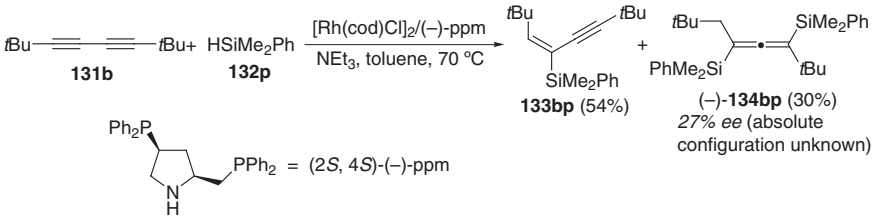


The hydrosilylation of several 1,4-disubstituted 1,3-butadiynes **131a–c** was reported using Ni(0)–butadiyne complexes as catalysts [109]. As shown for the Pt- and Rh-catalyzed reactions (see above), an allene **134aq** was formed in 92% yield as a sole product from **131a** and **132q** using the Ni complex **138a**. The di-*tert*-butyl-1,3-diyne **131b** was found to be less reactive and the product was obtained as a mixture of **133bq** (1%) and **134bq** (80%) with the complex **138b** as a catalyst. The diphenylbutadiyne **131c** showed a different regioselectivity and no allenic product was detected after a reaction with **132q** using **138b** (Scheme 3.69).



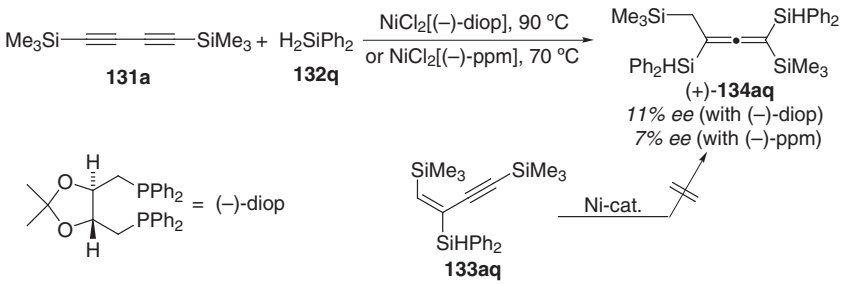
Scheme 3.69

Catalytic asymmetric synthesis of axially chiral allenes was achieved by the double hydrosilylation of 1,3-butadiynes **131a** and **131b** using chiral rhodium or nickel catalysts [110, 111]. A species generated in situ from $[Rh(cod)Cl]_2$ and (2*S*,4*S*)-(–)-ppm was the best catalyst for the asymmetric double hydrosilylation of **131b** with **132p** in terms of the enantioselectivity. It was found that presence of a small amount of NEt_3 increased the enantioselectivity. Under the optimized conditions, the highest *ee* value of 27% was observed for the reaction, although the chemical yield of the axially chiral allene **134bp** was low (30%; Scheme 3.70).



Scheme 3.70

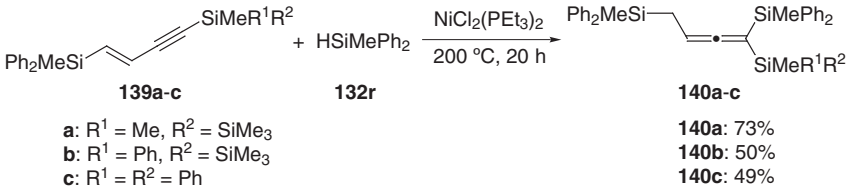
For the reaction between **131a** and **132q**, $NiCl_2$[(–)-diop] and $NiCl_2$[(–)-ppm] were examined and the axially chiral allene **134aq** was obtained in 11% (11% *ee*) and 49% (7% *ee*), respectively [111]. The allene **134aq** was not formed when the enyne **133aq** was reacted with **132q** in the presence of the Ni catalyst. Accordingly, the Ni-catalyzed hydrosilylation was proposed to be a concerted reaction and not a two-step reaction as suggested by Hiyama and co-workers for the Rh- and Pt-catalyzed hydrosilylation of **131a** (Scheme 3.71) [107, 108].



Scheme 3.71

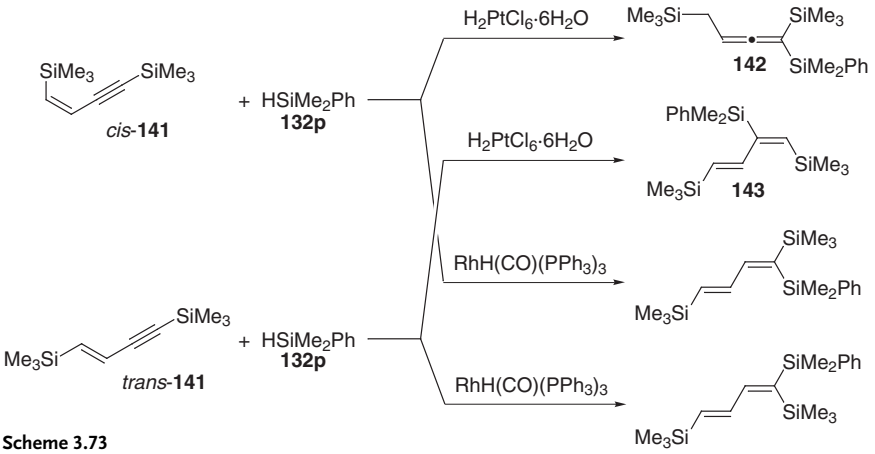
3.3.1.2 1,4-Addition of Hydrosilanes to Conjugated Enynes

An early example of 1,4-hydrosilylation of conjugated enynes appeared in 1992 [112]. Addition of $HSiMePh_2$ (**132r**) to (*E*)-1-silyl-4-disilanylbut-1-en-3-ynes (**139a–c**) was catalyzed by $NiCl_2(PEt_3)_2$ (8.5 mol%) and corresponding allenes **140a–c** were obtained as sole products in moderate yields. In all cases, the silyl moiety from **132r** added to the sp-carbon atom bearing a silyl (or disilanyl) substituent (Scheme 3.72).



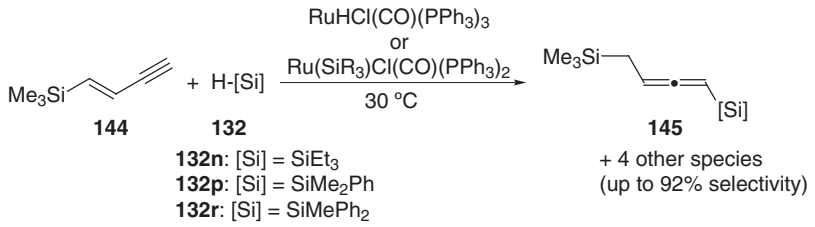
Scheme 3.72

The hydrosilylation of 1,4-bis(trimethylsilyl)but-3-en-1-yne (**141**) was beautifully controlled and four different isomeric products could be prepared independently with 93–96% selectivity by a proper choice of geometric isomers of **141** and transition metal catalysts [113]. One of the four products from the reaction of **141** with **132p** was allene **142**, which was obtained as a mixture (**142**:**143** = 96:4) in 93% yield (Scheme 3.73).



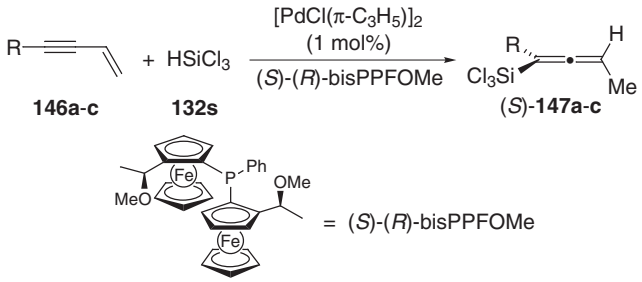
Scheme 3.73

The ruthenium-catalyzed hydrosilylation of 1-(trimethylsilyl)but-1-en-3-yne (**144**) also afforded an allenic species **145** as a main product [114]. A product mixture of five species was formed and the allene **145** was obtained with up to 92% selectivity (Scheme 3.74).



Scheme 3.74

In 2001, a palladium-catalyzed asymmetric hydrosilylation of 4-substituted-but-1-en-3-ynes (**146**) was reported by Hayashi and co-workers [115]. It was found that a monodentate bulky chiral phosphine, (*S*)-(*R*)-bisPPFOMe, was effective for the asymmetric synthesis of the axially chiral allenes **147** and up to 90% *ee* was achieved (Scheme 3.75). The bulky substituent at the 4-position in **146** is essential for the selective formation of the allene **147**: the reaction of nC$_6$H$_{13}$C≡CCH=CH$_2$ gave a complex mixture of hydrosilylation products which consisted of <20% of the allenylsilane.



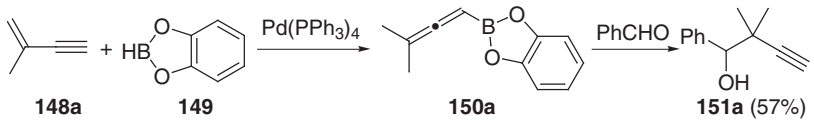
146a-c **132s** (*S*)-**147a-c**

R in 146	Conditions	yield (%)	% *ee* (config)
*t*Bu (**146a**)	0 °C, 160 h	37 (**147a**)	90 (*S*)
mesityl (**146b**)	20 °C, 64 h	90 (**147b**)	77 (*S*)
$SiMe_2$*t*Bu (**146c**)	20 °C, 160h	40 (**147c**)	68 (*S*)

Scheme 3.75

3.3.1.3 1,4-Addition of Hydroboranes to Conjugated Enynes

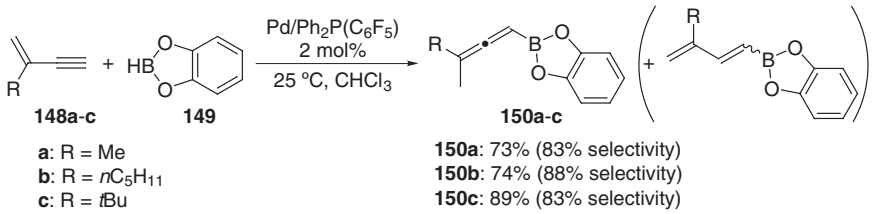
A single example of allene formation was briefly described for a reaction of 2-methylbut-1-en-3-yne (**148**) with catecholborane (**149**) [116]. The allenylborane **150** was not isolated but converted into the homopropargyl alcohol **151** in 57% yield by quenching with benzaldehyde (Scheme 3.76).



148a **149** **150a** **151a** (57%)

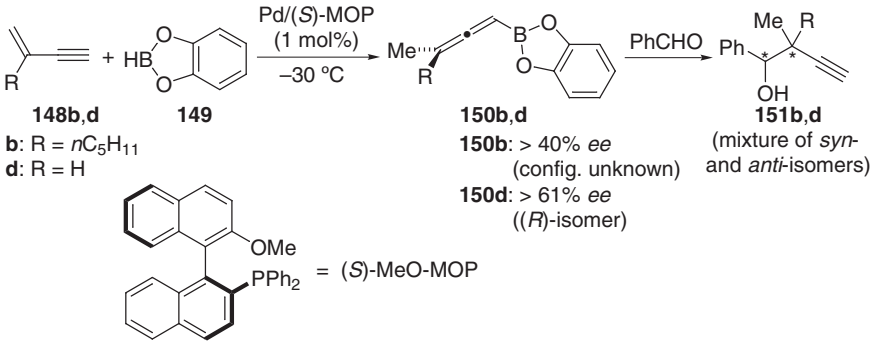
Scheme 3.76

The hydroboration reaction was investigated in detail and it was shown that the selectivity of allene formation was greatly affected by the choice and amount of the supporting ligand in the palladium catalyst [117]. With 2 mol% of the palladium catalyst generated from $Pd_2(dba)_3 \cdot CHCl_3$ and $Ph_2P(C_6F_5)$ (2 equiv. with respect to Pd) the allenylboranes **150a–c** were obtained in 73–89% yield with good selectivity (Scheme 3.77). The 1,4-hydroboration was observed only for the enynes lacking substituents at the 1- and 4-positions. Enynes substituted at the 1-position underwent selective 1,2-addition to the triple bond, whereas alkyl substitution at the 4-position inhibited the catalytic hydroboration.



Scheme 3.77

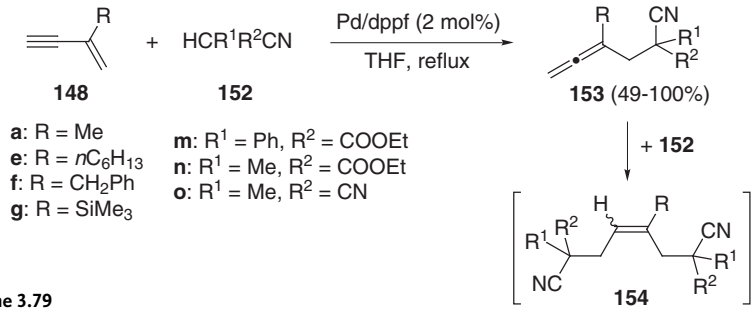
An asymmetric version of the Pd-catalyzed hydroboration of the enynes was reported in 1993 [118]. The monodentate phosphine (*S*)-MeO-MOP was used as a chiral ligand for the palladium catalyst. Enantioselectivity of the asymmetric hydroboration was estimated from the enantiopurity of homopropargyl alcohols, which were obtained from the axially chiral allenylboranes and benzaldehyde via an S_E' pathway (Scheme 3.78).



Scheme 3.78

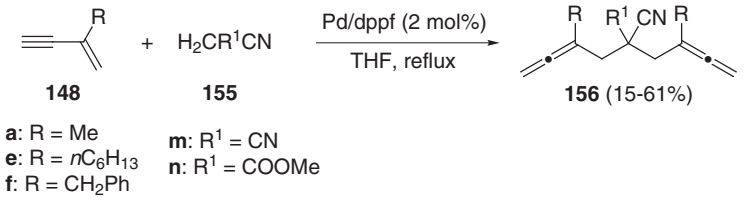
3.3.1.4 1,4-Addition of Carbon Pronucleophiles to Conjugated Enynes

The palladium-catalyzed reaction of the conjugated enynes **148** with certain carbon pronucleophiles **152** proceeded in a 1,4-addition manner to give the corresponding allenes **153** in good yields (Scheme 3.79) [119, 120]. A palladium species generated from $Pd_2(dba)_3 \cdot CHCl_3$ (2 mol% Pd) and dppf (5 mol%) showed excellent catalytic activity. As pronucleophiles, activated methines having at least one CN substituent were found to be appropriate and were more active than activated methylenes for the reaction. In the presence of an excess of **152**, the bis-adduct **154** was isolated. The second step giving **154** was slower than the first step, hence the formation of **154** could be suppressed provided that a small excess of **148** was added to **152**. The addition of **152** to **148** proceeded regioselectively; the CR^1R^2CN moiety in **152** added to the terminal carbon of the double bond. If there was a substituent at either terminal carbons of the enyne substrate, the reaction was slow and did not proceed at all in some cases.



Scheme 3.79

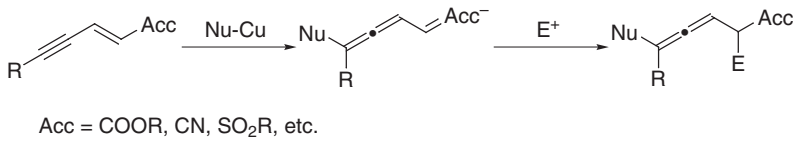
With 0.5 equiv. (with respect to **148**) of activated methylene pronucleophiles **155m–n**, double addition proceeded to give bis-allenes **156** (Scheme 3.80) [120]. The reactions with **155m–n** were sluggish and the yields of **156** were relatively low (15–61%).



Scheme 3.80

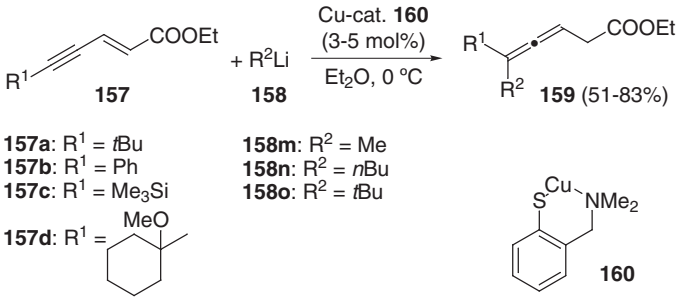
3.3.2
1,6-Conjugate Addition to Enynylcarbonyl Compounds

The conjugate addition of an organocopper reagent to an acceptor-substituted enyne proceeds via 1,6-addition to give an allenic species (Scheme 3.81) [121].



Scheme 3.81

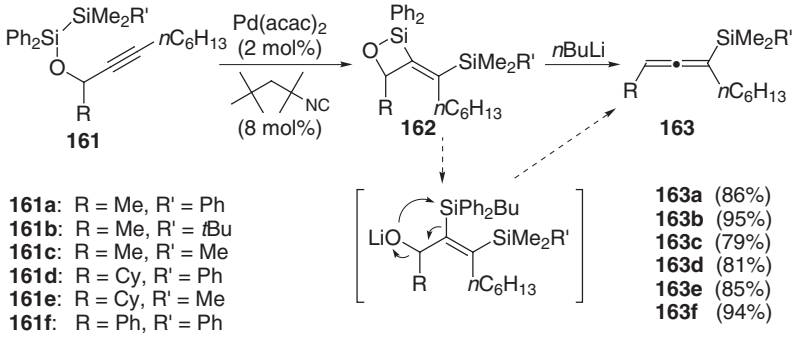
The 1,6-addition reaction can also be conducted with catalytic amounts of copper; however, very carefully controlled reaction conditions were required to minimize the competitive 1,2-addition reaction [122]. Using 3–5 mol% of copper (2-dimethylaminomethy)thiophenolate (**160**) suspended in diethyl ether, simultaneous addition of the substrate **157** and an organolithium reagent **158** at 0 °C resulted in the formation of various substituted β-allenylcarboxylates **159** (Scheme 3.82). The yields from the catalytic reactions were comparable to those from analogous stoichiometric procedures.



Scheme 3.82

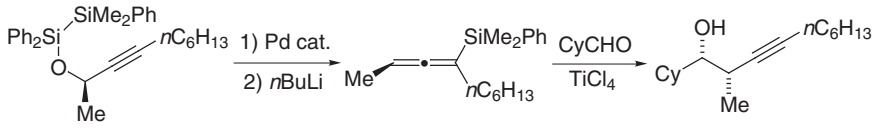
3.4
Formation of Allenes by Elimination Reactions

Palladium-catalyzed intramolecular bis-silylation of disilanyl propargyl ethers **161a–f** and successive *syn*-elimination of the siloxy group by BuLi treatment give a series of allenylsilanes **163a–f** in good yields (Scheme 3.83) [123]. For the bis-silylation reaction, a palladium species prepared from $Pd(acac)_2$ (2 mol%) and 1,1,3,3-tetramethylbutyl isocyanide (8 mol%) was used. The formation of the intermediary four-membered cyclic siloxanes **162** was confirmed by NMR analysis, but they were used without isolation/purification owing to their high reactivity.



Scheme 3.83

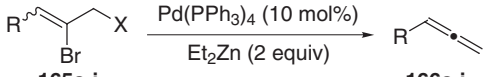
When the enantiomerically enriched disilanyl propargyl ether (*R*)-**161a** (96.7% *ee*) was applied to the reaction, the optically active axially chiral allene (–)-**163a** was obtained. Although the enantiopurity of (–)-**163a** could not be determined, treatment of (–)-**163a** with cyclohexanecarboxaldehyde in the presence of $TiCl_4$ gave the homopropargyl alcohol **164** of shown absolute configuretion with 93.2% *ee* (Scheme 3.84). This result indicateds that the chirality transfer from (*R*)-**161a** to (–)-**163** proceeded with >95% transfer efficiency and (–)-**163** possesses the *R*-configuration [123].



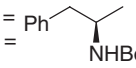
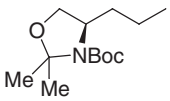
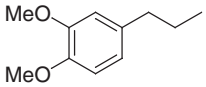
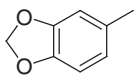
(*R*)-**161a** (96.7% *ee*) (–)-**163a** (86%) **164** (76%, 93.2% *ee*)
syn : *anti* = 95 : 5

Scheme 3.84

Treatment of 2-bromoallyl esters **165** with $Pd(PPh_3)_4$ (10 mol%) and Et_2Zn (2 equiv.) in THF at room temperature gave the terminal allenes **166** in good yields (Scheme 3.85) [124, 125]. Et_2Zn is required to reduce the Pd(II) species, which was formed during the elimination of the Br and X groups from **165**. Both *Z*- and *E*-isomers of **165** could be converted into the corresponding allenes **166** by the reaction. In a relatively large-scale reaction, the catalyst loading could be reduced, i.e. **166a** was prepared in 69% yield with 4 mol% of $Pd(PPh_3)_4$ starting from 4 g of **165a**. The reaction proceeded slowly for an acetate: with **165i**, a higher temperature (45 °C) and prolonged reaction time were needed. In contrast, the reactivity of the trichloroacetate **165j** was comparable to that of a mesylate.



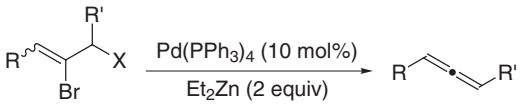
165a-j **166a-i**

165a: R = **165b**: R = $TsNHCH_2CH_2$-	(*Z*), X = OMs (*E*), X = OMs	69% (**166a**)[a] 66% (**166a**)
165c: R = **165d**: R = 	(*Z*), X = OMs (*E*), X = OMs	82% (**166c**) 83% (**166c**)
165e: R = 	(*Z*), X = OMs	69% (**166e**)
165f: R = **165g**: R = $PhCH_2CH_2$-	(*Z*), X = OMs (*E*), X = OMs	78% (**166f**) 62% (**166f**)
165h: R = 	(*Z*), X = OMs	69% (**166h**)
165i: R =  **165j**: R =	(*Z*), X = OAc (*Z*), X = $OCOCCl_3$	60% (**166i**) 69% (**166i**)

[a] 4 mol% of $Pd(PPh_3)_4$ was used

Scheme 3.85

The synthetic method was also applicable to the conversion of secondary alcohol derivatives **167** into the corresponding internal allenes **168** (Scheme 3.86).



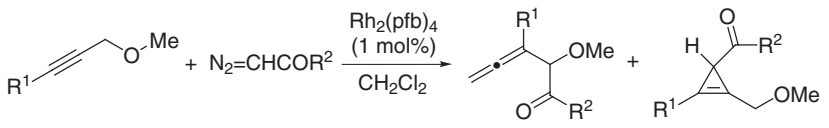
167a-f **168a,b, or e**

167a: (*Z*), R = nC_8H_{17}, R' = nC_4H_9, X = OMs	77% (**168a**)
167b: (*Z*), R = Ph, R' = Ph, X = OAc	66% (**168b**)
167c: (*Z*), R = Ph, R' = Ph, X = $OCOCCl_3$	83% (**168b**)
167d: (*E*), R = Ph, R' = Ph, X = $OCOCCl_3$	47% (**168b**)
167e: (*Z*), R = Ph, R' = Me, X = $OCOCCl_3$	53% (**168e**)
167f: (*E*), R = Ph, R' = Me, X = $OCOCCl_3$	55% (**168e**)

Scheme 3.86

3.5 Other Miscellaneous Methods of Preparing Allenes

The rhodium(II)-catalyzed reaction of propargyl compounds **169** and diazo compounds **170** gave corresponding functionalized allenes **171** together with cyclopropenes **172** (Scheme 3.87) [126]. $Rh_2(pfb)_4$, where pfb represents perfluorobutyrate, was found to be an excellent catalyst for preparing the allenes **171**. An analogous rhodium(II) complex, $Rh_2(OAc)_4$, afforded mainly **172** with only a trace amount of **171** (<5%).

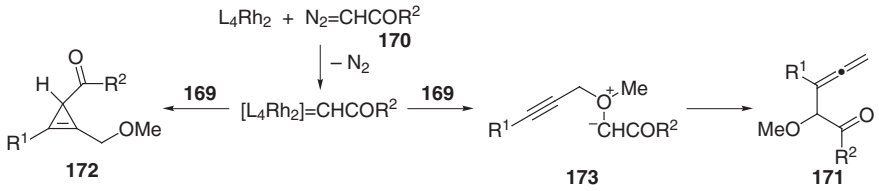


169 **170** **171** **172**

R^1 in 169	R_2 in 170	yield (%)	171 : 172
H	Ph	80	82 : 18
H	OEt	67	61 : 39
*n*Bu	Ph	67	90 : 10
*n*Bu	OEt	83	80 : 20
$SiMe_3$	OEt	80	93 : 7

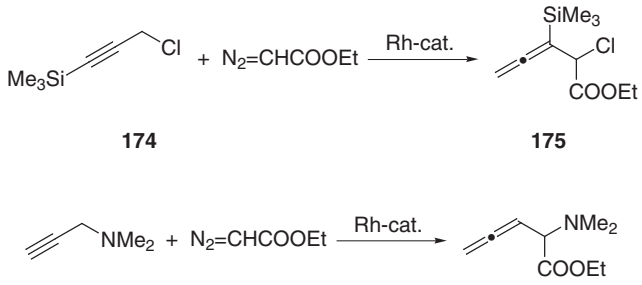
Scheme 3.87

As shown in Scheme 3.88, an initially formed Rh–carbene species reacted with **169** to give either **172** or an oxonium ylide, **173**. The latter underwent a [2,3]sigmatropic rearrangement to form the allene **171** (Scheme 3.88).



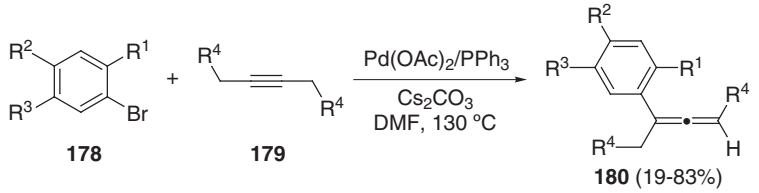
Scheme 3.88

The reaction could be applied to propargyl chloride **174** and propargylamine **176** and corresponding allenes **175** and **177** were obtained in 63 and 85% yields, respectively (Scheme 3.89) [126].



Scheme 3.89

In 1997, Miura and co-workers reported a palladium-catalyzed reaction of aryl bromides with dialkylacetylenes [127]. The reaction is similar to the well-known Heck reaction of alkenes. In the presence of $Pd(OAc)_2$ (2.5 mol%), PPh_3 (10 mol%) and Cs_2CO_3, the reactions of **178** and **179** in DMF proceeded smoothly at 130 °C to give allenes **180** in moderate to good yields (Scheme 3.90). The choice of the base is one of the most important factors determining the reaction efficiency: with Na_2CO_3 or Bu_3N, the yield of **180** was greatly diminished. Generally, aryl bromides **178** having an *ortho*-substituent afforded good yields. The highest yield of 83% was reported for the reaction of **178a** with **179o**.



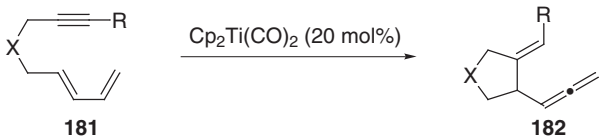
178 **179** **180** (19-83%)

178a: $R^1 = R^3 = Me$, $R^2 = H$
178b: $R^1 = Et$, $R^2 = R^3 = H$
178c: $R^1 = R^3 = H$, $R^2 = Me$
178d: $R^1 = R^3 = H$, $R^2 = OMe$
178e: $R^1 = OMe$, $R^2 = R^3 = H$
178f: $R^1 = R^2 = R^3 = H$

179m: $R^4 = Et$
179n: $R^4 = n$Pr
179o: $R^4 = i$PrCH$_2$

Scheme 3.90

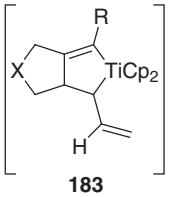
Titanocene-catalyzed cycloisomerization of dienynes **181** provided terminal allenes **182** in moderate yields (Scheme 3.91) [128]. The reaction proceeded via the titanacycle **183** and the allene **184** was formed via loss of a β-hydrogen atom from the allyltitanium species.



181 **182**

181a: X = $(EtO_2C)_2C$, R = Me
181b: X = $(t$BuO$_2$C$)_2$C, R = Me
181c: X = PhN, R = nC$_5$H$_{11}$

182a (54%)
182b (44%)
182c (36%)



183

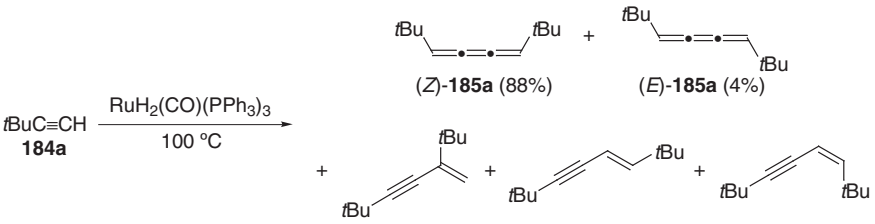
Scheme 3.91

3.6 Formation of 1,2,3-Butatrienes

Several examples are known of the transition metal-catalyzed synthesis of 1,2,3-butatrienes, which possess one more cumulated C=C double bond than allenes. Most of the reported examples of the butatriene synthesis involve dimerization of terminal alkynes and conjugated enynes are typical side products of the reactions.

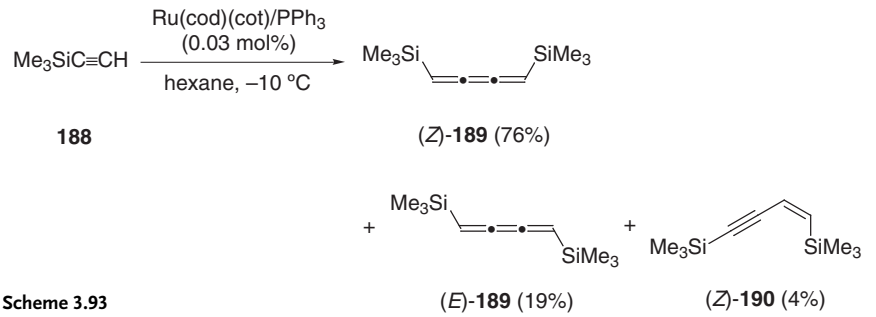
The first example of a butatriene preparation via dimerization of a 1-alkyne was reported in 1976 [129]. Treatment of a benzene solution of tBuC≡CH (**184a**) at

100 °C (in a sealed tube) in the presence of a catalytic amount of $RuH_2(CO)(PPh_3)_3$ (~8 mol%) gave a mixture of five compounds (Scheme 3.92). The main product, (*Z*)-1,4-di-*t*Bu-1,2,3-butatriene [(*Z*)-**185a**], was formed with 88% selectivity [130]. The mechanism of the reaction was thoroughly investigated and clarified [131–133].



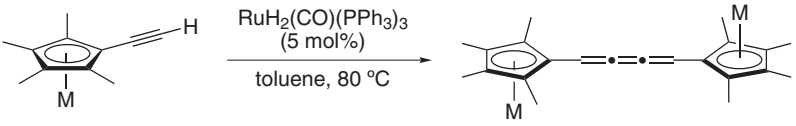
Scheme 3.92

For the dimerization of trimethylsilylacetylene (**188**), $RuH_2(CO)(PPh_3)_3$ was not an appropriate catalyst. An Ru(0) species generated from Ru(cod)(cot) and PPh_3 (6 equiv with respect to Ru) was an active catalyst for the stereoselective dimerization of **188**, giving 1,4-bis(trimethylsilyl)-1,2,3-butatriene (**189**) [133, 134]. The dimeric product was obtained in 92% yield using 0.03 mol% of the Ru catalyst at –10 °C. The product contained three isomers in the molar ratio (*Z*)-**189**:(*E*)-**189**:(*Z*)-**190** = 76:19:6 (Scheme 3.93).



Scheme 3.93

The Ru-catalyzed reaction was applied to the dimerization of (η^5-ethynylcyclopentadienyl)metal complexes [135]. Using 5 mol% of $RuH_2(CO)(PPh_3)_3$, **191a–c** were converted into the corresponding 1,2,3-butatrienes **192a–c** in moderate yields (Scheme 3.94). The butatrienes **192** were obtained as mixtures of *Z*- and *E*-isomers; however, the *E*:*Z* ratios were not determined. The sterically less demanding alkynylferrocene ($HC{\equiv}CC_5H_4$)FeCp did not afford a butatriene derivative under identical conditions.

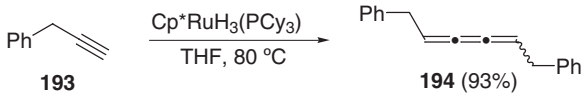


191a: M = Rh(cod)
191b: M = Ir(cod)
191c: M = Fe(C_5HMe_4)

192a (45%)
192b (48%)
192c (53%)

Scheme 3.94

Another example of a ruthenium-catalyzed reaction appeared in 1996 for the dimerization of $PhCH_2C{\equiv}CH$ (**193**) [136]. The catalyst used for the reaction was $Cp^*RuH_3(PCy_3)$ and the butatriene **194** was obtained as a single isomer in 93% yield with >95% selectivity; however, the geometry of **194** could not be determined unambiguously (Scheme 3.95).

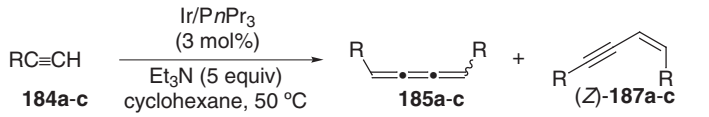


193

194 (93%)

Scheme 3.95

The Ir-catalyzed reaction of terminal acetylenes **184a–c** was another route to butatrienes [137]. The dimerization catalyst was generated from $[Ir(cod)Cl]_2$ (1.5 mol%) and P*n*Pr_3 (6 mol%) in cyclohexane. In the presence of 5 equiv of Et_3N, the terminal acetylenes were converted into the butatrienes **185a–c** with 78–93% selectivity (Scheme 3.96).

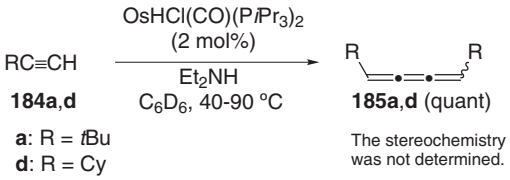


		yield of **185**+**187**
a: R = *t*Bu	(*Z*)-**185a** : (*Z*)-**187a** = 93 : 7	74%
b: R = CMe_2Ph	**185b**[a] : (*Z*)-**187b** = 84 : 16	83%
c: R = $CMe_2(OSiMe_2tBu)$	**185c**[a] : (*Z*)-**187c** = 78 : 22	71%

[a] The stereochemistry was not determined.

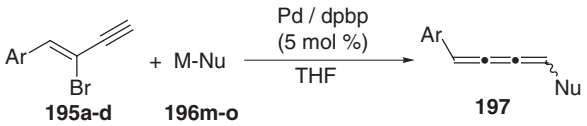
Scheme 3.96

In the presence of diethylamine, the complex $OsHCl(CO)(PiPr_3)_2$ catalyzed the dimerization of terminal alkynes **184a** and **184d** [138]. The reaction gave the 1,2,3-butatrienes **185a** and **185d** quantitatively (Scheme 3.97). Although the products were obtained as single isomers, the stereochemistry was not determined.

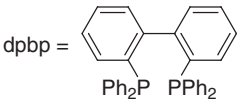


Scheme 3.97

A completely different approach to butatrienes was reported in 2000 [139]. Treatment of 1-aryl-2-bromo-1-buten-3-ynes **195** with a variety of carbon soft nucleophiles **196** in the presence of 5 mol% of a Pd–dpbp catalyst gave the corresponding 1,2,3-butatrienes **197** in moderate yields (Scheme 3.98). The reactions showed essentially no *E*/*Z*-selectivity: all the butatrienes were obtained as mixtures of the two isomers.



	yield (%)	(*E*)/(*Z*)
195a : Ar = Ph	45 (**197am**)	52/48
195b : Ar = 1-naphthyl	46 (**197bm**)	51/49
195c : Ar = *p*-CF_3-C_6H_4	73 (**197cm**)	60/40
195d : Ar = *p*-MeO-C_6H_4	29 (**197dm**)	54/46
196m : Na[CMe(COOMe)$_2$]	64 (**197cn**)	50/50
196n : Na[CMe(COMe)(COOEt)]	~10 (**197co**)	----
196o : Na[CMe(COMe)$_2$]		



Scheme 3.98

3.7 Conclusion

This chapter has discussed the transition metal-catalyzed synthesis of allenes. Because allenes have attracted considerable attention as useful synthons for synthetic organic chemistry, effective synthetic methods for their preparation are desirable. Some recent reports have demonstrated the potential usefulness of optically active axially chiral allenes as chiral synthons; however, methods for supplying the enantiomerically enriched allenes are still limited. Apparently, transition metal-catalyzed reactions can provide solutions to these problems. From the economics point of view, the enantioselective synthesis of axially chiral allenes from achiral precursors using catalytic amounts of chiral transition metal catalysts is especially attractive. Considering these facts, further novel metal-catalyzed reactions for the preparation of allenes will certainly be developed in the future.

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[130] The geometry of the main product was reported as the *E*-isomer in the original report [129]; however, the authors reformulated it as the *Z*-isomer in a subsequent paper [131].

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4
Enantioselective Synthesis of Allenes

Hiroaki Ohno, Yasuo Nagaoka, and Kiyoshi Tomioka

4.1
Introduction

Allene is a versatile functionality because it is useful as either a nucleophile or an electrophile and also as a substrate for cycloaddition reactions. This multi-reactivity makes an allene an excellent candidate for a synthetic manipulations. In addition to these abilities, the orthogonality of 1,3-substitution on the cumulated double bonds of allenes enables the molecule to exist in two enantiomeric configurations and reactions using either antipode can result in the transfer of chirality to the respective products. Therefore, the development of synthetic methodology for chiral allenes is one of the most valuable subjects for the synthetic organic chemist. This chapter serves as an introduction to recent progress in the enantioselective syntheses of allenes. Several of the earlier examples are presented in excellent previous reviews [1].

4.2
Chirality Transfer from Propargylic Compounds

4.2.1
Organocopper-Mediated Alkylation of Propargyl Alcohol Derivatives

One of the most standard and convenient synthetic methods for enantiomerically enriched allenes is the conversion of non-racemic propargylic substrates with organocopper reagents, because of the availability of propargyl alcohols in an enantiomerically pure form. Following the pioneering work on the organocopper-mediated synthesis of allenes by Roma and Crabbé in 1968 [2], many reports have been published describing modified reactions [3]. In this section, recent developments in the organocopper-mediated synthesis of enantioenriched allenes during the period 1984–2002 are summarized.

In 1984, Corey and Boaz rationalized the *anti* stereochemistry observed in most of the organocopper-mediated S_N2' displacements [4]. The stereoelectronic effect arising from a 'bidentate' binding involves a d-orbital of a nucleophilic copper and

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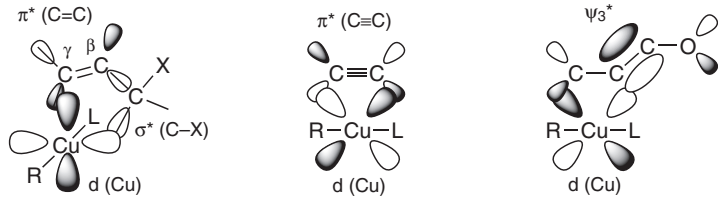
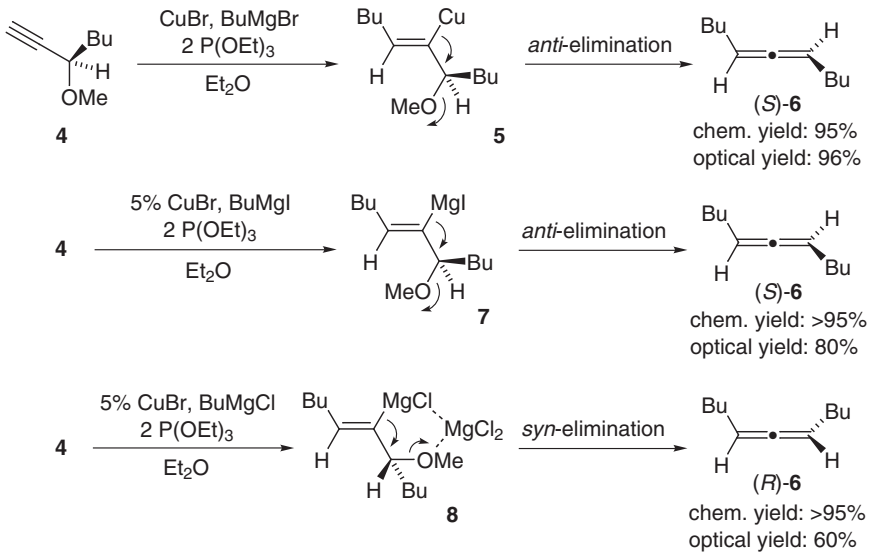
π* and σ* orbitals of the substrates and consequently prefers an *anti*-S_N2' displacement. The simple allylic substrate **1** is shown in Scheme 4.1. This argument can also be applied to allenic and propargylic substrates. The extension of this idea to other reactions of organocuprates including additions to acetylenes and enones is also shown as the transition states **2** and **3**.



Scheme 4.1 Bidentate binding of a d-orbital of copper with π*, σ* or ψ_3* orbitals of the substrates.

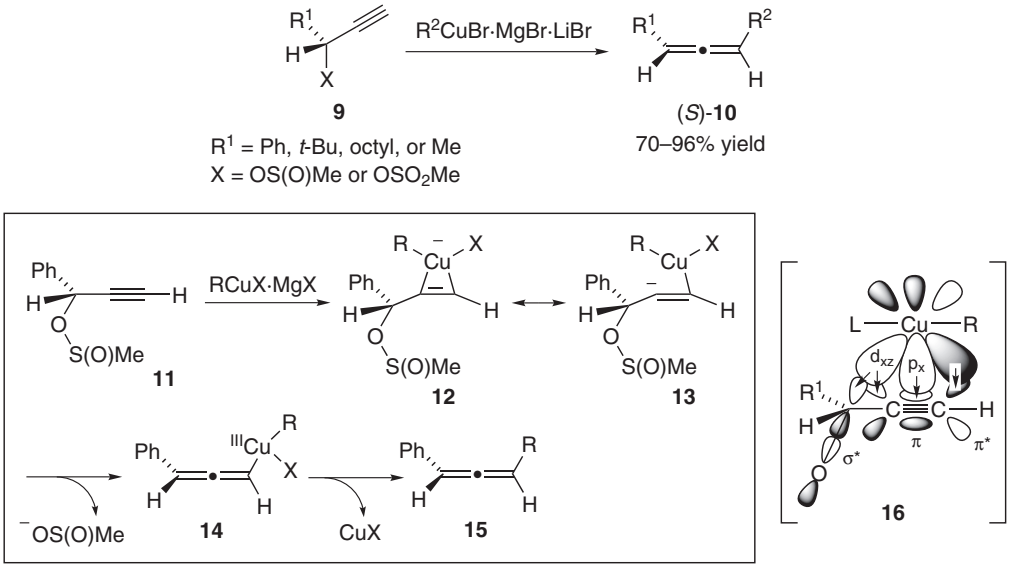
Alexakis and co-workers found an interesting stereochemical course of copper-mediated S_N2' substitution (Scheme 4.2) [5]. Treatment of chiral propargyl ether **4** (37–58% *ee*), synthesized by the asymmetric reduction of the corresponding ynone using $LiAlH_4$/Darvon alcohol and subsequent methylation with a stoichiometric amount of an organocopper reagent gave a chiral allene, (*S*)-**6**, in 96% optical yield through the purely *anti* β-elimination of the intermediate **5**. In contrast, on treat-



Scheme 4.2 Halogen effect of the copper(I)-catalyzed reaction of propargyl ether **4**.

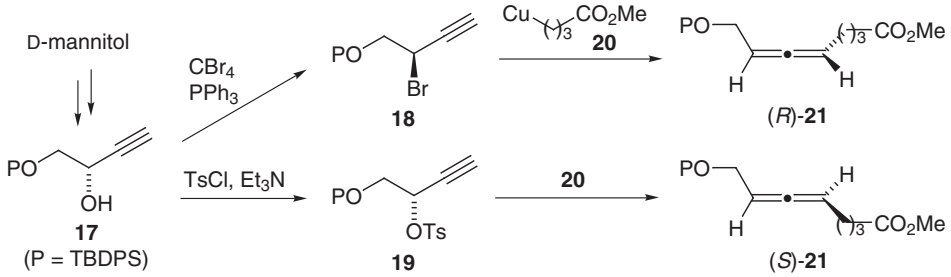
ment with a Grignard reagent RMgX and a catalytic amount of Cu(I) salt, allene (*S*)-**6** or (*R*)-**6** was selectively obtained through an *anti* or *syn* overall process, respectively. The crucial step is the stereoselective β-elimination of the intermediate **7** or **8**, which is of *anti* type with RMgI and of *syn* type with RMgCl. The small size and the electronegativity of the chlorine atom allow the cyclic transition state **8**, where the greater Lewis acidity of $MgCl_2$ favors a *syn* elimination. On the other hand, the size of the iodine atom does not allow such a cyclic arrangement and the elimination becomes predominantly *anti*. Propargyl acetates also afford allenes through a Cu(III) intermediate that are not sensitive to this halogen effect.

The reaction of chiral propargyl mesylates **9** or sulfinates with organocopper(I) reagents at low temperatures in THF gave chiral 1,3-dialkylallenes **10** of high enantiomeric purity (Scheme 4.3) [6]. Organocopper(I) regents of the type RCuX·M were used rather than diorganocuprate R_2CuM because of the racemization of the allenes by the latter reagent [7]. The 1,3-substitution reactions of esters **9** with the cuprates, prepared in situ from $LiCuBr_2$ and an equimolar amount of the appropriate Grignard reagent, are generally fast; typically, complete conversion is achieved within a few minutes at –60 °C and proceed with high *anti* stereoselectivities to afford the nearly optically pure allenes **10**. The stereochemical outcome of the reaction was proposed as follows: the reaction of organocopper with **11** gives a π-complex **12**, which equilibrates with **13**. Elimination affords the allenylcopper(III) intermediate **14** (see **16**), which undergoes reductive elimination of CuX affording the allene **15** stereospecifically.



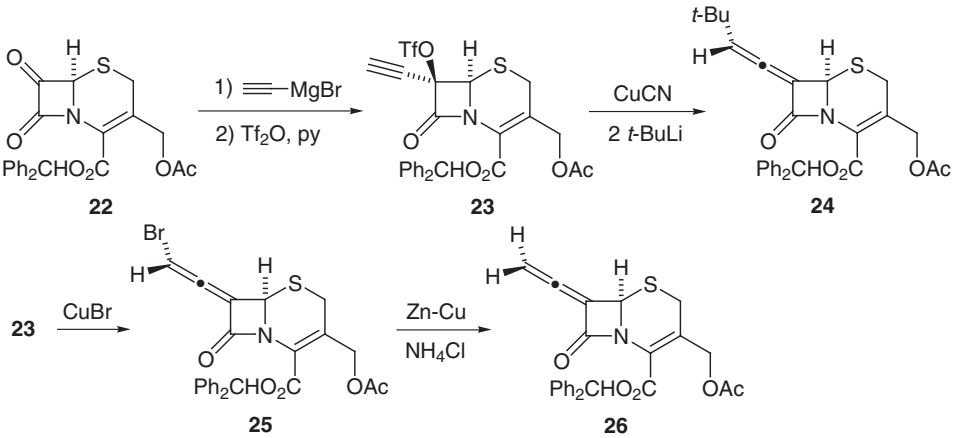
Scheme 4.3 Organocopper-mediated stereospecific substitution of propargyl esters.

Gooding et al. reported a general, high-yield synthesis of chiral allenic alcohols starting from D-mannitol (Scheme 4.4) [8]. Reaction of a bromide **18** or a tosylate **19** with a functionalized organocopper reagent **20** (prepared from the corresponding iodide by the reaction with Zn–Cu and CuBr·DMS) at room temperature yielded allene (*R*)-**21** (88% yield) or (*S*)-**21** (96% yield), respectively. Deprotection of (*R*)-**21** with tetra-*n*-butylammonium fluoride (TBAF) afforded the antifungal constituent of *Sapium japonicum*. The ^{13}C NMR spectral analysis of the corresponding Mosher esters guaranteed an *ee* of >94%.



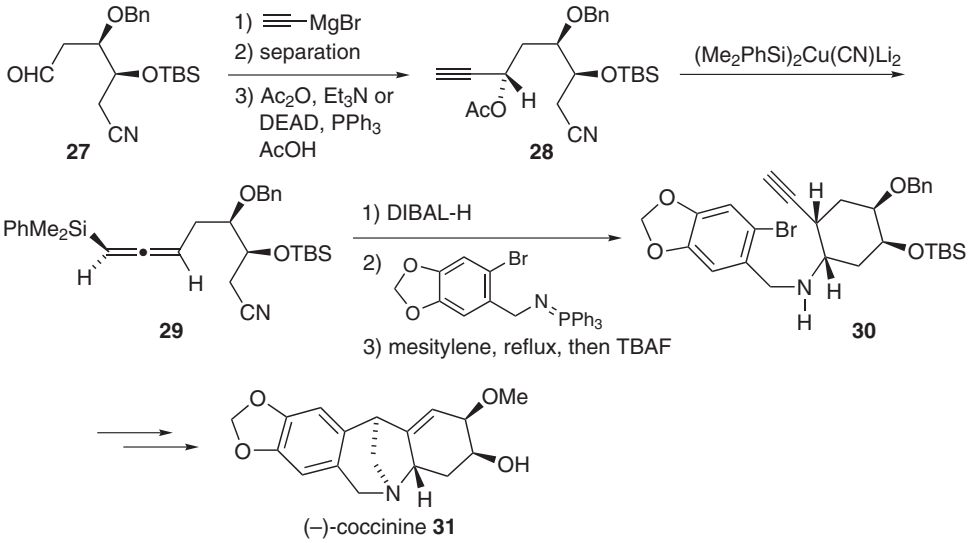
Scheme 4.4 Synthesis of both enantiomers of allene **21** from a single enantiomer **17**.

Buynak et al. reported the synthesis of representative 7-vinylidenecephalosporine derivatives bearing an axial allene chirality (Scheme 4.5) [9]. A chiral allene **24** was prepared stereoselectively utilizing the reaction of an organocopper reagent with propargyl triflate **23**, obtained by a diastereoselective ethynylation of the ketone **22** with ethynylmagnesium bromide. Terminally unsubstituted allene **26** was synthesized via bromination of the triflate **23** followed by reduction of the bromide **25** with a zinc–copper couple.



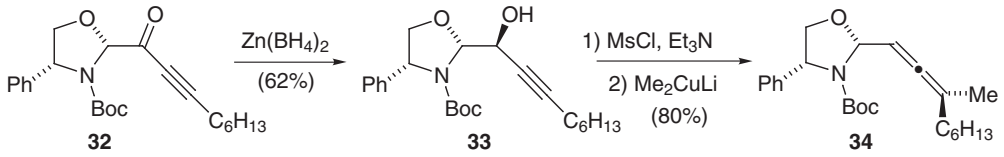
Scheme 4.5 A highly diastereoselective synthesis of vinylidenecephem derivatives **24** and **26**.

Jin and Weinreb reported the enantioselective total synthesis of 5,11-methanomorphanthridine *Amaryllidaceae* alkaloids via ethynylation of a chiral aldehyde followed by allenylsilane cyclization (Scheme 4.6) [10]. Addition of ethynylmagnesium bromide to **27** produced a 2:1 mixture of (*S*)- and (*R*)-propargyl alcohols **28**. Both of these isomers were separately converted into the desired same acetate **28** by acetylation or Mitsunobu inversion reaction. After the reaction of **28** with a silyl cuprate, the resulting allene **29** was then converted into (–)-coccinine **31** via an allenylsilane cyclization.

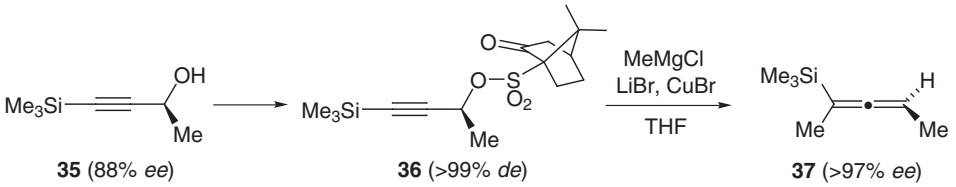


Scheme 4.6 Enantioselective total synthesis of the 5,11-methanomorphanthridine alkaloid (–)-coccinine via chiral allenylsilane **29**.

Diastereoselective reduction of a ketone is also a useful method for the asymmetric synthesis of allenes by way of the produced chiral propargyl alcohol. Reduction of 2-acyloxazolidine **32** with zinc borohydride gave a diastereomerically pure propargyl alcohol **33**, from which chiral allene **34** was obtained in 80% yield (Scheme 4.7) [11]. Chiral allene **37** (>97% *ee*) was synthesized by a combination of an enantioselective asymmetric reduction of a ketone and enantioenrichment of the resulting propargyl alcohol (Scheme 4.8) [12]. The alcohol **35** (88% *ee*) was obtained from reduction of the corresponding ketone using Alpine borane and the recrystallization of the camphorsulfonate **36** afforded diastereomerically pure **36**, which was treated with methyl Grignard reagent and copper bromide to yield the allenylsilane **37** stereospecifically. The silylallene **37** obtained is a useful chiral nucleophile toward aldehydes for the synthesis of homopropargyl alcohols.

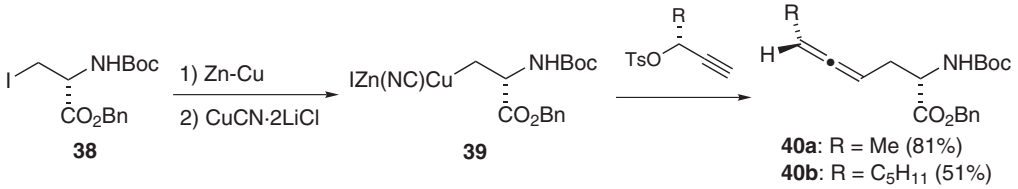


Scheme 4.7 Asymmetric synthesis of allene via a diastereoselective reduction.



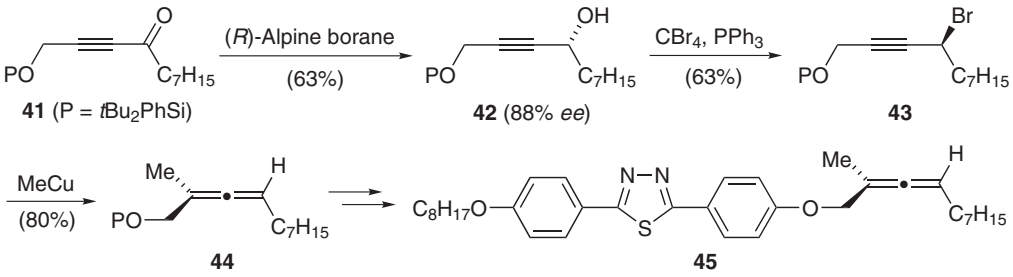
Scheme 4.8 Synthesis of chiral allene **37** from propargyl camphorsulfonate **36**.

In 1995, Jackson and co-workers reported a useful synthetic method for β-aminoallenes using the serine-derived zinc–copper reagents **39** (Scheme 4.9) [13]. This reagent was easily prepared by insertion of zinc into the carbon–iodine bond of a protected iodoalanine **38** followed by treatment with CuCN·2LiCl. Reaction of **39** with enantiomerically enriched propargyl tosylates, prepared from the corresponding acetylenic ketones by an asymmetric reduction with (*R*)-Alpine borane, gave rise to protected allenic amino acids **40** in 51–81% yields.



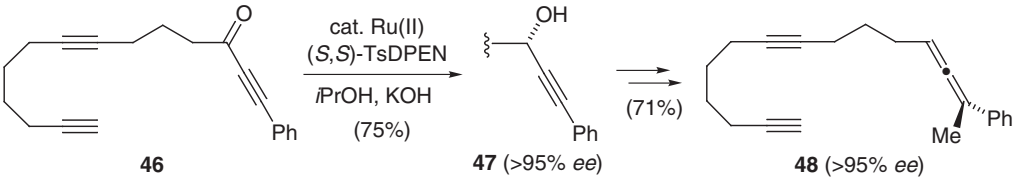
Scheme 4.9 Synthesis of chiral allenic amino acids **40**.

The synthesis of chiral liquid-crystalline allenes was reported by Tschierske and co-workers (Scheme 4.10) [14]. An asymmetric reduction of **41** with Alpine borane was a key step to an enantioenriched allene **44**. After removal of the silyl group, the allenic alcohol was etherified by the Mitsunobu method to give **45**, the first liquid-crystalline allene derivatives.



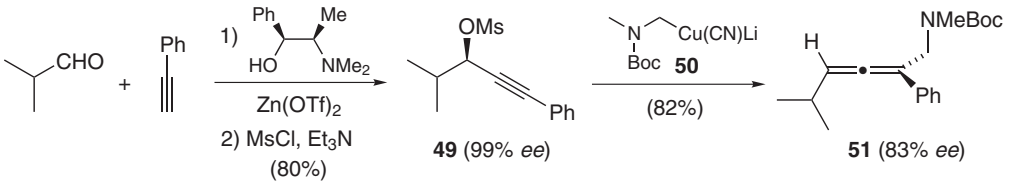
Scheme 4.10 Synthesis of liquid-crystalline allene **45**.

The asymmetric synthesis of allenes via enantioselective hydrogenation of ketones with ruthenium(II) catalyst was reported by Malacria and co-workers (Scheme 4.11) [15, 16]. The ketone **46** was hydrogenated in the presence of *i*PrOH, KOH and 5 mol% of a chiral ruthenium catalyst, prepared from $[(p\text{-cymene})RuCl_2]_2$ and (*S*,*S*)-TsDPEN (2 equiv./Ru), to afford **47** in 75% yield with 95% *ee*. The alcohol **47** was converted into the corresponding chiral allene **48** (>95% *ee*) by the reaction of the corresponding mesylate with MeCu(CN)MgBr. A phosphine oxide derivative of the allenediyne **48** was proved to be a substrate for a cobalt-mediated [2 + 2 + 2] cycloaddition.



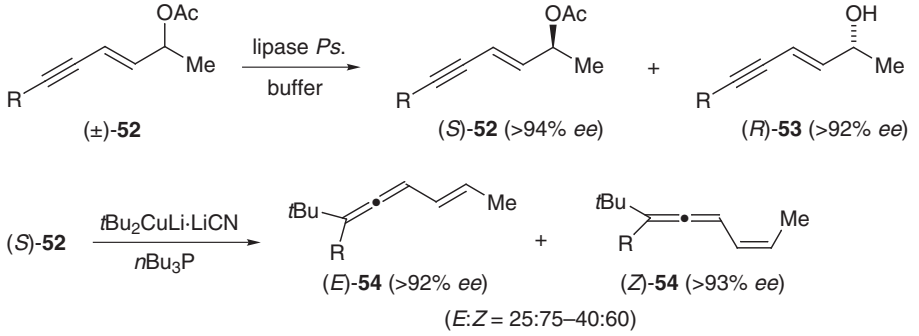
Scheme 4.11 Asymmetric synthesis of allene via a ruthenium(II)-catalyzed reduction.

Carreira and co-workers developed a highly efficient enantioselective addition of terminal alkynes to aldehydes giving propargyl alcohols by the mediation of zinc triflate and *N*-methylephedrine [17]. This reaction serves as a convenient and powerful synthetic route to a wide variety of enantioenriched allenes via propargyl alcohols. Dieter and Yu applied this alkynylation to the asymmetric synthesis of allenes (Scheme 4.12) [18]. Reaction of phenylacetylene with isobutyraldehyde afforded the propargyl alcohol in 80% yield with 99% *ee*, which was mesylated to **49** in quantitative yield. Reaction of **49** with the cyanocuprate **50** afforded the desired allene **51** with 83% *ee*.



Scheme 4.12 Asymmetric synthesis of allene **51** via Carreira's alkynylation.

An interesting remote stereocontrol for the synthesis of vinylallenes was reported by Krause and co-workers (Scheme 4.13) [19]. The requisite chiral enyne acetates **52** were obtained with good enantiomeric excesses (>92% *ee*) by a lipase-catalyzed kinetic resolution of the racemic acetates (±)-**52** and subsequent acylation of the alcohols (*R*)-**53**. Reactions of (*S*)-**52** with cyano-Gilman reagent $t\text{Bu}_2\text{CuLi}\cdot\text{LiCN}$ were unsatisfactory, giving **54** with a poor *ee* (*E*:*Z* = 25:75; 8–76% *ee* for the *E*-isomer and 28–95% *ee* for the *Z*-isomer), owing to a racemization of the vinylallene **54** by the cuprate or other reactive species. However, addition of $n\text{-Bu}_3\text{P}$ or $(\text{EtO})_3\text{P}$ dramatically improved the selectivity: both *E*- and *Z*-isomers of the vinylallenes **54** with excellent enantiomeric excesses were obtained (>91% *ee*). This is one of the few examples of efficient 'remote 1,5-stereocontrol' in organocopper chemistry.



Scheme 4.13 Asymmetric synthesis of vinylallenes by the remote stereocontrol.

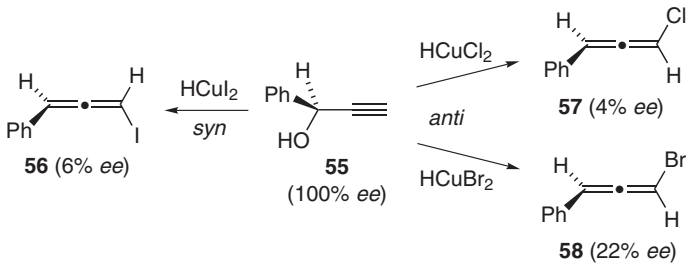
The organocopper-mediated synthesis of allenes by ring-opening reactions is summarized in Section 4.2.6.

4.2.2
Copper-Mediated Halogenation of Propargyl Alcohol Derivatives

Chiral haloallenes are extremely useful in organic synthesis. Haloallenes undergo organocopper-mediated substitutions, palladium-catalyzed cross-coupling reactions [20] and the formation of nucleophilic allenylmetal reagents. It is known that the conversion of propargyl alcohols with a halocuprate species, prepared from HX and CuX (Landor reagent), into the allenes proceeds preferentially in the *syn* 1,3-substi-

tution mode (S_Ni' process) [21], whereas that of 3-chloro-3-phenyl-1-propyne with tetrabutylammonium dichlorocuprate takes place mainly as an *anti* 1,3-substitution [22]. In 1980, Montury and Goré developed a highly efficient halocuprate reagent $LiCuX_2$, which converts racemic propargyl mesylates into the corresponding haloallenes under very mild conditions [23]. Elsevier et al. found that a highly *anti*-selective 1,3-substitution of chiral propargyl mesylates to haloallenes with high enantiomeric excesses was accomplished under similar reaction conditions [24]. Today, a halocuprate of the type $LiCuX_2$ is the most commonly used reagent for the haloallene synthesis.

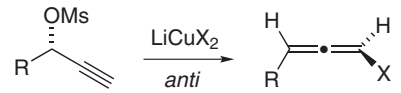
Elsevier and Vermeer reported that the reaction of propargyl alcohols with Landor reagents ($HCuX_2$) proceeded selectively through both *syn* and *anti* 1,3-substitution depending on the halogen in the reagent (Scheme 4.14) [25]. Treatment of optically pure propargyl alcohol **55** with $HCuI_2$, prepared by mixing equimolar amounts of CuI and HI in water as a solvent, produced nearly quantitatively the iodoallene **56** via a *syn* substitution pathway. In contrast, the reaction with $HCuCl_2$ or $HCuBr_2$ proceeded with *anti* selectivity although in low stereospecificities (4–22% *ee*). These results are in striking contrast to Landor's observation that *syn* substitution is preferred in the reaction of 3,4,4-trimethyl-1-pentyn-3-ol. Hence it is possible that the nature of the substituents at the propargylic center of the starting alcohols substantially influences the stereochemical course of the allene formation.



56 (6% *ee*) **55** (100% *ee*) **57** (4% *ee*) **58** (22% *ee*)

Scheme 4.14 *Anti*-stereoselectivity for the formation of haloallenes **57** and **58** using Landor reagent.

A general synthesis of enantioenriched 3-alkyl-1-haloallenes **60** was achieved from **59** by reaction with a halocuprate reagent of the type $LiCuX_2$ (Scheme 4.15) [26]. From the experimental results and optical rotations of the resulting haloallenes, the literature parameters λ (for the calculation of molar rotations Φ_D) for chlorine were revised and adequate numerical values for those of bromine and iodine were proposed. Treatment of a chiral propargyl mesylate with $LiCuI_2$ gave the corresponding iodoallene, applicable for the precursor to an allenylindium [27].

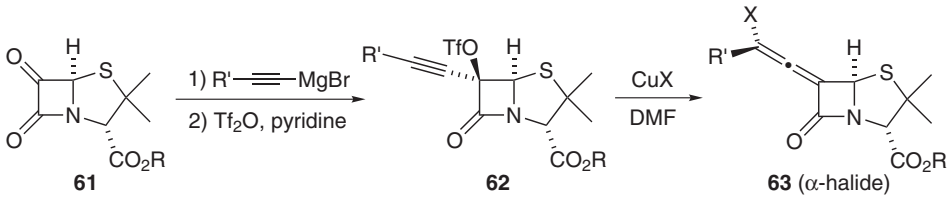


59 (22–38% *ee*) **60** (22–38% *ee*) $\Phi_D = [\lambda(R^1)-\lambda(R^2)][\lambda(R^3)-\lambda(R^4)]$

X	λ (X)
Cl	+21.5
Br	+29.5
I	+54.0

Scheme 4.15 A highly *anti*-selective synthesis of haloallenes and prediction of stereochemistry of haloallenes by optical rotations with revised parameters.

Stereoselective alkynylation of **61** and subsequent triflation gave **62**, a good precursor for conversion to **63** with copper(I) halides in DMF (Scheme 4.16) [28].

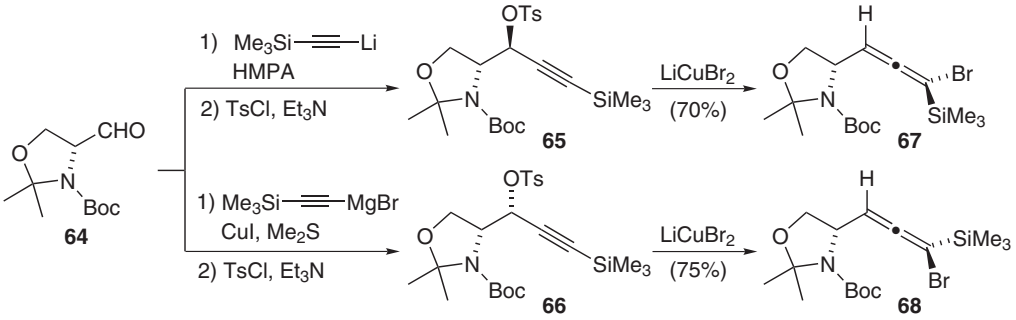


61 **62** **63** (α-halide)

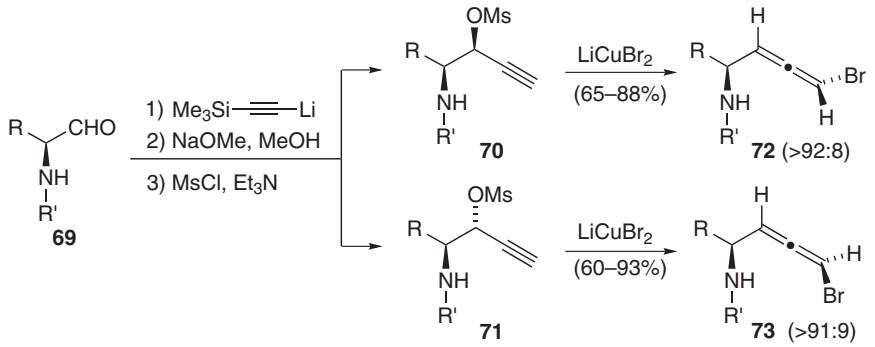
R' = H: 30–78% yield, α:β = 100:0

Scheme 4.16 Synthesis of 6-bromovinylidenepenams.

Ethynylation of Garner's aldehyde **64** with lithium acetylide in the presence of HMPA or with ethynyl Grignard reagent in the presence of copper(I) salt gave, after tosylation, *anti*-**65** or *syn*-**66**, respectively (Scheme 4.17) [29]. Subsequent bromination with $LiCuBr_2$ afforded silylated bromoallenes **67** or **68** stereospecifically. Similar conversion starting from various amino acids was recently reported by Ohno and co-workers (Scheme 4.18) [30]. Whereas mesylates **70** and **71** derived from L-valine, L-phenylalanine or L-alanine gave the corresponding bromoallenes **72** and **73** (R = *i*Pr, Bn or Me) in good selectivities (>99:1–91:9), mesylates **70** or **71** derived from L-serine (R = $TBSOCH_2$) afford allenes with relatively low diastereoselectivities (72:25–89:11).

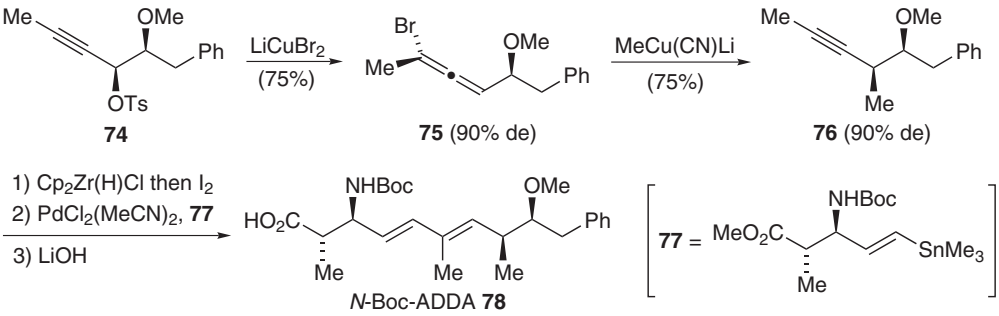


Scheme 4.17 Synthesis of serine-derived enantiomerically pure bromoallenes.

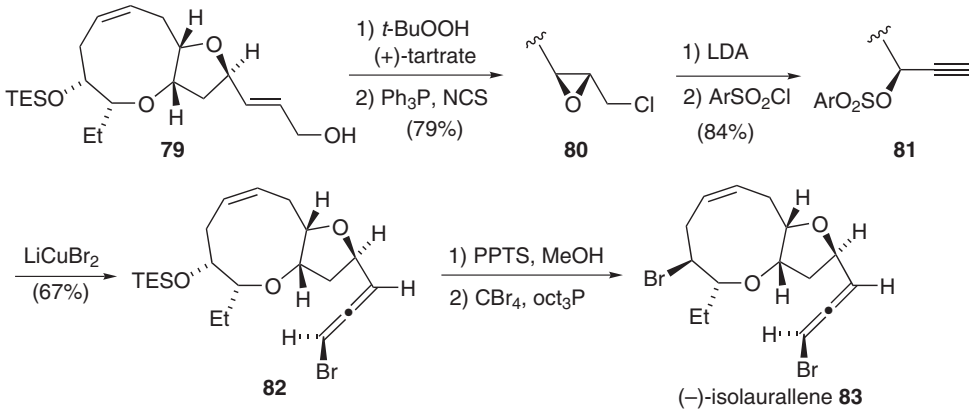


Scheme 4.18 Synthesis of bromoallenes from various α-amino acids.

A bromoallene **75** was prepared from **74** following the standard procedure and used in the natural product synthesis [31] of **78** (Scheme 4.19) [32]. Crimmins and Emmitte succeeded in the construction of the chiral bromoallene moiety of isolaurallene **83** by bromination of propargyl sulfonate **81** with $LiCuBr_2$ as a key step (Scheme 4.20) [33] (cf. Section 18.2.3).



Scheme 4.19 Synthesis *N*-Boc-ADDA **78** via bromoallene **75**.

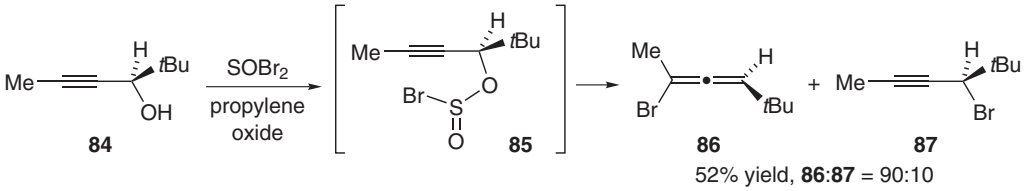


Scheme 4.20 Asymmetric total synthesis of (–)-isolaurallene.

4.2.3

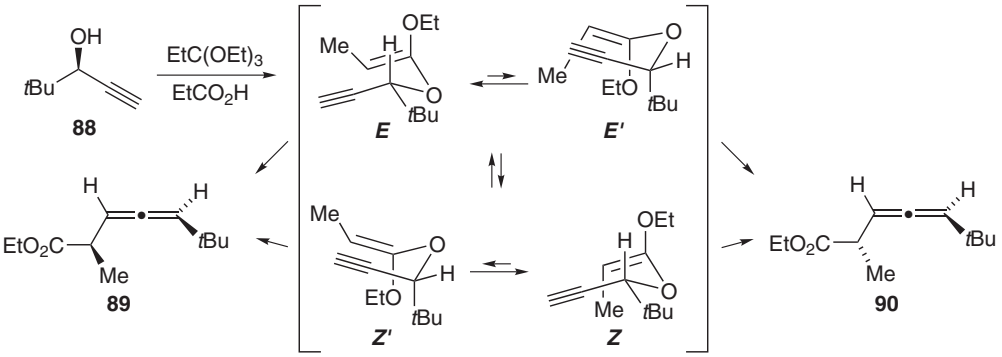
Rearrangement of Propargyl Alcohol Derivatives

In 1963, an asymmetric synthesis of chloroallenes was reported by the S_Ni' reaction of propargyl alcohols with thionyl chloride [34]. Since then, rearrangement of propargylic precursors has been one of the most useful methodologies for the synthesis of allenes [35]. Treatment of **84**, obtained by asymmetric reduction with $LiAlH_4$–Darvon alcohol complex, with thionyl bromide gave **86** as the major product via **85** (Scheme 4.21) [36].

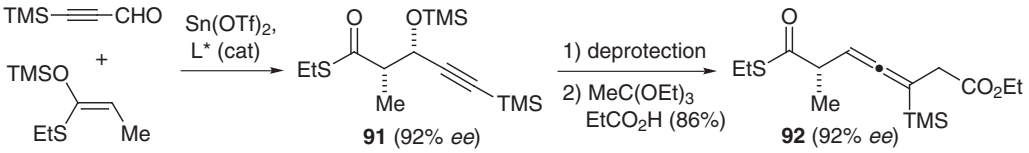


Scheme 4.21 Asymmetric synthesis of bromoallenes with thionyl bromide.

The asymmetric synthesis of allenes by the orthoester Claisen rearrangement was first reported by Henderson and Heathcock (Scheme 4.22) [37]. The chiral propargyl alcohol **88** was treated under the conditions of the orthoester Claisen rearrangement to give a 9:1 mixture of **89** and **90** (>68% *ee*). A rearrangement reaction from (*E*)-ketene acetal was proposed to be responsible for the formation of **89**. Mukaiyama et al. reported the asymmetric synthesis of allene **92** by a catalytic asymmetric aldol reaction and subsequent Claisen rearrangement (Scheme 4.23) [38]. Acetylenic aldehydes enantioselectively reacted with a silyl enol ether of a thioester to afford the corresponding propargyl alcohol **91** in 92% *ee*, which was subjected to the rearrangement conditions, giving the allene **92** with 92% *ee*. This type of Claisen rearrangement was successively applied to the asymmetric synthesis of enprostil **95** by using

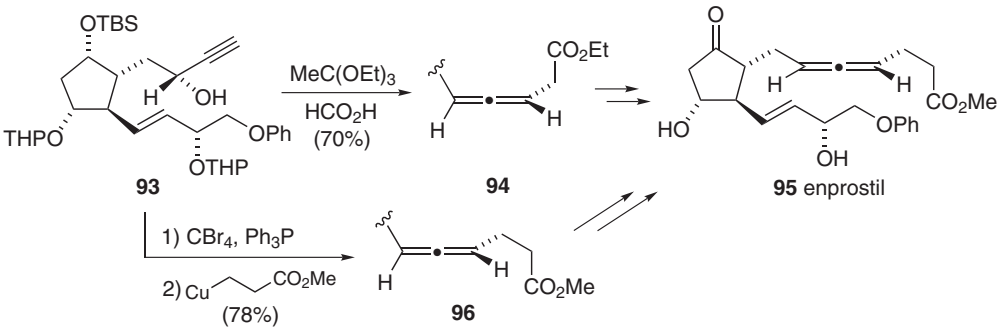


Scheme 4.22 Asymmetric synthesis of allene **89** by the orthoester Claisen rearrangement.

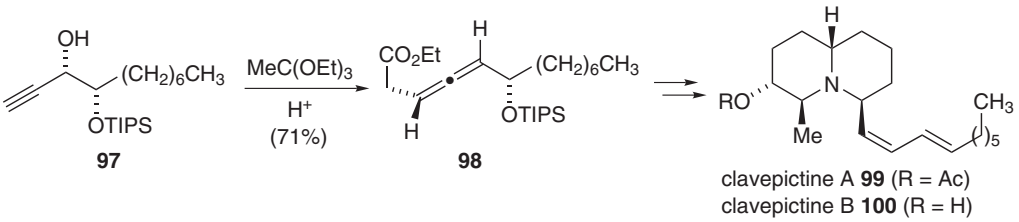


Scheme 4.23 Chiral allene synthesis via asymmetric aldol reaction and Claisen rearrangement.

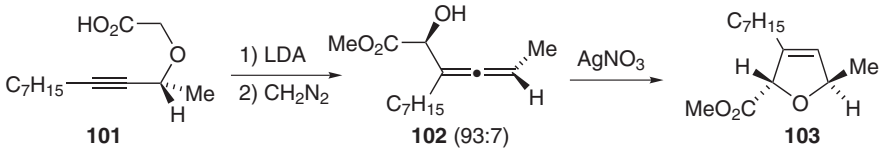
a rearrangement of **93** to **94** (Scheme 4.24) (cf. Section 18.3.2) [39]. This synthetic route suffers from the need to add one carbon to the chain. Improved synthesis of enprostil **95** was accomplished by bromination of **93** with CBr_4 and Ph_3P followed by organocopper-mediated *anti*-S_N2' substitution of the resulting bromide to afford **96**. A Claisen rearrangement of **97** gave an allene **98**, which was converted to clavepictine A (**99**) and B (**100**) (Scheme 4.25) [40]. Couty and co-workers synthesized chiral allenes by the Claisen rearrangement utilizing their efficient *N*-Boc-2-acyloxazolidine methodology [41]. A [2,3]-Wittig rearrangement [42] of bispropargyl ethers **101** to **102** was reported in a synthesis of 2,5-dihydrofuran **103** by Marshall and coworkers (Scheme 4.26) [43].



Scheme 4.24 Asymmetric synthesis of enprostil **95** via Claisen rearrangement.

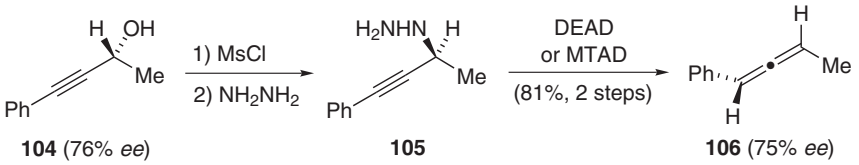


Scheme 4.25 Asymmetric synthesis of clavepictines **99** and **100** via Claisen rearrangement.

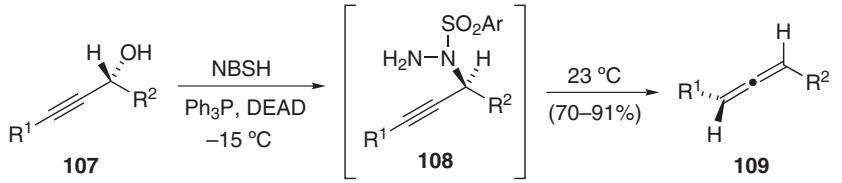


Scheme 4.26 [2,3] Wittig rearrangement for asymmetric synthesis of allenic alcohol **102**.

Myers et al. developed a novel synthesis of allenes from alkynyl hydrazines in 1989 (Scheme 4.27) [44]. A hydrazine derivative **105** underwent a smooth oxidative rearrangement with diethyl azodicarboxylate (DEAD) or 4-methyl-1,2,4-triazoline-3,5-dione (MTAD), presumably via a propargyldiazene intermediate to form the allene **106**. Carreira and co-workers applied this allene synthesis to an intramolecular [2 + 2] photocycloaddition of 1,3-disubstituted allenes with enones and enoates [45]. Although this method did provide a stereospecific preparation of allenes, it was lengthy, unsuccessful in the preparation of trimethylsilyl-substituted allenes and proceeded with 48–81% yields. In 1996, a highly efficient modified reaction was reported by the same group for the synthesis of allenes in a single step from propargyl alcohols (Scheme 4.28) [46]. Reaction of propargyl alcohols **107** with *o*-nitrobenzenesulfonylhydrazine (NBSH) under Mitsunobu conditions (Ph_3P, DEAD) led to the stereospecific formation of allenes **109** in 70–91% yield. The increased acidity of arenesulfonylhydrazine improved the efficiency of the Mitsunobu reaction and accelerated the thermal decomposition of **108**.

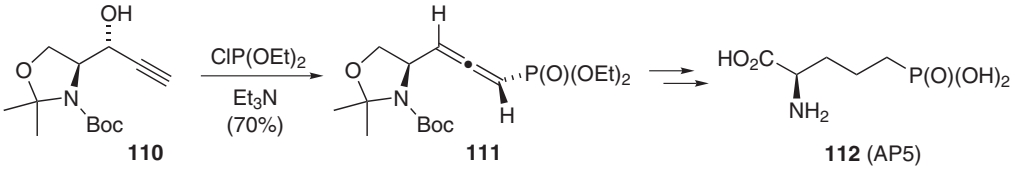


Scheme 4.27 Asymmetric synthesis of allenes by oxidative rearrangement.



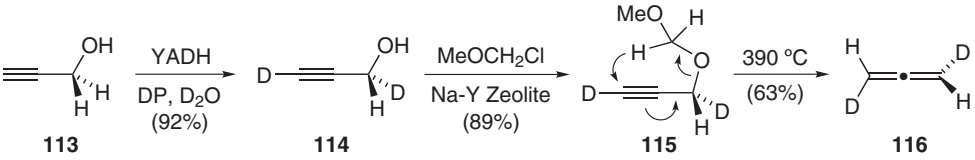
Scheme 4.28 A modified single-step synthesis of allenes under Mitsunobu conditions.

A potent and selective *N*-methyl-D-aspartate (NMDA) antagonist, AP5 **112**, was synthesized from **111**, which was a pseudo-Claisen [2,3] rearrangement product of **110** (Scheme 4.29) [47].



Scheme 4.29 Synthesis of AP5 via a thermal pseudo-Claisen [2,3] rearrangement of **110** to **111**.

In 1997, the synthesis of 1,3-dideuteroallene **116**, the lightest chiral molecule composed of stable elements, was reported utilizing enzymatic deuteration of **113** and thermal rearrangement of **115** to **116** (Scheme 4.30) [48].



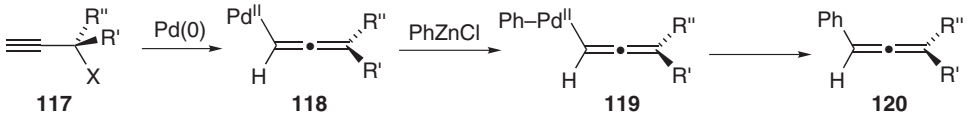
Scheme 4.30 Enantioselective synthesis of 1,3-dideuteroallene.

4.2.4

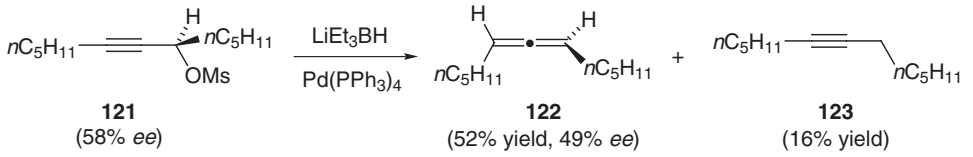
Palladium(0)-Catalyzed Reactions of Propargyl Alcohol Derivatives

The synthesis of racemic allenes by the reaction of propargyl substrates with Grignard reagents under palladium(0) catalysis was first reported by Leffery-Luong and Linstrumelle in 1980 [49]. Almost at the same time, a similar type of palladium(0)-catalyzed synthesis of allenes with the use of organozinc reagents was developed [50]. The *anti* stereoselectivity in the formation of **120** from **117** (*anti*:*syn* = 82:12–98:2) was attributed to a palladation of **117** to **118** with inversion, subsequent phenylation to **119** and reductive elimination to **120** (Scheme 4.31) [51]. The palladium(0)-catalyzed stereoselective reduction of propargyl mesylate **121** with lithium triethylborohydride was reported to give **122** with high *anti* selectivity (Scheme 4.32) [52]. Lipase-catalyzed resolution of (±)-**124** provided (*S*)-**124**, which was a good

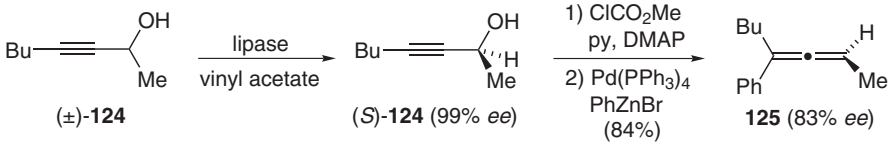
substrate for the palladium-catalyzed allene synthesis (Scheme 4.33) [53]. The fluorine-containing propargyl mesylates **126** were converted into allenes **127** (96% *ee*) by palladium-catalyzed phenylation with PhZnCl (Scheme 4.34) [54].



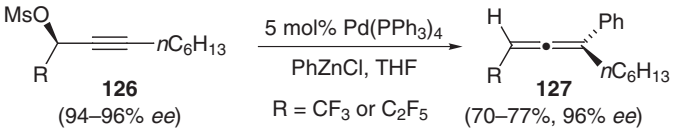
Scheme 4.31 Palladium(0)-catalyzed synthesis of allenes with *anti* stereoselectivity.



Scheme 4.32 Palladium(0)-catalyzed reduction of propargyl mesylates forming allenes.

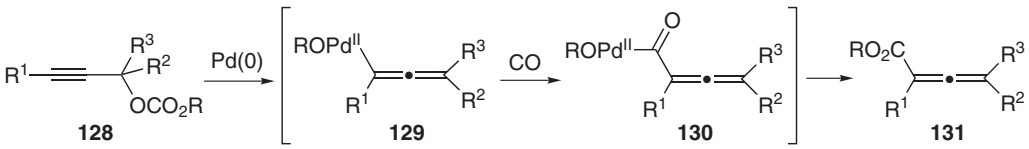


Scheme 4.33 Asymmetric synthesis of allenes by lipase- and palladium(0)-catalyzed reactions.

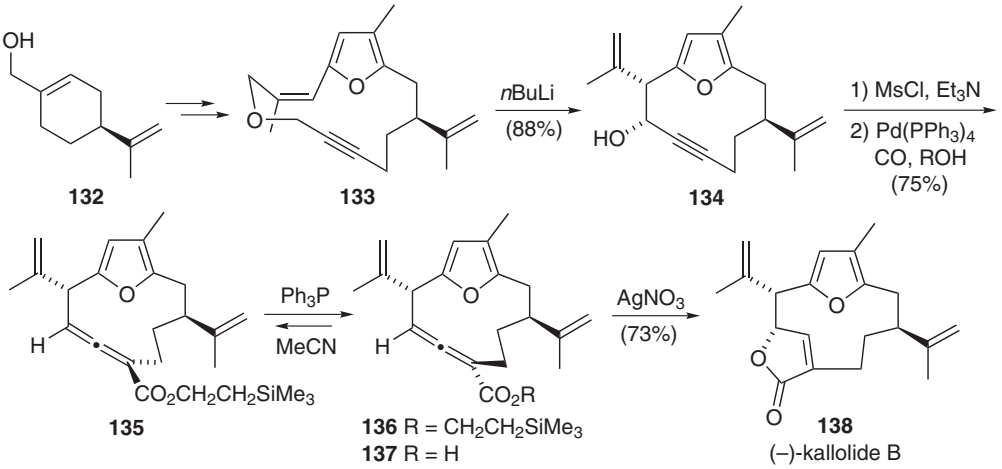


Scheme 4.34 Asymmetric synthesis of fluorine-containing allenes.

In 1986, Tsuji et al. developed the palladium(0)-catalyzed alkoxycarbonylation of racemic or achiral propargyl carbonates **128** in an alcohol solvent to afford **131** via carbonylation of **129** to **130** (Scheme 4.35) [55]. Palladium(0)-catalyzed alkoxycarbonylation of **134** and isomerization to **136** were key steps for the total synthesis of (–)-kallolide B **138** (Scheme 4.36) [56].

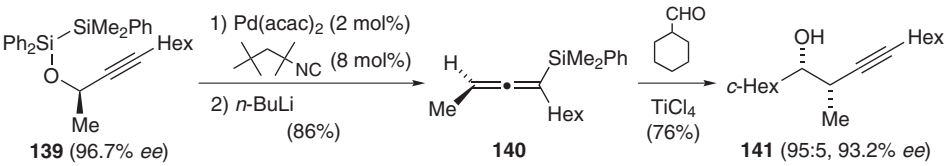


Scheme 4.35 Palladium-catalyzed alkoxycarbonylation of **128** giving **131**.



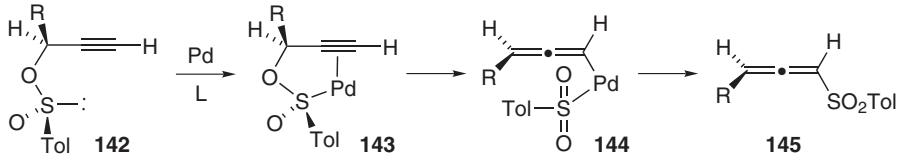
Scheme 4.36 Asymmetric total synthesis of (–)-kallolide B via allenic esters **135** and **136**.

Ito and co-workers discovered an interesting synthetic method for allenylsilanes **140** by palladium(0)-catalyzed intramolecular bis-silylation of propargyl alcohols (Scheme 4.37) [57]. Disilanyl ether **139** with 96.7% *ee* was heated in the presence of a palladium catalyst, prepared from $Pd(acac)_2$ (2 mol%) and 1,1,3,3-tetramethylbutyl isocyanide (8 mol%), to give allenylsilane **140** via 1,2-oxasiletane formed by *cis*-addition of the Si–Si bond to the carbon–carbon triple bond of **139**. The $TiCl_4$-mediated reaction of the enantioenriched allene **140** with cyclohexanecarboxaldehyde gave *syn*-homopropargyl alcohol **141** with high diastereoselectivity (95:5).



Scheme 4.37 Palladium-catalyzed bis-silylation of propargyl alcohol **139** to form an allenylsilane.

Recently, Hiroi and co-workers reported a palladium-catalyzed asymmetric transformation of chiral 2-alkynyl sulfinates **142** into allenyl sulfones **145** (Scheme 4.38) [58]. Treatment of **142** with $Pd(OAc)_2$ in the presence of a phosphine ligand afforded allenylsulfones **145** with high stereospecificities (73–89%) in good yields, probably through intermediates **143** and **144**.



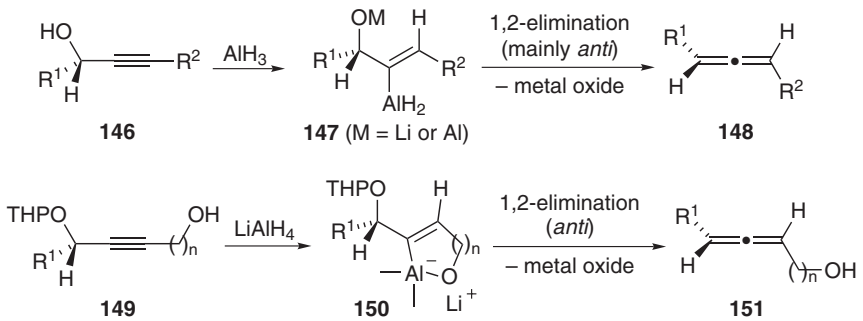
Scheme 4.38 Synthesis of allenylsulfones by palladium-catalyzed rearrangement.

4.2.5

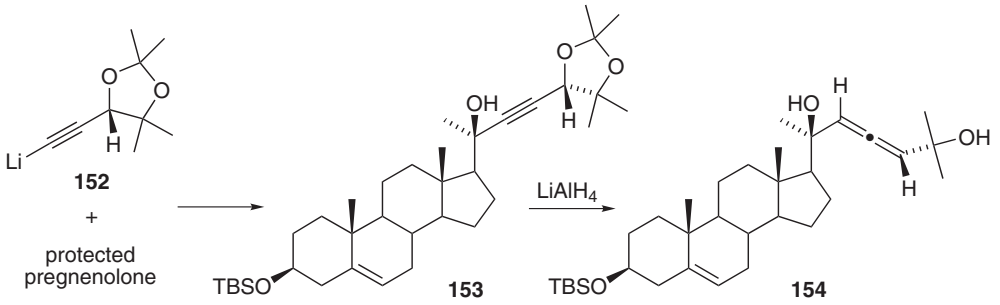
S_N2' Reduction of Propargyl Alcohol Derivatives

The first synthesis of allenes using an S_N2' reduction of propargylic substrates dates back to 1954: reduction of pent-4-en-2-yn-1-ol with $LiAlH_4$ to yield an allenic alcohol was reported by Bates and et al. [59]. Miki and Hara discovered the $LiAlH_4$-reduction of substituted 2-butyne-1,4-diol to afford allenic alcohols [60]. In 1969, Borden and Corey reported the synthesis of optically active allenes by the reaction of an enantiomerically pure camphorsulfonate of a propargyl alcohol with $LiAlH_4$ in the presence of $AlCl_3$ to yield enantioenriched 1,3-di-*tert*-butylallene as the sole product [61]. Almost at the same time, Landor developed a hydroxyl group-assisted S_N2' reduction of mono-*O*-tetrahydropyran-2-yl derivatives of 2-butyne-1,4-diols with $LiAlH_4$ to yield allenic alcohols [62]. Since then, several asymmetric syntheses of allenes via reduction of propargyl alcohols [63] or 2-butyne-1,4-diol derivatives [64] have been reported.

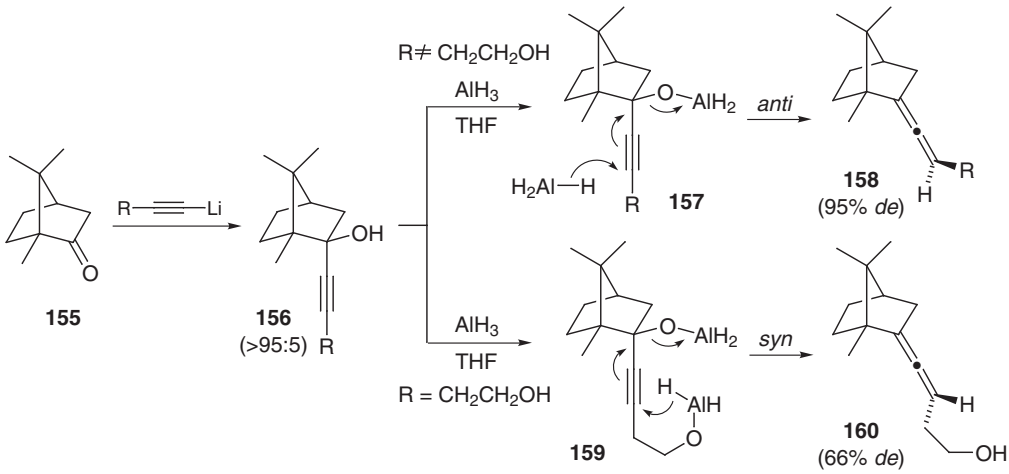
Reaction of AlH_3 (or $AlCl_3$–$3LiAlH_4$) with propargyl alcohols **146** yielded allenes **148** with overall *syn* stereochemistry via 1,2-*anti* elimination of metal oxide from the intermediate **147** (Scheme 4.39) [65]. Mono-*O*-tetrahydropyran-2-yl derivatives **149** of butyne-1,4-diols were converted to **151** via stepwise reduction to **150** and *anti* elimination [64]. Cholesterylallene **154** was synthesized in 88% yield by the $LiAlH_4$ reduction of **153** (Scheme 4.40) [66]. AlH_3 reduction of the propargyl alcohols **156** stereoselectively provided **158** and **160** via **157** and **159** (Scheme 4.41) [67].



Scheme 4.39 The S_N2'-reduction of propargyl alcohols followed by *anti*-elimination, giving allenes **148** and **151**.

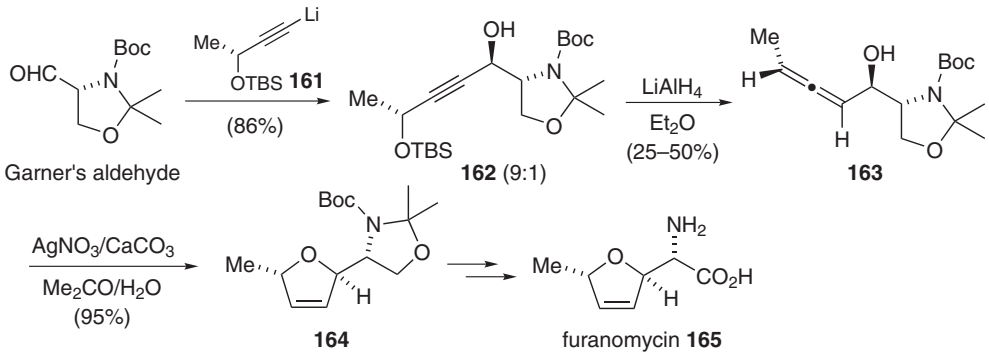


Scheme 4.40 Stereoselective synthesis of cholesteryl allene **154** by $LiAlH_4$ reduction.



Scheme 4.41 Stereoselective synthesis of camphor-based allenes by AlH_3 reduction.

The stereospecific reduction of a 2-butyne-1,4-diol derivative and silver(I)-mediated cyclization of the resulting allene were successively applied to a short total synthesis of (+)-furanomycin **165** (Scheme 4.42) [68]. Stereoselective addition of lithium acetylide **161** to Garner's aldehyde in the presence of zinc bromide afforded **162** in 77% yield. The hydroxyl group-directed reduction of **162** with $LiAlH_4$ in Et_2O produced the allene **163** stereospecifically. Cyclization followed by subsequent functional group manipulations afforded (+)-furanomycin **165**.



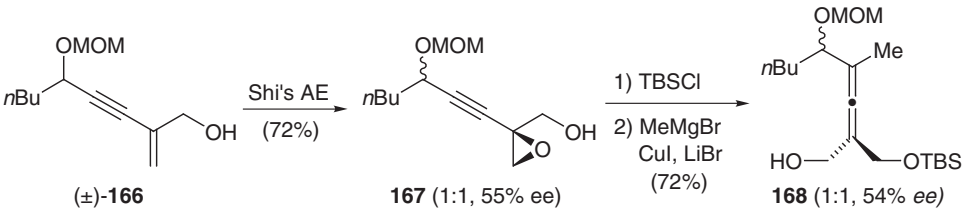
Scheme 4.42 Total synthesis of furanomycin using the S_N2'-reduction and allene cyclization.

4.2.6

Ring-Opening Reactions of Propargyl Epoxides and Related Compounds

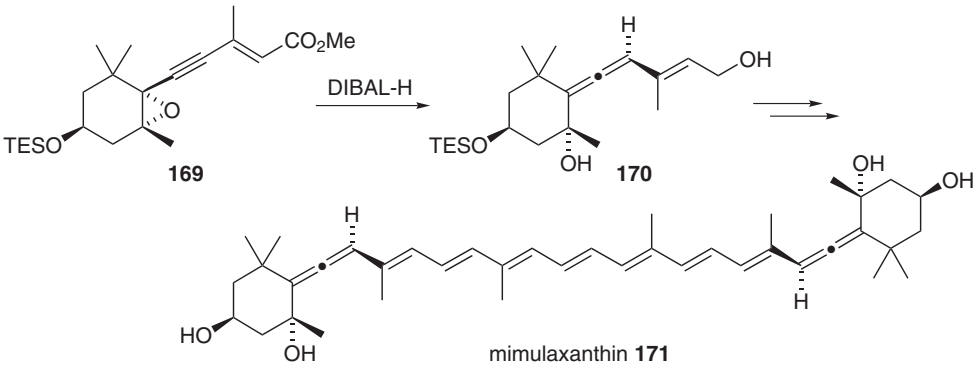
Although syntheses of allenes by ring-opening reaction of epoxides with organocopper [69] or $LiAlH_4$ [70] have been reported, the stereochemical course of these reactions was not addressed initially. A highly stereoselective synthesis of chiral allenes by the reaction of epoxides with organocopper reagents was first reported by Oehlshlager and Czyzewska in 1983 [71]. The stereochemistry of the reaction was exclusively *anti* to give diastereomerically pure dihydroxyallenes in the reaction with $R_2CuM \cdot Me_2S$ (M = Li or MgBr). In contrast, Alexakis and co-workers reported that the *syn* diastereomer is better obtained with RMgCl and copper(I) bromide, whereas the *anti* diasteromer is preferentially obtained with RMgBr and a complexed copper(I) salt [72, 73] (cf. Chapter 2). These results are comparable to those with propargyl ethers (Scheme 4.2).

Spino and Frechette reported the synthesis of non-racemic allenic alcohol **168** by a combination of Shi's asymmetric epoxidation of **166** and its organocopper-mediated ring-opening reaction (Scheme 4.43) [74]. Reduction of the ethynyl epoxide **169** with DIBAL-H stereoselectively gave the allenic alcohol **170**, which was converted to mimulaxanthin **171** (Scheme 4.44) [75] (cf. Section 18.2.2). The DIBAL-H reduction was also applied in the conversion of **173** to the allene **174**, which was a synthetic intermediate for peridinine **175** (Scheme 4.45) [76]. The S_N2' reduction of ethynyl epoxide **176** with DIBAL-H gave **177** (Scheme 4.46) [77].



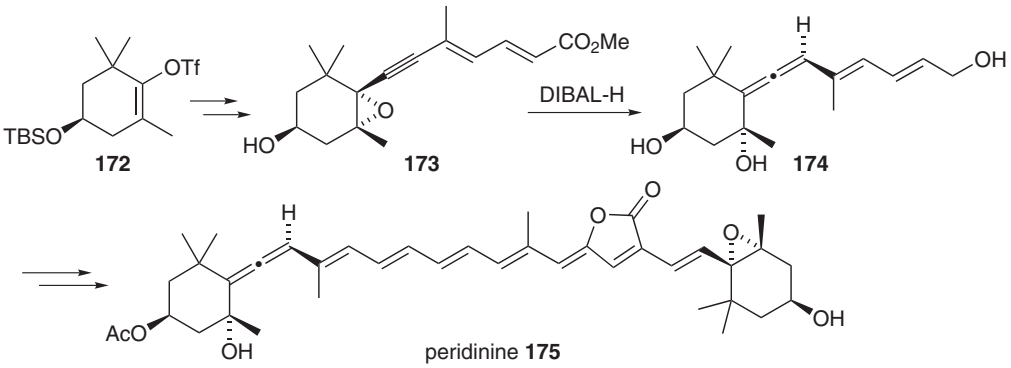
(±)-**166** **167** (1:1, 55% ee) **168** (1:1, 54% *ee)*

Scheme 4.43 Ring-opening reaction of epoxides prepared by Shi's asymmetric epoxidation.



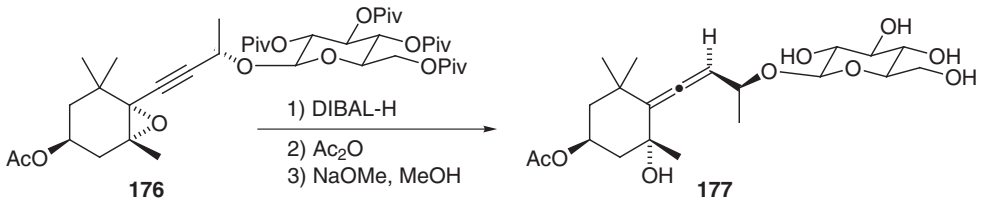
169 **170** mimulaxanthin **171**

Scheme 4.44 Total synthesis of mimulaxanthin via ring-opening reduction of epoxide **169**.



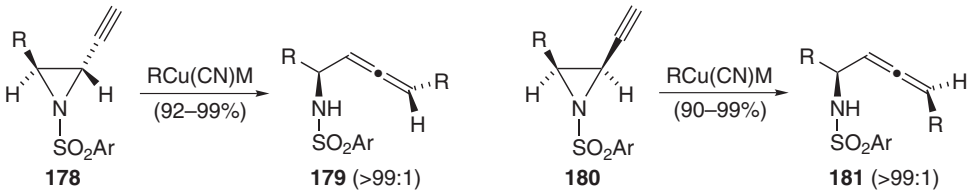
172 **173** **174** peridinine **175**

Scheme 4.45 Total synthesis of peridinine via ring-opening reduction of epoxide **173**.



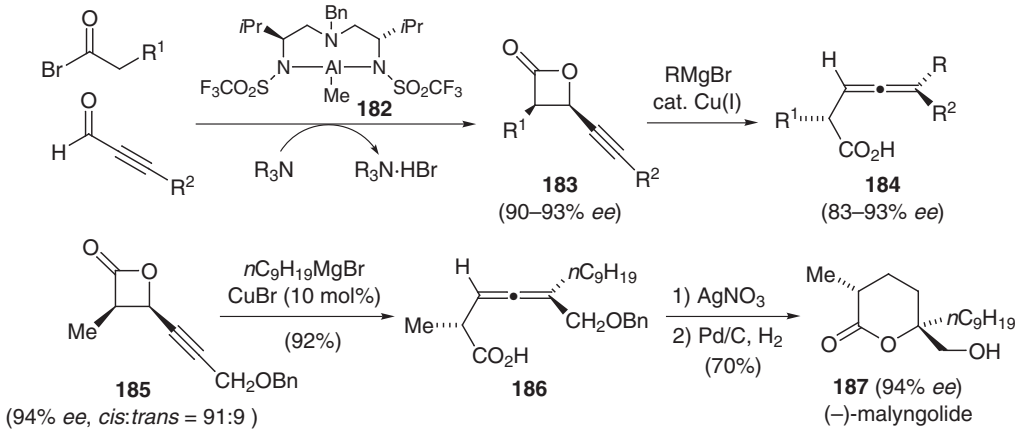
Scheme 4.46 Synthesis of glucosidic damascenone by the S_N2' reduction.

Aminoallenes constitute an important class of functionalized allenes with interesting chemical properties. They are known as attractive substrates for constructing three- to six-membered azacycles [78]. In 1999, Ohno and co-workers reported the stereoselective synthesis of chiral α-aminoallenes **179** and **181** by RCu(CN)M-mediated *anti*-S_N2' substitution of chiral 2-ethynylaziridines **178** and **180** (Scheme 4.47) [79]. The X-ray data and specific rotations of the allenes were consistent with a net *anti*-S_N2' substitution reaction.



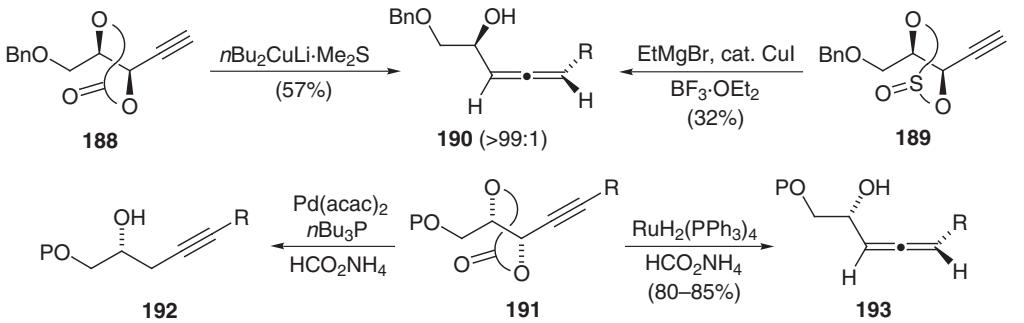
Scheme 4.47 Synthesis of α-aminoallenes by ring-opening reaction of 2-ethynylaziridines

In 2000, Wan and Nelson reported a synthesis of optically active allenes **184** and **186** from β-lactone templates **183** and **185** with organocopper reagents (Scheme 4.48) [80]. A series of optically active alkynyl-substituted β-lactones **183** (90–93% *ee*) were prepared by asymmetric acyl halide–aldehyde cyclocondensation reactions (AAC reactions) catalyzed by Al(III) catalyst **182**. Copper-catalyzed substitution of various organometallic nucleophiles with **183** uniformly proceeded in high yields (79–94%) and with consistent chirality transfer (83–93% *ee*) to give β-allenic acids **184**. The copper-catalyzed ring opening reaction of **185** with nonyl Grignard reagent delivered the trisubstituted allene **186**. The expected 6-*endo-trig* cyclization of **186** in the presence $AgNO_3$ (10 mol%) and $i Pr_2NEt$ (5 mol%) followed by hydrogenation afforded synthetic (–)-malyngolide **187**.



Scheme 4.48 Asymmetric synthesis of β-allenic acids **184**, **186** and (–)-malyngolide **187** via β-lactones.

Cyclic carbonates **188** and **191** and sulfites **189** are attractive ring-opening substrates for the synthesis of α-allenic alcohols **190** and **193** (Scheme 4.49) [81]. Interestingly, cyclic propargyl carbonates **191** were reduced with ammonium formate in the presence of a palladium catalyst to give the S_N2 reduction product **192**. In contrast, reduction of **191** with ammonium formate in the presence of $RuH_2(PPh_3)_4$ gave allenic alcohols **193** in 80–85% yields as the sole product [82].

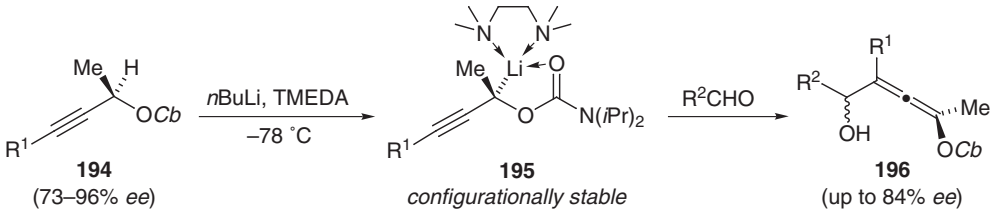


Scheme 4.49 Asymmetric synthesis of allenic alcohols from cyclic carbonates or sulfites

4.2.7
Chiral Propargyl– or Allenyl–Metal Reagents

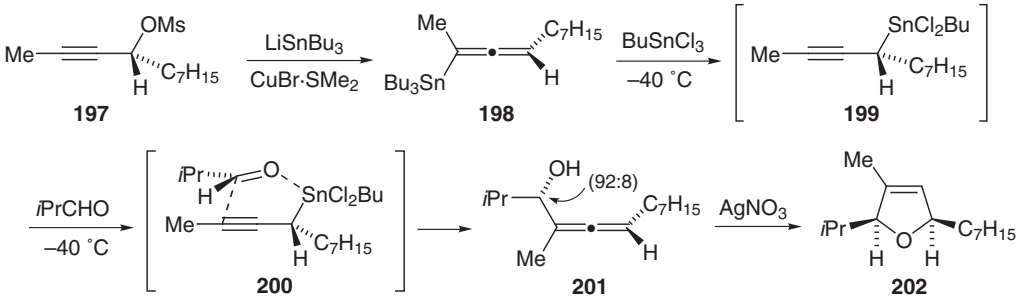
Most of the synthetic routes to allenes utilize the reaction of propargylic compounds as electrophiles. In contrast, if the propargylic compounds serve as nucleophiles, a wide variety of substituted allenes, which are not easily accessible by the reaction of propargylic compounds with nucleophiles, are available. However, in order to synthesize enantioenriched allenes by this method, it is necessary to generate configurationally stable propargyl or allenylmetal reagents (cf. Chapter 9).

In 1991, Hoppe and co-workers reported the synthesis of enantiomerically enriched allenes **196** using chiral, configurationally stable 1-lithio-2-alkynyl carbamates **195** (Scheme 4.50) [83]. Lithiation of **194** with *n*BuLi in the presence of TMEDA at –78 °C afforded the configurationally stable lithium intermediates **195** available for a nucleophilic addition to an aldehyde, giving allenes **196** with up to 84% *ee*. Although the carbamate **195** (R^1 = Me or Me_3Si) was not configurationally stable, in situ generation allowed the use of **195** (84–88% chirality transfer to **196**). The related (–)-sparteine-mediated lithiation of achiral propargyl carbamates with *n*BuLi and allene synthesis have been reported recently [84].



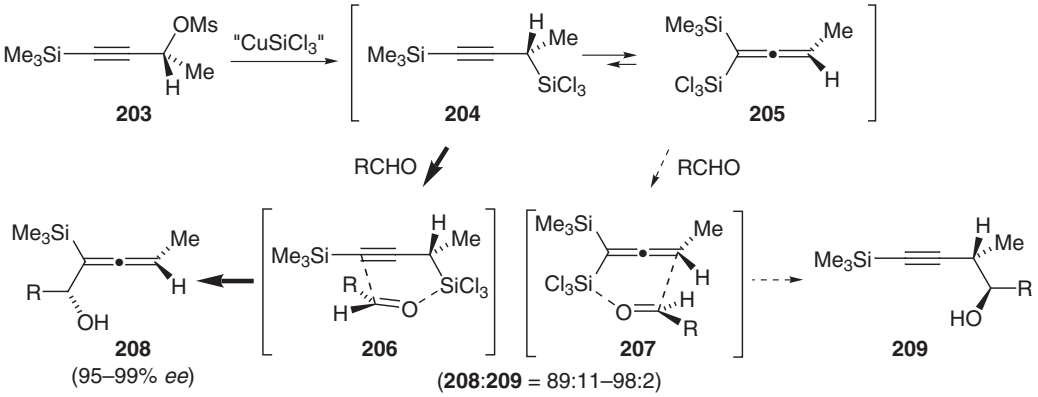
Scheme 4.50 Asymmetric synthesis of allenes via stable propargyllithium intermediates

Marshall et al. reported the diastereo- and enantioselective synthesis of allenic alcohols **201** through S_E2' addition of the transient non-racemic propargylstannane **198** to an aldehyde (Scheme 4.51) [85]. The non-racemic allenylstannane **198** was prepared by S_N2' displacement of a mesylate **197** with Bu_3SnLi–$CuBr \cdot SMe_2$. Treatment of this stannane with $BuSnCl_3$ followed by addition of isobutyraldehyde at –40 °C afforded the *syn*-allenic alcohol **201** (β-OH:α-OH = 92:8) in 72% yield, which was a good precursor of *cis*-2,5-dihydrofuran **202**. In contrast, when $BF_3 \cdot OEt_2$ was employed instead of $BuSnCl_3$ as the Lewis acid, the regioselectivity of the nucleophilic addition of **198** was dramatically changed to give the corresponding homopropargyl alcohol.



Scheme 4.51 Asymmetric synthesis of allenes via propargylstannane reagents.

Marshall and Adams reported the diastereo- and enantioselective synthesis of allenic alcohols **208** via propargyltrichlorosilane **204** and allenylsilane **205** (Scheme 4.52) [86]. Reaction of a propargyl mesylate **203** (bearing a trimethylsilyl group on the acetylene terminus) with $HSiCl_3$ and catalytic amounts of CuCl in the presence of Hünig's base, followed by addition of an aldehyde in DMF afforded the allenic alcohols **208** as the major products (**208**:**209** = 89:11–98:2), with excellent chirality transfer (95–99% *ee*). In contrast, when terminal acetylenes were employed, the corresponding homopropargyl alcohols of the type **209** were the major products. These results were rationalized as follows: the starting mesylate **203** would undergo an S_N2 or S_N2' displacement by a Cl_3Si cuprate (formally iPrNEt·HCl·$CuSiCl_3$) to afford the intermediate chlorocuprates, which on reductive elimination gave **204** and **205** with retention of configuration. Addition to the aldehyde is envisioned to take place through transition states **206** or **207** to afford the allenes **208** or homopropargyl alcohols **209**. In contrast, Fleming and Pang reported that chiral propargyltrimethylsilanes reacted with aldehydes in the presence of $TiCl_4$ in *anti* S_E2' reactions, but with a low level of stereoselectivity (75:25–50:50) [87].

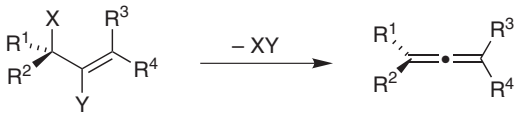


Scheme 4.52 Asymmetric synthesis of allenes via the allenyl- or propargylsilanes.

4.3
Elimination Reactions of Chiral Allylic Compounds

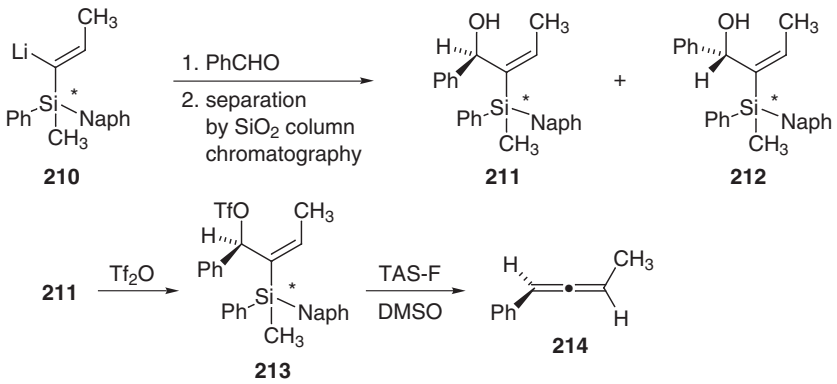
4.3.1
Chirality Transfer from Allylic Position

The stereoselective elimination reaction of suitably substituted allylic compounds is a reasonable approach to the construction of the propadiene framework. Central chirality at the allylic position is transferred to axial chirality of the allene by stereoselective β-elimination (Scheme 4.53).

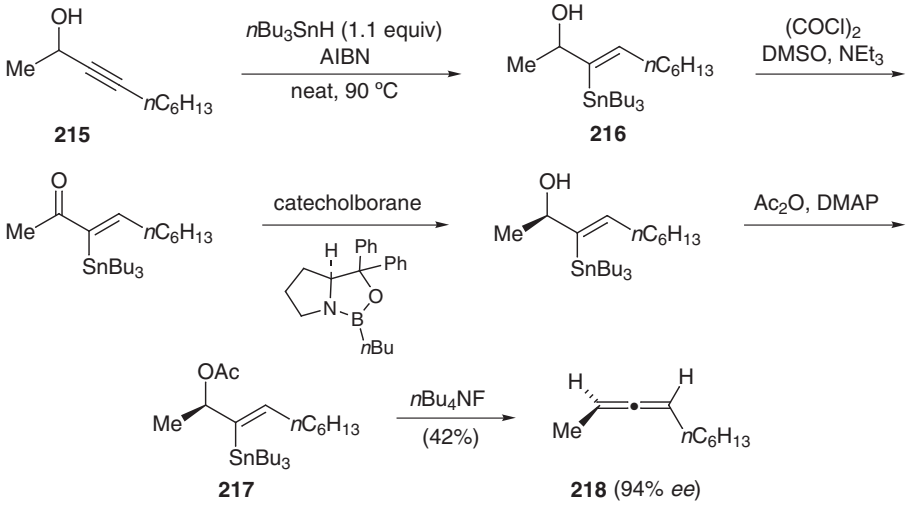


Scheme 4.53 Formation of allenes by stereoselective elimination of chiral allylic compounds.

McGarvey and co-workers prepared chiral allylic silyl trifluoromethanesulfonate **213** by the reaction of **210** with benzaldehyde and following triflation (Scheme 4.54) [88]. Fluoride ion-induced elimination of **213** with tris(dimethylamino)sulfurtrimethylsilicon difluoride (TAS-F) gave 1-phenyl-1,2-butadiene **214** of 18% *ee* in 50% yield. The poor *ee* was ascribed to low *anti*-selectivity of the elimination step. On the other hand, Konoike and Araki accomplished a highly stereoselective fluoride ion-induced deoxystannylation of the optically active β-stannyl allylic acetate **217** to the allene **218** in 42% yield with excellent 94% *ee* by treatment with tetrabutylammonium fluoride (Scheme 4.55) [89]. The configuration of the resulting allene demonstrated the complete *anti*-selectivity of the β-elimination of **217**. By the synthesis of a chiral allene using this method, Kitching and co-workers identified the structure of naturally occurring allenic hydrocarbons produced by Australian melolonthine scarab beetles [90].

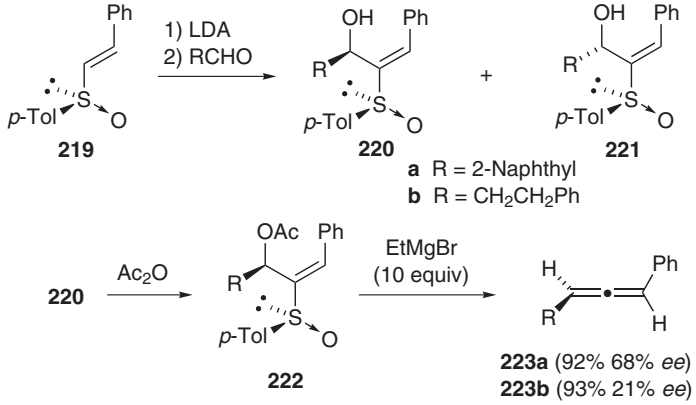


Scheme 4.54 Formation of chiral allene via fluoride-induced elimination of chiral allylic silyl triflate **213**.

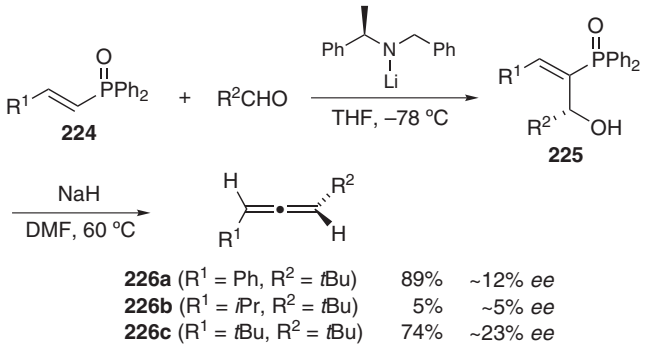


Scheme 4.55 A chiral allene via highly stereoselective deoxystannylation.

Treatment of chiral allylic sulfinyl acetate **222a** with 10 equiv. of EtMgBr at –25 °C resulted in a stereospecific *anti*-elimination of a β-acetoxysulfoxide, giving allene **223a** in 92% yield and 68% *ee* (Scheme 4.56) [91]. The same treatment of **222b** afforded the allene **223b** in 93% yield and only 21% *ee*. Horner–Wadsworth–Emmons (HWE)-type olefination of allylic phosphonyl alcohols **225** is an alternative way to construct 1,2-dienes **226**. Thus, treatment of **225** [92] with NaH gave **226** with moderate to poor enantioselectivities (Scheme 4.57) [93].



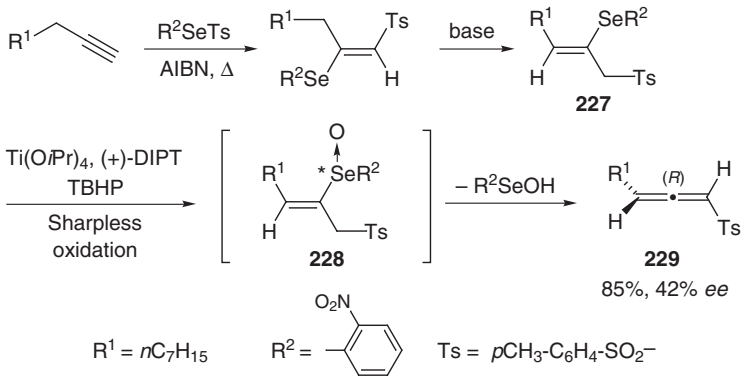
Scheme 4.56 Chiral allenes via elimination of chiral allylic sulfoxides.



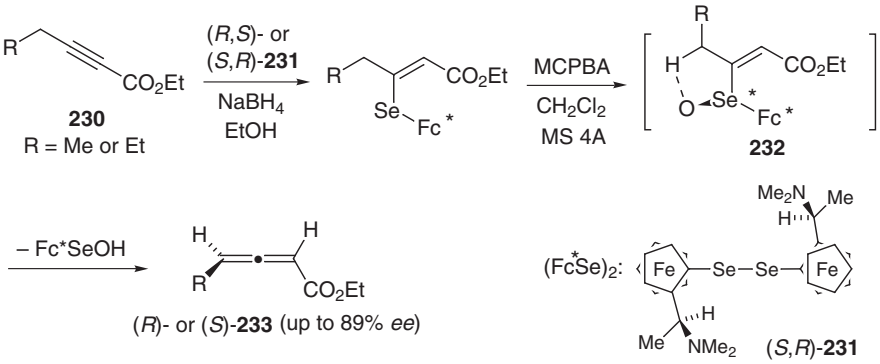
Scheme 4.57 Chiral allenes by an asymmetric Baylis–Hillman type reaction.

4.3.2
Elimination Reactions of Allylic Compounds Having a Chiral Leaving Group

Uemura and co-workers opened up a new synthetic route to chiral allenes **229** in up to 42% *ee* using an asymmetric oxidation of aryl vinyl selenide **227** to **228** with Sharpless or Davis oxidants (Scheme 4.58) [94]. The axial chirality in the resulting allenic sulfone is derived from optically active selenoxide leaving groups. This is completely different from most other chiral allene syntheses, in which chirality of an allenic skeleton is directly transferred from a chiral sp^3 carbon through stereoselective rearrangement of propargylic groups or β-elimination of allylic groups. They also reported enantioselective elimination reactions of intermediate chiral selenoxides **232** prepared from the reaction of ethyl propionate derivatives with a newly developed chiral diferrocenyl diselenide, (*R,S*)-**231** or (*S,R*)-**231**, in the presence of $NaBH_4$ followed by oxidation with *m*-chloroperbenzoic acid (MCPBA). Reaction of (*R,S*)-**231** and (*S,R*)-**231** gave chiral allene carboxylates (*R*)-**233** and (*S*)-**233**, respectively, with high enantioselectivity of up to 89% *ee*. The best selectivity was obtained by the use of CH_2Cl_2 as a solvent at low temperature in the presence of 4 Å molecular sieves to remove traces of water (Scheme 4.59) [95].



Scheme 4.58 Chiral allenic sulfones from asymmetric selenoxide elimination.

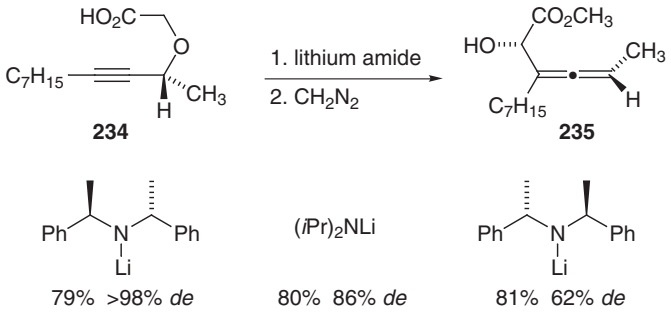


Scheme 4.59 Synthesis of chiral allenecarboxylates **233** using chiral diferrocenyl diselenides **231**.

4.4
Synthesis of Allenes Using Chiral Reagents

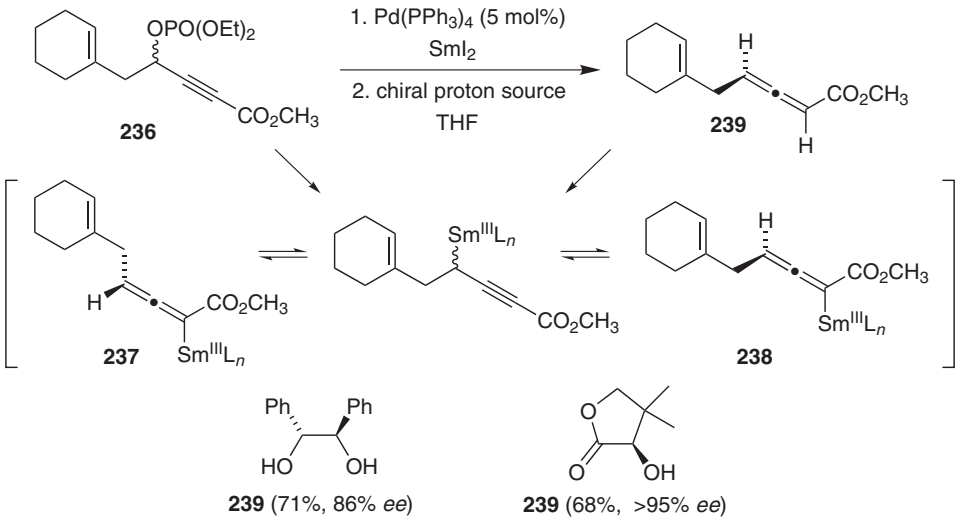
4.4.1
Asymmetric Deprotonation–Protonation

The [2,3]-Wittig rearrangement of chiral **234** (90–92% *ee*) with (*R*,*R*)- and (*S*,*S*)-lithium amide gave the allene **235** in 98 and 62% *de*, respectively, indicating the dependence of the selectivity on the configuration of the lithium amide (Scheme 4.60) [96].



Scheme 4.60 Chiral base-induced [2,3]-Wittig rearrangement of α-(propargyloxy)acetic acid **234**.

The enantioselective synthesis of an allenic ester using chiral proton sources was performed by dynamic kinetic protonation of racemic allenylsamarium(III) species **237** and **238**, which were derived from propargylic phosphate **236** by the metalation (Scheme 4.61) [97]. Protonation with (*R*,*R*)-(+)-hydrobenzoin and *R*-(–)-pantolactone provided an allenic ester **239** with high enantiomeric purity. The selective protonation with (*R*,*R*)-(+)-hydrobenzoin giving *R*-(–)-allenic ester **239** is in agreement with the

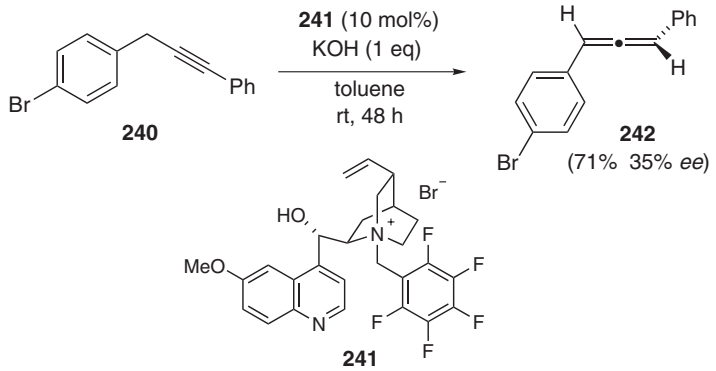


Scheme 4.61 Enantioselective protonation of **237/238**, giving allene **239**.

proposed transition-state model, in which steric repulsion between the alkyl groups in the allenylsamarium(III) species and in the chiral proton source play a key role.

Shioiri and co-workers developed a catalytic asymmetric synthesis of allenes by isomerization of the alkyne **240** to allene **242** under the control of a chiral phase-transfer catalyst **241** (Scheme 4.62) [98]. Although the enantiomeric excess is not high (35% *ee*), this is the first example of the asymmetric isomerization of alkynes under phase-transfer catalyzed conditions.

The (–)-sparteine-mediated lithiation of achiral propargyl carbamates with *n*BuLi and allene synthesis has already been described in Section 4.2.7 [84].

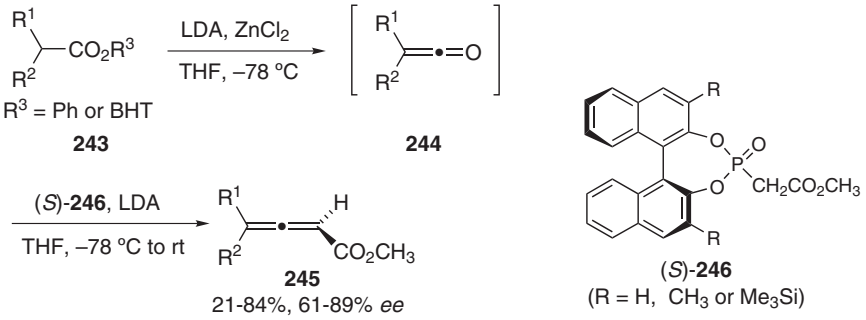


Scheme 4.62 Asymmetric allene synthesis via isomeration of alkyne **240** with the chiral phase-transfer catalyst **241**.

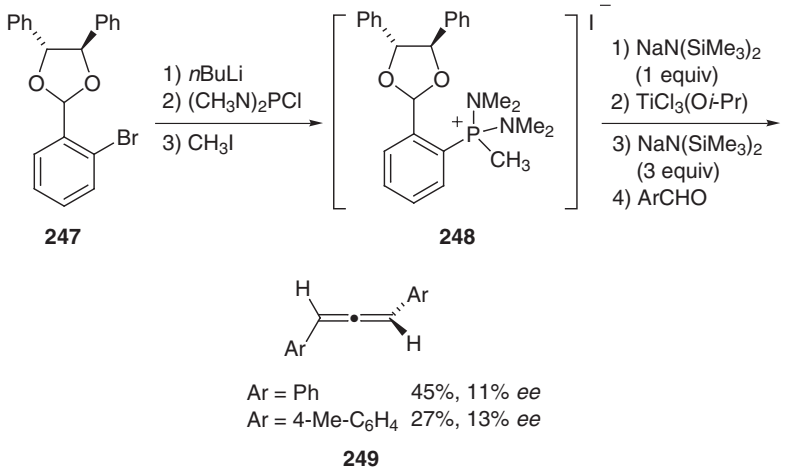
4.4.2

Asymmetric Horner–Wadsworth–Emmons and Related Reactions

A variety of optically active 4,4-disubstituted allenecarboxylates **245** were provided by HWE reaction of intermediate disubstituted ketene acetates **244** with homochiral HWE reagents **246** developed by Tanaka and co-workers (Scheme 4.63) [99]. α,α-Disubstituted phenyl or 2,6-di-*tert*-butyl-4-methylphenyl (BHT) acetates **243** were used for the formation of **245** [100]. Addition of $ZnCl_2$ to a solution of the lithiated phosphonate may cause binding of the rigidly chelated phosphonate anion by Zn^{2+}, where the axially chiral binaphthyl group dictates the orientation of the approach to the electrophile from the less hindered *si* phase of the reagent. Similarly, the aryl phosphorus methylphosphonium salt **248** was converted to a titanium ylide, which was condensed with aromatic aldehydes to provide allenes **249** with poor *ee* (Scheme 4.64) [101].



Scheme 4.63 Chiral allenecarboxylates by the asymmetric HWE reaction.

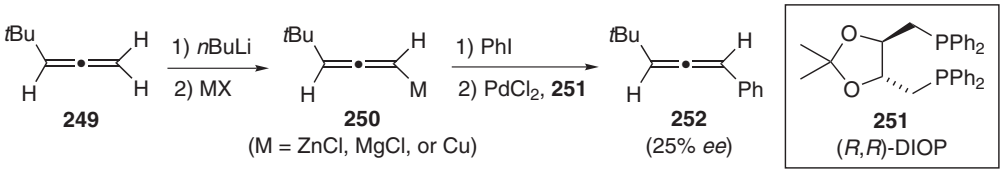


Scheme 4.64 Chiral allenes **249** via olefination using titanium-substituted ylide.

4.5
Direct Asymmetric Synthesis of Allenes Using an External Chiral Catalyst

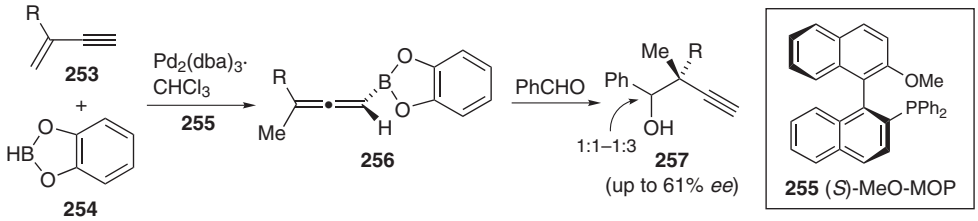
The asymmetric synthesis of allenes by stereoselective manipulations of enantiomerically pure or enriched substrates relies on the availability of such optically active substrates. In contrast, a direct synthesis of allenes by the reaction of prochiral substrates in the presence of an external asymmetric catalyst is an almost ideal process [102]. Most of the catalytic asymmetric syntheses in organic chemistry involve the creation of chiral tetrahedral carbon centers [103], whereas the asymmetric synthesis of allenes requires the construction of an axis of chirality.

The catalytic asymmetric synthesis of allenes was first achieved by Elsevier and co-workers in 1989 [104]. A palladium-catalyzed cross-coupling reaction of an allenylmetal compound **250** (M = ZnCl, MgCl or Cu) with iodobenzene in the presence of DIOP **251** gave **252** in 25% *ee* (Scheme 4.65). The synthesis of **252** by the reaction of **250** (M = Br) with phenylzinc chloride in the presence of a chiral palladium catalyst gave a quantitative conversion but very low enantiomeric excesses (3–9% *ee*).



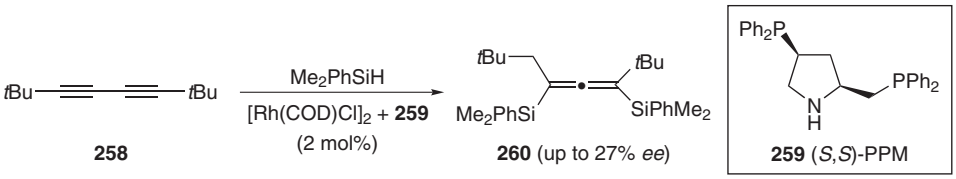
Scheme 4.65 First catalytic asymmetric synthesis of allene **252** with a chiral palladium catalyst.

In 1993, Hayashi and co-workers reported a catalytic asymmetric synthesis of allenylboranes **256** by palladium-catalyzed hydroboration of conjugated enynes **253** (Scheme 4.66) [105]. Reaction of but-1-en-3-ynes **253** with catecholborane **254** in the presence of a catalyst, prepared from $Pd_2(dba)_3 \cdot CHCl_3$ (1 mol%) and a chiral monodentate phosphine ligand (*S*)-MeO-MOP **255** (1 mol%), gave an allenylborane **256**. The *ee* of **256** was determined by the reaction with benzaldehyde affording the corresponding optically active homopropargyl alcohols **257** with up to 61% *ee* (*syn*:*anti* = 1:1–3:1).



Scheme 4.66 Catalytic asymmetric synthesis of allenylboranes by a chiral palladium catalyst.

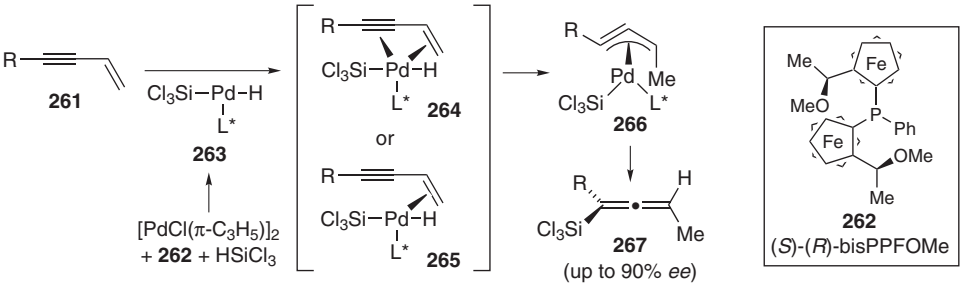
Tillack and co-workers developed a rhodium-catalyzed asymmetric hydrosilylation of butadiyne **258** to afford allenylsilane **260** (Scheme 4.67) [106]. Among more than 30 chiral phosphine ligands investigated, the highest enantioselectivity was observed when the catalyst was prepared from $[Rh(COD)Cl]_2$ (1 mol%) and (*S*,*S*)-PPM **259** (2 mol%) to afford the optically active allene **260** with 27% *ee*. Other metals such as Ir, Pd, Pt or Ni were less effective: for example, a nickel catalyst prepared from $NiCl_2$ and (*R*,*R*)-DIOP **251** or (*S*,*S*)-PPM **259** gave the allene **260** with 7–11% *ee*.



258 **260** (up to 27% *ee*) **259** (*S*,*S*)-PPM

Scheme 4.67 Asymmetric synthesis of allene **260** by rhodium-catalyzed hydrosilylation of diyne **258**.

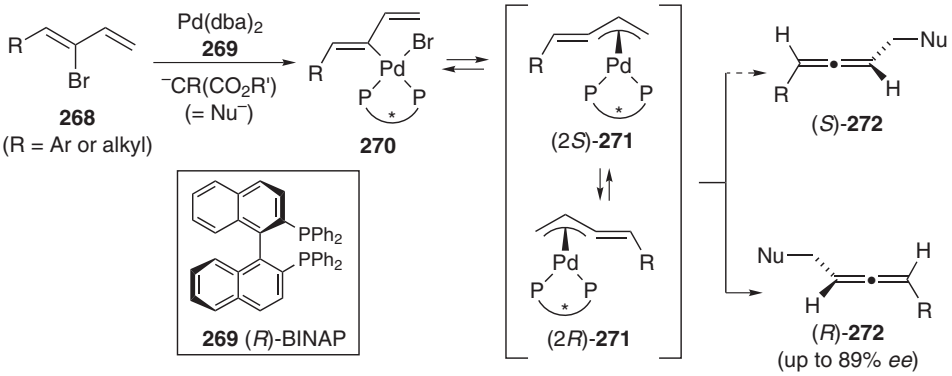
An excellent preparation of axially chiral allenylsilanes **267** by enantioselective palladium catalysis was reported recently by Hayashi and co-workers (Scheme 4.68) [107]. The asymmetric hydrosilylation of enynes **261** bearing a bulky substituent (R = *t*Bu, mesityl or TBS) with trichlorosilane was catalyzed by a palladium complex **263** prepared from $[PdCl(\pi\text{-}C_3H_5)]_2$ (1 mol%) and (+)-(*S*)-(*R*)-bisPPFOMe **262** (2.2 mol%) to give allenylsilanes **267** in good to high yields with up to 90% *ee*. This asymmetric hydrosilylation of enynes was proposed to proceed through a catalytic cycle involving hydropalladation of the double bond of **261**, forming a π-propargyl-(silyl)palladium intermediate **266**. The steric bulkiness of the substituent at the 4-position is important in retarding the hydropalladation of the alkyne moiety. The allenyl(trichloro)silanes **267** obtained were allowed to react with benzaldehyde to give the corresponding homopropargyl alcohols. The reaction of bromodienes **268** with a malonate was catalyzed by $Pd(dba)_2$ and (*R*)-BINAP **269** to give the enantioenriched allenes (*R*)-**272** in up to 89% *ee* (Scheme 4.69) [108]. Interestingly, reaction of **268** (R = Ph) with $Pd[(R)\text{-binap}]_2$ (10 mol%) gave a chiral allene (*R*)-**272** (R = Ph) in 91% yield with only 11% *ee*. The presence and absence of dibenzylideneacetone (dba) make the difference between these two reactions. NMR study revealed that



261

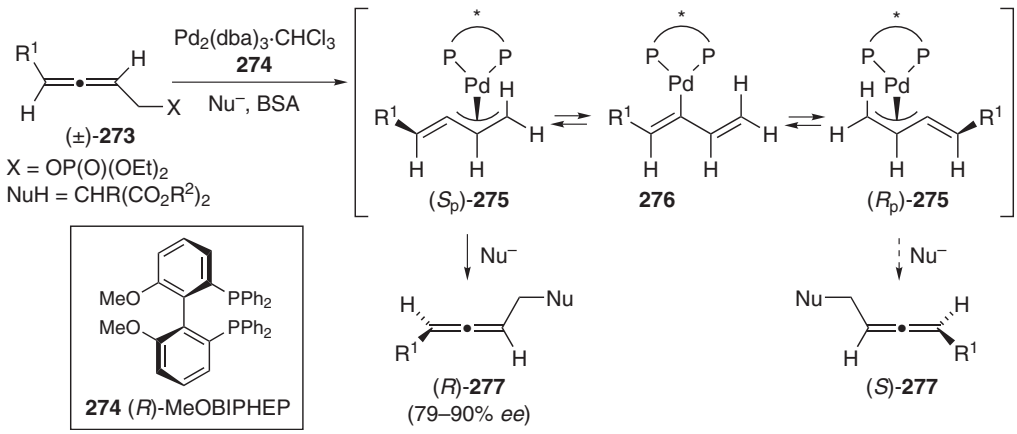
Scheme 4.68 Palladium-catalyzed asymmetric hydrosilylation of enynes **261** forming allenylsilanes **267**.

coexisting dba accelerates the equilibrium between the two diastereomers (2*S*)- and (2*R*)-**271**. Similarly, axially chiral (allenylmethyl)silanes was also prepared from (3-bromopenta-2,4-dienyl)trimethylsilane utilizing this chemistry [109].



Scheme 4.69 Highly enantioselective synthesis of allenes **272** by palladium-catalyzed substitution.

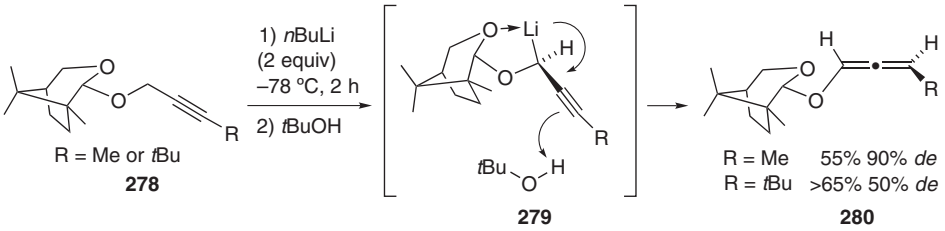
The synthesis of optically active 2-(2,3-alkadienyl)malonates **277** by a palladium-catalyzed asymmetric alkylation of racemic 2,3-alkadienyl phosphates **273** was reported by Murahashi and co-workers (Scheme 4.70) [110]. Alkylation of phosphates (±)-**273** with soft carbon nucleophiles such as substituted diethyl malonate in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and a palladium catalyst prepared from $Pd_2(dba)_3 \cdot CHCl_3$ (1 mol%) and (*R*)-MeOBIPHEP **274** (4 mol%) in THF afforded enantiomerically enriched allenes **277** in good yields with 69–90% *ee*. An equilibrium is present between two diastereomeric η^3-1,3-alkadienylpalladium complexes (S_p)-**275** and (R_p)-**275** through η^1-1,3-alkadienylpalladium complex **276**. Preferential nucleophilic attack of malonate anion to (S_p)-**275** from the opposite side to the palladium is thought to give the optically active allenes (*R*)-**277**.



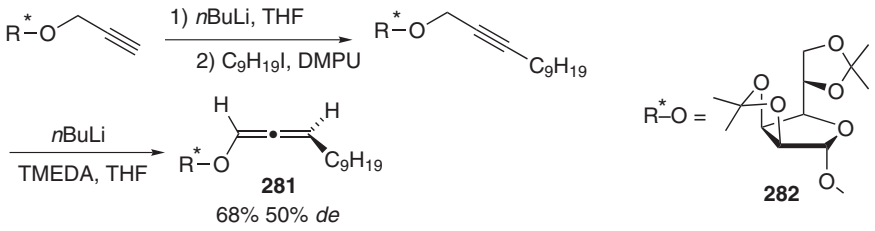
Scheme 4.70 Palladium-catalyzed asymmetric alkylation of 2,3-alkadienyl phosphates **273**.

4.6
Synthesis of Allenes Using Internal Chiral Auxiliaries

Asymmetric induction using internal chiral auxiliaries is one of the most promising methods for asymmetric syntheses. Tius and co-workers succeeded in the preparation of enantio-enriched alkoxyallenes **280** by a base-induced isomerization of propargyl ethers **278** bearing a camphor-derived auxiliary (Scheme 4.71) [111]. Treatment of **278** with *n*BuLi resulted in the selective abstraction of the pro-*S* propargylic proton, leading to an internally chelated structure **279**, which was protonated with *t*BuOH to give **280**. The chiral camphor auxiliary is removable after playing its role. Reissig and co-workers examined six chiral carbohydrate auxiliaries in a similar isomerization reaction to **281** (Scheme 4.72) [112]. At best, the two diastereomers of **281** are formed in a 75:25 ratio in favor of the R_a-isomer when fructose-derived auxiliary **282** was used.



Scheme 4.71 Camphor-derived auxiliary for the asymmetric synthesis of chiral allene ether **280**.

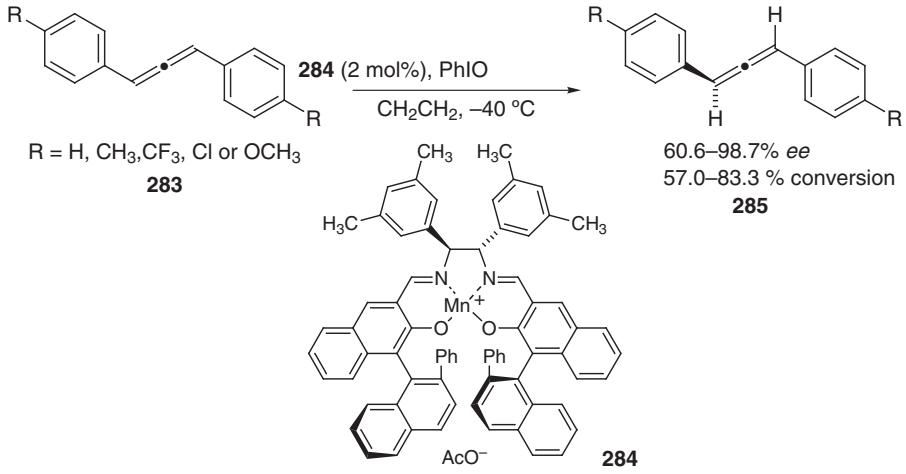


Scheme 4.72 Fructose-derived auxiliary for the synthesis of chiral allene ethers **281**.

4.7
Kinetic Resolution

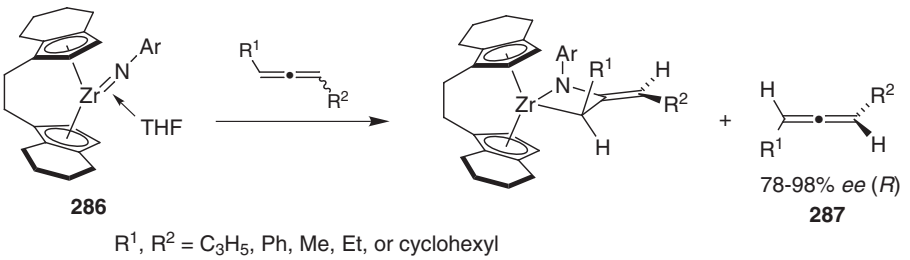
Resolution of a racemic mixture is still a valuable method involving fractional crystallization [113], chiral stationary phase column chromatography [114] and kinetic resolutions. Katsuki and co-workers demonstrated the kinetic resolution of racemic allenes by way of enantiomer-differentiating catalytic oxidation (Scheme 4.73) [115]. Treatment of racemic allenes **283** with 1 equiv. of PhIO and 2 mol% of a chiral (salen)manganese(III) complex **284** in the presence of 4-phenylpyridine *N*-oxide resulted

in partial asymmetric oxidation, which led to the recovery of enantioenriched allenes **285**. This method was useful especially for the resolution of 1,3-diarylallenes **283** in up to 98.7% *ee* and 83.3% conversion.

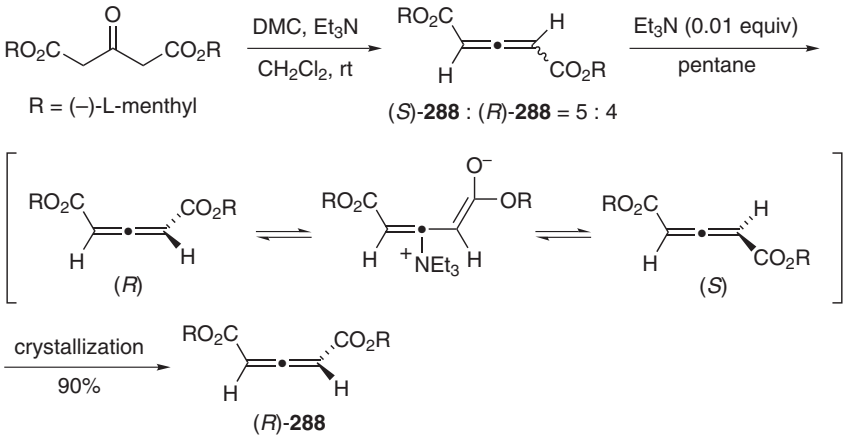


Scheme 4.73 Kinetic resolution of racemic allenes **283** by enantiomer-differentiating oxidation.

The kinetic resolution using a chiral zirconocene–imido complex **286** took place with high enantioselectivity to result in chiral allenes **287** (up to 98% *ee*) (Scheme 4.74) [116]. However, a potential drawback of these methods is irreversible consumption of half of the allene even if complete recovery of the desired enantiomer is possible. Dynamic kinetic resolutions avoid this disadvantage in the enantiomer-differentiating reactions. Node et al. transformed a di-(–)-L-menthyl ester of racemic allene-1,3-dicarboxylate [(*S*)- and (*R*)-**288**] to the corresponding chiral allene dicarboxylate (*R*)-**288** by an epimerization–crystallization method with the assistance of a catalytic amount of Et_3N (Scheme 4.75) [117].

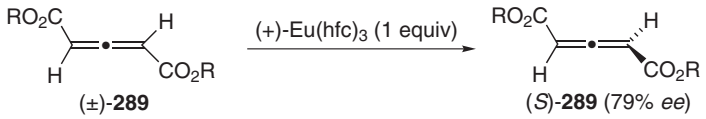


Scheme 4.74 Kinetic resolution by using chiral zirconocene-imido complexes **286**.



Scheme 4.75 Synthesis of a chiral allene dicarboxylate **288** through asymmetric transformation (DMC= 2-chloro-1,3-dimethylimidazolinium chloride).

Chiral Lewis acids are also applicable in the deracemization of racemic allene dicarboxylates **289**. Treatment of dimethylallene-1,3-dicarboxylate **289** with a chiral organoeuropium reagent, (+)-Eu(hfc)$_3$, gave the corresponding optically active allene in 79% *ee* (Scheme 4.76) [118]. Unfortunately the chiral allene could not be isolated from the reaction mixture without loss of its optical purity.



Scheme 4.76 Europium-mediated enantioselective deracemization of **289** (R = Me).

4.8 Conclusion

The most standard and convenient method for the asymmetric synthesis of allenes is the manipulation of chiral propargyl alcohol derivatives, for which the asymmetric alkynylation of aldehydes recently developed by Carreira and co-workers, and other methods, would provide a wide variety of chiral starting materials. Other transformations such as the elimination of chiral allylic compounds and reactions using chiral reagents also provide a number of reliable methods for the asymmetric synthesis of allenes. However, the direct asymmetric synthesis of allenes using an external chiral catalyst has the great advantage that it requires only a catalytic amount of chiral compounds. Further asymmetric syntheses of allenes aimed at improving the *ee* of the allenes, the efficacy of the reactions and the atom economy of the synthetic route will be reported.

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II
Special Classes of Allenes

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5
Allenic Hydrocarbons – Preparation and Use in Organic Synthesis

Henning Hopf

5.1
Introduction

Although allenes have been known for more than 100 years to organic chemists – the first organic molecule with a cumulenic double bond system, allene (propadiene) itself, was prepared by Gustavson and Demjanov in 1888 [1] – these unsaturated compounds and their higher cumulogs for a long time were not more than laboratory curiosities, used more often to demonstrate stereochemical principles predicted by van't Hoff than employed in organic synthesis. Recently this situation has changed dramatically, as indicated, inter alia, by a growing increase in the review literature during recent decades [2]. Responsible for this increased awareness is the unique capability of allenes to profit from most of the major developments in modern synthetic organic chemistry. Their unique stereochemistry – many allenes are axially chiral – makes them interesting substrates for stereoselective synthesis or processes requiring stereocontrol, the acidity of their hydrogen atoms permits easy functionalization and their most characteristic reactions, additions and isomerizations, are also the chemical transformations cherished in reaction sequences with a high atom economy. Furthermore, since allenes are energy-rich compounds – their conjugated isomers are thermodynamically much more stable – they can serve very well as intermediates in multi-step processes (domino reactions, tandem reactions) [3]. Their high reactivity is also a good prerequisite for their use as reaction partners in multi-component reactions. Allenes share many of these properties with their acetylenic isomers and it is therefore not surprising that both types of hydrocarbons have experienced a phenomenal growth in synthesis [4].

This review concentrates on preparative developments in allenic hydrocarbon chemistry that have taken place during the last 15–20 years, thus allowing a nearly uninterrupted connection with the older review literature [2]. For reasons of space this chapter is restricted largely to pure hydrocarbon systems. After presenting a 'combinatorial' approach to generate synthetically interesting and useful allenic hydrocarbons, the major routes to the preparation of these hydrocarbons will be discussed. The main part of this chapter will then concentrate on the preparation of these hydrocarbons and their use in organic synthesis, trying to avoid too much overlap with other chapters concerned with synthetic applications.

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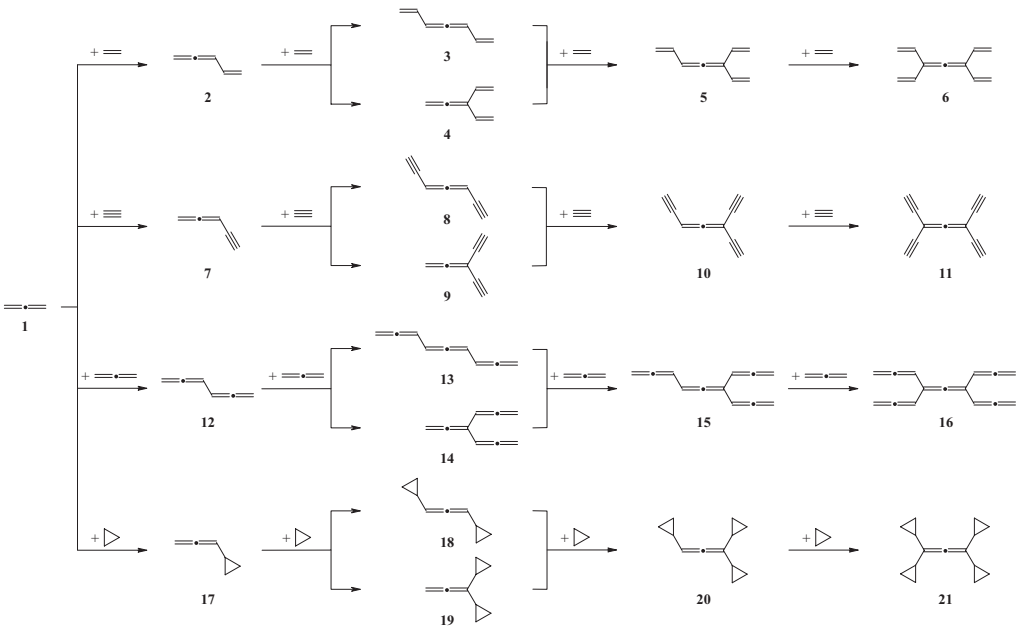
5.2
Allenic Hydrocarbons from Simple Building Blocks

Allene (**1**) and its alkyl and aryl derivatives have long been used in organic synthesis, especially in cycloaddition reactions, whether these are thermally [5] or photochemically induced and involve metal catalysis or polar reagents [2]. Potentially more interesting derivatives arise when the allene group is connected with other unsaturated 'building blocks' as shown in Scheme 5.1.

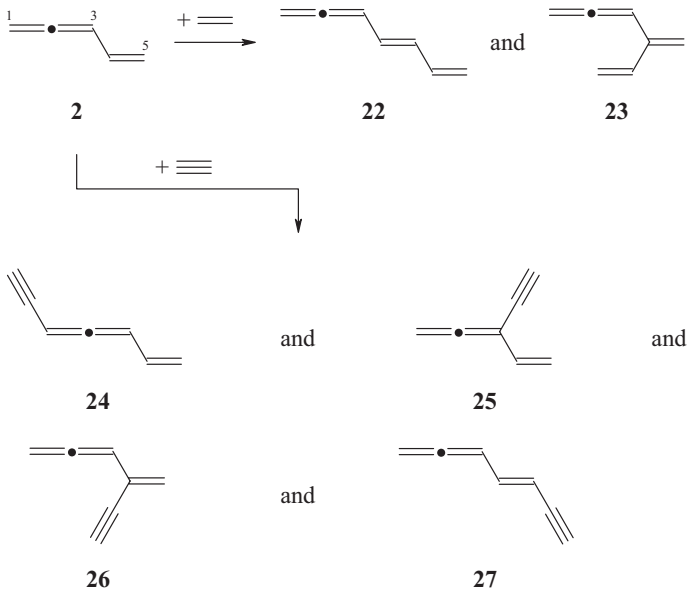


Scheme 5.1

Combining **1** with an additional, non-cumulenic double bond provides vinylallene (1,2,4-pentatriene) (**2**), and analogously 1,2-pentadien-4-yne (ethynylallene) (**7**), 1,2,4,5-hexatetraene (biallenyl) (**12**) and cyclopropylallene (**17**) are obtained when a triple bond, a second allene group and a cyclopropane ring, respectively, are used as substituents for **1**. The resulting hydrocarbons have two options for binding the same building block to the allene core again and thus either linear derivatives **3**, **8**, **13** and **18** are generated or the branched allene structures **4**, **9**, **14** and **19**. These last four hydrocarbons are all cross-conjugated [6], as are all remaining ones produced on introduction of a third (**5**, **10**, **15**, **20**) and fourth (**6**, **11**, **16**, **21**) identical substituent. Whereas the majority of the hydrocarbons with one or two additional substituents to the allene group have been prepared, this is not the case for the highly unsaturated compounds collected in the last two rows of Scheme 5.1. From experience with other p-electron-rich systems, one would expect most of these parent systems to be very unstable and unisolable. Still, this has not prevented attempts to prepare

them. For example, allenetetrayne **11** has been proposed as a new building block for novel carbon allotropes [7] and the first precursors of this hydrocarbon have in fact been prepared (see Section 5.3.4), although the parent system has so far escaped all preparative efforts (see Section 5.3.4). Many of the compounds summarized in Scheme 5.1 offer themselves as components for cycloaddition reactions, and, indeed, these have been carried out successfully and led to interesting and important results (see Section 5.5).

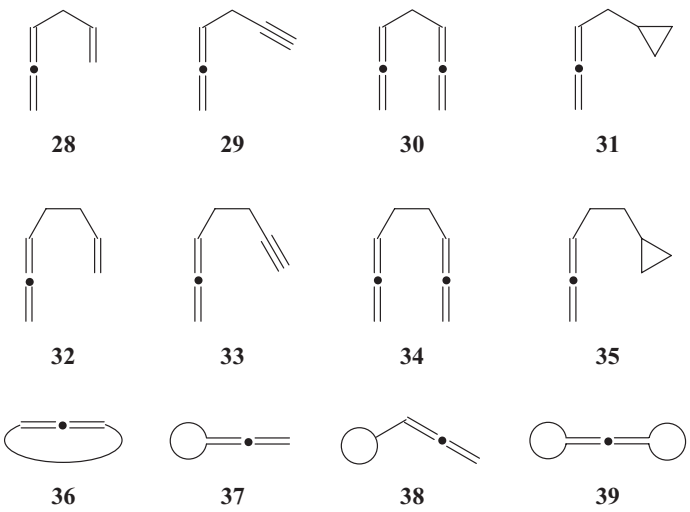
The structural variety increases if the second (and further) substituent(s) is (are) not bound to the allene nucleus. For vinylallene (**2**), the additional vinyl group can be introduced at C-5, leading to 1,2,4,6-heptatetraene (**22**; only *E*-isomer shown) or at C-4, providing 4-methylene-1,2,5-hexatriene (**23**), the former being an important substrate for cyclization reactions, as will be discussed in Section 5.5 (Scheme 5.2).



Scheme 5.2

Of course, the additional substituents need not be of the same type. Beginning with vinylallene (**2**) again and adding an ethynyl group, the four combinations **24**–**27** arise (Scheme 5.2). Again, the last hydrocarbon is an interesting substrate for cyclization reactions (see Section 5.5).

A direct connection between the allene group and another unsaturated functional group is no prerequisite for interesting chemical behavior, as illustrated for hydrocarbons **28**–**31** in Scheme 5.3, in which the allene unit and the above four substituents are connected either by a methylene group or by an ethano bridge, as for allenes **32**–**35**.



Scheme 5.3

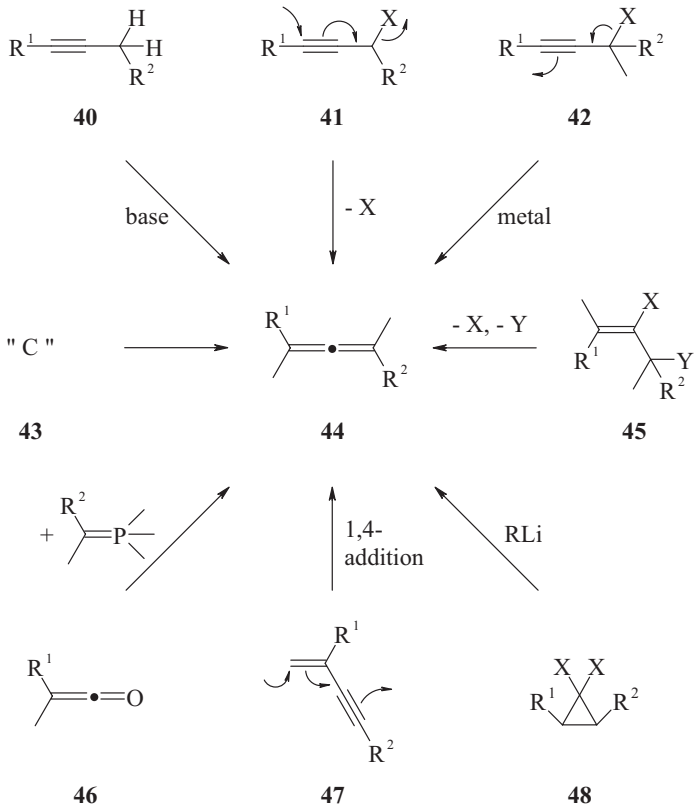
Most of these hydrocarbons have been prepared and their chemical behavior has been investigated. Many of them undergo mechanistically and preparatively interesting Cope-type isomerizations (see below).

The principle of this simple combinatorial game is obvious by now; it can be easily extended using other hydrocarbon building blocks. The three-membered ring, for example, can be enlarged and also be anchored to other positions of the allene element, of course, thus yielding ring structures such as **36–39**. However, these will not be discussed comprehensively in this Chapter to keep its limits acceptable. Besides, cycloallenes (**36**) are dealt with separately in Chapter 6.

5.3 Preparation of Allenic Hydrocarbons

5.3.1 General Methods

The number of fundamentally new preparative methods for synthesizing allenes has not increased significantly in the last two decades. Hence the by now classical routes summarized in Scheme 5.4 still form the main approaches to allenic hydrocarbons.



Scheme 5.4

Very often the carbon framework of the future allene is already present in the substrate and often it is propargylic in nature. For example, base-catalyzed isomerizations of acetylenic hydrocarbons – with the triple bond in a non-terminal (**40**) or terminal position – were often used to prepare allenic hydrocarbons in the early days of allene chemistry [8]. The disadvantage of this approach consists in the thermodynamic instability of the allenes produced: if not prohibited for structural reasons, the isomerizations do not stop at the allene but proceed to the more stable conjugated diene stage. In practice, complex mixtures are often formed [9] (see also Chapter 1).

When the propargyl derivatives carry a good leaving group, S_N2'-type substitutions can occur as symbolized by structure **41** in Scheme 5.4. Alternatively, as shown in **42**, the propargyl derivative may be employed for the preparation of a metal organic intermediate which can be trapped to the allene **44** out of its allenic form, the structure often preferred by propargylic organometallic compounds. Since allenes are a special type of olefins, it is hardly surprising that eliminations are also often used to prepare them. The substitution pattern of the starting material **45** is often encountered, but isomeric arrangements have also been used. The dehalo-

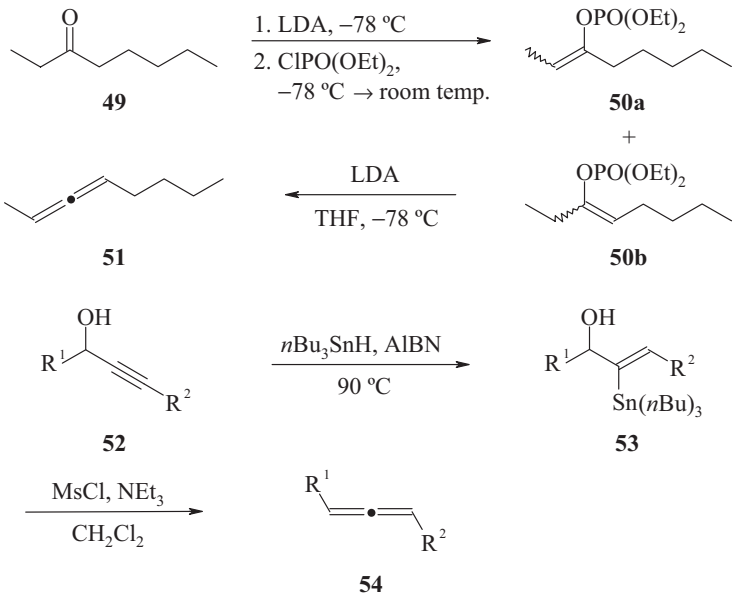
genation/rearrangement of 1,1-dihalocyclopropane derivatives **48**, the so-called Doering–Moore–Skattebøl synthesis (DMS synthesis of allenes) has also very often been exploited to prepare allenic hydrocarbons [2], whether they contain one or more allene groups or are acyclic or mono- or polycyclic (see Chapter 6). The reaction is accompanied by side-reactions, however (insertions, rearrangements), as has been pointed out again in a recent review devoted to the use of cyclopropane derivatives other than **48** for the preparation of allene derivatives [10, 11].

The 1,4-addition to conjugated enynes, symbolized by structure **47**, is of particular preparative value when organolithium compounds are added to the alkenyne and the resulting allenyl lithium derivative is quenched by a suitable electrophile [12]; if this is a proton, allenic hydrocarbons result, of course. Wittig and Wittig-type processes, **46** → **44**, are another import from olefin to allene chemistry. Both combinations, ketene plus methylenphosphorane – as shown – and ketone plus vinylidenphosphorane have been reported (see Section 5.3.7). With **43**, the 'naked' carbon atom, is meant the addition of atomic carbon to olefins on the one hand, a reaction known for a long time [13], but on the other hand also the use of certain C_1 reagents (CO_2, CCl_4, CBr_4, active methylene groups) that eventually provide the sp-carbon atom of the assembled allene group (see below). Needless to say, the above scheme is not complete; it does not mention, for example, the use of cycloreversions and fragmentations to prepare allenes [2], the synthesis of allenes from other allenes or their preparation by various photochemical routes [14].

In summary, a broad range of synthetic methods are available today to allow the synthesis of practically any required acyclic allenic hydrocarbon. We can therefore turn to the preparation of specific target molecules and we preferentially select these from the hydrocarbons collected in Schemes 5.1–5.3. Before doing that, however, some recent approaches to alkyl-substituted allenes are considered.

5.3.2
Alkylallenes

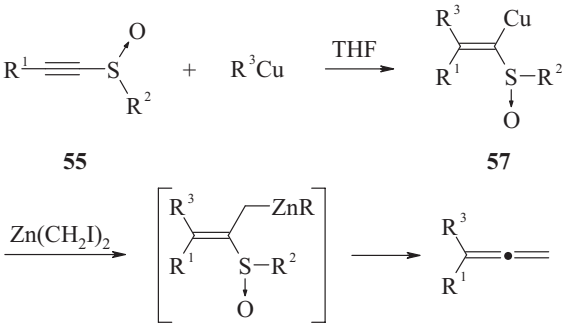
Many of the reactions assembled in Scheme 5.4 are of undiminished interest in modern allene chemistry when relatively simple alkyl derivatives are the preparative goal. For example, β-eliminations of enolphosphates prepared from saturated ketones constitute a simple route to 1,3-dialkylated allenes. Thus 3-octanone (**49**), on LDA treatment followed by quenching the generated enolate ions with diethyl chlorophosphate, affords a mixture of the enolphosphates **50**. When these are treated with further LDA in THF at low temperatures, 2,3-octadiene (**51**) is produced in 50% yield (Scheme 5.5) [15].



Scheme 5.5

In another elimination sequence, the propargyl alcohols **52** are first subjected to hydrostannation, a radical process, and the resulting vinylstannanes **53** are subsequently deoxystannylated by treatment with mesyl chloride in the presence of triethylamine (Scheme 5.5). In practically all cases the yields were in the range 70–80% and the two-step, one-pot process could also be applied to prepare chiral allenes of high enantiomeric purity from enantiomerically pure propargylic alcohols [16].

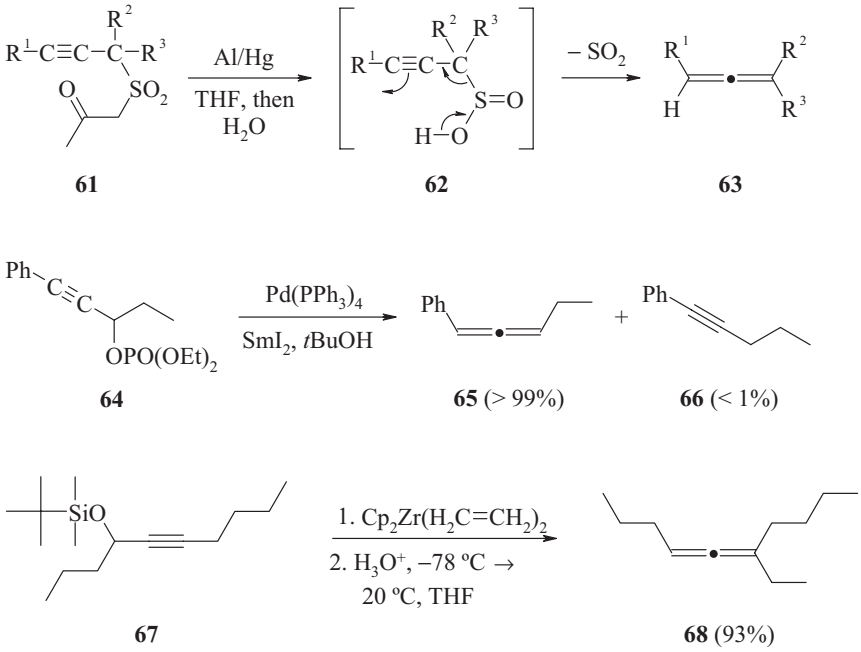
Sometimes the construction of the intermediate to undergo the β-elimination process appears to be fairly involved, but actually can often be carried out as a one-pot operation providing the desired allenes in excellent yield (65–95%), as illustrated in Scheme 5.6 by a new approach described recently [17].



Scheme 5.6

Here an alkynyl sulfoxide **55** is first carbocuprated with an organocopper reagent **56** to provide a vinylcopper intermediate **57**, which is then zinc homologated with the primary zinc sp^3-carbenoid **58** to yield the allylzinc intermediate **59**. This, in a spontaneous *syn*-β-elimination, gives the corresponding allene **60**. This protocol could also be adopted to the preparation of chiral allenes.

That propargylic starting materials are often employed in modern allene hydrocarbon chemistry is not surprising and the following examples are just a small selection from a much larger synthetic effort. Thus, the sulfones **61** are first cleaved in an aluminum amalgam-mediated reduction to the intermediates **62**, which lose sulfur dioxide under the reaction conditions and furnish the trisubstituted allenes **63** in good to excellent yields (75–95%) (Scheme 5.7) [18].



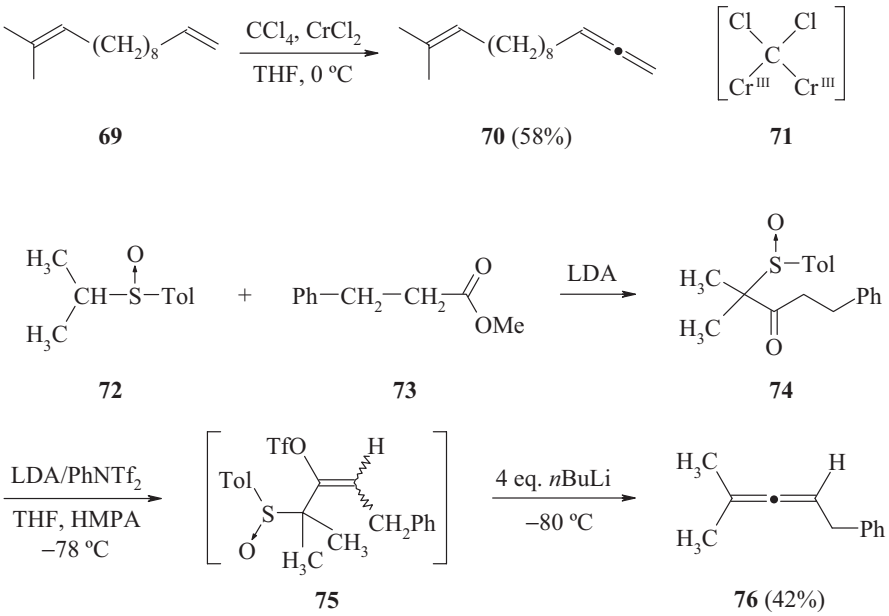
Scheme 5.7

In another reduction, the propargylic phosphate **64** is reduced with samarium(II) iodide in the presence of tetrakis(triphenylphosphine)palladium and *tert*-butanol as a proton source; the allene **65** is produced almost exclusively, <1% of the isomeric alkyne **66** being present in the product mixture [19].

Ethylene and styrene derivatives react with various propargylic silyl ethers in the presence of zirconocene(II) to afford allenic products in high yield (Scheme 5.7). For example, substrate **67** was transformed into the trisubstituted allene hydrocarbon **68** in 93% yield under the reaction conditions [20]. In the synthesis of various tetraalkylated allenes, in which several of the alkyl substituents also contained triple bonds, allowing these substrates to be cyclized intramolecularly into aromatic com-

pounds by treatment with $CpCo(CO)_2$, the coupling of propargylic mesylates with suitably functionalized cuprates is the decisive step [21].

As far as the construction of allenes from C_1 precursors (as discussed above regarding Scheme 5.4) is concerned, the transformations summarized in Scheme 5.8 are instructive.



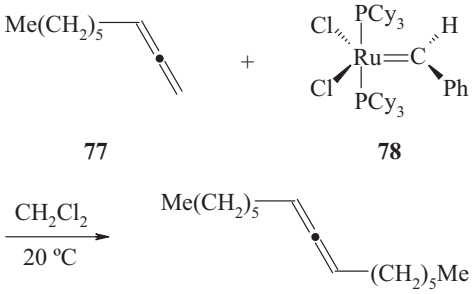
Scheme 5.8

When the diolefin **69** was treated with tetrachloromethane in the presence of a large excess of $CrCl_2$ (4 equiv.) in THF, the terminal allene **70** was produced in acceptable yield [22]. The process is thought to involve the dichlorocarbene equivalent **71** in which the electron-deficient center is stabilized by two Cr(III) ligands. It appears that this reactive intermediate selectively attacks terminal olefins to give the corresponding cyclopropylidene carbenoids that readily ring open to the corresponding allenes. Interestingly, when **69** is subjected to the DMS allene synthesis (see above), the more highly substituted olefinic double bond is converted into an allene group.

In the second example, one carbon atom of the future allene group is contributed by the sulfoxide **72**, which is first converted to the ketone **74** by LDA treatment followed by quenching of the resulting carbanion with methyl 3-phenylpropanoate (**73**). To convert the now complete carbon framework into a central allene unit, the enol triflate of **74**, intermediate **75**, is produced under the conditions given in the scheme. Ultimate butyllithium treatment of **75** then furnishes the alkylated allene **76** [23].

The olefin metathesis reaction apparently has rarely been applied to allene synthesis so far, or at least the potential of this important process has not been exploited

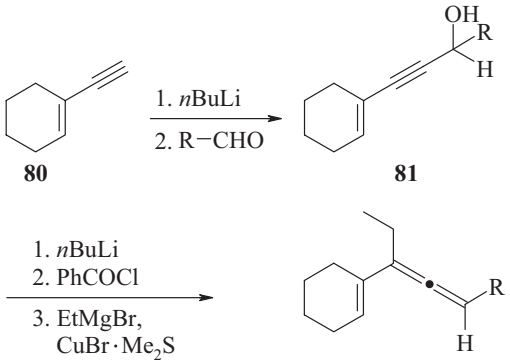
in this area of chemistry to any extent. Still, as shown in Scheme 5.9, the Grubbs catalyst **78** was shown to catalyze the cross-metathesis of the monosubstituted allene **77** to the 1,3-disubstituted derivative **79**. Although the yield for the preparation of other allenes was not as high as in this specific case (70%), the process clearly deserves further attention [24].



Scheme 5.9

5.3.3 Vinylallenes

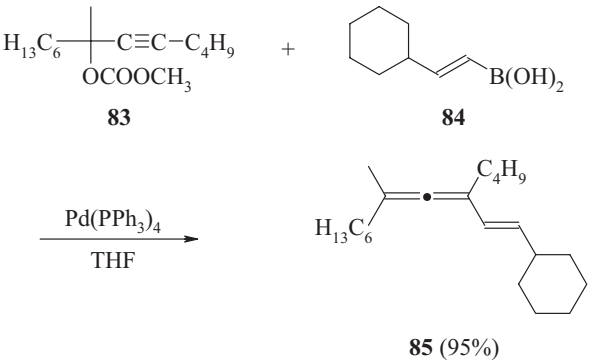
Among the conjugated allenes, vinylallenes belong to the most important ones because of their rich – and not at all fully explored – chemistry (see below). The parent molecule was prepared in 1958 by either coupling vinylmagnesium bromide with propargyl bromide [25] or by base-catalyzed isomerization of 1-pent-4-yne and stopping the process at the vinylallene stage [26]. Substituted vinylallenes have been obtained recently by conventional and by more modern protocols. An example of the former approach is described in Scheme 5.10, where 1-ethynylcyclohexene (**80**) is first converted into the propargyl alcohol **81**, which is subsequently esterified to allow a propargylic substitution with Grignard reagents to lead to the vinylallenes **81** (Scheme 5.10) [27].



Scheme 5.10

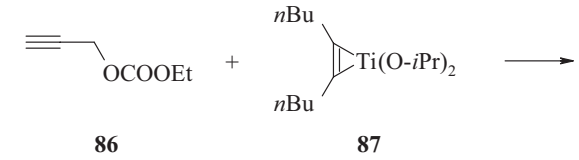
82 (R = Me, Ph)

Many of the modern vinylallene syntheses involve metal-mediated coupling reactions, as shown by several typical examples summarized in Scheme 5.11. The treatment of the propargyl carbonate **83** with the alkenylborane **84** in the presence of a palladium catalyst furnished the substituted vinylallene **85** in excellent yield (Scheme 5.11) [28].

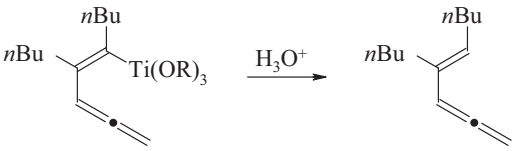


83 **84**

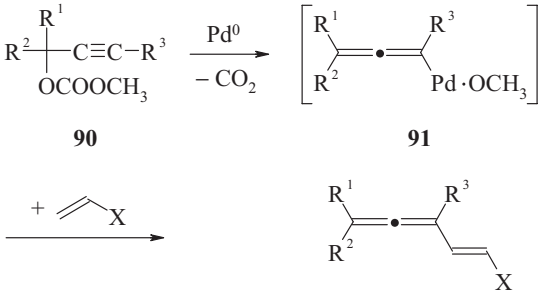
85 (95%)



86 **87**



88 **89**



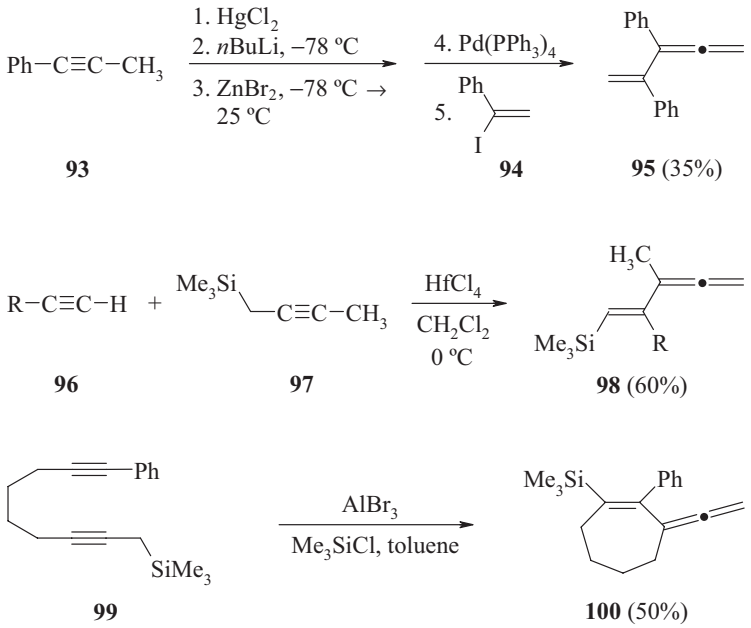
90 **91**

92

Scheme 5.11

In other examples, also involving propargyl carbonates, the parent derivative **86** was first coupled with **87** – obtained by reaction of 5-octyne with the titanium diisopropoxide – propene complex at –50 °C, providing the titanated vinylallene **88**, which on hydrolysis furnished the vinylallenes **89** in good yield [29]. Carbonate **90** in the presence of a Pd^0 catalyst readily decarboxylated and yielded the allenylpalladium intermediate **91**, which could be coupled with various vinyl derivatives to afford the vinylallenes **92**. Since X represents a functional group (ester, acetyl), functionalized vinylallenes are available by this route [30].

Various intermolecular coupling reactions involving acetylene hydrocarbons have been reported to lead to vinylallenes. For example, 1-phenylpropyne (**93**), after activation with Hg(II) chloride, is first metalated by butyllithium treatment, then transmetalated with zinc bromide and finally coupled with 1-iodo-1-phenylethene (**94**) in the presence of tetrakis(triphenylphosphine)palladium to provide the diphenylvinylallene **95** in moderate yield (Scheme 5.12) [31].



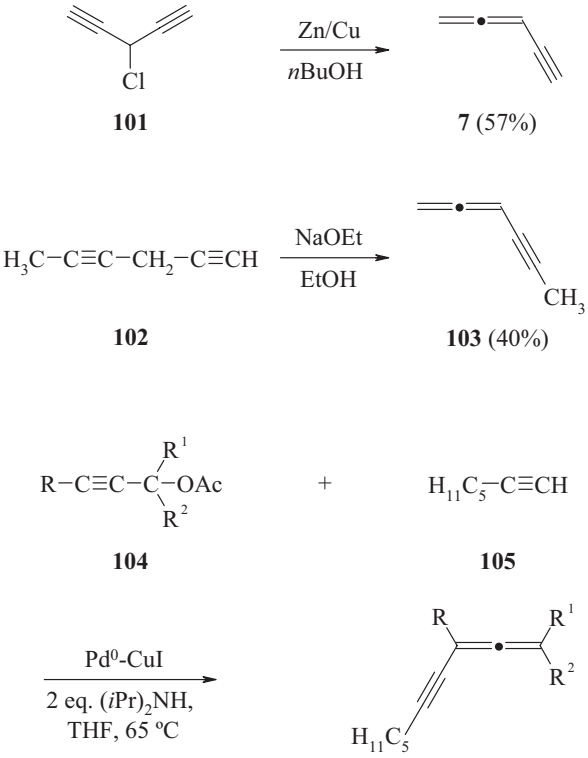
Scheme 5.12

When the terminal alkynes **96** are treated with the trimethylsilylalkyne **97** in the presence of $HfCl_4$ as a Lewis acid, the silylated vinylallenes **98** are produced in acceptable yields. In an intramolecular variant of this process, **100** was obtained from the diyne **99** [32]. Vinylallenes, incorporated into a cyclic framework and hence of restricted conformational mobility, are of interest for photochemical studies [33] and are among the photoproducts in ring-enlargement reactions of polycyclic allenes [34].

The higher vinylallenes **5** and **6** are apparently unknown.

5.3.4
Ethynylallenes

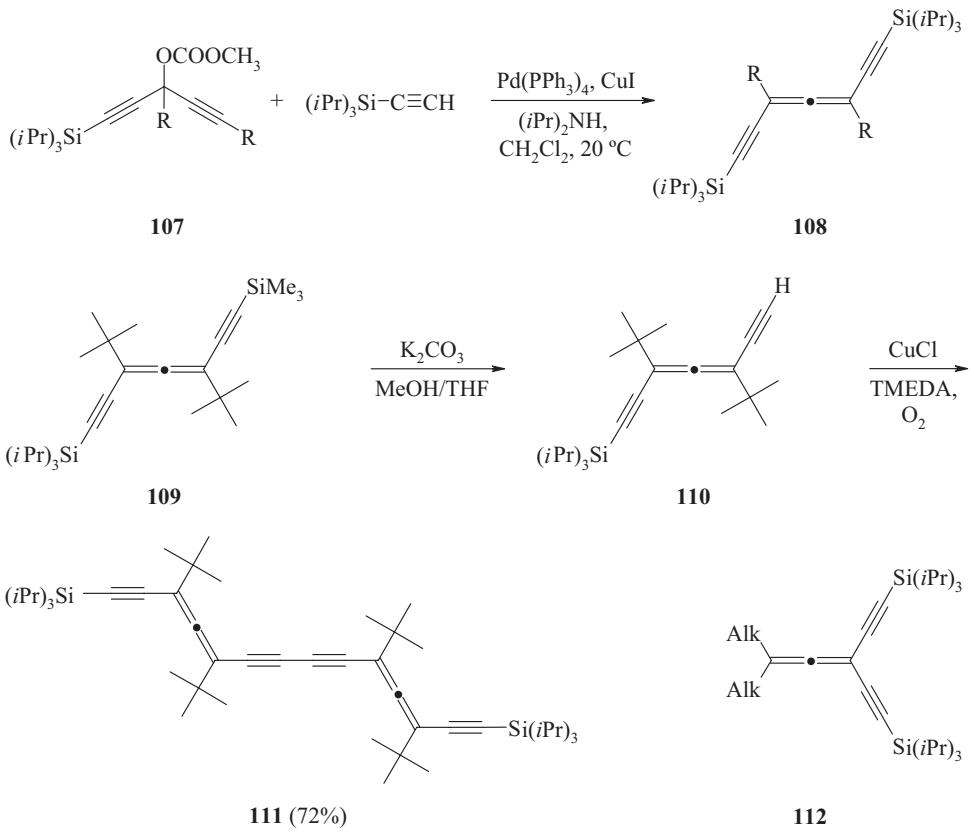
Ethynylallenes [35], the didehydro analogs of vinylallenes, have also been known for some time, the parent system **7** having been obtained in 1960 by reduction of 3-chloro-1,4-pentadiyne (**101**) with zinc–copper couple in butanol [36] and the 5-methyl derivative **103** by base-catalyzed isomerization of 1,4-hexadiyne (**102**) with sodium ethoxide in ethanol (Scheme 5.13) [9].



Scheme 5.13

With the recent increased interest in allene chemistry, these highly unsaturated hydrocarbons have also moved into focus again. For example, propargyl acetates **104** (or halides or tosylates) can be cross-coupled with terminal alkynes such as 1-heptyne (**105**) in the presence of a Pd^0 catalyst and cuprous chloride (Scheme 5.13) [37]. The resulting di- to tetraalkylated ethynylallenes are produced in 50–75% yield and even better results are obtained with propargyl chlorides and by working in benzene or toluene or even in pure diisopropylamine as the solvent (81%). In a similar approach, but starting from optically active propargyl carbonates, optically active ethynylallenes could be prepared in up to 85% *ee* [38].

1,3-Diethynylallenes, i.e. derivatives of the parent system **8** in Scheme 5.1, are obtained when the propargylic substrate already contains an additional triple bond as shown in Scheme 5.14. Here the bispropargyl carbonate **107** – for example with R = *n*-hexyl – is coupled with tris(isopropyl)silylacetylene to provide the protected hydrocarbon **108** in excellent yield (94%) [39, 40].



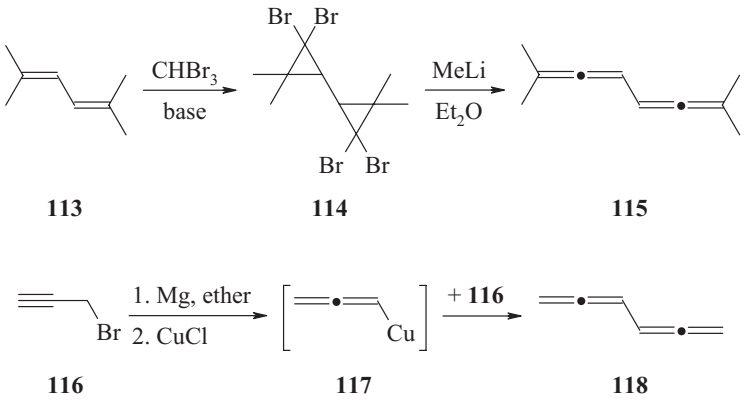
Scheme 5.14

With its two different protective groups, derivative **109** could be selectively deprotected to the 'free' acetylene **110** that, on Glaser–Hay coupling, furnished the highly unsaturated dimer **111** (72%), probably as a mixture of two diastereomers. Although comparable approaches to prepare derivatives of the parent hydrocarbon **10** and **11** (Scheme 5.1) have so far failed, with the protected 1,1-diethynylallene **112** a first representative of the cross-conjugated diethynylallene **9** could be synthesized [40].

5.3.5
Conjugated Bisallenes

Omitting conjugated bisallenes that are produced as reactive intermediates [41], basically two routes have been used to prepare this interesting class of hydrocarbons: the DMS method and coupling reactions of propargylic derivatives or substrates derived therefrom. Once a bisallene has been synthesized, it may be substituted/functionalized by exploiting the acidity of its allenic hydrogen atoms [42].

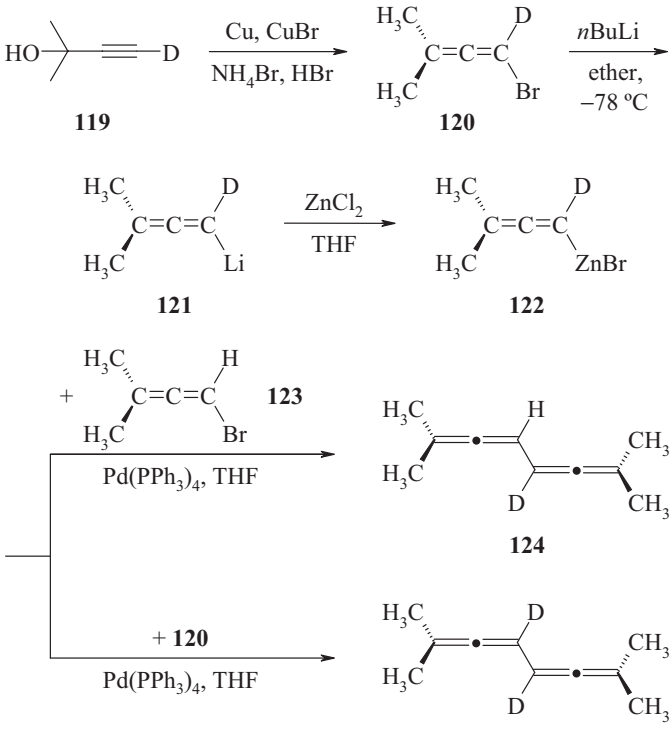
The classical examples of these two routes are the conversion of 2,5-dimethyl-2,4-hexadiene (**113**) via the bisdibromocarbene adduct **114** into the terminally fully methylated bisallene **115** (Scheme 5.15) [43] and the reductive coupling of propargyl bromide (**116**).



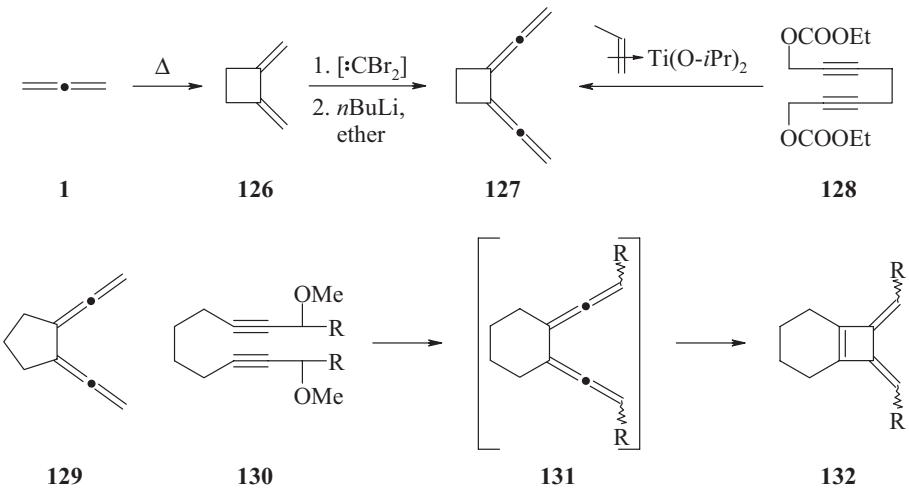
Scheme 5.15

To prepare the parent bisallene **118**, **116** is first converted into its Grignard reagent (known from spectroscopic studies to possess the allenic structure), from which, presumably, by the addition of cuprous chloride the organocopper intermediate **117** is generated. Addition of further **116** subsequently provides a mixture of **118** and propargylallene (1,2-hexadien-5-yne) (**29**) (see below) in a 2:3 isomer ratio [44].

In another route to (specifically deuterated) **115**, the 3-deuteriopropargyl alcohol **119** was converted to the bromoallene **120** first, which, on butyllithium treatment in diethyl ether, provided the allenyllithium intermediate **121** (Scheme 5.16) [45].



Scheme 5.16



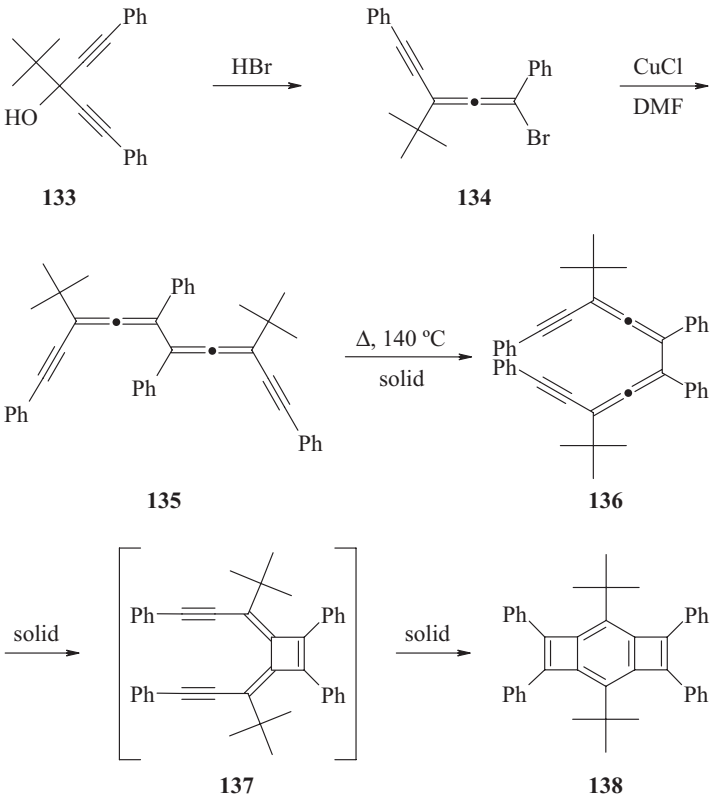
Scheme 5.17

After transmetalation of **121** with zinc chloride in THF, the resulting **122** could either be coupled with the undeuterated bromoallene **123** to the monodeuterio derivative **124** or with **120** to the dideuterated hydrocarbon **125**.

The conformationally locked [46] bisallene **127** was first prepared by subjecting the allene dimer **126** to the DMS allene synthesis (Scheme 5.17) [47].

In a more recent approach, the bispropargyl carbonate **128** was treated with (η^2-propene)Ti(O*i*Pr)$_2$ to provide **127** by a novel cyclization reaction. The method is general and can be applied to other tethered bispropargyl derivatives, thus providing cyclic allenes such as **129** and several of its derivatives. In the case of six- and seven-membered rings, bicyclic bismethylencyclobutenes were obtained, presumably via bisallenic intermediates as illustrated in the sequence **130** → **131** → **132** (Scheme 5.17) [48].

Remarkable single-crystal to single-crystal interconversions could be observed with various highly substituted and hence stable bisallene derivatives (Scheme 5.18). Thus, hydrocarbon **135**, a chiral bisallene, obtained by treating the tertiary alcohol **133** with hydrobromic acid and dimerizing the resulting allenic bromide with cuprous chloride in DMF, is first converted from its *s-trans* conformation **135** into the *s-cis* form **136** on heating in the crystalline state [49, 50].



Scheme 5.18

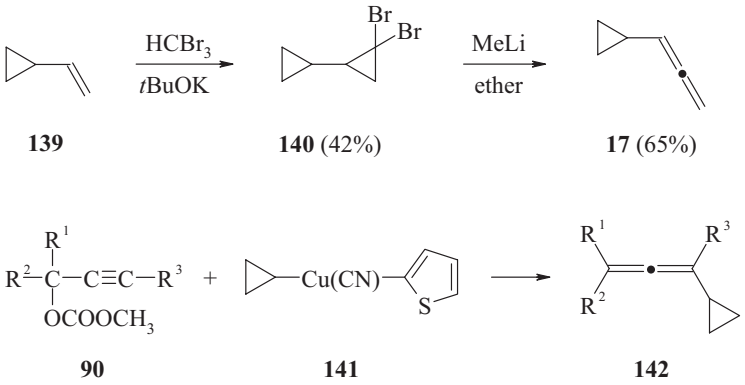
Hydrocarbon **136** subsequently cyclizes to a bismethylencyclobutene again, **137**, in which the triple bonds of the substituent are so close that they can engage in a [2 + 2] cycloaddition, leading to the doubly annelated hydrocarbon **138**. For less highly unsaturated bisallenes, a similar behavior is observed and they allowed the determination of the stereochemistry of the first ring-closure step [51].

Although conjugated bisallenic hydrocarbons display a rich chemistry (see Section 5.5), more and more functionalized derivatives are being described in the chemical literature [52, 53].

Not surprisingly, the higher bisallenes **15** and **16** are unknown.

5.3.6
Cyclopropylallenes

Generally, cycloproylallenes are prepared by the same methods as employed for the synthesis of other allenic hydrocarbons. Thus, cyclopropylallene (**17**) itself has been obtained from vinylcyclopropane (**139**) via its dibromocarbene adduct **140** using the DMS method (Scheme 5.19) [54].

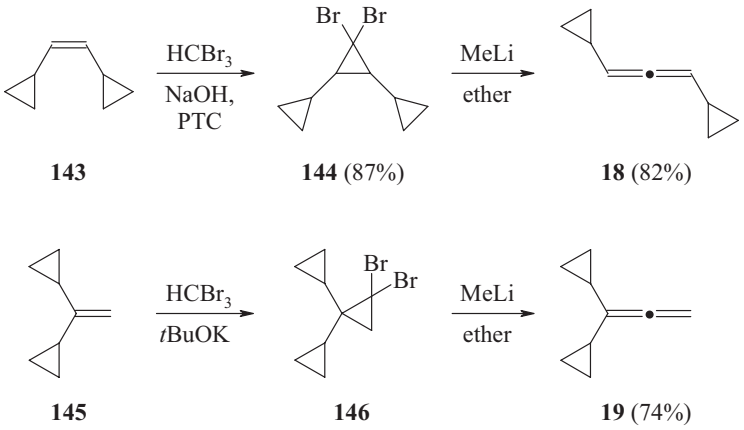


Scheme 5.19

With substituted vinylcyclopropanes, the corresponding cyclopropylallenes are formed in comparable yields [55].

A richer structural variety is realized when the propargyl carbonates **90** are treated with cyclopropyl(cyano)thienyl cuprates [56] such as **141**, allowing the preparation of allenes with up to four different substituents (Scheme 5.19) [57].

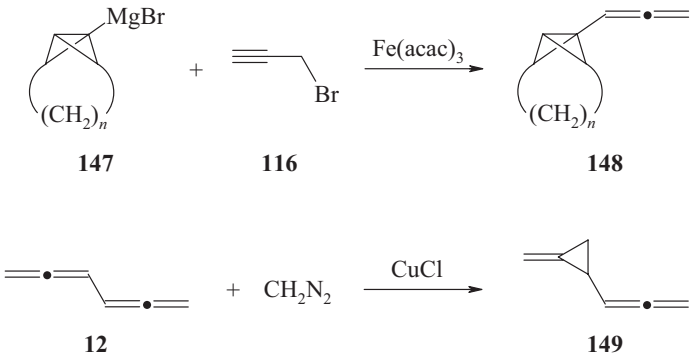
An efficient new synthesis of 1,3-dicyclopropylallene (**18**) (overall yield 68%) has been developed starting from dicyclopropylacetylene. This hydrocarbon was first reduced to the olefin **143**, which was subsequently converted via **144** into the target molecule (Scheme 5.20) [58].



Scheme 5.20

The 1,1-isomer **19** was prepared from 1,1-dicyclopropylethene (**145**) via **146** by an analogous route by different workers who have also studied its chemical behavior [59].

Among the more exotic cyclopropylallenes, the polycyclic hydrocarbons **148** ($n = 2, 3$) may be cited, which are available by coupling the Grignard reagents **147** with propargyl bromide (**116**) in the presence of various metal catalysts, $Fe(acac)_3$ leading to the highest yields (Scheme 5.21) [60].



Scheme 5.21

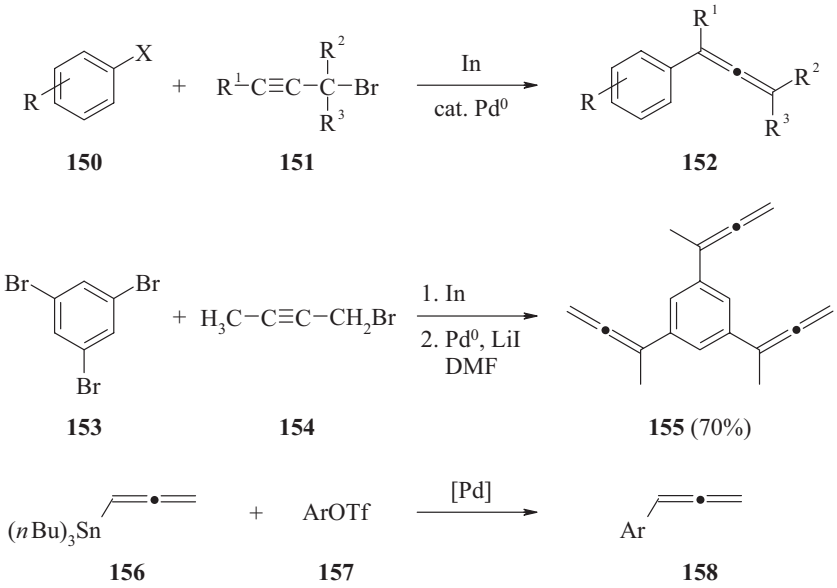
In principle, the direct cyclopropanation of vinylallenes and related substrates also allows the preparation of cyclopropylallenes. However, because of low or no discrimination between the differrent double bonds, complex product mixtures are to be expected. A case in point is provided by 1,2,4,5-hexatetraene (**12**), which yields the cyclopropylallene **149** on diazomethane/CuX treatment – but only in a (difficult to separate) mixture with all other cyclopropanation products of **12** (Scheme 5.21) [61].

No attempt seems to have been undertaken to prepare the cyclopropylallenes **20** and **21**.

5.3.7
Arylallenes

Allenes carrying aryl substituents constitute probably the largest known group of allenic hydrocarbons. The reason is simple: aryl substituents stabilize the allene group considerably, hence make the preparation and especially the separation and purification of arylallenes easier than those of other allenic hydrocarbons, especially when the latter carry highly unsaturated substituents. Although the methodological variety for preparing this group of allenes has increased considerably in modern times, often the same preparative principles as in classical allene synthesis and summarized in Scheme 5.4 in Section 5.3.1 are employed. This will be illustrated by the following examples that have been published recently.

In an indium-mediated process, the aromatic substrates **150** (X = Br, I, OTf) can be coupled in the presence of catalytic amounts of a Pd^0 catalyst with the propargyl bromides **151** to yield the arylallenes **152**, the reaction most likely proceeding via an allenylindium intermediate (Scheme 5.22) [62].

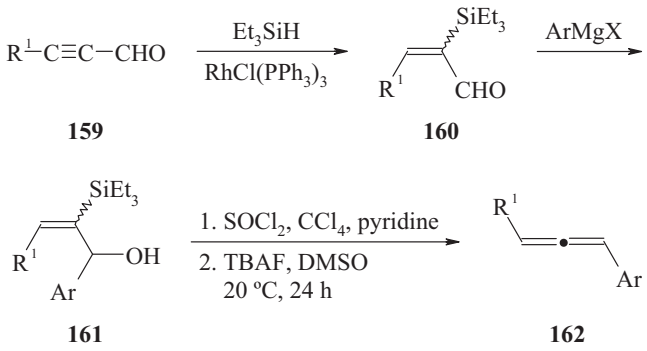


Scheme 5.22

Changing to a trisubstituted aromatic precursor such as 1,3,5-tribromobenzene (**153**) yields the trisallene **155** when 1-bromo-2-butyne (**154**) is used as the coupling partner. When leaving groups of different reactivity are present in the aromatic substrate, such as in 1-bromo-4-iodobenzene, different propargyl halides can be connected to the aromatic core, resulting in the formation of arylallenes with different allene substituents.

In a reaction analogous to a Stille coupling, *n*-tributylallenylstannane (**156**) is cross-coupled in the presence of a palladium catalyst to various aryltriflates **157** to furnish the arylallenes **158** in yields between 20 and 70% (Scheme 5.22) [63].

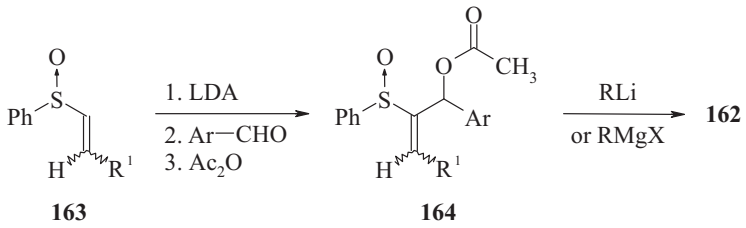
β-Elimination routes are also popular in this area of allene hydrocarbon chemistry. For example, hydrosilylation of ynals **159** with triethylsilane in the presence of a rhodium catalyst leads to the α-triethylsilylenals **160** (Scheme 5.23) [64].



Scheme 5.23

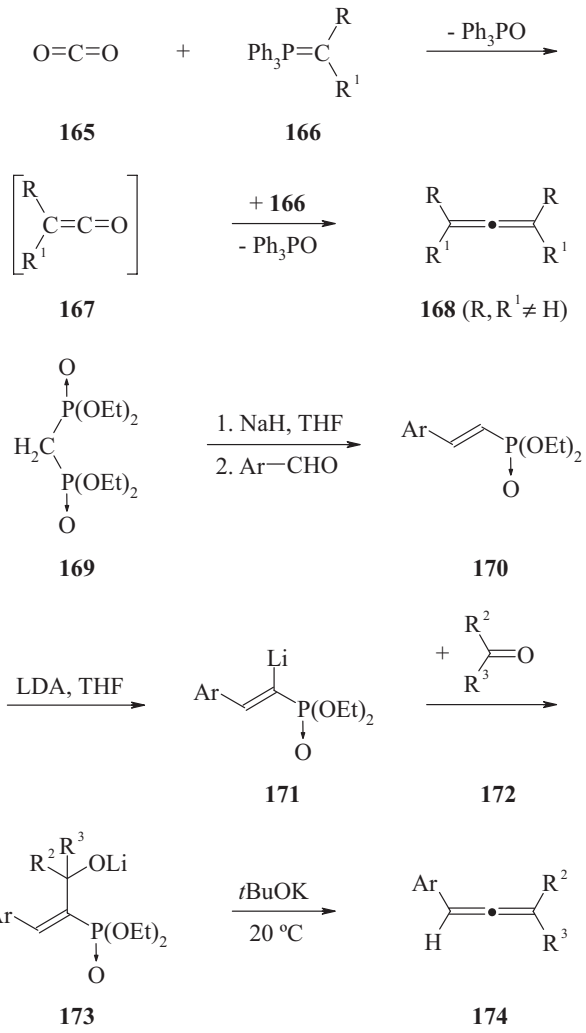
Subsequent addition of aryl Grignard reagents then provides the secondary alcohols **161**, which easily undergo elimination under the conditions shown in the scheme to provide the 1,3-disubstituted allenes **162** in excellent yields (~90%).

Likewise, the sulfoxide–metal exchange reaction of β-acetoxy sulfoxides **164** (β-mesyloxy sulfoxides can also be used), which are prepared from alkenyl aryl sulfoxides **163** and aromatic aldehydes, with a Grignard or alkyllithium reagent at low temperatures gives the allenes **162** in good to excellent yield (Scheme 5.24) [65].



Scheme 5.24

The concept of employing three components, all of which contribute one carbon atom to the final allene unit (see Scheme 5.4), is illustrated in its purest form by the reaction of carbon dioxide (**165**) with 2 equiv. of an alkylidenetriphenylphosphorane **166**, the process very likely involving the generation in the first step of a ketene intermediate **167**, which subsequently reacts with further **166** to yield the allene product **168** (Scheme 5.25) [66].

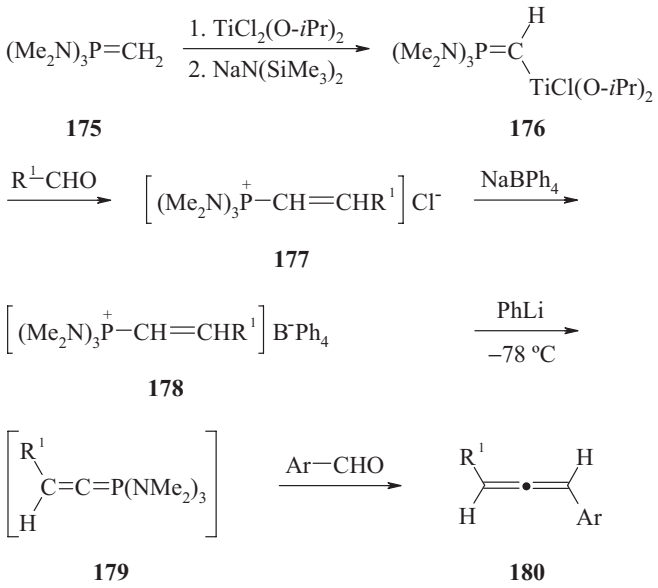


Scheme 5.25

The nature of the reagent eventually providing the central carbon atom of the allene unit, the ylid and the ketene intermediate have been varied considerably over the years, as shown by the following selection of examples.

When methylene bisphosphonate (**169**) is reacted in a Horner reaction with an aromatic aldehyde, the alkenyl phosphonate **170** is produced (Scheme 5.25). By metalation with LDA in THF, this is converted to the vinyllithium intermediate **171** that, with the ketone **172**, affords a Baylis–Hillman reaction-type product, **173**; on base treatment, this is converted to the arylallene **174** [67].

The titanated ylid **176** has been prepared from the phosphorane **175** under the conditions shown in Scheme 5.26 [68].



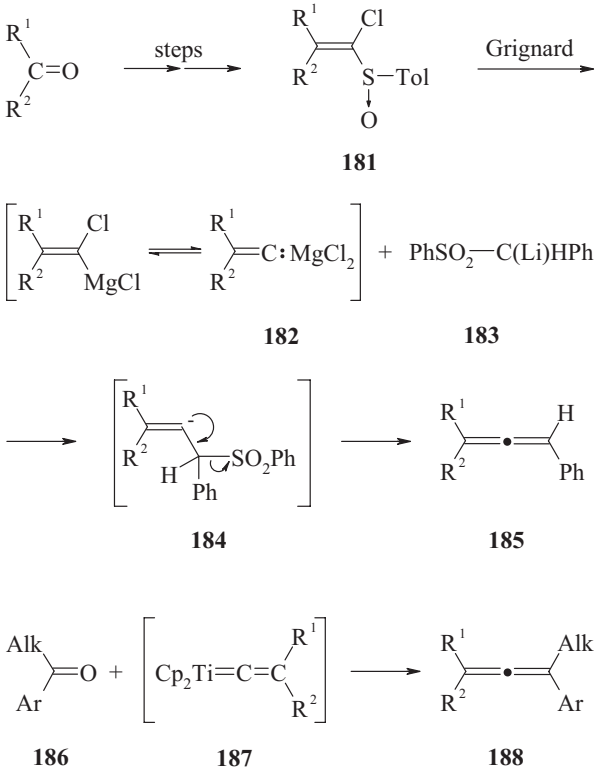
Scheme 5.26

Reaction with a first aldehyde transforms **176** into the vinylphosphonium chloride **177**, which for practical reasons is subjected to an anion-exchange process, leading to the phosphonium salt **178**. From this, phenyllithium treatment liberates the allenic phosphorane **179**, an intermediate that has previously been used to prepare allenes from aldehydes [69], in the present case providing the products **180**. The same protocol has also been applied to *o*-alkynylbenzaldehydes to yield allenes of interest as model compounds for the study of Schmittel and Myers-type cyclization reactions [70].

In another three-component process, 1-chlorovinyl *p*-tolylsulfoxides **181** are first prepared from ketones (Scheme 5.27) [71].

Treating **181** with a Grignard reagent causes sulfoxide–magnesium exchange and produces the magnesium alkylidene carbenoids **182**. When the latter are intercepted by lithiated sulfones **183**, the allenes **185** are produced via **184** in average to good yield.

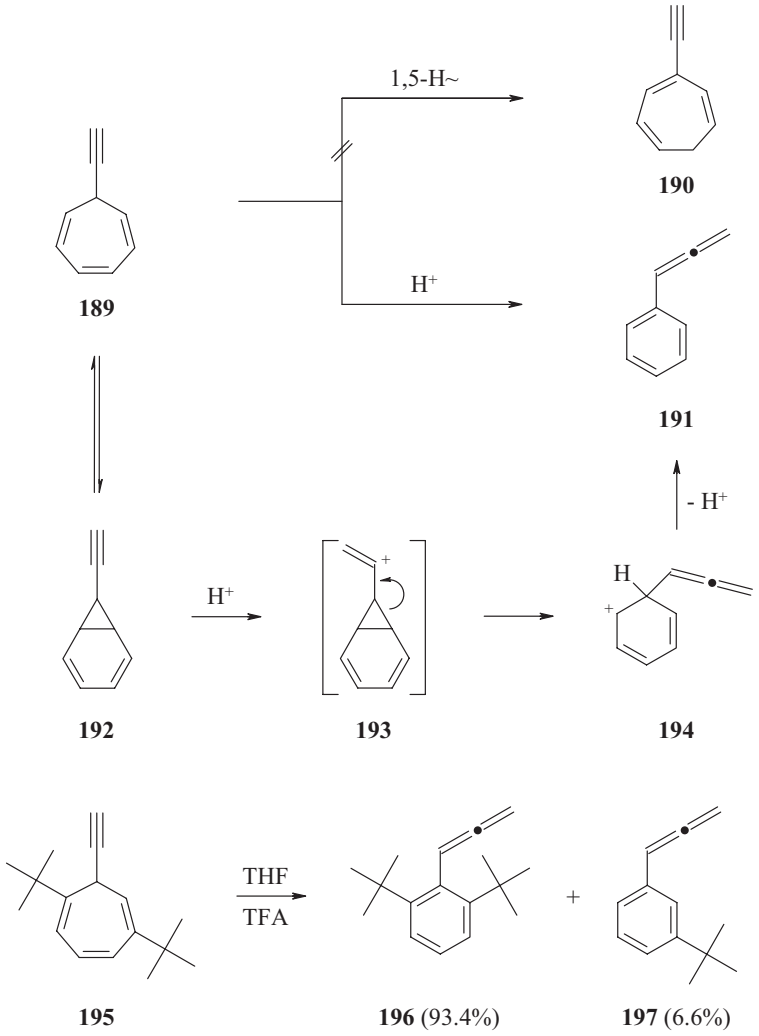
The titanocene alkylidene complex **187** may be regarded formally as a metal equivalent of a ketene; it requires no further activation and reacts directly with aromatic ketones **186** to give the arylallenes **188** (Scheme 5.27) [72], the yields being excellent (80–90%).



Scheme 5.27

This section concludes with a curious transformation, the isomerization of 7-ethynylcycloheptatrienes to arylallenes. For example, the parent system **189**, rather than undergoing a 1,5-hydrogen shift to **190**, rearranges to phenylallene (**191**) in the presence of acid (Scheme 5.28) [73].

It appears likely that this ring contraction reaction begins with a cycloheptatriene → norcaradiene cyclization, **189** → **192**, followed by protonation of the triple bond and acid-catalyzed ring opening as shown in **193**; the resulting cation **194** finally aromatizes to **191** by proton loss. Analogously, the di-*tert*-butyl derivative **195** cyclizes to **196** and **197** in the presence of trifluoroacetic acid in THF, the formation of the latter hydrocarbon obviously requiring the loss of a *tert*-butyl substituent.



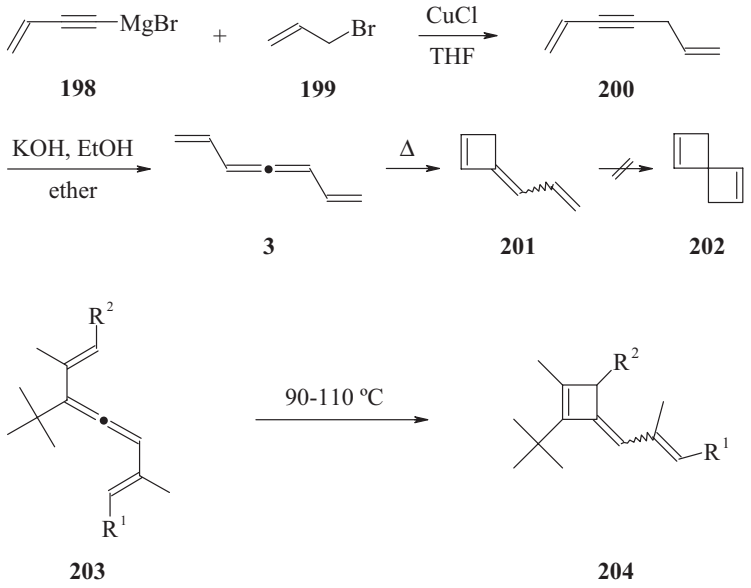
Scheme 5.28

5.3.8
Allenes Carrying Other Unsaturated Substituents

A large number of allenes are known in which the unsaturated substituents possess a different structure than in the cases discussed so far. Rather than trying to be comprehensive, a number of representative cases will be discussed.

Beginning with vinylallene (**2**) as a prototype, four 'double bond extended' hydrocarbons can be constructed: **3**, **4**, **22** and **23**. They have all been prepared and characterized or generated as reactive intermediates.

The chiral 1,3-divinylallene (1,3,4,6-heptatetraene) (**3**) is obtained when the vinylacetylene Grignard reagent **198** is first coupled to allyl bromide (**199**) and the resulting skipped enyne is subsequently isomerized under basic conditions (Scheme 5.29) [74].

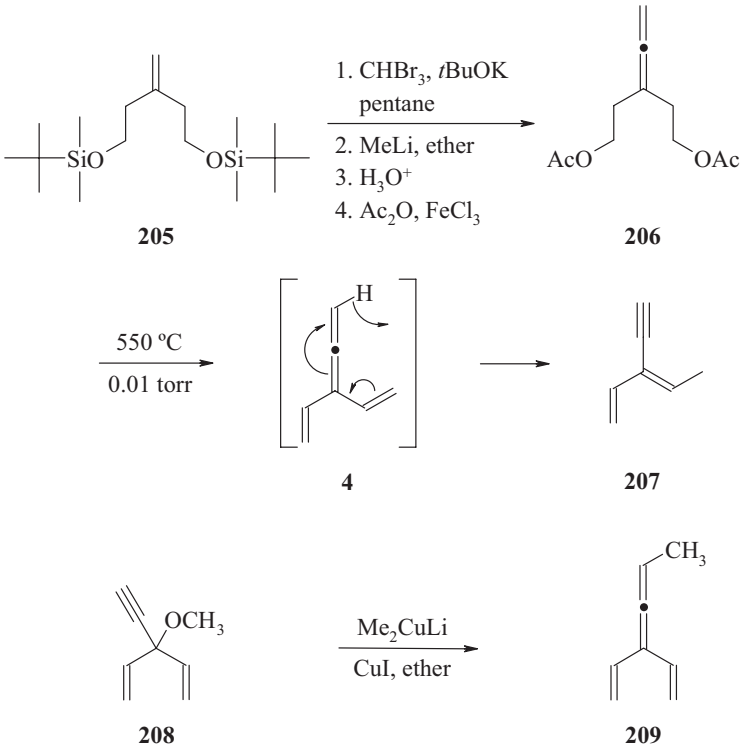


Scheme 5.29

Higher alkylated derivatives of **3** have recently been prepared and their thermal ring closure has been investigated. Formation of methylencyclobutenes (see below) takes place at the sterically more congested vinylallene subunit as shown by the formation of **204** from **203**, the process displaying a high torquoselectivity [75]. As for the parent compound, the cyclization stops at the monocyclic stage, e.g. both **201** and **204** do not cycloisomerize further to their spiro isomers, such as **202** [74].

To prepare the cross-conjugated isomer 3-vinyl-1,2,4-pentatriene (**4**), the route summarized in Scheme 5.30 was taken [76]. Starting with the protected bishomoallyl alcohol **205**, its double bond was first extended to an allene group by the DMS method. Hydrolysis and esterification of the resulting diol then provided the bisacetate **206**, which was pyrolyzed at 550 °C under flash vacuum conditions.

Unfortunately, the desired **4** undergoes a 1,5-hydrogen shift reaction at these high temperatures to yield **207** as the only diastereomer. Since vinylallene (**2**) rearranges under comparable conditions to (*Z*)-2-penten-4-yne (see below) [77], it appears reasonable to postulate the intermediate generation of **4**. That 1,1-divinylallenes are isolable under milder conditions was demonstrated by the preparation of the methyl derivative **209**, which is produced when the highly unsaturated ether **208**



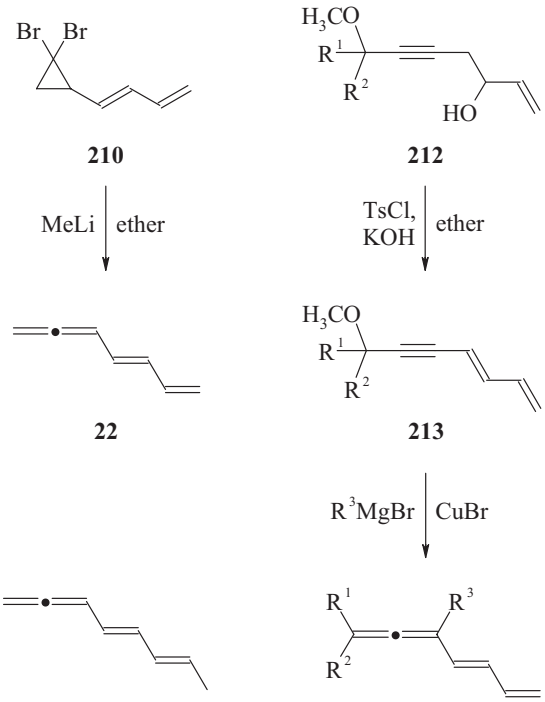
Scheme 5.30

is treated with lithium dimethylcuprate in diethyl ether, product **209** being a highly instable, yet characterizable hydrocarbon [76].

The other possible linear vinylallene vinylog, 1,2,4,6-heptatetraene (**22**), has been prepared by the DMS route from the mono dibromocarbene adduct to 1,3,5-hexatriene, **210** [78], practically simultaneously with the methyl derivative **211** [79] and several higher alkylated derivatives of **22**, **214** (Scheme 5.31) [80].

The reaction sequence to the latter hydrocarbons is the most flexible one and starts from the allenic alcohols **212**, which are first converted to the 1,3-hexadien-5-ynes **213** by an elimination reaction; the allene group is then generated by a propargylic rearrangement initiated by the addition of a Grignard reagent.

Many hydrocarbon derivatives of **22** have since been prepared [81, 82]; they are mostly of interest because of their thermal cyclization reactions (see below) [8, 83, 84], although their behavior in cycloaddition reactions could also lead to new preparative insights [79].



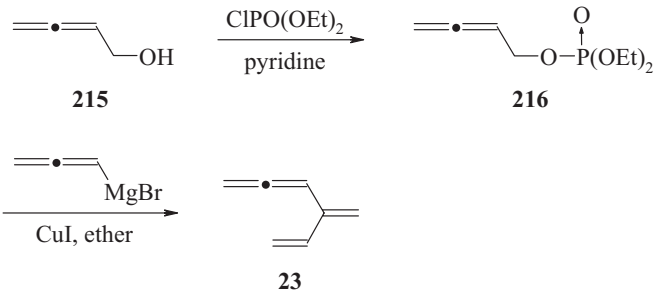
Scheme 5.31

To prepare the other cross-conjugated allene, 4-methylene-1,2,5-hexatriene ('2-allenyl-1,3-butadiene') (**23**), the allene alcohol **215** was first converted into the phosphate **216**, that readily underwent an S_N2'-type substitution with allenylmagnesium bromide to yield the target hydrocarbon as a highly reactive allene derivative (Scheme 5.32) [76].

Of the four 'ethynylated' vinylallenes **24**–**27** (Scheme 5.4), only the last one has received attention so far; in fact, all other combinations of the vinylallene framework and a triple bond appear to be unknown.

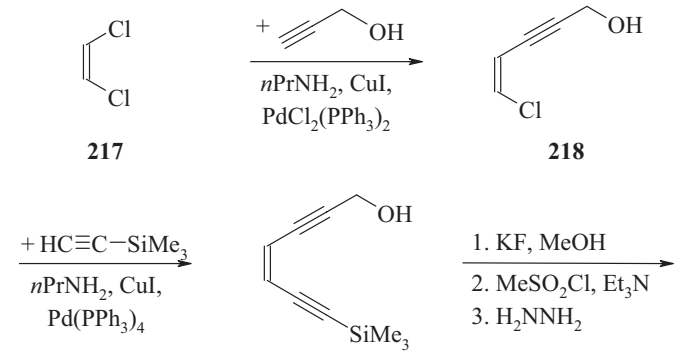
The acetylene **27** became of interest since it undergoes a novel type of thermal cyclization reaction, later to be called the Myers or Myers–Saito cyclization (see Chapter 20 for a discussion of its relevance). The *Z*-diastereomer of 1,2,4-heptatrien-6-yne (**27**) was prepared by the sequence summarized in Scheme 5.33 [85].

Coupling of excess (*Z*)-1,2-dichloroethene (**217**) with propargyl alcohol first led to the enyne **218**, which, when subjected to a second Pd-catalyzed coupling step with trimethylsilylacetylene, provided the 'mixed' diacetylene **219**. With all carbon atoms assembled, the allene function was generated by first producing the (unprotected) hydrazine derivative **220**, which on treatment with either diethyl azodicarboxylate (DEAD) or 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) under anaerobic conditions at 0 °C yielded the hydrocarbon **27**. According to mechanistic studies, the latter process leads first to a mixture of (*E*)- and (*Z*)-diazenes. Sigmatropic elimination of

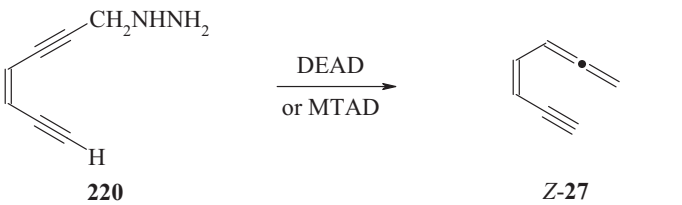


215 **216** **23**

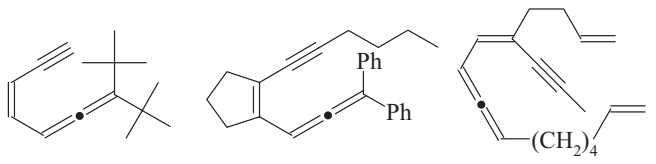
Scheme 5.32



217 **218** **219**



220 ***Z*-27**



221 **222** **223**

Scheme 5.33

nitrogen from the *Z*-diastereomer forms the allene **27** directly, whereas the *E*-isomer must first undergo a rate-limiting $E \rightarrow Z$-isomerization [86].

In later studies by various groups, the enyneallene motif was incorporated into more complex hydrocarbon structures, allowing not only a better understanding of the Myers cyclization but also the generation of polycyclic hydrocarbons, some of them resembling the steroid core unit. Conceptually, these latter cyclizations are reminiscent of Johnson's biomimetic cyclization reactions with the main difference that here radical intermediates are involved rather than carbocations. Typical starting materials in these studies are the allenes **221** [87], **222** [88] and **223** [89], their cyclization behavior being discussed in Chapter 20.

As in the other 'extensions' of vinylallene (**2**), there are also four ways to connect an additional allene group to **2**, of which two apparently have been described in the chemical literature.

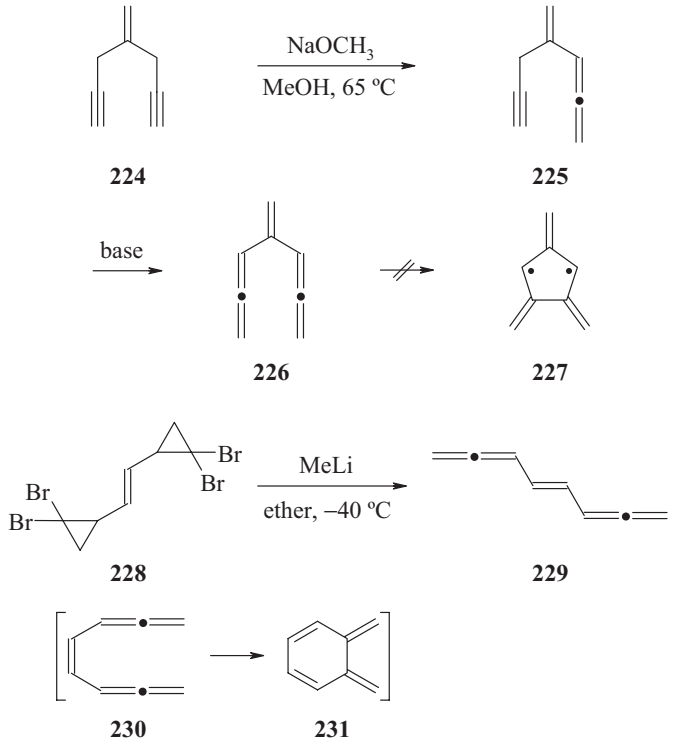
The cross-conjugated bisallene **226** is obtained when the diacetylene **224** is treated with potassium *tert*-butoxide in THF at –78 °C for 30 min (Scheme 5.34) [76].

Presumably the reaction takes place via the monoallene **225**, which can be made the sole isomerization product if the rearrangement is carried out with sodium methoxide in methanol at 65 °C (yield 60%) [76]. The intended intramolecular [2 + 2] cycloaddition to the diradical **227**, a hybrid of trimethylenemethane and tetramethyleneethane, could so far not be detected.

The linear isomer of **225**, (*E*)-1,2,4,6,7-octapentaene (**229**), is formed in addition to other products on treatment of the bisdibromocarbene adduct to (*E*)-1,3,5-hexatriene with methyllithium in diethyl ether at –40 °C; like **226**, it is a highly unstable hydrocarbon [90]. Several attempts to characterize the *Z*-isomer **230** [90, 91] also met with failure. Although very likely generated as an intermediate in these experiments, **230** immediately cyclized to *o*-xylylene (**231**), which can be trapped, e.g., as a Diels–Alder addition product.

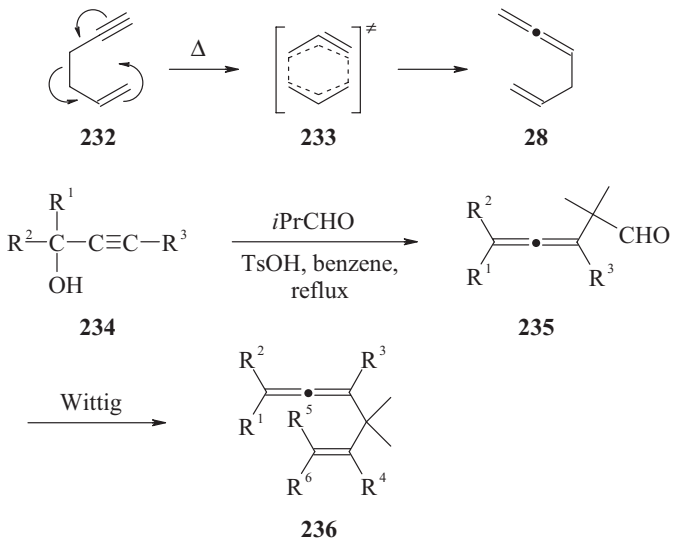
When one begins to separate the allene group from other unsaturated functional groups within the same molecule by inserting saturated carbon atoms, as demonstrated for hydrocarbons **28**–**35** in Scheme 5.3, one would expect chemical interactions (bond formation) between the respective p-systems as long as the separator unit or linker does not precede C_3 (propane), but to fall off quickly once the distance between these groups becomes larger. This is indeed the case and for many years there has therefore been interest in synthesizing skipped and/or C_2- and C_3-separated allenes. Again, the discussion presented here makes no attempt at being comprehensive but just mentions a number of characteristic cases.

The skipped enallene **28** is easily prepared by gas-phase pyrolysis of 1-hexen-5-yne (**232**), which under high-temperature conditions undergoes a Cope-type isomerization via transition state **233** (Scheme 5.35) [41, 92].



224 **225** **226** **227** **228** **229** **230** **231**

Scheme 5.34

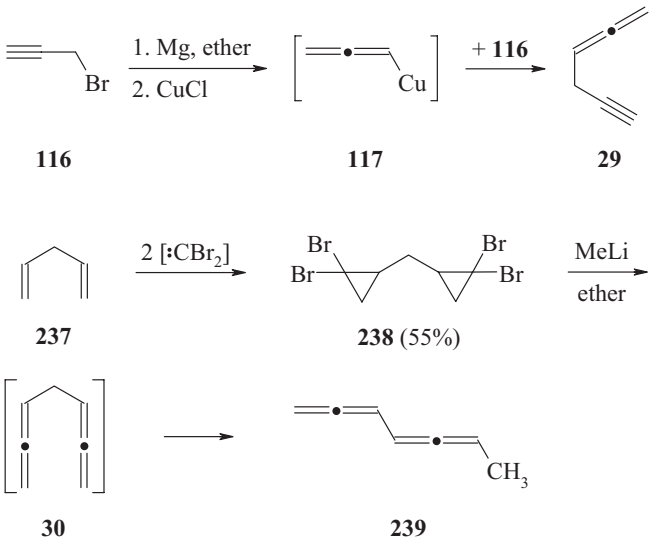


232 **233** **28** **234** **235** **236**

Scheme 5.35

More highly substituted (alkylated) derivatives of **28** are available when the propargyl alcohols **234** are first reacted with isobutyraldehyde and the resulting hemiacetals are dehydrated by in situ treatment with *p*-toluenesulfonic acid. The enol ether produced subsequently undergoes a Claisen-type isomerization yielding the allenic aldehyde **235**. This can either be converted directly into **236** by a Wittig reaction or subjected to a Grignard reaction followed by PCC oxidation. The ketones produced can be easily transformed into a (more highly) substituted derivative of **236** by another Wittig reaction [93].

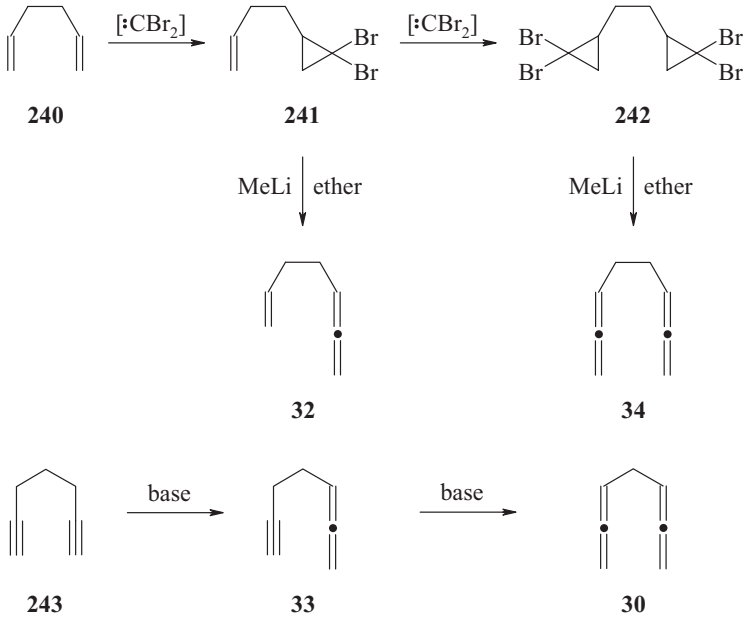
Propargylallene (1,2-hexadien-5-yne) (**23**) is the other main product obtained when the allenyl copper reagent **117** is coupled with propargyl bromide (**116**; see above) (Scheme 5.36) [44, 94].



Scheme 5.36

1,2,5,6-Heptatetraene (diallenylmethane) (**30**) is produced in 1% yield in the base-catalyzed isomerization of 1,6-heptadiyne (**243**; see below). Its preparation from the bisdibromocarbene adduct **238** to 1,4-pentadiene (**237**) failed: rather than **30**, its isomerization product **239**, a derivative of **12**, was isolated [95] in poor yield and was accompanied by 1- and 6-methylfulvene, respectively [96].

The next higher homologs of **28**–**30** have all been prepared without difficulty as shown in Scheme 5.37. Single and double addition of dibromocarbene to 1,5-hexadiene (biallyl) (**240**) leads to the adducts **241** and **242**, respectively, which on methyllithium treatment are debrominated/rearranged to **32** and **34** in the usual way [43, 96, 97].



Scheme 5.37

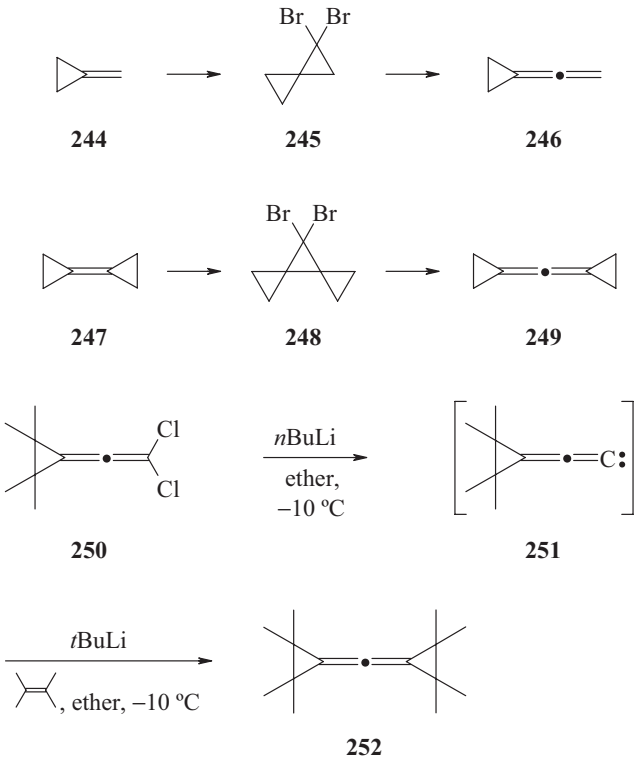
The dienyne **33** is produced by base-catalyzed isomerization of 1,6-heptadiyne (**243**) [98] in a mixture with other C_7H_8 hydrocarbons, among them traces of diallenylmethane (**30**). The still higher homolog 1,2,7,8-nonatetraene has also been described [99].

Apparently neither the cyclopropane derivative **31** nor **35** has been reported in the chemical literature.

5.3.9
Semicyclic Allenic Hydrocarbons

In semicyclic allenic hydrocarbons, one of the terminal allene carbon atoms is part of an alicyclic ring system, as illustrated by the general structure **37** in Scheme 5.3. Numerous hydrocarbons of this type are known, some of them carrying more than one allene group, such as in the case of the conjugated bisallenes **127** and **129** (see Scheme 5.17), and many of them are described in the review literature [2] and will not be repeated here. However, since Chapter 6 on cycloallenes does not treat these derivatives, some new developments in this area will be briefly presented, limited to the two cases in which cyclopropane rings form the end groups of the allene moiety, i.e. **246** and **249**.

Both hydrocarbons have been known for some time, having been prepared from **244** via **245** [100] and from **247** via **248** [101] by the DMS approach (Scheme 5.38).



Scheme 5.38

However, more recent reinvestigations have shown the process to be more complex, its outcome (formation of side products), for example, being dependent on the reaction temperature [102]. A cleaner hydrocarbon **249** is obtained in 43% yield as the sole product when bis(1-bromocyclopropyl) ketone is treated with titanium trichloride and zinc–copper couple [103].

An old approach to preparing hydrocarbons such as **246** and **249** consists in the cycloaddition of ethenylidene carbenes to olefins [104]. In a recent application, such a carbene, **251**, was generated from the dichloride **250** by *n*-butyllithium treatment; trapping with 2,3-dimethyl-2-butene then led to the permethylated hydrocarbon **252** in 40% yield [103].

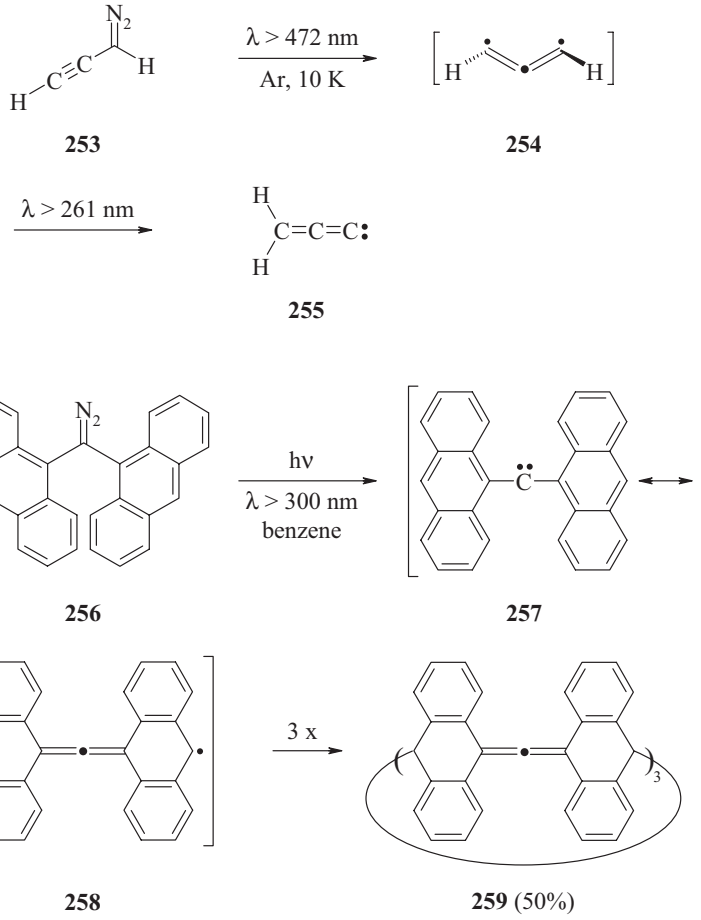
5.4
Allenic Hydrocarbons as Reaction Intermediates

Allenic hydrocarbons have often been postulated or observed as reaction intermediates in chemical transformations. In most cases these are cycloallenes of the endocyclic type **36** (Scheme 5.3) and they are treated in Chapter 6.

As far as acyclic allene hydrocarbon intermediates are concerned, these begin with a C_3H_2 species, **254**, about which there has been considerable discussion since it has also been detected in radioastronomy studies to belong to the (growing) number of organic compounds present in interstellar and circumstellar space [105].

In the laboratory **254** has inter alia been obtained in an argon matrix by irradiation of diazopropyne (**253**) at 10 K [106]. Matrix isolation ESR and IR studies and *ab initio* calculations show it to be a 1,3-diradical with C_2 symmetry, as indicated in Scheme 5.39 [107]. Irradiation with shorter wavelength light induces a 1,3-hydrogen shift by which the triplet propynylidene **254** is converted into the singlet propadienylidene **255**, the parent system of unsaturated carbenes such as **251** (Scheme 5.39) [108].

Another interesting allenic intermediate is generated when di(9-anthryl)diazomethane (**256**) is deazotized by irradiation in benzene (Scheme 5.39). The carbene produced, **257**, belongs to the long-sought persistent triplet carbenes, although its

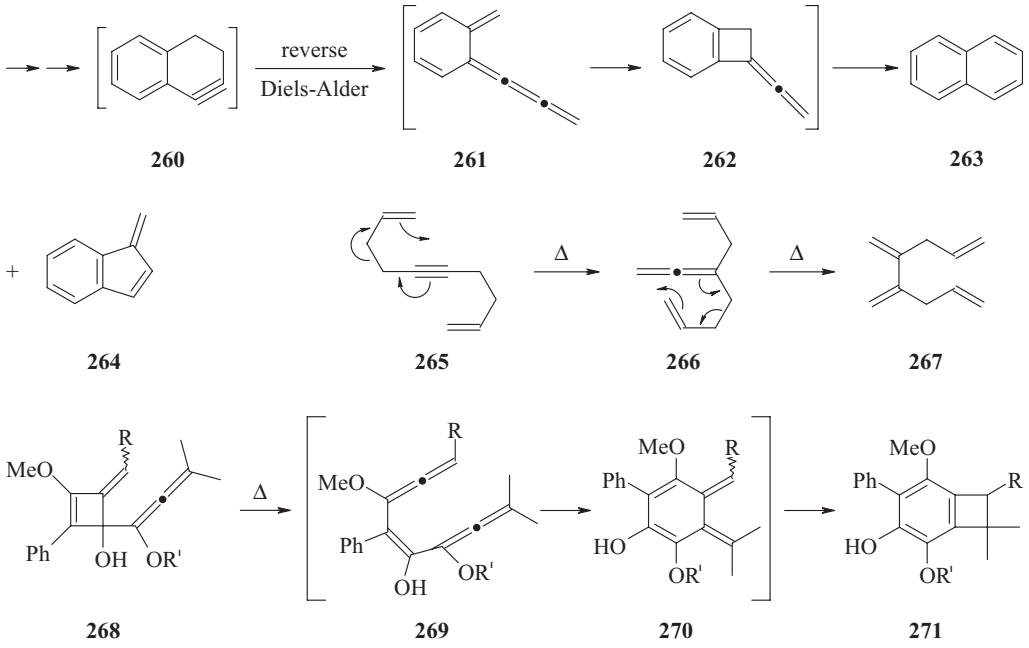


253 **254** **255** **256** **257** **258** **259** (50%)

Scheme 5.39

lifetime is only 0.5 μs [109]. Part of the reason of the still high reactivity of **257** derives from the fact that the unpaired electrons reside largely at the 10,10′-positions – see resonance structure **258** – which, in a sense, is an extended version of **254**. Interestingly, under the reaction conditions **258** trimerizes to the cyclic trisallene **259**. When the 10- and 10′-positions carry phenyl substituents, a dramatic stability increase is observed: With a half-life of 19 min at room temperature, the corresponding hydrocarbon is the most persistent diarylcarbene triplet known to date [110].

Allenic hydrocarbon intermediates have also often been observed in thermal isomerization reactions, some of which are summarized in Scheme 5.40.



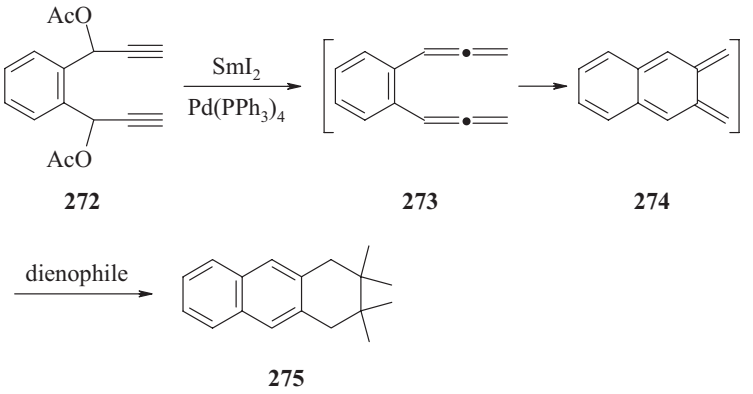
Scheme 5.40

When the cyclic acetylene **260** is generated from a suitable precursor, it undergoes an isomerization reaction spontaneously generating naphthalene (**263**) and benzofulvene (**264**) as the finally isolable products. Very likely the process begins with a retro-Diels–Alder reaction to the [3]cumulene **261**, which in a cascade reaction via the semicyclic allene **262** rearranges to **263** and **264** [111].

1,9-Decadien-5-yne (**265**) in a tandem process first produces, by a Cope-type isomerization, the allene intermediate **266**, which has the structural and electronic prerequisites to undergo this sigmatropic process a second time, yielding 2,3-bisallyl-1,3-butadiene (**267**) [112].

Although not involving a 'pure' hydrocarbon, the thermal isomerization of the methylenecyclobutene **268** to the benzocyclobutene **271** shows some typical allene hydrocarbon behavior (see below). In the first step of this sequential reaction, the substrate opens to give a 'vinylallene', **269**, which, at the same time is also a derivative of the (*Z*)-bisallene **230** already referred to. As such, it readily electrocyclizes to the *o*-xylylene **270**, which, in a last and also characteristic step, ring closes to **271** [113].

Derivatives incorporating the **230**/**269** motif as a substructure have often been invoked as reactive intermediates. An example is the reduction of the bisacetate **272** with samarium diiodide in the presence of a palladium catalyst (see above) (Scheme 5.41) [114].



272 **273** **274** **275**

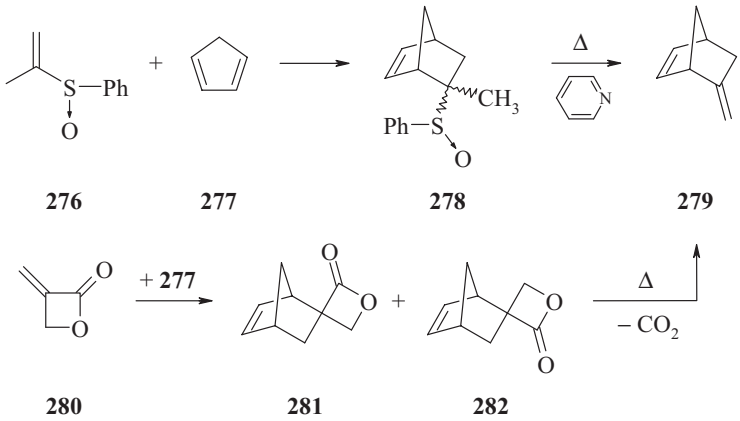
Scheme 5.41

The initially generated *o*-diallenylarene **273** electrocyclizes to the annelated *o*-xylylene **274**, which can either ring close to a naphtho[*b*]cyclobutene or be trapped with a dienophile to yield the Diels–Alder adduct **275**. Instead of the terminal hydrogen atom, the ethynyl functions can also carry alkyl and aryl substituents.

In closing this section, the use of allene equivalents will also be mentioned briefly; although in these cases the allene is never generated as such – it is present in latent form and hence comparable to an unisolated intermediate.

Cycloaddition between the vinyl sulfoxide **276** and 1,3-cyclopentadiene (**277**) takes place readily to yield the Diels–Alder adduct **278**, which, when heated in pyridine, undergoes a β-elimination to provide **279**, the formal adduct of allene (**1**) to **277** (Scheme 5.42) [115].

Likewise, α-methylene-β-lactones, **280**, can serve as allene equivalents since they cycloadd to conjugated dienes to provide the expected [2 + 4] products, e.g. **281** and **282**, which on heating fragment with carbon dioxide loss to furnish the allene adduct **279** again [116].



Scheme 5.42

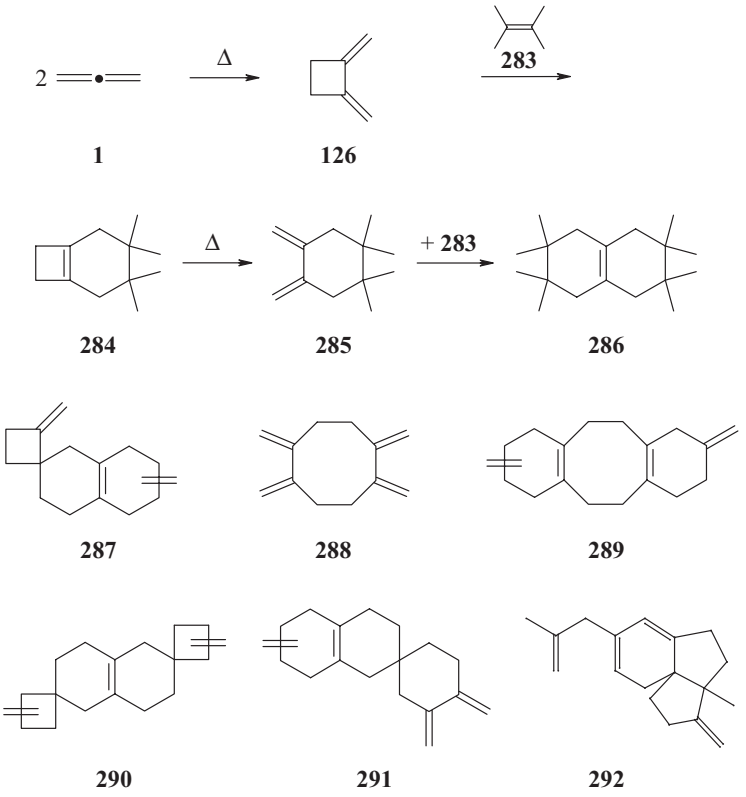
5.5
Why Allenic Hydrocarbons Are of Interest in Preparative Organic Chemistry

As demonstrated in most of the other chapters of this book, there is a countless – and growing – number of applications of allenes in preparative organic chemistry. A need for an extra section on the use of allenic hydrocarbons in synthesis may therefore not be apparent. However, since this chapter concentrates on the construction and then preparation of novel π-systems – neglecting all non-hydrocarbon substituents – some general remarks on the preparative usefulness of the parent systems seem to be in order.

Beginning with allene (**1**) itself, its thermal dimerization to 1,2-bismethylenecyclobutanes (**126**) constitutes one of the oldest allene reactions known. Although the yield is only moderate (in the region of 30%, depending on the pyrolysis conditions), the dimerization generates a very useful diene from a readily available starting material (Scheme 5.43) [117].

Reacting **126** with dienophiles **283** produces Diels–Alder adducts **284**, which, as cyclobutenes, can thermally be ring opened to the conjugated dienes **285**, ready for a repetition of the cycloaddition step to provide the 2:1 adducts **286**. Hence the whole sequence represents a diene-transmissive Diels–Alder protocol [118].

The comparatively low yield of the initial dimerization of allene is also caused by further addition of **1** to **126** and other allene oligomers produced subsequently in the pyrolysis. A reinvestigation of the reaction has revealed that not only are new tetramers such as **287** and **288** formed in the reaction, but also numerous hexamers such as **289**–**292**, the latter certainly not giving an indication that it originates from **1** [119]. Since some of these products still contain conjugated diene subunits – see, e.g., **291** – further 'growth' appears likely; *tert*-butylallene behaves similarly [120].



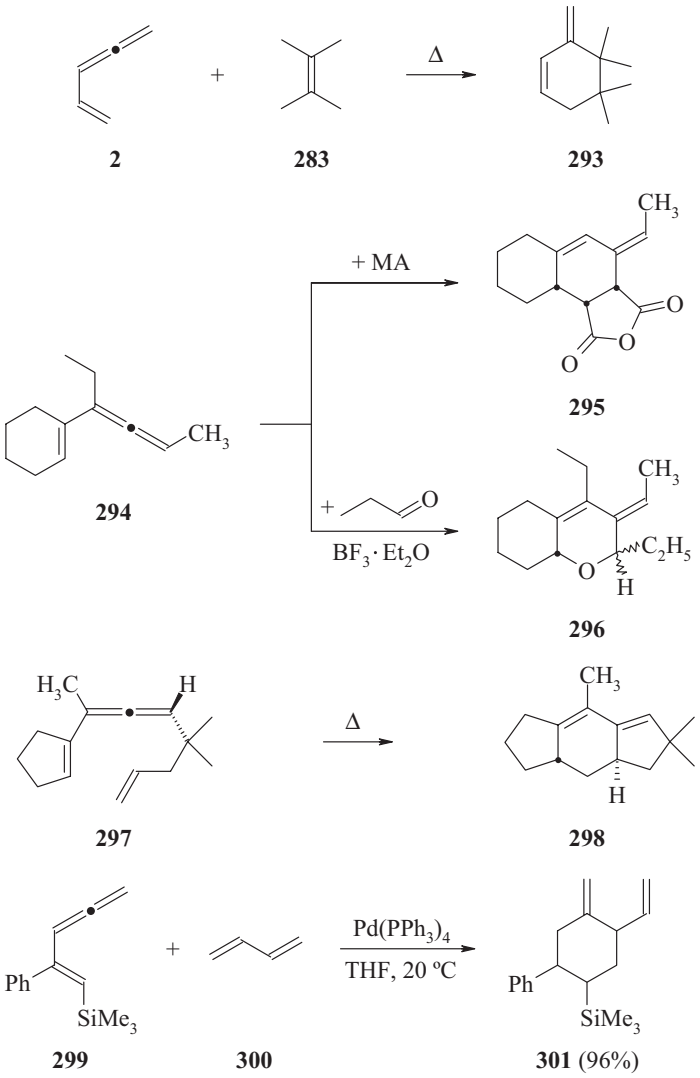
Scheme 5.43

The stereochemistry of the dimerization is complex and has been studied for numerous alkyl and aryl derivatives.] [117, 121].

Moving on to vinylallene (**2**) and its derivatives as substrates, the situation becomes rapidly more complex – and more interesting. The possibility of using vinylallenes as diene components in Diels–Alder additions was recognized many years ago [5]. As shown in Scheme 5.44, the [2 + 4] cycloaddition of a 'generalized' dienophile **283** to **2** yields 3-methylencyclohexene adducts **293**.

As a specific example of the vinylallenes, **294** demonstrates that not only can common dienophiles such as maleic anhydride (MA) be added (to furnish adduct **295** with a rich functionality) [122], but also carbonyl compounds such as propanal to afford **296** when the reaction is carried out in the presence of a Lewis acid catalyst [27].

Of course, the cycloaddition can also be performed intramolecularly, as shown by the conversion of **297** into **298**. Since there are other structural possibilities to connect dienes and dienophiles, a great variety of cycloadducts may be generated [123].



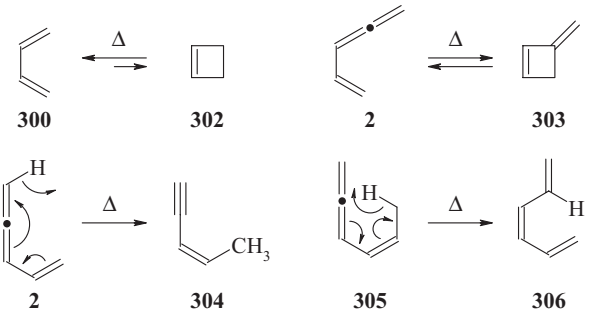
Scheme 5.44

In another recent development, Pd-catalyzed [2 + 4] cycloadducts of numerous vinylallenes to conjugated dienes have been studied; the formation of **301** from **299** and 1,3-butadiene (**300**) is typical, with regard to both regioselectivity and yield [124].

The second pericyclic process of vinylallenes involves their cyclization to methylencyclobutenes already referred to in passing above. Compared with the 1,3-butadiene to cyclobutadiene equilibrium, **300** ⇄ **302**, which because of the far greater thermodynamic stability of the open chain isomer lies completely to the left, vinylallenes and its derivatives, because the endothermicity of the allene substituent, just offset the ring strain of the cyclobutene ring, and establish an equilibrium between

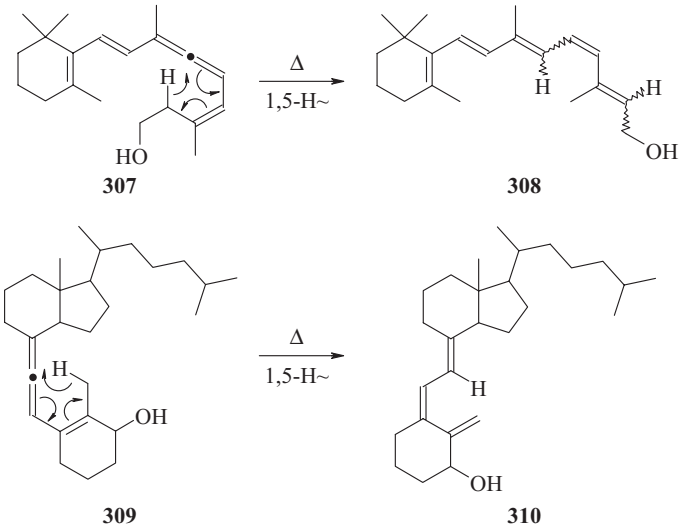
the open form **2** and the closed form **303** [125]. This ring closure was first observed for 4-methyl-1,2,4-pentatriene [126], then for the parent hydrocarbon **2** itself [127, 128] and later for many derivatives, making 3-methylenecyclobutene derivatives readily available four-membered ring systems [129].

A third symmetry-allowed transformation in which vinylallenes participate involves sigmatropic hydrogen shifts. As shown in Scheme 5.45, two types of these concerted processes have so far been observed.



Scheme 5.45

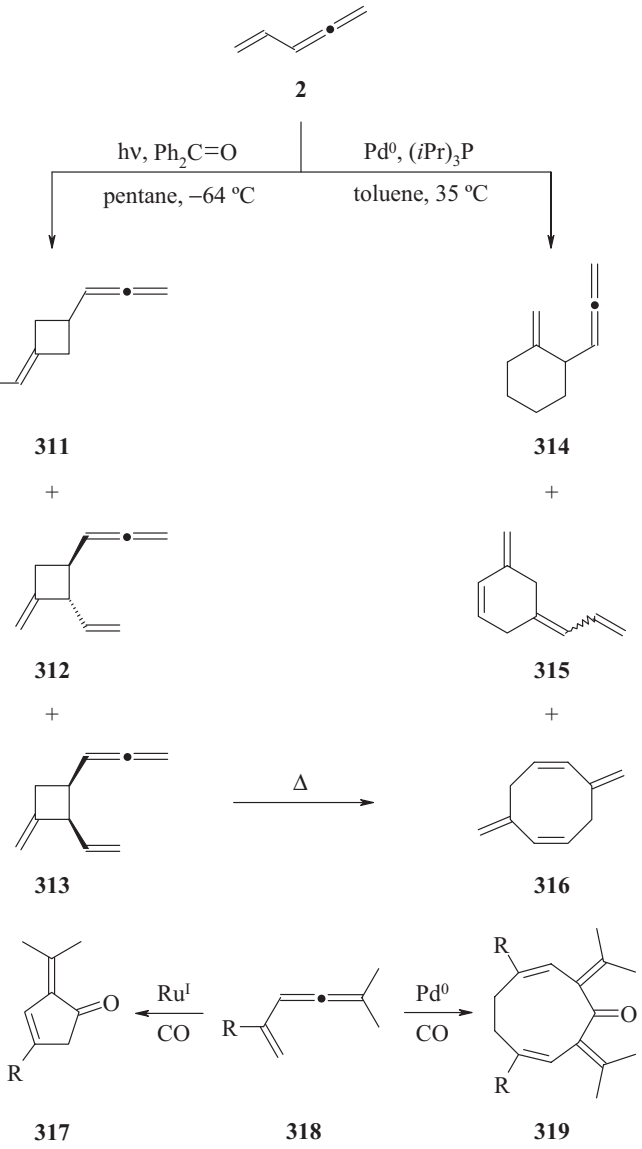
In the first [1,5]hydrogen shift, one of the hydrogen atoms of the allene group migrates to the terminal double bond of **2**, thus generating the *Z*-configurated enyne **304** [77]. If, however, the vinylallene carries a *Z*-oriented alkyl substituent in the 5-position, as in **305**, a hydrogen shift to the central allene carbon atom becomes possible and the result is a (*Z*)-1,3,5-hexatriene, e.g. **306**. This reaction has been put to extensive preparative use in the retinoid and calciferol field, two examples being presented in Scheme 5.46 [130].



Scheme 5.46

As shown in the scheme, the 11-*cis*-vitamin A isomers **308** are available from the precursor vinylallene **307** and the vitamin D analogue **310** from substrate **309**.

Irradiation of vinylallene (**2**) in the presence of the triplet sensitizer benzophenone in pentane at low temperatures with a medium-pressure mercury lamp induces [2 + 2] photoaddition, leading to the primary products **311–313** (Scheme 5.47) [127].



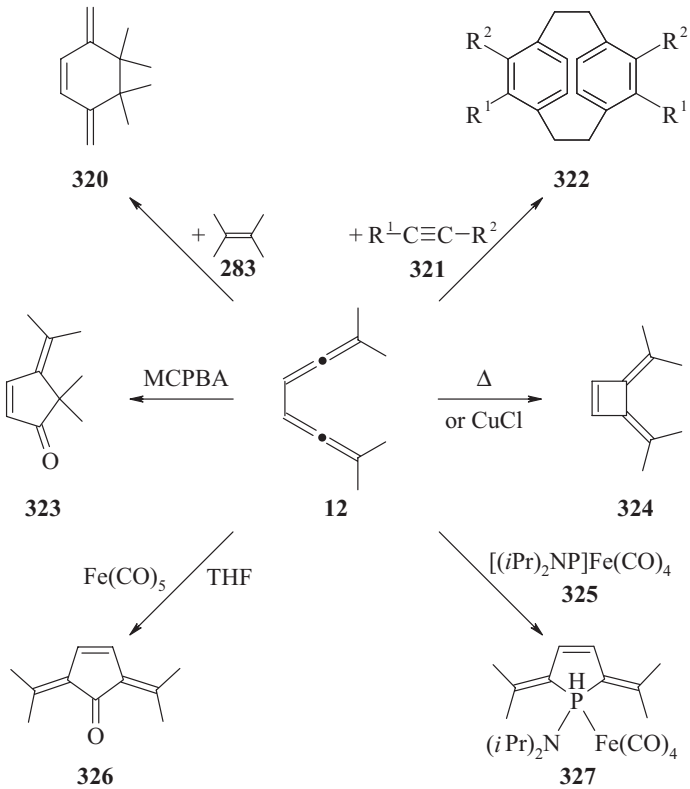
Scheme 5.47

That the also produced eight-membered ring hydrocarbon **316** is a (thermal) secondary product was shown by repetition of the reaction at room temperature, where the relative amount of **316** had increased significantly at the expense of the *cis*-isomer **313**.

The Pd^0-catalyzed dimerization of **2** leads to the 'Diels–Alder' adduct **314** as the main product (81%), for whose formation only one allene group has participated in the dimerization process, in addition to the dimer **315** (14%), in which no allene group has survived; in addition, several other dimers are produced in trace amounts [131].

An interesting dependence on the nature of the transition metal catalyst employed for the dimerization has been observed for the substituted vinylallene **318** (R = phenyl or vinyl). Whereas its carbonylation in the presence of Rh(I) leads to the [4 + 1] cycloadduct **317**, the change to Pd^0 opens up a [4 + 4 + 1]route which furnishes the nine-membered ring ketone **319**, the yields being good to excellent in both cases [132].

Depending on the reaction conditions, 1,2,4,5-hexatetraene (**12**) and its alkyl derivatives can be transformed into four-, five- or six-membered carbo- or heterocyclic ring compounds, as illustrated by the transformations shown in Scheme 5.48.



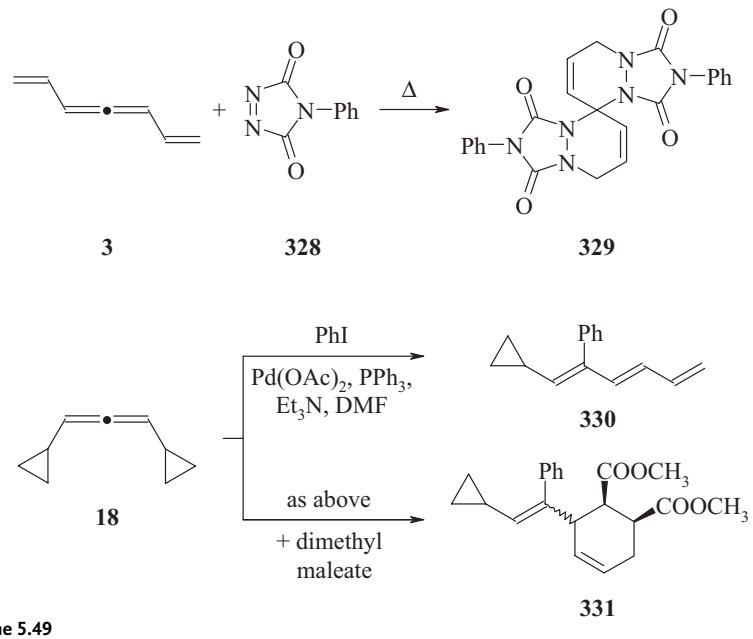
Scheme 5.48

Diels–Alder additions with numerous dienophiles **283** lead to the conjugated trienes **320** [133], whereas the use of activated triple bonded dienophiles **321** ($R^1 = R^2 = CO_2CH_3$, CN, CF_3, etc.; R^1 = CHO, CN, $COOCH_3$, etc., R^2 = H) constitutes the simplest route to functionalized [2.2]paracyclophanes, **322**, the primary *p*-xylylene adducts dimerizing under the reaction conditions [134, 135].

That the thermal isomerizations of these substrates lie completely on the side of the cyclic structures **324** comes as no surprise after what has been said about the energetics of the allene cyclization reactions above [125]; the cycloisomerization may also be induced by metal salts, such as cuprous chloride, incidentally [136].

Five-membered ring compounds are obtained from conjugated bisallenes under a variety of conditions. Whereas oxidation with *m*-chloroperbenzoic acid (MCPBA) provides ketones of type **323** [137], carbonylation by iron pentacarbonyl in THF at 50 °C leads to the symmetrical dialkylidene cyclopentenones **326** [45]. With phosphinidene complexes such as **325**, biallenyls react in a stepwise process that eventually leads to adducts such as **327** [138], mimicking the behavior of singlet carbenes [139].

1,3-Divinylallene (**3**), whose thermal cyclization behavior has already been referred to above, is formally a double diene system in which the two conjugated subsystems share the central (allenic) carbon atom. The molecule is chiral and a double Diels–Alder addition should lead to a spiro system. Although both tetracyanoethylene (TCNE) and maleic anhydride are not reactive enough to reach this goal – the addition process stops at the 1:1 adduct stage – the highly reactive dienophile *N*-phenyltriazolindione (**328**) provides the desired double adduct **329** (Scheme 5.49) [74].



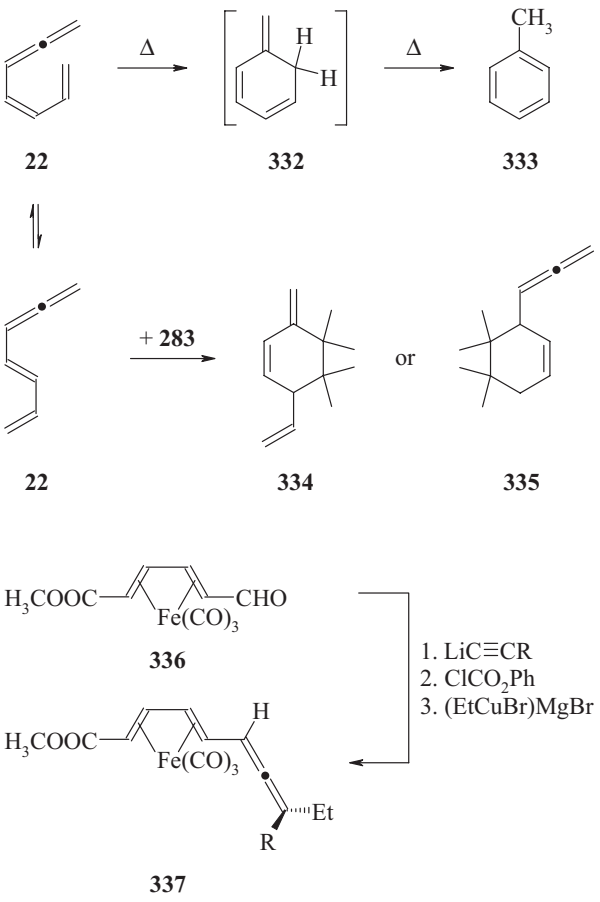
3 **328** **329**

18 **330** **331**

Scheme 5.49

The cyclopropanated version of **3**, 1,3-di(cyclopropyl)allene (**18**), has been used as a coupling partner in Heck-type reactions. For example, with iodobenzene the conjugated cyclopropylhexatriene **330** is obtained whereas repetition of the experiment in the presence of dimethyl maleate yields the Diels–Alder adduct **331** [58].

Although 1,2,4,6-heptatetraene (**22**) and its derivatives have largely been studied because of the mechanism of their thermocyclization to alkyl aromatics – in the simplest case, **22** isomerizes to toluene (**333**) via isotoluene (**332**) as an intermediate (Scheme 5.50) [8, 79, 80, 83] – other reactions of this interesting combination of conjugated and cumulated p-systems are also known.



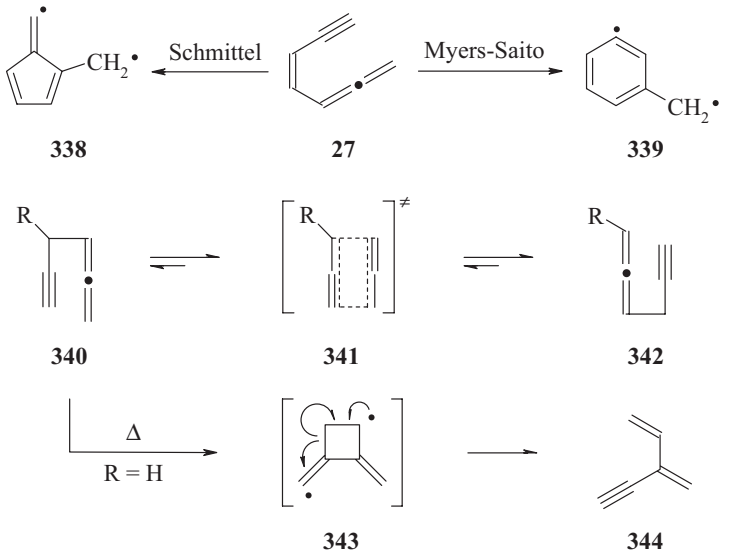
Scheme 5.50

As can be seen from the 'double-cisoid' conformation in Scheme 5.50, a Diels–Alder addition (with the 'generalized' dienophile **283**) could in principle yield either the mono-adduct **334** or the alternative **335**. At least for the reaction with 1,2,4,6-octatetraene (**211**), it was shown that the former addition mode is preferred, the driv-

ing force being provided by the removal of an allene group while simultaneously maintaining a conjugated diene subsystem [79].

Metal complexes such as **337** of various butadienylallenes have been obtained in a straightforward manner from the aldehydes **336** by first reacting these with lithium acetylides and subsequently converting the obtained propargyl alcohols into allenes in the usual way (see Scheme 5.50 and earlier) [140].

Many of the allenic parent systems mentioned in Schemes 5.1–5.3 have been of interest in mechanistic studies. Thus, the *Z*-isomer of **27** can either cyclize by the Myers–Saito route to the aromatic diradical **339** or under the so-called Schmittel cyclization conditions to yield the fulvene diradical **338** (Scheme 5.51) [141], both processes being discussed thoroughly in Chapters 13 and 20.

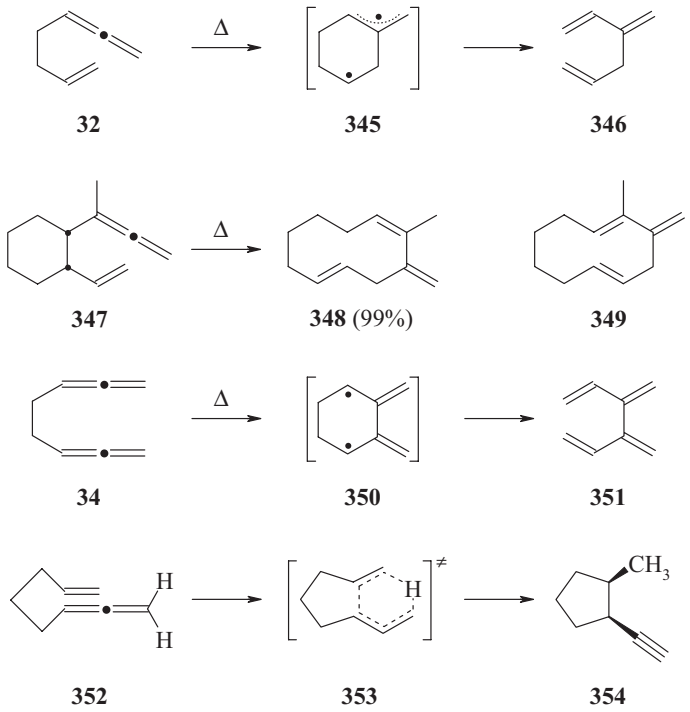


Scheme 5.51

The skipped allenynes **340**, propargylallenes, are subject to two interesting thermal isomerizations. At lower temperatures (150–210 °C), a [3.3]-sigmatropic isomerization takes place which can be studied when the degeneracy of the process is lifted by the introduction of substituents R differing from hydrogen. This propargyl-Cope rearrangment proceeds via the transition state **341** and is characterized by activation parameters typical for such pericyclic processes (low Arrhenius activation energy of 30.8 kcal mol^{-1}, negative entropy of activation of –11.7 e.u, log*A* = 10.84) [142]. Preparatively, this isomerization has not been exploited so far; it could be of considerable use once functional groups are introduced into the propargylallene framework.

At higher temperatures, **29** (360–500 °C, R = H) undergoes a formal 1,3-ethynyl shift yielding the cross-conjugated enyne 2-ethynyl-1,3-butadiene (**344**). Deuterium-labeling studies indicate that species such as **343** or hydrocarbons derived therefrom could be intermediates in the process [143].

Much experimental and theoretical work has been performed with the two allenes 1,2,6-heptatriene (**32**) and 1,2,6,7-octatetraene (**34**). Thermal isomerization of **32** leads to 3-methylene-1,5-hexadiene (**346**), a process that at first sight looks like a typical Cope rearrangement. However, trapping experiments with either oxygen or sulfur dioxide have shown that at least half of the rearrangement passes through the diradical **345** (Scheme 5.52) [144].



Scheme 5.52

The other half of the isomerization takes place directly bypassing a trappable intermediate, as recently confirmed by extensive theoretical calculations [B3LYP, CASPT 2, (8/8)CASSCF] [145].

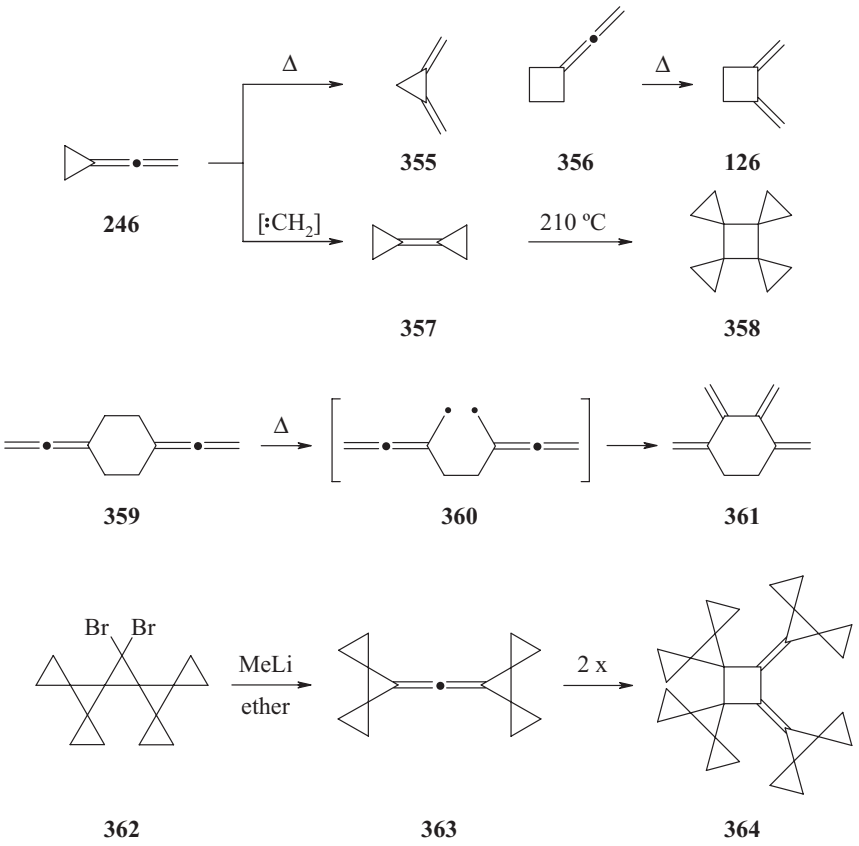
Bridging allenes such as **32** in the 4- and 5-positions by a butano fragment results in either the *cis*-cyclohexane derivative **347** or its *trans*-isomer. When the former is thermally isomerized the 10-membered ring system **348** is generated in practically quantitative yield, whereas *trans*-**347** yields the diastereomer **349** [146].

One of the ways to generate the tetramethylenethane-type diradical **350**, an important reference compound in connection with non-Kekulé hydrocarbons [147], consists in the thermal isomerization of hydrocarbon **34** at ~100 °C [43, 148]. Under the reaction conditions, the six-membered ring of **350** ruptures to yield [4]dendralene (3,4-bismethylene-1,5-hexadiene) (**351**).

For the enallene **352**, it has been observed that the intramolecular [2 + 2] cycloaddition route competes with an also intramolecular ene reaction leading to *cis*-1-ethynyl-2-methylcyclopentane (**354**) via transition state **353** (Scheme 5.52) [149].

Cylizations to numerous functionalized five-membered ring systems starting from allenes have recently been described; in most cases they make use of Pauson–Kand or other metal-mediated ring-forming protocols (see Chapter 16 for a discussion of these useful cyclizations) [150].

Semicyclic allenes, especially when they incorporate three- or four-membered rings and hence combine the inherent thermodynamic instability of the allene group with the strain of a small carbocyclic ring, have frequently been used as starting materials for other hydrocarbon systems. Thus, both vinylidencyclopropane (**246**) and vinylidencyclobutane (**356**) on thermolysis isomerize to the conjugated dienes 1,2-bismethylencyclopropane (**355**) [100, 151] and 1,2-bismethylencyclobutane, respectively (**126**, Scheme 5.53) [152].

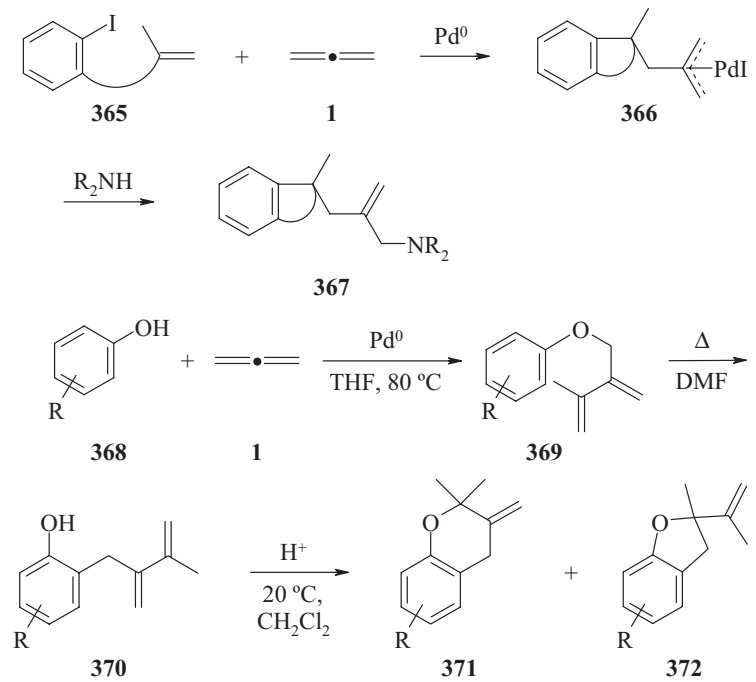


Scheme 5.53

Cyclopropanation of **246** leads to bicyclopropylidene (**357**), which dimerizes to [4]rotane (**358**) on heating [100]. The allene → radialene connection which is hinted at by the conversions of **246** and **356** becomes even more obvious by the thermal isomerization of the bisallene **359**, which lacks the strain of its small-ring homologs but possesses two energy-rich allene groups: on heating to 500 °C it rearranges to 1,2,3,4-tetramethylencyclohexane (**361**), the diradical **360** presumably passed en route [152, 153].

In another synthesis leading to a complex polycyclic hydrocarbon that even contains 12 cyclopropane rings, the allene **363**, obtained from the dibromocyclopropane derivative **362** by the DMS approach [154] and itself a derivative of bicyclopropylidenemethane (**249**) (see Section 5.3.9), shows typical allene behavior and thermally dimerizes at 0 °C (reaction time 1 year – but in 100% yield) to the 1,2-bismethylencyclobutane derivative **364** [155], thus establishing a connection between the allenes and the triangulanes [156], another class of hydrocarbons of high current interest.

Another synthetically very promising area deals with the use of allenes in multicomponent reactions. For example, the aryl iodide **365** after oxidative addition and cyclization can insert allene (**1**) to yield the p-allylpalladium(II) species **366**. When this is subsequently captured by a secondary amine the functionalized benzo-fused 5–8-membered ring systems **367** are produced in good yield (Scheme 5.54) [157].



Scheme 5.54

When, furthermore, phenols (**368**) are coupled with **1** in the presence of a Pd^0 catalyst, the phenoxy-methyl-1,3-dienes **369** are produced [158]. As aryl allyl ethers, these can be made to undergo a Claisen rearrangement (205 °C, DMF) and the ensuing 2-(1,3-dienylmethyl)phenols **370** finally cyclize in the presence of a trace of acid to a mixture of *exo*-methylene chromans **371** (major product) and dihydrobenzofurans **372** – a remarkable generation of functional and structural complexity from simple starting materials with 100% atom economy and underlining impressively the synthetic versatility of modern allene chemistry!

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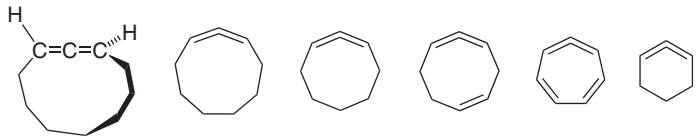
6
Cyclic Allenes Up to Seven-Membered Rings

Manfred Christl

6.1
Introduction

Apart from the treatment in general articles on allenes, this subject has been specifically reviewed by Johnson [1] in 1989 and Balci and Taskesenligil [2] in 2000.

Because of the linear arrangement of the carbon atoms and the orthogonal disposition of the bonding planes of the termini relative to each other in the equilibrium geometry, the three carbon atoms of an allene moiety can be accommodated without strain only in rings of at least 10 carbon atoms [1]. Thus, 1,2-cyclodecadiene (**1**) (Scheme 6.1) should behave as a non-cyclic 1,3-dialkylallene. The strain is still not significant in 1,2-cyclononadiene (**2**), since it is stable at room temperature and dimerizes only on heating at temperatures above 100 °C [3]. In contrast, 1,2-cyclooctadiene (**3**) cannot be isolated owing to its rapid dimerization at room temperature [4, 5]. However, NMR spectra of **3** [6] and 1,2,5-cyclooctatriene (**4**) [7] were obtained at low temperatures. This was not possible with cyclic allenes containing less than eight carbon atoms, except for 1,2,4,6-cycloheptatetraene (**5**) incarcerated in a molecular container [8].



1 **2** **3** **4** **5** **6**

Scheme 6.1 A selection of carbocyclic allenes.

Beyond dimerization and oligomerization, [2 + 2]- and [4 + 2]-cycloadditions with conjugated dienes and styrenes and the addition of nucleophiles are typical reactions of strained cyclic allenes. These transformations have been studied most thoroughly with 1,2-cyclohexadiene (**6**) and its derivatives [1, 2]. Concerning the cycloadditions, a theoretical study had the surprising result that even the [4 + 2]-cycloadditions should proceed in two steps via a diradical intermediate [9]. In the case of nucleophiles, the sites of attack at several 1,2-cyclohexadiene derivatives having an

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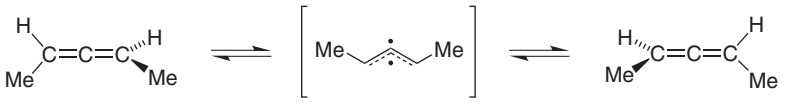
oxygen or a nitrogen atom next to the allene moiety in the ring deviate from those of homocyclic 1,2-cyclohexadienes [10–14]. Since 1,3-disubstituted allenes and hence cyclic allenes are chiral, the enantiomerization has received much attention. The corresponding barrier of 2,3-pentadiene (**7**) (Scheme 6.2) has been determined experimentally to be 46.2 kcal mol^{-1} [15]. Derived from the observation of highly excited torsional vibrations, the torsional barrier of allene agrees well with this value [16]. According to quantum-chemical calculations, the transition state should be the allyl diradical **8** [17]. Based on the results of trapping experiments, Roth and Bastigkeit [7] considered **8** as an intermediate.



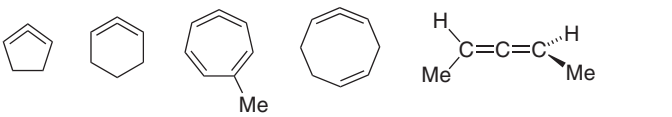
(*M*)-**7** **8** (*P*)-**7**

(intermediate[a] or transition state[b])

(a) Ref. 7; (b) ref. 17.

Scheme 6.2 The enantiomerization of 2,3-pentadiene (**7**).

Anyway, on going from **7** to **8**, a bending of the molecule at the central atom and a planarization have to occur. Both movements are already partially enforced in strained cyclic allenes, which is why smaller enantiomerization barriers have to be expected than that of **7**. As early calculations have shown, the bond angle at the central allene carbon atom decreases from 170° in **2** to 121° in 1,2-cyclopentadiene (**9**). Simultaneously, the dihedral angle H1–C1–C2–C3 is reduced from 34° (45° in **1** and **7**) to 13° [1, 18, 19]. Correspondingly, the barrier to enantiomerization should diminish in this series. Although there are not many data, this expectation is corroborated by the experimental values for **4** [7] and 5-methyl-1,2,4,6-cycloheptatetraene (**10**) [20] as well as calculated values for **6** [13] and **9** [19] (Scheme 6.3). The large difference of ~20 kcal mol^{-1} between the activation energies of **4** and **10** and the much smaller one of only 2–5 kcal mol^{-1} between those of **10** and **6** can be explained by the structure of the transition states. That of **10** experiences a special stabilization by the conjugated π-bonds, which are absent in **4** and **6**.

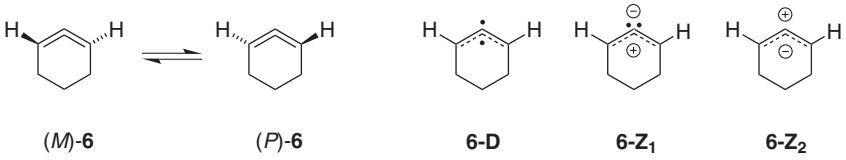


	9	**6**	**10**	**4**	**7**	
E_a	2–5[a]	15–18[b]	19.6, 20.3[c]	40.8[d]	46.2[e]	kcal mol^{-1}

(a) Calculated values from ref. 19; (b) calculated values from ref. 13;
(c) experimental values from ref. 20; (d) experimental value from ref. 7;
(e) experimental value from ref. 15.

Scheme 6.3 Activation energies (kcal mol^{-1}) to enantiomerization of several cyclic allenes of different ring size and of 2,3-pentadiene (**7**).

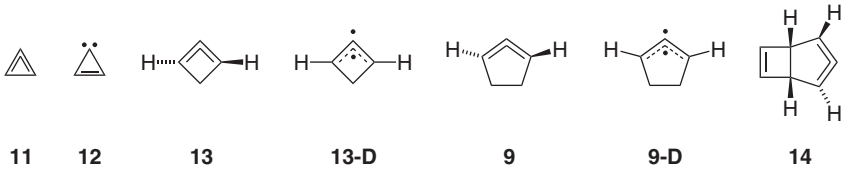
Quantum-chemical calculations of the transition state of the enantiomerization of **6**, that is, for the interconversion of (*M*)-**6** and (*P*)-**6**, support the diradical **6-D** [13, 18] (Scheme 6.4). Most probably, its singlet state is a few kcal mol^{-1} more stable than the triplet state. The zwitterions **6-Z$_1$** and **6-Z$_2$** are excited states [1]. However, if a methylene group directly attached to the allene system in **6** is replaced by an appropriate heteroatom, either **6-Z$_1$** or **6-Z$_2$** may be strongly stabilised (see Section 6.3.5).



Scheme 6.4 Different states of 1,2-cyclohexadiene (**6**).

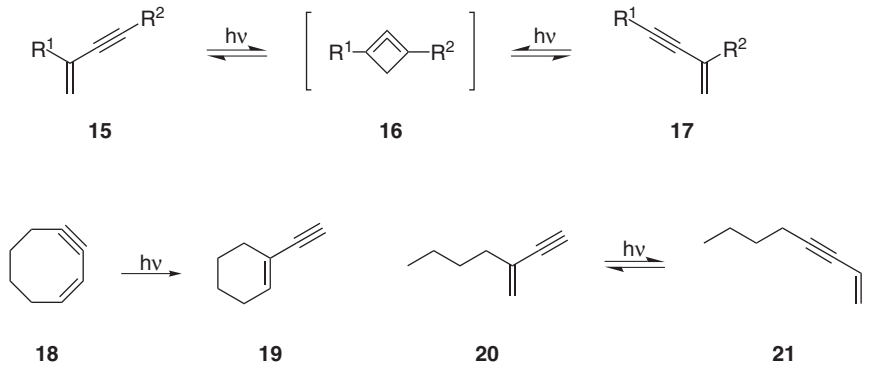
6.2
Three-, Four- and Five-Membered Rings

The formula of the smallest ring including a complete allene moiety is that of cyclopropadiene (**11**) (Scheme 6.5). However, this structure does not seem to be an energy minimum at the C_3H_2 hypersurface [21]. Cyclopropylidene (**12**) was calculated to be the most stable species followed by open-chain isomers [22].



Scheme 6.5 Isomerism of three-, four- and five-membered cyclic allenes.

However, there is already experimental evidence for the existence of derivatives of 1,2-cyclobutadiene (**13**). Indeed, the unsensitized irradiation of conjugated enynes **15** does give the rearranged enynes **17**, sometimes establishing an equilibrium (Scheme 6.6). This type of reaction was discovered by Meier and König [23], who studied cyclic enynes. For example, they obtained 1-ethynylcyclohexene (**19**) from cyclooct-1-en-3-yne (**18**). Non-cyclic substrates were investigated by Johnson et al. [24], e.g. the interconversion of 2-ethynyl-1-hexene (**20**) and oct-1-en-3-yne (**21**), who postulated 1,2-cyclobutadiene derivatives **16** as intermediates. The ring closures **15** → **16** and **17** → **16** are analogous to the photochemical formation of cyclobutene from 1,3-butadiene and the two possibilities to reopen the ring of **16** correspond to the thermal reverse reaction.



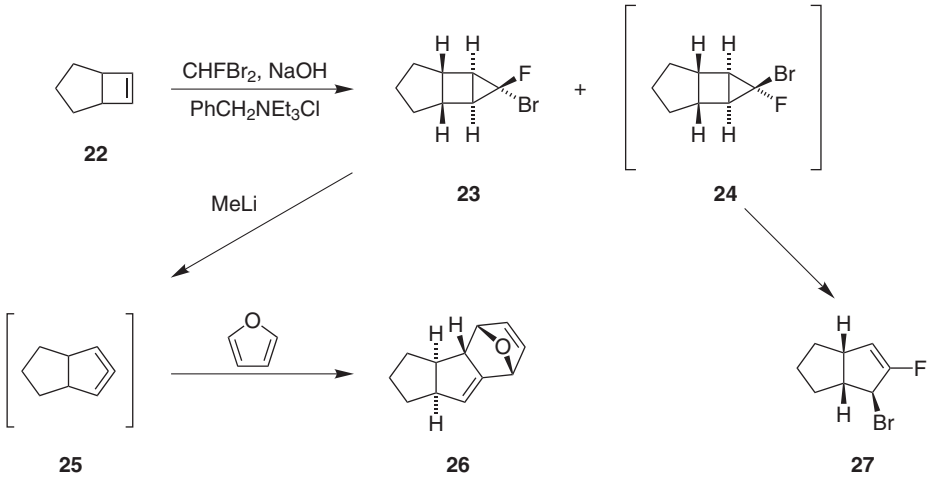
Scheme 6.6 Photochemical isomerizations of conjugated enynes with 1,2-cyclobutadiene derivatives **16** as possible intermediates.

Quantum-chemical calculations furnished very similar energies of 1,2-cyclobutadiene (**13**) and the diradical **13-D** (Scheme 6.5), with a small preference for the latter. Since the ring opening of **13** or **13-D** was estimated to be highly exothermic (74.5 kcal mol^{-1}) because of the inherent strain, the barrier for this step must be low [24].

In view of the similar energies of **13** and **13-D**, the allene structure has to be expected as the global minimum for the next higher homologue. Thus, the diradical **9-D** (Scheme 6.5) should serve as transition state for the equilibration of the enantiomers of 1,2-cyclopentadiene (**9**). Theoretical work by Johnson et al. [1, 19] is in line with this prediction. Calculations at the highest level used gave an energy difference of 4.9 kcal mol^{-1}. The range shown in Scheme 6.3 covers the results of different computational methods [19]. By calculations at a much higher level, *cis*-bicyclo[3.2.0]-hepta-2,3,6-triene (**14**) was predicted to be a true allene [25]. The dihedral angles H–C–C–C of the allene moiety were obtained as 23 and 28° and hence much larger than that computed for **9** (13°) previously [19].

A number of futile attempts to generate **9** or one of its derivatives have been summarised recently [2]. In these experiments, cyclopentenes were chosen as substrates exclusively and methods were employed that had proven successful in the case of 1,2-cyclohexadiene (**6**). Only the application of the Doering–Moore–Skattebøl (DMS) reaction, probably the most general procedure for synthesizing allenes [26], led to the first liberation of a derivative of **9**, that is, bicyclo[3.3.0]octa-2,3-diene (**25**) (Scheme 6.7) [27]. Since dichloro- and dibromocarbene adducts of cyclobutene and its derivatives are unstable and rearrange to 2,3-dihalocyclopentenes even under the conditions of their preparation [28–31], bicyclo[3.2.0]hept-6-ene (**22**) was treated with bromofluorocarbene [27]. The addition proceeded from the *exo*-face of **22** with formation of the diastereomeric products **23** and **24**. As expected, instead of the latter, its ring-expanded isomer **27** was obtained, whereas the former proved to be persistent [27], because the C–F bond would have to be cleaved heterolytically simultaneously with the disrotatory opening of the three-membered ring [32, 33]. This is

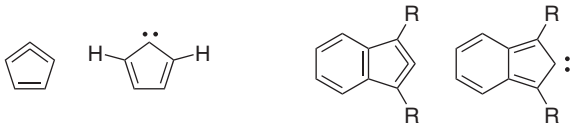
prevented by the strength of the C–F bond, which has a bond dissociation energy larger than that of a C–Br bond by ~40 kcal mol^{-1} [34]. The reaction of bromofluorocarbene with cyclic alkenes whose dibromocarbene adducts are not isolable is a general strategy to prepare stable precursors of short-lived cyclic allenes. It was published for the first time on the occasion of the generation of 1-oxa-2,3-cyclohexadiene (**351**) (Section 6.3.6), 1,2,4-cyclohexatriene (**162**) and 3δ^2-1*H*-naphthalene (**221**) (Section 6.3.4) [35].



Scheme 6.7 Generation and interception of the 1,2-cyclopentadiene derivative **25** by Balci and co-workers.

The treatment of **23** with methyllithium in the presence of furan gave rise to the tetracyclic product **26**, which is obviously a [4 + 2]-cycloadduct of furan to the 1,2-cyclopentadiene derivative **25** [27]. The feature that the oxanorbornene system of **26** carries its saturated substituent in the *endo*-position is analogous to the [4 + 2]-cycloadducts of furan to all six-membered cyclic allenes (see Section 6.3). Balci et al. [36] also provided evidence for the generation of 1-phenyl-1,2-cyclopentadiene. They postulated this species to be an intermediate in the reaction of 1-phenyl-2-iodocyclopentene with potassium *tert*-butoxide in benzene at 240 °C, which resulted in the formation of 1-phenyl- and 1,2-diphenylcyclopentene. Both products were considered as evidence in favor of the diradical nature rather than the allene structure of 1-phenyl-1,2-cyclopentadiene.

In comparison with **9**, the additional double bond of 1,2,4-cyclopentatriene (**28**) (Scheme 6.8) could destabilize the allene structure and make the cyclopentadienylidene **29** a viable species. Experimental results and quantum-chemical calculations support a triplet ground state for such a C_5H_4 molecule. The closed-shell state of lowest energy belongs to a carbene **29** having C_s symmetry [37]. In three investigations, the allene **28** could not be identified as an energy minimum [37–39]. However, according to another one [40], **28** lies only <1 kcal mol^{-1} above the C_s symmetric **29** and is separated from this species by a barrier of 14 kcal mol^{-1}. Within the pair



28 **29** **30** **31**

Scheme 6.8 1,2,4-Cyclopentatriene (**28**) or 2,4-cyclopentadienylidene (**29**), that is the question.

30–31, which is analogous to **28–29**, the allene structure **30** should be stabilized by the aromaticity of the six-membered ring and could well be favored over the singlet carbene **31** [41]. The species **30–31** with R = 2,4,6-trimethylphenyl [42] and R = phenyl [43] have been studied experimentally.

6.3 Six-Membered Rings

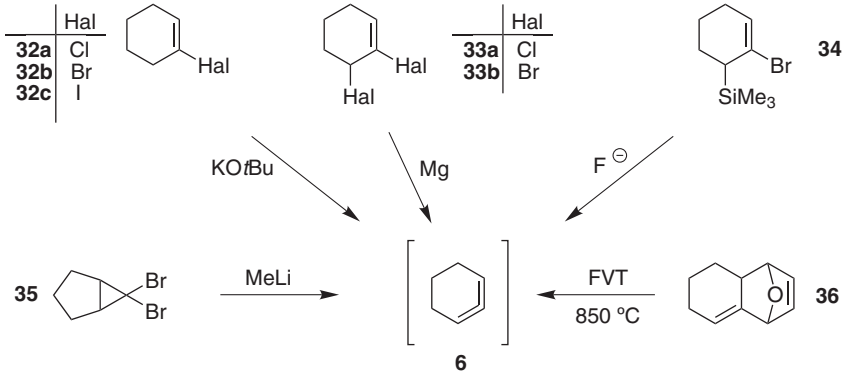
An enormous amount of work has been dedicated to six-membered cyclic allenes. This justifies the organization of the subject in several subsections: unsubstituted 1,2-cyclohexadiene (**6**) (6.3.1), substituted 1,2-cyclohexadienes (6.3.2), bridged and annulated 1,2-cyclohexadienes (6.3.3), 1,2,4-cyclohexatriene (**162**), $3\delta^2$-1*H*-naphthalene (**221**) and their derivatives (6.3.4), heterocyclic derivatives of 1,2,4-cyclohexatriene and $3\delta^2$-1*H*-naphthalene (6.3.5) and heterocyclic derivatives of 1,2-cyclohexadiene (6.3.6).

6.3.1 Unsubstituted 1,2-Cyclohexadiene (6)

Owing to the high reactivity of **6**, early workers [4b, 44] assumed a structure with a planar 'allene' moiety, that is, the allyl diradical **6-D** or the zwitterion **6-Z$_1$** (Scheme 6.4). After the chirality of the species had been established [45, 46], theoretical studies corroborated its allene nature **6** [13, 19, 47–49]. In line with previous work, the most recent calculations ascribed **6** C_1 symmetry only slightly distorted from C_2 symmetry and came to a C–C–C bond angle and H–C–C–C dihedral angles of the allene subunit of 133 and 37°, respectively. The barrier to enantiomerization was predicted to lie between 15 and 18 kcal mol^{-1} (see Scheme 6.3), with the magnitude depending on the theoretical method used and the C_s symmetric diradical **6-D** serving as transition state [13]. A value of ~15 kcal mol^{-1} for this barrier was estimated as early as 1985 [19].

After the first attempts of a Russian school to prepare **6** [1], Ball and Landor [4] also did not arrive at a conclusive result when they treated 1-chlorocyclohexene (**32a**) with sodium amide. Wittig and Fritze [50] were the first to demonstrate clearly the existence of **6**. After the reaction of 1-bromocyclohexene (**32b**) (Scheme 6.9) with potassium *tert*-butoxide (KO*t*Bu) in dimethyl sulfoxide (DMSO), they isolated the dimer **38** (Scheme 6.10) of **6** in 7% yield and, when the elimination was performed

in the presence of 1,3-diphenylisobenzofuran (DPIBF), the [4 + 2]-cycloadducts **50** (Scheme 6.14) of **6** in 38% yield. The same products **50** in the same ratio were also obtained on treatment of 1,6-dibromocyclohexene (**33b**) with magnesium [51] and of 1-bromo-6-(trimethylsilyl)cyclohexene (**34**) with cesium fluoride [52] or tetrabutylammonium fluoride [53] in the presence of DPIBF. In addition, **6** could be generated from 1,6-dichlorocyclohexene (**33a**) with magnesium and intercepted with activated alkenes [54]. However, the DMS method [26] provides by far the best possibility to prepare oligomers and cycloadducts of **6**. Accordingly, 6,6-dibromobicyclo[3.1.0]hexane (**35**), the dibromocarbene adduct of cyclopentene, was treated with methyllithium in the absence and presence of activated alkenes, respectively [44, 54, 55]. The ring enlargement of the cyclopropylidene derived from **35** to **6** was studied theoretically and an extremely low activation barrier of 0.2 kcal mol^{-1} predicted [49].



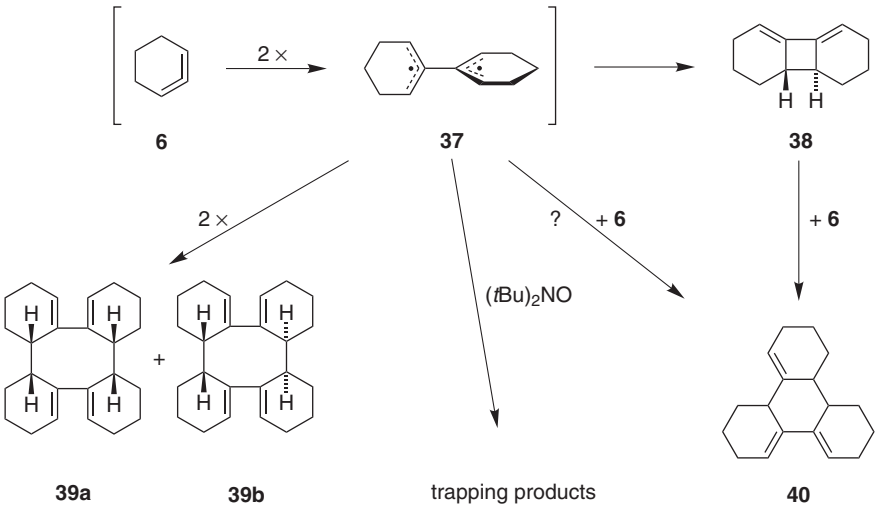
Scheme 6.9 Methods to generate 1,2-cyclohexadiene (**6**).

Werstiuk et al. [48] observed **6** by means of ultraviolet photoelectron spectroscopy as product of the flash vacuum thermolysis (FVT) at 850 °C of **36**, the [4 + 2]-cycloadduct of furan to **6** [54]. The first two vertical ionization energies were measured to be 8.4 and 10.4 eV and agree well with the calculated values [48]. Possibly this is the only study providing direct experimental data for **6**, although two further papers claimed to do so. Thus, the product of the FVT of bicyclo[3.1.0]hexane-6-carbonyl chloride, trapped in an argon matrix at –262 °C, gave an IR absorption [56] close to calculated values for **6** (AM1, 1817 cm^{-1}[47]; DFT, MP2, 1818–1874 cm^{-1} [49]). However, the result of the experiment could not be repeated, as the FVT of the ketene appearing as an intermediate yielded only ethylene and vinylacetylene [57], the products of the [4 + 2]-cycloreversion of **6**. Also, the pyrolysate of 6-bromo-6-(trimethylstannyl)bicyclo[3.1.0]hexane, trapped at –263 °C in argon, showed, in addition to IR signals of ethylene and vinylacetylene, an absorption in the region expected for **6** [58], which was identified later as originating from trimethylstannane [57]. A number of experiments were performed to isolate in a matrix volatile products of the reactions of 1,6-dibromocyclohexene (**33b**) and 6,6-dibromobicyclo[3.1.0]hexane (**35**) with methyllithium or alkali metals and led to the observation of a common IR band at 1976 cm^{-1}. Whether or not this signal belongs to **6** is considered uncertain [57].

The reversal of the thermal decomposition of **6** to ethylene and vinylacetylene cannot be utilized to generate **6**, since, according to a quantum-chemical analysis, the reaction is slightly endergonic and requires a large free activation enthalpy (0.9 and 42 kcal mol^{-1}, respectively) [59]. The intramolecular variant of this process as well as the addition of typical dienophiles of the normal Diels–Alder reaction to divinylacetylenes will be discussed at the end of Section 6.3.3.

If liberated in the absence of a trapping reagent, **6** undergoes oligomerization and the kind depends on the procedure of the generation and the conditions. Thus, a 7% yield of the dimer **38** (Scheme 6.10) was obtained on treatment of 1-bromcyclohexene (**32b**) with KO*t*Bu in DMSO [50]. The detailed investigation of this reaction uncovered a wealth of further products [60], inter alia the [4 + 2]-cycloadduct **54** and the [2 + 2]-cycloadduct **55** of **6** to 1,3-cyclohexadiene (Scheme 6.15), with the latter probably being formed by the base-catalyzed conversion of **32b** into 3-bromocyclohexene followed by the elimination of hydrogen bromide. Major products of the action of KO*t*Bu on 1-iodocyclohexene (**32c**) in DMSO were *tert*-butyl cyclohex-1-en-1-yl ether (**41**) (Scheme 6.11), **38** and the trimer **40** (Scheme 6.10) of **6** in yields of 10, 32 and 25%, respectively. Monitoring the course of the reaction led to the conclusion that **40** emerged from **38**. When the reaction was carried out in the presence of di-*tert*-butyl nitroxide [$(t\text{Bu})_2$NO], the products formed directly from **6** were found as in the previous experiment, but **38** and **40** were no longer observed. This indicates that two molecules of **6** give rise to the diradical **37**, which undergoes ring closure with formation of **38** in the absence of $(t\text{Bu})_2$NO, but is efficiently trapped in the presence of this radical. The analogous sequence starting from 5-methyl-1,2-cyclohexadiene (**81**) is discussed in Section 6.3.2, Scheme 6.24 [61].

Moore and Moser [44] obtained **38** and the tetramers **39** of **6** as products of the reaction of **35** with methyllithium in diethyl ether. The best yield of **38** (55%) resulted at 35 °C, whereas only a trace of **38** was observed at –80 °C, at which temper-



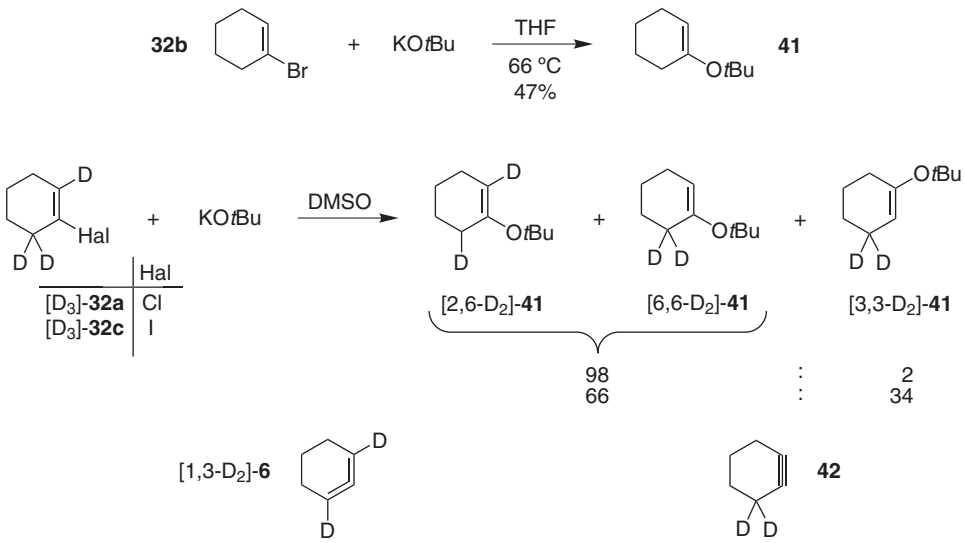
Scheme 6.10 Oligomerization of 1,2-cyclohexadiene (**6**).

ature **39a** and **39b** in a ratio of 3:1 were the major products (61%). A possible reason for the relatively good yields of oligomers in the α-elimination from **35** as compared with those of the β-elimination from **32** could be that, owing to the tetrameric nature of methyllithium in diethyl ether, higher local concentrations of **6** are produced. At low temperature, the dimerization of the diradical **37** to give **39** is obviously considerably favored over the ring closure resulting in **38**. Trimers of **6** played only a minor part in these experiments [44]. It is unknown if these were formed directly from **37** or via **38**. By using [1-D]-**35**, [1-D]-**6** was generated and furnished three isotopomeric dimers [D]-**38**. Their ratio allowed the determination of the composite intramolecular kinetic isotope effect of $k_H/k_D = 1.04$ in terms of formation of the doubly allylic bond of **38** [62]. The ring closure of **37** has to be considered as a least-motion process smoothly giving rise to the *trans* configuration of the product (**38**) [44].

Considering the reaction of 1-halocyclohexenes **32** with a strong base, the question arises if instead of **6** or in addition to **6** cyclohexyne is formed. Under the influence of the base, this strained acetylene could be isomerized to **6** or the trapping products of cyclohexyne could be rearranged to those of **6**. In the case of the cycloadducts **50** of DPIBF (Scheme 6.14), it was proved, however, that they do not result via the adduct of cyclohexyne [50]. The general problem was systematically investigated by trapping the intermediates by nucleophiles. Also methyl derivatives of **32** were utilized, as described in Section 6.3.2. It turned out that the relative rates of the elimination leading to **6** and the cyclohexyne depend on the kind of halogen in **32**, the base and the solvent. The attack of the nucleophile at the central allene carbon atom of **6** is highly characteristic, giving rise to an allyl anion derivative, from which the isolated products are formed.

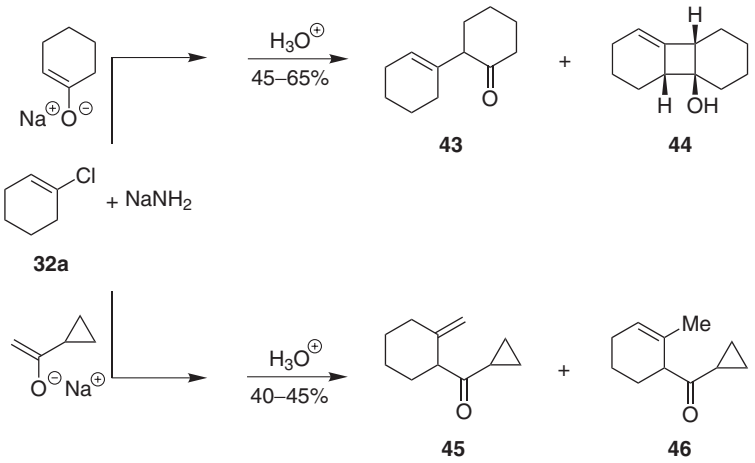
Caubère et al. [63, 64] treated **32a** with sodium amide–sodium *tert*-butoxide ($NaNH_2$–NaO*t*Bu) in tetrahydrofuran (THF) in the presence of secondary amines and obtained enamines. Analogously, the corresponding thioenol ethers were formed from **32a** and sodium amide–sodium thiolate in the presence or absence of NaO*t*Bu. It was shown, however, that cyclohexyne rather than **6** is the decisive intermediate en route to the enamines as well as the thioenol ethers [63b, 64]. As already mentioned above, the enol ether **41** arises inter alia from **32b** and KO*t*Bu in DMSO. The best yield (47%) was obtained in refluxing THF (Scheme 6.11) [60].

The mechanism of this substitution was scrutinized by treatment of 2,6,6-trideutero-1-chloro- ([D_3]-**32a**) and -1-iodocyclohexene ([D_3]-**32c**) with KO*t*Bu in DMSO. In the case of [D_3]-**32a**, the products [2,6-D_2]-**41** and [6,6-D_2]-**41**, which bear the functional group at the same carbon atom as the substrate, on one side and [3,3-D_2]-**41** on the other resulted in a ratio of 98:2, whereas when using of [D_3]-**32c** this ratio was 66:34. These findings allow the conclusion that the intermediates [1,3-D_2]-**6** and [3,3-D_2]-cyclohexyne (**42**), determining the products, emerge from [D_3]-**32a** and [D_3]-**32c** in ratios of 96:4 and 32:68, respectively. In **32**, a chlorine atom clearly favors the generation of **6** whereas a bromine and an iodine atom in this order increasingly cause the formation of cyclohexyne. Among the solvents, DMSO promotes the route to **6** better than THF and diglyme [60].



Scheme 6.11 Formation of *tert*-butyl cyclohex-1-enyl ether (**41**) from 1-halocyclohexenes (**32**) and KO*t*Bu.

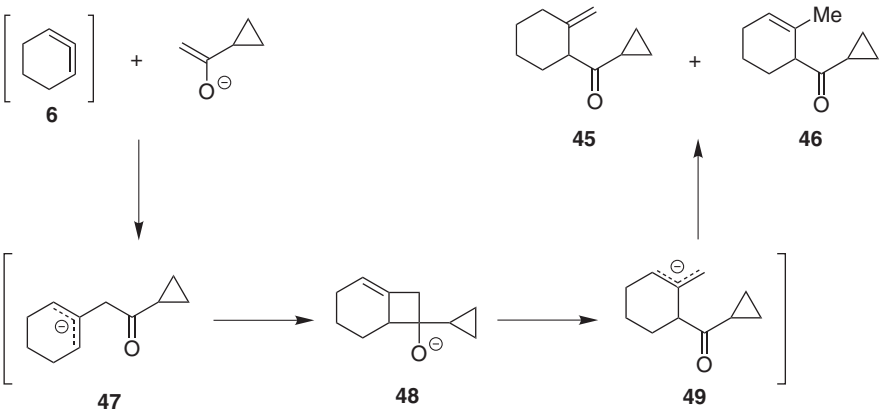
Caubère et al. [64, 65] also employed enolates as nucleophiles to intercept the intermediates produced from **32a** and the mixture of sodium amide and a sodium enolate. Scheme 6.12 illustrates the results obtained by using the enolates of cyclohexanone and cyclopropyl methyl ketone. The former furnished only the ketone **43** in hexamethylphosphoric triamide as solvent, but almost exclusively the cyclobuta-



Scheme 6.12 Reactions of 1-chlorocyclohexene (**32a**) with complex bases from sodium amide and sodium enolates, according to Caubère and co-workers.

nol **44** in THF, whereas dimethoxyethane brought about a 63:37 mixture of **43** and **44**. On the other hand, the enolate of cyclopropyl methyl ketone gave rise to a 70:30 mixture of the β,γ-unsaturated ketones **45** and **46** in THF [65a].

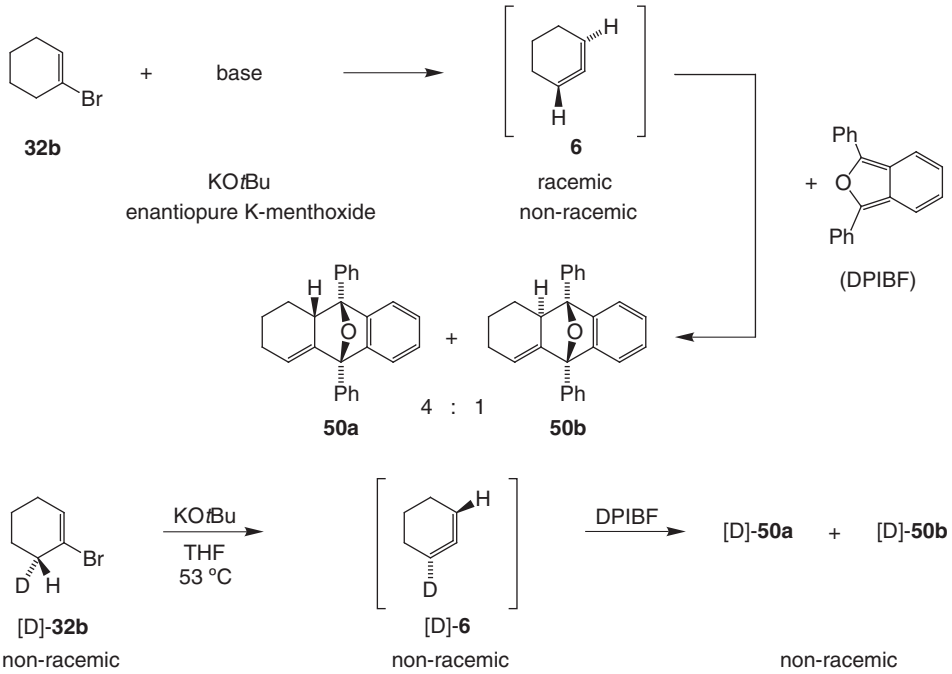
On the basis of the products observed after the reaction of a number of methyl derivatives of **32a** (see Section 6.3.2), the mechanistic course displayed in Scheme 6.13 was proposed [64]. Accordingly, the elimination of hydrogen chloride from **32a** by the complex bases leads mainly to the cyclic allene **6**. Then the enolate attacks the central allene carbon atom of **6** with formation of **47**, whose allyl anion subunit closes a four-membered ring by addition to the carbonyl group. Thus generated, the cyclobutanolate **48** opens up the four-membered ring in an alternative way to give the new allyl anion **49**, the protonation of which leads to **45** and **46**. In the case of cyclohexanone, the reaction proceeds only to the anions corresponding to **47** and **48**, which are the precursors to **43** and **44**, respectively.



Scheme 6.13 Mechanism of the formation of the β,γ-unsaturated ketones **45** and **46** from **6** and the enolate of cyclopropyl methyl ketone.

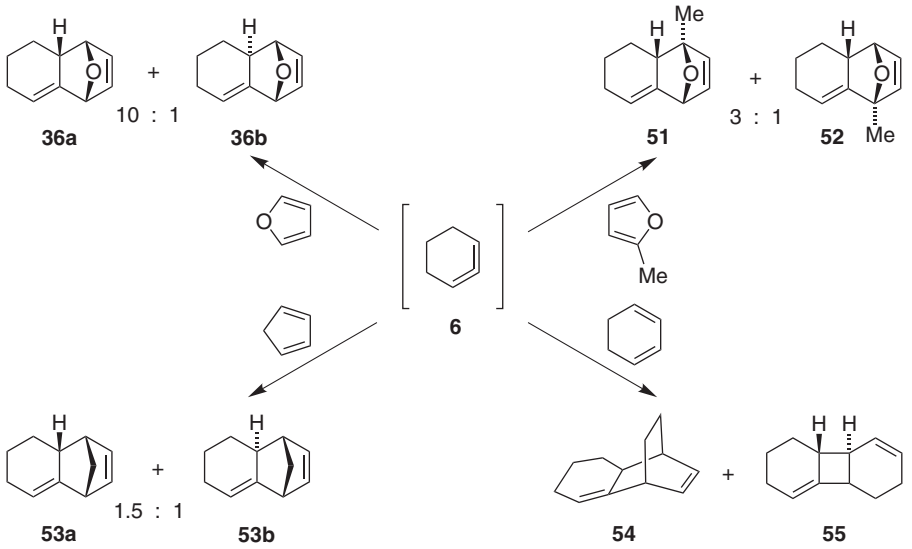
Cycloadditions with activated alkenes constitute the third characteristic type of reaction of **6** besides oligomerization and the interception by nucleophiles. These conversions not only attract great mechanistic interest, but also offer a preparative potential owing to the considerable variability. [4 + 2]-Cycloaddition with 1,3-diphenylisobenzofuran (DPIBF) was used by Wittig and Fritze [50] for the first conclusive demonstration of the existence of **6** (Scheme 6.14). The products **50a** and **50b**, obtained in the ratio of 4:1 in 38% yield on treatment of **32b** with KO*t*Bu in the presence of DPIBF [50], served also as proof of the generation of **6** from other precursors [51–53]. Balci and Jones took advantage of this reaction to establish that **6** is chiral. In their first study [45], relying on the H/D-isotope effect, they liberated [D]-**6** at 53 °C from nonracemic [D]-**32b** and isolated optically active [D]-**50** (Scheme 6.14). This showed that [D]-**6** is chiral and was formed as a non-racemic mixture of enantiomers. Performing the experiment at 100 °C gave racemic products [D]-**50**, however. Obviously, at 100 °C the racemization of [D]-**6** is faster than the interception by

DPIBF, which does not apply at 53 °C. These findings are in line with a calculated barrier to enantiomerization of 15–18 kcal mol^{-1} (see Scheme 6.3). In their second investigation, Balci and Jones [46] eliminated hydrogen bromide from **32b** at 53 °C with a pure enantiomer of potassium menthoxide in the presence of DPIBF, which gave rise to optically active products **50**. Again, racemic products were formed on repetition of the experiment at 100 °C. Here, the base causes an enantioselective elimination from **32b** with formation of non-racemic **6**, which is trapped at 53 °C before complete racemization occurs.



Scheme 6.14 Trapping of **6** with 1,3-diphenylisobenzofuran (DPIBF) and proof of the chirality of **6** by formation of non-racemic products **50**.

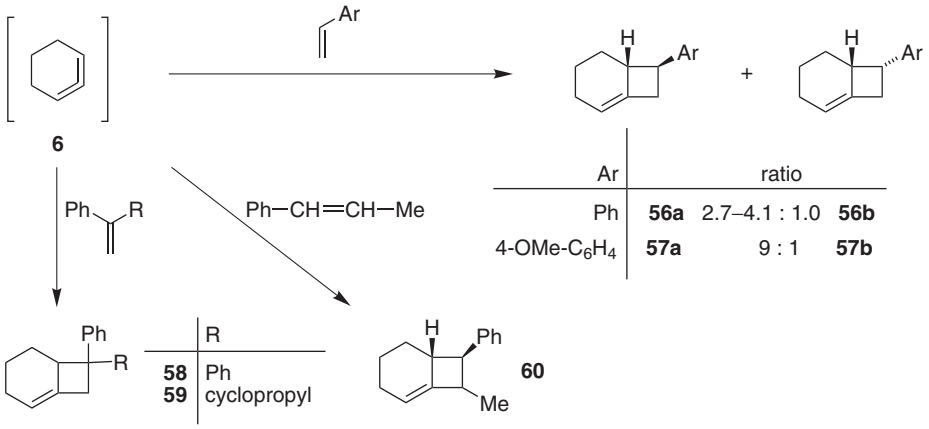
Generating **6** from 6,6-dibromobicyclo[3.1.0]hexane (**35**) with methyllithium in the presence of styrene, Moore and Moser [55] observed the first [2 + 2]-cycloadditions of **6**. Bottini et al. extended the variety of compounds able to trap **6** to 1,3-cyclohexadiene [54, 60], furan, 2-methylfuran, 1,3-cyclopentadiene and methyl-substituted 1,3-butadienes [54]. In all these reactions, the dimer **38** of **6** is a byproduct or, as in the case of the less reactive trapping agents, even the main product. Hence it is advisable to use a reaction partner of **6**, if it is a liquid, as the solvent.



Scheme 6.15 Cycloadditions of **6** with furan, 2-methylfuran, 1,3-cyclopentadiene and 1,3-cyclohexadiene.

The results of the cycloadditions of **6** to furan, 2-methylfuran, 1,3-cyclopentadiene and 1,3-cyclohexadiene are presented in Scheme 6.15. Furan gave a 10:1 mixture of **36a** and **36b**, the *endo*- and *exo*- [4 + 2]adduct, respectively, in 57% yield. The products formed from 2-methylfuran were originally considered as diastereomers [54]. On the basis of the results of the reaction of 2-methylfuran with 3δ^2-chromene [12] (**258**) (see Section 6.3.5) and also 1-oxa-2,3-cyclohexadiene [66] (**351**) (see Section 6.3.6), it is more likely that a 3:1 mixture of the regioisomers **51** and **52** was present, however. 1,3-Cyclopentadiene gave a high yield of the diastereomeric [4 + 2]-cycloadducts **53a** and **53b** in the ratio of 1.5:1. For the reaction with 1,3-cyclohexadiene, **6** was generated from 1-halocyclohexenes (**32**) [60], 1,6-dichlorocyclohexene (**33a**) or **35** [54] and furnished two [4 + 2]-cycloadducts **54** and the [2 + 2]-cycloadduct **55** in the ratio 1:10:5. By using **35** as precursor of **6**, the repetition of the reaction led to a 10:1 mixture of **54** and **55** as well as **38** in 22 and 44% yield, respectively [67].

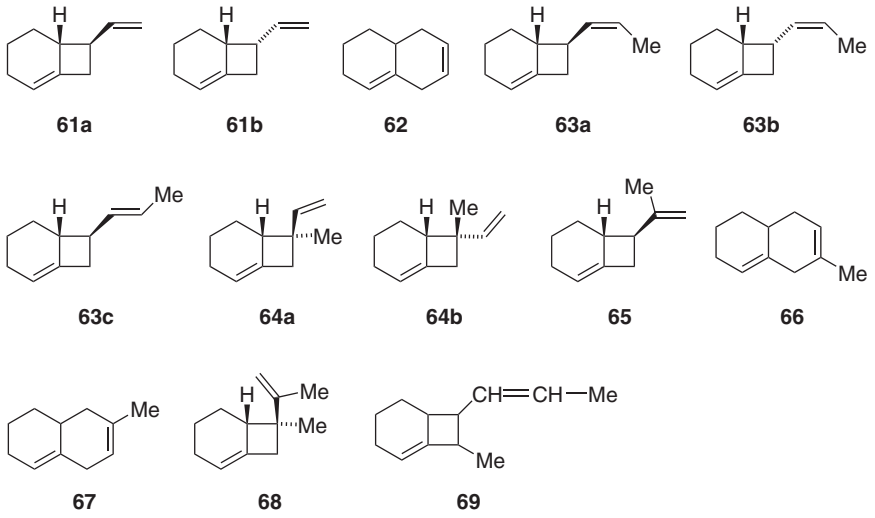
As shown in Scheme 6.16, **6** is intercepted by styrene to give the diastereomeric [2 + 2]-cycloadducts **56**. According to Moore and Moser [55], the yield is 76%. The *exo*:*endo* ratio for **56a**:**56b** depends on the temperature of the reaction: 4.1:1.0 at –45 °C and 2.7:1.0 at +42 °C. The equilibrium between **56a** and **56b** could be established by heating at 140 °C and the corresponding ratio **56a**:**56b** = 13:1 indicates that the formation of these products from **6** proceeds under kinetic control [68]. A 23% yield of the diasteromers **57a** and **57b** in the ratio 9:1 was obtained by trapping of **6** with 4-methoxystyrene [68]. A Hammett study was conducted by generating **6** in the presence of a mixtures of styrene and a substituted styrene. As the latter, 3- and 4-halostyrenes, 3- and 4-methylstyrenes and 4-alkoxystyrenes were employed. The ρ value was determined as +0.79 and indicates that **6** is acting as a nucleophile, but



Scheme 6.16 Cycloadditions of **6** with styrene and styrene derivatives.

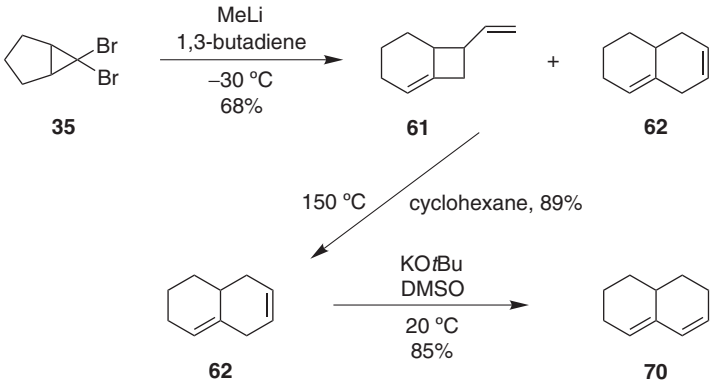
the small magnitude indicates only a small amount of charge separation in the transition state [69]. 1,1-Diphenylethylene and the commercial *E,Z* mixture of the 1-phenylpropenes trapped **6** to give the methylenecyclobutanes **58** and **60** in yields of 12 and 5%, respectively [68]. Both diastereomers **59** in the ratio of 2:1 resulted from the addition of α-cyclopropylstyrene to **6** [70].

1,3-Butadiene and a number of its methyl derivatives have also been utilized to intercept **6**. The formulas of the products are collected in Scheme 6.17. The unsubstituted diene gave rise to an 8:1:4 mixture of the [2 + 2]-cycloadducts **61a** and **61b** and the [4 + 2]-cycloadduct **62** in 68% yield [71, 72]. Only [2 + 2]-cycloadducts of the vinyl group emerged from the 1,3-pentadienes with the interesting feature that the configuration of the propenyl moiety was completely retained. Thus, the two diastereomers **63a** and **63b** in the ratio of 15:1 resulted from (*Z*)-1,3-pentadiene in 26% yield [54, 67], whereas the third diastereomer **63c** was formed exclusively from (*E*)-1,3-pentadiene in 17% yield [71]. Isoprene furnished a 43% yield of five products, the [2 + 2]-cycloadducts **64a**, **64b** and **65** and the [4 + 2]-cycloadducts **66** and **67** in a ratio of 9:2:2:1:1 [71]. In contrast, 2,3-dimethyl-1,3-butadiene gave rise to a single compound in 46% yield, namely the [2 + 2]-cycloadduct **68** [54,71]. Bottini et al. [54] reported that **6** was trapped by a mixture of the 2,4-hexadienes at –15 °C to produce two diastereomeric [2 + 2]-cycloadducts **69** in a ratio of 1.3:1. An attempt to repeat this experiment by using pure (*E,E*)-2,4-hexadiene at –30 °C failed to give any **69** and yielded only the dimer **38** of **6** [67].



Scheme 6.17 Structures of the cycloadducts of **6** with 1,3-butadiene, (*Z*)- and (*E*)-1,3-pentadiene, isoprene, 2,3-dimethyl-1,3-butadiene and 2,4-hexadiene.

The hexahydronaphthalene derivatives **62**, **66** and **67** are genuine [4 + 2]-cycloadducts of **6** as they are formed generally at temperatures as low as –15 °C. However, all [2 + 2]-cycloadducts in Scheme 6.17 except **69** have been shown to rearrange to the corresponding hexahydronaphthalenes above 130 °C [71]. Thus, the trapping of **6** by 1,3-butadienes has a preparative potential, although product mixtures are formed in most cases, but the number of components is greatly reduced on thermolysis of these mixtures. In particular, this was demonstrated with the mixture of **61a**, **61b** and **62**, 23 g of which were obtained from 60 g of the precursor **35** of **6** according to Scheme 6.18 [72]. It is noteworthy that **35** can be prepared in batches of several hundred grams [44]. The thermolysis of 10 g of **61a**, **61b** and **62**, dissolved in cyclo-



Scheme 6.18 Example for the preparative potential of 1,2-cyclohexadiene (**6**), which is the intermediate in the conversion of **35** to **61** and **62**.

hexane, at 150 °C furnished an 89% yield of pure 1,2,3,5,8,8a-hexahydronaphthalene (**62**) [72], multigram quantities of which could be converted to 1,2,3,7,8,8a-hexahydronaphthalene (**70**) by KO*t*Bu in DMSO [67, 71]. So far, this reaction sequence provides the only access to **62**, while other routes to **70** lead to an isomeric [73] or otherwise complex mixture [74].

Taking advantage of the competition principle, Bottini et al. [54] determined relative rate constants (k_{rel}) for the interception of **6** by conjugated dienes and styrene. Three precursors of **6** were employed, **32b**, **33a** and **35** (see Scheme 6.9), and also the solvent and the temperature were varied. If the polymerization of styrene and the dimerization of 1,3-cyclopentadiene are taken into account, the various sets of k_{rel} values agree well with each other and indicate the same reactive intermediate **6** under all conditions tried. Obviously, **6** is uncomplexed rather than associated with a metal halide, formed on generation of **6**, or magnesium, which is the reagent for the liberation of **6** from **33a**. The k_{rel} values obtained from experiments with **35** are summarized in Scheme 6.19.

allenophile	k_{rel}
2-methylfuran[a]	1.00
furan[a]	1.42
2,4-hexadiene[a]	1.42
(*Z*)-1,3-pentadiene[a]	4.42
2,3-dimethyl-1,3-butadiene[a]	≡ 8.33
1,3-cyclohexadiene[a]	15.4
1,3-butadiene[b]	15.8
styrene[a]	19.6
1,3-cyclopentadiene[a]	392

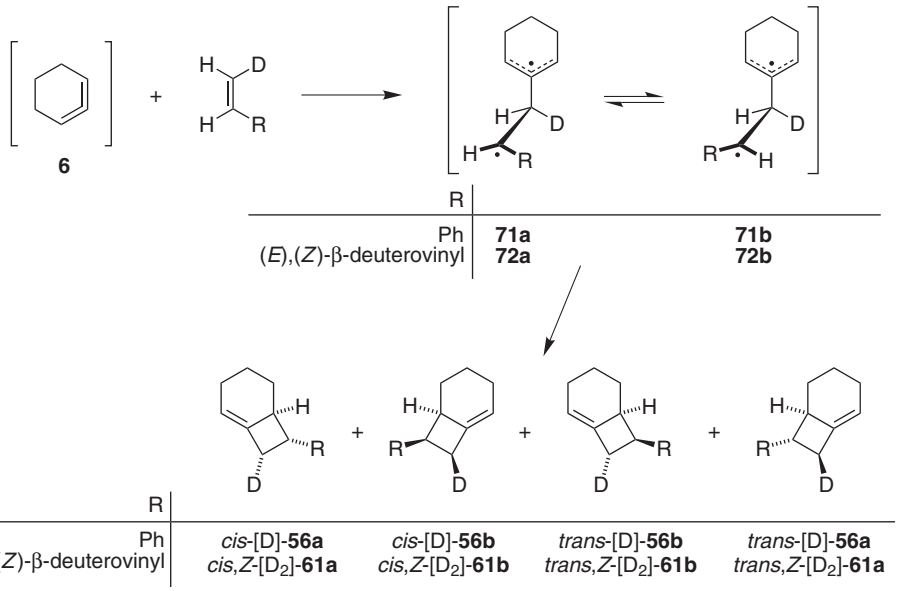
(a) At 0 °C, taken from ref. 54; (b) at –20 °C, taken from ref. 71.

Scheme 6.19 Relative rate constants (k_{rel}) for the reactions of 1,2-cyclohexadiene (**6**), generated from **35**, with conjugated dienes and styrene.

Insights into the mechanisms of the cycloadditions of **6** were gained by studying the steric course of the reactions by means of deuterium-labeled allenophiles. Two groups [68, 69] found independently that the addition of (*Z*)-β-deuterostyrene proceeds with complete loss of the stereochemical information. A concerted cycloaddition is hence excluded and a two-step reaction via the diradical **71** seems to be likely. As shown in Scheme 6.20, the central allene carbon atom of **6** should attack the β-position of (*Z*)-β-deuterostyrene and bring about the conformation **71a** of the diradical **71**, which is perfectly stabilized owing to its nature as an allyl and a benzyl radical. Since both products [D]-**56a** and [D]-**56b** result as a 1:1 isotopomeric mixture (*cis*-[D]-**56a**:*trans*-[D]-**56a** = 1:1, *cis*-[D]-**56b**:*trans*-[D]-**56b** = 1:1), the conformations **71a** and **71b** have to equilibrate completely prior to the ring closure.

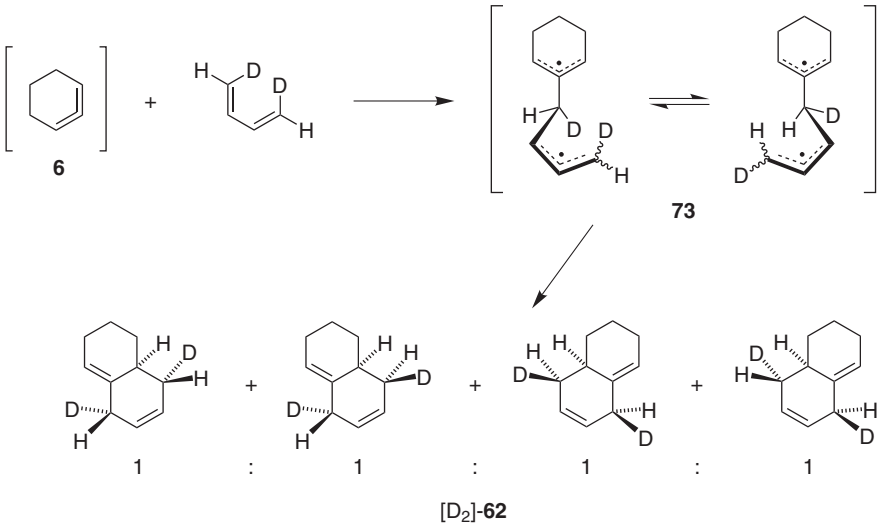
The reaction of (*Z,Z*)-1,4-dideutero-1,3-butadiene provided mechanistic details on the [2 + 2]- and the [4 + 2]-cycloaddition of **6** [72]. Concerning the former, Scheme 6.20 illustrates that the stereochemical information with regard to the deuterovinyl group that becomes part of the four-membered ring is entirely lost, whereas that of the second deuterovinyl group is completely retained. The former observation is in

accord with the result of the reaction of (*Z*)-*β*-deuterostyrene and the latter had to be expected because of the retention of the configuration on addition of (*E*)- and (*Z*)-1,3-pentadiene to **6** (see Scheme 6.17). Therefore, it is assumed that **6** attacks the *s-trans* conformer of the diene to give the conformation **72a** of the diradical **72**, which equilibrates completely with the conformation **72b** before the ring closure occurs to yield *cis*- and *trans*,(*Z*)-[D_2]-**61a** and *cis*- and *trans*,(*Z*)-[D_2]-**61b** each with an isotopomeric ratio of 1:1. The diradical **72** bears a special feature in the configuration of the non-cyclic allyl radical subunit, which is believed to be *E* and *Z* with regard to the CHD and deuterium substitutent, respectively, and not subject to isomerization.



Scheme 6.20 Steric course of the [2 + 2]-cycloadditions of 1,2-cyclohexadiene (**6**) to (*Z*)-*β*-deuterostyrene and (*Z,Z*)-1,4-dideutero-1,3-butadiene.

The product of the [4 + 2]-cycloaddition of (*Z,Z*)-1,4-dideutero-1,3-butadiene to **6** also proved to be an isotopomeric mixture. A detailed ananlysis characterized it as consisting of the four isotopomers [D_2]-**62** of Scheme 6.21 in the ratio 1:1:1:1, indicating that the sterochemical information of the allenophile had now been totally lost [72]. This finding is in line only with a stepwise mechanism via **73**, which is completely equilibrated with regard to its conformations and the configurations of the CHD group of the non-cyclic allyl radical subunit, but does not change its configuration (*Z*) as to the CHD substituent. Considering both the [2 + 2]- and the [4 + 2]-cycloaddition of (*Z,Z*)-1,4-dideutero-1,3-butadiene, it is proposed that the diradical **72** (Scheme 6.20) is generated by addition of **6** to the *s-trans* conformer of the allenophile exclusively, whereas **73** emerges from the addition to the *s-cis* conformer exclusively. Further, an interconversion of **72** and **73** would not be in accord with the experimental results.

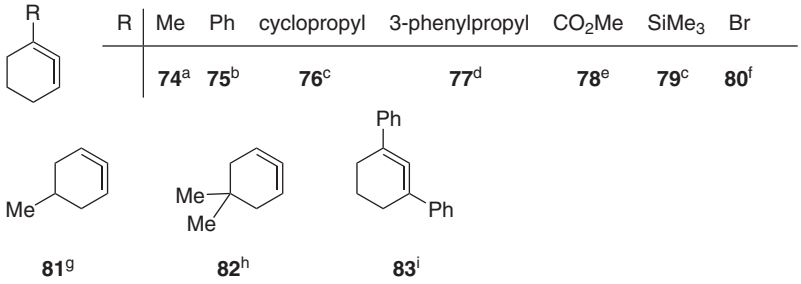


Scheme 6.21 Steric course of the [4 + 2]-cycloaddition of 1,2-cyclohexadiene (**6**) to (*Z*,*Z*)-1,4-dideutero-1,3-butadiene.

Quantum-chemical calculations distinctly favor the stepwise formation of the hexahydronaphthalene **62** from **6** and 1,3-butadiene via a diradical such as **73** over a concerted [4 + 2]-cycloaddition [9]. Whereas for the latter the energies of the *endo*- and *exo*-transition structures lie ~7 kcal mol^{-1} above that of the reactants, a transition structure en route to the diradical analogous to **73** could not be localized. However, its energy has to be very close to that of the reactants and thus significantly lower than that of the transition structures of the concerted pathways, since the formation of the diradical analogous to **73** was computed to be exothermic by 27.6 kcal mol^{-1}. The theoretical studies furnished similar results for the reaction of **6** with furan to give **36** (Scheme 6.15) and of the unsubstituted allene (C_3H_4) with 1,3-butadiene to give 4-methylencyclohexene. Invariably, a stepwise course via diradicals such as **73** was found to be preferred over a concerted process [9], although the latter was previously considered to be likely on the basis of secondary kinetic isotope effects [75].

6.3.2
Substituted 1,2-Cyclohexadienes

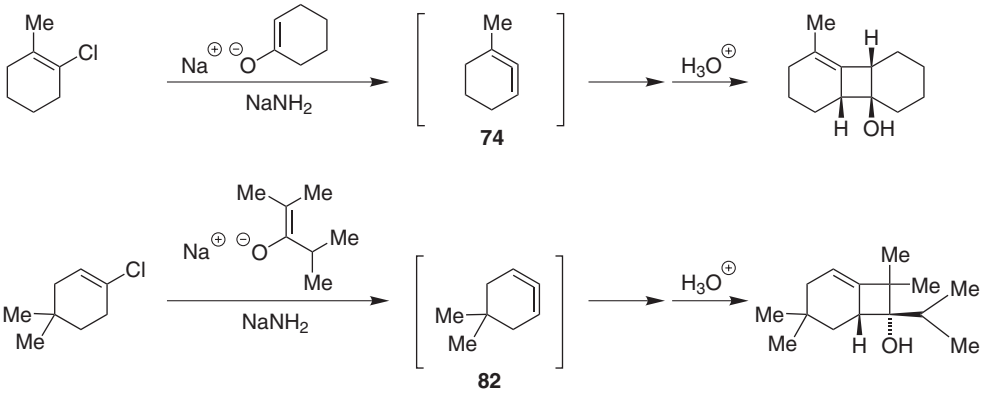
The formulas of the substituted 1,2-cyclohexadienes heretofore successfully generated and trapped are collected in Scheme 6.22. It seems that a theoretical study has been performed only with 1-phenyl-1,2-cyclohexadiene (**75**), predicting it to be a true allene with a C1–C2–C3 bond angle of 134° [76], which is very similar to that of **6**.



(a) Refs. 60, 64, 68, 71, 77; (b) refs. 76, 78, 79; (c) ref. 70; (d) ref. 78; (e) ref. 9; (f) ref. 50b; (g) refs. 60, 61; (h) refs. 64, 77; (i) ref. 76.

Scheme 6.22 Substituted 1,2-cyclohexadienes that have been successfully generated and trapped.

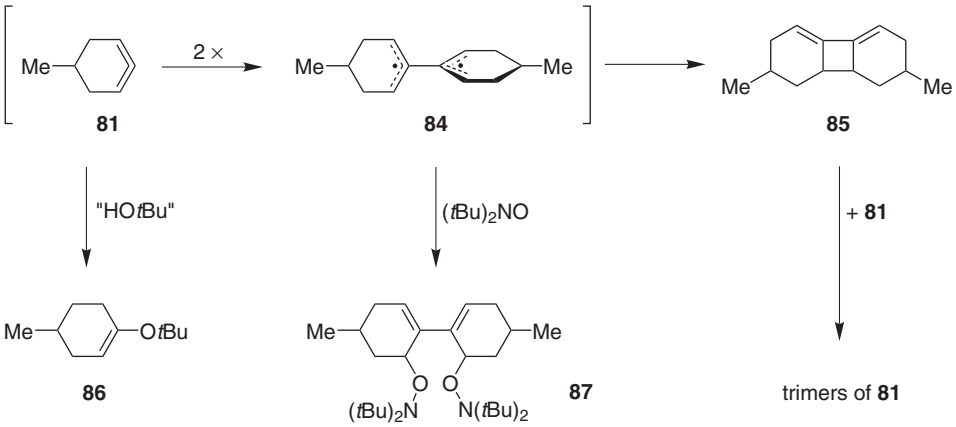
Together with **6**, its methyl derivatives **74**, **81** and **82** were liberated from the respective 1-halocyclohexenes by β-elimination to answer the query of how the competing formations of the 1,2-cyclohexadiene and the corresponding cyclohexyne depend on the reaction conditions. The treatment of 1-chloro-, 1-bromo- and 1-iodo-4-methylcyclohexene with KO*t*Bu in DMSO furnished *tert*-butyl 4-methyl- (**86**) (Scheme 6.24) and 5-methylcyclohex-1-en-1-yl ether in ratios of 98:2, 86:14 and 75:25, respectively, and thus corroborated the results obtained with deuterium-labeled 1-halocyclohexenes (see Scheme 6.11). Whereas a chlorine atom strongly favored the formation of **81** over 4-methylcyclohexyne (96:4), an iodine atom allowed both intermediates to be generated to the same extent (50:50). In THF and diglyme as solvents, the proportion of **81** was decreased relative to that of 4-methylcyclohexyne [60]. The elimination from 1-bromo-6-methyl- and 1-iodo-6-methylcyclohexene in THF gave rise to 1-methyl-1,2-cyclohexadiene (**74**) and 3-methylcyclohexyne in ratios of 50:50 and 20:80, respecttively, as was concluded from the ratios of the resulting *tert*-butyl methylcyclohexenyl ethers [60].



Scheme 6.23 3-Methylenecyclobutanol derivatives from the interception of the methyl-substituted 1,2-cyclohexadienes **74** and **82** by the enolates of cyclohexanone and diisopropyl ketone, respectively.

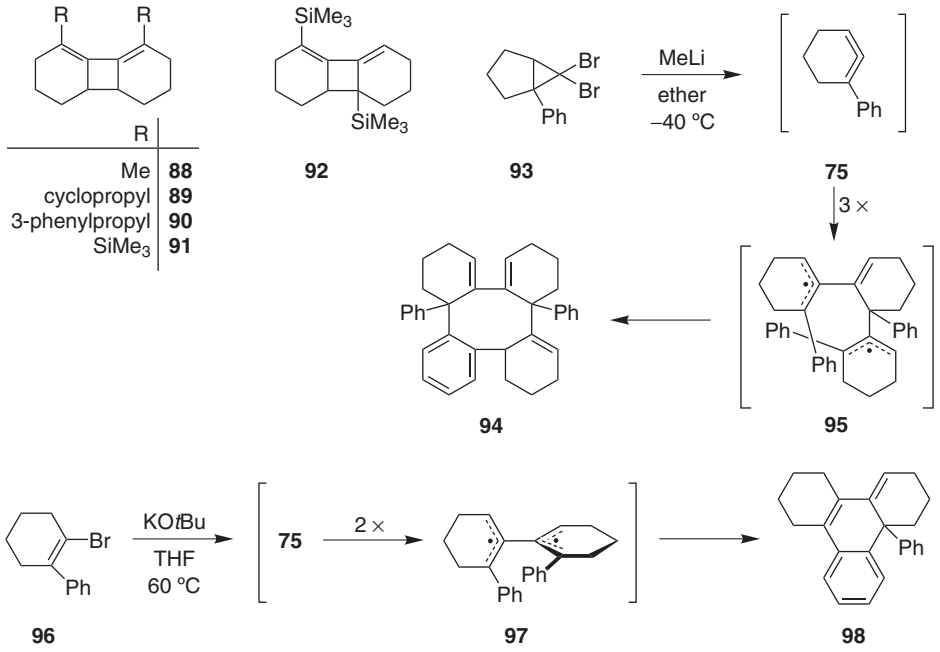
In analogy with reactions discussed with the examples of Schemes 6.12 and 6.13, **74** and **82** were trapped by enolates. Without exception, the enolate β-carbon atom attacked the central carbon atom of the allene moiety with eventual formation of 3-methylenecyclobutanol derivatives as major products in most cases [64, 77]. This type of reaction is illustrated in Scheme 6.23 by two examples.

In addition to the *tert*-butyl enol ethers mentioned above (15% yield), the action of KO*t*Bu on 1-iodo-4-methylcyclohexene in DMSO furnished the dimers **85** and trimers of **81** in 30 and ~25% yield (Scheme 6.24). As in the case of **6** (see Scheme 6.10), the formation of oligomers of **81** was completely suppressed on performance of this reaction in the presence of $(t\text{Bu})_2\text{NO}$, whereas the enol ethers (**86** and its 5-methyl isomer, with the former originating in part and the latter totally from 4-methylcyclohexyne) were observed as in the reaction in the absence of the stable radical. Instead of the dimers **85** and the trimers of **81**, a mixture of the hydroxylamine derivatives **87** was isolated in 38% yield. These findings indicate that **81** has no diradical character, in contrast to its immediate dimer **84**, which is hence trapped quantitatively by $(t\text{Bu})_2\text{NO}$ [61].



Scheme 6.24 Formation of the enolether **86** and of oligomers from 5-methyl-1,2-cyclohexadiene (**81**) and trapping of the diradical **84** by di-*tert*-butyl nitroxide, according to Bottini and co-workers.

The cycloadditions of 1-substituted 1,2-cyclohexadienes and among them their dimerization are of interest because of the position selectivity. Does the reaction occur at the substituted or the unsubstituted ethylene subunit? For that question to be answered, 1-methyl- (**74**), 1-phenyl- (**75**), 1-cyclopropyl- (**76**), 1-(3-phenylpropyl)- (**77**) and 1-trimethylsilyl-1,2-cyclohexadiene (**79**) were generated from the corresponding 1-substituted 6,6-dibromobicyclo[3.1.0]hexanes with methyllithium. Several of these dibromides are thermolabile, which particularly applies to the phenyl (**93**) [76] and the cyclopropyl derivative [70]. In those cases, it is advisable or necessary to prepare the dibromide in situ, that is, the dibromocarbene is liberated from tetrabromomethane with methyllithium at –60 °C in the presence of the respective cyclopentene. Without workup, from the thus formed 6,6-dibromobicyclo[3.1.0]hexane, the 1,2-cyclohexadiene is then generated by addition of methyllithium at ~ –30 °C.

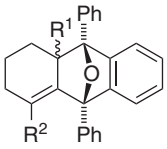


Scheme 6.25 Dimers and a trimer of 1-substituted 1,2-cyclohexadienes.

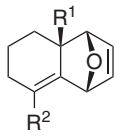
Scheme 6.25 shows the formulas of the compounds **88** [68], **89** [70], **90** [78], **91** and **92** [70], which emerge from the dimerization of **74**, **76**, **77** and **79**, respectively. The structure is of the same type as that of the dimer **38** of **6** (Scheme 6.10). The configuration has not been determined, but it is assumed to be *trans* as in the case of **38**. Hence the cyclization of the tetramethyleneethane diradicals of type **37** (Scheme 6.10), the immediate precursors of the isolated dimers, should proceed as a least-motion process at the unsubstituted radical centers. Only the trimethylsilyl group causes a predominantly alternative course, since the dimers **91** and **92** were obtained in a ratio of 1:2.

Oligomers of another type are brought about by 1-phenyl-1,2-cyclohexadiene (**75**) and even different products arise from different sources of **75**. The treatment of **93** with methyllithium furnished mainly the trimer **94** of **75** in addition to unidentified material, whereas the dimer **98** emerged (31% yield) from 1-bromo-2-phenylcyclohexene (**96**) and KO*t*Bu (Scheme 6.25). In both cases, the initial step should be the dimerization of **75** giving rise to the diradical **97**. Originating from **96**, **97** cyclizes with participation of a phenyl group and furnishes a methylene-1,3-cyclohexadiene derivative, which is isomerized to yield **98** under the influence of KO*t*Bu. Possibly caused by the high local concentration of **75**, connected to the tetrameric nature of methyllithium, **75** may not have time enough to cyclize with formation of the progenitor to **98** but adds to another molecule of **75**. Thus produced, the diradical **95** undergoes ring closure with participation of a phenyl group and, after a 1,3-hydrogen shift, the product is **94** [79].

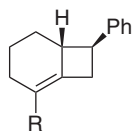
Scheme 6.26 contains the formulas of cycloadducts of 1-substituted 1,2-cyclohexadienes to furan, 1,3-diphenylisobenzofuran (DPIBF), styrene and 1,1-diphenylethylene. Wittig and Fritze [50b] obtained the [4 + 2]-cycloadduct **99** of **80** from the reaction of 1,2-dibromocyclohexene with KO*t*Bu in the presence of DPIBF and suspected the formation of the positional isomer **100** and its in situ conversion to a second product isolated. With an excess of base, **99** was converted to a 1,2-cyclohexadiene derivative, which also was trapped by DPIBF. The compounds **101** were prepared from different precursors to 1-phenyl-1,2-cyclohexadiene (**75**) and DPIBF [76]. One was **93** and the other the anion formed from 1-chloro-2-phenylcyclohexene and KO*t*Bu in DMSO, which was irradiated or thermolyzed in the presence of DPIBF. The performance of the latter procedure in the presence of furan gave rise to the [4 + 2]-cycloadduct **102** in 50% yield. The method of liberating the strained allene from a 2-chloroallyl anion was also applied to 1-chloro-2,6-diphenylcyclohexene and the resulting 1,3-diphenyl-1,2-cyclohexadiene (**83**) was intercepted by furan to furnish **103**. Methyl 1,2-cyclohexadiene-1-carboxylate (**78**) was generated in the conventional manner from a mixture of methyl 2-chlorocyclohex-2-ene- and methyl 2-chlorocyclohex-1-enecarboxylate by KO*t*Bu and trapped by furan to give the positional isomers **104** and **105** in a ratio of 3.4:1 in 68% yield [9]. If instead of the methyl ester **78** the corresponding L-menthyl and L-bornyl esters were exposed to furan, no diastereoselectivity could be observed in the products analogous to **104** and **105**.

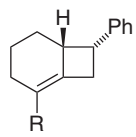


	R^1	R^2
99	H	Br
100	Br	H
101	Ph	H

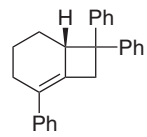


	R^1	R^2
102	Ph	H
103	Ph	Ph
104	CO_2Me	H
105	H	CO_2Me





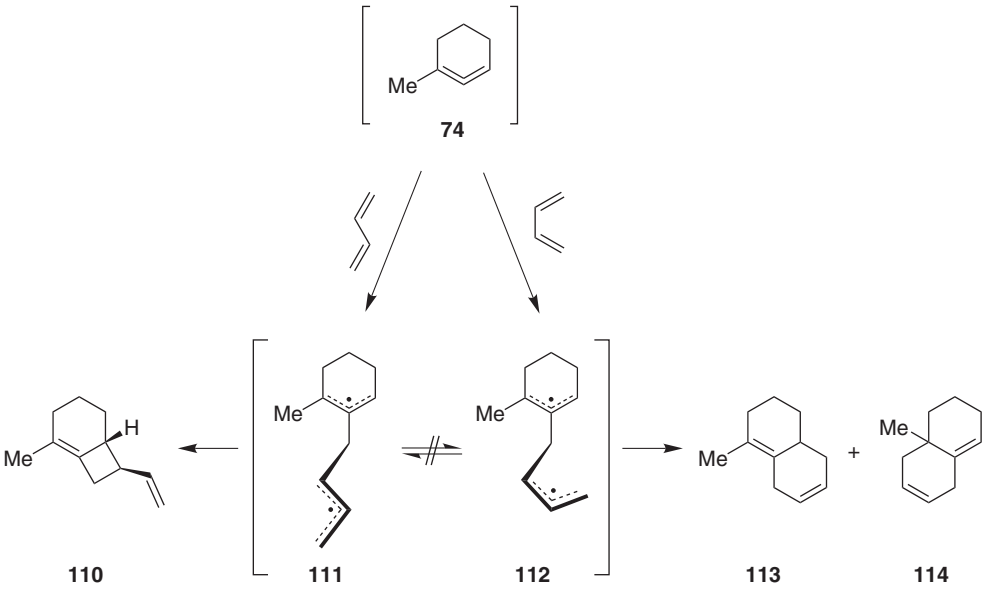
R				
Me	**106a**	4	: 1	**106b**
Ph	**107a**	1	: 1	**107b**
$SiMe_3$	**108a**	1.4	: 1	**108b**



109

Scheme 6.26 Cycloadducts of furans and styrenes to 1-substituted 1,2-cyclohexadienes.

The methylenecyclobutane derivatives **106a**,**b** (54% yield) [68], **107a**,**b** (24%) [78] and **108a**,**b** (28%) [70] were the products from styrene addition to 1-methyl- (**74**), 1-phenyl- (**75**) and 1-trimethylsilyl-1,2-cyclohexadiene (**79**), all of them generated by the DMS method. The triphenyl compound **109** was obtained in 34% yield from **75** and 1,1-diphenylethylene [78]. In addition to the methylenecyclobutane derivative **110** (29% yield), the two methylhexahydronaphthalenes **113** (1%) and **114** (2%) were formed on exposure of **74** to 1,3-butadiene (Scheme 6.27) [71].



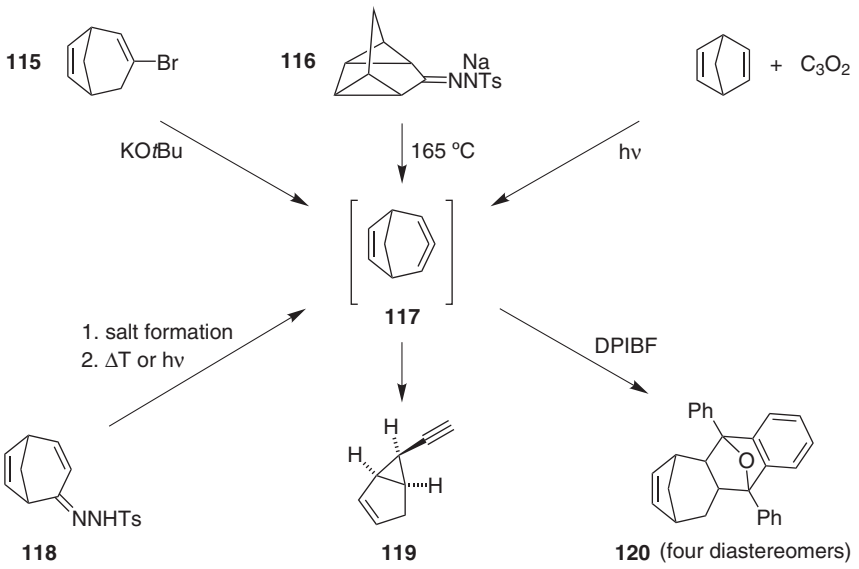
Scheme 6.27 Proposal of the mechanisms governing [2 + 2]- and [4 + 2]-cycloadditions using the example of the reaction between 1-methyl-1,2-cyclohexadiene (**74**) and 1,3-butadiene.

Concerning the positional selectivity of the above cycloadditions, the unsubstituted double bond of the allene is strongly preferred in the [2 + 2]-cycloadditions, with the already mentioned exception of the dimerization of **79**. In the case of the [4 + 2]-cycloadditions, the substituted double bond seems to be the more reactive. Given the two-step course of all these reactions [9], the explanation of the positional selectivity is restricted to the question of the site of the ring closure of the diradical intermediates. This is illustrated in Scheme 6.27 by the addition of **74** to 1,3-butadiene giving rise initially to **111** and **112**, having a non-cyclic allyl radical subunit with an *E*- and a *Z*-configuration, respectively. They should be formed in separate ways, **111** from the *s-trans* and **112** from the *s-cis* conformer of 1,3-butadiene. Probably, they do not interconvert and, with high selectivity, close a four-membered and a six-membered ring to furnish **110** and **113**–**114**, respectively. If the spin density of the cyclic allyl radical subunit of **111** and **112** were decisive exclusively, the positional selectivity would be the same for [2 + 2]- and [4 + 2]-cycloadditions, which is not true. Probably, steric interactions between the substituents at the six-membered ring of **111** and **112** also play an important part.

6.3.3
Bridged and Annulated 1,2-Cyclohexadienes

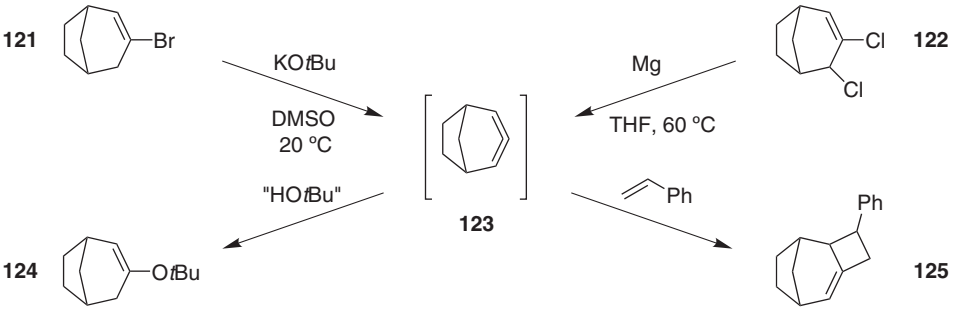
Bergman and Rajadhyaksha [80] were the first to generate bicyclo[3.2.1]octa-2,3,6-diene (**117**), but they considered it as a homoconjugated carbene rather than a cyclic allene. They used two routes directed to **117**: β-elimination from 3-bromobicyclo[3.2.1]octa-2,6-diene (**115**) with KO*t*Bu in DMSO at room temperature and thermolysis of the tetracyclo[3.2.1.$0^{2,7}$.$0^{4,6}$]octan-3-one tosylhydrazone sodium salt (**116**). Of course, **117** could not be observed, but rearranged to *endo*-6-ethynylbicyclo[3.1.0]-hex-2-ene (**119**) (Scheme 6.28), which was isolated in moderate yields. Obviously, the conversion into **119** can compete with oligomerization of **117**, a dimer of which has not been described. A small amount of **119** was also obtained on photolysis of a mixture of norbornadiene and carbon suboxide [81]. The intermediacy of **117** is highly likely there as it is in the thermal and photochemical decomposition of salts of bicyclo[3.2.1]octa-3,6-dien-2-one tosylhydrazone (**118**). The latter reactions furnished complex product mixtures containing **119** [82].

That the precursor to **119** must be the cyclic allene **117** was proved by Balci and Jones [46], who treated **115** at 53 °C with KO*t*Bu in THF in the presence of DPIBF and came to four diastereomeric [4 + 2]-cycloadducts **120** of **117** in 53% yield (Scheme 6.28). Apparently, the rearrangement of **117** to **119** is considerably slower than the trapping by DPIBF. The replacement of KO*t*Bu by enantiopure potassium menthoxide gave rise to optically active products **120**. On conducting this experiment at 100 °C, **120** was shown to be racemic. These findings indicate that **117** is chiral and undergoes enantiomerization with about the same ease as 1,2-cyclohexadiene (**6**) [45, 46]. When the reaction of **115** with potassium menthoxide at 53 °C was carried out in the absence of



Scheme 6.28 Precursors and reactions of bicyclo[3.2.1]octa-2,3,6-triene (**117**).

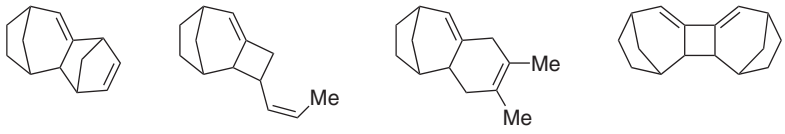
DPIBF, the resulting **119** was optically active. This suggests that the progenitor of **119** has the allene structure **117** rather than other conceivable constitutions [80, 81]. Even early quantum-chemical calculations on **117** showed a strongly bent, chiral structure, although the enantiomerization barrier was not correctly estimated [19].



Scheme 6.29 Generation of bicyclo[3.2.1]octa-2,3-diene (**123**) and trapping by KO*t*Bu and styrene.

Bicyclo[3.2.1]octa-2,3-diene (**123**) (Scheme 6.29), the dihydro derivative of **117**, was described for the first time by Devaprabhakara et al. [83], who isolated the enol ether **124** in 62% yield after the treatment of 3-bromobicyclo[3.2.1]oct-2-ene (**121**) with KO*t*Bu in DMSO. When this reaction was performed in the presence of styrene, two [2 + 2]-cycloadducts of **123** were obtained in 50% yield. The claim that regioisomers were present [83] seems unlikely in view of the styrene addition to **6** (Scheme 6.16) and its 1-substituted derivatives (Scheme 6.26). Rather, a mixture of diastereomers **125** of the same kind should have been formed as it was collected in 82% yield by Bottini and Hilton [84] after the reaction of the dichloride **122** with magnesium in the presence of styrene. However, the possibility was not excluded that bicyclo[3.2.1]oct-2-yne results instead of **123** when **121** undergoes a β-elimination. The trapping product of the strained acetylene by styrene could then be isomerized by the base to give **125**, thus pretending the intermediacy of **123**. Indeed, extended studies on the reaction of **121** with KO*t*Bu revealed that the allene **123** plays only a minor part en route to **124** and that the major quantity of **124** results from the formal addition of HO*t*Bu to bicyclo[3.2.1]oct-2-yne [85, 86]. Concerning the formation of enamines in the reactions of 3-chlorobicyclo[3.2.1]oct-2-ene with mixtures of $NaNH_2$, NaO*t*Bu and morpholine, diethylamine or *N*-methylaniline in THF, Caubère et al. [87] also concluded that bicyclo[3.2.1]oct-2-yne is the most important intermediate. Further, the elimination observed on treatment of 3-chloro- and 3-bromo-4-(2-hydroxyethoxy)bicyclo[3.2.1]oct-2-ene with KO*t*Bu was considered to generate mainly the bicycloalkyne and the corresponding bicycloallene to only a small extent [88].

In addition to styrene, Bottini and Hilton [84] employed 1,3-cyclopentadiene, (*Z*)-1,3-pentadiene and 2,3-dimethyl-1,3-butadiene to intercept **123**, which was generated from **122**. 1,3-Cyclopentadiene gave rise to three [4 + 2]-cycloadducts **126** (Scheme 6.30) and (*Z*)-1,3-pentadiene furnished mainly one [2 + 2]-cycloadduct **127**. In the case of 2,3-dimethyl-1,3-butadiene, the major product was a mixture of three



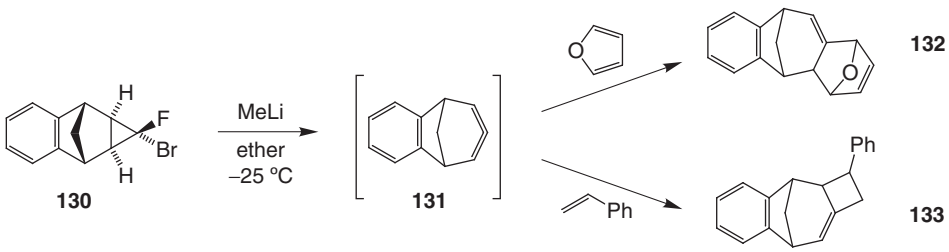
126 **127** **128** **129**

Scheme 6.30 Structure of the trapping products of bicyclo[3.2.1]-octa-2,3-diene (**123**) with 1,3-cyclopentadiene, (*Z*)-1,3-pentadiene and 2,3-dimethyl-1,3-butadiene and of the dimers of **123**.

dimers **129** of **123** and, in addition, a [4 + 2]-cycloadduct **128** was obtained. Stereochemical assignments to these products were not attempted, but relative rate constants of the cycloaddition of the allenophiles to **123** have been determined in THF at 60 °C: 1,3-cyclopentadiene, $k_{rel} = 22$; 2,3-dimethyl-1,3-butadiene, ≡ 5.6; styrene, 3.3; and (*Z*)-1,3-pentadiene, 1.0. Compared with the reactivity towards 1,2-cyclohexadiene (**6**) (see Scheme 6.19), the exchange of the order of 2,3-dimethyl-1,3-butadiene and styrene is remarkable.

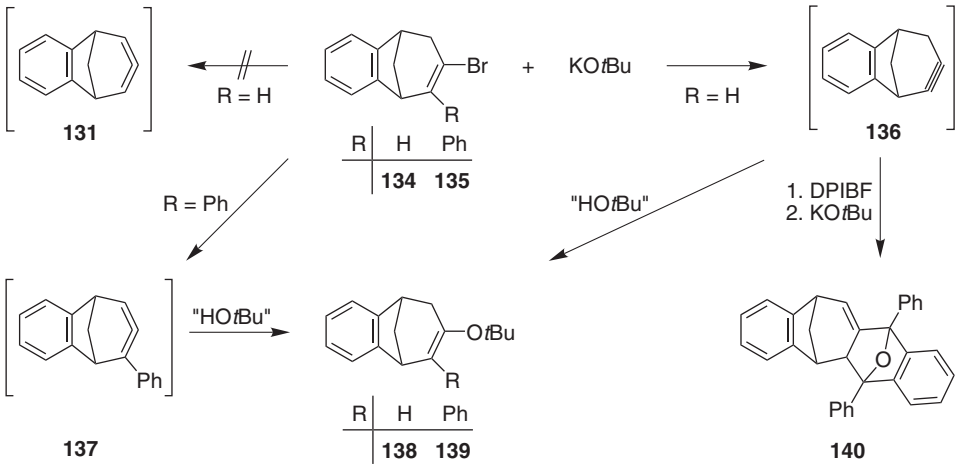
The DMS method has not been employed yet for the generation of **117** and **123**, since the dibromocarbene adducts of norbornadiene and norbornene rearrange under the usual conditions for the preparation [89]. However, they could be synthesized at –60 °C by taking advantage of tetrabromomethane and methyllithium as a source of the carbene [90] and could prove stable enough to serve as precursors of **117** and **123**. On the other hand, the adducts of bromofluorocarbene to norbornadiene and norbornene having the fluorine atom in a *cis*-orientation should be isolable at room temperature and hence be usable as stable precursors of **117** and **123**. These variations of the DMS method were published on the occasion of the preparation of cycloadducts of 1-oxa-2,3-cyclohexadiene (**351**) (Section 6.3.6) [35, 91], 1,2,4-cyclohexatriene (**162**) and 3δ^2-1*H*-naphthalene (**221**) (Section 6.3.4) [35, 92].

The bromofluorocarbene adduct **130** of benzonorbornadiene proved to be a reliable precursor of 3δ^2-1,5-dihydro-1,5-methanobenzocycloheptene (**131**), the benzo derivative of **117**. Exposure of **130** to methyllithium in the presence of furan and styrene gave rise to cycloadducts of **131**, namely two [4 + 2]-cycloadducts **132** and several [2 + 2]-cycloadducts **133** in 45 and 30% yield, respectively (Scheme 6.31) [93].



130 **131** **132** **133**

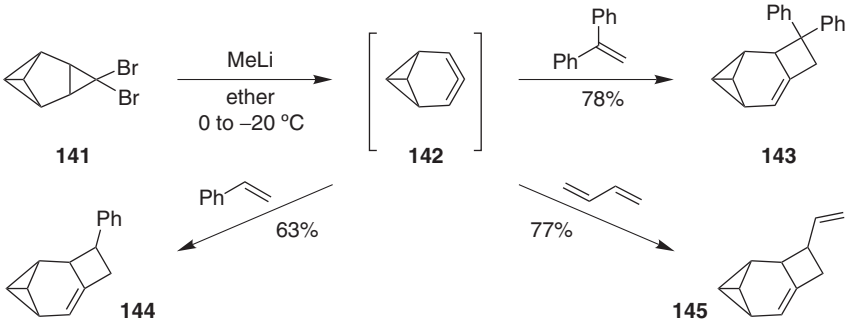
Scheme 6.31 Generation of 3δ^2-1,5-dihydro-1,5-methano-benzocycloheptene (**131**) and its interception by furan and styrene.



Scheme 6.32 β-Elimination of hydrogen bromide from the 3-bromo-4,5-dihydro-1,5-methano-1*H*-benzocycloheptenes **134** and **135** by KO*t*Bu and trapping of the intermediates.

In previous experiments, Balci et al. [2] had tried to liberate **131** from 3-bromo-6,7-benzobicyclo[3.2.1]octa-2,6-diene (**134**) by β-elimination of hydrogen bromide with KO*t*Bu. Both the trapping products **140** of the intermediate with DPIBF and the enol ether **138** appeared to provide evidence in favor of **131**, but did not exclude the cycloalkyne **136** [94]. The generation of **136** in the presence of DPIBF by two routes that cannot lead to **131** gave rise to cycloadducts different from **140**, which were converted into **140** on treatment with KO*t*Bu, however [95, 96]. On the basis of these results and further investigations [97, 98], the formation of **131** from **134** is considered unlikely. Instead of **131**, **136** seems to arise and to be the source of the products observed. In contrast, the phenyl derivative **137** of **131** is the obvious intermediate in the reaction of **135** with KO*t*Bu, which furnished the enol ether **139** [2].

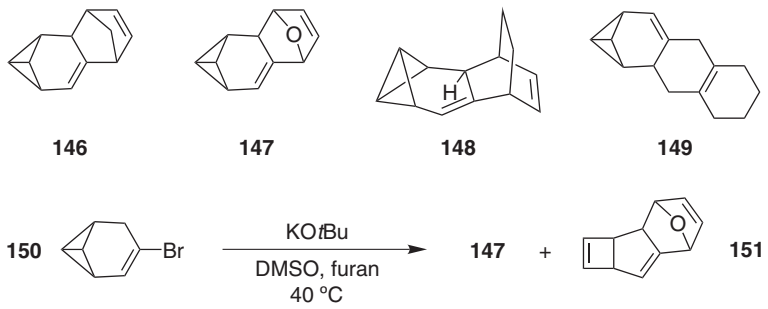
7,7-Dibromotetracyclo[4.1.0.0^{2,4}.0^{3,5}]heptane (**141**), the dibromocarbene adduct of benzvalene, turned out to be an efficient starting material for the synthesis of trapping products of tricyclo[4.1.0.0^{2,7}]hepta-3,4-diene (**142**) (Scheme 6.33) [99]. The isolation of **141** is possible, since it rearranges to 4,5-dibromotricyclo[4.1.0.0^{2,7}]hept-3-enes only at 80 °C [100], but appropriate safety precautions are necessary owing to its tendency to detonate [101]. Although quantum-chemical calculations have not been carried out, **142** should be a real allene having C_2 symmetry rather than a diradical as was presumed previously [99b]. The efficiency of the interception by activated alkenes seems to be a good criterion for an allene ground state of a 1,2-cyclohexadiene derivative. If such a species is a zwitterion or if the energy of the zwitterionic state lies only a few kcal mol^{-1} above that of the allene state, the sensitivity towards nucleophiles (KO*t*Bu) seems to prevent cycloadditions (see Section 6.3.5).



Scheme 6.33 Liberation of tricyclo[4.1.0.0^{2,7}]hepta-3,4-diene (**142**) from 7,7-dibromotetracyclo[4.1.0.0^{2,4}.0^{3,5}]heptane (**141**) and formation of [2 + 2]-cycloadducts of **142**.

The [2 + 2]-cycloadditions of **142** are collected in Scheme 6.33. 1,1-Diphenylethylene furnished the tetracyclononene **143** in 78% yield. Styrene gave rise to a 5:1 mixture of two diastereomers **144**, in the major product of which the phenyl group should occupy the *trans*-position relative to the bicyclobutane system. The same configuration is the most probable one for **145**, which resulted as a single compound (77% yield) from the trapping of **142** by 1,3-butadiene [99b].

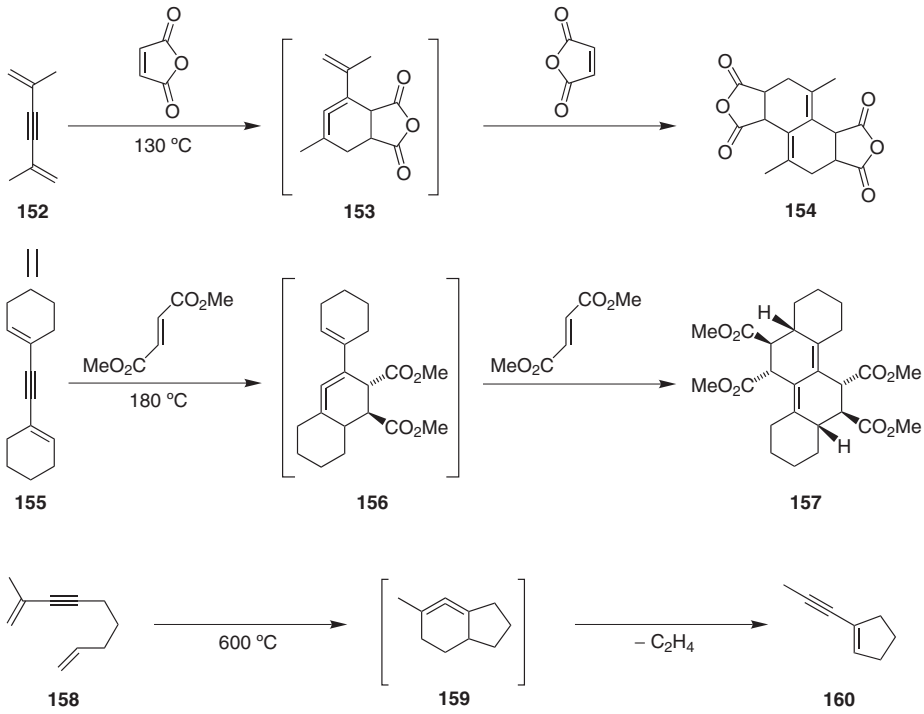
The 1,3-dienes cyclopentadiene, furan, cyclohexadiene and 1,2-bismethylenecyclohexane converted **142** to two diastereomers **146** (1:1, 73% yield), two diastereomers **147** (9:1, 54%), **148** (37%) [99b] and **149** (41%) [102], respectively (Scheme 6.34). A mixture of several isomers was formed in 63% yield on addition of 1,3,5-cycloheptatriene to **142** [99b]. The treatment of **141** with methyllithium in the absence of a reagent for **142** led to a complex mixture, probably consisting of higher oligomers of **142**. An experiment to generate **142** by β-elimination from 4-bromotricyclo[4.1.0.0^{2,7}]hept-3-ene (**150**) with KO*t*Bu in DMSO at 40 °C in the presence of furan gave rise to the products **147** and **151** [102]. It is believed that **151** originates from **147** by thermal rearrangement, since separate studies revealed such transformations



Scheme 6.34 [4 + 2]-Cycloadducts of tricyclo[4.1.0.0^{2,7}]hepta-3,4-diene (**142**) and the generation of **142** from 4-bromotricyclo-[4.1.0.0^{2,7}]hept-3-ene (**150**) in the presence of furan.

on heating of **146–148** [103], whereas the [2 + 2]-cycloadducts **144** and **145** of **142** were shown to produce derivatives of 1,3,5-cycloheptatriene at 80 °C [102, 104]. Whether the β-elimination from **150** creates the allene **142** exclusively or also produces the corresponding tricycloalkyne was not investigated.

The formal [4 + 2]-cycloaddition of conjugated enynes to alkenes, sometimes called a 'dehydro' Diels–Alder reaction, leads to 1,2-cyclohexadiene (**6**) and derivatives thereof. Such processes take place if the product is able to undergo a reaction that provides a stable compound. Miller et al. [105, 106]. quoted a number of such cycloadditions recently and revisited two examples from the 1930s and 1940s. They showed that the acetylene subunit is changed initially in the acid-catalyzed process and hence derivatives of 1,2-cyclohexadiene cannot be intermediates. However, the reaction of a divinylacetylene with 2 equivalents of a typical dienophile is best described in terms of two consecutive concerted [4 + 2]-cycloadditions. This type of reaction was discovered by Butz et al. [107a] in 1940 and supported by further examples in later years [107b–f]. Remarkably, the authors proposed the 1,2-cyclohexadiene derivative **153** to be the intermediate of the conversion of 2,5-dimethylhexa-1,5-dien-3-yne (**152**) by maleic anhydride to the tetracyclic product **154** (Scheme 6.35) as early as in their first paper [107a].

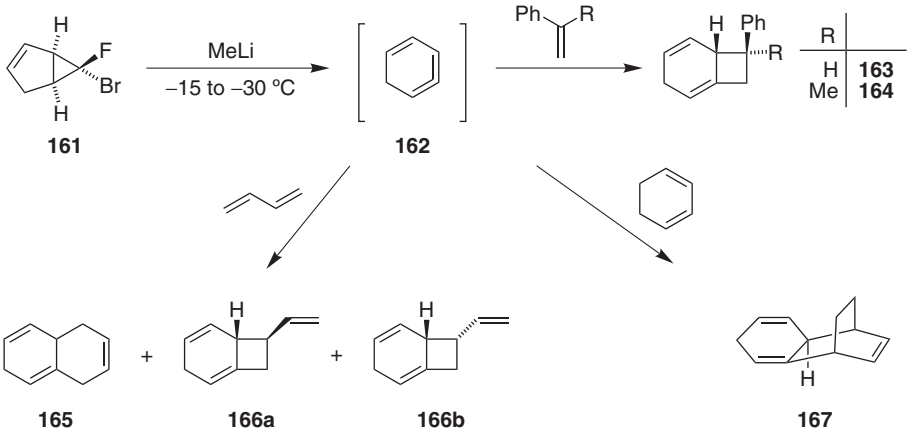


Scheme 6.35 'Dehydro' Diels–Alder reactions of conjugated enynes with alkenes.

The reaction of bis(cyclohex-1-en-1-yl)acetylene (**155**) with dimethyl fumarate, proceeding at 180 °C via **156** and yielding **157** [107d], was repeated by Miller et al. [106], who established the configuration of **157** and that of the analogous product from **155** and maleic anhydride. In these processes, the intermediates such as **153** and **156** have the possibility of undergoing a [4 + 2]-cycloaddition, this time a regular Diels–Alder reaction and thereby to convert smoothly into a stable product. Such a reaction, taking advantage of the high strain of the 1,2-cyclohexadiene system, is not available to **6**, the formal [4 + 2]-cycloadduct of butenyne to ethylene, since, for example, a thermal 1,3-hydrogen shift, which would produce 1,3-cyclohexadiene from **6**, is not allowed. Therefore, reliable examples of intermolecular additions of conjugated enynes without a second conjugated ethylene moiety at the acetylene subunit to an alkene are not known [105, 106]. However, Johnson et al. [59] have shown by the gas-phase pyrolysis of 2-methylnona-1,8-dien-3-yne (**158**) (Scheme 6.35) that the intramolecular [4 + 2]-cycloaddition can be enforced. The resulting 1,2-cyclohexadiene **159** was subject to a retrograde 'dehydro' Diels–Alder reaction giving rise to the propynylcyclopentene **160** and ethylene.

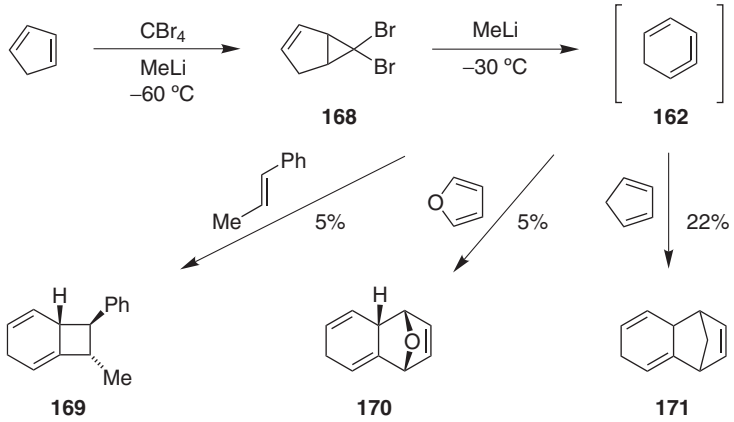
6.3.4
1,2,4-Cyclohexatriene (162), 3δ^2-1*H*-Naphthalene (221) and Their Derivatives

Since 1,2,4-cyclohexatriene (**162**) is an isomer of benzene and 3δ^2-1*H*-naphthalene (**221**) an isomer of naphthalene, these intermediates attracted much attention and may be called the isobenzene **162** and the isonaphthalene **221**. Although the relationship of **162** to 1,2-cyclohexadiene (**6**) is obvious, it took 23 years from the first clear evidence of **6** [50a] to that of **162** [35]. That is because possible precursors of **162** that are analogous to those of **6** were unknown and had to be synthesized just for the purpose of the generation of **162**. Since the adduct **168** of dibromocarbene to 1,3-cyclopentadiene had not been described in the literature, the diene was exposed to bromofluorocarbene. For the reason discussed in Section 6.2, the *endo*-fluoro compound **161** (20% yield) proved to be stable at room temperature, whereas the *exo*-fluoro isomer was converted into fluorobenzene under the reaction conditions. It turned out that **161** is a perfect substrate in the DMS reaction. Accordingly, the addition of methyllithium to a solution of **161** in an activated alkene furnished annulated derivatives of 1,4-cyclohexadiene, which obviously are cycloadducts of **162** (Scheme 6.36). Styrene and α-methylstyrene gave the [2 + 2]-cycloadducts **163** [92] and **164** [66] in 65 and 51% yield, respectively. 1,3-Butadiene brought about a 30% yield of a 6:3:1 mixture of the [4 + 2]-cycloadduct **165** and the [2 + 2]-cycloadducts **166a** and **166b**. On heating this mixture in refluxing cyclohexane, it was converted into pure 1,4,6,8a-tetrahydronaphthalene (**165**) in high yield, which was hitherto unknown and is now readily accessible. 1,3-Cyclohexadiene trapped **162** to give the [4 + 2]-cycloadduct **167**, which was isolated in 14% yield in addition to the product of its dehydrogenation (dihydrobenzobarrelene, 19%) [67].



Scheme 6.36 Trapping of 1,2,4-cyclohexatriene (**162**), generated from *exo*-6-bromo-*endo*-6-fluorobicyclo[3.1.0]hex-2-ene (**161**), by styrenes, 1,3-butadiene and 1,3-cyclohexadiene.

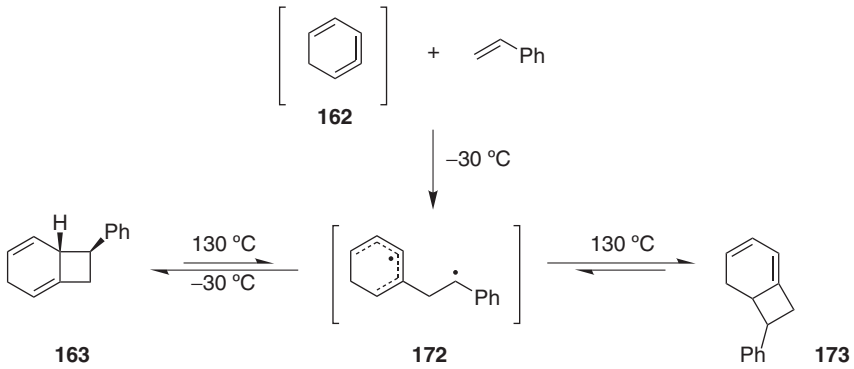
Since the yield of **161** is only 20%, the overall yields of the cycloadducts with reference to 1,3-cyclopentadiene are rather modest. Therefore, it was tested whether or not 6,6-dibromobicyclo[3.1.0]hex-2-ene (**168**) is after all stable enough to serve as progenitor of **162**. To that end, dibromocarbene was generated from tetrabromomethane by methyllithium [90] at –60 °C in the presence of 1,3-cyclopentadiene. Low-temperature NMR spectra revealed that **168** remains intact in the solution up to 0 °C. On the basis of this observation, a one-pot procedure was developed for the synthesis of the trapping products of **162** from 1,3-cyclopentadiene. As illustrated in Scheme 6.37, **168** was prepared at –60 °C, then an allenophile and methyllithium in succession were added to the mixture at –30 °C. In this way, the adducts of **162** to



Scheme 6.37 One-pot reactions, starting from 1,3-cyclopentadiene, to prepare the products of the interception of 1,2,4-cyclohexatriene (**162**) by (*E*)-1-phenylpropene, furan and 1,3-cyclopentadiene.

(*E*)-1-phenylpropene, furan and 1,3-cyclopentadiene were obtained. The yields of **169**, **170** and **171** (*endo*:*exo* ≈ 2:1) amounted to 5, 5 and 22%, respectively [92]. Analogously, **163** and also to **165** and **166** were synthesized in 49% [92] and 11% [67] overall yield.

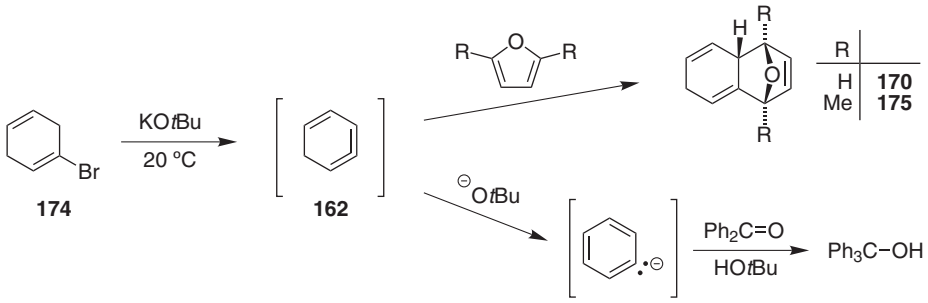
All cycloadditions of **162** proceed at the allene π-bond that is conjugated to the vinylene group. Although a concerted mechanism of the [4 + 2]-cycloadditions was assumed previously [92], two-step processes via diradical intermediates are more likely on the basis of quantum-chemical calculations [9], as in the case of the [2 + 2]-cycloadditions. With respect to the part stemming from **162**, these intermediates are cyclohexadienyl radicals with a side-chain in the 2-position, which contains an allyl or a benzyl radical subunit. Thus, on interception of **162** by styrene, the diradical **172** should result and undergo ring closure employing the central carbon atom of the pentadienyl radical moiety to give **163** (Scheme 6.38). That the final step proceeds under kinetic control follows from the thermolysis of **163** at 130 °C, which yields a 1:3 mixture of **163** and **173**. Most probably, **172** is regenerated at 130 °C and undergoes ring closure using the proximate terminal carbon atom of the pentadienyl radical moiety now as well with formation of **173**, that is, under thermodynamic control.



Scheme 6.38 Mechanism of the formation and the thermolysis of the cycloadduct **163** of styrene to **162**.

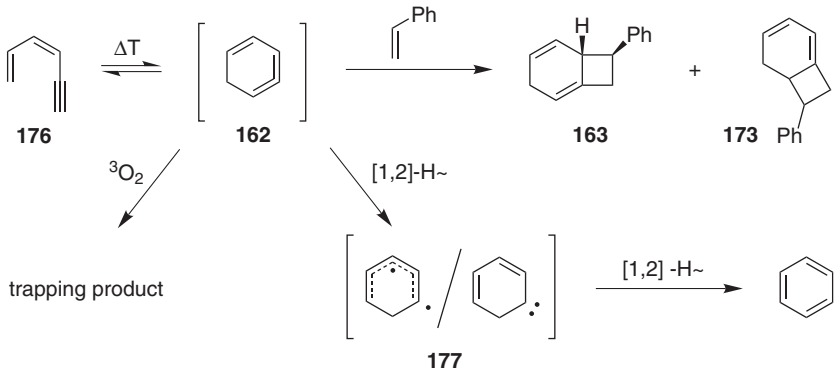
In the case of the [4 + 2]-cycloadditions, the diradical analogous to **172** should contain an allyl radical subunit in the side-chain having the *Z*-configuration. There the closure of the six-membered ring occurs also employing the central carbon atom of the pentadienyl radical system. A quantum-chemical study reproduced the preference of the step **172** → **163** over that from **172** to **173** [47]. This may have its origin in the higher spin density at C3 of the cyclohexadienyl radical as compared with C1 and C5 [108].

In spite of the fact that the yields of the trapping products of **162** are far from quantitative, a dimer of **162** or an oligomer has never been observed. Most probably, **162** oligomerizes unspecifically or polymerizes.



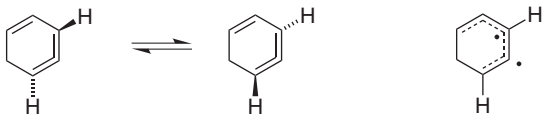
Scheme 6.39 Generation of **162** by β-elimination from 1-bromo-1,4-cyclohexadiene (**174**), trapping of **162** by furan and 2,5-dimethyl-furan and deprotonation of **162** by KO*t*Bu.

It was an interesting question whether **162** can also be generated by β-elimination. For that purpose, 1-bromo-1,4-cyclohexadiene (**174**) was synthesized and treated with KO*t*Bu in furan and also 2,5-dimethylfuran, whereupon the products **170** and **175** (Scheme 6.39), respectively, were isolated in 30 and 13% yield [109]. Since **170** had already been obtained by the DMS reaction of **168** (Scheme 6.37) in the presence of furan, it seems reasonable to suppose that the same intermediate, **162**, had a fleeting existence in both reactions. Remarkably, the possible deprotonation of **162** by the rather strong bases methyllithium and KO*t*Bu does not prevent the interception by allenophiles, although the thermodynamic acidity of **162** should be high owing to the formation of an aromatic species, namely the phenyl anion. Whether its protonation product benzene was present in the reaction mixtures was not analyzed, but a test for the phenyl anion was conducted by treatment of **174** with KO*t*Bu in the presence of benzophenone. The product triphenylmethanol, isolated in 5% yield, clearly points to the intermediacy of phenylpotassium [109]. No evidence is available for the reaction of KO*t*Bu as nucleophile with **162**, which should have furnished *tert*-butyl 1,4-cyclohexadien-1-yl ether, although this product was not searched for.



Scheme 6.40 Formation of **162** by electrocyclization of (*Z*)-hexa-1,3-dien-5-yne (Hopf cyclization), interception of **162** by styrene and rearrangement of **162** to benzene.

In 1969, Hopf and Musso [110] reported the thermal conversion of hexa-1,3-dien-5-yne to benzene at about 200 °C. It was proved 28 years later that in the course of this rearrangement the *Z*-isomer **176** undergoes an electrocyclization with formation of **162** (Hopf cyclization) followed by a hydrogen migration in the latter to give benzene. Conclusive evidence for **162** was obtained by conducting the reaction in the presence of styrene, which trapped **162** to yield the [2 + 2]-cycloadducts **163** and **173** (Scheme 6.40) [111]. The activation parameters for the isomerization **176** → benzene in the gas phase were determined to be $\Delta H^{\neq} = 40.3\,\text{kcal mol}^{-1}$ and $\Delta S^{\neq} = -10.3\,\text{cal K}^{-1}\,\text{mol}^{-1}$ [112]. Interestingly, the formation of benzene was suppressed when the reaction was performed in the presence of triplet oxygen ($^3O_2$), which is believed to trap **162**. The measurement of the reaction rates of defined mixtures of **176** and $^3O_2$ allowed the determination of the energy profile of the two-step reaction **176** → **162** → benzene under the assumption that the interception of **162** by $^3O_2$ proceeds with encounter control, that is, without an activation energy. For the step **176** → **162**, the activation parameters turned out to be $\Delta H^{\neq} = 30.3\,\text{kcal mol}^{-1}$ and $\Delta S^{\neq} = -17.9\,\text{cal K}^{-1}\,\text{mol}^{-1}$. The standard heat of formation ($\Delta H_f°$) of **162** was derived to be larger than that of benzene by 85 kcal mol^{-1} by means of $\Delta H_f°$ of **176** and the reaction enthalpy. This value agrees well with an estimate for the diradical structure **162-D** (Scheme 6.41) based on group increments [113].



(*M*)-**162** (*P*)-**162** **162**-D

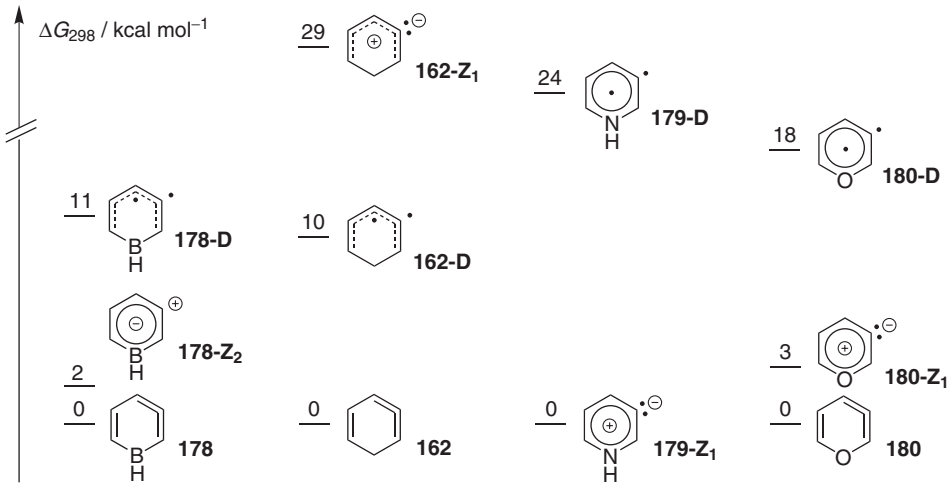
Scheme 6.41 Structures of the enantiomers **162** and of the transition state (**162-D**) for their enantiomerization.

However, high-level quantum-chemical calculations disagreed with this $\Delta H_f°$ value and, moreover, invariably ascribed the allene structure **162** (C_1 symmetry) to the species [13, 47, 114–117] Three of these studies also dealt with the energy difference between **162** and **162-D** and recognized **162-D** as the transition state for the enantiomerization of **162** [13, 47, 117], the energy of which was calculated to be close to 10 kcal mol^{-1} above that of the **162**-enantiomers (Scheme 6.41) [13, 117]. Hence the barrier to enantiomerization of **162** is smaller by 5–8 kcal mol^{-1} than that of 1,2-cyclohexadiene (**6**), which nicely reflects the difference between the resonance energies of the allyl and the pentadienyl radical [118]. The $\Delta H_f°$ value of (*M*)- and (*P*)-**162** was obtained to be in the range 76–78 kcal mol^{-1} above that of benzene [13, 116, 117]. By using this range and group increments [119], an estimation of the strain energy leads to values of 32–34 kcal mol^{-1}. In the equilibrium geometry, the bond angle C1–C2–C3 is 130.8° and the dihedral angles H1–C1–C2–C3/H3–C3–C2–C1 are 33.6/34.2° (see Scheme 6.60 in Section 6.3.5) [13]. In comparison with **6**, the allene subunit of **162** is somewhat more strongly bent, since the tether across the allene termini is shorter owing to the C=C double bond in **162**. In addition, the allene subunit of **162** is slightly closer to planarity, because the energetic distance to

the transition state, which has a planar 'allene' subunit, is considerably reduced relative to **6**.

The discrepancy between calculated and experimental $\Delta H_f°$ value of **162** was resolved as it turned out that the latter has to be considered as the upper limit resulting from the assumption of the interception of **162** by $^3O_2$ under encounter control. However, the numerical simulation of the experimental rate data was also perfectly successful by imposing an activation barrier of 7 kcal mol^{-1} on the trapping step [13]. This brought the $\Delta H_f°$ of **162** down to 78 kcal mol^{-1} above that of benzene [13], in good agreement with calculated values [13, 116, 117].

The energy of the triplet state of **162-D** lies about 2 kcal mol^{-1} above that of the singlet state [13, 117], which is the ground state of the system in the planar arrangement (C_s symmetry). As the first excited singlet state with this geometry, the zwitterion **162-Z$_1$** was calculated, which contains a pentadienyl cation and a vinylanion subunit. In Scheme 6.42, it is depicted that the free enthalpy of this state is 29 kcal mol^{-1} above that of the allene state (**162**). In addition, in Scheme 6.42, the free enthalpies of the different states of **162** are compared with those of its analogues in which the CH_2 group is replaced by a heteroatom or a heteroatom group of the second row of the periodic table (**178–180**) [120].

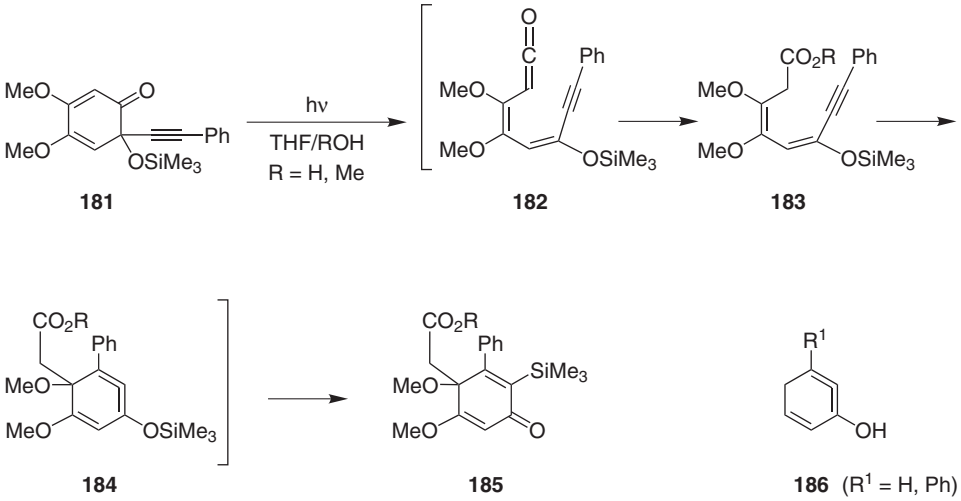


Scheme 6.42 Calculated free enthalpies of various states of the isobenzene **162** and its analogues having the CH_2 group replaced by a BH group, an NH group or an oxygen atom, according to Engels and co-workers.

A [1,3]- or [1,5]-H shift is formally required for the rearrangement of **162** to benzene (Scheme 6.40). Quantum-chemical calculations predict that the hydrogen atom migrates in two steps, that is, in consecutive [1,2]-H shifts, with the species **177** being the intermediate, which has to be described either as a diradical [117] or a carbene [116, 117]. The experimental activation enthalpy for the conversion of **176** into benzene [112] was correctly simulated by the energy of the transition state separat-

ing **162** and **177** [116, 117]. Also, the calculated value [117] of the activation enthalpy of the electrocyclization **176**→**162** agrees well with the experimental value [113].

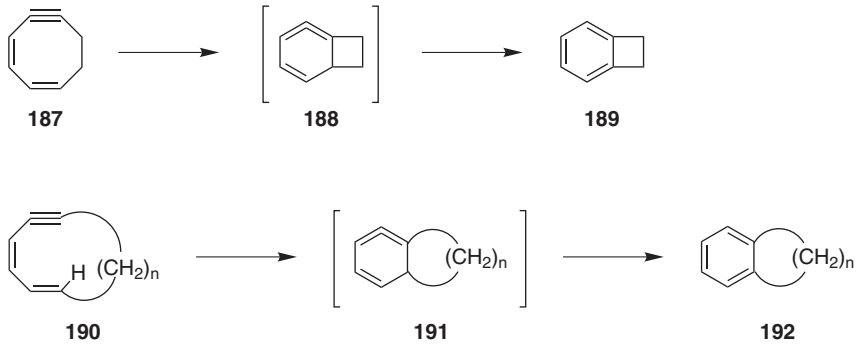
Highly substituted derivatives **184** of **162** were recently postulated as intermediates in the photolysis of the alkynylcyclohexadienones **181** in aqueous or methanolic THF (Scheme 6.43). The 2,5-cyclohexadienones **185** were the products isolated. The irradiation should convert **181** to the ketenes **182**, which react with water and methanol to give the acid and ester **183**, respectively. These compounds are believed to undergo electrocyclization leading to **184**, from which the products **185** arise by a 1,3-shift of the trimethylsilyl group. By using simplified models such as **186**, a theoretical study suggested that the cyclic allenes **184** rather than the corresponding diradicals are the intermediates and that only a small activation energy is required for the conversion **184**→**185** [121]. Diederich et al. [122] observed a deep-seated rearrangement of a 1,2-bismethylenecyclobutane derivative bearing two trimethylsilylethynyl groups at one of the exocyclic methylene groups and postulated a Hopf cyclization to be possibly the initial step.



181 **182** **183** **184** **185** **186** (R^1 = H, Ph)

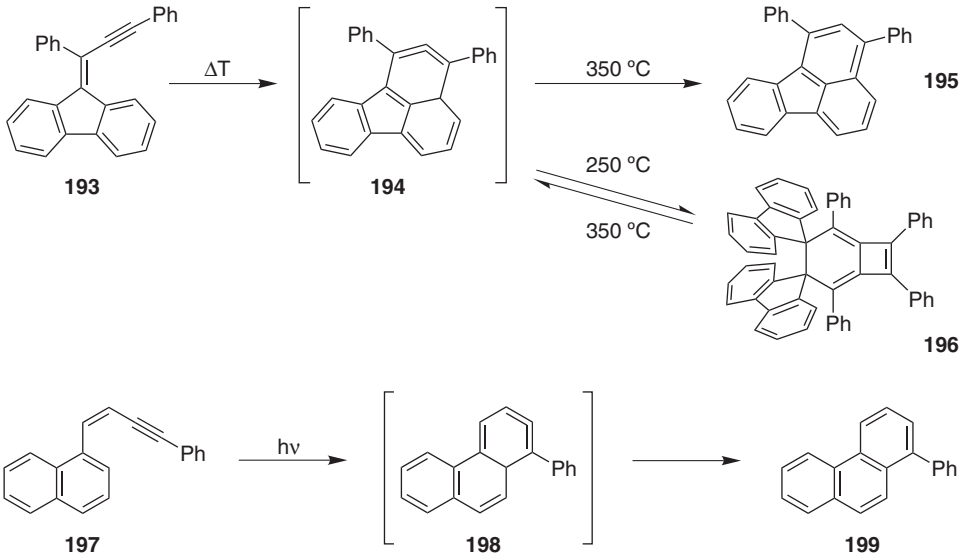
Scheme 6.43 1,2,4-Cyclohexatriene derivatives **184** as intermediates in the conversion of alkynyl-3,5-cyclohexadienones **181** into 2,5-cyclohexadienones **185**.

Cyclic derivatives of **176** such as cycloocta-1,3-dien-5-yne (**187**) and the compounds **190** may rearrange to give benzocycloalkenes **189** and **192** (Scheme 6.44). The 1,2,4-cyclohexatriene derivatives **188** and **191**, respectively, are the most likely intermediates. Generated from a precursor by thermolysis at 140–180 °C, **187** could not be isolated, but gave rise to **189** right away [123]. In contrast, the hydrocarbons **190** with $n > 4$ were found to be stable at room temperature, whereas **190** with $n = 4$ began to cyclize at room temperature. The tendency that the cyclization rate decreases with increasing n could be reproduced by quantum-chemical calculations with the assumption of the intermediacy of **191** [117].



Scheme 6.44 Hopf cyclizations of cyclic hexa-1,3-dien-5-ynes to give eventually benzocycloalkenes.

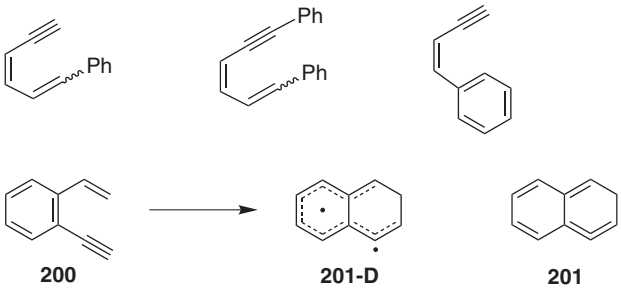
Scheme 6.45 presents two examples of cyclizations of hexa-1,3-dien-5-ynes whose terminal ethylene subunits are part of a benzo group. The thermolysis of the dibenzofulvene **193** took a particularly spectacular course as the benzocycbutene derivative **196** was formed entirely unexpectedly in 87% yield at 250 °C. It is believed that the initially generated cyclic allene **194** dimerizes in the usual manner and that the resulting 1,2-bismethylenecyclobutane derivative undergoes an unprecedented rearrangement to give **196**. However, heating of either **193** or **196** at 350 °C furnished a high yield of 1,3-diphenylfluoranthene (**195**), the product of the hydrogen shift expected of **194**. Thus, **196** seems to be in equilibrium with **194** at higher temperatures. Three phenylethynyldibenzofulvenes substituted differently than **193** were



Scheme 6.45 Hopf cyclization of aromatic hydrocarbons having a (*Z*)-4-phenylbut-1-en-3-ynyl side-chain.

thermally converted to dimers of type **196** as well [111]. A detailed investigation of the photochemical conversion of 1-(4-phenylbut-1-en-3-ynyl)naphthalene (**197**) and related compounds into 1-phenylphenanthrene (**199**) and analogous products, respectively, led to the conclusion that 1,2,4-cyclohexatrienes such as **198** are the decisive intermediates [124].

Additional hexa-1,3-dien-5-yne derivatives that were subjected to high-temperature thermolysis (>500 °C) are depicted in Scheme 6.46. Labeling experiments disclosed that the cycloaromatization occurs via three competing pathways, of which the Hopf cyclization plays only a minor part, with **200** being the only exception. However, if the ethynyl hydrogen atom of **200** was replaced by a phenyl or a trimethylsilyl group, the contribution of the electrocyclization as the initial step of the cycloaromatization decreased drastically [125]. A theoretical study of the route from **200** to naphthalene had the interesting result that the Hopf cyclization requires an activation that is only slightly greater than that of the parent system (**176**) and that the ensuing intermediate does not have the allene structure **201** but is the diradical **201-D**. The first [1,2]-H migration step en route from **201-D** to naphthalene then has a significantly higher activation barrier than the step **162** → **177** (Scheme 6.40) [117].



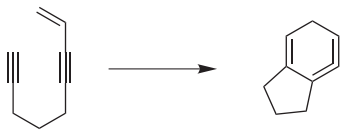
Scheme 6.46 Hexa-1,3-dien-5-yne derivatives undergoing cycloaromatization on thermolysis.

If both ethylene subunits of a 1,3-hexadien-5-yne derivative are members of benzene entities, the cycloaromatization, caused by flash vacuum thermolysis, may give rise to bowl-shaped molecules such as corannulene or semibuckminsterfullerene. However, in those cases, the initial step is not a Hopf cyclization but an isomerization of the ethynyl to a vinylidenecarbene group [125].

In addition to the Hopf cyclization of **176**, there is a second pericyclic reaction leading to **162**, that is, the 'dehydro' Diels–Alder reaction of butenyne with acetylene (Scheme 6.47). The theoretical treatment of this process by Johnson et al. [59] predicted a free reaction enthalpy and a free activation enthalpy, both at 25 °C, of –13.4 and 42.0 kcal mol^{-1}, respectively. Ananikov [116] arrived at a similar result for the intramolecular case of non-1-en-3,8-diyne (**202**) and calculated the same quantities to be –15.3 and 30.9 kcal mol^{-1} for the formation of the isoindane **203**. As already discussed regarding Scheme 6.40, the conversion of **162** into benzene and likewise that of **203** into indane have to be considered as a sequence of two [1,2]-H shifts 116, 117], whose highest transition state has a significantly lower energy than that for the formation of **162** and **203** by the 'dehydro' Diels–Alder reaction.

162

ΔH_R = –25.4 $\Delta H^{\ddagger}$ = 31.5 kcal mol^{-1}
ΔS_R = –40.3 $\Delta S^{\ddagger}$ = –35.2 cal K^{-1} mol^{-1}
ΔG_R (25 °C) = –13.4 $\Delta G^{\ddagger}$ (25 °C) = 42.0 kcal mol^{-1}

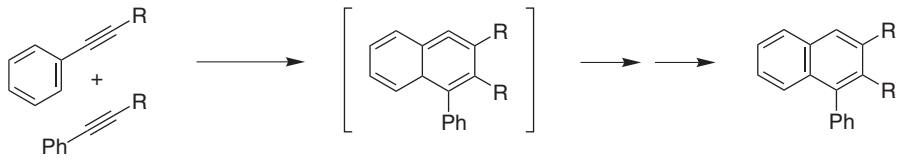


202 203

ΔG_R (25 °C) = –15.3 $\Delta G^{\ddagger}$ (25 °C) = 30.9 kcal mol^{-1}

Scheme 6.47 Calculated thermodynamic and kinetic data for the 'dehydro' Diels–Alder reaction of butenyne with acetylene and non-1-ene-3,8-diyne.

The cycloaddition of butenyne to acetylene according to Scheme 6.47, which would eventually lead to benzene, has not been observed yet experimentally. However, a number of reactions of that kind are known [1] and the first example was discovered in the 19th century. Michael and Bucher [126] heated phenylpropiolic acid in acetic anhydride under reflux and obtained 1-phenylnaphthalene-2,3-dicarboxylic acid anhydride (**206a**) (Scheme 6.48). This type of reaction proceeds undisturbed by a variety of functional groups on the aromatic rings and its mechanism was probed [127]. Although a pathway via a cationic intermediate was proposed [127], the involvement of the 1,2,4-cyclohexatriene derivative **205a** is not excluded [105]. Ethyl phenylpropiolate (**204b**) was shown to dimerize to give **206b** on heating at 200 °C [128]. Thermolysis and photolysis of 2,2′-bis(phenylethynyl)biphenyl (**204c**) and 1,8-bis(phenylethynyl)naphthalene (**204d**) caused the same cyclizations and furnished 9-phenyldibenz [*a*,*c*]anthracene (**206c**) [129] and 7-phenylbenz [*k*]fluoranthene (**206d**) [130], respectively. The bicyclo[3.3.0]octane derivative **204e** rearranged accordingly on heating at 150 °C and gave **206e** [131]. In all these reactions, the generation of an intermediate **205** should be the initial step followed by two consecutive [1,2]-H shifts, rather than a [1,3]- or [1,5]-H migration as previously assumed [131], to produce the aromatics **206**.



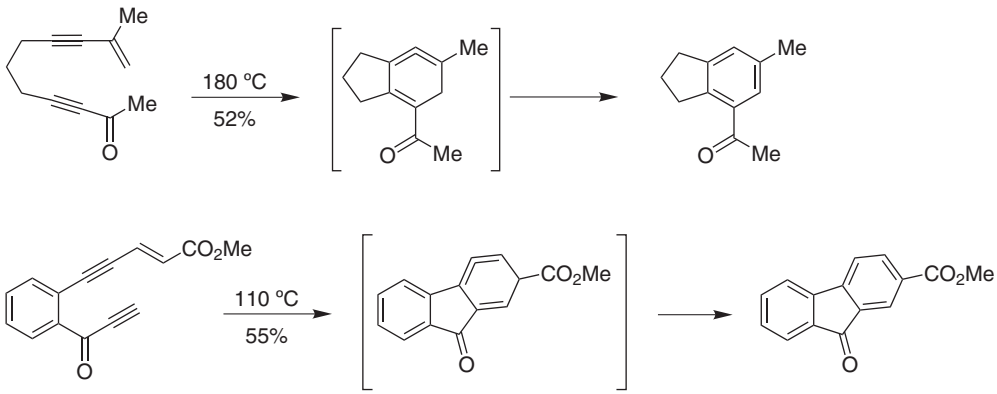
204 205 206

a: R, R = CO–O–CO; **b**: R = $CO_2C_2H_5$; **c**: R, R = biphenyl-2,2′-diyl; **d**: R, R = [1,8]naphto;
e: R, R = (1α,2α,4α,5α,6α,8α)-2,6-dicyano-4,8-dihydroxy-1,5-dimethylbicyclo[3.3.0]octane-4,8-diyl

Scheme 6.48 Formation of 2,3-disubstituted 1-phenylnaph-thalenes **206** by 'dehydro' Diels–Alder reaction of a pair of phenylacetylene moieties such as **204**.

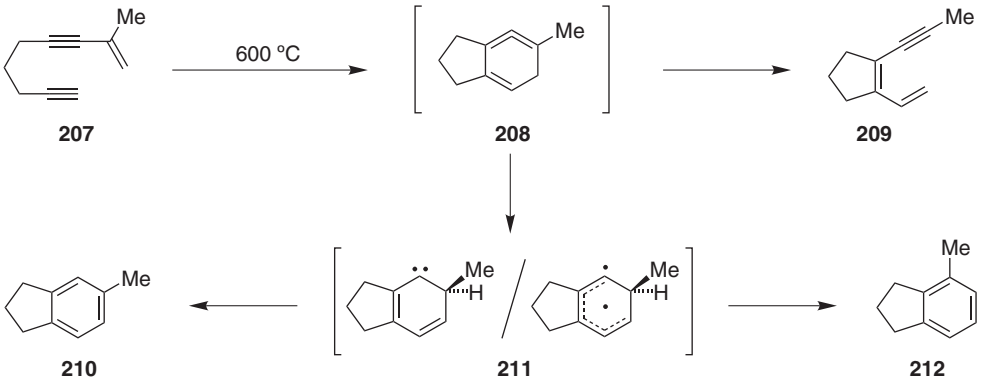
Recently, further examples for 'dehydro' Diels–Alder reactions were published, which are believed to proceed via intermediates of the type **205**. To explain the formation of products besides those of the type **206**, the authors [132] proposed a remarkable reaction cascade and supported it by quantum-chemical calculations. Accordingly, an isonaphthalene of the type **205** undergoes an electrocyclic ring expansion to give a 1,2-dehydro[10]annulene derivative, in which a configurational isomerization occurs followed by an electrocyclic ring closure, yielding a further isonaphthalene of the type **205**, and aromatization.

Danheiser et al. [133] reported a variety of intramolecular [4 + 2]-cycloadditions of a butenyne subunit with a remote acetylene moiety by thermolysis of the substrates, with the best yields being obtained in the presence of phenolic additives. Two examples are presented in Scheme 6.49. Of particular significance with regard to synthetic utility is the observation that protic and Lewis acids were powerful promoters of these reactions. The intermediacy of 1,2,4-cyclohexatriene derivatives, as shown in Scheme 6.49, is highly likely, at least in the non-catalyzed cases.



Scheme 6.49 Intramolecular 'dehydro' Diels–Alder reactions of conjugated enynes with a remote acetylene subunit furnishing annulated benzene derivatives, according to Danheiser and co-workers.

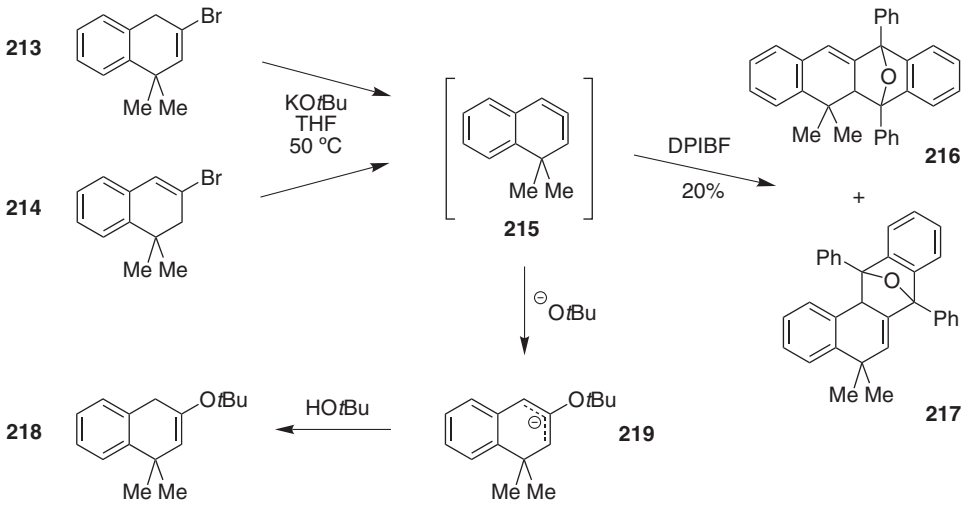
Particularly instructive is the result of the flash vacuum thermolysis of 2-methylnon-1-ene-3,8-diyne (**207**) (Scheme 6.50) [59]. Three isomers of the substrate were isolated in a ratio of 1:3.5:1, namely 1-(1-propynyl)-2-vinylcyclopentene (**209**), 5-methylindane (**210**) and 4-methylindane (**212**). They provide powerful support for the isoindane derivative **208** generated in the initial step. By a reverse Hopf cyclization, **209** should result from **208**, whereas the formation of **212** indicates that the carbene or diradical **211** is a further intermediate, ensuing **208** by a [1,2]-H shift (see also Scheme 6.40). Since in **211** a hydrogen atom or the methyl group may migrate to yield a stable compound, the production of both indanes **210** and **212** is in agreement with expectation [59]. The same migration of a methyl group would be possible in a number of reactions in solution, but was never observed [133].



Scheme 6.50 Thermolysis of 2-methylnon-1-ene-3,8-diyne (**207**) at 600 °C in a flow reactor by Johnson and co-workers.

A variety of palladium-catalyzed dimerizations of conjugated enynes and their additions to diynes and triynes gave rise to styrene and phenylacetylene derivatives, respectively. Inter alia, 1,2,4-cyclohexatrienes have been invoked as intermediates in these reactions [134]. 5,6-Diphenyl-1,2,4-cyclohexatriene has been proposed as an intermediate in the rearrangement of 4,4-diphenylcyclohexa-2,5-dienylidene to *o*-terphenyl and its possible existence was supported by quantum-chemical calculations [135].

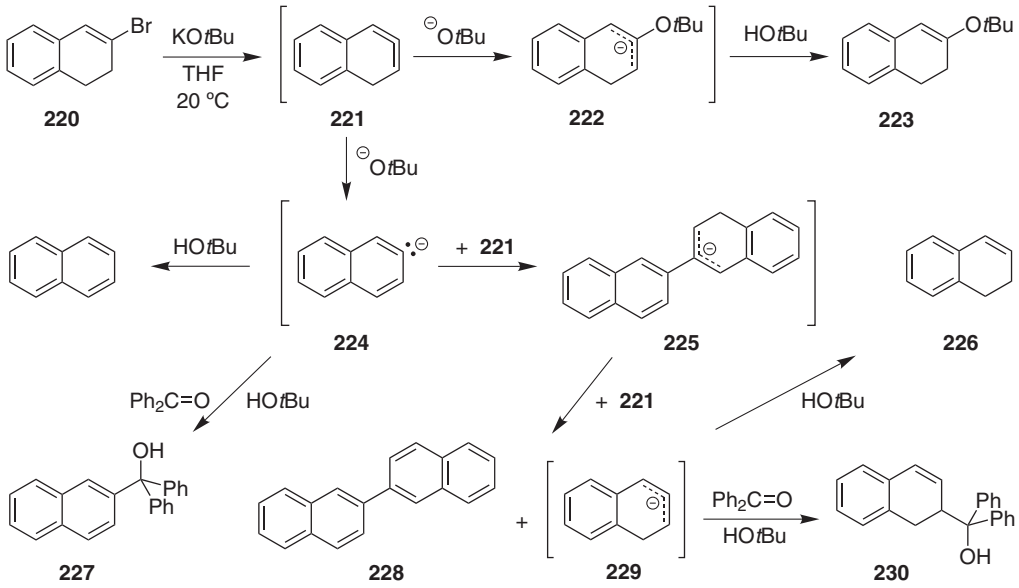
Miller and Shi [136] were the first to demonstrate the intermediacy of a benzo derivative of **162**, that is, the dimethylisonaphthalene **215** (2,3-dehydro-1,2-dihydro-1,1-dimethylnaphthalene or 1,1-dimethyl-3δ^2-1*H*-naphthalene) (Scheme 6.51). They treated the bromodimethyldihydronaphthalenes **213** and **214** with KO*t*Bu in the presence of 1,3-diphenylisobenzofuran (DPIBF) and obtained the pentacyclic compounds **216** and **217** in 20% yield in a ratio of 3:2. Obviously, **215** was generated by β-elimination of hydrogen bromide from **213** and **214** and trapped by DPIBF in terms of [4 + 2]-cycloadditions to the different double bonds of the allene subunit. In addition to a mixture of hydrocarbons, which did not allow the isolation of a specific compound, the enol ether **218** resulted in the reaction in the absence of DPIBF. Its formation is best rationalized by the nucleophilic addition of KO*t*Bu to the central allene carbon atom of **215**, leading to the allyl anion **219**, which is protonated under kinetic control to give **218**. The structures of the products **216–218** are a plausible consequence of the intermediacy of the allene **215** and cannot be readily brought into agreement with the corresponding cycloalkynes that could conceivably result instead of **215**.



Scheme 6.51 Generation and trapping of 1,1-dimethyl-3δ^2-1*H*-naphthalene (**215**) by Miller and Shi.

Now the interesting question arose of whether the intermediate analogous to **215** but devoid of the methyl groups, that is, 3δ^2-1*H*-naphthalene (**221**), would also be interceptable, because **221** should show a high thermodynamic acidity owing to its conversion into the 2-naphthyl anion (**224**) on deprotonation and because of the use of the strong base KO*t*Bu for the liberation of **221** from 3-bromo-1,2-dihydronaphthalene (**220**) (Scheme 6.52). In the event, the major product was indeed naphthalene. However, there were further products, namely the enol ether **223** and small quantities of 2,2′-binaphthyl (**228**) as well as 1,2-dihydronaphthalene (**226**). The overall yield amounted to 92% [137].

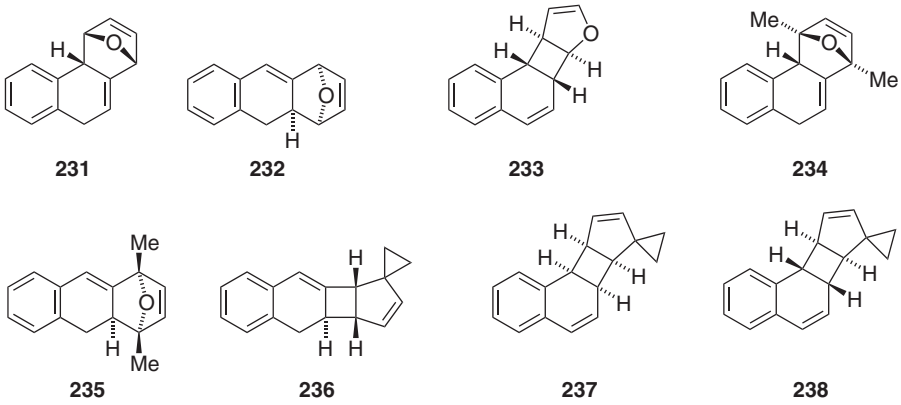
These results support the β-elimination from **220** to give **221**, towards which KO*t*Bu acts as a base and a nucleophile. As in the case of **215**, the addition occurs at the central allene carbon atom leading the allyl anion **222**, which is protonated to yield **223**. On the other hand, the deprotonation of the methylene group brings about **224**, whose major amount is converted to naphthalene, but a small proportion, behaving as a nucleophile, traps **221**, giving rise to the allylanion **225**, which in turn reacts with **221** and, by a hydride transfer, furnishes **228** and the allyl anion **229**. By protonation, the latter is converted into **226**. By conducting this experiment in the presence of benzophenone, this mechanistic model was confirmed as the tertiary alcohols **227** and **230** were obtained in addition to naphthalene, **223** and **228**. Apparently, the anions **224** and **229** were intercepted in part or totally, respectively, by benzophenone (Scheme 6.52) [137].



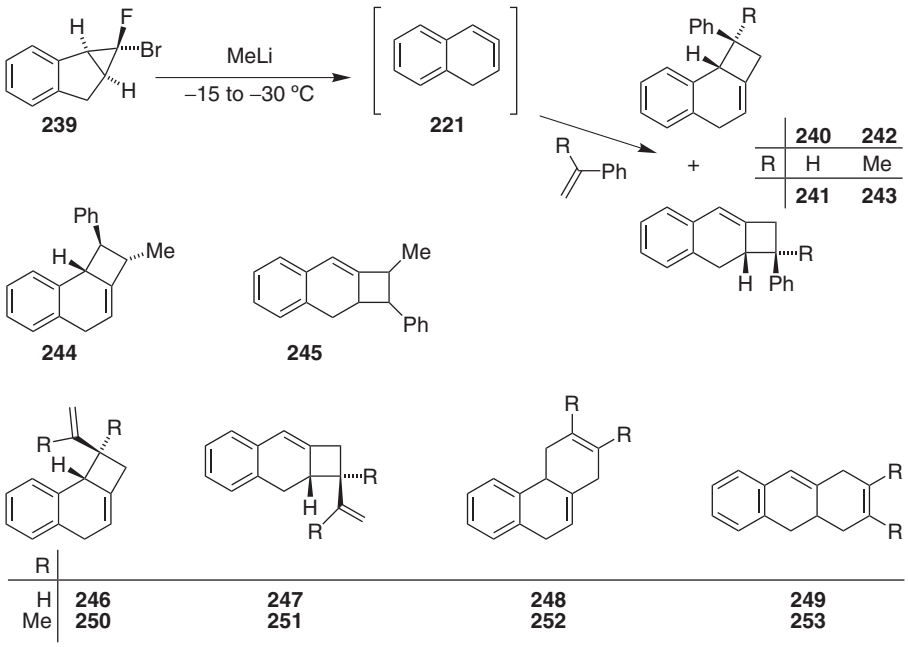
Scheme 6.52 Generation of $3\delta^2$-1*H*-naphthalene (**221**) by β-elimination from 3-bromo-1,2-dihydronaphthalene (**220**) and reaction sequences started by attacks of KO*t*Bu at **221**.

The efficient transformations of **221** by KO*t*Bu are the dominant processes even if the liberation of **221** is performed in the presence of activated alkenes, but cycloadditions are not entirely suppressed. The structures of the products of such reactions are depicted in Scheme 6.53. When **220** was treated with KO*t*Bu in pure furan, the [4 + 2]-cycloadducts **231** and **232** in addition to the cyclobutane derivative **233** were obtained in yields of 11, 8 and 2%, respectively. Resulting from a [2 + 2]-cycloaddition to **221**, the progenitor of **233** should be subject to a base-catalyzed double bond migration. Major products were naphthalene and phenanthrene in yields of 46 and 26%, respectively, with the latter probably originating from **231** by a base-catalyzed dehydration. 2,5-Dimethylfuran gave rise to the [4 + 2]-cycloadducts **234** and **235**, whereas only [2 + 2]-cycloadducts were apparently formed from spiro[2,4]hepta-4,6-diene. Only **236** is a genuine cycloadduct, whereas **237** and **238** are regarded as consecutive products of diastereomeric cycloadducts, which undergo a double-bond shift under the influence of the base [137].

For the preparation of cycloadducts, the generation of **221** according to the DMS method is much more suitable than the β-elimination from **220**. However, the dibromocarbene adduct **254** of indene cannot be isolated. Under the usual conditions of its preparation, it is converted into 2-bromonaphthalene [138]. Therefore, indene was exposed to bromofluorocarbene and the *endo*-fluoro compound **239** (Scheme 6.54) could be isolated in 16% yield. The treatment of **239**, dissolved in styrene, with MeLi furnished a 14:1 mixture of the [2 + 2]-cycloadducts **240** and **241** of **221** in 63% yield [35, 92]. α-Methylstyrene gave rise to a 45% yield of **242** and **243** in a ratio of 10:1 [66]. From (*E*)-1-phenylpropene a 3:1 mixture of **244** and **245** in 50% yield resulted [139]. The use of 1,3-butadiene as trapping reagent for **221** led to a 40% yield of the [2 + 2]- and the [4 + 2]-cycloadducts **246**–**249**, respectively, in a ratio of 10:1:2:1. Even at room temperature **246** and **247** rearranged slowly to **248** and **249** in a ratio of 2:1 [67, 92]. In the case of 2,3-dimethyl-1,3-butadiene, the proportion of the [2 + 2]- (**250**, **251**) as compared with the [4 + 2]-cycloadducts (**252**, **253**) was higher than with 1,3-butadiene [66]. Concerning the efficiency of the preparation of cycloadducts, the comparison of the liberation of **221** from **220** as well as **239** in the presence of 2,5-dimethylfuran is revealing. Whereas the use of **220** gave a 33:1 mixture of **234** and **235** (Scheme 6.53) in 9% yield, the same products arose from **239** in 42% yield [139].

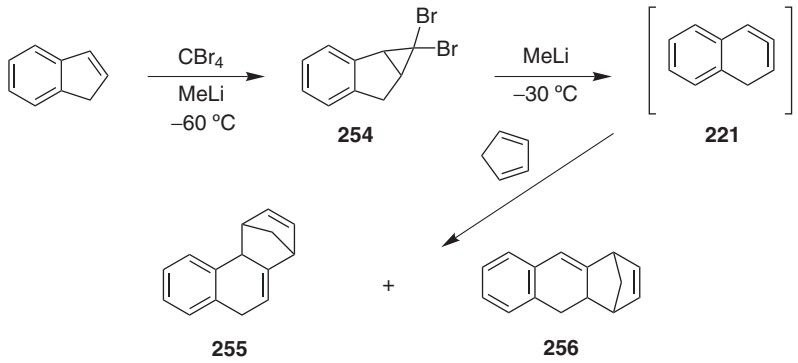


Scheme 6.53 Products formed by cycloadditions of 3δ^2-1*H*-naphthalene (**221**), liberated from **220** by KO*t*Bu, with furan, 2,5-dimethylfuran and spiro[2.4]hepta-4,6-diene.



Scheme 6.54 Cycloadducts of 3δ^2-1*H*-naphthalene (**221**), generated from the bromofluorocyclopropane **239** by methyllithium (MeLi), to styrenes and 1,3-butadienes.

Because of the yield of only 16% in the synthesis of **239**, the overall yields of cycloadducts with reference to indene according to Scheme 6.54 are rather low, however. A substantial improvement was achieved by the development of a one-pot procedure, which starts from indene and takes advantage of its dibromocarbene adduct (**254**) (Scheme 6.55). This was prepared at –60 °C with tetrabromomethane and MeLi as source for the carbene and remained unchanged in solution up to temperatures around 0 °C [92]. If an activated alkene and MeLi were added sequentially to such a solution at –30 °C, cycloadducts of **221** were isolated in a number of cases in relatively good yields. In Scheme 6.55, this procedure is illustrated by the example of 1,3-cyclopentadiene, which furnished the [4 + 2]-cycloadducts **255** and **256**, both as a mixture with *endo*:*exo* = 2:1, in the ratio of 8:1 in 23% yield with reference to indene [67]. Analogously, the products from **221** and styrene, 1,3-butadiene [92] and 2,3-dimethylbutadiene [66], namely the compounds **240**, **241**, **246**–**249** and **250**–**253**, were obtained in yields of 40, 24 and 25%, respectively, by means of the one-pot procedure from indene.



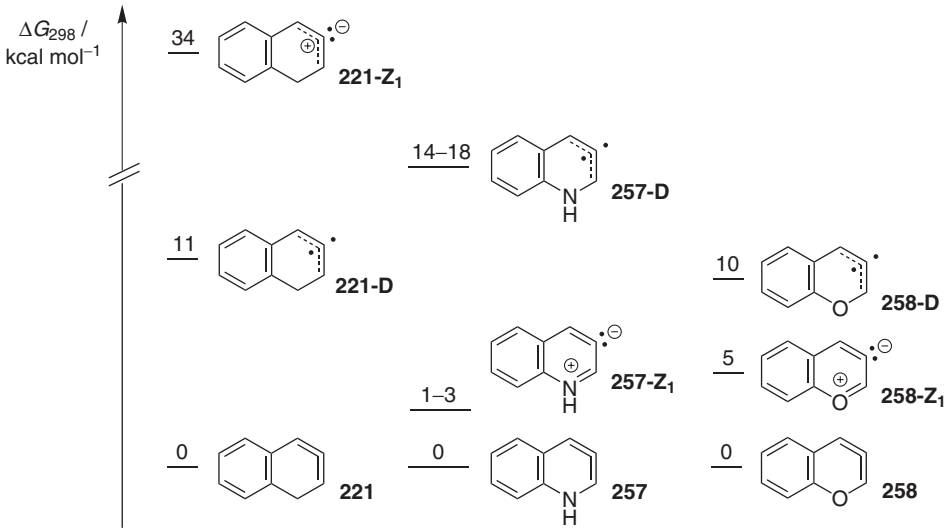
Scheme 6.55 One-pot procedure, starting from indene, for the preparation of the cycloadducts of 3δ^2-1*H*-naphthalene (**221**) to 1,3-cyclopentadiene.

There are cases known in which the use of different precursors of **221** was not equally successful in the synthesis of a certain cycloadduct. Thus, when the bromofluorocyclopropane **239** and 1,3-cyclopentadiene were employed as source and trapping reagent for **221**, respectively, the diene was deprotonated to a large extent [66, 139], whereas this process did not play a major part on utilization of the dibromocyclopropane **254** (Scheme 6.55). Further, an experiment to prepare the furan adducts **231**–**233** (Scheme 6.53) from **239** failed [66], probably because of the metalation of furan by MeLi or the carbenoid resulting from **239**.

The positional selectivity on formation of the cycloadducts from **221** is less pronounced than that of the isobenzene **162**, but it is the conjugated double of the allene moiety as well that predominantly undergoes the reaction. As demonstrated by the thermolysis of several products, these are formed from **221** under kinetic control. For example, on heating, the styrene adduct **240** and the furan adduct **231** rearranged virtually completely to **241** and **232**, which are formally the cycloadducts to the non-conjugated double bond of the allene subunit of **221** [92, 137]. The cause of the selectivity may be the spin-density distribution in the phenylallyl radical entity of the diradical intermediates.

It seems plausible that the electronic nature of the allene subunit of **221** is intermediate between that of 1,2-cyclohexadiene (**6**) and that of the isobenzene **162**. Two reasons may be advanced in favor of this suggestion. First, **221** suffers from less strain than **162**, since the C_2 entity common to both rings must have a longer bond than the vinylene group of **162** owing to the aromatic delocalization in the benzo group. Second, the stabilization of the allyl radical subunit of **221-D** (Scheme 6.56) by the benzo group should be smaller than that of **162-D** by the vinylene group, since the resonance energy of the benzyl radical is not as large as that of an allyl radical [118]. Both effects increase the difference between the energies of the allene and the diradical state. Compared with the pair **162**/**162-D** (Scheme 6.42), this difference should be larger for **221**/**221-D** but not as large as that of **6**/**6-D** (15–18 kcal mol^{-1}; see Section 6.3.1). Indeed, quantum-chemical calculations gave a $\Delta\Delta G_{298}$ value of ~11 kcal mol^{-1} (Scheme 6.56) in the case of the singlet state of

221-D and only a corresponding difference of ~9 kcal mol^{-1} for **162**/**162-D** [13]. The value of 10 kcal mol^{-1} for the latter pair, given in Scheme 6.42, was calculated by a slightly different method [120].

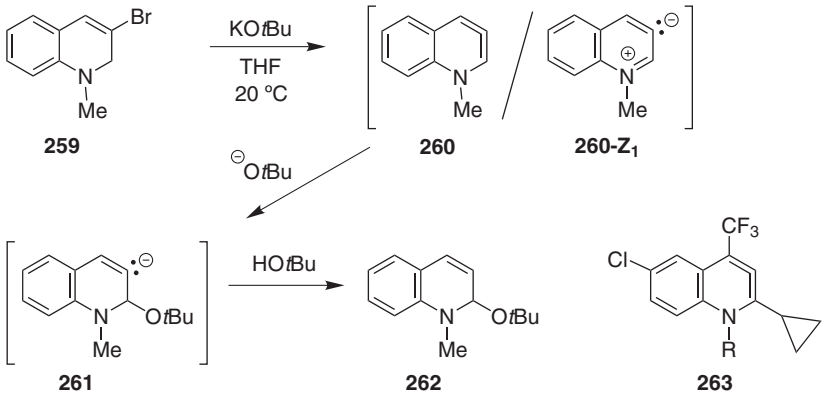


Scheme 6.56 Calculated values of the relative free enthalpies of the various states of the isonaphthalene **221**, the quinoline **257** and the chromene **258**.

6.3.5
Heterocyclic Derivatives of 1,2,4-Cycloheptatriene (162) and 3δ^2-1*H*-Naphthalene (221)

Apart from the diphosphaisobenzenes **300** and **307** and a briefly mentioned isopyridazine [140a], only compounds in which the methylene group of **162** or **221** is replaced by a heteroatom or a heteroatom group are dealt with in this section. At best, theoretical studies are known on other isoaromatic cyclic allenes [140b].

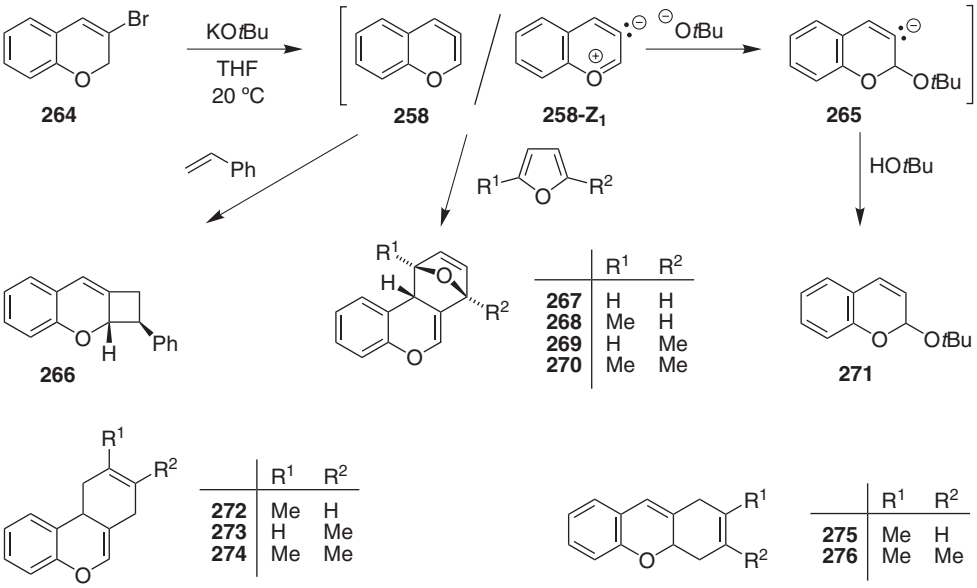
The quantum-chemical calculation of 3δ^2-1*H*-quinoline indicated that the ground state still possesses allene character (**257**); however, the energy of the zwitterionic state **257-Z$_1$** lies only 1–3 kcal mol^{-1} above that of **257** (Scheme 6.56) [14]. The interconversion of the **257** enantiomers proceeds via **257-Z$_1$**. The singlet diradical **257-D** is an excited state in the case of the planar molecular geometry. Whereas the ΔG_{298} values in Scheme 6.56 are valid in the gas phase, **257-Z$_1$** is possibly more stable than **257** in solution and hence the allene structure may no longer correspond to an energy minimum in solution [14]. The energetic similarity of **257** and **257-Z$_1$** is based on the circumstances that both species encompass the same number of bonding electron pairs and **257-Z$_1$** experiences a special stabilization by the aromaticity of the 10 π-electron system.



Scheme 6.57 $3\delta^2$-1*H*-Quinoline derivatives **260**/**260-Z$_1$** and **263** as reactive intermediates.

Experimental studies on **257** are not known, but its *N*-methyl derivative was liberated by β-elimination of hydrogen bromide from 3-bromo-1-methyl-1,2-dihydroquinoline (**259**). Independent of the presence or absence of furan and styrene, the only compounds observed were the *N*,*O*-acetal **262** and its consecutive products. As depicted in Scheme 6.57, the intermediate is probably trapped by the *tert*-butoxide ion to give the vinylanion **261**, which is eventually protonated yielding **262**. Unlike the reaction of the isonaphthalene **221**, the site of the addition to the intermediate is not the central carbon atom of the allene subunit but a terminal one. This is evidence for a polar nature of the intermediate in terms of the zwitterion **260-Z$_1$**, the reactivity of which has to be expected based on its quinolinium ion character. Whether **260-Z$_1$** or the allene structure **260** represents the ground state of the species is an open question, but the calculations on **257**/**257-Z$_1$** are in line with the behavior of **260**/**260-Z$_1$**. Apparently, its sensitivity towards KO*t*Bu is very high, which is why cycloadditions with furan or styrene cannot compete [14]. The possible intervention of highly substituted derivatives of **260**/**260-Z$_1$** such as **263** in the thermolysis of 1-(2-amino-5-chlorophenyl)propargyl carboxylates has recently been advanced [141].

The generation of $3\delta^2$-chromene (2,3-didehydro-2*H*-1-benzopyran, **258**), the oxygen analogue of **257**, and its trapping by KO*t*Bu proceeded as in the case of **260**/**260-Z$_1$**. Thus, on treatment of 3-bromo-2*H*-chromene (**264**) with KO*t*Bu in THF, the acetal **271** (Scheme 6.58) was obtained in 79% yield [12]. However, when the liberation of **258** was carried out in an activated alkene as solvent, only small amounts of **271** were observed and the major products were the respective cycloadducts of **258**. Styrene gave rise to the [2 + 2]-cycloadduct **266** in 41% yield. Furan, 2-methylfuran and 2,5-dimethylfuran furnished the [4 + 2]-cycloadducts **267** (59%), **268** and **269** in a ratio of 2.5:1 (28%) and **270** (41%), respectively [12]. Isoprene and 2,3-dimethylbutadiene led to the [4 + 2]-cycloadducts **272**, **273** and **275** in a ratio of 1:3:6 (37%) and **274** and **276** in a ratio of 1:2 (15%) [139].



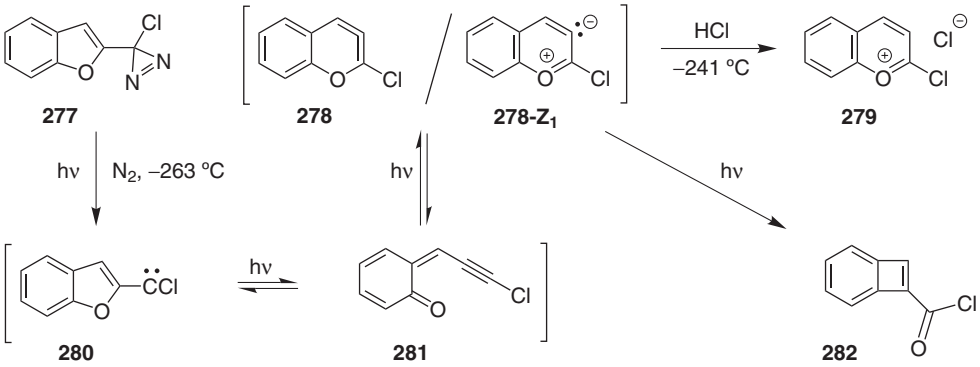
Scheme 6.58 Generation of $3\delta^2$-chromene (**258**) and its interception by the *tert*-butoxide ion and various activated alkenes.

The positional selectivity of the cycloadditions appears not to be uniform, but probably there is a preference as in the previous cases. This is demonstrated by the adducts of the furans, where the formation under kinetic control is obvious as **267**–**270** rearranged to the formal [4 + 2]-cycloadducts to the allene double bond of **258** next to the oxygen atom on heating at 110 °C [12]. In the case of styrene, isoprene and 2,3-dimethylbutadiene, it is conceivable that the products isolated are those of thermodynamic control. [2 + 2]-Cycloadducts to the allene double bond of **258** remote from the oxygen atom had been expected, but they may be subject to rearrangement already at room temperature owing to the strain inherent in the four-membered ring. The low persistence of **266** at room temperature may be evidence for its conversion into the diradical that has to be assumed to be the intermediate on formation of **266** from **258** and styrene [12]. If indeed [2 + 2]-cycloadducts of the methyl-1,3-butadienes to the 3,4-double bond of **258** are initially produced, their rearrangement would be accompanied by ring enlargement of the vinylcyclobutane to cyclohexene subunits with formation of **272**–**276** (see **61**→**62**, Scheme 6.18 and **246**/**247**→**248**/**249**, Scheme 6.54). As already invoked on the occasion of the addition to **162** and **221**, the spin-density distribution in the intermediate diradical may be the cause of the positional selectivity.

The formation of the acetal **271** is evidence for a polar nature of **258** in terms of the zwitterions **258-Z$_1$**, whose pyrylium-ion character explains the attack of the *tert*-butoxide ion to give the vinyl anion **265** (Scheme 6.58). In contrast to **260**/**260-Z$_1$**, **258** does prefer cycloadditions if it is generated in the presence of an activated

alkene. Therefore, the ground state of the species should be the allene **258** in spite of its polarization. Quantum-chemical calculations support this view, as they gave a free enthalpy of **258-Z$_1$**, the transition state for the interconversion of the **258** enantiomers, that lies 5 kcal mol^{-1} above that of **258** (Scheme 6.56) [13]. The larger energy difference between these states as compared with **257** and **257-Z$_1$** is presumably caused by the lower donor ability of an oxygen atom relative to that of an NH group.

Khasanova and Sheridan [142] reported the observation of a strikingly rich cascade of reactive intermediates after photolysis of 2-benzofurylchlorodiazirine (**277**) isolated in an N_2 matrix at –263 °C. Two isomers of the carbene **280** were formed. Depending on the wavelength used, transformations could selectively and reversibly be caused from **280** to the quinone methide **281** and from **281** to 2-chloro-3δ^2-chromene (**278**). Prolonged irradiation at 313 nm ultimately converted **278**, **280** and **281** into the benzocyclobutadiene **282**. Warming an HCl-doped N_2 matrix to –241 °C converted **278** to the pyrylium salt **279**. All the transient species were identified by comparing experimental and quantum-chemical calculated IR spectra. The protonation of **278** to give **279** indicates a polar ground state of **278**. Indeed, theory predicted a difference of only 2.5 kcal mol^{-1} between the allene structure **278**, being the ground state, and the zwitterion **278-Z$_1$**, which serves as a transition state for the enantiomerization of **278** [142]. This result agrees well with that of calculations on the parent system **258** (see Scheme 6.56) [13].

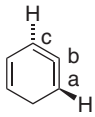
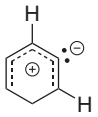
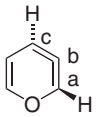
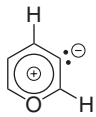


Scheme 6.59 Generation of 2-chloro-3δ^2-chromene (**278**) by irradiation of the diazirine **277** and reactions of **278**, according to Khasanova and Sheridan.

The replacement of the methylene group of the isobenzene **162** by an oxygen atom leads to the pyran derivative **180** (3δ^2-pyran, Scheme 6.42). This substitution has two important consequences. First, the strain of the allene structure **180** should increase relative to that of **162** since C–O bonds are shorter than C–C bonds. Second, the interaction of the oxygen atom with the allene subunit should strongly stabilize the zwitterionic structure **180-Z$_1$** owing to the aromatic character of the resulting π-electron system. In fact, the theoretical treatment furnished a $\Delta\Delta G_{298}$ of only 1 kcal mol^{-1} between **180** and **180-Z$_1$** [13]. As depicted in Scheme 6.42, a slightly

modified calculation gave a difference of 3 kcal mol^{-1} [120]. In both cases, **180** is the ground state and **180-Z$_1$** the transition state for the interconversion of the **180** enantiomers. These energetics are valid for the gas phase, but the estimation of the free enthalpy of solvation led to a stronger stabilization of **180-Z$_1$**, with the consequence that **180** is no longer an energy minimum [13]. The diradical **180-D** is the first excited singlet state of planar geometry. Its ΔG_{298} value in the gas phase is higher by 18 kcal mol^{-1} than that of **180**.

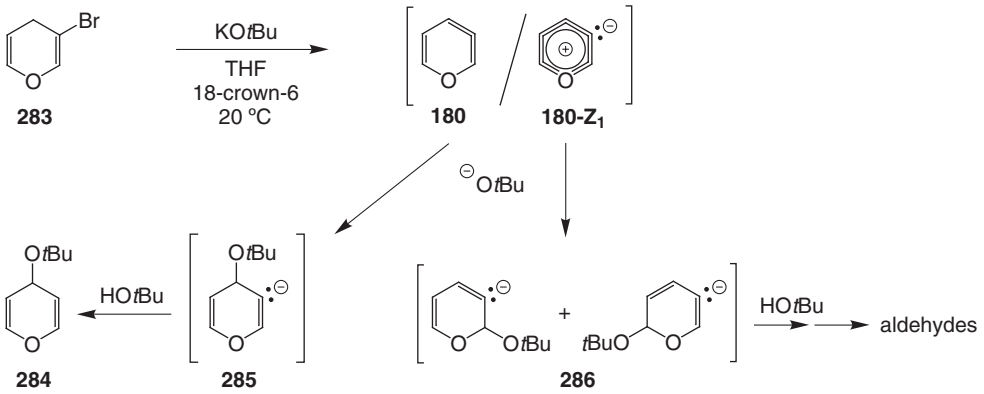
Owing to the similarity of the energies of **180** and **180-Z$_1$**, their geometric parameters are much closer to each other than those of the isobenzene **162** and **162-Z$_1$**. This is demonstrated in Scheme 6.60 by calculated values of the bending and the dihedral angles of the allene moieties. The zwitterions are characterized by small values of the bond angles of 109.5 and 110.7°, respectively, which originate from the closed-shell repulsion between the lone pair of the anionic carbon atom and the neighboring C–C bonds. Within the allene structures, these angles are larger by 21.3° in **162** but only 4.9° in **180**. Similarly, the dihedral angles of **180** are much closer to 0° than those of **162**. Because of a free enthalpy difference of 29 kcal mol^{-1} between **162** and **162-Z$_1$**, these states are not closely related, whereas **180** possesses already a substantial part of the properties of **180-Z$_1$** owing to a $\Delta\Delta G_{298}$ of only 1 or 3 kcal mol^{-1} [13, 120].

angle				
	162	**162-Z$_1$**	**180**	**180-Z$_1$**
Ca-Cb-Cc	130.8	109.5	115.6	110.7
Ha-Ca-Cb-Cc	33.6	0.0	9.6	0.0
Hc-Cc-Cb-Ca	34.2	0.0	16.0	0.0
C-Ca-Cb-Cc or O-Ca-Cb-Cc	16.2	0.0	10.9	0.0
Ca-Cb-Cc-C	18.2	0.0	11.2	0.0

Scheme 6.60 Selected bond and dihedral angles (degrees) of the isobenzene **162**, **162-Z$_1$**, the pyran **180** and **180-Z$_1$**.

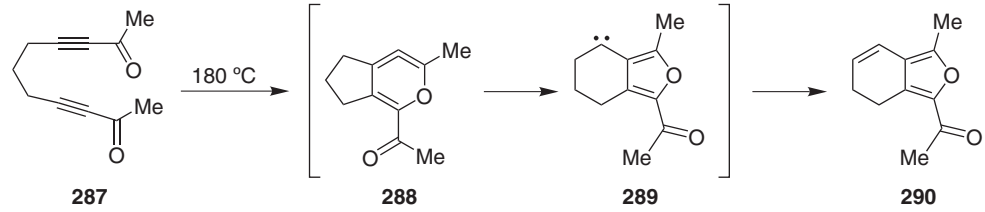
This is manifest in the reactivity of **180**/**180-Z$_1$**, which was generated from 3-bromo-4*H*-pyran (**283**) by β-elimination of hydrogen bromide with KO*t*Bu (Scheme 6.61). Whether or not this reaction was conducted in the presence of styrene or furan, the only product identified was *tert*-butyl 4*H*-pyran-4-yl ether (**284**). This is in line with the relationship of the intermediate to a pyrylium ion. Thus, the addition of the *tert*-butoxide ion to **180**/**180-Z$_1$** has to be expected at the 4-position with formation of the vinyl anion **285**, which is then protonated to give **284**. Likewise, the attack of the nucleophile is predicted at C2 and C6 leading to the vinyl anions **286**, which

ultimately should give rise to *tert*-butyl 2*H*-pyran-2-yl ether. That this compound was not observed is not unexpected, since 2*H*-pyrans are well known to undergo readily an electrocyclic ring opening yielding aldehydes. Indeed, the NMR spectrum of the product contained signals of aldehydes in addition to those of **284** [13]. As in the case of the quinoline **260/260-Z$_1$**, KO*t*Bu is so reactive towards **180/180-Z$_1$** that cycloadditions with activated alkenes cannot compete.



Scheme 6.61 Generation of 3δ^2-pyran (**180**) and trapping by the *tert*-butoxide ion.

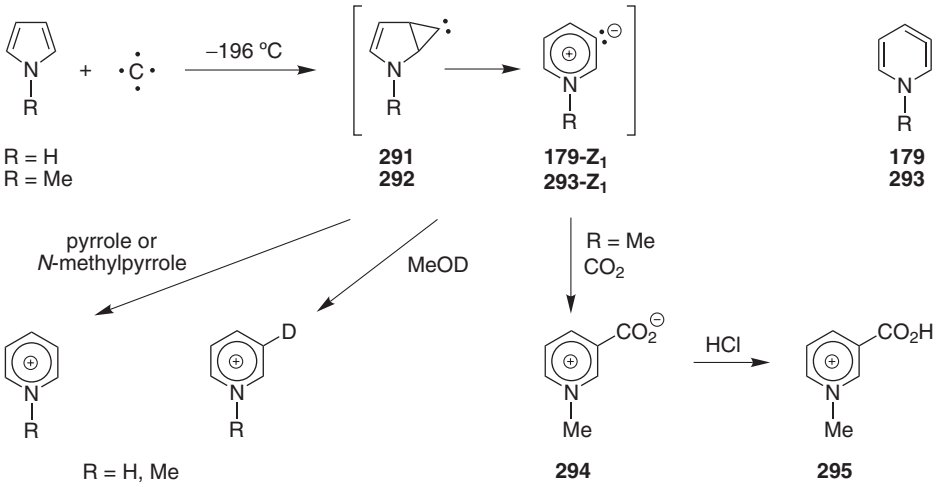
Derivatives of **180** have been invoked as intermediates in the thermal cyclization of conjugated ynones such as **287** (Scheme 6.62). The first step is believed to be an intramolecular [4 + 2]-cycloaddition of the conjugated ynone moiety with the second acetylene functionality giving rise to the 3δ^2-pyran **288**. This step is analogous to the [4 + 2]-cycloaddition of conjugated enynes generating derivatives of the isobenzene **162** as illustrated in Schemes 6.47–6.50. Because of the structure of the furan **290** isolated in 80% yield, the rearrangement of **288** to the carbene **289** was suggested, followed by a [1,2]-H migration in the latter [143]. In view of the cyclization of the conjugated enynone **281** to the carbene **280** (Scheme 6.59), the direct formation of **289** from **287**, without the intermediacy of **288**, is conceivable.



Scheme 6.62 The 3δ^2-pyran derivative **288** as a possible intermediate in the thermal cyclization of undeca-3,8-diyne-2,10-dione (**287**).

The isopyridine **179** ($3\delta^2$-1*H*-pyridine) is the result if the oxygen atom of **180** is replaced by an NH group. Owing to the better electron-donor quality relative to that of an oxygen atom, the NH group could have the effect that the zwitterion **179-Z$_1$** is more stable than the allene structure **179**, even in the gas phase. Experiments and quantum-chemical calculations support this expectation.

Emanuel and Shevlin [144] exposed pyrrole to atomic carbon at –196 °C and observed the formation of pyridine (Scheme 6.63). Supported by calculations, labeling studies revealed that initially the cyclopropylidene **291** is generated, which is converted to **179-Z$_1$** by a ring enlargement. Proton transfer to **179-Z$_1$** from pyrrole, which was present in a large excess, brings about the pyridinium ion and therefrom finally pyridine. The treatment of *N*-methylpyrrole with atomic carbon had an analogous result as *N*-methylpyridinium chloride was found after addition of hydrogen chloride to the reaction mixture [145]. Thus, the intermediates **292** and **293-Z$_1$** are plausible. If the reaction of **179-Z$_1$** and **293-Z$_1$** with electrophiles other than pyrrole and *N*-methylpyrrole were intended, these electrophiles had to be co-condensed with atomic carbon and the substrates. With MeOD, [3-D]pyridine or the [3-D]-*N*-methylpyridinium ion were observed and carbon dioxide gave rise to the betaine **294**, as was concluded from the formation of the acid **295** [144, 145]. The first generation of **293-Z$_1$** proceeded by thermolysis of **294** [146], which decarboxylated remarkably fast at 150 °C in benzonitrile [147].



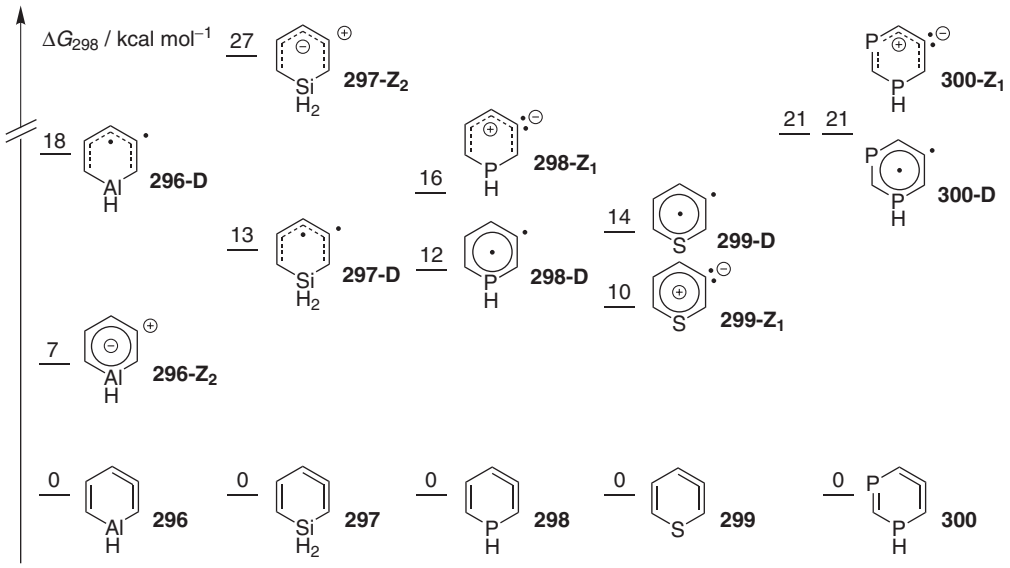
Scheme 6.63 Addition of atomic carbon to pyrrole and *N*-methylpyrrole and interception of the zwitterions **179-Z$_1$** and **293-Z$_1$** by electrophiles, according to Shevlin and co-workers.

These reactions point to the polar character of **179-Z$_1$** and **293-Z$_1$**. Already the first calculations resulted in a virtually planar geometry and thus in the conclusion that **179-Z$_1$** and likewise **293-Z$_1$** are the ground states [144]. In consequence, the allene structures **179** and **293** are not energy minima. Utilizing a higher level of theory,

more recent calculations corroborated the previous finding [14, 120, 140b]. Single-point calculations at the CASPT2 level favor **179-Z$_1$** over **179** by 1–2 kcal mol^{-1} in the gas phase [14], and it is expected that the solvent effect will enhance this difference. As illustrated in Scheme 6.42, the diradical **179-D** represents the first excited state having a ΔG_{298} value higher by 24 kcal mol^{-1} than that of **179-Z$_1$** [120]. An isopyridazine derivative related to **179-Z$_1$** and **293-Z$_1$** was claimed to be generated on thermolysis of (2-ethynylphenyl)triazenes [140a].

In addition to the energetics of **162**, **179-Z$_1$** and **180**, Scheme 6.42 contains those of the boraisobenzene **178**, which represents the last possible system of that kind with one heteroatom of the second row of the periodic table. The allene structure **178** was indeed calculated to be the ground state, but ΔG_{298} of the zwitterion **178-Z$_2$** is only 2 kcal mol^{-1} greater. The polarization of that state is opposite to that of **179-Z$_1$**. To allow an aromatic π-electron sextet to form, the σ-orbital at the central carbon atom of the 'allene system' must remain empty [120]. Experiments directed towards the observation of **178** or a derivative thereof seem to be unknown.

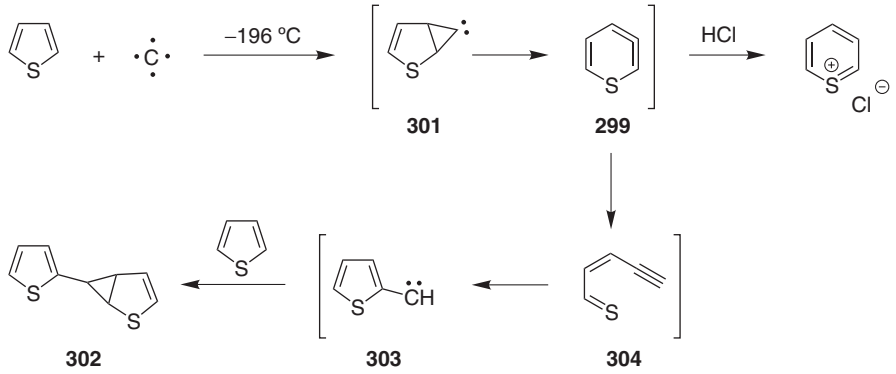
The results of the calculations of the higher homologues of the species contained in Scheme 6.42 are summarized in Scheme 6.64. The diphosphaisobenzene **300** was included in this study [120], since a substituted derivative thereof is known [148]. A previous investigation of the sulfur compound **299** arrived virtually at the same conclusions [149]. In all cases, the allene structure was found to be the ground state with a considerable energy gap to the next stable state. This has its origin in the greater length of the heteroelement–carbon bonds, reducing the strain inherent in the bent allene subunit in comparison with the system containing heteroelement atoms of the second row (Scheme 6.42). Further, relative to their lower homologues, the zwitterions **296-Z$_2$**, **298-Z$_1$** and **299-Z$_1$** suffer from the disadvantage that the ability of third-row elements to form π-bonds and hence participate in an aromatic π-electron sextet is strongly decreased. This effect is most clearly evident in the monophosphorus system, in which ΔG_{298} of **298-Z$_1$** is larger by 16 kcal mol^{-1} than the value of the allene state **298**. In consequence, the diradical **298-D** serves as a transition state for the enantiomerization of **298** and **298-Z$_1$** represents the first excited singlet state of the system with coplanar CH groups. At variance with this situation, the zwitterion **179-Z$_1$** is the ground state of the isopyridine species. A peculiarity is revealed by the silicon compound **297**. Being the lowest zitterionic state, **297-Z$_2$**, has a ΔG_{298} value that lies as much as 27 kcal mol^{-1} above that of the allene structure, but its polarization is opposite to that of the carbon system (**162-Z$_1$**) and the same as that of the most stable zwitterions of the boron and the aluminum systems (**178-Z$_2$**, **296-Z$_2$**). This is rationalized by the β-silicon effect, providing a significant stabilization for a carbocationic center by a silicon atom in the β-position [150]. Experimental studies of the systems in Scheme 6.64 have been carried out only for the sulfur compound **299** [151] and the tetra-*tert*-butyl derivative of the phosphorus compound **300** [148].



Scheme 6.64 Calculated relative free enthalpies of various states of derivatives of the isobenzene **162**, which contain a heteroatom or a heteroatom group of the third row of the periodic table instead of the methylene group of **162**. The species **300**, having two phosphorus atoms, has been included because of a known derivative thereof.

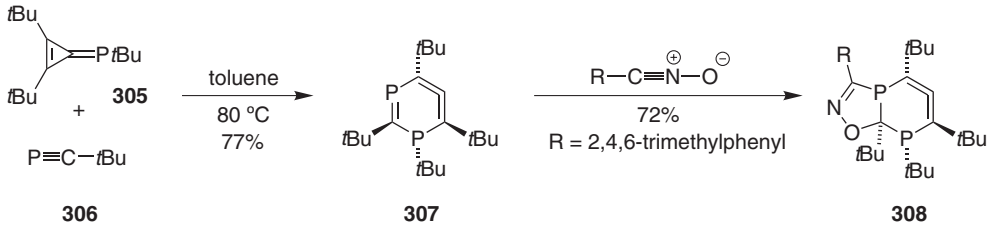
Shevlin et al. [151] co-condensed atomic carbon, thiophene and hydrogen chloride and observed thiopyrylium chloride as a major product. The utilization of ^{13}C-enriched carbon vapor revealed that carbon atoms attack thiophene at several positions. One of the main pathways is the addition to the π-electron system leading to the cyclopropylidene **301**, which rapidly undergoes ring expansion to generate the cyclic allene **299**. The hydrogen chloride present converts **299** into the thiopyrylium salt. If the experiment was carried out in the absence of hydrogen chloride, **299** did not have a long lifetime either as it rearranged to 2-thienylcarbene (**303**), which gave rise to the cyclopropane derivative **302** by addition to thiophene. A number of steps of the reaction cascades starting from atomic carbon and thiophene were studied theoretically [149]. Inter alia, the results suggest that the transformation of **299** to **303** proceeds via the thioaldehyde **304** as an intermediate. Caused by irradiation, such a reaction sequence was also observed starting from the $3\delta^2$-chromene **278** (Scheme 6.59) [142].

In spite of the C–S bonds of **299** being rather long (176 and 178 pm), the allene moiety is still strongly bent (C–C–C bond angle 132°), preventing the isolation of the species. In the phosphorus compound **298**, this angle has a value of 144° and amounts to even 153° in the diphosphaisobenzene **300** [120].



Scheme 6.65 Addition of atomic carbon to thiophene giving rise to 3δ^2-thiopyran (**299**) and reactions of **299**.

Regitz et al. [148] took advantage of the reduced strain energy of **300** and the massive kinetic stabilization provided by four *tert*-butyl groups, allowing the isolation of **307** (Scheme 6.66) as a stable compound at room temperature. It arose in 77% yield in a mechanistically obscure reaction on heating of the phosphatriafulvene **305** and the phosphaalkyne **306**. The low reactivity of the allene system of **307** is manifest in the 1,3-dipolar cycloaddition to 2,4,6-trimethylbenzonitrile *N*-oxide, which did not take place at a C–C but at the C–P double bond furnishing **308**, whose structure was determined by X-ray diffraction. As compared with **6** or the isobenzene **162**, the bending of the allene system of **308** is strongly reduced as the angle was found to be 155.8°. However, the angle between the planes defined by the C–P bonds and the proximate ethylene moiety of the allene system has a value of 40.7° and thus still deviates considerably from that of an unstrained allene (90°). Bands at 1865 and 1846 cm^{-1} in the IR spectrum have been assigned to the allene moiety of **307** and at 1865 and 1830 cm^{-1} to that of **308**.

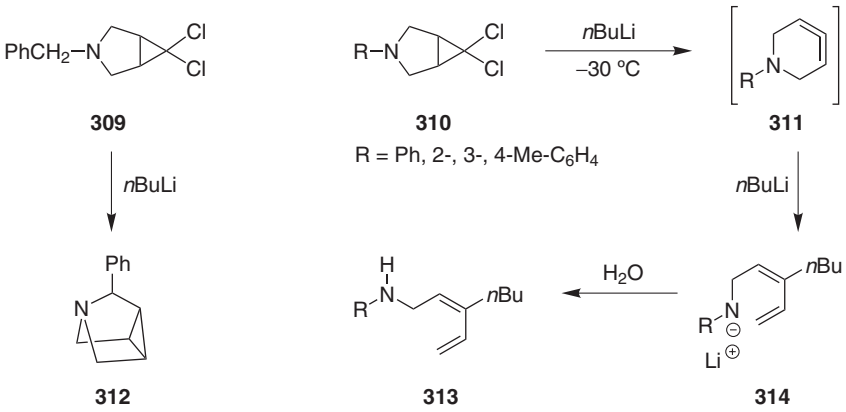


Scheme 6.66 Synthesis of the 5δ^2-1*H*-diphosphinin **307** and its 1,3-dipolar cycloaddition to 2,4,6-trimethylbenzonitrile *N*-oxide, according to Regitz and co-workers.

6.3.6
Heterocyclic Derivatives of 1,2-Cyclohexadiene (6)

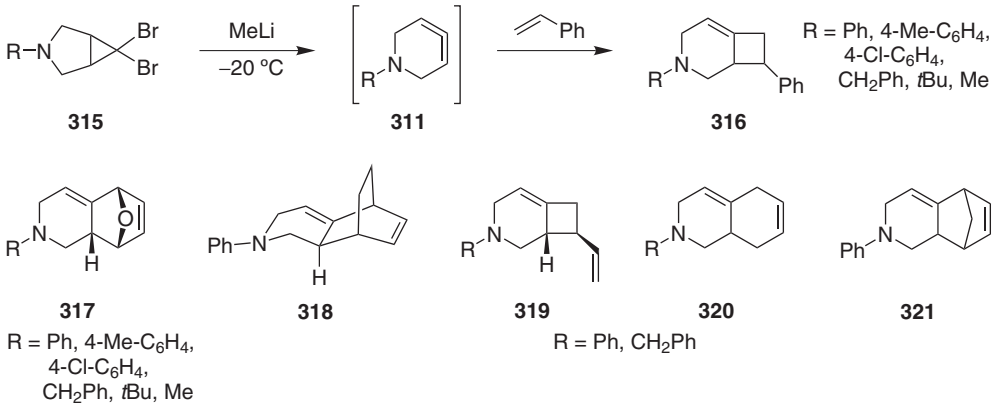
In this section, compounds are described that differ from **6** by the replacement of one or more methylene groups by heteroatoms or heteroatom groups. Quantum-chemical calculations on such species have not been carried out. However, on the basis of the results discussed in the above sections and depicted in Schemes 6.42 and 6.64, there is no doubt that all reactive intermediates under consideration are genuine allenes. After all, the tether across the allene subunit is larger in the corresponding compounds in this section than in $3\delta^2$-1*H*-pyridine (**179**), $3\delta^2$-pyran (**180**) and $3\delta^2$-thiopyran (**299**) owing to the absence of a double bond. Thus, compared with these models, the allene structures in this section suffer from less strain and are hence stabilized relative to their zwitterionic states.

The first reaction that could have led to a 1-aza-3,4-cyclohexadiene **311** was described by Boswell and Bass [152]. They treated 3-benzyl-6,6-dichloro-3-azabicyclo[3.1.0]hexane (**309**) with butyllithium (*n*BuLi) and obtained the tricyclic compound **312** (Scheme 6.67). Apparently, the carbenoid or carbene intermediate resulting from **309** does not undergo ring expansion to generate **311** (R = CH_2Ph) according to the DMS reaction [26], but prefers insertion into a C–H bond of the benzyl methylene group yielding **312**. To avoid such an insertion, the *N*-phenyl [153] and *N*-tolyl derivatives **310** [66] were synthesized. The action of *n*BuLi converted them into the aryl-3-butylpentadienylamines **313**, isolated in yields of 59–68%. This result points to the occurrence of the DMS reaction, but the cyclic allenes generated interact on their part with *n*BuLi, as they are attacked at the central allene carbon atom by the butyl nucleophile. In an S_N2'-process, the lithium amides **314** are formed and subsequently hydrolyzed to give **313**. The presence of an activated alkene in the reaction mixture had no influence on the outcome. This result indicates a high sensivity of **311** towards *n*BuLi, which prevents cycloadditions to activated alkenes.



Scheme 6.67 Reactions of *N*-substituted 6,6-dichloro-3-azabicyclo-[3.1.0]hexanes (**309**, **310**) with *n*-butyllithium.

For the latter reaction to take place, 6,6-dibromo-3-azabicyclo[3.1.0]hexanes **315** had to be synthesized and treated with MeLi [153, 154], which is considerably less reactive as a nucleophile than *n*BuLi. Indeed, the addition of MeLi to **315**, dissolved in an activated alkene, smoothly furnished the expected cycloadducts of **311**. Six species **311** were trapped by styrene and furan (Scheme 6.68). The styrene adducts **316** were isolated in yields ranging from 59% (R = Ph) to 14% (R = Me) and consisted exclusively of two diastereomers with the *exo*-compound as the major product. The addition of furan gave the *endo*-[4 + 2]-cycloadducts **317** in yields from 69% (R = 4-MeC_6H_4) to 6% (R = Me). Only in the case of R = *t*Bu was **317** accompanied by some of its diastereomer. 1,3-Butadiene was accepted by **311** with R = Ph and CH_2Ph and led to a 2:1 mixture of the [2 + 2]- and [4 + 2]-cycloadducts **319** and **320** in yields of 66 and 16%, respectively. Analogous to the behavior of the corresponding [2 + 2]-cycloadducts of **6**, **162** and **221**, **319** rearranged on thermolysis to furnish **320**. The interception by 1,3-cyclohexadiene and 1,3-cyclopentadiene was tried only with **311** (R = Ph) and gave rise to the [4 + 2]-cycloadducts **318** and **321** (*endo–exo* mixture) in 25 and 33% yield [153, 154].

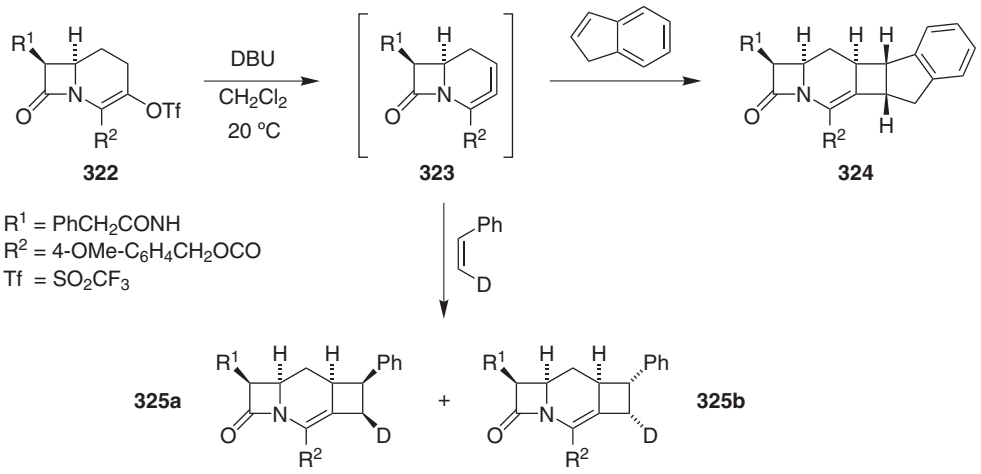


Scheme 6.68 Generation of various N-substituted 1-aza-3,4-cyclohexadienes (**311**) from the corresponding 6,6-dibromo-3-azabicyclo[3.1.0]hexanes (**315**) and cycloadducts of **311** to styrene, furan, 1,3-cyclohexadiene, 1,3-butadiene and 1,3-cyclopentadiene.

The utilization of the dibromides **315** permitted the generation of **311** by MeLi. Since MeLi is less reactive as a nucleophile than *n*BuLi, the ring opening of **311** by addition of the methyl anion analogous to the formation of **314** (Scheme 6.67) was of no importance. However, in the case of **315** (R = CH_2Ph), the intramolecular insertion of the transient carbenoid or carbene, leading to **312**, was the main reaction and hence the cause of low yields of the respective cycloadducts **316**, **317**, **319** and **320**. Whether such an insertion has to be blamed for the very modest yields of **316** and **317** with R = Me could not be proved [154].

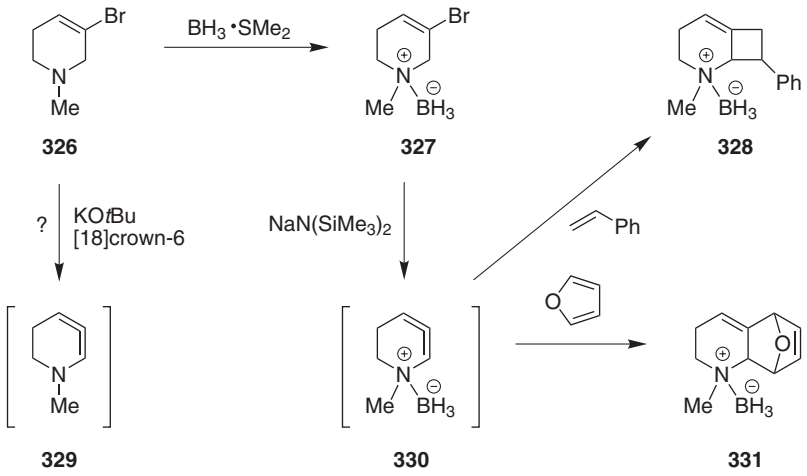
An intermediate containing the 1-aza-2,3-cyclohexadiene system, which is isomeric to the skeleton of **311**, was described for the first time in 1997. The action of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) on the carbacephalosporin triflate **322** in

the presence of indene and (*Z*)-β-deuterostyrene furnished the annulated carbacephalosporins **324** in 53% yield and **325a**,**b** as a 1:1 mixture in 20% yield (Scheme 6.69) [155]. Plausibly, it was assumed that DBU causes the β-elimination of triflic acid from **322**, generating the 1-aza-2,3-cyclohexadiene derivative **323**, which undergoes [2 + 2]-cycloadditions to the activated alkenes. The mechanistic consequences of the complete retention of the stereochemical information introduced by (*Z*)-β-deuterostyrene, namely the *cis*-orientation of the phenyl group and deuterium atom in **325**, will be discussed in the context of the corresponding trapping reactions of 1-oxa-2,3-cyclohexadiene (**351**) (Scheme 6.78) and the cephalosporin derivative **417** (Scheme 6.87).



Scheme 6.69 Generation of 4-methoxybenzyl (6*R*,7*S*)-8-oxo-7-(phenylacetamido)-1-azabicyclo[4.2.0]octa-2,3-diene-2-carboxylate (**323**) from the carbacephalosporin triflate **322** and the interception of **323** by indene and (*Z*)-β-deuterostyrene.

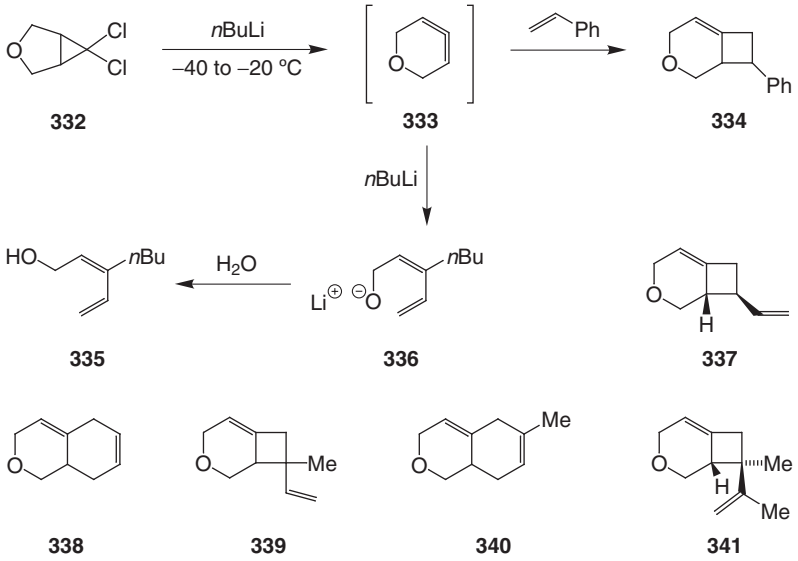
Attempts to liberate 1-methyl-1-aza-2,3-cyclohexadiene (**329**) from 3-bromo-1-methyl-1,2,5,6-tetrahydropyridine (**326**) by KO*t*Bu in the presence of [18]crown-6 and furan or styrene did not lead to products that could have been ascribed to the intermediacy of **329** (Scheme 6.70) [156]. Even if there is no doubt as to the allene nature of **329** on the basis of the calculations on the isopyridine **179** and 3δ^2-1*H*-quinoline (**257**), it is conceivable that the zwitterion **329-Z$_1$** is only a few kcal mol^{-1} less stable than **329**. This relationship could foster the reactivity of **329** towards the *tert*-butoxide ion to an extent that cycloadditions to activated alkenes would be too slow to compete. On the other hand, the ultimate product of the trapping of **329** by KO*t*Bu could have been an *N*,*O*-acetal or a vinylogous *N*,*O*-acetal, which might not have survived the workup (see, for example, the sensitivity of the *N*,*O*-acetal **262** [14], Scheme 6.57).



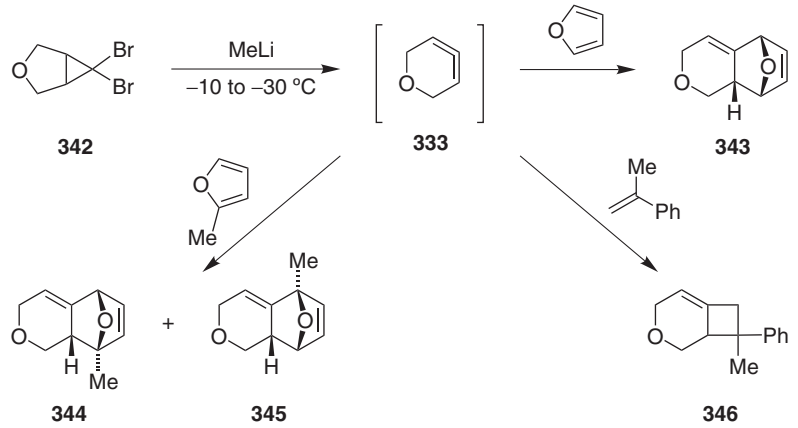
Scheme 6.70 Generation of 1-methyl-1-azacyclohexa-2,3-diene(*N*,*B*)borane (**330**) and its trapping by styrene and furan.

By chance, the existence of the borane complex **330** of **329** was discovered. The liberation of **330** occurred with the best efficiency with sodium bis(trimethylsilyl)-amide from the borane complex **327** of **326**. When styrene or furan was used as the solvent, three diastereomeric [2 + 2]-cycloadducts **328** and [4 + 2]-cycloadducts **331**, respectively, were obtained in 30 and 20% yield (Scheme 6.70) [156]. With no lone pair on the nitrogen atom, **330** cannot be polarized towards a zwitterionic structure, which is why its allene subunit, apart from the inductive effect of the nitrogen atom, resembles that of 1,2-cyclohexadiene (**6**) and hence undergoes cycloaddition with activated alkenes. It is noted that the carbacephalosporin derivative **323** (Scheme 6.69) also does not have a lone pair on the nitrogen atom next to the allene system because of the amide resonance.

As illustrated in Scheme 6.71, the symmetrical isopyran **333** (1-oxa-3,4-cyclohexadiene) was liberated for the first time from 6,6-dichloro-3-oxabicyclo[3.1.0]hexane (**332**) using *n*BuLi. The use of styrene as solvent led to the formation of two distereomeric [2 + 2]-cycloadducts **334** (*exo*:*endo* = 10:1) in 52% yield. 1,3-Butadiene, isoprene and 2,3-dimethyl-1,3-butadiene gave rise to [2 + 2]-cycloadducts and in part also [4 + 2]-cycloadducts: **337** and **338** in 60 and 18% yield, two diastereomers **339** (ratio 10:1) and **340** in 42 and 2% yield, **341** in 52% yield. All [2 + 2]-cycloadducts of the 1,3-butadienes were smoothly converted into the corresponding formal [4 + 2]-cycloadducts of **333** by heating at 165 °C. The interception of **333** by furan was unsuccessful under the conditions described above. Instead of the expected product **343** (Scheme 6.72), the butylpentadienol **335** was isolated in 49% yield. Competing for **333**, furan apparently does not react fast enough to outpace *n*BuLi, which, as a nucleophile, attacks the central allene carbon atom and brings about the lithium alcoholate **336** and eventually **335** [157].



Scheme 6.71 Generation of 1-oxa-3,4-cyclohexadiene (**333**) from 6,6-dichloro-3-oxabicyclo[3.1.0]hexane (**332**) by *n*-butyllithium and interception of **333** by *n*-butyllithium, styrene, 1,3-butadiene, isoprene and 2,3-dimethyl-1,3-butadiene.

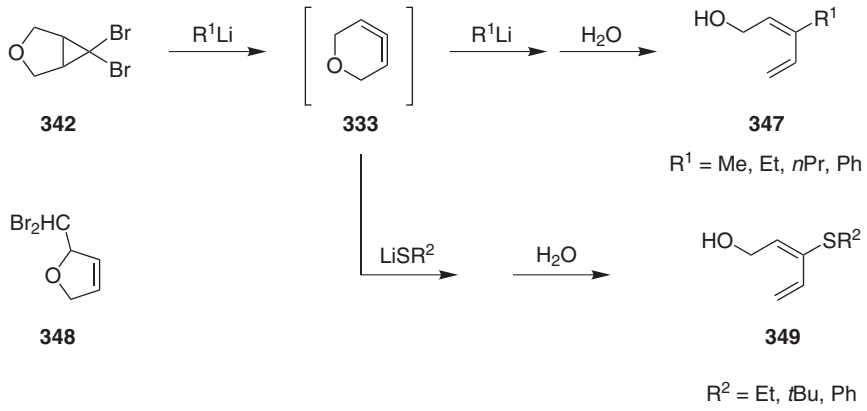


Scheme 6.72 1-Oxa-3,4-cyclohexadiene (**333**) from 6,6-dibromo-3-oxabicyclo[3.1.0]hexane (**342**) and methyllithium and interception of **333** by furan, 2-methylfuran and α-methylstyrene.

However, the furan adduct **343** could be prepared in 21% yield from 6,6-dibromo-3-oxabicyclo[3.1.0]hexane (**342**) as the source for **333** (Scheme 6.72). This allowed the utilization of MeLi as the reagent, which is less nucleophilic than *n*BuLi and now furan competed successfully for **333** [157]. Generated from **342**, **333** was also

trapped with 2-methylfuran and α-methylstyrene. In the former case, a 6.5:3.5:1 mixture (35% yield) of **344**, **345** and a third [4 + 2]-cycloadduct, probably a diastereomer of **344** or **345**, was formed. α-Methylstyrene furnished two [2 + 2]-cycloadducts **346** in a ratio of 10:1 in 54% yield [66].

The observation of the reaction of *n*BuLi with **333** yielding **335** led to the elaboration of a general synthesis for 3-substituted 2,4-pentadienols, whose hydroxymethyl and vinyl groups are *cis*-orientated relative to one another (Scheme 6.73). Accordingly, the dropwise addition of **342** to an excess of methyl-, ethyl-, *n*-propyl- or phenyllithium gave rise, after hydrolysis, to the pentadienols **347** in 50–70% yield [66]. When a mixture of MeLi and lithium ethane-, 2-methylpropane-2- or benzenethiolate was analogously treated with **342**, the thioenol ethers **349** resulted in 20–43% yield. In the case of **349**, R = Ph, a 1:1 mixture of both diastereomers was obtained, probably because phenylthio radicals, readily formed by exposure of thiophenol, present in trace amounts, to air, catalyzed the isomerization of the initially formed *E*-isomer [158].

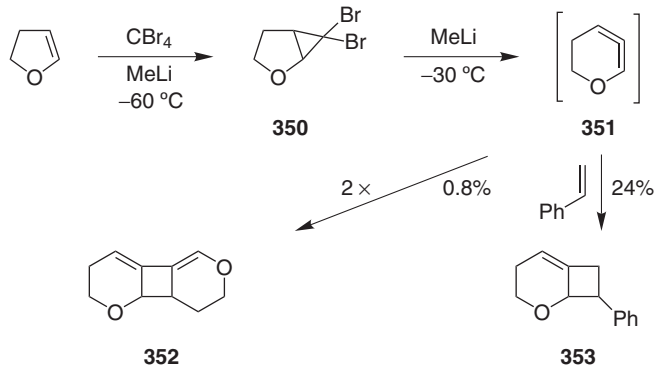


Scheme 6.73 Preparation of 3-substituted 2,4-pentadienols **347** and **349** via the symmetrical isopyran **333**.

The precursors **332** and **342** of **333** are prepared by addition of dichloro- and dibromocarbene to 2,5-dihydrofuran. As a parallel reaction, the insertion of the carbene to give **348** or the corresponding dichloro compound plays a non-negligible role. This requires an additional separation step. As procedures for the separation of **332** and **342** from the insertion products, the chemical transformation of the latter and the isolation of **332** and **342** from the resulting mixtures as well as separation by gas chromatography have been reported [159, 160], but neither was very efficient. Therefore, better procedures were looked for in the case of the **342**–**348** mixture. Virtually quantitative separations were achieved by distillation at 0.05 Torr by using an effective column [161] or by flash chromatography on silica gel with light petroleum ether–diethyl ether (20:1) as eluant [158].

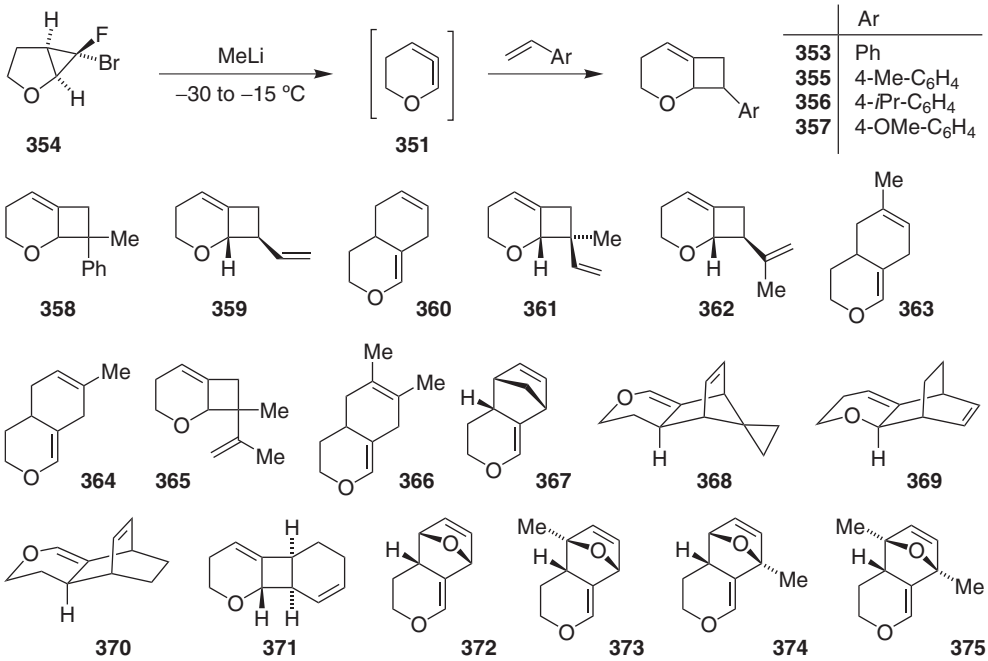
The substrate **332** for the liberation of **333** is one of the rather rare 1,1-dichlorocyclopropanes that allow a smooth DMS reaction [26]. Therefore, 6,6-dichloro-2-oxabi-

cyclo[3.1.0]hexane was tried first to serve as a precursor for the unsymmetrical isopyran **351** (1-oxa-2,3-cyclohexadiene). The treatment of this compound, dissolved in styrene, with *n*BuLi furnished the [2 + 2]-cycloadduct **353** of **351**, but the yield was only 7% [91]. Since 6,6-dibromo-2-oxabicyclo[3.1.0]hexane (**350**) cannot be isolated [160], it was prepared in situ from 2,3-dihydrofuran, tetrabromomethane and MeLi at –60 °C. Styrene and MeLi were added to the solution in that order at –30 °C to give a 1:1 mixture of the cycloadducts **353** in 24% yield relative to tetrabromomethane (Scheme 6.74) [91]. Experiments designed for the analogous synthesis of the furan and the 1,3-cyclopentadiene adducts **372** and **367**, respectively, of **351** were unsuccessful. In both cases, the formation of *exo*-6-bromo-2-oxabicyclo[3.1.0]hexane was observed. Apparently, the carbenoid resulting from **350** and MeLi did not eliminate LiBr to give **351**, but was protonated by furan or 1,3-cyclopentadiene [67].



Scheme 6.74 Generation of 1-oxa-2,3-cyclohexadiene (**351**) from 6,6-dibromo-2-oxabicyclo[3.1.0]hexane (**350**), dimerization of **351** and its trapping by styrene.

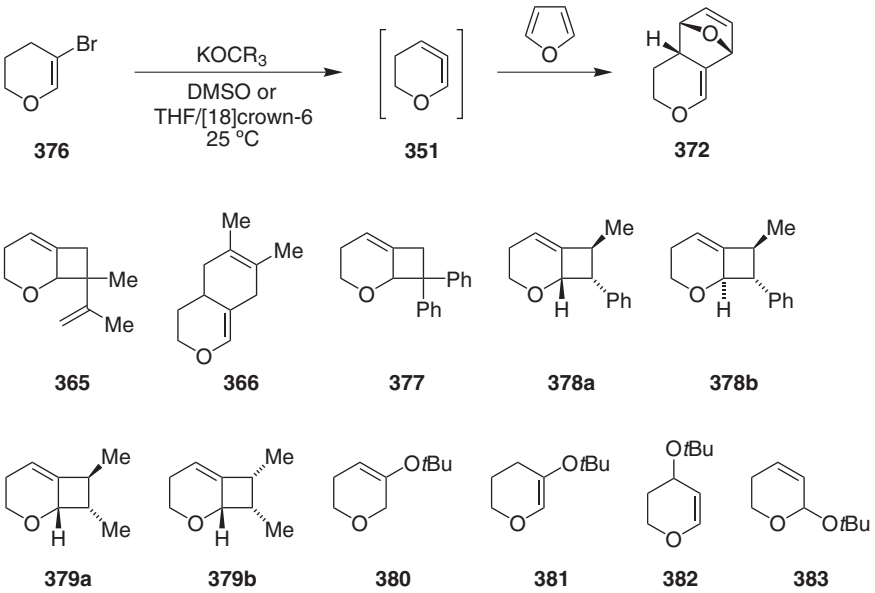
The dimer **352** of **351** was isolated from the product mixtures of two experiments conducted to trap **351** by alkenes, one with **350** and the other with **354** as substrate. Although no cycloadduct with the alkene was observed in one case, the yield of **352** amounted to only 0.8%. Nevertheless, the structure of **352** is interesting, since it suggests that the tetramethyleneethane diradical assumed to be the intermediate undergoes ring closure preferentially between two different allyl-radical termini.



Scheme 6.75 Products of the cycloadditions of 1-oxa-2,3-cyclohexadiene (**351**), liberated from *exo*-6-bromo-*endo*-6-fluoro-2-oxabicyclo[3.1.0]-hexane (**354**), to styrenes, 1,3-butadiene, isoprene, 2,3-dimethyl-1,3-butadiene, 1,3-cyclopentadiene, spiro[2.4]hepta-4,6-diene, 1,3-cyclohexadiene, furan, 2-methyl-furan and 2,5-dimethylfuran.

exo-6-Bromo-*endo*-6-fluoro-2-oxabicyclo[3.1.0]hexane (**354**) turned out to be a versatile and isolable precursor of **351**. It was prepared in 25% yield from 2,3-dihydrofuran, dibromofluoromethane and NaOH under phase-transfer catalysis [35, 91]. The treatment of solutions of **354** in a number of styrenes and 1,3-dienes at –30 to –15 °C with MeLi furnished the cycloadducts of **351** represented in Scheme 6.75. Styrene and three of its 4-substituted derivatives gave the methylenecyclobutanes **353** and **355–357** as 1:1 mixtures of diastereomers in yields of 54–59%. On thermolysis of these mixtures, the *endo*-isomer was converted almost completely to the *exo*-isomer in each case. α-Methylstyrene furnished a 2.5:1 mixture of *exo*- and *endo*-phenyl-**358**, whose ratio increased to 20:1 on heating at 170 °C [66, 91]. A 2:1 mixture of the [2 + 2]-cycloadduct **359** and the [4 + 2]-cycloadduct **360** resulted in 80% yield from 1,3-butadiene [91]. Analogously, isoprene gave rise to the [2 + 2]-cycloadducts **361** and **362** and a mixture of the [4 + 2]-cycloadducts **363** and **364** in a ratio of 2:1:1 in 61% yield, whereas the [2 + 2]-cycloadduct **365** was the predominant product (**365**:**366** = 8:1, 57%) in the case of 2,3-dimethyl-1,3-butadiene [66, 91]. Only one [4 + 2]-cycloadduct each was obtained from 1,3-cyclopentadiene (**367**, 10%) [67] and spiro[2.4]hepta-4,6-diene (**368**, 53%) [66]. The [4 + 2]-cycloadducts **369** and **370** and the [2 + 2]-cycloadduct **371** in a ratio of 3:1:1.4 and traces of a diastereomer each of

370 and **371** were formed from 1,3-cyclohexadiene and **351** in 55% yield [67]. Furan, 2,5-dimethylfuran and 2-methylfuran furnished only [4 + 2]-cycloadducts: **372** (31%), **375** (37%) [91] and **373** and **374** (1.5:1, 57%) [66], respectively.



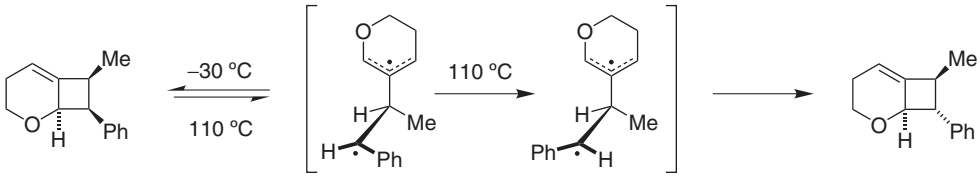
Scheme 6.76 Generation of 1-oxa-2,3-cyclohexadiene (**351**) from 5-bromo-3,4-dihydro-2*H*-pyran (**376**) and trapping products of **351** obtained from furan, 2,3-dimethyl-1,3-butadiene, 1,1-diphenyl-ethylene, (*E*)-1-phenylpropene, (*E*)-2-butene, (*Z*)-2-butene and '*tert*-butyl alcohol', according to Schlosser and co-workers.

5-Bromo-3,4-dihydro–2*H*-pyran (**376**) is also an easily accessible and efficient precursor to **351** [10, 11, 162, 163]. Schlosser et al. employed it to prepare the cycloadducts of **351** that are represented in Scheme 6.76. To that end, **376** was treated with KO*t*Bu and in one case with potassium 5-butyl-5-nonanolate in DMSO or in THF–[18]crown-6 in the presence of furan (**372**, 50% yield), 2,3-dimethyl-1,3-butadiene (**365** and **366** in the ratio of 4:1, 46%), 1,1-diphenylethylene (**377**, 43%) [11, 162], (*E*)-1-phenylpropene (**378a**,**b** in the ratio of 2:1, 19%), (*E*)-2-butene (**379a**, 6%) and (*Z*)-2-butene (**379b**, 8%) [11]. In the absence of the above trapping reagents, the *tert*-butoxypyrans **380** (8% yield), **381** (traces), **382** (7%) and **383** (traces) were formed in addition to small amounts of dimers or dihydrodimers [11], among them probably **352**.

It is remarkable that furan and 2,3-dimethyl-1,3-butadiene were used to trap **351** when it was generated from **354** as well as **376**. In both cases, the same products resulted and even the **365**:**366** ratios were closely similar in view of the different reaction conditions. This is convincing evidence for **351** existing as a separate species, unassociated with LiF or KBr, the second products of the eliminations from the progenitors en route to **351**. The first successful use of unactivated alkenes [(*E*)- and

(*Z*)-2-butene] as reaction partners of a strained cyclic allene was a highly surprising result.

Schlosser et al. [11] reported also the complete retention of configuration in the cycloadditions of **351** to (*E*)-1-phenylpropene and (*E*)- and (*Z*)-2-butene with formation of **378a**,**b**, **379a** and **379b**, respectively. By employing the precursor **354** of **351**, these trapping reactions were repeated and the results found to be correct [67]. Even though the yields were <1%, (*E*)- and (*Z*)-2-butene specifically gave rise to **379a** and **379b**, respectively. (*E*)-1-Phenylpropene furnished a 2:1 mixture of **378a** and **378b** in 47% yield, heating of which at 110 °C converted **378a** completely into **378b**. The use of (*Z*)-1-phenylpropene led to **378a**, **378b** and **378c** (Scheme 6.77) in a ratio of 2:1:20 in 5% yield. On heating this mixture, **378a** and **378c** rearranged to give **378b**. Whether the small quantities of **378a** and **378b** indicate a stereochemical leakage is unknown, since these compounds could originate from a small admixture (<1%) of (*E*)-1-phenylpropene to the *Z*-isomer. This seems possible on the basis of the substantially different yields of 47% from (*E*)- and only 5% from (*Z*)-phenylpropene, suggesting significantly different reaction rates [67].



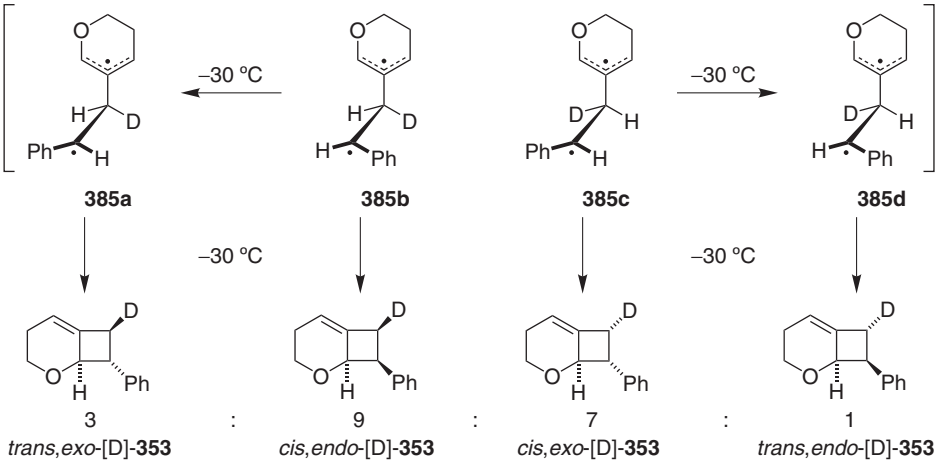
378c **384a** **384b** **378b**

Scheme 6.77 Proposal for the mechanisms of the addition of 1-oxa-2,3-cyclohexadiene (**351**) to (*Z*)-1-phenylpropene and of the thermolysis of the product **378c**.

Because of the retention of the configuration on addition of (*E*)- and (*Z*)-2-butene to **351**, Schlosser et al. [11] proposed a one-step mechanism and believed it to be similar to the [2 + 2]-cycloadditions of ketenes. According to quantum-chemical calculations, such reactions are concerted, but highly asynchronous [164], or proceed stepwise via an extremely short-lived diradical as intermediate [165]. Owing to the relationship of **351** to 1,2-cyclohexadiene (**6**) and the similarity of their reactivity as well as their trapping products, concerted [2 + 2]-cycloadditions seem unlikely. Diradical intermediates are well in accord with the stereochemical outcome, provided that they collapse to yield the four-membered ring faster than a rotation occurs around the C–C single bond that emerges from the C–C double bond of the allenophile. The height of the barrier to such a rotation is doubtless of a magnitude (several kcal mol^{-1}) that can explain the high stereoselectivities, as is illustrated for the cases of the addition of (*Z*)-1-phenylpropene (Scheme 6.77) and (*Z*)-β-deuterostyrene (Scheme 6.78) to **351**.

The strongly predominating formation of **378c** on addition of (*Z*)-1-phenylpropene requires the diradical intermediate **384a** and its ring closure without a change of the conformation at –30 °C (Scheme 6.77). Since **378c** rearranges to give the *trans*-

diastereomer **378b** on heating at 110 °C [67], **378c** should revert to **384a** on thermolysis and **384a** should now undergo a conformational change. The resulting **384b** should then collapse to furnish **378b**, which is the thermodynamic sink of the system. On addition of (*E*)-1-phenylpropene to **351**, **384b** should initially be formed besides its conformer, in which the pyran subunit is rotated by 180° and which should collapse to give **378a**.



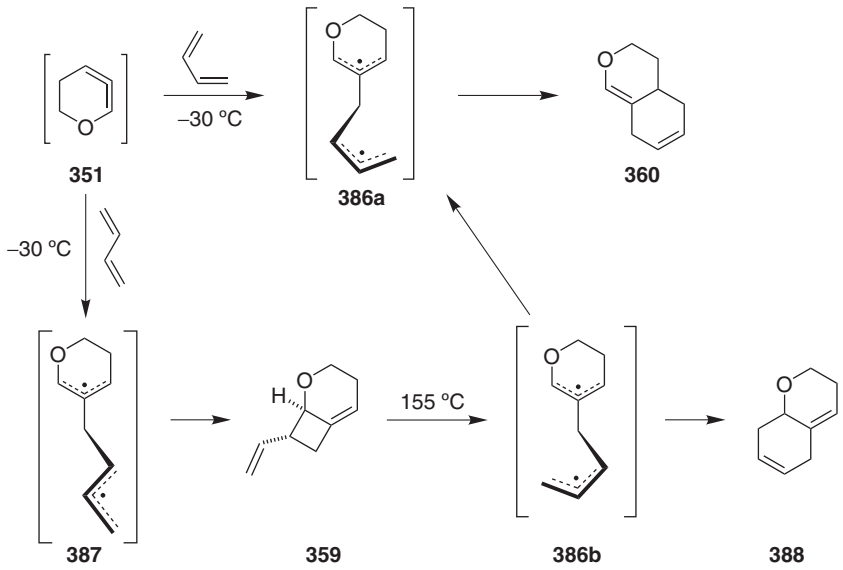
Scheme 6.78 Proposal for the mechanism of the addition of 1-oxa-2,3-cyclohexadiene (**351**) to (*Z*)-*β*-deuterostyrene.

The stereochemical course of the addition of styrene to **351** was probed with (*Z*)-*β*-deuterostyrene (Scheme 6.78) [166]. At variance with the reaction of **6** (Scheme 6.20), the stereochemical information was not entirely lost now. The products *trans,exo-*, *cis,endo-*, *cis,exo-* and *trans,endo*-[D]-**353** resulted in a ratio of 3:9:7:1, which suggests the same ratio for the diradicals **385a–d**. The combination of **351** and (*Z*)-*β*-deuterostyrene can lead only to **385b** and **385c** (and their enantiomers) initially. If the conformational barrier is high enough, the interconversion of **385b** and the enantiomer of **385c** can be negligible (see the absence of the *exo*-phenyl isomer of **378c**, Scheme 6.77). Provided that these assumptions are valid, the ratios of conformational change and ring closure of **385b** (→ **385a** and *cis,endo*-[D]-**353**) and **385c** (→ **385d** + *cis,exo*-[D]-**353**) are calculated to be 1:3 and 1:7, respectively, and are evidence for extremely low activation barriers to ring closure of the diradicals of the type **385** as well as **384**. This mechanistic model also explains the ratio *endo*-**353**:*exo*-**353** = 1:1 (Schemes 6.74 and 6.75), although their relative thermodynamic stability is characterizd by a ratio of 1:20.

The positional selectivity of the cycloadditions of **351** is of particular interest, since the [2 + 2]-cycloadditions proceed exclusively at the double bond bearing the oxygen atom, whereas the [4 + 2]-cycloadditions occur at the double bond remote of the oxygen atom with the exception of the major product resulting from 1,3-cyclohexadiene (**369**, Scheme 6.75). Supposing diradical mechanisms, these findings require that

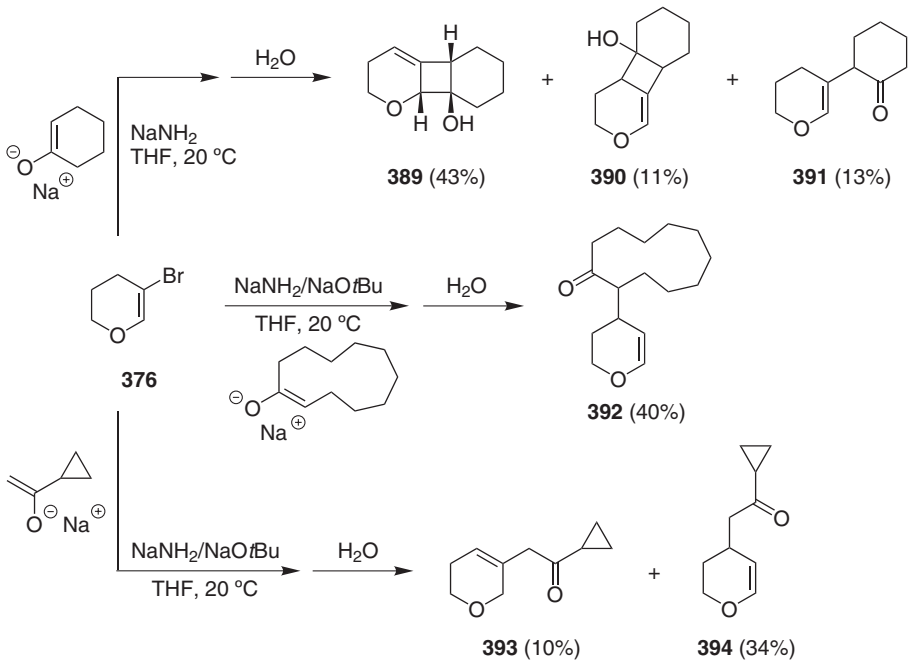
the 1,4-diradicals in Schemes 6.77 and 6.78 cyclize with high selectivity using the allyl-radical terminus of the pyran moiety that is bound to the oxygen atom. The greater spin density at that atom relative to the other allyl terminus may be the origin of the phenomenon [91]. In addition, a polarization of these diradicals due to the ability of the oxygen atom to donate an electron pair could contribute to the selectivity.

Initially, the pathways of the [4 + 2]-cycloadditions were taken to be concerted because of the positional selectivity [11, 91]. Since all 1,3-dienes used can be considered to be electron rich, the involvement of the double bond of **351** that is the less electron rich is well in accord with the rationalization of the reactivity of concerted [4 + 2]-cycloadditions on the basis of frontier-orbital energies. However, the quantum-chemical treatment of the [4 + 2]-cycloadditions of **6** to 1,3-butadiene and furan favors two-step reactions via diradical intermediates [9]. Based on that model, Scheme 6.79 illustrates the mechanisms of the addition of 1,3-butadiene to **351**. The diradical **387**, having an allyl subunit with an *E*-configuration in the side-chain, should result from **351** and *s-trans*-1,3-butadiene and should collapse to give the [2 + 2]-cycloadduct **359**. On the other hand, the interaction with *s-cis*-1,3-butadiene should lead to **386a**, in which the allyl subunit of the side-chain has the *Z*-configuration and is distant from the oxygen atom, thus furnishing **360** exclusively on 1,6-cyclization. The thermolysis of **359** at 155 °C gave rise to a 1:1 mixture of **360** and **388** [67, 91]. Plausibly, the conformation **386b** of **386a** has to be assumed as progenitor of **388**. Simultaneously, the high temperature could allow conversion to **386a** and ultimately to **360**. Accordingly, diradicals of type **386a** rather than **386b** would have to be the intermediates in most cases en route to the [4 + 2]-cycloadducts of cyclic 1,3-dienes.



Scheme 6.79 Proposal for the mechanisms of the trapping of 1-oxa-2,3-cyclohexadiene (**351**) by 1,3-butadiene and of the thermolysis of the [2 + 2]-cycloadduct **359** at 155 °C.

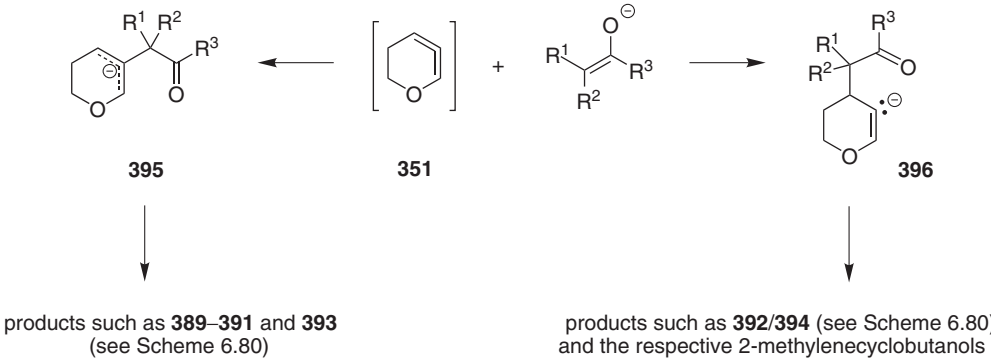
With respect to the cycloadditions, **6** and **351** behave similarly with the significant addition of positional selectivity in the case of **351**. Likewise, the reactions of **351** with nucleophiles offer an aspect supplementary to the phenomena observed with **6**. Schlosser et al. [11] obtained the *tert*-butoxypyrans **380–383** as products of the action of KO*t*Bu on **376** (Scheme 6.76), indicating that the *tert*-butoxide ion attacked not only the central carbon atom of the allene subunit of **351** but also the terminal ones. The former process is analogous to the behavior of **6** and leads to allyl anions whose protonation gives rise to the enol ethers **380** and **381**, whereas the latter brings about vinyl anions that are the progenitors of the allyl ether **382** and the acetal **383**. The formation of **382** and **383** parallels the reaction of $3\delta^2$-pyran (**180**, Scheme 6.61), $3\delta^2$-chromene (**258**, Scheme 6.58) and $3\delta^2$-1*H*-quinoline (**260**, Scheme 6.57) with KO*t*Bu and provides evidence that the ground state of **351** has some polar character despite its allene nature. In comparison with the zwitterionic state **258-Z$_1$**, the respective state of **351** should be destabilized owing to the absence of the aromatic π-electron system. On the basis of calculations on **258** and **258-Z$_1$** (Scheme 6.56), the free enthalpy of the zwitterionic state of **351** should lie significantly more than 5 kcal mol^{-1} above that of the allene state.



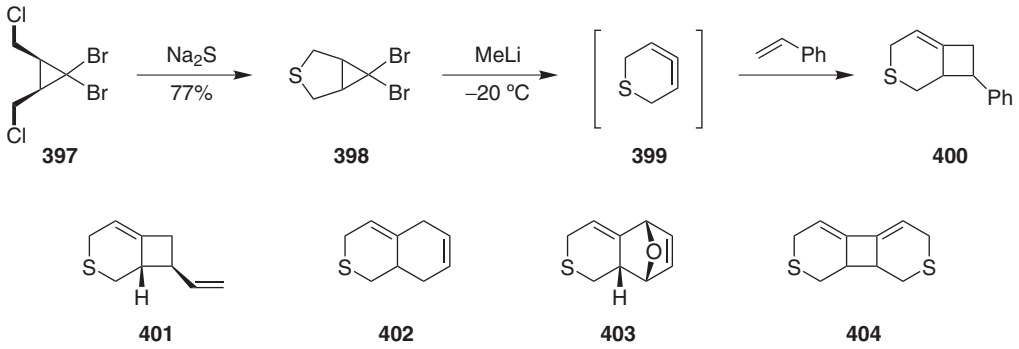
Scheme 6.80 Reactions of 5-bromo-3,4-dihydro-2*H*-pyran (**376**) with complex bases composed of $NaNH_2$ or $NaNH_2$–NaO*t*Bu and enolates of ketones, according to Caubère and co-workers.

The interception of **351** by enolate ions corroborates this conception of **351**. Caubère et al. [10, 163] treated **376** with complex bases consisting of $NaNH_2$ or $NaNH_2$–NaO*t*Bu and enolates of a variety of ketones. A selection of the results are depicted in Scheme 6.80. Cyclohexanone furnished the 3-methylenecyclobutanols **389** and **390** in addition to the ketone **391** in yields of 43, 11 and 13%, respectively. Cyclopentanone, cycloheptanone and several substituted cyclohexanones brought about analogous products in yields of 30–86%. In contrast, cycloundecanone and cyclododecanone gave rise to the ketone **392** (40%) and the higher homologue (60%). The ketones **393** (10%) and **394** (34%) resulted from cyclopropyl methyl ketone. From propiophenone, diethyl ketone and diisopropyl ketone, mixtures of products such as **389**, **391**, **392**/**394** and 2-methylenecyclobutanols corresponding to **392**/**394** were obtained in yields of up to 83%.

There is no doubt that the reactions of Scheme 6.80 proceed via 1-oxa-2,3-cyclohexadiene (**351**), which results by β-elimination from **376**, in particular in view of the generation of **6** from 1-halocyclohexenes and its interception by enolates (see Schemes 6.12, 6.13 and 6.23). The liberation of the cycloalkyne isomeric to **351** seems not to interfere. Although the authors [10] prefer concerted or quasi-concerted pathways, such courses are not very likely, which is why two-step processes are drawn in Scheme 6.81. The attack of the enolate β-carbon atom at the central carbon atom of the allene subunit gives rise to the allyl anion **395**, which explains the formation of products such as **389**–**391** and **393**. While this mechanism is just a transfer of that proposed for the reaction of **6** with enolates, another one is possible owing to the polar character of **351**. The addition of the enolate at C4 of **351** leads to the vinyl anion **396**, which should be the progenitor of compounds such as **392**/**394** and of 2-methylenecyclobutanols that emerge from the cyclization of **396** eventually. However, it remains unexplained why no products were found that could have resulted from an attack of an enolate at C2 of **351**.



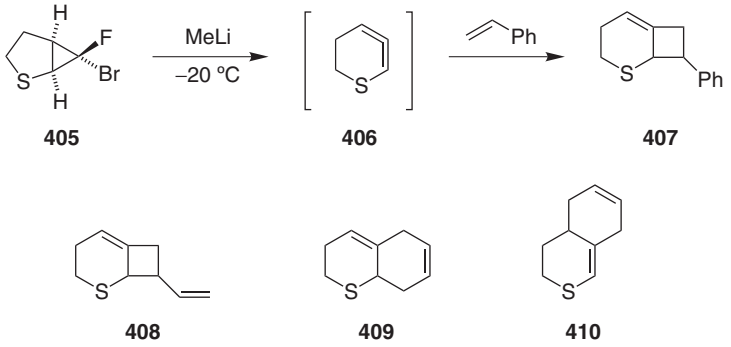
Scheme 6.81 Mechanisms of product formation from 1-oxa-2,3-cyclohexadiene (**351**) and enolates.



Scheme 6.82 Treatment of 6,6-dibromo-3-thiabicyclo[3.1.0]hexane (**398**) with methyllithium, trapping of the resulting 1-thia-3,4-cyclo-hexadiene (**399**) by styrene, 1,3-butadiene and furan and the structure of the dimer **404** of **399**.

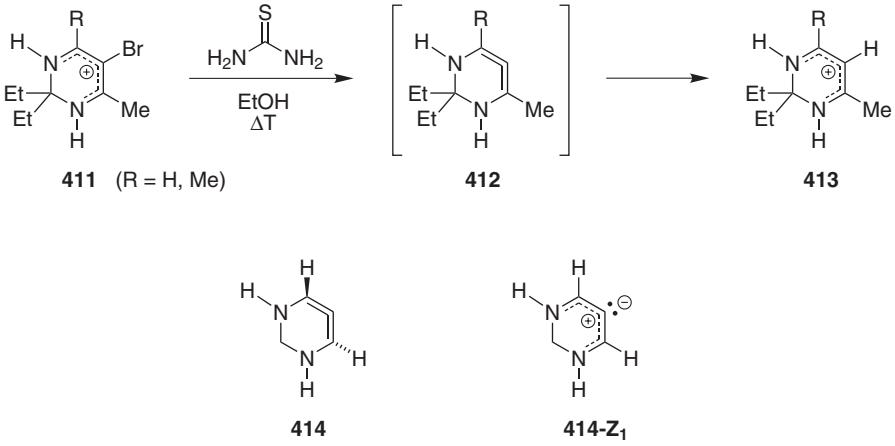
The higher homologues of the isopyrans **333** and **351**, 1-thia-3,4- (**399**) and 1-thia-2,3-cyclohexadiene (**406**) have also been investigated [154]. As precursor to **399**, 6,6-dibromo-3-thiabicyclo[3.1.0]hexane (**398**) was employed (Scheme 6.82). It was prepared in 77% yield from *cis*-1,1-dibromo-2,3-bis(chloromethyl)cyclopropane (**397**) and sodium sulfide monohydrate in H_2O–$CHCl_3$ in the presence of tetrabutylammonium bromide. The treatment of **398**, dissolved in styrene, with MeLi furnished the [2 + 2]-cycloadducts **400** (*exo*:*endo* = 4:1) of **399** in 23% yield. 1,3-Butadiene instead of styrene gave rise to a 1:1 mixture of the [2 + 2]-cycloadduct **401** and the [4 + 2]-cycloadduct **402** in 10% yield, whereas only a 2% yield of **403** was obtained from furan and **399**. The low yields are caused by side reactions, whose products resulted in significant amounts, namely the dimer **404** of **399** [167], and consecutive products of the carbenoid that is brought about from **398** and MeLi and whose conversion into **399** seems to be not very efficient [154].

Since the addition of dibromocarbene to 2,3-dihydrothiophene was unsuccessful, bromofluorocarbene was utilized, leading to *exo*-6-bromo-*endo*-6-fluoro-2-thiabicyclo[3.1.0]hexane (**405**), isolated in 16% yield (Scheme 6.83). The treatment of its solution in styrene with MeLi gave the [2 + 2]-cycloadduct **407** (*exo*:*endo* = 5:1) in 26% yield. An 8:1:2 mixture of the *exo*- and *endo*-isomers of the [2 + 2]-cycloadduct **408** and the [4 + 2]-cycloadduct **409** resulted in a 22% yield from 1,3-butadiene instead of styrene. In spite of the modest yields, further products could not be identified, which may be taken as an indication that the oligomerization or polymerization is the major reaction of **406**. An attempt to trap **406** by furan was unsuccessful. Concerning the positional selectivity of the cycloadditions of **406**, that of the [2 + 2]additions (**407**, **408**) is the same as that of the oxygen homologue **351**, whereas that of the [4 + 2] addition (**409**) is at variance with that of **351**. The thermolysis of *exo*-**408** at 90 °C proceeded as in the case of the oxygen analogue **359** and furnished a 1:1 mixture of the tetrahydrobenzothiopyrans **409** and **410**. In contrast, *endo*-**408** was converted into **410** exclusively, which is why this transformation may be viewed as a Cope rearrangement [154].



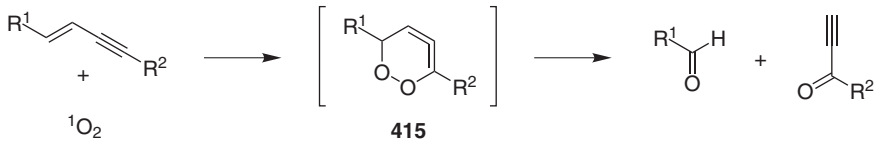
Scheme 6.83 Generation of 1-thia-2,3-cyclohexadiene (**406**) from *exo*-6-bromo-*endo*-6-fluoro-2-thiabicyclo[3.1.0]hexane (**405**) by methyllithium and trapping of **406** by styrene and 1,3-butadiene.

Two types of derivatives of 1,2-cyclohexadiene with two heteroatoms were proposed as reactive intermediates more than 20 years ago. Lloyd and McNab [168] observed the reaction of the 5-bromo-1,2-dihydropyrimidinium ions **411** with thiourea in refluxing ethanol to give the bromine-free cations **413**. Suspected as intermediates, the 5δ^2-dihydropyrimidines **412** were initially considered as zwitterions of the type **414-Z$_1$**. However, quantum-chemical calculations on the parent systems suggested an unambiguous preference of the allene structure **414** over the zwitterion **414-Z$_1$** [169].

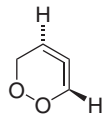


Scheme 6.84 Protodebromination of the 5-bromo-1,2-dihydropyrimidinium ions **411** believed to proceed via the 5δ^2-dihydropyrimidines **412**.

Lee-Ruff et al. [170] treated conjugated enynes with singlet oxygen and obtained aldehydes or methyl formate and acylacetylenes (Scheme 6.85). They explained the outcome by 'dehydro' Diels–Alder reactions with formation of the 1,2-dioxa-3,4-cyclohexadienes **415** followed by the retrograde 'dehydro' Diels–Alder reactions to give two carbonyl compounds. A theoretical study of the parent **415d** of the intermediates **415a–c** and its fragmentation showed that this species is a genuine allene and that its conversion into formaldehyde and propynal is exothermic by 63 kcal mol^{-1} [170]. These processes supplement the picture of the 'dehydro' Diels–Alder reactions of conjugated enynes with alkenes and acetylenes, which have been discussed in Sections 6.3.3 and 6.3.4 (Schemes 6.35 and 6.47–6.50).



	R^1	R^2
a	Ph	Ph
b	4-MeO-C_6H_4	Ph
c	OMe	H

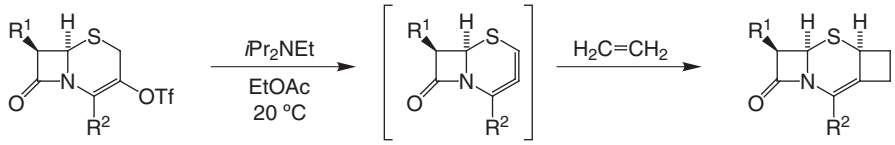


415d

Scheme 6.85 Formation of 1,2-dioxa-3,4-cyclohexadienes (**415**) by addition of singlet oxygen to conjugated enynes and retrograde 'dehydro' Diels–Alder reaction of **415**.

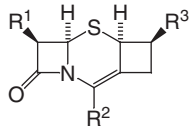
Intense efforts toward the synthesis of new cephalosporin derivatives, possibly useful as drugs, led to the unintended discovery of a particularly interesting bishetero-1,2-cyclohexadiene system, that is, the dihydro-5δ^2-1,3-thiazine nucleus annulated to a β-lactam entity (**417**, **444**) (Schemes 6.86 and 6.91) [155, 171, 172]. For example, species of that kind emerge from the vinyl triflate **416** and the vinyl mesylate **443** by β-elimination caused by a tertiary amine. For the first time, these mild conditions allowed the successful use of functionalized alkenes and acetylenes to trap a six-membered cyclic allene with formation of cycloadducts [155, 171a]. Because of the aggressiveness of MeLi and KO*t*Bu, the standard reagents for the liberation of six-membered cyclic allenes, functionalized alkenes and acetylenes were found to be incompatible with such reaction conditions. In addition, **417** is of an unprecedented reactivity, allowing the cycloaddition of unactivated alkenes and even that of unsubstituted ethylene and acetylene to give the corresponding 3-methylenecyclobutane and 3-methylenecyclobutene, respectively, in excellent yields [155].

Scheme 6.86 displays the generation of **417** from the cephalosporin triflate **416** and the formulas of the trapping products with ethylene, monosubstituted ethylenes, 1,1-disubstituted ethylenes and 1,1-dimethylallene [155]. It was shown for two such reaction partners (styrene and phenyl vinyl thioether) that the exchange of the



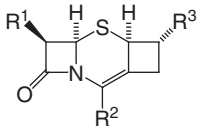
416 **417** **418**

R^1 = $PhCH_2CONH$, R^2 = 4-MeO-$C_6H_4CH_2OCO$, Tf = SO_2CF_3



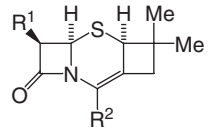
419

R^3 = *n*Bu, cyclohexyl, CH_2SiMe_3, CH_2OH, OEt, OAc, 2-oxopyrrolid-1-yl, cyclopropyl, Ph, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 3-Cl-C_6H_4, CN, CO_2Me, SPh

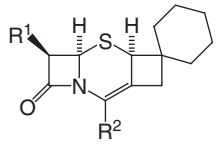


420

R^3 = cyclopropyl, Ph, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 3-Cl-C_6H_4, CN, CO_2Me, SPh



421



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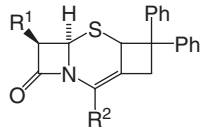

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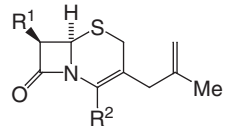

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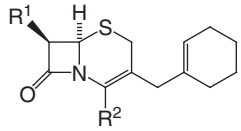
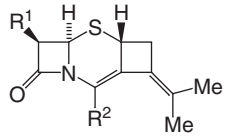


425



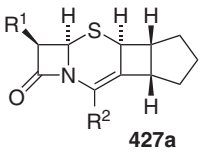
426

Scheme 6.86 Generation of 4-methoxybenzyl (6*R*,7*R*)-8-oxo-7-(phenylacetamido)-1-aza-5-thiabicyclo[4.2.0]octa-2,3-diene-2-carboxylate (**417**) from the cephalosporin triflate **416** and products of the trapping of **417** by ethylene, monosubstituted ethylenes, 1,1-disubstituted ethylenes and 1,1-dimethylallene, according to Elliott and co-workers.

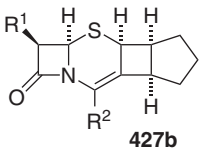
phenylacetyl group by a benzoyl group does not disturb the cycloadditions. Scheme 6.87 contains the structures of the cycloadducts of **417** with cycloalkenes and 1,2-disubstituted ethylenes. Methylene chloride was routinely used as a solvent, in which the β-elimination from the triflate **416** by ethyldiisopropylamine was relatively fast. Acetone gave an equally rapid reaction, whereas **416** was consumed much slower in ethyl acetate (EtOAc) and THF. These four solvents gave the best yields, and in ethanol and dimethylformamide the yields were considerably lower. Ethyldiisopropylamine ($i\mathrm{Pr_2NEt}$) proved to be the base of choice for the generation of **417**. Stronger bases such as DBU and sterically less hindered bases, e.g. triethylamine, gave lower yields. The use of K_2CO_3 was superior to that of $i\mathrm{Pr_2NEt}$ with regard to the yields, but the reactions were much slower.

For the addition of ethylene, EtOAc as solvent was particularly advantageous and gave **418** in 60% yield (Scheme 6.86). The monosubstituted ethylenes 1-hexene, vinylcyclohexane, allyltrimethylsilane, allyl alcohol, ethyl vinyl ether, vinyl acetate and *N*-vinyl-2-pyrrolidone furnished [2 + 2]-cycloadducts of the type **419** in yields of 54–100%. Mixtures of [2 + 2]-cycloadducts of the types **419** and **420** were formed with vinylcyclopropane, styrene and derivatives substituted at the phenyl group, acrylonitrile, methyl acrylate and phenyl vinyl thioether (yields of 56–76%), in which the diastereomers **419** predominated up to a ratio of 2.5:1 except in the case of the styrenes, where this ratio was 1:1. The Hammett ρ value for the addition of the styrenes to **417** turned out to be –0.54, suggesting that there is little charge separation in the transition state [155]. In the case of **6**, the ρ value was determined as +0.79 (see Section 6.3.1) and indicates a slight polarization in the opposite direction. This astounding variety of substrates for **417** is contrasted by only a few monosubstituted ethylenes whose addition products with **417** could not be observed or were formed in only small amounts: phenyl vinyl ether, vinyl bromide, (perfluorobutyl)-ethylene, phenyl vinyl sulfoxide and sulfone, methyl vinyl ketone and the vinylpyridines.

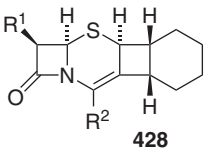
Isobutene, methylenecyclohexane and 1,1-diphenylethylene gave rise to the related [2 + 2]-cycloadducts **421**, **422** and **423**, respectively, in yields of 47–77%, which were accompanied by small quantities of the non-cyclized products **424** and **425** in the case of isobutene and methylenecyclohexane. A 34% yield of the [2 + 2]-cycloadduct **426** was obtained from the interception of **417** with 1,1-dimethylallene. A 1.8:1 mixture of the diastereomeric [2 + 2]-cycloadducts **427a**,**b** resulted in a 55% yield from cyclopentene. Cyclohexene brought about the single product **428** (39%). The reactions of **417** with 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran proceeded similarly, but with better yields (73, 62%) and gave **429a**,**b** and **430**. The same regioselectivity of the cycloaddition as styrene revealed indene, benzofuran, benzothiophene *S*,*S*-dioxide and *N*-acetylindole. They furnished products of the type **431** in yields of 90, 63, 34 and 33%, respectively. On addition of (*E*)-2-butene, (*E*)-2-pentene, (*E*)-stilbene and (*E*)-1-methoxybut-1-en-3-one to **417**, the configuration was retained and the *trans*-substituted 3-methylenecyclobutanes of type **432** were the products isolated in yields of 56–91%. The use of (*Z*)-2-butene and (*Z*)-2-pentene was impaired by small impurities of the *E*-isomers, which react with **417** about 25times as fast as the *Z*-compounds. The *cis*-disubstituted [2 + 2]-cycloadducts of type **433**



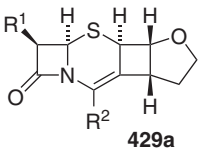
427a



427b

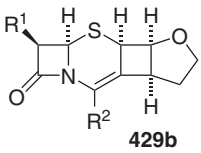


428

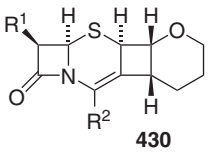


429a

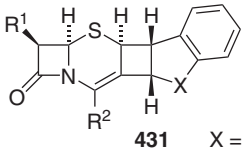
R^1 = $PhCH_2CONH$, R^2 = 4-MeO-$C_6H_4CH_2OCO$



429b

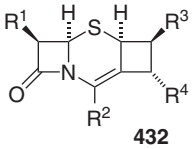


430



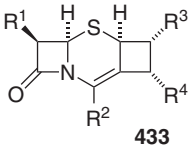
431

X = CH_2, O, SO_2, NAc



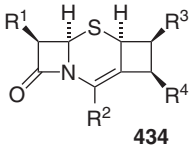
432

R^3	Me	Me	Et	Ph	OMe
R^4	Me	Et	Me	Ph	COMe



433

R^3	Me	Me	Et	Ph	Ph	OMe
R^4	Me	Et	Me	D	OMe	Ph



434

R^3	Me	Ph
R^4	Me	D

Scheme 6.87 Trapping products of cephalosporin derivative **417** with cycloalkenes and 1,2-disubstituted ethylenes.

and **434** resulted predominantly (ratios of 7:1 and 4:1), but the *trans*-isomers of type **432** were also formed well. (*Z*)-*β*-Methoxystyrene and (*Z*)-*β*-deuterostyrene were converted into the products (two regioisomers of type **433** in a ratio of 3:1 and diastereomers of the type **433** and **434** in a ratio of 1:1) without a stereochemical leakage.

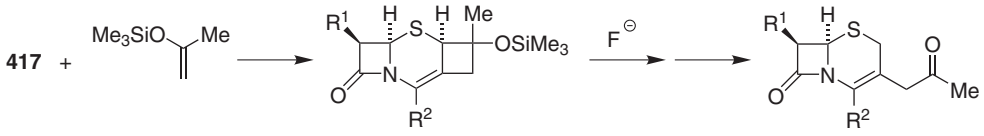
In view of the retention of the configuration on addition of (*Z*)-*β*-deuterostyrene to **323** (Scheme 6.69), **417** and **450** (Scheme 6.92), and the failure to observe products resulting from the opening of the three-membered ring in the case of the reaction of vinylcyclopropane with **417**, Elliott et al. [155] excluded two-step mechanisms with diradical intermediates and preferred concerted cycloadditions to the allenes of the $[_\pi 2_s + {}_\pi 2_a]$type. This conclusion is not a necessary one. As has been discussed concerning the reactions of 1-oxa-2,3-cyclohexadiene (**351**), which adds (*Z*)-2-butene with complete retention of the configuration and (*Z*)-*β*-deuterostyrene with predominant but not complete retention, a diradical intermediate would have to collapse just faster than the rotation around the single bond occurs that resulted from the double bond of the alkene. Thus, a two-step course also would explain the phenomena. On the other hand, the barrier to the rearrangement of the cyclopropylcarbinyl into the homoallyl radical was determined as 7 kcal mol^{-1} [173]. If the barrier to the ring closure of the diradical possibly formed from **417** and vinylcyclopropane is just 2 kcal mol^{-1} smaller, the opening of the cyclopropane moiety will not be observed

and hence the two-step mechanism is also able to rationalize the formation of the [2 + 2]-cycloadducts **419** and **420**, R = cyclopropyl.

That the reactions of **417** with isobutene and methylenecyclohexane yield small amounts of the 1,4-pentadiene derivatives **424** and **425**, respectively, in addition to the 3-methylenecyclobutanes **421** and **422** was explained by ene reactions, which could take place parallel to the cycloadditions [155]. An alternative mechanism invokes the diradicals that could well emerge from the addition of **417** to the olefinic methylene groups of isobutene and methylenecyclohexane. The collapses to give **421** and **422** would then compete with hydrogen atom transfers from the subunits originating from the allenophils to the allyl radical moiety, leading to **424** and **425**. Such hydrogen atom transfers are well known from photochemically generated 1,4-diradicals. For example, the irradiation of chloranil in the presence of isobutene furnished products [174] analogous to **421** and **424**. This has to be considered as support for diradical intermediates in the [2 + 2]-cycloadditions of **417**.

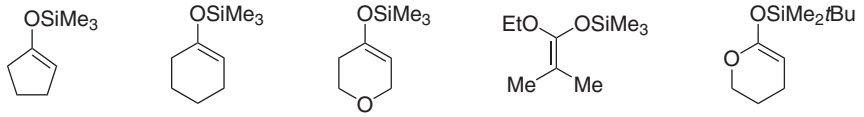
Elliott et al. [155] proposed a concerted cycloaddition also for the reaction of **417** with 1,1-dimethylallene to yield **426**. However, even the 1,2-bismethylenecyclobutane entity of **426** provides support for a diradical intermediate, since it is characteristic of the dimers of many allenes (see, for example, Schemes 6.10 and 6.25). It is generally accepted that these [2 + 2]-cycloadditions proceed via diradicals as intermediates.

The efficiency of the [2 + 2]-cycloadditions of **417** was utilized in a strategy for the synthesis of cephalosporin derivatives that carry an acetone or acetic acid ester group in the 3-position (Scheme 6.88) [175]. Liberated in the presence of 2-(trimethylsilyloxy)propene, **417** underwent cycloaddition leading to **435**, treatment of which with tetrabutylammonium or hydrogen fluoride furnished the Δ^3-cephalosporin **436** admixed with the Δ^2-isomer. This mixture was converted to pure **436** by an oxidation–reduction sequence. In addition to the trimethylsilylenol ether of acetone, the



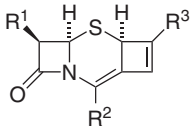
435 **436**

R^1 = $PhCH_2CONH$, R^2 = 4-MeO-$C_6H_4CH_2OCO$



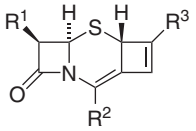
Scheme 6.88 Silylenol ethers and silyl keteneacetals that were used to trap the cyclic allene **417**. The [2 + 2]-cycloadducts such as **435** were converted into products of the type **436**.

silylenol ethers and silyl keteneacetals derived from cyclopentanone, cyclohexanone, tetrahydropyran-4-one, ethyl isobutyrate and γ-valerolactone, respectively, were employed.



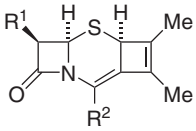
437

R^3 = H, Ph, CO_2Me, *n*Bu, CH_2OH, CH_2Br, OEt, $SiMe_3$



438

R^3 = H, Ph, CO_2Me



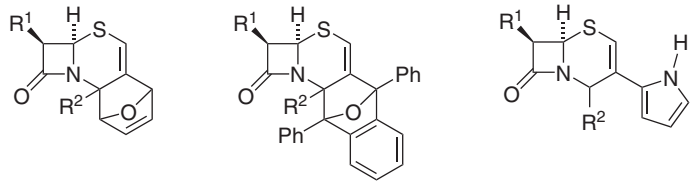
439

R^1 = $PhCH_2CONH$, R^2 = 4-MeO-$C_6H_4CH_2OCO$

Scheme 6.89 [2 + 2]-Cycloadducts of the cyclic allene **417** with acetylenes, according to Elliott and co-workers.

Cycloadditions of acetylenes to six-membered cyclic allenes remained unknown until the work of Elliott et al. [155, 171a]. The reactions of **417** furnished astonishingly high yields in several cases. Scheme 6.89 displays the formulas of the corresponding methylenecyclobutenes. Unsubstituted acetylene gave a 1:4.2 mixture of the diastereomers of type **437** and **438** in 42% yield. Phenylacetylene (95%, 1:2.3) and methyl propiolate (35%, 2.5:1) behaved similarly. Single products of the type **437** emerged from 1-hexyne (50%), 2-propyn-1-ol (34%), propargyl bromide (16%), ethoxyacetylene (36%) and (trimethylsilyl)acetylene (69%). Even from 2-butyne, which reacts rather sluggishly in cycloadditions in general, the respective methylenecyclobutene (**439**) resulted in 57% yield.

The investigation of 1,3-dienes as trapping reagents for **417** was less extensive. 1,3-Butadiene, 1,3-cyclopentadiene and 1,3-cyclohexadiene gave rise to complex mixtures, which probably contained [2 + 2]- and [4 + 2]-cycloadducts, but which were neither separated nor characterized [155]. In view of up to five products that were formed from **6** with 1,3-butadiene (Scheme 6.17), **221** with 1,3-cyclopentadiene (Scheme 6.55) and **351** with 1,3-cyclohexadiene (Scheme 6.75), the variety of the possible products is not surprising owing to the chirality centers of **417**. A shown in Scheme 6.90, furan and 1,3-diphenylisobenzofuran furnished a single [4 + 2]-cycloadduct each, **440** (49% yield) and **441** (67%) [155, 171b]. An attempt to intercept **417** with pyrrole did not cause a cycloaddition but, with regard to pyrrole, a substitution that could be electrophilic in nature. Accordingly, as a nucleophile, pyrrole would attack the central allene carbon atom of **417** and the resulting zwitterion would be converted into **442** (91% yield) by proton transfer from the cationic pyrrole to the allyl-anion subunit.

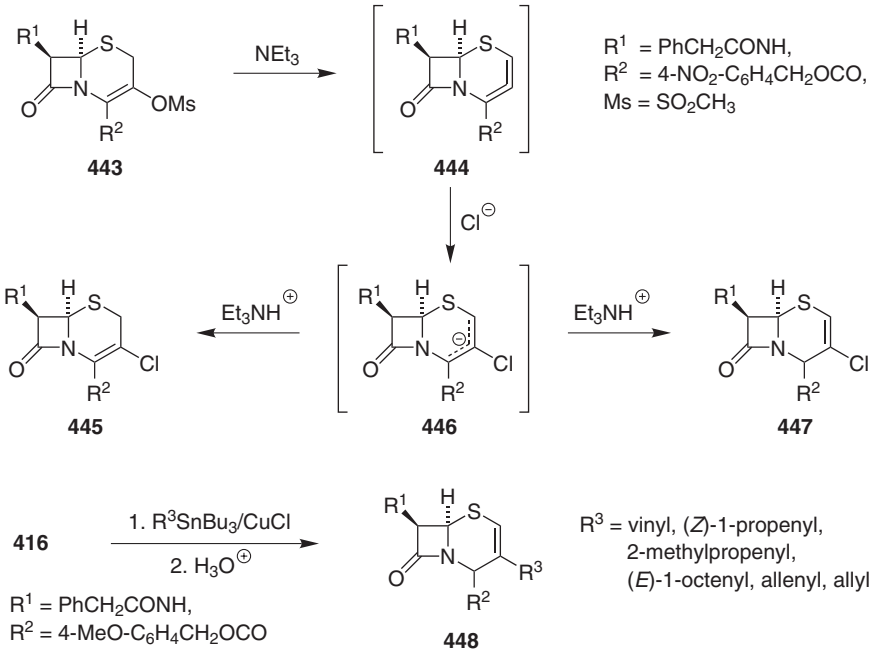


440 **441** **442**

R^1 = $PhCH_2CONH$, R^2 = 4-MeO-$C_6H_4CH_2OCO$

Scheme 6.90 Products of the reactions of the cyclic allene **417** with furan, 1,3-diphenylisobenzofuran and pyrrole.

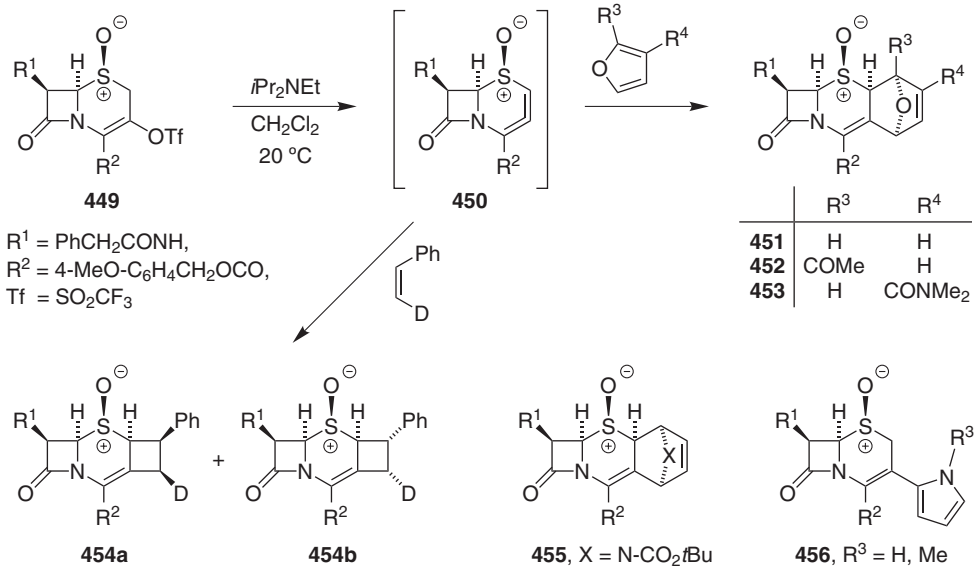
A nucleophilic attack at an allene system of the type of **417** was described for the first time by Cainelli et al. [172], namely at **444** with the chloride ion as the nucleophile (Scheme 6.91). After the treatment of the mesylate **443** with triethylamine in the presence of lithium, sodium or tetrabutylammonium chloride, mixtures of the vinyl chlorides **445** and **447** were isolated in high yields. Since the reaction did not proceed in the absence of triethylamine, the first step should be a β-elimination of methanesulfonic acid from **443** to generate **444**, which would accept a chloride ion at the central allene carbon atom. A proton transfer to either allyl terminus of the anion thus formed (**446**) would lead to the products **445** and **447**.



Scheme 6.91 Nucleophilic substitutions at the cephalosporin triflate **416** and mesylate **443**, believed to proceed via the cyclic allenes **417** and **444**, respectively.

An analogous mechanism was proposed for the conversion of the triflate **416** to the vinyl-, allyl- and allenyl-Δ^2-cephems **448** in yields of 47–71% by the respective tributyltin compounds in the presence of cuprous chloride (Scheme 6.91) [176]. Accordingly, the cyclic allene **417** should be liberated from **416** in the first step. Then, the organocopper species would transfer a hydrocarbon group to the central allene carbon atom of **417**, leading to an allyl anion derivative, which is protonated during the workup. These reactions of **416** and **443** indicate that the cyclic allenes **417** and **444** behave toward nucleophiles as 1,2-cyclohexadiene (**6**) (Schemes 6.11–13) and its non-polar derivatives such as **215** (Scheme 6.51), **221** (Scheme 6.52), **311** (Scheme 6.67) and **333** (Schemes 6.71 and 6.73), that is, they interact with nucleophiles at the central carbon atom of the allene system exclusively.

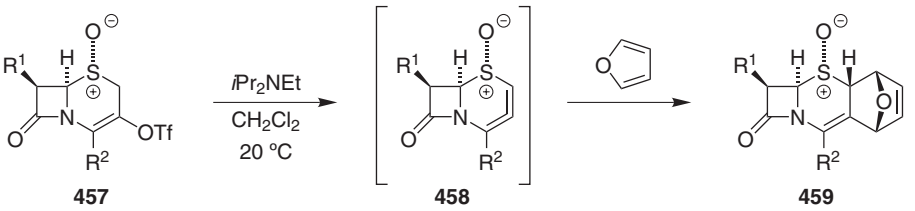
As with the sulfide triflate **416**, the sulfoxide triflate **449** underwent β-elimination with ethyldiisopropylamine to generate a cyclic allene, namely **450**, which was intercepted by (*Z*)-β-deuterostyrene to give a 1:1 mixture of the diastereomeric [2 + 2]-cycloadducts **454a**,**b** in 43% yield (Scheme 6.92) [155, 171b]. The stereospecifity of the reaction does not exclude a two-step mechanism as has been discussed with regard to the corresponding addition of **417** (Scheme 6.87). The trapping of **450** was also achieved with furan, 2-acetylfuran and furan-3-carboxylic acid dimethylamide leading to the [4 + 2]-cycloadducts **451**–**453** in yields of 66, 10 and 52%, respectively.



Scheme 6.92 Generation of the cephalosporin-derived cyclic allene **450** from the cephalosporin β-S-oxide triflate **449** and trapping of **450** by (*Z*)-β-deuterostyrene, furan, 2-acetylfuran, furan-3-carboxylic acid dimethylamide, *N*-*tert*-butoxycarbonylpyrrole, pyrrole and *N*-methylpyrrole.

Hence the positional selectivity is different from that of the furan additions to **417** (Scheme 6.90). Assuming diradical intermediates for these reactions [9], the different types of products are not caused by the nature of the allene double bonds of **417** and **450** but by the properties of the allyl radical subunits in the six-membered rings of the intermediates. Also *N-tert*-butoxycarbonylpyrrole intercepted **450** in a [4 + 2]-cycloaddition and brought about **455** in 29% yield. Pyrrole itself and *N*-methylpyrrole furnished their substituted derivatives of type **456** in 69 and 79% yield [155, 171b]. Possibly, these processes are electrophilic aromatic substitutions with **450** acting as electrophile, as has been suggested for the conversion of **417** into **442** by pyrrole (Scheme 6.90).

Being a diastereomer of **450** with respect to the configuration of the sulfur atom, **458** was liberated from the triflate **457** by ethyldiisopropylamine and trapped by furan (Scheme 6.93). The resulting [4 + 2]-cycloadduct **459** was isolated in 62% yield and is a diastereomer of **451** [155, 171b]. Typical for virtually all furan adducts of six-membered cyclic allenes, **451** and **459** display the *endo*-configuration with respect to the 7-oxanorbornene skeleton.

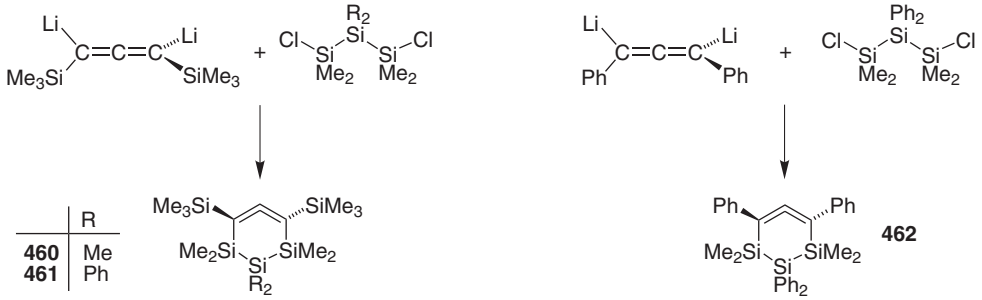


457 **458** **459**

R^1 = $PhCH_2CONH$, R^2 = 4-MeO-$C_6H_4CH_2OCO$, Tf = SO_2CF_3

Scheme 6.93 Generation of the cephalosporin-derived cyclic allene **458** from the cephalosporin a-*S*-oxide triflate **457** and trapping of **458** by furan.

The first derivatives of 1,2-cyclohexadiene (**6**) stable at room temperature were prepared simultaneously by Barton et al. [177] and Ando et al. [178]. These are the 1,2,3-trisila-4,5-cyclohexadienes **460**, **461** [177] and **462** [178], which were obtained in yields of 90, 67 and 11%, respectively, by treatment of the dilithium derivatives of 1,3-bis(trimethylsilyl)- and 1,3-diphenylallene with 1,3-dichlorohexamethyltrisilane and 1,3-dichloro-1,1,3,3,-tetramethyl-2,2-diphenyltrisilane (Scheme 6.94). The structures of **461** and **462** were determined by X-ray diffraction. Accordingly, the bond angle at the central allene carbon atoms is 166.4° in **461** and 161° in **462** and hence of similar magnitude to the calculated value for 1,2-cyclooctadiene (**3**) [19]. Also, the dihedral angels Si1–C6–C4–Si3, amounting to 64.6 and 52.2°, deviate only moderately from the ideal value for an unstrained allene (90°). This is a consequence of the greater length of C–Si and Si–Si bonds compared with C–C bonds in 1,2-cyclohexadiene (**6**). In view of the short lifetime of **3** at room temperature [4, 5], the persistence of **460**–**462** has to be ascribed to a kinetic stabilization by the substituents at the allene subunits ($SiMe_3$, Ph). Most likely this is also the cause of the failure of **460** to react with 1,3-diphenylisobenzofuran and 2,3-dimethyl-1,3-butadiene, even



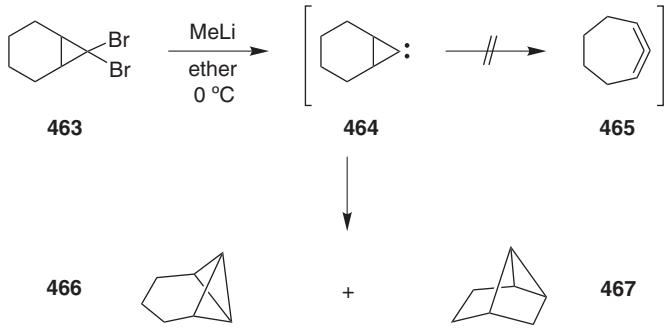
Scheme 6.94 Syntheses of the 1,2,3-trisila-4,5-cyclohexadienes **460**–**462**.

on prolonged heating [177]. The IR bands of the allene moieties of **460**–**462** were found at 1840, 1846 and 1856 cm^{-1}, respectively. On the basis of the data obtained by X-ray diffraction, the 1,3-diphospha-4,5-cyclohexadiene derivative **308** (Scheme 6.66) is more strained than **461** and **462**.

6.4 Seven-Membered Rings

As discussed in the preceding section, the by far predominating number of all six-membered ring compounds with a formal allene subunit is characterized by a genuine allene nature. Only a few heterocyclic systems are zwitterions or close to a zwitterionic state, which possess a coplanar arrangement of all atoms of the formal allene system. Owing to the reduced strain energy because of the larger ring, the analogous seven-membered compounds can safely be regarded as true allenes.

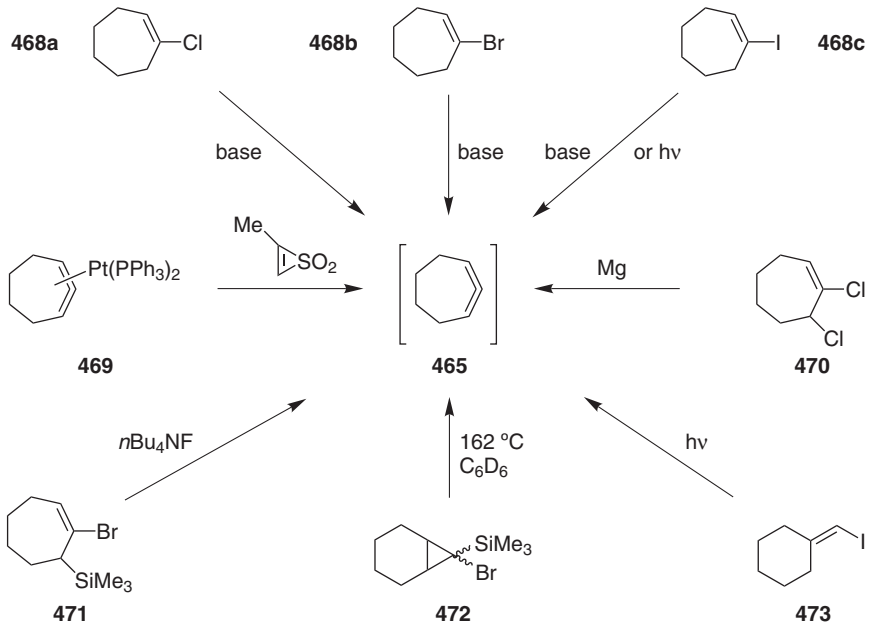
Whereas the reactivities of six- and seven-membered cyclic allenes are similar and hence the mechanisms for the formation of the products agree to a great extent, there is a substantial difference as to their access. The DMS reaction is the method of choice for the generation of 1,2-cyclohexadiene (**6**) and many of its derivatives, but it can be employed only for the liberation of a few 1,2-cycloheptadiene derivatives, since intramolecular insertion reactions of the intermediate 7-bicyclo[4.1.0]-heptylidenes outstrip the ring enlargement. Accordingly, the treatment of 7,7-dibromonorcarane (**463**) with methyllithium (MeLi) in diethyl ether at 0 °C does not give a consecutive product of 1,2-cycloheptadiene (**465**) but the tricycloheptanes **466** and **467** in a ratio of 23:1 in 40% yield (Scheme 6.95) [179, 180]. Compared with the same reaction of 6,6-dibromobicyclo[3.1.0]hexane (**35**) (Scheme 6.9), this result is surprising and was hence studied theoretically [49]. While the cyclopropylidene derived from **35** converts into **6** almost without an activation energy, a barrier of 14.6 kcal mol^{-1} was calculated for the ring enlargement of **464** to yield **465**, which is caused by the necessary conformational change. However, the insertion reactions of the carbene center of **464** into C–H bonds of methylene groups to produce **466** and **467** require activation energies of only 6.4 and 9.1 kcal mol^{-1}, respectively.



Scheme 6.95 Reaction of 7,7-dibromobicyclo[4.1.0]heptane (**463**) with methyllithium (MeLi) in ether at 0 °C, according to Moore and co-workers.

6.4.1
1,2-Cycloheptadiene (465) and Its Simple Derivatives

After an erroneous report about the isolation of **465** from 1936 [181], Ball and Landor [4] were the first to prove the existence of this species. They treated 1-chlorocycloheptene (**468a**) (Scheme 6.96) with $NaNH_2$ in liquid ammonia and isolated the dimer **474** of **465** (Scheme 6.97) in 32% yield. By employing THF as solvent and $NaNH_2$ or $NaNH_2$–NaO*t*Bu as the base, Caubère et al. [87] achieved a 65% yield of **474**. Its configuration was elucidated by Criegee and Reinhardt [182]. Wittig and Meske-Schüller [183] eliminated hydrogen bromide from 1-bromocycloheptene (**468b**) by KO*t*Bu in DMSO at 40 °C and obtained a 2:1 mixture of **474** and an isomer thereof (69% yield), which, according to Bottini et al. [184], is most likely a consecutive product of **474**. When this elimination was performed in the presence of 1,3-diphenylisobenzofuran (DPIBF), the [4 + 2]-cycloadducts **475** (Scheme 6.97) were isolated in 59% yield with an *endo*:*exo* ratio of 10:1 [183]. Balci and Jones took advantage of this interception of **465** to prove its chirality by two sets of experiments. In the first, they synthesized non-racemic 7-deutero-1-bromocycloheptene ([7-D]-**468b**) and treated it in THF with KO*t*Bu in the presence of DPIBF [45]. In the second, **468b** was subjected to elimination by enantiopure potassium menthoxide in the presence of DPIBF [46]. The isolated products [D]-**475** and **475**, respectively, were optically active, leading to the conclusion that the intermediates [D]-**465** and **465** must have been chiral and non-racemic. In the first case the H/D isotope effect and in the second the different rates of detachment of the enantiotopic protons (H7) of **468b** by the enantiopure base caused the formation of the respective non-racemic intermediate. Both eliminations were performed at 53 and 100 °C and the former even at 140 °C. The higher temperatures did not lead to a significant loss of the optical activity of the product, which is at variance with the results achieved with 1,2-cyclohexadiene (**6**) (Scheme 6.14) and in line with the expectation that the barrier to enantiomerization should be substantially higher in **465** than in **6**.



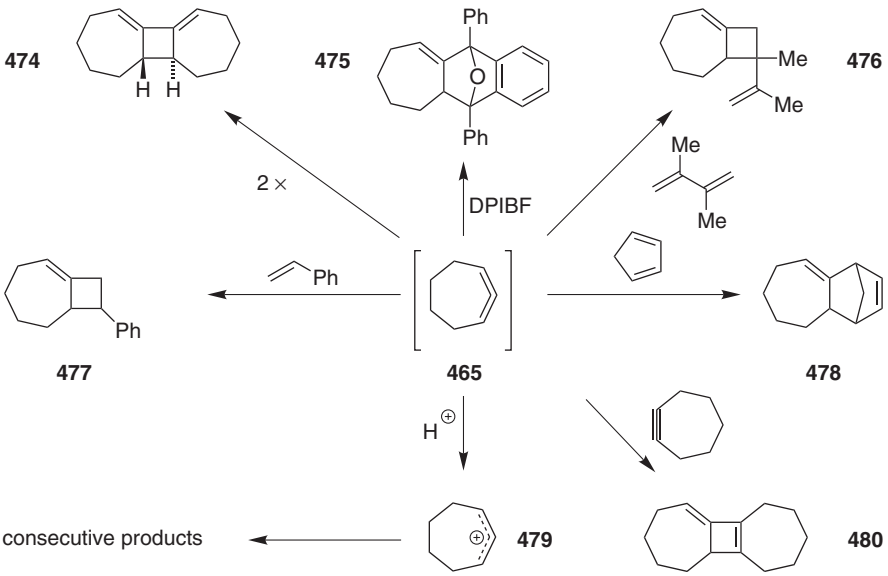
Scheme 6.96 Methods of generation of 1,2-cycloheptadiene (**465**).

Visser and Ramakers [6] liberated **465** by the action of 2-methylthiirene 1,1-dioxide on the bis(triphenylphosphane)platinum complex **469** (Scheme 6.96) and observed a dimer, probably **474**, or several dimers. The synthesis of **469** was accomplished by dehydrobromination of **468b** in the presence of bis(triphenylphosphane)(ethylene)platinum and was believed to proceed via the trapping of **465** by the platinum complex. Jones et al. [185] doubted this opinion and regarded the reversed sequence as more likely, that is, the complexation of **468b** by $(PPh_3)_2Pt$ followed by the dehydrobromination.

As shown by the formation of **474**, Bottini and Hilton [84] generated **465** in THF from 1-chlorocycloheptene (**468a**) by KO*t*Bu and also from 1,6-dichlorocycloheptene (**470**) by magnesium. The presence of 2,3-dimethyl-1,3-butadiene in the reaction mixture in the former case gave rise to the [2 + 2]-cycloadduct **476** of **465**. On liberation of **465** from **470**, it could be intercepted by styrene and 1,3-cyclopentadiene yielding the [2 + 2]- and [4 + 2]-cycloadducts **477** and **478**, respectively. By using the competition method, the rate constants for the trapping of **465** by 2,3-dimethyl-1,3-butadiene, styrene and 1,3-cyclopentadiene were determined to conform to a ratio 1:7.5:150.

The generation of **465** is also possible from 1-bromo-7-(trimethylsilyl)cycloheptene (**471**) and tetrabutylammonium fluoride. This was shown by the reaction in the presence of DPIBF furnishing **475** [53]. These products also resulted when both 7-bromo-7-(trimethylstannyl)norcaranes (**472**), admixed with DPIBF, were heated at 162 °C in C_6D_6 [186]. In the absence of DPIBF, the dimer **474** of **465** was formed in

high yield. If these thermolyses were carried out in the presence of methanol, the production of **474** was suppressed totally in the case of *exo*-Br-**472**, but only in part with *endo*-Br-**472**. It was concluded from detailed studies that *exo*-Br-**472** is initially converted into 7-bicyclo[4.1.0]heptylidene (**464**), which surmounts the relatively high barrier to ring enlargement to yield **465** [49] without interference of the insertions leading to **466** and **467** owing to the high temperature. However, in the presence of methanol, **464** is quantitatively quenched to give methyl 7-norcaranyl ether [186]. The decomposition of *endo*-Br-**472** is believed to occur via a different route without the intermediacy of **464**. The heterolytic cleavage of the C–Br bond of *endo*-Br-**472** with concomitant disrotatory opening of the three-membered ring should lead to an ion pair that transforms to trimethyltin bromide and **465**. The latter does not dimerize completely, since some part is protonated generating the cycloheptenyl cation **479**, from which the additional products are derived.

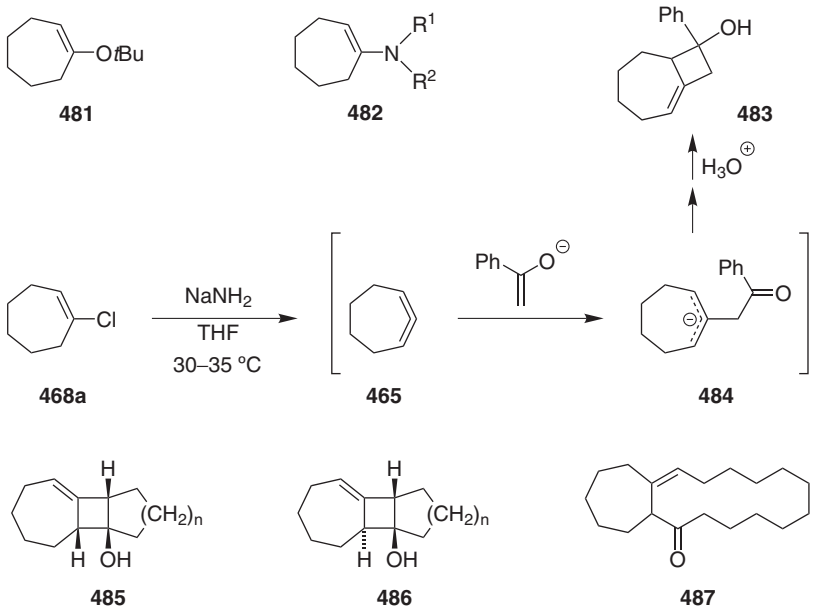


Scheme 6.97 Products of dimerization, cycloadditions and protonation of 1,2-cycloheptadiene (**465**).

The protonation of **465** to give **479** was invoked for the first time by Kropp et al. [187] on the occasion of the photolysis of 1-iodocycloheptene (**468c**) and (iodomethylene)cyclohexane (**473**) (Scheme 6.96). It is assumed that the 1-cycloheptenyl cation is liberated in the first step followed by a deprotonation–protonation sequence resulting, with **465** as intermediate, in **479**, from which several minor products are derived.

Two groups [64, 184] have pursued the query of whether the base-induced dehydrohalogenations of the 1-halocycloheptenes **468** generate also cycloheptyne besides **465**. This does occur but the extent depends on the substrate (**468a**, **b** or **c**), the solvent and the kind of the base. Bottini et al. [184] treated **468a–c** at 65 °C with KO*t*Bu in THF and also in DMSO as solvent. In all cases, **474** was the major product, indi-

cating the intermediacy of **465**. However, the reactions of **468b**,**c** in THF also brought about the isomer **480** of **474**, whose formation is explained as a [2 + 2]-cycloaddition of **465** onto cycloheptyne. By using DMSO, no **480** was observed, which is taken as evidence that cycloheptyne emerges to a certain extent only in the eliminations performed in THF. Support for this hypothesis came from the finding that *tert*-butyl 1-cycloheptenyl ether (**481**) (Scheme 6.98) resulted in yields of up to 5% only in THF as solvent, whereas just traces appeared in DMSO. Thus, **481** is predominantly formed by way of interception of cycloheptyne rather than **465** by the *tert*-butoxide ion. Compared with KO*t*Bu, sodium pyrrolidide is a stronger nucleophile. On reaction with **468a**,**b**, it furnished the corresponding enamine **482** in yields of 28 and 24%, respectively, and only small amounts of **474**. The utilization of [1-^{14}C]**468a** revealed that 70% of it was converted into [1-^{14}C]cycloheptyne and 30% into [2-^{14}C]**465**.



Scheme 6.98 Products of the reactions of 1-halocycloheptenes, for example **468a**, with KO*t*Bu, substituted sodium amides and sodium enolates.

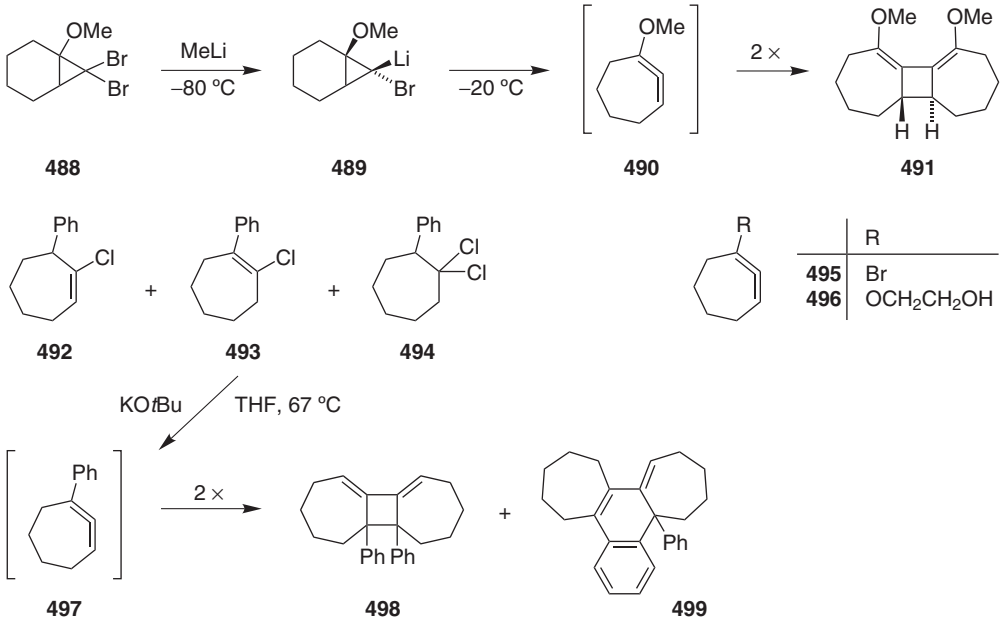
Caubère et al. [87] exposed **468a**,**b** to mixtures of morpholine and $NaNH_2$ or $NaNH_2$–NaO*t*Bu in THF. The major product was **474**, but its yield was significantly reduced compared with the reaction without morpholine (65%), in fact by the amount in which the corresponding enamine **482** was formed. This indicates that sodium morpholidide competed successfully for the cyclic allene **465**, whose dimerization was hence restrained. The exchange of morpholine by piperidine furnished an analogous result, when **468a** and $NaNH_2$–NaO*t*Bu were used. However, diethyl- and diisopropylamine gave only small quantities of enamines **482**. In contrast, sodium *N*-methylanilide, either pure or admixed with $NaNH_2$–NaO*t*Bu, converted

468a to the corresponding enamine **482** in yields of 65 and 55%, respectively, and the dimer **474** of **465** could not be observed. It was not established whether **465** or cycloheptyne acted as the decisive intermediate.

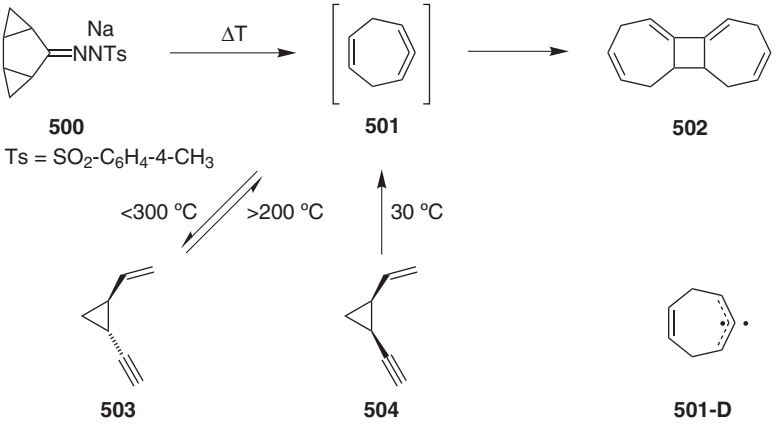
The reactions between **468a** and mixtures of $NaNH_2$ with sodium enolates of ketones in THF or 1,2-dimethoxyethane (DME) gave rise, after hydrolylsis, to the formal [2 + 2]-cycloadducts of the enol to **465** almost exclusively. Scheme 6.98 illustrates the use of acetophenone, whose enolate attacks the central allene carbon atom of **465** to form the allyl anion **484**. Its cyclization involving the carbonyl group furnishes the alcoholates of the 3-methylenecyclobutanols **483**, which are protonated to give a 1:1 mixture of the diasteromers **483** in 44% yield. Analogous products were obtained from diisopropyl ketone under the same conditions in 42% yield, with the difference that the *endo*-OH compound predominated (≧75%) [188].

By empoying cyclic ketones, the results were similar, namely 3-methylenecyclobutanols of the types **485** and **486**. With the series from cyclopentanone through cyclooctanone, yields of 40–55% were achieved. Apart from cyclohexanone, the isomers **486** were preferably produced, but the **485**:**486** ratio increased on extension of the reaction time. Cyclododecanone furnished a further diastereomer in addition to **485** and **486**, ($n = 8$) and the major product (14% yield) was bicyclo[12.5.0]nonadec-13-en-2-one (**487**) [65d]. After deprotonation of the alcohols of the types **483**, **485** and **486**, the ring opening of the alcoholates is possible in two directions leading to an allyl anion of type **484** and another one, which can give rise to a total of three β,γ-unsaturated ketones including those of type **487**. Catalyzed by the strong base of the reaction mixtures, the β,γ-unsaturated ketones may isomerize to α,β-unsaturated ketones. Such β,γ- and α,β-unsaturated ketones were found at best in small amounts with the use of acetophenone, diisopropyl ketone and the members of the series from cyclopentanone to cyclooctanone in the solvents THF and DME, but resulted in increased quantities or even as the major products in hexamethylphosphoric triamide [65d].

Only a few simply substituted 1,2-cycloheptadiene derivatives are mentioned in the literature. They are represented in Scheme 6.99. 1-Bromo-1,2-cycloheptadiene (**495**) was generated by β-elimination from 1,2-dibromocycloheptene in the presence of DPIBF to give a small yield of a [4 + 2]-cycloadduct and a consecutive product of a second one [183]. In addition to the corresponding cycloheptyne, 1-(2-hydroxyethoxy)-1,2-cycloheptadiene (**496**) was postulated as an intermediate on treatment of 1-halo-7-(2-hydroxyethoxy)cycloheptene with KO*t*Bu [88]. 1-Methoxy-1,2-cycloheptadiene (**490**) seems to be the only seven-membered cyclic allene that can be synthesized efficiently by taking advantage of the DMS reaction. Thus, Taylor et al. [189] prepared the carbenoid **489** from the dibromonorcarane **488** and MeLi. Having been stable at –80 °C, **489** decomposed above –20 °C to give the dimer **491** of **490** in high yield. Two dimers were formed when 1-phenyl-1,2-cycloheptadiene (**497**) was liberated by KO*t*Bu from a mixture of the chloro compounds **492–494**, which were obtained from 2-phenylcycloheptanone and phosphorus pentachloride [79]. Wheras **498** (8% yield) possesses the common structure of allene dimers, one phenyl group participated in the cyclization en route to **499** (17% yield) in the same way as already discussed with regard to the dimerization of 1-phenyl-1,2-cyclohexadiene (**75**) (Scheme 6.25).



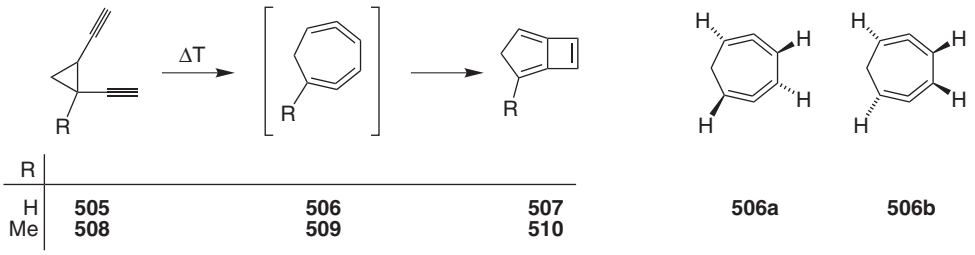
Scheme 6.99 Known 1-substituted 1,2-cycloheptadienes and generation and dimerization of 1-methoxy- (**490**) and 1-phenyl-1,2-cycloheptadiene (**497**).



Scheme 6.100 Formation and dimerization of 1,2,5-cycloheptatriene (**501**).

Obviously being the dimer of 1,2,5-cycloheptatriene (**501**), the tricyclic hydrocarbon **502** resulted in high yields on pyrolysis at 250–500 °C of the *syn*- and the *anti*-isomer of the tosylhydrazone sodium salt **500** (Scheme 6.100) [190]. In addition to **502**, small amounts of *trans*-ethynylvinylcyclopropane (**503**) and 4-ethynylcyclopentene were formed depending on the temperature of the reaction. On decomposition of **500** at 160–200 °C, the volatile diazo compounds generated initially could be isolated at –80 °C. They decomposed at low temperature and furnished the corresponding azines and **504** besides **502**. That **504** converted into **502** at a temperature as low as 30 °C is evidence in favor of a Cope rearrangement giving rise to **501**, which then dimerized. It can therefore be assumed that at high temperatures **501** emerges from **500** entirely via the diazo compounds and **504**, whereas **503** is formed reversibly from **501**. In line with this mechanistic scheme, **503** converted quantitatively to **502** in solutions heated at temperatures above 200 °C. The results regarding **504** were corroborated by an independent synthesis of **504** and its gas-phase thermolysis [7]. The activation parameters for the rearrangement of **504** were determined as $\Delta H^{\neq} = 19.3$ [190], 22.1 kcal mol^{-1} [7] and $\Delta S^{\neq} = -15$ [190], –8.6 cal K^{-1} mol^{-1} [7]. Both groups of authors [7, 190] considered the possibility that the intermediate in question is the allyl diradical **501-D** instead of the allene **501**. This is highly unlikely in view of the energetics of 1,2,4,6-cycloheptatetraene (**5**) (see Section 6.4.2) and **501-D** has to be regarded as the transition state for the enantiomerization of **501**, with an energy difference significantly greater than 20 kcal mol^{-1}.

cis-Diethynylcyclopropane (*cis*-**505**) was converted to the bicyclo[3.2.0]heptatriene **507** under relatively mild conditions. Most probably generating 1,2,4,5-cycloheptatetraene (**506**), the first step has to be regarded as a Cope rearrangement [191a–c]. At substantially higher temperatures, *trans*-**505** also yielded **507** [191c, d]. The gas-phase pyrolysis of **508** gave rise to the methylbicycloheptatriene **510**, presumably via **509** [191e]. Quantum-chemical calculations revealed two energy minima for 1,2,4,5-cycloheptatetraene, namely the *dl*-isomers **506a** (C_2 symmetry) and the *meso*-isomer **506b** (C_s symmetry) [192]. Both torsional and angle strain contribute to the gap of 4 kcal mol^{-1} between their energies, with **506b** being the less stable species. The greater angle strain of **506b** is manifest in the bond angles at the central allene carbon atoms that were estimated to amount to 149.7° in **506a** but only 146.4° in **506b**.

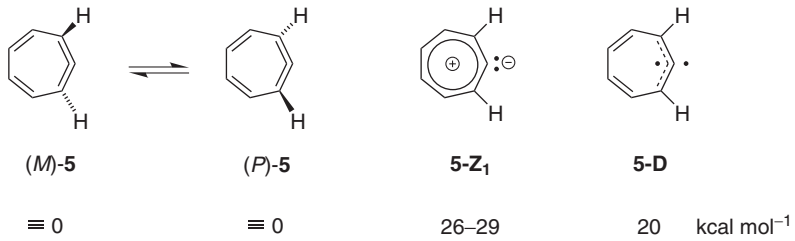


Scheme 6.101 Intermediacy of 1,2,4,5-cycloheptatetraene (**506**) and its methyl derivative **509** in the thermolysis of diethynylcyclopropanes.

6.4.2

1,2,4,6-Cycloheptatetraene (5) and Its Simple Derivatives

1,2,4,6-Cycloheptatetraene (**5**) is probably the cyclic allene that has received the most attention. Originally, **5** was not searched for at all, since the nucleophilic carbene **5-Z$_1$** (Scheme 6.102) was the species that should be generated and trapped. It was believed almost three decades that this goal had been reached [193, 194]. When the investigations of the species in question in argon matrices at very low temperatures [195] and the proof of its chirality [196] had shown the nature of the intermediate to be the allene **5**, a mobile equilibrium between **5** and **5-Z$_1$** was postulated for the explanation for the reactivity [1]. However, in 1996, three theoretical studies came to the reliable conclusion that, in agreement with earlier calculations [21], **5-Z$_1$** is not an energy minimum [197–199], which is why the reactivity is interpreted exclusively by means of the allene structure **5** in the following.

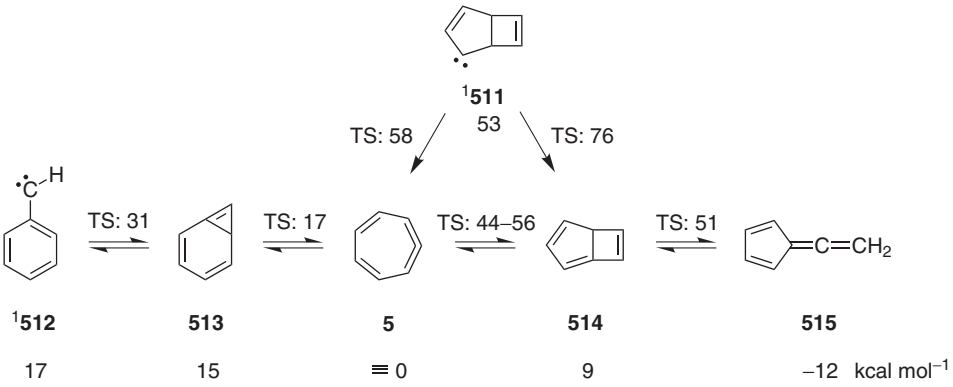


Scheme 6.102 Calculated relative energies of 1,2,4,6-cycloheptatetraene (**5**), the closed-shell 2,4,6-cycloheptatrienylidene (**5-Z$_1$**) and the open-shell **5-D**.

The relative energies of **5** (C_2 symmetry), the closed-shell 2,4,6-cycloheptatrienylidene (**5-Z$_1$**, C_{2v}) and the open-shell cycloheptatrienylidene singlet **5-D** (C_{2v}) are summarized in Scheme 6.102, as they have been estimated by high-level quantum-chemical calculations [197–199]. The most stable species are the enantiomers **5**. The energy of the diradical **5-D** lies 20 kcal mol^{-1} above that of **5** and **5-D** serves as transition state for the enantiomerization of **5**. Surprisingly, the energy of the nucleophilic carbene **5-Z$_1$** is greater by 6–9 kcal mol^{-1} than that of **5-D**, although the spin pairing would bring about an aromatic π-electron sextet as in the tropylium ion. The origin for this seems to be the small bond angle of 119° of the carbene carbon atom, which results from closed-shell repulsion (see Scheme 6.60) and imposes more strain energy on **5-Z$_1$** than on **5-D** (corresponding bond angle of 140°), while the aromatic stabilization of **5-Z$_1$** is compensated by the repulsion of the electrons within the lone pair [197]. A hydrogen bond, for example donated by methanol, may well stabilize **5-Z$_1$** better than the allene state **5** [200], but an energy difference of ~20 kcal mol^{-1} still remains. At the triplet energy hypersurface, two species were localized (C_{2v} symmetry), which are very similar in energy and several kcal mol^{-1} less stable than **5-D**. Hence the latter is the ground state at the planar molecular geometry [197–199]. Two papers report on the experimental observation of a **5**-triplet by ESR spectroscopy on irradiation of diazo-2,4,6-cycloheptatriene, which is not easily accessible, in argon

matrices at –261 [201] and –252 °C [202]. Since the spectra of the two studies are not the same, one must be in error, which has been documented [198, 199] for ref. 202.

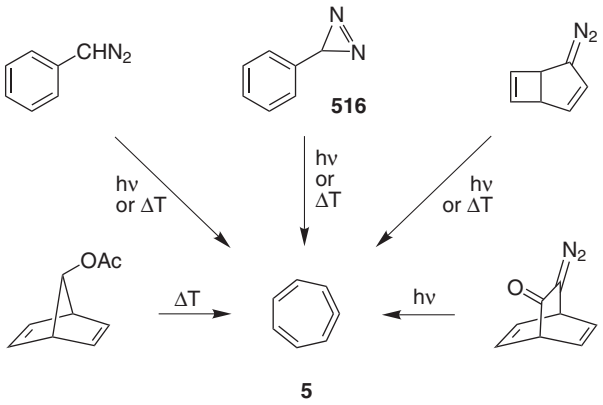
In addition to **5**, **5-D** and **5-Z$_1$**, further species C_7H_6 were calculated, from which **5** can emerge and which can result from **5**. Scheme 6.103 represents some of these species, their relative energies and those of the transition states (TS) separating two species each. Since the flash vacuum thermolysis (FVT) of phenyldiazomethane is an excellent method to generate **5**, if this is to be observed directly in a matrix at very low temperatures (see below) [195], the pathway of the transformation of singlet phenylcarbene (**^{1}512**) to **5** was studied in detail [197–199]. It was computed to be a two-step process and exothermic by 17 kcal mol^{-1}. The intermediate is bicyclo[4.1.0]-hepta-2,4,6-triene (**513**), which is formed by an electrocyclization (allylcarbene → cyclopropene) from **^{1}512** and converted into **5** by a retrograde electrocyclization (1,3-cyclohexadiene → 1,3,5-hexatriene). Because of a barrier of only 2 kcal mol^{-1} to the last step, the prospects to observe **513** directly are not promising. Apart from the reverse reaction to **513**, the only intramolecular process open to **5** is the electrocyclization (1,3-butadiene → cyclobutene) to yield bicyclo[3.2.0]hepta-1(2),3,6-triene (**514**). Since the corresponding TS has a similar relative energy (44–56 kcal mol^{-1}) [25, 198] as the TS (51 kcal mol^{-1}) to the transformation of **514** to fulvenallene (**515**) [198], **514** also has not been directly observed yet. In contrast, **515** and its consecutive products, the ethynyl-1,3-cyclopentadienes, are well known to be formed on FVT of phenyldiazomethane [203]. As a precursor to **5**, 2-diazobicyclo[3.2.0]hepta-3,6-diene (Scheme 6.104) is also suitable. On photolysis or FVT, it was smoothly converted to **5** without the bicyclic carbene **511** being observed [195b], which is not surprising in view of low barrier to ring enlargement of **511**, calculated to be only 5 kcal mol^{-1} [25]. The intramolecular reaction of **5** with the lowest barrier is doubtless the ring contraction to give **513** and the energy of the TS for the rearrangement of **513** to phenylcarbene (**^{1}512**) is still much lower than that for the ring closure to yield **514**. In con-



Scheme 6.103 Calculated relative energies of species C_7H_6 and transition states (TS) separating them, leading from singlet 2-bicyclo-[3.2.0]hept-3,6-dienylidene (**^{1}511**) and singlet phenylcarbene (**^{1}512**) to fulvenallene (**515**) via 1,2,4,6-cycloheptatetraene (**5**).

sequence, the formation of **5** from ^{1}**512** should be reversible at high temperatures, if intermolecular processes of **5** are avoided. This was confirmed by using isotopically labeled phenylcarbenes [204].

The direct observation of **5** was accomplished at very low temperatures in argon matrices [195] and recently at room temperature, when **5** was incarcerated in a molecular container [8, 200]. The reactions employed for the isolation of **5** in an argon matrix are summarized in Scheme 6.104 [195b]. Accordingly, the irradiation ($\lambda > 478$ nm) of an argon matrix of phenyldiazomethane gave rise to the phenylcarbene triplet (ESR spectrum), which is the ground state of phenylcarbene. Its irradiation ($\lambda > 416$ nm) caused the isomerization to **5** as observed by a strong decrease in the ESR signal and the appearance of the IR spectrum of **5**. The agreement of the experimental [195, 197] and calculated IR spectra [197] leaves no doubt as to the identity of **5**. Its bands at 1824 and 1816 cm^{-1}, with the latter being a combination band, are characteristic for the allene subunit. The same IR spectrum resulted when phenyldiazomethane was subjected to FVT at 375 °C and the pyrolysate was co-condensed with argon. This matrix did not show a triplet ESR signal, but its irradiation ($\lambda > 278$ nm) brought about that of phenylcarbene, indicating a small steady-state concentration of this species. The photolysis ($\lambda > 338$ nm) of matrix-isolated phenyldiazirine (**516**) yielded mainly phenyldiazomethane and phenylcarbene plus a small quantity of **5**. This mixture could be converted almost completely into **5** as described above. On irradiation of its argon matrix or on FVT at 250 °C, 2-diazobicyclo[3.2.0]-hepta-3,6-diene [195b, 205] furnished **5**, as did 7-acetoxynorbornadiene on FVT and 8-diazobicyclo[2.2.2]octa-2,5-dien-7-one on photolysis of its argon matrix [195b].

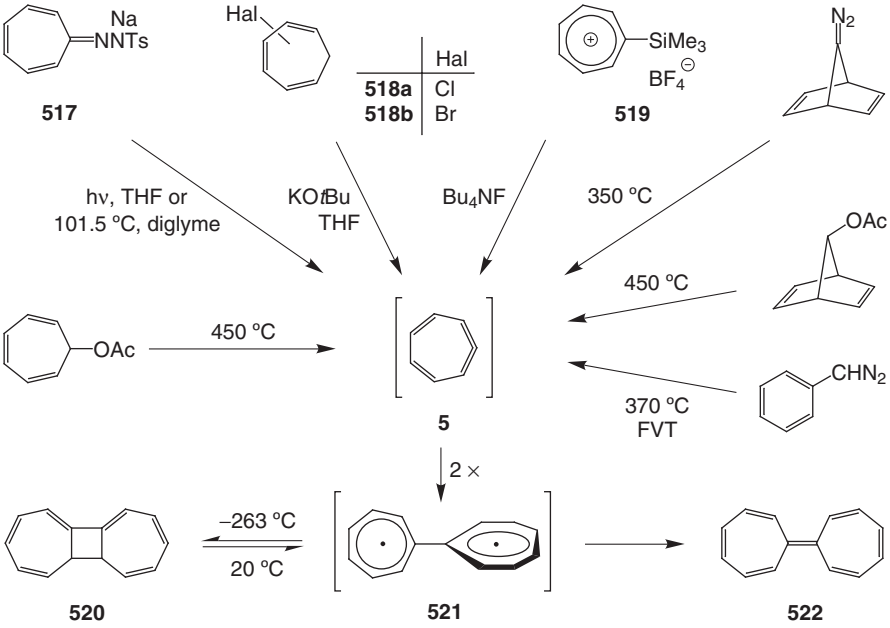


Scheme 6.104 Methods of generation of 1,2,4,6-cycloheptatetraene (**5**) for its direct observation by IR spectroscopy in an argon matrix at temperatures ranging from –263 to –258 °C, according to Chapman and co-workers.

The compounds *α*-, *o*-, *m*- and *p*-deuterophenyldiazomethane were photolyzed and thermolyzed as phenyldiazomethane and the products studied in argon matrices. Whereas the photolyses gave rise specifically to [1-D]-**5**, [1-D]- and [4-D]-**5**, [4-D]- and [5-D]-**5** and only [5-D]-**5**, respectively, as has to be expected on the basis of Scheme 6.103,

the thermolyses of all substrates at 500 °C yielded a 1:1:1 mixture of all three [D]-**5**. This is evidence for the complete reversibility of the conversion of ^{1}**512** into **5** [195b].

For the performance of intermolecular reactions of **5**, its generation from the sodium salt of tropone tosylhydrazone (**517**) and from halo-1,3,5-cycloheptatrienes (**518**) are most suitable, but other precursors can also be employed, as illustrated in Scheme 6.105. In view of the product structures, some reactions of **5** give results that deviate from those of typical allene processes, and this is even valid for the dimerization (Scheme 6.105).

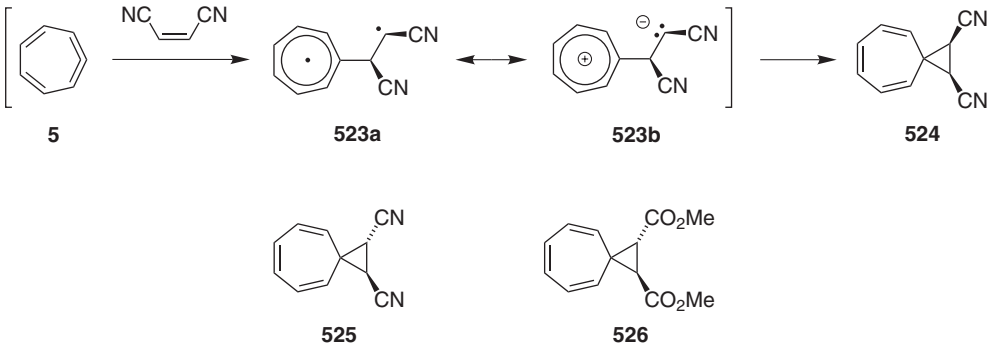


Scheme 6.105 Formation of the dimer **522** of 1,2,4,6-cycloheptatetraene (**5**) generated from various precursors of **5**.

Thus, heptafulvalene (**522**) was isolated in 33 and 65% yield after thermolysis of **517** in diglyme and its photolysis in THF, respectively [193]. An almost quantitative yield of **522** resulted when a mixture of 1-, 2- and 3-chloro-1,3,5-cycloheptatriene (**518a**) was treated with KO*t*Bu in THF [206]. Even on variation of the concentration of the starting material and the temperature of the reaction, **522** turned out to be the exclusive product [207]. Also, the treatment of (trimethylsilyl)tropylium tetrafluoroborate (**519**) with tetrabutylammonium fluoride [208] and the gas-phase pyrolysis of 7-acetoxynorbornadiene and 7-acetoxy-1,3,5-cycloheptatriene [209] afforded high yields of **522**. Further, **522** was observed on FVT of *N*-nitroso-*N*-(7-norbornadienyl)-urea at 350 °C, which is believed to be converted into 7-diazonorbornadiene initially. Its decomposition should proceed via 7-norbornadienylidene to bicyclo[3.2.0]hepta-1(2),3,6,-triene (**514**) (Scheme 6.103) and then on to **5** [210]. The intermediacy of **514** is also suspected in the formation of **522** from 7-acetoxynorbornadiene.

When the pyrolysate of the FVT of phenyldiazomethane was condensed at –263 °C without argon, the IR spectrum did not show the presence of **5**, but that of a new substance, which was converted into **522** on warming to 20 °C. Possibly this new substance was **520** [195b], whose structure corresponds to that of regular allene dimers. An indication to **520** was also described by Jones et al. [211, 212], who observed a beige deposit on condensation of the pyrolysate of **517** at low temperatures that irreversibly turned into the almost black solid of **522** on warming. As a derivative of 7,7′-bis(1,3,5-cycloheptatrienyl), **520** would be expected to be very labile. In the case of the parent hydrocarbon, the dissociation into two tropenyl radicals is endothermic by only 33.5 kcal mol^{-1} [213]. If allowance is made for the strain energy of the bismethylenecyclobutane system amounting at least to 27 kcal mol^{-1}, the ring opening of **520** to generate the diradical **521** has an energy requirement of only several kcal mol^{-1} and hence should occur even in the case of a moderate activation barrier already at rather low temperatures. In the first place, **521** should be formed by the approach of two molecules of **5** along their C_2 axes in the crossed arrangement and smoothly undergo a least-motion ring closure to yield **520**. To be converted to heptafulvalene (**522**), **521** has to reach a coplanar geometry of the two rings. Because of the large resonance stabilization of the two tropenyl-radical entities [213] of **521**, the central π-bond of **522** is also rather weak, which explains the ready decomposition of **522** [193b].

Irradiation of the sodium salt **517** in a solution of maleonitrile in THF gave a 30% yield of the *cis*-spiro[2.6]nonatrienedicarbonitrile **524** (Scheme 6.106). Analogously, fumaronitrile led to the *trans*-diastereomer **525** exclusively in 29% yield [193b], which was also obtained from (trimethylsilyl)tropylium tetrafluoroborate (**519**) as precursor of **5** [208]. The interception of **5** by dimethyl fumarate succeeded by generating **5** from **517** by either photolysis [193] or thermolysis [193, 194] and from **519** [208] and afforded the dimethyl *trans*-dicarboxylate **526** in yields of 50, 40 and 42%, respectively. Liberation of **5** in the presence of dimethyl maleate led also to **526** [194, 214]. In this reaction, the isomerization of dimethyl maleate to fumarate could have interfered and hence pretended the loss of the stereochemical information, since



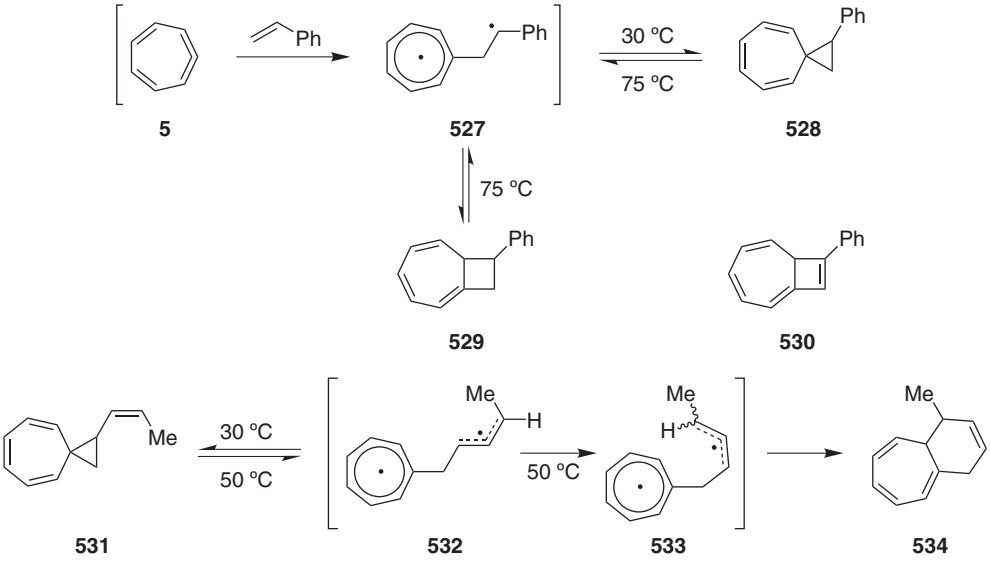
5 523a 523b 524 525 526

Scheme 6.106 [2 + 1]-Cycloadducts of 1,2,4,6-cycloheptatetraene (**5**) to maleonitrile, fumaronitrile, dimethyl fumarate and dimethyl maleate.

dimethyl fumarate was found to add onto **5** 175 times as fast as dimethyl maleate. In contrast, fumaro- and maleonitrile trapped **5** equally fast and twice as fast as dimethyl fumarate [214].

The products **524–526** were considered as cycloadducts of the nucleophilic carbene **5-Z$_1$** [193, 194, 214]. However, **5-Z$_1$** has been calculated not to be an energy minimum [197–199], which is why the allene **5** undergoes these reactions. Since stepwise courses are the most likely, as suggested by quantum-chemical calculations [9], the interaction of **5** with maleonitrile could generate the diradical **523a**, which might well be polarized according to the resonance structure **523b**. The stereospecific formation of **524** can then be explained by a ring closure of **523** that proceeds significantly faster than the rotation around the single bond between the carbon atoms bearing the nitrile groups.

Concerning the structure, the cyclopropane derivatives **524–526** deviate from the generally observed cycloadducts of cyclic allenes with monoalkenes (see Scheme 6.97 and many examples in Section 6.3). The difference is caused by the different properties of the diradical intermediates that are most likely to result in the first reaction step. In most cases, the allene subunit is converted in that step into an allyl radical moiety that can cyclize only to give a methylenecyclobutane derivative. However, **5** is converted to a tropenyl-radical entity, which can collapse with the radical center of the side-chain to give a methylenecyclobutane or a cyclopropane derivative. Of these alternatives, the formation of the three-membered ring is kinetically favored and hence **524–526** are the products. The structural relationship between both possible product types is made clear in Scheme 6.107 by the example of the reaction between **5** and styrene.



Scheme 6.107 Cycloadducts of 1,2,4,6-cycloheptatetraene (**5**) to styrene, phenylacetylene, (*Z*)-1,3-pentadiene and (*E*)-1,3-pentadiene.

Whereas **5** could not be intercepted with non-activated alkenes such as (*Z*)-2-butene and cyclohexene, the spirononatrienes **528** (28% yield) and **531** (22%) resulted on irradiation of **517** at about 30 °C in the presence of styrene and (*Z*)-1,3-pentadiene, respectively. Under the same conditions, (*E*)-1,3-pentadiene gave rise to a mixture of both bicycloundecatetraenes **534** (Scheme 6.107), however, and some **522**. The thermolysis of **517** in diglyme at 100 °C in the presence of (*E*)- or (*Z*)-1,3-pentadiene led also to **534** in ~40% yield [215]. A yield of 8% of the bicyclononatetraene **530** was achieved when a mixture of **517**, phenylacetylene and diglyme was heated at 120 °C [216].

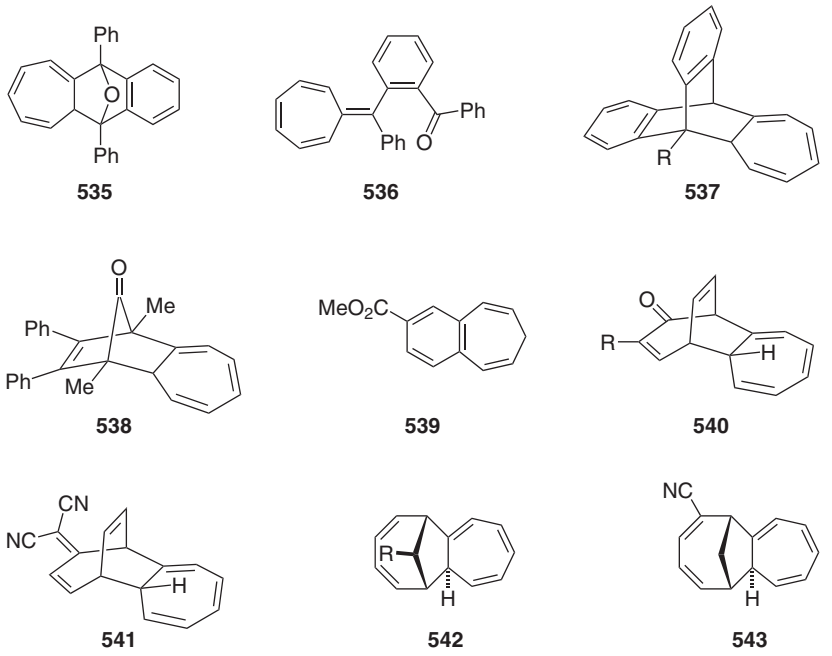
It is reasonable to assume that **5** and styrene generate the diradical **527**, which collapses to give **528** at 30 °C under kinetic control. At temperatures of 75 °C and above, the last step is reversible and an equilibrium is established in that **528** and the methylenecyclobutane derivative **529** maintain a ratio of 1:6 [215]. The [2 + 2]-cycloadduct **530** of **5** to phenylacetylene should be formed analogously via a diradical of the type **527** and is closely related in its structure to the cephalosporin derivatives **437** and **438** (R = Ph, Scheme 6.89). In addition to **530**, 2-phenylindene was obtained, which has to be considered as the product of the thermal rearrangement of **530** [216]. Akin to such a process, **526** [194] and **529** [215] were converted into indane derivatives on heating.

The diradical **532** should be the intermediate emerging from **5** and (*Z*)-1,3-pentadiene and undergo ring closure to yield **531** under kinetic control. The quantitative formation of both bicycloundecatetraenes **534** from **531** at 50 °C indicates that the step **532** → **531** must be reversible at that temperature and that the diastereomerization of the allyl-radical subunit of **532** to give **533** has to occur under these conditions. The diastereomer of **532**, with regard to the location of the methyl group, should be expected as the first intermediate on addition of **5** to (*E*)-1,3-pentadiene. However, the product of its collapse, that is, the diastereomer of **531**, was not observed. Either this step is reversible even at 30 °C and the diradical then isomerizes to **533** or the latter is formed directly from the reaction partners and closes the six-membered ring to give **534**. These mechanistic possibilities have already been discussed with regard to the interception of 1,2-cyclohexadiene (**6**) with (*Z*,*Z*)-1,4-dideutero-1,3-butadiene (Schemes 6.20 and 6.21). The retention of the configuration as in **531** has also been experienced in the trapping of **6** with (*Z*)-1,3-pentadiene (Scheme 6.17).

The spirononatriene **528** was prepared from styrene and other precursors to **5** than **517** as well, namely from the chlorocycloheptatrienes **518a** with KO*t*Bu in THF at 20 °C [206] and from **518b** with the bromine atom in the 3-position with KO*t*Bu in DMSO at 40 °C [102]. The photolysis of **517** in THF at 30 °C [217] and the treatment of **518a** with KO*t*Bu in THF at 20 °C [206] were employed to generate **5** in the presence of mixtures of styrene and a substituted styrene (3-Br, 4-Me, 4-OMe, 4-Cl, 4-Br with **517**; 4-Me, 4-OMe, 4-F, 4-Cl, 4-Br with **518a**). Determined from the ratio of the products, the relative rate constants of the styrenes correlated well with the Hammett equation. Virtually the same ρ values were obtained from both substrates, that is, +1.05 from **517** and +1.02 from **518a**, which provides further support for **5** being the intermediate in both reactions. The sign of the ρ value is the same as in the case

of **6** [69] and the magnitude indicates a slightly larger charge separation in the transition state than there.

In addition to **534**, further [4 + 2]-cycloadducts of **5** were prepared by using 1,3-dienes, some of which are well known as trapping reagents of short-lived cyclic allenes and cycloalkynes. Further, cycloadditions could be achieved with tropone and several 2-substituted tropones, 8,8-dicyanoheptafulvene, 1,3,5-cycloheptatriene and a few of its 7-substituted derivatives. The products of these reactions are represented in Scheme 6.108.



Scheme 6.108 Products of the interception of 1,2,4,6-cycloheptatetraene (**5**) with 1,3-diphenylisobenzofuran, anthracenes, 2,5-dimethyl-3,4-diphenylcyclopenta-2,4-dien-1-one, methyl 2-pyrone-5-carboxylate, tropones, 8,8-dicyanoheptafulvene and 1,3,5-cycloheptatrienes.

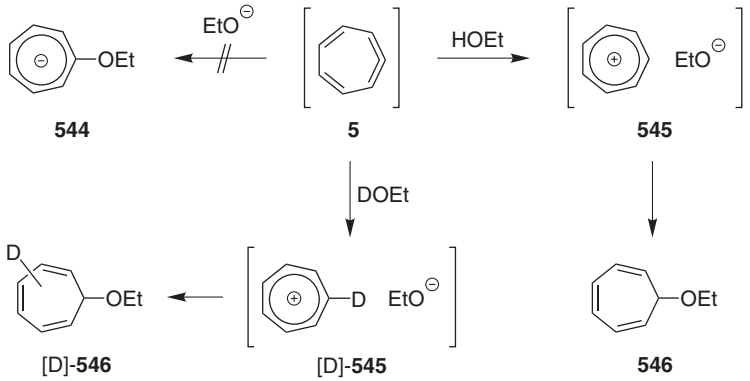
Saito et al. [216, 218] thermolyzed **517** in diglyme at 120 °C in the presence of 1,3-diphenylisobenzofuran (DPIBF) and isolated the *endo*- and *exo*-[4 + 2]-cycloadduct **535** of **5** in 28 and 3% yield, respectively. The heptafulvene **536** was an additional product (4% yield), which can be taken as evidence for a stepwise formation of **535**, as the diradical that should emerge from the attack of **5** at DPIBF can collapse to give **535** as well as open the heterocycle to yield **536**. Harris and Jones [196] employed the interception by DPIBF to prove the chirality of **5**. To that end, they took advantage of the same approaches as those used to probe the structure of 1,2-cyclohexadiene (**6**), bicyclo[3.2.1]octa-2,3,6-triene (**117**) and 1,2-cycloheptadiene (**465**) (Sections 6.3.1, 6.3.3 and 6.4.1). In one set of experiments, solutions of the bromocycloheptatrienes **518b** in THF were treated with enantiopure potassium menthoxide

in the presence of DPIBF at 0, 45 and 65 °C and the products **535** exhibited optical activity. In the second set, eliminations of hydrogen bromide were carried out with the non-racemic 7-deuterobromocycloheptatrienes [7-D]–**518b** with KO*t*Bu in the presence of DPIBF in THF at 25 and 53 °C and also in diglyme at 100 °C and again the products were optically active. There, the primary kinetic isotope effect was the cause of the predominant generation of non-racemic deutero-1,2,4,6-cycloheptatetraenes ([D]-**5**). Even if it was somewhat reduced, the optical activity was clearly discernible in the case of the product prepared at 100 °C. This points to an enhanced barrier to enantiomerization of **5** as compared with 1,2-cyclohexadiene (**6**). The liberation of [D]-**5** from [7-D]-**518b** in the presence of styrene gave rise to racemic [D]-**528**, indicating an achiral intermediate such as diradicals **527** deuterated in the seven-membered ring.

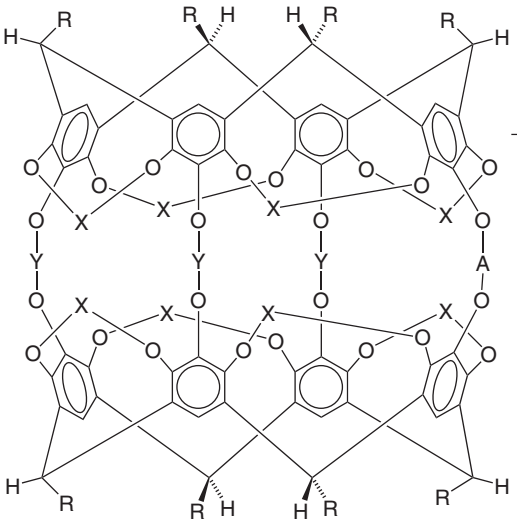
When **517**, dissolved in diglyme, was heated at 120 °C in the presence of anthracene, the [4 + 2]-cycloadduct **537** (R = H) of **5** could be isolated in 21% yield [216, 218]. Analogous products **537** resulted on trapping of **5** by 9-methyl-, 9-phenyl-, 9-acetyl-, 9-cyano-, 9-chloro-, 9-bromo- and 9-nitroanthracene in yields of 4–25% [219]. 2,5-Dimethyl-3,4-diphenylcyclopenta-2,4-dien-1-one reacted with **5** to give the *endo*- and *exo*-[4 + 2]-cycloadducts **538** in yields of 12 and 2%, respectively, and, in addition, a consecutive product of them formed by decarbonylation and aromatization. Further, tetraphenylcyclopentadienone and two tetracyclic diphenylcyclopentadienones were employed, which gave rise to compounds analogous to **538** or to consecutive products of them or to mixtures of both [220]. The thermolysis of **517** in the presence of methyl 2-pyrone-5-carboxylate furnished the benzocycloheptene **539** in 15% yield, which emerged from an unobserved [4 + 2]-cycloadduct by decarboxylation and aromatization, and a second benzocycloheptene that resulted from a skeletal rearrangement. The latter compound was the exclusive product from the interception of **5** by methyl 2-pyrone-3-carboxylate [221]. Tropone interacted with **5** to give the [4 + 2]-cycloadduct **540** (R = H) in 51% yield and analogous products **540** were formed from 2-phenyl-, 2-methyl- and 2-chlorotropone. Compound **541** was obtained in a yield of only 2% on generation of **5** in the presence of 8,8-dicyanoheptafulvene [222, 223]. [6 + 2]-Cycloadducts of the type **542** resulted in yields of 5–19% from the trapping of **5** by 1,3,5-cycloheptatriene and its 7-methyl, 7-ethyl and 7-methoxy derivatives. The structure of the [6 + 2]-cycloadduct **543** indicates that 1,3,5-cycloheptatriene-7-carbonitrile underwent a tautomerization prior to the reaction with **5** [223].

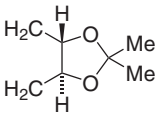
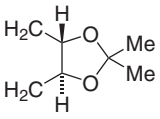
Mukai et al. [194] thermolyzed **517** in refluxing ethanol and isolated 2,4,6-cycloheptatrienyl ethyl ether (**546**) (Scheme 6.109) in 60% yield. The photolysis of **517** in *O*-deuteroethanol (DOEt) gave rise to such an ether with random distribution of the deuterium atom among all positions of the cycloheptatriene system ([D]-**546**) [224]. On treatment of the chlorocycloheptatrienes **518a** with NaOEt–DOEt, [D]-**546** was also obtained in 50% yield. These results were considered to be in agreement only with the intermediacy of cycloheptatrienylidene **5-Z$_1$**. An important argument against the allene **5** as intermediate was [224] that strained cyclic allenes react with KO*t*Bu–HO*t*Bu to give vinyl ethers. As elaborated above, this is valid for **6** (Scheme 6.11), **215** (Scheme 6.51) and **221** (Scheme 6.52), but there are deviations from that

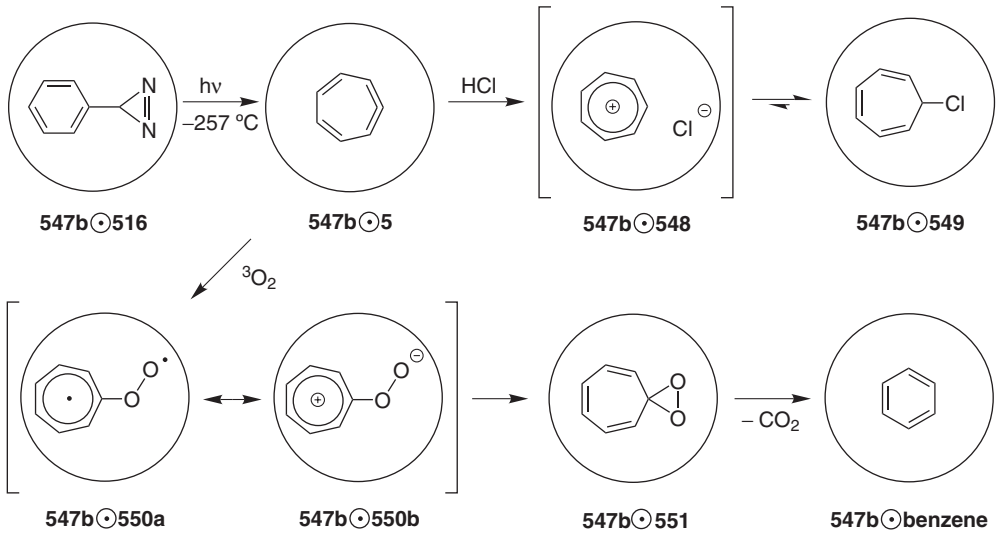
rule. The heterocyclic allenes **180** (Scheme 6.61), **260** (Scheme 6.57) and **258** (Scheme 6.58) bring about allyl ethers exclusively with this reagent and mixtures of allyl and vinyl ethers result from **351** (Scheme 6.76). On the other hand, the reactivity of **5** toward nucleophiles should be particulary low, since there is no activation to an attack at a terminal carbon atom of the allene subunit such as that by the heteroatoms of **180**, **260**, **258** and **351** and the attack at the central carbon atom would lead to a cycloheptatrienyl anion, for example **544** in the case of the ethoxide ion as the nucleophile, whose antiaromatic character puts this step at a disadvantage. The unsubstituted 2,4,6-cycloheptatrienyl anion is unknown to date, although its alleged preparation has been reported [225], but the respective experiment could not be repeated [226]. Only 2,4,6-cycloheptatrienyl anions with potent electron-acceptor substituents could be prepared and were studied by NMR spectroscopy [227]. In contrast, the protonation of **5** at the central carbon atom of the allene moiety gives rise to the tropylium ion, whose aromatic character favors this process. Apparently, the basicity of **5** is high enough to cause its smooth conversion by HOEt and DOEt into tropylium ethoxide (**545**) and deuterotropylium ethoxide ([D]-**545**), respectively, from which the products **546** and [D]-**546** emerge. In this connection, it is worth noting that two groups [186, 187] have invoked the protonation of 1,2-cycloheptadiene (**465**) to give the cyclohept-2-enyl cation (**479**) (Scheme 6.97) in order to rationalize reaction products.



Scheme 6.109 Reaction of 1,2,4,6-cycloheptatetraene (**5**) with ethanol and *O*-deuteroethanol.



	R	X	Y	A
547a	$(CH_2)_4Me$	CH_2	$(CH_2)_4$	$(CH_2)_4$
547b	$(CH_2)_4Me$	CD_2	$(CH_2)_4$	$(CH_2)_4$
547c	$(CH_2)_4Me$	CD_2	$(CH_2)_4$	
547d	$(CH_2)_2Ph$	CD_2	$(CD_2)_4$	



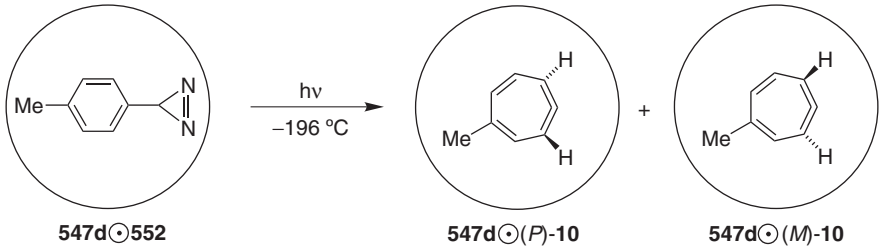
Scheme 6.110 Structure of the hemicarcerands **547** that Warmuth and Marvel used to prepare isolated molecules of 1,2,4,6-cycloheptatetraene (**5**) and its 5-methyl derivative (**10**) to make them observable at room temperature and to study their reactions with hydrogen chloride and triplet oxygen.

Taking advantage of the methodology of the inner-phase stabilization of reactive intermediates, which proved fruitful with species such as 1,3-cyclobutadiene and 1,2-dehydrobenzene [228], Warmuth and Marvel [8, 200] succeeded in the direct observation of 1,2,4,6-cycloheptatetraene (**5**) at room temperature and in the elucidation of its reactivity. By incarceration of phenyldiazirine (**516**) in the molecular container (hemicarcerand) **547a**, the hemicarceplex **547a⊙516** (Scheme 6.110) was prepared. Its photolysis furnished mainly the insertion product of the phenylcarbene (**512**) into an acetal C–H bond of **547a**. The performance of the irradiation at low temperatures also brought about a small quantity of **5** incarcerated in **547a**. The insertion reaction could be restrained somewhat by employing the partially deuterated hemicarceplex **547b⊙516**, which increased the yield of **5** in the form of **547b⊙5** to 31% on photolysis at –257 °C. When [D_8]acetophenone was present during the reaction, the yield of **547b⊙5** even amounted to 60%. This characterizes the incarcerated singlet phenylcarbene (**512**) as the species that prefers the insertion, whereas triplet **512** undergoes ring enlargement to give **5**. On exclusion of oxygen, **547b⊙5** is persistent at room temperature. Exhibiting a coupling constant $J_{1,3} = -9.8$ Hz, the ^{1}H NMR spectrum of **5** is typical for an allene.

The hemicarceplex **547b⊙551** was the result of the reaction of **547b⊙5** with triplet oxygen ($^3O_2$). Its ^{1}H NMR spectrum was recorded at –10 °C, since the fragmentation into **547b⊙benzene** and carbon dioxide proceeded at room temperature [8, 200]. The formation of **547b⊙551** should start with the addition of $^3O_2$ to the central allene carbon atom of **5** inside the molecular container. This step is promoted by the enormous resonance energy of the tropenyl radical [213] and should yield the triplet state of the diradical **547b⊙550a**. The intersystem crossing transforms it to a carbonyloxide that is represented by the resonance structures **547b⊙550a** and **547b⊙550b**, whose collapse gives rise to the incarcerated dioxirane **547b⊙551** [8, 200]. Incarcerated 7-chloro-1,3,5-cycloheptatriene **547b⊙549** emerged from the addition of hydrogen chloride to **547b⊙5** [8]. Surprisingly, the covalent molecule **549** was formed rather than incarcerated tropylium chloride (**548**), which can be explained by the low polarity of the inner phase of **547b**. On heating at 120 °C, a coalescence of the ^{1}H NMR signals of **549** occurred, suggesting a fast equilibration of **547b⊙549** and **547b⊙548** [228]. In analogy with the reaction of free **5** in ethanol (Scheme 6.109), **547b⊙548** should result by proton transfer from HCl to the central allene carbon atom of **547b⊙5**, which did not react with methanol, however [8]. Most probably, the acidity of methanol does not suffice to create the ion pair $(CH)_7^+$ MeO^- in the nonpolar inner phase of **547b**.

The diastereomeric hemicarceplexes **547c⊙(*M*)-5** and **547c⊙(*P*)-5** were the result of the irradiation of **516** inside the enantiopure molecular container **547c**. Heating of this mixture did not lead to the observation of a coalescence of the ^{1}H NMR signals of the **5** enantiomers, which is why the direct determination of the barrier to enantiomerization of (*M*)- and (*P*)-**5** was not possible [200]. An attempt was made to estimate this barrier on the basis of the experimental values of the incarcerated enantiomers of 5-methyl-1,2,4,6-cycloheptatetraene (**547d⊙10**) (see below) [20]. However, it is doubtful whether the assumptions that were made regarding the transition state are correct. As such, the carbene **5-Z$_1$** was presumed, although quan-

tum-chemical calculations [197–199] had suggested that the diradical **5-D** (Scheme 6.102) serves as transition state.



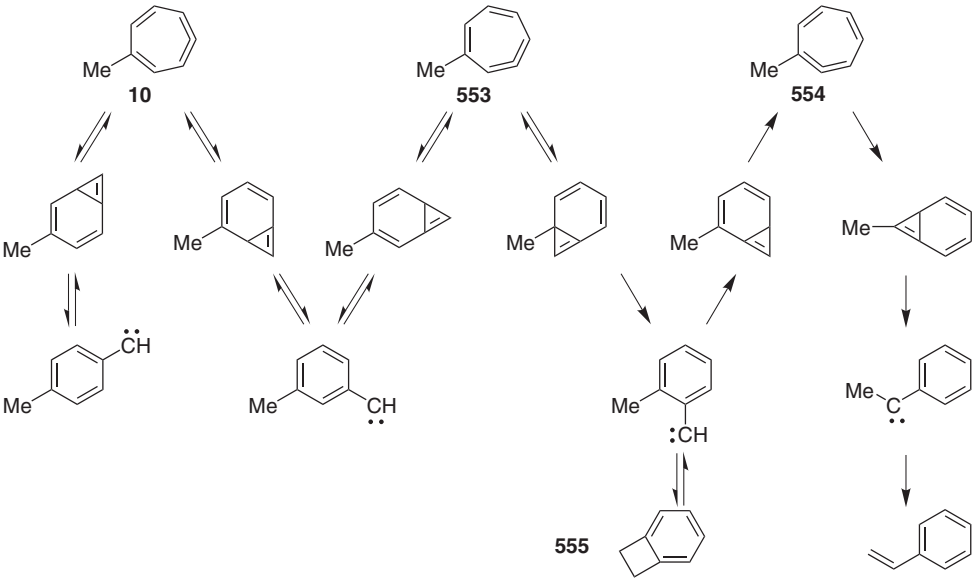
Scheme 6.111 Photolysis of *p*-tolyldiazirine (**552**) within the enantiopure molecular container **547d** giving rise to the diastereomeric carceplexes **547d⊙10**.

The photolysis of incarcerated *p*-tolyldiazirin **547d⊙552** at –196 °C furnished the diastereomeric carceplexes **547d⊙10** (Scheme 6.111) in a ratio of 1:1.15, which slowly turned to 1:1.9 at –10 °C. Monitoring of this equilibration at different temperatures gave rate constants as did the lineshape analysis of the methyl group signals in the ^{1}H NMR spectrum, the broadening of which above 98 °C indicated a dynamic exchange of both forms of **547d⊙10**. From the rate constants, the activation energies were determined as 19.6 and 20.3 kcal mol^{-1} for the conversion of the minor into the major diastereomer and vice versa [20]. These data are in excellent agreement with the value estimated by quantum-chemical calculations for **5** [197–199]. Akin to **547b⊙5**, **547d⊙10** reacted smoothly with $^3O_2$ at –10 °C, giving rise to incarcerated toluene and carbon dioxide [20].

Chapman et al. [229] observed the IR spectrum of **10** in an argon matrix at –258 °C in 1988. Photolysing ($\lambda > 470$ nm) *p*-tolyldiazomethane, they generated the respective triplet carbene, which was converted to **10** on further irradiation ($\lambda > 416$ nm). Analogously, from *m*-tolyldiazomethane, a mixture of **10** and 4-methyl-1,2,4,6-cycloheptatetraene (**553**) was obtained and *o*-tolyldiazomethane yielded only 1-methyl-1,2,4,6-cycloheptatetraene (**554**). Previously, several groups (see references cited in ref. 229) had reported the production of benzocyclobutene (**555**) and styrene on gas-phase thermolysis of the isomeric tolyldiazomethanes. After FVT of *p*-tolyldiazomethane and co-condensation of the pyrolysate with argon, **10** and **553** were observed by IR spectroscopy in addition to styrene and **555** [229]. In the same way, *m*-tolyl- and *o*-tolyldiazomethane as well as 1-phenyldiazoethane were investigated. Further, trideuteromethyl derivatives were utilized in all cases. Scheme 6.112 summarizes the interpretation of the results, which is valid for the gas phase at temperatures above 250 °C. The route from *p*-tolulcarbene to **555** leads via *m*- and *o*-tolylcarbene and, on formation of styrene, 1-phenylethylidene is the intermediate. The carbene–carbene rearrangements just mentioned proceed via the six isomeric methylbicyclo[4.1.0]hepta-2,4,6-trienes and the three methyl-1,2,4,6-cycloheptatetraenes (**10**, **553** and **554**) [229].

The results of the gas-phase pyrolysis of the sodium salts of 2- and 4-methyltropone tosylhydrazone at 350 °C/3 Torr and 450 °C/6 Torr, respectively, are in line with the mechanisms in Scheme 6.112. From the salt of 2-methyltropone tosylhydrazone, which should liberate **554** directly, only styrene was formed, whereas the 4-methyl

isomer produced a 1:1 mixture of styrene and **555** [212]. Also, the gas-phase photolysis of *o*-, *m*- and *p*-tolyldiazomethane yielded styrene and **555** [212].

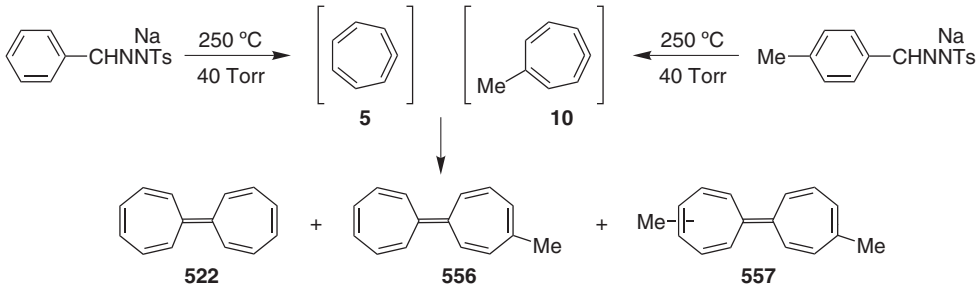


Scheme 6.112 The three methyl-1,2,4,6-cycloheptatetraenes (**10**, **553**, **554**) as key intermediates in the transformations of the tolylcarbenes in the gas phase.

Deviations of the experimental results from those expected based on the mechanisms in Scheme 6.112 were summarized by Gaspar et al. [230]. To probe these mechanisms, the authors subjected (3,5-dimethylphenyl)- and (3,4,5-trimethylphenyl)diazomethane to FVT, which should have generated dimethyl- and trimethyl-1,2,4,6-cycloheptatetraenes, respectively, as intermediates. The formation of certain styrenes and benzocyclobutenes led to the development of a hypothesis modifying the mechanisms in Scheme 6.112 [230]. However, the use of [*o*-(trideuteromethyl)-phenyl]diazomethane yielded results that strongly support Scheme 6.112 [229].

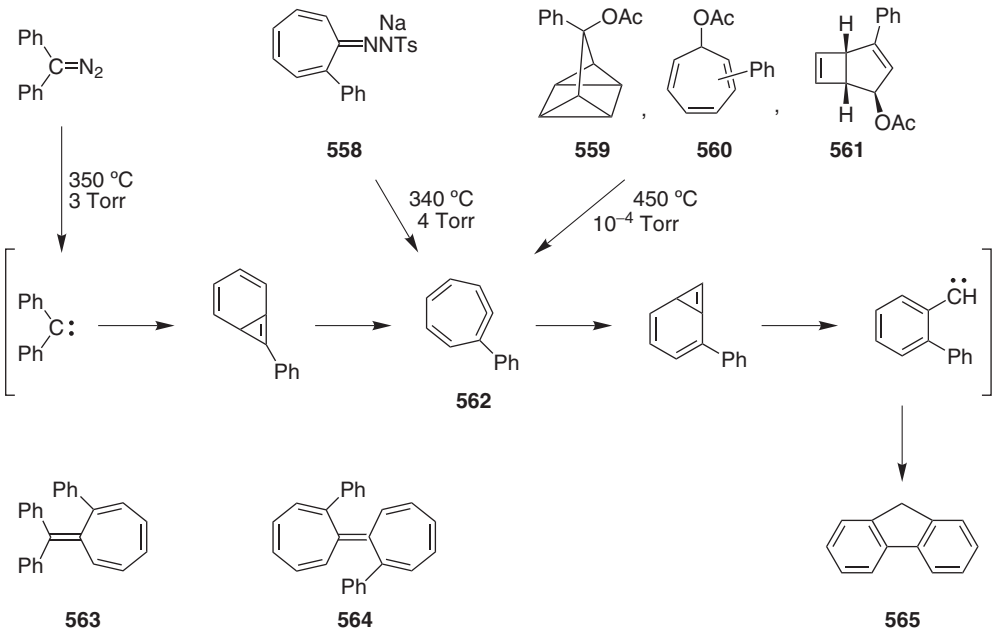
The generation of phenylcarbene (**512**) and *p*-tolylcarbene at 250 °C/40 Torr in the gas phase brought about only the ring expansion to give **5** and **10**, respectively and their dimerization yielding **522** and **557** (Scheme 6.113). The co-thermolysis of the sodium salts of benzaldehyde and *p*-methylbenzaldehyde tosylhydrazone also gave rise to the mixed heptafulvalene **556**. With a ratio of 1:2:1, the amounts of **522**, **556** and **557** verified the expectation based on statistics [212].

Diphenylcarbene also undergoes a ring expansion of the above kind. When it was generated in the gas phase at 350 °C/3 Torr, small quantities of tetraphenylethylene, the triphenylheptafulvene **563** and the diphenylheptafulvalene **564** were formed in addition to fluorene (**565**), which was obtained in 29% yield. As illustrated in



Scheme 6.113 Formation of heptafulvalene (**522**), its methyl derivative **556** and its dimethyl derivatives **557** on co-thermolysis of the sodium salts of benzaldehyde and *p*-methylbenzaldehyde tosylhydrazones.

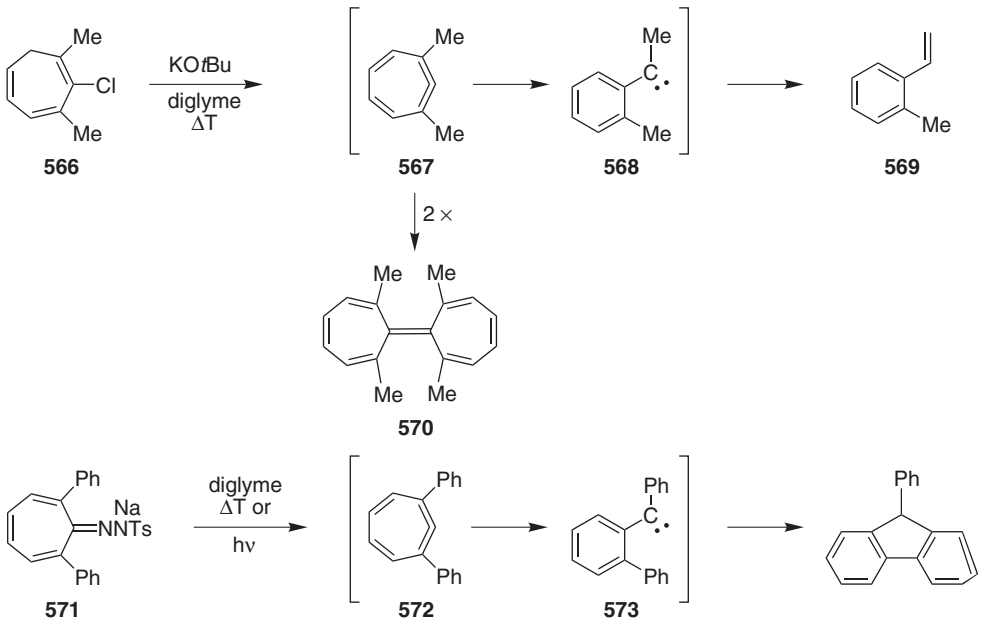
Scheme 6.114, a carbene–carbene rearrangement transforms diphenylcarbene to *o*-phenylphenylcarbene, which is the progenitor of **565**. Two phenylbicyclo[4.1.0]-hepta-2,4,6-trienes and 1-phenyl-1,2,4,6-cycloheptatetraene (**562**) have to be assumed as further intermediates. The participation of **562** is supported by the structure of the products **563** and **564**, which should result from the addition of **562** to diphenylcarbene and the dimerization of **562**, respectively. By thermolysis of the sodium salt of 2-phenyltropone tosylhydrazone, **562** was generated directly. At 100 °C in diglyme as solvent, **564** was identified as the only product and at 340 °C/4 Torr in the gas



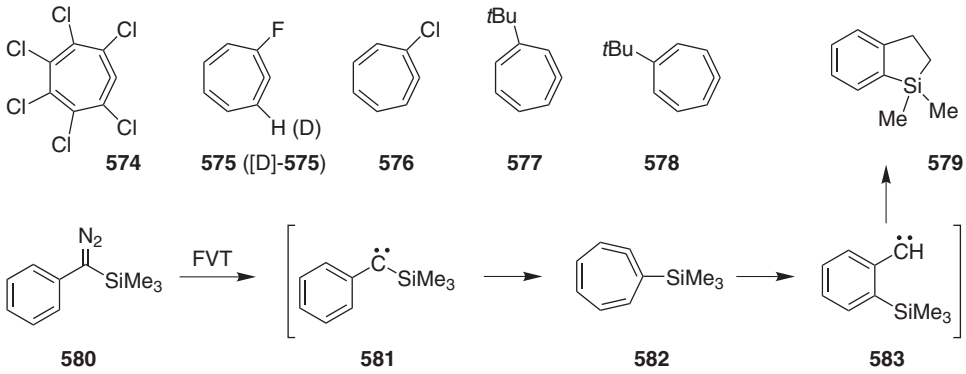
Scheme 6.114 Formation of fluorene (**565**) via 1-phenyl-1,2,4,6-cyclo-heptatetraene (**562**), generated from various precursors.

phase, **564** and **565** were obtained in yields of 50 and 15% [212]. The gas-phase pyrolysis at 450 °C of 7-phenyl-7-quadricyclyl acetate (**559**) and its isomers **560** and **561** also gave high yields of **565**. Owing to the very low pressure, the dimerization of **562** could not compete with its rearrangement to **565** [231]. In agreement with the mechanism presented in Scheme 6.114, the thermolysis of phenyl-*p*-tolyl-, *p*-anisylphenyl- [212] and *p,p′*-ditolyldiazomethane [232] produced the corresponding 2-substituted fluorenes and 2,7-dimethylfluorene.

As described above, the reorganization of a 1,2,4,6-cycloheptatetraene to the corresponding phenylcarbene could only be accomplished in the gas phase, because the dimerization to yield a heptafulvalene is the preferred reaction in solution. However, in 1,3-disubstituted 1,2,4,6-cycloheptatetraenes, the bias to dimerize is strongly hindered owing to overcrowding and thus the rearrangement even occurs in solution (Scheme 6.115). Although the liberation of 1,3-dimethyl-1,2,4,6-cycloheptatetraene (**567**) from 2-chloro-1,3-dimethyl-1,3,5-cycloheptatriene (**566**) by KO*t*Bu in diglyme at 100 °C gave the tetramethylheptafulvalene **570** in 92% yield, about the same amount of **570** and *o*-methylstyrene **569** were formed at 150–160 °C. The latter product indicated the conversion of **567** into the carbene **568**, which should be the progenitor of **569** [207]. 1,3-Diphenyl-1,2,4,6-cycloheptatetraene (**572**) was generated from the sodium salt of 2,7-diphenyltropone tosylhydrazone (**571**) in diglyme either by heating at 145 °C or by irradiating at 10 °C. That under both conditions 9-phenylfluorene resulted exclusively provides ample support for the complete rearrangement of **572** to the carbene **573** [207].



Scheme 6.115 Generation of 1,3-dimethyl- (**567**) and 1,3-diphenyl-1,2,4,6-cycloheptatetraene (**572**) and their ability to rearrange to a carbene even in solution.



Scheme 6.116 Substituted 1,2,4,6-cycloheptatetraenes that were observed or assumed in addition to those in Schemes 6.111–6.115.

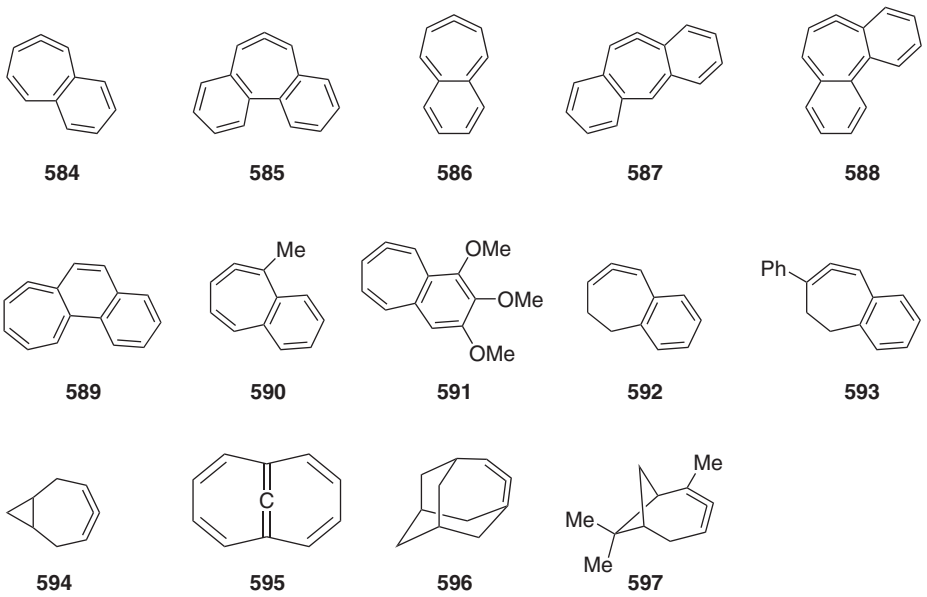
In Scheme 6.116, the formulas of further substituted 1,2,4,6-cycloheptatetraenes are collected, for which there is experimental evidence. The 1-fluoro (**575**) and 1-chloro (**576**) derivatives were prepared by photolysis of the respective 3-halo-3-phenyldiazirines or *o*-halophenyldiazomethanes and characterized in argon matrices at –258 °C by their IR spectra. Also, the FVT of the 3-halo-3-phenyldiazirines and of *o*-fluorophenyldiazomethane and the co-condensation of the pyrolysate with argon led to the observation of **575** and **576**. The IR bands of the allene subunits appeared at 1810 cm^{-1} (**575**), 1809 cm^{-1} (**576**) and, in the case of the deuterated fluoro compound [D]-**575**, at 1799 cm^{-1} [195b]. All these values agree well with the spectrum of the unsubstituted compound **5** [195b].

The *tert*-butylcycloheptatetraenes **577** and **578** are assumed to be formed by the action of atomic carbon at *tert*-butylbenzene, which initially should give rise to a number of carbenes owing to insertions into all types of C–H bonds. Then, the ring enlargement of 3- and (4-*tert*-butylphenyl)carbene should furnish **577**/**578** and pure **578**, respectively. This was concluded from the results of the treatment of the products that were brought about by atomic carbon, enriched in ^{13}C and frozen at –196 °C with tetrafluoroboric acid. Resulting from protonation of **577** and **578**, ^{13}C-labeled *tert*-butyltropylium ions were observed. Analogously, from benzene instead of *tert*-butylbenzene, the unsubstituted tropylium salt was obtained, which supports the intermediacy of **5** [233].

The formation of the benzosilacyclopentene **579** on gas-phase pyrolysis of (trimethylsilyl)phenyldiazomethane (**580**) provided evidence for the existence of 1-trimethylsilyl-1,2,4,6-cycloheptatetraene (**582**) (Scheme 6.116). A ^{13}C-labeling study suggested that **582** results from **580** via the carbene **581** and the corresponding bicyclo[4.1.0]hepta-2,4,6-triene and rearranges to **579** via a second bicyclo[4.1.0]hepta-2,4,6-triene and the carbene **583** [234]. Hexachloro-1,2,4,6-cycloheptatetraene (**574**) is likely to be the intermediate in the reaction of octachloro-1,3,5-cycloheptatriene with metal carbonyls, which furnished *syn*-perchloroheptafulvalene in good yield [235].

6.4.3
Annulated and Bridged Derivatives of 1,2-Cycloheptadiene

The possible benzo and dibenzo derivatives of 1,2,4,6-cycloheptatetraene (**5**) and its tribenzo derivative were studied theoretically fairly early [236a]. Some of these systems and a few naphthoannulated compounds were subject to an improved treatment later [236b]. Accordingly, the allene states **584**, **585** and **589** are strongly preferred over the corresponding 2,4,6-cycloheptatrienylidene states, whereas the energies of **586–588** are approached rather closely by those of the respective cycloheptatrienylidenes (Scheme 6.117). This situation was corroborated for **584** by a recent investigation, in which the calculated IR spectrum was shown to agree well with an experimental spectrum, recorded for this species isolated in an argon matrix at –263 °C [237]. Waali et al. [238] obtained cycloadducts of **584** with furan and styrene. Kirmse and Sluma [239] studied the trapping of **584–586** with NaOMe–HOMe. The experimental study of **589** afforded two heptafulvalene dimers and trapping products with activated alkenes [236b].



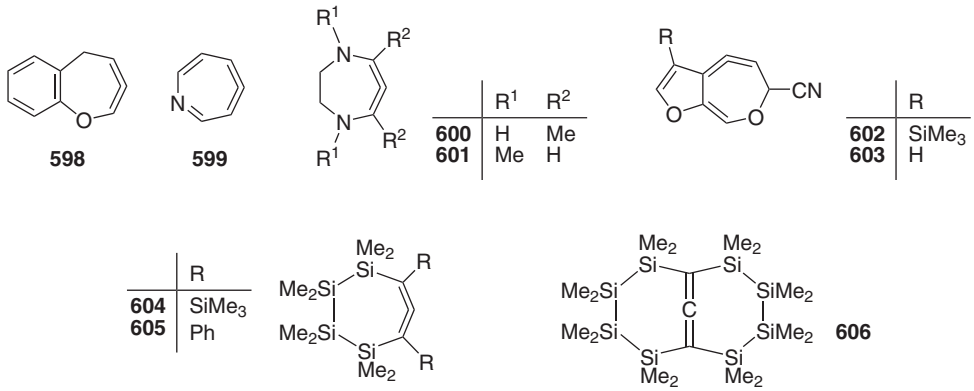
Scheme 6.117 Structures of annulated and bridged derivatives of 1,2-cycloheptadiene.

Dimers with a 1,2-bismethylenecyclobutane structure were obtained from **585** [240], **590** [238], **591** [241], **592** [242], **593** [243] and from the pinene derivative **597** [244]. The interception of **592** by 1,3-diphenylisobenzofuran (DPIBF) afforded two diastereomeric [4 + 2]-cycloadducts [245]. Bicyclo[5.1.0]octa-3,4-diene (**594**) was generated by β-elimination and trapped by sodium pyrrolidide because of the question of the extent to which the corresponding bicyclooctyne is formed in addition to **594** [184]. Liberated by β-elimination from 11,11-dichloro-1,6-methano[10]annulene in

the presence of DPIBF, the [4.4]betweenallene **595** gave rise to the [4 + 2]-cycloadduct of a valence isomer of **595** [246]. 3,4-Homoadamantadiene (**596**) was generated from 3-bromo-4-iodo-4-homoadamantene by dehalogenation and furnished two dimers in addition to a [4 + 2]-cycloadduct with DPIBF [247].

6.4.4
Heterocyclic Derivatives of 1,2-Cycloheptadiene

It was concluded from the formation of a dimer that **598** emerged by a DMS reaction in addition to a bicyclo[1.1.0]butane derivative [248]. The azacycloheptatetraene **599**, trapped in an argon matrix kept at –261 °C, was observed by IR spectroscopy after photolysis of 3- and 4-diazomethylpyridine [249]. According to quantum-chemical calculations, the protodebromination of the respective bromodihydrodiazepinium ions is believed to proceed via the 1,4-diaza-5,6-cycloheptadienes **600** and **601** as intermediates [169, 250].



Scheme 6.118 Structures of heterocyclic derivatives of 1,2-cycloheptadiene.

The 1-oxa-2,4,5-cycloheptatrienes **602** and **603** were postulated to be intermediates in the rearrangement of certain (ethynylfuryl)oxiranes to furo[3,4-*b*]furans [251]. The replacement of the methylene groups of 1,2-cycloheptadiene (**465**) by $SiMe_2$ groups and the introduction of substituents at the allene moiety allowed the preparation of isolable seven-membered ring allenes. Thus, Barton et al. [177] obtained **604** and Ando et al. [178] **605**. A few reactions of these systems have also been studied [177, 252]. Both groups [178, 253] synthesized the [4.4]betweenallene **606** and determined its structure by X-ray diffraction.

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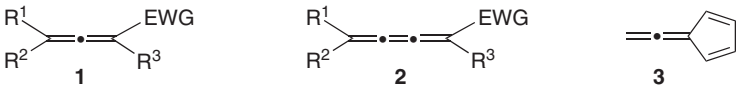
7
Acceptor-Substituted Allenes

Klaus Banert and Jens Lehmann

7.1
Introduction

The allenes **1** directly connected with an electron-withdrawing substituent have been used successfully as synthetic building blocks for more than four decades (see Scheme 7.1). The polarization of the C=C double bonds by the acceptor substituent allows a wide and very useful range of subsequent reactions, for example nucleophilic additions, cycloadditions and miscellaneous syntheses of heterocycles.

The electron-withdrawing group (EWG) substituents of greatest importance prove to be mainly the carbonyl groups of aldehydes, ketones, carboxylic acids, carboxylic acid esters and amides, but also nitriles, sulfones, sulfoxides, phosphane oxides and phosphonates (Scheme 7.1). In rather rare cases, the acceptor group EWG can represent perfluoroalkyl (R_F), isonitrile, imine, oxime and hydrazono groups, ammonium or sulfonium salts, sulfine amines, sulfonic acid esters and phosphonic acid diamides or dichlorides. Additionally, butatrienes with electron-withdrawing substituents **2** and ethenylidenecyclopentadienes of type **3** will be included in the present summary.



EWG = CHO, C(O)R, CO_2H, CO_2R, $CONRR^1$, CN, SO_2R,
S(O)R, $P(O)R_2$, $P(O)(OR)_2$,

R_F, NC, $C(R)=NR^1$, $C(R)=NOR^1$, $C(R)=N–NR^1R^2$, $\overset{\oplus}{N}RR^1R^2$,
$\overset{\oplus}{S}R^1R^2$, $S(O)–NR_2$, SO_2OR, $P(O)(NR_2)_2$, $P(O)Cl_2$

Scheme 7.1

In the 1980s, the complete chemistry of allenes was summarized in several very informative books [1–5] and excellent reviews were published covering the most important functionalized allenes such as sulfones [6], phosphonates [7] and phos-

Modern Allene Chemistry. Edited by N. Krause and A.S.K. Hashmi

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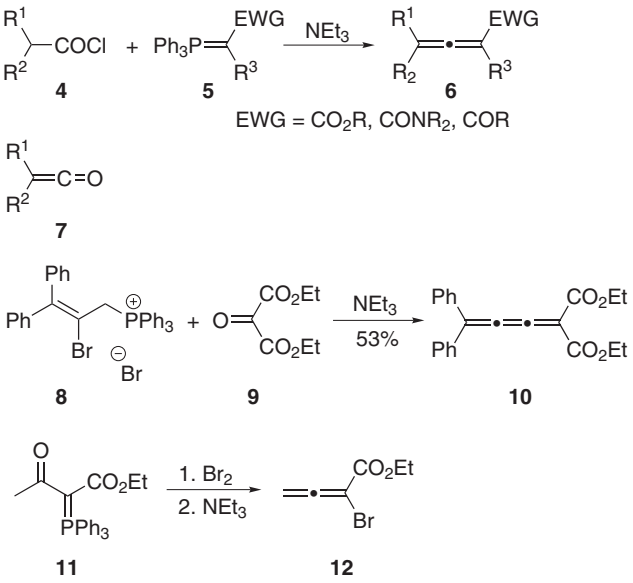
phorylated allenes [8]. Hence this summary focuses mainly on the results of the last 20 years. However, well-known and very important syntheses and reactions of acceptor-substituted allenes will be presented with new examples.

7.2
Synthesis of Acceptor-Substituted Allenes

There is not just one predominating method for the generation of allenes with at least one electron-withdrawing group, but a number of important routes. Even for the synthesis of allenes with a given acceptor function, for example allenic esters, different routes are often used such as the Wittig reaction, prototropic isomerization or alkoxycarbonylation.

7.2.1
Methods with Building Up of the Carbon Skeleton of the Allene

One of the old [9] but still one of the most powerful methods of making acceptor-substituted allenes uses the Wittig reaction of carboxylic acid chlorides **4** with phosphorane **5** containing already the electron-withdrawing substituent (Scheme 7.2). Lang and Hansen [10] elaborated procedures for the synthesis of esters of type **6** (EWG = CO_2R), which were used by several other groups to synthesize various further allenic esters, usually in good yields [11–18]. By variation of the component **5**, this method is also applicable to lactams [19] and ketones [20]. In some cases, a



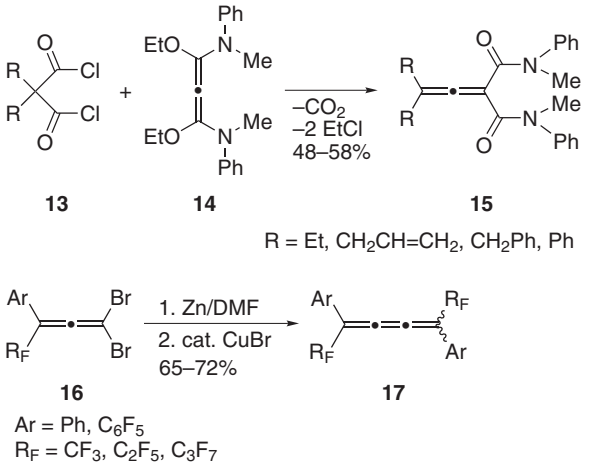
Scheme 7.2

ketene of type **7** was used instead of the acid chloride **4**, yielding ketones, esters [21], nitriles [22, 23] and carboxylic acid amides [24, 25] of type **6**. A phosphonate carbanion and a phosphinate carbanion were also reacted with ketenes to give allenic esters [26, 27]. Starting from the phosphonium salt **8** and the mesoxalic ester **9**, the butatriene **10** can be synthesized in the presence of triethylamine [28]. In contrast to the Wittig reactions mentioned above, the phosphorane **11** contains already all carbon atoms important for the allene skeleton in the synthesis of **12** [14].

Unusual transallenation reactions were discovered by Saalfrank et al. [29] during the reaction of the substituted malonyl chlorides **13** with the nucleophilic allene **14** (Scheme 7.3). In this case, **14** contributes only one and **13** the remaining two carbon atoms to the allene framework of the product **15**.

The dimerization of vinyl carbenoids, generated from the precursors **16**, allows the building of butatrienes with perfluoroalkyl groups (R_F) [30, 31]. The products **17** are obtained as *E*–*Z* mixtures.

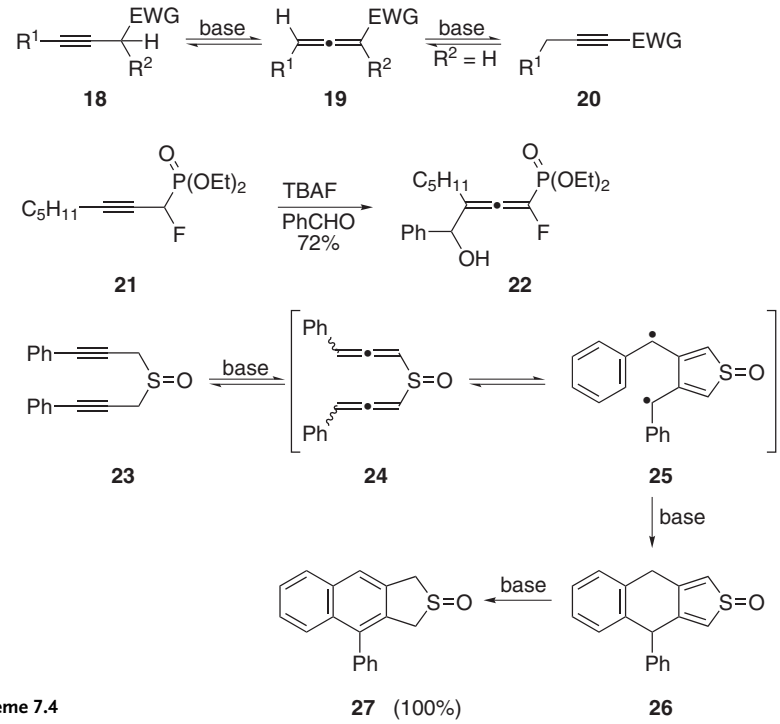
The photochemical reaction of diiron μ-alkenylide complexes with diazo compounds leads to μ-allene complexes, which can be cleaved by several methods to yield allenes, for example allenic esters [32].



Scheme 7.3

7.2.2
Prototropic Isomerization of Propargyl Compounds

The acidity of the propargylic proton of the starting compound **18** allows the equilibration with the allene **19** induced by bases such as tertiary amines or alcoholates (Scheme 7.4). Such prototropic rearrangements furnish the title compounds **19** with at least one proton at the terminal carbon atom, often in good yields. The EWG group involves carboxylic acids [33], esters [34], ketones [35, 36], isonitriles [37], sulfones [38], sulfoxides [39, 40] and phosphonates [41]. The oxidation of easily accessi-

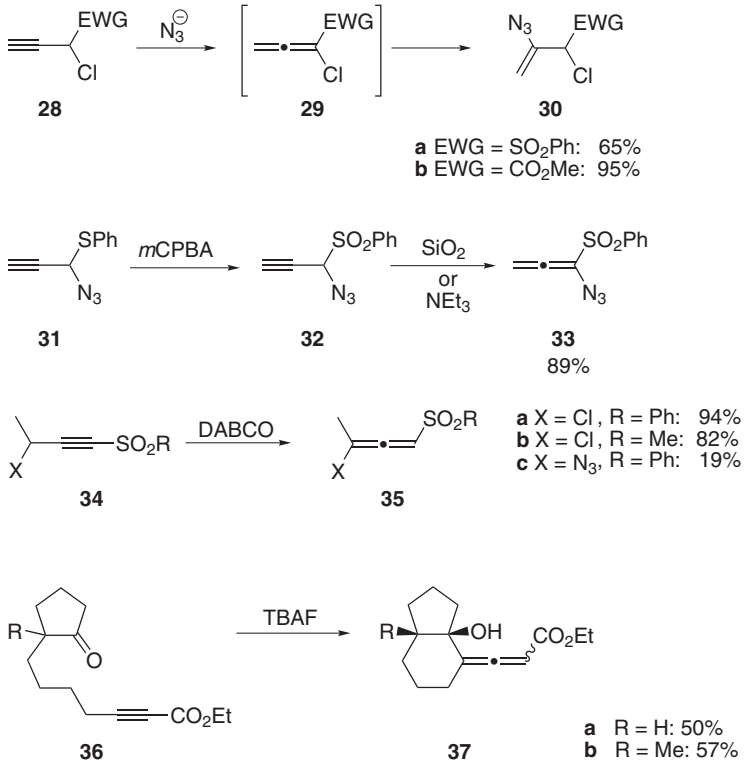


Scheme 7.4

ble homopropargylic alcohols yields ketones already rearranged to structure **19**, especially if the Dess–Martin procedure or Swern reactions are chosen [42–47].

Only a few examples exist describing the products from the allenylic/propargylic carbanion resulting from the deprotonation of **18** and reaction with other electrophiles instead of protons which lead to products analogous to **19** [48]. Thus, treating the propargyl compound **21** with tetrabutylammonium fluoride (TBAF) in the presence of benzaldehyde furnishes the C,C-connected compound **22** [41].

In the case of carboxylic acids [33], ketones [47] or sulfones [49], it was possible to prove a further prototropic rearrangement of allenes **19** with $R^2 = H$ yielding the alkynes **20**. In other examples, the prototropic isomerization of the triple bond leads to conjugated dienes directly; thus the allene of type **19** could only be postulated as an intermediate [50]. Braverman et al. showed that the allenes generated by prototropic isomerization of dipropargylic sulfones or sulfoxides, for example **24**, are unstable. They are transferred rapidly via diradical intermediates to polycycles such as **27** [51–53].



Scheme 7.5

No propargyl or allenyl azides could be found when the chloro compounds **28** were treated with azide reagents, even under many different conditions (Scheme 7.5). The resulting vinyl azides **30**, which were formed instead, are explained easily by the prototropic rearrangement **28** → **29**, for example, caused by the base sodium azide and the subsequent rapid nucleophilic addition of HN_3 (see Section 7.3.1) [54]. However, allenylazides, which are otherwise difficult to access [55–58], can be prepared by prototropic isomerization of propargylic compounds if the EWG is generated after introduction of the azido group. For instance, the oxidation of thioether **31** combined with prototropic rearrangement of **32** provides good access to the allenyl azide **33** [59].

The equilibrium **19**⇄**20** is not only a succeeding reaction of the acceptor-substituted allenes **19**, but can also be used to synthesize the title compounds starting from **20**. Whereas the isomerization of the chloro compounds **34a** and **34b** furnishes the allenes in good yields, the conversion of **34c** leads to the unstable azide **35c** with low yield [59].

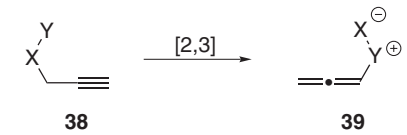
Another method using starting materials of type **20** includes ring closure via nucleophilic attack at cyclic ketones [60]. Thus, on treatment of compounds **36** with tetra-*n*-butylammonium fluoride (TBAF), the products **37** were isolated. If cyclohex-

anones or cycloheptanones analogous to **36** were utilized, the yields of the bicyclic products similar to **37** were even better (80–95%).

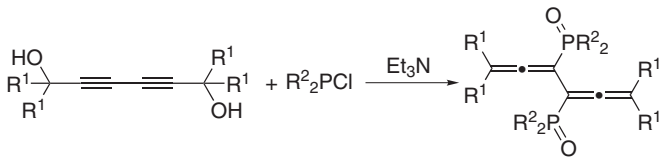
7.2.3
[2,3]-Sigmatropic Rearrangement of Propargyl Compounds

The isomerization reactions of alkynes via [2,3]- or [3,3]-sigmatropic rearrangements are probably among the most important methods available for the introduction of the allene group into an organic molecule. The usefulness of this synthetic method [61, 62] and the access to new functionalized allenes [63] have been reviewed recently.

The [2,3]-sigmatropic rearrangements of phosphinous esters **38** (X–Y = OPR_2, Scheme 7.6) to phosphane oxides of type **39** [64–69] and of phosphites **38** [X–Y = $OP(OR)_2$] to allenic phosphonates **39** [7, 70–78] have been well known for a long time as convenient routes to acceptor-substituted allenes. Such reactions were used by several groups to prepare the stable diallenes **42** [79–81] as well as more newly substituted allenephosphonates [79, 82, 83] [**39**, $Y^+–X^- = P(O)(OR_2)$] and allenylphosphine oxides [79] of type **39** [$Y^+–X^- = P(O)R_2$]. Similar sigmatropic rearrangements allow also the synthesis of allenephosphonic diamides [84] [**39**, $Y^+–X^- = P(O)(NR_2)_2$] and allenyldichlorophosphane oxides [84–87] [**39**, $Y^+–X^- = P(O)Cl_2$].



38 **39**



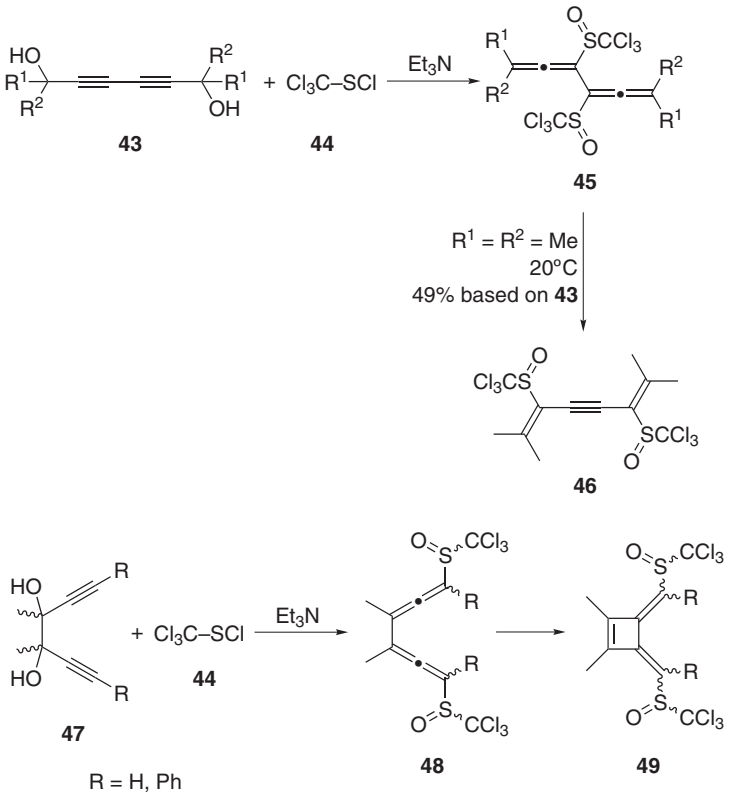
40 **41** **42**

a $R^1–R^1 = (CH_2)_5$, R^2 = OEt: 74%
b R^1 = Me, R^2 = OEt: ca. 90%
c R^1 = H, R^2 = Ph: 40 %
d R^1 = Me, R^2 = Ph: 75 %
e R^1 = H, R^2 = Et: 95%

Scheme 7.6

Along with the [2,3]-sigmatropic migrations of phosphorus-containing functional groups, the analogous rearrangements via sulfur-containing functional groups are known, for example the rapid rearrangement of propargyl sulfenates to allenyl sulfoxides [88–93] and the isomerization of propargyl sulfinates to allenyl sulfones [94–

100]. Nevertheless, new examples have also been reported of allenyl sulfoxides [101] and especially allenyl trichloromethyl sulfoxides [**39**, $Y^+–X^- = S(O)CCl_3$] [102]. There have been many trials to use these sigmatropic rearrangements for the synthesis of diallenes (compare **40** → **42**), e.g. the reaction of the diols **43** with trichloromethanesulfenyl chloride **44** to the diallenes **45** (Scheme 7.7) [103].



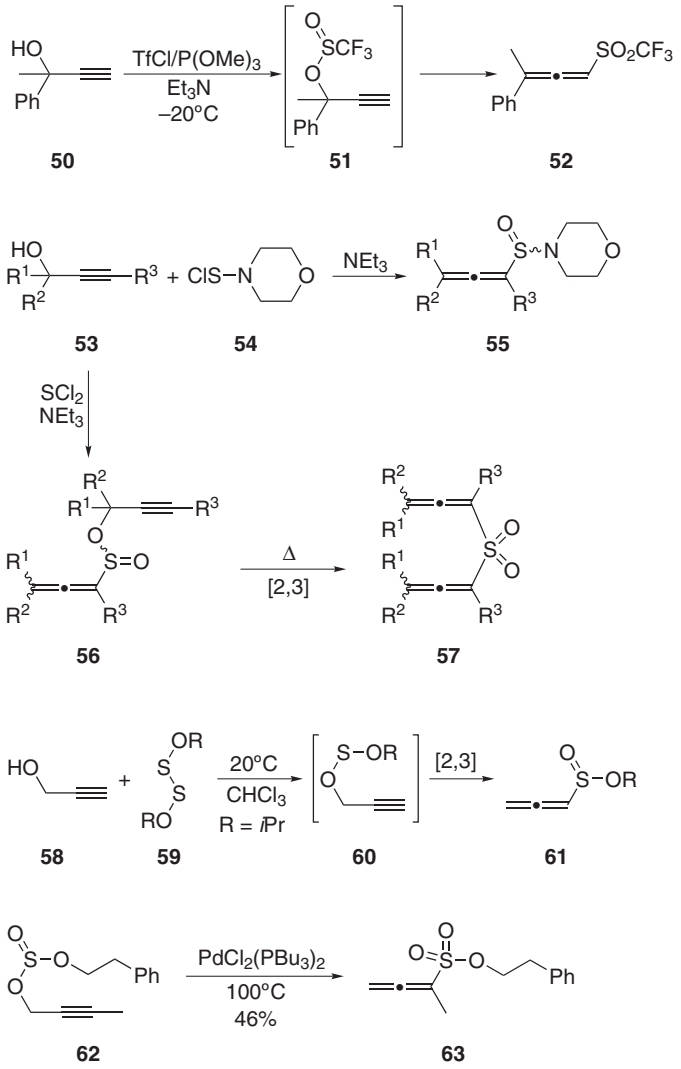
Scheme 7.7

We found that **43** ($R^1 = R^2 = Me$) and **44** lead to a mixture of the diallenes *meso*- and *rac*-**45**, which can be characterized by spectroscopy without doubt at low temperature [104]. The isolation of **45** ($R^1 = R^2 = Me$) failed because this compound rearranged rapidly at room temperature most probably to the dienyne **46**. Braverman et al. [105] analyzed spectroscopically the diallenes **48** resulting from diols **47** and the reagent **44**. In one case, even isolation was possible. However, the cumulenes **48** cyclize irreversibly to mixtures of the stereoisomers of the stable compounds **49** at room temperature, mostly at lower temperature.

Because of the usually high temperatures required to rearrange propargyl sulfinates to allenyl sulfones, a report about such palladium-catalyzed transformations seems to be promising [106]. Even at low temperatures the synthesis and isomerization of trifluoromethanesulfinate **51** are possible if, during the reaction of the ter-

tiary alcohol **50** with trifluoromethanesulfonyl chloride (TfCl), in addition to the base triethylamine also the reducing agent trimethyl phosphite is present (Scheme 7.8) [107]. Whilst the rapid rearrangement of **51** allows no isolation of this ester, the analogous isomerization of sulfinates resulting from secondary propargyl alcohols requires distinctly higher temperatures.

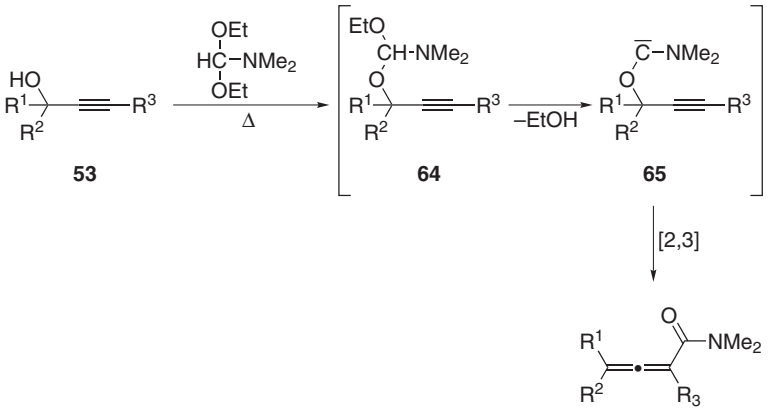
The reaction of the propargyl alcohols **53** with the reagent **54** furnished the *S*-allenylsulfinylamines **55** in good to excellent yields [108, 109]. Furthermore, the propargyl alcohols can be transformed with sulfur dichloride to the *S*-allenylsulfinates **56**, which isomerize on heating in solution to the diallenyl sulfones **57** [79, 110, 111].



Scheme 7.8

Recently, Braverman and Pechenick reported another method to generate in situ propargyl sulfoxylates, which rearrange rapidly to give allenesulfinates. For example, treatment of dialkoxy disulfide **59** (R = *i*Pr) with propargyl alcohol **58** leads to the allene **61** via [2,3]-isomerization of the intermediate **60** [112]. Several similar starting materials of type **59**, including dipropargyloxy disulfides and diallyloxy disulfides, are also converted into propargyl sulfoxylates and finally into allenesulfinates, on reaction with the appropriate alcohols. However, dipropargyloxy disulfides can also generate functionalized allenes as short-lived intermediates via direct [2,3]-sigmatropic rearrangement [113]. In this case, more complex bicyclic final products are formed. Whereas the rearrangement of propargyl sulfites to allenesulfonates could be only postulated at first [114], the transformation of the sulfite **62** to the isolable product **63** was successful by using a Pd(II) catalyst [115]. However, this rearrangement reaction allows acceptable yields in only a few cases.

The allenic amide **66**, obtained from the reaction of propargyl alcohol **53** with dimethylformamide diethyl acetal, could be explained by an unusual [2,3]-sigmatropic rearrangement (Scheme 7.9) [116]. The authors assume that after a transesterification via the intermediate **64** and an α-elimination of ethanol, a [2,3]-migration of the resulting nucleophilic carbene **65** completes the reaction. Treatment of *O*-propargylcyanohydrins with an excess of lithium diisopropylamide resulted in the formation of lithium cyanide and allenyl ketones by [2,3]-sigmatropic isomerization (Wittig rearrangement) [117].

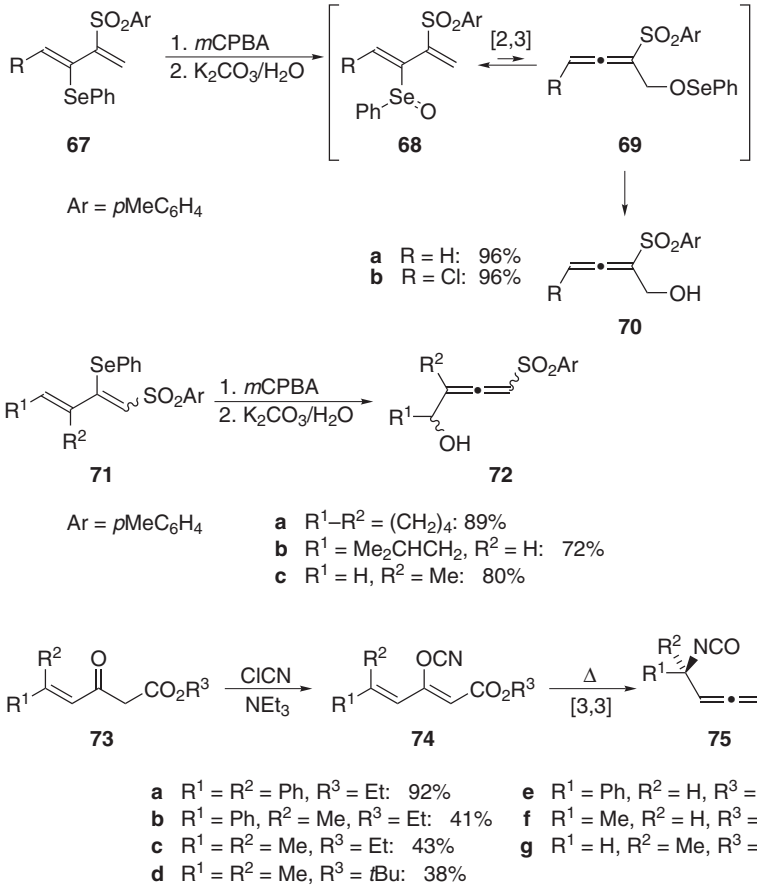


Scheme 7.9

7.2.4 Other Rearrangement Reactions

Not only propargyl precursors but also acceptor-substituted 1-methyleneallyl compounds such as **67**, **71** or **74** can be used to produce the target allenes by sigmatropic reactions (Scheme 7.10). After oxidation of selenium compounds **67** followed by equilibration of the resulting selenoxides **68** and selenenic esters **69**, hydrolysis

leads to the allenic alcohols **70**. In a similar way, starting materials **71** were transformed to the products **72** [118]. Cyanates **74**, which are easily accessible from β-keto esters **73**, afford allenic esters **75** by irreversible [3,3]-sigmatropic migration of the cyanato group [119, 120]. In the case of **74a–d**, these reactions were performed by heating solutions of the starting materials, whereas volatile **74e–g** were transformed to less stable **75e–g** by flash vacuum pyrolysis.

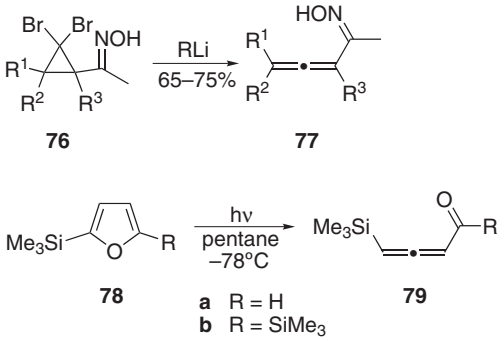


Scheme 7.10

The rearrangements **67** → **70**, **71** → **72** and **74** → **75** include the transformation of conjugated dienes to cumulenes. Nevertheless, these reactions take place with very high yields in some cases, because either an irreversible step of hydrolysis such as **69** → **70** is involved or the very exothermic transformation from cyanates to isocyanates is used. Comparison of the energies, calculated by *ab initio* methods [121], shows that, for example, the energy of methyl isocyanate is lower than that of methyl cyanate by 26.8 kcal mol^{-1} and that of vinyl isocyanate is lower than that of vinyl cyanate by 28.1 kcal mol^{-1}.

The allene moiety of the products **70b**, **72** and **75** is in each case chiral and, furthermore, an additional chiral center is created in **72a**,**b** and **75b**,**e**–**g**, thereby leading to the possible formation of diastereomers. However, the concerted nature of such sigmatropic processes should result in suprafacial migrations and formation of the racemate of only one diastereomer in each case, as shown for **74** → **75** in Scheme 7.10. High stereoselectivity can really be found for the reaction of (*E*)-**71a** and **74b**,**e**,**f**, but not for other examples of type **71** and for **74g**, which lead to mixtures of diastereomers.

The Doering–Moore–Skattebøl method including a cyclopropylidene–allene rearrangement is often used for the synthesis of allenes. However, the reaction conditions applied are often not compatible with acceptor substituents. One of the rare exceptions is the transformation **76** → **77** (Scheme 7.11) [122]. The oximes **77** are not accessible by the classical route starting from allenyl ketone and hydroxylamine (see Section 7.3.2).



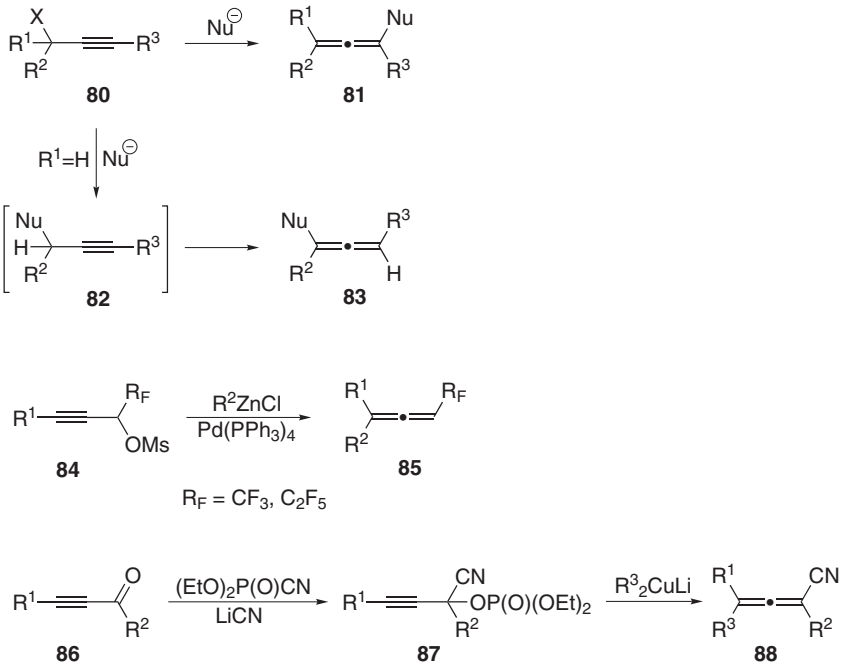
Scheme 7.11

The photolysis of the furan derivatives **78** yielded the butadienals **79** as the main products [123]. Further isomerizations leading to allenic esters used the radiation of a cyclopropene-1-carboxylic acid ester [124] or applied flash vacuum pyrolysis to 3-ethoxycyclobut-2-en-1-one [125].

7.2.5
Nucleophilic Substitution of Propargyl Compounds

The cyanoallenes **81** (Nu = CN) can be prepared directly from tertiary propargyl alcohols **80** (X = OH) in the presence of copper powder, potassium cyanide, copper(I) cyanide and aqueous hydrochloric acid or hydrobromic acid (Scheme 7.12) [126]. In a more recent version, propargyl carbonates (X = OCO_2Me or OCO_2Et) were treated with trimethylsilyl cyanide in the presence of catalytic amounts of tetrakis(triphenylphosphane)palladium(0) to give also cyanoallenes **81** in partly very good yields [127]. Primary and secondary propargyl halides **80** (X = Cl, Br) react with cyanide in the presence of catalytic amounts of copper(I) salts in aqueous solution to give the allenes **81** (Nu = CN) or the products of direct displacement **82** (Nu = CN). Under these reaction conditions, the compounds **82** are converted, at least partially, to the

cyanoallenes **83** by prototropic isomerization (see Section 7.2.2) [128–131]. In the case of $R^1 = H$ and $R^2 \neq R^3$, the product **83** is an isomer of **81**. Similar results can be obtained from the reaction of propargyl bromide **80** (X = Br) and diethyl phosphite or diphenylphosphane oxide yielding allenephosphonates and allenylphosphane oxides of type **83** [Nu = $P(O)(OEt)_2$ and $P(O)Ph_2$, respectively] in addition to other products [132, 133].



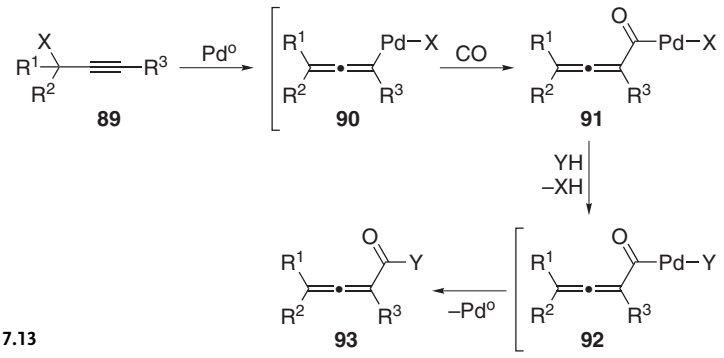
Scheme 7.12

The nucleophilic substitution of propargyl substrates already containing an acceptor group can also be used to synthesize the target allenes. For example, the reaction of zinc–organic reagents with perfluoroalkyl-substituted propargyl mesylates **84** in the presence of catalytic amounts of tetrakis(triphenylphosphane)palladium(0) furnishes the allenes **85** mostly in good yields [134]. Starting from enantiomerically pure substrates **84**, the transformation to the products **85** occurs without loss of the optical purities.

Cyanohydrin diethyl phosphates **87**, easily accessible from propargyl aldehydes or ketones of type **86**, reacted with lithium dialkylcuprates or similar reagents via an S_N2' process to give cyanoallenes in moderate to good yields [135]. The transformations **80** → **81** and **84** → **85** are only formally also S_N2' reactions. Thus, plausible catalytic cycles, which include different short-lived palladium intermediates, have been postulated to explain these nucleophilic substitution reactions [127, 134].

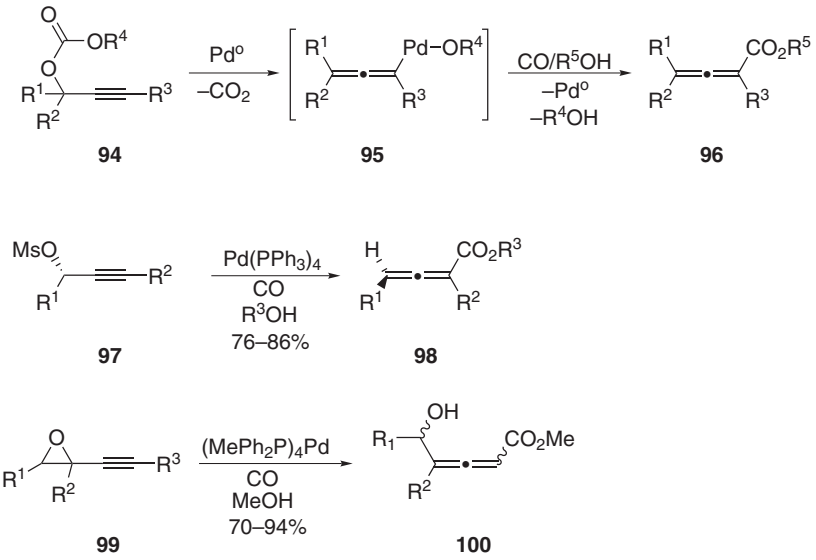
7.2.6
Palladium-catalyzed Carbonylation of Propargyl Compounds

Carbonylation reactions, particularly important in organic synthesis, belong to the numerous palladium-catalyzed reactions of propargyl compounds, reviewed by Tsuji and Mandai [136]. Esters **89**, derived from propargylic alcohols like their acetates and phosphates or preferably mesylates and carbonates [X = OCOMe, $OP(O)(OR)_2$, OSO_2Me, OCO_2R], serve as starting materials (Scheme 7.13). Partly drastic reaction conditions are necessary if propargylic compounds of type **89** with X = OH, Br, Cl, NRR′ are used. In many cases, the catalyst tetrakis(triphenylphosphane)palladium(0) is applied. However, the essential palladium(0) species can also be generated in situ by reduction of palladium(II) compounds such as palladium(II) acetate. Starting from reactive substrates **89** and palladium catalysts, it is often possible to obtain the products **93** in good to very good yields using mild reaction conditions without higher pressure of carbon monoxide. Probably, the conversions proceed by oxidative addition of **89** to the palladium(0) species furnishing the palladium(II) complex **90**. This complex reacts to give the intermediate **91** by insertion of carbon monoxide into the palladium–carbon σ-bond. After possibly exchange of X to the group Y, the reductive elimination completes the transformation with generation of the functionalized allenes **93** and recovery of the palladium(0) species.



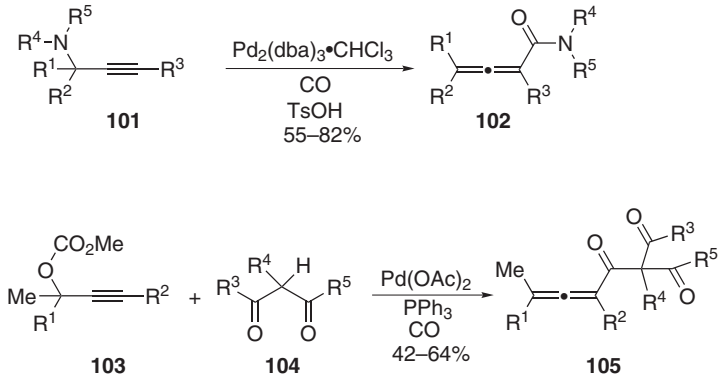
Scheme 7.13

Not least for the syntheses of natural products, alkoxycarbonylations with formation of allenic esters, often starting from mesylates or carbonates of type **89**, are of great importance [35, 137]. In the case of carbonates, the formation of the products **96** occurs by decarboxylation of **94** to give the intermediates **95** (Scheme 7.14). The mesylates **97** are preferred to the analogous carbonates for the alkoxycarbonylation of optically active propargylic compounds in order to decrease the loss of optical purity in the products **98** [15]. In addition to the simple propargylic compounds of type **89**, cyclic carbonates or epoxides such as **99** can also be used [138]. The obtained products **100** contain an additional hydroxy function.



Scheme 7.14

Aside from alkoxycarbonylations, hydroxycarbonylations in the presence of water to yield allenic carboxylic acids [15] (**93**, Y = OH) and aminocarbonylations in the presence of amines to give the analogous amides [139] (**93**, Y = NRR′) have also been carried out, respectively (Scheme 7.13). These products of structure **102** can also be obtained if using the propargylamines **101** with R^1 = Ph or $R^3 \neq H$ as starting materials (Scheme 7.15) [140]. Additionally, hydroxycarbonylations, also termed carboxylations, are successful without palladium catalysis by reaction of propargyl halides and carbon monoxide in the presence of nickel(II) cyanide under phase-transfer conditions [141, 142].

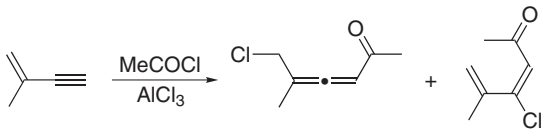


Scheme 7.15

Finally, the synthesis of allenyl ketones is also possible by carbonylation if carbonates **103** are treated with C–H acidic compounds **104** such as β-diketones or derivatives of malonic ester to yield products of type **105** [143].

7.2.7
1,4-Addition to Enynes

The $AlCl_3$-mediated acylation of but-1-en-3-ynes such as **106** to give mixtures of allenyl ketones of type **107** and 1,2-addition products such as **108** have been published several times (Scheme 7.16) [144, 145]. In the case of other substitution patterns of the starting enynes, the stereochemistry of the resulting allenyl ketones was investigated [146].



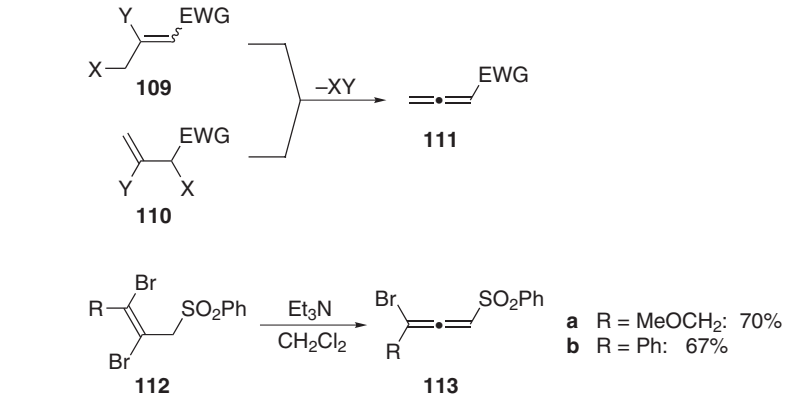
106 **107** 60% **108** 19%

Scheme 7.16

Not only electrophilic 1,4-addition, as shown above, but also radical 1,4-addition to conjugated enynes such as selenosulfonation is known to yield acceptor-substituted allenes [118]. Finally, monotitanation of conjugated diynes followed by treatment with benzaldehyde and aqueous workup leads to an ester of penta-2,3,4-trienoic acid, which is formally also a product of 1,4-addition [147].

7.2.8
Elimination and Cleavage Reactions

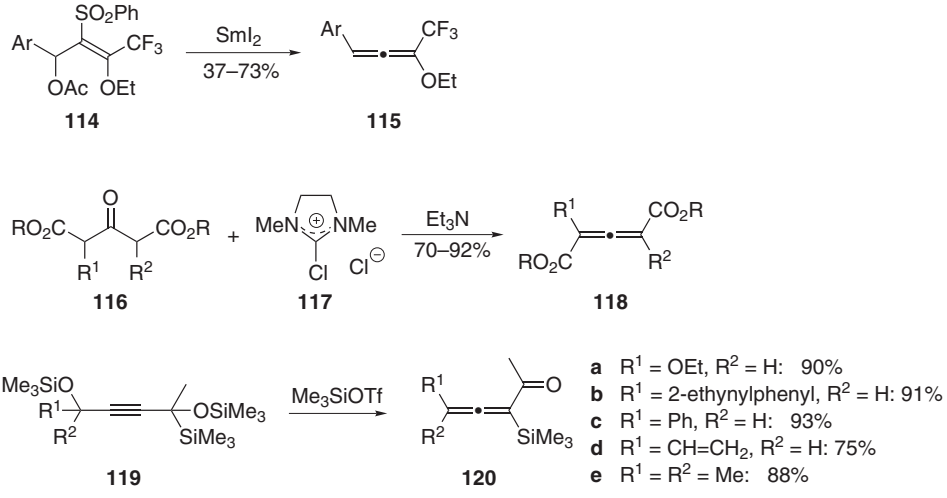
Starting with precursors of type **109**, β-elimination of the groups X and Y leads to the formation of the terminal C=C bond of the products **111**, that is the double bond of the allene which is not conjugated with the EWG (Scheme 7.17). In most cases, a base is used to split off XY with Y often representing Cl, Br, I and with X = H. For example, allenic aldehydes [148], allenyl ketones [149, 150] or allenyl sulfones [151] are formed by this route. Diethyl phosphate, when using enol phosphates [152] or benzeneselenenic acid (PhSeOH), generated by decomposition of vinyl selenoxides [153–155] arising from oxidation of the corresponding seleno ethers, can also be the molecules XY to split off. If starting compounds of type **110** are chosen, the non-terminal (internal) double bond of product **111** is formed by β-elimination. In this way, allenic esters [156] are prepared by removal of hydrochloric acid and allenyl sulfones [155] are formed by the oxidation–elimination route from vinyl selenides mentioned above. In almost all cases of starting materials **109** and **110**, Y means a leaving group and X stands for H. Only this orientation allows one to utilize the enhanced acidity of the protons, caused by the acceptor-substituent EWG, to split off HY. For example, elimination reaction of starting material **112**,



Scheme 7.17

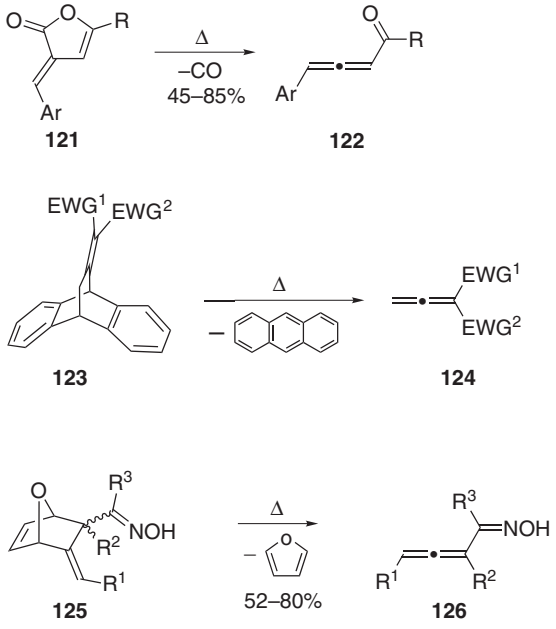
easily accessible from bromine and the appropriate propargyl compounds, leads to the allenes **113** [59].

The elimination reactions of β-acetoxy sulfones **114** to give the donor–acceptor-substituted allenes **115** by a Julia–Lythgoe process are less conventional (Scheme 7.18) [157]. A new one-step synthesis of allene-1,3-dicarboxylates **118** from acetone derivatives **116** was developed by the use of 2-chloro-1,3-dimethylimidazolinium chloride **117** [158, 159]. This elimination of water follows also the general Scheme 7.17 if a derivative of the enol, resulting from **116**, is assumed as an intermediate for an elimination step. More complex processes of starting materials **119** furnished allenyl ketones **120** in high yields [160–162].



Scheme 7.18

Another method to prepare allenyl ketones uses flash vacuum pyrolysis of the heterocycles **121** (Scheme 7.19) [163]. This elimination of carbon monoxide is at least formally a cheletropic reaction. Highly reactive allenes such as esters and nitriles of type **124** or unsubstituted butadienal can be generated if retro-Diels–Alder reaction of **123** or similar precursors, respectively, is performed by flash vacuum pyrolysis [164].



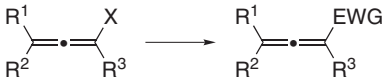
Scheme 7.19

The analogous transformation of **125**, also realized by flash vacuum pyrolysis, gave rise to allenic oximes **126** [165], which are not directly accessible by the classical route starting from allenyl ketones and hydroxylamine (see Section 7.3.2) [122]. Because compounds **125** are prepared from allenyl ketones and furan by [4 + 2]-cycloaddition followed by treatment with hydroxylamine, the retro-Diels–Alder reaction **125** → **126** is in principle the removal of a protecting group (see also Scheme 7.46).

7.2.9
Introduction of the Acceptor Substituent into the Allene

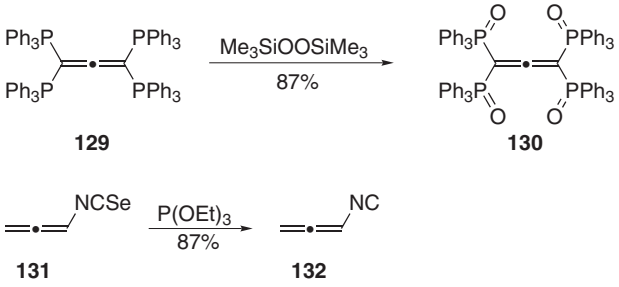
The functionalized allenes **127** bearing the group X, which does not have the properties of an EWG, can be transformed into the target allenes **128** by several different methods (Scheme 7.20). The oxidation of a functional group is one of the mainly used possibilities to generate an acceptor from a non-acceptor substituent. Many examples exist of the oxidation of primary and secondary alcohols [**127**,

X = CH(OH)R] to butadienals [166–168] and allenyl ketones [137, 169–171], respectively. Using particularly the Swern or Dess–Martin oxidation methods, very high yields can be achieved [166, 172, 173].



Scheme 7.20

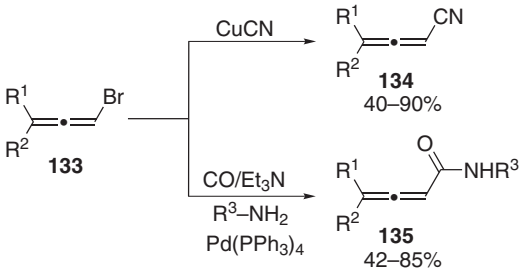
Schmidbaur and co-workers were successful in synthesizing the allene **129**, which could be converted to the fourfold phosphane oxide **130** and also to the analogous thio and seleno compounds (Scheme 7.21) [174–178]. Not only the addition but also the removal of chalcogens can contribute to the introduction of EWGs, as shown in the example **131** → **132** [179]. The photolysis of a 4-azidobuta-1,2-diene including the hydrolysis of the resulting imine to the aldehyde can also be used to generate the target allenes [180].



Scheme 7.21

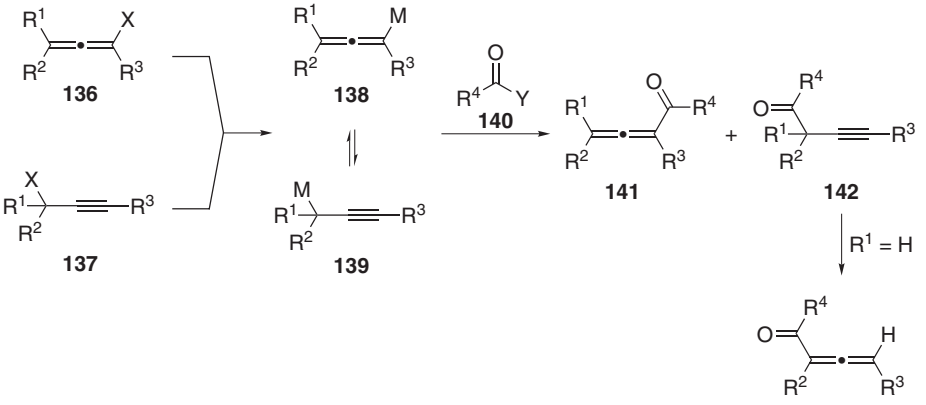
Starting with bromoallenes **133**, nucleophilic substitution supported by the use of cuprous cyanide lead to cyanoallenes of type **134** (Scheme 7.22) [126, 131, 181]. Propargyl precursors and also cumulenes of type **133** can be utilized for palladium-catalyzed aminocarbonylation to give allenic amides **135** (cf. Section 7.2.6) [182].

The introduction of an acceptor group into an allene is successful not only if the precursor is attacked by a nucleophile (see **133** → **134**) but also if the allenic starting



Scheme 7.22

material itself, for example an organometallic compound **138**, is acting as a nucleophile (Scheme 7.23). Precursors of **138** are haloallenes (**136**, X = Br, I) or hydrocarbons (**136**, X = H) which are transferred to allenyllithium compounds (**138**, M = Li) by halogen-metal exchange or by deprotonation, respectively [183–185]. However, such lithium reagents are also available by multiple lithiation of the unsubstituted allene [186, 187] or by metal-metal exchange reactions [15]. In addition to allenyllithium compounds, allenylmagnesium bromide (**138**, M = MgBr) was also used [188] to react with the electrophile **140** to give products of type **141**. Instead of the precursors **136**, the propargyl compounds **137**, where X is mostly halogen, are often applied to synthesize the organometallic reagents. These are not only lithium [189] and magnesium [190] compounds but also zinc [191, 192], indium [193], mercury [36], aluminum [194] or boron [194] derivatives. In these cases, direct preparation of the reagents from the halogen compound and the metal represents a further method in addition to those already mentioned [195, 196]. The particular organometallic reagent can be either in the allene form **138** or a propargyl structure **139**. Even if spectroscopic data show a great ratio of the latter compounds within the equilibrium **138**⇄**139**, high yields of allenic products of type **141** can be achieved by reaction with electrophiles [194]. In other cases of the reaction with **140**, the amounts of homopropargylic compounds **142** obtained were much higher [191, 192]. These products can isomerize to the allenes **143** by prototropic rearrangement (cf. Section 7.2.2) during their synthesis if $R^1 = H$ [190]. The cumulene obtained in this way is isomeric with **141** only for $R^2 \neq R^3$. The electrophiles **140**, used for the reaction with the organometallic reagents **138**/**139**, are acyl chlorides [191, 192], partially in the presence of aluminum trichloride [36], but also acyl cyanides [193], carboxylic esters [188] and amides [183], especially dimethylformamide [184, 189], as well as carboxylates [186, 187], to give allenic aldehydes and ketones of type **141**. In addition to **140**, carbon dioxide [15, 185, 194] and isocyanates [190] can also be applied as electrophiles to generate carboxylic acids and their amides, respectively. Instead of common organometallic reagents, a propargylsilane (**139**, M = $SiMe_3$) can be transferred

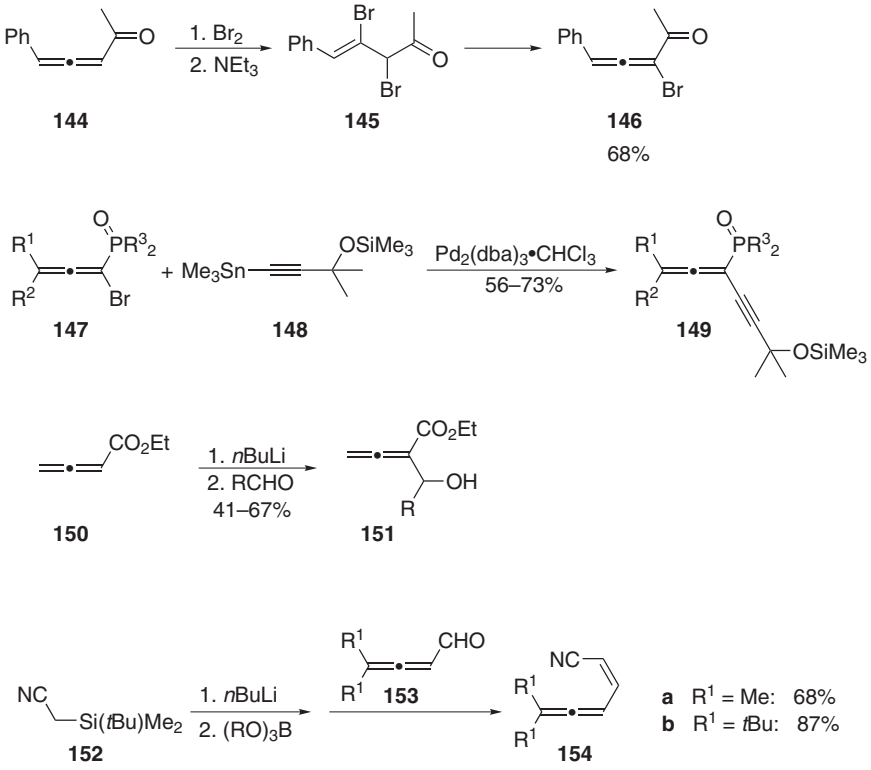


Scheme 7.23

to the allenyl ketone **141** in the presence of acetyl chloride and aluminum trichloride [197]. Finally, acceptor-substituted allenes were also prepared via **138**/**139** starting from **137** which contained the EWG $R^1 = CF_3$ [198].

7.2.10
Synthesis from Other Acceptor-substituted Allenes

Several trivial but highly useful reactions are known to convert one acceptor-substituted allene into another. For example, the transformation of allenic carboxylic acids is possible both via the corresponding 2,3-allenoyl chlorides or directly to 2,3-allenamides [182, 185]. Allenylimines were prepared by condensation of allenyl aldehydes with primary amines [199]. However, the analogous reaction of allenyl ketones fails because in this case the nucleophilic addition to the central carbon atom of the allenic unit predominates (cf. Section 7.3.1). Allenyl sulfoxides can be oxidized by *m*-CPBA to give nearly quantitatively the corresponding allenyl sulfones [200]. The reaction of the ketone **144** with bromine yields first a 2:1 mixture of the addition product **145** and the allene **146**, respectively (Scheme 7.24). By use of triethylamine, the unitary product **146** is obtained [59]. The allenylphosphane oxides and allene-



Scheme 7.24

phosphonates **147** with R^3 = Ph and R^3 = OEt, respectively, underwent Stille cross-coupling on treatment with stannylalkyne **148** to give ynallenes **149** [83]. Treatment of ester **150** with *n*-butyllithium at low temperature followed by reaction with aldehydes gave moderate yields of the alcohols **151**. The same transformation, which is like the Baylis–Hillman reaction, can also be performed if DABCO is used as a catalyst instead of *n*-butyllithium [201]. Furthermore, analogous modifications of allenyl sulfoxides are possible by metallation with *n*-butyllithium followed by the reaction with a variety of electrophiles [202]. Condensation reactions of **152** and butadienals **153** afforded the enallenes **154**, which are not simply acceptor-substituted allenes but vinyl analogues of these target allenes [203].

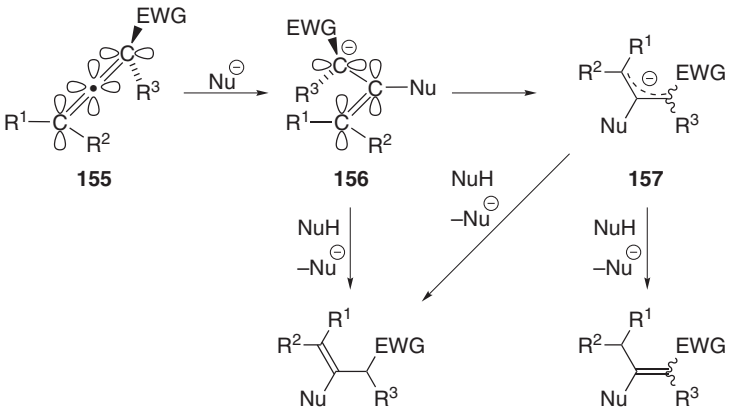
7.3 Reactions of Acceptor-substituted Allenes

The reactions of acceptor-substituted allenes are as manifold as their syntheses. The electron deficiency of the 'inner' C=C double bond prove to be the predominating property of these allenes. Therefore, nucleophilic addition at the central carbon atom is an important first step inducing many reactions of the electron-deficient allenes.

7.3.1 Nucleophilic Addition

The nucleophilic addition of alcohols [130, 204–207], phenols [130], carboxylates [208], ammonia [130, 209], primary and secondary amines [41, 130, 205, 210, 211] and thiols [211–213] was used very early to convert several acceptor-substituted allenes **155** to products of type **158** and **159** (Scheme 7.25, Nu = OR, OAr, O_2CR, NH_2, NHR, NRR′ and SR). While the addition of alcohols, phenols and thiols is generally carried out in the presence of an auxiliary base, the reaction of allenyl ketones to give vinyl ethers of type **159** (Nu = OMe) is successful also by irradiation in pure methanol [214]. Using widely varying reaction conditions, the addition of hydrogen halides (Nu= Cl, Br, I) to the allenes **155** leads to reaction products of type **158** [130, 215–220]. Therefore, this transformation was also classified as a nucleophilic addition. Finally, the nucleophiles hydride (such as lithium aluminum hydride–aluminum trichloride) [211] and azide [221] could also be added to allenic esters to yield products of type **159**.

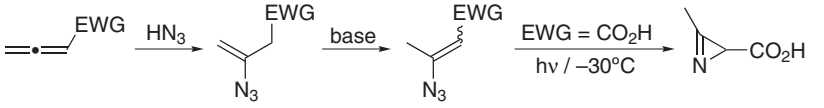
It was recognized in early examples of nucleophilic addition to acceptor-substituted allenes that formation of the non-conjugated product **158** is a kinetically controlled reaction. On the other hand, the conjugated product **159** is the result of a thermodynamically controlled reaction [205, 215]. Apparently, after the attack of the nucleophile on the central carbon atom of the allene **155**, the intermediate **156** is formed first. This has to execute a torsion of 90° to merge into the allylic carbanion **157**. Whereas **156** can only yield the product **158** by proton transfer, the protonation of **157** leads to both **158** and **159**.



Scheme 7.25

The formal addition of hydrazoic acid to the simple acceptor-substituted allenes **160a–e** yielded first the isolable vinyl azides **161a–e**, which isomerize under basic reaction conditions to the conjugated products **162a–e** (Scheme 7.26) [81]. Some of the final products of type **162** were prepared earlier from the allenes **160** without observing the intermediates **161** [221–223]. In the case of the carboxylic acid **160a**, the almost neutral reaction conditions facilitate the isolation of **161a** during the reaction with sodium azide in water or aqueous acetic acid [81]. In the presence of sodium hydroxide, **161a** rearranges to **162a** irreversibly. By photolysis, the latter vinyl azide yields racemic azirinomycin **163a** [81], a well-known [224, 225], antibiotically active natural product. The succeeding reaction **161** → **162** can be suppressed if the allenes **160b–e** were reacted with sodium azide not in pure DMF but in a mixture of DMF and acetic acid or by use of less basic *N*,*N*,*N*′,*N*′-tetramethylguanidinium azide (TMGA).

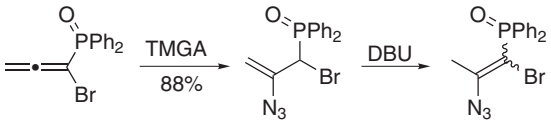
Electron-deficient allenes bearing additional substituents do not behave in all cases completely analogously to the parent compounds **160a–e**. Whereas **160f** reacts with TMGA first to give the isolable intermediate **161f** [81] and then to the final product **162f**, the analogous reaction of **160g** yields only the product **162g** without a detectable intermediate [59]. On the other hand, especially high yields of the vinylazides **161h–k** are obtained if the sulfonylallenes **160h–k** are treated with TMGA [59].



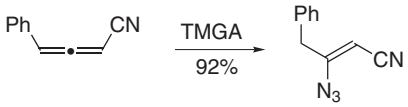
160 **161** **162** **163a**

(±)-azirinomycin

a EWG = CO_2H **d** EWG = $P(O)Ph_2$
b EWG = CO_2Et **e** EWG = CN
c EWG = $P(O)(OEt)_2$



160f **161f** **162f**



160g **162g**

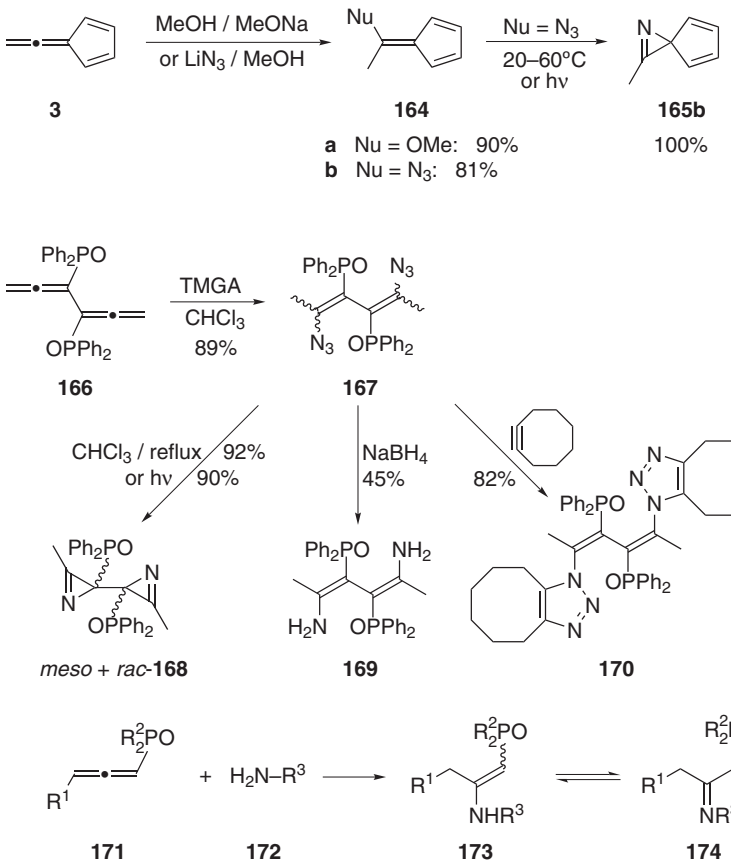
160 **161**

h R^1 = Me, R^2 = Cl, R^3 = Ph: 97% (*E*)/(*Z*) = 1.5
i R^1 = Me, R^2 = Cl, R^3 = Me: 98% (*E*)/(*Z*) = 3.3
j R^1 = $MeOCH_2$, R^2 = Br, R^3 = Ph: 95%
k R^1 = Ph, R^2 = Br, R^3 = Ph: 92%

Scheme 7.26

The addition of methanol or hydrazoic acid to ethenylidenecyclopentadiene **3** demonstrates that **3** behaves like an acceptor-substituted allene (Scheme 7.27) [226, 227]. More examples of nucleophilic additions to alkyl-substituted derivatives of **3** were reported by Hafner [228]. Photoelectron spectroscopy of the spirocyclic compound **165b**, easily accessible from azide **164b**, shows that the lone-pair orbital n(N) of the 2*H*-azirine nitrogen atom interacts strongly with the π_1-orbital of the cyclopentadiene ring [227].

Treatment of diallene **166** with TMGA allows access to the long-sought [229] 1,4-diazidobuta-1,3-dienes [81], which are obtainable by an alternative route only with effort [230]. Compound **167** can be used for several interesting succeeding reactions, for example the thermal or photochemical generation of bi-2*H*-azirin-2-yls *meso*- and *rac*-**168**. Recrystallizing the mixture of the geometric isomers of **167** gives easily



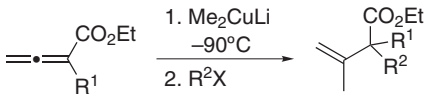
Scheme 7.27

pure (*E*,*E*)-**167**, which yields the enamine **169** after reduction with sodium borohydride and the cycloaddition product **170** on treatment with cyclooctyne [81, 104].

Whereas the reactions of allenephosphonates **171** (R^2 = OEt) with primary aliphatic and aromatic amines **172** and the reactions of the phosphane oxides **171** (R^2 = Ph) with aliphatic amines **172** afford the conjugated addition products **173** always in good yields, the addition of anilines to **171** (R^2 = Ph) leads to an equilibrium of the products **173** and **174** [231]. However, treatment of both phosphane oxides and phosphonates of type **171** with hydroxylamines **172** ($R^3 = OR^4$) yields only the oximes **174** [232, 233]. The analogous reaction of the allenes **171** with diphenylphosphinoylhydrazine furnishes hydrazones of type **174** [$R^3 = NHP(O)Ph_2$] [234].

The attack of carbon nucleophiles such as Grignard reagents [116, 235, 236], cuprates [183, 237–242] and C–H acidic compounds [212] on allenes **155** leads generally to the non-conjugated products **158**. However, it was observed early that **158** is the product of a kinetically controlled reaction also in these cases, whereas the thermodynamically more stable product **159** is formed at longer reaction times or subse-

quently by prototropic isomerization [240]. If the reaction mixture resulting from the attack of an organometallic reagent on allene **155** is worked up not with water but first with a carbon electrophile such as an alkyl halide [241] or carbon dioxide [236], the products obtained instead of compound **158** are formed by multiple C,C bond linking. For example, the successsive application of lithium dimethylcuprate and alkylating reagent (R^2X = MeI or CH_2=$CHCH_2Cl$) to the allenic esters **175** furnishes the products **176** in good yields (Scheme 7.28) [241].

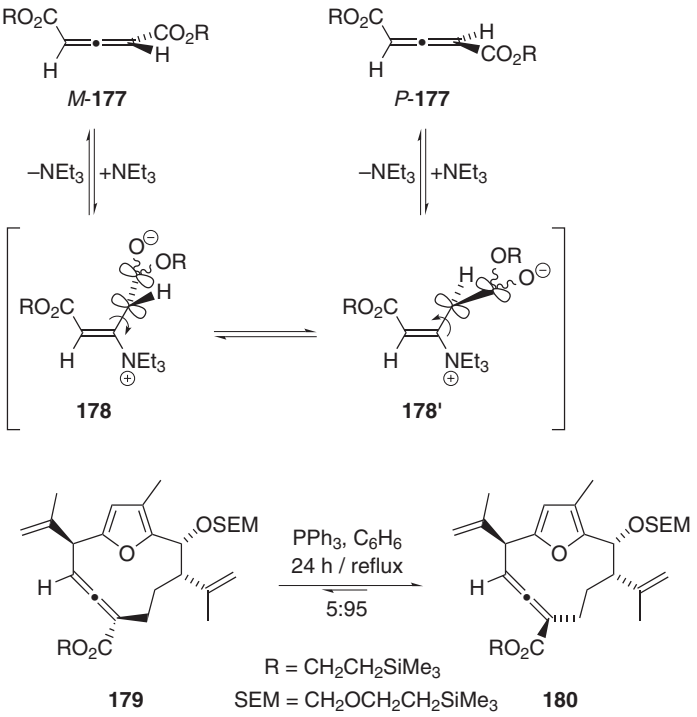


175 75–95% **176**

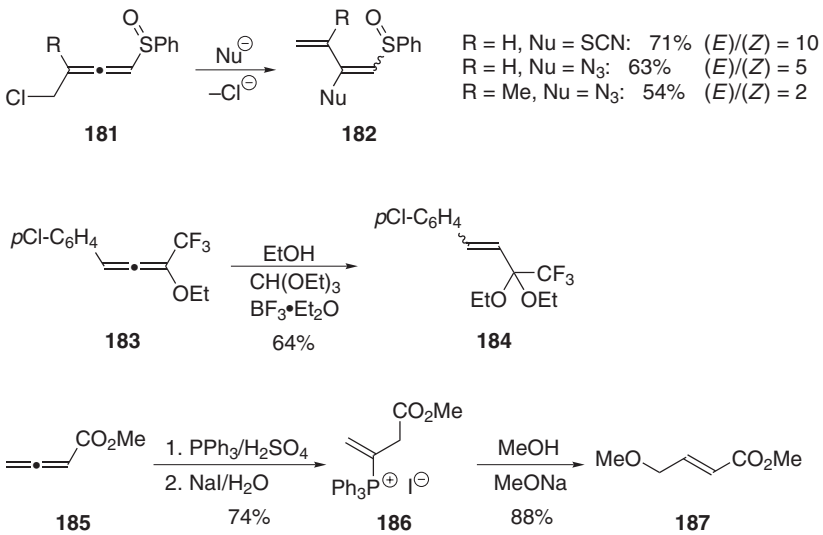
Scheme 7.28 R^1 = H, Me

Based on nucleophilic addition, racemic allenyl sulfones were partially resolved by reaction with a deficiency of optically active primary or secondary amines [243]. The reversible nucleophilic addition of tertiary amines or phosphanes to acceptor-substituted allenes can lead to the inversion of the configuration of chiral allenes. For example, an optically active diester **177** with achiral groups R can undergo a racemization (Scheme 7.29). A 4:5 mixture of (*M*)- and (*P*)-**177** with R = (–)-L-menthyl, obtained through synthesis of the allene from dimenthyl 1,3-acetonedicarboxylate (cf. Scheme 7.18) [159], furnishes (*M*)-**177** in high diastereomeric purity in 90% yield after repeated crystallization from pentane in the presence of catalytic amounts of triethylamine [158]. Another example of a highly elegant epimerization of an optically active allene based on reversible nucleophilic addition was published by Marshall and Liao, who were successful in the transformation **179** → **180** [35]. Recently, Lu et al. published a very informative review on the reactions of electron-deficient allenes under phosphane catalysis [244].

The attack of the nucleophile on the acceptor-substituted allene usually happens at the central sp-hybridized carbon atom. This holds true also if no nucleophilic addition but a nucleophilic substitution in terms of an S_N2' reaction such as **181** → **182** occurs (Scheme 7.30) [245]. The addition of ethanol to the allene **183** is an exception [157]. In this case, the allene not only bears an acceptor but shows also the substructure of a vinyl ether. A change in the regioselectivity of the addition of nucleophilic compounds NuH to allenic esters can be effected by temporary introduction of a triphenylphosphonium group [246]. For instance, the ester **185** yields the phosphonium salt **186**, which may be converted further to the ether **187**. Evidently, the triphenylphosphonium group induces an electrophilic character at the terminal carbon atom of **186** and this is used to produce **187**, which is formally an abnormal product of the addition of methanol to the allene **185**. This method of umpolung is also applicable to nucleophilic addition reactions to allenyl ketones in a modified procedure [246, 247].

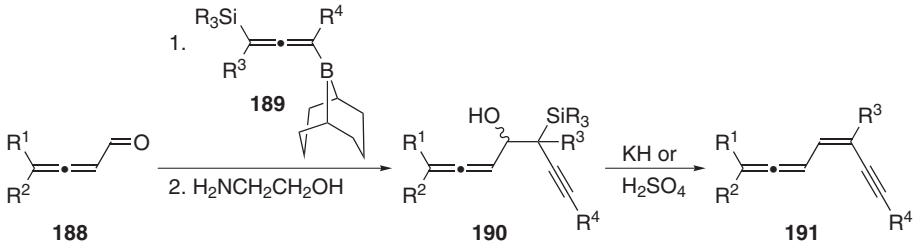


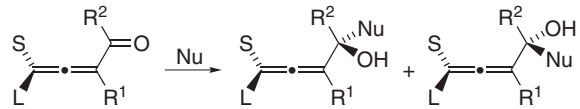
Scheme 7.29



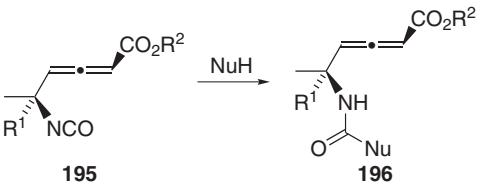
Scheme 7.30

The nucleophilic attack on an acceptor-substituted allene can also take place at the acceptor itself, especially in the case of carbonyl groups of aldehydes, ketones or esters. Allenic esters are reduced to the corresponding primary alcohols by means of diisobutylaluminum hydride [18] and the synthesis of a vinylallene (allenene) by Peterson olefination of an allenyl ketone has also been reported [172]. The nucleophilic attack of allenylboranes **189** on butadienals **188** was investigated intensively by Wang and co-workers (Scheme 7.31) [184, 203, 248, 249]. The stereochemistry of the obtained secondary alcohol **190** depends on the substitution pattern. Fortunately, the synthesis of the desired *Z*-configured hepta-1,2,4-trien-6-ynes **191** is possible both by *syn*-elimination with the help of potassium hydride and by *anti*-elimination induced by sulfuric acid. Analogous allylboranes instead of the allenes **189** can be reacted also with the aldehydes **188** [250].





a R^2 = H
b R^2 = Me



a [Nu = PhNH]: 38%
a [Nu = N_3]: 42%
b [Nu = Me_2CHNH]: 97%
b [Nu = $CH(CO_2Et)_2$]: 59%

a R^1 = Me, R^2 = *t*Bu
b R^1 = H, R^2 = Et

Scheme 7.31

Not only the stereochemistry of the products of a nucleophilic attack on the central carbon atom of electron-deficient allenes [211] but also the stereochemical result after the nucleophilic addition to the carbonyl group of chiral butadienals and allenyl ketones have been investigated [167]. Only in some cases of very large discrimination between the small group S and the large group L, e.g. S = H and L = *t*Bu or S = Me, *n*Bu and L = *t*BuPh$_2$Si, high diastereoselectivities in favor of the product **193** are observed during the reaction of **192a** with methyllithium or Grignard reagents and on treatment of **192b** with lithium tri-*sec*-butylborohydride.

Finally, the attack of a nucleophile can fail to occur both on the electron-deficient allene and on the acceptor, and instead of this it can take place at another part of the substrate. For example, the allenic esters **195** yield products of type **196** by addition of different nucleophiles at the more reactive isocyanato group [120].

7.3.2 Nucleophilic Addition Including Ring Closure

Different strategies all including nucleophilic addition to acceptor-substituted allenes have been used for the synthesis of cyclic compounds, mostly heterocycles. Thus, it is obvious to release a nucleophile already existing within the allenic compound in a protected form. For example, treatment of silyl ethers **197** with tetrabutylammonium fluoride (TBAF) leads to the intermediates **198**, which yield the dihydrofurans **199** by nucleophilic addition (Scheme 7.32) [251].

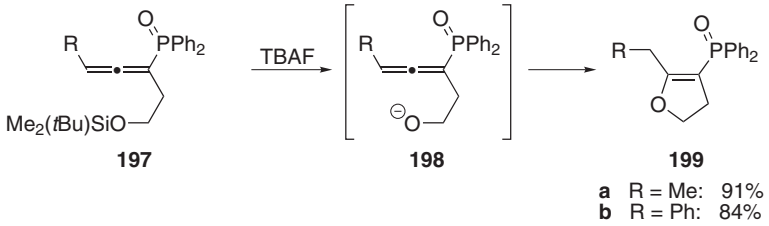
However, an existing nucleophile can also cause the ring closure after building up the electron-deficient allene. By methoxycarbonylation (cf. Section 7.2.6) of ethynyloxiranes **200**, the allenic esters **201** are formed first, which react immediately to give the heterocycles **202** or **203**, depending on the substitution pattern of the starting material [138].

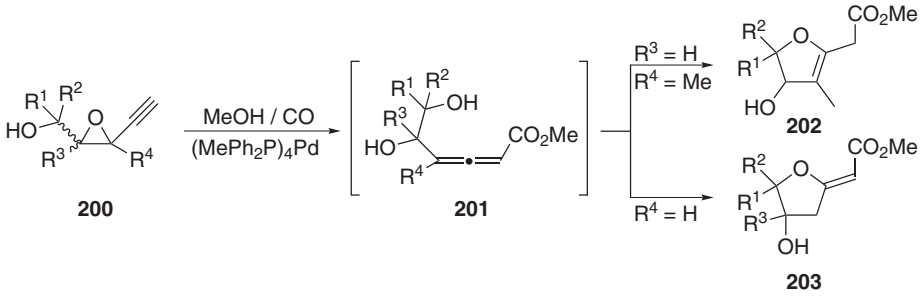
The heterocycles **205** are accessible by addition of the reagents NuH$_2$, acting as double nucleophiles, to the diallenes **204** [104]. Compound **206** can also be prepared by this method and C,H-acidic compounds can serve as double nucleophiles as well.

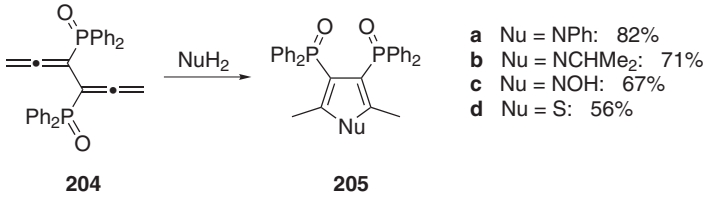
It was recognized early that reagents such as hydroxylamines and hydrazines, also reacting twice as nucleophiles, lead to isoxazoles and pyrazoles, respectively, by reaction with cyanoallenes [130]. The analogous reactions of hydrazines or hydroxylamine with allenyl ketones to give pyrazoles [252] or isoxazoles [122], respectively, is also well-known. In these cases, after the nucleophilic attack on the central carbon atom of the allene, a second attack follows on the cyano group or the carbonyl group. Thus, the formation of heterocycles such as **209** is easy to understand with the help of the intermediate **208** (Scheme 7.33) [253]. If phenylhydrazine instead of hydrazine is used, an additional [3,3]-sigmatropic rearrangement can lead to a different reaction path. In this case the indole derivative **213** results and the reaction shows strong similarities to the Fischer indole synthesis [254].

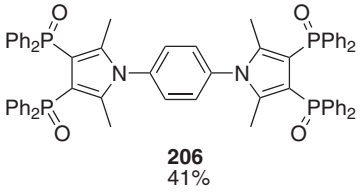
The transfer of such sequences to various acceptor-substituted allenes **214** and to *O*-deprotonated *N*-phenylhydroxylamines **215** was investigated thoroughly by Blechert [255, 256]. After the nucleophilic addition forming the intermediate **216**, the [3,3]-sigmatropic isomerization takes place at low temperature in only a few minutes

owing to the weak N–O bond, the formation of a C=O bond and the acceleration by a carbanion. The ketones **218** can be isolated or they are converted directly by a one-pot procedure to the indoles **219**. If both *ortho*-positions (positions 2 and 6) of **215** are substituted, e.g. by methyl groups, rearomatization by tautomerism of **217** is impossible. Thus, instead of **218**, the indan-2-one derivatives **220** or **221** are formed via intramolecular attack of the carbanion **217** at position 1 or 3, respectively [257, 258].

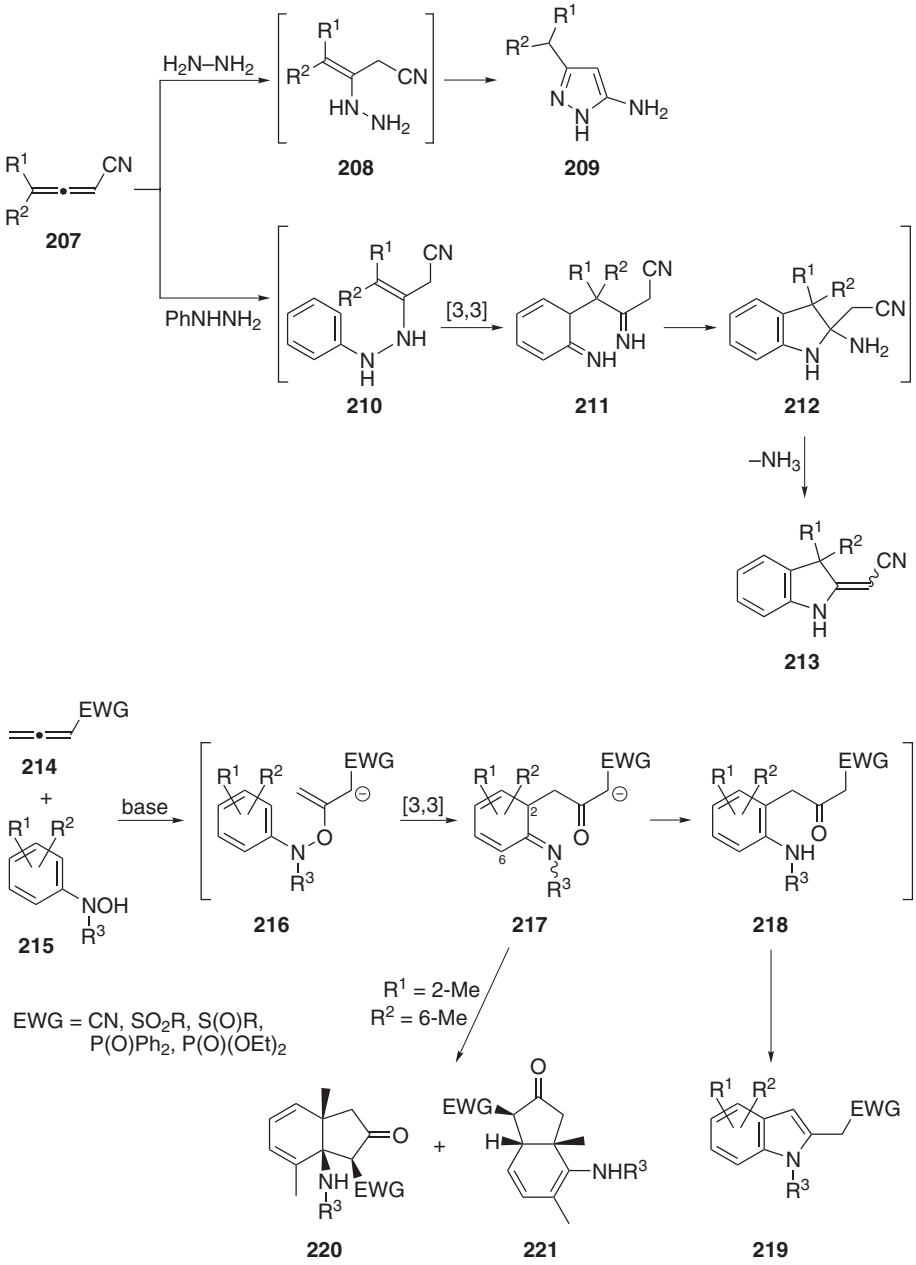




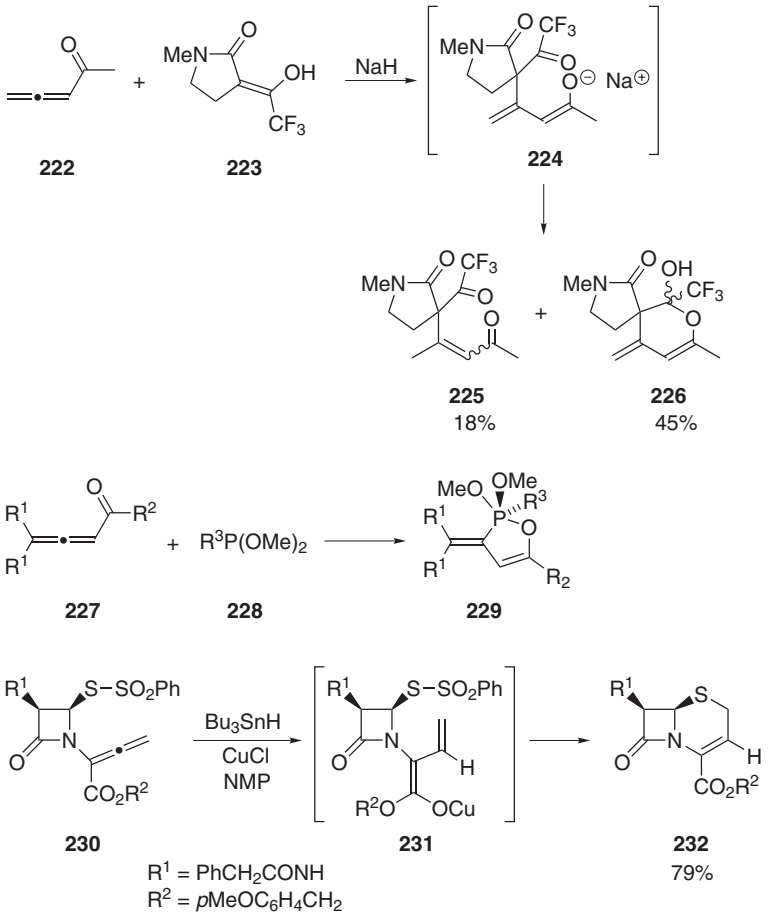




Scheme 7.32


H2N–NH2
PhNHNH2
[3,3]
–NH3
base
EWG = CN, SO2R, S(O)R, P(O)Ph2, P(O)(OEt)2
R1 = 2-Me
R2 = 6-Me
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221

Scheme 7.33



Scheme 7.34

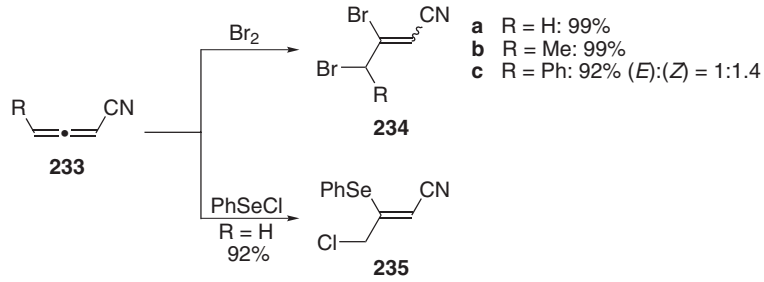
Intermediates such as **224** resulting from the nucleophilic addition of C,H-acidic compounds to allenyl ketones such as **222** do not only yield simple addition products such as **225** by proton transfer (Scheme 7.34) [259]. If the C,H-acidic compound contains at least one carbonyl group, a ring closure is also possible to give pyran derivatives such as **226**. The reaction of a similar allenyl ketone with dimethyl malonate, methyl acetoacetate or methyl cyanoacetate leads to α-pyrones by an analogous route; however, the yields are low (20–32%) [260]. The formation of oxaphospholenes **229** from ketones **227** and trivalent phosphorus compounds **228** can similarly be explained by nucleophilic attack at the central carbon atom of the allene followed by a second attack of the oxygen atom of the ketone at the phosphorus atom [261, 262]. Treatment of the allenic ester **230** with copper(I) chloride and tributyltin hydride in *N*-methylpyrrolidone (NMP) affords the cephalosporin derivative **232** [263]. The authors postulated a Michael addition of copper(I) hydride to the electron-

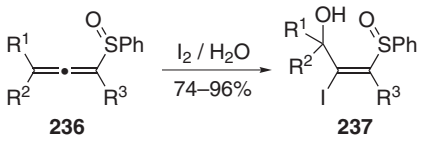
deficient allene **230** and a subsequent intramolecular nucleophilic attack of the resulting copper enolate **231** at the sulfur atom. In the case of allenylsulfonium salts, generated in situ by prototropic rearrangement of propargyl precursors, double nucleophilic attack of enolates stabilized by conjugative groups leads to highly substituted furans [264, 265]. Finally, the double nucleophilic attack at the central carbon atom of the electron-deficient allene also gives heterocyclic products. Landor and co-workers [266–268] reported on the reactions of cyanoallenes with ethylene- and *o*-phenylenediamines and several other double nucleophiles which yield 2-alkylimidazolines and 2-alkylbenzimidazoles or further heterocycles, respectively, by elimination of one molecule of acetonitrile.

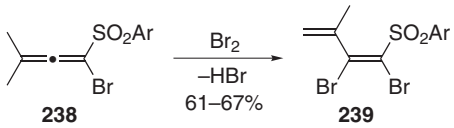
7.3.3 Electrophilic Addition

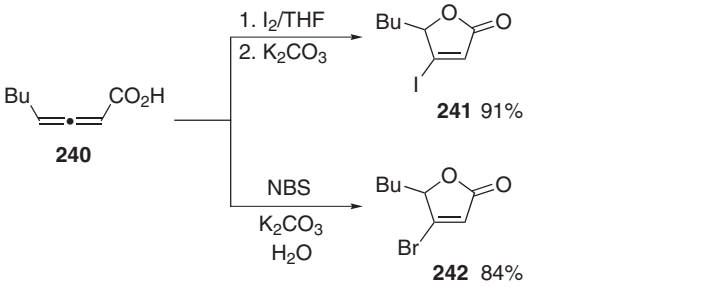
Because the nucleophilic addition to acceptor-substituted allenes occurs usually at the electron-deficient 'inner' C=C double bond, at least for the primary step, it is obvious that electrophilic additions take place at the more electron-rich 'terminal' C=C double bond. This is indeed observed, for example, during the electrophilic addition of bromine or other halogens or phenylselenenyl chloride to the cyanoallenes **233** (Scheme 7.35) [59, 81, 130]. The bromination of allenic esters [269] and the iodination of allenephosphonates [41] run in a similar way. In only a few cases, a competitive electrophilic addition also to the C=C double bond conjugated to the acceptor has been reported [270]. Not only during the formation of **235** [81], but also during the iodohydroxylation **236** → **237** [271], the electrophilic group is transferred to the central carbon atom of the allene furnishing good yields and also excellent regio- and stereoselectivity.

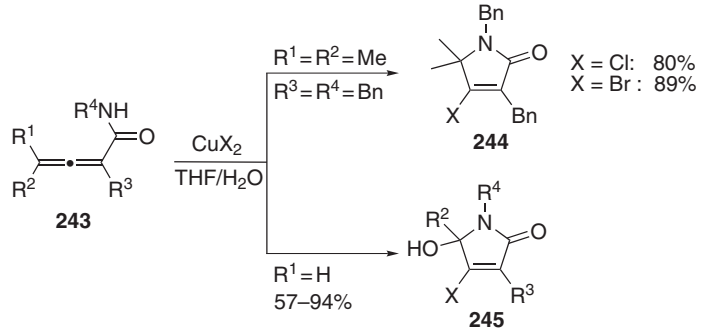
The bromination of allenyl sulfones **238** is connected with elimination of hydrogen bromide yielding the 1,3-dienes **239** [79]. The electrophilic addition to electron-deficient allenes forming five-membered heterocycles was investigated early by several working groups using the examples of allenic sulfones [272], esters and sulfinates [111, 273] and also allenic phosphonic acids [87] and allenephosphonates [274–277]. Not only oxaphospholenes [79, 278] are readily available, as shown by newer examples of such ring closure reactions, but also access to butenolides or imino lactones starting from allenic esters or amides and iodine monobromide, respectively, has been demonstrated [139]. The β-halobutenolides **241** and **242** can be prepared in good yields from the carboxylic acid **240** [279]. Analogous products are obtained on treatment of allenic acids with copper(II) halides [280, 281] and even similar iodolactonizations to give β-iodobutenolides are possible starting with appropriate esters and iodine monobromide [15]. In both cases, the chirality of the allenes can be transferred effectively to the β-halobutenolides. If allenic amides **243** are treated with copper(II) chloride or bromide, the structure of the heterocyclic product depends on the substitution pattern of the starting material. Allenes **243** with R^1, $R^2 \neq H$ afford 4-halopyrrol-2(5*H*)-ones such as **244**, whereas starting materials with at least $R^1 = H$ lead to compounds **245** by a sequential halolactamization–hydroxylation [282].


Br2
PhSeCl
R = H
92%
a R = H: 99%
b R = Me: 99%
c R = Ph: 92% (E):(Z) = 1:1.4
233
234
235


I2 / H2O
74–96%
236
237


Br2
–HBr
61–67%
238
239


1. I2/THF
2. K2CO3
NBS
K2CO3
H2O
240
241 91%
242 84%

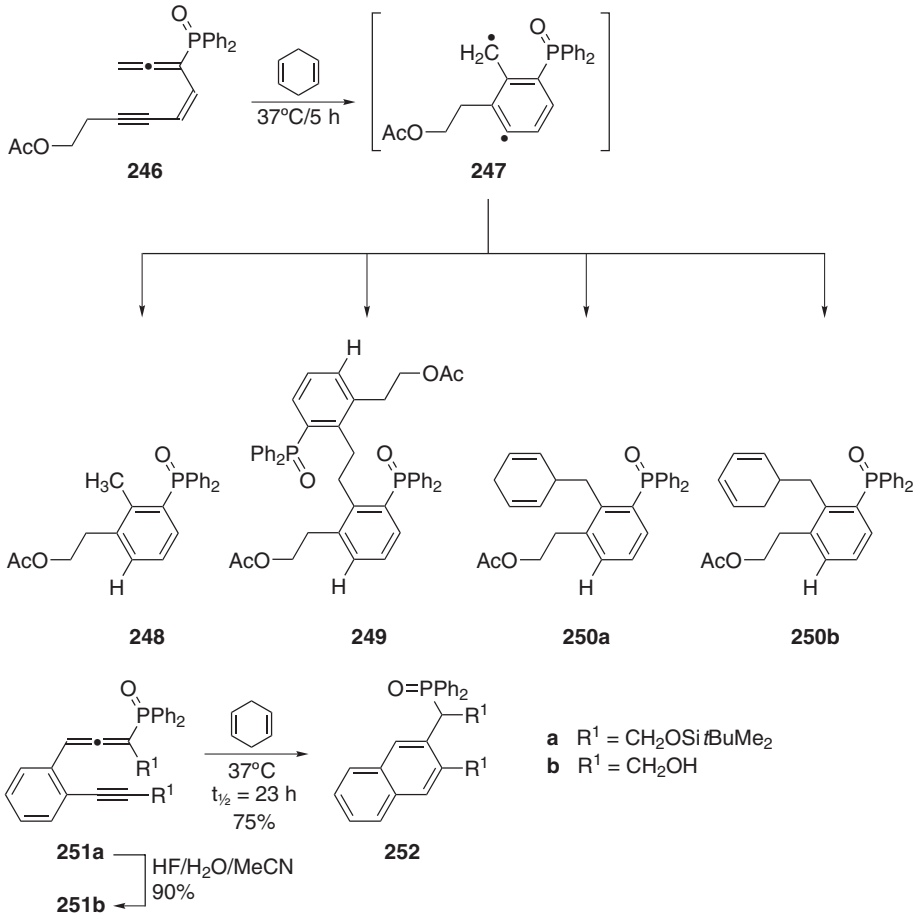

CuX2
THF/H2O
R1 = R2 = Me
R3 = R4 = Bn
R1 = H
57–94%
X = Cl: 80%
X = Br : 89%
243
244
245

Scheme 7.35

Less common addition reactions such as the bromination of trifluoromethyl-substituted butatrienes [30] or the reaction of tetrafluoroallene with boron trifluoride have also been reported [283]. Especially the interaction of phosphorylated allenes with electrophiles was summarized in a review by Alabugin and Brel [8], whereas Smadja [284] published a more general overview about the electrophilic addition to allenic derivatives.

7.3.4
Ring Closure to Form Carbocycles

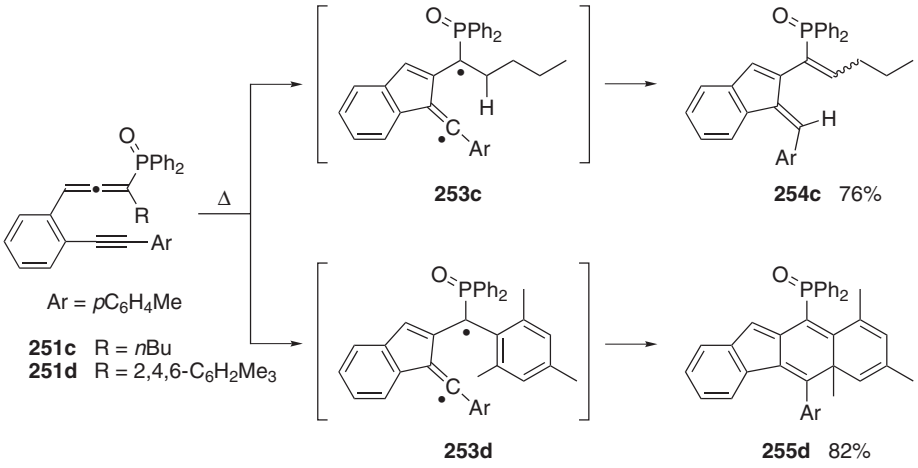
Allenes linked with a *cis*-but-1-en-3-ynyl or a 2-ethynylphenyl group can undergo a Meyers–Saito cycloaromatization [285–288]. The first examples of this ring closure include the reactions of allenylphosphane oxides suitable substituted such as **246** and **251** (Scheme 7.36) (see also Chapter 20).



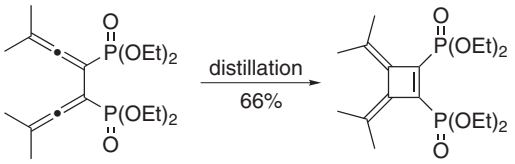
Scheme 7.36

At low temperatures in the presence of the hydrogen donor cyclohexa-1,4-diene, the substrate **246** furnishes the products **248** (32% yield), **249** (4%) and **250** (**250a**,**b** together 17%). They can be explained plausibly by a mechanism via the diradical intermediate **247** [289]. The transformation **251a** → **252** runs in a similar way with 75% yield [290]. It was mentioned early that such diradical intermediates of type **247** resemble the reactive benzenoid diradical species generated by Bergman-type cyclization [289]. Thus, conjugated *cis*-enyneallenes could act similarly to enediyne antibiotics [291, 292], such as neocarzinostatin, esperamicin and calichemicin, as antitumor antibiotics, by hydrogen abstraction from the DNA sugar backbone. Indeed, **251b** and related compounds show the expected properties of DNA cleavage and antitumor activity. These properties might not be caused by the hydrogen abstraction alone but also by the nucleophilic addition of DNA to the central carbon atom of the allene [290]. Starting materials such as **246** and **251** and a variety of similar [293] allenylphosphane oxides, which can be used for Meyers–Saito cyclization, were prepared from the reaction of propargyl alcohols with chlorodiphenylphosphane (see Section 7.2.3). However, allenyl sulfones bearing a 2-ethynylphenyl group [293] or analogous allenyl ketones [161] are also suitable for this cycloaromatization.

Schmittel and co-workers observed that the introduction of an aryl group at the acetylene terminus of 2-ethynylphenylallene changes the direction of the thermally induced ring closure reaction [294, 295]. For example, the substrates **251c** and **251d** cyclize to **254c** and **255d**, respectively, but these carbocycles are only the formal products of an intramolecular ene reaction and such a Diels–Alder reaction (Scheme 7.37). Thorough investigations show that **254c** and **255d** cannot be explained by a concerted mechanism but via the diradical intermediates **253c** and **253d**, respectively.

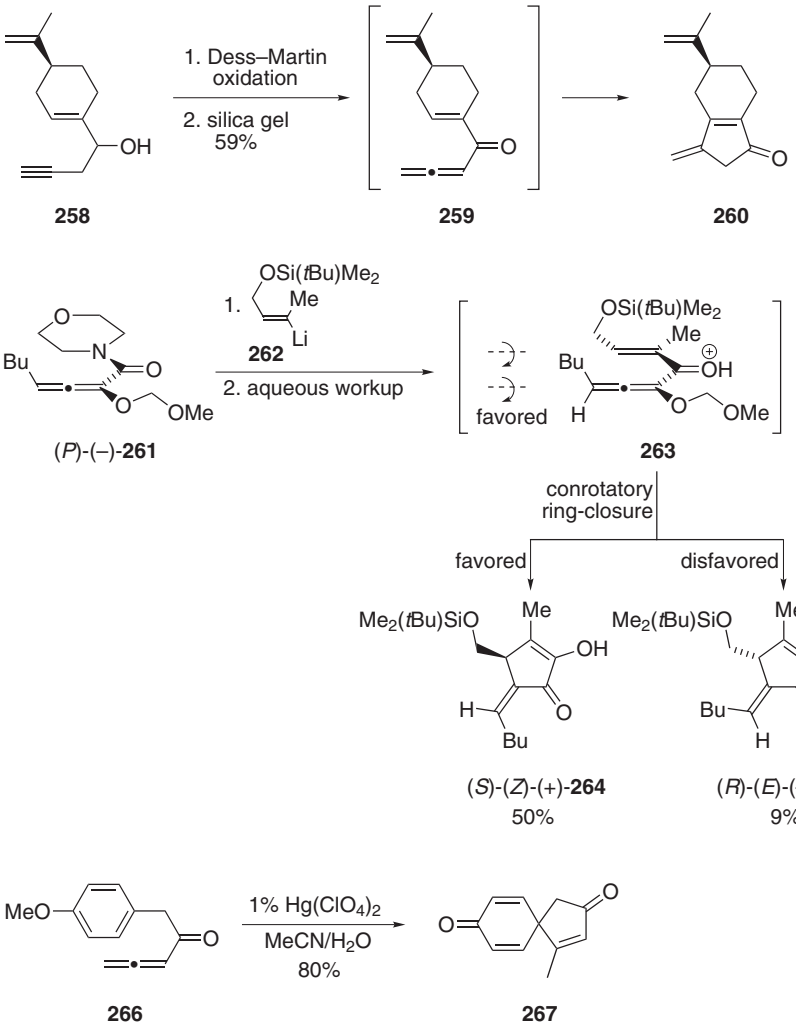


Scheme 7.37



256 **257**

Scheme 7.38



258 **259** **260**

(*P*)-(–)-**261** **263**

(*S*)-(*Z*)-(+)-**264** 50%

(*R*)-(*E*)-(–)-**265** 9%

266 **267**

Scheme 7.39

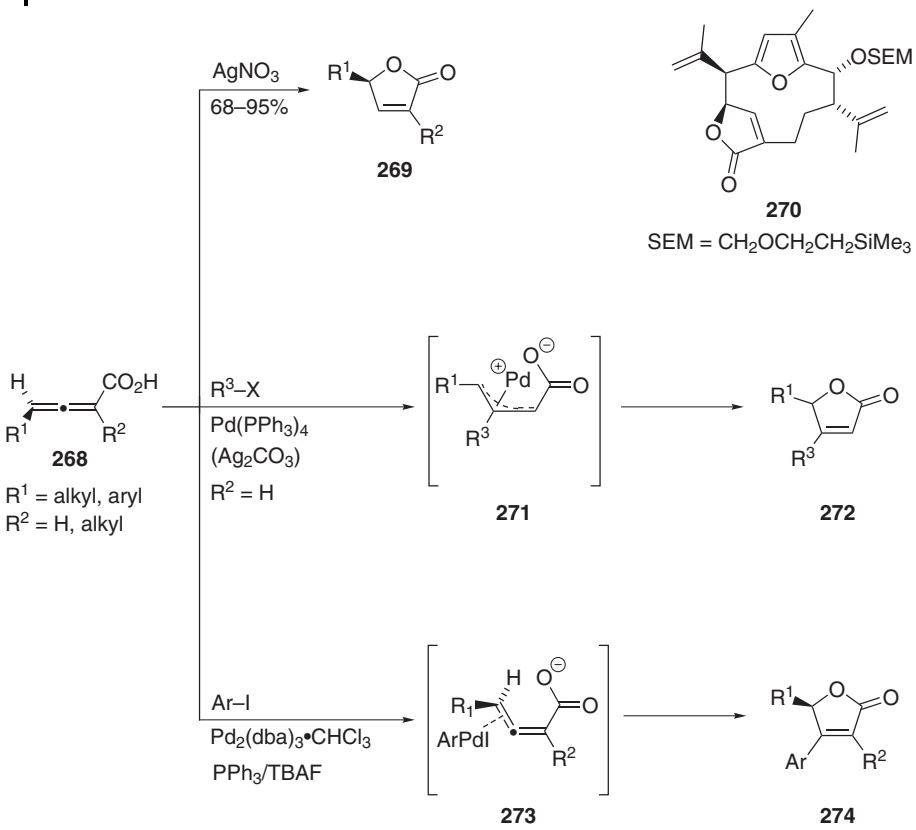
Diallenes such as **256** can lead to carbocycles by electrocyclic ring closure (Scheme 7.38) [80]. Whereas **257** is formed on distillation of **256** at ~160 °C, other diallenes cyclize at significantly lower temperatures to produce dimethylenecyclobutenes (see Scheme 7.7) [105].

Modified Nazarov cyclizations to transform allenyl vinyl ketones into cyclopent-2-enones were investigated by several groups [46, 185, 296]. In most cases, the former ketones were not isolated but transformed directly to carbocycles during workup. For instance, the Dess–Martin periodinane oxidation of the homopropargylic alcohol **258** yields the ketone **259** (cf. Section 7.2.2), which cyclizes to the product **260** in the presence of silica gel (Scheme 7.39) [46]. Highly efficient chirality transfer from an allene to tetrahedral carbon has also been realized during the course of a modified Nazarov cyclization. Thus, treatment of allene (*P*)-(–)-**261** with reagent **262** followed by aqueous workup gave a mixture of the major product (*S*)-(*Z*)-(+)-**264** and the minor product (*R*)-(*E*)-(–)-**265**. These results can be explained by two different conrotatory cyclization pathways of the intermediate **263** favoring torquoselectively the rotation of the butyl group to the outside [185]. Finally, ring closure of *p*-methoxybenzyl allenyl ketones such as **266** to yield spirocyclic diketones was successfully performed in the presence of catalytic amounts of Lewis acids which tolerate water [297].

7.3.5
Ring Closure to Produce Heterocycles

The transformation of functionalized allenes into heterocycles, especially to products with five-membered rings, is well-known and has been reviewed recently [298]. If the acceptor functionality of an electron-deficient allene includes a hydroxyl group, for example in the case of allenic phosphonic acids or carboxylic acids, oxygen heterocycles such as oxaphospholenes or butenolides, respectively, are formed. Cyclization of allene phosphonic acids, which is acid-catalyzed [86] or performed in the presence of epoxidation reagents [299], was already investigated extensively by Macomber's group. The acid-catalyzed [300, 301] or base-induced [301] isomerization of phenyl-substituted allenic carboxylic acids, which are generated in situ by hydrolysis of esters in some cases, is an even older method to produce butenolides. The transfer of the chirality of the allenes to the cyclization products is successful only in favorable cases [302, 303]. On the other hand, the isomerization of allenic acids **268** (R^1 = alkyl; R^2 = H, alkyl) in the presence of silver nitrate, introduced by Marshall et al., furnishes not only the butenolides **269** in good to excellent yields but also allows additionally an effective transfer of the chirality to these products (Scheme 7.40) [15]. Starting from cyclic allenes, this ring closure reaction can also be used to synthesize bridged butenolides, for example the kallolide A precursor **270** (see also Scheme 7.29) [35, 137].

The ring closure to form butenolides by palladium(0) catalysis can be combined with C,C bond linking, as shown by Ma and co-workers. If using tetrakis(triphenylphosphane)palladium(0), the products **272** are obtained from **268** (R^1 = alkyl, R^2 = H) and vinyl iodides or aryl bromides and iodides R^3X [304]. The authors assume that



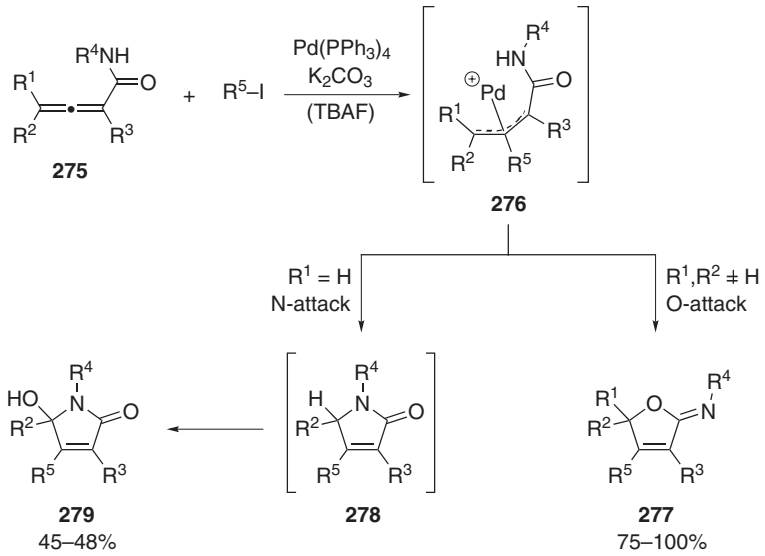
Scheme 7.40

the π-allylpalladium species **271** is formed after the oxidative addition of R^3X to the palladium(0) species and intramolecular carbopalladation of the allene. The yield of **272** can be increased to 59–79% by addition of silver carbonate. A 3-silverbut-2-enolide intermediate, as it could occur also during the isomerization **268** → **269**, is held responsible for this result. If the allenes **268** react with aryl iodides in the presence of tris(dibenzylideneacetone)dipalladium(0) chloroform adduct [$Pd_2(dba)_3 \cdot CHCl_3$], triphenylphosphane and tetrabutylammonium fluoride (TBAF), the resulting heterocycles **274** are obtained in yields of 55–90% [305]. In order to optimize the chirality transfer, the authors used to advantage, instead of **268**, its 1:1 salt, for example with Hünig's base or chinonidine, wherein the intermediate **273** should play a role.

By treatment of allenic esters with *N*-benzylideneaniline and boron trifluoride, ring closures to but-2-enolides with introduction of a carbon substituent at position 3 are also possible [306]. However, both the number of examples and the yields are low.

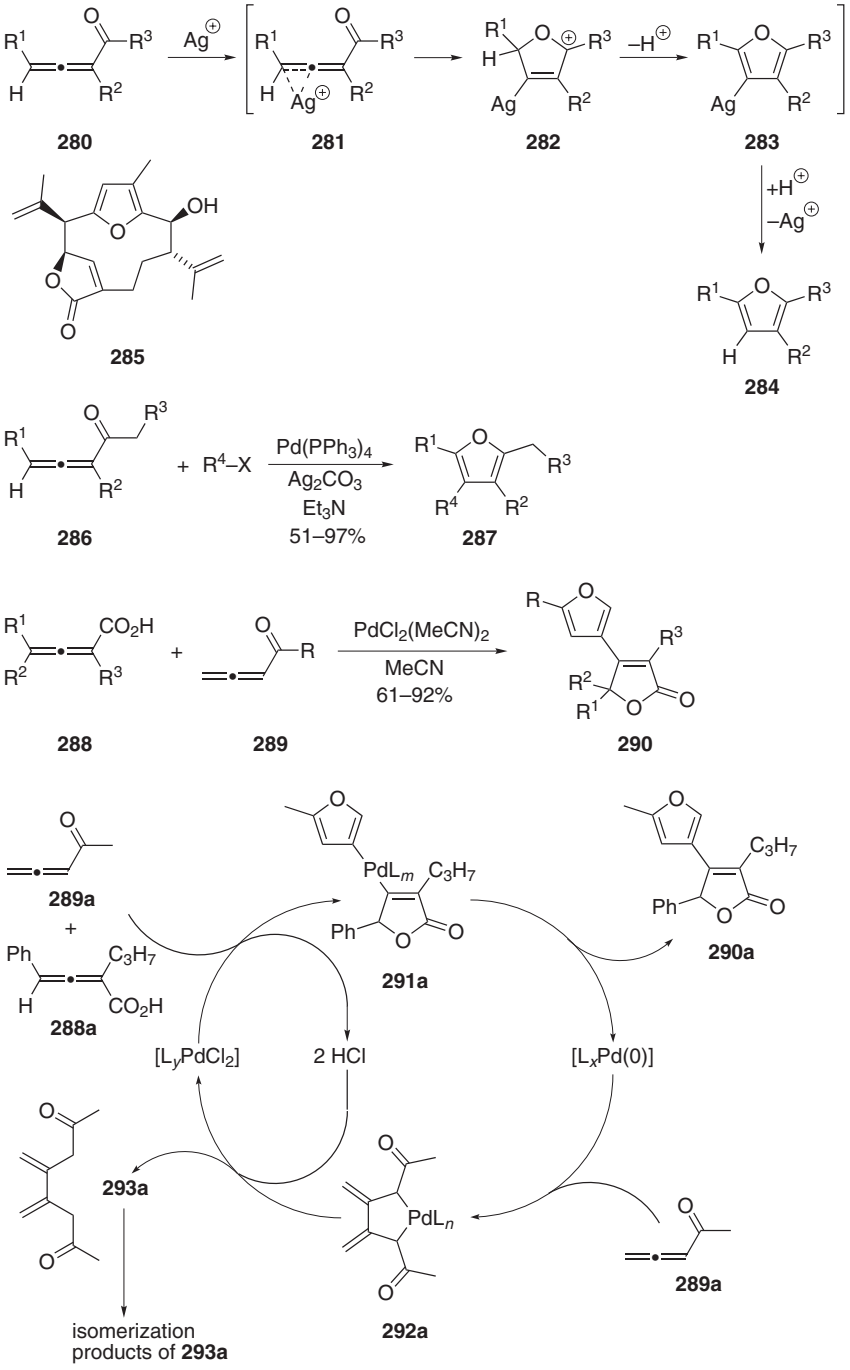
With catalysis by tetrakis(triphenylphosphane)palladium(0), the reaction of allenic amides **275** and aryl or vinyl iodides afforded *Z*-configured iminolactones **277**

stereoselectively in excellent yields using a mixture of potassium carbonate and tetrabutylammonium fluoride as the base (Scheme 7.41) [182]. The authors postulated a mechanism via oxidative addition of R^5I to the palladium(0) catalyst, formation of a π-allylpalladium intermediate **276** and an exclusive intramolecular nucleophilic attack of the carbonyl oxygen followed by the loss of a proton. However, starting materials with $R^1 = H$ lead to γ-hydroxy-γ-lactams **279** in lower yields by intramolecular nucleophilic attack of the nitrogen atom and subsequent oxidation (cf. Scheme 7.35).



Scheme 7.41

The rearrangement of allenyl ketones to furans on flash vacuum pyrolysis at high temperatures is well-known [307, 308]. In the special case of 1,4-bis(trimethylsilyl)-buta-2,3-dienone, heating in solution or a mild palladium-catalyzed reaction lead to an isomeric furan [123]. The ring closures of allenals and allenones **280**, established by Marshall and co-workers, mostly performed with the help of silver nitrate or tetrafluoroborate, or rarely with tris(triphenylphosphane)rhodium(I) chloride, are broadly applicable and furnish in good to excellent yields the products **284** (Scheme 7.42) [43, 166]. This cyclization is suitable especially for the generation of 2,5-bridged furano macrocyclic compounds [43, 137, 173, 309] such as kallolide A **285** [35]. A mechanism via the intermediates **281**, **282** and **283** is assumed for the isomerization **280** → **284**, which is also compatible with deuterium labeling experiments [44]. Ring closure of allenyl ketones to yield furans is also possible with the help of gold(III) chloride [310]. Substrates incompatible with the commonly used silver catalysts, for example allenyl ketones bearing an additional terminal alkyne, can be converted to furans using special cyclic palladium(II) catalysts [45].


Ag⊕
–H⊕
+H⊕
–Ag⊕
280
281
282
283
284
285
286
287
288
289
290
Pd(PPh3)4
Ag2CO3
Et3N
51–97%
+ R4–X
PdCl2(MeCN)2
MeCN
61–92%
289a
288a
291a
290a
[LyPdCl2]
2 HCl
[LxPd(0)]
293a
292a
isomerization
products of 293a

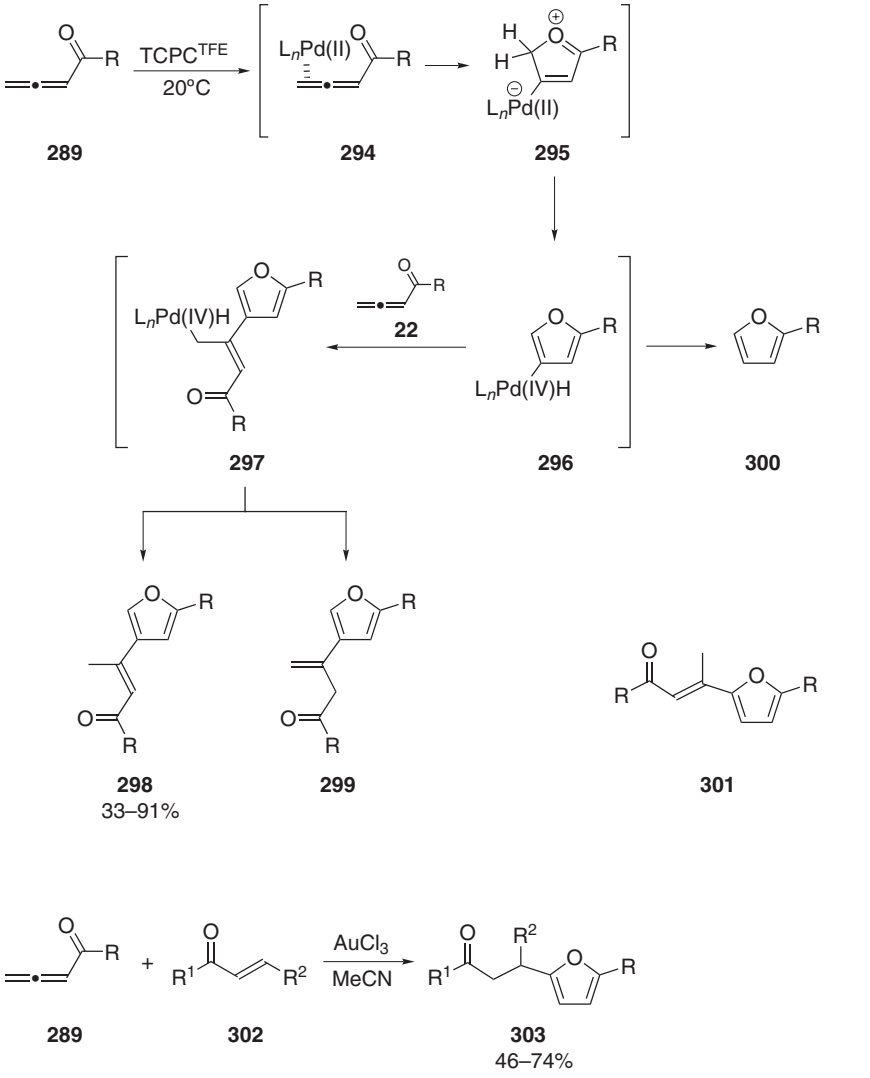
Scheme 7.42

With catalysis by tetrakis(triphenylphosphane)palladium(0) and silver carbonate, the cyclization of allenyl ketones **286** can be combined with the introduction of a carbon substituent into the 3- or 4-position of the resulting furan **287** using aryl or vinyl halides R^4X [311]. Furthermore, the formation of butenolides from allenic carboxylic acids **288** (cf. Scheme 7.40) and the ring closure of allenyl ketones **289** can also be combined to give the product **290** if the catalyst bis(acetonitrile)palladium(II) chloride and a threefold excess of **289** are used (Scheme 7.42) [312]. The catalytic cycle proposed to explain at least the product **290a** includes the intermediate **291a**, which leads to **290a** and a palladium(0) species on reductive elimination. This species reacts with 2 equivalents of **289a** to form the cyclic palladium intermediate **292a**, which can be protonated with 2 equivalents of hydrogen chloride generated in advance to form **293a** and subsequently its isomerization products. The bis(acetonitrile)palladium(II) chloride is regenerated and can re-enter the catalytic cycle.

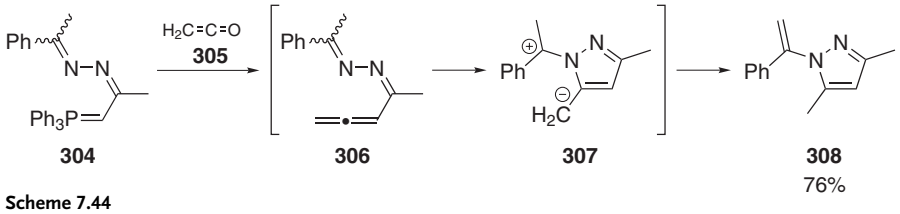
The reaction of allenyl ketones **289** bearing no substituents at the allene unit with palladium(II) catalysts, such as palladium(II) acetate, bis(acetonitrile)palladium(II) chloride or tetrakis[(2,2,2-trifluoroethoxy)carbonyl]palladacyclopentadiene ($TCPC^{TFE}$), was introduced by Hashmi and co-workers and yields stereoselectively the *E*-configured products **298** (Scheme 7.43) [45, 47, 188, 313]. This formal dimerization of **289** can be explained by the intermediates **294**, **295**, **296** and **297**. The simple furans **300** were observed as by-products which are accessible selectively from allenyl ketones and silver(I) catalysts (cf. Scheme 7.42). Sometimes the palladium(II)-catalyzed reactions yield, in addition to the dimers **298**, also the isomeric products **299**, which contain a methylene group isolated from the carbonyl function instead of the conjugated alkene unit [314]. If gold(III) chloride is used as the catalyst, the allene **289** is converted both to **300** and to the dimer **301**, isomeric with **298** [310]. This catalyst allows also the synthesis of furans to be combined with the linkage of these heterocycles to α,β-unsaturated ketones **302**, yielding the 2,5-disubstituted furans **303**.

Recently, the highlights of new transition metal catalyzed reactions of allenes were summarized by Hashmi [315], and Zimmer et al. published a comprehensive review of palladium-catalyzed reactions of allenes [316].

A few decades ago, Braverman and Segev showed that diallenyl sulfones, which are accessible by [2,3]-sigmatropic rearrangements (see Section 7.2.3), cyclize to thiophene 1,1-dioxides via diradical intermediates [110]. Syntheses and ring closure reactions of diallenyl sulfones are demonstrated also by newer examples [79]. The cyclization of diallenyl sulfoxides, generated in situ by prototropic isomerization of dipropargyl sulfoxides, takes place via diradicals. Finally, these electron-deficient allenes furnish thiophene 1-oxides and their succeeding products (cf. Scheme 7.4) [51–53]. Compounds with nitrogen-containing five-membered rings are also available from acceptor-substituted allenes. For example, the ring closure of allenic oximes can yield 1-hydroxypyrroles (cf. Scheme 7.11) [122]. If the phosphonium ylide **304** is allowed to react with ketene **305**, it affords the pyrazole **308** (Scheme 7.44) [317]. This transformation is explained by Wittig reaction of **304** and **305** (cf. Scheme 7.2) followed by cyclization of the resulting allenic azine **306**. Starting with **304** or similar phosphonium ylides and substituted ketenes instead of **305**, fused pyrazole derivatives such as pyrazoloisoquinolines can be prepared.



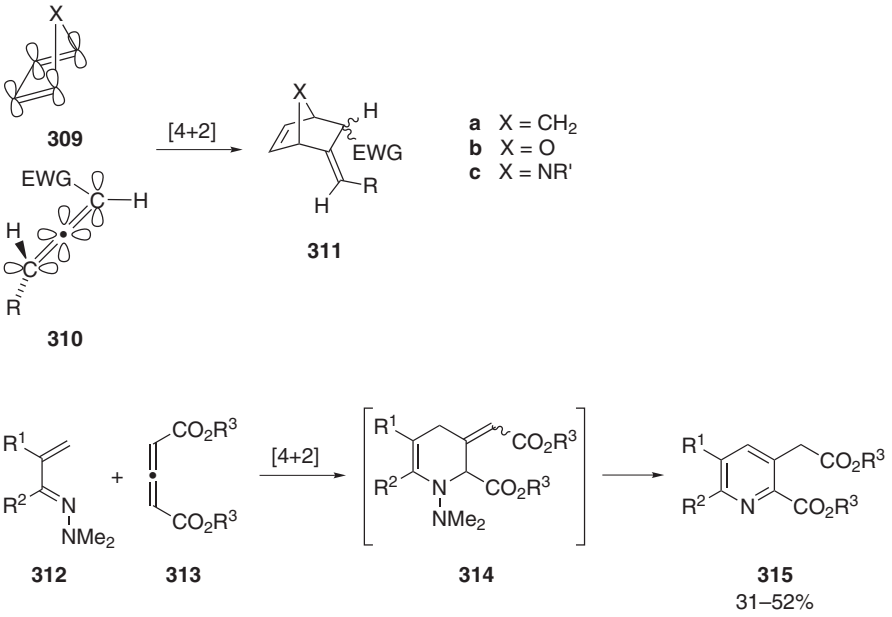
Scheme 7.43



Scheme 7.44

7.3.6
Diels–Alder Reactions

[4 + 2]-Cycloaddition utilizing allenes as dienophiles provides a convenient way of synthesizing a variety of 4-methylenecyclohexenes (cf. Chapter 12). However, the application of allenes to the Diels–Alder reaction was considered to be severely limited because of the unreactive nature of allenes as dienophiles owing to their high-lying LUMO [200, 318, 319]. Nevertheless, the reactions of acceptor-substituted allenes **310**, for example cyanoallene [130] and also buta-2,3-dienoic acid and penta-2,3-dienedioic acid [320], with cyclopentadiene **309a** were early successful to yield [4 + 2]-cycloadducts of type **311a** (Scheme 7.45). In addition to the mentioned nitrile and carboxylic acids, also allenic esters [13, 158, 319, 321–325], allenyl ketones [165] and sulfones [151, 200, 318, 326, 327] can be utilized as dienophiles. Allenic sulfoxides show sufficient reactivities only if they bear an additional acceptor group at the sulfur atom, for example a 2-nitrophenyl group [328]. The Diels–Alder reaction of **309a** and allenyl trichloromethyl sulfoxides is successful if supported by ultrasound irradiation [102].



Scheme 7.45

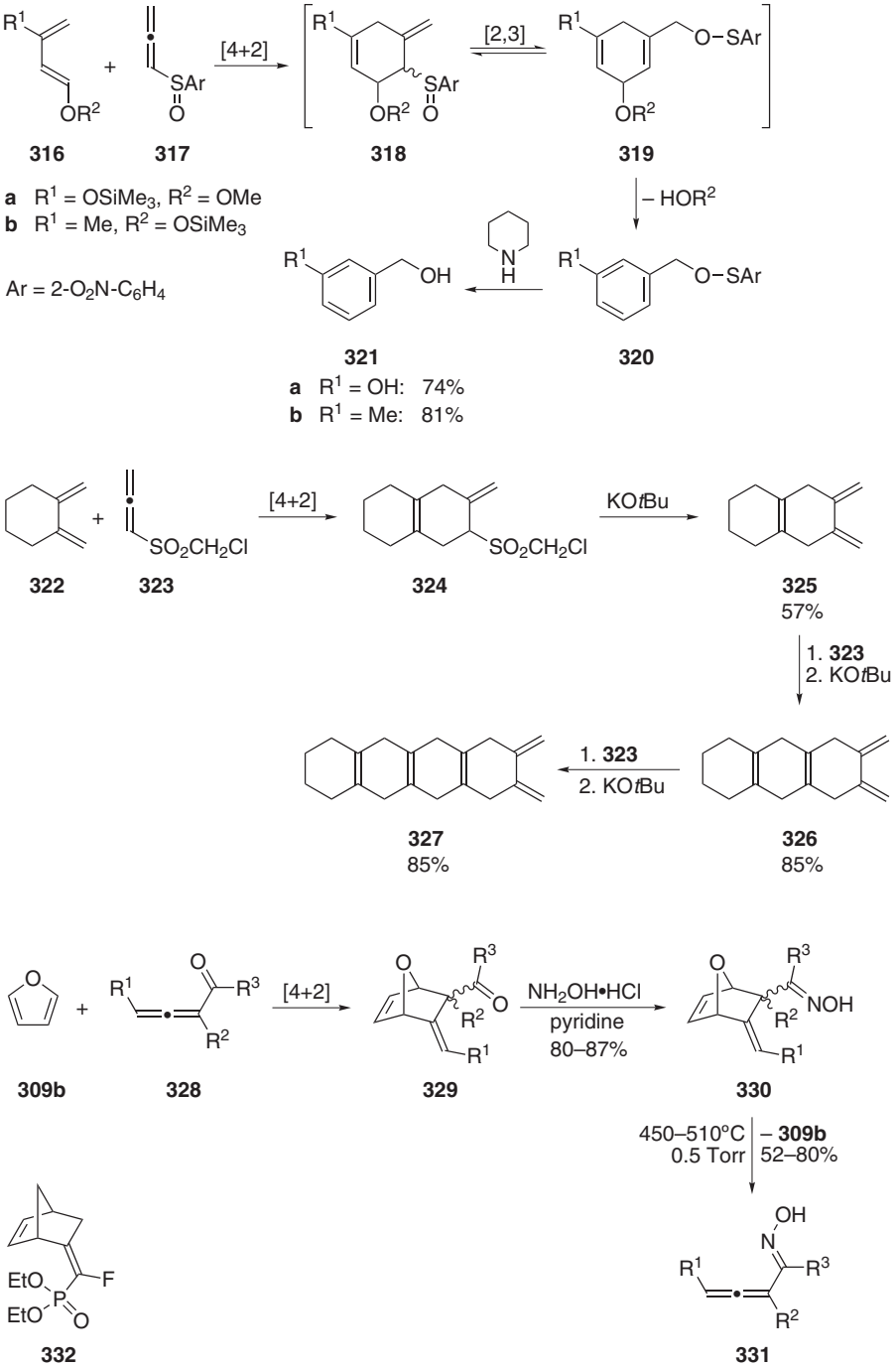
Apart from cyclopentadiene **309a**, furan [151, 165, 321–323, 327, 329] and pyrrole derivatives [158, 325] **309b** and **309c**, respectively, are also often used as dienes. Recently, the synthetic applications of furan Diels–Alder chemistry were reviewed comprehensively [330]. In the case of α,β-unsaturated hydrazones **312**, isomerization and elimination of dimethylamine convert the Diels–Alder products **314**, which

are formed regioselectively, spontaneously into the pyridine derivative **315** [331]. If tetraphenylcyclopentadienone [319] or reactive open-chain dienes such as Danishefsky's diene [(*E*)-1-methoxy-3-trimethylsiloxybuta-1,3-diene] **316a** (cf. Scheme 7.46), are treated with acceptor-substituted allenes [332], the initially formed [4 + 2]-cycloadducts lead to benzene derivatives on rearrangement and loss of carbon monoxide or cleavage of ethers, respectively. The cycloadducts **318** likewise regioselectively formed react immediately via a [2,3]-sigmatropic rearrangement to give the intermediates **319**, which lead to the isolable sulfenates **320** by elimination [328]. Their cleavage is possible with excess of piperidine to obtain the benzyl alcohols **321** in good overall yield. The products **321** correspond to a cycloaddition–elimination sequence starting from **316** and propargyl alcohol, which itself shows to low dienophilic reactivity but serves as a precursor of **317** (see Section 7.2.3).

The Diels–Alder product **324** resulting from the diene **322** and the allenyl sulfone **323** can be used together with potassium *tert*-butoxide directly in a Ramberg–Bäcklund reaction [333]. In this case, a diene permanently in the cisoid conformation is regenerated to make the polycyclic compounds **326** and **327** available by the same Diels–Alder/Ramberg–Bäcklund sequence.

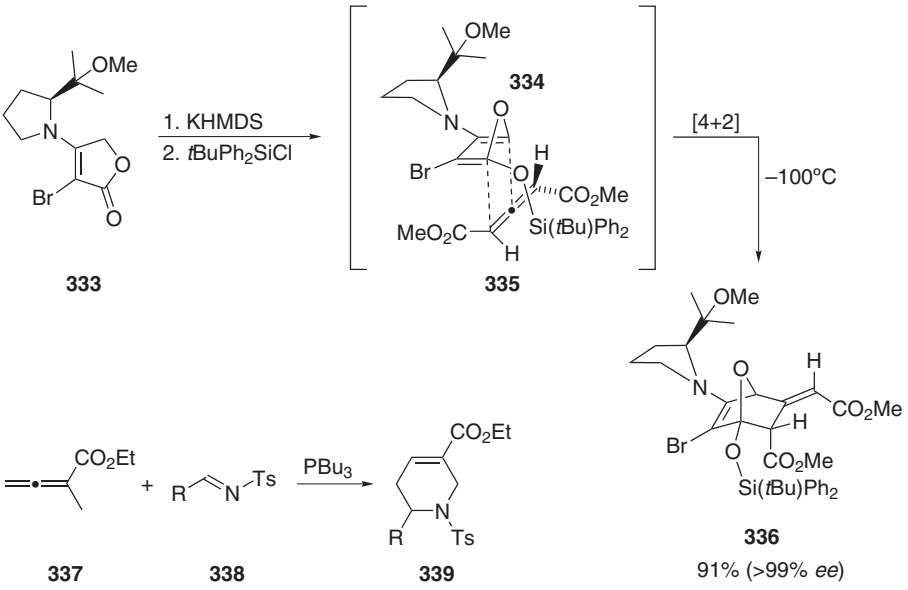
Particularly good yields of the cycloadduct **329** are obtained if $R^1 = R^2 = H$ is valid for the allenyl ketone **328** [165]. The Diels–Alder products **329** can undergo many chemical transformations, for example to the oximes **330**, which yield the modified allenes **331** after a subsequent flash vacuum pyrolysis. The oximes **331** generated by retro-Diels–Alder reaction are not available from ketones **328** and hydroxylamine hydrochloride directly [122] (see also Scheme 7.19).

Only the double bond of the electron-deficient allenes, which is conjugated to the acceptor, reacts as a dienophile during Diels–Alder reactions recognizable in the products **311**, **318**, **324** and **329**. This is also valid for acceptor-substituted butatrienes [28, 30]. Exceptions are rare [319], but one was observed during the synthesis of **332** [41]. If sulfones of type **310** and cyclic dienes **309** undergo Diels–Alder reactions, the *endo*/*exo* selectivities range from an almost balanced *endo*/*exo* ratio to the exclusive formation of the *endo* products **311** [151, 200, 318, 325, 326]. The analogous reaction of esters of type **310** also leads to very different diastereoselectivities [321, 325]. In this case, the *endo* selectivity can be increased if the esters result from sterically demanding alcohols [158] and the cycloadditions are performed using Lewis acid catalysis [322, 324, 334] at low temperature [323]. Starting with allenyl ketones [165] or allenic esters [319, 321, 325] of type **310** with $R \neq H$, different configurations at the exocyclic C=C double bond of the [4 + 2]-cycloaddition products are possible. However, the geometric isomers shown for **311**, **329** and **336** are normally dominant, which can plausibly be explained by steric effects. In the case of allenyl sulfones, more balanced *E*/*Z* ratios are often found for products of type **311** [151, 200, 326]. The diastereoselectivities described above can be used to prepare selectively non-racemic Diels–Alder products **311** starting with the achiral diene **309** and the optically active allene **310** [158, 200, 324, 326, 334]. On the other hand, treatment of an excess of the racemic allene **335** with the non-racemic furan derivative **334**, generated from **333** by deprotonation with the help of potassium bis(trimethylsilyl)amide (KHMDS) followed by silylation of the resulting enolate, leads to the [4 + 2]-cyclo-


R1
OR2
SAr
O
[4+2]
[2,3]
O–SAr
316
317
318
319
a R1 = OSiMe3, R2 = OMe
b R1 = Me, R2 = OSiMe3
Ar = 2-O2N-C6H4
– HOR2
N
H
OH
321
320
a R1 = OH: 74%
b R1 = Me: 81%
SO2CH2Cl
KOtBu
322
323
324
325
57%
1. 323
2. KOtBu
327
85%
326
85%
309b
328
329
NH2OH•HCl
pyridine
80–87%
330
NOH
450–510°C
0.5 Torr
– 309b
52–80%
EtO
EtO
P
F
332
331

Scheme 7.46

adduct **336** with high yield and enantioselectivity (Scheme 7.47) [323]. The product **336** arises from a double diastereofacially selective reaction in which kinetic resolution of the allenic diester **335** occurs.

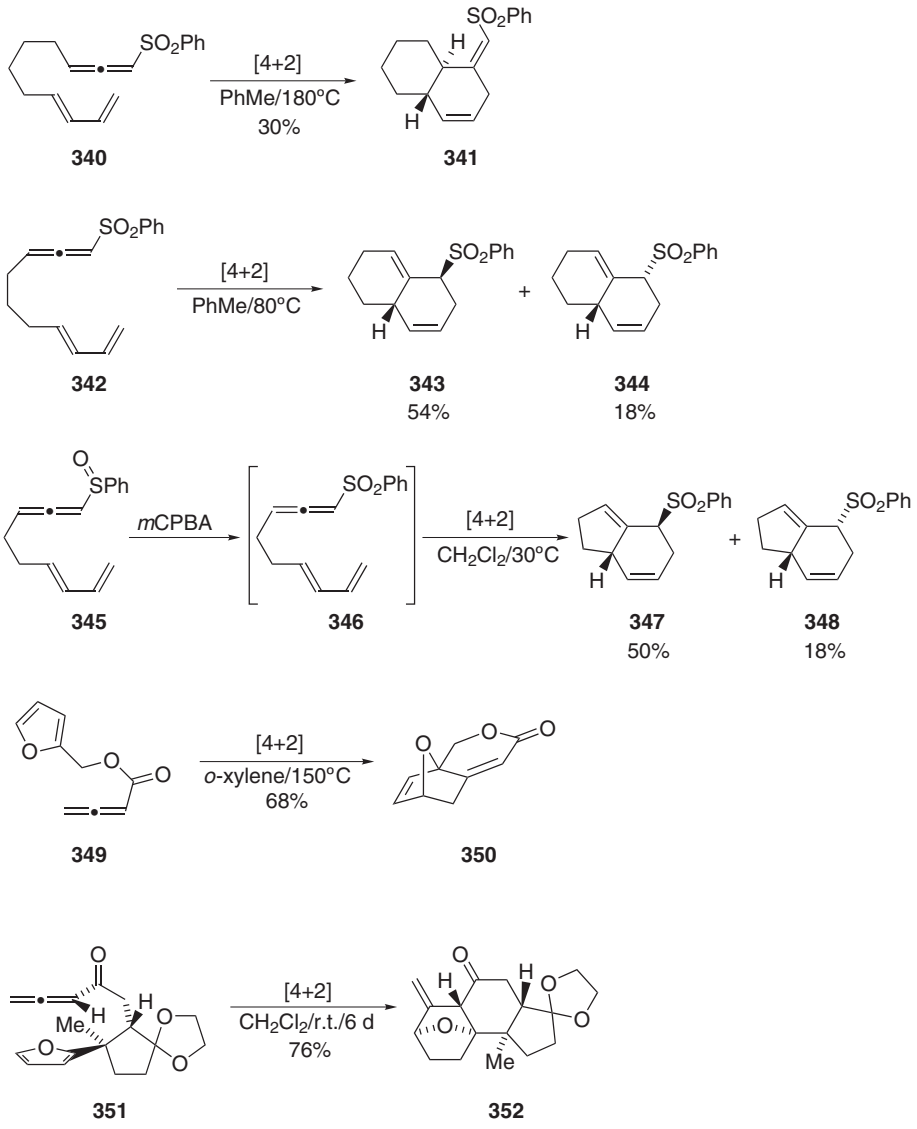


Scheme 7.47

Some cases are known in which Diels–Alder reactions of electron-deficient allenes and dienes compete with [2 + 2]-cycloadditions (see also Section 7.3.7) [12, 151, 335, 336]. Recently, a phosphane-catalyzed [4 + 2]-annulation starting from allenic ester **337** and *N*-tosylaldimines **338** was published [337]. However, the formation of the tetrahydropyridines **339** isolated in excellent yields is explained by a multistep mechanism and only resembles a Diels–Alder reaction.

Allenes as versatile synthons including Diels–Alder reactions and especially intramolecular cycloadditions of this type were reviewed by Aso and Kanematsu [338]. In some cases of intramolecular Diels–Alder reactions of open-chain starting materials such as **340** [339], **342** [339] and similar acceptor-substituted allenes [156], the formation of two new six-membered rings seems to be favorable if possible (Scheme 7.48). The non-activated cumulated C=C bond of **340** takes part in the [4 + 2]-cycloaddition and hence the necessary reaction temperature is high. On the other hand, the progressive truncation of the tether and the electron deficiency of the allenic C=C bond involved give rise to a remarkable Diels–Alder reactivity of the sulfone **346** generated in situ from sulfoxide **345** [339].

Allenic esters such as **349** [12] or allenyl ketones such as **351** [42] are able to undergo intramolecular [4 + 2]-cycloadditions with participation of both the inactivated or the activated C=C bond of the allene, respectively. The latter starting material is consumed at room temperature, yielding only one product. However, similar

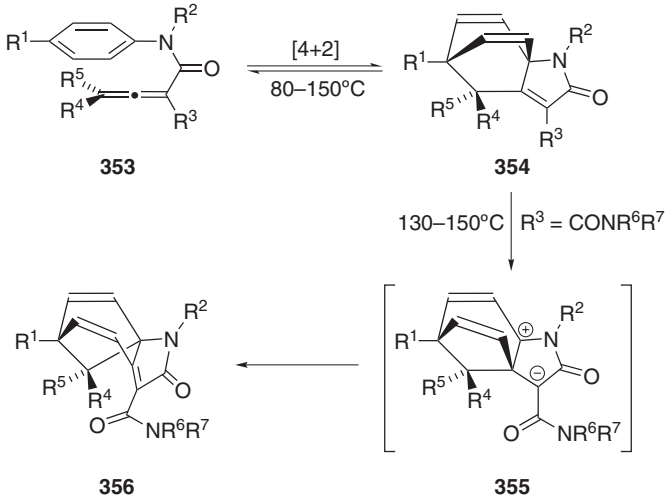


Scheme 7.48

transformations of allenyl ketones bearing a furan unit need heating and furnish a mixture of diastereomeric Diels–Alder products [42, 186, 187].

Himbert and co-workers discovered the interesting intramolecular [4 + 2]-cycloaddition of allenecarboxanilides **353**, which is possible even with monosubstituted benzenes ($R^1 = H$, Scheme 7.49) [25, 340]. During heating, partially an equilibrium between the allene **353** and the cycloadduct **354** is established. This Diels–Alder reaction can be applied to the corresponding *N*-(3-pyridyl) [335] or *N*-(1-naphthyl)

compounds [190] and also to the analogous aryl allenecarboxylates [11] and allenephosphonates [336]. In the case $R^3 = CONR^6R^7$, the Diels–Alder products **354** can undergo a rearrangement to afford high yields of **356** [24, 29]. This isomerization was explained by a 1,2-shift of one of the etheno bridges of **354** followed by a Wagner–Meerwein migration of the methano group of the resulting dipolar intermediate **355**.

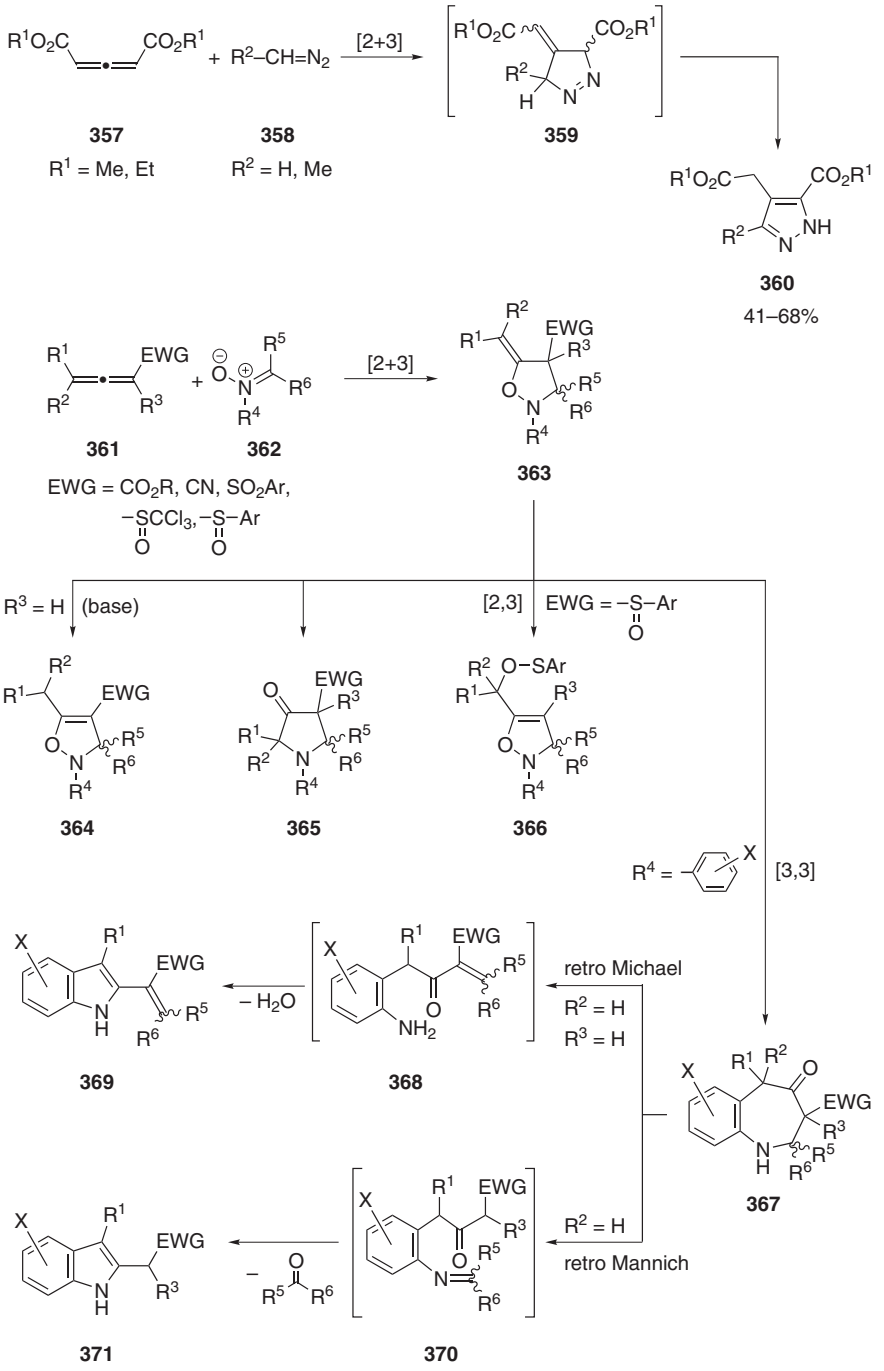


Scheme 7.49

7.3.7
Other Cycloaddition Reactions

The cycloaddition of different 1,3-dipoles such as azides [331, 341] and diazoalkanes [342–344] to acceptor-substituted allenes was thoroughly investigated early and has been summarized in a comprehensive review by Broggini and Zecchi [345]. The primary products of the 1,3-dipolar cycloadditions often undergo subsequent fast rearrangements, for example tautomerism to yield aromatic compounds. For instance, the five-membered heterocycles **359**, generated regioselectively from allenes **357** and diazoalkanes **358**, isomerize to the pyrazoles **360** (Scheme 7.50) [331].

The nitrones **362** are always added to the electron-deficient C=C bond of acceptor-substituted allenes **361** furnishing the 5-methyleneisoxazolidines **363**. The regiochemistry has been explained in terms of maximum orbital overlap between the nitrone HOMO and the allene LUMO [346]. A deviation from this regiochemistry, caused by steric hindrance and the formation of 4-methyleneisoxazolidines, is only seldom found. The products **363** ($R^3 = H$) can isomerize to the heterocycles **364** by proton shift, supported by bases [346]. 5-Methyleneisoxazolidines of type **363** often rearrange to the pyrrolidin-3-ones **365** via homolytic cleavage of the labil N–O bond and reorganization of the resulting diradical species [347]. If a sulfoxide with


[2+3]
357
358
359
360
41–68%
361
362
363
EWG = CO2R, CN, SO2Ar,
−SCCl3, −S−Ar
R3 = H
(base)
[2,3]
EWG = −S−Ar
364
365
366
R4 =
[3,3]
retro Michael
R2 = H
R3 = H
− H2O
369
368
367
R2 = H
retro Mannich
371
370

Scheme 7.50

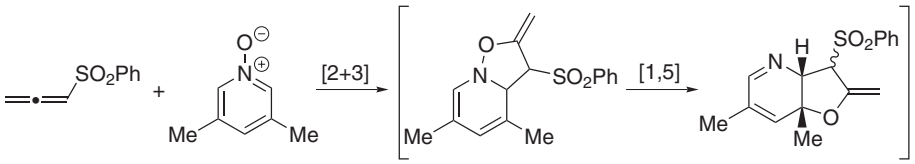
EWG = –S(O)Ar is chosen as the electron-poor allene **361**, the reaction with **362** to form cycloadduct **363** is followed by a spontaneous [2,3]-sigmatropic rearrangement to yield the sulfenate **366** [328]. Because **361** is prepared from propargylic alcohols and the sulfenates **366** can easily be hydrolyzed to alcohols, this reaction pathway via **363** and **366** corresponds formally to a 1,3-dipolar cycloaddition of nitrones to propargylic alcohols, which themselves possess too low dipolarophilic reactivities. If the nitrone **362** introduces an aryl group by the substituent R^4, the [2 + 3]-cycloaddition is followed by rapid ring expansion, **363** → **367**. The latter process was explained as a [3,3]-sigmatropic rearrangement with subsequent proton shift [348, 349], but also as a homolytic cleavage of the weak N–O bond and formation of a diradical [350] or via dipolar intermediates [351]. In some cases, the often unstable benzazepin-4-ones **367** can be isolated (36–75% yield) [348–351]. The reaction of **361** and **362** is used for the one-pot synthesis of 2-vinylindoles **369** because **367** ($R^2 = R^3 = H$) is frequently transformed to the short-lived intermediate **368** via a retro-Michael reaction under the reaction conditions [348, 349, 352]. Additionally, depending on the substitution pattern, the heterocycles **367** can form the final products **371** via the intermediates **370** by a retro-Mannich reaction [348, 349, 351, 353]. Products of type **371** are also generated if the electron-poor allenes **361** are treated with *N*-phenylhydroxylamines in terms of a nucleophilic addition (cf. Scheme 7.33).

At room temperature, the reaction of the allene **372** with pyridine *N*-oxide **373** yields a mixture of the 1:1 and 2:1 products **376** and **377**, respectively (Scheme 7.51) [354]. Most likely, **376** is formed via the intermediates **374** and **375**, i.e. by [2 + 3]-cycloaddition, followed by a [1,5]-sigmatropic shift of the oxygen and a final proton shift. The azetidine **377** is formally a [2 + 2]-cycloaddition product of **372** and **376**. However, it is also possible that **377** is generated from **372** and **376** via a regio- and stereoselective Diels–Alder reaction with subsequent [3,3]-sigmatropic rearrangement. Tandem reactions combining cycloadditions with sigmatropic rearrangement processes were summarized in a review by Neier et al. [355].

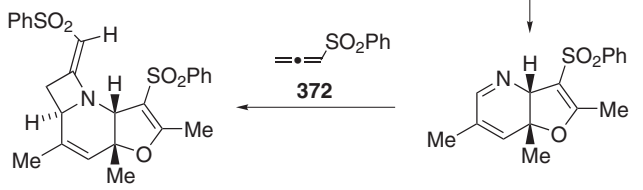
1,3-Dipolar cycloadditions to electron-deficient allenes are not regioselective, taking place at the electron-poor C=C bond, in all cases. For example, the reaction of **372** with nitrile oxide **378** furnishes a mixture of products **379**–**383** [356]. Obviously, **379**, **380** and **381** result from different [2 + 3]-cycloadditions followed by tautomerism, whereas **382** and **383** are formed from the primary products of the 1,3-dipolar cycloaddition via addition of a second equivalent of **378** to the remaining exocyclic C=C bond.

Intramolecular 1,3-dipolar cycloadditions to acceptor-substituted allenes are rare [357]. The synthesis of triazole **386** from the precursor **384** is one of the few examples [120].

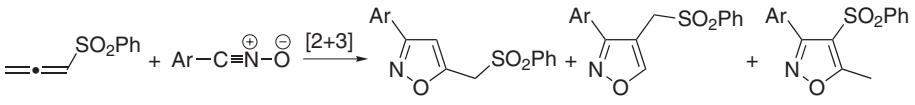
Allenic esters such as **185** can act not only as dipolarophiles but also, at least formally, as 1,3-dipoles, which was shown by Xu and Lu during the phosphane-catalyzed reaction with *N*-tosylimines **387** (Scheme 7.52) [358, 359]. The heterocycles **388** are formed at least in moderate and mostly in excellent yields, if R^1 is an aryl or a vinyl group. The formation of the products can be explained by reversible nucleophilic addition of the phosphane to **185** (cf. Section 7.3.1) followed by nucleophilic addition of the resulting intermediate to the imine **387**.



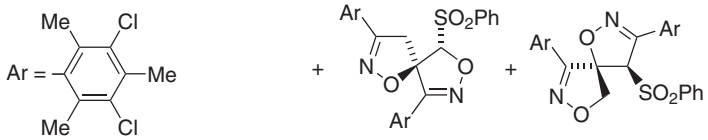
372 **373** **374** **375**



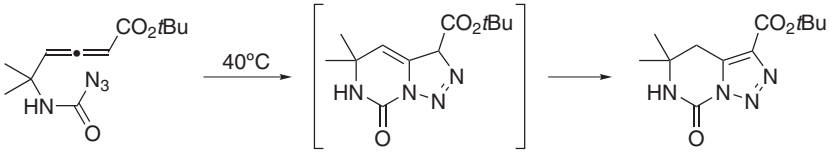
377 15% **376** 15%



372 **378** **379** 23% **380** 21% **381** 2.5%

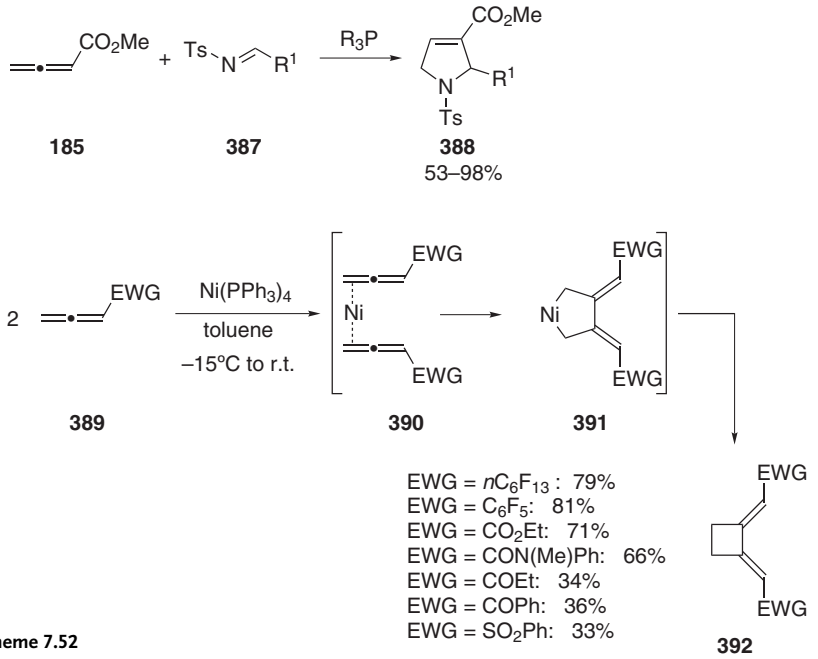


382 4% **383** 1.8%



384 **385** **386** 34%

Scheme 7.51



Scheme 7.52

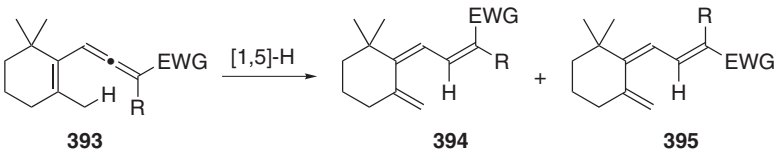
In some cases, [2 + 2]-cycloadditions occur competitively during Diels–Alder reactions or 1,3-dipolar cycloadditions of acceptor-substituted allenes [12, 151, 335, 336]. Heating of butatrienes bearing trifluoromethyl groups leads to mixtures of stereoisomeric [4]radialenes [31]. In contrast, the nickel-catalyzed [2 + 2]-annulations of monosubstituted electron-deficient allenes **389** proceed in a highly regioselective manner under very mild conditions to give the head-to-head cyclodimerization products **392** as single stereoisomers in moderate to good yields [360]. The formation of the bismethylenecyclobutanes **392** is explained by selective generation of the intermediate **390** and the metallacycle **391**, which would be controlled by the electronic and steric effects of the EWG unit of **389**.

If epoxidation is accepted as [2 + 1]-cycloaddition, then the rare transformation of an allenyl ketone to an isolable allene oxide should be mentioned [170]. The Pauson–Khand reaction, probably the best known of the [2 + 2 + 1]-cycloadditions, can also be performed using an alkyne and an allene, the latter replacing a simple alkene. These reactions were summerized recently by Brummond also including acceptor-substituted allenes [361].

7.3.8

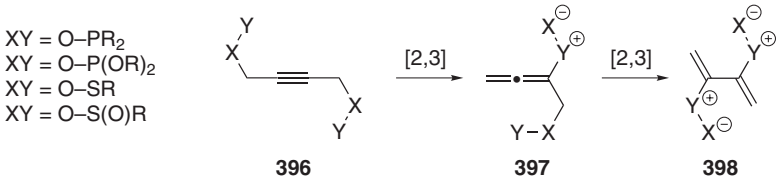
Sigmatropic Rearrangement Reactions

The [1,5]-sigmatropic hydrogen shift of (*Z*)-hexa-1,2,4-trienes is accelerated by acceptors at the terminal position of the allene unit. For example, Okamura and co-workers found for sulfone **393a** an ~700-fold acceleration of the sigmatropic rearrangement in comparison with the vinylallene without an acceptor (**393**, R = EWG = H, Scheme 7.53) [362, 363]. The sulfoxides **393b**, generated from the corresponding propargylic alcohols (cf. Section 7.2.3), isomerize in a similar way. In these cases, an analogous acceleration by a factor of 104–131 (R = H) and 186 (R = *t*Bu), respectively, is observed compared with the hydrocarbon vinylallenes (EWG = H). Whereas **393a** and some other vinylallenes yield similar amounts of the geometric isomers **394** and **395**, the rearrangement of each of the two diastereomers of the sulfoxides **393b** is connected with significant π-facial selectivity in favor of product **394**. The [1,5]-sigmatropic hydrogen shift of similar allenyl sulfoxides generated in situ can be used for the stereocontrolled synthesis of conjugated pentaenes [364].

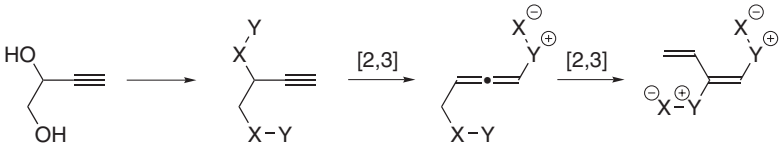


393 **394** **395**

a EWG = SO_2Ph, R = H
b EWG = S(O)Ph, R = H, Me, Et, *i*Pr, *t*Bu



396 **397** **398**



399 **400** **401** **402**

a XY = O–PPh_2
b XY = O–SAr
c XY = O–S(O)*p*Tol

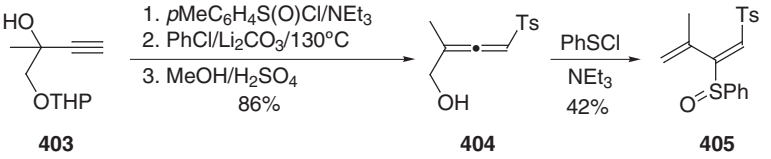
Scheme 7.53

Acceptor-substituted allenes such as **397** produced by [2,3]-sigmatropic rearrangement (cf. Section 7.2.3) can be short-lived intermediates owing to a rapid second [2,3]-sigmatropic shift. Starting with esters of but-2-yne-1,4-diols **396**, a well-known sequence of two [2,3]-sigmatropic isomerizations gives rise to doubly functionalized buta-1,3-dienes **398**. Although many examples of these tandem reactions have been studied [365], for instance conversion of phosphinous esters to phosphane oxides [YX = $P(O)R_2$] [366] or similar rearrangements [367], transformations of phosphites to phosphonates [YX = $P(O)(OR)_2$] [69, 73], sulfenates to sulfoxides [YX = S(O)R] [93, 98] and sulfinates to sulfones [YX = SO_2R] [98], direct evidence such as spectral data for allenic intermediates of type **397** is rare [66] or unknown.

The hydroxyl groups of but-3-yne-1,2-diols such as **399** can be easily transformed into esters of type **400** and thus into isomerizable functional groups. The sequence of [2,3]-sigmatropic rearrangements **400** → **401** → **402** provides a convenient approach to 1,2-difunctionalized buta-1,3-dienes [368]. Thus, the diol **399** furnishes the phosphine oxide **402a** [YX = $P(O)Ph_2$, 25% yield] or the sulfoxides **402b** [YX = S(O)Ar, 44–66%] by a one-pot reaction with chlorodiphenylphosphane or arylsulfenyl chlorides, respectively, even below room temperature. In contrast, the sulfinate **400c** generated from **399** has to be heated in solution to 130 °C to rearrange to the sulfone **402c** (YX = Ts, 55% based on **399**). The allenic intermediate of type **401** can be proved directly by spectroscopy only in the case of **401c** [245]. Not only the parent compounds **402** but also products bearing additional substituents on the buta-1,3-diene chain are always formed with a *trans* configuration of the two YX groups.

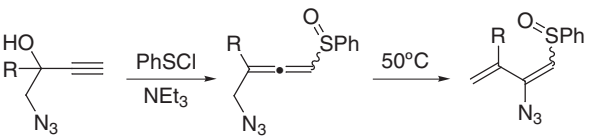
Buta-1,3-dienes with two different functional groups in positions 1 and 2 are also available by sigmatropic rearrangement of allenes. Thus, the half-protected diol **403** is first transformed to an allenyl sulfone via [2,3]-isomerization of the corresponding sulfinate (Scheme 7.54). After deprotection, the resulting intermediate **404** is converted to **405** through [2,3]-rearrangement of the sulfenate [368]. The sulfoxides **407**, easily prepared from propargyl alcohols **406** with the help of a [2,3]-sigmatropic shift, are transferred to the products **408** by [3,3]-migration of the azido group. In the case of the synthesis of **412**, a [2,3]-sigmatropic isomerization of sulfinate **410**, which is accessible from alcohol **409**, and a Cope rearrangement of allenyl sulfone **411** are involved [368]. Sequences of sigmatropic rearrangement reactions leading to functionalized buta-1,3-dienes via allenes have been reviewed [63].

Treatment of allenic sulfinates **413** with vinylic Grignard reagents **414** at low temperature gives rise to allenyl sulfoxides **415**, which undergo a rapid [3,3]-sigmatropic rearrangement under mild conditions to produce thioketone *S*-oxides **416** as mixtures of geometric isomers [369]. In some cases with $R^3 = H$, significant amounts of **415** can be detected within the crude mixture of products and the resulting thioaldehyde *S*-oxide (**416**, $R^3 = H$) tends to undergo rapid succeeding reactions. If sulfinates of type **413** are treated with allylic Grignard reagents, the allenyl allyl sulfoxides generated in situ isomerize spontaneously via an analogous [3,3]-sigmatropic process to afford (2-methylenebut-3-enyl)thioketone *S*-oxides.



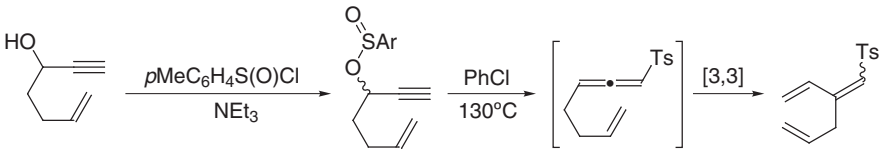
403 **404** **405**

THP = tetrahydropyranyl



406 **407** **408**

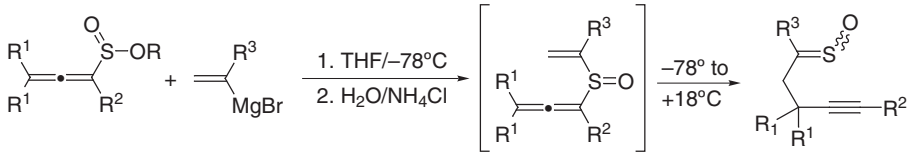
a R = H, (*E*):(*Z*) = 4:1
48% (based on **406**)
b R = Me, (*E*):(*Z*) = 2:1
54% (based on **406**)



409 **410** **411** **412**

Ar = *p*MeC$_6$H$_4$

(*E*):(*Z*) = 1: 1.6
63% (based on **409**)



413 **414** **415** **416**

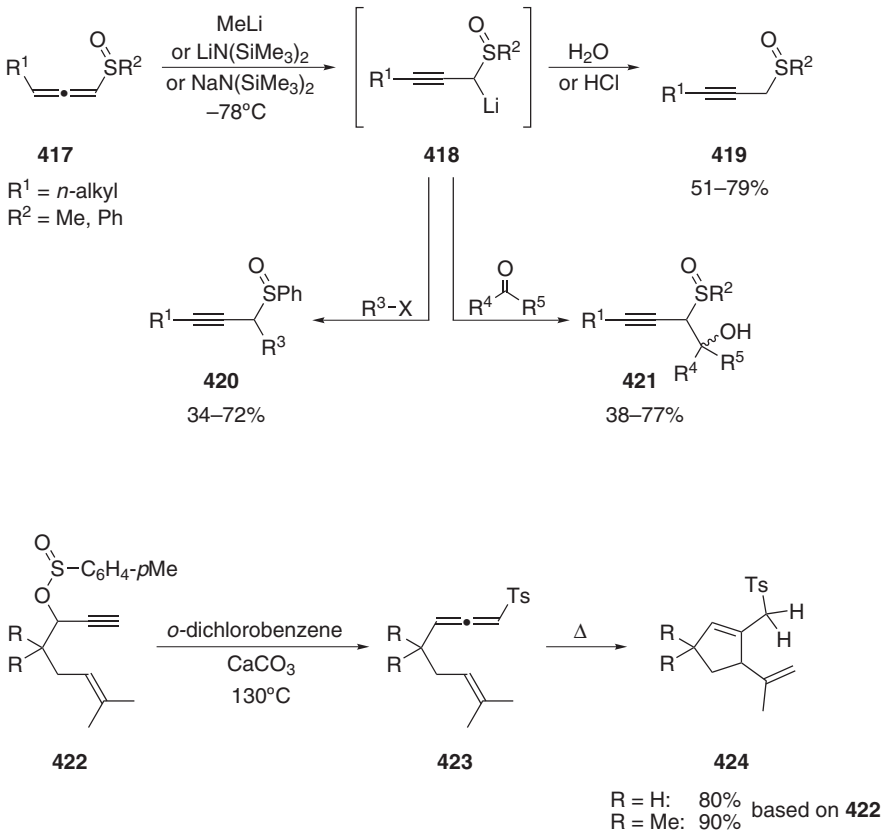
	R	R^1, R^1	R^2	R^3	Yield (%)	(*E*):(*Z*)
a	Et	Me, Me	Me	Me	94	65:35
b	Me	Me, Me	Ph	Me	70	85:15
c	Me	Me, Me	Me	Ph	96	92:8
d	Me	–(CH$_2$)$_5$–	Me	Ph	94	95:5

Scheme 7.54

Quaternary allenylallylammonium salts, produced in situ by prototropic isomerization of propargyl precursors (see Section 7.2.2), can undergo a 3-aza-Cope rearrangement [370]. The resulting intermediates are hydrolyzed under the reaction conditions to yield 2-methylenepent-4-enals.

7.3.9 Other Rearrangement Reactions

Acceptor-substituted allenes can be prepared from the corresponding propargyl precursors by prototropic isomerization (see Section 7.2.2). Conversely, such allenes can also be used to synthesize propargyl compounds. For example, treatment of the sulfoxides **417** with 1 equivalent of a lithiation reagent leads to the intermediates **418**, which furnish propargyl sulfoxides **419** by hydrolysis (Scheme 7.55) [101]. If the electrophiles used are not protons but primary alkyl halides or carbonyl compounds, the products **420** or **421**, respectively, are formed by C,C linkage.



Scheme 7.55

It has been known for a long time that allenes bearing at one carbon atom an acceptor and a hydrogen atom are in a base-catalyzed equilibrium with propynes, bearing the acceptor in position 1 (cf. Scheme 7.4). Thus, allenyl phenyl sulfone can be generated by treating phenyl prop-1-ynyl sulfone with triethylamine in benzene [49]. On the other hand, but-2-ynoic acid is prepared by heating buta-2,3-dienoic acid

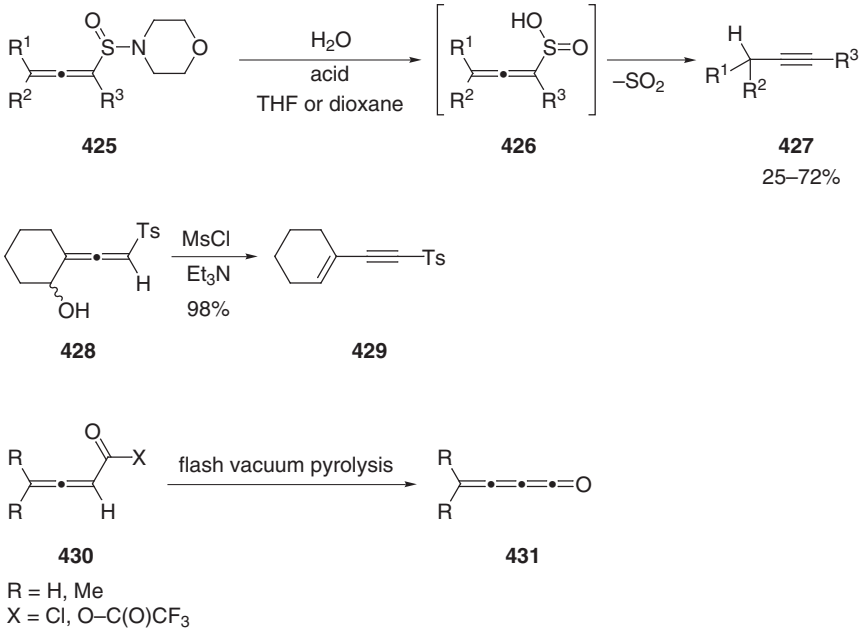
in the presence of aqueous potassium carbonate [33]. Allenecarboxylic acids should be involved in the prototropic rearrangement of octa-3,5- or octa-2,6-diynedioic acid to produce octa-2,4-dien-6-ynedioic acid [50]. Finally, isomerization of 2-methylocta-4,5,7-trien-3-one to give 2-methyloct-7-en-4-yn-3-one and 2-methyloct-6-en-4-yn-3-one has also been reported [169].

Allenes containing an allyl unit at a suitable position within the molecule can undergo an intramolecular ene reaction. Thus, allenyl sulfones **423**, prepared by oxidation of the corresponding sulfoxides, lead to ring closure products **424** on heating [371]. If propargyl sulfinates **422** are thermolyzed, the same carbocycles **424** are formed via [2,3]-sigmatropic rearrangement followed by intramolecular ene reaction.

7.3.10
Miscellaneous Reactions

Acid-catalyzed hydrolysis of *S*-allenylsulfinylamines **425**, easily accessible from propargyl alcohols (cf. Scheme 7.8), provides the alkynes **427** (Scheme 7.56) [108, 109]. This transformation is postulated to proceed via the intermediate allenic sulfinic acid **426**. However, in some cases with $R^1 = R^2 =$ alkyl, more complicated products are formed instead of simple alkynes **427** [372].

Whereas enyne **429** is formed in excellent yield from allenyl sulfone **428** as a stable product of 1,4-elimination of water [118], short-lived butatrienones **431** can only be characterized by argon matrix infrared spectroscopy after 1,2-elimination of HX from precursors **430** by flash vacuum pyrolysis [373, 374].



425 **426** **427**

428 **429**

430 **431**

Scheme 7.56

Allenic esters can be generated by palladium-catalyzed carbonylation of propargyl compounds (see Section 7.2.6). Under the reaction conditions applied, however, succeeding reactions occur directly in many cases, for instance by introduction of a second ester function. Many examples of such carbonylation reactions of allenic esters were summarized in a review by Tsuji and Mandai [136].

7.4 Conclusions

Although this review is by no means comprehensive, it should give an impression of the great number of feasible syntheses of acceptor-substituted allenes and their possibilities of reactions. The unique combination of the C=C=C unit and the acceptor group often allows not only the common reactions of these parts but also specific transformations into a variety of very different products. Much attention was paid to the results of the last 20 years, but we have tried to mention all important facts about the chemistry of the title compounds. At the latest during the last two decades, it turned out that acceptor-substituted allenes are not only compounds for experts in organic chemistry but also very useful and general tools in synthetic chemistry.

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8
Donor-Substituted Allenes

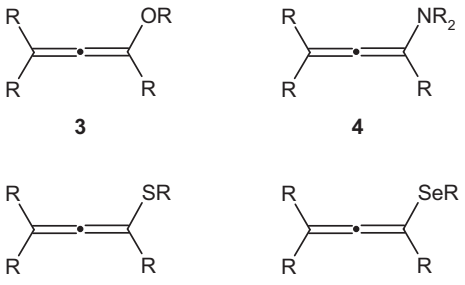
Reinhold Zimmer and Hans-Ulrich Reissig

8.1
Introduction

Donor- and acceptor-substituted allenes with general structures **1** or **2** (Scheme 8.1) have the most obvious synthetic potential among functionalized allene derivatives and therefore they serve as versatile building blocks in many synthetic endeavors [1]. As expected, the reactivity of the double bonds of **1** or **2**, which are directly connected to the activating substituents, are strongly influenced by these groups. Hence there is enol ether or enamine reactivity of **1** and Michael acceptor type chemistry of **2**. In addition, the terminal double bonds are also influenced by these functional groups.

Scheme 8.1 **1** **2**

In this chapter we shall deal with donor-substituted allenes of type **3**, **4**, **5** and **6** (Scheme 8.2), among which oxygen-substituted allene derivatives **3** are of major importance. They have been utilized for numerous syntheses of interestingly func-



3 **4**

5 **6**

Scheme 8.2

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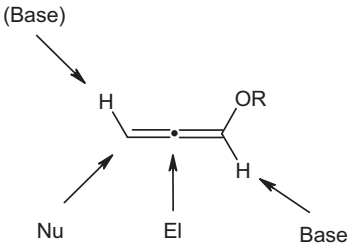
tionalized acyclic, carbocyclic or heterocyclic compounds [2–9]. In addition, they have become increasingly important for the synthesis of natural products or biologically active compounds [2]. The chemistry of nitrogen-, sulfur- or selenium-substituted allene derivatives is still under development and it is expected that their importance will increase in the future [10].

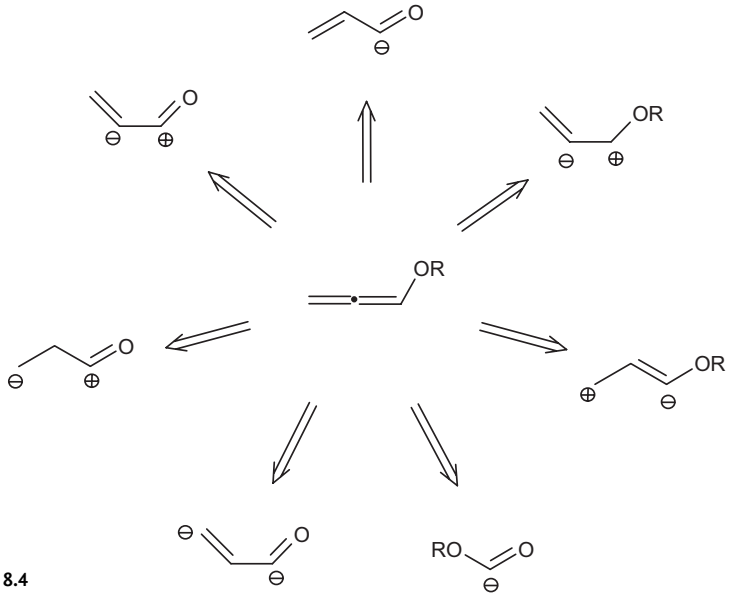
As mentioned above, the reactivity of alkoxyallenes is governed by the influence of the ether function, which leads to the expected attack of electrophiles at the central carbon C-2 of the cumulene. However, the alkoxy group also activates the terminal double bond by its hyperconjugative electron-withdrawing effect and makes C-3 accessible for reactions with nucleophiles (Scheme 8.3). This feature is of particular importance for cyclizations leading to a variety of heterocyclic products. The relatively high CH-acidity at C-1 of alkoxyallenes allows smooth lithiation and subsequent reaction with a variety of electrophiles. In certain cases, deprotonation at C-3 can also be achieved.



Scheme 8.3

The substitutions at C-1 can be classified as processes with umpolung of reactivity since a negatively charged carbon directly connected to oxygen is involved. A variety of synthons with umpolung of reactivity are therefore derived from simple alkoxyallenes as summarized in Scheme 8.4. The rich and often very surprising chemistry of these unique, but easily available, building blocks is still under development and it is expected that even more new synthons derived from alkoxyallenes will be detected in the future.

Several reviews on various aspects of the chemistry of these allenes have been published [1–10] and therefore this chapter concentrates on the presentation of principle reaction patterns, on important applications of known processes and on new developments in this area.

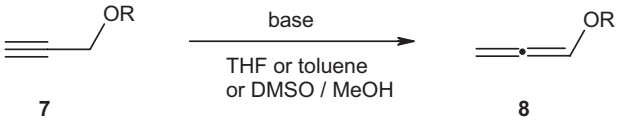


Scheme 8.4

8.2
O-Substituted Allenes

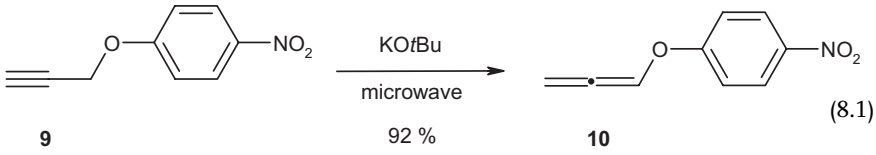
8.2.1
Synthesis of *O*-Substituted Allenes

The first investigations in the 1960s [11, 12] established the base-induced isomerization of alkyne precursors as the most practical and general route for the synthesis of alkoxy- and aryloxyallenes. In the meantime, a number of monosubstituted allenes **8** bearing an achiral or a chiral group R is smoothly accessible by this efficient procedure (Scheme 8.5) [1, 2, 13–19]. Beside the most commonly used base potassium *tert*-butoxide, other bases, e.g. *n*-butyllithium, are also applicable for this isomerization. Recently, the yields of alkyne-allene isomerizations could be significantly increased, in particular with aryloxy-substituted allenes, by using microwave irradiation (Eq. 8.1) [20].



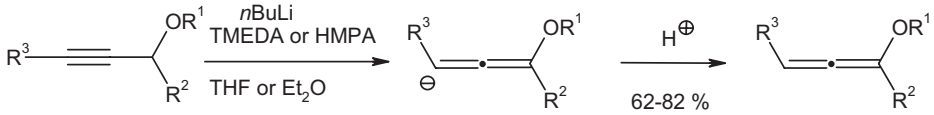
R = Me, Et, *n*Bu, *t*Bu, Bn, Ph, $CH_2CH_2SiMe_3$, MOM, CHMeOEt, THP, DAG, DAF, menthyl
base: KO*t*Bu or *n*BuLi, TMEDA

Scheme 8.5



9 10 (8.1)

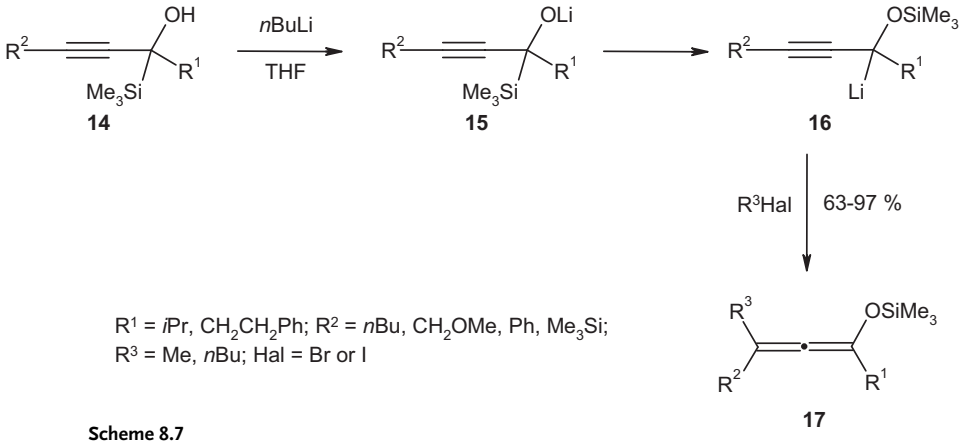
Base-induced isomerizations of alkyne precursors are also useful to produce more functionalized 1,2-dienes. Accordingly, 3-substituted 1-alkoxyallenes and 1-siloxyallenes **13** and **17** can smoothly be prepared in good yields from disubstituted alkynes **11** and **14** (Schemes 8.6 and 8.7) [21–24]. In general, these procedures involve the isomerization of lithiated prop-2-ynyl ethers to the corresponding lithiated allenyl ethers followed by regioselective protonation or alkylation which form 1,3-di- or 1,1,3-trisubstituted allenes, respectively. The lithiated 1-siloxyalkynes **16** were formed in situ by migration of the trimethylsilyl group in **15** from carbon to oxygen, which occurs smoothly under the reaction conditions employed. It should be mentioned that protonation of intermediates **12** with $R^2 = H$ is generally not regioselective. In order to effect a clean conversion of **11** into **13**, the addition of TMEDA or HMPA is mandatory [22, 23].



11 **12** **13**

R^1 = Me, Me_3Si, DAG, DAF; R^2 = H, *i*Pr, Me_3Si, CH_2CH_2Ph;
R^3 = nonyl, *n*Bu, Ph, Me_3Si, CH_2OMe

Scheme 8.6

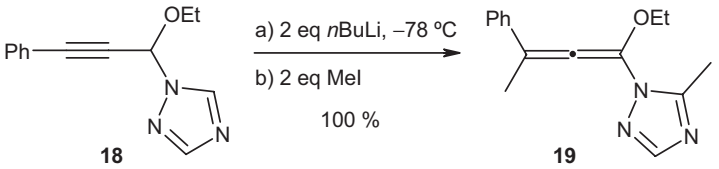


14 **15** **16** **17**

R^1 = *i*Pr, CH_2CH_2Ph; R^2 = *n*Bu, CH_2OMe, Ph, Me_3Si;
R^3 = Me, *n*Bu; Hal = Br or I

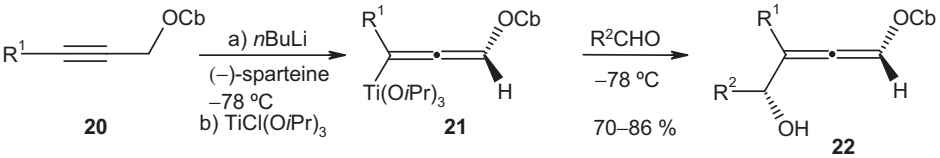
Scheme 8.7

A related method was reported by Katritzky et al. [25], who prepared 1-alkoxy-1-(1,2,4-triazol-1-yl)allenes from the corresponding triazole-substituted alkynes, e.g. the reaction of **18** to **19** in Eq. 8.2. In this case the generated allenyl anion was trapped with methyl iodide.



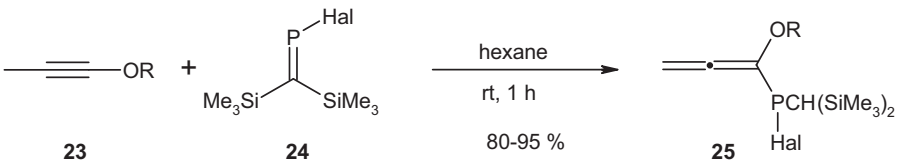
(8.2)

In recent years, Hoppe's group has considerably extended the isomerization-addition methodology, especially for the highly regio- and stereoselective synthesis of 1,2-alkadienyl carbamates. It involves deprotonation of alkynyl carbamates, transmetalation into a titanium species and subsequent reaction with carbonyl compounds [26–30]. This group recently described the preparation of enantiomerically enriched 4-hydroxyallenyl carbamates **22** by sparteine-mediated lithiation of alkynyl carbamates **20** [29]. Impressive examples of these transformations are summarized in Scheme 8.8.



Scheme 8.8

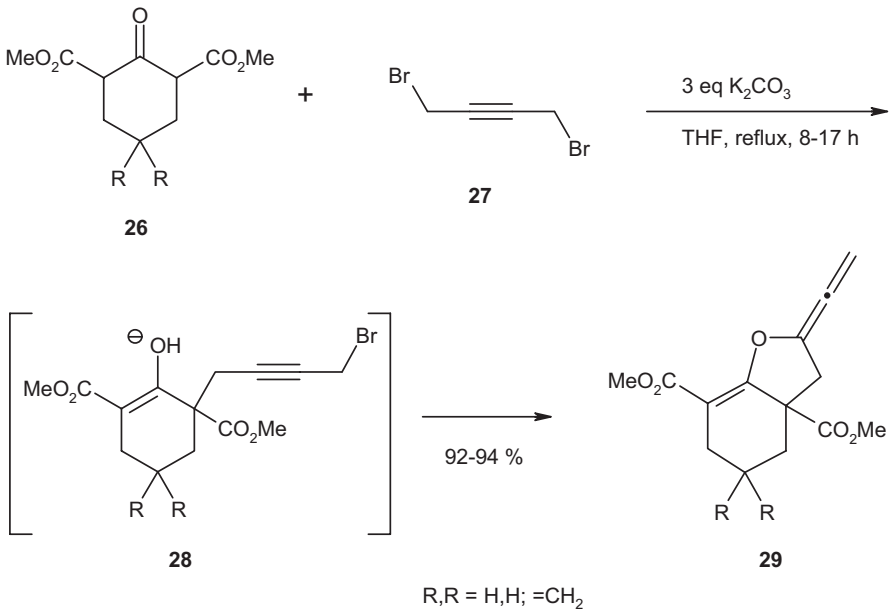
An exceptional approach to phosphorus-substituted alkoxyallenes via isomerization of alkynes was introduced by Beletskaya's group. The treatment of 1-alkoxy-1-propynes **23** with 1-halo-2,2-bis(trimethylsilyl)phosphaethen **24** furnished alkoxyallenes **25** (Scheme 8.9) [31].



Scheme 8.9

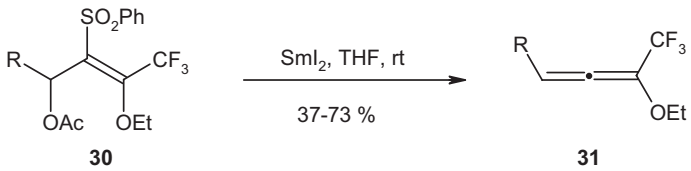
R = Me, Et; Hal = Cl, Br

So far, the formation of cyclic alkoxyallenes bearing an exocyclic or endocyclic allenyl unit has been less developed. Several examples with this structural feature are described as unstable compounds or highly reactive intermediates [32–35]. However, in the 1990s, Lavoisier-Gallo and Rodriguez demonstrated a useful one-pot protocol for the synthesis of 2-vinylidenedihydrofurans such as **29** involving a tandem C-O cycloalkylation of stabilized carbanion intermediates **28** as crucial step (Scheme 8.10) [36, 37].

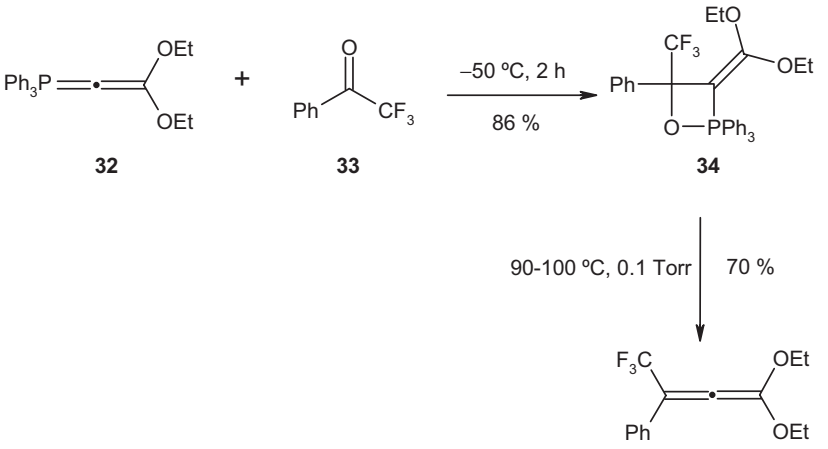


Scheme 8.10

Two convenient methods have been developed for the preparation of trifluoromethyl-substituted alkoxyallenes. Reductive elimination of allylic acetates **30** with samarium diiodide leads to **31** (Scheme 8.11) [38], whereas reaction of Wittig cumulene **32** with phenyl trifluoromethyl ketone (**33**) and thermolysis of the intermediate **34** provides **35** (Scheme 8.12) [39].

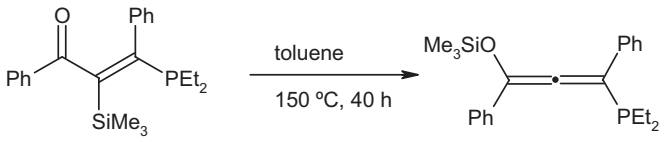


Scheme 8.11

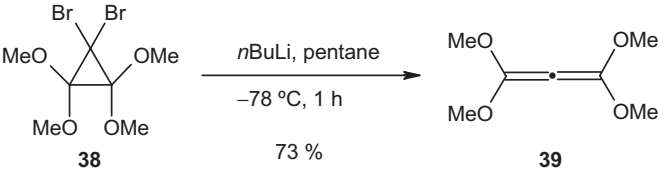


Scheme 8.12

In a single case, thermal treatment of enone **36** induced a 1,3-sigmatropic silyl shift which led to the formation of the rearranged product **37** (Eq. 8.3) [40]. So far, only one example of a ring-opening reaction of a cyclopropane **38** has been reported which furnished tetramethoxy-substituted allene **39** (Eq. 8.4) [41].



(8.3)



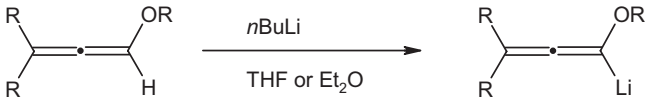
(8.4)

8.2.2
Deprotonation of Alkoxyallenes and Reaction with Electrophiles – Ring-Closing Reactions

8.2.2.1 Synthesis of Primary Allene Adducts

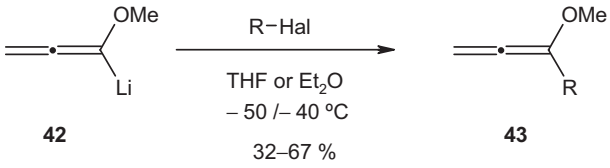
Due to the synthetic versatility of donor-substituted allenes, it is of great importance to modify these compounds by substitution reactions at C-1. The CH-acidity at the α-carbon of alkoxyallenes allows their smooth lithiation [12, 42] which conveniently

delivers highly nucleophilic intermediates **41** (Eq. 8.5). Their reactions with different classes of electrophiles have been utilized for a variety of synthetic applications [2–5]. Of particular importance are suitably substituted alkoxyallenes which can undergo cyclization to carbocycles and heterocycles [2, 4, 43].



40 **41** (8.5)

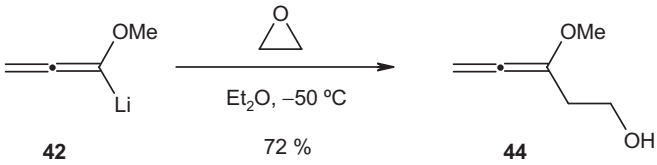
Scheme 8.13 and Eqs. 8.6–8.10 reveal that lithiated methoxyallene **42** is sufficiently reactive towards a variety of electrophiles such as alkyl halides [44, 45], ethylene oxide [12c], tosylated aziridine **45** [46], dimethyl disulfide [12b], trialkylstannyl and trialkylsilyl chlorides [47, 48] and iodine [49]. These substitution reactions proceed with excellent regioselectivity and the corresponding α-functionalized products are obtained in good to high yields. An exceptional case was found by treatment of **42** with a guanidinium salt, which led to a 60:40 mixture of α- and γ-adducts **50** and **51** (Eq. 8.11) [50].



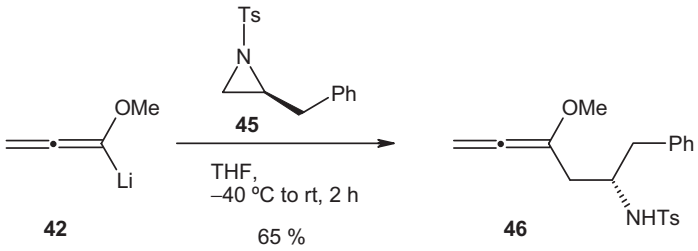
42 **43**

R = Me, *n*Pr, *n*Bu, Bn, $CH_2CH{=}CH_2$; Hal = Br, I

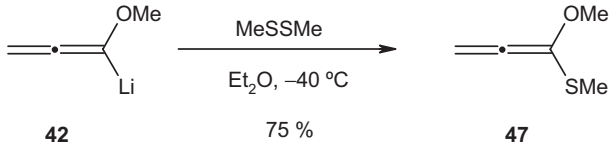
Scheme 8.13



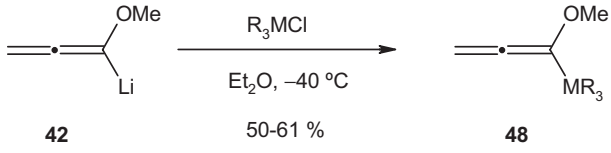
42 **44** (8.6)



42 **46** (8.7)

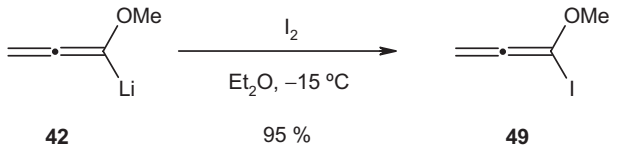


42 75 % **47** (8.8)

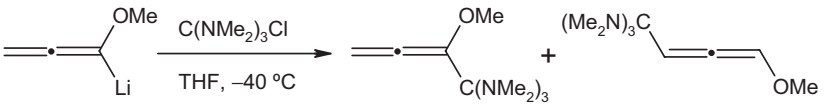


42 50-61 % **48** (8.9)

(M = Si, Sn; R = Me, *n*Bu)

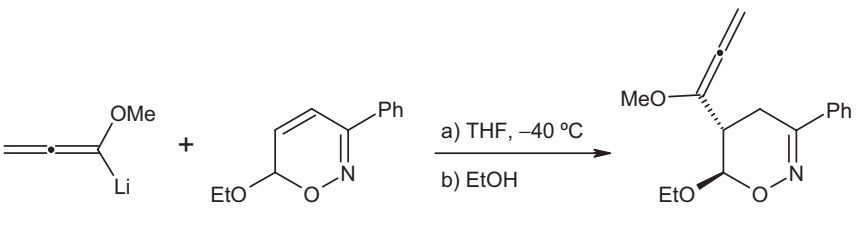


42 95 % **49** (8.10)

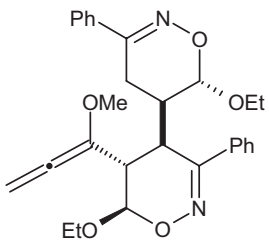


42 69 % **50** (60:40) **51** (8.11)

The Michael-type addition of **42** to 6*H*-1,2-oxazine **52** afforded heterocycle **53** in 45% yield together with bis-adduct **54** as a minor component (Eq. 8.12) [51].

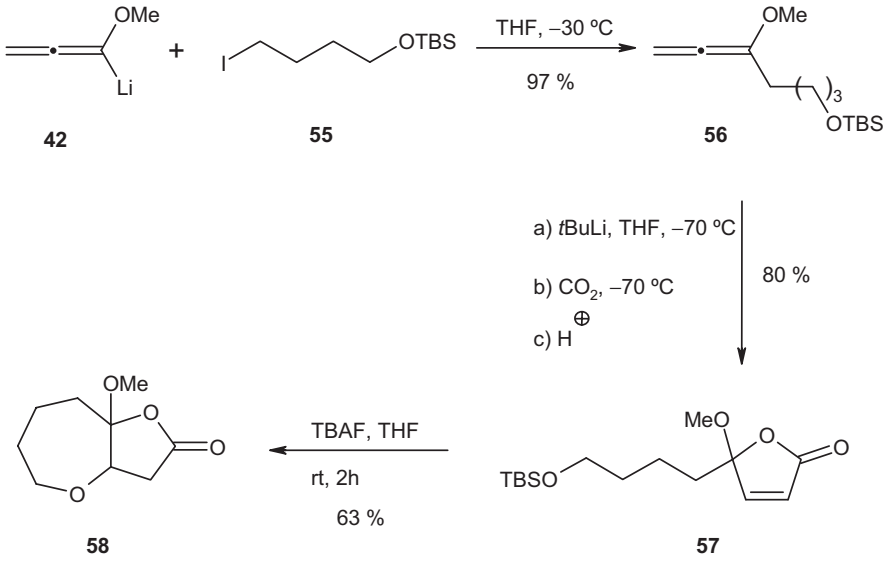


42 **52** **53** (45 %)



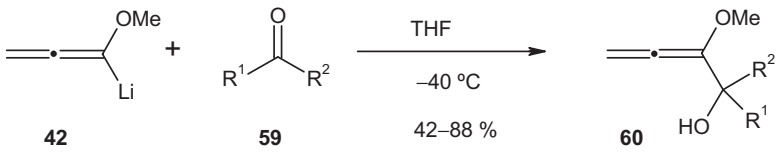
54 (18 %) (8.12)

The synthetic usefulness of reactions of lithiated methoxyallene **42** with suitable electrophiles was demonstrated by several syntheses of bioactive natural products or substructures thereof [52–58]. An interesting application was described by Fall et al. [52]: after addition of alkyl iodide **55** to lithiated methoxyallene **42**, deprotonation by *tert*-butyllithium and addition of carbon dioxide occurred at the terminal γ-carbon and thus provided butenolide **57** after acidic workup. Desilylation of this intermediate with TBAF finally gave bicyclic oxepane derivative **58** in good overall yield (Scheme 8.14).



Scheme 8.14

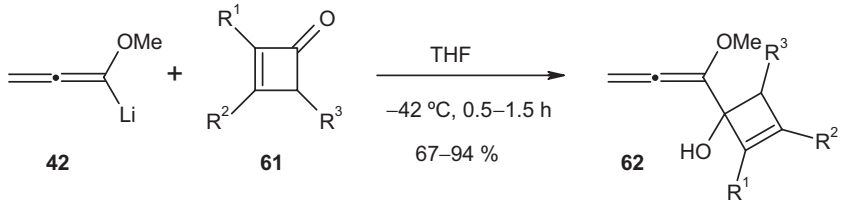
Among the many useful electrophiles, carbonyl compounds and their derivatives lead to products of the highest value for synthetic endeavors. First experiments with aldehydes and ketones were performed by Hoff, Brandsma and Arens (Scheme 8.15) [12b]. The primary allenyl adducts **60**, which are isolable in moderate to excellent yields [12b, 47], serve as starting materials for subsequent cyclizations (see Section 8.2.2.2).



R^1 = H, Me, Et, Ph; R^2 = Me, Et, Ph, CH=CHPh; R^1,R^2 = $(CH_2)_n$, n = 4-5

Scheme 8.15

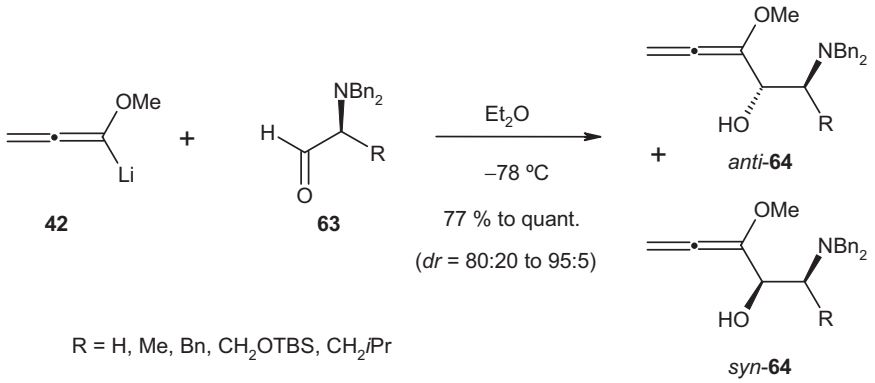
An interesting application was described by Liebeskind and Stone, who prepared 1-(methoxy-1,2-propandienyl)-2-cyclobuten-1-ols **62** by treatment of cyclobutenones **61** with lithiated methoxyallene **42** (Scheme 8.16) [59]. The authors used these primary adducts in a subsequent acid-catalyzed ring-enlargement providing 5-hydroxy-5-vinyl-2-cyclopenten-1-ols.



R^1 = H, Me; R^2 = Me, *n*Bu, Me_3Si, OEt; R^3 = H, Me, Cl

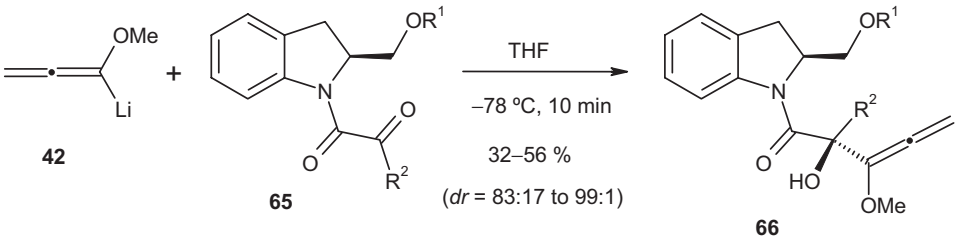
Scheme 8.16

Experiments with chiral carbonyl compounds demonstrated that lithiated alkoxyallenes display good diastereofacial selection. One of the first additions of lithiated methoxyallene **42** to a chiral ketone, a 2-acetylpyrrolidine derivative, was employed by Overman et al. as a crucial key step of the synthesis of allopumiliotoxin 267A [60]. More detailed investigations with chiral aldehydes were performed by Hormuth and Reissig [61–64]. The nucleophilic addition of **42** to *N*-protected α-aminoaldehydes **63** was shown to be highly flexible and largely independent of the nitrogen protective group or the substituent R. The good to excellent *anti* selectivity leading to products **64** results from the preferred Felkin-Anh addition (Scheme 8.17). The stereochemical outcome was unambiguously verified by an X-ray analysis of a subsequent cyclization product derived from the major *anti*-isomer of **64** (see also Scheme 8.27) [65].



Scheme 8.17

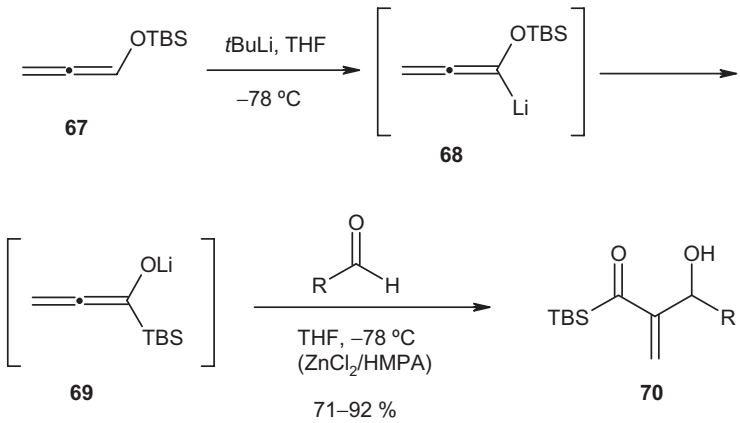
Similarly, diastereoselective addition of **42** to chiral α-ketoamides **65** afforded primary allene adducts **66** in moderate yields but with a high level of stereoselectivity (Scheme 8.18) [55].



R^1 = Me, TBS; R^2 = Me, Et, *n*Hexyl, Ph

Scheme 8.18

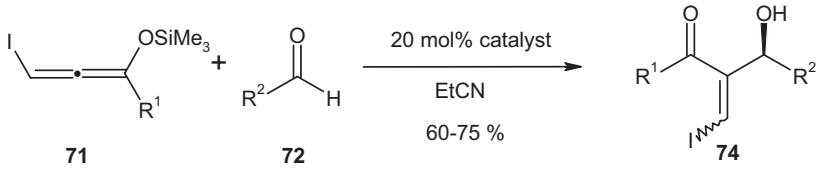
The addition of carbonyl compounds towards lithiated 1-siloxy-substituted allenes does not proceed in the manner described above for alkoxyallenes. Tius and co-workers found that treatment of 1-siloxy-substituted allene **67** with *tert*-butyllithium and subsequent addition of aldehydes or ketones led to the formation of α,β-unsaturated acyl silanes **70** (Scheme 8.19) [66]. This simple and convenient method starts with the usual lithiation of allene **67** at C-1 but is followed by a migration of the silyl group from oxygen to C-1, thus forming the lithium enolate **69**, which finally adds to the carbonyl species. Transmetalation of the lithiated intermediate **69** to the corresponding zinc enolate provided better access to acylsilanes derived from enolizable aldehydes. For reactions of **69** with ketones, transmetalation to a magnesium species seems to afford optimal results.



R = Bn, *i*Pr, *n*Pent, CH_2CH_2Ph, $C_6H_3(OMe)_2$, pXC_6H_4 (X = NMe_2, OMe)

Scheme 8.19

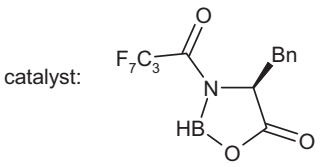
Li's group reported the first asymmetrically catalyzed addition of 1-siloxy-substituted 3-iodoallenes **71** to carbonyl compounds employing *N*-heptafluoropropyloxazaborolidine **73** as a chiral catalyst (Scheme 8.20) [67]. The resulting β-iodo Baylis–Hillman-type adducts **74** are available in good yield and with enantioselectivities up to 98% *ee*.



71 **72** **74**

E/*Z* = 1:1.8 to >1:20
ee = 66-98 %

R^1 = Me, *n*Pr, Ph, *p*MeC$_6$H$_4$; R^2 = Et, *n*Pr, *i*Bu, Ph, PhCH=CH, *p*XC$_6$H$_4$ (X = Me, OMe)

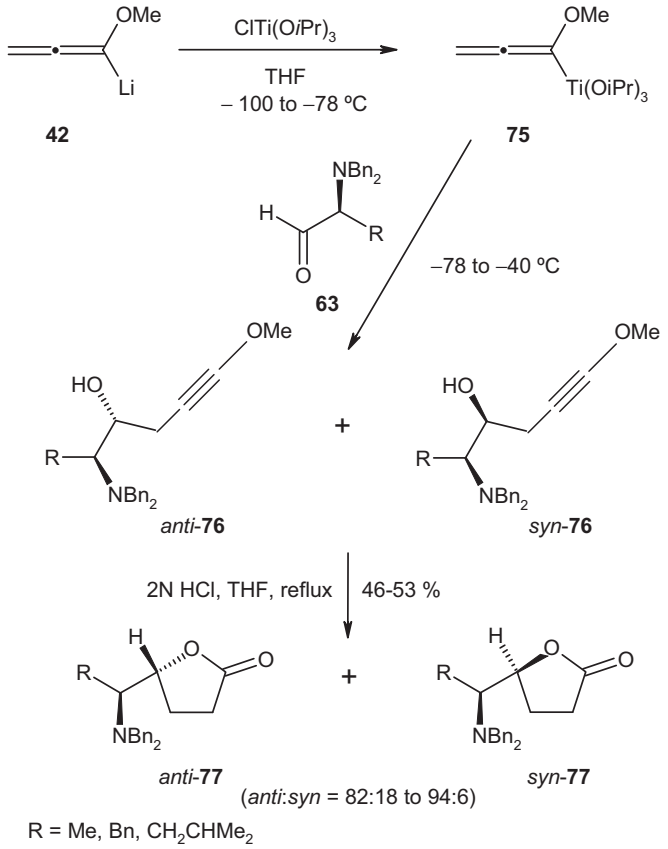


73

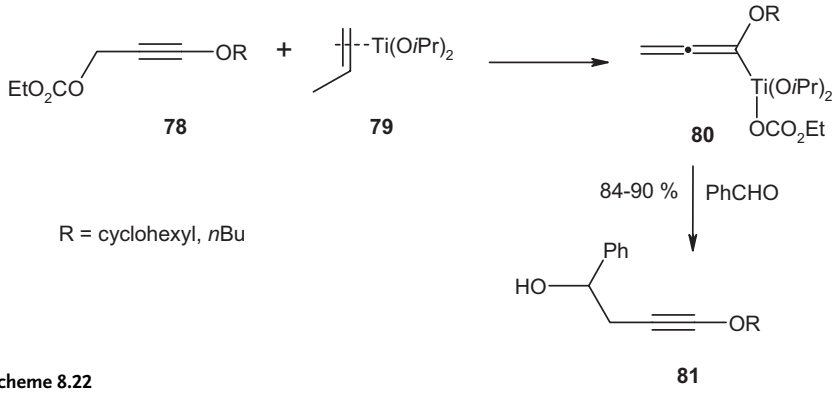
Scheme 8.20

In contrast to lithiated allenes, the corresponding titanium species and carbonyl compounds furnished the regioisomeric γ-addition products [68,69]. Thus, reaction of α-aminoaldehydes **63** with the titanated intermediate **75** gave methoxyalkynes **76**, which smoothly cyclized in the presence of acid and provided lactones **77**, again with high *anti* selectivity (Scheme 8.21) [69]. The regioselectivity depends on the aldehyde used.

An alternative formation of titanated alkoxyallenes could be achieved by reaction of 3-alkoxy-2-propyn-1-yl carbonates **78** with (η^2-propene)titanium diisopropoxylate (**79**). Successive addition of **80** to benzaldehyde afforded the corresponding addition products **81** in high yield (Scheme 8.22) [70]. The results demonstrate that titanium species **75** and **80** can serve as easily available ester homoenolate equivalents. Notably, conversion of lithiated alkoxyallenes to the magnesium species by treatment with $MgBr_2$ followed by addition to chiral carbonyl compounds resulted in a mixture of α- and γ-products [71].

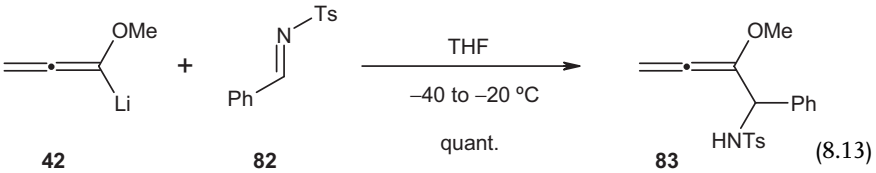


Scheme 8.21

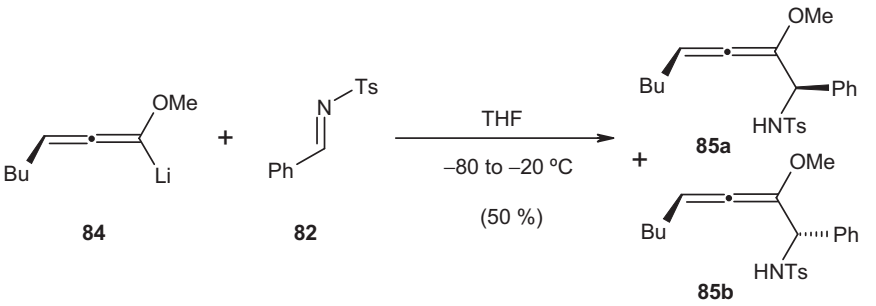


Scheme 8.22

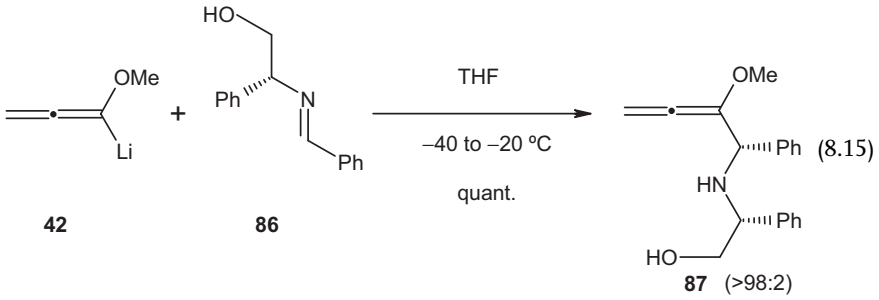
The successful application of carbonyl compounds as reaction partners of lithiated alkoxyallenes has stimulated the investigation of a variety of electrophiles containing C=N units. Surprisingly, the first systematic investigations were reported only in the late 1990s [72–76] when achiral and chiral imines generally turned out to be very suitable electrophiles for addition to lithiated methoxyallene **42**. The expected allenyl amines were formed in good to excellent yields. As typical examples, adducts **83**, **87**, **89** and **91** are represented in Eqs 8.13 and 8.15–8.17. A similar result was obtained using the in situ-formed 3-butyl-1-lithio-1-methoxyallene (**84**) (Eq. 8.14), but unfortunately this addition led to an unselective formation of the two diastereomeric trisubstituted allenes **85** [74]. In case of imines with chiral nitrogen substituents, the stereochemical outcome of their reaction with lithiated methoxyallene **42** depends strongly on the nature of the nitrogen substituents. With the phenylglycinol-derived imine **86** only one diastereomer of **87** was detected (Eq. 8.15) [77]. SAMP-derived hydrazones **88** provided the corresponding primary adducts **89** in excellent yields and high diastereomeric purity. These intermediates can be converted into enantiomerically pure dihydropyrrole derivatives [75]. Lithiated methoxyallene **42** and *N*-phenyl-protected glyceraldehyde-derived imine **90** furnished the adduct **91** with good *syn*-diastereoselectivity, an example which demonstrates that a chiral centre at the α-carbon atom of the imine can also efficiently control the stereochemistry of these addition reactions [77].



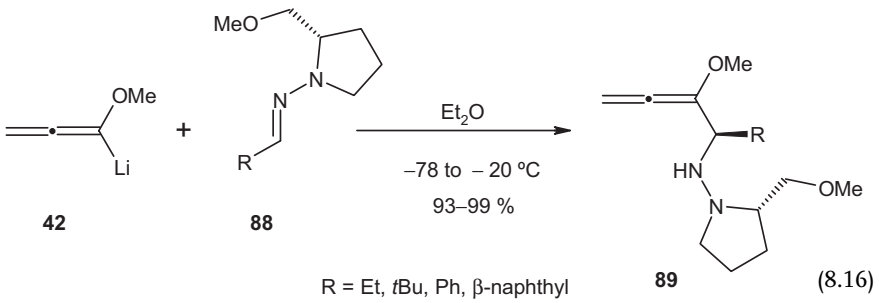
42 **82** **83** (8.13)



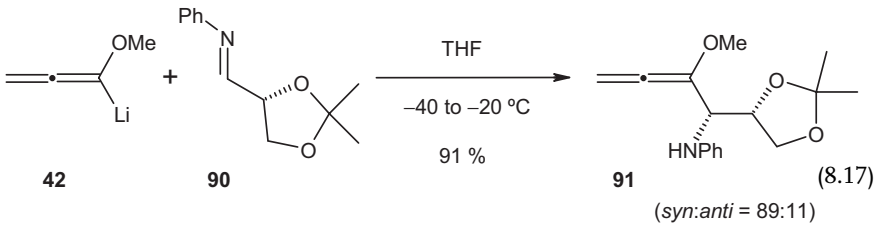
84 **82** (1:1) (8.14)



(8.15)

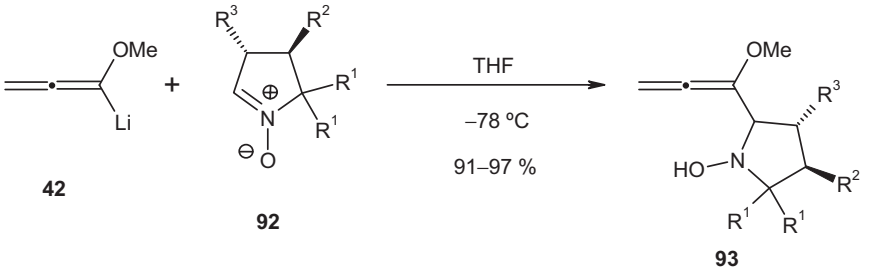


(8.16)



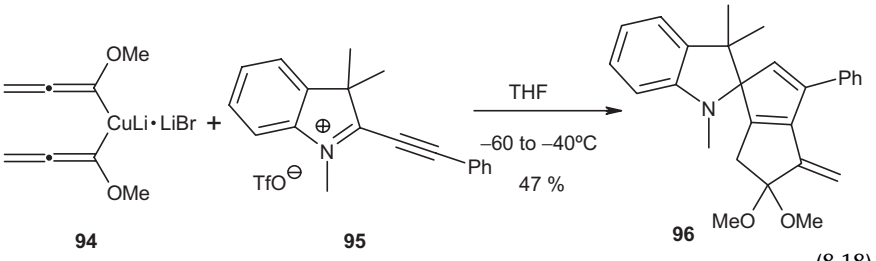
(8.17)

In several additions of lithiated methoxyallene **42** to sterically hindered nitrones **92**, *N*-hydroxypyrrolidines **93** were obtained in high yield and with excellent diastereoselectivity (Scheme 8.23) [72, 76]. Primary products **93** smoothly cyclize to give bicyclic compounds as shown in Eqs 8.25 and 8.26.



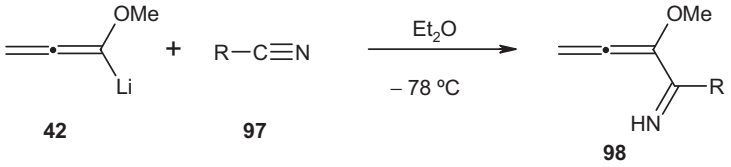
Scheme 8.23

In a single reaction, Maas and co-workers used iminium salt **95** as an electrophile for the addition to 1-methoxyallenyl cuprate **94**, which was prepared by transmetalation of lithiated methoxyallene **42** (Eq. 8.18) [78]. Spiro compound **96** was isolated in moderate yield.



94 **95** **96** (8.18)

Reaction of lithiated methoxyallene **42** with nitriles **97** provided the expected allenylimines **98** (Scheme 8.24); however, these products are very labile and only singular examples could be cyclized to afford the expected pyrroles (see Scheme 8.37) [79].



42 **97** **98**

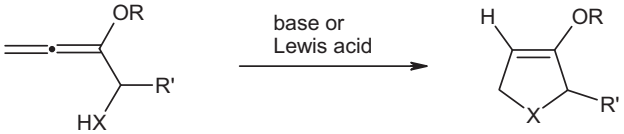
R = *i*Pr, *t*Bu, Ph

Scheme 8.24

8.2.2.2 Subsequent Ring-Closing Reactions of the Primary Allene Adducts

The primary allene adducts of general structure **99** as introduced in Section 8.2.2.1 generally are able to undergo (Baldwin disfavored) 5-*endo-trig* cyclizations to furnish products of type **100**. These isomerizations are either promoted by bases or catalyzed by Lewis acids or transition metal complexes.

The oxygen- or nitrogen-substituted allene adducts as described in the previous section are of major interest because of the possible subsequent cyclization leading to very valuable oxygen- or nitrogen-containing heterocycles (Scheme 8.25). The syn-

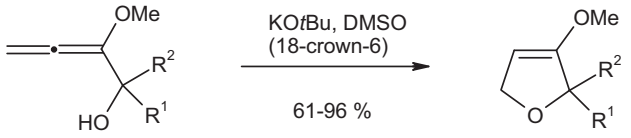


99 X = O, NR **100**

Scheme 8.25

thetic usefulness of such ring formations of primary allenyl adducts as precursors was demonstrated by the synthesis of several natural products and other compounds with biological activity.

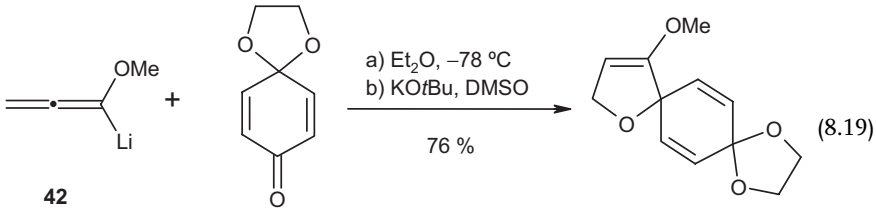
The first cyclization of α-hydroxyalkoxyallenes goes back to the pioneering experiments of Brandsma, Hoff and Arens, who found that dihydrofuran derivatives **102** are formed by treatment of **101** with KO*t*Bu in DMSO (Scheme 8.26) [12c]. This reaction protocol was successfully applied by others [61, 63, 64, 80–83], for example in the preparation of spiro compound **104** (Eq. 8.19) [83] and in the cyclization of **64** leading to α-amino acid-derived dihydrofurans **105** (Scheme 8.27) [61, 63]. Acidic hydrolysis of dihydrofurans furnished 3(2*H*)-dihydrofuranones, which could be used again as carbonyl components in the repetitive addition of lithiated methoxyallene **42**. This concept was employed in syntheses of racemic [82] and enantiomerically pure [64] primary helical spirocycles.



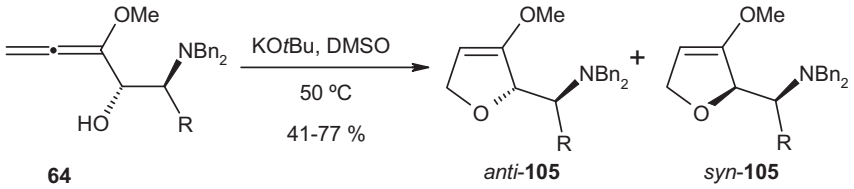
101 **102**

R^1,R^2 = H, alkyl, aryl, cycloalkyl

Scheme 8.26



42 **103** **104** (8.19)



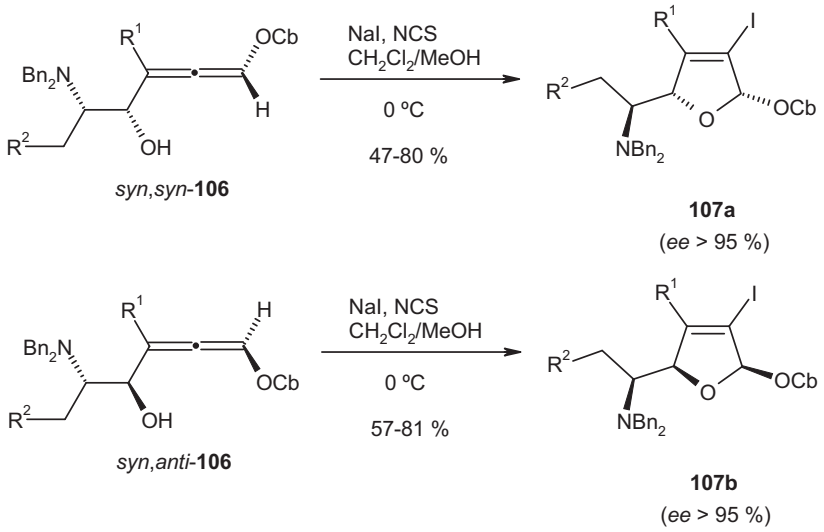
64 *anti*-**105** *syn*-**105**

(*anti*:*syn* = 80:20 to >99:1)

R = H, Me, Bn, CH_2*i*Pr

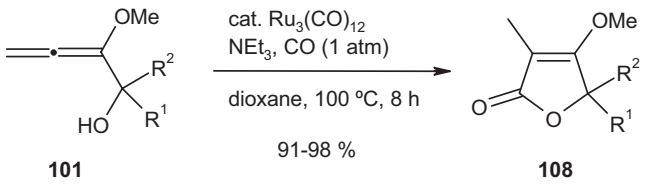
Scheme 8.27

An alternative synthesis of dihydrofurans was recently described by Hoppe and co-workers [84]. The easily accessible 4-hydroxy-1,2-alkadienyl carbamates **106** were treated with NaI in the presence of NCS, which resulted in the formation of 3-iodo-2,5-dihydrofurans **107** (Scheme 8.28). *Syn,syn*-**106** and *syn,anti*-**106** gave the corresponding enantiopure 3-iodo compounds **107a,b** in moderate to good yield. By treatment of *syn,syn*-**106** with iodine in DMSO at 90 °C, the authors obtained the corresponding 3-iodofuran [84].



Scheme 8.28 R^1 = Me, Me_3Si; R^2 = *i*Pr, Ph

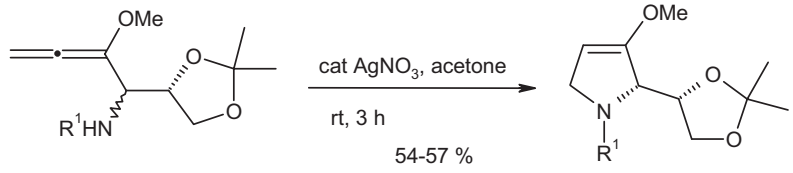
Another interesting cyclization employing 2-hydroxy-substituted methoxyallenes **101** was reported by Takahashi et al. (Scheme 8.29) [85]. Their novel $Ru_3(CO)_{12}$-catalyzed carbonylation reaction of allenyl alcohols **101** furnished γ-lactones **108** in almost quantitative yields.



R^1 = H, Me; R^2 = Me, Et, Ph; R^1,R^2 = $(CH_2)_5$

Scheme 8.29

In analogy with α-hydroxy-substituted alkoxyallene adducts, the corresponding allenylamines, e.g. **109** in Scheme 8.30 and **85** in Eq. 8.20, can be cyclized to dihydropyrrole derivatives either under basic conditions [43, 74, 75] or by treatment with catalytic amounts of $AgNO_3$ in acetone or acetonitrile [43, 73, 74].



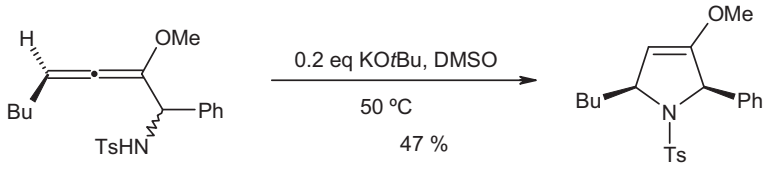
109a,b

a: *syn*:*anti* = 89:11
b: only *syn*

a: R^1 = Ph,
b: R^1 = Bn

110a,b

Scheme 8.30

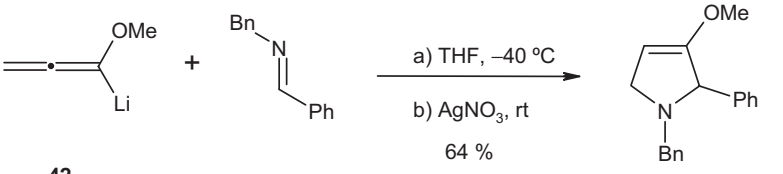


(8.20)

85

syn-**111**
(+ 10 % *anti*-**111**)

Many other examples, even with less reactive imine precursors as electrophiles, demonstrate that this type of dihydropyrrole synthesis has a very broad range. Eqs 8.21–8.24 present selected examples of the addition of lithiated methoxyallene **42** to *N*-alkyl- and *N*-aryl-substituted acyclic or cyclic imines and the subsequent cyclizations providing the heterocyclic target compounds [74, 79].

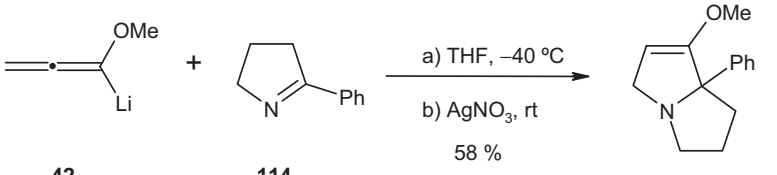


(8.21)

42

112

113

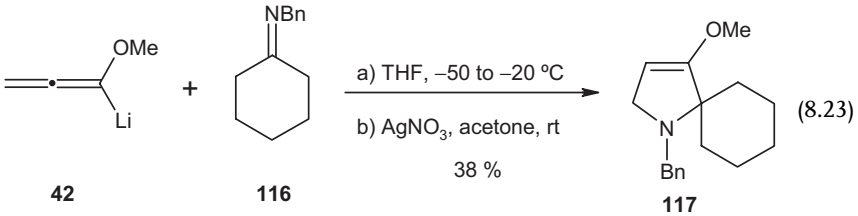


(8.22)

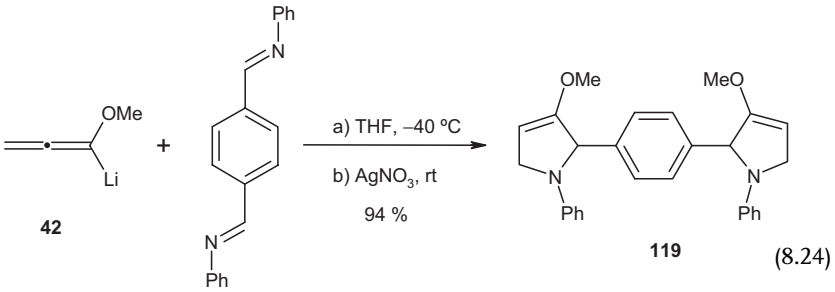
42

114

115

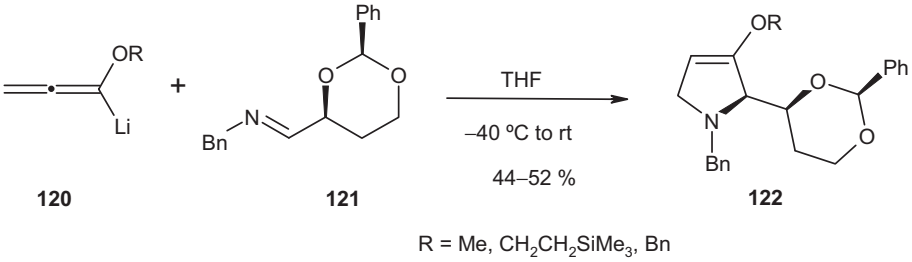


42 116 117 (8.23)



42 118 119 (8.24)

The efficient addition–cyclization sequence described above could be successfully applied to the preparation of the polyhydroxylated γ-amino acid (–)-detoxinine [73]. The crucial key step in this fairly short synthesis is the chelate-controlled addition of lithiated benzyloxyallene **120** (R = Bn) to the chiral *N*-benzyl-substituted imine **121** as shown in Scheme 8.31. The required skeleton of the natural product was generated in good overall yield.



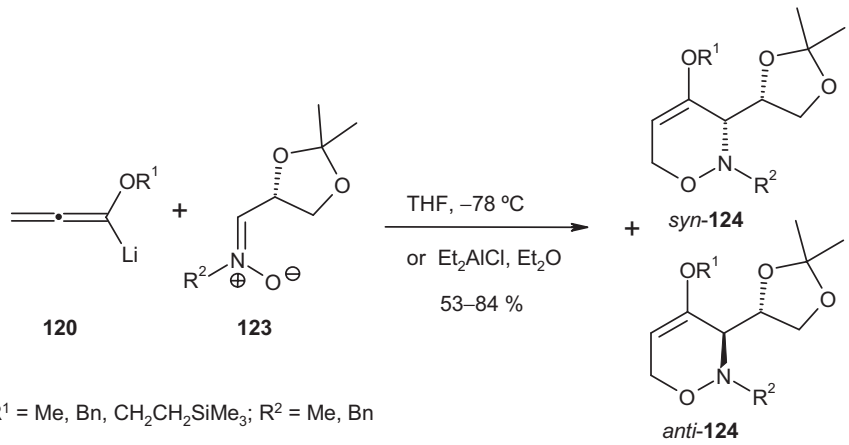
120 121 122

R = Me, $CH_2CH_2SiMe_3$, Bn

Scheme 8.31

The substrate-controlled diastereoselective addition of lithiated alkoxyallenes to chiral nitrones such as **123**, **125** and **126** (Scheme 8.32) furnish allenylhydroxylamines as unstable products, which immediately cyclize to give enantiopure mono- or bicyclic 1,2-oxazines (Eqs 8.25 and 8.26) [72, 76]. Starting with (*R*)-glyceraldehyde-derived nitrone **123**, cyclization products **124** were formed with excellent *syn* selectivity in tetrahydrofuran as solvent, whereas precomplexation of nitrone **123** with

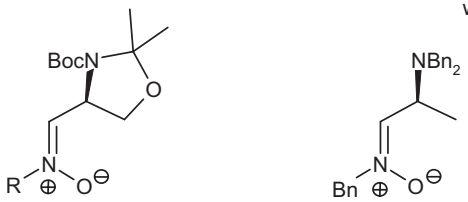
Et_2AlCl in diethyl ether led to *anti*-configured 1,2-oxazines **124** with high preference [72]. The few isolable allenylhydroxylamines, e.g. **127** and **130**, readily cyclized on standing at room temperature (several days) to give bicyclic compounds **128** and **131** in high yields. The cyclization of intermediate **127** also provided bicyclic amine oxide **129** as a byproduct. Surprisingly, the ratio of the two cyclization products depends on the concentration of the solution and on the solvent employed [76]. It should be mentioned that the products of these formal [3 + 3] cyclizations as presented in Scheme 8.32 and Eqs 8.25 and 8.26 are excellent precursors for optically active pyrrolidines, acyclic amino alcohols or other compounds with potential biological activity [86].



120 **123**

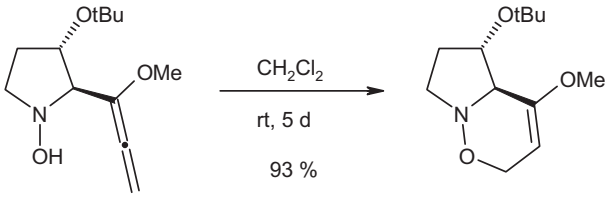
R^1 = Me, Bn, $CH_2CH_2SiMe_3$; R^2 = Me, Bn

without Et_2AlCl: *syn*:*anti* = 94:6 to 98:2
with Et_2AlCl: *syn*:*anti* = 3:97

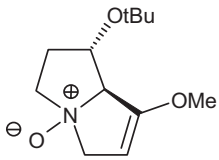


125 (R = Me, Ph) **126**

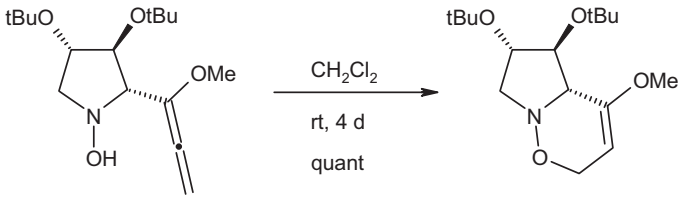
Scheme 8.32



127 **128** (8.25)

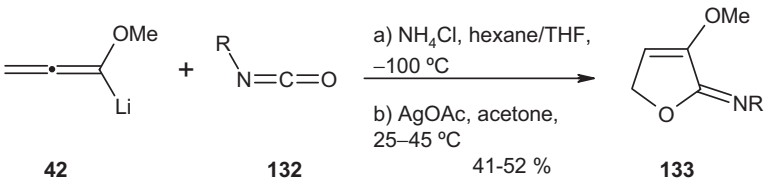


129



130 **131** (8.26)

Additions of lithiated alkoxyallenes to alkyl-substituted isocyanates and isothiocyanates as electrophiles were recently disclosed by Nedolya and co-workers [87–91]. A short route to *N*-[2(5*H*)-furanylidene]amines **133** consists in the addition of lithiated methoxyallene **42** to alkyl isocyanates **132** and silver acetate-mediated cyclization of the intermediate (Scheme 8.33) [87].

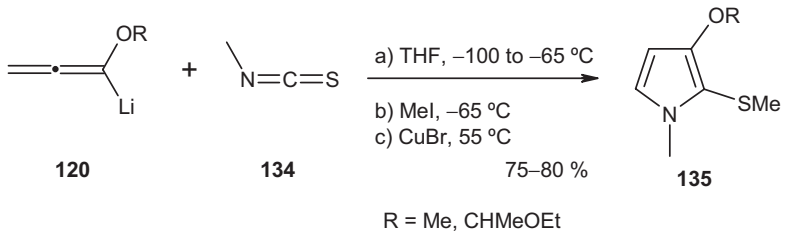


42 **132** **133**

R = *n*Pr, *i*Pr

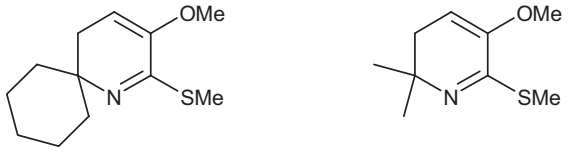
Scheme 8.33

These authors also demonstrated that the outcome of analogous additions of lithiated alkoxyallenes **120** to isothiocyanates is highly dependent on the nature of the alkyl group in the isothiocyanates as depicted in Schemes 8.34 and 8.35 [88, 91]. Whereas methyl isothiocyanate **134** leads to pyrrole derivative **135**, the correspond-



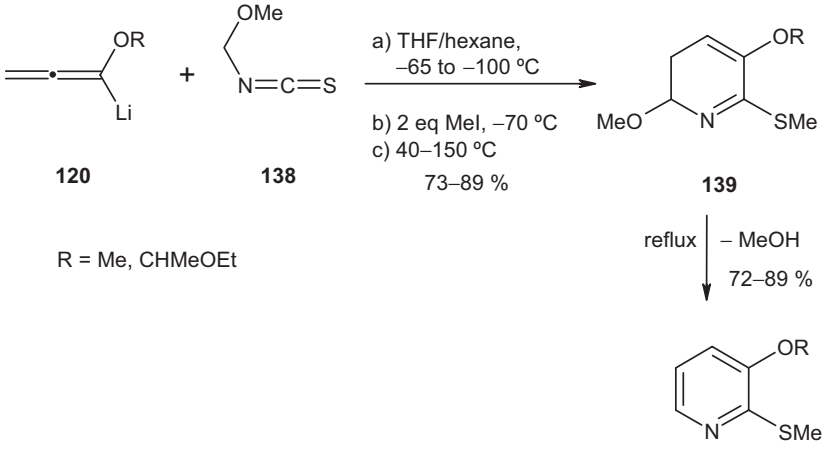
120 **134** **135**

R = Me, CHMeOEt



136 **137**

Scheme 8.34



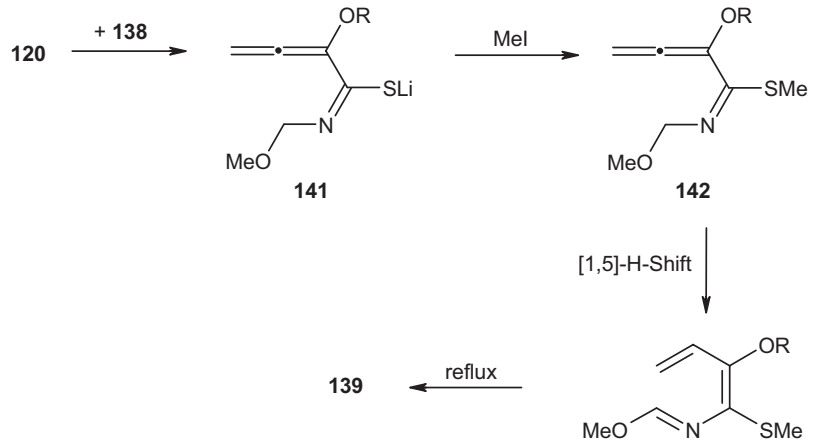
120 **138** **139**

R = Me, CHMeOEt

140

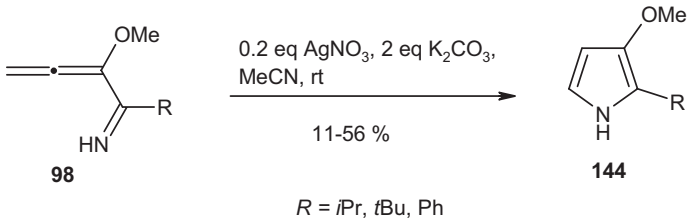
Scheme 8.35

ing cyclohexyl, isopropyl and methoxymethyl isothiocyanates give predominantly 2,3-dihydropyridines **136**, **137** and **139**. As shown in Scheme 8.36, the authors suggest that the reaction proceeds through the formation of allenyl adduct **141** followed by methylation at the thiolate function to give 2,3-butadieneimidothioate **142**. The resulting intermediate **142** isomerizes to the 1,3-butadiene **143**, which affords pyridine derivative **139** by electrocyclization.



Scheme 8.36

The allenylimines **98** can be cyclized in the presence of silver nitrate to provide the electron-rich and rather sensitive 3-methoxypyrrole derivatives **144** in low to moderate yield [79].

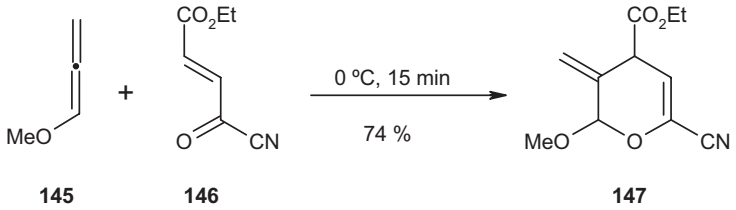


Scheme 8.37

8.2.3 Cycloadditions and Cyclizations

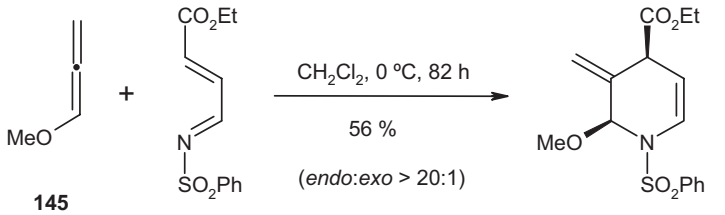
8.2.3.1 [4 + 2], [3 + 2] and [2 + 2] Cycloadditions

Cycloadditions and cyclization reactions are among the most important synthetic applications of donor-substituted allenes, since they result in the formation of a variety of carbocyclic and heterocyclic compounds. Early investigations of Diels–Alder reactions with alkoxyallenes demonstrated that harsh reaction conditions, e.g. high pressure, high temperature or Lewis acid promotion, are often required to afford the corresponding heterocycles in only poor to moderate yield [12b, 92–94]. Although α,β-unsaturated carbonyl compounds have not been used extensively as heterodienes, considerable success has been achieved with activated enone **146** (Eq. 8.27) or with the electron-deficient tosylimine **148** (Eq. 8.28). Both dienes reacted under



(8.27)

145 **146** **147**



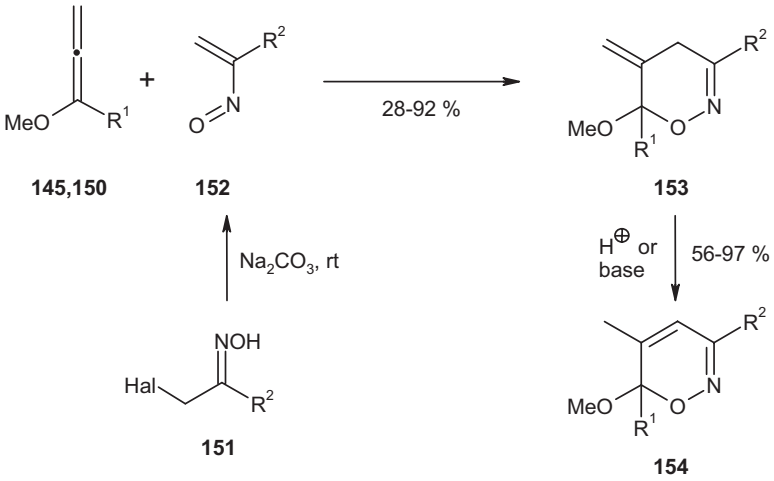
(8.28)

145 **148** **149**

fairly mild conditions with methoxyallene **145** yielding 3,4-dihydro-2*H*-pyran **147** [93b] and 1,2,3,4-tetrahydropyridine **149**, respectively [95].

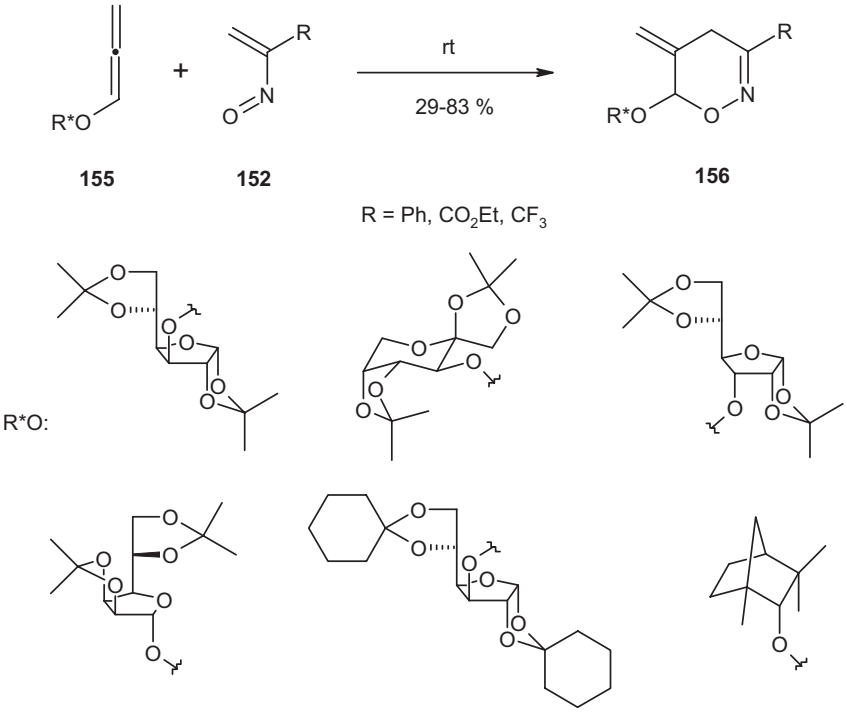
An important application of donor-substituted allenes in cycloadditions leads to six-membered *N,O*-heterocycles [15, 47, 96–99]. As depicted in Scheme 8.38, a series of hetero-Diels–Alder reactions were performed by trapping highly reactive α-nitrosoalkenes **152**, generated in situ by base treatment of α-halogen oximes **151**, with methoxyallene **145** and its C-1-substituted derivatives **150** [15, 47, 96–98]. The isomerization of the primary cycloadducts **153** to 6*H*-1,2-oxazines **154** was achieved by either base or acid catalysis [47]. The use of chiral starting materials in asymmetric hetero-Diels–Alder reactions allows the preparation of optically active 1,2-oxazines [15, 99]. Easily available alkoxyallenes **155** bearing carbohydrate auxiliaries are well suited as precursors in the asymmetric synthesis of 1,2-oxazines **156** (Scheme 8.39) [99]. Diacetoneglucose-derived alkoxyallene turned out to be the best dienophile in these hetero-Diels–Alder reactions, furnishing the corresponding 5,6-dihydro-4*H*-1,2-oxazine **156** with a diastereomeric ratio of ~90:10.

In the [4 + 2] cycloadditions discussed so far, the enol ether double bond of alkoxyallenes is exclusively attacked by the heterodienes, resulting in products bearing the alkoxy group at C-6 of the heterocycles. This regioselective behavior is expected for [4 + 2] cycloadditions with inverse electron demand considering the HOMO coefficients of methoxyallene **145** [100]. In contrast, all known intramolecular Diels–Alder reactions of allenyl ether intermediates occur at the terminal C=C bond [101], most probably because of geometric restrictions.



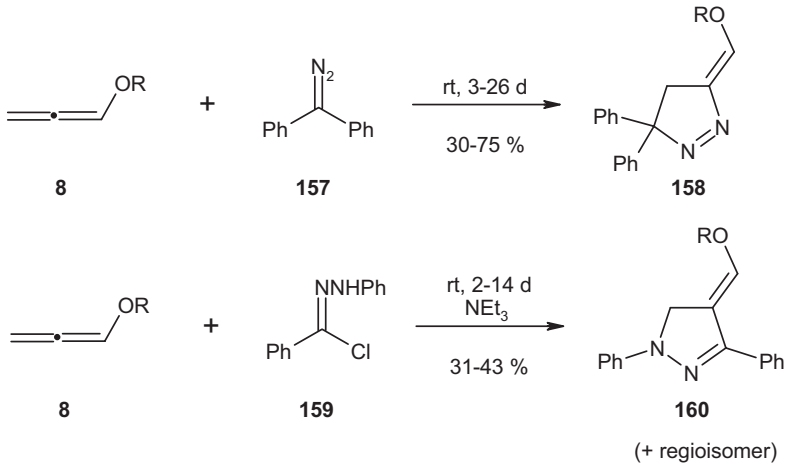
R^1 = H, Me, allyl, CMe_2OH, CHMeOH, CHMeOTBS, CHPhOH,
R^2 = Ph, aryl, CO_2Et, CF_3, $HC{=}CHCO_2Me$; Hal = Cl or Br

Scheme 8.38



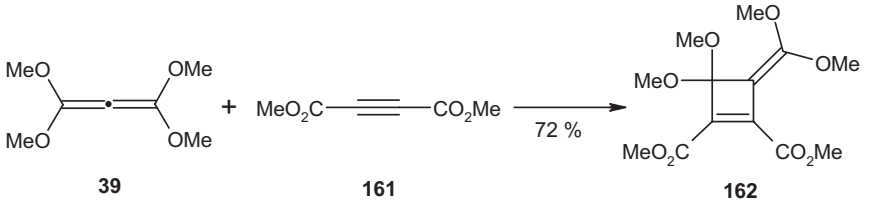
Scheme 8.39

Less frequently applied are [3 + 2] and [2 + 2] cycloadditions of oxygen-substituted allenes [102–104]. Battioni et al. described only a limited number of [3 + 2] cycloadditions of phenyloxy- and methoxyallene with diphenyldiazomethane (**157**) and the nitrile imine derived from diphenylhydrazonoyl chloride (**159**) (Scheme 8.40) [102]. Both 1,3-dipoles exclusively attack the terminal C=C bond, furnishing cycloadducts **158** and **160**. Padwa et al. reported [3 + 2] cycloadditions of methoxyallene **145** with two nitrones which afforded isoxazolidines in low yield [103].

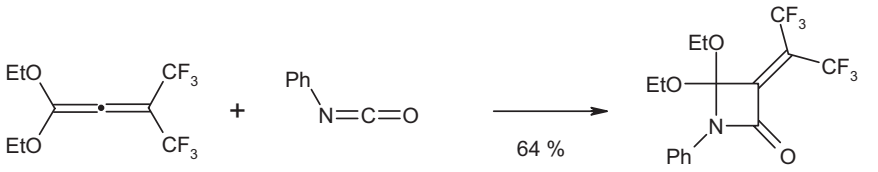


Scheme 8.40

The few reported [2 + 2] cycloadditions of alkoxyallenes illustrated in Eqs 8.29 and 8.30 are probably of less synthetic importance. Cyclobutene derivative **162** could be prepared in good yield by cycloaddition of tetramethoxyallene **39** and acetylenedicarboxylate **161** [105], whereas the reaction of 1,1-diethoxyallene **163** and phenylisocyanate (**164**) gave the expected β-lactam **165** [106]. Another example for a [2 + 2] cycloaddition is the dimerization of **39** described by Saalfrank et al. [107].



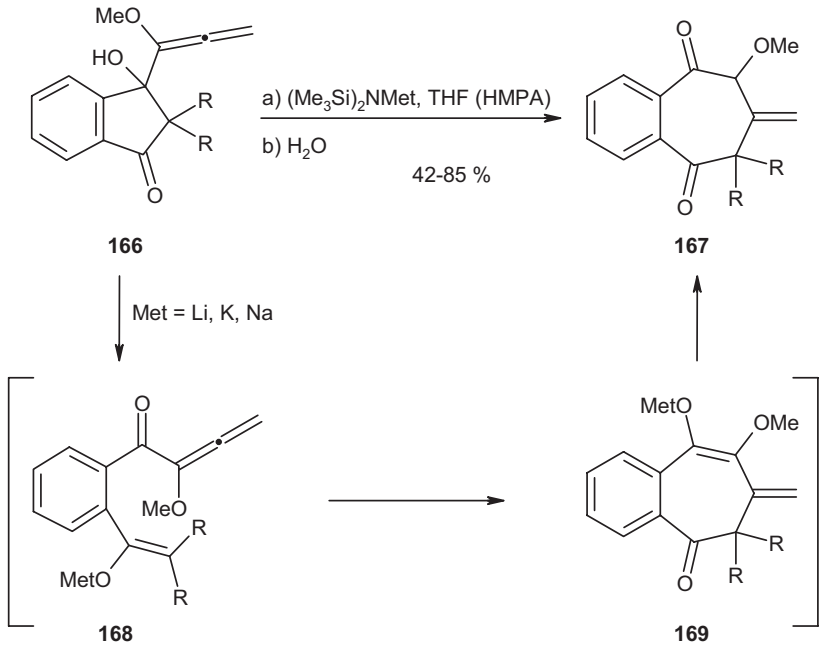
(8.29)



(8.30)

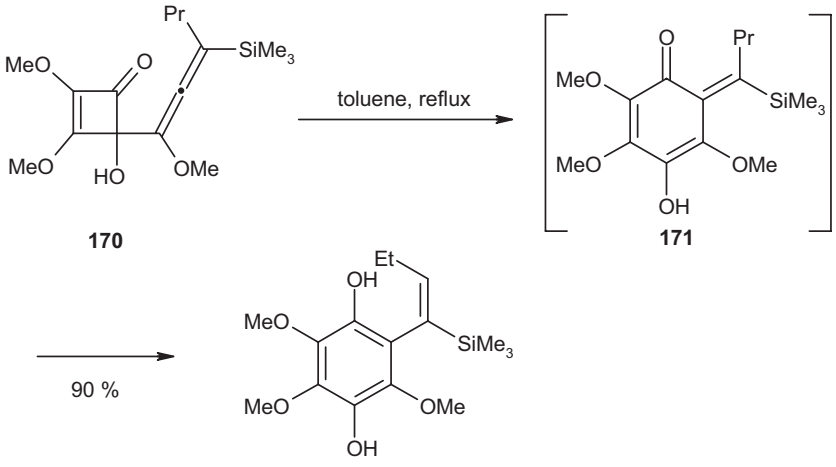
8.2.3.2 Other Cyclization Reactions

In addition to the cycloadditions described in the previous section, a series of electrocyclic ring closures, ring expansions, cyclopentannelations, etc., were performed with oxygen-substituted allenes. They allow the stereoselective construction of highly functionalized carbocyclic compounds. It has been shown that 3-hydroxy-3-(1-methoxyallenyl)indanone derivatives **166** are transformed into benzocyclohepten-1,5-diones **167** by base-induced intramolecular tandem two-carbon ring expansion (Scheme 8.41) [108]. This ring expansion process can be explained by ring opening of **166** leading to allenyl ketone intermediate **168**, followed by a Michael-type addition to form **167** via **169**. Interestingly, this group also developed a related palladium-catalyzed ring expansion leading to 4-oxo-α-tetralones (see Chapter 14).



Scheme 8.41

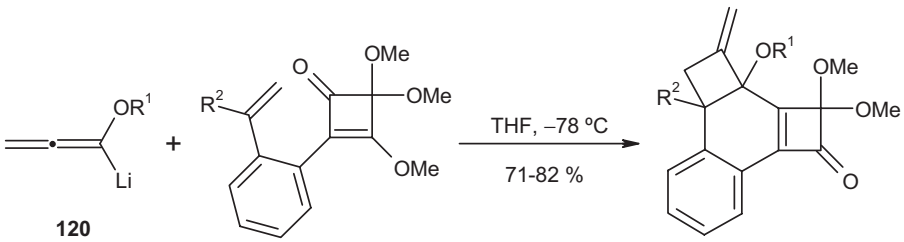
The groups of Liebeskind and Moore independently explored the ring expansion of allenyl-substituted cyclobutenol derivatives. This allows either the preparation of 5-alkylidene-2-cyclopentenones, which are substructures of naturally occurring bioactive compounds [59], or the generation of *o*-quinone methides, which are very attractive intermediates in the synthesis of hexahydrocannabinols [109]. As shown in Scheme 8.42, the ring expansion of the tetrasubstituted methoxyallene derivative **170** furnished the vinylhydroquinone **172** in high yield [109].



170 **171** **172**

Scheme 8.42

An interesting possibility for the construction of a tetracyclic system **174** with two cyclobutane rings arises by addition of lithiated alkoxyallenes **120** to **173** followed by two consecutive electrocyclic reactions. Products such as **174** are useful precursors for benz[*a*]anthracene-7,12-diones (Scheme 8.43) [110].

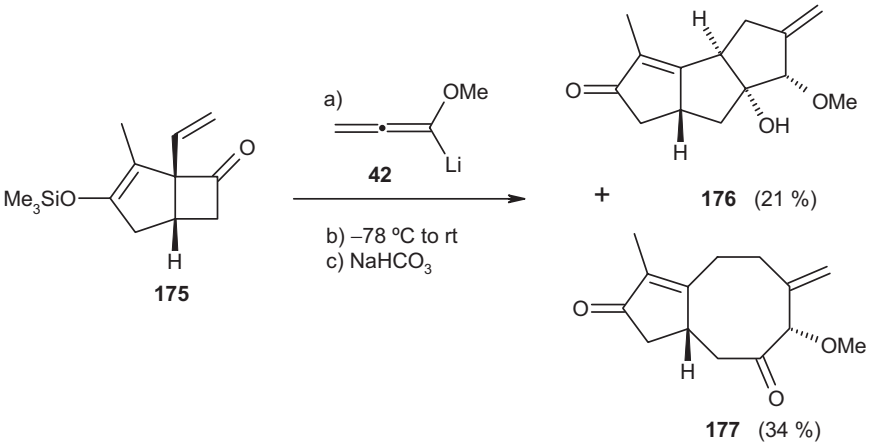


120 **173** **174**

R^1 = Me, *t*Bu; R^2 = H, Me

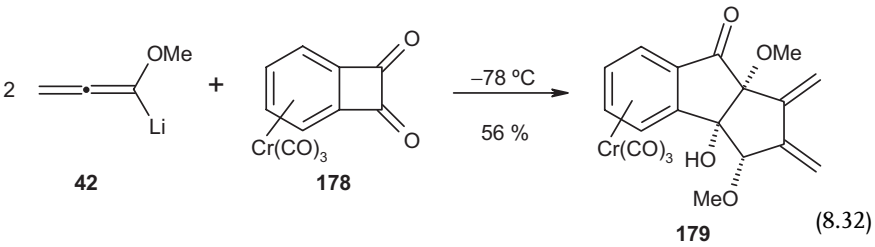
Scheme 8.43

Just one reaction has been described where lithiated methoxyallene **42** reacted with bicyclo[3.2.0]heptenone **175** to form the triquinane derivative **176** via a tandem oxy-Cope–transannular ring closure sequence (Eq. 8.31) [111]. However, cyclooctanone **177** was isolated as a major product, which is unusual since other alkenyllithium compounds and **175** provide only triquinanes. The authors assumed that the additional sp^2-hybridized C-atom in the eight-membered ring intermediate (enolate of **177**) induces a conformation which is less susceptible to transannular ring closure.



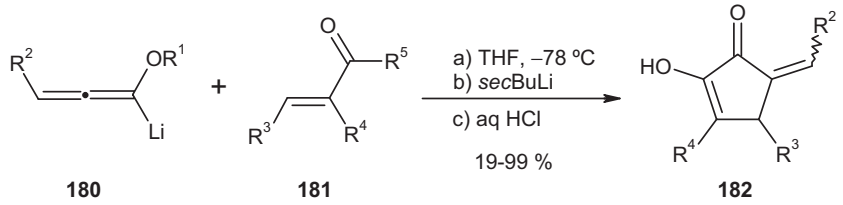
(8.31)

Butenschön and co-workers nicely demonstrated that treatment of (benzocyclobutendione)tricarbonylchromium(0) (**178**) with an excess of lithiated methoxyallene **42** gives the tricyclic complex **179**. It is the result of a dianionic oxy-Cope rearrangement and a subsequent intramolecular aldol addition (Eq. 8.32) [112].



(8.32)

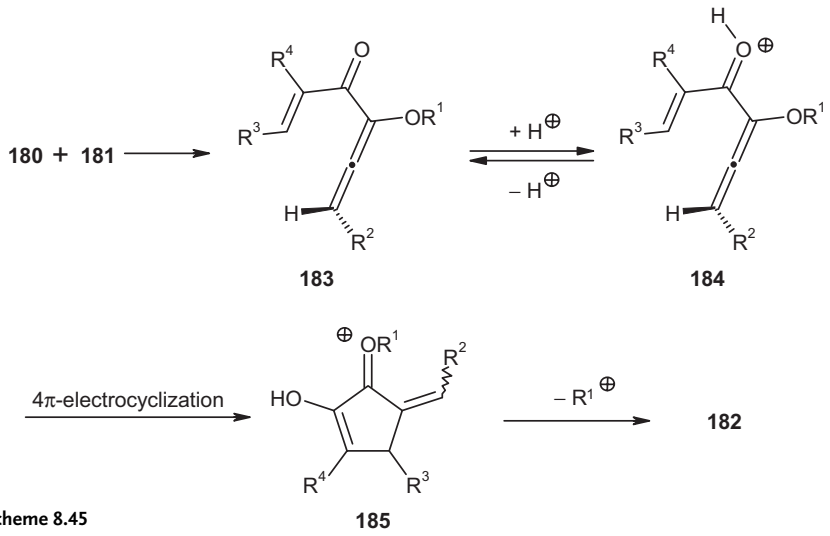
Tius and co-workers investigated a number of cationic cyclopentannelations of allenyl ethers [113] and found that 1-lithio-1-alkoxyallenes **180** react with α,β-unsaturated carbonyl compounds **181** leading to highly functionalized cyclopentenones **182** (Scheme 8.44). The primary products are α-allenyl ketones **183**, which form pentadienyl cations **184** by protonation. The latter undergo a thermally allowed 4π-conrotatory ring closure to intermediates **185**, which with elimination of R^1 finally lead to the expected products **182** (Scheme 8.45).



180 181 182

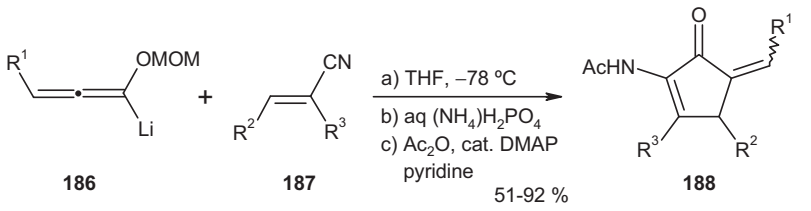
R^1 = Me, CH_2OMe, Cb; R^2 = H, Me, CH_2CH_2OH, *t*Bu;
R^3 = H, Me, Et, *i*Pr, Ph, *p*$MeOC_6H_4$; R^4 = Me, Ph, $CH_2CH_2CH{=}CH_2$, F, Br, OEt;
R^5 = NMeOMe

Scheme 8.44



Scheme 8.45

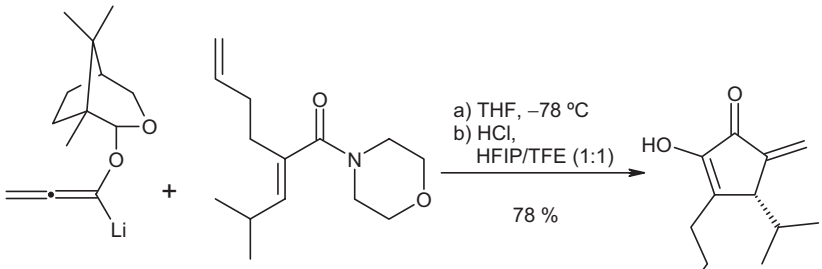
Tius and others have considerably extended this 4π-electrocyclization process, which was summarized in a comprehensive review [113h]. Recently, this powerful strategy was extended to α,β-unsaturated nitriles **187**, which can undergo an imino-Nazarov reaction as exemplified in Scheme 8.46 [113b]. Eq. 8.33 displays the successful asymmetric version of this cyclopentannelation which was carried out with 1-lithioallenes bearing camphor- or carbohydrate-derived auxiliaries such as **189** and **192**. The resulting cyclopentenones were formed with *ee* >85%. First efforts to synthesize enantioenriched 5-alkylidene-2-cyclopentenones **195** using chiral lithiated allenyl carbamates **193** were reported by Tius, Hoppe and co-workers (Eq. 8.34) [113c].



186 **187** **188**

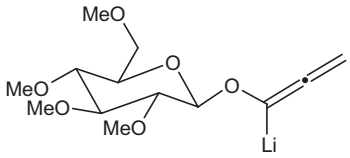
R^1 = H, Me; R^2 = Ph, *p*MeOC_6H_4; R^3 = Me;
R^2,R^3 = $CH_2CHPhCH_2CH_2$, $(CH_2)_{10}$, $O(CH_2)_3$

Scheme 8.46



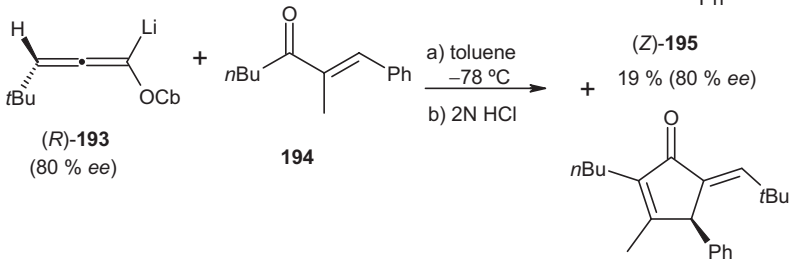
189 **190** **191**

(86 % ee)



192

(8.33)



(*R*)-**193**
(80 % *ee*)

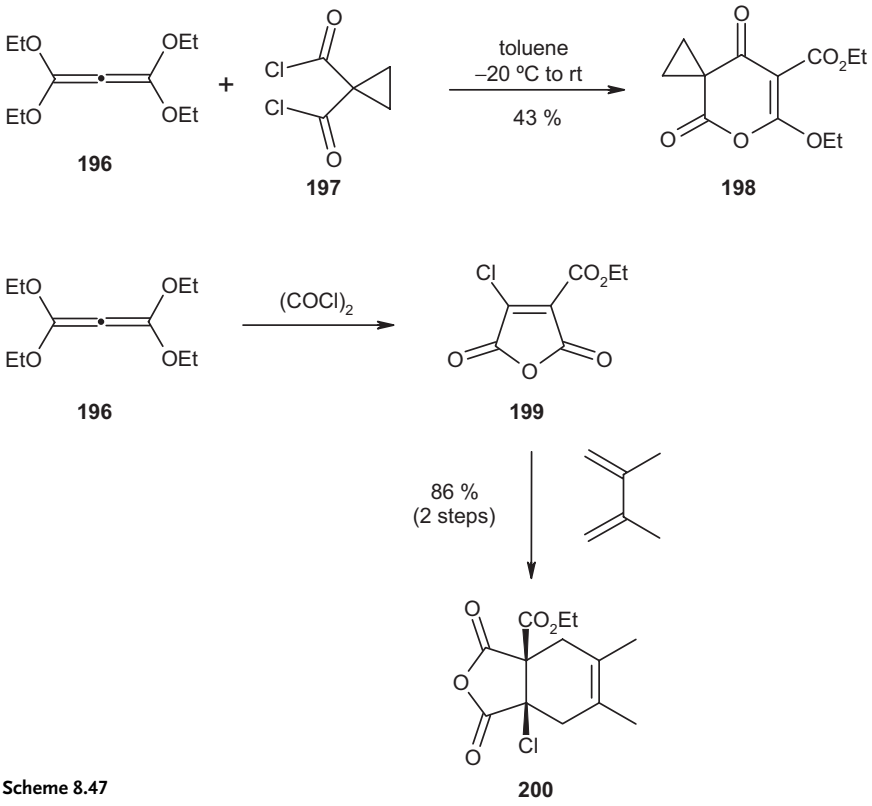
194

(*Z*)-**195**
19 % (80 % *ee*)

(*E*)-**195**
38 % (77 % *ee*)

(8.34)

Saalfrank, Hoffmann and co-workers performed a number of reactions with tetraalkoxyallenes such as **196** (Scheme 8.47) [1, 41, 105, 114–116] and demonstrated that this class of donor-substituted allenes can serve as a 1,3-dianion equivalent of malonic acid. Treatment of **196** with cyclopropyldicarboxylic acid dichloride **197** produces 2,4-dioxo-3,4-dihydro-2*H*-pyran **198** through release of two molecules of ethyl chloride [115]. Similarily, the reaction of this allene **196** with oxalyl chloride gives 3-chloromalonic acid anhydride derivative **199**. This intermediate is a reactive dienophile which accepts 2,3-dimethyl-1,3-butadiene in a subsequent [4 + 2] cycloaddition to afford cycloadduct **200** in good yield [116].



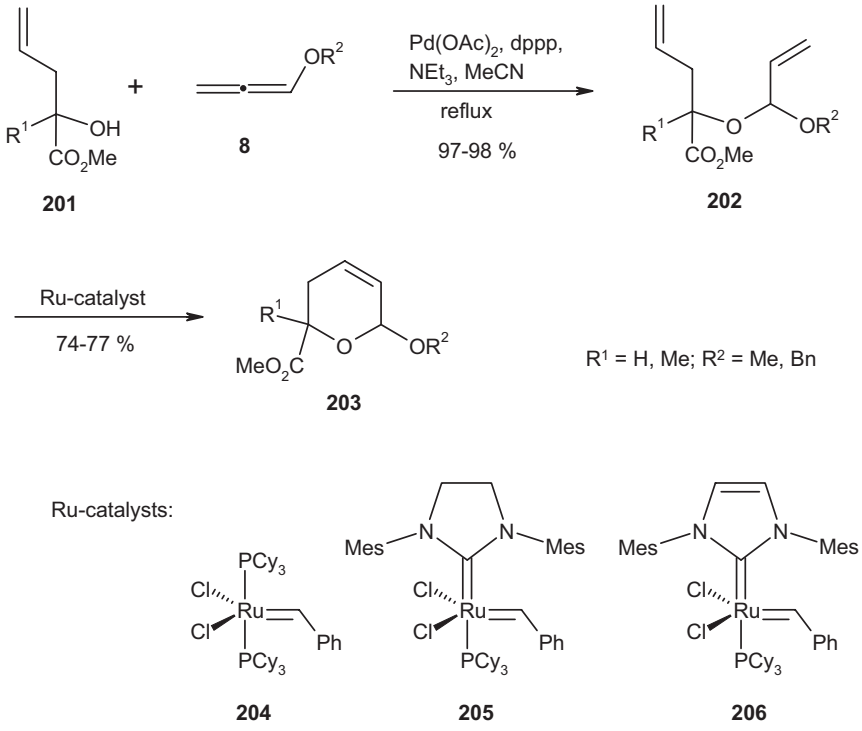
Scheme 8.47

8.2.4

Formation of Acetals and Subsequent Metathesis Reactions

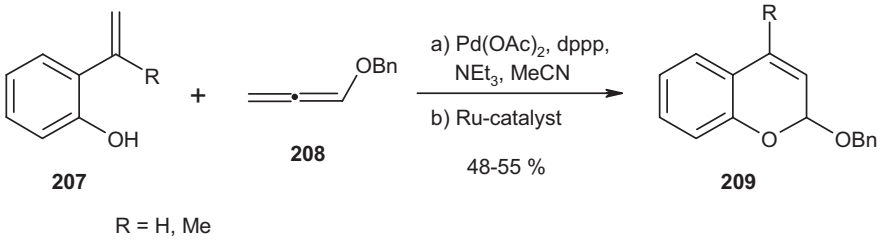
The olefin ring-closing metathesis (RCM) has been developed into an important synthetic method which is frequently employed in many synthetic endeavors. In many applications the popular Grubbs compound **204** or advanced complexes such as **205** and **206** were used as catalysts [117]. Rutjes and co-workers [118] and Okuro and Alper [119] elegantly used oxygen-substituted allenes to prepare precursors for the

synthesis of functionalized dihydropyrans. Treatment of homoallyl alcohols **201** with alkoxyallenes **8** in the presence of Pd(II) acetate, dppp and triethylamine in acetonitrile afforded the desired acetals **202** in excellent yields (Scheme 8.48) [118]. Subsequent RCM of intermediates **202** with Ru catalysts such as **204–206** provided dihydropyrans **203** as a mixture of diastereomers. Milder reaction conditions could be applied to phenols such as **207**, which allowed the preparation of benzopyrans **209** (Scheme 8.49) [118, 120].



201 **8** **202** **203** **204** **205** **206**

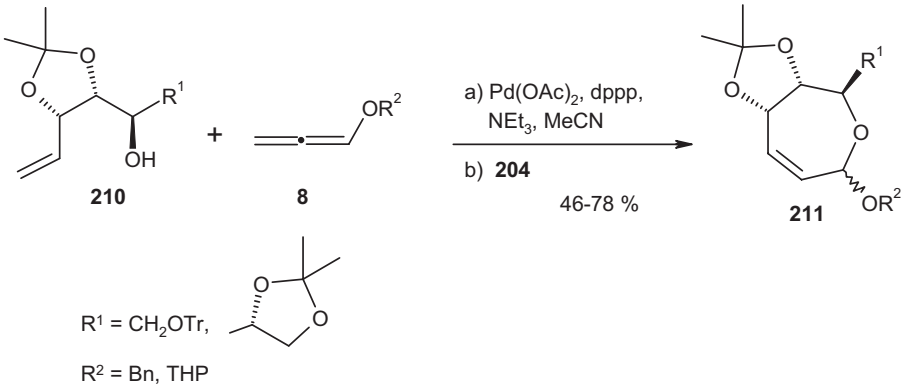
Scheme 8.48



207 **208** **209**

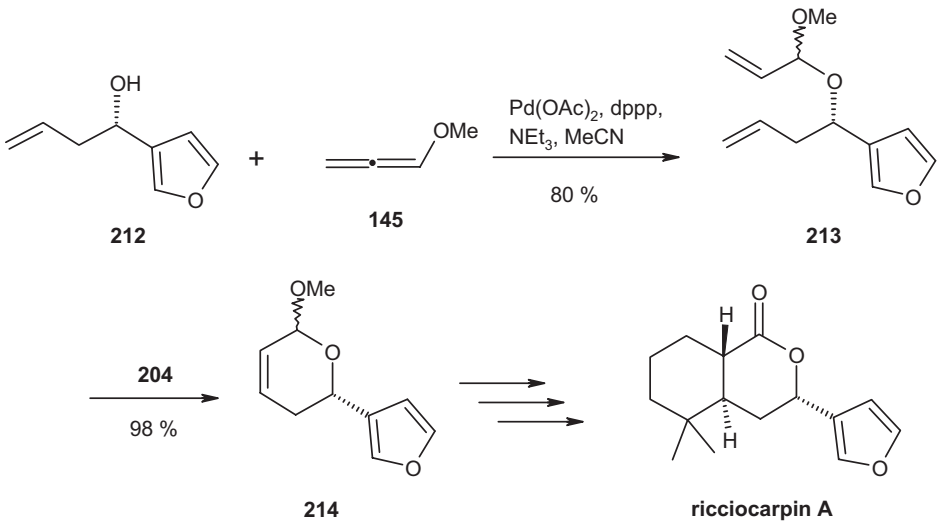
Scheme 8.49

Van Boom and co-workers published an expeditious route to chiral oxepines with monosaccharide derivatives as precursors. The synthesis was accomplished by treatment of **210** with alkoxyallenes **8** under Rutjes's optimized reaction conditions (Scheme 8.50) [121].

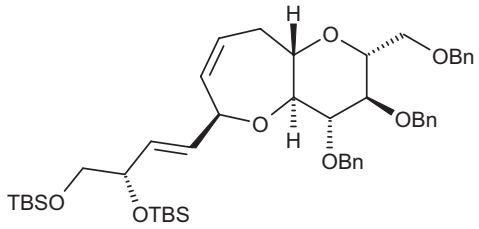


Scheme 8.50

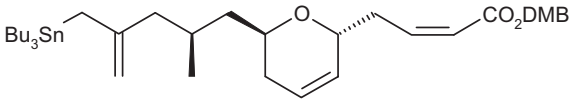
The oxypalladation method mentioned above was introduced as a crucial step in the synthesis of several natural products. As shown in Scheme 8.51, Metz and co-workers used this strategy in an enantioselective synthesis of ricciocarpin A [122]. Other impressive applications including the acetalization–RCM sequence have been employed in the synthesis of the AB ring of ciguatoxin [123] and of the C_1–C_{14} fragment of laulimalide [124] (Scheme 8.52).



Scheme 8.51



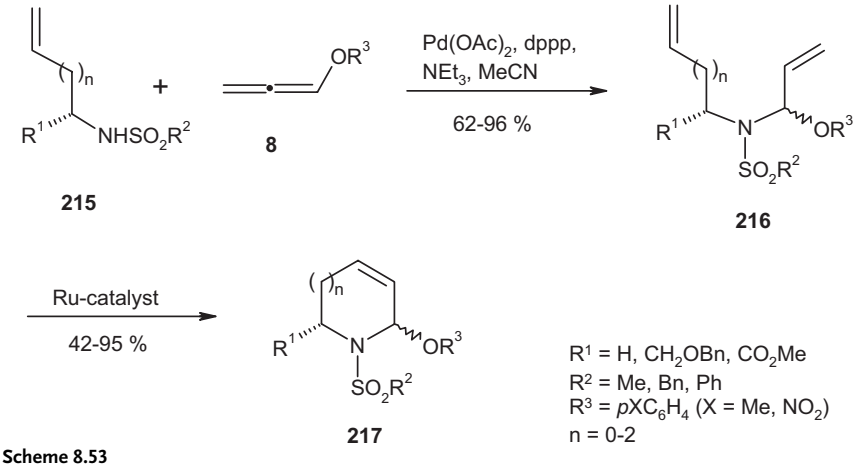
AB ring of **ciguatoxin**



C_1-C_{14} fragment of **laulimalide**

Scheme 8.52

The protocol mentioned above for the preparation of dihydropyrans was also applied to the amidopalladation of allenes **8** and the subsequent RCM of *N,O*-acetal intermediates **216**. This method leads to the expected five-, six- and seven-membered nitrogen-containing heterocycles **217** with good efficiency (Scheme 8.53) [118a].



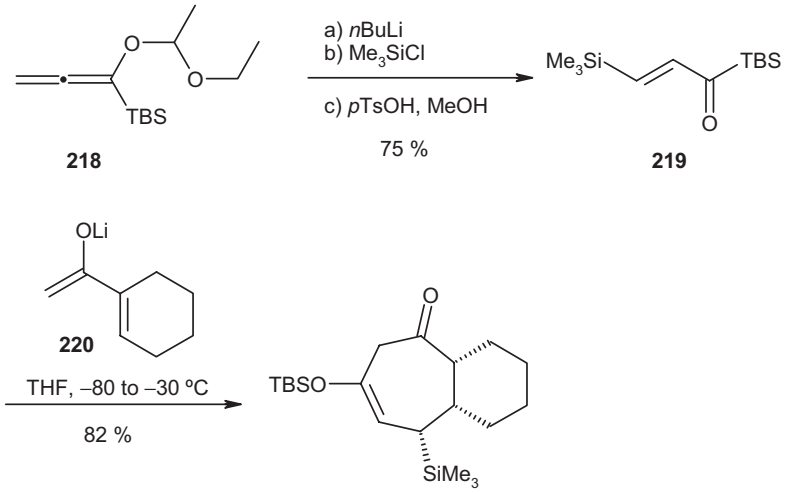
215 **8** **216** **217**

R^1 = H, CH_2OBn, CO_2Me
R^2 = Me, Bn, Ph
R^3 = pXC_6H_4 (X = Me, NO_2)
n = 0-2

Scheme 8.53

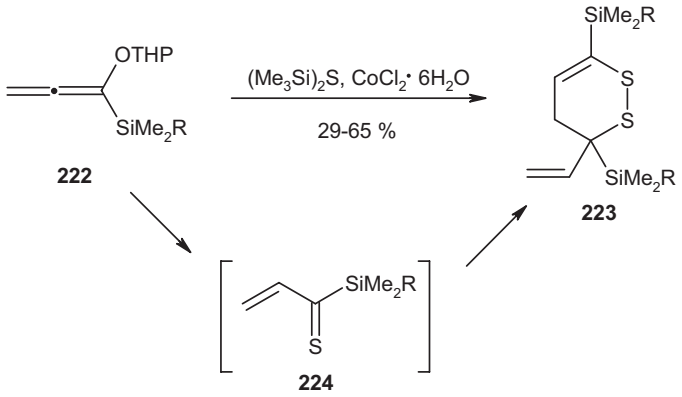
8.2.5
Miscellaneous Reactions of *O*-Substituted Allenes

Considerable attention has been devoted to the preparation and chemistry of α,β-unsaturated carbonyl compounds, which are valuable intermediates in organic synthesis [125]. Acid-promoted hydrolysis of alkoxyallenes has therefore frequently been employed to prepare a variety of functionalized α,β-unsaturated carbonyl compounds [12b, 41, 44, 60, 126]. A recent example is illustrated in Scheme 8.54 with C-1-silylated alkoxyallene **218** as a convenient starting material for the synthesis of bicyclo[5.4.0]undec-4-en-2-one **221**. Sequential deprotonation and silylation at the terminal C=C bond efficiently transformed **218** into a 1,3-disilylated allene which was converted into the acryloylsilane **219** under acidic conditions. A [3 + 4] annulation of intermediate **219** with lithium dienolate **220** furnished bicyclic compound **221** in good yield [127].



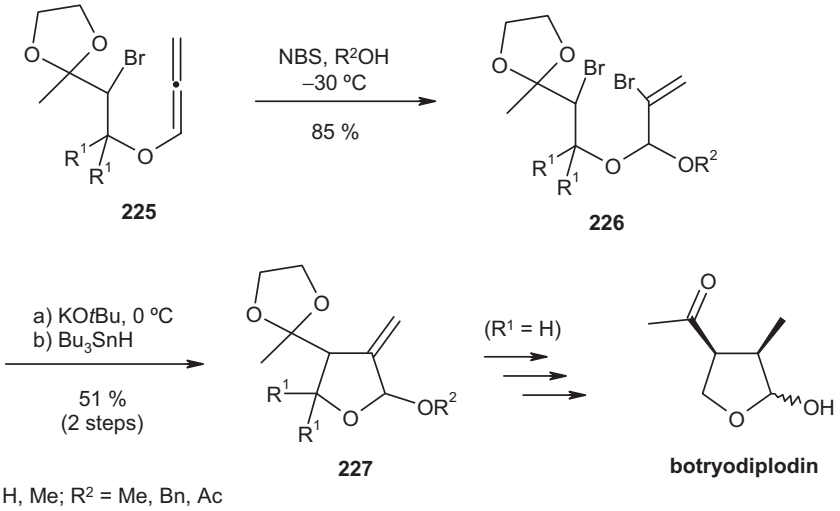
Scheme 8.54

Capperucci and co-workers investigated the dimerization of α,β-unsaturated thioacylsilanes **224**, which are generated in situ from 1-silylated alkoxyallenes **222** using bis(trimethylsilyl) sulfide and cobalt(II) chloride hexahydrate as reagents. The resulting 1,2-thiins **223** are isolated as major products in 29–65% yield [128] (Scheme 8.55).



Scheme 8.55

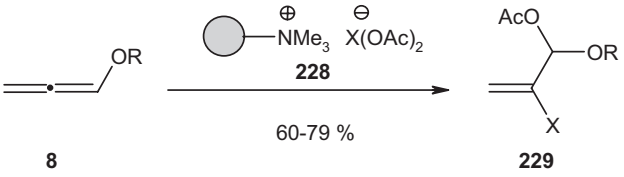
Allenyl ethers are useful key building blocks for the synthesis of α-methylene-γ-butyrolactones [129, 130]. The synthesis of the antileukemic botryodiplodin was accomplished with the crucial steps briefly presented in Scheme 8.56. Bromoallenyl ethers **225** were easily prepared by base-induced isomerization from the corresponding β-bromoalkyl alkynyl ether compounds and then subjected to electrophilic bromination with NBS. The resulting acetals **226** were converted into 2-alkoxy-3-methylenetetrahydrofurans **227** by dehydrohalogenation of the alkenyl bromide unit to an alkyne and subsequent radical cyclization employing tributyltin hydride [130].



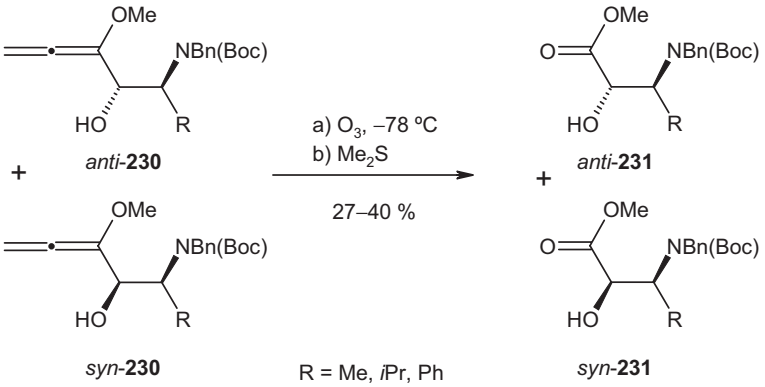
Scheme 8.56

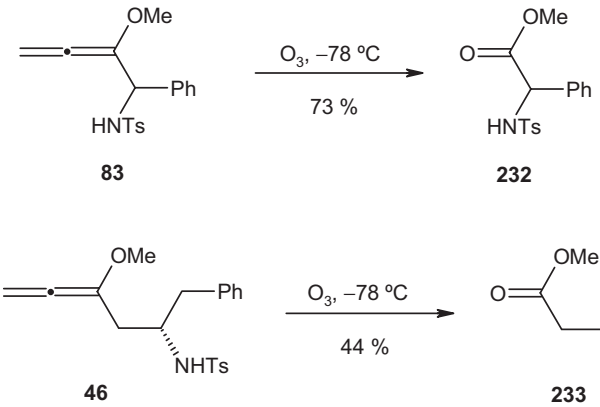
As an example of the use of a polymer-bound reagent **228**, the transformation of alkoxyallenes **8** into vinyl halides **229** is depicted in Scheme 8.57 [131].

Alkoxyallenes have also been subjected to oxidative reaction conditions [46, 62, 74, 132–134]. Ozonolysis of the already mentioned α-hydroxy-substituted methoxyallenes **230** provided a *syn–anti* mixture of α-hydroxy esters **231** (Scheme 8.58) [62].



Scheme 8.57 R = Me, Bn; X = Br, I

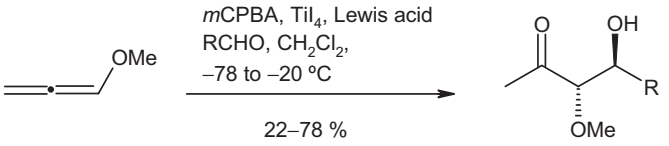




Scheme 8.58

Similarly, treatment of α-tosylamino-substituted allene **83** provided the expected α-amino ester **232** in good yield [74]. The analogous reaction could also be performed with methoxyallene–aziridine adduct **46**, which furnished enantiomerically pure β-amino acid **233** [46]. Although the ozonolysis approach seems to constitute a versatile and flexible method for the construction of α-amino and α-hydroxy esters, only a few examples have been reported so far.

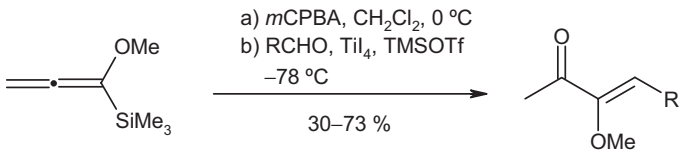
Hayakawa and Shimizu developed a novel C–C bond-forming reaction by epoxidation of methoxyallene **145** with *m*-chloroperbenzoic acid, which provides a methoxyallene oxide intermediate capable of adding to aldehydes. This reaction sequence provides 3-hydroxy-2-methoxy ketones **234** (Scheme 8.59) [133]. The best *anti*/*syn* selectivity was obtained by application of a 1:1 mixture of TiI_4 and $Ti(OiPr)_4$. They also observed the formation of α,β-unsaturated ketones **236** under comparable reaction conditions when 1-silylated methoxyallene **235** was employed as starting material (Scheme 8.60) [134].



145 **234**

R = Bn, cyclohexyl, *t*Bu, C_6F_5, CH_2CH_2Ph, CH=CHPh, pXC_6H_4 (X = OMe, Br, Cl, F, NO_2); Lewis acid = BF_3 etherate, $TiCl_4$, $Ti(OiPr)_4$

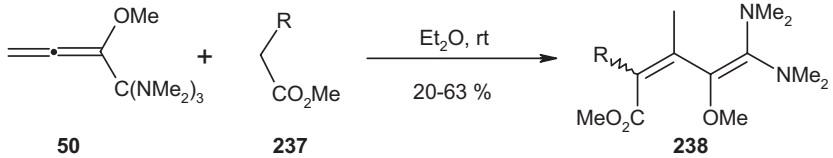
Scheme 8.59



235 **236**

R = Ph, 1-naphthyl, pXC_6H_4 (X = Cl, OMe), $oMeC_6H_4$

Scheme 8.60

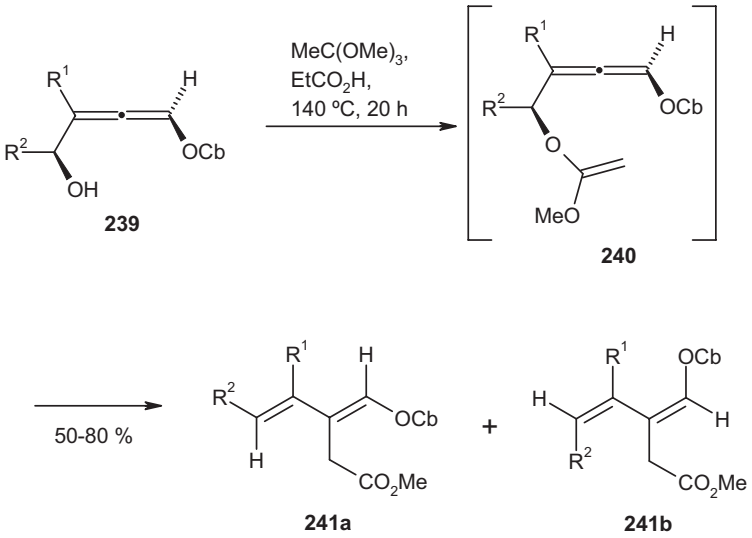


50 **237** **238**

R = CN, CO_2Me

Scheme 8.61

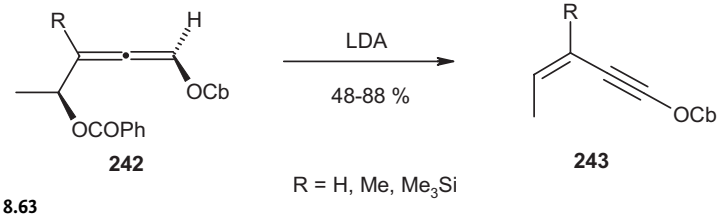
Alkoxyallenes turned out to be excellent starting materials also for the synthesis of highly functionalized 1,3-dienes, two examples being depicted in Schemes 8.61 and 8.62. As described by Kantlehner et al., 1,3-dienes such as **238** were obtained from methoxyallene derivative **50** by condensation with CH-acidic compounds **237** [135]. Hoppe and co-workers explored the stereochemical course of the allene Claisen rearrangement under Johnson's conditions, e.g. the reaction of **239** with trimethyl orthoacetate, which furnished intermediate **240** followed by rearrangement to the isomeric dienes **241a**,**b** [136].



Ratio: **a**:**b** = 70:30 to >95:5
R^1 = H, Me, Me_3Si; R^2 = Me, *i*Pr

Scheme 8.62

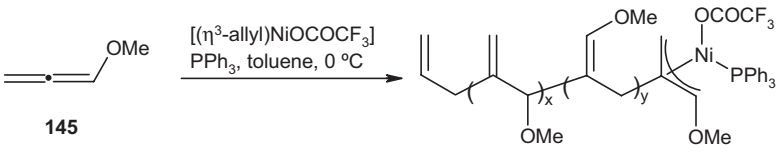
Hoppe and Gonschorrek also reported the interesting formation of an enyne structure [137]. Deprotonation of allenyl carbamates **242** bearing a benzoyloxy group caused a 1,4-elimination of lithium benzoate, furnishing 1-alkynyl carbamates **243** in moderate to good yield (Scheme 8.63).



R = H, Me, Me_3Si

Scheme 8.63

Finally, methoxy- and phenoxyallene are also attractive monomers to produce reactive polymers bearing *exo*-methylene units [138–140]. For example, Endo and coworkers described the polymerization of **145** leading to polymer **244** in high yield. Its molecular weight (M_n) was determined as 18 100 g mol^{-1} (Scheme 8.64) [140].



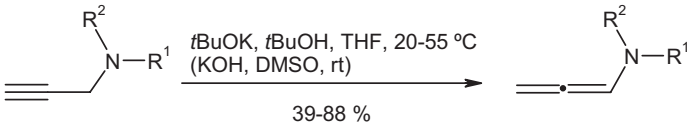
145 **244**

Scheme 8.64

8.3
N-Substituted Allenes

8.3.1
Synthesis of *N*-Substituted Allenes

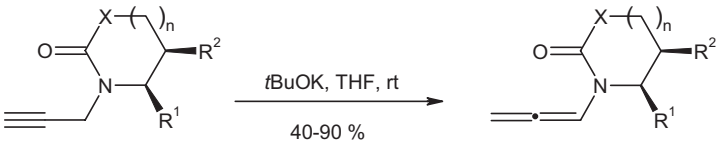
In analogy with the synthesis of oxygen-substituted allenes, 1,2-dienes bearing a nitrogen functionality are accessible by isomerization of the corresponding alkyne precursors [1,10]. A few examples of base-induced transformations are shown in Schemes 8.65 and 8.66 [141–145] and Eq. 8.35 [146]. In general, it is known that simple dialkyl(aryl)aminoallenes are prone to hydrolysis and polymerization, resulting in difficulties during preparation, whereas allenylamides are considerably more stable and easier to handle [10].



245 **246**

R^1 = Me, Et, Bz; R^2 = Et, Ph; R^1,R^2 = $CH_2CH_2OCH_2CH_2$

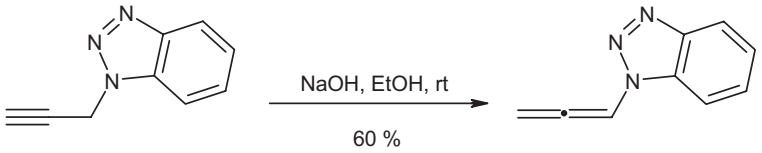
Scheme 8.65



247 **248**

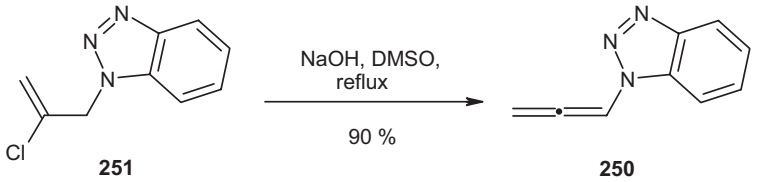
R^1 = Ph, Bn, $CHPh_2$; R^2 = H, Me, Ph; X = O, NMe, CH_2; n = 0-2

Scheme 8.66



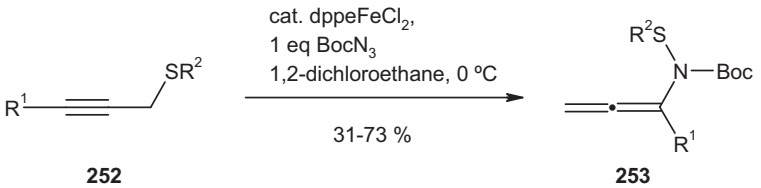
249 **250** (8.35)

An alternative and more efficient preparation is achieved in the case of 1-allenylbenzotriazole (**250**), which proceeds by dehydrochlorination of 1-(2-chloroallyl)benzotriazole (**251**) by NaOH in dimethyl sulfoxide under reflux (Eq. 8.36) [147].



251 **250** (8.36)

An intriguing approach to nitrogen-substituted allenes such as **253** was reported by van Vranken and co-workers (Scheme 8.67) [148]. Iron(II)-catalyzed sulfimidation of propargyl sulfides **252** and subsequent [2,3]-sigmatropic rearrangement furnish **253** in moderate to good yields.

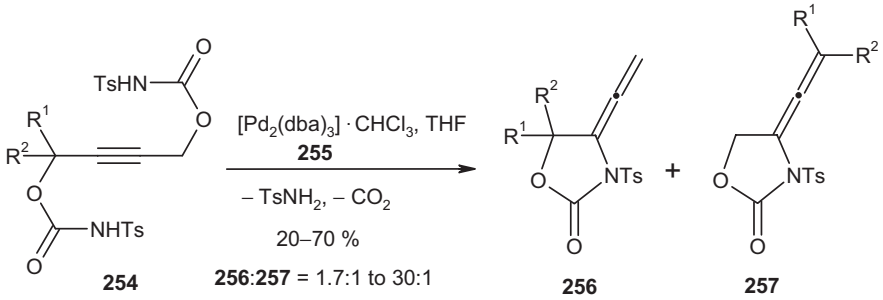


252 **253**

R^1 = H, Me, Me_3Si, CHPhOR (R = H, Me_3Si); R^2 = Ph, CH_2CH_2Ph

Scheme 8.67

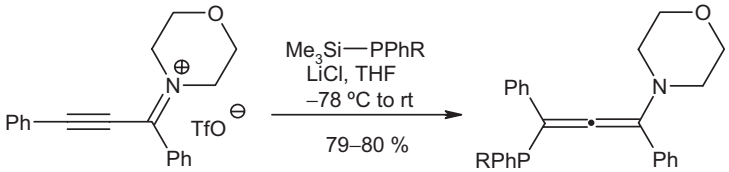
The palladium-catalyzed elimination–cyclization reaction of biscarbamates **254** opens up a further route to nitrogen-substituted allenes (Scheme 8.68) [149]. This transformation proceeds for certain substitution patterns with surprisingly high regioselectivity, favoring allenes **256** with a terminally unsubstituted C=C bond.



R^1 = Me, Et, *i*Pr, cyclohexyl, *t*Bu, Ph; R^2 = H, Me;
R^1,R^2 = $(CH_2)_n$ (n = 4 or 5), 2-adamantyl

Scheme 8.68

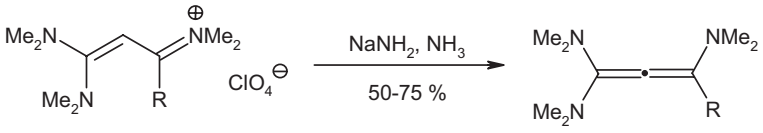
Treatment of propyne iminium triflate **258** with silylated phosphorus nucleophiles such as $Me_3SiPPhR$ affords (3-morpholinoallenyl)phosphanes **259** in high yield (Scheme 8.69) [150].



R = Ph, *n*Pent

Scheme 8.69

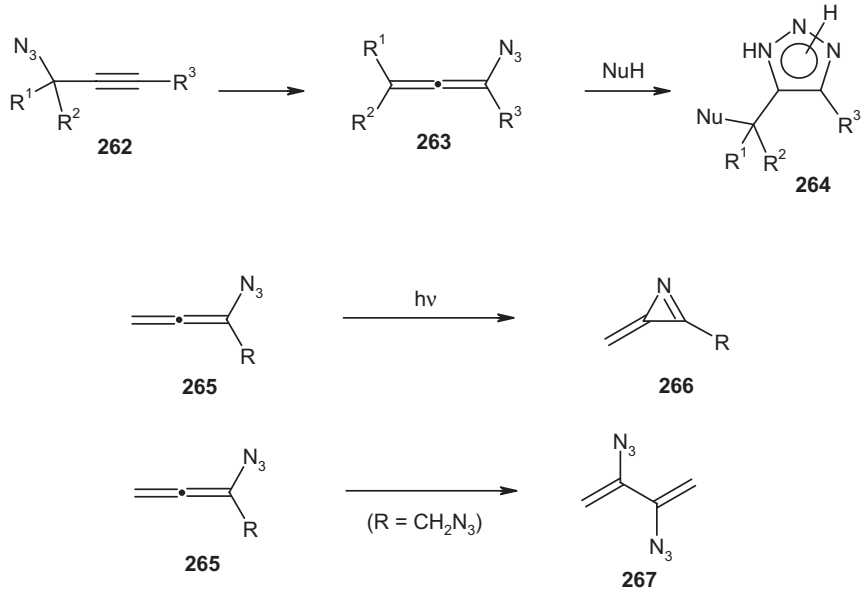
Early investigations dealing with the synthesis and reactions of tri- and tetraamino-substituted allenes were performed by Gompper and co-workers [151]. Scheme 8.70 illustrates a typical method for the preparation of **261** by deprotonation of propenylidene ammonium salt **260**. However, this chemistry has not been developed further during the last three decades.



R = *t*Bu, Ph

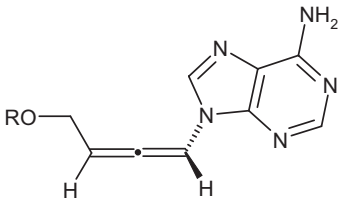
Scheme 8.70

Interesting highly reactive 1-azidoallenes such as **263** and **265** are accessible by a [3 + 3]-sigmatropic isomerization of 3-azido-1-alkyne precursors **262** (Scheme 8.71) [152]. Due to the synthetic potential of this class of allenes, the scope and limitations of their transformations were explored in detail by Banert and co-workers [153].



Scheme 8.71

A few nitrogen-substituted allenes themselves are known as biologically active compounds [154]. For example, the 9-(4′-hydroxy-1′,2′-butadienyl)adenine (**268a**) was found to inhibit in vitro replication and cytopathic effects of human immunodeficiency viruses HIV-1 and HIV-2 [155]. More recently, an increase in the anti-HIV activity in cell cultures using the adenallene phosphotriester derivative **268b** was reported (Scheme 8.72) [156].



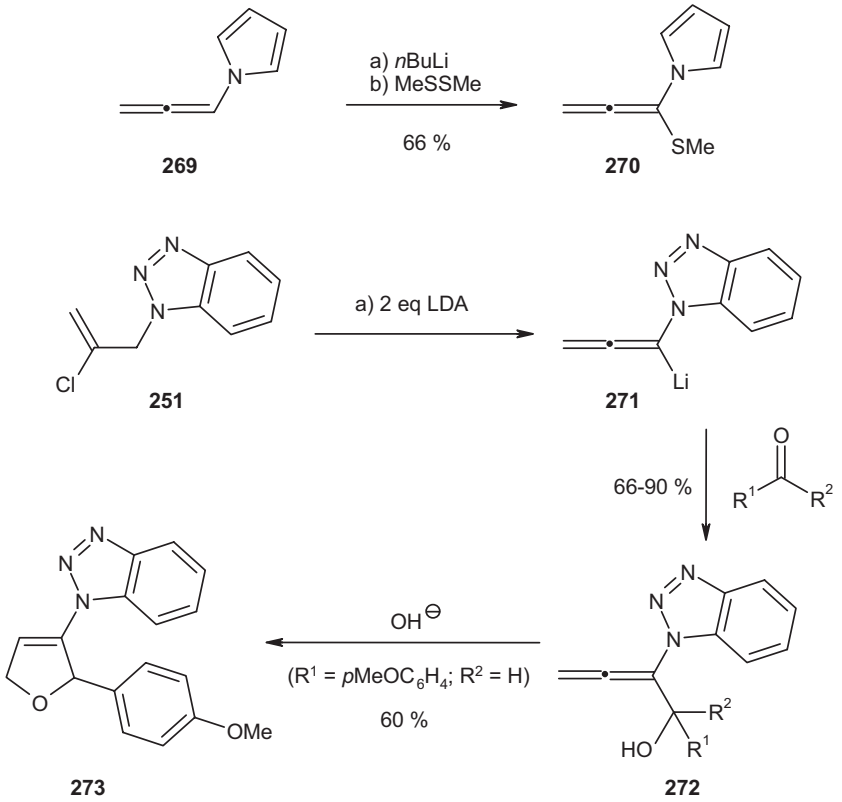
a: R =H
b: R = P(O)(OCH$_2$CH$_2$SCO*t*Bu)$_2$

Scheme 8.72

8.3.2

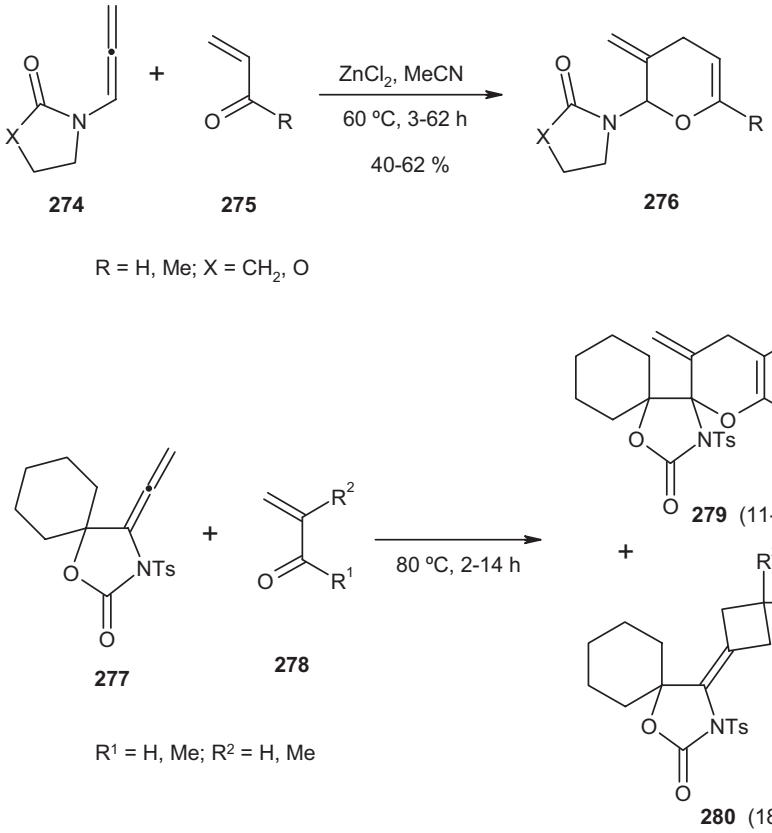
Reactions of *N*-Substituted Allenes

In contrast to the rich chemistry of alkoxy- and aryloxyallenes, synthetic applications of nitrogen-substituted allenes are much less developed. Lithiation at the C-1 position followed by addition of electrophiles can also be applied to nitrogen-containing allenes [10]. Some representative examples with dimethyl sulfide and carbonyl compounds are depicted in Scheme 8.73 [147, 157]. α-Hydroxy-substituted (benzotriazole)allenes **272** are accessible in a one-pot procedure described by Katritzky and Verin, who generated allenyl anion **271** and trapped it with carbonyl compounds to furnish products **272** [147]. The subsequent cyclization of **272** leading to dihydrofuran derivative **273** was achieved under similar conditions to those already mentioned for oxygen-substituted allenes.



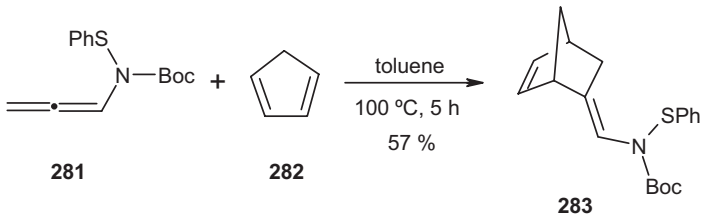
Scheme 8.73

Cycloadditions of *N*-substituted allenes are well investigated reactions of this class of 1,2-dienes. Several [4 + 2] and [3 + 2] cycloadditions and a few [2 + 2] cycloadditions of this allene subclass are known [10]. By taking advantage of the enamide functionality, Diels–Alder reactions with α,β-unsaturated carbonyl compounds **275** can easily be performed in the presence of catalytic amounts of zinc chloride (Scheme 8.74) [158,159]. Notably, chiral *N*-allenamides can be used in [4 + 2] cycloadditions with inverse electron demand, resulting in cycloadducts formed with good to high diastereoselectivity (70–90% *de*) [158,160]. When 4-vinylidene-2-oxazolidinone **277** was subjected to thermal cycloaddition with α,β-unsaturated aldehydes or ketones, a competition between [4 + 2] and [2 + 2] cycloaddition was discovered [149], with the [2 + 2] cycloadduct **280** being the major component in many cases.



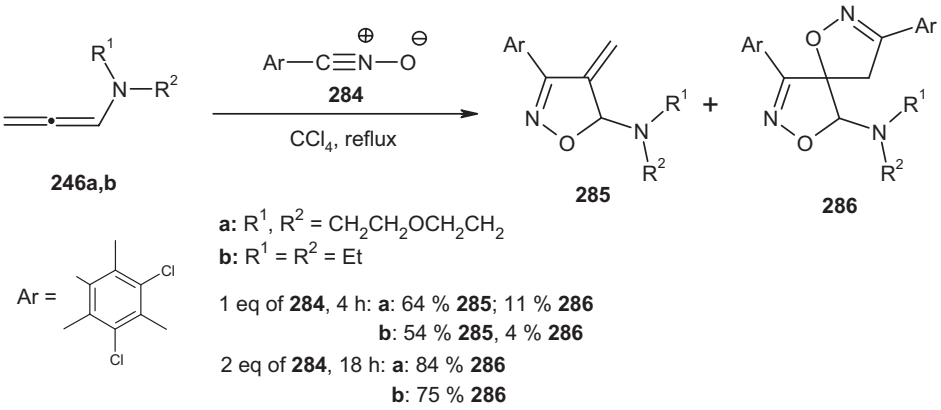
Scheme 8.74

In contrast to the above-mentioned cycloadditions, normal electron demand Diels–Alder reactions exclusively form products where the terminal C=C bond of the allene was attacked by the diene. For example, cycloaddition of *N*-allenylsulfenimide **281** with cyclopentadiene (**282**) affords norbornene derivative **283** (Eq. 8.37) [148].



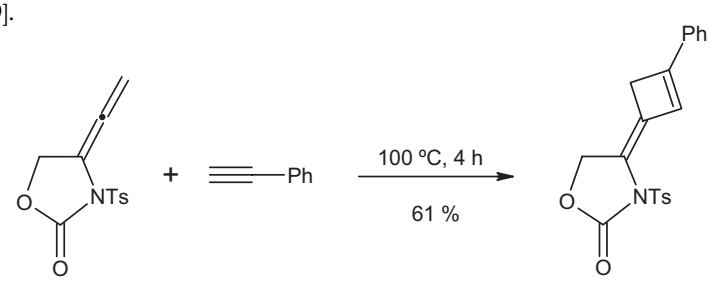
281 **282** **283** (8.37)

Zecchi and co-workers also reported 1,3-dipolar cycloadditions with nitrogen-substituted allenes. As illustrated in Scheme 8.75, the expected isoxazoline derivatives **285** were obtained by [3 + 2] cycloaddition reaction of aminoallenes **246** and nitrile oxide **284** [141, 142]. Bis-adducts **286** became the major products when 2 equiv. of nitrile oxide **284** were applied with prolonged reaction times.



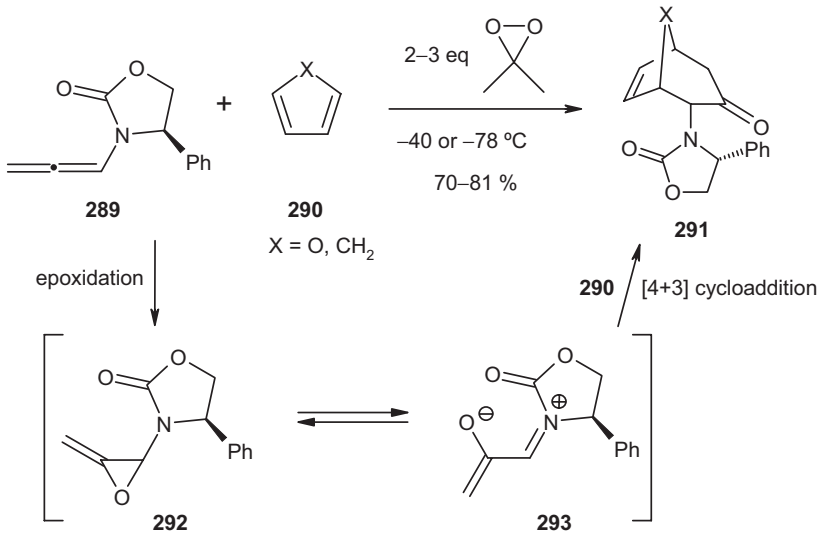
Scheme 8.75

As exemplified in Eq. 8.38, thermal [2 + 2] cycloadditions of 4-vinylidene-2-oxazolidinone **287** and alkynes such as phenylacetylene result in the formation of 3-phenyl-substituted methylenecyclobutene **288** [149]. The authors confirmed by NMR analysis that only the *Z*-configuration isomer was formed. It is worth noting that the [2 + 2] cycloaddition of allenes **287** is not restricted to alkynes; even olefins such as acrylic esters or silyl enol ethers furnish the corresponding methylenecyclobutanes [149].



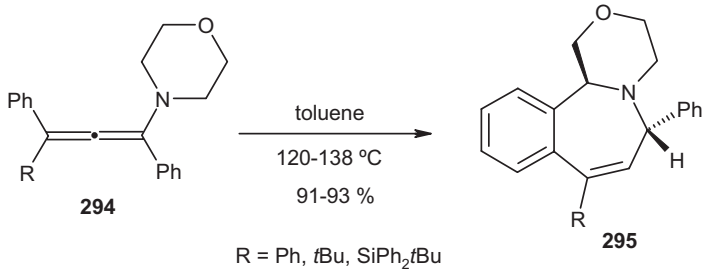
287 **288** (8.38)

Hsung and co-workers described the first epoxidation of 1-amidoallenes leading to highly reactive intermediate **292** (Scheme 8.76) [159]. Formation of bicyclic products **291** occurs via iminium enolate **293**, which was trapped by cyclopentadiene **290** (X = CH_2) or furan **290** (X = O). [4 + 3] Cycloaddition of the intermediate **293** furnished **291** in good yield as a mixture of *endo*-diastereoisomers (~75:25). The best diastereoselectivity was found when the reaction was performed in the presence of 2 equiv. of zinc chloride (>96:4).



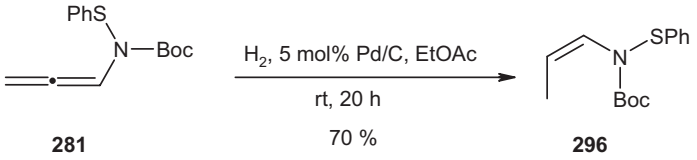
Scheme 8.76

Mayer and Maas reported an interesting thermal isomerization of nitrogen-substituted allenes which involves an azomethine ylide [161]. Heating of *N*-functionalized allenes **294** in toluene at 120–138 °C provides 3,4,5,12b-tetrahydro-1*H*-[1,4]oxazino[4,3-*a*][2]benzazepines **295** in almost quantitative yield (Scheme 8.77).



Scheme 8.77

Only a few reactions have been studied with *N*-allenylsulfenimides. Despite the presence of a sulfur function in allene **281**, van Vranken and co-workers carried out its heterogeneous catalytic hydrogenation (Eq. 8.39) [148]. The reaction occurs only at the terminal C=C bond, providing the *Z*-configuration enamide **296** in 70% yield.



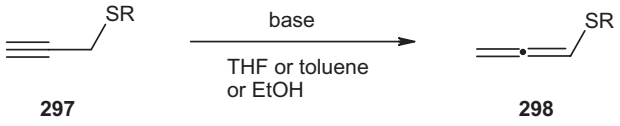
281 **296** (8.39)

8.4
S- and *Se*-Substituted Allenes

Sulfur-containing allenes can be subdivided into donor-functionalized allenes such as allenyl thioethers and into acceptor-functionalized allenes such as allenyl sulfoxides and sulfones. In this section only the synthesis and chemistry of donor-substituted sulfur-containing allenes will be summarized.

8.4.1
Synthesis of *S*-Substituted Allenes

In general, sulfur-substituted allenes are accessible starting from alkyne precursors by a variety of transformations such as isomerization, rearrangement or addition reactions. The standard method for the synthesis of donor-substituted allenes is again the base-induced isomerization of alkynes. This very first method was applied for the preparation of achiral [11, 162, 163] and chiral [164] *S*-functionalized 1,2-dienes (Scheme 8.78).

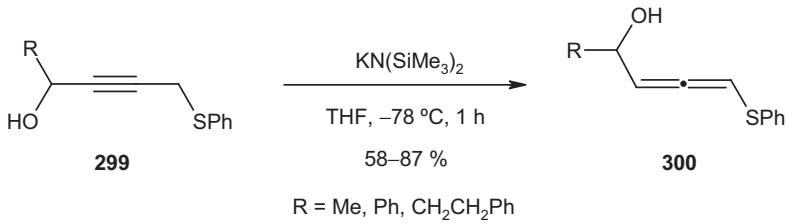


297 **298**

R = H, alkyl, aryl, propargyl; base: KO*t*Bu, NaO*t*Bu, NaOH

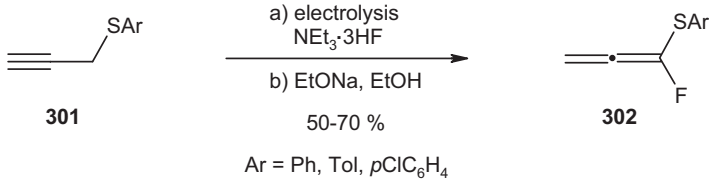
Scheme 8.78

Some interesting modifications with respect to the base-induced isomerization have recently been developed. For example, conversion of 4-hydroxy-1-thiophenyl-2-alkynes **299** into the corresponding 4-hydroxy-substituted thiophenylallenes **300** was achieved by treatment with potassium hexamethyldisilazide at low temperature (Scheme 8.79) [165]. If the hydroxyl group is protected as the THP ether an elimination reaction occurred, resulting in the formation of an enyne instead of allene **300**.



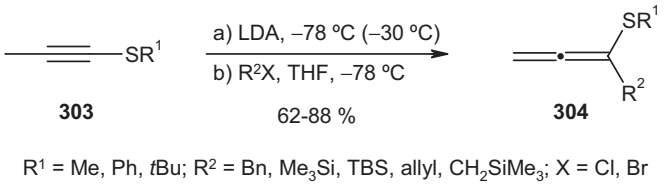
Scheme 8.79

Fuchigami and co-workers utilized the regioselective anodic fluorination of aryl propargyl sulfides **301** for the preparation of fluorinated alkyne intermediates, which were subsequently isomerized by sodium ethoxide to furnish 1-fluoro-1-arylthioallenes **302** (Scheme 8.80) [166].



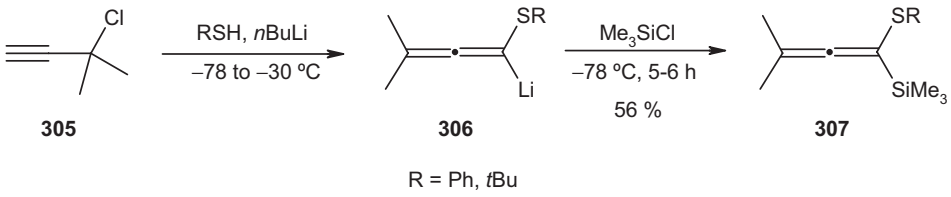
Scheme 8.80

Another modification of the deprotonation/isomerization sequence starts with easily accessible 1-thio-substituted 1-propynes **303**. Their deprotonation at the γ-position generates allenyl anions that could be trapped regioselectively by different electrophiles R^2X (Scheme 8.81) [167–169]. The resulting C-1-substituted allenyl sulfides **304** were obtained in high yields.



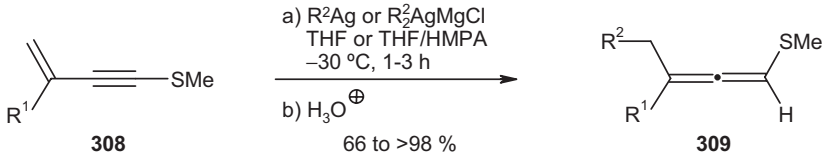
Scheme 8.81

Gasking and Whitham described the one-pot preparation of 1-silylated 3,3-dimethyl-substituted allenyl sulfides **307** (Scheme 8.82) [170]. Treatment of alkyne **305** with lithium thiolate generates allenyllithium species **306**, which is subsequently silylated by trimethylsilyl chloride. Formation of lithiated intermediate **306** is based on a procedure developed by Clinet and Julia [171].



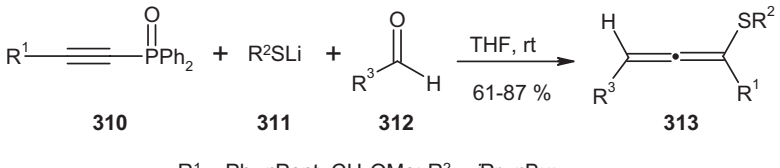
Scheme 8.82

Investigations by Vermeer and co-workers have shown that 3-substituted allenyl methyl thioethers **309** can be prepared by regioselective addition of an alkyl silver species to the terminal C=C bond of enyne sulfides **308** (Scheme 8.83) [172]. Remarkably, this method can also be applied to the preparation of several allenylphosphines starting from the corresponding phosphorus-substituted alkynes.



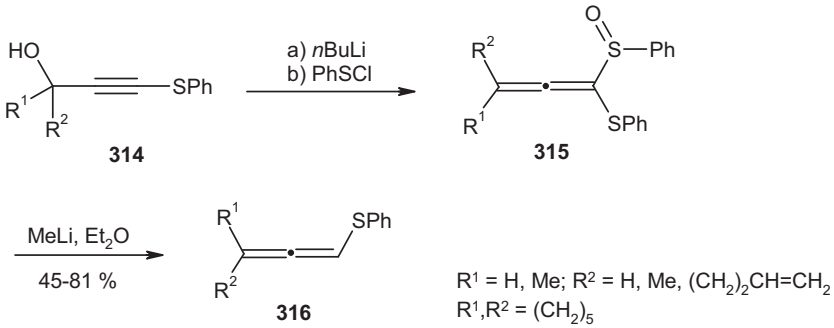
Scheme 8.83

An interesting approach to allenyl thioethers has been reported by Huang and Xiong, which is based on a novel three-component reaction. Treatment of 1-alkynylphosphine oxides **310** with lithium alkylthiolates **311** in the presence of an aldehyde **312** provides the expected highly substituted allenyl thioethers **313** in good yield (Scheme 8.84) [173]. Unfortunately, this procedure could not be extended to arylthiolates.



Scheme 8.84

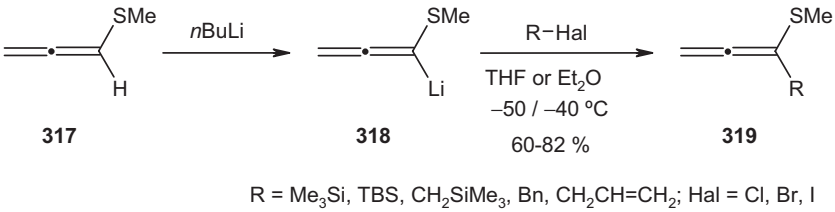
Cutting and Parsons described the transformation of acetylenic alcohols **314** into allenyl phenyl thioethers **316** by a two-step procedure (Scheme 8.85) [174]. Deprotonation of alkynes **314** with *n*-butyllithium is followed by addition of phenylsulfenyl chloride, forming sulfenyloxy intermediates which subsequently rearrange to allenic sulfoxides **315**. Treatment of allenes **315** with methyllithium results in loss of the sulfoxide moiety to form allenyl sulfides **316** in reasonable yields.



Scheme 8.85

8.4.2
Reactions of *S*-Substituted Allenes

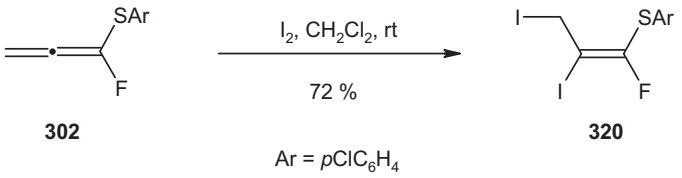
Sulfur-containing acyclic and cyclic compounds have been prepared from allenyl sulfides in numerous transformations such as substitutions, additions, cycloadditions and other cyclization reactions. Like the other donor-substituted allenes, allenyl sulfides are suitable substrates for regioselective lithiation and substitutions as exemplified in Scheme 8.86 [168, 169, 175].



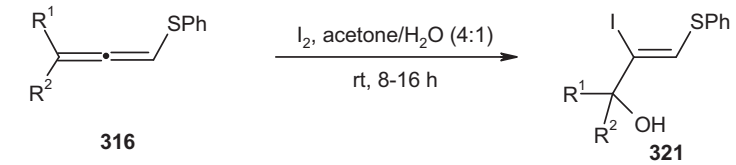
Scheme 8.86

Fuchigami and co-workers showed that α-fluoroallenyl sulfide **302** can be smoothly converted into (*E*)-configured vinyl iodide **320** by addition of iodine in dichloromethane at ambient temperature (Scheme 8.87) [166]. Ma et al. [176] treated

sulfur-substituted allene **316** with iodine in an aqueous acetone solution and obtained with excellent stereoselectivity *Z*-configured iodo compounds **321**, which are equipped with two synthetically useful functionalities such as an allylic alcohol and a vinyl iodide unit (Scheme 8.88). In few cases the formation of regioisomeric addition products affording α,β-unsaturated aldehydes **323** was observed. These reactions regioselectively add iodine across the C-2–C-3 bond to afford products **321**



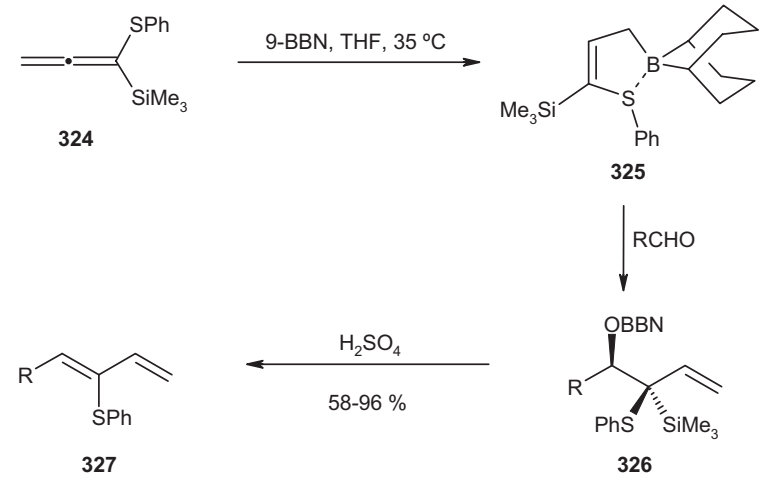
Scheme 8.87



Scheme 8.88

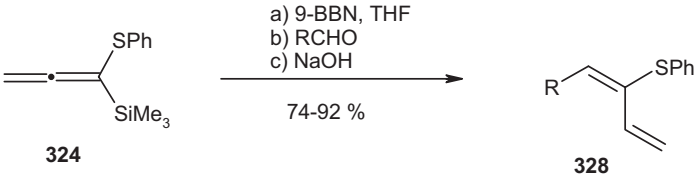
and **323**. The suggested mechanism involves the formation of iodonium ion **322** followed by attack of water at the alkyl-substituted carbon atom.

A stereoselective route to 2-(phenylthio)-1,3-butadienes such as **327** or **328** was developed by Pearson et al. [167] with allylboranes as crucial intermediates. Addition of 9-BBN to allenyl sulfide **324** gives the allylborane intermediate **325**, which subsequently adds to aldehydes (Scheme 8.89). Typical of Peterson olefinations, this reaction can also be terminated by two different work-up procedures, either acidic conditions leading to *anti*-elimination, which affords *Z*-configuration of dienes **327**, or basic work-up resulting in a *syn*-elimination to form (*E*)-dienes **328**.



324 **325** **326** **327**

R = *n*Pent, octyl, *i*Pr, cyclohexyl, Ph, Bn, $(CH_2)_nX$ (n = 4,5, X = Br, N_3)

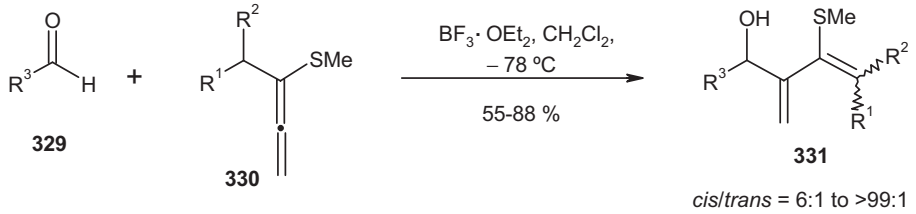


324 **328**

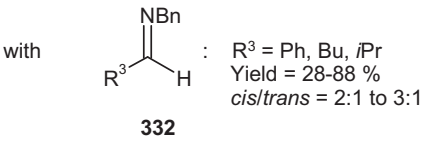
R = *n*Pent, octyl, *i*Pr, cyclohexyl, Ph, Bn, $(CH_2)_nX$ (n = 4,5, X = Br, N_3), CH=CHPh

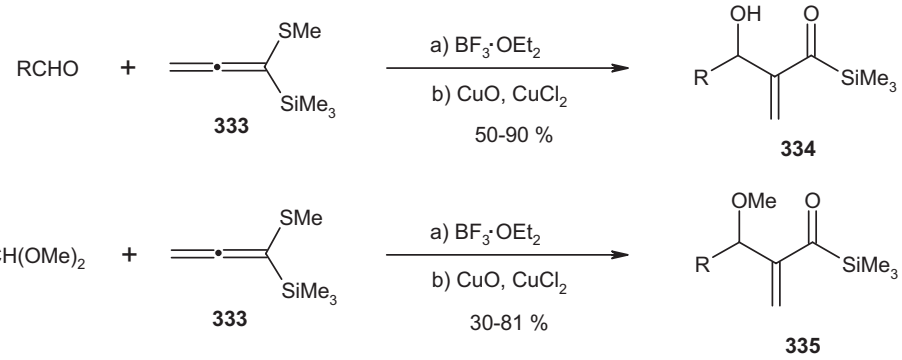
Scheme 8.89

Lewis acid-catalyzed ene reactions proceed between allenyl sulfides, e.g. **330**, and aldehydes **329** to afford *cis–trans* mixtures of 1,3-butadienes **331** (Scheme 8.90) [168, 175b]. Similar ene reactions observed with imines such as **332** provide the corresponding allylamines [168,177]. It was also found that the ene reaction of 1-silylated allenyl sulfide **333** with various aldehydes (or acetals) furnishes α,β-unsaturated acyl compounds such as **334** and **335** under BF_3-etherate catalysis [175b].



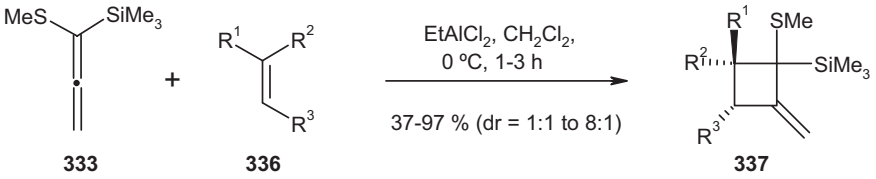
R^1 = Ph, H, Me; R^2 = H, Me; R^3 = Ph, CH_2CH_2Ph, *i*Pr, cyclohexyl, CH=CHPr





Scheme 8.90 R = alkyl or aryl

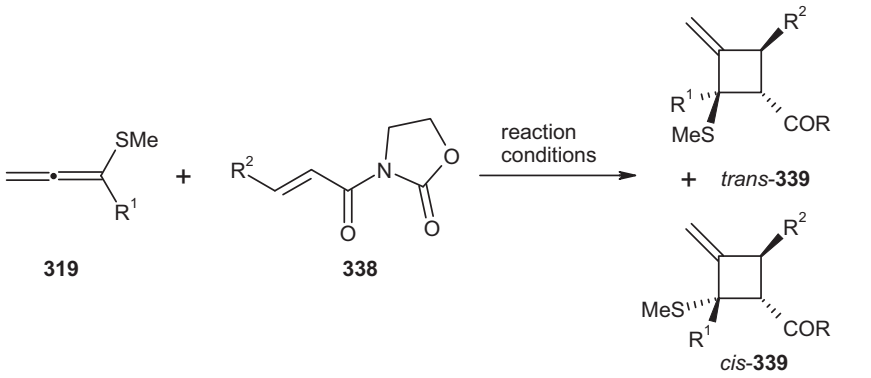
In contrast to the limited success with vinyl sulfides as components of [2 + 2] cycloadditions, allenyl sulfides show wide applicability. As illustrated in Scheme 8.91, Lewis acid-catalyzed [2 + 2] cycloadditions of 1-trimethylsilyl-1-methylthio-1,2-propadiene (**333**) with a variety of electron-deficient olefins **336** provide cycloadducts **337** with excellent regioselectivity but with moderate stereoselectivity [175c]. Narasaka and co-workers reported the first Lewis acid-catalyzed asymmetric [2 + 2] cycloaddition of C-1-substituted allenyl sulfides **319** with α,β-unsaturated compounds **338** using a chiral TADDOL-titanium catalyst. The corresponding cycloadducts **339** were obtained with 88–98% *ee*, but a low level of *trans*/*cis* selectivity (Scheme 8.92) [169, 175d].



333 **336** **337**

R^1 = CN, CO_2Me; R^2 = H, Me; R^3 = Me, Ph, CN, CO_2Me

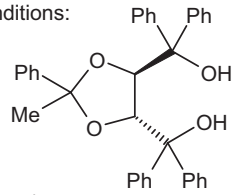
Scheme 8.91



319 **338**

(R = 2-oxo-1,3-oxazolidin-3-yl)

reaction conditions:



20 mol%

$TiCl_2(OiPr)_2$, 4 Å MS

R^1 = Me, *i*Pr, $(CH_2)_nCH{=}CH_2$ (n = 1-4), $CH_2CH_2C{\equiv}CH$,
R^2 = H, CO_2Me

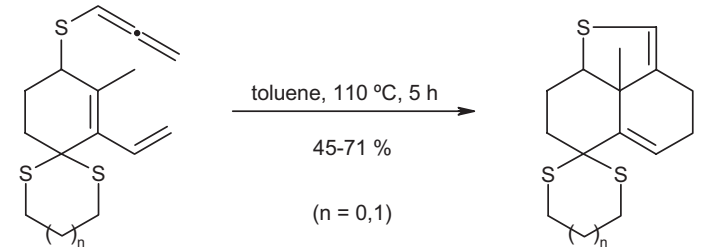
Yield = 85-98 %
trans/*cis* = 50:50 to 80:20

Exceptions: R^1 = Me_3Si, $SiMe_2Allyl$: *trans*/*cis* <2:>98

ee *trans*: 91-98 %
cis: 88 to >98 %

Scheme 8.92

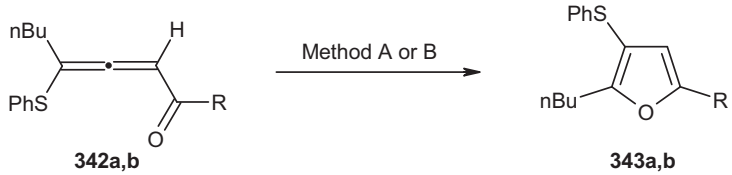
Tricyclic sulfur heterocycles **341** were prepared utilizing an intramolecular [4 + 2] cycloaddition. Heating of allenyl sulfides **340** to 110 °C leads to Diels–Alder products **341** in reasonable yields (Scheme 8.93) [163]. Unfortunately, this method does not allow general access to these heterocycles, since a particular substitution pattern of the substrate is required. No reaction occurred with substrates lacking the thioacetal moiety.



340 **341**

Scheme 8.93

An interesting transformation of allenyl sulfides bearing a carbonyl group was recently described by Gevorgyan and co-workers. This conversion incorporates a 1,2-migration of the phenylthio group. While allene **342a** carrying a phenyl ketone group quantitatively cyclizes to **343a** under thermal reaction conditions (method A), the same cyclization with **342b** having an alkyl ketone moiety occurs only under CuI catalysis (method B) (Scheme 8.94) [178]. The cyclization is often more effective starting from the corresponding alkyne precursors where the allenyl intermediates are formed in situ.

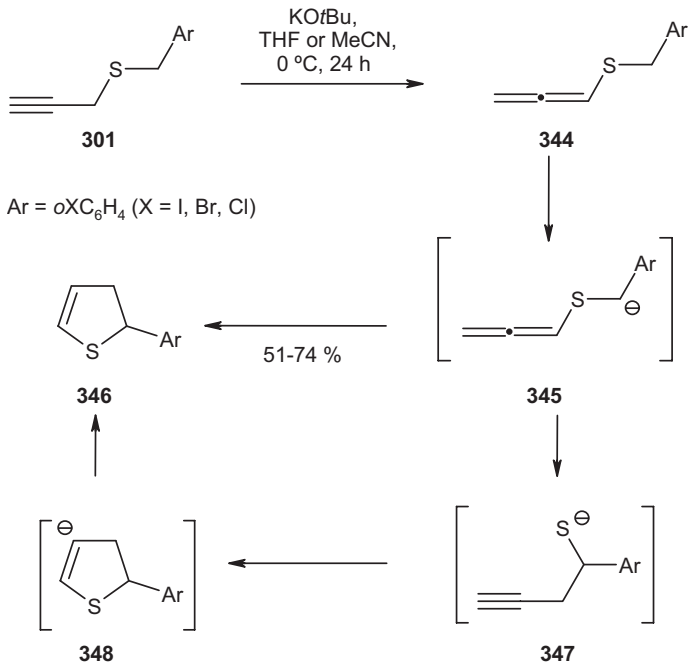


342a,b **343a,b**

a: R = Ph:	Method A: 130 °C, 2 h	100 %
b: R = $(CH_2)_3OMOM$:	Method B: rt, 5 mol% CuI, 36 h	82 %

Scheme 8.94

A base-induced cyclization of benzyl alkynyl sulfides **301** allows the synthesis of 2-aryl-2,3-dihydrothiophenes **346** (Scheme 8.95) [179]. The authors suggest smooth isomerization of **301** to allenyl sulfide **344**, followed by deprotonation at the benzylic position. The resulting anion **345** probably undergoes 5-*endo-trig* cyclization furnishing heterocycle **346**. Alternatively, **345** could rearrange via a [2,3]-thia-Wittig-like sigmatropic reaction leading to the final product **346** via cyclic carbanion **348**.

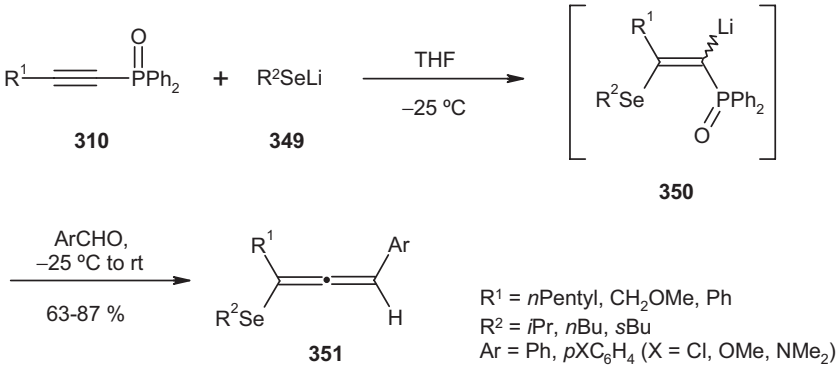


Scheme 8.95

8.4.3

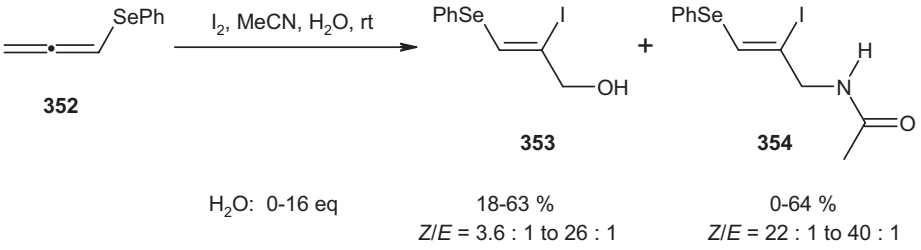
Synthesis and Reactions of *Se*-Substituted Allenes

In comparison with the already discussed classes of donor-substituted allenes, much less is known about their selenium analogs [11, 180]. The standard method for synthesizing donor-substituted allenes is the base-induced isomerization of the corresponding alkyne precursors [11]. In addition, selenium-substituted allenes such as **351** can be prepared by a novel tandem Michael/Horner–Wadsworth–Emmons reaction, which was already successfully applied to sulfur analogs (Scheme 8.96). Thus, treatment of 1-alkynylphosphine oxides **310** with lithium alkylselenoates **349** generates alkenyllithium intermediates **350**, which react with a variety of aldehydes and finally produce selenium-substituted allenes **351** generally in high yield [181].



Scheme 8.96

One of the rare applications of selenium-substituted allenes was recently reported by Ma et al. [182]. The allenyl selenide **352** undergoes an iodohydroxylation or iodoamination, depending on the amount of water used, leading to the formation of allyl alcohol **353** and allylacetamide **354** (Scheme 8.97). When the reaction is performed with 12–16 equiv. of water, allyl alcohol **353** is exclusively formed, whereas the use of 1 equiv. of water exclusively provides the amide **354** in 64% yield.



Scheme 8.97

8.5 Conclusion

The examples illustrated in the almost 100 schemes in this chapter demonstrate how versatile donor-substituted allenes can be in synthetic processes. The major applications concern addition reactions and cycloadditions to the allenic double bonds, which furnish products with valuable functional groups. Of particular interest are metalations – usually at C-1 of the allene unit – followed by reactions with electrophiles that deliver compounds which can often be used for cyclization reactions. A variety of highly substituted and functionalized heterocycles arises from these flexible methods, which cannot be obtained by other reactions. Many of these transformations proceed with good regioselectivity and excellent stereoselection.

Fairly recently, an increase in the use of allenyl amides bearing chiral auxiliaries could be observed. Many interesting and synthetically useful results can be expected in this area. Sulfur- and selenium-substituted allenes have rarely been employed, although many of their subsequent products would feature unique properties. Hence it should be possible to switch the donor property of a sulfur substituent to an electron-accepting group by various oxidation methods.

So far, axially chiral donor-substituted allenes have rarely been used although they should be capable of transferring their stereochemical information to a new center of chirality. This lack may be due to the difficulties of generating axially chiral donor-substituted allenes with high enantiomeric purity. We expect that this gap will be filled in near future.

Addendum (July 1st, 2004)

Additional references for Section 8.2.2 [183–186], Section 8.2.3 [187–190], Section 8.2.4 [191], Section 8.3.1 [192–194] and Section 8.3.2 [195, 196].

Abbreviations

9-BBN	9-Borabicyclo[3.3.1]nonane
DAF	Diacetonefructose
DAG	Diacetoneglucose
dba	Dibenzylideneacetone
dppe	1,2-Bis(diphenylphosphino)ethane
dppp	1,3-Bis(diphenylphosphino)propane
HFIP	Hexafluoro-2-propanol
HMPA	Hexamethylphosphoric triamide
MOM	Methoxymethyl
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
RCM	Ring-closing metathesis
TBAF	Tetra-*n*-butylammonium fluoride
TFE	Trifluoroethanol
TMEDA	Tetramethylethylendiamine

References

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9
Synthesis and Reactions of Allenylmetal Compounds

James A. Marshall, Benjamin W. Gung, and Melissa L. Grachan

9.1
Introduction

'Organometallic allenes: although these are interesting from a chemical viewpoint, they have as yet found little synthetic use.' [1] 'Propargyl and allenyl organometallics: unfortunately, the utility of this methodology is limited by the tendency of propargylic metal derivatives to combine with carbonyl compounds (and other electrophiles) to produce both allenic and alkynic products.' [2] So begin the two most recent reviews of allenic and propargylic organometallic compounds, which appeared in 1984 and 1991. Not surprisingly, a great deal has transpired in the last decade to refute those earlier statements and beliefs. This review will survey the most common and useful allenylmetal compounds currently employed as synthetic reagents. Particular emphasis will be placed on the more interesting and practical synthetic applications. Coverage will be thorough but not exhaustive and subject to the personal preferences and opinions of the authors.

9.1.1
Preparation

The most general routes to allenylmetal compounds involve metal–halogen exchange or propargylic deprotonation. Typically the starting halide for the former process is propargylic rather than allenic (Scheme 9.1). Depending on the nature of R^1 and R^2, the allenic or propargylic organometal derivative or a mixture of the two is formed. In general, the allenic isomer is favored, especially when the metal is located at the less substituted position. The initial propargylic/allenic metal compound can often be transmetallated to produce a new allenic/propargylic metal species in situ. Transmetallations are commonly carried out on allenyllithium and tin compounds.

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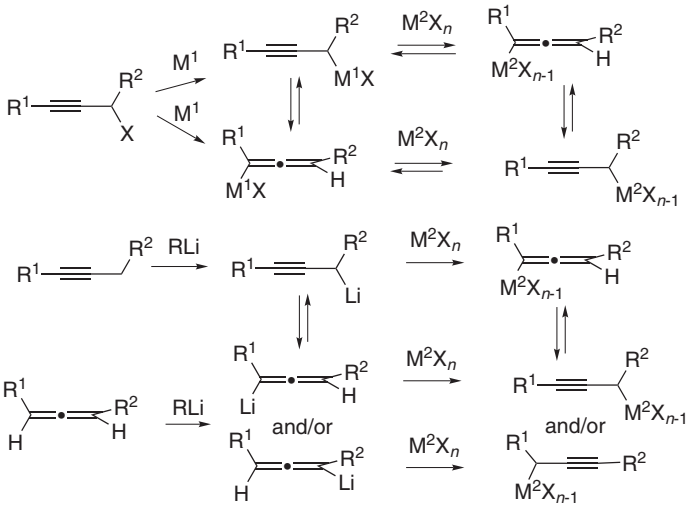
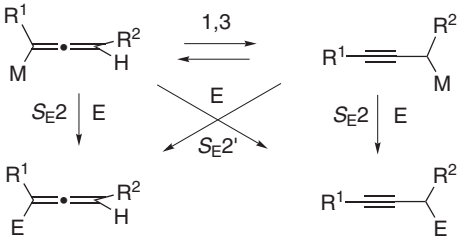


Scheme 9.1 Synthesis of allenylmetal compounds from propargylic halides, alkynes, and allenes.

9.1.2
Reaction Characteristics

Regiochemistry

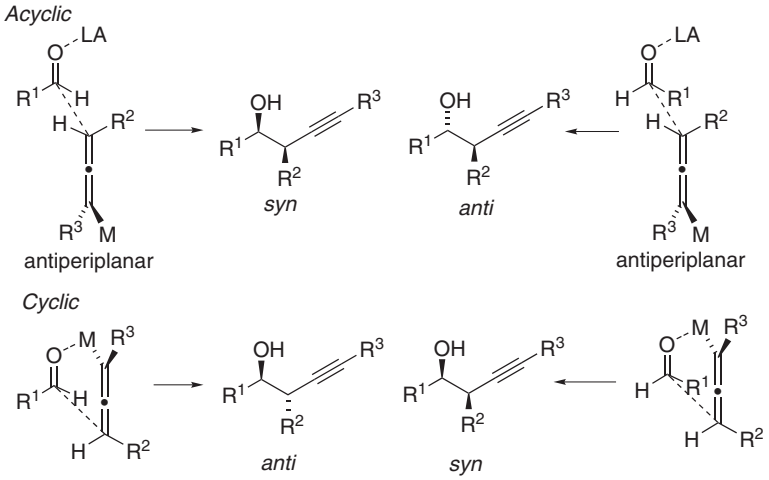
As noted above, metallations or deprotonations of propargylic precursors lead to allenic and/or propargylic organometal species, generally as an equilibrium mixture (Scheme 9.1). Reactions of such mixtures with electrophiles often lead to isomeric product mixtures, the composition of which reflects the relative transition-state energies of the substitution reactions (Scheme 9.2). It is possible for equilibration of the organometal reagents to be faster or slower than the subsequent substitution reactions depending on the reagent, electrophile and reaction conditions. The substitution process itself can proceed by either an S_E2 or an S_E2' pathway.



Scheme 9.2 Reaction of allenylmetal reagents with electrophiles.

Diastereoselectivity

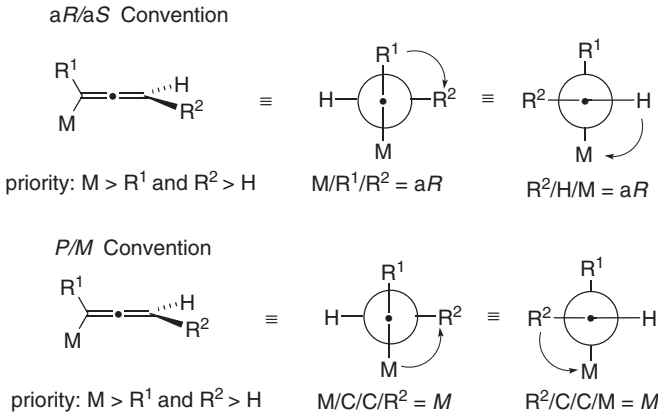
One of the most important reactions of allenylmetal reagents is their S_E2' addition to aldehydes to form homopropargylic alcohols. Reactions of γ-substituted allenylmetal reagents can produce diastereomeric S_E2' addition products. Two distinct transition states, acyclic and cyclic, have been identified; both are controlled by steric factors (Scheme 9.3). In the former, interactions between the aldehyde and allenic substituents, R^1 and R^2, favor the arrangement leading to the *syn* isomer. Similar considerations favor the *anti* product from additions involving a cyclic transition state. The preference for acyclic versus cyclic transition states is largely governed by the Lewis acidity of the metal substituent. Typically, halometal reagent additions proceed through cyclic transition states whereas the alkylmetal analogues follow an acylic pathway. In the latter case, Lewis acids are required in stoichometric or greater amounts to activate the carbonyl center.



Scheme 9.3 Transition states for additions of allenylmetal reagents to aldehydes.

Chirality

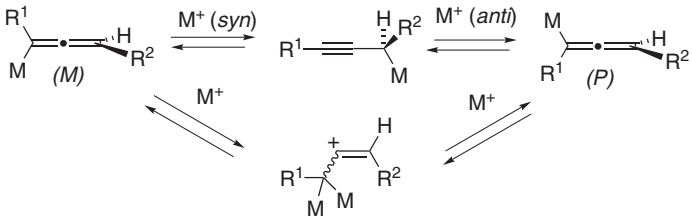
Allenylmetal compounds with a substituent at the γ-position are chiral. Two chirality descriptors have been employed for assigning configuration. The first of these, referred to as 'axial chirality', is based on the Cahn–Ingold–Prelog (C–I–P) *R*/*S* convention. Accordingly, the substituents at each of the two termini of the allene are assigned C–I–P priorities based on atomic number. The observer then sights down the allene chirality axis and traces a path from the higher to lower priority substituent on the near sp^2 center and continues to the higher priority substituent on the far sp^2 center. If the path from the near higher-priority to near lower-priority to far higher-priority substituent is clockwise, the allene is designated a*R* (axial *R*). A counterclockwise path would be traced for the a*S* enantiomer. It should be noted that the assignment of configuration is independent of the choice of near and far termini (Scheme 9.4).



Scheme 9.4 Configuration assignments for allenylmetal compounds (M = metal).

A more recent (and preferred) alternative convention for designating the chirality of allenes is based on their inherent helicity. By this convention one again identifies higher and lower priority substituents on each of the allene termini. A path is then traced from the higher priority group on one of the termini through the three allenic carbons to the higher priority group on the second allene terminus. A clockwise path defines the *P* (plus) configuration and a counterclockwise the *M* (minus). While the two conventions are unambiguous, they convey the opposite sense of chirality in that an a*R* allene (clockwise path) would be designated as *M* (counterclockwise path) by the helicity convention and vice versa.

The configurational stability of chiral allenylmetal reagents depends to a large extent on the nature of the metal substituent. The mechanism of the racemization process has not been studied in detail, but two reasonable pathways can be proposed, based on known reactivity characteristics of these compounds. The first entails reversible intermolecular $S_{E'}$ rearrangement to the propargylic isomer. This process could proceed by a pure *syn* or *anti* pathway, in which case no racemization would take place. However, the occurrence of both pathways would result in racemization (Scheme 9.5).

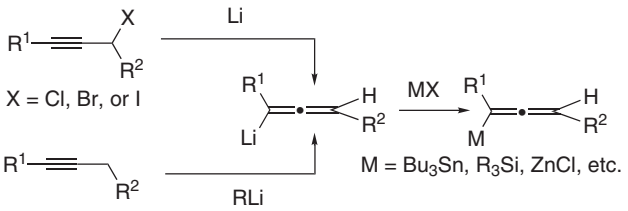


Scheme 9.5 Possible racemization pathways for chiral allenylmetal compounds.

Racemization could also take place by addition of a metal cation to the vinylic M double bond of the allenylmetal reagent. The resulting achiral vinylic cation intermediate would collapse to the racemic product through loss of M^+. Analogous pathways could account for metal exchange reactions of allenylmetal compounds. For this reversible process the position of the transmetallation equilibrium would be determined by thermodynamic considerations. Depending on the mechanistic pathway, the exchange could occur with retention or inversion of configuration and with partial or total racemization.

9.2 Allenyllithium Reagents

Allenyllithium reagents are commonly prepared through lithiation of propargylic halides or by deprotonation of alkynes or certain allenes (Eq. 9.1). Lithiated allenes often serve as precursors to stable allenylmetal compounds such as stannanes or silanes. They can also be employed for the in situ synthesis of allenylzinc, -titanium and -boronate compounds, which can be further transformed to substitution products not accessible from their allenyllithio precursors.

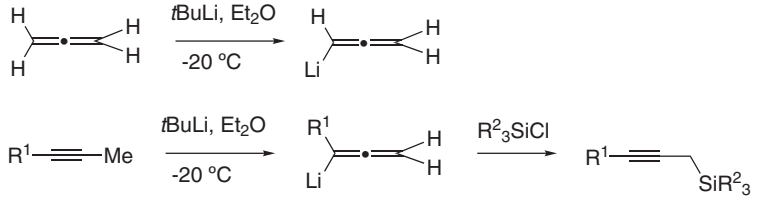


(9.1)

9.2.1 Structure

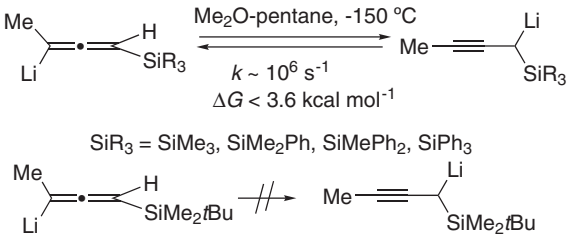
Since allenyllithium compounds are the quintessential allenylmetal reagents, it is not surprising that they have received extensive investigations of their structure. Recent variable-temperature ^{13}C and ^{7}Li NMR studies have been particularly enlightening [3]. These studies were conducted on allenyllithium itself and several 3-lithioallenes. The former was prepared through deprotonation of allene and the latter by deprotonation of appropriate 1-methyl-3-alkyl-2-alkynes in dimethyl ether with *t*-butyllithium at low temperature (Eq. 9.2). Of the various allenyllithium derivatives in Eq. 9.2, all were monomeric except allenyllithium itself, which was present as a dimer–monomer mixture. NMR data were consistent with a monomer:dimer equilibrium ratio of 2:1 at –140 °C and 2:3 at –80 °C. The monomeric methyl-, isopropyl- and *tert*-butyl-substituted allenyllithium derivatives all showed ^{13}C and ^{7}Li spectral characteristics of the allenyl structure. The ^{13}C–^{7}Li linewidth of the propargylic CH signals at 44 ppm were 3.5–4 Hz. These values are considerably less than the calculated value of 48 Hz for a pure propargyllithium isomer. By assuming that the lithiated propargyl and allenyl structures are rapidly interconverting, it can be sur-

mised that no more than 5% of the propargyllithium isomer could be present in the equilibrium mixtures of the alkyl-substituted lithioallenes (Eq. 9.2).



(9.2)

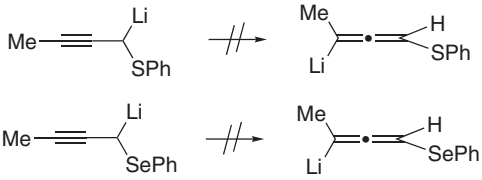
Silylated allenyllithium reagents, prepared by lithiation of various propargylic silanes (Eq. 9.2), were also examined (Eq. 9.3). The ^{13}C NMR spectrum of the TBS derivative showed chemical shift data consistent with the allenyl structure. Furthermore, the allenyl position was strongly coupled to the lithium substituent and the linewidths of both sp^2 centers were the same, as would only be expected if the propargyl isomer were absent. The spectra of the trimethylsilyl (TMS) and various phenyl-substituted silylated derivatives contained signals whose chemical shifts were intermediate between those expected for the allenyl and propargyl isomers, suggestive of a rapidly equilibrating mixture of the two. This conclusion was corroborated by infrared spectral data showing absorptions at both 2179 (alkyne) and 1894 cm^{-1} (allene). Variable-temperature ^{13}C–^{7}Li J value analysis was employed to derive an estimated rate constant of $10^6\ s^{-1}$ and a $\Delta G^{\ddagger}$ of ~3.6 kcal mol^{-1} for this interconversion in the TMS-substituted lithioallene.



(9.3)

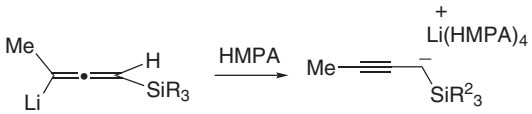
It was suggested that the silyl substituent of these lithium reagents stabilizes charge localized at the propargylic center. However, this stabilization is partially counterbalanced by unfavorable steric interactions. The steric effect is greatest in the TBS derivative, where it completely subverts the stabilizing influence of the silyl substituent, leading to exclusive formation of the allenyl isomer (Eq. 9.3). The TMS group exerts a smaller steric effect and, as a result, both the electronically favored propargylic and sterically favored allenyl isomer are present at equilibrium. The phenyl-substituted silanes require additional explanation. Based solely on the steric argument, the phenylsilanes would be predicted to favor the allenyl structures. However, it is proposed that the electron-withdrawing phenyl substituents enhance the charge-stabilizing effect of the silicon in the propargyl isomer of these lithiated derivatives, thereby offsetting the destabilizing steric effect. Consequently, both iso-

mers are observed at equilibrium. Electron-withdrawing substituents such as SPh and SePh are known to favor the propargylic lithio isomer to the exclusion of the allene (Eq. 9.4) [3].



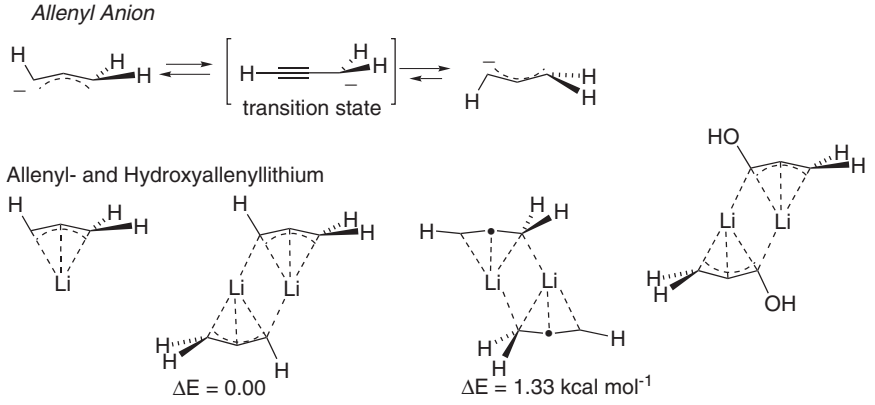
(9.4)

Solvation of the lithio cation of the silylated reagents by HMPA leads to solvent-separated ion pairs (Eq. 9.5). Titration experiments indicate coordination by four HMPA molecules. These solvated complexes, including the TBS derivative, exist entirely as the propargyl structures, emphasizing the importance of the silyl group to charge stabilization.



(9.5)

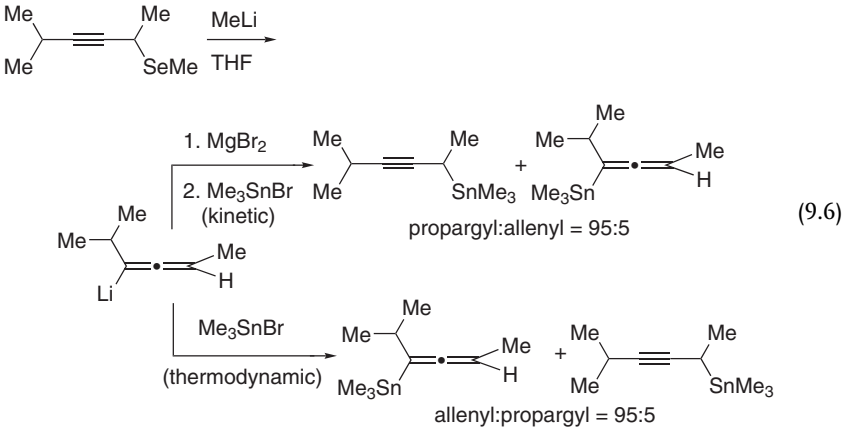
Ab initio calculations on the allenyl anion reveal a strong preference for a bent structure (Scheme 9.6) [3]. The localized propargyl anion represents a transition state for allenyl inversion. However, calculations on lithioallene predict a single monomeric structure and two dimers. The monomer resembles the bent allene anion with a somewhat greater C1–C2–C3 angle (173 versus 157°). All three lithioallenes possess a 1,3-lithium bridge. The lower energy dimer is largely allenic whereas a slightly higher energy species shows significant pyramidalization at the CH_2 terminus, in keeping with a propargylic structure. The hydroxy analogue, a computational surrogate for methoxyallenyllithium, converged to a single minimized dimer structure with considerable allenic character.



Scheme 9.6 Calculated structures for the allenyl anion and allenyl and hydroxyallenyllithium.

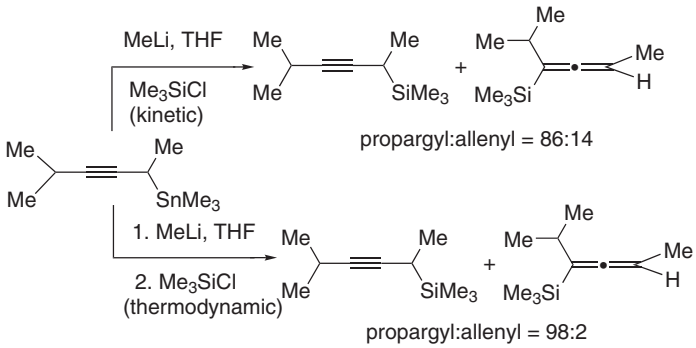
9.2.2
Regioselectivity of Silylation

An earlier study addressed the issue of regioselectivity in reactions of allenyl- or propargyllithium reagents with silyl chlorides [4]. These lithio derivatives were derived from stannane precursors, which in turn were prepared by successive transmetallations of 2-selenomethyl-5-methyl-3-hexyne (Eq. 9.6). Accordingly, lithiation followed by lithium-magnesium exchange and subsequent treatment of the intermediate allenylmagnesium bromide with trimethyltin bromide yielded the kinetically favored propargylic stannane. The thermodynamically favored allenic isomer was obtained from reactions in which the allenic lithium intermediate was trapped in situ with Me_3SnBr.



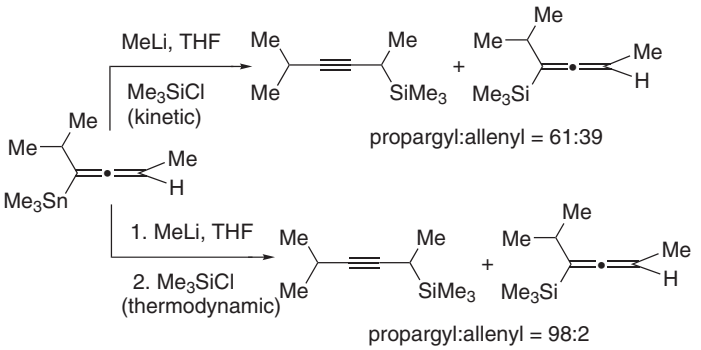
(9.6)

Lithiation of the allenic stannane in the presence of Me_3SiCl gave rise to an 86:14 mixture of propargylic and allenic silanes (Eq. 9.7). Sequential lithiation followed by addition of Me_3SiCl, on the other hand, afforded the propargylic silane to the near exclusion of the allenic isomer.



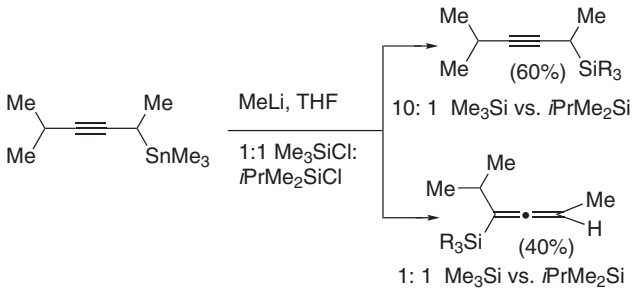
(9.7)

Comparable treatment of the allenic stannane resulted in a similar outcome, producing a mixture of regioisomers from the in situ silylation and near exclusive formation of the allenylsilane from the sequential addition (Eq. 9.8).



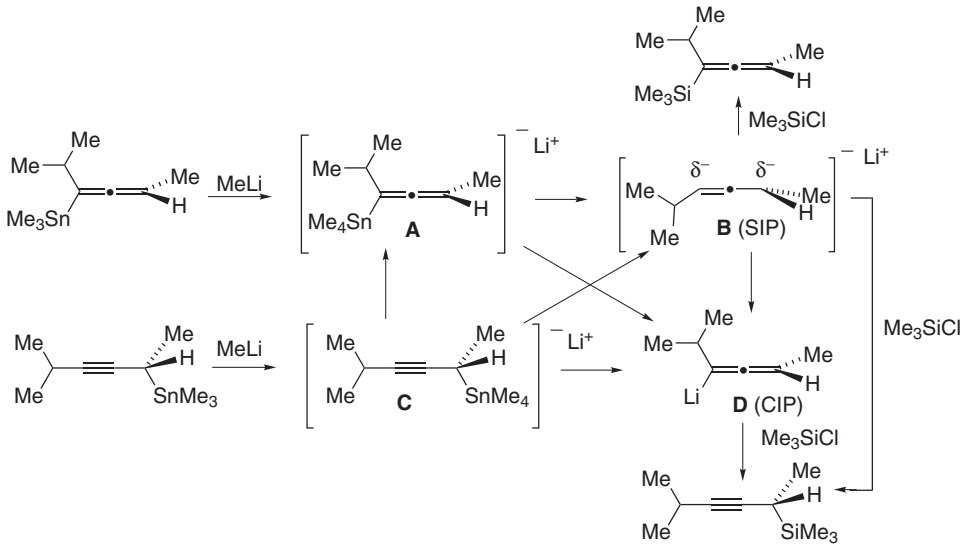
(9.8)

A competition experiment clarified the nature of the intermediates leading to the two silylated products (Eq. 9.9). Accordingly, lithiation of the propargylic stannane in the presence of a 1:1 mixture of Me_3SiCl and iPrMe$_2$SiCl (kinetic trapping) afforded a 60:40 mixture of propargylic and allenic silanes, in accord with the results of Eq. 9.8. The propargylic product consisted of a 10:1 mixture favoring the trimethylsilyl derivative. The allenic product, in contrast, was a nearly 1:1 mixture of trimethylsilyl and isopropyldimethylsilyl derivatives.



(9.9)

These findings can be reconciled with the reaction sequence depicted in Scheme 9.7. Accordingly, the tin ate complexes **A** and **C** are the immediate precursors of the respective lithio reagents. The allenic isomer **A** can undergo S_E2 substitution with the lithio cation to afford the stable contact ion-pair (CIP) allenyllithium intermediate **D**, which reacts by an S_E2' reaction with Me_3SiCl to produce the propargylic silane. A second pathway for **A** would be dissociation to a solvent-separated ion-pair (SIP) intermediate **B**, which could collapse to the thermodynamically favored allenyllithium contact ion-pair **D** or react with Me_3SiCl to yield the allenylsilane. Because of the short lifetime of **B**, this reaction would only be possible if the tin–lithium exchange were conducted in the presence of the silyl chloride. The propargylic tin ate complex **C** could similarly dissociate to **B** or react with Li^+ to form



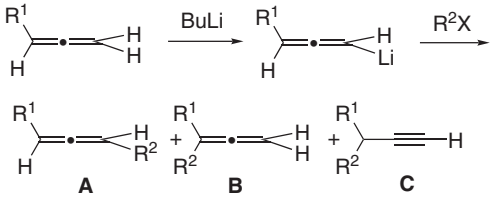
Scheme 9.7 Mechanistic pathways for reactions of stannane-derived allenyl- and propargyllitihum intermediates with silyl chlorides.

the allenyllithium intermediate **D**, which would react with Me_3SiCl already present or subsequently added.

It is thought that a large fraction of the allenylsilane product is formed from the solvent-separated ion pair **B**. The expectedly high reactivity of this species would minimize steric effects associated with the silylation, thus explaining the lack of selectivity observed for Me_3Si versus iPrMe$_2$Si in the competition experiment.

The tin–lithium exchange reactions are thought to proceed with retention of stereochemistry. However, as the stannanes employed in this study were racemic, there is no evidence in support of this pathway.

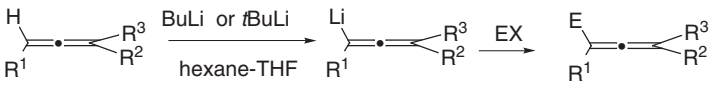
Allenes are deprotonated by organolithium bases to yield allenyllithium intermediates. Subsequent treatment of these intermediates with various reactive carbon electrophiles can follow several pathways. An early study showed that terminal allenes bearing a free CH_2 substituent afford mainly the direct S_E2 substitution product **A** upon treatment first with BuLi and then with various unbranched alkyl iodides (Table 9.1) [5]. A negligible amount of the S_E2' propargylic product **C** was formed under these conditions Small amounts of regioisomeric allene alkylation products **B** were presumed to arise from 1,3-dilithioallenes.



R^1	R^2X	**A**:**B**:**C**
Me	$C_8H_{17}I$	84:15:1
Pr	BuI	91:7:2
C_6H_{13}	MeI	93:6:1
C_8H_{17}	MeI	94:5:1

Table 9.1 Deprotonation and Alkylation of terminal allenes.

Additional allene homologues were prepared by using this methodology with a variety of electrophiles (EX, Table 9.2) [6]. For reactions requiring removal of a secondary allenic proton the base of choice was *t*BuLi. Only allenic products were formed except in the reaction with cyclopentanone, in which a small amount of the homopropargylic alcohol product was produced (last entry).

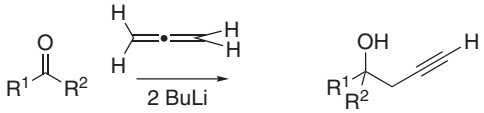


R^1	R^2	R^3	EX	yield,%
H	H	Pr	Me_3SiCl	90
Bu	Me	Me	Me_3SiCl	95
H	H	C_8H_{17}	MeSSMe	76
H	H	Pr		83
H	H	H	CO_2	62
H	H	C_8H_{17}		95[a]

[a] an 86:14 mixture of allenic and propargylic isomers

Table 9.2 Lithiation of allenes and subsequent reaction with electrophiles.

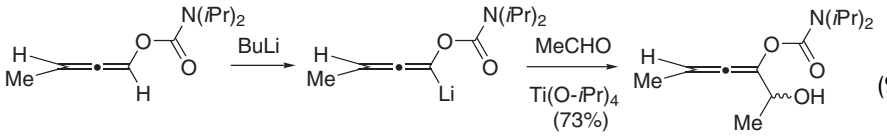
Treatment of allene (1,2-propadiene) with 2 equiv. of butyllithium leads to an intermediate dilithio species which adds to ketones and aldehydes to afford homopropargylic alcohols in high yield (Table 9.3) [7]. This intermediate also reacts with geranyl chloride to afford the alkynyl coupling product uncontaminated by the allene regioisomer.



R^1	R^2	Yield, %
Ph	Me	93
Ph	Ph	90
Ph	C_3H_5	90
Me	$CH{=}CH_2$	80
Ph	H	93

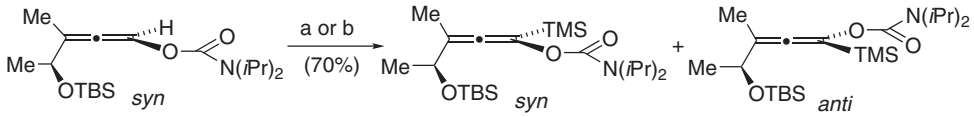
Table 9.3 Additions of a dilithioallene to ketones and aldehydes.

1,2-Butadienyl carbamates can be deprotonated with BuLi [8]. Subsequent treatment with $Ti(OiPr)_4$ and acetaldehyde give the allenyl addition product in 73% yield as a 60:40 mixture of diastereomers (Eq. 9.10).



(9.10)

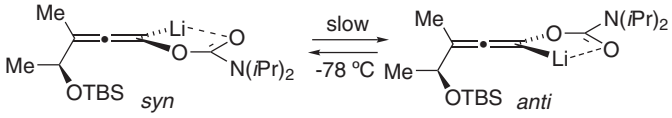
The stereochemistry of the process was examined by analysis of the products resulting from trapping the lithioallene from a chiral allenylcarbamate with Me_3SiCl (Eq. 9.11). Sequential lithiation with BuLi followed by addition of Me_3SiCl at –78 °C afforded a 75:25 mixture of the *syn* and *anti* adducts in 70% yield. On the other hand, deprotonation with LDA at –78 °C in the presence of excess Me_3SiCl gave rise to the *syn* adduct as the sole product in 70% yield. It could therefore be surmised that (1) lithiation proceeds with retention of stereochemistry and (2) syn/*anti* isomerization of the putative allenyllithium intermediate at –78 °C is slower than silylation (Eq. 9.12).



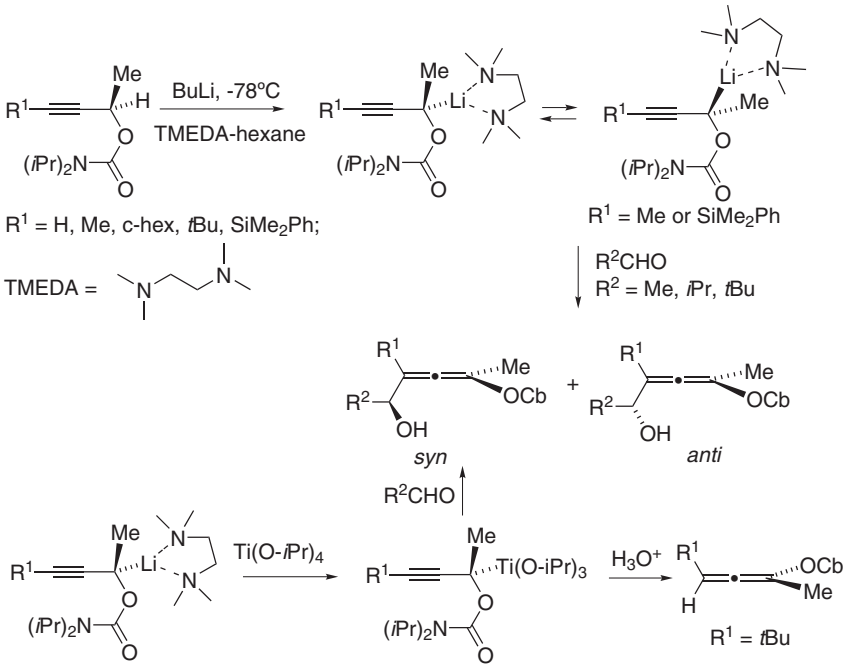
a) 1. BuLi, Et_2O, -78 °C; 2. Me_3SiCl; *syn:anti* = 75:25,

b) LDA, Me_3SiCl, Et_2O, -78 °C ; *syn:anti* = 100:0

(9.11)

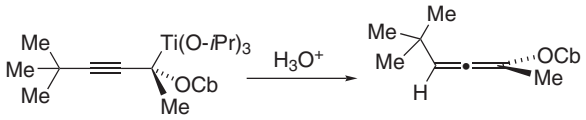


(9.12)



Scheme 9.8 Lithiation of enantioenriched propargylic cabamates and their subsequent conversion to chiral allenylcarbinols [OCb = $(iPr)_2NCOO$].

In a related study, enantioenriched propargylic carbamates were prepared in order to evaluate the configurational stablility of the lithio derivatives, formed through deprotonation and their subsequent reaction with aldehydes (Scheme 9.8) [9]. The allenyllithium derived from the methyl-substituted propargyl carbamate ($R^1 = Me$) afforded a 36:64 mixture of racemic *syn* and *anti* adducts in 50% yield. The $PhMe_2Si$-substituted derivative likewise gave racemic products with a slight preference for the *syn* isomer (58:42, 50% yield). In contrast, reaction of the *t*-butyl derivative ($R^1 = tBu$) with acetaldehyde afforded an 82:18 mixture of *anti* and *syn* adducts with no racemization. Comparable results were obtained with isobutyraldehyde as the electrophile. It was also found that these ratios were unchanged when $Ti(OiPr)_4$ was added to the lithioallene prior to addition of the aldehyde. Protonolysis of the presumed propargylic titanium species afforded the allenylcarbamate of inverted configuration (Eq. 9.13).

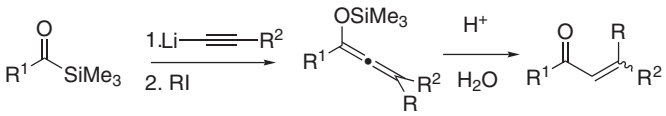


(9.13)

The following conclusions were drawn from this study:

1. Lithiation proceeds with retention of configuration.
2. The lithiated propargyl carbamate is configurationally stable at –78 °C as long as a bulky substituent (R^1) is present at the remote alkynyl position.
3. Groups that stabilize a negative charge at the lithiation site cause racemization.
4. Transmetallation by $Ti(OiPr)_4$ occurs with retention of configuration.
5. The aldehyde additions proceed by a *syn* S_E2' cyclic transition states.
6. Protonolysis of the propargylic titantium intermediate prefers an *anti* S_E2' pathway.

Whereas deprotonation and halogen–lithium exchange represent the most common methods to access allenic and propargylic lithium intermediates, several less direct routes to more functionalized analogues have also been reported. Additions of various lithium acetylides to acylsilanes followed by MeI or EtI afforded alkylated allenyl silyl ethers (Table 9.4) [10]. The adducts were analyzed after hydrolysis to the related enones.

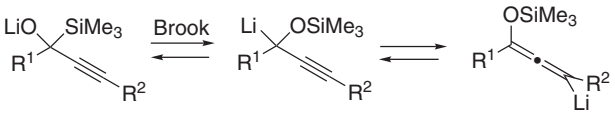


R^1	R^2	R	Yield, %[a]
$PhCH_2CH_2$	Bu	Me	71
$PhCH_2CH_2$	Pr	Et	60
$PhCH_2CH_2$	Ph	Me	70
$PhCH_2CH_2$	Ph	Et	54
Et	Bu	Me	74

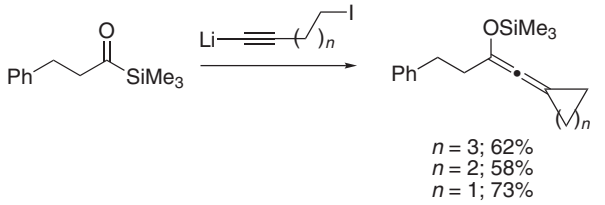
[a] After hydrolysis to the enone

Table 9.4 Formation of allenyllithium intermediates by a Brook rearrangement sequence.

These reactions are thought to proceed by initial formation of the lithio propargylic alcohol adduct, which undergoes a reversible Brook rearrangement (Eq. 9.14). The resulting propargyllithium species can equilibrate with the allenyl isomer and subsequent reaction with the alkyl iodide electrophile takes place at the allenic site. An intramolecular version of this alkylation reaction leads to cyclic allenylidene products (Eq. 9.15).



(9.14)



(9.15)

An allenyllithium intermediate was implicated in the reaction of BuLi with an alkynylated cyclohexene epoxide (Table 9.5) [11]. It was found that addition of 2 equiv. of BuLi to the alkynyloxirane in the presence of 5 mol% $CuBr \cdot 2PPh_3$ led, after quenching with H_2O, not to the expected S_N2' butylated allene, but instead to the protonolysis product. Likewise, quenching the reaction with MeI or MeSSMe led to the methylated and thiolated allenes, respectively. Furthermore, the putative lithioallene could be trapped by CO_2 or PhCHO to yield the expected adducts.

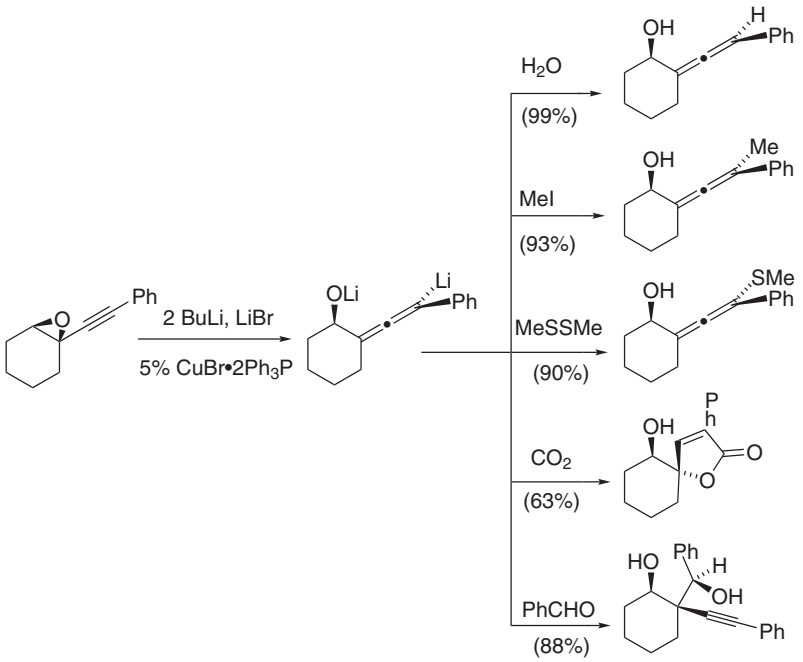
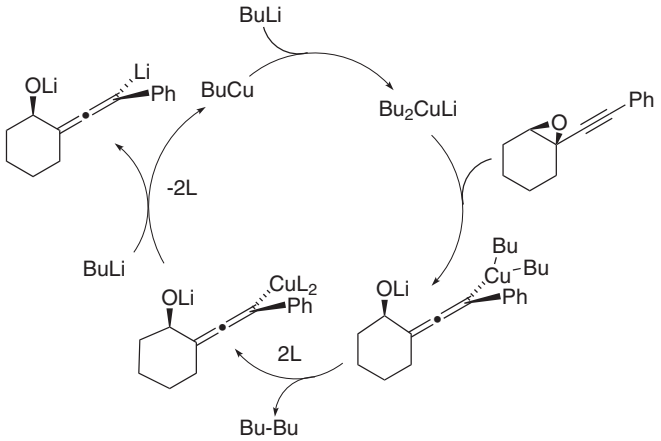


Table 9.5 Lithiation of an alkynyloxirane.

A priori, an allenyl cuprate intermediate might account for the observed products. However, the reaction was carried out in two stages with only 5 mol% of CuBr. Thus, if a cuprate intermediate was the reactive species, a theoretical yield of 5% would have been expected. However, the reaction did not take place in the absence of the copper catalyst. Accordingly, a catalytic cycle was proposed in which the initial dibutyl cuprate effects a well precedented S_N2' displacement on the vinyloxirane,

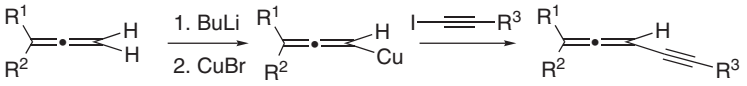
but the subsequent reductive elimination step proceeds by extrusion of octane rather than transfer of a butyl group from the Cu(III) species to the allene (Scheme 9.9). The allenyl Cu(I) intermediate then undergoes transmetallation with BuLi to form BuCu and the allenyllithium intermediate.



Scheme 9.9 Catalytic cycle for S_N2' lithiation of an alkynyloxirane.

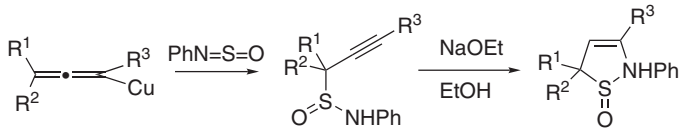
9.3 Allenylcopper Reagents

Allenylcopper reagents can be generated from allenyllithium precursors by treatment with stoichiometric amounts of CuBr (Table 9.6) [12]. These intermediates were not characterized, per se, but subsequent reaction with alkenyl iodides led to allenynes in high yield. Thus it is assumed that the reagents are allenic rather than propargylic. The same intermediates afford 2-alkynylsulfinamides on treatment with *N*-sulfinylaniline (Table 9.7) [13]. Cyclization to the *N*-phenyldihydroisothiazole *S*-oxides proceeds in nearly quantitative yield on treatment with base.



R^1	R^2	R^3	Yield, %
H	H	TMS	85
H	H	Ph	89
Me	Me	TMS	80
Me	Me	Ph	90
*t*Bu	H	Me	75
*t*Bu	H	TMS	77
*t*Bu	H	Ph	90

Table 9.6 Generation of allenyl-Cu(I) reagents and their reaction with alkynyl iodides.

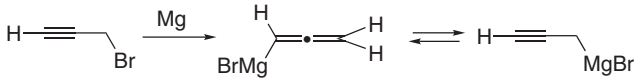


R^1	R^2	R^3	Yield, %	Yield, %
H	H	H	95	-
Me	Me	H	85	95
*t*Bu	H	H	81	95
Me	Me	Ph	72	95

Table 9.7 Reaction of allenyl-Cu(I) reagents with *N*-sulfinylaniline.

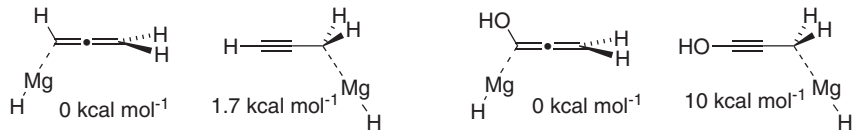
9.4
Allenylmagnesium Halides

The first allenylmetal reagent was prepared from propargyl bromide and magnesium in 1950 by Prévost et al. (Eq. 9.16) [14]. Subsequent studies showed that the product of this reaction is best represented by the allenic structure in rapid equilibrium with minor amounts of the propargyl isomer [15]. Allenylmagnesium bromide has proven to be a useful reagent for the synthesis of homopropargylic compounds [16]. However, higher homologues have not found significant utility.



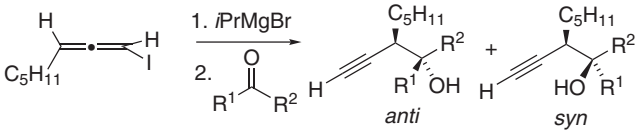
(9.16)

Recent *ab initio* calculations confirm the allenic nature of allenylmagnesium hydride, a computational surrogate for the Grignard reagent [17]. An energy difference of 1.7 kcal separates the allenyl structure from its higher energy propargyl counterpart (Scheme 9.10). An even larger energy difference was calculated for 1-hydroxyallenylmagnesium hydride and its propargyl isomer. This calculation was performed to evaluate the structural preference for the reagent derived from methoxyallene.



Scheme 9.10 Calculated relative energies for minimized structures of allenyl- and propargylmagnesium hydride and the related hydroxy analogues.

In situ magnesiation of an allenyl iodide with isopropylmagnesium bromide gives rise to a transient allenyl Grignard reagent, which adds to aldehydes and ketones to afford mainly homopropargylic alcohol adducts (Table 9.8) [18]. The *anti* diastereomers are favored, especially with sterically demanding aldehydes. Additions to ketones are less selective.



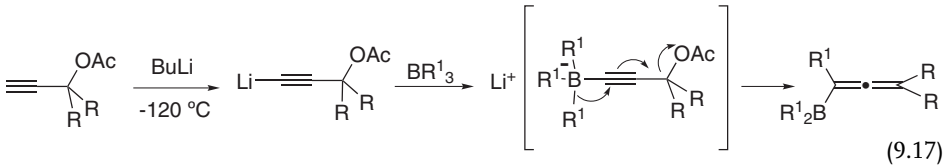
R^1	R^2	*anti:syn*	Yield, %
H	Bu	89:11	72
H	*t*Bu	99:1	58
H	Ph	57:43	80
Me	Ph	75:25	88[a)]
Me	Bu	53:47	67

[a)] A 92:8 mixture of propargyl and allene isomers

Table 9.8 In situ preparation and reactions of an allenylmagnesium iodide reagent.

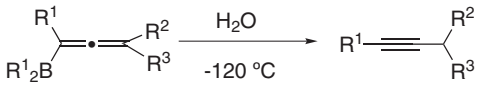
9.5 Allenylboron Reagents

Allenylboranes can be prepared by treatment of propargylic acetates with butyllithium and a trialkylborane [19]. The reaction proceeds by initial formation of an alkynylboronate followed by migration of an alkyl group from boron to carbon (Eq. 9.17).



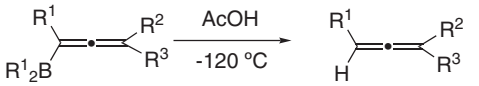
(9.17)

Protonolysis of these allenylboranes can be effected by addition of water or acetic acid. In the former case the reaction occurs by an S_E2' pathway affording alkynes in high yield (Table 9.9). In contrast, acetic acid effects protonolysis without isomerization to yield the corresponding allenes, also in high yield (Table 10).



		yield, %		
R^2	R^3	R^1 = Bu	R^1 = *i*Bu	R^1 = *s*Bu
Me	Me	80	90	76
C_5H_{11}	H	87	92	92
C_6H_5	H	94	91	90
$C_6H_5CH{=}CH$	H	64		
$MeCH{=}CH$	H	87		

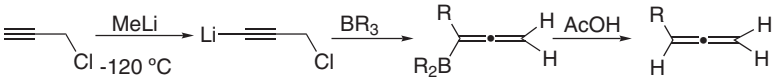
Table 9.9 Conversion of allenylboranes to alkynes.



	Yield, %	
R^2, R^3	R^1 = Bu	R^1 = *i*Bu
Me, Me	87	-
C_6H_5, H	91	91
MeCH=CH, H	60	-
$(CH_2)_5$	84	-

Table 9.10 Conversion of allenylboranes to allenes.

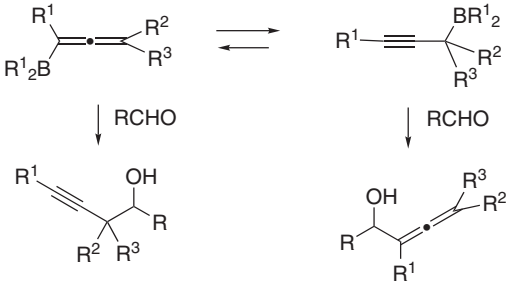
Allenylboranes can also be prepared from lithiated propargyl chloride [20]. As noted above, these intermediates react with acetic acid to afford allenes (Table 9.11).



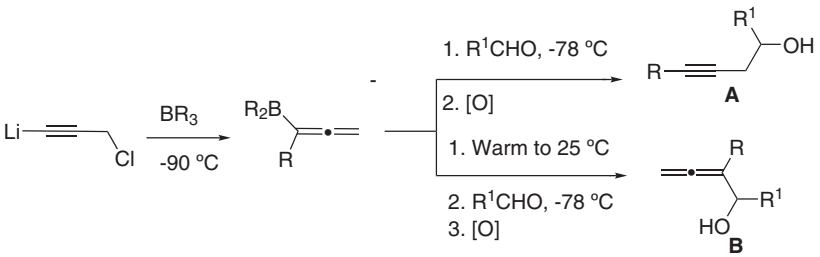
R	Yield, %
butyl	73
3-hexyl	74
cyclopentyl	75
2-methylcyclopentyl	76
cyclohexyl	77

Table 9.11 Synthesis of allenes from propargyl chloride.

Reactions with aldehydes at –78 °C afford homopropargylic alcohols (Eq. 9.18) [21]. On warming to 25 °C, allenylboranes rearrange to the propargylic isomers, which react with aldehydes at –78 °C to yield allenylcarbinols. Accordingly, isomeric alcohol products can be prepared from a single allenylborane through control of the reaction conditions. If an aldehyde is added to the initially formed allenylborane at –78 °C, the product obtained is a homopropargylic alcohol (Table 9.12). If, however, the initially formed allenylborane is allowed to warm to room temperature, then recooled to –78 °C before the aldehyde is added, the adduct obtained is the allenycarbinol, derived from the thermodynamically favored propargylic borane (Table 9.12).



(9.18)

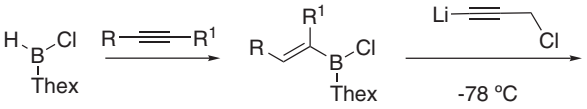


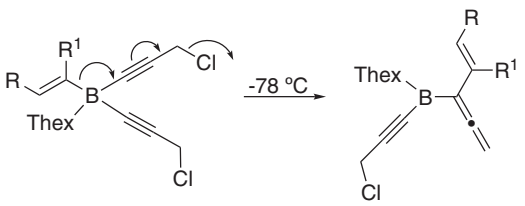
R	R^1	**A**, %	**B**, %
cC_5H_9	Et	89	80
cC_5H_9	C_6H_{11}	88	86
cC_5H_9	*t*Bu	86	79
cC_5H_9	C_6H_5	86	85
cC_5H_9	CH_2=CH_2	75	84
C_6H_{11}	Et	-	77
C_6H_{13}	Et	85	73

Table 9.12 Conversion of lithio propargyl chloride to allenic carbinols and homopropargylic alcohols.

These reactions proceed in high yield and afford isomerically pure products. Although both propargylic and allenic boranes react with aldehydes, only allenic boranes add to ketones. Apparently, the allenic borane is more reactive than the propargylic isomer. A shortcoming of the method is the inefficent utilization of only one of the three alky groups of the trialkylborane. Attempts to circumvent this requirement through use of a 9-borabicyclo [3.3.1]nonane (9-BBN) dummy ligand were unsuccessful, as the 9-BBN group was preferentially transferred in the reaction leading to the allenylborane intermediate. However, if the borane was substituted by a thexyl and a primary alkyl substituent, then migration of the primary group to afford the alkyl-substituted allenylborane was favored. Unfortunately, extension of this modification to a secondary alkyl substituent was not feasible as the thexyl group migrated preferentially.

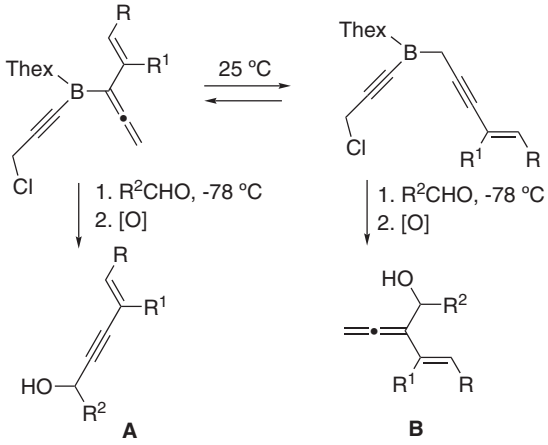
In contrast to the previous results with secondary alkyl substituents, the thexyl group of mixed secondary vinylic-substituted allenyl or propargyl boranes, prepared according to Eq. 19, is effectively inert and the reagent reacts with aldehydes to afford propargylic or allenic carbinols [22]. Both the thexyl and propargylic chloride substituents serve as dummy ligands in this reaction and the alkenyl group migrates with retention of stereochemistry. As previously noted, the structure of these boranes is dependent on temperature. If the initial allenylborane is allowed to equilibrate at room temperature prior to addition of the aldehyde, the thermodynamically more stable propargylic borane predominates. Consequently, the allenic carbinol is formed on addition of the aldehyde. The method is applicable to a variety of alkenyl groups, propargylic chlorides and aldehydes. The alcohol products of these sequential reactions were obtained in moderate yield (Table 9.13).





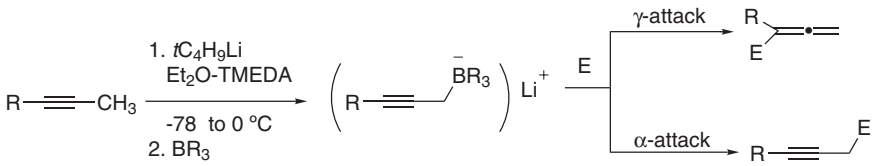
(9.19)

Extension of this reaction to electrophiles other than aldehydes was unsuccessful [22, 23]. However, propargylic boronates were found to react with allylic halides and various carbonyl compounds [23]. The boronates were prepared by lithiation of a methyl-substituted alkyne with *t*-butyllithium followed by treatment with a trialkylborane. The propargylic boronate preferentially reacts with the electrophile at the γ-position to yield propargylic products (Eq. 9.20). The methodology has also been applied to alanates with comparable results.



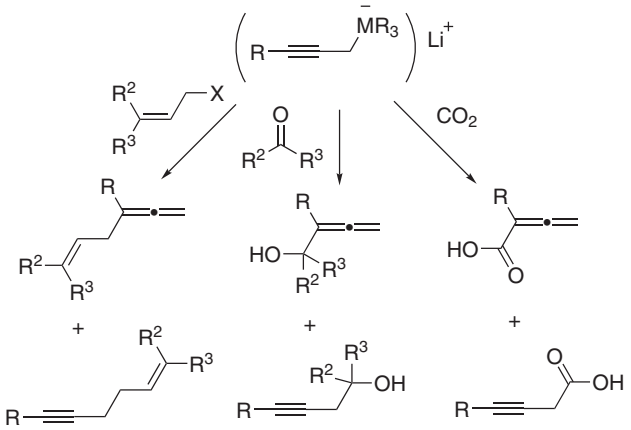
R	R^1	R^2	**A**, %	**B**, %
Bu	H	Et	60	74
Bu	H	*i*Pr	-	76
Bu	H	*t*Bu	70	88
Bu	H	CH_2=CH	72	71
C_6H_{11}	H	Et	-	80
*t*Bu	H	Et	-	88
Et	Et	Et	-	61

Table 9.13 Synthesis of 1,2,4-trienols and 1,3-enynols.



(9.20)

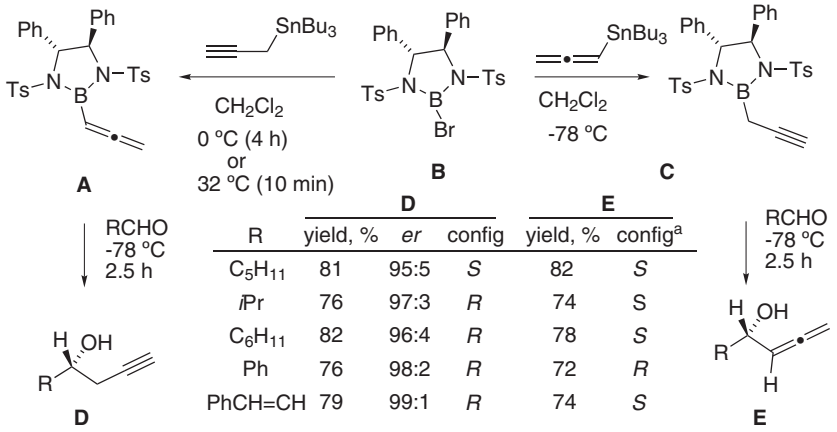
Although both boronates and alanates react with allylic bromides, aldehydes and CO_2 to afford allenic products in satisfactory yield, the alanates are more efficient in additions to ketones (Table 9.14). Boronate reagents do not require a B–C alkyl migration for their preparation. Thus the starting acetylene possesses the structural elements of the product. Additionally, the issue of dummy ligands is irrelevant.



M	R	Electrophile	Allene:alkyne	Yield, %
B	Bu	CH_2=$CHCH_2Br$	83:17	74
B	Bu	Me_2C=$CHCH_2Br$	99:1	84
B	Bu	EtCHO	99:1	86
B	*t*Bu	EtCHO	62:38	21
B	Bu	Me_2CO	48:52	35
B	Bu	CO_2	98:2	76
Al	Bu	Me_2C=$CHCH_2Br$	99:1	84
Al	*t*Bu	EtCHO	97:3	71
Al	Bu	Me_2CO	95:5	73
Al	Bu	CO_2	92:8	80

Table 9.14 Reaction of propargyl boronates and alanates with various electrophiles.

The enantiomerically enriched allenic and propargylic boron reagents **A** and **C** have been prepared by treatment of the (*R,R*)-bromoboron intermediate **B** with the appropriate propargyl or allenyltin reagent [24]. Allenic and propargylic adducts are

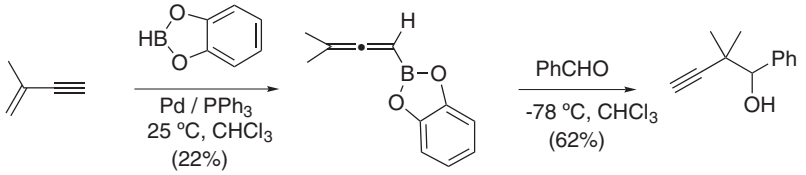


R	D yield, %	D *er*	D config	E yield, %	E config[a]
C_5H_{11}	81	95:5	*S*	82	*S*
*i*Pr	76	97:3	*R*	74	S
C_6H_{11}	82	96:4	*R*	78	*S*
Ph	76	98:2	*R*	72	*R*
PhCH=CH	79	99:1	*R*	74	*S*

Table 9.15 Enantioselective synthesis of allenic and propargylic carbinols.

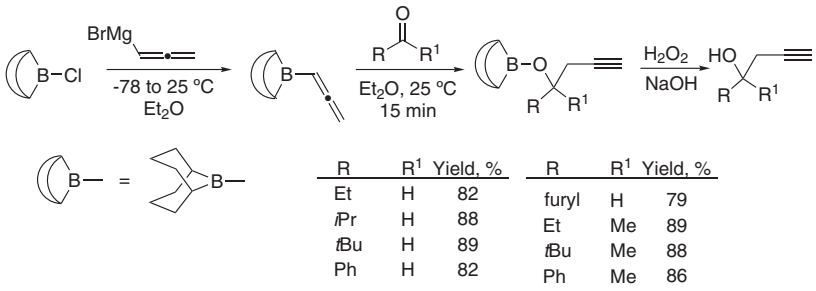
obtained on treatment of these borane reagents with a range of aldehydes. Both products were produced in high yield and enantiomeric purity (Table 9.15).

Catechol allenylboranes have also been used to synthesize homopropargylic alcohols [25]. These reagents are prepared by hydroboration of an enyne with catecholborane in the presence of a Pd(0) catalyst possessing monodentate phosphine ligands. Dienylboranes were formed as minor products. Optimum results were obtained by treatment of the catecholborane with molar equivalents of triphenylphosphine and the palladium catalyst. Although several allenylboranes were prepared, only the dimethyl reagent was further examined. Treatment of that borane with benzaldehyde afforded the homopropargylic alcohol in 62% yield (Eq. 9.21).



(9.21)

Various homopropargylic alcohols have been synthesized from 9-allenyl-9-BBN and a variety of aldehydes and ketones (Table 9.16) [26]. The additions occur rapidly with a high degree of regioselectivity to afford borinic esters, which are cleaved by oxidation with alkaline hydrogen peroxide. The 9-BBN reagent is prepared from *B*-chloro-9-BBN and can be easily stored. This reagent selectively forms homopropargylic alcohols upon additions to ketones, in contrast to the corresponding allenylmagnesium and allenyldibutylboronate reagents, which yield a mixture of propargylic and allenic adducts. Successful application to ketones as the electrophilic partner is a useful extension of these reactions.

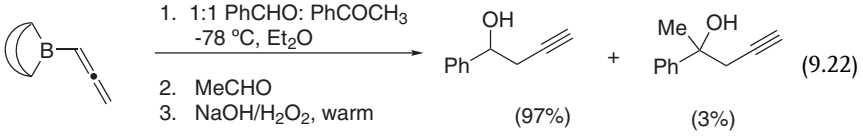


R	R¹	Yield, %
Et	H	82
*i*Pr	H	88
*t*Bu	H	89
Ph	H	82

R	R¹	Yield, %
furyl	H	79
Et	Me	89
*t*Bu	Me	88
Ph	Me	86

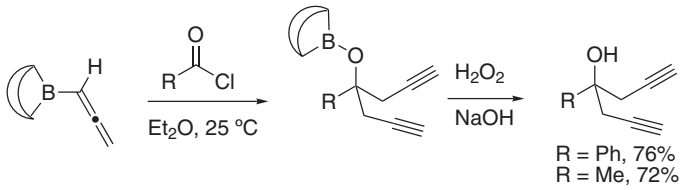
Table 9.16 Synthesis of homopropargylic alcohols from *B*-allenyl-9-BBN.

B-Allenyl-9-BBN has also been shown to react cleanly and efficiently with other electrophiles [27]. Not surprisingly, aldehydes show the highest reactivity. In a competition experiment between benzaldehyde and acetophenone at –78 °C, the aldehyde adduct predominated by more than 30:1(Eq. 9.22). Competition experiments with other carbonyl compounds showed a similar bias for aldehyde adducts.



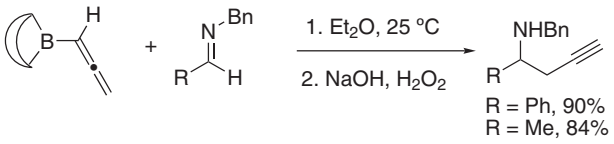
(9.22)

Acid chlorides were also shown to be reactive electrophiles. *B*-Allenyl-9-BBN affords tertiary bis-homopropargylic alcohols in satisfactory yields upon reaction with acetyl or benzoyl chloride (Eq. 9.23).



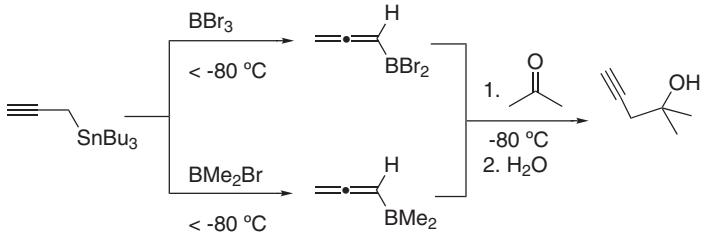
(9.23)

A tertiary homopropargylic alcohol could also be prepared by treatment of ethyl acetate with two equivalents of *B*-allenyl-9-BBN. However, the reaction proceeded slowly and was not general for other esters, which proved to be unreactive, as were tertiary amides and alkyl halides. However, homopropargylic amines could be prepared in high yield and with minimal allenic byproduct through allenylboration of imines with *B*-allenyl-9-BBN (Eq. 9.24).



(9.24)

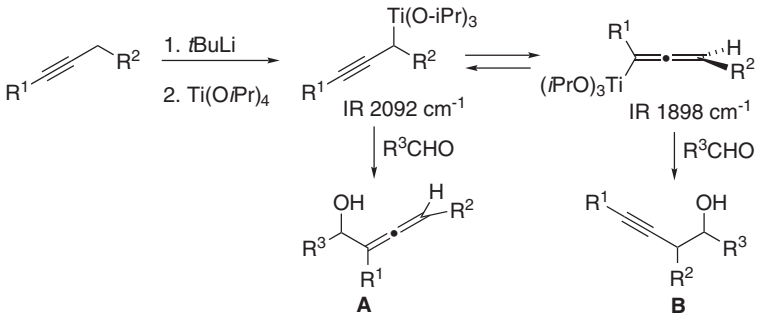
Allenyldibromoborane was obtained in 34% yield by the reaction of boron tribromide with allenyltributylstannane below –80 °C [28]. Allenyldimethylborane was likewise prepared in 84% yield from dimethylboron bromide. In neither case was the propargylborane observed. Both allenylboranes react with acetone to yield 2-methyl-4-pentyn-2-ol after hydrolysis (Eq. 9.25).



(9.25)

9.6 Allenyltitanium Reagents

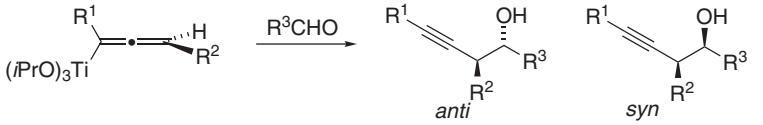
One of the earliest syntheses of allenic and propargylic titanium reagents employed a two-step procedure in which an alkyne was subjected to propargylic deprotonation with *t*BuLi and the lithiated intermediate was allowed to react with titanium tetraisopropoxide (Table 9.17) [29]. The infrared spectrum indicated a propargylic structure for those titanium intermediates derived from methyl-substituted alkynes and an allenic structure for higher homologues. Terminal alkynes would expectedly undergo preferential deprotonation of the alkynyl hydrogen and were therefore not examined. Alkynes with two non-equivalent propargylic substituents have the potential to form mixtures of allenic and propargylic titanium intermediates. Reactions of these reagents with aldehydes proved highly regioselective for S_E2' addition products.



R^1	R^2	R^3	**A**:**B**	Yield, %
Me_3Si	H	C_6H_{11}	99:1	93
Me_3Si	CH_3	C_6H_{11}	1:99	69
CH_3	H	C_6H_{11}	99:1	90
CH_3CH_2	CH_3	C_6H_{11}	1:99	42
C_6H_5	CH_3	C_6H_{11}	6:94	89
Me_3Si	H	C_6H_5	99:1	87

Table 9.17 Addition of propargylic and allenic titanium reagents to aldehydes.

Propargylic ethers undergo directed lithiation and subsequent transmetallation to afford oxygenated allenyl titanium reagents. Subsequent addition of aldehydes gives rise to various homopropargylic alcohol adducts as mixtures favoring the *anti* diastereomers (Tables 9.18 and 9.19) [29, 30]



R^1	R^2	R^3	*anti*:*syn*	Yield, %
Me_3Si	CH_3	C_6H_{11}	89:11	69
Me_3Si	OTHP	C_6H_{11}	90:10	67
Me_3Si	OTHP	C_5H_{11}	88:12	65
CH_3	OTHP	C_6H_{11}	94:6	81
CH_3	OTHP	C_5H_{11}	95:5	76

Table 9.18 Stereoselective addition of allenic titanium reagents to aldehydes.

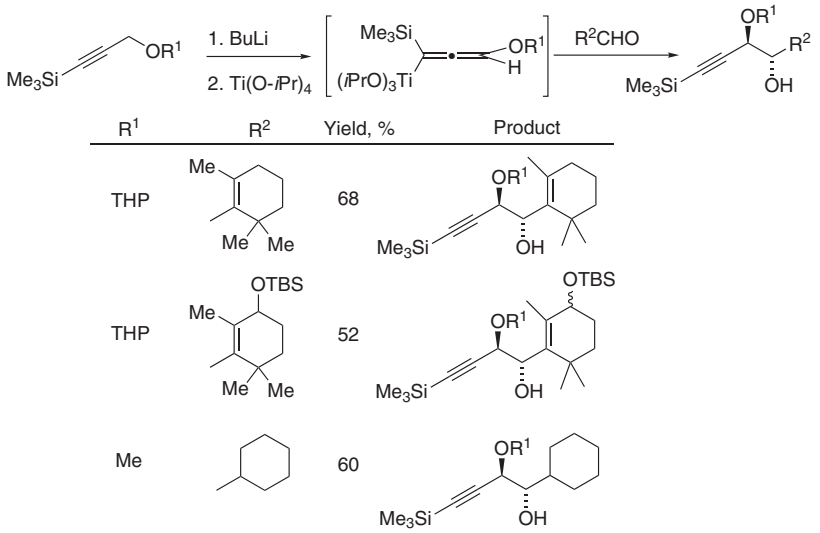
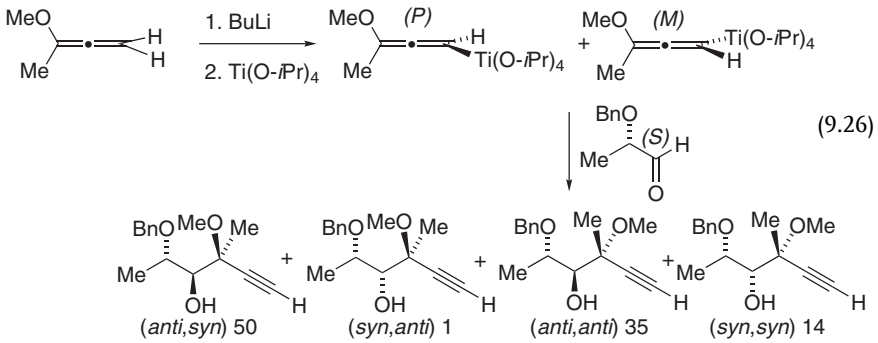


Table 9.19 Oxygenated allenyltitatium additions to aldehydes.

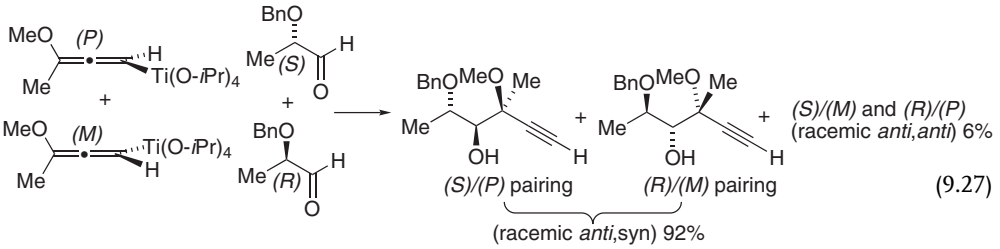
Deprotonation of 3-methoxy-3-methylallene with BuLi followed by metal exchange with $Ti(OiPr)_4$ affords a chiral allenyltitanium reagent [31]. Addition of this reagent to enantioenriched (*S*)-2-benzyloxypropanal afforded a mixture of four diastereomeric products in which the *anti,syn* and *anti,anti* adducts predominated (Eq. 9.26) [31]. The former was shown to derive from the matched pairing of the (*S*)-aldehyde with the (*P*)-enantiomer of the allenic titanium reagent. The latter is the major diastereomer of the mismatched (*S*)/(*M*) pairing.



(9.26)

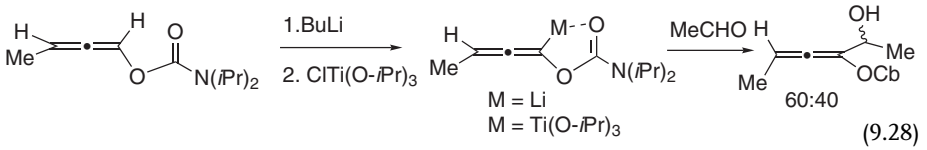
Addition of the racemic allenyltitanium reagent to racemic 2-benzyloxypropanal, on the other hand, afforded a 92:6 mixture of racemic *anti,syn* and *anti,anti* adducts as a result of preferred (*S*)/(*P*) and (*R*)/(*M*) pairing (Eq. 9.27) In both cases, *anti* adducts are favored. These two experiments show that the allenyltitanium reagent does not racemize under the reaction conditions. If racemization had taken place,

the non-racemic *anti,syn* adduct would have been formed from the (*S*)-aldehyde in >50% yield (kinetic resolution).



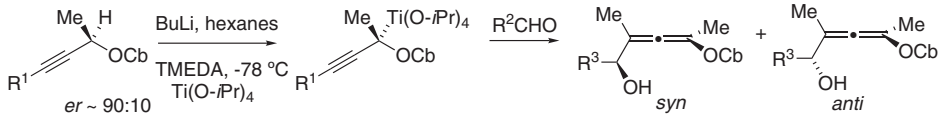
(9.27)

Carbamate substituents have also been found to permit the direct removal of allylic, propargylic and allenic protons by organolithium reagents [32, 33]. In the latter case, the resulting lithioallenes can be converted to the allenyltitanium reagents with $ClTi(OiPr)_3$ (Eq. 9.28) [8]. As illustrated, subsequent addition to acetaldehyde proceeds with only modest diastereoselectivity.



(9.28)

A measure of enantiomeric stability was provided by experiments in which various non-racemic propargylic carbamates were deprotonated by BuLi and the lithiated propargylic intermediates were treated with $Ti(OiPr)_4$ followed by addition of an aldehyde (Table 9.20) [34]. The *er* of the adducts was determined and compared with that of the starting propargylic carbamate, a 90:10 mixture of *R* and *S* enantiomers. In all cases, adducts of enantiopurity comparable to that of the propargylic precursor of the allenyltitanium reagent were obtained, indicating that both these reagents and the lithioallene precursors are not appreciably racemized under the conditions of the experiment.

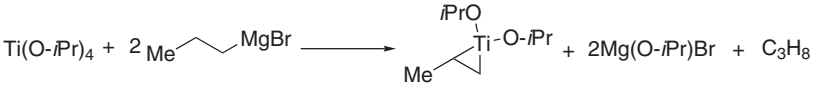


R^1	R^2	*syn*, %	*anti*, %	*er*
C_6H_{11}	*t*Bu	29	30	80:20
*t*Bu	Me	13	58	90:10
*t*Bu	*i*Pr	15	55	90:10
*t*Bu	*t*Bu	31	38	86:14
*t*BuPh$_2$Si	*t*Bu	29	21	0
*t*BuPh$_2$Si	*t*Bu	13	10	90:10[a)]

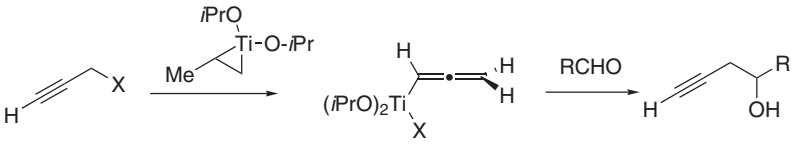
[a)] Aldehyde added first

Table 9.20 Additions of chiral carbamoy propargylic titanium reagents to aldehydes.

In a more direct approach to allenyltitanium reagents, titanium tetraisopropoxide is converted into a propene complex by reaction with propylmagnesium bromide (Eq. 9.29) [35]. This complex undergoes ligand exchange and in situ elimination (a net oxidative addition) on reaction with various propargylic halides and esters (Tables 9.21–9.23) [36]. Either allenic or propargylic titanium intermediates are formed, depending on the substituents present in the propargylic starting material. Terminal alkynyl compounds favor allenic reagents, which react with aldehydes to afford unbranched homopropargylic alcohols (Table 9.21) [37]. A substituent on the alkynyl terminus tends to favor the propargylic titanium reagent (Table 9.22). Subsequent addition to an aldehyde yields the allenylcarbinol adduct. If both the alkynyl terminus and the propargylic position are substituted, the allenic titanium reagent is produced. As before, addition to an aldehyde yields the homopropargylic alcohol adduct (Table 9.23) [37]. In these additions, mixtures of diastereomeric adducts are produced favoring the *anti* isomers.

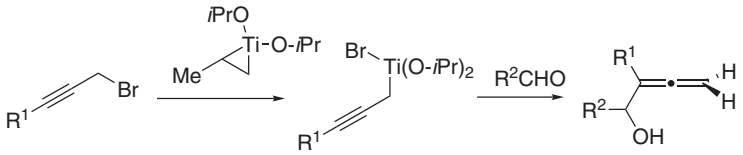


(9.29)



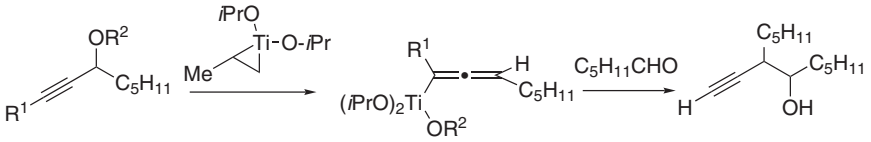
X	R	Yield, %
Br	Ph	85
Cl	Ph	82
OCO_2Et	Ph	74
Br	C_8H_{17}	91
Br	PhCH=CH	74

Table 9.21 Effect of propargylic leaving group on the efficiency of allenyltitanium additions to aldehydes.



R^1	R^2	Yield, %
Me	Ph	89
Me_3Si	Ph	83
Me_3Si	*p*$MeOC_6H_4$	79
Ph	Ph	86

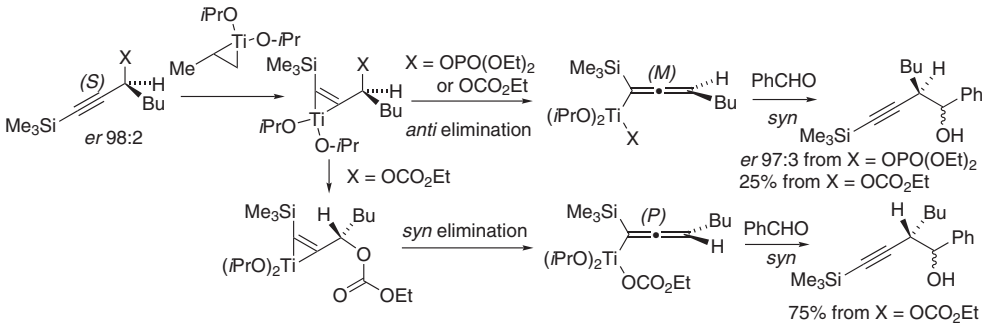
Table 9.22 Effect of alkynyl substituent of the efficiency of propargyltitanium additions to aldehydes.



R^1	R^2	Yield, %	*anti:syn*
Me_3Si	CO_2Et	70	80:20
Me_3Si	Ac	77	80:20
H	CO_2Et	89	75:25
C_6H_{13}	CO_2Et	89	75:25

Table 9.23 Effect of substituents on additions of allenyltitanium reagents to hexanal.

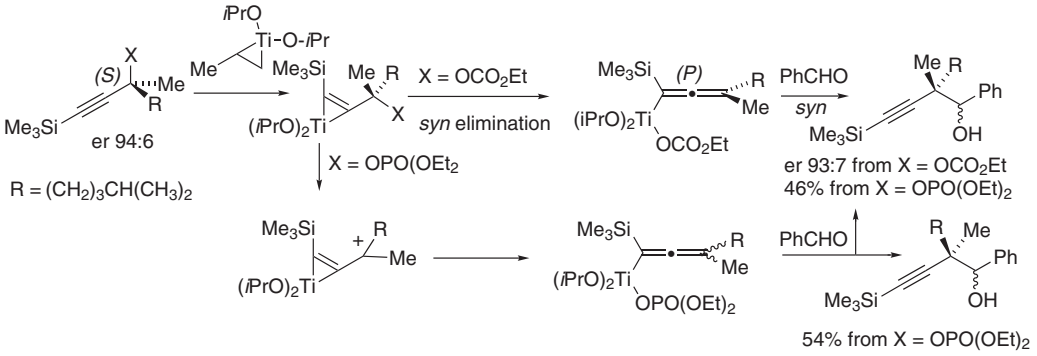
A measure of enantioselectivity for these reactions was obtained from experiments involving enantioenriched propargylic phosphates and carbonates (Eqs. 9.5 and 9.6) [38]. Generation of the allenic titantium reagent in the presence of benzaldehyde led to the expected homopropargylic alcohols as mixtures of diastereoisomers. However, the enantiomeric ratios and reaction pathways varied with the nature and substitution of the propargylic leaving groups. The secondary phosphate (Eq. 9.30) yielded the allenic titanium intermediate by an *anti* elimination pathway. Subsequent addition to benzaldehyde afforded a mixture of diastereomers with the *R* configuration at the propargylic center. The secondary carbonate was converted to a 75:25 mixture of the (*S*)- and (*R*)-propargylic adducts (Eq. 9.30). It is postulated that the carbonate, possibly because of its poorer leaving group ability or enhanced basicity relative to phosphate, is converted to a mixture of enantiomeric allenyltitanium intermediates by both *anti* and *syn* elimination pathways. As a result, the alcohol adducts are partially racemized at the propargylic position.



(9.30)

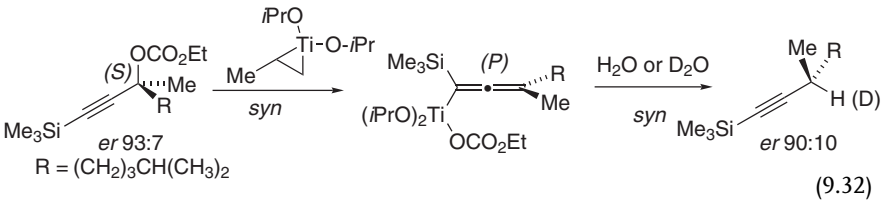
The preference for a *syn* elimination pathway is higher for tertiary versus secondary carbonates, as illustrated in Eq. 9.31. The two-step sequence of allenyltitanium formation followed by addition to benzaldehyde affords the homopropargylic alcohol adduct with essentially complete retention of configuration. In contrast, the phosphate derivative yields a benzaldehyde adduct in which the propargylic center is

nearly completely racemized. This outcome is thought to result from a stepwise elimination pathway for the reaction leading to the allenyltitanium intermediate (Eq. 9.31).

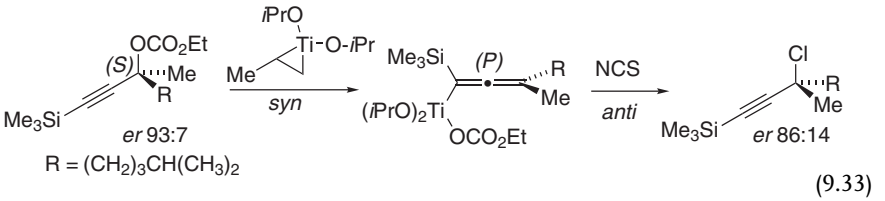


(9.31)

These trends were further confirmed through reactions of the foregoing chiral carbonate and phosphate derivatives with other electrophiles (Eqs. 9.32–9.34) [39]. For example, on protonolysis or deuterolysis, the allenyltitanium intermediate derived from the tertiary carbonate of Eq. 9.32 afforded an alkyne of 90% enantiopurity. Based on the configuration of this product and the assumption of a *syn* elimination to form the allenyltitanium, the protonolysis was suggested to take place by a *syn* S_E2' pathway. In contrast, chlorination of this allenyltitanium intermediate follows an *anti* pathway (Eq. 9.33).

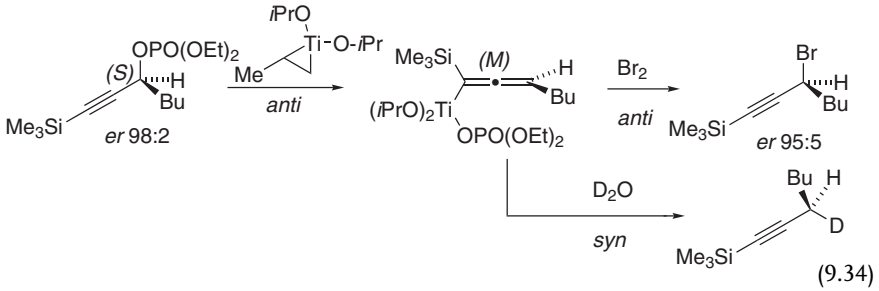


(9.32)



(9.33)

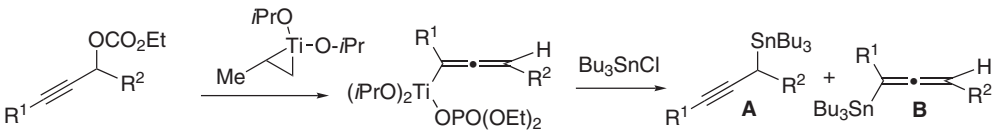
Halogenantion of the allenyltitanium intermediate derived from the chiral secondary phosphate likewise follows an *anti* course (Eq. 9.34). As the initial phosphate elimination also occurs by an *anti* process, the propargylic product must have the same configuration as the phosphate precursor. In contrast, deuterolysis of the fore-



(9.34)

going titanium intermediate takes place by a *syn* pathway. Both reactions are highly enantioselective.

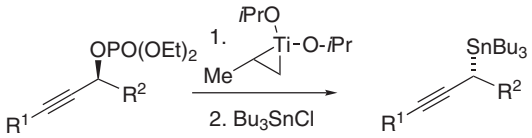
Stannylation of various allenyltitanium intermediates can be effected with Bu_3SnCl. The reaction favors the propargyl stannane regioisomers, unless the alkynyl group is unsubstituted (Table 9.24) [12].



R^1	R^2	Yield, %	**A:B**
C_5H_{11}	H	66	96:4
H	Bu	71	2:98
Bu	Bu	80	98:2
Bu	Ph	57	63:37
Ph	Bu	85	53:47
Me	C_5H_{11}	72	97:3
C_7H_{15}	Me	77	98:2

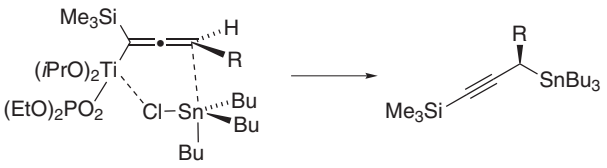
Table 9.24 Stannylation of allenyltitanium intermediates.

The steric course of this two-step process was examined with several chiral secondary propargylic phosphates (Eq. 9.35) [40]. The derived propargylic stannanes were found to be formed with net inversion of configuration. Based on previous evidence that the initial formation of the allenyltitanium intermediate occurs with inversion, it can be deduced that stannylation proceeds by a *syn* pathway. This surprising result was attributed to coordination between the chlorine substituent of the Bu_3SnCl and the electropositive titanium center (Scheme 9.11).

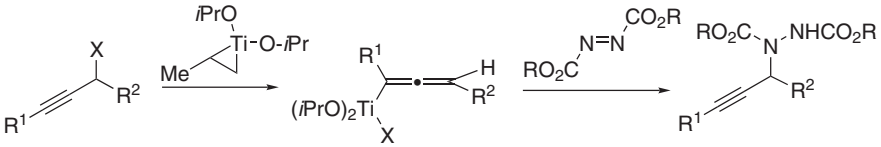


(9.35)

R^1 = Me, R^2 = Bu (78%) > 90% enantioselective
R^1 = Bu, R^2 = Me (79%)
R^1 = Me_3Si, R^2 = Bu (80%)



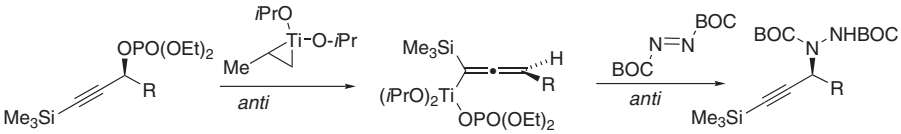
Scheme 9.11 Proposed transition state for the *syn* stannylation of an allenyltitanium reagent.



X	R^1	R^2	R^3	Yield, %
OCO_2Et	Me_3Si	H	*t*Bu	49
OCO_2Et	C_5H_{11}	H	*t*Bu	51
$OPO(OEt)_2$	Me_3Si	*i*Bu	*t*Bu	75
$OPO(OEt)_2$	Me_3Si	*i*Bu	Et	52
$OPO(OEt)_2$	Me	*i*Bu	*t*Bu	62

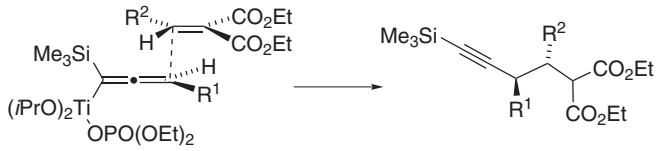
Table 9.25 Reaction of allenyltitanium reagents with diazodicarboxylates.

Allenyltitanium intermediates have also been found to react with diazo dicarboxylates to afford propargylic hydrazides (Table 9.25) [41]. The reaction proceeds with overall retention of configuration. The enantioselectivity of the process decreases with increasing steric demands of the propargylic substituent of the phosphate precursor (Eq. 9.36).

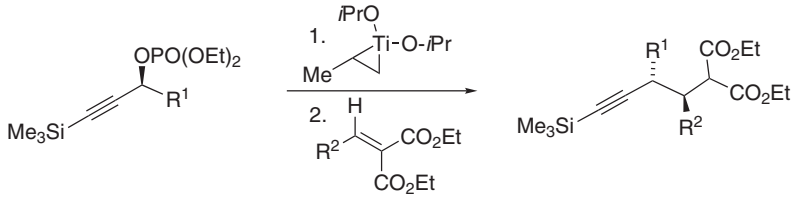


R = Me, 81% (13% racemization)
R = Bu, 73% (53% racemization)
R = *i*Bu, 74% (72% racemization) (9.36)

Chiral allenyltitanium reagents, prepared from propargylic phosphates as outlined, react with alkylidene malonates to afford 1,4-adducts with excellent *anti* diastereoselectivity (Table 9.26) [42]. The addition is presumed to take place through an open antiperiplanar transition state (Scheme 9.12).



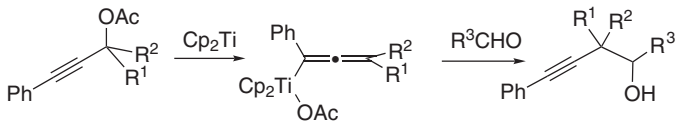
Scheme 9.12 Proposed transition state for 1,4-additions of allenyltitanium reagents to alkylidene malonates.



R^1	R^2	Yield, %	*anti:syn*
Me	Me	92	97:3
Me	Bu	89	98:2
Me	Ph	96	>99:1
Bu	Me	85	97:3

Table 9.26 1,4-Additions of allenyltitanium reagents to conjugated esters.

An alternative, but related, route to allenic titanium reagents from propargylic esters has been reported recently. Reaction of titanocene dichloride with BuMgCl *and* Mg yields a reactive titanocene intermediate, formulated as Cp_2Ti. This reduced Ti species reacts in situ by oxidative addition to propargylic acetates. The allenyltitanium reagents thus produced add to aldehydes and ketones, as expected, to afford homopropargylic alcohols (Table 9.27) [43].

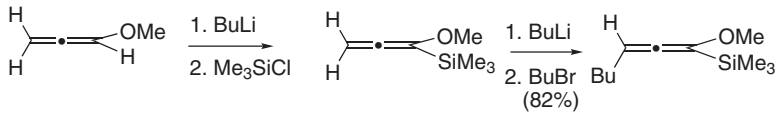


R^1	R^2	R^3	Yield, %
Me	Me	Ph	72
$(CH_2)_4$		Ph	72
$(CH_2)_4$		Pr	52
Me	H	Ph	65
Me	H	C_6H_{11}	56
C_6H_{13}	H	Ph	69

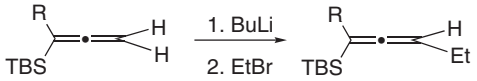
Table 9.27 Additions of Cp_2 allenyltitanium reagents to aldehydes and ketones.

9.7
Allenylsilanes

The preparation of allenylsilanes by silylation of allenic and propargylic lithium reagents has been noted previously in connection with structural and reactivity studies on these intermediates (Eqs. 9.7 and 9.8). Some additional examples are depicted in Eqs. 9.37 and 9.38 [44, 45].



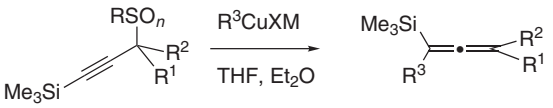
(9.37)



(9.38)

R = Me (84%)
R = C_6H_{11} (84%)

A more general route involves the S_N2' displacement of trimethylsilyl-substituted propargylic derivatives with organocopper reagents (Table 9.28) [46]. Reactions with propargylic sulfinates or sulfonates yield allenylsilane products. Minor amounts of propargylic silanes are obtained with *t*-butyl cuprates, but otherwise the reactions are highly regioselective.

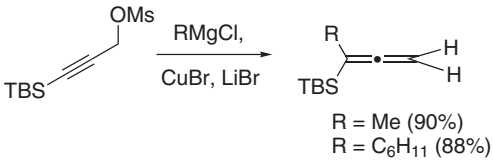


R	*n*	R^1	R^2	R^3	Yield, %	R	*n*	R^1	R^2	R^3	Yield, %
Me	2	H	H	Et	90	Me	2	Me	Me	Et	96
Me	2	H	H	*i*Pr	95	Me	2	Me	Me	*i*Pr	97
Me	2	H	H	*t*Bu	[a]	Me	2	Me	Me	*t*Bu	95
pMeC_6H_4	3	H	H	*t*Bu	[b]	Me	2	$(CH_2)_4$		Me	90
Me	2	*t*Bu	H	Bu	91	Me	3	$(CH_2)_5$		Me	98
Me	3	*t*Bu	H	*s*Bu	90						

[a] A 70:30 mixture of alkyne and allene
[b] An 85:15 mixture of allene and alkyne

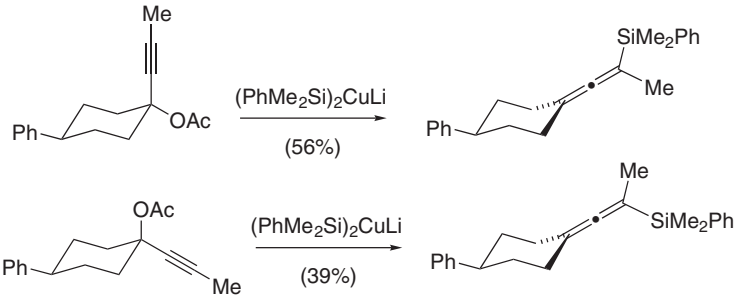
Table 9.28 Synthesis of propargylic silanes by S_N2' displacement of propargylic sulfinates.

The route has also been applied to TBS-substituted propargylic mesylates (Eq. 9.39) [45]. Interestingly, the isomeric propargylic silanes are not formed despite the more attractive steric environment for a direct S_N2 displacement at the primary center.

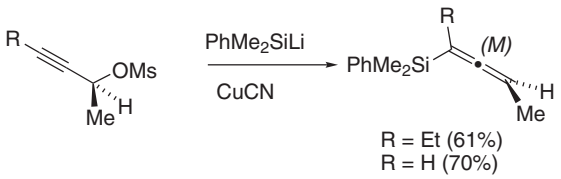


(9.39)

An alternative S_N2' strategy utilizes a silylcuprate reagent. The highest yields are obtained with reagents derived from $PhMe_2SiLi$ [47]. Cuprate derivatives of trialkylsilanes are more basic and give rise to unproductive side reactions. Reactions of cuprates with certain propargylic acetates and chiral propargylic mesylates have been shown to proceed by an *anti* pathway (Eqs. 9.40 and 9.41) [47, 48].

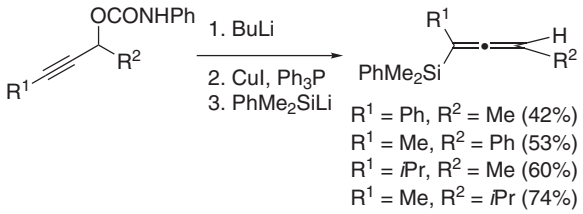


(9.40)



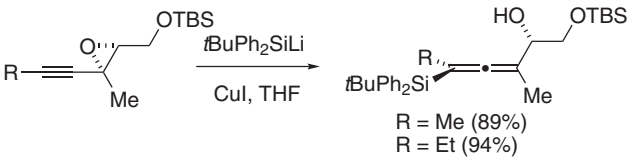
(9.41)

Carbamates also serve as satisfactory starting materials for this methodology (Eq. 9.42) [49]. In this variation, lithiation of the carbamic amide precedes displacement by the cuprate reagent.



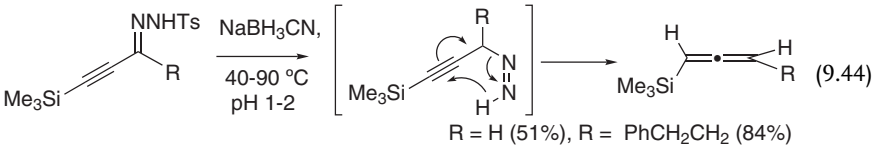
(9.42)

A cuprate prepared in situ from tBuPh$_2$SiLi and CuI has been found to react with alkynyl epoxides to afford allenylsilanes (Eq. 9.43) [50]. Enantioenriched alkynyl epoxides, which are readily prepared in high yield through Sharpless asymmetric epoxidation [51], afford chiral allenylsilanes with *anti* stereoselectivity.



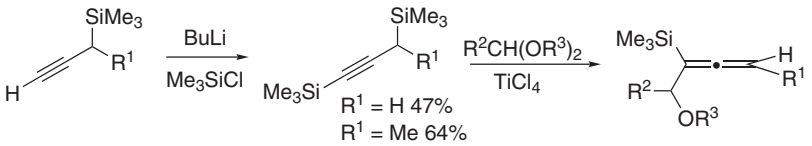
(9.43)

A little-explored route to allenylsilanes utilizes tosylhydrazone derivatives of trimethylsilyl alkynyl ketones [52]. Treatment with $NaBH_3CN$ in acidic medium leads to transient propargylic diazines, which rearrange with loss of nitrogen (Eq. 9.44).



(9.44)

A number of additional methods involve the addition of alkynylsilanes to electrophiles with concomitant 1,3-isomerization to afford allenylsilanes geminally substituted with the electrophile moiety. The first of these methods employed a trimethylsilyl-substituted propargylic silane as the alkynylsilane and various acetals as the electrophile precursors (Table 9.29) [53]. The allenylsilanes are formed without contamination by alkynyl isomers.

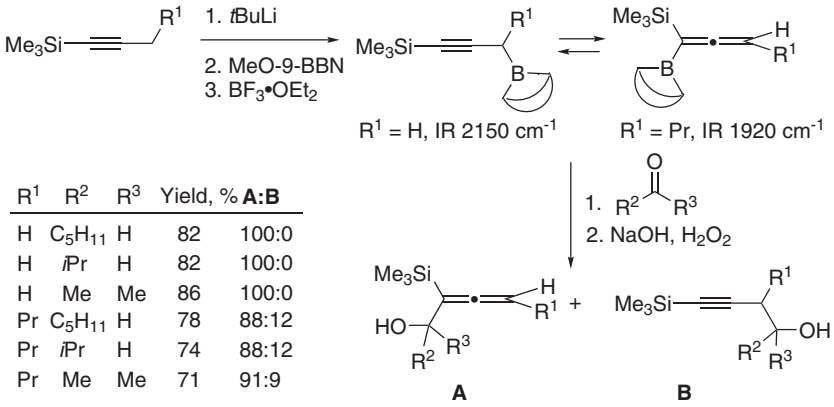


R^1	R^2	R^3	Yield, %
H	*i*Bu	Et	31
H	Ph	Me	56
Me	*i*Bu	Et	79
Me	Ph	Me	68
Me	H	Bu	43
Me	CH_2=CCH_2	Et	81

Table 9.29 Synthesis of allenylsilanes from propargylic 1,3-*bis*-silanes.

A related method utilizes trimethylsilyl-substituted propargylic boranes [54]. These react with aldehydes through a presumed cyclic transition state to yield the allenylsilanes (Table 9.30). The unsubstituted propargylborane reagent leads exclusively to the allenic product whereas the more substituted secondary analogues afford mixtures of allenic and propargylic isomers. The additions are most selective when conducted at –78 °C and become less so at higher temperatures. The infrared spectrum of the intermediate borane precursor of the allenic silane **A** shows a diagnostic adsorption band at 2150 cm^{-1} indicative of an alkynyl moiety. In the spectrum

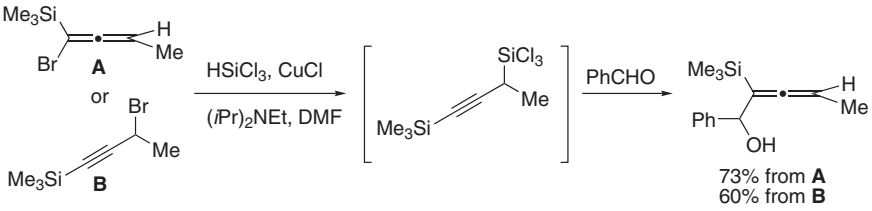
of the more substituted borane, this adsorption is joined by one at 1920 cm^{-1} indicative of the allenylborane isomer. It is suggested that the propargylic borane is the more stable but less reactive isomer. At low temperature, equilibration of the isomeric boranes is fast relative to addition, thus accounting for the predominance of allenic silanes from both allenic and alkynyl boranes.



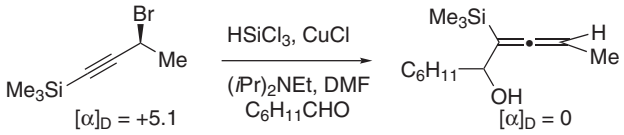
R^1	R^2	R^3	Yield, %	**A:B**
H	C_5H_{11}	H	82	100:0
H	*i*Pr	H	82	100:0
H	Me	Me	86	100:0
Pr	C_5H_{11}	H	78	88:12
Pr	*i*Pr	H	74	88:12
Pr	Me	Me	71	91:9

Table 9.30 Synthesis of allenylsilanes from propargylic boranes.

It is also possible to employ trimethylsilyl-substituted propargylic trichlorosilanes in electrophilic substitution reactions leading to allenylsilanes (Eq. 9.45) [50]. The trichlorosilanes can be prepared by S_N2' or S_N2 displacement of allenic or propargylic bromides by a trichlorosilyl copper reagent. The overall process, starting from an enantioenriched propargylic bromide of unknown enantiopurity, afforded a racemic allenylsilane (Eq. 9.46)



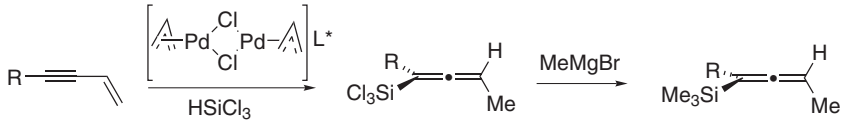
(9.45)



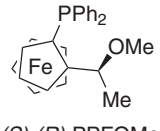
(9.46)

Hydrosilation of conjugated enynes with $HSiCl_3$ in the presence of a chiral palladium catalyst provides a route to enantioenriched allenyltrichlorosilanes [55]. A bulkyl alkynyl substituent such as *t*Bu is most effective in directing facial and regioselectivity (Table 9.31). Two chiral ferrocenyl ligands, (*S*)-(*R*)-PPFOMe and (*S*)-(*R*)-bis-

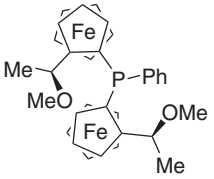
PPFOMe, were developed for this reaction. The chlorosilanes can be purified by distillation. Reaction with MeMgBr converts them to trimethylsilanes.



R	L*	yield,%	er
*t*Bu	*(S)-(R)*-PPFOMe	81	86:14
*t*Bu	*(S)-(R)-bis*-PPFOMe	59	92:8
2,4,6-$Me_3C_6H_2$	*(S)-(R)-bis*-PPFOMe	90	88:12
TBS	*(S)-(R)*-PPFOMe	94	81:19



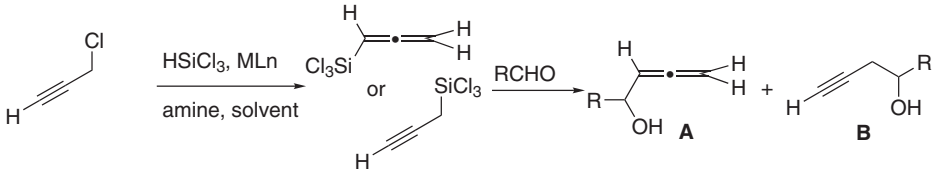
(S)-(R)-PPFOMe



(S)-(R)-bis-PPFOMe

Table 9.31 Asymmetric hydrosilylation of vinylacetylenes.

Allenyltrichlorosilanes can also be prepared by S_N2' displacement of propargylic chlorides with a Cu or Ni complex of $HSiCl_3$ [56]. The reaction requires an amine base and a donor solvent such as THF or propionitrile (Table 9.32). Conditions can be adjusted to favor the propargylic or allenic silane, which is not isolated, but treated directly with various aldehydes to afford allenylcarbinols (**A**) or homopropargylic alcohols (**B**). These reactions presumably proceed by an S_E2' pathway, such that the allenyl products arise from the propargylic silane and vice versa.



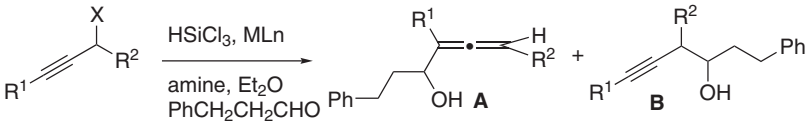
MLn	Amine	Solvent	R	Yield, %	**A**:**B**
CuCl	*i*Pr_2NEt	Et_2O-EtCN	$PhCH_2CH_2$	71	>30:1
CuCl	*i*Pr_2NEt	Et_2O-EtCN	C_8H_{17}	77	>30:1
NiL_2[a)]	*i*Pr_2NEt	THF	$PhCH_2CH_2$	58	<1:30
NiL_2[a)]	b)	THF	$PhCH_2CH_2$	80	<1:30
NiL_2[a)]	b)	THF	Ph	79	<1:30

[a)] L = $MeCOCH_2CO_2Et$

[b)] Amine = 1,2,2,6,6-pentamethylpiperidine

Table 9.32 In situ additions of trichloallenyl/propargylsilane to aldehydes.

The regioselectivity is maintained with mono- and even disubstituted propargylic chlorides (Table 9.33) [56]. The copper complex affords allenylcarbinols (**A**) and the nickel complex favors homopropargylic alcohols (**B**). In the latter case, the *syn* adducts are predominant, suggestive of an acylic transition state.

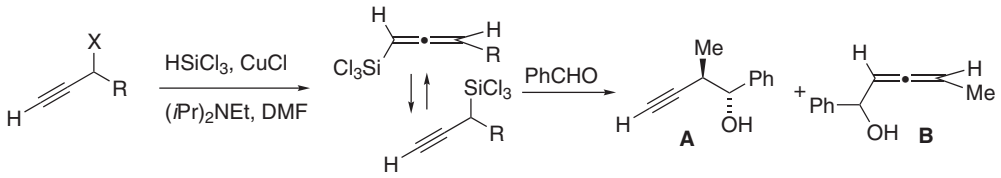


R^1	R^2	MLn	Amine	Yield, %	**A**:**B**
Me	H	CuCl	*i*Pr$_2$NEt	94	>30:1
Me	H	NiL$_2$[a)]	[b)]	11	1:12
Ph	H	CuCl	*i*Pr$_2$NEt	84	>30:1
H	Me	NiL$_2$[c)]	[b)]	84	<1:30[c)]

[a)] L = MeCOCH$_2$CO$_2$Et
[b)] Amine = 1,2,2,6,6-pentamethylpiperidine
[c)] 7:1 *syn:anti*

Table 9.33 In situ additions of trichloallenic and/or propargylic silane to aldehydes.

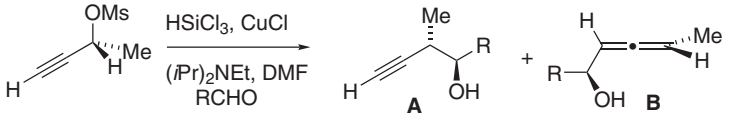
When the propargylic position of the halide is substituted and the alkynyl terminus is not, the homopropargylic adducts are favored (Eq. 9.47) [50]. Bromides and iodides yield *anti* homopropargylic adducts under conditions previously reported to favor *syn* isomers (Table 9.6). The cause of this discrepancy is not known. In the more recent applications of Eq. 9.47, a large R group increases regioselectivity.



X = I, R = C_5H_{11}; 86% yield, **A**:**B** = 96:4, **A** = 85:15 *anti*:*syn*
X = Br, R = Me; 77% yield, **A**:**B** = 86:14, **A** = 80:20 *anti*:*syn*

(9.47)

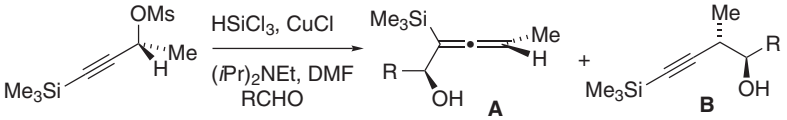
Not surprisingly, the aldehyde substituent also plays a role in determining the regio- and stereoselectivity. Because of the dynamic nature of these additions, which involve equilibrating allenyl and propargylic silanes, regiochemical control is related to aldehyde reactivity whereas diastereoselectivity can be correlated with steric requirements (Table 9.34) [50]. It should be noted that non-racemic propargylic mesylates can also be employed in these reactions. The additions take place with essentially complete chirality transfer. The presumed pathway involves an initial *anti* S_N2' displacement of the mesylate by the cuprate species followed by ensuing aldehyde addition through a cyclic transition state.



R	Yield, %	**A**:**B**	*anti:syn* (**A**)
C_6H_{11}	72	96:4	98:2
C_6H_{13}	79	95:5	89:11
(E)-BuCH=CH	80	99:1	70:30
$DPSOCH_2CH_2$	92	86:14	92:8

Table 9.34 Synthesis and in situ addition of chiral allenic trichlorosilanes to aldehydes.

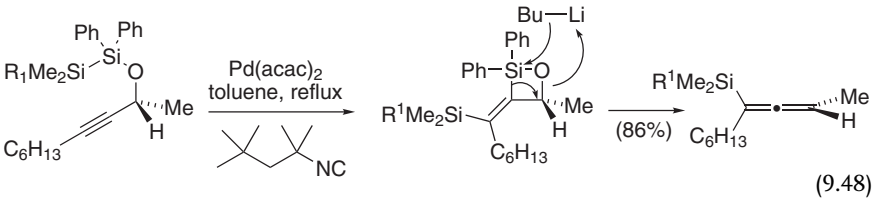
Introduction of a trimethylsilyl group at the terminal alkynyl position of the foregoing chiral mesylates reverses the regiochemistry of the addition reactions (Table 9.35) [50]. In these systems, the allenyl adducts are strongly favored in additions that are highly diastereo- and enantioselective.



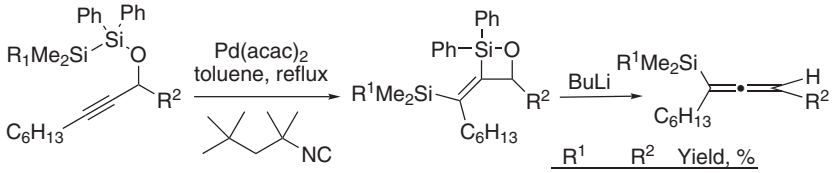
R	Yield, %	**A**:**B**
C_6H_5	92	89:11
C_6H_{11}	55	98:2
C_6H_{13}	67	95:5
$PhCH_2CH_2$	67	98:2

Table 9.35 Synthesis and in situ addition of chiral trimethylsilylpropargylic trichlorosilanes to aldehydes.

A novel intramolecular bis-silylation of propargylic disilanyl ethers followed by a Peterson-type *syn* elimination provides access to a variety of allenylsilanes (Table 9.36) [57]. The elimination is initiated by treatment of the presumed four-membered siloxane intermediate with BuLi. This intermediate could not be isolated, but spectral data were in accord with the assigned structure. The cycloaddition and elimination steps were shown to take place stereospecifically (Eq. 9.48).



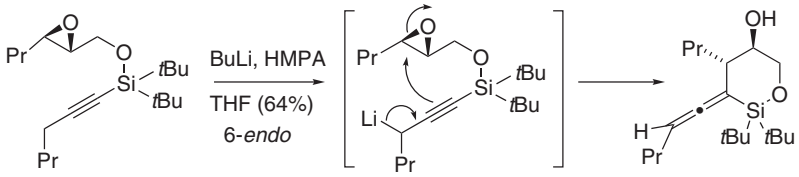
(9.48)

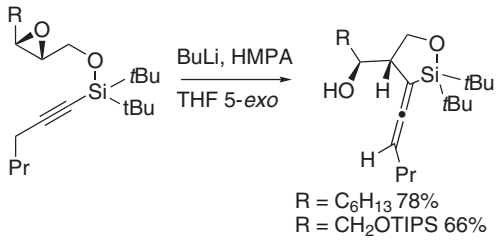


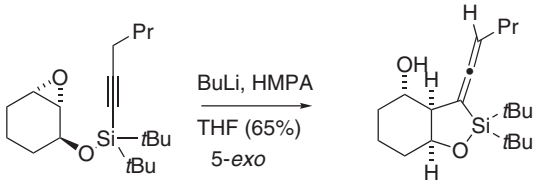
R^1	R^2	Yield, %
Ph	Me	86
*t*Bu	Me	95
Me	Me	79
Ph	C_6H_{11}	81
Me	C_6H_{11}	85
Ph	Ph	94

Table 9.36 Intramolecular *bis*-silylation of propargylic oxydisilanes.

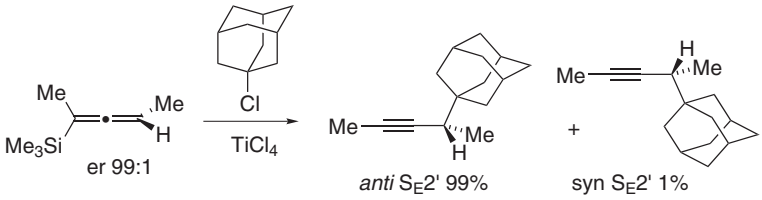
Five- and six-membered cyclic allenylidenesiloxanes have been prepared by internal displacements of siloxane epoxides by lithiated propargylic siloxanes (Eqs. 9.49–9.51) [58]. The mode of attack is related to the stereochemistry of the epoxide. A *trans* epoxide (Eq. 9.49) give rise to a six-membered siloxane by a 6-*endo* pathway, whereas *cis* epoxides (Eqs. 9.50 and 9.51) undergo 5-*exo* cleavage.



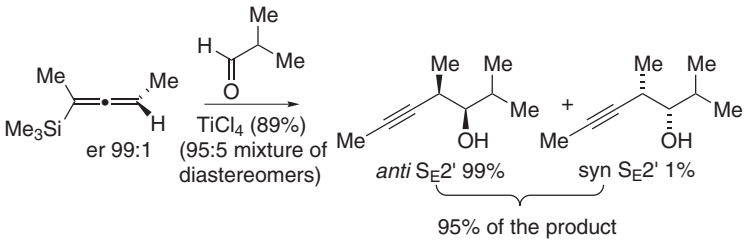




Additions of electrophiles to allenylsilanes have been shown to proceed by an *anti* S_E2' process (Eqs. 9.52 and 9.53) [59]. Reactions of enantiopure allenylsilanes yield propargylic adducts with <1% racemization.

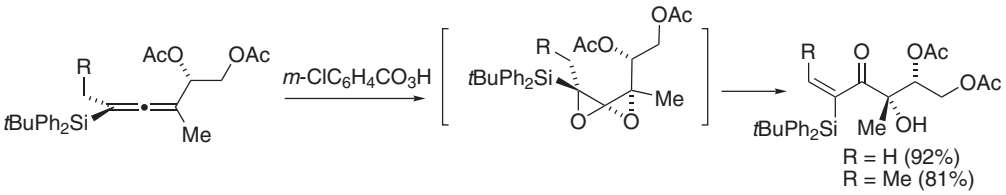


(9.52)



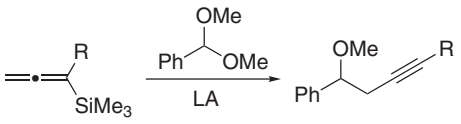
(9.53)

Epoxidations of chiral allenylsilanes are also highly stereoselective, especially if the silyl group is spatially demanding (Eq. 9.54) [60]. A bis-epoxide intermediate is formed which rearranges to an α,β-unsaturated α'-hydroxy ketone. Such products are of interest as branched carbohydrate analogues.



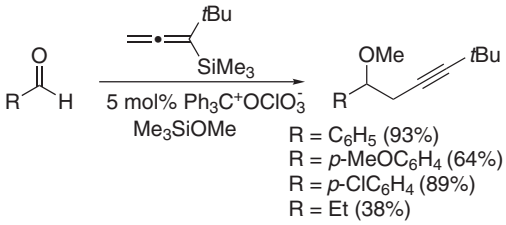
(9.54)

Allenylsilanes react with acetals to afford homopropargylic ethers (Table 9.37) [61]. These reactions are promoted by silyl and carbocation species. A variation of this conversion involves in situ formation of the acetal from an aldehyde and Me_3SiOMe (Eq. 9.55). The success of this method indicates that conversion of the aldehyde to the acetal and its subsequent reaction with the silane must be faster than direct reaction of the aldehyde with the silane.



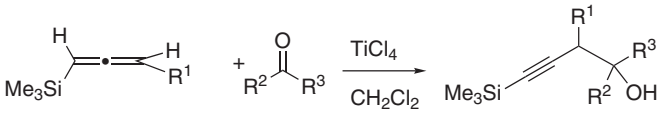
R	LA	Yield, %
*t*Bu	$Ph_3C^+OClO_3^-$	99
*t*Bu	TMSOTf	81
DPS	$Ph_3C^+OClO_3^-$	85
Et	TMSOTf	4

Table 9.37 Addition of benzaldehyde dimethyl acetal to allenylsilanes.



(9.55)

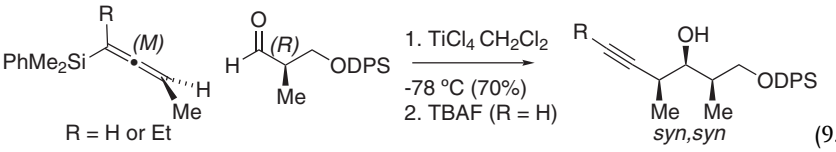
In general, allenic silanes are less reactive than their stannane counterparts. Whereas allenic stannane additions to aldehydes are promoted by the comparatively mild Lewis acid $BF_3 \cdot OEt_2$ or even $MgBr_2$, the corresponding silanes require $TiCl_4$ or $AlCl_3$. Some of the early studies are summarized in Table 9.38 [52].



R^1	R^2	R^3	Yield, %
H	$PhCH_2CH_2$	H	84
H	$(CH_2)_5$		89
H	$PhCH_2CH_2$	Me	72
$PhCH_2CH_2$	Me	Me	38
$PhCH_2CH_2$	$(CH_2)_5$		49

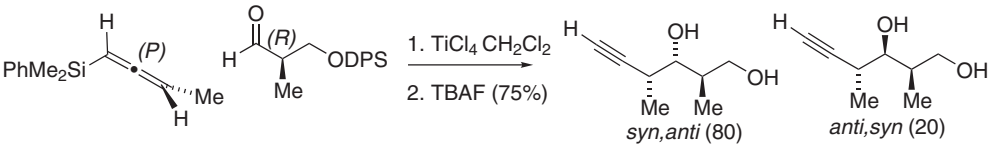
Table 9.38 Additions of allenylsilanes to ketones and aldehydes.

Reactions of chiral silanes with chiral aldehydes exhibit matching and mismatching characteristics (Eqs. 9.56 and 9.57) [48]. The additions proceed through an acyclic transition state, which favors *syn* adducts. The matched (*M*)/(*R*) pairing of Eq. 9.56 proceeds by way of a favorable Felkin–Anh arrangement to afford the *syn,syn* homopropargylic alcohol product. However, if the silanes possess an α-hydrogen, a vinylic chloride intermediate is formed, as shown in Scheme 9.13. Subsequent treat-

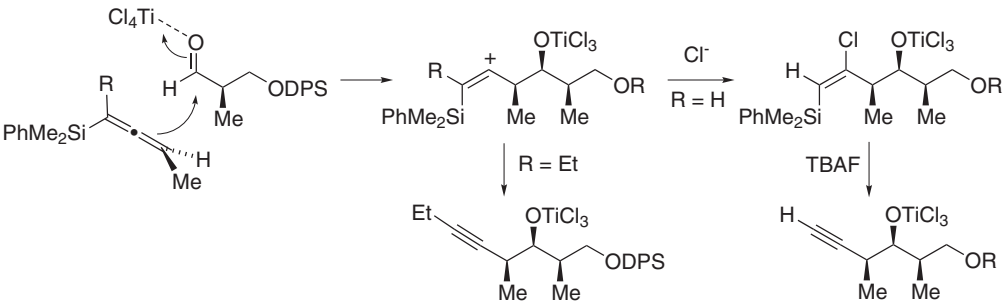


(9.56)

ment with TBAF effects elimination to the homopropargylic alcohol adducts. The (*P*)/(*R*) mismatched combination affords an 80:20 mixture of the *syn,anti* and *anti,-syn* adducts (Eq. 9.57).

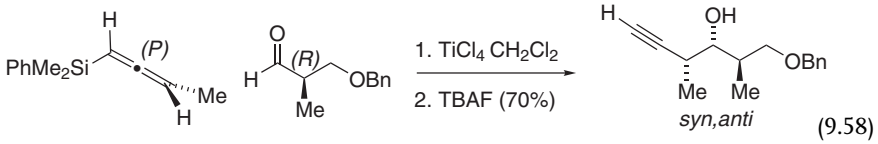


(9.57)

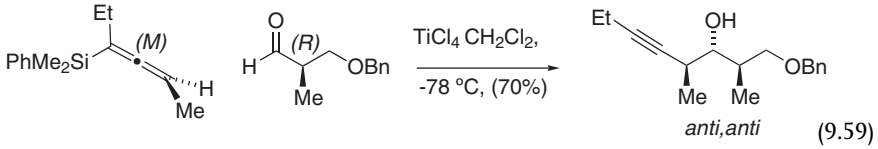


Scheme 9.13 Proposed pathway for additions of chiral allenylsilanes to aldehydes.

Chiral α-methyl aldehydes bearing a β-OBn substituent afford diastereomeric homopropargylic alcohol adducts with negligible mismatching upon reaction with enantiomeric allenylsilanes (Eqs. 9.58 and 9.59). As noted above, a two-step process is required for silanes bearing an α-hydrogen. The (*P*)/(*R*) combination (Eq. 9.58) is able to adopt the Felkin–Anh arrangement through an acyclic transition state to afford the *syn,anti* adduct. In the (*M*)/(*R*) combination, a Felkin–Anh transition state is disfavored for steric reasons. However, chelation of the aldehyde carbonyl and the OBn oxygen with $TiCl_4$ gives rise to a low-energy transition state for the *anti,anti* adduct (Eq. 9.59) [48]. This process does not intervene in the case of the mismatched β-ODPS aldehyde (Eq. 9.57) because of the diminished chelating ability of the ODPS grouping.

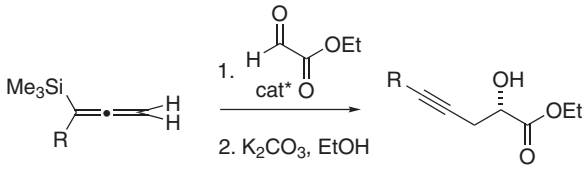


(9.58)



(9.59)

Allenyltrimethylsilanes add to ethyl glyoxalate in the presence of a chiral pybox scandium triflate catalyst to afford highly enantioenriched homopropargylic alcohols or dihydrofurans, depending on the nature of the silyl substituent (Tables 9.39 and 9.40) [62]. The trimethylsilyl-substituted silanes give rise to the alcohol products whereas the bulkier *t*-butyldiphenylsilyl (DPS)-substituted silanes yield only the [3 + 2] cycloadducts. A bidentate complex of the glyoxalate with the scandium metal center in which the aldehyde carbonyl adopts an axial orientation accounts for the observed facial preference of both additions.



R	Yield, %	*er*
Me	95	99:1
Bu	90	97:3
C_6H_{11}	95	95:5
*i*Pr	96	96:4
Ph	63	98:2

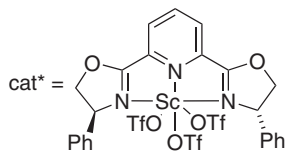
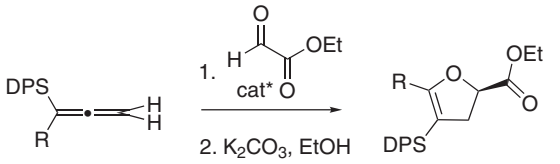


Table 9.39 Chiral scandium triflate-catalyzed additions of trimethylsilyl-substituted-allenes to aldehydes.



R	Yield, %	*er*
Me	91	96:4
Et	81	97:3
Pr	86	96:4
Bu	89	96:4
C_6H_{11}	63	96:4
Ph	32	92:8

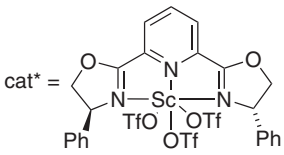
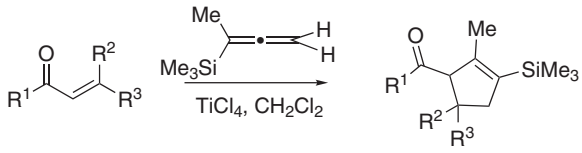


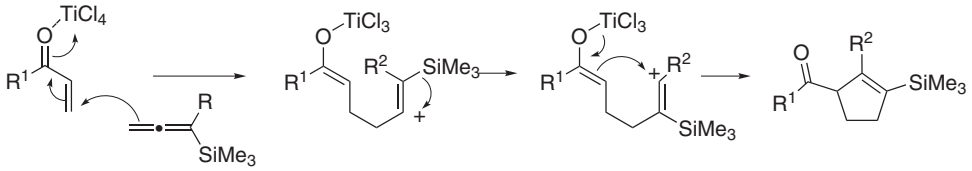
Table 9.40 Chiral scandium triflate-catalyzed [3+2] cycloadditions of DPS-allenes to aldehydes.

Conjugated ketones and esters react with allenylsilanes to yield acylcyclopentenes (Eq. 9.60) [63]. These products are formed by initial 1,4-addition to the conjugated double bond to afford a silyl-stabilized vinyl cation intermediate. 1,2-Silyl migration gives rise to a second silyl-stabilized vinyl cation which cyclizes to the acyl cyclopentene (Scheme 9.14).



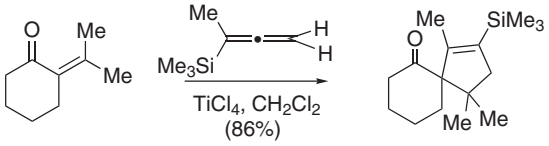
(9.60)

R^1 = Me, R^2 = R^3 = H (75%)
R^1 = R^2 = R^3 = Me (65%)
R^1 = OMe, R^2 = R^3 = H (49%)

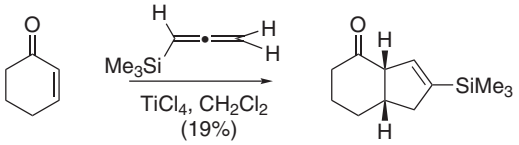


Scheme 9.14 Proposed pathway for the reaction of allenylsilanes with conjugated ketones leading to acylcyclopentenes.

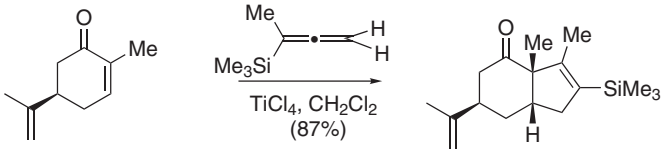
Spirocyclic and fused-ring ketones have been prepared by this method (Eqs. 9.61 and 9.62) [63]. In the latter case, *cis*-fused bicyclic adducts are favored (Eqs. 9.62 and 9.63).



(9.61)

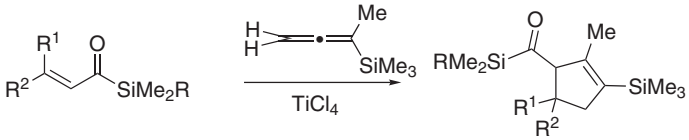


(9.62)



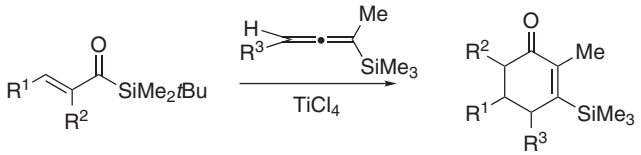
(9.63)

Conjugated silyl ketones are likewise converted to acylcyclopentenes (Eq. 9.64) [64]. In some additions an isomeric cyclohexenone is formed (Eq. 9.65). This latter product is postulated to arise from ring expansion of the initial acylcyclopentene as illustrated in Scheme 9.15.



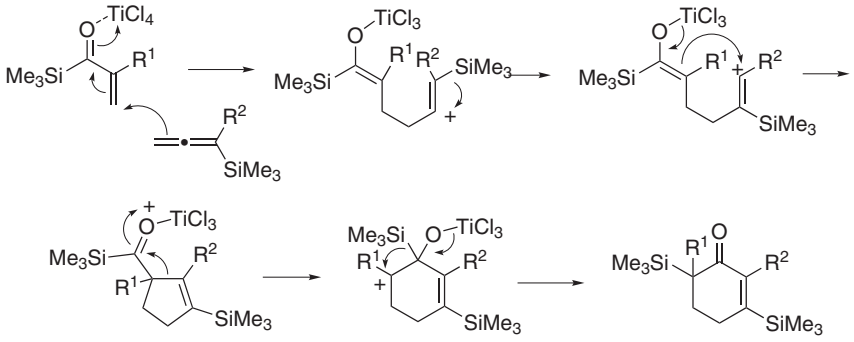
(9.64)

$R^1 = R^2 = H$, R = *t*Bu (72%)
R^1 = H, R^2 = Me, R = *t*Bu (66%)
$R^1 = R^2 = R$ = Me (74%)



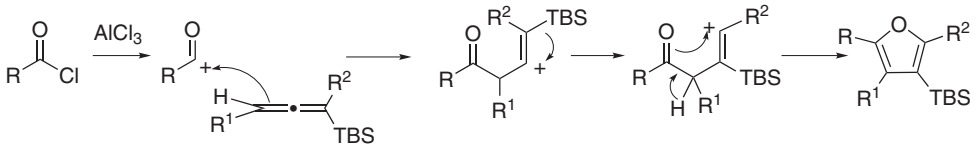
(9.65)

$R^1 = R^3$ = H, R^2 = Me (56%)
R^1 = H, $R^2 = R^3$ = Me (41%; 70:30 *cis:trans*)
$R^1 = R^2$ = Me, R^3 = H (66%; 57:43 *trans:cis*)

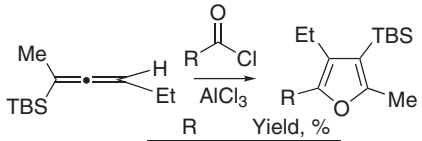


Scheme 9.15 Proposed pathway for the reaction of allenylsilanes with conjugated acylsilanes leading to acylcyclopentenes and cyclohexenones.

The reaction of acylsilanes with acid chlorides in the presence of $AlCl_3$ leads to furans (Table 9.41) [45]. In these reactions an acyl cation initiates the addition with ensuing silyl migration yielding an intermediate vinyl cation. Attack of the carbonyl oxygen followed by proton loss affords the observed products (Scheme 9.16). An analogous reaction with nitrosyl fluoroborate provides a route to oxazoles (Table 9.42) [65]. The nitrosyl cation serves as the electrophile in this application.

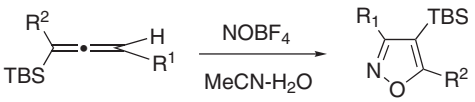


Scheme 9.16 Proposed pathway for the reaction of allenylsilanes with acyl chlorides leading to furans.



R	Yield, %
$PhCH_2$	79
C_6H_{11}	66
Me	68
*t*Bu	35
$Me_2C{=}CH$	58

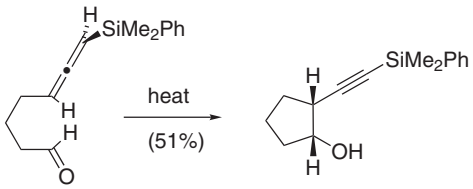
Table 9.41 Synthesis of furans from acyl chlorides and allenylsilanes.



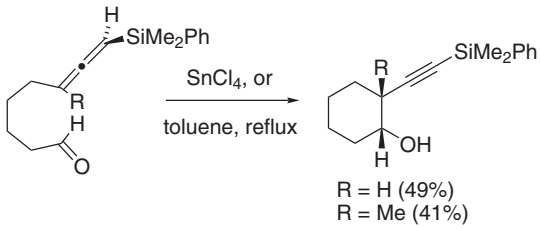
R^1	R^2	Yield, %
H	C_6H_{11}	66
Me	C_6H_{11}	63
Et	Me	59
H	Me	87

Table 9.42 Synthesis of isoxazoles from nitrosyl fluoroborate and allenylsilanes.

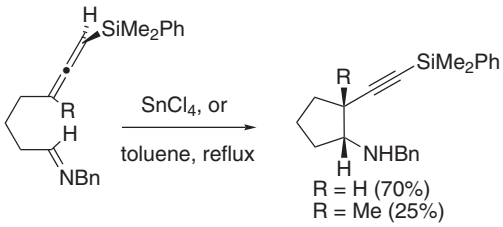
Allenylsilanes undergo intramolecular additions to appropriately positioned aldehydes, imines, conjugated esters and alkenes to afford various alkynylcyclopentane and cyclohexane derivatives (Eqs. 9.66–9.70) [66]. The reactions are promoted by $SnCl_4$ or by thermolysis. The stereochemistry of these cyclization reactions is consistent with a concerted sigmatropic process as illustrated in Scheme 9.17.



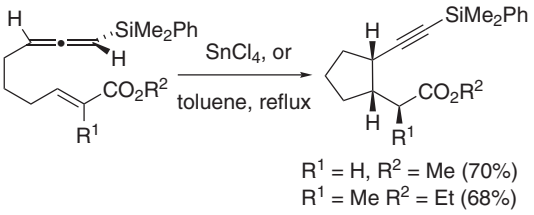
(9.66)



(9.67)

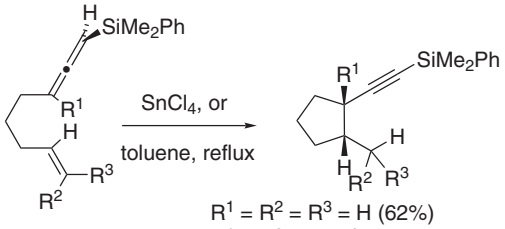


(9.68)



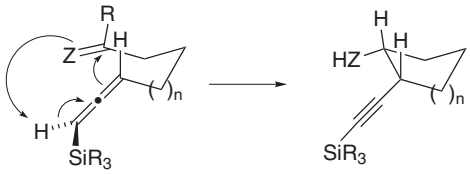
(9.69)

R^1 = H, R^2 = Me (70%)
R^1 = Me R^2 = Et (68%)



(9.70)

$R^1 = R^2 = R^3$ = H (62%)
$R^1 = R^3$ = H, R^2 = H (62%)
R^1 = H, $R^2 = R^3$ = Me (35%)
R^1 = Me, $R^2 = R^3$ = H (75%)



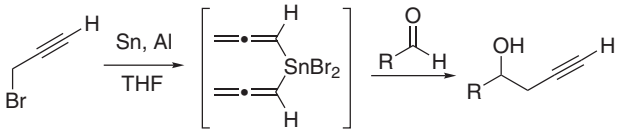
Z = NBn, O, $C(R^1)CO_2R^2$, CR^1R^2
R = H, Me

Scheme 9.17 Proposed ene pathway for intramolecular allenylsilane additions.

9.8
Allenylstannanes

9.8.1
Allenyltin Halide Reagents

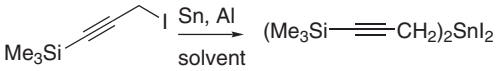
Allenyltin halides are not isolable but can be prepared in situ through reaction of a propargylic halide with a mixture of tin and aluminum metal, usually in powdered form. For example, propargyl bromide is converted to diallenyltin dibromide (Eq. 9.71). This intermediate reacts with aldehydes to produce homopropargylic alcohols in high yield. Allenyl adducts are not formed in this reaction [67].



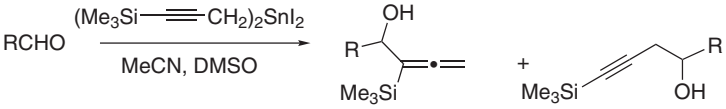
(9.71)

R = Ph (94%), C_6H_{13} (77%), *(E)*-MeCH=CH (72%)

Trimethylsilyl-substituted propargyl iodide undergoes a similar metal–halogen exchange, in the presence of coordinating solvents, to afford an intermediate formulated as bis(trimethylsilyl propargyl)tin diiodide (Eq. 9.72) [67]. Reaction with aldehydes yields mixtures of allenyl and propargyl adducts (Eqs. 9.73 and 9.74). The ratio of the two products is solvent dependent. The allenyl isomer is favored in the dipolar–aprotic solvent pair MeCN–DMSO whereas propargyl adducts dominate in DME ($MeOCH_2CH_2OMe$).

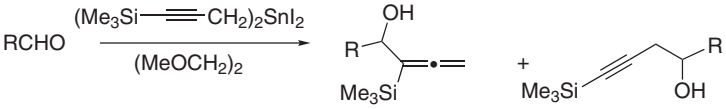


(9.72)



(9.73)

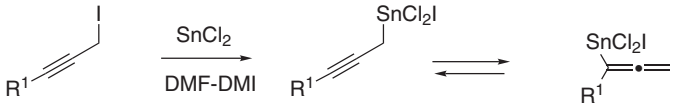
R = C_6H_{13} (89%), 95:5
R = Ph (88%), 90:10
R = *(E)*-MeCH=CH, (60%) 92:8



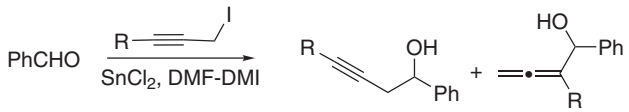
(9.74)

R = C_6H_{13} (75%), 8:92
R = Ph (69%), 11:89
R = *(E)*-MeCH=CH, (64%) 9:91

A related method of preparation involves the oxidative addition of a tin(II) salt to propargylic iodides, which yield mixtures of allenyl- and propargyltin halides on treatment with $SnCl_2$ in DMF–DMI (1,3-dimethylimidazol-2-one) (Eq. 9.75) [68]. These intermediates react in situ with aldehydes to afford mixtures of propargylic and allenic carbinols via a cyclic S_E2' process (Eqs. 9.76 and 9.77). As explained in the Introduction, the ratio of these two products reflects the relative transition-state energies of the addition reactions.

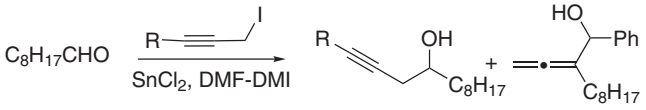


(9.75)



(9.76)

R = H (98%), 52:48
R = Me (79%) 3:97
R = $SiMe_3$ (67%) 40:60

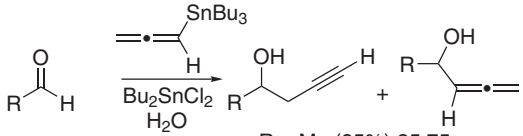


(9.77)

R = H (92%), 30:70
R = Me (79%) 2:98
R = $SiMe_3$ (76%) 0:100

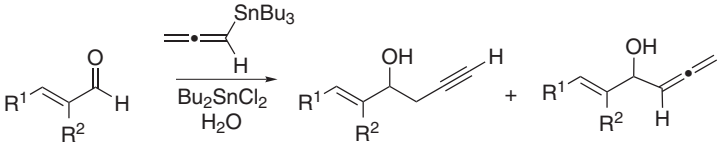
A third route to allenyltin halides involves transmetallation of isolable allenyltributyltin compounds, as exemplified by the reaction of allenyltributyltin with Bu_2SnCl_2 [68]. The resulting mixture of allenyl- and propargyldibutyltin chlorides reacts with various aldehydes to afford mixtures of propargyl- and allenylcarbinols (Eqs. 9.78 and 9.79). The yields of these additions are uniformly high, but the selectivity depends on the nature of the aldehyde substituent. The transmetallation route to allenyltin and -indium halides will be discussed in more detail in a later section.

An alternative transmetallation procedure employs Grignard reagents, such as allenylmagnesium bromide, which reacts with Bu_2SnCl_2 in ether to afford dibutyl-



(9.78)

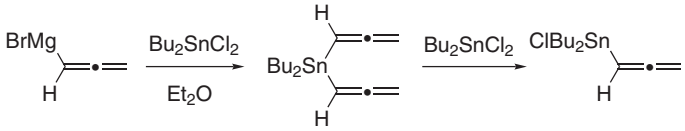
R = Me (95%) 25:75
R = *i*Pr (97%) 25:75
R = *t*Bu (95%) 40:60



(9.79)

$R^1 = R^2 = H$ (98%) 90:10
R^1 = Me, R^2 = H (95%) 95:5
R^1 = H, R^2 = Me (90%) 65:35

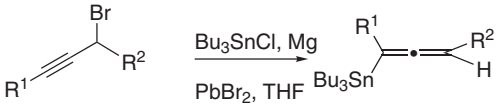
diallenyltin [69]. A second transmetallation with excess Bu_2SnCl_2 leads to dibutylallenyltin chloride (Eq. 9.80).



(9.80)

9.8.2 Trialkylallenyltin Reagents

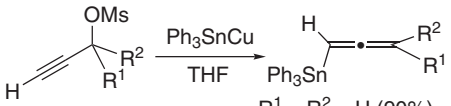
The foregoing allenyl/propargyltin halide reagents are generated in situ where they react with aldehydes. Although the regioselectivity can be high, a means for controlling this aspect of the reaction has not yet been developed. In contrast, trialkylallenyl and -propargyltin reagents are stable, isolable substances. Their reactions with aldehydes have received detailed study and methodology has been developed for addition reactions that proceed with high levels of regio- and stereoselectivity. One of the most direct preparations of these reagents involves stannylation of propargylic halides with Bu_3SnCl in the presence of reducing metals such as Mg or Al. The reaction of propargylic bromides with Mg and Bu_3SnCl is illustrative (Eq. 9.81) [70]. This reaction is accelerated by $PbBr_2$.



R^1 = H, CO_2Me
R^2 = H, Me

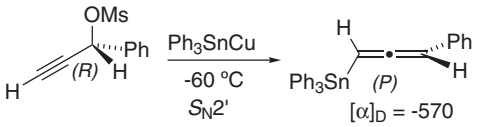
(9.81)

Trialkyl- or triarylallenyltin compounds can also be prepared by S_N2' displacement of propargylic mesylates with various stannylcopper reagents in THF (Eq. 9.82) [71]. This reaction is postulated to proceed by an *anti* S_N2' pathway based on the stereochemical relationship between the enantioenriched mesylate and the allenic product (Eq. 9.83). The allene obtained from the reaction of the mesylate of (*R*)-3-phenyl-1-propyn-3-ol with Ph_3SnCu was assigned the (*P*) configuration from a consideration of the observed optical rotation and an application of Brewster's rules [71].



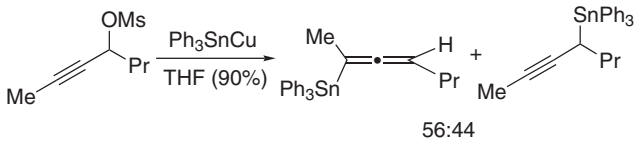
$R^1 = R^2$ = H (90%)
R^1 = H, R^2 = Ph (90%)
R^1 = H, R^2 = *t*Bu (80%)
$R^1 = R^2$ = Me (95%)

(9.82)



(9.83)

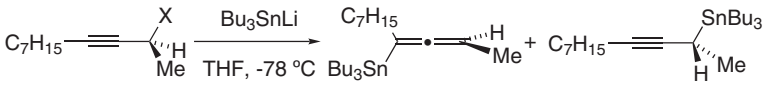
Whereas tin cuprate displacements of terminal propargylic mesylates lead exclusively to allenic stannanes (Eqs. 9.82 and 9.83), the reaction of an internal propargylic mesylate with Ph_3SnCu afforded a mixture of allenic and propargylic isomers (Eq. 9.84) [71].



(9.84)

56:44

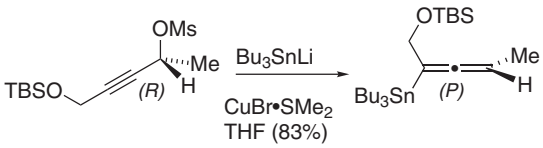
The reaction of Bu_3SnLi with an internal propargylic bromide or mesylate also yielded mixtures of regioisomeric products (Eq. 9.85) [72]. The preference for the allenyl- over the propargylstannane in reactions of terminal alkynyl mesylates may be the result of steric factors, which tend to favor the product with the bulky tin substituent at the less hindered position. Interestingly, the product ratio is affected by the nature of the propargylic leaving group (Eq. 9.85).



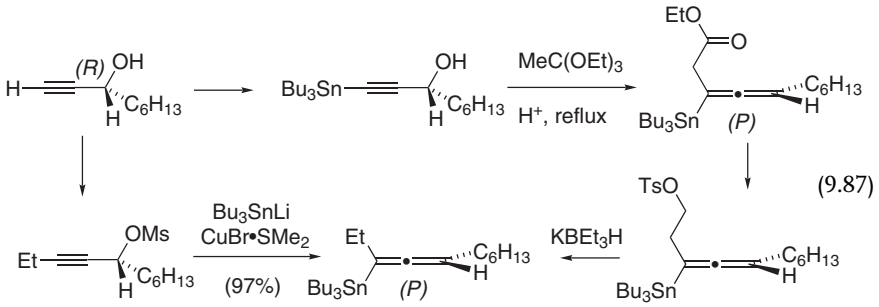
(9.85)

X = Br 50:50
X = OMs 90:10

Later work showed that displacements of internal propargylic mesylates by $Bu_3SnLi \cdot CuBr \cdot SMe_2$ yield only the allenic products (Eq. 9.86) [72]. An independent synthesis of one of the allenyl products (Eq. 9.87) supported the assumption that the S_N2' reaction proceeds by an *anti* pathway. An explanation for the differing regiochemical outcomes of the internal propargylic mesylate displacements has not been advanced. However, propargylic stannanes have been found to isomerize to the allenyl isomers upon passage through silica gel, implying that the latter are the more stable isomers. Hence it could be postulated that the observed regioselectivity of the cuprate reactions is the consequence of partial equilibration, perhaps catalyzed by copper salts. However, this postulate has not been tested.



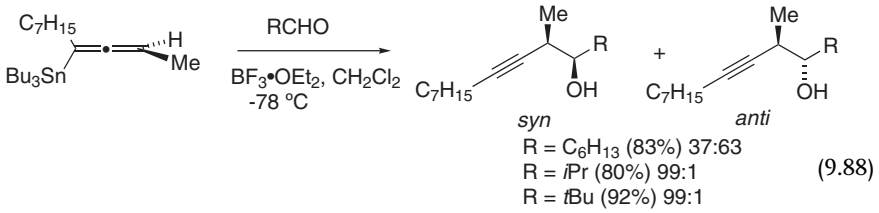
(9.86)



(9.87)

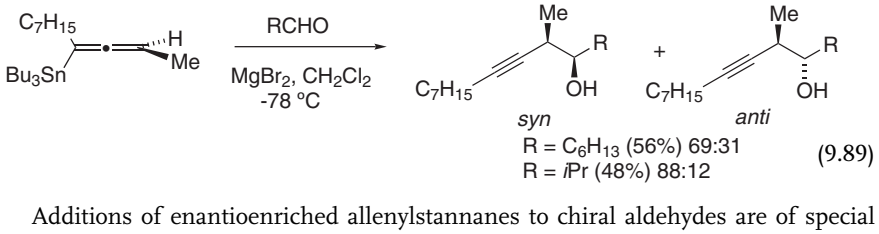
9.8.3
Reactions of Chiral Allenyltin Reagents

Alkyl-substituted allenyltin reagents do not add to typical aldehydes without initiation by a strong Lewis acid. The most effective is $BF_3 \cdot OEt_2$, which is commonly employed in moderate excess (Eq. 9.88). This Lewis acid, unlike $SnCl_4$, $TiCl_4$ and $InCl_3$, serves to activate the carbonyl group toward addition without transmetallation of the allenyltin reagent. $MgBr_2$ has also been used to promote these additions, albeit somewhat less efficiently (Eq. 9.89).



R = C_6H_{13} (83%) 37:63
R = *i*Pr (80%) 99:1
R = *t*Bu (92%) 99:1

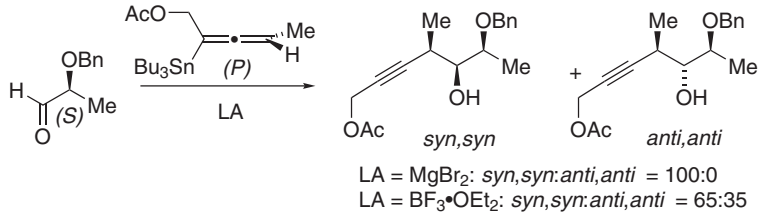
(9.88)



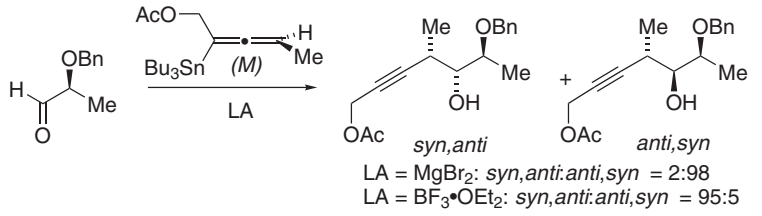
R = C_6H_{13} (56%) 69:31
R = *i*Pr (48%) 88:12

(9.89)

Additions of enantioenriched allenylstannanes to chiral aldehydes are of special interest. The products of these reactions often serve as intermediates for the synthesis of polyketide and related natural products. The factors that control the stereochemistry of such additions can be illustrated with two types of aldehydes in which an oxygenated substituent is either α or β to the carbonyl group. $MgBr_2$-promoted additions are highly diastereoselective for both enantiomeric stannanes whereas $BF_3 \cdot OEt_2$-promoted additions display the more common matching/mismatching characteristics (Eqs. 9.90 and 9.91) [73]. In the former case an acylic transition state involving a chelated aldehyde offers the best explanation for the observed selectivity



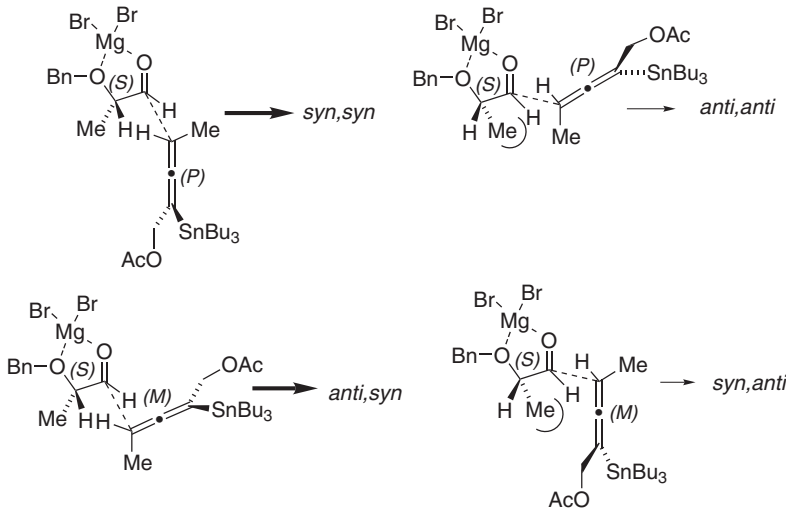
(9.90)



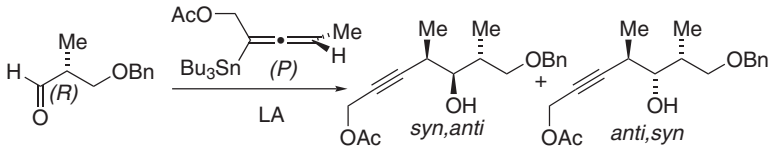
(9.91)

(Scheme 9.18). The $BF_3 \cdot OEt_2$-promoted additions also proceed via acyclic transition states but the diastereoselectivity results from Felkin–Anh control.

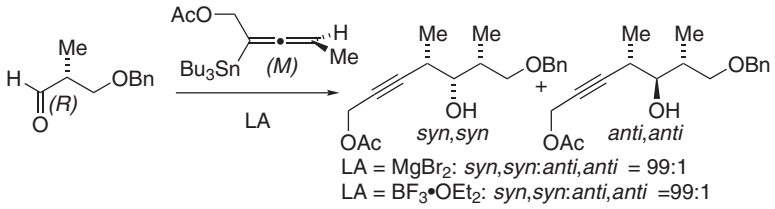
β-Oxygenated aldehydes also show excellent diastereoselectivity in $MgBr_2$-promoted additions (Eqs. 9.92 and 9.93) [74]. In these reactions, internal coordination of the aldehyde would involve six-membered Mg complexes, which are less favorable than the five-membered chelates pictured in Scheme 9.18. Nonetheless, the reaction between the (*P*)-allenyltin reagent and the (*R*)-aldehyde proceeds via the chelated aldehyde to afford the *syn,anti* product. The corresponding BF_3-promoted reaction must involve an acyclic non-chelated Felkin–Anh transition state, which in this pairing is mismatched, resulting in the formation of an 83:17 mixture of the *syn,anti*



Scheme 9.18 Transition states for $MgBr_2$-promoted additions of a (*P*) and (*M*)-allenylstanane to (*S*)-*O*-benzyllactic aldehyde.

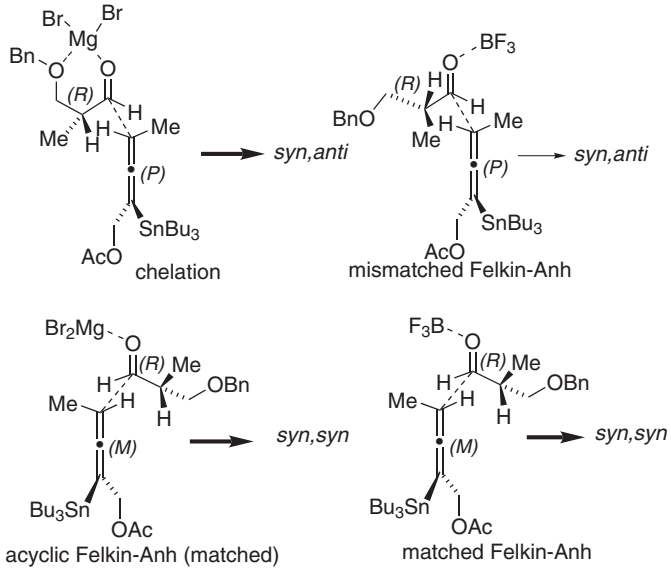


(9.92)



(9.93)

and *anti,syn* products (Scheme 9.19). The (*M*)/(*R*) pairing of allenyltin reagent and aldehyde can adopt a matched Felkin–Anh acyclic transition state for both $MgBr_2$- and BF_3-promoted reactions giving rise to the *syn,syn* diastereoisomer with high selectivity.

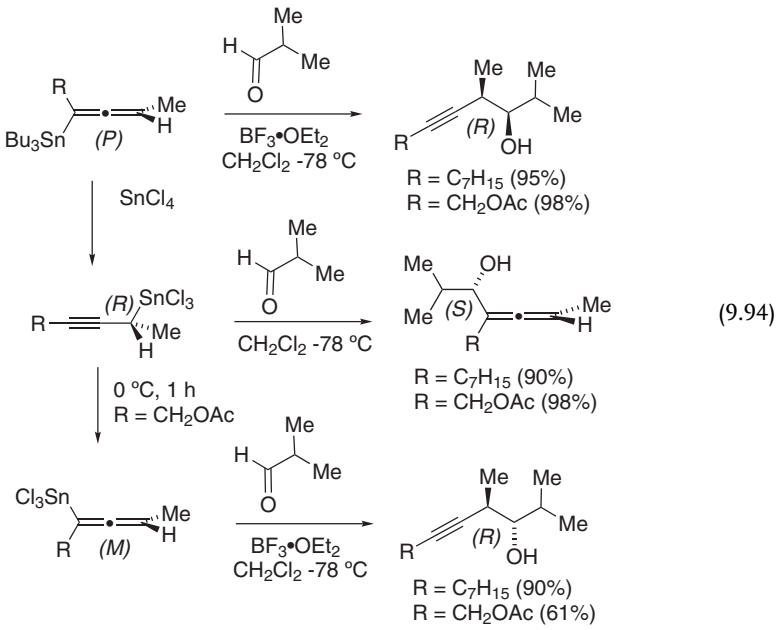


Scheme 9.19 Transition states for $MgBr_2$ and BF_3-promoted-promoted additions of a (*P*)- and (*M*)- allenylstannane to an (*R*)-α-methyl-β-benzyloxypropionaldehyde.

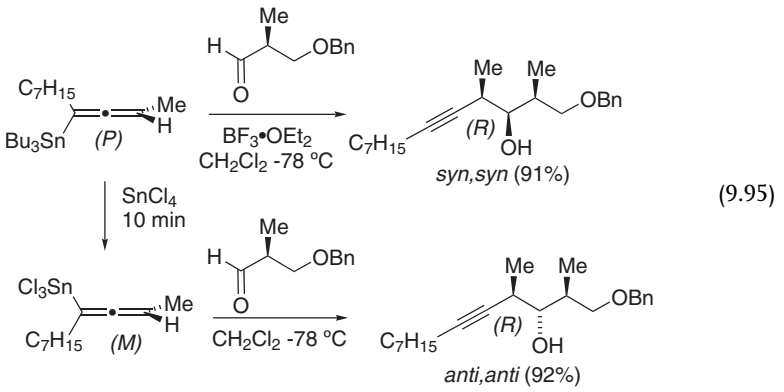
9.8.4

Synthesis and Reactions of Chiral Allenyltin Halides

Chiral allenyltributyltin reagents undergo transmetallation upon treatment with $SnCl_4$ to afford transient propargylic trichlorotin intermediates [74]. These intermediates react with aldehydes at –78 °C to yield chiral allenylcarbinols of high enantiopurity (Eqs. 9.94 and 9.95). Upon warming to 0 °C or prolonged standing at –78 °C, the propargylic trichlorotin intermediates isomerize to allenyltrichlorotin species, which afford *anti* adducts upon addition to aldehydes.

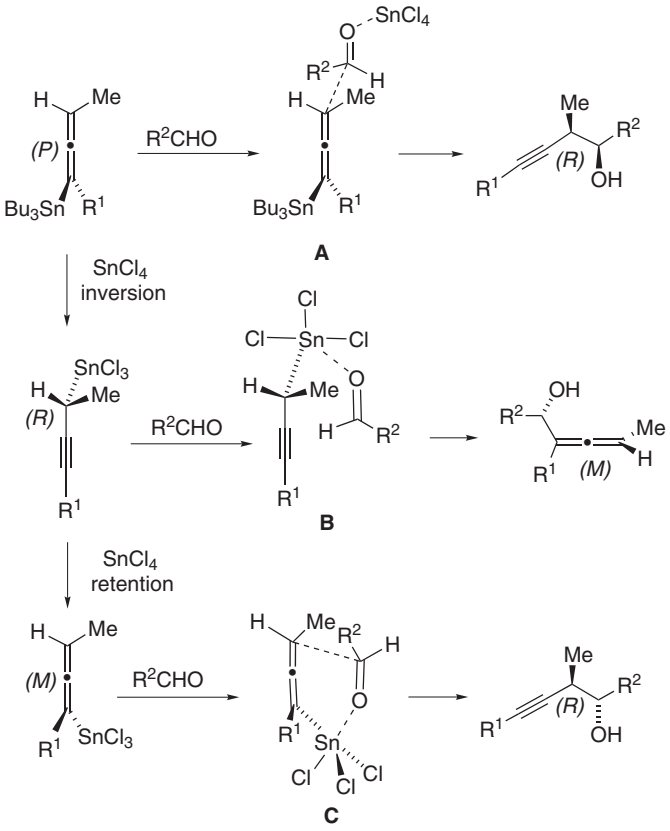


(9.94)



(9.95)

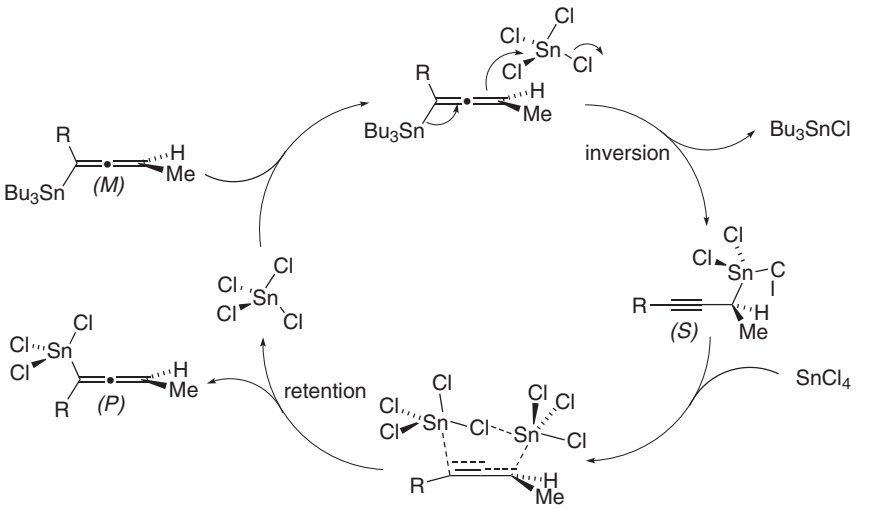
A possible pathway for this sequence is illustrated in Scheme 9.20. As stated previously, tributylallenyltin compounds react with aldehydes in the presence of $BF_3 \cdot OEt_2$ or other Lewis acids, by way of an acylic transition state such as **A** to minimize steric interactions between the aldehyde substituent R^2 and the Me group of the allenyl reagent. The Bu_3Sn group adopts an *anti* orientation to the forming C–C bond for stereoelectronic reasons. The resulting product has a *syn* arrangement between the Me and OH adjacent substituents.



Scheme 9.20 Possible reaction pathways for additions of allenyltributylstannanes to aldehydes in the presence of $SnCl_4$.

The first exchange of Bu_3Sn for Cl_3Sn takes place with inversion to afford a propargylic trichlorotin intermediate, which reacts with an aldehyde through a cyclic transition state, as in **B**, to yield the allenic carbinol product. These additions are highly diastereoselective.

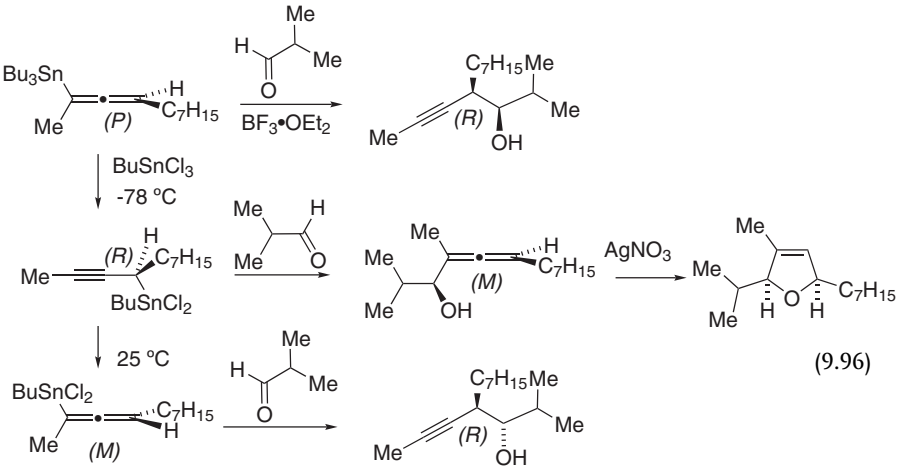
The propargylic trichlorotin intermediate isomerizes to the more stable allenyltrichlorotin species on standing or being warmed to 0 °C. The isomerization, which is highly stereoselective, takes place with retention. A possible transmetallation and isomerization pathway is illustrated in Scheme 9.21.



Scheme 9.21 Transmetallation of allenyltributyltin with $SnCl_4$.

The allenyl trichlorotin intermediate reacts with aldehydes to yield *anti* homopropargylic adducts by a cyclic transition state as in **C** (Scheme 9.20). Steric interactions between the aldehyde substituent R^2 and the allenyl Me most likely control the stereochemistry of these additions.

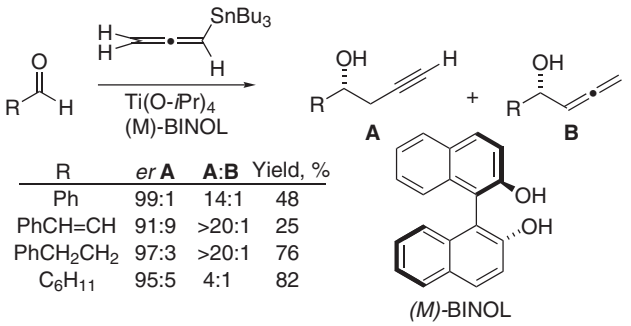
The foregoing transmetallation sequence provides an efficient highly diastereoselective route to diastereomeric adducts starting from a single allenyltributyltin precursor. However, the use of this method to prepare chiral allenylcarbinols is problematic owing to the tendency of the transient propargylic trichlorotin species to rearrange to the more stable allenyl isomer. A solution to this problem lies in the use of $BuSnCl_3$ as the transmetallation reagent [75]. The reaction with an allenyltributyltin leads to a propargylbutyldichlorotin intermediate which is slow to isomerize. In this way it is possible to prepare a variety of allenylcarbinols with excellent diastereoselectivity and in high yield (Eq. 9.96). These adducts are converted to 2,5-dihydrofurans on exposure to 10% $AgNO_3$ in acetone or 10% $AgNO_3$ on silica gel.



(9.96)

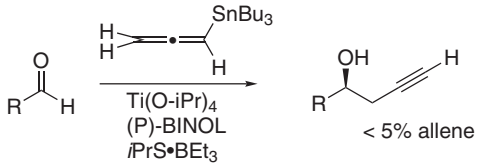
9.8.5
Chiral Catalysis

Tributylstannylallene adds to aldehydes in the presence of a chiral Lewis acid derived from $Ti(OiPr)_4$ and (*P*)- or (*M*)-binaphthol to give homopropargylic alcohols of high enantiopurities (Table 9.43) [76]. The reaction is slow, requiring 72–100 h and 0.5–1.0 mol equiv. of the titanium complex. It was subsequently found that $iPrS \cdot BEt_3$ accelerates the addition (Table 9.44) [77]. With this additive, reaction times are reduced to <18 h and only 10 mol% of the titanium complex is required. Furthermore, the homopropargylic alcohol products contain <2% of the allenic isomers.



R	*er* **A**	**A**:**B**	Yield, %
Ph	99:1	14:1	48
PhCH=CH	91:9	>20:1	25
$PhCH_2CH_2$	97:3	>20:1	76
C_6H_{11}	95:5	4:1	82

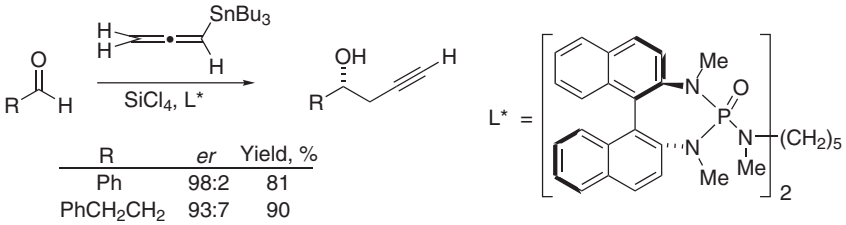
Table 9.43 Enantioselective additions of alleny tributyl tin to aldehydes.



R	*er*	Yield, %
Ph	96:4	52
$PhCH_2CH_2$	97:3	86
$(Me)_2CHCH_2$	97:3	61
C_6H_{11}	95:5	73

Table 9.44 Acceleration of allenyl tributyl tin additions.

A novel chiral phosphonic amide–$SiCl_4$ complex has also been found to serve as a catalyst for additions of allenyltributyltin to aldehydes (Table 9.45) [78]. The reaction is limited to aromatic aldehydes because of competing formation of silylated chlorohydrins from aliphatic aldehydes and the $SiCl_4$ reagent.

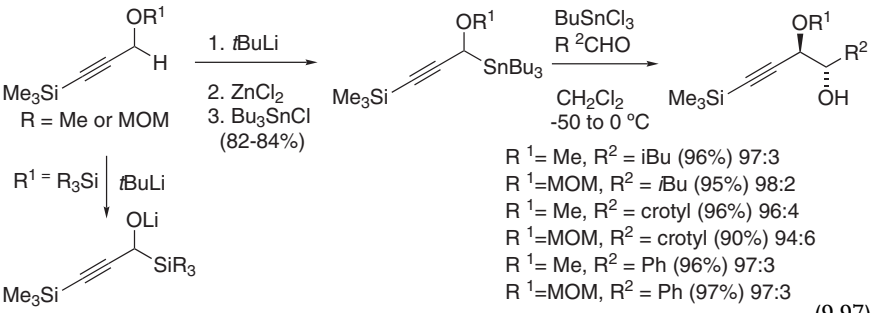


R	*er*	Yield, %
Ph	98:2	81
$PhCH_2CH_2$	93:7	90
2-Naphthyl	96:4	95

Table 9.45 Enantioselective additions of allenyl tributyl tin to aldehydes catalyzed by a Lewis acid–chiral base complex.

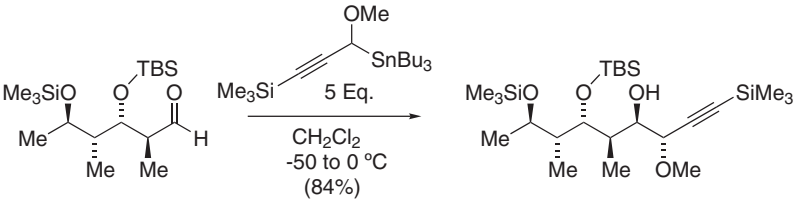
9.8.6
Oxygenated Allenyltin Halides

Certain trimethylsilyl-substituted propargylic ethers are converted to α-oxygenated propargylic stannanes upon lithiation followed by conversion to the allenylzinc reagent with $ZnCl_2$ and ensuing transmetallation with Bu_3SnCl [79, 80] (Eq. 9.97). Transmetallation of the tributyltin intermediates with $BuSnCl_3$ in the presence of various aldehydes leads to *anti* adducts in high yield and excellent diastereoselectivity. Attempts to prepare silyloxy analogues by this sequence could not be achieved because of a competing Brook rearrangement in the lithiation step.



(9.97)

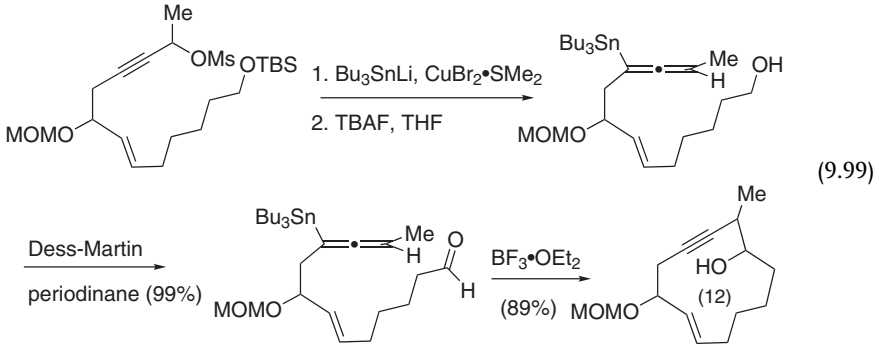
Although the foregoing allenylstannane reagents are racemic, it was possible to effect a useful kinetic resolution upon treatment of an enantiopure aldehyde with a five-fold excess of the propargylic ether (Eq. 9.98).

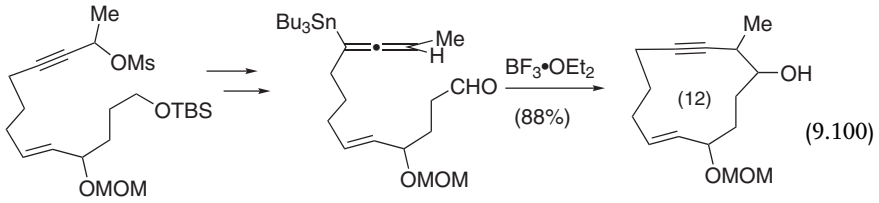


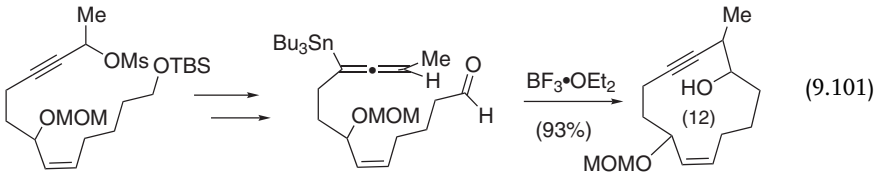
(9.98)

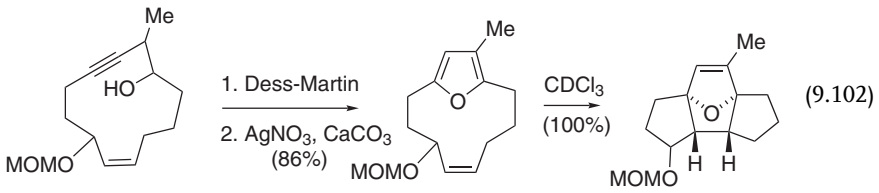
9.8.7
Intramolecular Additions

Because trialkylallenylstannanes are isolable and relatively stable compounds, it is possible to prepare intermediates in which an allenyltin and an aldehyde function are both present, leading to the possibility of Lewis acid-promoted intramolecular addition reactions. The feasibility of this scenario has been demonstrated on a series of allenylaldehydes, resulting in the efficient synthesis of several cyclododecynyl derivatives as mixtures of diastereomers (Eqs. 9.99–9.101) [81]. The *cis*-enyne product was oxidized to an allenone, which was converted to a furanocycle in high yield by treatment with $AgNO_3$ (Eq. 9.102). This intermediate underwent a remarkably facile intramolecular Diels–Alder cyclization on standing in $CDCl_3$ overnight.

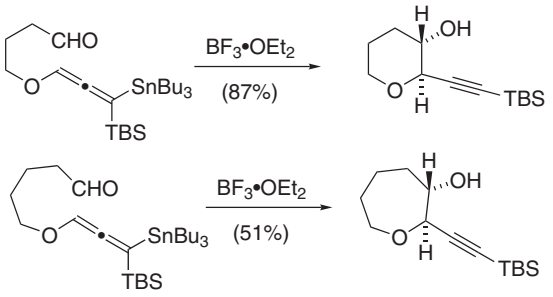






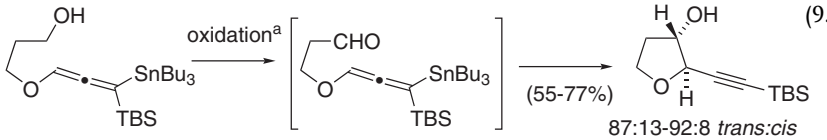


Oxygenated allenylstannanes have also been employed in intramolecular additions to aldehydes [82]. Both six- and seven-membered cyclic ethers have been synthesized with high diastereoselectivity by this route (Eq. 9.103).



(9.103)

Attempted preparation of the aldehyde precursor of the five-membered ether product through oxidation of the corresponding alcohol led not to the aldehyde, but instead the cyclic ether itself (Eq. 9.104). Evidently the cyclization reaction is facile in this case.

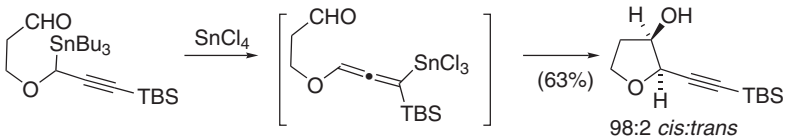


(9.104)

87:13-92:8 *trans:cis*

[a] SO_3-pyridine, DMSO, Et_3N or *i*PrOMgBr, ADD

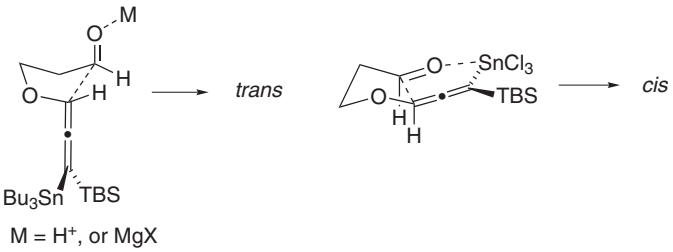
The isomeric propargylic stannylated aldehyde intermediate, on the other hand, could be prepared from the alcohol precursor without competing cyclization to an seven-membered enol ether product (Eq. 9.105). Treatment of this stannane with $SnCl_4$ afforded the *cis*-disubstituted tetrahydrofuran stereoselectively. Presumably, this reaction proceeds through an allenyl trichlorostannane intermediate.



(9.105)

98:2 *cis:trans*

The differing steric outcomes of these cyclizations can be understood on the basis of an acyclic transition state in the former case and a coordinated cyclic transition state in the latter (Scheme 9.22).

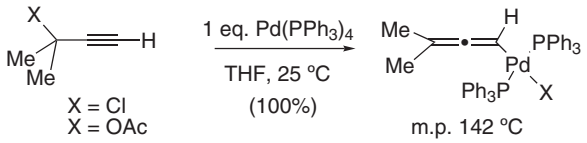


Scheme 9.22 Transition-state orientations for allenylstannane cyclizations.

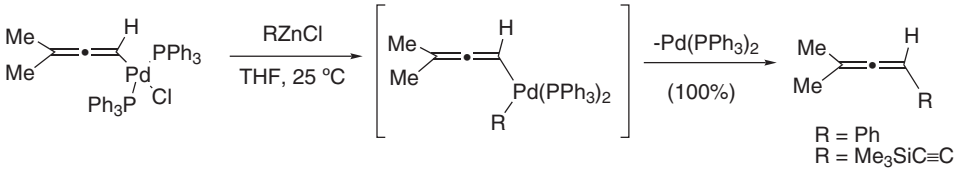
9.9 Allenylpalladium Reagents

9.9.1 Synthesis

Some synthetically important allenylmetallics, such as allenylzinc and allenylindium reagents, are prepared from allenylpalladium intermediates. These reactions are discussed in appropriate sections of this chapter. This section covers the reactions of allenylpalladium compounds without further transmetallation. Allenylpalladium complexes can be prepared from propargylic halides, acetates, carbonates, mesylates, alcohols and certain alkynes [83–87]. The allenylpalladium compound prepared from 3-chloro-3-methyl-1-butyne has been isolated and characterized spectroscopically (Eq. 9.106) [83]. It was found to couple with organozinc chlorides to produce homologated allenes quantitatively (Eq. 9.107).

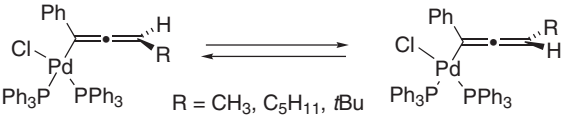


(9.106)



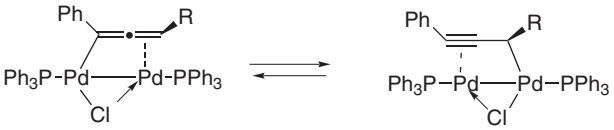
(9.107)

Chiral allenylpalladium complexes have been prepared from non-racemic propargylic chlorides and $Pd_2(dba)_3$–PPh_3 [88]. Although nominally stable, these complexes were found to racemize under certain conditions (Eq. 9.108). Reagents prepared under oxygen-free conditions racemize more slowly than those prepared in



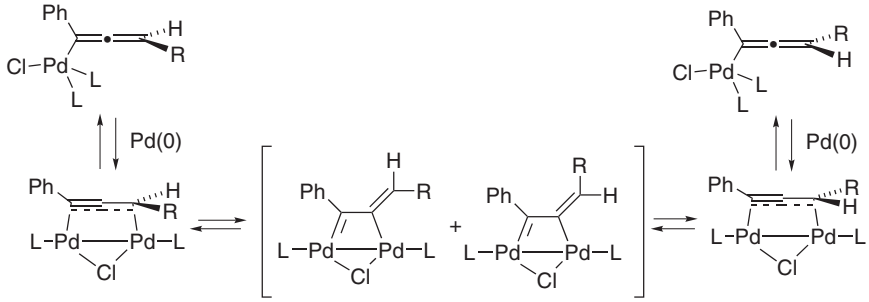
(9.108)

air. The addition of Ph_3P suppressed the rate of racemization. A dinuclear palladium complex and $Ph_3P{=}O$ were isolated from the allenylpalladium intermediate prepared in air (Scheme 9.23).



Scheme 9.23 Proposed structure for the dinuclear palladium complex derived from a chiral propargyl chloride.

Based on the above observations, a plausible mechanism for the racemization was proposed [88]. The rate-determining step was shown to involve a dinuclear complex which could invert by way of an achiral vinyldipalladium intermediate (Scheme 9.24). Ligands such as Ph_3P were found to suppress the formation of the dinuclear complex and the accompanying racemization.

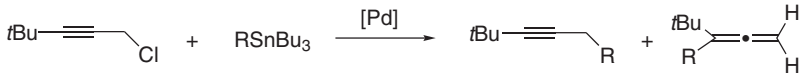


Scheme 9.24 Racemization pathway for chiral allenylpalladium compounds.

9.9.2
Cross-Coupling Reactions

Stille cross-couplings between allenylpalladium complexes and organotin compounds can afford alkynyl or allenyl products. The product ratio and yield, not surprisingly, are affected by the choice of catalyst and the structure of the coupling partners [89]. With $Pd(PPh_3)_4$ the reaction of $PhSnBu_3$ and the allenylpalladium prepared from tBuC≡CCH$_2$Cl was slow and inefficient (Eq. 9.109). On the other hand, with $Pd_2(dba)_3$ as the catalyst precursor and 2 equiv. of the PPh_3 ligand, the yield was markedly improved. In these reactions, the alkyne was the major product. How-

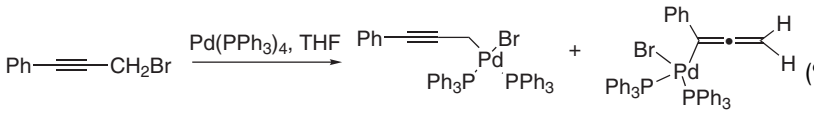
ever, when PhC≡CSnBu$_3$ was used in the coupling reaction, the allenic product predominated. The observed preference for the alkynyl product was attributed to steric hindrance in the case of PhSnBu$_3$. The allenic product is favored when PhC≡CSnBu$_3$ is used because of the sterically less demanding PhC≡C group and a greater electronic preference for coupling at the sp^2 versus sp^3 carbon of the palladium reagent.



[Pd] = $Pd_2(dba)_3$ + 2PPh_3 R = Ph, alkyne/allene = 96:4 (95%)
[Pd] = $Pd(PPh_3)_4$ R = Ph, alkyne/allene = 99:1 (26%)
[Pd] = $Pd_2(dba)_3$ + 2PPh_3 R = PhC≡C, alkyne/allene = 3:97 (100%)
[Pd] = $Pd(PPh_3)_4$ R = PhC≡C, alkyne/allene = 4:96 (73%)

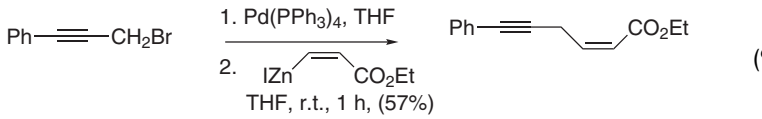
(9.109)

A 1.7:1 mixture of propargyl and allenylpalladium complexes was obtained when phenylpropargyl bromide was treated with $Pd(PPh_3)_4$ in THF at room temperature (Eq. 9.110) [87, 90]. This mixture reacted with a vinylzinc iodide to produce the enyne coupling product exclusively (Eq. 9.111) [87]. On the other hand, the reaction of the same mixture of palladium complexes with phenylzinc bromide gave 1,1-diphenylallene in 60% yield (Eq. 9.112). When the palladium complex derived from 1-trimethylsilylpropyne was treated with (*E*)- or (*Z*)-vinyl iodides, the enyne coupling products were produced with retention of the double bond geometry (Eq. 9.113).

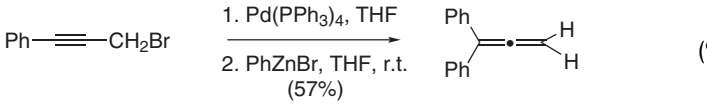


(1.7 : 1)

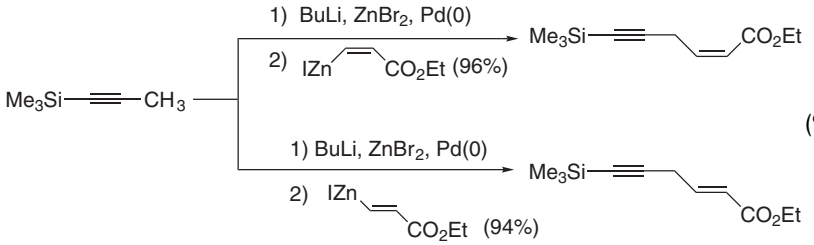
(9.110)



(9.111)

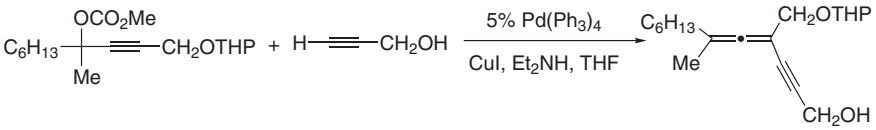


(9.112)



(9.113)

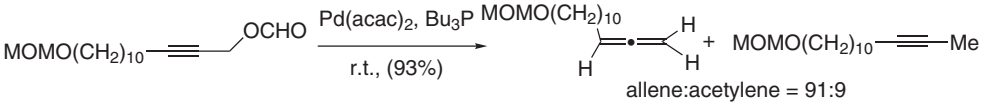
Substituted propargylic carbonates react with terminal acetylenes in the presence of a catalytic amount of $Pd(PPh_3)_4$ and CuI to produce Sonogashira-type cross-coupling products (Eq. 9.114) [84]. Presumably, the reaction proceeds through an allenylpalladium complex. Addition of a salt, such as KBr, increased the yield of the coupling product. Only tetrasubstituted allenes could be obtained by this procedure.



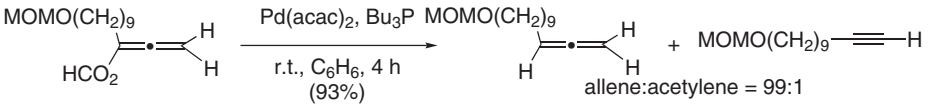
(9.114)

9.9.3 Decarboxylation

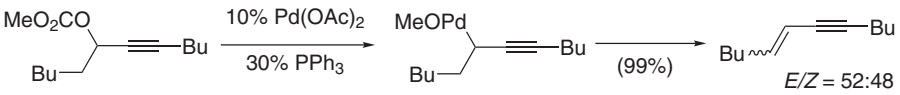
Primary propargylic formates decarboxylate in the presence of $Pd(acac)_2$ and Bu_3P at room temperature to give mainly allenic products (Eq. 9.115) [91]. Initial formation of a propargylic palladium complex, which rearranges to the more stable allenylpalladium species, accounts for this transformation. Under similar conditions, a terminal allenyl formate afforded a 99:1 mixture of allene and acetylene product (Eq. 9.116) [91]. However, a mixture of enyne elimination products was formed when a secondary propargylic carbonate was treated with a palladium catalyst (Eq. 9.117).



(9.115)



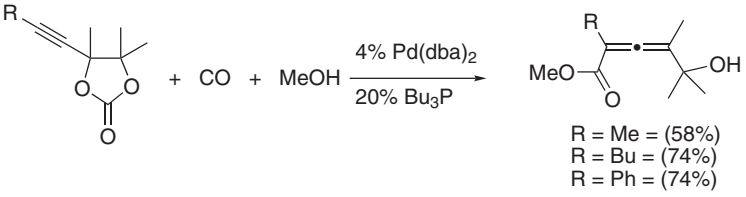
(9.116)



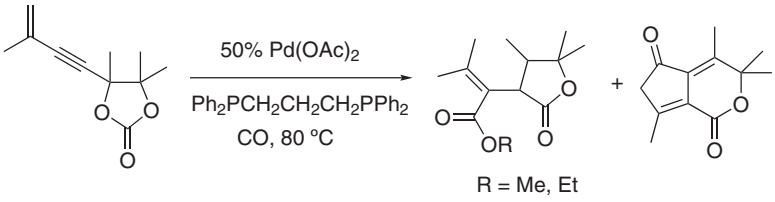
(9.117)

9.9.4 Carbonylation

Cyclic alkynyl carbonates undergo carbonylation in the presence of a palladium catalyst and carbon monoxide (5 MPa) in MeOH to give allenic carboxylates (Eq. 9.118) [92]. Bu_3P proved superior to Ph_3P as the catalyst ligand. An enynyl cyclic carbonate underwent double vicinal carbonylation at 80 °C to produce a five-membered lactone product in 52% yield (Eq. 9.119). When the reaction was performed at 50 °C, the bicyclic enone lactone was produced in 75% yield along with 10% of the γ-lactone.

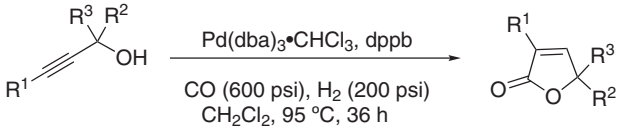


(9.118)



(9.119)

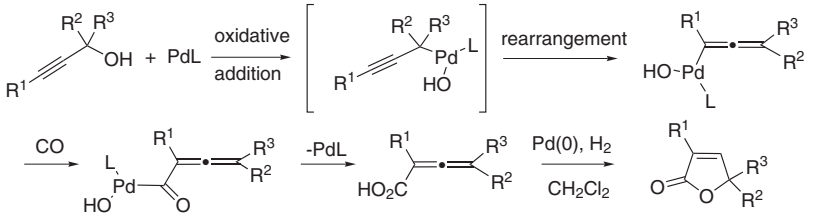
Substituted propargylic alcohols were found to undergo direct carbonylation to the corresponding butenolides in 67–98% yield (Eq. 9.120) [86]. This reaction requires a catalytic amount of $Pd_2(dba)_3$–$CHCl_3$ (4%) and 1,4-bis(diphenylphosphino)butane (8%) in CH_2Cl_2 under an atmosphere of CO (600 psi) and H_2 (200 psi) at 95 °C for 36 h. The cyclocarbonylation reaction is believed to proceed via an allenylpalladium intermediate, which is formed by initial insertion of Pd(0) into the C–O bond of the alkynol followed by rearrangement (Scheme 9.25).



R^1 = H, alkyl, phenyl and vinyl
R^2, R^3 = H or alkyl

(67-98%)

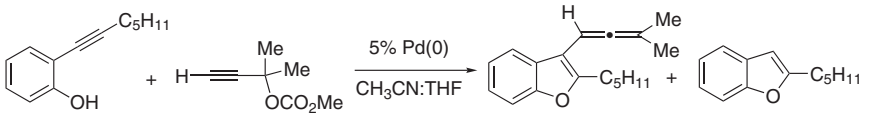
(9.120)



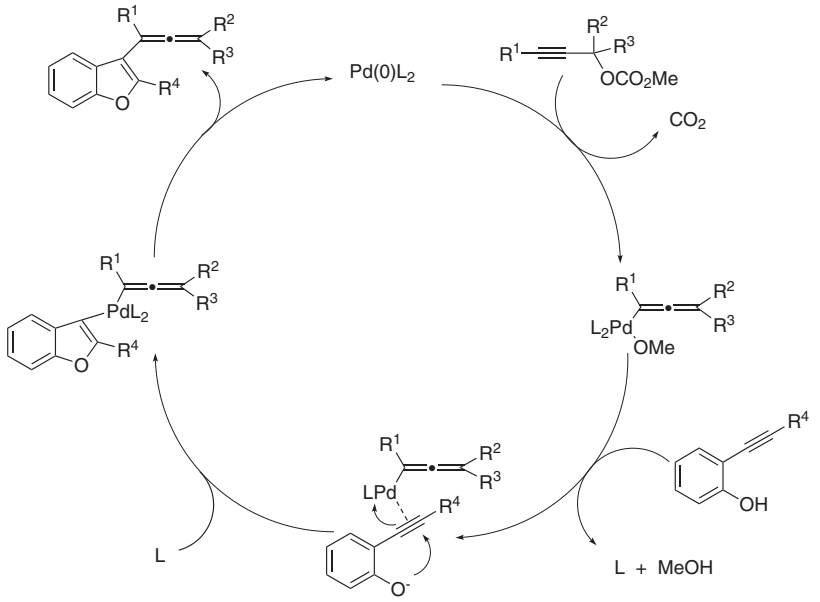
Scheme 9.25 Possible mechanism for Pd-catalyzed alkynol cyclocarbonylation.

9.9.5
Cyclizations and Cascade Reactions

The reaction of 2-alkynylphenols with tertiary propargyl carbonates in the presence of a Pd(0) catalyst gave 2-substituted 3-allenylbenzo [*b*]furans in moderate to high yields (Eq. 9.121) [93]. This heteroannulation is thought to proceed by a σ-allenylpalladium complex (Scheme 9.26).



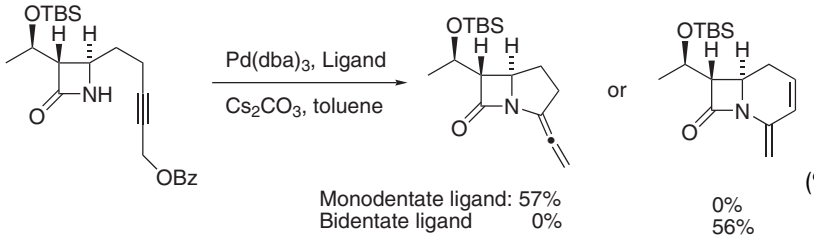
(77%) (11%) (9.121)



Scheme 9.26 Possible mechanism for heteroannulation promoted by a σ-allenylpalladium intermediate.

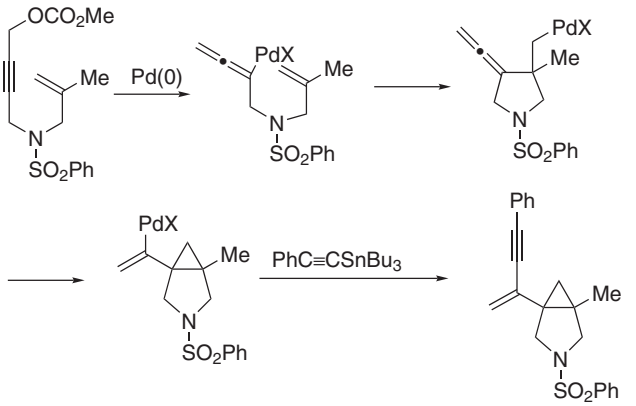
According to the proposed mechanism, an S_N2'-type reaction of the palladium complex with the propargyl carbonate generates an allenylpalladium methoxide. A proton exchange between the phenol and the methoxide anion follows and the next step is the coordination of the triple bond to palladium through ligand displacement. Intramolecular attack of the phenoxide anion on the triple bond from the opposite side of the activating σ-allenylpalladium complex generates the benzofuranyl allenylpalladium complex. Subsequent coupling of the σ-allenyl and the benzofuranyl moiety through reductive elimination of Pd(0) gives the 3-allenylbenzo[*b*]furan and regenerates the active catalytic species.

When a THF solution of a β-lactam having a propargylic benzoate side-chain was warmed in the presence of 5% $Pd_2(dba)_3$–$CHCl_3$ and 20% of a bidentate ligand at 40 °C, a carbapenam was produced in high yield (Eq. 9.122) [94, 95]. In this reaction, the lactam nitrogen attacks the central sp carbon of the σ-allenylpalladium complex, which was formed from the propargyl ester and Pd(0). The type of ligand on the allenylpalladium complex plays an important role in determining the ring size of the product. Monodentate ligands gave the cyclized product via a palladacycle, while bidentate ligands gave a ring-expanded product via an η^3-propargylpalladium complex.



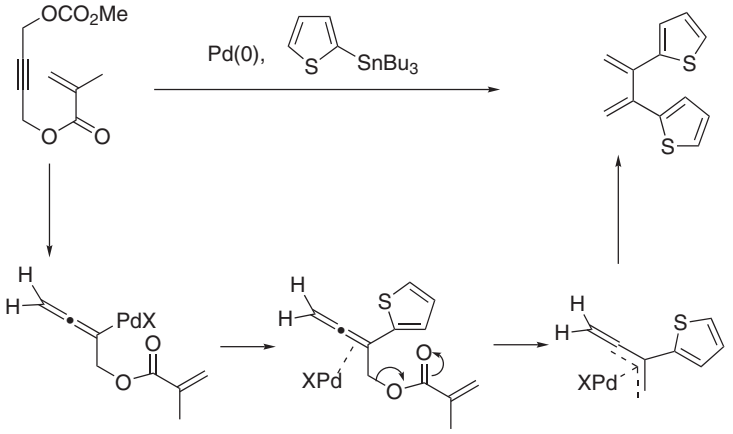
(9.122)

Enynes with stategically located triple and double bonds undergo a cascade reaction in the presence of a palladium catalyst [96, 97]. One such reaction is depicted in Eq. 9.123. Formation of an allenylpalladium intermediate is followed by a 5-*exo*-trig cyclization generating a five-membered ring. The normal preference for attack of an organopalladium (II) species at the central carbon of the allene is prevented by the geometric constraints imposed by the ring. Cyclization occurs at the near terminus of the allene to produce a vinylpalladium intermediate, which then undergoes a coupling reaction with an organotin compound [96, 97].



(9.123)

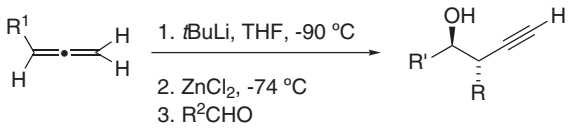
Another interesting reaction was discovered serendipitously in a study of cascade reactions of allenylpalladium intermediates [97]. A carbonic, methacrylic diester of 2-butyne-1,4-diol was found to yield a 1,3-diene on Stille coupling with a thiophene stannane. (Eq. 9.124). A plausible mechanism involves initial formation of an allenylpalladium intermediate followed by cross-coupling with the organotin compound. Loss of the acryloyloxy group then generates a π-allyl species, which reacts with a second equivalent of the tin reagent to give the diene.



(9.124)

9.10 Allenylzinc Reagents

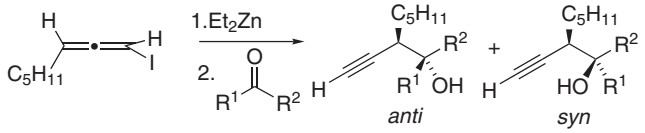
An early synthesis of allenylzinc reagents employed a two-step procedure in which monosubstituted allenes were subjected to lithiation in THF with *t*BuLi at –90 °C and the resulting allenyllithium intermediates were treated with $ZnCl_2$. The allenylzinc reagents thus generated react in situ with aldehydes to afford mainly *anti* homopropargyl alcohols (Table 9.46) [98].



R^1	R^2	Yield, %	*anti:syn*
Et	C_6H_{13}	95	96:4
*i*Pr	C_6H_{13}	86	99:1
Et	C_6H_{11}	80	98:2
C_3H_7	C_3H_7	95	93:7

Table 9.46 Additions of allenylzinc reagents to aldehydes.

A direct zinc–halogen exchange has been used to convert allenyl iodides into allenylzinc reagents (Table 9.47) [98]. These react with aldehydes and ketones to yield mainly *anti* homopropargylic adducts in modest yield. The selectivity is highest with aliphatic aldehydes.

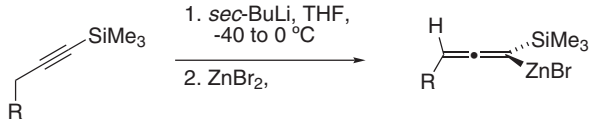


R^1	R^2	*anti:syn*	Yield, %
H	Bu	87:13	63
H	*t*Bu	99:1	44
H	Ph	63:37	58
Me	Ph	86:14	61
Me	Bu	52:48	62

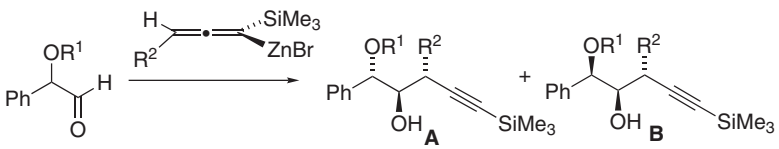
Table 9.47 In situ preparation of an allenylzinc reagent.

9.10.1
Racemic Allenylzinc Reagents

Terminal trimethylsilylacetylenes are deprotonated at the propargylic position by using *s*BuLi to yield a lithiated species which undergoes transmetallation with $ZnBr_2$ to afford the allenylzinc reagent (Eq. 9.125) [99]. Additions to α-alkoxyaldehydes are relatively unselective (Table 9.48), whereas additions to α-alkoxy imines are highly *anti* selective (Eq. 9.126).

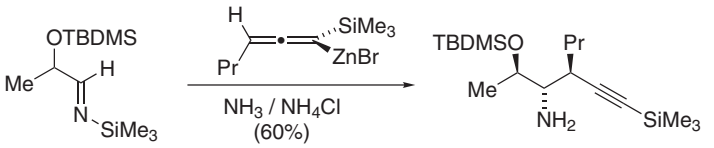


(9.125)



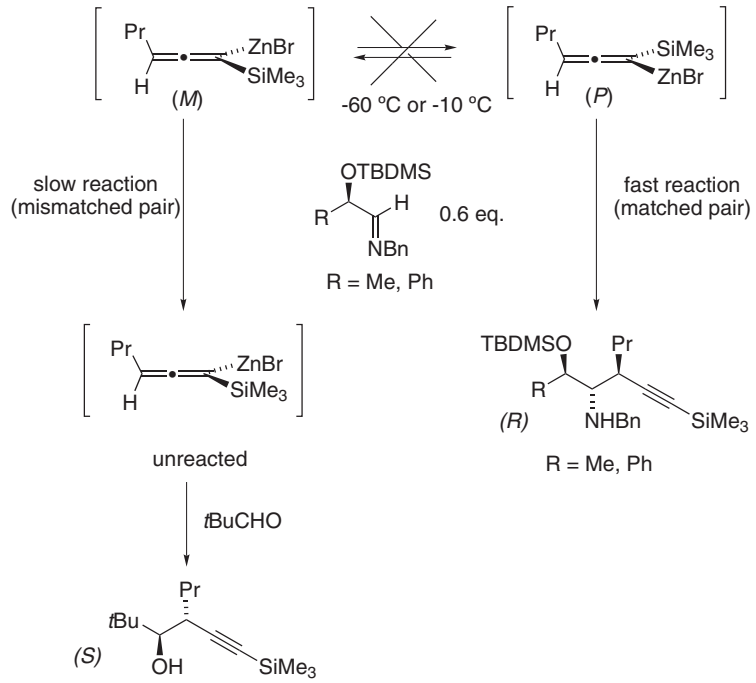
R^1	R^2	**A**:**B**
TIPS	Me	53:47
TBS	Me	55:45
DPS	Me	58:42
TBS	Pr	58:42
DPS	Pr	67:33

Table 9.48 Additions of non-racemic silylated allenylzinc reagents to racemic silylated mandelic aldehyde.



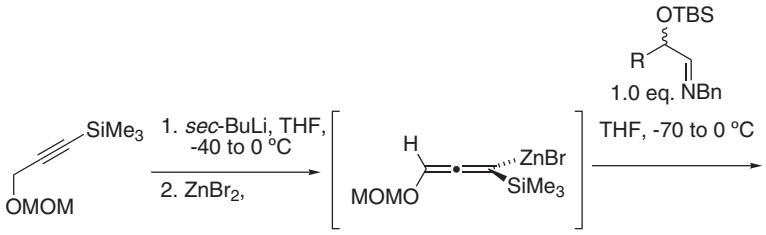
(9.126)

A kinetic resolution can be performed on the racemic allenylzinc reagent by using enantiomerically enriched α-alkoxyimines (Scheme 9.27) [100]. The resolved allenylzinc reagent was subjected to the Hoffmann test for configurational stability and it was found that at –60 to–10 °C, racemization does not occur at a significant rate [101, 102]. When 0.6 equiv. of the chiral (*R*)-imine was added to the racemic allenylzinc reagent, the matched (*P*)-reagent was consumed rapidly and the mismatched (*M*)-enantiomer was left unchanged. Addition of *t*BuCHO to the reaction mixture yielded the adduct of the (*M*)-reagent of nearly 100% enantiomeric purity.

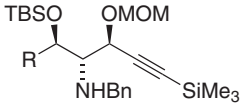


Scheme 9.27 Kinetic resolution of an allenylzinc reagent using a chiral imine.

A 3-alkoxyallenylzinc reagent can be prepared by treating the MOM ether of trimethylsilylpropargyl alcohol with *s*BuLi followed by $ZnBr_2$ (Eq. 9.127) [103]. This reagent adds to aldehydes affording protected propargylic diols in high yields but with low diastereoselectivity (*dr* < 4:1) [104–106]. However, addition to benzylimines of lactic and mandelic aldehydes leads to *anti*,*anti*-2-amino-1,3-diol derivatives with high diastereoselectivity (Eq. 9.127) [103].

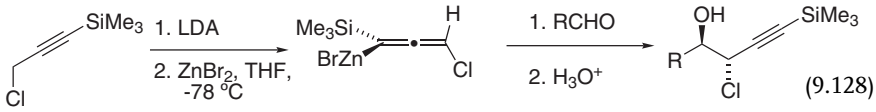


(9.127)

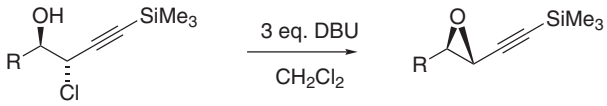


R = Me, Ph, (60-75%), *dr* > 40:1

A related allenylzinc reagent was prepared by the addition of LDA to a solution of trimethylsilylpropargyl chloride and $ZnBr_2$ in THF at –78 °C (Eq. 9.128) [107]. *Anti* propargylic chlorohydrins adducts were obtained when aldehydes were allowed to react with this reagent. Subsequent treatment with DBU gave the alkynyloxiranes (Eq. 9.129).

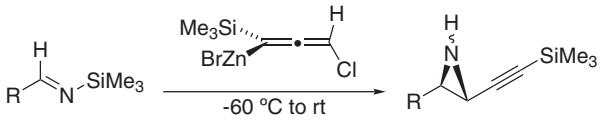


(9.128)



(9.129)

Propargylic aziridines were obtained in one step on reaction of this allenylzinc reagent with imines (Eq. 9.130) [108, 109].

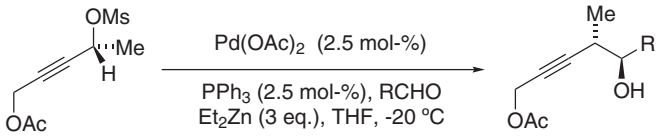


(9.130)

9.10.2
Enantioenriched Chiral Allenylzinc Reagents

A mild approach that avoids the use of BuLi has been developed for enantioenriched chiral allenylzinc reagents. Configurationally predictable reagents can be prepared through reaction of a chiral mesylate with Et_2Zn in the presence of a palladium catalyst, usually $Pd(OAc)_2$ and PPh_3 [110–112]. The reagent reacts in situ with an alde-

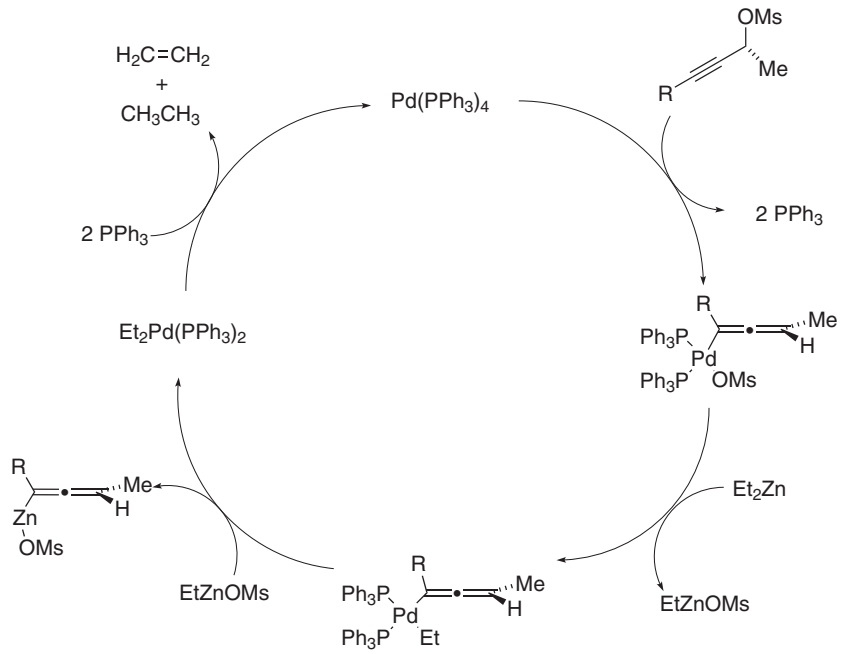
hyde to yield non-racemic *anti* homopropargyl alcohols of high enantiomeric purity (Eq. 9.131).



(9.131)

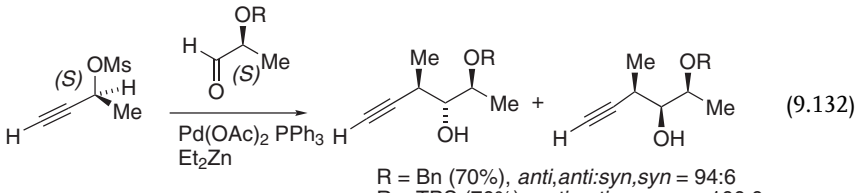
R = C_6H_{11} (75%), *anti:syn* = 95:5
R = C_6H_{13} (74%), *anti:syn* = 88:12
R = *i*Pr (75%), *anti:syn* = 95:5
R = *E*-BuCH=CH (57%), *anti:syn* = 72:28

The palladation of propargylic mesylates is known to occur with inversion of configuration [113]. The predominant formation of *anti* products strongly suggests a cyclic transition state for the addition. It can therefore be surmised that the zincation reaction proceeds with retention of configuration. A possible catalytic cycle is shown in Scheme 9.28 [110].



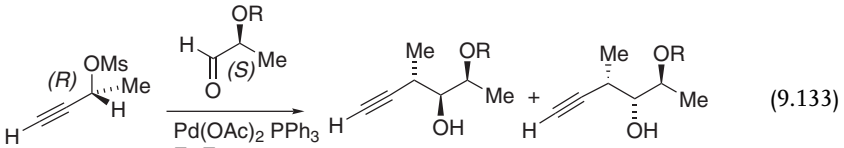
Scheme 9.28 Possible catalytic cycle for the Pd(0)-catalyzed zincation of propargylic mesylates.

Additions of enantioenriched allenylzinc reagents to chiral aldehydes provide intermediates that can be employed in the synthesis of polyketide natural products. Matched and mismatched pairing of reagent and substrate can result in enhanced or diminished diastereoselectivity (Eqs. 9.132 and 9.133) [114].



(9.132)

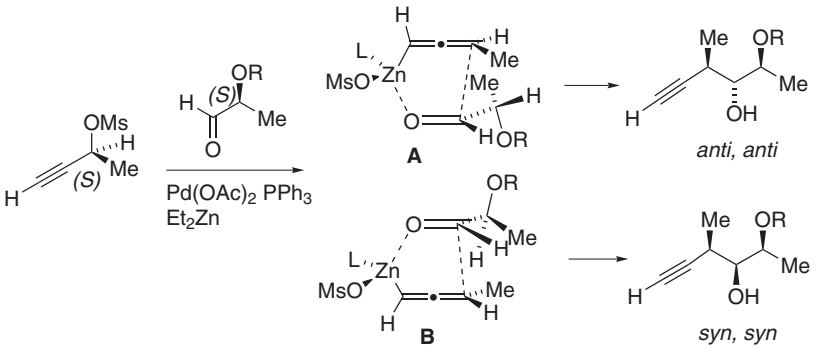
R = Bn (70%), *anti,anti:syn,syn* = 94:6
R = TBS (70%), *anti,anti:syn,syn* = 100:0



(9.133)

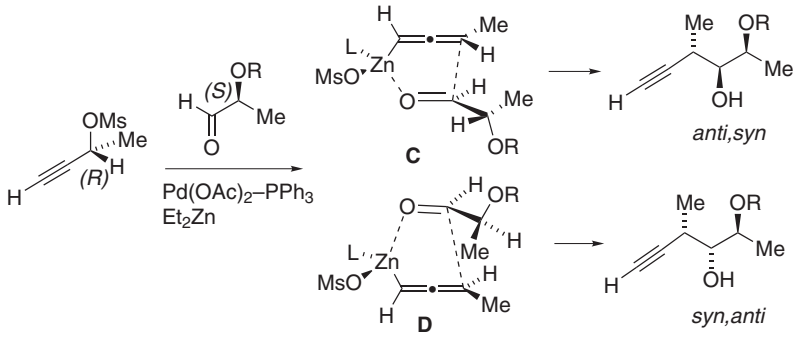
R = Bn (70%), *anti,syn:syn,anti* = 86:14
R = TBS (75%), *anti,syn:syn,anti* = 85:15

The factors that control the stereochemical outcome of such rections can be illustrated by additions of enantiomeric allenylzinc reagents to (*S*)-lactic aldehyde derivatives [114]. The matched *S*/*S* pairing proceeds via the cyclic transition state **A** in which addition to the aldehyde carbonyl assumes the Felkin–Anh orientation with an *anti* arrangement of the allenyl methyl and aldehyde substituents (Scheme 9.29). The alternative arrangement **B** is disfavored both by the anti-Felkin–Anh arrangement and eclipsing of the allenylmethyl and aldehyde substituents.



Scheme 9.29 Possible transition states for additions of the matched (*S*)/(*S*) pairing of allenylzinc to lactaldehyde.

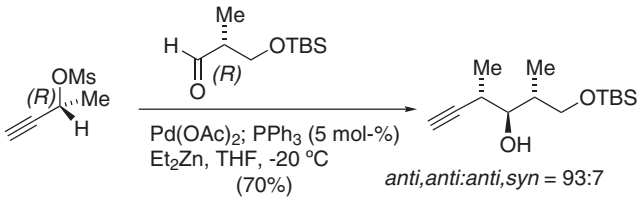
The mismatched *R*/*S* pairing could lead to the *anti,syn* adduct through transition state **C** and the *syn,anti* adduct via **D** (Scheme 9.30). The former pathway entails non-Felkin–Anh addition but *anti* disposed methyl and aldehyde substituents. Transition state **D** proceeds through the Felkin–Anh mode of carbonyl addition but requires eclipsing of the methyl and aldehyde substituents. This interaction is the more costly one and thus disfavors the *syn,anti* adduct.



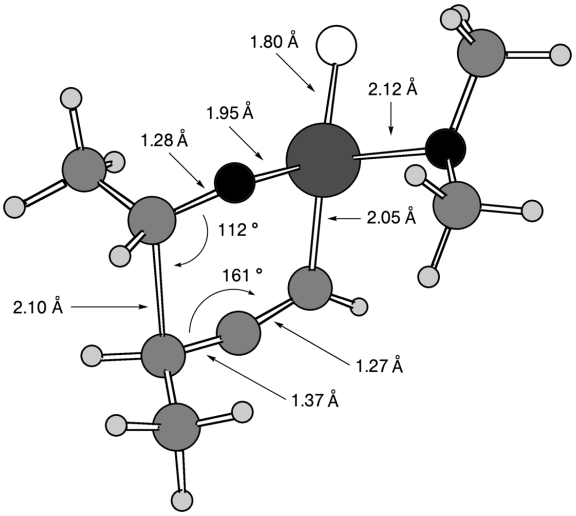
Scheme 9.30 Possible transition states for additions of the mismatched (*R*)/(*S*) pairing of allenylzinc to lactaldehyde.

A computational study supports the proposed transition state geometry for the addition [115]. Transition-state structures for the reaction of an (*M*)-1,2-butadienylzinc reagent and acetaldehyde were located at the B3LYP/6–31G* and HF/6–31++G** levels of theory (Scheme 9.31). A tetrahedrally-coordinated zinc atom with a dimethyl ether ligand is found to give energy differences that are most consistent with the observed results. This arrangement allows staggering of the bonding sp^2 carbons, thus avoiding eclipsing of the aldehyde and the allenyl substituents. The allenyl moiety is slightly bent ($\angle C{=}C{=}C \approx 162°$). A relatively 'late' transition state is proposed for this reaction based on comparisons with *ab initio* transition states for dialkylzinc and allylborane additions. The computational study suggests that steric interactions between the aldehyde and allene substituents control the diastereoselectivity of the reaction and also influence the *syn* or *anti* complexation of the zinc atom with the aldehyde carbonyl.

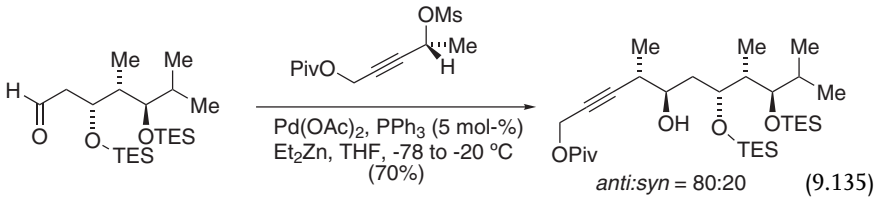
The efficiency and convenience of the chiral allenylzinc reagents are demonstrated in the synthesis of subunits of several natural products. In a total synthesis of bafilomycin V_1, seven of the 13 stereogenic centers were introduced by means of allenylzinc chemistry [112]. Three centers of chirality in the C5–C11 fragment were constructed from the precursor (*R*)-mesylate and the (*R*)-aldehyde (Eq. 9.134). The TBS protecting group of the aldehyde is important for high diastereoselectivity. Four of the five stereogenic centers in the C15–C25 subunit were likewise established (Eq. 9.135).



(9.134)

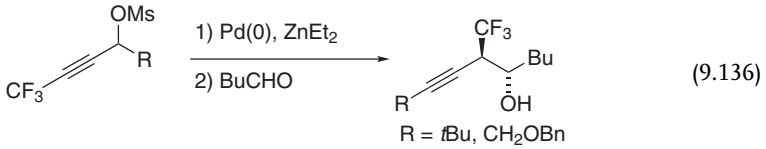


Scheme 9.31 Cyclic transition states for the (M)-1,2-butadienylzinc additions to acetaldehyde calculated at the B3LYP/6–31G* level of theory.

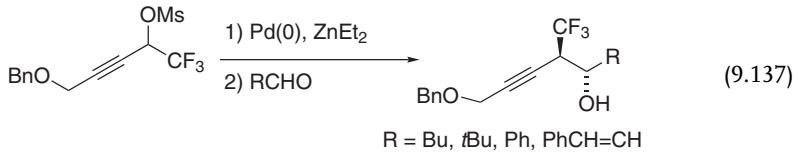


(9.135)

The application of this method to trifluoromethyl analogues has been reported [116]. Trifluoromethylpropargylic mesylates undergo highly selective conversion to allenylzinc reagents, which add in situ to aldehydes producing the expected *anti* homopropargyl alcohols (Eqs. 9.136 and 9.137).

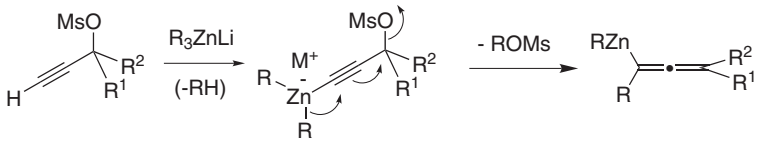


(9.136)

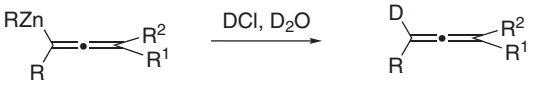


(9.137)

Terminal propargylic mesylates are converted to alkylallenylzinc compounds by reaction with lithiotrialkylzincate reagents (Scheme 9.32) [117]. The latter are formed in situ from dialkylzinc and alkyllithium species. Deuterolysis of the allenylzinc intermediates gave rise to deuterated allenes (Eq. 9.138).

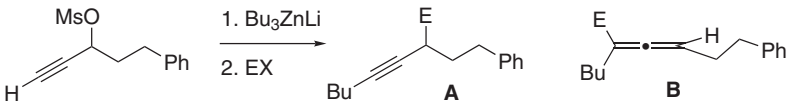


Scheme 9.32 Synthesis of allenylzinc reagents from propargylic mesylates.



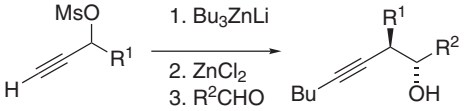
(9.138)

Reaction of the transient zinc intermediates with various electrophiles yielded the acetylenic substitution products and only minor amounts of allenes (Table 9.49). Reactions with aldehydes were non-selective, affording mixtures of stereo- and regioisomeric adducts. However, prior addition of $ZnCl_2$ resulted in the formation of the homopropargylic alcohol adducts with high preference for the *anti* adduct, as would be expected for an allenylzinc chloride intermediate (Table 9.50).



EX	Yield, %	**A**:**B**
I_2	87	93:7
NCS	86	98:2
Me_3SiCl	90	90:10
$PhMe_2SiCl$	88	96:4
MeCOCl	80	89:11
BuCOCl	90	88:12
*t*BuCOCl	91	95:5

Table 9.49 Electrophilic substitution of a butyl-allenylzinc reagent.

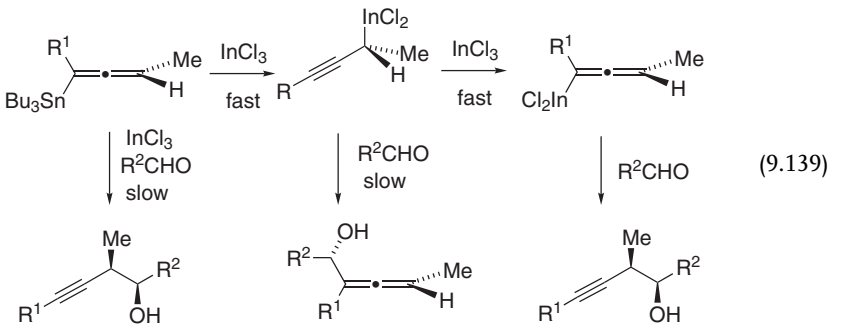


R^1	R^2	Yield, %	*anti:syn*
Me	*i*Pr	89	98:2
C_8H_{17}	*i*Pr	85	99:1
C_8H_{17}	$PhCH_2CH_2$	86	95:5
C_6H_{11}	Et	89	97:3

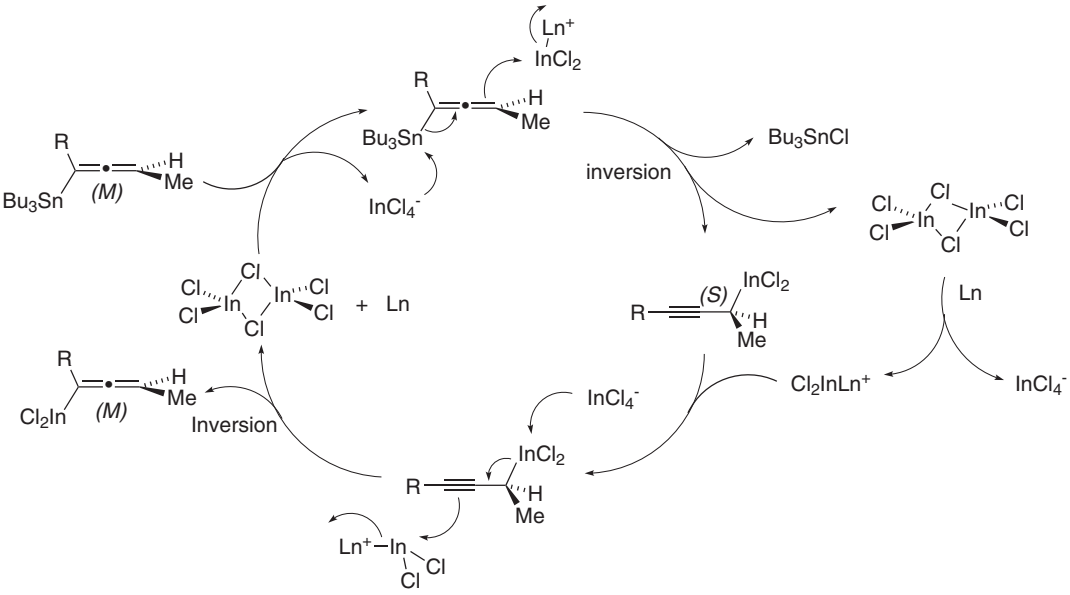
Table 9.50 Additions of butyl-allenylzinc reagents to aldehydes.

9.11 Allenylindium Reagents

Allenic tributylstannanes undergo transmetallation to allenylindium intermediates on treatment with $InCl_3$ (Eq. 9.139) [117]. Although analogous to that previously described for $SnCl_4$ or $BuSnCl_3$, the overall process differs in two important respects: (1) the transmetallation can be conducted in the presence of aldehydes without the formation of allenylcarbinols and (2) the configuration of the major propargylic alcohol adducts is opposite to that produced in the tin halide reactions. Therefore, it is concluded that the transmetallation–isomerization process is fast compared with addition of the allenyltributylstannane to the aldehyde and that isomerization of the transient propargylic indium chloride is also fast compared with its addition to the aldehyde substrate. The stereochemical outcome requires that the transmetallation proceeds mainly with net retention of configuration. A possible pathway for this process is illustrateds in Scheme 9.33. It is assumed that the indium chloride dimer is the source of electrophilic indium, but a solvated monomer could also be envisioned. Presumably steric interactions prevent a *syn* 1,3-In transfer along the lines suggested for the analogous transmetallation of allenylstannanes with $SnCl_4$ (Scheme 9.21).

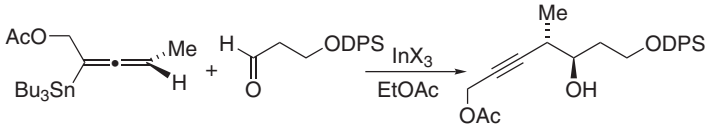


(9.139)



Scheme 9.33 Hypothetical pathway for the transmetallation of allenyltributyltin reagents with $InCl_3$.

The transmetallations appear to be rapid but the ensuing aldehyde addition is relatively slow. Furthermore, *anti* adducts of only low or modest *ee* are obtained. Evidently chiral allenylindium chlorides are more prone to racemize than the corresponding allenyltin species. Racemization was less extensive with $InBr_3$ and InI_3 (Table 9.51).

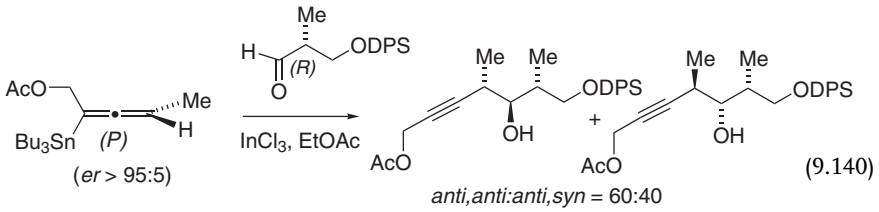


X	T, °C	Time, h	Yield, %	*ee*, %
Cl	rt	0.5	75	20
Br	rt	0.25	60	75
Br	-78...rt	10	83	40
I	rt	0.5	60	80

Table 9.51 Enantioselectivity of allenylindium additions.

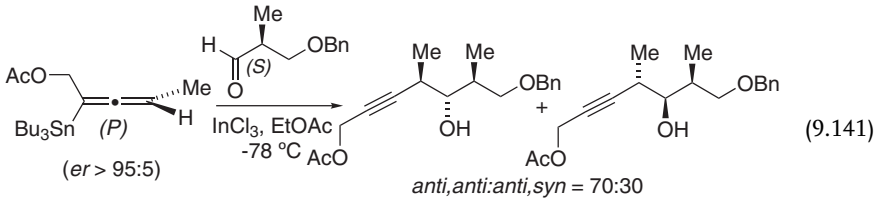
Insight regarding the configurational stability of the putative allenylindium intermediates was obtained from experiments employing (*R*)-α-methyl-β-ODPS-propanal (Eq. 9.140). Addition of the allenylindium chloride derived from a (*P*)-allenylstannane of >95% enantiopurity yielded a 60:40 mixture of *anti,anti* and *anti,syn* adducts. When the racemic allenylstannane was employed in the foregoing addition, a 55:45 mixture of these two adducts was formed. Use of the (*S*)-aldehyde led to a

40:60 mixture of the *anti,anti* and *anti,syn* adducts. Hence it can be concluded that (1) substrate control (Felkin–Anh or chelation) is only modest in these reactions and (2) the rate of racemization is only slightly less than the rate of addition.



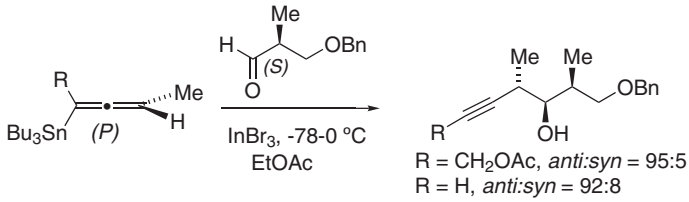
(9.140)

Addition of the indium reagent derived from the foregoing (*P*)-allenylstannane to β-benzyloxy-α-methylpropanal as the aldehyde substrate at low temperature afforded a 70:30 mixture of *anti,anti* and *anti,syn* adducts (Eq. 9.141). The improved diastereoselectivity in this case can be attributed to substrate control, reflecting the chelating ability of an OBn versus an ODPS group. The lower temperature may also account for the improved diasteroselectivity.



(9.141)

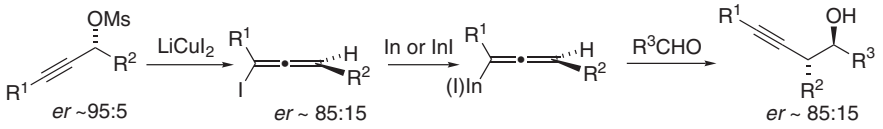
Significantly higher diastereoselectivity was observed when $InBr_3$ was employed as the transmetallating species (Eq. 9.142). These additions were appeciably faster than those employing $InCl_3$.



(9.142)

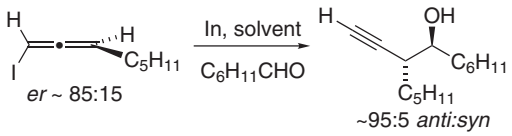
9.11.1
Metal–Halogen Exchange

Allenyl iodides can be prepared from propargylic mesylates by S_N2' displacement with $LiCuI_2$ (Eq. 9.143) [118]. The reaction proceeds primarily by an *anti* pathway with slight racemization. Metallation of these iodides with powdered indium in various donating solvents leads to transient allenylindium intermediates which react in situ with aldehydes to afford *anti* homopropargylic alcohols (Table 9.52). Additions



(9.143)

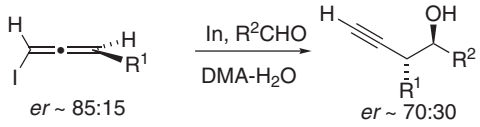
to α-branched aldehydes are highly *anti* selective whereas additions to unbranched or conjugated aldehydes are only modestly so (Table 9.53). The metallation and ensuing addition reactions proceed with negligible racemization.



Solvent	Yield, %	*er*
THF-5%H_2O	96	85:15
DMF-5%H_2O	95	75:25
DMA-5%H_2O	98	85:15
THF	99 [a)]	85:15

[a)] $InBr_3$/Zn at -78 °C

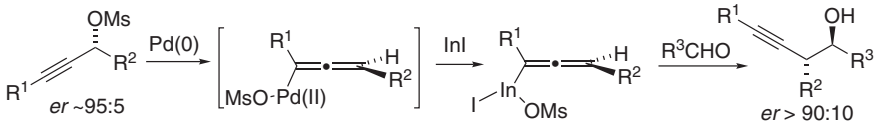
Table 9.52 Effect of solvent on enantioselectivity of allenylindium additions.



R^1	R^2	Yield, %	*anti:syn*
C_5H_{11}	C_6H_{11}	98	95:5
C_5H_{11}	C_6H_{13}	91	87:13
C_5H_{11}	(E)-BuCH=CH	88	71:29
C_5H_{11}	2-furyl	96	52:48
CH_3	C_6H_{11}	84	95:5
CH_3	(E)-BuCH=CH	89	69:31

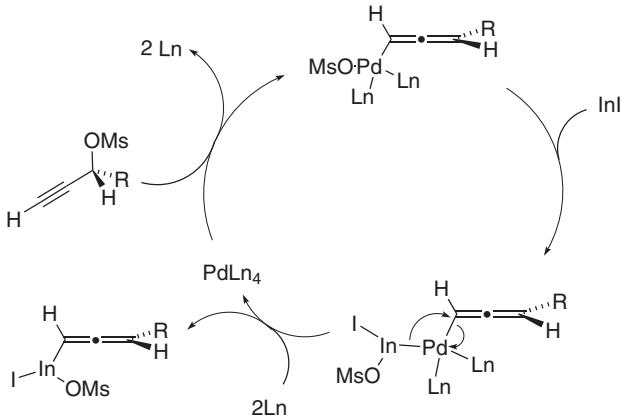
Table 9.53 Diastereoselectivity of allenylindium additions.

A more satisfactory sequence, which also starts with enantioenriched propargylic mesylates, generates the allenylindium intermediate by oxidative transmetallation of an allenylpalladium precursor with InI. This catalytic process takes place in the presence of an aldehyde. The reaction employs 5–10 mol% of the palladium catalyst and a stoichiometric quantity of InI. Based on the stereochemistry of the starting



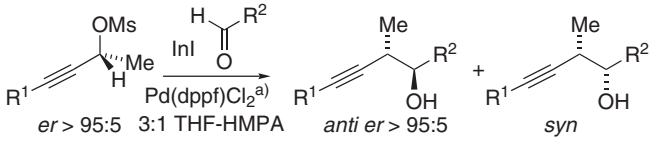
(9.144)

propargylic mesylate and the *anti* homopropargylic alcohol product, it can be surmised that palladation occurs by an *anti* S_E2' process and the ensuing transmetallation occurs with retention of configuration (Eq. 9.144, Scheme 9.34).



Scheme 9.34 Oxidative transmetallation of allenylpalladium intermediates with InI.

Not surprisingly, these additions favor the *anti* products in ratios that reflect the steric requirement of the aldehyde substituent (Table 9.54). Additions to chiral α-methyl-β-oxygenated propanals show remarkable reagent control (Eq. 9.145). The *anti* adducts are formed to the exclusion of the *syn* diastereomers when enantiomeric mesylates are employed with the (*R*)-aldehyde.

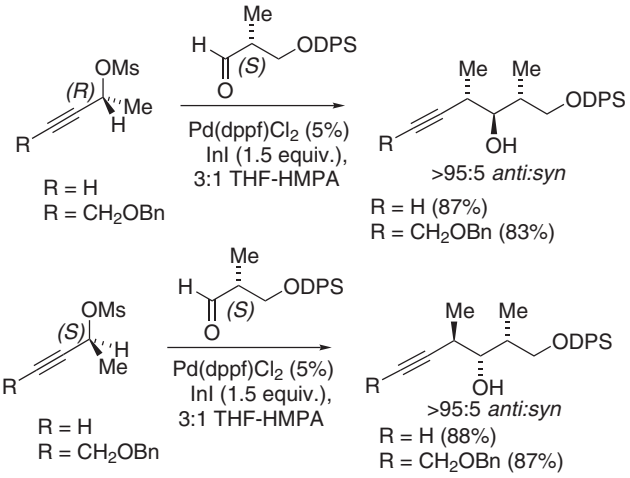


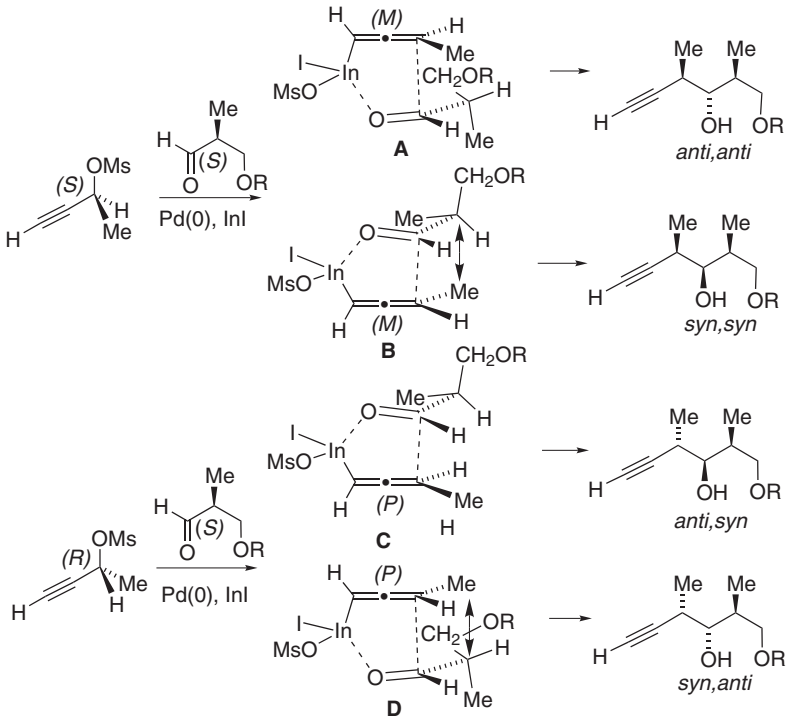
R^1	R^2	Yield, %	*anti:syn*
H	cC_6H_{11}	76	95:5
H	C_6H_{13}	73	82:18
H	1-Heptynyl	62	72:28
CH_2OBn	cC_6H_{11}	81	96:4
CH_2OBn	C_6H_{13}	72	82:18

[a] dppf = diphenylphosphinoferrocene.

Table 9.54 Additions of transient chiral allenylindium reagents to representative achiral aldehydes.

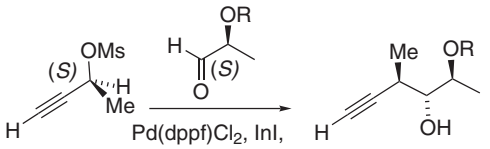
Likely transition states for these additions are shown in Scheme 9.35. The normally favored Felkin–Anh arrangement in the *M*/*S* pairing **B** is strongly disfavored



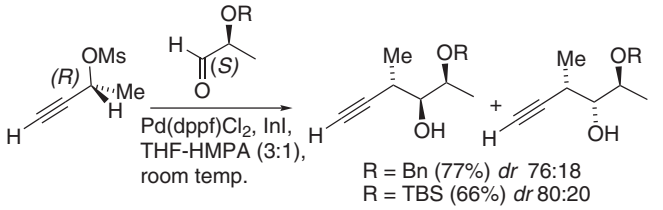


Scheme 9.35 Transition states for additions of allenyl-M reagents to α-methyl-β-oxygenated aldehydes.

by an eclipsing interaction between the aldehyde substituent and the methyl group of the allene (arrow). In the *P*/*S* pairing **C**, Felkin–Anh control is possible without such an eclipsing interaction.

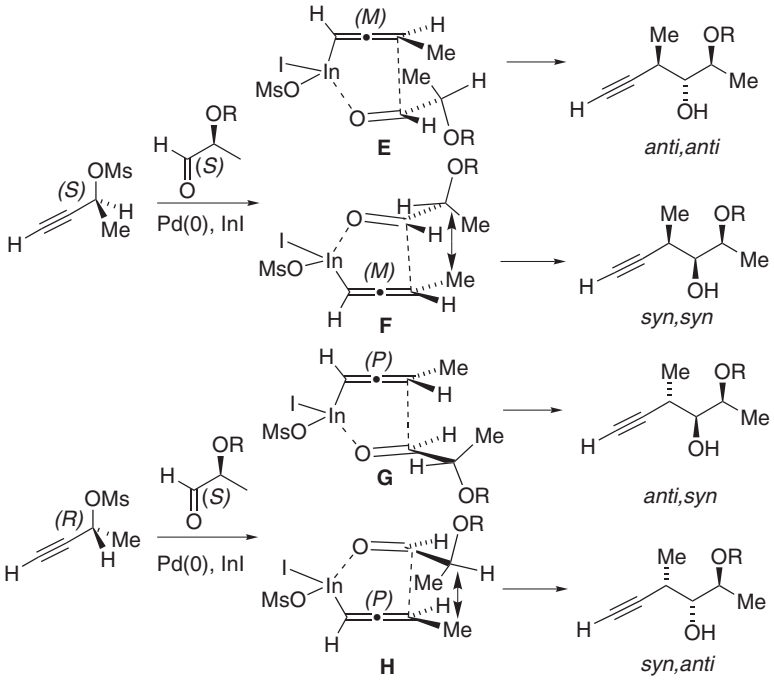


(9.146)



(9.147)

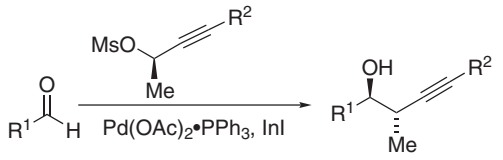
Additions to chiral α-oxygenated aldehydes exhibit more typical matching/mismatching behavior [114]. The *M*/*S* pairing of aldehyde and mesylate leads to *anti,-anti* adducts exclusively (Eq. 9.146). The *P*/*S* pairing is mismatched and both *anti,syn* and *syn,anti* adducts are formed, with the former predominant (Eq. 9.147).



Scheme 9.36 Transition states for additions of allenyl indium reagents to a-oxygenated aldehydes.

Possible transition states for these additions are pictured in Scheme 9.36. The matched *M*/*S* pairing can react through the Felkin–Anh and sterically favored arrangement **E** to yield the *anti,anti* adduct, whereas the Felkin–Anh array **H** of the *P*/*S* pairing is disfavored by steric eclipsing. This effect is absent in the alternative arrangement **G** for the *P*/*S* combination. Although more favorable than **H**, the arrangement in **G** places the aldehyde methyl substituent into the trajectory of the attacking allenyl group. Hence the *P*/*S* pairing is mismatched.

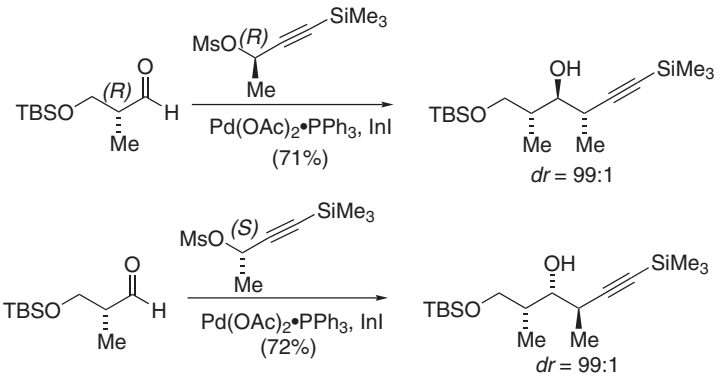
Propargylic mesylates show only modest diastereoselectivity in Pd(0)/InI-mediated additions to unbranched and conjugated aldehydes [118]. However, the presence of a terminal trimethylsilyl substituent on the alkynyl grouping greatly improves the diastereoselectivity of such additions (Table 9.55) [119].



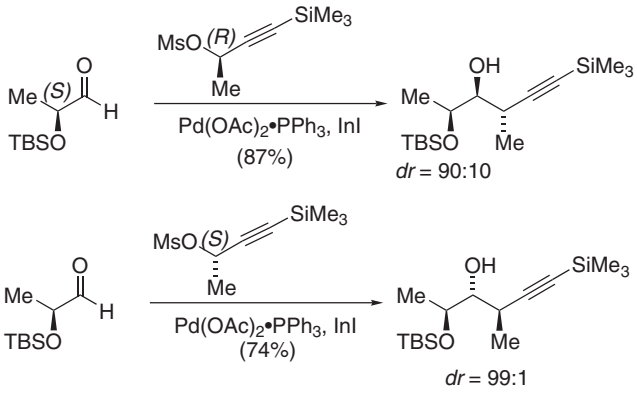
	R^2 = TMS		R^2 = H	
R^1	Yield, %	*anti:syn*	Yield, %	*anti:syn*
cC_6H_{11}	75	>99:1	86	95:5
*i*Pr	89	98:2	-	-
$Ph(CH_2)_2$	69	>99:1	71	77:23
C_6H_{13}	80	98:2	71	93:7
(E)-BuCH=CH	73	99:1	78	60:40

Table 9.55 Additions of silylated and non-silylated allenylindium reagents to achiral aldehydes.

The silyl effect is also seen for chiral α-methyl-β-silyloxypropanals (Eq. 9.148), although the improvement from >95:5 (Eq. 9.145) to 99:1 is not dramatic. Additions to chiral α-oxygenated aldehydes are also more diastereoselective with the TMS-substituted reagent (Eq. 9.149). The origin of this effect remains to be discovered.

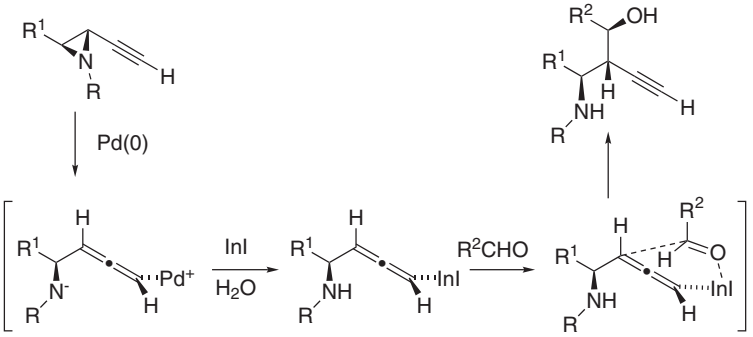


(9.148)



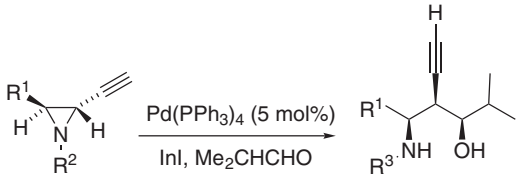
(9.149)

Sulfonic amides of alkynylaziridines can also be converted to allenylindium reagents by oxidative transmetallation of transient allenylpalladium complexes. When the reaction is perfomed in the presence of an aldehyde the expected adducts are produced stereoselectively (Eq. 9.150) [120].



(9.150)

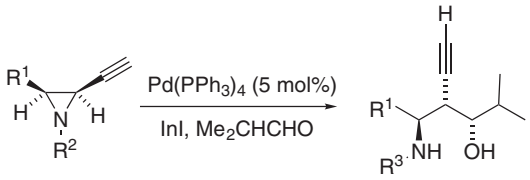
The allenylindium intermediates are prepared by treatment of the aziridines with $Pd(PPh_3)_4$ in THF–HMPA containing 1 equivalent of water. In the presence of isobutyraldehyde the expected adducts were formed with excellent diastereoselectivity (Tables 9.56 and 9.57). Interestingly, the reaction did not proceed in the absence of water. It is suggested that water is needed to protonate the sulfonamide anion of the initially formed allenyl palladium species (Eq. 9.150).



R^1	R^2	Yield, %
*i*Pr	Mts	42
Bn	Mts	62
Bn	Mtr	57
$TBSOCH_2$	Mts	68
*i*Pr	Boc	43

Mts = 2,4,6-$Me_3C_6H_2SO_2$, Mtr = 4-MeO-2,3,6-$Me_3C_6HSO_2$

Table 9.56 In situ formation of allenylindium reagents from *trans*-alkynylaziridines and their addition to isobutyraldehyde.

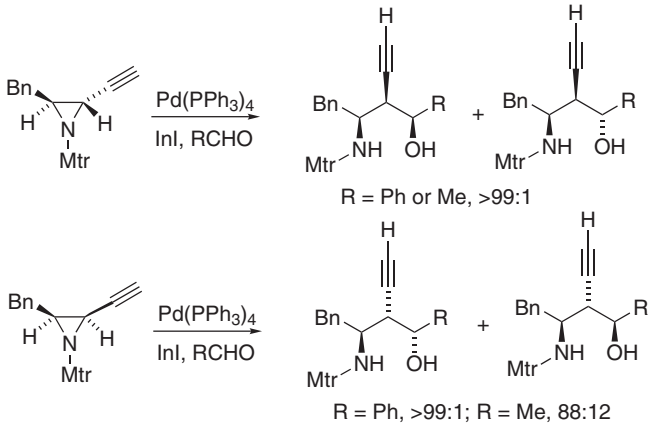


R^1	R^2	Yield, %
*i*Pr	Mts	59
Bn	Mtr	62
$TBSOCH_2$	Mts	70
*i*Pr	Boc	45

Mts = 2,4,6-$Me_3C_6H_2SO_2$, Mtr = 4-MeO-2,3,6-$Me_3C_6HSO_2$

Table 9.57 In situ formation of allenylindium reagents from *cis*-alkynylaziridines and their addition to isobutyraldehyde.

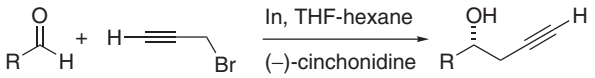
In the foregoing examples, the reaction proceeds through a highly organized transition state in which the aldehyde substituent and the allenyl component adopt an *anti* orientation. The formation of the *anti* isomer is in accord with a reaction pathway in which the intermediate allenylindium reagent is formed with inversion and the subsequent addition proceeds through a cyclic transition state in which the aldehyde and allenyl substituents adopt an *anti* arrangement (Eq. 9.150). Reaction of the benzyl-substituted *cis*- and *trans*-aziridines with benzaldehyde was also highly *anti* selective. Interestingly, the indium reagent derived from the *trans*-aziridine afforded the *anti* isomer upon addition to acetaldehyde but reaction with the corresponding reagent obtained from the *cis*-aziridine led to an 88:12 mixture of *anti* and *syn* adducts (Eq.151).



(9.151)

9.11.2
Chiral Lewis Acids

In situ formation of allenylindium bromide in the presence of (+)- or (–)-cinchonidine and subsequent addition of various aldehydes provides a direct route to homopropargylic alcohols of modest enantiopurity (Table 9.58) [121]. The additions were conducted in strictly anhydrous THF–hexanes as traces of water resulted in diminished product yields. Allenylcarbinols were not detected in these reactions.

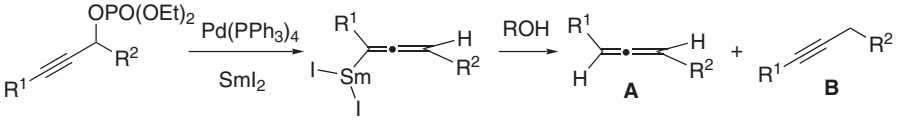


R	*er*	Yield, %
Ph	86:14	71
PhCH=CH	68:32	76
$PhCH_2CH_2$	88:22	63
C_8H_{17}	84:16	70
C_6H_{11}	83:17	72
CCl_3	92:8	49

Table 9.58 Enantioselective in situ addition of allenylindium bromide to aldehydes mediated by (–)-cinhonidine.

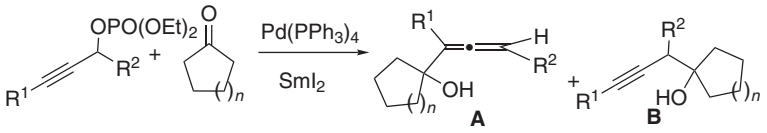
9.12
Miscellaneous Allenylmetal Reagents

In situ transmetallation of allenylpalladium intermediates with SmI_2 provides a route to allenylsamarium reagents [123]. These undergo protonolysis with alcohols to afford mainly allenes (Table 9.59). Additions to ketones yield either allenylcarbinols (**A**) or homopropargylic alcohols (**B**) depending on the allene substituents (Table 9.60).



R	R^1	R^2	Yield, %	**A**:**B**
*i*Pr	Ph	Et	66	98:2
*t*Bu	Ph	Et	80	>99:1
*i*Pr	Bu	$PhCH_2CH_2$	84	>99:1
*t*Bu	Bu	$PhCH_2CH_2$	89	>99:1

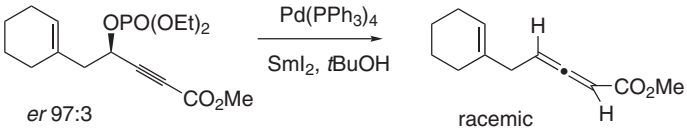
Table 9.59 Protonolysis of allenylsamarium iodide reagents.



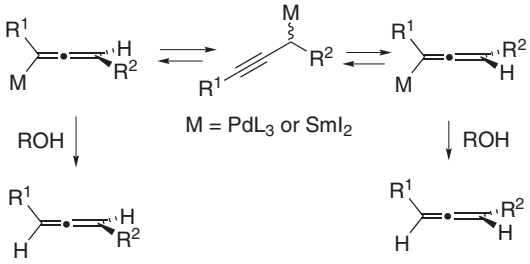
R^1	R^2	*n*	Yield, %	**A**:**B**
Ph	Et	2	71	94:6
Bu	Me	2	49	94:6
Bu	H	2	84	2:98
Bu	H	1	45	4:96

Table 9.60 Addition of allenylsamarium reagents to ketones.

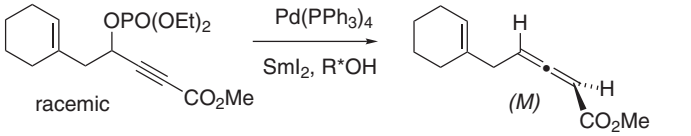
An enantioenriched propargylic phosphate was converted to a racemic allene under the foregoing reaction conditions (Eq. 9.152) [124]. It is proposed that the racemization pathway involves equilibration of the allenyl enantiomers via a propargylic intermediate (Scheme 9.37). Both the allenylpalladium precursor and the allenylsamarium reagent could racemize by this pathway. When a chiral alcohol was used as the proton source, the reaction gave rise to enantiomerically enriched allenes (Table 9.61) A samarium alcohol complex is thought to direct the protonolysis (Scheme 9.38).



(9.152)



Scheme 9.37 Proposed racemization pathway for allenylsamarium intermediates.



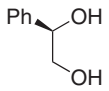
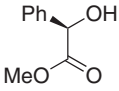
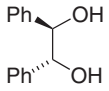
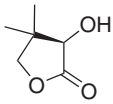
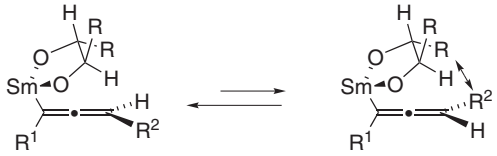
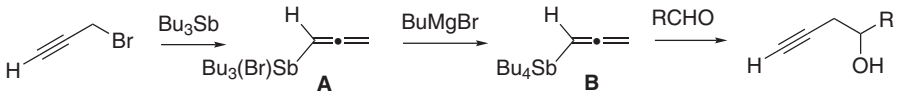
R*OH	*er* of allene	Yield, %	R*OH	*er* of allene	Yield, %
	56:44	86		84:16	71
	93:7	71		97:3	68

Table 9.61 Dynamic kinetic protonation of chiral racemic allenylsamarium intermediates.



Scheme 9.38 Proposed ligand-directed equilibration of allenylsamarium reagents.

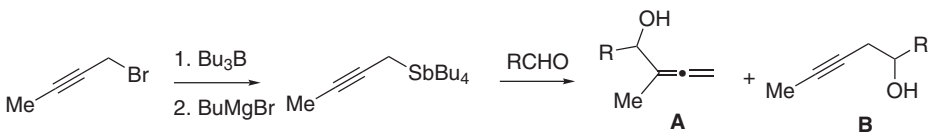
Propargyl bromide reacts with tributylstibine to form an intermediate allenylstibinate (**A**) (Table 9.62) [124]. This intermediate fails to react with aldehydes at temperatures as high as 120 °C. However, addition of BuMgBr produces a reactive allenylantimony reagent (**B**), which reacts with aldehydes to yield homopropargylic alcohols.



R	Yield, %
Ph	91
*p*MeC$_6$H$_4$	90
*p*MeOC$_6$H$_4$	78
*p*ClC$_6$H$_4$	92
PhCH=CH	90
C$_9$H$_{19}$	89

Table 9.62 Synthesis of homopropargylic alcohols from an allenylantimony reagent.

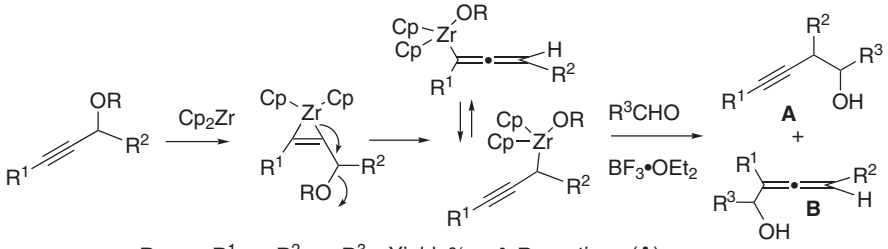
In contrast, when 1-bromo-2-butyne is employed in this sequence, allenylcarbinols are the major adducts (Table 9.63). In the former case, the allenyl antimony reagent is presumed to prevail whereas in the latter sequence, the terminal Me substituent causes the equilibrium to shift toward the sterically favored propargylic isomer.



R	Yield, %	**A**:**B**
Ph	89	97:3
*p*MeC$_6$H$_4$	86	97:3
*p*ClC$_6$H$_4$	86	97:3
C$_6$H$_{11}$	87	65:35
C$_8$H$_{17}$	85	77:23

Table 9.63 Synthesis of allenylcarbinols from a propargylic antimony reagent.

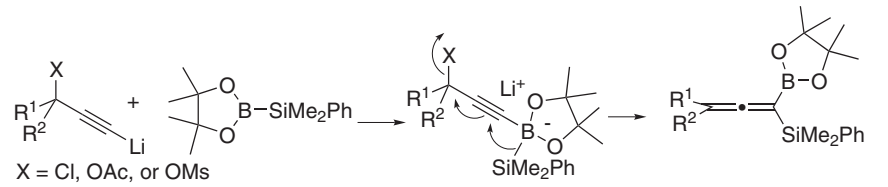
In a process analogous to that described for allenyltitanium compounds, Cp$_2$Zr reacts with propargylic ethers to afford allenylzirconium reagents [126]. In situ additions to aldehydes yield mixtures of propargylic and allenic adducts **A** and **B** with the former predominant (Table 9.64). The *anti* adduct **A** is the major propargylic product of these additions.



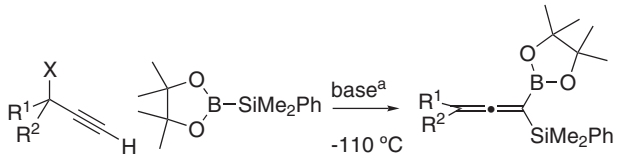
R	R^1	R^2	R^3	Yield, %	**A:B**	*anti:syn* (**A**)
Bn	Ph	Me	Ph	80	86:14	75:25
Bn	Ph	Me	C_6H_{11}	76	94:6	99:1
Me	Ph	Me	C_6H_{11}	65	95:5	97:3
TBS	Ph	Me	C_6H_{11}	73	>98:2	96:4
Bn	Ph	*i*Pr	Ph	89	98:2	75:25
Bn	Ph	*i*Pr	C_6H_{11}	86	>98:2	98:2
Bn	Me_3Si	Me	Ph	49	80:20	67:33
Bn	Me_3Si	Me	C_6H_{11}	49	78:22	83:17

Table 9.64 In situ formation of allenylzirconium reagents and addition to aldehydes.

Reaction of lithiopropargylic halides, acetates or mesylates with a silylboronate reagent has recently been reported to yield silylated allenylboronates. [127]. The reaction is thought to proceed by formation of a lithioboronate intermediate followed by migration of the silyl substitiuent to the adjacent alkynyl center with loss of the X leaving group along the lines in Scheme 9.39. The pathway is analogous to that proposed for the formation of alkyl-substituted allenylboranes from lithiated propargylic acetates (Eq. 9.17). The reaction is conducted at –110 °C. The lithioalkyne is either preformed from BuLi and the alkyne followed by addition of the silylboronate reagent or in situ with LDA in the presence of the two reactants. In the latter case pre-equilibration of the propargylic mesylate with TMSCl before addition of LDA enhances the reaction rate and leads to increased product yields (Table 9.65).



Scheme 9.39 Proposed pathway for the addition of a silylboronate reagent to lithioalkynes.

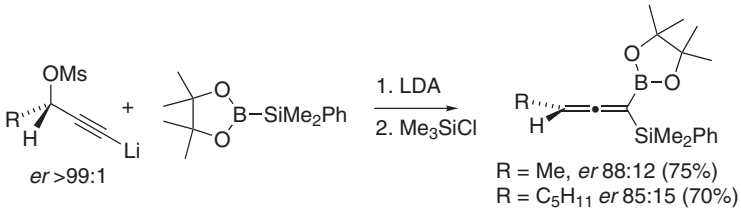


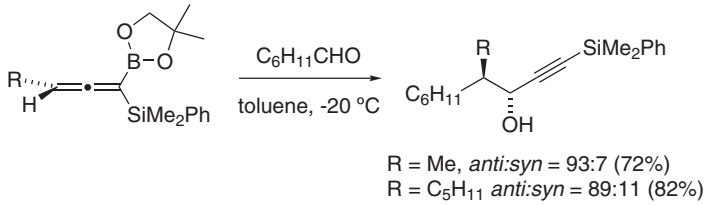
R^1	R^2	X	Base[a)]	Yield, %
Me	Me	Cl	BuLi	70
Me	Me	OAc	BuLi	77
$(CH_2)_5$		OAc	BuLi	53
$(CH_2)_5$		OAc	LDA	60
Ph	H	Cl	LDA	52
Me	H	Cl	LDA	52
Me	H	OMs	LDA[b)]	75

[a)] BuLi was added to the alkyne followed by the boronate reagent. LDA was added to a mixture of the alkyne and the boronate reagent.
[b)] Me_3SiCl was added to the mixture of boronate and alkyne before LDA was introduced.

Table 9.65 Synthesis of silylated allenylboronates from propargylic halides and esters.

Evidence for the mainly S_N2' pathway for the silyl migration was obtained from reactions of enantioenriched mesylates (Eq. 9.153). The connfigurations of the allenylboronate intermediates were deduced from their reactions with cyclohexanecarboxaldehyde to afford the *anti* products of known configuration (Eq. 9.154). It is assumed that these reactions proced by way of a cyclic transition state.





Acknowledgment

Thanks are due to Craig Gibeau, Miami University, for providing ChemDraw structures for the allenylzinc and -palladium sections of this chapter.

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III
Reactions of Allenes

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10
Ionic Additions to Allenes

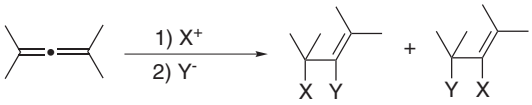
Shengming Ma

In this chapter, both intermolecular and intramolecular electrophilic [1] and nucleophilic additions [2, 3] to allenes will be discussed. For electrophilic addition, the regio- and stereoselectivity depend on the steric and electronic effects of the substituents on the allenes and the nature of the electrophiles. However, nucleophilic addition usually occurs at the central carbon atom with very limited exceptions.

10.1
Unfunctionalized Allenes

10.1.1
Electrophilic Additions

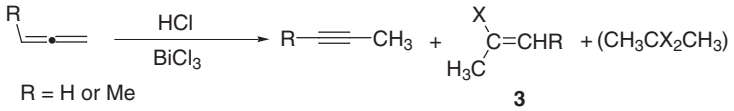
The electrophilic addition of alkyl-substituted allenes may afford terminal attack and center attack products, depending on the structures of allenes and electrophiles (Scheme 10.1).



1 **2**

Scheme 10.1

The reaction of propadiene or 1,2-butadiene with HX afforded the product of a terminal attack **3** [4].



3

Scheme 10.2

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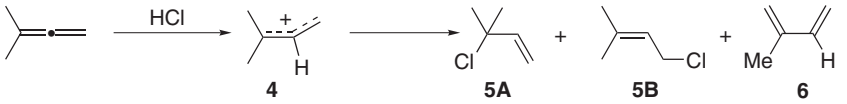
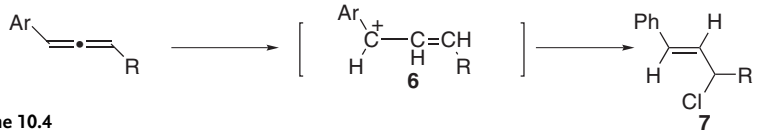
However, it is interesting that the corresponding reaction of 3-methyl-1,2-butadiene affords the corresponding center attack products allylic chlorides **5A**/**5B** and 2-methyl-1,3-butadiene **6**, probably owing to the strong stabilization effect of the two methyl groups on the cationic center in **4** [4].



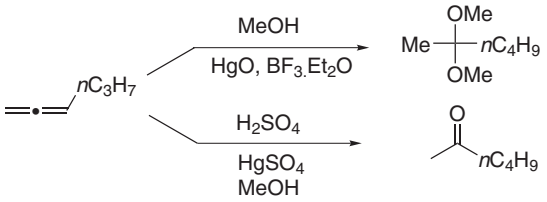
Scheme 10.3

The hydrochlorination of 1-aryl-1,2-alkadiene gives *trans*-1-alkyl-3-aryl-2-propenyl chloride for the same reasons [5].



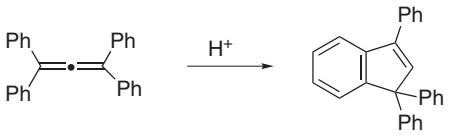
Scheme 10.4

Under the catalysis of mercuric oxide and boron trifluoride–diethyl ether, the reaction of methanol with 1,2-hexadiene afforded 2,2-dimethoxyhexane [6]. Hydration with sulfuric acid led to methyl *n*-butyl ketone [6].



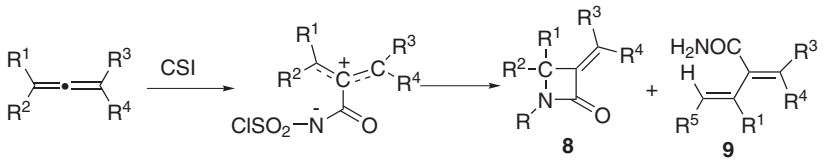
Scheme 10.5

Using a strong acid, 1,1,3,3-tetraphenylallene afforded 1,1,3-triphenylindene by an electrophilic *ortho* attack of the intermediate allyl cation [7].



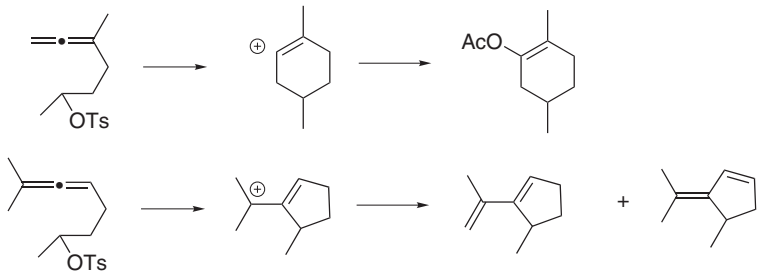
Scheme 10.6

Simple allenes can also react with chlorosulfonyl isocyanate (CSI) to afford α-alkylidene-β-lactams **8** and 2-carboxamido-1,3-butadienes **9** [8].



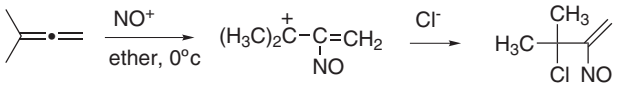
Scheme 10.7

Solvolysis of γ-allenic tosylates afforded cyclic compounds with the regioselectivity determined by the steric effect of the two C=C bonds of the allene moiety [9].



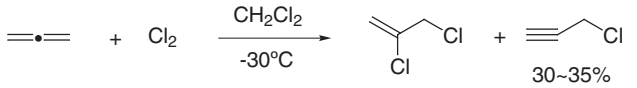
Scheme 10.8

The electrophilic addition of nitrosyl chloride with 3-methyl-1,2-butadiene at 0 °C afforded 2-nitroso-3-chloro-3-methyl-1-butene, in which the nitrosyl group was connected to the central carbon atom [10].



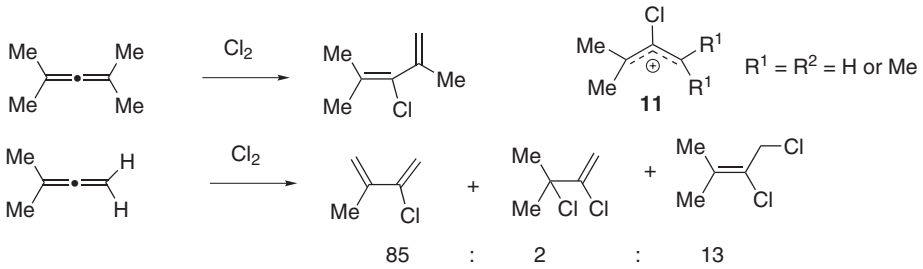
Scheme 10.9 **10**

Chlorination of simple allenes in CH_2Cl_2 with or without BF_3 afforded a mixture of 2,3-dichloro-1-propene and propargyl chloride [11, 12].



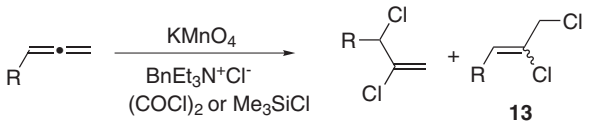
Scheme 10.10

Dichlorination of tetramethylallene afforded 3-chloro-2,4-dimethyl-1,3-pentadiene as the single product, whereas the same reaction of 1,1-dimethylallene yielded a mixture of 2-chloro-3-methyl-1,3-butadiene, 2,3-dichloro-3-methyl-1-butene and 1,2-dichloro-3-methyl-2-butene, indicating the intermediacy of the 2-chloroallylic cationic intermediate **11** [13].



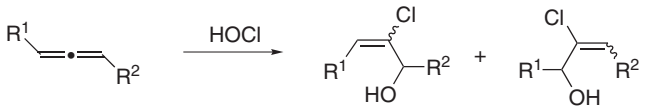
Scheme 10.11

Boyes and Wild reported the manganese-mediated regioselective chlorination of allenes [14]. For the dichlorination of cyclo-1,2-nonadiene, the dichloride was obtained as the major product whereas the reaction of monosubstituted allene afforded a mixture of regiosomers of the dichlorination products with 2,3-dichloro-1-alkene **12** being the major one. The yield with oxalyl chloride is better than that with TMSCl.



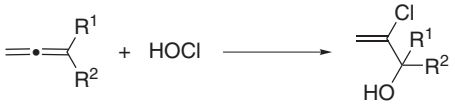
Scheme 10.12

The reaction of HOCl with allenes also yielded a mixture of regioisomeric allylic alcohols with the chlorine atom connected to the central carbon atom and the OH connected to the more substituted carbon atom [15].



Scheme 10.13

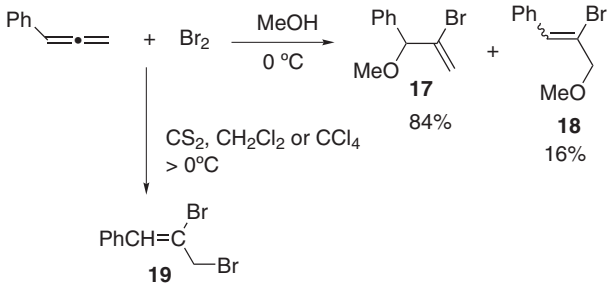
Even the reaction with 1,1-disubstituted allenes delivered 2-chloroallyl alcohols **16** with the hydroxyl group connected to the more substituted terminus [15].



Scheme 10.14

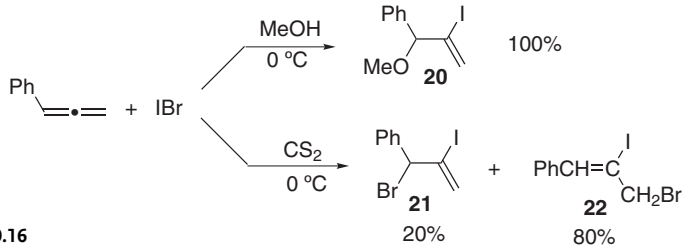
The bromination of phenyl-1,2-propadiene in MeOH at 0 °C led to a regioisomeric mixture of 2-bromoallylic methyl ethers **17** and **18** with the product **17**, in which the methoxy group was attached to the benzylic position, being the major route (Scheme 10.15) [16].

However, in a non-polar solvent such as CS_2 only 2,3-dibromo-1-phenyl-1-propene was formed. A control experiment indicated that at –70 °C 2,3-dibromo-3-phenyl-1-propene was also formed, which would isomerize to 2,3-dibromo-1-phenyl-1-propene **19** at higher temperatures [16].



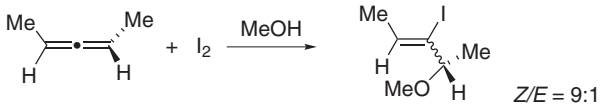
Scheme 10.15

The reaction of phenyl-1,2-propadiene with iodine bromide in MeOH afforded a 100% yield of 2-iodo-3-phenyl-3-methoxy-1-propene whereas the reaction in CS_2 at 0 °C provided a 1:4 mixture of 2-iodo-3-phenyl-3-bromo-1-propene and 1-phenyl-2-iodo-3-bromo-1-propene [16]. The corresponding chlorination shows a lower regioselectivity.



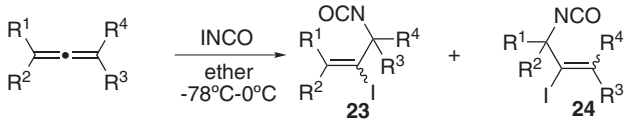
Scheme 10.16

The reaction of 2,3-pentadiene with I_2 in MeOH afforded a 9:1 *Z*:*E* ratio of 3-iodo-4-methoxy-2-pentene [17].



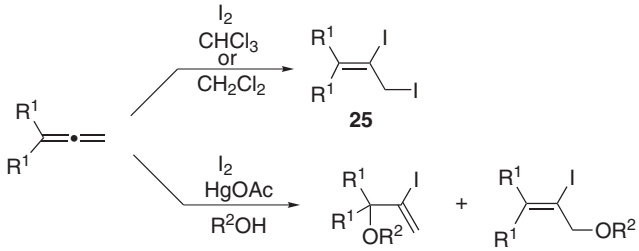
Scheme 10.17

The reaction with iodine isocyante (INCO) produced a mixture of 2-iodoallylic isocyantes **23** and **24** [18]. The ratio of **23** and **24** depends on the reaction temperature and the structures of allenes. In the case of 1,1-dimethylallene, the reaction affords preferentially the diiodination product of the unsubstituted C=C bond.



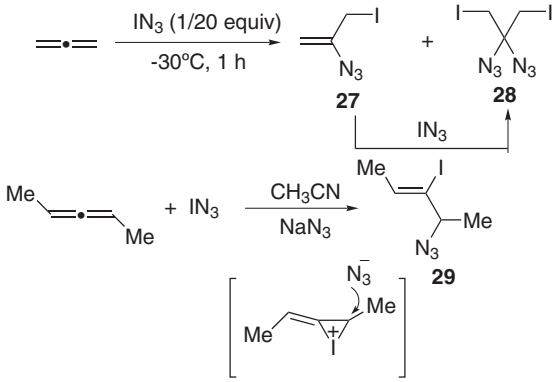
Scheme 10.18

Direct reaction of I_2 with allenes formed 2-iodoallylic iodide **25** in $CHCl_3$ or CH_2Cl_2 whereas in the presence of $Hg(OAc)_2$ in MeOH the reaction afforded a regioisomeric mixture of 2-iodoallylic ethers **26A** and **26B** [19].



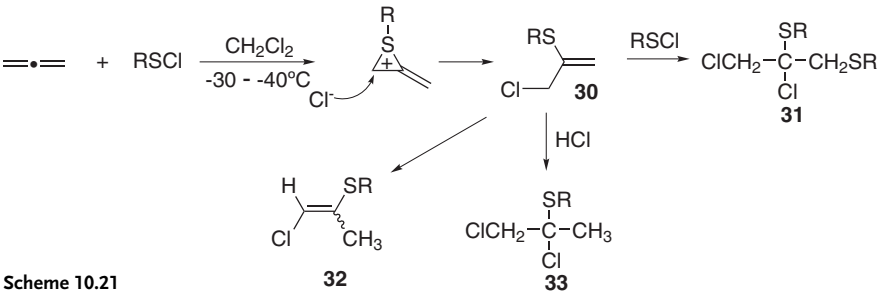
Scheme 10.19

IN_3 can also react with propadiene to afford 3-iodovinylic azide **27** [20], which further reacted with IN_3 to afford the 2:1 adduct **28**. In this reaction the regioselectivity is unique. In contrast, the reaction of a substituted allene, i.e. 2,3-pentadiene, afforded the normal product **29**.



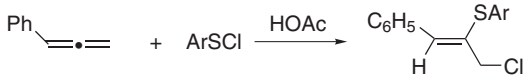
Scheme 10.20

Sulfenyl chloride reacts with allene to afford a mixture of 2-sulfenylallyl chloride **30**, 2:1 adduct **31**, 2-sulfenyl-1-chloro-1-propene **32** and dichloride **33** [21].



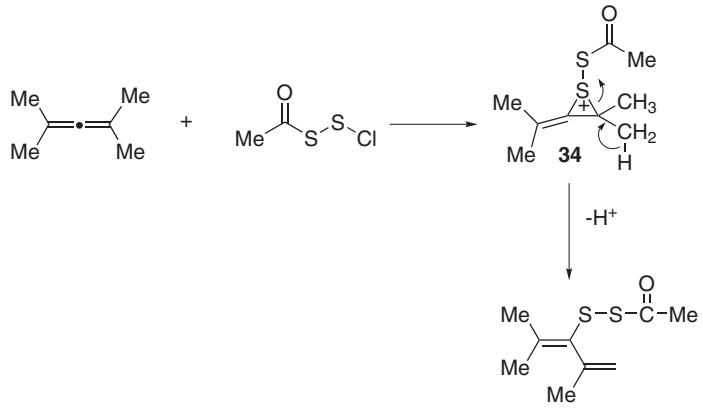
Scheme 10.21

With ArSCl 2-sulfinyl-3-phenyl-2-(*Z*)-propenyl chloride was formed [21b].



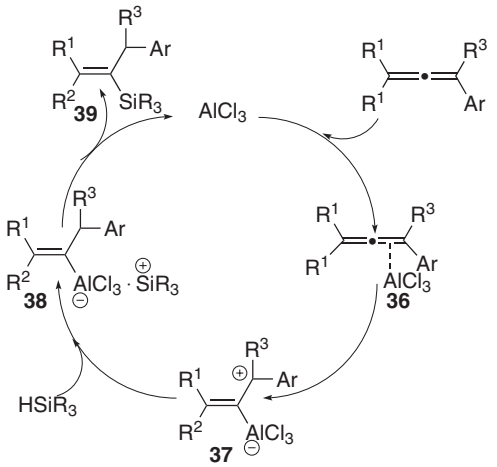
Scheme 10.22

The reaction of tetramethylallene with acetylthiosulfenyl chloride gave 2-acetylthiosulfenyl-1,3-diene **35** [21a].



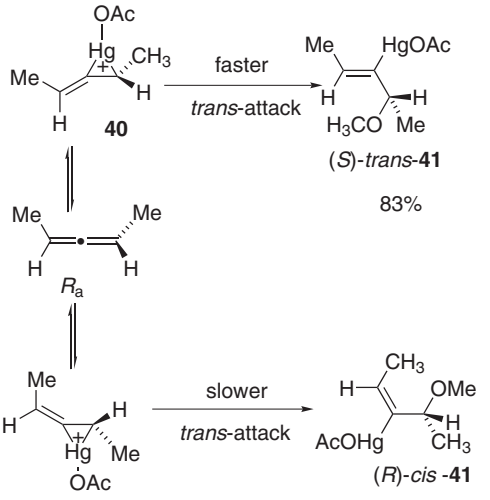
Scheme 10.23

$AlCl_3$ can interact electrophilically with allenes to form zwitterionic intermediate **37**, which would react with $HSiR_3$ to produce the (*E*)-vinylic silane **39** by a hydrosilylation [22]. This hydrosilylation shows *trans*-diastereoselectivity.



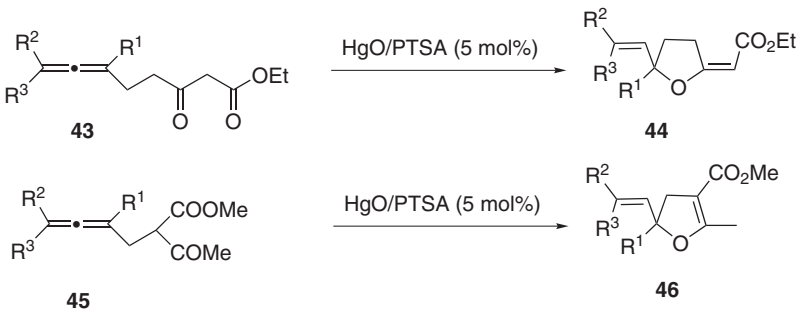
Scheme 10.24

$Hg(OAc)_2$ easily reacts with allene to yield methoxymercuration products, i.e. vinylmercury compound **41**, with the *trans* isomer being the major product. The chirality of allene was transferred into the final products, indicating the intermediacy of a σ-bridged mercurinium ion [23–26]. The stereoselectivity of this reaction was determined by the relative stability of intermediates **40** and **42** and steric hindrance for the incoming methoxy group.



Scheme 10.25

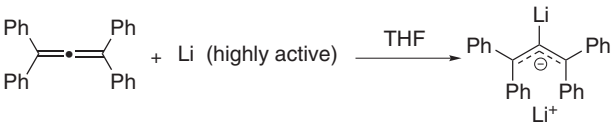
Under the catalysis of mercury(II) oxide and *p*-toluenesulfonic acid, allenic β-keto esters **43** and **45** afforded the furan derivatives **44** and **46** [27].



Scheme 10.26

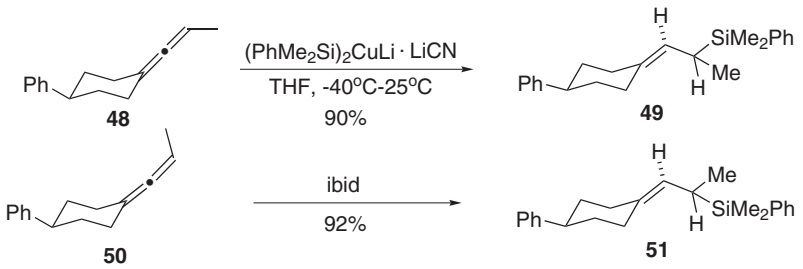
10.1.2 Nucleophilic Additions

Tetraphenylpropadiene can accept an electron from lithium to form lithium 2-lithio-1,1,3,3-tetraphenylpropenide **47** [28].



Scheme 10.27

Fleming et al. reported that allenes **48** and **50** undergo highly stereoselective silylcupration with $(PhMe_2Si)_2CuLi \cdot LiCN$, allylic silanes **49** and **51** being formed [29].

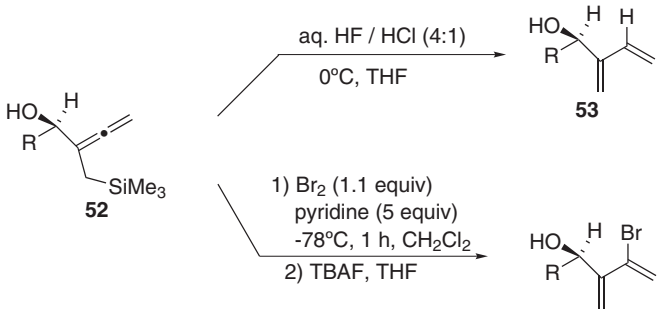


Scheme 10.28

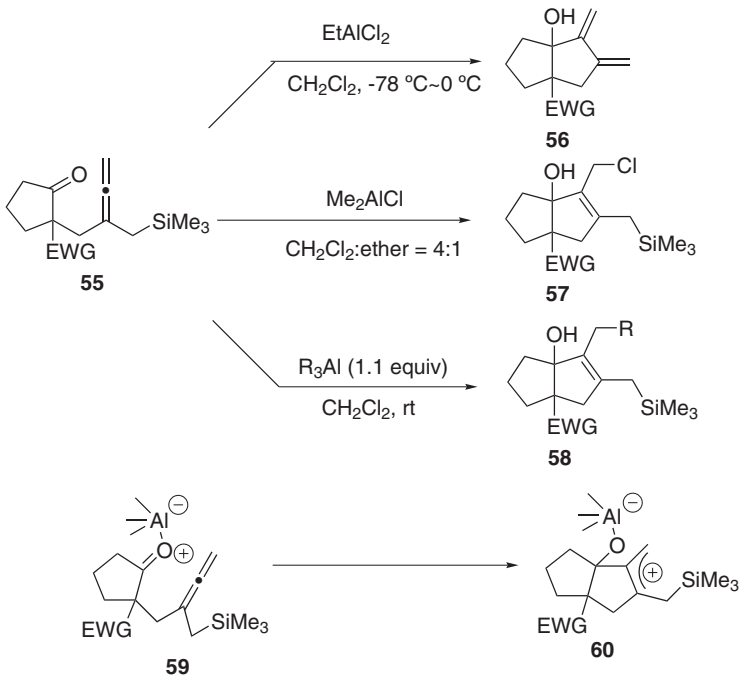
10.2
Allenylsilanes

10.2.1
Electrophilic Additions

2-(1′-Hydroxylalkyl)-2,3-butadienyltrimethylsilane **52** reacted with H^+ or Br_2 to give 2-methylene-3-alken-1-ols **53** or 2-methylene-3-bromo-3-alken-1-ols **54**, respectively [30]. Both reactions are accompanied by an elimination of the silyl substituent.



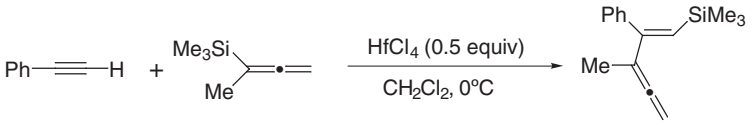
Scheme 10.29



Scheme 10.30

In the presence of an aluminum reagent, 2,3-butadienyltrimethylsilane can also accept the intramolecular electrophilic attack of the ketone–aluminum complex to afford bicyclic products via intermediate **60** [31]. The structures of the products depend on the aluminum reagent used [31].

An $HfCl_4$-catalyzed carbosilylation of phenylacetylene with 3-(trimethylsilyl)-1,2-butadiene giving the 1,3,4-pentatrienylsilane **61** was also reported [32]. In this reaction, 3-(trimethylsilyl)-1,2-butadiene may be converted by $HfCl_4$ to 2-butynyltrimethylsilane, which reacted further with an alkyne to afford the vinylic allene **61**.

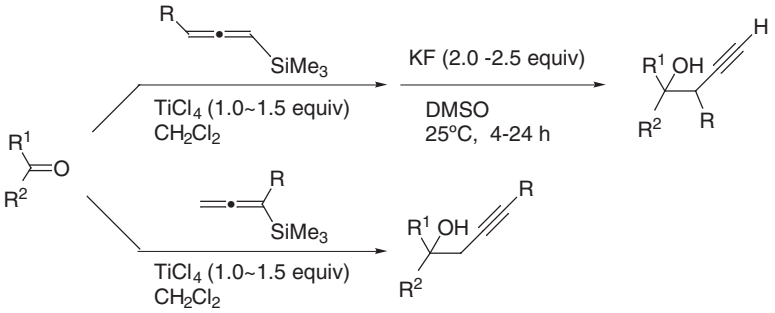


61

50%

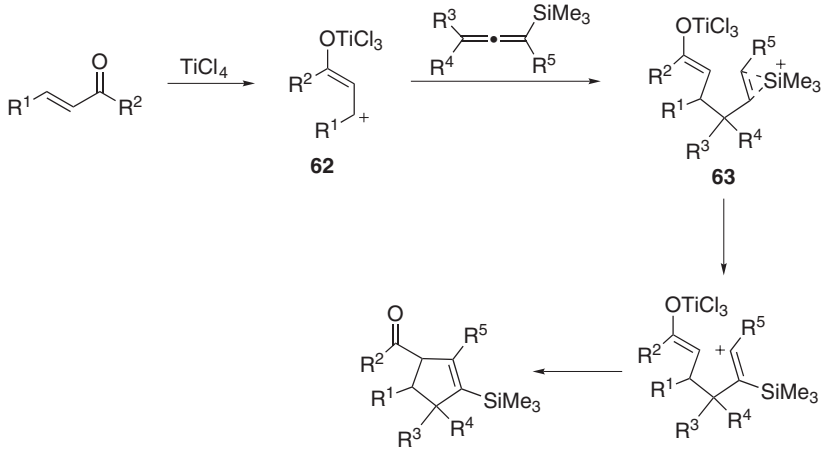
Scheme 10.31

In the presence of $TiCl_4$, 1,2-allenylsilanes can react with aldehydes, ketones or acetals to give homopropargyl alcohols or ethers [33].



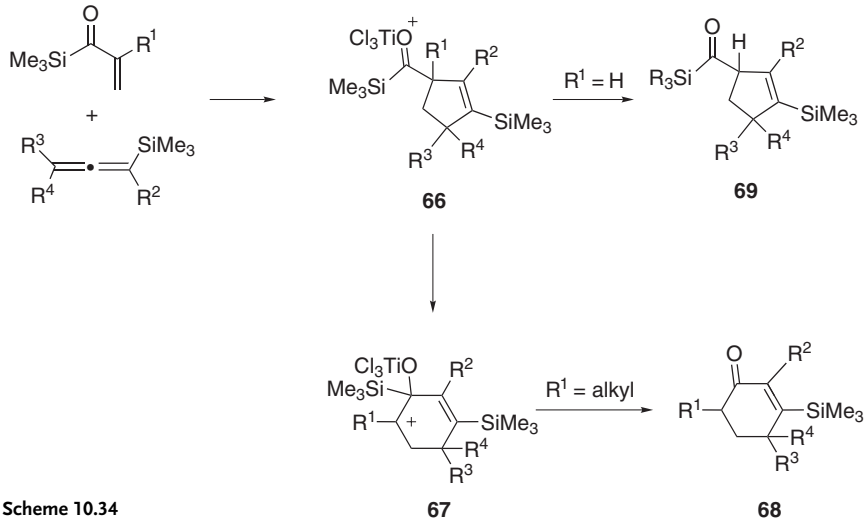
Scheme 10.32

However, the reaction of α,β-unsaturated enones, 1,2-allenylsilane and $TiCl_4$ in CH_2Cl_2 afforded five-membered vinylic silanes **65** via the formation of **62**, regioselective electrophilic addition and 1,2-shift of the trimethylsilanyl group and cyclization [34].



Scheme 10.33

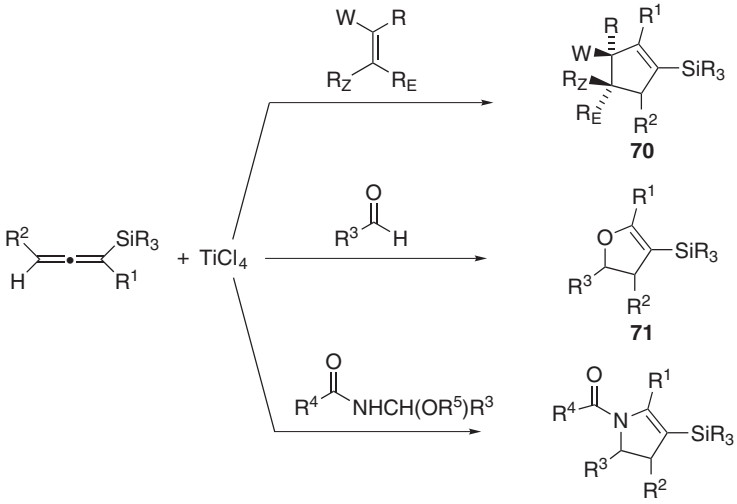
With α-substituted-α,β-unsaturated trimethylsilyl ketones, six-membered β-(trimethylsilyl)-α,β-unsaturated cyclic enones **68** were formed, probably owing to the stabilization of the R^1 group for the six-membered cationic intermediates **67** [35].



Scheme 10.34

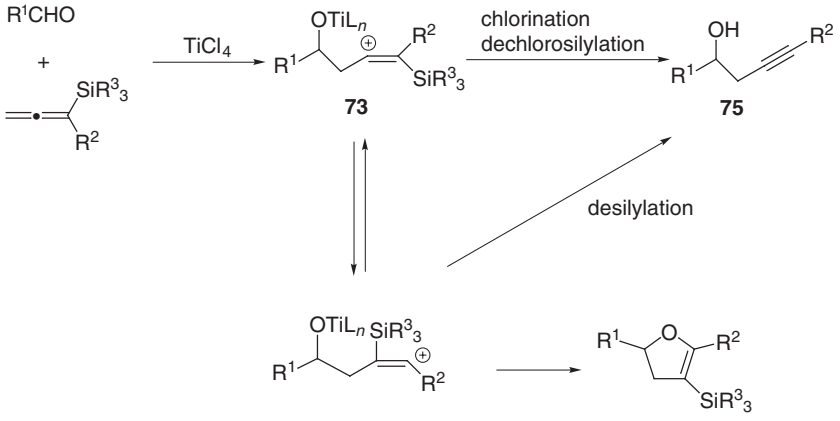
In addition to electron-deficient alkenes, under the catalysis of $TiCl_4$, 1,2-allenylsilanes can react with aldehydes or *N*-acyliminium ion to afford five-membered vinylic silanes **71** and **72**. Here the carbocations generated by a Lewis acid regiospecifically attack the C_3 of the 1,2-allenylsilanes to produce a vinyl cation stabilized by hyper-

conjugative interaction with the adjacent carbon–silcon bond. A subsequent 1,2-cationic transfer of the silyl group followed by an intramolecular nucleophilic trapping afforded the cyclic products **70–72** [36].



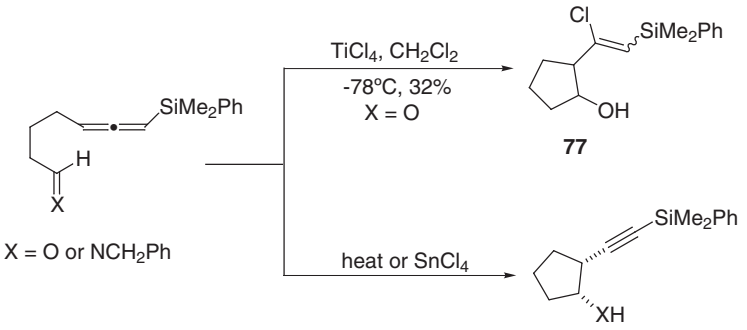
Scheme 10.35

As discussed previously [33–36], the Lewis acid-mediated reaction of 1,2-allenyl silanes with aldehydes or ketones can also afford homopropargylic alcohols **75** or five-membered 2,3-dihydrofurans **76** [37]. The type of reaction depends on the structure of the allenylsilanes, the substituent of the silyl group and the reaction conditions.



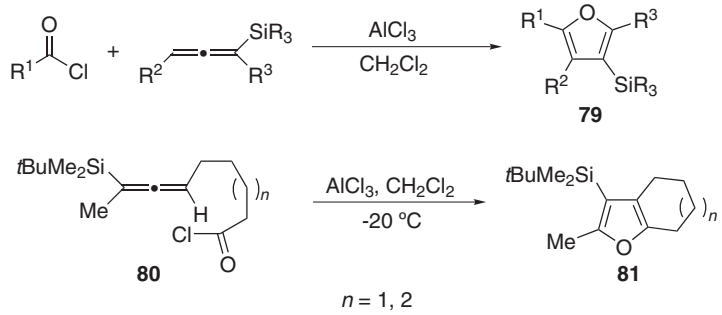
Scheme 10.36

An intramolecular version of this reaction leading to cyclic alcohols or amines **77** and **78** has also been reported [38].



Scheme 10.37

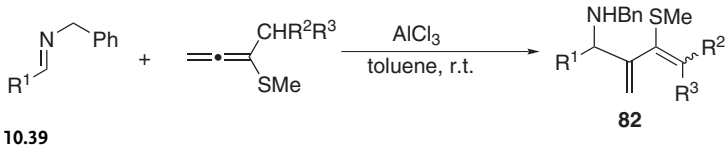
A similar reaction was also observed with acyl chlorides, which afforded polysubstituted furans **79** [39]. An intramolecular version of this reaction behaved similarly to afford anellated furan products **81**.



Scheme 10.38

10.3
1,2-Allenyl Sulfides

A similar ene-type reaction was also observed with 1,2-allenyl sulfides to afford 2-methylene-3-thio methylalk-3-enylamines [40].

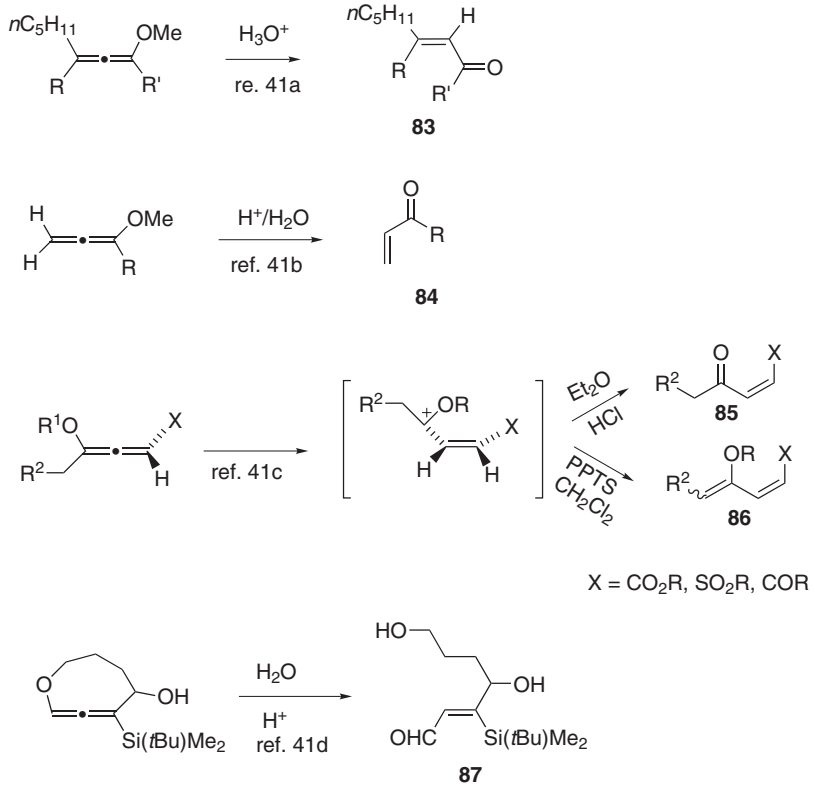


Scheme 10.39

10.4
1,2-Allenyl Ethers

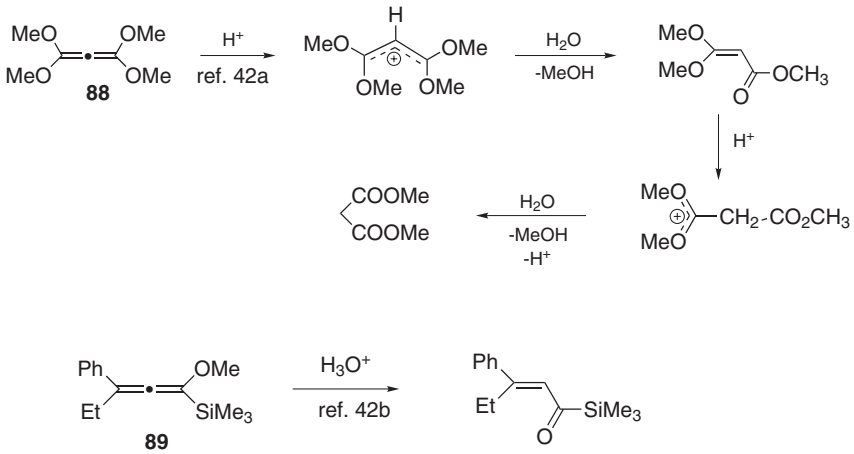
10.4.1
Electrophilic Additions

Protonation of 1,2-allenyl ethers ultimately delivers α,β-unsaturated enones or enals **83–87** [41].



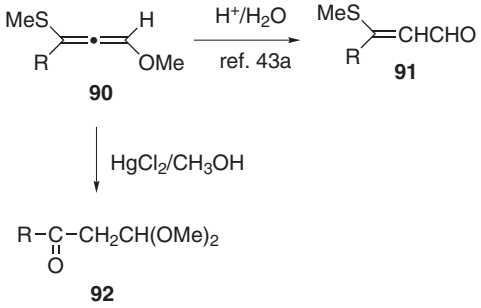
Scheme 10.40

1,1,3,3-Tetramethoxypropadiene **88** or 1-methoxy-1-(trimethylsilyl)-3-phenyl-1,2-pentadiene **89** may be easily protonated and then leads to dimethyl malonate or 1-trimethylsilyl-3-phenyl-2-penten-1-one [42].



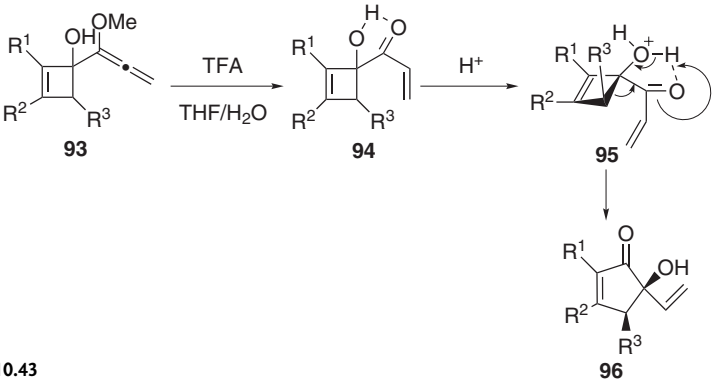
Scheme 10.41

The protonation of 3-thio methyl-1-methoxy-1,2-allenes **90** affords 3-methylthioenals **91** [43]. Hydrolysis can, on the other hand, be directed to the thioether moiety with $HgCl_2$–MeOH leading to 1,1-dimethoxy-3-ketones **92** [43].



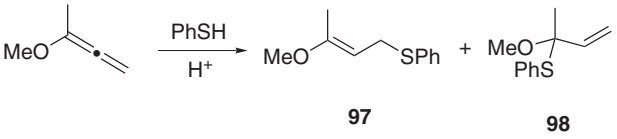
Scheme 10.42

In the protonation of 1-(1′-methoxy-1′,2′-propadienyl)-2-cyclobuten-1-ols **93**, the α,β-unsaturated enones **94** formed by protonation can be further converted to 5-hydroxy-5-vinyl-2-cyclopentenones **96** by a ring-expansion reaction under the action of H^+ [44].



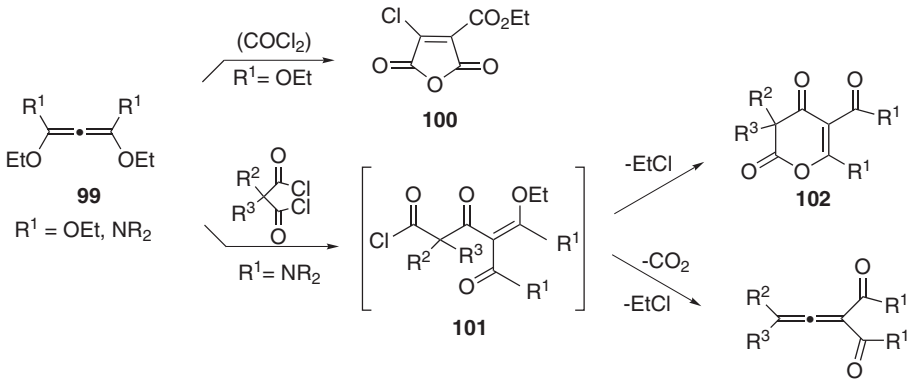
Scheme 10.43

The protonated 1,2-allenyl ether can also be attacked by nucleophiles such as thiols to afford 3-methoxy-2-butenyl sulfide **97** and 3-methoxy-3-thiophenyl-1-butene **98**, with the former being the major isomer [45, 46].



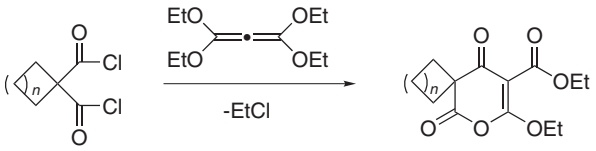
Scheme 10.44

1,3-Diethoxy-1,2-allene can also accept the electrophilic attack of oxalyl chloride or malonyl chloride to afford cyclic anhydride **100** and dioxopyrans **102** or 2-(alkoxycarbonyl or amido)-2,3-allenoates or allenamides **103**, depending on the structures of both starting materials [47].



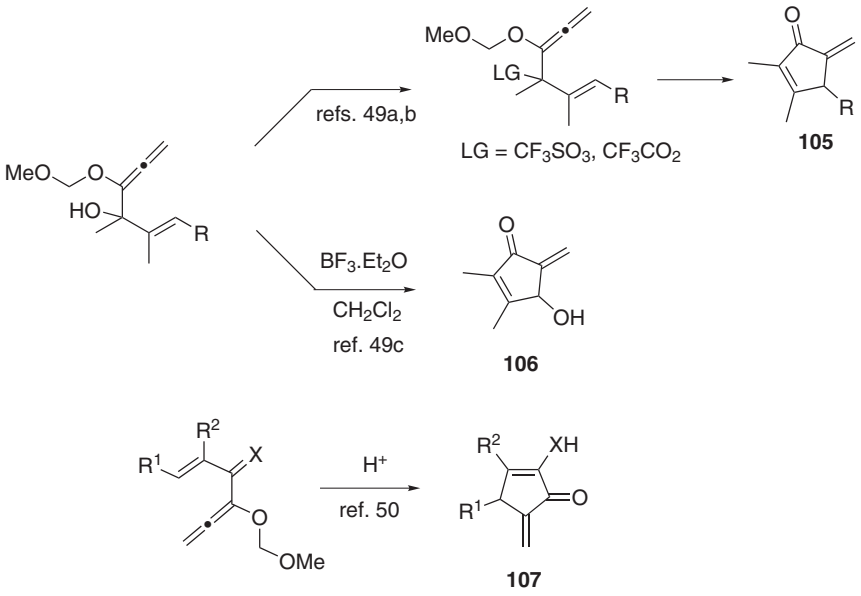
Scheme 10.45

The reaction of 1,1,3,3-tetraethoxypropadiene with cyclic 1,1-dicarbonyl dichloride also affords dihydro-2,4-dioxo-2*H*-pyrans [48].



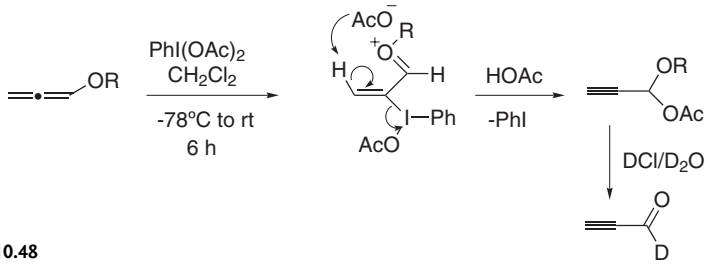
Scheme 10.46 **104**

Nazarov cyclizations of methoxymethoxylallene deliver α-methylenecyclopent-2-enone derivatives **105–107** [49, 50].



Scheme 10.47 X = O or NH

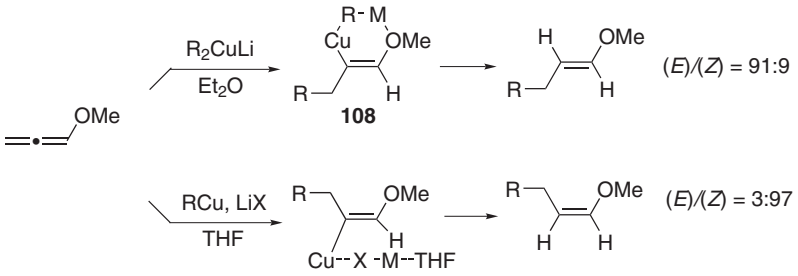
Electrophilic addition of $PhI(OAc)_2$ to 1,2-allenyl ether led to the formation of 3-acetoxy-3-alkoxy-1-propyne [51].



Scheme 10.48

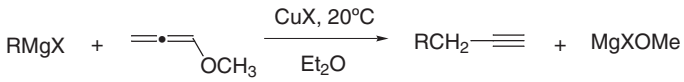
10.4.2
Nucleophilic Additions

The carbocupration of methoxyallene affords a (*Z*)- or (*E*)-enol ether depending on the solvent used [52]. In THF, the reaction exhibits *Z*-selectivity because the coordination ability of THF excludes the intramolecular chelation effect of the methoxy group, which may be responsible for the *E*-selectivity for the reaction in ether (Scheme 10.49).



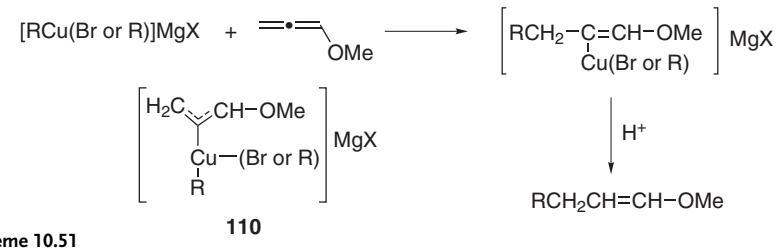
Scheme 10.49

The CuBr-catalyzed reaction of a Grignard reagent with 1,2-allenyl ether in Et_2O at 20 °C afforded terminal alkynes [53].



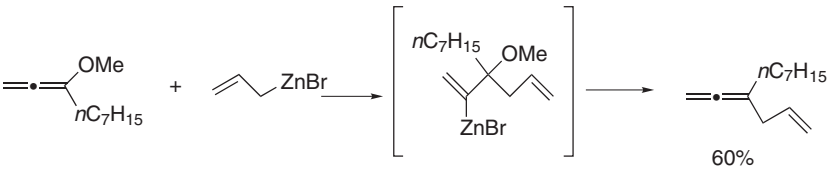
Scheme 10.50

If the reaction was carried out in THF with R_2CuMgX or [RCuBr]MgX as the organometallic reagent, a vinylic compound was prepared upon protonation. The *E*:*Z* ratio of the product depends strongly on the type of organocopper reagent used. The reaction may proceed via the attack of Cu on the central carbon atom of the allene moiety, followed by transfer of the R group from Cu to the terminal carbon atom [54].



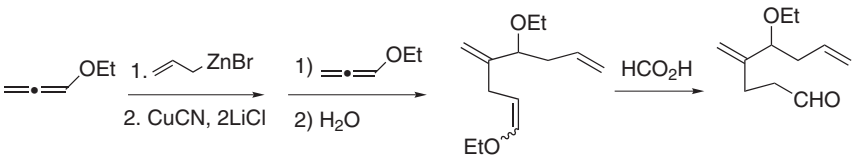
Scheme 10.51

However, with allylzinc bromide the reaction afforded the vinylic metal intermediate **111** with the allyl group connected to the carbon linked to a methoxy group, which may afford a new allenic product via β-elimination.



Scheme 10.52 **111**

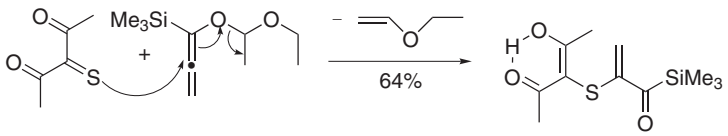
With ethoxypropadiene, the vinylic copper intermediate formed via the allylzinccation reacts with another molecule of ethoxyallene leading to the formation of enol ether **112** as an *E*–*Z* mixture [55].



112

Scheme 10.53 66% ((*Z*)/(*E*) = 70:30)

With thione **113**, 1-(trimethylsilyl)-1-(1′-ethoxy)ethoxypropadiene affords α,β-unsaturated acyl silane **115** [56].



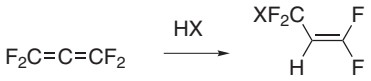
113 **114** **115**

Scheme 10.54

10.5
1,2-Allenyl Halides

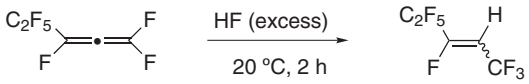
10.5.1
Electrophilic Additions

With electrophiles such as hydrogen halides, perfluoropropadiene affords products with the central carbon atom of the allene moiety being protonated [57]. Although HX are normally considered as electrophiles, these reactions with tetrafluoropropadiene may be nucleophilic in nature [57].



Scheme 10.55 X = F (20°C, 99%), Cl (20°C, 99%), Br (-45°C, 89%)

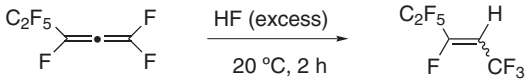
The reaction of HF with perfluoropenta-1,2-diene delivered a 65:35 *E*–*Z* mixture of 2*H*-nonafluoropent-2-ene [58].



Scheme 10.56

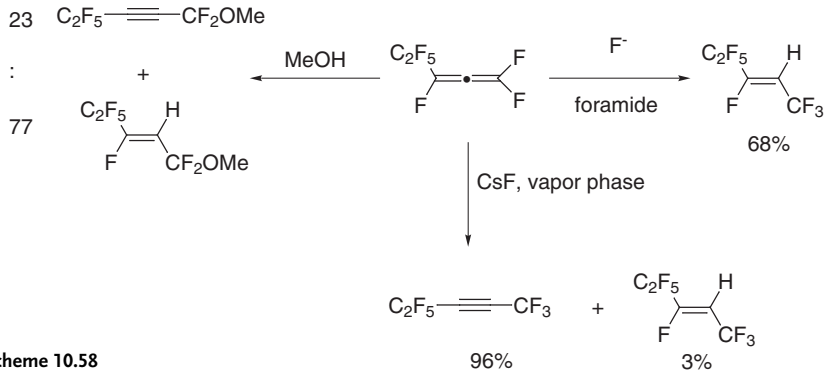
10.5.2
Nucleophilic Additions

Perfluoropropadiene can also react with nucleophiles such as ROH and F^- to provide the product with the nucleophilic moiety connected to the terminal carbon atom [57].



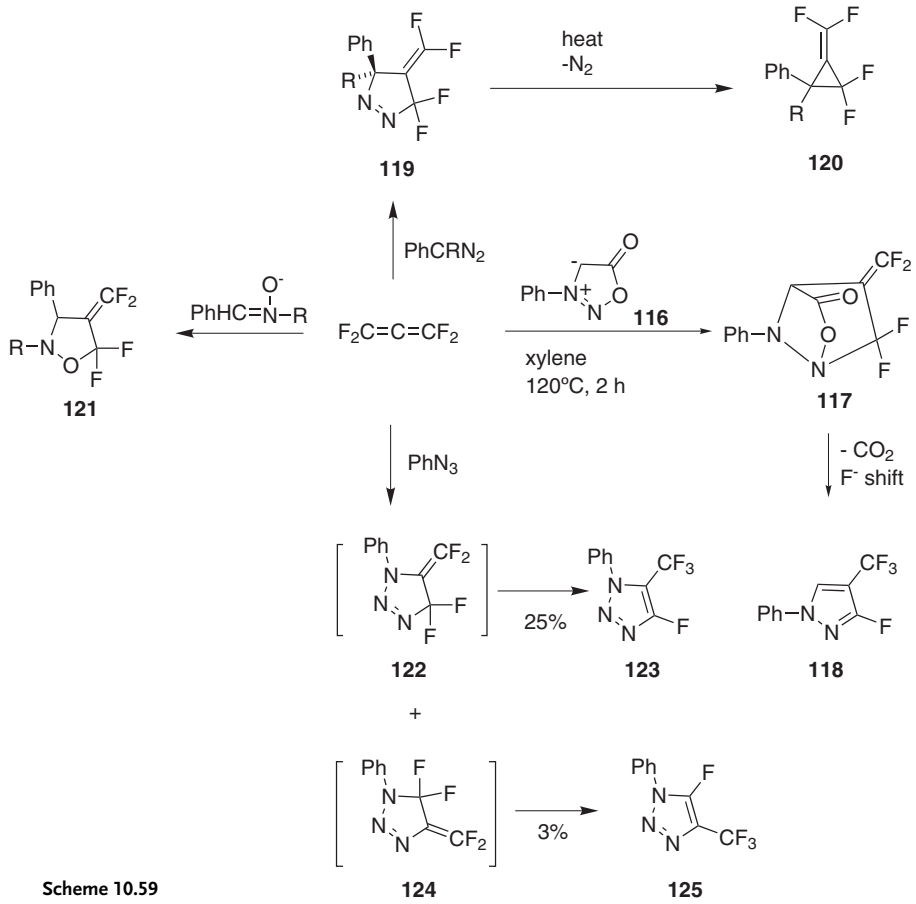
Scheme 10.57

The reaction of perfluoropenta-1,2-diene with cesium fluoride in foramide led to nonafluoropent-2-ene [58]. With anhydrous CsF the reaction in the vapor phase affords perfluoro-2-pentyne; with MeOH, the reaction affords 1-methoxy-2-perfluoropentyne and 1-methoxy-2*H*-octafluoro-2-(*Z*)-pentene [58].



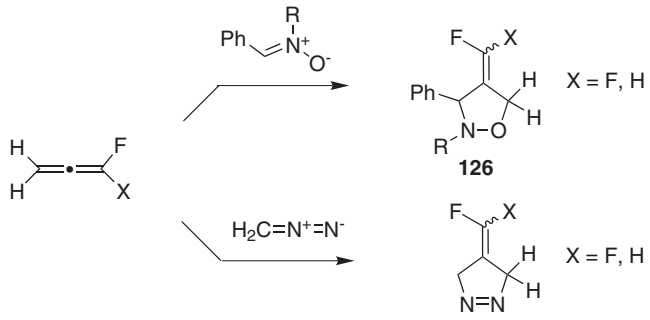
Scheme 10.58

N-Phenylsydnone **116** reacts readily with perfluoropropadiene to form pyrazoles **118** in 63% yield [59, 60]. Actually, perfluoropropadiene reacts with a whole series of 1,3-dipolar reagents providing an efficient entry to hetero- and carbocycles **119**, **121**, **123** and **125**.



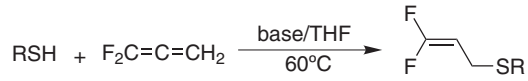
Scheme 10.59

Reactions of 1,1-difluoropropadiene or monofluoropropadiene and a 1,3-dipolar reagent such as diazo compounds, nitrones, nitrile oxides and carbonyl ylides are an excellent route to five-membered heterocycles, such as **126** and **127** [61–63].



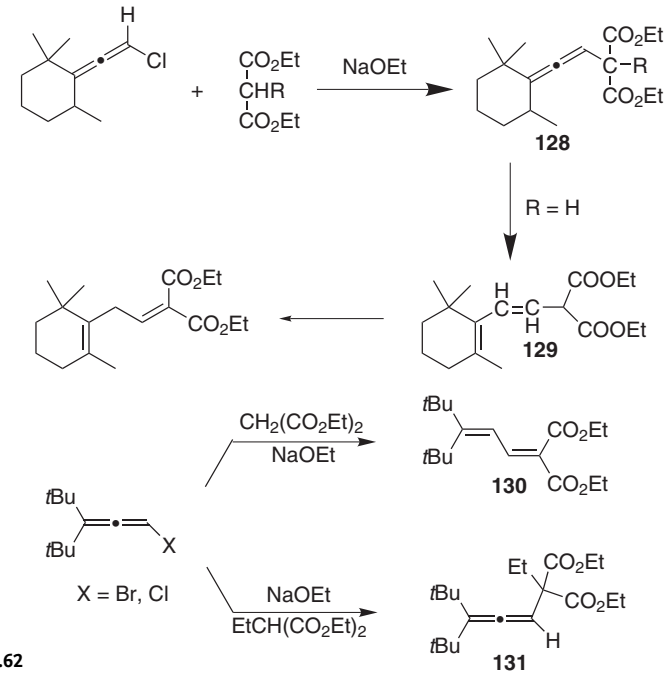
Scheme 10.60

1,1-Difluoropropadiene can accept the nucleophilic attack of thiols; 3,3-difluoroallyl thioethers are the final product [64].



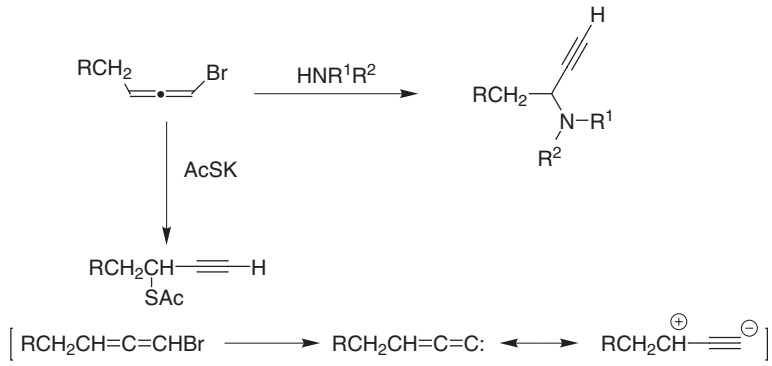
Scheme 10.61

1,2-Allenic halides can also react with monosubstituted malonates to afford 2-(1′,2′-allenyl)malonates **128** and **131**. With an unsubstituted malonate the migration of the C=C bond was observed to form 1,3-dienes **129** and **130** [65].



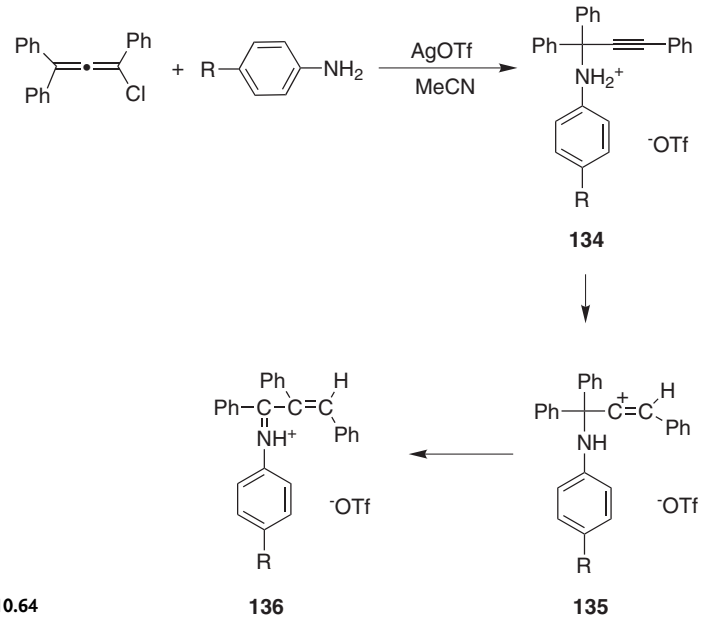
Scheme 10.62

1,2-Allenyl bromide accepts the nucleophilic attack of amines or potassium thioacetate leading to propargylic amines or thioesters via the alkenylidenecarbene **132** or zwitterion intermediate **133** [66].



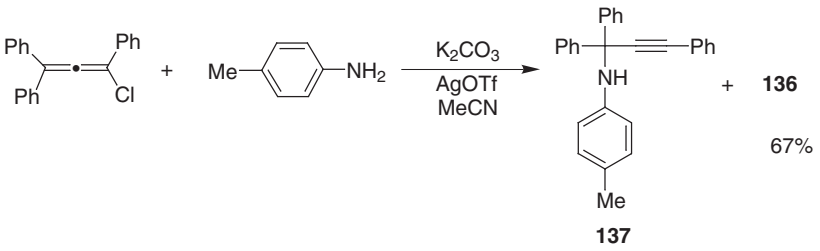
Scheme 10.63 **132** **133**

In the presence of AgOTf, the reaction of 1,3,3-triphenylpropadienyl chloride with an amine in CH_3CN resulted in the formation of iminium triflate **136** via a 1,2-phenyl shift process [67].



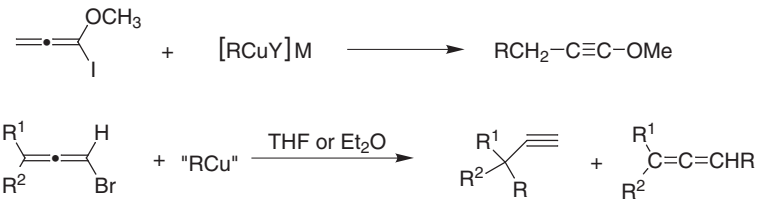
Scheme 10.64

In the presence of K_2CO_3, the reaction afforded propargylic amine **137** together with the corresponding iminium triflate **136** [67].



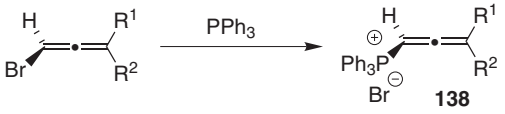
Scheme 10.65

A copper reagent can also react directly with 1,2-allenyl halides to provide alkynes and/or allenes[68, 69].



Scheme 10.66

1,2-Allenyl bromides can also react with PPh_3 to afford 1,2-allenylphosphonium bromide **138** [70].



Scheme 10.67

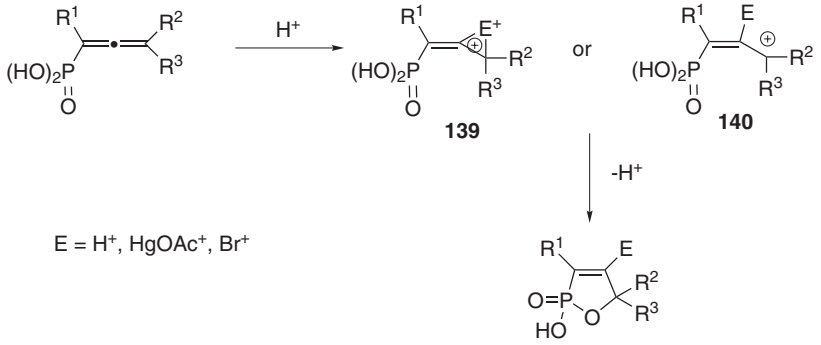
10.6 Phosphorus-Containing Allenes

1,2-Allenic phosphonic acids, phosphonates and phosphine oxides can be easily prepared from propargylic alcohols and phosphinyl chloride (see Chapter 1). They readily react with both electrophilic reagents and nucleophilic reagents.

10.6.1 Electrophilic Addition

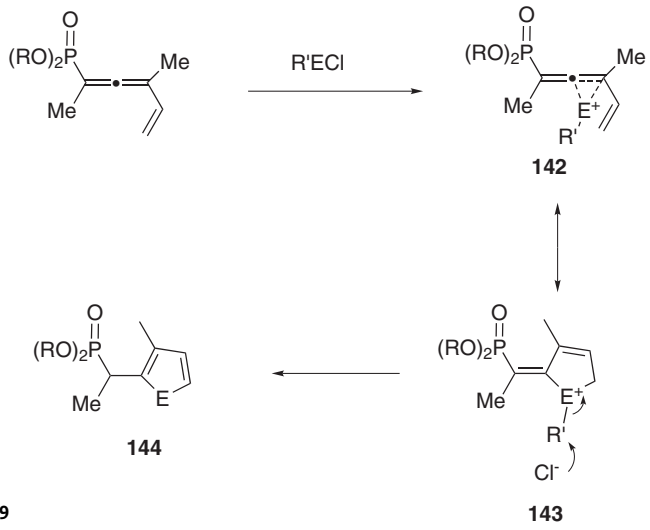
1,2-Allenic phosphonic acids undergo cyclization reactions in the presence of electrophilic reagents, i.e. proton, bromine (in $CHCl_3$) and $Hg(OAc)_2$ (in HOAc), to afford five-membered cyclic compounds [71]. The reaction rate depends greatly on the struc-

ture of the electrophile and the substitution patterns of R^2 and R^3. With R^2 and/or R^3 = alkyl the reaction proceeded readily, whereas with R^2 and R^3 = H the reaction is difficult or suppressed (Scheme 10.68). The reaction of optically active 1,2-allenic phosphonic acids showed that the reaction is highly regio- and stereoselective (*trans*).



Scheme 10.68

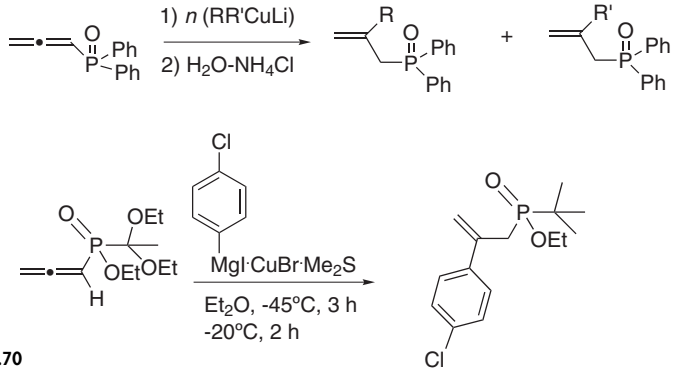
Sulfenyl chlorides and halogens react with 1,2-alkadienylphosphonic acids to afford phosphorus-containing heterocycles [72]. However, the electrophilic addition of dialkyl 4-methyl-2,3,5-hexatrien-2-yl phosphonates with sulfenyl or selenyl chloride afforded 2-thienyl methylphosphonates or the seleno analogues [73, 74]. The conjugate addition of sulfenyl or selenyl chloride with the 2,4-diene moiety in the starting allene leads to the formation of the five-membered skeleton (Scheme 10.69).



Scheme 10.69

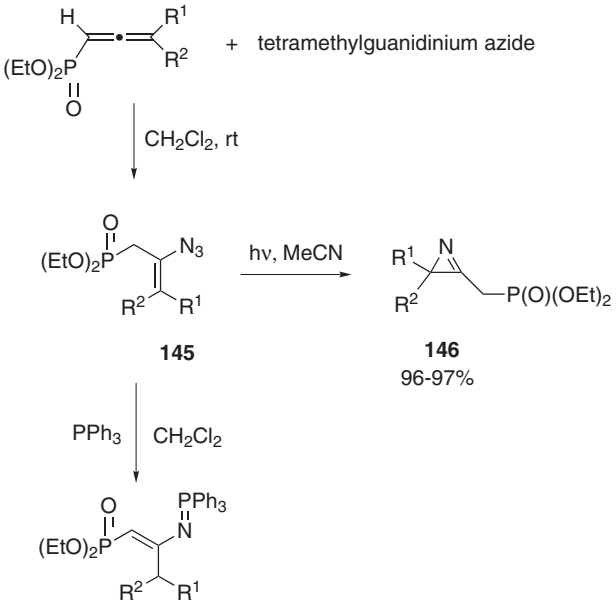
10.6.2
Nucleophilic Addition

1,2-Propadienylphosphine oxide or phosphonate is a very good Michael acceptor, reacting with organometallic reagents to afford 2-substituted-2-propenyl phosphine oxides or phosphonates (Scheme 10.70) [75].



Scheme 10.70

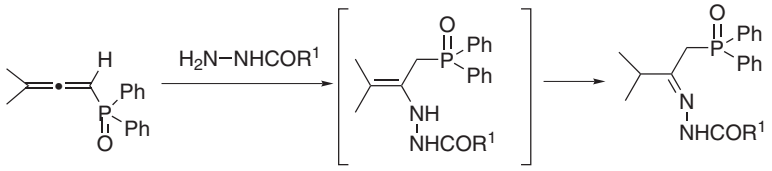
The nucleophilic addition of NaN_3 leads to 2-azido-2-alkenyl phosphonates **145**, which would react further with PPh_3 to afford phosphinimine **147**. The migration of the C=C bond in **145** was not observed. Upon photolysis, **145** can also cyclize to afford azirine **146** (Scheme 10.71) [76].



145 **146** 96-97% **147**

Scheme 10.71

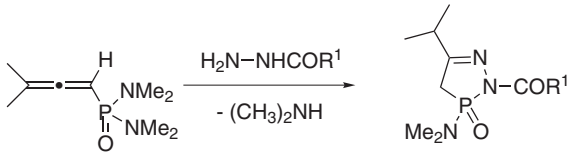
The reaction of monoacylhydrazide with 1,2-allenic phosphine oxide **148** afforded β-iminylphosphine oxide **150**. Here the unreacted C=C bond in the allylic phosphine oxide **149** tautomerized to form a C=N bond during the reaction (Scheme 10.72) [77].



148 **149** **150**

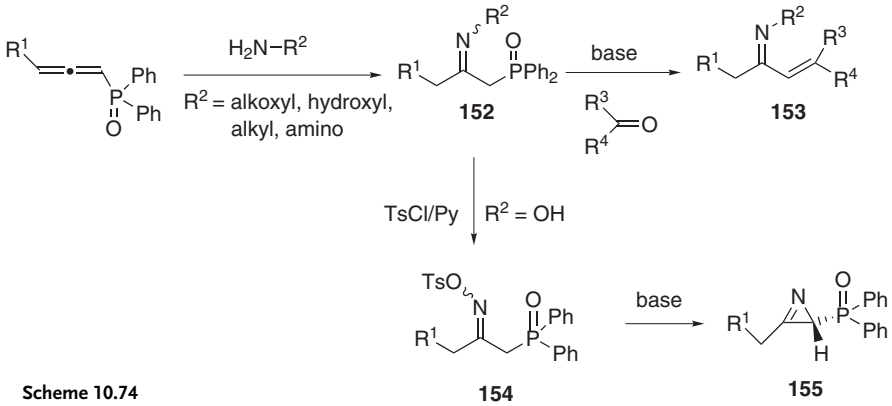
Scheme 10.72

A similar reaction of monoacyl hydrazide with 1,2-allenylphosphonamide led to the formation of five-membered cyclic product **151** (Scheme 10.73) [77].



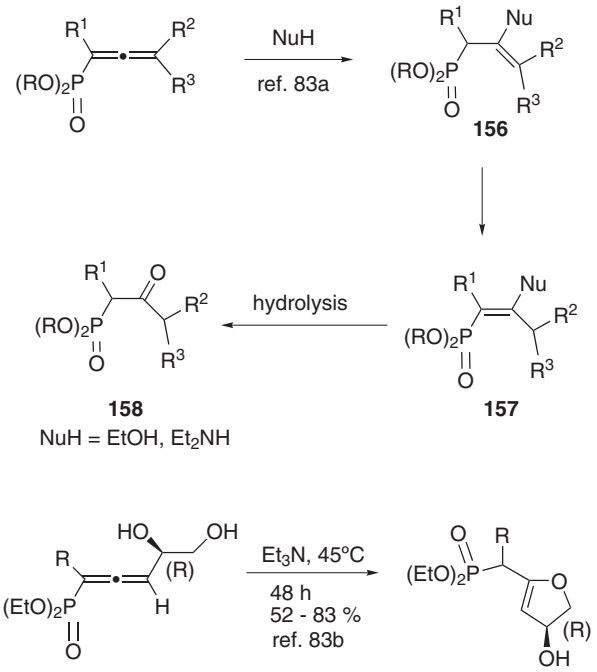
Scheme 10.73 **151**

The migration of a C=C bond to form a C=N bond was also observed with hydroxylamine [78, 79], hydrazine [80, 81] and primary amines [82]. The β-iminylphosphine oxide formed in the reaction may serve as a Wittig reagent in the presence of a base to react with a ketone or an aldehyde leading to α,β-unsaturated alkenylimines **153** (Scheme 10.74). The phosphorus group can be a phosphonium salt as well as a phosphonate.



Scheme 10.74 **152** **153** **154** **155**

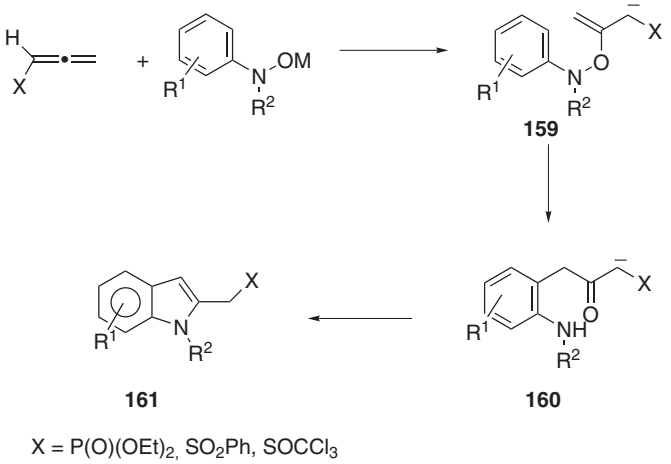
Since the migration of a C=C bond to form a C=N bond is impossible, the corresponding reaction with diethylamine afforded 2-amino-2-alkenyl phosphonates (Scheme 10.75) [83a].



Scheme 10.75

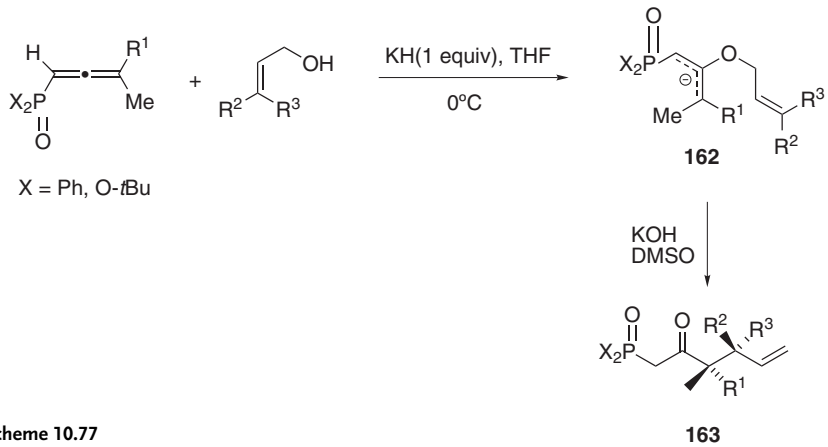
The nucleophilic addition of 1,2-allenic phosphonates with EtOH followed by hydrolysis leads to the formation of β-ketophosphonates (Scheme 10.75) [83a]. Intramolecular nucleophilic addition of a hydroxyl group with 1,2-allenic phosphonate was also observed to produce 2,3-dihydrofurans [83b].

The corresponding reaction of diethyl 1,2-propadienyl phosphonates (sulfones or sulfoxides) with *N*-phenylhydroxylamine afforded α-anionic *N*-phenylvinyloxyamine **159**, which upon [3,3]-sigmatropic rearrangement led to anionic 2-(2′-oxoalkyl)phenylamine **160**. Further cyclization provides an efficient synthesis of indole derivatives **161** [84].



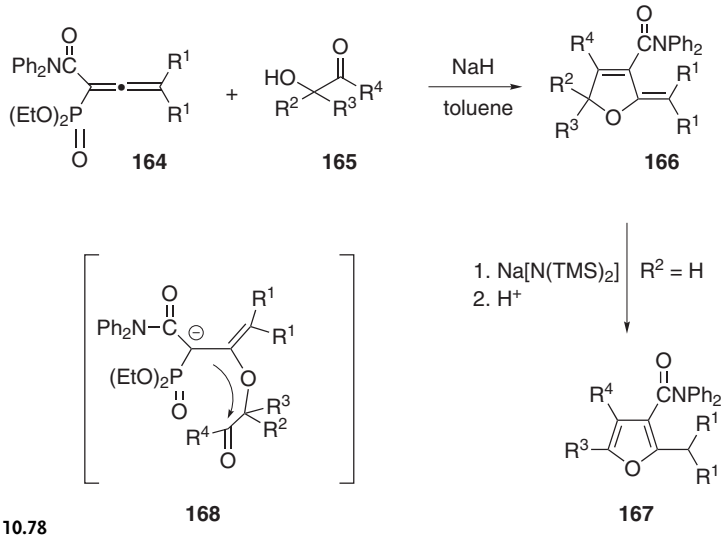
Scheme 10.76

The intermediate product **162**, formed from the nucleophilic addition of 1,2-allenic phosphonate or 1,2-allenic phosphine oxide with allylic alcohol, would also undergo a Claisen rearrangement to form 2-oxo-5-alkenyl phosphonate or phosphine oxide **163** [85]. The rearrangement is accelerated by the carbanionic nature of the intermediate **162**. For the conjugate addition step, the reaction temperature is crucial since the reaction at 0 °C afforded mainly β,γ-unsaturated product whereas α,β-unsaturated products were formed at 20 °C.



Scheme 10.77

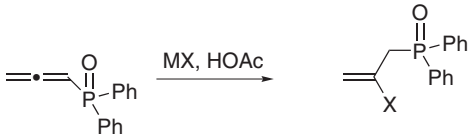
1-Amido-1,2-allenic phosphonate **164** reacted with α-hydroxy ketone **165** to give 2-alkylidene-2,5-dihydrofuran **166** via a sequential conjugate nucleophilic addition and a Wittig–Horner reaction. On treatment with a base, **166** was converted to tetrasubstituted furans (Scheme 10.78) [86].



164 **165** **166** **168** **167**

Scheme 10.78

Reaction of 1,2-propadienyl diphenylphosphine oxide and MX (M = Na, Li, X = Cl, Br, I) in HOAc leads to 2-halo-2-propenyl diphenylphosphine oxides in 58–75% yields. With substituent(s) in the allene moiety, the reaction is very slow. The corresponding reaction with HX gives low yields [87].



169 **170**

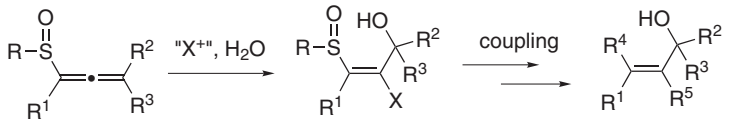
Scheme 10.79

10.7
1,2-Allenyl Sulfoxides

These compounds can easily be prepared; see Chapter 1.

10.7.1
Electrophilic Additions

The iodohydroxylation of 1,2-allenyl sulfoxide **171** with I_2 in the presence of H_2O exhibits *E*-selectivity leading to (*E*)-2-iodo-3-hydroxy-1-alkenyl sulfoxide [88]. By using Br_2, $CuBr_2$ or NBS, (*E*)-2-bromo-3-hydroxy-1-alkenyl sulfoxide is produced. For the chlorohydroxylation of a sulfoxide, $CuCl_2$ and silica gel were used to mix with the sulfoxide to deliver the (*E*)-chlorohydroxylation products highly stereoselectively [88]. The chirality in the allene moiety can be efficiently transferred to the final allylic alcohols. Under the catalysis of a Pd or Ni complex, the C–X and C–S bonds can be coupled to introduce different substituent(s) into the different locations of the C=C bond.

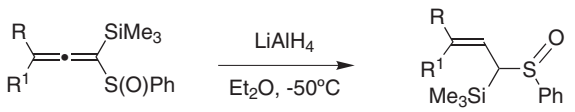


171 **172** **173**

Scheme 10.80

10.7.2
Nucleophilic Additions

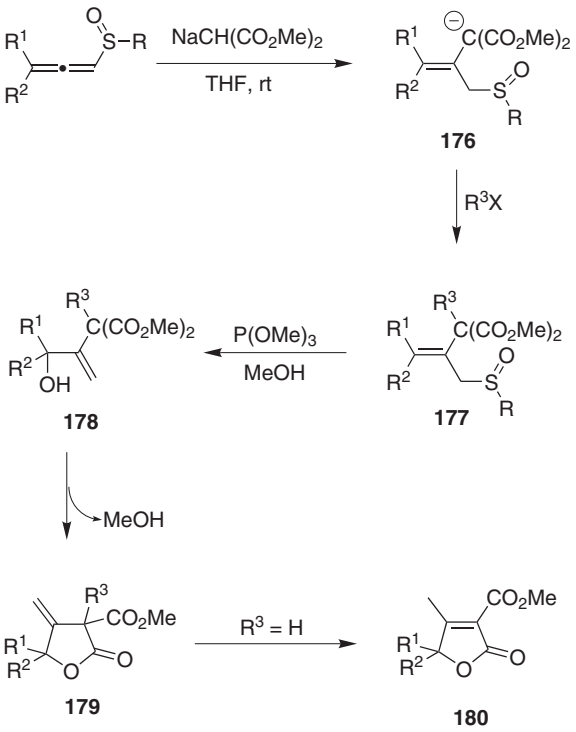
1-Trimethylsilyl-1,2-alkadienyl sulfoxide **174** reacted with $LiAlH_4$ to afford 2-alkenyl sulfoxides **175** with an allylsilane substructure [89].



174 **175**

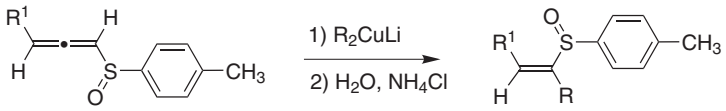
Scheme 10.81 21 - 68%

The reaction of 1,2-allenyl sulfoxides with sodium malonate also afforded 2-[bis (methoxycarbonyl)methyl]-2-alkenyl sulfoxides **177**, which upon further transformation would provide an efficient access to butenolide derivatives **180** [90, 91].



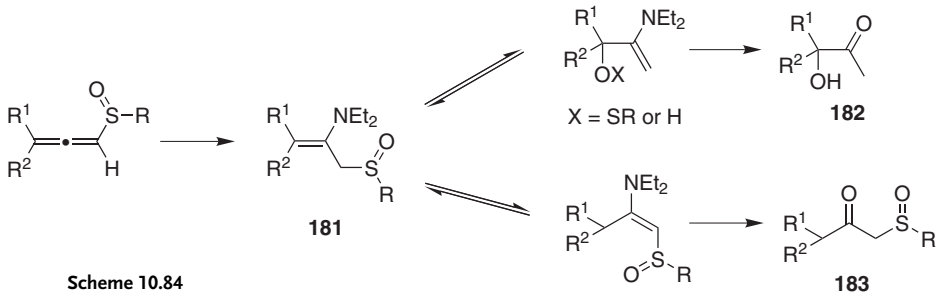
Scheme 10.82

R_2CuLi is a good nucleophile to introduce an alkyl group into the 2-position of allylic sulfoxides with a preference for the *Z*-isomer [92, 93].



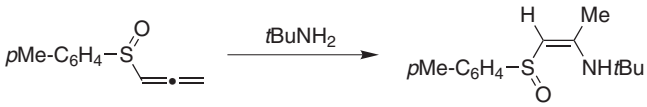
Scheme 10.83

Diethylamine can readily undergo nucleophilic addition with 1,2-allenyl sulfoxides to afford 2-diethylamino-2-enyl sulfoxides **181**, which can be easily converted to α-hydroxy ketones **182** or β-keto sulfoxides **183** [94].



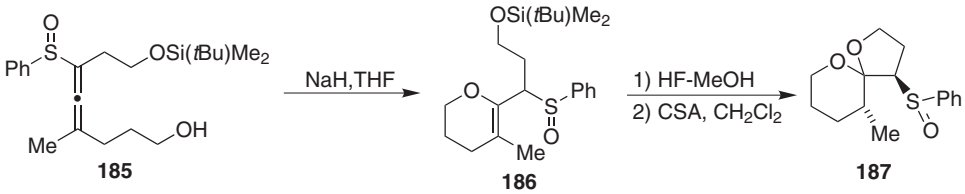
Scheme 10.84

The reaction of 1,2-propadienyl *p*-tolyl sulfoxide with *tert*-butylamine gave a (*Z*)-enamine, indicating that the C=C bond migrated from the β,γ-position to the α,β-position [95]. The stereoselectivity may be explained by the intramolecular hydrogen bonding in (*Z*)-**184**.



Scheme 10.85

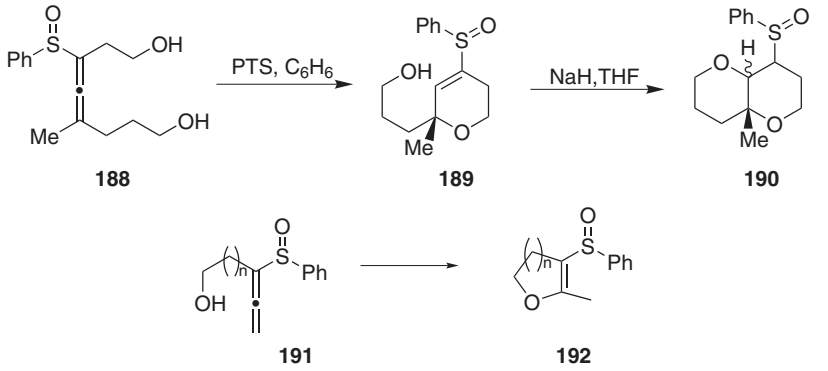
In 1987, Parsons et al. reported the intramolecular addition of alcohols to 1,2-allenyl sulfoxides in the presence of NaH [96].



Scheme 10.86

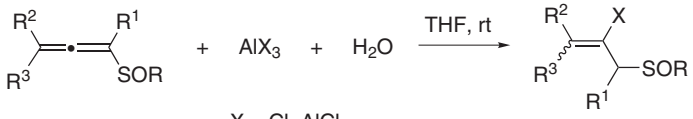
When the reaction of **188** was catalyzed by PTS, first an electrophilic addition may produce **189**, which would then undergo an intramolecular 1,4-conjugate addition leading to **190** [96].

Under the catalysis of *t*BuOK in *t*BuOH, a hydroxyl group can also attack intramolecularly to the central carbon atom, which was followed by C=C bond migration leading to cyclic vinylic sulfoxides **192** (Scheme 10.87) [97].



Scheme 10.87 n = 1, 2, 3, 4

Direct hydrohalogenation of 1,2-allenic sulfoxides with MX in HOAc failed. AlX_3 was found to be a good X^- donor to afford 2-haloallylic sulfoxides in 56–89% yields. In this reaction, an Al^{3+} species activates the reactivity of the allene moiety by its interaction with the sulfinyl group [87, 98].



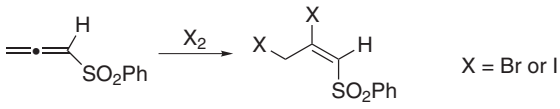
Scheme 10.88

10.8
1,2-Allenyl Sulfones

By the methods described in Chapter 1, these compounds are also readily available.

10.8.1
Electrophilic Additions

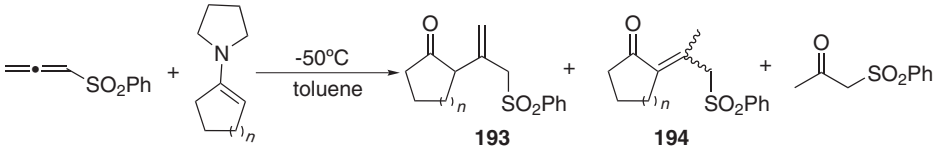
In 1990, Padwa et al. reported that by the reaction of halogens (X = Br, I) with propadienyl sulfone, the dihalogenation products of the relatively election-rich terminal C=C bond can be synthesized [99–101].



Scheme 10.89

10.8.2
Nucleophilic Additions

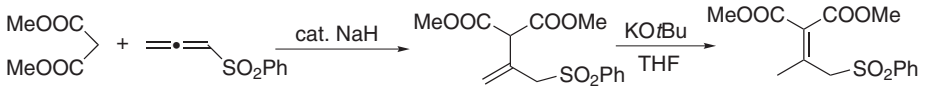
1,2-Propadienyl phenyl sulfone can accept enamines of cyclic ketones as nucleophiles to afford β,γ- or α,β-unsaturated ketones **193** and **194** as the major products [102].



Scheme 10.90

α,β-Unsaturated enone **194** was formed from the migration of the C=C bond in **193**. Due to the presence of a trace amount of pyrrolidine, its direct reaction with 1,2-propadienyl sulfones followed by hydrolysis afforded 2-oxopropyl phenyl sulfoxide [102].

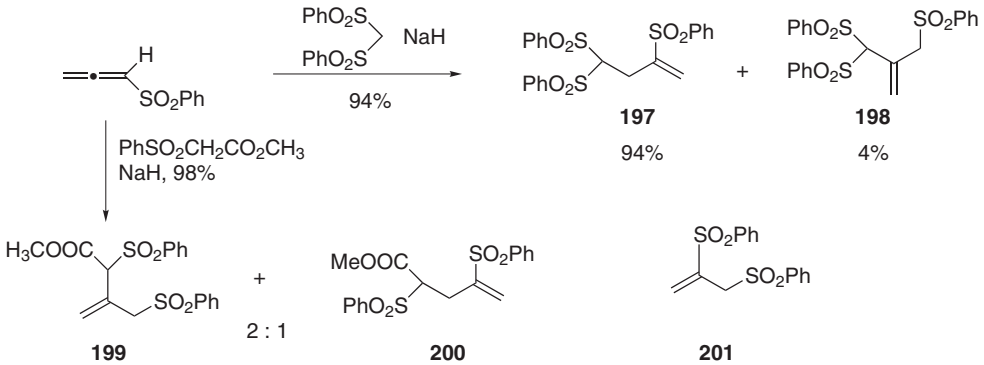
Malonate can react with 1,2-propadienyl phenyl sulfone in the presence of a trace amount of NaH to give 2-[bis(methoxycarbonyl)methyl]-2-propenyl sulfone **195**, which was converted to 2-methyl-3,3-[bis(methoxycarbonyl)]-2-propenyl sulfone **196** by the migration of the C=C bond mediated by KO*t*Bu [103].



Scheme 10.91

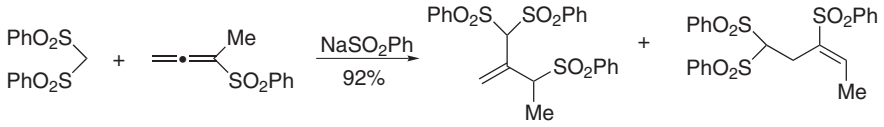
195 **196**

However, it is interesting that the same reaction with bis(phenylsulfonyl)methane in the presence of NaH afforded 3-nucleophile-substituted-2-(phenylsulfonyl)-1-propene **197** and the expected 2-[bis(phenylsulfonyl)methyl]-2-propenyl sulfone **198** in 94 and 4% yields, respectively. A similar reaction with methyl phenylsulfonylacetate afforded **199** and **200** in a ratio of 2:1.



Scheme 10.92

These two products must be formed via an S_N2'-type substitution of intermediate **201**, which may be formed by the nucleophilic attack of benzenesulfinate with 1,2-propadienyl phenyl sulfone. This was further supported by the reaction of 1-methyl-1,2-propadienyl sulfone with bis(phenylsulfonyl)methane in the presence of sodium benzenesulfinate, in which allylic sulfone **202** and vinylic sulfone **203** were formed [103].

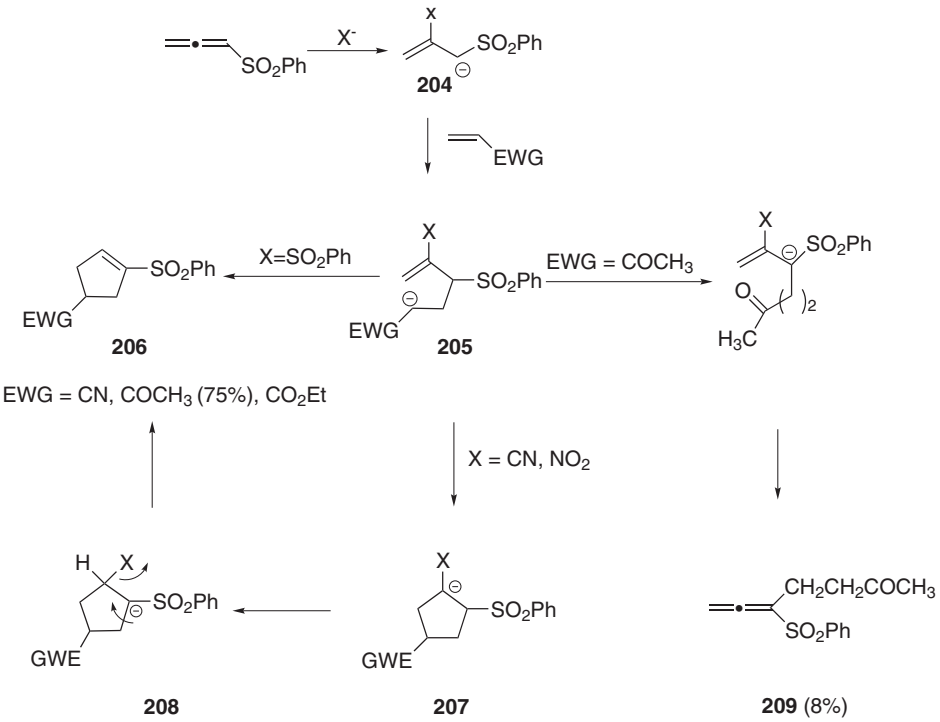


202 : **203**

1 : 1

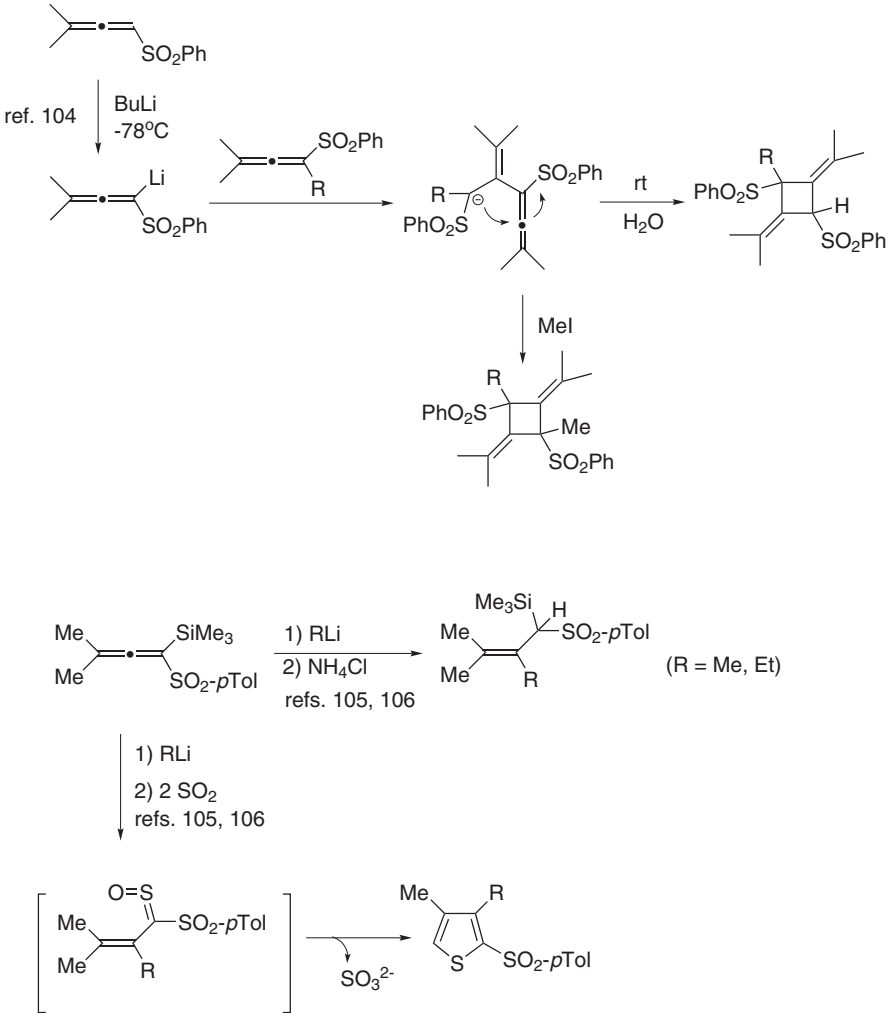
Scheme 10.93

Such a reaction was utilized to promote the anionic [3 + 2]-cycloaddition [103]. With KCN as the catalyst, the reaction of propadienyl phenyl sulfone with methyl vinyl ketone provided **206** (E = $COCH_3$) in 80% yield as the only product. The reaction is stepwise since 1-(3′-oxobutyl)-1,2-propadienyl phenyl sulfonyl **209** was formed together with **206** (E = COMe) in a 1:1 ratio when lithium benzenesulfinate was used as the promoter.

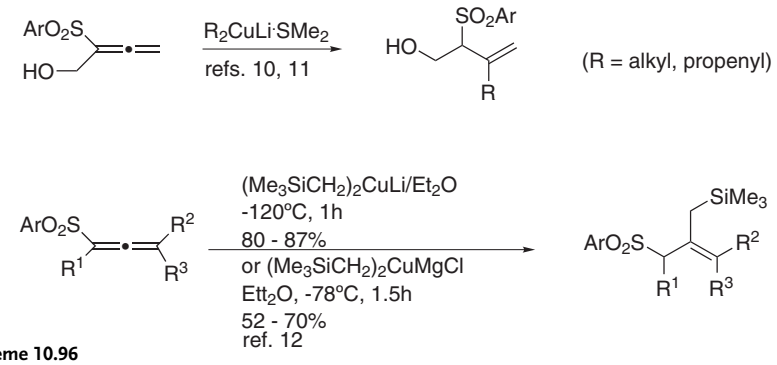


Scheme 10.94

1,2-Allenyl sulfones can also readily accept the nucleophilic attack of alkyl lithium [104–106]. No migration of the C=C bond was observed. R_2CuLi reacts with 1,2-allenylsulfones similarly [107–109].

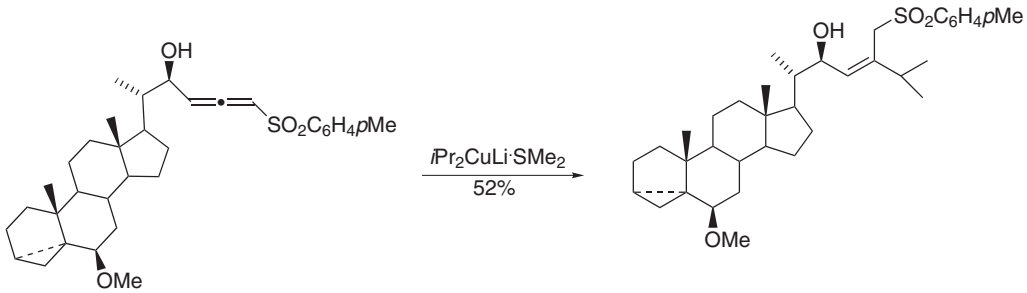


Scheme 10.95



Scheme 10.96

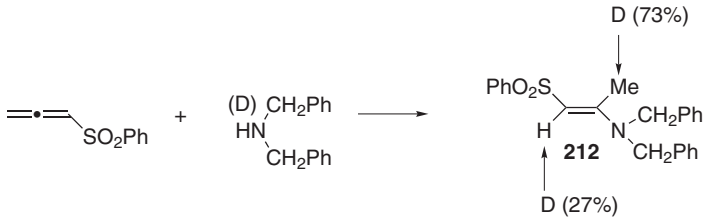
In case of 3-substituted 1,2-allenyl sulfones, e.g. **210**, the carbocupration reaction exhibits *Z*-selectivity, indicating that the nucleophile attacks from the less hindered side [110, 111].



210 **211**

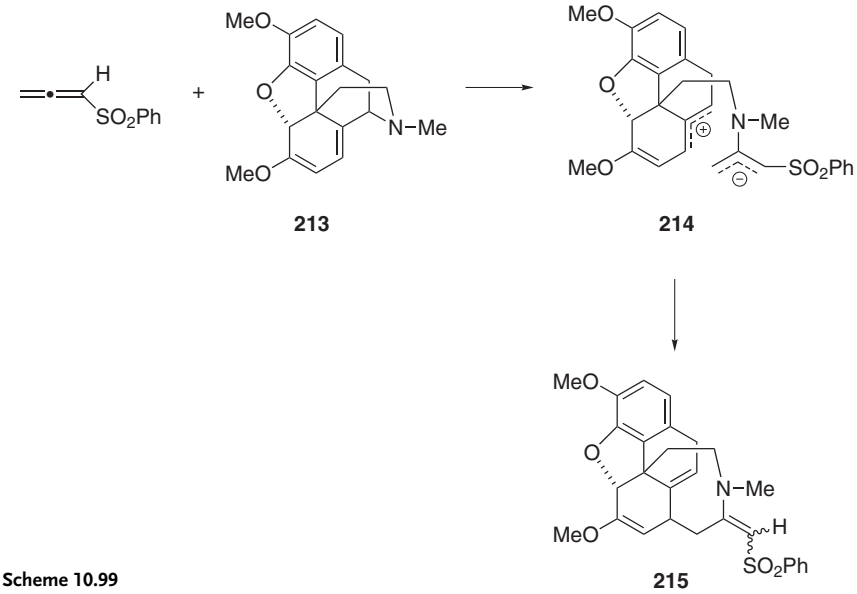
Scheme 10.97

The reaction of 1,2-allenylphenylsulfone with dibenzylamine afforded (*E*)-2-(dibenzylamino)-1-propenylphenyl sulfone **212** [112]. Based on this reaction, racemic allenic sulfones can be partially resolved with optically active amines [113].



Scheme 10.98 (*E*)-isomer

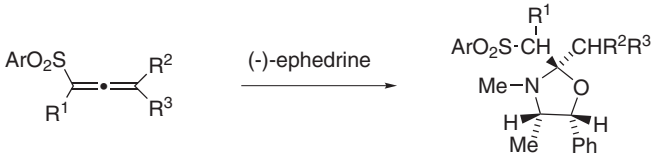
Phenylsulfonylpropadiene can even react with certain tertiary amines such as **213** via cleavage of the allylic C–N bond in the amine followed by conjugate addition and coupling to afford vinylic sulfones **215** [114].



213 **214** **215**

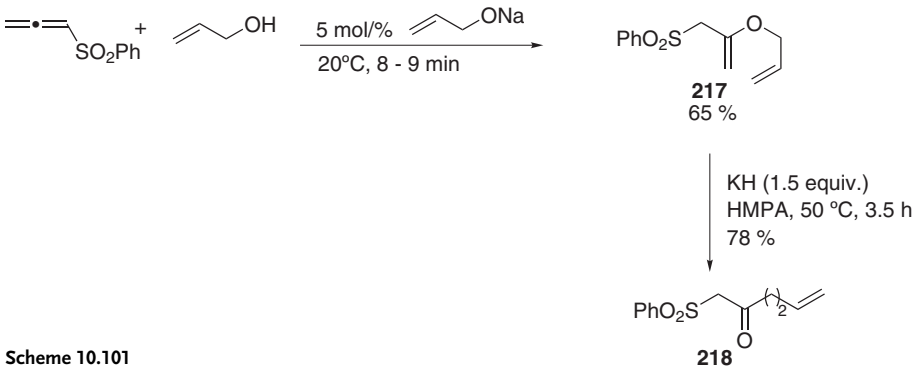
Scheme 10.99

The reaction of 1,2-allenyl sulfones with (–)-ephedrine led to enantiomerically pure 1,3-oxazolidines **216** via the formation of a conjugated enamine and subsequent intramolecular Michael addition [115].



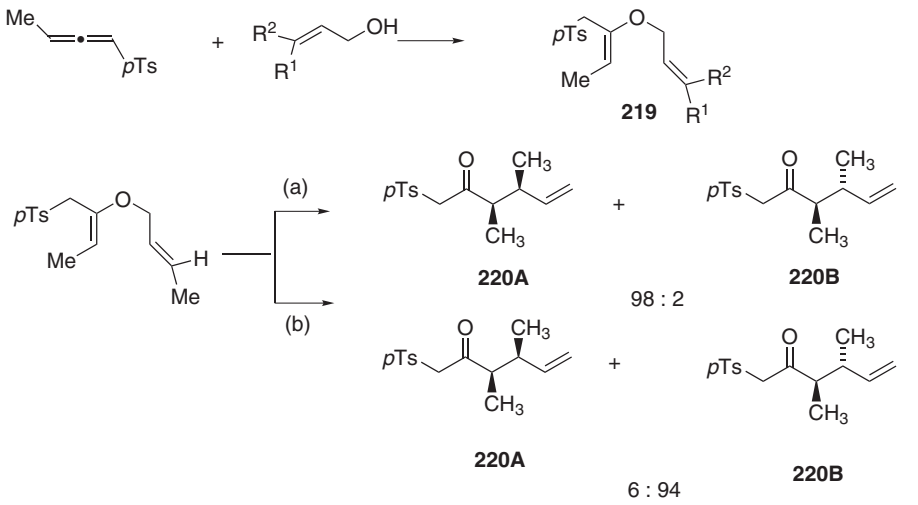
Scheme 10.100 **216**

Denmark and Harmata studied the reaction of 1,2-allenyl sulfones and 2-propenols under the catalysis of 5 mol% of sodium alkoxide affording 2-alloxy-2-propenyl sulfone **217**, which can be converted to 2-oxo-5-alkenyl sulfone **218** by treatment with 1.5 equiv. of KH in HMPA, a carbanion-accelerated Claisen rearrangement [116, 117].



Scheme 10.101

With 3-substituted-1,2-allenyl sulfones, the 1,4-addition reaction with alcohols also afforded *E*-isomers, which can be converted to different diastereomeric 3,4-disubstituted-2-oxoalkenyl sulfones **220** highly stereoselectively under different conditions [118].



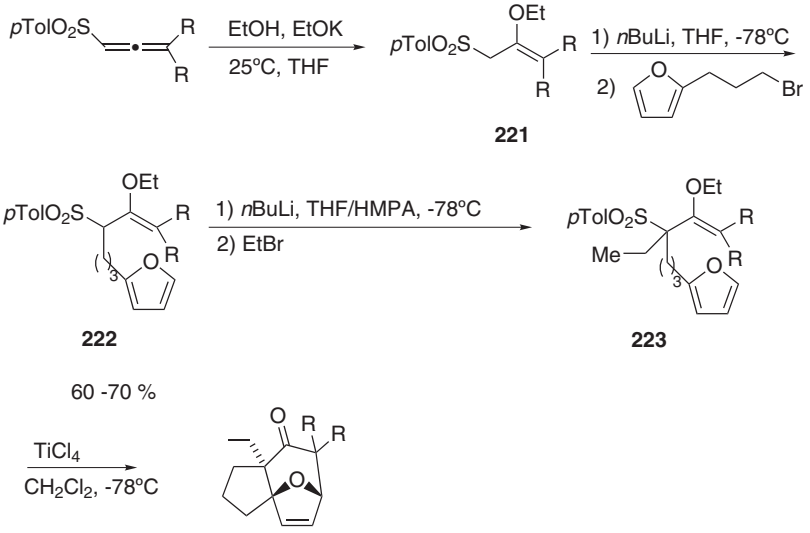
(a) NaH (2.2 equivs) DMSO, 20°C, 4 h, 85%
(b) KH (2.6 equivs)/LiCl (15 equiv.), DMSO, 50°C, 1.5 h, 45%

Scheme 10.102

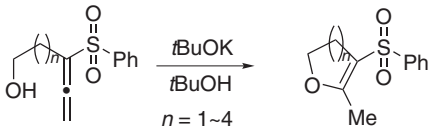
In this addition reaction with a higher concentration of the base and a longer reaction time, the C=C bond in the initially formed products may migrate to form the thermodynamically more stable α,β-unsaturated products [119].

The reaction of 1,2-allenyl sulfones with EtOH in the presence of a catalytic amount of EtOK afforded 2-ethoxy-2-alkenyl sulfones **221**, which can be easily alky-

lated to prepare useful synthetic intermediates [120–122]. An intramolecular version of such a reaction has also been observed [97].

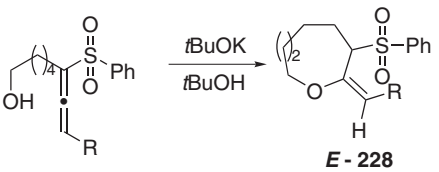


Scheme 10.103 **224**



Scheme 10.104 **225** **226**

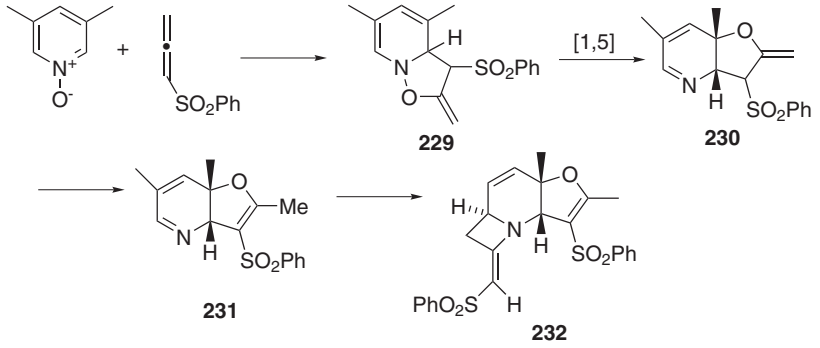
In the above reaction, the migration of the C=C bond was observed. With the introduction of a substituent to the 3-position of 1,2-allenyl sulfones, the C=C bond did not migrate [97] and the expected (*E*)-**228** was isolated.



***E* - 228**

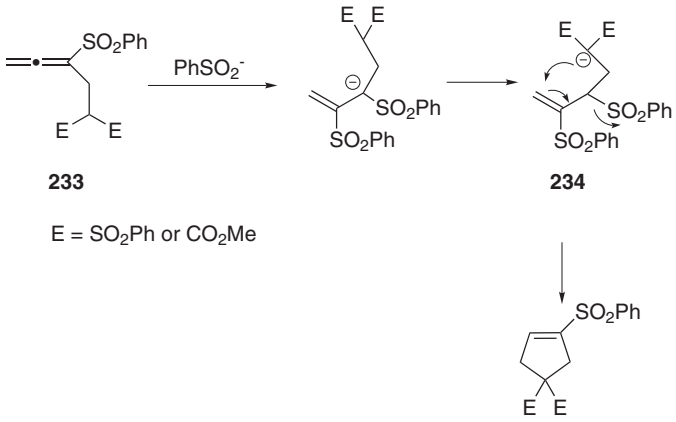
Scheme 10.105 **227**

3,5-Dimethylpyridine *N*-oxide and 1,2-allenyl sulfone in $CHCl_3$ at room temperature gave the 1,3-dipolar cycloaddition product **229**, which subsequently underwent a [1,5]-sigmatropic rearrangement and a migration of the C=C bond to afford **231**. The [2 + 2]-cycloaddition of the C=N bond in **231** with the terminal bond in propadienyl sulfone would deliver the tricyclic product **232** [123].



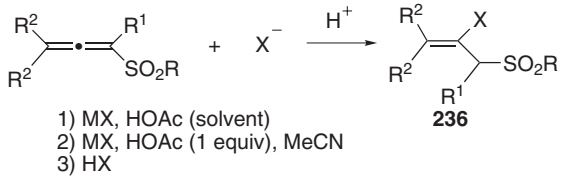
Scheme 10.106

The reaction of $PhSO_2^-$ with 2-(2′-phenylsulfonyl)-2′,3′-butadienylmalonate **233** affords the five-membered cyclic alkenyl sulfone **235** via a 1,4-addition, intramolecular deprotonation and a S_N2'-substitution process [124, 125].



Scheme 10.107

1,2-Allenyl sulfones can also readily undergo hydrohalogenation reactions with MX (M = Na, Li; X = Cl, Br, I) to afford 2-haloallylic sulfones **236** [87, 126]. The reactivity depends greatly on the substitution pattern of the allene moiety.

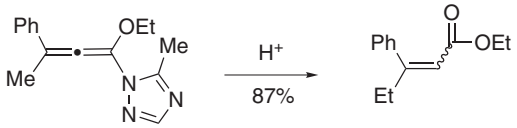


Scheme 10.108

10.9
Allenylamines

10.9.1
Electrophilic Additions

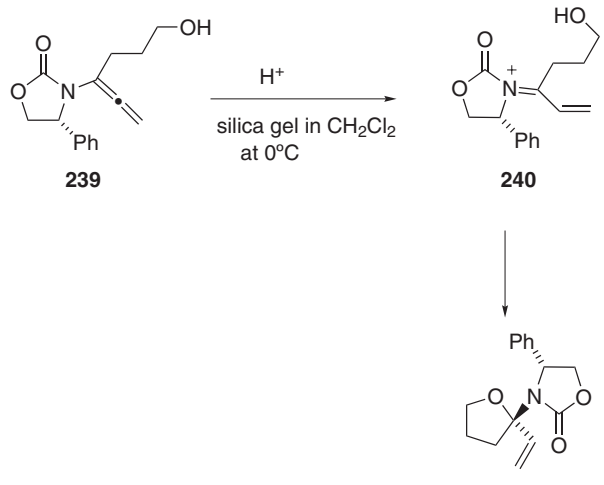
Protonation of triazole-substituted 1,2-allenyl ether **237** affords the α,β-unsaturated enoate **238** [127].



237 **238**

Scheme 10.109 (*E*)/(*Z*) = 1:4

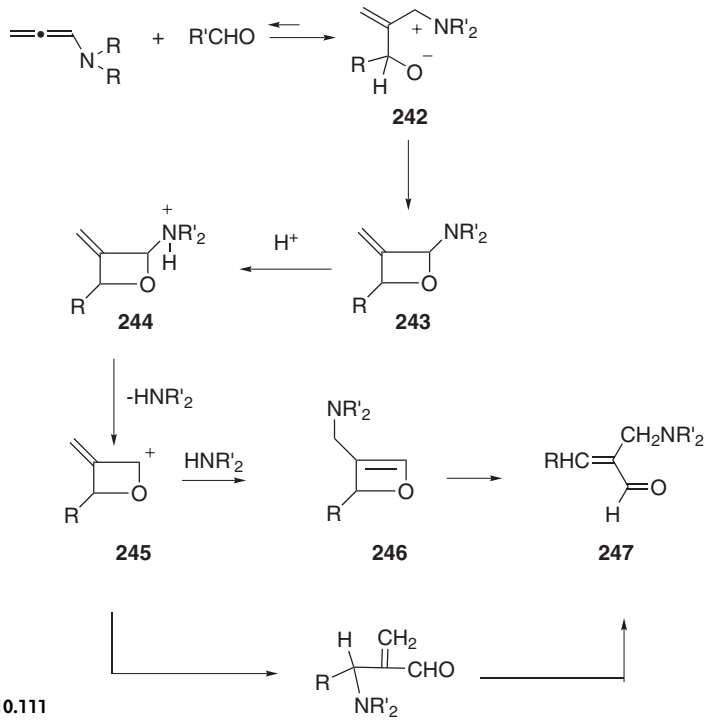
Allenamide **239** and a proton form the iminonium intermediate **240**, which then is attacked intramolecularly by a hydroxyl group to form dumbell-type bicyclic compounds **241** [128].



239 **240** **241**

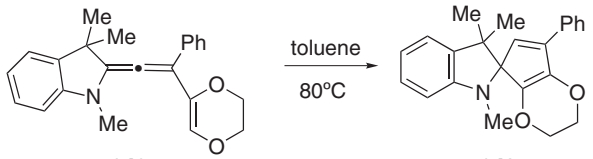
Scheme 10.110

1,2-Allenylamines can also serve as an enamine and react with an aldehyde to afford 2-(aminomethyl)-2-enals **247** [129].



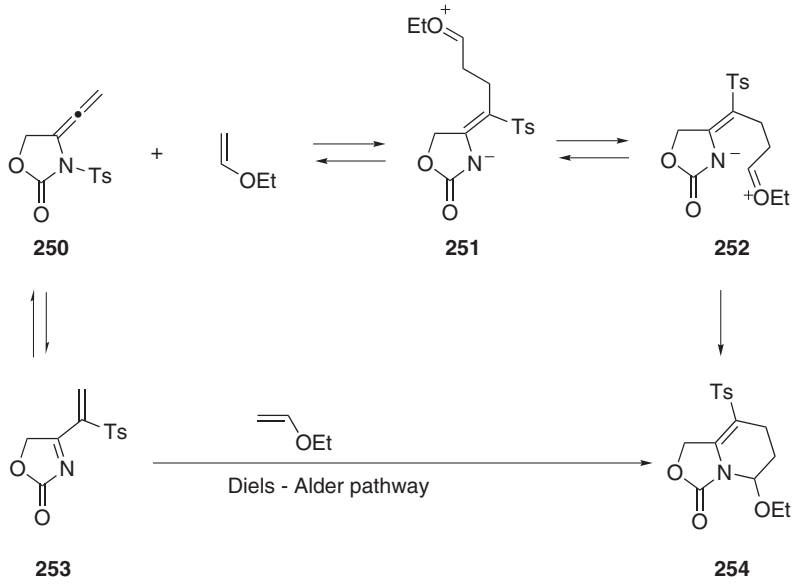
Scheme 10.111

1,2-Allenylamine **248** reacts intramolecularly with an enol ether to give the cyclic compound **249** [130].



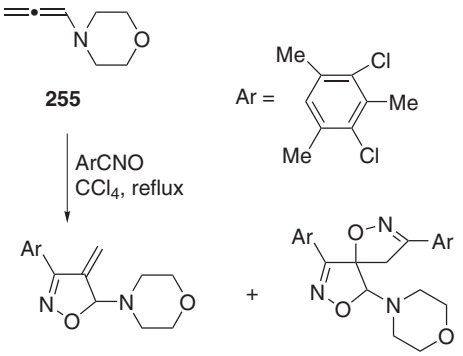
Scheme 10.112

An intermolecular reaction of *N*-sulfonyl-1,2-propadiene **250** with ethyl vinyl ether leading to tetrahydropyridine **254** was observed [131].



Scheme 10.113

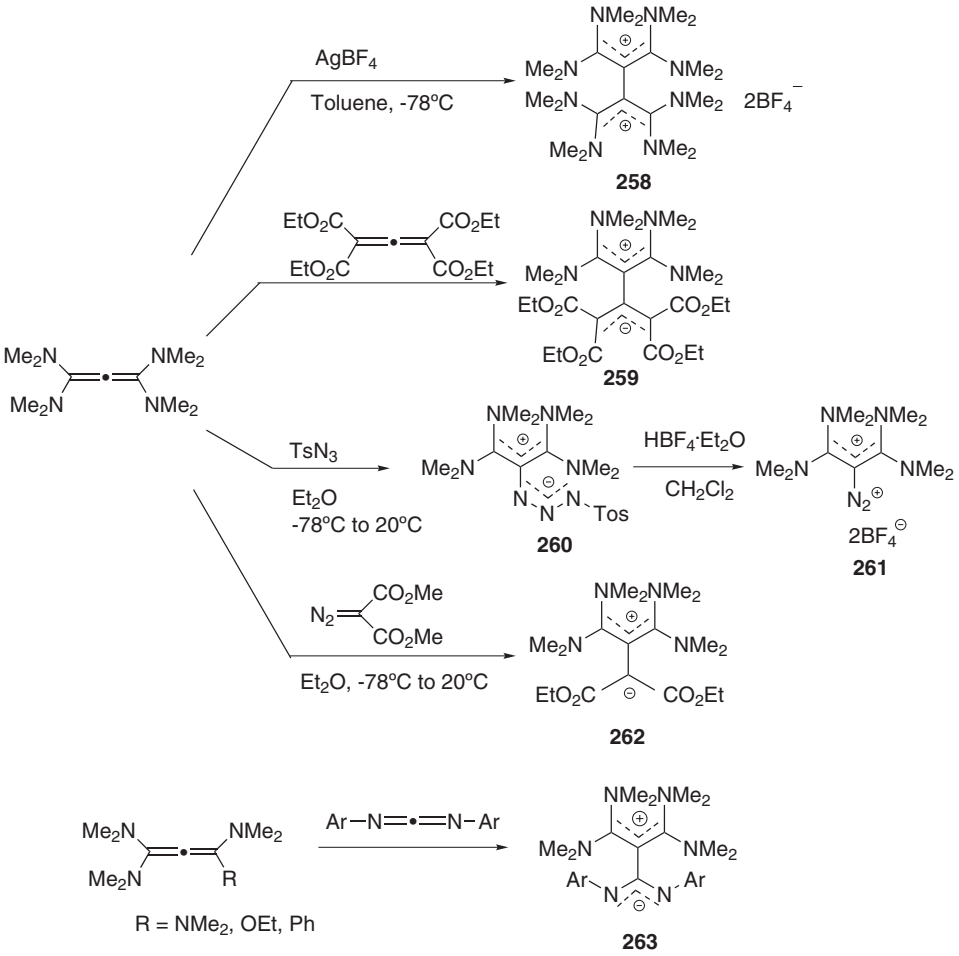
The reaction of 1,2-allenylamine **255** with 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide in boiling CCl_4 provided 4-methylene-4,5-dihydroisoxazoles **256** and **257** [132].



1 equiv	64 %	11%
2 equivs	-	84 %

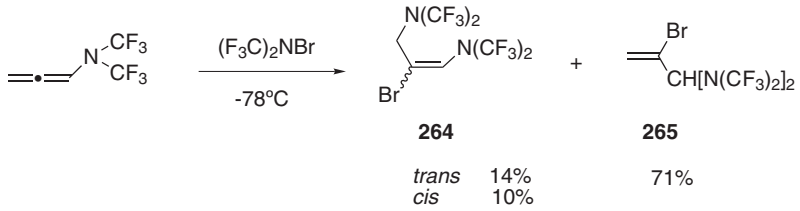
Scheme 10.114

The reactivity of 1,1,3-tri(dimethylamino)propadiene and 1,1,3,3-tetra(dimethylamino)propadiene towards electrophiles has also been demonstrated [133].



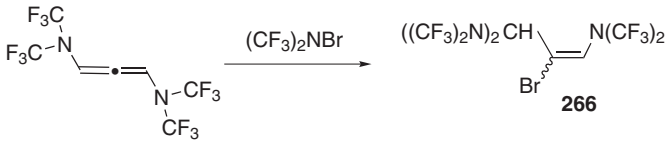
Scheme 10.115

N,N-Bis(trifluoromethyl)propadienylamine or 1,3-bis[*N,N*-bis(trifluoromethyl)]-aminopropadiene reacted with di(trifluoromethyl)amino bromide to give the center-attack products **264–266** [134].



264 **265**

trans 14% 71%
cis 10%

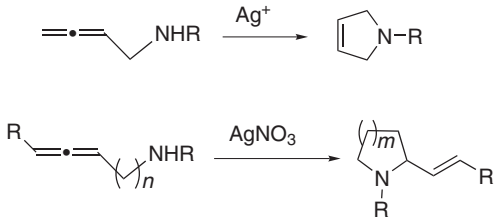


266

trans 54%
cis 44%

Scheme 10.116

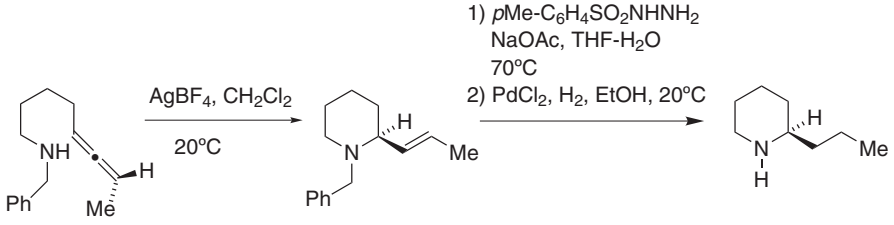
Under catalysis of Ag^+, 2,3-allenylamines can undergo cycloisomerization to afford *N*-containing heterocycles [135, 136]. Such metal-mediated isomerizations are discussed in detail in Chapter 15.



n = 3, 4 *m* = 1 or 2

Scheme 10.117 **267**

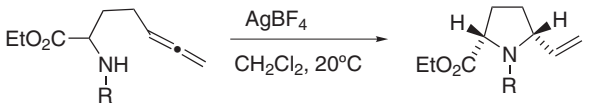
By applying this cycloisomerization protocol, (*R*)-(–)-coniline was synthesized in 11 steps starting from optically active 2,3-pentadienol [137].



268 **269** **270**

Scheme 10.118

In the cycloisomerization reaction of **271**, high diastereoselectivity was also observed, depending on the nature of the R group connected to the nitrogen atom [138].

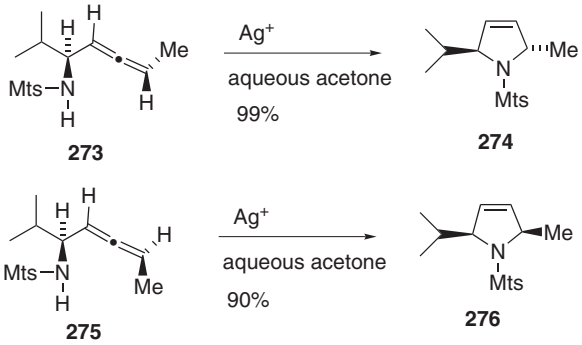


271 **272**

R = SO_2Tol, CH_2Ph, Boc *cis* / *trans* > 50 : 1 70 - 100%
R = H *cis* / *trans* 1 : 1, yield: 60%

Scheme 10.119

By starting from optically active 2,3-allenylamines **273** and **275**, the Ag(I)-catalyzed cycloisomerization afforded *trans*- or *cis*-pyrroline derivatives **274** and **276**, depending on the absolute configurations of the starting compounds [139].

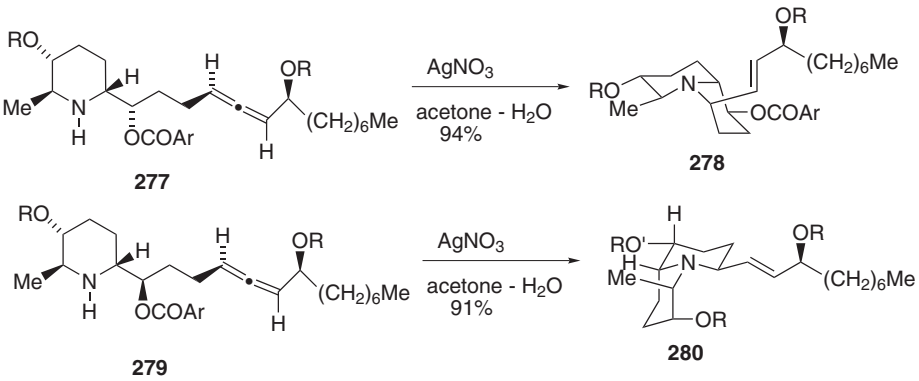


273 **274**

275 **276**

Scheme 10.120

Ha and Cha applied this reaction for the total synthesis of clavepictines A and B [140].

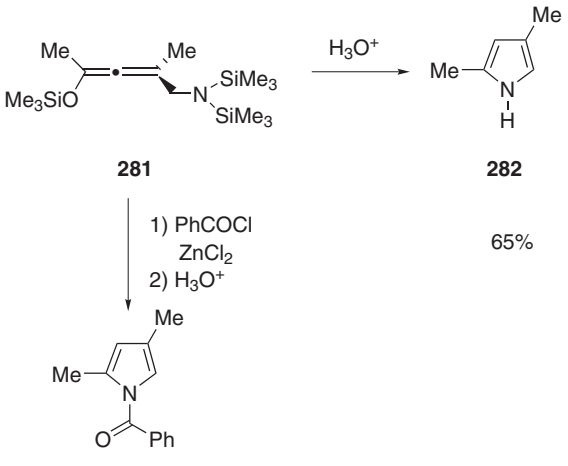


277 **278**

279 **280**

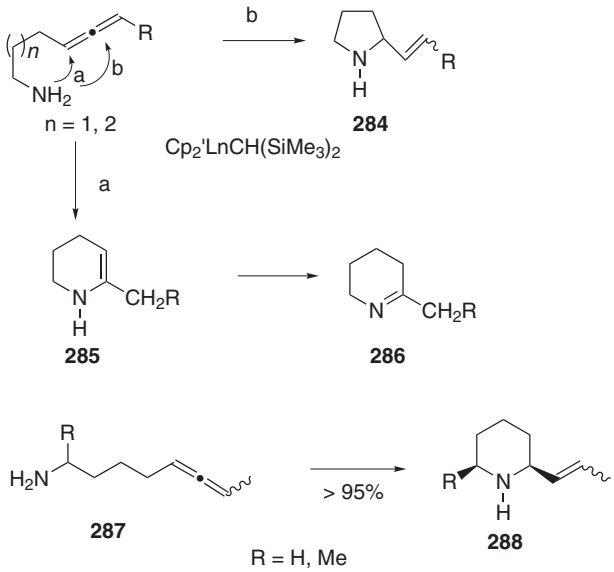
Scheme 10.121

This cycloisomerization of 4-siloxy-2,3-pentadienylamine can also be mediated by H^+ or PhCOCl–$ZnCl_2$ to afford pyrroles **282** and **283**, respectively [141].



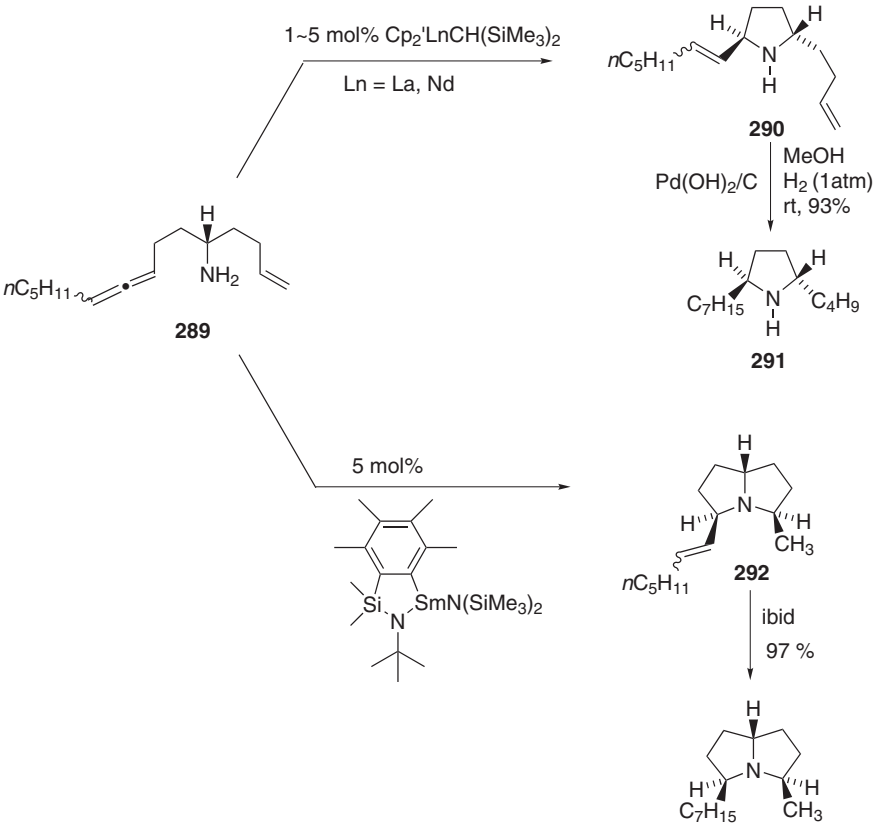
Scheme 10.122

Organolanthanide-catalyzed cycloisomerizations have also been realized [142, 143]. Regioselectivity is an issue here; with R being H, six-membered compounds are the major products while with R = alkyl, the reaction proceeded via path b affording **284**.



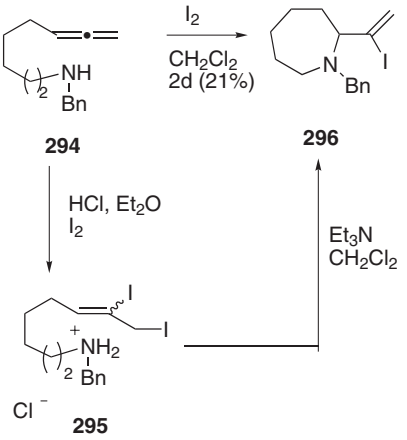
Scheme 10.123

Catalyzed by a samarium complex, the cycloisomerization of 1-(3′-butenyl)-4,5-allenylamine **289** would lead to bicyclic product **292** by a two-fold cyclization reaction [143].



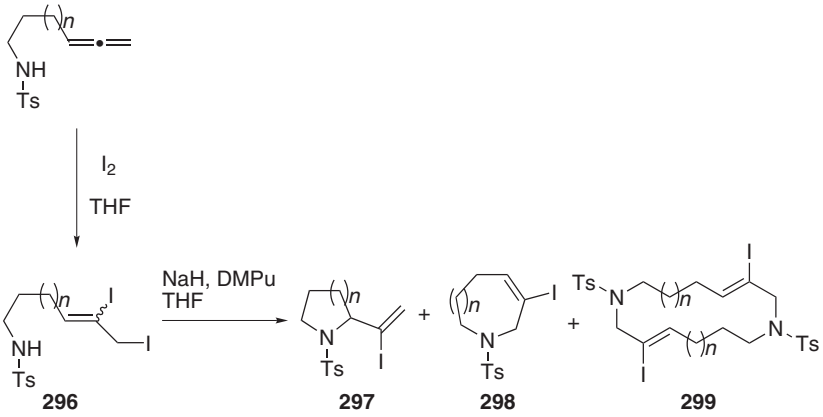
Scheme 10.124

Treatment of *N*-benzyl-6,7-octadienylamine **294** with I_2 afforded hexahydroazepine [144]. This transformation may also be conducted as a two-step procedure (17% overall).



Scheme 10.125

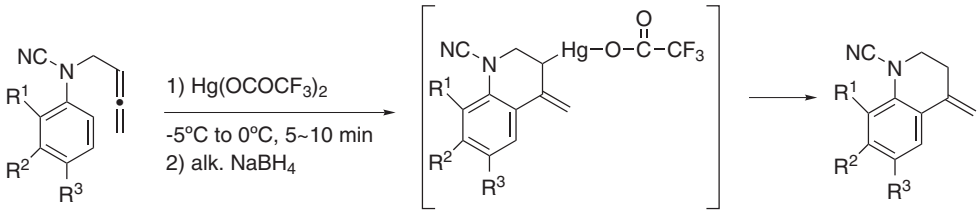
For the cyclization of the less nucleophilic sulfonamides, this conversion can only be achieved via this two-step protocol. The addition of I_2 was highly regioselective, addressing the terminal C=C bond, whereas the second step could deliver several products including the S_N2-substitution, S_N2'-substitution and bimolecular double substitution products **297–299**, depending on the length of the tether connecting the amine and the allene moiety [144, 145].



$n = 1$	83%	10% (*E*)	
$n = 2$	13%	13%	23%
$n = 3$	0	38% ((*E*)/(*Z*) = 1:1)	20%
$n = 4$	0	15% ((*E*)/(*Z*) = 1:1.5)	40%
$n = 5$	0	10% ((*E*)/(*Z*) = 1:3)	30%

Scheme 10.126

Hg^{2+} interacts with the allene moiety to mediate the cyclization of amine **300** [146]. Finally the C–Hg bond in **301** can be cleaved by reduction with $NaBH_4$.

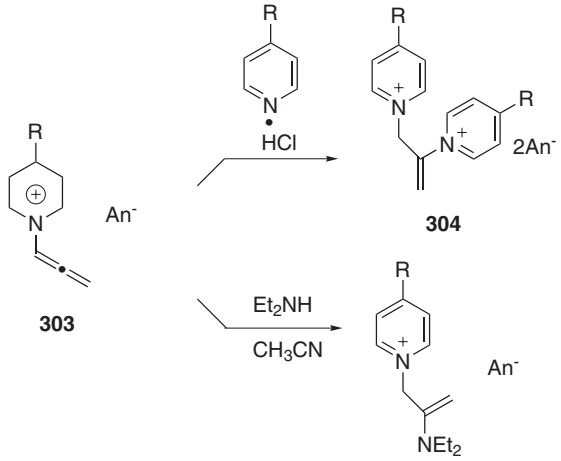


300 **301** **302**

Scheme 10.127

10.9.2 Nucleophilic Additions

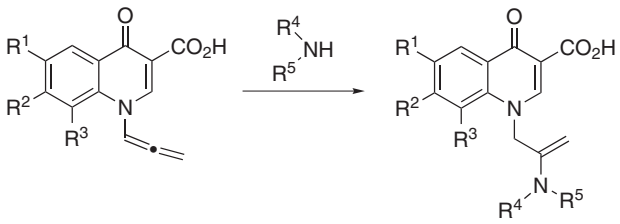
1,2-Allenyl pyridinium salts **303** are a class of electron-deficient allenes, of which the center carbon atom can accept nucleophilic addition of diethylamine and pyridine derivatives [147, 148].



303 **304** **305**

Scheme 10.128

1,2-Allenylquinolone **306** can also behave in a similar way to react with amines to afford 2,3-diamino-1-propene **307** [149].

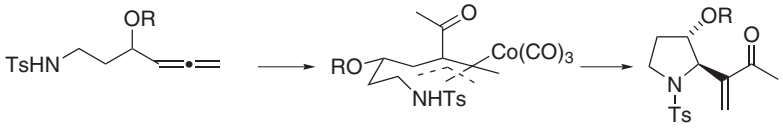


306 307

R^1, R^2 = OCH_2O, R^3 = H
R^1 = F, R^2 = Cl, R^3 = H
R^1 = F, R^2 = 4-methyl-1-piperazinyl, R^3 = H
R^1 = R^2 = R^3 = F

Scheme 10.129

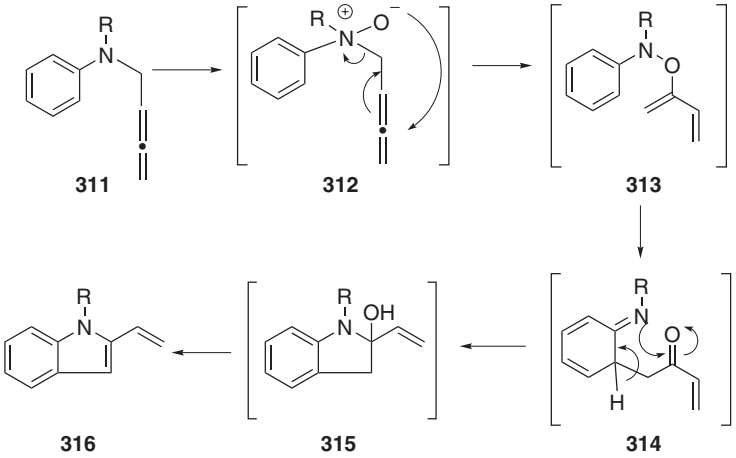
The allene moiety of *N*-(3-alkoxy-4,5-dienyl)toluenesulfonamide **308** is attacked by acetyltetracarbonylcobalt to form a π-allyl–Co intermediate **309**, which may be converted to *trans*-pyrrolidine derivatives **310** via an intramolecular nucleophilic substitution [150, 151].



308 **309** **310**

Scheme 10.130

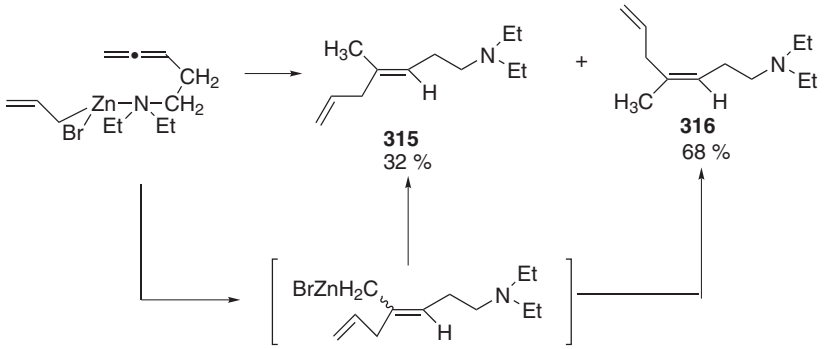
When *N*-alkyl-*N*-allenylaniline **311** was treated with magnesium monoperoxyphthalate in aqueous MeOH, the corresponding *N*-oxides **312** were formed initially, which would then undergo sequential [2,3]- and [3,3]-sigmatropic rearrangement and aromatization to afford *N*-alkyl-2-ethenylindoles **316** [152].



311 **312** **313** **314** **315** **316**

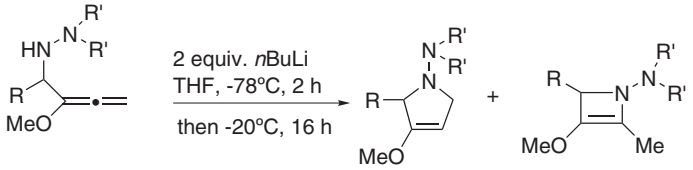
Scheme 10.131

With allylzinc bromide, 3,4-allenylamines delivered a mixture of *trans*- and *cis*-allylation products [153].



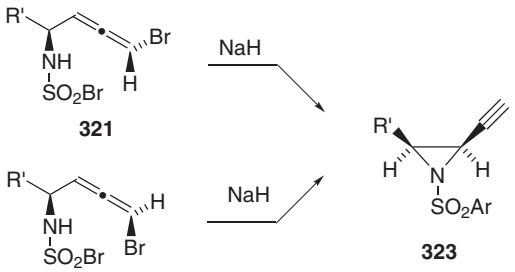
Scheme 10.132

In the presence of 2 equiv. of *n*BuLi, 2-methoxy-2,3-alkadienylhydrazines **318** undergo a cyclization reaction to afford *N*-(dialkylamino)-3-pyrrolines **319** [154]. In some cases a minor product, which was assigned as an azetidine **320**, was also detected.



Scheme 10.133

When the allene moiety of 2,3-allenylamines was substituted with Br, an intramolecular nucleophilic substitution reaction led to a chiral 2,3-*cis*-ethynylaziridine **323**. The diastereoselectivity depends on the absolute configuration of the allene moiety, i.e. typically for a matched–mismatched pair the *S*,a*R*-isomer afforded the product with much higher stereoselectivity [155, 156].

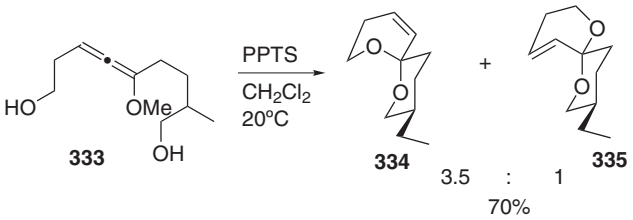


Scheme 10.134

10.10
2,3-Allenols

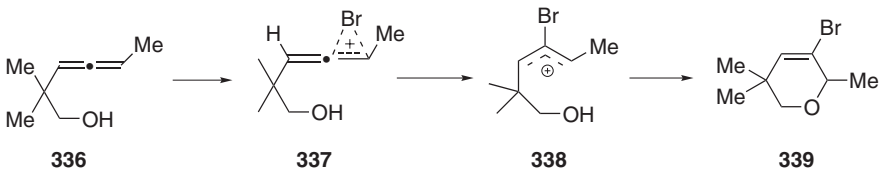
10.10.1
Electrophilic Additions

An acid-mediated cyclization of 3,4-dienol **333** to spiroketals **334** and **335** has been observed [157].



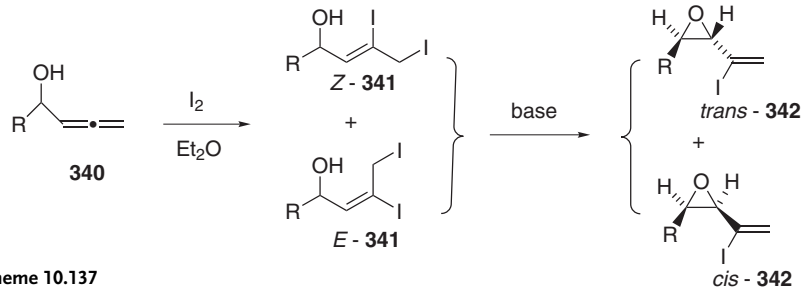
Scheme 10.135

The reaction of Br_2 with 2,2-dimethyl-3,4-hexadienol **336** afforded the pyran derivative **339** [158].



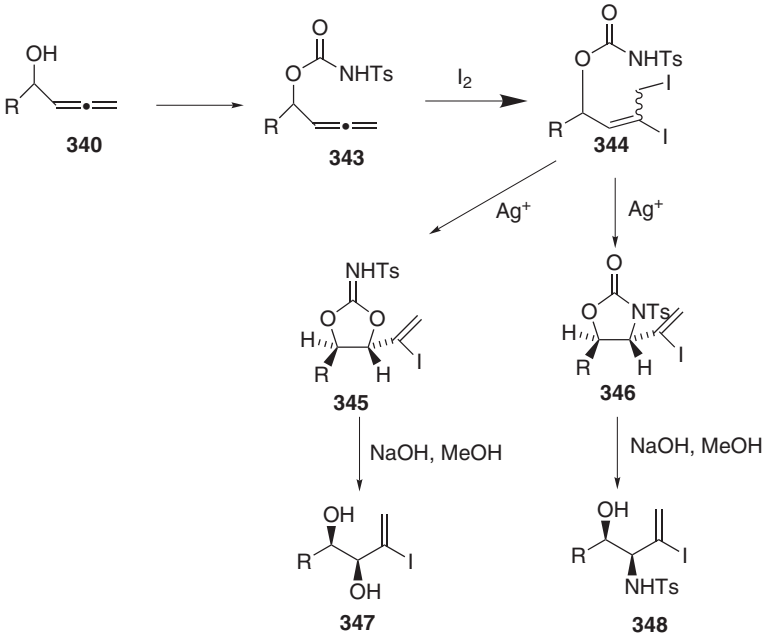
Scheme 10.136

The electrophilic addition of I_2 to 2,3-allenols **340** in Et_2O was highly regioselective with respect to the terminal C=C bond, leading to the diiodination products **341** with a preponderance of the *Z*-isomer. The diiodide **341** may be further converted to *trans*/*cis* vinylic epoxide **342** upon the treatment with a base (Scheme 10.137) [159].

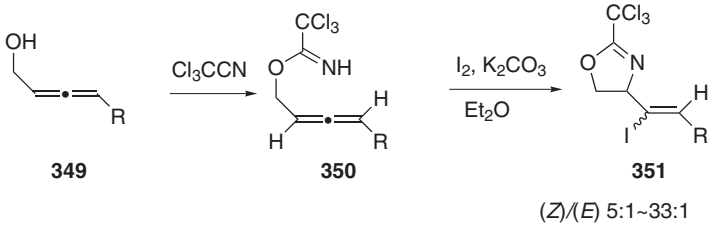


Scheme 10.137

Friesen et al. reported that 2,3-allenols **340** can be converted to the corresponding carbamate derivatives **343**, in which the terminal C=C bond of the allene moiety can be iodinated to afford diiodides **344**. Under the catalysis by an Ag^+ salt, compounds **344** react to give iminocarbonates **345** and oxazolindinones **346**, leading to diols **347** and amino alcohols **348**, respectively, after hydrolysis (Scheme 10.138) [160–162]. A similar reaction was observed with trichloroacetimidates **350** [163].

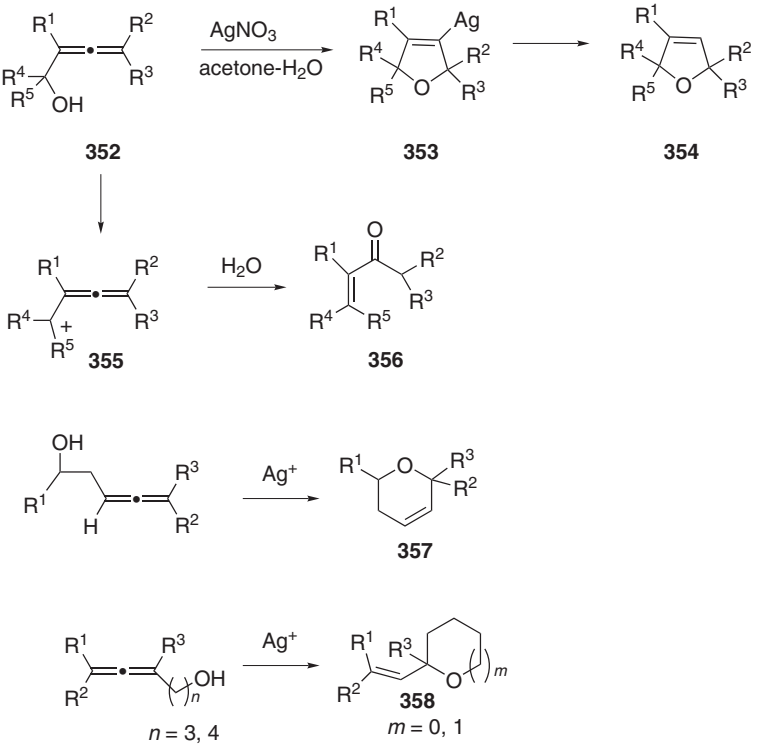


Scheme 10.138



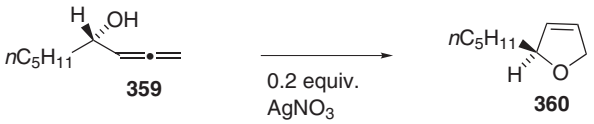
Scheme 10.139

The allene moiety of 2,3- or 3,4-allenols can also interact with Ag^+ to induce cyclization, affording 2,5-dihydrofurans **354** and 5,6-dihydro-2*H*-pyrans **357** [164, 165]. Starting from optically active 2,3-allenols, optically active 2,5-dihydrofurans were formed in a highly stereoselective manner [164 f, g]. In some cases, $AgNO_3$ may interact with the OH group to form a cationic intermediate **355**, leading to the formation of α,β-unsauturated enone **356** upon further hydrolysis [164 a, 165].



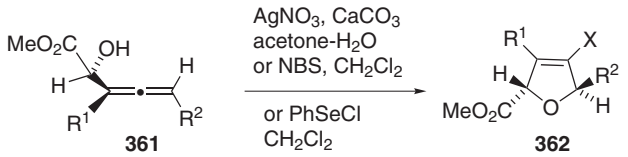
Scheme 10.140

The reaction pathway depends on the steric hindrance and/or the electron density of the allene moiety. With alcohols bearing a less or unsubstituted allene moiety, the addition of $CaCO_3$ may help the cyclization [166, 167].



Scheme 10.141

The allene moiety can also interact electrophilically with NBS or PhSeCl followed by intramolecular attack of the hydroxyl group leading to 3-heteroatom-substituted 2,5-dihydrofurans **362**. The chirality in the starting compounds can be efficiently transferred to the 2,5-positions of 2,5-dihydrofurans [167].



361 362

Scheme 10.142 X = H, Br, SePh

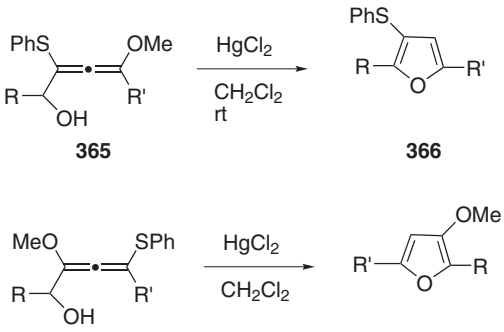
This transformation can also be affected by HCl gas or acid AberlysEt 15 resin [168]. Recently, $AuCl_3$ was shown to be a superier catalyst for this cyclization [168].

363 364

Scheme 10.143 22 mol% $AgNO_3$, 7 mol% $AuCl_3$; mixture, 95 %

Chapter 15 contains more of the transition metal-catalyzed cycloisomerizations of allenes.

Under the catalysis of 1 mol% of $HgCl_2$, 4-methoxy-2-thiophenyl-2,3-allenols **365** and **367** can undergo cyclization to afford 3-phenylthiofurans **366** and **368** (Scheme 10.144) [169]. In this cycloelimination reaction, the methoxy or phenylthio substituent served as the leaving group.

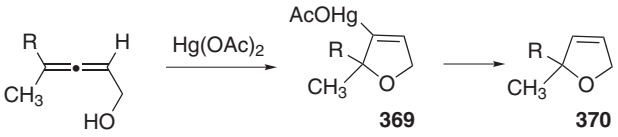


365 366

367 368

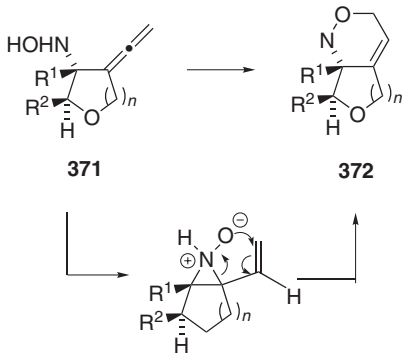
Scheme 10.144

It is interesting that the reaction under the catalysis of $Hg(OAc)_2$ led to 2,5-dihydrofurans [170].



Scheme 10.145

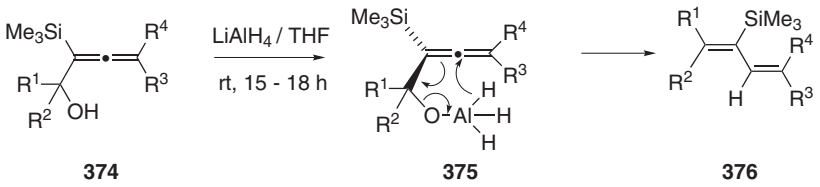
In 1998, an uncatalyzed cyclization of *N*-2,3-dienylhydroxylamine affording bicyclic products was also observed. The reaction was believed to proceed via a reverse Cope elimination [171].



Scheme 10.146

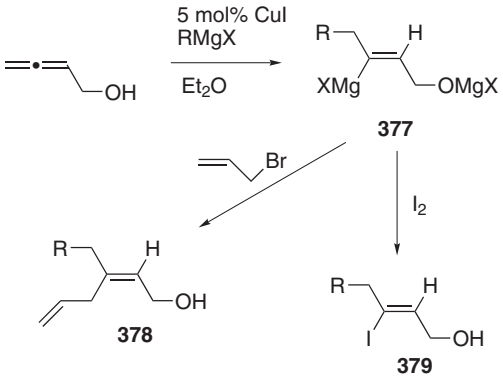
10.10.2 Nucleophilic Additions

The reduction of α-allenic alcohols with lithium aluminum hydride afforded 1,3-dienes **376** via the intramolecular transfer of hydride from aluminum to the central carbon atom of the allene moiety [172].

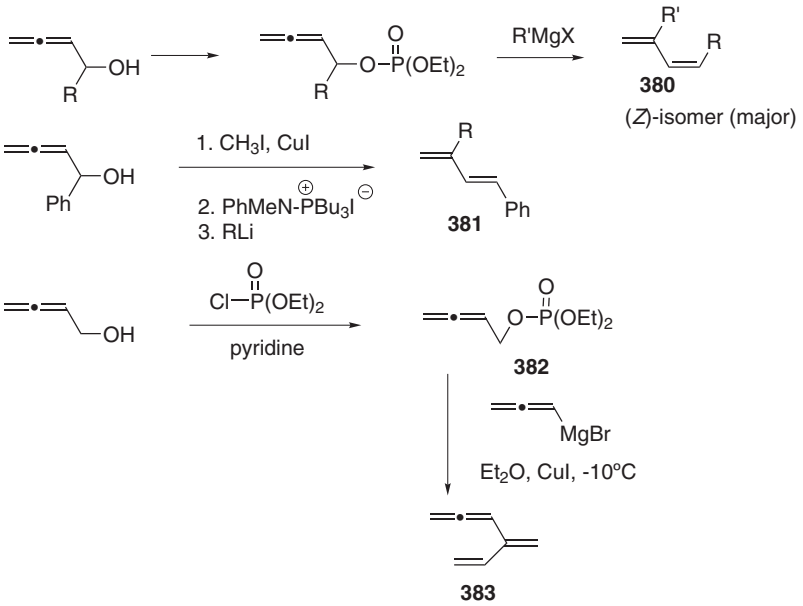


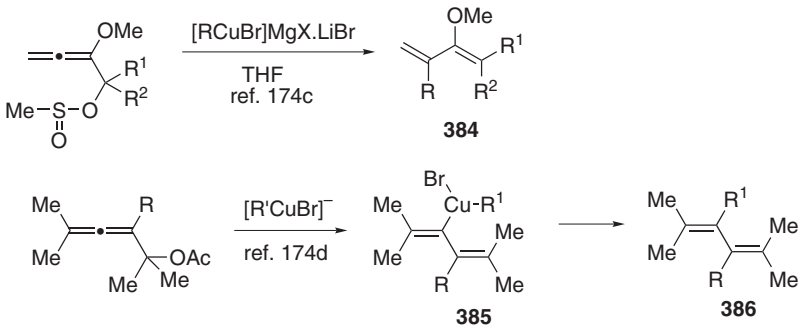
Scheme 10.147

2,3-Allenols can react directly with Grignard reagents under the catalysis of 5 mol% of CuI to afford vinylic magnesium intermediate **377**, which upon treatment with allyl bromide or I_2 afforded allylic alcohols **378** and **379**, respectively [173]. It should be noted that the R group of RMgX was introduced into the terminal carbon atom of buta-2,3-dienol.



Scheme 10.148

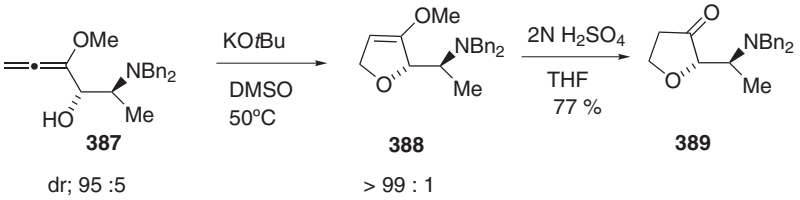




Scheme 10.149

When the hydroxy group is converted to a leaving group, the allene moiety can accept the nucleophilic attack leading to the formation of 1,3-dienes **380**, **381**, **383** and **386** [174].

In the presence of *t*BuOK in DMSO, 2-(N,N-dibenzyl)-4-methoxy-4,5-hexadien-3-ol **387** cyclizes to afford 3-methoxy-2,5-dihydrofuran **388,** probably via a SET mechanism involving DMSO [175].

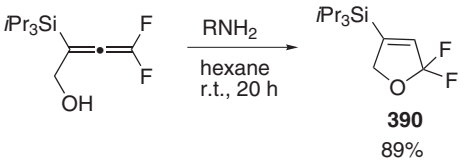


387 **388** **389**

dr; 95 :5 > 99 : 1

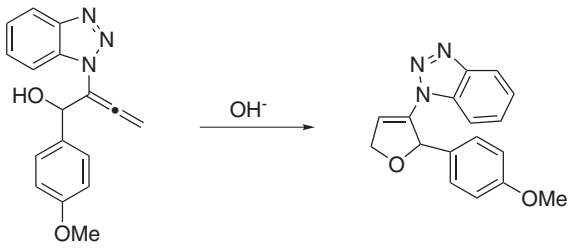
Scheme 10.150

With hexylamine at room temperature, 4,4-difluorobuta-2,3-dienols also cyclize to 2,5-dihydrofuran **390** [176]. A similar cyclization was also observed with 2-benzotriazole-substituted-2,3-allenol **391** [177].



390

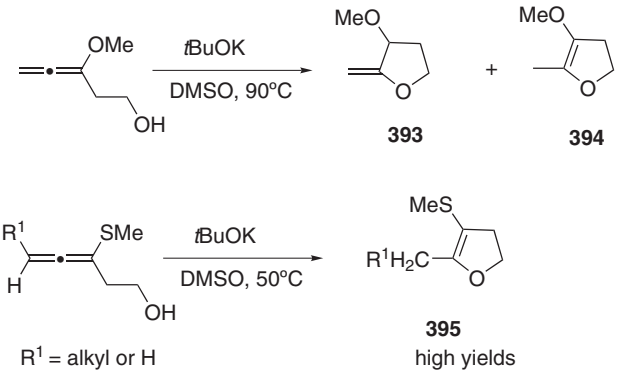
89%



391 **392**

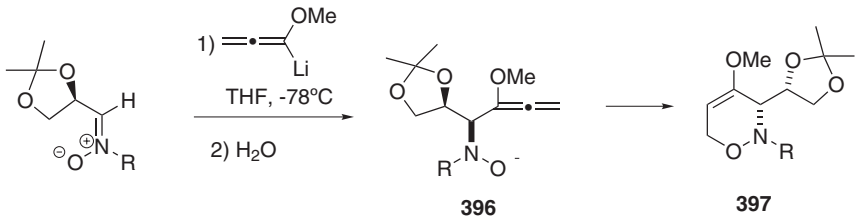
Scheme 10.151

The cyclization of 3-methoxy(or thio methyl)-3,4-pentadienol with KO*t*Bu also afforded five-membered ring compounds **393–395** [175c].



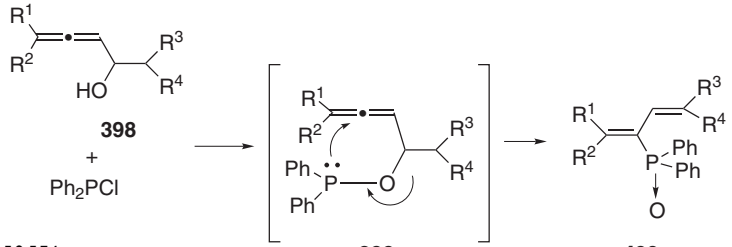
Scheme 10.152

4-Nitronyl-3-methoxy-1,2-alkadiene **396** cyclized to afford 1,2-oxazine derivatives **397** [178].



Scheme 10.153

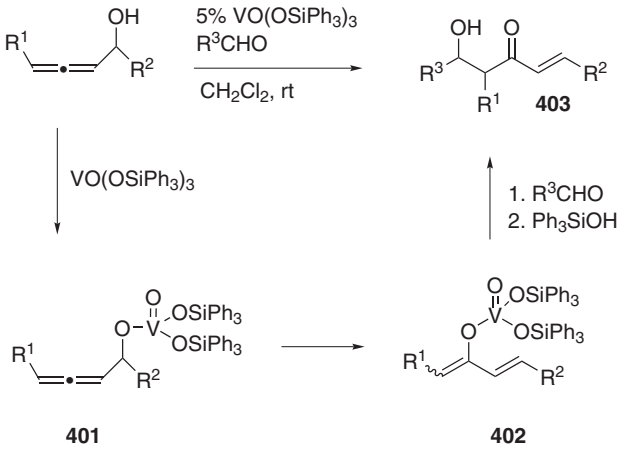
The reaction of 2,3-allenols **398** with Ph_2PCl afforded dienyl phosphine oxide **400** via the intramolecular nucleophilic attack of the phosphorus atom in **399** [179].



Scheme 10.154

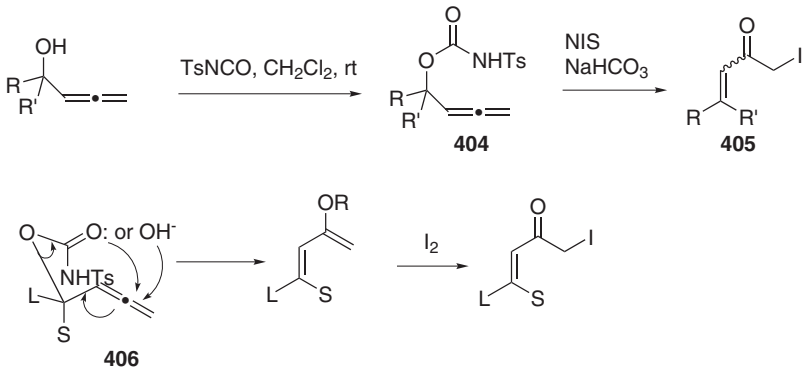
Many more of these examples can be found in Chapter 1.

Recently, Trost et al. reported the vanadium-catalyzed addition reaction of 2,3-allenols [180]. Here the oxygen in **401** served as an intramolecular nucleophile to attack the center carbon atom of allene to form a vanadium enolate **402**. Aldol condensation of **402** with an aldehyde afforded (2-hydroxy)alkyl vinylic ketones **403**.



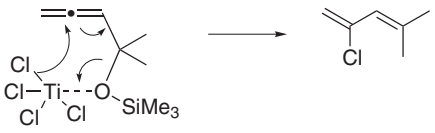
Scheme 10.155

With NIS and aqueous $NaHCO_3$, the carbamates of tertiary 2,3-allenols **404** reacted to give 4,4-dialkyl-1-iodo-3-buten-2-ones **405** via the sequential intramolecular attack of the carbonyl oxygen or intermolecular attack of OH in **406** and iodination [181].



Scheme 10.156

The reaction of an allenoxylsilane, generated in situ from the reaction of propargyltrimethylsilane with carbonyl compounds, with $TiCl_4$ led to the formation of 2-chloro-1,3-diene via the Ti-mediated nucleophilic attack of the chlorine atom [182].

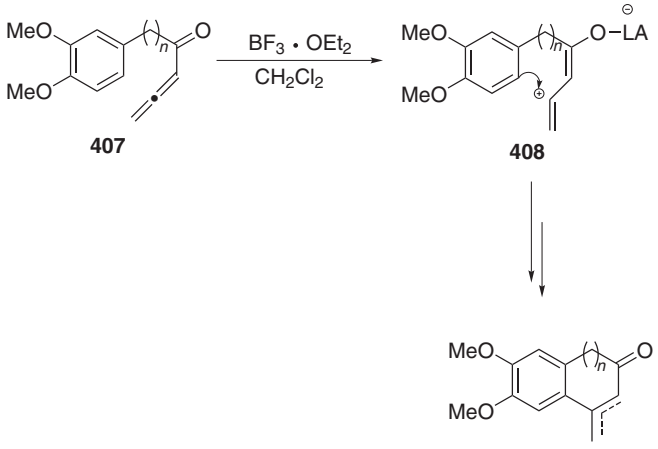


Scheme 10.157

10.11
1,2-Allenic Ketones

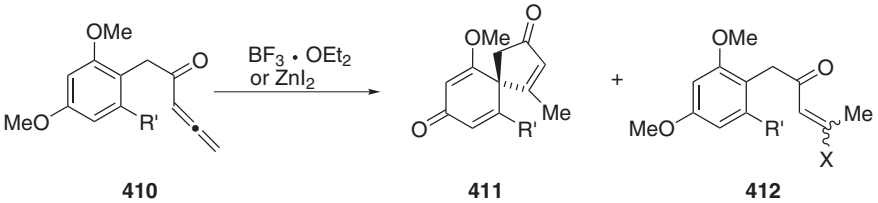
10.11.1
Electrophilic Additions

Under the catalysis of a Lewis acid, 1,2-allenyl ketones **407** can undergo 5-*endo* mode cyclization to benzo cycloketones **409** [183, 184]. The interaction of the Lewis acid with the carbonyl group leads to the formation of a cationic intermediate **408**, which attacks the aromatic ring as an electrophile (Scheme 158). In this reaction, the position of the C=C bond in the products depends on the length of the tether connecting the aryl group and the carbonyl group.



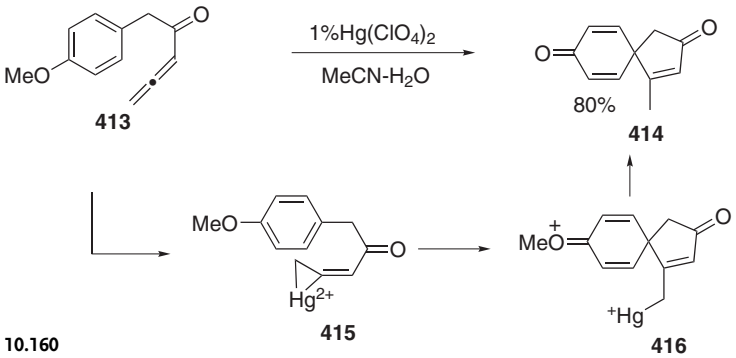
Scheme 10.158

In these reactions, the cyclization mode is also determined by the substitution patterns of the aryl ring. If one or both *ortho*-positions are occupied by a methoxy group, the reaction affords spiro-*endo* mode cyclization products **411** (Scheme 10.159) [185]. The formation of a **408**-type intermediate was supported by the fact that 2-halo-1-alkyl ketones **412** were formed in some cases [184, 185].



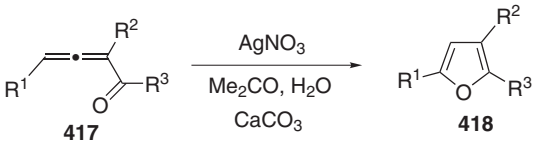
Scheme 10.159

A limitation of this cyclization is that at least two methoxy substituents should be on the aryl ring. Hashmi et al. [186] observed that by using 1 mol% of $Hg(ClO_4)_2$, the reaction of *p*-methoxybenzyl 1,2-propadienyl ketone **413** also went smoothly to afford the spiro-*endo* mode cyclization product **414** (Scheme 10.160). Here the presence of water is important. The high efficiency shown by Hg(II) may be due to the fact that Hg(II) can coordinate with both the carbonyl oxygen and the terminal C=C bond.

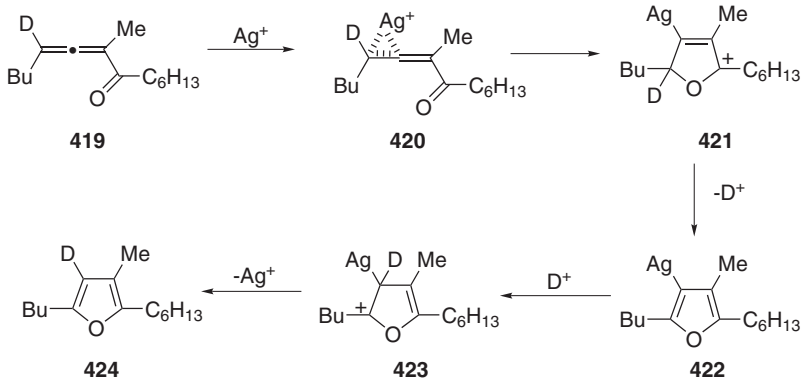


Scheme 10.160

Marshall et al. noted that under the catalysis of Ag^+ or Rh^+, 1,2-allenyl ketone or aldehyde **417** may undergo cycloisomerization to afford furans **418**. The reaction proceeded via the interaction of Ag^+ or Rh^+ with the relatively electron-rich C=C bond in the allene moiety followed by nucleophilic attack of the carbonyl oxygen [187]. Through a labeling study, it was found that the reaction proceeds by the mechanism shown in Scheme 10.162 [188].



Scheme 10.161



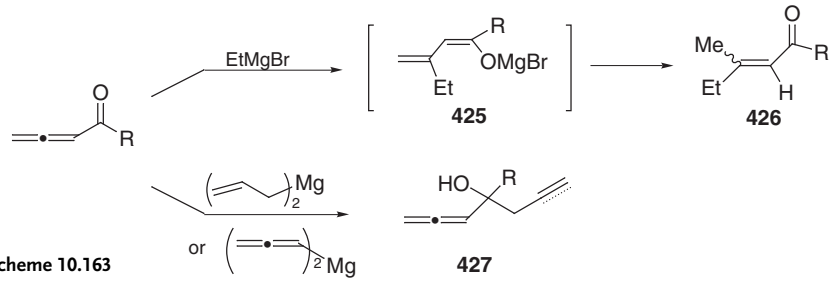
Scheme 10.162

Again, more details on these transition metal-catalyzed reactions are discussed in Chapter 15.

10.11.2 Nucleophilic Additions

Due to the strong electron-withdrawing ability of the carbonyl group, a 1,2-allenyl ketone is a very good Michael acceptor. Hence it can undergo 1,4-addition with all kinds of nucleophiles.

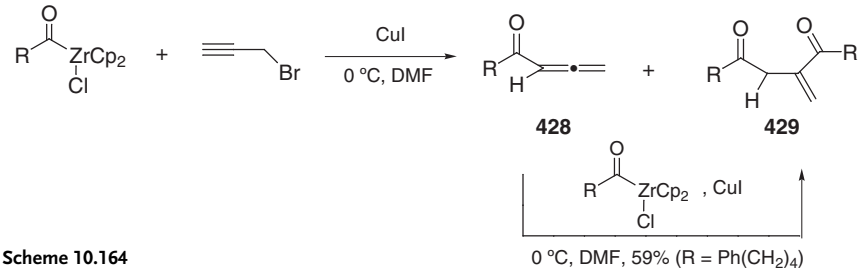
Grignard reagents can react with 1,2-allenyl ketones in a 1,2- or 1,4-addition manner depending on the reactivity of the Grignard reagents. The reaction with ethylmagnesium bromide involves 1,4-addition followed by migration of the C=C bond from the β,γ-position to the α,β-position whereas that with an allyl or propargyl Grignard reagent undergoes 1,2-addition with the carbonyl group to afford tertiary alcohols **427** (Scheme 10.163) [189].



Scheme 10.163

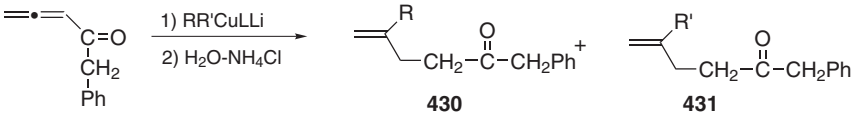
Similar 1,2-addition reactions were also observed in the reaction of 2,3-allenal with organolithiums, Grignard reagents or the reduction of 1,2-allenyl ketones with metal hydrides [190].

Recently, Hanzawa et al. reported that, catalyzed by Cu(II), the reaction of an acylzirconium with propargyl bromide affords 1,2-allenyl ketones **428**, which may undergo a further conjugate addition with acylzirconocene to give 2-methylene 1,4-diketones **429** [191].



Scheme 10.164

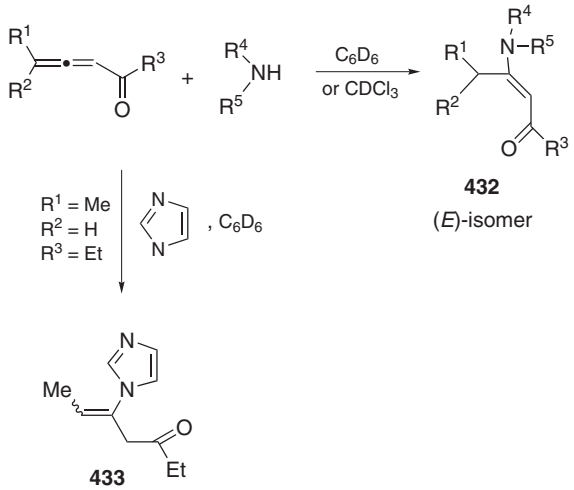
The reaction of 1,2-allenyl ketones with organocuprates afforded β,γ-unsaturated enones. The reaction with mixed cuprates RR′CuLi delivered, depending on the properties of R and R′, two products **430** and **431** [192].



430 **431**

Scheme 10.165

β-Nucleophile substituted (*E*)-α,β-unsaturated enones can be synthesized by the reaction of 1,2-allenyl ketones with t-$BuNH_2$ or pyrrolidine, whereas the reaction with imidazole afforded the corresponding β,γ-unsaturated enones [193, 194]. The ratio of α,β- to β,γ-products reflects the regioselectivity of the addition reaction. However, the reaction of aniline afforded (*Z*)-α,β-unsaturated enones, probably owing to the strong hydrogen bond between the amino group and the initially formed dienolate oxygen.

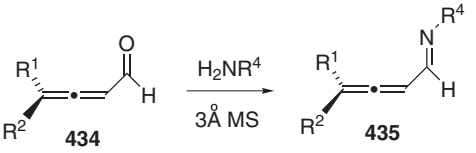


432
(*E*)-isomer

433

Scheme 10.166

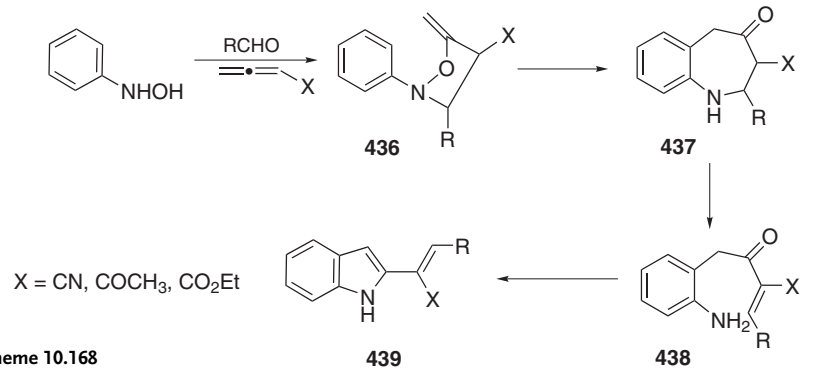
The reaction of disubstituted 2,3-allenals **434** with primary amines leads to the predominant formation of 1,2-allenylimines in THF, CCl_4, toluene, etc. [194].



434 **435**

Scheme 10.167

With phenylhydroxylamine and an aldehyde, 1,2-propadienyl methyl ketone afforded indole derivatives via the intermediacy of **437**; the latter was formed by a sequential addition, *in situ* aldol condensation and sigmatropic rearrangement process [195].

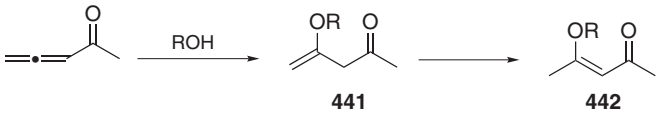


Scheme 10.168

Hydrolysis of 1,2-allenyl ketones affords 1,3-diketones [196].

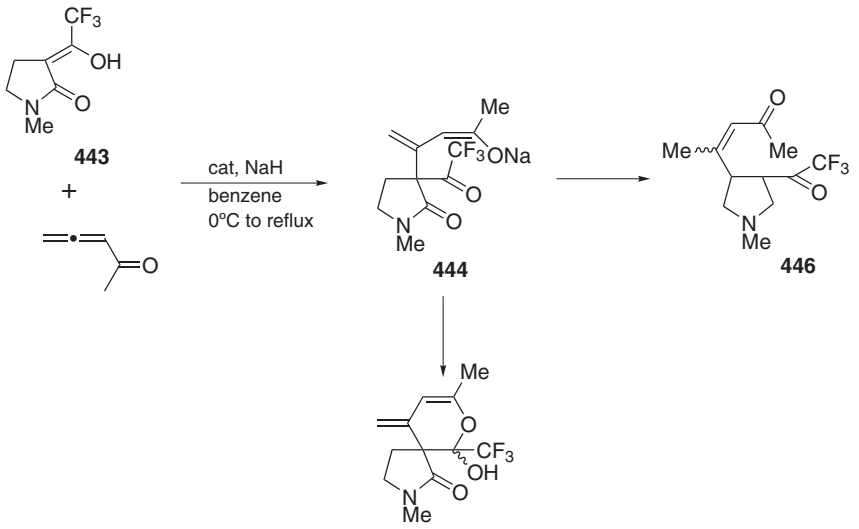
Scheme 10.169

Under the catalysis of MeONa, MeOH can react with 1,2-allenyl ketones to give β-methoxy-β,γ-unsaturated enones **441**, which undergo migration of the C=C bond to afford the more favorable β-methoxy-α,β-unsaturated enones [197–199].



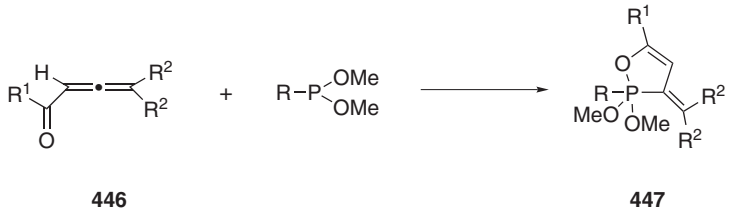
Scheme 10.170

1,4-Addition products **444** are obtained from 3-(1′-hydroxy-2′,2′,2′-trifluoroethylidenyl)-1-methylpyrrolidin-2-one and acylallene. They may further react with the C=O group connected to CF_3 to afford bicyclic compound **445** via intramolecular nucleophilic attack of oxygen on the C=O group connected to CF_3 and **446** via protonation of sodium enolate **444** [200].



Scheme 10.171

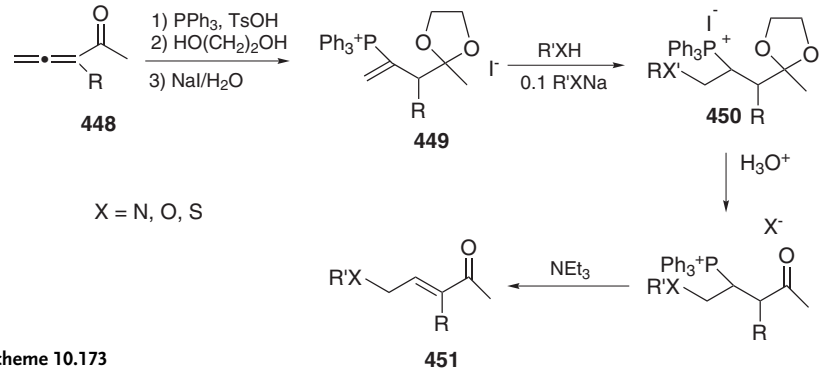
In 1972, Buono et al. observed that tricoordinated phosphorus compounds $RP(OMe)_2$ (R = Me, Ph, $CH{=}CH_2$, SMe, CN, OPh, NMe_2) or Ph_2POMe reacted with 1,2-propadienyl ketone **446** to afford 3-alkylidene-Δ^4-1,2-oxaphospholenes **447** [201, 202].



446 **447**

Scheme 10.172

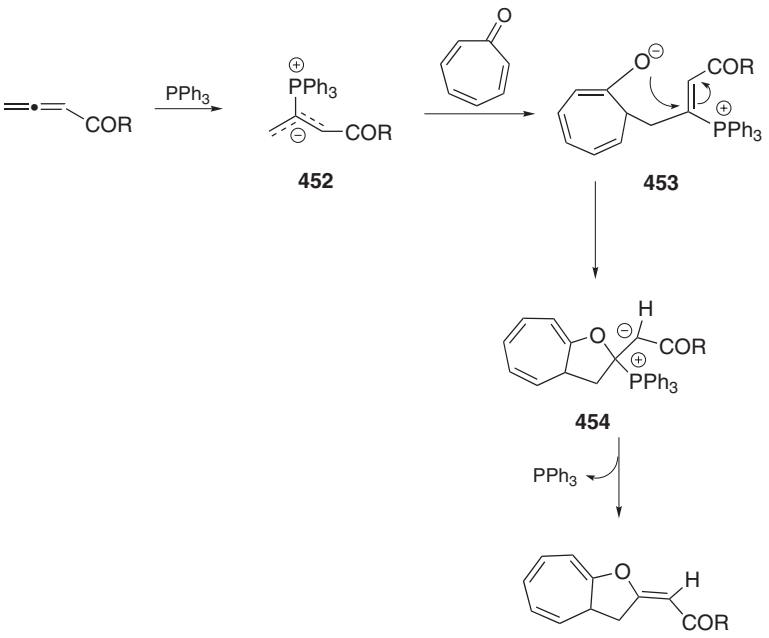
It is interesting that the reaction of triphenylphosphine with a 1,2-allenyl ketone leads to the formation of a vinyl phosphonium salt **449**, which upon protection of the carbonyl group would accept nucleophilic attack followed by elimination in the presence of Et_3N to afford γ-nucleophile substituted-α,β-unsaturated enones **451** [197].



448 449 450 451

Scheme 10.173

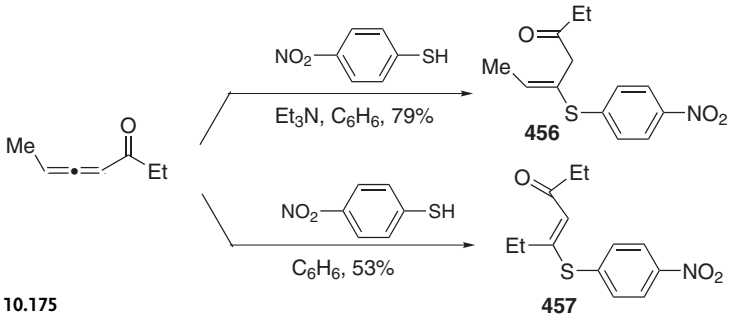
The intermediate **452** resulting from the direct reaction of PPh_3 with an allenyl ketone can also serve as an all-carbon 1,3-dipole to undergo [8 + 2]-annelation with tropone to yield fused bicyclic tetrahydrofuran derivatives **455** [203].



452 453 454 455

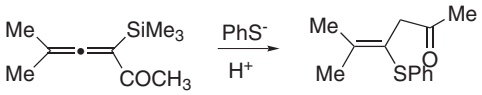
Scheme 10.174

With thiol in the presence of Et_3N in $CDCl_3$, allenyl ketones give β,γ-unsaturated enones. However, in the absence of Et_3N, the same reaction affords α,β-unsaturated enones [193].



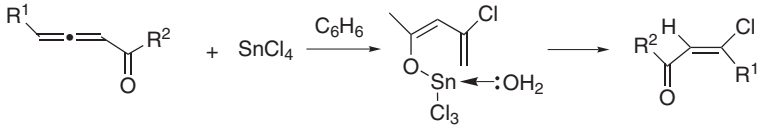
Scheme 10.175

The effect of base is interesting since the reaction of **458** with lithium thiophenolate also produced a β,γ-unsaturated enone **459** [204]. In the presence of a base, anionic RS^- attacks the β-C to form a dienolate intermediate, in which the π-bonds are orthogonal to each other. The γ-protonation needs a 90° rotation of the α,β-C–C single bond to form α,β-unsaturated enones; thus the reaction afforded a β,γ-unsaturated enone via α-protonation [193].



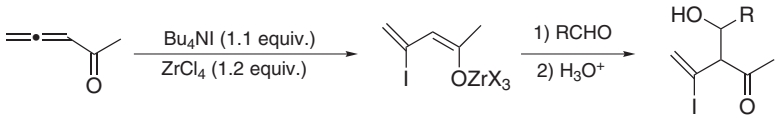
Scheme 10.176 **458** **459**

The reaction of $SnCl_4$ with 1,2-allenyl ketones afforded *trans*-β-chloro-α,β-unsaturated enones **461** via the hydrolysis of **460** [205].



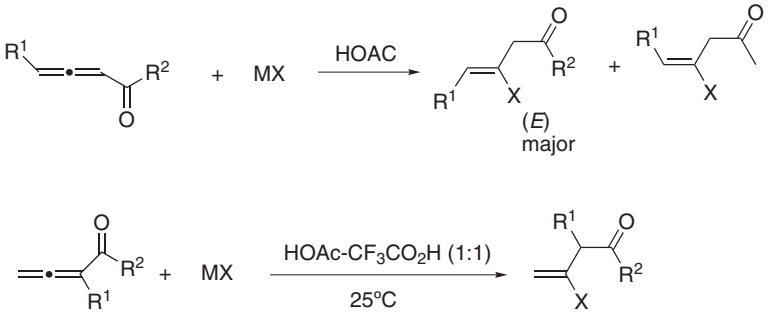
Scheme 10.177 **460** **461**

Zhang and Lu observed that the sequential reaction of an allenyl ketone, Bu_4NI, $ZrCl_4$ and an aldelyde in CH_2Cl_2 at –78 °C afforded 3-(1′-hydroxyalkyl)-4-iodo-4-en-2-one **463** via conjugate addition and a subsequent aldol process [206].



Scheme 10.178 **462** **463**

Ma et al. reported the hydrohalogenation of 1,2-allenyl ketones leading to β-halo-β,γ-unsaturated enones [87, 207]. The reaction of 3-substituted-1,2-allenyl ketone with MX in HOAc affords (*E*)-2-halo-2-alkenyl ketones as the major product. In HOAc, the reaction of 1-substituted-1,2-allenyl ketones affords a mixture of β-halo-α,β- and -β,γ-unsaturated enones whereas in CF_3CO_2H–HOAc (1:1) the same reaction affords β,γ-unsaturated enones.

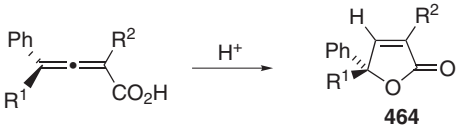


Scheme 10.179

10.12
2,3-Allenoic Acids and 2,3-Allenoates

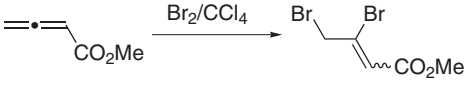
10.12.1
Electrophilic Additions

In an acidic medium, optically active 3-phenylallenecarboxylic acids can cyclize to the chiral butenolides **464** [208].



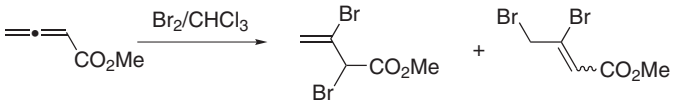
Scheme 10.180 **464**

The relatively electron-rich terminal carbon atom in 2,3-allenoates can be dibrominated to afford 3,4-dibromo-2-butenoate **465** with the *E*-isomer being the major product [209–211].



Scheme 10.181 **465**

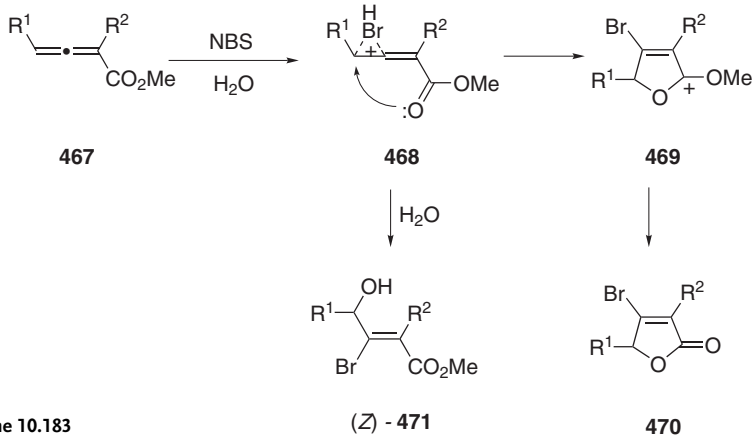
However, it is interesting that the same reaction in $CHCl_3$ afforded a mixture of dibromination products of both C=C bonds [212].



466 **465**

			(*E*)/(*Z*) (%)
	-30°C	27%	27/46
Scheme 10.182	rt	6%	18/76

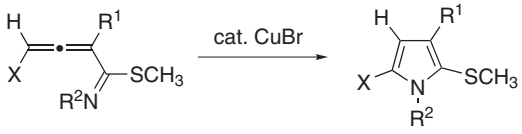
The bromolactonization product **470** was obtained by the reaction of γ-monoalkyl-substituted allenoates **467** with NBS in H_2O or Br_2 at room temperature. Here the carbonyl oxygen served as an intramolecular nucleophile. The *Z*-isomer of the bromohydroxylation product was also formed in 4% yield (R^1 = Me, R^2 = H) [211, 213, 214]. The absence of the *Z*-isomer may be ascribed to the easy conversion of the *E*-isomer to butenolide **470**.



467 **468** **469**

Scheme 10.183 (*Z*) - **471** **470**

In the presence of a catalytic amount of CuBr, thiomethyl-substituted-1,3,4-azatriene **472** underwent cyclization to afford tetrasubstituted pyrroles **473** [215].

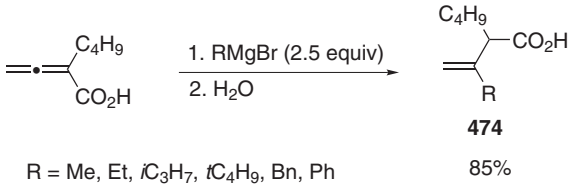


472 **473**

Scheme 10.184 X = OR^1, NR^2

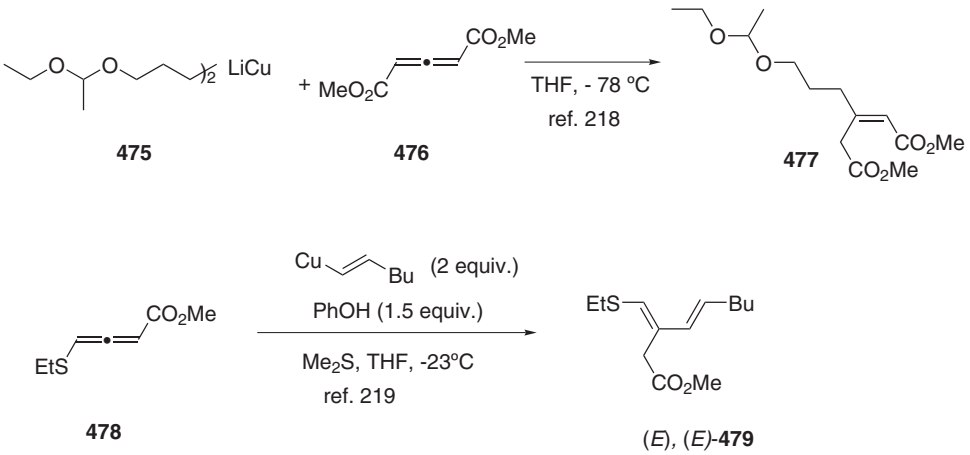
10.12.2
Nucleophilic Additions

In 1952, Wotiz and co-workers reported the reaction of ethylmagnesium bromide with 2-butyl-2,3-butadienoic acid affording 3-alkenoic acid **474** via a 1,4-addition process [216, 217].



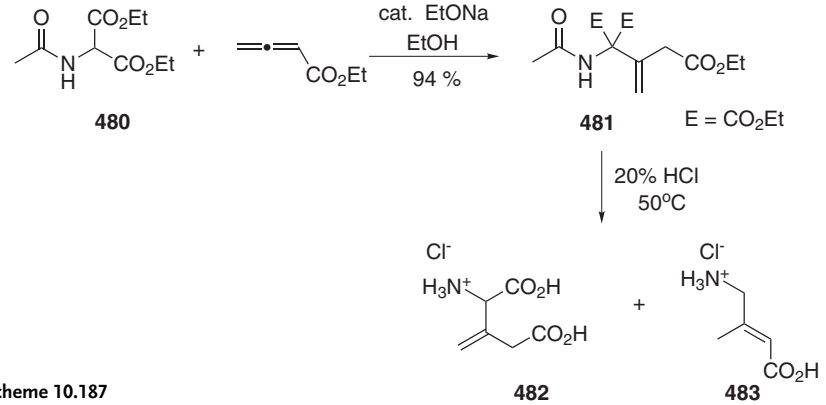
Scheme 10.185

The 1,4-conjugate addition of dialkyl cuprate to 4-methoxycarbonyl-2,3-butadienoate **476** or 4-thioethyl-2,3-butadienoate **478** leads to the 3-(*E*)-alkenoates **477** and **479** with high diastereoselectivity [218, 219].



Scheme 10.186

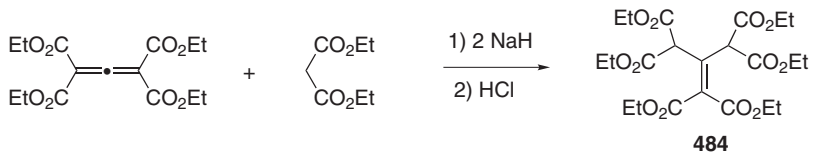
Sodium salt of diethyl acetamidomalonate **480** reacts with ethyl 2,3-butadienoate in the presence of a catalytic amount of EtONa to afford β,γ-unsaturated enoate **481**, which can be easily decarboxylated leading to β-methyleneglutamic acid hydrochloride **482** [220].



Scheme 10.187

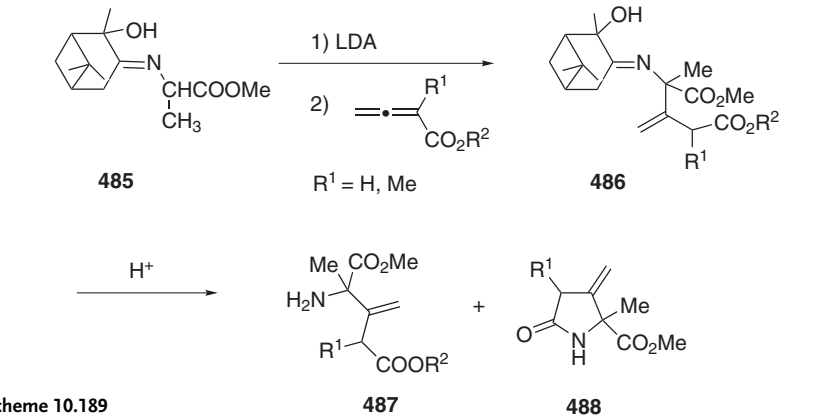
In the first step, the terminal C=C bond was kept in its original position. However, in the second step, further decarboxylation and partial migration of the C=C bond affording **483** were observed [220].

Compound **484** was synthesized by the reaction of malonate with propadienetetracarboxylate in the presence of NaH [221].



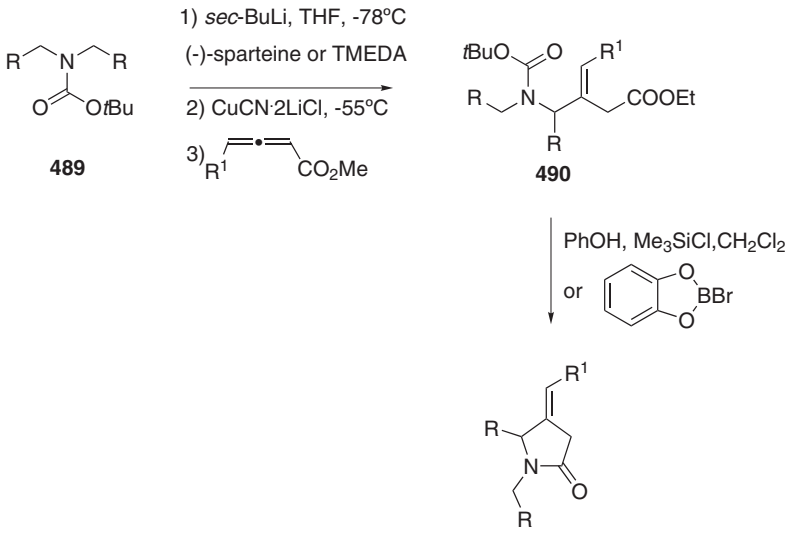
Scheme 10.188

Similarly, the lithium salt of α-iminyl carboxylate **485** can attack the β-position of 2,3-alkadienoates to provide β,γ-unsaturated enoates **486**, which upon protonation or hydrolysis afforded **487** and **488** [222].



Scheme 10.189

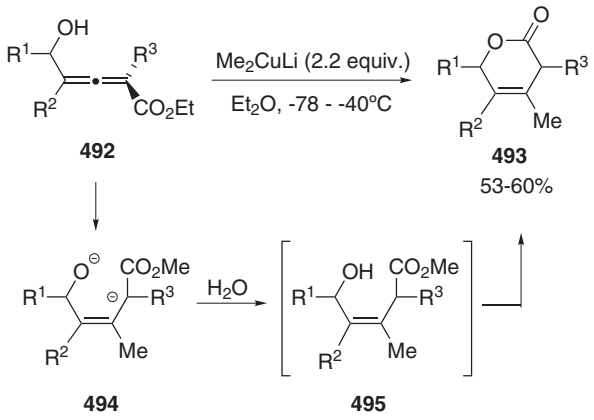
The addition of α-aminoalkyl cuprates to 2,3-alkadienoates leads to 3-(aminoalkyl)-3-(*E*)-alkenoates **490** with high stereoselectivity [223].



489 **490** **491**

Scheme 10.190

In 2000, Knight et al. reported the 1,4-conjugate addition of Me_2CuLi with 4-(1′-hydroxyalkyl)-2,3-alkadienoate **492** followed by a lactonization to δ-lactones **493**. Here, the stereoselective introduction of the methyl group is important for the subsequent lactonization [224].

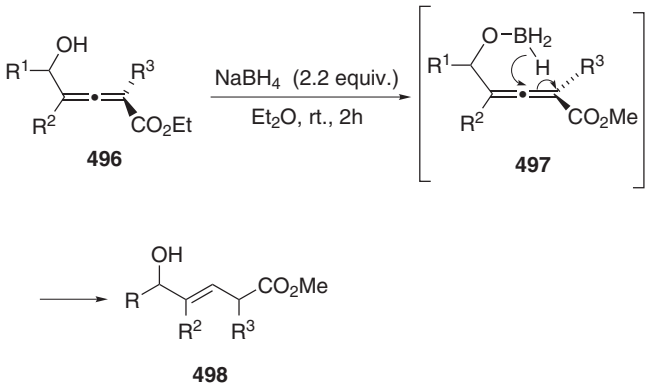


492 **493** 53-60%

494 **495**

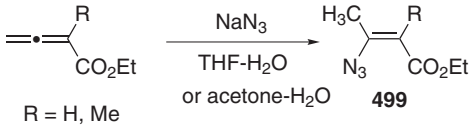
Scheme 10.191

5-Hydroxyl-2,3-allenoate **496** can also react with H^- to reduce the α,β-C=C bond highly selectively [224].



Scheme 10.192

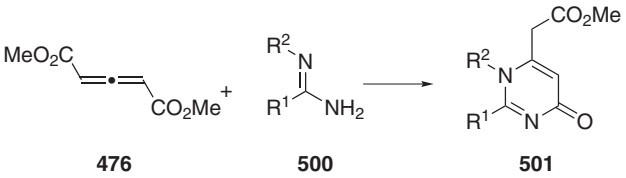
An excess of sodium azide reacts with 2,3-allenoates to give α,β-unsaturated enoates **499**. No reaction was observed with 4,4-disubstituted 2,3-allenoates [225].



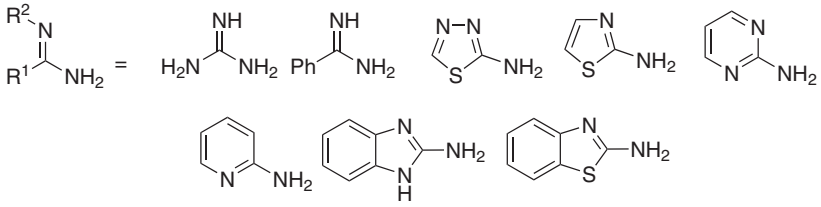
Scheme 10.193

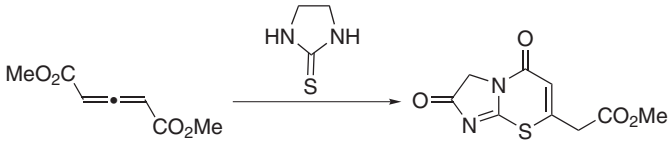
Dimethyl allene-1,3-dicarboxylate **476** can react with a variety of nucleophiles with an 'N=C–NH_2' substructure to afford monocyclic or bicyclic compounds **501**. In this reaction the iminyl nitrogen first attacks the center carbon atom of the allene moiety to afford 3-amino-4-(methoxycarbonyl)-2-butenoate, in which the other nitrogen atom and the conjugated carboxylate undergo an aminolysis reaction to afford the cyclic product [226].

Benzylaniline can aslo react with dimethyl allene-1,3-dicarboxylate to yield (*E*)-β-amino-γ-methoxycarboxyl-α,β-unsaturated enoate (*E*)-**506** as the single stereoisomer [226, 227].

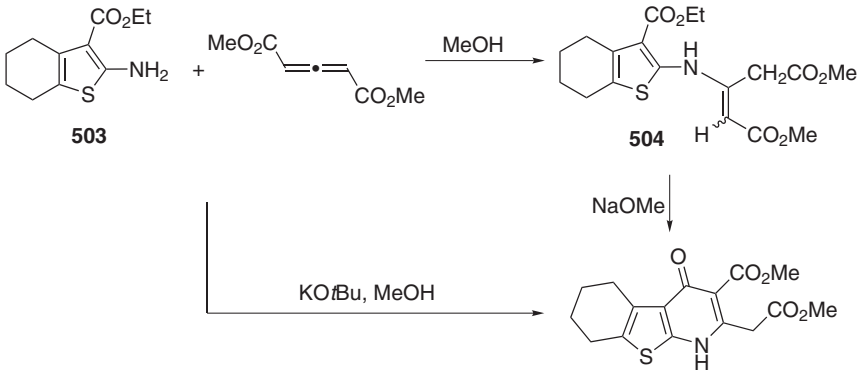


476 500 501



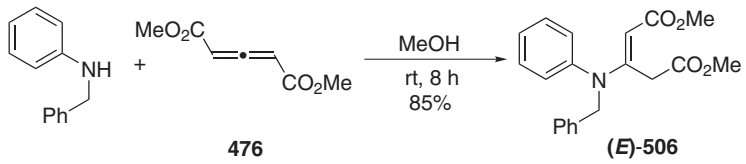


502



503 504 505

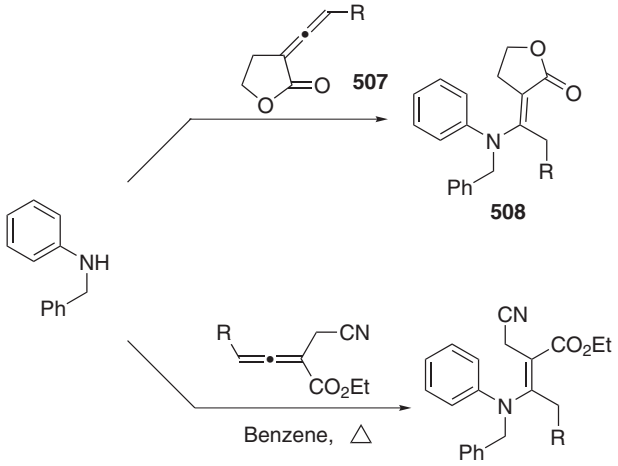
Scheme 10.194



476 (*E*)-506

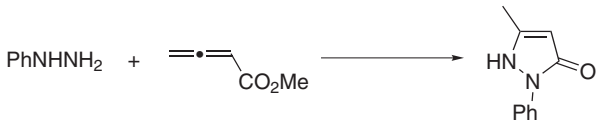
Scheme 10.195

Such stereoselectivity was also observed with cyclic monoester **507**; the C=C bond migrated from the β,γ- to the α,β-position [193, 228–230].



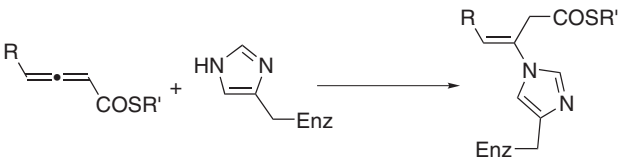
Scheme 10.196

It is interesting that the reaction of phenylhydrazine affords 3-methyl-1-phenyl-pyrazolone **510** [230, 231].



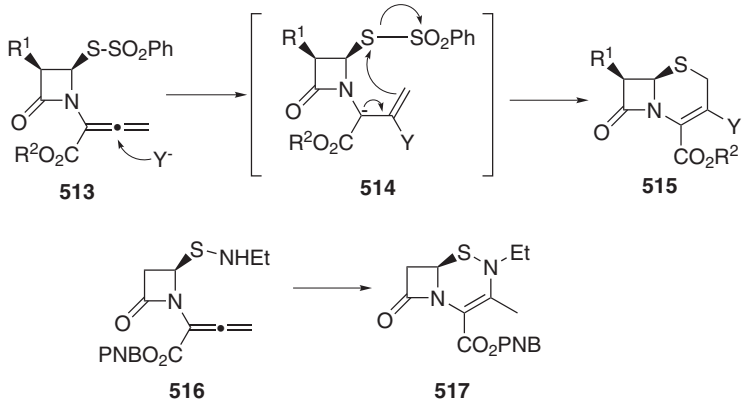
Scheme 10.197

Allenyl thioesters can also react with imidazole derivative **511** leading to the formation of the thioesters of β,γ-unsaturated enoic acids **512** [232].



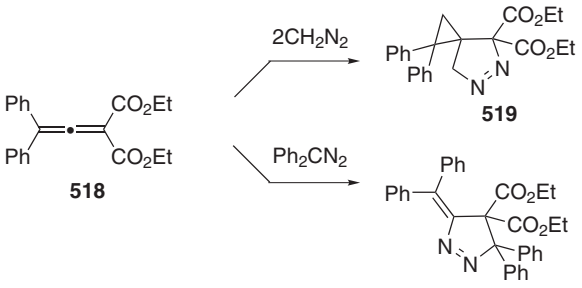
Scheme 10.198

Morpholine, pyrrolidine and sodium azide can also be also used as nucleophiles in the synthesis of 3-substitututed Δ^3-cephems **515** via the conjugate addition of the 2,3-allenoate moiety in **513** [233].



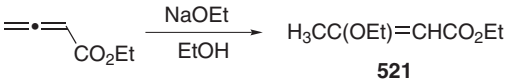
Scheme 10.199

1,3-Dipolar cycloaddition of ethyl 2-(ethoxycarbonyl)-4,4-diphenyl-2,3-butadienoate **518** with CH_2N_2 or Ph_2CN_2 afforded bicyclic or monocyclic products **519** and **520**, respectively. The possibility of extra cyclopropanation depends on the steric effect of the diazo compound [234].



Scheme 10.200

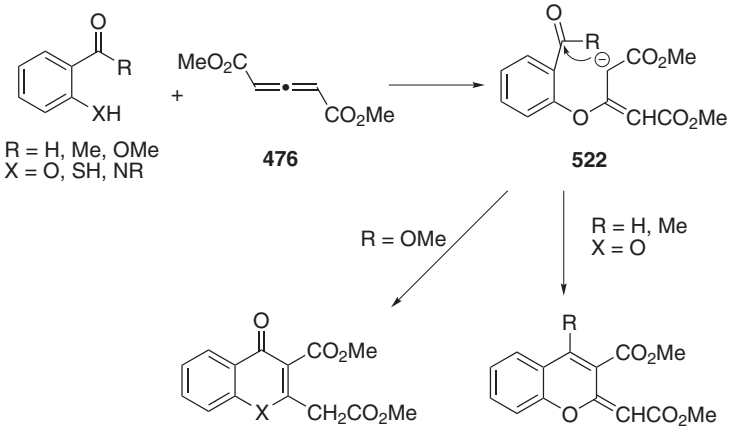
In 1954, Eglinton et al. [235] reported the reaction of ethyl 2,3-butadienoate with NaOEt in EtOH. It was observed that the product is ethyl 2-ethoxy-2-butenoate, showing that the C=C bond migrated from the β,γ-position to the α,β-position under the basic conditions [235].



Scheme 10.201

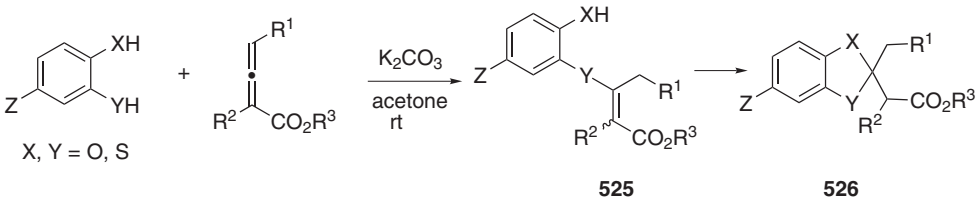
In 1983, Nixon and Scheimann reported that 2-acyl(or formyl, methoxycarbonyl)-phenol can add to 4-(methoxycarbonyl)-2,3-butenoate to yield 4-(methoxycarbonyl)-3-(phenoxy)-3-buteneate **522**. *o*-Hydroxyphenyl ketone, *o*-hydroxybenzaldehyde or *o*-hydroxybenzoic acid esters reacted with 4-methoxycarbonyl-2,3-butenoate in a

Michael addition and intramolecular aldol condensation–elimination process to afford coumarin derivatives **523** and **524**, respectively [236].



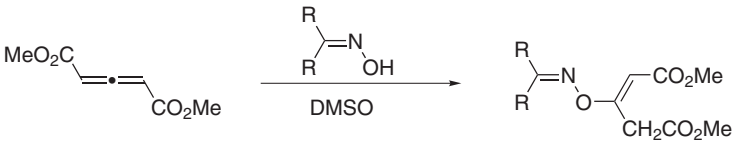
Scheme 10.202

Due to the migration of C=C bond, the conjugated esters formed can accept the attack of a second nucleophile. Thus, by applying different difunctionalized benzenes, benzo-fused five-membered heterocyclic compounds **526** can be prepared efficiently [237].



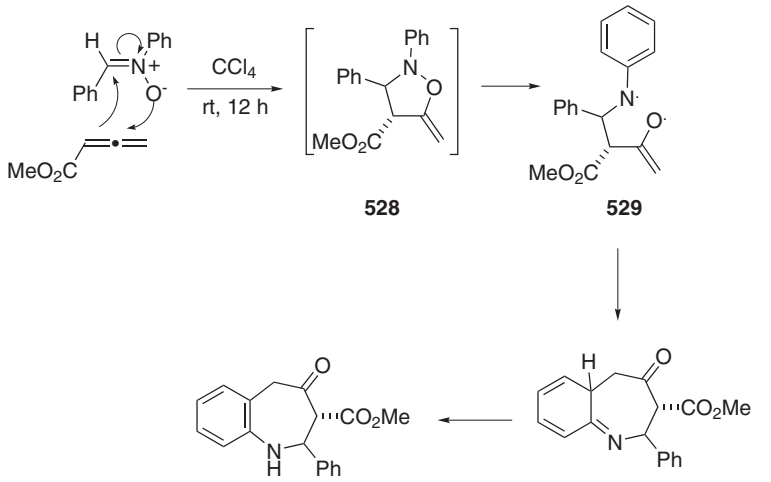
Scheme 10.203

The reaction of ketoximes with monoactivated allenes is either slow or complicated. However, the reaction with allene-1,3-carboxylate **476** afforded addition product (*E*)-**527** highly stereoselectively [238].



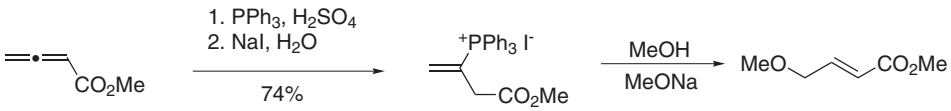
Scheme 10.204

Methyl 2,3-butadienoate can undergo 1,3-dipolar cycloaddition with nitrones leading to the formation of **528**, which would undergo homolytic cleavage of the N–O bond followed by radical rearrangement and coupling to afford benzazepinone **531** [239].



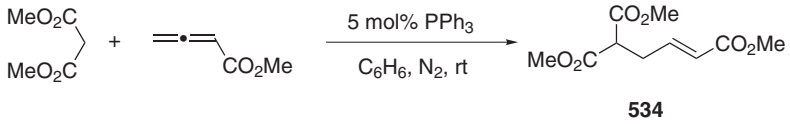
Scheme 10.205

In 1985, Cristiau et al. reported that the reaction of methyl 2,3-butadienoate with PPh_3 followed by the addition of NaI afforded phosphonium iodide **532**, which makes the γ-carbon prone to nucleophilic attack, leading to the formation of 4-methoxy-2-enonate **533** [197a].



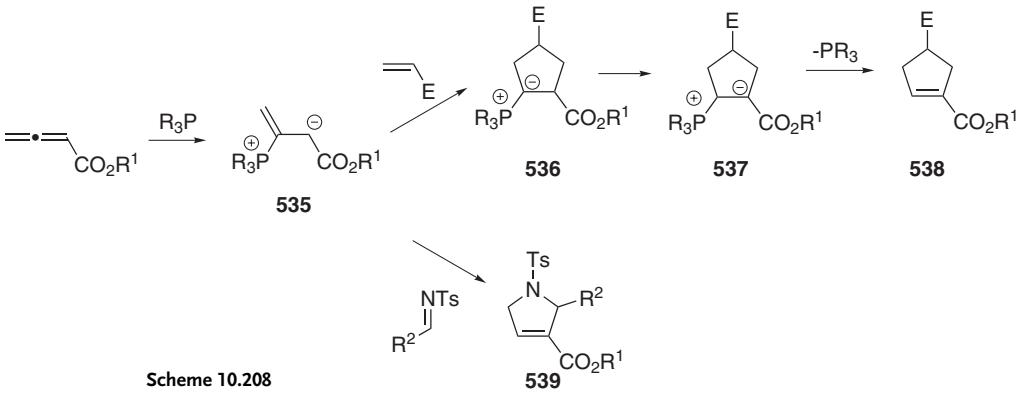
Scheme 10.206

In 1995, Lu et al. developed the PPh_3-catalyzed reaction of 2,3-butadienoate with dimethyl malonate [240]. A similar catalytic reaction was also observed with PhOH and benzyl alcohol leading to the γ-addition product **534** [241].



Scheme 10.207

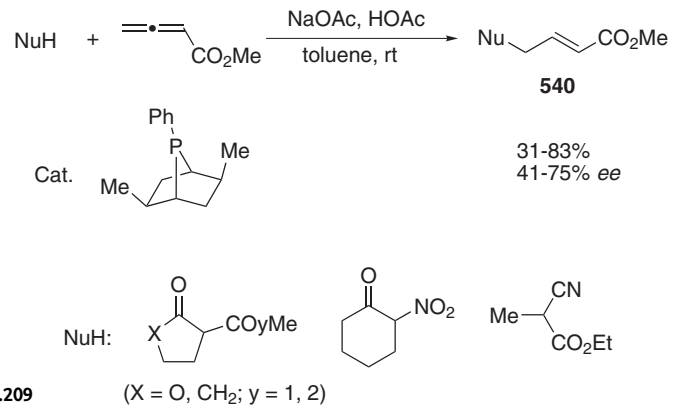
Based on this, Lu et al. developed the PPh_3-catalyzed [3 + 2]-cycloaddition of 2,3-allenoates with electron-deficient alkenes [242, 243] and imines [244, 245], leading to the formation of five-membered compounds **538** and **539**.



Scheme 10.208

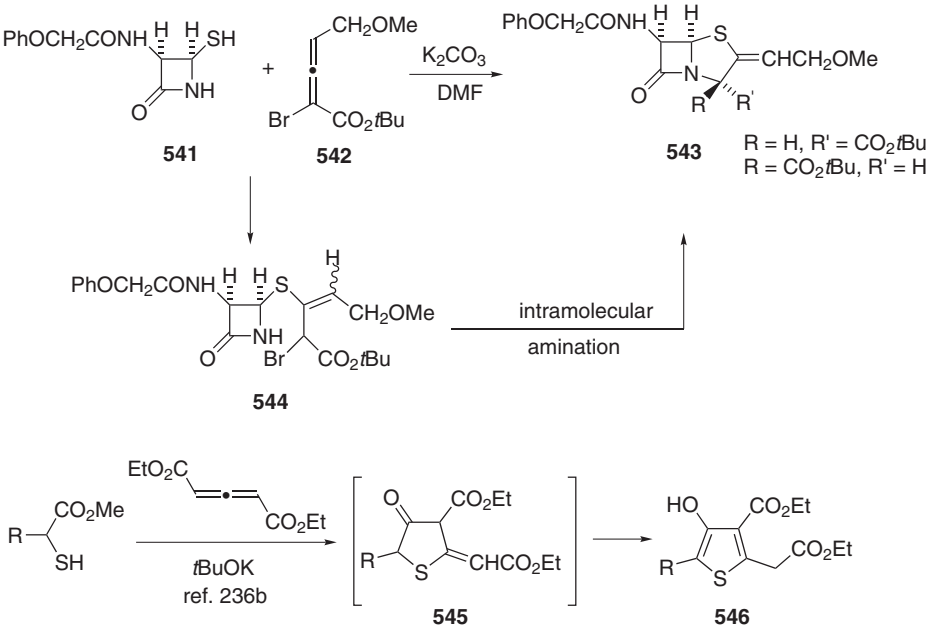
This reaction principle has even been applied to the [3 + 2]-cycloaddition of 2,3-allenoates to 60-fullerene [246, 247].

Zhang et al. developed the enantioselective chiral phosphine-catalyzed addition of 2,3-allenoates with carbon-centered nucleophiles and electron-deficient olefins leading to efficient enantioselective C–C bond formation [248, 249].



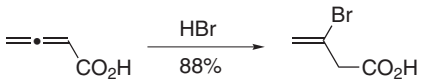
Scheme 10.209

Conjugate additions of thiols to a 2,3-allenoate proceed easily [236b, 249, 250].



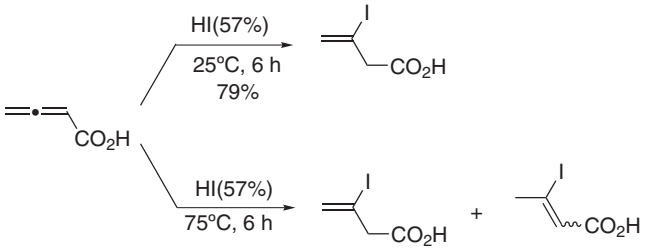
Scheme 10.210

The addition reaction of HBr to 2,3-allenoic acids afforded 2-bromo-2-propenoic acid [251].



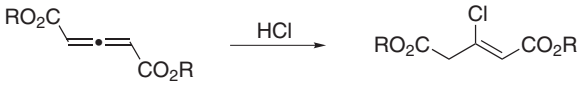
Scheme 10.211

The reaction with HI at 25 °C gave the iodo analogue. However, if the reaction was run at a higher temperature, a mixture of 2-iodo-3-propenoic acid and 2-iodo-2-propenoic acid was formed [252].



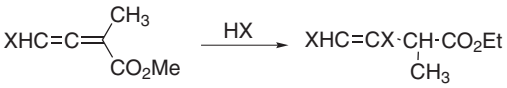
Scheme 10.212

With HCl, allene-1,3-dicarboxylates afford (*Z*)-3-chloro-4-(alkyoxycarboxyl)-2-butenoates [253].



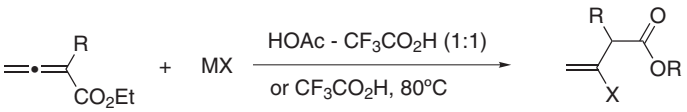
Scheme 10.213 **547**

4-Substituted 2,3-allenoates react with HX to afford 3-halo-3-enoates [254].



Scheme 10.214

The hydrohalogenation reaction can also be performed with MX in HOAc [207a]. The reaction of 4-substituted-2,3-allenoates affords a mixture of (*E*)- and (*Z*)-β-halo-β,γ-unsaturated enoates [87]. With 2-substituted-2,3-allenoates, the reaction should be carried out in HOAc–CF_3CO_2H (1:1) or CF_3CO_2H to form β-halo-β,γ-unsaturated enoates with high regioselectivity [255].

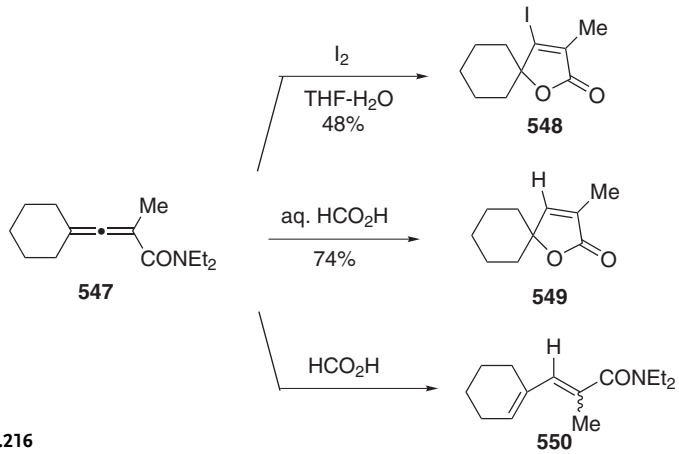


Scheme 10.215

10.13 2,3-Allenamides

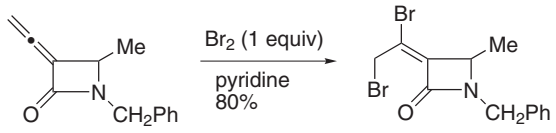
10.13.1 Electrophilic Additions

The reaction of 2,3-allenamide **547** with I_2 and aqueous formic acid in aqueous THF afforded β-iodobutenolides **548** and butenolides **549**, respectively. With anhydrous formic acid, 2,4-alkadienamide **550** was formed via a protonation and deprotonation process [256].



Scheme 10.216

In 2,3-allenamide **551**, with its β-lactam substructure, dibromination of the relatively electron-rich C=C bond was observed [257].

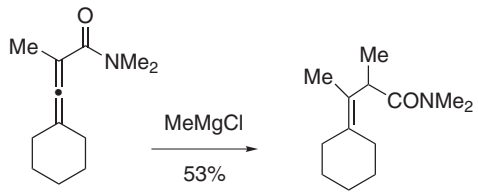


551 **552**

Scheme 10.217

10.13.2 Nucleophilic Additions

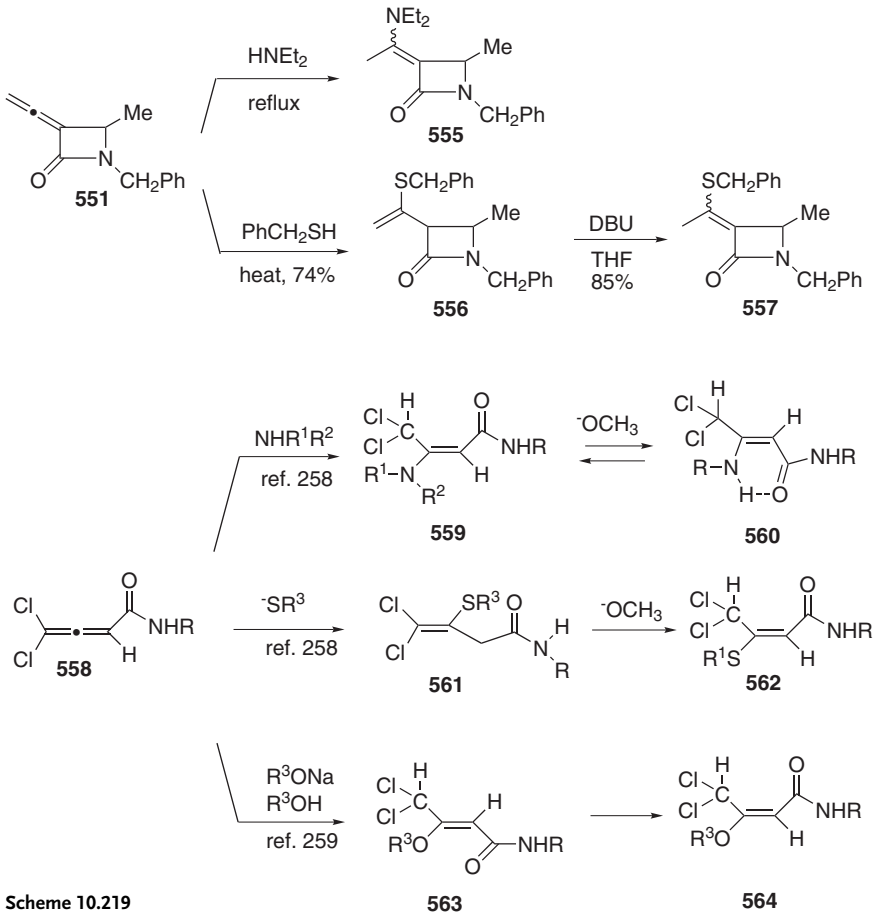
Methylmagnesium chloride can react with 2,3-allenamide **553** to give the β-methyl-β,γ-unsaturated enamide **554** [256].



553 **554**

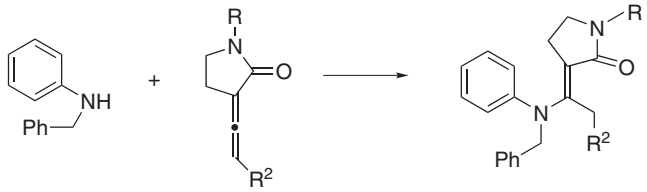
Scheme 10.218

The reaction of diethylamine or alcohol with 2,3-allenamide **551** affords β-diethylamino-α,β-unsaturated enamide **555**, indicating the migration of the C=C bond under basic conditions. The corresponding reaction of **551** with benzyl thiol proceeded to afford β-thiobenzyl-β,γ-unsaturated enamide **556**; the β,γ-C=C bond can migrate to the α,β-position on the treatment with DBU in THF to afford **557** [257]. In reactions of 4,4-dichloro-2,3-butenamide **558** with amines, thiolates and alcohols, α,β-unsaturated enamides **560–564** are always formed on treatment with a base [258, 259].



Scheme 10.219

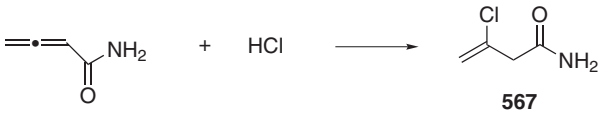
The nucleophilic addition of amines to cyclic 2,3-allenamides **565** leads to (*E*)-3-amino-2-enamides **566** [260].



565 **566**

Scheme 10.220

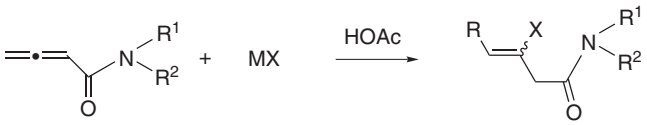
The reaction of HCl with 2,3-butadienamide afforded 3-chloro-3-butenamide [261].



567

Scheme 10.221

The hydrohalogenation reaction of 2,3-allenoamide with MX also delivers β-halo-β,γ-unsaturated enamides. The *Z*- and *E*-isomers can be easily separated [87].



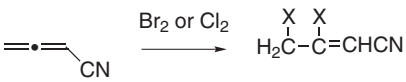
568

Scheme 10.222

10.14 2,3-Allenyl Nitriles

10.14.1 Electrophilic Additions

The electrophilic addition of Br_2 or Cl_2 to 2,3-butadiene nitrile afforded 3,4-dihalo-2-butenenitriles [261].

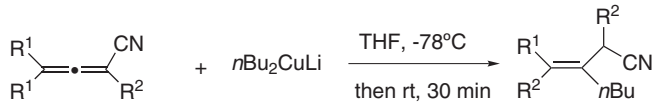


569

Scheme 10.223

10.14.2
Nucleophilic Additions

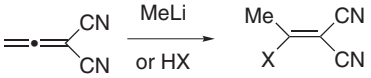
2,3-Allenic nitriles **570** reacted with nBu$_2$CuLi to give β,γ-unsaturated allylic nitriles **571** [262].



570 **571**

Scheme 10.224

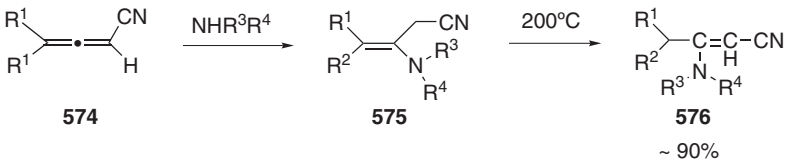
The reaction of 2-cyano-2,3-butadienenitrile **572** with MeLi or HX afforded α,β-unsaturated 2-cyano-3-substituted-2-butenenitrile **573** [263].



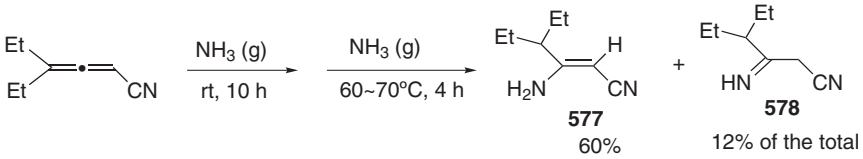
572 **573**

Scheme 10.225 X = Me, OMe, NHPh, NMe$_2$

At temperatures between –33 and 0 °C, 1-cyano-1,2-allenes **574** can react with primary or secondary amines to afford unconjugated enaminic nitriles **575**, which can be converted to conjugated enamines **576** at 200 °C [264, 265]. The corresponding reaction of ammonia is relatively slow and was conducted at 60–70 °C to afford 3-amino-4-ethyl-2-hexenenitrile **577** together with a small precentage of iminyl nitrile **578** [264, 265].



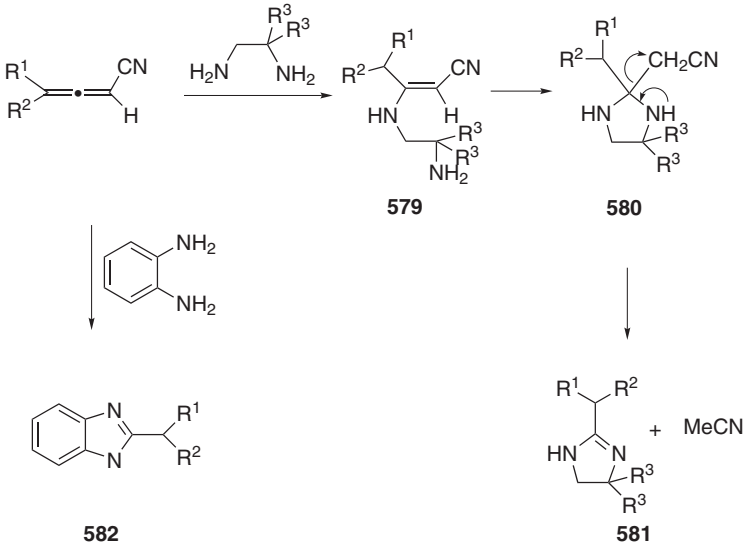
574 **575** **576**
~ 90%



577 60%
578 12% of the total

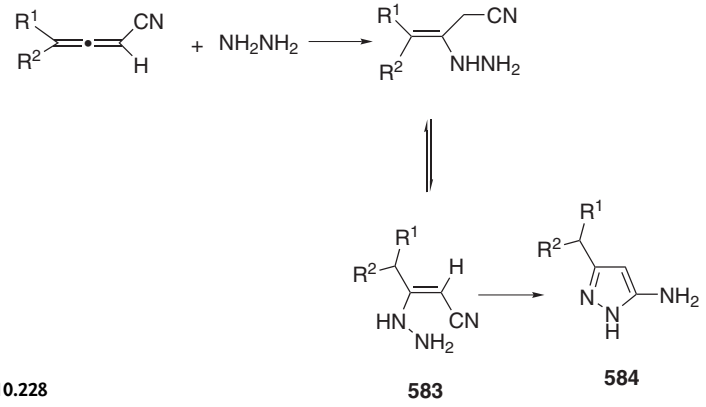
Scheme 10.226

By using diamines, the 2-alkyl-(benzo)imidazolines **581** and **582** were formed by a double Michael addition reaction and subsequent elimination of MeCN [266, 267].



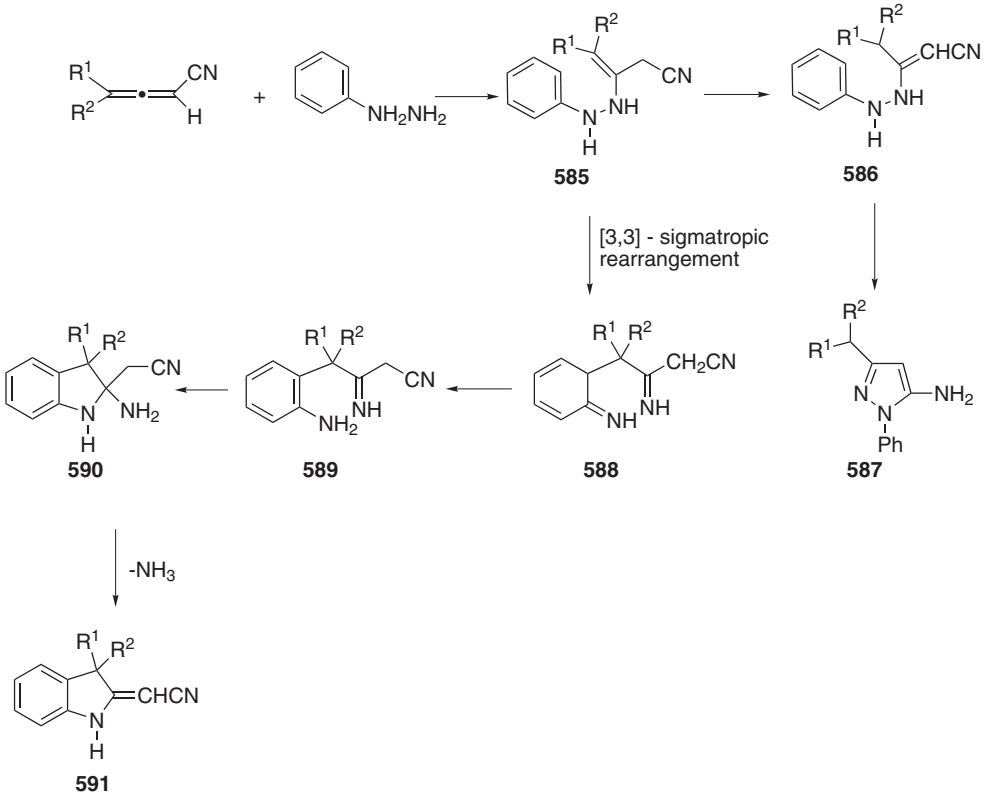
Scheme 10.227

By using hydrazine, 3-alkyl-5-aminopyrazoles **584** were formed in excellent yields via conjugate addition, C=C bond migration and intramolecular amination of the C–N triple bond [268].



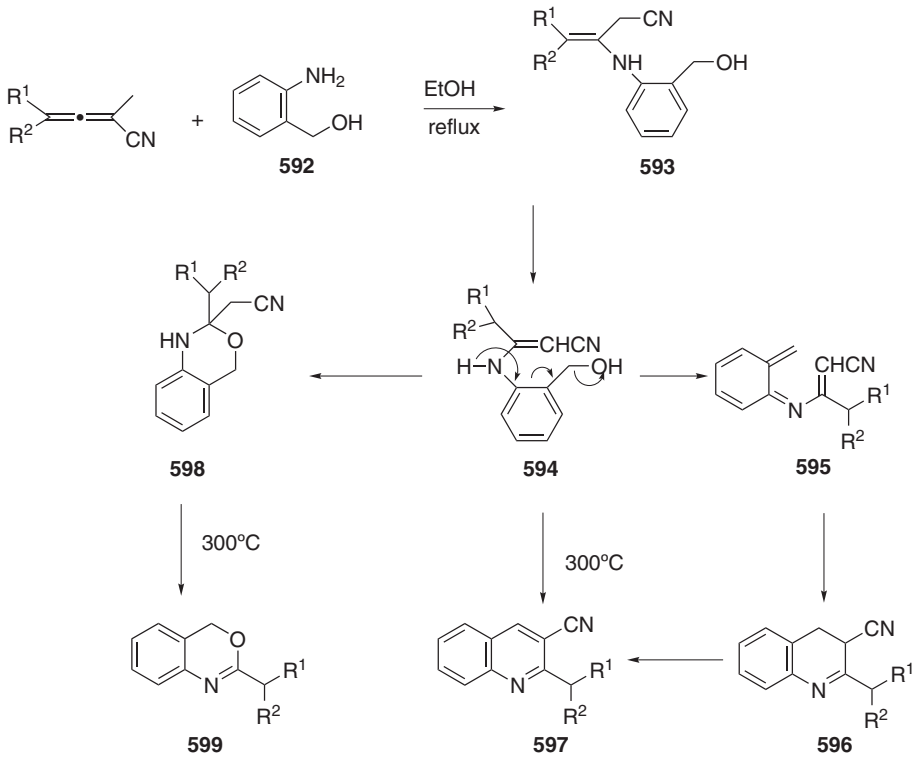
Scheme 10.228

With phenylhydrazine, a mixture of pyrazoles **587** and 3*H*-indoles **591** were formed via conjugate addition, C=C bond migration and cyclic amination of the nitrile group or [3,3]-sigmatropic rearrangement of 3-amino-3-alkenenitriles **585**, respectively [268a].



Scheme 10.229

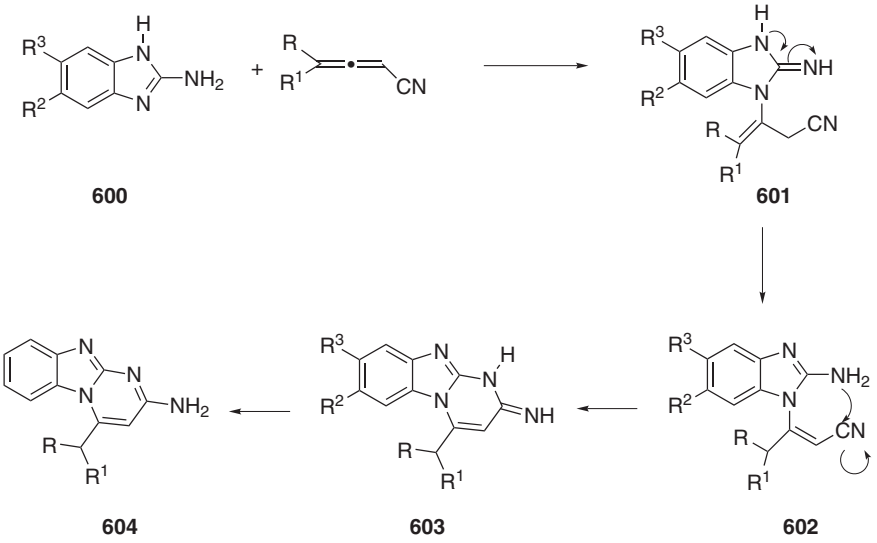
The reaction of 1-cyano-1,2-allenes with *o*-aminobenzyl alcohol afforded a mixture of conjugated 2-enenitriles **594** and dihydro-4*H*-3,1-benzoxazines **598**. On heating to 300 °C, **598** eliminates MeCN to give the 4*H*-3,1-benzoxazines **599**. However, under similar conditions, **594** affords 2-alkyl-3-cyanoquinolines **597** as the major product [269].



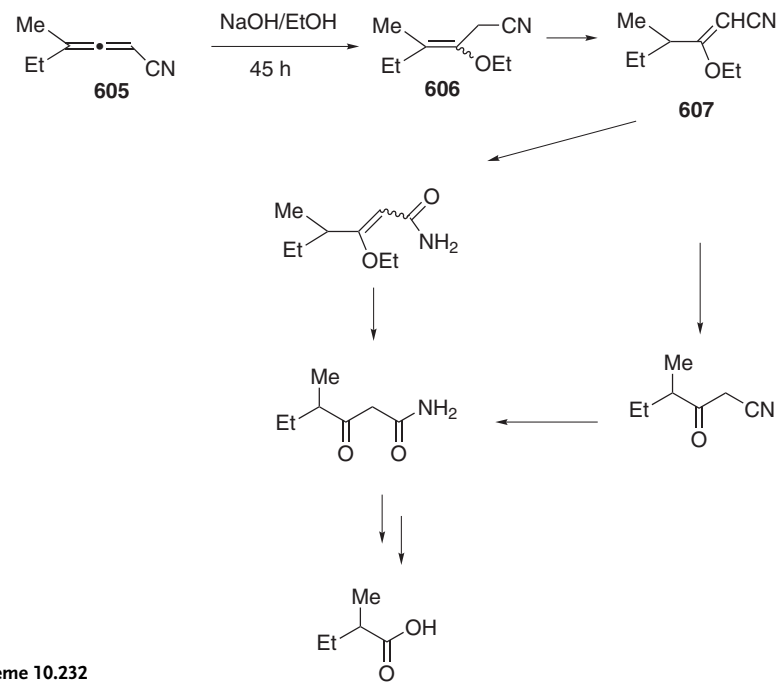
Scheme 10.230

The reaction of 2-aminobenzimidazoles **600** with 2,3-allenenitriles led to pyrimidobenzimidazoles **604** via initial attack of the unsaturated nitrogen atom in the imidazole ring followed by a 1,3-H shift to form **602**. Intramolecular amination of the nitrile group in **602** and a subsequent 1,3-H shift afforded the final product **604** [270].

The reaction of 2,3-allenenitrile **605** with EtOH in the presence of NaOH afforded the β-ethoxy-β,γ-unsaturated enenitrile **606**, which was isomerized and hydrated to afford a mixture of β-ethoxy-α,β-unsaturated enenitrile, enamide carboxylic acid or α-cyano ketone [271].

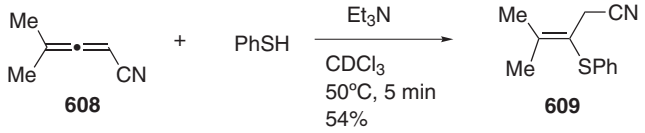


Scheme 10.231



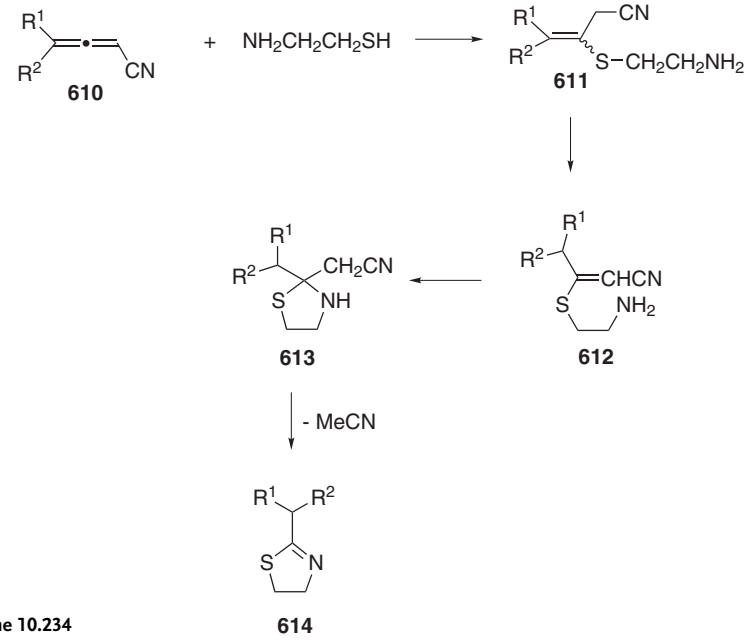
Scheme 10.232

In the presence of a base such as triethylamine, 2,3-allenenitrile **608** reacted with thiols to give the β,γ-unsaturated enenitrile **609** [193, 272].



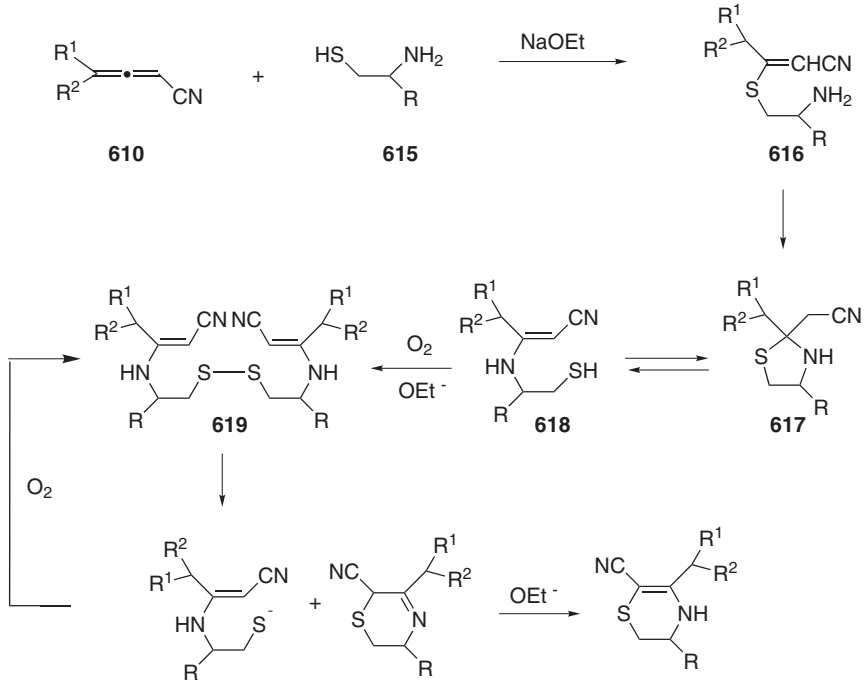
Scheme 10.233

With amino thiols, the amino group can serve as the second nucleophile to induce further conjugate nucleophilic attack to form heterocyclic compounds **614** [273, 274].



Scheme 10.234

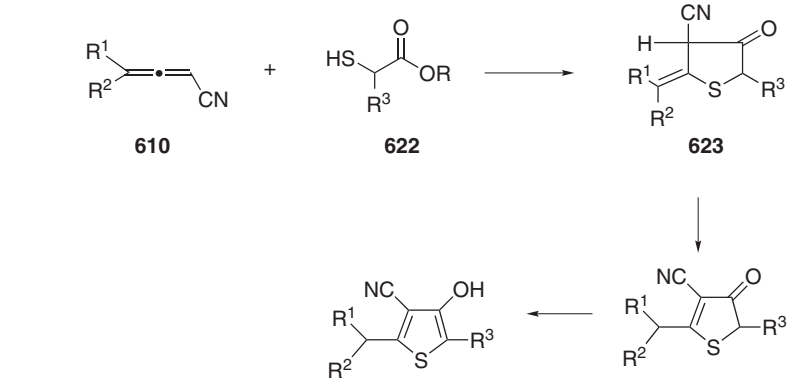
If the same reaction was carried out in refluxing EtOH using 0.5 equiv. of NaOEt in the presence of oxygen, 3-alkyl-5,6-dihydro-4*H*-thiazine-2-carbonitrile **621** was formed in >90% yield [275].



610 615 616 619 618 617 620 621

Scheme 10.235

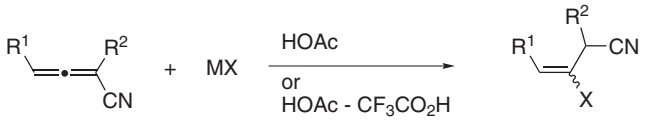
2-Alkyl-3-cyano-4-hydroxythiophenes **625** were obtained from the reaction of 2,3-allenenitriles **610** with mercaptoacetates **622**. The presence of the ester group leads to the formation of cyclic ketones **623**, which undergo migration of the C=C and C=O bonds to form thiophenes **625** [276].



610 622 623 624 625

Scheme 10.236

The hydrohalogenation of 1-cyano-1,2-allenes with MX affords β,γ-unsaturated enenitriles [87, 277]. For the 4-alkyl-substituted 2,3-allenenitriles, the stereoselectivity is low; however, the *Z*- and *E*-isomers can be easily separated to provide easy access to the pure (*Z*)- and (*E*)-β-halo-β,γ-unsaturated enenitriles.



Scheme 10.237

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11
Fundamentals and Application of Free Radical Addition to Allenes

Jens Hartung and Thomas Kopf

11.1
Introduction

Almost one century has passed since Moses Gomberg realized that organic free radicals, i.e. reactive intermediates with an unpaired electron, may exist under conventional laboratory conditions in solution [1]. This observation was followed by extensive efforts to uncover the principles of radical reactivities and selectivities [2]. In the last few decades of the 20th century, carbon radical-based transformations finally became one of the cornerstones of organic synthesis [3]. At that time, all elementary reactions of free radicals had been thoroughly studied in physical organic and in kinetic investigations [4]. This information had been supplemented by knowledge about selectivity control using polar and/or steric substituent effects in inter- and, particularly, intramolecular transformations [5, 6]. Guidelines have emerged that allow the reliable prediction of radical selectivities in, for instance, diastereoselective or even enantioselective carbon–carbon bond formations that proceed via efficient chain reactions under mild and neutral conditions [7–9].

The cumulated π-system of allenes has been described as consisting of two comparatively unperturbed double bonds with regard to its reactivity towards nucleophiles or electrophiles [10]. Early reports on radical additions to 1,2-dienes, however, already pointed to peculiarities of the allene system concerning its reactivity towards intermediates with unpaired electrons [11–14]. It was soon realized that no such correlation between polar and steric substituent effects existed, similar to what had been uncovered for the reaction of radicals with olefins, in order to predict selectivities in radical additions to cumulated dienes [4, 15].

In recent years, interest in radical-based transformations of allenes has been renewed for two major reasons. First, a number of useful intramolecular additions of carbon-centered radicals to 1,2-dienes have been reported, which allowed syntheses of complex natural product-derived target molecules to be accomplished in instances where other methods have failed to provide similar selectivities. Further, a large body of kinetic and thermochemical data has become accessible from results of experimental and theoretical investigations in order to predict selectivities in addition reactions to allenes more precisely. Such contributions originated predominantly from (i) studies directed towards an understanding of the incineration process,

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which provides, under pyrolysis conditions, a great diversity of radical intermediates in addition to allene itself [16], and (ii) the interest in fundamental transformations of atmospheres with a significant concentration of hydrocarbons – conditions that exist on Titan today and may have existed initially on Earth [17, 18].

In view of this background, it is the aim of this chapter to organize the fundamentals of radical additions to 1,2-dienes and to present its state of the art in organic synthesis. All aspects of enyne allene cyclizations [19, 20] have been omitted since this topic is addressed in Chapter 20. In order to simplify the mechanistic discussion, the positions and π-bonds of allenes have been consistently numbered using the nomenclature outlined in Figure 11.1.

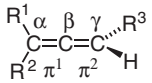


Figure 11.1 Indexing of key positions and bonds in substituted allenes.

11.2 Basic Principles

11.2.1 FMO Analysis of 1,2-Dienes

Transition states of radical additions to olefins are, in most instances, located early on a reaction coordinate [21]. Therefore, FMO theory may be applied in order to rationalize the preferred site of radical addition [4]. A significant stabilization upon the approach of reactants in the transition state requires that interacting FMOs exhibit small energy differences. Relevant orbitals to take into account for this analysis are the SOMO of the radical and either the HOMO (approach of an electrophilic radical) or the LUMO (in the case of a nucleophilic radical) of the olefin (see Figure 11.2). The olefinic carbon atom which contributes with the largest coefficient to the relevant π- or π*-type FMO is the preferred site for subsequent σ-bond formation [22]. In order to identify whether or not radical additions to allenes may be treated in a similar way, FMO energies and orbital coefficients of 1,2-dienes have been investigated using photoelectron spectroscopy (PES) in combination with *ab initio* calculations. PES ionization potentials (*IP*) of 10.07 and 10.64 eV have been measured for propadiene (**1a**) (Jahn–Teller-splitting) [23]. These values are close to the corresponding *IP* obtained of ethene (10.51 eV) [10]. The LUMO energy of allene **1a** (–1.9±1 eV) has been derived from electron affinity measurements via electron transmission spectroscopy [24]. Methyl substitution lowers the correspondding PES *IP* from propadiene (**1a**) via buta-1,2-diene (**1b**) (9.33, 10.06 eV), penta-2,3-diene (**1c**) (9.13, 9.65 eV), 3-methylbuta-1,2-diene (**1d**) (8.95, 9.86 eV), 2-methylpenta-2,3-diene (**1e**) (8.69, 9.24 eV) to 2,4-dimethylpenta-2,3-diene (**1f**) (8.47, 8.96 eV) [25]. A more significant change in calculated orbital energies is seen on replacement of a hydrogen

atom in diene **1a** by OH, F, CHO or CN [15]. Resonance donating groups (F, OH), methyl substituents (hyperconjugation) and a vinyl group (mesomeric interaction) raise the energy of the filled orbital π^1 and lower the energy levels of π^2 and of the two virtual orbitals π^{*1} and π^{*2}. Such groups act as electron-withdrawing functionalities with respect to π^2. Substituents that exhibit a negative resonance effect, i.e. CN, CHO, lower the energy of all filled and virtual π-type FMOs. The effects of α-substituents on π^1 and π^{*1} follow the same trends that have been found for the corresponding ethylene derivatives. The largest FMO coefficients are almost consistantly located at C_γ and therefore refer to π^2 and π^{*2}. In general, σ-donors and π-acceptors stabilize an allene, whereas π-donors and σ-acceptors lead to a destabilization [26].

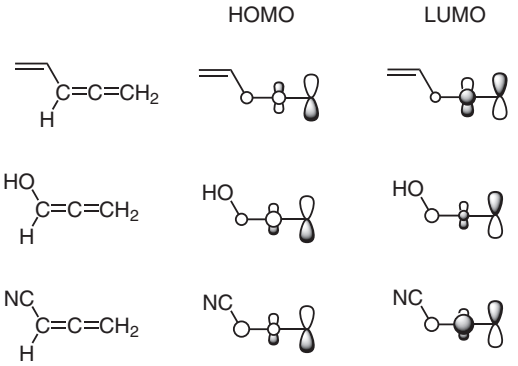
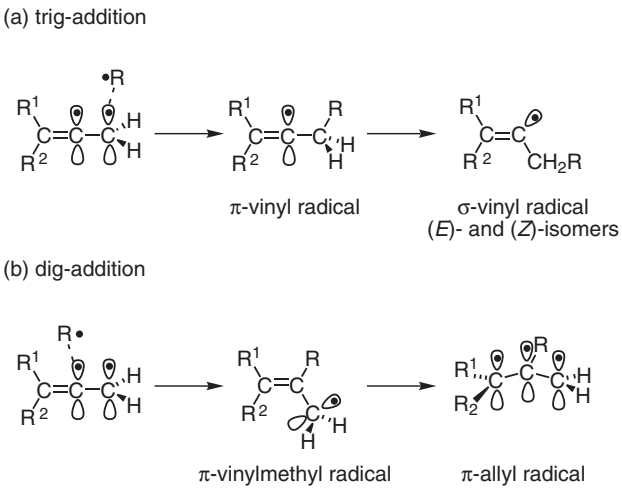


Figure 11.2 Schematic presentation of FMOs of selected 1-substituted propadienes [15].

11.2.2
Radical Addition to the Cumulated π-System in Allenes

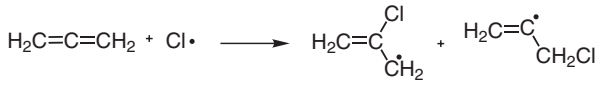
Addition of carbon- [27], tin- [28], nitrogen- [29], phosphorus- [30], sulfur- [14] and selenium-centered radicals [31] to allenes have been investigated on an experimental and a theoretical level (see Scheme 11.1). Moreover, the reactions of atoms such as halogen ($Cl^\bullet$, $Br^\bullet$) [13, 16], hydrogen [32], oxygen [33] or metal atoms [34] to molecules with cumulated π-bonds have been studied. The principle of least motion requires that addition to C_α or C_γ provides a π-type vinyl radical. This intermediate may isomerize to adopt the energetically favored σ-vinyl radical structure (Scheme 11.1). Addition to the central carbon atom of an allene (i.e. C_β) furnishes a π-type vinylmethyl radical that, upon rotation of the methylene group by 90°, acquires the geometry of an allylic π-radical in order to gain full resonance stabilization (59 ± 8 kJ mol^{-1} for the 1-propenyl radical) [35].



Scheme 11.1 Schematic presentation of intermediates involved in radical additions to allenes.

11.2.2.1 Addition of Halogen Atoms to 1,2-Dienes

The chlorine atom adds in the gas phase to propadiene (**1a**) with a rate constant that is close to the gas-kinetic limit. According to the data from laser flash photolysis experiments, this step furnishes exclusively the 2-chloroallyl radical (**2a**) [16, 36]. A computational analysis of this reaction indicates that the chlorine atom encounters no detectable energy barrier as it adds either to C_α or to C_β in diene **1a** to furnish chlorinated radical **2a** or **3a**. A comparison between experimental and computed heats of formation points to a significant thermochemical preference for 2-chloroallyl radical formation in this reaction (Scheme 11.2). Due to the exothermicity of both addition steps, intermediates **2a** and **3a** are formed with considerable excess energy, thus allowing isomerizations of the primary adducts to follow.



	1a	**2a**	**3a**
calcd[a].:	$_fH_0$:	≡0.0	+94.7
exp.:	$\Delta_fH^0_{298.15}$:	+139 ± 7	+238 ± 5

Scheme 11.2 Products of chlorine atom addition to propadiene (**1a**) and heats of formation [kJ mol^{-1}] of addition products **2a** and **3a** [16].
[a] QCISD(T)/6–311+G(d,p)//QCISD(T)/6–31+G(d,p); MP2/6–31+G(d,p) for calculation of the zero point vibrational energy.

If photolyzed with light of the intensity I, HBr adds to propadiene (**1a**) in the gas phase with a rate given by $v = k_{exp}[HBr]I^{0.5}$. This transformation affords within the detection limit (GC) 2-bromo-1-propene (**5a**) as sole reaction product (Table 11.1). The conversion of methyl-substituted allenes, such as **1c** and **1f**, under these conditions follows the same kinetic expression [37]. Results from competition experiments indicate that the reactivity of an allene towards HBr increases progressively with the number of methyl substituents from propadiene (**1a**) (≡ 1.00) to 2,4-dimethylpenta-2,3-diene (**1f**) (1.65). In all instances, $Br^{\bullet}$ addition occurs exclusively at C_{β} to furnish substituted allyl radicals, which were trapped in the rate determining step by HBr.

Table 11.1 Selectivity data for HBr addition to allenes in solution and in the gas phase [13, 37].

α β
$H_2C{=}C{=}CH_2$ **1a**

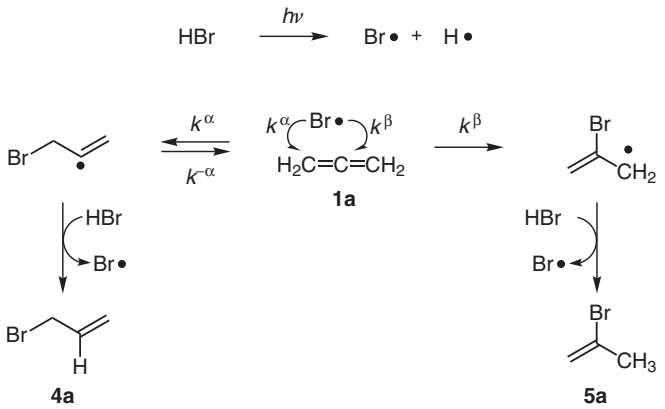
α β
$(H_3C)HC{=}C{=}CH(CH_3)$ **1c**

α β
$(H_3C)_2C{=}C{=}C(CH_3)_2$ **1f**

Entry	Allene	k^{rel}	[α] : [β][b]	
			Gas phase	Solution
1	**1a**	≡1.0[a]	< 1 : 99[c]	67 : 33
2	**1c**	1.56	4 : 96	-[d]
3	**1f**	1.65	< 1 :99[c]	-[d]

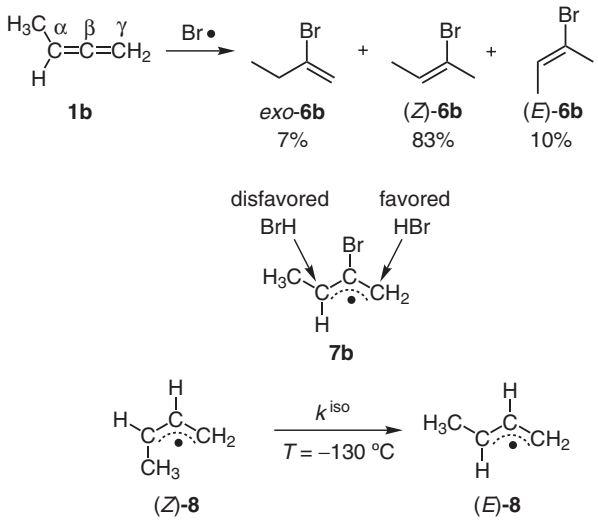
[a] Refers to 60 °C.
[b] The hydrogen atom transfer consistently occurred at C_{γ}.
[c] No α-adduct was detected (GC).
[d] Not investigated.

In solution, products of central *and* terminal $Br^{\bullet}$ addition to propadiene (**1a**) are formed (Scheme 11.3) [13, 37]. The latter are promoted by high reactant ratios [HBr]:[C_3H_4] and low reaction temperatures. Under conditions of kinetic control, the reaction between diene **1a** and HBr furnishes a 67:33 ratio of allyl bromide **4a** versus 2-bromopropene **5a**. These investigations also revealed that α-addition of $Br^{\bullet}$ is reversible, but the β-addition is not. The reversible addition to C_{α} has been used to explain the preference for allyl bromide formation from substrate **1a** and HBr at low temperatures, since the $Br^{\bullet}$ loss profits from elevated temperatures.



Scheme 11.3 Mechanism of addition of HBr to propadiene (**1a**) in solution [13, 37].

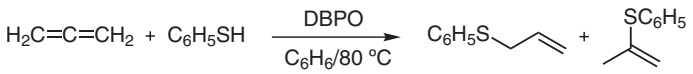
Free radical addition of HBr to buta-1,2-diene (**1b**) affords dibromides *exo*-**6b**, (*E*)-**6b** and (*Z*)-**6b**, which consistently originate from $Br^{\bullet}$ addition to the central allene carbon atom [37]. The fact that the internal olefins (*E*)-**6b** and (*Z*)-**6b** dominate among the reaction products points to a thermodynamic control of the termination step (see below). The geometry of the major product (*Z*)-(**6b**) has been correlated with that of the preferred structure of intermediate **7b**. The latter, in turn, has been deduced from an investigation of the configurational stability of the (*Z*)-methylallyl radical (*Z*)-**8**, which isomerizes with a rate constant of $k^{iso} = 10^2\ s^{-1}$ (–130 °C) to the less strained *E*-stereoisomer (*E*)-**8** (Scheme 11.4) [38].



Scheme 11.4 Products of HBr addition to buta-1,2-diene (**1b**) in the gas phase (top), preferred site of hydrogen atom trapping of 2-bromobutenyl radical **7b** (center) and isomerization of methylallyl radical (*Z*)-**8** (bottom) [13, 37, 38].

11.2.2.2 Reactivity and Selectivity of Oxygen-, Sulfur- and Selenium-Centered Radicals Towards Allenes

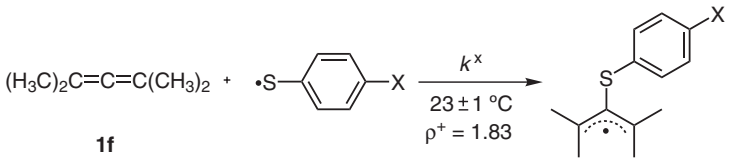
The *tert*-butoxyl radical prefers hydrogen atom abstraction to addition to propadiene (**1a**) and its methyl derivatives [39]. Based on competition experiments, it has been concluded that the reactivity of C–H bonds towards *tert*-butoxyl radicals decreases in the series allenic ≈ propargylic > allylic. Alkyl- and arylsulfanyl radicals, which may be generated upon photolyzing thiols or treatment of such compounds in the presence of an initiator, readily add to cumulated π-bonds [14, 40–45]. In most instances, products of mono- and of twofold addition are formed from a thiol and propadiene (**1a**). According to results from computational studies, the $HS^{\bullet}$ addition to 1-donor- and 1-acceptor-substituted allenes is considerably exothermic [15]. With regard to the regioselectivity of sulfanyl radical attack on allenes, the tendency for β-addition increases along the series $HS^{\bullet} < MeCOS^{\bullet} < RS^{\bullet}$ (R = alkyl) < $C_6H_5S^{\bullet}$. The α-addition of $C_6H_5S^{\bullet}$ to propadiene (**1a**) is almost freely reversible, whereas the β-attack is not [14]. At C_6H_5SH concentrations above 3 M thioethers **9a** and **10a** are obtained in a constant ratio of 3:1 (Scheme 11.5). On the other hand, the addition of $C_6H_5S^{\bullet}$ to C_β *and* C_α of methyl-substituted allenes proceeds irreversibly. The significance of the β-attack increases with the number of methyl substituents present in the allene.



1a **9a** 75% **10a** 25%

Scheme 11.5 Addition of thiophenol (3 M) to propadiene (**1a**) in the presence of dibenzoyl peroxide (DBPO) [14, 44].

According to results from laser flash photolysis, the *p*-(methoxyphenyl)sulfanyl radical adds exclusively to the central atom in of 2,4-dimethylpenta-2,3-diene (**1f**) with a rate constant of $1.1 \times 10^5\ M^{-1}\ s^{-1}$ (23 ± 1 °C) (Scheme 11.6) [45]. A correlation between the measured rate constants for addition of *para*-substituted arylsulfanyl radicals to allene **1f** was feasible using Brown and Okomoto's σ^+ constant [46]. The ρ^+ value of 1.83, which was obtained from this analysis, was interpreted in terms of a polar transition state for C–S bond formation with the sulfanyl radical being the electrophilic part [45]. This observation is in agreement with an increase in relative rate constant for phenylsulfanyl radical addition to 1-substituted allene in the series of methoxyallene **1g**, via dimethylallene **1d**, to phenylsulfanylallene **1h**, to ester-substituted 1,2-diene **1i** (Table 11.2).

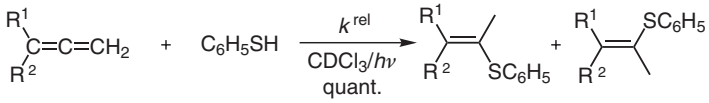


1f

X =	Br	Cl	H	$(H_3C)C$	CH_3	OCH_3
k^x_{rel} =	46	30	16	5.3	4.4	≡1.0

Scheme 11.6 Selectivity and relative rate constants for arylsulfanyl radical addition to 2,4-penta-2,3-diene (**1f**) [45].

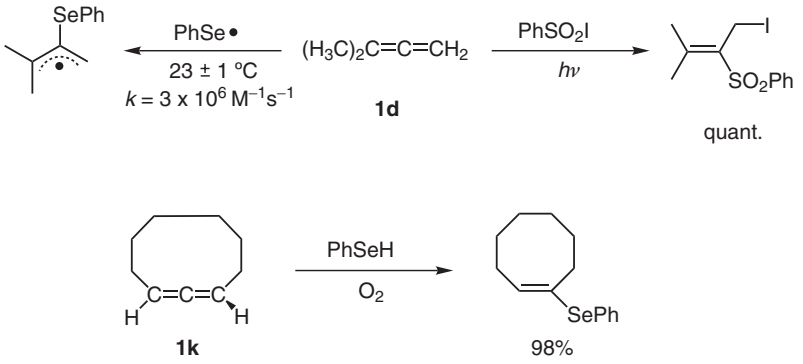
Table 11.2 Selectivity of product formation and relative rate constants for thiophenol addition to 1-substituted allenes **1d** and **1g–i** [44].



1 (*E*)-**11** (*Z*)-**11**

Entry	R^1	R^2	**1**	k^{rel}	*E* : *Z*
1	CH_3	CH_3	**1d**	≡1.0	–
2	OCH_3	H	**1g**	2.34	18 : 82
3	SC_6H_5	H	**1h**	0.88	60 : 40
4	CO_2CH_3	H	**1i**	< 0.09	72 : 28

Aryl- and alkylsulfonyl radicals have been generated from the corresponding iodides and added to, e.g., propadiene (**1a**), enantiomerically enriched (*P*)-(+)-propa-2,3-diene [(*P*)-(**1c**)] and (*P*)-(–)-cyclonona-1,2-diene [(*P*)-(**1k**)] [47]. Diaddition of sulfonyl radicals may compete considerably with the monoaddition [48,49]. Also, products of diiodination have been purified from likewise obtained reaction mixtures, which points to a more complex reactivity pattern of these substrates towards cumulated π-bonds. An analysis of regioselectivities of arylsulfonyl radical addition to allenes is in agreement with the familiar trend that α-addition occurs in propadiene (**1a**), whereas alkyl-substitution at the cumulated π-bond is associated with a marked increase in formation of β-addition products (Scheme 11.7).



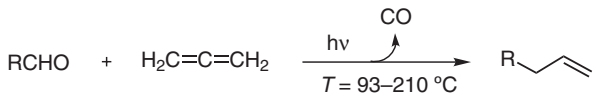
Scheme 11.7 Free radical-based transformations of 2-methylbuta-1,2-diene (**1d**) (top) and nona-1,2-diene (**1k**) (bottom): formation of C–S and C–Se bonds [31, 45, 49].

The phenylselenyl radical adds irreversibly to the central carbon atom of 2-methylbuta-1,2-diene (**1d**) with a rate constant of $3 \times 10^6\,M^{-1}\,s^{-1}$ (23 ± 1 °C) (Scheme 11.7) [45]. On a synthetic scale, $PhSe^{\bullet}$ addition to cumulated π-bonds has been investigated by oxidizing phenylselenol with air in the presence of mono-, 1,1-di- or 1,3-disubstituted allenes to provide products of selective β-addition. Trapping of 2-phenylselenyl-substituted allyl radicals with O_2 did not interfere with the hydrogen atom delivery from PhSeH (Scheme 11.7) [31].

11.2.2.3 Addition of C_1–C_3 Carbon and Tin Radicals to Allenes

The methyl radical adds to the terminal carbon of propadiene (**1a**) with a rate constant $k = 1 \times 10^4\,M^{-1}\,s^{-1}$ [27]. This elementary reaction requires an activation energy of 34 kJ mol^{-1} based on an Arrhenius analysis of data recorded in the temperature range 100–210 °C. Comparable results were obtained for ethyl and isopropyl radical addition to substrate **1a** (Table 11.3) [27].

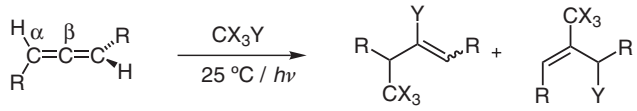
Table 11.3 Rate constants and activation parameters for additions of alkyl radicals to propadiene (**1a**) [27].



Entry	R	T [°C]	k (142°C) [$M^{-1}s^{-1}$]	E_a [kJ mol^{-1}]
1	CH_3	100–210	1 x 10^4	34
2	C_2H_5	101–198	5 x 10^3	39
3	$CH(CH_3)_2$	93–200	5 x 10^3	30

The α-selectivity for carbon radical addition to propadiene (**1a**) is retained on substituting chlorine or fluorine for hydrogen in radicals of the type $CX_3^\bullet$ (X = F, Cl), no matter whether the reaction is conducted in the liquid or in the gas phase (Table 11.4) [14, 49–51]. β-Selective addition to allenes becomes progressively more important for the $CCl_3^\bullet$ radical with an increase in number of methyl substituents [14, 47]. For example, treatment of optically active (*P*)-(+)-2,4-dimethylpenta-2,3-diene [(*P*)-(**1c**)] with $BrCCl_3$ affords a 59:41 mixture of α- and β-monoadducts [47]. The α-addition product consists of a 20:80 mixture of *E*- and *Z*-stereoisomers, whereas the product of β-addition exclusively exhibits the *Z*-configuration. The fraction of 2,4-dimethylpenta-2,3-diene (*P*)-(**1c**) that was recovered from this reaction mixture had completely retained its optical activity. These results indicate that the α-*and* the β-$CCl_3^\bullet$ addition proceed under kinetic control. If one of the addition steps were reversible, at least partial racemization would inevitably have taken place.

Table 11.4 Product formation for $CX_3^\bullet$ radical addition (X = F, Cl) to allenes [14, 47, 50, 51]



1

Entry	**1**	R	X	Y	Yield [%]	α : β
1	**1a**	H	F	I	quant.	> 99 : 1[a]
2	**1c**	CH_3	F	I	91[b]	> 99 : 1[a]
3	**1a**	H	Cl	Br	67[c]	> 99 : 1[a]
4	**1c**	CH_3	Cl	Br	quant.	59[d] : 41

[a] No β-product was detected (GC).
[b] *E*:*Z* = 22:78.
[c] In addition: 33% of α,γ-diaddition product.
[d] *E*:*Z* = 20:80.

Based on the significance of organotin reagents as mediators in radical chain reactions, the addition of $Me_3Sn^\bullet$ to allenes has been investigated in detail [28]. For example, treatment of propadiene (**1a**) at 100 °C with trimethyltin hydride at a reactant ratio of $[Me_3SnH]:[C_3H_4] = 0.5$ provided exclusively monoadducts with a selectivity of $\alpha:\beta = 55:45$ (Figure 11.3). According to a kinetic analysis, both modes of addition proceed irreversibly. The β-selectivity for $Me_3Sn^\bullet$ attack increases with the number of methyl substituents. Trapping of β-adducts with the tin hydride furnishes internal olefins as major products (Figure 11.3) [28].

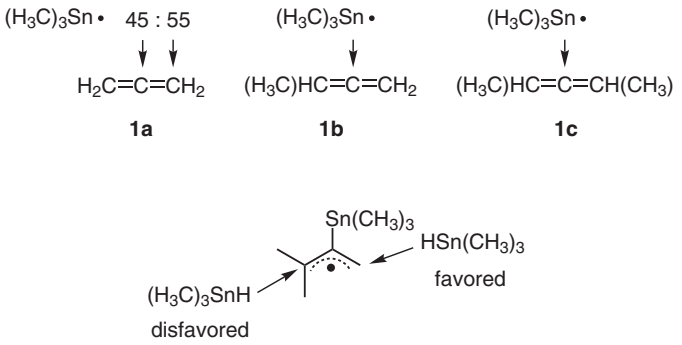


Figure 11.3 Selectivity for (i) tin radical addition to allenes (top) and (ii) hydrogen atom trapping of 2-stannyl-substituted allyl radicals (bottom) [28].

11.2.2.4 Guidelines for Predicting Regioselectivities in Radical Additions to Allenes

The preferred site for radical addition to a cumulated π-system of a 1,2-diene depends on (i) the degree of substitution of the allene, (ii) the nature of the attacking radical and (iii) reaction parameters such as temperature and initial reactant concentrations.

FMO Interactions

It has not been possible to correlate FMO energies and orbital coefficients with the observed reactivities and selectivities, in particular for thiyl radical additions to α-substituted propadienes (Figure 11.2) [15]. Therefore, it must be concluded that the addition is guided by thermodynamic factors, and hence the relative stabilities of adduct radicals.

α-Addition to Allenes

Selective α-addition to a cumulated π-bond is restricted to reactions with propadiene (**1a**), regardless of the the nature of the radical (i.e. from second-, third- or fourth-row elements). The phenomenon of reversible addition of the bromine atom and the phenylsulfanyl radical to C_α is striking but lacks in a thorough explanation at the moment [13, 14]. The activation energy for methyl radical addition to propadiene (**1a**) is 6 kJ mol^{-1} higher than that for addition to propene [27, 52]. This finding may be indicative of a transition state for the $CH_3^\bullet$ addition to allene **1a**, which is located later on the reaction coordinate than would have been expected on the basis of theoretical investigations [53]. The persistent α-selectivity of $CX_3^\bullet$ (X = H, F, Cl) in additions to propadiene (**1a**) has been applied to argue against the significance of polar effects in this type of reaction [10–12], since all three radicals exhibit different ionization potentials and hence SOMO energies [54].

β-Addition to Allenes

Substituents at the allene in general and methyl groups in particular favor β-addition of radicals, which leads to the formation of allylic and therefore stabilized intermediates. Results from computational studies predict that $CH_3^\bullet$ addition to C_β of

propadiene (**1a**) occurs along a trajectory that is orthogonally arranged with respect to the axis that aligns the three allenic carbon atoms (Figure 11.4) [53].

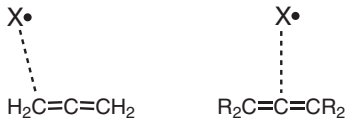


Figure 11.4 Models and guidelines for predicting selectivities in radical additions to allenes. R = H and/or alkyl, OH, SC_6H_5, CO_2CH_3. X = CX_3 (X = H, F, Cl), C_2H_5, $CH(CH_3)_2$, $Sn(CH_3)_3$, SC_6H_5, SeC_6H_5, Cl, Br.

11.2.2.5 **Trapping of Vinyl and Allyl Radicals**

Based on data from competition experiments, trapping of vinyl radicals occurs via a σ-type intermediate, which is lower in energy than the alternative π-radical structure [55, 56]. Stabilization of σ-radicals via hyperconjugation is small, which causes vinyl radicals to be more reactive than e.g. the methyl radical. *E*/*Z*-Isomerization of a strained σ-vinyl radical proceeds with a rate constant $k \approx 3 \times 10^8$–$10^{10}\ s^{-1}$ to provide the thermodynamically most favorable geometry [56].

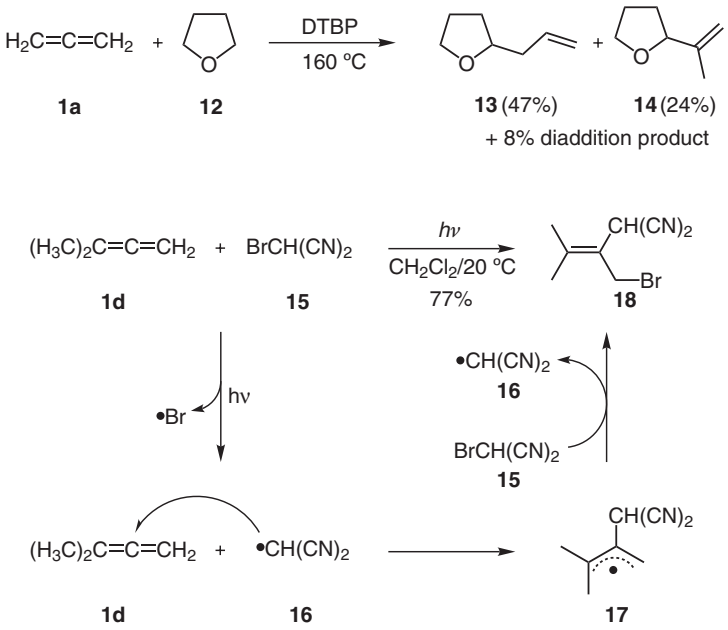
Trapping of an allyl radical is slower than that of structurally similar alkyl radicals. The origin of this decrease in reactivity has been related to the resonance stabilization of allyl radicals. According to EPR investigations, the largest SOMO coefficient of 1-substituted allyl radicals is located at C1 [57]. An analysis of reaction products from radical additions to allenes, however, indicates that the final step of allyl radical trapping does not occur at the highest substituted carbon, i.e. C1, but at the least hindered site, thus favoring the formation of the most stabilized olefin. Based on this argument, it must be concluded that this step proceeds under thermodynamic control [15]. The ratio of *E*- to *Z*-configured internal olefins from this step may provide insight into the preferred allyl radical configuration, unless additions of arylsulfonyl iodides or thiols are investigated. In the latter cases, the reversible addition of $I^\bullet$ and $ArS^\bullet$ to olefins causes an equilibration of the primary reaction product [47].

11.3 Intermolecular Additions of Alkyl Radicals to Allenes

Synthetic applications of carbon radical additions to allenes cover aspects of polymerization, selective 1:1 adduct formation and homolytic substitutions. If heated in the presence of, e.g., di-*tert*-butyl peroxide (DTBP), homopolymerization of phenylallene is observed to provide products with an average molecular weight of 2000 (not shown) [58]. IR and ^1H NMR spectroscopic analyses of such macromolecules point to the preferential carbon radical addition to C_γ and hence selective polymerization across the 2,3-double bond of the cumulene. Since one of the olefinic π-bonds from the monomer is retained, the polymer consists of styrene-like subunits and may be

subjected to further selective crosslinking or functionalization reactions. Methoxyallene, on the other hand, polymerizes under similar conditions to form a macromolecule that consists of 1,2- *and* 2,3-linked monomers.

Tetrahydrofuran (**12**) adds to propadiene when heated in the presence of DTBP to 160 °C to afford a minor fraction of diadduct in addition to 71% of a mixture of monoaddition products **13** and **14** (Scheme 11.8). The reaction proceeds via the nucleophilic 2-tetrahydrofuryl radical (not shown) that adds with a low α-selectivity to propadiene (**1a**), thus leading after hydrogen atom trapping to a 66:34 ratio of functionalized heterocycles **13** and **14** [59].

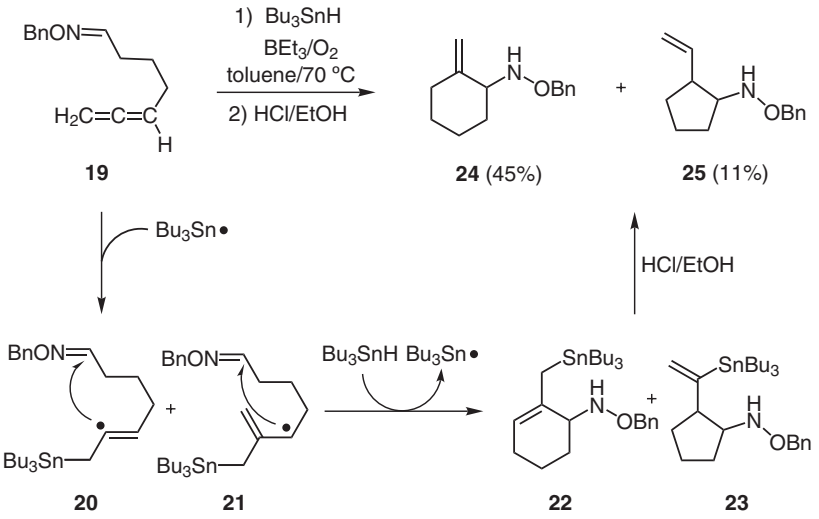


Scheme 11.8 Addition of tetrahydrofuran (**12**) and 2-bromomalodinitrile (**15**) to 1,2-dienes [59, 60].

Addition of the dicyanomethyl radical to propadiene (**1a**) occurs exclusively at C_α (not shown in Scheme 11.8) [60]. On the other hand, methyl-substituted allenes, e.g. **1d**, undergo β-selective reactions with 2-bromomalodinitrile (**15**). The significant β-selectivity has been associated with the steric demand of the incoming radical **16**, which favors addition to the sterically least hindered site at the diene **1d** to provide allylic radical **17**. However, it seems likely that a stabilization of an intermediate allylic radical, e.g. **17**, by methyl substituents contributes significantly to the observed regioselectivity of product formation. Trapping of intermediate **17** with bromine atom donor **15** proceeds at the least substituted carbon to afford allylic bromide **18**.

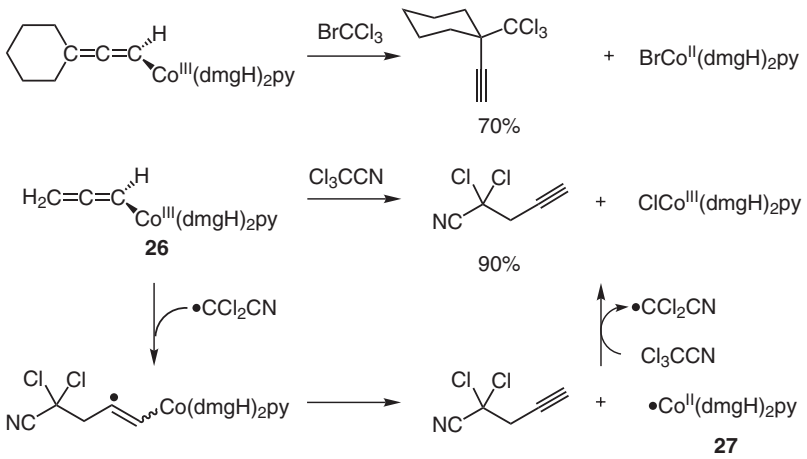
The propensity of trialkyltin radicals to add to the terminal position of allenes has been applied in the synthesis of substituted hydroxylamines from *N*-oximinoallenes,

e.g. **19** (Scheme 11.9) [61]. Thus, γ-selective addition of $Bu_3Sn^{\bullet}$ to the cumulated π-bond of substrate **19** affords vinyl radical **20** as major intermediate. A 6-*endo*-trig-selective ring closure of the latter intermediate follows to provide after hydrogen atom trapping stannylmethyl-substituted cyclohexene **22**. In in similar way, the minor β-addition product **21** cyclizes to yield vinyltin derivative **23**. Acidic hydrolysis of the primary products **22** and **23** then provides destannylated hydroxylamines **24** and **25** as target compounds.



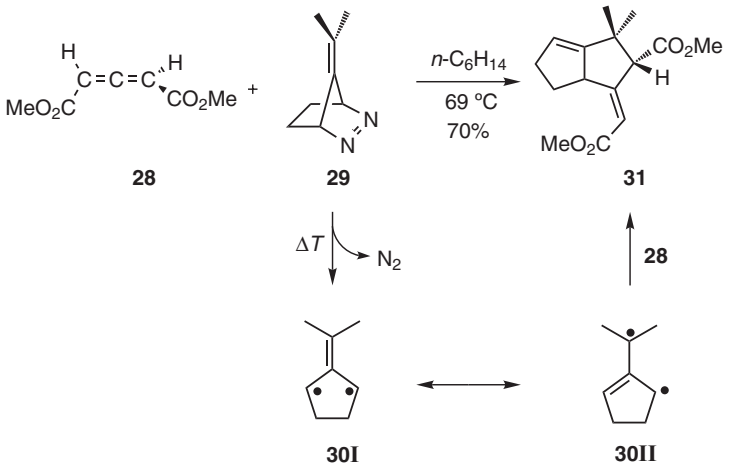
Scheme 11.9 Formation of *N*-substituted hydroxylamines **24** and **25** [61].

Allenylcobaloximes, e.g. **26**, react with bromotrichloromethane, carbon tetrachloride, trichloroacetonitrile, methyl trichloroacetate and bromoform to afford functionalized terminal alkynes in synthetically useful yields (Scheme 11.10). The nature of the products formed in this transformation points to a γ-specific attack of polyhaloethyl radicals to the allenyl group, with either a concerted or a stepwise formation of cobaloxime(II) **27** and the substituted alkyne [62, 63]. Cobalt(II) radical **27** abstracts a bromine atom (from $BrCCl_3$) or a chlorine atom (e.g. from Cl_3CCN), which leads to a regeneration of the chain-carrying radical. It is worth mentioning that the reverse reaction, i.e. the addition of alkyl radicals to stannylmethyl-substituted alkynes, has been applied in the synthesis of, e.g., allenyl-substituted thymidine derivatives [64].



Scheme 11.10 Synthesis of terminal alkynes from allenylcobaloximes [62, 63].

In studies directed towards the development of biologically more potent taxol analogues, diradical additions to allenes have been investigated. Thus, nitrogen extrusion from diazene **29** in hot hexanes, for example, furnishes diradical **30**, which adds to dimethyl glutinate (**28**) to afford cycloadduct **31** in 70% yield (Scheme 11.11) [68]. The configuration of this product was deduced from results of single-crystal X-ray diffraction analysis. Optimized conditions for the synthesis of bicyclic compound **31** require low concentrations of both the allene **28** and the diradical precursor **29**, in order to minimize formation of oligomers. The mechanism of this reaction has been interpreted as proceeding via addition of a secondary radical center of intermediate **30** to the central carbon of allene **28** to furnish a singlet diradical adduct. Given the short lifetimes of singlet diradicals, it was concluded that the optimized yield of target product **31** under low reactant concentrations originates from an intersystem crossing and thus the formation of a triplet diradical intermediate that cyclizes in a succeeding and comparatively slow step.



Scheme 11.11 Addition of diradical **30** to dimethyl glutinate (**28**) [65].

11.3.1
Conclusion

Intermolecular carbon radical additions to allenes proceed regioselectively. The α-addition is favored for propadiene (**1a**), whereas β-selective additions dominate for substituted allenes. Exceptions to this guideline are seen in (i) tin radical additions to the terminal position in monosubstituted allenes and (ii) homolytic substitutions in allenylcobaloximes(III).

11.4
Intramolecular Radical Additions to Cumulated Double Bonds

Radical cyclizations onto allenes have been applied so far in order to construct carbon–carbon (alkyl radicals) or carbon–nitrogen bonds (iminyl radicals). The selectivity guidelines for intermolecular reactions would favor formation of the β-adduct since, in principle, a monosubstituted allene is the least substituted cumulated π-system to serve as substrate in ring closure reactions. The experimental results, however, indicate that the distance between the reacting entities is a major factor of regiocontrol being, wherever possible, in favor for the construction of five-membered rings (Figure 11.5). It should be noted that in selected instances products of other ring sizes have been prepared in good (cyclohexene derivatives) to poor yields (a substituted cyclopropane or a functionalized cycloheptene) [66].

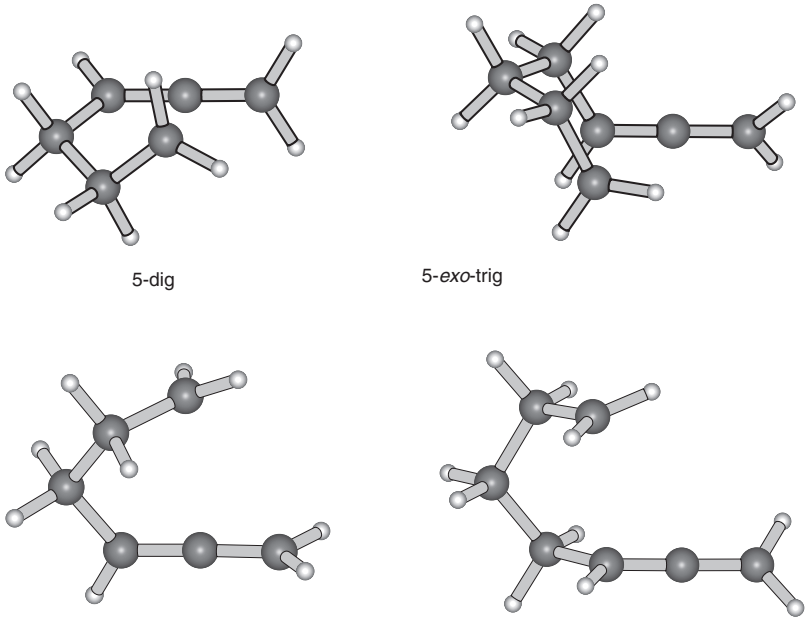
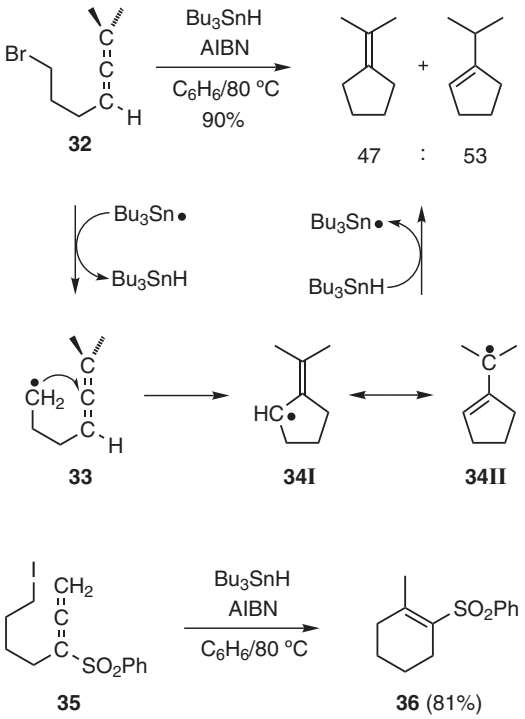


Figure 11.5 Ball-and-stick transition state models for (i) the 5-dig-cyclization of the hexa-4,5-dien-1-yl radical (left) and the 5-*exo*-trig-cyclization of the hepta-5,6-dien-1-yl radical (right).

11.4.1
Cyclizations on to the Central Carbon Atoms of Allenes

Allenyl radicals undergo cyclizations related to those of their olefinic counterparts. The efficiency of such transformations, if conducted in the presence of Bu_3SnH as reactive hydrogen atom donor, depends substantially on the chain length separating both reactive entities. The 6-methyl-4,5-heptadien-1-yl radical (**33**), for example, cyclizes efficiently via addition to the central allenic carbon atom [67]. Based on the knowledge that additions to π-bonds follow stereoelectronic control, the cyclization may be classified as 5-*exo*-dig addition, thus leading to radical **34II**. However, in view of the fact that intermediates **34I** and **34II** represent two mesomeric formulae of the same structure, it is reasonable to restrict the nomenclature for dig-cyclizations onto allenes to the ring size and the geometry of the reaction center. Competition experiments have indicated that the rate of cyclization **33** → **34** exceeds that of the 5-hexen-1-yl radical 5-*exo*-trig reaction by a factor of 90 at 80 °C. The higher homologue, i.e. the 7-methyl-5,6-octadien-1-yl radical (not shown), cyclizes by a factor of at least 100 slower than intermediate **33** to afford, after 6-dig-ring closure and subsequent hydrogen atom delivery from Bu_3SnH, 27% of 1-isopropylcyclohexene and 4% of isopropenylidenecyclohexane. The efficiency of the latter mode of cyclization may be increased with the aid of substituents located at the α-position of the allene

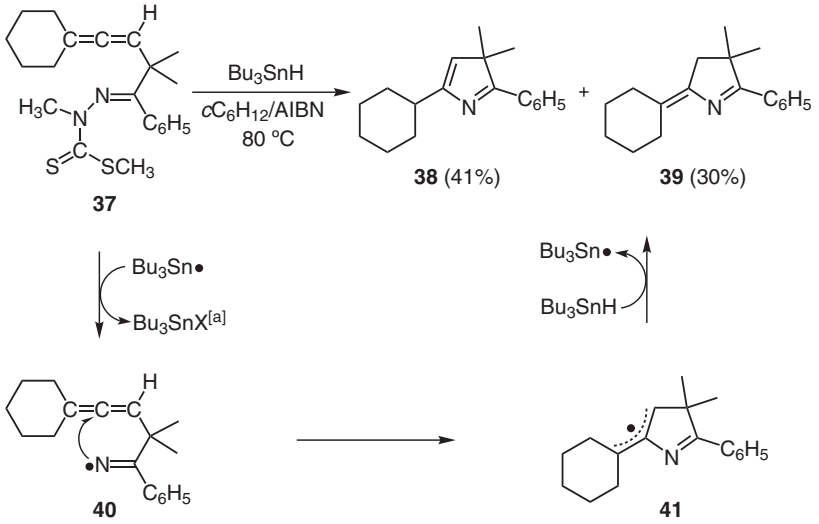
(Scheme 11.12, bottom). 3-Phenylsulfonyl-ω-iodobutylallene (**35**), for example, provides 81% of 1-phenylsulfonyl-2-methylcyclohexene (**36**) when treated with Bu_3SnH and AIBN in hot C_6H_6 [67].



Scheme 11.12 Modes of ring closure of 3-(ω-bromopropyl)- and 3-(ω-iodobutyl)-substituted allenes **32** and **35** in the presence of Bu_3SnH and AIBN [66, 67].

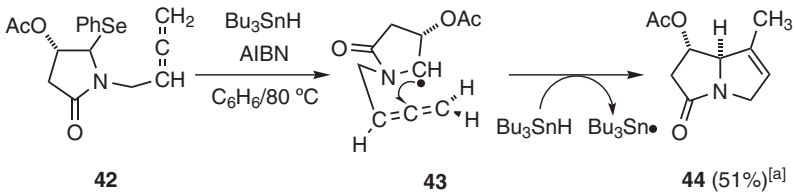
The 5-dig-mode of cyclization has been applied in the synthesis of *N*-heterocycles. For example, treatment of the β-allenyl dithiosemicarbazide **37** with Bu_3SnH and AIBN in hot benzene furnishes the substituted 3*H*-pyrrole **38** in 41% yield and the isomeric heterocycle **39** in 30% yield (Scheme 11.13) [68]. Iminyl radical **40** is formed via $Bu_3Sn^{\bullet}$ addition to the thiocarbonyl group of the radical precursor **37** and fragmentation of the adduct (not shown). Nitrogen-centered radical **40** adds 5-dig-selectively to provide substituted allyl radical **41**. The latter intermediate is trapped by Bu_3SnH to furnish preferentially product **38** with an endocyclic double bond.

Selective ring closure of cyclic secondary alkyl radicals onto the central carbon atom of allenes have been investigated in the course of pyrrolizidine alkaloid syntheses [69]. Thus, reduction of the phenylselenyl-substituted *N*-(1,2-buten-4-yl)pyrrolidone **42** with Bu_3SnH via a radical chain mechanism provides 51% of target compound **44** as a 78:22 mixture of diastereomers (Scheme 11.14). The stereoselectivity



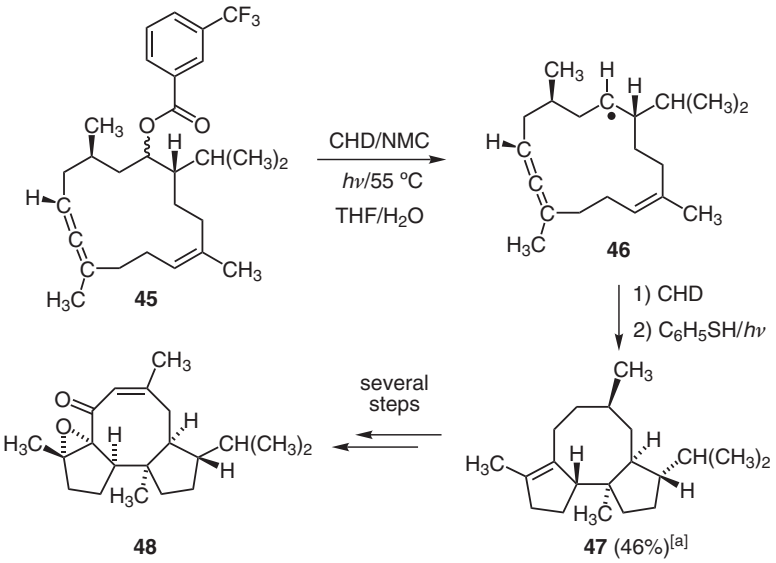
Scheme 11.13 Formation of pyrrole derivatives via iminyl radical cyclization on to a cumulated π-bond [68]. [a)] $X = S–C(NCH_3)(SCH_3)$.

of the underlying 5-dig ring closure of intermediate **43** may be rationalized by adapting the Beckwith–Houk model for this purpose: The major product originates from a chair-like transition structure, which is considered to represent the conformer with the least torsional strain upon an approach of reacting entities [70, 71]. On the assumption of an irreversible addition of carbon radicals to either site of an allene, likewise obtained relative energies of competing transition states are suited in order to rationalize the origin of observed diastereoselectivities in cyclizations. The major product from the reductive deselenation of substituted pyrrolidone **42** was converted in three steps with an overall yield of 15% into (+)-heliotridine, a necine base that is present in almost 20 mono- and diester derivatives of pyrrolizidine alkaloids, such as echinatine, heliosupine and heliotrine [69].



Scheme 11.14 The synthesis of building block **44** in the total synthesis of (+)-heliotridine, a necine base present in a large diversity of pyrrolizidine alkaloids [69]. [a)] 78:22 mixture of diastereomers.

The utility of radical additions to allenes was probed in a cascade reaction starting from a mixture of diastereomeric esters **45**, which was photolyzed in the presence of 1,4-cyclohexadiene (CHD) and *N*-methylcarbazole (NMC) in a solution of THF and water (Scheme 11.15) [72]. Under these conditions, macrocyclic allenic radical **46** is formed, which undergoes two consecutive intramolecular additions, one being a conventional 5-*exo*-trig cyclization on to an olefinic π-bond and the other a radical addition to a central allenic carbon atom. The cascade is terminated via hydrogen atom trapping from CHD to furnish a tricyclic reaction product that consists of a mixture of olefin isomers. Equilibration of this mixture is feasible, if treated with C_6H_5SH, to provide target compound **47**. The diastereoselectivities of the carbon–carbon bond-forming steps from the cascade reaction have been investigated using the Spellmeyer–Houk method [71], i.e. by estimating relative transition-state energies by means of force field calculations. In all instances, the observed selectivities were in agreement with the results obtained from the model calculations. Finally, product **47** from the cascade reaction was transformed into the natural product 7,8-epoxy-4-basmen-6-one (**48**) [73].

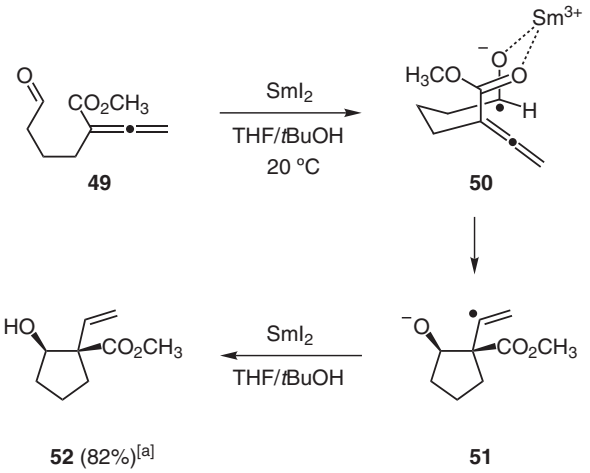


Scheme 11.15 Application of transannular cyclizations in the total synthesis of 7,8-epoxy-4-basmen-6-one (**48**) [72]. [a)]The yield of **47** refers to macrocycle **45** as starting material.

11.4.2
Cyclizations via Radical Addition to C_α

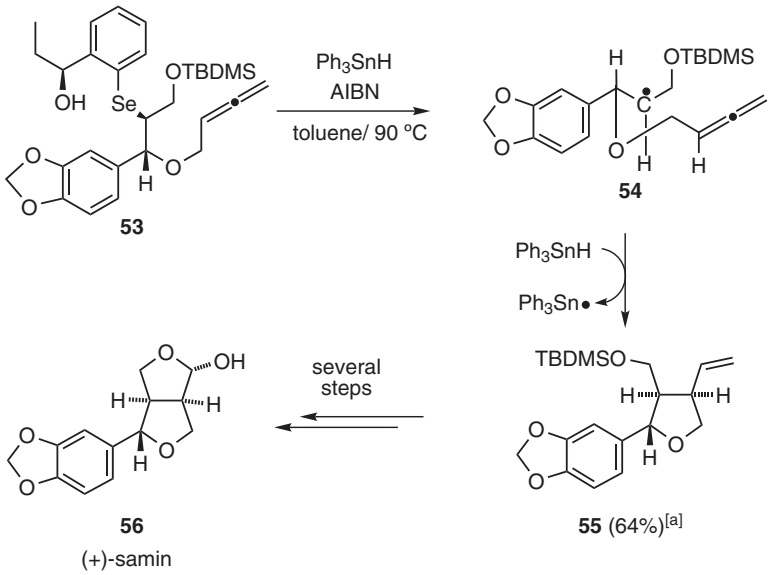
In view of the propensity of carbon radicals to favor in cyclizations the formation of five-membered products, the mechanistic approach for conducting *exo*-trig-selective

ring closures is based on the use of δ-allenic instead of γ-allenic intermediates. Treatment of methoxycarbonyl-substituted allenic aldehyde **49** with 2 equiv. of both SmI_2 and *tert*-C_4H_9OH provided methyl 2-hydroxy-1-vinylcyclopentanecarboxylate (**52**) in 82% yield as a 94:6 mixture of diastereomers (Scheme 11.16). The transformation starts with the generation of a ketyl radical anion. The approach of the reacting entities is facilitated by means of chelation of two oxo functionalities to the Sm^{3+} ion, thus affording presumably a chair-like structure **50** as the energetically lowest transition state. This arrangement is set up for 5-*exo*-trig selective ring closure, for stereoelectronic reasons. The intramolecular C–C bond formation affords *cis*-configured vinyl radical oxyanion **51** as major product. Further reduction of this intermediate with the second equivalent of SmI_2 and protonation with the aid of *tert*-C_4H_9OH leads to the formation of cyclopentane derivative **52**. This strategy has been extended in order to prepare methyl 2-hydroxy-1-vinylcyclohexanecarboxylate (78%, *cis*:*trans* = 86:14) via a 6-*exo*-trig cyclization [74].



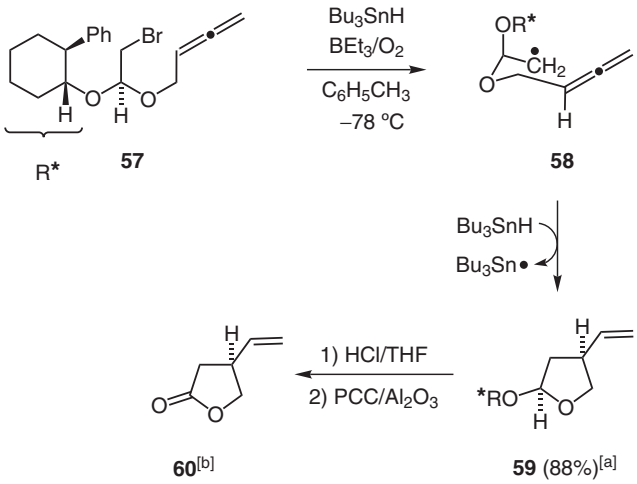
Scheme 11.16 Diastereocontrol via chelate effect: stereoselective 5-*exo*-trig cyclization on to a cumulated π-bond of a chelated ester-substituted ketyl radical anion **50** [74].
[a] 94:6 mixture of diastereomers.

The 5-*exo*-trig mode of cyclization onto allenes has been applied in the total synthesis of the lignane (+)-samin (**56**) (Scheme 11.17) [75]. The furofuran (i.e. 3,7-dioxabicyclo[3.3.0]octane) skeleton of the target compound **56** was constructed from functionalized selenide **53** by treatment with Ph_3SnH and AIBN in hot toluene. Under these conditions, intermediate **54** is formed that preferentially undergoes 5-*exo*-trig-selective ring closure to afford, after hydrogen atom trapping, 64% of trisubstituted tetrahydrofuran **55**. The cyclization disfavors the product which is required for completion of the (+)-samin synthesis, whereas guidelines for selective carbon radical ring closure reactions state that cyclizations of the 1-methyl-substituted 5-hexen-1-yl radical, i.e. the 6-hepten-2-yl radical (not shown), proceed, for reasons of secondary orbital interactions, *cis*-selectively [76].



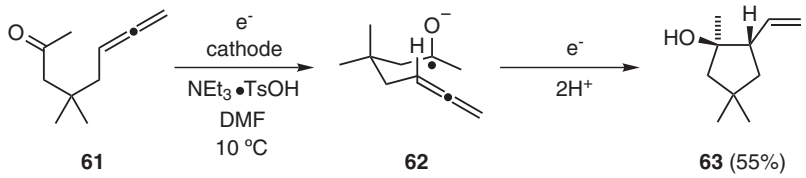
Scheme 11.17 Diastereoselective formation of a tetrahydrofuran nucleus via 5-*exo*-trig alkyl radical cyclization on to an allene functionality in the course of a total synthesis of (+)-samin (**56**) [75]. [a] 33:67 mixture of diastereomers.

The control of facial selectivity in 5-*exo*-trig additions to cumulated π-bonds has been achieved using chiral auxiliaries, e.g. in a Ueno–Stork-type reaction (Scheme 11.18) [77, 78]. Treatment of bromoacetal **57** with Bu_3SnH and BEt_3–O_2 at –78 °C leads to the formation of carbon radical **58** that undergoes a 5-*exo*-trig-selective ring closure. The preference for radical attack onto the *Si*-face at C_α of the allenic entity is governed by the acetal substituent, which, on the basis of results from computational studies, favors the pseudoaxial position [79]. Hydrogen atom trapping of the cyclization product affords vinyl-substituted acetal **59** in 88% yield (90:10 mixture of diastereomers), which has been converted into optically active building block **60**. Similar transformations have provided a novel access to (–)-botryodiplodin, a natural product that has been purified from *Botryodiplodia theobromae* and from a fermentation broth of *Penicillium roqueforti*.



Scheme 11.18 Auxilliary control in an Ueno–Stork-type 5-*exo*-trig cyclization in the synthesis of an enantiomerically pure lactone **60** [77].
[a] 90:10 mixture of diastereomers. [b] >99% *ee*.

Electrolysis of δ-allenic ketone **61** at a controlled cathode potential of –2.43 V (versus Ag/AgI) in anhydrous DMF using tetraethylammonium *p*-toluenesulfonate as co-electrolyte provides the derived ketyl radical that undergoes a 5-*exo*-trig selective ring closure, presumably via transition structure **62** (Scheme 11.19). The cyclization product is further reduced and subsequently protonated to afford *trans*-configured cyclopentanol **63** as single diastereomer in a total yield of 55% [80].



Scheme 11.19 Selective formation of functionalized cyclopentanol **63** via electrochemical reduction of allenic ketone **61** [80].

11.4.3 Conclusion

Radical cyclizations onto allenes are feasible via the dig (addition to C_β) or the *exo*-trig mode of ring closure (addition to C_α). The significance of the α-addition is more pronounced in the case of the intramolecular pathway than in its intermolecular counterpart owing to (i) the chain length between the reacting entities and (ii) the stereoelectronic prerequisites for a radical attack on a π-bond [4].

11.5 Summary and Perspectives

Radical additions to allenes constitute challenging and synthetically useful transformations for constructing a large variety of building blocks in organic synthesis. Fields of application cover aspects of selective heteroatom functionalization, homolytic substitutions, cycloadditions, cascade reactions and polymerizations. A strict separation between transformations of propadiene (**1a**) and its substituted derivatives, e.g. **1b–k**, is necessary in order to uncover guidelines for predicting selectivities in radical additions to cumulated π-bonds. Seemingly regardless of their polarity, radicals of different rows and groups of the Periodic Table add α-selectively to the propadiene (**1a**), whereas substituents already present at the 1,2-diene direct the incoming radical preferentially to the central carbon. In the latter case, selectivities of radical additions are predictable by considering relative stabilities of the corresponding intermediates. Therefore, it must be concluded that thermochemistry guides radical additions to allenes, whereas FMO theory serves to rationalize selectivities of radical additions to olefins and aromatic π-systems.

In a time when the biological activity of organic compounds is a major driving force for preparing target compounds it is worth mentioning that the cornerstones of this field of research originate from physical- and physical organic-oriented studies. In the last few years, however, applications of radical-based transformations of allenes, in particular for constructing five-membered rings as parts of natural product syntheses that required an olefinic π-system next to the newly formed bond in either the target compound or a synthetic intermediate, have become more and more important. Many of the more recent examples, such as the construction of the bicyclic substructure of azadirachtin, a highly oxidized diterpene which has been isolated from the Indian tree *Azadirachta indica*, and new bi- and tricyclic β-lactams, have indicated that researchers are willing to apply radical additions to allenes in instances where ionic transformations have failed to provide similar selectivities [81, 82]. In order to uncover the full potential of this chemistry it may be necessary, however, to return to its roots, i.e. to devise new reactivity and selectivity experiments that allow a more precise classification of factors that contribute to the marked difference between olefins and allenes in the seemingly well-rationalized elementary reaction of the radical addition to a π-bond.

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12
Cycloadditions of Allenes

Masahiro Murakami and Takanori Matsuda

12.1
Introduction

The heat of hydrogenation of one carbon–carbon double bond of allene is 41 kcal mol^{-1}, whereas that of an ordinary alkene is around 29 kcal mol^{-1}. Thus the cumulated double bond of allene liberates 12 kcal mol^{-1} more than that of a simple alkene on hydrogenation. Accumulation of two carbon–carbon double bonds imparts an extra reactivity to allene, making it a remarkably active component participating in a variety of cycloaddition reactions as a two-carbon unit.

$$H_2C{=}C{=}CH_2 \xrightarrow[\Delta H = -41\ \text{kcal/mol}]{H_2} CH_3{-}CH{=}CH_2 \xrightarrow[\Delta H = -29\ \text{kcal/mol}]{H_2} CH_3{-}CH_2{-}CH_3 \qquad (12.1)$$

This chapter focuses on cycloaddition reactions in which at least two new σ-bonds are formed between allene derivatives and other unsaturated organic molecules. Intramolecular cycloaddition reactions are also described. The reactions are categorized according to assembly modes, such as [$m + n$]-cycloaddition, where the variables m and n simply denote the number of atoms that each component contributes to the ring construction. Some electrocyclic reactions of allene derivatives are also included.

12.2
[2 + 2]-Cycloaddition of Allenes

12.2.1
Dimerization of Allenes

12.2.1.1 Intermolecular Dimerization

Unlike ordinary olefins, allene (1,2-propadiene) (**1**) undergoes *thermal* dimerization to afford 1,2-dimethylenecyclobutane (**2**), first reported by Lebedev in 1913 [1]. The yield of the dimer **2** was improved up to 95% by Dolbier, who used a benzene solution of **1** for the dimerization reaction [2].

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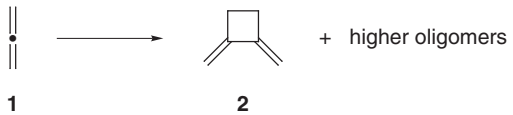
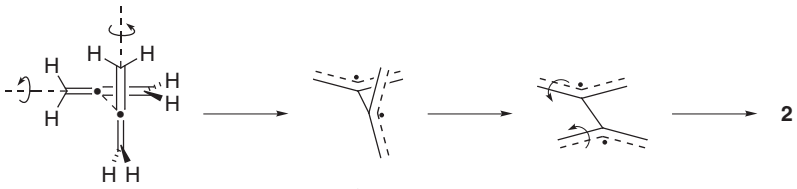


1 **2** (12.2)

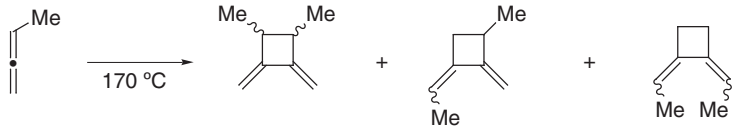
neat (140–150 °C): 5%
gas-phase (500–510 °C): 50%
solution (130–200 °C): 95%

The [2 + 2]-cycloaddition of allene proceeds via a stepwise diradical mechanism rather than a concerted one-step mechanism. The allenes come together in a 'crossed' configuration. The bond formation between the central sp carbon atoms is accompanied by a simultaneous conrotatory twisting leading to a 'perpendicular' 2,2′-bisallyl diradical **3**. Rotation about the central bond of **3** gives the planar diradical and a disrotatory closure leads to the formation of dimer **2**. The stereochemistry of some of the following examples is explained by this mechanism.



3 (12.3)

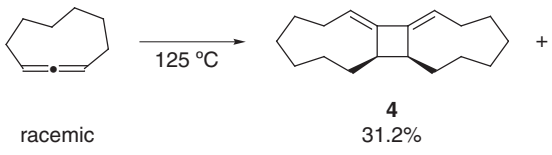
Thermal dimerization of methylallene yielded a mixture of seven possible cisoid conjugated dienes [3].

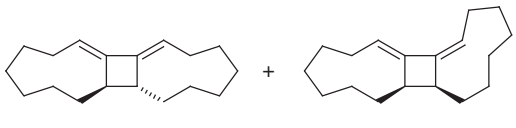


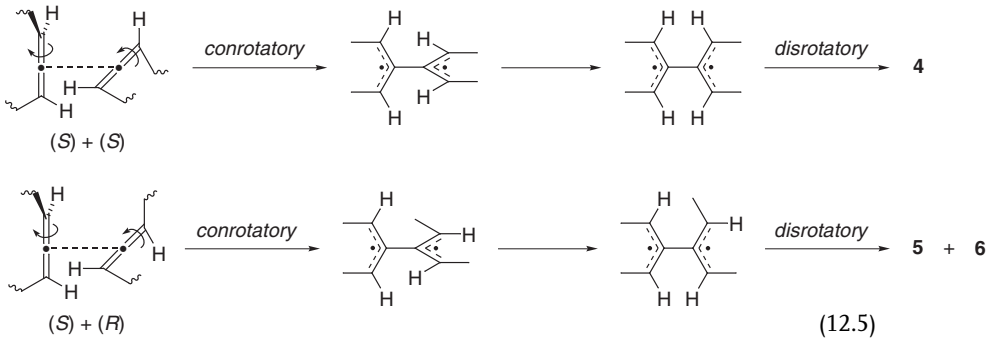
(12.4)

head-to-head (h-h) head-to-tail (h-t) tail-to-tail (t-t)
cis:*trans* = 14:86 *Z*:*E* = 67:33 *ZZ*:*EZ*:*EE* = 79:18:3
h-h:h-t:t-t = 29:55:16

1,2-Cyclononadiene is the smallest isolable cyclic allene with a chirality axis. Heating the racemic mixture without solvent at 125 °C afforded an essentially quantitative yield of a mixture of three isomers **4**–**6** [4]. The combination of (*S*)-allene with (*S*)-allene [or (*R*) with (*R*)] gives **4**, while the cross-combination of (*S*)-allene with (*R*)-allene gives **5** and **6** (cf. Chapter 6).

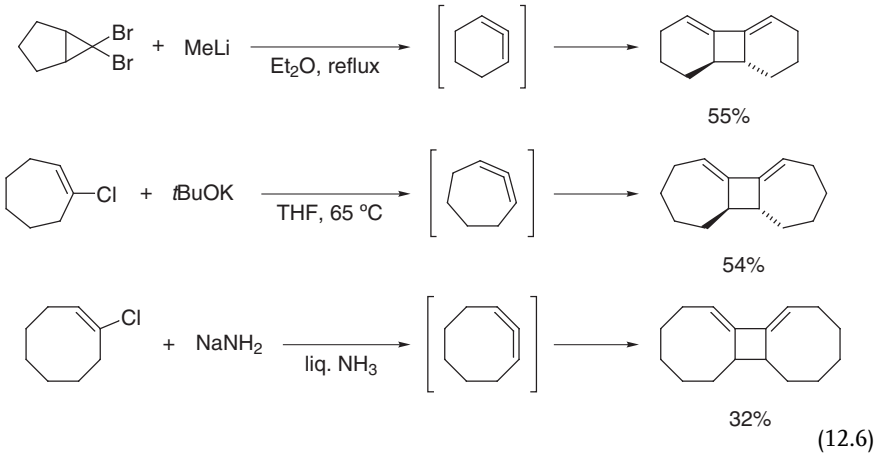






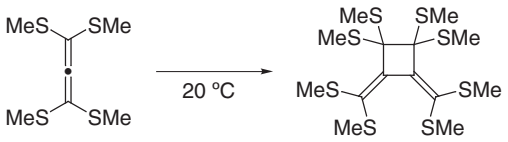
(12.5)

Six- to eight-membered cyclic allenes are too strained to be isolated. Spontaneous [2 + 2]-cycloaddition occurs with these allenes to give the dimer as soon as they are generated in solution [5, 6].



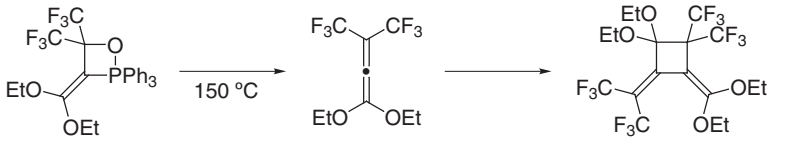
(12.6)

A variety of allenes having functional groups also undergo thermal dimerization. Examples are shown below. Tetrakis(methylthio)allene was reactive enough to dimerize at 20 °C [7].



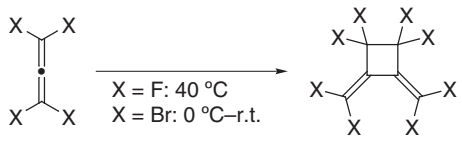
48% (12.7)

Thermolysis of an oxaphosphetane afforded allene **7**, possessing electron-donating and electron-accepting substituents at each end. Spontaneous head-to-tail dimerization took place with the formation of **8** [8].



7 **8** 85% (12.8)

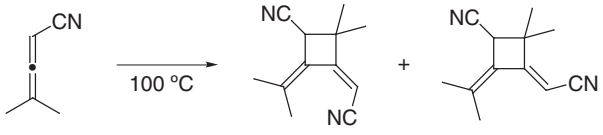
Halogen-substituted allenes undergo [2 + 2]-homodimerization under relatively mild conditions to afford 1,2-bis(halomethylene)cyclobutene derivatives in good yields [9].



X = F, Br

X = F: 83%
X = Br: 85% (12.9)

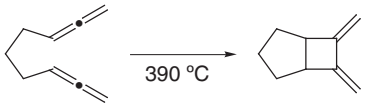
Allenic nitrile **9** gave unsymmetrical head-to-tail cycloadduct **10** as a mixture of *Z*- and *E*-isomers [10].



9 (*Z*)-**10** 85% (*E*)-**10** 5% (12.10)

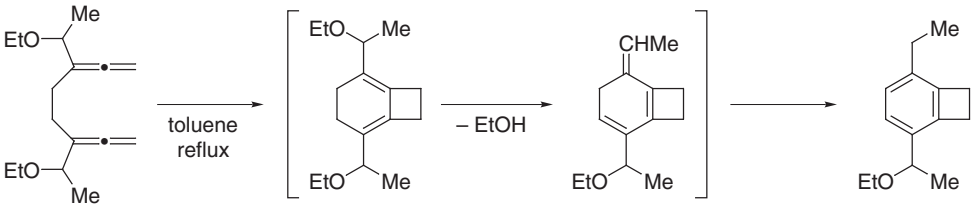
12.2.1.2 **Intramolecular [2 + 2]-Cycloaddition of Bisallenes**

With bisallene **11** having a three-carbon chain between the allenic parts, the intramolecular [2 + 2]-cycloaddition occurred at the inner carbon–carbon double bonds to afford 6,7-dimethylenebicyclo[3.2.0]heptane **12** [11].



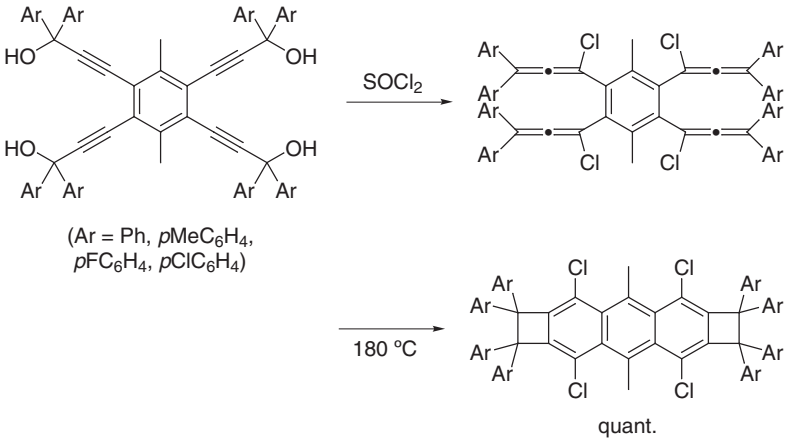
11 **12** 32% conv. (12.11)

On the other hand, bisallene **13** having a two-carbon tether underwent dimerization at the terminal carbon–carbon double bonds at lower temperature. Aromatic compound **14** was ultimately formed through elimination and a hydrogen shift [12].



13 **14** 82% (12.12)

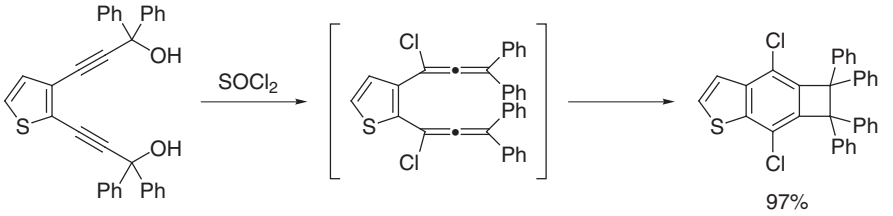
Analogous reactions were used for the preparation of various benzocyclobutene derivatives [13–15].



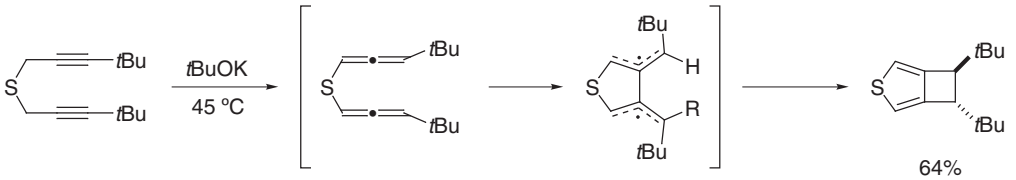
(Ar = Ph, *p*MeC$_6$H$_4$, *p*FC$_6$H$_4$, *p*ClC$_6$H$_4$)

quant.

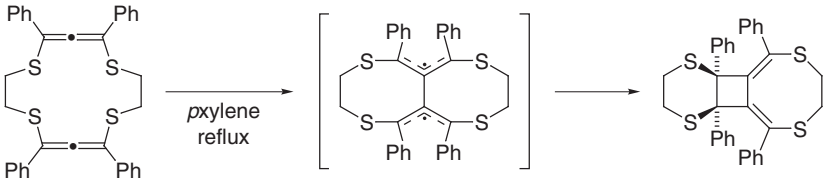
(12.13)



97%



64%



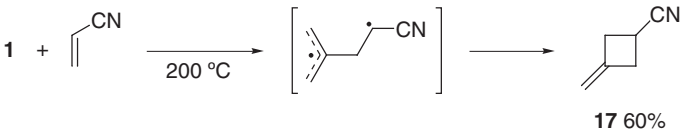
dl-**15**
meso-**15**

16 quant. (from *dl*)
quant. (from *meso*)

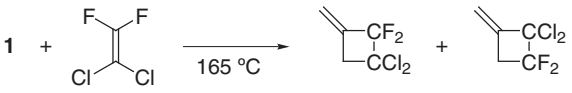
12.2.2
Cycloaddition with Olefins

12.2.2.1 Thermal Cycloaddition

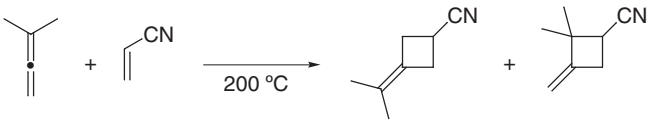
Electron-deficient olefins such as acrylonitrile can participate in the cross [2 + 2]-cycloaddition with allenes. 3-Methylenecyclobutanecarbonitrile (**17**) was obtained in 60% yield by the reaction of allene with a large excess of acrylonitrile under autogenous pressure at 200 °C [16]. Initial bond formation takes place between the central carbon of allene and the terminal carbon of acrylonitrile to give a diradical species, which cyclizes to form the cycloadduct [17].



17 60%



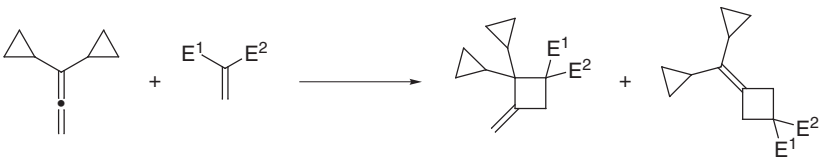
18 75% (95:5) (12.14)



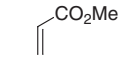
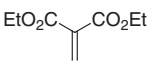
36% 30%

1,1-Dicyclopropylallene reacts with olefins activated by ester groups at 200 °C to yield the adducts **20** predominantly (Table 12.1). In contrast, the reactions with methylenemalononitrile occurred at *room temperature* with selective production of the adduct **19** [18]. A dipolar mechanism is assumed for the latter reaction.

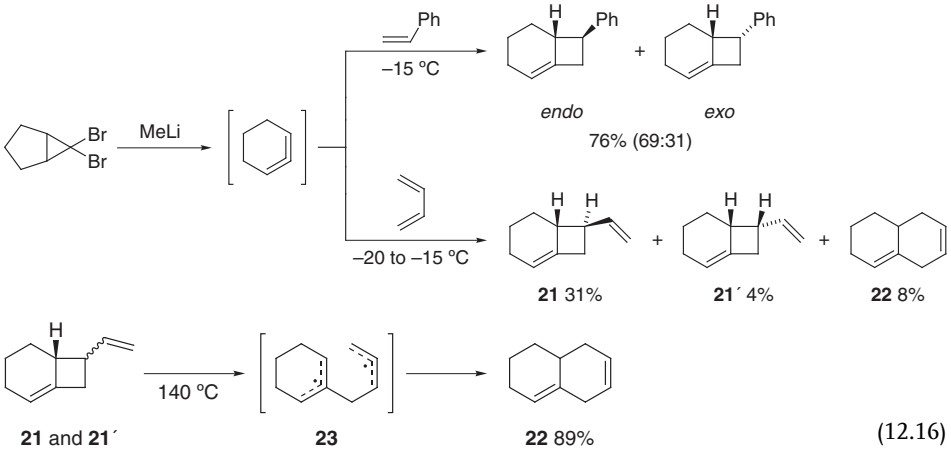
Table 12.1 Reactions of 1,1-dicyclopropylallene with activated olefins.



19 **20** (12.15)

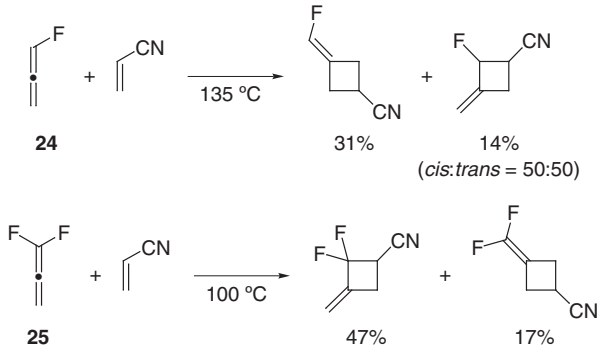
	Temperature (°C)	Yield (%)	19:20
	200	69	11:89
	200	84	5:95
	r.t.	66	93:7

1,2-Cyclohexadiene, generated by the reaction of MeLi with the dibromide formed from cyclopentene and dibromocarbene, is so reactive as to add to styrene and 1,3-butadiene [19]. Hexahydronaphthalene **22** was formed by thermolysis of **21** and **21′** via diradical **23** [20].



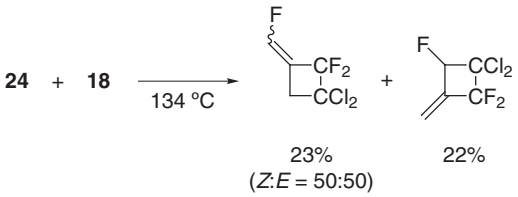
(12.16)

Cycloaddition reactions of monofluoroallene (MFA) (**24**) and 1,1-difluoroallene (DFA) (**25**) with acrylonitrile occurred at either C1–C2 or C2–C3 bond of the fluoroallenes, respectively, affording 3-methylenecyclobutanecarbonitrile derivatives [21].



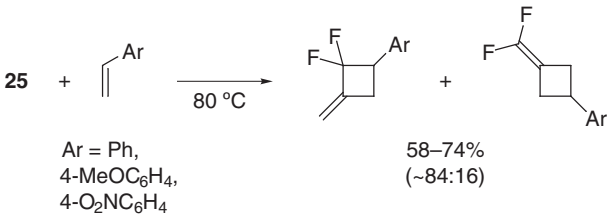
(12.17)

The central carbon atom of MFA is bound to the difluoro-substituted carbon atom in the [2 + 2]-cycloaddition of MFA with **18** [22].



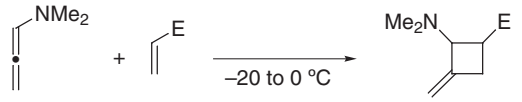
(12.18)

DFA reacts with a 10-fold excess of styrene derivatives to afford a regioisomeric mixture of two methylenecyclobutanes [23].



(12.19)

(Dimethylamino)allene is so reactive that [2 + 2]-cycloaddition reactions with acrylonitrile and methyl acrylate are complete only in 30 min at –20 to 0 °C [24].

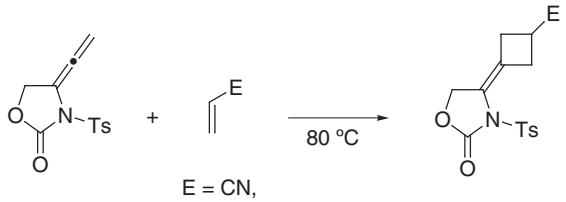


(12.20)

26 E = CN, CO_2Me

E = CN: 97% (*cis*:*trans* = 30:70)
E = CO_2Me: 93% (*cis*:*trans* = 9:91)

On the other hand, 4-vinylidene-1,3-oxazolidin-2-one **26** undergoes a facile [2 + 2]-cycloaddition with electron-deficient olefins regioselectively at the terminal double bond to furnish methylenecyclobutane derivatives [25].



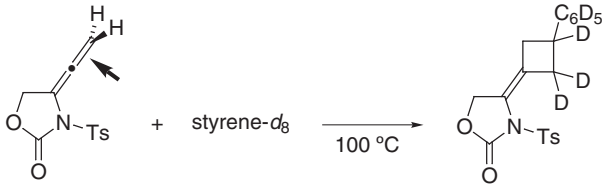
26

E = CN, CO_2Me, $CONMe_2$

71–88%

(12.21)

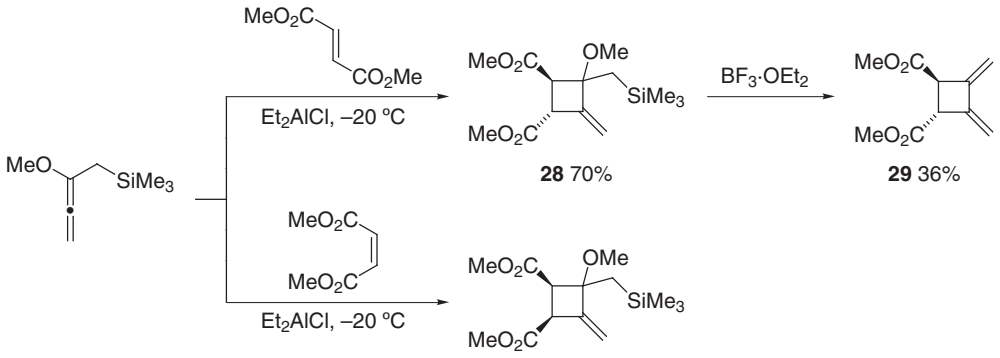
The reaction of the oxazolidinone with styrene-d_8 led to the selective formation of (*Z*)-**27**. Thus, styrene adds to the terminal double bond from the more congested face *syn* to the *N*-tosyl group.



(*Z*)-**27** 80%
(*Z*:*E* > 45:1)

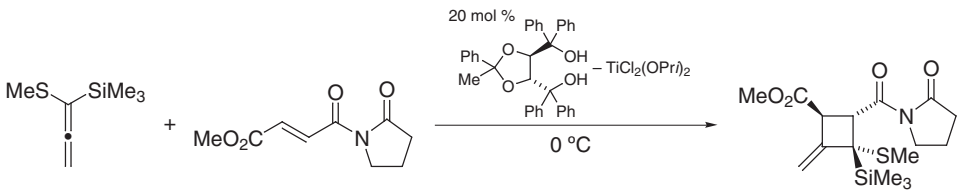
(12.22)

Lewis acids can promote the [2 + 2]-cycloaddition by activating substrates having ester groups. 2-Methoxyallenylmethylsilane reacts with methyl fumarate and methyl maleate in the presence of Et_2AlCl to give cyclobutanes with retention of the double bond configuration. The cycloadduct **28** was converted to the corresponding 1,2-dimethylenecyclobutane **29** through 1,2-elimination of the methoxy and silyl groups [26].



(12.23)

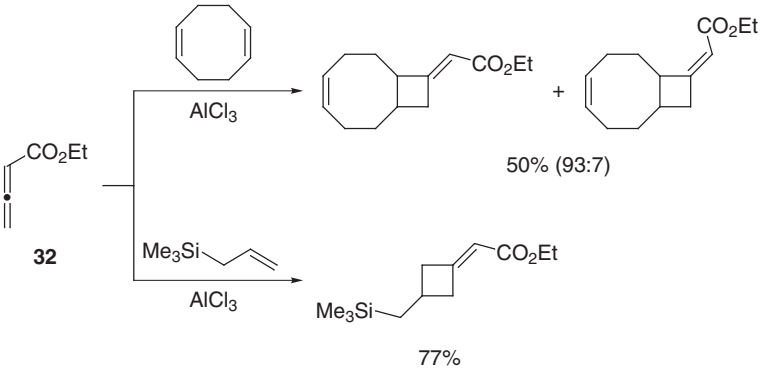
A Ti-catalyzed enantioselective [2 + 2]-cycloaddition between allenyl sulfide **30** and **31** afforded the adduct with a high optical purity [27].



30 **31** 98% (>98% *ee*)

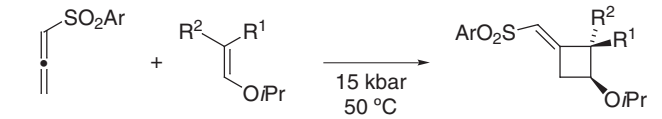
(12.24)

[2 + 2]-Cycloaddition reactions of electron-deficient allenes are also known. In the presence of $AlCl_3$, ethyl 2,3-butadienoate (**32**) reacts with alkenes to give cyclobutylideneacetic esters at room temperature [28].



(12.25)

High-pressure conditions also promote the [2 + 2]-cycloaddition. (4-Methylphenylsulfonyl)allene and enol ethers give the [2 + 2]-adducts in a regioselective and stereospecific way [29].

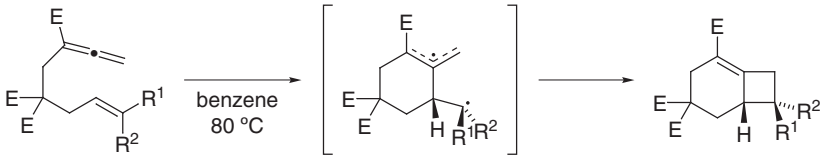


(Ar = 4-MeC_6H_4)

R^1 = H, R^2 = Me: 75%
R^1 = Me, R^2 = H: 62%

(12.26)

Thermal intramolecular [2 + 2]-cycloadditions of phenylsulfonyl-substituted allenes **33** gave **34** stereoselectively. An initial carbon–carbon bond formation occurred at the central allenic carbon and the proximal olefinic carbon. The resulting non-allylic radical **35** is unstable and cyclizes rapidly, which may account for the high stereoselectivity [30].



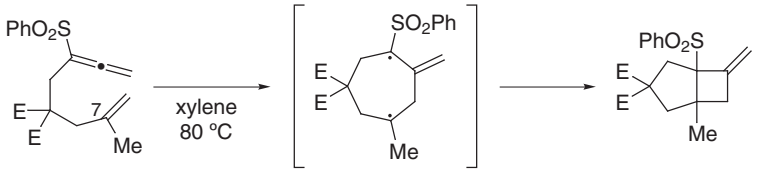
33: E = SO_2Ph,
R^1 = H, R^2 = Me;
R^1 = Me, R^2 = H

35

34 80–98%

(12.27)

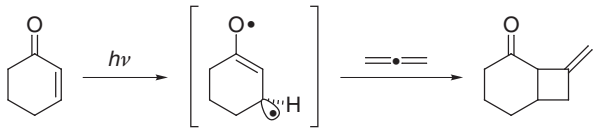
An interesting variation in the regioselectivity was observed with enallene **36** having a substituent at the 7-position. The presence of the substituent shifted the position of the initial C–C bond formation and accordingly, the position of the ring closure [30b].



36 74% (12.28)

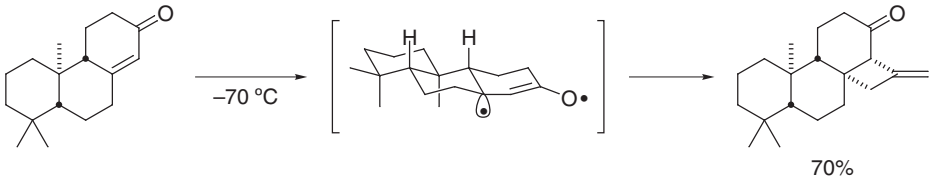
12.2.2.2 **Photocycloaddition with Enones**

The [2 + 2] photocycloaddition reaction of enones with allenes was first reported in 1966. A diradical intermediate is formed from a triplet enone via an exciplex. The triplet diradical cyclizes to the product after spin inversion to the singlet state [31, 32].



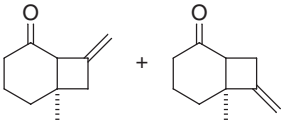
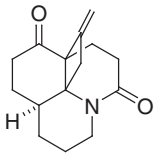
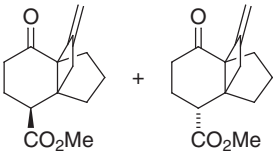
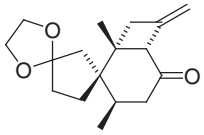
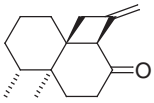
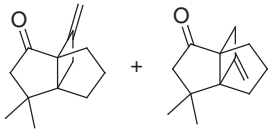
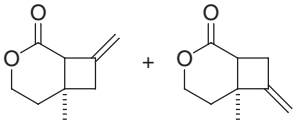
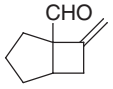
55% (12.29)

Since then, the photocycloaddition reaction has been extensively studied and has become a powerful tool for the construction of complex polycyclic molecules. High stereoselectivities are observed in some cases. The configuration of the diradical intermediate determines the stereochemistry of the adduct [33]. Typical examples are given in Table 12.2 [34].

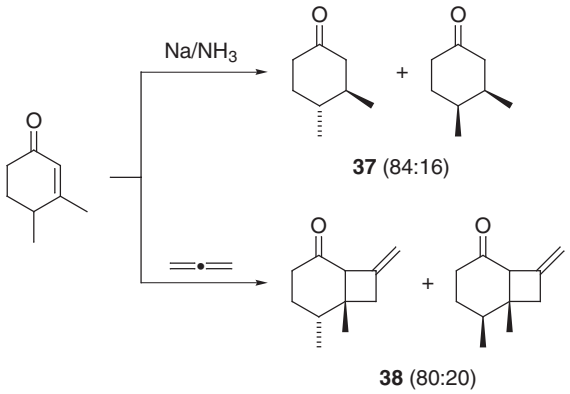


70% (12.30)

Table 12.2 Photocycloaddition reactions of enones.

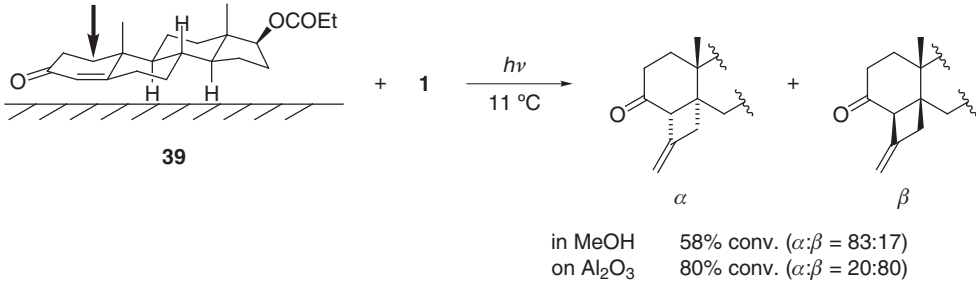
Compounds	Ref.	Compounds	Ref.
 82% (63:37)	[35]	 54%	[36]
 80% (93:7)	[37]	 83%	[38]
 75%	[39]	 94% (82:18)	[40]
 83% (60:40)	[35]	 41%	[41]

The stereochemistry of the photocycloadducts can be predicted from the result of a dissolving metal reduction of the same α,β-unsaturated ketone. For example, sodium/ammonia reduction of 3,4-dimethylcyclohexenone yielded *trans*- and *cis*-dimethylcyclohexanone **37** in a ratio of 84:16, which was similar to the ratio of the two photocycloadducts **38** (80:20) [33b, 42].



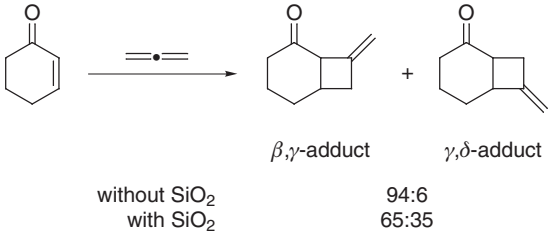
(12.32)

The stereochemical outcome of the reaction of steroidal enone **39** changed when adsorbed on alumina [43]. Photocycloaddition in methanol occurred from the α side (83:17). In contrast, the β product was favored when the reaction was carried out on alumina. The observed β selectivity can be accounted for by the preferential adsorption of the sterically less hindered α side of the enone to the gel surface.



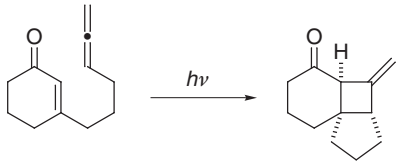
(12.33)

Interestingly, the ratio of the β,γ-adduct to the γ,δ-adduct formed from 2-cyclohexenone and allene also changed in favor of the latter on a silica gel surface [44].

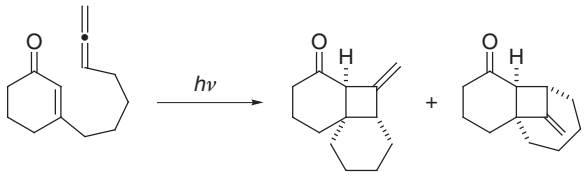


(12.34)

Intramolecular [2 + 2]-cycloadditions of allenes and enones occur with fair to good site- and regioselectivities. Thus, cyclohexenone **40** bearing an allenic side-chain at the C3 position was irradiated and a single product **41** was isolated in 95% yield [45].

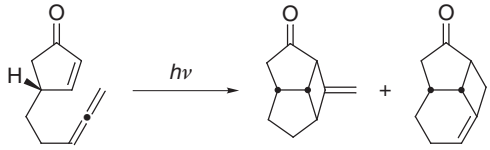


40 **41** 95%

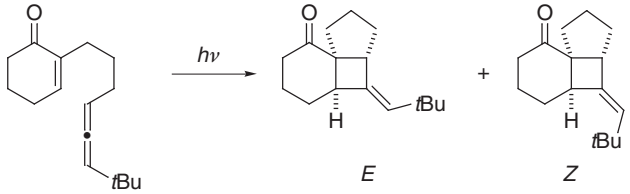


quant. (85:15)

(12.35)



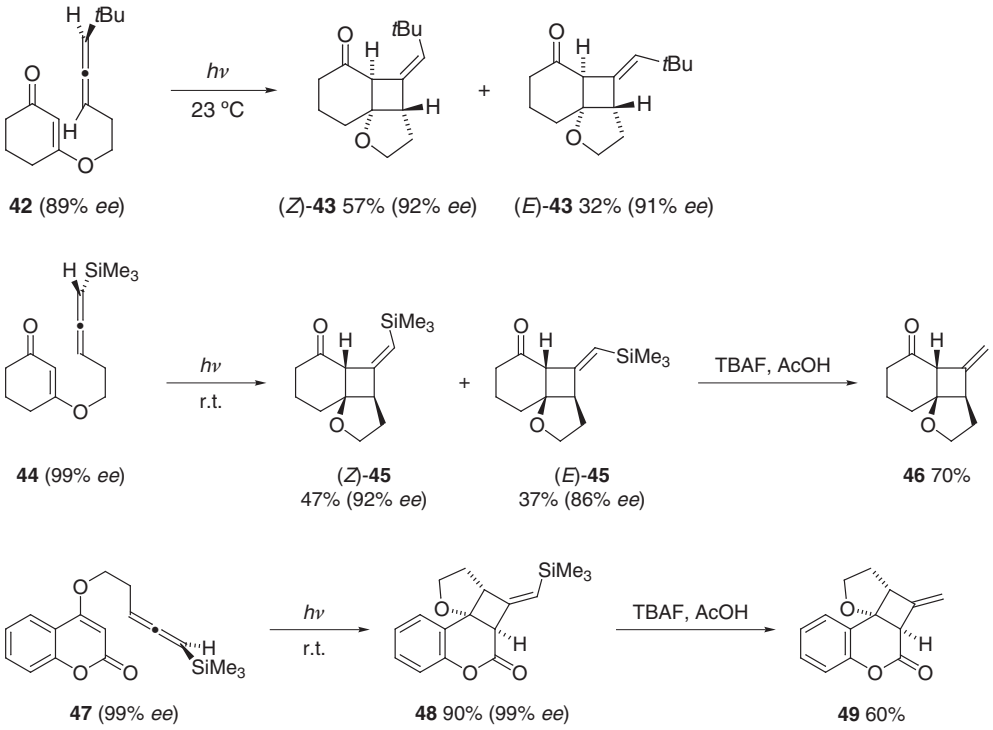
93% conv. (87/13)



E *Z*

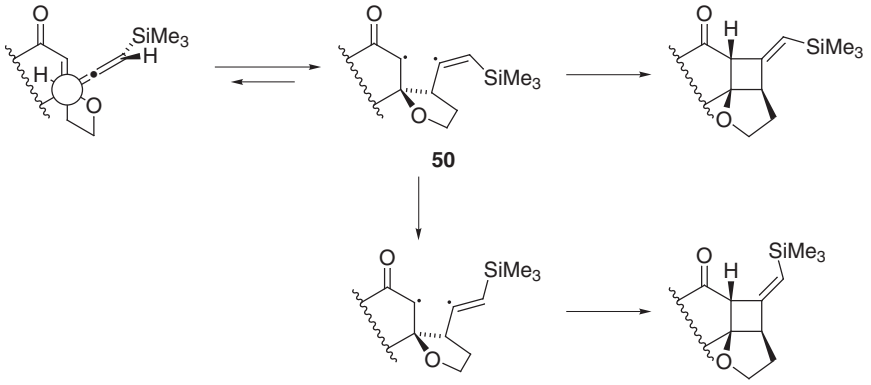
>90% (*E*:*Z* = 10:1)

Irradiation of the enantiomerically enriched allenenone **42** afforded alkylididecyclobutane **43** with high levels of chirality transfer. The silyl moiety of optically active allenylsilanes **44** and **47** functioned as a removable auxiliary to control the stereochemistry. Thus, the silyl-substituted photoadducts **45** and **48** underwent protodesilylation on treatment with TBAF to give the unsubstituted *exo*-methylenecyclobutanes **46** and **49**, respectively [46].



(12.36)

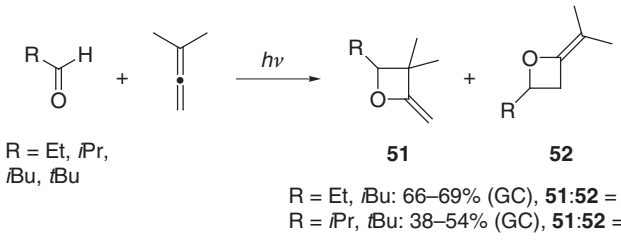
The efficient chirality transfer is accounted for by assuming that the enone in its excited state approaches the allene from the less hindered face. The stereoisomeric adduct (*Z*)-**45** arises via inversion of the resulting 1,4-diradical intermediate **50** before ring closure.



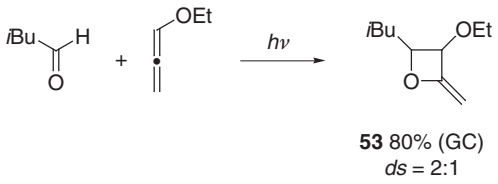
(12.37)

12.2.3
Photocycloaddition with Ketones and Aldehydes

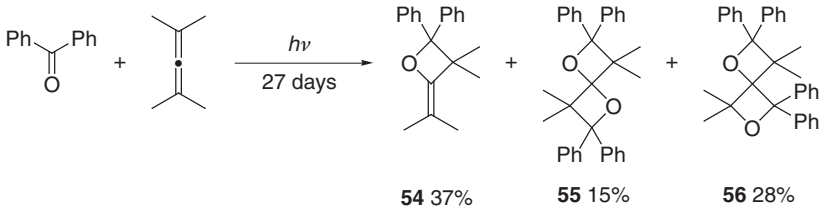
Irradiation of 1,1-dimethylallene and aliphatic aldehydes afforded 2-methyleneoxetanes **51** and **52** with low regioselectivities [47]. In contrast, ethoxyallene reacted with isovaleraldehyde at the internal C=C bond with complete regioselectivity to give **53** as a 2:1 mixture of diastereomers.



(12.38)



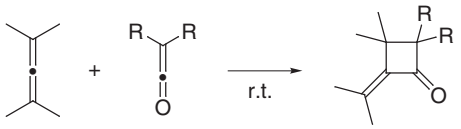
In the case shown below, the initially formed oxetane **54** further reacted with benzophenone forming 1,5- and 2,5-dioxaspiro[3.3]heptane derivatives (**55** and **56**) [48].



(12.39)

12.2.4
Cycloaddition with Ketenes

Ketene is also a suitable partner for [2 + 2]-cycloaddition with allenes. Diphenylketene and dimethylketene react readily with tetramethylallene at room temperature to give 2-isopropylidenecyclobutanones in good yields [49].



R = Me, Ph

R = Me: 68%
R = Ph: 73%

(12.40)

Other examples are given in Table 12.3. The cycloaddition reactions take place even at 0 °C. A regioisomeric mixture was obtained from 1,1-dimethylallene [50]. As for the mechanism of the allene–ketene [2 + 2]-cycloaddition, it is not clear whether the reaction proceeds via a concerted process (ketene antrafacial) or a two-step process.

Table 12.3 Examples of cycloaddition with ketenes.

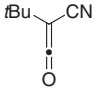
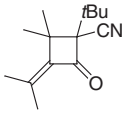
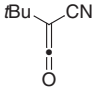
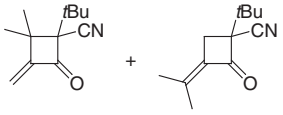
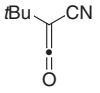
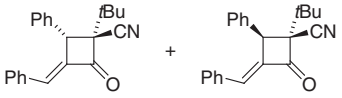
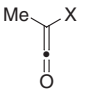
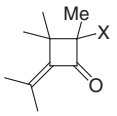
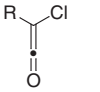
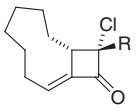
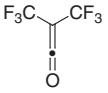
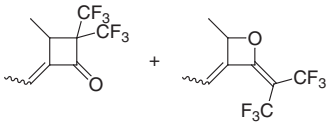
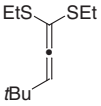
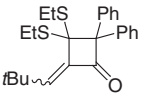
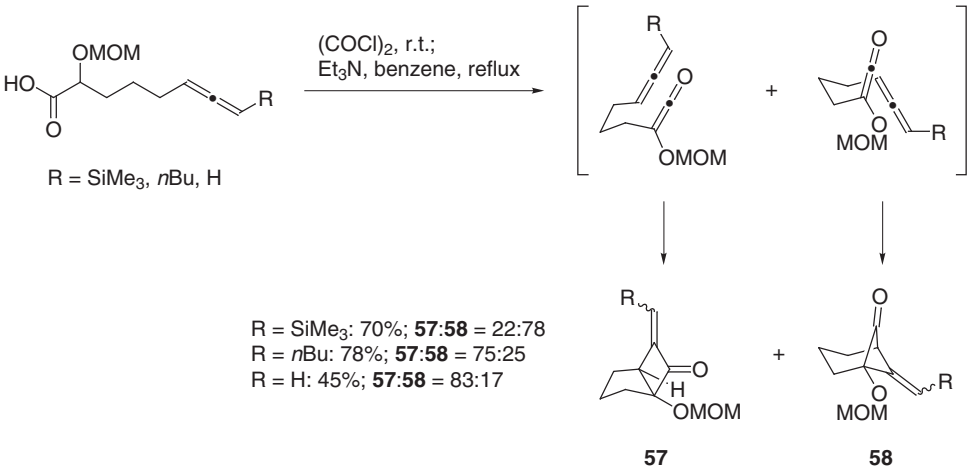
Allene	Ketene	Temp.	Product	Ref.
		Benzene reflux	 77%	
		0 °C	 62% (65:35)	
		20 °C	 49% (77:23)	[51]
		pentane reflux or hexane reflux	 X = Cl: 72% X = Br: 65%	[52]
		pentane reflux or hexane reflux	 R = Me: 72% R = Cl: 75%	

Table 12.3 (continued)

Allene	Ketene	Temp.	Product	Ref.
		100 °C	 65% 17%	[53]
		r.t.	 **65** 66%	[54]

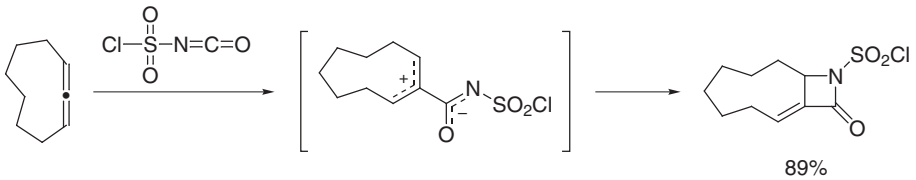
Although an intramolecular thermal [2 + 2] allene–ketene cycloaddition reaction was reported, the regioselectivity was moderate [55].



(12.42)

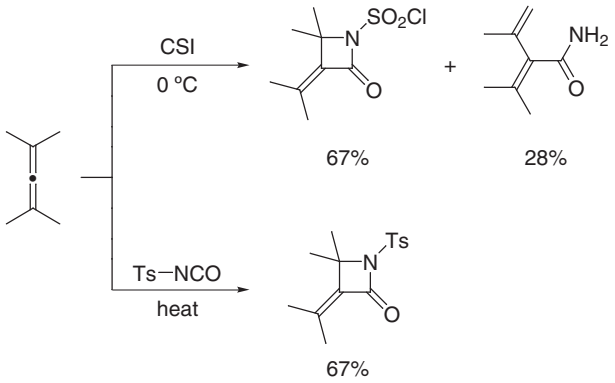
12.2.5
Cycloaddition with Isocyanates

Allenes react with isocyanates to give the α-alkylidene-β-lactams. The highly reactive chlorosulfonyl isocyanate (CSI) is often used. Initial nucleophilic attack of the central allenic carbon atom to the central isocyano carbon atom produces an allylic cation intermediate, which cyclizes to the β-lactam.



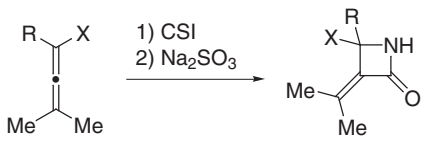
(12.43)

In the example shown, a 2-carboxamido-1,3-diene was formed as the byproduct [56]. *p*-Toluenesulfonyl isocyanate can be also used [57].



(12.44)

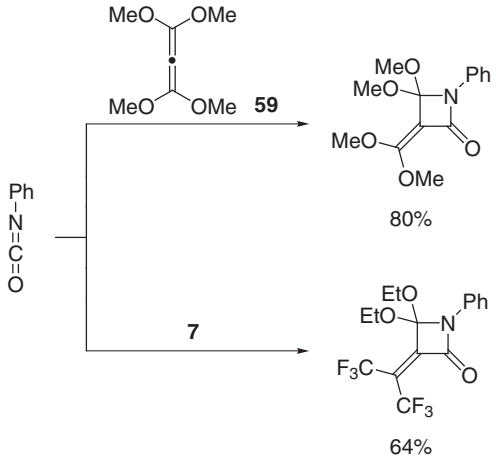
Good regioselectivities were observed in the [2 + 2]-cycloaddition of heteroatom-substituted allenes [58].



(12.45)

X = OAc, R = H: 23%
X = SC_6H_4Cl-*p*, R = $(CH_2)_2OTBS$: 66%
X = SC_6H_4Cl-*p*, R = $SiMe_3$: 87%

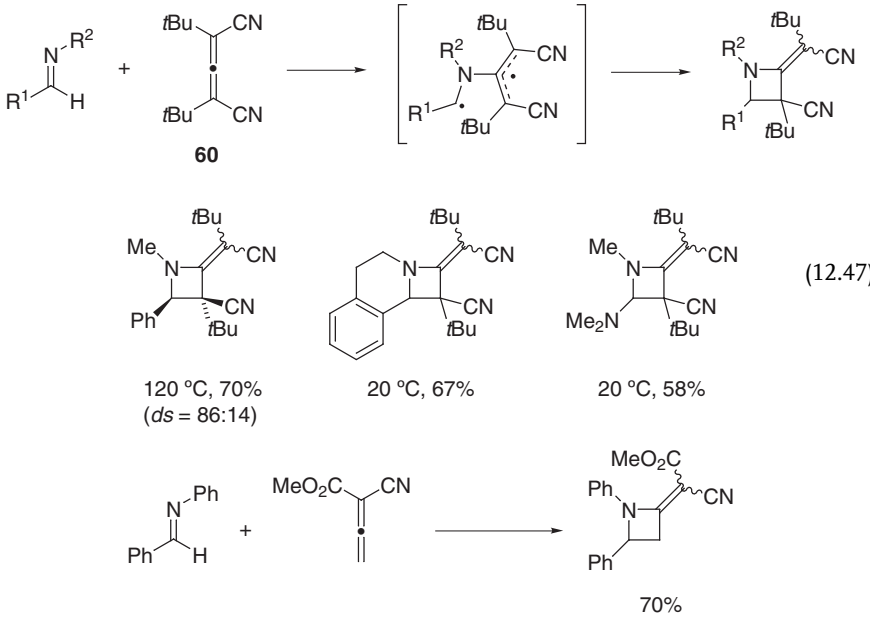
Phenyl isocyanate reacted with highly reactive allenes **59** and **7** to give the corresponding [2 + 2]-cycloadducts [59].



(12.46)

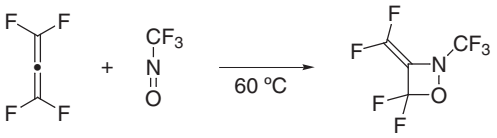
12.2.6
Cycloaddition with Other X=Y Bonds

The [2 + 2]-cycloaddition reactions of 1,3-di-*tert*-butylallene-1,3-dicarbonitrile (**60**) with imines afford azetidines [60]. The nitrogen atom of the imine was attached to the central carbon atom of the allene to give 2-methyleneazetidines.



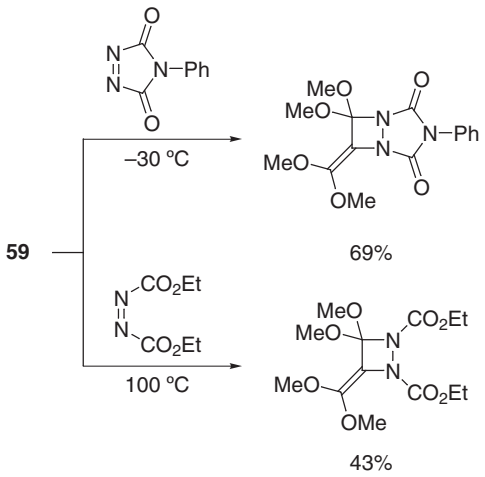
(12.47)

The [2 + 2]-cycloaddition of trifluoronitrosomethane with tetrafluoroallene (**61**) (excess) proceeded in the vapor phase to give 1,2-oxazetidine in moderate yield [61].



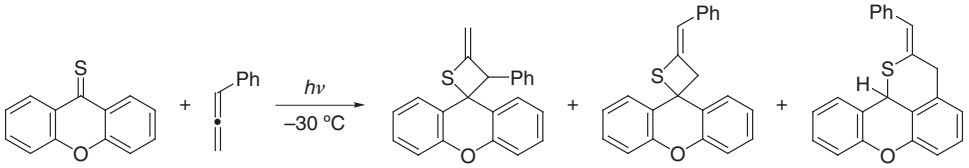
61 43% (12.48)

The reaction of azodicarboxylic acid derivatives with tetramethoxylallene (**59**) affords diazetidines [59a].



(12.49)

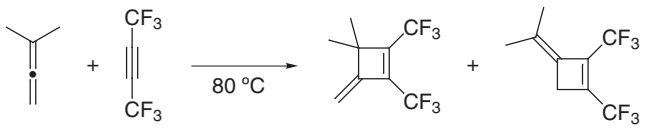
Irradiation of xanthenethione (**62**) with phenylallene (excess) and pyridine (1%) at –30 °C afforded a mixture of the [2 + 2]-adducts **63** and **64**, together with [4 + 2]-adduct **65** [62].



62 **63** 70% **64** 20% **65** 5% (12.50)

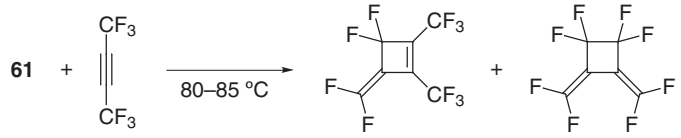
12.2.7
Cycloaddition with Alkynes

The highly reactive hexafluoro-2-butyne reacted with 1,1-dimethylallene to afford methylenecyclobutanes [63].



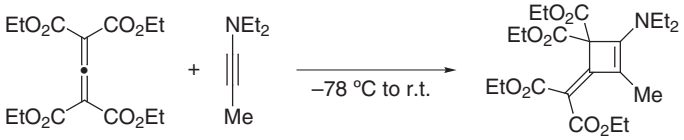
97% (75:25) (12.51)

The reaction of tetrafluoroallene (**61**) with hexafluoro-2-butyne (5 equiv.) under autogenous pressure gave a mixture containing the desired [2 + 2]-cycloadduct **66** and the allene dimer **67** [64].

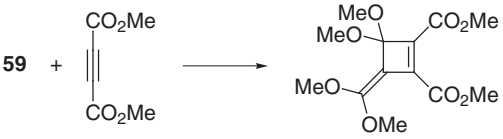


66 50% **67** 42% (12.52)

The facile [2 + 2]-cycloaddition took place at lower temperatures with a combination of an allene and an alkyne of opposite electronic bias [65]. An electron-rich allene **59** reacted with an electron-deficient alkyne to give a [2 + 2]-cycloadduct in good yield [59a].

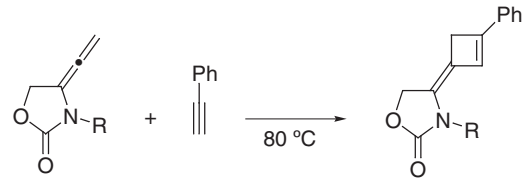


81% (12.53)



72%

4-Vinylideneoxazolidin-2-ones reacted with phenylacetylene in a regio- and stereoselective manner to yield the [2 + 2]-cycloadducts [25]. It is noteworthy that the addition of the alkyne occurred from the more crowded side of the allene bond.

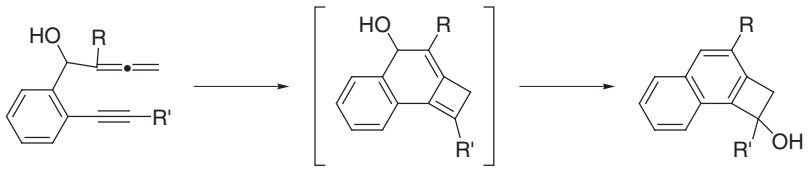


(R = Ts, Bz)

R = Ts: 60%
R = Bz: 55%

(12.54)

The thermal [2 + 2]-cycloaddition of allenyne **68** was used for the preparation of a naphtho[*a*]cyclobutene skeleton **69** [66].



68
R = Ph, R' = C≡CSiMe$_3$
R = C≡CPh, R' = SiMe$_3$
R = C≡CPh, R' = C≡CSiMe$_3$

69
93%
79%
quant.

(12.55)

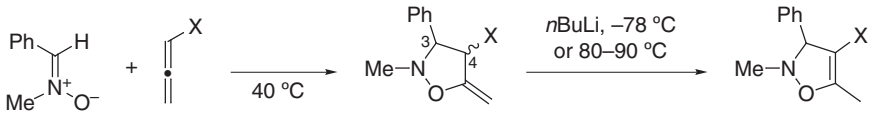
12.3 [3 + 2]-Cycloaddition of Allenes

The [3 + 2]-cycloaddition reactions of allenes with 1,3-dipoles are useful for the construction of a variety of five-membered heterocycles with a high degree of regio- and stereochemical control [67]. Generally, the dipolar cycloaddition reactions are concerted and synchronous processes with a relatively early transition state. The stereoselectivities and regiochemistries are accounted for by the FMO theory: The reaction pathway is favored when maximal HOMO–LUMO overlap is achieved.

12.3.1 Cycloaddition with Nitrones

Like the nitrone–olefin [3 + 2]-cycloaddition, the nitrone–allene [3 + 2]-cycloaddition also takes place regioselectively to furnish methylene-substituted isoxazolidine derivatives. The substituents of the 3- and 4-positions of the cycloadducts **72a** and **72b** are disposed *cis*; in contrast, the reaction of **70** with allenyl sulfone **71c** gives rise to the *trans*-cycloadduct **72c** exclusively (Table 12.4). On treatment with base or heating, methyleneisoxazolidines **72** readily rearrange to isoxazolines via a 1,3-hydrogen shift.

Table 12.4 Cycloadditions with nitrones.



70 **71a–c** **72a–c**

(12.56)

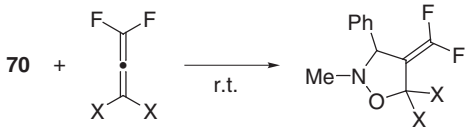
71 (X)	Product 72 (% yield, stereo)	Ref.
71a (CO_2Me)	**72a** (80, *cis*)	[68]
71b (CN)	**72b** (99, *cis*)	[69]
71c (SO_2Ph)	**72c** (98, *trans*)	[69, 70]

On the other hand, 4-methyleneisoxazolidines are formed from methoxyallene (**73**) and monofluoroallene (**24**) as a mixture of *E*- and *Z*-isomers [71, 72].

73: X = OMe — 90 °C — 58% (*E*:*Z* = 48:52)
24: X = F — r.t. — 95% (*E*:*Z* = 82:18)

(12.57)

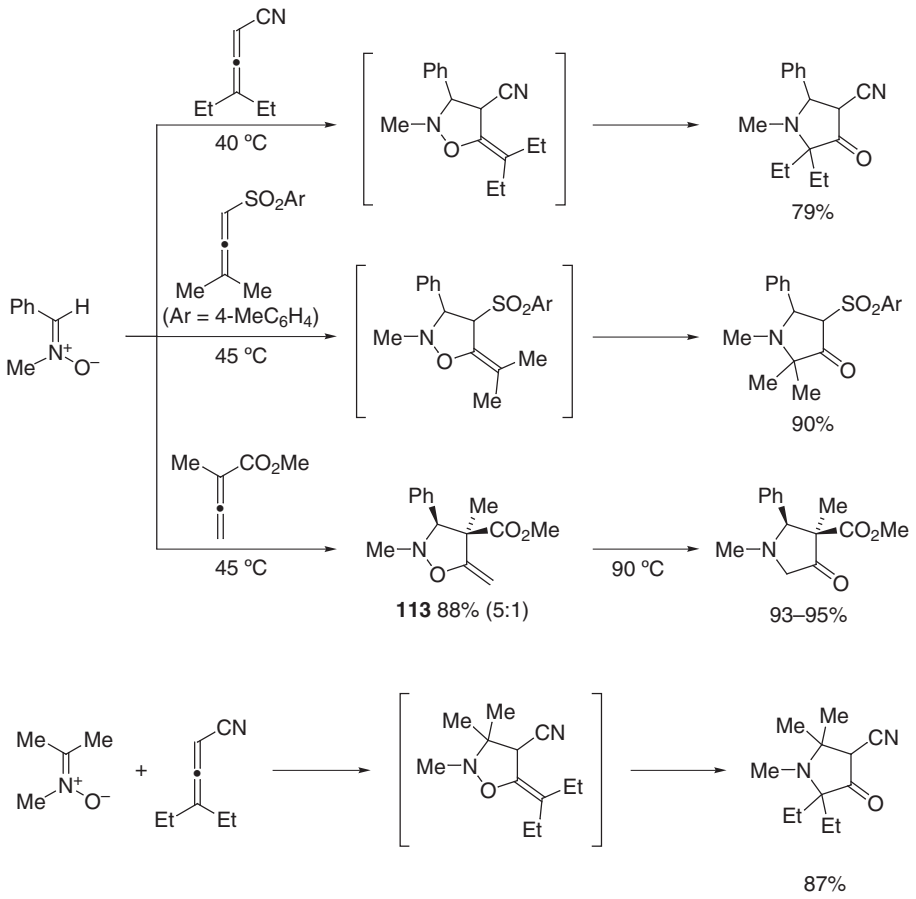
Fluoroallenes **25** and **61** react with **70** smoothly at room temperature to afford the corresponding isoxazolidines [72b, 73].



25: X = H — X = H: 95%
61: X = F — X = F: 71%

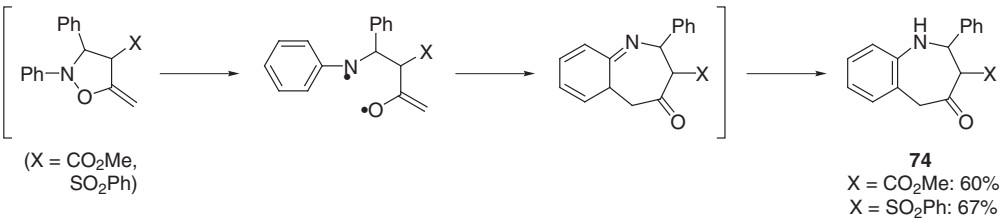
(12.58)

In the following cases, the initially formed cycloadducts rapidly rearrange to pyrrolidinones [68, 69]:



(12.59)

When *N*-phenyl-*C*-phenylnitrone was used as the 1,3-dipole in the reaction with activated allenes, benzazepin-4-ones **74** were obtained as the major product [74]. The isoxazolidine initially formed undergoes N–O bond cleavage and the resulting diradical recyclizes by attack at the *ortho*-position of the *N*-phenyl group.

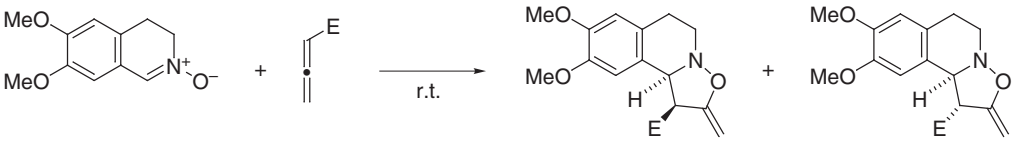


(X = CO_2Me, SO_2Ph)

74
X = CO_2Me: 60%
X = SO_2Ph: 67%

(12.60)

The 1,3-dipolar cycloaddition reaction of 3,4-dihydroisoquinoline *N*-oxides **75** with **71b** and **32** proceeded regioselectively to give diastereomeric mixtures of isoxazolidines **76** and **77** [75].

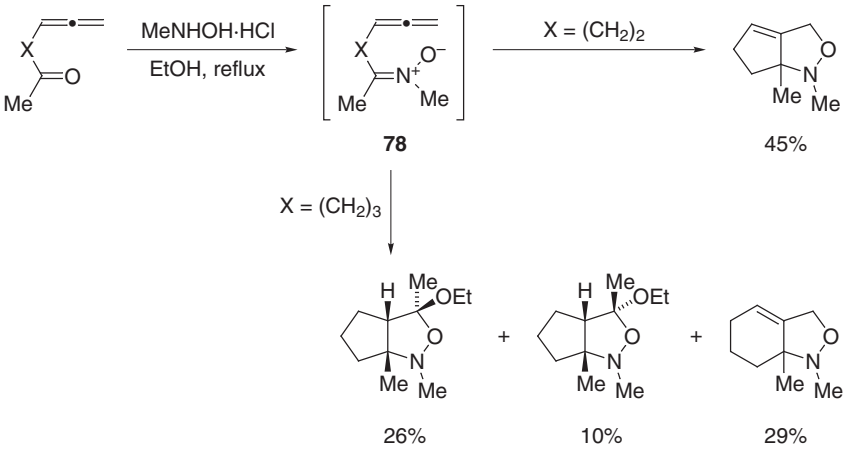


75 **71b**: E = CN; **32**: E = CO_2Et **76** **77**

E=CN: 78% (62:38)
E = CO_2Et: 80% (50:50)

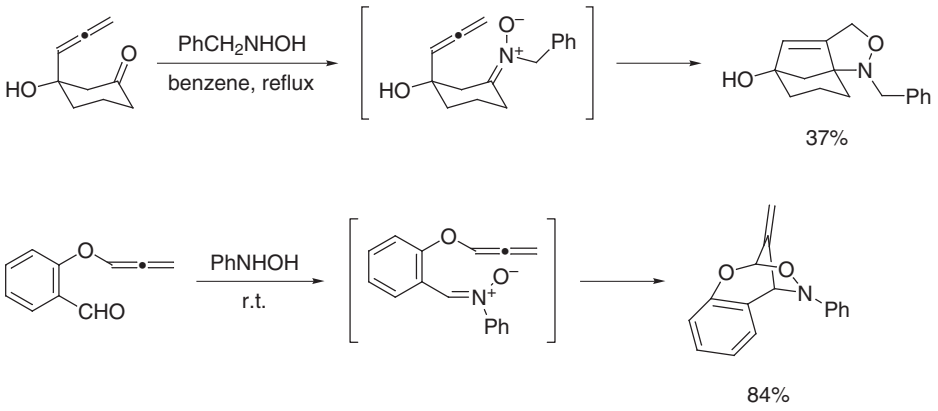
(12.61)

The intramolecular dipolar cycloaddition of a nitrone with an unactivated allene was also studied [76]. Treatment of 5,6-heptadien-2-one with *N*-methylhydroxylamine in refluxing ethanol yielded allenyl nitrone **78**, which cyclized with the terminal allenic C=C bond to give an unsaturated bicyclic isoxazolidine. On the other hand, the site selectivity decreased with an allenic ketone having a trimethylene tether.



(12.62)

An intramolecular [3 + 2]-cycloaddition reaction occurred at either the terminal or internal C=C bond in the following examples [77, 78]:



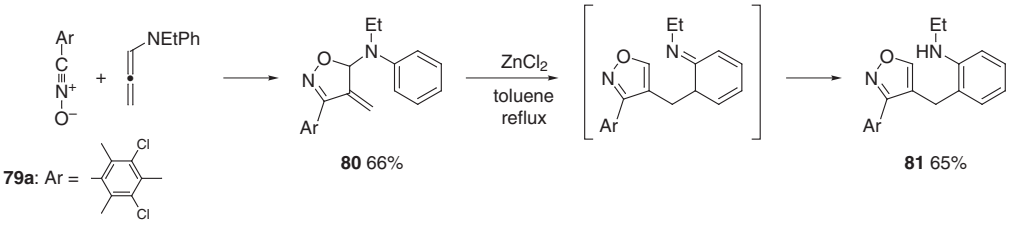
(12.63)

12.3.2

Cycloaddition with Nitrile Oxides

Nitrile oxides also undergo [3 + 2]-cycloaddition with allenes. As shown below, a variety of products were formed depending on the substituents of both nitrile oxide and allene [72b, 79]. The cycloadduct **80** was slowly converted to the isomeric isoxazole **81** in the presence of $ZnCl_2$ via a sigmatropic rearrangement [79a].

In the cycloaddition of nitrile oxide **79a** with 1,1-diphenyllallene, the nitrile carbon atom of **79a** is selectively attached to the central carbon atom (C2) of the allene. The cycloaddition takes place at both the C1–C2 and C2–C3 double bonds of the allene to give a mixture of 4-methylene-2-isoxazolines [80].



79a: Ar =

80 66%

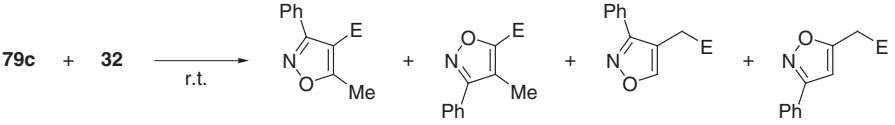
81 65%

79b: Ar = mesityl

83%
(*Z*:*E* = 96:4)

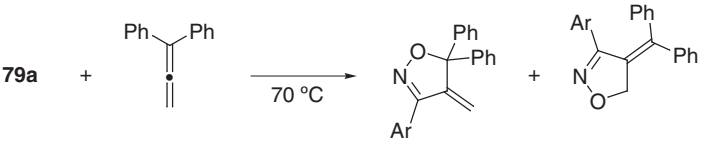
79c

52%



33% (33:24:10:33)
(E = CO_2Me)

(12.64)

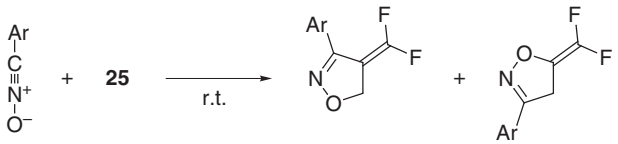


20% 12%

(Ar = 3,5-dichloro-2,4,6-trimethylphenyl)

(12.65)

The reaction of 1,1-difluoroallene (**25**) with benzonitrile oxide (**79c**) gave a mixture of the regioisomers (56:44), whereas the cycloaddition with 2,4,6-trimethylbenzonitrile oxide (**79b**) afforded only one regioisomer in high yield [72b].



(12.66)

79b: Ar = mesityl
79c: Ar = Ph

Ar = mesityl: 94% (>99:1)
Ar = Ph: 75% (56:44)

4-Vinylideneoxazolidin-2-one **82** reacted smoothly with nitrile oxide **79b** at the internal C=C bond at room temperature to afford a diazadioxaspiro compound [25b].

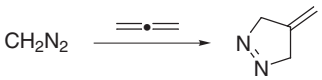
(12.67)

82

60%
(Ar = mesityl)

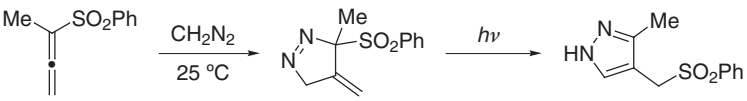
12.3.3
Cycloaddition with Diazo Compounds

The addition of allene to an ethereal solution of diazomethane gave 4-methylene-1-pyrazoline [81].



(12.68)

A reaction of 3-(phenylsulfonyl)-1,2-butadiene and diazomethane gave pyrazoline **83** in good yield. Upon irradiation, a 1,3-sulfonyl shift occurred to provide the disubstituted pyrazole **84** [82].

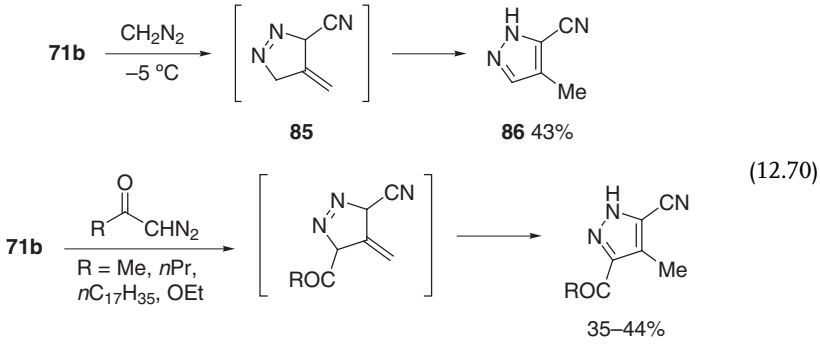


(12.69)

83 80%

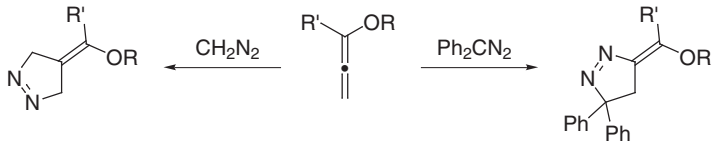
84 86%

Addition of diazomethane to cyanoallene took place at the internal C=C bond of the cyanoallene to give 4-methylenepyrazoline **85**. The following isomerization via 1,3-hydrogen shifts afforded 4-methyl-5-cyanopyrazole **86** [83]. α-Diazo carbonyl compounds reacted in an analogous way [84].



(12.70)

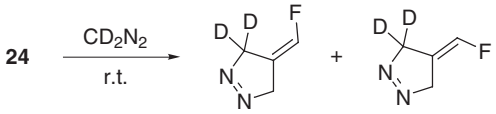
Alkoxyallenes react with diazomethane at the terminal C=C bond to give 4-methylenepyrazoline **87**, whereas the reaction with diphenyldiazomethane affords 3-methylenepyrazoline **88** [85].



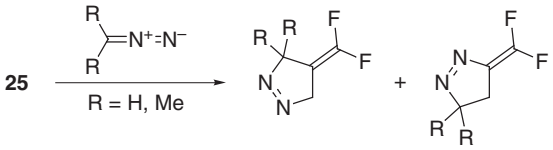
87		**88**
61%	R = Me, R' = H	73%
69%	R = Ph, R' = H	75%
60%	R = Ph, R' = Me	43%

(12.71)

The 1,3-dipolar cycloaddition of diazomethane to MFA (**24**) occurred exclusively at the C2–C3 π-bond to give 4-(fluoromethylene)pyrazolines. The methylene group of diazomethane was regioselectively attached to the C2 carbon atom of **24** with a *syn*:*anti* ratio of 88:12 [72b]. DFA (**25**) similarly reacted with diazomethane to give 4-(difluoromethylene)pyrazoline **89** selectively [72b, 86]. The cycloaddition reaction of bulkier 2-diazopropane with DFA was less regioselective.



54% (88:12)

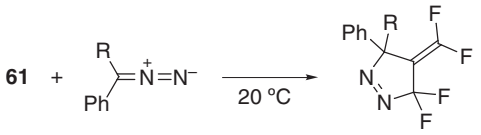


89 **90**

R = H: 95% (NMR, >99:1)
R = Me: 99% (NMR, 61:39)

(12.72)

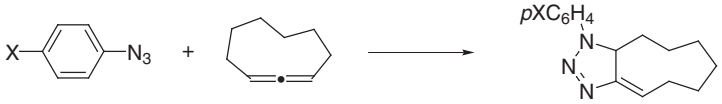
The [3 + 2]-cycloaddition of tetrafluoroallene (**61**) with diazoalkanes produced exclusively 4-methylenepyrazolines [73].

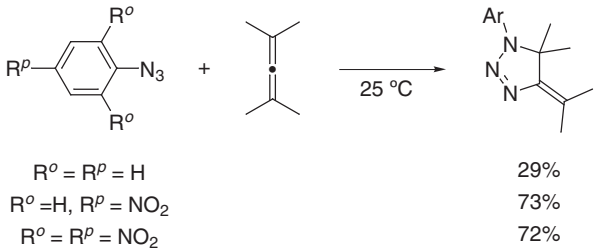


(12.73)

12.3.4
Cycloaddition with Azides

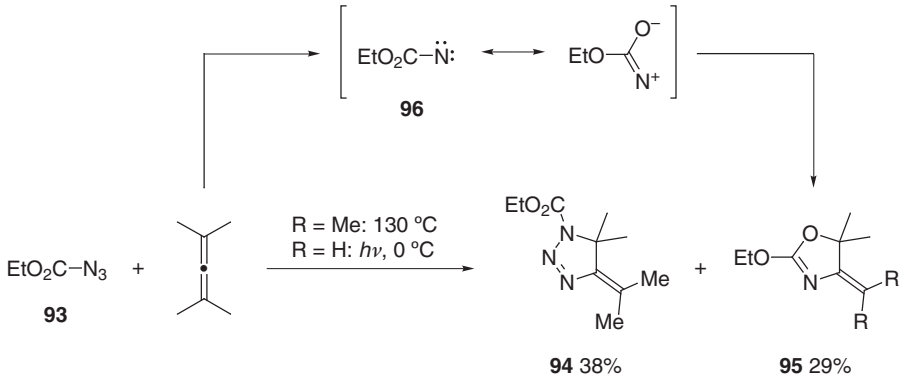
1,2-Cyclononadiene reacted with aryl azides **91** regioselectively to give triazolines **92** [87]. In the cycloaddition reactions of aryl azides with tetramethylallene (excess), electron-deficient azides afforded better yields of triazolines [88].





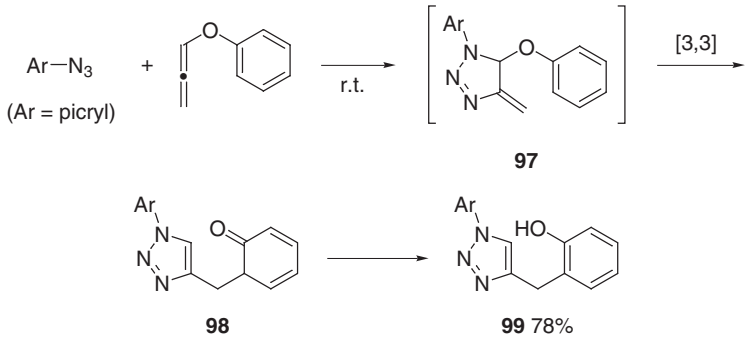
(12.74)

The reaction of ethyl azidoformate (**93**) with tetramethylallene yielded triazoline **94** and oxazoline **95** [88]. The triazoline **94** was formed by [3 + 2]-cycloaddition of azide **93** to the allene. The oxazoline **95** may result from [3 + 2]-cycloaddition of carbethoxynitrene (**96**), which is formed from **93** by nitrogen evolution, to the allene or by the [2 + 1] addition of the nitrene and subsequent rearrangement.



(12.75)

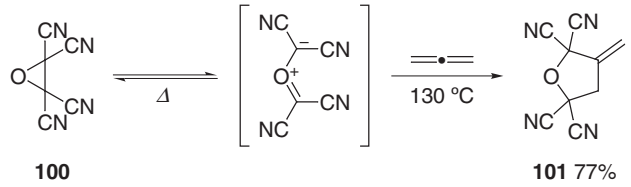
The cycloaddition of picryl azide with phenoxyallene took place at the C1–C2 double bond of the allene exclusively to give the triazoline intermediate **97** [89]. This intermediate underwent a facile Claisen rearrangement to yield cyclohexadienone **98**, which rapidly tautomerized to phenol **99**.



(12.76)

12.3.5
Cycloaddition with Other 1,3-Dipoles

Tetracyanoethylene oxide (**100**) added to allene through cleavage of the epoxide ring to give 3-methylene-2,2,5,5-tetracyanotetrahydrofuran (**101**) in good yield [90].

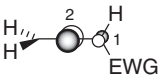


(12.77)

12.4
[4 + 2]-Cycloaddition of Allenes

12.4.1
Intermolecular Cycloaddition of Activated Allenes

Allenes participate in the Diels–Alder-type [4 + 2]-cycloaddition mostly as an electron-deficient dienophile. The LUMO energy level of an allene is lowered by the introduction of an electron-withdrawing unsaturated substituent. The largest LUMO coefficient locates on the central carbon (C2) and the next largest on the substituted carbon (C1). Thus, [4 + 2]-cycloadditions of activated allenes take place at the internal C=C bond of the allene.

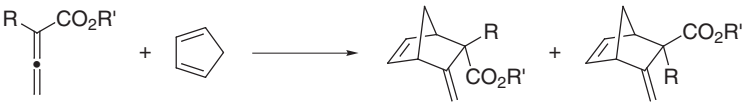


LUMO (12.78)

12.4.1.1 Allenic Esters

Allenic esters react with cyclopentadiene to give the two [4 + 2]-cycloadducts *endo*- and *exo*-**102** in high yields (Table 12.5) [28, 91]. The use of a Lewis acid lowers the reaction temperature and improves the yield and *endo* selectivity.

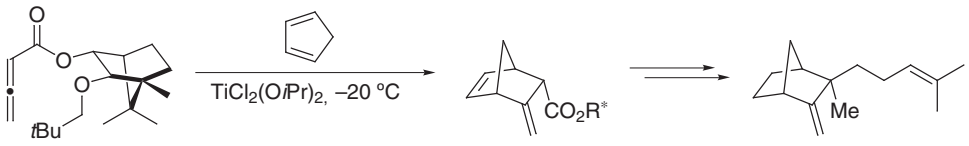
Table 12.5 Reactions of allenic esters.



endo-**102** *exo*-**102** (12.79)

R	R′	Conditions	Yield (%)	*endo*:*exo*
H	Et	Benzene, 80 °C	90	64:36
H	Et	$AlCl_3$, benzene, 25 °C	95	86:14
Me	Me	Benzene, 80 °C	~80	40:60
Me	Me	$AlCl_3$, benzene, 25 °C	90	76:24

The Lewis acid-promoted [4 + 2]-cycloaddition reaction of the allenic ester **103** having a camphor-derived chiral auxiliary with cyclopentadiene provided the adduct with excellent π-facial selection, leading to an enantioselective synthesis of (–)-β-santalene [92].

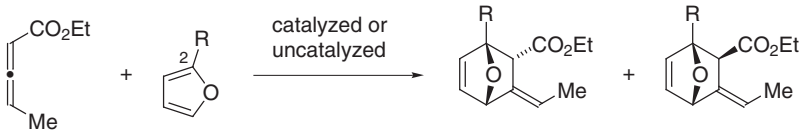


103 98%, 99% de, *endo*:*exo* = 98:2 (–)-β-santalene

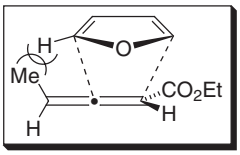
(12.80)

Both uncatalyzed and catalyzed [4 + 2]-cycloaddition reactions of furans with the allenic esters have been reported (Table 12.6) [93]. The allene adds from the less hindered C1–C2 π-face. The unfavorable steric interaction between the α-hydrogen atom of the furan and the methyl group at C4 of the allene is responsible for this selectivity. The more reactive 2-methylfuran adds to the allenic ester also in a regioselective manner. The C2 carbon atom of 2-methylfuran was exclusively attached to the C1 carbon atom of the allenic ester, providing a mixture of *endo*- and *exo*-adducts.

Table 12.6 Uncatalyzed and catalyzed cycloaddition reactions of furans with allenic esters



endo *exo* (12.81)

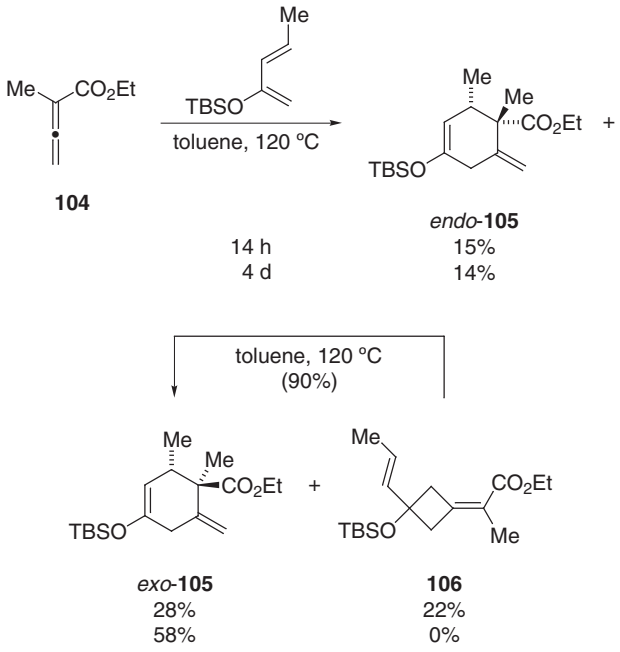


R	Conditions[a)]	Yield (%)	*endo*:*exo*
H	Uncatalyzed	40	75:25
H	Catalyzed	70	100:0
Me	Uncatalyzed[b)]	70	52:48
Me	Catalyzed	80	70:30

a) Uncatalyzed, furan (excess), reflux; catalyzed, 1 mol% $Eu(fod)_3$ or $Pr(fod)_3$ at room temperature

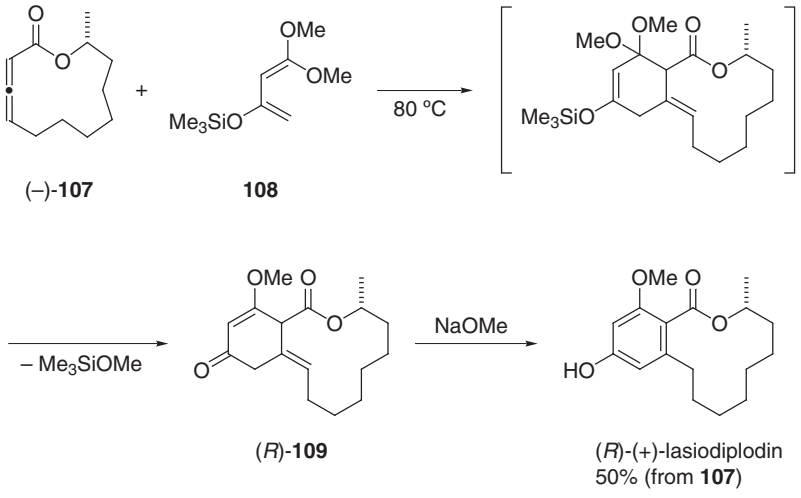
b) Benzene, reflux

The reaction of allenecarboxylate **104** with a siloxydiene at 120 °C afforded a mixture of three cycloadducts, *endo*-**105** (15%), *exo*-**105** (28%) and the [2 + 2]-cycloadduct **106** (22%) [94]. A thermal rearrangement of **106** to *exo*-**105** took place at 120 °C, ultimately leading to the formation of only the two [4 + 2]-cycloadducts after 4 days.



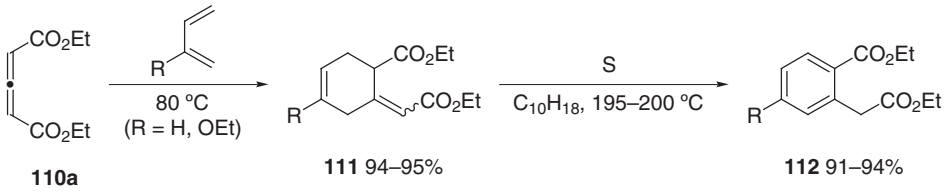
(12.82)

An analogous reaction sequence starting with (–)-**107** and 1,1-dimethoxy-3-trimethylsilyloxy-1,3-butadiene (**108**) led to (*R*)-(+)-lasiodiplodin via the adduct (*R*)-**109** [95].

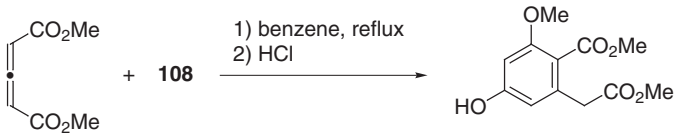


(12.83)

Allene-1,3-dicarboxylates **110** are also useful dienophiles for [4 + 2]-cycloadditions. They react with 1,3-dienes to give 4-methylenecyclohexene derivatives **111**. The aromatization shown produced homophthalic derivatives **112** and **113** [96].



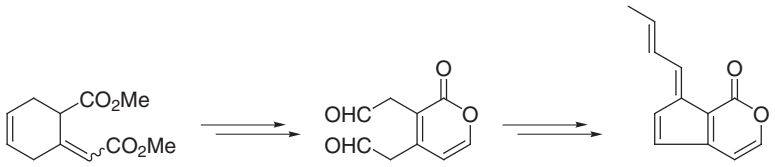
110a **111** 94–95% **112** 91–94%



110b **113** 72%

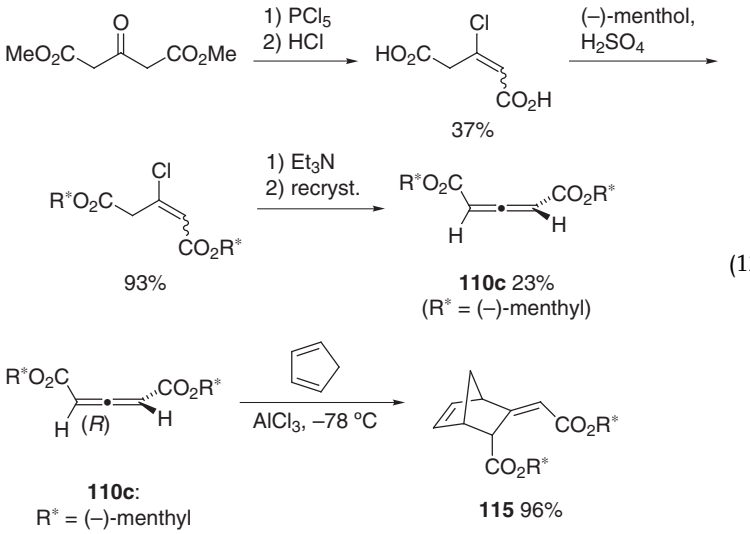
(12.84)

Alternatively, ozonolysis of the [4 + 2]-adduct **114** led to the total synthesis of fulvoplumierin [97].



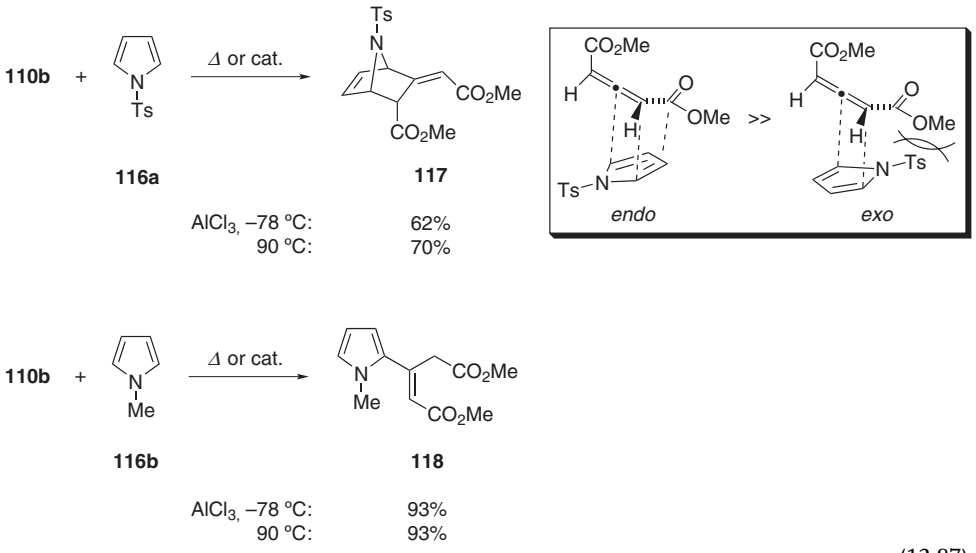
114 fulvoplumierin (12.85)

Optically pure 1,3-allenedicarboxylate **110c** possessing central and axial chirality was prepared from dimethyl acetonedicarboxylate by incorporation of menthol as a chiral auxiliary [98]. The [4 + 2]-cycloaddition reaction of **110c** with cyclopentadiene in the presence of $AlCl_3$ proceeded with high diastereoselectivity to afford adduct **115**.



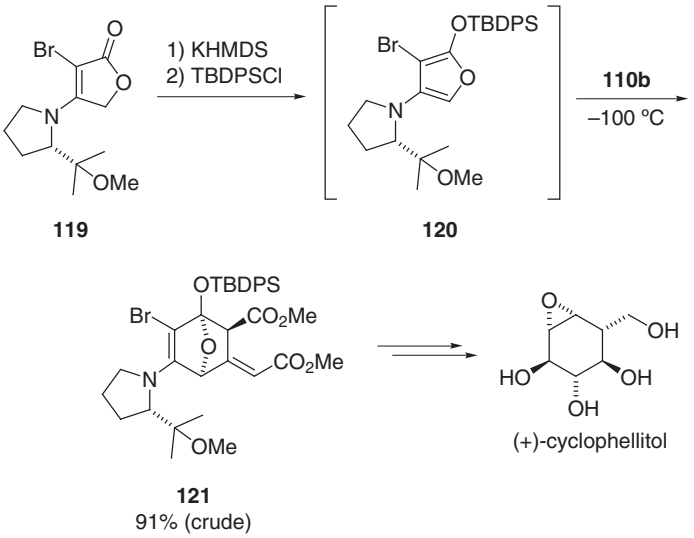
(12.86)

The reaction of 1,3-allenedicarboxylate **110b** with *N*-tosylpyrrole (**116a**) took place at 90 °C to give the Diels–Alder product **117** [99]. The same [4 + 2]-cycloaddition reaction occurred at –78 °C in the presence of $AlCl_3$. The exclusive formation of the *endo*-adduct with **116a** can be attributed to the severe steric repulsion between the tosyl and ester moieties. On the other hand, the reactions of the electron-rich *N*-methylpyrrole **116b** with **110b** exclusively gave 2-alkenylated pyrrole **118**.



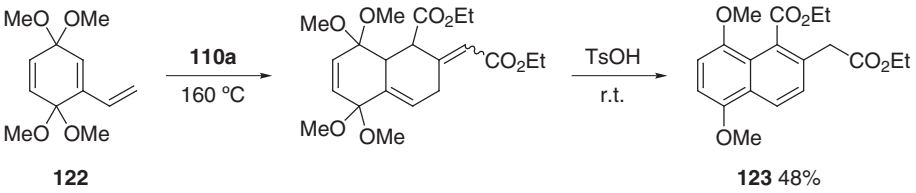
(12.87)

The chiral furan **120**, prepared from **119**, underwent a Diels–Alder reaction with racemic **110b** (4 equiv.) at –100 °C. Kinetic resolution of the allenic diester efficiently occurred to afford the oxabicyclic enamine adduct **121** stereoselectively [100]. The adduct was transformed to (+)-cyclophellitol.



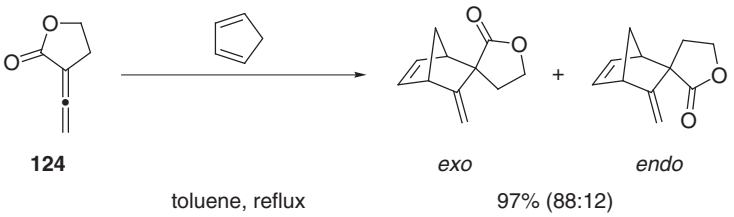
(12.88)

The cycloadduct of the reaction of vinylquinone ketal **122** with diester **110a** afforded naphthalene derivative **123** via aromatization [101].



(12.89)

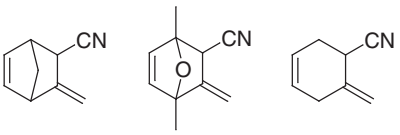
The cycloaddition of allenic lactone **124** with cyclopentadiene was carried out under thermal conditions and also in the presence of a Lewis acid catalyst [102]. In both cases, the *exo*-adduct was formed predominantly.



(12.90)

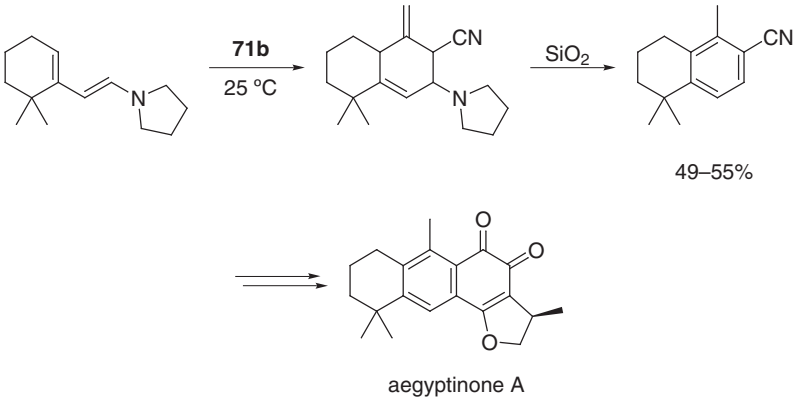
12.4.1.2 Cyanoallenes

[4 + 2]-Cycloaddition reactions of cyanoallene with 1,3-dienes gave the corresponding adducts (*endo*:*exo* ratios are not given) [103].



(12.91)

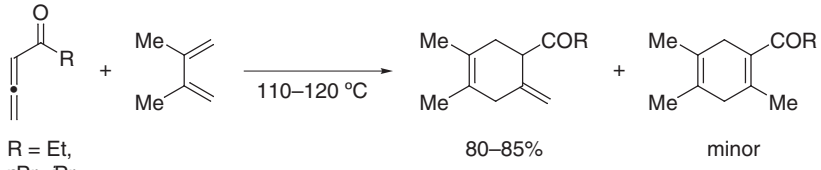
The cyanoallene cycloaddition with an enamine was used in the synthesis of aegyptinones A and B [104].



(12.92)

12.4.1.3 Allenic Ketones

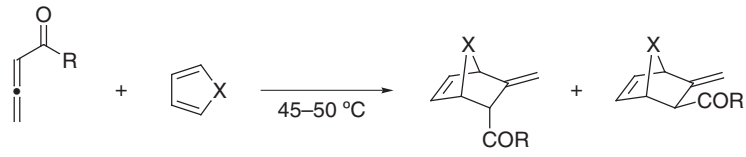
Allenic ketones undergo a thermal cycloaddition reaction with 1,3-dienes. The carbon–carbon double bond proximal to the carbonyl group reacts exclusively as in the case of allenic esters [105].



(12.93)

Cyclic dienes such as cyclopentadiene and furan react with allenic ketones at a lower temperature (Table 12.7) [105, 106]. Preferential formation of the *endo* adducts was observed for the both dienes.

Table 12.7 Reactions of cyclic dienes with allenic ketones.

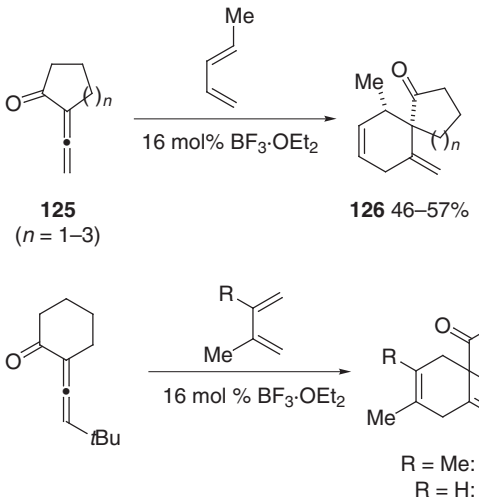


(12.94)

R = *n*Pr, *i*Pr X = CH_2, O *endo* *exo*

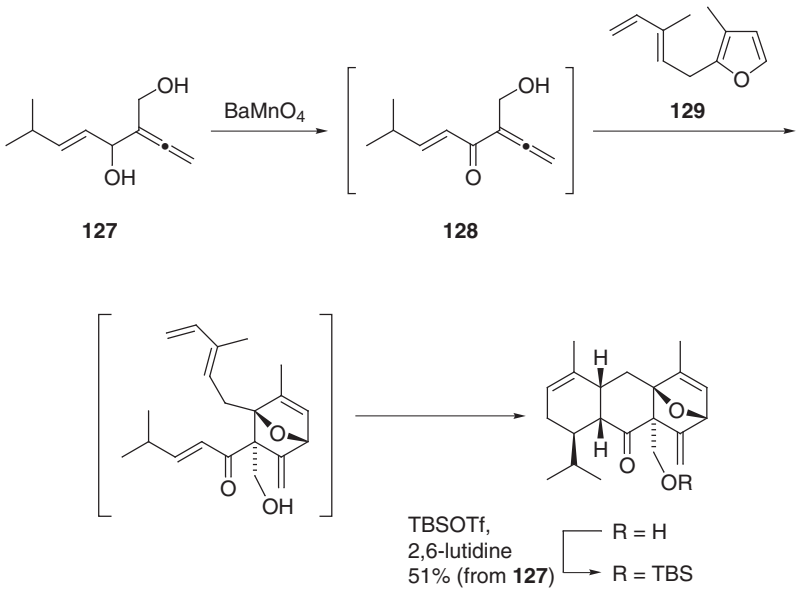
X	R	Yield (%)	*endo*:*exo*
CH_2	*n*Pr	95	85:15
CH_2	*i*Pr	94	90:10
O	*n*Pr	70	64:36
O	*i*Pr	94	70:30

Vinylidenecycloalkanones **125** undergo cycloadditions with 1,3-dienes in the presence of a Lewis acid catalyst to give spirocyclic dienones **126** [107]. Good regio- and stereoselectivities were observed for unsymmetrical dienes.



(12.95)

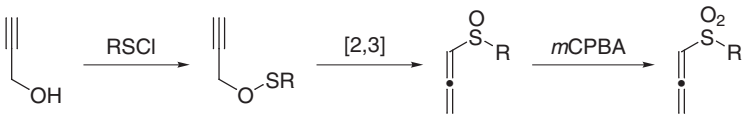
The tandem Diels–Alder reaction of bisdiene **129** and bisdienophile **128** led to the production of a highly complex molecule as a single stereoisomer. Three new rings and six new stereogenic centers were created during the process [108].



(12.96)

12.4.1.4 **Sulfonylallenes**

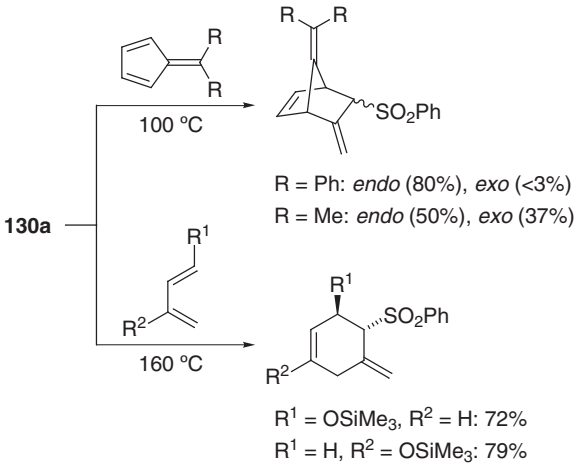
Sulfonylallenes **130a–c** are easily prepared from propargyl alcohol via sulfenation, [2,3]-sigmatropic rearrangement and *m*CPBA oxidation (see Chapter 1).



(12.97)

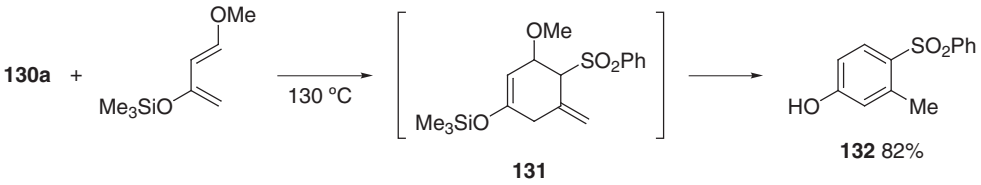
130a: R = Ph
130b: R = CCl_3
130c: R = CH_2Cl

These sulfonylallenes undergo the Diels–Alder reaction with electron-rich dienes at the proximal C–C double bond in a regioselective manner [109].



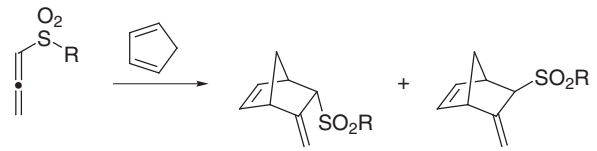
(12.98)

Danishefsky's diene also reacted with **130a** at 130 °C to give phenol derivatives **132**, which might arise from the initially formed adduct **131** through hydrolysis and subsequent aromatization.



(12.99)

Table 12.8 Reaction of allenyl phenyl sulfones with cyclopentadiene.



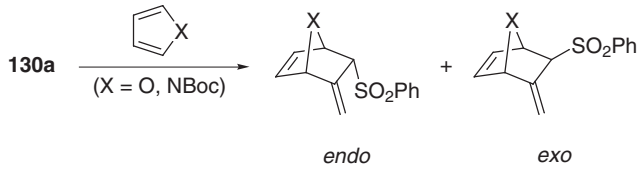
(12.100)

130a: R = Ph
130b: R = CCl_3

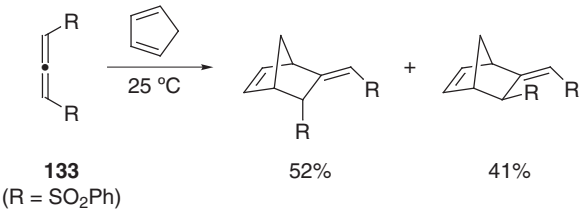
R	Temperature (°C)	Yield (%)	*endo*:*exo*	Ref.
Ph	80	90	65:35	[111]
CCl_3	25	100	90:10	[112]
CCl_3	0[a)]	85	90:10	[113]

[a)] Ultrasound irradiation

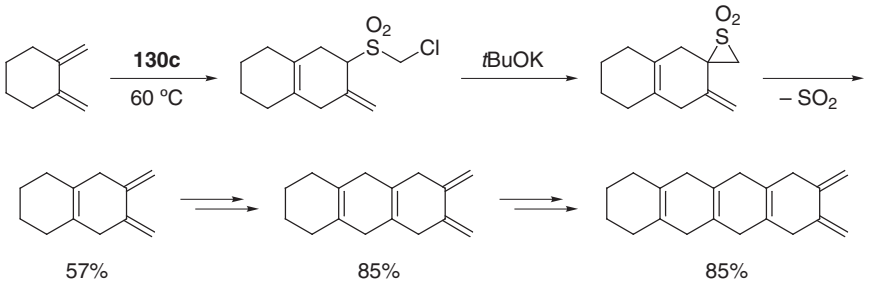
The [4 + 2]-cycloaddition reaction of allenyl phenyl sulfone **130a** with cyclopentadiene afforded a mixture of *endo* and *exo* adducts (65:35) (Table 12.8). The corresponding trichloromethyl sulfone **130b** reacted at a lower temperature to give better *endo* selectivities. The allene **133** possessing two sulfonyl groups was also reactive [110, 114].



(12.101)

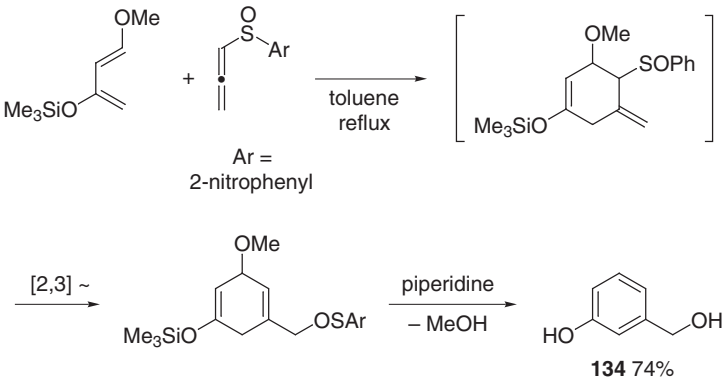


The cycloaddition reaction of the allenyl chloromethyl sulfone **130c** was successfully applied to an iterative ring-annulation procedure [115].



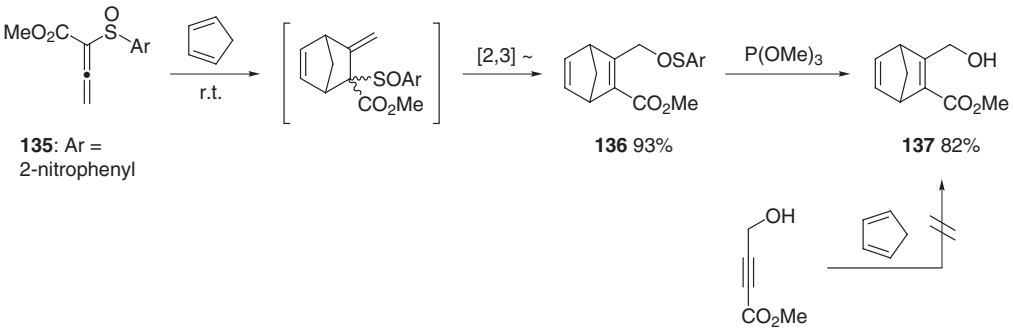
(12.102)

In contrast to allenyl sulfones, allenyl phenyl sulfoxide failed to react with the Danishefsky's diene even at an elevated temperature [116]. Introduction of an electron-withdrawing nitro group on the aromatic ring, however, lowered the LUMO energy level and facilitated the cycloaddition, providing phenol **134**.



(12.103)

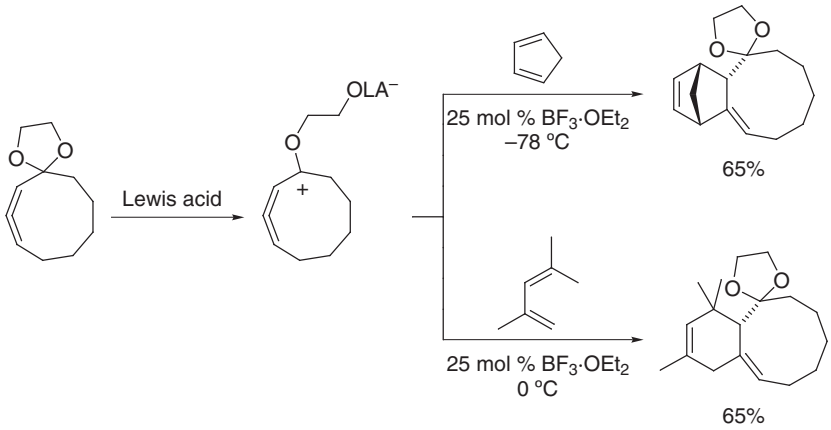
The cycloaddition of allenyl sulfoxide **135** and cyclopentadiene occurred at room temperature, giving the single adduct **136**. The initially formed allylic sulfoxide underwent a rapid [2,3]-sigmatropic rearrangement. Treatment of **136** with trimethyl phosphite furnished alcohol **137**. It should be noted that the reaction of methyl 4-hydroxy-2-butynoate with cyclopentadiene failed to give **137**. Thus, the allene **135** is considered as a masked and more reactive alkyne equivalent.



(12.104)

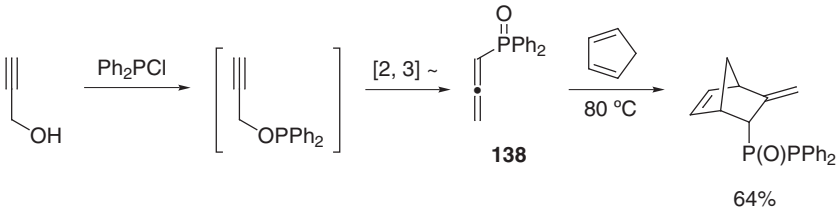
12.4.1.5 **Miscellaneous**

1,2-Cyclononadien-4-one itself is a poor dienophile, but its ethylene glycol acetal undergoes [4 + 2]-cycloaddition reactions with 1,3-dienes in the presence of Lewis acid at low temperatures [117]. Treatment of the acetal with $BF_3 \cdot OEt_2$ generated a carbocation adjacent to the allenyl moiety. The powerful electron-withdrawing nature of the carbocation enhanced the rate of the cycloaddition.



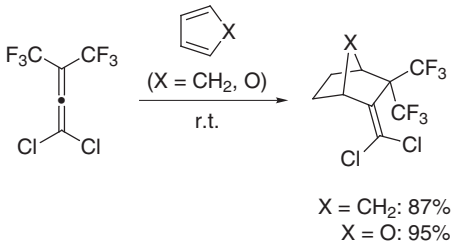
(12.105)

The cycloaddition of allenes carrying an electron-withdrawing phosphorus substituent has also been studied [118]. Allenyl phosphine oxide **138** is prepared in a manner analogous to allenyl sulfoxide. The [4 + 2]-cycloaddition reaction of **138** with cyclopentadiene proceeded with a high *endo* selectivity.



(12.106)

1,1-Dichloro-3,3-bis(trifluoromethyl)allene undergoes efficient [4 + 2]-cycloaddition reactions regioselectively at the trifluoromethyl-substituted double bond [119].



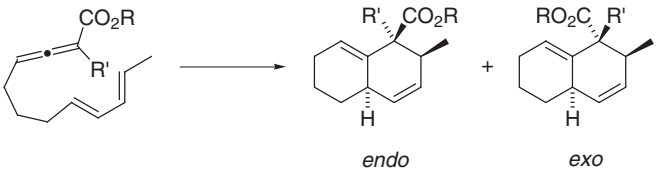
(12.107)

12.4.2
Intramolecular Cycloaddition of Activated Allenes

12.4.2.1 Allenic Esters

Intramolecular [4 + 2]-cycloaddition reactions of allenic acids and esters proceeded in refluxing toluene to give bicyclic compounds with the *exo*-isomer predominating (Table 12.9) [120]. When a Lewis acid was used as a promoter, the [4 + 2]-cycloaddition occurred at 0 °C and the *endo*-isomer was favored.

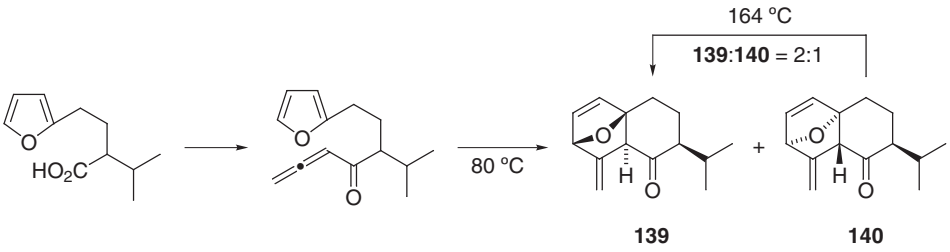
Table 12.9 Cycloaddition reactions of allenic acids and esters.



(12.108)

R, R′	Conditions	Yield (%)	*endo*:*exo*
H, Me	Toluene, 111 °C	87	35:65
Me, Et	Toluene, 111 °C	83	34:66
H, Me	Et_2AlCl, CH_2Cl_2, 0 °C	65	87:13
Me, Et	Et_2AlCl, CH_2Cl_2, 0 °C	49	87:13

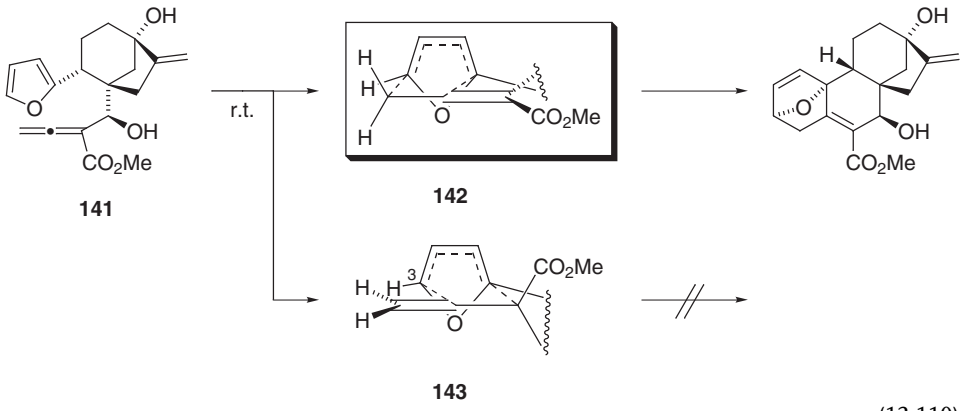
The intramolecular allene–furan cycloaddition led to the formation of a mixture of two *exo*-adducts, **139** and **140** (5:4) [121]. Heating the mixture at reflux in mesitylene gave an equilibrium mixture of **139** and **140** in a ratio of 2:1.



59% (**139**:**140** = 5:4)

(12.109)

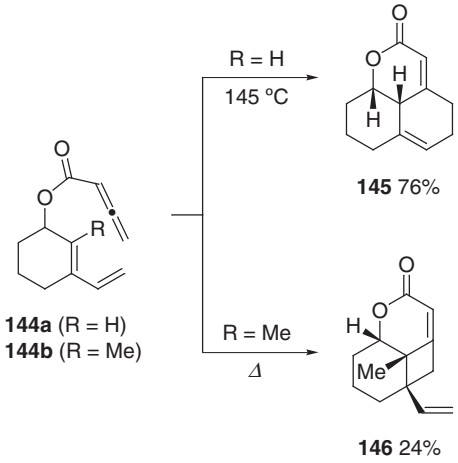
With **141**, the allenic π-bond that is distal to the ester group added to furan spontaneously upon concentration [122]. The observed site-selective addition can be attributed to steric reasons. The transition state geometry **143** is destabilized by a repulsive non-bonding interaction between H-3 and the *exo*-methylene group.



141 **142** **143**

(12.110)

Allene carboxylate **144a** afforded the product **145** through an intramolecular [4 + 2]-cycloaddition [123]. On the other hand, allene carboxylate **144b** gave the [2 + 2]-cycloadduct **146** exclusively. The switching of the reaction pathway is ascribed to the conformational stability of the transition state.



144a (R = H)
144b (R = Me)

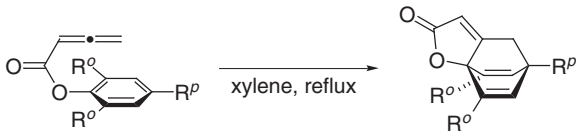
145 76%

146 24%

(12.111)

A benzene ring can act as the diene in the intramolecular [4 + 2]-cycloaddition with an activated allene. Thus, aryl allene carboxylates **147** gave tricyclic lactones **148** (Table 12.10) [124].

Table 12.10 Reactions of aryl allenecarboxylates **147.**



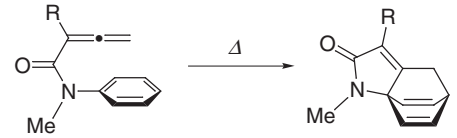
(12.112)

147 **148**

R^o	R^p	Yield (%)
H	H	63
H	Br	60
H	Me	60
Me	H	80

12.4.2.2 **Allenic Amides**

The aromatic rings of allene carboxanilides **149** also acted as the diene to furnish the tricyclic lactams **150** in refluxing xylene or benzene [125].

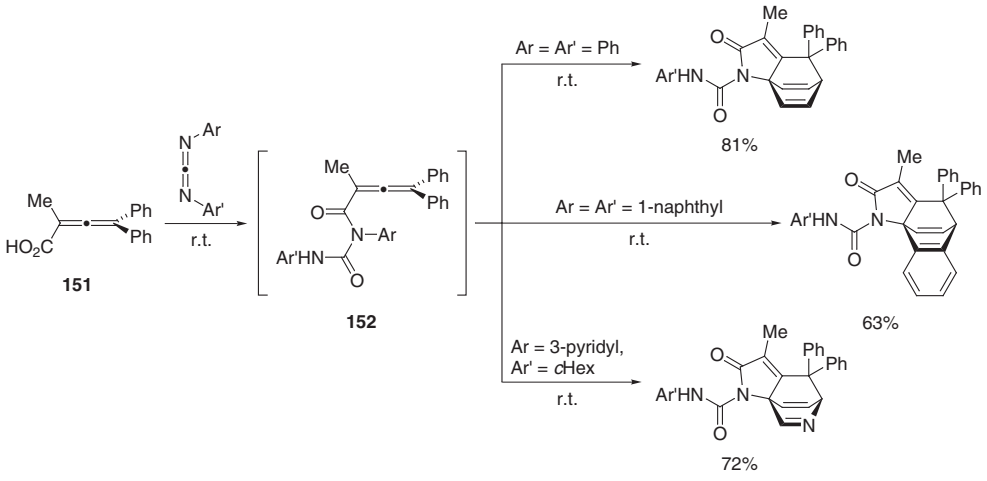


(12.113)

149
(R = H, Me, $SiMe_3$, CONHPh)

150 61–90%

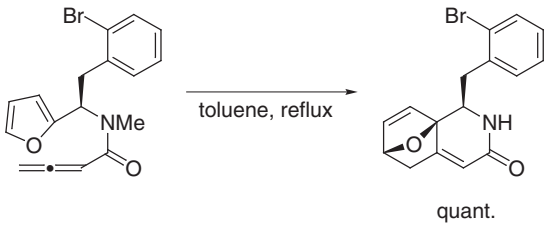
Allenic acylureas **152**, prepared in situ from the corresponding allenic acid **151** and carbodiimides, afforded lactams in good yields [126].



151 **152**

(12.114)

The intramolecular Diels–Alder reaction of a furan allenamide was most conveniently carried out in refluxing toluene [127].



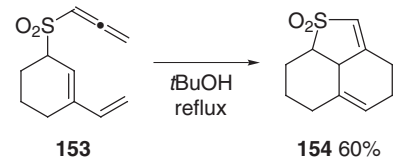
(12.115)

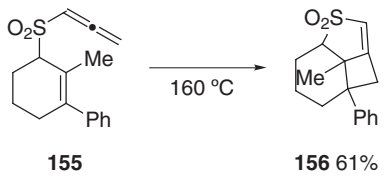
12.4.2.3 **Sulfonylallenes**

A furyl-substituted sulfonylallene readily underwent a [4 + 2]-cycloaddition to give the adduct [30].

(12.116)

Sulfonylallene **153** afforded the [4 + 2]-cycloadduct **154** on heating in refluxing *t*BuOH [128]. In contrast, the phenyl derivative **155** underwent the [2 + 2]-cycloaddition reaction selectively to give **156** as the sole product.

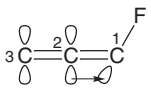




(12.117)

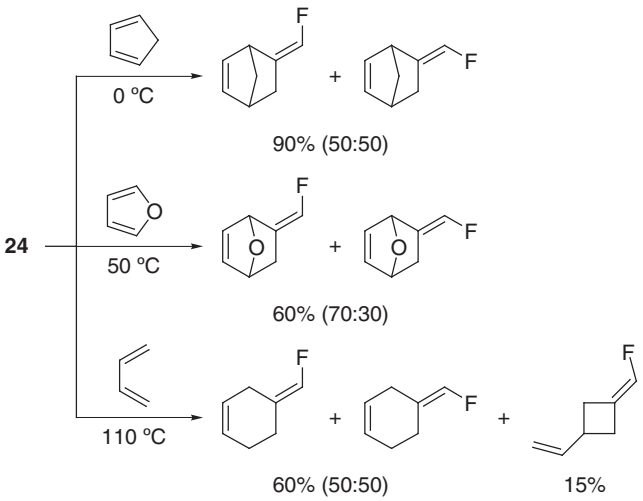
12.4.3 Fluoroallenes

Fluorine can exercise ambivalent electronic effects on an organic compound; fluorine accepts electron density from carbon since it is more electronegative. In addition, the unoccupied antibonding orbital of a C–F linkage is energetically low-lying and may accept electron density by hyperconjugation. On the other hand, fluorine is the best π-donor among halogens because of the effectiveness of overlap of a 2p orbital of fluorine with a 2p orbital of carbon. In fluoroallenes, these ambivalent characters of fluorine operate in different ways on their two orthogonal π-bonds. Although the lone-pair electrons of fluorine are delocalized into the C1–C2 double bond, this electron-donating effect is canceled by its inductive electron-withdrawing effect. Empirically, the C2–C3 π-orbital is electron-deficient owing to hyperconjugation as well as the simple inductive effect and, therefore, more reactive as the dienophile.



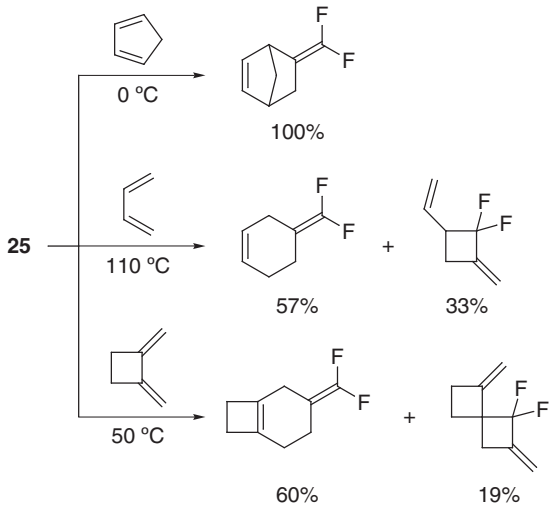
(12.118)

Monofluoroallene (**24**) underwent site-selective [4 + 2]-cycloadditions at the C2–C3 bond with some 1,3-dienes, although with little face selectivities [21, 129].



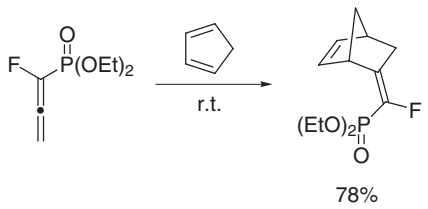
(12.119)

Likewise, 1,1-difluoroallene (**25**) afforded the [4 + 2]-cycloadducts. [2 + 2]-Cycloadducts were also formed in some cases.



(12.120)

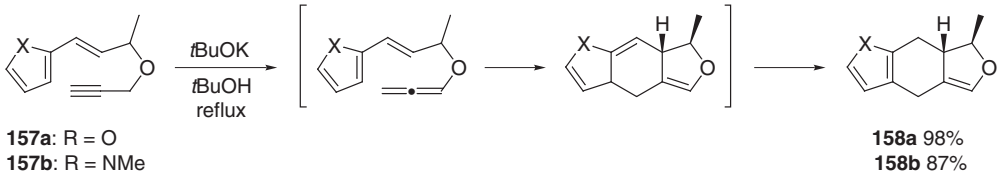
α-Fluoroallenylphosphonate reacted with cyclopentadiene at room temperature to furnish the *endo* adduct selectively [130]. A favorable interaction of the phosphonate moiety and the incoming diene may be responsible for the *endo* selectivity.

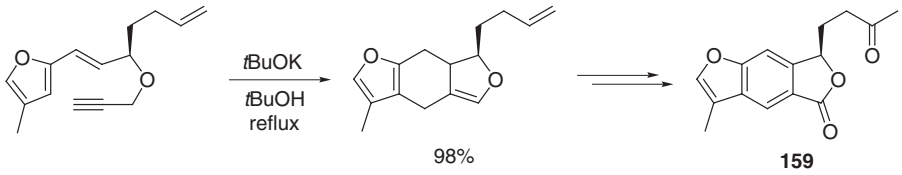


(12.121)

12.4.4
Alkoxyallenes

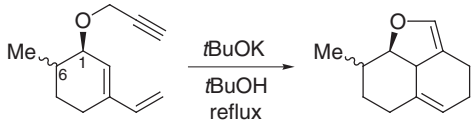
Intramolecular [4 + 2]-cycloaddition reactions, which involve base-induced isomerization of a propargyl ether to an allenyl ether, have been extensively studied. Treatment of **157** with a base caused an intramolecular Diels–Alder reaction of the intermediate allenyl ether to give tricyclic compounds **158** [131]. An asymmetric synthesis of benzofuran lactone **159** was achieved by an analogous procedure [132].





(12.122)

The following reactions of propargyl 3-vinyl-2-cyclohexenyl ethers **160** also involved initial isomerization to an alkoxyallene. The terminal allenic C=C double bond participated in an intramolecular [4 + 2]-cycloaddition [133].

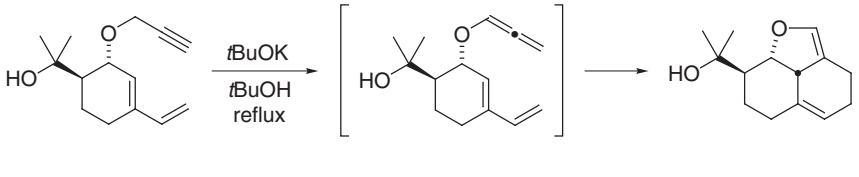


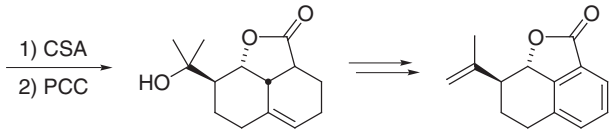
160
(1,6-*cis* or 1,6-*trans*)

1,6-*cis:* 81%
1,6-*trans*: 76%

(12.123)

Tricyclic lactone systems were synthesized by the analogous intramolecular [4 + 2]-reaction followed by hydration and oxidation of the resulting dihydropyran ring. This isomerization–cycloaddition sequence was successfully applied to the synthesis of (+)-platyphyllide [134].



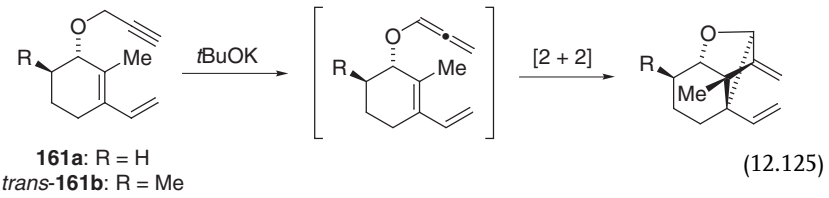


77%

(+)-platyphyllide

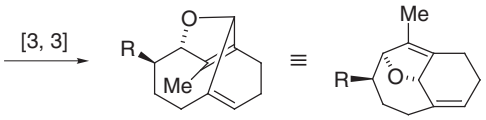
(12.124)

The introduction of a substituent on the C2 position changed the reaction pathway. In the case of the *trans*-**161b**, tandem [2 + 2]-cycloaddition at the internal C=C bond and [3,3]-sigmatropic rearrangement proceeded exclusively [133, 135].



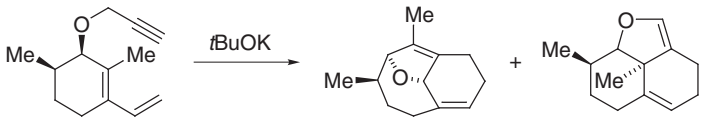
161a: R = H
trans-**161b**: R = Me

(12.125)



162a 88%
162b 90%

On the other hand, 1,6-*cis*-substituted propargyl ether *cis*-**161b** afforded a mixture of the [4 + 2]-adduct and the [2 + 2]/[3,3]-adduct.



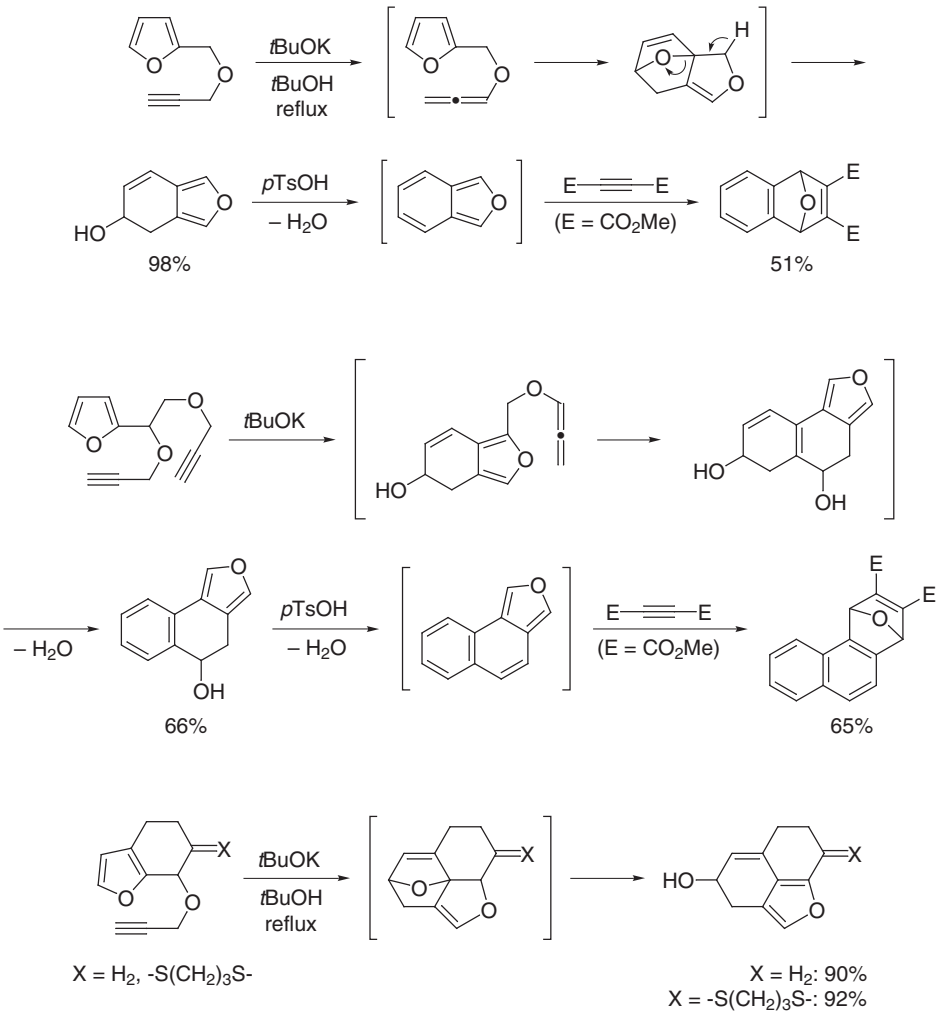
cis-**161b**

[2+2]/[3,3]: 50%

[4+2]: 20%

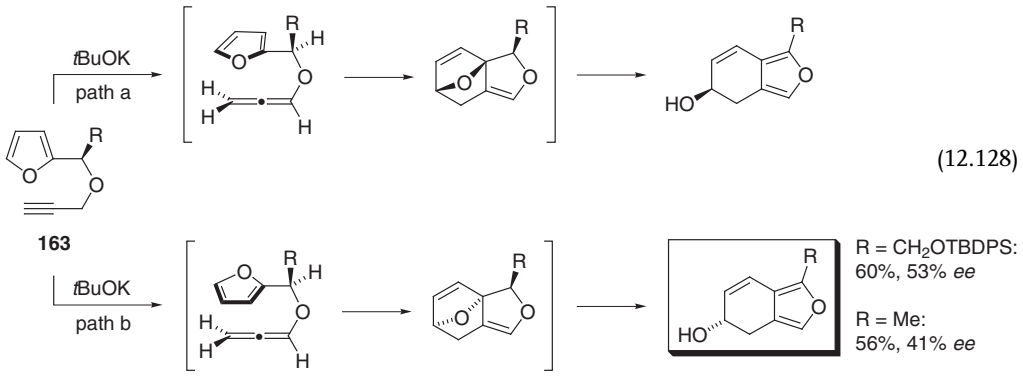
(12.126)

A formal transfer of a furan ring was achieved by the tandem intramolecular Diels–Alder reaction and base-catalyzed ring-opening of the adduct [136].



(12.127)

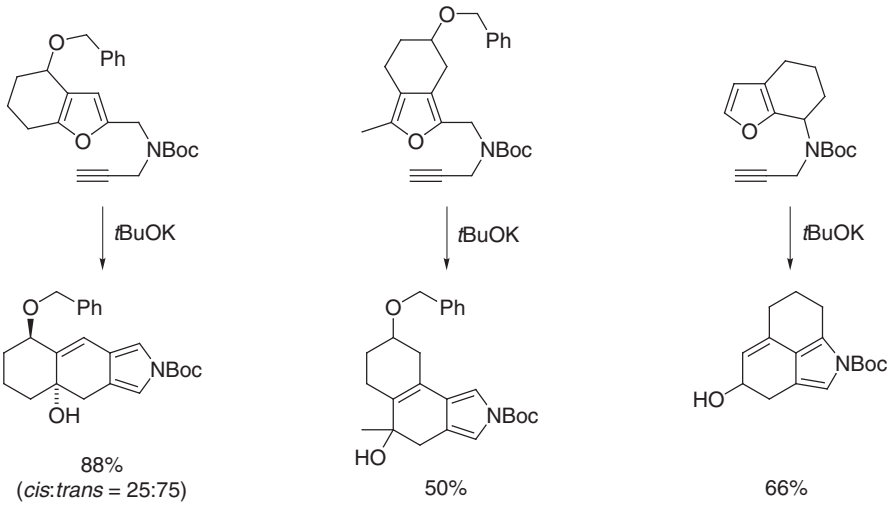
In a furan ring transfer reaction of **163**, a chirality transfer was observed from the starting material to the allylic carbon atom in the bicyclic allylic alcohols. The major enantiomer was formed through path b [137].



163

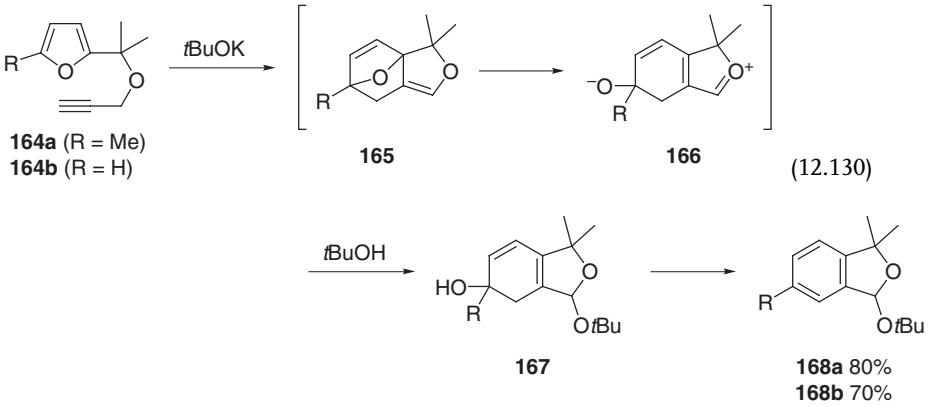
(12.128)

The furan transfer reaction was extended to the furan–pyrrole ring exchange reaction by using propargylamines [138].



(12.129)

Heating the propargyl ethers **164** with *t*BuOK in refluxing *t*BuOH gave acetals **168** [139]. It was proposed that the highly strained cycloadducts **165** easily undergo a ring opening of the bridged oxygen to form zwitterions **166** as the reaction intermediate. Protonation of the alkoxide ion and nucleophilic attack on the oxonium ion occurred to afford the intermediates **167**, which underwent aromatization.



164a (R = Me)
164b (R = H)

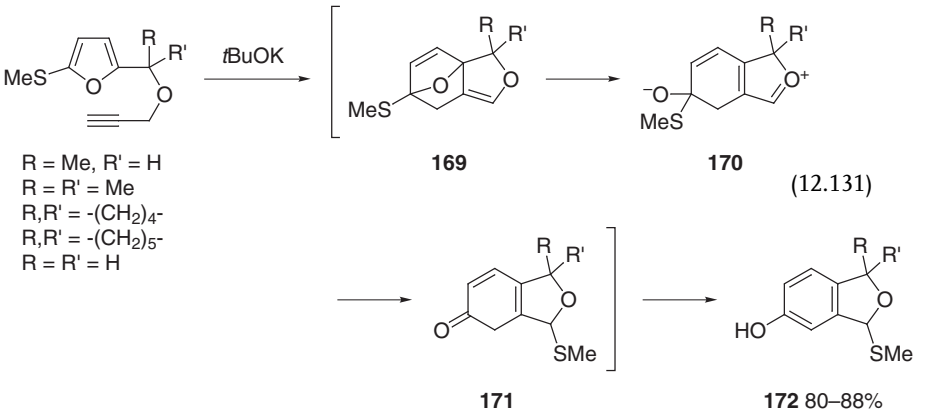
165 **166**

(12.130)

167

168a 80%
168b 70%

The results with furfuryl propargyl ethers having a methylthio group at the 5-position are consistent with this mechanistic hypothesis [140]. Heating the propargyl ether with *t*BuOK gave the rearranged products, presumably via the corresponding cycloadducts **169** and zwitterions **170**. Elimination of the methylthio group followed by nucleophilic attack on the oxonium ion gave the rearranged intermediates **171**, which underwent aromatization to afford **172**.



R = Me, R' = H
R = R' = Me
R,R' = -$(CH_2)_4$-
R,R' = -$(CH_2)_5$-
R = R' = H

169 **170**

(12.131)

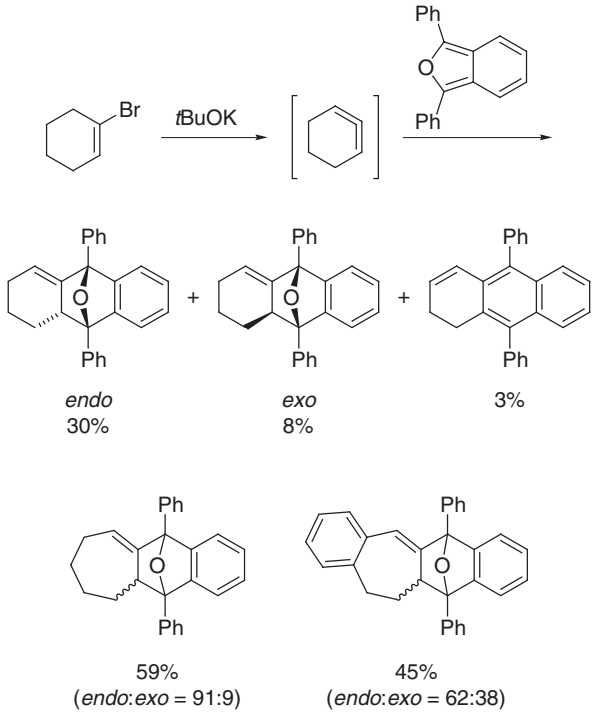
171

172 80–88%

12.4.5

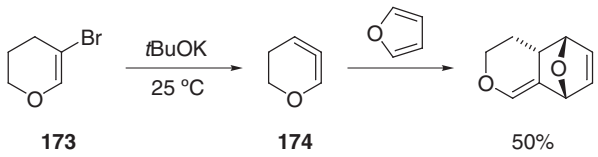
Cycloaddition of Strained Cyclic Allenes

Strained cyclic allenes, in situ generated by dehydrobromination of 1-bromocycloalkenes with *t*BuOK, react with diphenylisobenzofuran (DPIBF) to give the [4 + 2]-adducts. Preferential formation of *endo* adducts was observed [141].



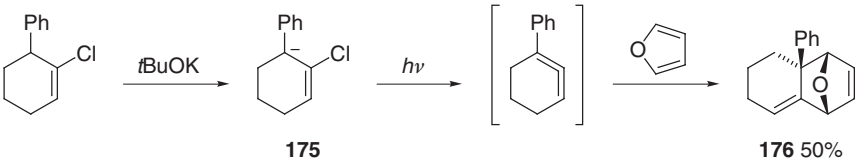
(12.132)

Dehydrobromination of **173** with *t*BuOK gave rise to the 1-oxa-2,3-cyclohexadiene intermediate **174**, which was trapped by furan to give the cycloadduct [142].



(12.133)

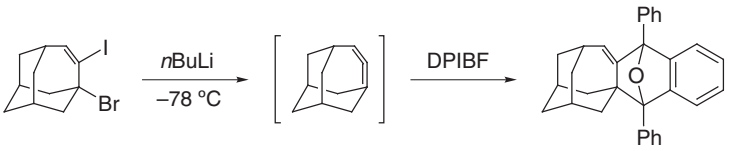
A cyclic allene generated by photodehalogenation of chlorocarbanion **175** reacted with furan to yield the *endo* adduct **176** [143].



175 **176** 50%

(12.134)

The reaction of **177** with *n*BuLi in the presence of DPIBF at –78 °C produced the [4 + 2]-adduct in good yield. The bridgehead double bond of **178** served as the dienophile [144].

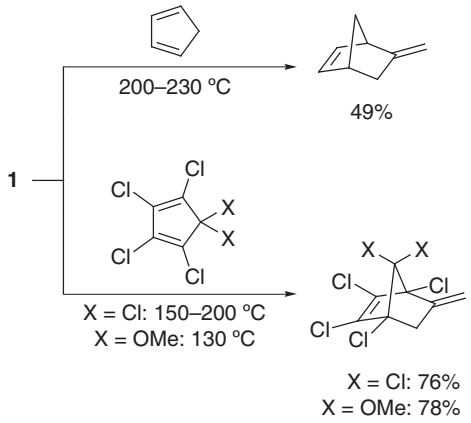


177 **178** 79%

(12.135)

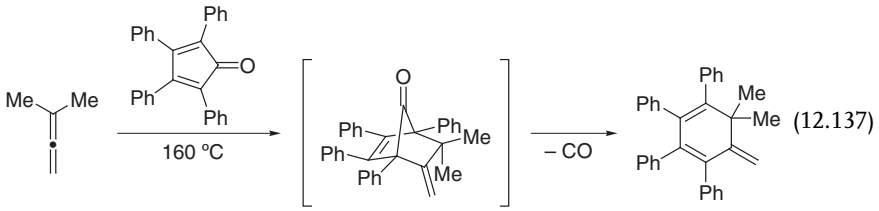
12.4.6
Cycloaddition of Unactivated Allenes

Although allene itself is reluctant to react with ordinary 1,3-dienes, it underwent successful [4 + 2]-cycloadditions with relatively reactive cyclopentadienes to afford 5-methylenebicyclo[2.2.1]hept-2-ene derivatives [145].



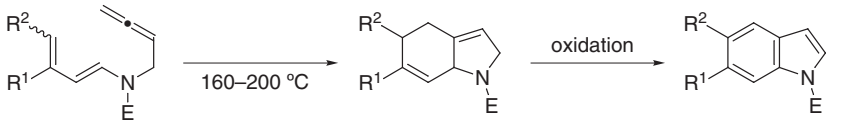
(12.136)

1,1-Dimethylallene reacted with tetraphenylcyclopentadienone to produce methylenecyclohexadiene derivative **180** [146]. The cycloaddition occurred at the more substituted double bond of the allene, which was followed by extrusion of carbon monoxide from the intermediate **179**.



179 **180** quant. (12.137)

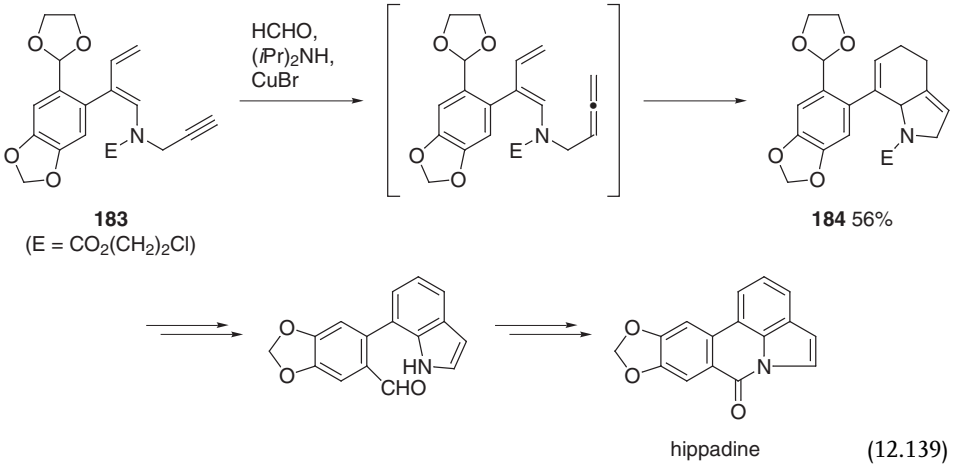
An intramolecular Diels–Alder reaction of allenic dienamide **181** provided the tetrahydroindole ring system **182**, which was oxidized with DDQ or MnO_2 to give indole derivatives [147].



181 (E = CO_2Et) **182** 50–80%

$R^1 = R^2 = H$: 100%
$R^1 = H$, $R^2 = Et$: 76%
$R^1 = Me$, $R^2 = H$: 100%
$R^1,R^2 = -(CH_2)_4-$: 100% (12.138)

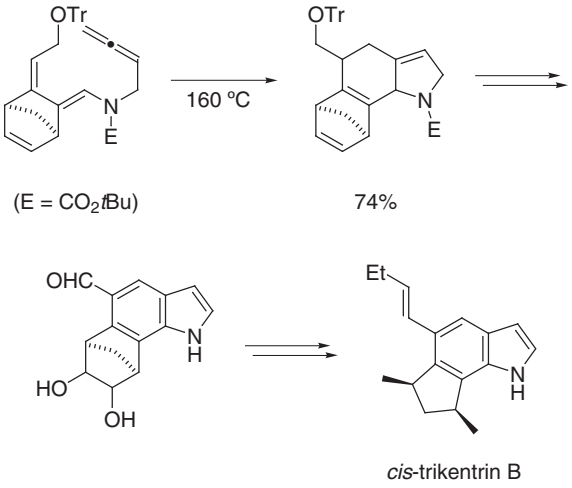
When propargylamine **183** was subjected to a homologative allenylation (Crabbé reaction) at 100 °C, the resulting allene underwent a spontaneous Diels–Alder reaction to give the adduct **184**. This intramolecular cycloaddition–oxidation sequence provided a simple route to indole alkaloids such as hippadine and *cis*-trikentrin B [148].



183 (E = $CO_2(CH_2)_2Cl$) **184** 56%

hippadine (12.139)

Natural *cis*-trikentrin B was synthesized enantioselectively by cycloaddition of the allenic dienamide [149].



(12.140)

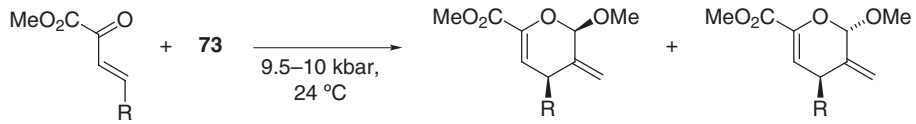
12.4.7
Hetero-Diels–Alder Reaction

[4 + 2]-Cycloaddition reactions of electron-rich allenes with some heterodienes take place at the C1–C2 bond of the allene to yield heterocycles. α,β-Unsaturated carbonyl compounds **185** react with the internal C=C bond of ethoxyallene to afford dihydropyrans in moderate yields [150].

185
(R = H, Me)

R = H: 41%
R = Me: 19%

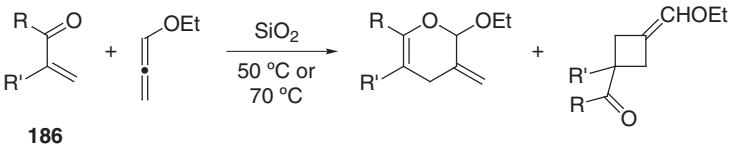
(12.141)



(R = OMe, Ph)

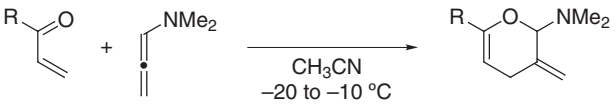
R = OMe: 51% (50:50)
R = Ph: 49% (75:25)

Hetero-Diels–Alder reactions of α,β-unsaturated carbonyl compounds **186** with ethoxyallene are promoted by acid-free silica gel to give the [4 + 2]-adducts along with a small amount of [2 + 2]-adducts [151].



186 (12.142)

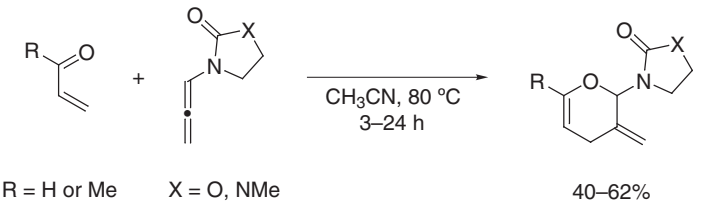
With more reactive (dimethylamino)allene, the reactions were complete within a few minutes at –10 °C [24].



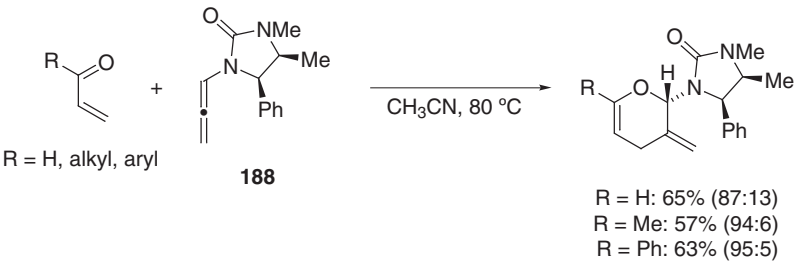
(12.143)

Allenamides are more stable and hence easier to handle in synthetic manipulations [152]. When allenamide **187** was heated with 2 equiv. of acrolein or methyl vinyl ketone (MVK), cycloadducts were isolated as single regioisomers. Allenamides containing either an oxazolidinone or imidazolidinone moiety also reacted with these α,β-unsaturated carbonyl compounds under thermal conditions.

(12.144)

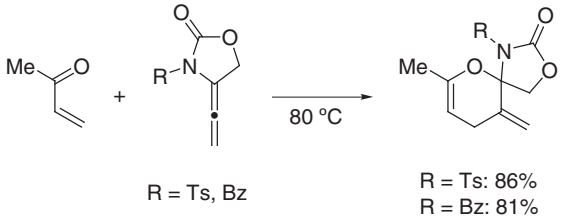


Allenamide **188** having a chiral auxiliary was successfully applied to stereoselective [4 + 2]-cycloaddition reactions with α,β-unsaturated carbonyl compounds at 80 °C to give pyranyl heterocycles with high enantioselectivities [153].



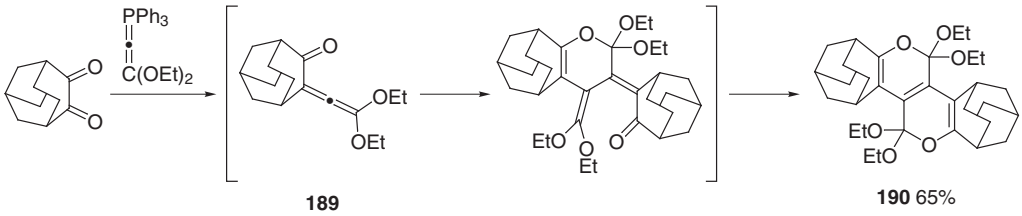
(12.145)

N-Tosyl- and *N*-benzoyl-4-vinylidene-2-oxazolidinones underwent [4 + 2]-cycloadditions with MVK at the enamide double bond to furnish the spiro adducts [154].



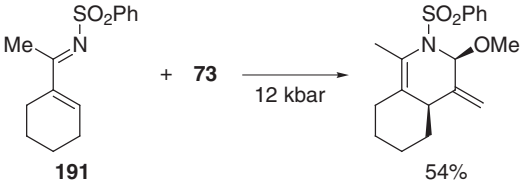
(12.146)

The unsymmetricall allene **189** dimerized to give pyranopyran **190**. A hetero-Diels–Alder reaction was followed by the subsequent electrocyclic ring closure reaction [8].



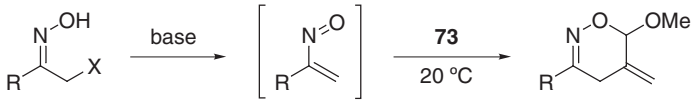
(12.147)

A regioselective and *endo*-selective [4 + 2]-cycloaddition reaction of *N*-benzenesulfonylimine **191** was promoted by pressure to yield a tetrahydropyridine derivative [155].



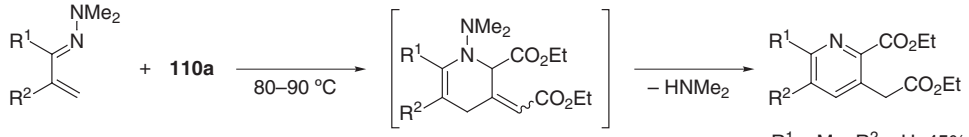
(12.148)

Nitrosoalkenes **192**, generated in situ from α-halo oximes, reacted with methoxyallene in a [4 + 2] fashion to give 6*H*-1,2-oxazines [156].



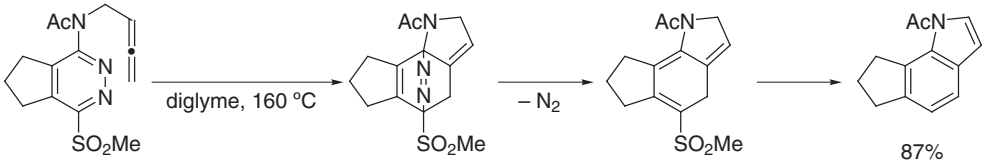
(12.149)

Electron-deficient allenes also undergo hetero-Diels–Alder reactions. *N,N*-Dimethylhydrazones **193** reacted with allenedicarboxylate **110a** in refluxing acetonitrile to give 2-carboxy-3-pyridineacetic acid diesters [157].



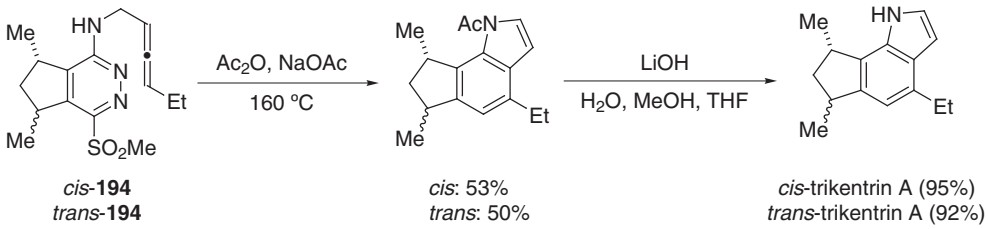
(12.150)

A thermal intramolecular allene 1,2-diazine Diels–Alder reaction proceeded at 160 °C to afford indole derivatives [158].



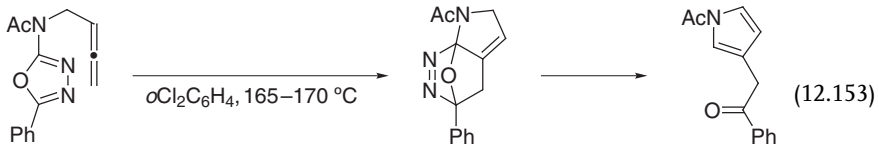
(12.151)

This strategy was applied to the total synthesis of (±)-*cis*- and (±)-*trans*-trikentrin A [159]. Treatment of **194** with acetic anhydride at 160 °C provided indole derivatives via an *N*-acylation–[4 + 2]-cycloaddition cascade. Deacylation afforded trikentrin A.



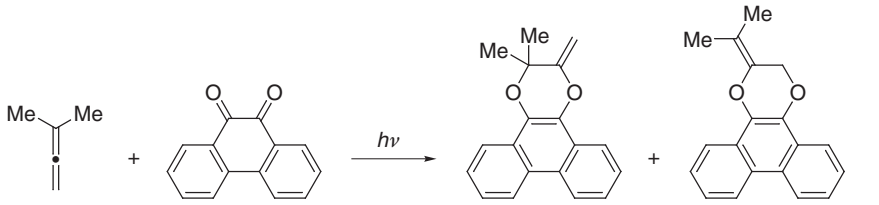
(12.152)

A [4 + 2]-cycloaddition reaction of 1,3,4-oxadiazole **195** was followed by isomerization and elimination of dinitrogen to provide a pyrrole [160].



195 65% (12.153)

Phenanthraquinone (**196**) added photochemically to 1,1-dimethylallene to give a mixture of isomeric dihydrodioxin derivatives **197a** and **197b** [161]. The cycloaddition reaction took place at the more substituted C=C bond preferentially, affording **197a** as the major product.



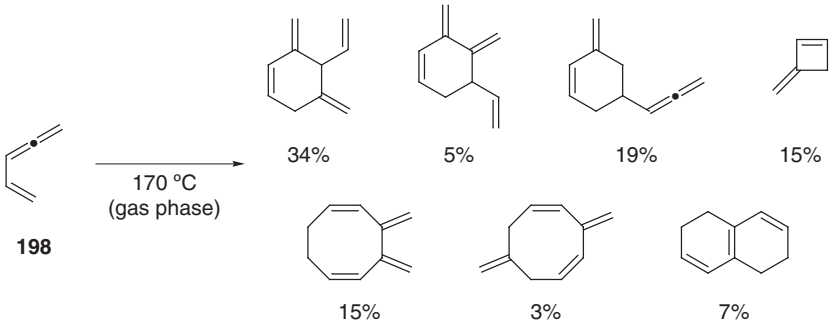
196 **197a** 51% **197b** 17% (12.154)

12.5 Vinylallenes and Bisallenes

Vinylallenes and bisallenes participate in the Diels–Alder-type cycloaddition as the diene component, providing a powerful tool for the construction of complex ring systems. They also undergo thermal electrocyclic ring closure to form methylenecyclobutene derivatives.

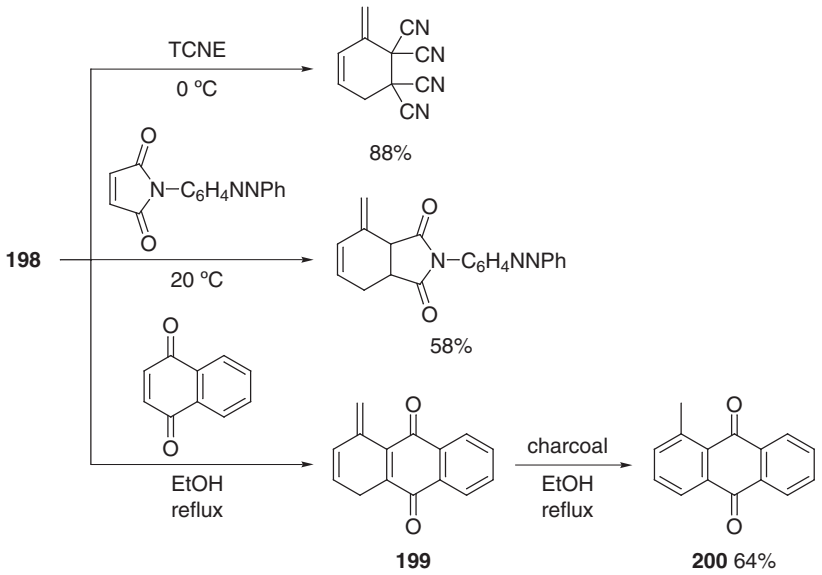
12.5.1 Intermolecular [4 + 2]-Cycloaddition of Vinylallenes

Vinylallene **198** itself undergoes a variety of dimerization and cycloisomerization reactions on heating at 170 °C in the gas phase [162].



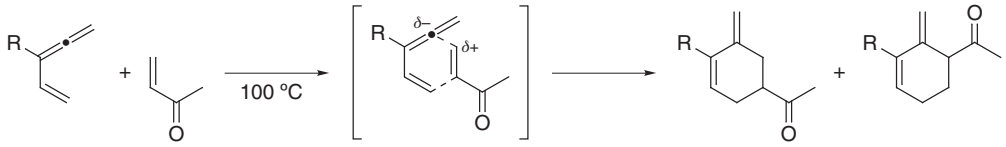
(12.155)

In the presence of electron-deficient dienophiles such as tetracyanoethylene (TCNE), however, vinylallene **198** acts as a diene to afford cross [4 + 2]-cycloadducts. In the case of 1,4-naphthoquinone, the adduct **199** was converted to 1-methylanthraquinone **200** in the presence of charcoal [163].



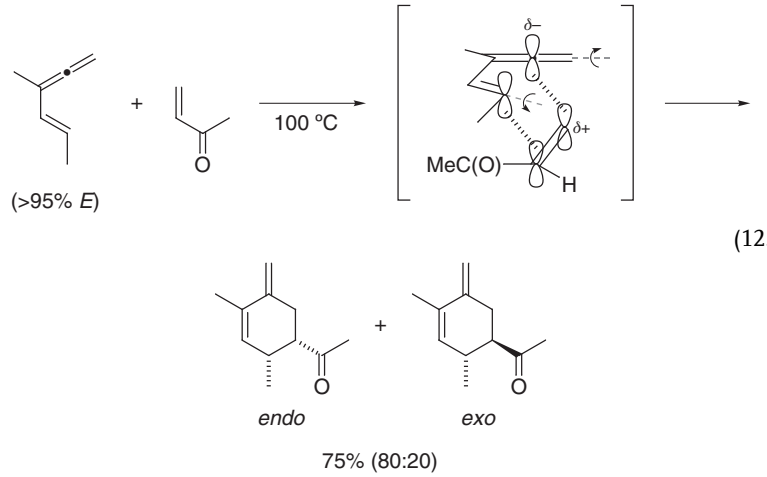
(12.156)

With an unsymmetrical electron-deficient dienophile, the electron-rich central carbon of vinylallene preferentially adds to the more electron-deficient carbon of the dienophile. Moderate regioselectivities were observed in the reactions of methyl vinyl ketone with vinylallenes at 100 °C [164].



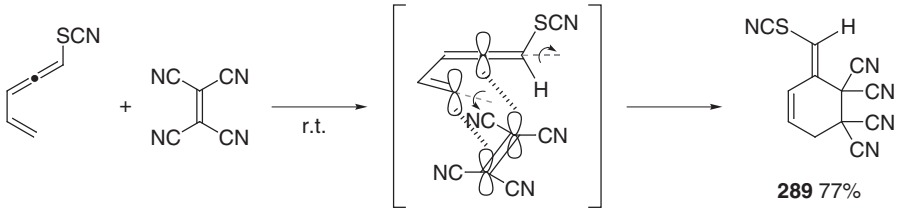
(12.157)

If the vinylallene possesses a substituent at the vinylic terminal position, an *endo* adduct is preferentially obtained owing to the secondary orbital overlap. Only the *E*-isomer of propenylallene underwent the regio- and stereoselective cycloaddition with methyl vinyl ketone to afford the *endo*-isomer as the major product. The *Z*-isomer was unreactive because it preferred the transoid conformation [165].



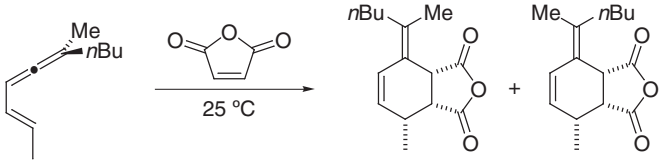
(12.158)

When a vinylallene bears a substituent at the allene terminus, a dienophile approaches from the less hindered face of the vinylallene in an *s-cis* conformation. Thus, the [4 + 2]-cycloadduct possesses an *E*-configuration [166].



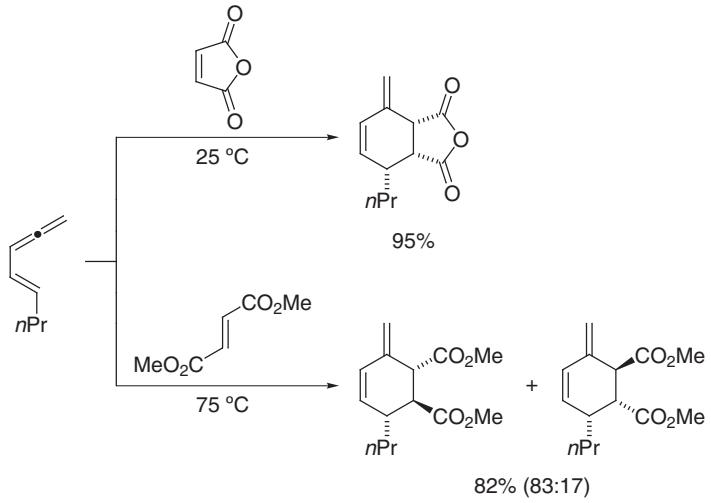
(12.159)

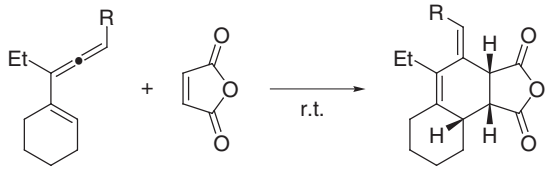
Cycloaddition of vinylallene **201** having methyl and *n*-butyl substituents at the terminal allenic carbon gave a moderate ratio of geometric isomers owing to the small steric difference between the two substituents [167].



201 82% (3:1) (12.160)

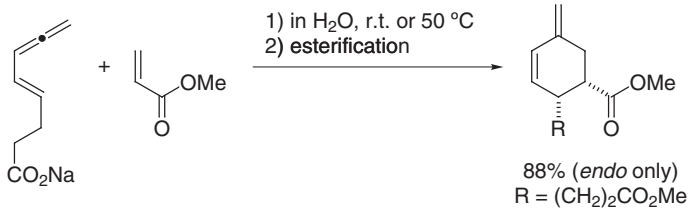
Examples of the stereoselective cycloaddition are shown below. The *trans* disubstitution is kept in the reaction with dimethyl fumarate [168].





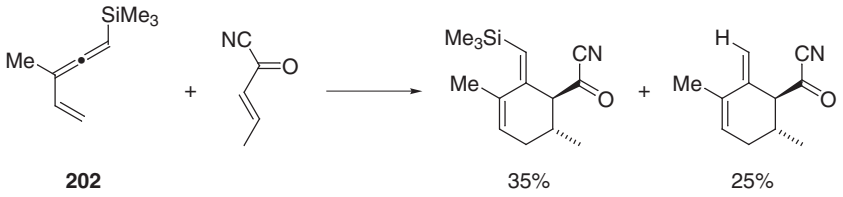
R = Me, Ph >90% (12.161)

The reaction of sodium 1,2,4-octatrienoate occurred at a relatively low temperature in water [169].



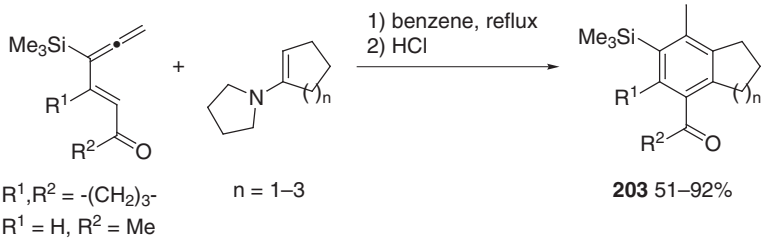
(12.162)

The condensation of vinylallene **202** with (*E*)-crotonoyl cyanide gave the corresponding [4 + 2]-cycloadduct and the desilylated product in 35 and 25% yields, respectively. The regiochemistry was opposite to that of the reaction with α,β-enones, suggestive of a stepwise ionic mechanism [170].



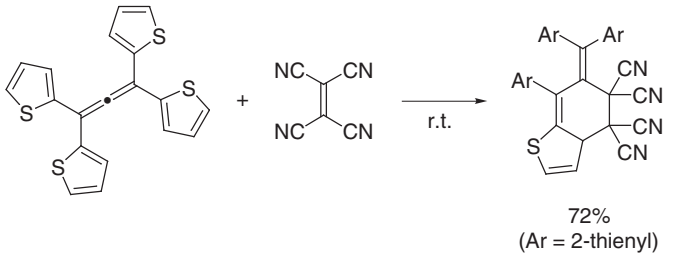
(12.163)

Regioselective condensations of vinylallenones with enamines gave highly substituted arylsilanes **203** after acidic workup [171].



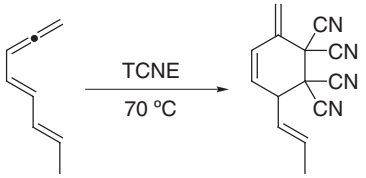
(12.164)

Tetrakis(2-thienyl)allene reacted smoothly with TCNE at room temperature to form the [4 + 2]-cycloadduct. One of the thienyl groups was incorporated as the part of the diene [172].



(12.165)

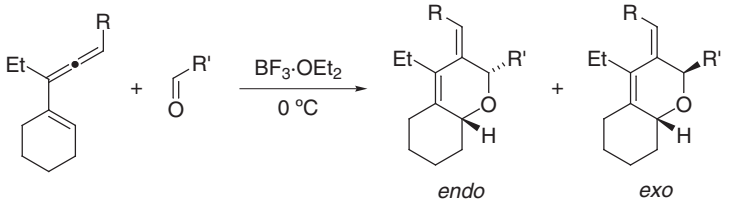
The [4 + 2]-cycloaddition reaction of dienylallene **204** with TCNE took place at 70 °C to give the adduct **205** in good yield [173]. The dienylallene behaved not as butadiene but vinylallene, partly owing to the thermodynamic stability of the adduct.



(12.165)

204 **205** 88%

Hetero-Diels–Alder-type cycloaddition reactions of the vinylallenes with aldehydes proceeded in the presence of $BF_3 \cdot OEt_2$ (1.1 equiv.) at 0 °C to give the adducts in a moderate *endo*:*exo* ratio. The cycloaddition took place from the less hindered face of the vinylallene [168].

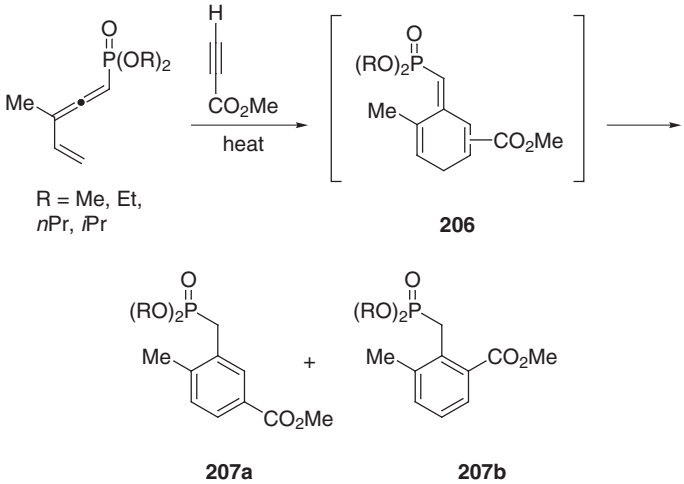


(12.167)

R = Me, Ph R' = Et, *i*Pr, Ph

R = Me: 50–70% (64:36–74:26)
R = Ph: 36–54% (66:34–75:25)

The reactions of allenylphosphonates with methyl propiolate gave the benzylphosphonates via aromatization of the initially formed cycloadducts **206**. The product **207a** was formed selectively [174].



R = Me, Et, *n*Pr, *i*Pr

206

(12.168)

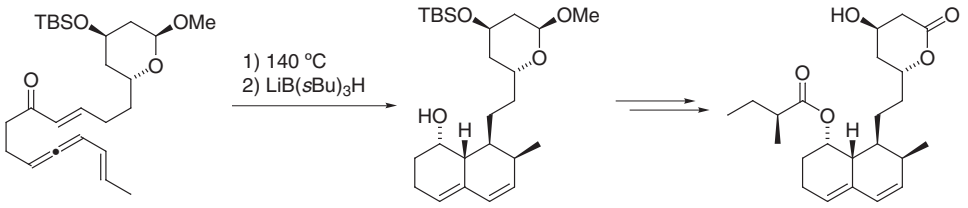
207a **207b**

62-81% (96:4–100:0)

12.5.2

Intramolecular [4 + 2]-Cycloaddition of Vinylallenes

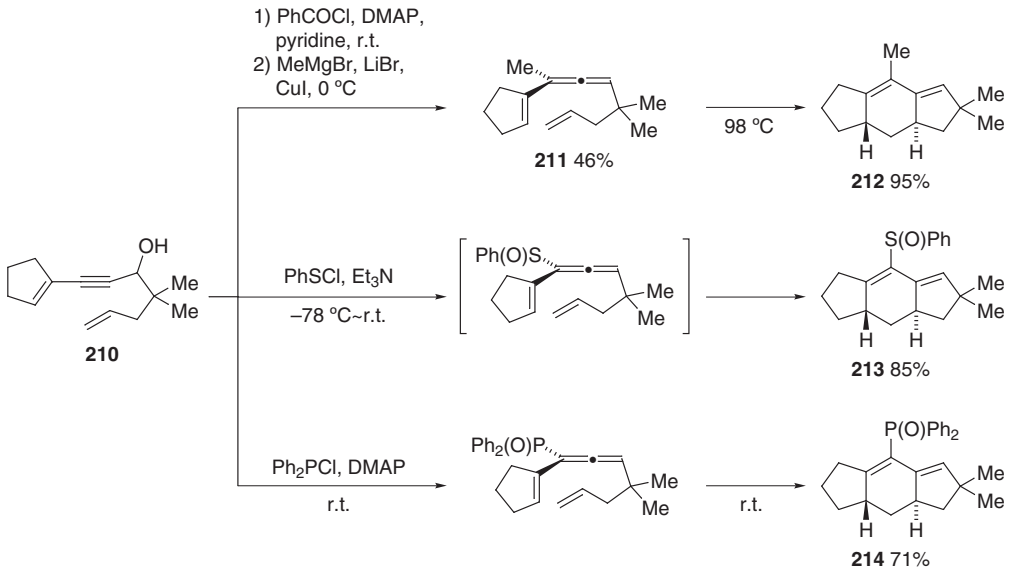
Intramolecular [4 + 2]-cycloadditions of vinylallenes have been utilized in the synthesis of complex molecules including natural products such as compactin. Heating the vinylallene **208** at 140 °C gave hexahydronaphthalene **209**. The crude mixture was immediately reduced with $LiB(sBu)_3H$ because of the instability of β,γ-unsaturated ketones [175].



208 **209** 84% (diastereomeric mixture) (+)-compactin

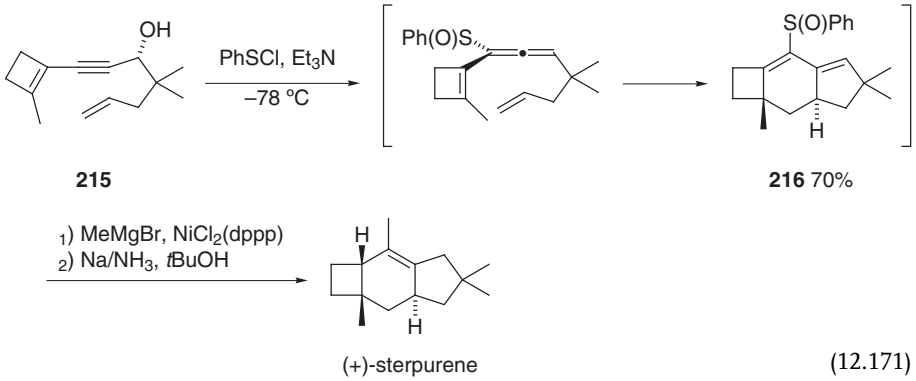
(12.169)

The intramolecular [4 + 2]-cycloaddition reactions of vinylallenes were also used for the synthesis of hydrindanes. Vinylallene **211** was prepared by benzoylation of propargylic alcohol **210** followed by S_N2' displacement with MeMgBr. Heating of **211** at 98 °C for 3 h afforded **212** as a single diastereomer. When the propargyl alcohol was treated with benzenesulfenyl chloride in the presence of triethylamine, a [2,3]-sigmatropic rearrangement occurred and diene sulfoxide **213** was obtained as a mixture of two sulfoxide diastereomers, which were epimeric at sulfur. Treatment of the propargyl alcohols with chlorodiphenylphosphine in the presence of DMAP gave the phosphinite ester, which spontaneously rearranged to vinylallene and subsequently cyclized at room temperature to afford phosphine oxide **214**. Both the S(O)Ph (~140 times faster than **211**) and $P(O)Ph_2$ (~30 times faster than **211**) groups accelerated the reactions. These accelerating effects can be attributed to their electron-withdrawing nature [176].



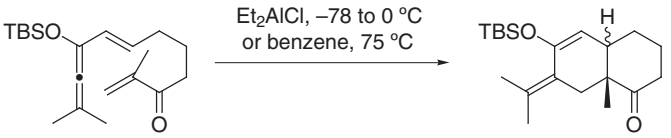
(12.170)

The propargyl alcohol **215** having a cyclobutene ring similarly underwent a [2,3]-sigmatropic rearrangement/[4 + 2]-cycloaddition sequence to give the corresponding adduct **216** in good yield. Cross-coupling with MeMgBr followed by Birch reduction of the diene yielded (+)-sterpurene [177].



(12.171)

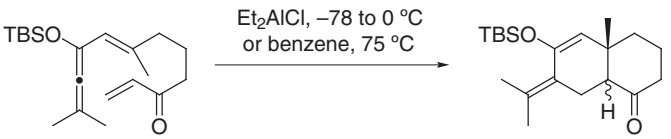
In the cycloaddition of vinylallenes **217** and **218**, both Lewis acid catalysis and thermal conditions gave analogous results in terms of stereoselectivities [178].



217

Lewis acid: 51% (*cis*:*trans* = 2:1)
Δ: 42% (*cis*:*trans* = 1:1)

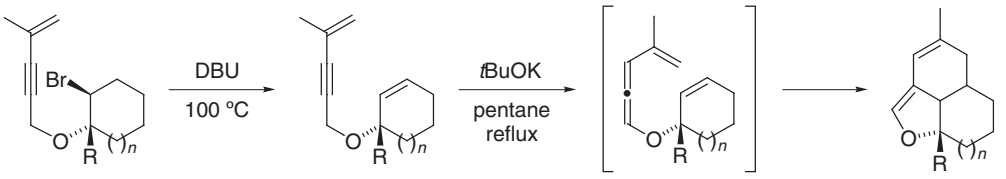
(12.172)



218

Lewis acid: 51% (*cis*:*trans* = 1:1)
Δ: 23% (*cis*:*trans* = 1:1)

Dehydrobromination of **219** with DBU gave rise to allyl propargyl ethers **220**, which underwent a base-catalyzed isomerization–[4 + 2]-cycloaddition sequence to afford tricyclic enol ethers **221** [179].



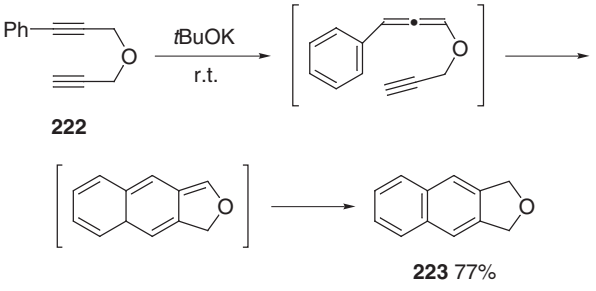
219
n = 0, R = H
n = 1, R = H
n = 2, R = H
n = 1, R = Me

220 72–97%

221 90–95%

(12.173)

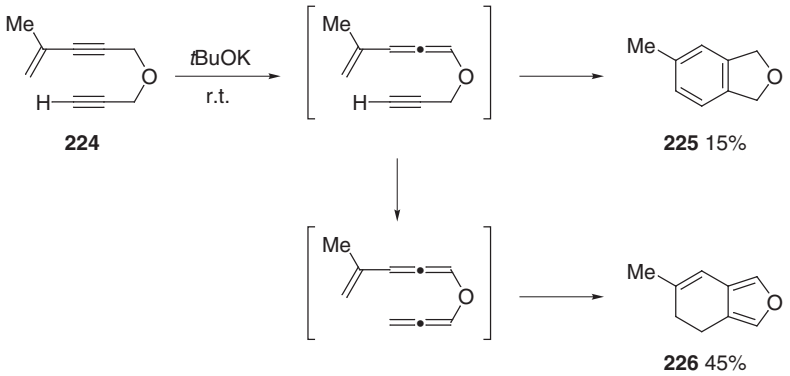
Bispropargyl ether **222** isomerized on treatment with *t*BuOK into the naphthalene **223** via the intramolecular [4 + 2]-cycloaddition of the phenylallene with the acetylene moiety. Similar reactions of enynyl propargyl ether **224** took place at room temperature to give two isomeric isobenzofurans, **225** and **226**. The major product **226** presumably arises from the intramolecular [4 + 2]-cycloaddition of the bisallenyl ether, whereas the minor product **225** is formed by the [4 + 2]-cycloaddition of the monoallenyl ether [180].



222

223 77%

(12.174)

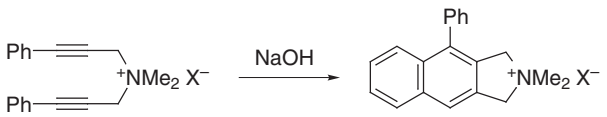


224

225 15%

226 45%

The analogous reaction of bis(propargyl)ammonium salt **227** in the presence of sodium hydroxide in an aqueous solution gave the naphthalene derivative **228** in high yield [181].



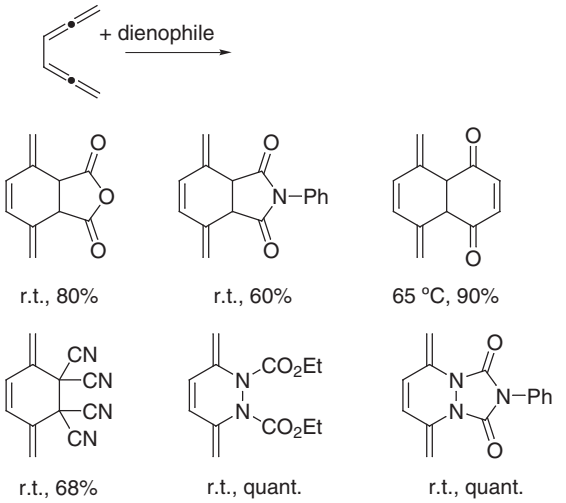
227

228 96%

(12.175)

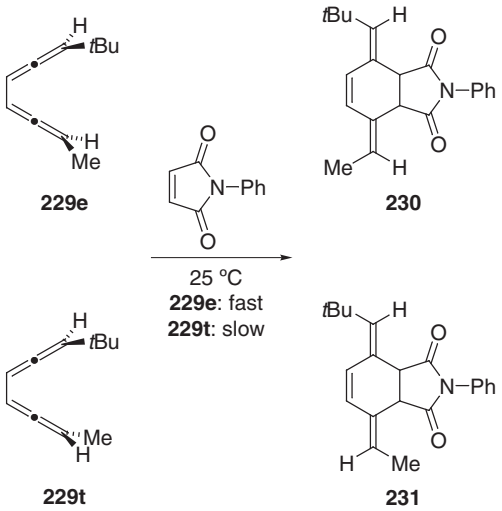
12.5.3
[4 + 2]-Cycloaddition of Bisallenes

Bisallene (1,2,4,5-hexatetraene) reacts with reactive dienophiles to afford the corresponding [4 + 2]-adducts [182].



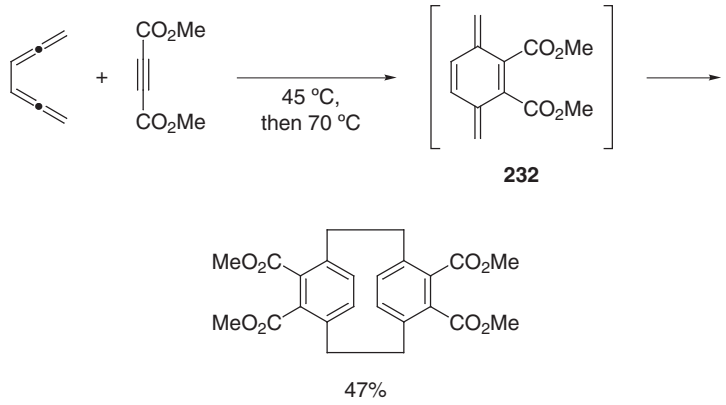
(12.176)

When a mixture of *erythro*- and *threo*-bisallenes (1 equiv., **229e**:**229t** = 60:40) was stirred with *N*-phenylmaleimide (NPMI) (1 equiv.), only **229e** reacted to afford the [4 + 2]-cycloadduct **230**, leaving **229t** unchanged. The **229t** that remained reacted with NPMI slowly to produce the cycloadduct **231**. In both cases the cycloadducts were formed by a concerted [4 + 2]-cycloaddition process in which the NPMI approaches from the less hindered face of the bisallene in an *s-cis* conformation [183].



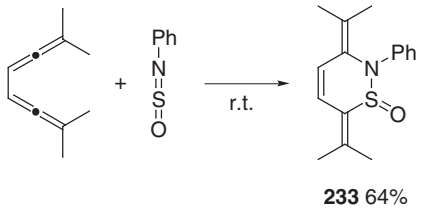
(12.177)

A [2.2]paracyclophane was prepared by dimerization of *p*-quinodimethane **232**, which was obtained by a [4 + 2]-cycloaddition reaction of bisallene with DMAD [184]. This sequence represents one of the most general approaches to functionalized paracyclophanes.



(12.178)

The reaction of tetramethylbisallene with *N*-sulfinylaniline gave the [4 + 2]-adduct **233** as the only isolable product [185].

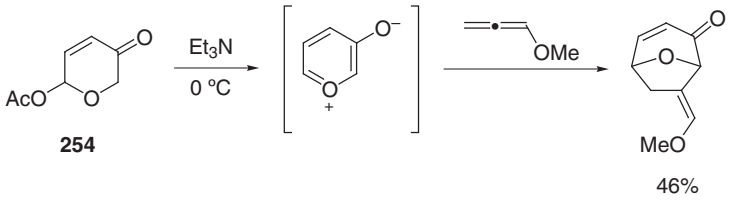


(12.179)

12.6 Miscellaneous Cycloaddition Reaction of Allenes

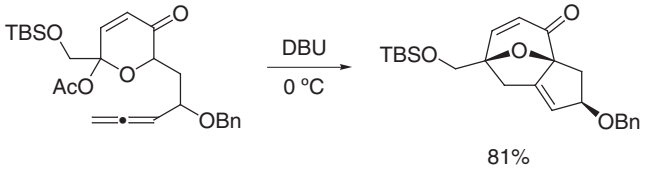
12.6.1 [5 + 2]-Cycloaddition of Allenes

Like alkenes, methoxyallene undergo [5 + 2]-cycloaddition with the oxidopyrylium ion formed from the precursor **254** and triethylamine. The allenic terminal C=C bond adds from its sterically less encumbered face to afford the [5 + 2]-cycloadduct [186].



(12.180)

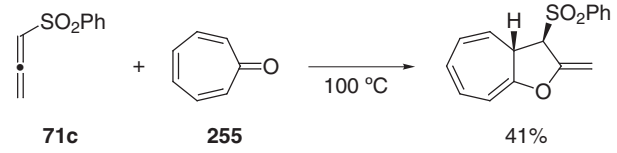
The corresponding intramolecular allene–oxidopyrylium cycloaddition gave the [5 + 2]-cycloadduct as a single diastereomer.

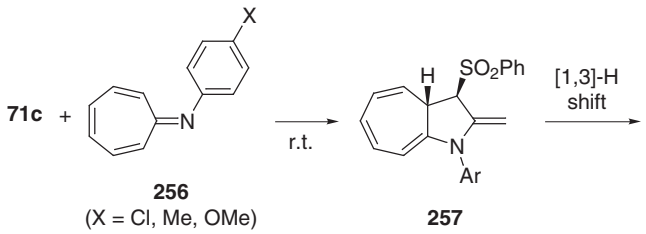


(12.181)

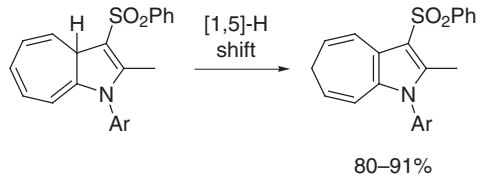
12.6.2
Cycloaddition of Allenes with Tropones

Tropone (**255**) cycloadds to allene **71c** to construct a 5,7-fused ring system, probably via a concerted mechanism [109]. The reaction of **71c** with azaheptafulvenes **256** took place much more readily at room temperature to produce the relatively unstable adducts **257**, which isomerized gradually to the stable pyrroles.

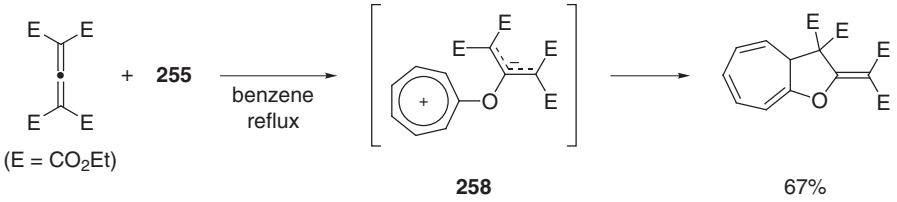




(12.182)

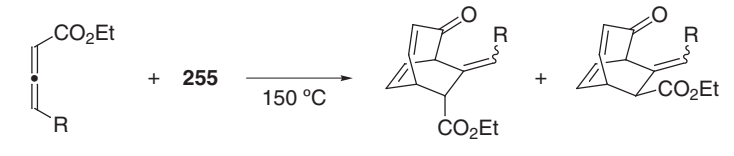


An allenic tetraester also reacted with **255** to afford the corresponding cycloadduct, probably via a zwitterionic intermediate **258** [65].



(12.183)

In contrast, the reaction of allenic esters **259** with **255** proceeded in a different manner to yield [4 + 2]-cycloadducts as the major products [187].

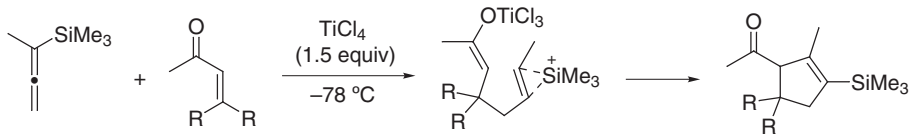


(12.184)

259
(R = H, Me, Et)

12.6.3
[3 + 2]-Cycloaddition of Allenylsilanes

A regioselective [3 + 2]-cycloaddition approach to substituted 5-membered carbocycles was made available by the use of allenylsilanes [188]. The reaction involves regioselective attack of an unsaturated ketone by (trimethylsilyl)allene at the 3-position. The resulting vinyl cation undergoes a 1,2-silyl migration. The isomeric vinyl cation is intercepted intramolecularly by the titanium enolate to produce a highly substituted (trimethylsilyl)cyclopentene derivative.

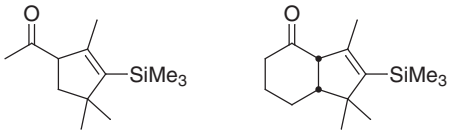


R = H, Me

R = H: 71–75%
R = Me: 65%

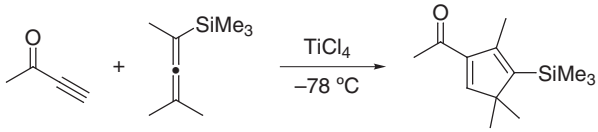
(12.185)

The (trimethylsilyl)cyclopentene annulation proceeds most efficiently with the use of 1-substituted (trimethylsilyl)allenes. Even the fully methyl-substituted (trimethylsilyl)allene reacted with both cyclic and acyclic enones to provide the corresponding cyclopentenes in good yields.



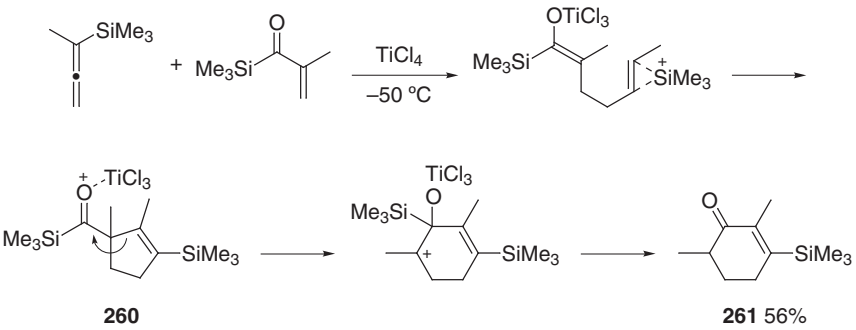
80% 61–63% (12.186)

An analogous annulation reaction of an acetylenic ketone provides an access to a cyclopentadiene derivative.



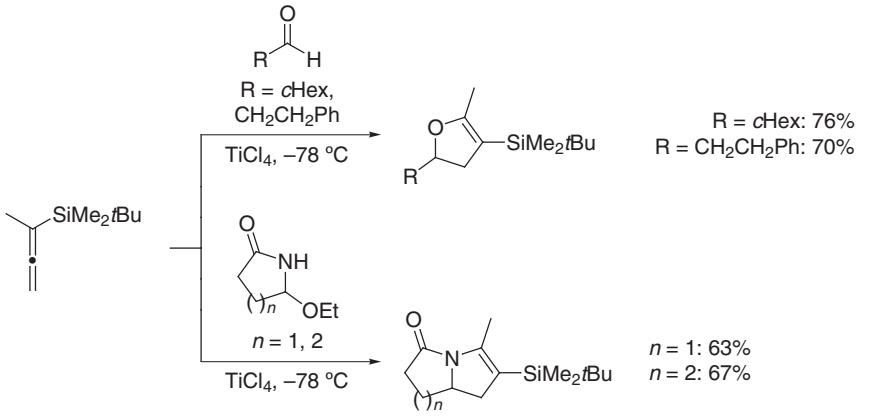
53% (12.187)

The reaction of allenylsilanes with α,β-unsaturated acylsilanes presents a new [3 + 3]-cycloaddition approach to a six-membered carbocycle [189]. Lewis acid-promoted ring expansion of the [3 + 2]-annulation product **260** is followed by a second cationic 1,2-silyl migration to produce the cyclohexenone **261** after desilylation.



260 **261** 56% (12.188)

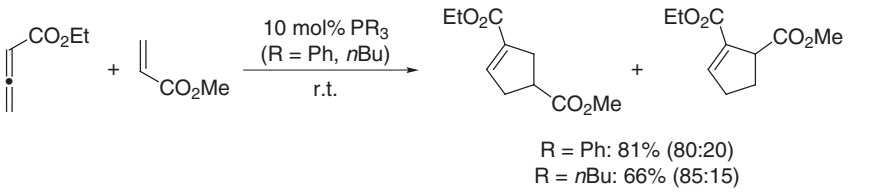
A (*tert*-butyldimethylsilyl)allene reacted with aldehydes and *N*-acylimine in the presence of $TiCl_4$ to afford the five-membered heterocycles [190].



(12.189)

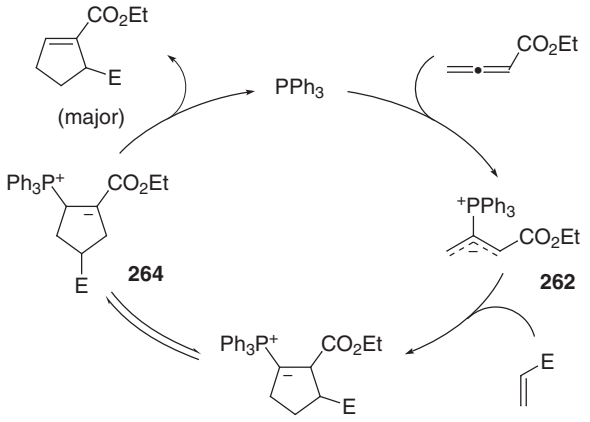
12.6.4
Phosphine-Catalyzed Cycloaddition of Allenes

In the presence of a catalytic amount of phosphine, the reaction of ethyl 2,3-butadienoate with methyl acrylate took place at room temperature to afford a regioisomeric mixture of the [3 + 2]-cycloadducts in good yield [191].



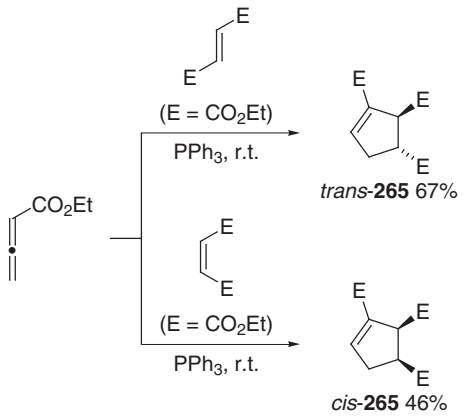
(12.190)

As shown in Scheme 12.1, reaction of the phosphine with an allenic ester gives all-carbon 1,3-dipole **262**. This dipolar intermediate reacts at the α-position to form the cyclic intermediate **263**, which is in equilibrium with **264** via hydrogen shift. Finally, the reaction affords the cycloadduct along with the regeneration of PPh_3 as the catalytically active species.



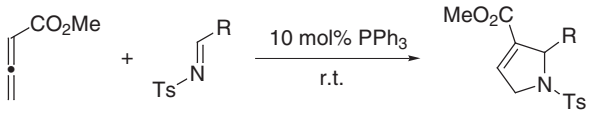
Scheme 12.1

Diethyl fumarate and diethyl maleate reacted with the allenic ester to yield *trans*- and *cis*-**265**, respectively, as the single product.



(12.191)

N-Tosylimines also afforded the [3 + 2]-cycloaddition products [192].

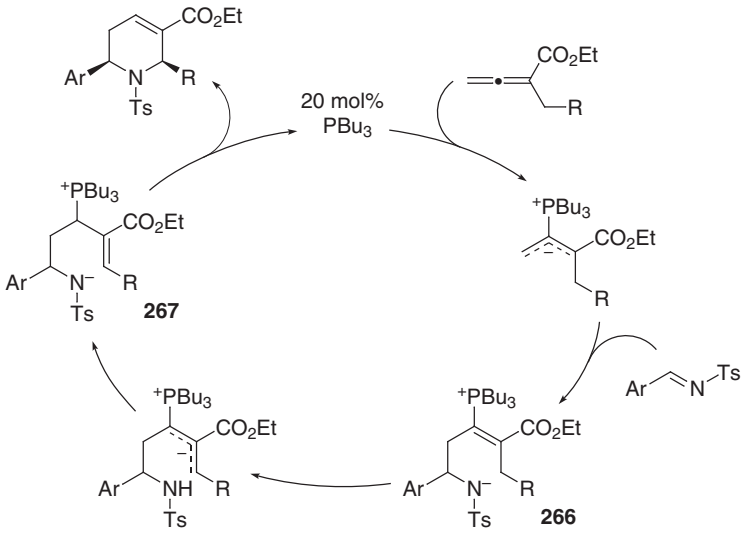


R	
Ph	98%
*o*MeOC$_6$H$_4$	96%
cinnamyl	53%

(12.192)

When the allenic esters bear α-substituents, the hydrogen shift occurred with intermediate **266**. The resultant intermediate **267** undergoes a 6-*endo* cyclization followed by expulsion of PBu_3 to generate tetrahydropyridine (Table 12.11) [193].

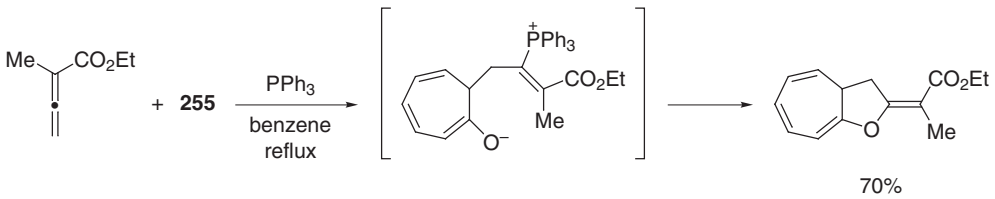
Table 12.11 Cyclization of intermediate **267.**



(12.193)

Ar	R	Yield (%)	*dr*
Ph	H	98	–
2-Furyl	H	97	–
Ph	3-$MeOC_6H_4$	99	98:2

An allenic ester–tropone annulation is also catalyzed by a phosphine in refluxing benzene, providing a single stereoisomer in good yield [194].

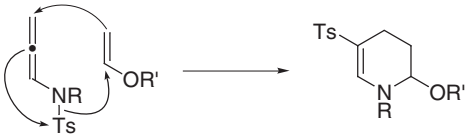


(12.194)

12.6.5

[4 + 2]-Cycloaddition of *N*-Allenylsulfonamides Involving a 1,3-Sulfonyl Shift

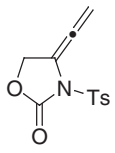
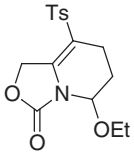
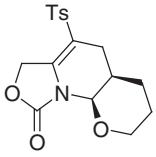
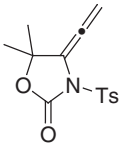
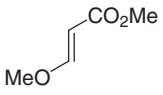
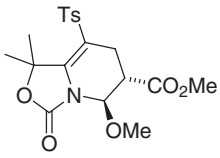
Electron-rich alkenes like an enol ether react with *N*-allenylsulfonamides to assist a 1,3-shift of the sulfonyl group, eventually furnishing formal [4 + 2]-cycloaddition products, tetrahydropyridine derivatives. The sulfonyl group migrates from the nitrogen to the central allenyl carbon atom [25b, 195]



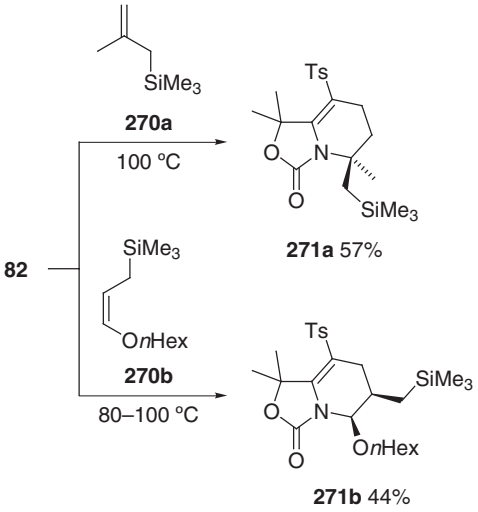
(12.195)

Enol ethers **268a–c** reacted with *N*-tosyl-4-vinylidene-1,3-oxazolidin-2-ones to give bicyclic tetrahydropyridine derivatives **269a–c** (Table 12.12). Methyl β-methoxyacrylate afforded **269c** without formation of the [2 + 2] adduct.

Table 12.12 Reactions of enol ethers **268**.

Sulfonamide	Nucleophile 268	Temperature (°C)	Product 269	Yield (%)
 (**26**)	 (**268a**)	100	 (**269a**)	92
	 (**268b**)	80	 (**269b**)	89
 (**82**)	 (**268c**)	70	 (**269c**)	72

Allylsilanes also serve as a two-carbon component for the analogous formal [4 + 2]-cycloaddition to provide tetrahydropyridines [188]. The reaction of **270b** with **82** provided **271b**, indicating that the enol ether moiety rather than the allylsilane moiety determines the orientation of the cycloaddition reaction.



(12.197)

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13
Cyclizations of Allenes

Marcus A. Tius

13.1
Introduction

Most, perhaps all, of the reactions that simple alkenes undergo are also available to allenes. By virtue of their strain and of the small steric requirement of the sp-hybridized carbon atom, the reactions of allenes usually take place more easily than the corresponding reactions of olefins. Because the allenes can also be chiral, they offer opportunities for control of the reaction products that are not available to simple alkenes. Finally, some reaction pathways are unique to allenes. For example, deprotonation of allenes with alkyllithium reagents to form allenyl anions is a facile process that has no counterpart in simple alkenes. These concepts will be illustrated by the discussion of cyclization reactions of allenes that follows.

13.2
Nazarov and Related Reactions

Allenyl ethers are easily prepared by isomerizing the corresponding propargyl ethers with potassium *tert*-butoxide according to Brandsma's protocol [1]. The allenyl ethers are acidic and can be deprotonated with strong base, so as to produce allenyllithium species, such as **1** (Eq. 13.1). The allenyllithiums are excellent nucleophiles and their addition to ketones proceeds smoothly. For example, addition of **1** to 3-methyl–3-buten–2-one **2** leads to tertiary alcohol **3** in 88% yield [2]. Exposure of **3** to an excess of trifluoroacetic anhydride and 2,6-lutidine at –20 °C leads to methylenomycin B **5** in 74% yield. As is the case for the conventional Nazarov cyclization, the reaction presumably takes place through the pentadienyl carbocation that results from ionization of the tertiary, bis-allylic alcohol group in **3** [3]. A conrotatory electrocyclization follows, which generates **4**. Loss of methoxymethyl cation from **4** leads to the observed product.

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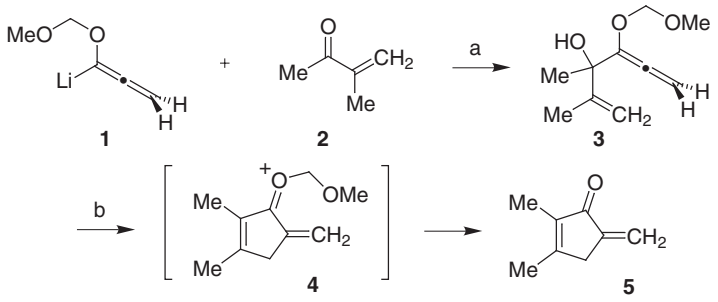
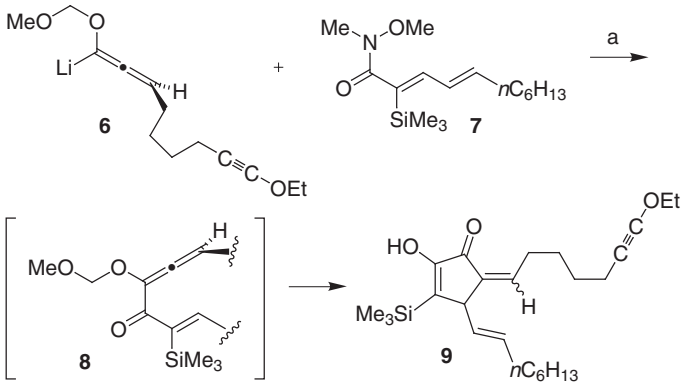


(13.1)

(a) 4 equiv. **1**, THF, Et_2O, –78 °C; 88%;
(b) 3 equiv. TFAA, 5 equiv. 2,6-lutidine, CH_2Cl_2, –20 °C; 74%

The addition of allenyl ether-derived anions to Weinreb [4] or to morpholino amides [5] follows a slightly different pathway (Eq. 13.2). For example, the addition of lithioallene **6** to Weinreb amide **7** at –78 °C, followed by quenching the reaction with aqueous NaH_2PO_4 and allowing the mixture to warm to room temperature leads to cyclopentenone **9** in 80% yield [6]. The presumed intermediate of this reaction, allenyl vinyl ketone **8**, was not isolated, as it underwent cyclization to **9** spontaneously [7]. These are exceptionally mild conditions for a Nazarov reaction and are probably a reflection of the strain that is present in the allene function, and also the low barrier for approach of the sp and sp^2 carbon atoms. What is also noteworthy is the marked kinetic preference for the formation of the *Z*-isomer of the exocyclic double bond in **9**. Had the Nazarov cyclization of **8** been conducted with catalysis by strong acid, it is unlikely that the kinetic product would have been observed.

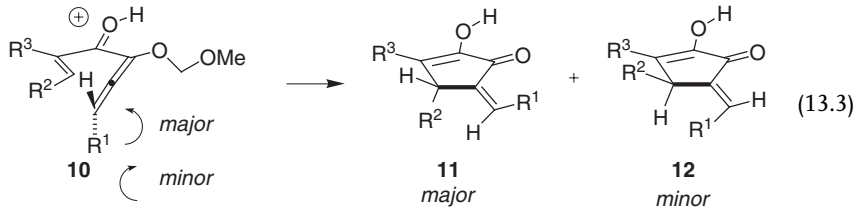


(13.2)

(a) THF, Et_2O, –78 °C; (b) aq. NaH_2PO_4; 80%

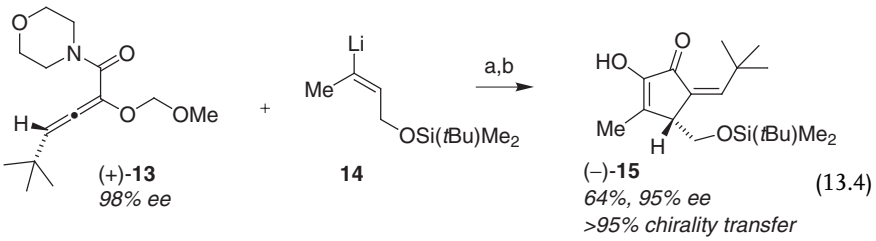
The origin of this preference is illustrated by Eq. 13.3. When the allene is terminally substituted, as it is in **6**, it is axially chiral. Consequently, there are two reaction pathways that the allenyl vinyl ketone (**10** in Eq. 13.3) can follow. The major reaction pathway for **10** involves counterclockwise conrotation, leading to **11**, whereas the

minor pathway involves clockwise conrotation leading to **12**. The major pathway is the one in which the steric bulk of R^1 moves away from R^2 [8]. Cyclopentenones **11** and **12** are diastereomeric and differ in the geometry of the exocyclic double bond and also in the stereochemistry of the sp^3-hybridized ring carbon atom. This latter observation suggests that if the allene function in **10** is non-racemic, one should be able to transfer the axial chirality of the allene to tetrahedral chirality of the ring carbon atom. Thus, groups with a larger steric demand, either R^1 or R^2, should lead to greater levels of asymmetry transfer. This has been shown to be the case.



(13.3)

Allenamide (±)-**13** was prepared by trapping the corresponding lithioallene with carbon dioxide, followed by conversion of the carboxylate to the amide. Chromatographic resolution of the enantiomers of **13** was easily accomplished on a 10 × 250 mm Chiralcel OD HPLC column. Addition of vinyllithium **14** to (+)-**13**, followed by quenching the reaction with aqueous NaH_2PO_4, led to cyclopentenone (–)-**15** in 64% yield with >95% chirality transfer (Eq. 13.4). The absolute stereochemistry of (–)-**5** is consistent with the mechanistic hypothesis put forth in Eq. 13.3 [8].

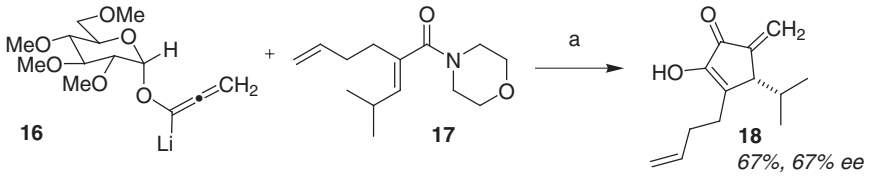


(13.4)

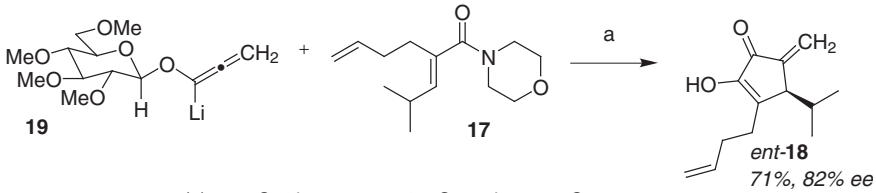
(a) THF, –78 °C, 30 min; (b) aq. NaH_2PO_4; 64%, 95% *ee*

Cyclizations that lead to cyclopentenones that are not substituted at the exocyclic carbon atom proceed through the intermediacy of non-stereogenic allenes (cf. **10**, $R^3 = H$); therefore, alternative means to control the absolute stereochemical course of the cyclization must be found. An obvious approach is to incorporate a chiral auxiliary in the allene. It should be pointed out at this juncture that there is a restriction on the structure of the allene substituent, namely that the group must be part of an acetal. There are apparently two reasons for this. First, the group must be able to depart from the cationic cyclic intermediate (cf. **4**, Eq. 13.1) as a stable cation. This cleavage step must take place rapidly, otherwise the cation can undergo undesired rearrangements. Second, the acetal oxygen atom may play a role in stabilizing the

transition state for the cyclization. The first chiral auxiliary that was chosen was derived from permethylated α-D-glucose (**16**, Eq. 13.5) [9]. Chiral auxiliaries are only useful if both enantiomeric forms are available. They must also be reasonably cheap. Auxiliary **16** would seem to be a poor choice, since L-glucose is neither readily available nor cheap. As will be seen, however, *both* enantiomeric forms of the cyclopentenones are available from D-glucose-derived auxiliaries. When lithioallene **16** was combined with morpholinoenamide **17**, cyclopentenone **18** was isolated in 67% yield and in 67% *ee* (Eq. 13.5). Lithioallene **19**, which differs from **16** only in the stereochemistry of the anomeric carbon atom, combines with enamide **17** to give *ent*-**18** in 71% yield and in 82% *ee* (Eq. 13.6). Therefore, both enantiomeric forms of the cyclopentenones are available from cheap D-glucose-derived auxiliaries.



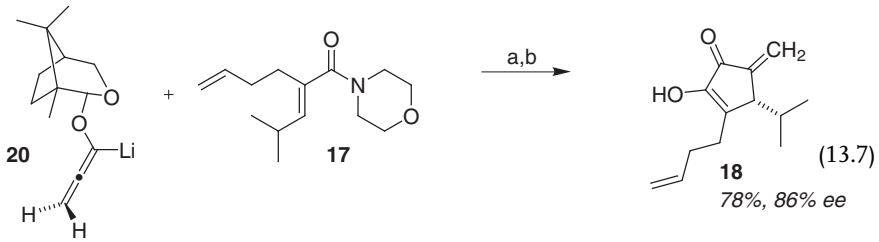
(a) –78 °C, 1 h; HCl, EtOH, –78 °C; 67%, 67% *ee* (13.5)



(a) –78 °C, 1 h; warm to –40 °C; cool to –78 °C;
HCl, 1,1,1,3,3,3-hexafluoro-2-propanol, 0 °C; 71%, 82% *ee* (13.6)

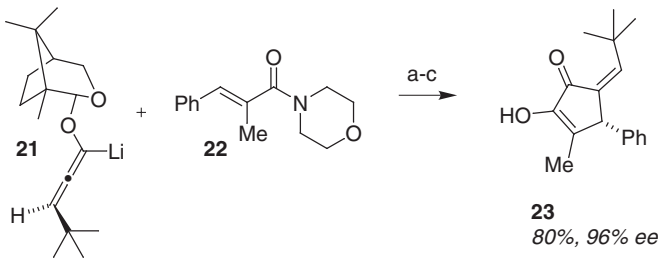
There are some problems associated with the use of sugar-derived auxiliaries **16** and **18**. The nucleophilicity is much lower than for **1**, possibly because of the presence of multiple ether functions that can complex lithium ion. It was necessary to include 4 equiv. of LiCl in the addition reactions of **16** and **19** to enamides, otherwise yields were low. A more serious problem associated with **16** is the erosion of the *ee* of products that was observed when the reactions were scaled up from 0.2 to 4 mmol. Fortunately, a chiral auxiliary that is prepared from camphor does not have these shortcomings [10].

Auxiliary **20** was prepared in four steps. Addition of **17**, followed by cyclization in situ as before, led to cyclopentenone **18** in 78% yield and 86% *ee* (Eq. 13.7). Unlike the sugar-derived auxiliaries, the reactions of **20** scaled up without any erosion of the *ee* of the products.



(13.7)

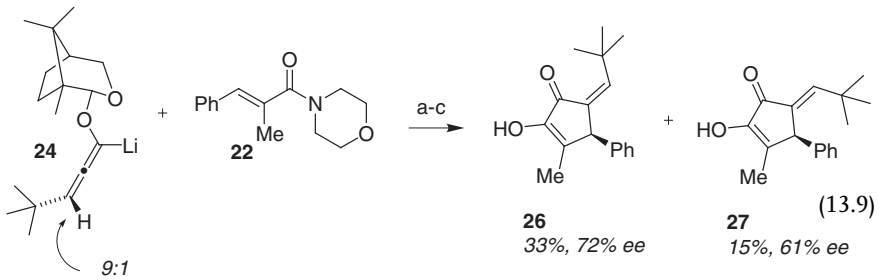
(a) –78 to –30 °C, 1 h; (b) HCl, 1,1,1,3,3,3-hexafluoro-2-propan-ol–trifluoroethanol (1:1), –78 °C; 78%, 86% *ee*



(13.8)

(a) *n*BuLi, THF, –78 °C; (b) add **22**; –20 °C; –78 °C;
(c) HCl, 1,1,1,3,3,3-hexafluoro-2-propanol–trifluoroethanol (11), –78 °C; 80%, 96% *ee*

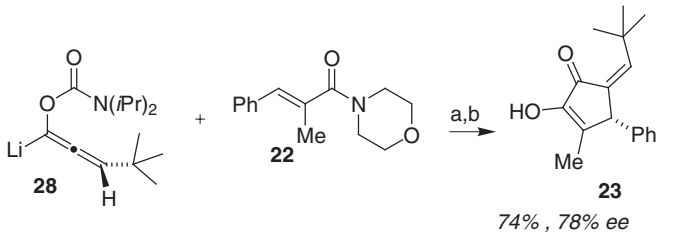
A question that arises is whether enhanced levels of asymmetry transfer during the Nazarov cyclization might be observed from axially chiral allenes bearing the camphor-derived auxiliary (Eq. 13.8). Accordingly, *tert*-butylallenyllithium species **21** was prepared and was allowed to react with enamide **22** [11]. Cyclization led to cyclopentenone **23** in 80% yield and 96% *ee*. The high level of asymmetry transfer is a consequence of the matching of the chirality of the auxiliary with the axial chirality of the allene. Note also that the product is isolated as the *Z*-isomer of the exocyclic double bond. This reflects the large preference for rotation of the bulky *tert*-butyl group away from the phenyl (cf. Eq. 13.3). It is clear that the axial chirality of the allene in **21** exerts the dominant effect on the stereochemistry of the product, as the mismatched case proves (Eq. 13.9).



(13.9)

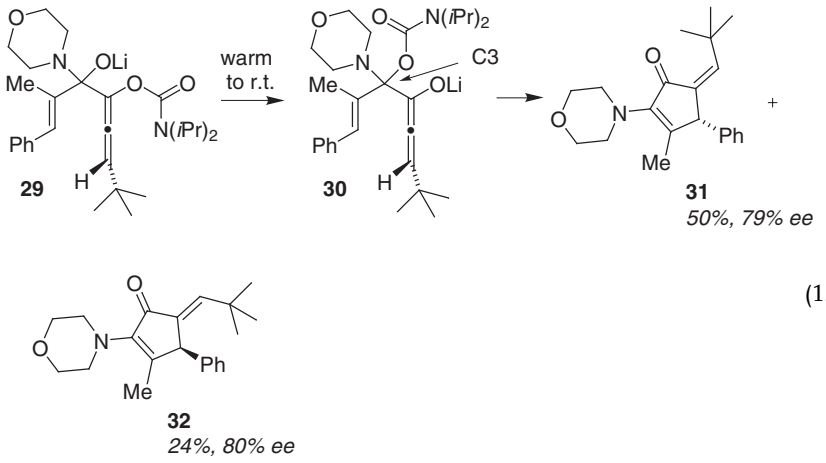
(a) *n*BuLi, THF, –78 °C; (b) add **22**; –20 °C; –78 °C; (c) HCl, 1,1,1,3,3,3-hexafluoro-2-propanol-trifluoroethanol (1:1), –78 °C; **26** 33%, 72% *ee*; **27** 15%, 61% *ee*

Lithioallene **24** differs from **21** only in the sense of the axial chirality of the allene. When combined with enamide **22**, two products are formed, cyclopentenones **26** and **27**, which have the *opposite* stereochemistry at the ring carbon as **23** [11]. Significantly, the enantiomeric excess of both products is lower than for **23**. This shows that the effect of the auxiliary on the absolute stereochemistry of the products is overwhelmed by the effect of the *tert*-butyl group. This is also evident from the work of Hoppe and co-workers, who used sparteine-mediated enantioselective deprotonation to prepare lithioallene **28** (Eq. 13.10) [12]. When combined with enamide **22**, cyclopentenone **23** was formed in 74% yield with 98% chirality transfer. In this case, the enantioselectivity of the reaction is due solely to the presence of the *tert*-butyl group. The mechanistic complexity inherent in this system can be appreciated by considering the results of Eq. 13.11. When adduct **29**, from the reaction of **22** and **28**, is allowed first to warm to room temperature for 1 h and is then treated with 2 M HCl, the two morpholinocyclopentenones **31** and **32** were isolated rather than hydroxycyclopentenone **23**. Apparently, intramolecular migration of the diisopropylcarbamoyl group takes place at room temperature to give **30** as a mixture of diastereomers. What is surprising is that the stereochemical course of the cyclization of Eq. 13.11 is determined by the stereochemistry at C3 (see **30**), rather than the axial chirality of the allene: **31** and **32** have *opposite* absolute stereochemistry at the sp^3 carbon atom of the ring.



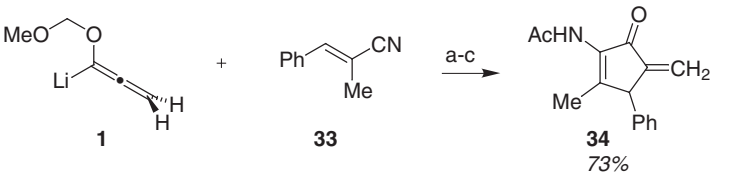
(13.10)

(a) PhMe, 2.5 h, –78 °C; (b) transfer rapidly to 5% HCl in EtOH; 74%, 78% *ee*



(13.11)

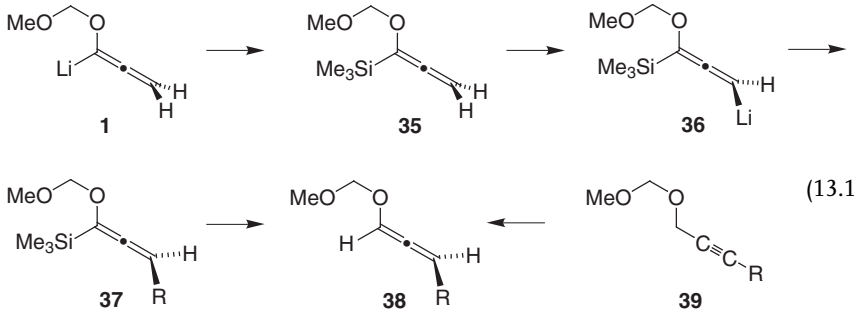
There is another approach that can be used to prepare α-aminocyclopentenones from the cyclopentannelation reaction. Addition of allenyllithium **1** to (*E*)-α-methylcinnamonitrile **33**, followed by quenching of the reaction with saturated aqueous $(NH_4)H_2PO_4$, led to the α-aminocyclopentenone (Eq. 13.12) [13]. Since the products of this reaction have a tendency to polymerize through Michael addition of the amino group of one molecule to the exocyclic methylene group of another, **34** was isolated as the acetamide derivative in 73% overall yield from **33**. The reaction is general and is noteworthy because it represents an imino-Nazarov reaction. Calculations by Smith and Ulmer [14] have shown that the classical imino-Nazarov reaction is disfavored energetically, because the acyclic divinylimminium ion is more stable than the cyclic 2-aminoallyl carbocation. The amino group is able to stabilize the acyclic cation by electron pair donation, but cannot do so in the cyclic product. In the case of Eq. 13.12, the reaction presumably succeeds so well because the unfavorable equilibrium for ring closure can be overcome by irreversible loss of methoxymethyl cation from the cyclic intermediate (cf. **4**, Eq. 13.1). Relief of strain associated with loss of the allene function during the cyclization also helps this reaction.



(13.12)

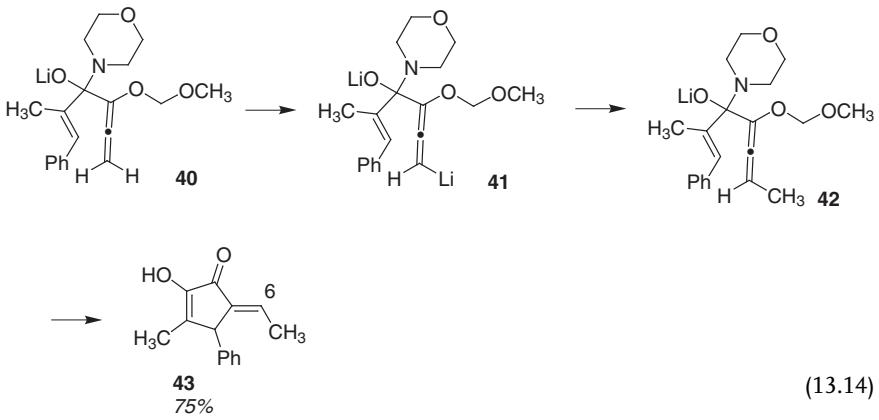
(a) THF, –78 °C; (b) aq. $(NH_4)H_2PO_4$; (c) EtOAc, pyr, DMAP (cat.), Ac_2O; 73%

Although the preparation of the substituted allene ether substrates for the Nazarov reaction is not the topic of this chapter, it is necessary to mention a few aspects of their synthesis. Lithioallene **1** (Eq. 13.13) can be trapped with chlorotrimethylsilane to give **35** [6]. Exposure of **35** to *sec*- or *tert*-butyllithium leads to allenyllithium **36**, which can be trapped with alkyl halides or other electrophiles to give **37**. Desilylation of **37** leads to **38**. This is somewhat laborious, but it leads to allene **38** uncontaminated by propargyl ether **39**. Exposure of **39** to *n*-butyllithium, followed by quenching with acid, typically produces mixtures of **38** and **39** that are difficult to separate. Fortunately, one need not prepare allenes **38** in order to access the C6-sub-

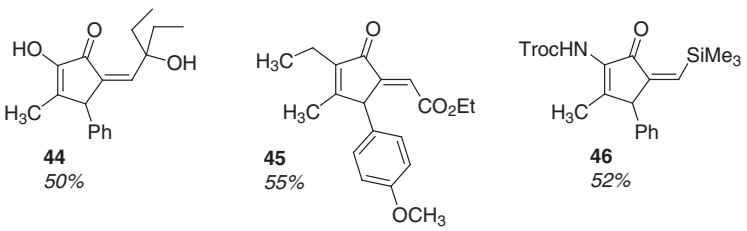


(13.13)

stituted cyclopentenones. By exploiting the acidity of allenyl protons, it is possible to deprotonate **40**, the intermediate that one obtains from the addition of **1** to **22**, thereby converting it to **41** (Eq. 13.14). Trapping of **41** with iodomethane leads to **42**, which is cyclized to **43** in the presence of aqueous HCl in 75% overall yield from **22** [15]. This represents a significant simplification of the original method. Moreover, the approach of Eq. 13.14 provides access to cyclopentenones that cannot be prepared directly. For example, trapping **41** with 3-pentanone, followed by cyclization, produces **44** in 50% yield. Cyclopentenones **45** and **46** are prepared by trapping the appropriate lithioallenes with ethyl cyanoformate and trimethylchlorosilane, respectively. In these cases (**43**–**46**), the geometry of the exocyclic double bond depends on the conditions for cyclization. Longer contact times or stronger acids generally result in isomerization of the kinetic *Z*-products to the thermodynamically favored *E*-isomers. Significantly, the method of Eq. 13.14 is also successful in the asymmetric series. For example, camphor-derived allenyllithium **20** (Eq. 13.7) can be combined with enamide **22**, deprotonated, methylated and cyclized, to provide (*R*)-**43** in 70–75% yield and in 78% *ee*.

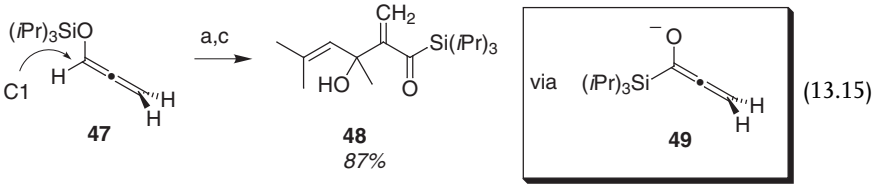


(13.14)



The alkyl allenyl ethers whose chemistry has been discussed are readily prepared and are useful for the synthesis of diverse cyclopentenones, as racemates or in enantiomerically enriched form. It is worth noting that *silyl* allenyl ethers allow entry into a distinct mechanistic manifold [16]. Triisopropylsilyloxyallene **47** can be deprotonat-

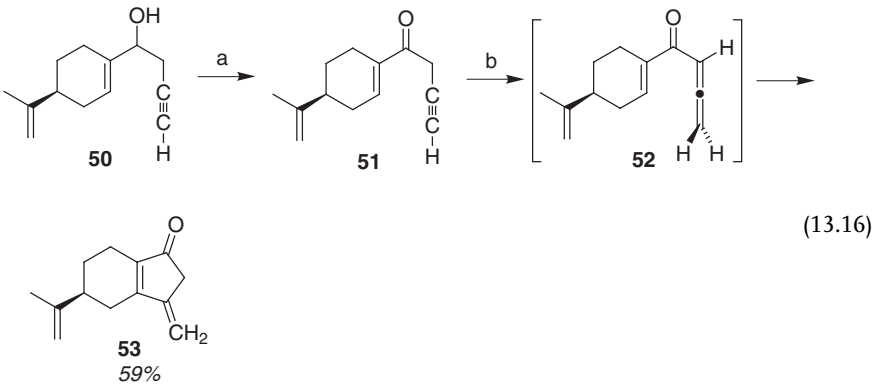
ed with *tert*-butyllithium (Eq. 13.15). Transmetallation from lithium to magnesium, followed by addition of mesityl oxide, leads to α,β-unsaturated acylsilane **48** in 87% yield [17]. The putative mechanism for this process is by initial deprotonation at C1 of **47**, followed by a reverse Brook rearrangement leading to allenolate **49**. The rearrangement is probably a bimolecular process. Addition of **49** to ketones or aldehydes leads to acylsilanes in good yield.



(13.15)

(a) *t*BuLi, THF, –78 °C; (b) $MgBr_2$; (c) mesityl oxide; 87%

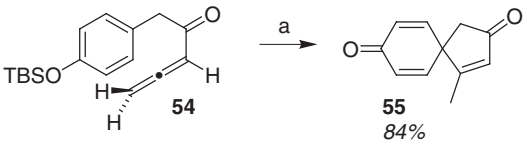
A very unusual Nazarov cyclization of propargyl vinyl ketones has been reported by Hashmi et al. (Eq. 13.16) [18]. Propargyl alcohol **50** was oxidized to ketone **51** with the Dess–Martin periodinane. Attempts to purify **51** by column chromatography on silica gel led to cyclopentenone **53** in 59% isolated yield. This suggests that the solid support catalyzed the isomerization of **51** to allenyl vinyl ketone **52**, which was not isolated, but which underwent spontaneous cyclization to **53**. This result is consistent with earlier observations of the great ease with which allenyl vinyl ketones undergo the Nazarov reaction (cf. **8**, Eq. 13.2).



(13.16)

(a) Dess–Martin periodonane; (b) SiO_2 column chromatography; 59%

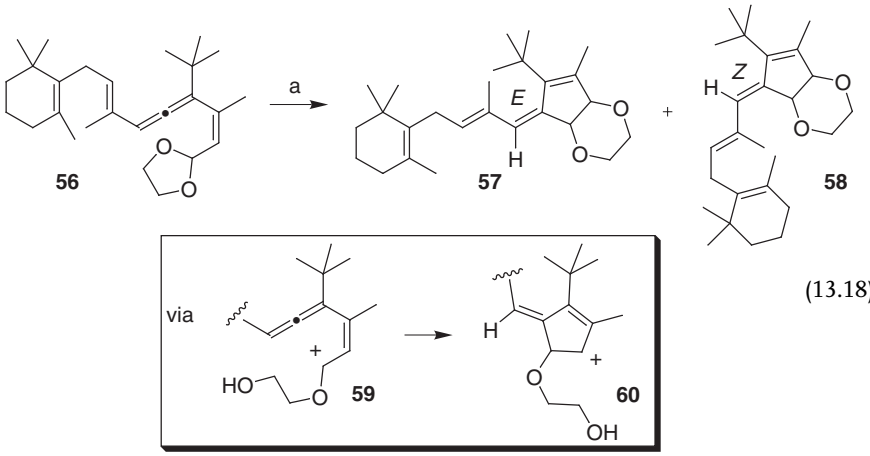
The reactivity of allenyl ketones is also manifested in the Hg(II)-catalyzed *ipso* substitution that converts **54** to spirodione **55** (Eq. 13.17) [19]. The reaction presumably involves activation of the allene by Hg(II), followed by intramolecular electrophilic attack on the aromatic ring. Hydrolytic cleavage of the metal from the intermediate product of the reaction, followed by rearrangement leads to the observed spirocyclic dione.



(13.17)

(a) 1% $Hg(ClO_4)_2$, MeCN, H_2O (2 equiv.); 84%

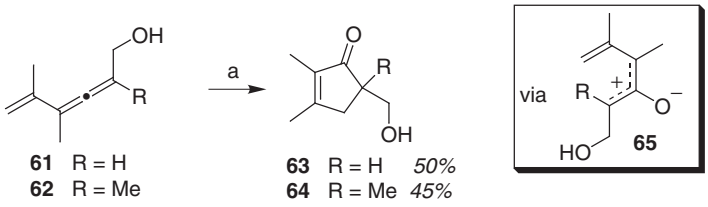
An alternative approach for generating the pentadienyl carbocation that is needed for the Nazarov cyclization has been demonstrated by de Lera and co-workers [20, 21] (Eq. 13.18). Vinylallene acetal **56** is converted to a ca 1:1 mixture of cyclopentenes **57** and **58** upon exposure to toluenesulfonic acid in acetone at room temperature. The reaction presumably involves initial generation of carbocation **59** that undergoes conrotation to give **60**. Intramolecular trapping of the carbocation by the pendant hydroxyl group leads to the observed product. Depending on whether the conrotation in **59** takes place clockwise or counterclockwise, *E*- (**57**) or *Z*-(**58**) products are formed.



(13.18)

(a) TsOH, acetone, 25 °C.

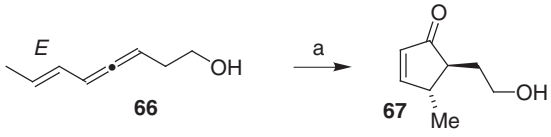
Vinylallenes can also be cyclized oxidatively. Vinylallene **61** when treated with vanadyl acetonacetonate and *tert*-butyl hydroperoxide in benzene produced cyclopentenone **63**, the immediate precursor of methylenomycin B (cf. **5**, Eq. 13.1), in 50%



(13.19)

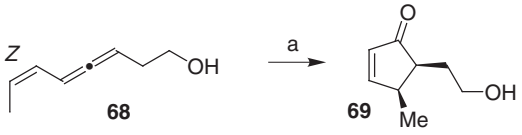
(a) *t*BuOOH, PhH, $VO(acac)_2$, 1–3 h, 20–50 °C; **63**, 50%; **64** 45%

yield [22]. Similar treatment of **62** led to cyclopentenone **64** (45% yield). Although the mechanism for the cyclization is not exactly the same as for the Nazarov reaction, the two are conceptually related. In the present instance, hydroxyl group-directed epoxidation of the allene produces an allene oxide that rearranges to zwitterion **65** [23] and cyclizes to the cyclopentenone products. One of the reasons for the interest in the mechanism stems from the fact that it is the presumed key step in the biosynthesis of the clavulones, a family of unusual cross-conjugated cyclopentenone marine natural products [24]. Epoxidation of either alkene unit of the allene leads to the same zwitterion **65**. It is likely that the mechanism is either concerted or at least fast and stepwise, because the stereochemistry of the alkene portion of the vinylallene is preserved in the product. For example, vanadyl acetonacetonate-catalyzed epoxidation of (*E*)-vinylallene **66** leads exclusively to *trans*-cyclopentenone **67** (Eq. 13.20), whereas (*Z*)-vinylallene **68** gives *cis*-cyclopentenone **69** (Eq. 13.21) [25]. These reactions are reported to take place in 40–70% yield and are initiated by hydroxyl-directed epoxidation of the allene in the first step.



66 **67** (13.20)

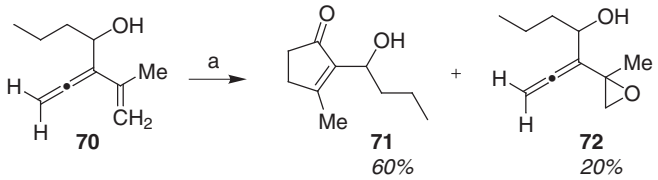
(a) *t*BuOOH, CH_2Cl_2, $VO(acac)_2$, r.t.



68 **69** (13.21)

(a) *t*BuOOH, CH_2Cl_2, $VO(acac)_2$, r.t.

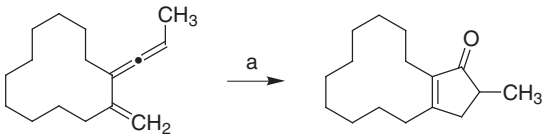
A hydroxyalkyl substituent on the internal carbon atom of the allene can also be used to direct the epoxidation reaction (Eq. 13.22) [26]. In the case of vinylallene **70**, hydroxyl-directed epoxidation, followed by cyclization of the allene oxide, leads to cyclopentenone **71** in 60% yield, along with 20% of epoxide **72**. The greater reactivity of the allene ensures that the epoxidation step will be selective; however, in this case the selectivity is not complete.



70 **71** *60%* **72** *20%* (13.22)

(a) *t*BuOOH, CH_2Cl_2, $VO(acac)_2$; **71** 60%; **72** 20%

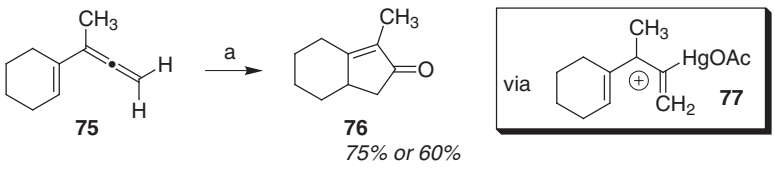
The oxidative cyclization of vinylallenes need not be directed by a pendant hydroxyl group in order to succeed. The higher reactivity of the allene compared with the exocyclic methylene group in **73** (Eq. 13.23) with monoperphthalic acid leads primarily to the allene oxide which rearranges to cyclopentenone **74** [27]. Inevitably some epoxidation of the alkene also takes place during the reaction. When *m*-CPBA is used as the oxidant, another side reaction is associated with *m*-chlorobenzoic acid-mediated decomposition of the intermediate epoxide. It is possible to overcome this problem by performing the epoxidation in dichloromethane in a two-phase system with aqueous bicarbonate so as to buffer the acid [28].



73 **74** (13.23)

(a) monoperphthalic acid, CH_2Cl_2–Et_2O (60:40)

Mercuric acetate and thallic acetate have also been used for the oxidative cyclization of vinylallenes (Eq. 13.24) [29]. Exposure of vinylallene **75** to stoichiometric mercuric acetate in acetic acid led to cyclopentenone **76** in 75% yield. With thallium acetate as the oxidant, the yield of **76** was 60%. The presumed mechanism of the oxidative cyclization involves a Nazarov cyclization of acetoxymercury intermediate **77**.

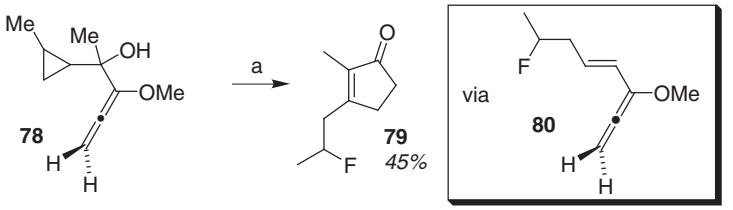


75 **76** *75% or 60%* (13.24)

(a) 1 equiv. $Hg(OAc)_2$, HOAc, 30 min at r.t., cat. $HClO_4$; 1 h at 70 °C or 1.1 equiv. $Tl(OAc)_3$, HOAc, cat. conc. HCl, 40 °C; 75 or 60%

An unusual type of Nazarov cyclization that apparently proceeds through the intermediacy of a vinyl *methoxy*allene is shown in Eq. 13.25 [30]. Exposure of allenyl alcohol **78** to HF–pyridine in the presence of sodium fluoride leads to fluorinated cyclopentenone **79** in 45% yield. It is reasonable to postulate acid-catalyzed ionization of the tertiary cyclopropylmethyl carbinol function in **78**, followed by nucleophilic ring-opening of the cyclopropane ring by fluoride, leading to vinyl allene **80**. Sodium fluoride was necessary for the success of the reaction by providing a nucleophilic source of fluoride. The cyclopropane C–C bond is apparently partially broken in the transition state leading to **80**, since attack by fluoride takes place preferentially at the more highly substituted ring carbon atom. Conversion of **80** to **79** requires

transfer of a proton from the reaction medium to the sp-hybridized allene carbon atom, thereby generating the pentadienyl carbocation that undergoes the Nazarov cyclization. The retrosynthetic recognition of the sequential rearrangements leading backwards from **79** to **78** is challenging.

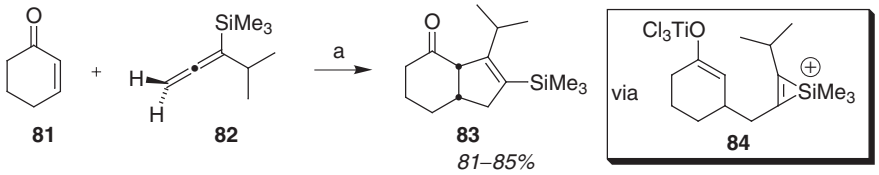


(13.25)

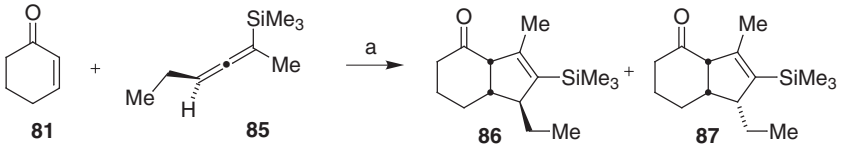
(a) CH_2Cl_2, 0 °C, NaF, $(HF)_n$·pyr; 45%

13.3
Annulations Making Use of Trialkylsilyl Allenes (Danheiser Reactions)

A fundamentally different type of ring-forming reaction takes place between α,β-unsaturated ketones and trialkylsilylallenes, under the influence of strong Lewis acid (Eq. 13.26) [31]. Exposure of a mixture of cyclohexenone **81** and allene **82** to $TiCl_4$ leads to hydroindanone **83** in excellent yield. The reaction is very general; however, it fails for β-substituted endocyclic enones. Activation of the enone by the Lewis acid is followed by Michael addition of the unsubstituted carbon atom of the allene with formation of a vinyl carbocation that is stabilized by the β-trialkylsilyl group. Rearrangement to silacyclopropenium ion **84** is followed by intramolecular nucleophilic attack by the titanium enolate, leading to **83**. During this process the trialkylsilyl group migrates to the central carbon atom of the allene. Both the trialkylsilyl group and the strain inherent to the allene function presumably contribute to overcoming what would otherwise be unfavorable energetics for the formation of a vinyl cation. In the case of 1,3-dialkyl-1-trialkylsilylallenes (**85**, Eq. 13.27) the annulation proceeds in excellent yield and diastereoselectivity [31].



(a) 1.5 equiv. $TiCl_4$, CH_2Cl_2, –78 °C, 1 h; 81–85% (13.26)



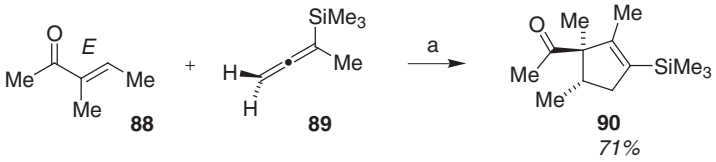
81 85 86 87

95:5, 79%

(13.27)

(a) 1.5 equiv. $TiCl_4$, CH_2Cl_2, –78 °C, 1 h; 95:5, 79%

The annulation evidently proceeds much more rapidly than conformational interconversion of the intermediate cations. For example, the annulation of (*E*)-3-methyl-3-penten-2-one **88** with allene **89** leads to acetylcyclopentene **90** as the sole reaction product in 71% yield (Eq. 13.28) [32]. The stereochemical relationship of the two methyls is preserved in the product. When the reaction is repeated with (*Z*)-3-methyl-3-penten-2-one **91** (Eq. 13.29), acetylcyclopentene **92** is isolated as the major product, along with a small amount of **90** [32].

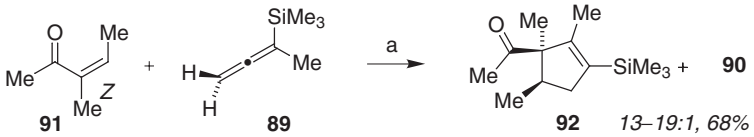


88 89 90

71%

(13.28)

(a) $TiCl_4$, CH_2Cl_2, –78 °C; 71%

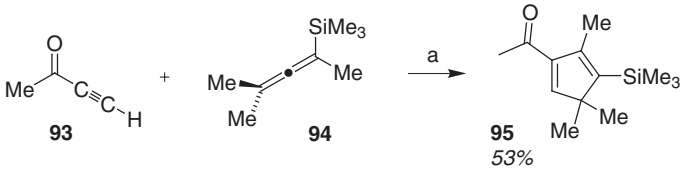


91 89 92 13–19:1, 68%

(13.29)

(a) $TiCl_4$, CH_2Cl_2, –78 °C; 13–19:1, 68%

Butynone **93** and tetrasubstituted allene **94** combine to form acetyl cyclopentadiene **95** (Eq. 13.30) [32]. The annulation does not proceed in satisfactory yield in the case of unsubstituted trimethylsilyl allene **96** (Eq. 13.31) [32]. This is presumably due to diminished stabilization of the cationic intermediates in the case of **96**, which allows competing reaction pathways to erode the yield.

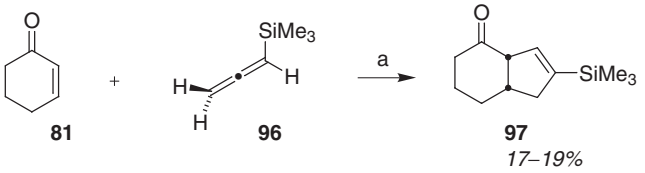


93 94 95

53%

(13.30)

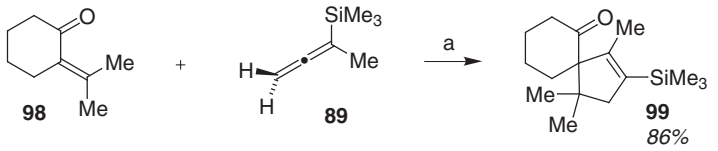
(a) $TiCl_4$, CH_2Cl_2, –78 °C; 53%



(13.31)

(a) $TiCl_4$, CH_2Cl_2, –78 °C; 17–19%

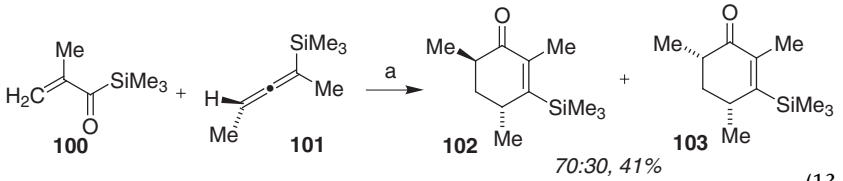
Whereas the annulation fails with most hindered enones, such as isophorone, the reaction of **89** with 2-isopropylidenecyclohexanone **98** takes place to provide spiro fused product **99** in 86% yield (Eq. 13.32) [33].



(13.32)

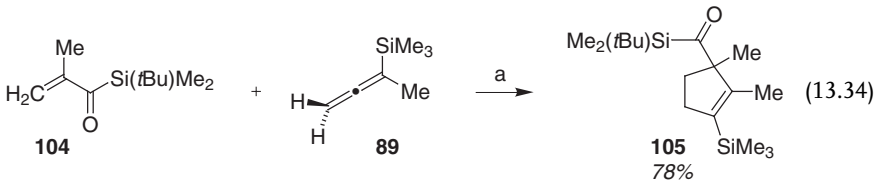
(a) $TiCl_4$, CH_2Cl_2, 25 °C; 86%

The annulation of trialkylsilyl allenes with α,β-unsaturated acylsilanes proceeds much faster than with ketones. It is also mechanistically more complex. The titanium tetrachloride-catalyzed annulation of acylsilane **100** with allene **101** (Eq. 13.33) takes place at 0 °C and leads to diastereomeric cyclohexenones **102** and **103** in 41% yield in a ratio of 70:30 [34]. This result should be contrasted with that summarized in Eq. 13.34. Acylsilane **104**, which differs from **100** only in one of the alkyl groups on the silicon atom, undergoes annulation with silylallene **89** to produce cyclopentenone **105** in 78% yield [34]. Cyclopentenes such as **105** that bear a non-hydrogen substituent at the carbon atom α to the acylsilane carbonyl undergo rearrangement to cyclo*hexenones* on treatment with $TiCl_4$ at temperatures above –78 °C. This suggests that the [3 + 2]-annulation products, the cyclopentenones, are formed kinetically and that they rearrange to the [3 + 3] products, which are thermodynamically favored. A plausible mechanism that rationalizes these results is summarized in Eq. 13.35. The intermediate of the $TiCl_4$-catalyzed Michael addition of allenylsilane **101** to acylsilane **100** is **106**. The 1,2-migration of TMS leads to ion **107** that is intercepted by the titanium enolate function to give **108**, the kinetic [3 + 2] product. This intermediate can rearrange by ring expansion to **109**. The greater migratory aptitude of the vinyl group ensures the specificity of this process.



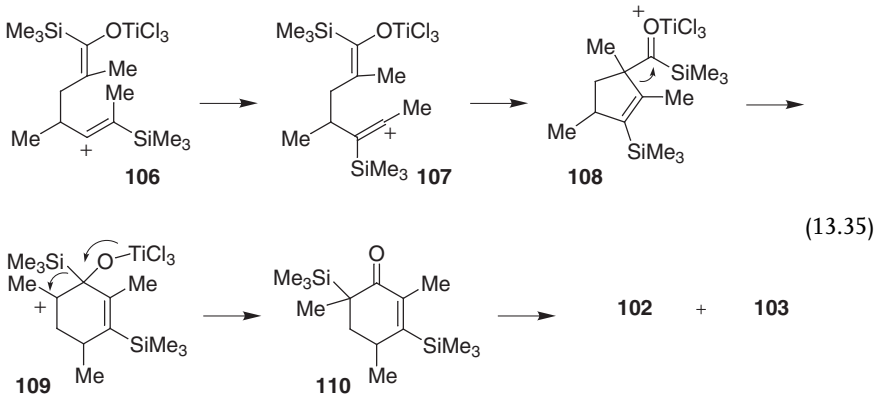
(13.33)

(a) $TiCl_4$, CH_2Cl_2, 0 °C, 1 h; 70:30, 41%

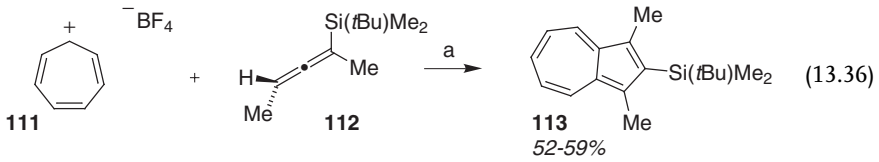


(a) $TiCl_4$, CH_2Cl_2, –78 °C; 78%

A second 1,2-migration of the TMS group in **109** leads to cyclohexenone **110**. Protiodesilylation during workup gives the final product as a mixture of diastereomers **102** and **103**. If the cyclopentene is the desired product, the ring expansion and rearrangement can be suppressed by keeping reaction times <2 min, not allowing the reaction temperature to warm more than –78 °C and by using *tert*-butyldimethylsilyl- rather than trimethylsilylacylsilanes [34].

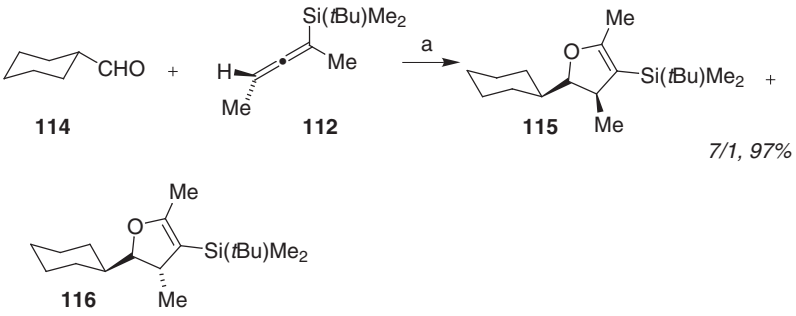


The allenylsilanes are excellent nucleophiles and they can react with a variety of electrophilic species in annulation processes that provide access to diverse products. Allenylsilane **112** (Eq. 13.36) reacts with tropylium fluoroborate **111** to provide azulene **113** [35]. The reaction is slow and it is necessary to use an acid scavenger so as to inhibit protiodesilylation by the fluoroboric acid that is generated during the course of the annulation. The excess tropylium salt abstracts a hydride from the reaction intermediate leading to the azulene. There are relatively few direct methods for the synthesis of azulenes.



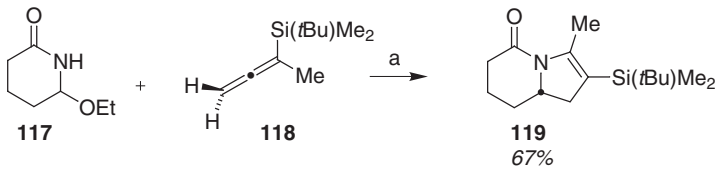
(a) 2 equiv. **111**, poly(4-vinylpyridine), MeCN, 25 °C, 24 h; 52–59%

Allenylsilanes can be used for a very wide variety of [3 + 2] annulations that lead to heterocyclic products. Silane **112** adds to cyclohexane carboxaldehyde **114** to give a mixture of diastereomeric dihydrofurans **115** and **116** in excellent yield (Eq. 13.37) [36]. The mechanism follows the same paradigm that has been discussed in the context of all the Danheiser reactions, namely Lewis acid-catalyzed addition of the allenylsilane to the carbonyl carbon atom of **114**, 1,2-silicon migration and ring closure. The reaction can be used to prepare pyrrolines (Eq. 13.38) [36]. The *N*-acyliminium ion that is formed by the reaction of **117** with $TiCl_4$ is trapped by allenylsilane **118** to give indolizidine **119**. By allowing the allenylsilane to react with acid halides, one can easily prepare tetrasubstituted furans (Eq. 13.39) [37]. In the presence of $AlCl_3$, 3-methylbut-2-enoyl chloride **120** is converted to a reactive electrophile that is trapped by allenylsilane **121**. 1,2-Silicon migration and proton loss from the reaction intermediate lead to furan **122** in 58% yield. The trialkylsilyl substituent offers opportunities for further functionalization. This represents one of the very best syntheses of polysubstituted furans extant.



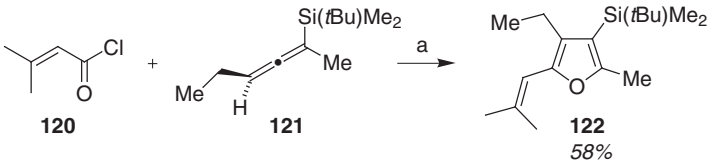
(13.37)

(a) $TiCl_4$, CH_2Cl_2, –78 °C; 7:1, 97%



(13.38)

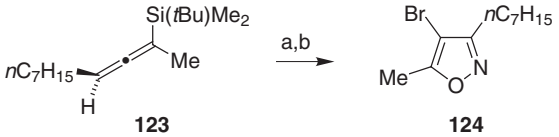
(a) $TiCl_4$, CH_2Cl_2, 0–25 °C; 67%



(13.39)

(a) $AlCl_3$, CH_2Cl_2, –20 °C, 2 h; quench with Et_3N, pentane; 58%

Nitronium fluoborate also reacts with silylallenes, as indicated in Eq. 13.40 [38]. Attack of the electrophile at the allene carbon atom distal to the silicon atom, 1,2-silicon migration and ring closure lead to a silyloxazole. Exposure of this material to bromine in a second step gives **124** in 72% overall yield from **123**. This annulation is best performed with *tert*-butyldimethylsilylallenes. With trimethylsilyl compounds, protodesilylation is a competing side reaction.



123 **124** *72%* (13.40)

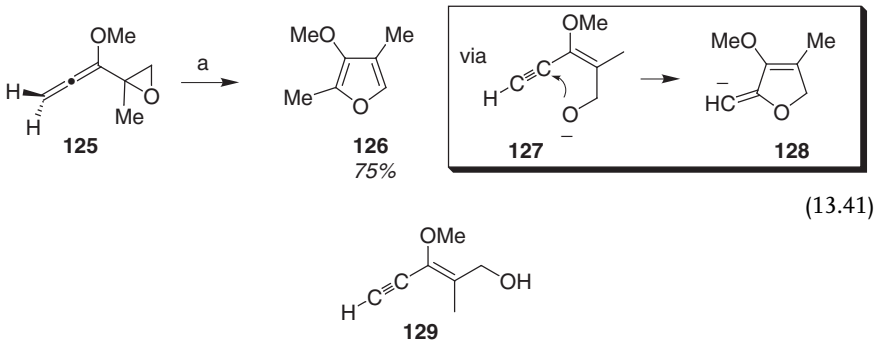
(a) $NOBF_4$, MeCN, –30–25 °C; (b) Br_2, CCl_4, 25 °C, 24 h; 72%

In summary, the Danheiser reactions are a family of [3 + 2] annulations that take place between allenylsilanes and diverse electrophiles. The products can be carbocycles or heterocycles. In all cases, the annulations proceed most efficiently when the allenylsilane has a non-hydrogen substituent on the carbon atom bearing the silicon. This is a consequence of the common mechanistic pathway that proceeds through a vinyl carbocation intermediate.

13.4
Allene Cyclizations Leading to Dihydrofurans, Furans, Pyrrolines and Pyrroles

A large number of reaction conditions have been defined for the rearrangement of various allene derivatives into small heterocycles. The rearrangements have been accomplished variously with acids, bases or oxidatively.

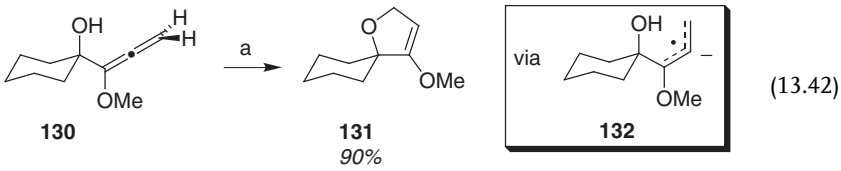
A mechanistically interesting rearrangement of allenyloxirane **125** to methoxyfuran **126** has been described by Brandsma and co-workers (Eq. 13.41) [39]. Brief treatment of **125** with potassium *tert*-butoxide in DMSO leads to furan **126** in 75% yield. The first step in the process is abstraction of one of the allenic protons by the strong base, to give alkoxide **127** after epoxide ring opening. Intramolecular attack of the negatively charged oxygen atom in **127** on the alkyne gives vinyl anion **128** as a transient intermediate. Prototropy leads to **126**. Indirect evidence for this mechanism comes from the reaction of **125** with KOH in DMSO, which leads to a mixture of **126** and **129**. The first step in the reaction of **125** with KOH in DMSO evidently produces a mixture of double-bond isomers, only one of which can cyclize. In the presence of potassium *tert*-butoxide in DMSO, a much stronger base than KOH, deprotonation of the vinyl methyl group in the alkoxide of **129** can also take place, thereby providing a pathway for isomerization to **127**. The reaction in Eq. 13.41 is mechanistically interesting, but of limited utility in synthesis: the C4 methyl group is required for a high yield of product.



(13.41)

(a) *t*BuOK, DMSO, 20–30 °C, 45 min; 75%

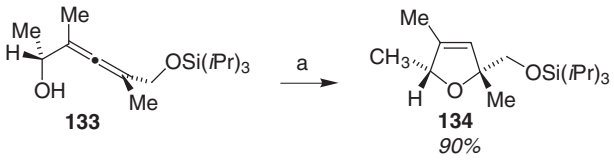
A slightly different process involving a methoxyallene derivative and potassium *tert*-butoxide in DMSO is summarized in Eq. 13.42 [40]. Exposure of tertiary alcohol **130** to strong base leads to dihydrofuran **131** in 90% yield. The mechanism of this intriguing cyclization that has been postulated by Magnus apparently involves single electron transfer from dimsylate anion to give allenyl radical anion **132** and dimsyl radical, which then abstracts a hydrogen atom from the hydroxyl of **132**. Intramolecular radical recombination and proton transfer completes the process. Support for this mechanism is provided by the observation that molecular oxygen inhibits the cyclization and that in DMSO-d_6 only the vinyl hydrogen of **131** is replaced by deuterium. The reaction in Eq. 13.42 suggests the existence of an unexplored reaction manifold for allenes [41].



(13.42)

(a) *t*BuOK, DMSO or *t*BuOK, *tert*BuOH, 18-C-6; 90%

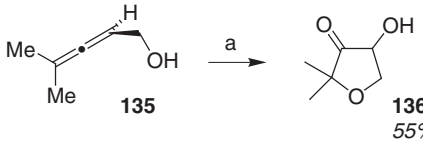
Allenyl alcohols have been used as starting materials for a different kind of dihydrofuran synthesis. This is a process with great generality and utility in total synthesis. An example of the process is shown in Eq. 13.43 [42]. Treatment of allenyl alcohol **133** with silver nitrate in aqueous acetone at room temperature leads stereospecifically to dihydrofuran **134** in excellent yield. A similar reaction occurs with allenyl ketones, leading to furans. The isomerization is known to take place with Rh(I) [43], Ag(I) [44, 45] Pd(II) [46], Au(III) [47, 48] Cu(I) [49] or Hg(II) [50, 51].



(13.43)

(a) $AgNO_3$, acetone, H_2O, $CaCO_3$, dark, r.t., 20 h; 90%

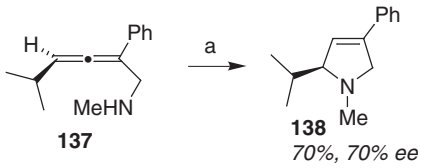
The oxidative cyclization of allenyl alcohol **135** with a small excess of dimethyldioxirane leads to an intermediate diepoxide that rearranges to hydroxyfuranone **136** in 55% yield (Eq. 13.44) [52]. If the oxidative cyclization is conducted in the presence of 0.5 equiv. of toluenesulfonic acid, the major product is the furanone lacking the α-hydroxy group of **136**. Hydroxyfuranones or pyranones are available from the same kinds of reactions of 5-methylhexa-3,4-dien-1-ol.



(13.44)

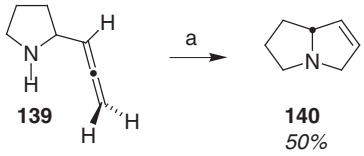
(a) acetone, >3 equiv. dimethyldioxirane, 10 min; 55%

3-Pyrrolines and pyrroles can be readily prepared from the rearrangement of α-aminoallenes. Optically enriched α-aminoallene **137** is rearranged to pyrroline **138** by catalytic silver nitrate (Eq. 13.45) [53]. The yield of the reaction is high and the cyclization occurs with high levels of asymmetry transfer. Annulated 3-pyrroline **140** is the product of rearrangement of allenyl pyrrolidine **139** (Eq. 13.46) [53].



(13.45)

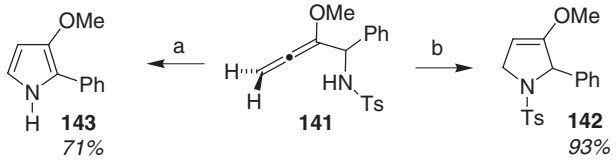
(a) 0.2 equiv. $AgNO_3$, acetone, dark, r.t.; 70%, ≥70% *ee*



(13.46)

(a) 0.2 equiv. $AgNO_3$, acetone, dark, r.t.; 50%

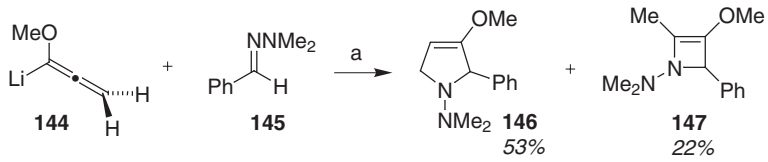
The cyclization can also be carried out on α-tosylaminoallenes, in which case the choice of reaction conditions determines whether the product is the *N*-tosyl-3-pyrroline or whether elimination of toluenesulfonic acid acid gives the pyrrole. For example, in the presence of catalytic silver nitrate, allene **141** (Eq. 13.47) rearranges to *N*-tosylpyrroline **142** in excellent yield, whereas when **141** is treated with potassium *tert*-butoxide in DMSO, pyrrole **143** is formed in 71% yield [54]. Warming the lithium salt of **141** in DMSO also leads to **143**. The rearrangement of **141** to **143** may be mechanistically related to the conversion of **130** to **131** (Eq. 13.42).



(13.47)

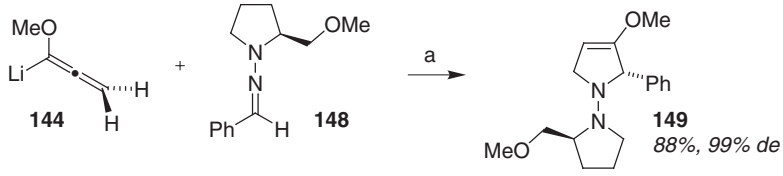
(a) 1.5 equiv. *t*BuOK, DMSO, 50 °C; 71%; (b) 0.27 equiv. $AgNO_3$, acetone, r.t.; 93%

The addition of α-lithiomethoxyallene **144** [55] to benzaldehyde dimethylhydrazone **145** (Eq. 13.48) leads to a mixture of pyrroline **146** and dihydroazete **147** [56]. The cyclization in this case, which takes place in the same operation as the addition to the hydrazone, follows two distinct pathways, with attack of the nitrogen atom taking place at the inner, in addition to the terminal, carbon atom of the allene. A similar reaction of **144** with SAMP-hydrazone **148** (Eq. 13.49) leads to 3-pyrroline **149** in 88% yield and excellent diastereoselectivity [57]. Cleavage of the chiral auxiliary group from **149** takes place in two steps (1, methyl chloroformate; 2, Raney nickel, 50 bar, 50 °C) in 74% overall yield. When the addition of **144** to **148** is conducted in diethyl ether, cyclization of the adduct does not take place. Surprisingly, the hydrazones of aliphatic aldehydes react with **144** in poor yield in THF, but react quantitatively and diastereoselectively in diethyl ether to give the (uncyclized) allenyl hydrazone products.



(13.48)

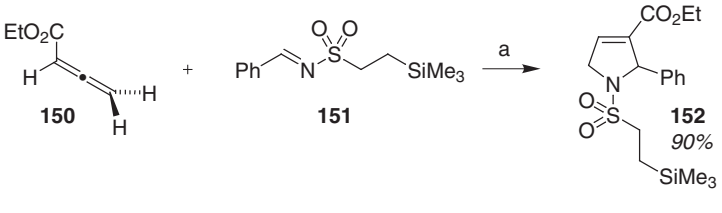
(a) THF, –78 °C, 2 h then r.t. 16 h; **146** 53%, **147** 22%



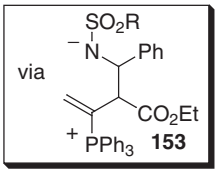
(13.49)

(a) THF, –78 °C; 88%, 99% *de*

A fundamentally different approach to the synthesis of 3-pyrrolines is evidenced in the annulation in Eq. 13.50 [58]. Ethyl 2,3-butadienoate **150** reacts with *N*-sulfonylimine **151** in the presence of triphenylphosphine under very mild conditions to give *N*-protected 3-pyrroline **152** in 90% yield. The mechanism that has been postulated is related to that of the Baylis–Hillman reaction. Michael addition of triphenylphosphine to the allenyl ester generates a zwitterion that combines with the imine to give **153** in a non-concerted process. This is followed by ring closure, proton exchange and expulsion of triphenylphosphine to give **152**. This annulation is successful only for aromatic or cinnamyl imines [59].

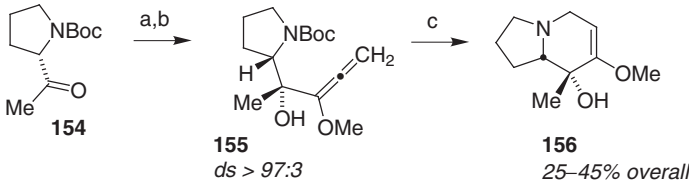


(13.50)



(a) PPh_3, PhH, r.t.; 90%

The most convincing proof of the utility of a synthetic method is its application in a total synthesis. Equation 13.51 shows the key cyclization step in Overman's enantioselective synthesis of the allopumiliotoxin A alkaloids 267A and 339B [60]. Exposure of **154** to trifluoroacetic acid cleaves the Boc group and gives an ammonium trifluoroacetate salt that is allowed to react with an excess of **144**, leading to allene **155** with high diastereoselectivity. Exposure of **155** to toluenesulfonic acid in acetonitrile gives indolizidine **156** in 25–45% overall yield from **154**.

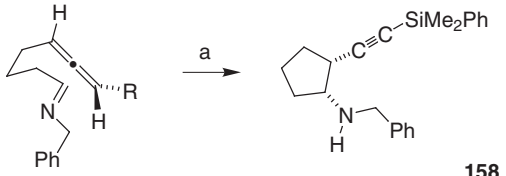


(13.51)

(a) TFA, PhOMe; (b) 5 equiv. **144**, –78 °C; (c) TsOH, MeCN; 25–45% overall

13.5
Ene Reactions of Allenes

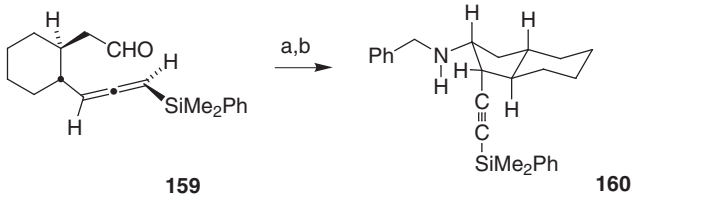
Allenes and allenylsilanes have excellent reactivity in the ene reaction and can combine with alkene enophiles, in addition to aldehydes and imines [61]. Iminoallene **157** (R = $SiMe_2Ph$) is converted to cyclopentane **158** on heating in toluene solution or on treatment with stannic chloride in benzene (Eq. 13.52) [62]. In both cases the yield is 70%. The silyl substituent on the allene is necessary, since exposing **157** (R = H) to heat or Lewis acid, even under forcing conditions, does not lead to cyclic products. This suggests that the reaction proceeds by means of a polar transition state and that the trialkylsilyl group stabilizes the developing positive charge on the sp-hybridized carbon atom of the allene. This has the effect of lowering the transition state energy relative to the case in which R is hydrogen or alkyl. In this regard there is a similarity between the role of silicon in this ene process and its role in the Danheiser reaction (see Eq. 13.26). Nevertheless, unlike the Danheiser reaction, the ene process is not an ionic, stepwise process, but instead appears to follow a concerted pericyclic mechanism. Several pieces of evidence suggest that this is so. The final products are silylacetylenes and not terminal alkynes. Furthermore, the ene reaction is completely stereospecific.



157 **158** *70%* (13.52)

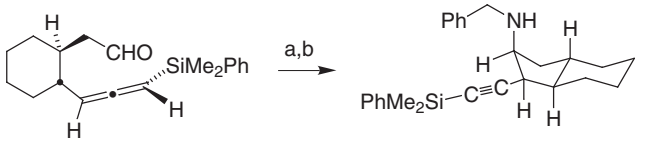
(a) $SnCl_4$, PhH, 0 °C to r.t. or PhMe, heat; 70%

Allenylsilanes **159** (Eq. 13.53) and **161** (Eq. 13.54) differ in the axial stereochemistry of the allene function. In each case, formation of the benzyl imine, followed either by treatment with tin(IV) chloride in benzene at room temperature or heating in toluene, leads to diastereomeric products **160** and **162** [63]. Significantly, there is no crossover, pointing to a concerted (or fast, stepwise) process. Since the absolute stereochemistry of the allenylsilanes is easily controlled, the methodology is ideal for applications in total synthesis. Weinreb and co-workers have used the reaction for his synthesis of the marine natural product (–)-papuamine.



159 **160** *87% or 70%* (13.53)

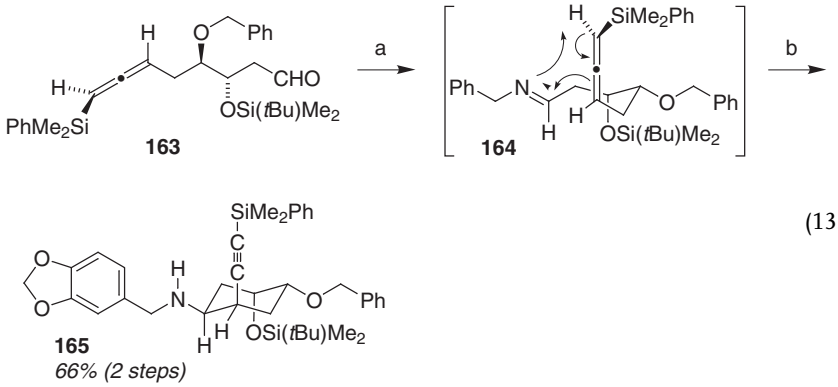
(a) $PhCH_2NH_2$; (b) $SnCl_4$, PhH, r.t. or PhMe, heat; 87 or 70%



161 **162** *84% or 67%* (13.54)

(a) $PhCH_2NH_2$; (b) $SnCl_4$, PhH, r.t. or PhMe, heat; 84 or 67%

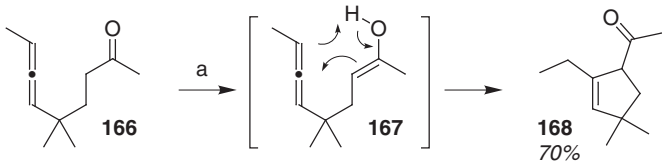
The allenylsilane ene reaction is also well suited for the synthesis of cyclohexane rings. Jin and Weinreb have described the process of Eq. 13.55 in a synthesis of 5,11-methanomorphanthridine, an Amaryllidaceae alkaloid [64]. Conversion of aldehyde **163** to imine **164** with piperonylamine took place in situ. Heating the solution of imine at reflux in mesitylene for 2 h led to cyclization through the conformer shown. The yield of **165** from aldehyde **163** was 66%.



(13.55)

(a) piperonylamine, mesitylene, r.t., 4 Å sieves; (b) mesitylene, reflux, 2 h; 66% (2 steps)

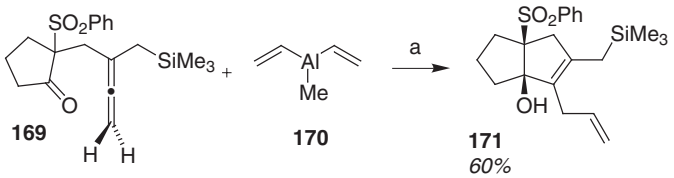
Allenyl ketones can undergo a Conia-ene cyclization, as shown in Eq. 13.56 [65]. Heating ketone **166** at 275 °C for 15 min leads to acetylcyclopentene **168** in 70% yield. Cyclization presumably takes place through a pericyclic mechanism involving enol **221**.



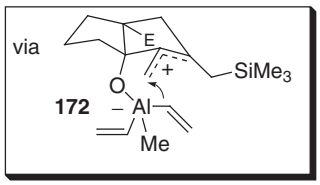
(13.56)

(a) 275 °C, 15 min; 70%

A rather different allene cyclization that takes place in tandem with an alkylative process has been described by Trost and Urabe [66] (Eq. 13.52). Exposure of ketoallene **169** to divinylmethylaluminum **170** in dichloromethane solution leads to **171** in 60% yield. The mechanism of this alkylative cyclization involves complexation of the Lewis acidic aluminum to the carbonyl oxygen atom, followed by ring closure, leading to zwitterion **172**. Intramolecular transfer of a vinyl group from aluminum to carbon completes the process.



(13.57)

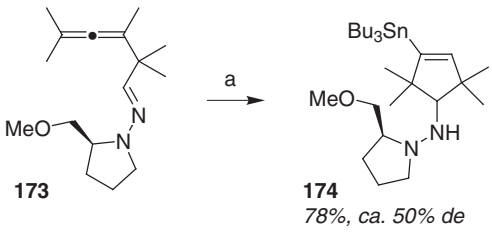


(a) CH_2Cl_2, r.t.; 60%

As is the case for Diels–Alder cycloadditions, the high reactivity of the allene function provides low activation barrier pathways for a number of synthetically useful ene reactions.

13.6 Miscellaneous Cyclizations of Allenes

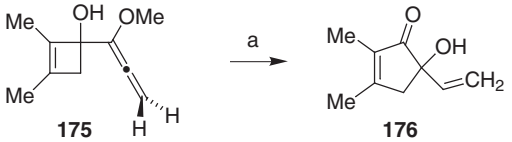
Equation 13.58 describes the radical cyclization of SAMP hydrazone **173** [67]. In the presence of tributyltin hydride and a radical initiator, cyclization to **174** takes place in 78% yield. It is not clear what the full scope of this reaction is or what its utility in synthesis might be.



(13.58)

(a) 2 equiv. Bu_3SnH, AIBN, PhH; 78%, ~50% *de*

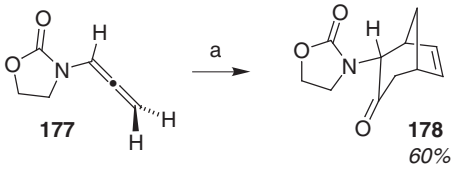
The addition of allenyllithium **144** to 2,3-dimethyl–2-cyclobutenone gives tertiary alcohol **175** (Eq. 13.59) [68]. Exposure of this material to trifluoroacetic acid gives rise to a ring expansion with formation of cyclopentenone **176** in 76% yield. This process is interesting, since it appears likely that there are two mechanisms that operate to convert **175** to **176**. One mechanism is an ionic 1,2-alkyl migration, whereas the other mechanism involves conrotatory cyclobutene ring opening with the hydroxyl moving outward, followed by electrocyclization to form the five-membered ring. Spectroscopic evidence for the ring-open intermediate of the second pathway has been obtained.



(13.59)

(a) CF_3COOH, THF, H_2O; 76%

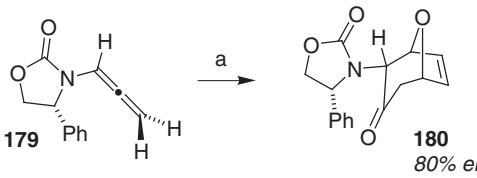
Epoxidation of amidoallenes with dimethyldioxirane leads to allene oxides as reactive intermediates which can be trapped with dienes in a [4 + 3]-cycloaddition reaction. Exposure of a mixture of amidoallene **177** with cyclopentadiene to a small excess of dimethyldioxirane at –45 °C produced *endo*-bicyclooctanone **178** in 60% yield (Eq. 13.60) [69]. The allene oxide is electrophilic, since no reaction takes place with methyl acrylate.



(13.60)

(a) 2–3 equiv. dimethyldioxirane, THF, –45 °C, 10 equiv. cyclopentadiene, 8–10 h; 60%, only *endo*

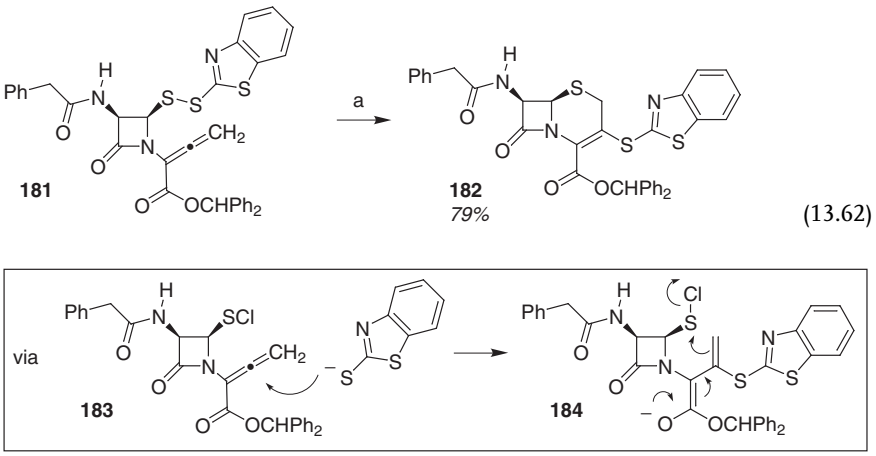
Use of a chiral auxiliary on the allene results in excellent control of product stereochemistry. For example, epoxidation of allene **179** in the presence of furan leads to **180** in 80% yield (Eq. 13.61). The ratio of *endo* to *exo* isomers was 96:4 [69].



(13.61)

(a) 2–3 equiv. dimethyldioxirane, THF, –78 °C, 2.0 equiv. $ZnCl_2$, furan; 80%, only *endo*, *dr* =96:4.

N-Allenylazetidinone **181** rearranges to cephalosporin **182** in the presence of lithium chloride (Eq. 13.62) [70]. This is a very unusual reaction that is presumed to be initiated by chloride ion-induced cleavage of the disulfide to give sulfenyl chloride **183**. Thiolate attack at the allene sp carbon atom of **183** generates ester enolate **184**, which cyclizes to **182**. The reactivity of the allene function in **181** ensures the success of the reaction.



(13.62)

(a) 3.0 equiv. LiCl, THF, –20 to 0 °C, 2 h; 79%

13.7 Conclusion

The coverage of the material in this chapter, although broad, is not all-encompassing, nor can it be, owing to the limitations of space. An effort has been made to give examples of the most useful and also the most interesting ring-forming reactions that make use of allenes. An attempt has been made to present the work within a mechanistic framework. Results that have been published subsequent to Schuster and Coppola's 1984 monograph on allenes [71] have been emphasized.

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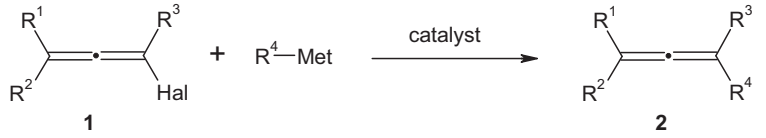
14
Transition Metal-Catalyzed Cross-Couplings of Allenes

Reinhold Zimmer and Hans-Ulrich Reissig

14.1
Introduction

Metal-catalyzed cross-coupling reactions have been developed into useful preparative methods during the past three decades and now belong to the most efficient processes forming carbon–carbon bonds [1]. Among these, palladium-catalyzed reactions have emerged as particularly powerful synthetic tools and have become one of the most extensively studied reactions of the organic chemist's synthetic arsenal [2, 3]. Transition metal-catalyzed cross-couplings of alkenes and alkynes are very important synthetic transformations which proceed fairly conveniently, thus increasing the applicability of these reactions for the construction of a wide range of simple and complex molecules. Following this trend, investigations were extended to transition metal-catalyzed cross-couplings with allenes as substrates. They offer attractive possibilities for carbon–carbon bond formation and for the preparation of important synthetic precursors [4–7]. From this point of view, substitutions at allenes by cross-couplings seem to be a very useful aim.

In principle, three basically different types of reaction modes are applied for cross-coupling reactions of allenes. First, cross-couplings of allenes with suitable halogen or metal substituents at one of the sp^2-hybridized carbons furnish products still bearing the intact cumulene π-system. On this basis, numerous reactions for conversions of precursor **1** or **3** into substituted allenes **2** have been developed (Schemes 14.1 and 14.2).



Scheme 14.1

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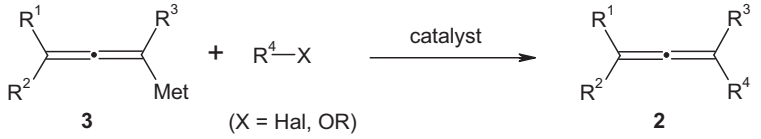
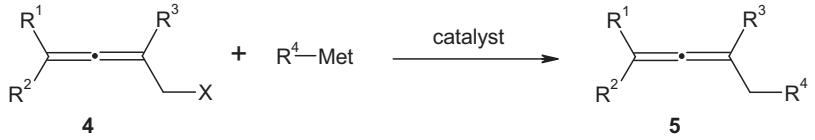


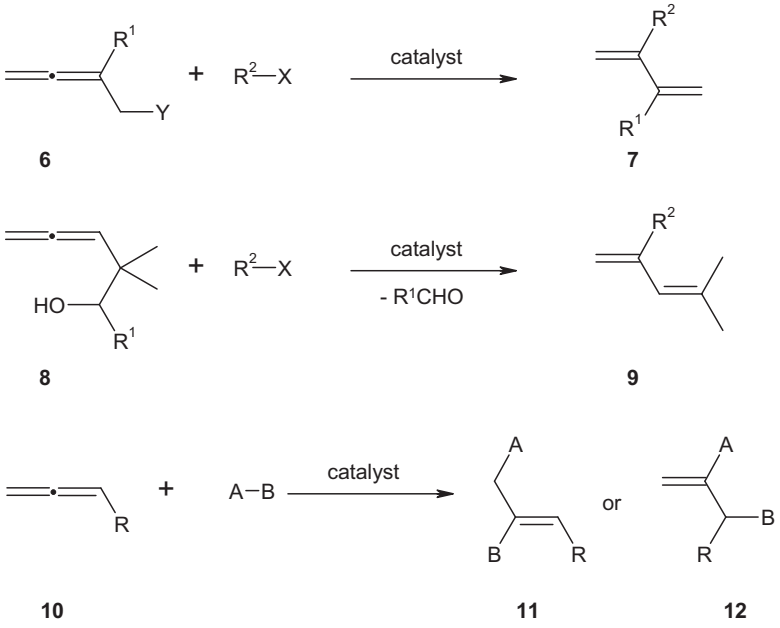
Scheme 14.2

Second, substitution reactions of suitably α-functionalized allenes **4** result in compounds **5** which also still contain the unchanged cumulene system (Scheme 14.3).



Scheme 14.3

Third, in contrast to these processes, transition metal-catalyzed couplings at the central allene carbon are often accompanied by subsequent reactions, mostly attack of a nucleophile or elimination of a fragment, both providing products ruling out the cumulene π-system. General examples of this reaction mode are given in Scheme 14.4. 1,3-Dienes such as **7** or **9** are produced starting from allenes bearing leaving groups.



Scheme 14.4

The closely related transition metal-catalyzed additions leading to general structures **11** and/or **12** will not be treated in this chapter, since these synthetically useful additions are discussed separately in Chapter 16. Transformations of allenes involving coupling reactions are often accompanied by subsequent ring-closing reactions of the intermediates, which afford carbocycles and heterocycles. These processes are also part of Chapter 16; in addition, fairly recent comprehensive reviews summarizing these elegant and useful transformations should be mentioned [4–8].

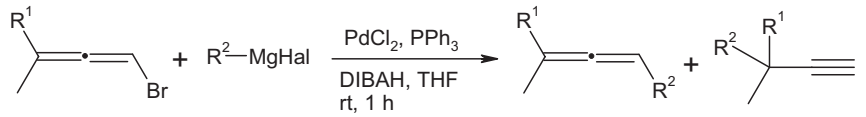
In this chapter, we attempt to provide an overview of the varying structures of suitable reaction partners in cross-couplings. Important recent developments and applications of the aforementioned reaction types will be discussed.

14.2
Cross-Coupling Reactions of Allenes Producing Compounds with an Intact 1,2-Diene Moiety

14.2.1
Cross-Coupling Reactions of Allenyl Halides

14.2.1.1 Palladium-Catalyzed Reactions

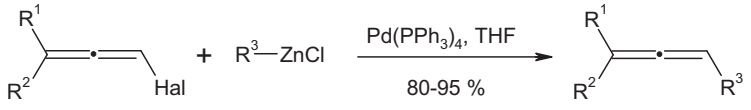
In the early 1980s, one of the first preparations of substituted allenes was reported, which employed a palladium-catalyzed cross-coupling reaction of allenyl halides [9]. In this study, allenyl bromides **13** and various Grignard reagents **14** were coupled in the presence of catalytic amounts of a Pd(0) species, generated in situ by reduction of a Pd(II) salt. Trisubstituted allenes **15** were obtained with high regioselectivity (allene **15**:alkyne **16** = 90:10 to 99:1) (Scheme 14.5).



(R^1 = H or Me; R^2 = Octyl, Tolyl; Hal = Cl or Br)

Scheme 14.5

Unfortunately, the use of Grignard reagents in cross-couplings with allenyl halides is restricted to only a few examples [9, 10]. These reactions do not proceed cleanly because of the competing halogen–metal exchange at the allenes by Grignard compounds. Vermeer and co-workers have observed that organozinc compounds, e.g. phenylzinc chloride (**18a**) and vinylzinc chloride (**18b**), are more convenient as precursors in palladium(0)-catalyzed cross-couplings of allenyl bromides and iodides **17** giving allenes **19** in excellent yields (Scheme 14.6) [11]. In these examples no alkyne side products could be detected.

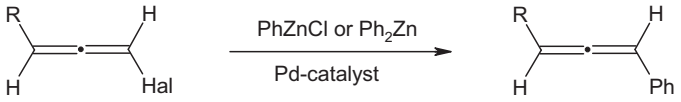


17 **18a** R^3 = Ph **18b** R^3 = Vinyl **19**

(R^1,R^2 = **a**: H,H; **b**: H, Me; **c**: Me, Me; Hal = Br or I)

Scheme 14.6

The stereochemical outcome of palladium(0)-catalyzed conversions of easily accessible enantioenriched allenyl halides [12] into 1,3-disubstituted allenes was also examined by using phenylzinc compounds (Scheme 14.7, Table 14.1) [13, 14]. Thus, $Pd(PPh_3)_4$-catalyzed reactions of allenyl chloride (*R*)-**20a** and allenyl bromides (*R*)-**20b** or (*R*)-**22b** with phenylzinc chloride or diphenylzinc afforded phenyl-substituted allenes (*S*)-**21** and (*S*)-**23**, respectively, with inversion of configuration (entries 1–3 and 5 in Table 14.1). It should be mentioned that Ph_2Zn, which was prepared in situ by mixing of 1 equiv. of PhMgBr with 0.5 equiv. of $ZnCl_2$, led to the expected allenes with a significantly lower stereoselectivity [e.g. only 36% *ee* for the transformation of (*R*)-**20a** into (*S*)-**21**].



20 (R = Ph) **22** (R = *t*Bu) **21** (R = Ph) **23** (R = *t*Bu)

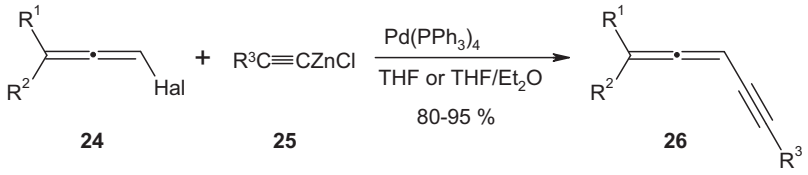
Scheme 14.7 (Hal: **a**: Cl; **b**: Br; **c**: I)

Table 14.1 Palladium-catalyzed reactions.

Entry	Substrate	Reagent	Product	*ee* (%)
1	(*R*)-**20a**	PhZnCl	(*S*)-**21**	62
2	(*R*)-**20a**	Ph_2Zn	(*S*)-**21**	67
3	(*R*)-**20b**	PhZnCl	(*S*)-**21**	80
4	(*R*)-**20c**	PhZnCl	(*R*)-**21**	12
5	(*R*)-**22b**	Ph_2Zn	(*S*)-**23**	73
6	(*R*)-**22c**	PhZnCl	(*R*)-**23**	73
7	(*R*)-**22c**	Ph_2Zn	(*R*)-**23**	68

The attempt of chiral induction in the cross-coupling of racemic 1-bromo-4,4-dimethyl-1,2-pentadiene (**22b**) with PhZnCl in the presence of the chiral palladium complex Pd[(*R*,*R*)-DIOP]$_2$ was disappointing. Although the expected disubstituted allene **23** was formed in quantitative yield, the enantiomeric excess was at best 9% *ee* [15].

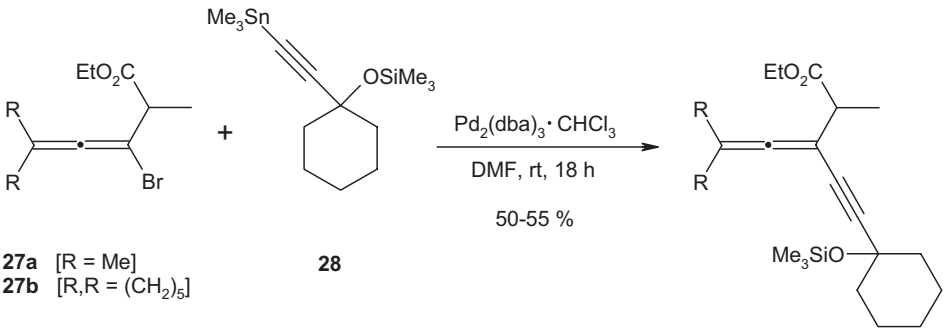
The cross-coupling reactions of allenes with components containing sp-carbon atoms are useful synthetic transformations since they provide yne-allenes and enyne-allenes, respectively. Due to the synthetic potential of these classes of carbon-rich unsaturated compounds, the scope and limitations were systematically investigated [1, 16–18]. The first synthetic application was reported in 1981, describing the preparation of alkynyl-substituted allenes by coupling of alkynylzinc chlorides with allenyl halides (Scheme 14.8) [11].



24 **25** **26**

Scheme 14.8 (R^3 = Me_3Si; Ph; H_2C=CMe; HC≡C)

A convenient route for the preparation of yne-allenes was recently described by Saalfrank et al. [19]. Products **29a/b** were formed by Stille cross-coupling of allenyl bromides **27a/b** with alkynylstannanes such as **28** (Scheme 14.9). Allenyl phosphonates such as **30** were also suitable substrates in palladium-catalyzed couplings with propargylstannane **31** (Eq. 14.1). Bisstannylated acetylene **33** as alkyne component furnished the expected yne-bisallene **34** in reasonable yield, but without any diastereoselectivity (*meso*-**34**: (*R*,*R*)-/(*S*,*S*)-**34** ≈50:50) (Eq. 14.2).

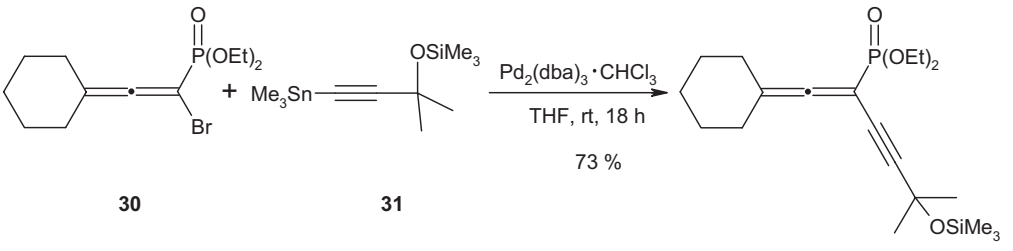


27a [R = Me]
27b [R,R = $(CH_2)_5$]

28

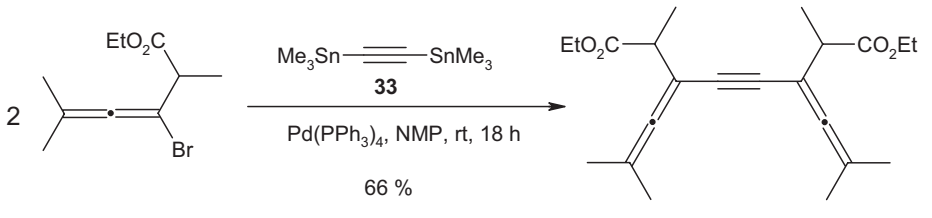
29a/b

Scheme 14.9



30 **31** **32**

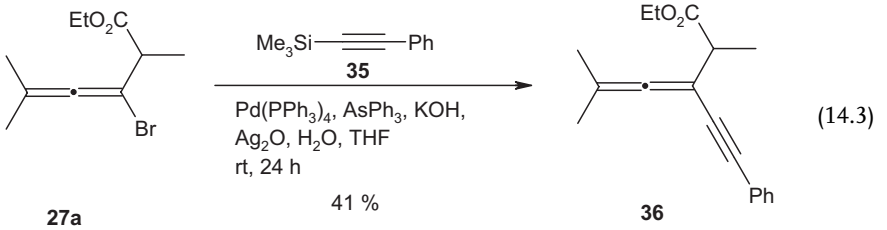
(14.1)



27a **34**

(14.2)

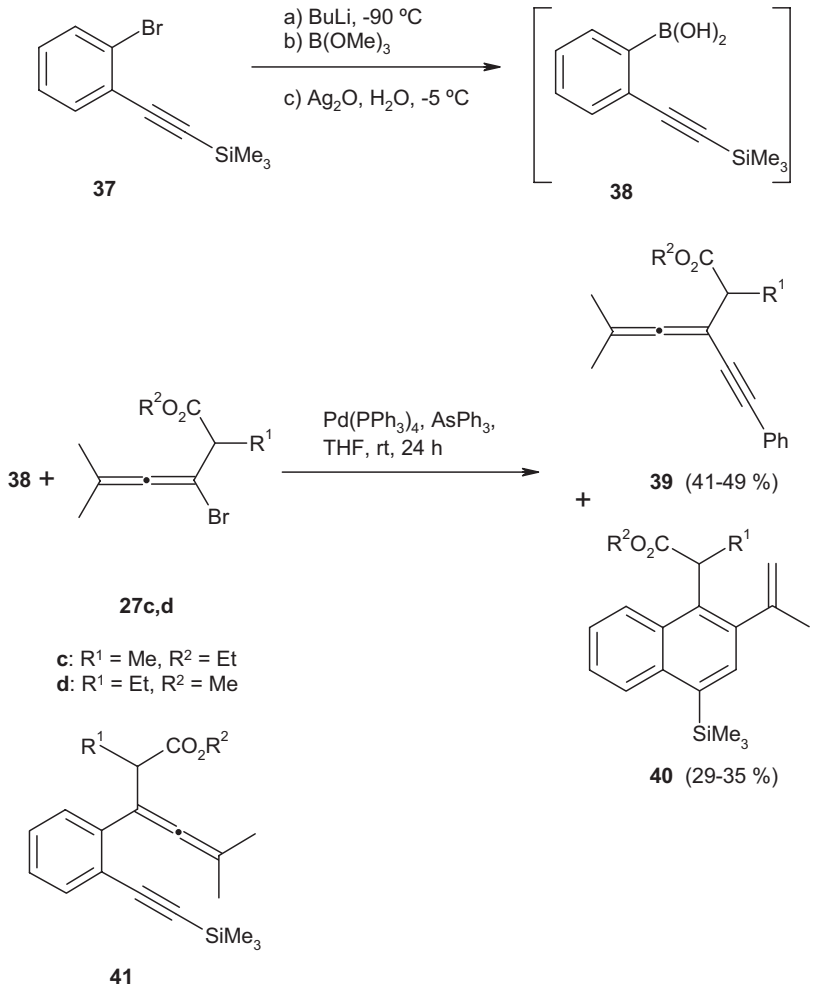
Treatment of bromoallene **27a** and phenylethynyltrimethylsilane (**35**) with a reagent cocktail as given in Eq. 14.3 afforded yne-allene **36** in moderate yield [19]. The key intermediate in the formation of the tetrasubstituted allene **36** is phenylacetylene, which is generated in situ by spontaneous desilylation of **35** by potassium hydroxide.



27a **36**

(14.3)

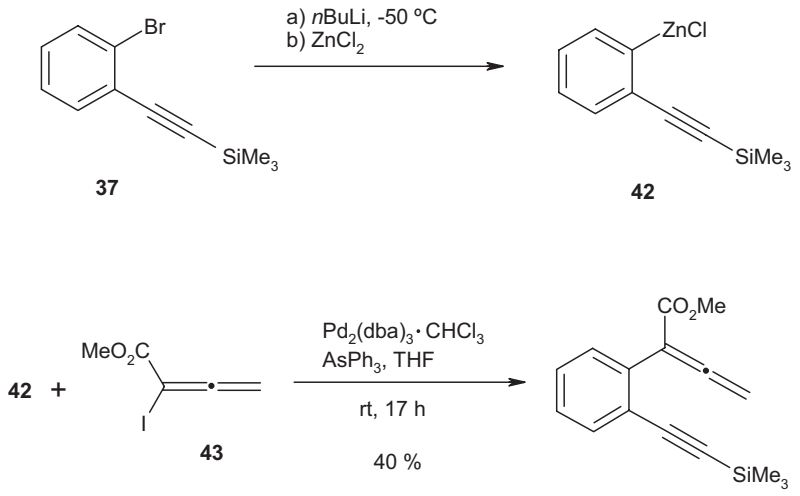
Prompted by the discovery of enediyne antibiotics, several research groups attempted to synthesize other unsaturated structures that could cyclize to give biradical species [20]. Thus, development of elegant and efficient methods for construction of enyne-allenes became a formidable task. Saalfrank's group described the Suzuki coupling of allenyl bromides **27c/d** with boronic acid **38**, generated from the corresponding aryl bromide **37**, which led to the formation of naphthalene derivatives **40** and of yne-allenes **39** (Scheme 14.10) [21]. The suggested pathway involves the generation of the expected intermediate **41**, which suffers cycloaromatization under the reaction conditions used. The isolation of yne-allenes **39** suggests that



Scheme 14.10

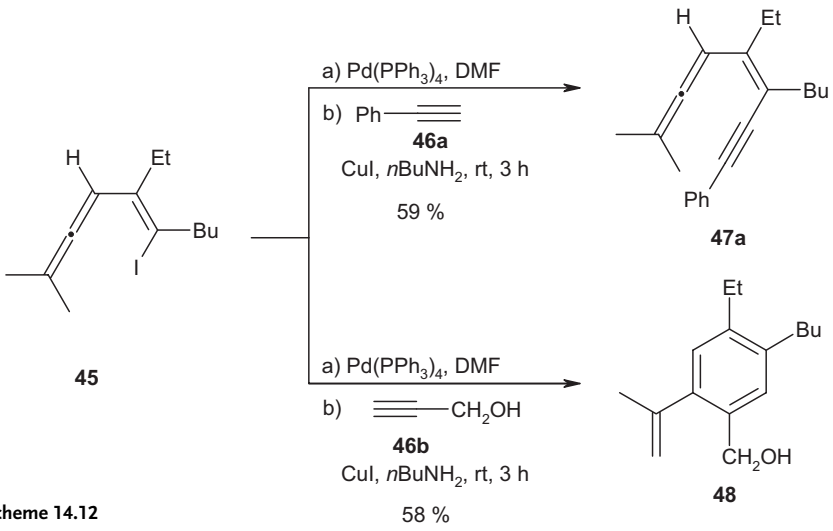
phenylacetylene is formed from **38** and subsequently couples with **27c/d**. Compounds **39** were independently prepared by the [Pd(0)/Ag(I)]-catalyzed reaction of phenylacetylene and **27c/d**.

Gillmann's synthesis of enyne-allenes started with conversion of aryl bromide **37** into arylzinc chloride **42**, which reacted with allenyl iodide **43** under $Pd_2(dba)_3 \cdot CHCl_3/AsPh_3$ catalysis to form the enyne-allene **44** in 40% yield (Scheme 14.11) [22]. According to the general protocol established by Suzuki, coupling of allenyl iodide **43** with various arylboronic acids could be applied successfully with $Pd(PPh_3)_4$ as catalyst and Na_2CO_3 as base, which provided compounds such as **44** in moderate to excellent yields [22, 23].



Scheme 14.11

Wang's approach for the synthesis of enyne-allenes focused on ene-allenyl iodide **45** (Scheme 14.12) [24]. Palladium-catalyzed Sonogashira reaction of **45** with terminal alkynes **46** (R = Ph or CH_2OH) proceeded smoothly under mild reaction conditions in the presence of the cocatalyst cuprous iodide and *n*-butylamine. The initially formed enyne-allene **47b** with substituent R = CH_2OH cyclized spontaneously to the corresponding α-methylstyrene derivative **48**.

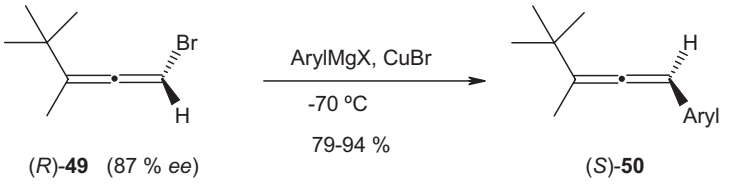


Scheme 14.12

Finally, it should be noted that the synthesis of methyl 2,3-butadiene-1-carboxylate can be achieved by the palladium-catalyzed carbonylation of 1-bromoallene with carbon monoxide in methanol [25]. Similarly, 2,3-allenamides are accessible from bromoallenes, carbon monoxide and primary amines or ammonia [26].

14.2.1.2 Copper-Catalyzed Reactions

Copper-mediated cross-couplings of allenyl halides have also been studied extensively, but these reactions mostly require the presence of stoichiometric amounts of cuprates [27]. Only a few reports have been presented for the application of copper-catalyzed reactions of allenyl halides. CuBr-catalyzed couplings of the enantioenriched allene (*R*)-**49** with various aryl Grignard compounds proceeded with excellent regioselectivity and under inversion of configuration, as represented by the examples depicted in Scheme 14.13 [12e, 28]. However, alkyl-substituted Grignard reagents instead of the aryl-substituted species did not react with similarly high regioselectivity. Here a mixture of allene and alkyne as side product was observed (cf. Scheme 14.5) [27e]. Formation of the undesirable alkyne component can only be suppressed by use of stoichiometric amounts of Gilman's cuprate such as nBu$_2$CuLi.



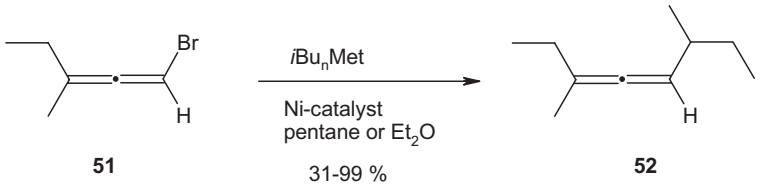
(*R*)-**49** (87 % *ee*) (*S*)-**50**

ee: Aryl = Ph (84 %); *p*FC$_6$H$_4$ (83 %); 1-Naphthyl (56 %); *p*MeOC$_6$H$_4$ (63 %)

Scheme 14.13

14.2.1.3 Nickel-Catalyzed Reactions

In contrast to palladium- and copper-catalyzed cross-couplings of allenyl halides, only one publication describes nickel-catalyzed reactions of these substrates [29]. Alkyl-substituted bromoallenes such as **51** were coupled with a variety of isobutylmetal reagents with high chemo- and regioselectivity (Scheme 14.14). The best results in terms of yield and selectivity were obtained with Ni(dppe)Cl$_2$ and Ni(dppp)Cl$_2$ as catalysts in coupling reactions of iBu$_3$Al, whereas the phosphine-free catalyst Ni(mesal)$_2$ was found to be more efficient with iBuMgCl, iBu$_2$Zn and iBuZnCl as coupling partners of **51**. The solvent plays an important role in the reactivity of these organometallic compounds. Cross-couplings with iBu$_3$Al and iBu$_2$Zn require hydrocarbon solvents such as pentane, whereas iBuMgCl or iBuZnCl react readily in coordinating solvents such as diethyl ether.

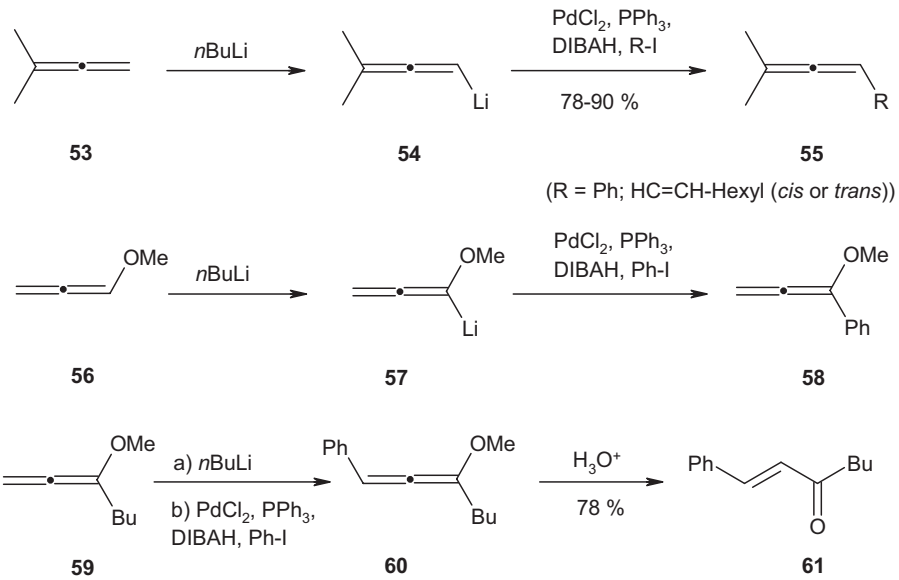


Scheme 14.14 (Met = Al, MgCl, Zn or ZnCl)

14.2.2
Cross-Coupling Reactions of Allenylmetal Compounds

14.2.2.1 Palladium-Catalyzed Reactions

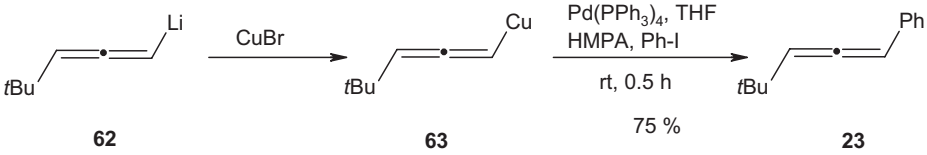
A complementary approach for cross-couplings with allenes was applied by using metallated allene species instead of allenyl halides, which have already been discussed in Sect. 14.2.1. Since allenyllithium compounds are readily available by deprotonation of allenes with *n*-butyllithium, successful cross-coupling reactions between lithiated allenes such as **54** or **57** and aryl or vinylic halides allowed convenient routes to aryl- and vinyl-substituted allenes, e.g. **55**, **58** and **60** (Scheme 14.15) [30].



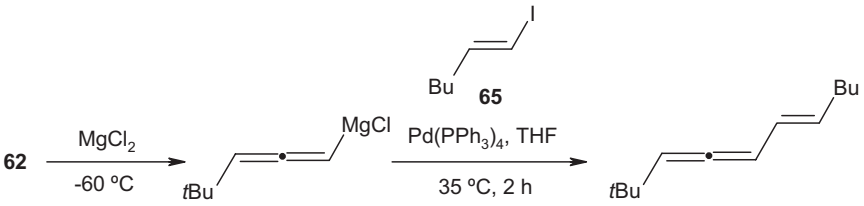
Scheme 14.15

The straightforward generation of lithiated allenes [31], in particular lithiated donor-substituted allenes [32], has opened up smooth and efficient routes to further metallated functionalized allenes. By transmetallation, metals such as magnesium,

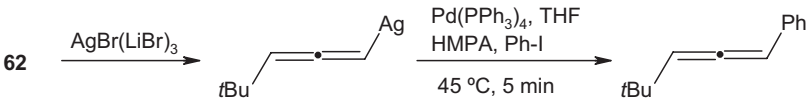
copper, silver, boron and especially zinc could be introduced, which generated more suitable metallated allenes for the coupling step [33–35]. Simple addition of the corresponding metal salt to a THF solution of the in situ-generated lithioallene leads to the transmetallated species, which reacts under palladium catalysis with various aryl and vinylic halides (Eqs 14.4–14.7 and Scheme 14.16).



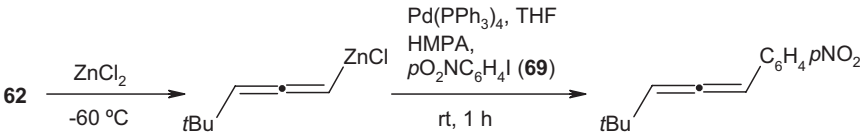
62 **63** **23** (14.4)



64 **66** (14.5)

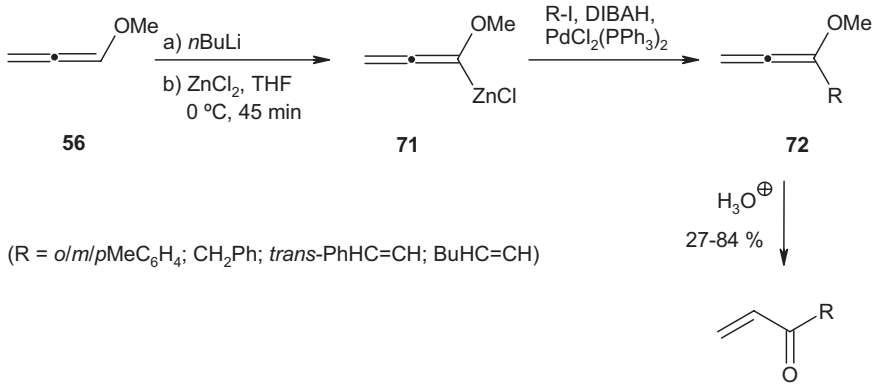


67 **23** (14.6)



68 **70** (14.7)

Additional examples of palladium-catalyzed cross-couplings, in particular with allenylzinc compounds, can be found elsewhere [11, 15, 36]. A systematic study comparing several chiral palladium phosphine catalysts in the reaction of 4,4-dimethyl-1,2-pentadienylzinc chloride and iodobenzene revealed that an enantiomeric excess of only 25% was obtained from the best catalyst combination $PdCl_2$ and (*R,R*)-DIOP [15]. The synthetic value of these transformations of donor-substituted allenes as precursors is documented by the preparation of α,β-unsaturated carbonyl



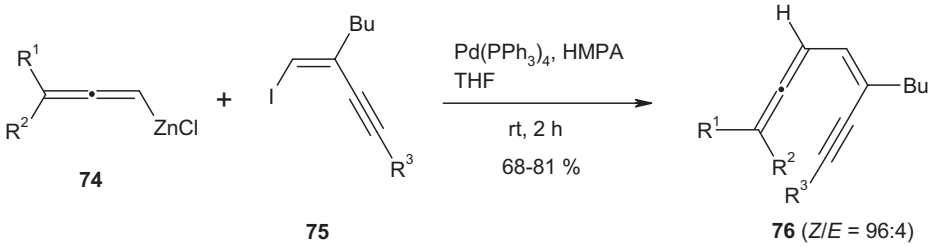
56 **71** **72** **73**

(R = *o*/*m*/*p*MeC$_6$H$_4$; CH$_2$Ph; *trans*-PhHC=CH; BuHC=CH)

Scheme 14.16

compounds, e.g. **61** and **73** (Schemes 14.15 and 14.16) which are themselves important synthetic intermediates [37].

Wang's synthesis of enyne-allenes by cross-coupling of ene-allenic iodides with alkynes has already been mentioned in Sect. 14.2.1.1 (Scheme 14.12). In a continuation of this work, the same group developed an alternative coupling reaction of allenylzinc chlorides **74** with enyne iodides **75** catalyzed by Pd(PPh$_3$)$_4$, which provided the expected enyne-allenes **76** in high yield and with excellent *Z*/*E* selectivity (Scheme 14.17) [38].

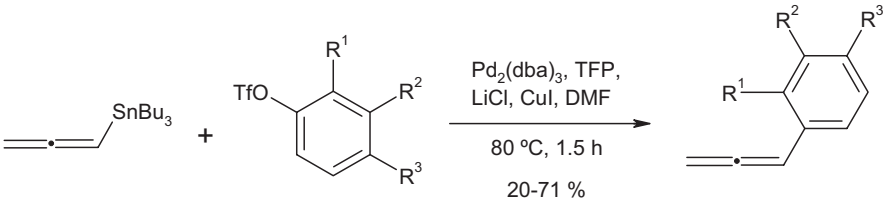


74 **75** **76** (*Z*/*E* = 96:4)

(R^1 = H, Me; R^2 = Me, Hexyl; R^3 = *n*Bu, Ph)

Scheme 14.17

In 1994, Badone et al. reported that the Stille coupling of allenylstannane **77** and aryl triflates **78** resulted in formation of various aryl-substituted allenes **79** in moderate to good yield (Scheme 14.18) [39]. The choice of catalyst was certainly a crucial issue in this process for optimizing yield and rate. The best results could be obtained employing a catalyst cocktail of Pd$_2$(dba)$_3$–TFP–LiCl–CuI. Similar Stille coupling reactions with stannylated allenes and aromatic iodides as substrates were described by Aidhen and Braslau [40a] and Huang et al. [40b].



77 78 79

Scheme 14.18 (R^1 = H, Ph, CO_2Et; R^2 = H, OMe; R^3 = H, Ph)

In spite of these first successful results, so far Stille cross-couplings have rarely reported employing functionalized stannylated allenes such as easily available donor-substituted allene **80a** or allenyl esters such as **81** (Scheme 14.19) [19, 41, 42]. A single palladium-catalyzed annulation reaction with **80b** as precursor leading to an α-pyrone derivative was reported [43].

80a (R = Me)
80b (R = *n*Bu)

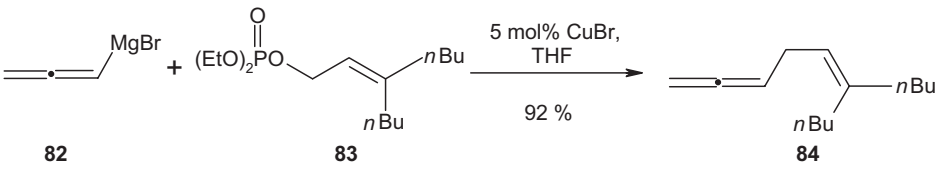
81

Scheme 14.19

14.2.2.2 Other Transition Metal-Catalyzed Reactions

Only a few attempts have been made to use $Ni(PPh_3)_4$ and $Pt(PPh_3)_4$ as catalysts in cross-coupling reactions of zinc-substituted allene **68** with phenyl iodide (cf. Eq. 14.7). In both cases the resulting coupling product **70** was formed in <5% yield [33].

Surprisingly, only a single application of a copper(I)-catalyzed cross-coupling of metallated allenyl species has been reported [44]. The CuBr-catalyzed coupling of allenylmagnesium bromide (**82**) with allyl phosphate **83** provided 6-butyldeca-1,2,5-triene (**84**) in high yield, as depicted in Eq. 14.8.



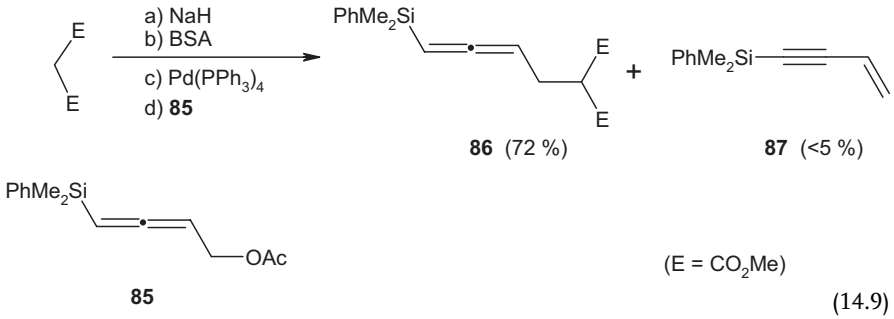
82 83 84

(14.8)

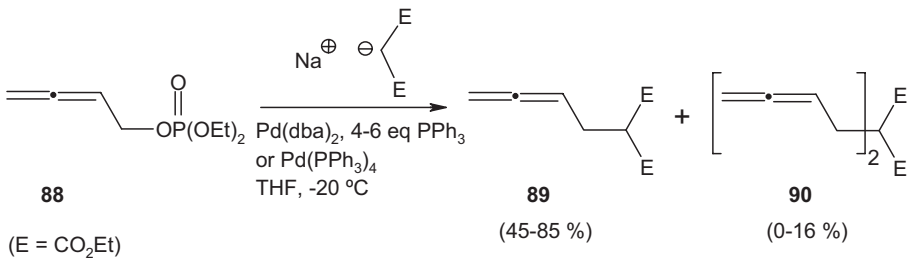
14.2.3

Cross-Coupling Reactions of α-Substituted Allenes

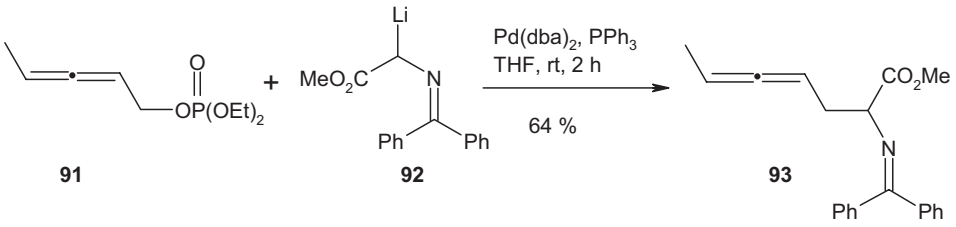
If allenes bear a potential leaving group in the α-position to the cumulene system, they are very attractive substrates for palladium-catalyzed substitutions. Examples are α-allenic acetates and particularly α-allenic phosphates, which react under palladium(0) catalysis with carbanions derived from β-diesters, β-keto esters, α-phenylsulfonyl esters and glycine ester derivatives. They lead to β-functionalized allenes such as **86**, **89** and **93** (Eqs. 14.9–14.11) [45–48].



(14.9)

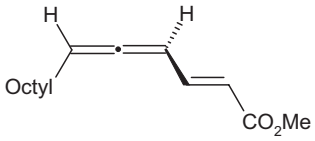


(14.10)

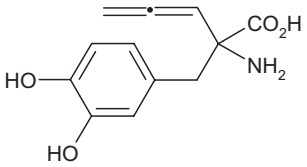


(14.11)

Some observed side-products (**87** or **90**) can be suppressed, for example by the use of modified catalysts ($Pd(dba)_2$/4–6 equiv. PPh_3 instead of $Pd(PPh_3)_4$ in Eq. 14.10). Additional model studies demonstrated the utility of α-allenyl acetates and phosphates by the successful synthesis of pheromone (*R*)-**94** [47] and of enzyme inhibitor **95** [48] (Scheme 14.20).



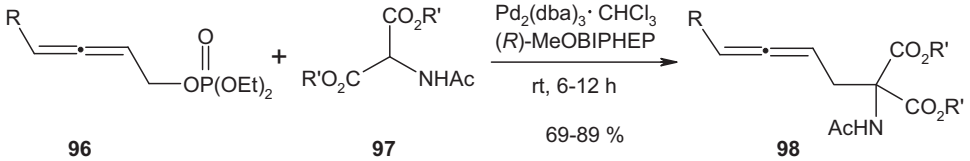
(*R*)-**94**



95

Scheme 14.20

Based on these reactions, Imada et al. reported the first enantioselective alkylation of 2,3-alkadienyl phosphates **96** by employing malonate derivatives **97** in the presence of palladium complex catalysts bearing MeOBIPHEP or BINAP as ligand (Scheme 14.21) [49]. The highest enantioselectivity (90% *ee*) was obtained by the catalyst combination $Pd_2(dba)_3 \cdot CHCl_3$ and (*R*)-MeOBIPHEP.



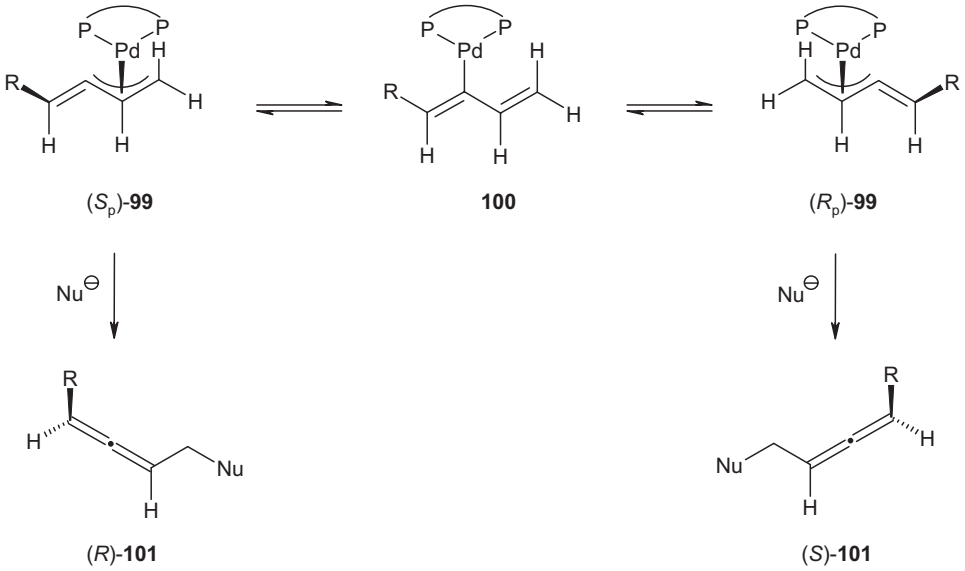
96 **97** **98**

(up to 90 % ee)

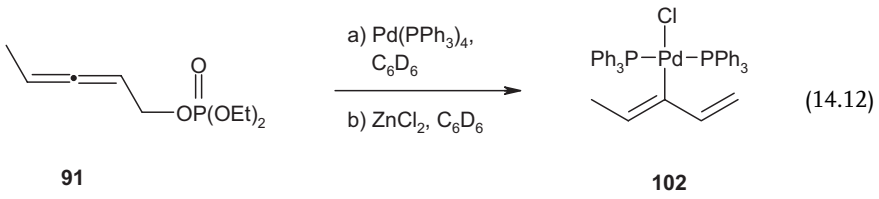
(R = Me, *i*Pr, *t*Bu, Pentyl, Ph; R' = Me, Et)

Scheme 14.21

The stereochemical outcome can be rationalized by the mechanism illustrated in Scheme 14.22. The formation of an enantiomeric pair of allylpalladium complexes (S_P)/(R_P)-**99** offers two possibilities for the attack of the nucleophile in the subsequent addition leading to the formation of the stereoisomers (*R*)- and (*S*)-**101**. It should be mentioned that the structure of intermediate **102**, prepared from α-allenic phosphate **91**, could be proved by both NMR spectroscopy and single-crystal X-ray analysis and therefore serves as evidence for the formation of intermediate **100** (Scheme 14.22 and Eq. 14.12) [49].

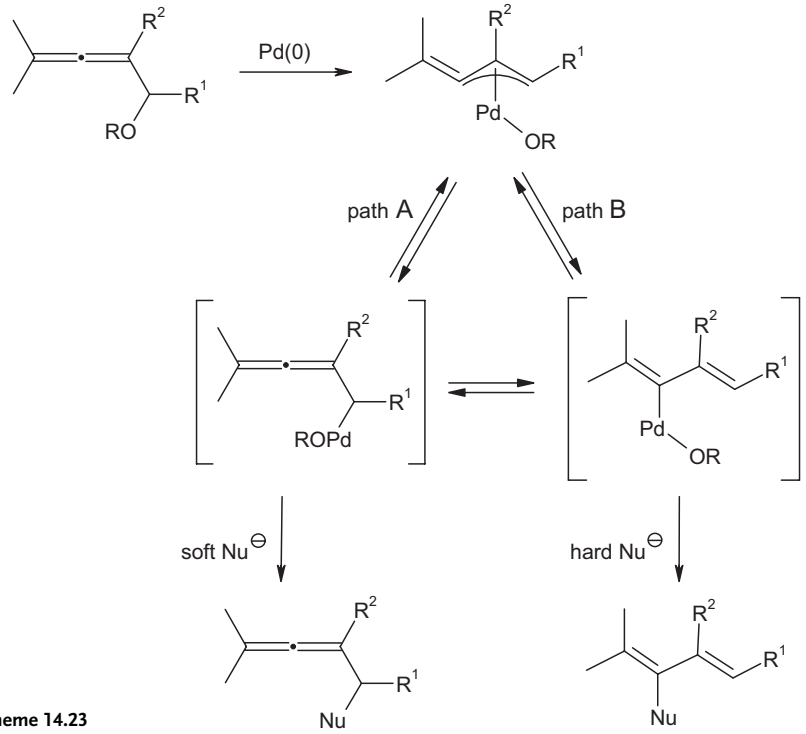


Scheme 14.22



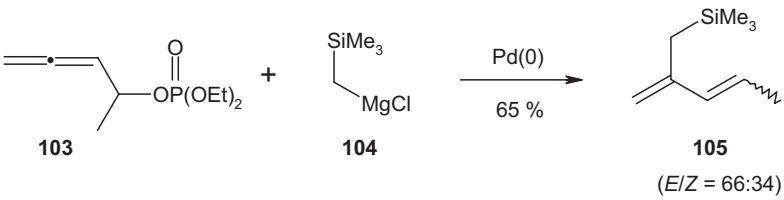
14.3
Cross-Coupling Reactions of Allenes at the Central Position

The generation of stereo- and regio-defined alkenylpalladium intermediates offers attractive options for the preparation of conjugated dienes. Several useful procedures for the synthesis of 1,2-dienes have been developed by employing α-substituted allenes as substrates in palladium-catalyzed cross-couplings. The nucleophilicity of the coupling partner is crucial for the outcome of the reaction. Whereas soft carbon nucleophiles such as malonate derivatives (see Section 14.2.3) react with α-attached allenyl acetates, phosphates and carbonates with the formation of α-substituted 2,3-dienes, hard carbon nucleophiles such as organomagnesium or organozinc halides furnish 1,3-dienes (Scheme 14.23) [50].



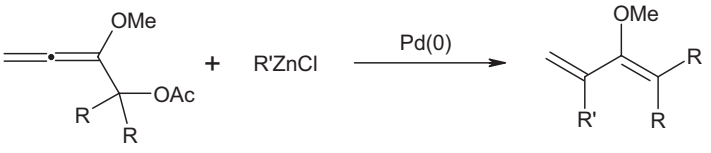
Scheme 14.23

Goré and co-workers developed a convenient experimental procedure for the conversion of α-phosphate-substituted allene **103** to the preferentially formed *E*-configured 1,3-pentadiene **105** (Eq. 14.13) [46, 47, 51]. In a similar manner, Vermeer and co-workers converted α-acetate-substituted allenes **106** into the corresponding 1,3-dienes **107** in moderate to good yields by simple treatment with organozinc chlorides in the presence of Pd(0) catalyst (Eq. 14.14) [52].

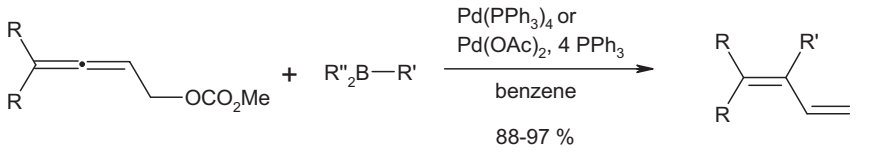


103 **104** **105** (14.13)

(*E*/*Z* = 66:34)



106 **107** (14.14)

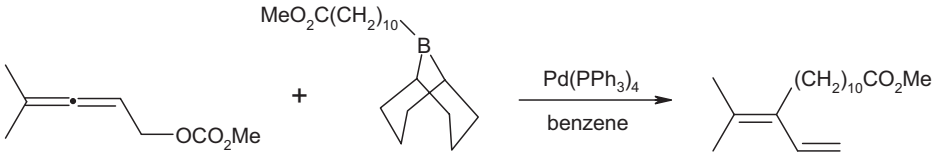


108
(R = H or Me)

109
(R' = aryl, vinyl, alkyl)

Scheme 14.24

The application of in situ-generated (alkoxy)palladium(II) species (Scheme 14.23) can be extended to reactions of α-carbonates with organoboron compounds. Cross-couplings of allenes **108** with aryl (or alkenyl) boron acids or their esters catalyzed by a palladium(0) complex afforded the 2-aryl(alkenyl)-1,3-butadienes **109** in excellent yields (Scheme 14.24) [53]. The coupling reactions of 9-BBN-derived intermediates such as ester **111** can be accelerated by applying K_3PO_4 as additive (Eq. 14.15).

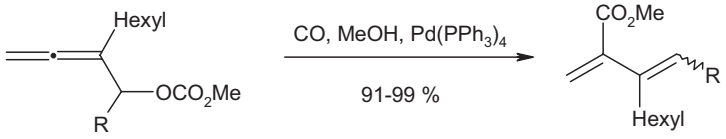


110 **111** **112**

without K_3PO_4 60 %
with 1.2 eq. K_3PO_4 79 %

(14.15)

Tsuji and co-workers carbonylated α-carbonate-substituted allenes **113** with carbon monoxide and methanol, which provided **114** in excellent yields (Scheme 14.25) [54]. They found that allenylic carbonates are more reactive than simple allylic carbonates and that the reaction proceeded rapidly even at ambient temperature under atmospheric pressure of carbon monoxide. Unfortunately, the poor *E*/*Z* selectivity diminishes the synthetic value of this very efficient carbonylation reaction.

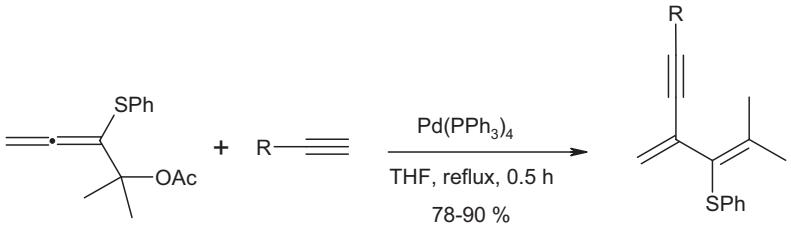


113

114
(*E*/*Z* = 2:1 to 1:1)

Scheme 14.25 [R = Pentyl, Ph, H, $(CH_2)_3CO_2Me$]

Ni and Padwa developed an interesting method for the construction of sulfur-containing 1,3-dienes **116** using **115** as precursor of a palladium-catalyzed reaction, which was executed in the absence of an amine base (Scheme 14.26) [55].

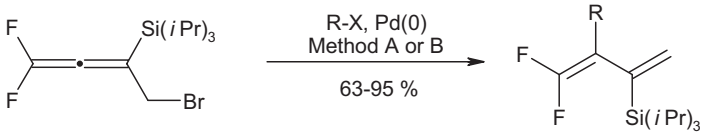


115 **116**

(R = $Me_3SiC{\equiv}C$; $HOCH_2C{\equiv}C$; $Me(CH_2)_3C{\equiv}C$)

Scheme 14.26

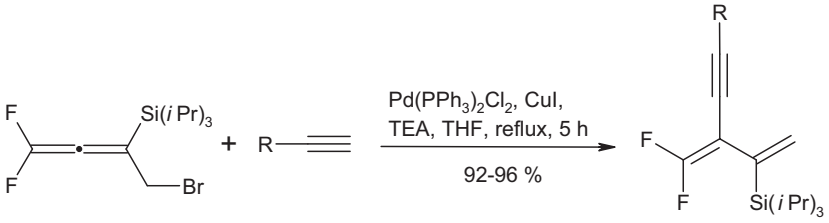
In recent reports Hammond and co-workers described couplings of the terminally bisfluorinated allene **117** with aryl (hetaryl) iodides (Scheme 14.27) [56–58]. They suggested the generation of a 2,3-butadienylzinc iodide species which rapidly isomerizes to the thermodynamically more stable 1,3-dien-2-ylzinc species (**118**, R = ZnI). Reactions of **118** under Suzuki or Sonogashira conditions afforded the corresponding fluorinated 1,3-dienes **118** (R = aryl or hetaryl) and **119**, respectively, in good to almost quantitative yields. When the aryl halide is substituted by strongly electron-withdrawing functions such as a nitro group, the yields were considerably lower [56, 57].



117 **118**

Method A [for X = I]: Zn, $Pd(PPh_3)_4$, DMF, 60 °C, 5 h
Method B [for X = $B(OH)_2$]: $Pd_2(dba)_3$, PPh_3, toluene, Na_2CO_3, 100 °C, 5-16 h

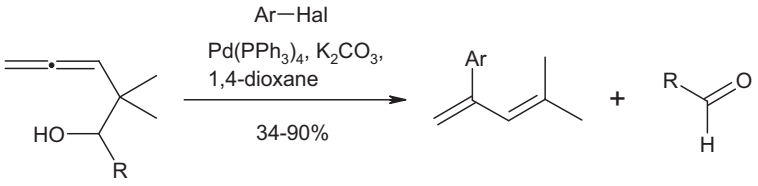
(R = aryl, hetaryl)



117 **119**

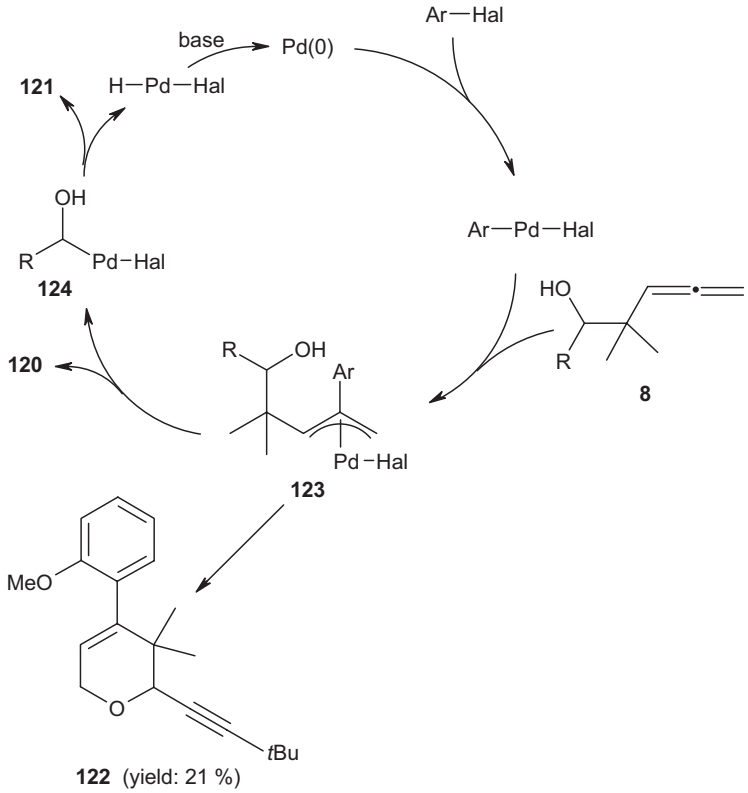
(R = Ph, Me_3Si, *n*Bu)

Scheme 14.27



Scheme 14.28

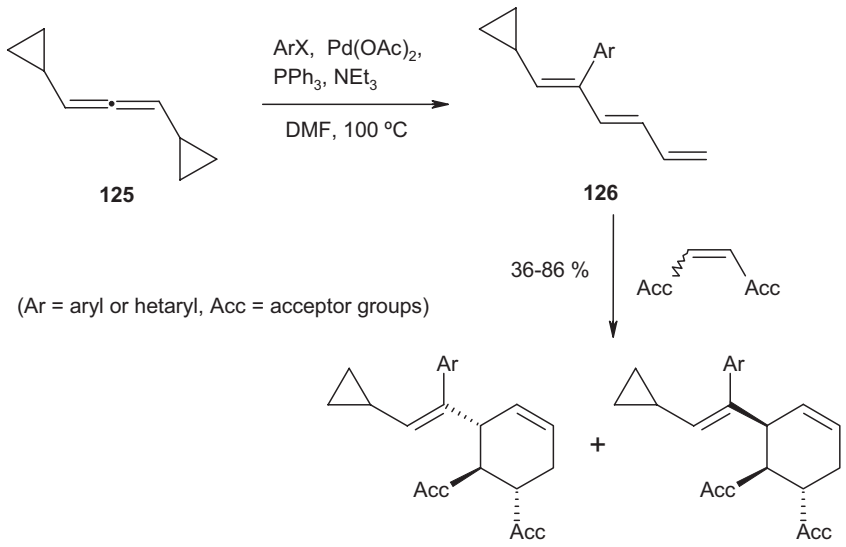
An unusual palladium-catalyzed arylative fragmenation process of β-hydroxy-substituted allenes was observed by Oh et al. [59]. Compounds such as **8** reacted with aryl bromides and iodides in the presence of $Pd(PPh_3)_4$ and K_2CO_3 as base to give 1,3-dienes **120** and aldehydes **121** as second fragment (Scheme 14.28). The initially expected cyclization product, dihydropyran **122** (Scheme 14.29), was usually not formed.



Scheme 14.29

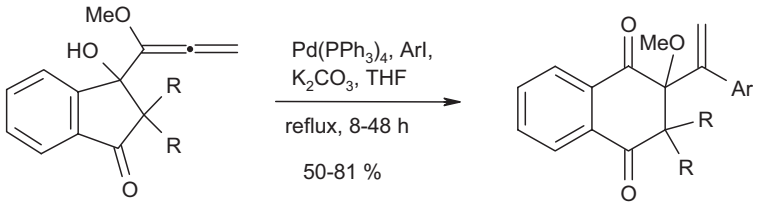
The proposed mechanism involves the usual oxidative addition of the aryl halide to the Pd(0) complex affording a Pd(II) intermediate (Ar–Pd–Hal), subsequent coordination of allene **8** and migratory insertion of the allene into the Pd–C bond to form the π-allylpalladium(II) species **123**. A remarkable C–C bond cleavage of **123** leads by decarbopalladation to 1,3-diene **120** and α-hydroxyalkylpalladium species **124**. β-H elimination of **124** affords aldehyde **121** and the H–Pd–Hal species, which delivers Pd(0) again by reaction with base (Scheme 14.29). The originally expected cyclization of intermediate **123** by employment of the internal nucleophilic hydroxyl group to form a pyran derivative **122** was observed in a single case only (Scheme 14.29).

Knoke and de Meijere [60] recently developed a highly flexible domino Heck–Diels–Alder reaction of a symmetrically substituted cumulene **125**, which also involves cross-couplings of an allene at the central position. Both aryl and hetaryl halides react efficiently with 1,3-dicyclopropyl-1,2-propadiene (**125**) and furnish 1,3,5-hexatriene derivatives **126** as intermediates, which are usually trapped by acceptor-substituted olefins in a subsequent cycloaddition, providing adducts **127a/b** in moderate to good overall yields (Scheme 14.30).



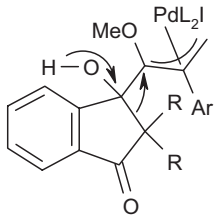
Scheme 14.30 **127a** **127b**

4-Oxo-α-tetralones **129** were synthesized starting from hydroxy-substituted methoxyallenylindanones **128** (Scheme 14.31) [61–65]. The mechanism of this intramolecular tandem carbopalladation–carbocyclic ring-expansion reaction involves the formation of π-allylpalladium intermediate **130** and its subsequent ring expansion as illustrated in Scheme 14.31. This strategy was successfully extended to the stereoselective construction of α-disubstituted cyclopentanones with the corresponding allenylcyclobutanols serving as precursors [66].



128 **129**

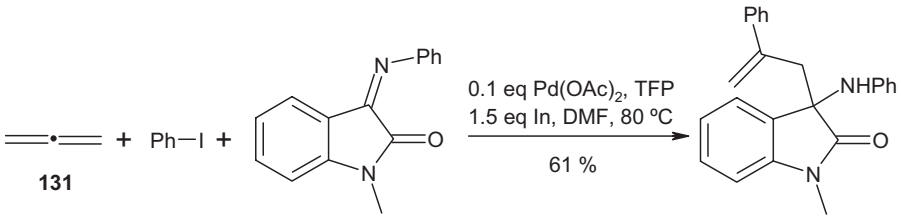
(R = Me, Et, *n*Pr, Bn; Ar = Ph, *p*Tolyl, *p*$NO_2C_6H_4$)



130

Scheme 14.31

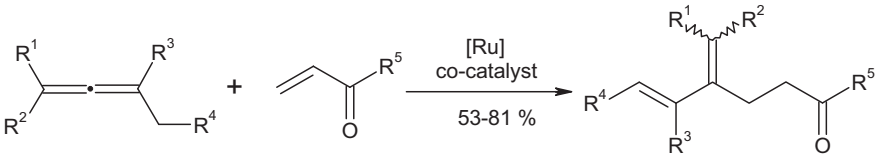
Grigg and co-workers described a novel three-component indium–palladium-mediated allylation reaction [67]. As exemplified by Eq. 14.16, 3,3-disubstituted oxindole derivative **133** was obtained smoothly from phenyl iodide, the easily available isatin imine **132** and 1,2-propadiene (**131**). Excellent levels of diastereoselectivity were obtained in this cascade reaction employing imines derived from enantiopure sulfinamides.



131 **132** **133**

(14.16)

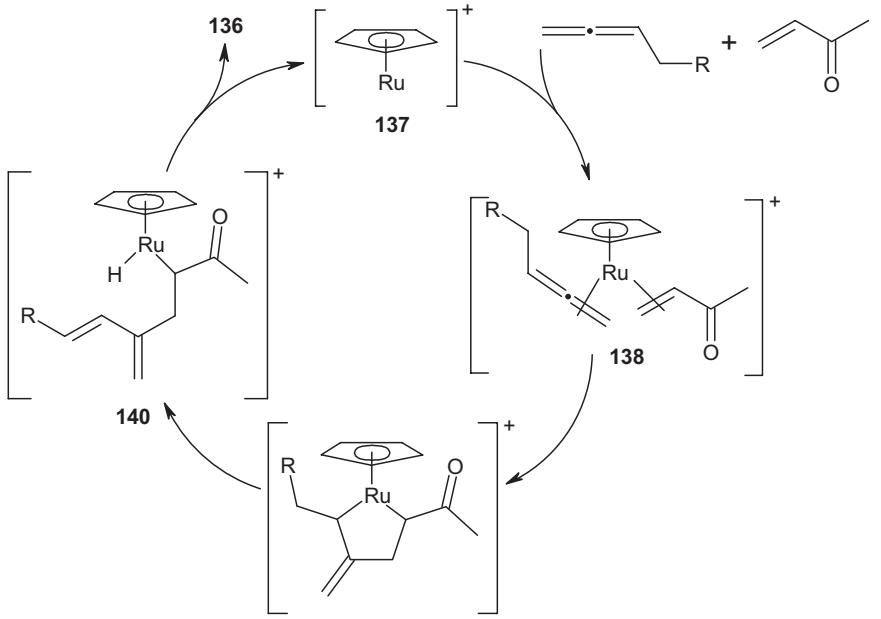
Trost and co-workers published a series of papers dealing with ruthenium-catalyzed two-component reactions which provide functionalized 1,3-dienes [68–71]. Various substituted allenes **134** were combined with vinyl ketones **135**, leading to 1,3-dienes **136** in reasonable to good yields (Scheme 14.32). The reaction is catalyzed by cationic ruthenium complexes [$CpRu(MeCN)_3PF_6$ or CpRu(COD)Cl] and promoted by a Lewis acid co-catalyst, e.g. $SnCl_4$ and $CeCl_3$. It should be mentioned that 1,3-dienes **136** serve as valuable intermediates and have been efficiently applied in a coupling–Diels–Alder cycloaddition reaction sequence, producing [4 + 2]-cycloadducts with excellent chemo- and regioselectivity [68, 71].



134 **135** **136**

Scheme 14.32

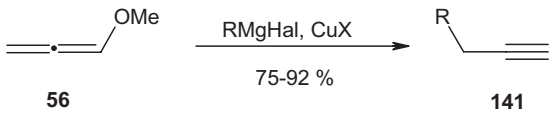
The proposed mechanism involves coordination of allene and α,β-unsaturated ketone to the cationic cyclopentadienylruthenium species **137**. Subsequent formation of the ruthenacycle **139**, followed by β-hydride elimination, generates the ruthenium hydride species **140**. Finally, reductive elimination closes the cycle and regenerates the ruthenium intermediate **137** (Scheme 14.33) [68, 71].



Scheme 14.33

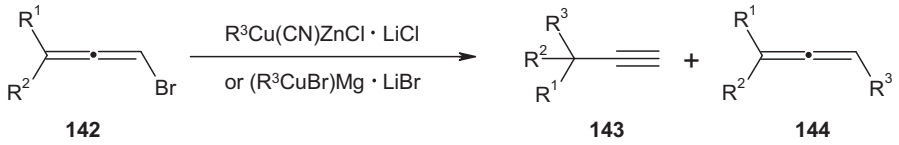
14.4 Synthesis of Alkynes

To date, less effort has been made in the transition metal-catalyzed conversion of allenes into alkynes. Almost 30 years ago, Meijer and Vermeer developed a convenient synthesis of monosubstituted alkynes **141**. They started from methoxyallene (**56**) and treated this allene derivative with Grignard reagents in the presence of catalytic amounts of copper(I) halides thus generating **141** in good to excellent yields (Scheme 14.34) [72]. It was suggested that the reactive species in this coupling are heterocuprates (RCuX)MgX. Attempts to achieve an extension of this catalytic process to other donor-substituted allenes failed. In contrast, conversion of 1-iodo-1-methoxyallene to the corresponding 1-alkynyl methyl ether was successful when 0.5–1 equiv. of copper(I) salt was employed [10].



Scheme 14.34 (Hal = Br, I; X = Cl, Br, I)

More attractive copper-catalyzed (mediated) transformations of allenes into alkynes were reported by Caporusso and co-workers [27f, 73–75]. Allenes **142** were converted into alkynes **143** by treatment with stoichiometric amounts of a cuprate species, as exemplified in Scheme 14.35. The problem of regioselective formation of either alkyne **143** or allene **144** was solved by the proper choice of the organometallic species. Preferential formation of alkynes **143** could be achieved employing cuprates such as $R^3Cu(CN)ZnCl \cdot LiCl$, which are prepared from organozinc compounds. On the other hand, reactions of organomagnesium derived cuprates $(R^3CuBr)Mg \cdot LiBr$ mostly provided allenes **144** as major components.

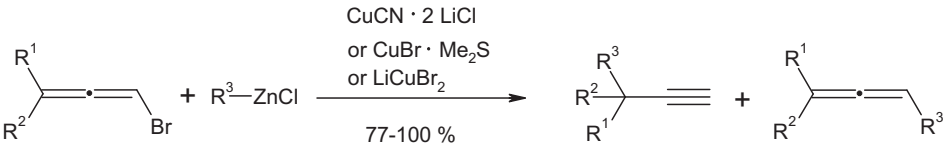


(R^1 = H, Me; R^2 = Et, *n*Pr, *t*Bu, Ph; R^3 = *i*Pr, *n*Bu, $ClMgO(CH_2)_n$ [n = 3-4], $RC{\equiv}C(CH_2)_2$ [R = H, Me_3Si])

Scheme 14.35

The coupling process, which has been extended successfully to functionalized cuprates, can also be performed with alkylzinc chlorides in the presence of catalytic amounts of cuprous salts (e.g. $CuCN \cdot 2LiCl$, $CuBr \cdot Me_2S$ and $LiCuBr_2$), providing products with excellent alkyne/allene selectivity (**143**:**144** = 91:9 to 100:0) (Scheme

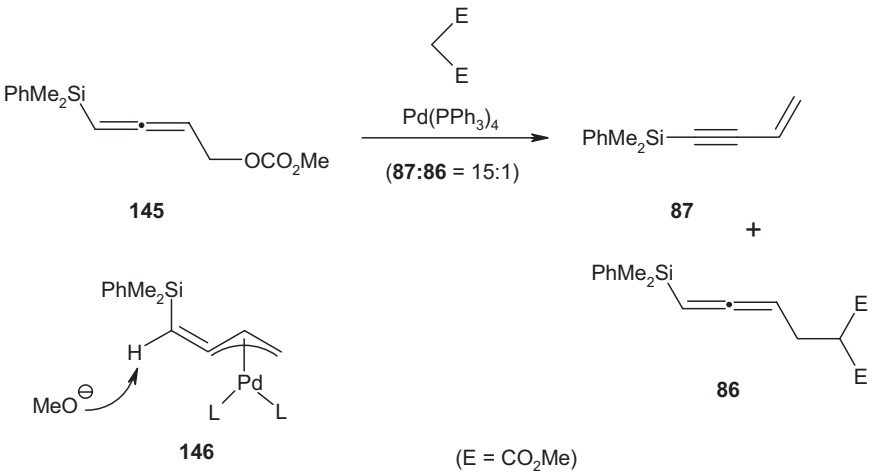
14.36) [73]. Similarly, an efficient procedure of general applicability was described for the synthesis of propargylamines by copper(I)-catalyzed amination of bromoallenes [75]. It should be mentioned that by use of an enantioenriched allene **142** ($R^1 = n$Pr, R^2 = Me), the optical purity was completely transferred to alkyne **143** ($R^3 = n$Bu) [73].



(R^1 = H, Me; R^2 = Et, *n*Pr, *t*Bu, Ph; R^3 = *i*Pr, *i*Bu, *n*Bu, $ClMgO(CH_2)_n$ [n = 3-4], $H_2C{=}CH(CH_2)_2$)

Scheme 14.36

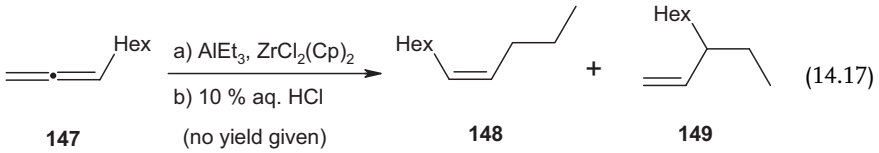
A single reaction has been described in which a palladium-catalyzed reaction was employed to form an alkyne [45]. Thus, attempted alkylation of carbonate **145** with dimethyl malonate in the presence of $Pd(PPh_3)_4$ gave a mixture of enyne **87** and the alkylation product **86** in a 15:1 ratio (Scheme 14.37). Methoxide caused an elimination in (π-allyl)palladium intermediate **146**, which is apparently faster under these conditions than a reaction with the nucleophile (cf. Eq. 14.9). The synthetic importance of this process seems to be limited.



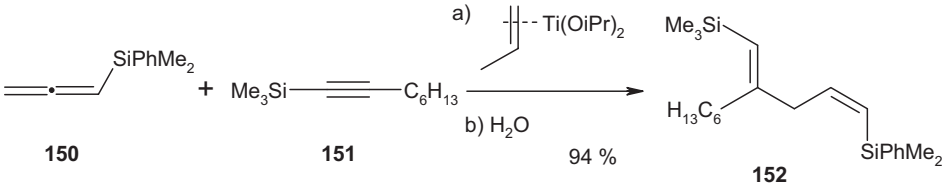
Scheme 14.37

14.5 Miscellaneous Reactions

The zirconium-catalyzed cross-coupling reaction of 1,2-nonadiene (**147**) and triethylaluminum afforded alumacyclopentanes, which were subsequently hydrolyzed to give olefins such as **148** and **149** (Eq. 14.17) [76].

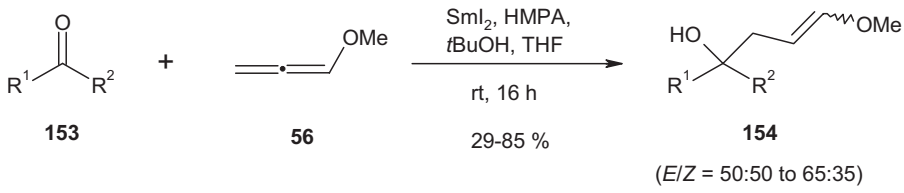


Several stoichiometric methods for transition metal-promoted transformations of allenes have been studied, involving metals such as iron [77] and titanium [78, 79]. The titanium-mediated reactions developed by Sato and co-workers have probably the greatest synthetic impact, as exemplified by the conversion of silylated allene **150** to 1,4-diene **152** (Scheme 14.38) [78].



Scheme 14.38

An interesting novel coupling reaction of allenes with carbonyl compounds mediated by a lanthanide metal species was reported recently [80]. The samarium(II) iodide-mediated reaction of various ketones or aldehydes **153** with methoxyallene (**56**) afforded exclusively γ-addition products 4-hydroxy-1-enol ethers **154** in moderate to good yields with low *cis*/*trans* selectivity (Scheme 14.39).



[R^1/R^2 = H/Hexyl; Me/Me; Et/Et; $(CH_2)_n$, n = 4-6]

Scheme 14.39

14.6 Conclusion

The transition metal cross-couplings of allenes described here offer practical solutions for the modification of 1,2-dienes and access to the preparation of highly functionalized 1,3-dienes, alkynes and alkenes, which are often not easily accessible in a regio- and stereoselective manner by classical methods. Some of the prepared alkynes or functionalized allenes serve as important intermediates in syntheses of natural products, biologically active compounds, e.g. enynes and enyne-allenes, and new materials. It can be predicted that further synthetic efforts will surely be focused on new applications of allenes in transition metal-catalyzed cross-coupling reactions.

Addendum (July 1st, 2004)

Additional references for Section 14.1 [81], Section 14.2.1 [82, 83], Section 14.2.2 [84, 85] and Section 14.3 [86–89].

Abbreviations

9-BBN	9-borabicyclo[3.3.1]nonane
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
COD	cyclooctadiene
Cp	cyclopentadiene
dba	dibenzylideneacetone
DIOP	2,3-*O*-isopropylidine-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphanyl)ethane
dppp	1,3-bis(diphenylphosphanyl)propane
MeOBIPHEP	(6,6′-dimethoxybiphenyl-2,2′-diyl)bis(diphenylphosphine)
mesal	*N*-methylsalicylaldimine
TEA	triethylamine
TFP	tris(*O*-furyl)phosphane
TIPS	tri(isopropyl)silyl

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15
Transition Metal-Catalyzed Cycloisomerizations of Allenes

A. Stephen K. Hashmi

15.1
Introduction

Cycloisomerizations are one of the most popular methods for the formation of carbo- and heterocyclic compounds [1, 2]. Although in most cases alkenes and/or alkynes are still involved, there now exist a significant number of similar applications of allenes which benefit from the higher reactivity of the allene-unit.

Most of these isomerization reactions probably follow one of the following four mechanistic possibilities:

1. Activation of one the double bonds of the allene by coordination to an electrophilic metal center such as Hg(II), Ag(I), Pd(II), Rh(I), Cu(I) or Au(III). Then an intramolecular nucleophile can attack and the product is formed by protodemetallation of the intermediate (Scheme 15.1). Depending on electronic and steric factors, either the proximal or the distal π-bond of the allene **1** is activated in that way (**2** and/or **3**). For each of these two possibilities now an *exo* or *endo* attack of the nucleophile is conceivable, leading to intermediates **4**–**7**. An equilibrium between both **5** and **6** and **9** is possible. Finally, from **4** the vinyl-substituted **8** is formed. From **5**, **6** or **9** the exocyclic alkene **10** and/or the endocyclic alkene **11** can be observed. Compound **7** would deliver the endocyclic alkene **12**.

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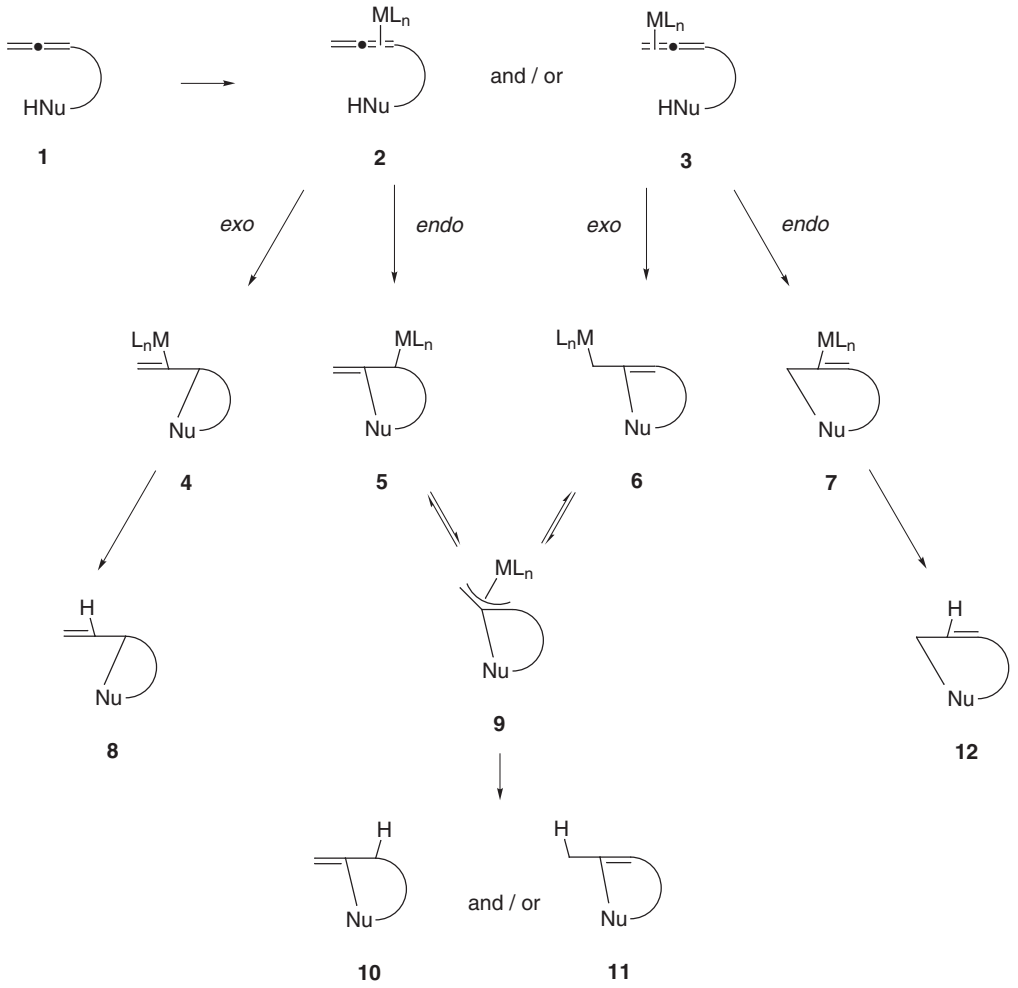
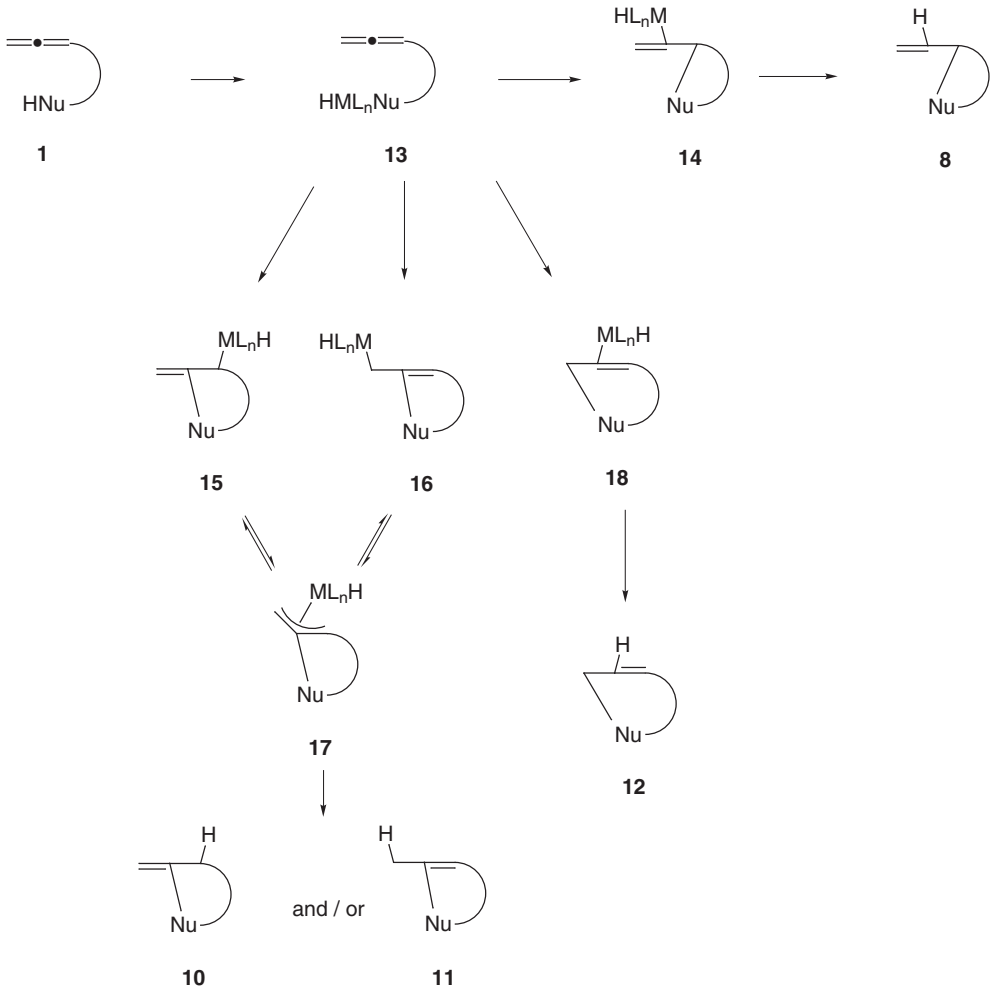


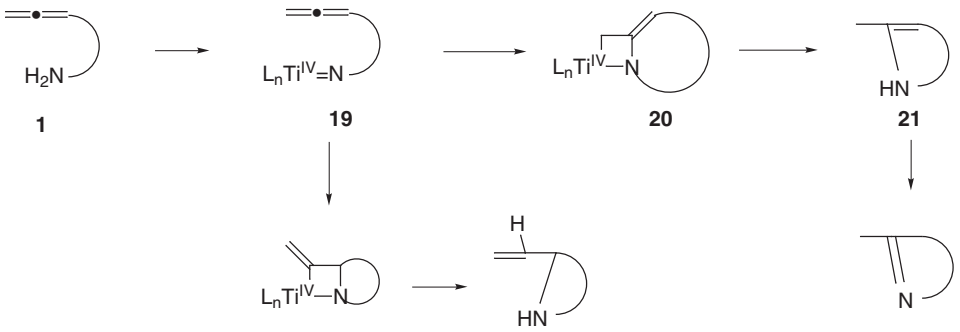
Scheme 15.1

2. An activation of the nucleophile by insertion of the transition metal species into a nucleophile–hydrogen bond. Here typical metals are Pd(0), Y(III), La(III) and Sm(III). Then one π-bond of the 1,2-diene in **13** inserts intramolecularly into the nucleophile–metal bond (Scheme 15.2). Depending on the regioselectivity of this insertion either **14**, the possible equilibrium between **15**, **16**, **17** or **18** will be the next intermediates. Reductive elimination finally delivers **8** from **14**, **10** and/or **11** from **15**, **16** or **17** and **12** from **18**.



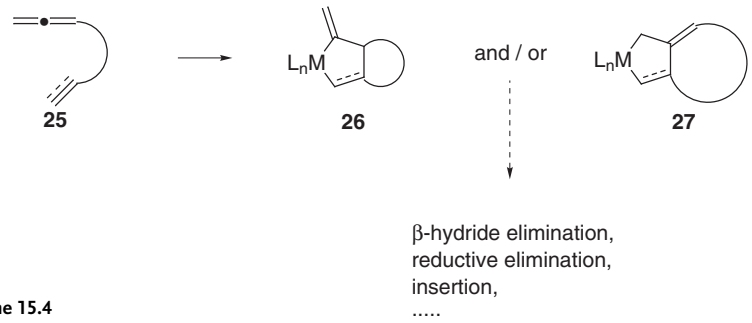
Scheme 15.2

3. The nucleophile is activated by the formation of a titanium(IV)–imido complex **19**. The next step is a [2 + 2] cycloaddition with one of the π-bonds of the allene, depending on the regioselectivity leading to either **20** or **22**. Compound **20** then delivers **21** by twofold stepwise proto-demetallation and the latter enamine tautomerizes to the imine **24** (Scheme 15.3). Compound **22**, on the other hand, should provide allylamines **23**, but as we shall see, there are no examples of that mode of reaction known so far.



Scheme 15.3

4. In this case the reaction takes place with other C–C multiple bonds rather than with a nucleophile (substrates of type **25**). Cyclometallation of the π-bonds leads either to metallacycle **26** or **27** (Scheme 15.4). Then different pathways are possible, for example *β*-hydride elimination and reductive elimination are known.



Scheme 15.4

Only in some cases does the presumed reaction mechanism deviate slightly from the mechanistic schemes sketched above; see, for example, Scheme 15.8. In this chapter the term 'catalyzed' is used in a very broad sense, basically in such a way that the metal species is not intrinsically consumed or changed in a stoichiometric way during the reaction; still, reactions discussed here might need as much as 20 mol% or even several equivalents of 'catalyst' owing to a very slow reaction rate (for example, the Ag(I) catalysts and the heterogeneous reactions on the surface of yellow HgO).

As one can also see, different mechanisms might lead to the same products. Hence the mechanism is not a good criterion for the organization of this chapter. The product also is not a good choice, because the same starting material would often deliver different product types (for example, different ring sizes depending on the catalyst, the substituents or the solvent; see, for example, the reactions of compounds **103**, **141** and **247**). Therefore, the chapter is organized by the different types of starting materials.

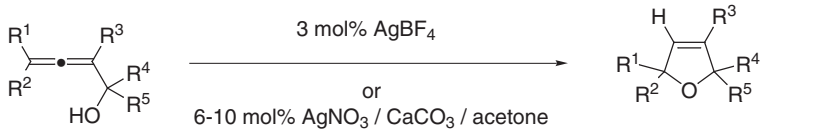
Some of the reactions covered here are in principle also possible under strongly acidic or strongly basic conditions or as concerted pericyclic reactions at high temperatures [3]; for polyfunctional substrates in the synthesis of complex products the advantage of transition metal catalysis under neutral conditions and at low temperatures is obvious.

Smaller parts of this chapter have been covered in sub-sections of different reviews of other subjects in recent years [4–9].

15.2 Alcohols as Nucleophiles

The field was initiated by mercury(II) serving as a catalyst for the cycloisomerization of allenylcarbinols; Gelin and Albrand's investigation of this reaction was limited to substrates with alkyl substituents on the allene [10–12].

Compared with the direct use of strong acids, the benefit of the metallic electrophile, which is exchanged for a proton later by a proto-demetallation step, is higher selectivities of the reactions [13]. Efforts to circumvent the disadvantages of mercury then led to the use of silver(I). After Bertrand et al. initially observed that silver is active [14], this was developed to a useful synthetic protocol shown for the transformation of **28** to **29** by Olsson and Claesson (Scheme 15.5) [15].

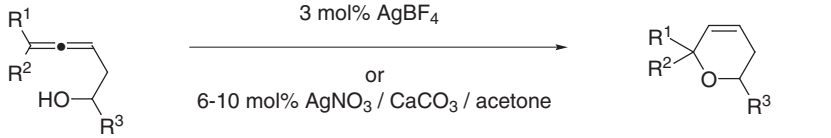


28 **29** (20-63%)

R^1,R^2,R^3,R^4,R^5 = H, alkyl

Scheme 15.5

The higher homologue also reacts in an *endo-trig* mode at the distal allenic double bond; thus from **30** the dihydropyran **31** is formed (Scheme 15.6) [15–17].



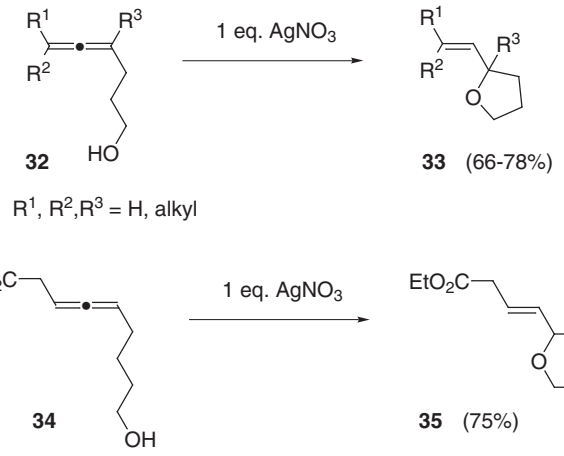
30 **31** (40-85%)

R^1,R^2,R^3 = H, alkyl

Scheme 15.6

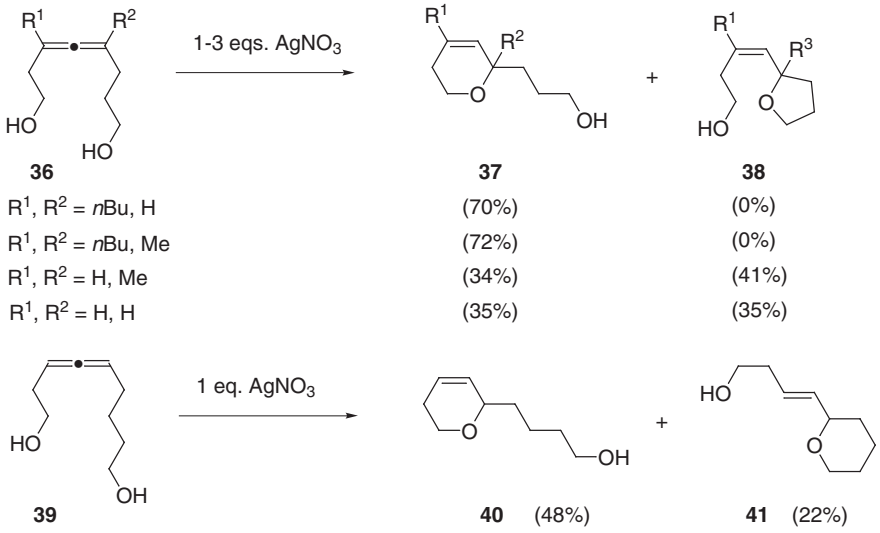
Extending the bridge between the hydroxyl group and the allene to three carbon atoms as in **32** then led to vinyltetrahydrofurans **33** by an *exo-trig* cyclization at the

proximal allenic double bond; here Gore et al. needed one or more equivalents of $AgNO_3$ (Scheme 15.7) [17, 18]. With a four-carbon tether in **34**, by a similar reaction the vinyltetrahydropyrans **35** were formed [18–20].



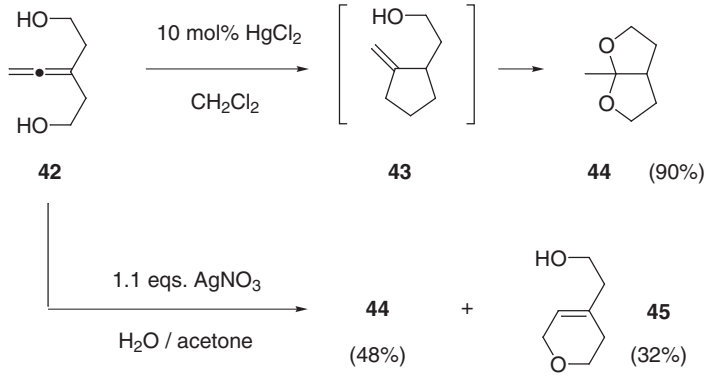
Scheme 15.7

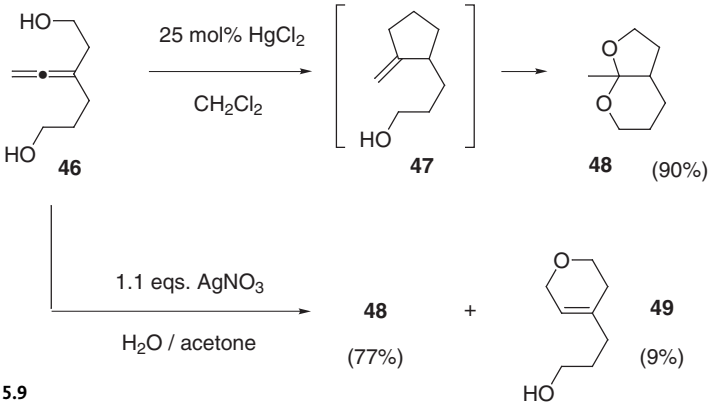
The same group also conducted a series of competition experiments with diols such as **36**, which show that $AgNO_3$ and $HgCl_2$ behave similarly; in Scheme 15.8, the results for $AgNO_3$ are depicted [17]. It is obvious that a selective cyclization to a dihydropyran **37** is dependent on an alkyl chain such as R^1; with $R^1 = H$, for both $R^2 = H$ and $R^2 =$ alkyl an almost 1:1 mixture of **37** and tetrahydrofuran **38** was observed. The competition of a two-carbon chain with a four-carbon chain in **39** leads to a 2:1 mixture of the dihydropyran **40** as the major product and the tetrahydropyran **41** as the minor product.



Scheme 15.8

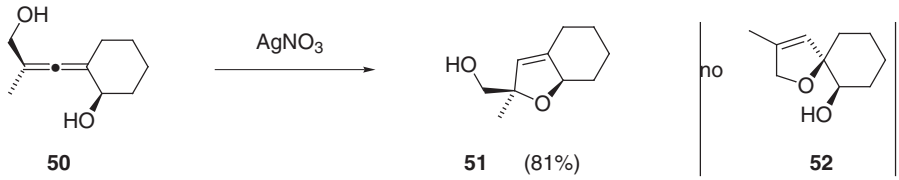
Further experiments with diols such as **42** and **46** showed that bicyclic acetals **44** and **48** are formed (Scheme 15.9) [21]. With $AgNO_3$ the dihydropyrans **45** and **49** were always observed as side-products.





Scheme 15.9

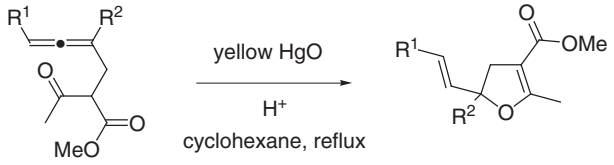
Even the competition of two different allenylcarbinols can be highly selective; the conversion of **50** to **51** only is one example investigated by Marshall and Pinney (Scheme 15.10) [22]. The secondary alcohol and not the primary one cyclizes; a possible explanation is the preferential complexation of Ag(I) at the less congested double bond of the allene [23].



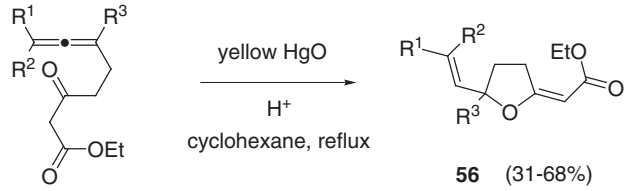
50 **51** (81%) **52**

Scheme 15.10

The vinyldihydrofuran **54** and the vinylalkylidenetetrahydrofuran **56** were accessible from the enol form of β-keto esters **53** and **55** by *exo-trig* cylizations (Scheme 15.11) [24].



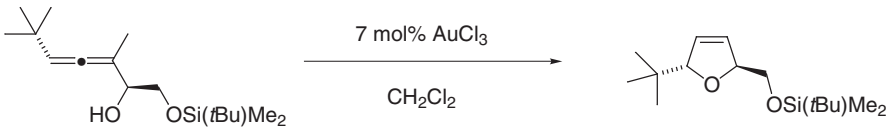
53 R^1,R^2 = H, alkyl **54** (72-74%)



55 R^1,R^2,R^3 = H, alkyl **56** (31-68%)

Scheme 15.11

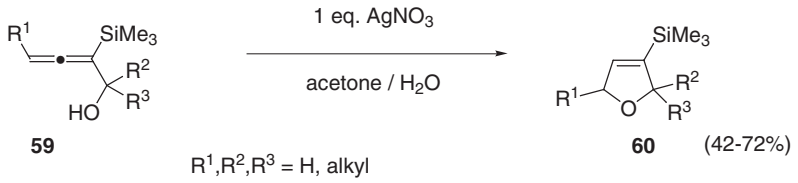
Allenylcarbinols that show a sluggish reaction with Ag(I) can react efficiently with gold(III) chloride [25, 26] as the catalyst. For example, Krause and co-workers demonstrated that the substrate **57** with 7 mol% $AuCl_3$ delivered 95% of the desired **58** whereas $AgNO_3$ only delivered a complex mixture (Scheme 15.12) [27, 28].



57 **58** (95%)

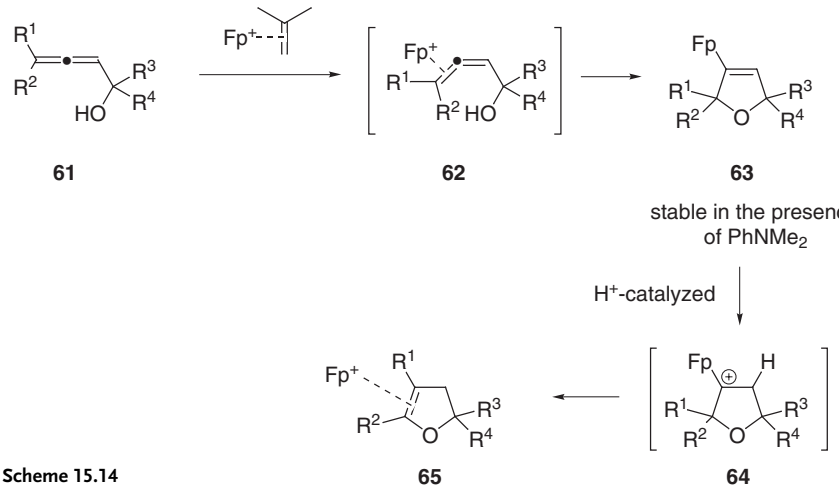
Scheme 15.12

Timethylsilyl-substituted allenylcarbinols also react; in the presence of $AgNO_3$, the trisubstituted allenes **59** deliver dihydrofurans **60**, which are sensitive towards air oxidation to the furans, as reported by Wang et al. (Scheme 15.13) [29].



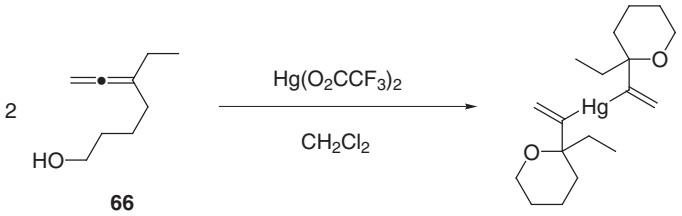
Scheme 15.13

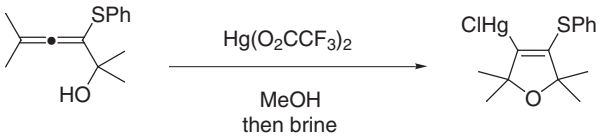
Interesting direct evidence for the reaction pathway of these metal-catalyzed reactions was obtained from stoichiometric reactions of allenylcarbinols such as **61** with the $[\eta^5\text{-}C_5H_5Fe(CO)_2]^+$ (Fp^+) complex. From the isobutene adduct of Fp^+ and **61** the π-complex **65** was obtained. The complex **65** was suspected to be the product of an acid-catalyzed rearrangement; indeed, in the presence of *N,N*-dimethylaniline as a base, **63** was isolated (Scheme 15.14) [30].



Scheme 15.14

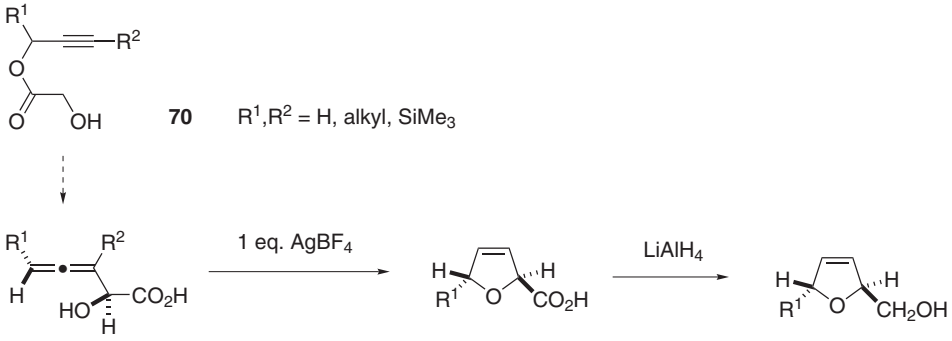
Especially with Hg(II) it was often possible to obtain directly the vinylmercury species as a stable compound, for example in the cyclization of **66** to **67** [20] or the formation of **69** from **68** (Scheme 15.15) [31]. This is in complete accord with the intermediate **7** in the mechanistic model for the intramolecular addition of nucleophiles to the allene unit (Scheme 15.1).





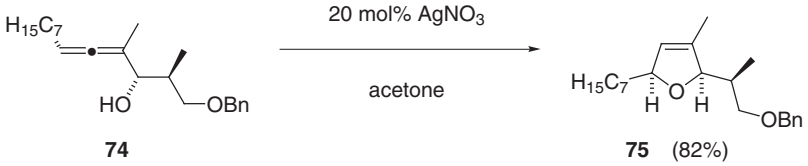
Scheme 15.15 **68** **69** (32%)

Several applications of this methodology are known. For the determination of the relative configuration of the stereocenter and the axial chiral unit of **71**, the product of a diastereoselective ester enolate Claisen rearrangement of **70**, with $AgBF_4$ a cyclization to **72** was initiated. Then the carboxylic acid was reduced to alcohol **73** and the position of the substituents was investigated by NMR and by the use of NMR shift-reagents (Scheme 15.16) [32]. Control experiments ensured the stereospecificity of the cyclization and the reduction step. There are further examples of this strategy [33].



Scheme 15.16

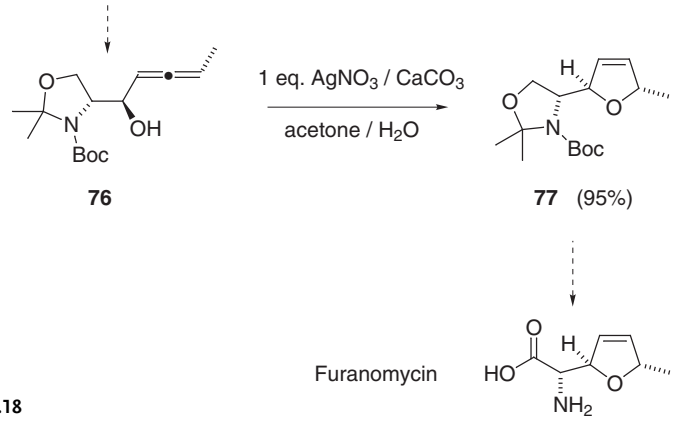
The stereospecificity of the reaction was already mentioned around 1990 [34, 35]. Since enantiomerically pure allenes are available by a number of methods [36, 37], this clean axial to central chirality transfer is very useful in organic synthesis. Several further examples can be found in the literature [38, 39], one example being the cyclization of **74** to **75** (Scheme 15.17) [40].



74 **75** (82%)

Scheme 15.17

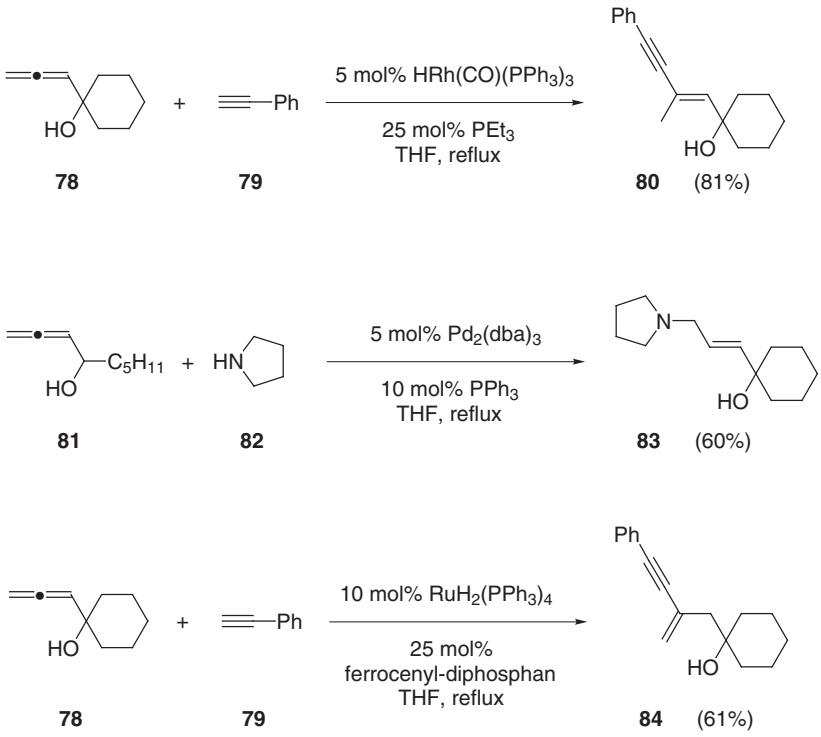
In a synthesis of furanomycin, this reaction was a stereospecific key step for the construction of the dihydrofuran ring **77** from the chiral non-racemic precursor **76** (Scheme 15.18) [41].



76 **77** (95%)

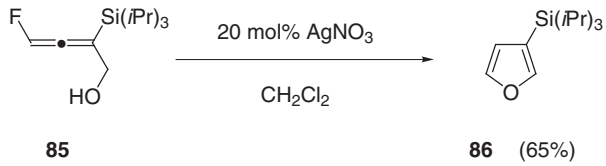
Scheme 15.18

From the results presented here, one could get the impression that such allenes with hydroxyl groups in the substituents will always form heterocycles in the presence of transition metal catalysts, but in the presence of other substrates even allenylcarbinols can react to give different products. Examples are the rhodium-catalyzed reaction of allenylcarbinol **78** and phenylacetylene **79** to **80** [42], the palladium-catalyzed reaction of **81** and pyrrolidine **82** to **83** [43] and the ruthenium-catalyzed reaction of **78** and **79** to **84**, an isomer of the rhodium-catalyzed reaction of the same substrates mentioned above [44] (Scheme 15.19).



Scheme 15.19

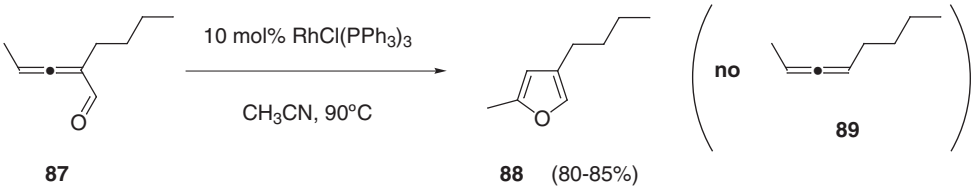
In the case of the fluorine-substituted allene **85** with Ag(I) catalyst, only the product of a cyclization/elimination process, the furan **86**, was produced (Scheme 15.20) [45].



Scheme 15.20

15.3
Allenyl Ketones

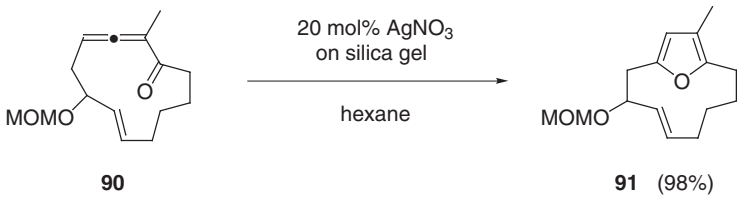
In efforts to decarbonylate the allenylaldehyde **87** with Wilkinson's catalyst, Marshall and Robinson observed the formation of the furan **88** rather than the desired hydrocarbon, the allene **89** (Scheme 15.21) [46].



Scheme 15.21

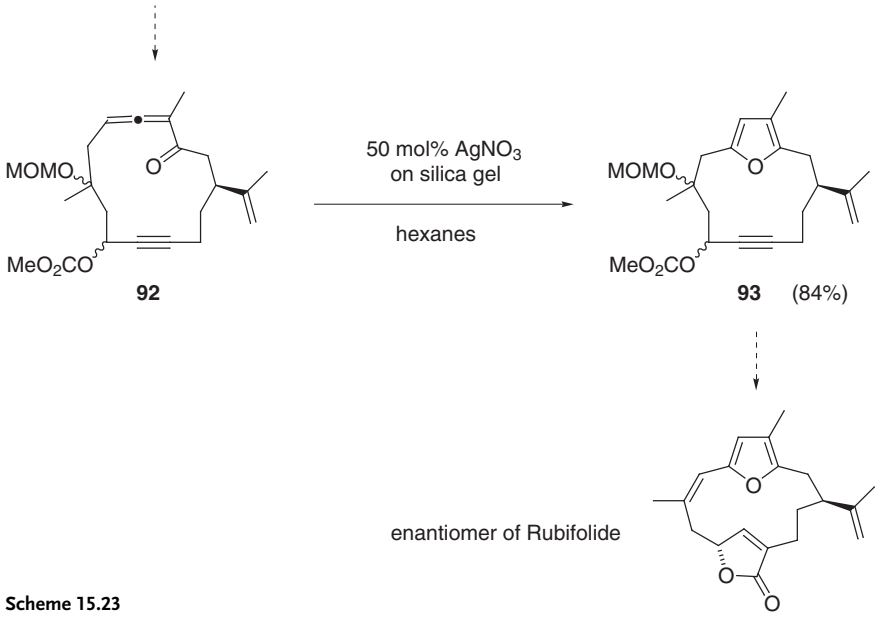
Other π-coordinating Lewis acids were investigated and $AgNO_3$ and $AgBF_4$ were found to be effective, but for an efficient conversion 20 mol% or more of the silver salt was necessary. Then almost quantitative yields can be obtained. This transformation was known, but the conditions of the transition metal catalysis were much milder than those of flash vacuum pyrolysis at 500–800 °C [47, 48]. In addition to methodological work [49–51], a very interesting mechanistic investigation was conducted [52]. The latter, for example, proved that the $CaCO_3$ additive used in the earlier work was not necessary at all and that the migration of the hydrogen atom from the end of the allene to the central carbon during the cycloisomerization is protic and not intramolecular. The silver catalyst could even be reused [39].

Challenging applications in the field of macrocyclic furans have been investigated. The major synthetic advantage is the cyclization to the furan after the macrocyclization. This will avoid a problematic ring closure to macrocycles (to 1,3-furanophanes) with a furan substrate ('furan latest strategy'). Test substrates demonstrated the viability of this concept [50], as shown below for the synthesis of the [8]furanophane **91** from the macrocyclic ketone **90** (Scheme 15.22) [39].



Scheme 15.22

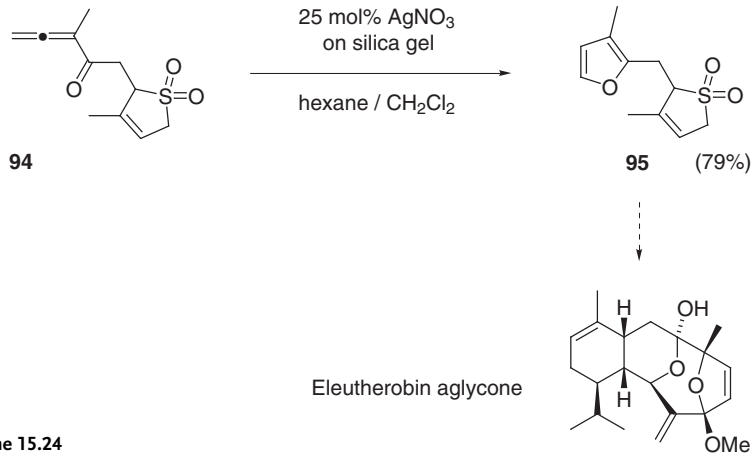
Steps in total syntheses are the conversion of the macrocycic allenyl ketone **92** to the furanophane **93** in the synthesis of the enantiomer of rubifolide (Scheme 15.23) [53] and different steps in other references [54, 55].



92 93 (84%)

Scheme 15.23

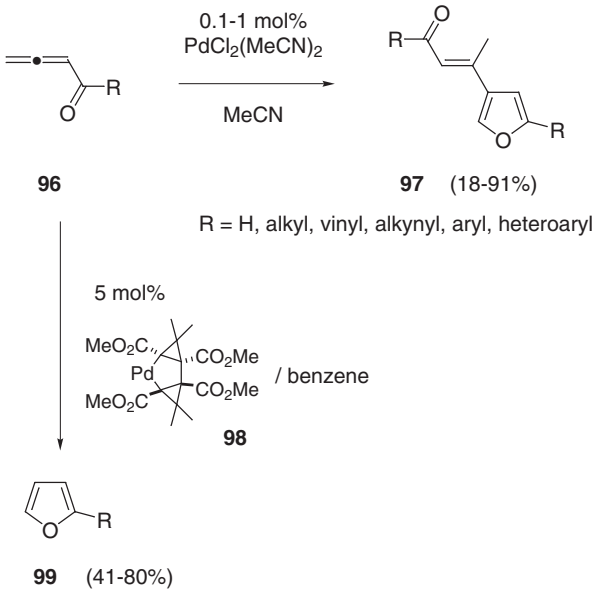
For a tandem Diels–Alder/fragmentation approach to the eleutherobin aglycone, Winkler et al. used Marshall's protocol in an early step of the synthesis. The building block **95** was prepared in that way (Scheme 15.24) [56].



94 95 (79%)

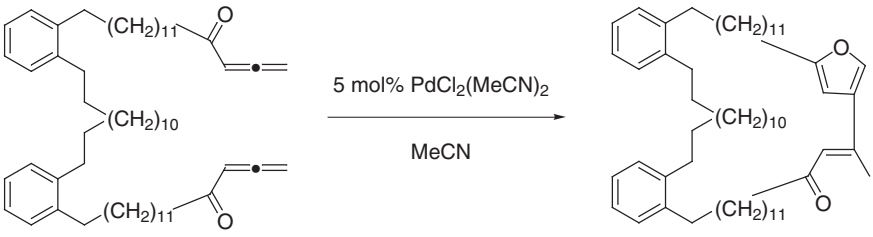
Scheme 15.24

Hashmi et al. investigated a number of different transition metals for their ability to catalyze reactions of terminal allenyl ketones of type **96**. Whereas with Cu(I) [57, 58] the cycloisomerization known from Rh(I) and Ag(I) was observed (in fact the first observation that copper is also active for cycloisomerizations of allenes), with different sources of Pd(II) the dimer **97** was observed (Scheme 15.25). Under optimized conditions, **97** was the major product. Numerous substituents are tolerated, among them even groups that are known to react also in palladium-catalyzed reactions. Examples of these groups are aryl halides (including iodides!), terminal alkynes, 1,6-diynes, 1,6-enynes and other allenes such as allenylcarbinols. This chemoselectivity might be explained by the mild reaction conditions.



Scheme 15.25

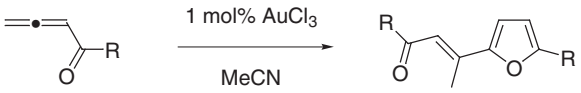
With the bulky metallo-organic Pd(II) catalyst **98**, on the other hand, selective formation of **99** was possible; here functional groups are tolerated that would react with an Ag(I) catalyst (for example, terminal alkynes, alkyl chlorides, alkyl bromides and alkyl iodides) [59]. With 1,*n*-diallenyl diketones (**100**), easily accessible by a bidirectional synthesis, up to 52-membered macrocycles (**101**) could be prepared in an end-group differentiating intramolecular reaction (Scheme 15.26) [60]. For ring sizes lager than 12 only the *E*-diastereomer is formed; overall yields of the macrocycles varied between 17 and 38%. Only with tethers shorter than 11 carbon atoms could the *Z*-diastereomer of the products be observed, a stereoisomer unknown from the intermolecular dimerization reactions of **96**.



100 **101** (20%)

Scheme 15.26

Limitations of the Pd(II)-catalyzed cycloisomerization/dimerization are strongly coordinating groups such as pyridyl groups, amines, thioethers or halogens on the allene [61]. With **96**, $AuCl_3$ delivered products **102**, which are constitutional isomers of the dimers of the Pd(II)-catalyzed reactions (Scheme 15.27) [62]. Compounds **102** are always accompanied by the monosubstituted furans **99**. Furthermore, these catalysts were highly reactive and allowed a much faster reaction than Ag(I) or Pd(II) under the same conditions.



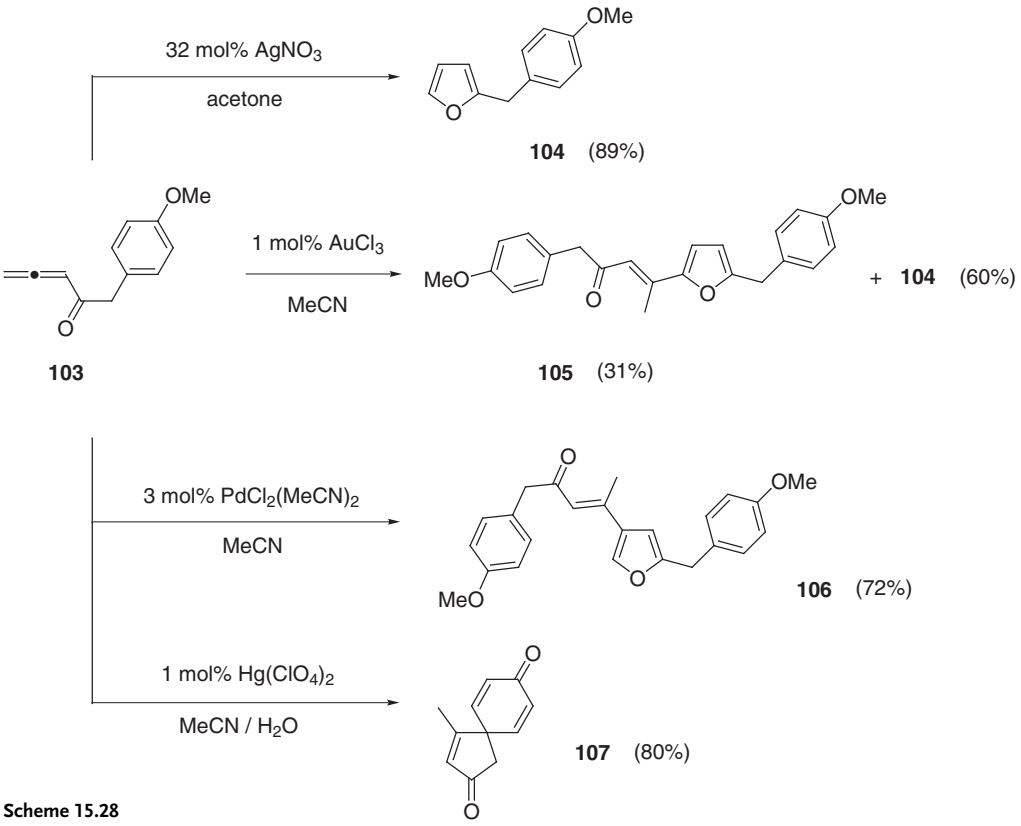
96 **102** (4-51%)

R = alkyl, aryl

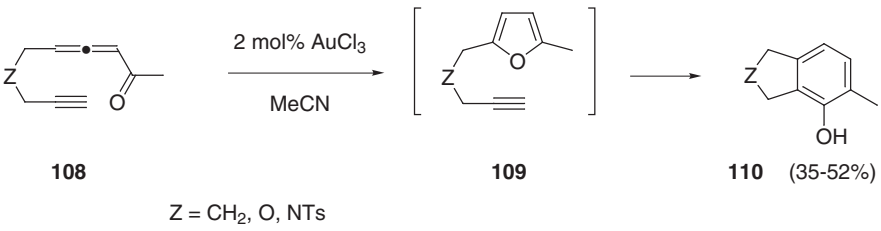
Scheme 15.27

With certain substitution patterns such as in the *p*-methoxybenzyl allenyl ketone **103**, the products from reactions with Ag(I), Au(III), Pd(II) and Hg(II) are entirely different; **104**, the dimers **105** or **106** or even **107** were formed (Scheme 15.28) [63, 64].

When a terminal alkyne is offered intramolecularly as in allenyne **108**, the highly substituted phenols **110** were formed (Scheme 15.29) [65]. The reaction proceeds through an initial isomerization to the corresponding furan **109**, which could be proved by the direct use of that furans [66–68].

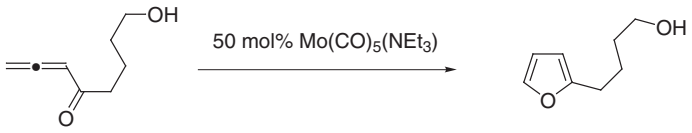


Scheme 15.28



Scheme 15.29

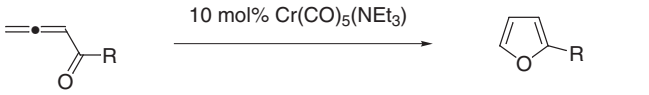
The $Mo(CO)_5(NEt_3)$ complex isomerizes the allenyl ketone **111** to the furan **112**; even the free hydroxyl group is tolerated, but with 50% of 'catalyst' a 28% yield is not too (effective turnover number (TON) = 0.5; Scheme 15.30) [69].



111 **112** (28%)

Scheme 15.30

A similar isomerization of an allenyl ketone, catalyzed by a $Cr(CO)_5L$ complex, is most probably the mechanistic key step of the palladium-catalyzed conversion of chromium carbene complexes and propargyl bromide to furans. In control experiments different aryl and alkyl allenyl ketones **96** isomerized to the furans **99** in the presence of 10 mol% of $Cr(CO)_5(NEt_3)$ in good yields (Scheme 15.31) [70].

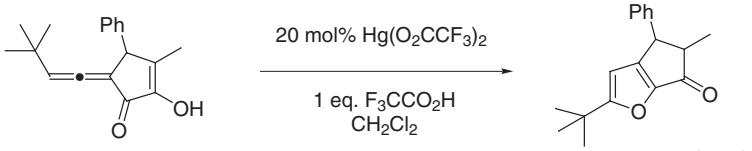


96 R = 4-$MeOC_4H_4$, CH_2CH_2Ph **99** (85-100%)

Scheme 15.31

Gevorgyan and co-workers demonstrated that allenyl imines can be formed in situ by treating alkynylimines with a base (see Section 15.8, compound **185**) [71, 72]. The same principle also works for the in situ formation of allenyl ketones from alkynyl ketones and their conversion to furans with a copper(I) catalyst [71, 72]. That Cu(I) would catalyze the isomerization of an allenyl ketone was known from work of Hashmi et al. [57, 58].

Although, as shown above, a number of metals [Hg(II), Rh(I), Ag(I), Pd(II), Au(III) and Cu(I)] are active for the cycloisomerization of allenyl ketones, some substrates are still restricted to the use of Hg(II); as Leclerc and Tius demonstrated recently for **113**, the cyclopentane-anellated furan **114** was only accessible with the mercury catalyst (Scheme 15.32) [73].



113 **114** (71%)

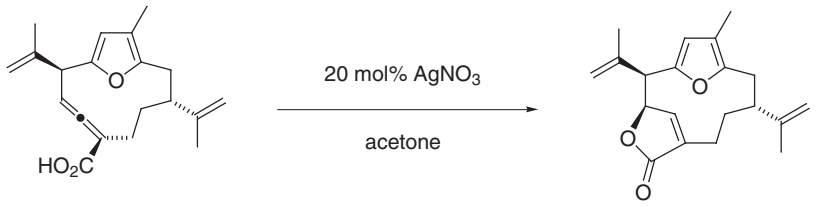
Scheme 15.32

In other Pd(II)-catalyzed reactions, combining a cyclization with a coupling reaction, the furans which stem from a simple cycloisomerization reaction without coupling are often observed as side-products, occasionally in significant yield. Several examples have been reported by Ma and co-workers [74, 75].

15.4
Allenic Carboxylic Acids

As early as 1940, Kohler and Whitcher reported the acid-catalyzed cyclization of 1,2-allenyl carboxylic acids [76].

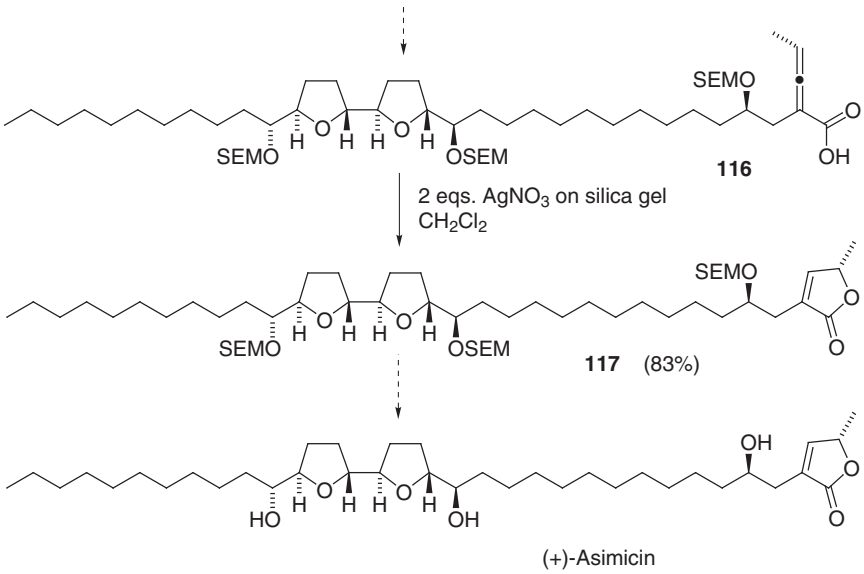
Marshall and co-workers used the silver-catalyzed version of this cycloisomerization as the final step in the synthesis of (–)-kallolide B from precursor **115** (Scheme 15.33) [51, 54]. Again, the reaction is stereospecific, as has also been demonstrated in the synthesis of kallolide A [55] and other examples [77].



115 (-)-Kallolide B (68%)

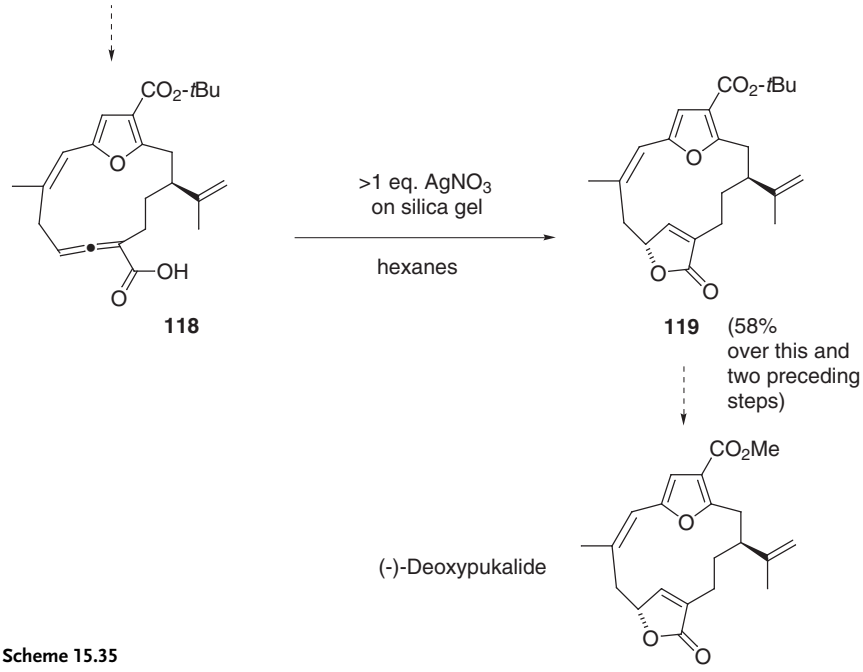
Scheme 15.33

The total synthesis of (+)-asimicin also uses this methodology for the introduction of the butenolide in one of the final steps, the formation of **117** from **116** (Scheme 15.34) [78]. Owing to the small scale (18 μmol), an excess of catalyst had to be used.



Scheme 15.34

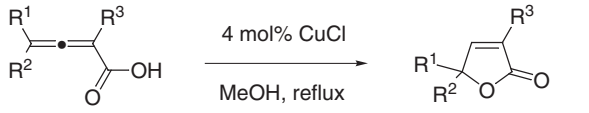
Other applications include the synthesis of (–)-deoxypukalide by Marshall and Van Devender, where an Ag(I)-catalyzed cycloisomerization of **118** to **119** again is very late in the sequence (Scheme 15.35) [79], and the synthesis of rubifolide [53]. Furthermore, studies on the synthesis of pseudopterane analogues have been conducted [80].



118 **119**

Scheme 15.35

In Pd(II)-catalyzed reactions targeting cyclization/oxidative coupling products, the butenolides often were formed as side-products, but only in low yield [81, 82]. The cyclization of a series of 1,2-allenylcarboxylic acids **120** to butenolides **121** was acomplished with 4 mol% of CuCl, a comparable cheap catalyst, in methanol (Scheme 15.36) [83].

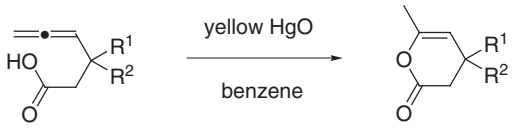


120 **121** (77-97%)

R^1 = alkyl, aryl
R^2 = H, alkyl
R^3 = alkyl, allyl, benzyl

Scheme 15.36

The only substrate of that type with a longer bridge between the carboxylic acid and the allene is **122**, which was isomerized in an *exo-dig* manner to the six-membered lactone **123** on the surface of yellow HgO in benzene (Scheme 15.37) [84].

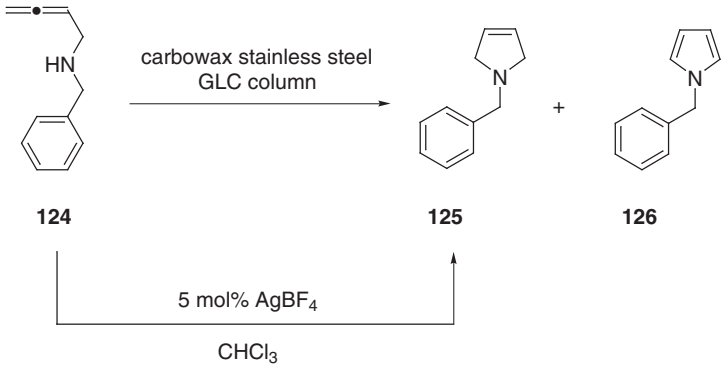


122 R^1,R^2 = H,Me **123** (100%)

Scheme 15.37

15.5 Amines as Nucleophiles

In 1979, Claesson et al. observed the formation of the dihydropyrrole **125** and the pyrrole **126** when trying to purify the amine **124** by GLC [85]. They suspected that an initial cycloisomerization first leads to **125** and a subsequent dehydrogenation then delivers **126**. Guided by other intramolecular nucleophilic additions to alkynes that are catalyzed by $AgBF_4$, they discovered that this catalyst efficiently allowed the transformation of **124** to **125** (Scheme 15.38). Reissig et al. found that with enantiomerically pure substrates of that kind a cyclization without racemization is possible with Ag(I) catalysts [86].

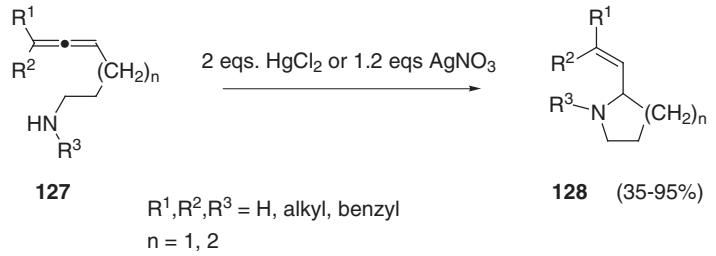


124 **125** **126**

(100%)

Scheme 15.38

Arseniyadis and Gore investigated the cyclization of secondary dialkylamines **127** with both $HgCl_2$ and $AgNO_3$ in stoichiometric amounts. Tetrahydropyrroles or hexahydropyridines **128**, both bearing vinyl substituents, were obtained; with Ag(I) the yield was always better than with Hg(II) (Scheme 15.39) [87].



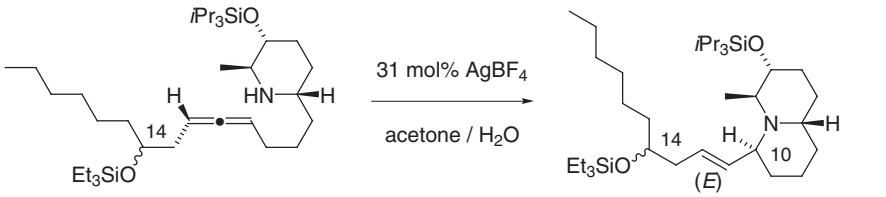
127 **128** (35-95%)

R^1,R^2,R^3 = H, alkyl, benzyl
n = 1, 2

Scheme 15.39

The first to discover that Cu(I) salts, in this case CuI, are also active for that reaction were Balasubramanian et al. [88].

Application of silver-catalyzed cyclization is a key step in the synthesis of clavepictines A and B, a synthesis which also established the absolute configuration for these compounds. With regard to the allene unit and the heterocycle, enantiomerically pure precursor **129** was prepared and then cyclized to the quinolizidine **130** with $AgNO_3$ in a diastereoselective manner (Scheme 15.40) [89, 90]. The synthesis was conducted with an inseparable 1:1 mixture of diastereomers at C-14; from the diastereomerically pure allene with regard to the axial chirality of the allene a 7:1 mixture of diastereomers (at C-10) was formed.

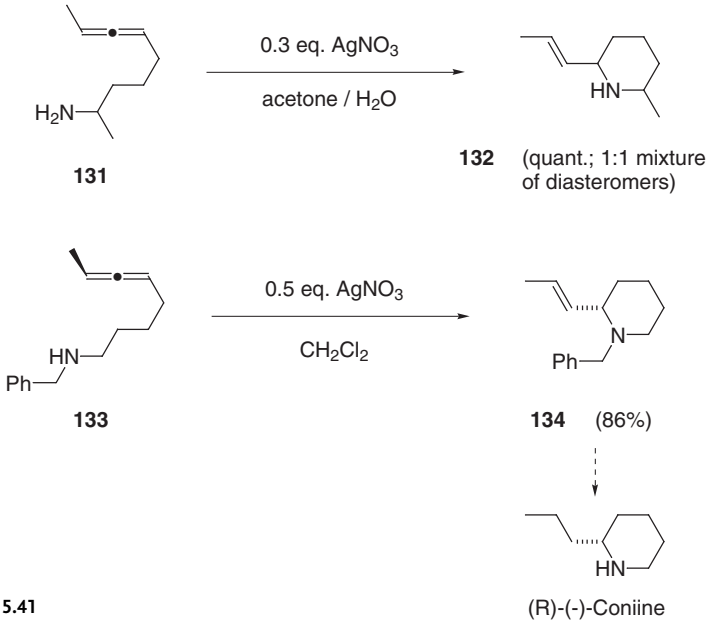


129 (*dr* = 1:1 at C-14)

130 (54%) (*dr* = 1:1 at C-14
dr = 7:1 at C-10)

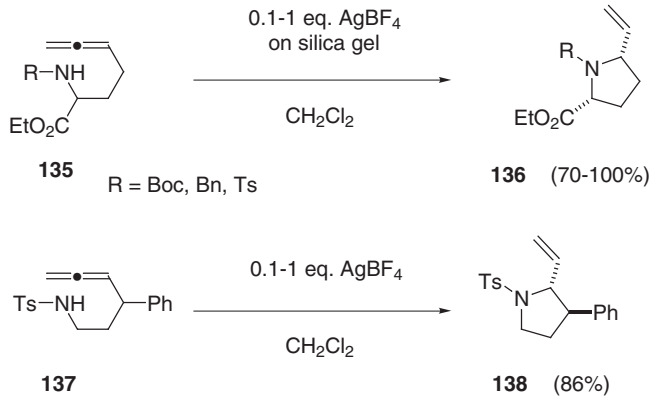
Scheme 15.40

Further applications include the synthesis of (±)-pinidine **132** (Scheme 15.41) [91] and the synthesis of (*R*)-(–)-coniine via an axial to central chirality transfer in the cyclization of enantiomerically pure **133** to **134** [92].



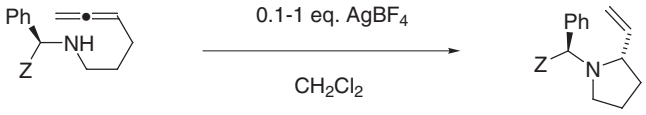
Scheme 15.41

As the examples above show, the stereoselectivity of these cycloisomerizations is an important issue, and Gallagher *and co-workers* focused on this in different investigations. Substrates **135** in most cases showed a clear preference for the formation of the *cis*-diastereomer **136** with a selectivity better than 50: 1 (only for R = H is the *cis*:*trans* ratio 1:1; Scheme 15.42) [93, 94]. For a phenyl substituent instead of the ester group, the same phenomenom was observed. Moving the phenyl group one position away from the nitrogen, on the other hand, delivers a 1:1 mixture of diastereomers. Finally, placing the phenyl group next to the allene, as in **137**, leads to the *trans*-diastereomer **138** [95].



Scheme 15.42

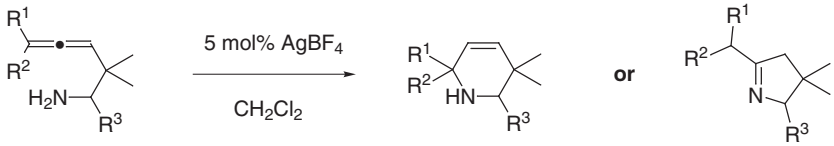
A chiral center not in the tether but on nitrogen is also capable of inducing a certain configuration of a stereogenic center of the ring. This was investigated with substrates **139**, which deliver 33–80% *de* in the products **140**, depending on the group Z. The best *de* values were obtained with strongly coordinating groups Z such as amines and an amide (Scheme 15.43) [96, 97].



139 Z = Me, CO_2Me, CH_2OH, CONHMe, CH_2NHMe **140** (80-97%, *de* 33-80%)

Scheme 15.43

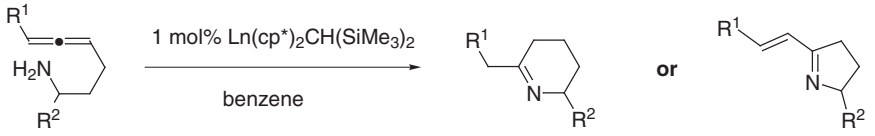
The regioselectivity is an issue in substrates **141**. With two alkyl substituents on the distal position, tetrahydropyridines **142** are the product. With only one alkyl substituent, the cyclic imine **143** was isolated; for these rearrangement products it is unknown whether they stem from the enamine generated from a 5-*endo-trig* or 5-*exo-dig* cyclization (Scheme 15.44) [98].



141 R^1,R^2,R^3 = H, alkyl **142** (50-75%) for R^1 and R^2 = alkyl **143** (30%) for R^1 or R^2 = H

Scheme 15.44

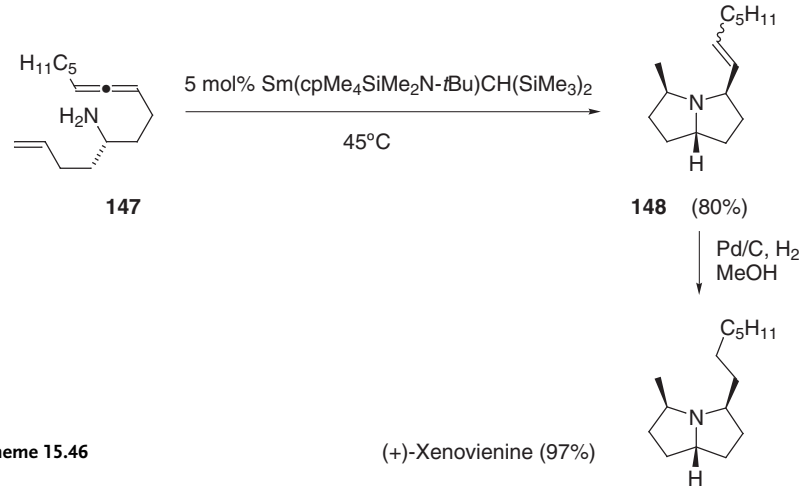
Marks et al.'s organolanthanide catalysts show a strong dependence on the substitution of the allene [99]. Terminal allenes **144** with three carbons in the tether deliver the tetrahydropyridines **145**. 1,2-Disubstituted allenes with the same length of the tether lead to the vinylpyrrolines **146** (Scheme 15.45).



144 **145** (91-95%) for R^1 = H R^2 = alkyl **146** (>95%) for R^1 = alkyl R^2 = H, alkyl

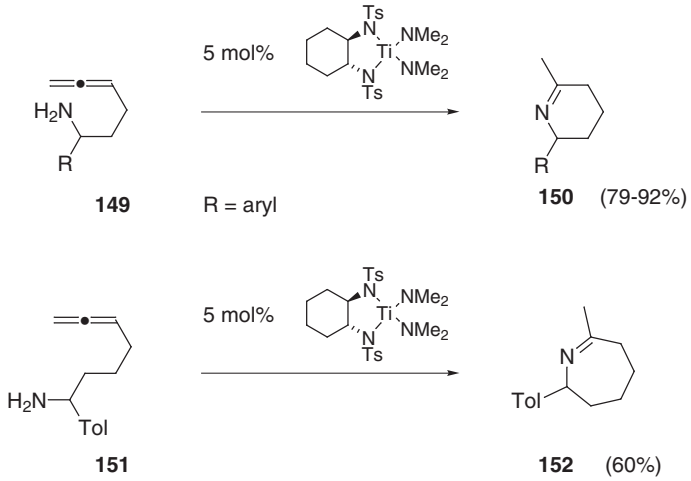
Scheme 15.45

Such lanthanide catalysts were also used in hydroamination/cyclization strategies for the synthesis of the alkaloid (+)-xenovenine. This reaction of enantiomerically pure **147** leading to **148** via two C–N bond formations was used in a late step of the synthesis; after a hydrogenation, the natural product was isolated (Scheme 15.46) [100].



Scheme 15.46

Ackermann and Bergman developed a highly reactive titanium precatalyst for the intramolecular hydroamination of allenes **149** [101]. The products **150** and in one case even the seven-membered cyclic imine **152** were obtained (from **151**) in reasonable yield (Scheme 15.47).

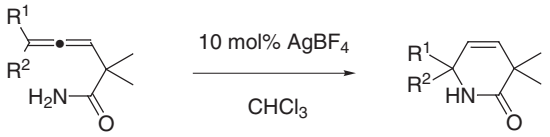


Scheme 15.47

The next two sections will cover compounds with acceptors on nitrogen.

15.6
Amides as Nucleophiles

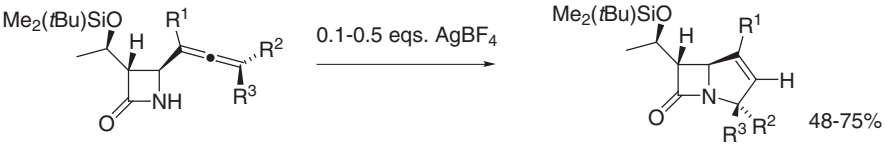
In 1986, Grimaldi and Cormons reported that with a catalytic amount of $AgBF_4$, substrates **153** readily deliver lactams **154** (Scheme 15.48) [102].



153 R^1,R^2 = H, alkyl **154** (>60%)

Scheme 15.48

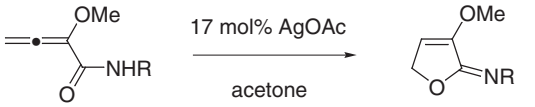
The reaction of azetidinones **155** with $AgBF_4$ as a catalyst leads to carbapenems **156** (Scheme 15.49) [103].



155 R^1,R^2,R^3 = H, alkyl **156**

Scheme 15.49

Starting from the metallated methoxyallene, the amide **157** was obtained easily, as Brandsma et al. showed [104]. The latter selectively delivered the dihydrofurans **158**; no isomeric dihydropyrroles were detected (Scheme 15.50).

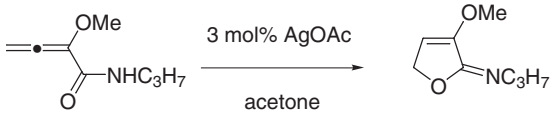


157 **158** (58-83%)

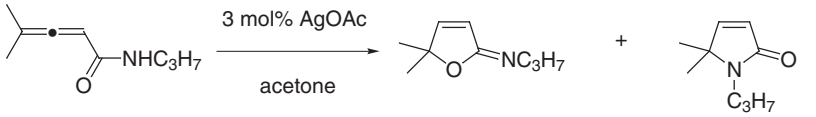
R = Pr, *i*Pr

Scheme 15.50

With related substrates **159** and a silver catalyst, the furanylidenamines **160** were formed; with other substitution patterns as in **161** similar products **162** were accompanied by pyrrolinones **163** (Scheme 15.51) [105].

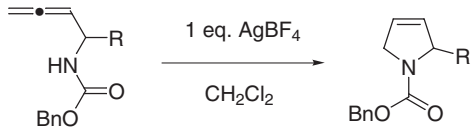


159 **160** (83%)



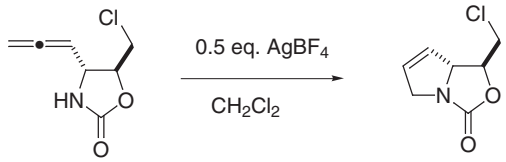
161 **162** (no yield given) **163** (10%)

Scheme 15.51

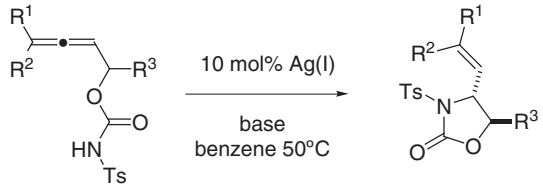


164 **165** (69-84%)

R = alkyl, aryl



166 **167** (81%)



168 **169** (34-91%)

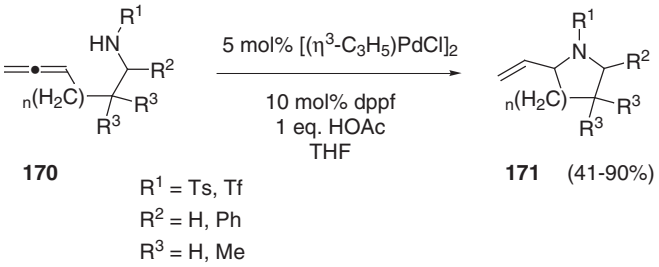
R^1,R^2,R^3 = alkyl, aryl *trans* : *cis* = 30 :1 to 1.5 : 1

Scheme 15.52

The carbamates **164** also deliver dihydropyrroles; compounds **165** are obtained in good yields with 1 equiv. of $AgBF_4$ (Scheme 15.52) [106]. A related reaction with a cyclic carbamate **166** bearing a chloromethyl group in the side-chain was also reported to react without any problem; even with the use of 0.5 equiv. of $AgBF_4$ the chorine remains in the product [107]. The diastereoselectivity of such reactions of carbamates **168** was investigated by Tamaru et al. [108]. The bulkier the substituent R^3, the higher is the preference for the *trans*-isomer in the product **169**. Here, in addition to the carbamate unit, which leads to the oxazolidinone ring in **169**, we also encounter a tosyl group, which will be the focus of the next section.

15.7 Sulfonamides as Nucleophiles

The intramolecular hydroamination of substrates **170** is catalyzed by a Pd(0) catalyst which is generated in situ from a Pd(II) precursor and a phosphane. One equivalent of acetic acid has to be added for efficient catalysis; this is a hint of a hydropalladation mechanism. Meguro and Yamamoto obtained good yields of the vinyltetrahydropyrroles or the vinylhexahydropyridines **171** in that way (Scheme 15.53) [109].



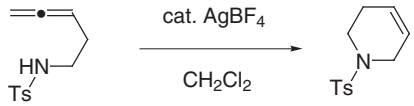
170 **171** (41-90%)

R^1 = Ts, Tf
R^2 = H, Ph
R^3 = H, Me
n = 1, 2

Scheme 15.53

Related reactions were described by Vernon and Gallagher [110] and *endo-trig* cyclization to dihydropyrroles by Ibuka et al. [111].

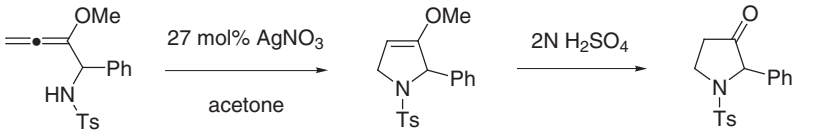
Tetrahydropyridines can be obtained from the tosylamides **172** with $AgBF_4$ in dichloromethane; **173** was isolated in excellent yield (Scheme 15.54) [112].



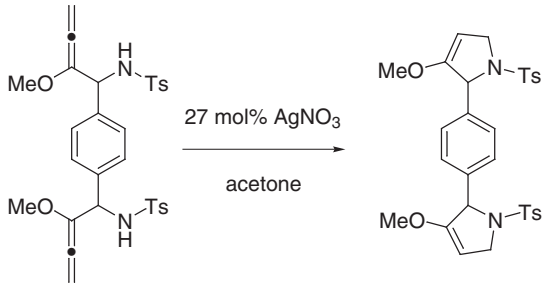
172 **173** (92%)

Scheme 15.54

The nucleophilic addition of lithiated methoxyallene to *N*-tosylimines delivers tosylamides **174**. Treatment of the latter with $AgNO_3$ leads cleanly to dihydropyrroles **175**, which under acidic conditions provide pyrrolidin-3-ones **176**. Another example is the reaction of **177** to **178** (Scheme 15.55) [113].



174 **175** (93%) **176** (96%)

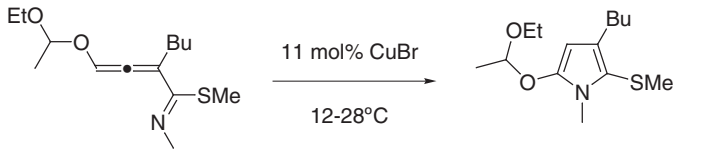


177 **178** (94%)

Scheme 15.55

15.8 Imines and Related Groups as Nucleophiles

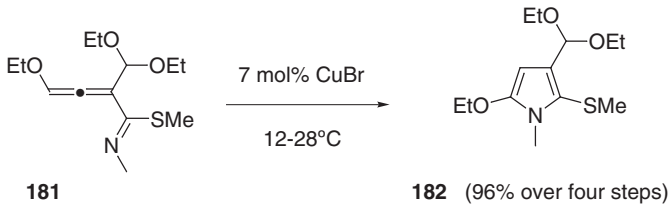
The imine-related precursor **179** was readily cyclized by CuBr or CuI as the catalyst to the highly fuctionalized pyrrole **180** (Scheme 15.56) [114–116].



179 **180** (51% over four steps)

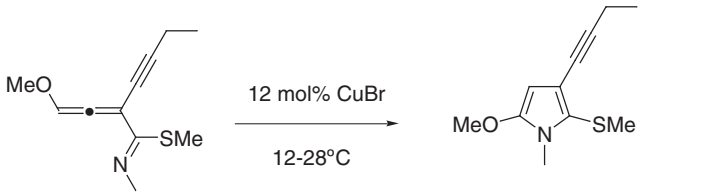
Scheme 15.56

Another example of a similar reaction leading to **182** was reported by Brandsma et al. (Scheme 15.57) [117]. Furthermore, alkynylpyrroles **183** can be prepared in that way (Scheme 15.58) [118]. More examples were given by Brandsma et al. [119].



181 **182** (96% over four steps)

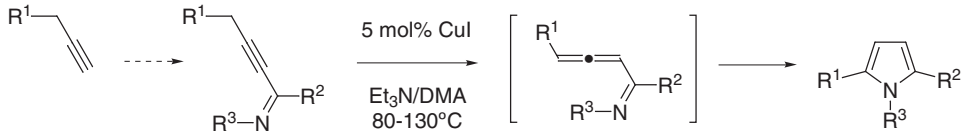
Scheme 15.57



183 **184** (19% over five steps)

Scheme 15.58

Allenylimines **186** are not easily accessible, and the most elegant approach is the reaction of alkynylimines **185** with triethylamine to generate **186** in situ; the copper(I) catalyst which is also present then catalyzes the cycloisomerization to the pyrrole **187** (Scheme 15.59) [120]. The method also is applicable to the imine substructure in 2-alkynylpyridines and related substrates, thus opening up a very elegant access to condensed aromatic nitrogen heterocycles.



185 **186** **187** 51-93%

R^1,R^2 = H, alkyl, alkenyl, aryl
R^3 = alkyl, Tr, EB

Scheme 15.59

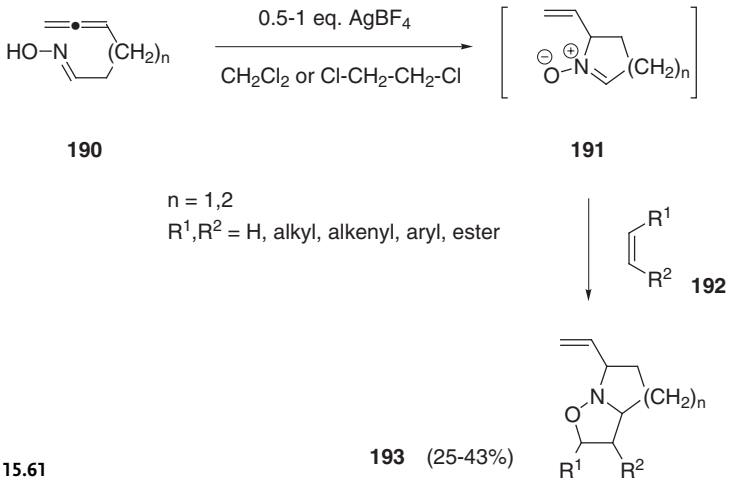
15.9
Oximes as Nucleophiles

An interesting access to the seven-membered 4,7-dihydro-1,2-oxazepines **189** is the $AgBF_4$-catalyzed cyclization of the oximes **188** [121]. Unfortunately, this paper lacks any information on the amount of catalyst used and only a very rough description of the yield is given (Scheme 15.60).

188 **189** ("about 70%")

Scheme 15.60 R^1,R^2,R^3 = H, alkyl

In 1985, Lathbury and Gallagher reported the in situ synthesis of nitrones **191** from oximes **190**; the 1,3-dipoles then could be trapped by a number of different alkenes **192** and thus the bicylic **193** was obtained (Scheme 15.61) [122].

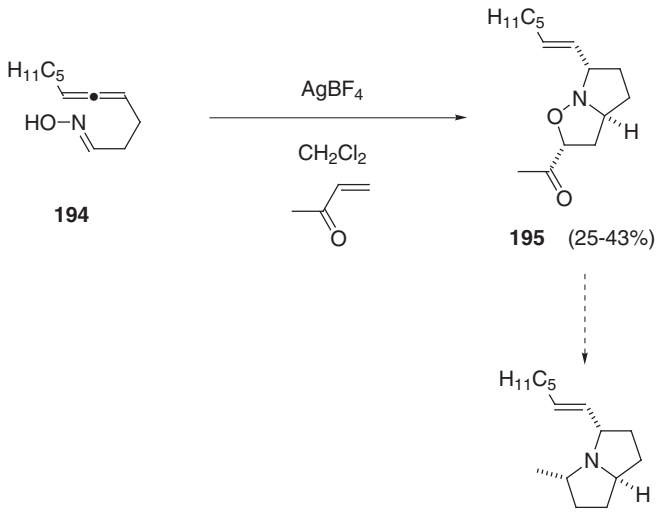


190 **191**

193 (25-43%)

Scheme 15.61

This methodology has been applied to the diastereoselective synthesis of the pyrrolizidine alkaloid **196** from **194** via **195** (Scheme 15.62) [123]. Furthermore, the diastereoselectivity of these reactions for different dipolarophiles has been investigated in detail [124] and could be extended to a ring closure to seven-membered nitrogen heterocycles [125, 126].

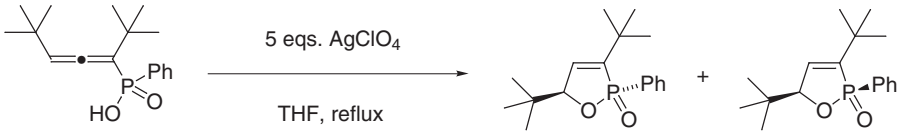


194 **195** (25-43%) **196**

Scheme 15.62

15.10 Phosphonic Acids

The phenylphosphonic acid **197** reacts with 5 equiv. of $AgClO_4$ to deliver the 1,2-oxaphosphol-3-ene-2-oxide **198** in an 80% total yield of the *Z*- and *E*-isomers (Scheme 15.63) [127]. For related reactions, see also [128]. With a phosphonic acid and $Hg(OAc)_2$, the mercurated intermediate, a 4-acetoxymercury 1,2-oxaphosphol-3-ene and the corresponding chloride after ligand exchange were isolated [129].



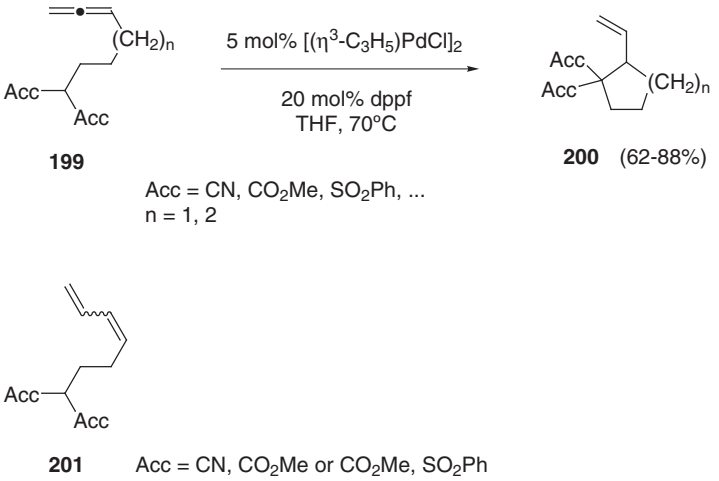
197 (*Z*)-**198** (*E*)-**198**

Scheme 15.63

15.11
Activated C–H Bonds

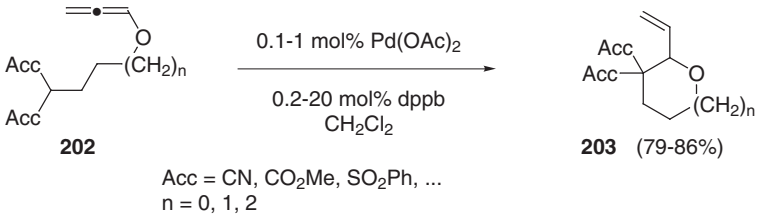
Not only heteroatom–H bonds but also activated C–H bonds can add to the π-system of an allene. Since carbon lacks a free electron pair, the transition metal catalyst must first activate the C–H bond; the new species formed will then react with the C=C double bond. For efficient activation of that kind, two acceptors (typically esters, nitriles and/or sulfones) are necessary. In accord with this mechanistic picture is the fact that the reaction does not benefit from an additional base (which would deprotonate the pronucleophile). Hence neutral conditions are even better.

Yamamoto et al. [130] reported an intramolecular hydrocarbonation of allenes **199** to five- and six-membered carbocyles **200**. In the case of $n = 2$ with the catalyst in the presence of *t*-BuOK only 10% yields were obtained, and without the base 62%! With both the three and the four carbon bridges only an *exo-trig* cyclization was observed. In some examples 1,3-dienes **201** were formed. This is good evidence for a hydridopalladium intermediate, at least for the formation of **201**. On the other hand, this does not necessarily mean that the same reaction pathway is responsible for the formation of the normal product **200** (Scheme 15.64) [130].



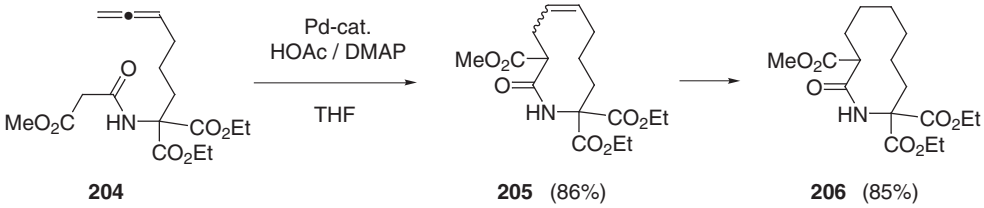
Scheme 15.64

Allenyl ethers **202**, which are easily accessible by the methods described in Chapter 1, consequently lead to cyclic ethers **203**. The alkoxyallenes were much more reactive than the alkylallenes from the previous example. Thus the amount of catalyst could be reduced to 0.1 mol% and 820 turnovers were reached. Five- to seven-membered rings were isolated (Scheme 15.65) [131].



Scheme 15.65

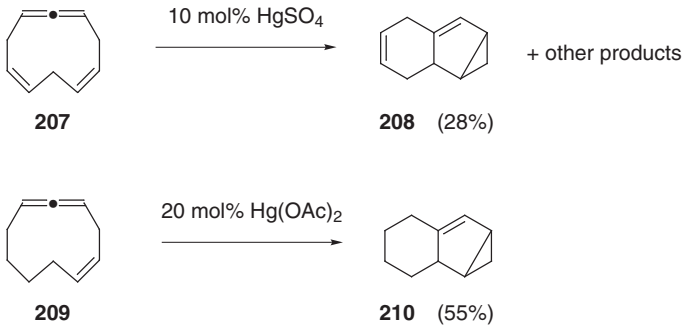
A highly efficient method for the synthesis of medium-sized rings (examples of 17-, 15-, 10- and 5-membered carbocycles, lactones and lactams) without high-dilution conditions was developed by Trost et al.; for example, precursor **204** with a palladium catalyst led to an *E*–*Z* mixture of **205** in 86% yield, and subsequent hydrogenation then provided the 10-membered lactam ring **206** in 85% yield (Scheme 15.66) [132].



Scheme 15.66

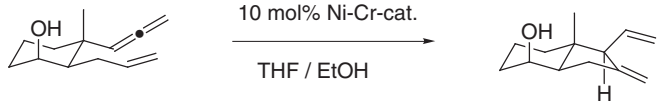
15.12
Reaction with Other C–C Multiple Bonds

Probably the earliest example of such a reaction is the cycloisomerization of hydrocarbons **207** and **209** when treated with $HgSO_4$. Thies et al. observed the formation of the tricyclic vinylcyclopropanes **208** and **210** (Scheme 15.67) [133].



Scheme 15.67

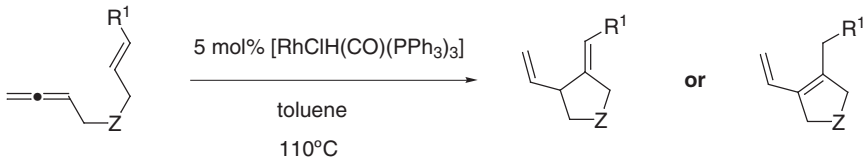
In 1988, Trost and Tour published the cycloisomerization of an ene-allene using a nickel–chromium catalyst [134]. For example, **211** diastereoselectively led to **212** (Scheme 15.68). In the total synthesis of (±)-petiodial, this nickel–chromium system failed, but a palladium catalyst was successful [135].



211 **212** (77%)

Scheme 15.68

Depending on the substrate, the enallenes **213** react with a ruthenium–hydrido catalyst to give either the initial product the methylenecyclopentanes **214** with a 1,4-diene substructure or to the conjugated vinylcyclopentenes **215**. The latter are formed by a subsequent ruthenium-catalyzed isomerization of the initial cycization product **214** (Scheme 15.69) [136].



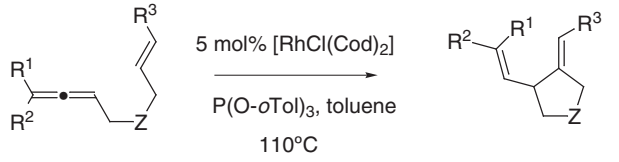
213 **214** (56-75%) **215**

$Z = CR^2_2, NR^2, O$

$R^1 = H, CO_2Et$

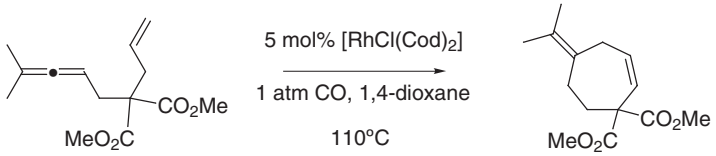
Scheme 15.69

Another rhodium-catalyzed isomerization, by Makino and Itoh [137], allows the conversion of enallenes **216** and **218** to either five-membered methylenecyclopentanes **217** or, under a CO atmosphere in dioxane, seven-membered alkylidenecycloheptenes **218** (Scheme 15.70). With one more carbon in the bridge (in **220**), methylenecyclohexane **221** was accessible, but as much as 20 mol% of catalyst was necessary. A more recent paper also covers this reaction [138].

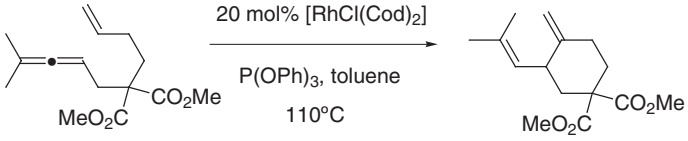


216 **217** (32-97%)

Z = CR^4_2, NR^4, O
R^1,R^2 = H, alkyl
R^3 = H, alkyl, aryl, $SiMe_3$



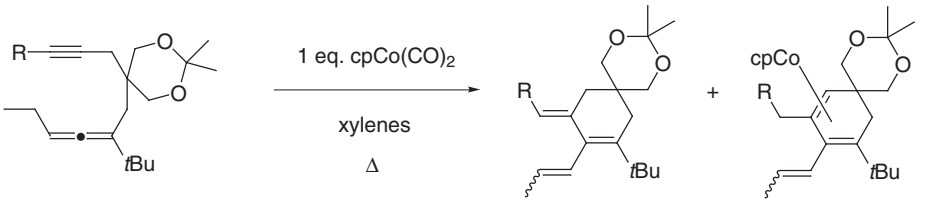
218 **219** (80%)



220 **221** (83%)

Scheme 15.70

In 1996, Malacria et al. [139] reported on cobalt-mediated reactions of the related allenynes. Heating the allenyne **222** in the presence of $cpCo(CO)_2$ accompanied by a photochemical activation of this organometallic compound delivered the cross-conjugated trienes **223** (Scheme 15.71). The second triple bond present in the substrate did not participate in the reaction, underlining the higer reactivity of the allene unit.



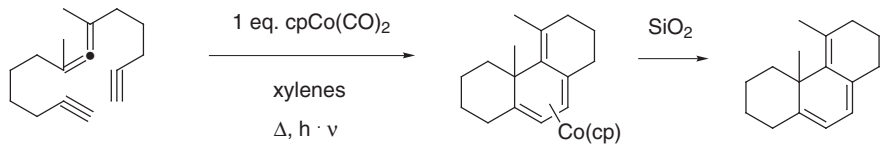
222 **223** **224**

R = $(CH_2)_3$-CC-$SiMe_3$
R = H

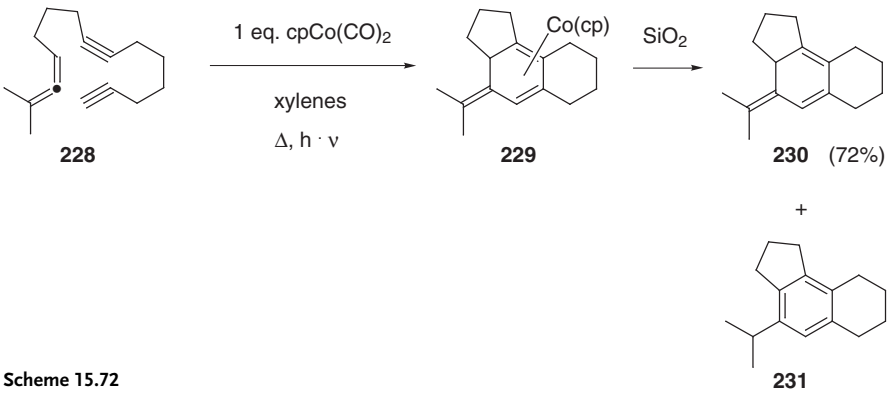
2 : 3 (49%; (*E*):(*Z*) = 7 : 3)
(60%; no ratio given)

Scheme 15.71

With two alkynes in **225** and **228**, tricyclic products such as **227** or **230** were obtained after liberation from the cpCo fragment by chromatography on silica gel (Scheme 15.72) [140–142]. In the case of **228** the desired product **230** forms an inseparable mixture with **231**, the product of an aromatization of the initial product.



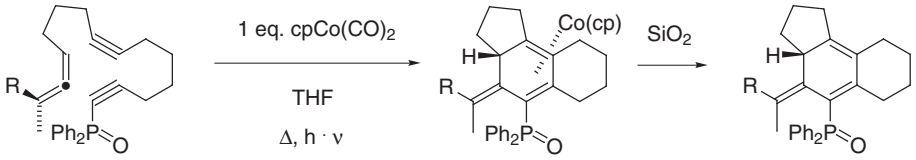
225 **226** **227** (42%)



228 **229** **230** (72%) **231**

Scheme 15.72

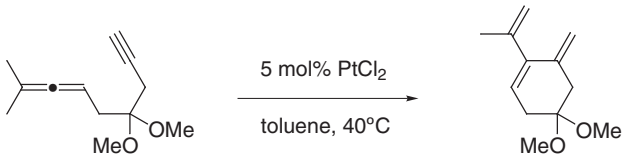
In these reactions a clean axial to central chirality transfer can be achieved. The phosphine oxide **232** cleanly delivers **234** as a single diastereomer; the relative configuration shown was determined by single-crystal X-ray analysis (Scheme 15.73) [143].



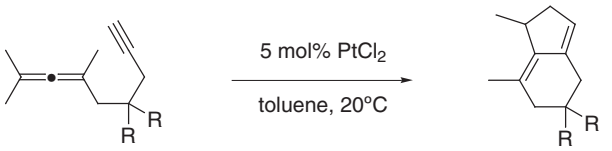
232 R = Me, Ph **233** **234** (66-100%)

Scheme 15.73

Furthermore, $PtCl_2$ prove to be active for the conversion of allenynes. New types of products are then observed. Depending on the substrate, here either the cross-conjugated **236** or the bicylic 1,3-dienes **238** are the products (Scheme 15.74) [144].



235 **236** (54%)

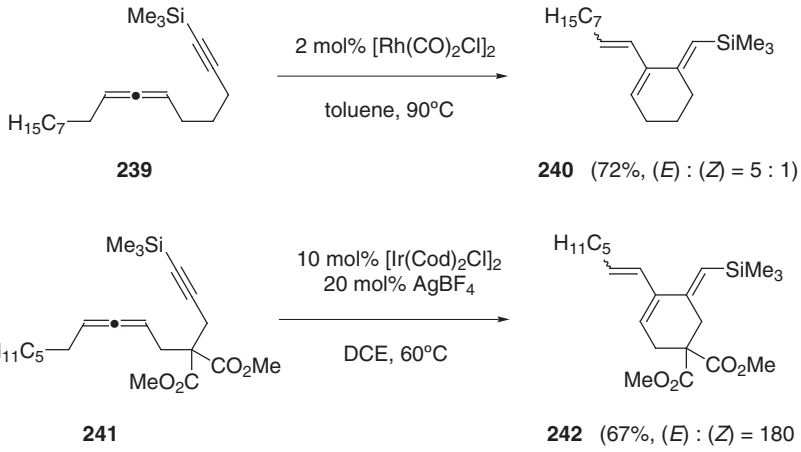


237 **238** (60-80%)

R = CH_2OMe, CO_2Me, ...

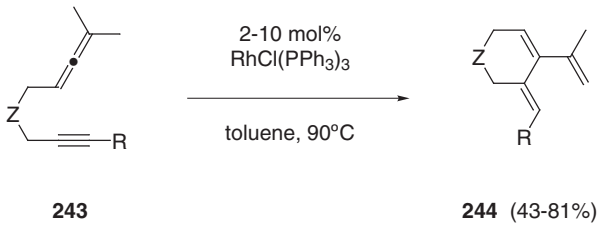
Scheme 15.74

Cross-conjugated compounds of type **240** are isolated after treating substrates **239** with $[Rh(CO)_2Cl]_2$ in toluene at 90 °C. Even unprotected hydroxymethyl groups are tolerated; on the other hand the control of the double bond geometry was not perfect. Switching to the $[Ir(COD)Cl]_2/AgBF_4$ catalyst system then gave a clear preference of the *E*-configuration product with selectivities up to 180:1 as determined by GC analysis of **242** (Scheme 15.75) [145].



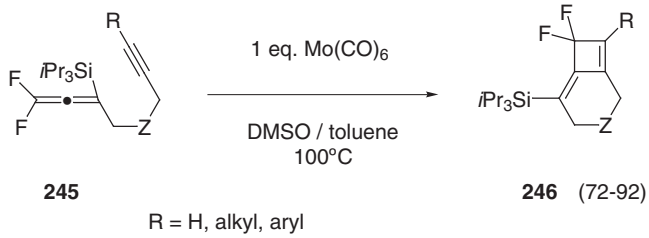
Scheme 15.75

Wilkinson's catalyst also allows the intramolecular cycloisomerization of allenynes **243** to interesting cross-conjugated trienes **244** (Scheme 15.76) [146]. Similar compounds are observed as side-products in Pauson–Khand reactions of allenynes [147].



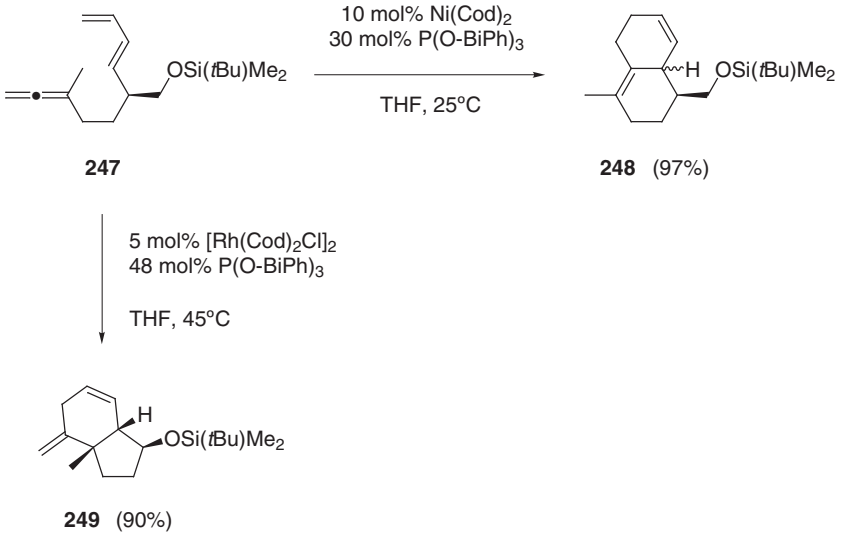
Scheme 15.76

With the silyl-substituted difluoroallene **245** and molybdenum hexacarbonyl, the expected [2 + 2 + 1] cycloaddition is not observed. CO is not incorporated and the cyclobutene derivatives **246** can be isolated in good yields (Scheme 15.77) [148].



Scheme 15.77

Transition metal-catalyzed [4 + 2]-cycloadditions of diene-allenes **247** can lead to different results. With a nickel catalyst Wender et al. isolated the anellated system of two six-membered rings **248**; with a rhodium catalyst the anellation of a five- and a six-membered ring **249** was possible (Scheme 15.78) [149]. Both transformations proceed readily at low temperatures whereas the uncatalyzed thermal reaction requires 185 °C. Even an anellation of a six- and a seven-membered ring was achieved.

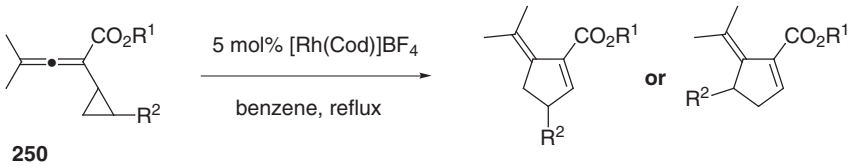


247 **248** (97%)

249 (90%)

Scheme 15.78

In 1998, Saigo et al. [150] discovered the Rh(I)-catalyzed allenic version of the vinylcyclopropane rearrangement. With a subsituent on the cyclopropane ring two different isomers can be formed depending on which of the different allylic C–C bonds in the three-membered ring is broken. Depending on R^2, different regioselectivites were obtained with **250**. Alkyl-substituted substrates lead to **251** and aryl-substituted substrates to **252** (Scheme 15.79) [150].



250

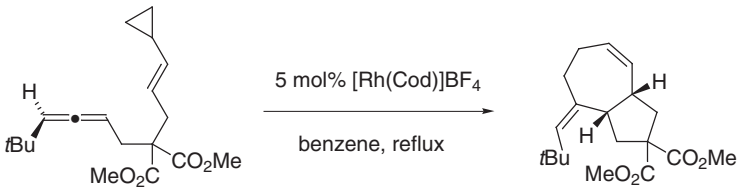
R^1 = Bn, R^2 = Pr **251** (89%)

R^1 = Me, R^2 = Ph **252** (95%)

Scheme 15.79

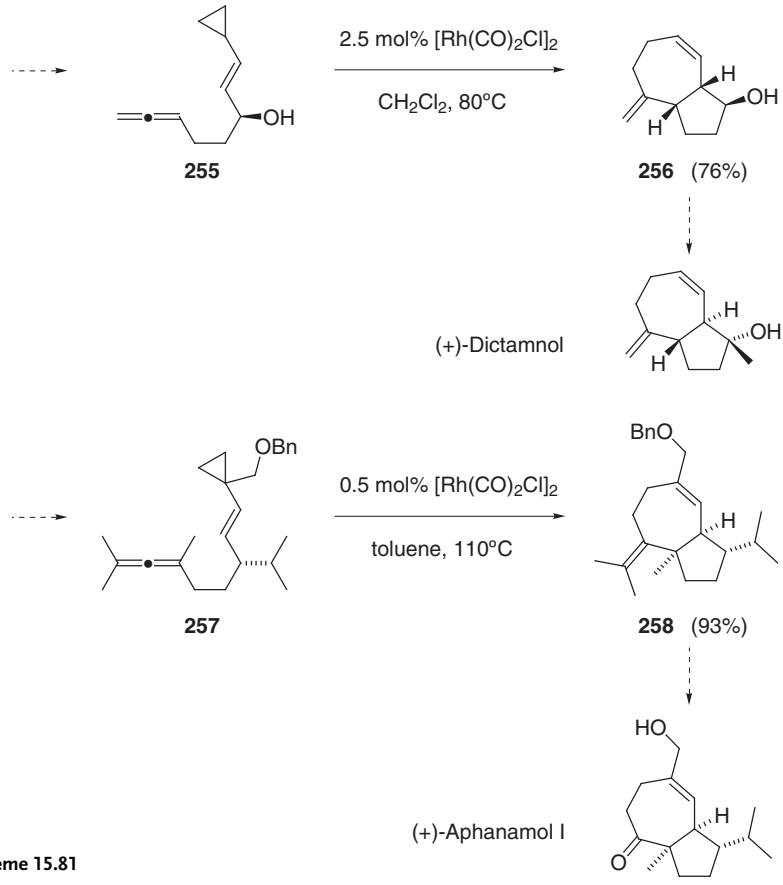
Wender et al. intensively studied the intramolecular Rh(I)-catalyzed [5 + 2] cycloaddition of allenes and vinylcyclopropanes to yield fused systems of five- and seven-membered rings [151]. A typical example is the reaction of the enantiomerically

enriched axial chiral **253** leading to *cis*-fused product **254** (Scheme 15.80) [152]. The natural products (+)-dictamnol (transformation **255** to **256** as key step) [153] and (+)-aphanamol I (transformation **257** to **258** as key step) [154] were synthesized in that way (Scheme 15.81).



253 (91% *ee*) **254** (96%, 91% *ee*)

Scheme 15.80

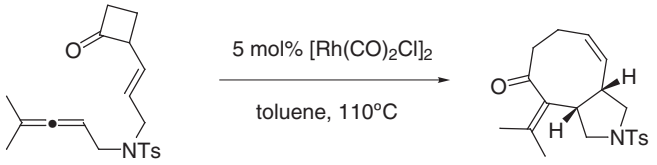


255 **256** (76%)

257 **258** (93%)

Scheme 15.81

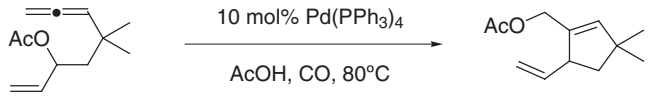
An extension to the synthesis of eight-membered rings such as **260** via a [6 + 2] cycloaddition by use of 2-vinylcyclobutanones **259** was also possible (Scheme 15.82) [155]. In order to obtain a good yield, a concentration lower than 0.05 M must be used.



259 **260** (91%)

Scheme 15.82

In 1996, Yamamoto et al. investigated the intramolecular Pd(0)-catalyzed reactions of allylic acetates with allenes and observed the isomerization of triene **261** to the cyclic diene **262** (Scheme 15.83) [156]. The reaction probably proceeds via oxidative addition to Pd(0), insertion of the allene and return of the acetate.



261 **262** (64%)

Scheme 15.83

15.13 Conclusion

Although numerous examples of cycloisomerizations of allenes have been reported in the literature, many more similar reactions of alkynes are known. For many of the examples the detailed mechanism or the origin of a changed selectivity with a change in conditions or catalyst is still unknown; for all this often a descriptive style is found in the publications. Here there is still much scope for detailed investigation. Although the transfer of axial to central chirality is frequently covered and different aspects of diastereoselectivity have often interested the investigators, the possibility of conducting some of the reactions in a catalytic asymmetric manner has so far barely attracted any attention. This is also likely to change in the near future.

Abbreviations

Ac	Acetyl
atm	Atmosphere
BiPh	Biphenyl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bu	Butyl
Cod	1,4-Cyclooctadienyl
cp	Cyclopentadienyl
cp*	Pentamethylcyclopentadienyl
dba	Dibenzylideneacetone
DCE	1,2-Dichloroethane
DMA	*N*,*N*-Dimethylacetamide
DMAP	*N*,*N*-Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
dppb	1,4-Diphenylphosphanylbutane
dppf	1,1′-Bis(diphenylphosphanyl)ferrocene
Et	Ethyl
EB	3-Ethylbutyryl
eq.	Equivalent
Fp	η^5-Cyclopentadienyldicarbonyliron
GLC	Gas–liquid chromatography
Me	Methyl
MOM	Methoxymethyl
Nu	Nucleophilic group
Ph	Phenyl
Pr	Propyl
quant.	Quantitative
SEM	(Trimethylsilylethoxy)methyl
Tf	Trifluoromethylsulfonyl
THF	Tetrahydrofuran
Ts	*p*-Toluenesulfonyl
Tol	Tolyl
Tr	Trityl

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16
Transition Metal-Catalyzed Addition/Cycloaddition of Allenes

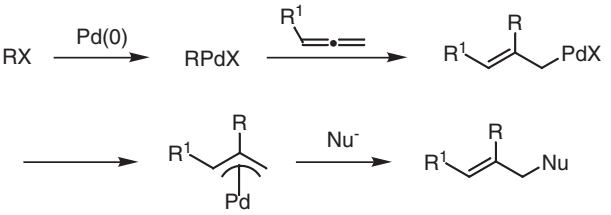
Tadakatsu Mandai

16.1
Introduction

An allene, a very interesting compound with a hybrid character of an olefin and an acetylene, has proved to be very reactive toward a wide range of transition metals. Hence a large number of transition metal-catalyzed reactions of allenes have been developed so far and thereby have paved the way for the widespread use of allenes in organic synthesis. Palladium-catalyzed reactions of allenes, in particular, have enjoyed popularity over the last two decades owing to their wide applicability in organic synthesis and two comprehensive reviews are now available [1, 2]. Owing to space limitations, this review covers only transition metal-catalyzed reactions of high synthetic value, including palladium-catalyzed reactions, that appeared after the above reviews.

16.2
Reactions via Carbopalladation

An organic halide, RX (R = aryl or vinyl) adds oxidatively to Pd(0) species to form a RPdX species. An allene readily undergoes carbopalladation of the species to generate a π-allylpalladium intermediate [3] in a highly regioselective manner. Finally, an allylic compound is produced by a nucleophile attack (Scheme 16.1).



Scheme 16.1 Formation of a π-allylpalladium complex via carbopalladation of an allene.

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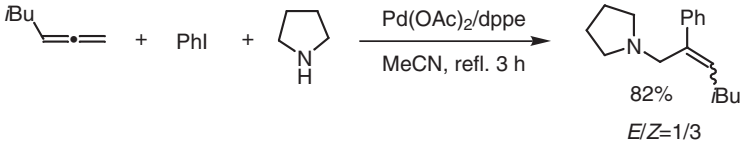
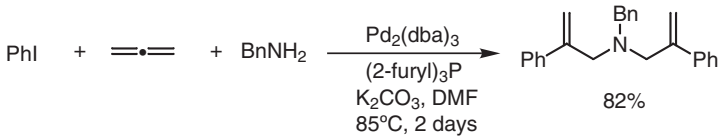
Shimizu and Tsuji [4] reported the first highly regioselective synthesis of 1,2-disubstituted allylic amines through capture of a π-allylpalladium complex by pyrrolidine (Scheme 16.2). This methodology has since been extended to a wide range of amines and allenes [5].



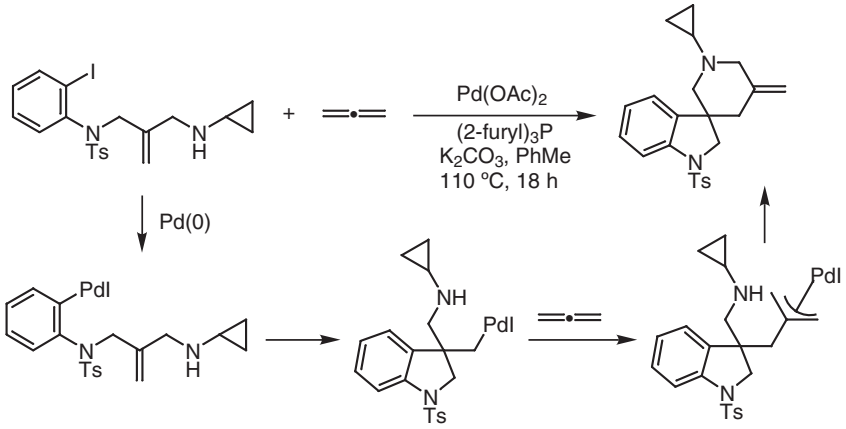
Scheme 16.2 Preparation of an allylic amine.

A related approach was employed in the synthesis of tertiary amines (Scheme 16.3) [6, 7].



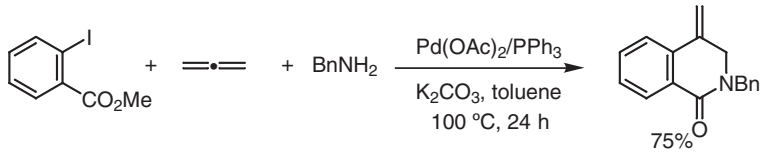
Scheme 16.3 Preparation of a tertiary amine.

The reaction was further applied to the synthesis of spiro heterocycles (Scheme 16.4) [8]. The oxidative addition of an iodide to a Pd(0) species generates an ArPdI species, into which an internal olefin inserts to form an alkylpalladium complex otherwise difficult to access. Allene participates in the reaction at this stage to provide a π-allylpalladium complex, which is attacked by the amine intramolecularly to afford the procuct.



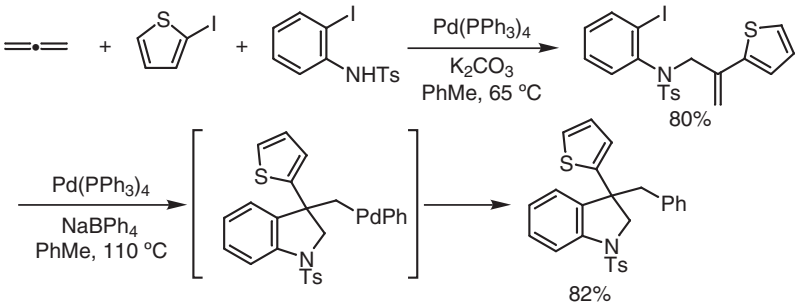
Scheme 16.4 Preparation of a spiro heterocycle.

N-Substituted 4-methylene-3,4-dihydro-1-(2*H*)-isoquinolin-1-ones are synthesized by means of a palladium-catalyzed three-component process (Scheme 16.5) [9].



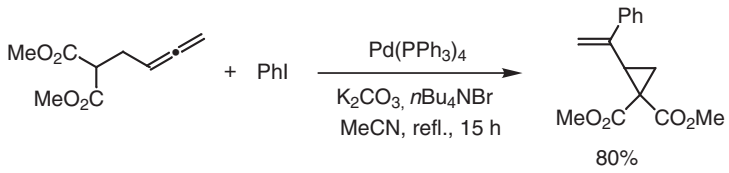
Scheme 16.5 Preparation of a lactam.

A one-pot synthesis of 3,3-disubstituted indolines was achieved by taking advantage of a sequential carbopalladation of allene, nucleophile attack, intramolecular insertion of an olefin and termination with $NaBPh_4$ (Scheme 16.6) [10]. First, a Pd(0) species reacts with iodothiophene selectively to afford ArPdI, probably because the oxidative addition step is facilitated by coordination with the adjacent sulfur atom. Second, the ArPdI adds to allene, giving a π-allylpalladium complex, which is captured by a 2-iodoaniline derivative to afford an isolable allylic compound. Under more severe conditions, the oxidative addition of iodide to Pd(0) followed by the insertion of an internal olefin takes place to give an alkylpalladium complex, which is transmetallated with $NaBPh_4$ to release the product.



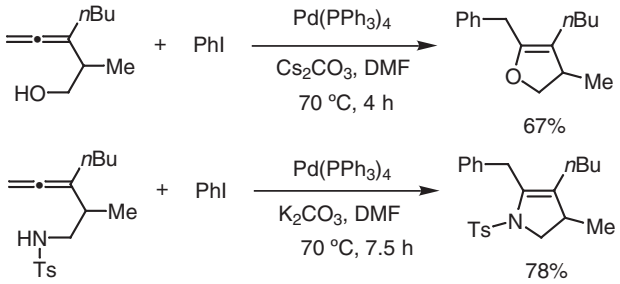
Scheme 16.6 One-pot synthesis of a 3,3-disubstituted indoline.

The palladium-catalyzed reaction of iodobenzene and an allenyl malonate provided vinylcyclopropane in a highly regioselective manner (Scheme 16.7) [11, 12]. A π-allylpalladium complex, generated by the addition of PhPdI to a 2-allenyl malonate, can be trapped by an internal malonate anion to afford a vinylcyclopropyl derivative. The site selectivity in this cyclization is dependent on the nature of the entering RX groups, catalytic systems involving phosphine ligands, solvents and bases.



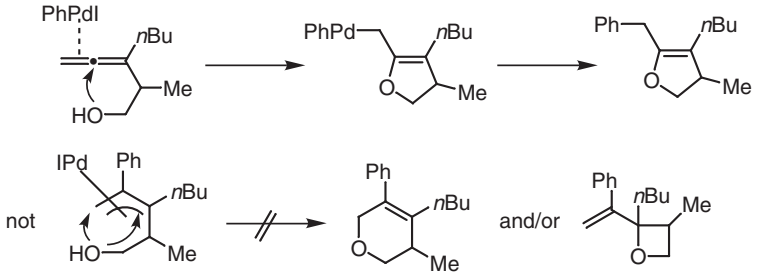
Scheme 16.7 Synthesis of a vinylcyclopropane.

Palladium-catalyzed reaction of a 3,4-allenol with iodobenzene proceeds through an oxypalladation–reductive elimination sequence to give a 2,3-dihydrofuran efficiently (Scheme 16.8) [13, 14].



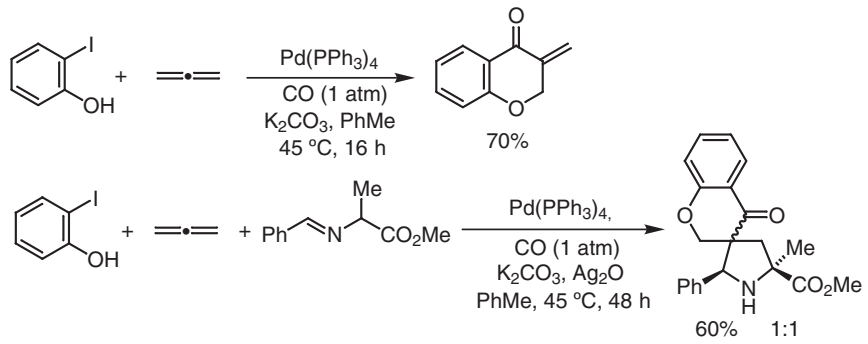
Scheme 16.8 Synthesis of five-membered heterocycles.

The possibility of π-allylpalladium complex formation through carbopalladation is excluded from the observation that no four- and/or six-membered rings are produced. The reaction apparently proceeds via an alternative pathway which involves a sequence of π-coordination of PhPdI to an allenic terminal double bond, oxypalladation and ensuing reductive elimination (Scheme 16.9).



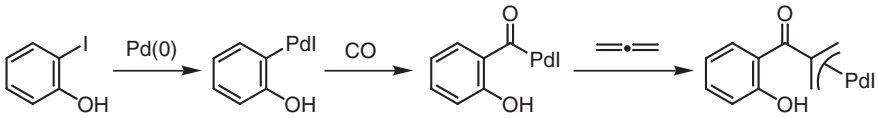
Scheme 16.9 Mechanism of a five-membered ring formation.

A palladium-catalyzed three-component assembly process of an aryl iodide, carbon monoxide and allene offers a facile synthesis of heterocycles bearing an *α-exo*-methylene ketone moiety (Scheme 16.10) [15, 16].



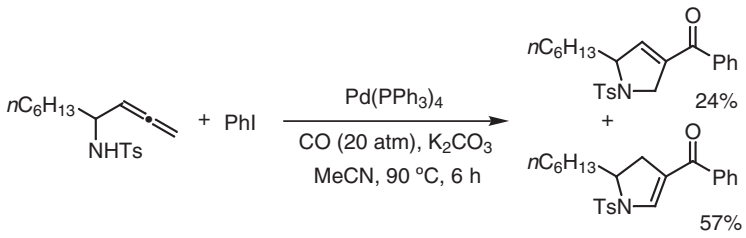
Scheme 16.10 Preparation of heterocycles via a three-component assembly process.

First, oxidative addition of 2-iodophenol to a Pd(0) species gives rise to an arylpalladium complex, which in turn undergoes carbonylation followed by insertion of allene to generate a 2-acyl–π-allylpalladium complex. Attack by an internal hydroxyl group gives an *α-exo*-methylene ketone (Scheme 16.11).

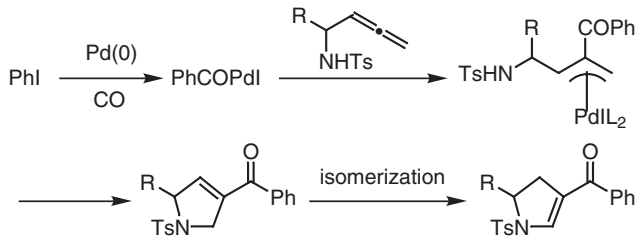


Scheme 16.11 Reaction pathway via a 2-acyl–π-allylpalladium complex.

An α-allenic sulfonamide undergoes Pd-catalyzed carbonylative cyclization with iodobenzene, affording a mixture of isomeric heterocycles (Scheme 16.12) [17]. The coupling reaction of an allene with a PhCOPdI species takes place at the allenyl central catrbon to form a 2-acyl–π-allylpalladium complex, which is attacked by an internal sulfonamide group in an *endo* mode, affording a mixture of isomeric heterocycles (Scheme 16.13).

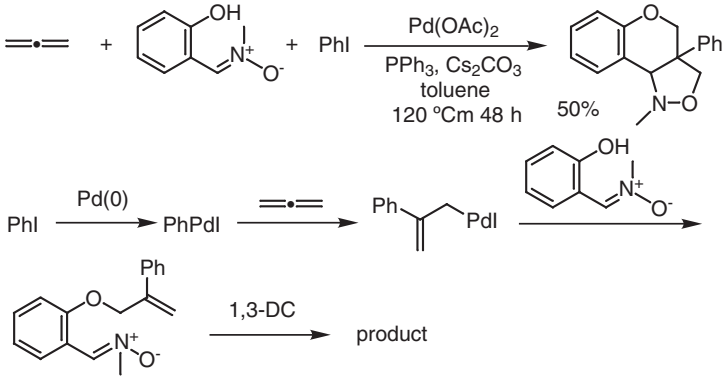


Scheme 16.12 Preparation of five-membered nitrogen heterocycles.



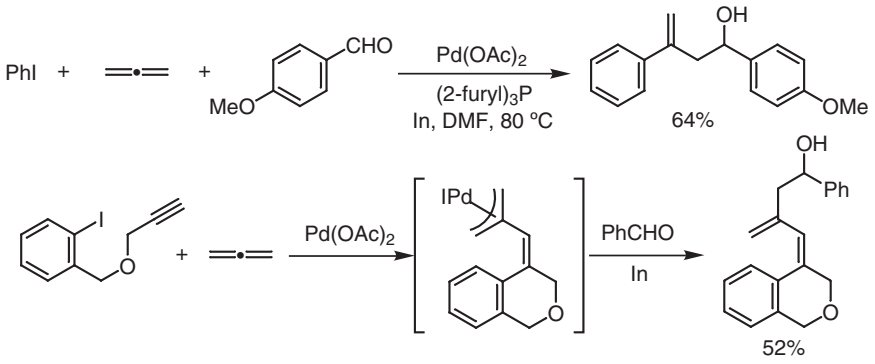
Scheme 16.13 Preparation of a 2-acyl–π-allylpalladium complex.

Fused isooxazolidines can be prepared efficiently in a one-pot procedure, which involves a sequence of a Pd-catalyzed reaction of iodobenzene with allene, nucleophilic substitution and nitrone 1,3-dipolar cycloaddition (1,3-DC) (Scheme 16.14) [18].



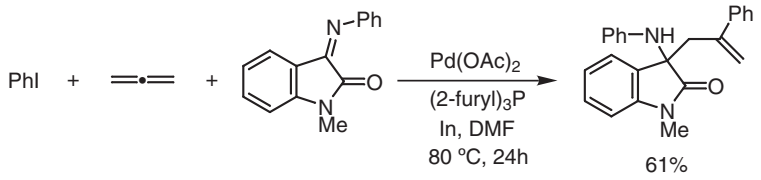
Scheme 16.14 Formation of an isooxazolidine

Homoallylic alcohols are provided by Pd-catalyzed reaction of iodobenzene, allene and aldehydes (Scheme 16.15) [19, 20]. A nucleophilic allylindium intermediate is generated through transmetallation of a π-allylpalladium species with indium. Such a π-allylpalladium complex can alternatively be provided through carbopalladation of ArPdI to a proximate acetylene followed by insertion of allene.



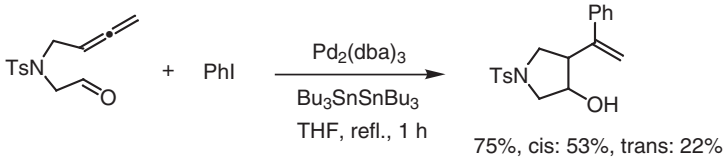
Scheme 16.15 Formation of homoallylic alcohols.

This methodology can be extended to imines, providing tertiary amines (Scheme 16.16) [21].

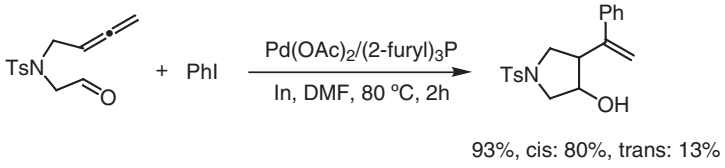


Scheme 16.16 Preparation of a homoallylic amine.

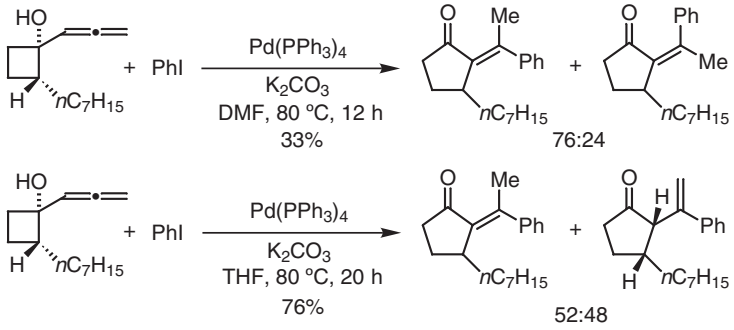
A cyclic homoallylic alcohol is efficiently provided by a sequence of π-allylpalladium complex formation, transmetallation with hexa-*n*-butyldistannane and intramolecular allylation (Scheme 16.17) [22]. The same transformation can be conducted by means of indium (Scheme 16.18) [23].



Scheme 16.17 Formation of a heterocycle via arylative cyclization using hexa-*n*-butyldistannane.

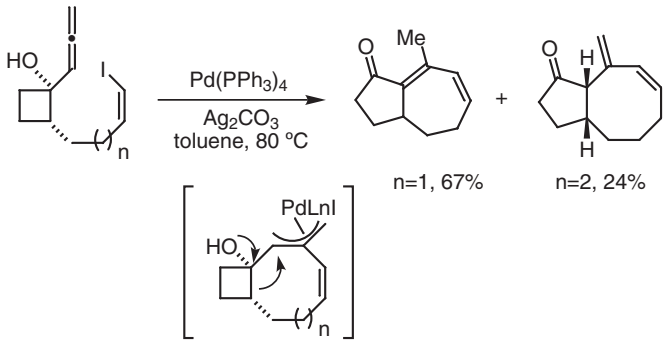


Scheme 16.18 Formation of a heterocycle via arylative cyclization using indium.



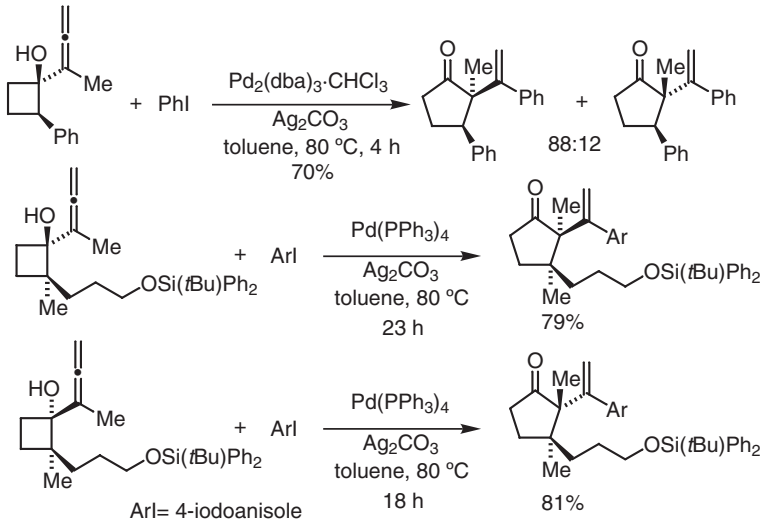
Scheme 16.19 A sequential carbopalladation and ring expansion of an allenylcyclobutanol.

A sequential process of carbopalladation and ring expansion of allenylcyclobutanols provides five-membered rings (Scheme 16.19) [24]. The intramolecular version of this approach offers a facile synthetic method for 5,7- and 5,8-fused ring frameworks (Scheme 16.20) [24].



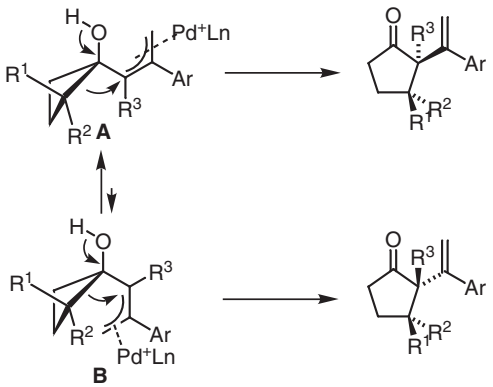
Scheme 16.20 Intramolecular carbopalladation and ring expansion of allenylcyclobutanols.

The above method has been applied to a stereoselective synthesis of cyclopentanones with quaternary carbon centers (Scheme 16.21) [25].



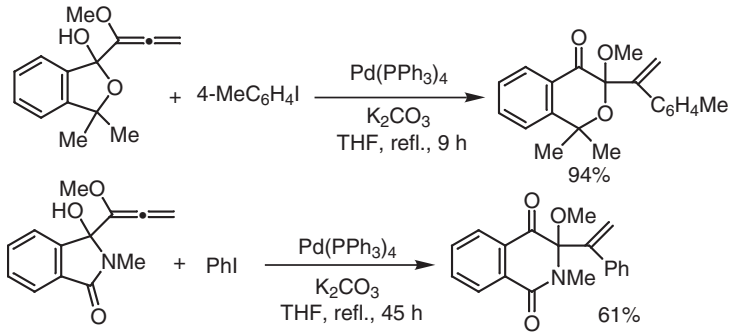
Scheme 16.21 Formation of cyclopentanones with quaternary carbon centers.

The reaction of an allenylcyclobutanol with ArPdI would provide four possible π-allylpalladium complexes, that is, two *anti*- and two *syn*-isomers. The rearrangement would, however, take place more favorably via two *anti*-isomers, **A** and **B**, which are equilibrated. Consequently, the products can be provided in a highly diastereoselective manner via thermodynamically more stable intermediate **A** (Scheme 16.22) [26].



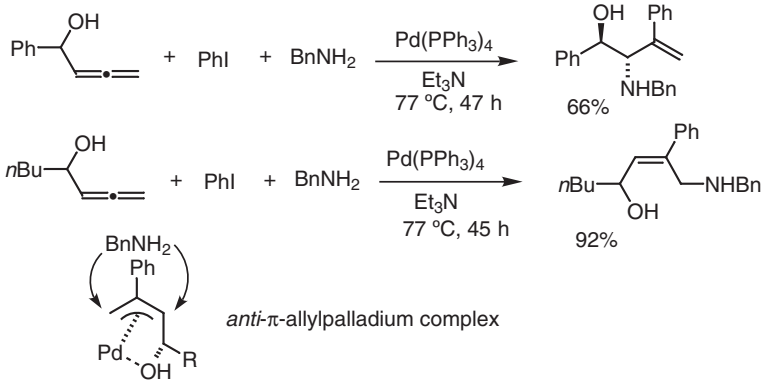
Scheme 16.22 A proposed reaction mechanism via an *anti*-π-allylpalladium complex.

Heteroatoms can also participate in the ring expansion reaction mentioned above. For example, a hydroxyl methoxyallenylphthalan gave rise to a 4-isochromanone derivative. A hydroxymethoxyallenylisoindolinone afforded an isoquinolinedione derivative efficiently (Scheme 16.23) [27, 28].



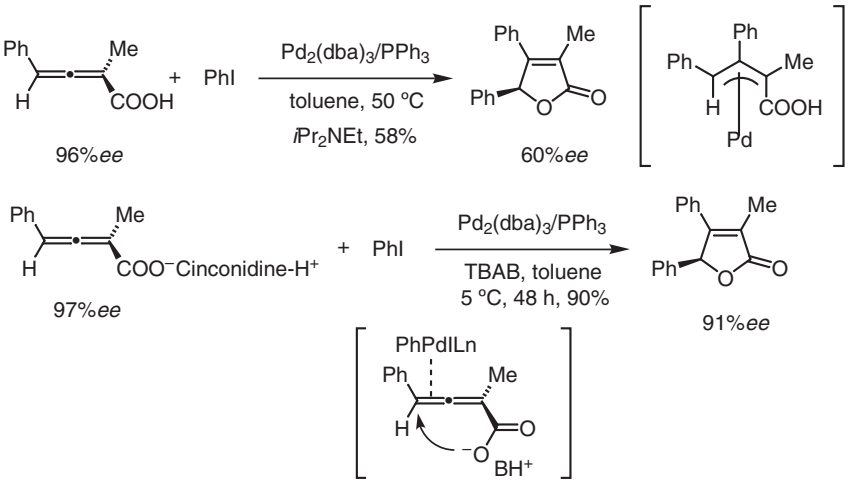
Scheme 16.23 Preparation of heterocycles via the ring expansion method.

Ma and Zhao reported a highly regio- and diastereoselective synthetic method for 2-amino-3-alken-1-ols and 4-amino-2-(*E*)-alken-1-ols by the palladium-catalyzed reaction of 2,3-allenols, aryl iodides and amines (Scheme 16.24) [29]. Carbopalladation of PhPdI to the allene probably generates a thermodynamically more stable *anti*-π-allylpalladium species for steric reasons. Regioselectivity of the amine attack depends largely on the stereoelectronic effect on the α-substituents.



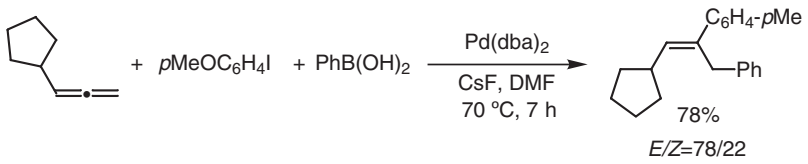
Scheme 16.24 Preparation of 1,2- and 1,4-amino alcohols.

The efficiency of chirality transfer of chiral 2,3-allenic acids can be much increased by switching the π-allylpalladium mechanism to a coordinative cyclization–reductive elimination route (Scheme 16.25) [30].



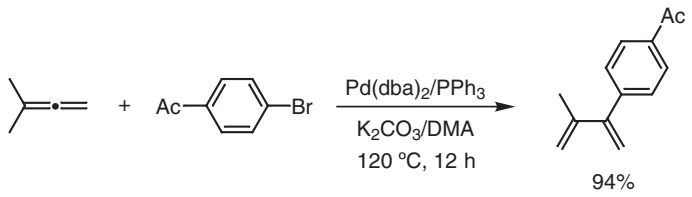
Scheme 16.25 Asymmetric synthesis of a butenolide.

Three-component assembly of allenes, organic halides and arylboronic acids has been reported in which Suzuki coupling of a π-allylpalladium complex with an organoboronic acid is utilized (Scheme 16.26) [31]. Addition of phosphorus ligands to the reaction mixture greatly decreases either the product yields or *E*/*Z* ratios. The decrease in *E*/*Z* ratio may be explained based on the fact that donor ligands readily promote *anti–syn* rearrangement of a π-allylpalladium species via a σ-allylpalladium intermediate.



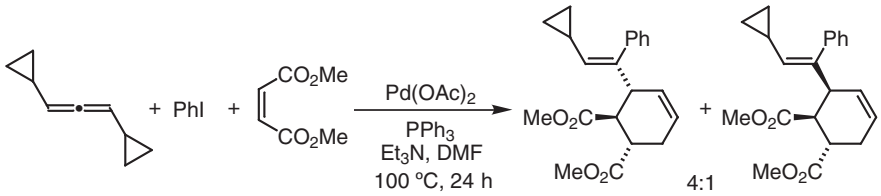
Scheme 16.26 Carbon–carbon bond formation via Suzuki coupling.

In the absence of a nucleophile, the reaction of allenes with aryl bromides provides 1,3-dienes in good yield (Scheme 16.27) [32]. The reaction is very sensitive to the reaction temperature, solvent, base and amount of phosphine used. The formation of a 1,3-diene may be explained by either β-hydrogen elimination or deprotonation at the α-carbon of the π-allylpalladium intermediate.



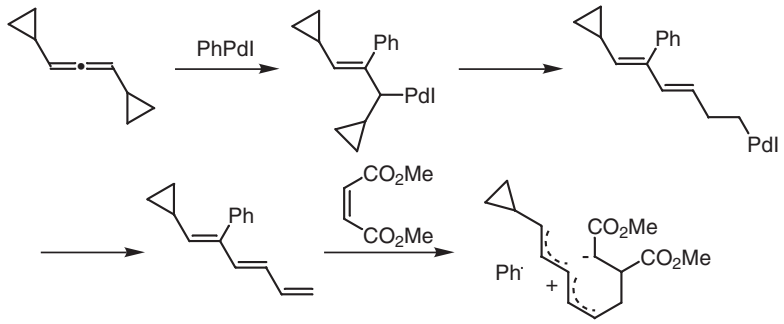
Scheme 16.27 Preparation of 1,3-dienes.

Domino Heck–Diels–Alder type reaction has been demonstrated by the reaction of 1,3-dicyclopropyl-1,2-propadiene with iodobenzene in the presence of dimethyl maleate under palladium catalysis (Scheme 16.28) [33].



Scheme 16.28 Domino Heck–Diels–Alder reaction.

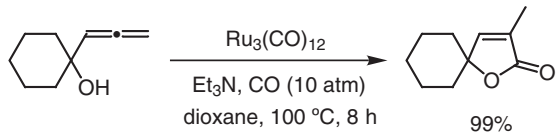
Addition of PhPdI to the allene triggers cyclopropyl ring opening to generate a σ-palladium species, which readily leads to a 1,3,5-triene through β-elimination. From the observed diastereoselectivities, the reaction seemingly proceeds stepwise via the well-stabilized zwitterionic intermediate.



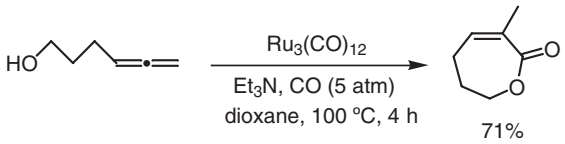
Scheme 16.29 Formation of a 1,3,5-triene and Diels–Alder reaction.

16.3 Carbonylation

$Ru_3(CO)_{12}$ catalyzes the carbonylation of the sp carbon of allenyl alcohols, giving rise to γ- and δ-lactones in good yields (Scheme 16.30) [34]. The methodology was successfully applied to the syntheis of seven- and eight-membered lactones (Scheme 16.31) [35].

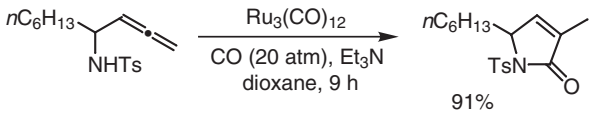


Scheme 16.30 Formation of a butenolide via Ru-catalyzed cyclocarbonylation.

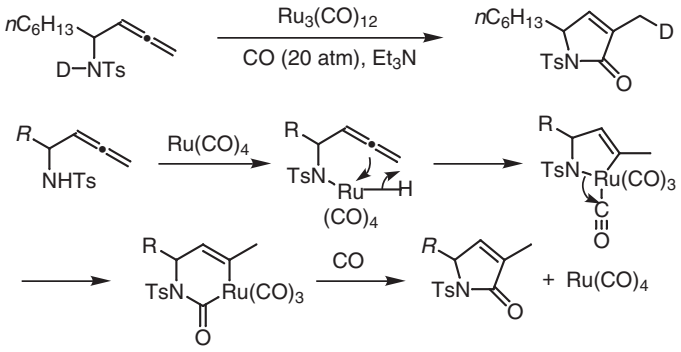


Scheme 16.31 Formation of a seven-membered lactone via Ru-catalyzed cyclocarbonylation.

The Ru-catalyzed cyclocarbonylation of α-allenic sulfonamides proceeds in the presence of Et_3N under a CO atmosphere (20 atm) to yield α,β-unsaturated lactams (Scheme 16.32) [36]. In order to gain an insight into the reaction mechanism, a deuterium-substituted α-allenic sulfonamide was subjected to the carbonylation. The deuterium was found to be totally transferred to the methyl group. Based on this observation, a mechanism has been proposed which involves a ruthenacycle derived from addition of the Ru–H to the terminal double bond of allene (Scheme 16.33).

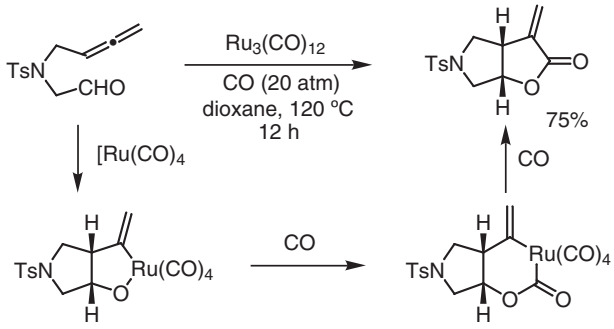


Scheme 16.32 Formation of α,β-unsaturated lactams.



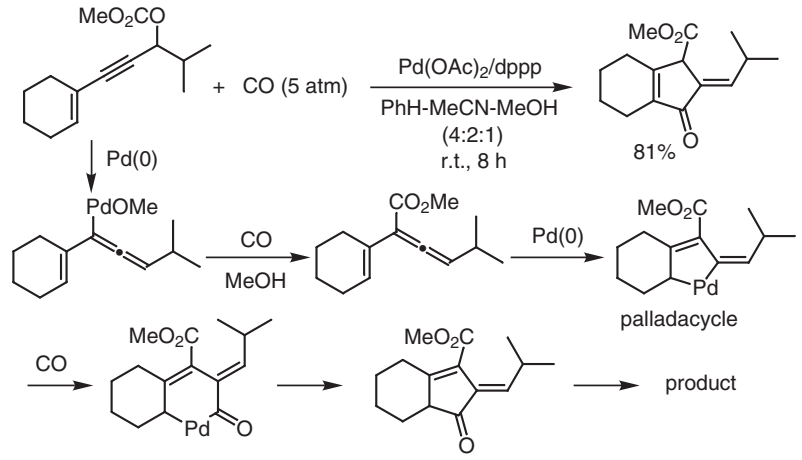
Scheme 16.33 Reaction mechanism of Ru-catalyzed cyclocarbonylation.

An allenylaldehyde can be transformed efficiently into an α-methylene-γ-butyrolactone by a ruthenium-catalyzed carbonylative cycloaddition process (Scheme 16.34) [37]. The reaction mechanism may involve a metallacyclopentene, which undergoes insertion of CO and reductive elimination leading to the product.



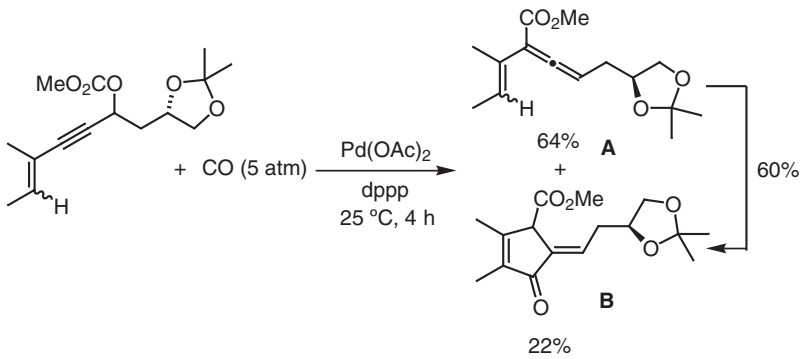
Scheme 16.34 Preparation of an α-methylene-γ-butyrolactone.

Carbonylation of 4-en-2-ynyl carbonates offers a novel synthetic method for cross-conjugated 4-oxo-5-alkylidene-2-cyclopentenecarboxylates (Scheme 16.35) [38]. The primary product of the process appears to be a 2-vinyl-2,3-dienyl ester, leading to a palladacycle, which in turn follows CO insertion into the Pd–sp^2 carbon, reductive elimination of Pd(0) species and isomerization, leading to the final product.



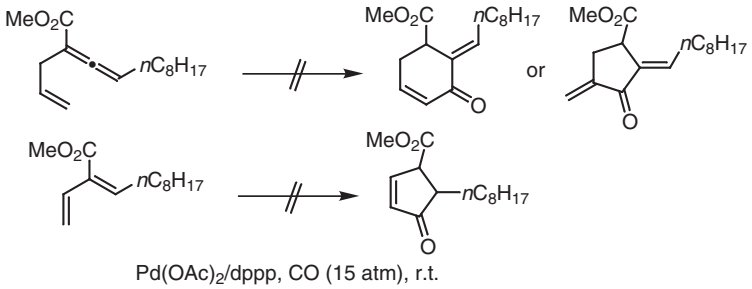
Scheme 16.35 Formation of a cross-conjugated 4-oxo-5-alkylidene-2-cyclopentencarboxylate.

Isolation of 2-vinyl-2,3-dienyl esters as the hypothetical intermediate was unsuccessful in most cases. As the only exception, 2-vinyl-2,3-dienyl ester **A** was isolated (64%) as a mixture with enone **B** (22%) after 4 h of reaction. Compound **A** was converted to **B** in 60% yield on further exposure to the carbonylation conditions, indicating that **A** is a precursor of **B** (Scheme 16.36).



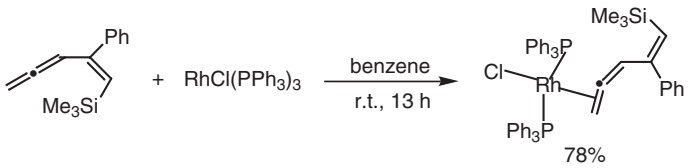
Scheme 16.36 2-Vinyl-2,3-dienyl ester as a precursor.

In order to gain more insight into the intervention of the palladacycle, the following two substrates were subjected to the carbonylation with an icreased pressure of CO (15 atm). As a result, the starting materials were recovered intact without giving the cyclized products, which led to the definite conclusion that the 2-vinyl-2,3-dienyl ester is undoubtedly a precursor of the palladacycle (Scheme 16.37).



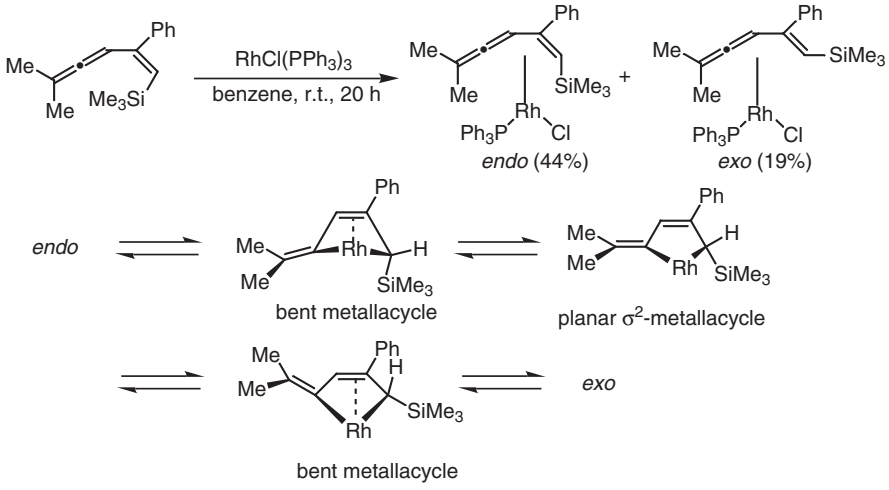
Scheme 16.37 Possible precursors for a palladacycle.

Murakami et al. elucidated the behavior of a vinylallene towards a rhodium complex. A vinylallene that has no substituents at the terminal allenic carbon is treated with $RhCl(PPh_3)_3$ in benzene at room temperature to give a (η^2-vinylallene)rhodium(I) complex in 78% yield (Scheme 16.38) [39].



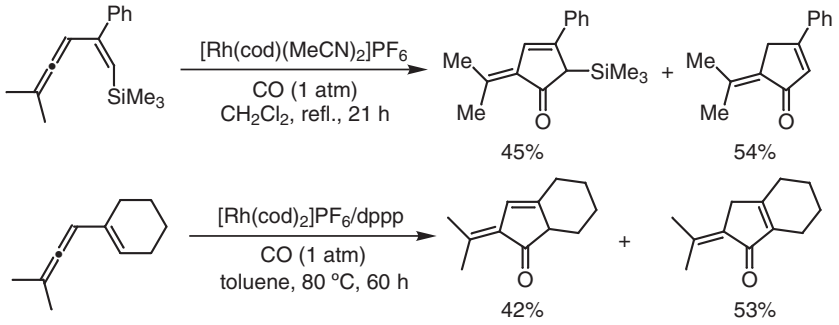
Scheme 16.38 Synthesis of a η^2-(vinylallene)rhodium complex.

In sharp contrast, a vinylallene bearing two methyl groups at the allenic terminusl is treated with $[RhCl(PPh_3)_3]$ to give (η^4-vinylallene)rhodium(I) complexes as an isolable mixture of *endo* and *exo* isomers. The *endo* isomer is found to isomerize thermally to the *exo* isomer (Scheme 16.39) [39, 40].



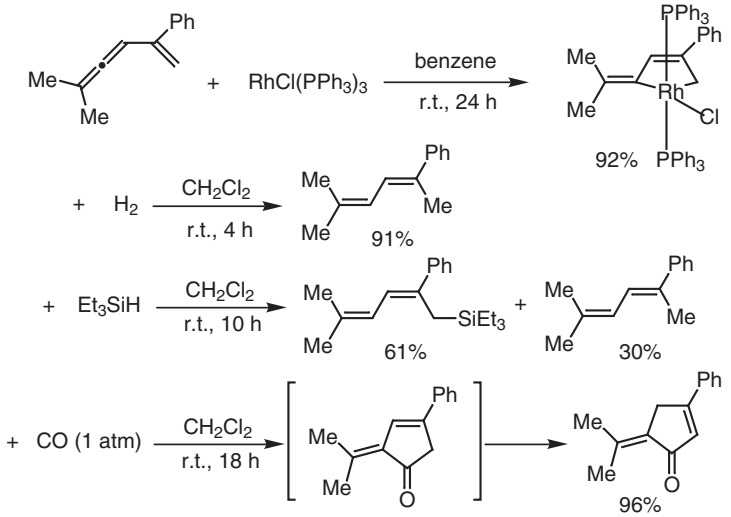
Scheme 16.39 Synthesis of η^4-(vinylallene)rhodium complexes.

An Rh-catalyzed [4 + 1]-cycloaddition reaction of vinylallenes with carbon monoxide provies an efficient synthetic method for cross-conjugated cyclopentenones (Scheme 16.40) [39, 40].



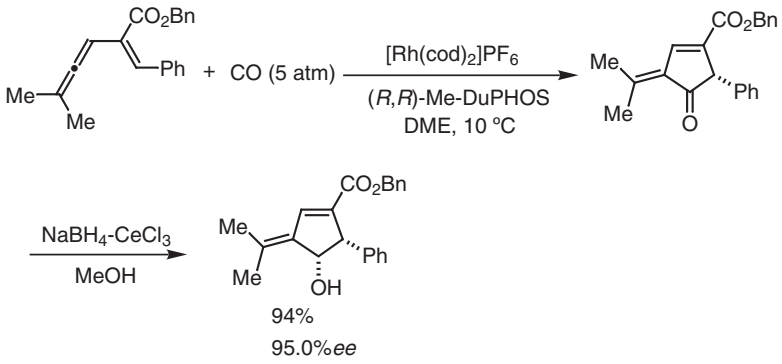
Scheme 16.40 Rh-catalyzed [4 + 1]-cycloaddition of vinylallenes with carbon monoxide.

The binding mode of a vinylallene and a rhodium(I) complex depends greatly on the substitution patterns, probably for steric reasons. The reaction of a vinylallene lacking substituents at the vinylic terminus with $RhCl(PPh_3)_3$ provides a σ^2-bonded (vinylallene)rhodium complex having an essentially planar structure. Several stoichiometric reactions of the complex have been examined (Scheme 16.41) [41].



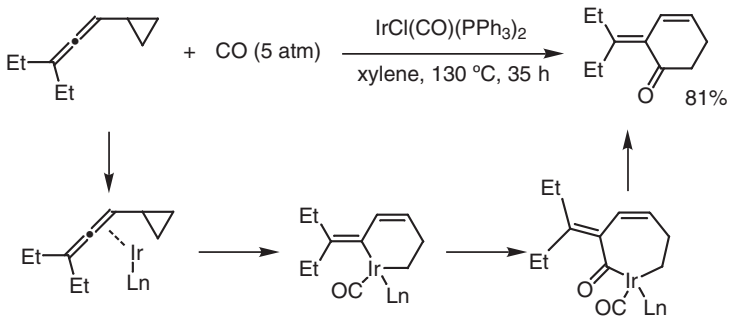
Scheme 16.41 Synthesis of (vinylallene)rhodium(III) complex of planar structure.

An Rh-catalyzed asymmetric [4 + 1]-cycloaddition of vinylallenes with carbon monoxide was realized for the first time to furnish chiral 5-substituted 2-alkylidene-3-cyclopentenones (Scheme 16.42) [42].



Scheme 16.42 Rhodium-catalyzed asymmetric [4 + 1]-cycloaddition.

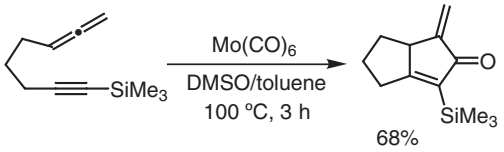
Carbonylative [5 + 1]-cycloaddition of allenylcyclopropanes was successfully achieved by use of an Ir(I) catalyst to yield (2-alkylidene)cyclohexenones in good yields (Scheme 16.43) [43]. No carbonylative [5 + 1]-cycloaddition was observed in the case of an allenylcyclopropane lacking substituents at the allenic terminus. It can be deduced that the metal is too distant to open the cyclopropane ring, probably owing to the preferred η^2-coordination at the allenic π-bond distal to the cyclopropyl group.



Scheme 16.43 Ir-catalyzed [5 + 1]-cycloaddition.

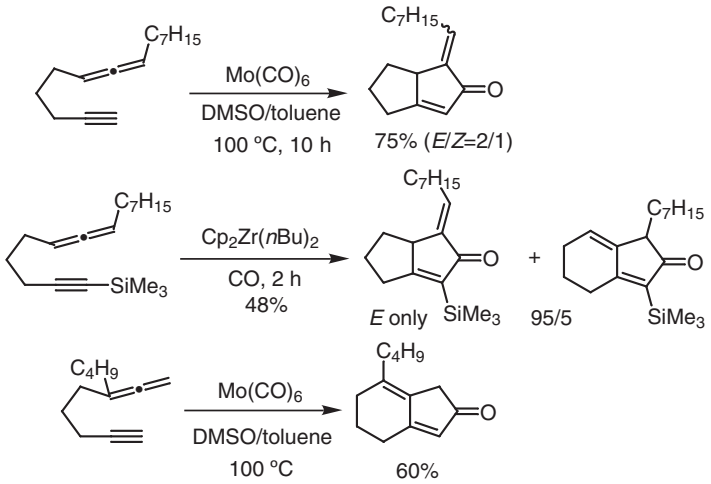
16.4
Pauson–Khand Reactions

Alkynylallenes have proved to be viable substrates for Pauson–Khand reactions (PKR), providing α-methylenecyclopentenones (Scheme 16.44) [44, 45]. It has been found that a combination of $Mo(CO)_6$ and dimethyl sulfoxide (DMSO) is an effective catalytic system. The most commonly used $Co_2(CO)_8$ catalyst for PKR is not effective since it causes polymerization.



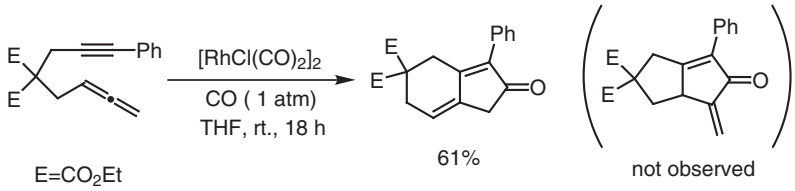
Scheme 16.44 Pauson–Khand reaction of an alkynylallene.

It has been reported that the π-bond selectivity of an allene is greatly influenced by the substitution pattern of an allene(Scheme 16.45) [46]. Reaction of a 1,3-disubstituted allenyne with $Mo(CO)_6$–DMSO gives a mixture of *E*- and *Z*-isomers of the bicyclo[3.3.0]octane ring systems in 75% yield. When the cyclization was effected in the presence of $Cp_2Zr(n\text{Bu})_2$, the (*E*)-bicyclo[3.3.0]octane ring system was obtained as the major product in moderate yield. Cyclization of a 3,3-disubstituted allenyne gave a bicyclo[4.3.0]nonane ring system as the sole product in 60% yield.



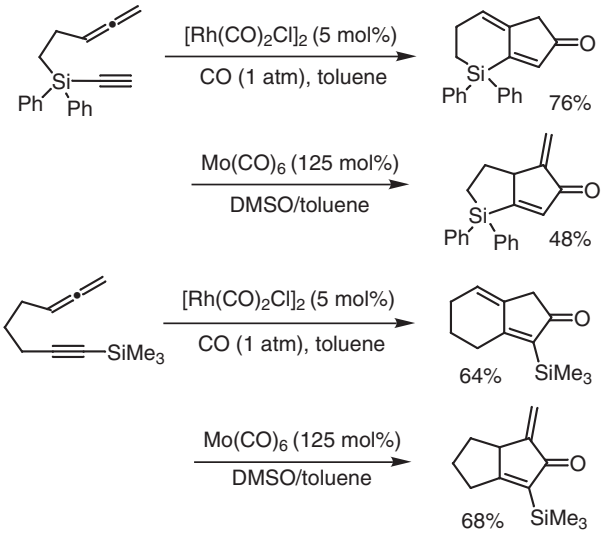
Scheme 16.45 Influence of the substituents on the π-bond selectivity.

Narasaka and co-workers found that the PKR of an allenyne proceeds at room temperature under atmospheric pressure of CO, affording a bicyclo[4.3.0]nonane skeleton (Scheme 16.46) [47].



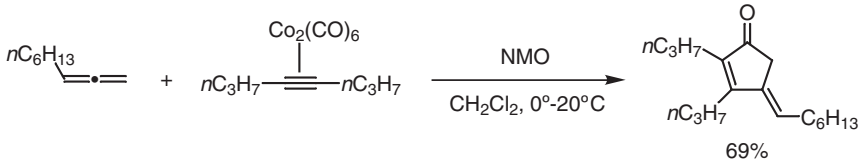
Scheme 16.46 Highly site-selective Pauson–Khand reaction.

It was found later that the controlling factor inducing preferential cyclization with the terminal π-bond of the allene is not the substitution pattern but the catalyst used. $[Rh(CO)_2Cl]_2$ is probably the best catalyst for the effective formation of bicyclo[4.3.0]nonane ring systems (Scheme 16.47) [48, 49].



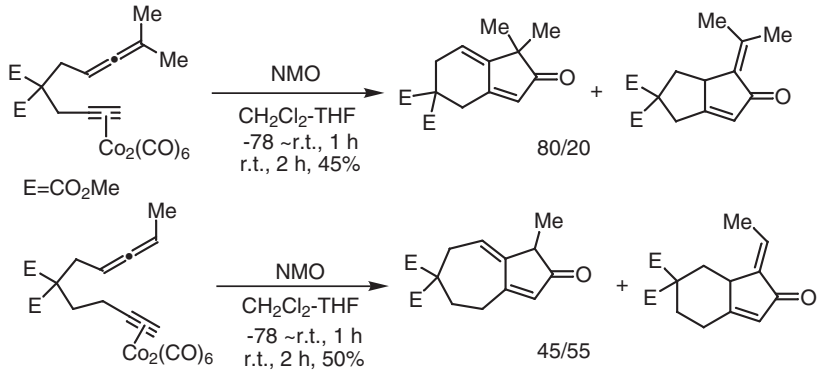
Scheme 16.47 Effect of the catalyst on the site selectivity.

The intermolecular PKR of an allenic compound with an alkyne $Co_2(CO)_6$ complex takes place under very mild conditions when *N*-methylmorpholine oxide (NMO) is used as a promoter, giving rise to (*E*)-4-heptylidene-2,3-dipropyl-2-cyclopentenone in 69% yield (Scheme 16.48) [50–53].



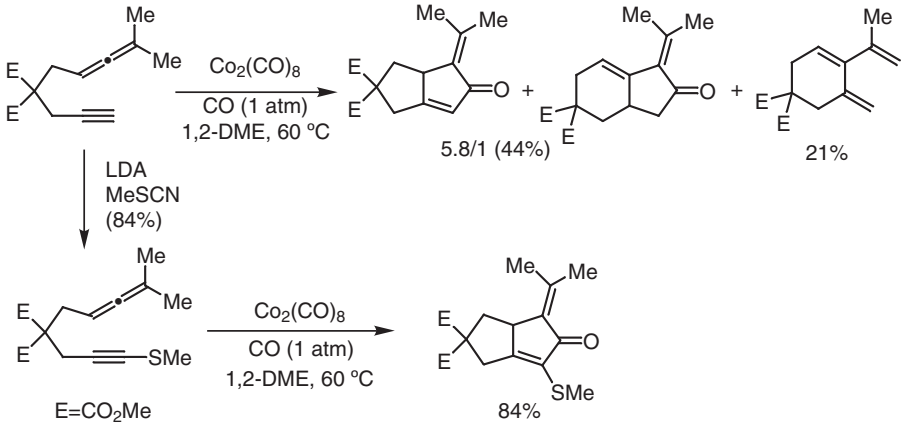
Scheme 16.48 Intermolecular Pauson–Khand reaction using NMO as a promoter.

The promoter is also effective for the intramolecular PKR of following hexacarbonyldicobalt complexes of α,ω-allenynes (Scheme 16.49) [54].



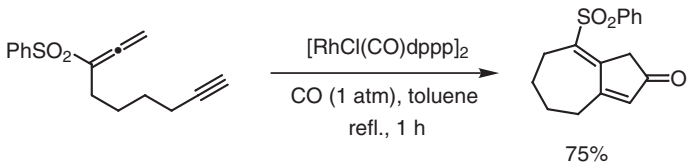
Scheme 16.49 Intramolecular Pauson–Khand reactions using NMO as a promoter.

Livinghouse and co-workers reported that a (methythio)alkyne is a superior substrate for $Co_2(CO)_8$-catalyzed PKR of allenynes (Scheme 16.50) [55].



Scheme 16.50 Remarkable effect of a (methylthio)alkyne moiety on the Pauson–Khand reaction.

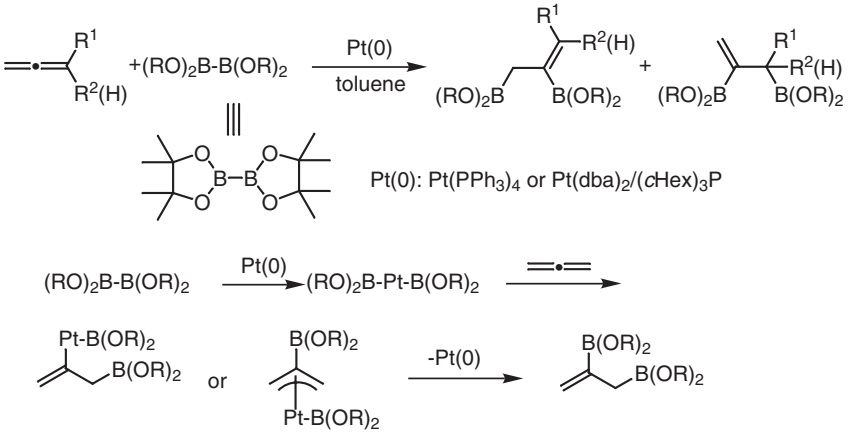
An improved synthetic method for bicyclo[5.3.0]dec-1,7-diene-9-one derivatives has recently been reported, in which $[RhCl(CO)dppp]_2$ is utilized as the catalyst (Scheme 16.51) [56].



Scheme 16.51 Synthesis of a 5,7-fused ring.

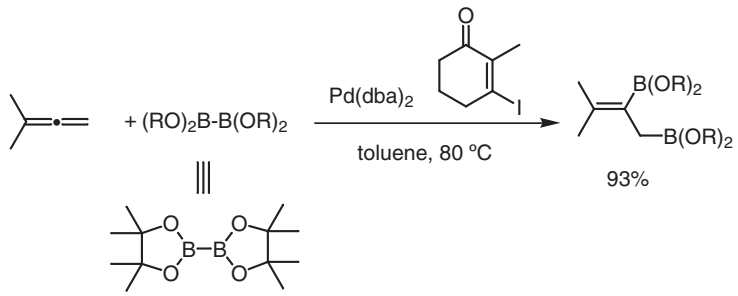
16.5
Carbon–Metal Bond Formation

Miyaura and co-workers reported the platinum-catalyzed diboration of allenes with bis(pinacolato)diboron (Scheme 16.52) [57]. The catalytic cycle involves a sequence of oxidative addition of bis(pinacolato)diboron to Pt(0), insertion of an allene into the B–Pt bond and reductive elimination of an allylic boronate, re-producing the Pt(0) species. (*Z*)-Allylic boronates are formed stereoselectively in the reaction with monosubstituted allenes, which strongly suggests a pathway via a vinylplatinum species rather than a π-allylplatinum species.



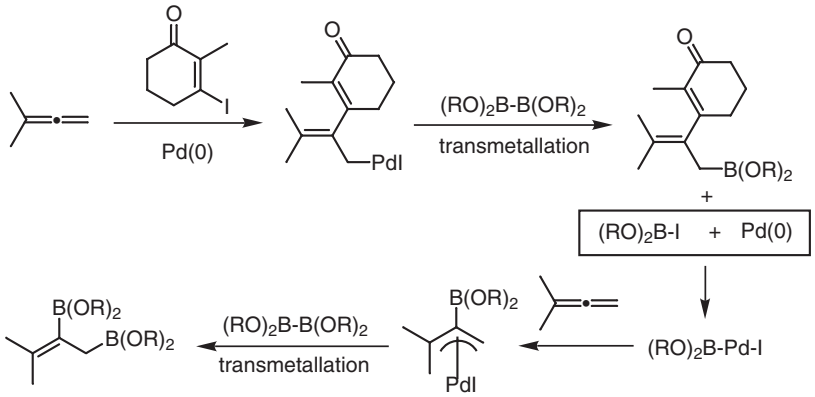
Scheme 16.52 Pt-catalyzed diboration.

A stable *cis*-$Pt(BO_2C_2Me_4)_2(PPh_3)_2$ complex has been isolated and characterized by X-ray analysis, whereas the corresponding Pd(0) complex is not known. Compatibly, no Pd-catalyzed diboration is known. However, Yang and Cheng reported for the first time a palladium-catalyzed diboration of allenes using an aryl, alkenyl iodide or I_2 as a co-catalyst (Scheme 16.53) [58].



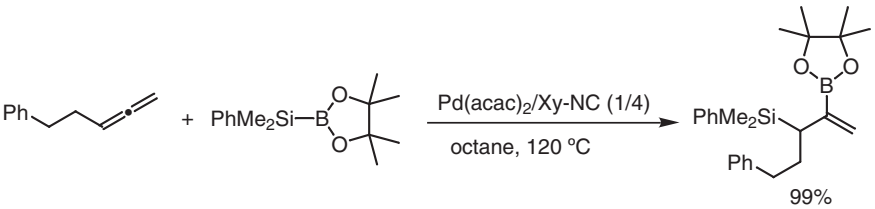
Scheme 16.53 Pd-catalyzed diboration.

The basis of the method lies in the generation of $(RO)_2B$–Pd–I as a highly reactive species toward allenes (Scheme 16.54). The palladium-catalyzed reaction of an alkenyl iodide with an allene routinely gives rise to a π-allylpalladium complex, which readily undergoes transmetallation with $(RO)_2BB(OR)_2$ to afford $(RO)_2BI$ as the real active co-catalyst. Oxidative addition of $(RO)_2BI$ to Pd(0) generates $IPdB(OR)_2$, to which an allene inserts regioselectively to form a π-allylpalladium species having a boron group on the central carbon atom. Finally, the biboronic compound is produced through transmetallation of the π-allylpalladium intermediate with $(RO)_2B$-$B(OR)_2$ followed by reductive elimination, leaving the Pd(0) species.



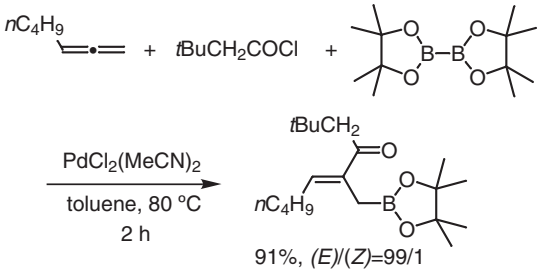
Scheme 16.54 Catalytic cycle of Pd-catalyzed diboration.

Silaboration of 3-substituted 1,2-dienes takes place smoothly at the internal double bond in the presence of the catalytic $Pd(acac)_2$–2,6-xylyl isocyanide complex and the boryl group is regioselectively introduced to the central carbon atom of an allene (Scheme 16.55) [59, 60]. The same regioselectivity is observed with the catalytic system $Pd_2(dba)_3$–$P(OCH_2)_3CEt$ [59].



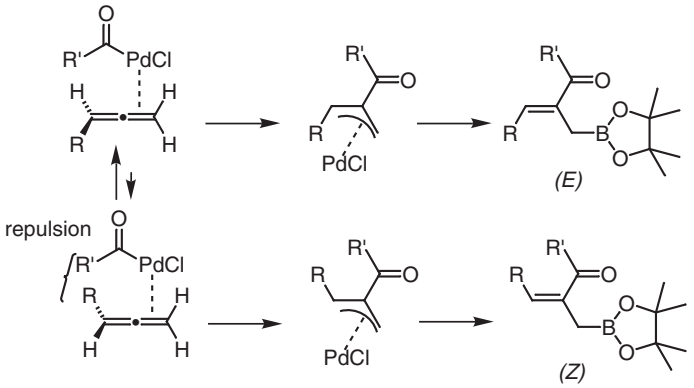
Scheme 16.55 Pd-catalyzed silaboration.

2-Acyl-allylboronates are smoothly provided through a palladium-mediated three-component assembly reaction of an acyl chloride, an allene and a diboron with high regioselectivity and *E*-stereoselectivity (Scheme 16.56) [62].



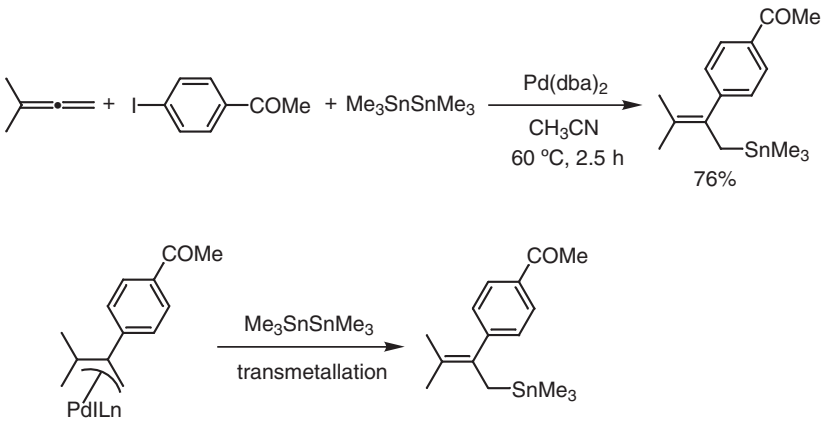
Scheme 16.56 Pd-catalyzed acylboration of allenes.

The high *E*-stereoselectivity can be explained by the face-selective coordination of an allene to an acylpalladium complex (Scheme 16.57).



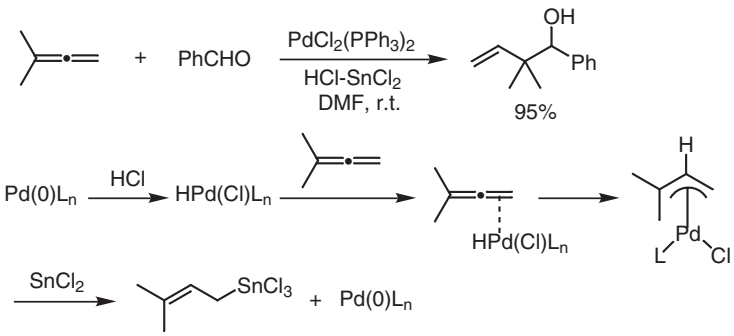
Scheme 16.57 Mechanism of acylboration.

Synthetically useful allylstannanes are provided by palladium-catalyzed carbostannylation using hexamethylditin (Scheme 16.58) [63]. The reaction mechanism can be rationalized by transmetallation between ditin and a π-allylpalladium complex produced by reaction of an allene with an arylpalladium iodide. In this process, hexamethylditin is added to the reaction mixture slowly via a syringe pump to suppress its high reactivity towards the arylpalladium species leading to an arylstannane.



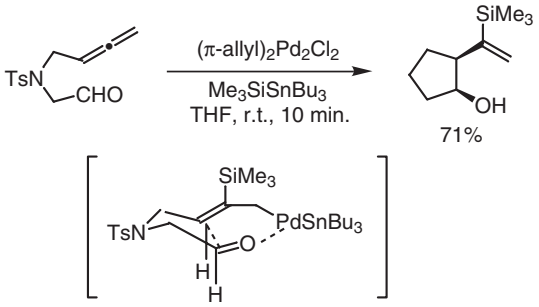
Scheme 16.58 Pd-catalyzed stannylation.

An allene undergoes hydrostannylation in the presence of $PdCl_2(PPh_3)_2$, HCl and $SnCl_2$ to give an allylltrichlorotin, which reacts smoothly with an aldehyde to afford a homoallylic alcohol (Scheme 16.59) [64]. The reduction of $PdCl_2(PPh_3)_2$ with $SnCl_2$ may initiate the catalytic reaction, giving rise to a Pd(0) species, which undergoes oxidative addition of HCl to generate an $HPd(Cl)L_n$ species. Coordination and ensuing insertion of 1,1-dimethylallene into a $HPd(Cl)L_n$ species produces a π-allylpalladium species, which is transformed into an allyltrichlorotin that is reactive towards an aldehyde.



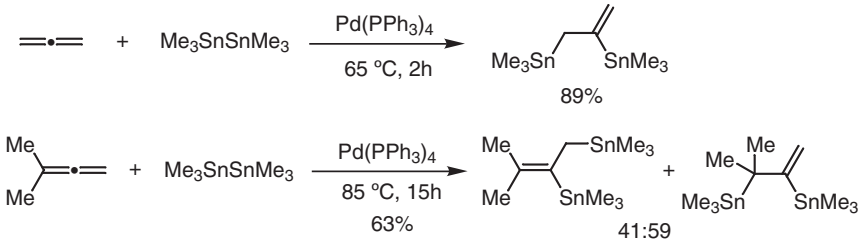
Scheme 16.59 Formation of an allyltrichlorotin.

An allenylaldehyde undergoes regioselective silastannylation to give a π-allylpalladium complex that adds to an aldehyde to afford a *cis*-cyclopentanol (Scheme 16.60) [65].



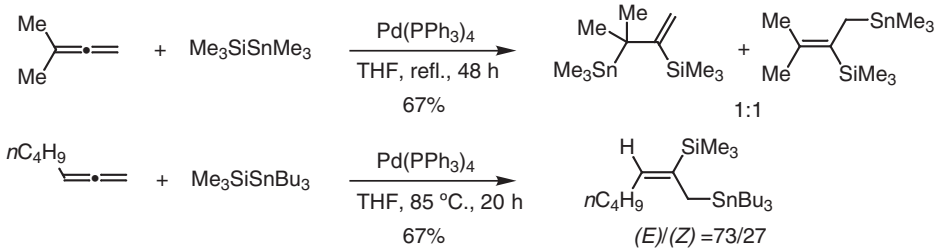
Scheme 16.60 Pd-catalyzed silastannylation.

Hexamethylditin readily adds to allene in the presence of $Pd(PPh_3)_4$ to give an allyltin compound. An unsymmetrically substituted allene such as 1,1-dimethylallene undergoes kinetically controlled addition at lower temperatures, whereas at higher temperatures thermodynamically more stable products are formed (Scheme 16.61) [66].



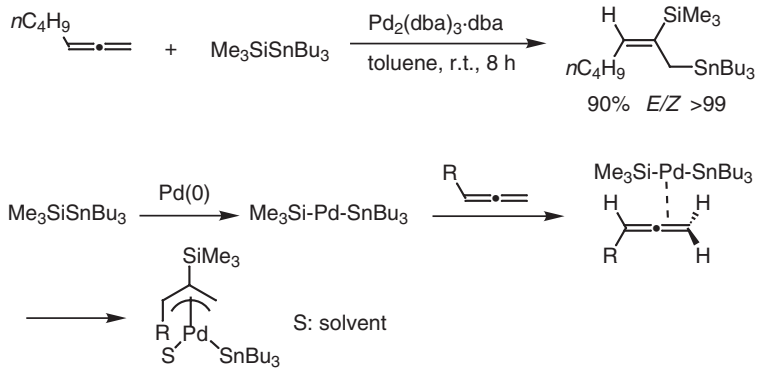
Scheme 16.61 Pd-catalyzed addition of hexamethylditin to allenes.

$Me_3SiSnMe_3$ adds to 1,1-dimethylallene in refluxing THF to give two isomeric allylstannanes without regioselectivity (Scheme 16.62) [67, 68]. The addition is only regiospecific with respect to the Me_3Si group. The proportion of the primary allylic stannane can be increased to ~80% by heating the distilled product mixture at 90 °C for 15 h in the presence of 1 mol% $Pd(PPh_3)_4$. The reaction with *n*-butylallene affords *E*-isomers with moderate stereoselectivity.



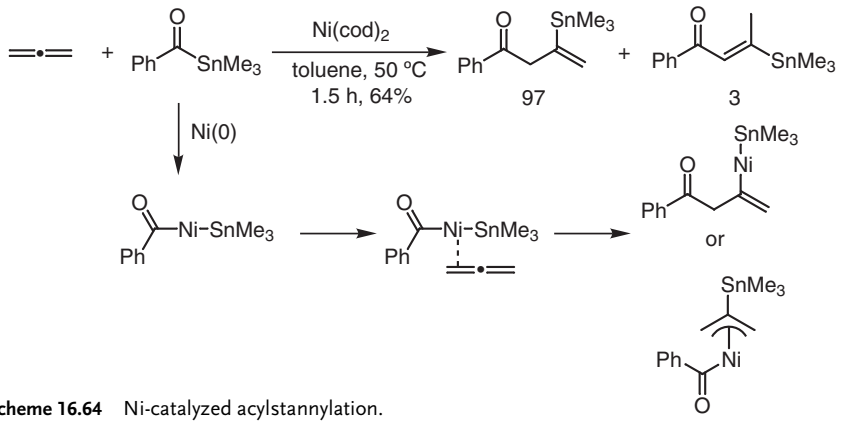
Scheme 16.62 Pd-catalyzed addition of (trimethylsilyl)trimethylstannane.

The poor regio- and stereoselectivities of the silylstannylation mentioned above are greatly improved by use of phosphine-free palladium complexes. $Pd_2(dba)_3 \cdot dba$ is a superior catalyst to other phosphine-free palladim salts such as $PdCl_2$, $Pd(acac)_2$ and $Pd(OAc)_2$. The silylstannation occurs efficiently at the allenic terminal double bond to give allylstannanes in such a way that the stannyl group always connects to the terminal carbon with excellent stereoselectivity (Scheme 16.63) [69]. A Me_3Si–Pd–$SnBu_3$ species, generated from Pd(0) and $Me_3SiSnBu_3$, adds to an allenic terminal double bond in a highly regio- and face-selective manner to give rise to a π-allylpalladium complex with the R group *anti* to the $SiMe_3$, which would be solely responsible for the exclusive formation of a (*E*)-vinylsilane derivative.



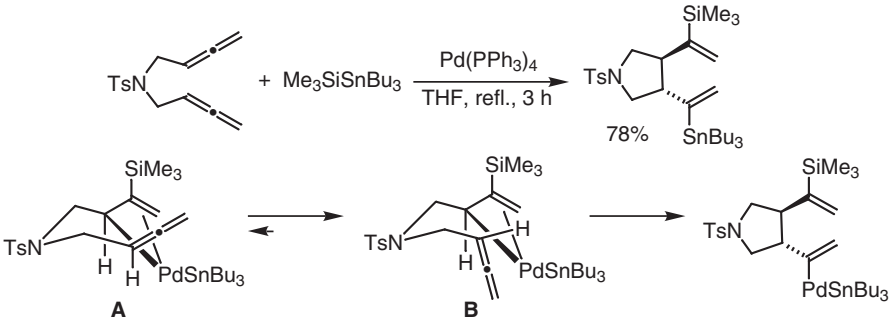
Scheme 16.63 Pd-catalyzed highly regio-and stereoselective silastannylation of allenes.

$Ni(cod)_2$ is an effective catalyst for the acylstannylation of allenes to give a wide range of α-(acylmethyl)vinylstannanes (Scheme 16.64) [70]. The catalytic reaction would be initiated by oxidative addition of an acylstannane to an Ni(0) complex to generate an acyl nickel complex. Addition of the acyl nickel complex to an allene would provide two possible intermediates leading to α-(acylmethyl)vinylstannanes.



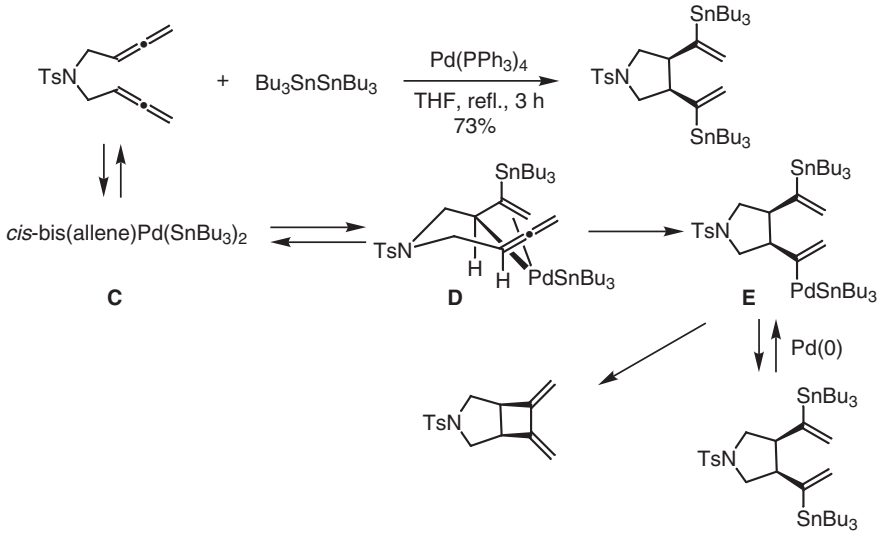
Scheme 16.64 Ni-catalyzed acylstannylation.

Palladium-catalyzed carbocyclization via silastannylation and distannylation of bisallenes provides access to silylstannane- and distannane-incorporated five-membered ring systems (Scheme 16.65) [71]. An $Me_3SiPdSnBu_3$ species adds to an allenic moiety to form a σ- or π-allylpalladium complex. Insertion of another tethered allene moiety may proceed through intermediate **B** not **A**, probably owing to the steric hindrance of the neighboring Me_3Si group.



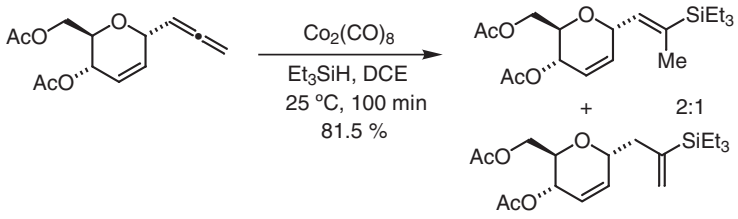
Scheme 16.65 Pd-catalyzed carbocyclization-silastannylation of bisallenes.

On the other hand, the reaction of bisallenes with $Bu_3SnSnBu_3$ may generate *cis*-bisallene $Pd(SnBu_3)_2$ (**C**) and/or a chelated σ-allylpalladium complex **D** reversibly. The fast carbocyclization of these intermediates would give rise to a vinylpalladium complex **E**, which then yields a *cis*-compound by reductive elimination and/or a *cis*-bicyclodiene through σ-bond metathesis as a kinetically controlled product (Scheme 16.66).



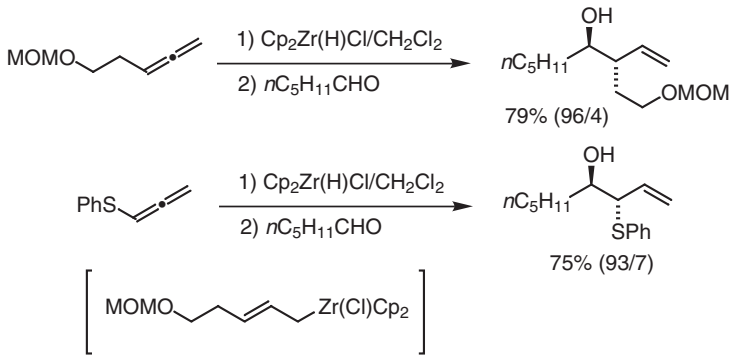
Scheme 16.66 Pd-catalyzed carbocyclization–distannylation of bisallenes.

$Co_2(CO)_8$-mediated hydrosilylation of a sugar allene proceeds under very mild conditions to give vinylsilanes as a mixture of regioisomers in good yields (Scheme 16.67) [72].



Scheme 16.67 Co-catalyzed hydrosilylation of a sugar allene.

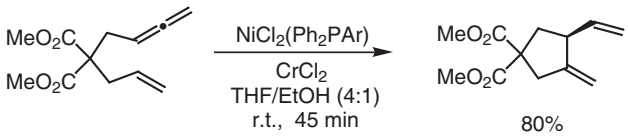
Hydrozirconation of monosubstituted allenes offers easy access to allylzirconocene chlorides, which react with carbonyl compounds to afford homoallylic alcohols in a highly regio- and stereoselective manner (Scheme 16.68) [73–75].



Scheme 16.68 Hydrozirconation of allenes.

16.6 Allenic Alder Ene Reaction and Cycloisomerization

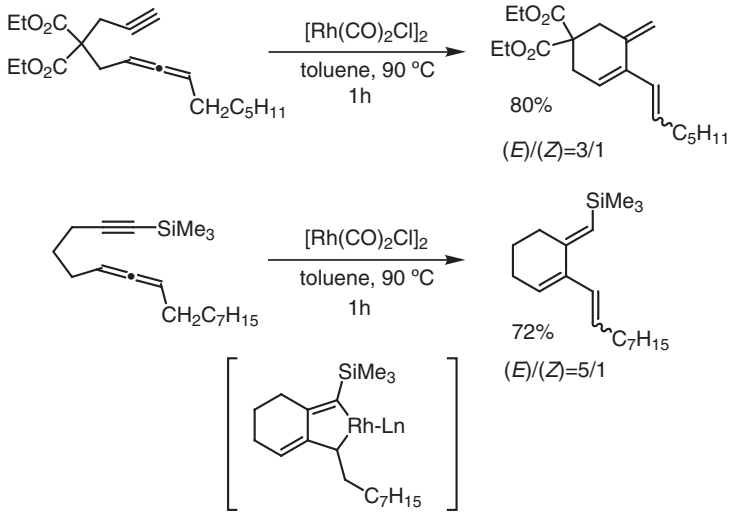
An allene serves as an excellent functional group for cyclization via isomerization with the use of a novel nickel–chromium bimetallic catalyst (Scheme 16.69) [76].



Ph_2PAr: *p*-diphenylphosphanylpolystyrene

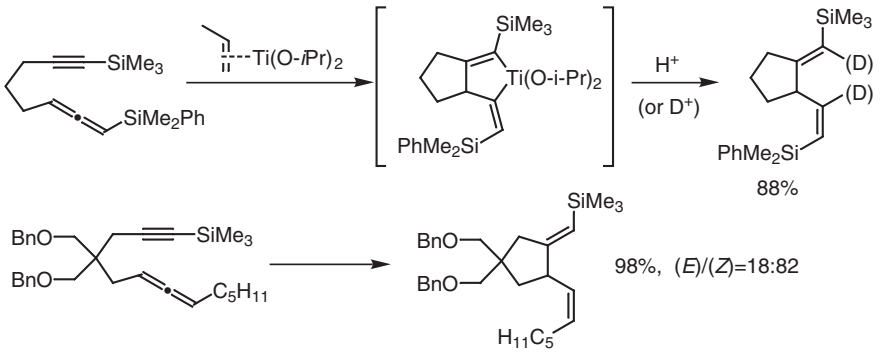
Scheme 16.69 Ni–Cr-catalyzed cyclization of enallenes.

A rhodium-catalyzed allenic Alder ene reaction effectively provides cross-conjugated trienes in very good yields (Scheme 16.70) [77]. The reaction most likely involves β-hydride elimination of an intermediate rhodium metallacycle to afford an appending olefin and ensuing reductive elimination of a metallohydride species to give the exocyclic olefin.



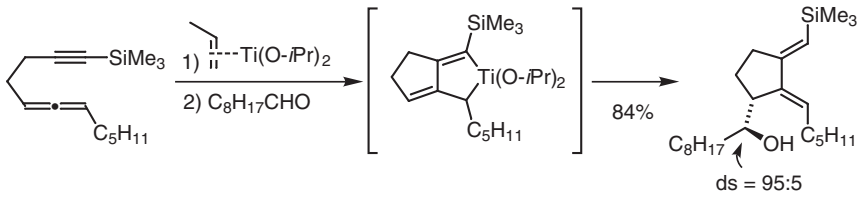
Scheme 16.70 Rh-catalyzed formal allenic Alder ene reaction.

A bis-silylated 1,2-octadien-7-yne undergoes very clean cyclization with a slight excess of (η^2-propene)Ti(O*i*Pr)$_2$, prepared in situ from Ti(O*i*Pr)$_4$ and *i*PrMgCl, at –50 °C for 2 h to give a 1,4-diene as a single isomer after hydrolytic workup (Scheme 16.71) [78]. Deuteration of the reaction mixture afforded exclusively the bis-deuterated product, confirming the presence of an intermediate titanacycle. This reaction seems to be general for other allenes with diverse substitution patterns.



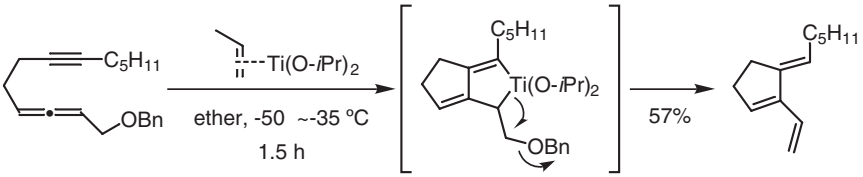
Scheme 16.71 Ti-mediated allenyne cyclization.

Ti-mediated cyclization of a 1,2-dien-6-yne generates a new allylic titanacycle, which reacts with an aldehyde to give a homoallylic alcohol with high diastereoselectivity (Scheme 16.72) [78].



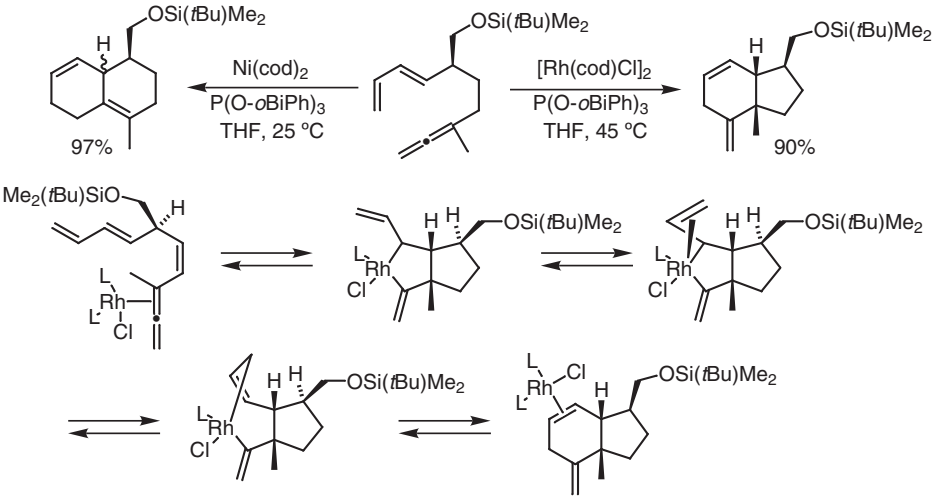
Scheme 16.72 Ti-mediated allenyne cyclization followed by condensation with an aldehyde.

Ti-mediated cyclization of an allenynes having a leaving group provides a five-membered ring with cross-conjugated trienes which might be produced by the elimination of an alkoxy group from a titanacycle (Scheme 16.73) [79].



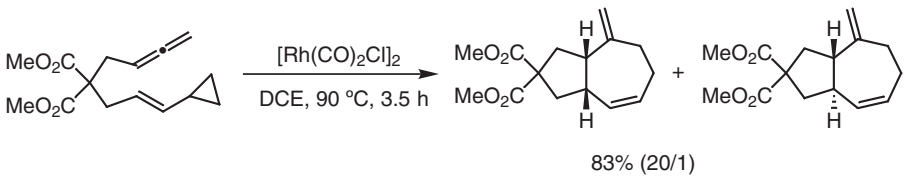
Scheme 16.73 Stereoselective preparation of cyclic cross-conjugated trienes.

Angularly substituted bicyclo[4.3.0] systems can be synthesized efficiently through a rhodium-catalyzed intramolecular [4 + 2] diene–allene cycloaddition protocol (Scheme 16.74) [80].



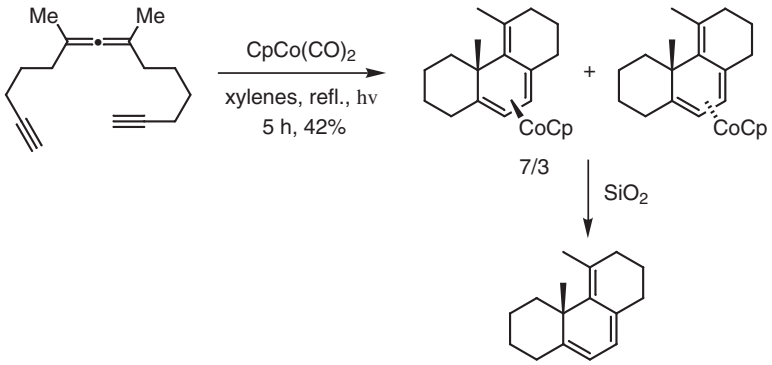
Scheme 16.74 Intramolecular [4 + 2]-cycloadditions of diene–allene.

Rhodium-catalyzed [5 + 2]-cycloaddition of an allene and a vinylcyclopropane proceeds with complete chemo-, *endo*/*exo*- and diastereoselectivity, representing an effective general route to bicyclo[5.3.0]decane derivatives (Scheme 16.75) [81]. This cycloaddition protocol has been applied successfully to asymmetric total syntheses of natural products [82, 83].



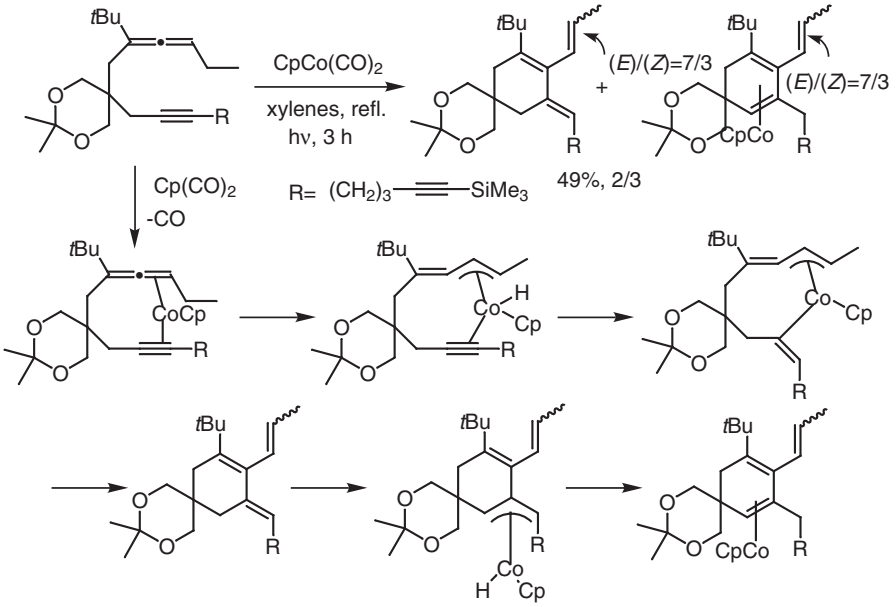
Scheme 16.75 Rh-catalyzed intramolecular [5 + 2]-cycloadditions of allenes and vinylcyclopropanes.

An allene is a very promising unsaturated partner in cobalt-mediated [2 + 2 + 2]-cycloaddition reactions. Exposure of an allenediyne to a stoichiometric amount of $CpCo(CO)_2$ in boiling xylenes under irradiation for 5 h furnishes red–brown complexes in 42% isolated yield (Scheme 16.76) [84–87]. Treatment of a 7:3 mixture of the two diastereomers thus obtained with silica gel provides an oxygen-sensitive cobalt-free tricyclic compound.



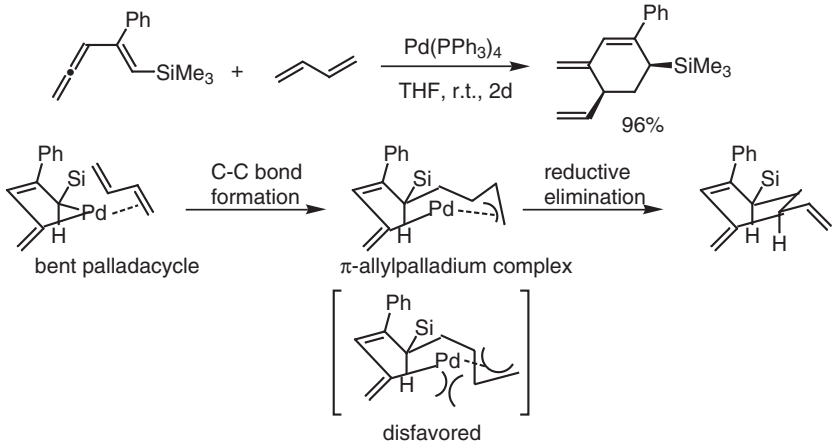
Scheme 16.76 Cobalt-mediated intramolecular [2 + 2 + 2]-cycloaddition.

A cobalt-mediated formal Alder ene reaction of an allenyne takes place to give a mixture of adducts and (η^4-cyclohexadiene)cobalt complexes (Scheme 16.77) [88]. The reaction may proceed via coordination and ensuing π-allyl complex formation.



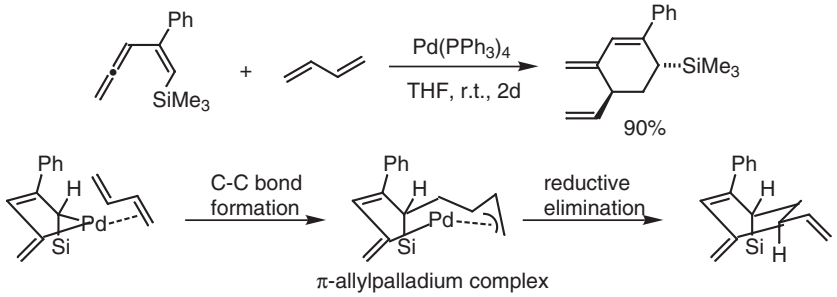
Scheme 16.77 Cobalt-mediated formal Alder ene reaction of an allene.

A vinylallene undergoes an intermolecular [4 + 2]-cycloaddition reaction with butadiene in the presence of Pd(0) catalyst under extremely mild reaction conditions, affording a cyclohexene derivative in a highly regio- and stereoselective manner (Scheme 16.78) [89]. Interestingly, the vinylallene contributes a four-carbon unit to the six-membered ring. Conversely, butadiene acts as a dienophile to provide a two-carbon complement in a regioselective manner. The reaction mechanism is as follows. Initially, there is a five-membered bent palladacycle having the trimethylsilyl group in a pseudoequatorial orientation. Then, butadiene in an *s-trans* form coordinates to the palladium and inserts concurrently to generate a π-allyl complex. The observed regio- and stereochemical outcome can be regarded as a consequence of the selective formation of this π-allylpalladium complex. A pathway leading to a π-allyl complex with the alternative stereochemistry is disfavored because of a repulsive steric interaction between the pseudo-axial vinyl group and the pseudo-axial hydrogen atom.



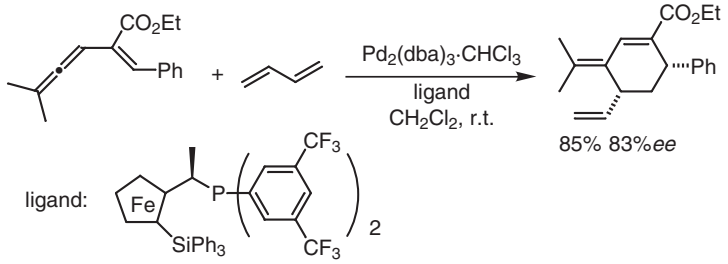
Scheme 16.78 [4 + 2]-Cycloaddition of an allene with butadiene.

A geometric isomer of the vinylallene mentioned above also undergoes [4 + 2]-cycloaddition with butadiene to furnish a cyclohexene derivative in 90% yield with excellent diastereomeric purity (>99:1). The preferred formation of a π-allylpalladium complex from the axially oriented complex accounts for the *trans* selectivity (Scheme 16.79) [89].



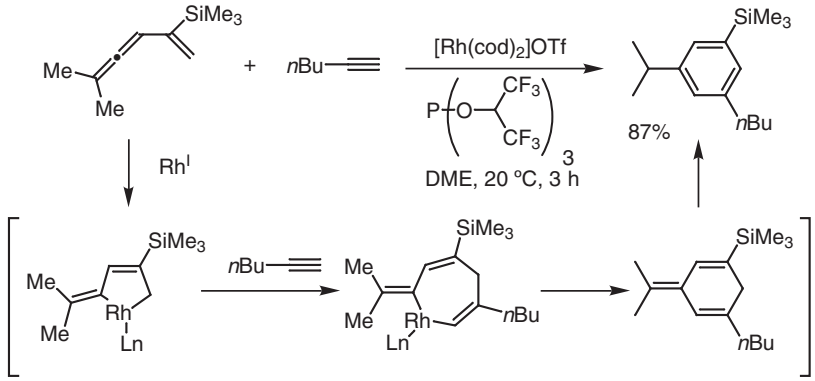
Scheme 16.79 [4 + 2]-Cycloaddition of an allene with butadiene.

A catalytic asymmetric [4 + 2]-cycloaddition of a vinylallene with butadiene has been achieved successfully, in which a palladium complex modified by a ferrocene-derived chiral monophosphine ligand proved to be a superior catalyst transferring chirality to the product (Scheme 16.80) [90].



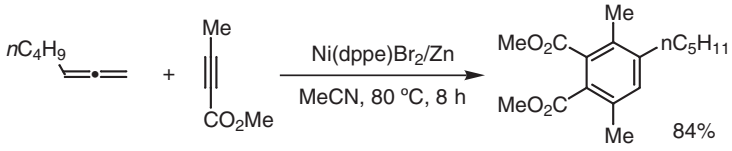
Scheme 16.80 Rh-catalyzed asymmetric [4 + 2]-cycloaddition of a vinylallene with butadiene.

Intermolecular [4 + 2]-cycloaddition of vinylallenes with alkynes is efficiently mediated by means of an electronically tuned rhodium catalyst (Scheme 16.81) [91]. A five-membered rhodacycle is formed from the vinylallene. Coordination followed by insertion of an alkyne to the rhodacycle generates a seven-membered rhodacycle, from which rhodium(I) is eliminated reductively to produce a cyclohexatriene, leading to the aromatic compound.



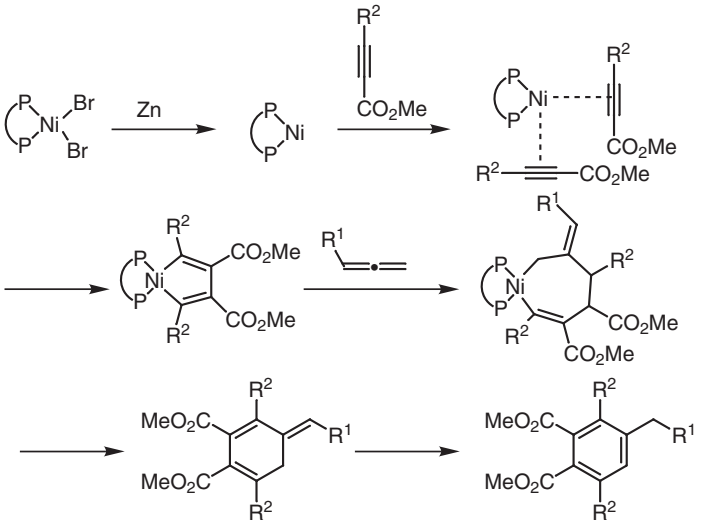
Scheme 16.81 Rh-catalyzed [4 + 2]-cycloaddition of a vinyl allene and a terminal alkyne.

A Ni(dppe)Br_2–Zn system effectively catalyzes co-cyclotrimerization of an allene with a propiolate. The reaction is highly regio- and chemoselective to afford a polysubstituted benzene derivative in good yield. (Scheme 16.82) [92]. From the observation that no desired [2 + 2 + 2] product is obtained for the reaction of 1-hexyne and phenylacetylene with *n*-butylallene under similar conditions, the presence of an electron-withdrawing CO_2Me group in the alkyne moiety is essential for the success of the present [2 + 2 + 2]-co-cyclotrimerization.



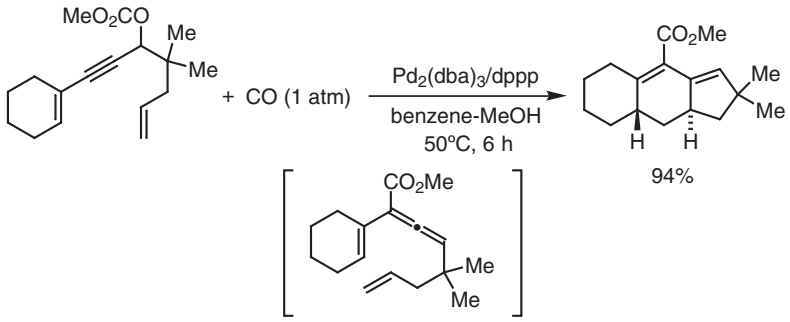
Scheme 16.82 [2 + 2 + 2]-Co-cyclotrimerization of an allene.

The proposed reaction mechanism is as follows (Scheme 16.83). Zinc metal reduces Ni(II) species to Ni(0). A nickelacyclopentadiene may be produced via coordination of two molecules of propiolates and regioselective head-to-head oxidative cyclometallation. Coordination and subsequent insertion of an allene into the Ni(II)–carbon bond give rise to a nickelacycloheptadiene intermediate. Finally, a benzene derivative is produced via reductive elimination followed by isomerization.



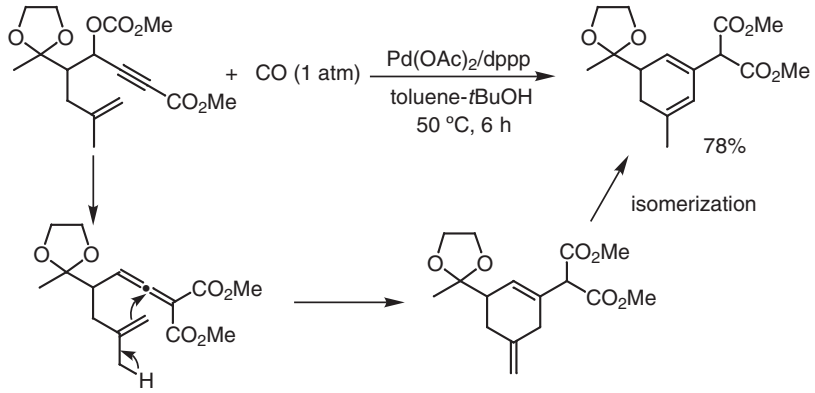
Scheme 16.83 Proposed reaction mechanism.

An allenyl bond conjugated to an ester group formed by the carbonylation of propargylic carbonates is highly reactive and undergoes an intramolecular [4 + 2]-cycloaddition reaction with a properly arranged olefin, providing a polycyclic compound in high yield (Scheme 16.84) [93].

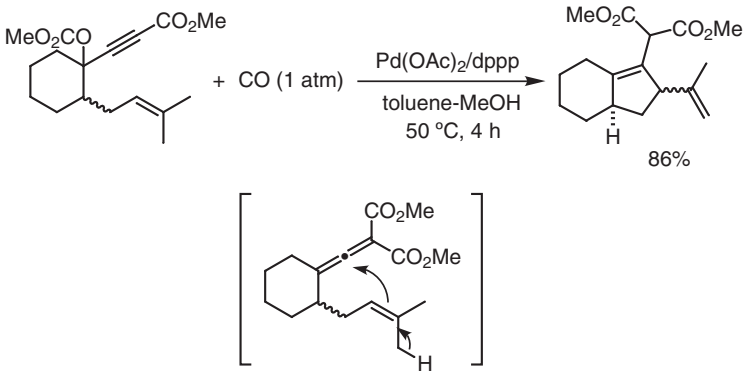


Scheme 16.84 Pd-catalyzed tandem carbonylation and intramolecular Diels–Alder reaction.

Sequential carbonylation and intramolecular ene reaction of 1-(2-methoxycarbonylethynyl)-4-alkenyl methyl carbonate proceed smoothly under CO (1 atm) in the presence of a Pd catalyst to give cyclohexadiene and cyclopentene derivatives in good yields (Schemes 16.85 and 16.86) [94]. An allenyl geminal diester would be formed as a reasonable initial product by the carbonylation. These geminal ester groups lower the LUMO level of the allenyl part, which may account for the remarkably high reactivity of the allenyl geminal diester as an enophile. It is ambiguous whether the palladium catalyst mediates the ene reaction or not.

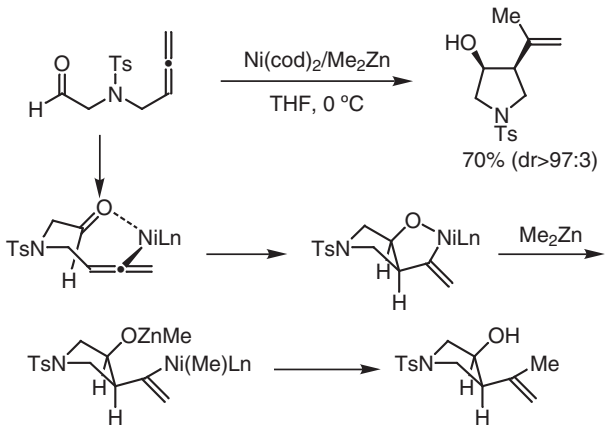


Scheme 16.85 Pd-catalyzed tandem carbonylation and intramolecular ene reaction.



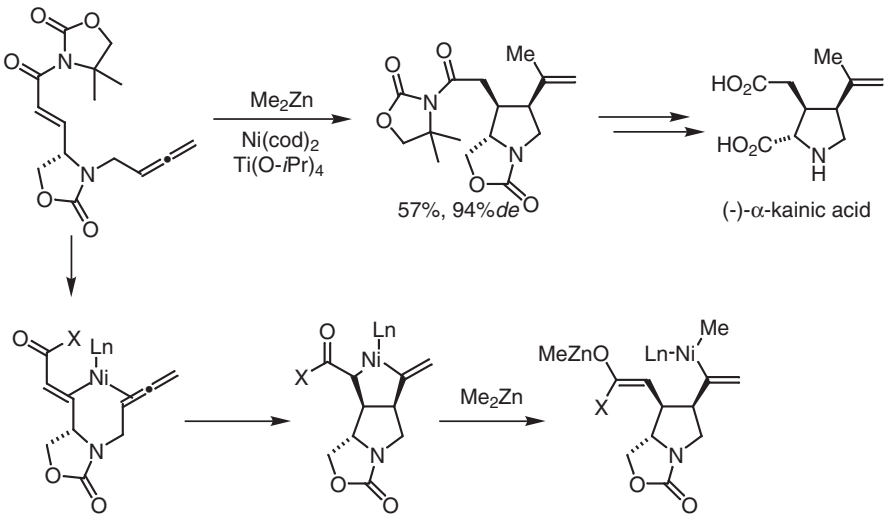
Scheme 16.86 Formation of a 5,6-fused ring.

A combination of $Ni(cod)_2$ and R_2Zn effects simultaneous nickel metallacycle formation and organozinc transmetallation, yielding a cyclic homoallyl alcohol (Scheme 16.87) [95].



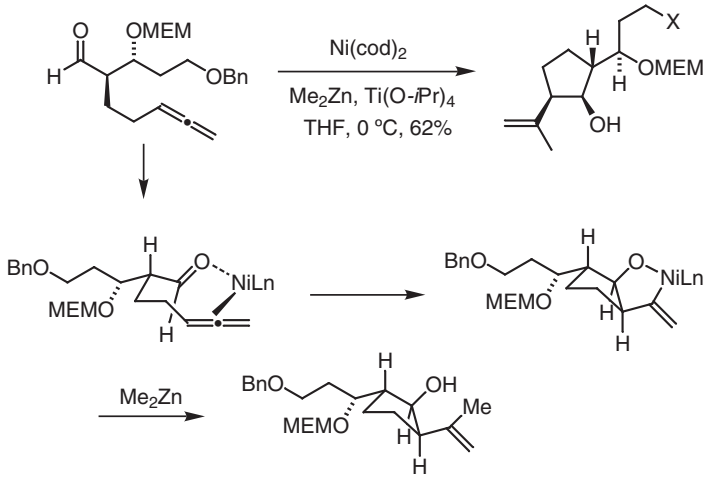
Scheme 16.87 Ni-catalyzed cyclization of an allenylaldehyde.

A novel $Ni(cod)_2$-catalyzed allene/alkene cyclization has been utilized in the synthesis of (–)-α-kainic acid (Scheme 16.88) [96]. A stereocontrolled metallacycle would be generated via coordination of Ni(0) species to both an alkene of the enone and a proximal allenyl double bond followed by oxidative cyclization of the Ni(0) complex. The metallacycle would be transformed into the product through transmetallation of Me_2Zn and ensuing reductive elimination.



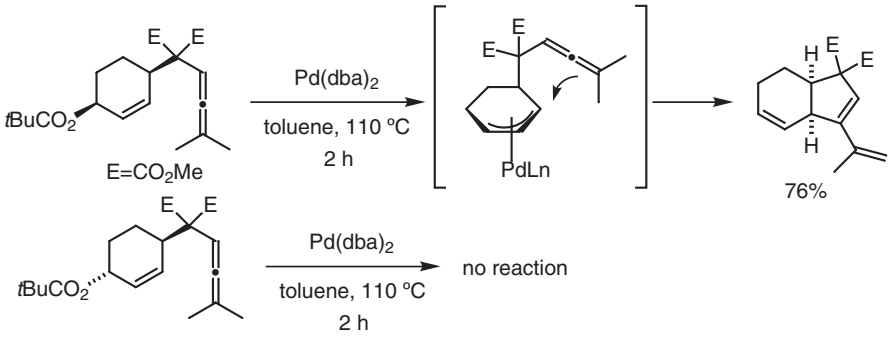
Scheme 16.88 Ni-catalyzed cyclization of an allene.

This protocol is also effective for the cyclization of an allenylaldehyde, the synthetic utility of which has been demonstrated in the synthesis of (+)-testudinariol A (Scheme 16.89) [97]. Cyclization of an allenylaldehyde provides a *cis*-cyclopentanol bearing a 2-propenyl group at the C2 position. The reaction mechanism may be accounted for by coordination of Ni(0) with both the aldehyde and the proximal allenyl double bond in an eclipsed fashion with a pseudo-equatorial orientation of the side chain, oxidative cyclization to a metallacycle, followed by Me_2Zn transmetallation and reductive elimination.



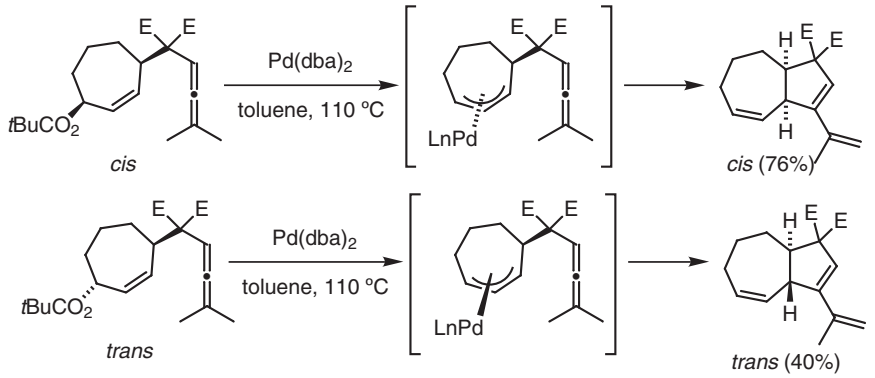
Scheme 16.89 Ni-catalyzed cyclization of an allenylaldehyde.

It has been shown that an allene acts as a π-nucleophile and attacks a π-allylpalladium complex on the face opposite to that of palladium (Scheme 16.90) [98]. An allenic allylic pivalate, *cis*-isomer, undergoes a smooth cyclization in the presence of catalytic amounts of $Pd(dba)_2$ in toluene to give a *cis*-fused 5,6-ring system. The reaction with the *trans*-isomer gives no cyclization product and the starting material is recovered.



Scheme 16.90 Ene reaction of an allene with a π-allylpalladium complex.

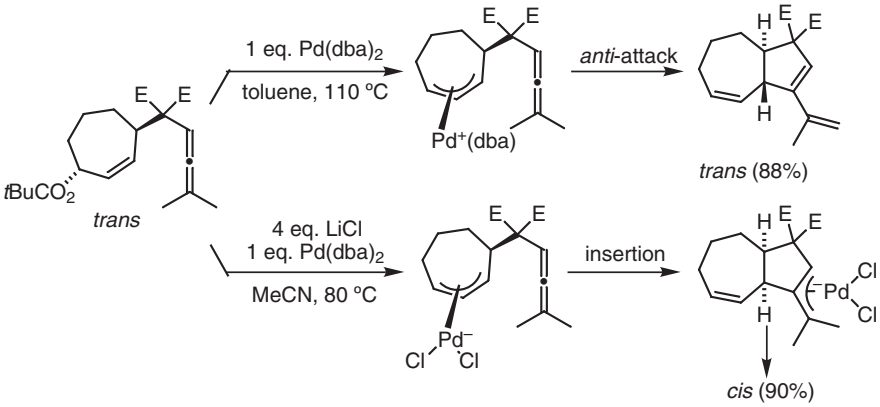
The stereoselectivity of the allene attack has been demonstrated by the catalytic reaction of *cis* and *trans* seven-membered allenic compounds, in which *cis*- and *trans*-fused 5,7-ring systems are provided in 76 and 40% yield, respectively, via π-allylpalladium intermediates (Scheme 16.91).



Scheme 16.91 Preparation of *cis*- and *trans*-fused 5,7-ring systems.

The following observations are intriguing from both mechanistic and synthetic viewpoints (Scheme 16.92). In the stoichiometric reactions, electron-withdrawing ligands (e.g. dba) on palladium are necessary for the olefinic double bond to attack a π-allylpalladium group. The resulting electrophilic π-allylpalladium group becomes

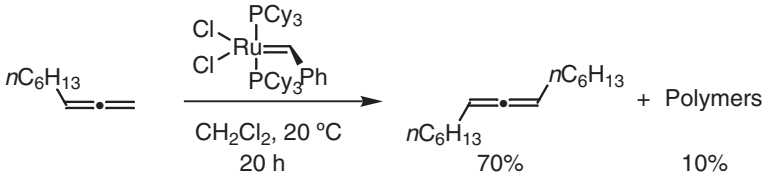
more susceptible to attack by the electron-rich double bond. In sharp contrast, nucleophilic attack of the external double bond is blocked severely upon addition of LiCl. Instead, double bond insertion of the allene into the allyl–palladium bond occurs to give a *cis*-fused 5,7-ring system.



Scheme 16.92 Effect of LiCl on the cyclization pathway.

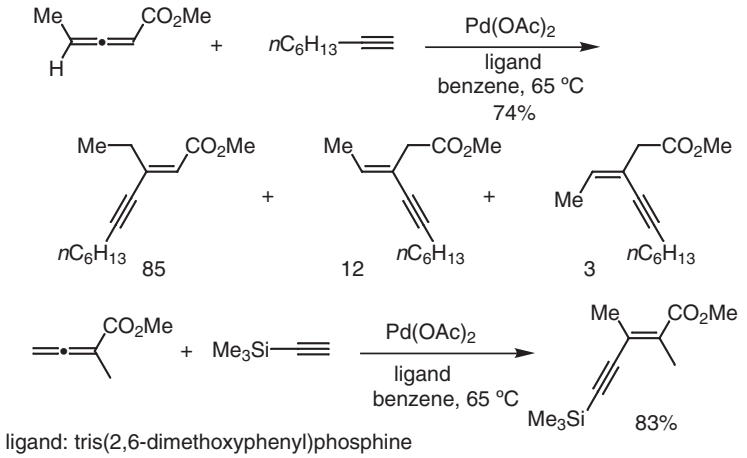
16.7
Homo- and Cross-Coupling Reactions

Exposure of a monosubstituted allene to a Grubbs carbene complex allows the formation of a 1,3-disubstituted allene accompanied with polymers (Scheme 16.93) [99]. The product distribution depends considerably on the alkyl substituents on the allene moiety and particularly the reaction of a series of phenylallenes undergoes complete conversion to polymers.



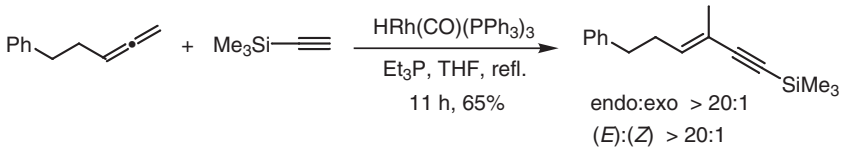
Scheme 16.93 Metathesis of an allene.

Methyl 2,3-alkadienoates undergoes cross-coupling reactions with terminal acetylenes to give enynes in a highly regioselective manner (Scheme 16.94) [100].



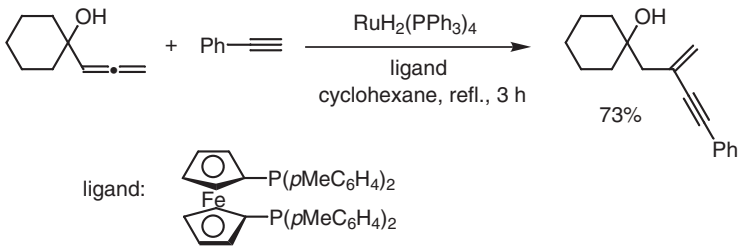
Scheme 16.94 Cross-coupling reaction of allenyl esters and terminal alkynes.

The cross-coupling reaction of unactivated allenes and 1-alkynes has been efficiently achieved by making use of catalysis with $HRh(CO)(PPh_3)_3$ and Et_3P, giving *endo*-(*E*)-enynes in high yields and selectivities (Scheme 16.95) [101].



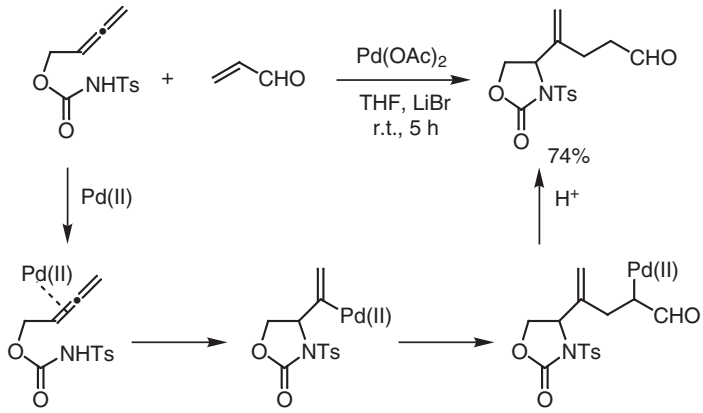
Scheme 16.95 Cross-coupling reaction of a terminal allene and silylacetylene.

A combination of $RuH_2(PPh_3)_4$ and ferrocenylphosphines catalyzes the cross-coupling reaction of α-hydroxyallenes and 1-alkynes to give *exo*-enynes selectively (Scheme 16.96) [102]. From the observation that *O*-protected allenes and 5-phenyl-1,2-pentadiene are inert to the cross-coupling reaction, the α-hydroxyl group in allenes plays an important role in this *exo*-selective reaction.



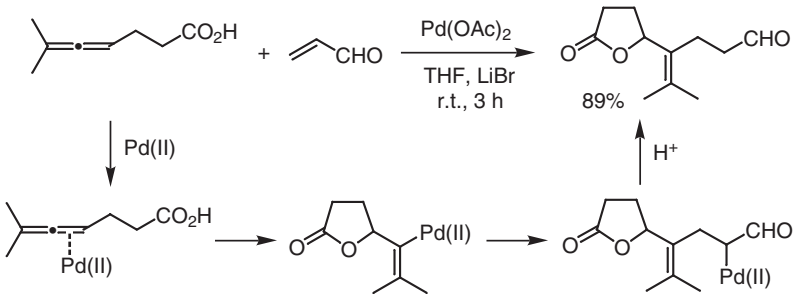
Scheme 16.96 Cross-coupling reaction of an α-allenyl alcohol and phenylacetylene.

A Pd(II)-catalyzed sequential cyclization–coupling reaction of allenyl *N*-tosylcarbamates and acrolein has been developed (Scheme 16.97) [103]. The proposed mechanism involves intramolecular aminopalladation of an allene, followed by insertion of acrolein and carbon–Pd bond protonolysis.



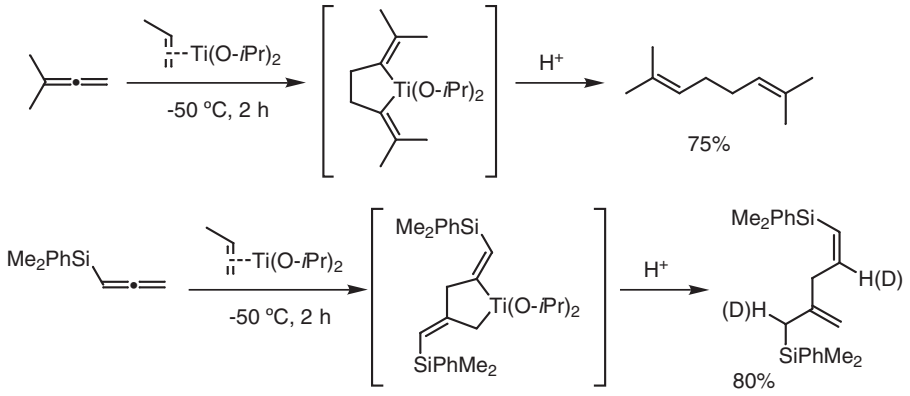
Scheme 16.97 Cross-coupling reaction of an allene and acrolein.

This approach is applicable to cross-coupling reactions of allenoic acids and acrolein, which lead to the synthesis of lactones (Scheme 16.98) [104]. The reaction proceeds via oxypalladation of an allenoic acid to give rise to a vinylpalladium species.



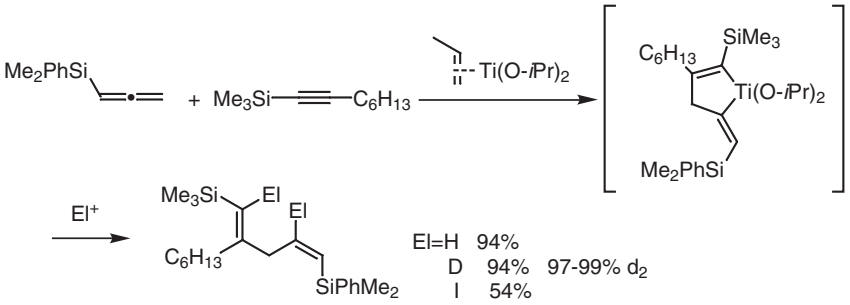
Scheme 16.98 Cross-coupling reaction of an allenoic acid and acrolein.

The homo-coupling reaction of 1,1-dimethylallene proceeds at –50 °C to give a symmetrically substituted diene in good yield (Scheme 16.99) [105]. In sharp contrast, the reaction of a monosubstituted allene proceeds via a titanabicycle to give an unsymmetrical diene.



Scheme 16.99 Ti-mediated coupling reaction of terminal allenes.

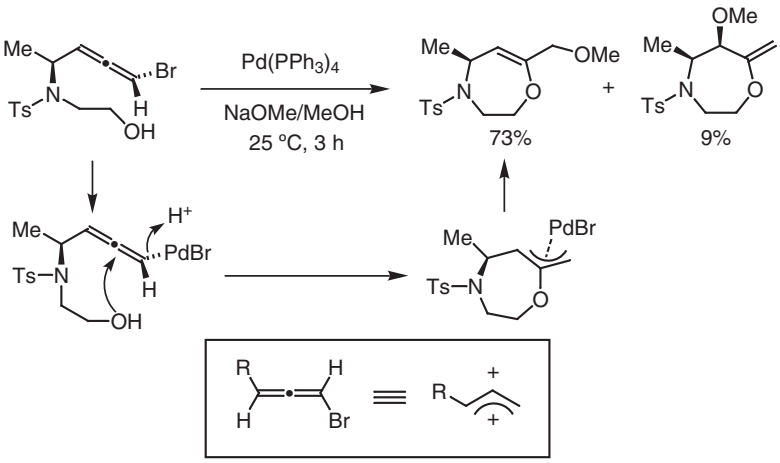
The cross-coupling reaction between an allene and an acetylene takes place at the terminal double bond of an allene to generate a titanacycle, which, on treatment with electrophiles, gives diverse 1,4-dienes in a highly stereoselective manner (Scheme 16.100) [105].



Scheme 16.100 Preparation of 1,4-dienes via Ti-mediated cross-coupling reaction.

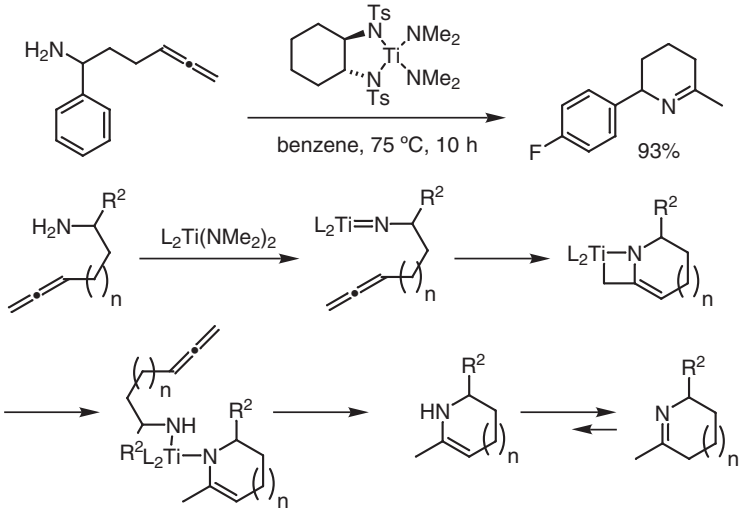
16.8 Miscellaneous Reactions

A bromoallene was demonstrated to act as an allyl dication equivalent. When treated with Pd(0) in an alcoholic solvent, an ω-hydroxybromoallene provides a medium-sized heterocycle (Scheme 16.101) [106]. The oxidative addition of a bromoallene to Pd(0) generates an allenylpalladium species, which is successively transformed into a π-allylpalladium complex through the attack of the hydroxyl group on the sp carbon followed by the protonation of the resulting Pd–carbene complex. Finally, the products are provided as a mixture of regioisomers by the nucleophilic attack of the external methanol.



Scheme 16.101 Preparation of a seven-membered heterocycle.

Highly regioselective intramolecular hydroamination of a γ-aminoallenes has been achieved using a titanium bis(sulfonamide) as a precatalyst (Scheme 16.102) [107].



Scheme 16.102 Ti-mediated intramolecular hydroamination of a γ-aminoallene.

16.9 Conclusions

A tremendous number of transformations of allenes have been reported owing to their high π-coordination ability towards transition metals. Among them, intramolecular cycloaddition reactions of allenes, in particular, appear to be a practical means of carbon–carbon bond formation in a complicated system. The allenic moiety, however, should be precisely designed for the synthetic purpose of more complex frameworks. A formidable challenge is the synthesis of diversely functionalized allenes of high chemical and/or enantiomerical purity.

Abbreviations

acac	acetylacetone
Cp	cyclopentadienyl
dba	dibenzylideneacetone
DCE	dichloroethane
DMA	*N*,*N*-dimethylacetamide
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppe	1,2-bis(diphenylphosphanyl)ethane
dppp	1,3-bis(diphenylphosphanyl)propane
NMO	4-methylmorpholine *N*-oxide

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17
Oxidation of Allenes

Attila Horváth and Jan-E. Bäckvall

17.1
Introduction

The addition of halogens or hypohalides to allenes has been known for a century, but oxidation by other means is a relatively new field of allene chemistry. In this book, oxidation reactions of allenes are divided into three mechanistically different groups. The first group deals with reactions that are initiated by an electrophilic species such as a halogen or sulfenyl or selenyl chloride followed by addition of a nucleophile such as a halide, an alcoholate, a carboxylate or an amide. These reactions are discussed in Chapter 10. In the second group, covered in the present chapter, reactions catalyzed by transition metals such as palladium, ruthenium and osmium are included. In this case only nucleophiles are added to the allenic double bond and the transition metal is reduced. Oxidation of the reduced metal closes the catalytic cycle. The third important group of reactions involves epoxidation reactions, including tungsten-catalyzed epoxidation, and is also discussed in this chapter. Reactions in this group begin with epoxidation of one or both allenic double bonds. The epoxide intermediate is then opened by a nucleophile or via rearrangement. At the end of the chapter, oxidation of allenes by elemental sulfur is discussed.

17.2
Palladium(II)-Catalyzed 1,2-Oxidations

Palladium(II) is one of the most important transition metals in catalytic oxidations of allenes [1]. Scheme 17.1 shows the most common reactions. Transformations involving oxidative addition of palladium(0) to aryl and vinyl halides do not afford an oxidized product and are discussed in previous chapters. The mechanistically very similar reactions, initiated by nucleophilic attack by bromide ion on a (π-allene)palladium(II) complex, do afford products with higher oxidation state and are discussed below. These reactions proceed via a fairly stable (π-allyl)palladium intermediate. Mechanistically, the reaction involves three discrete steps: (1) generation of the π-allyl complex from allene, halide ion and palladium(II) [2]; (2) occasional isomeriza-

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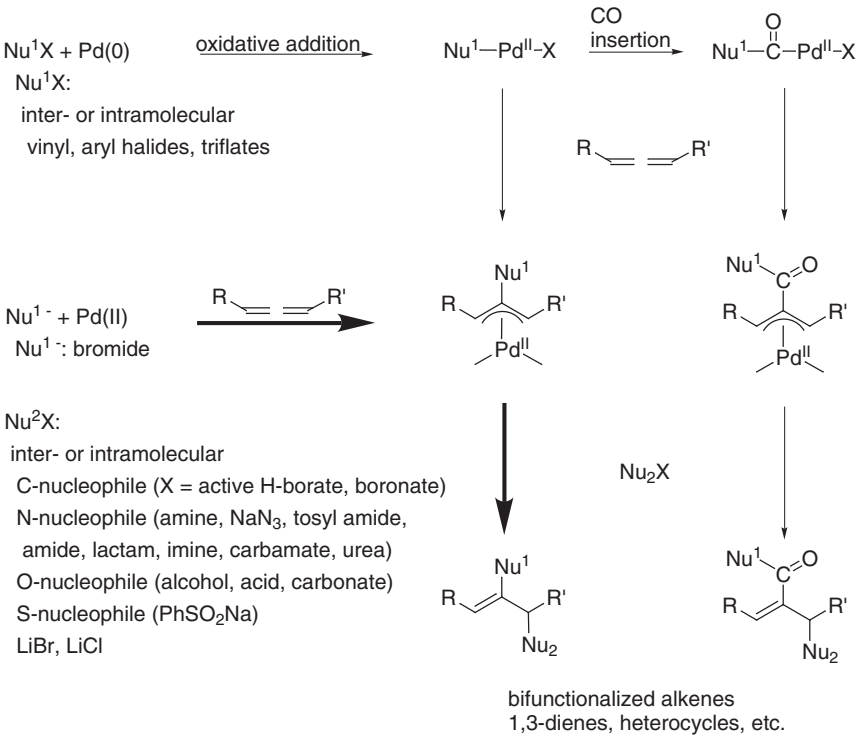
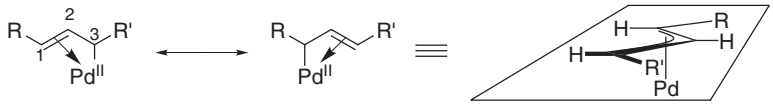
tion of the intermediate (π-allyl)palladium complex (see Scheme 17.3) and (3) product formation from the π-allyl complex and a second nucleophile. With the proper selection of the nucleophiles a variety of five- and six-membered heterocycles and several functionalized alkenes are accessible. A good process, however, has to be chemo-, regio- and stereoselective. This means that only one of the double bonds of the allene should be functionalized with high regioselectivity. Furthermore, the remaining double bond should be of either *Z*- or *E*-configuration in the product.



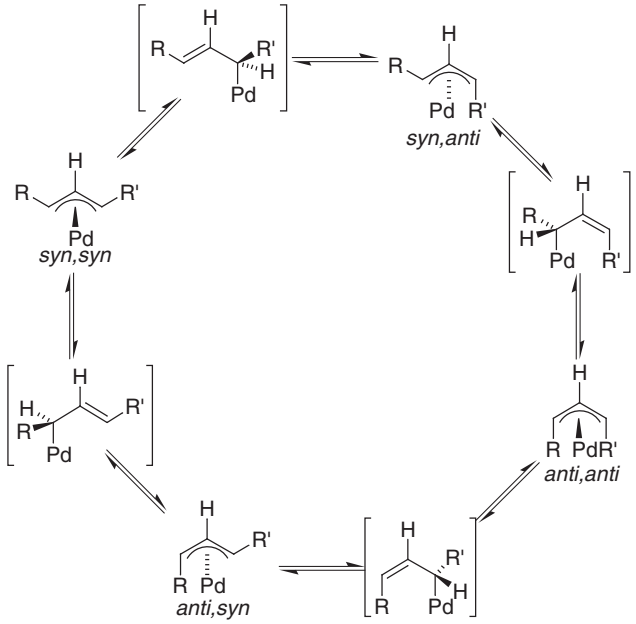
Scheme 17.1 Selected palladium-catalyzed reactions of allenes proceeding via π-allyl complexes.

The intermediate π-allyl complex is formally the palladium(II) complex of an allylic anion that can be represented by the two mesomeric forms shown in Scheme 17.2. It is important to note that this is not a fast equilibrium between two σ-allyl complexes but a stable species where palladium is simultaneously bound to both carbon-1 and carbon-3. All eight atoms of the π-allyl moiety are almost in the same plane. All three carbon atoms have sp^2 character and the rotation between the C1-C2 and C2-C3 bonds is blocked. As a consequence of the hindered rotation, four diastereomeric π-allyl complexes are possible. For example, in Scheme 17.2 both R and R′ are *syn* to the hydrogen on carbon-2, therefore this complex is called the *syn,syn* diastereomer.



Scheme 17.2 Structure of the π-allyl(palladium) complex.

In general the *syn,syn* complex is the most stable isomer but it is in equilibrium with the other three diastereomers (Scheme 17.3). The interconversion between the π-complexes proceeds via the less stable *σ*-complexes and is rather slow. Usually more than one π-allyl intermediate is present in the reaction mixture, which makes chirality transfer from an enantiomerically enriched allene to the product complicated.

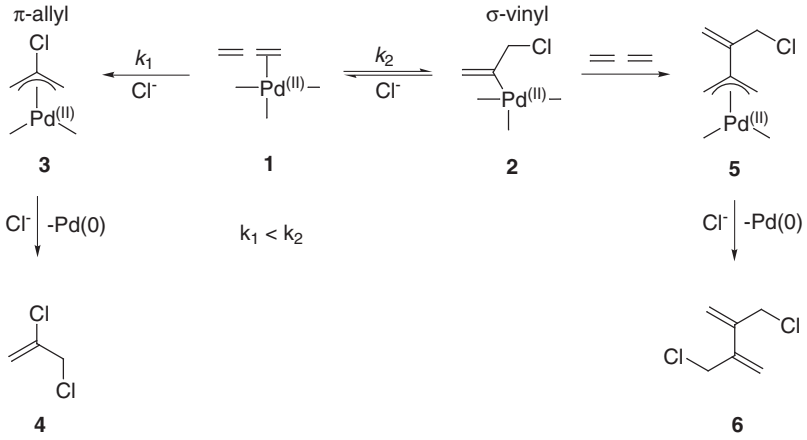


Scheme 17.3 Possible stereoisomers of the π-allyl(palladium) complex and the equilibrium between them via a π–*σ*–π rearrangement.

In Scheme 17.2 palladium is coordinated from below, but it is also possible that it coordinates from above and forms the other enantiomer of the chiral *syn,syn* π-allyl complex. If palladium has another chiral ligand then these π-allyl complexes become diastereomers. Thus, from an unsymmetrically substituted allene (R ≠ R′), eight diastereomeric π-allyl complexes can be formed. If one of the diastereomers is preferred then further reaction of the π-allyl moiety leads to an enantiomerically enriched product.

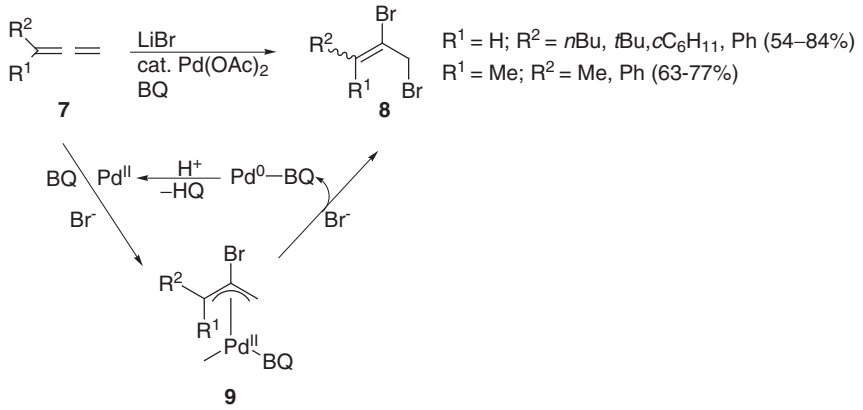
17.2.1 Dihalogenation

The palladium(II)-catalyzed oxidation of allenes with chloride was studied by Hegedus et al. [3]. In this reaction the dimeric products **4** and **6** as shown in Scheme 17.4 were obtained. The (allene)palladium(II) complex formed can react with chloride ions in two different ways (Scheme 17.4) [4]. Attack at the terminal carbon gives a vinylpalladium intermediate **2** whereas attack at the middle carbon produces a 2-chloro(π-allyl)palladium complex **3**. The former complex is the kinetic intermediate ($k_2 > k_1$) and is in equilibrium with the (allene)palladium complex. The 2-chloro(π-allyl)palladium complex is formed more slowly but is more stable and has been isolated [2]. The vinyl complex can undergo further reaction with excess allene to give a new (π-allyl)palladium complex, which undergoes attack with chloride to give the observed dimer **6** [3]. The dichloride from attack on the 2-chloro-(π-allyl)palladium complex **3** was not observed.



Scheme 17.4 Palladium(II)-induced reaction of allenes with chloride.

In 1997, Bäckvall and Jonasson published a procedure for the 1,2-oxidation of terminal allenes **7** [5]. In this case the reaction conditions were chosen so that the (vinyl)palladium complex equilibrates back to the allene complex. Using bromide instead of chloride as a nucleophile, the 2-bromo-π-allyl complex **9** is the major intermediate present in the reaction mixture. A catalytic reaction was developed with the use of 5 mol% palladium acetate and *p*-benzoquinone (BQ) as terminal oxidant (Scheme 17.5).

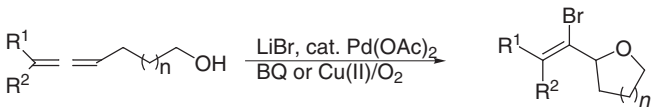


Scheme 17.5 Palladium(II)-catalyzed 1,2-bromination of terminal allenes.

The stereochemistry of the remaining double bond of **8** depends on the size of the substituent on the allene moiety (R^2 in Scheme 17.5). The (*E*)-alkene is the major product when a large substituent is present (*Z*:*E* = 3:7 when R^2 = *t*Bu) but the (*Z*)-alkene is formed preferentially when the substituent is sterically less demanding (*Z*:*E* = 87:13 when R^2 = *n*Bu). It is interesting that the regioselectivity of the palladium(II)-catalyzed dibromination is opposite to that obtained from bromination with Br_2 [6]. The reaction introduces two bromide nucleophiles into a terminal allene. Analogous palladium(II)-catalyzed 1,2-oxidations can be carried out with two different nucleophiles, one of them being intramolecular (see below).

17.2.2 Oxybromination

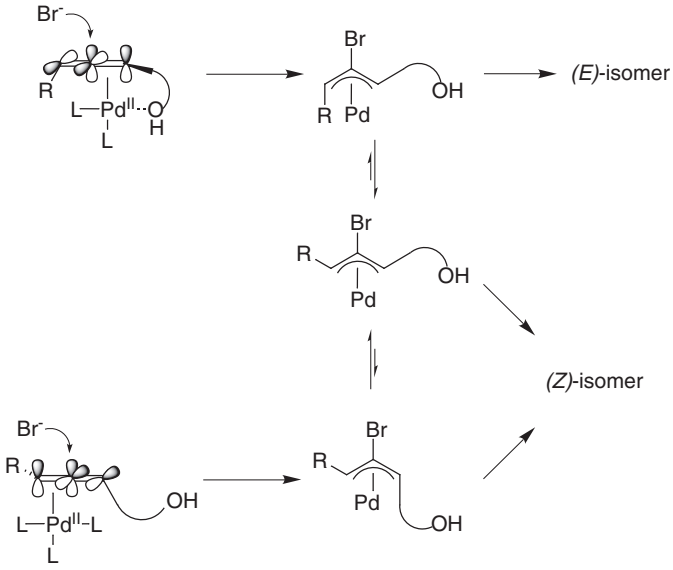
Allenyl alcohols **10** react with lithium bromide in the presence of a palladium(II) catalyst to afford tetrahydrofurans and tetrahydropyrans **11** in good yield (Scheme 17.6) [7]. The mechanism of the reaction is similar to that discussed in Sect 17.2.1. i.e. it proceeds via a 2-bromo(π-allyl)palladium(II) complex. In this case, however, the second nucleophile is not bromide ion but the alcohol moiety. As stoichiometric oxidant *p*-benzoquinone (BQ) or copper(II) together with oxygen can be used.



n = 1; R^2 = H; R^1 = *n*C_5H_{11}, *i*Pr, CH(C_2H_5)C_4H_9 (62–75%, *Z*:*E*=88:12–94:6)
n = 1; R^1 = R^2 = Me (70-71%)
n = 2; R^2 = H; R^1 = *n*C_5H_{11}, *i*Pr (70-78%, *Z*:*E*=94:6–96:4)

Scheme 17.6 Synthesis of tetrahydrofurans and tetrahydropyrans.

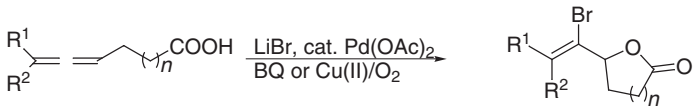
The remaining double bond has a strong preference for a *Z*-configuration in the product. This is due to a slow equilibrium between the different π-allyl intermediates, as shown in Scheme 17.7. When the attack of the second nucleophile is relatively slow then the intermediate complex has enough time to rearrange to the thermodynamically preferred isomer that will lead to the product with a *Z* double bond.



Scheme 17.7 Possible stereochemical outcome of the oxybromination reaction.

17.2.3
Bromolactonization

In analogy with the oxybromination reaction of allenyl alcohols, allenyl acids **12** afforded five- and six-membered lactones **13** on treatment with lithium bromide in the presence of palladium acetate (Scheme 17.8) [7, 8].



12 **13**

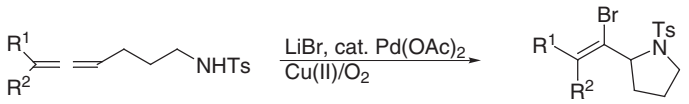
n = 1 or 2; R^2= H; R^1= nC_5H_{11}, *i*Pr (70–84%, *Z*:*E* = 76:24–92:8 with BQ in AcOH)
(83–90%, *Z*:*E* = 37:63–90:10 with Cu(II) in CH_3CN)
n = 1; R^1= Me, R^2= Me, C_2H_5 (67–68% *Z*:*E* = 59:41 with BQ in AcOH)
(74% with Cu(II) in CH_3CN)

Scheme 17.8 Bromolactonization of allenyl acids.

Good diastereoselectivity was obtained with BQ as the oxidant in acidic media but the reaction times were relatively long (1–2 days at 40 °C). Using the copper(II)–oxygen system in slightly basic media permits a much faster reaction (0.5–1 h at 20 °C) with better isolated yields but with poor or even reversed diastereoselectivity. The slower reaction with BQ as oxidant is due to the fact that this oxidant requires an acidic medium, which lowers the nucleophilicity of the acid moiety. It is also likely that BQ or copper(II) has to coordinate to palladium(II) before the second nucleophile can attack to make the π-allyl complex more electrophilic. Coordination of copper(II) would make a more electrophilic intermediate than coordination of BQ. The relation between reaction time and diastereoselectivity supports a mechanism analogous to that in Scheme 17.7.

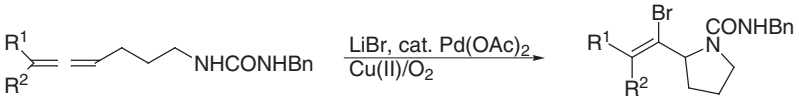
17.2.4 Bromoamidation

The oxybromination and bromolactonization reactions of allenes were extended to bromoamidation with the use of nitrogen nucleophiles [7, 9]. An electron-withdrawing substituent must be present on the nitrogen for the reaction to work. This substituent weakens the coordination of nitrogen to palladium and increases the acidity of the proton on nitrogen that is removed during the reaction. *N*-Tosyl amides **14** and ureas **16** were used successfully (Scheme 17.9) whereas carbamates and benzylamines afforded the corresponding pyrrolidines only in low yields. The copper(II)–oxygen system was the only efficient stoichiometric oxidant because the acidic conditions required by BQ lead to a slower reaction of the nitrogen nucleophile. The diastereoselectivity is good when one of the substituents is hydrogen ($R^1 = H$ in Scheme 17.9).



14 **15**

R^2 = H; R^1 = H, nC_5H_{11}, *i*Pr,CH(C_2H_5)C_4H_9 (69–80%, *Z*:*E* = 89:11–93:7)
R^1 = Me, R^2 = Me, C_2H_5 (70–71%, *Z*:*E* = 65:35)

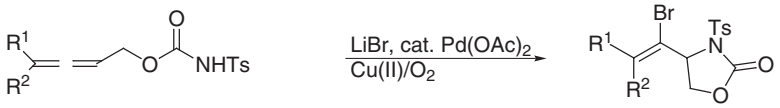


16 **17**

R^2 = H; R^1 = nC_5H_{11}, *i*Pr (69–78%, *Z*:*E* = 76:24–89:11)

Scheme 17.9 Synthesis of pyrrolidines.

In contrast to the carbamates, *N*-tosyl carbamates **18** reacted fast (1–2 h) with LiBr in the presence of copper(II)–oxygen and catalytic amounts of palladium acetate yielding oxazolidinones **19** (Scheme 17.10). The rate enhancement is due to the presence of two electron-withdrawing substituents on nitrogen and is, again, responsible for the diminished diastereoselectivity of the reaction. Attempts to prepare the homologous six-membered heterocycles gave only poor yields.

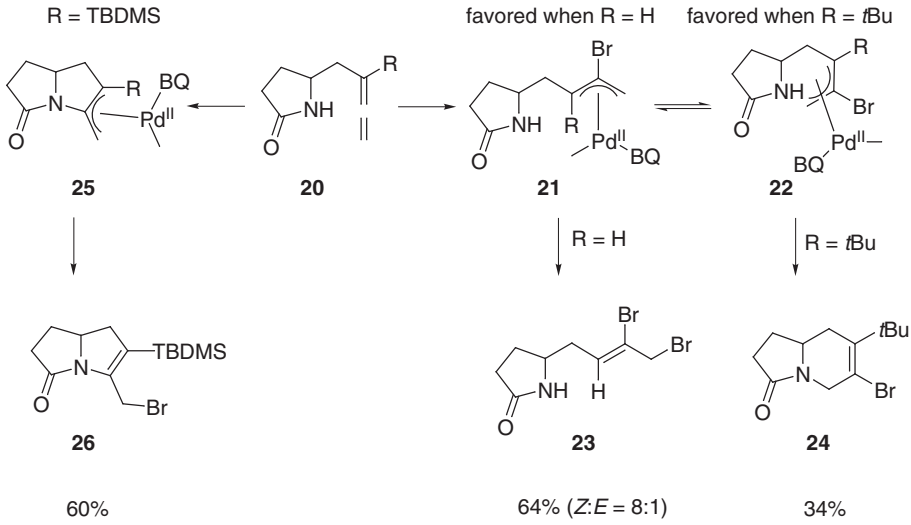


18 **19**

R^2 = H; R^1 = nC_5H_{11}, *i*Pr (68–70%, *Z*:*E* = 49:51–52:48)

Scheme 17.10 Synthesis of oxazolidinones.

Interesting results were obtained using pyrrolidinone-substituted terminal allenes **20** [9]. Three different products were formed depending on the nature of the other substituent on the allene moiety (R in Scheme 17.11). When R is the large *tert*-butyl group it will occupy the *syn* position in the intermediate complex, forcing the amide nitrogen close to the π-allyl moiety. After the second nucleophilic attack the expected six-membered ring product **24** is formed in 34% yield (the by-product was probably formed via a palladium-catalyzed intramolecular hydroamination reaction; see [10]). In the absence of a sterically directing group (R = H), the nitrogen will be too far from the π-allyl moiety in the intermediate complex **21**. Instead of cycliza-



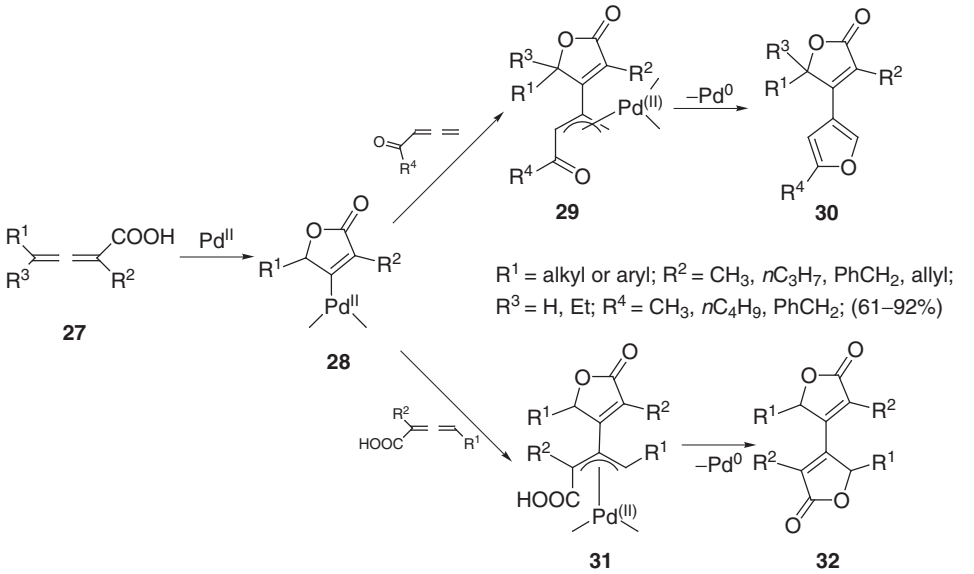
Scheme 17.11 Reactions of substituted 5-(β-allenyl)pyrrolidinone.

tion, a second bromide will attack in the final step to give the dibrominated product **23** (see Section 17.2.1). Finally, when R = *tert*-butyldimethylsilyl (TBDMS), the nitrogen attacks the central allenic carbon atom and a pyrrolizine derivative **26** is formed. Probably the increased electrophilicity of the sp carbon in the presence of the TBDMS substituent is responsible for this unique reaction.

17.2.5
Cyclization–Dimerization of α-Allenyl Acids and Ketones

The reaction of an allene with an aryl- or vinylpalladium(II) species is a widely used way of forming a π-allyl complex. Subsequent nucleophilic attack on this intermediate gives the product and palladium(0) (Scheme 17.1). Oxidative addition of palladium(0) to an aryl or vinyl halide closes the catalytic cycle that does not involve an overall oxidation. α-Allenyl acids **27**, however, react with palladium(II) instead of with palladium(0) to afford σ-vinylpalladium(II) intermediates **28** (Scheme 17.12). These σ-complexes than react with either an allenyl ketone [11] or with another allenyl acid [12] to form 4-(3′-furanyl)butenolides **30** or -dibutenolides **32**, respectively.

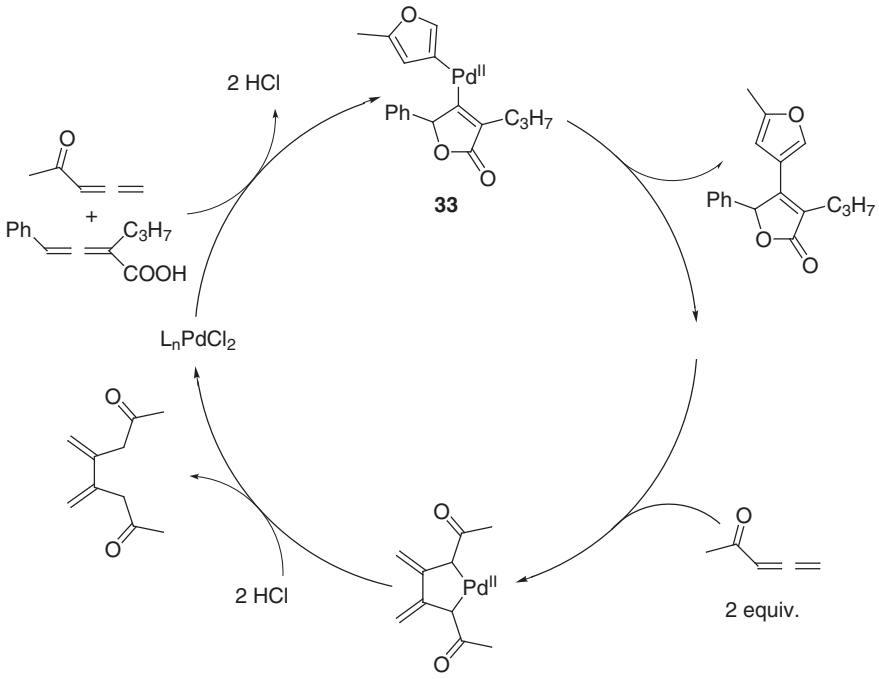
A likely mechanism of these reactions is that they proceed via a (π-allyl)palladium intermediate **29** or **31** as shown in Scheme 17.12. Intramolecular attack by either



Scheme 17.12 Cyclization–dimerization of α-allenyl acids and ketones.

keto or carboxyl groups on the π-allyl intermediate, respectively, affords the product. Ma and Yu [11, 13], however, suggest that the reaction proceeds via a bis(σ-vinyl)palladium(II) complex (Scheme 17.13). This would require that palladium in the vinylpalladium intermediate acts as an electrophile to induce nucleophilic attack on an allene, which seems less likely. In both mechanisms palladium(0) is reoxidized by 2 equiv. of the starting allenyl ketone (present in excess), which is reductively dimerized (shown only in the second mechanism, Scheme 17.13).

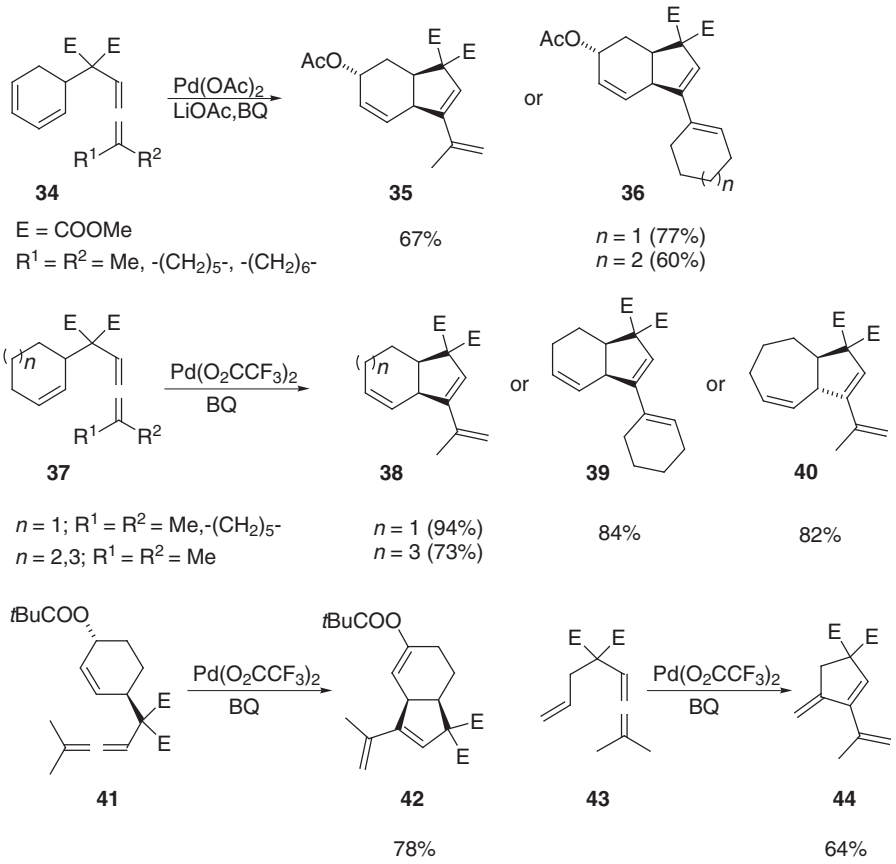
It is worth noting that in most of the reactions involving allenes with an internal nucleophile, σ-vinyl complexes are formed but their further reaction usually lead to unwanted by-products.



Scheme 17.13 Alternative mechanism for the cyclization–dimerization reaction of an α-allenyl acid and a ketone.

17.2.6
Cyclization of Alkenyl- and Dienylallenes

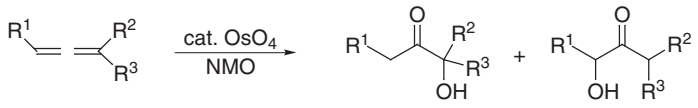
Oxidation of alkenes and dienes involving an allene substituent as a formal nucleophile is a conceptually new reaction. Allene-substituted 1,3-cyclohexadienes **34** undergo a palladium(II)-catalyzed oxidation to give bicyclic compounds **35** or **36** in good yields (Scheme 17.14) [14]. When γ-alkenylallenes, e.g. **37**, **41** and **43**, were treated with 1 mol% palladium trifluoroacetate, a similar oxidative carbocyclization took place [15]. In both reactions the new stereocenters are formed with high stereoselectivity.



Scheme 17.14 Cyclization of dienyl- and alkenylallenes.

17.3 Catalytic Osmylation

Unlike palladium(II), osmium tetraoxide and ruthenium tetraoxide catalyze the dihydroxylation of one or both double bonds of an allene. The osmium tetraoxide-catalyzed dihydroxylation of unsymmetrically substituted allenes **45** can lead to two different α-ketols, **46** and **47**, depending on which of the double bonds is oxidized. David et al. studied this reaction using NMO as a stoichiometric oxidant and found good product selectivity in a few cases, but the yields were only moderate (Scheme 17.15) [16]. They showed that the most substituted double bond was oxidized preferably when the bulkiness of the allene substituents did not interfere.



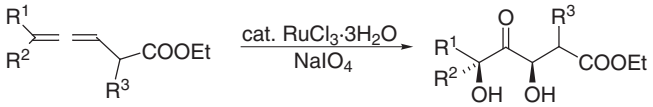
45 **46** **47**

R^1 = H; R^2 = R^3 = -C_5H_{10}- (48%, **46**:**47** = 100:0)
R^1 = R^2 = H; R^3 = Ph (35%, **46**:**47** = 100:0)
R^1 = R^2 = H; R^3 = C_7H_{15} (60%, **46**:**47** = 76:24)
R^1 = C_6H_{15}; R^2 = R^3 = Me (71%, **46**:**47** = 56:44)
R^1 = R^2 = H; R^3 = $CH_2CH(N{=}CPh_2)COOEt$ (41%, **46**:**47** = 100:1)
R^1 = R^2 = H; R^3 = $CH_2C(NHBoc)(COOEt)_2$ (31%, **46**:**47** = 1:100)
R^1 = R^2 = H; R^3 = $C_2H_4C(NHBoc)(COOEt)_2$ (65%, **46**:**47** = 74:26)

Scheme 17.15 Dihydroxylation of allenes.

17.4 Ruthenium-Catalyzed Oxidation

In 1997, Laux and Krause showed that ruthenium(III) chloride can catalyze the oxidation of allenes **48** to α,α'-dihydroxy ketones **49** [17]. They used sodium periodate as a stoichiometric oxidant and obtained the products in moderate to good yields, probably owing to overoxidation (Scheme 17.16). The dihydroxy compound was formed with high diastereomeric excess in one example when a chiral allene was oxidized.



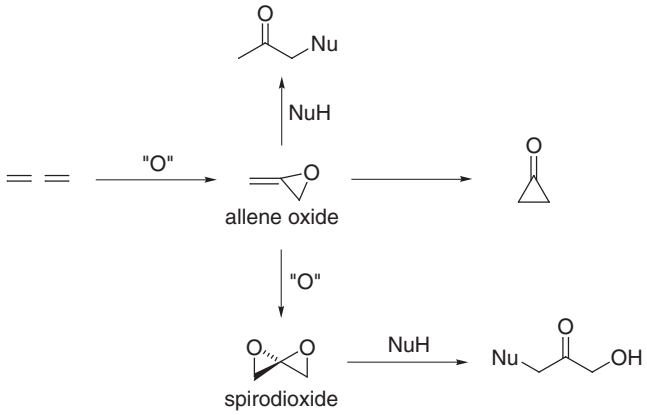
48 **49**

R^1 = R^2 = Me or *t*Bu; R^3 = H (24–32%)
R^1 = *t*Bu; R^2 = Me; R^3 = H (72%)
R^1 = *t*Bu; R^2 = Me; R^3 = OEt (45%, *de* = low)
R^1 = *t*Bu; R^2 = *n*Bu; R^3 = H (38%, *de* = 88%)

Scheme 17.16 Ruthenium-catalyzed oxidation of allenes.

17.5
Epoxidation

The reaction of allenes with peracids and other oxygen transfer reagents such as dimethyldioxirane (DMDO) or hydrogen peroxide proceeds via allene oxide intermediates (Scheme 17.17). The allene oxide moiety is a versatile functionality. It encompasses the structural features of an epoxide, an olefin and an enol ether. These reactive intermediates may then isomerize to cyclopropanones, react with nucleophiles to give functionalized ketones or participate in a second epoxidation reaction to give spirodioxides, which can react further with a nucleophile to give hydroxy ketones.

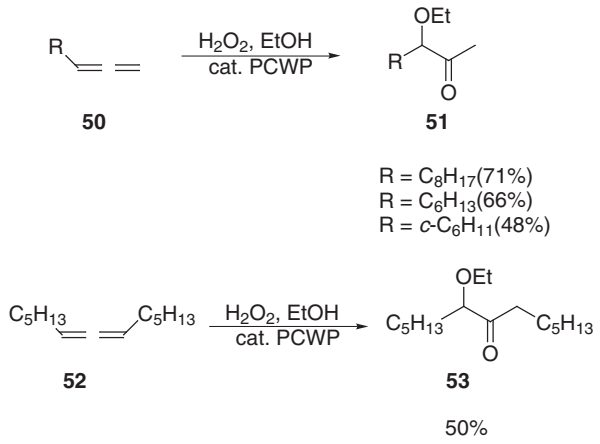


Scheme 17.17 Epoxidation of allenes.

Only a few isolated allene oxides have been synthesized from allenes and characterized. Most often peracids are used but the oxidative and acidic conditions usually result in a complex mixture of products. To overcome this problem, dimethyldioxirane (DMDO) can be used, which rapidly oxidizes allenes to spirodiepoxides. Several synthetically useful methods have been developed via in situ reaction of the intermediate allene oxide or spirodioxide with different nucleophiles.

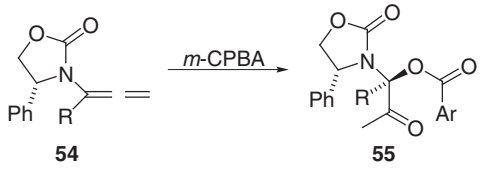
17.5.1
Epoxidation and Subsequent Intermolecular Ring Opening

Allenes react with hydrogen peroxide in the presence of 2 mol% peroxotungstophosphate (PCWP) and ethanol to afford α-ethoxy ketones in medium to good yields (Scheme 17.18) [18]. To achieve selective oxidation of only one of the two double bonds, e.g. **52**, terminal allenes **50** have to be used. Alternatively, oxidation of a symmetrically substituted allene leads also to a single product.



Scheme 17.18 Epoxidation followed by ring opening with EtOH.

In a recent study, reaction of chiral allenamides **54** with *m*-chloroperbenzoic acid (*m*-CPBA) led to an epoxidation and subsequent ring opening by *m*-chlorobenzoic acid [19] The resulting α-keto aminals **55** were obtained with high diastereoselectivity (Scheme 17.19).



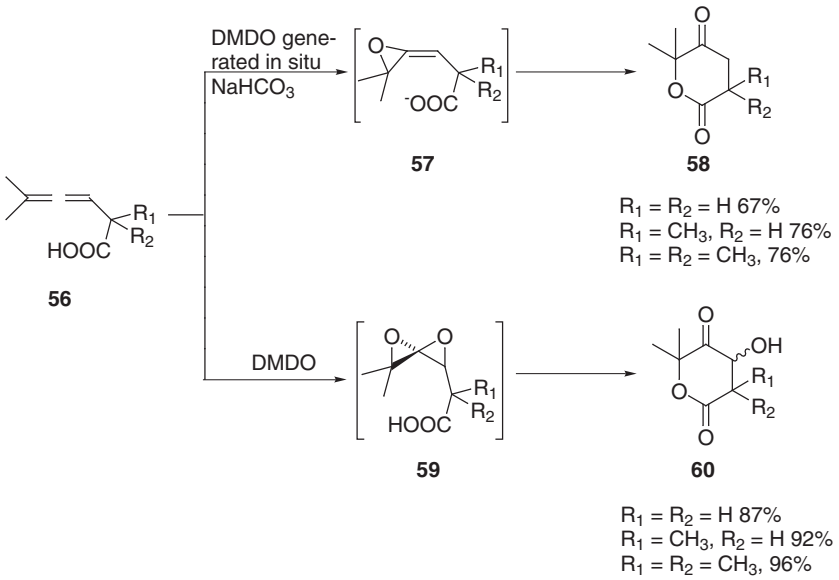
R = H (94%) S:R = 91:9
R = C_4H_8OH (58%) a single diastereomer

Scheme 17.19 Epoxidation of chiral allenamides by *m*-CPBA.

17.5.2
Epoxidation and Subsequent Intramolecular Ring Opening

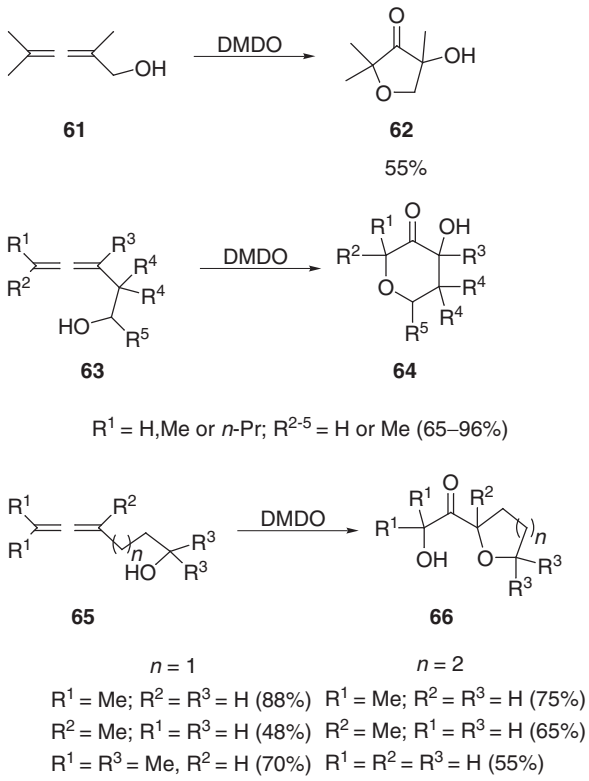
In situ epoxidation of allenyl alcohols [20], aldehydes [21], acids [22] and sulfonamides [23] followed by intramolecular ring opening of the intermediates was thoroughly investigated by Crandall and co-workers. They showed that products formed either from the allene oxide or the spirodioxide intermediate can be prepared selectively. Allenyl acids **56**, for example, react first with DMDO on their more substituted double bond. When the concentration of the oxidant is low (DMDO is formed

in situ) and the allenyl acid is deprotonated (i.e. becomes more nucleophilic), then the allene oxide intermediate **57** is opened by the acid moiety (Scheme 17.20). When DMDO is present in a higher concentration during the reaction with the free acid, the spirodioxide **59** formed undergoes reaction with the carboxylic group.



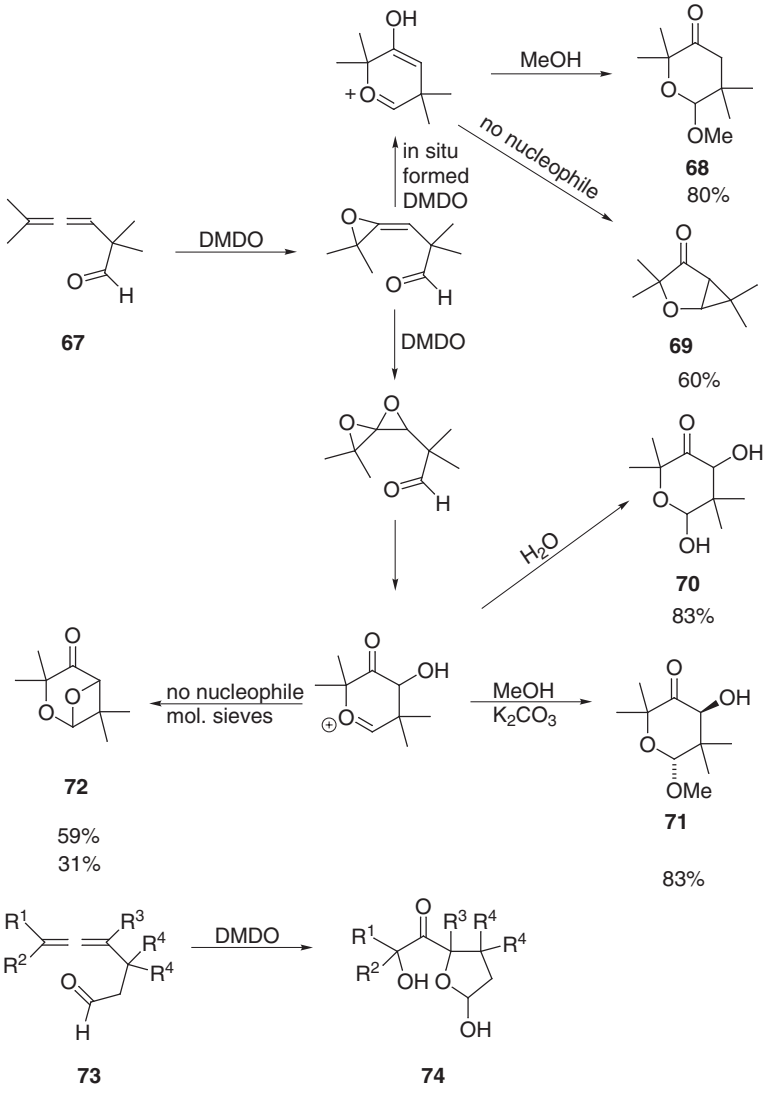
Scheme 17.20 Epoxidation of allenyl acids by DMDO.

The corresponding reactions of allenyl alcohols proceed mostly via the spirodioxide intermediate (Scheme 17.21) [20]. Whereas α-allenyl alcohol **61** gives the corresponding tetrahydrofuranone **62** in only moderate yield, β-allenyl alcohols **63** react much cleaner to afford tetrahydropyranones **64** in good yield. In the case of γ- and δ-allenyl alcohols **65** the spirodioxide intermediate is attacked intramolecularly on the carbon atom closer to the alcohol moiety, so that tetrahydrofurans and tetrahydropyrans **66** are formed.



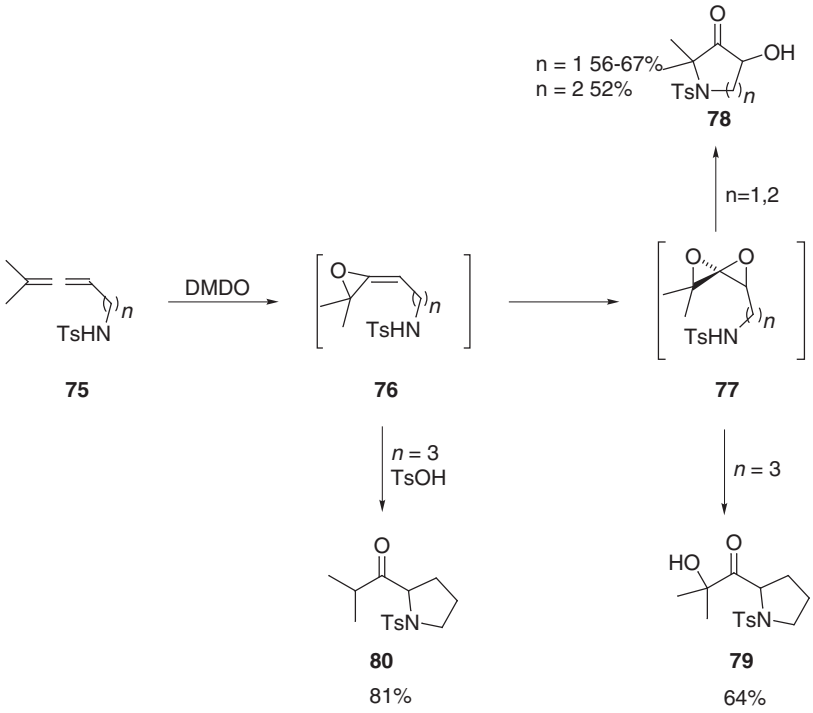
Scheme 17.21 Epoxidation of allenyl alcohols by DMDO.

When allenyl aldehydes are allowed to react with DMDO, the aldehyde moiety is not oxidized to the acid except for monosubstituted allenes [21]. In all other cases, the carbonyl oxygen participates as a nucleophile in the opening of the intermediate epoxide. From 2,2,5-trimethyl-3,4-hexadienal **67**, for example, five different products can be synthesized selectively under different reaction conditions (Scheme 17.22). When *p*-toluenesulfonic acid (TsOH) is present or DMDO is formed in situ, then the initially formed allene (mono)oxide reacts with the aldehyde moiety to give **68** or **69**. In the presence of excess DMDO and the absence of acid, three other products (**70**–**72**) can be formed via the spirodioxide intermediate. These reactions, however, seem to be less general compared with similar reactions of allenyl acids and allenyl alcohols. γ-Allenylaldehydes **73** can be cyclized to five-membered hemiacetals **74** via the spirodioxide intermediate.



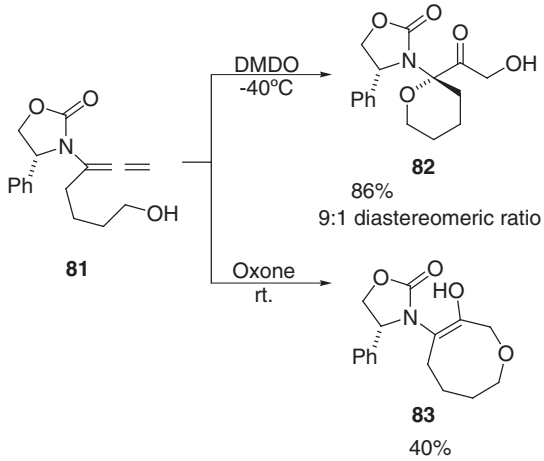
Scheme 17.22 Epoxidation allenylaldehydes by DMDO.

The oxidation of allenylsulfonamides **75** is also possible by using DMDO [23]. Unlike the corresponding reaction of allenyl acids, oxidation of allenyl sulfonamides usually cannot be stopped after the formation of the allene oxide **76** but proceeds further to the spirodiepoxide intermediate **77**, finally giving hydroxypyrrolidinone **78** and hydroxypiperidone **79**, respectively (Scheme 17.23). Similarly to γ-allenyl alcohols, aldehydes and acids, five-membered heterocycles, e.g. **80**, are also formed from γ-allenylsulfonamides. In the latter case the reaction can be terminated after the first epoxidation by addition of *p*-toluenesulfonic acid.



Scheme 17.23 Epoxidation of allenyl sulfonamides by DMDO.

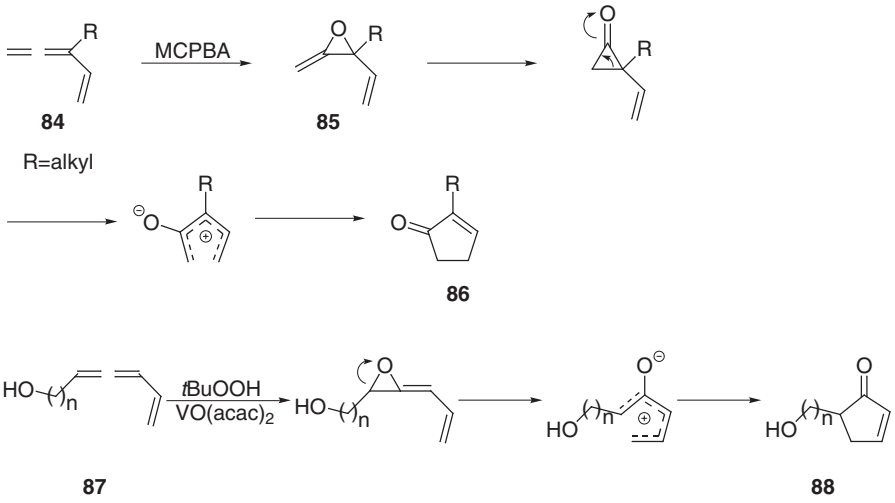
In a different study, a δ-allenyl alcohol **81** containing a chiral substituent was oxidized by DMDO and then cyclized to afford the substituted tetrahydropyran **82** with good diastereoselectivity [19] (Scheme 17.24). Interestingly, when oxone was used instead of DMDO, the eight-membered cyclic ether **83** was formed via the allene oxide intermediate.



Scheme 17.24 Selective epoxidation of an allenyl alcohol.

17.5.3
Epoxidation and Subsequent Ring Opening with Rearrangement

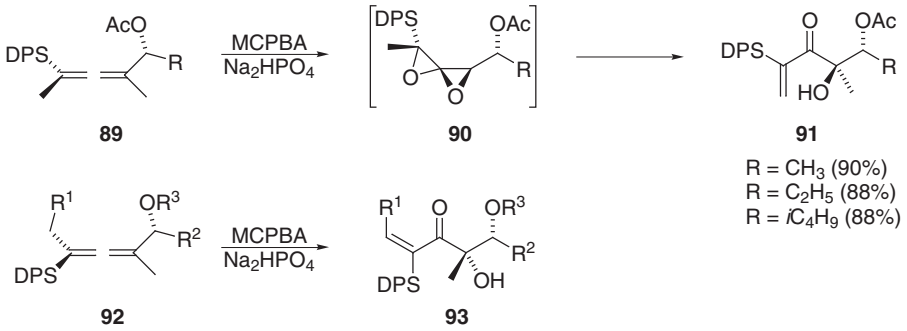
Allene oxides **85** generated from vinylallenes **84** can rearrange to cyclopentenones **86**. Among the oxidizing agents used are peracids [24, 25], peracids and $VO(acac)_2$ [26] and oxygen–*hν* [27]. Sufficient selectivity is obtained only when the isolated double bond is less reactive than the allene unit (i.e. the allenic double bond is more substituted) or a directing hydroxy group is present in the vicinity of the allene substrate **87** (Scheme 17.25).



Scheme 17.25 Proposed mechanisms for the epoxidation of vinylallenes.

Typical yields are in the range of 40–70% regardless of the method used. We should mention that the acetoxymercuration and acetoxythallation of vinylallenes also lead to cyclopentenones, albeit not via epoxide formation [28].

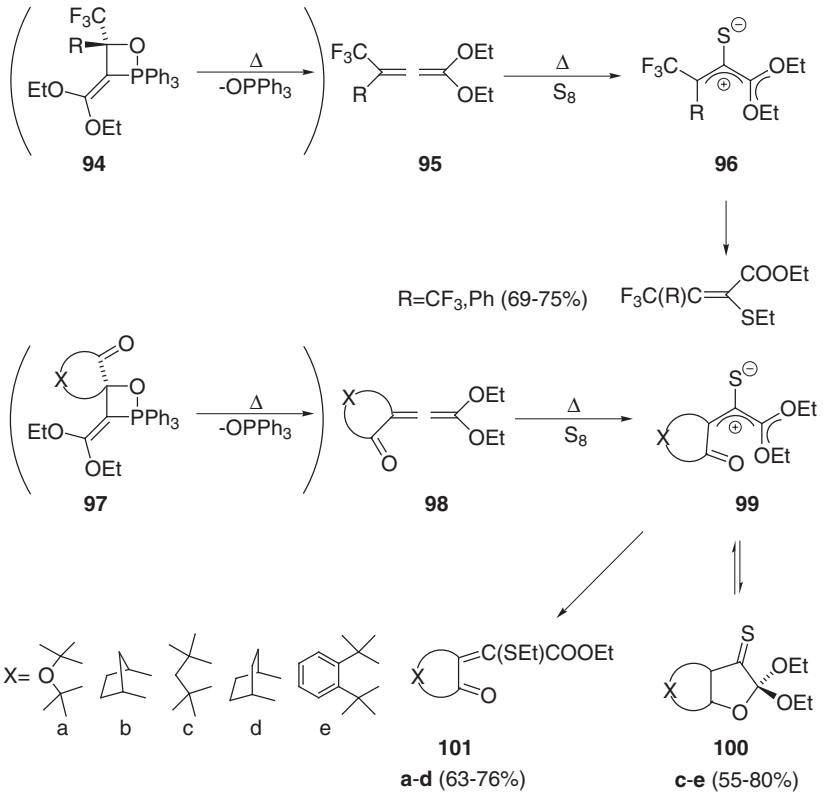
It is also possible to oxidize allenes **89** and **92** to unsaturated hydroxy ketones **91** and **93** via the spirodioxide intermediate **90** [29]. In this case the terminating step is a 1,5-proton shift. In the examples shown in Scheme 17.26, the formation of the spirodioxide intermediate is diastereoselective, as is the rearrangement to the unsaturated hydroxy ketone.



Scheme 17.26 Epoxidation followed by 1,5-proton shift.

17.6 Oxidation by Sulfur

Allenes **95** bearing an electron-withdrawing substituent on one side and two electron-releasing ethoxy groups on the other terminus react with elemental sulfur via a sulfidoallyl intermediate **96** [30]. This zwitterionic structure is then rearranged to the product **97**. The starting allene is prepared in a Wittig reaction via a fairly stable 1,2λ^5-oxaphosphetan intermediate **94** that is a convenient starting material for the whole oxidation reaction (Scheme 17.27). When the electron-withdrawing substituent has an α-keto group, the latter can also participate in the final rearrangement of the sulfidoallyl intermediate forming a five-membered ring product **100**. These compounds are not very stable and rearrange to the alternative thioether product **101**. Unfortunately, there was no comment on the stereochemistry of the remaining double bond, but from the given NMR data it seems that only one diastereomer is formed.



Scheme 17.27 Oxidation of allenes by sulfur.

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IV
Applications

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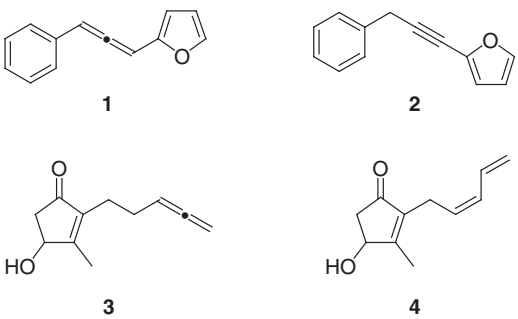
18
Allenic Natural Products and Pharmaceuticals

Norbert Krause and Anja Hoffmann-Röder

18.1
Introduction

For a long period, allenes [1] have been regarded mostly as chemical curiosities. As early as 1874–1875, Van't Hoff [2] had predicted, in one of the most relevant publications in the development of organic chemistry, the correct structures of allenes and higher cumulenes in line with the tetrahedral geometry of alkanes. However, even though the first experimental investigations in this area closely followed, most chemists had their doubts about Van't Hoff's predictions and considered such systems to be highly unstable – a common prejudice that can be even encountered nowadays. Not surprisingly, the first documented synthesis of an allene, carried out by Burton and von Pechmann [3] in 1887, was initially an attempt to prove the nonexistence of this class of compounds. At that time, however, with all the analytical tools available (mostly syntheses of derivatives), it was almost impossible to distinguish between allenes and the corresponding alkynes. Only when IR and Raman spectroscopy were introduced as tools for structural investigations was it possible to prove, by its characteristic allenic C–C vibration at about 1950 cm^{-1}, that Burton and von Pechmann had indeed synthesized an allenic molecule [4].

Similar problems were encountered in the characterization of certain allenic natural products [5] (Scheme 18.1). For example, Semmler [6] had proposed an allenic



Scheme 18.1 Proposed (left) and correct (right) structures of unsaturated natural products.

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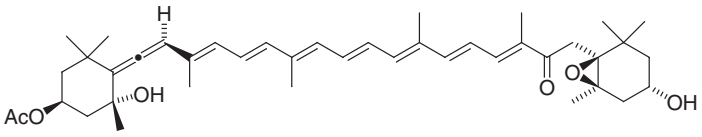
structure **1** for a furan derivative extracted from the roots of *Carlina acaulis* with the aid of Raman spectroscopy, which was corrected later in favor of the isomeric alkyne **2** [7]. Much wider known, however, is the case of the pyrothrolone from *Chrysanthemum cinerariaefolium*, for which Staudinger and Ruzicka [8] in 1924 had published the structure **3**. Also this assignment, relying on the cleavage of the natural product by ozonolysis, turned out to be incorrect and spectroscopic investigations finally revealed the conjugated diene moiety of **4** [9, 10].

Furthermore, for a large number of well-known natural products, the (correct) assignment of their allenic structure took place long after their isolation (Scheme 18.2). For example, the most abundant of all carotinoids, fucoxanthin (**5**), which occurs in brown algae and diatomes, was isolated by Willstätter and Page [11] in 1914, whereas its structural assignment was not achieved until almost 50 years later [12]. Even more strikingly, the closely related carotinoid peridinin (**6**), which plays an important role in the photo system of dinoflagellates, was isolated in 1890, but fully characterized only in 1971 [13].



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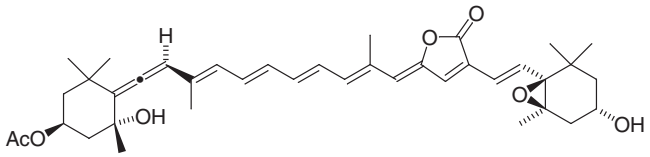


6

Scheme 18.2 Structure of the allenic carotinoids fucoxanthin (**5**) and peridinin (**6**).

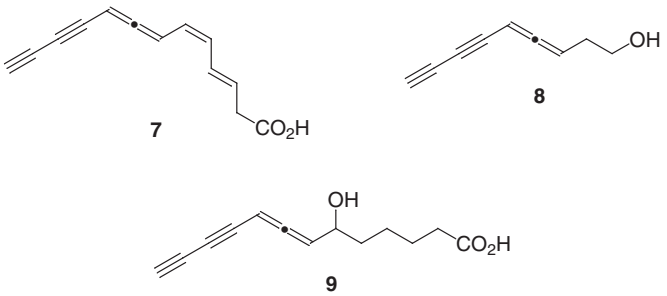
Nowadays, about 150 natural products comprising an allenic or cumulenic structure are known [14]. This number clearly proves that allenes cannot simply be considered as curiosities, but instead they represent important structural elements for a wide variety of different classes of compounds. The major part of these naturally occurring allenes can be divided into three classes: linear allenes, allenic carotinoids and terpenoids and bromoallenes. Moreover, almost all allenic natural products reported to date are chiral and were isolated in non-racemic form, albeit not necessarily as enantiomerically pure compounds (see below). A substantial number of these allenes show interesting biological activities and, in recent years, many attempts have been made to 'tune' further the biological and pharmacological properties of certain pharamacologically active compounds simply by introducing an allenic moiety into the existing backbone of the molecule.

In this chapter, we shall concentrate on recent developments in the field of allenic natural products and pharmaceuticals, emphasizing their (normally stereoselective) synthesis [1, 15], and investigations of their biological properties.

18.2
Allenic Natural Products

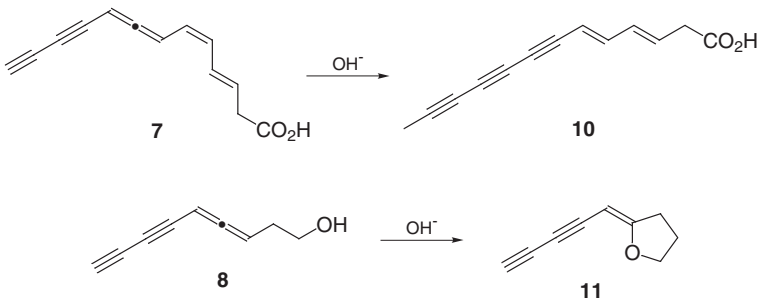
18.2.1
Linear Allenes

Linear allenes form the structurally simplest group of allenic natural products and comprise more than 30 compounds [5, 14] isolated from such diverse sources as microorganisms, fungi, higher plants and insects. Moreover, to this class belongs the first 'authentic' allenic natural product, the fungal metabolite mycomycin (**7**) [16], which shows {as the related marasin (**8**) [17]} high antibiotic activity (Scheme 18.3). Interestingly, both enantiomers of marasin can be found in nature, with (*R*)-(–)-marasin being isolated from *Marasmium ramealis*, whereas the (*S*)-(+)-enantiomer was found in *Aleurodiscus roseus*. To date an impressive number of naturally occurring linear allenes possessing a diyneallene structure [18, 19] has been characterized, such as the antibiotic diynoic allenol 07F275 (**9**) [18i], which was isolated from a fungus originating from Panama.



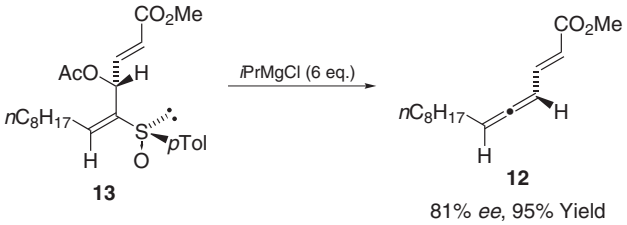
Scheme 18.3 Mycomycin (**7**), marasin (**8**) and 07F275 (**9**).

The low stability of these unbranched polyenynes, however, prevented any exploitation of their biological activity (Scheme 18.4). Whereas mycomycin (**7**) readily rearranges to the dienetriyne isomycomycin (**10**) [16b], the corresponding marasin (**8**) is cycloisomerized to the tetrahydrofuran analog isomarasin (**11**) [17a].



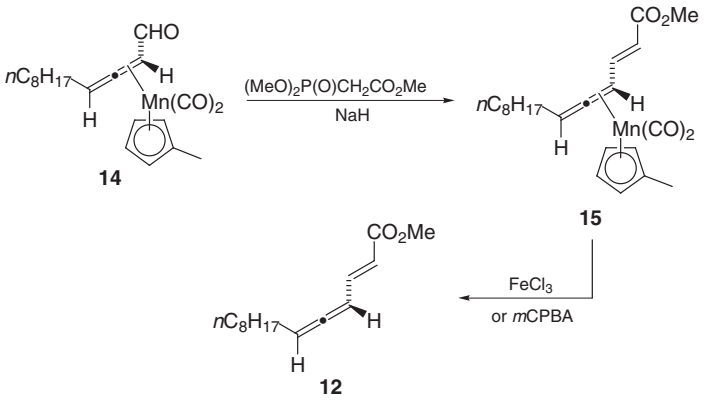
Scheme 18.4 Rearrangement of linear allenes.

With respect to crop protection, the insect pheromone methyl (*R*,*E*)-(–)-tetradeca-2,4,5-trienoate (**12**) also represents an interesting allenic target molecule. This compound was isolated in 1970 by Horler [20] from male 'dried bean beetles', *Acanthoscelides obtectus*. Interestingly, the beetle contains rather large amounts (~0.5%) of the chiral allene which does not occur in enantiomerically pure form but with an enantiomeric excess of about 80%. Although several syntheses of the racemic [21] and of the enantiomerically pure [22] allene are known, the pheromone was recently targeted again by differrent groups in order to probe newly developed stereoselective methods for the synthesis of such chiral allenes. For example, Satoh et al. [23] utilized the stereoselective sulfoxide–magnesium exchange of the chiral β-acetoxy sulfoxide **13** with isopropylmagnesium chloride, followed by subsequent elimination, for the generation of **12** with 81% *ee* (Scheme 18.5). The non-natural enantiomer of the insect pheromone was also obtained correspondingly with a very similar enantiomeric purity.



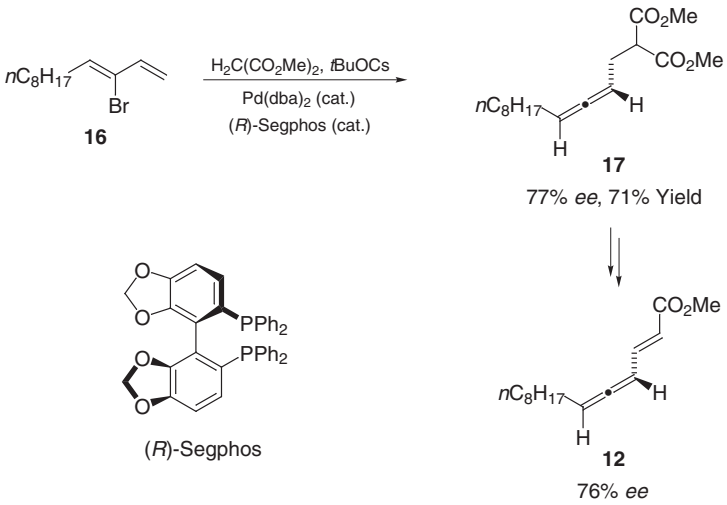
Scheme 18.5 Synthesis of the insect pheromone **12** from chiral sulfoxide **13** (*p*Tol = *p*-tolyl) [23].

In a different approach, Franck-Neumann et al. [24] utilized the manganese complex **14** (formed by deracemization) to obtain the enantiomerically pure target molecule **12** via Horner–Wadsworth–Emmons olefination and oxidative decomplexation of the intermediate vinylallene complex **15** (Scheme 18.6).

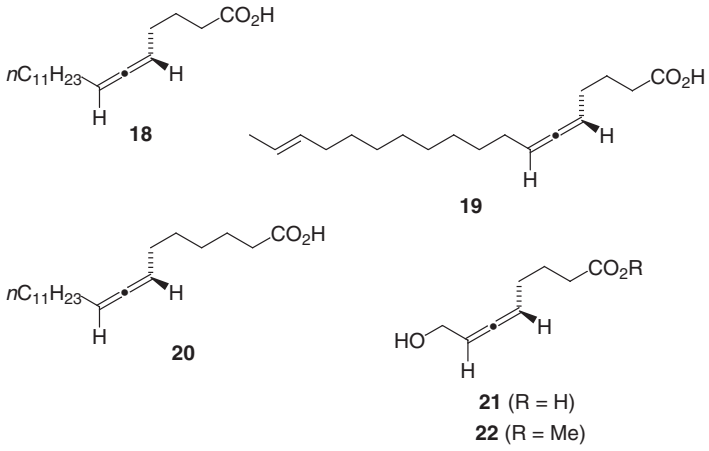


Scheme 18.6 Synthesis of the insect pheromone **12** from the manganese complex **14** (*m*CPBA = *m*-chloroperbenzoic acid) [24].

Furthermore, the first *catalytic* synthesis of allenes with high enantiomeric purity [15c, 25] was applied recently to the pheromone **12** by Ogasawara and Hayashi [26] (Scheme 18.7). Their palladium-catalyzed S_N2'-substitution process of the bromodiene **16** with dimethyl malonate in the presence of cesium *tert*-butanolate and catalytic amounts of the chiral ligand (*R*)-Segphos furnished allene **17** with 77% *ee*. Subsequent transformation into the desired target molecule **12** via decarboxylation and selenoxide elimination proceeded without appreciable loss of stereochemical purity and again (cf. Scheme 18.5) led to the formation of the allenic pheromone in practically the same enantiomeric ratio as in the natural sample.



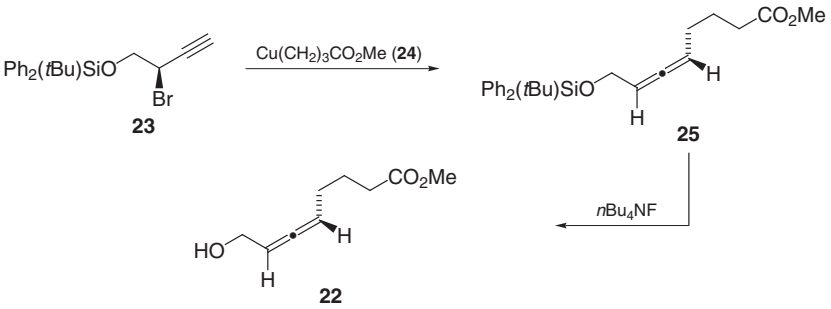
Scheme 18.7 Synthesis of the insect pheromone **12** by palladium-catalyzed S_N2'-substitution (dba = dibenzylideneacetone).



Scheme 18.8 Linear allenes isolated from seed oils.

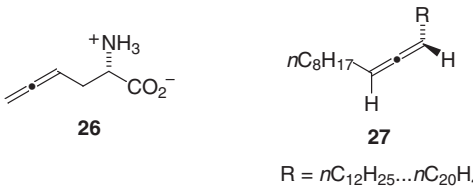
A number of closely related linear allenes have also been isolated from seed oils (Scheme 18.8). Examples are laballenic acid (**18**) [27], lamenallenic acid (**19**) [28] and phlomic acid (**20**) [29]. The hydroxy acid **21** was isolated as part of a triglyceride from the chinese tallow tree *Sapium sebiferum* [30] and as its methyl ester **22** from the related species *Sapium japonicum* [31], which is found in Japan.

As a consequence of its antifungal activity, which efficiently prevents infections of the leaves, allenic ester **22** had been the target of several non-stereoselective [32] and enantioselective syntheses. Whereas Huguet and del Carmen Reyes [33] in their synthesis of **22** relied on the S_N2'-reduction of a chiral propargylic ether with lithium aluminum hydride, Gooding et al. [34] took advantage of an *anti*-stereoselective S_N2'-substitution reaction using the propargylic bromide **23** and the functionalized organocopper compound **24** (Scheme 18.9).



Scheme 18.9 Synthesis of methyl (*R*)-8-hydroxyocta-5,6-dienoate (**21**l).

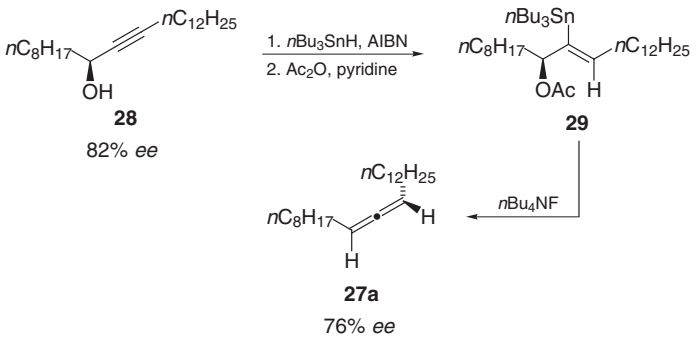
The amino acid **26**, which has been isolated from various *Amanita* fungi [35], is one of the few examples of a natural product with an achiral allene moiety (Scheme 18.10) and was prepared inter alia by Strecker synthesis and also substitution reactions of allenic bromides and phosphates [36]. Recently, even *unfunctionalized* allenes have been found in nature: seven allenic hydrocarbons **27** with chain lengths ranging from C_{23} to C_{31} were isolated from the skin of the Australian scarab beetle *Anitrogus consanguineus* and related species (Scheme 18.10) [37]. Also these allenes do not occur in enantiomerically pure form, but with enantiomeric excesses of 86–89% *ee*.



Scheme 18.10 Naturally occurring allenic amino acid (**26**) and allenic hydrocarbons (**27**).

A stereoselective synthesis of the enantiomerically enriched allenic hydrocarbons was described in 2001 (Scheme 18.11) [37]. For example, hydrostannylation of the chiral propargylic alcohol **28** (obtained with 82% *ee* by enantioselective reduction of

the corresponding ketone with a chiral oxazaborolidine) and subsequent esterification provided the stannyl acetate **29**, which was converted into the chiral allene **27a** (76% *ee*) by treatment with tetra-*n*-butylammonium fluoride.

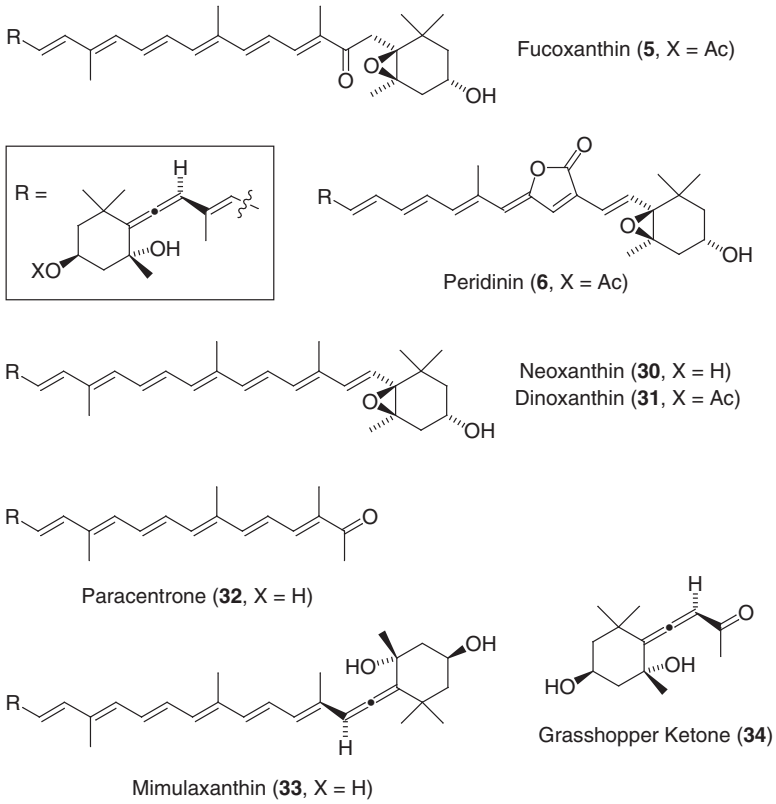


Scheme 18.11 Synthesis of (*R*)-(–)-tricosa-9,10-diene (**27a**) from chiral propargylic alcohol **28** (AIBN = azobisisobutyronitrile) [37].

18.2.2
Carotinoids and Terpenoids

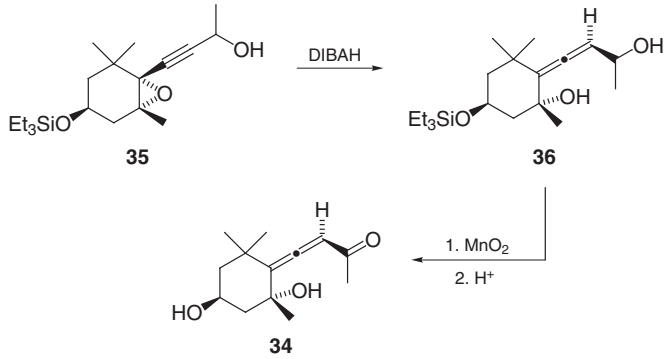
With nowadays more than 40 isolated compounds, carotinoids and terpenoids form the largest group of allenic natural products [5, 14]. As mentioned in the Introduction, the majority of these compounds have been known for a long time, whereas the structural assignments often were not accomplished until after the introduction of spectroscopic methods. As a common structural feature, most carotinoids bear a cyclohexylidene ring but differ in the structure of the second ring and its periphery (Scheme 18.12). Typical examples are {besides the already mentioned compounds fucoxanthin (**5**) [11, 12] and peridinin (**6**) [13]} neoxanthin (**30**) [38], dinoxanthin (**31**) [39] and paracentrone (**32**) [40], whereas mimulaxanthin (**33**) [41] finally represents a carotinoid even containing two allenic groups. One of the best known allenic natural products, the so-called 'grasshopper ketone' (**34**) [42], is probably a dietary metabolite of one or several of these allenic carotinoids.

Many allenic carotinoids are readily available in large amounts from natural sources and, consequently, early preparative work was concentrated mainly on their interconversions. Until now, total syntheses have been documented only for fucoxanthin (**5**), peridinin (**6**), neoxanthin (**30**), paracentrone (**32**), mimulaxanthin (**33**) and the grasshopper ketone (**34**) [43]. The last allenic terpenoid was isolated in 1968 from the defence secretion of the large flightless grasshopper *Romalea microptera*, which occurs in the southern USA (Scheme 18.12) [42]. The strong similarity to the carotinoids fucoxanthin (**5**) and neoxanthin (**30**), present in many plants suggests, that they are oxidatively metabolized in vivo to **34**, which could also be demonstrated by in vitro experiments [44].



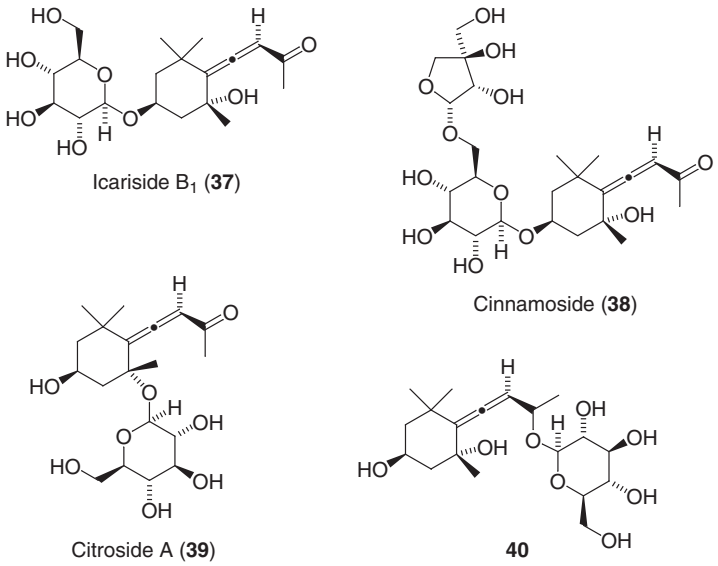
Scheme 18.12 Structures of allenic carotinoids und terpenoids.

The first synthesis of the racemic natural product **34** was described in 1969 [45] and numerous (also enantioselective [46]) syntheses can now be found in the literature. Here, the introduction of the allenic moiety was achieved either by photochemical oxidation of a β-ionol-type molecule with singlet oxygen or by reduction of appropiate propargylic electrophiles with complex hydrides. Thus, the key step in the synthesis of enantiomerically pure grasshopper ketone by Eugster and co-workers [46d] comprises an S_N2'-reduction of the propargylic oxirane **35** with diisobutylaluminum hydride (Scheme 18.13). The high *syn*-diastereoselectivity observed in this transformation is most presumably due to a precoordination of the aluminum hydride to the epoxide oxygen atom. Since allenyl ketones of type **34** are prone to undergo a facile light-induced epimerization, this reaction sequence also provides an efficient access to stereoisomers of the grasshopper ketone [46d].



Scheme 18.13 Synthesis of the grasshopper ketone (**34**) according to Eugster and co-workers [46d] (DIBAH = diisobutylaluminum hydride).

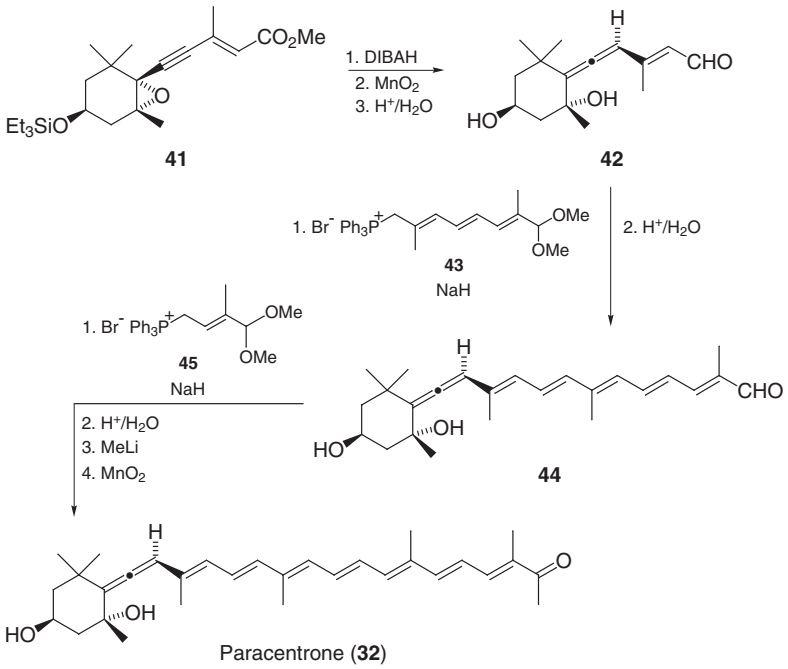
In addition to the free grasshopper ketone, the 3-*O*-acetyl derivative (apo-9′-fucoxanthinone) [47], as well as various glycosides, also occur in nature (Scheme 18.14). Thus, the terpenoid icariside B_1 (**37**), bearing a pyranose ring at the 3-position, was found in a variety of different plants [49], whereas the related disaccharide cinnamoside (**38**) has only been isolated from cinnamon (*Cinnamomum cassia*) [50]. This spice is used in Asian folk medicine as 'Goreisan' (China) or 'Kannan Keihi' (Japan) for the treatment of fever, pain and stomach trouble. Two further terpenoids, citroside A (**39**) and citroside B (the epimer with respect to the allenic chirality axis), bear



Scheme 18.14 Naturally occurring glycosides of the grasshopper ketone.

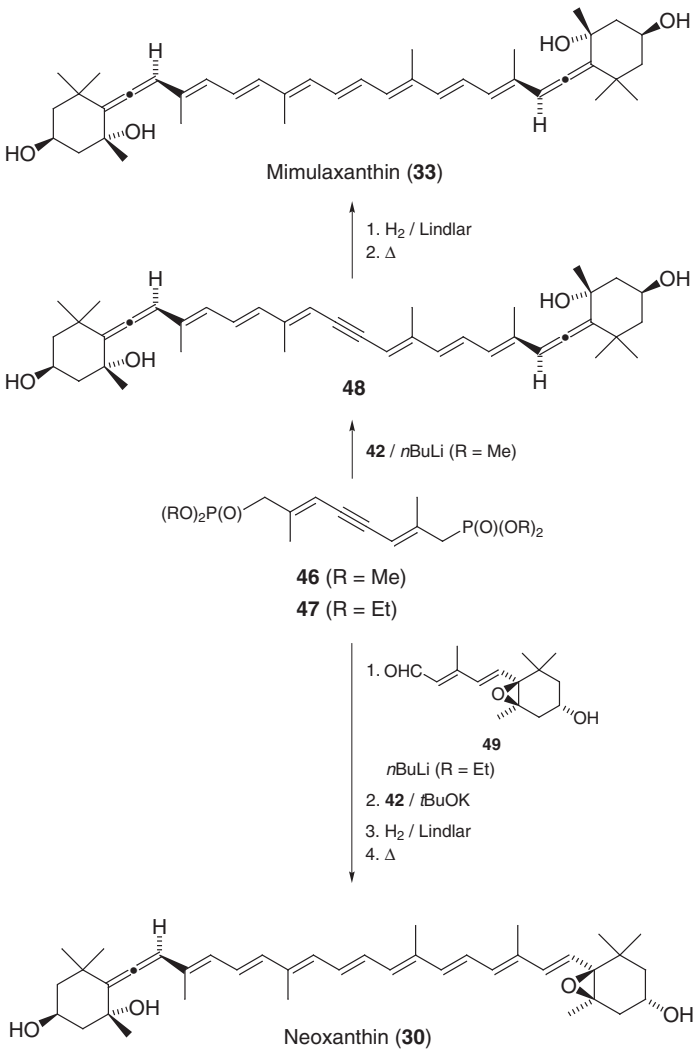
a pyranose ring at the 5-position and are contained in the leaves of the tangerine tree *Citrus unshiu* [51], wherease the terpenoid **40** (formally derived from the reduced grasshopper ketone by glycosylation in the 9-position) was isolated from the leaves of the solanaceous herb *Lycium halimifolium* [52]. The first syntheses of **40** and of derivatives of icariside B_1 (**37**) have been reported recently. Here, once again the allenic entity was formed via diastereoselective reduction of propargylic oxiranes using DIBAH [53].

The synthesis of higher allenic carotinoids could apparently benefit from the use of the grasshopper ketone (**34**) or related allenic carbonyl compounds as substrates for olefination reactions. Thorough investigations by Baumeler and Eugster [54], however, have shown not only that derivatives of **34** are very unreactive in Wittig olefinations, but also that the allene system may epimerize easily. Consequently, these reaction conditions are usually not suitable for the stereoselective synthesis of allenic carotinoids, although aldehyde **42** (available through *syn*-selective S_N2'-substitution reaction of the corresponding propargylic oxirane **41** with DIBAH and subsequent oxidation [54,55]) was employed successfully in the preparation of various carotinoids. In the sole reported synthesis of the C_{31}-apocarotinoid paracentrone (**32**) (isolated from the sea urchin *Paracentrotus lividus* [40]), olefination of **42** with the phosphonium salt **43** furnished aldehyde **44**, which after two further chain elongation steps (by another Wittig reaction with the C_5-building block **45** followed by MeLi addition) finally provided the desired target molecule **32** (Scheme 18.15) [56].



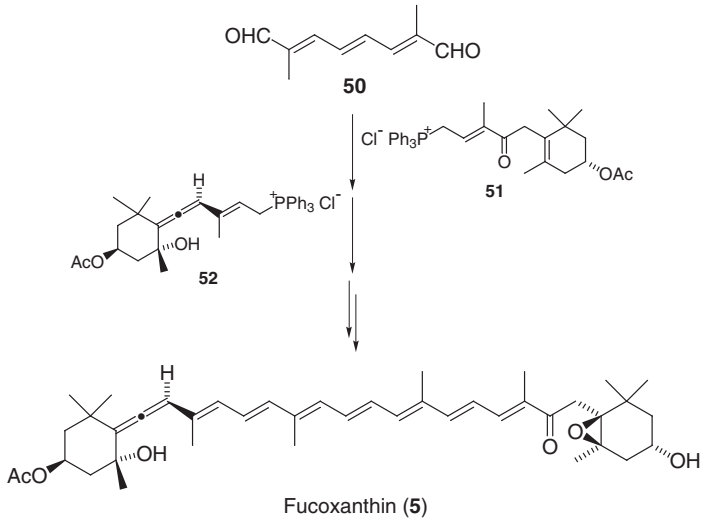
Scheme 18.15 Synthesis of the C_{31}-apocarotinoid paracentrone (**32**) [56] (DIBAH = diisobutylaluminum hydride).

Analogous olefination reactions were used by Eugster and co-workers during their syntheses of neoxanthin (**30**) [38, 57] and mimulaxanthin (**33**) [41, 54] (Scheme 18.16). Thus, Horner–Wadsworth–Emmons reaction of 2 equiv. of **42** with the bisphosphonate **46** according to the building block scheme C_{15} + C_{10} + C_{15} furnished the symmetrical product **48**, which was transformed into mimulaxanthin (**33**) by Lindlar hydrogenation and thermal isomerization of the central double bond [54]. In contrast, stepwise olefinations of the bisphosphonate **47** with the violaxanthin building block **49** and the allenic aldehyde **42** led to the formation of neoxanthin (**30**) [38, 57].



Scheme 18.16 Synthesis of neoxanthin (**30**) and mimulaxanthin (**33**) from the bisphosphonates **46**/**47** according to Eugster and co-workers [38, 54, 57]

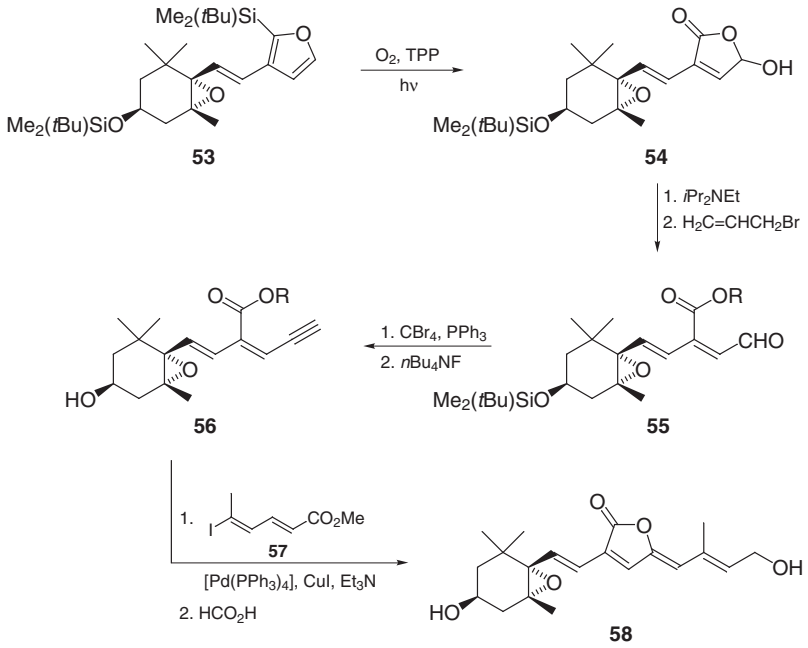
The sole synthesis (to date) of fucoxanthin (**5**) [11, 12] by Ito and co-workers [58] relied on the opposite building block scheme, i.e. the C_{10}-dialdehyde **50** was linked with the two C_{15}-phosphorane termini **51** and **52** (Scheme 18.17). However, several steps of this synthetic approach are hardly efficient; for example, the introduction of the epoxide ring carried out in the last step furnishes mainly the non-natural diastereomer.



Scheme 18.17 Synthesis of fucoxanthin (**5**) by Ito and co-workers [58].

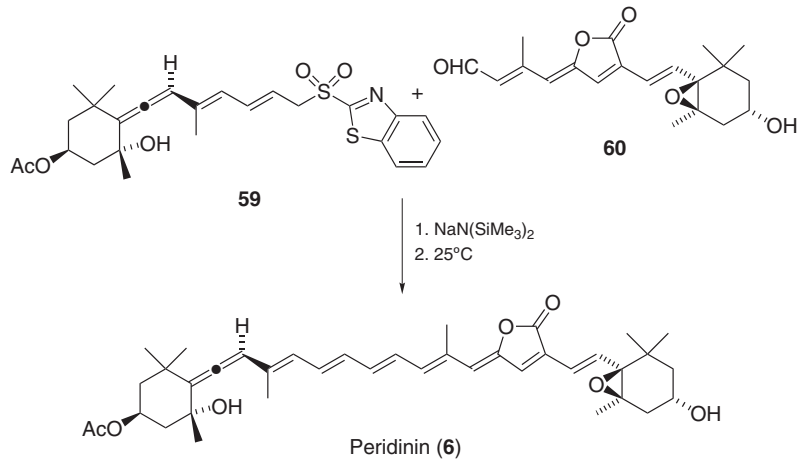
In contrast, the recently described first stereoselective [59] synthesis [43, 60] of peridinin (**6**) [13] can be regarded without exaggeration as a highlight in the chemistry of allenic natural products (Schemes 18.18 and 18.19). Several challenges had to be met in this synthesis, i.e. the stereoselective construction of the all-*trans*-polyene chain and of the chiral allene moiety, and also the generation of the (*Z*)-γ-alkylidene-butenolide ring. To generate the key building block **58**, the authors started with the silylfurane **53**, which was oxidized chemoselectively with singlet oxygen to the corresponding butenolide **54** (Scheme 18.18). Subsequent ring opening and esterification provided the aldehyde **55**, which was converted into the terminal alkyne **56** via the Corey–Fuchs reaction. The resulting alkyne **56** was then submitted to a Sonogashira coupling with the iododiene **57** and furnished, after reductive deallylation and stereoselective lactonization, the desired building block **58**. Remarkably, three of these subsequent steps were realized in an elegant one-pot procedure using different Pd(0) and Pd(II) catalysts.

To link the two half moieties of the molecule, a Julia–Kocienski olefination was carried out between the C_{19} building block **59** (again prepared by *syn*-S_N2'-substitution of a propargylic oxirane with DIBAH) and the C_{20} building block **60**, formed via oxidation of **58** with MnO_2 (Scheme 18.19). Although this reaction initially led to the formation of the *Z*-isomer as the major product, the latter was readily isomerized at room temperature to the desired all-*trans*-polyene peridinin (**6**).



53 54 55 56 58

Scheme 18.18 Synthesis of peridinin (**5**) [59]: formation of the key building block **58** (TPP = 5,10,15,20-tetraphenyl-21*H*,23*H*-porphin; R = allyl).

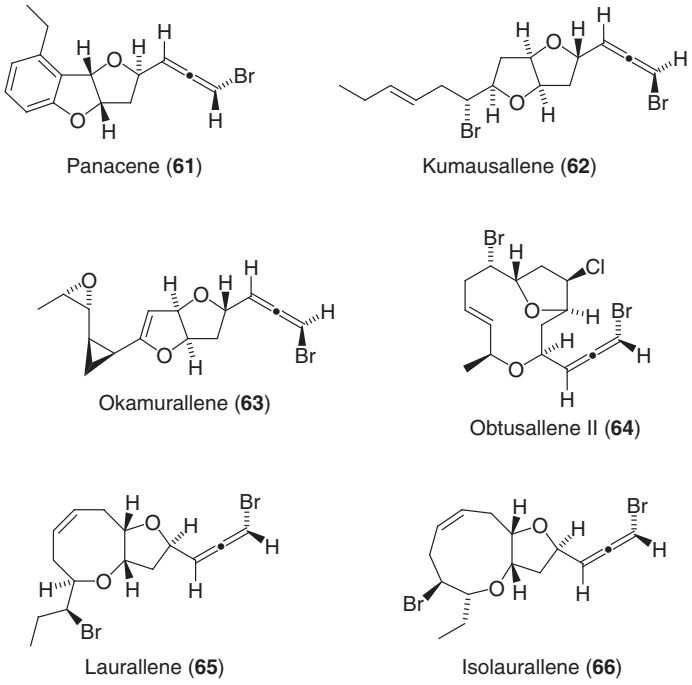


59 60

Scheme 18.19 Synthesis of peridinin (**5**) [59]: linking of the building blocks **59** and **60**.

18.2.3
Bromoallenes

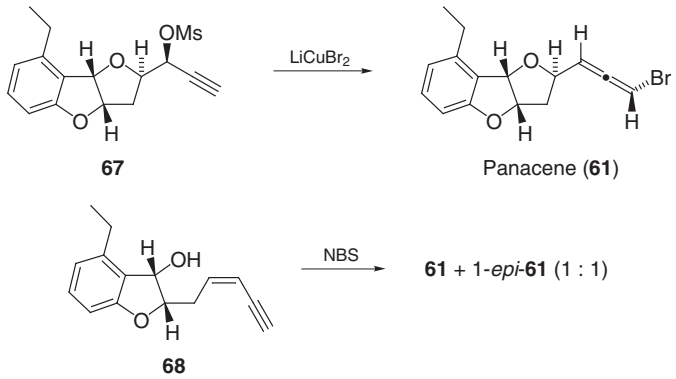
Among allenic natural products, bromoallenes form the most recently discovered group {the first example, panacene (**61**), was isolated in 1977 [61]} but comprise already more than 30 members [5, 14]. These are mainly C_{15}-dioxabicyclic compounds with an exocyclic bromoallene moiety [62], which were isolated from red algae or molluscs (Scheme 18.20).



Scheme 18.20 Naturally occurring bromoallenes.

The structural complexity of this class of natural products is highly impressive. The most abundant bicyclics are 2,6-dioxabicyclo[3.3.0]octanes [63] {panacene (**61**) [61], kumausallene (**62**) [64], okamurallene (**63**) [65], aplysiallene [66]} and 4,13-dioxabicyclo[8.2.1]tridecanes {dactylallene [67], obtusallene II (**64**) [68], obtusallenes III–IV and VII–IX [68,69]}. In addition to these bicyclo[6.3.0]undecanes {laurallene (**65**) [70], pannosallene [71], aplyparvunin [72]}, bicyclo[6.4.0]dodecanes (microcladallene A–C [73]), and bicyclo[7.3.0]dodecanes {isolaurallene (**66**) [74], neolaurallene [75]), bicyclo[7.3.1]tridecanes (obtusallene I, [68, 69] kasallene [76]) and even tricyclo[8.2.1.$1^{1,4}$]tetradecanes (obtusallene V–VI [69d]) have been observed. Of this large number of potential target molecules, so far only panacene (**61**), kumausallene (**62**), laurallene (**65**) and isolaurallene (**66**) have been the target of total syntheses.

Panacene (**61**) is a metabolite of the sea hare *Aplysia brasiliana* and acts as a fish antifeedent [61]. The synthesis of the racemic natural product, published by Feldman et al. [77] in 1982, takes advantage of the *anti*-selective S_N2'-substitution of the propargylic mesylate **67** with $LiCuBr_2$ (Scheme 18.21). In contrast, the later attempted biomimetic synthesis by treatment of the enyne **68** with NBS or 2,4,4,6-tetrabromocyclohexadienone did not proceed stereoselectively and led to a 1:1 mixture of the target molecule **61** together with its allenic epimer [78].



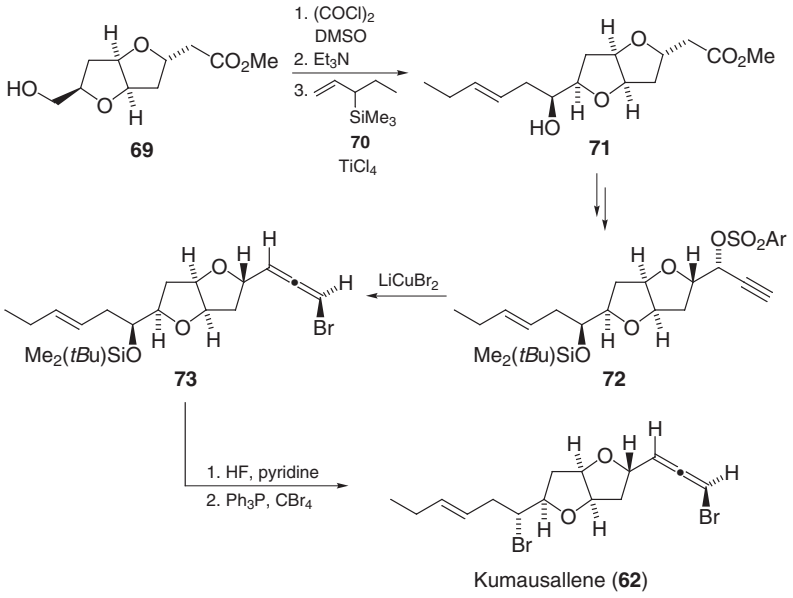
67 Panacene (**61**) 68

Scheme 18.21 Synthesis of (±)-panacene (**61**) [77, 78] (Ms = methanesulfonyl; NBS = *N*-bromosuccinimide).

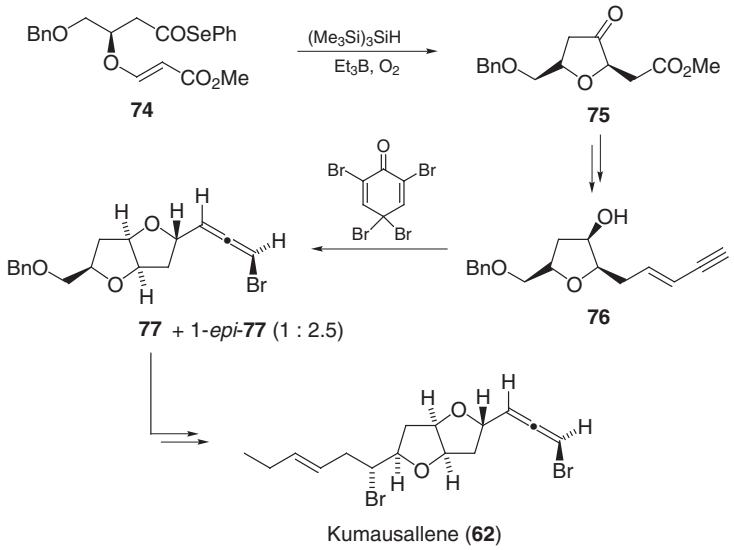
The bromoallene (–)-kumausallene (**62**) was isolated in 1983 from the red alga *Laurencia nipponica* Yamada [64a]. The synthesis of the racemic natural product by Overman and co-workers once again employed the S_N2'-substitution of a propargyl mesylate with lithium dibromocuprate (Scheme 18.22) [79]. Thus, starting from the unsymmetrically substituted 2,6-dioxabicyclo[3.3.0]octane derivative **69**, the first side chain was introduced by Swern oxidation and subsequent Sakurai reaction with the allylsilane **70**. The resulting alcohol **71** was protected and the second side chain was attached via diastereoselective addition of a titanium acetylide. The synthesis was concluded by the introduction of two bromine atoms: *anti*-selective S_N2'-substitution of the bulky propargyl mesylate **72** was followed by Appel bromination (tetrabromomethane–triphenylphosphine) of the alcohol derived from deprotection of the bromoallene **73**.

Two formal syntheses of (–)- [80] and (+)-kumausallene [81] followed this route and relied on the enantioselective preparation of the 2,6-dioxabicyclo[3.3.0]octane core **69** starting from diethyl tartrate or an appropriate chiral sulfoxide. In contrast, Evans et al. [82] used a distinct biomimetic approach in their enantioselective synthesis of the natural product (–)-**62** (Scheme 18.23).

In this approach, the *cis*-disubstituted tetrahydrofuranone **75** [accessible with high diastereoselectivity via radical cyclization of the acylselenide **74** with tris(trimethylsilyl)silane and triethylborane] was transformed into the corresponding enyne **76** by reduction and Wittig olefination. The subsequent electrophilic cyclization was carried out in analogy with the biomimetic synthesis of panacene (Scheme



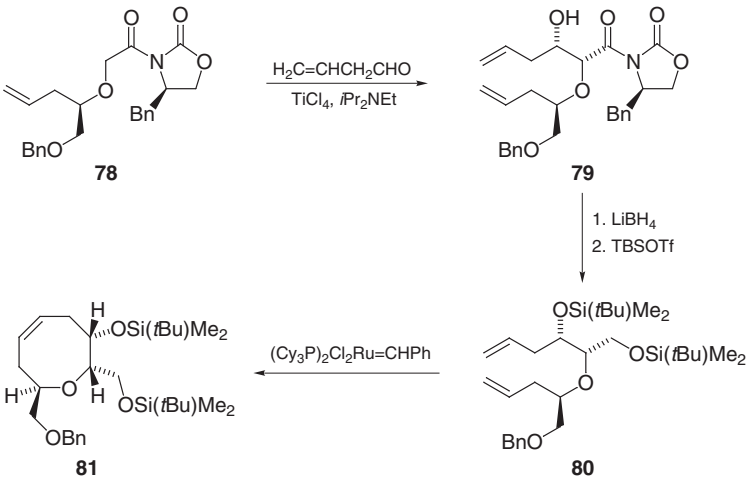
Scheme 18.22 Synthesis of (±)-kumausallene (**62**) [79] (Ar = 2,4,6-triisopropylphenyl).



Scheme 18.23 Synthesis of (–)-kumausallene (**62**) by Evans et al. [82] (Bn = benzyl).

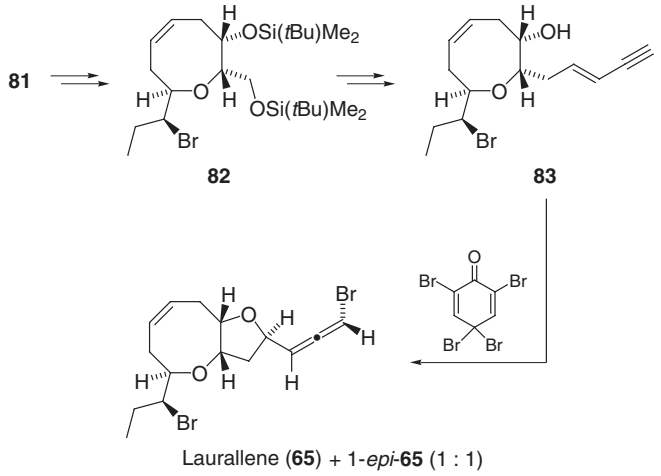
18.21) and led to the desired bicyclic bromoallene **77**, albeit with the non-natural epimer as the major product. However, the latter can be transformed into the desired intermediate **77** on treatment with samarium(II) iodide and 2,4,4,6-tetrabromocyclohexadienone. The final steps in the synthesis of (–)-kumausallene (**62**) again comprise a Sakurai reaction and Appel bromination (cf. Scheme 18.22).

The closely related bromoallenes laurallene (**65**) [70], isolaurallene (**66**) [74] and neolaurallene [75] (which is a stereoisomer of **66**) are likewise metabolites of *Laurencia nipponica* Yamada and other red algae. From a preparative point of view, interest in these natural products is mainly due to their challenging eight- and nine-membered cyclic ether structure. Moreover, in analogy with panacene and kumausallene, biomimetic studies suggest the enyne prelaureatin as the presumable precursor for laurallene [83]. However, the total syntheses of laurallene (**65**) [84] and isolaurallene (**66**) [85] published recently by Crimmins and co-workers do not follow this biomimetic pathway but use a ring-closing metathesis reaction for the formation of the eight- and nine-membered rings.

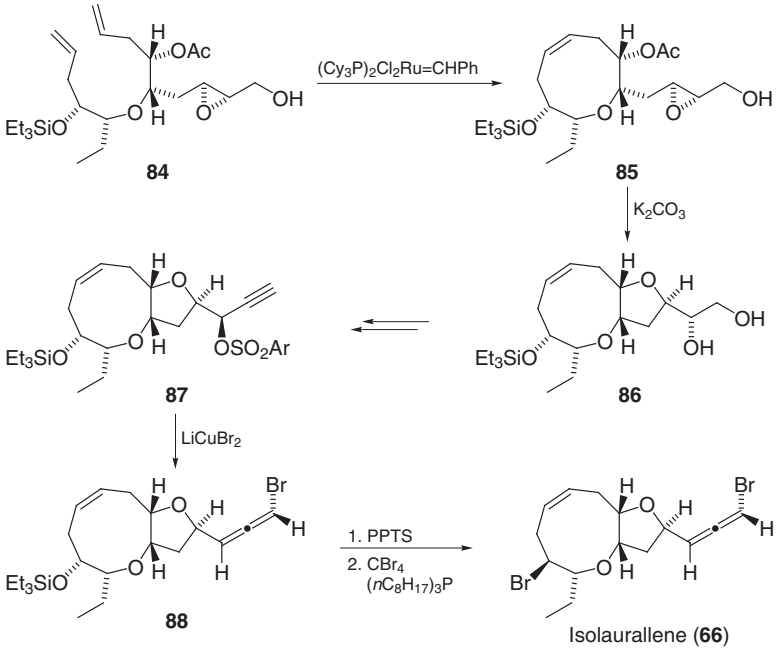


Scheme 18.24 Synthesis of laurallene (**65**) [84]: aldol reaction and ring-closing metathesis (Bn = benzyl).

To generate the two stereogenic centers of the bicyclic system, the synthesis of laurallene (**65**) in one of its key steps takes advantage of an aldol reaction between the titanium enolate formed from the chiral oxazolidinone **78** and but-3-enal (Scheme 18.24). Subsequent reduction and protection of the aldol adduct **79** led to the diene **80**, which was converted with an excellent chemical yield of 95% into oxocine **81** via ring-closing metathesis using the Grubbs-I catalyst. Subsequently, the construction of the bromopropane side chain and the formation of the enyne moiety was tackled with the aid of two Wittig reactions employing a C_1 and a C_3 building block (Scheme 18.25). Finally, another electrophilic cyclization (cf. Schemes 18.21 and 18.23) with 2,4,4,6-tetrabromocyclohexadienone converted enyne **83** into a 1:1 mixture of the target molecule laurallene (**65**) and its allenic epimer.



Scheme 18.25 Synthesis of laurallene (**65**) [84]: formation of the side chains and electrophilic cyclization.



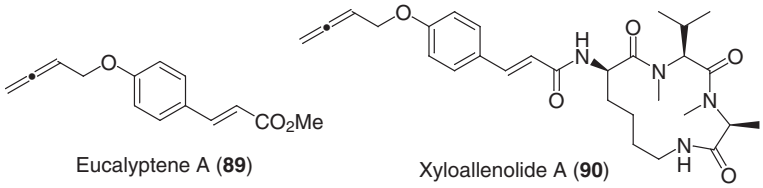
Scheme 18.26 Synthesis of isolaurallene (**66**) [85] (PPTS = pyridinium *p*-toluenesulfonate; Ar = 2,4,6-triisopropylphenyl).

In their total synthesis of isolaurallene (**66**), Crimmins and co-workers [85] relied on the *anti*-selective S_N2'-substitution of a propargylic sulfonate with $LiCuBr_2$ (cf. Schemes 18.21 and 18.22) instead of the enyne cyclization sequence, which had turned out to be unsatisfactory in terms of stereocontrol (Scheme 18.26).

Again, the formation of the nine-membered cyclic ether was accomplished via ring-closing metathesis of the diene **84** (formed by enantioselective alkylation and Sharpless epoxidation) with the Grubbs-I catalyst, proceeding with high efficiency (94% yield). Treatment of the cyclic product **85** with potassium carbonate led to the formation of the bicyclo[7.3.0]dodecane system and the resulting diol **86** was converted in several steps into the required propargylic sulfonate **87**. As expected, the formation of the bromoallene **88** by S_N2'-substitution took place with high *anti*-stereoselectivity, allowing the synthesis of the natural product to be concluded using the already outlined sequence of deprotection and incorporation of the secondary bromide via Appel bromination.

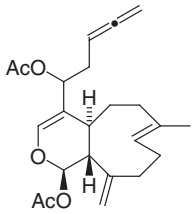
18.2.4
Other Naturally Occurring Allenes and Cumulenes

About 30 allenic natural products cannot be integrated into the three classes covered so far [5, 14]. These comprise compounds with an acyclic, often achiral allene group [86] such as the cinnamate eucalyptene A (**89**), which was isolated together with the *Z*-isomer eucalyptene B from the fungus *Citocybe eucalyptorum* (Scheme 18.27) [87]. Interestingly, a fungus of the *Xylaria* species not only contains **89** and the corresponding allenic carboxylic acid, but also the cyclic peptide **90**, which was labelled xyloallenolide A [88].

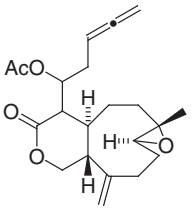


Scheme 18.27 Naturally occurring allenic cinnamates.

A further group of bicyclic natural products bearing a terminal allene moiety has been found in corals of the *Acalycigorgia* species [89]. Examples of these are ginamallene (**91**) and acalycixeniolide B–F (Scheme 18.28). A common structural feature of these compounds is a *trans*-bicyclo[7.4.0]tridecane system comprising an *E*-double bond in the larger ring that (as in acalycixeniolide E) can also be epoxidized. Several acalycixeniolides inhibit the growth of sea urchin eggs and are found to be cytotoxic against certain leukemia cell lines [89]. Furthermore, acalycixeniolide E (**92**) has been shown to possess strong anti-angiogenetic properties [90]. To date, however, no syntheses of these interesting allenic natural products have been described.



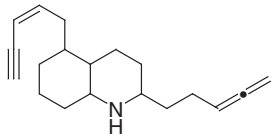
Ginamallene (**91**)



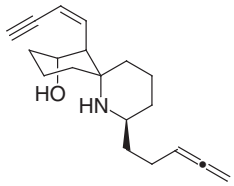
Acalycixeniolide E (**92**)

Scheme 18.28 Allenic natural products from *Acalycigorgia* corals.

The skin of several *Dendrobates* 'poison-dart frogs' from Columbia contains some allenic alkaloids with either a decahydroquinoline [91] or an azaspiro[5.5]undecane structure [92] (Scheme 18.29). The decahydroquinolines of type **93** exist as *cis*- and *trans*-isomers with regard to the decalin system and to the attached side chains. Since frogs raised in captivity do not form these toxins, they are probably part of their diet; indeed, related compounds were also found in the ant *Solenopsis azteca* [91b]. The allenic azaspiro[5.5]undecanes comprise isodihydrohistrionicotixin (**94**) and isotetrahydrohistrionicotixin, which bears instead of the enyne a 1,3-butadiene side chain [92]. Investigations of the interaction with ion channels of the nicotine acetylcholine receptor revealed strong similarities between the histrionicotixins with different side chains; the strongly unsaturated allenic natural products isodihydro- (**94**) and isotetrahydrohistrionicotixin, however, usually displayed the highest activities [92b]. Also for these allenic alkaloids no total syntheses have been reported so far.



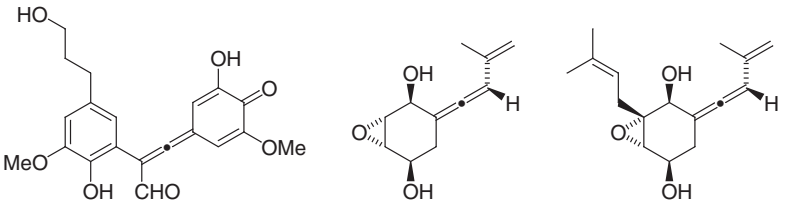
93



Isodihydrohistrionicotixin (**94**)

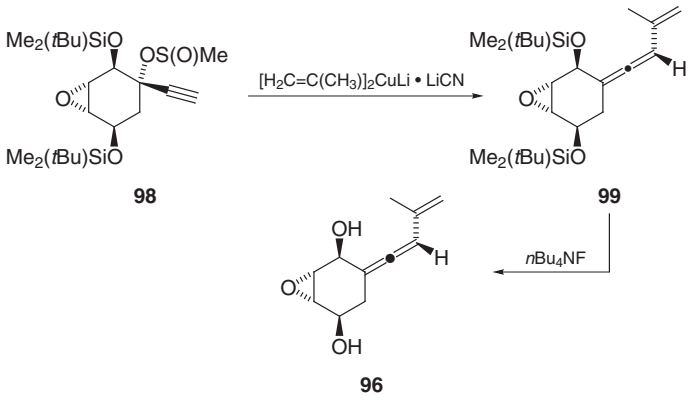
Scheme 18.29 Allenic alkaloids isolated from the skin of *Dendrobates* 'poison-dart frogs'.

The natural products **95–97** provide examples of exocyclic allenes which do not belong to the class of carotinoids and terpenoids (Scheme 18.30). For example, the quinone derivative **95** has been isolated recently from the bark of the tree *Brosimum acutifolium*, which occurs in the Amazon region [93]. This bark ('Murure') is used in Brazilian folk medicine because of its anti-inflammatory and anti-rheumatic properties. In contrast, the vinylallenes **96** [94] and **97** [95] represent once again fungal metabolites. Compound **96** has been isolated from the fungus *Eutypa lata*, which infects fruit trees and grapevines and causes the so-called eutypiosis desease that finally leads to the death of the plants.



Scheme 18.30 Naturally occurring exocyclic allenes.

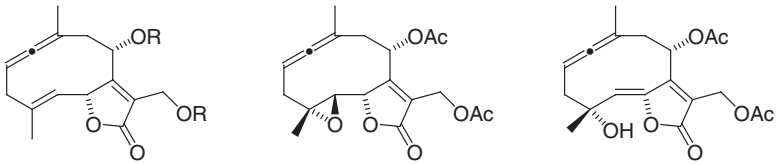
A diastereoselective synthesis of the racemic vinylallene **96** was described by Gordon and Tabacchi [96] in 1992 (Scheme 18.31). Here, the exocyclic allene was formed via *anti*-S_N2'-substitution of the propargylic sulfinate **98** with lithium diisopropenylcyanocuprate, which, however, was also found to undergo side reactions such as reduction and direct attack of the nucleophile at the sulfinate. Deprotection of the substitution product **99** (which was obtained with only 35% yield) finally provided the desired target molecule **96**.



Scheme 18.31 Synthesis of the exocyclic vinylallene **96** [96].

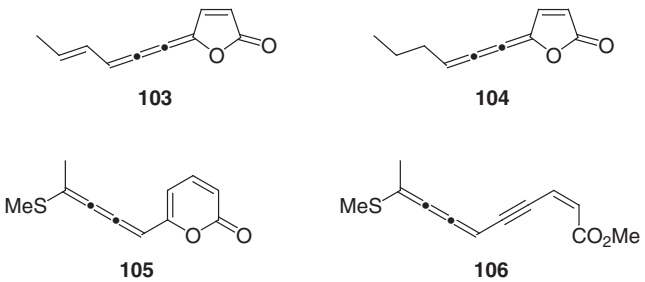
About 20 years ago, Bohlmann and co-workers examined South American plants of the widespread *Vernonia* species and found the first and (until now) only naturally occurring endocyclic allenes (Scheme 18.32) [97]. These are the bicyclic sesquiterpene lactones **100–102** bearing a 10-membered ring [98], in which the *E*-double bond of the larger ring can also be present in its oxidized form (**101**, **102**). As in other cases, these fascinating natural products have not been synthesized until now.

Bohlmann and co-workers furthermore described the sole natural products with a 1,2,3-butatriene sub-structure (Scheme 18.33) [99]. These compounds **103–106** (which were isolated between 1965 and 1971 from the roots of camomile and other plants) are highly unstable, which made their structural assignment difficult.



100 (R = H, Ac) **101** **102**

Scheme 18.32 Cyclic allenes isolated from *Vernonia* sp. [97].



103 **104** **105** **106**

Scheme 18.33 Naturally occurring cumulenes [99].

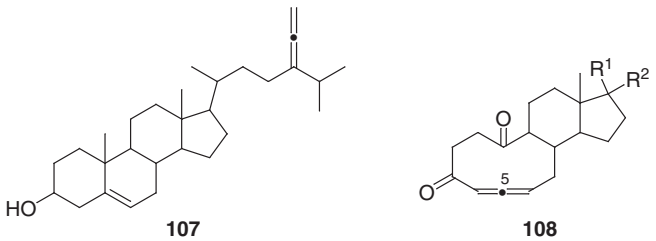
18.3 Pharmacologically Active Allenes

The manifold biological activities of the allenic natural products described in the previous sections might give the impression that it could be auspicious to include an allenic moiety also in (non-natural) pharmacologically active compounds. In order to estimate the potential benefit of such a cumulated double bond systems in pharmaceuticals, information about structure–activity relationships and the biogenesis of allenes should be helpful. Unfortunately, mostly (plausible) speculations but only very few experimental investigations are to be found in this field [5]. For example, it seems reasonable to ascribe the activity of the insect pheromone **12** to the allene topology (rigid C_3 unit with axial chirality), but the existence of a specific receptor for this structural element has not been proven so far. Similarly, experimental evidence is lacking for the biosynthesis of allenes which are usually thought to be formed via oxidative or reductive rearrangements of the corresponding alkynes [5, 100, 101] {cf. biomimetic syntheses of the bromoallenes panacene (**61**) [78], kumausallene (**62**) [82] and laurallene (**65**) [83]}. In spite of the lack of information about structure–activity relationships, a number of different allenic pharmaceuticals has been synthesized and examined in terms of their activity, with the results up to 1980 having already been reviewed [5]. Recent advances in this field focus mainly on the inhibition of enzymes by allenic steroids, prostaglandins and amino acid and

nucleoside analogs. In this respect, a 'mechanism-based inhibition' is frequently observed where a 'suicide substrate' is unmasked at the active site by the natural catalytic activity of the enzyme leading to the formation of a highly reactive acceptor-substituted allene, which then undergoes an irreversible Michael addition with a suitable nucleophilic group of the enzyme [5, 102].

18.3.1 Steroids

Pharmacologically active allenic steroids have already been examined intensively for about 30 years [5]. Thus, the only naturally occurring allenic steroid **107** had been synthesized 3 years *before* its isolation from *Callyspongia diffusa* and it had been identified as an inhibitor of the sterol biosynthesis of the silkworm *Bombyx mori* (Scheme 18.34) [86d]. At this early stage, allenic 3-oxo-5,10-secosteroids of type **108** were also used for the irreversible inhibition of ketosteroid isomerases in bacteria, assuming that their activity is probably caused by Michael addition of a nucleophilic amino acid side chain of the enzyme at the 5-position of the steroid [103, 104]. Since this activity is also observed in the corresponding β,γ-acetylenic ketones, it can be rationalized that the latter are converted *in vivo* into the allenic steroids **108** by enzymatic isomerization [104, 105].

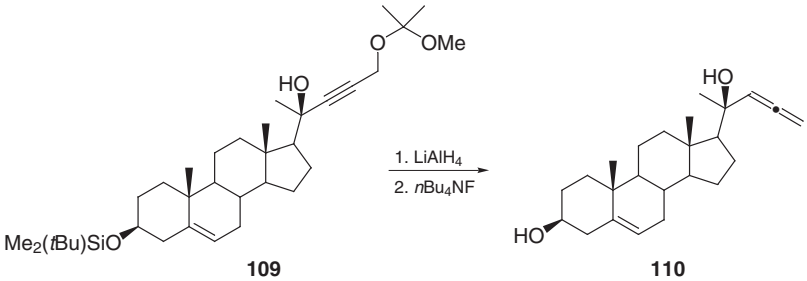


107 **108**

Scheme 18.34 Allenic steroids as inhibitors of sterol biosynthesis.

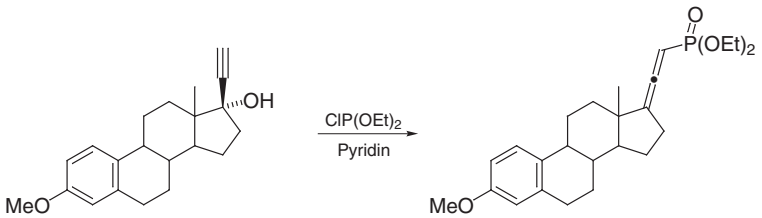
Most of the more recently described allenic steroids bear an allene group at the 17-position, which was usually formed by an S_N2' substitution [106] or reduction [86d] process of a suitable propargylic electrophile. Thus, reduction of the propargylic ether **109** with lithium aluminum hydride followed by deprotection of the silyl ether resulted in the formation of the allenic steroid **110**, which irreversibly inhibits the biosynthesis of the insect moulting hormone ecdysone (Scheme 18.35) [107].

Alternative, also stereoselective, routes to allenic steroids take advantage of cationic cyclization reactions [108] or [2,3]-sigmatropic rearrangements [109]. For example, the allenic Michael acceptor **112** was prepared with 57% chemical yield by reaction of mestranol (**111**) with diethyl chlorophosphite and was found to inhibit the sterol biosynthesis of the pathogen responsible for *Pneumocystis carinii* pneumonia (PCP), the most abundant AIDS-related disease (Scheme 18.36) [110].



109 **110**

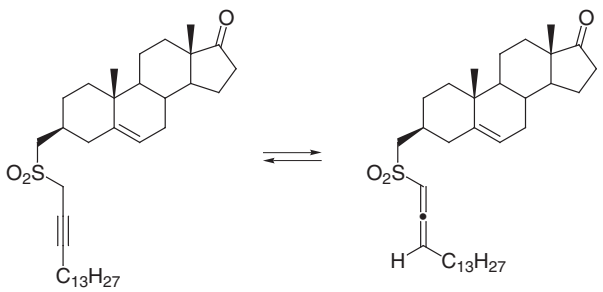
Scheme 18.35 Synthesis of the allenic steroid **110** by S_N2'-reduction [107].



111 **112**

Scheme 18.36 Synthesis of the allenic phosphonate **112** by [2,3]-sigmatropic rearrangement [110].

Further variations of allenic steroids include the introduction of an allene moiety at the 10- [111], 11- [112] or 3-position. Williams and Boehm [113] investigated a number of steroids with propargylic sulfone side chains as inhibitors for glucose-6-phosphate dehydrogenase (G6PDH) and observed the highest activity for substrates bearing lipophilic alkyl chains at the 3β-position (e.g. **113**; Scheme 18.37). Again, it is assumed that an isomerization to the allenic sulfone **114** occurs in the enzymatic active site, with the latter undergoing an irreversible Michael addition with nucleophilic amino acid side chains.

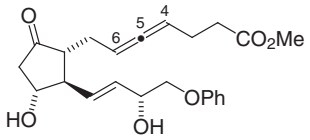


113 **114**

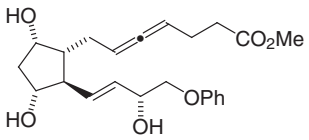
Scheme 18.37 3β-Substituted steroids as inhibitors of glucose-6-phosphate dehydrogenase.

18.3.2
Prostaglandins and Carbacyclins

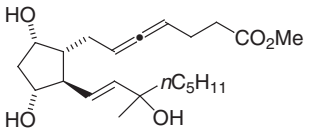
Variations of the prostaglandin and prostacyclin structures by introduction of an allenic group in the α- or ω-side chain have been the subject of much research activity in the last 30 years. Here, the major goals were not only a modulation of the pharmacological activity but also an improvement of the metabolic stability and bioavailibility of the molecules [114]. Although only a few examples (with minor biological activities) have been reported for prostaglandins with allenic ω-side chains so far [115], several compounds with an allenic entity in the 4–5–6-positions have been developed and marketed (Scheme 18.38) [114], the most noted example being enprostil (**115**).



Enprostil (**115**)



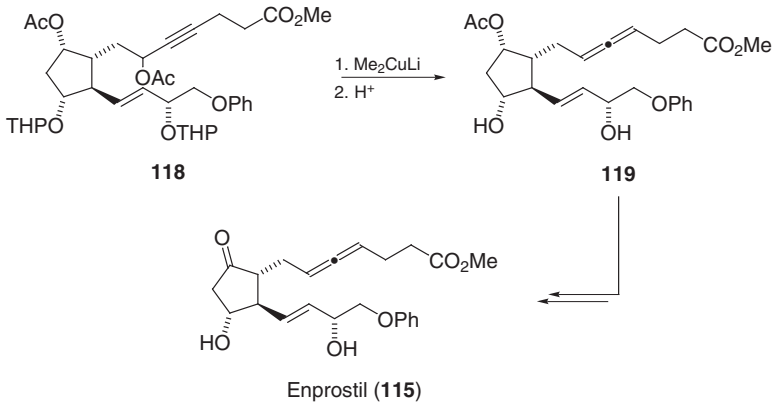
Fenprostalene (**116**)



Prostalene (**117**)

Scheme 18.38 Allenic prostaglandins introduced commercially.

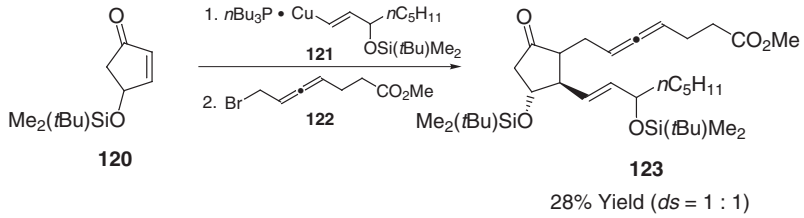
Enprostil (**115**) [114] is a PGE_2 analog with a strong inhibitory activity against gastric acid secretion [116, 117] and is (or was) marketed in several countries under the trade names Gardrin, Camleed or Syngard for the prevention and treatment of gastric and duodenal ulcers. The allene and phenoxy groups were introduced in order to decrease the metabolic susceptibility of the oral drug. Interestingly, the effect of either modification alone is modest whereas enprostil is over 600 times more potent than PGE_2 in inhibiting gastric acid secretion [118]. Enprostil is usually administered as a racemic mixture of diastereomers with respect to the allenic axis of chirality. In the first synthesis of this isomeric mixture (Scheme 18.39) [119], the allenic moiety was installed by an S_N2'-reduction of the propargylic acetate **118** with lithium dimethylcuprate [115, 120]. Subsequent manipulation of the protective groups of the product **119** and oxidation of the 9-hydroxy group finally provided the target molecule **115**.



118 119

Scheme 18.39 Synthesis of racemic enprostil (**115**) [119, 120] (THP = tetrahydropyranyl).

During the last decade, a substantial number of novel (sometimes even stereoselective) strategies for the preparation of allenic prostaglandins have been devised. The approach used by Patterson involves a three-component coupling via a 1,4-addition of the organocopper compound **121** to the enone **120**, followed by alkylation of the enolate formed with the bromide **122** (Scheme 18.40) [121]. However, due to the notoriously low reactivity in the alkylation of the mixed copper–lithium enolate formed during the Michael addition [122], the desired product **123** was obtained with only 28% chemical yield (the alkylation was not even stereoselective, giving **123** as a 1:1 mixture of diastereomers).

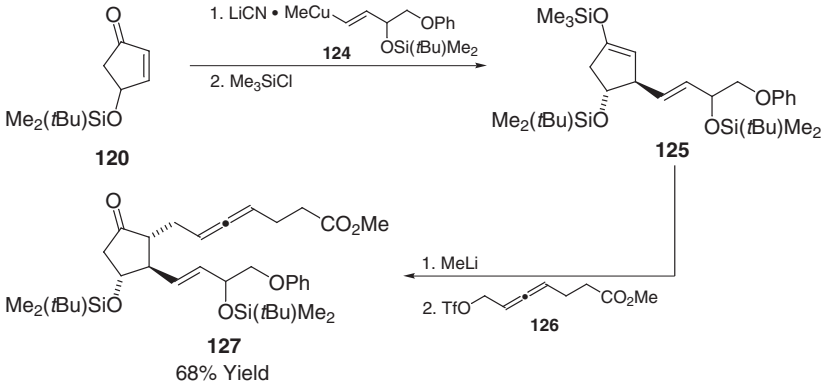


120 123

28% Yield (*ds* = 1 : 1)

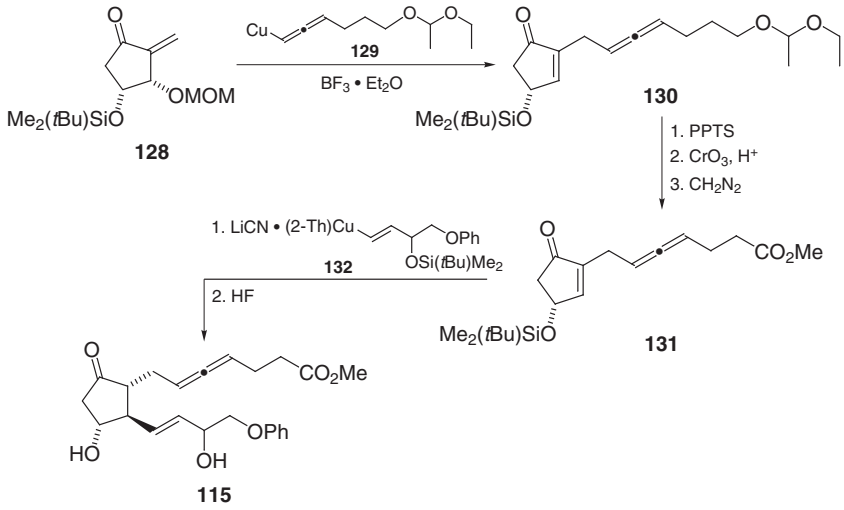
Scheme 18.40 Synthesis of the allenic prostaglandin **123** by three-component coupling [121].

A route involving trapping the enolate as a silyl enol ether, subsequent transmetallation to the corresponding lithium enolate and alkylation turned out to be more efficient (Scheme 18.41) [123]. Thus, treatment of **120** with the cuprate **124** and chlorotrimethylsilane furnished the silyl enol ether **125**, which was then converted into the desired enprostil derivative **127** with 68% yield over both steps by reaction with methyllithium and the allenic triflate **126**.

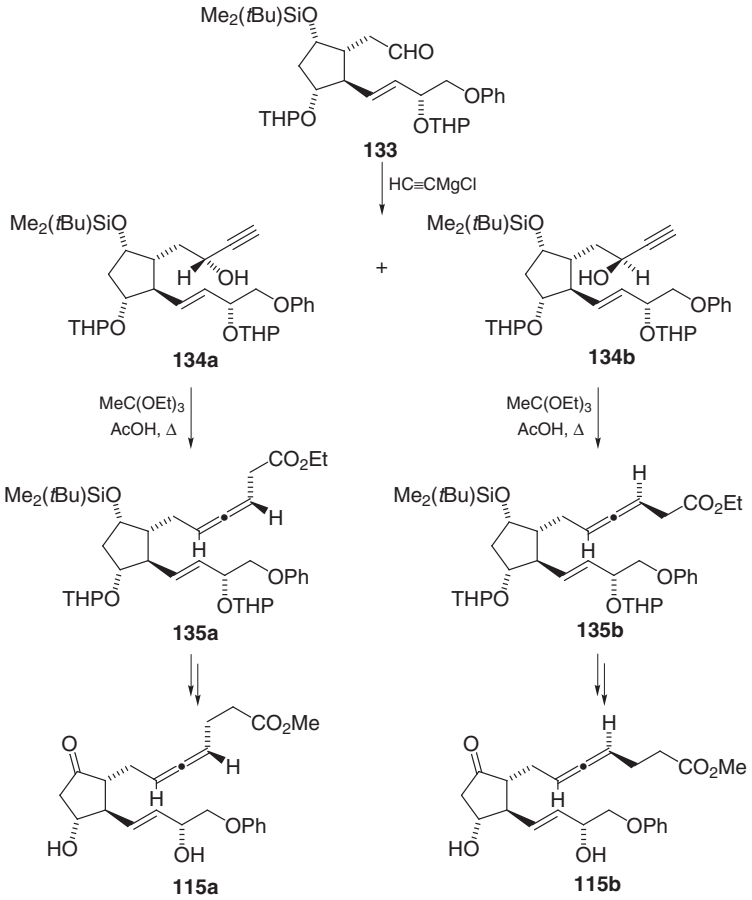


Scheme 18.41 Synthesis of the enprostil derivative **127** via silyl enol ether **125** [123] (Tf = trifluoromethanesulfonyl).

In contrast, Sato and co-workers [124] employed two consecutive 1,4-addition reactions of organocopper compounds for the assembly of the enprostil framework (Scheme 18.42). An addition–elimination reaction of the exocyclic enone **128** with the allenic copper compound **129** provided the endocyclic enone **130**, which was deprotected and oxidized. The resulting Michael acceptor **131** was then subjected to another 1,4-addition with the cuprate **132**, furnishing enprostil (**115**) after desilylation. Here, both the cuprate addition and the subsequent enolate protonation proceed with high diastereoselectivity to give the correct relative configuation of the three contiguous stereogernic centers at the five-membered ring.



Scheme 18.42 Synthesis of enprostil (**115**) by consecutive cuprate additions [124] (MOM = methoxymethyl; PPTS = pyridinium *p*-tuolenesulfonate; 2-Th = 2-thienyl).

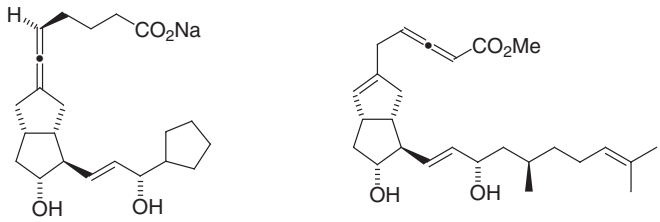


Scheme 18.43 Stereoselective synthesis of enprostil by orthoester–Claisen rearrangement [125a] (THP = tetrahydropyranyl).

Additionally, a selective synthesis of all four stereoisomers of enprostil was accomplished by Cooper et al. [125a] using an orthoester–Claisen rearrangement. (Scheme 18.43). Acetylide addition to the aldehyde **133** thus furnished a 3:2 mixture of the epimeric propargylic alcohols **134a** and **134b**, which were separated chromatographically and subjected to a *syn*-stereoselective Claisen rearrangement to furnish **135a** and **135b**, respectively. The pure enprostil isomers **115a** and **115b** were finally obtained through a sequence of homologization, oxidation and deprotection (their enantiomers were prepared correspondingly). Interestingly, of these four stereoisomeric prostaglandin analogs, **115a** exhibits by far the highest anti-secretoric activity [116b] and the strongest binding to PG receptors [117a].

The allenic $PGF_{2\alpha}$ analogs fenprostalene (**116**) and prostalene (**117**) are closely related to enprostil and are used in veterinary medicine for the synchronization of estrus. As in the synthesis of enprostil (Scheme 18.39), the allenic α-side chain is

formed by a copper-mediated S_N2'-reduction [114]. In addition to these prostaglandin analogs, some examples of hydrolytically more stable allenic prostacyclin analogs, namely the carbacyclin **136** and the isocarbacyclin **137** (Scheme 18.44), have been reported. Allene **136** is a promising anti-thrombotic agent [114] that was prepared through a [2,3]-sigmatropic rearrangement of a propargylic sulfenate and reaction of the resulting allenic sulfoxide with methyllithium [126]. In contrast, Mikami et al. [127] generated the allenic side chain of isocarbacyclin **137** by a palladium-catalyzed and samarium-mediated reduction of a secondary propargylic phosphate.



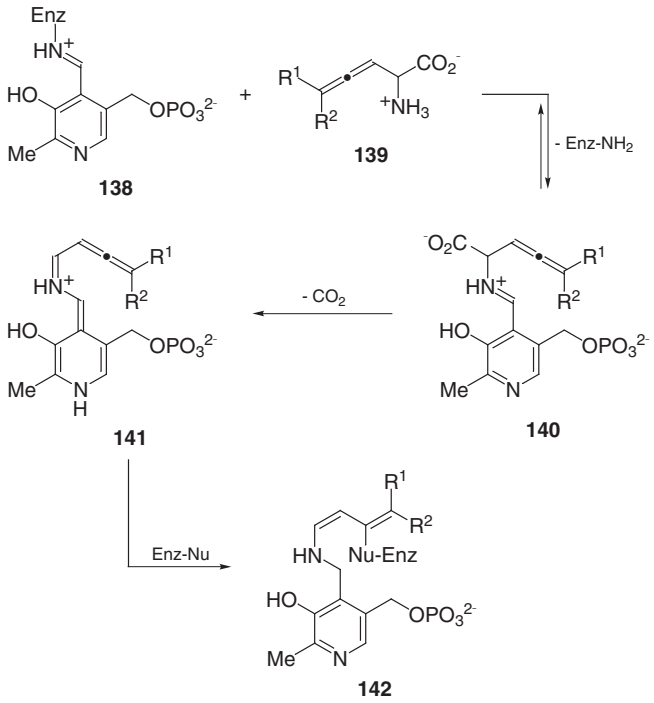
136 **137**

Scheme 18.44 Allenic carbacyclins.

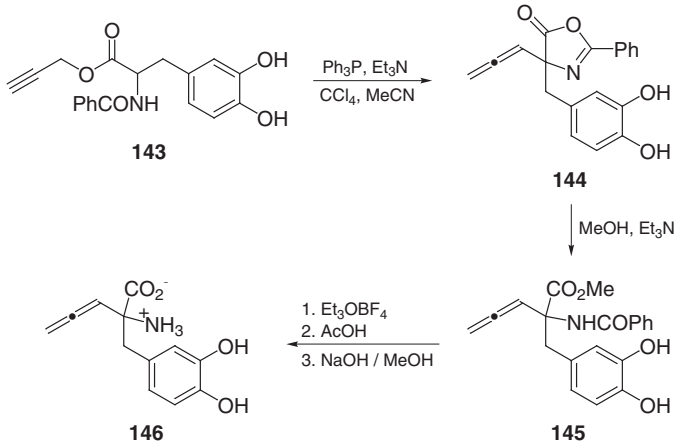
18.3.3 Amino Acids

Allenic amino acids belong to the classical 'suicide substrates' for the irreversible 'mechanism-based inhibition' of enzymes [5]. Among the different types of allenic substrates used for enzyme inhibition [128, 129], the deactivation of vitamin B_6 (pyridoxal phosphate)-dependent decarboxylases by α-allenic α-amino acids plays an important role (Scheme 18.45). In analogy with the corresponding activity of other β,γ-unsaturated amino acids [102, 130], it is assumed that the allenic amino acid **139** reacts with the decarboxylase **138** to furnish the imine **140**, which is transformed into a Michael acceptor of type **141** by decarboxylation or deprotonation. Subsequent attack of a suitable nucleophilic group of the active site then leads to inhibition of the decarboxylase by irreversible formation of the adduct **142** [131, 132].

The first syntheses of α-allenic α-amino acids [131,133] took advantage of Steglich's [134] protocol for the oxazole–Claisen rearrangement of unsaturated *N*-benzoylamino acid esters (Scheme 18.46). Thus, treatment of the propargylic ester **143** with triphenylphosphine and tetrachlormethane furnished the allenic oxazolone **144**, which was converted into the amino acid derivative **145** by methanolysis. Stepwise deprotection finally led to the allenic DOPA analog **146**, which shows a much higher decarboxylase-inhibiting activity than α-vinyl- and α-ethynyl-DOPA [133].

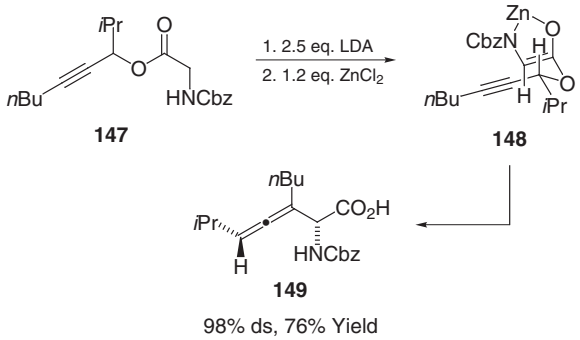


Scheme 18.45 Postulated inhibition mechanism of pyridoxal phosphate-dependent decarboxylases by α-allenic α-amino acids.



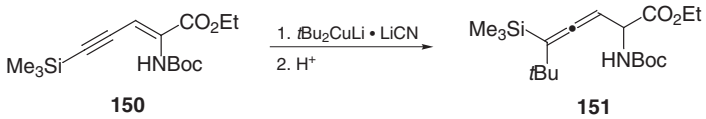
Scheme 18.46 Synthesis of α-allenyl-DOPA (**146**) [133].

Further variations of the Claisen rearrangement protocol were also utilized for the synthesis of allenic amino acid derivatives. Whereas the Ireland–Claisen rearrangement led to unsatisfactory results [133b], a number of variously substituted α-allenic α-amino acids were prepared by Kazmaier [135] by chelate-controlled Claisen rearrangement of ester enolates (Scheme 18.47). For example, deprotonation of the propargylic ester **147** with 2 equiv. of lithium diisopropylamide and transmetallation with zinc chloride furnished the chelate complex **148**, which underwent a highly *syn*-stereoselective rearrangement to the amino acid derivative **149**.



Scheme 18.47 Synthesis of the allenic amino acid derivative **149** by chelate-controlled Claisen rearrangement [135] (LDA = lithium diisopropylamide; Cbz = benzyloxycarbonyl).

Additional routes to α-allenic-α-amino acids were described more recently and utilize radical [136] or transition metal-catalyzed [137] allenylations, in addition to copper-promoted Michael additions [15b]. Thus, sterically demanding amino acid derivatives (e.g. **151**) are accessible via a 1,6-addition reaction of lithium di-*tert*-butylcyanocuprate with acceptor-substituted enynes of type **150** (Scheme 18.48).



Scheme 18.48 Synthesis of the allenic amino acid derivative **151** by 1,6-cuprate addition [15b] (Boc = *tert*-butoxycarbonyl).

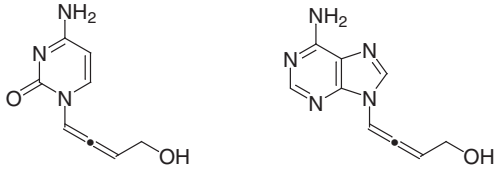
In addition to α-allenic α-amino acids, the corresponding allenic derivatives of γ-aminobutyric acid (GABA) have also been synthesized as potential inhibitors of the pyridoxal phosphate-dependent enzyme GABA-aminotransferase (Scheme 18.49) [131, 138–142]. The synthesis of γ-allenyl-GABA (**152**) and its methylated derivatives was accomplished through Crabbé reaction [131], aza-Cope rearrangement [138] and lactam allenylation [139], whereas the fluoroallene **153** was prepared by S_N2'-reduction of a propargylic chloride [141].

152 153

Scheme 18.49 Allenic derivatives of γ-aminobutyric acid (GABA).

18.3.4 Nucleoside Analogs

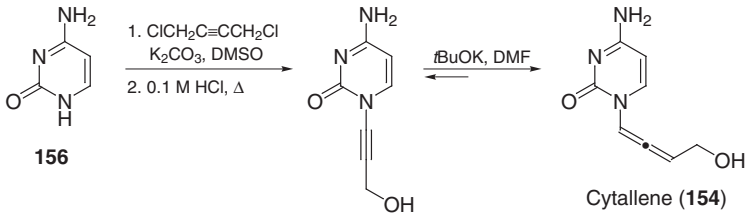
Allenic nucleoside analogs are currently of high interest as cytotoxic and antiviral agents. Prototypes of this class of compounds (Scheme 18.50) are the nucleoside analogs cytallene (**154**) and adenallene (**155**), which were developed by Zemlicka [143].



Cytallene (**154**) Adenallene (**155**)

Scheme 18.50 Allenic nucleoside analogs.

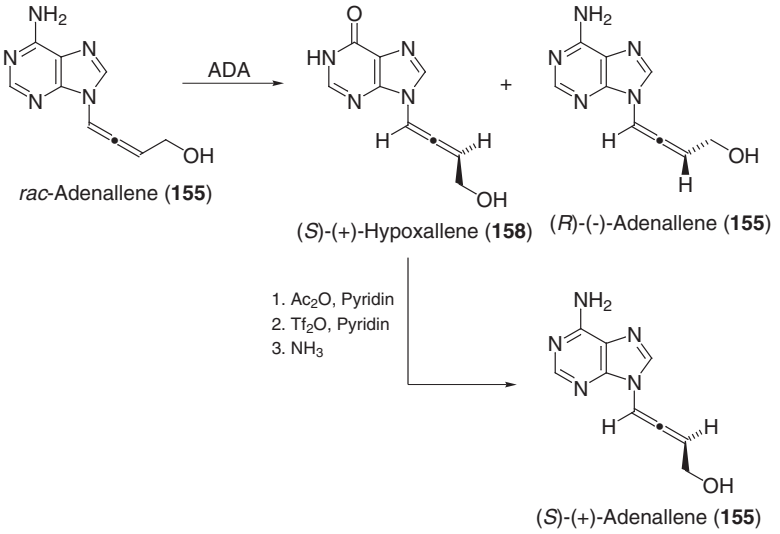
After the first reports of cytallene and adenallene in 1988, the array of allenic nucleoside analogs of this type was expanded by a large number of similar compounds (e.g. guanallene, hypoxallene) [143]. These allenic nucleoside analogs were selected as target molecules because of their close similarity to cytosine and adenosine (with the hydroxyallene side chain mimicking the topology of the ribose ring) and their ability to undergo in vivo phosphorylation of the free hydroxyl group. The synthesis of both nucleoside analogs was accomplished by alkylation of the free nucleobase (e.g. cytosine **156**) with 1,4-dichlorobut-2-yne, hydrolysis to the propargylic alcohols **157** and basic equilibration, followed by chromatographic separation of the allene **154** from the equilibrium mixture (Scheme 18.51) [144].



156 157 Cytallene (**154**)

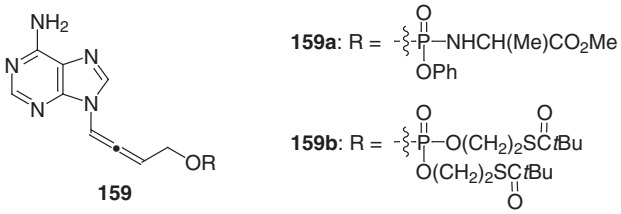
Scheme 18.51 Synthesis of racemic cytallene (**133**) [144].

A number of impressive biological activities were subsequently rapidly determined for cytallene and adenallene, including cytotoxicity and inhibition of the replication of HIV and other retroviruses [144]. In contrast, no antiviral activity could be detected for an adenallene analog bearing two terminal CH_2OH groups [145]. In order to investigate the dependence of the antiviral activity on the absolute configuration of the allenic side chain, the pure enantiomers of the allenic nucleoside analogs were prepared via kinetic deracemization. Whereas in the case of cytallene this could be accomplished through a simple lipase-catalyzed acylation reaction [146], a deamination catalyzed by adenosine deaminase had to be used for adenallene (Scheme 18.52) [147]. Hence the deamination reaction led to the formation of (*R*)-(–)-**155** and (*S*)-(+)-hypoxallene (**158**), with the latter being converted into (*S*)-(+)-adenallene by esterification, ammonolysis and ester hydrolysis.



Scheme 18.52 Kinetic deracemization of adenallene (**155**) by enzyme-catalysed deamination [147] (ADA = adenosine deaminase; Tf = trifluoromethanesulfonyl).

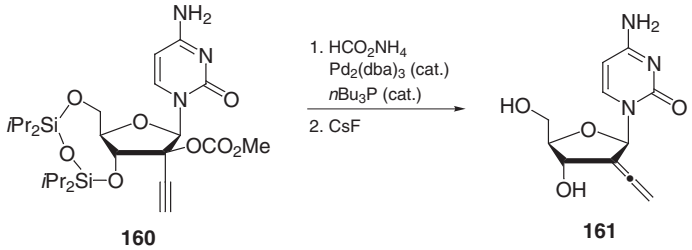
Attempts to inhibit HIV-1 with either enantiomer of cytallene and adenallene revealed that only the *R*-enantiomer is active [146, 147]. Moreover, (*R*)-(–)-cytallene is capable of inhibiting the replication of the hepatitis B virus [148]. The activation of these nucleoside analogs (which act as 'prodrugs') takes place via an enzymatic phosphorylation. Since cells resistant against antiviral agents such as AZT often lack the kinase necessary for the formation of the monophosphate [143c], a number of lipohilic phosphodiester derivatives of these allenic nucleoside analogs were designed for the inhibition of retroviruses. As expected, an increased anti-HIV activity was observed for the phosphorylated adenallene derivatives **159** (Scheme 18.53). Thus, the phosphodiester amidate **159a** is found to be 16 times (racemate) and 28 times (*R*-enantiomer) more active than adenallene itself [149]. Interestingly, this enhanced activity, albeit less pronounced, was also found determined for the



Scheme 18.53 Phosphodiester derivatives of adenallene.

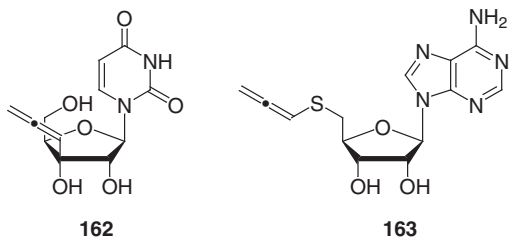
S-acylthioethylphosphate **159b** [150]. However, this increase in activity is accompanied by an enhanced cytotoxicity and a lower selectivity.

In addition to these nucleoside analogs bearing an allenic chain instead of the ribofuranose ring, a few derivatives with an intact sugar ring modified by introduction of an allenic substituent have been described. Thus, Jarvi and McCarthy [151] prepared 2′-desoxy-2′-ethenylidenecytidine (**161**) and the corresponding adenosine analog (which are of interest as possible inhibitors for the ribonucleotide reductase or *S*-adenosyl-L-homocysteine hydrolase) by palladium-catalyzed S_N2' reduction of the corresponding propargylic carbonates (e.g. **160**, Scheme 18.54).



Scheme 18.54 Synthesis of 2′-desoxy-2′-ethenylidenecytidine (**161**) [151].

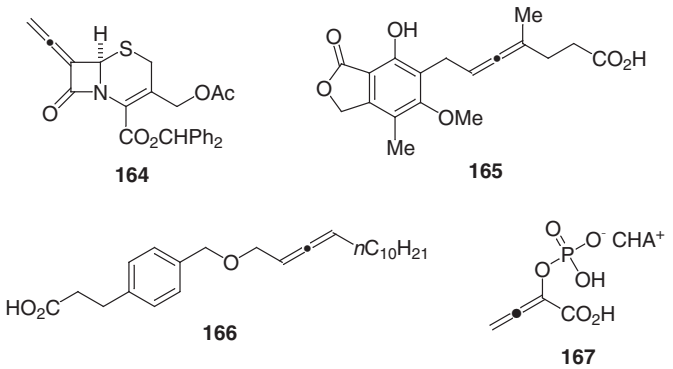
In contrast, 3′-allenyluridine (**162**) was synthesized by Crabbé homologization of the corresponding 3′-ethynyl derivative, but did not show any antitumor activity (Scheme 18.55) [152]. However, similarly to cytallene and adenallene, the allenic thioether **163** is active against the vaccinia virus and was prepared via basic isomerization of the corresponding propargylic thioether [153].



Scheme 18.55 Further allenic nucleoside analogs with a modified ribofuranose ring.

18.3.5
Other Pharmacologically Active Allenes

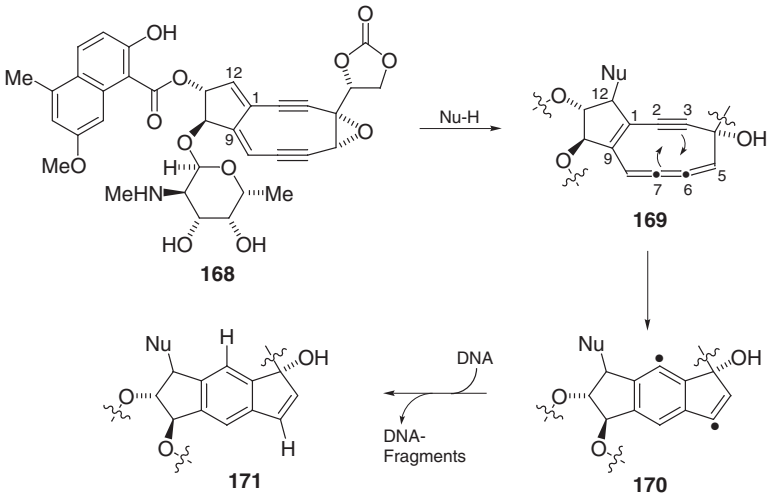
In addition to the aforementioned allenic steroids, prostaglandins, amino acids and nucleoside analogs, a number of other functionalized allenes have been employed (albeit with limited success) in enzyme inhibition (Scheme 18.56) [154–159]. Thus, the 7-vinylidenecephalosporin **164** and related allenes did not show the expected activity as inhibitors of human leukocyte elastase, but a weak inhibition of porcine pancreas elastase [156]. Similarly disappointing were the immunosuppressive activity of the allenic mycophenolic acid derivative **165** [157] and the inhibition of 12-lipoxygenase by the carboxylic acid **166** [158]. In contrast, the carboxyallenyl phosphate **167** turned out to be a potent inhibitor of phosphoenolpyruvate carboxylase and pyruvate kinase [159]. Hydrolysis of this allenic phosphate probably leads to 2-oxobut-3-enoate, which then undergoes an irreversible Michael addition with suitable nucleophilic side chains of the enzyme.



Scheme 18.56 Functionalized allenes used for enzyme inhibition (CHA^+ = cyclohexylammonium).

For a number of other pharmacologically active unsaturated compounds, it is assumed that a reactive allene is formed in situ by an alkyne isomerization [160] or an elimination reaction [161]. The prime example of the formation of such a highly reactive allene through chemical activation of an unsaturated precursor is the enediyne antibiotic neocarzinostatin (Scheme 18.57) [162].

The strong cytotoxicity of neocarzinostatin is ascribed to an activation of the neocarzinostatin chromophore (**168**) by attack of a nucleophile (usually a thiol) at the 12-position of the bicyclo[7.3.0]dodecane core. This induces a ring opening of the epoxide and the formation of the enynecumulene **169**, which under physiological conditions subsequently undergoes a Myers–Saito cyclization between C3 and C7 to give the aromatic biradical **170**. This radical is stabilized by abstraction of hydrogen atoms from the carbohydrate backbone of DNA, which causes fragmentation of the latter [162].



Scheme 18.57 Postulated mechanism of the DNA cleavage by the neocarzinostatin chromophore **168** [162].

Since the double bond between C5 and C6 of the enynecumulene **169** is not required for the Myers–Saito cyclization, a large number of enyneallenes have been synthesized as model compounds for the neocarzinostatin chromophore and tested for DNA-cleaving activity in recent years, with the results having already been summarized extensively (cf. Chapter 20) [162].

18.4 Conclusion

Starting 50 years ago, the chemistry of allenic natural products and pharmaceuticals has turned out to be a very attractive and prolific area of interest. Advances in the isolation and characterization of new allenic natural products were accompanied by the establishment of efficient synthetic procedures which also opened up an access to enantiomerically pure target molecules in many cases. Highlights of these developments are the enantioselective total syntheses of the allenic carotinoid peridinin and of the bromoallenes laurallene and isolaurallene.

Inspired by the intriguing biological activities of many allenic natural products, the systematic introduction of allenic moieties in pharmacologically active classes of compounds (steroids, prostaglandins, amino acids, nucleosides) was commenced about 30 years ago. The functionalized allenes thus obtained often exhibit interesting activities as mechanism-based enzyme inhibitors and cytotoxic or antiviral agents. Again, the progress achieved had to rely on the high 'state of the art' of stereoselective allene synthesis. Thus, allenes have been established as a pharmacologically important class of compounds and future exciting developments in this field can be expected.

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19
Allenes in Natural Product Synthesis

Kay M. Brummond and Hongfeng Chen

19.1
Introduction

The focus of this chapter is the incorporation of allenes in precursors that are used in the total synthesis of natural products. Incorporation of an allene functionality in a retrosynthetic fragment is still a process that can raise eyebrows but nevertheless one that has not only proven to be successful, but in many cases advantageous. If an author has made direct reactivity comparisons between an allene and another functional group, those comparisons are included in this review. We have divided the chapter into sections according to the type of reaction in which the allenyl group is a participant. The content of this review has mostly been taken from the literature since the publication of Schuster and Coppola's monograph on allenes in 1984 [1]. We have not included natural products possessing an allene functionality since this is the topic of Chapter 18 and consequently if the allene is incorporated in the natural product, it was most likely not involved in a key carbon–carbon bond-forming strategy of the synthesis. Moreover, allenes in natural product synthesis are rarely indexed as such in the literature. Therefore, retrieving them requires examination of individual publications. As a consequence of this search strategy, this review is not meant to be exhaustive but to provide an account highlighting many successful synthetic strategies whereby an allene has served as a key precursor in natural product synthesis.

19.2
Cycloaddition Reactions

Some of the earliest applications of allenes in natural product synthesis involved thermal- and photo-induced cycloaddition reactions. As a consequence of this and the fact that these types of reactions work so well, the use of allenes as cycloeducts in these types of reactions has been widespread. A variety of examples are showcased in the sections that follow.

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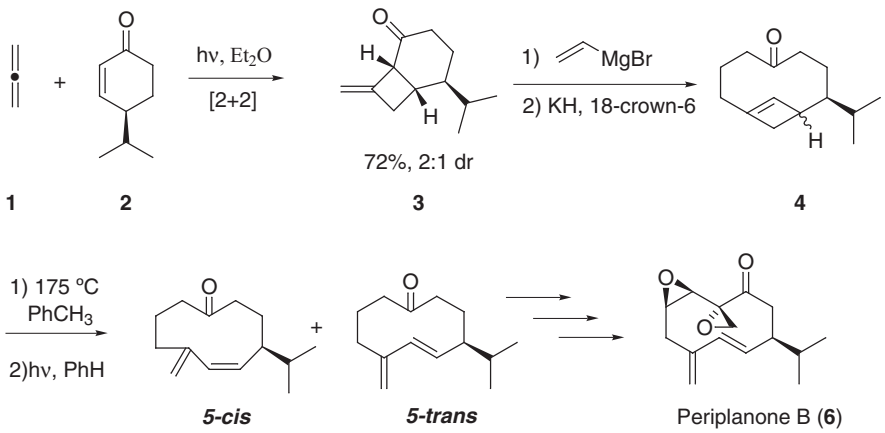
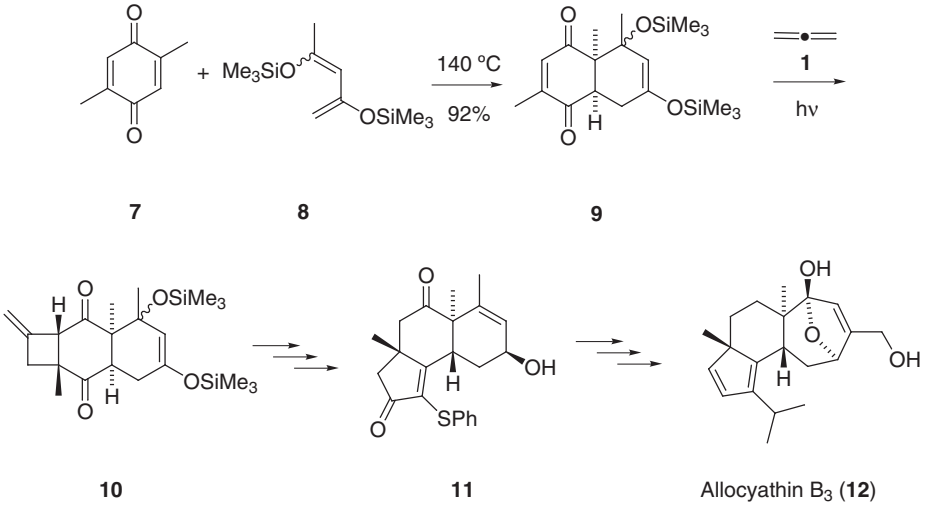
19.2.1
[2 + 2]-Cycloaddition Reactions

The power of the allenic photoinititated [2 + 2]-cycloaddition reaction has been elegantly demonstrated in Schreiber and Santini's total synthesis of periplanone B (**6**) (Scheme 19.1) [2]. Their synthesis began with a [2+2]-photocycloaddition between cyclohexenone **2** and 1,2-propadiene (**1**). Cycloadduct **3** was obtained as one regioisomer (head-to-head) but as a mixture of diastereomers (2:1). The low diastereomeric ratio was of no consequence since both diastereomers could be converted to compound **4**. Addition of vinylmagnesium bromide to ketone **3**, followed by KH and 18-crown-6, afforded an oxy-Cope rearrangement that gave the ring expansion product **4**. A thermal ring opening of the cyclobutene ring of **4** afforded a mixture of dienes, **5-*cis*** and **5-*trans***, which upon irradiation gave a 15:1 mixture favoring the desired **5-*trans*** in 75% yield. This diene was successfully converted to periplanone B (**6**). The allenic photocycloaddition step provided two new stereocenters and ultimately a bridgehead cyclobutene functionality that served as a latent 1,3-diene.



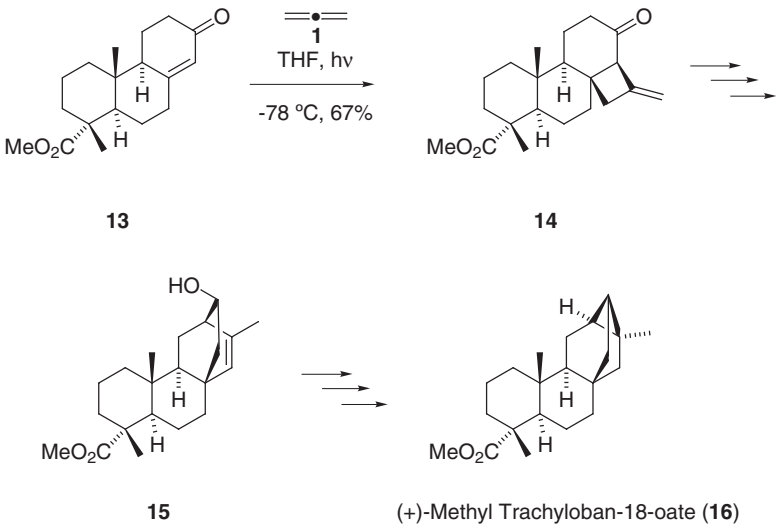
Scheme 19.1 Periplanone B.

A general approach to the cyathin diterpenes and a total synthesis of allocyathin B_3 (**12**) has been reported by Ward and co-workers and is depicted in Scheme 19.2 [3]. This unique approach involves a photo-initiated [2 + 2]-cycloaddition between the Diels–Alder adduct **9** (prepared from **7** and **8**) and 1,2-propadiene (**1**). The resulting [2 + 2]-cycloadduct **10** was obtained as a mixture of two regioisomers (4:1) with the desired one (head-to-head) predominating. Each regioisomer was obtained as a single stereoisomer as predicted by Wiesner and co-workers' empirical rule [4]. The methylidenecyclobutane group was used to convert **10** to the tricyclic compound **11** in four steps, which was eventually converted to the natural product **12**. The allenic [2 + 2]-cycloaddition provided a rapid and stereoselective assembly of the 6–5 ring system possessing a difficult angular methyl group.



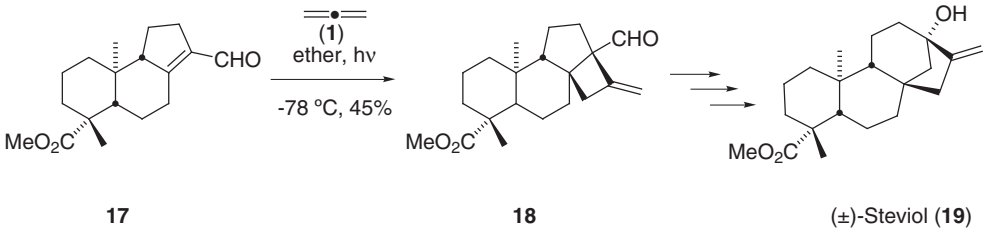
Scheme 19.2 Allocyathin B_3.

In Bettolo and co-workers' approach to (+)-methyl trachyloban-18-oate (**16**), enone **13** was subjected to a photocycloaddition with 1,2-propadiene (**1**) to afford the [2 + 2]-cycloadduct **14** as a single product in 67% yield (Scheme 19.3) [5]. The addition proceeded exclusively from the β-face. The resulting exocyclic olefin was eventually converted to a ketone using osmium tetroxide and $NaIO_4$ and taken on to **15**, constituting a formal total synthesis of **16**.



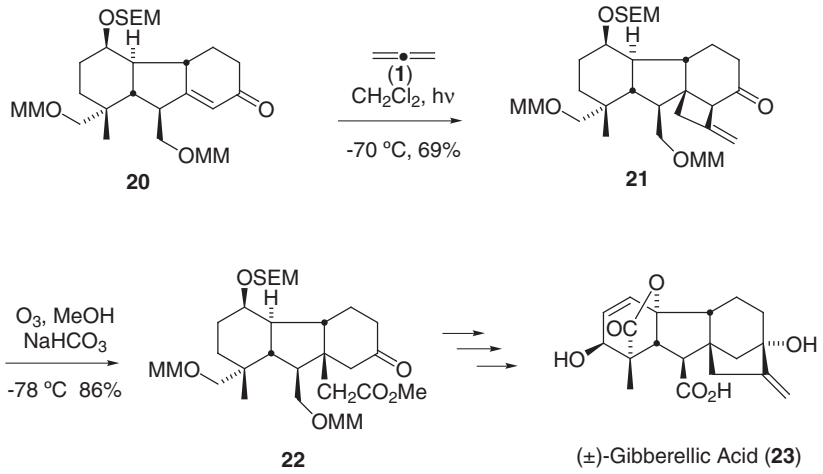
Scheme 19.3 A formal total synthesis of (+)-methyl trachyloban-18-oate.

In Ziegler and Kloek's synthesis of (±)-steviol methyl ester, irradiation of hydrindenal **17** and 1,2-propadiene (**1**) afforded the photocycloadduct **18** in 45% yield as a 14:1 mixture of diastereomers (Scheme 19.4) [6]. The major cycloadduct was subsequently converted to (±)-steviol methyl ester via a reduction of the aldehyde, followed by mesylation of the resulting alcohol and treatment with aqueous acetone in 2,6-lutidine. Unfortunately, steviol methyl ester **(19)** was obtained in only 3% yield.



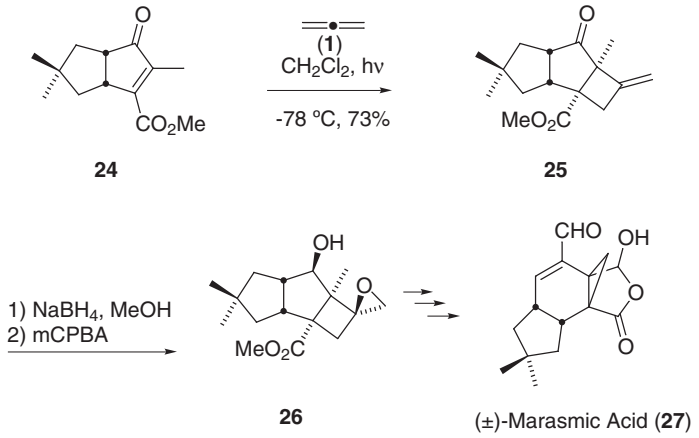
Scheme 19.4 (±)-Steviol methyl ester.

Yamada and co-workers reported stereoselective formation of the D-ring of gibberellic acid (**23**), which was accomplished via an allenic [2 + 2]-photocycloaddition between **1** and enone **20** (Scheme 19.5) [7]. The reaction occurred to give the cycloadduct **21** in 69% yield along with a 12% yield of a stereoisomer of **21**. The predominant isomer resulted from the reaction occurring from the less hindered face of the enone. Ozonolytic cleavage of **21** in the presence of methanol and $NaHCO_3$ provided the δ-keto ester **22** in 86% yield. This keto ester was taken on to complete the synthesis of (±)-gibberellic acid **(23)**.

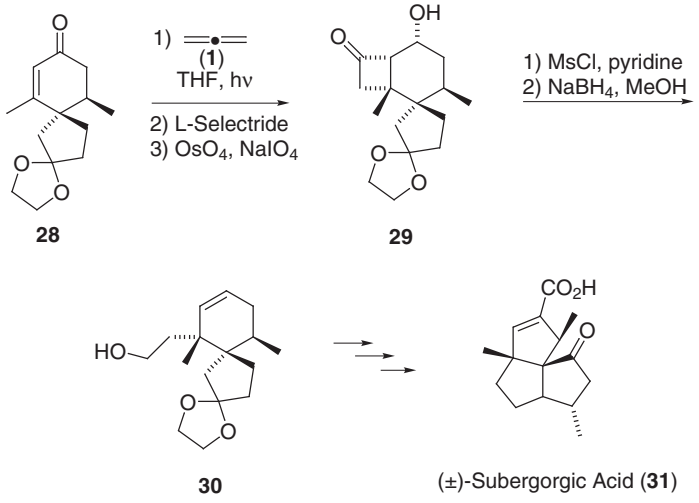


Scheme 19.5 (±)-Gibberellic acid.

The key intermediate in Tobe et al.'s synthesis of (±)-marasmic acid (**27**), 1-oxaspirohexane (**26**), was accessed via a photocycloaddition between enone **24** and **1** (Scheme 19.6) [8]. The photocycloadduct **25** was obtained in 73% yield with the desired isomer consisting of 91% of the material. The structure of the minor product obtained from this cycloaddition was not confirmed. Reduction of the carbonyl group of **25** and epoxidation of the exocyclic double bond gave **26**. An acid-catalyzed rearrangement of **26** afforded the core structure of marasmic acid and was subsequently taken on to complete the synthesis of this natural product.



Scheme 19.6 (±)-Marasmic acid.



Scheme 19.7 (±)-Subergorgic acid.

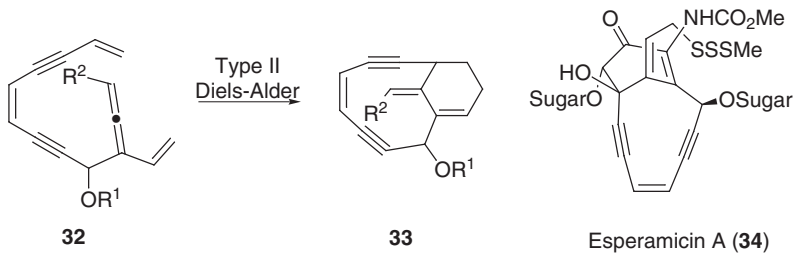
The angular triquinane (±)-subergorgic acid (**31**) was prepared by Iwata et al. from enone **28** and **1** (Scheme 19.7) [9]. The desired cycloadduct was obtained in 90% yield with only minor amounts of an unidentified product. Reduction of the carbonyl group and oxidative cleavage of the exocyclic double bond afforded **29**. Conversion of the hydroxyl group to a mesylate followed by treatment with $NaBH_4$ resulted in the formation of **30**, which was taken on to complete the synthesis of (±)-subergorgic acid (**31**). Interestingly, attempts to convert **28** directly to **30** by using a conjugate addition of an organometallic reagent or via an oxy-Cope rearrangement of the corresponding 1,2-addition product were not successful.

In summary, as can be seen in the examples depicted above, the resulting allenic [2 + 2]-photocycloadducts have been creatively transformed to a variety of functional groups appropriately positioned for conversion to biologically relevant compounds. In many cases, the stereoselectivities were good, although in most instances the minor by-products obtained during the cycloaddition were not characterized. Hence there is some uncertainty with regard to the structure of these minor by-products.

19.2.2 [4 + 2]-Cycloadditions

19.2.2.1 Allene as Diene Component

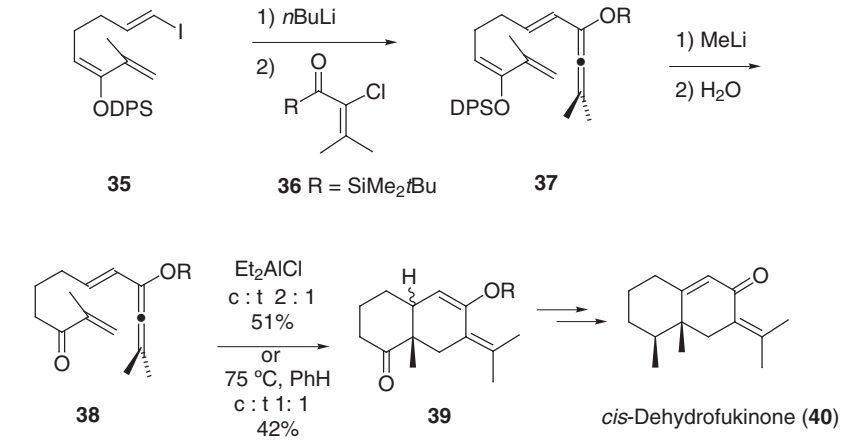
The use of vinylallenes as the diene component in Diels–Alder reactions is very common, thus resulting in their ubiquitous use in natural product synthesis. A vinylallene has even been proposed by Schreiber and Kiessling [10] as a biogenetic intermediate in the synthesis of the skeleton of esperamicin A (**32** → **33**). Their synthetic approach to esperamicin A (**34**) was modeled after this biogenetic proposal in which a Type II intramolecular Diels–Alder cycloaddition was used to gain access to the highly unsaturated bicyclic core of **34** (Scheme 19.8) [10].



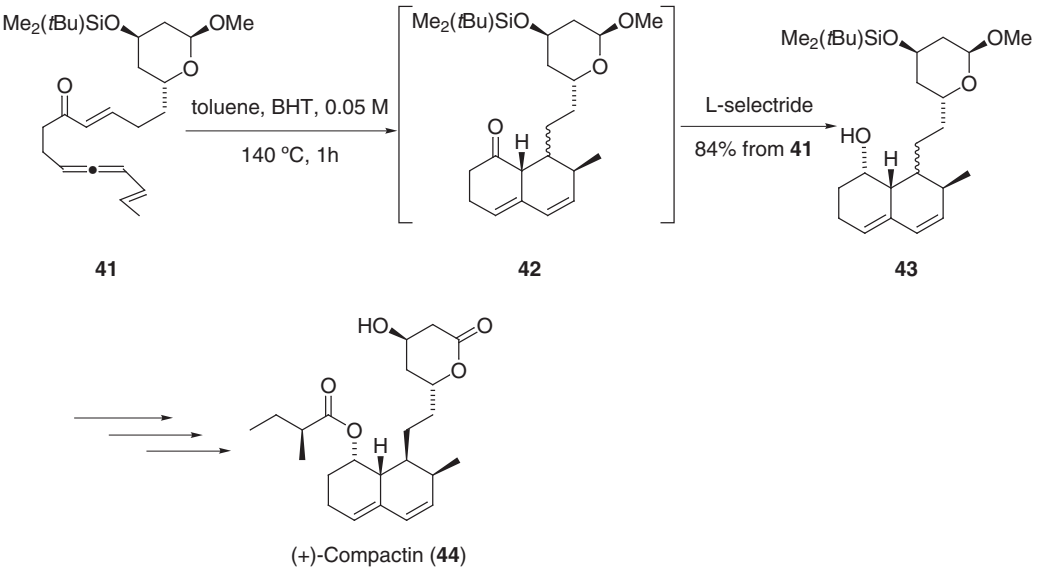
32 **33** Esperamicin A (**34**)

Scheme 19.8 Allenes proposed as biogenetic origins.

Reich et al. have shown that siloxyvinylallenes can be prepared in two ways and one of these methods was utilized in the synthesis of *cis*-dehydrofukinone (**40**) (Scheme 19.9) [11]. Addition of the vinyllitium reagent derived from **35** to the α-chloroacylsilane **36** resulted in the formation of vinylallene **37** via a Brook rearrangement. Exposure of **37** to methyllithium afforded a selective cleavage of the dimethylphenyl silyl ether to give **38**. Enone **38** was reportedly unstable and taken on directly to the Diels–Alder reaction to give a 51% yield of **39**. Lewis acid catalysis or thermal



Scheme 19.9 *cis*-Dehydrofukinone.



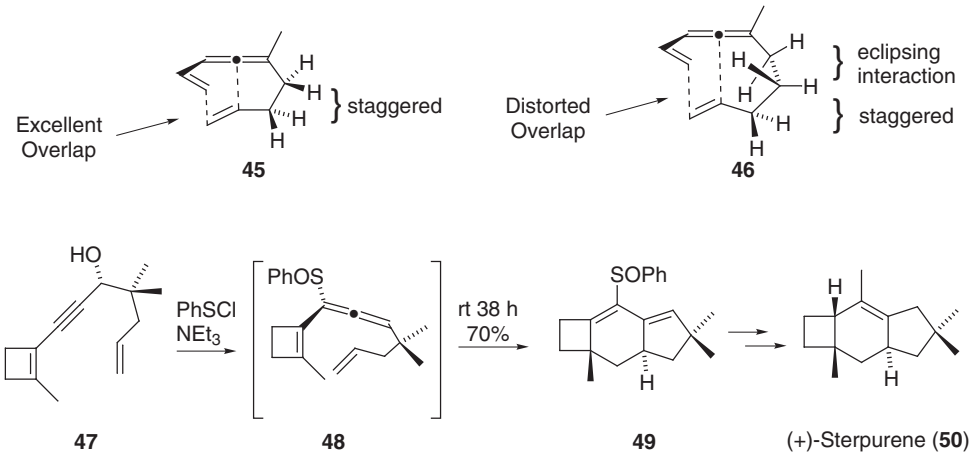
Scheme 19.10 A convergent synthesis of (+)-compactin.

conditions were used to effect the Diels–Alder reaction. Cycloadduct **39** was subsequently converted to **40**.

A well-designed synthesis of the bottom portion of (+)-compactin (**44**) was reported by Keck and Kachensky using a vinylallene as the diene in an intramolecular Diels–Alder reaction (Scheme 19.10) [12]. This was done at a time when there was very little literature precedent on the use of vinylallenes as dienes. Based on examination of molecular models, it was reasoned that the transition state for the

Diels–Alder reaction of **41** would adopt a conformation to give only the *exo* cycloaddition product. The *endo* cycloaddition mode could occur only if the C=C and C=O bonds of the enone exist at a 90° angle. As a result, the *trans* double bond geometry of the vinylallene was necessary to arrive at the correct relative stereochemistry of (+)-compactin (**44**), thus avoiding a *cis* double bond geometry that is known to participate in 1,5-hydrogen migrations. Heating the Diels–Alder precursor **41** at 140 °C for 1 h in toluene in the presence of BHT afforded the presumed intermediate **42**, which was immediately subjected to reduction conditions so as to inhibit the formation of a conjugated enone. The highly functionalized decalin **43** was obtained as a 1:1 mixture of diastereomers in 84% yield from **41**. The diastereomers were separated and, since the relative stereochemistry was unknown at this point, both diastereomers were advanced through the synthetic sequence independently. One of these compounds matched the spectral data of (+)-compactin (**44**) exactly.

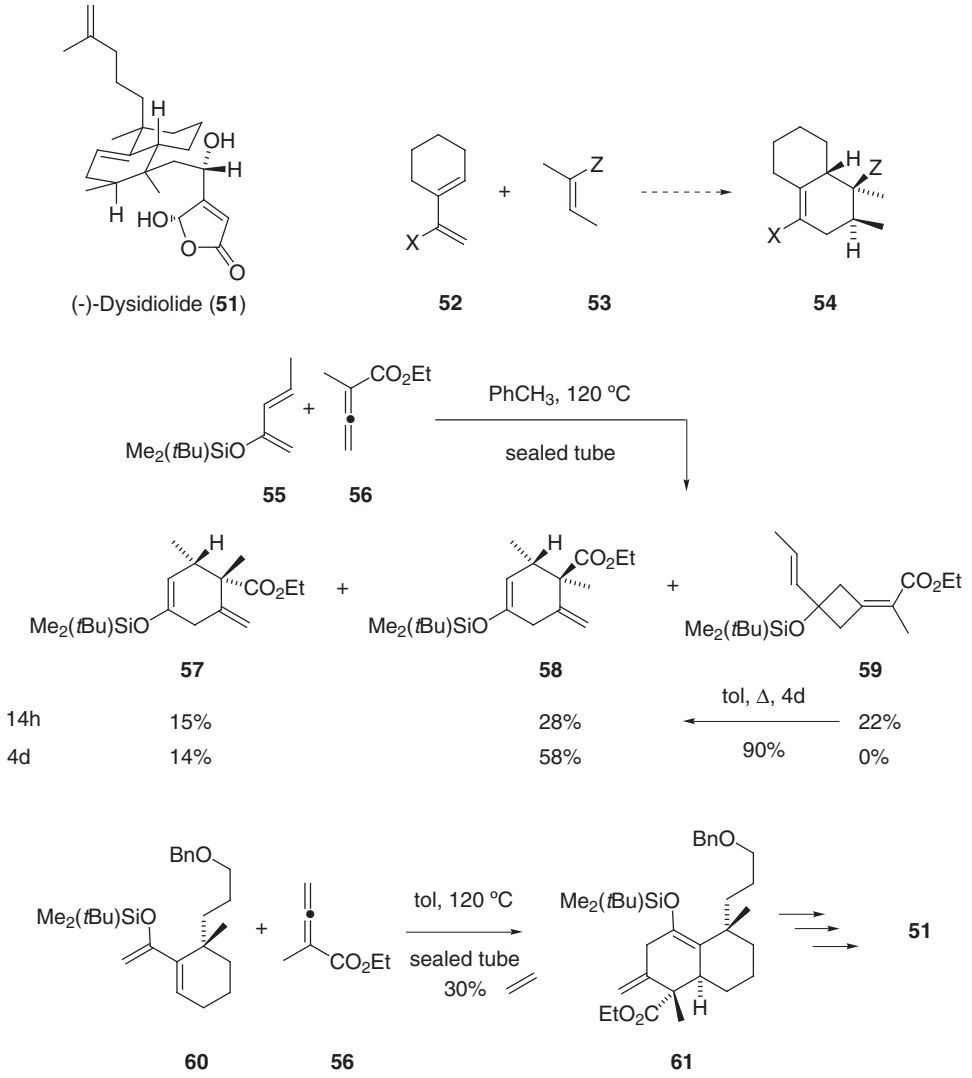
Okamura and co-workers have also taken advantage of the vinylallene group in a total synthesis of (+)-sterpurene (**50**) [13]. A chiral non-racemic allene was assembled and shown to transfer chiral information to an sp^3-hybridized carbon. This demonstrated for the first time a central–axial–central chiral element transfer process in the context of natural product synthesis. Moreover, they predicted that the intramolecular Diels–Alder reaction of **45** should be considerably faster than that of **46**. This reasoning was based on examination of molecular models, showing **46** to possess eclipsing interactions and distorted overlap between the diene and the dienophile. Treament of propargyl alcohol **47** with benzenesulfinyl chloride afforded vinylallene **48**. Cycloaddition of **48** to give **49** was exceedingly facile at room temperature with a half-life of 12.4 h. The sulfoxide was removed from **49** and the resulting compound converted to (+)-sterpurene (**50**). The Diels–Alder reaction was highly enantio- and diastereoselective. A systematic study reported in the paper showed that the facile Diels–Alder reaction had very little to do with the *gem*-dimethyl group, but that the pronounced reactivity depended on the tether length, the allene and the sulfoxide groups.



Scheme 19.11 (+)-Sterpurene.

19.2.2.2 **Allene as Dienophile Component**

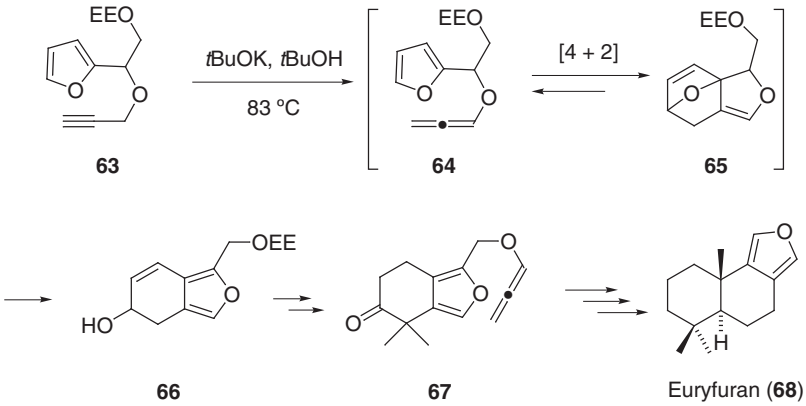
In an approach by Jung and Nishimura, the assembly of the dysidiolide decalin skeleton **54** was deemed possible via an intermolecular Diels–Alder reaction between cyclohexene **52** and dienophile **53** [14]. Based on precedent established by Wulff et al. [15] [where $Z = C(OCH_3)=Cr(CO)_5$], the cycloaddition should give predominantly the *exo* isomer as shown (Scheme 19.12). However, all attempts to effect the cycloaddition simply gave recovery of starting material. It was reasoned that steric hindrance was to blame. The steric hindrance associated with the dienophile was decreased by replacing one of the methyl groups with another double bond in the



Scheme 19.12 (–)-Dysidiolide.

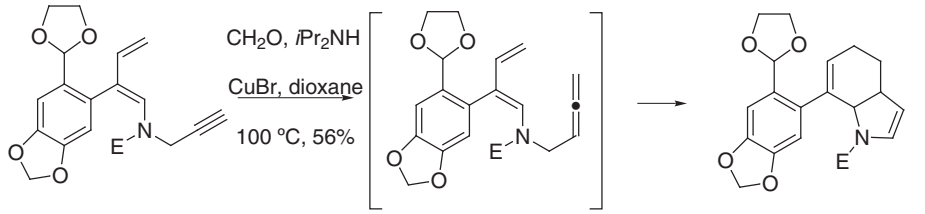
form of an allene. A model study was performed showing that a cycloaddition between diene **55** and allenic ester **56** afforded a mixture of the *endo* and *exo* Diels–Alder adducts and the [2 + 2]-cycloadduct, **57**, **58** and **59**, respectively. Interestingly, if the reaction mixture is heated for 4 days in toluene, rearrangement of the [2 + 2]-cycloadduct **59** occurs to give the *exo* Diels–Alder adduct **58**. Fully functionalized cyclohexene **60** was used in the Diels–Alder reaction to give six distinct compounds with the desired *exo* stereoisomer **61** isolated in 30% yield. Compound **61** was then transformed to an intermediate that constituted a formal total synthesis of (–)-dysidiolide (**51**).

Euryfuran (**68**) is a natural product possessing a 3,4-disubstituted furan ring, a substitution pattern that remains a synthetic challenge. Kanematsu and Soejims have effected a furan ring transfer reaction to access this general substructure (Scheme 19.13) [16]. Compound **63**, when heated with potassium *tert*-butoxide, afforded the isomerization product **64**. This allene then underwent a spontaneous intramolecular Diels–Alder reaction at 83 °C to give furan **65**. Next, the potassium *tert*-butoxide initiates a ring opening of **65** to give the furan transfer product **66**. Repeating this process by way of allene **67** affords the target **68**.

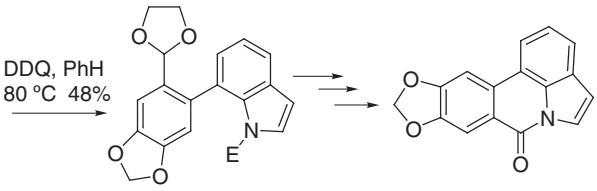


Scheme 19.13 Euryfuran via a sequential furan ring transfer.

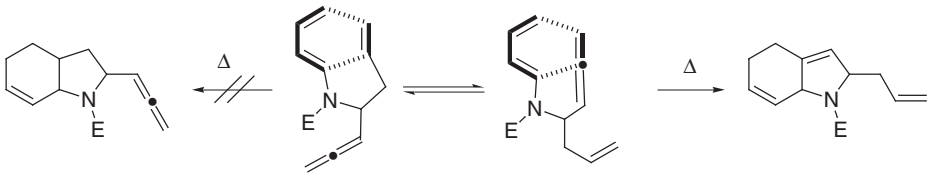
Kanematsu and co-workers have shown that this intramolecular allenic cycloaddition can be applied to the preparation of another very interesting class of heterocycles, the indoles [17]. Propargyl dienamide **69** was prepared and subjected to Crabbé's homologative allenylation (Scheme 19.14). The resulting allene **70** underwent a spontaneous Diels–Alder reaction to afford the cycloadduct **71** in 56% yield. Dehydrogenation using DDQ gave the desired indole **72**, which was subsequently converted to the natural product hippadine (**73**). Interestingly, with cycloeduct **75** possessing an olefinic dienophile and an allene, cycloaddition occurred exclusively with the allene to give **76** and none of **74** [18].



69 E = $CO_2CH_2CH_2Cl$ **70** **71**

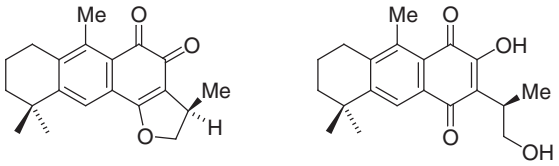


72 Hippadine (**73**)

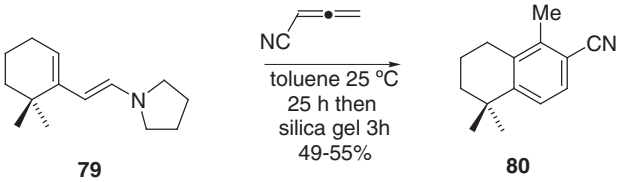


74 E = CO_2Et **75** **76**

Scheme 19.14 The total synthesis of hippadine.



Aegyptinone A (**77**) Aegyptinone B (**78**)

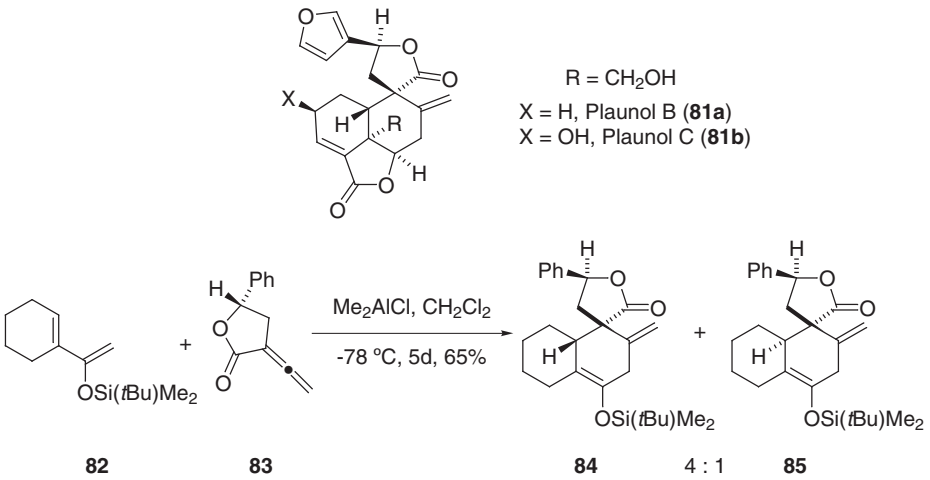


79 **80**

Scheme 19.15 Aegyptinone A and B.

Assembly of aegyptinone A (**77**) and B (**78**) by Danheiser et al. was facilitated by a benzannulation strategy using cyanoallene and diene **79**, which gave good yields of the benzonitrile **80** (Scheme 19.15) [19]. Attempts to effect the desired benzannulation process using 3-pentyn-2-one and methyl butynoate gave either no product or low yields.

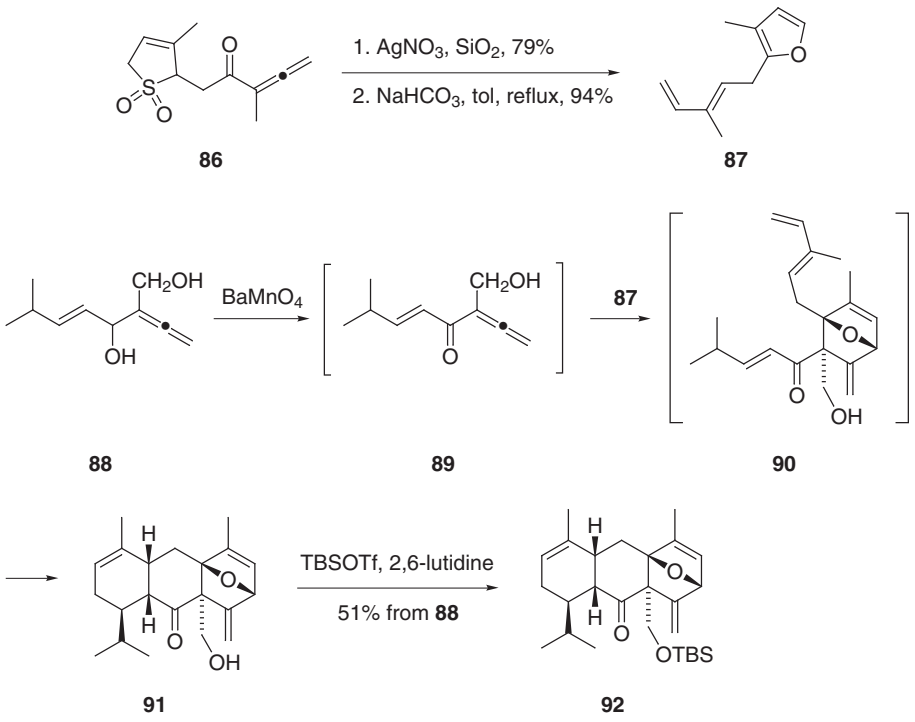
The key reaction in Jung et al.'s proposed assembly of Plaunol B (**81a**) and C (**81b**) was an intermolecular Diels–Alder reaction between a diene and an allenic lactone that should give the *exo*-methylene group in the natural product (Scheme 19.16) [20]. The phenyl-substituted lactone **83** was prepared as a model for the eventual furan lactone of the plaunols. Cycloaddition of **82** possessing a TBS enol ether and **83** using dimethylaluminum chloride gave a 65% yield of the *endo* and *exo* isomers **84** and **85** in a 4:1 ratio. The reaction proceeded with excellent stereodifferentiation with the diene approaching the phenyl-substituted allenic lactone away from the phenyl group.



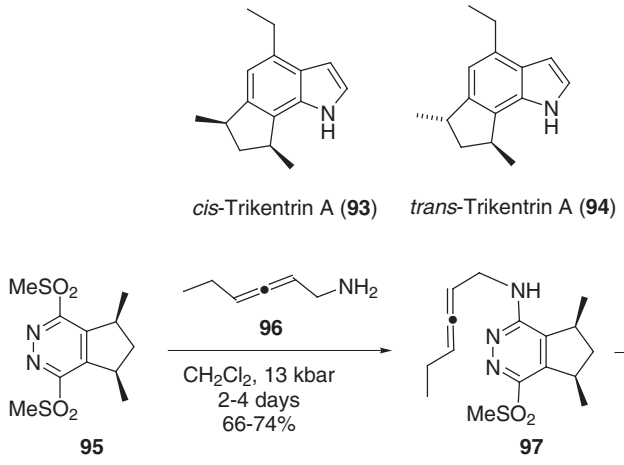
Scheme 19.16 Synthetic approach to plaunol B and C.

In an approach to eleutherobin by Winkler et al., a tandem Diels–Alder approach was investigated (Scheme 19.17) [21]. The required diene component **87** was assembled from the allene **86** using a Marshall protocol. The dienophile component was obtained from the diol **88**, which upon oxidation presumably afforded **89**, which was not isolated but treated immediately with diene **87**. Warming a neat mixture of **87** and **89** to 50 °C gave the tandem Diels–Alder cycloaddition product **91**, presumably via the intermediate **90**. In situ protection of the resulting alcohol **91** was applied to give the cycloadduct **92** as a single steroisomer in 51% overall yield from the diol **88**. The tandem process involves four chemical reactions, formation of three new rings and the creation of six stereogenic centers.

Boger and Zhang's assembly of the intramolecular Diels–Alder adduct **97** is carried out by reacting 1,2-diazine **95** and allene **96** at high pressure for an extended time (Scheme 19.18) [22]. On heating to 120 °C, an intramolecular Diels–Alder reac-

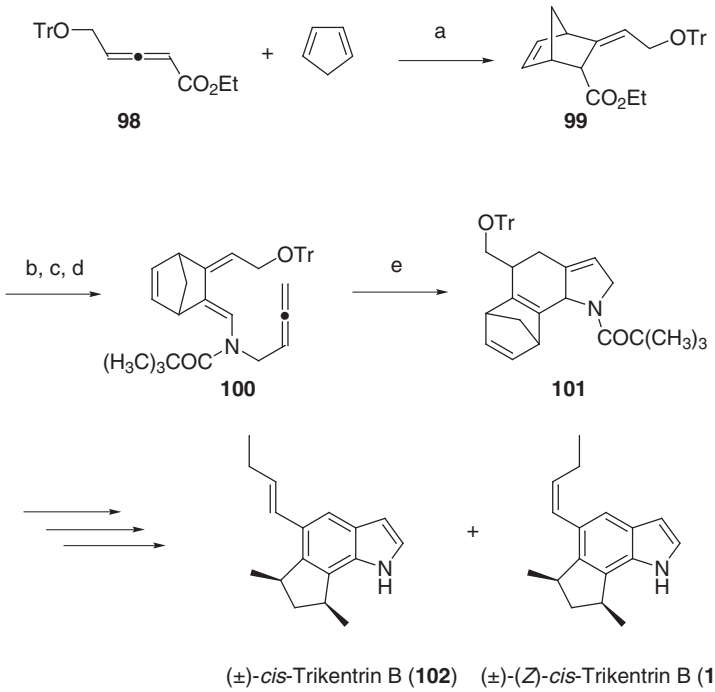


Scheme 19.17 A tandem Diels–Alder approach to eleutherobin.



Scheme 19.18 (±)-*cis*-Trikentrin A.

tion proceeds between the allene and heteroaromatic 1,2-diazine of **97**. The cycloadduct is not isolated but spontaneously undergoes a retro-Diels–Alder reaction with loss of nitrogen followed by thermal isomerization to the pyrrole then elimination of methanesulfinic acid to give the indole of (±)-*cis*-trikentrin A (**93**) directly. The use of an allene as the dienophile over an alkene or an alkyne allowed the Diels–Alder cycloaddition to be carried out under much milder conditions (90–160 °C). The corresponding alkenyl system required temperatures of 190 °C and the alkyne 220–230 °C.

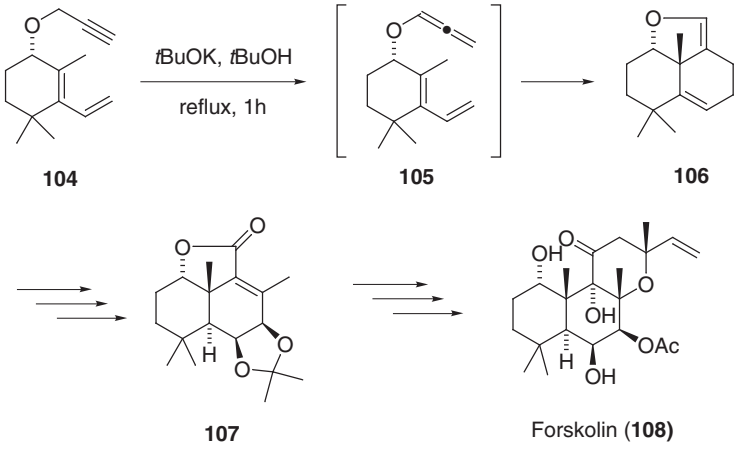


Scheme 19.19 (±)-*cis*-Trikentrin B. (a) Benzene, 80 °C, 3 h, 93%;
(b) (1) $LiAlH_4$, THF, 0 °C, 1 h; (2) PCC, CH_2Cl_2, 30 min, 78%;
(c) (1) propargylamine, 4 Å molecular sieves, diethyl ether, 3 h;
(2) NaH, DME, –18 °C, 10 min; (3) $(CH_3)_3CCOCl$, –18 °C to r.t. (45%);
(d) HCHO, iPr_2NH, CuBr, 1,4-dioxane, 101 °C, 5 h, 79%; (e) toluene, 160 °C, 2 h, 74%.

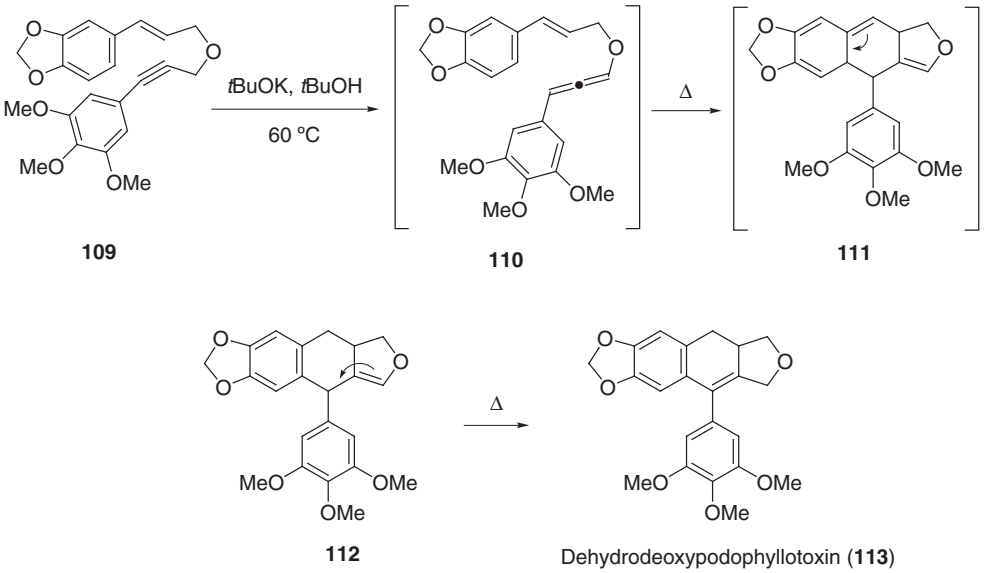
A synthesis of (±)-*cis*-trikentrin B has also been accomplished by Yasukouchi and Kanematsu using an intramolecular Diels–Alder reaction of a trisubstituted allenic dienamide (Scheme 19.19) [23]. The requisite dienamide **100** was prepared by a three-step protocol. First, an intermolecular Diels–Alder reaction between cyclopentadiene and ester **98** was effected to give **99**. Next, the ester **99** was converted to an aldehyde, then the aldehyde was treated with propargyl amine to give the enamide. Conversion of the propargyl group to the desired allene gave the intramolecular Diels–Alder precursor **100**. Heating this compound to 160 °C in toluene for 2 h gave the cycloadduct **101**. The diastereomeric ratio was not reported since the next step involved oxidation of the tetrahydroindole ring system to a substituted indole. Compound **101**

was then converted to the target substrate (±)-(*E*)-*cis*-trikentrin B (**102**) and (±)-(*Z*)-*cis*-trikentrin B (**103**), thus demonstrating a novel route to the synthesis of indoles.

An enantioselective synthesis of the Ziegler intermediate **107** of forskolin (**108**) has been achieved using an intramolecular allenic Diels–Alder reaction (Scheme 19.20) [24]. Treatment of propargyl ether **104** with potassium *tert*-butoxide in *tert*-butanol affords **106**, presumably through the intermediate allene **105**. Compound **106** was obtained as a single stereoisomer.



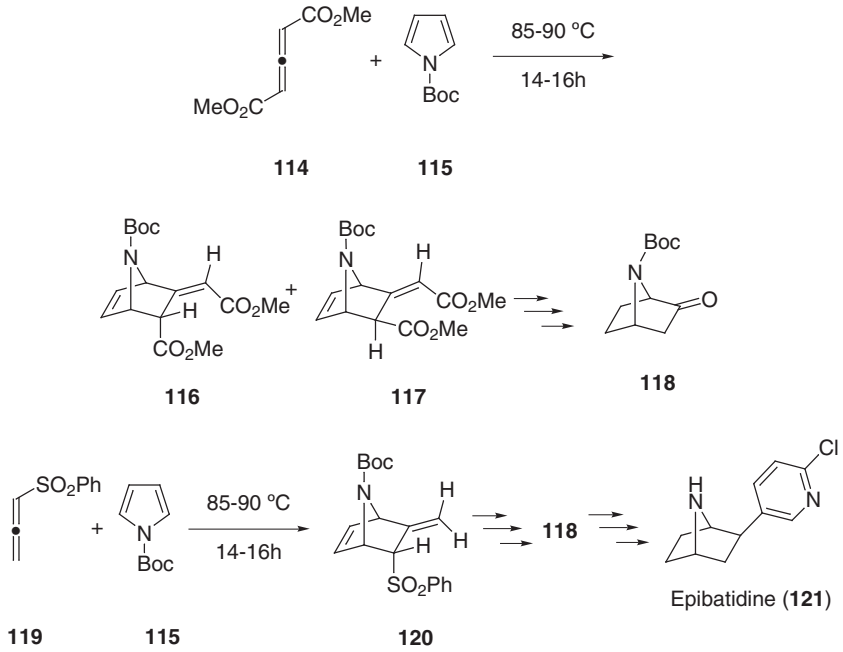
Scheme 19.20 Forskolin.



Scheme 19.21 Dehydrodeoxypodophyllotoxin.

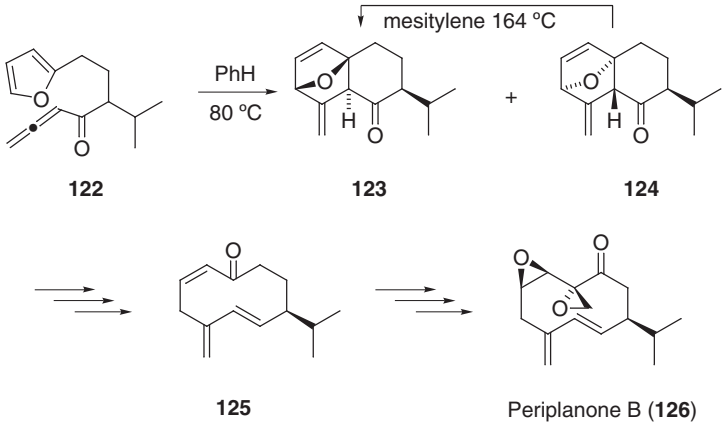
Lignans have been accessed using an intramolecular allenic Diels–Alder reaction (Scheme 19.21). Alkyne **109** was treated with potassium *tert*-butoxide at 60 °C to afford a mixture of **112** and **113** via intermediates **110** and **111** [25]. Cycloadduct **112** could eventually be transferred to isomer **113** at room temperature by way of a second sigmatropic hydrogen shift.

It had been previously reported that allenic esters undergo [4 + 2]-cycloaddition reactions with *N*-acylpyrroles and Pavri and Trudell investigated this route as an approach to epibatidine (**121**) [26]. The reaction between **114** and **115** required 14–16 h and heating (85–90 °C) (Scheme 19.22). Only two of the possible four isomers were obtained, where the *exo* isomer predominated slightly (**116**:**117** = 2:3). The resulting *endo* isomer **116** could be converted to an intermediate **118** that had previously been taken on to epibatidine (**121**) by many groups. Unfortunately, the *exo* isomer **117** could not be further manuipulated in such a way. Alternatively, a Diels–Alder reaction between 1-(benzenesulfonyl)-1,2-propadiene (**119**) and **115** gave the cycloadduct **120** in 45% yield as the sole product. Hydrogenation, ozonolysis and reductive removal of the benzenesulfonyl group gave the ketone **118** in 19% overall yield, which proved to be much more efficient and higher yielding than the allenic ester sequence. Interestingly, Node et al. were able to convert the corresponding *endo*-menthyl ester of **116** to ketone **118** [27].



Scheme 19.22 A formal synthesis of (±)-epibatidine.

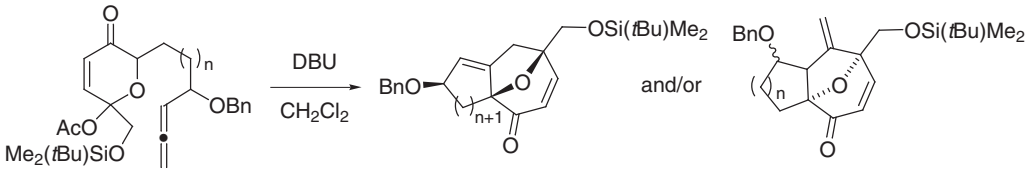
In another approach to periplanone B by Cauwberghs and De Clercq, an intramolecular Diels–Alder reaction of furan-allene **122** afforded a mixture of two *exo* adducts **123** and **124** and an *endo* adduct (not pictured) in 90% yield and a 5:4:1 ratio (Scheme 19.23) [28]. Refluxing the mixture in mesitylene (N_2, 164 °C) afforded a 2:1 equilibrium mixture of **123–124** through a cycloreversion process. The Diels–Alder adduct **123** was converted to **125** via a series of synthetic manipulations, which constituted a formal total synthesis of periplanone B (**126**).



Scheme 19.23 Periplanone B.

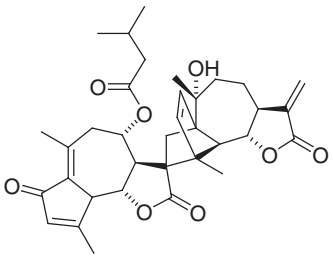
19.2.3
[5 + 2]-Cycloaddition Reactions

Intramolecular [5 + 2]-cycloaddition reactions between oxidopyrylium ions and allenes were examined by Lee with the incentive being its application to the synthesis of arteminolide (**130**) [29]. For each of the substrates shown in Scheme 19.24, only the tether length was varied. For **127a**, containing only a two-carbon tether, the cycloaddition took place with only the distal double bond of the allene to afford **128a** as a single diastereomer in 81% yield. When the tether length was increased to three carbons, the reaction of **127b** took place with only the proximal double bond to afford **129b** as a 2:1 mixture of diastereomers in 45% yield. Increasing the tether length to four carbons gave no cycloadduct. Intermolecular cycloaddition reactions were also examined but the products were obtained in low to moderate yields and only when electron-releasing substituents were present on the allene group.



127a-c **128a-c** **129a-c**

Substrate	n	product (yield)
127a	0	**128a** (81%)
127b	1	**129b** (45%); dr (α:β = 1:2)
127c	2	no cycloadduct obtained



Arteminolide (**130**)

Scheme 19.24 Arteminolide.

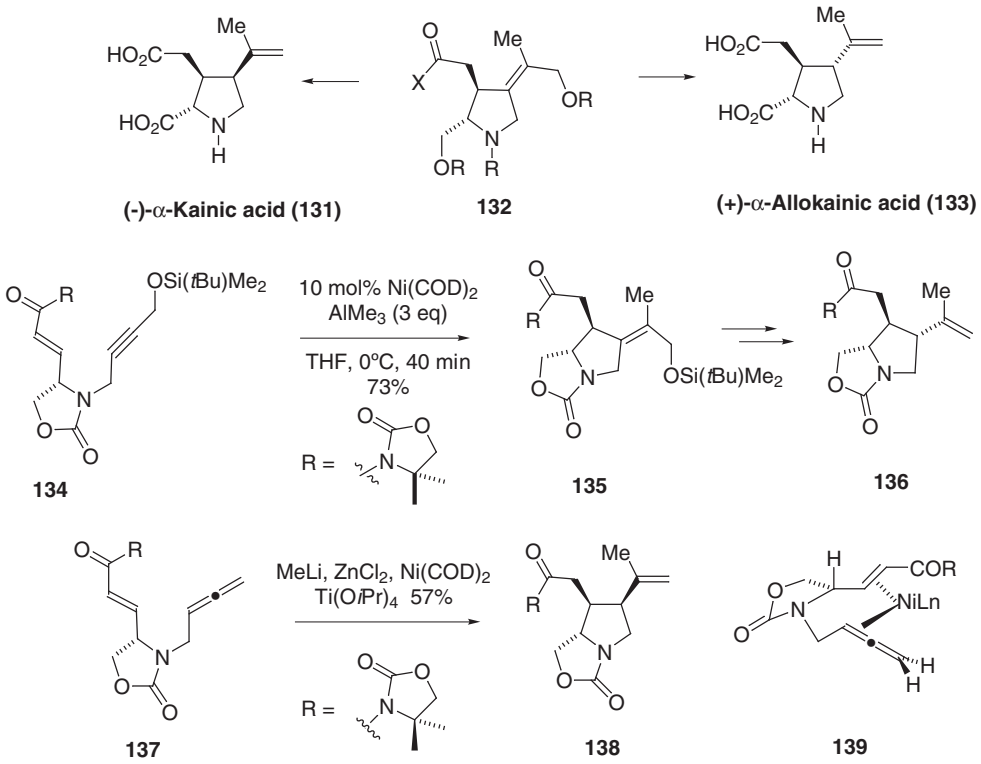
As evidenced by the many examples in Section 19.2, [2 + 2]- and [4 + 2]-cycloaddition reactions are by far the most common application of allenes in natural product synthesis. Far less common is the use of allenes in transition metal-catalyzed carbon–carbon bond-forming reactions, the topic of Section 19.3.

19.3 Transition Metal-Catalyzed Cycloadditions

Transition metal-catalyzed carbon–carbon bond-forming reactions have revolutionized strategies used to assemble complex organic structures from unsaturated precursors. However, the use of allenes in these processes have been slower in coming. There are many reasons for this but one factor that plays a major role in this dearth of activity is the selectivity factor associated with an allene [30]. For example, when performing a reaction with an allene, one must control regioselectivity, stereoselectivity, chemoselectivity and constitutional group selectivity. Hence control of elements leading to a single product can sometimes be a daunting task.

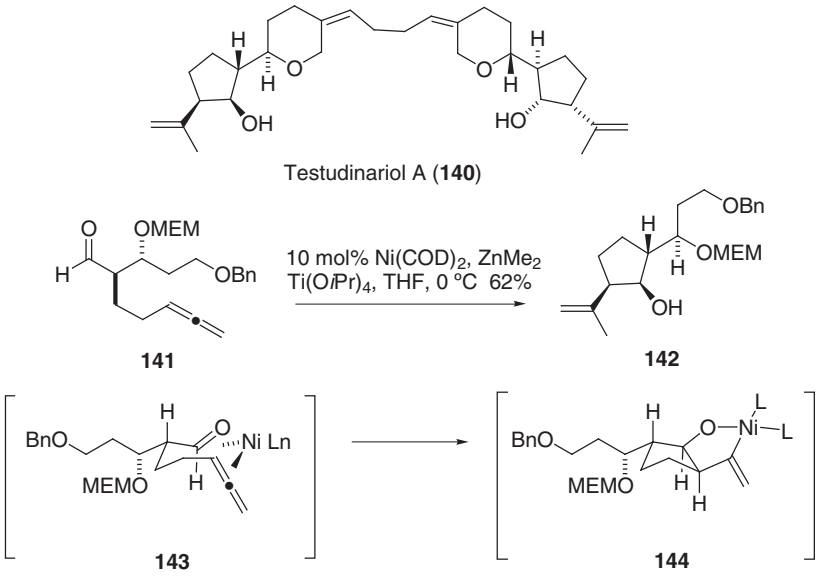
In many cases, allenes are used as creative solutions to problems encountered using more saturated counterparts. This is the situation in Chevliakov and Montgomery's approach to (–)-α-kainic acid (**131**) [31]. They reported a late-stage common intermediate **132** that could be taken on to both (–)-α-kainic acid (**131**) and (+)-α-allokainic acid (**133**) (Scheme 19.25). Intermediate **132** was to be obtained from enyne **134**. Indeed, treatment of **134** to conditions developed in their laboratories afforded the desired carboannulation to give **135**. However, this pyrrole could only be taken on to (+)-α-allokainic acid (**133**) owing to reduction of the olefin affording

the all-*trans* stereochemical relationship of the three pyrrolidine substitutents of **136**. Due to severe $A^{1,3}$ strain associated with the exocyclic double bond, the reduction could not be effected to give the desired stereochemistry for conversion to α-kainic acid. It was subsequently reasoned that replacement of the alkyne in **134** with an allene would give the carbocyclization with the correct stereochemistry of α-kainic acid directly. Treatment of **137** under nickel-catalyzed conditions indeed gave a 57% yield of **138** as a single stereoisomer. Transition-state structure **139** was proposed to explain the stereochemistry obtained. Compound **138** was subsequently taken on to (–)-α-kainic acid (**131**).



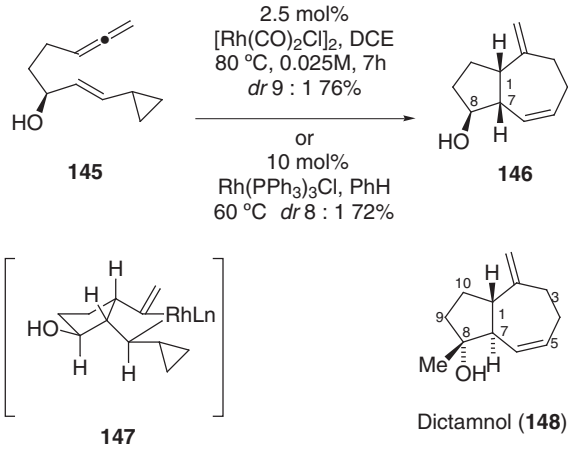
Scheme 19.25 (–)-α-Kainic acid and (+)-α-allokainic acid.

Amarasinghe and Montgomery have extended the scope of this reaction further by showing that allenylaldehydes also cyclize under the nickel-catalyzed conditions. They elegantly applied this synthetic strategy to the total synthesis of (+)-testudinariol A (**140**) [32]. Substrate **141** was reacted with dimethylzinc, titanium isopropoxide and 10 mol% $Ni(COD)_2$ in THF (Scheme 19.26). The carbocyclization proceeded in 62% yield to give **142** with 97% diastereoselectivity. The high diastereoselectivity is attributed to the transition-state structures **143** and **144** with the side chain in the pseudo-equatorial position.

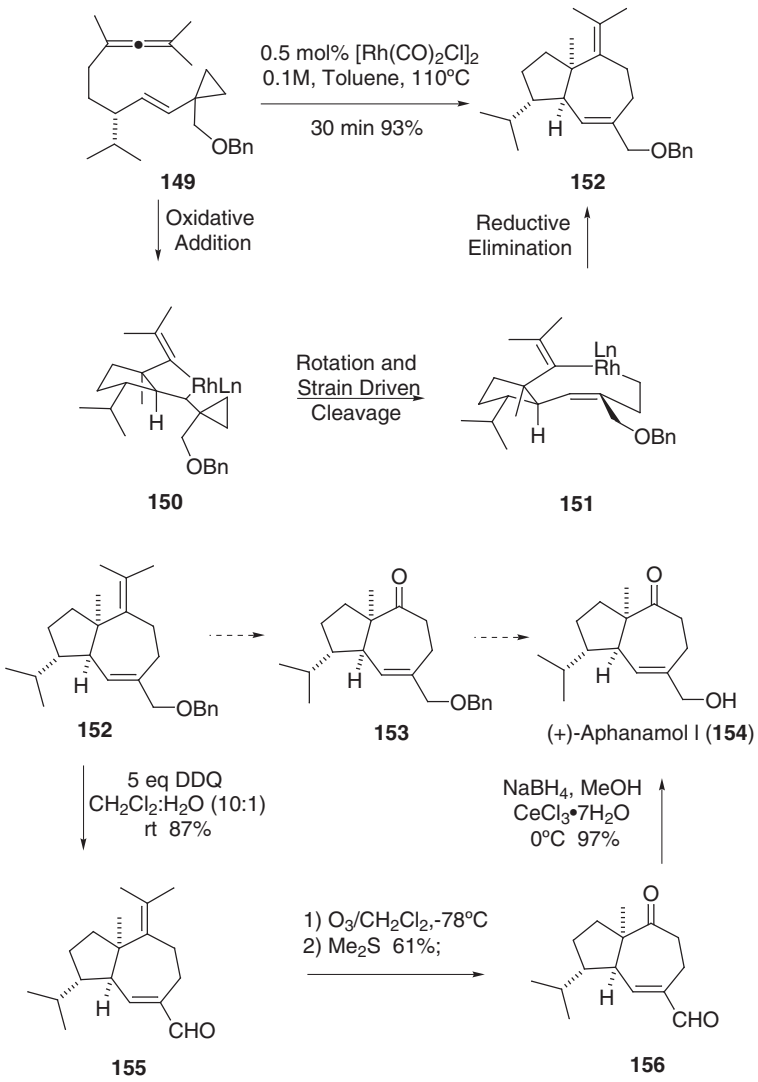


Scheme 19.26 (+)-Testudinariol A.

Wender et al. have demonstrated the power of the rhodium-catalyzed [5 + 2]-cycloaddition reaction discovered in their laboratories by synthesizing (+)-dictamnol (**148**) [33]. Allenylvinylcyclopropane **145** was treated with rhodium biscarbonyl chloride dimer or rhodium tris(triphenylphosphine) chloride (Scheme 19.27). Both catalysts provided the cycloadduct **146** in 70–76% yield and high diastereoselectivity (8–9:1). The diastereoselectivity was attributed to the C8 hydroxyl group assuming a position on the less sterically encumbered *exo* face of the transition-state structure **147**.



Scheme 19.27 (+)-Dictamnol.

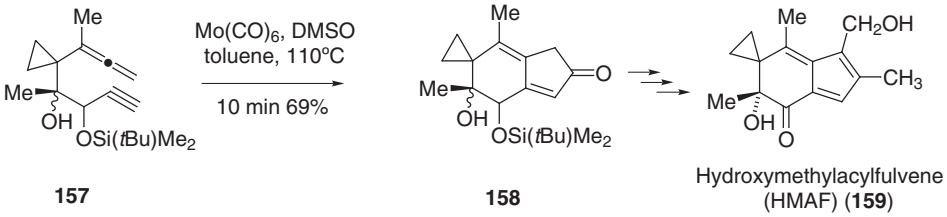


Scheme 19.28 (+)-Aphanamol I.

Wender et al.'s [5 + 2] metal-catalyzed annulation strategy has also been applied to the total synthesis of (+)-aphanamol I (**154**) [34]. The scope of this method was expanded by using a tetrasubstituted allene that resulted in the stereoselective formation of an angular methyl group. The reaction of allene **149** with 0.5 mol% of rhodium biscarbonyl choride dimer afforded the fused bicyclic product **152** in 93% yield with complete *exo*/*endo* and diastereoselectivity (Scheme 19.28). The stereoselectivity of this process was attributed to a preference for formation of the *cis*-fused metallo-

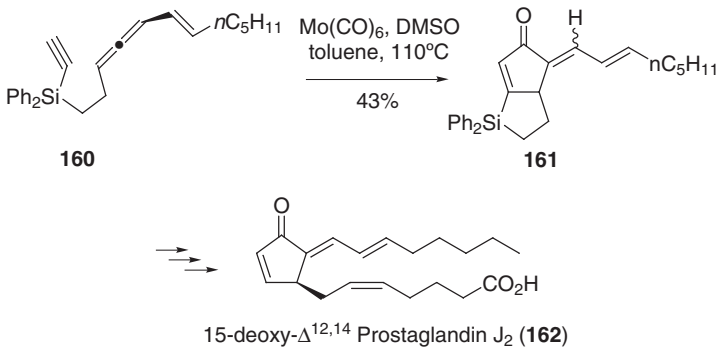
bicyclic intermediate **150** with the large isopropyl group on the sterically less encumbered *exo* face. Rotation and cleavage of the vinylcyclopropane affords the rhodium metallocycle **151** that undergoes a reductive elimination to give **152**. Attempts to ozonize the more substituted double bond directly to give **153** was not successful, so the allyl ether of **152** was deprotected and the hydroxyl group oxidized to give an α,β-unsaturated aldehyde **155**. The two double bonds of **155** were now easily differentiated chemically to give **156**, which was then converted to (+)-aphanamol I (**154**).

The potent antitumor agent hydroxymethylacylfulvene (**159**) was assembled by Brummond and co-workers in 11 steps from 2,4-pentanedione using an allenic Pauson–Khand carbocyclization strategy (Scheme 19.29) [35]. Alkynyl allene **157** was treated with molybdenum hexacarbonyl and dimethyl sulfoxide, affording the 6–5 bicyclic ring system **158** that was readily converted to the functionalized fulvene of **159**. An allene group was beneficial to the synthesis of HMAF since six-membered rings can be difficult to obtain via the Pauson–Khand reaction of an alkynylalkene.



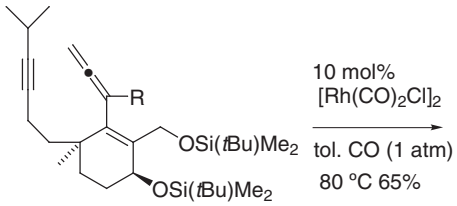
Scheme 19.29 Hydroxymethylacylfulvene.

In a similar manner, Brummond et al. demonstrated the first total synthesis of 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (**162**) that was completed using a silicon-tethered allenic Pauson–Khand reaction to obtain the highly unsaturated cyclopentenone substructure [36]. Treatment of alkynylallene **160** with molybdenum hexacarbonyl and dimethyl sulfoxide affords the desired cycloadduct **161** in 43% yield (Scheme 19.30). Trienone **161** was obtained as a 2:1 *Z*:*E* mixture of isomers in which the *Z*-isomer could be isomerized to the desired *E*-isomer. The silicon tether was cleaved and the resulting product converted to 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (**162**).

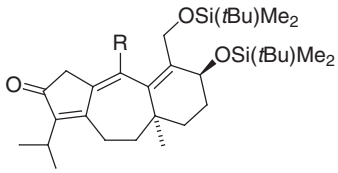


Scheme 19.30 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2.

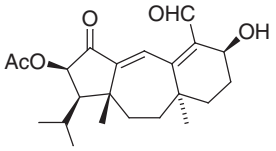
An interesting reversal in the π-bond selectivity of an allene in the allenic Pauson–Khand reaction has also been uncovered by Brummond's group. Using an Rh(I) catalyst in an intramolecular CO insertion, reaction always occurs with the distal double bond of the allene, even to yield seven-membered rings [37]. This result has subsequently been applied in an approach to guanacastepene A (**165**) (Scheme 19.31). Alkynylallene **163** cyclizes in the presence of 10 mol% rhodium biscarbonyl choride dimer to give a 65% yield of the tricyclic ring system **164**, possessing the core structure of guanacastepene A (Scheme 19.31) [38]. The allene group was required to effect the formation of the seven-membered ring.



163 R = $SiMe_2Ph$



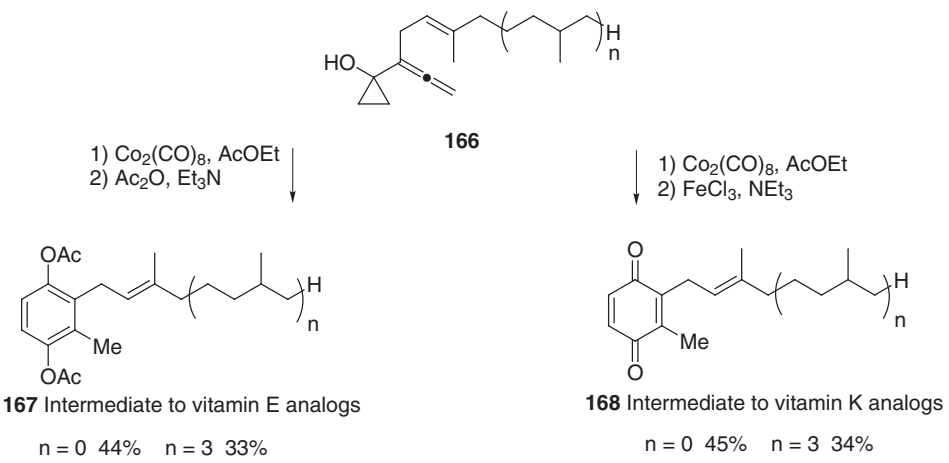
164



Guanacastepene A (**165**)

Scheme 19.31 Guanacastepene A.

Analogous to the conversion of the dicobalt hexacarbonyl complex of 1-alkynylcyclopropanol to cyclopentenones, allenyl cyclopropanols have been transformed by Iwasawa and co-workers into hydroquinones using cobalt conditions (Scheme 19.32) [39]. This approach has been used in the synthesis of vitamin E and K analogs. Allenylcyclopropanol **166** affords the acetylated hydroquinone **167** using the cobalt mediator and quenching with acetic anhydride. Alternatively, treatment of the same compound with dicobaltoctacarbonyl and then iron(III) chloride gives the benzoquinone **168**. A mechanism for this process is postulated whereby a carbonylated intermediate is formed followed by ring expansion, reductive elimination and tautomerization to give a hydroquinone that can then be oxidized to the benzoquinone.



167 Intermediate to vitamin E analogs

n = 0 44% n = 3 33%

168 Intermediate to vitamin K analogs

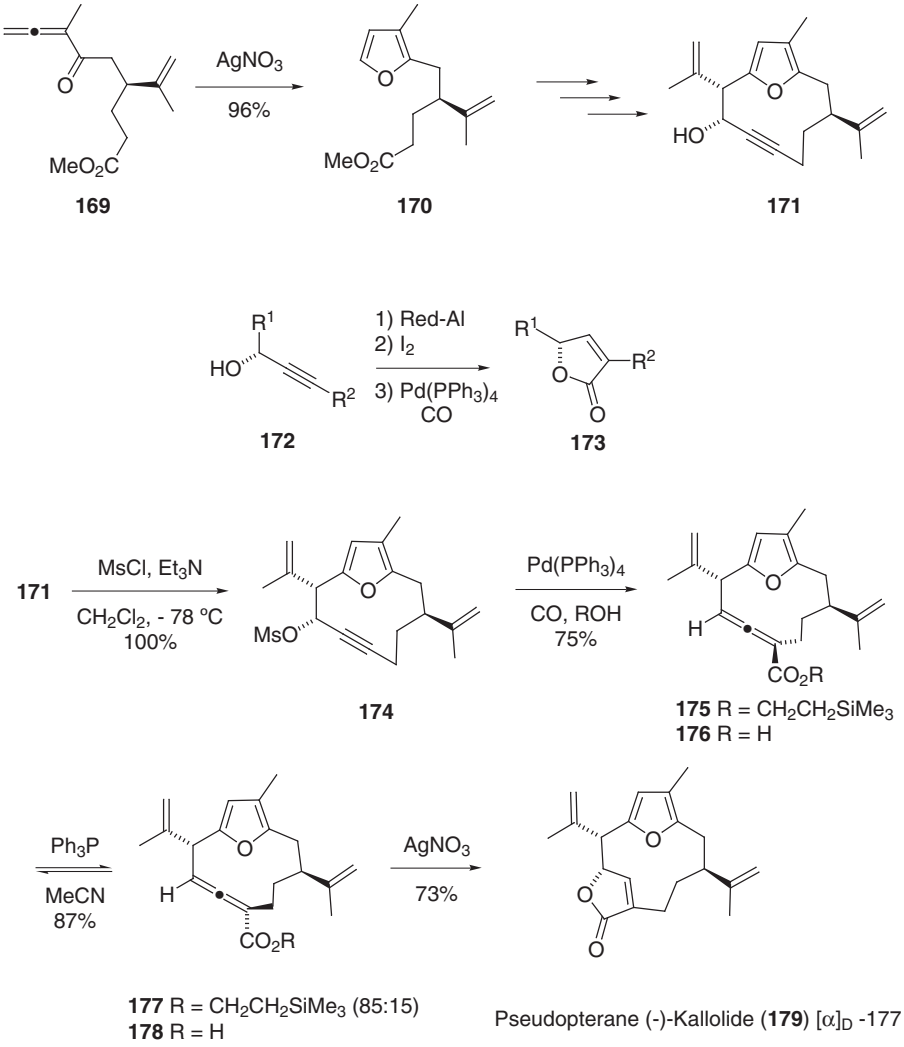
n = 0 45% n = 3 34%

Scheme 19.32 Vitamin E and K analogs.

19.4 Transition Metal-Promoted Heterocyclizations

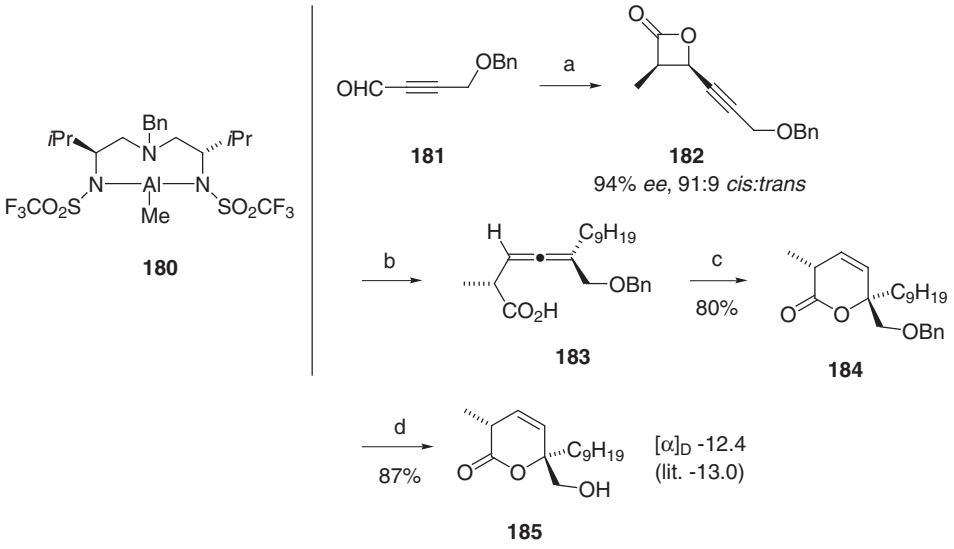
Marshall and colleagues have shown that conjugated allenones can be converted to furans using silver nitrate (Scheme 19.33) [40]. As can be seen, conversion of **169** to **170** was a very high-yielding process. Furan **170** was then further manipulated to give propargyl alcohol **171**. Based on previous unsuccessful attempts to convert propargyl alcohol **172** to lactone **173** via the sequence shown, alkyne **171** was instead converted to the mesylate **174** and then to the allenic ester **175**. The latter was subsequently isomerized to the diastereomeric allenic ester **177** with triphenylphosphine in acetonitrile. Cleavage of the β-TMS ethyl ester gave allenic acid **178**, which was treated with silver nitrate to afford the cyclized product, lactone **179**, constituting a synthesis of the enantiomer of (+)-kallolide B.

Recently, Wan and Nelson demonstrated the power of asymmetric acyl halide–aldehyde cyclocondensation (AAC) by applying this method to the asymmetric synthesis of (–)-malyngolide (**185**) (Scheme 19.34) [41]. β-Lactone **182** was prepared via an asymmetric AAC reaction of propionyl bromide and 4-benzyloxybutanal **181** using the Al(III) catalyst **180** discovered in their laboratories. Next, a copper-catalyzed ring opening of the lactone was effected to afford the non-racemic trisubstituted chiral allene **183**. Treatment of this allene with silver nitrate and Hünig's base at 80 °C resulted in the rapid formation of lactone **184**, which was then converted rapidly to (–)-malyngolide (**185**). The 6-*endo*-trig ring closure of **183** to **184** was favored over the 5-*exo*-dig ring closure owing to the enhanced stability of the developing positive charge at the allene terminus.

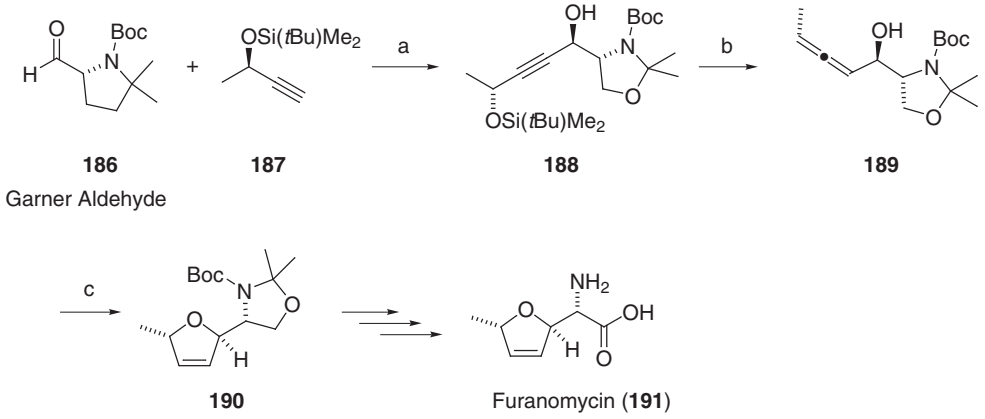


Scheme 19.33 Pseudopterane (–)-kallolide B enantiomer of natural (+)-kallolide B.

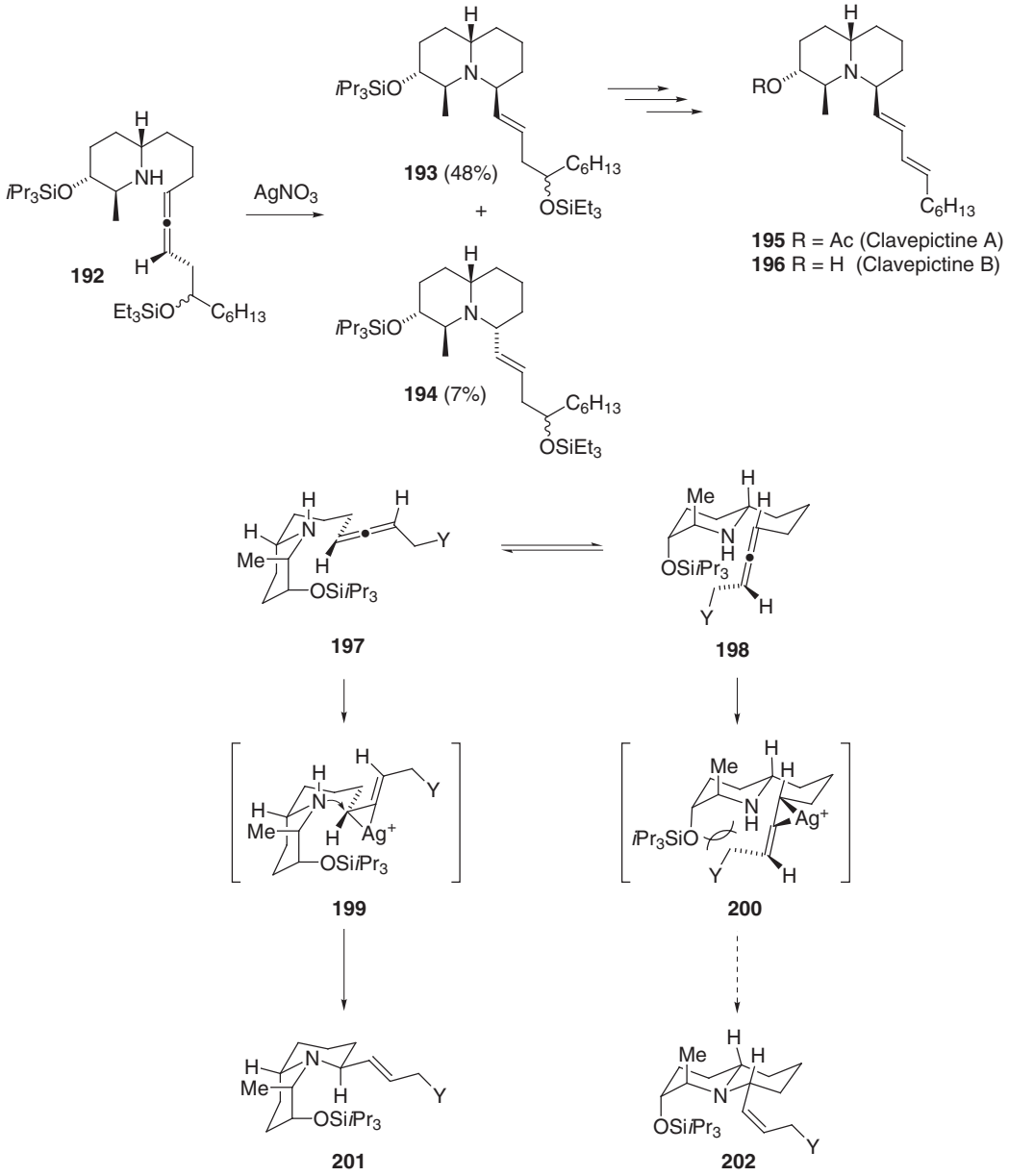
In Standaert and co-workers' approach to (+)-furanomycin (**191**), propargylic alcohol **188** was synthesized in high yield from the Garner aldehyde **186** and **187** (Scheme 19.35) [42]. Conversion of **188** to allene **189** was effected using either lithium aluminum hydride or RedAl. Unfortunately, neither of these reducing reagents gave very high yields (25–50%). The allene was then treated with silver nitrate and calcium carbonate to provide the cyclization product, dihydrofuran **190**. This furan was then converted to a translatable amino acid, (+)-furanomycin (**191**). This approach was suited for the preparation of multigram quantities of **191**.



Scheme 19.34 (–)-Malyngolide. (a) 10 mol% **180**, EtCOBr, iPr$_2$NEt, CH_2Cl_2, –50 °C; (b) $C_9H_{19}MgBr$, 10 mol% CuBr, THF, –78 °C; (c) 10 mol% $AgNO_3$, 5 mol% iPr$_2$NEt, 80 °C, MeCN; (d) H_2, Pd/C.



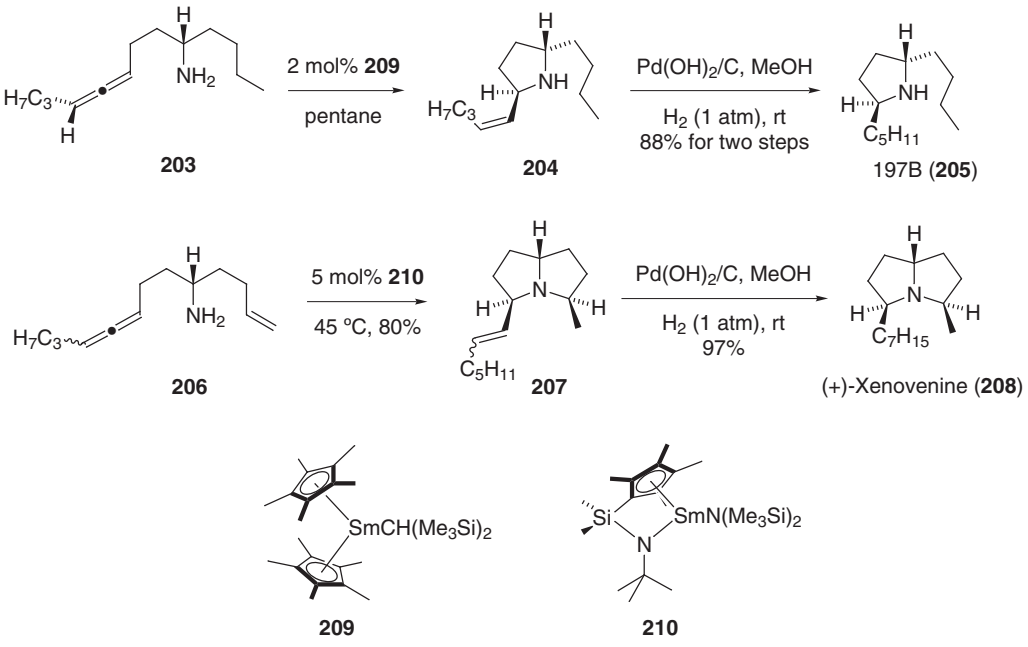
Scheme 19.35 (+)-Furanomycin. (a) nBuLi, THF, $ZnBr_2$ (3 equiv.), –78 to 25 °C, 86% (9:1 *dr*); (b) LAH, diethyl ether, –20 to 25 °C, 25–50%; (c) $AgNO_3/CaCO_3$, acetone/H_2O, dark, >95%.



Scheme 19.36 Clavepictine A and B.

Cha and co-workers reported that the silver nitrate-mediated heterocyclization of the diastereomerically pure aminoallene **192** gave the desired quinolizidine **193** and **194**, both possessing the *E* double bond geometry, as a 7:1 mixture of diastereomers (Scheme 19.36) [43]. Diastereomeric transition states **197** and **198** were proposed. The quinolizidine **201** was expected to form predominantly from **199**. They pointed out that interestingly, the cyclization of a 1:1 mixture of diastereomers of **192** gave a 1:2 mixture of **193** and **194**. Compound **193** was successfully converted to the target clavepictine A (**195**) and B (**196**).

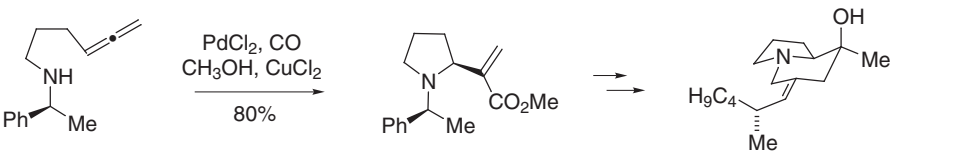
An extension of the alkyne and alkene intramolecular hydroamination/cyclization (IHC) reaction was investigated by McDonald and co-workers and subsequently applied to the synthesis of pyrrolidine and pyrrolizidine alkaloids (Scheme 19.37) [44]. The synthetic strategy involved an enantioselective preparation of a primary amine and a diastereoselective IHC reaction for the pyrrolidine alkaloid and a tandem IHC reaction for preparation of the pyrrolizidine ring system. Catalytic ring closure of **203** was effected by the organolanthanide complex **209**. The pyrrolidine **204** was obtained as the *trans* product and the carbon–carbon double bond was produced as only the *Z*-isomer. Hydrogenation of **204** produced pyrrolidine 197B (**205**) in 88% yield for the two steps. The tandem IHC reaction was not as cooperative. However, the 'constrained geometry' organolanthanide complex **210** was found to effect the tandem ring-closing reaction of **206**. Bicyclic pyrrolizidine **207** was obtained in 80% yield as a single stereoisomer. Reduction of the appending olefin using $Pd(OH)_2$/C



Scheme 19.37 197B and (+)-xenovenine.

and H_2 afforded (+)-xenovenine (**208**). The catalytic cycle for the IHC reaction has been proposed based on a variety of physical data and the preferred stereochemical pathway is discussed in the context of the transition-state structures. Not surprisingly, the kinetic data showed that the allene moiety is 20 times more reactive than the alkene.

Enantiomerically pure allenamine **211** was converted to the pyrrolidine **212** by Gallagher and co-workers in a synthesis of pumiliotoxin 251D (**213**) (Scheme 19.38) [45]. The chiral benzylic residue was to serve as a control element for the newly created asymmetric center. However, a diastereomeric ratio of 1:1 was observed under the palladium(II)-catalyzed conditions. This result is in contrast to reports using Ag(I) salts as an electrophilic trigger, which proceed with high diastereoselectivities. A variety of chiral non-racemic ligands were used to modify the palladium catalyst, but all were unsuccessful in increasing the stereoselectivity. Nevertheless, the α-methylbenzyl residue did serve as a resolving agent to give the desired diastereomer in 40% yield on a multigram scale and was subsequently converted to pumiliotoxin 251D (**213**).

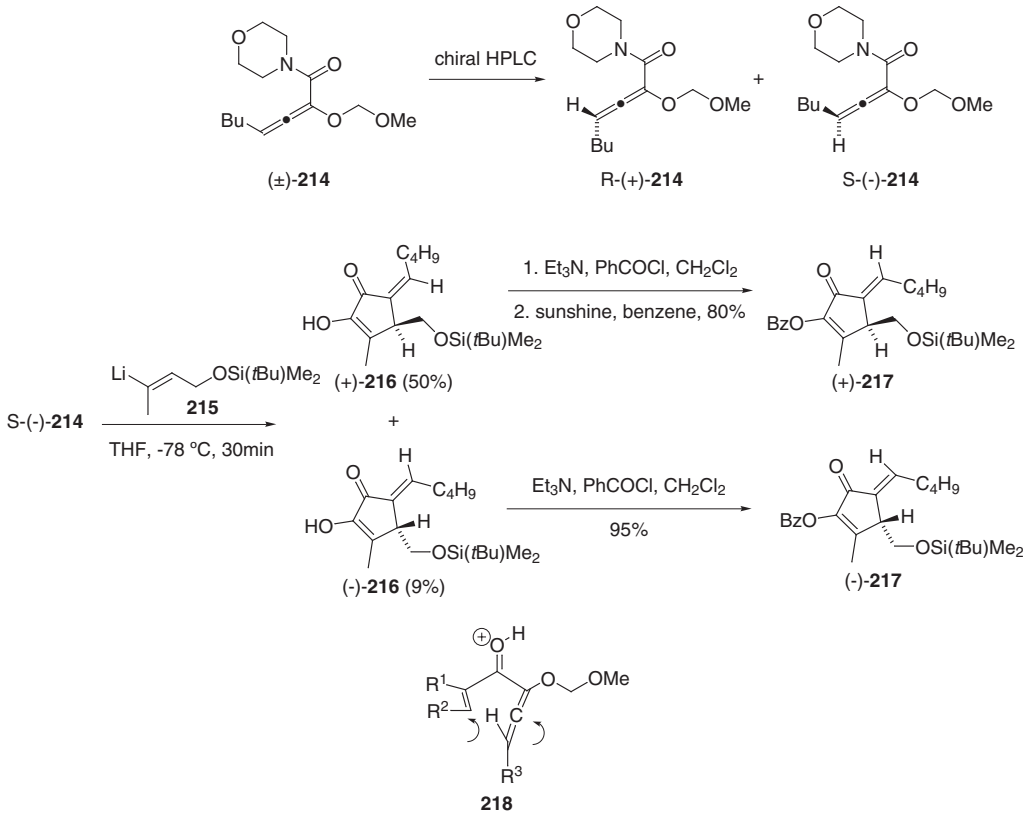


211 **212** Pumiliotoxin 251D (**213**)

Scheme 19.38 Pumiliotoxin 251D.

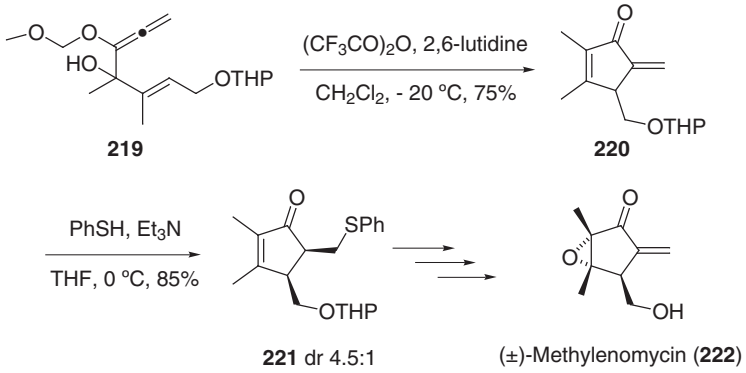
19.5 Acid-Catalyzed Rearrangements

Tius and co-workers elegantly applied a variant of the Nazarov reaction to the preparation of cyclopentenone prostaglandins (Scheme 19.39) [46]. Moreover, it was demonstrated that the chirality of non-racemic allenes is transferred to an sp^3-hybridized carbon atom. Preparation of allenic morpholinoamide **214** and resolution of the enantiomers by chiral HPLC provided (–)- and (+)-**214**. Compound (–)-**214** was exposed to the vinyllithium species **215** to afford a presumed intermediate which was not observed but spontaneously cyclized to give (+)- and (–)-**216** as a 5:1 mixture. Compound (+)-**216** was obtained with an 84% transfer of chiral information and (–)-**216** was obtained in 64% *ee*. The lower enantiomeric excess of (–)-**216** indicates that some *Z* to *E* isomerization took place. This was validated by the conversion of **216** to **217**, where the absolute configuration was established. The stereochemical outcome of this reaction has been explained by conrotatory cyclization of **218** in which the distal group on the allene rotates away from the alkene to give **216**.



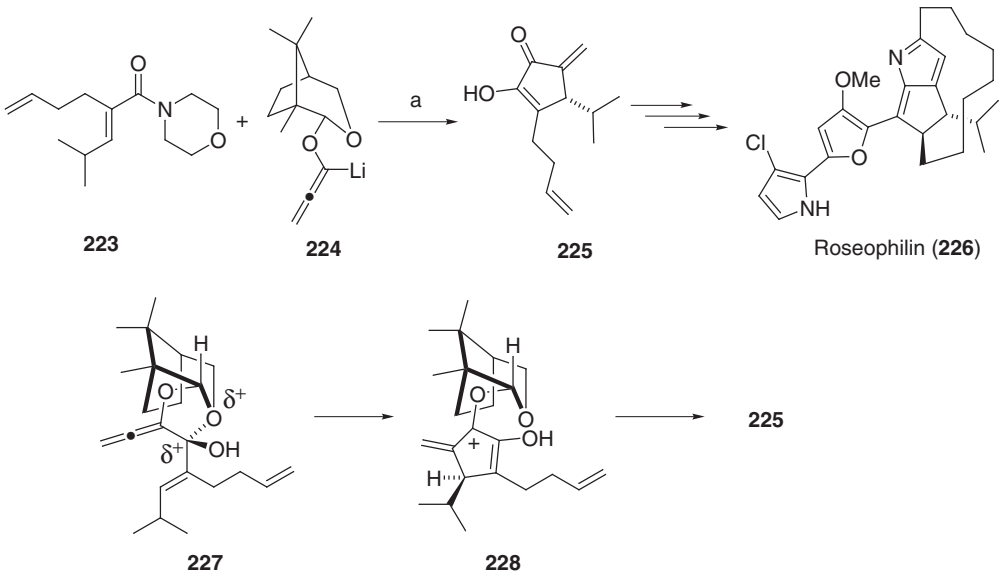
Scheme 19.39 Cyclopentenone prostaglandins.

A total synthesis of (±)-methylenomycin A (**222**) using Tius and Trehan's Nazarov cyclization strategy to form α-alkylidene cyclopentenones has been accomplished (Scheme 19.40) [47]. Treatment of **219** with trifluoroacetic anhydride and 2,6-lutidine (reagent of choice for the cationic cyclopentannulation reaction) gave cyclopentenone **220** in 75% yield. Further functional group manipulations were carried out by first protecting the exocyclic double bond by the addition of thiophenol to give **221**. The exocyclic double bond was later reinstalled by the oxidation of the thiophenoxy enone to the sulfone with mCPBA and DBU-promoted elimination.



Scheme 19.40 (±)-Methylenomycin A.

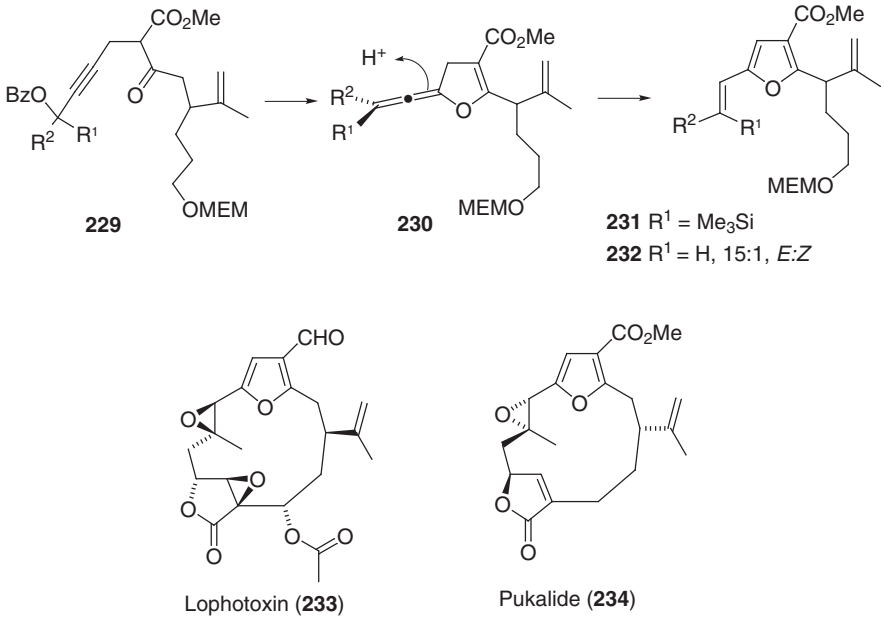
Harrington and Tius reported the first enantioselective total synthesis of roseophilin (**226**) using the allenyl Nazarov-type cyclization strategy (Scheme 19.41) [48]. The lithioallene **224** was added to the amide **223** and the mixture was warmed to room temperature. The key cationic cyclopentannelation reaction was performed using HCl in 1,1,1,3,3,3-hexafluoro-2-propanol and 2,2,2-trifluoroethanol. The highly unsaturated cyclopentenone **225** was afforded in 76% yield and 86% *ee*. It was previously established by the Tius group that these protic conditions were essential for the attainment of high enantiomeric excesses. It has been postulated



Scheme 19.41 Roseophilin. (a) (1) *n*BuLi, THF, –78 °C; (2) –78 to –30 °C, 1 h, **223**; (3) HCl, HFIP–TFE (1:1), –78 °C, 78%, 86% *ee*.

that these conditions have a beneficial effect on the reaction by increasing the rate of the irreversible cleavage of cation **227**. The use of the chiral auxiliary **224** represents a substantial improvement in the enantioselectivity compared with the first disclosure where a carbohydrate was used as a chiral auxiliary on the allene. To explain the origins of the enantioselectivity, a working hypothesis was proposed based upon the results from four sugar-derived chiral auxiliaries. Structure **227** shows stablization of the pentadienyl cation by donation of the axial electron pair of the pyran oxygen atom. This interaction limits the conformational mobility of **227** and brings the ethylene bridge of the auxiliary in closer proximity to the pentadienyl cation so as to block the α-face. The oxocationic intermediate **228** then undergoes a fragmentation to give **225**.

The Wipf group has shown that alkenylfurans are formed in one step from α-propargyl-β-keto esters under palladium catalysis or basic conditions via allenyl intermediate **230** (Scheme 19.42) [49]. Initially, this approach suffered from poor *E*/*Z* selectivity with regard to the alkenyl portion of the furan when R^1 was hydrogen. A solution to the problem involved the allenyl intermediate **230**. Selective protonation from one face of the allene should afford one alkene geometry. Thus replacement of R^1 with a bulkier TMS group afforded a 10:1–15:1 *E*/*Z* selectivity, depending on R^2. Progress is under way to convert **232** to pukalide (**234**) and lophotoxin (**233**).



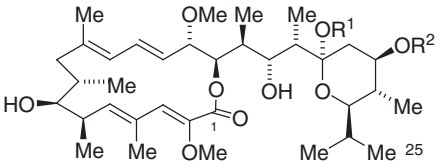
Scheme 19.42 Lophotoxin and pukalide.

19.6 Allenyl Organometallic Intermediates

The addition of allenyl metal reagents to aldehydes affords homopropargylic alcohols with contiguous OH- and Me-substituted stereocenters, which serves as a complementary approach to the aldol condensation for polyketide synthesis. Marshall has developed this method extensively and this work is the subject of a more detailed review (cf. Chapter 9) [50]. The applications of this method to the synthesis of naturally occurring compounds have also been wide-ranging and a few are highlighted below.

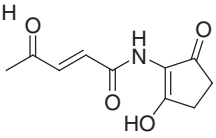
Marshall's approach to the bafilomycins (**235**) involves the stereoselective addition of chiral nonracemic allenyl zinc reagents to aldehydes **236**, **237** and **238** (Scheme 19.43) [51]. The *anti* stereochemistry is desired for each of these additions. Importantly, the resulting acetylenic unit plays a key role in further functionalizing these segments. For the synthesis of fragment C1–C11 of bafilomycin it was initially hoped that aldehyde (*R*)-**242** could be used so that an orthogonal protecting group strategy could be applied later in the synthesis. The low reactivity of aldehyde (*R*)-**242** proved to be a problem that necessitated higher temperatures and additional catalyst. The low *anti*,*anti*:*anti*,*syn* ratio was attributed to partial racemization of the allenyl zinc intermediate **244** derived from (*R*)-**239**. Thus aldehyde (*R*)-**243** was examined and as expected reacted at –20 to 0 °C to give the desired stereotriad **241** in 70% yield and with an *anti*,*anti*:*anti*,*syn* isomer ratio of 93:7.

Marshall's approach to the synthesis of the C15–C25 **250** subunit involved a similar stereo-defining step (Scheme 19.44). Addition of the allenylzinc reagent derived from mesylate **245** to aldehyde **246** provided the *anti* isomer **247** predominantly (95:5 *anti*:*syn*) in 76% yield. Functional group manipulation of **247** gave **248**, which was subjected to the allenylzinc species of **245**, affording **249** as an 80:20 *anti*:*syn* mixture of diastereomers. The low diastereoselectivity was of no consequence since the hydroxyl group is to be converted to a ketone. However, these low diastereoselectivities remain a drawback of the allenylzinc additions to unbranched aldehydes. Attempts were also made to install the *anti* 1,2-diol array and the alkyne for further elaboration of subunit **250**. However, treatment of a model aldehyde **251** under the allenylzinc conditions using the methoxy-substituted allenyl ether derived from **252** gave a 47:47:6 mixture of diastereomers of **253**. The major isomers were presumed to be *anti* since the addition is known to occur through a cyclic transition state. External additives such as (–)-sparteine or (–)-*N*-methylephedrine had no effect on the low selectivity. Subunit **250** was subsequently functionalized in another manner.

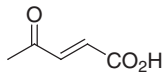


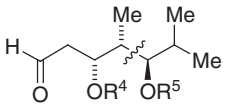
235

bafilomycin A_1; $R^1 = R^2 = H$
bafilomycin A_2; R^1 = Me, R^2 = H
bafilomycin B_1;R^1= H, R^2 =
bafilomycin B_2; R^1 = Me, R^2 =



bafilomycin C_1; R^1 = H, R^2 =
bafilomycin C_2; R^1 = Me, R^2 =





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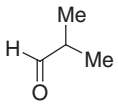

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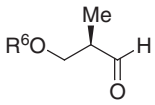

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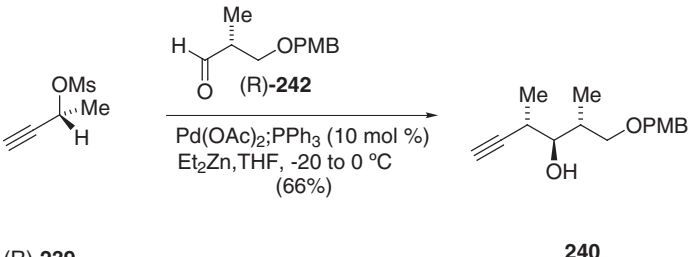
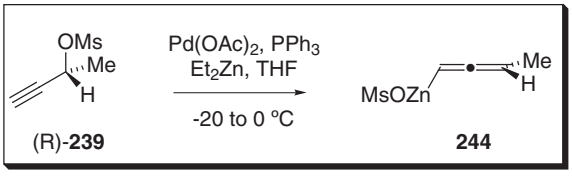
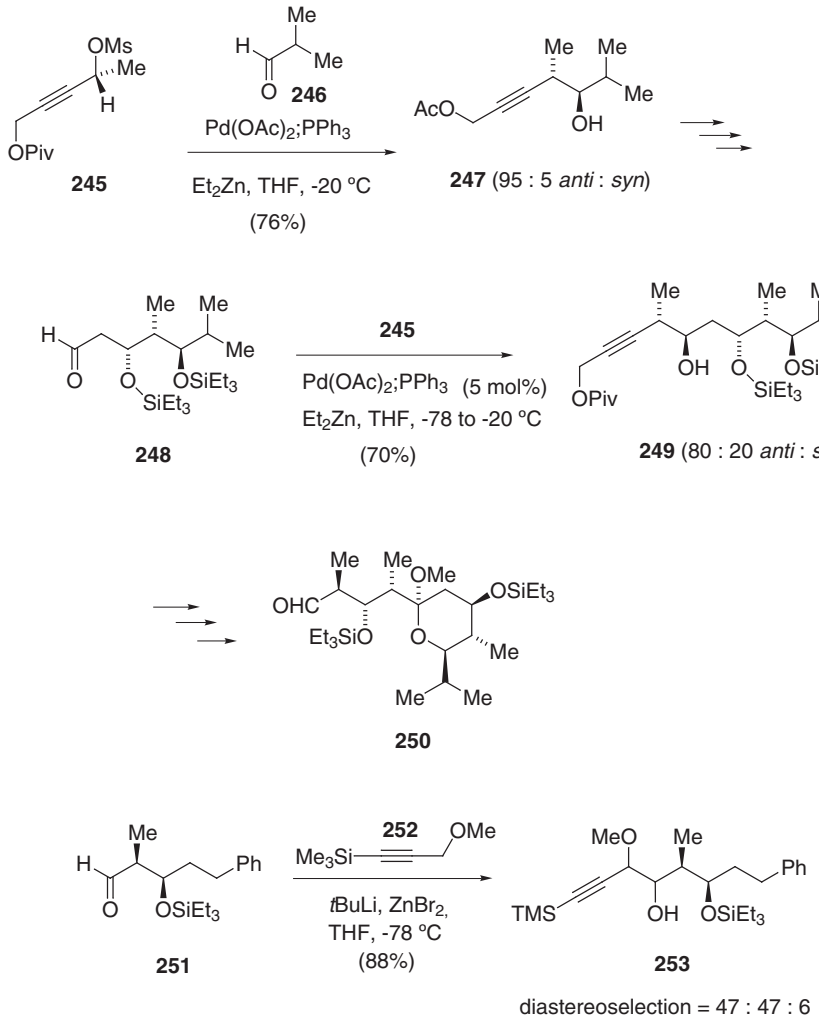


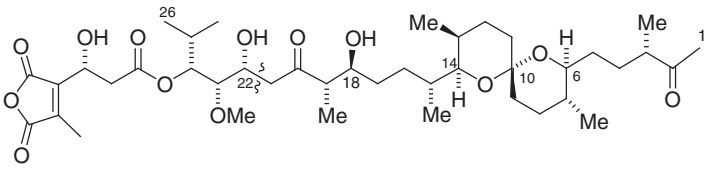


Scheme 19.43 Bafilomycins (C1–C11).

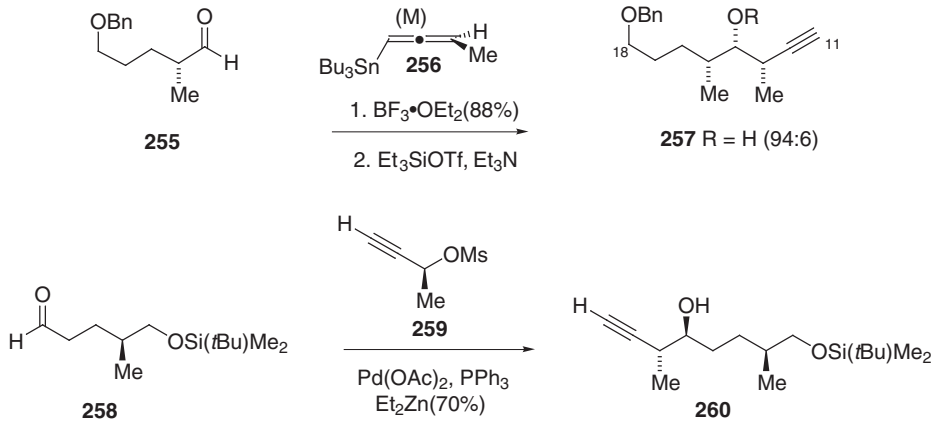


Scheme 19.44 Bafilomycins (C15–C25).

In Marshall's total synthesis of tautomycin (**254**) a convergent route was developed employing both enantioenriched allenyl stannanes and zinc reagents derived from (*S*)-3-butyn-2-ol methanesulfonates (Scheme 19.35) [52]. (*M*)-Allenylstannane **256** was obtained from the mesylate of (*S*)-3-butyn-2-ol by treatment with Bu_3SnLi–$CuBr \cdot DMS$ in THF. The $BF_3 \cdot OEt_2$-promoted addition to aldehyde **255** afforded the *syn*:*syn* stereotriad **257** as the major diastereomer (94:6). Addition of the (*M*)-allenylzinc reagent of **259** generated from (*S*)-3-butyn-2-ol to aldehyde **258** gave rise to the *anti* adduct **260** as the major component (85:15).

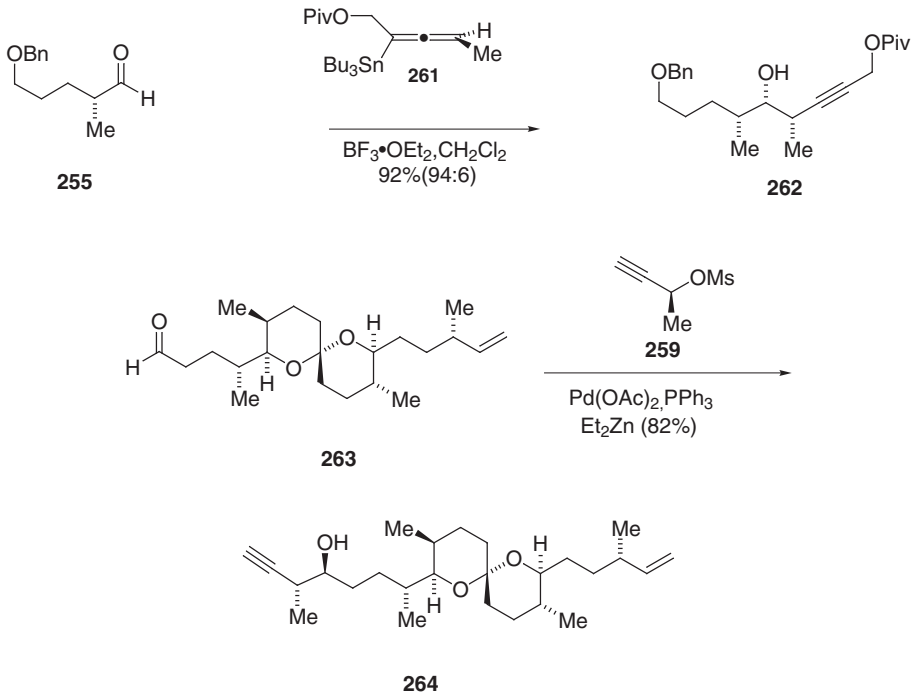


Tautomycin (**254**)

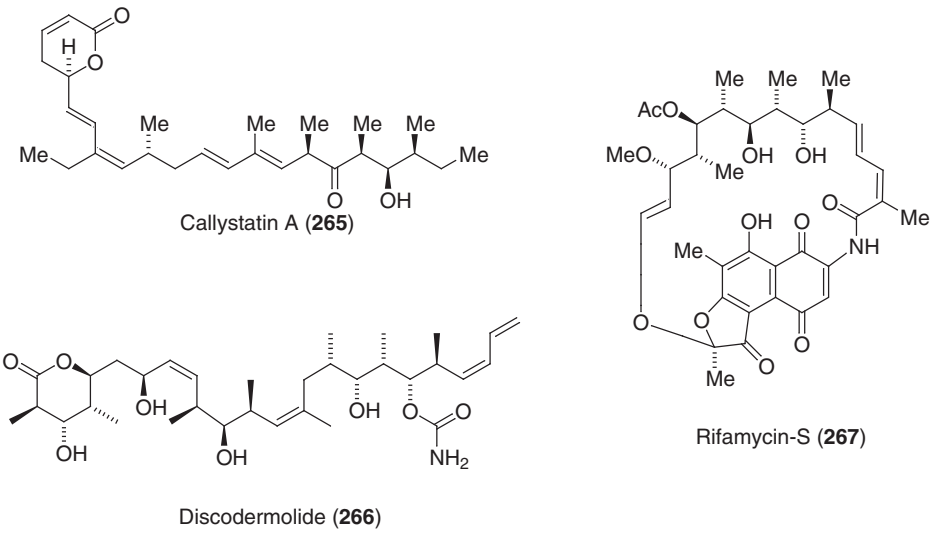


Scheme 19.45 Tautomycin.

During these investigations, a more convergent approach to a subunit derived from **257** was developed by the direct addition of the more substituted allenylstannane **261** to aldehyde **255** to give **262** (Scheme 19.46). One final chain extension was performed on aldehyde **263** to give the *anti* adduct **264** as an 86:14 mixture of diastereomers. Interestingly, the following step required the complete removal of residual palladium from the allenylzinc addition step to prevent exothermic polymer formation. As seen in the bafilomycin synthesis, the addition of allenyl metal species to unbranched aldehydes occurs with moderate diastereoselectivity. Allyl boronate or aldol counterparts proceed with only slightly higher diastereoselectivity [53]. Preference for the *anti* over the *syn* diastereomer can be attributed to an unfavorable eclipsing interaction between the allenylmethyl and the aldehyde R group in the transition state leading to the *syn* adduct. A systematic study was performed investigating the stereochemistry of a stereopentad for application to the naturally occurring callystatin.



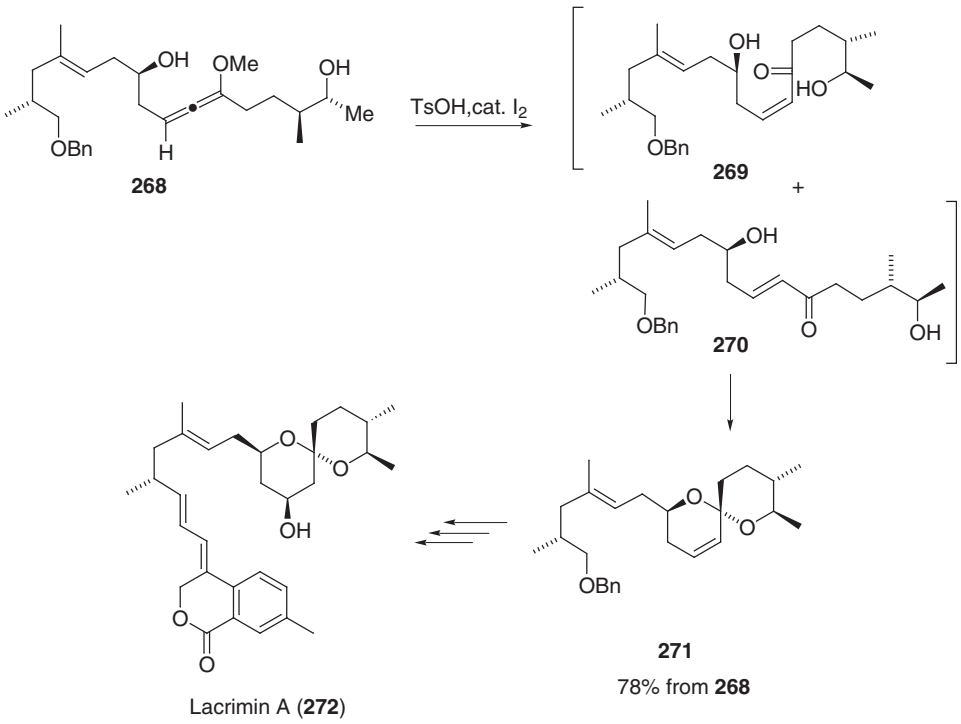
Scheme 19.46 Tautomycin-A: a more convergent approach.



Scheme 19.47 Callystatin, discodermolide and rifamycin S.

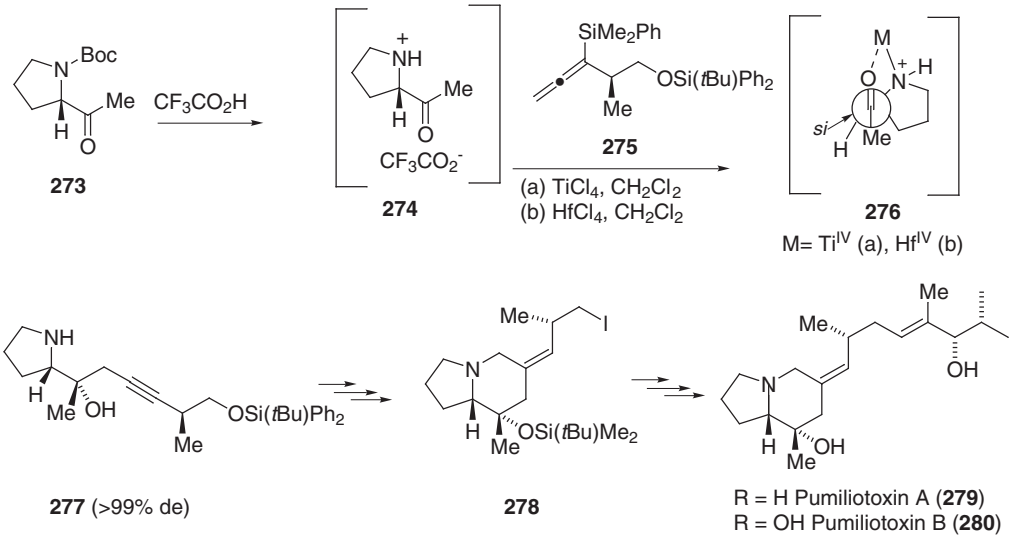
The power of this strategy has been demonstrated by Marshall's group, showing that callystatin (**265**) [54], discodermolide (**266**) [55] and rifamycin (**267**) [56] have all either been accessed using the synthetic protocols described above or it is under way (Scheme 19.47).

In Takle and Kocienski's total synthesis of lacrimin A (**272**), methoxyallene **268** was easily prepared via consecutive alkylations and subjected to acidic conditions to afford the presumed enone intermediates **269** and **270** (Scheme 19.48) [57]. Enone **269** underwent spontaneous spiroacetal formation to give a single stereoisomer **271** in 78% yield from **268**. This compound was taken on to complete a total synthesis of lacrimin A (**272**).



Scheme 19.48 Lacrimin A.

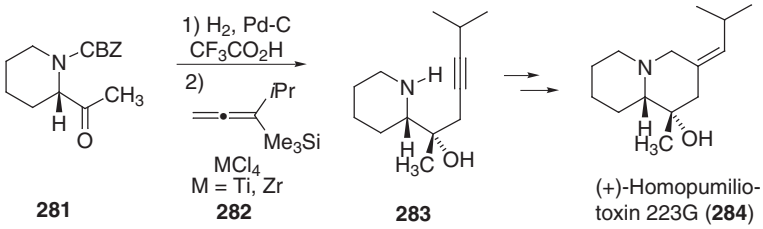
In Kibayashi and co-workers' convergent approach to the pumiliotoxin alkaloids, the *N*-Boc-protected substrate **273** was treated with triflic acid and allenylsilane **275** was added to the resultant intermediate **274** (Scheme 19.49) [58]. When titanium(IV) chloride was used to mediate this nucleophilic addition, the desired propargylic alcohol **277** was obtained with complete stereocontrol in 71% yield. The use of hafnium(IV) chloride as a Lewis acid also yielded a single product but in 92% yield. The facial selectivity realized in these propargylations was rationalized by invoking a Lewis acid chelate cyclic intermediate **276** involving the chelation of the NH and the carbonyl groups. Compound **277** was taken on to a common intermediate **278** that



Scheme 19.49 (+)-Pumuliotoxin A and B.

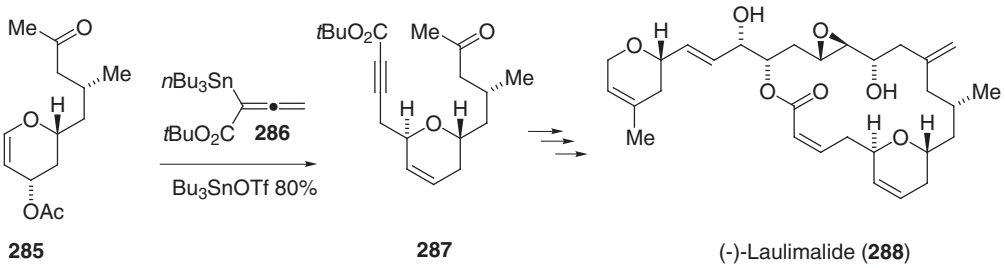
was used to access (+)-pumiliotoxin A (**279**) and B (**280**) and other members of the pumiliotoxin family.

In Kibayashi and co-workers' approach to homopumuliotoxin 223G (**284**), attempts to effect propargylation of **281** using 4-methyl-2-pentynylmagnesium bromide failed under a variety of conditions owing to an equilibrating mixture of allenic and propargylic nucleophiles [59]. An alternative method involved using a variant of Danheiser's protocol, with allenylsilane **282**. The homopropargylic alcohol **283** was obtained in 96% yield with complete diastereocontrol. $TiCl_4$ and $ZrCl_4$ performed equally as well in this reaction (Scheme 19.50).



Scheme 19.50 Homopumuliotoxin 223G.

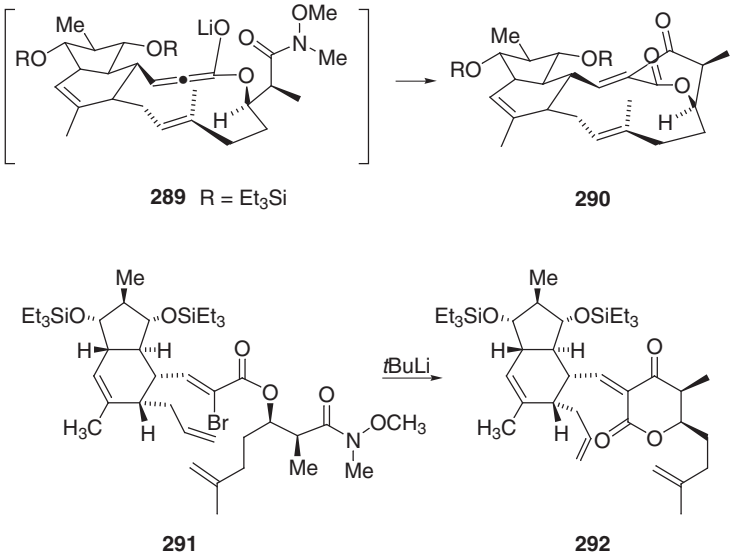
In a total synthesis of (–)-laulimalide (**288**), Nelson et al. were able to assemble rapidly the bottom synthon of the target by adding carboalkoxyallenylstannane **286** to glycal **285** [60]. The Lewis acid activator Bu_3SnOTf gave the best results, affording the *anti* S_N2' addition product in 80% yield (Scheme 19.51).



Scheme 19.51 (–)-Laulimalide.

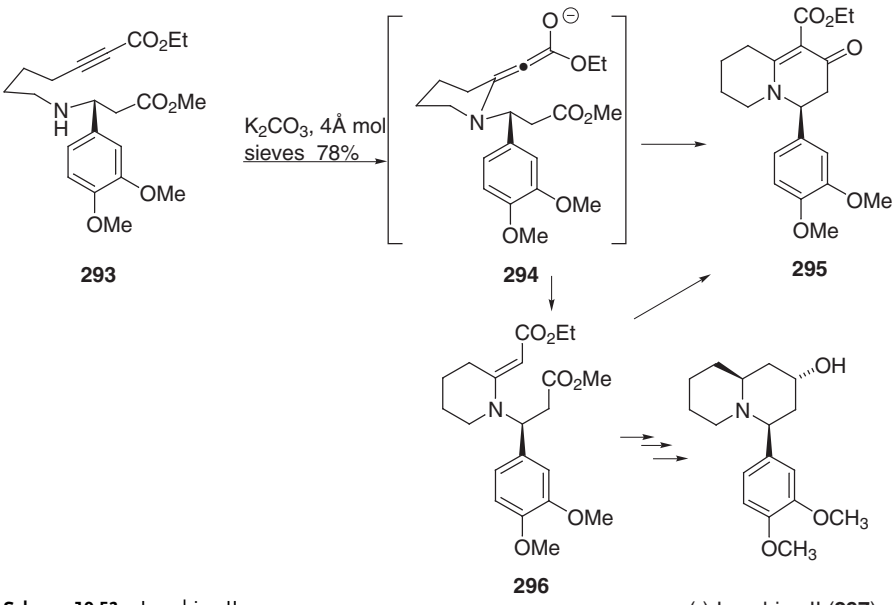
19.7 Allenoates

In an approach to FR182877, Sorensen and co-workers generated allenoate intermediate **289** from an α-bromo-α,β-unsaturated lactone and effected an intramolecular acylation to afford α-alkylidene-β-keto-γ-lactone **290** as a single stereoisomer (Scheme 19.52) [61]. Evidence for the allenoate intermediate was established by the treatment of α-bromoenoate **291** with *t*BuLi, which afforded the cyclized compound **292** as a single stereoisomer. Treatment of the isomeric bromoenoate of compound **291** also gave **292**. Hence this demonstrated a stereoselective but not stereospecific process.



Scheme 19.52 FR182877.

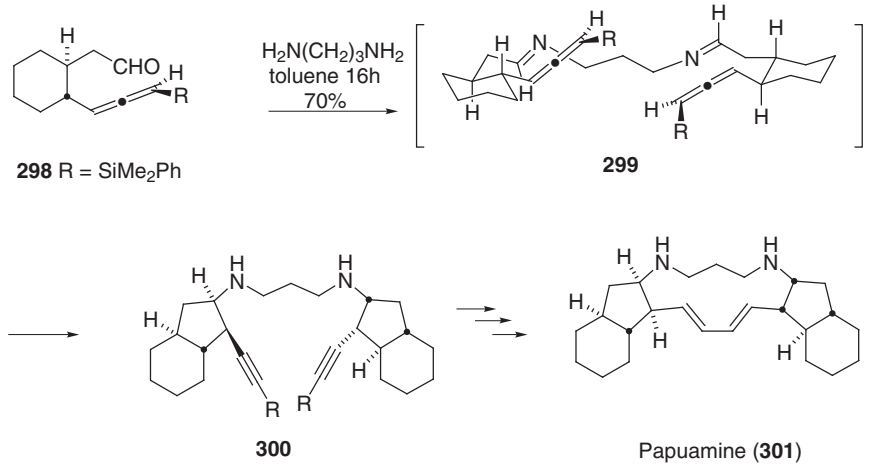
Enantiopure quinolizidinones and indolizidinones were obtained by Ma and Zhu in an intramolecular conjugate addition of the secondary amine of **293** to the alkynoate ester to provide the intermediate allenoate **294**, which was subsequently trapped in a condensation reaction to afford **295** (Scheme 19.53) [62]. In some instances, intermediate **296** was isolated, which could also be converted to **295**. This quinolizidinone intermediate was then converted in a concise manner to lasubine II (**297**).



Scheme 19.53 Lasubine II.

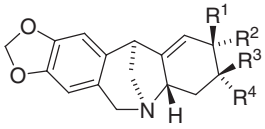
19.8 Imino–Ene Reactions

An elegant and concise synthesis of (–)-papuamine (**301**)was carried out by Weinreb and co-workers using an intramolecular imino–ene reaction (Scheme 19.54) [63]. Treatment of allenylaldehyde **298** with 1,3-diaminopropane and heating for 16 h provided a 70% yield of **300** as a single stereoisomer. The intermediate bisamine **299** presumably undergoes simultaneous imino–ene reactions. Interestingly, the reaction products are silylalkynes that are shown to be formed stereospecifically, suggesting that the reaction is a concerted process. The tetracycle **300** was easily converted to (–)-papuamine **301**.

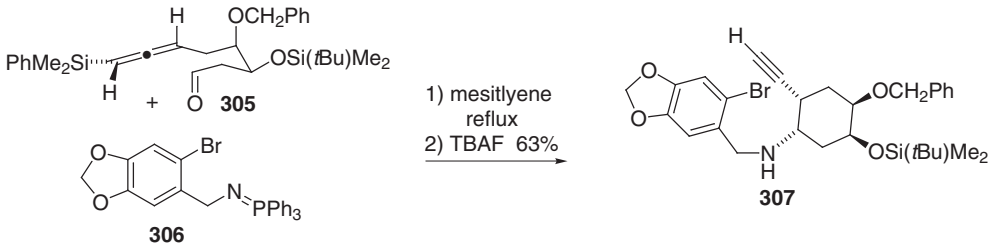


Scheme 19.54 (–)-Papuamine.

(–)-Montanine (**302**), (–)-coccinine (**303**) and (–)-pancracine (**304**) were synthesized by Jin and Weinreb also using the intramolecular imino–ene strategy (Scheme 19.55) [64]. Refluxing aldehyde **305** and iminophosphorane **306** in mesitylene gave a 63% yield of **307** after removal of the silyl group from the terminus of the alkyne. This intermediate was then taken on to complete the total synthesis of the natural product targets.



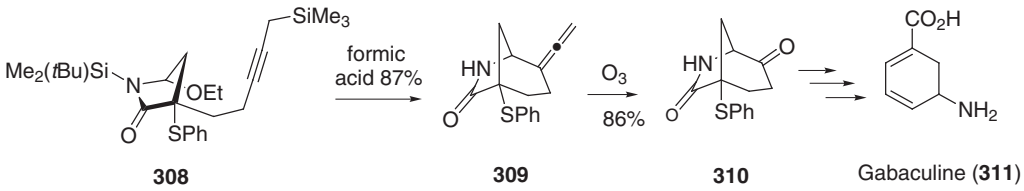
(-)-Montanine R^1, R^4 = H, R^2 = OMe, R^3 = OH (**302**)
(-)-Coccinine R^1= OMe R^4, R^2= H, R^3 = OH (**303**)
(-)-Pancracine R^1, R^4 = H, R^2, R^3 = OH (**304**)



Scheme 19.55 5,11-Methanomorphanthridine class of *Amaryllidaceae* alkaloids.

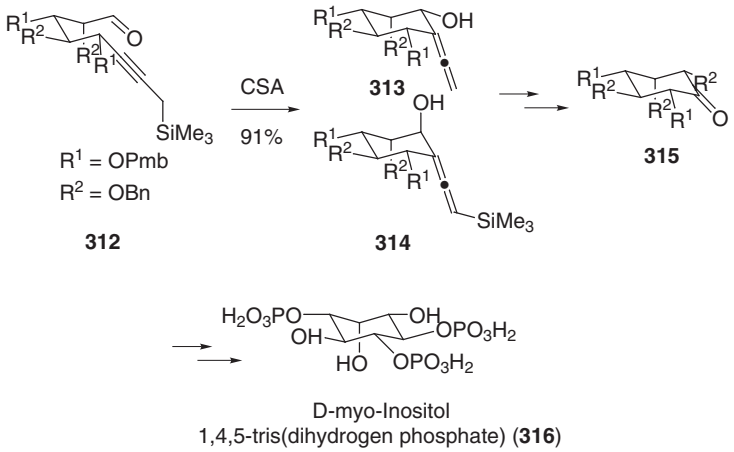
19.9
Oxidation of Allenes

Heimstra and co-workers have shown that it can be advantageous to use a less direct route involving a propargylsilane over a vinylsilane for certain ring closures [65]. All attempts to effect the ring closure shown in Scheme 19.56 with the corresponding vinyl silane met with failure, giving elimination of ethanol and or protodesilylation. However, reaction of **308** with formic acid provided an 87% yield of the bicycle **309**. Ozonolysis of allene **309** afforded bicyclic ketone **310** in 86% yield, which was subsequently converted to gabaculine (**311**).



Scheme 19.56 Gabaculine.

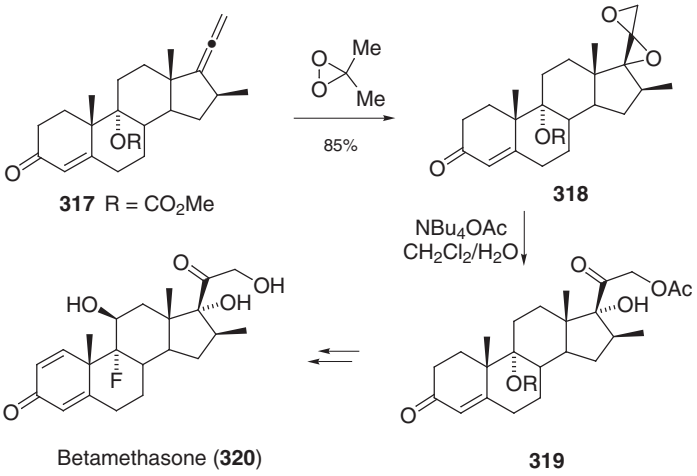
In Clive et al.'s formal synthesis of D-myo-inositol 1,4,5-tris(dihydrogenphosphate) (**316**), aldehyde **312** was prepared from D-glucose and then exposed to reagents predicted to be suitable for the formation of the allene **313** ($TiCl_4$, $BF_3 \cdot OEt_2$, CF_3CO_2H, TBAF) (Scheme 19.57) [66]. It turns out that storing compound **312** in $CDCl_3$ for a few days gave rise to the unexpected product **314**. The ene reaction was subsequently optimized to give a 91% yield of **314** by heating with camphorsulfonic acid. Interestingly, this reaction was examined in more detail on a vari-



Scheme 19.57 D-Myo-inositol 1,4,5-tris(dihydrogenphosphate).

ety of substrates and it was found that only the highly oxygenated substrates afforded products where the silyl group was retained. All other substrates gave the expected allenyl alcohols. The silyl group was removed and eventually the allene was subjected to ozonolysis to afford the desired ketone **315**. Ozonolysis of this allene was not well behaved since a deficiency of ozone was required.

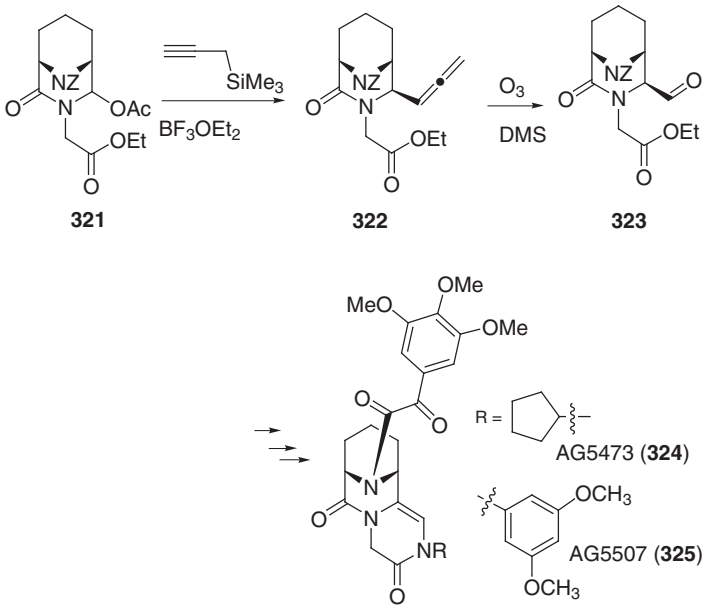
Andews and co-workers prepared allene **317** in 86% yield from the corresponding propargylic carbonate using the Tsuji protocol [$Pd(OAc)_2$–PBu_3, NH_4OCOH, 45 °C] (Scheme 19.58) [67]. Allene **317** was oxidized to the bisepoxide **318** using dimethyldioxirane to afford a mixture of diastereomers (2:1). The epoxides were then opened up using ammonium acetate to afford the keto acetate **319**, which was converted to betamethasone (**320**) using known protocols.



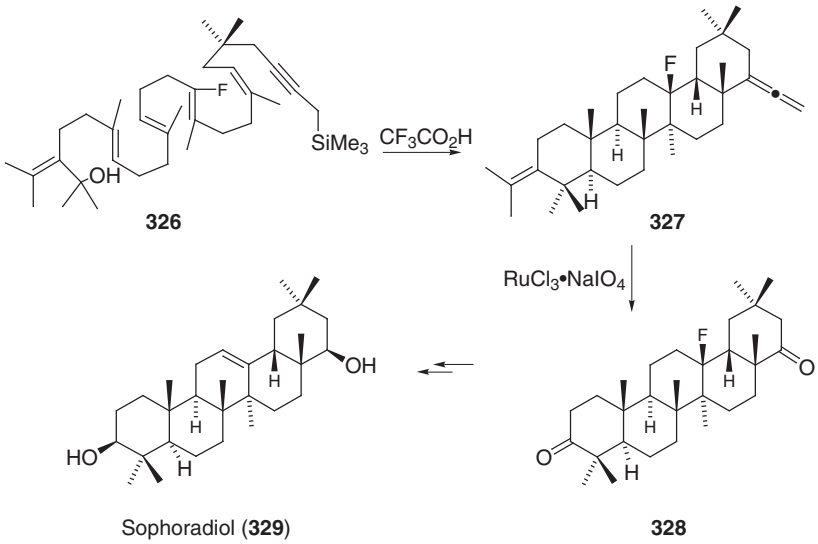
Scheme 19.58 Betamethasone.

In the synthesis of AG5473/5507 (**324**/**325**) by Guo et al., many attempts were made to homologate an aldehyde directly through an intermediate acyliminium ion, but without success [68]. Finally, a less direct route involving the addition of propargylsilane to **321** afforded the allene **322** with 10:1 diastereoselectivity (Scheme 19.59). Allene **322** was then ozonized to give aldehyde **323** in 90% yield.

Attempts by Fish and Johnson to effect a steroid synthesis using a standard epoxide-initiated pentacyclization of a polyene afforded complex mixtures [69]. Alternatively, the allyl alcohol **326** was synthesized and treated with TFA (Scheme 19.60). Protonation affords a symmetrical tetramethylallyl cation that undergoes cyclization to give pentacycle **327** in 31% yield. Simultaneous cleavage of the isopropylidene and vinylidene groups was carried out to furnish the diketone **328** in 88% yield, which was then converted to sophoradiol (**329**).



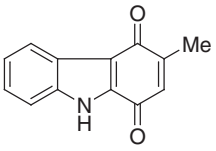
Scheme 19.59 AG5473/5507.



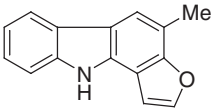
Scheme 19.60 Sophoradiol.

19.10
Electrocyclizations

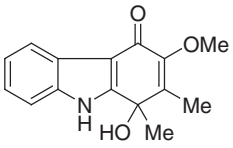
A variety of indole-containing natural products were accessed by Hibino and coworkers using an allene-mediated electrocyclization reaction (Scheme 19.61) [70]. Isomerization of the propargyl ether **335** to allene **336** was performed using potassium *tert*-butoxide. This dienylallene then underwent a spontaneous 6π electrocyclization to afford **337** after aromatization of the triene. Murrayaquinone (**330**), furostifoline (**331**), carbazomycin G (**332**), carazostatin (**333**) and hyellazole (**334**) were all accessed using this strategy.



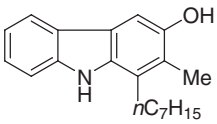
Murrayaquinone A (**330**)



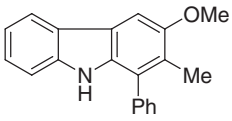
Furostifoline (**331**)



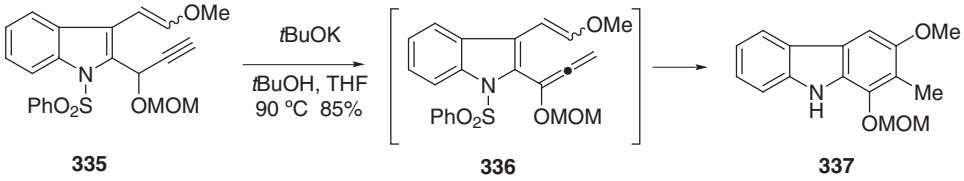
Carbazomycin G (**332**)



Carazostatin (**333**)



Hyellazole (**334**)



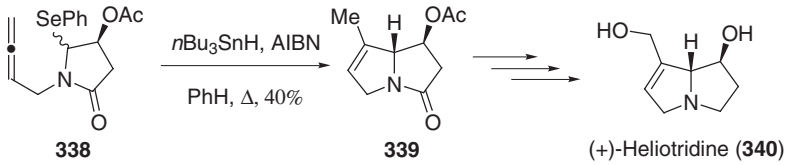
335 **336** **337**

Scheme 19.61 Naturally occurring indoles.

19.11
Miscellaneous

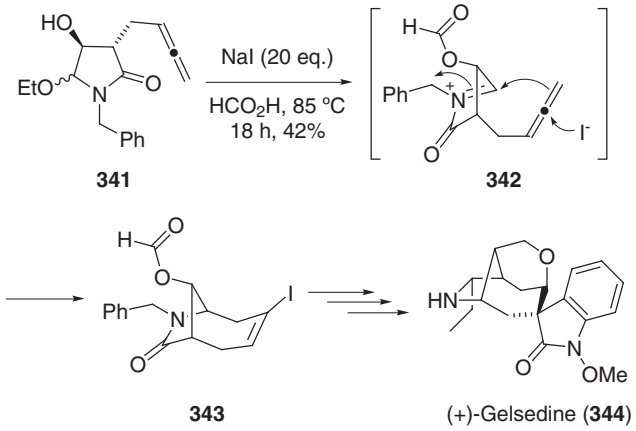
Allenes have also been used as substrates in free radical cyclizations. Dener and Hart demonstrated that such entries are valuable in constructing pyrrolizidine and indolizidine ring systems [71]. In a total synthesis of pyrrolizidine base (+)-heliotridine (**340**), compound **338** possessing an allene functionality was used as a key intermediate (Scheme 19.62). Tri-*n*-butyltin radical-mediated carbon–selenium bond homolysis of **338** followed by the addition of the free radical to the allene moiety

afforded a mixture of four cyclization products with the major product **339** isolated in 40% yield. Intermediate **339** was successfully converted to (+)-heliotridine **340** in only three steps.



Scheme 19.62 (+)-Heliotridine.

Hiemstra and co-workers reported the first example of an iodine-promoted allenyl *N*-acyliminium ion cyclization for the total synthesis of (+)-gelsedine, the enantiomer of the naturally occurring (–)-gelsedine [72]. Compound **341** was prepared from (*S*)-malic acid. When **341** was dissolved in formic acid with a large excess of NaI and heated at 85 °C for 18 h, **343** was found to be the major product isolated in 42% yield. The latter was then successfully converted to (+)-gelsedine in a multi-step manner. Other routes without the allene moiety failed to provide the desired stereoisomer. The successful one-step transformation of **341** to **343** was key to the success of this synthesis.



Scheme 19.63 (+)-Gelsedine.

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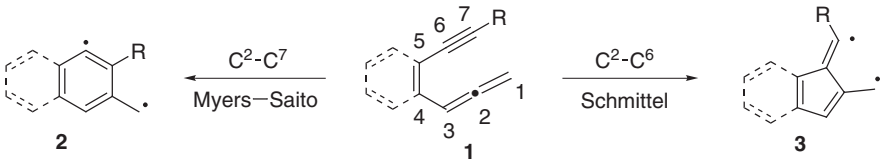
20
Enyne–Allenes

Kung K. Wang

20.1
Introduction

The ability of (*Z*)-1,2,4-heptatrien-6-ynes (enyne–allenes) and the benzannulated derivatives to undergo cyclization reactions under mild thermal conditions to produce biradicals has been the main focus of their chemical reactivities [1–5]. With the development of many synthetic methods for these highly conjugated allenes, a variety of biradicals are readily accessible for subsequent chemical transformations. Cyclization of the enyne–allene **1** could occur either via the C2–C7 pathway (Myers–Saito cyclization) leading to the α,3-didehydrotoluene/naphthalene biradical **2** [6–10] or via the C2–C6 pathway (Schmittel cyclization) producing the fulvene/benzofulvene biradical **3** [11] (Scheme 20.1).



Scheme 20.1 Biradicals from enyne–allenes.

The preferred course of cyclization is dictated by the nature of the substituent at the acetylenic terminus. With a hydrogen or a sterically non-demanding alkyl substituent, the Myers–Saito cyclization reaction is the preferred pathway. However, with the presence of an aryl substituent or a sterically demanding *tert*-butyl or trimethylsilyl group, the Schmittel cyclization reaction becomes the preferred pathway. The effect of the aryl substituent has been attributed to its ability to stabilize the alkenyl radical center in **3**. The sterically demanding group inhibits the Myers–Saito cyclization reaction because of the emergence of severe non-bonded steric interactions in the biradical **2**. The influence of the substituent on the reaction pathway and the energetics of the cyclization reactions and also the stability of the resultant biradicals have been extensively investigated using a variety of computational and theoretical methods [12–26].

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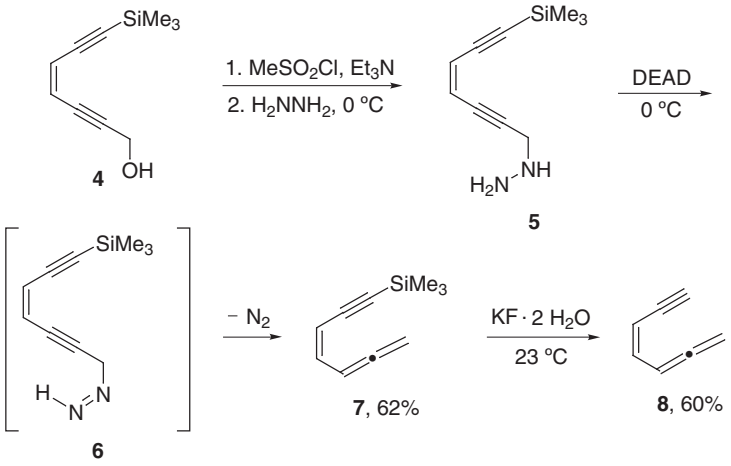
20.2
Synthesis and Cyclization

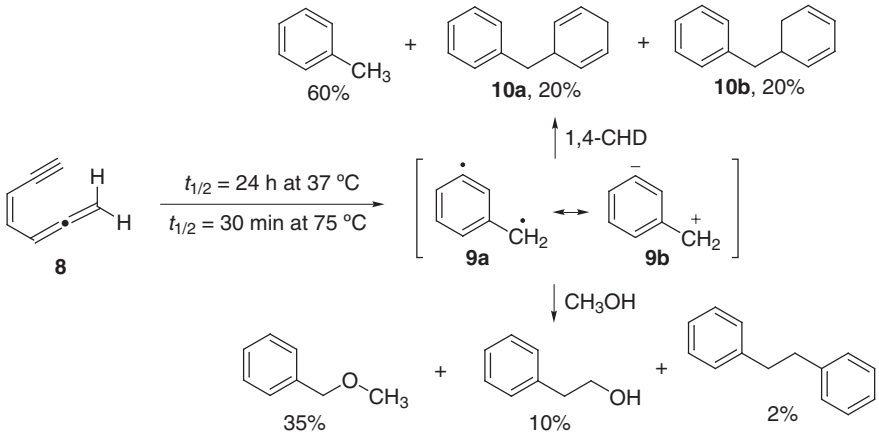
20.2.1
Rearrangement of Enediynyl Propargylic Diazenes

The parent enyne–allene **8** was synthesized from the enediynyl propargylic alcohol **4** (Scheme 20.2) [6–8, 27]. Treatment of **4** with methanesulfonyl chloride followed by hydrazine afforded the corresponding propargylic hydrazine **5**. Oxidation with diethyl azodicarboxylate (DEAD) produced the diazene **6**, which underwent a spontaneous sigmatropic rearrangement with extrusion of dinitrogen to produce **7**. Desilylation of **7** was achieved with potassium fluoride dihydrate in methanol at 23 °C. The mildness of the reaction conditions in the final stages of the synthetic sequence is ideally suited for the preparation of thermally labile enyne–allenes.



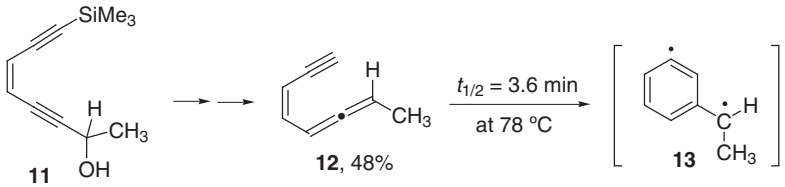
Scheme 20.2 Synthesis of (*Z*)-1,2,4-heptatrien-6-yne.

The Myers–Saito cyclization of **8** in deoxygenated 1,4-cyclohexadiene (1,4-CHD) produced toluene (60%) and combination products **10a** and **10b** (1:1, 40%) in quantitative yield (Scheme 20.3). The half-life of the transformation from **8** to the α,3-didehydrotoluene biradical **9a** was determined to be ~24 h at 37 °C. At 75 °C, the half-life of the reaction is reduced to 30 min. Although the transformation from **8** to **9** resulted in the net loss of one chemical bond, converting a π-bond in **8** to a σ-bond in **9** along with gains from aromaticity and benzylic resonance make the process energetically favorable. The reaction was estimated to be exothermic by ~15 kcal mol^{-1}. Thermolysis of **8** in methanol led to the formation of methyl benzyl ether (35%), 2-phenylethanol (10%) and bibenzyl (2%). The formation of methyl benzyl ether can best be accounted for by considering the biradical **9a** as the zwitterion **9b**. The use of light to initiate the photochemical Myers–Saito cyclization reaction has also been reported [28].



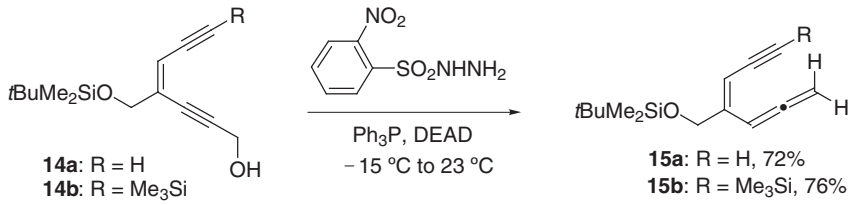
Scheme 20.3 The Myers–Saito cyclization reaction of (*Z*)-1,2,4-heptatrien-6-yne.

The enyne–allene **12** having a methyl substituent at the allenic terminus was likewise prepared from the corresponding enediynyl propargylic alcohol **11** (Scheme 20.4). The presence of a methyl group accelerates the rate of cyclization by approximately sixfold and **12** cyclizes with a half-life of ~3.6 min at 78 °C. The formation of a more stable secondary benzylic radical is apparently responsible for the rate enhancement.



Scheme 20.4 Synthesis and cyclization of (*Z*)-3,5,6-octatrien-1-yne.

An alternative one-step procedure involving treatment of the enediynyl propargylic alcohols **14a** and **14b** with triphenylphosphine, DEAD and finally *o*-nitrobenzenesulfonylhydrazine to give the corresponding enyne–allenes **15a** and **15b**, respectively, under mild thermal conditions has also been reported (Scheme 20.5)

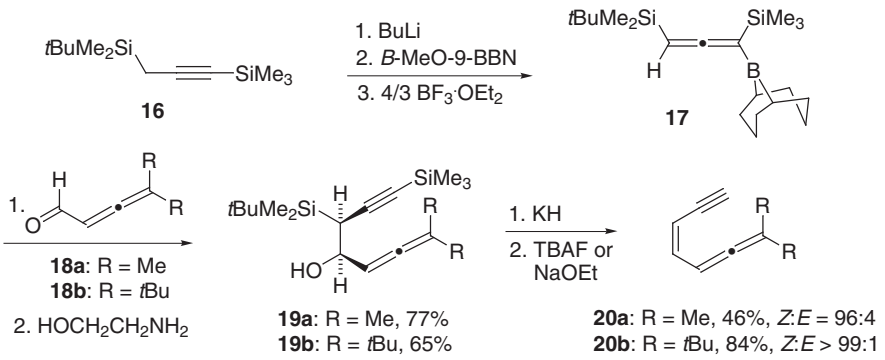


Scheme 20.5 One-step synthesis of enyne–allenes from enediynyl propargylic alcohols.

[29]. Apparently, the alkylated sulfonylhydrazines fragmented with the spontaneous elimination of *o*-nitrobenzenesulfinic acid to form the diazenes followed by the loss of dinitrogen leading to **15**. A benzannulated analog was likewise synthesized [30].

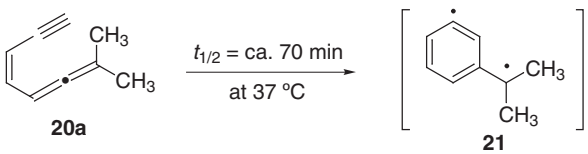
20.2.2
Condensation Between Allenic Aldehydes and [γ-(Trialkylsilyl)allenyl]boranes

A variety of enyne–allenic hydrocarbons were prepared by condensation between allenic aldehydes and [γ-(trialkylsilyl)allenyl]boranes to furnish the corresponding β-silyl alcohols, followed by elimination of the hydroxyl and the silyl groups to form the central carbon–carbon double bond. Specifically, the allenylborane **17** was prepared in situ by treatment of 3-(*tert*-butyldimethylsilyl)-1-(trimethylsily)-1-propyne (**16**) with *n*-butyllithium followed by *B*-methoxy-9-borabicyclo[3.3.1]nonane (*B*-MeO-9-BBN) and 4/3 equiv. of $BF_3 \cdot OEt_2$ (Scheme 20.6) [31]. Subsequent condensation with the conjugated allenic aldehydes **18** produced, after treatment with 2-aminoethanol, the β-silyl alcohols **19** with high diastereoselectivity. The achievement of high diastereoselectivity during condensation is crucial to forming the *Z* configuration of the central carbon–carbon double bond in the next step. The KH-induced *syn* elimination of hydroxy-*tert*-butyldimethylsilane from **19** followed by desilylation produced the enyne–allenes **20a** (*Z*:*E* = 96:4) and **20b** (*Z*:*E* > 99:1).



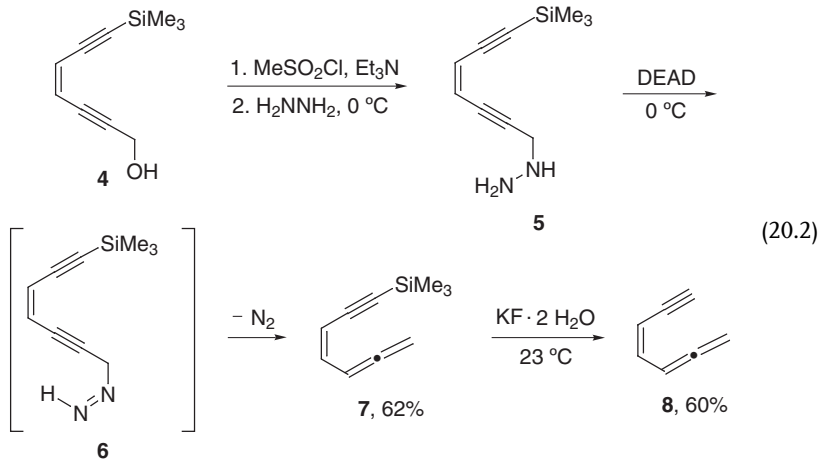
Scheme 20.6 Enyne–allenes from condensation between allenic aldehydes and a γ-(*tert*-butyldimethylsilyl)allenylborane.

With the presence of two methyl substituents at the allenic terminus of **20a**, the α,3-didehydrotoluene biradical **21** having a tertiary benzylic radical center was generated after cycloaromatization (Eq. 20.1). As a result, the half-life of the reaction is only ~70 min at 37 °C, which is significantly shorter than that of **8**.



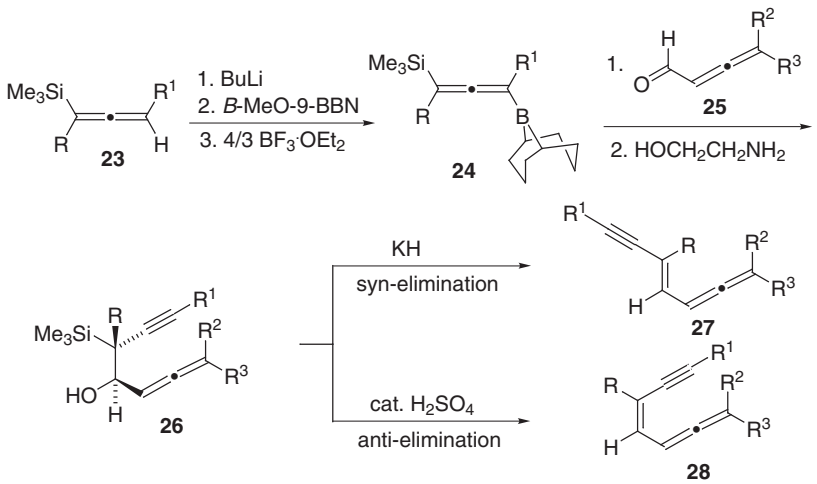
(20.1)

The enyne–allene **20b** having two sterically demanding *tert*-butyl groups exhibited a slower rate of cyclization ($t_{1/2} \approx 60$ min at 76 °C) when compared with **20a** (Eq. 20.2). It is worth noting that the benzylic radical center in **22** is an α,α-di-*t*-butylbenzylic radical, which has been shown to be persistent in dilution solution at room temperature for several days [32].



(20.2)

Condensation between the allenic aldehydes **25** and the allenylboranes **24**, derived from the allenylsilanes **23**, also exhibited high diastereoselectivity (Scheme 20.7) [33–35]. However, unlike **17**, a reversal of diastereoselectivity in favor of the *RR*/*SS* pair of the α-silyl alcohols **26** occurred. Consequently, treatment of **26** with potassium hydride to promote the *syn* elimination furnished the enyne–allenes **27** having predominantly the *E* configuration (*E*:*Z* ≥ 96:4) for the central carbon–carbon double



Scheme 20.7 Enyne–allenes from condensation between allenic aldehydes and γ-(trimethylsilyl)allenylboranes.

bond (Table 20.1). On the other hand, treatment of **26** with a catalytic amount of concentrated sulfuric acid to promote the *anti* elimination afforded **28** having predominantly the *Z* configuration (*Z*:*E* ≥ 96:4). The ability to prepare both isomers through a common α-silyl alcohol is an attractive feature of this synthetic method.

Table 20.1 Synthesis of the α-silyl alcohols **26** and the enyne–allenes **27** and **28**.

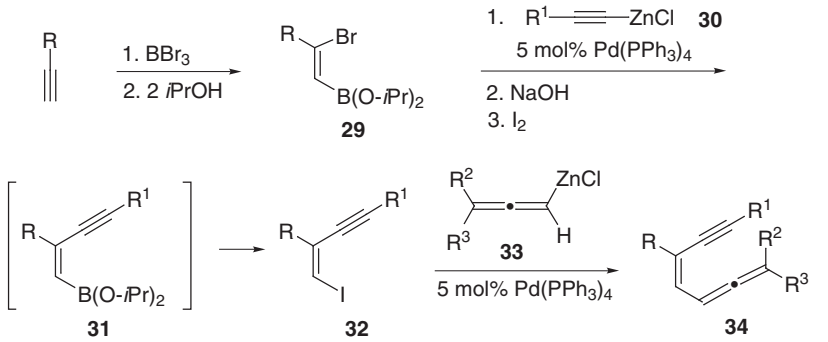
R	R^1	R^2	R^3	**26** (%)	**27** (%)	**28** (%)
Pr	H	Me	Me	**26a** (52)		**28a** (69)
Bu	H	Me	Me	**26b** (63)		**28b** (80)
$-(CH_2)_2CH(CH_3)_2$	H	Me	Me	**26c** (70)		**28c** (81)
$-(CH_2)_6CH=CH_2$	H	Me	Me	**26d** (56)		**26d** (87)
Me	Me	Me	Me	**26e** (89)	**27e** (90)	**28e** (91)
Me	Me	Bu	Bu	**26f** (90)	**27f** (92)	**28f** (82)
$-(CH_2)_2CH=CH_2$	Me	Me	Me	**26g** (92)	**27g** (91)	**28g** (92)
$-(CH_2)_2CH=CH_2$	Me	CD_3	CD_3	**26h** (89)		**28h** (88)
$-(CH_2)_2CH=CH_2$	Me	H	$-(CH_2)_4CH=CH_2$	**26i** (80)		**28i** (93)
$-(CH_2)_2C(CH_3)=CH_2$	Me	H	$-(CH_2)_4CH=CH_2$	**26j** (81)		**28j** (86)
$-(CH_2)_3CH=CH_2$	Me	H	$-(CH_2)_4CH=CH_2$	**26k** (68)		**28k** (81)
$-(CH_2)_3CH=CH_2$	Me	Me	Me	**26l** (68)		**28l** (84)
$-(CH_2)_2C(CH_3)_2CH=CH_2$	Me	H	$-(CH_2)_4CH=CH_2$	**26m** (62)		**28m** (73)
$-(CH_2)_2C(CH_3)_2CH=CH_2$	Me	Me	Me	**26n** (65)		**28n** (71)

The presence of a methyl substituent at the acetylenic terminus of the enyne–allenes **28e–n** appears to reduce the rate of cyclization, presumably for steric reasons. The higher thermal stability allows their isolation and purification at ambient temperature without special precautions.

20.2.3 Palladium-Catalyzed Cross-Coupling Reactions

Palladium-catalyzed cross-coupling reactions have also been employed for the synthesis of a variety of enyne–allenes. This strategy generally involved the use of an appropriately substituted alkene for subsequent couplings with alkynyl and allenyl derivatives. The (*Z*)-2-bromoalkenylboronic esters **29**, readily prepared from bromoboration of a terminal alkyne with tribromoborane followed by treatment with isopropyl alcohol, were found to be well suited for this purpose (Scheme 20.8) [33, 36]. Treatment of **29** with the alkynylzinc chlorides **30** in the presence of 5 mol% of $Pd(PPh_3)_4$ followed by iodination gave the enynyl iodides **32**. Subsequent coupling with the allenylzinc chlorides **33** then afforded the enyne–allenes **34** (Table 20.2).

The β-trimethyltin-substituted alkenylborane **36** was prepared in situ by treatment of triethylborane with 1-lithio-1-hexyne to form the lithium 1-alkynyltriethylborate **35** followed by trimethyltin chloride (Scheme 20.9) [37]. The trimethyltin chloride-induced migration of an ethyl group from boron to the adjacent acetylenic carbon is stereoselective with the boron and the tin substituents in **36** *cis* to each



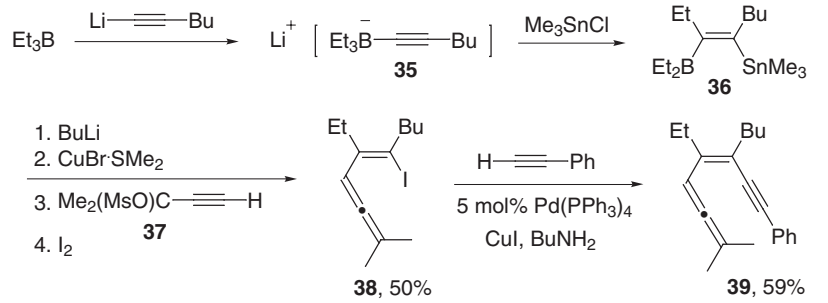
Scheme 20.8 Enyne–allenes from Pd-catalyzed couplings with (*Z*)-2-bromoalkenylboronic esters.

Table 20.2 Stereoselective synthesis of the enyne–allenes **34**.

R	R^1	R^2	R^3	Boronic esters 29 (%)	Enynyl iodides 32 (%)	Enyne–allenes 34 (%) *Z*:*E* ≥ 96:4
Bu	Bu	Me	Me	**29a** (79)	**32a** (55)	**34a** (78)
Bu	Bu	H	n-C_6H_{13}			**34b** (68)
Bu	Ph	Me	Me		**32c** (64)	**34c** (81)
Bu	Ph	H	n-C_6H_{13}			**34d** (74)
$-(CH_2)_2CH{=}CH_2$	Me	H	$-(CH_2)_4CH{=}CH_2$	**29e** (58)	**32e** (50)	**34e**[1] (64)
$-(CH_2)_2CH{=}CH_2$	Me	H	$-(CH_2)_3CH{=}CH_2$			**34f** (80)
$-(CH_2)_2CH{=}CH_2$	Me	H	$-(CH_2)_3C(CH_3){=}CH_2$			**34g** (89)

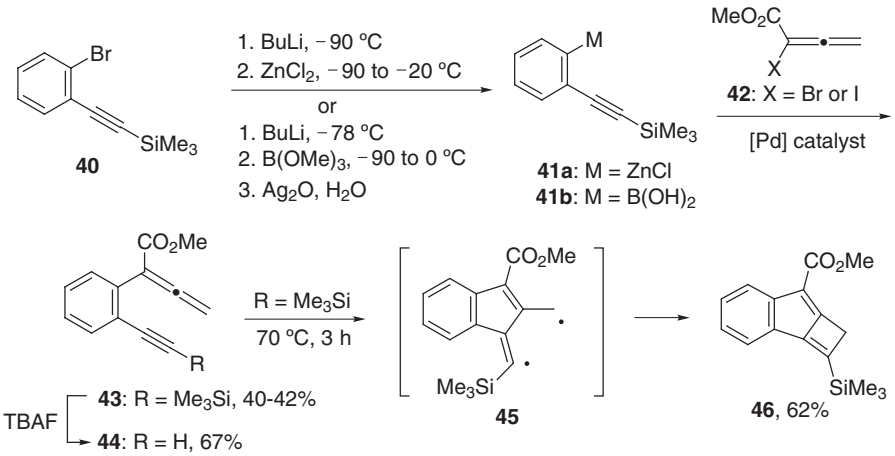
1) The structure of **34e** is identical with that of **28i**.

other. The alkenylborane moiety of **36** was then converted to the corresponding alkenylcopper for coupling with the propargylic methanesulfonate **37** to produce the ene–allenic iodide **38** in 50% overall yield from triethylborane in a single operation. Subsequent coupling with phenylacetylene afforded the enyne–allene **39**. Interestingly, an attempt to couple **38** with propargyl alcohol led to the direct formation of the cycloaromatized adduct.



Scheme 20.9 Enyne–allenes from a β-trimethyltin-substituted alkenylborane.

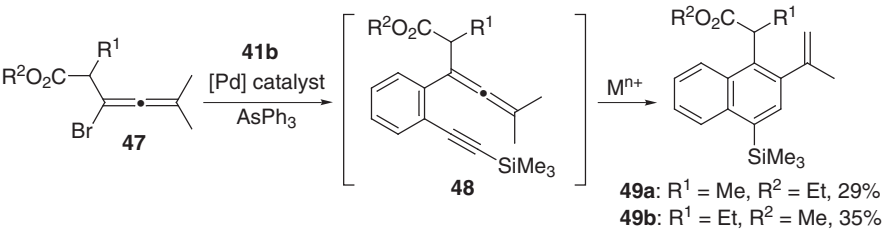
The aryl bromide **40**, prepared from cross-coupling between 1,2-dibromobenzene and (trimethylsilyl)acetylene, was converted to the corresponding arylzinc halide **41a** and arylboronic acid **41b** for subsequent coupling with the haloallenes **42** to produce the benzannulated enyne–allene **43** in ~40% yield (Scheme 20.10) [38]. Desilylation with tetrabutylammonium fluoride (TBAF) then afforded **44** in 67% yield.



Scheme 20.10 Synthesis of benzannulated enyne–allenes via Pd-catalyzed couplings.

Thermolysis of **44** produced products derived from the Myers–Saito cyclization reaction. However, when **43** having a trimethylsilyl substituent at the acetylenic terminus was subjected to heating in the presence of 1,4-CHD at 70 °C for 3 h, the 1*H*-cyclobut[*a*]indene **46** was produced. A reaction mechanism involving an initial Schmittel cyclization to generate the benzofulvene biradical **45** followed by an intramolecular radical–radical coupling was proposed to account for the formation of the formal [2 + 2]-cycloaddition product **46**.

The benzannulated enyne–allenes **48** were likewise synthesized in situ from coupling between **41b** and the bromoallene **47** (Scheme 20.11) [39]. Under the reaction conditions, **48** presumably underwent a spontaneous cation-mediated Myers–Saito cyclization reaction with a concomitant 1,2-shift of the trimethylsilyl group to give the naphthalene derivatives **49**.

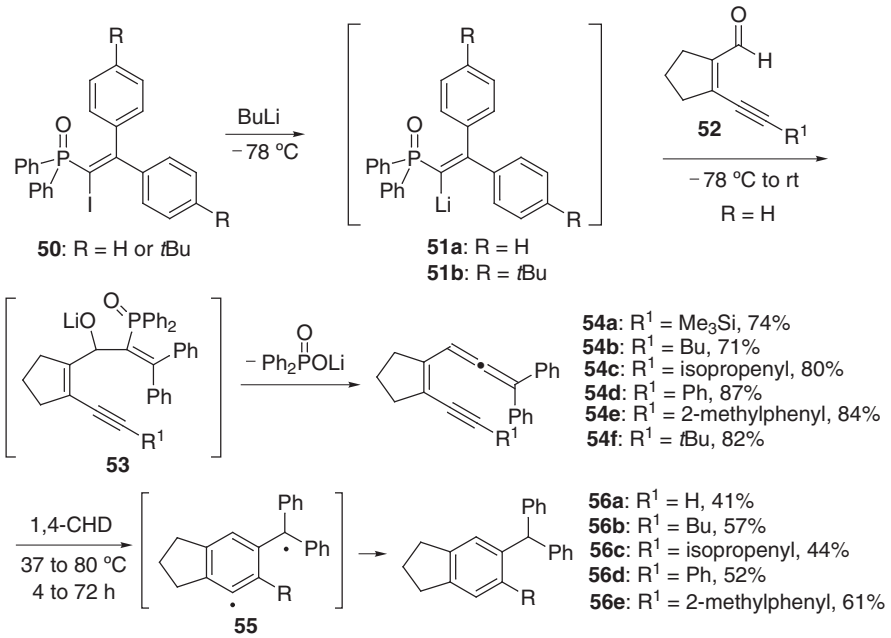


Scheme 20.11 Cation-mediated Myers–Saito cyclization reaction.

20.2.4

The Horner–Wittig and Related Reactions

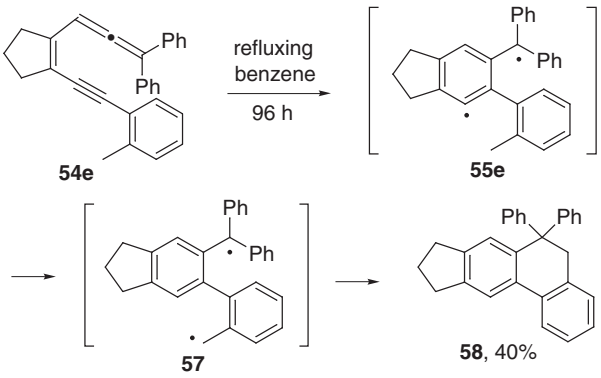
The Horner–Wittig and related reactions have also been adopted for the synthesis of enyne–allenes. The α-lithioalkenylphosphine oxides **51** were produced from **50** by lithium–halogen exchange for the Horner–Wittig reaction (Scheme 20.12) [40]. Condensation between **51a** and the enynyl aldehydes **52** produced **53**, which undergo spontaneous elimination to furnish the enyne–allenes **54**. The Myers–Saito cyclization of the desilylated adduct of **54a** and **54b–e** occurred readily between 37 and 80 °C to generate the biradicals **55**. Subsequent hydrogen atom abstractions from 1,4-CHD then afforded the cycloaromatized adducts **56**.



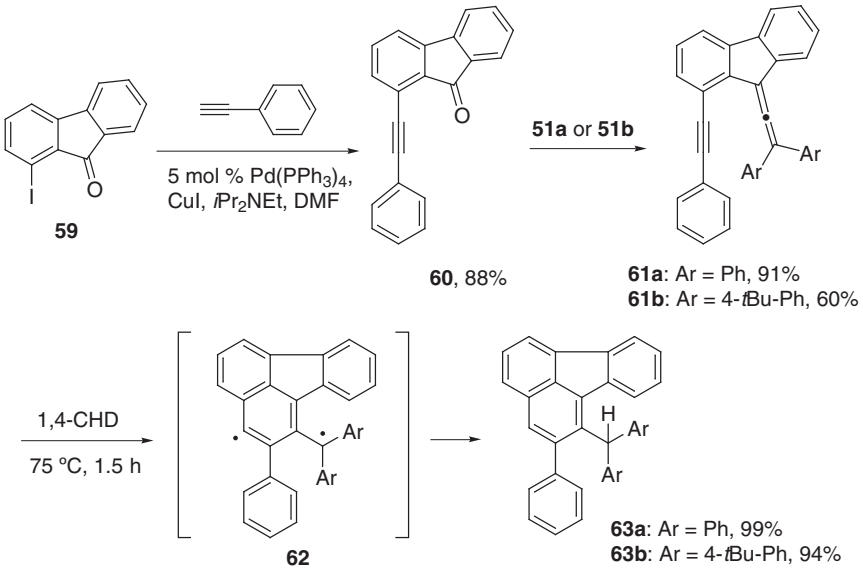
Scheme 20.12 Enyne–allenes via the Horner–Wittig reaction.

It is interesting that **54d** and **54e** undergo the Myers–Saito cyclization even though an aryl substituent is presence at the acetylenic terminus. This preference has been attributed to the emergence of substantial ring strain in the resulting biradicals having a bicyclo[3.3.0]octadienyl system had the reaction proceeded through the Schmittel cyclization [41, 42].

In the absence of 1,4-CHD, the biradical **55e** undergoes an intramolecular 1,5-hydrogen shift to form **57**, making it possible for an intramolecular radical–radical coupling to occur to produce **58** (Scheme 20.13). The fact that **58** was produced from **54e** lends support to the formation of the α,3-didehydrotoluene biradical **55e** as a transient reaction intermediate. It is also worth noting that the benzylic radical center in **55** is a stabilized triarylmethyl radical.



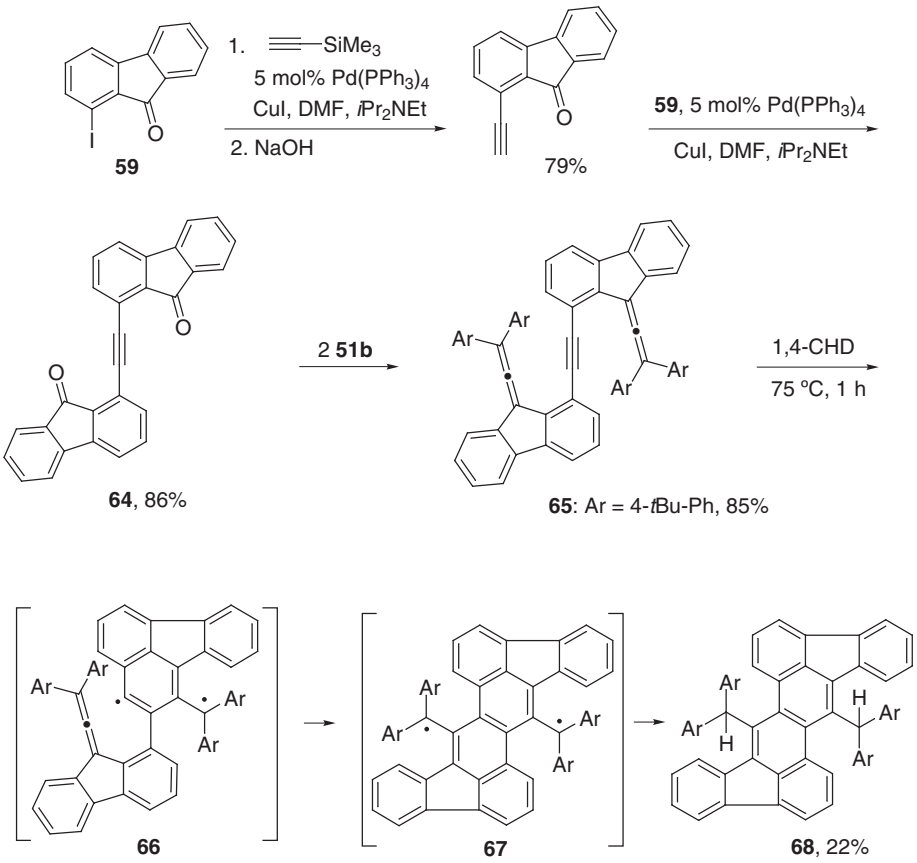
Scheme 20.13 Intramolecular 1,5-hydrogen shift of an α,3-didehydrotoluene biradical.



Scheme 20.14 α,3-Didehydrotoluene biradicals having a triarylbenzylic radical center.

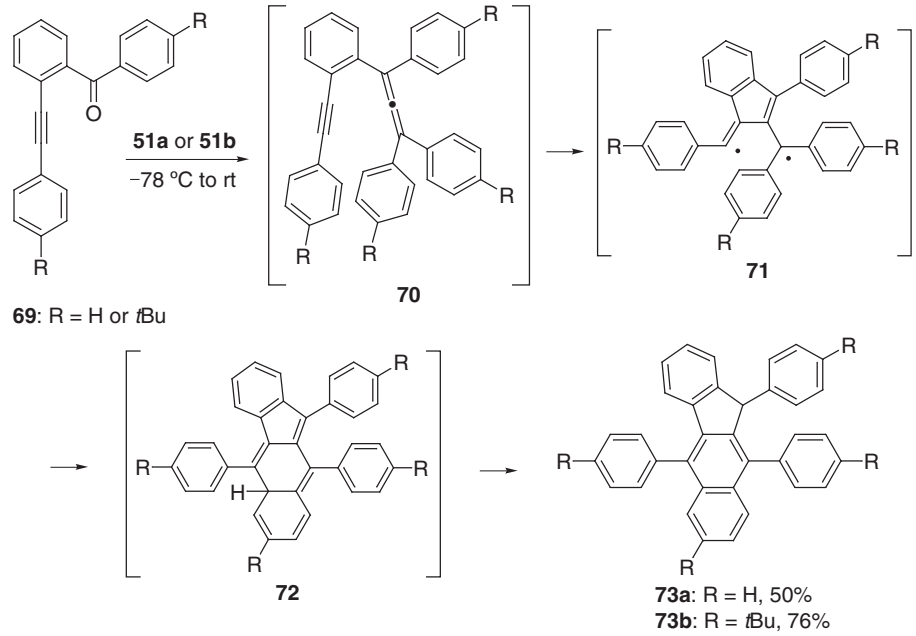
The use of 1-iodo-9-fluorenone (**59**) for cross-coupling with phenylacetylene produced **60**, which on treatment with **51** gave the benzannulated enyne–allenes **61** (Scheme 20.14) [43]. Thermolysis of **61** in 1,4-CHD at 75 °C promoted the Myers–Saito cyclization reaction, leading to **63** in excellent yields. Again, the benzylic radical center in **62** is a stabilized triarylmethyl radical.

The diketone **64** was also readily prepared from **59** as outlined in Scheme 20.15. Condensation between **64** and 2 equiv. of **51b** gave **65** in excellent yield. Thermolysis of **65** in 1,4-CHD at 75 °C also promoted the Myers–Saito cyclization reaction to generate the biradical **66**. The aryl radical center in **66** was then captured by the allenic moiety to form **67**, having two stabilized triarylmethyl radical centers. Subsequent hydrogen-atom abstractions from 1,4-CHD then furnished **68**.



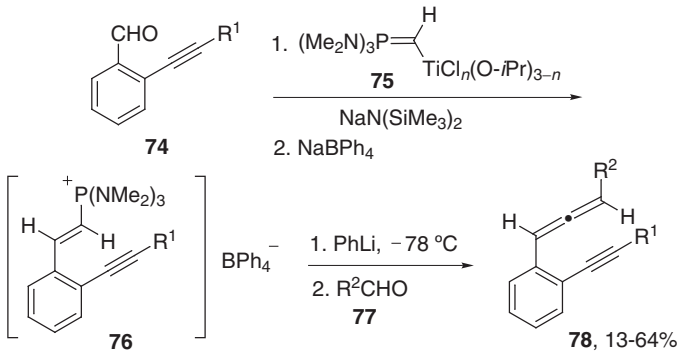
Scheme 20.15 Biradical having two triarylbenzylic radical centers.

As in **54**, the presence of the fused five-membered ring in **61** and **65** is crucial in directing the initial biradical-forming step toward the Myers–Saito pathway. Without the five-membered ring, the benzophenones **69**, on treatment with **51**, produced the 11*H*-benzo[*b*]fluorenes **73** (Scheme 20.16). Apparently, the initial Horner–Wittig reaction produced **70**, which then underwent a facile Schmittel cyclization at ambient or subambient temperature to form the benzofulvene biradicals **71**. The subsequent intramolecular radical–radical coupling then produced the formal Diels–Alder adducts **72** and subsequently, after a prototropic rearrangement, the 11*H*-benzo[*b*]-fluorenes **73**. Although the transformation from **70** to **72** could be considered as a concerted Diels–Alder reaction, theoretical [12–26], mechanistic [44–48] and DNA-cleaving [49] studies of analogous systems suggest a two-step biradical pathway.



Scheme 20.16 11*H*-Benzo[*b*]fluorenes via the Schmittel cyclization reaction.

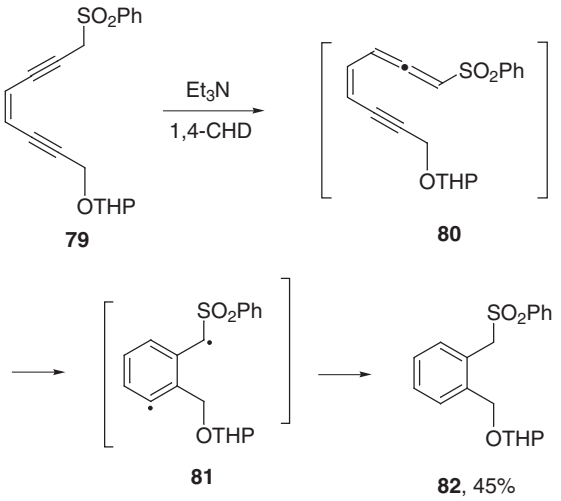
The metallated phosphorus methylide reagent **75**, capable of undergoing double olefination with aryl aldehydes to give enyne–allenes, has also been reported (Scheme 20.17) [50]. The doubly oxophilic ylide reagent was prepared in situ from $TiCl_2(OiPr)_2$, $(Me_2N)_3P{=}CH_2$ and $NaN(SiMe_3)_2$. Treatment of the acetylenic aldehydes **74** with the ylide **75** gave the vinylphosphonium salts **76**, which on treatment with phenyllithium followed by a second aldehyde **77** furnished **78**. Two other related procedures were also employed to prepare a variety of enyne–allenes for kinetic and mechanistic investigations of the Myers–Saito cyclization reaction.



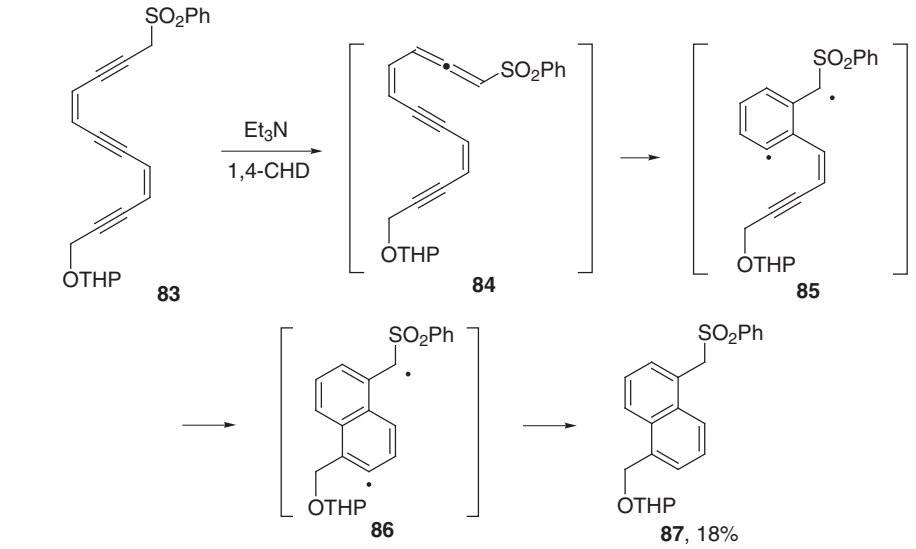
Scheme 20.17 Enyne–allenes via titanium-substituted ylides.

20.2.5
Prototropic Rearrangement

The prototropic rearrangement of enediynes represents a simple and direct synthetic pathway to enyne–allenes. The high acidity of the α-hydrogens of the enediynyl sulfone **79** permits the use of triethylamine to promote a prototropic rearrangement to form **80**, which then cyclizes to **81** and, after hydrogen-atom abstractions, **82** (Scheme 20.18) [51]. The enediynyl sulfone **83** was also prepared to allow the aryl radical center in **85** to be captured by the carbon–carbon triple bond intramolecularly, leading to the new biradical **86** and then **87** (Scheme 20.19) [52]. Other examples of the base-induced prototropic rearrangement of the enediynyl sulfones, including a cyclic system, have also been reported [53, 54].

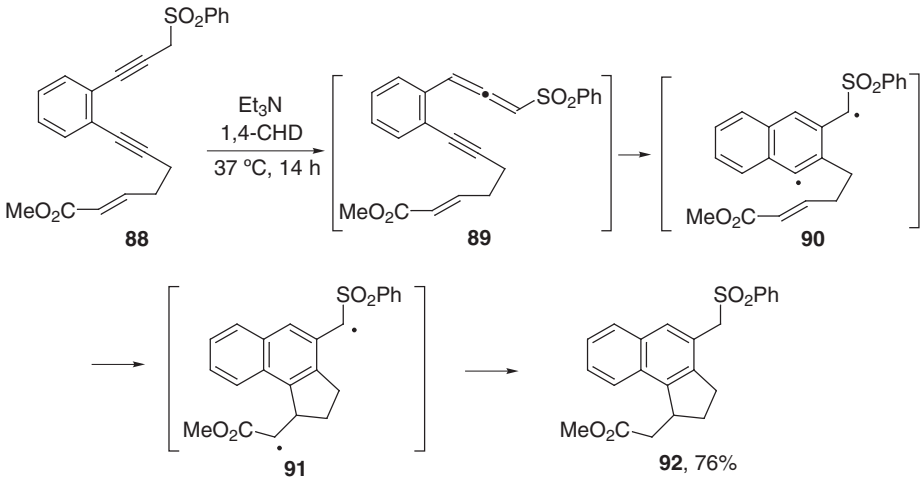


Scheme 20.18 Enyne–allenes via prototropic rearrangement of enediynyl sulfones.



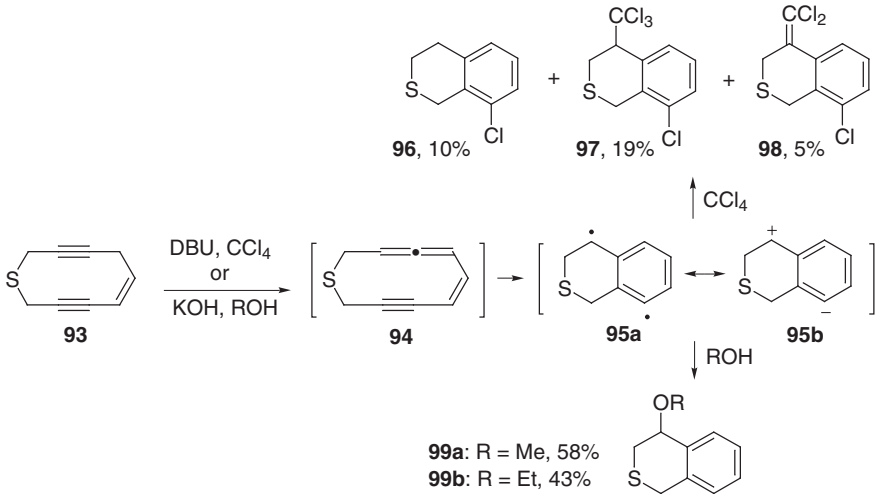
Scheme 20.19 Double cycloaromatization of an enediynyl sulfone.

The benzannulated analogs were also found to behave in a similar fashion. Attachment of a pendent olefin to the benzannulated enyne–allene system as depicted in **89** allowed the aryl radical in **90** to be captured in a 5-*exo* radical cyclization reaction leading to **91** and then the dihydrobenz[*e*]indene **92** (Scheme 20.20) [55, 56].



Scheme 20.20 Tandem enyne–allene and radical cyclizations.

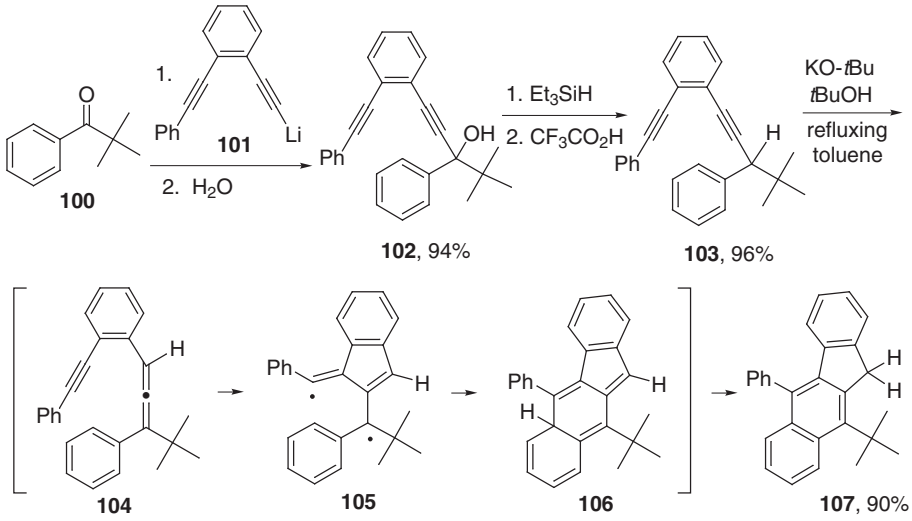
The cyclic enediynyl sulfide **93** is also prone to undergo prototropic rearrangement (Scheme 20.21) [57]. When the 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-induced isomerization was conducted in carbon tetrachloride, three cycloaromatized products, **96** to **98**, were isolated, indicating the formation of the biradical **95a** as a transient intermediate. In a polar solvent, such as methanol or ethanol, the formation of **99** can best be accounted for by regarding the biradical **95a** as the zwitterion ion **95b**. A related process involving the oxidation of **93** with selenium dioxide has also been reported [58].



Scheme 20.21 Synthesis and cyclization of a 10-membered ring enyne–allene.

A similar process involving an all-carbon cyclic system has also been investigated [59]. Other examples involving the prototropic rearrangement of enediynes having an imino or a keto substituent at the propargylic position to form the corresponding enyne–allenes have also been observed [60, 61].

The propargylic alcohol **102**, prepared by condensation between **100** and the lithium acetylide **101**, was efficiently reduced to the hydrocarbon **103**, which on treatment with potassium *tert*-butoxide was isomerized to the benzannulated enyne–allene **104** (Scheme 20.22) [62]. At room temperature, the formation of **104** was detected. In refluxing toluene, the Schmittel cyclization occurs readily to generate the biradical **105**, which then undergoes intramolecular radical–radical coupling to give **106** and, after a prototropic rearrangement, the 11*H*-benzo[*b*]fluorene **107**. Several other 11*H*-benzo[*b*]fluorenes were likewise synthesized from cyclic aromatic ketones.

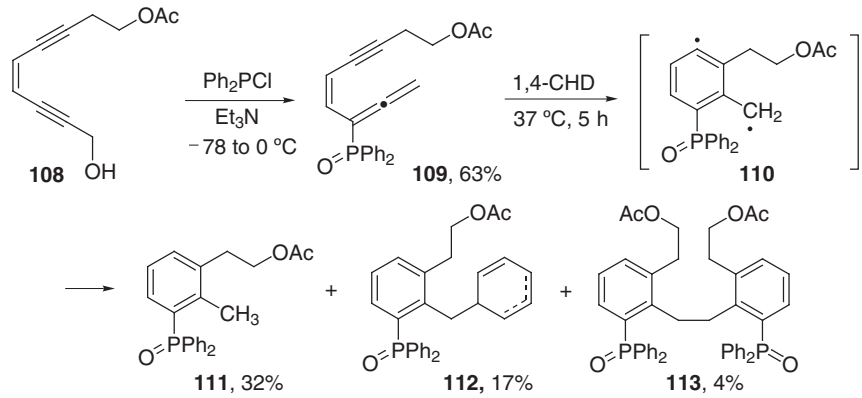


Scheme 20.22 Synthesis of 11*H*-benzo[*b*]fluorenes via prototropic rearrangement of benzannulated enediynes.

20.2.6

Phosphorus- and Sulfur-Substituted Enyne–Allenes

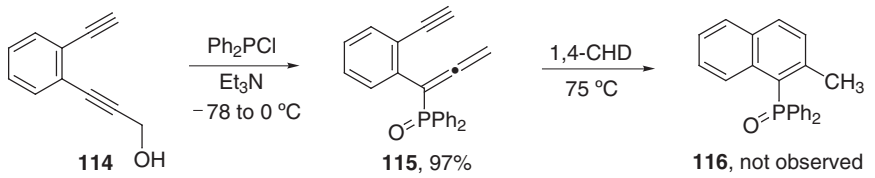
The use of chlorodiphenylphosphine to induce a [2,3]-sigmatropic rearrangement of enediynyl propargylic alcohols is one of the first synthetic methods adopted for the preparation of enyne–allenes. For instance, treatment of **108** with chlorodiphenylphosphine and triethylamine at –78 to 0 °C afforded the enyne–allenylphosphine oxide **109** in 63% isolated yield (Scheme 20.23) [9]. Thermolysis of **109** at 37 °C in the presence of 1,4-CHD generated the biradical **110**, leading to **111** and combina-



Scheme 20.23 Synthesis and cyclization of phosphorus-substituted enyne–allenes.

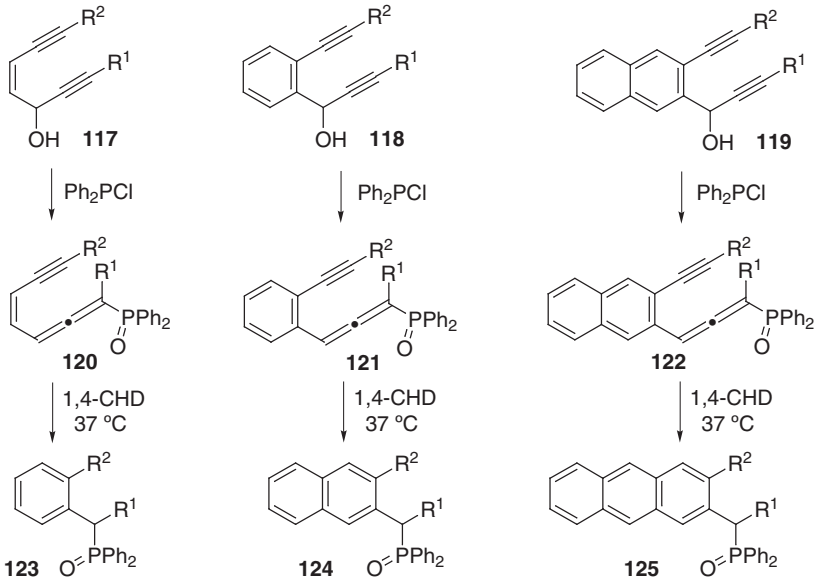
tion and coupling products **112** and **113**. The radical nature of the reaction was also demonstrated by capturing the aryl radical with a pendent carbon–carbon or carbon–nitrogen double bond [56].

The benzannulated analog **115** was likewise synthesized from **114** (Scheme 20.24) [56, 63]. However, unlike **109**, thermolysis of **115** resulted in its slow decomposition without the formation of the cycloaromatized adduct **116**. The lack of propensity for **115** to undergo the Myers–Saito cyclization reaction was attributed to unfavorable steric interactions between the diphenylphosphinyl group and the aryl ring of the benzannulated enyne–allene system, causing the allenic moiety to be rotated out of the plane defined by the aryl ring and preventing the cyclization reaction.



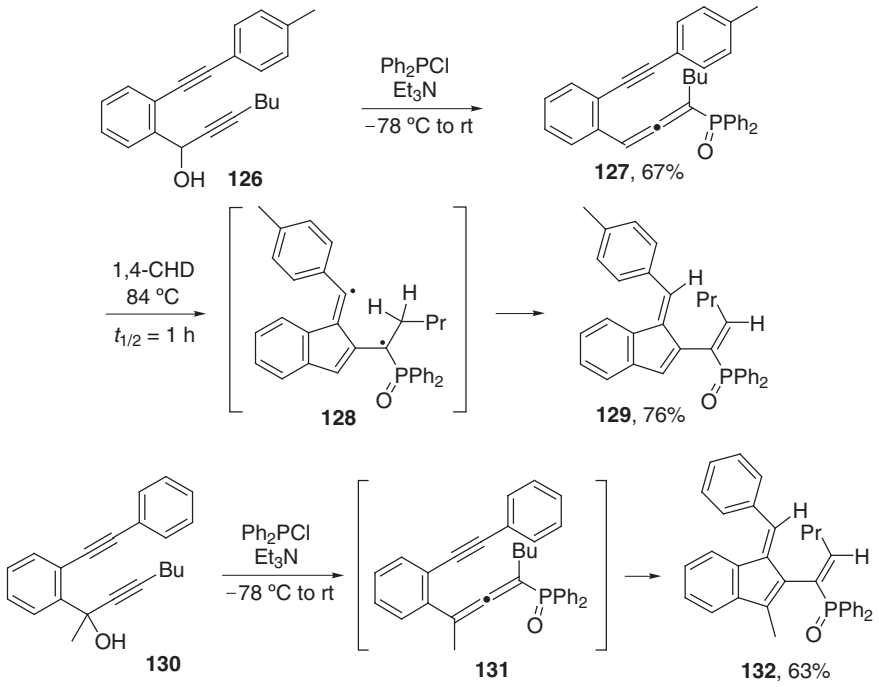
Scheme 20.24 Synthesis of phosphorus-substituted benzannulated enyne–allenes.

The enyne–allenylphosphine oxides **120** and the benzannulated and naphthannulated analogs **121** and **122** having the diphenylphosphinyl group at the allenic terminus were readily prepared from the corresponding enediynyl propargylic alcohols **117**, **118** and **119** (Scheme 20.25) [64]. Without the unfavorable steric interactions, these conjugated derivatives smoothly underwent the Myers–Saito cyclization reaction.



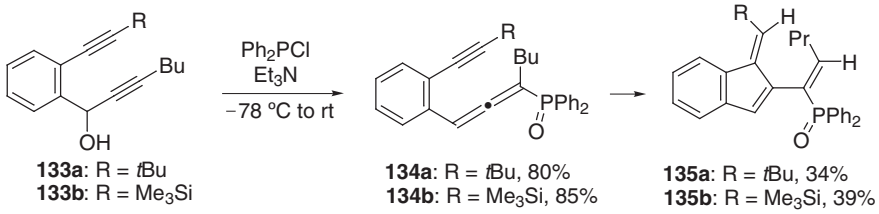
Scheme 20.25 Synthesis and cyclization of enyne–allenylphosphine oxides.

The switch from the Myers–Saito cyclization to the Schmittel cyclization was first discovered when the propargylic alcohols **126** and **130** having an aryl substituent at the acetylenic terminus were treated with chlorodiphenylphosphine (Scheme 20.26) [11]. Cyclization of **127** occurred at 84 °C with a half-life of 1 h to form the benzofulvene biradical **128**, which in turn underwent a 1,5-hydrogen shift to form **129**. Interestingly, unlike **115**, the presence of a methyl substituent at the internal position of the allenic moiety in **131** greatly enhances the rate of cyclization. Cyclization occurred much below ambient temperature and **132** was isolated in 63% yield. Although transformations from **127** to **129** and from **131** to **132** could also be considered as an intramolecular ene reaction, theoretical [12–26], mechanistic [44, 47] and DNA-cleaving studies [49] also suggest that the reaction proceeds through a two-step biradical pathway.



Scheme 20.26 Schmittel cyclization reactions of benzannulated enyne–allenes.

The presence of a sterically demanding *tert*-butyl or trimethylsilyl group at the acetylenic terminus also makes the Schmittel cyclization the preferred pathway (Scheme 20.27) [65]. This observation has been attributed to the emergence of severe non-bonded steric interactions in the naphthalene biradicals derived from the Myers–Saito cyclization.



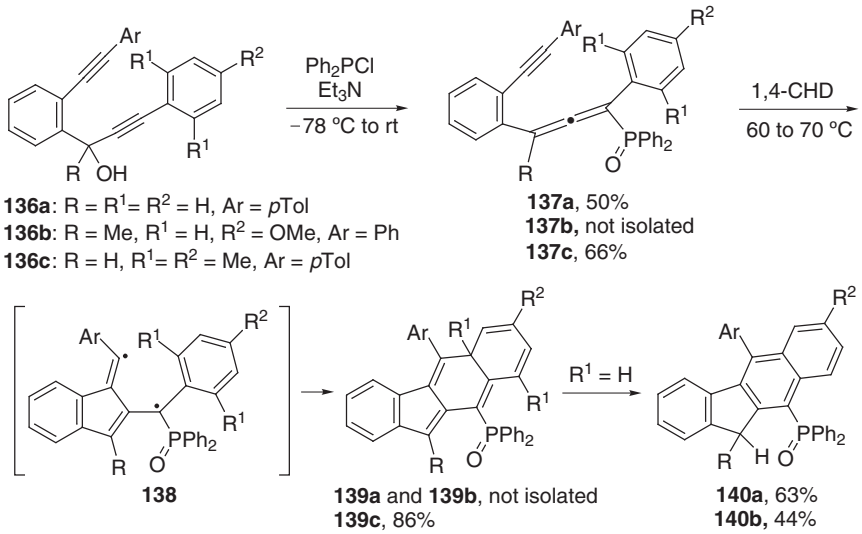
133a: R = *t*Bu
133b: R = Me_3Si

134a: R = *t*Bu, 80%
134b: R = Me_3Si, 85%

135a: R = *t*Bu, 34%
135b: R = Me_3Si, 39%

Scheme 20.27 Schmittel cyclization reactions of *tert*-butyl- and trimethylsilyl-substituted enyne–allenes.

Attaching an aryl substituent at the allenic terminus makes it possible for the intramolecular radical–radical coupling of the benzofulvene biradicals **138** to occur, leading to the 11*H*-benzo[*b*]fluorenes **140a** and **140b** and a related compound **139c** (Scheme 20.28) [45, 66]. The fact that the sterically demanding mesityl group in **137c** is involved in an unprecedented formal Diels–Alder reaction to produce **139c** also lends support to the two-step biradical pathway.



136a: R = R^1= R^2 = H, Ar = *p*Tol
136b: R = Me, R^1 = H, R^2 = OMe, Ar = Ph
136c: R = H, R^1= R^2 = Me, Ar = *p*Tol

137a, 50%
137b, not isolated
137c, 66%

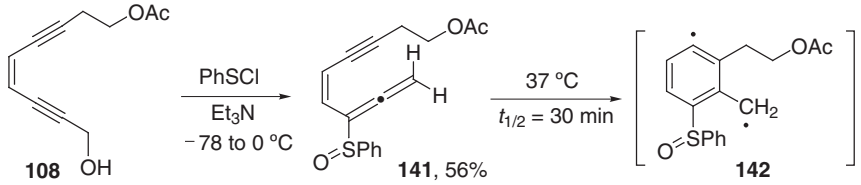
138

139a and **139b**, not isolated
139c, 86%

140a, 63%
140b, 44%

Scheme 20.28 11*H*-Benzo[*b*]fluorenes via phosphorus-substituted enyne–allenes.

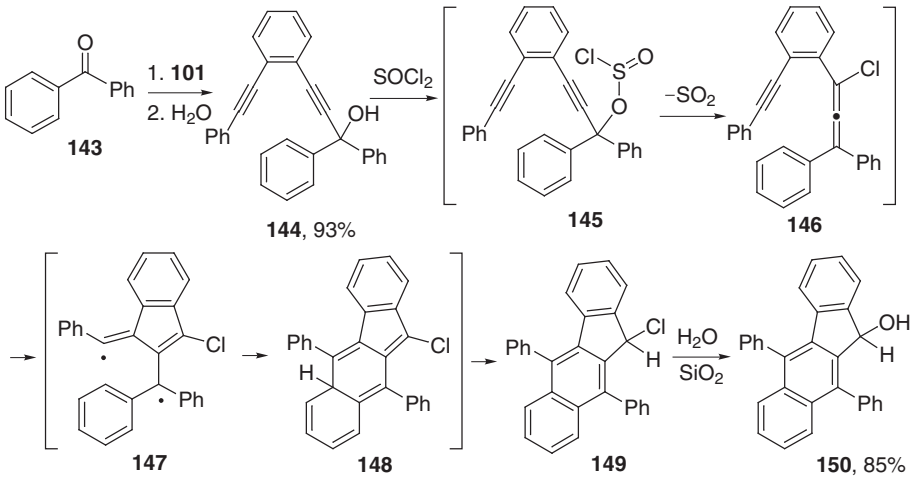
In addition to the sulfur-substituted enyne–allenes depicted in Schemes 20.18–20.20, the sulfoxide **141** was prepared by treatment of the enediynyl propargylic alcohol **108** with benzenesulfenyl chloride to induce a [2,3]-sigmatropic rearrangement (Scheme 20.29) [10]. The Myers–Saito cyclization of **141** occurs at 37 °C with a half-life of only 16 min.



Scheme 20.29 Synthesis and cyclization of an enyne–allenyl sulfoxide.

20.2.7
Chlorinated Enyne–Allenes

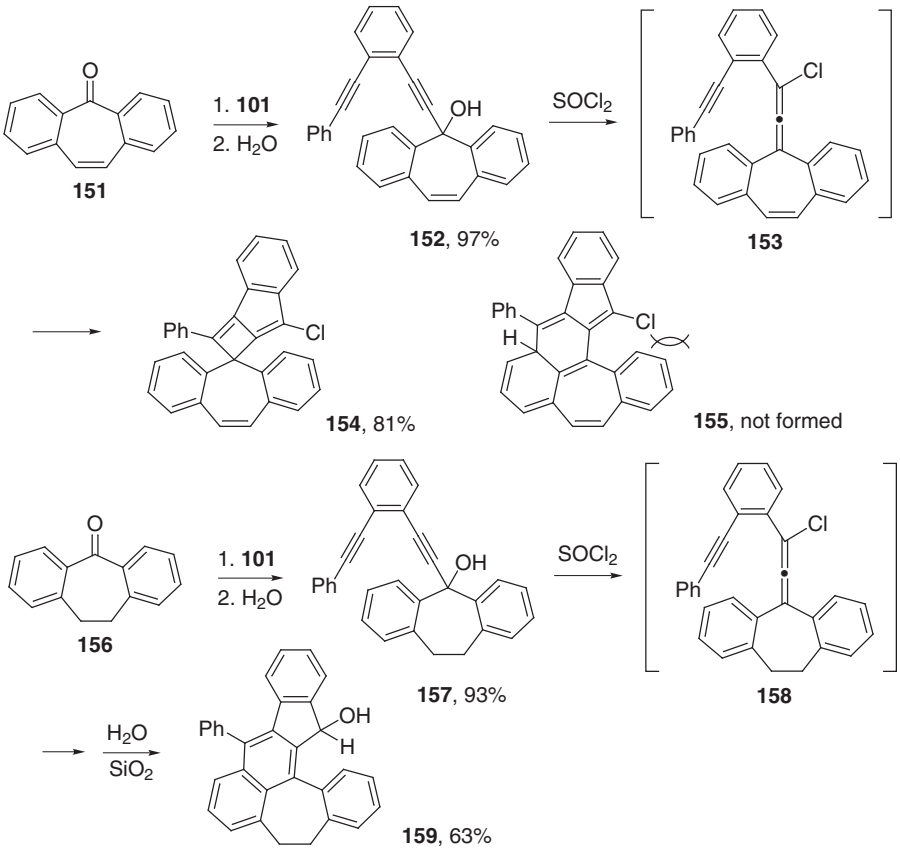
Treatment of the propargylic alcohol **144**, readily prepared from condensation between benzophenone (**143**) and the lithium acetylide **101**, with thionyl chloride promoted a sequence of reactions with an initial formation of the chlorosulfite **145** followed by an S_Ni' reaction to produce in situ the chlorinated and the benzannulated enyne–allene **146** (Scheme 20.30) [62]. A spontaneous Schmittel cyclization then generated the biradical **147**, which in turn underwent a radical–radical coupling to form the formal [4 + 2]-cycloaddition product **148** and subsequently, after a prototropic rearrangement, **149**. The chloride **149** is prone to hydrolysis to give the corresponding 11*H*-benzo[*b*]fluoren-11-ol **150** in 85% overall yield from **144**. Several other 11*H*-benzo[*b*]fluoren-11-ols were likewise synthesized from benzophenone derivatives.



Scheme 20.30 Synthesis and cyclization of chlorinated enyne–allenes.

Interestingly, when **152**, derived from dibenzosuberenone (**151**), was treated with thionyl chloride, the [2 + 2]-cycloaddition product **154** was produced exclusively (Scheme 20.31). Apparently, the [4 + 2]-cycloaddition product was not produced. On

the other hand, with **157**, derived from dibenzosuberone (**156**), the formal [4 + 2]-cycloaddition of the resultant chlorinated enyne–allene **158** was again the preferred pathway, leading to **159**. The change of the reaction pathway for **153** has been attributed to the emergence of unfavorable steric interactions as depicted in **155** between the chloro substituent and one of the neighboring benzene rings along the pathway toward the formal [4 + 2]-cycloaddition reaction. Replacing the central carbon–carbon double bond in **153** with the dimethylene linkage in **158** appears to reduce such a non-bonded steric interaction.

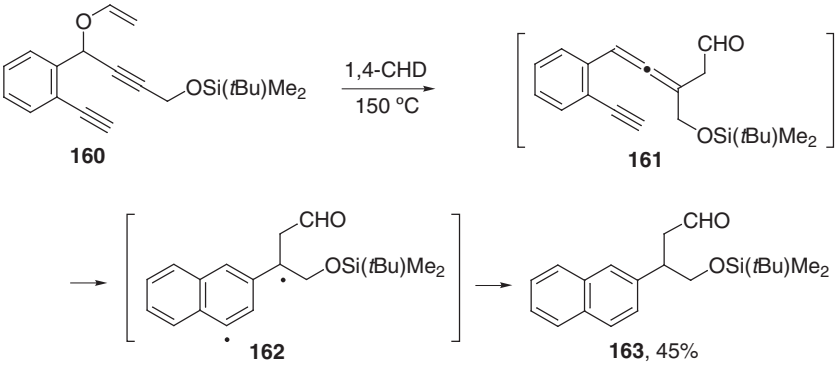


Scheme 20.31 Intramolecular [2 + 2]- versus [4 + 2]-cycloaddition reactions of benzannulated enyne–allenes.

20.2.8
[3,3]-Sigmatropic Rearrangements

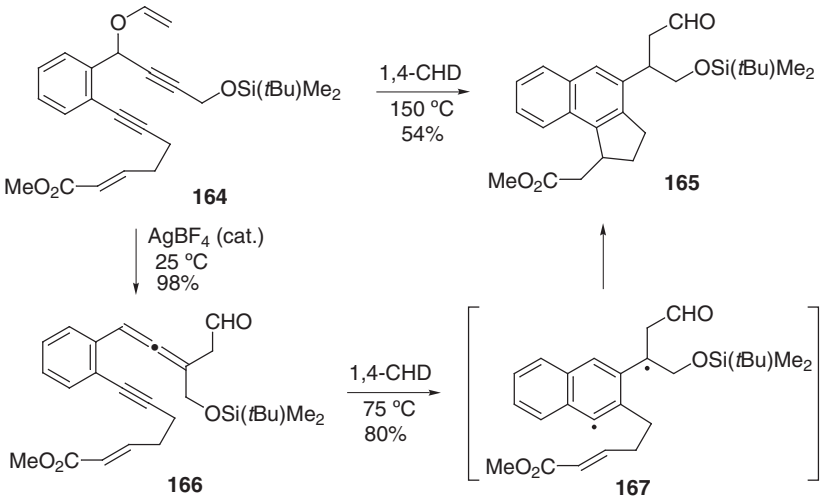
The synthetic strategy involving the use of a [3,3]-sigmatropic rearrangement of propargylic vinyl ethers for the preparation of enyne–allenes has also been investigated.

When **160** was heated at 150 °C in the presence of 1,4-CHD, the naphthalene derivative **163** was obtained in 45% yield (Scheme 20.32) [56, 67]. An initial [3,3]-sigmatropic rearrangement to form **161** followed by a Myers–Saito cyclization and hydrogen-atom abstractions from 1,4-CHD could account for the formation of **163**.



Scheme 20.32 Synthesis and cyclization of enyne–allenes via a [3,3]-sigmatropic rearrangement.

Thermolysis of **164** bearing a pendent olefin at 150 °C also allows the aryl radical in **167** to be captured in a 5-*exo* fashion, leading to **165** as a 1:1 mixture of diastereomers (Scheme 20.33). The corresponding Lewis acid-catalyzed [3,3]-sigmatropic rearrangement promoted by $AgBF_4$ was facile at room temperature, making it possible for **166** to be isolated. Thermolysis of **166** at 75 °C afforded **165** in 80% yield.

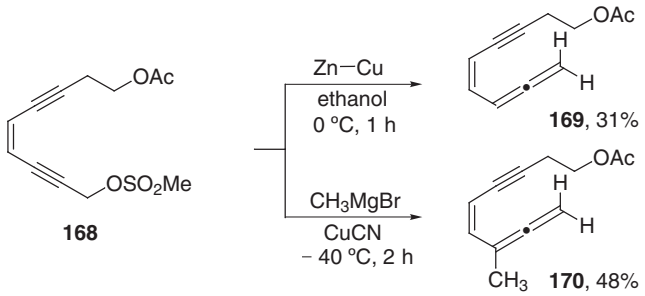


Scheme 20.33 Synthesis and cyclization of enyne–allenes via the silver(I)-catalyzed [3,3]-sigmatropic rearrangement.

20.2.9

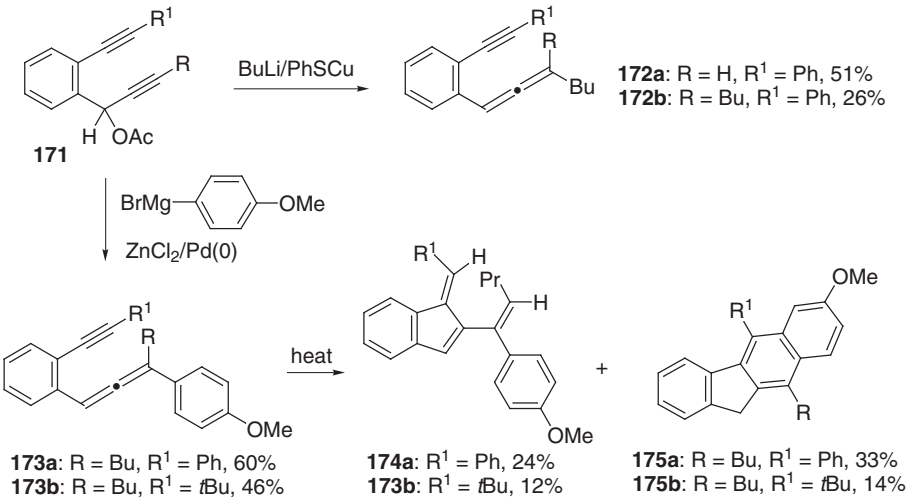
Nucleophilic Substitution with Rearrangement of Propargylic Derivatives

The use of the zinc–copper couple to effect the reduction of the methanesulfonate **168** with rearrangement furnished **169** (Scheme 20.34) [10]. Treatment of **168** with methylmagnesium bromide in the presence of copper(I) cyanide to induce an S_N2'-type reaction produced the methylated adduct **170**. The half-life of the Myers–Saito cyclization of **169** is 66 h at 37 °C, whereas that of **170** is 100 min. The faster rate of cyclization for **170** has been attributed to a steric effect favoring the requisite *s-cis* or twisted *s-cis* conformation.



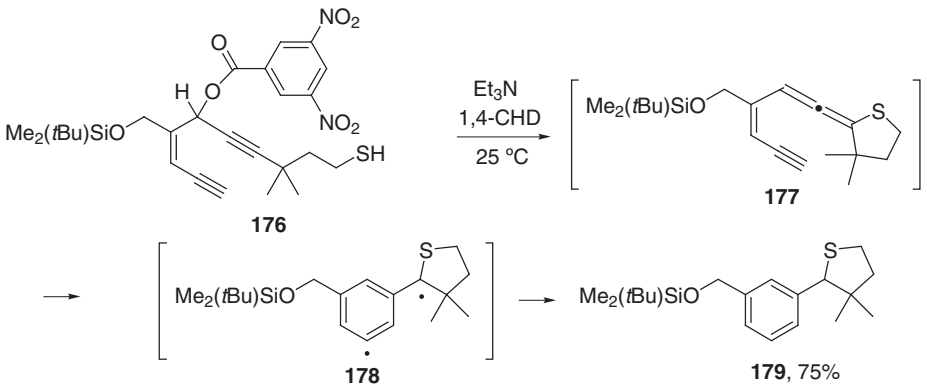
Scheme 20.34 Enyne–allenes via nucleophilic substitution with rearrangement.

Similarly, the benzannulated enyne–allenes **172** and **173** were prepared from the propargylic acetates **171** by cuprate addition or by Pd-catalyzed addition of arylzinc chloride (Scheme 20.35) [49]. The presence of a butyl group and a *p*-anisyl group at the allenic terminus of **173a** and **173b** permits competition between a formal ene reaction and a formal Diels–Alder reaction leading to **174** and **175**, respectively.



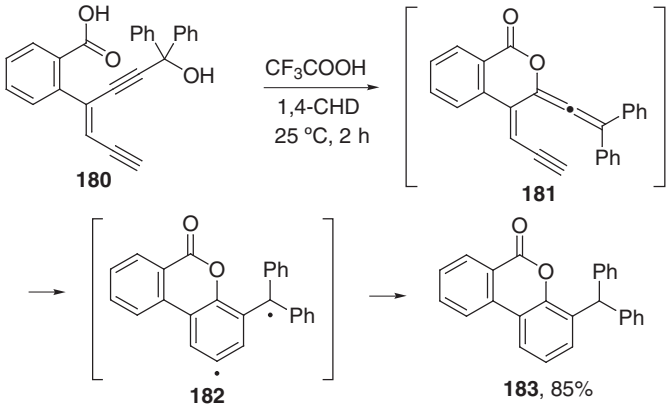
Scheme 20.35 Enyne–allenes via cuprate addition or Pd-catalyzed addition.

An elegant design using a based-induced internal S_N2' displacement reaction is depicted in Scheme 20.36 [7, 8]. Treatment of **176** with triethylamine in the presence of 1,4-CHD triggered the formation of the enyne–allene **177**, leading to the biradical **178** and, after hydrogen-atom abstractions, the cycloaromatized adduct **179**.



Scheme 20.36 Enyne–allenes via intramolecular S_N2' substitution.

Similarly, exposure of **180** to trifluoroacetic acid also promoted an internal S_N2' displacement reaction to form **181** (Scheme 20.37) [68]. The Myers–Saito cyclization generated the biradical **182** and, subsequently, **183**. As in the case of **55**, the benzylic radical center in **182** is a stabilized triarylmethyl radical. Several related transformations to produce enyne–allenes have also been reported [69, 70].

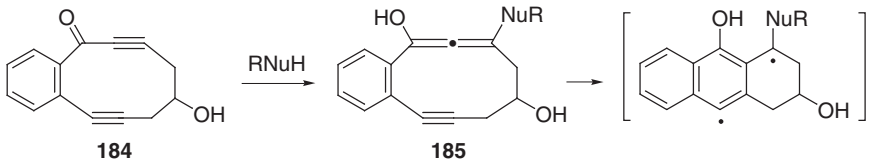


Scheme 20.37 Enyne–allenes via acid-catalyzed intramolecular S_N2' substitution.

20.2.10

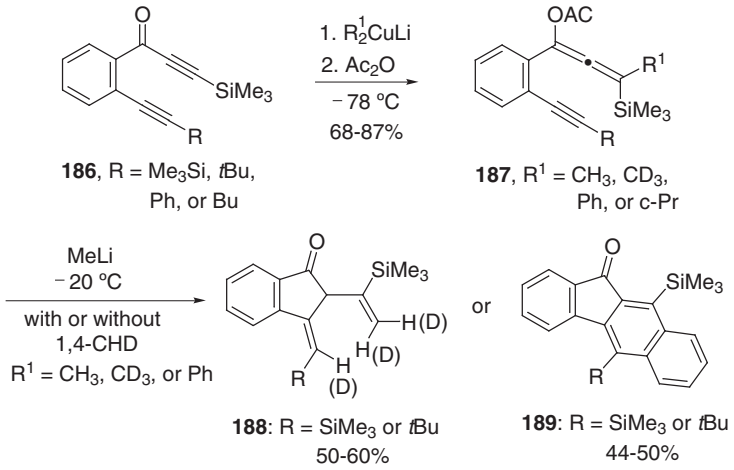
Nucleophilic Addition to Conjugated Systems

A nucleophilic attack on the acetylenic ketone functionality of golfomycin A (**184**) was proposed as a potential pathway to form the benzannulated enyne–allene **185** (Scheme 20.38) [71]. Subsequent biradical formation has been postulated as a possible mechanism to account for its DNA-cleaving properties and antitumor activity.



Scheme 20.38 Enyne–allenes via nucleophilic addition.

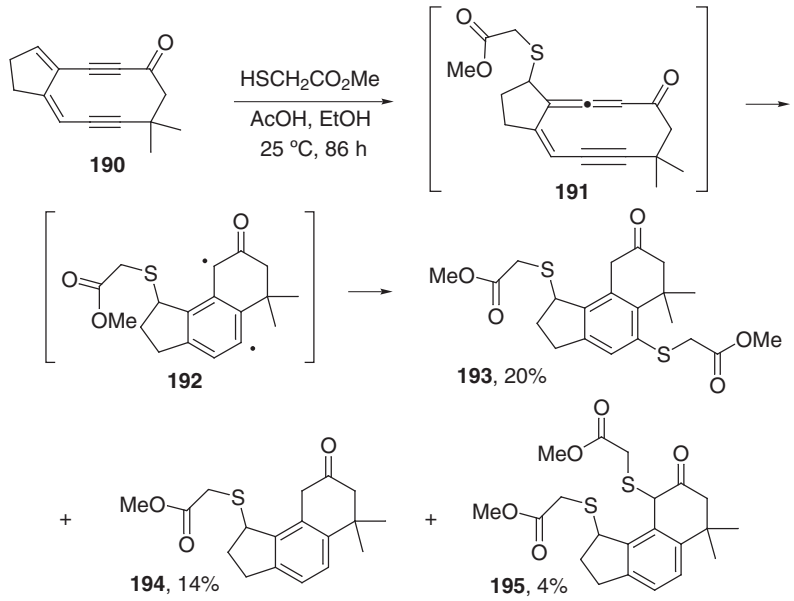
Treatment of the acetylenic ketones **186** with lithium dialkylcuprates and trapping the resultant enolates with acetic anhydride produced the enyne–allene **187** (Scheme 20.39) [72]. Regeneration of the oxyanion-substituted enyne–allene system using methyllithium at –20 °C led to the formation of either the indanones **188** or the benzofluorenones **189** through a Schmittel cyclization reaction.



Scheme 20.39 Enyne–allenes via conjugate addition of dialkylcuprates.

The oxyanion-substituted system appears to cyclize more rapidly than the neutral enol acetates **187**. For instance, the enol acetate **187** with R = *t*Bu and R^1 = Me undergoes cyclization at 50 °C with a half-life of 46 h, which is more than 45 times longer than that of the corresponding oxyanion.

Treatment of **190** with methyl thioglycolate also promoted a conjugate addition leading to the cyclic enyne–allene **191** (Scheme 20.40) [73]. Cyclization followed by hydrogen-atom abstraction and/or intermolecular radical–radical coupling with the thiyl radical derived from methyl thioglycolate then produced the tetrahydrobenz-[*f*]indanes **193**, **194** and **195**. Other analogous cyclic and acyclic enyne–allene systems were likewise prepared in situ by conjugate addition [74–76]. Conjugate addition to enynyl esters has also been reported to produce enyne–allenes [77].

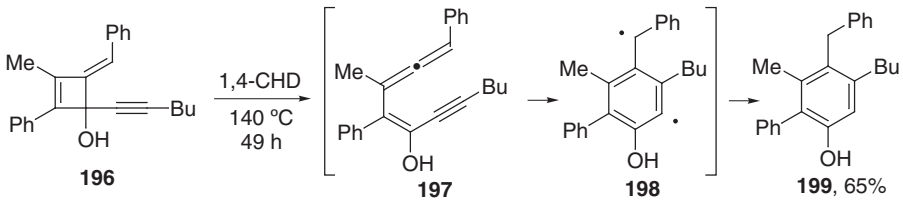


Scheme 20.40 Cyclic enyne–allene via conjugate addition.

20.2.11

Rearrangement of 4-Alkynyl-4-hydroxy-3-methylenecyclobutenes

The electrocyclic ring opening of the cyclobutene **196** at 140 °C in 1,4-CHD produced in situ the enyne–allene **197** (Scheme 20.41) [78]. Cycloaromatization to the biradical **198** followed by hydrogen-atom abstractions then produced the phenol **199**.

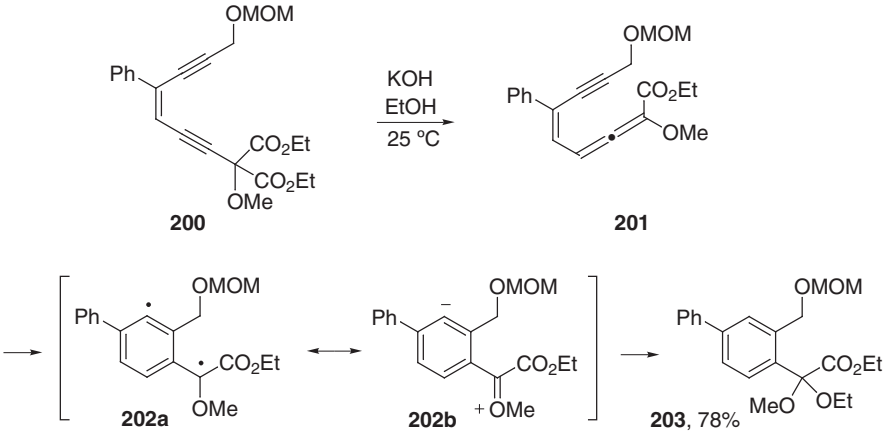


Scheme 20.41 Enyne–allene via rearrangement of a cyclobutene derivative.

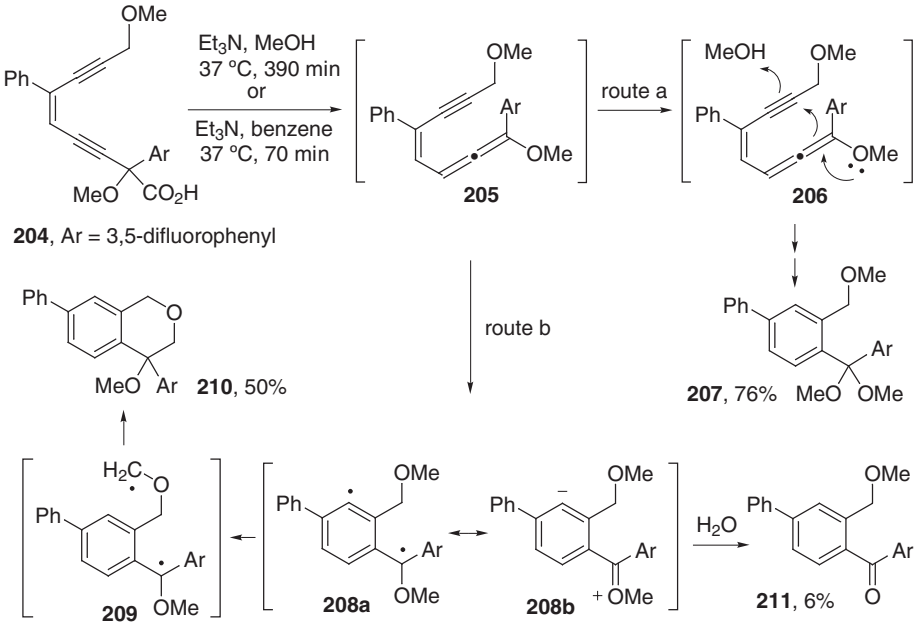
20.2.12

Hydrolytic Decarboxylation of α-Alkynylmalonates and α-Alkynylacetic Acids

Hydrolytic decarboxylation of the diethyl α-alkynylmalonate **200** with potassium hydroxide in ethanol was employed to produce in situ the enyne–allene **201** (Scheme 20.42) [79]. Cycloaromatization of **201** then generated the zwitterion **202b** leading to **203**.



Scheme 20.42 Enyne–allene via hydrolytic decarboxylation.

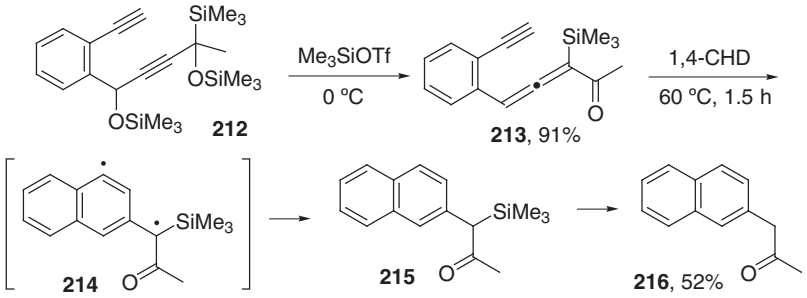


Scheme 20.43 Decarboxylative cycloaromatization of α-alkynylacetic acids.

Decarboxylative cycloaromatization of the α-alkynylacetic acid **204** was triggered on exposure to triethylamine in methanol to produce **207** (Scheme 20.43) [80]. Mechanistic studies suggest that the reaction proceeds through an ionic cyclization pathway (route a). On the other hand, in benzene the reaction undergoes the Myers–Saito cyclization to generate the biradical/zwitterion **208** (route b). The biradical **208a** undergoes an intramolecular 1,5-hydrogen shift to form **209**, which in turn undergoes an intramolecular radical–radical coupling to furnish **210**. The zwitterion **208b** was also captured by water to produce the diaryl ketone **211**.

20.2.13
Enyne–Allenes Having a Keto or an Aldehydic Substituent at the Allenic Terminus

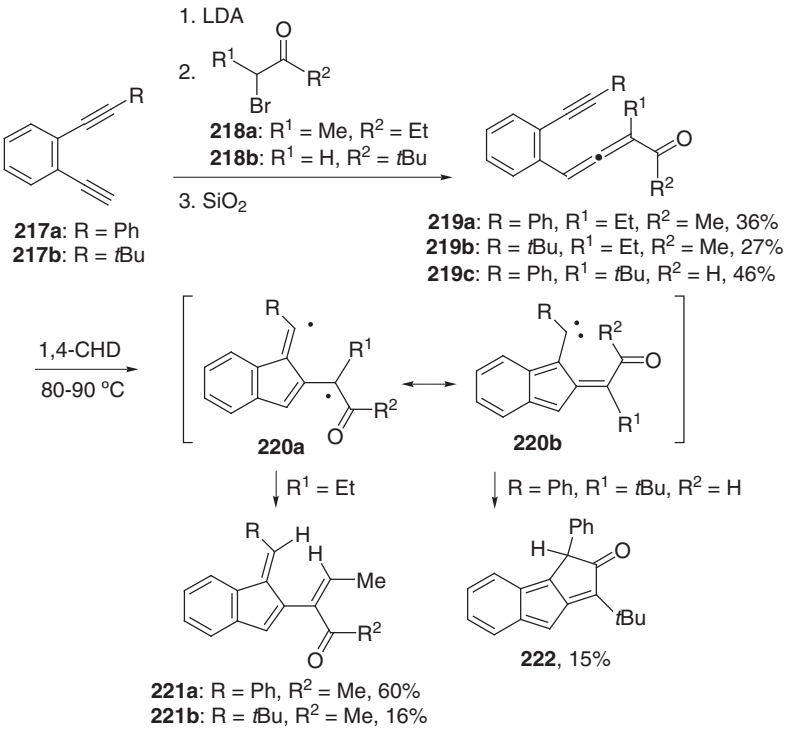
In addition to the example depicted in Scheme 20.40 and examples involving a prototropic rearrangement [61], the use of trimethylsilyl trifluoromethanesulfonate to induce the transformation of **212** afforded **213** bearing a keto substituent at the allenic terminus (Scheme 20.44) [81]. Thermolysis of **213** promoted the Myers–Saito cyclization leading to **216**.



Scheme 20.44 Enyne–allenes having a keto substituent.

Condensation between the lithium acetylides of **217** and the α-bromoketones **218** eventually leads to the formation of **219** (Scheme 20.45) [82]. Presumably following the attack on the carbonyl group, ring closure occurred to furnish the corresponding oxiranes, which were then converted to **219** with migration of the carbonyl group during column chromatography.

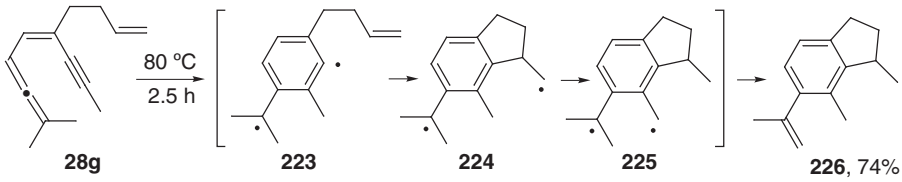
Thermolysis of **219a** and **219b** produced the benzofulvenes **221** as expected. However, the formation of **222** from **219c** can best be accounted for by regarding the biradical **220a** as the carbene **220b** to allow an intramolecular C–H insertion reaction. The presence of a carbonyl group in **219** also permits the use of samarium(II) iodide, samarium(III) chloride, boron trifluoride and trifluoroacetic acid to promote the Schmittel cyclization reaction.



Scheme 20.45 Synthesis and cyclization of carbonyl-substituted enyne–allenes.

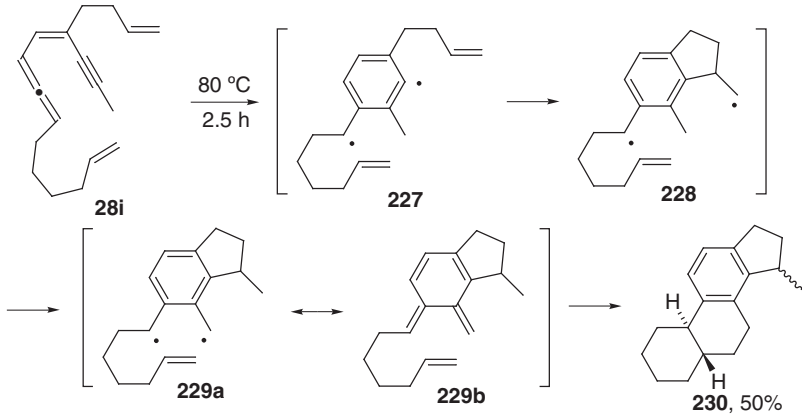
20.3
Cascade Radical Cyclizations of Biradicals Generated from Enyne–Allenes

The ability to generate biradicals from enyne–allenes under mild thermal conditions provides many opportunities for subsequent radical cyclizations. Several examples of such a tandem sequence have been illustrated in Schemes 20.13, 20.15, 20.19, 20.20 and 20.33. This strategy has also been adopted for the construction of structures containing multiple rings. Thermolysis of **28g** having a 3-butenyl substituent in refluxing benzene furnished the indan derivative **226** in a single operation (Scheme 20.46) [35]. Apparently, the aryl radical in **223** is captured in a typical 5-*exo* fashion to give **224**, which in turn undergoes a 1,5-hydrogen shift to form the *o*-quinodimethane **225** followed by a [1,5]-sigmatropic hydrogen shift to yield **226**.



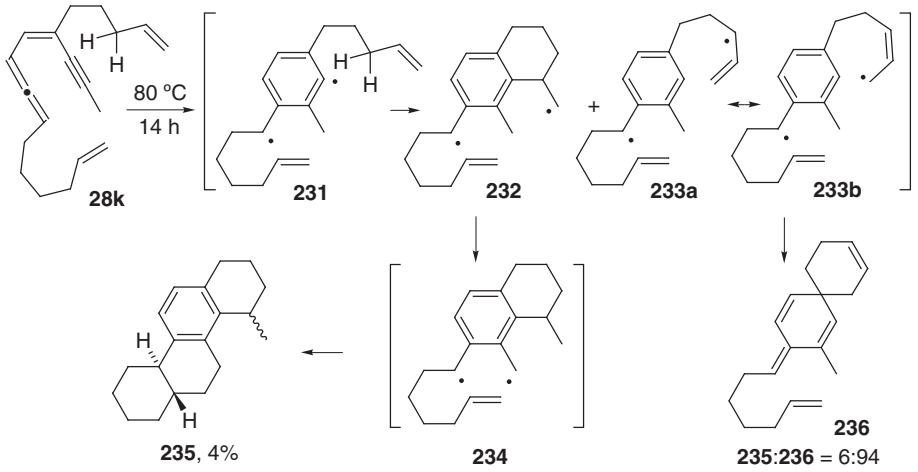
Scheme 20.46 Cascade radical cyclization leading to an indan derivative.

The presence of a 5-hexenyl substituent in **28i** allowed the *o*-quinodimethane **229b** to be captured in an intramolecular Diels–Alder reaction, producing **230**, having a tetracyclic steroidal skeleton, in a single operation (Scheme 20.47) [33, 34]. The fused tetracyclic 5,6,6,5-ring system was likewise produced from **34f** and **34g**.



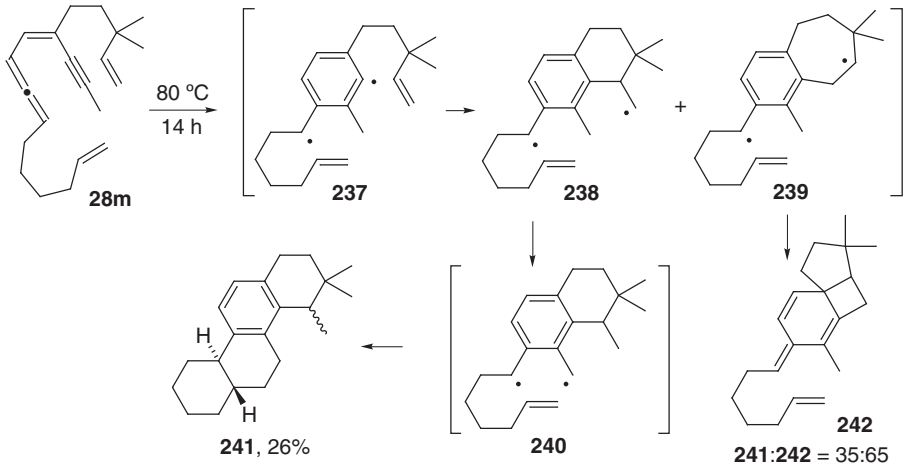
Scheme 20.47 Thermally induced one-step construction of the steroidal skeleton.

However, the use of **28k** bearing a 4-pentenyl group attached to the central carbon–carbon double bond of the enyne–allene system afforded only 4% of the expected tetracyclic compound **235** having the fused 6,6,6,6-ring system (Scheme 20.48) [33]. The major product was the bicyclic spiro derivative **236** (**235**:**236** = 6:94). Apparently, instead of capturing the aryl radical in **231** by the carbon–carbon double bond of the 4-pentenyl substituent in a 6-*exo* fashion to afford **232** leading to **235**, the majority of the reaction proceeded through a 1,5-hydrogen shift to furnish **233** having an allylic radical. The subsequent attack on the *ipso* carbon of the benzene ring by the terminus of the allylic radical led to hemolytic coupling that produced **236**.



Scheme 20.48 Formation of a bicyclic spiro hydrocarbon.

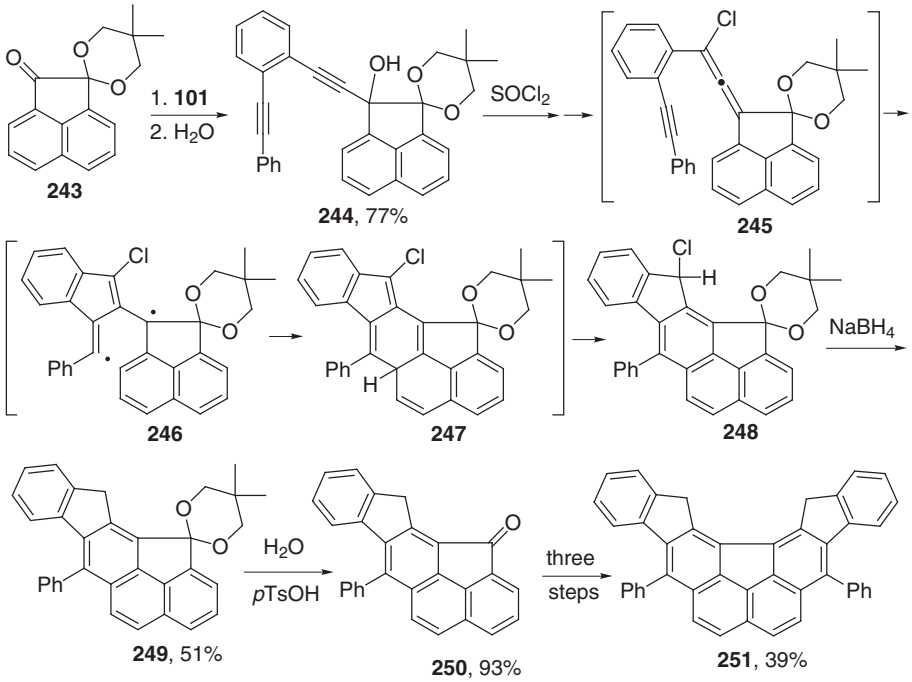
Replacing the two allylic hydrogens depicted in **28k** with two methyl groups as shown in **28m** improved the yield of the tetracyclic adduct **241** to 26% (Scheme 20.49) [33]. Interestingly, the angularly fused tricyclic derivative **242** was produced predominantly. Undoubtedly, **242** arises from a 7-*endo* ring closure of **237** to furnish **239** having a homobenzylic radical center, which in turn attacks the benzene ring to form the highly strained **242**.



Scheme 20.49 Formation of a strained tricyclic ring system.

20.4
Synthesis of a $C_{44}H_{26}$ Hydrocarbon Having a Carbon Framework Represented on the Surface of C_{60}

The reaction sequence outlined in Scheme 20.30 for the preparation of the chlorinated enyne–allenes was successfully adopted for the synthesis of the $C_{44}H_{26}$ hydrocarbon **251** having a carbon framework represented on the surface of C_{60} (Scheme 20.50) [83]. Condensation of the monoketal of acenaphthenequinone (**243**) with the lithium acetylide **101** afforded the propargylic alcohol **244**. On exposure to thionyl chloride, **244** underwent a cascade sequence of reactions as described in Scheme 20.30 to furnish the chloride **248**. Reduction followed by deprotection produced **250** to allow a repeat of condensation followed by the cascade transformation and reduction leading to **251**.

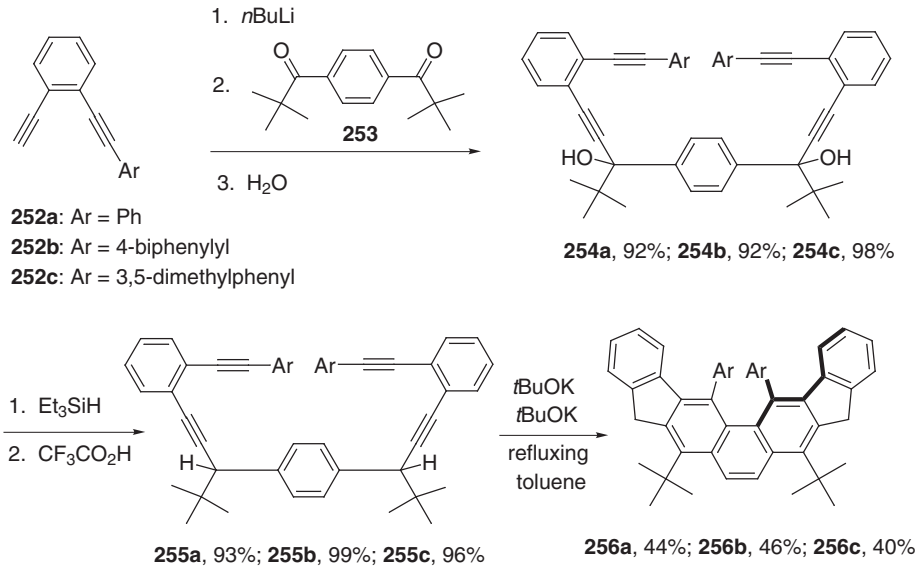


Scheme 20.50 Synthesis of a $C_{44}H_{26}$ hydrocarbon.

20.5
Synthesis of Twisted 4,5-Diarylphenanthrenes

The reaction sequence outlined in Scheme 20.22 also found application in the synthesis of twisted 4,5-diarylphenanthrenes **256** (Scheme 20.51) [84]. Condensation of the diketone **253** with 2 equiv. of the lithium acetylide of **252** produced the pro-

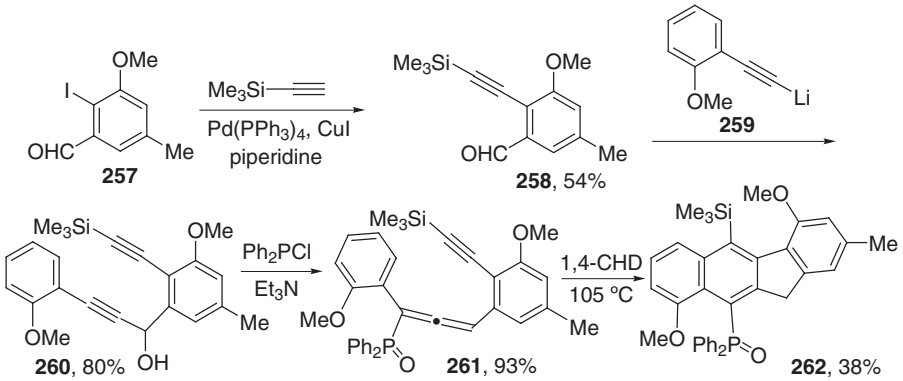
pargylic diols **254**. Reduction of **254** with triethylsilane in the presence of trifluoroacetic acid furnished **255**. Treatment of **255** with potassium *tert*-butoxide under refluxing toluene gave the 4,5-diarylphenanthrenes **256** in a single operation. Presumably, the reaction proceeds through prototropic rearrangements to form two units of benzannulated enyne–allene followed by two consecutive cascade radical cyclizations as described in Scheme 20.22.



Scheme 20.51 Synthesis of twisted 4,5-diarylphenanthrenes.

20.6
Synthesis of the Benzo[*b*]fluorene Core of the Kinamycins

The use of chlorodiphenylphosphine to promote a [2,3]-sigmatropic rearrangement of propargylic alcohols for subsequent Schmittel cyclization outlined in Scheme 20.28 was employed as a key step in the construction of the benzo[*b*]fluorene core of several metabolites structurally related to the kinamycin family of antibiotics (Scheme 20.52) [85]. The Pd-catalyzed cross-coupling between the aryl iodide **257** and (trimethylsilyl)acetylene gave **258**, which was treated with the lithium acetylide **259** to furnish **260**. Treatment of **260** with chlorodiphenylphosphine then gave the phosphorus-substituted enyne–allene **261**. Heating in the presence of an excess of 1,4-CHD in toluene furnished the benzo[*b*]fluorene **262**, having a structure resembling those of the kinamycins.



Scheme 20.52 Synthesis of the benzo[*b*]fluorene core of the kinamycins.

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