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Volume Editor J. Tsuji

Palladium in Organic Synthesis

Volume Editor

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Editorial Board

Preface

Organopalladium chemistry has made remarkable progress over the last 30 years. That progress is still continuing without any end in sight. I have published two books on organopalladium chemistry already in 1980 and 1995. In addition, several books and reviews treating various aspects of organopalladium chemistry have been published by other researchers.

The dramatic advances in that field in the last few years led me to publish in 2004 a book entitled "Palladium Reagents and Catalysts, New Perspectives for the 21 century" in which I summarize the key developments and important advances in that chemistry. A number of the novel Pd-catalyzed reactions discovered recently could not, however, be treated as extensively as they deserve, and they probably were not easy to understand from the rather short summaries in my last book.

I have thus come to feel that more comprehensive reviews of individual topics, written in detail by researchers who have made major contributions to them, are needed for a better understanding of this rapidly expanding area. Coincidentally, Springer Verlag asked me to edit a book entitled "Palladium in Organic Synthesis" , as one volume of the series "Topics in Organometallic Chemistry". I thought this was a timely project, and I agreed to be its editor.

I have selected a number of important topics in newly developed organopalladium chemistry, and have asked researchers who have made important contributions to these fields to review them. I am pleased that most of them have kindly accepted my request. For this book I have selected recent advances (covering mainly the last five years), most of which have not previously been the object of reviews. The book I am editing will cover Pd-catalyzed reactions that are novel, and entirely different from the more standard ones. Considerable patience will be required by readers when they face and try to understand topics such as β-carbon elimination, palladacycles, Pd/norbornene-catalyzed aromatic functionalizations, arylation of aromatics, three-component cyclizations of allenes, and cycloaddition of arynes, for example. I believe their efforts will be well rewarded.

I strongly feel that palladium is a remarkable metal. I hope that the book will have great appeal to researchers in organopalladium chemistry and stimulate further progress in that field.

Kamakura, February 2005

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Professor Emeritus
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Catalytic Processes Involving β-Carbon Elimination

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Abstract Palladium-catalyzed C–C bond cleavage via β-carbon elimination occurs in various cyclic and acyclic systems. Thus, the reaction can be utilized as one of fundamental and effective tools in organic synthesis. The recent progress in this field is summarized herein.

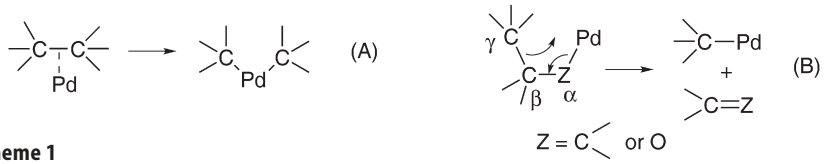
Keywords C–C bond cleavage · β-Carbon elimination · Ring opening · Palladium catalysts

Abbreviations

acac	Acetylacetonate
BARF	Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
CPC-Pd	Cyclopropylcarbinylpalladium
CP-Pd	Cyclopropylpalladium
Cy	Cyclohexyl
dba	Dibenzylideneacetone
dppp	1,3-Bis(diphenylphosphino)propane
MCP	Methylenecyclopropane
MS4A	Molecular sieves (4 Å)
Nap	Naphthyl

1
Introduction

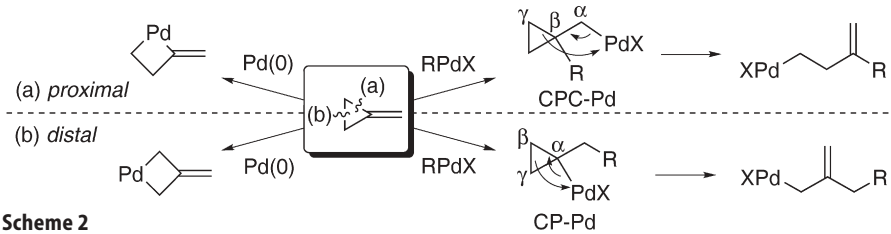
Palladium-catalyzed C–C bond formation is now recognized to be one of the most useful tools in organic synthesis [1–4]. Recently, the formally reverse reaction involving cleavage of a C–C single bond has also attracted considerable attention, because such a process may bring about new, direct synthetic routes in some cases [5–10]. Two typical modes for activating the relatively inert bond are known (Scheme 1). One of them, which involves metal insertion into the C–C bond (mechanism A), is usually observed in strained small ring systems [10]. Meanwhile, the reactions involving the other activation mode, that is, β-carbon elimination (mechanism B; formal deinsertion of alkenes or ketones), have recently been developed significantly and shown to occur widely, not only in three- and four-membered rings, but also in less-strained larger rings and even in some acyclic systems. This review focuses on the reactions involving β-carbon elimination under palladium catalysis. The reactions on carbon–carbon double bonds, such as alkene metathesis, as well as those over heterogeneous catalysts and in the vapor phase, are beyond the scope of this review.



Scheme 1

2
Reaction Involving Three-Membered Ring Opening

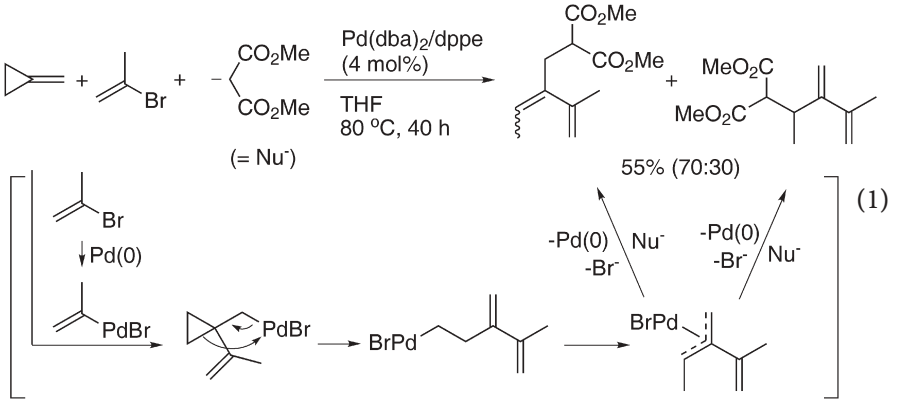
Among the compounds containing a strained three-membered ring, methylenecyclopropane (MCP) derivatives are particularly versatile and useful substrates for transition-metal-catalyzed reactions. Taking advantage of their availability [11], various kinds of reaction involving cleavage of their reactive cyclopropane bond have been explored [12]. Both the C–C bonds of MCP, that is, (a) proximal and (b) distal bonds, are known to be cleaved through the insertion of Pd(0) species (Scheme 2). The substrate may also undergo the



Scheme 2

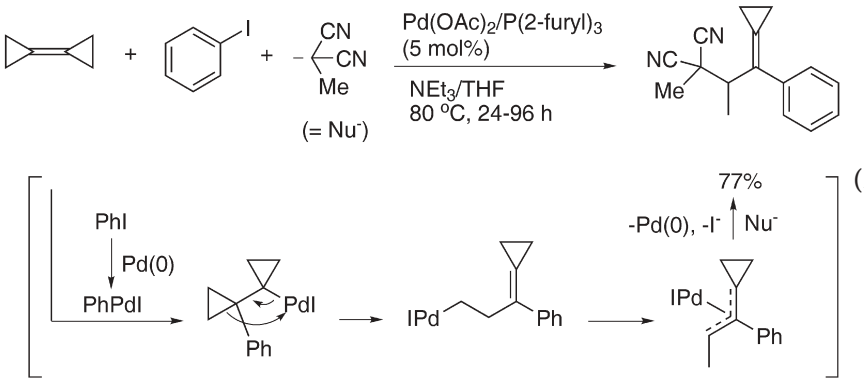
addition of R-Pd species to the *exo*-methylene double bond to give either a cyclopropylcarbinylpalladium (CPC-Pd) or a cyclopropylpalladium (CP-Pd) species. Then, C_β–C_γ bond cleavage, that is β-carbon elimination, takes place to give the corresponding alkylpalladium intermediates, which undergo further transformations to afford the final products.

Of the two reaction types involving β-carbon elimination, the former through CPC-Pd is relatively more common. For instance, in the Heck-type reaction of vinyl bromides with MCP (Eq. 1), carbopalladation on the *exo*-methylene moiety takes place to give a CPC-Pd intermediate. Then, β-carbon elimination, hydrogen migration, and reaction with a carbon nucleophile successively occur to give rise to three-component coupling products [13].



(1)

As shown in Eqs. 2 and 3, the carbopalladation of bicyclopropylidene [14, 15] and vinylcyclopropane [16] also gives the corresponding CPC-Pd intermediates, which readily undergo β-carbon elimination, hydrogen migration, and the subsequent inter- or intramolecular reaction with nucleophiles.



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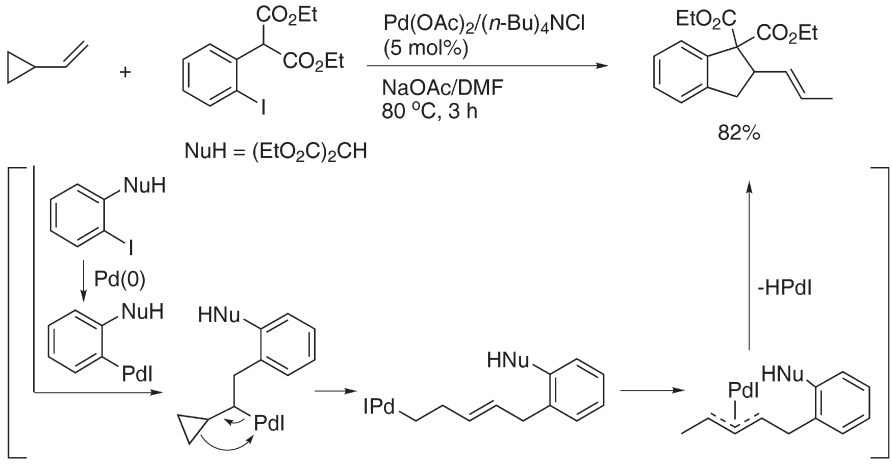
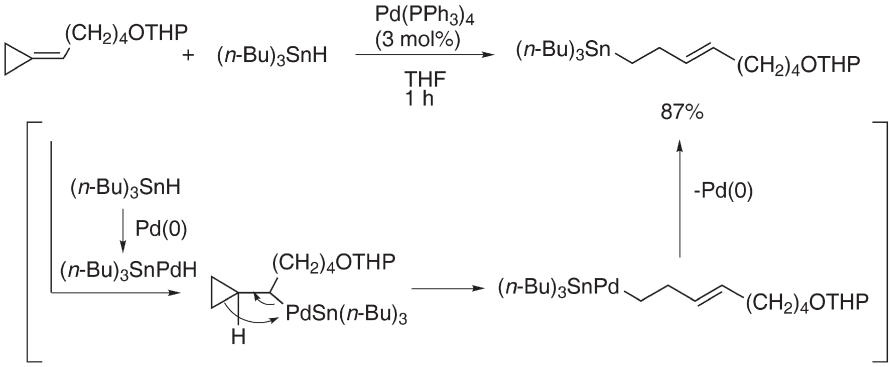


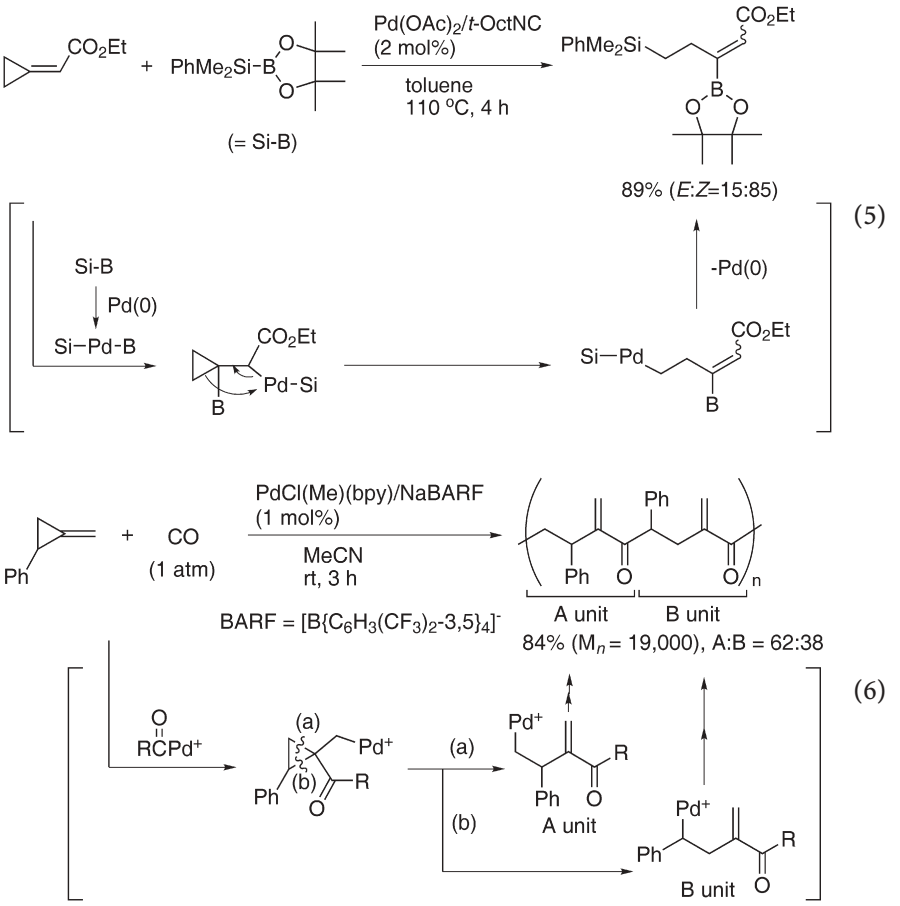
(3)

Similar mechanisms through CPC-Pd intermediates have been proposed for the hydrometalation and bismetalation of MCPs. For example, hydrostannation [17] and silaboration [18] involve the regioselective addition of H-Pd or B-Pd species, which is followed by β-carbon elimination and reductive elimination to yield the corresponding products (Eqs. 4 and 5).

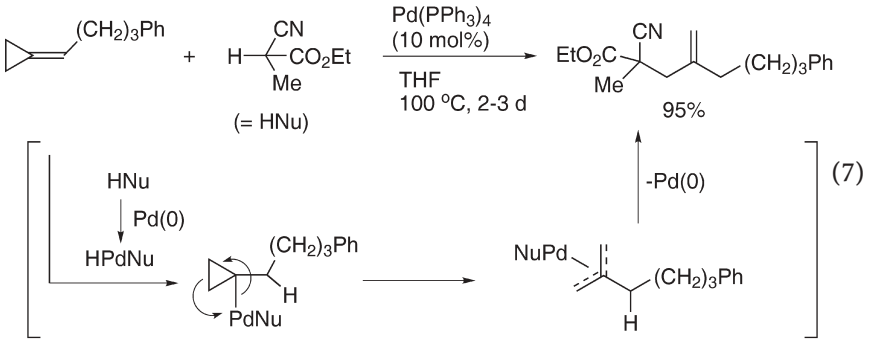


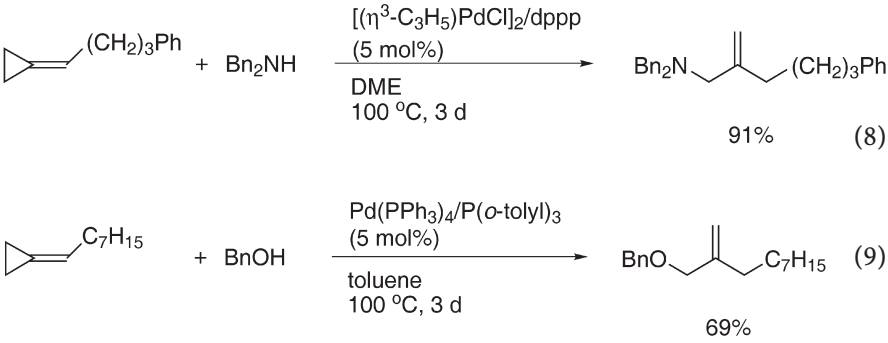
(4)

Ring-opening copolymerization of 2-arylated MCPs with CO also proceeds through CPC-Pd species to produce polyketones [19]. An example is shown in Eq. 6. Insertion of CO into the Pd–alkyl bond of a growing polymer gives an acylpalladium intermediate. The subsequent acylpalladation of the MCP affords the key CPC-Pd intermediate, which is followed by β-carbon elimination to regenerate the Pd–alkyl species. Cleavage of the less substituted C–C bond, that is, bond (a), leading to the A unit, is somewhat preferred rather than that of bond (b) leading to the B unit.



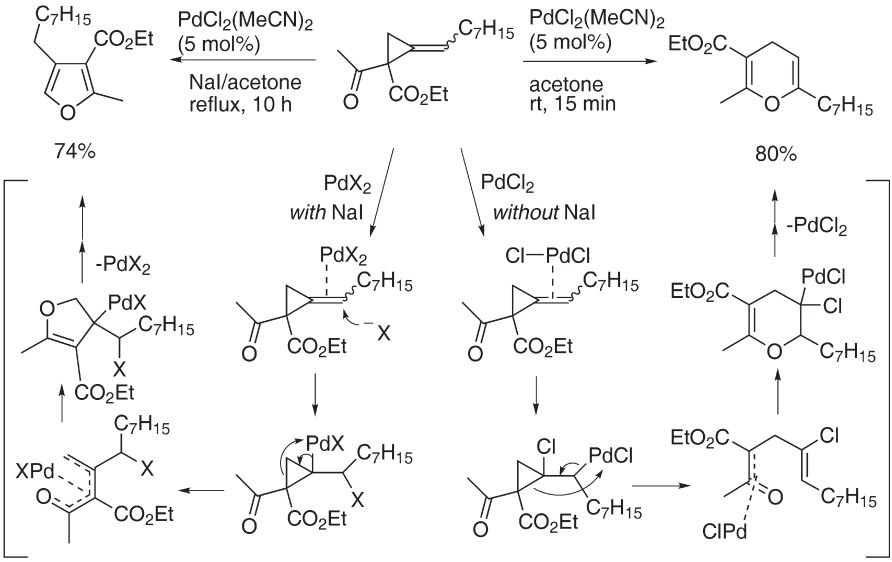
In contrast to the fact that there are many examples through an intermediary CPC-Pd species, a limited number of reactions involving a CP-Pd intermediate have appeared. As shown in Eqs. 7–9, it has been proposed that hydrocar-





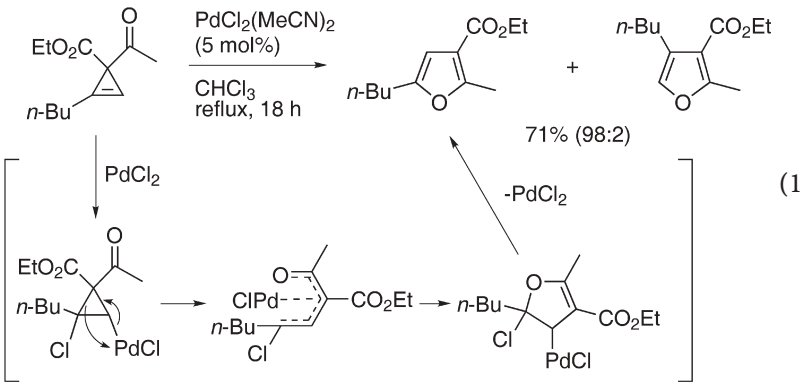
bonation [20, 21], hydroamination [22], and hydroalkoxylation [23, 24] of MCPs mainly proceed through hydropalladation, β-carbon elimination in the formed CP-Pd intermediates leading to distal bond cleavage, and subsequent reductive elimination.

The halopalladation of MCPs gives CP-Pd and CPC-Pd intermediates depending on the reaction conditions. Thus, the isomerization of alkylidene cyclopropyl ketones to 4*H*-pyran derivatives takes place in the presence of a palladium chloride catalyst via chloropalladation to form a CPC-Pd and the successive β-carbon elimination (Eq. 10) [25]. In contrast, the addition of NaI changes the reaction pathway dramatically. Under the conditions, the reaction proceeds through a CP-Pd intermediate and results in the formation of furan derivatives.



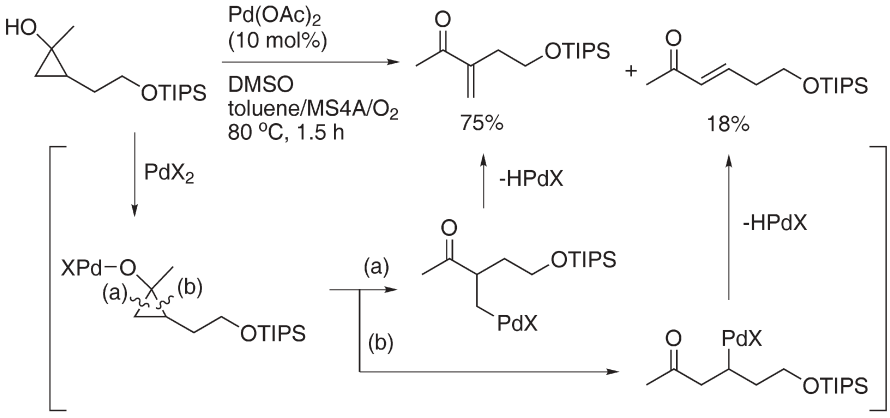
(10)

Cyclopropenyl ketones also undergo isomerization to produce furan derivatives (Eq. 11) [26]. It has been proposed that the initial chloropalladation on their unsymmetrically substituted double bond occurs regioselectively to give one of the possible CP-Pd intermediates predominantly, which undergoes β-carbon elimination and several subsequent reactions to yield the major products.



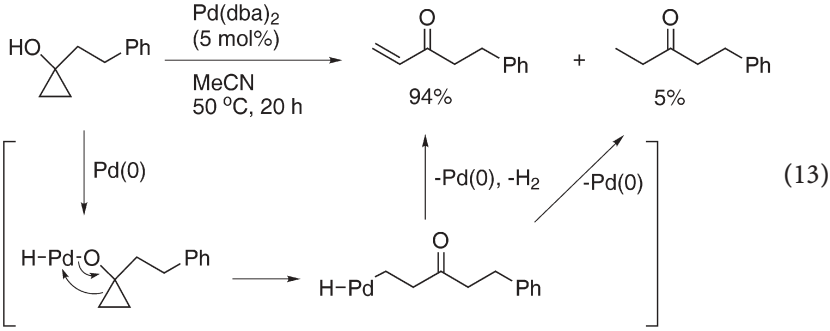
(11)

Treatment of *tert*-cyclopropanols with a Pd(II) catalyst gives cyclopropoxypalladium intermediates. While alkoxypalladium(II) species generated from the usual primary and secondary alcohols are known to undergo β-hydrogen elimination to afford aldehydes and ketones, respectively [27], the *tert*-cyclopropoxypalladium intermediates undergo ring-opening β-carbon elimination in a similar manner to that in CPC-Pd intermediates. In this step, the less substituted C–C bond, bond (a), is cleaved in preference to bond (b). Then, the resulting alkylpalladium intermediates undergo β-hydrogen elimination to afford enones and Pd(II)-H or Pd(0) species, which can be converted to active Pd(II) species by the presence of a reoxidant such as oxygen (Eq. 12) [28].



(12)

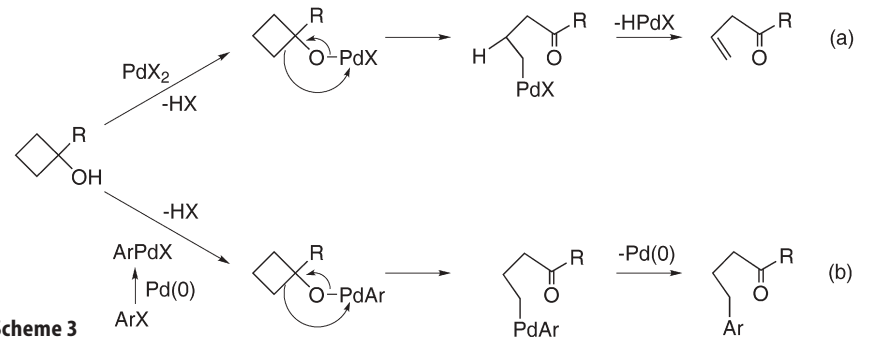
A similar reaction can also be performed by using a Pd(0) catalyst. In this case, it has been assumed that the cyclopropoxypalladium species is formed by oxidative addition of the O–H bond to Pd(0), which is followed by β-carbon elimination and successive β-hydrogen elimination or reductive elimination to give an enone and a saturated ketone, respectively (Eq. 13) [29].



(13)

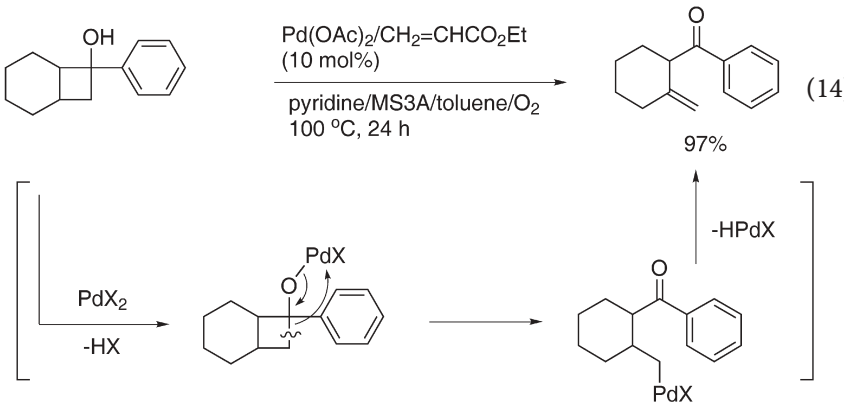
3
Reaction Involving Four-Membered Ring Opening

Strained four-membered rings also undergo ring opening readily under palladium catalysis. The reaction with *tert*-cyclobutanols has been studied extensively [27]. Depending on the conditions employed, (a) dehydrogenative or (b) arylative ring opening may occur (Scheme 3). The former takes place in the presence of a Pd(II) catalyst and a reoxidant [30, 31], essentially in the same manner to that of *tert*-cyclopropanols (Eq. 12). Thus, the hydroxy group coordinates to PdX_2 species to afford *tert*-cyclobutoxypalladium intermediates, which undergo β-carbon elimination and subsequent β-hydrogen elimination to give β,γ-unsaturated ketones. The palladium species formed in the last step, HPdX or Pd(0) generated by liberation of HX, are oxidized by the added reoxidant to regenerate active PdX_2 species and close the catalytic cycle.



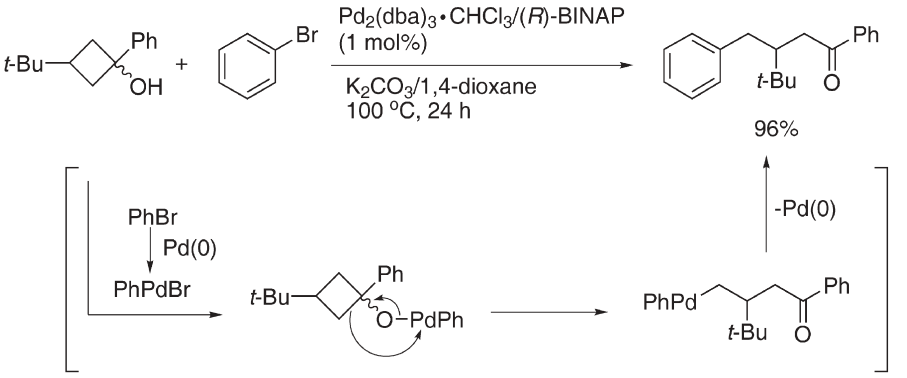
Scheme 3

An example of the dehydrogenative ring opening is shown in Eq. 14. In this case, there are two ring C–C bonds that may be cleaved. Of these, the less substituted C–C bond is cleaved exclusively. Such a tendency is also observed in the reaction of *tert*-cyclopropanols (Eq. 12), albeit with somewhat lower selectivity.



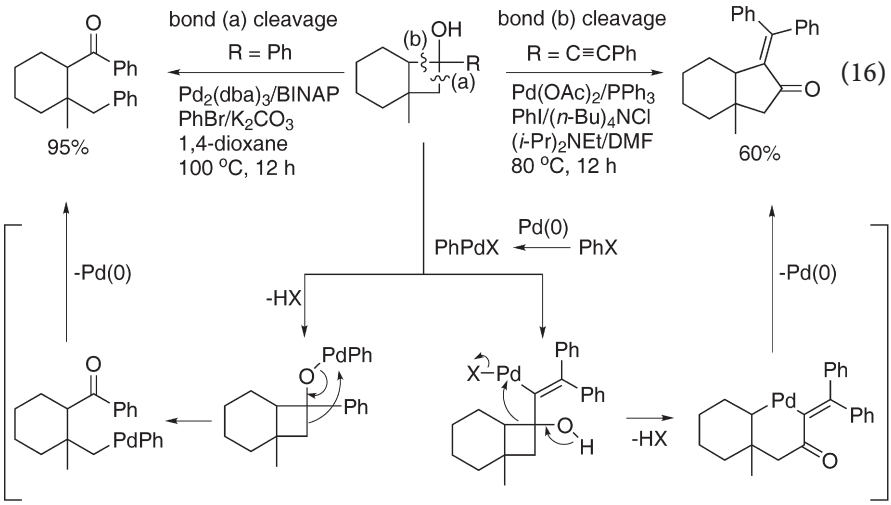
(14)

On the other hand, the arylative ring opening takes place in the presence of a Pd(0) catalyst, an aryl halide, and a base (Scheme 3, reaction b) [32–35]. Oxidative addition of aryl halides toward Pd(0) gives ArPdX species, which can readily interact with the alcohols affording arylpalladium alkoxide intermediates. Then, β-carbon elimination and subsequent reductive elimination occur to give γ-arylated ketones and regenarate Pd(0) species. An example is shown in Eq. 15.



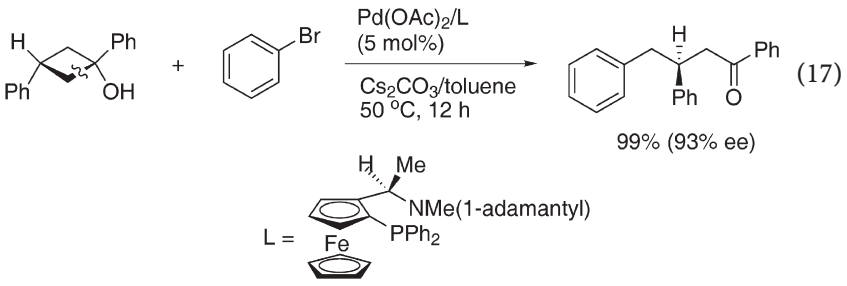
(15)

In this type of reaction of an unsymmetrically substituted cyclobutanol (Eq. 16, R=Ph) with bromobenzene, a single, regioisomeric product, is obtained via cleavage of the less hindered and more easily accessible C–C bond, bond (a), as in the dehydrogenative ring opening of the similar substrate (Eq. 14). The



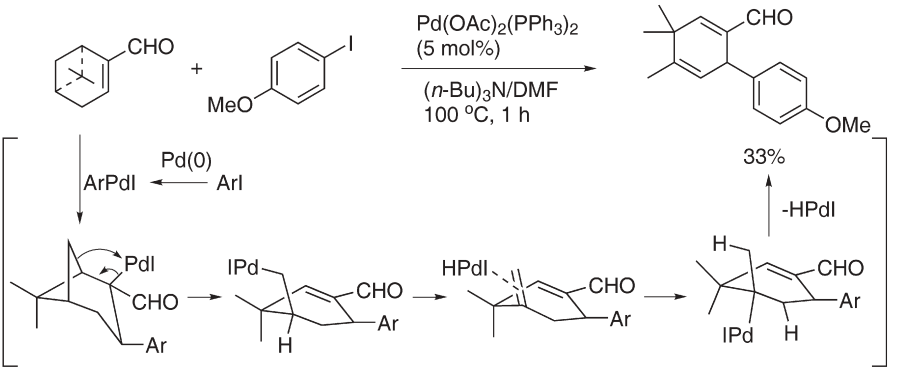
observed orientation is in contrast to that for the arylation–ring expansion reaction of the corresponding 1-(phenylethynyl)cyclobutanol (Eq. 16, R=C≡CPh) [36, 37]. The latter reaction producing a 2-alkylidenecyclopentanone derivative proceeds via the carbopalladation of the triple bond, ring expansion to release the ring strain, and subsequent reductive elimination. In the C–C cleavage step of this example, the more substituted, electron-rich carbon of the ring migrates to the electron-deficient palladium center to result in cleavage of bond (b). Similar selective C–C bond cleavages have been observed in the ring expansion reactions of other 1-alkynyl [36–38], 1-allenyl- [39, 40], and 1-dienylcyclobutanols [41].

In the arylative ring opening of 3-substituted cyclobutanols, enantioselective cleavage of the C–C bond has been achieved by using a palladium catalyst with a chiral ligand [33–35]. Particularly, the use of the chiral ferrocene-containing N,P-bidentate ligand shown in Eq. 17 leads to excellent enantioselectivity.



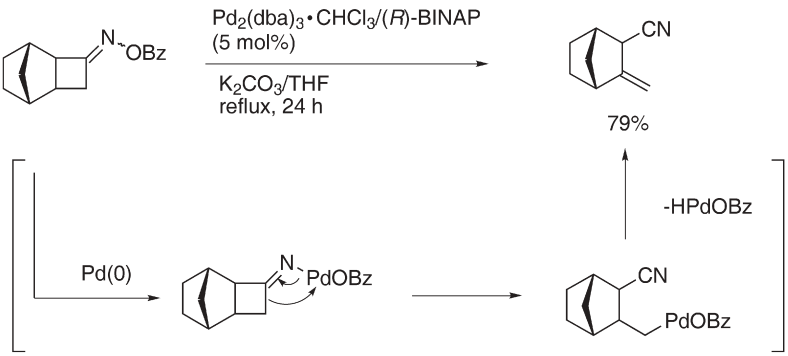
Other than cyclobutanols, the four-membered ring of myrtenal also undergoes the arylative ring opening to afford a monocyclic product with a moderate

yield (Eq. 18) [42]. The reaction proceeds via carbopalladation of the double bond of the substrate, β-carbon elimination with the less substituted alkyl moiety, hydrogen migration, and β-hydrogen elimination.



(18)

Cyclobutanone oximes undergo ring opening effectively upon treatment with a Pd(0) catalyst [43, 44]. An example is given in Eq. 19. The reaction is initiated by the oxidative addition of the substrate toward Pd(0) species to give a cyclobutaniminopalladium(II) intermediate, which is followed by β-carbon elimination to afford a γ-cyanoalkylpalladium species. The successive β-hydrogen elimination leads to formation of an unsaturated nitrile.

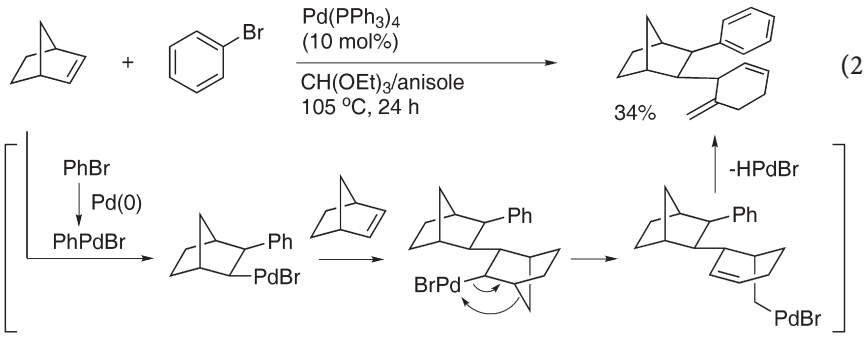


(19)

4
Reaction Involving Five-Membered or Larger Ring Opening

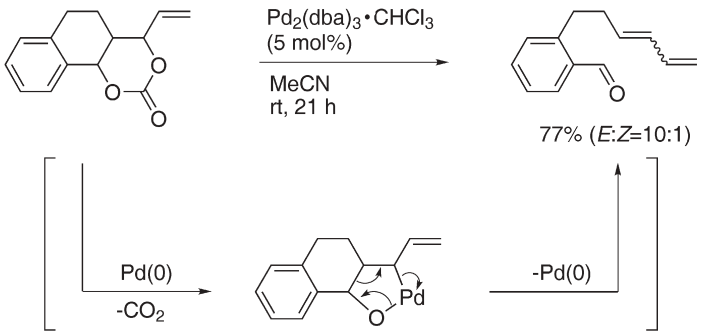
Examples involving the opening of less strained rings, five-, six-membered or larger ones, are relatively rare. An exceptional substrate is norbornene, which has a reactive five-membered ring and a strained carbon–carbon double bond, and a number of reactions involving its C–C bond cleavage have been found

[6]. Shown in Eq. 20 is an example, in which the ring opening by β-carbon elimination occurs on a norbornylpalladium intermediate formed by the insertion of the double bond of norbornene twice into PhPdBr [45].



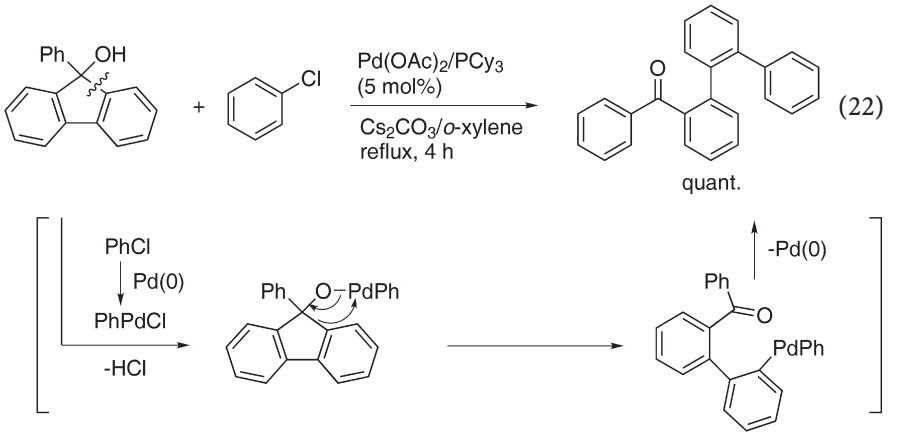
(20)

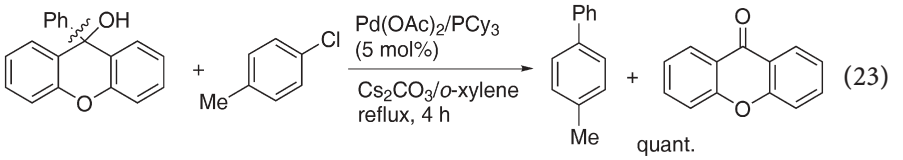
More generally, it has been reported that four-, five-, six-, eight-, and twelve-membered rings of bicyclic carbonates can be opened. An example of the six-membered ring opening is given in Eq. 21 [46]. In the reaction, oxidative addition of the allylic C–O bond toward Pd(0) species followed by decarboxylation affords a palladacycle intermediate. The subsequent β-carbon elimination results in the formation of a dienal.



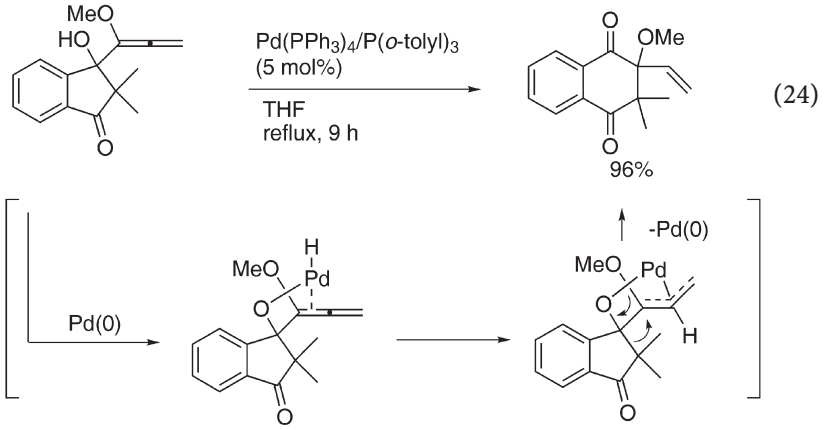
(21)

9-Phenylfluoren-9-ol, which may be regarded as a *tert*-cyclopentanol derivative, undergoes arylative ring opening via β-carbon elimination on an alkoxypalladium intermediate (Eq. 22) [47, 48], as do *tert*-cyclobutanols (Eqs. 15–17). Treatment of a related, but less strained six-membered substrate, 9-phenylxanthen-9-ol, under similar conditions results not in the ring opening but the selective β-carbon elimination of the *exo*-phenyl group to give the corresponding biaryl quantitatively accompanied by the formation of xanthone (Eq. 23). This kind of aryl–aryl coupling reaction is treated further in the next section.



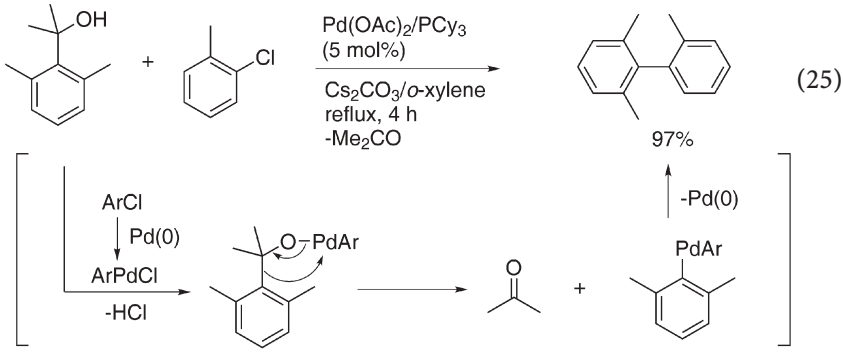


1-Hydroxy-1-allenylindanone derivatives as another type of cyclopentanol undergo ring expansion to give the corresponding 1,4-naphthoquinones (Eq. 24) [49, 50]. The reaction is presumed to proceed through oxidative addition of the hydroxy group to Pd(0), hydropalladation onto the allenyl moiety to yield a π-allylpalladium alkoxide, and subsequent β-carbon elimination.



5
Reaction in Acyclic Systems

β-Carbon elimination may occur even without the aid of ring strain, as is demonstrated by the reaction in Eq. 23. Actually, various α,α-disubstituted arylmethanols, even acyclic ones, undergo cleavage of the sp^2–sp^3 C–C bond [47, 48]. Thus, the reaction of the alcohols with aryl chlorides or bromides proceeds through the formation of an arylpalladium alkoxide intermediate, β-carbon elimination to release a ketone, and the subsequent reductive elimination of a biaryl (Eq. 25). The use of a bulky phosphine ligand such as PCy_3 (Cy=cyclohexyl) is essential for performing the reaction effectively and selectively. Since the substrates having *ortho* substituents tend to react efficiently, this coupling appears to provide a promising method, especially for preparing *ortho*-substituted biaryls. Indeed, a lot of examples have been reported [47, 48].

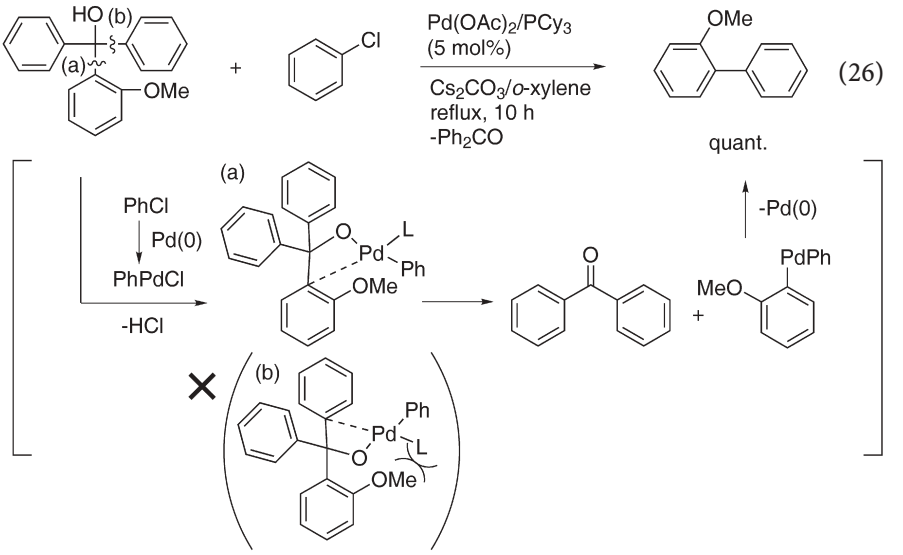


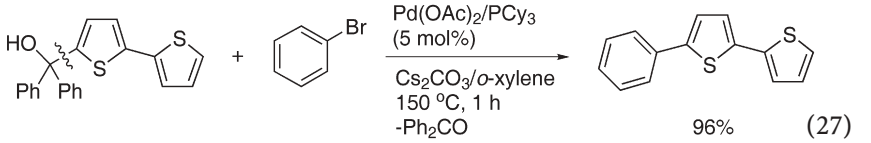
(25)

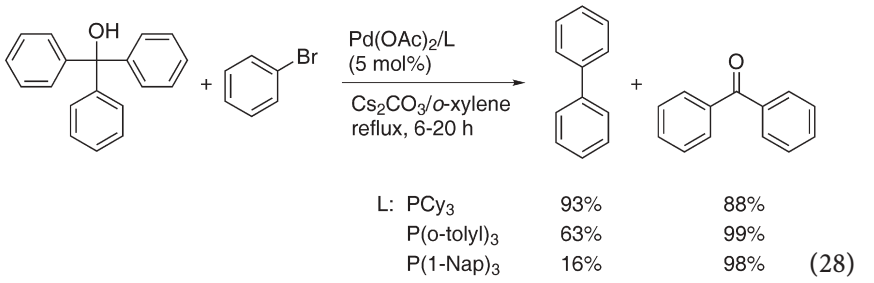
In monosubstituted triphenylmethanols, there are two kinds of C–C bond to be cleaved. Systematic studies with respect to factors determining the selectivity of the bond cleavage have indicated that substituent steric effects rather than electronic perturbations are significant [48]. Thus, as shown in Eq. 26, the aryl group having an *ortho* substituent, a methoxy group in this example, is eliminated selectively (via cleavage of bond (a)). The steric repulsion between the *ortho*-substituted phenyl group and the bulky ligand may make the transition state for the cleavage of bond (b) unfavorable.

In the reactions of (2-furyl)- and (2-thienyl)diphenylmethanols, the heteroaryl groups have also been found to be eliminated selectively [48]. This may be attributed to the coordination ability of the internal heteroatoms. It has been applied to the synthesis of 5-aryl-2,2′-bithiophenes (Eq. 27) [51].

As shown in Eqs. 25–27, $Pd(OAc)_2$-PCy_3 is an effective catalyst system for biaryl synthesis via β-carbon elimination. Thus, treatment of triphenylmethanol with bromobenzene using this catalyst gives biphenyl and benzophenone in good yields (Eq. 28). Using $P(o\text{-tolyl})_3$ instead of PCy_3 as ligand reduces the yield of biphenyl, although benzophenone is formed quantitatively. The

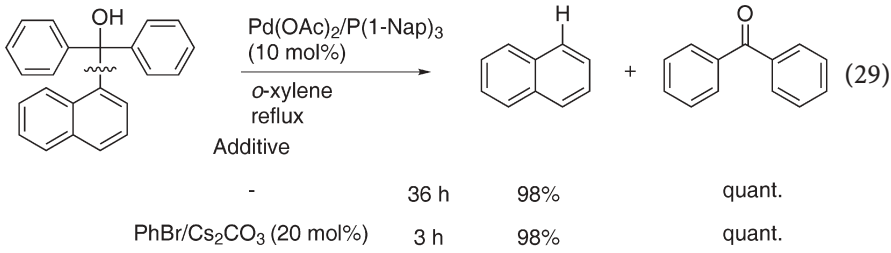




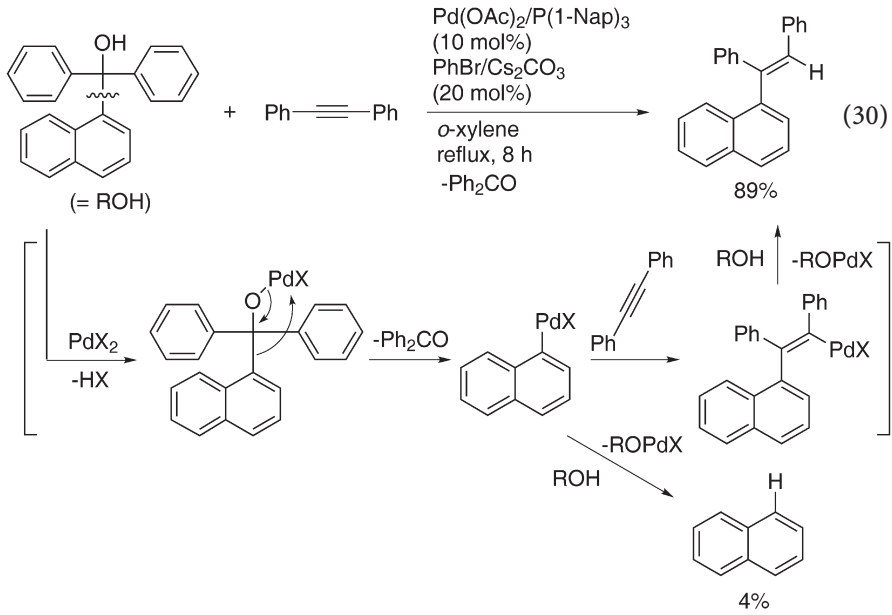


yield of biphenyl decreases further to 16% in the case employing $P(1\text{-Nap})_3$ (1-Nap=1-naphthyl) [52]. It may be conceived that dehydroarylation occurs predominantly to give benzene along with the ketone, especially when $P(1\text{-Nap})_3$ is employed.

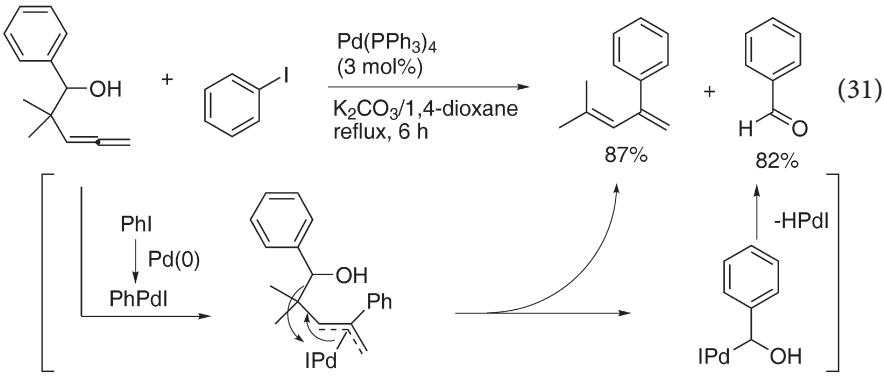
The hypothesis has been verified by the reaction of (1-naphthyl)diphenylmethanol using $P(1\text{-Nap})_3$ as ligand, in which naphthalene and benzophenone are produced quantitatively (Eq. 29) [52]. In this case, the addition of catalytic amounts of bromobenzene and Cs_2CO_3 promotes the reaction. Thus, one of the most bulky aromatic phosphines, $P(1\text{-Nap})_3$, appears to be a suitable ligand for the dehydroarylation of triarylmethanols, but to be too bulky for their aryl–aryl



coupling with aryl halides. The selective elimination of sterically hindered aryl groups in triarylmethanols is also seen in the dehydroarylation, as in the arylation of the alcohols. Interestingly, the hydroarylation of some unsaturated compounds occurs effectively by their addition to the reaction system. An example with (1-naphthyl)diphenylmethanol and diphenylacetylene is shown in Eq. 30. The reaction seems to proceed via coordination of the hydroxy group to PdX_2, selective β-carbon elimination of the bulky 1-naphthyl group, insertion of the alkyne into the formed aryl–palladium bond, and protonolysis of the resulting vinyl–palladium bond to afford the hydroarylation product and regenerate PdX_2. The simple dehydroarylation in Eq. 29 is explained by considering the protonolysis of the naphthyl–PdX intermediate. The catalytic amount of bromobenzene added may act as oxidant for adventitiously formed Pd(0) species.

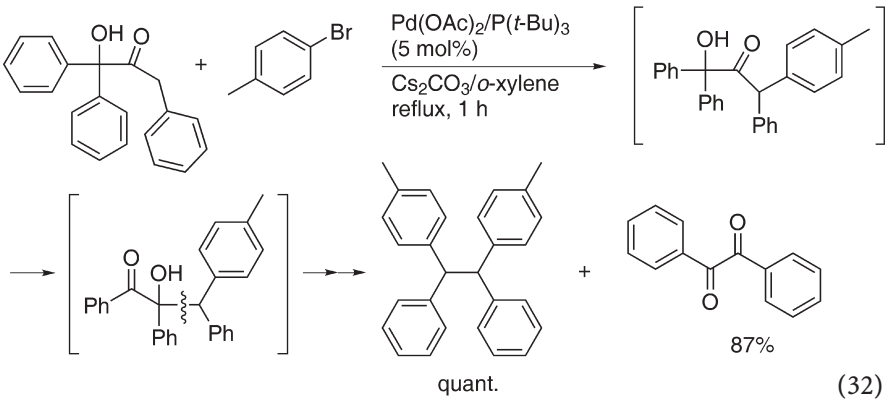


3-Allen-1-ols also undergo arylative fragmentation (Eq. 31) [53]. It has been proposed that the insertion of the allenyl group into an arylpalladium species



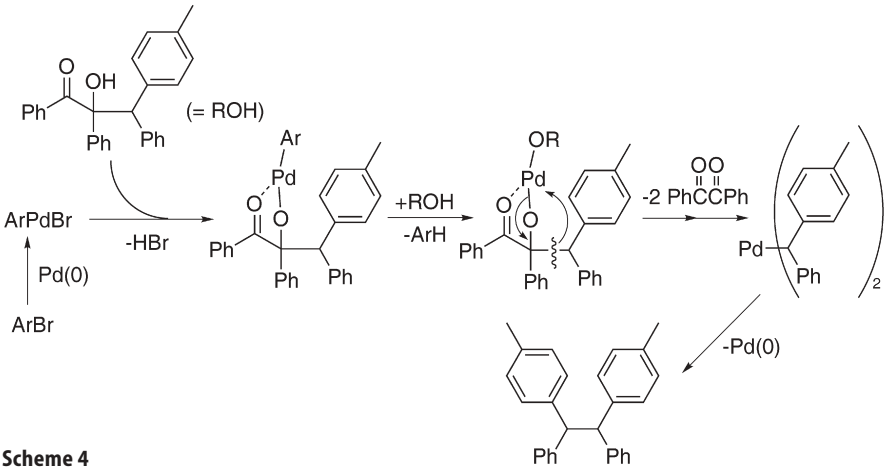
affords a π-allylpalladium intermediate. The successive β-carbon elimination leads to the formation of an arylated diene and an aldehyde. This example indicates that the sp^3–sp^3 C–C bond is also cleavable on the palladium catalyst.

Such a step, sp^3–sp^3 C–C bond cleavage, is also presumed to be involved in the unique arylative fragmentation of 1-hydroxy-1,1,3-triphenyl-2-propanone to give 1,2-diaryl-1,2-diphenylethanes and benzil (Eq. 32) [54]. The reaction seems to proceed via α-arylation [55] and subsequent α-ketol rearrangement to form an intermediary alcohol, 3-aryl-2-hydroxy-1,2,3-triphenyl-1-propanone [56]. Although the subsequent pathway leading to the final products is not well understood, one of the possible sequences is shown in Scheme 4.

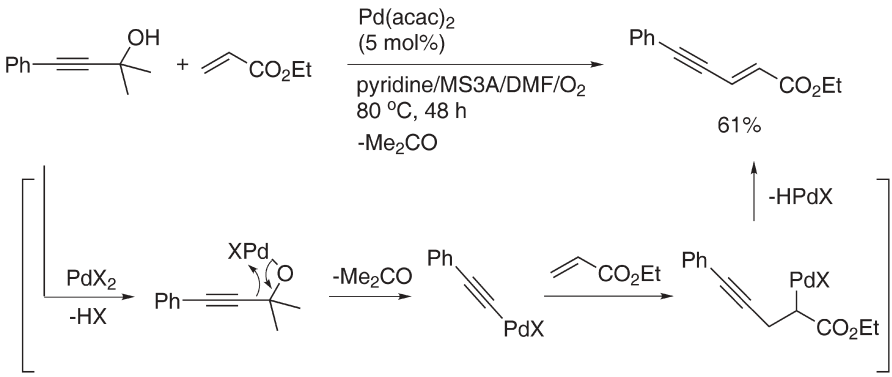


In addition to aryl and alkyl groups, alkynyl groups in tertiary alcohols are also detachable. Thus, as shown in Eq. 33, β-carbon elimination of an sp^3–sp^3 C–C bond in the reaction of propargyl alcohols with alkenes under an oxygen atmosphere gives an ene–yne product [57].

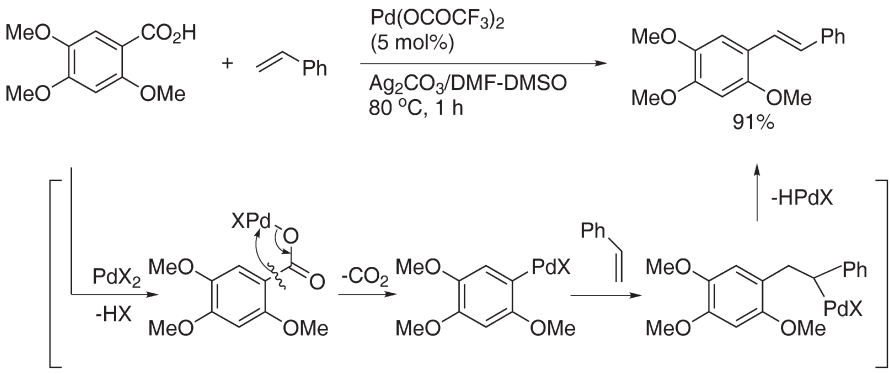
The decarboxylation of palladium(II) benzoates to give arylpalladium(II) species may be regarded as a β-carbon elimination. Such a reaction seems to be involved in the Heck-type coupling of benzoic acids and alkenes (Eq. 34) [58, 59].



Scheme 4



(33)



(34)

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Novel Methods of Aromatic Functionalization Using Palladium and Norbornene as a Unique Catalytic System

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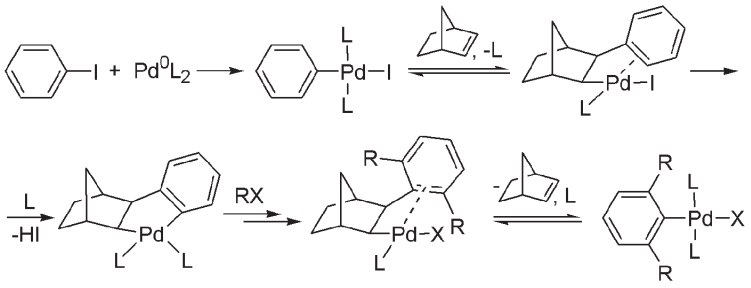
Abstract Ordered reaction sequences involving palladacycles in oxidation states (II) and (IV) are described. Insertion of rigid olefins into arylpalladium bonds followed by electrophilic attack on the aromatic ring leads to formation of palladium(II) metallacycles. The latter further reacts with alkyl or aryl halides with subsequent elimination or retention of the rigid olefins. A variety of termination processes lead to the final products with concomitant liberation of the palladium(0) species, which is able to start a new catalytic cycle by oxidative addition of aryl halides.

Keywords Aromatic functionalization · Palladacycles · Palladium · C–H activation · Homogeneous catalysis · Cross-coupling · Multicomponent reactions · Norbornene

Abbreviations
DMA Dimethylacetamide
NMP 1-Methyl-2-pyrrolidinone
TFP Tri-2-furylphosphine

1 Introduction

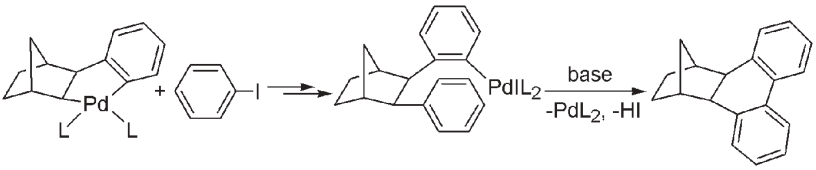
Palladium-catalyzed C–C bond-forming reactions have been the subject of extensive research [1]. The reactions described in the present review originate from the discovery that the insertion of olefins into an arylpalladium bond could give rise to a palladacycle if the usual β-H elimination process was unfavorable, and that the deinsertion process of the same olefins spontaneously occurred after *o*-dialkylation of the aromatic ring took place through the same palladacycle [2]. The required olefins are of the rigid and bulky type such as norbornene and bicyclooctene, which give a *cis*,*exo* insertion product [3] not able to undergo β-hydrogen elimination readily for steric reasons [4]. The process can be schematically represented for iodobenzene as follows (R=alkyl; X=halide; L=ligand: solvent or coordinating species) (Eq. 1).



(1)

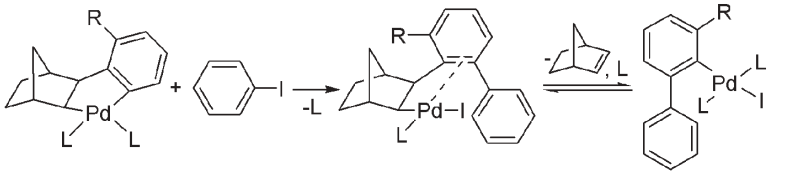
We shall see how this process could be made catalytic by further reacting the final palladium complex with suitable substrates able to afford an organic product together with palladium(0) [5].

We shall also see that the study of the reactivity of the intermediate palladacycle first led us to find that R=aryl migrated to the norbornyl site of the palladacycle and not to the aryl site, as for R=alkyl, and incorporated the norbornane structure into a ring (Eq. 2) [6].



(2)

Later we discovered an important feature of the chemistry of these palladacycles, namely the inversion of the migration site of aryl groups (no longer to the aliphatic but to the aromatic site) when an *ortho* substituent was present in the palladacyclic aromatic ring (Eq. 3) [7].



(3)

This behavior was exploited to obtain another series of catalytic reactions leading to organic products which contain the biphenyl structure [8].

2
Stoichiometric *o,o′*-Dialkylation of Aryl Iodides

The sequence of steps leading to selective alkylation starting from $Pd(OAc)_2$ has been analyzed step by step. The results are reported below.

2.1
Formation of Palladium(0) from Palladium(II)

It is well known that $Pd(OAc)_2$ can be reduced to palladium(0) through several reactions [9]. In particular the inner sphere reduction of $Pd(OAc)_2$ to palladium(0) in the presence of PPh_3 was examined in detail by Amatore and Jutand (Eq. 4) [10].

$$Pd(OAc)_2 + PPh_3 \rightarrow Pd^0 + AcOAc + PPh_3O \quad (4)$$

This is a model for other reduction processes of palladium(II) species commonly occurring at the expense of solvents, substrates, or reagents.

2.2 Oxidative Addition to Palladium(0)

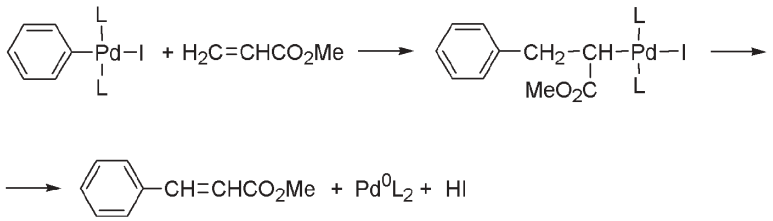
The species actually undergoing oxidative addition of iodobenzene has been shown by Amatore and Jutand [11] to involve palladium(0) anionic complexes such as $[Pd^0(PPh_3)_2OAc]^-$. The process is represented by Eq. 5.

$$[Pd^0(PPh_3)_2OAc]^- + PhI \rightarrow [PdPhI(PPh_3)_2OAc]^- \quad (5)$$

When no phosphinic ligand is present the solvent or norbornene can act as ligand [12]. As to the rate of oxidative addition, the series PhI>PhBr>PhCl [13] has been confirmed. To obtain reactions at mild temperatures aryl iodides have usually been used.

2.3 Olefin Insertion

Olefin insertion into arylpalladium bonds is a well-known process [14] which is usually terminated by β-hydrogen elimination, for example Eq. 6.



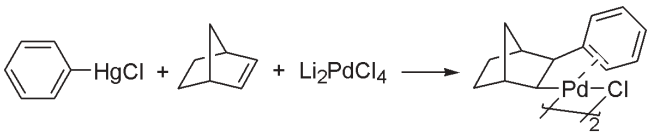
(6)

In our case the inserted norbornene molecule gives a *cis*,*exo* arylnorbornylpalladium adduct that is not able to undergo reductive elimination readily [4]. Although other rigid olefins such as bicyclooctene are able to give *cis*,*exo* insertion products [3] which cannot give reductive elimination readily, norbornene has the advantage of being strained so that its coordination to the metal is favored by steric strain relief [15].

The insertion process is promoted by acetate salts [16]. Reductive elimination, however, is possible through a bimolecular reaction with a base such as potassium phenoxide (Eq. 7) [17].

(7)

Besides monomeric complexes (Eq. 1) [3b,c], dimeric complexes have been isolated and characterized (Eq. 8) [3a,d].



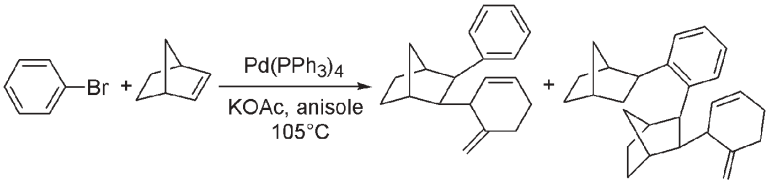
(8)

It has been shown previously [3b] that in monomeric complexes with PPh_3 as ligand, the aromatic ring is bound to palladium through η^2 coordination. This has been confirmed by detailed X-ray and NMR studies of dimeric complexes which have been carried out recently [3d]. Investigation of the analogous dimeric complex containing an *o*-methyl substituent has evidenced a shift toward η^1 coordination, which is not observed with *m*- or *p*-methyl groups. NMR and quantomechanical studies confirm the existence of η^1–η^2 coordination [3d]. These features are particularly relevant to the interpretation of the ring closure reaction to palladacycle to be treated in Sect. 2.4.

2.4 Palladacycle Formation and Reactivity

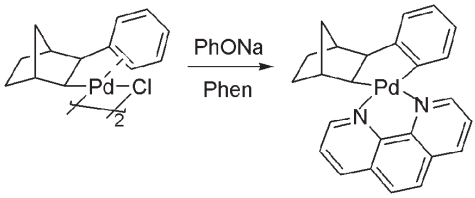
Palladacycles are amply reported in the literature [18]. We shall limit our review to those prepared by norbornene insertion and subsequent cyclization, which are relevant to the synthetic methods treated here.

The intermediacy of palladacycles in the reaction of bromobenzene with norbornene in the presence of $Pd(PPh_3)_4$ as catalyst and KOAc as a base in anisole as solvent was initially suggested by the isolation, among other products, of two compounds (Eq. 9), the former resulting from norbornene insertion into an alkylpalladium bond, the latter clearly deriving from palladium migration from the alkyl to the aryl site and double norbornene insertion. In both cases the termination step involved β,γ-C–C bond cleavage followed by β-H elimination. The stereochemistry of the norbornane unit invariably was *exo* [19].



(9)

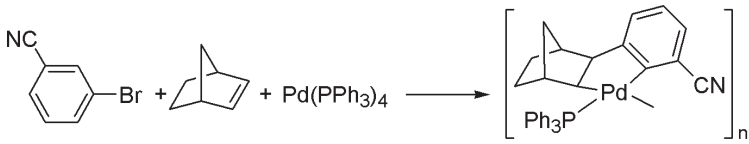
This pointed to the intermediacy of a palladacycle which was actually isolated from the reaction of phenylnorbornylpalladium chloride dimer with sodium phenoxide at room temperature by trapping it with phenanthroline (62% yield) (Eq. 10) [20].



(10)

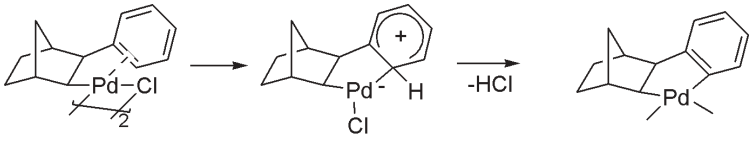
NMR spectroscopy showed that the phenanthroline ligand lies approximately on the palladacycle plane.

A direct way of preparing a palladacycle was found for the special case of *m*-bromocyanobenzene which was reacted with $Pd(PPh_3)_4$ and norbornene in anisole at 105 °C. The palladacycle precipitated in an oligomeric form from the reaction solution in good yields (67% on Pd). The complex contains one molecule of triphenylphosphine per palladium and a coordination site is occupied by the cyano group of another palladacycle unit. (Eq. 11) [21].



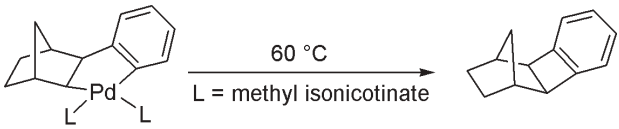
(11)

A study was carried out to get insight into the reaction of the ring-forming process. Palladacycle formation was found to be faster with *para* (with respect to the Pd–C bond) electron-releasing substituents than with the electron-withdrawing ones [22]. The process thus corresponds to an electrophilic aromatic substitution (Eq. 12).

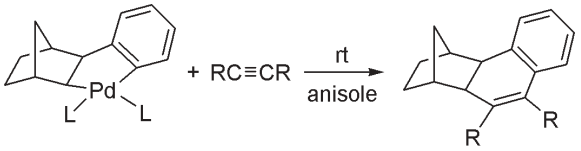


(12)

Palladacycle complexes of this type readily undergo ring closure (Eq. 13), particularly in the presence of bulky *ortho* substituents such as *t*-Bu [7, 17, 23]. Ring enlargement of the same complex can also be effected by reaction with internal acetylenes such as dimethyl acetylenedicarboxylate (R=CO_2Me, L= methyl isonicotinate) (Eq. 14) [24].

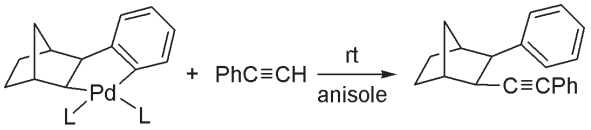


(13)



(14)

The use of a terminal alkyne such as phenylacetylene results in ring opening, likely through PhC≡CH oxidative addition and reductive elimination (Eq. 15).

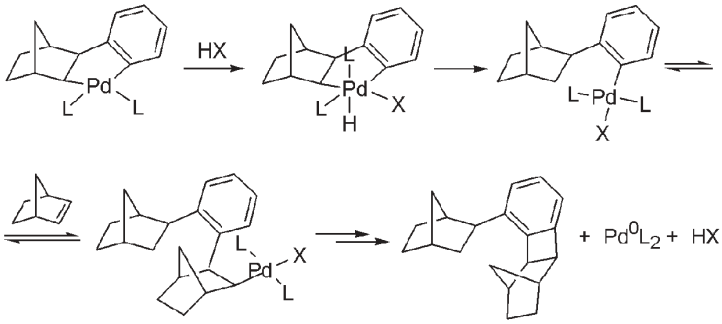


(15)

In the presence of the bidentate phenanthroline ligand, the palladacycle is rather stable and does not undergo ring contraction and expansion under the mild conditions reported.

2.5 Oxidative Addition of Protonic Acids or Alkyl Halides to Palladium(II) Metallacycles

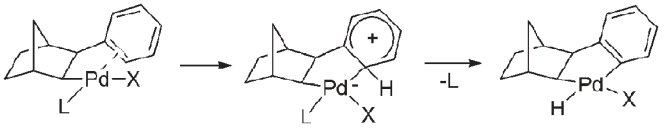
The presence of products derived not only from the reaction of the aliphatic palladacycle carbon, but also from the aromatic one as shown before (Eq. 9) [19b] and below [23, 25], suggested that an oxidative addition of a protonic acid HX to the palladium(II) metallacycle occurred with formation of palladium(IV) (Eq. 16).



(16)

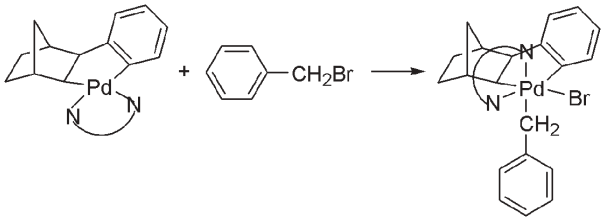
The HX species may also be generated intramolecularly, according to a mechanistic work carried out with an arylpalladium complex and norbornene (Eq. 17) [26].

The first alkylpalladium complex in oxidation state (IV) was isolated by Canty [27]. We obtained the first palladium(IV) metallacycles from the reaction



(17)

of a palladium(II) metallacycle with methyl iodide, and benzyl and allyl bromides or chlorides (N–N=phenanthroline) (Eq. 18, 78% yield) [20, 28].

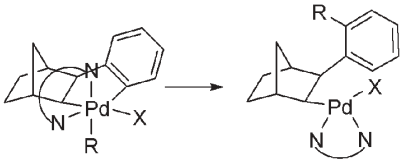


(18)

An approximate planar plane is defined by the palladacycle and by the two Pd–Br and Pd–N bonds, while the axial bonds are those with the other N atom and with the benzyl group. This isomer is formed selectively out of the ten possible.

2.6
Reductive Elimination from Palladium(IV) Metallacycles

The alkylpalladium(IV) complexes obtained by oxidative addition of alkyl (methyl, allyl, and benzyl) halides to the palladium(II) metallacycle spontaneously undergo reductive elimination. This implies migration of the alkyl group R onto the aromatic site of the palladacycle (Eq. 19, R=CH_2Ph, 72% yield).

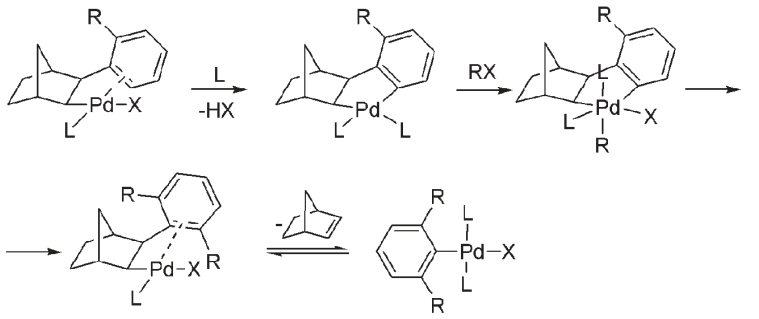


(19)

The reductive elimination process is likely to require that the coupling groups are placed in axial–equatorial rather than in equatorial–equatorial positions with respect to the plane defined by phenanthroline and palladium, and halide dissociation could favor this rearrangement [28b].

In the absence of phenanthroline as ligand the new palladium(II) complex thus obtained reiterates ring closure, oxidative addition, and reductive elimination (Eq. 20).

A selective double alkylation at the two *ortho* positions of the aryl group is thus achieved.

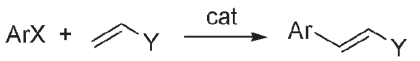


At this point the insertion equilibrium of norbornene into the *o*,*o*′-disubstituted aryl group is no longer favorable due to the steric effects exerted by substituents. As a consequence, norbornene spontaneously deinserts affording a new *o*,*o*′-disubstituted arylpalladium halide. The entire reductive elimination sequence has been proved unequivocally by NMR monitoring and isolation of the organometallic intermediates [2].

2.7
Palladium(0)-Forming Reactions of *o*,*o*′-Disubstituted Arylpalladium Complexes

To obtain a catalytic process from steps 2.1–2.6, it is necessary to add a terminal step that is able to liberate the palladium(0) required for the process initiation. Among the palladium-catalyzed processes reported in the literature some lend themselves to this task very well (Eqs. 21 to 24):

Hydrogenolysis [29] $\mathrm{ArX + 2H\text{-}donor \xrightarrow{cat} ArH + HX + 2donor}$ (21)

Heck reaction [30]  (22)

Suzuki reaction [31] $\mathrm{ArX + Ar'\text{-}B(OH)_2 \xrightarrow{cat} Ar\text{-}Ar' + X\text{-}B(OH)_2}$ (23)

Cassar–Sonogashira reaction [32]  (24)

3
Catalytic *o*,*o*′-Dialkylation of Aryl Halides

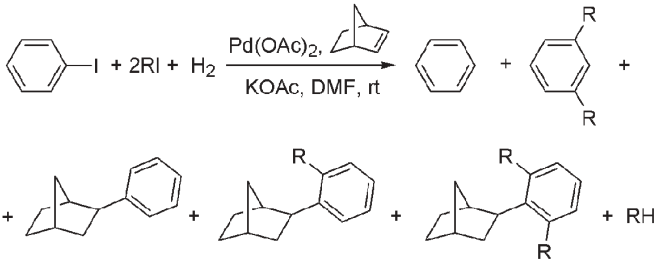
The combination of the elementary steps in the order shown in Sects. 2.1–2.6 leads to *o*,*o*′-disubstituted palladium complexes. At first sight the achievement of an ordered sequence appears problematic. Aryl iodides and alkyl iodides are

indeed both able to attack palladium in its oxidation states (0) and (II). Under appropriate conditions, however, in particular at room temperature, the reaction of aryl iodides with palladium(0) followed by norbornene insertion is preferred to that of alkyl halides. The latter instead react faster with palladium(II) than aryl iodides. This circumstance enabled us to obtain a selective sequence of steps starting from an initial molecular pool. It has also to be pointed out that norbornene or in general a rigid olefin, for example bicyclo[2.2.2]octene, is not incorporated in the final product and therefore acts catalytically. Thus, the aromatic dialkylation process is based on double catalysis by an inorganic and an organic species. This circumstance does not mean, however, that the organic species (norbornene) is employed in a low amount, because a mass action is useful to accelerate the norbornene insertion process. As to the inorganic catalyst (palladium), it must be made continuously available at the end of the desired reaction sequence. It is thus necessary to terminate the sequence with a reaction that liberates palladium in the initial zero oxidation state. This is not a straightforward task, however, because, in addition to the reactions that compete with the main sequence at any stage of the process, a further complication comes from the ability of the molecules used for terminating the sequence to interfere with all the steps where a C–Pd–X bond is present.

Since the type of difficulty that must be overcome to achieve a selective catalytic process depends on the types of substrates and reagents used, we shall describe the criteria adopted for each catalytic reaction.

3.1
Synthesis of *m*-Disubstituted Arenes

Dihydrogen was first used to obtain *m*-dialkylated aromatics according to the reaction of Eq. 25 exemplified for iodobenzene.

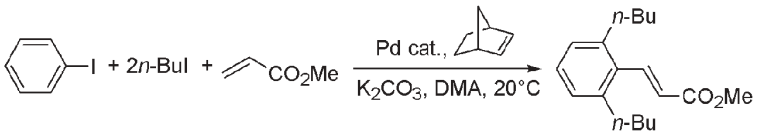


(25)

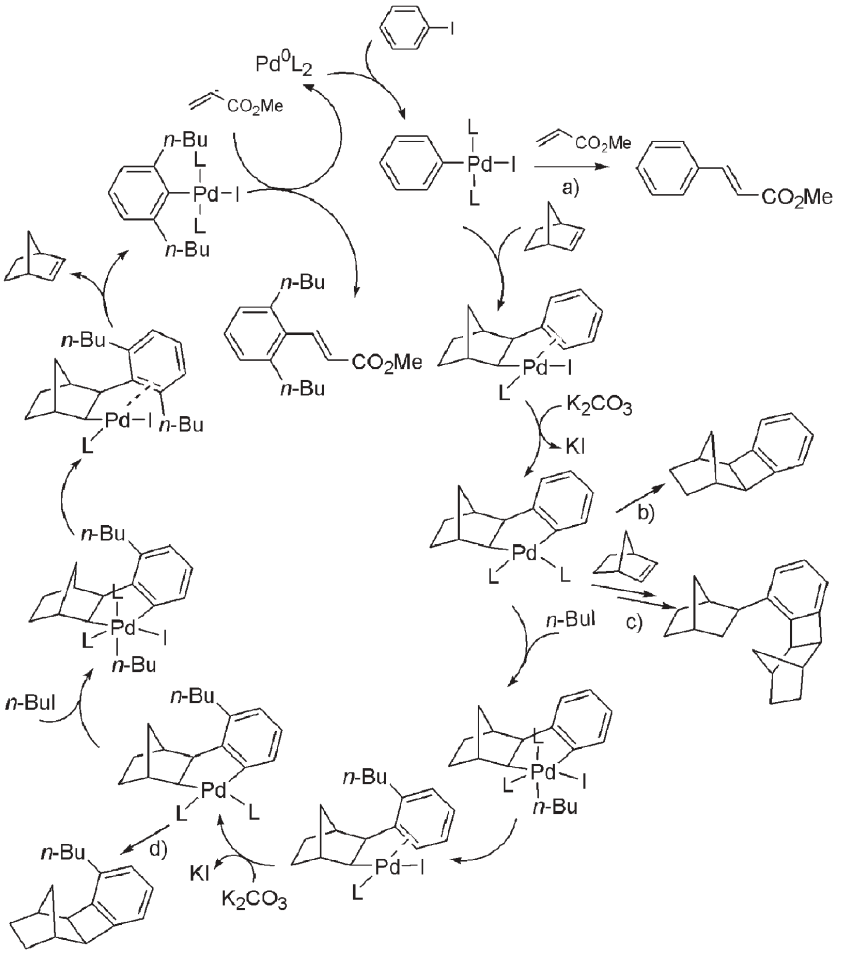
A complex mixture was formed, however, resulting from termination by hydrogen at various levels of the sequence. Satisfactory results were achieved by accelerating the ring closure steps by K_2CO_3 addition and by replacing hydrogen with a hydrogen-transfer agent such as sodium formate. In this way a 78% yield with R=*n*-Pr and a 76% yield with R=*n*-Bu could be reached [33].

3.2
Synthesis of *o,o′*-Disubstituted Vinylarenes

Much better results were obtained when we used olefins as terminating agents according to Eq. 26 (exemplified for iodobenzene, *n*-butyl iodide, and methyl acrylate; Pd cat=*cis*,*exo*-2-phenylnorbornylpalladium chloride dimer) [5].



(26)

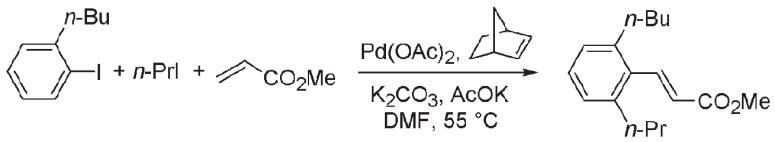


Scheme 1 Catalytic cycle for the synthesis of methyl *o,o′*-di-*n*-butylcinnamate; paths (a), (b), (c), and (d) may lead to secondary products

The reaction was performed using 1 equivalent of aryl iodide, 4 equivalents of *n*-BuI (to accelerate oxidative addition shown in Eq. 18 for benzyl bromide and curtail the competitive cyclobutene ring-forming reaction of Eq. 13), 1.5 equivalents of methyl acrylate, 3 equivalents of K_2CO_3 (to accelerate the metallacycle formation, Eq. 12), 1 equivalent of norbornene (to favor the insertion process, although it acts as a catalyst), and 0.05 equivalents of the palladium catalyst in DMA as the solvent at 20 °C. A 93% yield (on iodobenzene) of the methyl *o*,*o′*-di-*n*-butylcinnamate was obtained. The reaction was tolerant of substituents of various types on the aromatic ring and went very well with terminal olefins bearing an electron-withdrawing substituent. The alkyl halide did not undergo appreciable reductive elimination even in the case of β-phenylethyl iodide. The complete catalytic cycle is reported in Scheme 1.

3.3 Synthesis of *o*,*o′*-Differently Substituted Vinylarenes

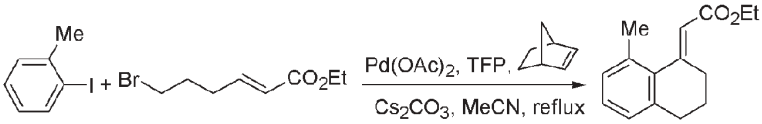
Much greater difficulties were met in the attempt to prepare vinylarenes containing different alkyl chains in the *ortho* position. Using different alkyl iodides all the possible combinations of the *ortho* substituents were obtained. To achieve a selective reaction we started from iodoarenes containing an *ortho* substituent and added the second *ortho* substituent through the reaction of an alkyl iodide with the norbornene-derived palladacycle. The required temperature was a little higher (55 °C), however, and the *ortho* substituent in the aryl iodide induced the elimination of hexahydromethanobiphenylene from the palladacycle (Eq. 13). It was necessary to add the alkyl iodide in large excess (6 equivalents per mol of palladium) in order to make its oxidative addition faster than the competitive reductive elimination. A drawback was the increased tendency of the alkyl iodide to react with palladium(0), and to prevent this reaction we found it advantageous to add half of the alkyl iodide together with half of the olefin gradually by means of a syringe pump [34]. Furthermore, KOAc (5 equivalents) was added to accelerate the reaction of arylpalladium iodide with norbornene (Eq. 7) [16]. With these modifications (Eq. 27) and using $Pd(OAc)_2$ (0.2 equivalents) it was possible to achieve satisfactory results. For example with *o*-*n*-butyliodobenzene, *n*-propyl iodide, and methyl acrylate a 76% yield of methyl 2-*n*-butyl-6-*n*-propylcinnamate was obtained.



(27)

Selective functionalization of aromatics with different groups opened the way to interesting applications. Lautens and coworkers worked out a modified procedure with tri-2-furylphosphine (TFP) as a ligand and Cs_2CO_3 as a base in

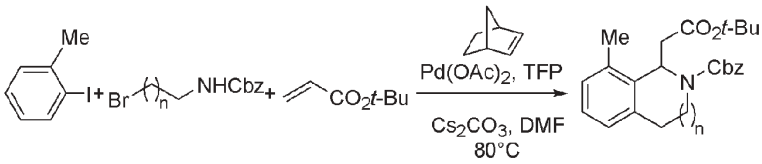
MeCN at reflux, which allowed the synthesis of a condensed ring, shown in Eq. 28 [35] for a specific reaction leading to a tetrahydrodecalin derivative with 92% yield.



(28)

The reaction is general and tolerant of several groups.

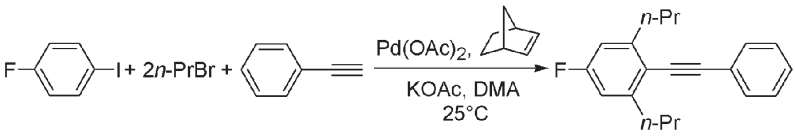
A three-component procedure was applied to the synthesis of nitrogen-containing rings, combining the sequential palladium-catalyzed *ortho* alkylation and vinylation with an aza-Michael reaction. Under the conditions shown in Eq. 29, tetrahydroisoquinoline (n=1) and tetrahydrobenzazepine (n=2) derivatives were obtained in 68 and 43% yield, respectively [36].



(29)

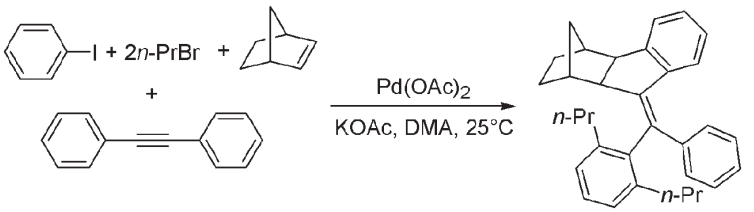
3.4
Synthesis of 2,6-Disubstituted Diarylacetylenes and Diarylalkylidenehexahydromethanofluorenes

Alkynes are known to undergo the Cassar–Sonogashira reaction, which consists of the palladium-catalyzed coupling of a terminal alkyne with an aryl halide [32]. We could thus expect that this reaction terminated the palladium- and norbornene-catalyzed reaction sequence in place of the acrylic ester or terminal olefins in general. Considerable difficulties were met, however, because the alkyne interacted with all the palladium complexes of the sequence, giving rise to a number of by-products. Starting from 1 equivalent of aryl iodide, 2 equivalents of alkyl bromide, 1 equivalent of norbornene, 0.3 equivalents of arylacetylene, 8 equivalents of KOAc, and 0.1 equivalent of $Pd(OAc)_2$ and adding gradually 2 equivalents of alkyl bromide and 0.7 equivalents of arylacetylene (to keep the concentration of the latter low) satisfactory results were obtained. Equation 30 reports the reaction with *p*-fluoroiodobenzene, *n*-propyl bromide, and phenylacetylene, which gave a 79% yield (71% with iodobenzene) [37].



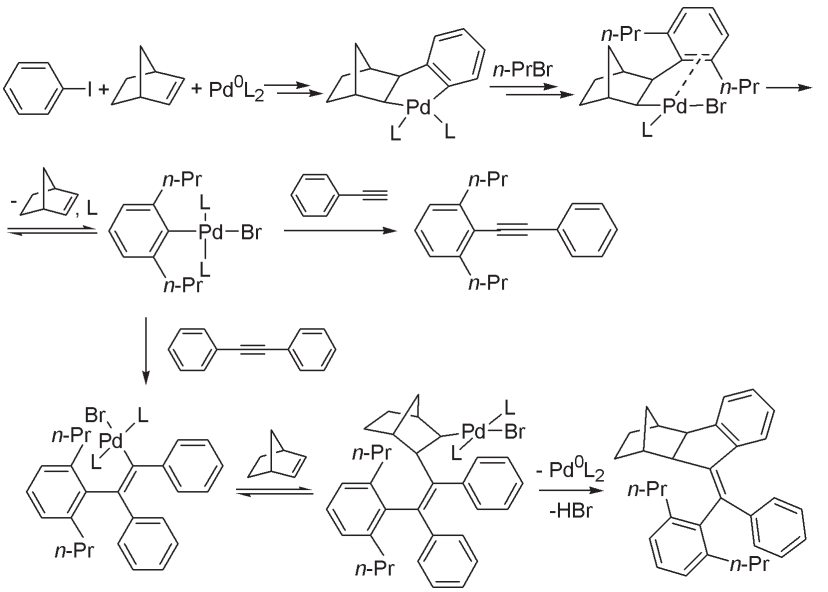
(30)

Under the reaction conditions diarylacetylene was also formed readily from phenylacetylene and the aryl iodide and reacted further by insertion into the terminal arylpalladium bond of the sequence. This gave rise to a new sequence leading to the diarylalkylidenehexahydromethanofluorene shown in Eq. 31 for iodobenzene, *n*-propyl bromide, and diphenylacetylene (formed in situ) [37].



(31)

The overall catalytic process, including both phenylacetylene coupling and diphenylacetylene insertion, is depicted in Scheme 2. The reaction proceeds according to the previously shown pattern until the *o*,*o*′-dialkylated arylpalladium complex is formed. At this point coupling with phenylacetylene occurs to the extent allowed by the concomitant formation of diphenylacetylene: as soon as phenylacetylene disappears diphenylacetylene is readily inserted. The resulting vinylpalladium species now reacts with norbornene and cyclization on one ring of diphenylacetylene affords the final product. It is worth noting



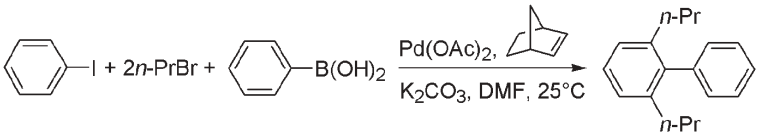
Scheme 2 Simplified catalytic cycles leading to the formation of 2,6-di-*n*-propyl-1,1′-(1,2-ethynediyl)bisbenzene and *E*-9-[1-(2″,6″-di-*i*-propylphenyl)-1-phenylmethylene]-1,2,3,4,4a,-9a-hexahydro-1,4-methano-1*H*-fluorene

that this sequential process includes three steps involving norbornene insertion, deinsertion, and again insertion. As previously explained steric hindrance controls the insertion–deinsertion process. When, however, diphenylacetylene insertion takes place with formation of a vinylpalladium bond, the situation again becomes favorable for norbornene insertion and the final irreversible ring formation further shifts the insertion equilibrium to the right.

The product of Eq. 31 forms in yields up to 15% at room temperature under the conditions adopted for the reaction of terminal alkynes leading to 2,6-disubstituted diarylacetylenes. To achieve selective reactions (yields up to 92%) diphenylacetylene was caused to react with 2,6-disubstituted aryl iodides in the presence of $Pd(OAc)_2$ and K_2CO_3 in DMF at 105 °C.

3.5 Synthesis of 2,6-Disubstituted 1,1′-Biphenyls

As anticipated above, owing to its versatility and simplicity, the Suzuki reaction [31] can be utilized to couple phenylboronic acids with the *o*,*o*′-disubstituted arylpalladium halides formed by norbornene elimination from the palladacycle. Working with 1 equivalent of iodobenzene, 4 equivalents of *n*-propyl bromide, 1.2 equivalents of phenylboronic acid, 6 equivalents of K_2CO_3, and 0.1 equivalent of $Pd(OAc)_2$, a 95% yield of 2,6-di-*n*-propyl-1,1′-biphenyl was obtained according to Eq. 32 [38].



(32)

Table 1 Reaction of an aryl iodide and an alkyl bromide with an arylboronic acid in the presence of $Pd(OAc)_2$ and norbornene as catalysts and K_2CO_3 as a base[a]

Substituent in aryl iodide	Alkyl bromide	Substituent in arylboronic acid	GC yield (%)[b]
H	*n*-Pr	H	95
H	*n*-Bu	H	83
4-CO_2Me	*n*-Bu	H	89
4-Me	*n*-Bu	H	74
4-Me	*n*-Bu	4-Me	86
H	*n*-Bu	4-Me	71
H	*n*-Bu	4-F	62
2-Me	*n*-Bu	H	89
2-*n*-Bu	*n*-Pr	H	70
2-*i*-Pr	*n*-Bu	H	82
2-*i*-Pr	*i*-Pr	H	71

[a] In DMF at rt for 72 h (144 h with 2-substituted aryl iodides) under nitrogen.
[b] On the aryl iodide.

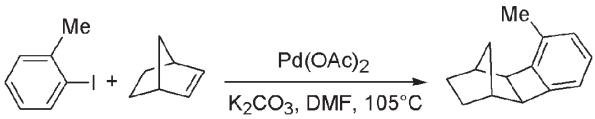
Table 1 shows that several substituents in the aromatic ring and in arylboronic acid are compatible and that different alkyl bromides can be used at room temperature in DMF. *o*-Substituents in the aromatic ring of the boronic acid exert a negative effect, likely for steric reasons.

4
Catalytic Formation of Rings Containing the Norbornane Structure

In several cases processes involving palladacycles containing the norbornane structure do not evolve toward norbornene expulsion. These cases will be examined in the following subsections.

4.1
Hexahydromethanobiphenylenes

As shown in stoichiometric experiments treated in Sect. 2.4, Eq. 13 hexahydromethanobiphenylenes are formed by reductive elimination from palladacycles. These compounds are often present as secondary products in the catalytic reactions shown. Path b of Scheme 1 is an example. In the absence of competitive reactants the palladacycle eliminates a hexahydromethanobiphenylene, forming palladium(0). A catalytic process was thus worked out starting with an aryl iodide or bromide, norbornene, $Pd(OAc)_2$, and K_2CO_3 [23]. Yields were good to excellent with *o*-substituted iodo- or bromobenzene (94% with *o*-Me, Eq. 33).



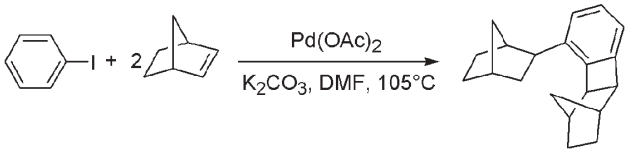
(33)

Bicyclo[2.2.2]octene could also be used in place of norbornene. Since it is not strained it has less tendency to coordinate to palladium compared to norbornene [15]. Thus it is reactive with *o*-iodo- rather than with *o*-bromotoluene to give an analogous product containing the bicyclooctane unit in place of the norbornane one (62%).

4.2
5-Norbornylhexahydromethanobiphenylenes

In Eq. 9 an intermediate palladacycle has been considered as responsible for the palladium migration from the alkyl to the aryl site. Further norbornene insertion resulted in the cleavage of a β,γ-C–C bond [19b].

Under different conditions (K_2CO_3 in DMF) or in the presence of appropriate substituents the process led to four-membered ring closure (Eq. 34, two diastereoisomers) [19b, 23, 25a,b].

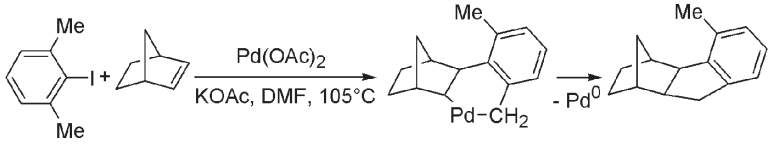


(34)

As mentioned before (Eqs. 16 and 17), this secondary reaction is connected to the presence of a protonic source in the reaction mixture or simply to direct hydrogen transfer from the arene to the norbornane site of the complex through palladium(IV).

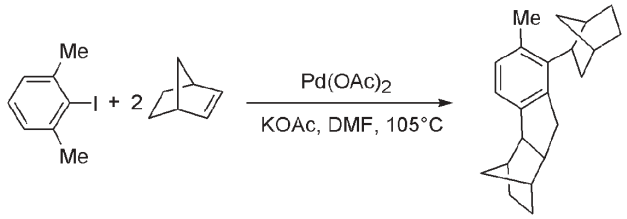
4.3
Hexahydromethanofluorenes

In Sect. 3 we have seen that *o*,*o*′-dialkylation via palladacycle is accompanied by norbornene deinsertion. Since this process is essentially due to the steric effects of the two *ortho* substituents, we could expect that norbornene deinsertion should be less favorable when steric hindrance is smaller and other reactants are absent. This is what happens with *o*,*o*′-methyl groups. At 105 °C in DMF *o*,*o*′-dimethyliodobenzene reacted with norbornene in the presence of $Pd(OAc)_2$ as catalyst and KOAc as a base to give a 60% yield of hexahydromethanofluorene. The reaction implies palladation of the *ortho* methyl group followed by reductive elimination (Eq. 35) [39].



(35)

Even more interesting, this reaction was accompanied by another one involving two molecules of norbornene (Eq. 36, 28% yield). The product was a mixture of two diastereoisomers.

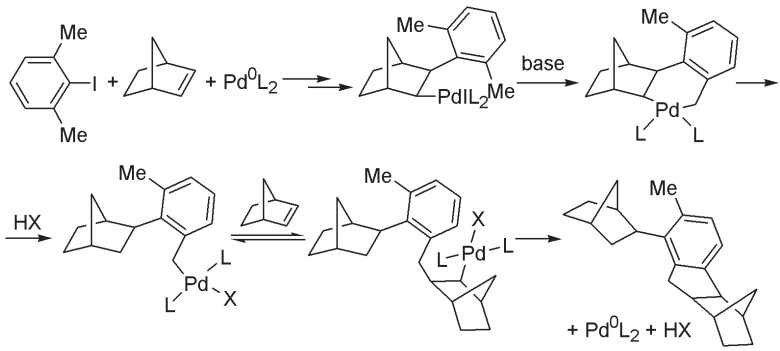


(36)

Reaction 36 involves palladium migration from an sp^3 to another sp^3 carbon. Palladium migration was observed in the norbornyl–aryl system [19b, 23, 25, 26] and in other systems not involving norbornene [40]; sp^2–sp^2 migrations

have also been described [41]. A related rhodium-catalyzed reaction involving the norbornyl–aryl system was reported by Miura [42].

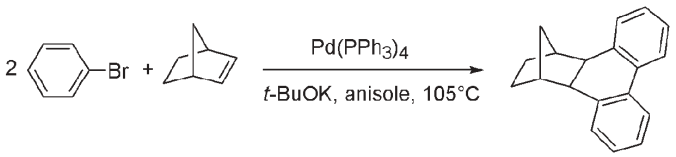
An important feature of reaction 36 (and also of reaction 35) is that it must involve a six-membered palladacycle to explain the formation of a condensed cyclopentene ring on the aromatic site, as shown in Scheme 3.



Scheme 3 Proposed pathway for the synthesis of hexahydromethanofluorene derivatives

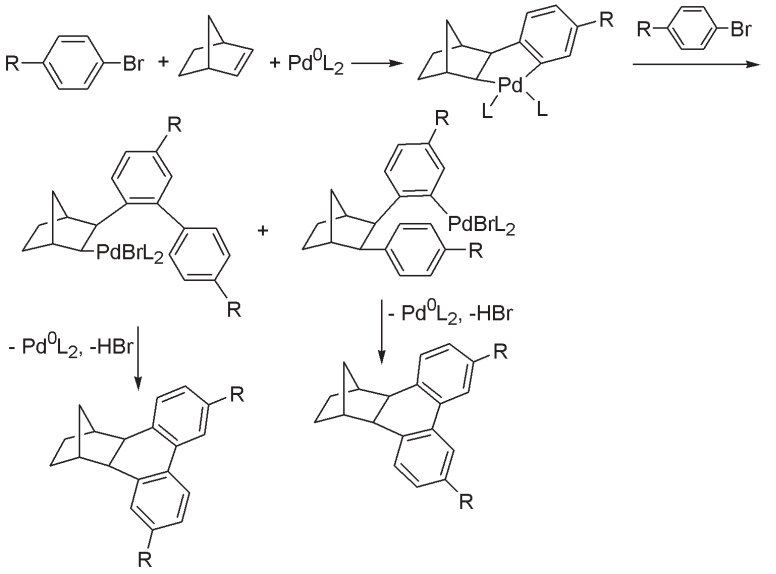
4.4 Hexahydromethanotriphenylenes

Reactions involving norbornene incorporation take place when aryl iodides are used in place of alkyl iodides for the attack on the metallacycle. An early reaction of bromo- or iodobenzene with norbornene and $Pd(PPh_3)_4$ in anisole at 105 °C in the presence of *t*-BuOK led to a 65% yield of the *cis*,*exo*-hexahydromethanotriphenylene shown in Eq. 37 [6].



(37)

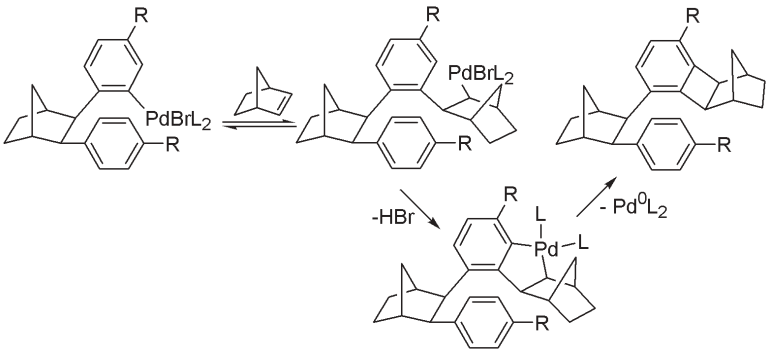
Biphenyl and hexahydromethanobiphenylene were the major by-products. To clarify the mechanism of this reaction a substituent was placed in the aromatic ring. It was thus found that two isomeric products were formed depending on whether the second aryl group attacked the aryl or the norbornyl site of the metallacycle, according to the mechanism shown in Scheme 4 (R=substituent, L=PPh_3). The two isomers formed to different extent depending on ligands, solvents, norbornene, R substituents, and reaction conditions. Thus, with R=F, PPh_3 as ligand, and anisole as solvent the product of aryl migration to the aryl site of the palladacycle was obtained in a 3:1 ratio (45% yield) to that of the norbornyl site. Using methyl *p*-iodobenzoate (R=CO_2Me) in a stoichiometric



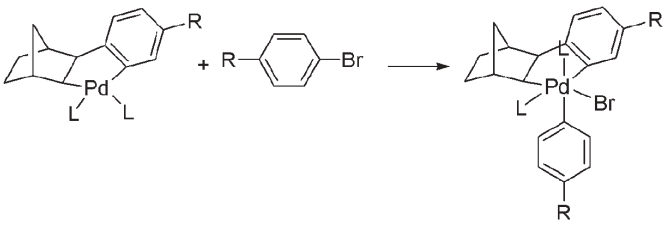
Scheme 4 Proposed pathway for the formation of isomeric hexahydromethanotriphenylene derivatives

reaction with phenylnorbornylpalladium chloride dimer and K_2CO_3 (which causes ring closure to palladacyle) in DMF at room temperature, migration to the norbornyl site occurred selectively (60% yield) [43].

The palladium complex isomer resulting from aryl migration to the norbornyl site was clearly the less reactive for ring closure to hexahydromethanotriphenylene and it could be trapped by norbornene itself, according to Scheme 5 [44]. The formation of the two isomers was interpreted as resulting from a common intermediate which forms by oxidative addition of the aryl halide to the palladacycle, according to Eq. 38.



Scheme 5 Trapping of the precursor of a hexahydromethanotriphenylene derivative with norbornene



(38)

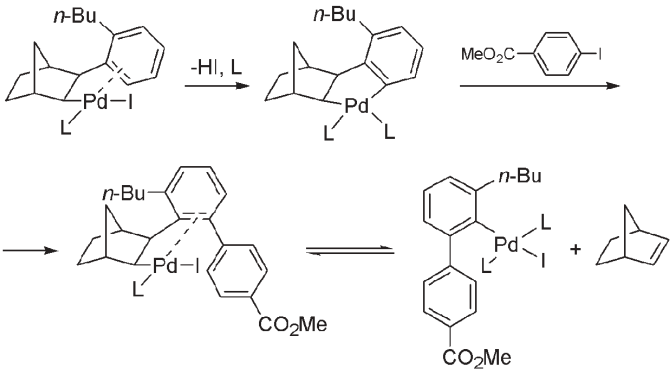
In contrast with the palladium(IV) metallacycle obtained by reaction with an alkyl halide (Eq. 18) the one shown in Eq. 38 could not be isolated, probably because reductive elimination is much faster. The literature, however, reports that diphenyliodonium triflate can arylate palladium(II) to form a palladium(IV) complex [45].

5
Stoichiometric *o′*-Arylation of *o*-Substituted Aryl Halides

Palladacycles lend themselves to attack by aromatic halides, as shown in Sect. 4.4. Depending on conditions the subsequent reductive elimination can affect the aryl or the norbornyl site. A selective behavior cannot be obtained except in the case of *ortho* substituents in the initial palladacycle.

5.1
The *ortho* Effect

It has been discovered that *o*-substituents in the palladacycle exert a steric effect that is able to orient the aryl group that attacks the palladacycle toward the aryl site of the palladacycle itself [7]. We have seen in Sect. 2.3, Eq. 8, that in the solid state an *o*-methyl group induces palladium to adopt an η^1 coordination and this probably is connected with some steric effect of the methyl group. The X-ray structure of the corresponding palladacycles stabilized by

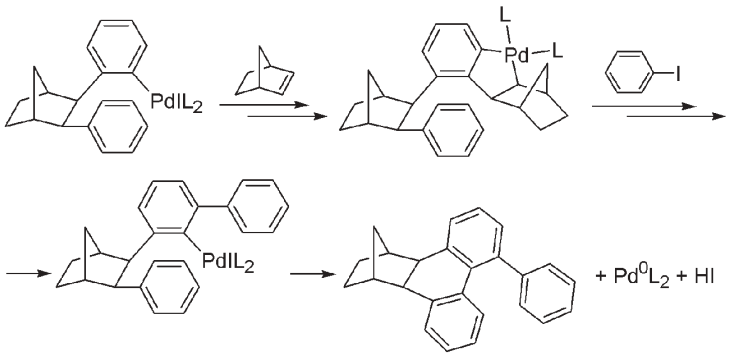


(39)

phenanthroline does not show significant changes in the Pd–C(norbornyl) and Pd–C(aryl) bonds in the presence and in the absence of an *o*-methyl substituent [46]; thus, the preferential cleavage of the latter should be traced to steric effects in the transition state for reductive elimination. The *o*-substituent effect appears to be quite powerful in that it reverses the predominant direction of addition of aryl groups in reductive elimination from the palladacycle. This change has a dramatic consequence: norbornene expulsion occurs, analogously to what is observed for *o*,*o*′-dialkylated arylpalladium complexes (Sect. 2.6), for example Eq. 39.

5.2 Reaction of Phenylnorbornylpalladium Chloride with Norbornene and Iodobenzene

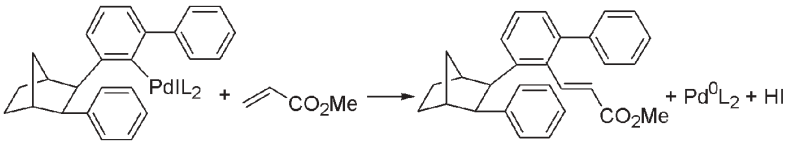
As mentioned before (Sect. 4.4) the stoichiometric reaction of phenylnorbornylpalladium chloride dimer with an aryl iodide in the absence of added norbornene gave hexahydromethanotriphenylene [43] (Scheme 4). When the same reaction was carried out in the presence of norbornene, the product derived from incorporation of another arene molecule was obtained (Scheme 6). This result could be explained as a consequence of the *ortho* effect. [7, 25c, 47].



Scheme 6 Simplified pathway of the introduction of an aryl group into the aromatic site of the palladacycle due to the bulkiness of the *ortho* substituent

As shown in Scheme 6 the palladium complex obtained by reaction of an aryl halide with the norbornyl site of the initial palladacycle, according to the catalytic reaction shown in Sect. 4.4, Scheme 5, is trapped by a new molecule of norbornene, which gives rise to a second palladacycle containing a bulky phenylnorbornyl group in the *ortho* position. Instead of giving the reductive elimination to a benzocyclobutene derivative, as observed at 105 °C [44], this time the palladacycle reacts with another molecule of iodobenzene, which attacks the aryl site selectively [7]. The final ring closure to phenylhexahydromethanotriphenylene is perfectly analogous to the one examined in

Sect. 4.4. These results explain satisfactorily the catalytic formation of 8-phenylhexahydromethanotriphenylene reported by de Meijere [47]. The precursor of the final product of Scheme 6 was also trapped by adding an acrylic ester (Eq. 40) [48].



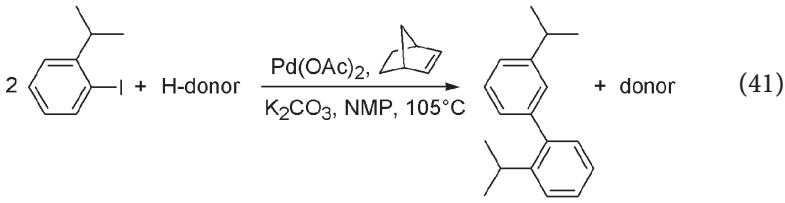
(40)

6
Catalytic *o′*-Arylation of *o*-Substituted Aryl Halides

The knowledge acquired from stoichiometric experiments on the *ortho* effect allowed a series of new sequential reactions leading to biphenyl-derived structures to be worked out.

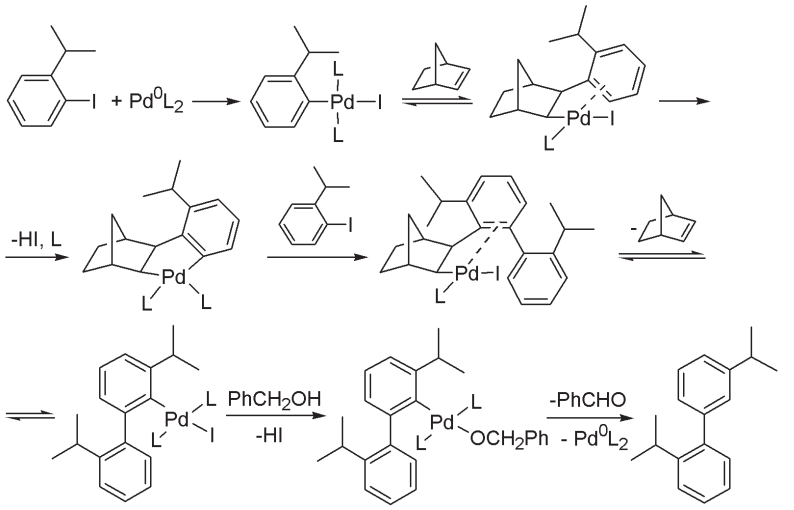
6.1
Synthesis of 2,3′-Disubstituted Biphenyls

The most simple termination of the sequence leading to a biphenylylpalladium halide complex consists of the reaction with dihydrogen or a hydrogen donor. Thus, starting from two molecules of *o*-*i*-propyliodobenzene it was possible to obtain an unsymmetrically substituted biphenyl containing the *i*-propyl group in the *ortho* position in one ring and in the *meta* position in the other (Eq. 41, NMP=*N*-methylpyrrolidinone) [49].



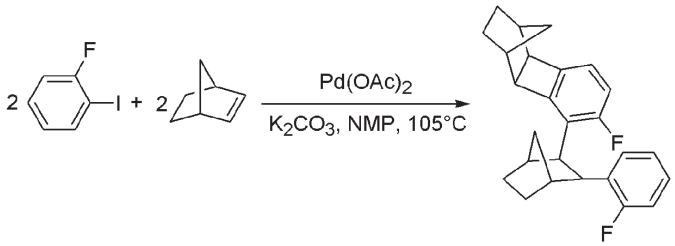
(41)

Selectivity, however, could not be readily achieved because of the possibility of alternative termination reactions and of the interaction of the H donor with each palladium complex of the sequence. Among several H donor tested, the highest selectivities were obtained with benzyl alcohol (86%) and benzhydrol (84%). Butanol (75%), isobutyl formate (72%), water (37%), and sodium formate (21%) followed. The reagents molar ratio was *o*-*i*-propyliodobenzene:H donor:K_2CO_3:norbornene:$Pd(OAc)_2$=80:80:160:20:1. Scheme 7 shows the reaction course for the *i*-propyl group as *ortho* substituent and benzyl alcohol as H donor (L=ligand: solvent, norbornene).



Scheme 7 Reaction pathway for the synthesis of 2,3′-di-*i*-propyl-1,1′-biphenyl from *o*-*i*-propyliodobenzene

The *o*-*i*-propyl group is the most effective, a moderate steric bulkiness being important. Accordingly the small size of F does not allow biphenyl formation with norbornene expulsion. A complex mixture was formed, containing predominantly a difluorinated compound (Eq. 42) [49, 50], which originates in accordance with Scheme 5, Sect. 4.4.



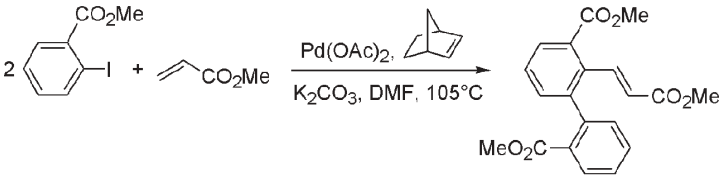
(42)

The steric effect of the *ortho* substituent is responsible for the formation of by-products resulting from reactions of the type shown in Eqs. 33 and 34 (Sect. 4.2). On the other hand, the tendency of the *ortho*-methyl group to form a cyclopentene ring (Sect. 4.3, Eqs. 35 and 36) leads to by-products containing the hexahydromethanofluorene unit.

6.2 Synthesis of 3,2′-Disubstituted Vinylbiphenyls

The reaction of terminal olefins, in particular acrylic esters, with the final biphenylylpalladium complex resulting from norbornene deinsertion led to the

achievement of another catalytic reaction of wide scope. In fact it was applied to many *o*-substituents in the starting aromatic iodide and in the olefin. One of the best examples is reported by Eq. 43 (98% yield) [50].



(43)

The reagents were used in molar ratio: aryl iodide:terminal olefin:K_2CO_3:norbornene:$Pd(OAc)_2$=40:24:40:12:1. As shown in Table 2, yields are good to excellent. Electron-withdrawing substituents both in the aryl iodide and in the olefin give the best results.

The positive effect of the electron-withdrawing substituent in the *ortho* position also allowed the use of the corresponding bromide in place of the iodide with comparable yields although for a longer time. Too-bulky groups such as *t*-butyl led to the exclusive formation of the hexahydromethanobiphenylene compound shown in Sect. 4.1, Eq. 33. Groups that interfere with palladium in arylnorbornylpalladium complexes, such as mono- and dimethylamino, hydroxy and acetoxy, inhibited the reaction.

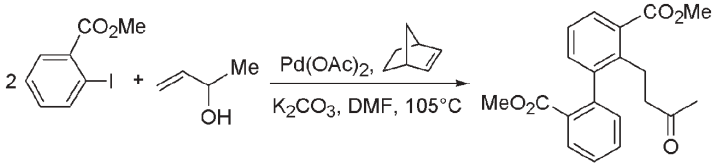
Table 2 Reaction of an *ortho*-substituted aryl iodide with a terminal olefin in the presence of $Pd(OAc)_2$ and norbornene as catalysts and K_2CO_3 as a base[a]

o-Substituent in aryl iodide	Substituent in the terminal olefin	Isolated yield (%)[b]
Me	CO_2Me	79
Et	CO_2Me	79
n-Pr	CO_2Me	76
i-Pr	CO_2Me	84
-$(CH)_4$-	CO_2Me	93
OMe	CO_2Me	88
CO_2Me	CO_2Me	98
Et	COMe	79
Et	Ph	87
Et	*n*-BuO	73[c]
Et	*n*-Hex	76[c]

[a] In DMF at 105 °C for 16 h under nitrogen.
[b] On the aryl iodide.
[c] After hydrogenation of the double bond.

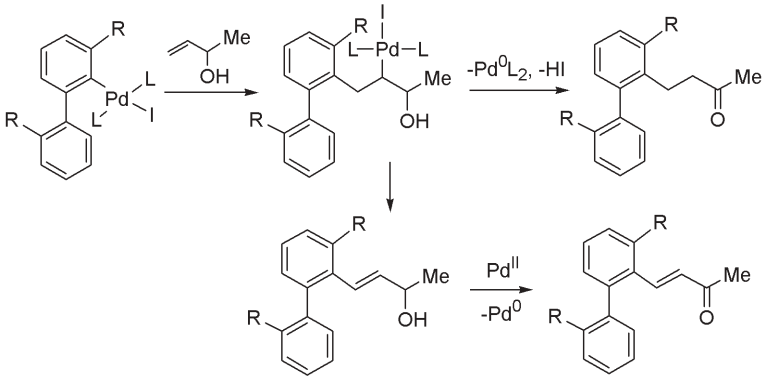
6.3
Synthesis of 3,2′-Disubstituted Biphenyls with an Oxoalkyl Chain

The utilization of allylic alcohols as terminating agents of the palladacycle reaction sequence offered new access to a class of ketones or aldehydes containing the selectively substituted biphenyl unit. An example of the reaction is given by Eq. 44 (93% yield) [51].



(44)

With substituents other than CO_2Me lower yields were obtained and the unsaturated alcohol and ketone were formed. Scheme 8 depicts the reaction of the biphenylylpalladium species with the allylic alcohol 3-buten-2-ol.

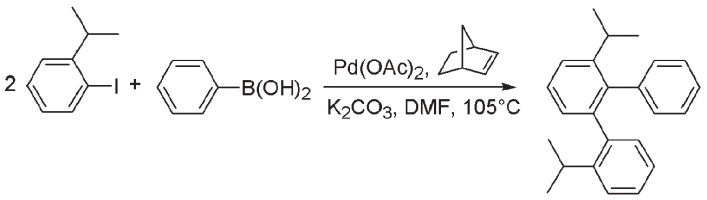


Scheme 8 Reaction pathways of biphenylylpalladium iodide with 3-buten-2-ol

6.4
Synthesis of 2,3′-Disubstituted *o*-Terphenyls

The versatile Suzuki reaction [31] was combined with the sequence leading to biphenylylpalladium iodide complexes to obtain aryl coupling [52]. Once again the best results were obtained with a moderately bulky *o*-substituent such as *i*-propyl (Eq. 45, 93%), which favors norbornene expulsion after formation of the biphenyl unit.

Table 3 reports the results obtained with different *o*-substituents in the aryl halide and with unsubstituted or substituted arylboronic acids. The molar ratio of the reagents was: aryl iodide:arylboronic acid:norbornene:$Pd(OAc)_2$:K_2CO_3=200:120:100:1:400. Analogously to the preceding synthetic procedure



(45)

Table 3 Reaction of an *ortho*-substituted aryl iodide with an arylboronic acid in the presence of $Pd(OAc)_2$ and norbornene as catalysts and K_2CO_3 as a base[a]

o-Substituent in aryl iodide	Substituent in arylboronic acid	Isolated yield (%)[b]
Me	H	88
Et	H	77
i-Pr	H	93
n-Bu	H	73
OMe	H	82
CO_2Me	H	89
n-Bu	4-Me	72
n-Bu	4-F	71
n-Pr	2-Me	73
i-Pr	2-Me	49

[a] In DMF at 105 °C for 90 h under nitrogen.
[b] On the aryl iodide; conversion was higher than 90% in all cases except in the last one (62%).

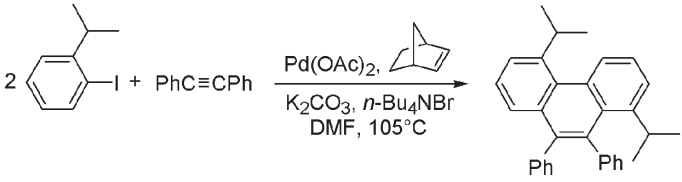
the process is tolerant of various substituents provided that they do not interfere with palladacycle formation, such as the methylamino, hydroxy, and acetoxy groups. By-products resulting from ring closure to hexahydromethanobiphenylenes (Sects. 4.1 and 4.2) were also present. A bromo derivative could be used in place of the iodo one in the case of *o*-CO_2Me.

The reaction is also compatible with the presence of an *ortho* substituent in the arylboronic acid, while arylboronic acid with two *ortho* substituents was not reactive. By-products from aryl scrambling and biaryl from homocoupling were not found. The reaction proceeds as previously indicated up to the formation of the biphenylylpalladium species and is terminated by the Suzuki coupling as in Eq. 45.

6.5 Synthesis of 1,5-Disubstituted Phenanthrenes

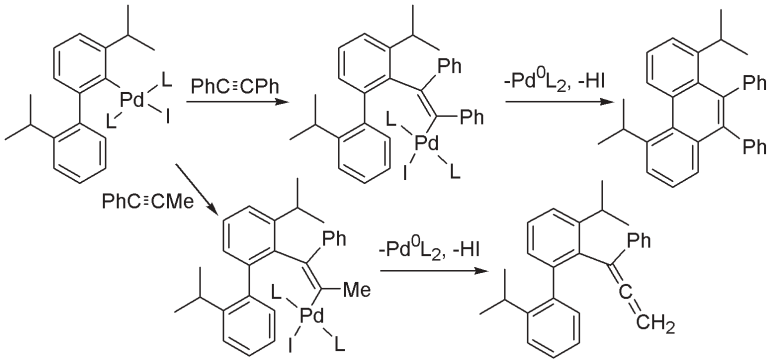
The reaction of diphenylacetylenes with aryl iodides was studied by various groups in order to synthesize phenanthrenes [41a, 53]. The new process here described follows a different logic, the biphenyl structure being formed step by step on the palladacycle and reacted with diphenylacetylene after norbornene

expulsion [54]. The reaction gave the best yield once again with the *o*-*i*-propyl group (Eq. 46) using the aryl iodide, norbornene, diphenylacetylene, K_2CO_3, *n*-Bu_4NBr, and $Pd(OAc)_2$ in the molar ratio 40:10:20:60:120:1.



(46)

The addition of the ammonium salt to the reaction mixture markedly enhanced the yield [53b]. DMF was the solvent of choice while DMA and MeCN gave poor results. While satisfactory results (yields higher than 80%) were obtained with the primary and secondary alkyl groups, the *t*-butyl group failed to react with the second molecule of aryl iodide and gave mostly the methanobiphenylene derivative (Sect. 4.1). Alkylphenylacetylenes could also be used but they transformed in part or totally into allenes by reductive elimination before ring closure (Scheme 9).

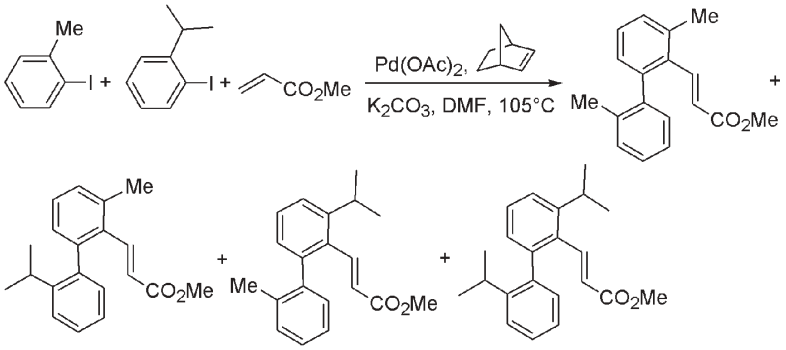


Scheme 9 Reaction pathway of biphenylylpalladium iodide with diphenylacetylene and methylphenylacetylene

6.6 Synthesis of Vinylbiphenyls Selectively Substituted by Different Substituents

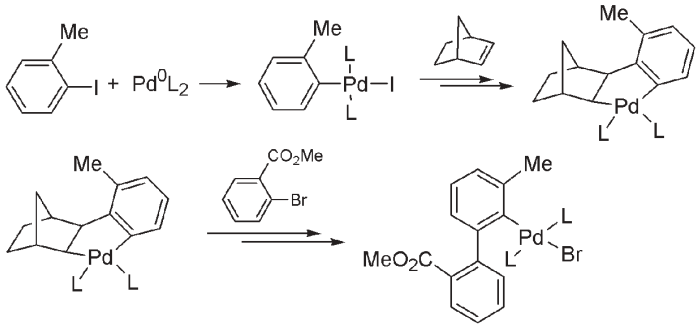
The task of introducing two different substituents in each ring of a vinylbiphenyl according to the methodology described in Sect. 6.2 seemed to be unfeasible in view of the results obtained with differently alkylated iodides. In fact, starting with *o*-iodotoluene and *o*-*i*-propylbenzene, all the possible isomers shown in Eq. 47 were formed in 37, 14, 17, and 31% yield, respectively.

An important step forward was taken when we realized that it was possible to discriminate between the first oxidative addition leading after norbornene



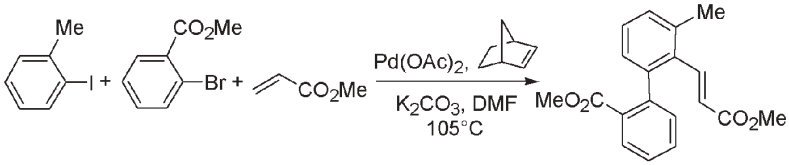
(47)

insertion to the palladium(II) metallacycle and the aryl halide attack on this species. Different requirements characterize the two sequential processes. As shown in Sect. 6.2, Table 2, an *ortho* electron-withdrawing substituent in the aryl iodide strongly enhances both processes. If, however, the corresponding aryl bromide is used, the ability to attack palladium(0) appears to be much lower while the ability to attack the palladium(II) metallacycle is still good (Scheme 10). By contrast an *o*-alkyl group in the aryl iodide can undergo oxidative addition to palladium(0) but it is not so effective for the attack on palladium(II).



Scheme 10 Preferential reaction of *o*-iodotoluene with palladium(0) and of methyl *o*-bromobenzoate with palladium(II) metallacycle

If, therefore, we combine *o*-bromobenzoate with *o*-iodotoluene the main product must be the mixed one. This was the criterion followed to achieve reaction 48 [55].



(48)

It essentially exploits the different behavior of aryl iodides bearing an *ortho* electron-releasing group and bromides containing an electron-withdrawing substituent in the attack to palladium(0) (followed by norbornene insertion) and palladium(II) (followed by norbornene deinsertion).

The reason why certain bromides are more active than iodides in the attack to palladium(II) is probably connected to steric effects. We ascertained that at room temperature the order of reactivity of aryl iodides and bromides with palladium(0) and palladium(II) is the same (I>Br), so the difference is likely to lie in the easier accessibility of the reaction center of the palladacycle to suitably activated bromo derivatives than to *o*-alkyl-substituted aryl iodides, which are considerably bulkier. We ascertained that several groups are compatible as shown in Table 4, referring to the reaction of *o*-substituted aryl iodides, substituted aryl bromides, norbornene, methyl acrylate, K_2CO_3, and $Pd(OAc)_2$ in the molar ratio 50:50:50:80:120:1.

Substituents in both the aryl iodide and the aryl bromide have a marked effect. While *o*-substituents are needed in the aryl iodide, *o*-, *m*-, and *p*-substituents can be present in the aryl bromide. The reaction tolerates methoxy and dimethylamino groups in the aryl iodide, but it is made difficult or inhibited by hydroxy, amino, or methylamino groups. As anticipated the success of the

Table 4 Reaction of an *ortho*-substituted aryl iodide and an aryl bromide with methyl acrylate in the presence of $Pd(OAc)_2$ and norbornene as catalysts and K_2CO_3 as a base[a]

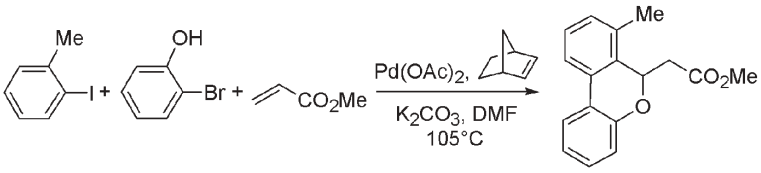
o-Substituent in aryl iodide	Substituent in aryl bromide	Isolated yield (%)[b]
Me	2-CO_2Me	80
i-Pr	2-CO_2Me	74
t-Bu	2-CO_2Me	37[c]
Ph	2-CO_2Me	73
OMe	2-CO_2Me	83
NMe_2	2-CO_2Me	82
CF_3	2-CO_2Me	77
Me	2-CF_3	Traces
Me	3-CF_3	71
Me	4-CF_3	80
Me	3-CO_2Me	37
Me	4-CO_2Me	71
Me	2-CN	13
Me	3-CN	62
Me	4-CN	79
Me	2-F	–
Me	3-F	24

[a] In DMF at 105 °C for 24 h under nitrogen.
[b] On the aryl iodide.
[c] The main product (42%) was the methanobiphenylene derivative.

reaction is due to the use of aryl iodides with an *ortho* electron-donating group and aryl bromides bearing an electron-withdrawing substituent. However, some anomalous behaviors were observed. As shown in Table 4, the trifluoromethyl group gave a satisfactory result in the reaction with *o*-bromobenzoate (77%) when present in the *ortho* position of the aryl iodide, while only traces of unsymmetrical coupling product were formed when *o*-trifluoromethylbromobenzene was used in combination with *o*-iodotoluene. This suggests an interaction between the *o*-CF_3 group and the palladacycle that is able to inhibit the following steps. In accordance with this hypothesis, the *meta* and *para* isomers gave good results. Other *ortho* substituents (*o*-F, *o*-CN) in the aryl bromides showed peculiar behavior and inhibited the reaction or led to the unsymmetrical product only in low yield. The different effect of the methoxycarbonyl group on reactivity is noteworthy. While comparable results were obtained when the substituent was in the *ortho* or *para* position of the aryl bromide, a lower reactivity was observed with the *meta* isomer. This can be related to the lower value of the Hammett constant (0.34) compared to that of the *para* isomer (0.46). Subtle electronic factors thus influence the reaction outcome.

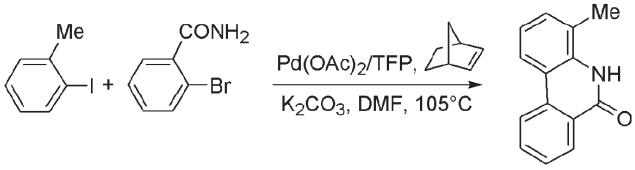
The terminal olefins can also be varied to a large extent from electron-withdrawing to electron-releasing substituents. Regioisomers derived from H elimination from different β sites were formed from alkyl chains as expected, and branched and linear isomers were obtained with electron-rich olefins.

Although the most effective substituents on the aryl bromide are the electron-withdrawing ones, *o*-bromophenol reacted satisfactorily, possibly because of the favorable effect of chelation, and led to the formation of a condensed cyclic compound by final Michael reaction. A 6*H*-dibenzopyran derivative was thus formed in 71% yield (Eq. 49) [55, 56].



(49)

The new coupling methodology was also extended to the synthesis of condensed nitrogen heterocycles. Using *o*-bromobenzamide in the reaction with *o*-iodotoluene in the presence of $Pd(OAc)_2$, tri-2-furylphosphine (TFP), and norbornene as catalyst in DMF at 105 °C, the corresponding phenanthridinone was obtained in 86% yield (Eq. 50) [57].



(50)

7
Conclusions and Perspectives

The reactions that have been illustrated should give an idea of the potential of a methodology which combines the criterion of multicomponent reactions with that of selectivity, usually difficult to reconcile. One key feature is the use of an olefin as a scaffold for the construction of a palladacycle that is able to direct aromatic functionalization selectively and can be easily removed at the end of the process. Another important feature is the use of different oxidation states of palladium to control reactivity. The combination of an inorganic catalyst (palladium) with an organic one (norbornene) leads to a variety of syntheses in one-pot reactions, which represent only the beginning of what may be expected to be a very fruitful development. Needless to say, any advancement in this area requires a thorough study of the reactivity of the organometallic species involved.

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Arylation Reactions via C–H Bond Cleavage

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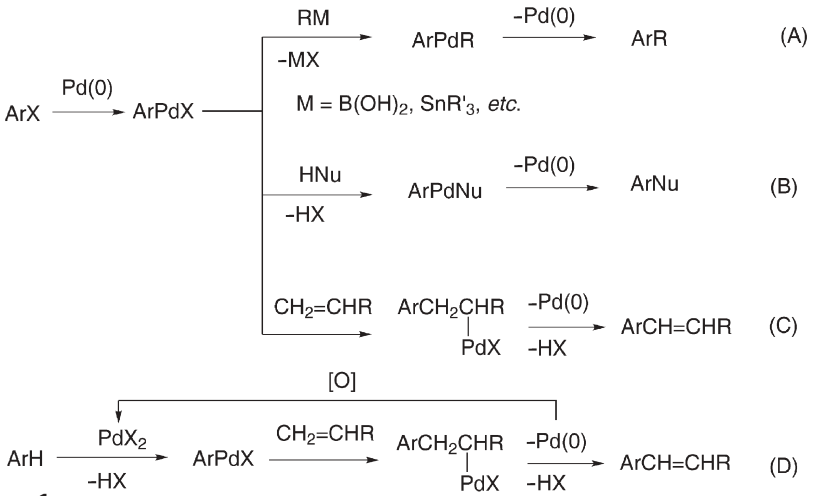
Abstract Various carbon nucleophiles having acidic C–H bonds, including active methylene compounds, ketones, aldehydes, esters, and so on, are arylated with aryl halides under palladium catalysis. Appropriately functionalized aromatic substrates also undergo inter- and intramolecular arylation reactions accompanied by cleavage of their unactivated C–H bonds. In this article is summarized the recent progress of these reactions as effective methods for preparing aromatic fine chemicals. A brief description of the progress of related direct arylation of unsaturated compounds with arenes is also given.

Keywords Aryl halides · Arylation · Palladium catalysts · Aromatic compounds · Carbonyl compounds

1 Introduction

The palladium-catalyzed cross-coupling of aryl halides with organometallic reagents is now recognized to be one of the most useful methods for the functionalization of aromatic compounds accompanied by carbon–carbon bond formation [1–3]. The Suzuki–Miyaura and Kosugi–Migita–Stille reactions of

aryl halides as well as vinyl halides with organoboron compounds and organostannanes, respectively, are very often employed in organic synthesis (Scheme 1, mechanism A). The Heck reaction with alkenes is also well known to be a versatile method for the synthesis of arylated alkenes (mechanism C) [1, 2, 4].



Scheme 1

On the other hand, the direct arylation of carbanionic species generated from substrates having relatively acidic hydrogens such as active methylene compounds and ketones can occur (mechanism B) [5, 6]. Aryl halides are also capable of coupling directly with appropriately functionalized aromatic substrates and five-membered heteroaromatic compounds as formal carbon nucleophiles via cleavage of their unactivated C–H bonds [5, 7–9]. The Fujiwra–Moritani reaction, which is the arylation of alkenes with arenes, is also useful for preparing arylalkenes without employing any halides (mechanism D) [10, 11].

The above reactions appear to have synthetically significant advantages, being able to be carried out without stoichiometric metalation of nucleophilic substrates or halogenation of arenes. Since we surveyed these direct methods for preparing aromatic fine chemicals [5], further impressive progress has been achieved. Consequently, an updated summary of the direct reactions is described herein.

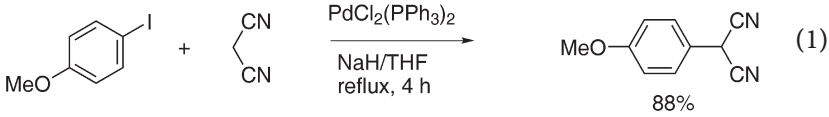
2
Arylation of Carbon Nucleophiles

Among common carbon–carbon bond formation reactions involving carbanionic species, the nucleophilic substitution of alkyl halides with active methylene compounds in the presence of a base, e.g., malonic and acetoacetic ester

syntheses, is one of the most well-documented important methods in organic synthesis. Ketone enolates and protected ones such as vinyl silyl ethers are also versatile nucleophiles for reaction with various electrophiles including alkyl halides. On the other hand, for the reaction of aryl halides with such nucleophiles to proceed, photostimulation or addition of transition metal catalysts or promoters is usually required, unless the halides are activated by strong electron-withdrawing substituents [12]. Of the metal species, palladium has proved to be especially useful, while copper may also be used in some reactions [13]. Thus, this type of catalytic reaction had been regarded as impossible or very difficult for a long time with the exception of some special cases; it has recently become a potential synthetic tool, and a variety of substrates having acidic C–H bonds can now be arylated effectively as described below.

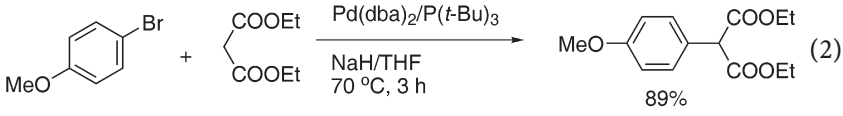
2.1
Active Methylene Compounds

As one of the first examples, Takahashi and coworkers reported the reaction of aryl iodides with malononitrile in the presence of $PdCl_2(PPh_3)_2$ using NaH as base (Eq. 1) [14, 15]. Cyanoacetate esters can be employed in place of malononitrile [16], but the use of other active methylene compounds having no cyano group such as malonates is not successful under similar conditions, while in the intramolecular version, various carbanion centers bearing two electron-withdrawing groups can be involved [17, 18].



(1)

Recently, the limitations of the intermolecular reaction have been significantly mitigated [19–25]. Use of sterically bulky and electron-rich phosphines as ligands, typically P(*t*-Bu)$_3$, allows the arylation of malonates as well as cyanoacetates even with aryl chlorides (Eqs. 2 and 3) [22]. The reaction of malonates at a somewhat elevated temperature affords arylacetates accompanied by dealkoxycarbonylation (Eq. 4) [26, 27].



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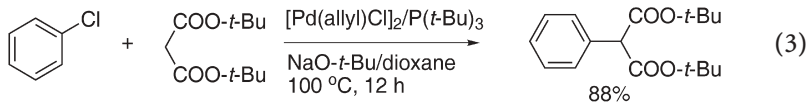

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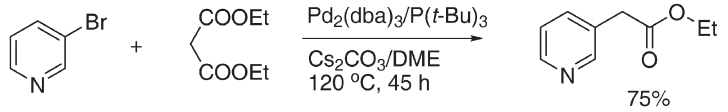


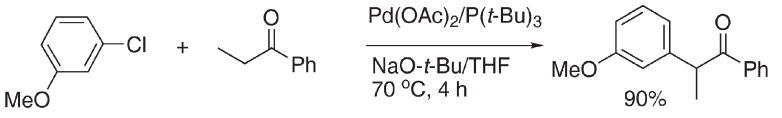
(4)

Various bulky phosphines and *N*-heterocyclic carbene ligands have proved to be effective in a number of palladium-catalyzed reactions of aryl chlorides and bromides [28–30], e.g., Mizoroki–Heck reaction, Suzuki–Miyaura reaction, Migita–Kosugi–Stille reaction, amination, and alkoxylation, as well as the reaction with various carbon nucleophiles as described below. The ligands are considered to enhance both the initial oxidative addition of aryl halides and the reductive elimination of products. The identity of bases is also an important factor to obtain satisfactory results commonly in the arylation of carbon nucleophiles; NaH, NaO-*t*-Bu, K_3PO_4, M_2CO_3 (M=K, Cs), and $MN(SiMe_3)_2$ (M= Li, Na, K) are typical choices.

2.2
Ketones, Aldehydes, Esters, and Amides

In the early examples of the α-arylation of ketones, masked ketone enolates such as silyl enol ethers [31] and enol acetates [32–34] were used in the presence of a tin source. The reactions involve tin enolates or acylmethyltins as intermediates, and thus proceed by transmetalation (Scheme 1, mechanism A).

The direct intermolecular α-arylation of relatively less acidic ketones with aryl halides, which proceeds by mechanism B, was reported concurrently in 1997 by the groups of Miura, Buchwald, and Hartwig [35–37]. The intramolecular version was also described by Muratake and coworkers in the same year [38, 39], while some intermolecular vinylation reaction had been reported [40, 41]. Taking advantage of this, the reaction of carbonyl compounds and related substrates has been studied extensively. Now a variety of ketones are known to be arylated by using appropriate ligands and bases [42–46]. The reaction usually takes place at a less hindered α position (Eqs. 5–7) [19, 20].



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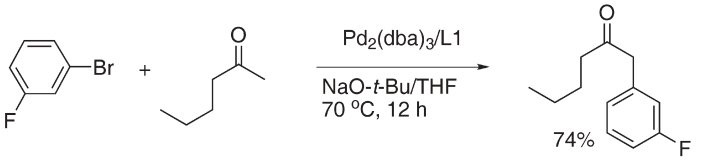

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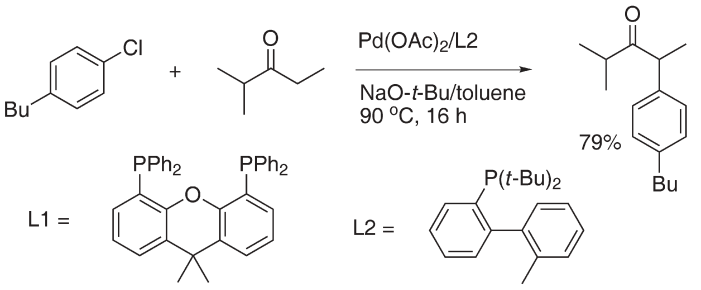
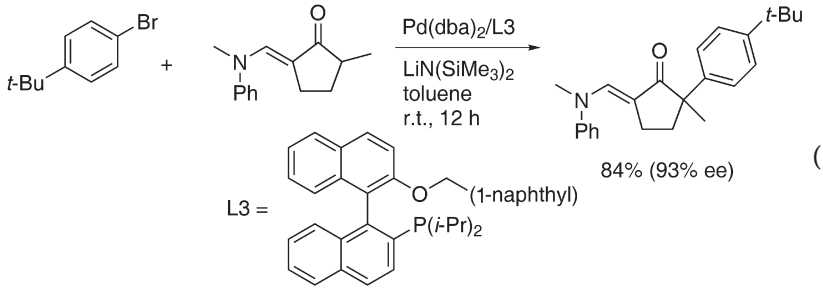


(7)

The asymmetric reaction of cyclic ketones can be performed with chiral binaphthylphosphines (Eq. 8) [47–50]. The reaction of acetophenones with *ortho*-bromonitrobenzenes followed by reduction affords indole derivatives (Eq. 9) [51]. The arylation of benzyl ketones has been applied to the synthesis of analogs of tamoxifen, which is a medicinal agent for breast cancer (Eq. 10) [52, 53].



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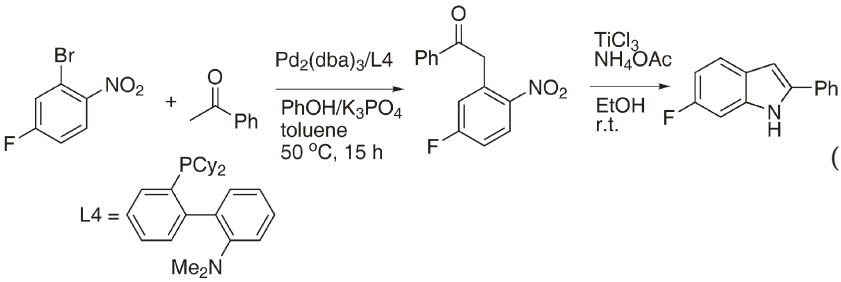

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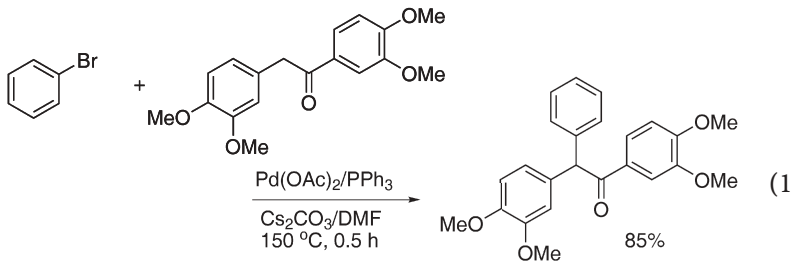
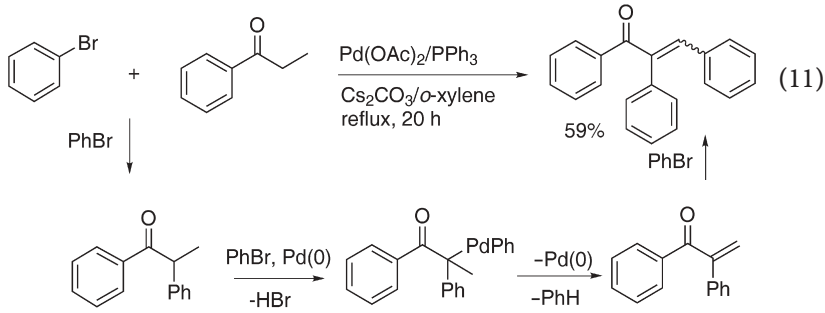


(10)

It has been found that treatment of propiophenone with an excess amount of bromobenzene gives rise to 1,2,3-triphenyl-2-propen-1-one (Eq. 11) [43]. In this reaction, α-arylation, unsaturation via β-hydrogen elimination, and Heck-type arylation occur successively. From the reaction of butyrophenone is obtained the corresponding triarylated product (Eq. 12). The reaction sequence involves α-arylation, unsaturation via β-hydrogen elimination, two times vinylogous arylation (γ-arylation), and double bond isomerization. It should be noted that α,β-unsaturated carbonyl compounds are generally arylated at their γ position (Eqs. 13 and 14) [54–56].



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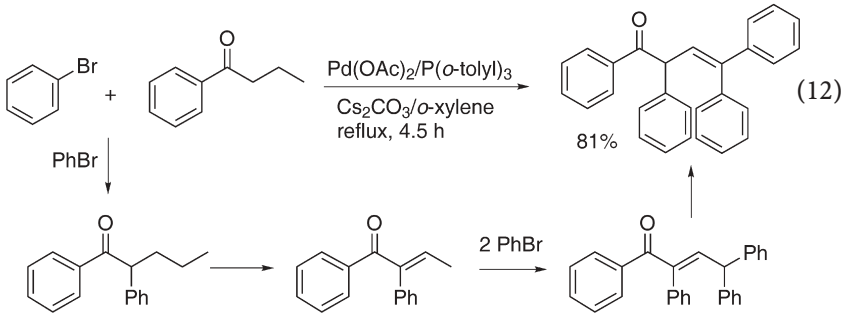
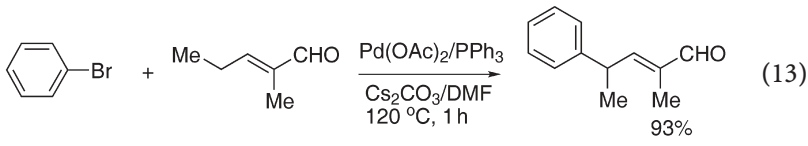


(12)



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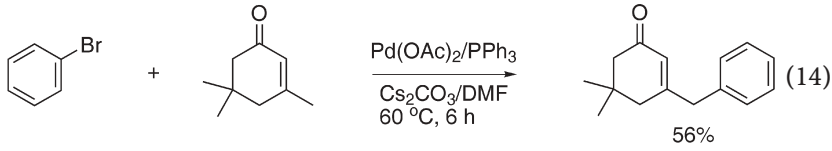
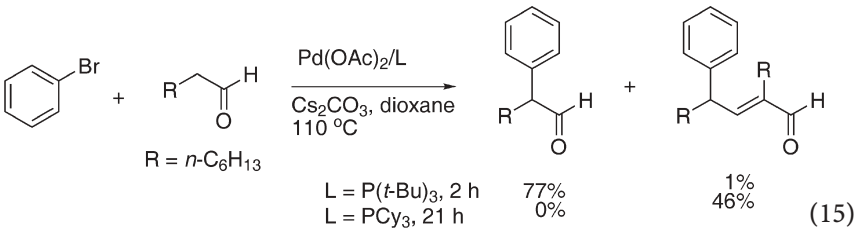


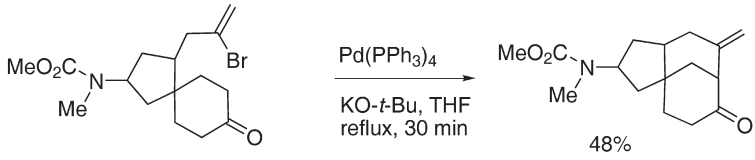
(14)

The α-arylation of aldehydes is also possible [57, 58]. The choice of ligand and solvent is important (Eq. 15) [57]. In the case when a less bulky ligand or a more polar solvent is used, aldol condensation occurs at first, which is follwed by γ-arylation to give a 1:2 coupling product.



(15)

The intramolecular coupling of haloaryl- or halovinyl-linked ketones and aldehydes as well as other carbonyl species is a useful tool for the construction of cyclic compounds including natural products [38–41]. The synthesis of the precursor of a natural immunosuppressant, FR901483, is a recent example (Eq. 16) [59]. It is noted that a novel Pd-catalyzed Grignard-type nucleophilic carbonyl arylation occurs competitively in some cases [60, 61]; the product ratio depends on the structure of the substrates (Eq. 17) [61].



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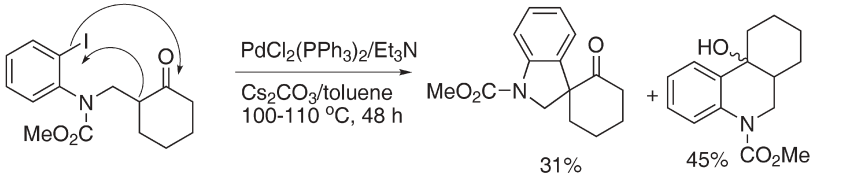
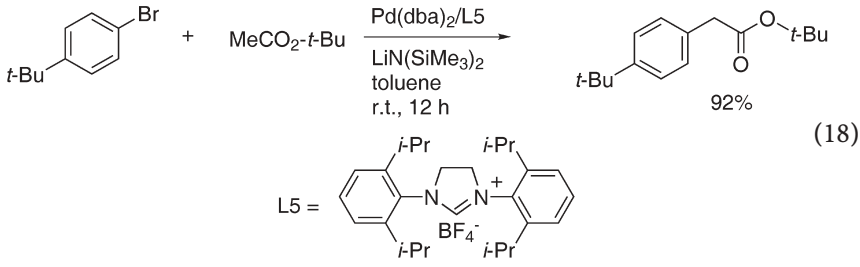


(17)

The arylation of esters is of importance as a synthetic method of arylacetic acids and 2-arylpropionic acids, which may exhibit antiinflammatory activity. Use of relatively bulky and strong bases such as hexamethyldisilazides has been reported to allow satisfactory results (Eqs. 18 and 19) [62–64]. The arylation of trimethylsilyl enolates of esters has also been described to occur effectively in the presence of a zinc(II) species, which proceeds via zinc enolates [65].

The reaction of protected glycines affords α-phenylglycine derivatives (Eq. 20) [63]. The intramolecular reaction of α-amino acid derivatives provides



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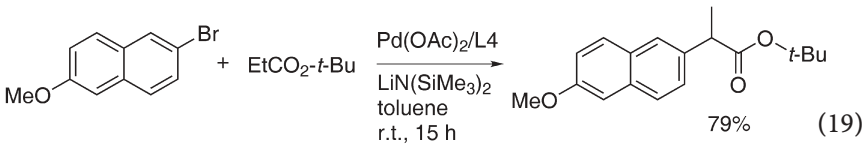
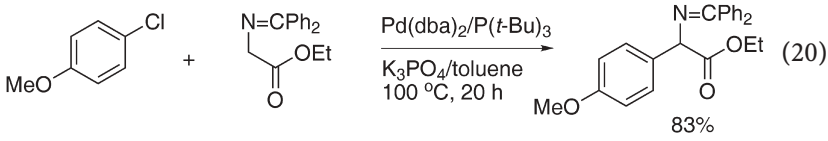


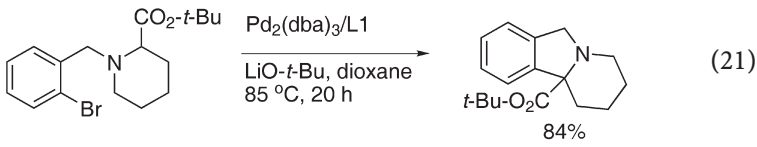
(19)



(20)

a useful method for preparing N-containing cyclic compounds (Eq. 21) [66]. Azlactone derivatives are also arylated (Eq. 22) [67].

Inter- and intramolecular arylations of amides have been described [68]. Use of zinc enolates of amides affords high yields in some cases (Eq. 23) [69]. In the



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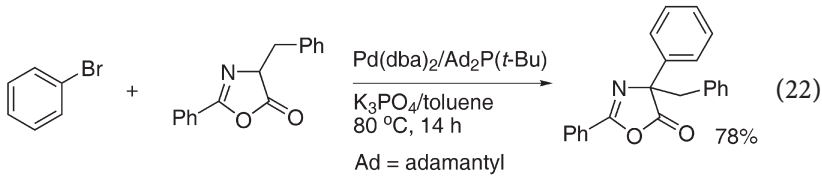

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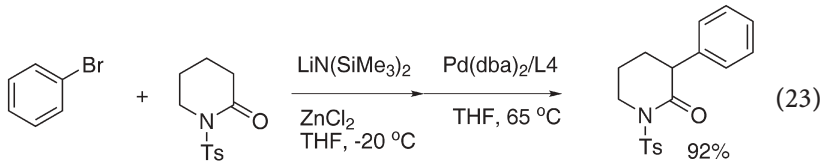
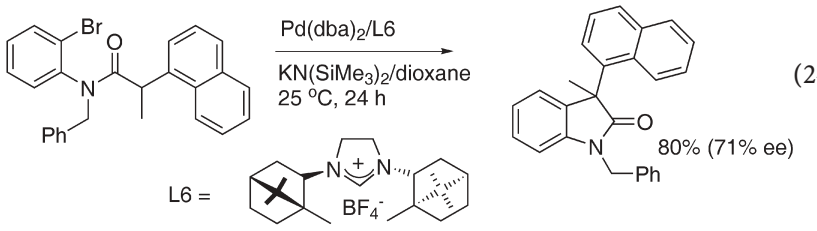


(23)

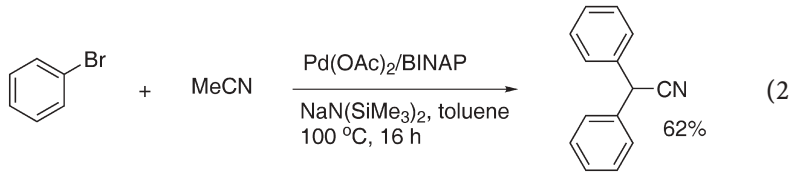
intramolecular version, asymmetric induction has been examined using various chiral ligands including *N*-heterocyclic carbenes (Eq. 24) [70].



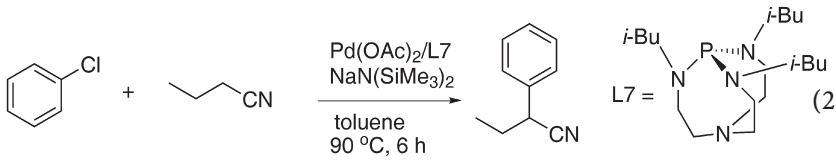
(24)

2.3 Miscellaneous Carbon Nucleophiles

The α-arylation of aliphatic nitriles proceeds effectively in the presence of a hexamethyldisilazide as base. Simple substrates such as acetonitrile undergo diarylation (Eq. 25) [71]. Monoarylation is possible by using a bulky proazaphosphatrane as ligand (Eq. 26) [24].

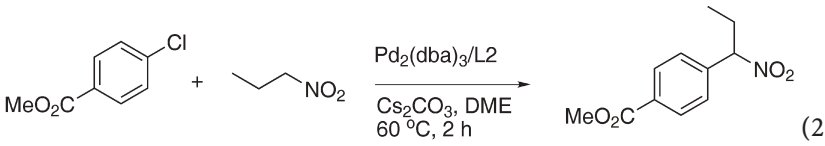


(25)



(26)

Nitroalkanes are monoarylated effectively by using a biphenylphosphine and Cs_2CO_3 as ligand and base, respectively (Eq. 27) [20, 72]. The intramolecular version has been reported [57]. Interestingly, 4-nitrotoluene undergoes formal vinylogous arylation, while 3-nitrotoluene is inactive [73]. Thus, 3,4-dimethylnitrobenzene is selectively arylated at the 4-methyl group (Eq. 28).



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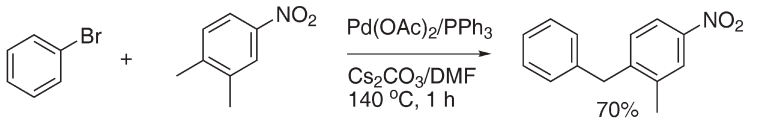
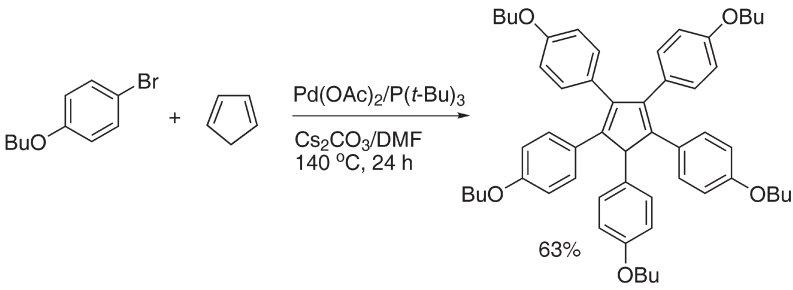


(28)

Cyclopentadiene, whose deprotonation in the presence of a base gives the relatively stable cyclopentadienyl anion, has been found to be a suitable substrate for palladium-catalyzed arylation [74, 75]. By using excess aryl bromides, it is completely arylated to produce pentaarylcyclopentadienes (Eq. 29). Metallocenes, typically zirconocene dichloride, are perarylated similarly [74, 76]. Pentaarylcyclopentadienes have been applied as the components of electroluminescent devices [77] and bulky metallocene ligands [78]. Di-*tert*-butylphosphinoferrocene is also pentaarylated efficiently (Eq. 30) [79]. In this case, another mechanism other than Scheme 1 (B) seems to be involved; possibly coordination-assisted palladation participates (see Sect. 3.2).



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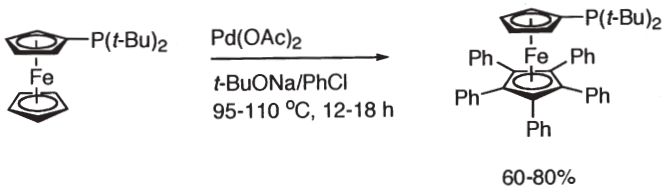


(30)

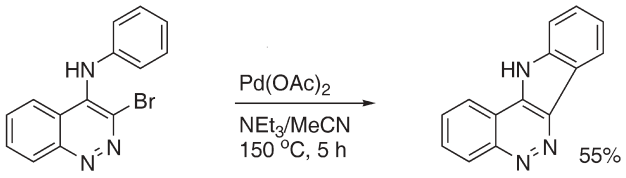
3 Arylation of Aromatics

Biaryl structures are found in a wide range of important compounds, including natural products and organic functional materials [8, 80, 81]. One of the most common and useful methods for preparing biaryls is the palladium-catalyzed coupling of aryl halides with arylmetals (Scheme 1, mechanism A). On the other hand, aryl halides have been known to couple directly with aromatic compounds as formal nucleophiles under palladium catalysis. While the intramolecular cases are particularly effective, certain functionalized aromatic compounds such as phenols and aromatic carbonyl compounds, as well as

five-membered aromatic heterocycles, can undergo intermolecular arylation on their aromatic rings.

3.1
Intramolecular Reaction of Aromatic Compounds

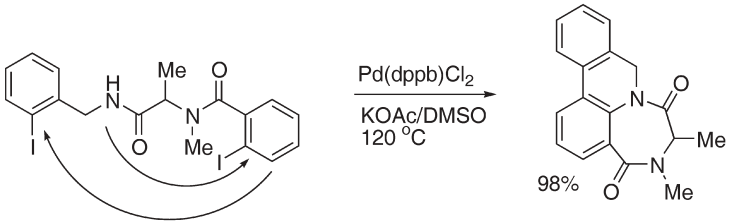
Ames et al. reported the cyclization of bromocinnolines as one of the early important examples of intramolecular aryl–aryl coupling (Eq. 31) [82–84]. This type of reaction is now a standard method for the synthesis of polycyclic compounds [7, 8, 81, 85].



(31)

Among the recent significant examples is the double cyclization of diiodo compounds by the combination of intramolecular aromatic arylation and *N*-arylation (Eq. 32) [86]. Interestingly, the reaction of *N*-(2-bromobenzyl)-1-naphthylamines selectively takes place at the *peri* position, not at the 2 position (Eq. 33) [87]. In this case, coordination of the nitrogen to Pd appears to be a key factor for forming the seven-membered ring. On the other hand, *N*-benzyl-*N*-chloroacetylaniline forms a five-membered ring exclusively (Eq. 34) [88]. Bowl-shaped polyaromatic hydrocarbons can be readily constructed by the cyclization method [89–91]. The reaction in Eq. 35 is an example [90].

It is often considered that such cyclization involves intramolecular electrophilic attack of the arylpalladium(II) moiety on another aromatic ring in the



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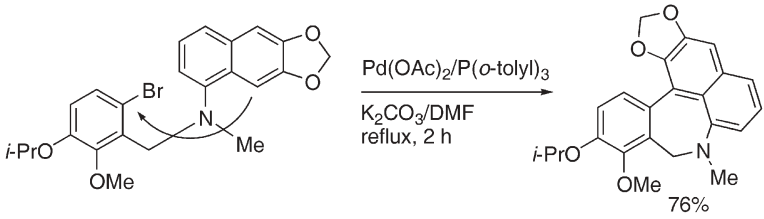
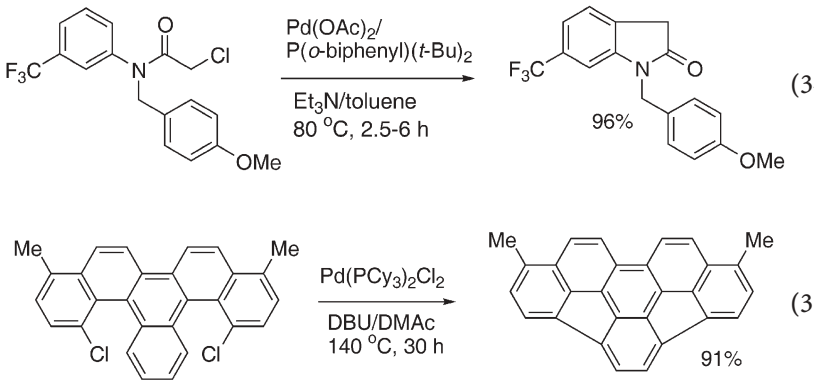
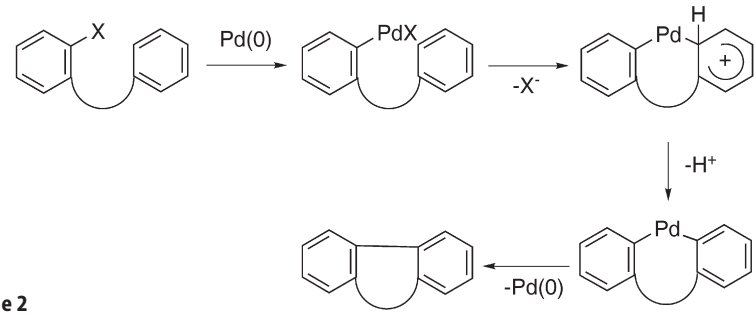


(33)



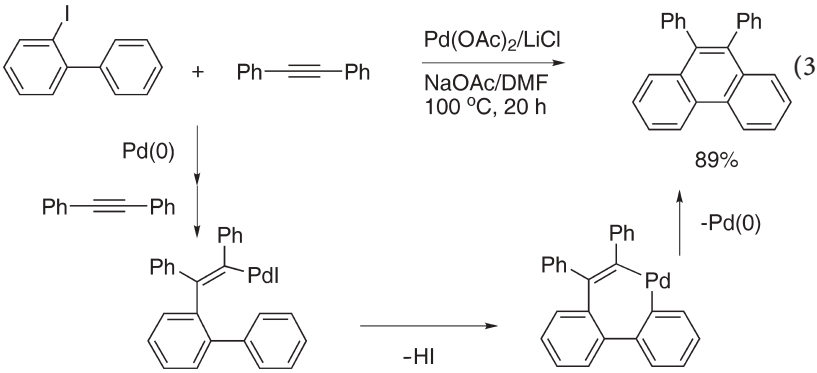
key intermediate (Scheme 2) [85, 92, 93]. However, the reaction of substrates having a strong electron-withdrawing substituent such as nitro group can occur effectively [91, 94]. Thus, another mechanism involving intramolecular aromatic C–H activation would also participate in the reaction. Other possibilities including carbopalladation have also been considered [85]. Therefore, it is likely that the mechanism is not a single route but that several pathways occur depending on the employed substrates, catalysts, and reaction conditions.



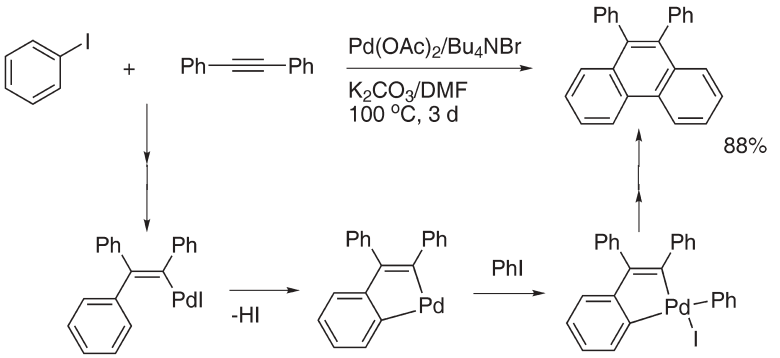
Scheme 2

The cyclization can be extended to the cross-annulation of aryl halides with unsaturated compounds [95, 96]. For example, 2-iodobiphenyl reacts with diphenylacetylene via a vinylpalladium intermediate to give a phenanthrene derivative (Eq. 36) [97, 98]. It is of particular interest that the same compound can be formed by the reaction with iodobenzene through a domino sequence (Eq. 37) [99, 100].

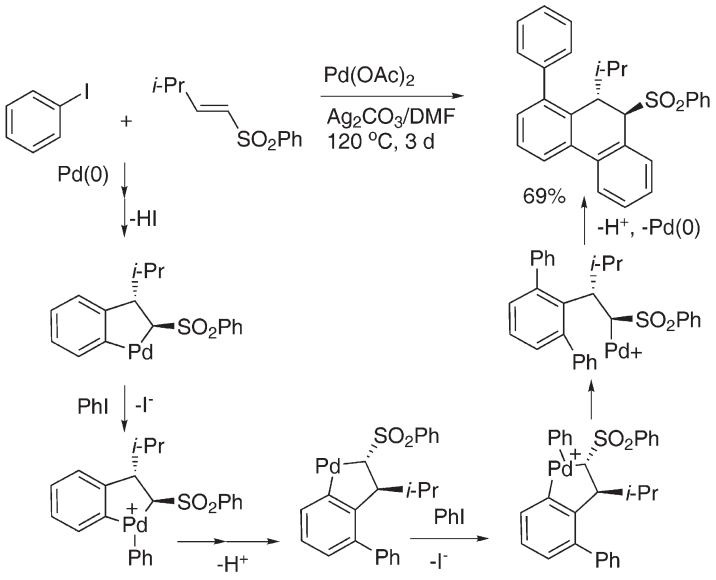
Similar sequential domino reactions occur using cyclic alkenes such as norbornene [101–105], indene [106], and dihydronaphthalene [107]. In these reactions, 3:1 coupling products can be formed. In the case of norbornene, up to 4:1 coupling is observed [104]. Notably, acyclic vinylsulfones specifically undergo 3:1 domino coupling (Eq. 38) [108].


Pd(OAc)2/LiCl
NaOAc/DMF
100 °C, 20 h
89%
Pd(0)
-HI
-Pd(0)

(36)

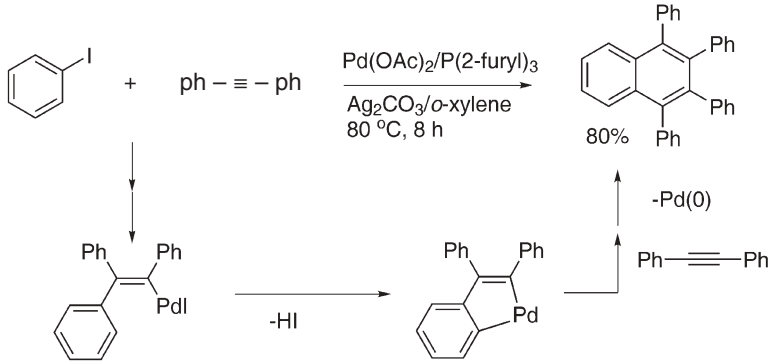

Pd(OAc)2/Bu4NBr
K2CO3/DMF
100 °C, 3 d
88%
-HI
PhI

(37)


Pd(OAc)2
Ag2CO3/DMF
120 °C, 3 d
69%
Pd(0)
-HI
PhI
-I-
-H+
-H+, -Pd(0)

(38)

It is worth mentioning that the reaction of iodobenzene with diphenylacetylene can also give 1:2 [100, 109, 110] and 1:1 [111] coupling products, i.e, naphthalene and fluorene derivatives, under somewhat different conditions (Eqs. 39 and 40) [110, 111]. The choice of bases is the key for the selective reactions.



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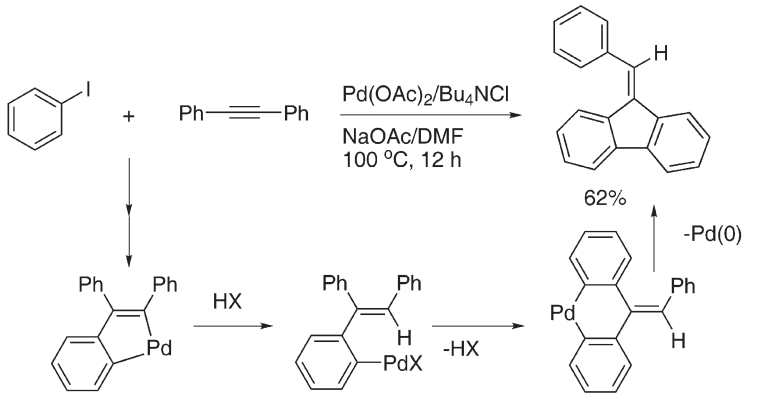
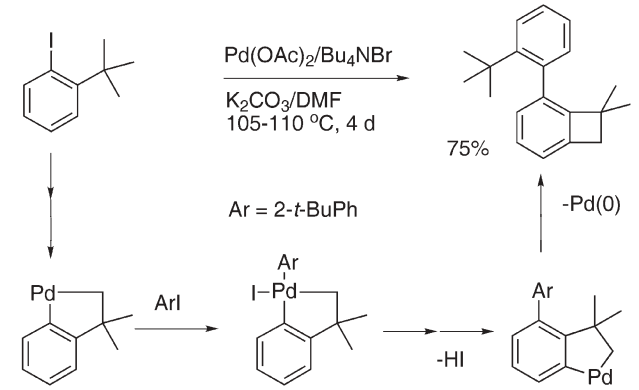


(40)

A number of di- or trimerization reactions of aryl and vinyl halides, which are mechanistically related to those in Eqs. 37 and 38 [7], have been reported. Interestingly, in the reaction of *o-tert*-butyliodobenzene, one of the aliphatic C–H bonds in the *ortho* substituent is intramolecularly activated and the successive reaction with another iodide molecule leads to a benzocyclobutene derivative (Eq. 41) [112]. A monomeric benzocyclobutene is produced selectively in the case of ethyl 2-(2-bromophenyl)-2-methylpropionate (Eq. 42) [113]. 2-(2-Bromophenyl)-2-ethylbutanoate undergoes an intramolecular redox reaction, that is, dehydrobromination–unsaturation (Eq. 43). The reaction has been proposed to proceed via C–H bond activation at one of the terminal methyl groups and β-hydrogen elimination.



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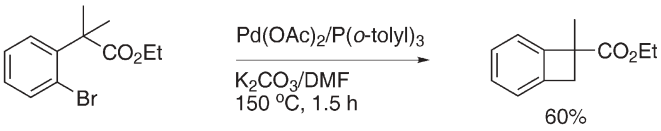

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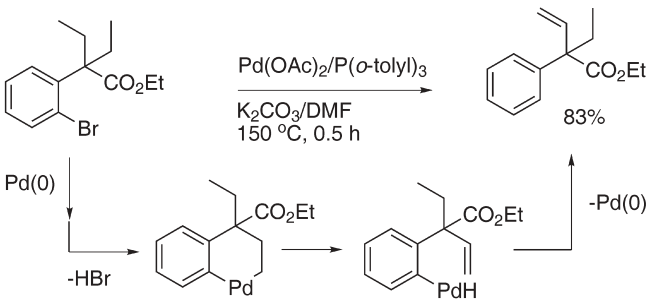
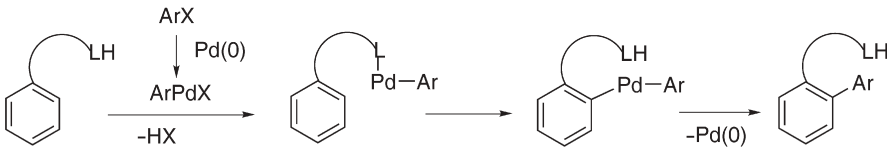


(43)

3.2 Intermolecular Reaction of Aromatic Compounds

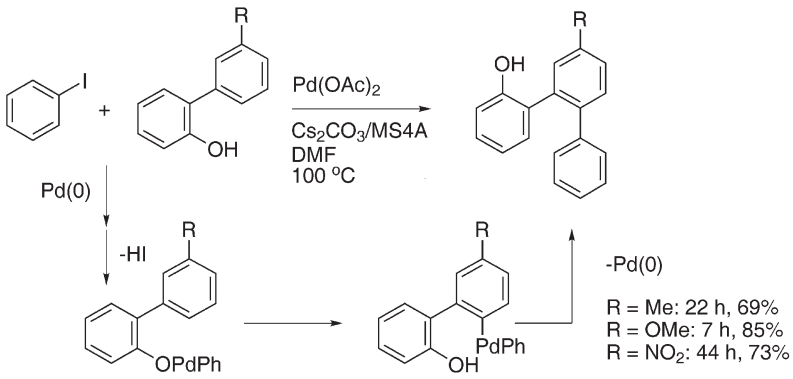
As described above, appropriately functionalized aromatic substrates such as phenols and aromatic carbonyl compounds undergo intermolecular arylation directly and regioselectively on treatment with aryl halides in the presence of palladium catalysts. As illustrated in Scheme 3, which is a proposed general



Scheme 3

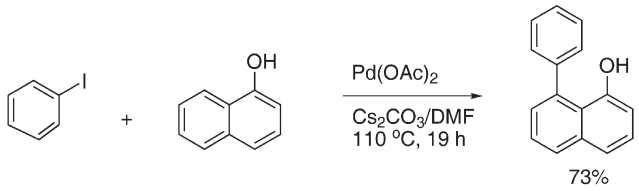
catalytic sequence, coordination of a given functional group to the metal center is the key for an effective coupling via C–H bond cleavage.

The arylation of 2-phenylphenols with aryl iodides (Eq. 44) is one of the first examples that proceeds by the sequence of Scheme 3 [35, 42]. The use of a relatively strong inorganic base such as Cs_2CO_3 is important for a smooth coupling. K_2CO_3 and Na_2CO_3 are less effective in this order.



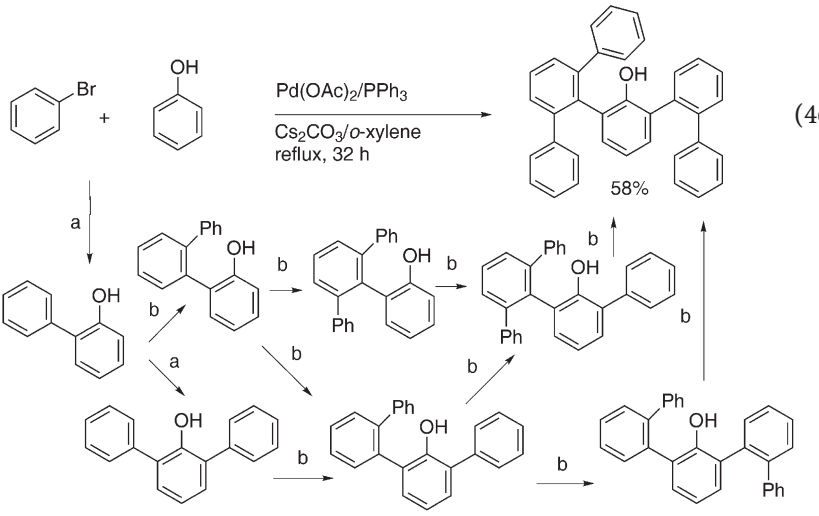
(44)

The C–H bond cleavage in the reaction may involve an electrophilic character as in the sequence of Scheme 2. The fact that the reactions of the substrates having an electron-donating substituent at the 5′ position proceed smoothly seems to be consistent with the mechanism. However, the strongly electron-withdrawing nitro group does not inhibit the reaction. Thus, the mechanism of the C–H bond cleavage is not a single pathway as in the intermolecular reaction. Anyway, the base appears to promote the reaction effectively.



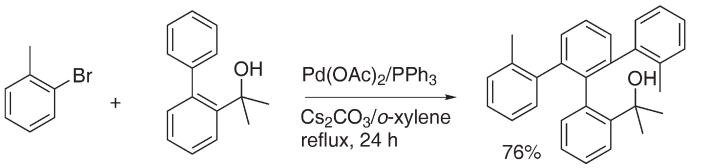
(45)

1-Naphthol is arylated at the *peri* position selectively (Eq. 45) [35, 42]. Interestingly, phenol itself and 4-substituted derivatives are multiply arylated around the oxygen up to five times in the presence of excess aryl bromides to selectively give 2-biphenyl-6-terphenylphenols (Eq. 46) [114]. The reaction is considered to involve two mechanistic patterns; i.e., the reactions of ArPd(II) intermediates with (a) phenolates at the *ortho* position, this being similar to the α-arylation of ketones, and (b) thus formed biphenyl-2-ols as in Eq. 44. While the latter proceeds in both DMF and xylene, use of the less polar solvent is essential for the former to effectively occur. A relevant coupling of phenols with



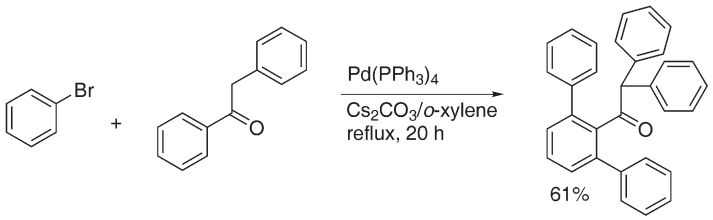
(46)

aryl halides in the presence of rhodium catalysts has been reported [115, 116]. A number of α,α-disubstituted benzyl alcohols undergo expected arylation via cleavage of the sp^2 C–H bond (Eq. 47) [117, 118]. Depending on the structure of the substrates and reaction conditions, however, another type aryl–aryl coupling predominantly takes place accompanied by cleavage of the sp^2–sp^3 C–C bond. The coupling is described in Sect. 5 of Catalytic Processes Involving β-Carbon Elimination.



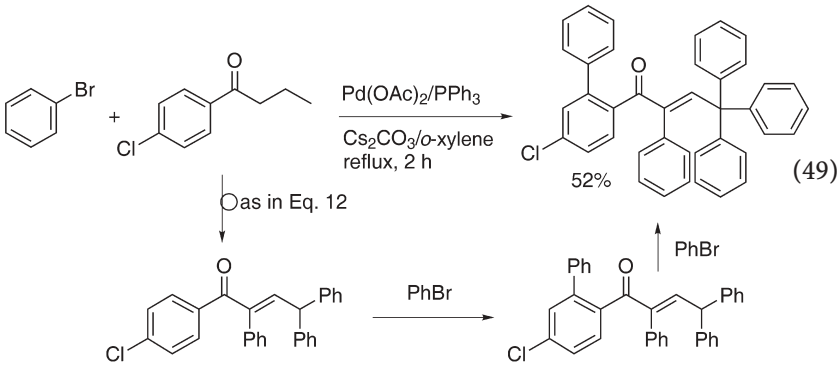
(47)

Acetophenones and benzyl phenyl ketones (Eq. 48) are arylated not only at the α position, but also at the two *ortho* positions by using excess aryl bromides [119]. The reaction proceeds via α-arylation of the ketone followed by aromatic *ortho*-arylation. The latter may occur via coordination of the enolate oxygen to an arylpalladium intermediate as in Scheme 3 and Eq. 44.

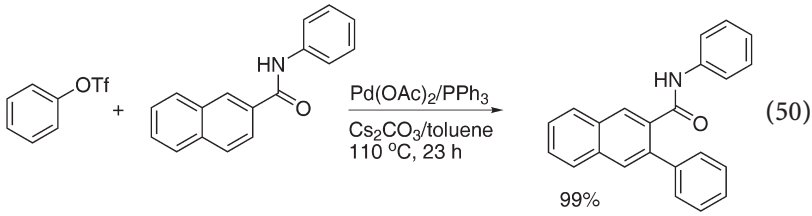


(48)

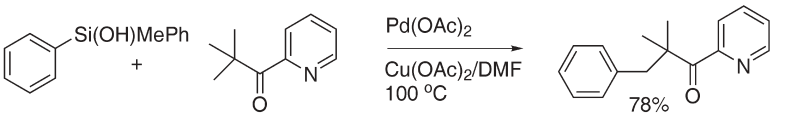
As described in Sect. 2.2, butyrophenone undergoes triarylation on the alkyl chain (Eq. 12) [43]. The ketone can also be further arylated at the *ortho* and γ positions in this order only by changing the ligands employed (Eq. 49). The bulkiness of ligands is an important factor in determining the degree of perarylation. The monoarylated product at the α position is obtained selectively with P(*t*-Bu)$_3$.



Benzanilide, which is a structural relative of benzyl phenyl ketone, is diarylated on the benzoyl moiety using aryl bromides or triflates [120]. *N*-Arylation [121] is not observed under the given conditions. *N*-(2-Naphthoyl)aniline undergoes monoarylation selectively at the 3 position (Eq. 50). This may be attributed to steric reasons.



Coordination-assisted aromatic arylation reactions using ruthenium [122–125] and rhodium [125, 126] catalysts have been reported. In the reactions, substrates having a neutral heteroatom such as pyridines and aromatic imines are usually employed and are reacted with aryl halides or arylmetal reagents. The palladium(II)-promoted arylation reaction of pyridines and imines having a *tert*-butyl group with arylsilanes is also known (Eq. 51) [127]. The reaction proceeds via initial transmetalation to form a PhPd(II) species, which is coordinated by the substrate, and then one of the aliphatic C–H bonds is activated.



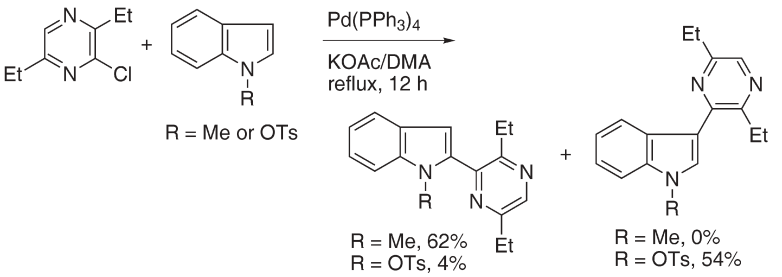
(51)

3.3 Intermolecular Reaction of Heteroaromatic Compounds

Various five-membered-ring heteroaromatic compounds involving one or two heteroatoms, even without having a functional group, are known to undergo arylation usually at their 2 and/or 5 position(s) on treatment with aryl halides under palladium catalysis. The reaction provides a useful tool for preparing aryl-substituted heterocycles, which may exhibit biological activity and have semiconducting and fluorescent properties.

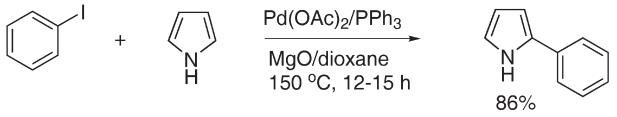
The arylation of pyrroles, furans, and thiophenes, which are generally susceptible to electrophiles, may be considered to proceed through an electrophilic mechanism involving the attack of ArPd(II) species, as judged by the usual substitution pattern [128]. However, other mechanisms seem to be capable of participating as in the above aromatic arylation.

One of the early significant examples is the coupling of 1-substituted indoles with 2-chloro-3,6-dialkylpyradines reported by Ohta and coworkers (Eq. 52) [129–131]. Depending on the 1-substituents, the reaction takes place selectively at the 2 or 3 position. The substitution at the 3 position is a rare instance, which appears to be caused by the electron-withdrawing tosyl group, while the precise mechanism is still not clear.



(52)

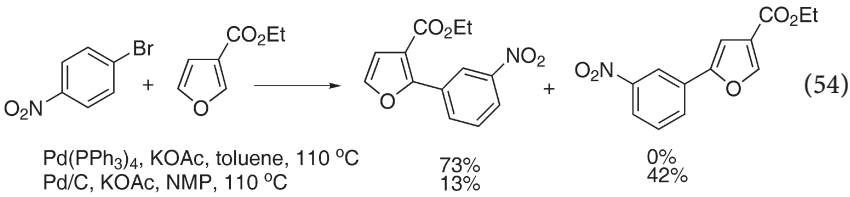
The reaction of pyrrole with iodobenzene proceeds selectively at the 2 position by using MgO as base, even without N protection (Eq. 53) [125, 132]. The



(53)

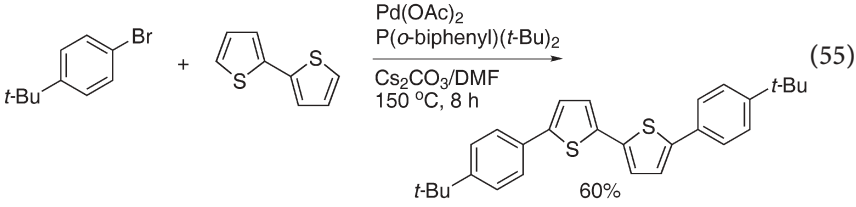
strong N–Mg interaction has been proposed to be the key for the effective coupling. As expected, N-unprotected indole is arylated selectively at the 2 position in the presence of MgO. The arylation of indolidines has also been reported [133].

The arylation of 3-ethoxycarbonylfuran and its thiophene analog occurs selectively at the 2 position in toluene, whereas the 5 position is attacked preferably in NMP (Eq. 54) [134]. It has been proposed that a Heck-type insertion mechanism and an electrophilic mechanism participate in the former and latter reactions, respectively.



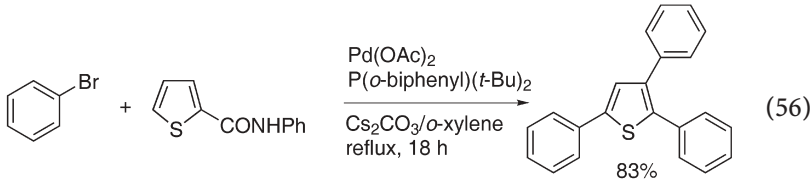
(54)

The selective monoarylation of unsubstituted thiophene and furan can be made by using an excess amount of the substrate [130]. It has been demonstrated that the use of AgF and DMSO as base and solvent, respectively, enables the reaction at 60 °C [135]. Various 2- or 3-substituted thiophenes and benzothiophenes have been subjected to the catalytic arylation [8,128, 130, 134–139]. 2,2′-Bithiophene can be arylated at the 5 and 5′ positions (Eq. 55) [137].



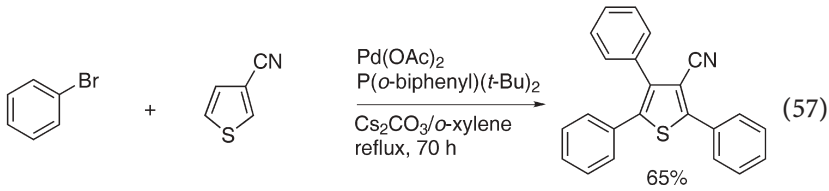
(55)

Interestingly, *N*-phenyl-2-thiophenecarboxamides undergo 2,3,5-triarylation accompanied by a formal decarbamoylation upon treatment with excess bromobenzene (Eq. 56) [136]. The reaction involves the initial coordination-assisted 3-arylation and successive decarbamoylation promoted by Pd(II) species and base in the medium. Introduction of an electron-withdrawing



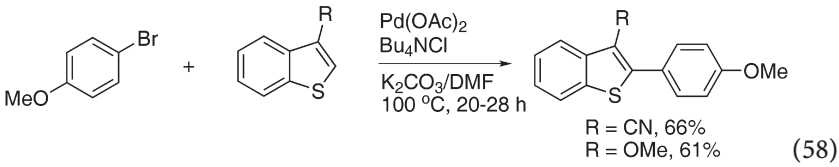
(56)

group to the 3 position of thiophene makes 4-arylation possible, while the reaction at the 2 and 5 positions occurs more readily (Eq. 57) [136]. Thus, the reaction of 3-cyanothiophene affords the corresponding 2,4,5-triarylated products. The mechanism for the 4-arylation is not definitive.



(57)

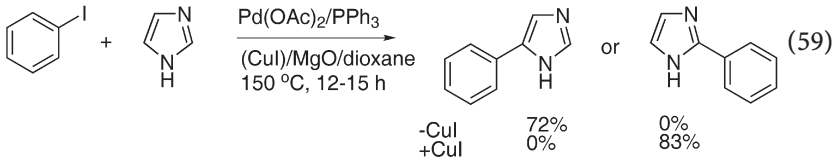
It has been proposed that the 2-arylation of 3-cyanobenzo[*b*]thiophene proceeds by the coordination of sulfur to palladium, whereas an electrophilic mechanism predominates in the reaction of 3-methoxybenzo[*b*]thiophene (Eq. 58) [139].



(58)

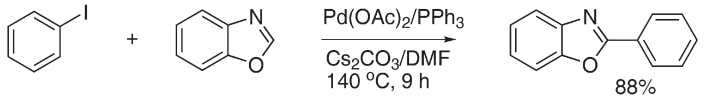
The arylation of azole compounds including imidazoles, oxazoles, and thiazoles at the electron-rich 5 position may be similar to that of pyrroles, furans, and thiophenes. On the other hand, the reaction at the 2 position is considered to proceed differently [128]. While the precise mechanism is still not clear, it may involve either base-assisted deprotonative palladation with ArPd(II) species or insertion of the C–N double bond into the Ar–Pd bond. The 5-arylation usually occurs faster than the 2-arylation. However, the reactivity order can be reversed by an additive such as a Cu(I) species [128].

4(5)-Phenyl- and 2-phenyl-1*H*-imidazoles can be obtained selectively by the reaction of 1*H*-imidazole itself with iodobenzene in the absence and presence of CuI, respectively (Eq. 59) [127, 132]. MgO is a suitable base for this reaction as in that of Eq. 53. The reaction of 1*H*-benzimidazole with iodobenzene also occurs at the 2 position. The same reaction can be carried out by using a rhodium catalyst [140]. The arylation of imidazo[1,2-*a*]pyrimidine has been reported [141].



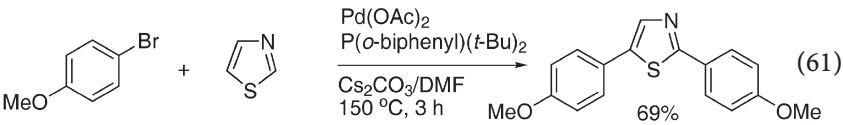
(59)

While the examples for the arylation of oxazole itself are limited, the reaction with 2-chloro-3,6-dialkylpyradines at the 5 position is known [131]. 2-Phenyloxazole and benzoxazole (Eq. 60) are good substrates for the direct arylation [128].

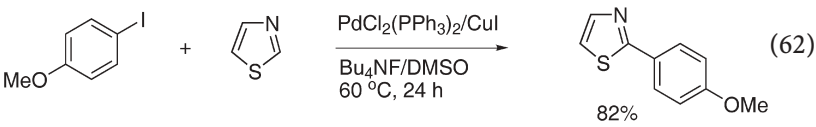


(60)

The 2,5-diarylation of thiazole can be carried out effectively with a bulky phosphine ligand. In this case, no monoarylated product is observed even in the early stage of the reaction, suggesting that the second arylation proceeds relatively fast (Eq. 61) [142]. The selective 2-arylation is accomplished by using CuI and Bu_4NF as cocatalyst and base, respectively (Eq. 62) [143]. By using a catalyst system of $Co(OAc)_2$-IMes (IMes=1,3-bis-mesitylimidazolyl carbene), the 5 position is arylated selectively [144]. The Pd-catalyzed arylation of thiazole and 1-methylpyrrole with a polymer-linked aryl iodide has been reported [145].



(61)

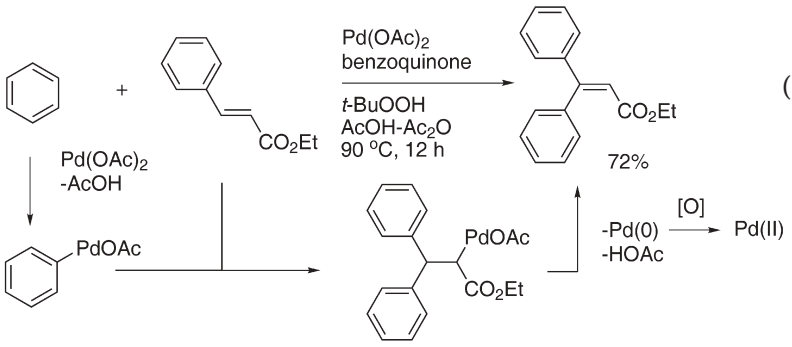


(62)

4
Direct Arylation of Unsaturated Compounds with Arenes

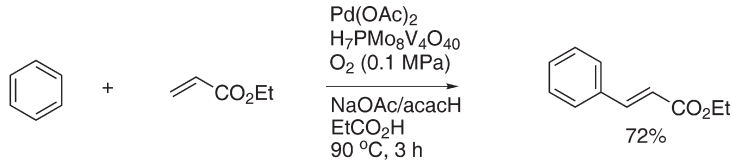
Aromatic compounds can react with Pd(II) species, typically $Pd(OAc)_2$, via cleavage of their C–H bonds to give arylpalladium(II) species (Scheme 1, mechanism D). Therefore, the arylation of alkenes can be performed directly using arenes and aromatic heterocycles [10, 11]. In this arylation, halogenation of arenes can be omitted, but an oxidizing reagent for the reoxidation of Pd(0) to Pd(II) should be added to make the reaction catalytic.

Thus, much effort has been made to find effective reoxidizing systems. The use of *tert*-BuOOH together with a catalytic amount of benzoquinone has been reported to be significantly effective (Eq. 63) [146]. Molecular oxygen is a more desirable oxidant. It has been found that the reaction of arenes with a number of alkenes proceeds efficiently in the presence of a catalytic amount of a hetero-

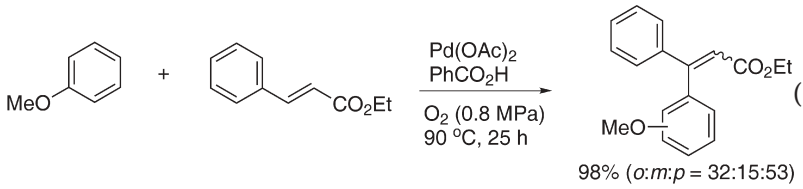


(63)

poly acid under a normal pressure of oxygen (Eq. 64) [147, 148]. Heteropoly acids work as mediators of the reoxidation. Under a pressurized oxygen atmosphere, the coupling proceeds without addition of any other metal species. Notably, benzoic acid and $Mn(OAc)_3$ work as good promoters for the reaction, while the role is not definitive (Eq. 65) [149].



(64)

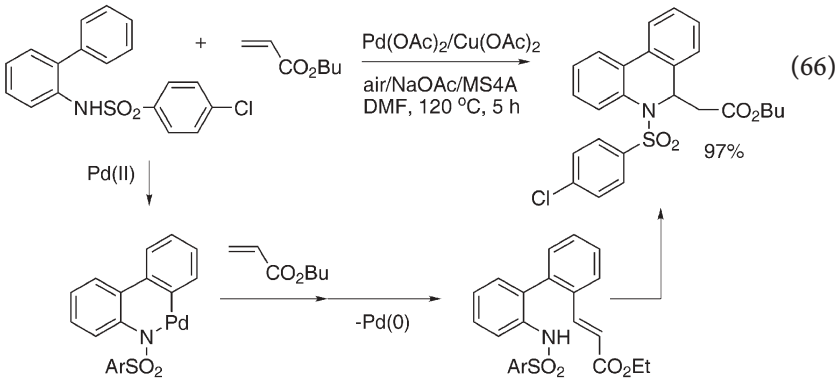


(65)

It is well known that aromatic compounds having an appropriate functional group readily ungergo palladation with Pd(II) species on their *ortho* position to form intramolecularly chelated arylpalladium complexes [1]. They can also react with various reagents including alkenes and alkynes. However, no effective catalytic version has been reported until recently. One of the possible reasons for this is due to the fact that the functional groups which give stable chelating complexes are susceptible toward oxidizing reagents.

It has been found that some functional groups having acidic hydrogen, including phenolic hydroxyl, carboxyl, and sulfonylamino groups, are suitable substituents to realize the direct catalytic arylation of alkenes [150, 151]. The reaction of 2-sulfonylaminobiphenyls is an example. The reaction with acrylate esters proceeds efficiently in the presence of $Cu(OAc)_2$–air as reoxidizing system, giving the corresponding products via regioselective vinylation followed

by nucleophilic cyclization (Eq. 66) [151]. *N*-Acetylanilines also undergo catalytic *ortho*-vinylation using benzoquinone as oxidant (Eq. 67) [152]. In this case, ionization of the functional group is not involved.



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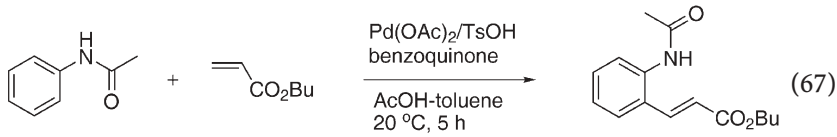
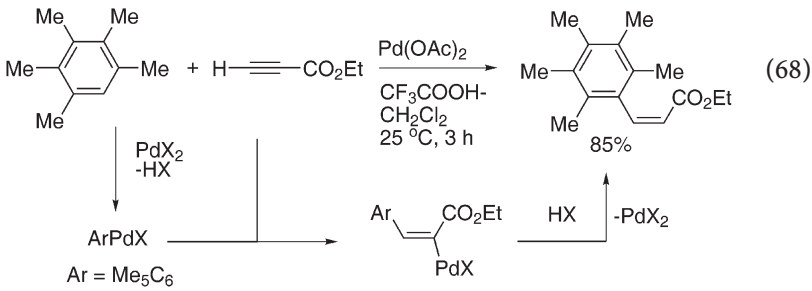


(67)

It should be noted that related coupling reactions have been developed for aromatic compounds having carbonyl- and nitrogen-containing functional groups with unsaturated compounds, especially by using ruthenium and rhodium catalysts, which involve precoordination of the neutral functional groups followed by *ortho*-C–H activation [7, 9, 153, 154].

Arenes, especially electron-rich ones, and five-membered-ring heteroaromatic compounds have been found to react with alkynes in the presence of Pd(II) or Pt(II) species in acidic solvents to give the corresponding hydroarylation products (Eqs. 68 and 69) [155–158]. The mechanism proposed for the reaction involves aromatic palladation to form ArPd(II) species, as in the Fujiwara–Moritani reaction [10], insertion of an alkyne, and protonolysis of the



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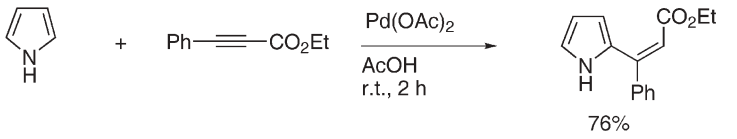
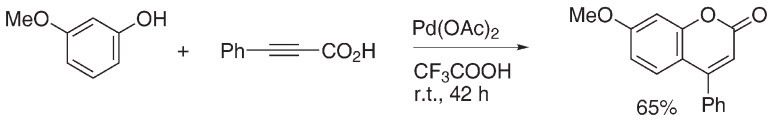


(69)

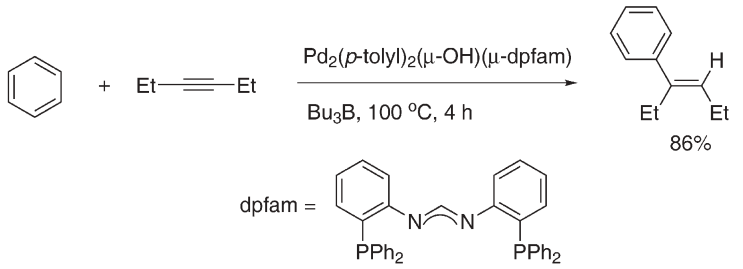
resulting vinylpalladium intermediate to give the product with the regeneration of catalytically active Pd(II) species.

The reaction of phenols having electron-donating groups with propiolic acids gives coumarin derivatives under similar conditions to those for Eq. 68 (Eq. 70) [159]. The same reaction has been found to occur using a Pd(0) species such as $Pd_2(dba)_3$ in formic acid [160]. In this case, different types of palladation mechanism by hydridopalladium species have been proposed.



(70)

Another interesting hydroarylation reaction of alkynes with arenes using a dinuclear palladium complex as catalyst has been reported (Eq. 71) [161], although the precise mechanism is unclear. Trialkylboranes act as effective promoters for this reaction.



(71)

5 Conclusion

The methods of direct arylation reactions via cleavage of activated and unactivated C–H bonds have developed significantly in recent years. Thus, various carbon nucleophiles can be directly and effectively arylated with aryl halides at their α position, irrespective of the fact that the acidities of these substrates are diverse [162]. Various aromatic and heteroaromatic compounds are also arylated directly with the halides. By using these reactions, rather complex molecules including polycyclic and polyaryl compounds can be prepared, which are of interest in pharmaceutical and material syntheses. Substantial progress has also been achieved in the arylation of unsaturated compounds with arenes

themselves. These direct methods, not requiring stoichiometric metalation or halogenation, are apparently useful and economical. Thus, much effort will be made continuously to improve catalytic efficiency and to develop new types of direct coupling.

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Palladium-Catalyzed Cross-Coupling Reactions of Unactivated Alkyl Electrophiles with Organometallic Compounds

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Abstract For many years, unactivated alkyl electrophiles that contain β hydrogens were generally regarded as unsuitable partners for palladium-catalyzed cross-coupling reactions. Recently, however, a series of studies have established that palladium complexes can in fact couple a range of alkyl electrophiles with a variety of organometallic reagents.

Keywords Cross-coupling · Homogeneous catalysis · Palladium · Alkyl halides

Abbreviations and Symbols

9-BBN	9-Borabicyclo[3.3.1.]nonane
Cy	Cyclohexyl
Cyp	Cyclopentyl
dba	*trans*, *trans*-Dibenzylidene acetone
DFT	Density functional theory
IMes·HCl	1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride
IPr·HCl	1,3-Bis(2,6-diisopropylphenyl)imidazolium chloride
MTBE	Methyl *t*-butyl ether
NHC	*N*-heterocyclic carbene
NMI	*N*-methylimidazole
NMP	*N*-methylpyrrolidinone

1 Introduction and Background

Transition metal-catalyzed cross-coupling reactions have matured into powerful, selective, and high-yielding techniques for the synthesis of organic compounds [1]. With respect to C–C bond-forming processes, which predominantly employ palladium and nickel catalysts, versatile methods have been described for couplings of aryl and alkenyl [i.e., C(sp^2)], as well as activated alkyl (e.g., allyl, benzyl, and α-halocarbonyl), electrophiles. In contrast, there have been relatively few reports of cross-couplings of unactivated alkyl halides/sulfonates, particularly those that contain β hydrogens [2]. Two of the reasons often cited for the lack of success with the latter family of electrophiles are: (1) palladium and nickel complexes are slow to oxidatively add alkyl halides/sulfonates; and (2) if oxidative addition does occur, the alkylmetal intermediate undergoes rapid intramolecular β-hydride elimination, rather than the desired intermolecular transmetalation (Fig. 1).

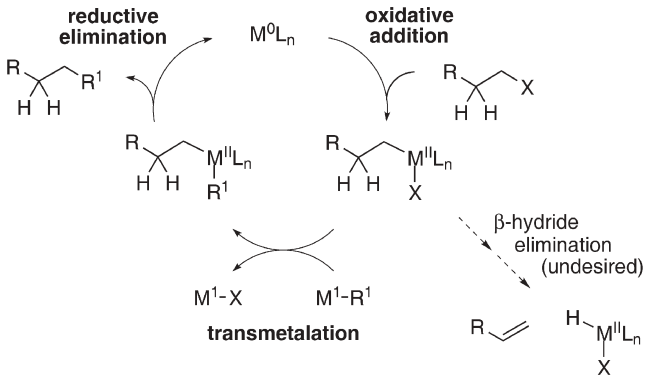
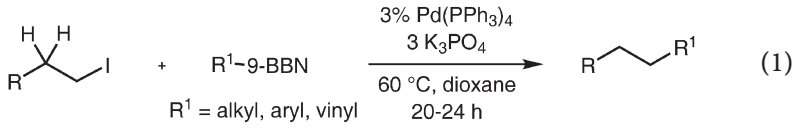


Fig. 1 Cross-coupling reaction of unactivated alkyl electrophiles showing intramolecular β-hydride elimination (undesired) and intermolecular transmetalation (desired).

Due to concern about these issues, in combination with early interest and success in coupling aryl and vinyl electrophiles, progress toward the development of palladium- or nickel-based methods for cross-coupling alkyl halides/sulfonates has been relatively slow. However, during the past decade (particularly the last few years), important advances have been described that clearly demonstrate that the aforementioned obstacles can be overcome and that the development of general catalysts for coupling alkyl electrophiles is a realistic objective.

In 1992, Suzuki provided the pioneering discovery in this area, a $Pd(PPh_3)_4$-catalyzed cross-coupling of an array of unfunctionalized and functionalized primary alkyl iodides with alkyl-, aryl-, and vinyl-9-BBN reagents (Eq. 1) [3]. Since this report, others have described a variety of nickel- [4–8] and palladium-catalyzed methods for coupling unactivated alkyl electrophiles with organometallic compounds [9–11]. In this chapter, we review the progress that has been achieved with palladium-based catalysts, highlighting the expansion of the scope of these processes from Suzuki reactions to cross-couplings that involve zinc-, zirconium-, tin-, silicon-, magnesium-, lithium-, and copper-based organometallic reagents.



(1)

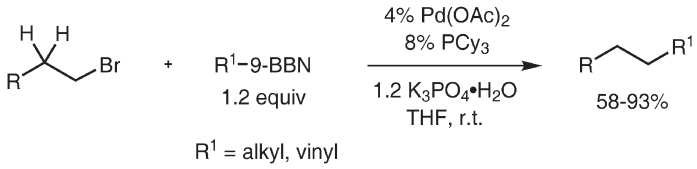
2
Suzuki Cross-Couplings

Nearly a decade elapsed between Suzuki's discovery of the $Pd(PPh_3)_4$-catalyzed cross-coupling of alkyl iodides with organoboranes (1992) and the next report of a palladium-based method for coupling an unactivated, β-hydrogen-containing alkyl electrophile (2001). However, since 2001, the rate of progress in this area has increased considerably, particularly with regard to the Suzuki reaction. As a consequence, it is now possible to cross-couple a range of primary alkyl halides and tosylates with an array of organoboranes. Thus far, two ligand classes have proved to be effective: trialkylphosphines and *N*-heterocyclic carbenes.

2.1
Phosphine Ligands

2.1.1
Couplings with 9-BBN Derivatives

In 2001, Fu reported the first examples of palladium-catalyzed Suzuki reactions of unactivated alkyl bromides (Eq. 2) [12]. This study arose from earlier investigations by Fu that had demonstrated the utility of bulky, electron-rich phos-



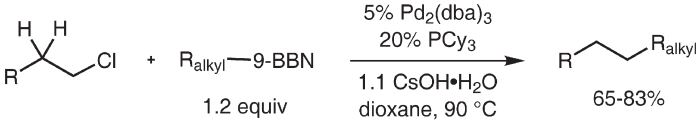
(2)

phines (e.g., P(*t*-Bu)$_3$ and PCy$_3$) in palladium-catalyzed couplings of aryl chlorides [13], substrates which, like alkyl electrophiles, were thought to be poor partners in cross-couplings due in part to their reluctance to undergo oxidative addition [14].

During the development of the catalyst system illustrated in Eq. 2, a diverse set of ligands and palladium sources was surveyed. Among the ligands that were examined, only PCy$_3$ and P(i-Pr)$_3$ furnished a substantial quantity of the desired alkyl–alkyl cross-coupling product; others (e.g., P(*t*-Bu)$_3$, P(*n*-Bu)$_3$, arsines, arylphosphines, bisphosphines, and phosphites) afforded <10% of the target compound, along with varying amounts of the olefin derived from β elimination. With respect to the organoborane coupling partner, only 9-BBN derivatives were reported to be effective participants under the described conditions (Eq. 2). Several examples of Pd/PCy$_3$-catalyzed, room-temperature Suzuki reactions of unactivated primary alkyl bromides are provided in Table 1 (entries 1–4), establishing the compatibility of the coupling with amines (entry 1), alkynes (entry 2), esters (entries 2 and 3), cyanides (entry 3), and alkyl chlorides (entry 4).

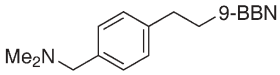
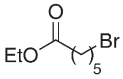
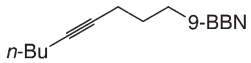
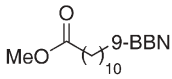
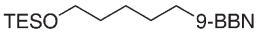
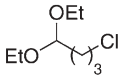
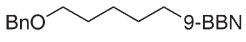
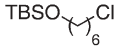
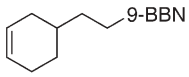
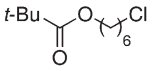
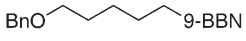
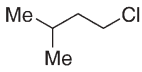
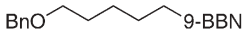
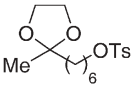
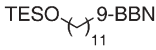
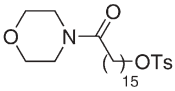
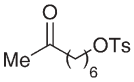
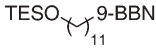
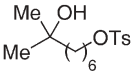
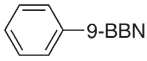
The presence of a small amount of water enhances the efficiency of these Suzuki reactions of alkyl bromides. Thus, if anhydrous K_3PO_4 rather than $K_3PO_4 \cdot H_2O$ is used, the cross-coupling proceeds much more slowly. ^{11}B NMR studies revealed that, in the presence of water, a hydroxy-bound boron "ate" complex is formed, which was suggested might be the species that participates in the transmetalation step of the catalytic cycle.

The development of methods for cross-coupling alkyl chlorides, which are less reactive electrophiles than the corresponding bromides or iodides, represents a significant challenge. This decreased reactivity provides both advantages (e.g., longer shelf life of the electrophile and lower toxicity) and disadvantages (e.g., slower oxidative addition). Fu has shown that Pd/PCy$_3$ can catalyze Suzuki reactions of primary, β-hydrogen-containing alkyl chlorides (Eq. 3) [15]. Under the conditions employed for cross-couplings of alkyl bromides (Eq. 2), very little of the desired product was obtained (<5% yield). However, by optimizing the reaction parameters, efficient carbon–carbon bond formation was achieved (Table 1, entries 5–8). Not surprisingly, a higher temperature is required for



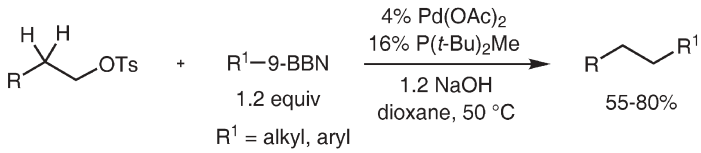
(3)

Table 1 Electrophiles and organoboron reagents for Suzuki reactions of alkyl bromides, alkyl chlorides, and alkyl tosylates

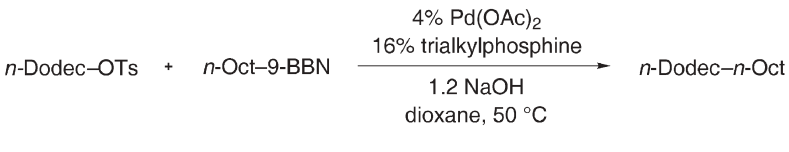
Entry	Alkyl electrophile	R–9-BBN	Yield (%)	Equation
1	*n*-Dodec-Br		78	2
2			58	2
3			81	2
4			81	2
5			70	3
6			72	3
7			65	3
8			74	3
9			67	4
10		*n*-Oct–9-BBN	76	4
11			55	4
12			63	4

cross-couplings of alkyl chlorides than for bromides (90 °C vs room temperature).

Unfortunately, attempts to extend the use of Pd/PCy_3 to Suzuki reactions of alkyl tosylates were unsuccessful. However, by modifying the conditions, it was possible to develop a catalyst system that is effective for cross-couplings of a range of primary tosylates (Eq. 4) [16]. Scheme 1 illustrates the remarkable sensitivity of the coupling reaction to the structure of the trialkylphosphine



(4)



for PCy_3: 46% yield

	R = *i*-Pr	Et	Me
PCy_2R	44%	70%	48%
$P(t\text{-Bu})_2R$	<2%	<2%	**78%**

Scheme 1 Suzuki reactions of alkyl tosylates catalyzed by Pd/trialkylphosphines

(e.g., $P(t\text{-Bu})_2Et$: <2% yield; $P(t\text{-Bu})_2Me$: 78% yield). Among the ligands that were examined, $P(t\text{-Bu})_2Me$ provided the highest yield. A rationale for some of the reactivity data in Scheme 1 is discussed in Sect. 8.2.

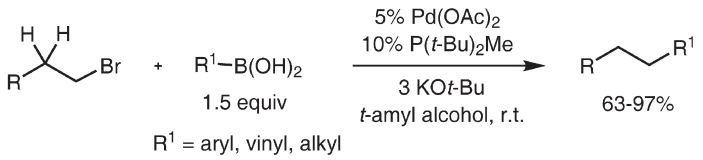
Several examples of $Pd/P(t\text{-Bu})_2Me$-catalyzed Suzuki couplings of primary, β-hydrogen-containing alkyl tosylates are illustrated in Table 1 (entries 9–12). Functional groups such as acetals (entry 9), amides (entry 10), ketones (entry 11), and tertiary alcohols (entry 12) are tolerated. Furthermore, both alkyl- and aryl-9-BBN compounds are suitable coupling partners. These Suzuki reactions of alkyl tosylates proceed in comparable yield at room temperature, albeit much more slowly.

A significant limitation to all three of these Pd/trialkylphosphine-based methods is their sensitivity to steric effects. To date, good yields have only been obtained for couplings in which neither the electrophile nor the organoborane is branched in the α or the β position.

2.1.2 Couplings with Boronic Acids

The attractiveness of organo-9-BBN derivatives as coupling partners is largely due to their accessibility via the hydroboration of alkenes and alkynes; on the other hand, they suffer from the drawbacks of not being easily manipulated in air or commercially available. In contrast, boronic acids are air-stable, and a large number and variety are commercially available. Consequently, the development of methods for cross-coupling alkyl electrophiles with boronic acids is undoubtedly an important objective.

In 2002, Fu described a Pd/P(*t*-Bu)$_2$Me-based catalyst that can achieve room-temperature cross-couplings of primary alkyl bromides with aryl-, vinyl-, and alkylboronic acids (Eq. 5) [17]. KO*t*-Bu was the best activator among those that were examined, and a protic solvent (*t*-amyl alcohol) was found to be optimal.

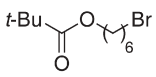
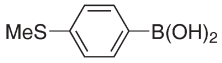
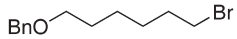
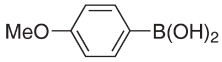
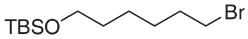
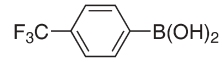
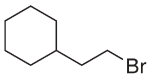
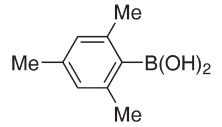
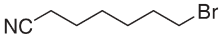
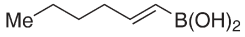
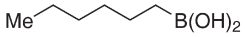


(5)

An electronically and sterically diverse array of arylboronic acids serve as useful reaction partners (Table 2, entries 1–4). In addition, vinylboronic acids can be cross-coupled in good yield (entry 5), although reactions of alkylboronic acids proceed with somewhat lower efficiency (entry 6). The catalyst tolerates a range of functional groups, including esters, thioethers, and cyanides.

It was demonstrated that [HP(*t*-Bu)$_2$Me]BF$_4$, an air-stable and commercially available phosphonium salt, can be used interchangeably with air-sensitive P(*t*-Bu)$_2$Me (Table 2). Under the reaction conditions, the phosphonium salt is

Table 2 Alkyl bromides and aryl-, vinyl-, and alkylboronic acids used in Suzuki cross-coupling reactions

Entry	Alkyl bromide	R^1-B(OH)$_2$	Yield (%)[a]
1			68 (66)
2			85 (84)
3			63 (67)
4			89 (91)
5			85 (87)
6	*n*-Dodec–Br		66 (62)

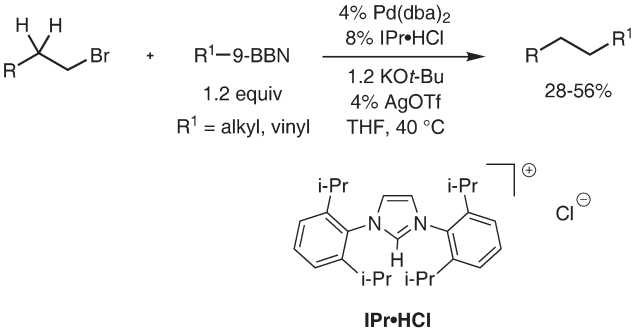
[a] The yield when P(*t*-Bu)$_2$Me is used [Eq. (5)] is shown without parantheses. The yield when [HP(*t*-Bu)$_2$Me]BF$_4$, rather than P(*t*-Bu)$_2$Me, is used is shown in parantheses.

deprotonated by KO*t*-Bu to liberate the phosphine, which binds to palladium to generate the active catalyst [18].

2.2 *N*-Heterocyclic Carbene Ligands

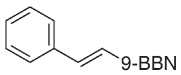
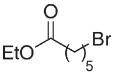
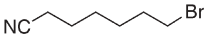
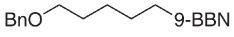
The Suzuki cross-coupling methods described in Sect. 2.1 establish that palladium complexes that bear electron-rich trialkylphosphines of the appropriate size can serve as effective catalysts for reactions of alkyl electrophiles. Naturally, it was of interest to determine if non-phosphine ligands that are bulky and electron-rich can also furnish active catalysts.

N-Heterocyclic carbenes (NHC) are examples of ligands that possess the desired attributes [19]. In 2004, Caddick and Cloke reported that a Pd/NHC-based catalyst cross-couples primary alkyl bromides with alkyl- and vinyl-9-BBN reagents (Eq. 6) [20]. A system composed of $Pd(dba)_2$/IPr·HCl/AgOTf (IPr·HCl=1,3-bis(2,6-diisopropylphenyl)imidazolium chloride) in the presence of KO*t*-Bu provides the most efficient catalyst. The yields of the cross-coupling products are modest (Table 3).



(6)

Table 3 Suzuki cross-coupling of primary alkyl bromides with alkyl- and vinyl-9-BBN reagents

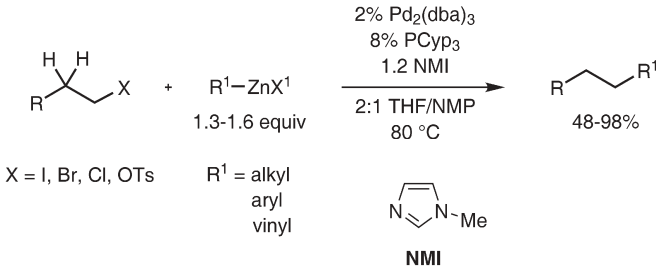
Entry	Alkyl bromide	R^1–9-BBN	Yield (%)
1	*n*-Dodec–Br		37
2		*n*-Hex-9-BBN	53
3		*n*-Hex-9-BBN	52
4	*n*-Dodec–Br		28

3
Negishi Cross-Couplings

3.1
Couplings with Organozinc Reagents

Organozinc halides are very attractive cross-coupling partners, since they are widely available from commercial sources and easily prepared from the corresponding organic halides [21]. Furthermore, they are compatible with a wide range of functional groups.

In 2003, Fu described the first palladium-catalyzed Negishi reactions of unactivated alkyl electrophiles, specifically, cross-couplings of primary iodides, bromides, chlorides, and tosylates with alkyl-, aryl-, and vinylzinc halides (Eq. 7) [22, 23]. The versatility of this method is unique; it is the only catalyst that can efficiently couple four families of alkyl electrophiles under a single set of reaction conditions. Several trialkylphosphines furnished similar yields in a representative Negishi cross-coupling (e.g., $P(t\text{-}Bu)_2Me$: 55%; $P(i\text{-}Pr)_3$: 59%; PCy_3: 65%; $PCyp_3$: 70%) (Cyp=cyclopentyl), with $PCyp_3$ emerging as the most effective ligand. In the absence of *N*-methylimidazole (NMI), the yield decreased by about 15%.

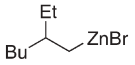
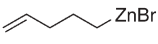
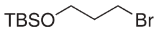
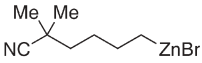
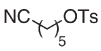
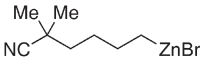
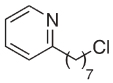
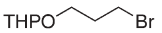
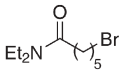
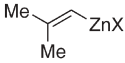
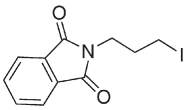
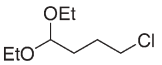
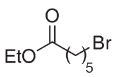
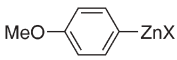


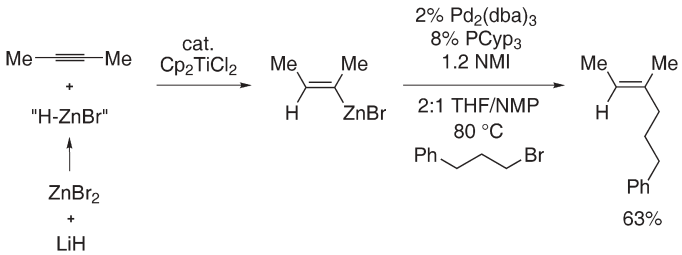
(7)

Examples of Negishi cross-couplings by this catalyst system are provided in Table 4. The method tolerates cyanides (entries 3 and 4), pyridines (entry 5), amides (entry 7), imides (entry 8), and esters (entry 10). Furthermore, hindered alkenylzincs (geminally or *cis*-substituted; entries 6–9) are suitable reaction partners. However, the effectiveness of the catalyst is compromised if the electrophile is hindered (e.g., branching in the α or β positions).

This method can be exploited as part of a one-pot "hydroalkylation" of an internal alkyne. Thus, titanium-catalyzed *syn* hydrozincation [24], followed by Negishi cross-coupling with an alkyl halide, stereospecifically generates a trisubstituted olefin (Eq. 8).

Table 4 Negishi cross-coupling reactions of alkyl electrophiles and organozinc halides

Entry	Alkyl electrophile	R^1–ZnX^1	Yield (%)
1	*n*-Dec-Br		89
2	*n*-Dec-Br		52
3			67
4			64
5		*n*-Bu-ZnBr	77
6			76
7			81
8			74
9			73
10			74

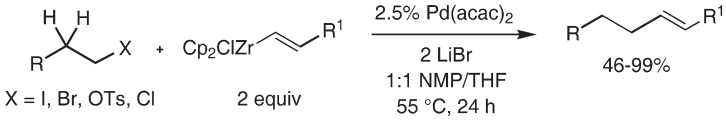


(8)

3.2 Couplings with Organozirconium Reagents

The hydrozirconation of alkynes with Cp_2ZrHCl (Schwartz's reagent) provides ready access to vinylzirconium reagents, which have been shown to be suitable partners in palladium-catalyzed cross-couplings ("zirconium-Negishi reaction") with aryl and vinyl electrophiles [1]. Recently, Fu disclosed the first

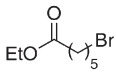
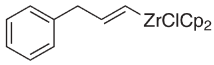
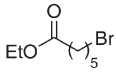
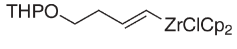
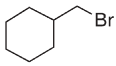
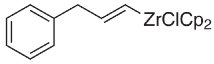
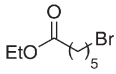
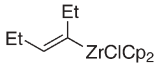
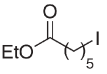
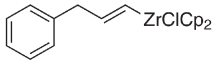
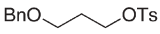
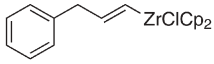
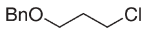
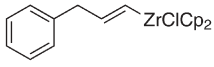
zirconium-Negishi reactions of unactivated alkyl electrophiles (Eq. 9) [25]. In contrast to all other palladium-catalyzed couplings of alkyl halides/sulfonates, the desired process can be achieved *in the absence of an added ligand*. Such "ligandless"[26] reactions are attractive from the standpoints of cost, simplicity, and ease of purification.



(9)

As illustrated in Table 5, the catalyst system can be applied to zirconium-Negishi reactions of primary alkyl bromides, iodides, and tosylates (entries 1–6); cross-couplings of chlorides can also be achieved, albeit in modest yield (entry 7). The coupling of a somewhat hindered β-branched alkyl bromide is noteworthy (entry 3), since the presence of β branching on the electrophile precludes efficient palladium-catalyzed cross-coupling with most other families of nucleophiles (e.g., organoboron and organozinc reagents). Zirconium-Negishi reactions of unactivated alkyl electrophiles also proceed well under microwave conditions; for example, when the reactants in entry 1 are irradiated (30-W microwave, 100 °C, 15 min), the cross-coupling product is generated in 94% yield.

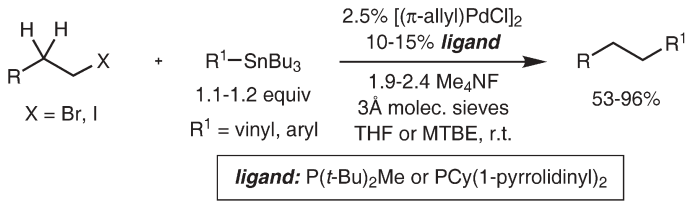
Table 5 Zirconium-Negishi reactions of primary alkyl bromides, iodides, tosylates, and chlorides

Entry	Alkyl electrophile	Zirconium reagent	Yield (%)
1			99
2			72
3			60[a]
4			85
5			82
6			83
7			46

[a] 5% $Pd(acac)_2$ was used. Reaction time: 48 h.

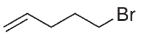
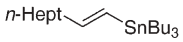
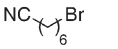
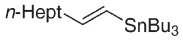
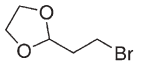
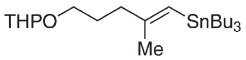
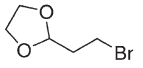
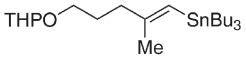
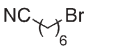
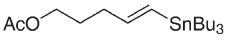
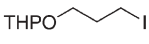
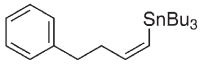
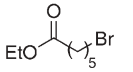
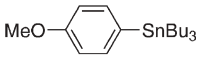
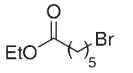
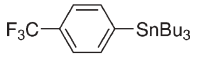
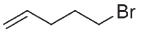
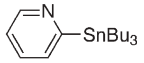
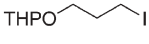
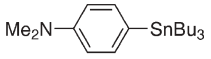
4
Stille Cross-Couplings

Two reports have described palladium-catalyzed Stille cross-couplings of unactivated alkyl electrophiles. Specifically, these investigations by Fu demonstrate that primary alkyl bromides and iodides can be coupled with vinylstannanes [27, 28] and arylstannanes [28] (Eq. 10).



(10)

Table 6 Stille couplings of alkyl bromides and iodides with vinyl- and arylstannanes

Entry	Alkyl halide	Stannane	Conditions[a]	Yield (%)
1			A	96
2			A	59
3			A	55
4			B	54
5			B	68
6			B	90
7			C	71
8			C	57
9			C	53
10			C	76

[a] Reaction conditions as described in Eq. (9). A: 15% P(*t*-Bu)$_2$Me, 1.9 equiv Me_4NF, THF; B: 15% PCy(1-pyrrolidinyl)$_2$, 1.9 equiv Me_4NF, THF; C: 10% PCy(1-pyrrolidinyl)$_2$, 2.4 equiv Me_4NF, MTBE.

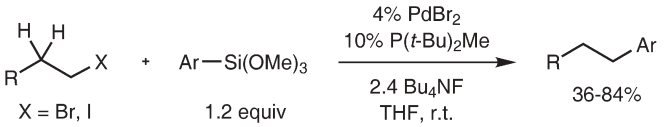
In the initial study, which focused on palladium-catalyzed cross-couplings of primary alkyl bromides with vinylstannanes, use of P(*t*-Bu)$_2$Me provided the best yields (solvent=THF) [27]. PCy$_3$ was slightly less effective, whereas a variety of other ligands, including *N*-heterocyclic carbenes, were essentially ineffective. The choice of activator (Me$_4$NF) and the presence of molecular sieves were important for the success of these reactions. Some examples of Pd/P(*t*-Bu)$_2$Me-catalyzed Stille couplings of alkyl bromides with vinylstannanes are provided in entries 1–3 of Table 6.

Unfortunately, this Pd/P(*t*-Bu)$_2$Me-based catalyst was not effective at cross-coupling alkyl halides with *aryl*stannanes. This limitation was subsequently addressed with a second-generation catalyst [28]. Motivated by studies by Woolins on the electron-donating ability of alkyldiaminophosphines [29], a family of such ligands was surveyed. As for Suzuki reactions of alkyl tosylates catalyzed by Pd/trialkylphosphines (Scheme 1), it was found that a change in the structure of just one of the groups on phosphorus can have a significant impact on reactivity. Thus, in a test Stille cross-coupling of an alkyl bromide with an arylstannane, as the R substituent of PR(1-pyrrolidinyl)$_2$ increased in size (Me→Et→Cy→*t*-Bu), the efficiency of the reaction first improved and then deteriorated, with the Cy-substituted ligand furnishing the highest yield.

Pd/PCy(pyrrolidinyl)$_2$ proved to be effective for room-temperature cross-couplings of an array of primary alkyl bromides and iodides with both vinyl- and arylstannanes (Table 6, entries 4–10). These examples establish that the desired carbon–carbon bond formation proceeds in the presence of functional groups such as cyanides (entry 5), esters (entries 5, 7, and 8), and pyridines (entry 9).

5
Hiyama Cross-Couplings

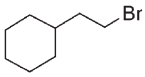
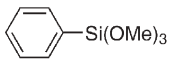
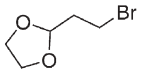
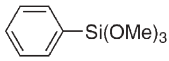
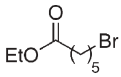
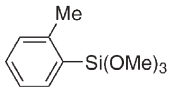
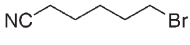
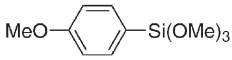
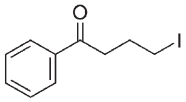
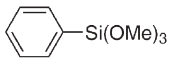
Fluoride is a common activating agent for C(sp^2)–C(sp^2) Hiyama couplings, presumably generating a hypervalent silicate intermediate that is more reactive toward transmetalation with palladium than the tetravalent organosilane precursor [1]. Unfortunately, Fu found that the fluoride-containing catalyst system that was employed for the cross-coupling of alkyl halides with organostannanes (Sect. 4) was ineffective for the analogous reactions of organosilanes. However, by adjusting the conditions, it was possible to achieve the desired Hiyama reactions of unactivated alkyl electrophiles (Eq. 11) [30].



(11)

With regard to the silicon-based coupling partner, only *aryltrimethoxy*silanes could be effectively cross-coupled; allyl- and vinyltrimethoxysilanes, as well as

Table 7 Hiyama cross-coupling of primary alkyl bromides and iodides with aryltrimethoxysilanes

Entry	Alkyl halide	Ar–Si(OMe)$_3$	Yield (%)
1			81
2			71
3			59
4			82
5			73

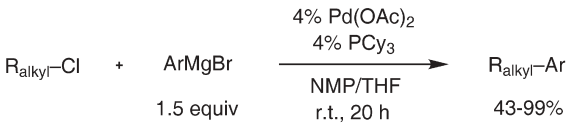
$ArSiCl_3$ and $ArSiMe_2Cl$, did not react in significant yield. P(*t*-Bu)$_2$Me was the best ligand among those that were examined. Interestingly, some Hiyama coupling was observed in the presence of an *N*-heterocyclic carbene (generated from 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (IMes·HCl)), although the yield was modest (36%).

Table 7 provides examples that illustrate the scope of this room-temperature Hiyama cross-coupling of unactivated primary alkyl bromides and iodides. The method is compatible with functional groups such as esters, cyanides, and ketones.

6 Kumada–Murahashi Cross-Couplings

Grignard reagents are attractive coupling partners because a large number are commercially available, and many others can readily be synthesized. On the other hand, their relatively high nucleophilicity and Brønsted basicity can lead to undesired reactions with a number of common functional groups [31]. Nevertheless, in recent years important progress has been reported in developing catalysts for cross-coupling Grignard reagents with unactivated alkyl electrophiles.

In 2002, Beller reported the first palladium-catalyzed couplings of aryl Grignard reagents with primary alkyl chlorides (Eq. 12) [32]. Among the catalyst systems that were examined, Pd/PCy$_3$ proved to be the best. Interestingly, the use of P(*o*-tol)$_3$ and P(*t*-Bu)$_3$ also led to cross-coupling, albeit in low yield

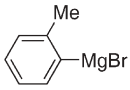
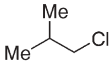
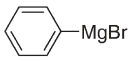
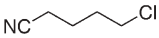
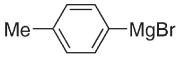
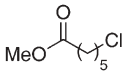
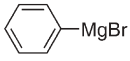
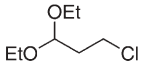
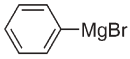
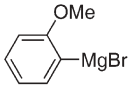
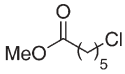
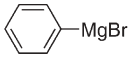
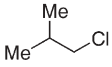
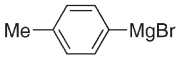
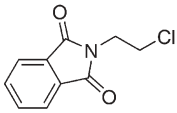
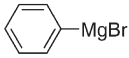


(12)

(11 and 27%, respectively). Although these ligands do not provide synthetically useful methods, it is noteworthy that they furnish palladium complexes capable of activating an alkyl chloride.

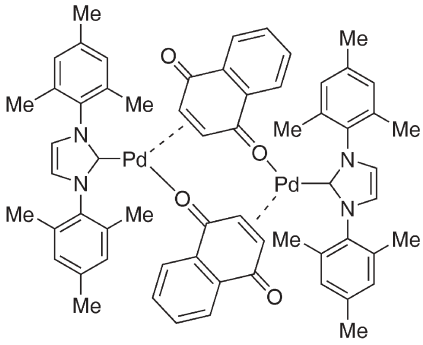
Representative examples of the application of Pd/PCy$_3$ to Kumada–Murahashi couplings of primary alkyl chlorides are illustrated in Table 8 (entries 1–5). In contrast to most other palladium-based methods for cross-coupling alkyl electrophiles, the reaction proceeds well even for a β-branched alkyl halide (entry 2).

Table 8 Kumada–Murahashi couplings of primary alkyl chlorides with aryl Grignard reagents

Entry	Alkyl chloride	Aryl grignard	Conditions[a]	Yield (%)
1	*n*-Hex-Cl		A	83
2			A	72
3			A	99
4			A	58
5			A	74
6	*n*-Hex-Cl		B	61
7			B	92
8			B	99
9			B	45

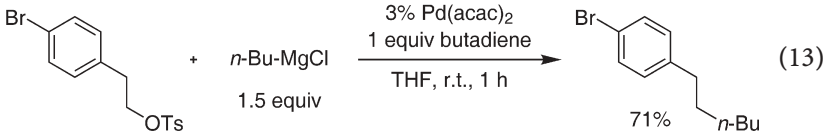
[a] A: Reaction conditions as in Eq. (12); B: Reaction conditions as in Eq. (12), with 2 mol% **1** (instead of Pd(OAc)$_2$ and PCy$_3$) and a reaction time of 1 h.

Beller later reported that a dimeric Pd/IMes complex (**1**) furnishes similar yields, but in a shorter time (typically 1 h), as compared with Pd/PCy_3 [33]. Another NHC ligand, IPr, was also investigated, but it was considerably less effective. Entries 6–9 of Table 8 provide a sampling of Kumada–Murahashi reactions that are catalyzed by Pd/IMes. Esters (entry 7) and imides (entry 9) are compatible with this second-generation method.



1

Kumada–Murahashi cross-couplings of primary alkyl bromides and tosylates have been described by Kambe [34]. $Pd(acac)_2$/butadiene was employed as the catalyst, and couplings of alkyl and aryl Grignard reagents were achieved. The reactions proceed in the presence of an aryl chloride, an aryl bromide, and a styrenyl group. A typical cross-coupling is illustrated in Eq. 13.



(13)

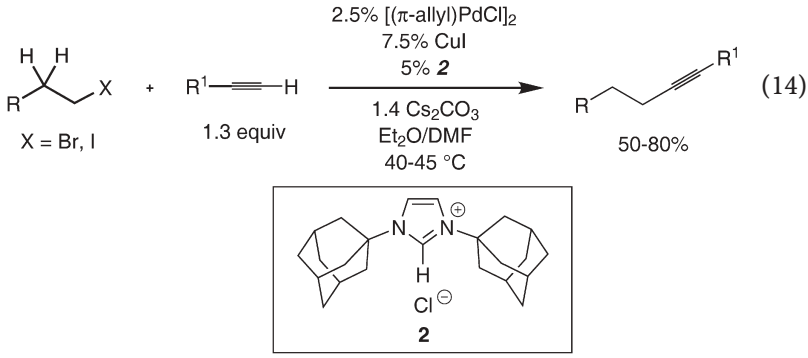
7
Cross-Couplings of Terminal Alkynes

7.1
Sonogashira Cross-Couplings

Many of the methods that have been reported for coupling alkyl electrophiles with terminal alkynes require a strong base and therefore have limited functional-group compatibility [35]. In contrast, the Sonogashira reaction, which is widely used to cross-couple aryl and vinyl electrophiles with terminal alkynes, employs a mild base (e.g., an amine). Expanding the scope of Sonogashira couplings to include alkyl electrophiles would be a welcome advance in alkyne chemistry.

In most cross-coupling processes, a *stoichiometric* amount of an organometallic coupling partner is added to the reaction mixture (e.g., Sects. 2–6); in contrast, in Sonogashira couplings, the transmetalating species (generally believed to be an alkynylcopper reagent) is produced in situ in low concentration. In view of the need to partition effectively between *intra*molecular β-hydride elimination (undesired) and *inter*molecular transmetalation (desired) (Fig. 1), the low concentration of the alkynylcopper makes the discovery of a method for achieving Sonogashira reactions of alkyl electrophiles a particularly interesting challenge.

Recently, Fu has developed a catalyst for Sonogashira cross-couplings of unactivated primary alkyl bromides and iodides with an array of alkynes (Eq. 14) [36]. Through a survey of a number of Pd/ligand combinations, Pd/NHC-based systems were found to possess the desired activity. Interestingly, organic bases such as NEt_3, which are commonly used in Sonogashira reactions of aryl electrophiles, were ineffective under the conditions described in Eq. 14.



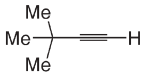
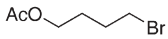
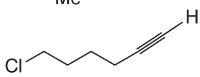
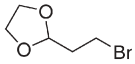
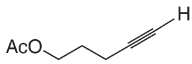
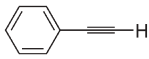
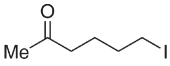
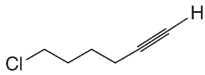
(14)

This catalyst system exhibits excellent functional-group tolerance: cross-couplings proceed in the presence of alcohols (Table 9, entry 1), cyanides (entries 2 and 5), esters (entries 3 and 4), and ketones (entry 6). Alkyl bromides and iodides are selectively coupled in the presence of alkyl chlorides (entries 3 and 6). Finally, even very hindered alkynes are suitable cross-coupling partners (e.g., *t*-butylacetylene, entry 2).

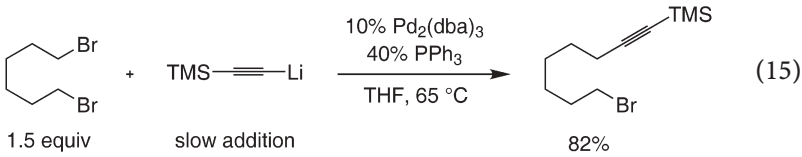
7.2 Alkynylmetal Cross-Couplings

While alkynyllithiums react with primary alkyl halides in the presence of diamines or HMPA to afford the coupled products [35], this reaction proceeds slowly in the absence of these additives, even at elevated temperature. Luh has described a Pd/PPh_3 catalyst that facilitates the cross-coupling of alkynyllithiums and alkynyl Grignard reagents with primary alkyl bromides and iodides (e.g., Eq. 15) [37].

Table 9 Sonogashira cross-couplings of primary alkyl bromides and iodides with alkynes

Entry	Alkyl Halide	Alkyne	Yield (%)
1			59
2			70
3			73
4			58[a]
5			61[b]
6			70

[a] Reaction was conducted at 60 °C.
[b] 7.5% [(π-allyl)PdCl]$_2$, 22.5% CuI, and 15% **2** were employed.



(15)

One of the challenges in developing this chemistry was to avoid palladium-mediated oxidative coupling of the alkynylmetal to form diynes. Luh determined that this side product can be disfavored by slow addition of the alkynylmetal to the reaction mixture. Interestingly, PPh_3 was found to be the best ligand; the use of trialkylphosphines such as P(*t*-Bu)$_2$Me led to increased homocoupling. As illustrated in Eq. 15, Luh was able to achieve the selective monoalkynylation of linear α,ω-dibromoalkanes (chain lengths from 3 to 12) in good yield.

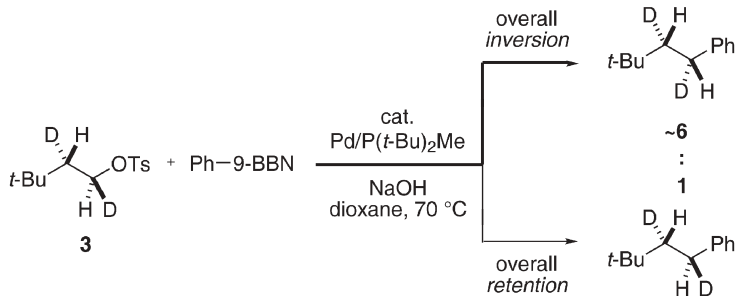
8
Mechanistic Studies

8.1
Stereochemistry of Oxidative Addition to Pd/PR$_3$

Pioneering studies by Stille in the 1970s established that the oxidative addition of benzyl chlorides and bromides (activated alkyl electrophiles) to Pd(0)/PPh_3 complexes occurs predominantly with inversion of stereochemistry at the elec-

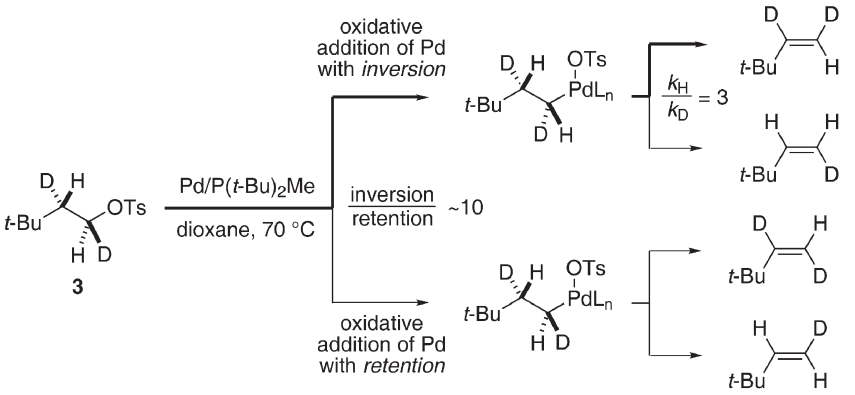
trophilic carbon [38–40]. It was therefore concluded that, for these reactants, oxidative addition is most likely occurring via an S_N2-like mechanism.

As part of an investigation of Pd/P(*t*-Bu)$_2$Me-catalyzed Suzuki cross-couplings of alkyl tosylates with organo-9-BBN reagents (Sect. 2.1.1), Fu described evidence that oxidative addition in this system also occurs with inversion of configuration at carbon [16]. Based on a strategy originally reported by Whitesides [41], diastereomerically pure tosylate **3** was coupled with phenyl-9-BBN, and the stereochemistry of the product was determined by $^1H\{^2H\}$ NMR spectroscopy (Scheme 2). The ratio of inversion:retention at the carbon undergoing substitution was ~6:1. Based on the assumption that reductive elimination proceeds with retention of configuration, as is well-precedented [42], it was concluded that oxidative addition of primary alkyl tosylates to Pd/P(*t*-Bu)$_2$Me occurs predominantly with inversion of configuration at the electrophilic carbon.



Scheme 2 Stereochemistry of the Suzuki coupling of tosylate **3** with phenyl-9-BBN

In a second stereochemical investigation of the mechanism of oxidative addition, tosylate **3** was treated with Pd/P(*t*-Bu)$_2$Me in the absence of a coupling partner (Scheme 3). With no transmetalation pathway available to the alkyl-

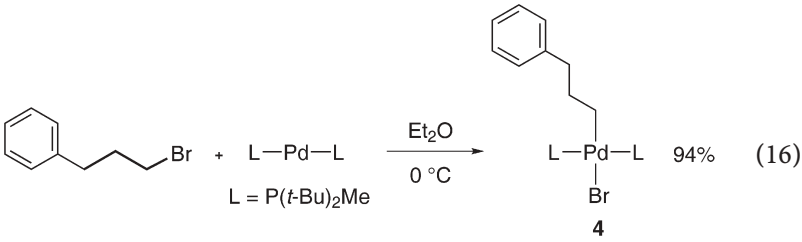


Scheme 3 Stereochemistry of the oxidative addition of tosylate **3** with Pd/P(*t*-Bu)$_2$Me

palladium(II) intermediate, β-hydride elimination occurred. An analysis of the distribution of the resulting olefins by ^{1}H NMR indicated again that oxidative addition proceeds predominantly with inversion of configuration (~10:1 inversion:retention; k_H/k_D ~3) [43, 44].

8.2 Kinetic Studies of Oxidative Addition to Pd/PR$_3$

During a study of Pd/P(*t*-Bu)$_2$Me-catalyzed Suzuki cross-couplings of primary alkyl bromides with boronic acids, Fu examined the stoichiometric reaction of Pd(P(*t*-Bu)$_2$Me)$_2$ with an alkyl bromide (Eq. 16) [17]. Interestingly, not only was oxidative addition facile at 0 °C, but the adduct (**4**) could be isolated in excellent yield and even crystallographically characterized.

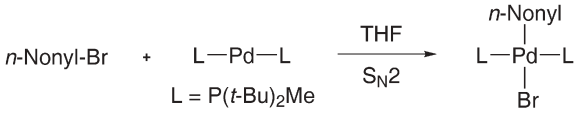


(16)

Upon warming, alkylpalladium complex **4** underwent β-hydride elimination to generate allylbenzene and Pd(P(*t*-Bu)$_2$Me)$_2$HBr. This process was inhibited by the presence of excess P(*t*-Bu)$_2$Me, consistent with a pathway that involves initial dissociation of a phosphine [45]. Oxidative-addition adduct **4** reacted with one equivalent of *o*-tolylboronic acid to generate the coupling product in 94% yield; in addition, it served as a competent catalyst for cross-couplings of alkyl bromides and arylboronic acids.

Kinetics studies of the oxidative addition of a variety of unactivated primary alkyl electrophiles to several PdL$_2$ complexes (L=trialkylphosphine) have been described [46]. For the reaction depicted in Eq. 17, the activation parameters are: $\Delta G^{\ddagger}$=20.8 kcal mol^{-1} (20 °C); $\Delta H^{\ddagger}$=2.4 kcal mol^{-1}; $\Delta S^{\ddagger}$=–63 eu. The large negative $\Delta S^{\ddagger}$ value that is observed is consistent with an associative pathway for oxidative addition. The rate of addition increases as the solvent polarity increases, as would be expected for the postulated S_N2 mechanism, and is not affected by added P(*t*-Bu)$_2$Me, indicating that the alkyl bromide oxidatively adds to PdL$_2$ (not PdL$_1$ or PdL$_3$) [47].

As anticipated, the better the leaving group, the faster the oxidative addition: *k*(I)>*k*(Br)>*k*(OTs)>*k*(Cl)>*k*(F) (e.g., $t_{1/2}$ for reactions of *n*-nonyl-X: X=I (2.2 h at –60 °C); X=Cl (2.0 days at 60 °C)). Furthermore, the activation barrier for

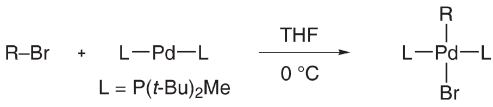


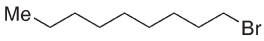
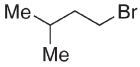
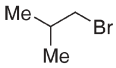
(17)

oxidative addition to $Pd(P(t\text{-}Bu)_2Me)_2$ has been measured for an array of alkyl bromides, manifesting the sensitivity of the process to the steric demand of the electrophile (Table 10). The reluctance of secondary bromides to oxidatively add, even at elevated temperature (entry 4), is consistent with the inability of $Pd/P(t\text{-}Bu)_2Me$ to cross-couple this family of electrophiles.

Finally, the dependence of the rate of oxidative addition on the choice of trialkylphosphine has been quantified (Table 11). Consistent with the reactivity patterns that have been observed in Pd/trialkylphosphine-catalyzed cross-coupling processes of alkyl electrophiles (e.g., Scheme 1), PdL_2 complexes derived from $P(t\text{-}Bu)_2Me$ and PCy_3 undergo relatively facile oxidative addition (entries 1 and 2), whereas those based on $P(t\text{-}Bu)_2Et$ and $P(t\text{-}Bu)_3$ are essentially unreactive (entries 3 and 4).

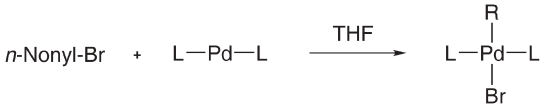
Table 10 Relative rates of oxidative addition of alkyl bromides to $Pd(P(t\text{-}Bu)_2Me)_2$



Entry	R–Br	k_{rel}	$\Delta G^{‡}$ (kcal mol^{-1})
1		1.0	19.5
2		0.19	20.3
3		0.054	21.0
4		<0.0001	>24.0[a]

[a] Extrapolated from a reaction run at 60 °C.

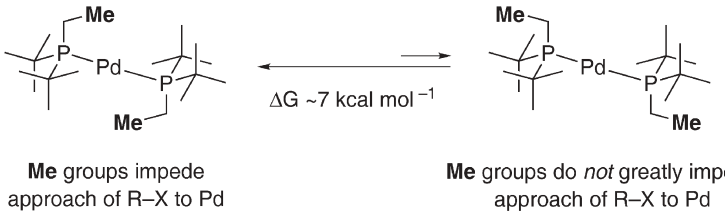
Table 11 Dependence of the rate of oxidative addition on the choice of trialkylphosphine



Entry	L	$\Delta G^{‡}$ (kcal mol^{-1}) [a]
1	$P(t\text{-}Bu)_2Me$	19.5 (0 °C)
2	PCy_3	20.0 (0 °C)
3	$P(t\text{-}Bu)_2Et$	25.4 (60 °C)
4	$P(t\text{-}Bu)_3$	>28.4 (60 °C)

[a] The temperature at which $\Delta G^{‡}$ was measured is noted in parentheses.

The difference in activation barriers between the P(*t*-Bu)$_2$Me and the P(*t*-Bu)$_2$Et complexes (Table 11, entry 1 vs entry 3), corresponding to k_{rel}~10^4, is particularly striking. A DFT computational study that examined the conformations of the Pd/phosphine adducts provided a reasonable rationale for this initially surprising result: the desire to minimize *syn*-pentane-like interactions between the Et and the *t*-Bu groups of P(*t*-Bu)$_2$Et leads to a preferred conformation that greatly encumbers approach of an electrophile to Pd(P(*t*-Bu)$_2$Et)$_2$ (Scheme 4).



Scheme 4 Effect of the conformations of the Pd/phosphine adducts on the approach of an electrophile

9 Summary and Outlook

In a short period, the palladium-catalyzed cross-coupling of unactivated alkyl electrophiles has been transformed from a process for which there was little expectation for synthetic utility into a very promising area of research. Examples of couplings of alkyl halides/sulfonates with most of the key organometallic reaction partners (e.g., organoboron, -zinc, -tin, -silicon, and -magnesium reagents) have now been described. The obstacles of slow oxidative addition and rapid β-hydride elimination, which many thought would preclude efficient carbon–carbon bond formation, have proved to be surmountable. Importantly, mechanistic investigations are beginning to furnish insight into the workings of these new catalysts.

At the same time, many interesting challenges have yet to be successfully ‘addressed. Currently, only primary alkyl electrophiles are suitable partners in these palladium-catalyzed cross-coupling processes. Drastic changes in ligand design may be necessary to expand the scope of these reactions to secondary and tertiary alkyl electrophiles. Once this objective has been accomplished, the door will then be open to exciting new opportunities in asymmetric catalysis. Thus, while significant progress has recently been achieved toward the development of methods for cross-coupling alkyl electrophiles, a wealth of important problems remains to be solved.

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Palladium-Catalyzed Cycloaddition Reactions of Arynes

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Abstract The transition-metal-catalyzed cyclotrimerization of alkynes has been used extensively in synthesis during the past 25 years. However, until recently there have been no procedures for the cyclotrimerization of arynes. This chapter shows that this transformation can be efficiently achieved with palladium catalysts, and that it opens new avenues in the synthesis of polycyclic aromatic hydrocarbons.

Keywords Palladium catalysts · Aryne cyclotrimerization · Cycloalkyne cyclotrimerization

Abbreviations

Ac	Acetyl
Ar	Aryl
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
BPPM	*tert*-Butyl-4-(diphenylphosphino)-2-(diphenylphosphinomethyl)-1-pyrrolidinecarboxylate
Bu	Butyl
t-Bu	*tert*-Butyl
cat	Catalyst
cod	Cyclooctadiene
Cp	Cyclopentadienyl
Cp*	Pentamethylcyclopentadienyl
Cy	Cyclohexyl
dba	Dibenzylideneacetone
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DMAD	Dimethylacetylene dicarboxylate
DMSO	Dimethyl sulphoxide
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1′-Bis(diphenylphosphino)ferrocene
ee	Enantiomeric excess
equiv	Equivalent(s)
Et	Ethyl
FVP	Flash vacuum pyrolysis
h	Hours
Hex	Hexyl
HBT	Hexabenzotriphenylene
HMDS	Hexamethyldisilazane
Ln	Ligands
Me	Methyl
min	Minute(s)
mol	Mole(s)
NBS	*N*-bromosuccinimide
NMR	Nuclear magnetic resonance
PAH	Polycyclic aromatic hydrocarbons
Ph	Phenyl
Pr	Propyl
rt	Room temperature
Tf	Trifluoromethanesulphonyl
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Tol	Tolyl
Tol-BINAP	2,2′-Bis[di(*p*-tolyl)phosphino]-1,1′-binaphthyl

1
Introduction and Background

1.1
Arynes

Arynes are formed when the loss of two mutually *ortho* substituents by an aromatic ring results in the formation of a triple bond [1–3]. Benzyne (**1**) is the parent member of a series that today comprises a huge number of substituted and unsubstituted monocyclic, polycyclic and heterocyclic compounds [2, 3]. Figure 1 includes some illustrative examples of these structures: 3-methoxy-1,2-didehydrobenzene (3-methoxybenzyne, **2**); 9,10-didehydrophenanthrene (9,10-phenanthryne, **3**); and 3,4-didehydropyridine (3,4-pyridyne, **4**). Although not properly arynes, some members of the closely related class of cycloalkynes, such 1,2-didehydroacenaphthylene (acenaphthyne, **5**), will also be mentioned in this chapter.

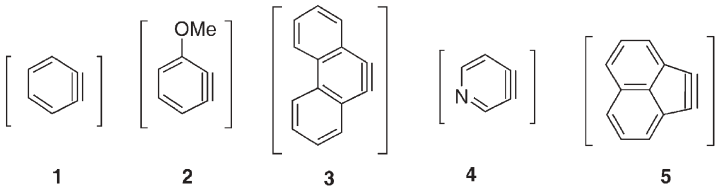


Fig. 1 Benzyne (**1**) and related substituted and unsubstituted monocyclic, polycyclic and heterocyclic compounds

In solution, benzyne and its derivatives are strained, short-lived intermediates which react with a broad array of nucleophiles, including carbanions, amines, alcohols and their salts, water, and even ethers. They also undergo pericyclic reactions such as Diels–Alder cycloadditions, 1,3-dipolar cycloadditions or ene reactions. The instability of benzyne and its derivatives is due to the strain caused by the deformation of the linear geometry of the formal sp-hybridized carbons of the triple bond to the angles close to 120° imposed by the ring geometry [2, 3].

1.2
Organometallic Chemistry of Arynes: Complexes with Transition Metals

It is well known that alkynes form stable π complexes with many transition metals and that this complexation changes the geometry of the alkyne from linear to angular. In view of this, the coordination of arynes to transition metals should relax part of the strain, possibly even resulting in stable species.

The first mention of the formation of aryne–metal complexes is due to Wittig, who formulated these species as possible intermediates in the formation

of benzyne by metallation of *o*-dihalobenzenes [4]. Since then, complexes of arynes with a wide array of transition metals have been prepared, but in most cases only for structural studies [5–9] (Fig. 2). Aryne complexes are usually represented in the forms **6** or **7**. Some authors prefer the former for late and the latter for early transition metals. However, for the sake of simplicity representation **6** will be use throughout this chapter.

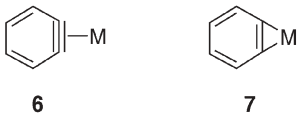


Fig. 2 Aryne complexes with transition metals

1.2.1 Aryne Complexes of Early Transition Metals

The intermediacy of aryne–metal complexes in many organometallic reactions has been postulated on the basis of the structures of the reaction products. This mechanistic hypothesis received strong support in 1979 with Schrock and co-workers' isolation of complex **8** and its structural characterization by X-ray crystallography [10]. Since then, many aryne complexes of early transition metals have been prepared, including complexes of Ti, Zr, Nb, Mo, W, Re, V, and even the actinoid elements U and Th. Figure 3 shows some representative examples of aryne complexes of early transition metals that have been characterized by X-ray diffraction studies.

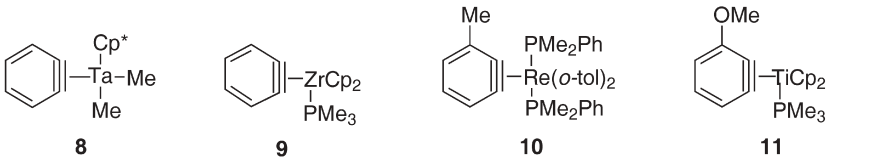
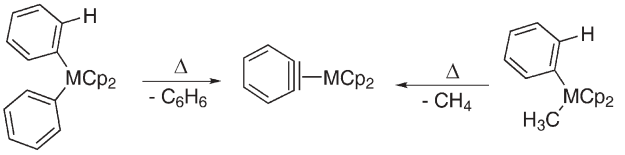
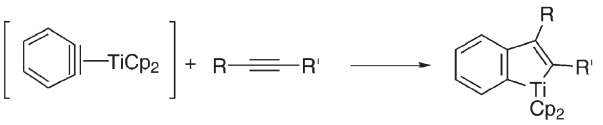


Fig. 3 Aryne complexes of early transition metals

The most useful procedure for the preparation of early transition metal complexes of type **13** is the thermal elimination of benzene or methane from diphenyl or arylmethyl compounds, respectively (**12** and **14** in Scheme 1) [5–9]. At the end of the 1960s, the first studies of the reactivity of such a complex, specifically the aryne–titanocene complex **15**, showed that it reacts with species such as alkynes, CO_2, N_2 or selenium to form titanacycles [7]. Particularly interesting for the aim of this chapter is the insertion of alkynes to form titanacyclopentadienes **16**. This reaction takes place in moderately good yields with both electron-rich and electron-poor alkynes (Scheme 2) [13–15].

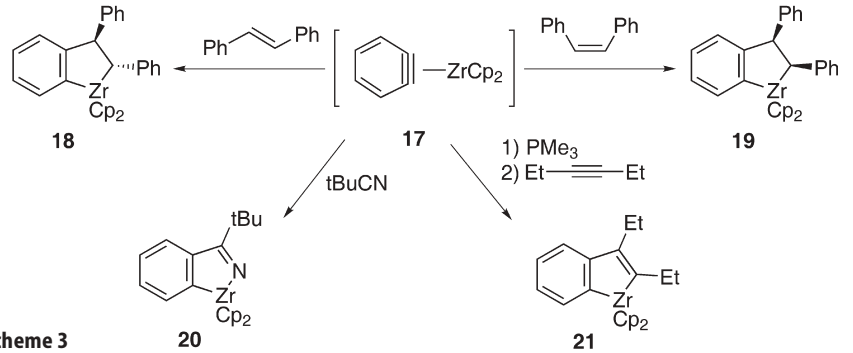


Scheme 1 12 13 14



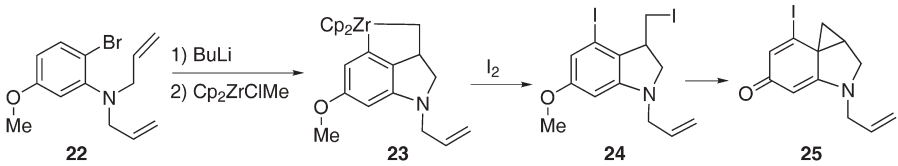
Scheme 2 15 16

However, the most useful complexes from the synthetic point of view are those of zirconium. The early work of Erker [16, 17] and later extensive studies by Buchwald [5, 8] have shown that the aryne–zirconium complex **17** is susceptible to insertion of a variety of unsaturated species to give the corresponding zirconacycles (Scheme 3). The insertion of substituted olefins such as stilbene is stereospecific, since *trans*-stilbene reacts with **17** to afford metallacycle **18**, while *cis*-stilbene affords **19** [17]. The reaction of *t*BuCN takes place with high regioselectivity to form metallacycle **20**, which can be hydrolysed to the corresponding ketone [18, 19]. Alkynes have been inserted both into **17** (the resulting metallacycles being transformed without isolation into benzothiophenes by treatment with SCl_2 [20]), and into complex **9** (obtained from **17** by treatment with excess of PMe_3), affording **21** [11].



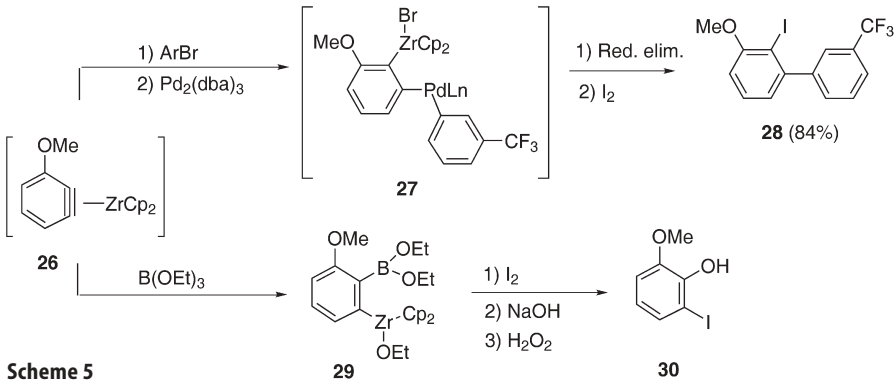
Scheme 3 18 17 19 20 21

Zirconium–aryne complexes have found applications in organic synthesis. For example, treating diallylamine **22** with BuLi and zirconocene(methyl) chloride forms an aryne–zirconium complex that undergoes intramolecular olefin insertion to yield metallacycle **23**, and trapping this metallacycle with iodine gives **24**, further manipulation of which allows rapid construction of **25**, an analogue of the pharmacophore of the antitumour agent CC-1065 [21] (Scheme 4).



Scheme 4

Zirconocene–aryne complexes can also be transmetallated, opening the way to a broad spectrum of synthetic operations such as oxidation, halogenation and cross-coupling (Scheme 5). For example, transmetallation of zirconocene–aryne complex **26** with the palladium complex generated from Pd(0) and *m*-bromo(trifluoromethyl)benzene regioselectively affords palladium(II) complex **27**, which after reductive elimination can be iodinated to **28** [22]. Alternatively, treatment of **26** with $B(OEt)_3$ results in the formation of **29**, and its iodination and oxidation leads to **30** [23].

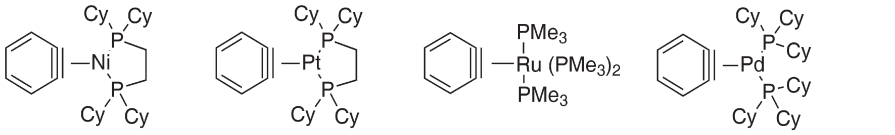


Scheme 5

1.2.2
Aryne Complexes of Late Transition Metals

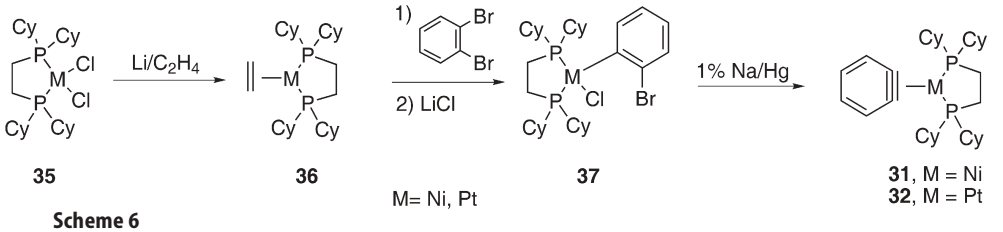
The evolution of the chemistry of late transition metal complexes is due principally to the efforts of Bennett and co-workers [6, 7], and runs parallel to that sketched above for early transition metals. Figure 4 shows some representative examples of aryne complexes of late transition metals that have been characterized by X-ray diffraction studies.

Ruthenium complex **33** has been prepared by thermolysis as shown in Scheme 1 for early transition metals [25]. However, this procedure is not applicable to nickel, platinum and palladium complexes because they undergo reductive elimination, rather than beta elimination. Complexes **31** and **32** have been prepared by sodium amalgam reduction of the corresponding σ-complex **37**, as shown in Scheme 6 [6, 7, 24].



31 Bennett, 1985 [24] **32** Bennett, 1989 [6,7] **33** Bergman, 1989 [25] **34** Bennett, Wenger, 2002 [26]

Fig. 4 Aryne complexes of late transition metals

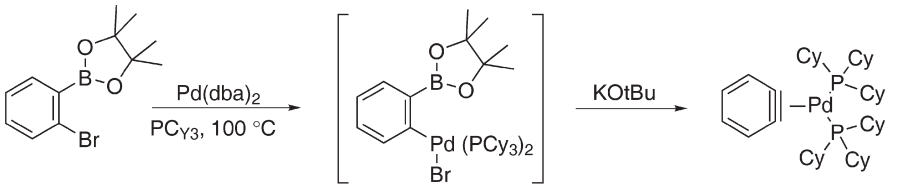


35 **36** **37** **31**, M = Ni **32**, M = Pt

M= Ni, Pt

Scheme 6

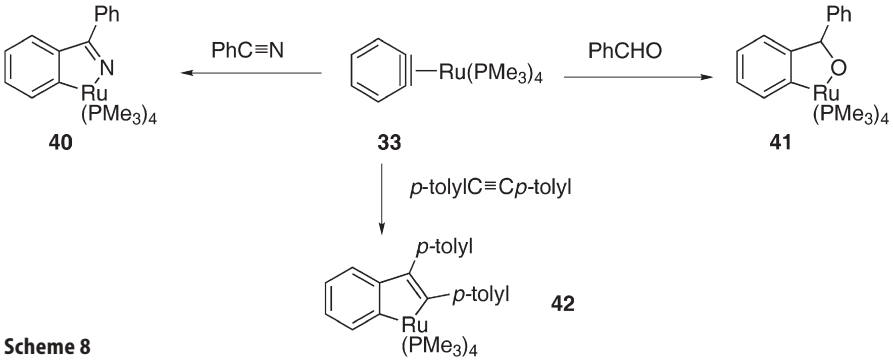
A more sophisticated procedure has recently allowed the preparation of palladium complex **34**, based on an intramolecular Suzuki coupling. The key intermediate **39** is generated by oxidative addition of palladium(0) to **38**, and treatment of **39** with base promotes a Suzuki-type intramolecular reaction leading to **34** (Scheme 7) [26]. The same procedure is applicable to the synthesis of benzyne–nickel complexes with a variety of ligands (PPh_3, PCy_3, PEt_3) [26].



38 **39** **34**

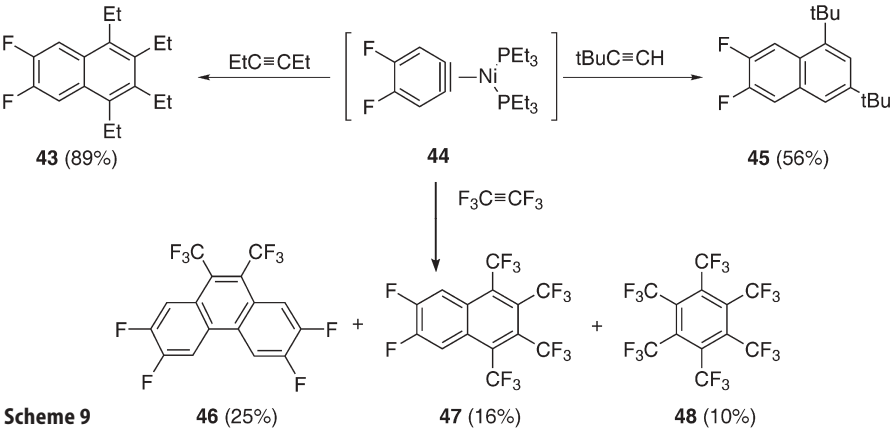
Scheme 7

Aryne complexes of late transition metals are very reactive towards both nucleophiles (amines, alcohols, water) and electrophiles (iodine). They also undergo insertion reactions with CO, alkenes and alkynes, but while the behaviour of ruthenium complexes is somewhat similar to that of titanium or zirconium complexes, the reactivity of nickel complexes is rather different [6, 8]. Examples of these reactions that are particularly interesting for the purposes of this chapter are shown in Schemes 8 and 9. Ruthenium complex **33** undergoes insertion of a molecule of benzonitrile, benzaldehyde or di(*p*-tolyl)acetylene to yield metallacycles **40**, **41** and **42**, respectively (Scheme 8). Further insertion of a second unsaturated molecule into these metallacycles has not been observed [25, 27].



Scheme 8

Aryne–nickel complexes, which were carefully studied by Bennett [6, 7], show a different reactivity, since following the insertion of a first unsaturated species, the metallacycles so formed usually undergo a second insertion and subsequent reductive elimination (Scheme 9). Thus, complex **44** undergoes the insertion of two molecules of 3-hexyne to afford **43** in good yield, and double insertion of the asymmetric alkyne *t*-butylacetylene into complex **44** yields naphthalene **45** with a high regioselectivity attributed to steric factors. Interestingly, the reaction of **44** with the more electron-deficient alkyne hexafluoro-2-butyne leads to a mixture of **46**, **47** and **48** [28, 29]; phenanthrene **46** might be formed by insertion of a second aryne molecule into an intermediate nickelacycle.



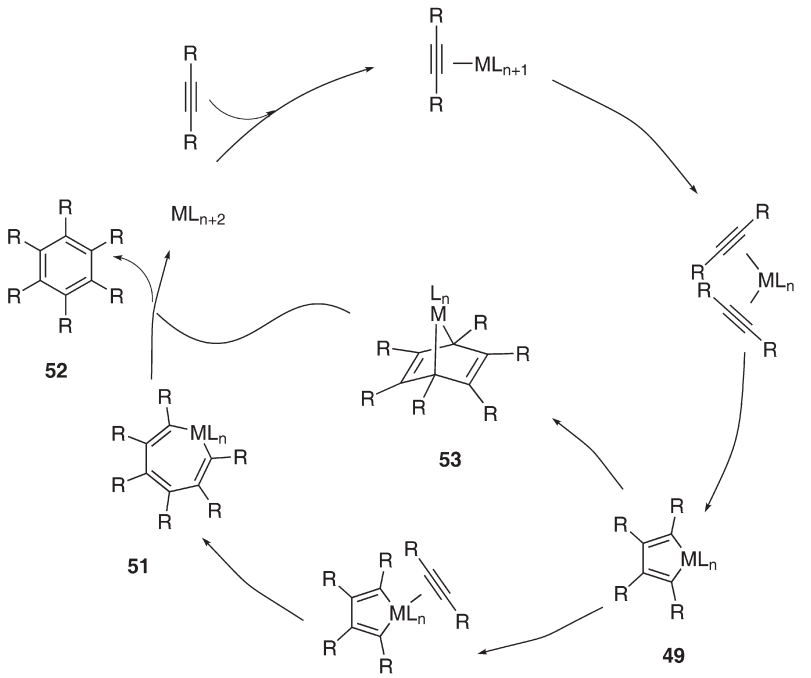
Scheme 9

Despite all this work, until the end of the 1990s the only aryne–metal complexes for which synthetic applications had been developed were a few zirconium complexes. The principal drawback of this chemistry was the use of stoichiometric amounts of metal complexes and, as a consequence, its poor atom economy (in both ligands and metals) and high cost.

2
Palladium-Catalyzed Cyclotrimerization of Arynes

2.1
Cyclotrimerization of Benzyne

Catalysis of the [2+2+2] cycloaddition of alkynes by transition metal complexes has been extensively exploited for the synthesis of complex organic molecules [30–34]. The accepted mechanism for this transformation, shown in Scheme 10, involves coordination of two alkyne molecules to the metal centre followed by oxidative coupling to form the coordinatively unsaturated metallocyclopentadiene **49**, which can coordinate a third molecule of alkyne to afford **50**. Insertion of the alkyne in a metal–carbon bond of this complex leads to metallocycloheptadiene **51**, and reductive elimination then affords cyclotrimer **52** and regenerates the catalytic species. Alternatively, the transformation of **49** into **52** might involve a Diels–Alder reaction giving intermediate **53**, followed by reductive elimination [35].

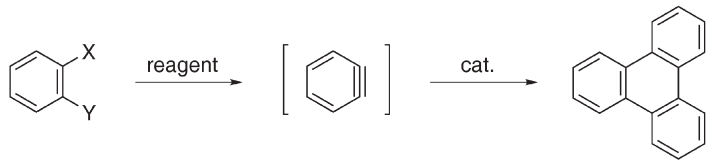


Scheme 10

These catalytic cyclotrimerizations of alkynes can be promoted by many transition metals. Complexes of Ni, Pd, Pt, Rh and, in particular, Co have found wide application in organic synthesis. However, even by the end of the 1990s very little was known about similar cyclotrimerization reactions of arynes. The formation

of triphenylene (**56**) had been observed in certain aryne reactions, especially when benzyne was generated from main-group organometallic species [2, 36, 37], and the same compound had been reported as the product of the decomposition of a benzyne–platinum complex [38], but arynes were not known to undergo any metal-catalyzed reaction. The predictable difficulties associated with this kind of transformation derived from the instability of species such as benzyne, which must be generated in situ by some method compatible with the use of metal complexes. Furthermore, the catalyst has to be able to coordinate arynes, but without forming complexes that are so stable as to block the catalytic cycle.

In 1998, Guitián, Pérez and co-workers reported that the cyclotrimerization of benzyne (**1**) to triphenylene (**56**) is efficiently catalyzed by palladium(0) complexes (Scheme 11) [39]. This was the first time an aryne had been the substrate in a metal-catalyzed process. The success of the reaction was based on a judicious choice of the reaction conditions, particularly with regard to the catalytic system and the method of generating the aryne. Some significant results of this seminal study are shown in Table 1. After some preliminary experiments in which nickel complexes were used as catalysts (entry 1), it was found that nucleophilic palladium(0) complexes efficiently promote the desired [2+2+2] cycloaddition of the strongly electrophilic substrate **1** (entries 2–6) [40]. At the same time, a systematic study of benzyne generation conditions showed that Kobayashi's method



54, X=Y=Br
55, X=TMS, Y=OTf

1

56

Scheme 11

Table 1 Metal-catalyzed synthesis of triphenylene (**56**, see Scheme 11)[a]

Entry	Aryne precursor	Reagent	Catalyst (0.1 equiv)	Additives	Yield (%)[b]
1	**54**	BuLi	$Ni(cod)_2$	–	10
2	**54**	BuLi	$Pd(PPh_3)_4$	–	40
3	**55**	CsF	$Pd(PPh_3)_4$	–	83
4	**55**	Bu_4NF	$Pd(PPh_3)_4$	–	71
5	**55**	CsF	$Pd_2(dba)_3$	dppe	70
6	**55**	CsF	$Pd_2(dba)_3$	$P(o\text{-tol})_3$	60
7	**55**	CsF	–	–	–
8	**55**	–	$Pd(PPh_3)_4$	–	–

[a] Reaction conditions: THF, 0 °C, 12 h (entries 1, 2, 4); CH_3CN, rt, 12 h (entries 3, 5–8).
[b] Yield of isolated product.

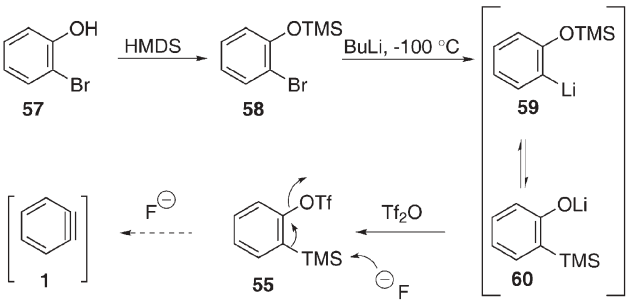
[fluoride-induced decomposition of 2-(trimethylsilyl)phenyl trifluoromethanesulphonate, (**55**)], is the method of choice [41].

The best yield of triphenylene (83%) is obtained when 2-(trimethylsilyl)-phenyl triflate (**55**) is treated at room temperature with caesium fluoride in acetonitrile in the presence of 10 mol% of $Pd(PPh_3)_4$ (entry 3). The combination of acetonitrile and caesium fluoride, which is only partially soluble in this solvent, results in a slow rate of benzyne generation and a correspondingly low concentration of this reactive species in the reaction medium, which is optimal for the catalytic transformation. Faster generation rates, which can be achieved by addition of a crown ether or by the use of a more soluble fluoride source, such as nBu_4NF, usually result in lower yields of cyclotrimer (entry 4). With regard to the catalyst, best results are obtained with $Pd(PPh_3)_4$, although the use of $Pd_2(dba)_3$ in combination with other phosphines, such as P(*o*-tol)$_3$ or dppe, also gives satisfactory yields of **56** (entries 5 and 6). As will be discussed later, for the trimerization of more complex arynes leading to strained products the use of $Pd_2(dba)_3$ in the absence of phosphines is usually more effective.

Triphenylene is not isolated in significant yields in the absence of the metal catalyst (entry 7), and when **55** is treated with $Pd(PPh_3)_4$ in the absence of fluoride it is recovered unchanged (entry 8), providing good evidence of the intermediacy of benzyne as the reactive species in the cyclotrimerization reaction.

2.2 Cyclotrimerization of Substituted Monocyclic Arynes

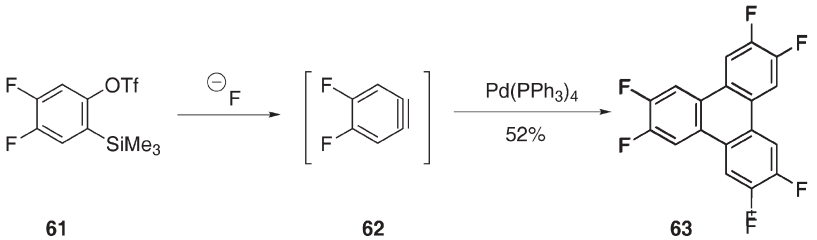
As will be discussed below, the methodology described in the preceding subsection has been extended to the trimerization of substituted benzyne derivatives, polycyclic arynes, and related species. As a prerequisite for the broad applicability of the method, its authors developed a straightforward general procedure for the synthesis of the required aryne precursors. Substituted *o*-(trimethylsilyl)aryl triflates are efficiently prepared from the corresponding *o*-bromophenols by the procedure shown in Scheme 12 for the synthesis of **55** [42, 43]. Silylation of bromophenol **57** with hexamethyldisilazane quantitatively affords **58**, which is converted into triflate **55** through a transformation that is an interesting example of silyl migration: metal–halogen exchange on **58** (induced by treat-



Scheme 12

ment with BuLi at –100 °C) affords aryl carbanion **59**, which undergoes migration of the TMS group from the oxygen to the *o*-carbon to yield phenoxide **60**, which is finally trapped with Tf_2O to give triflate **55**. In general, the transformation of bromophenols into the final triflates is accomplished in one pot with good overall yields [42].

The mild reaction conditions optimized for the cyclotrimerization of benzyne have been applied to substituted *o*-(trimethylsilyl)aryl triflates with a variety of electronic and steric characteristics, affording the corresponding triphenylenes. For example, cyclotrimerization of triflate **61,** in which the ring bears electron-withdrawing groups, affords hexafluorotriphenylene **63**, presumably through aryne **62** (Scheme 13) [39]. It should be mentioned that many such triphenylenes, and other planar aromatic compounds with core like **56**, undergo self-association to form columnar mesophases of great interest in the field of optoelectronics [44].

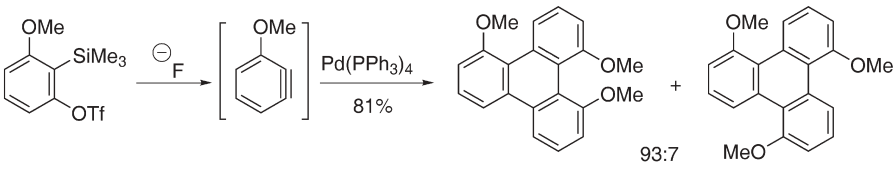


61 **62** **63**

Scheme 13

A limitation of the scope of this reaction has been observed when attempting its application to 6-nitro-2-(trimethylsilyl)phenyl triflate. The excessively strong electron-withdrawing effect of the nitro group promotes nucleophilic attack by the fluoride on the sulphur atom of the triflate, cleaving the S–O bond and expelling the phenoxide.

The use of precursors of asymmetrically substituted arynes introduces the question of regioselectivity, since two products of cyclotrimerization are possible. However, the cyclotrimerization of asymmetrically substituted aryne **2**, generated from 3-methoxy-2-(trimethylsilyl)phenyl triflate (**64**), proceeds in good yield and with high regioselectivity, affording a 93:7 mixture of regioisomers **65** and **66** (Scheme 14) [39].



64 **2** **65** **66**

Scheme 14

Experimental Procedure for Preparation of Aryne Precursors

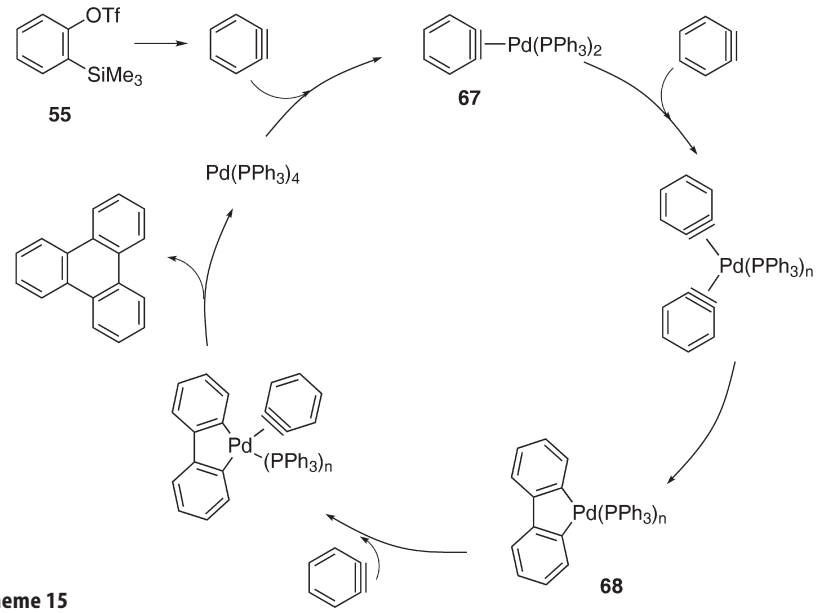
A mixture of *o*-bromohydroxyarene and HMDS (0.6 equiv) is stirred at 80 °C for 45 min in a flask protected with a $CaCl_2$ tube. Volatile products (NH_3, TMS-NH_2 and unreacted HMDS) are then removed under vacuum, and after ^{1}H NMR confirmation of the quantitative formation of the corresponding silyl ether, the crude product is dissolved in THF (0.15 M), the solution is cooled to –100 °C (external temperature, liquid N_2/ether bath) and *n*-BuLi (1.1 equiv) is added dropwise. Stirring is kept up for 20 min while the temperature reaches –80 °C. Then the mixture is again cooled to –100 °C, Tf_2O (1.2 equiv) is added dropwise, and stirring is again kept up for 20 min while the temperature returns to –80 °C. Cold saturated aqueous $NaHCO_3$ is added, the phases are separated, and the aqueous layer is extracted with Et_2O. The combined organic layers are dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2) affords the corresponding triflate.

Experimental Procedure for the Cyclotrimerization of Monocyclic Arynes

A solution of the *o*-(trimethylsilyl)aryl triflate (1 mmol) in dry acetonitrile (2 mL) is added to a suspension of finely powdered anhydrous CsF (2 mmol) and $Pd(PPh_3)_4$ (0.1 mmol) in the same solvent (10 mL). After stirring for 12 h at room temperature under argon, the solvent is evaporated and the residue purified by column chromatography.

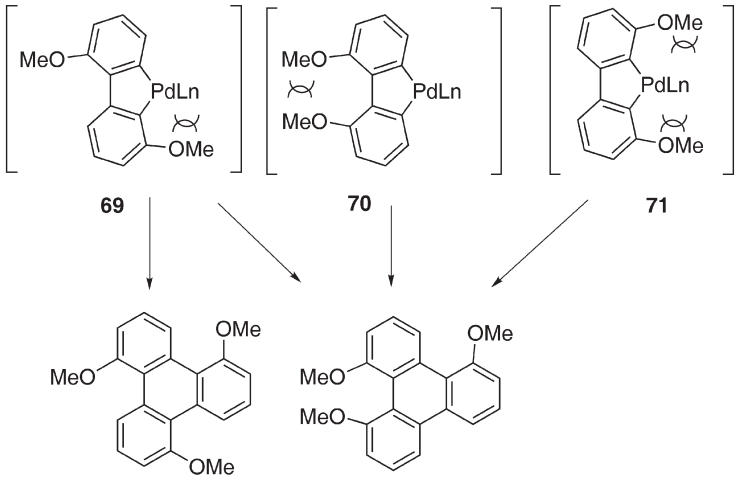
2.3 Hypothesized Mechanism

For the palladium-catalyzed cyclotrimerization of arynes, a mechanism similar to the accepted mechanism for [2+2+2] cycloaddition of alkynes may be proposed (Scheme 15). Though it has not been studied in depth, some experimental results support it. Firstly, aryne-forming conditions are necessary for the reaction to proceed (see Table 1, entry 8); no reaction of triflate **55** takes place at room temperature in the presence of the catalyst if fluoride is absent, which rules out a mechanism initiated by the oxidative addition of the aryl triflate to palladium. Data obtained in the closely related cocycloadditions of benzyne with alkynes, discussed below, likewise point to benzyne as the reactive species. Secondly, the benzyne–palladium complex **67** is a plausible initial intermediate because the ability of group 10 metals to coordinate benzyne is well known (see Sect. 1.2.2), and although benzyne complexes of palladium have eluded isolation (apparently because of their instability) [7, 26], they may well be able to exist as transient intermediates in a catalytic cycle such as that shown in Scheme 15. Thirdly, it is known that benzyne complex **34** can form metallacycles similar to **68**, albeit with dcpe as ligand instead of PPh_3 [26].



Scheme 15

Regarding the regioselectivity of the cyclotrimerization of the asymmetrically substituted aryne **2**, further experimental work and/or calculations are needed to find a rational explanation. It is not a trivial problem. If the cyclotrimerization of **2** proceeds via the mechanism of Scheme 15, intermediates **69**, **70** and **71** might be formed (Scheme 16). All three can be transformed into **65**, but **66** can only be formed from **69**.



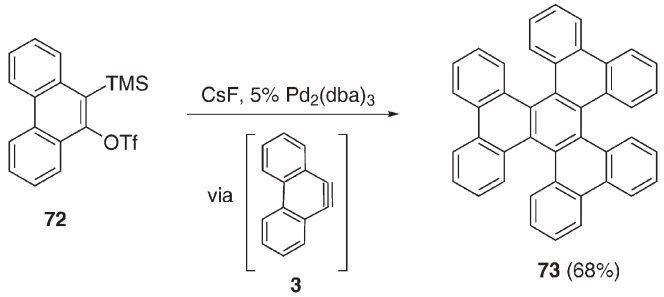
Scheme 16 **66** (7%) **65** (93%)

2.4
Cyclotrimerization of Polycyclic Arynes

2.4.1
Synthesis of Sterically Congested Polycyclic Aromatic Hydrocarbons (PAHs)

The palladium-catalyzed cyclotrimerization reaction is not limited to monocyclic arynes. On the contrary, a very interesting field of application of this reaction is the synthesis of extended PAHs from polycyclic aryne precursors.

An example that shows the potential of this methodology is the synthesis of hexabenzotriphenylene (HBT, **73**), which had previously been synthesized by Pascal in 5% yield by FVP of 9,10-phenanthrenedicarboxylic anhydride [45]. When the cyclotrimerization protocol is applied to 10-(trimethylsilyl)-9-phenanthrenyl triflate (**72**), HBT is formed in a remarkable 68% yield, presumably via 9,10-didehydrophenanthrene (**3**, Scheme 17) [46, 47]. It is important to note that in this case, and in the synthesis of other sterically congested PAHs, $Pd_2(dba)_3$ is the catalyst of choice, $Pd(PPh_3)_4$ being ineffective.



Scheme 17

HBT is a strained hydrocarbon that, to avoid the van der Waals interaction between the external aromatic rings, adopts a non-planar structure. It is interesting that while Pascal characterized his product as the more stable of its two possible conformers, the D_3-symmetric form **I** (Fig. 5) [45], the product of the palladium-catalyzed cyclotrimerization is the less stable kinetic product, the C_2-symmetric conformer **II** [47] (which has also been prepared from a 9,10-didehydrophenanthrene–nickel complex, and characterized by X-ray crystallography [48]).

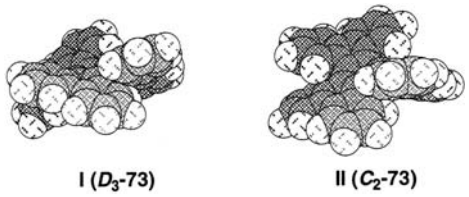
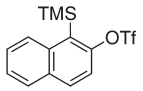
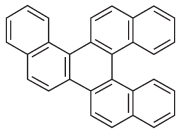
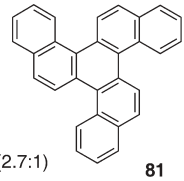
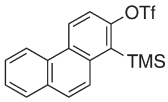
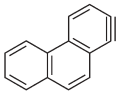
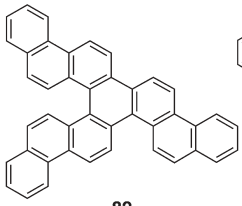
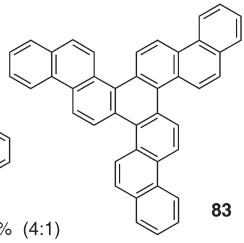
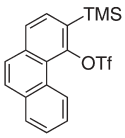
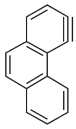
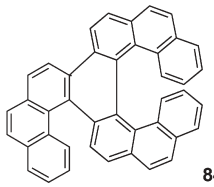


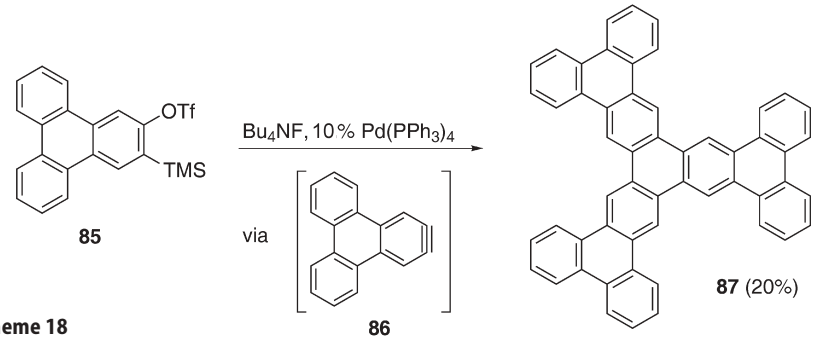
Fig. 5 The D_3- and C_2-symmetric conformers of hexabenzotriphenylene

The synthesis of HBT (**73**), which contains three [5]helicene units, illustrates the power of the cyclotrimerization of polycyclic arynes for the synthesis of helicenes. More examples are shown in Table 2. Again, $Pd_2(dba)_3$ is the catalyst of choice for trimerization of the asymmetric arynes **77–79**, which are generated from the corresponding *o*-(trimethylsilyl)aryl triflates **74–76**. In the reactions of 1,2-didehydronaphthalene (**77**) and 1,2-didehydrophenanthrene (**78**), mixtures of regioisomers are obtained, whereas **84** is the only isomer isolated from the cyclotrimerization of **79**. Compounds **80** and **82** contain a [5]helicene unit, while compound **84** is the first example of a double helicene formed by a pentahelicene and a heptahelicene with two rings in common.

The palladium-catalyzed cyclotrimerization of arynes can also be used to construct flat hydrocarbons with extended conjugation, such as hexabenzotrinaphthylene (supertriphenylene, **87**). In this case the required aryne **86** was generated in the presence of palladium by treatment of triflate **85** with tetrabutylammonium fluoride, and afforded trimer **87** in 20% isolated yield from **85** (Scheme 18) [51]. As in other cases (see below), the use of a soluble fluoride source was necessary because the extended planar reaction product is extremely

Table 2 Palladium-catalyzed cyclotrimerization of asymmetric polycyclic arynes

Aryne precursor	Aryne	Products	Ref
 **74**	 **77**	 **80** 60% (2.7:1)  **81**	46
 **75**	 **78**	 **82** 48% (4:1)  **83**	49
 **76**	 **79**	 **84** 26%	50

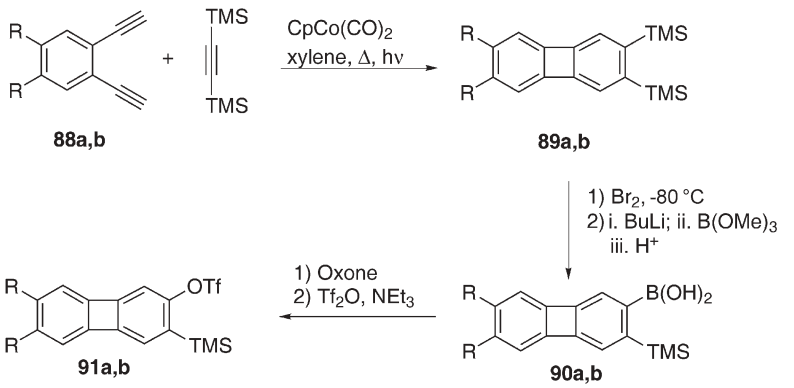


Scheme 18

insoluble and had to be isolated from the reaction medium by simple filtration. It should be noted that substituted derivatives of **87** form thermotropic columnar mesophases [52].

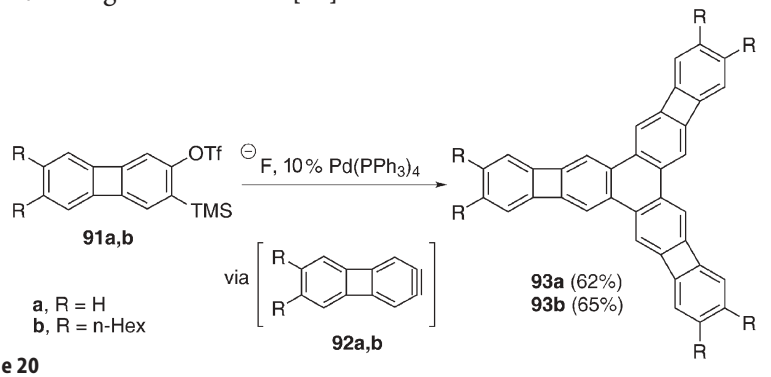
2.4.2 Cyclotrimerization of Arynes Derived from Biphenylene

Palladium-catalyzed cyclotrimerization has recently been applied to arynes derived from biphenylene in order to synthesize novel polycyclic architectures with potential interest as functional organic materials. The *o*-(trimethylsilyl)-biphenylenyl triflates **91a** and **91b**, which are required as aryne precursors, are efficiently prepared by the route shown in Scheme 19. 2,3-Di(trimethylsilyl)-biphenylenes **89a** and **89b**, obtained by cobalt-catalyzed [2+2+2] cycloaddition of diethynylarenes **88a** and **88b** to bis(trimethylsilyl)acetylene, are selectively monobrominated, and the resulting bromide is treated with *n*-BuLi and $B(OMe)_3$, affording boronic acids **90a** and **90b**. Oxidation, and trapping of the resulting biphenylenols with Tf_2O, gives triflates **91a** and **91b** in good overall yields [53].



Scheme 19

Treatment of **91a** with Bu_4NF in acetonitrile at room temperature generates 2,3-didehydrobiphenylene (**92a**), which in the presence of 10 mol% $Pd(PPh_3)_4$ cyclotrimerizes in 62% yield to tris(benzocyclobutano)triphenylene **93a**, a highly insoluble bright yellow solid that is difficult to purify and characterize. The soluble hexakis-substituted derivative **93b** is obtained with similar efficiency from triflate **91b** (Scheme 20) [53]. Trimers **93** are the first members of a novel class of compounds that are structurally related to the [*N*]phenylenes, a family of polycyclic hydrocarbons that have received great attention because of their unique combination of aromatic and antiaromatic character and because their physical properties offer promise for the development of conducting and/or magnetic materials [54].

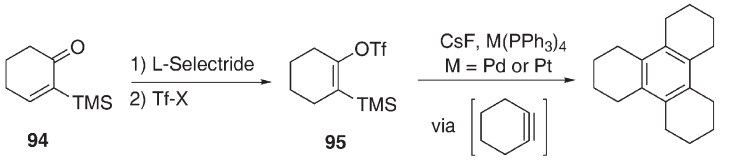


Scheme 20

2.4.3 Cyclotrimerization of Strained Cycloalkynes

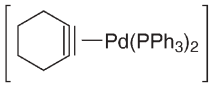
Although they are not arynes, and are therefore not covered by the title of this chapter, it is perhaps not inappropriate to note here that transition-metal-catalyzed cyclotrimerization has been successfully applied to a number of strained cycloalkynes. For example, cyclohexyne (**96**) undergoes [2+2+2] cycloaddition to form dodecahydrotriphenylene (**97**) in 65% yield, a reaction that can be promoted by either $Pd(PPh_3)_4$ or $Pt(PPh_3)_4$ with identical efficiency [55]. In this case the synthesis of the cycloalkyne precursor **95** requires a modified procedure, involving the conjugate addition of hydride to ketone **94** and trapping of the resulting enolate with *N*-phenyltriflimide (Scheme 21) [56].

Interestingly, when this reaction is monitored by ^1H NMR, there is a signal at δ=2.61 ppm that disappears upon completion of the reaction and has been



Scheme 21

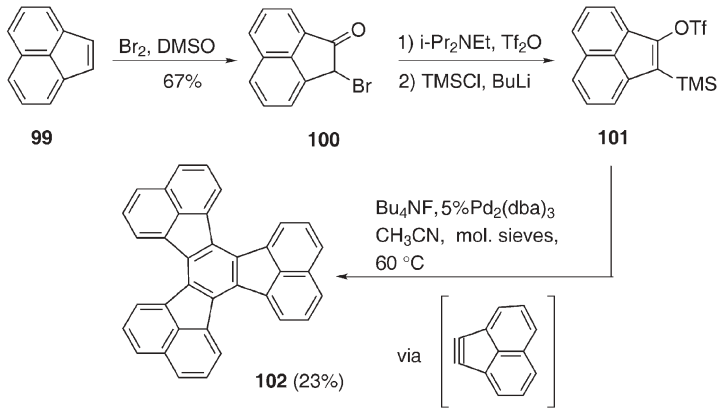
attributed to the transient formation of the known cyclohexyne–palladium complex **98** [57], which would be in keeping with a mechanism similar to that previously proposed for benzyne (Fig. 6).



98

Fig. 6 Cyclohexyne–palladium complex

A further test of this methodology was the cyclotrimerization of the more severely strained cycloalkyne **5**. The synthesis of the corresponding triflate **101** involves some modification of the general procedure. It starts with the transformation of acenaphthylene (**99**) into bromoketone **100** by one-pot bromination–oxidation with bromine and DMSO. The transformation of **100** into **101** is accomplished by enolization with Hünig's base and trapping with Tf_2O, followed by lithium–bromine exchange and silylation of the resulting carbanion with TMSCl. Attempts at generation and trimerization of the highly strained acenaphthyne **5** in the reaction conditions developed for arynes and cyclohexyne [CsF, $Pd(PPh_3)_4$, acetonitrile, rt] afforded very low yields of cyclotrimer, but forced reaction conditions involving Bu_4NF as fluoride source, $Pd_2(dba)_3$ as catalyst and higher reaction temperature gave decacyclene (**102**) in acceptable yields (Scheme 22) [55]. Although the reaction is thought to involve cycloalkyne **5**, an alternative mechanism involving the initial oxidative addition of the C–OTf bond to palladium cannot be ruled out, particularly considering the higher reaction temperatures at which this reaction takes place.



99 **100** **101**

102 (23%)

5

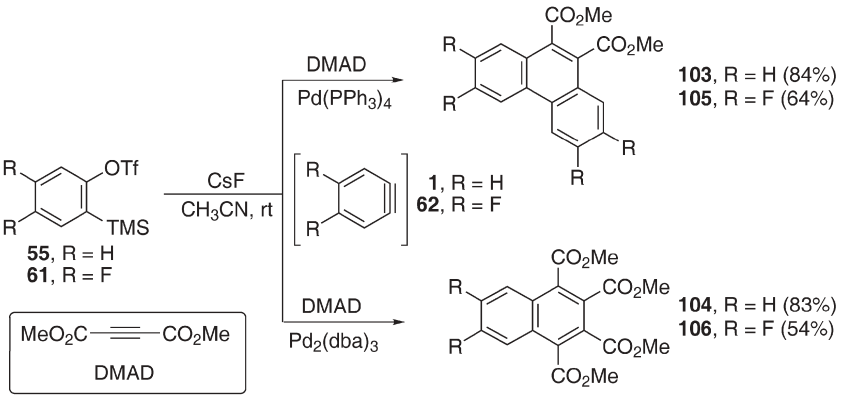
Scheme 22

3
Palladium-Catalyzed Cocycloaddition of Arynes and Alkynes

After discovering that arynes undergo palladium-catalyzed cyclotrimerizations in a similar way as alkynes [39], it is reasonable to wonder with what generality it is possible to carry out mixed [2+2+2] cycloadditions, that is, cocycloadditions of arynes and alkynes or other unsaturated species. They are certainly possible, the insertion of two molecules of alkyne into a metal–benzyne complex to obtain naphthalene derivatives being a known process (Scheme 9) [28, 29]. Intermolecular [2+2+2] cycloadditions of different alkynes usually take place with poor chemoselectivity, leading to mixtures of all possible cocycloaddition products, which limits the synthetic utility of these reactions. Previous solutions to this problem have consisted in partial intramolecular cyclotrimerizations of α,ω-diynes with monoalkynes [30] or in reaction of a preformed metallacyclopentadiene with a third alkyne [58, 59]. Purely intermolecular selective cocyclotrimerizations are rare, and the known examples are usually based on the individual alkynes having very different reactivities for simple cyclotrimerization [60]. Now analysis of the literature on palladium-catalyzed cyclotrimerizations suggests that arynes and alkynes have very different reactivities: while arynes, which are strongly electrophilic, are efficiently cyclotrimerized by Pd(0) catalysts [39], there are few examples of efficient cyclotrimerization of alkynes using these complexes [61, 62]. This difference in reactivity between arynes and alkynes in Pd-catalyzed cyclotrimerizations, rather than being a disadvantage, provides the chemoselectivity required for their cocyclization to be synthetically useful. Interestingly, cocyclizations of arynes and alkynes frequently show marked dependence on factors such as the electronic nature of the alkyne, the catalyst structure, or the reaction conditions.

3.1
Palladium-Catalyzed [2+2+2] Cocycloaddition of Arynes and DMAD

Electron-deficient alkynes and arynes often have similar reactivities, in particular when they act as dienophiles in cycloaddition reactions or as ligands of electron-rich metals such as palladium. Nevertheless, the palladium-catalyzed cocycloaddition of benzyne (**1**) and dimethylacetylene dicarboxylate (DMAD) is remarkably chemoselective, although all four possible [2+2+2] cycloaddition products are found to some extent in the reaction mixture [63]. When the cycloaddition is promoted by 10 mol% of $Pd(PPh_3)_4$ in acetonitrile at room temperature, phenanthrene **103**, resulting from the cocyclization of two aryne units and one alkyne, is obtained in 84% yield, while naphthalene **104**, resulting from the reaction of one aryne unit and two alkynes, is obtained in only 7% yield (Scheme 23). Small amounts of triphenylene (**56**, 2% yield) are also obtained. Remarkably, even the use of a large excess of the alkyne (10 equiv) fails to afford naphthalene **104** as the major product of the reaction under these reaction conditions. Even more astonishing is that when 5 mol% of $Pd_2(dba)_3$ is used as



Scheme 23

catalyst under similar conditions, the chemoselectivity is completely inverted, naphthalene **104** being obtained as the major product (83% yield) together with only small amounts of phenanthrene **103** (10% yield).

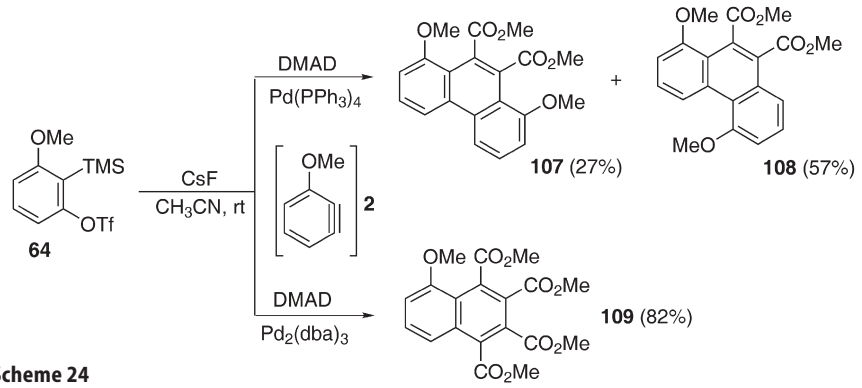
Experimental Procedures for the Palladium-Catalyzed Cocycloaddition of Arynes and DMAD

Procedure a (cycloaddition of two molecules of aryne with one molecule of DMAD) – A solution of the aryne precursor (0.5 mmol) in CH_3CN (5 mL) is added to a suspension of finely powdered anhydrous CsF (2 equiv), DMAD (1.4 equiv) and $Pd(PPh_3)_4$ (0.1 equiv) in CH_3CN (5 mL). The mixture is stirred under argon at room temperature for 12 h. The solvent is evaporated, and the residue is subjected to column chromatography to isolate the products. Procedure b (cycloaddition of one molecule of aryne with two molecules of DMAD) – As for procedure a, but using a larger excess of DMAD (5 equiv) and $Pd_2(dba)_3{\cdot}CHCl_3$ (0.05 equiv) as catalyst.

The same chemoselectivity is observed in the reaction of substituted arynes with DMAD [63]. The cocycloaddition of 4,5-difluorobenzyne (**62**), when promoted by $Pd(PPh_3)_4$, affords phenanthrene **105** as major product (64%), accompanied by minor amounts of naphthalene **106** (8%) and hexafluorotriphenylene (**63**, 8%). However, using $Pd_2(dba)_3$ the selectivity is inverted, naphthalene **106** being obtained in 54% yield and phenanthrene **105** in 9% yield (Scheme 23).

The cocycloaddition of 3-methoxybenzyne (**2**), though complicated by the formation of regioisomers, also proceeds with high chemoselectivity. The use of $Pd(PPh_3)_4$ as catalyst affords a mixture of phenanthrenes **107** and **108** (overall yield 84%) and small amounts of naphthalene **109** (7%), while $Pd_2(dba)_3$ promotes the formation of naphthalene **109** in 82% yield (Scheme 24) [63].

It is possible to explain this high chemoselectivity by once more assuming a mechanism similar to the one generally accepted for alkyne cyclotrimeriza-



Scheme 24

tions, and the formation of different intermediate palladium complexes depending on the nature of the ligands coordinated to palladium in each complex. In the experiments carried out using $Pd(PPh_3)_4$ there takes place the initial formation and eventual disappearance of complex **110** [64], which is assumed to be one of the intermediates involved in the formation of the phenanthrenes by reaction of DMAD with two molecules of aryne. The presence of strongly coordinated triphenylphosphine as ligand prevents the coordination and subsequent reaction of another molecule of DMAD with complex **110** (Fig. 7). By contrast, the "lightly stabilized" complex $Pd_2(dba)_3$ is expected to form complex **111** [61, 62, 65], which upon reaction with a molecule of aryne would directly afford the naphthalenes.

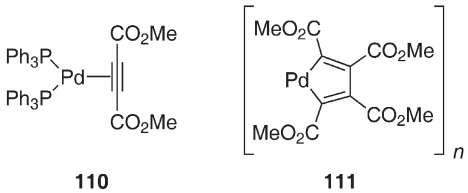
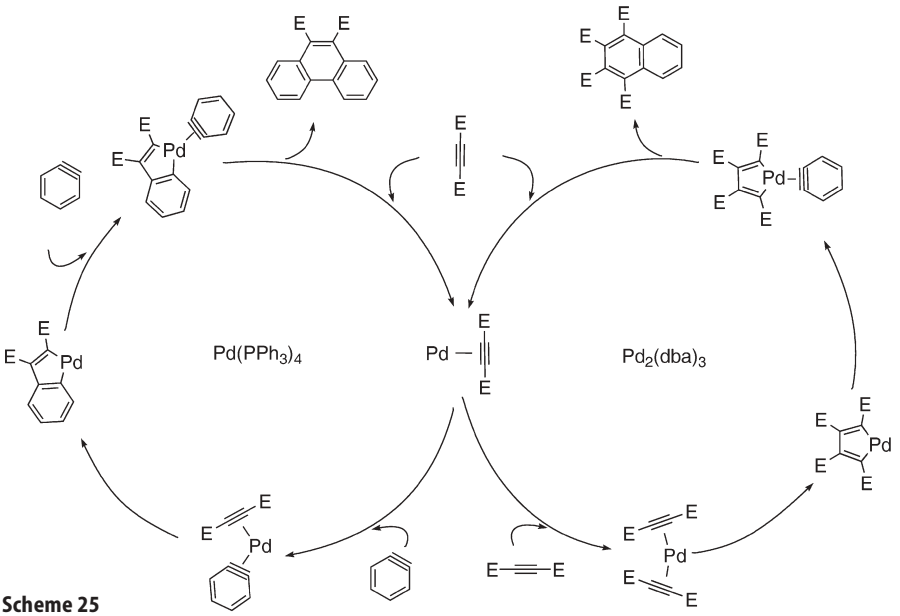


Fig. 7 Intermediates in the palladium-catalyzed [2+2+2] cocycloaddition of arynes and DMAD

Scheme 25 shows plausible mechanisms for both the $Pd(PPh_3)_4$-catalyzed and the $Pd_2(dba)_3$-catalyzed cocycloadditions of benzyne and DMAD. Although further investigation is needed to determine these mechanisms in detail, a pathway similar to the one generally accepted for alkyne cyclotrimerization is consistent with reports on the reactivity of aryne complexes of group 10 elements [66].

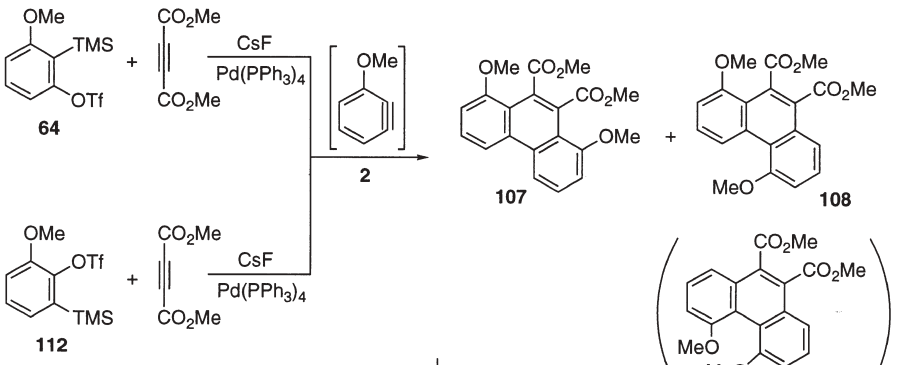
An alternative mechanism, initiated by oxidative addition of the aryl triflate to palladium, cannot be completely ruled out but is unlikely, since in the absence of CsF the starting materials remain unaltered even in the presence of



Scheme 25

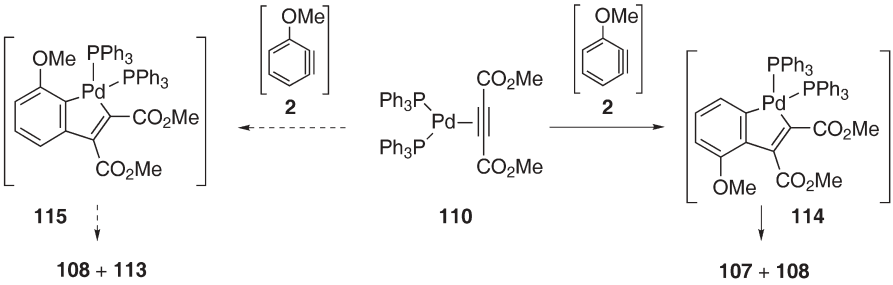
other bases such as triethylamine, or when alkenes are used as reaction partners. Additional evidence for a mechanism involving the free aryne is shown in Scheme 26. The $Pd(PPh_3)_4$-catalyzed cocycloaddition of DMAD with triflates **64** and **112**, both of which are precursors of 3-methoxybenzyne (**2**), leads to the isolation of the same regioisomers (**107** and **108**) in nearly identical ratios (approx. 1:2) [67], which strongly suggests that both reactions are mediated by **2**.

On the basis of the mechanism shown in Scheme 25, the isolation of phenanthrenes **107** and **108** but not **113** can be explained as due to the formation of



Precursor	108/ 107
64	2.1
112	1.9

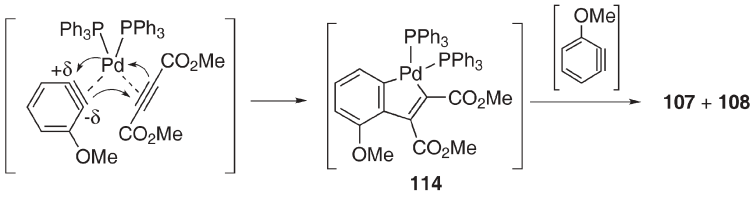
Scheme 26



Scheme 27

palladacycle **114** as intermediate (Scheme 27). The formation of the other possible palladacycle (**115**) would be inhibited by unfavourable steric interaction between the methoxy group of the aryne moiety and the triphenylphosphine coordinated to the metal centre. Subsequent reaction of complex **114** with 3-methoxybenzyne (**2**) would afford **107** or **108**.

In the selective formation of palladacycle **114**, electronic factors may also play a role. It is known that the presence of a 3-methoxy substituent in an aryne gives the triple bond a partial positive charge *meta* to the methoxy group [2, 3]. It is therefore reasonable to expect an electron-rich metal to attack at this position, resulting in the formation of intermediate **114** (Scheme 28).

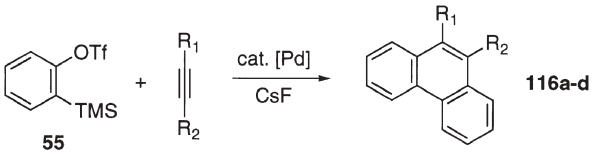


Scheme 28

3.2
Palladium-Catalyzed [2+2+2] Cocycloaddition of Arynes and Other Alkynes

Application of the reaction conditions optimized for DMAD to other alkynes affords somewhat lower yields of the cycloaddition products, and can elicit different chemoselectivities [63]. While the $Pd(PPh_3)_4$-catalyzed reaction of benzyne with hexafluoro-2-butyne affords the corresponding phenanthrene **116a** in good yield (entry 1 in Table 3), the reaction with ethyl 2-butynate only gives **116b** with $Pd_2(dba)_3$ as catalyst, suggesting that triphenylphosphine prevents the coordination of less electrophilic alkynes (entry 2). Small amounts of the corresponding naphthalenes are also detected in both cases. More electron-rich alkynes (entries 3 and 4) afford the corresponding products **116c,d** in poor yield even with $Pd_2(dba)_3$ as catalyst and a large excess of alkyne (but see below).

Table 3 Palladium(0)-catalyzed cocycloaddition of arynes and alkynes

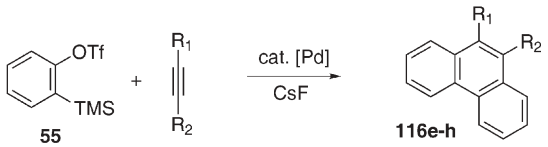


Entry	Alkyne	cat. [Pd]	Procedure	**116a-d** (% yield)	Triphenylene (**56**)
1	R_1=R_2=CF_3	$Pd(PPh_3)_4$	A	**116a** (65)	20
2	R_1=Me, R_2=CO_2Et	$Pd_2(dba)_3$	B	**116b** (63)	10
3	R_1=R_2=Et	$Pd_2(dba)_3$	B	**116c** (28)	23
4	R_1=R_2=Ph	$Pd_2(dba)_3$	A	**116d** (34)	26

A: 10 mol% [Pd], CsF (2 equiv), 18-crown-6 (3 equiv), toluene, rt.
B: 5 mol% [Pd], CsF (2 equiv), CH_3CN, rt.

Yamamoto and co-workers developed a catalytic system [$Pd(OAc)_2$/P(*o*-tol)$_3$ in CH_3CN, 60 °C] which turns out to be especially useful for cocycloaddition of electron-rich alkynes and arynes [68]. It allows phenanthrenes **116e–h** to be obtained in reasonable yields, accompanied by only trace amounts of triphenylene (**56**, Table 4).

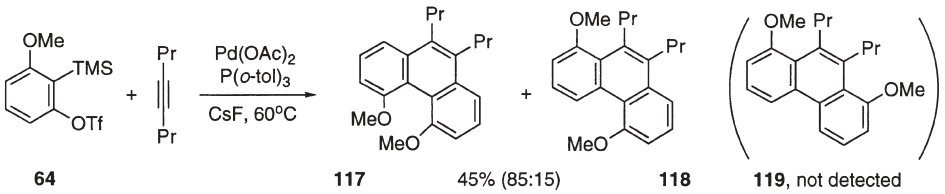
Table 4 Palladium(II)-catalyzed cocycloaddition of arynes and alkynes



Entry	Alkyne	**116e-h** (% yield)
1	R_1=R_2=*n*-Pr	**116e** (63)
2	R_1=R_2=CH_2OMe	**116f** (59)
3	R_1=Ph, R_2=Me	**116g** (67)
4	R_1=Ph, R_2=COMe	**116h** (76)

Proc.: 5 mol% $Pd(OAc)_2$, 5 mol% P(*o*-tol)$_3$, CsF (2 equiv), CH_3CN, 60 °C.

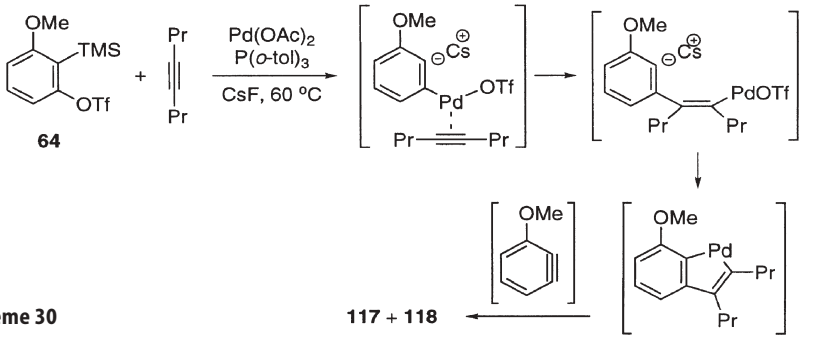
Curiously, the mixture of regioisomers obtained in the reaction of the benzyne precursor **64** under these conditions (Scheme 29) is not the same as is obtained under the conditions mentioned above for cocycloadditions of DMAD (Scheme 26). This result, together with the participation of electron-rich alkynes and the requirement of higher reaction temperatures, suggests that the



Scheme 29

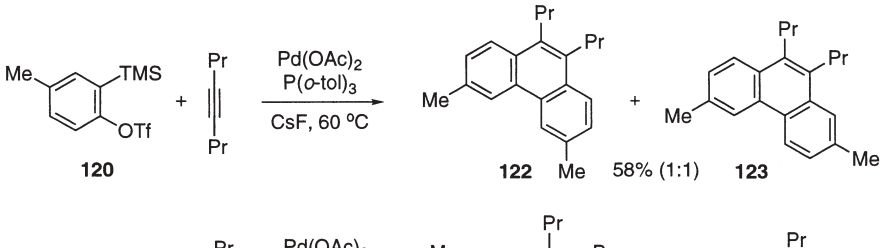
mechanism of this transformation differs from that of the reaction with Pd(0) complexes at room temperature (discussed above).

Under Yamamoto's conditions the reaction probably takes place by oxidative addition of the C–OTf bond to Pd(0) and subsequent carbopalladation of the aryl–Pd bond to the triple bond of the alkyne, as shown in Scheme 30 [69].



Scheme 30

The hypothesis of a mechanism involving oxidative addition of the aryl triflate bond to palladium is further supported by comparing the mixtures of phenanthrenes that are obtained when the $Pd(OAc)_2/P(o\text{-tol})_3$ catalytic system is applied to the regioisomeric triflates **120** and **121**. Since both these triflates

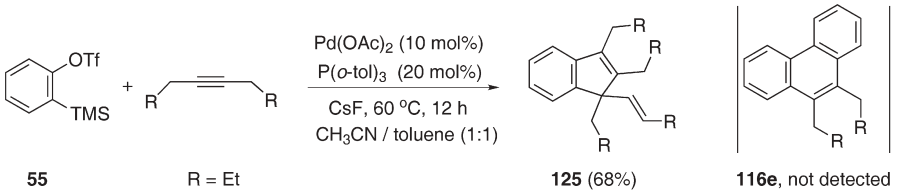


Scheme 31

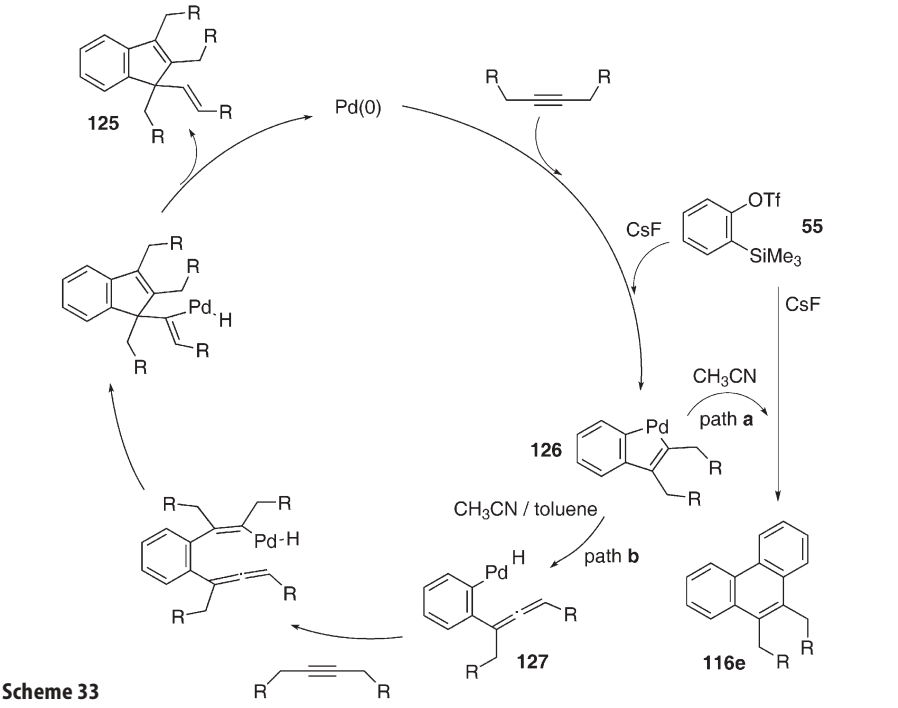
lead to the same aryne (4-methylbenzyne), the mechanism of Scheme 25, in which the triflate serves only to generate this aryne, would afford the same regioisomeric phenanthrenes in similar ratios. However, under Yamamoto's conditions triflate **120** actually leads to phenanthrenes **122** and **123**, while triflate **121** affords **123** and **124** (Scheme 31).

Moreover, the results obtained using Yamamoto's catalytic system are remarkably sensitive to the solvent. When a 1:1 mixture of CH_3CN and toluene is used, the reaction of **55** and 4-octyne affords indene **125** instead of the expected phenanthrene **116e** (Scheme 32).

This unexpected result is plausibly due to the rate of generation of benzyne depending on the solvent used [69]. As in Scheme 30, the key intermediate is presumed to be the result of an oxidative addition–carbopalladation sequence, i.e. palladacycle **126.** In CH_3CN, this metal complex would react with benzyne



Scheme 32



Scheme 33

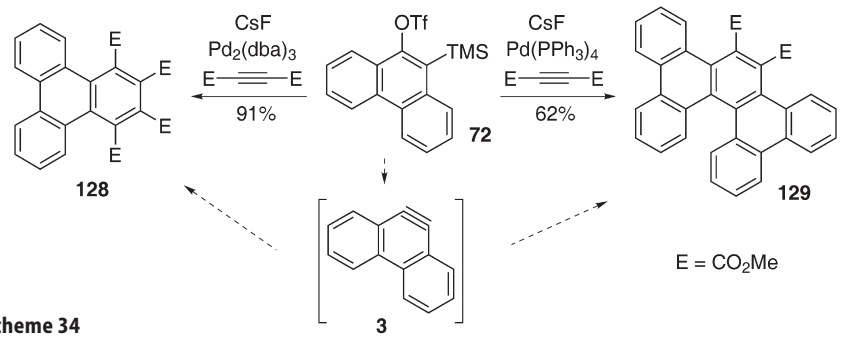
following path **a** to afford phenanthrene **116e.** However, in a mixture of CH_3CN and toluene, the solubility of CsF drops significantly. Therefore the generation of benzyne is slower and palladacycle **126** would evolve via path **b**, which means β-hydride elimination to generate allenyl intermediate **127.** Alkyne insertion into the aryl–Pd bond of **127** followed by carbopalladation of the alkenyl–Pd bond to the aryl-substituted double bond of the allenyl moiety, and reductive elimination of Pd(0), would lead to the indene derivative **125** (Scheme 33).

3.3 Synthetic Applications of Palladium-Catalyzed Cocycloaddition of Arynes and Alkynes

Although the palladium-catalyzed cocyclization of arynes and alkynes is still in its infancy, the synthetic potential of this novel methodology has already been explored.

3.3.1 Synthesis of Polycyclic Aromatic Hydrocarbons

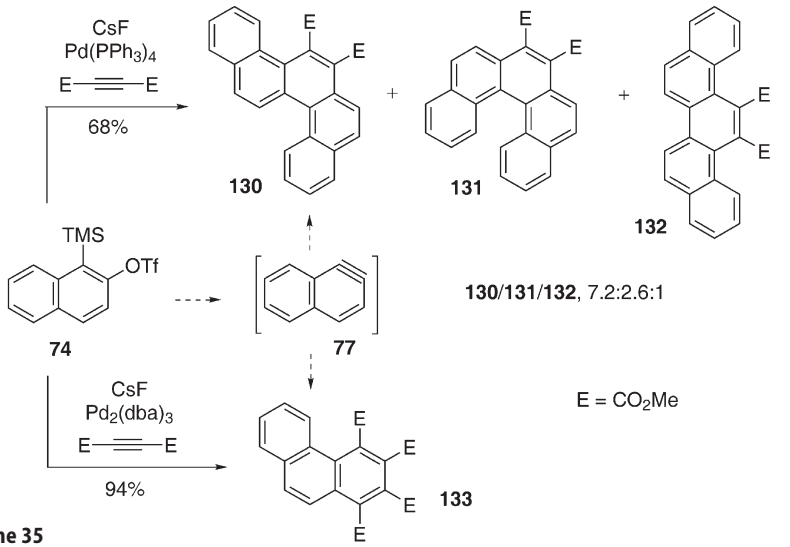
Palladium catalysts have been used for cycloaddition of dimethylacetylene dicarboxylate (DMAD) to polycyclic arynes **3**, **77** and **79** (Schemes 34–36). All these reactions exhibit the same reactivity pattern as is observed in the [2+2+2] cycloaddition of benzyne to DMAD (see Sect. 3.1): $Pd_2(dba)_3$ leads selectively to the cocycloaddition of one molecule of aryne and two molecules of DMAD, while $Pd(PPh_3)_4$ induces the reaction of two molecules of aryne with one molecule of DMAD. Both reactions afford the corresponding polycyclic aromatic hydrocarbons in good yields and with high chemoselectivity, constituting a novel and versatile method for the synthesis of functionalized PAHs under mild reaction conditions [70–72] (Scheme 34).



Scheme 34

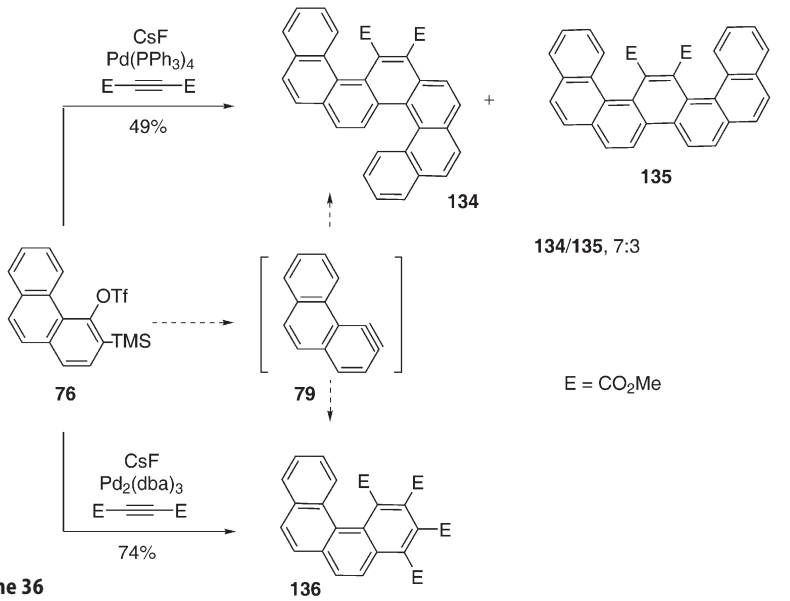
In the cocyclization of two molecules of the asymmetric aryne **77** and one molecule of DMAD, a mixture of all the possible regioisomers is formed

(Scheme 35) [70]. As in the cyclotrimerizations of arynes, there is no clear explanation for the regioselectivity of this reaction.



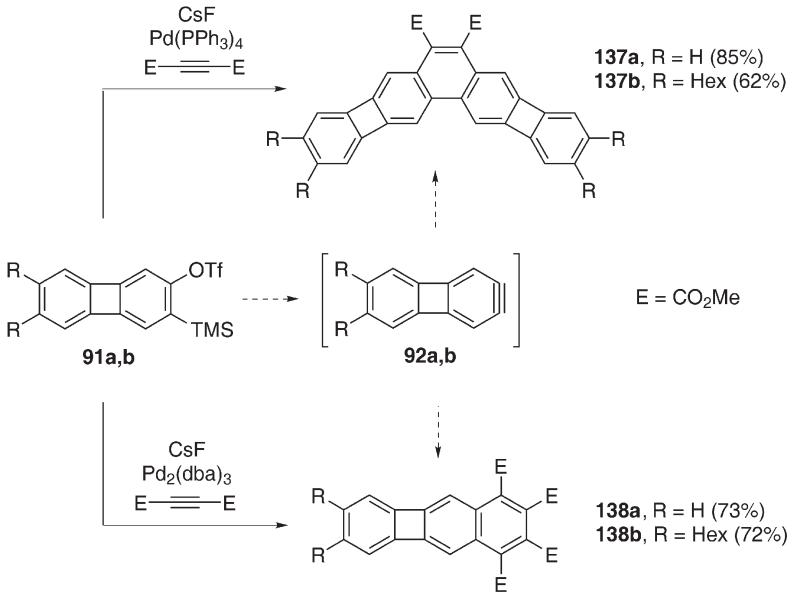
Scheme 35

The same is true of the cocyclization of two molecules of aryne **79** and one molecule of DMAD, in which only the formation of regioisomers **134** and **135** is observed (Scheme 36) [70].



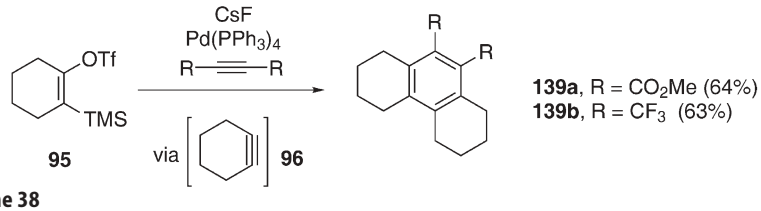
Scheme 36

2,3-Didehydrobiphenylenes **92a** and **92b** also exhibit the above chemoselectivity pattern in their reactions with DMAD. Thus, the use of $Pd(PPh_3)_4$ as catalyst affords bis(benzocyclobutadiene)phenanthrenes **137a** and **137b** as major products, while $Pd_2(dba)_3$ yields benzobiphenylenes **138a** and **138b** in good yields (Scheme 37)[53].



Scheme 37

This cocycloaddition is also effective in the reaction of two molecules of cyclohexyne (**96**) with electron-poor alkynes, which afford octahydrophenanthrenes **139a** and **139b** (Scheme 38). In this case, however, it was not possible to direct the reaction to the construction of the corresponding tetrahydronaphthalenes, by using $Pd_2(dba)_3$ as catalyst, even when a large excess of alkyne was employed [72].

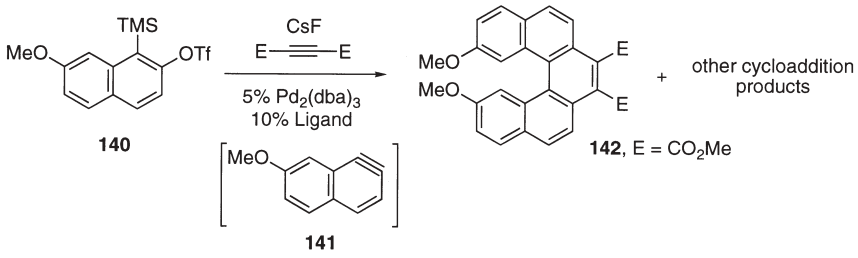


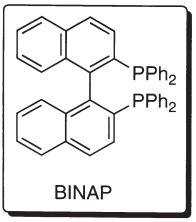
Scheme 38

3.3.2
Enantioselective Synthesis of Helicenes

Several polyarenes obtained by palladium-catalyzed cocycloaddition of arynes and DMAD are conformationally stable chiral helicenes. For example, cocycloaddition of aryne **141** and DMAD affords a mixture of polyarenes from which helicene **142** can be isolated in yields up to 30%. Furthermore, this reaction proceeds with good enantioselectivity when performed in the presence of chiral bidentate ligands such as BINAP, which leads to an ee of 67% when the solvent is THF (Table 5, entry 2) [73].

Table 5 Palladium-catalyzed enantioselective synthesis of helicenes





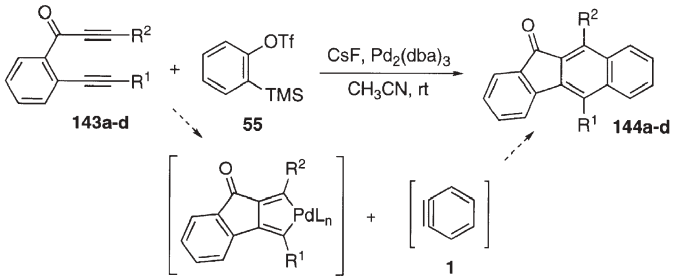
Entry	Ligand	**142** (ee, %)	Major enantiomer
1	(*R*)-BINAP	42	M
2	(*R*)-BINAP	67	M
3	(*R*)-Tol-BINAP	17	M
4	(-)-DIOP	27	P
5	(2*S*,4*S*)-BPPM	5	P
6	(*S*,*S*)-CHIRAPHOS	5	M
7	(*R*,*R*)-Me-DuPhos	-	-

Using CH_3CN as solvent, except entry 2 (THF)

3.3.3
Partially Intramolecular [2+2+2] Cocycloaddition of Arynes and Diynes

Intramolecular or partially intramolecular cycloaddition reactions are extremely useful tools in the synthesis of polycyclic molecules, since they can allow the construction of several rings in a single step. Preliminary studies indicate that this general principle also holds for partially intramolecular versions of the palladium-catalyzed cocycloaddition of arynes and alkynes. For example, benzo[*b*]fluorenones **144a–d**, which constitute the polycyclic skeleton of the kinamycin family of antitumour antibiotics, can be obtained by [2+2+2] cy-

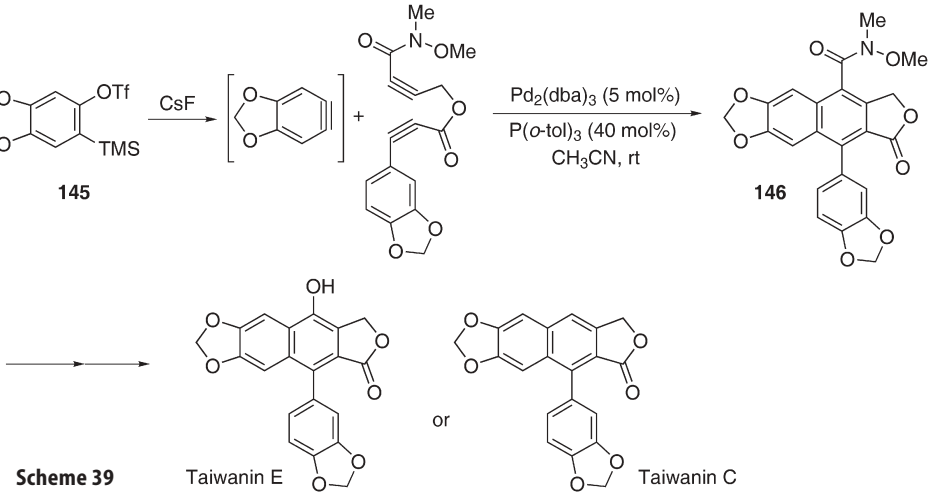
Table 6 Partially intramolecular cocycloaddition of arynes and alkynes



Entry	Benzodiyne **143a-d**	**144a-d** (% yield)
1	R^1 = Pr, R^2 = CO_2Et	**144a** (38)
2	R^1 = *t*-Bu, R^2 = CO_2Et	**144b** (24)
3	R^1 = Ph, R^2 = CO_2Et	**144c** (54)
4	R^1 = R^2 = Pr	**144d** (9)

cloaddition of benzyne (**1**) and benzodiynes **143a–d**, the yield of the reaction depending on the steric and electronic properties of the diyne (Table 6) [74].

Arylnaphthalene skeletons (**146**) can also be synthesized by partially intramolecular palladium-catalyzed [2+2+2] cocycloaddition of arynes and diynes. Indeed, this reaction is the key step in an elegant convergent total synthesis of taiwanins C and E (Scheme 39) [75].



Scheme 39

4
Other Metal-Catalyzed Cycloadditions of Arynes

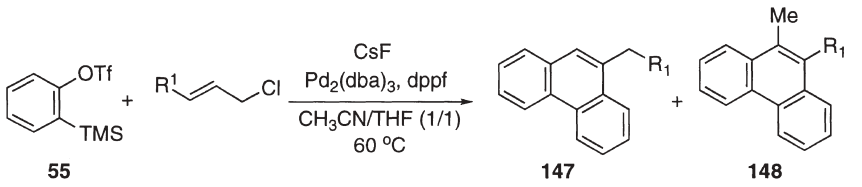
Although interest in metal-catalyzed cycloaddition reactions of arynes has mostly focused on reactions with alkynes, they have also proved synthetically useful in reactions with other species, such as allyl derivatives, CO or allenes.

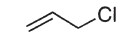
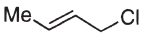
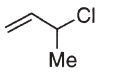
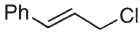
4.1
Palladium-Catalyzed Cycloaddition of Benzyne with Allyl Derivatives

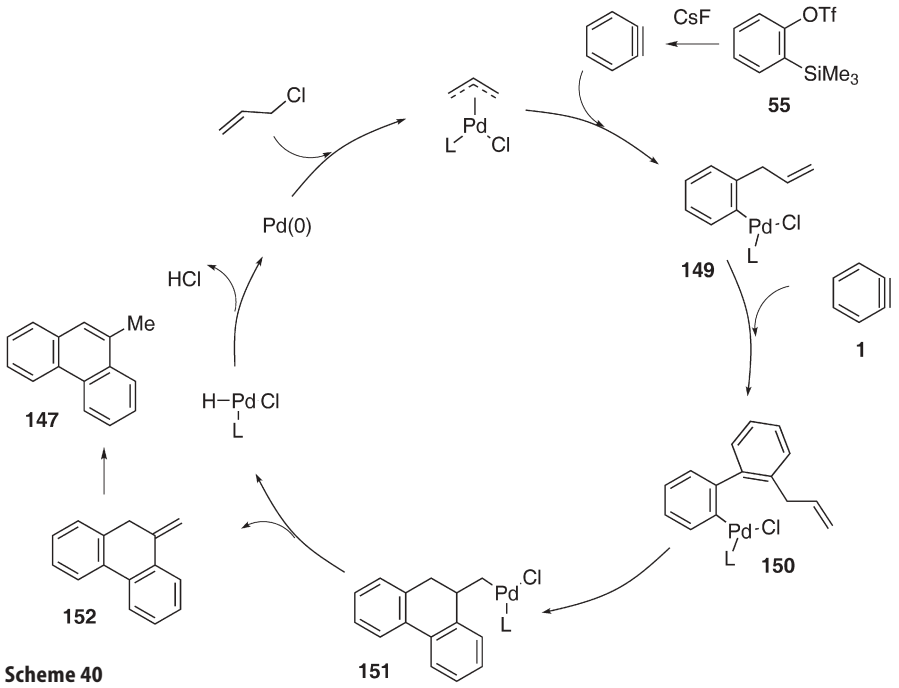
Benzyne is highly reactive as a carbopalladation partner of π-allyl palladium chloride, producing phenanthrene derivatives **147** and **148** (Table 7) [76]. A plausible mechanism for this benzyne–benzyne–alkene insertion is shown in Scheme 40. Initially a π-allyl palladium complex is formed by reaction of the allyl chloride derivative with palladium. Insertion of benzyne in a carbon–metal bond then affords the intermediate **149** (in the case of substituted allyl chlorides, two regioisomers are produced at this stage, leading to the final mixture of phenanthrenes **147** and **148**). A second benzyne insertion, this time into the Pd–aryl bond of **149**, now gives complex **150**, which undergoes intramolecular carbopalladation of the alkene affording intermediate **151**. Finally, β-hydride elimination produces **152**, which isomerizes to phenanthrene **147** [69, 76].

An interesting generalization of the above reactions consists in the inclusion of an alkyne among the reagents. Since π-allyl palladium complexes have low reactivity as regards the intermolecular insertion of ordinary alkynes, this makes controlled benzyne–alkyne–alkene insertion possible (Scheme 41) [76].

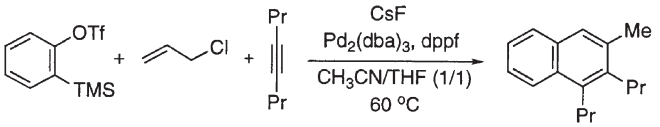
Table 7 Palladium-catalyzed cycloaddition of benzyne with allyl derivatives



Entry	Allyl chloride	R_1	Yield (**147**/**148**)
1		H	69
2		Me	66 (58:42)
3		Me	70 (65:35)
4		Ph	56 (70:30)



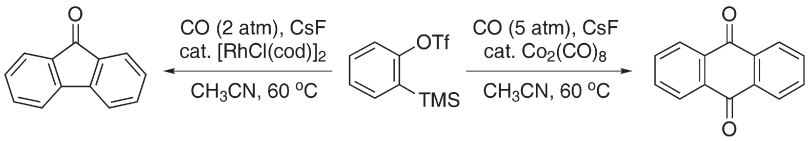
Scheme 40



Scheme 41 **55** **153** (47%)

4.2 Metal-Catalyzed Carbonylative Cycloaddition Reactions of Benzyne

Metal-catalyzed cocycloaddition of arynes and other unsaturated species, such as CO, has also been accomplished [77]. Generation of benzyne from *o*-(trimethylsilyl)phenyl triflate (**55**) under CO in the presence of catalyst based on Rh, Pd or Pt leads to moderate yields of fluorenone (**154**) through

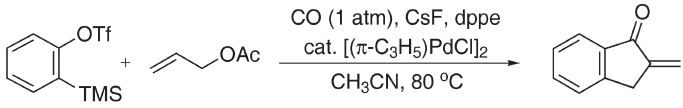


154 (30%) **55** **155** (71%)

Scheme 42

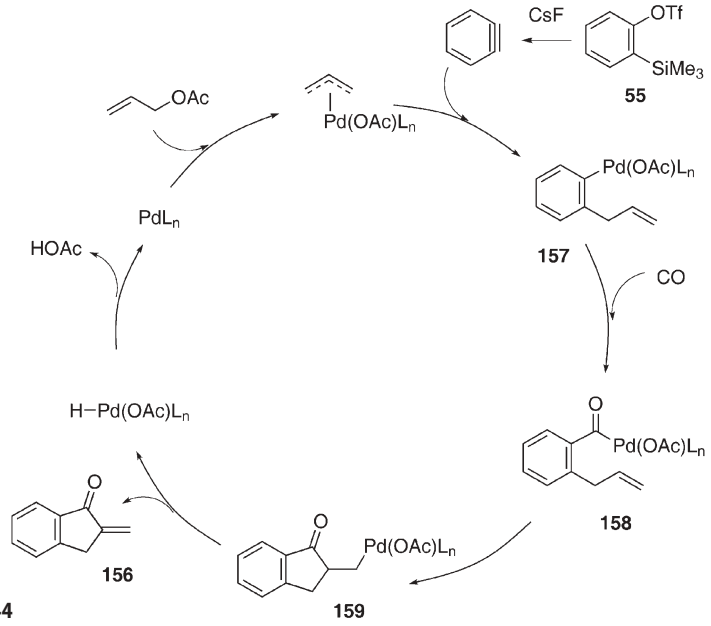
a formal [2+2+1] cycloaddition reaction, and catalysis by $Co_2(CO)_8$ gives the [2+2+1+1] cycloaddition product anthraquinone (**155**) as the major product [78] (Scheme 42).

Remarkably, the use of a palladium catalyst for cocycloaddition of benzyne and allyl acetate under CO results in a new type of carbonylation, affording 2-methylindanone (**156**) in a three-component cycloaddition reaction [78] (Scheme 43).



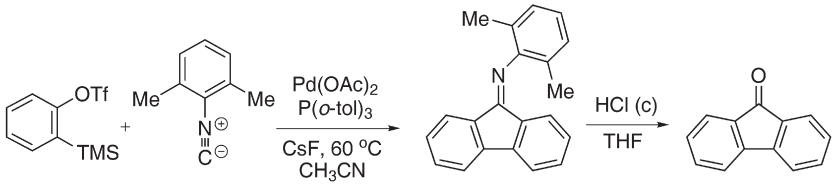
Scheme 43 **55** **156** (80%)

According to the proposed reaction mechanism (Scheme 44), carbopalladation of benzyne with the π-allyl palladium complex gives intermediate **157**. Insertion of CO in the palladium–aryl bond then leads to the acyl palladium complex **158**, which undergoes intramolecular cyclization and subsequent β-hydride elimination, affording indanone **156** [78].



Scheme 44

Palladium-catalyzed reactions of arynes with isocyanides also afford the corresponding [2+2+1] cycloaddition products [67]. For instance, reaction of triflate **55** with isocyanide **160** leads to fluorenimine (**161**), which can be hydrolysed to fluorenone (**154**) (Scheme 45).

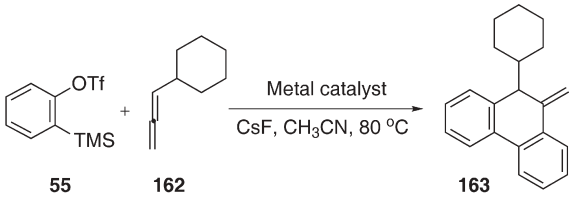


55 **160** **161** (40%) **154** (89%)

Scheme 45

4.3
Metal-Catalyzed Cocyclotrimerization of Arynes and Allenes

Another family that can participate in metal-catalyzed cocyclotrimerization with arynes are the terminal allenes (e.g. **162**). This cocycloaddition is best catalyzed by Ni(0), and leads in the case of **162** to 9-cyclohexyl-10-methylene-9,10-dihydrophenanthrene (**163**). For monosubstituted allenes the reaction appears to be highly selective, since only the internal C–C double bond of the allene participates in the cocyclotrimerization. With disubstituted allenes, mixtures of the two possible regioisomers are obtained as the result of the participation of both C–C double bonds in the cycloaddition reaction [79, 80] (Scheme 46).



55 **162** **163**

Metal catalyst	Yield
$NiBr_2$(dppe) / Zn	67%
$Pd(PPh_3)_4$	34%

Scheme 46

Acknowledgements Financial support from the DGES (BQU2000-0464) and PGIDT (01PXI20902PN) is gratefully acknowledged.

References

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Palladium-Catalyzed Annulation of Alkynes

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Abstract Palladium readily catalyzes the cross-coupling of functionally substituted aryl or vinylic halides and alkynes to afford a wide variety of heterocycles and carbocycles in one efficient step. Terminal alkynes presumably initially generate aryl (vinylic) alkynes, which under the reaction conditions are rapidly cyclized by the palladium or copper salts employed in the first step to produce the final product. Internal alkynes apparently react by carbopalladation of the alkyne and subsequent intramolecular nucleophilic substitution of the palladium moiety to generate the observed products. A variety of other closely related processes have also been reported, including the simultaneous annulation of alkynes and car-

bon monoxide to produce carbonyl products. The reactions generally tolerate considerable functionality, proceed in good yields, and generate a wide variety of hetero- and carbocyclic products, making these processes extremely valuable in organic synthesis.

Keywords Palladium · Catalysis · Alkyne · Heterocycle · Carbocycle

Abbreviations

Ac	Acetyl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
cod	*cis*,*cis*-1,5-Cyclooctadiene
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMA	*N*,*N*-Dimethylacetamide
DMF	*N*,*N*-Dimethylformamide
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1′-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
L	Ligand
MOM	Methoxymethyl (CH_3OCH_2)
NBS	*N*-Bromosuccinimide
phen	1,10-Phenanthroline
PMB	*p*-Methoxybenzyl
PPA	Polyphosphoric acid
Tf	Trifluoromethanesulfonyl
Ts	*p*-Toluenesulfonyl

1 Introduction

Annulation reactions are among the most important processes in organic synthesis, because they rapidly generate organic structures with substantially increased molecular complexity. In previous work, we and others have demonstrated the ease with which palladium can catalyze a wide variety of annulations involving: functionally substituted aromatic or vinylic halides and 1,2-, 1,3-, or 1,4-dienes; unsaturated cyclopropanes or cyclobutanes; cyclic or bicyclic alkenes; and alkynes. Much of that work was reviewed in 1999 [1, 2]. Considerable work has appeared recently on the palladium-catalyzed annulation of both terminal and internal alkynes by functionally substituted aryl and vinylic halides to produce a wide variety of heterocycles and carbocycles. That work will be the focus of this review.

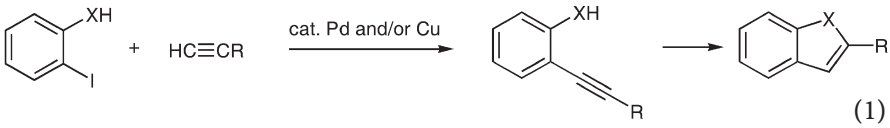
This review will not attempt to cover the many important reactions of functionally substituted alkynes where Pd(II) salts or organopalladium compounds (RPdX) react with the alkyne to promote cyclization onto the functionality already residing in the alkyne unit. That work has recently been reviewed by the present author in a separate book chapter, along with a large number of other

electrophilic cyclizations of alkynes. Annulations closely related to those reported here, but employing metals other than palladium, will only be included when they effect essentially the same transformation described here. The many other related transition metal-catalyzed annulation processes reported in recent years will not be covered here.

2
Annulation of Terminal Alkynes

2.1
Introduction

Palladium-catalyzed annulations of terminal alkynes by functionally substituted aromatic or vinylic halides or triflates often employ copper salts and most likely proceed by initial cross-coupling to produce the corresponding aryl alkyne or enyne (Eq. 1).

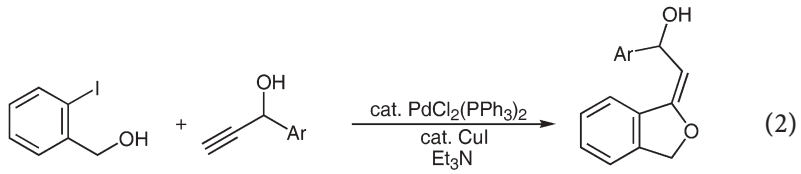


(1)

This process is commonly known as the Sonogashira reaction and has proven extraordinarily useful for the synthesis of a wide variety of aryl alkynes or enynes. When neighboring functionality exists, Pd and Cu salts are well known to effect cyclization to the corresponding hetero- or carbocycle. Thus, the reaction of terminal alkynes and aryl or vinylic halides bearing neighboring functionality often leads directly to heterocycles or carbocycles, providing a particularly useful synthesis of benzofurans and indoles.

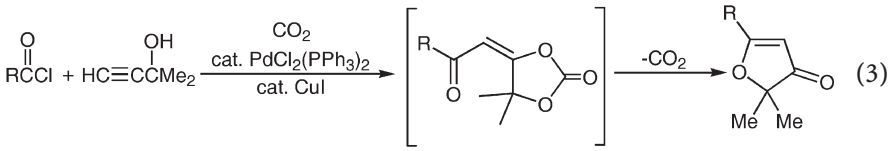
2.2
Annulation of Acetylenic Alcohols

There are only a couple of examples of the Pd-catalyzed annulation of terminal acetylenic alcohols. *o*-Iodobenzyl alcohol reacts with acetylenic carbinols in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI, plus Et_3N, to produce 1-alkylidene-1,3-dihydroisobenzofurans (Eq. 2) [3].



(2)

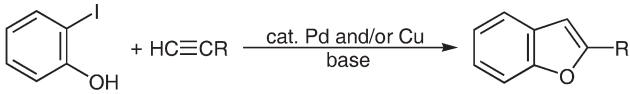
Using the same Pd and Cu catalysts, one can react acid halides and 2-methyl-3-butyn-2-ol, plus CO_2, to generate 3(2*H*)-furanones (Eq. 3) [4]. This reaction apparently proceeds by initial formation of a cyclic carbonate that subsequently undergoes decarboxylative rearrangement.



(3)

2.3 Annulation by o-Halophenols

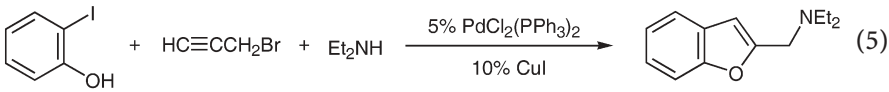
The reaction of *o*-halophenols and terminal alkynes in the presence of Pd and/or Cu catalysts provides a very convenient, direct route to benzofurans (Eq. 4).



(4)

The most commonly used catalyst system consists of $PdCl_2(PPh_3)_2$, CuI, and Et_3N [5–11], although $Pd(OAc)_2(PPh_3)_2$ [12] and piperidine [12] or tetramethylguanidine [13, 14] have also been used with CuI. The tetramethylguanidine procedure has also been employed on a solid support [15]. The combinations 10% Pd/C, CuI, PPh_3 plus prolinol in water [16]; 2.5% $Pd(OAc)_2$, 5% $P(C_6H_4SO_3Na\text{-}m)_3$, and Et_3N in aqueous MeCN [17]; and 37% Pd powder, 37% CuI, KF/Al_2O_3, and PPh_3 plus microwave irradiation [18] also work well. Alternatively, one can employ simply 10% $[Cu(phen)(PPh_3)_2]NO_3$ and Cs_2CO_3 [19], or substantial amounts of Cu_2O in pyridine [20, 21] or stoichiometric amounts of copper acetylides [22–25] to effect the same transformation.

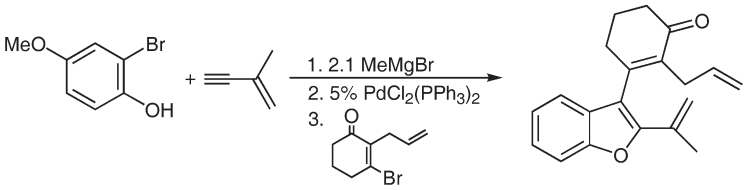
The reaction of *o*-iodophenol, propargyl bromide, and Et_2NH in the presence of the standard $PdCl_2(PPh_3)_2$/CuI catalyst provides the corresponding (diethylaminomethyl)benzofuran in good yield (Eq. 5) [26].



(5)

Recently, the sequential, one-pot Pd-catalyzed coupling of an *o*-halophenol and a terminal alkyne, followed by cross-coupling with a vinylic halide has provided an efficient approach to a complex benzofuran-containing natural product (Eq. 6) [27].

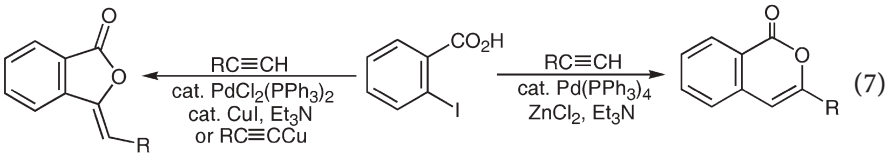
The Pd(II)-catalyzed reaction of simple phenols and 2-alkynoate esters provides a novel approach to coumarins, which will be discussed later in Sect. 3.2.



(6)

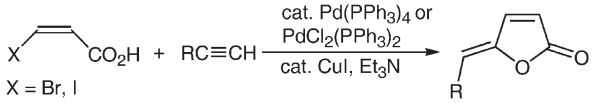
2.4 Annulation by Halo Carboxylic Acids

o-Halobenzoic acids react with terminal alkynes and a Pd catalyst to afford either phthalides or isocoumarins depending on the additional metal salt added to the reaction (Eq. 7). Thus, when CuI and Et_3N are added, phthalides are obtained in good yields [28, 29].



(7)

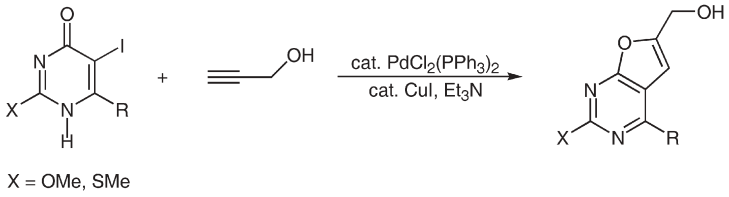
Replacing the CuI with $ZnCl_2$ affords primarily isocoumarins [30]. The direct reaction of *o*-halobenzoic acids with copper acetylides also affords phthalides [22–24]. The reaction of (*Z*)-3-halopropenoic acid and terminal alkynes in the presence of a palladium catalyst and catalytic amounts of CuI provides a convenient synthesis of alkylidene butenolides (Eq. 8) [31, 32].



(8)

2.5 Annulation by Halo Amides

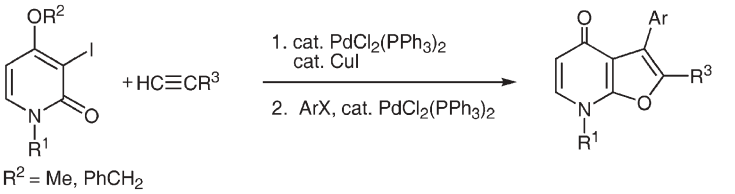
The Pd/Cu-catalyzed reaction of iodopyrimidinones and propargyl alcohol has been reported to give products in which cyclization has occurred on the carbonyl oxygen (Eq. 9) [33].



X = OMe, SMe

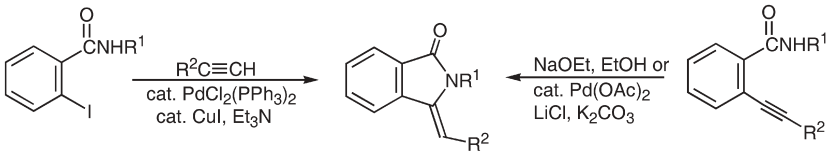
(9)

Similarly, the cross-coupling of terminal alkynes and 4-alkoxy-3-iodo-2-pyridones, followed by Pd-catalyzed arylation produces furo[2,3-*b*]pyridones (Eq. 10) [34].



(10)

All other cross-couplings involving terminal alkynes and halo amides have involved ring closure on nitrogen. Thus, *o*-halobenzamides react with simple terminal alkynes in the presence of a Pd/Cu catalyst to afford either (*Z*)-3-aryl(alkyl)idene isoindolin-1-ones or the corresponding 2-(1-alkynyl)benzamides, which are readily cyclized by NaOEt/EtOH or $Pd(OAc)_2$ catalyst to give isoindolin-1-ones (Eq. 11) [35, 36]. When acetylenic aryl carbinols are employed as the alkynes, 3-(acylmethyl)isoindolin-1-ones are obtained instead (Eq. 12) [37].



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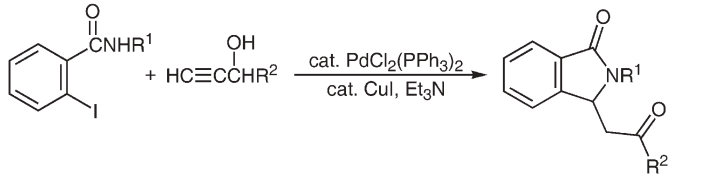
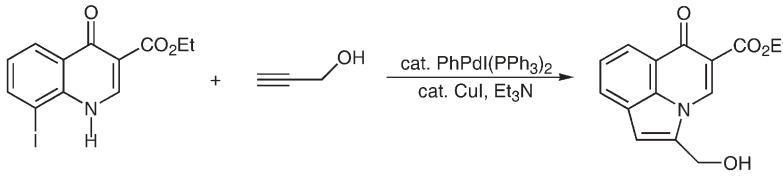


(12)

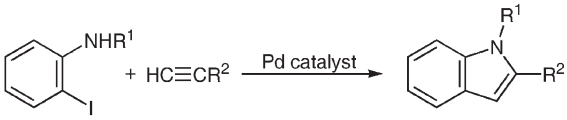
2.6
Annulation by Halo Amines and Derivatives

The Pd-catalyzed reaction of terminal alkynes and iodoquinolones and derivatives has been reported to produce pyrroloquinolones (Eq. 13) [38].



(13)

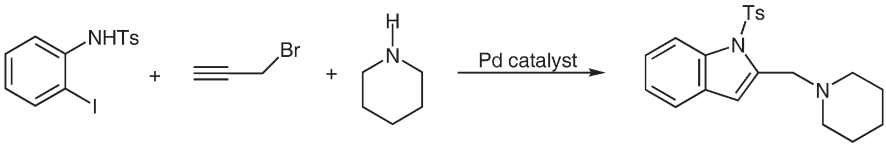
The Pd-catalyzed coupling of *o*-haloanilines and terminal alkynes tends to produce either the 2-(1-alkynyl)aniline or mixtures of the alkynylanilines and the corresponding indoles [17, 18]. However, *N*-benzyl-2-iodoaniline has recently been cross-coupled with terminal alkynes to afford the corresponding benzylindoles using a Pd zeolite catalyst (Eq. 14) [39]. One can also employ stoichiometric amounts of copper acetylides to effect this transformation [22–24].



(14)

The direct cross-coupling of terminal alkynes to produce indoles has been much more successful using derivatives of the 2-haloanilines. Thus, the Pd zeolite catalyst cross-couples terminal alkynes and acetanilides to indoles in good yields [39]. The corresponding tosylamides give somewhat lower yields. A catalyst consisting of Pd powder, CuI, and PPh_3, plus KF-Al_2O_3, has been used to cross-couple an acetanilide to an indole in a modest yield, while related trifluoroacetanilides afford mixtures of 2-(1-alkynyl)anilines and deprotected indoles, and a methanesulfonamide derivative gives a high yield of deprotected indole [18]. *o*-Iodotrifluoroacetanilide has been allowed to react with a terminal alkyne in the presence of $Pd(OAc)_2$ plus a sulfonated phosphine to generate a good yield of a mixture of the corresponding protected and deprotected indoles [17]. Acetanilides have also been cross-coupled with terminal alkynes in the presence of $PdCl_2(PPh_3)_2$, CuI, and tetramethylguanidine to produce deprotected indoles in high yields [40]. Methanesulfonamides also give high yields using this procedure and tetramethylguanidine [14] or triethylamine [41].

This indole synthesis has been extended to solid supports. Libraries of indoles have been prepared by cross-coupling sulfonamide derivatives of 2-iodoanilines on solid supports, where the indole is attached through either the benzene ring of the indole [42] or the sulfonamide linkage [43–45], using $PdCl_2(PPh_3)_2$, CuI, and Et_3N. This catalyst system has also been used to prepare pyrrolo[2,3-*d*]pyrimidines from methanesulfonamides [46] and to cross-couple a tosylamide, propargyl bromide, and piperidine (Eq. 15) [26].

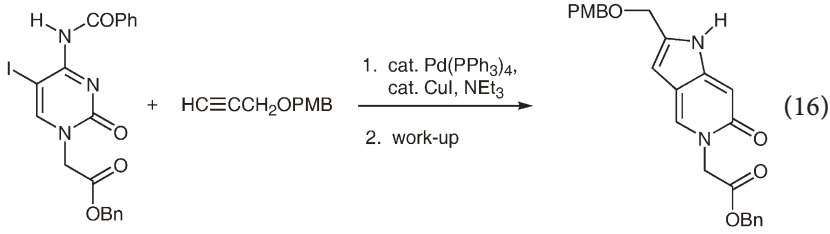


(15)

This catalyst system effects cross-coupling, but fails to cyclize carbamate derivatives to indoles [41]. However, by employing $Pd(OAc)_2$, PPh_3, LiCl, and

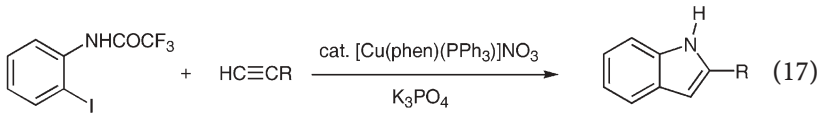
K_2CO_3, the Boc derivative of 4-amino-3-iodopyridine has been cross-coupled and cyclized to the corresponding 5-azaindole [47].

A protected propargyl alcohol has recently been annulated by a benzoyl-protected 5-iodocytosine derivative (Eq. 16) [48].



(16)

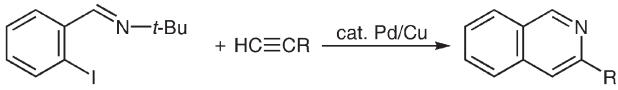
Recently, copper salts alone have been reported to effect the direct annulation of terminal alkynes by *N*-(*o*-iodophenyl)trifluoroacetamide (Eq. 17) [49] and the analogous formation of pyrrolo[2,3-*b*]quinoxalines [50] with loss of the trifluoroacetyl group.



(17)

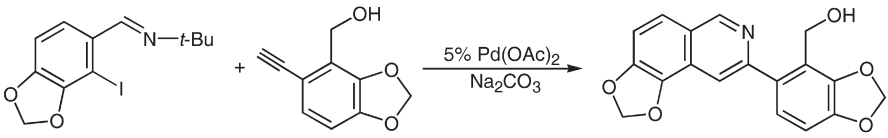
2.7
Annulation by Halo Imines and Nitro Derivatives

The *t*-butylimines of *o*-iodobenzaldehydes and 3-halo-2-alken-1-ones can be reacted with terminal alkynes in the presence of a Pd/Cu catalyst to afford isoquinolines and pyridines in a process which apparently involves aryl alkyne formation, followed by cyclization with fragmentation of the *t*-butyl group (Eq. 18) [51, 52].



(18)

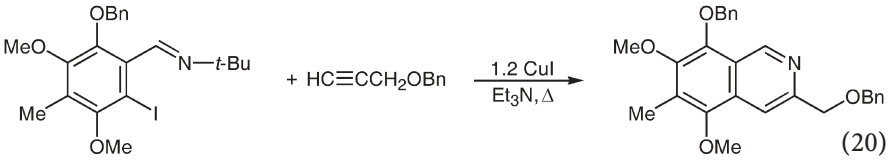
While this process works well in a limited number of examples, it is best carried out in two steps, first employing the Sonogashira coupling of the alkyne to produce the corresponding aryl alkyne and then cyclizing this substrate



(19)

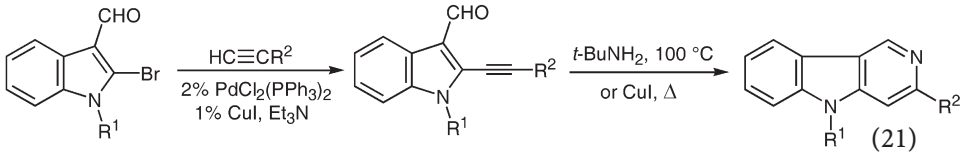
either thermally or using CuI catalyst. This general process has provided an efficient synthesis of the isoquinoline alkaloid decumbenine B (Eq. 19) [52].

More recently, it has been found that simply heating with 1.2 equiv of CuI will effect the cross-coupling and cyclization of an analogous imine (Eq. 20) [53].



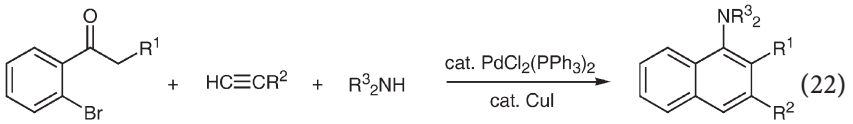
(20)

This imine annulation strategy has been extended to the synthesis of β- and γ-carbolines, where facile thermal cyclization during imine formation has been observed (Eq. 21) [54, 55].



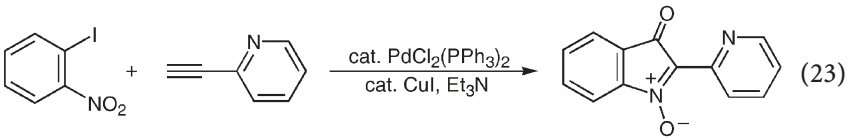
(21)

Naphthylamines have been prepared by the cross-coupling of terminal alkynes, amines, and bromoketones, presumably through the corresponding acetylenic enamine (Eq. 22) [56].



(22)

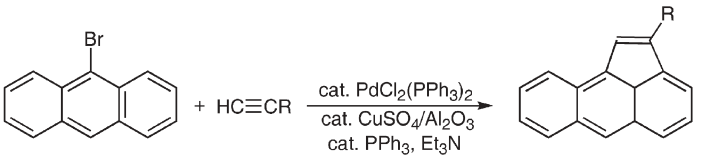
Finally, the Sonogashira coupling of 2-ethynylpyridine and *o*-iodonitrobenzene affords a nitrone directly (Eq. 23) [57].



(23)

2.8 Annulation by Haloarenes

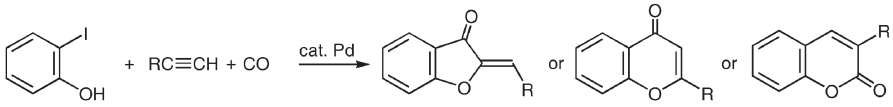
9-Bromoanthracene reacts with terminal alkynes in the presence of Pd and Cu catalyst to produce aceanthrylenes (Eq. 24) [58–60].



(24)

2.9 Annulation by CO and Aryl Halides

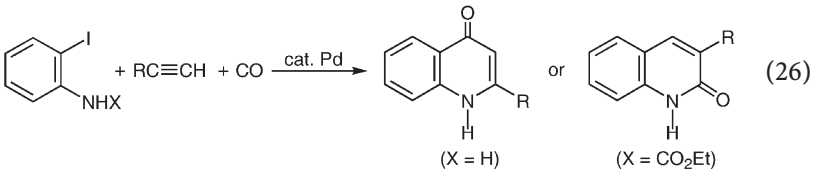
o-Halophenols react with terminal alkynes plus CO to produce either aurones, chromones, or coumarins depending on how the reaction is run (Eq. 25).



(25)

When using $Pd(PPh_3)_4$ as the catalyst, KOAc as the base, and anisole as the solvent, phenylacetylene apparently gives the aurone in an 82% yield [61, 62]. When $Pd(OAc)_2(dppf)_2$, DBU, and DMF are employed under 1 atm of CO at 60 °C, mixtures of aurones and chromones are obtained [63]. On the other hand, $PdCl_2(dppf)$ [64] or $PdCl_2(PPh_3)_2$ [65] and Et_2NH under 20 atm of CO at 120 °C afford 2-substituted chromones. 2-Iodophenyl acetates also react with terminal alkynes and 1 atm of CO in the presence of a 1:1:1 complex of $PdCl_2(PPh_3)_2$–thiourea–dppp plus Et_2NH and DBU at 40 °C to produce good yields of chromones [66]. We have observed that coumarins substituted in either the 3 or 4 position can be obtained in low yields by allowing *o*-iodophenols, terminal alkynes, and 1 atm of CO to react in the presence of 5% $Pd(OAc)_2$, pyridine, and *n*-Bu_4NCl [67].

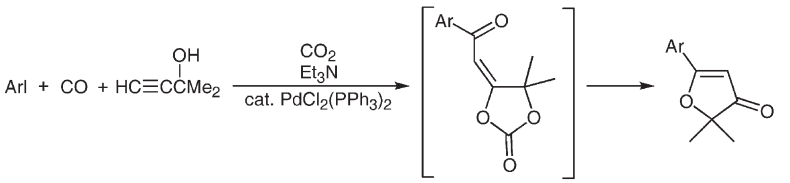
In a similar manner, 4- and 2-quinolones have been obtained from terminal alkynes, CO, and *o*-iodoaniline and derivatives (Eq. 26).



(26)

Using catalytic amounts of $PdCl_2(PPh_3)_2$ or $PdCl_2(dppf)$, Et_2NH, and relatively high temperatures and pressures, 4-quinolones have been reported as the sole products from *o*-haloanilines [68–70]. Employing analogous carbamate derivatives, 5% $Pd(OAc)_2$, pyridine, and *n*-Bu_4NCl, we have observed modest yields of mixtures of 3- and 4-substituted 2-quinolones in which the carboalkoxy group is lost during annulation [67].

Finally, 3-(2*H*)-furanones have been obtained by the Pd-catalyzed coupling of 2-methyl-3-butyn-2-ol, CO, CO_2, and aryl halides (Eq. 27) [71]. The reaction apparently first generates cyclic carbonates, which rearrange during the reaction.

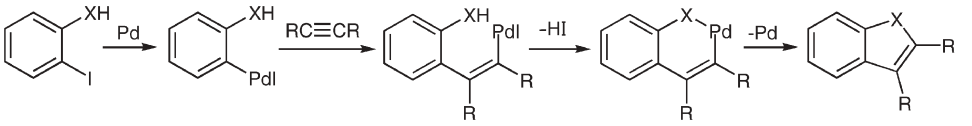


(27)

3
Annulation of Internal Alkynes

3.1
Introduction

Internal alkynes will also readily undergo palladium-catalyzed annulation by functionally substituted aromatic or vinylic halides to afford a wide range of heterocycles and carbocycles. However, the mechanism here appears to be quite different from the mechanism for the annulation of terminal alkynes. In this case, it appears that the reaction usually involves (1) oxidative addition of the organic halide to Pd(0) to produce an organopalladium(II) intermediate, (2) subsequent insertion of the alkyne to produce a vinylic palladium intermediate, (3) cyclization to afford a palladacycle, and (4) reductive elimination to produce the cyclic product and regenerate the Pd(0) catalyst (Eq. 28).

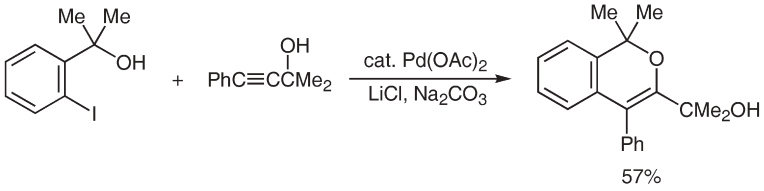


(28)

In much of this organopalladium chemistry, the Pd(0) catalyst is generated by adding a Pd(II) salt to the reaction and allowing it to be reduced under the reaction conditions. The regiochemistry of the annulation of unsymmetrical alkynes is usually easily predicted by simply looking at the steric bulk of the substituents on the ends of the carbon–carbon triple bond. The organopalladium intermediate usually adds the Pd moiety to the more hindered end of the triple bond, where the longer carbon–palladium bond is presumably more favorable energetically than the shorter carbon–carbon bond that is formed. Certain functional groups, like an ester, can control the regiochemistry when the steric effects are otherwise pretty comparable. This overall process has proven to be a very valuable route to heterocycles, particularly indoles, where it has found widespread use in the pharmaceutical industry.

3.2
Annulation by Halo Alcohols, Halo Phenols, and Phenols

o-Iodobenzylic alcohols readily annulate internal alkynes to generate benzopyrans (Eq. 29) [72]. This chemistry can also be applied to alcohol-containing vinylic halides (Eq. 30) [73]. With appropriately substituted allylic alcohols, furans are obtained by isomerization of the carbon–carbon double bond (Eq. 31) [73].



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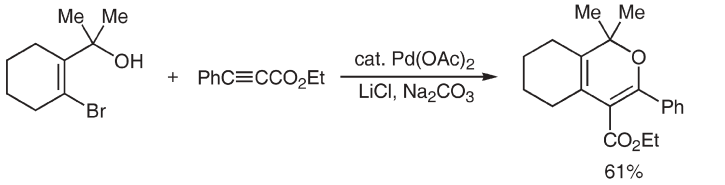

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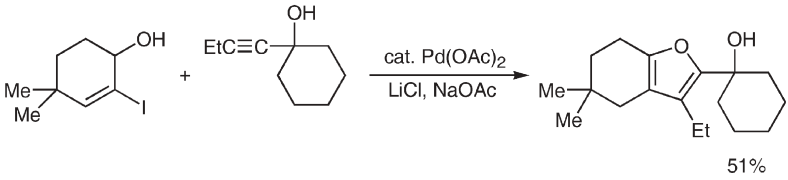
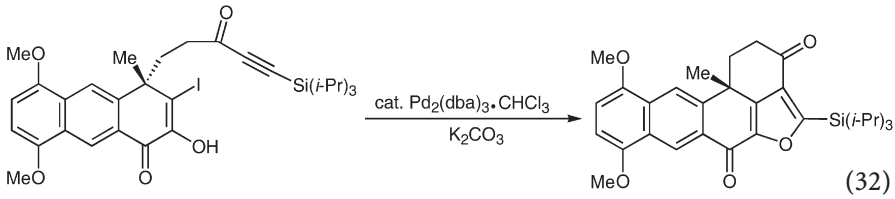


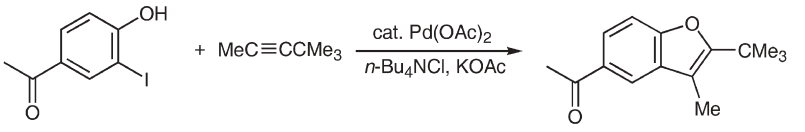
(31)

An intramolecular version of this chemistry has been employed as a key step in the synthesis of halenaquinone and halenaquinol (Eq. 32) [74].

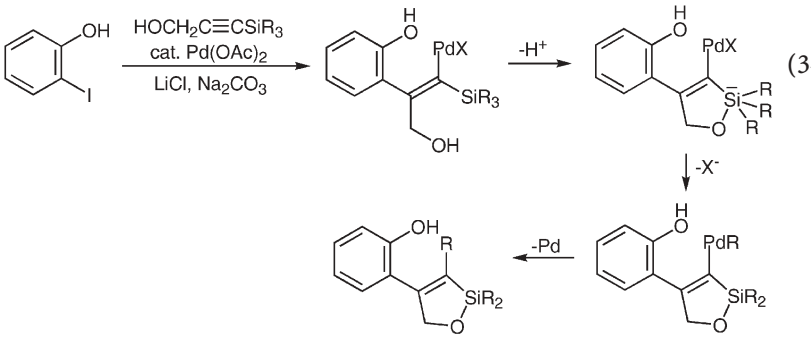


(32)

o-Iodophenols have been employed in the annulation of internal alkynes to generate a range of benzofurans (Eq. 33) [72]. When 1-silyl-1-alkynes are employed, good yields of 2-silylbenzofurans are generally obtained [72]. However, silyl-substituted alkynols have been reported to generate 1-oxa-2-silacyclopent-3-enes in low yields by an interesting alkyl migration process (Eq. 34) [75].

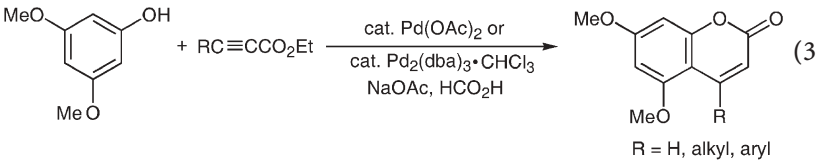


(33)



(34)

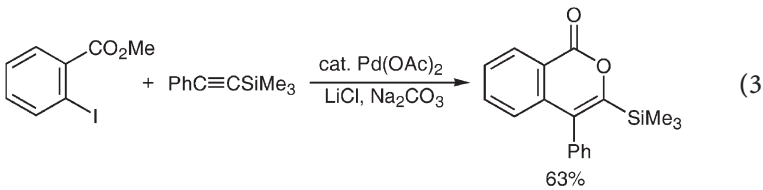
The reaction of 2-alkynoate esters and electron-rich phenols in the presence of formic acid and catalytic amounts of either $Pd(OAc)_2$ or $Pd_2(dba)_3{\cdot}CHCl_3$ provides an efficient way to synthesize coumarins (Eq. 35) [76]. This chemistry has been utilized to synthesize the natural products fraxinol methyl ether, ayapin, herniarin, xanthoxyletin, and alloxanthoxyletin. The reaction appears to involve a Pd(0) catalyst and the formation of hydridopalladium intermediates.



(35)

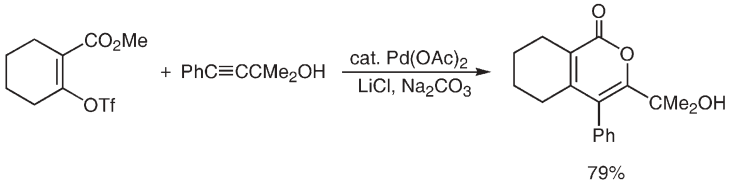
3.3 Annulation by Halo Esters

Although ester groups do not normally participate in organopalladium reactions, *o*-halobenzoate esters react with internal alkynes in the presence of a palladium catalyst to produce good yields of isocoumarins (Eq. 36) [72, 77, 78].



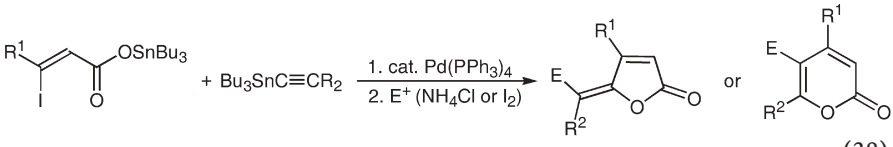
(36)

This process is successful because the vinylic palladium intermediate is able to react in an intramolecular fashion with the neighboring ester group. This reaction most likely involves attack on the carbonyl oxygen, since a wide variety of different esters give similar results. In an analogous manner, vinylic chlorides, bromides, iodides, and triflates can be utilized to generate α-pyrones (Eq. 37) [78–80].



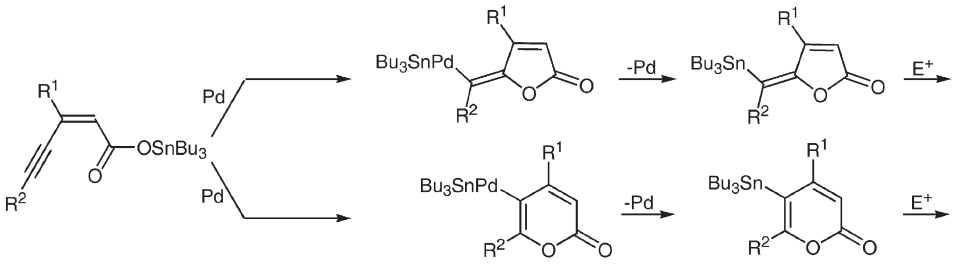
(37)

The palladium-catalyzed cross-coupling of 1-stannyl-1-alkynes with the tributylstannyl esters of (*Z*)-3-iodoalk-2-enoic acids affords either stannyl butenolides or α-pyrones depending on the nature of the substituents present on the alkyne (Eq. 38) [81].



(38)

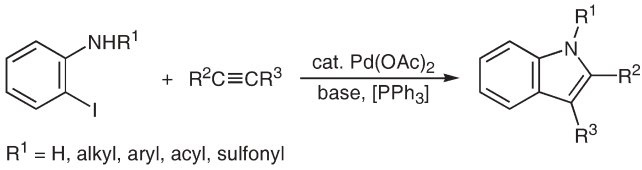
If the initial product is treated with NH_4Cl, one obtains the corresponding proton-substituted products. If I_2 is employed, the corresponding vinylic iodides are obtained. This reaction is suggested to proceed by initial cross-coupling to form an enyne, followed by cyclization by palladium, and finally electrophilic cleavage of the carbon–tin bond (Eq. 39).



(39)

3.4
Annulation by Haloanilines and Derivatives

We first reported that the palladium-catalyzed annulation of internal alkynes by *o*-haloanilines and their amide and sulfonamide derivatives provides a very versatile route to 2,3-disubstituted indoles (Eq. 40) [82, 83].

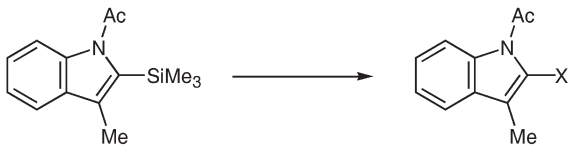


(40)

R^1 = H, alkyl, aryl, acyl, sulfonyl

The reaction usually employs $Pd(OAc)_2$ as the catalyst precursor, and various alkali metal acetate, bicarbonate, or carbonate bases are usually added to the reaction. The addition of LiCl or *n*-Bu_4NCl, and possibly PPh_3, sometimes facilitates reaction, but it is hard to predict when it is desirable to add these reagents or even what base to use. The success of the process is highly dependent on the choice of appropriate reaction conditions.

The process is quite versatile as far as the nature of the substituents that can be utilized on the nitrogen or aromatic ring of the aniline and on either end of the alkyne is concerned. The substituent remaining on the nitrogen of the indole can be a hydrogen, alkyl, aryl, acyl, or sulfonyl group. The reaction is generally quite regioselective, the major or only product being the indole with the bulkiest group of the alkyne in the 2 position. The alkyne used can contain a wide variety of substituents, including alkyl, aryl, functionally substituted alkyl or aryl, ester, or silyl groups. 1-Silyl-1-alkynes are particularly useful, since the bulky silyl group directs the regiochemistry of the alkyne insertion, generating exclusively the 2-silylindole, and these compounds readily undergo further substitution by hydrogen, halogen, or palladium to effect a number of very useful synthetic transformations (Eq. 41) [82, 83].



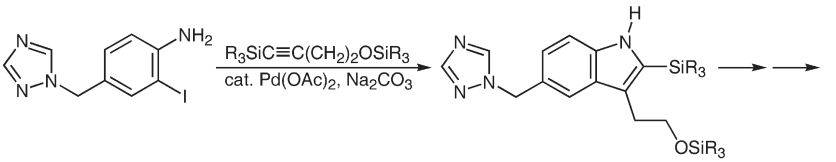
(41)

X = H [88%; $AlCl_3$, then H_2O]; Br [70%; NBS]; *E*- $CH{=}CHCO_2Et$ [75%; $H_2C{=}CHCO_2Et$, $Pd(OAc)_2$]

This indole synthesis has been widely employed by others in academia and the pharmaceutical industry. For example, syntheses of the potent 5-HT_{1D} receptor agonist MK-0462 [84], of interest for the treatment of migraine headaches, and an acetic acid metabolite of MK-0462 [85] have both employed the annulation of a silylalkyne (Eq. 42).

In a similar manner, another antimigraine drug candidate **1** has been prepared using a silylalkyne [86]. Here it was found that 2,4,6-trimercapto-*s*-triazine provides a very useful way to remove residual palladium. A number of tryptophan analogues have been prepared using this same silylalkyne chemistry, followed by protodesilylation [87–93] (Eq. 43).

In one tryptamine synthesis, the rate of annulation was enhanced by microwave irradiation [94]. In two tryptamine syntheses, the silyl group was



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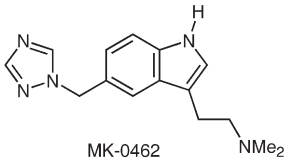
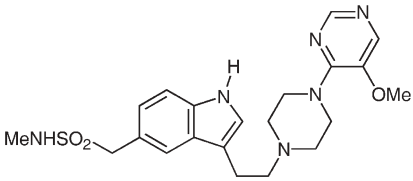


MK-0462



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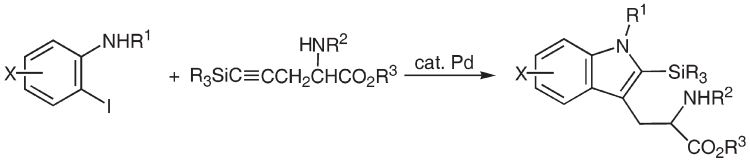
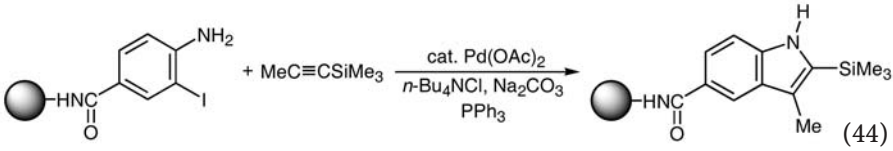


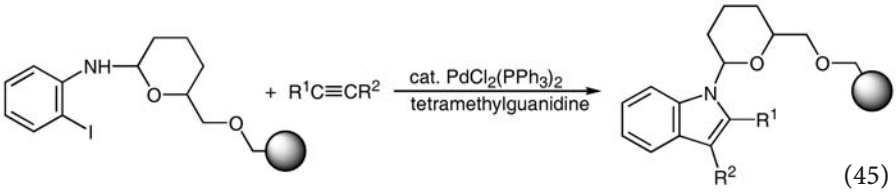
(43)

removed by halogenation [94, 95] and subsequent Suzuki coupling has also been utilized [95].

This indole synthesis has been employed on solid supports to generate libraries of indoles. In one case, the indole was attached through an amide group in the benzene ring of the indole (Eq. 44) [45, 96, 97]. In another case, the indole was attached to the resin through the nitrogen moiety by a tetrahydropyranyl ether linkage (Eq. 45) [98].

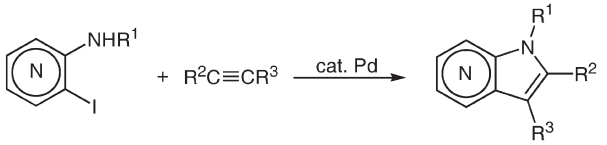


(44)



(45)

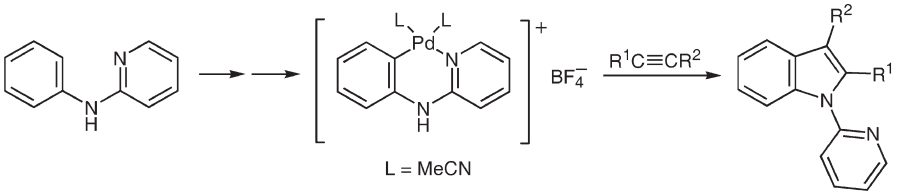
A number of heteroatom-substituted indoles have been prepared by this annulation methodology. For example, starting with various substituted pyridines, 5- [99–101], 6- [99, 100, 102, 103], and 7-azaindoles [100, 101, 103, 104] can be readily prepared (Eq. 46).



(46)

In a similar fashion, thieno[3,2-*b*]pyrroles and pyrrolo[2,3-*d*]pyrimidines have been prepared by starting with the appropriate 3-amino-2-iodothiophenes and 4-amino-5-iodopyrimidines, respectively [99]. The annulation of silylalkynes by 2-amino-3-iodoquinolines [105, 106] and 4-amino-3-iodoquinolines [107, 108] affords the corresponding pyrrolo[2,3-*b*]quinolines and pyrrolo[3,2-*c*]quinolines, respectively.

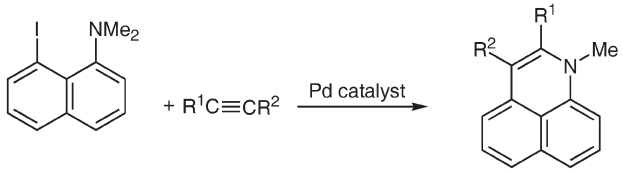
A similar annulation process has been reported using the cyclopalladated product of 2-(phenylamino)pyridine and internal alkynes (Eq. 47) [109]. Unfortunately, this process requires stoichiometric amounts of palladium.



(47)

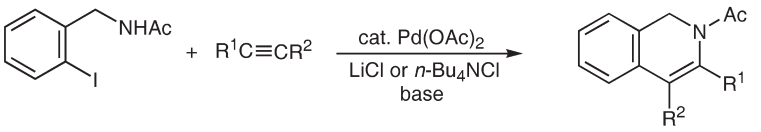
3.5
Annulation by Other Halo Amines and Derivatives

The palladium-catalyzed annulation of alkynes by a couple of other haloamine/amide systems has been reported to provide a useful route to nitrogen heterocycles. For example, 8-dimethylamino-1-iodonaphthalene reacts with internal alkynes in the presence of a cyclopalladation catalyst to afford *N*-methylbenzo[*d*,*e*]quinolines (Eq. 48) [110].



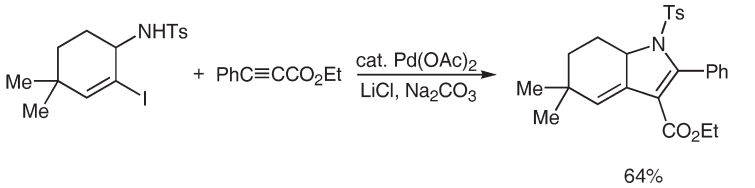
(48)

N-(2-Iodobenzyl)acetamide reacts with internal alkynes in the presence of catalytic amounts of $Pd(OAc)_2$ and a base to produce good yields of 1,2-dihydroisoquinolines (Eq. 49) [72].



(49)

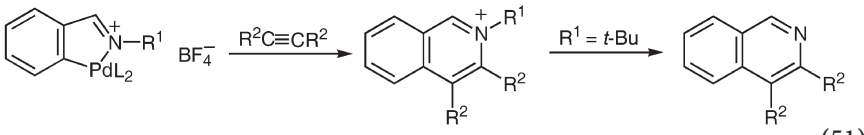
Finally, halogen-containing allylic tosylamides have been employed in the annulation of internal alkynes to generate 2,3-dihydropyrrole derivatives (Eq. 50) [73].



(50)

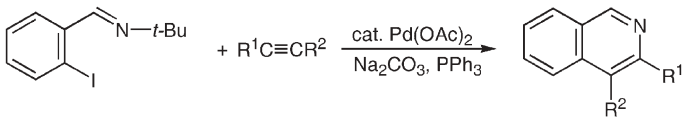
3.6 Annulation by Halo Imines

In 1987, Heck reported that cyclopalladated benzaldimine salts bearing an *N*-methyl, *N*-benzyl, or *N*-aryl substituent react with 3-hexyne to give isoquinolinium salts, but that the *N*-*tert*-butyl derivative reacts with diphenylacetylene to give the corresponding isoquinoline (Eq. 51) [111].



(51)

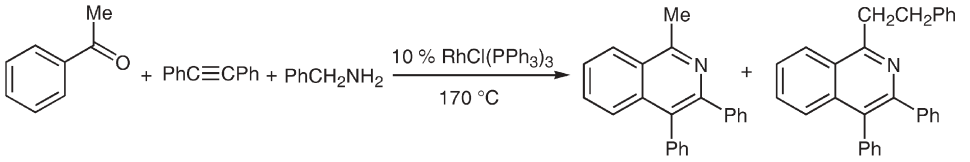
We subsequently reported that the *tert*-butyl imines of *o*-iodobenzaldehydes readily annulate internal alkynes in the presence of a palladium catalyst, affording a very nice synthesis of isoquinolines (Eq. 52) [112, 113].



(52)

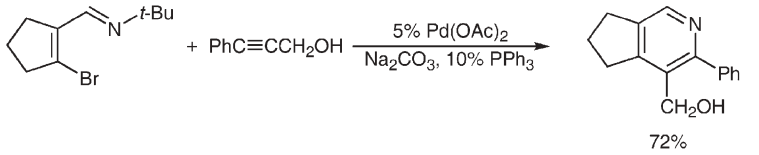
This reaction probably proceeds via the isoquinolinium salt, which under the reaction conditions presumably fragments to isobutylene.

A similar isoquinoline synthesis has recently been reported using a rhodium catalyst to effect a one-pot coupling of an aryl ketone, an amine, and an internal alkyne (Eq. 53) [114].



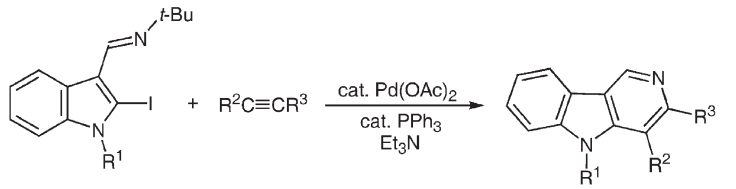
(53)

One can also employ the corresponding imines of 3-halo-2-alkenals to generate highly substituted pyridines (Eq. 54) [112, 113].



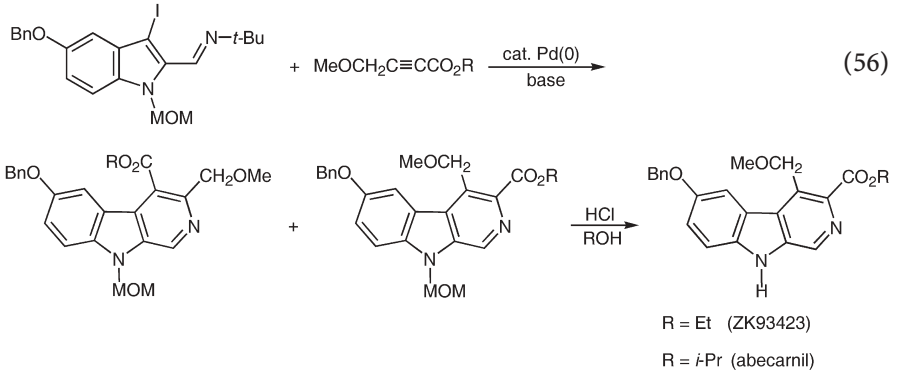
(54)

If one employs indole-containing imines and a slight variation in the reaction conditions, one can readily prepare β- and γ-carbolines (Eq. 55) [55, 115].



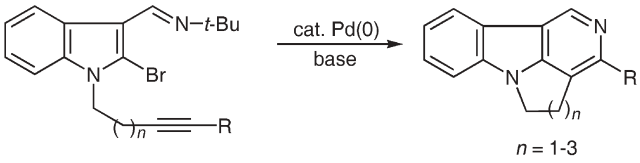
(55)

This process has been employed in the synthesis of two biologically interesting β-carboline alkaloids, ZK93423 and abecarnil (ZK112119) (Eq. 56) [55].



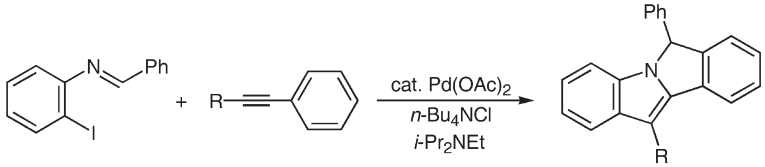
(56)

This methodology has been used to showcase new methodology for catalyst and reaction optimization employing nonaqueous capillary-array electrophoresis coupled with microreaction technology [116]. By tethering the alkyne to the nitrogen of the indole ring, one can readily prepare polycyclic substrates (Eq. 57) [117, 118].



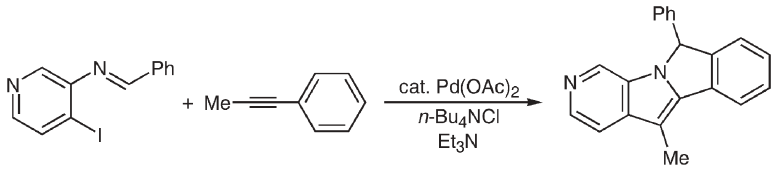
(57)

Imines derived from *o*-iodobenzaldehydes and *o*-iodoaniline have been utilized in the annulation of aryl alkynes to produce isoindolo[2,1-*a*]indoles (Eq. 58) [119, 120].



(58)

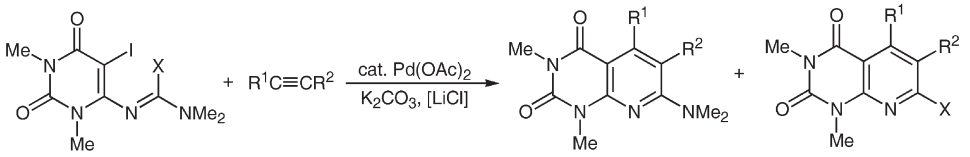
This unique process apparently involves (1) oxidative addition of the aryl iodide to Pd(0), (2) alkyne insertion, (3) addition of the resulting vinylic palladium intermediate to the C–N double bond of the imine, (4) either electrophilic palladation of the resulting σ-palladium intermediate onto the adjacent aromatic ring originating in the internal alkyne or oxidative addition of the neighboring aryl C–H bond, and (5) reductive elimination of the tetracyclic product with regeneration of the Pd(0) catalyst. This reaction generates three new bonds and two new rings in a single step, and exhibits unusual regioselectivity in substitution on the aromatic ring, which originates in the alkyne. If one employs an iodopyridine starting material, one can easily prepare pyridopyrrolo[2,1-*a*]isoindoles (Eq. 59) [121].



(59)

Iodouracils bearing a formamidine or acetamidine moiety react with alkynes to produce pyrido[2,3-*d*]pyrimidine derivatives (Eq. 60) [122].

The formamidine derivative reacts with terminal and internal alkynes to afford mixtures of products in which the major product is always the dimethylamine-containing product. In some cases, it is the exclusive product. The

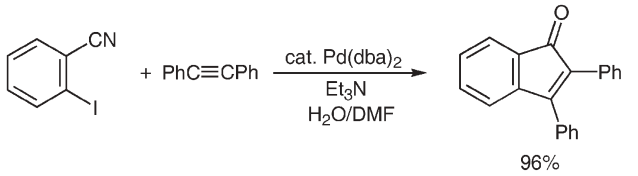


(60)

acetamidine derivative reacts with internal alkynes to afford exclusively the methyl-containing products. None of the dimethylamine product is reported. The ratio of products is affected by the presence or absence of LiCl. The exact mechanism of this process is not clear at this time.

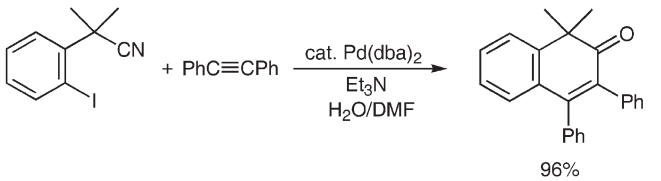
3.7 Annulation by Halo Nitriles

The nitrile group is another functional group that normally does not react with organopalladium compounds. However, when held in close proximity to an organopalladium intermediate, nitrile groups can readily undergo addition, producing some very useful synthetic chemistry. For example, *o*-iodobenzonitriles react with internal alkynes and certain bicyclic alkenes, like norbornene, in the presence of a palladium catalyst and aqueous DMF as solvent to afford ketone products arising by organopalladium addition to the nitrile, followed by imine hydrolysis (Eq. 61) [123, 124].



(61)

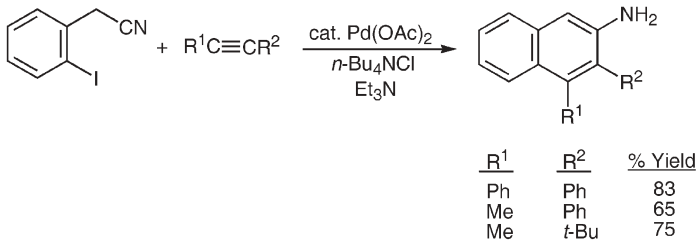
The reagent responsible for reduction of the intermediate Pd(II) salt back to Pd(0) is not obvious, although Et_3N is a good bet. This reaction also works well for the formation of a six-membered-ring ketone (Eq. 62) [123, 124].



(62)

However, the analogous acetonitrile derivative without the methyl groups affords good yields of β-naphthylamines instead (Eq. 63) [123, 125].

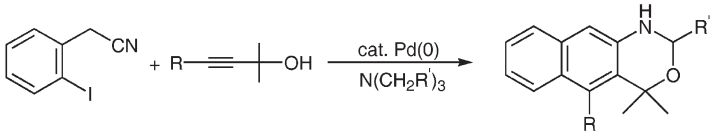
In this case, the intermediate imine apparently tautomerizes to the corresponding amine faster than it undergoes hydrolysis. When hindered propar-



R^1	R^2	% Yield
Ph	Ph	83
Me	Ph	65
Me	*t*-Bu	75

(63)

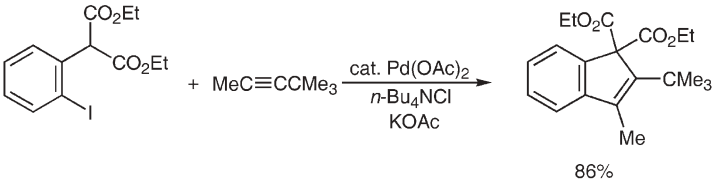
gylic alcohols are employed in this process, the amine added to the reaction participates in the process, affording low yields of 1,3-benzoxazines (Eq. 64) [125].



(64)

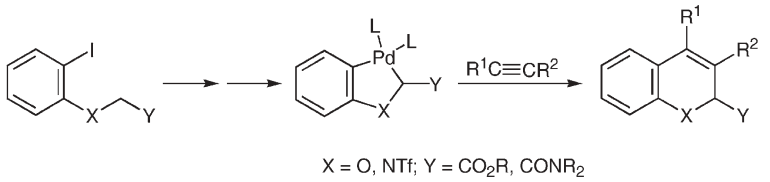
3.8 Annulation by Haloarenes Bearing Carbanions

We have observed that aryl halides bearing a neighboring functionality that readily stabilizes a carbanion will nicely undergo carboannulation of internal alkynes in the presence of a palladium catalyst and a mild base to generate highly substituted indenes (Eq. 65) [126].



(65)

Analogous chemistry utilizing stoichiometric arylpalladium intermediates has been employed to generate 2*H*-1-benzopyrans and 1,2-dihydroquinolines (Eq. 66) [127, 128]. When intermediates bearing chiral diamine ligands are utilized, high enantiomeric excesses can be obtained [128].

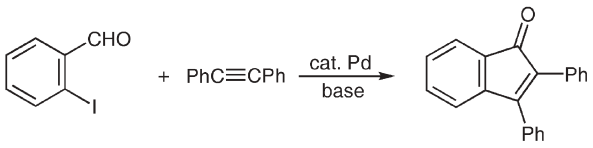


X = O, NTf; Y = CO_2R, $CONR_2$

(66)

3.9
Annulation by Halo Aldehydes and Ketones

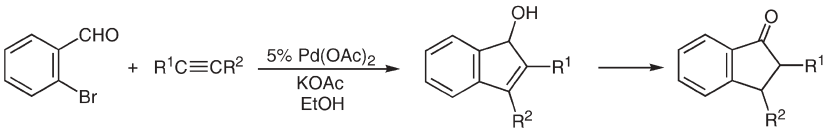
In 1989, Heck reported that the reaction of *o*-iodobenzaldehyde and diphenylacetylene in the presence of a palladium catalyst and NaOAc affords a 58% yield of 2,3-diphenylindenone (Eq. 67) [77].



(67)

We subsequently optimized the reaction conditions (5% $Pd(OAc)_2$, NaOAc, or Na_2CO_3; *n*-Bu_4NCl in DMF or DMA) and explored the scope of this process [129]. While the scope is somewhat limited and the yields are only moderate, this process provides a very direct and convenient route to 2,3-disubstituted indenones that would be quite hard to prepare by most other procedures. Mechanistically, it is not clear if this reaction proceeds by addition of the vinylic palladium intermediate across the aldehyde moiety and subsequent β-hydride elimination, or whether the aldehyde C–H bond undergoes oxidative addition to the vinylic palladium intermediate and two subsequent reductive eliminations generate the final indenone product. Related stoichiometric arylpalladium compounds have been reported to react with alkynes to afford both indenones and indenols [109, 130].

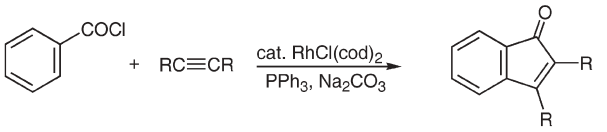
Yamamoto and coworkers subsequently found that these same reactants afford good yields of indenols when the reaction is run in the presence of 5% $Pd(OAc)_2$ and KOAc in EtOH under an argon atmosphere (Eq. 68) [131].



(68)

Heating some of the indenols to 100 °C for 24–36 h generated the corresponding indanones. *o*-Bromoacetophenone and related haloaryl ketones will also undergo this alkyne annulation process to provide good yields of the corresponding indenols [132]. Thus, it clearly appears that the vinylic palladium intermediates can add intramolecularly to the carbonyl group of an aldehyde or ketone.

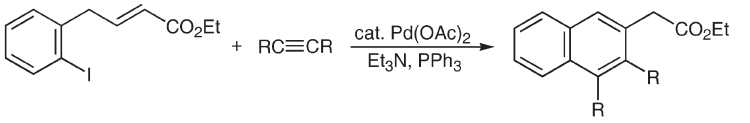
In recent years several closely related transition metal processes have been reported. For example, both catalytic amounts of CoI_2(dppe) [133, 134] and $NiBr_2$(dppe) [135] in the presence of Zn metal and acetonitrile will effect this same indenol synthesis from *o*-haloaryl aldehydes or ketones and alkynes. Similarly, rhodium will catalyze the formation of indenones from simple aroyl chlorides and internal alkynes (Eq. 69) [136].



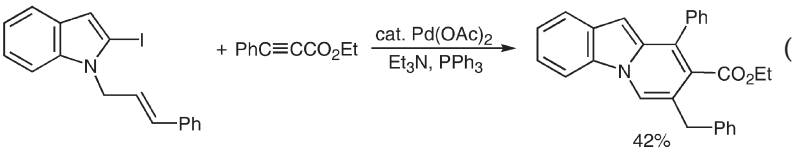
(69)

3.10 Annulation by Olefin-Containing Aryl Halides

A number of naphthalenes and carbazoles have been prepared by the palladium-catalyzed annulation of internal alkynes by aryl halides containing neighboring olefin functionality (Eqs. 70 and 71) [137, 138].



(70)

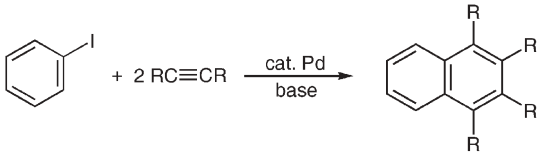


(71)

This process no doubt involves arylpalladium addition to the alkyne, followed by intramolecular olefin insertion. The resulting alkylpalladium intermediate may rearrange to an allylic palladium compound, which can undergo direct β-hydride elimination to the naphthalene or carbazole product or this intermediate may undergo direct β-hydride elimination, in which case subsequent double bond isomerization is required to produce the observed products.

3.11 Annulation by Simple Aryl and Vinylic Halides

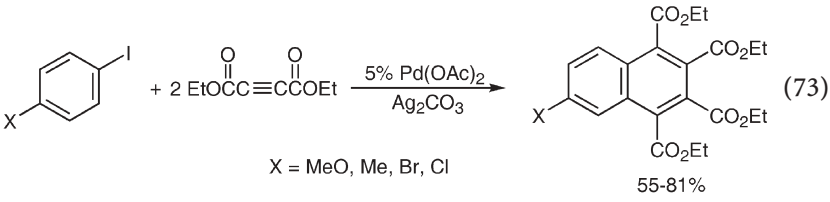
There are several reports of the reaction of simple aryl halides with internal alkynes producing naphthalenes, in which two molecules of the alkyne have been inserted and cyclization back onto the aromatic ring has taken place (Eq. 72) [77, 111, 139].



(72)

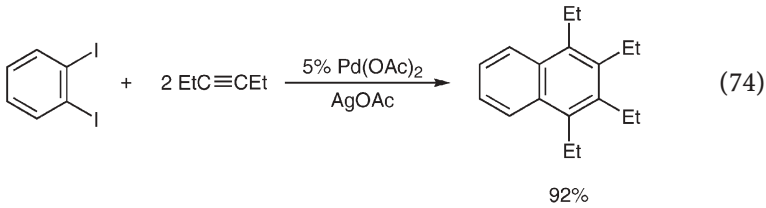
However, the yields of naphthalenes have usually been quite low and complex side products often accompany the naphthalene. Only recently has a procedure

been reported which provides reasonable yields of naphthalenes from a variety of simple aryl halides and either diphenylacetylene or diethyl acetylenedicarboxylate (Eq. 73) [140].



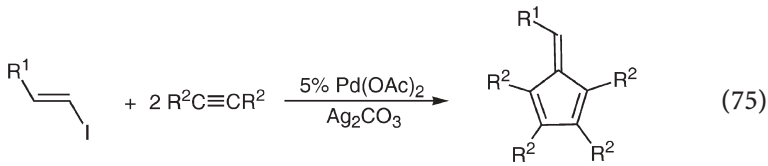
(73)

Quite recently, a procedure has also been reported which affords good yields of alkyne double-insertion products from a variety of dialkyl alkynes and 1,2-diiodoarenes (Eq. 74) [141].



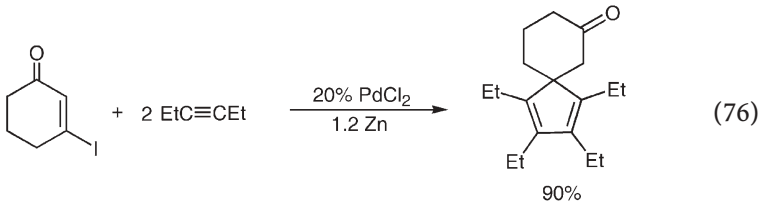
(74)

Vinylic halides have been reported to react with internal alkynes in the presence of a palladium catalyst to afford fulvenes (Eq. 75) [111, 142–144].



(75)

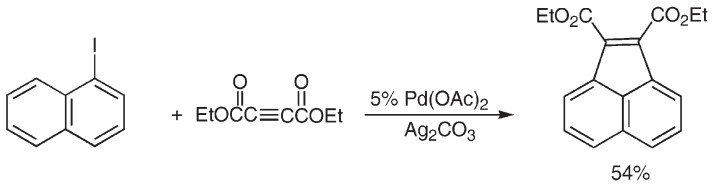
Excellent yields of fulvenes can now be obtained [142]. This process no doubt involves two consecutive *cis* insertions of the two molecules of alkyne into the carbon–palladium bond of the initial vinylpalladium intermediate, and then intramolecular addition of the resulting 1,3,5-alkatrienylpalladium species to



(76)

the internal carbon–carbon double bond arising for the vinylic halide. Subsequent palladium β-hydride elimination affords the fulvene. It has also been reported that spirocyclic ketones can be prepared by the reaction of appropriate iodoalkenones and alkynes in the presence of either a nickel or palladium catalyst (Eq. 76) [145].

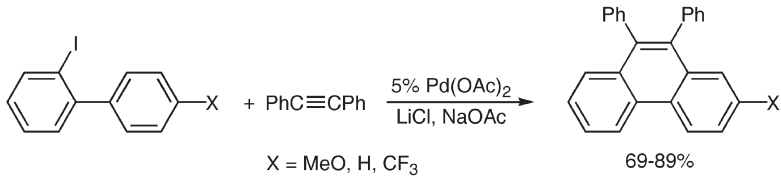
A number of acenaphthylene derivatives have been prepared by the palladium-catalyzed annulation of internal alkynes by iodonaphthalenes. For example, 1-iodonaphthalene affords a decent yield of a product derived from a single insertion of the alkyne (Eq. 77) [140].



(77)

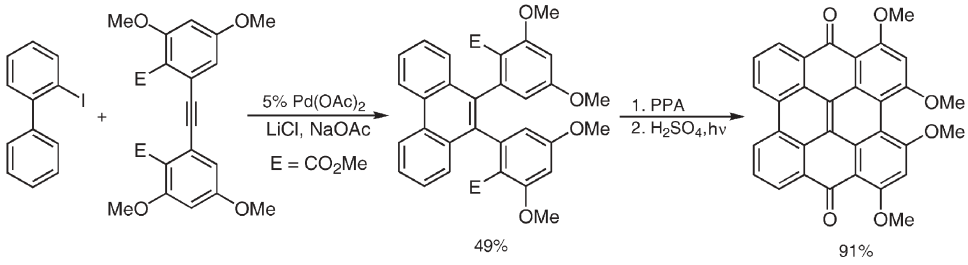
1,8-Diiodonaphthalene has also been reported to react with diaryl and dialkyl alkynes, as well as dimethyl acetylenedicarboxylate, to produce modest yields of these same types of acenaphthylenes [146].

In 1987 Heck reported that the reaction of 2-iodobiphenyl and diphenylacetylene provide a very low yield of 9,10-diphenylphenanthrene [111]. We subsequently improved the procedure to the point where it provides good yields from a wide variety of iodobiaryls and internal alkynes (Eq. 78) [147].



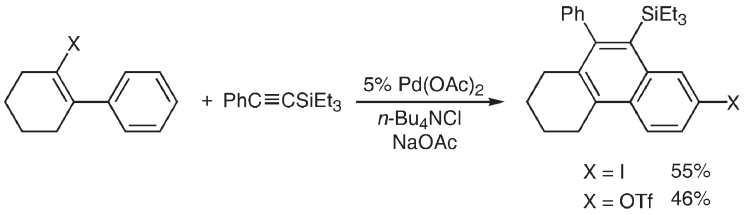
(78)

We have employed this process to prepare analogues of the biologically interesting antiviral agents hypericin and hypocrellin (Eq. 79) [148].



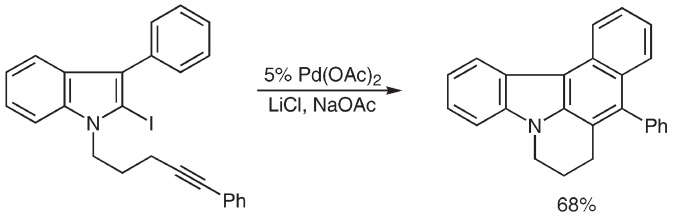
(79)

One can readily employ vinylic iodides and triflates in this process and obtain a wide range of polycyclic aromatic hydrocarbons (Eq. 80) [147, 149].



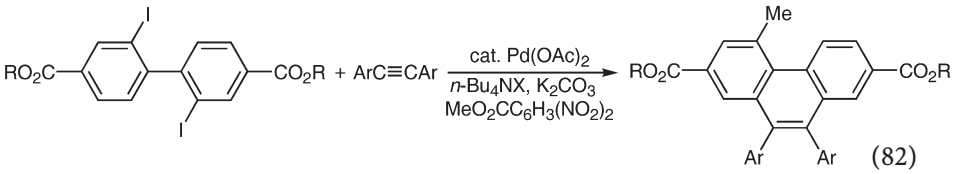
(80)

We have recently reported an intramolecular variant of this annulation process using an alkyne tethered to an indole (Eq. 81) [117, 118].



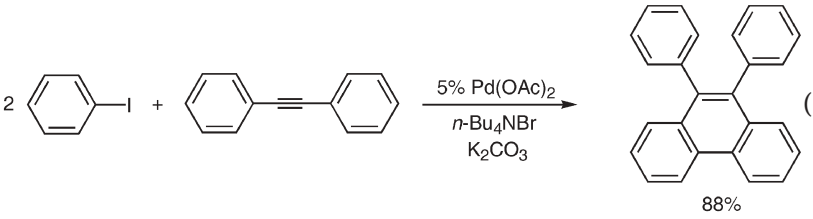
(81)

Apparent attempts to effect a double annulation using a diiodobiphenyl have been reported to produce a single alkyne insertion product, in which the second iodo group has been replaced by a methyl group from added methyl 3,5-dinitrobenzoate (Eq. 82) [150].



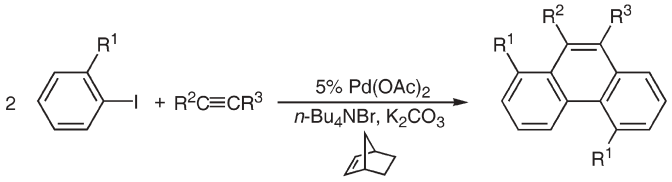
(82)

By simply modifying the reaction conditions and employing an excess of the aryl iodide, one can readily obtain 9,10-diarylphenanthrenes from the reaction of aryl iodides and diphenylacetylene (Eq. 83) [146, 151, 152].

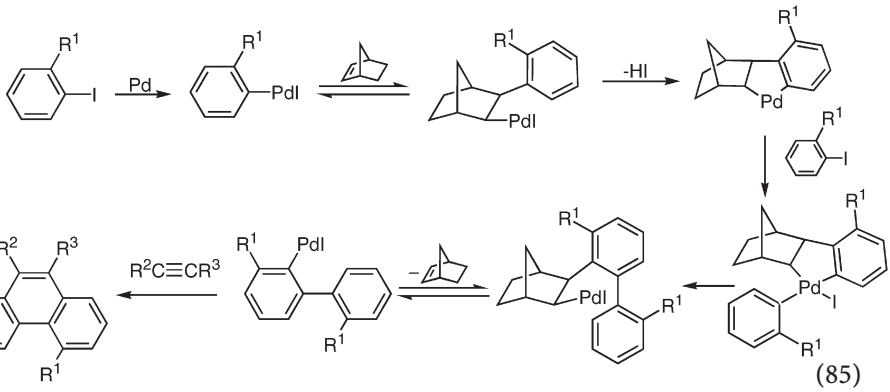


(83)

Recently this process has been extended to *ortho*-substituted aryl iodides and diphenyl- and alkylphenylacetylenes by adding norbornene (Eq. 84) [153]. This process proceeds by a mechanistically complicated series of insertion, deinsertion, and cross-coupling steps (Eq. 85).

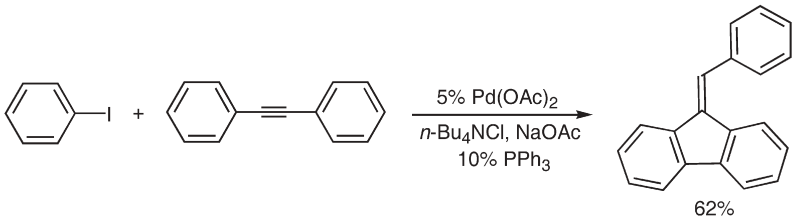


(84)



(85)

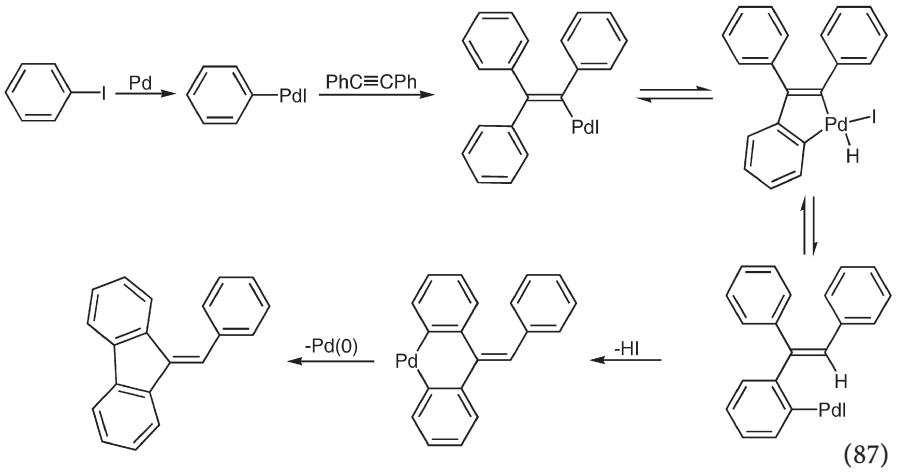
We have observed that by simply changing the base from K_2CO_3 to NaOAc in the phenanthrene synthesis shown in Eq. 83, we can obtain good yields of 9-alkylidene-9*H*-fluorenes instead (Eq. 86) [154, 155].



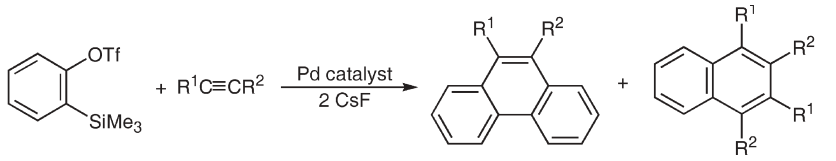
(86)

After optimization of the procedure, we have been able to employ a wide range of aryl alkynes and aryl halides in this process. This reaction involves a novel Pd migration from a vinylic position to an aryl position and subsequent ring closure (Eq. 87).

o-Silylaryl triflates have recently been shown to react with internal alkynes in the presence of a palladium catalyst to generate either phenanthrene products derived from two aryl units and one alkyne or naphthalenes derived from one aryl unit and two alkynes (Eq. 88) [156–158]. This reaction appears to involve an aryne intermediate.



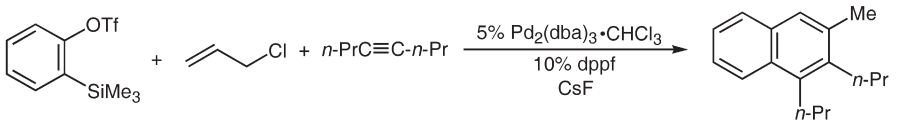
(87)



R^1, R^2 = CO_2Me, CO_2Me; CF_3, CF_3; CO_2Et, Me; Et, Et; Ph, Ph (88)

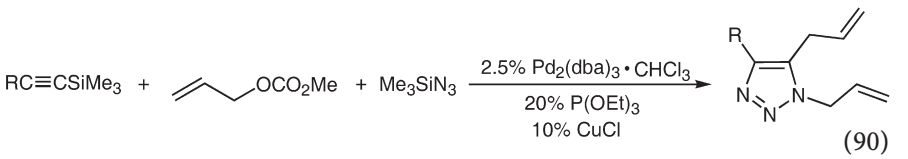
The catalyst $Pd(PPh_3)_4$ favors phenanthrene formation, while $Pd_2(dba)_3$ generates primarily the naphthalene product.

The cross-coupling of *o*-(trimethylsilyl)phenyl triflate, allyl chloride, and 4-octyne by a palladium catalyst has also been reported to generate a naphthalene product (Eq. 89) [159].



47% (89)

This process has been proposed to proceed by addition of π-allylpalladium chloride to benzyne, followed by a second insertion of benzyne, and cyclization of the resulting biphenylpalladium intermediate onto the allyl unit.



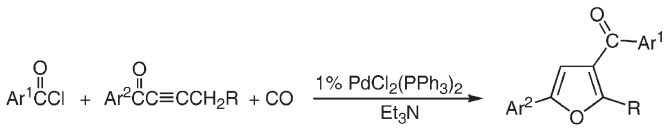
(90)

Finally, Yamamoto has recently reported the cross-coupling of a silylalkyne, allyl methyl carbonate, and trimethylsilyl azide to produce a diallyltriazole (Eq. 90) [160].

It is suggested that a copper acetylide reacts with either allyl azide or π-allylpalladium azide to generate the triazole ring.

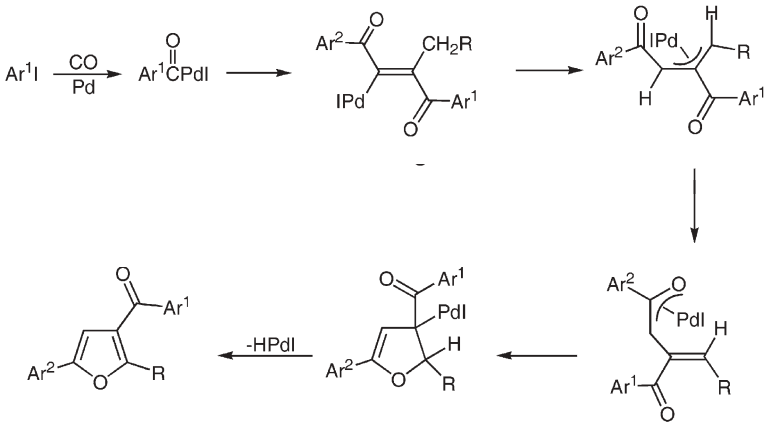
3.12 Annulation by CO and Aryl or Acyl Halides

The reaction of aryl halides and 1-aryl-2-alkyn-1-ones in the presence of a palladium catalyst and CO affords good yields of aroylfurans (Eq. 91) [161].



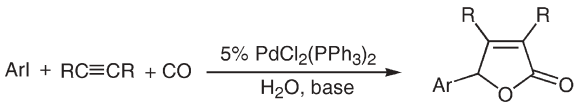
(91)

It has been suggested that this process involves the addition of an aroylpalladium intermediate to the alkyne, and an unusual 1,3-hydrogen shift to form a π-allylpalladium compound, which subsequently cyclizes and undergoes a hydride elimination (Eq. 92).



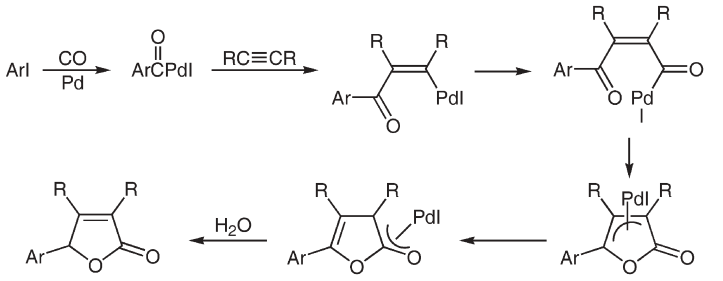
(92)

Simple aryl iodides and internal alkynes have been reported to react with one equivalent of water, CO, and a palladium catalyst to produce butenolides in modest yields (Eq. 93) [162].

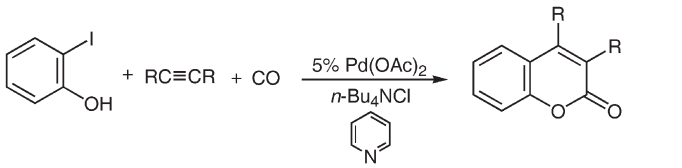


(93)

This reaction appears to proceed by aroylpalladium addition to the alkyne, CO insertion, and cyclization of the acylpalladium species, followed by protonation by water (Eq. 94).

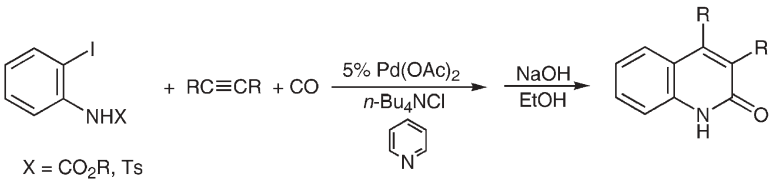


We have disclosed the facile synthesis of coumarins by the palladium-catalyzed coupling of *o*-iodophenols, internal alkynes, and CO (Eq. 95) [163, 164].



The key to the success of the reaction is the presence of pyridine. The reaction appears to proceed by generation of an arylpalladium intermediate and sequential insertion of the alkyne and CO, followed by lactone formation. This sequence is a bit unusual, since the literature suggests that CO should insert more readily than the alkyne. It may well be that CO insertion does indeed occur first, but that it is reversible and that alkyne insertion is not reversible.

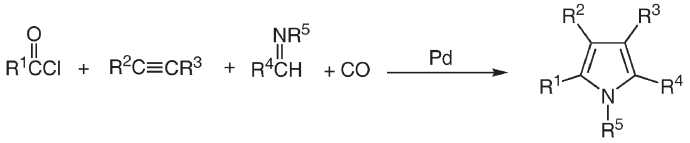
We have also observed that this alkyne/CO double-insertion process can be employed to synthesize 2-quinolones as well (Eq. 96) [165].



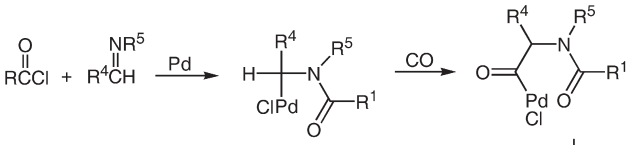
In this case, the nitrogen needs to be protected as a carbamate or tosylamide, but the protecting group is partially removed during the reaction and completely removed during the workup.

Finally, acyl halides, aldehyde imines, and internal alkynes have recently been shown to react in the presence of CO and a palladium catalyst to gener-

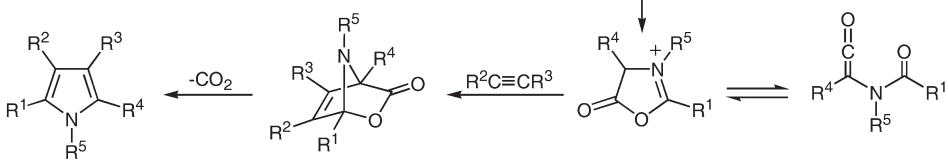
ate good yields of pyrroles (Eq. 97) [166]. This reaction appears to proceed as shown in Eq. 98.



(97)



(98)



4 Conclusions

Palladium has been shown to catalyze a large number of alkyne annulation processes, which afford a wide range of heterocycles and carbocycles. Most processes are initiated by the oxidative addition of an aryl or vinylic halide to Pd(0) and subsequent reaction with either a terminal or internal alkyne. Although the products are often very similar from terminal and internal alkynes, the mechanisms for the two processes are generally quite different. The reactions of terminal alkynes usually involve initial cross-coupling to form an aryl alkyne, which then undergoes a copper- or palladium-catalyzed cyclization. On the other hand, internal alkynes usually react by organopalladium addition to the triple bond of the alkyne to generate a vinylic palladium intermediate, followed by some type of cyclization process. These processes have proven extremely valuable for the synthesis of oxygen- and nitrogen-containing heterocycles, particularly benzofurans and indoles. In the future, one can expect a steady stream of new palladium-catalyzed processes and numerous applications of this methodology to the synthesis of natural products and pharmacologically interesting substrates to be reported.

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Palladium-Catalyzed Two- or Three-Component Cyclization of Functionalized Allenes

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Abstract This review summarizes the Pd-catalyzed cyclization of an allene bearing a nucleophilic functionality with an organic or inorganic halide, and the cyclization involving two allene moieties or an allene–alkene, allene–1,3-diene, allene–alkyne, allene–aldehyde, or allene–ketone combination in the presence or absence of an organic halide. The cyclic compounds were formed highly selectively via (1) intermolecular carbopalladation–intramolecular allylic substitution, (2) intramolecular nucleopalladation–intermolecular carbopalladation, or (3) an intermolecular carbopalladation (hydropalladation, etc.)–intramolecular insertion mechanism. The selectivity of these reactions largely depends on the substitution pattern of the allene moiety and the nature of the palladium catalyst. In all these reactions, the regeneration of the catalytically active palladium species is the key for a catalytic reaction.

Keywords Allenes · Cyclization · Nucleophile · Selectivity · Mechanism

Abbreviations

BQ	Benzoquinone
DBA	Dibenzylideneacetone
DMA	Dimethylacetamide
DMF	Dimethylformamide
Mts	2,4,6-Trimethylphenylsulfonyl

o-Ns	*o*-Nitrophenylsulfonyl
TBAB	Tetrabutylammonium bromide
$TCPC^{TFE}$	Tetrakis[(2,2,2-trifluoroethoxy)carbonyl]palladacyclopentadiene
THF	Tetrahydrofuran
Ts	4-Toluenesulfonyl

1 Introduction

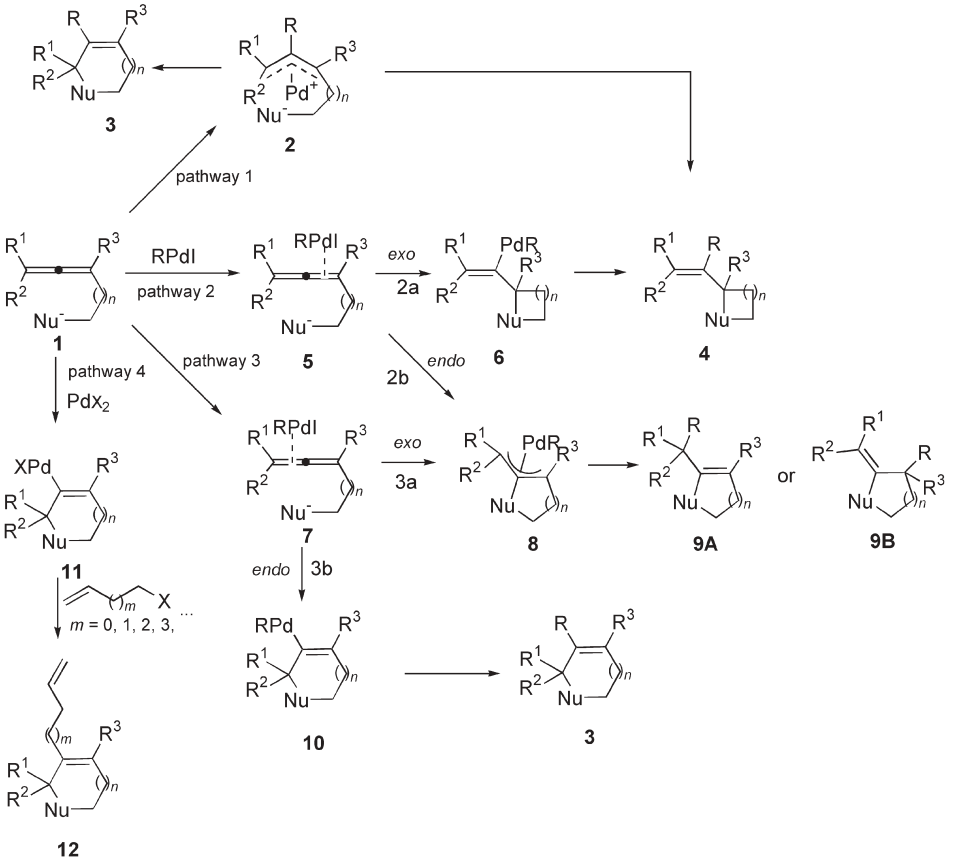
Allenes are a class of compounds with unique reactivity due to the presence of the cumulated diene unit, which also makes the chirality of allenes [1]. For a long period of time, this class of compounds has been considered as very unstable [2]. In reality allenes are not so unstable; recent observations have shown that allenes possess good reactivity and selectivity in organic synthesis [3]. Since some of the most recent advances in the chemistry of allenes have been summarized in several reviews and accounts, this chapter will summarize the typical advances in Pd-catalyzed two- or three-component cyclization of functionalized allenes, which have not been included in these reviews and accounts [3].

2 Two- or Three-Component Cyclization of Allenes Bearing a Nucleophilic Functionality with Organic or Inorganic Halides

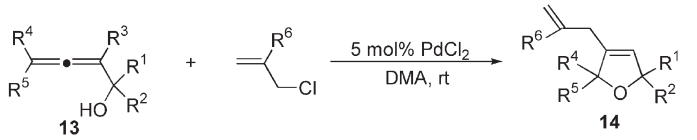
In the Pd-catalyzed cyclization of allenes with a nucleophilic functionality, there are two types of reactions: (1) the carbopalladation of the allene **1** leading to a π-allyl intermediate **2**, and (2) intramolecular nucleopalladation leading to the intermediates **6**, **8**, **10**, or **11** depending on the nature of the catalyst and the starting allenes (Scheme 1).

It is known that under the catalysis of a Pd(0) complex, the reaction of 2,3-allenols with organic halides would afford *trans*-vinylic epoxides [4]. However, under the catalysis of Pd(II) catalysts, such as $PdCl_2$, $PdCl_2(MeCN)_2$, $Pd(OAc)_2$, or $[(\pi\text{-}C_3H_5)PdCl]_2$, the reaction of 2,3-allenols with allylic halides in DMA or DMF afforded five-membered-ring 3-allylic 2,5-dihydrofurans **14** in moderate to good yields highly selectively (Scheme 2). The formation of the corresponding epoxides was not observed [5].

The yield of 2,5-dihydrofurans depends largely on the substitution patterns of the allene moiety: (1) R^3 can be H or an alkyl, aryl, or ethoxycarbonyl group; R^4 and R^5 can be H or alkyl; 4,4-disubstituted-2,3-allenols were also successfully applied; (2) R^1 or R^2 can be an aryl or alkyl group. Primary, secondary, and tertiary alcohols all underwent this coupling cyclization. However, for unsubstituted allenols, the reaction is rather complicated, affording 3-allyl-2,5-



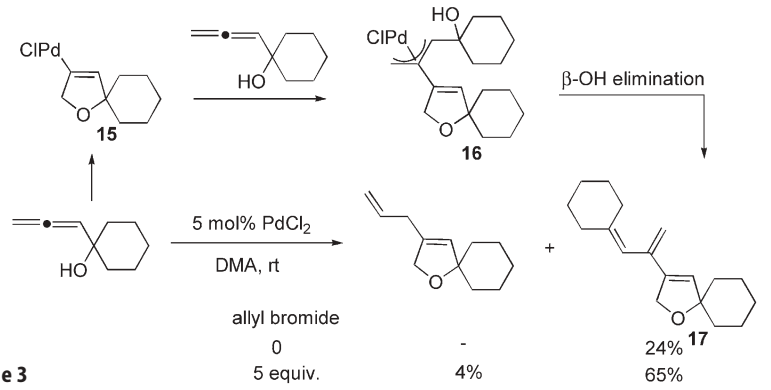
Scheme 1



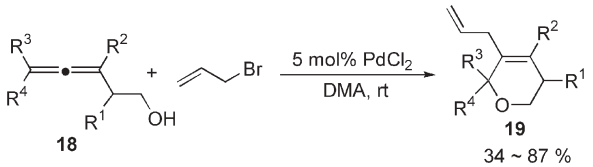
Scheme 2

dihydrofurans in rather low yields. The reaction of 1-(propadienyl)cyclohexanol afforded the bimolecular cyclized homocoupling product **17**, which was formed via the oxypalladation–insertion–β-OH elimination mechanism (Scheme 3) [5].

3,4-Allenols behaved similarly affording 5,6-dihydro-2*H*-pyrans **19** (Scheme 4). No expected product was found for the 3,4-allenols with $R^2=R^3=R^4=H$. Through control experiments with π-allylic Pd complexes it is believed that the reaction proceeded via the sequential intramolecular oxypalladation–intermolecular carbopalladation–β-dehalopalladation process (pathway 4, Scheme 1).

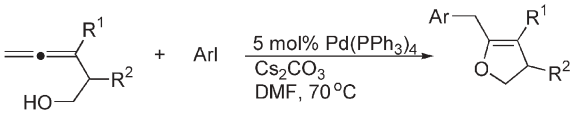


Scheme 3



Scheme 4

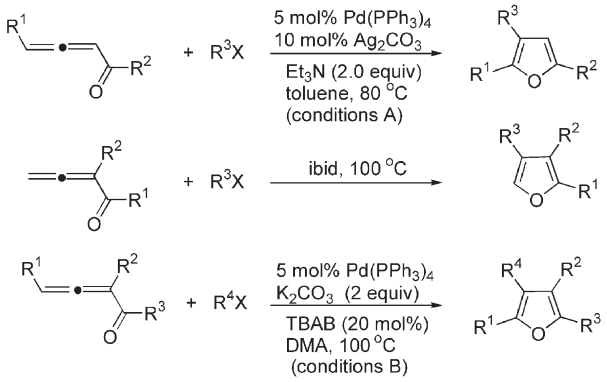
Under the catalysis of $Pd(PPh_3)_4$, the reaction of 3,4-allenols with phenyl iodide in DMF afforded 2,3-dihydrofurans exclusively (Scheme 5) [6]. The products may be formed via oxypalladation forming intermediate **8** and a subsequent highly regioselective reductive elimination mechanism (pathways 2b and 3a, Scheme 1).



Scheme 5

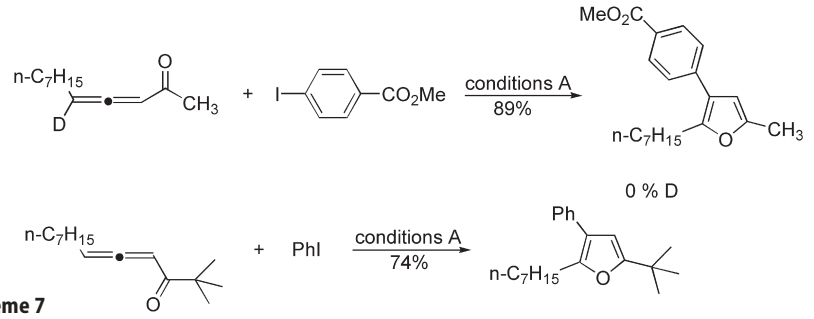
We have also shown that under the catalysis of $Pd(PPh_3)_4$ and Ag_2CO_3, the coupling cyclization of 1,2-allenyl ketones with organic halides afforded polysubstituted furans (Scheme 6). The diversity of the reaction depends on the structures of the two starting materials, i.e., once the expected substituent is in a certain location of two starting materials, it can be assembled into the expected location of polysubstituted furans. However, for the synthesis of tetrasubstituted furans, the reaction should be carried out in the presence of 20 mol% of n-$Bu_4N^+Br^-$ in DMA (conditions B).

The coupling cyclization of 3-deuterated 1,2-decadienyl methyl ketone with iodobenzoate under the conditions A afforded nondeuterated 2,3,5-trisubstituted furans in 89% yield (Scheme 7). Furthermore, *t*-butyl 1,2-decadienyl ketone can also undergo coupling cyclization with PhI under the conditions A



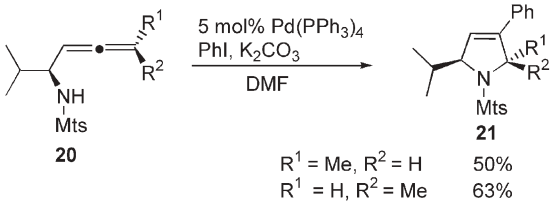
Scheme 6

to afford the corresponding product in 74% yield, indicating that the carbonyl group may act directly as a nucleophile or participate in the insertion reaction with the π-allyl Pd intermediate, which was formed via the carbopalladation of the electron-deficient allenes [7].



Scheme 7

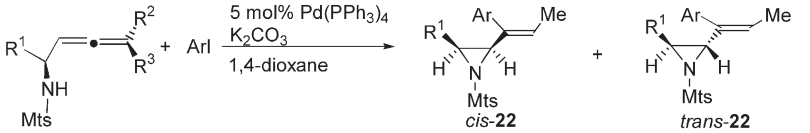
Ibuka et al. observed that under the catalysis of $Pd(PPh_3)_4$ (4–20 mol%), optically active 2,3-allenyl amines **20** can be cyclized in the presence of aryl halides in DMF (Scheme 8). The chirality of the allene moiety was smoothly transferred into the final products, i.e., 2,5-dihydropyrrole [8].



Scheme 8

However, it is quite interesting to note that the same reaction in dioxane afforded the *cis*- or *trans*-aziridines **22** as the major products depending on the absolute configuration of the allene moiety (Scheme 9). In some cases the

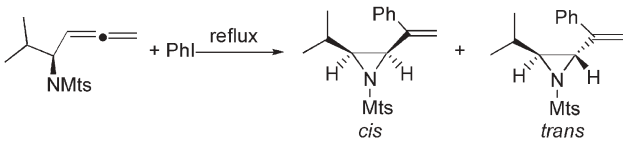
low-yielding formation of 2,5-dihydropyrroles was also observed. With R^2=R^3=H, the stereoselectivity depends on the reaction time. Obviously the *cis* isomer is the thermodynamically more stable product (Scheme 10).



R^1 = *i*-Pr, Bn, $TBSOCH_2$; R^2 = Me, R^3 = H or R^2 = H, R^3 = Me
Ar = phenyl, *p*-methylphenyl

Scheme 9

R^1 = *i*-Pr, R^2 = Me, R^3 = H	80%	82	:	18
R^1 = *i*-Pr, R^2 = H, R^3 = Me	79%	2	:	90

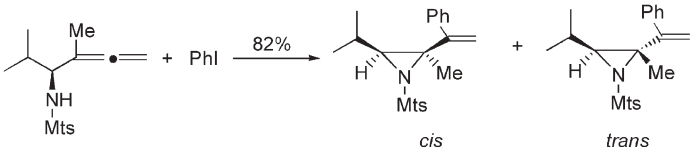


Scheme 10

1.5 h	80%	74	:	26
2.5 h	79%	94	:	6

The reaction of the α-methyl-substituted allenylamine **23** afforded the *trans* product with a de ratio of 94/6 (Scheme 11). 3,4-Allenyl amines **24** underwent the same transformation in DMF to afford the four-membered-ring *cis*-alkenyl azetidines **25** (Scheme 12). The reaction of **24** with R^2=*o*-Ns in DMF or R^2=Mts in dioxane afforded the same products with relatively low stereoselectivity. Formation of a π-allylpalladium intermediate and cyclic allylic substitution was proposed for this reaction (pathway 1, Scheme 1).

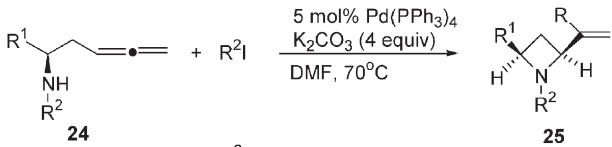
In 1999, Hiemstra et al. demonstrated that the $Pd(PPh_3)_4$-catalyzed reaction of 1-methoxycarbonyl-3,4-allenyl amines **26** with aryl iodides (triflates) or



Scheme 11

23

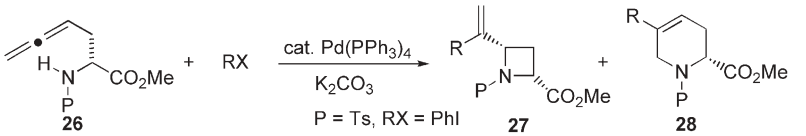
6	:	94



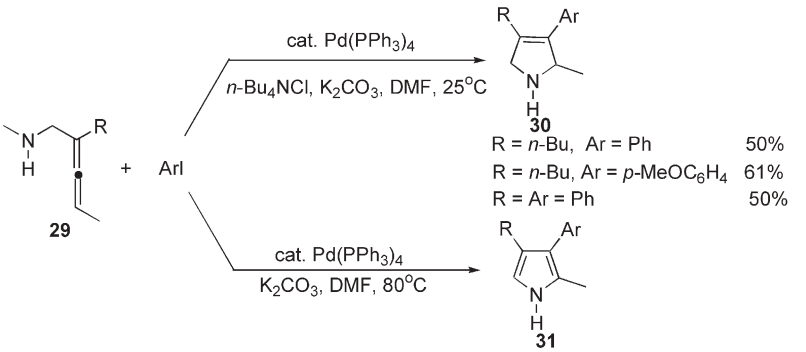
24 **25**

Scheme 12 R^2 = Mts, Ts, *o*-Ns, Ts

vinylic triflates afforded the four-membered-ring *cis*-vinylic azetidines **27** and six-membered-ring tetrahydropyridine derivatives **28** (Scheme 13) [9]. The yield and selectivity depend on the protecting group of the amino group and solvent as well as the reaction temperature. Dieters et al. observed that the reaction of 2,3-allenyl amines **29** with aryl iodides afforded pyrrolines **30** or pyrroles **31** depending on the reaction conditions (Scheme 14) [10].

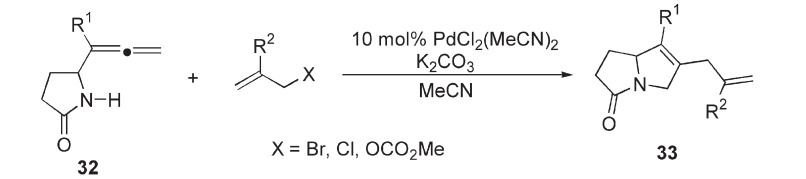


Scheme 13



Scheme 14

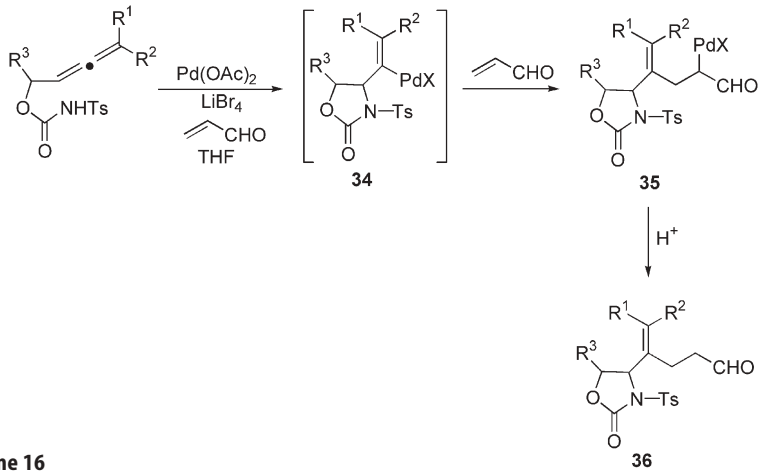
Hiemstra et al. studied the Pd(II)-catalyzed reaction of ɣ-allenyl-ɣ-lactams **32** with allylic halide or carbonate, affording fused bicyclic products **33** (Scheme 15) [11]. With R^1 as H, the expected product was not formed. Based on these experimental observations, a Pd(II)-catalyzed intramolecular azapalladation–intermolecular carbopalladation of the C=C bond in allylic halides (or carbonates)–β-deheteroatom palladation was proposed (pathway 4, Scheme 1).



Scheme 15

However, the same product can also be formed by using a stoichiometric amount of $[(\pi\text{-}C_3H_5)PdCl]_2$ as the allylating agent, which indicates that a Pd(0)-catalyzed mechanism may also be possible (pathway 1, Scheme 1).

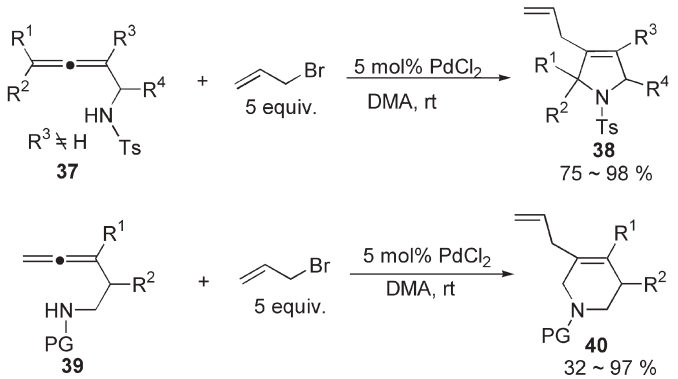
Lu et al. also observed that the vinylic palladium intermediate **34** formed by the Pd(II)-catalyzed azapalladation can be trapped by using α,β-unsaturated enals to afford aldehyde derivatives **36** (Scheme 16) [12]. In this reaction the



Scheme 16

Pd(II) catalyst was regenerated via protonation of the C–Pd bond in **35**, which was obviously facilitated by the presence of the CHO group.

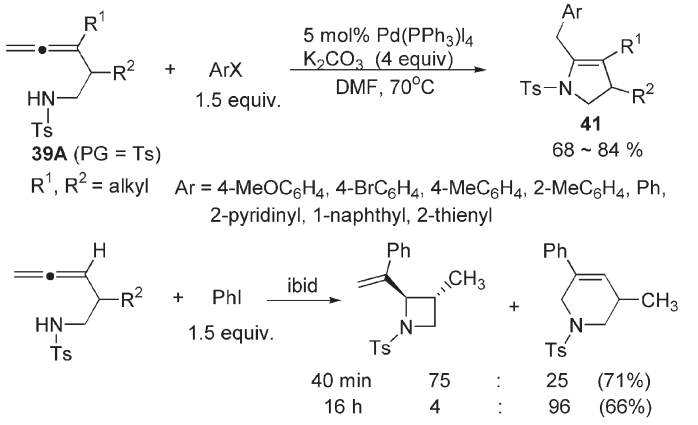
We have shown that *N*-(2,3-allenyl)toluenesulfonamides **37** or *N*-(3,4-allenyl)toluenesulfonamides **39** can undergo coupling cyclization with allylic halides, leading to 3-allylic 2,5-dihydropyrroles **38** and 1,2,5,6-tetrahydropyridines **40**, respectively (Scheme 17) [13]. Control experiments of the reactions of *N*-(2-methyl-2,3-decadienyl)toluenesulfonamide with 2-butenyl chloride/3-



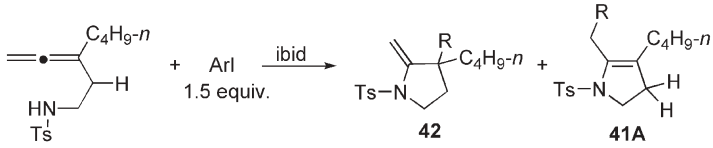
Scheme 17 PG = Ts, Ns, Ac

buten-2-yl chloride or π-allylic palladium species and optically active allenylamines excluded the possibility of a π-allylic palladium intermediate. Thus, a Pd(II)-catalyzed mechanism (pathway 4, Scheme 1) was proposed for this reaction.

We have also observed that under the catalysis of $Pd(PPh_3)_4$, the reaction of 3,4-allenyl toluenesulfonamides with aromatic halides afforded 2,3-dihydropyrroles **41** or a mixture of vinylic azetidines and 1,2,3,6-tetrahydropyridines, depending on the substituent at the 3 position of the 3,4-allenyl group (Scheme 18) [14]. With R^1 being *n*-butyl and R^2 being H, the reaction afforded two isomeric products **42** and **41A**, referring to the positions of the C=C bond and the R group in the products (Scheme 19). The ratio is 85:15 with 2,3-dihydropyrroles **41A** being the major product.

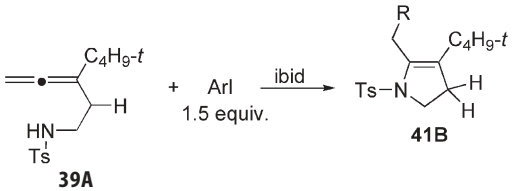


Scheme 18



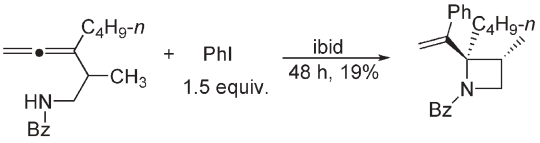
Scheme 19

The reaction of **39A** with R^1 being *t*-butyl and R^2 being H afforded 2,3-dihydropyrroles **41B** as the only product, probably due to the steric effect of the bulky *t*-butyl group (Scheme 20). However, it is quite interesting to observe that



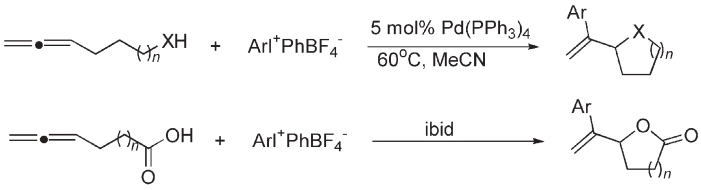
Scheme 20

the reaction of *N*-(2-methyl-3-butyl-3,4-pentadienyl)benzamide **39B** with PhI under similar reaction conditions afforded *trans*-vinylic azetidine as the only product, albeit in only 19% yield (Scheme 21) [14].

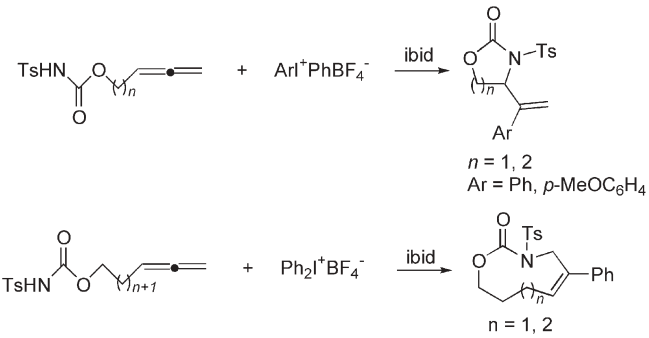


Scheme 21 **39B**

Kang et al. showed that under the catalysis of $Pd(PPh_3)_4$ (5 mol%) the reactions of 4,5- or 5,6-allenyl alcohols/toluenesulfonamides and 4,5- or 5,6-allenoic acids with hypervalent iodonium salts led to the formation of five- or six-membered-ring heterocyclic products (Schemes 22 and 23) [15, 16]. With *N*-(3,4-pentadienyl)toluenesulfonamide, a mixture of four- and six-membered-ring products was also formed.

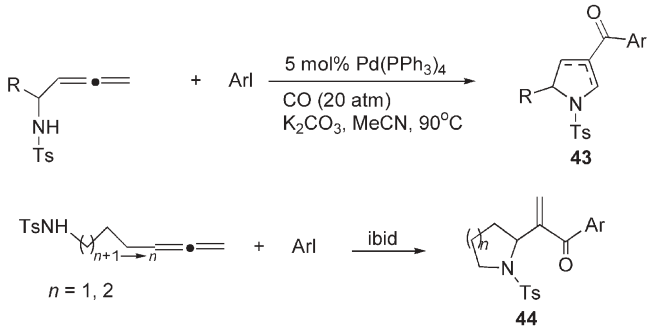


Scheme 22



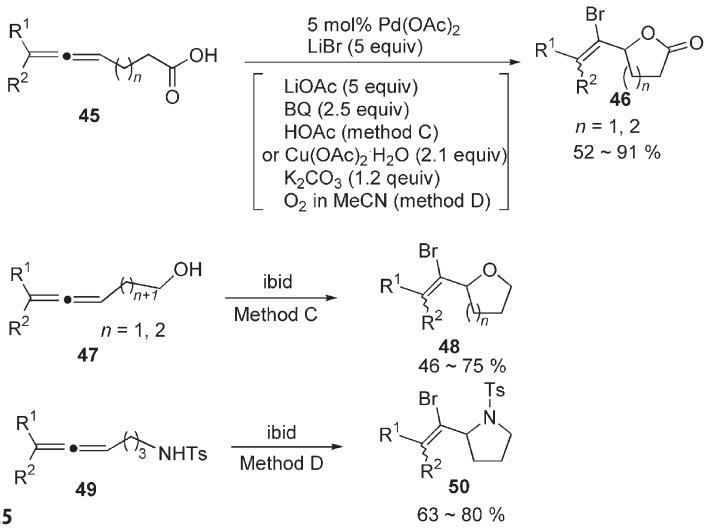
Scheme 23

Kang et al. also demonstrated that in the presence of CO (20 atm), the carbonylative coupling cyclization of 2,3-, 4,5-, or 5,6-allenylamines with ArI can be realized to afford aroyl-substituted N-containing heterocycles **43** and **44** (Scheme 24) [17]. The reaction proceeded via aroylpalladation of the allene moiety leading to a π-allyl palladium intermediate, which underwent an intramolecular nucleophilic attack to form the product (pathway 1, Scheme 1).



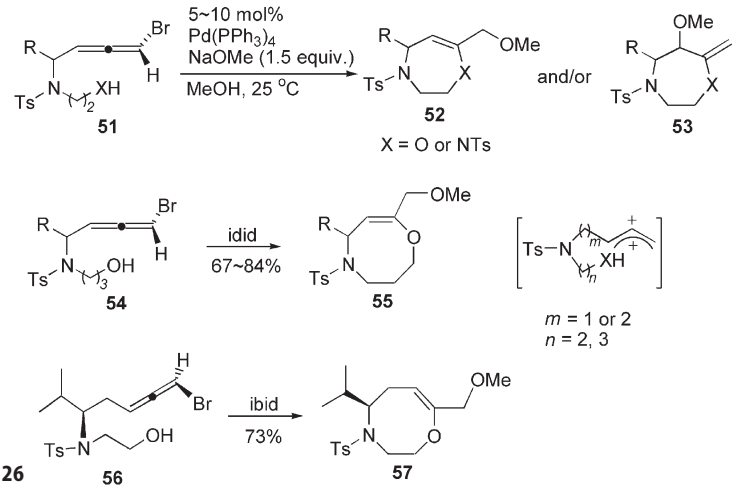
Scheme 24

Bäckvall et al. demonstrated the Pd(II)-catalyzed cyclizations of 4,5- or 5,6-allenoic acids **45**, 3,4- or 4,5-allenols **47**, and 4,5-allenyltoluenesulfonamides **49** with LiBr (Scheme 25). The reaction was initiated with bromopalladation of the allene moiety affording a 2-bromo-substituted π-allylic palladium intermediate, which underwent intramolecular nucleophilic substitution to afford the heterocyclic products and Pd(0) (pathway 1, Scheme 1). The in situ generated Pd(0) was oxidized to the catalytically active Pd(II) species by its reaction with benzoquinone [18].

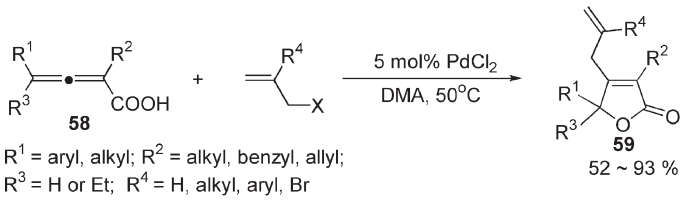


Scheme 25

Tanaka et al. established the chemistry of using the bromoallene moiety as the equivalent of allyl dications.This dication can react with an intermolecular nucleophile (MeOH) and an intramolecular nucleophile to form heterocyclic alkenes (Scheme 26) [19]. The $PdCl_2$-catalyzed reaction of 2,3-allenoic acids **58** with allylic halides in DMA at 50 °C afforded 4-allylic-substituted 2(5*H*)-furanones **59** in moderate to excellent yields (Scheme 27) [20].

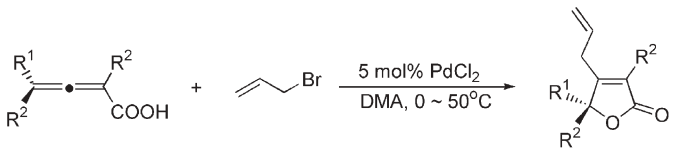


Scheme 26



Scheme 27

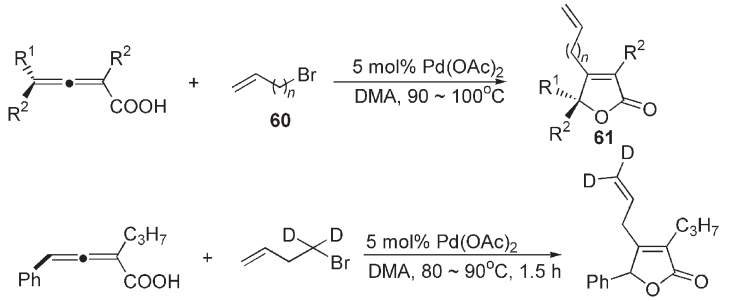
The chirality of the allene moiety in the starting acid can be transferred into the chiral center of β-allylic butenolides without obvious racemization (Scheme 28), indicating a Pd(II)-catalyzed oxypalladation–carbopalladation–dehalopalladation mechanism (pathway 4, Scheme 1) [20].



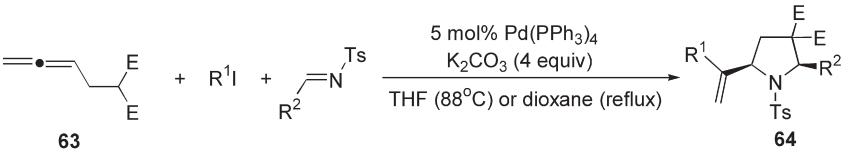
Scheme 28

$Pd(OAc)_2$ can catalyze the reaction of 2,3-allenoic acids with non-allylic alkenyl bromides with a terminal C=C bond leading to β-alkenyl butenolides **61** and **62** (Scheme 29). The reaction proceeded via oxypalladation–carbopalladation, repeated β-dehydropalladation/hydropalladation–dehalopalladation, in which Pd(II) is the catalytically active species [21].

We have also established the three-component tandem double addition–cyclization reaction of 2-(2,3′-dienyl)malonates **63**, imines, and organic halides,



Scheme 29

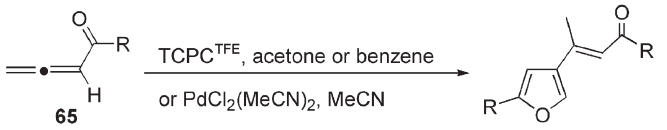


Scheme 30

leading to the highly stereoselective formation of *cis*-pyrrolidine derivatives **64** (Scheme 30) [22].

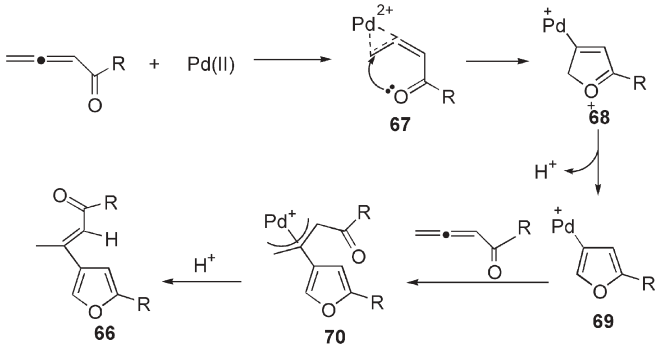
3
Cyclization Involving Two Allene Moieties

In 1997, Hashmi et al. observed the Pd-catalyzed homodimerization of 1,2-allenyl ketones affording 2-substituted 4-(4′-oxo-2′-alken-2′-yl)furans (Scheme 31) [23]. The reaction may proceed via intramolecular oxypalladation involving the carbonyl oxygen, leading to the formation of furanylpalladium intermediate **69**, followed by intermolecular carbopalladation with a second molecule of 1,2-allenyl ketone. Protonation of the C–Pd bond in **70** afforded the product **66** and regenerated Pd(II) (Scheme 32).

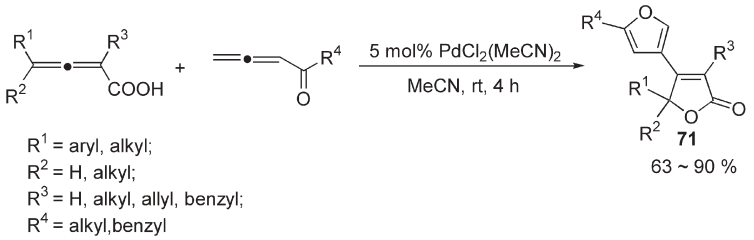


Scheme 31

We have demonstrated the first example of oxidative dimeric cyclization between two different classes of allenes, i.e., 2,3-allenoic acids and 1,2-allenyl ketones. The product is a dumb-bell-type bicyclic product 4-(3′-furanyl)-butenolide **71** (Scheme 33) [24].

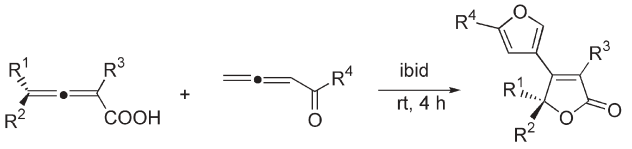


Scheme 32

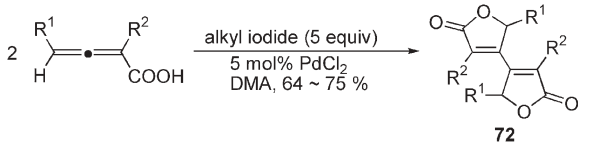


Scheme 33

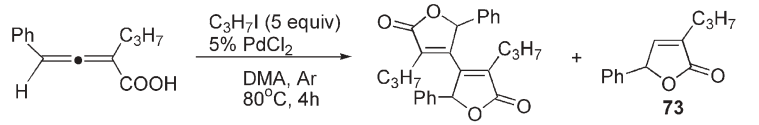
From optically active 2,3-allenoic acids the corresponding optically active butenolides can be prepared in high yields and ee values. In this reaction excess 1,2-allenyl ketone (5 equiv) was applied in order to regenerate the catalytically active Pd(II) species via cyclometalation and protonation (Scheme 34) [24]. In the presence of an excess amount of alkyl iodide, the $PdCl_2$-catalyzed homodimeric cyclization of 2,3-allenoic acids in DMA at 80 °C afforded bi-butenolides **72** in high yields (Scheme 35) [25]. When the reaction was conducted under an atmosphere of argon, the bi-butenolide was formed in low yield together with the cycloisomerization product butenolide **73** (Scheme 36). It is believed that the in situ generated Pd(0) may be oxidized to the catalytically active Pd(II) by the action of alkyl iodide and O_2 in air [25].



Scheme 34

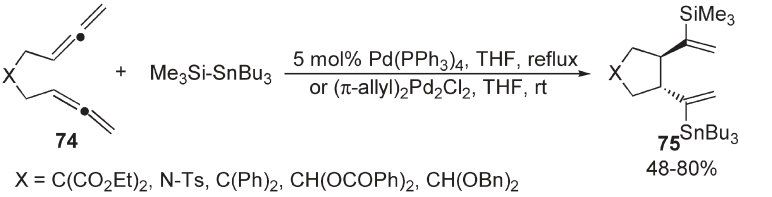


Scheme 35

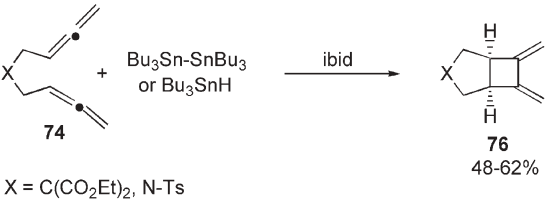


Scheme 36

Kang et al. showed that $Pd(PPh_3)_4$ can catalyze the cyclization of bis(allenes) **74** with Me_3SiSnR_3 in THF affording *trans*-1-trimethylsilylethenyl-2-trialkylstannyl-substituted five-membered cyclic products **75** highly stereoselectively (Scheme 37) [26]. However, it is quite unique to note that the same reaction with $(Bu_3Sn)_2$ or Bu_3SnH afforded fused bicyclo[3.2.0]heptane **76** (Scheme 38).



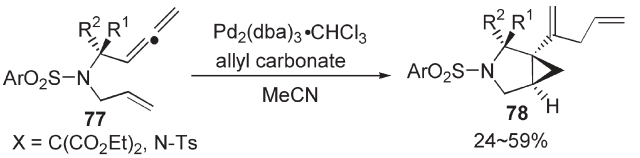
Scheme 37



Scheme 38

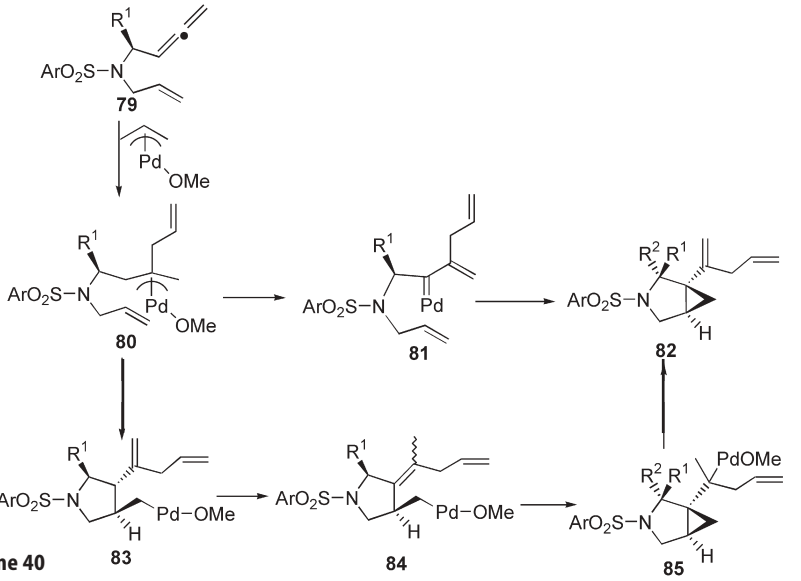
4
Cyclization of Allene–Alkene Combinations

In 2003, Ohno and Tanaka et al. observed that 3-azabicyclo[3.1.0]hexane **78** can be prepared from the $Pd_2(dba)_3{\cdot}CHCl_3$-catalyzed reaction of *N*-allyl-*N*-(2,3-dienyl)toluenesulfonamides **77** with allylic carbonate in MeCN (Scheme 39) [27]. The reaction may proceed via the carbopalladadtion of π-allylpalladium species generated from the interaction of Pd(0) and allyl carbonate with the allene moiety to afford a new π-allyl palladium species **80.** This π-allylpalladium



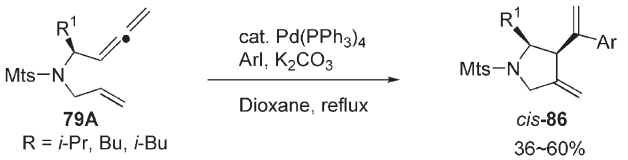
Scheme 39

intermediate may undergo rearrangement to form the metallocarbene intermediate **81**, followed by intramolecular cyclopropanation to afford the final product **82.** An alternative is the subsequent carbopalladation of the C=C bond to form the sp^3 C–Pd intermediate **83,** which underwent a C=C bond migration to form intermediate **84.** Intramolecular carbopalladation formed the bicyclic intermediate **85**, which led to the final production via dehydropalladation (Scheme 40).

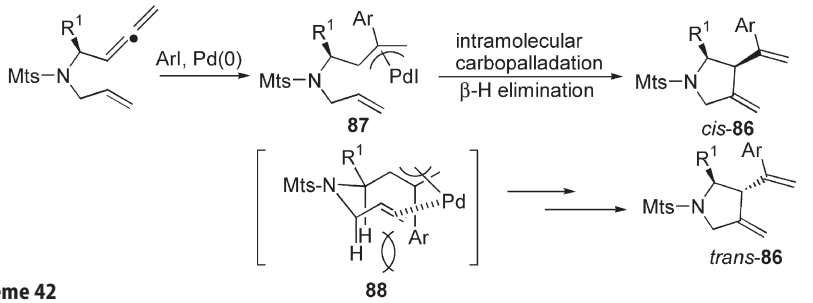


Scheme 40

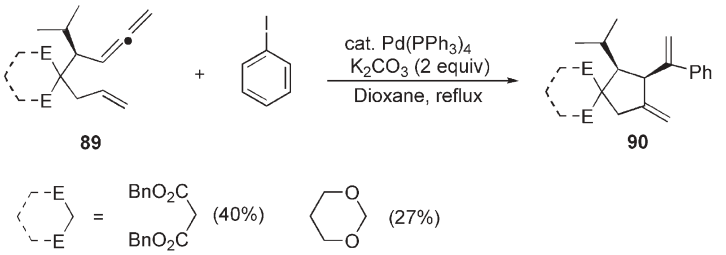
A similar reaction of *N*-allyl-*N*-(2,3-allenyl)mesitylenesulfonamides **79A** with aryl halides in dioxane afforded *cis*-2-alkyl-3-(1′-arylethenyl)-4-methylenepyrrolidines **86** via carbopalladation–stereoselective intramolecular carbopalladation–dehydropalladation (Scheme 41) [28]. Here the diastereoselectivity may be determined by the unfavorable steric interaction between the pseudoaxial hydrogens and the aromatic group in intermediate **88**, which would lead to the formation of the *trans* product **86** (Scheme 42). This chemistry has been extended to the carbon-tethered allenenes **89** (Scheme 43) [28]. In cases of more substituted C=C bonds, further cyclization with the aromatic ring from ArI was observed to afford fused tricyclic products **91** or tetracyclic products **92** (Scheme 44) [29].



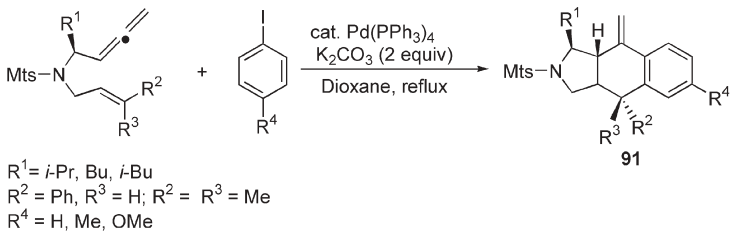
Scheme 41

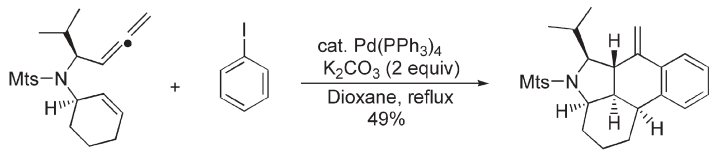


Scheme 42



Scheme 43

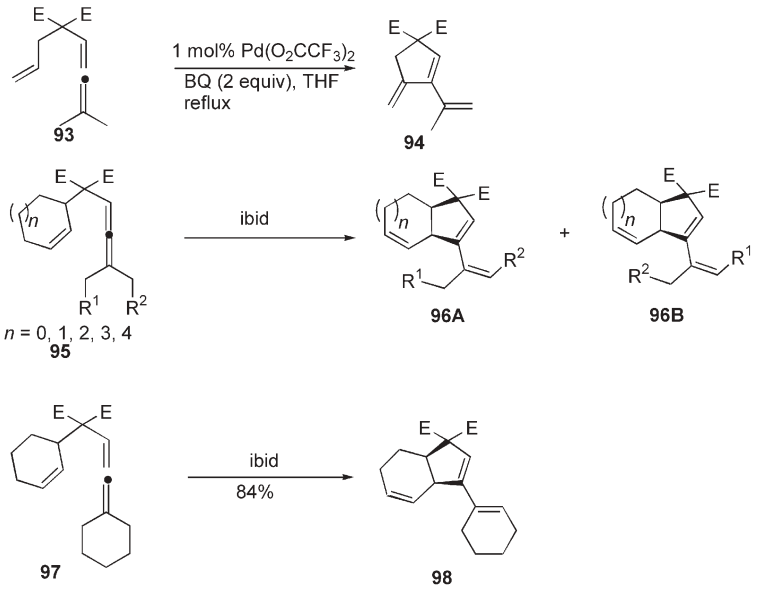




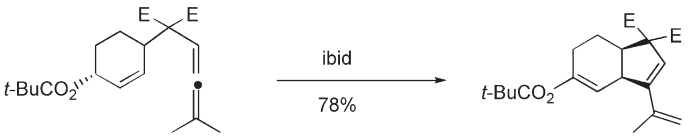
Scheme 44

Bäckvall et al. studied Pd(II)-catalyzed cyclization between the allene moiety and the alkene moiety in 2-allylic-2-(1′,2′-allenyl)malonates **93**, **95**, and **97** in the presence of two equivalents of benzoquinone in THF (Scheme 45) [30]. The reactions of **95** and **97** leading to cyclopentene-containing fused bicyclic products showed an excellent *cis* stereoselectivity, probably due to the formation of the cyclopentene ring.

Due to the presence of the Pd(II) catalyst, the allylic carboxylate moiety in **99** can also survive under these reaction conditions to afford bicyclic vinylic ester **100** (Scheme 46). The reaction was believed to proceed via the attack of



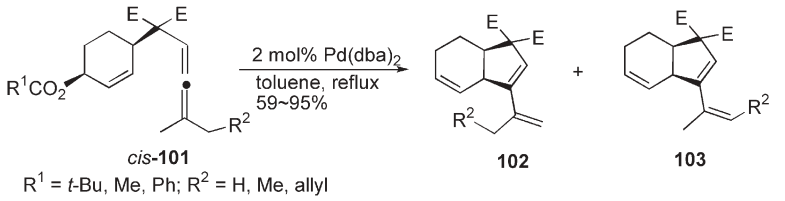
Scheme 45



Scheme 46

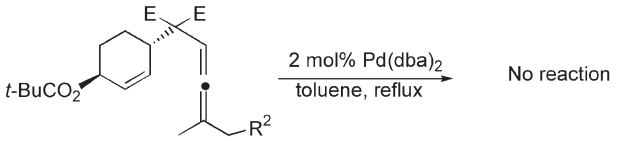
the allene moiety on Pd(II), affording a 1,3-dienylpalladium intermediate. This intermediate can further intramolecularly react with the alkene moiety to form the cyclopentene ring. The final step consisting of β-H elimination would afford the products.

Actually it is true that under the catalysis of a Pd(0) species, i.e., $Pd(dba)_2$, the *cis*-cyclohexyl carboxylate-allene **101** afforded the bicyclic trienes **102** and **103** via the oxidative addition of the allylic carboxylate moiety forming a π-allylic Pd intermediate, which underwent intramolecular carbopalladation and β-H elimination to afford the *cis* fused bicyclic products **102** and **103** (Scheme 47)



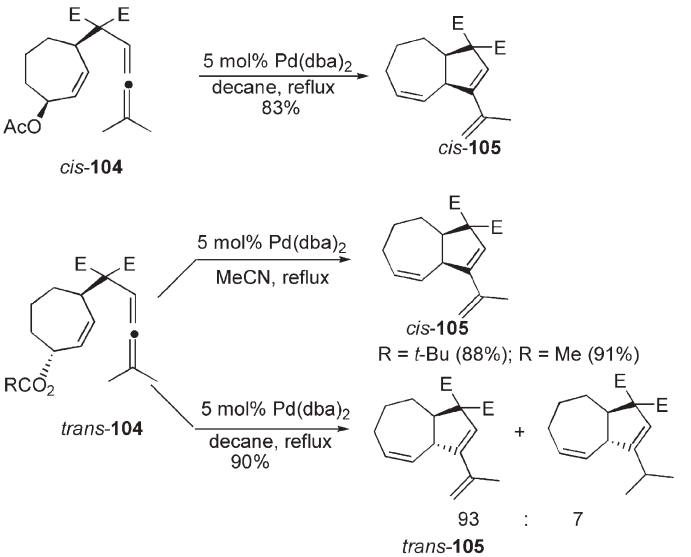
Scheme 47

[31]. The *cis* stereoselectivity is also determined by the formation of the cyclopentene ring. Under the same reaction conditions, no reaction was observed with the *trans* isomer **101** (Scheme 48).



Scheme 48 *trans*-**101**

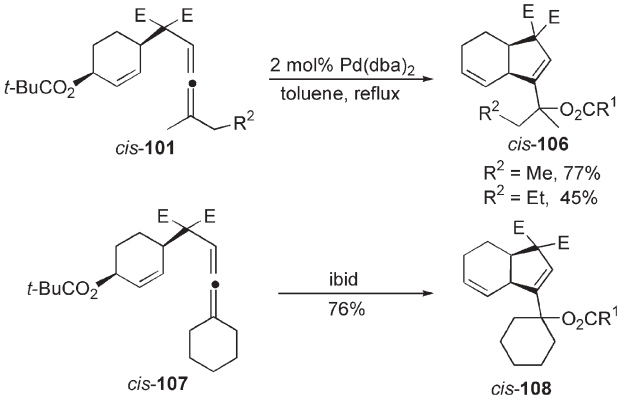
For a starting material containing a seven-membered ring, i.e., cycloheptadienyl carboxylate-allene **104**, both the *cis* isomer and the *trans* isomer can be cyclized to afford the *cis*- or *trans*-fused bicyclic product **105** highly stereoselectively depending on the solvent applied (Scheme 49). The formation of the *trans*-fused product **105** is made possible due to the flexibility of the seven-membered ring [31].



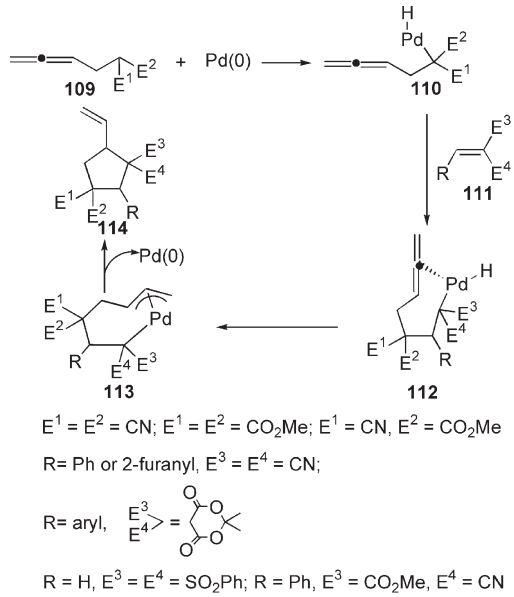
Scheme 49

When the reaction of *cis*-cyclohexyl carboxylates **101** and **107** was conducted in the presence of maleic anhydride (1 equiv) in toluene, a cycloisomerization affording *cis*-fused bicyclic alkyl carboxylates **106** and **108** was observed (Scheme 50) [31].

Yamamoto et al. developed the Pd-catalyzed [3+2] cycloaddition reaction of 2-(2′,3′-allenyl)malonates **109** with electron-deficient olefins bearing two geminal electron-withdrawing groups **111** (Scheme 51). The reaction proceeded via the oxidative addition of the C–H bond at the 2 position of the starting



Scheme 50



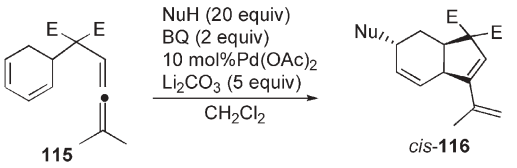
Scheme 51

malonate with Pd(0) to generate a palladium hydride species **110**, which underwent carbopalladation with the electron-deficient C=C bonds leading to the formation of a 5,6-allenyl palladium hydride **112**. Sequential hydropalladation and reductive elimination afforded the vinylic cyclopentane **114** [32].

5 Cyclization of Allene–1,3-Dienes in the Presence of a Nucleophile

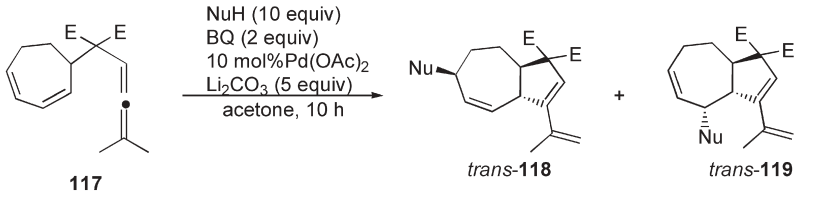
In the presence of benzoquinone (2 equiv), the allene-1,3-cyclohexdiene **115** afforded the *cis*-fused bicyclic triene **116** under the catalysis of $Pd(OAc)_2$

(Scheme 52) [33]. When this reaction was extended to allene-1,3-cycloheptadiene **117**, with HOAc as the nucleophile, both *trans*-fused bicyclic 1,4 and 1,2 products **118** and **119** were formed (Scheme 53). Further studies showed that the selectivity depends on the structures of the nucleophiles: with C_6F_5OH only the *trans*-1,4 product **118** was formed while the reaction with *t*-$BuCO_2H$ afforded *trans*-1,2-**119** as the only product.



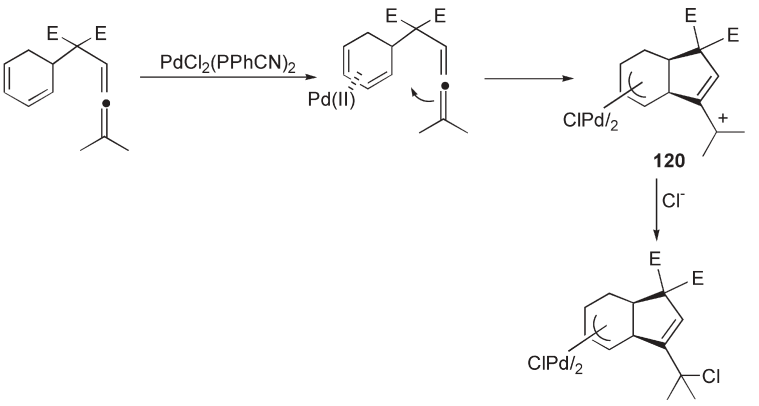
Scheme 52

NuH: HOAc (79%), C_6F_5OH (85%), $PhCO_2H$ (50%), $EtCO_2H$ (42%), *i*-$PrCO_2H$ (15%), *t*-$BuCO_2H$ (trace)



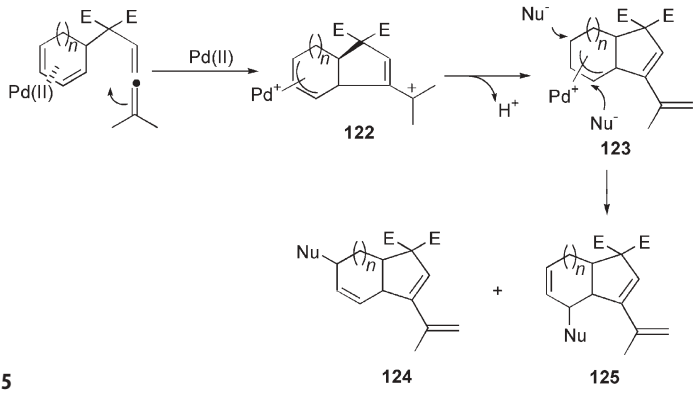
NuH		1,4-product **118**		1,2-product **119**
HOAc	90%	1	:	1
C_6F_5OH	87%	100	:	0
t-$BuCO_2H$	65%	0	:	100

Scheme 53

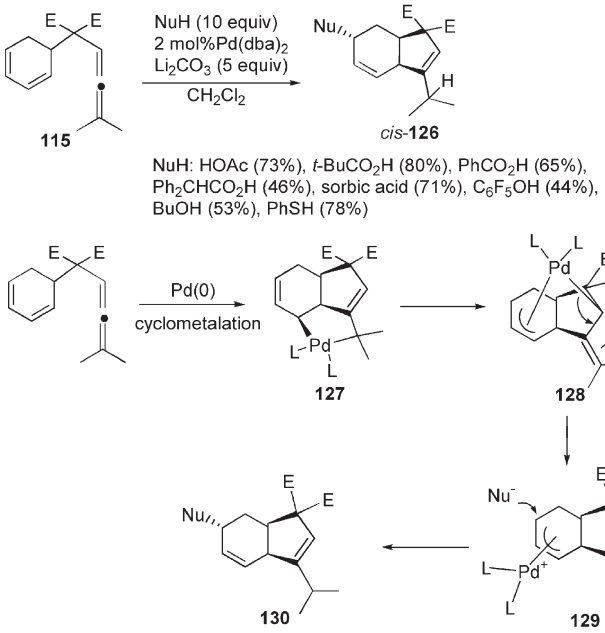


Scheme 54

The reaction of a stoichiometric amount of $PdCl_2(PhCN)_2$ with 2-(2′,4′-cyclohexadienyl)-2-(3′-methyl-1′,2′-butadienyl)malonate indicated that the Pd(II)-catalyzed reaction was initiated by nucleophilic attack of the allene moiety on the Pd(II) species leading to a cationic π-allylic palladium dimer **120**, which could be trapped by the Cl^- in the reaction mixture to afford bicyclic π-allylic palladium dimer **121** (Scheme 54) [34]. Thus, for the Pd(II)-catalyzed reaction the first step is the attack of allene on the Pd(II)-coordinated 1,3-diene moiety affording cationic π-allylic palladium intermediate **122**, which underwent deprotonation leading to a π-allylpalladium intermediate **123**. External trapping with a nucleophile afforded the regioisomeric products **124** and/or **125** (Scheme 55).



Scheme 55

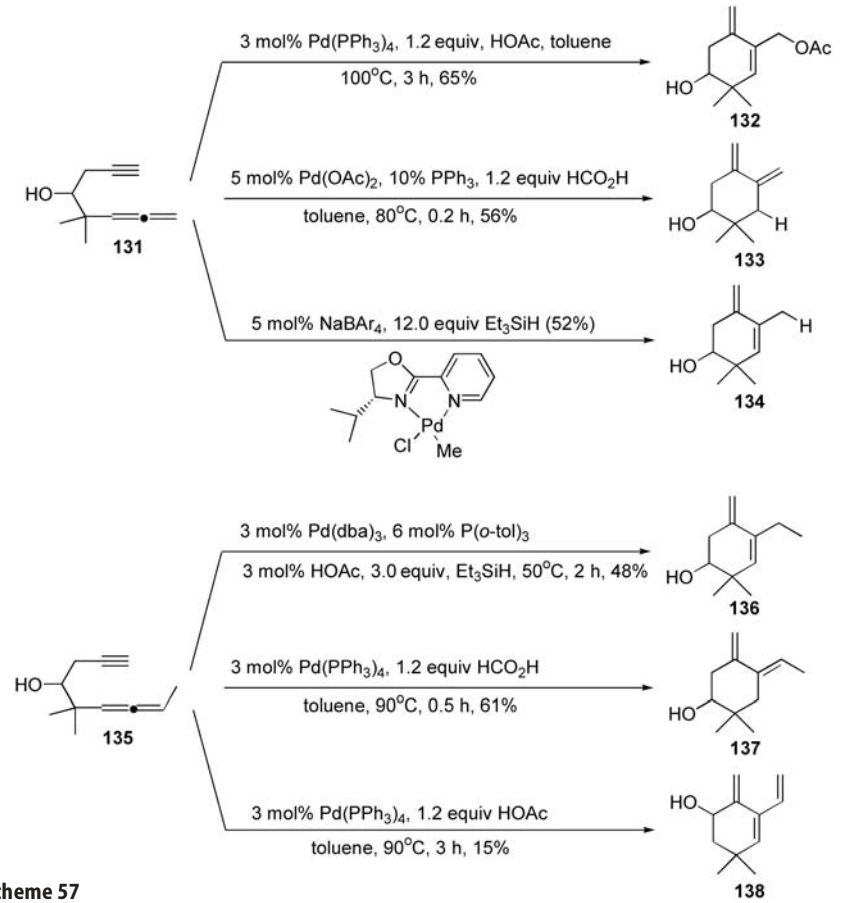


Scheme 56

In the presence of a nucleophile, the $Pd(dba)_2$-catalyzed reaction of allene-1,3-diene **115** afforded *cis*-**126** [33]. This Pd(0)-catalyzed reaction underwent cyclometalation to afford palladatricyclic intermediates **127** and **128**. Intermediate **128** underwent protonolysis to afford π-allylic intermediate **129**, which was followed by an allylic nucleophilic substitution reaction to afford the *cis*-fused bicyclic products **130** (Scheme 56).

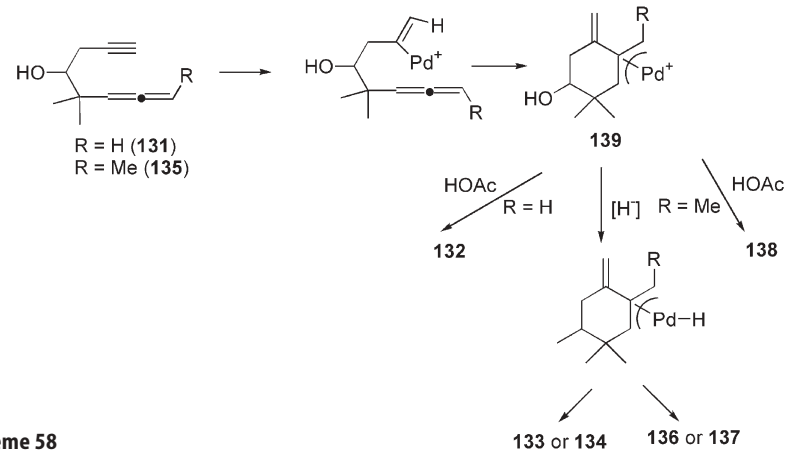
6
Cyclization of Allene–Alkyne Combinations

Oh et al. observed that 1,6-allenynes **131** and **135** underwent cyclization to afford six-membered-ring products **132–134** and **136–138** depending on the catalyst and additives used (Scheme 57) [35]. These products may be formed via the intermediacy of π-allyl palladium intermediate **139**, which was formed



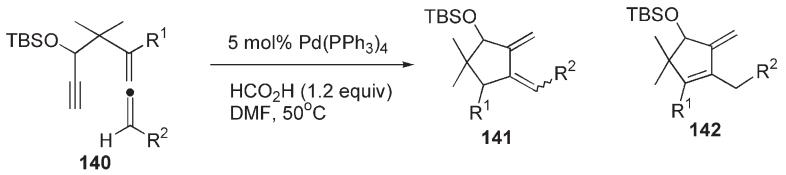
Scheme 57

by the hydropalladation of the terminal C–C triple bond and the subsequent intramolecular carbopalladation of the allene moiety (Scheme 58).



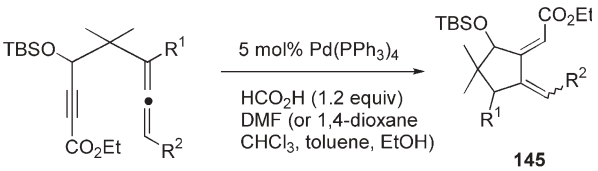
Scheme 58

They also studied the $Pd(PPh_3)_4$-catalyzed intramolecular reaction of an allene moiety with an alkyne in 1,5-alkyne-allene **140** in DMF in the presence of HCO_2H affording cyclopentane derivatives **141** [36]. The reaction demonstrated an interesting solvent effect, i.e., the reaction in dioxane afforded a mixture of regioisomers referred to the C=C bond in **141** and **142** (Scheme 59). However, if the terminal alkyne was further substituted with the ethoxycarbonyl group, i.e., allene-alkynoate **143**, the solvent effect is not obvious in terms of the selectivity, as only one product, i.e., bis(alkylidenyl)cyclopentane **145** was formed (Scheme 60). The yields in DMF are much higher.



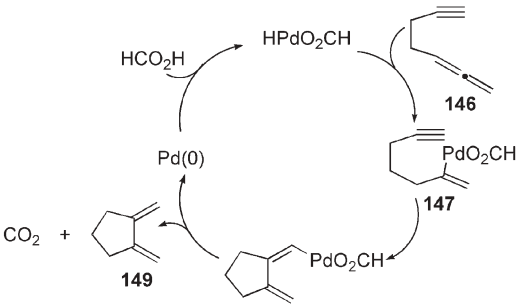
$R^1 = R^2$ =H (76%); R^1 = Me, R^2 = H (75%); R^1 =H , R^2 = Me (92%)

Scheme 59



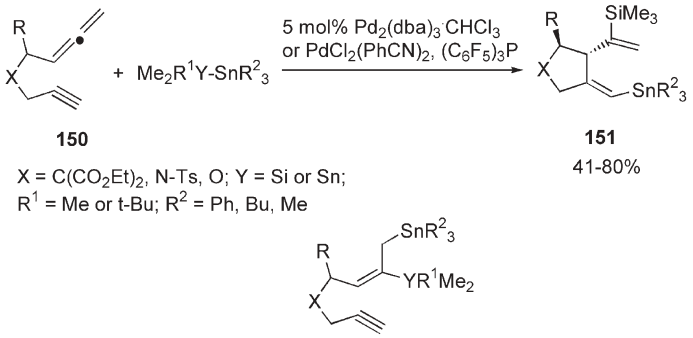
Scheme 60

Due to the higher reactivity of the allene moiety toward hydropalladation in 1,6-allenynes, the reaction may proceed via a hydropalladation of the allene moiety of **146** affording a vinylic palladium intermediate **147**. Subsequent intramolecular carbopalladation of the C–C triple bond moiety would lead to the 1,3-dienyl palladium formate **148**. Releasing of CO_2 and reductive elimination afford the final product **149** and Pd(0). Pd(0) would react with HCO_2H to afford HCO_2PdH, which is the catalytically active species (Scheme 61) [36].



Scheme 61

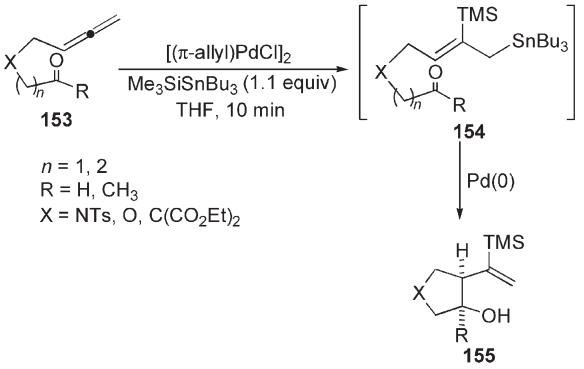
RajanBabu et al. reported that the $Pd_2(dba)_3{\cdot}CHCl_3$ or $PdCl_2(PhCN)_2$/$(C_6F_5)_3P$-catalyzed cyclization of 1,7-allenynes **150** in the presence of $Me_2RSiSnR'_3$ or $Me_3SnSnMe_3$ afforded the five-membered carbocycles or heterocycles **151** (Scheme 62) [37]. Under certain reaction conditions the acyclic silyl(or stannyl)stannylation products of the allene moiety **152** can be isolated, which may be further converted into the cyclized products **151** with prolonged reaction time or higher reaction temperature, indicating that the reaction started with the silyl(or stannyl)palladation of the allene moiety.



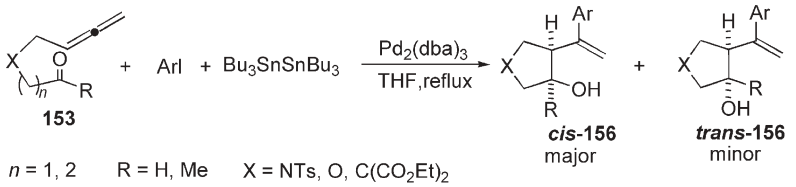
Scheme 62

7
Pd-Catalyzed Intramoleculer Reaction of Allenes with Aldehydes or Ketones

The $[(\pi\text{-allyl})PdCl]_2$-catalyzed reactions of allene-aldehydes or -ketones **153** with $Me_3SiSnBu_3$ led to the cyclic 2-vinylic alcohols **155** via the formation of an aldehyde- or ketone-containing 2-trimethysilyl-2-alkenyl tin intermediate **154** (Scheme 63) [38]. In the presence of an aryl iodide, $Pd_2(dba)_3$ could catalyze the coupling cyclization of allene-aldehydes or -ketones **153** with $Bu_3SnSnBu_3$ leading to the cyclic 2-(1′-arylvinyl) cyclic alcohols **156** stereoselectively with the *cis* isomer being the major product (Scheme 64) [39].



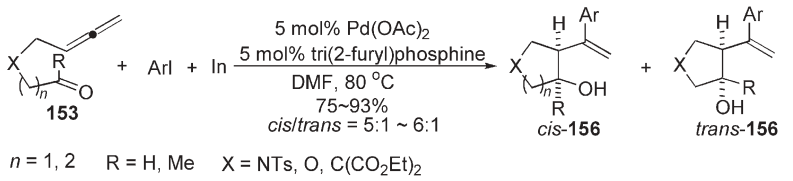
Scheme 63



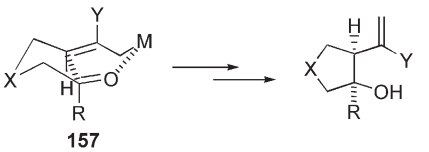
Scheme 64

The same products can be prepared from the Pd-catalyzed reaction of allene-aldehydes or -ketones **153** with ArI in the presence of metallic indium (Scheme 65) [40, 41]. The *cis* stereoselectivity of these reactions was probably determined by the chairlike conformation of the intermediate **157** (Scheme 66).

In conclusion, the palladium-catalyzed two- or three-component coupling reactions involving allenes have been established as powerful tools for the efficient synthesis of cyclic compounds. Reaction patterns involving all three carbon atoms of the allene moiety have been observed, with the selectivity depending on the structures of the starting materials, nature of the catalyst, and



Scheme 65



Scheme 66

the reaction conditions. It is believed that the transition metal-catalyzed chemistry of allenes will have a bright future in organic chemistry.

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Nucleophilic Attack by Palladium Species

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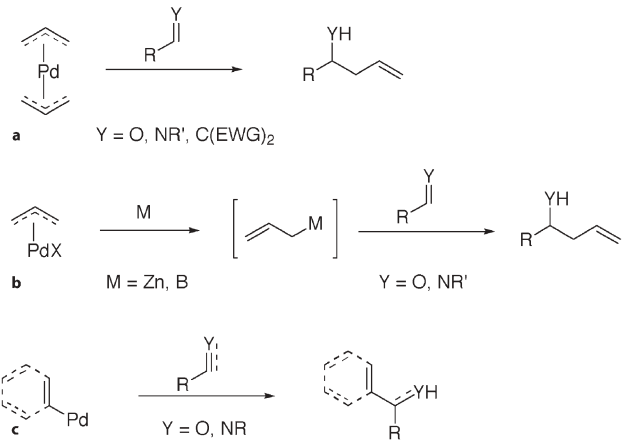
Abstract Recent researches have revealed that certain allyl-, vinyl-, and arylpalladium intermediates show a nucleophilic nature and react with various electrophiles. The bis-π-allylpalladium species not only exhibits nucleophilic reactivity but also behaves as an amphiphilic reagent, undergoing bis-allylation. Allyl-, propargyl-, and allenylmetals, which are catalytically generated from allyl-, propargyl-, and allenylpalladium in the presence of reductants, such as Zn and SmI_2, or organometallics, such as Et_2Zn and Et_3B, react with various electrophiles. Vinyl- and arylpalladium intermediates, which are formed by oxidative addition of a carbon–halogen or –pseudohalogen bond to palladium(0) or by insertion of alkynes into the R–Pd bond, react with carbon–heteroatom multiple bonds in a nucleophilic manner.

Keywords Nucleophilic attack · Amphiphilic reaction · Bis-π-allylpalladium · Umpolung · Vinylpalladium

Abbreviations
bpy 2,2′-Bipyridyl
dba Dibenzylideneacetone
DMA *N*,*N*-Dimethylacetamide
dppe 1,2-Bis(diphenylphosphino)ethane
dppf 1,1′-Bis(diphenylphosphino)ferrocene
TBAF Tetrabutylammonium fluoride

1
Introduction

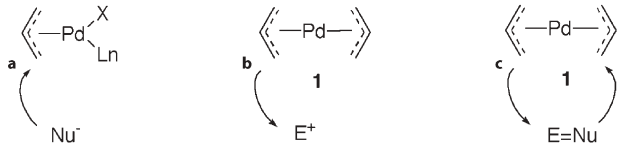
Palladium-catalyzed reactions have been widely investigated and have become an indispensable synthetic tool for constructing carbon–carbon and carbon–heteroatom bonds in organic synthesis. Especially, the Tsuji–Trost reaction and palladium(II)-catalyzed cyclization reaction are representative of palladium-catalyzed reactions. These reactions are based on the electrophilic nature of palladium intermediates, such as π-allylpalladium and (π-alkyne)palladium complexes. Recently, it has been revealed that certain palladium intermediates, such as bis-π-allylpalladium, vinylpalladium, and arylpalladium, act as a nucleophile and react with electron-deficient carbon–heteroatom and carbon–carbon multiple bonds [1]. Palladium-catalyzed nucleophilic reactions are classified into three categories as shown in Scheme 1: (a) nucleophilic and amphiphilic reactions of bis-π-allylpalladium, (b) nucleophilic reactions of allylmetals, which are catalytically generated from π-allylpalladium, with carbon–heteroatom double bonds, and (c) nucleophilic reaction of vinyl- and arylpalladium with carbon–heteroatom multiple bonds. According to this classification, recent developments of palladium-catalyzed nucleophilic reactions are described in this chapter.



Scheme 1

2
Nucleophilic and Amphiphilic Reactions of Bis-π-Allylpalladium

π-Allylpalladium complexes are useful synthetic intermediates since they can participate in reactions with a wide range of reaction partners to form C–C and C–heteroatom bonds in a highly stereo- and regioselective way (Scheme 2). It is widely accepted that the π-allylpalladium complex, which is a key intermediate of the Tsuji–Trost reaction, has an electrophilic nature and reacts with nucleo-

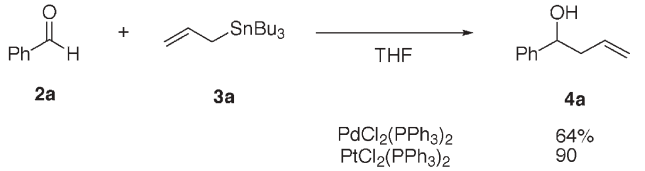


Scheme 2

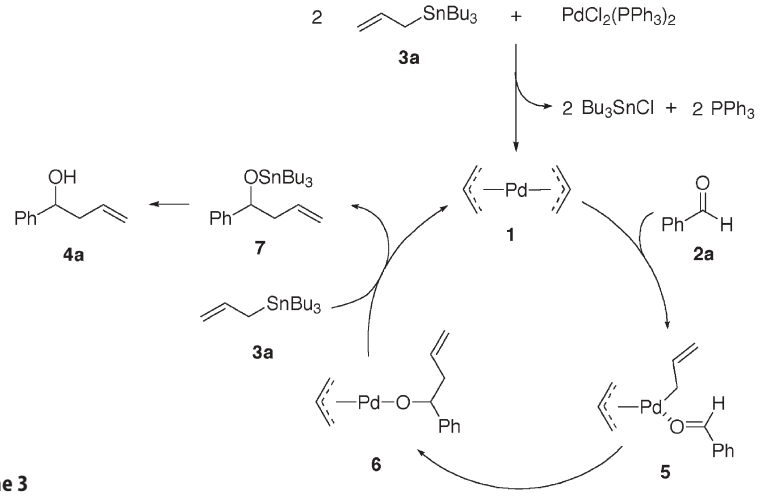
philes, such as diethyl malonate sodium salt and certain enolates, to afford the corresponding allylation products (type a) [2]. Recently, it was found that bis-π-allylpalladium complex **1** behaves as a nucleophile and reacts with various electrophiles, such as aldehydes and imines (type b). Furthermore, it was revealed that bis-π-allylpalladium **1** acts as an amphiphilic catalytic allylating reagent upon reaction with Michael acceptors and related substrates, producing the bis-allylated products (type c).

2.1
Nucleophilic Reactions of Bis-π-Allylpalladium

The palladium-catalyzed reaction of aldehydes with allylstannanes gives the corresponding homoallylic alcohols in good to high yields (Eq. 1) [3]. The reaction of benzaldehyde **2a** and allyltributylstannane **3a** in the presence of 10 mol% of $PdCl_2(PPh_3)_2$ affords 1-phenyl-3-buten-1-ol **4a** in 64% yield. This



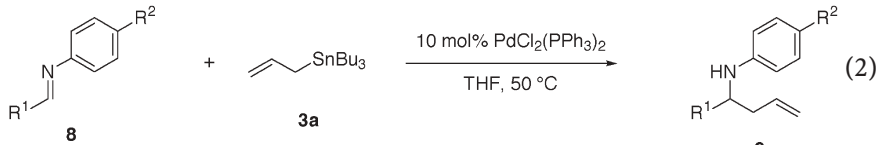
(1)



Scheme 3

reaction is catalyzed also by $PtCl_2(PPh_3)_2$, giving **4a** in 90% yield. The catalytic cycle proceeds as shown in Scheme 3. Bis-π-allylpalladium **1** is generated by transmetalation of $PdCl_2(PPh_3)_2$ with allylstannane **3a**. Aldehyde **2a** coordinates to **1**, forming the π-allyl-σ-allylpalladium intermediate **5**. Nucleophilic attack of the σ-allyl group on the carbon–oxygen double bond of the aldehyde produces the π-allylhomoallyloxypalladium species **6**, which reacts with **3a** to give **1** and the homoallyloxystannane **7**. Hydrolysis of the Sn–O bond takes places in the isolation process using column chromatography.

Imines also react very smoothly with allylstannanes (Eq. 2) [4]. The reaction of the aromatic imines **8a** and **8b** with allyltributylstannane **3a** proceeds in the presence of 10 mol% of $PdCl_2(PPh_3)_2$ in THF at 50 °C and the corresponding homoallylic amines **9** are obtained in good to high yields. The reaction of the aliphatic imines **8c** and **8d** also proceeds very smoothly.

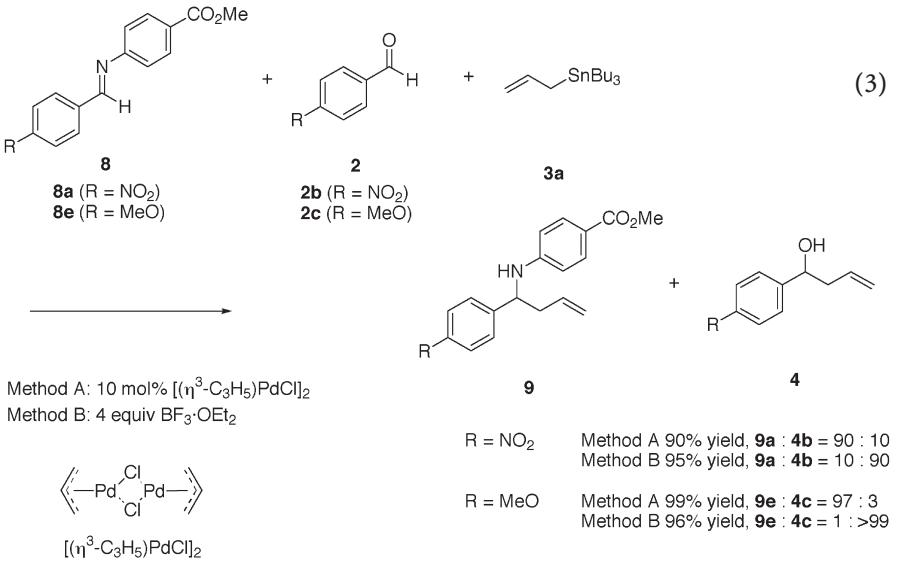


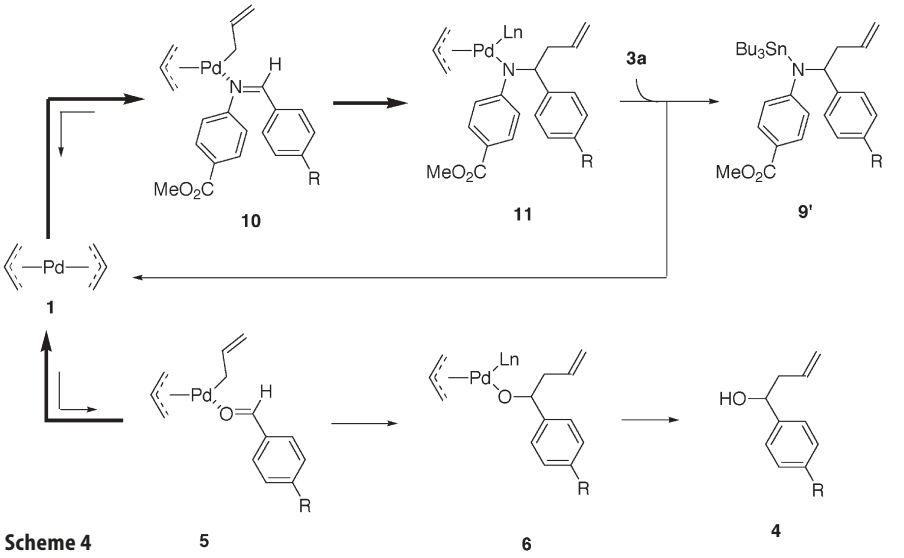
(2)

8a (R^1 = *p*-$NO_2C_6H_4$, R^2 = CO_2Me)
8b (R^1 = Ph, R^2 = CO_2Me)
8c (R^1 = *i*-Pr, R^2 = CO_2Me)
8d (R^1 = *c*- Hex, R^2 = MeO)

9a (R^1 = *p*-$NO_2C_6H_4$, R^2 = CO_2Me) 77%
9b (R^1 = Ph, R^2 = CO_2Me) 98
9c (R^1 = *i*-Pr, R^2 = CO_2Me) 81
9d (R^1 = *c*- Hex, R^2 = MeO) 72

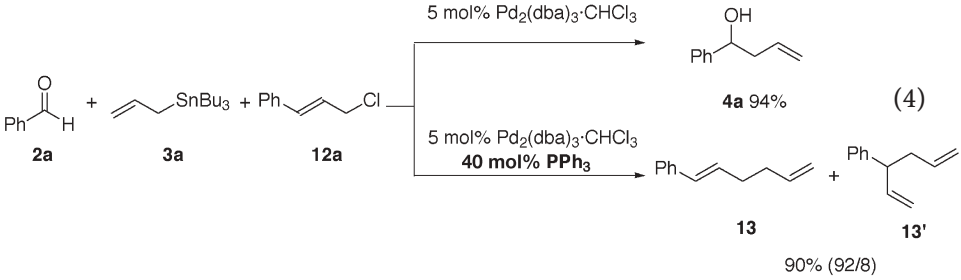
Very interestingly, imines are allylated chemoselectively in the presence of aldehydes in the reaction with allylstannanes using a π-allylpalladium chloride dimer catalyst (Eq. 3) [4]. Reasonably high chemoselectivity is obtained in the allylation of arylaldehydes **2** and their imine partners **8**; when π-allylpalladium chloride dimer is used as a catalyst the homoallylamines **9** are obtained chemoselectively, while the reaction using 4 equivalents of $BF_3{\cdot}OEt_2$ affords mainly **4**. This unprecedented chemoselectivity is explained by the difference of the coordination ability between nitrogen and oxygen atoms to the transition metal (Scheme 4). In general, a nitrogen atom can coordinate to a transition metal more strongly than an oxygen atom. Catalytic amounts of bis-π-allylpalladium intermediate **1** react with imines more predominantly than with aldehydes to give **10**, which affords **9′** via **11**. The key intermediate **1** is regenerated by the reaction of **11** and **3a**. On the other hand, excess amounts of Lewis acid (>2 equiv) can coordinate to both aldehydes and imines, activating both electrophiles in the same manner; the resulting aldehyde–Lewis acid complex is more electrophilic than the imine complex. The use of 1 equivalent of $BF_3{\cdot}OEt_2$ in the reaction between **8a** and **2b** gives a ca. 50:50 ratio of **9a** to **4b**. The regeneration of **1** via the catalytic process in addition to the strong coordinative preference of the N atom becomes a key to this unusual chemoselectivity; the Lewis acid-promoted reaction never proceeds in a catalytic manner.



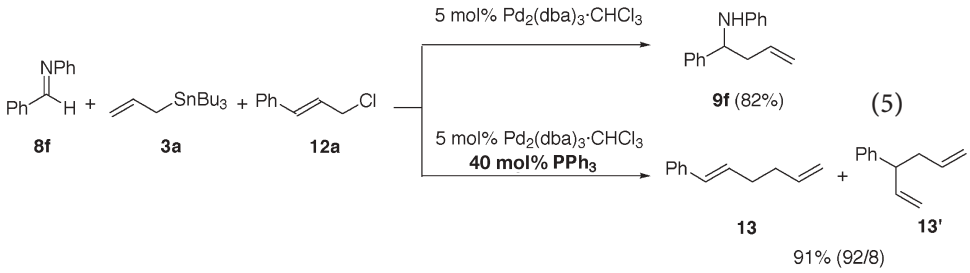


Scheme 4

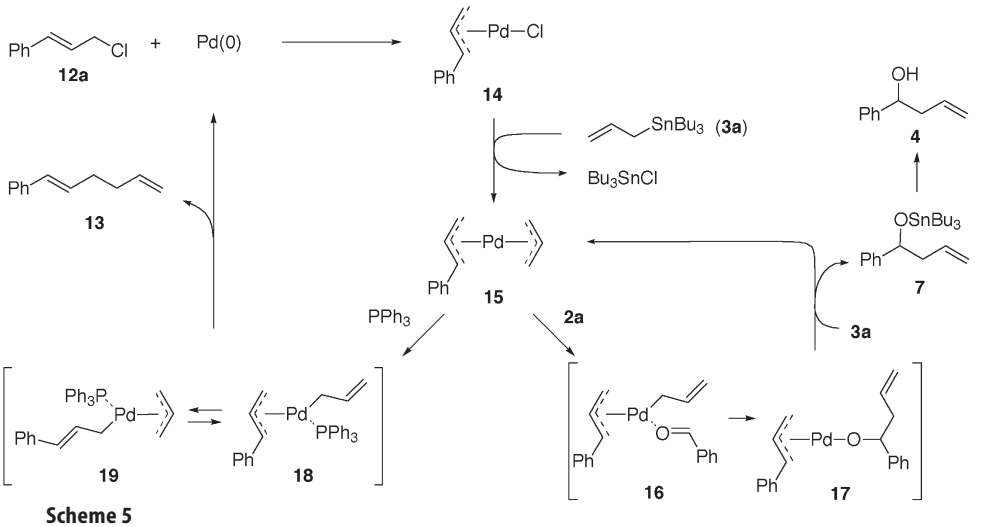
The fate of bis-π-allylpalladium complex in the presence of aldehydes and allylic chloride, in which triphenylphosphine ligand plays a key role in controlling the chemoselectivity, has been clarified [5]. The reaction of **12a** and allyltributylstannane **3a** with benzaldehyde **2a** in the absence of PPh_3 gives the homoallyl alcohol **4a** in 94% yield, and **12a** is recovered in essentially quantitative yield (Eq. 4 top), whereas the reaction in the presence of 4 equivalents of PPh_3 (relative to Pd) gives a 92/8 mixture of **13** and **13′** in 90% yield, and



benzaldehyde **2a** is recovered quantitatively (Eq. 4 bottom). A key role of PPh_3 in controlling the chemoselectivity is also observed in the reaction of the imines. In the absence of the phosphine ligand, the reaction of **8f**, allyltributylstannane **3a**, and **12a** gives the allylation product **9f** in 82% yield, and **12a** is recovered (Eq. 5 top), whereas in the presence of 4 equivalents of PPh_3, a 92/8 mixture of **13** and **13′** is obtained in 91% yield, and the imine **8f** remains unchanged (Eq. 5 bottom).

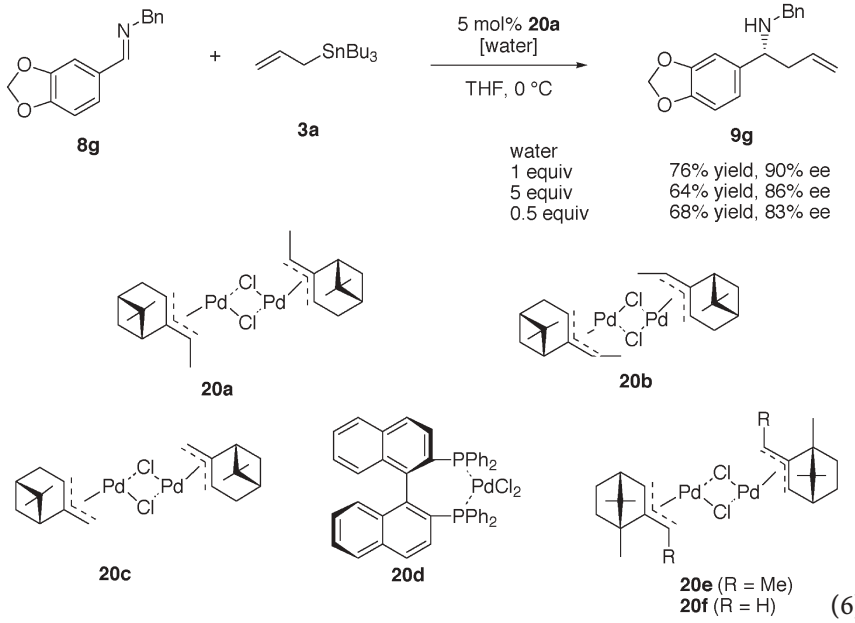


A plausible mechanism is shown in Scheme 5. Oxidative addition of **12a** to palladium(0) gives π-allyl(chloro)palladium complex **14**, and transmetalation of **14** with allyltributylstannane **3a** produces the bis(π-allyl)palladium complex **15**. In the absence of PPh_3, benzaldehyde **2a** coordinates to palladium(II) to produce the homoallyloxypalladium complex **17** via **16**. The transmetalation of **17** with allyltributylstannane **3a** produces the corresponding homoallyloxytin compound **7** and regenerates the bis(π-allyl)palladium intermediate **15**. In the allylation reaction, the unsubstituted π-allyl group of **15** undergoes nucleophilic addition to benzaldehyde **2a**, while the phenyl-substituted allyl group acts as a nontransferable π-allyl ligand. Therefore, only catalytic amounts of cinnamyl chloride **12a** react initially with allyltributylstannane **3a** to afford the bis(π-allyl)palladium intermediate **15**, and large amounts of **12a** remain in the reaction medium. However, in the presence of PPh_3, the phosphine ligand coordinates to **15** to give the σ-allyl-π-allylpalladium intermediates **18** and/or **19**. Reductive elimination from **18** and/or **19** (or perhaps more preferably from the corresponding σ-allyl-σ-allylpalladium intermediate) gives the Stille coupling products **13** (together with the minor product **13′**) and regenerates palladium(0).

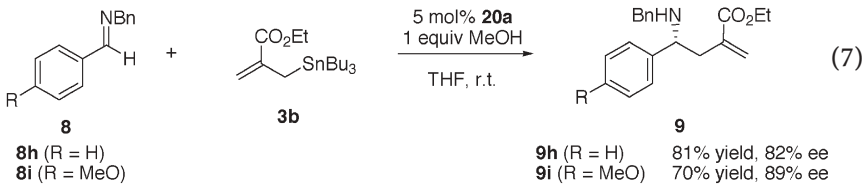


Scheme 5

Catalytic asymmetric allylation of imines **8** with allyltributylstannane **3a** is achieved by the use of the chiral π-allylpalladium complex **20a** as a catalyst (Eq. 6) [6]. The reaction of imine **8g** with 1.25 equivalents of allyltributylstannane **3a** in the presence of 5 mol% of **20a** and 1 equivalent of water in THF gives **9g** in 76% yield with 90% ee. Repeated recrystallization of the chiral catalyst **20a** is important to obtain high enantioselectivity, since the reaction employing the



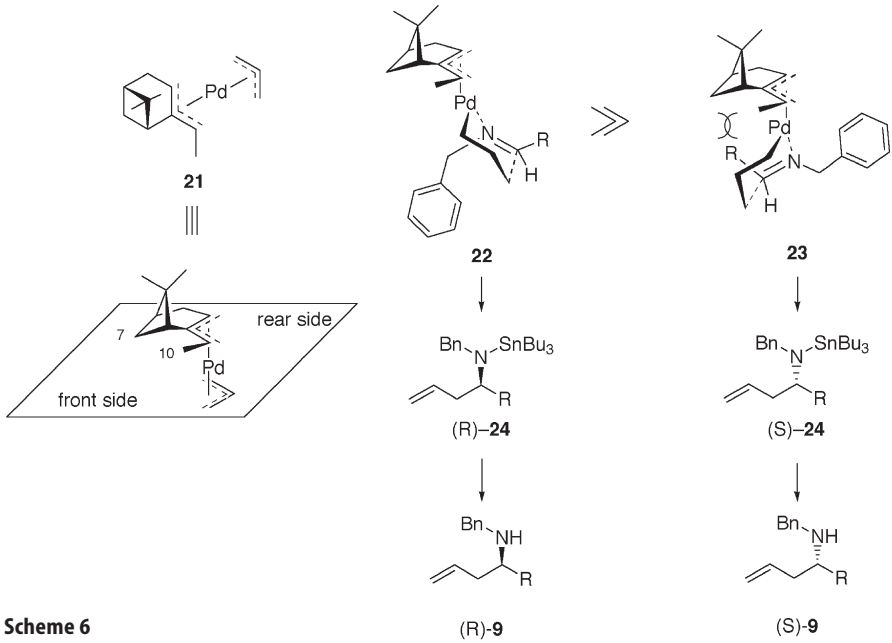
(6)



(7)

stereoisomeric catalyst **20b** leads to a poor yield and unsatisfactory enantioselectivity (42% yield, 17% ee). It is revealed that the use of 1 equivalent of water is important to get high enantioselectivities and reproducible results. Excess of water (5 equiv) or less than 1 equivalent (0.5 equiv) gives inferior results. In the absence of water, nonreproducible results are obtained. The use of other catalysts **20c–f** results in very low enantiomeric excesses.

A plausible mechanism for the asymmetric allylation is shown in Scheme 6. The bis-π-allylpalladium **21** is the reactive intermediate, in which an allyl ligand acts as a transferable intermediate and the other nontransferable allyl group determines the stereocontrol of allylation. The front side of the η^3-10-methylpinene group of the palladium catalyst is highly crowded by the methyl group at the C-10 position, and thus an imine is forced to approach from the less hindered rear side. The nitrogen of the imine **8** coordinates to the palladium atom of **21** and C–C bond formation occurs through the six-membered cyclic chairlike transition state. In the case of **23**, there is severe steric repulsion between the R group of the imine and the C-7 methylene group. Accordingly,

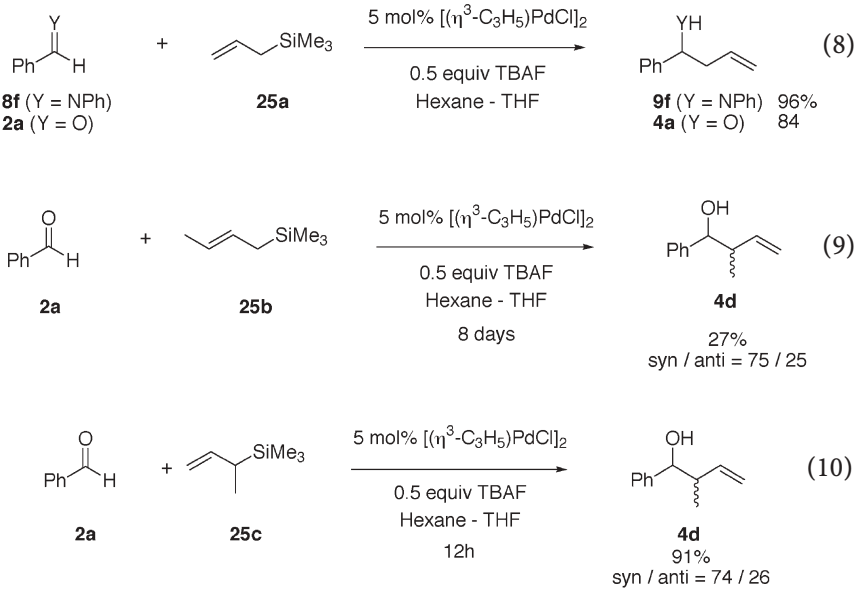


Scheme 6

the reaction proceeds through a transition state model **22** to give the (*R*)-homoallylamine **9** predominantly. The role of water in this reaction could be to form the precoordinate allylstannane, in which water coordinates to tetravalent stannane **3a**, and thereby facilitates C–Sn bond cleavage and enhances the transmetalation step. Water could also promote the facile protonation of the Sn–N bond of **24**. This contributes to a faster reaction rate and higher yields.

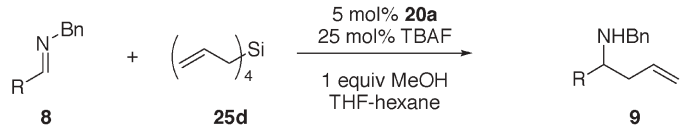
Carbethoxyallylstannane **3b** is employed in the presence of the chiral bis-π-allylpalladium catalyst **20a** to achieve a useful conversion of prochiral imines to chiral 2-(2-aminoethyl)acrylates, which are important building blocks for further asymmetric synthesis of a wide range of compounds (Eq. 7) [7]. The reaction of imines **8** with 1.5 equivalents of carbethoxyallylstannane in the presence of 5 mol% of **20a** and 1 equivalent of methanol gives **9** in good yields with high enantioselectivities.

It is found that allylsilanes, which are more desirable than allylstannanes from the point of green chemistry, work as an allylating reagent and react with imines and aldehydes using a palladium–TBAF cocatalyst system [8]. The reaction of imine **8f** with 2 equivalents of allyltrimethylsilane **25a** proceeds smoothly at room temperature in the presence of catalytic amounts of π-allylpalladium chloride dimer and 0.5 equivalent of TBAF in *n*-hexane–THF (4:1) cosolvent, giving the corresponding homoallylamine **9f** in 96% yield (Eq. 8). Benzaldehyde **2a** is also allylated under the same conditions. The reaction of benzaldehyde with **25b** is very sluggish at room temperature, and after 8 days the γ-addition product **4d** is obtained regioselectively only in 27% yield (Eq. 9). Interestingly, the reaction of **25c** is faster than that of **25b** and is completed in 12 h, giving selectively the α-addition product **4d** in 91% yield (Eq. 10). Fur-



thermore, in both cases, the *syn*/*anti* diastereomer ratios of the product **4d** are almost same. These results suggest that the rate-determining step of the allylation reaction is the transmetalation step; transmetalation from **25b** is very slow whereas that from **25c** is faster, and the same bis-π-allylpalladium is produced from **25b** and **25c**.

The enantioselective allylation of aldimines **8** with the tetraallylsilane–TBAF–MeOH system with use of the chiral bis-π-allylpalladium catalyst **20a** under catalytic, non-Lewis acidic, essentially neutral, and very mild reaction conditions has been achieved (Eq. 11) [9]. The reaction of imines **8** with 1.2 equivalents of tetraallylsilane **25d** in the presence of 5 mol% of the chiral bis-π-allylpalladium catalyst **20a**, 25 mol% of TBAF, and 1 equivalent of methanol in THF–hexane (1:2) cosolvent furnished the corresponding homoallylamines **9** in high yields and good to excellent enantioselectivities.



(11)

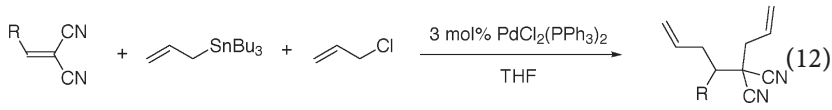
8 **25d** **9**

8h (R = Ph)
8i (R = *p*-anisyl)
8j (R = *p*-tolyl)

9h (R = Ph)	86% yield, 91% ee
9i (R = *p*-anisyl)	84% yield, 94% ee
9j (R = *p*-tolyl)	92% yield, 92% ee

2.2 Amphiphilic Reactions of Bis-π-Allylpalladium

Bis-π-allylpalladium acts as an amphiphilic reagent and reacts with both nucleophilic and electrophilic carbons of activated olefins **26** at once to produce the double allylation products **27** in good to high yield (Eq. 12) [10]. The reaction of ethylidenemalononitriles **26** (1 equiv), allyltributylstannane **3a** (1.2 equiv), and allyl chloride **12b** (1.2 equiv) in the presence of 3 mol% of $PdCl_2(PPh_3)_2$ gives the double allylated products **27** in good to high yields. A mechanistic rationale which accounts for the unprecedented double allylation of activated olefins is illustrated in Scheme 7. The transmetalation of allyltributylstannane **3a** to palladium produces bis-π-allylpalladium **1**, which reacts with activated olefins **26** to give the π-allylpalladium intermediate **28**. The first allylation proceeds in a nucleophilic manner. The reductive coupling from **28** gives the corresponding 1,7-octadienes **27** and palladium(0) species. At this stage, the

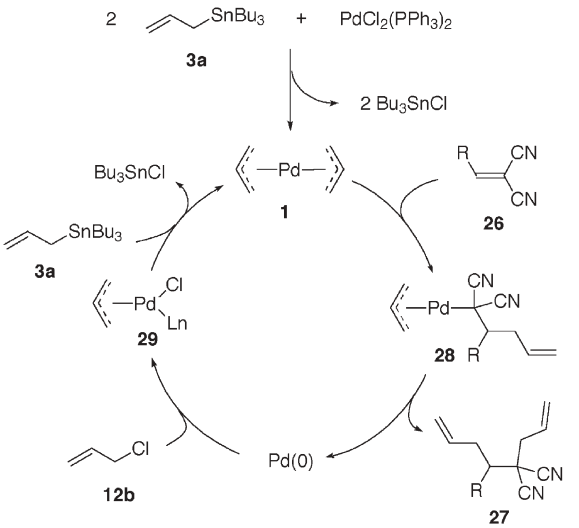


(12)

26 **3a** **12b** **27**

26a (R = Ph)
26b (R = 2-furyl)
26c (R = *i*-Pr)

27a (R = Ph)	91%
27b (R = 2-furyl)	91
27c (R = *i*-Pr)	82

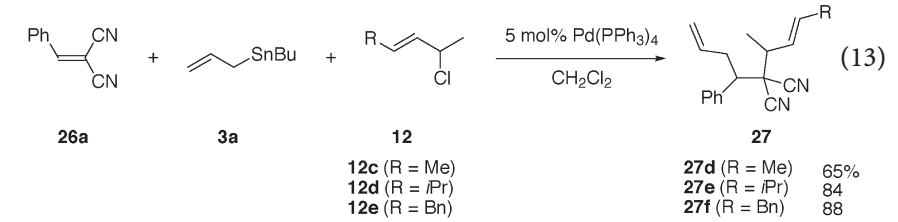


Scheme 7

second allylation proceeds in an electrophilic fashion. The oxidative insertion of Pd(0) into allyl chloride produces the π-allylpalladium complex **29**. The reaction of **29** with allyltributylstannane **3a** produces **1** and Bu_3SnCl.

The reaction of the dialkyl-substituted allyl chlorides **12c–e** with allyltributylstannane **3a** and benzylidenemalononitrile **26a** gives the corresponding regioselective double allylation products **27** [11] (Eq. 13). The regioselective bis-allylation of **26a** with 2 equivalents of cinnamyl chloride **12a** takes place in the presence of hexamethylditin **30** [12] (Eq. 14).

The bis-allylation reaction is extended to the intramolecular reaction [13]. The reaction of 8-chloro-2,6-octadienyltributylstannane **31** with **26** gives a mix-

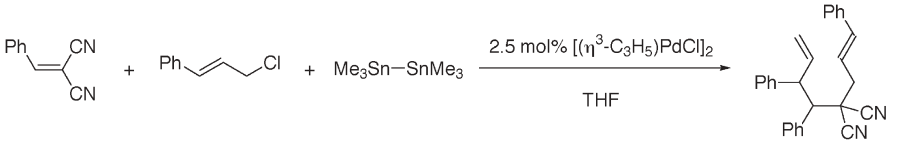


26a **3a** **12** **27**

12c (R = Me)
12d (R = *i*Pr)
12e (R = Bn)

27d (R = Me) 65%
27e (R = *i*Pr) 84
27f (R = Bn) 88

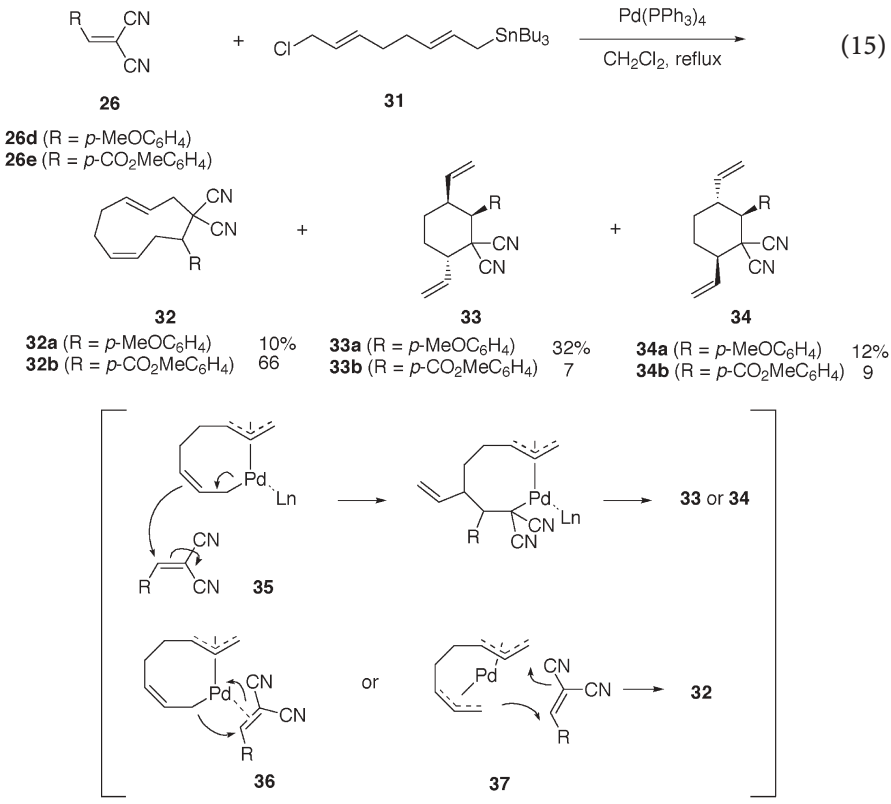
(13)



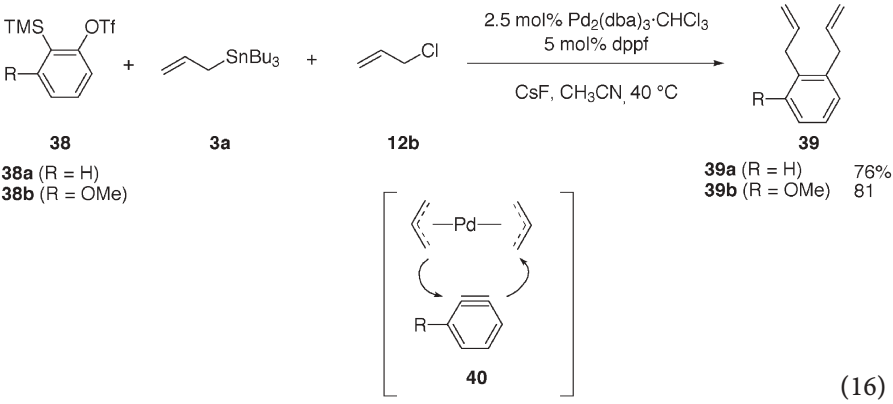
26a **12a** **30** **27g** 60%

(14)

ture of the regioisomeric cycloadducts, [8+2] (**32**) and [4+2] cycloaddition products (**33** and **34**). The [8+2] adduct **32a** is produced as the minor product in the reaction of the activated alkene **26d** having an anisyl group, whereas **32b** is obtained as the major product in the reaction with the activated alkene **26e** bearing an electron-withdrawing group at the *para* position (Eq. 15). In the case of **26e**, the coordination of the electron-deficient alkene to Pd(II) becomes much stronger favoring a pathway via **36** or **37**. Accordingly, the [8+2] adduct **32b** is obtained predominantly. In the reaction of **26d**, a pathway through the alkene–Pd coordination in **36** and **37** competes with the ordinary nucleophilic addition pathway via **35**, giving a mixture of the [8+2] and [4+2] adducts.



The triple bond of arynes reacts with bis-π-allylpalladium in an amphiphilic fashion (Eq. 16) [14]. The reaction of the aryne precursors **38** with allyltributylstannane **3a** and allyl chloride **12b** in acetonitrile in the presence of 2 equivalents of CsF and 2.5 mol% of $Pd_2(dba)_3{\cdot}CHCl_3$-dppf catalyst at 40 °C for 12 h affords the 1,2-diallylbenzenes **39** in good to high yields. The reaction proceeds through the addition of two allyl groups of bis-π-allylpalladium to the benzyne triple bond as shown in **40**.



38
38a (R = H)
38b (R = OMe)

3a

12b

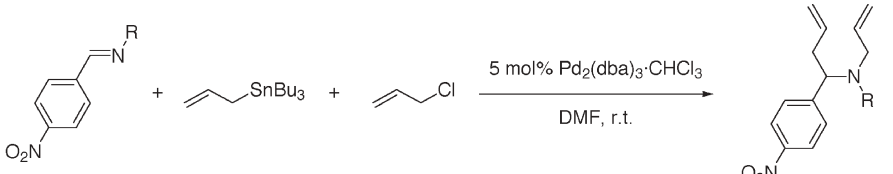
40

39
39a (R = H) 76%
39b (R = OMe) 81

(16)

Not only the activated C–C unsaturated compounds, but also certain activated C–N unsaturated compounds such as imines and isocyanates undergo the amphiphilic bis-allylation reaction. The reaction of the aromatic imines **8k–m**, derived from 4-nitrobenzaldehyde and alkylamines, with allyltributylstannane **3a** and allyl chloride **12b** proceeds very smoothly in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ catalyst in DMF at room temperature, giving *N*-allyl-*N*-alkyl-1-(4-nitrophenyl)-3-butenylamines **41a–c** in 81–53% yields (Eq. 17) [13]. Tosyl isocyanate **42** [13, 15] and carbon monoxide [16] also undergo a similar type of reaction with allylstannanes **3a** and allyl chlorides **12** in the presence of catalytic amounts of palladium (Eqs. 18 and 19).

The palladium-catalyzed reaction of allyltributylstannane **3a** with the aldehydes (or imines) **45** containing allyl halide in the same molecule proceeds



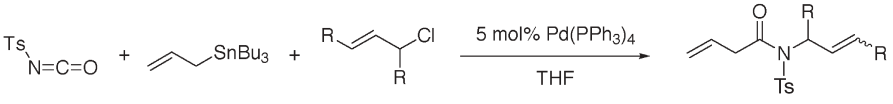
8
8k (R = Me)
8l (R = Bu)
8m (R = Bn)

3a

12b

41
41a (R = Me) 81%
41b (R = Bu) 74
41c (R = Bn) 53

(17)



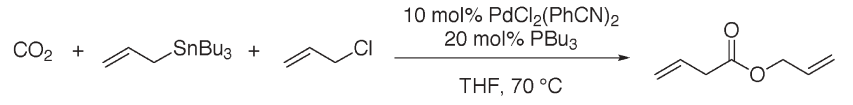
42

3a

12
12b (R = H)
12c (R = Me)

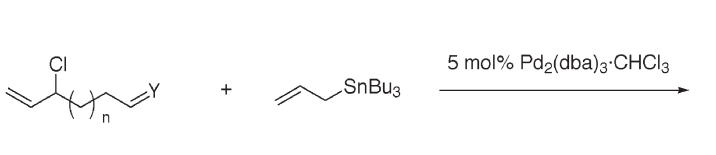
43
43a (R = H) 65%
43b (R = Me) 62

(18)



(19)

through the nucleophilic allylation of the C=Y group followed by heterocyclization, giving the five- and six-membered ring heterocycles **46** in good to high yields (Eq. 20) [17].



(20)

45

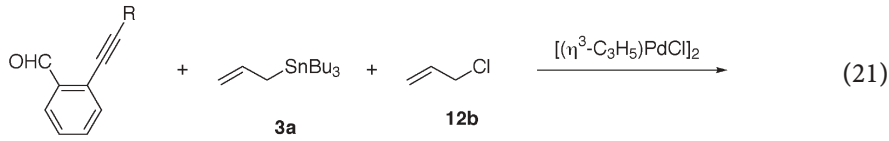
45a (Y = O, n = 1)
45b (Y = NBn, n = 1)
45c (Y = NBn, n = 2)

3a

46

46a	(Y = O, n = 1)	64%
46b	(Y = NBn, n = 1)	67
46c	(Y = NBn, n = 2)	67

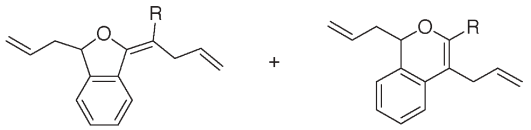
The reaction of the *ortho*-alkynylarylaldehydes **47** with allyltributylstannane **3a** and allyl chloride **12b** proceeds very smoothly in an amphiphilic manner, giving the corresponding diallylated heterocycles in good to high yields (Eq. 21) [18]. The reaction of **47a** and **47b**, which have a bulkier group at the alkynyl position, proceeds mainly through the 5-*exo* cyclization leading to **48**, while the reaction of **47c** bearing a normal alkyl group proceeds via the 6-*endo* cyclization to give **49c**.



(21)

47

47a (R = Ph)
47b (R = TMS)
47c (R = *n*-Bu)



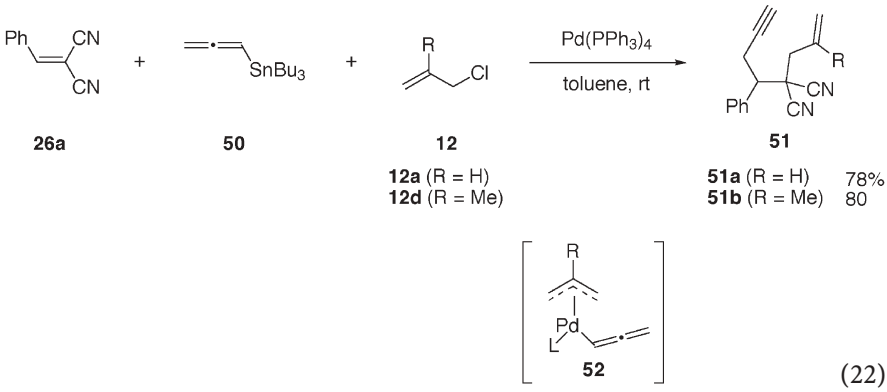
48

48a (R = Ph)	86%
48b (R = TMS)	94
48c (R = *n*-Bu)	25

49

49a (R = Ph)	10 %
49b (R = TMS)	6
49c (R = *n*-Bu)	59

Palladium-catalyzed three-component assembly of benzylidenemalononitrile **26a**, allylic chlorides **12**, and allenyltributylstannane **50** leading to the formation of the 1,7-enyne derivatives **51** is reported [19] (Eq. 22). The reaction proceeds



26a **50** **12** **51**

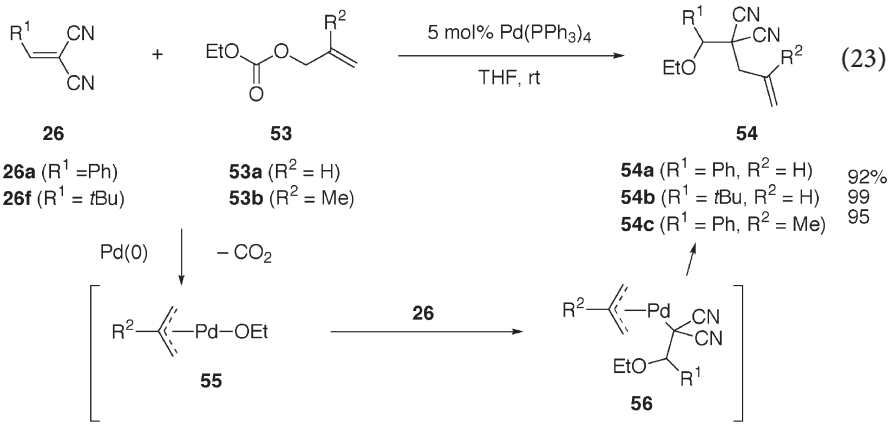
12a (R = H)
12d (R = Me)

51a (R = H) 78%
51b (R = Me) 80

(22)

through formation of σ-allenyl-π-allylpalladium intermediate **52** followed by regioselective alkylation of **26a** with **52.**

It is disclosed that, similar to bis-π-allylpalladium, alkoxy-π-allylpalladium and π-allylpalladium azide show amphiphilic reactivity toward E=Nu species and react with carbon–carbon and carbon–heteroatom multiple bonds in a catalytic manner. The reaction of the allyl carbonates **53** and the activated olefins **26** gives the alkoxyallylation products **54** in good to high yields (Eq. 23) [20]. This reaction proceeds through the formation of the ethoxy-π-allylpalladium species **55,** which is generated by oxidative addition of the allylic C–O bond of **53** to Pd(0) followed by decarboxylation. Nucleophilic attack of the ethoxy group on the β position of the activated olefin gives the π-allylpalladium intermediate **56.** Reductive elimination of palladium(0) affords the product **54.** The reaction of **26a** with **53a** in the presence of 10 equivalents of the external alcohols ROH **57** gives the products **58,** which have the RO group at the β position of **26a** (Eq. 24). In the case of benzyl alcohol **57c,** benzyloxy allylated product **58c** is obtained predominantly in 78% yield, even by the use of 1 equivalent of **57c.**



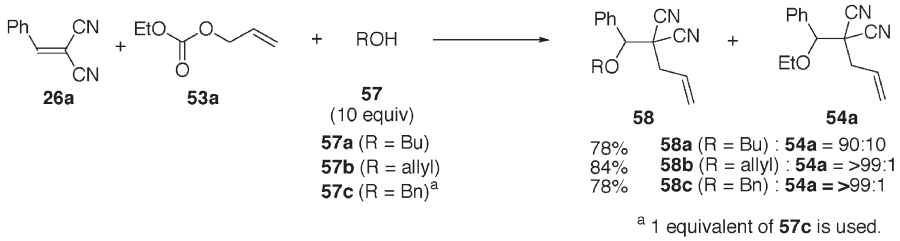
26 **53** **54**

26a (R^1 =Ph)
26f (R^1 = *t*Bu)

53a (R^2 = H)
53b (R^2 = Me)

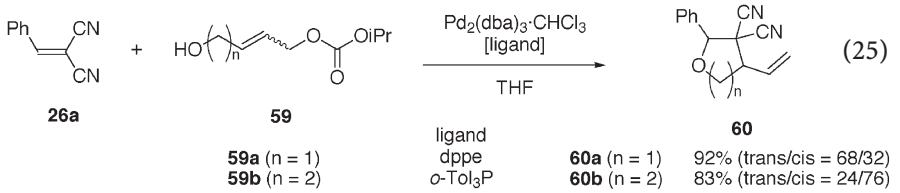
54a (R^1 = Ph, R^2 = H) 92%
54b (R^1 = *t*Bu, R^2 = H) 99
54c (R^1 = Ph, R^2 = Me) 95

(23)

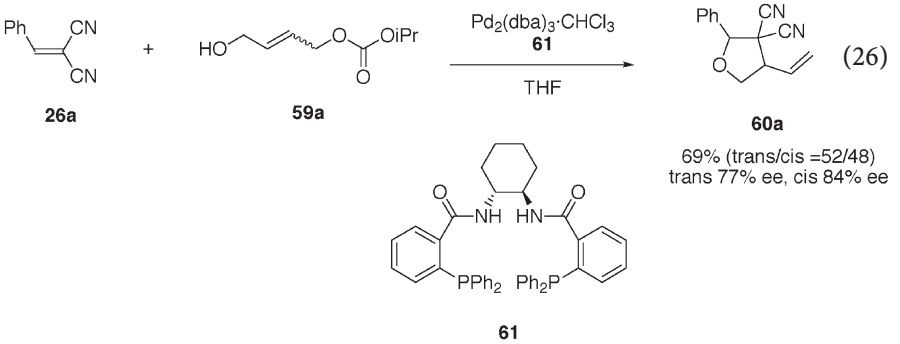


(24)

The reaction of the allyl carbonates **59**, which have a hydroxy group at the end of the carbon chain, with the activated olefin **26a** produces the corresponding cyclic ethers **60** in good to high yields (Eq. 25) [21]. The highly enantioselective alkoxyallylation of the activated olefin **26a** is achieved by the use of the chiral phosphine ligand **61** (Trost ligand, Eq. 26).



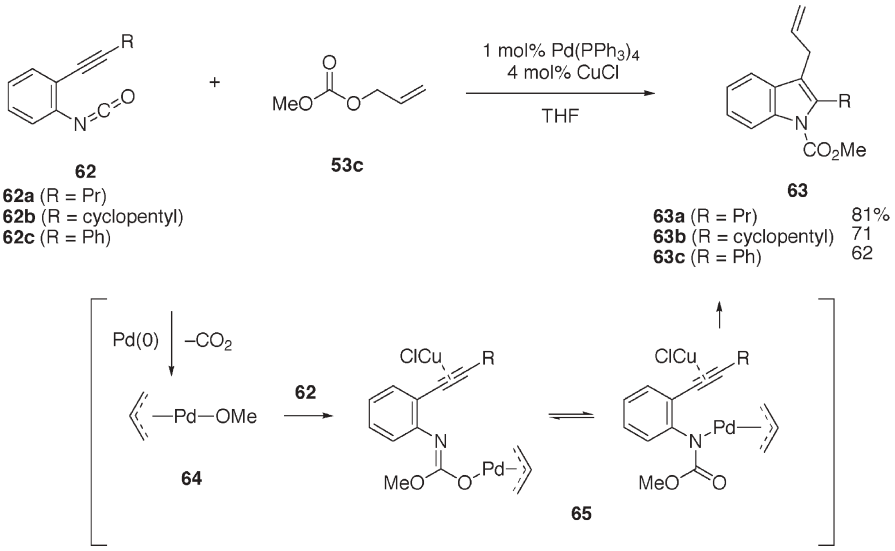
(25)



(26)

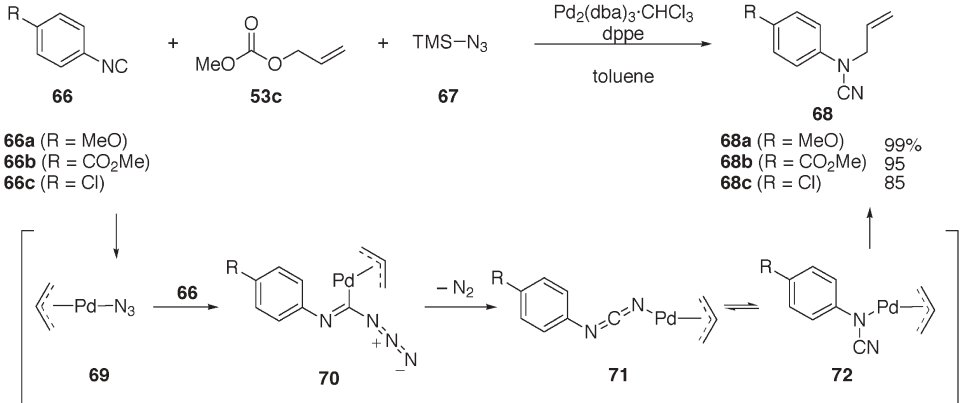
Methoxy-π-allylpalladium **64** reacts with *o*-alkynylphenylisocyanates **62** in an amphiphilic manner, giving the 3-allylindoles **63** in good to high yields (Eq. 27) [22]. Nucleophilic attack of the methoxy group of **64** on the carbon atom of the isocyanate group of **62** leads to the π-allylpalladium intermediate **65**. Insertion of the alkyne gives the product **63**. Copper chloride behaves as a Lewis acid activating the C–C triple bond through π coordination in order to facilitate carbopalladation.

π-Allylpalladium azide **69**, which is catalytically generated from allyl methyl carbonate **53c** and trimethylsilyl azide **67**, reacts with the arylisocyanides **66** to

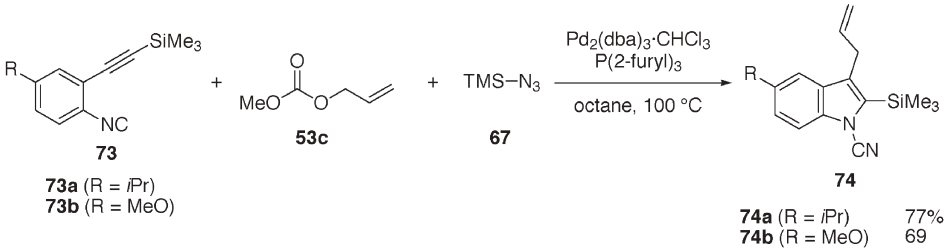


(27)

give the corresponding cyanoamides **68** in good to excellent yields (Eq. 28) [23]. Nucleophilic attack of the azide group of **69** on the isocyanides **66** followed by elimination of a nitrogen molecule from the resulting azide species **70** gives the π-allylpalladium–carbodiimide complex **71.** Curtius-type rearrangement of the π-allylpalladium group of **70** from the α-carbon to the β-nitrogen produces **71.** The 1,3-shift of the π-allylpalladium group of **71** gives the palladium–cyanamide complex **72,** and the reductive elimination of Pd(0) affords **68.** The reaction of the *o*-alkynylarylisocyanides **73** with allyl methyl carbonate **53c** and trimethylsilyl azide **67** affords the corresponding *N*-cyanoindoles **74** in good to high yields (Eq. 29) [23b].



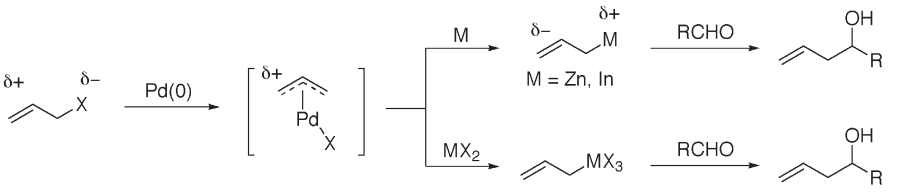
(28)



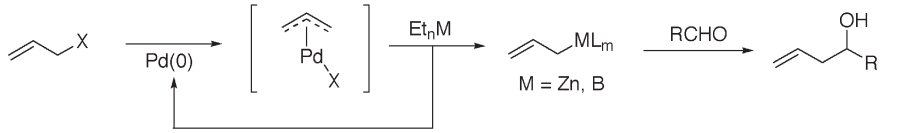
(29)

3
Nucleophilic Reactions of Allyl-, Propargyl-, and Allenylmetals Generated from π-Allyl-, Propargyl-, and Allenylpalladium

The ordinary electrophilic reactivity of π-allyl-, propargyl-, and allenylpalladium complexes is converted to nucleophilic reactivity by transmetalating them into other organometallics or by reducing them with electrochemical means [24]. In situ generation of nucleophilic allylmetal species or allyl anion from π-allylpalladium complexes leads to the reversal of reactivity; this is so-called umpolung. Reduction of π-allylpalladium complexes with metals, such as zinc and indium, and with low-valent metal salts, such as tin(II) chloride and samarium(II) iodide, forms the corresponding allylmetals, which behave as nucleophilic reagents and react with electrophiles, such as aldehydes and acetals (Scheme 8) [25–35]. Recent developments belonging to this category are summarized in Table 1. Transmetalation of π-allylpalladium intermediates with organometallics, such as diethylzinc and triethylborane, also generates nucleophilic allylmetal species in situ (Scheme 9), and representative examples are shown in Table 2 [36–41]. Umpolung of propargyl- and allenylpalladium complexes can be accomplished in a similar manner (see: Table 1, entries 6 and 7; Table 2, entries 4 and 5). Schemes 8 and 9 demonstrate that the starting allyl

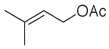
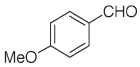
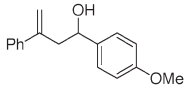
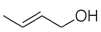
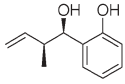
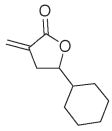
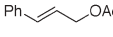
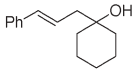
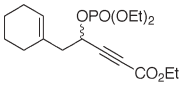
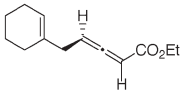
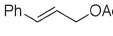
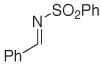
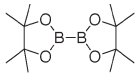
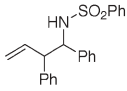


Scheme 8



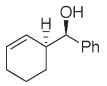
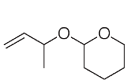
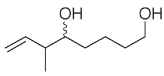
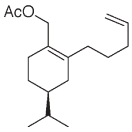
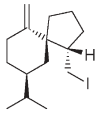
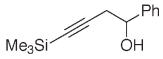
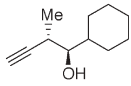
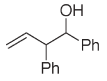
Scheme 9 – CH_3–CH_3, CH_2=CH_2, etc.

Table 1 Umpolung of π-allyl-, π-propargyl-, and allenylpalladium by reduction

entry	allyl source	electrophile	palladium	reductant	product	yield	ref.
1		PhCHO	$Pd(PPh_3)_4$	Zn		99%	[25]
2	PhI		$Pd(OAc)_2$ $P(2\text{-furyl})_3$	In		64%	[26]
3			$PdCl_2(PhCN)_2$	$SnCl_2$		74% syn:anti = 94:6	[27]
4			$PdCl_2(PhCN)_2$	$SnCl_2$		61%	[28]
5			$Pd(PPh_3)_4$	SmI_2		75%	[29]
6		H–O*i*Pr	$Pd(PPh_3)_4$	SmI_2		95%	[30]
7			$Pd(PPh_3)_4$	SmI_2		68% >95% ee	[31]
8		PhCHO	$Pd(PPh_3)_4$	SnF_2 Et_2AlCl_2		95%	[32]
9			$Pd_2(dba)_3$			91%	[33]
10		Me_3SiCl	$Pd(PPh_3)_4$	ne^{-} [a]		82%	[34]
11		PhCHO	$PdCl_2(PPh_3)_2$	ne^{-} [a] $ZnCl_2$		77%	[35]

[a] ne^{-} = electrochemical reduction.

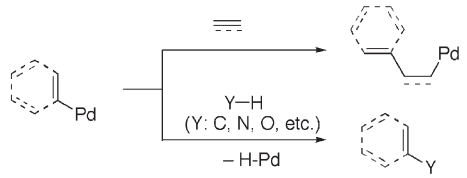
Table 2 Umpolung of π-allyl-, π-propargyl-, and allenylpalladium by transmetallation with organometallics

entry	allyl source	electrophile	palladium	organometal	product	yield	ref.
1		PhCHO	$Pd(PPh_3)_4$	Et_2Zn		76%	[36]
2			$Pd(OAc)_2$ PBu_3	Et_2Zn		97% anti:syn = 2:1	[37]
3		I_2	$Pd(OAc)_2$ PBu_3	Et_2Zn		90% d.r. 95:5	[38]
4		PhCHO	$Pd(PPh_3)_4$	Et_2Zn		80%	[39]
5			$Pd(PPh_3)_4$	Et_2Zn		85% anti:syn = 95:5 95% ee	[40]
6		PhCHO	$Pd(PPh_3)_4$	Et_3B		83% anti:syn = 2.2:1	[41]

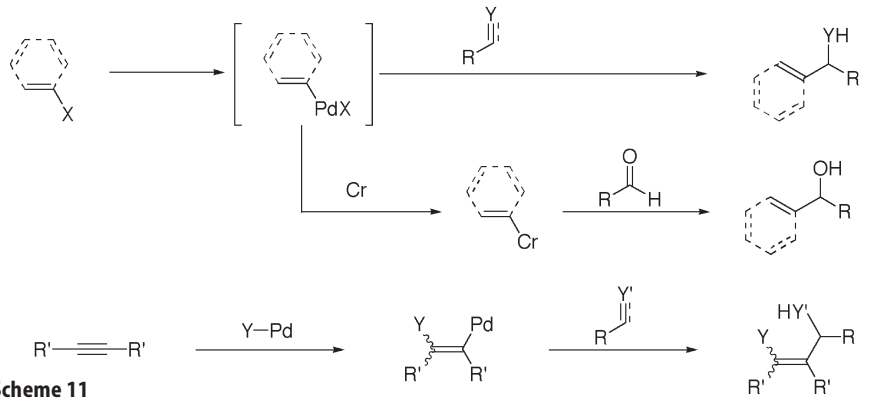
substrates, in which the allyl group is electrophilic, are converted to nucleophilic allylmetals via electrophilic π-allylpalladium complexes, which react with aldehydes to give homoallyl alcohols.

4
Nucleophilic Reactions of Vinyl- and Arylpalladium

In contrast to the diverse chemistry of allylpalladium complexes, vinylpalladium intermediates have been involved mainly in the vinylpalladation of carbon–carbon unsaturated systems and in the insertion into carbon–hydrogen and heteroatom–hydrogen bonds (Scheme 10). It is found that a vinylpalladium species reacts with carbon electrophiles such as aldehydes, ketones, and nitriles (Scheme 11, type a). Oxidative addition of vinyl–halogen and –pseudohalogen bonds to Pd(0) is the common way to generate the vinylpalladium species. Vinyl-



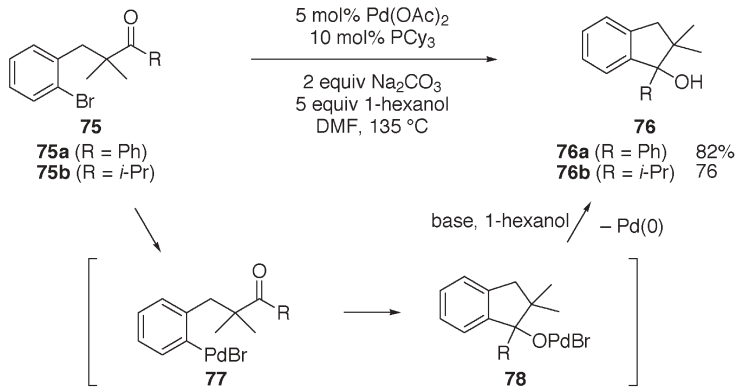
Scheme 10



Scheme 11

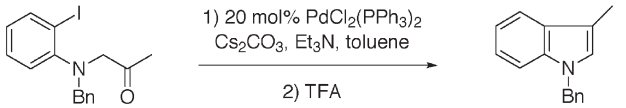
and arylchromates, which are catalytically generated by transmetalation of vinyl- and arylpalladium complexes with a chromium salt, act as a nucleophile and react with aldehydes (Nozaki–Hiyama–Kishi coupling, type b). Insertion of a carbon–carbon triple bond into the carbon–palladium or heteroatom–palladium bond (Y–Pd) is an alternative way to form the vinylpalladium intermediate, which reacts with aldehydes, ketones, and nitriles in a nucleophilic fashion (type c).

Intramolecular nucleophilic addition of aryl bromides to ketones proceeds very smoothly in the presence of palladium catalyst to give the corresponding cyclic alcohols in good to high yields [42] (Eq. 30). The reaction of the *o*-bromophenyl ketones **75** in the presence of $Pd(OAc)_2$, PCy_3, Na_2CO_3, and 1-hexanol



(30)

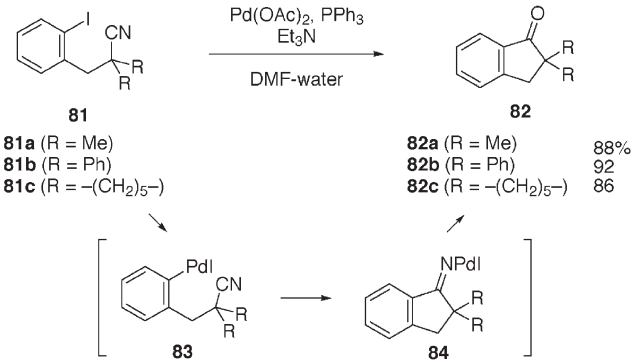
under argon atmosphere in DMF gives the indanols **76** in high yields. The reaction starts from oxidative addition of the C–Br bond of **75** to palladium(0). The resulting arylpalladium **77** attacks the carbonyl group in a nucleophilic manner. The product **76** and palladium(0) are formed by reduction of **78** with Na_2CO_3 and 1-hexanol. This reaction is a Grignard-type reaction using a palladium catalyst. The Pd-catalyzed nucleophilic cyclization of α-(2-iodoanilino)ketone **79** followed by treatment with TFA affords 3-methylindole **80** [43] (Eq. 31).



79 **80** 83%

(31)

Intramolecular cyclization of the 3-(2-iodoaryl)-propanenitriles **81** affords the indanones **82** in high yields [44] (Eq. 32). The reaction proceeds through nucleophilic attack of arylpalladium **83** on the nitrile group, forming the iminopalladium intermediate **84**.



81

81a (R = Me)
81b (R = Ph)
81c (R = –(CH$_2$)$_5$–)

82

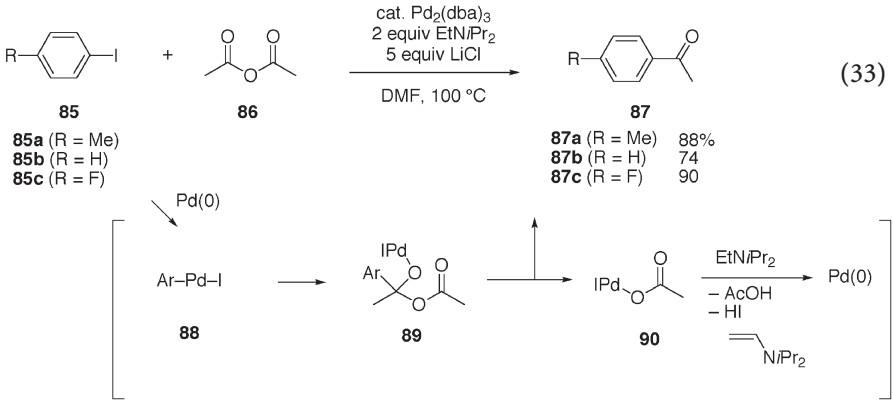
82a (R = Me) 88%
82b (R = Ph) 92
82c (R = –(CH$_2$)$_5$–) 86

83 **84**

(32)

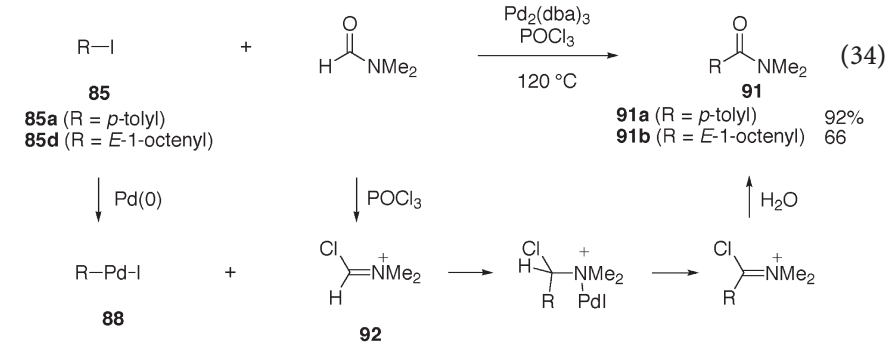
Intermolecular nucleophilic addition of the arylpalladium complexes **88** to acetic anhydride **86** gives the acetophenones **87** in good to high yields [45] (Eq. 33). The reaction of aryl iodides **85** and 5 equivalents of acetic anhydride **86** proceeds in the presence of catalytic amounts of $Pd_2(dba)_3{\cdot}CHCl_3$, 2 equivalents of EtN*i*Pr$_2$, and 5 equivalents of LiCl in DMF at 100 °C, affording the corresponding acetophenones **87** in high yields. Nucleophilic attack of the arylpalladium species **88**, which are generated by oxidative insertion of Pd(0) into the C–I bond of **85**, on the carbon–oxygen double bond of **86** leads to the alkoxypalladium intermediates **89**. The acetophenone products **87** are formed by elimination of the acetoxypalladium species **90**. Palladium(0) is regenerated by reduction with EtN*i*Pr$_2$.

Aminocarbonylation of the aryl and alkenyl iodides **85** with DMF proceeds via nucleophilic attack of the aryl- and alkenylpalladium intermediates **88** [46]



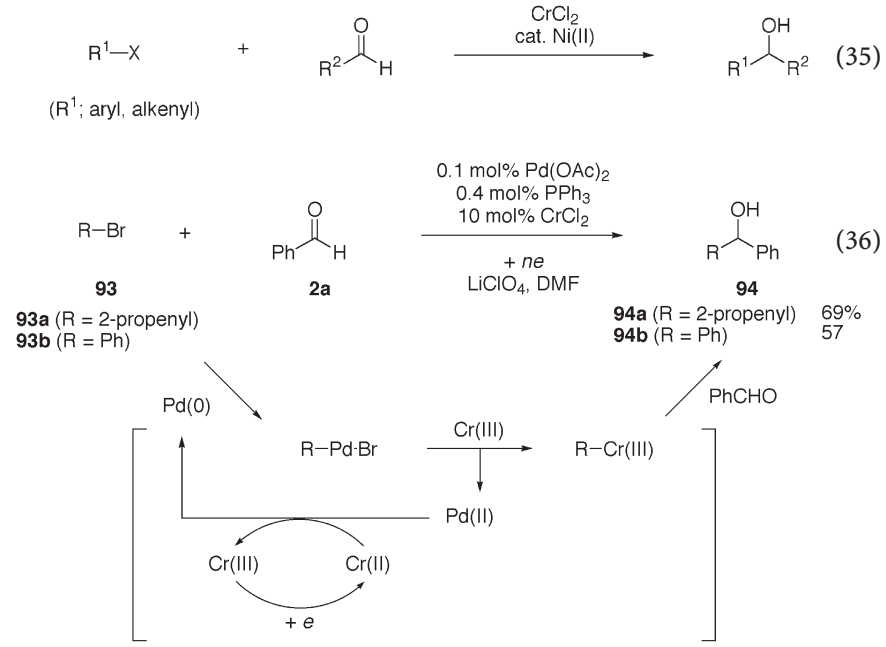
(33)

(Eq. 34). The reaction of aryl and alkenyl iodides **85** with excess amounts of DMF in the presence of 2.5 mol% of $Pd_2(dba)_3{\cdot}CHCl_3$ and 2 equivalents of $POCl_3$ produces the corresponding amides **91** in good to high yields. Nucleophilic attack of the sp^2 carbon–palladium bond **88** on the iminium salt **92**, which is generated from DMF and $POCl_3$ (so-called Vielsmeier reagent), occurs in the catalytic cycle.

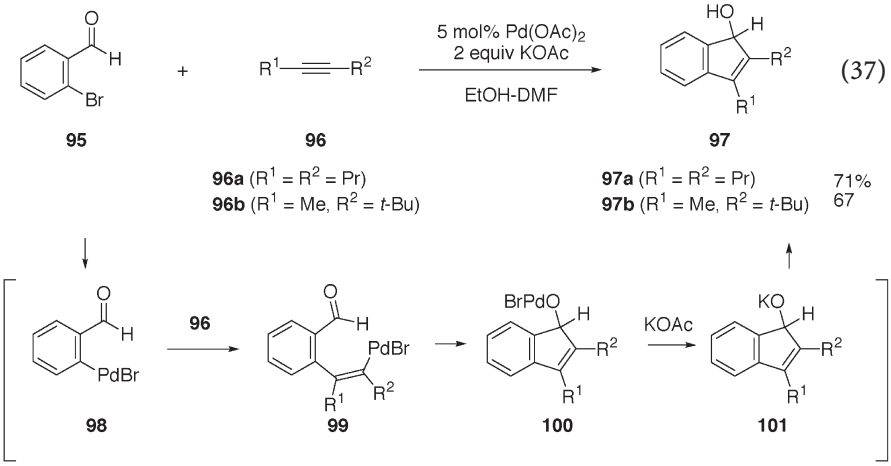


(34)

The reaction of alkenylchromium reagents, which are catalytically generated from alkenyl halides and pseudohalides with chromium(II), with aldehydes has been widely utilized in organic synthesis and been recognized as the Nozaki–Hiyama–Kishi reaction [47] (Eq. 35). Although nickel complexes have been generally used as a catalyst, palladium can promote a similar C–C bond-forming reaction between **93** and **2a** under electrochemical conditions, producing the corresponding alcohols **94** in good yields [48] (Eq. 36). The reaction proceeds through formation of an sp^2 carbon–palladium bond followed by transmetalation with chromium(III), generating an sp^2 carbon–chromium bond. Nucleophilic addition to the C=O bond of benzaldehyde **2a** gives the alcohol **94**. Palladium(0) is regenerated by reduction with chromium(II), which is reoxidized electrochemically.

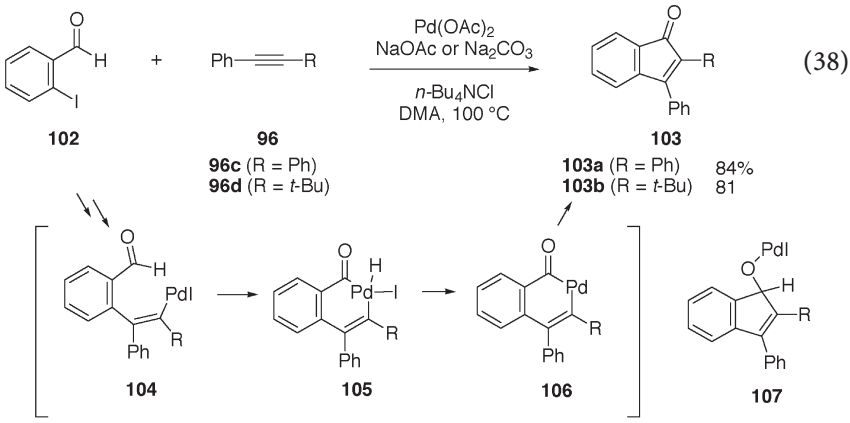


o-Bromobenzaldehyde **95**, in the presence of palladium catalyst, smoothly undergoes consecutive intermolecular carbopalladation with the internal alkynes **96** and then the intramolecular nucleophilic addition of the resulting vinylpalladium to the aldehyde function produces the indenol derivatives **97** in high yields [49–51] (Eq. 37). The reaction of *o*-bromobenzaldehyde **95** with the alkynes **96** in the presence of $Pd(OAc)_2$ (5 mol%), KOAc (2 equiv), and EtOH in DMF affords the indenols **97** in 67–71% yield. Insertion of the alkynes **96** into the



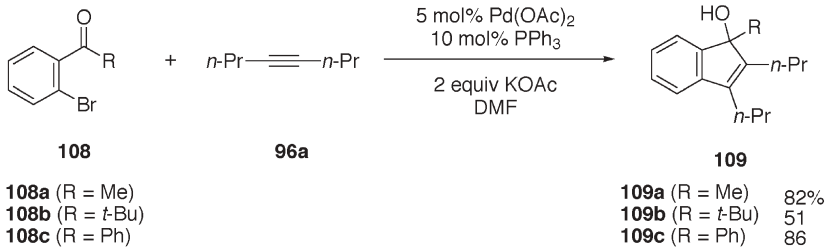
aryl–Pd bond of **98**, which is formed by oxidative addition of the C–Br bond of **95** to palladium(0), produces the vinylpalladium intermediates **99**. The intramolecular nucleophilic addition of **99** to the aldehyde group leads to the indenyloxypalladium species **100**. Excess amounts of KOAc transmetalate **100** into the alkoxides **101**, which give the reaction products **97** after subsequent protonolysis.

By contrast, the reaction of *o*-iodobenzaldehyde **102** with the arylalkynes **96** in the presence of $Pd(OAc)_2$, Na_2CO_3, and *n*-Bu_4NCl in DMA gives the corresponding indenones **103** in good to high yields [52] (Eq. 38). The reaction proceeds through the oxidative insertion of the resulting Pd(II) intermediates **104** into the aldehyde C–H bond to form the palladium(IV) intermediates **105**. Elimination of HI by base, and the reductive elimination of palladium(0) from the resulting Pd(II) species **106** gives **103**. There is an alternative mechanism in which β-hydrido elimination from the indenoxypalladium intermediates **107**, which are produced via the nucleophilic addition of vinylpalladium **104** to the aldehyde carbon, gives the indenone products **103** [50].

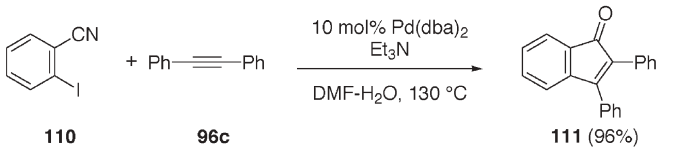


(38)

Nucleophilic cyclization of the *o*-bromophenyl ketones **108** and *o*-iodobenzonitrile **110** with the internal alkynes **96** occurs in the presence of palladium catalysts, producing the indenols **109** and indenones **111**, respectively[53, 54] (Eqs. 39 and 40).

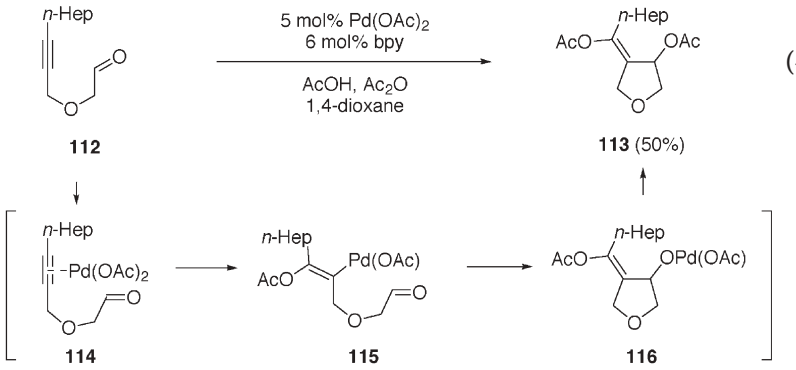


(39)



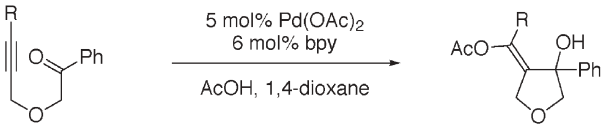
110 **96c** **111** (96%) (40)

Palladium-catalyzed cyclization of the alkynes containing an aldehyde (**112**), ketone (**117**), or nitrile group (**119**) gives the corresponding heterocycles in good to high yields [55] (Eqs. 41–43). The reaction of the alkynal **112** with acetic



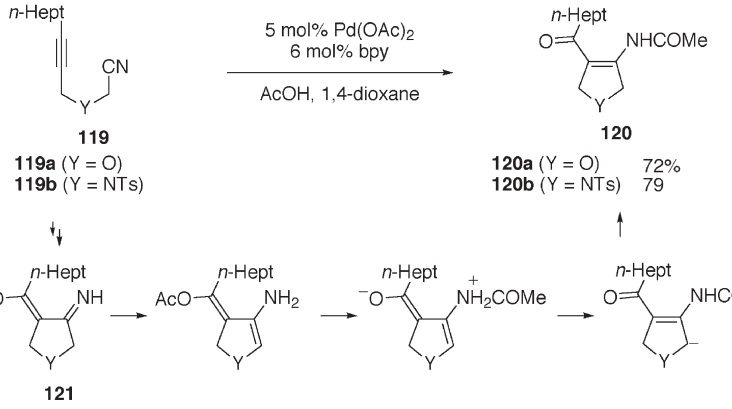
112 **113** (50%)

114 **115** **116** (41)



117
117a (R = *n*-Hept)
117b (R = *n*-Pent)

118
118a (R = *n*-Hept) 71%
118b (R = *n*-Pent) 80 (42)



119
119a (Y = O)
119b (Y = NTs)

120
120a (Y = O) 72%
120b (Y = NTs) 79

121 (43)

acid and acetic anhydride in the presence of catalytic amounts of $Pd(OAc)_2$ and bpy affords the corresponding tetrahydrofuran derivative **113** in 50% yield (Eq. 41). The reaction proceeds through coordination of the triple bond to palladium(II) (**114**) followed by *trans*-acetoxypalladation. Nucleophilic attack of the resulting vinylpalladium **115** on the carbonyl group produces the oxypalladium species **116**, which reacts with Ac_2O to give the product **113**. The alkynones **117** are also converted to the corresponding alcohols **118** (Eq. 42). In the reaction of the cyanoalkynes **119**, the corresponding expected products **121** are isomerized to the amides **120** (Eq. 43).

5 Perspective

In general, the π-allyl group of π-allylpalladium complexes (π-allylX, X=OAc, halogen, OCO_2R, …) acts as an electrophilic allyl moiety. However, bis-π-allylpalladium ($(\pi\text{-allyl})_2Pd$) acts as a nucleophilic allylating agent to carbonyl compounds. The ordinary electrophilic reactivity of π-allyl-, propargyl-, and allenylpalladium complexes is converted to nucleophilic reactivity through appropriate manipulation. Although the nucleophilic addition of Grignard reagents and organolithium compounds to aldehydes and ketones is a very common and useful reaction, the addition of organopalladiums to such carbonyl compounds has been an uncommon reaction. However, this type of addition is becoming popular in palladium chemistry. As can be seen from this chapter, one of the characteristics of palladium chemistry lies in its diversity. The reactivity of main group organometallics, such as Grignard reagents (RMgX) and organolithium compounds (RLi), is rather straightforward. The R group exhibits nucleophilic reactivity in most cases, and to the best of our knowledge it is not possible to produce electrophilic reactivity of the R group. However, by a simple manipuation, switching the electrophilic reactivity to a nucleophilic one is rather easy in the palladium complexes. This is a strong and beneficial point of palladium species when they are applied in organic synthesis. The diverse reactivities of organopalladium compounds will continue to be further uncovered, and it is expected that clever and smart application of the diversity in organic synthesis will be achieved in the future.

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The Use of *N*-Heterocyclic Carbenes as Ligands in Palladium-Mediated Catalysis

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Abstract Recent developments in the use of N-heterocyclic carbenes (NHC) as ligands in palladium-mediated transformations are described. These versatile ligands afford steric and electronic control of the metal environment, just as tertiary phosphines, yet they also allow synthetic access and operational catalytic advantages compared to metal–tertiary phosphine-centered transformations.

Keywords N-heterocyclic carbene · Palladium · Ligand · Cross-coupling · Catalysis

Abbreviations

Bu_4NOAc	Tetrabutylammonium acetate
Cp*	Pentamethylcyclopentadienyl
CO	Carbon monoxide
dba	Dibenzylideneacetone
DMAc	Dimethylacetamide
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
IAd	1,3-Bis(adamantyl) imidazol-2-ylidene
IMes	1,3-Bis(2,4,6-trimethylphenyl) imidazol-2-ylidene
IPrHCl	1,3-(2,6-Diisopropylphenyl) imidazolium chloride
IR	Infrared
KO^tAm	Potassium *tert*-amylate
KO^tBu	Potassium *tert*-butoxide
MeCN	Acetonitrile
MeOH	Methanol
NaH	Sodium hydride
NaO^tBu	Sodium *tert*-butoxide
NHC	N-heterocyclic carbene
OAc	Acetate
PCy_3	Tricyclohexylphosphine
$P(o\text{-tolyl})_3$	Tri(*o*-tolyl)phosphine
PPh_3	Triphenylphosphine
P^iPr_3	Triisopropylphosphine
ppm	Parts per million
SIPrHCl	1,3-(2,6-Diisopropylphenyl)-4,5-dihydroimidazolium chloride
TBAF	Tetrabutylammonium fluoride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Tmiy	1,3,4,5-Tetramethylimidazolin-2-ylidene
TON	Turnover number
ΔH	Enthalpy

1 Introduction

Among transition metal catalysts, palladium-centered transformations are found to be most versatile, with a wide range of applications on both industrial and laboratory scales [1]. As a result of the growing importance of cross-coupling reactions in organic synthesis over the past few decades, Pd-catalyzed C–X (X=C, N, O, S) bond formation has emerged as an intensively studied area [2]. This catalytic methodology has become more popular in organic synthesis as more efficient catalysts have been developed, and has permitted the synthesis of a wide variety of organic compounds ranging from polymers, materials, and liquid crystals [3] to pharmaceuticals and natural products [4].

To this end, monodentate phosphine or bidentate PX (X=P, N, O) ligands have usually been employed as ancillary ligands for transition-metal-catalyzed reactions, with bulky tertiary alkyl phosphines proving particularly effective. Significant advances have been achieved in the use of less active aryl chlorides (bond strength: C–Cl>C–Br>C–I) as chemical feedstock [5], with a number of processes mediated by palladium–bulky phosphine systems. This success is often explained by the effect of bulk and electron richness at the metal center along the catalytic cycle depicted in Fig. 1 [6].

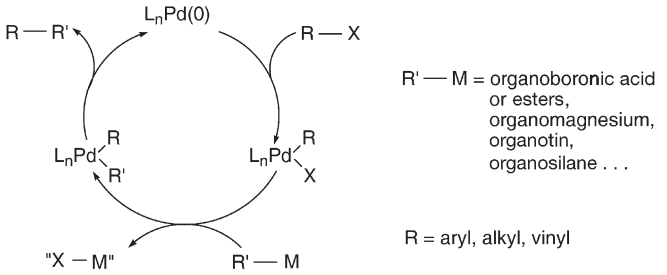


Fig. 1 General catalytic cycle for cross-coupling reactions

Despite their effectiveness in controlling reactivity and selectivity in organometallic chemistry and homogeneous catalysis [7], tertiary phosphines are often air-sensitive and are subject to P–C bond degradation at elevated temperatures. As a consequence, the use of a higher phosphine concentration in such catalytic processes is often required [8]. Phosphine oxidation can take place not only in the presence of oxygen but also intramolecularly if proper substituents are present. It is known that palladium/tertiary phosphine/acetate complexes lack stability due to a propensity to oxidize the supporting phosphine ligand via an intramolecular process. Triphenylphosphine is a classical example where the reaction of $Pd(OAc)_2$ with excess PPh_3 leads to $Pd(PPh)_4$ and $O{=}PPh_3$ [9].

N-heterocyclic carbenes (NHC) and their metal complexes have a relatively short but continually expanding history of applications. Since their discovery

in the early 1960s [10], carbene complexes derived from heterocycles such as imidazole, dihydroimidazole, and triazole have attracted considerable attention [11]. A true explosion in the field was catalyzed by the isolation of stable, "bottleable", imidazol-2-ylidene carbene in the early 1990s [12]. These ligands appear to have several advantages over the commonly utilized phosphines: the complexes display high thermal stability and exhibit in general a resistance to ligand dissociation from the metal center. Therefore an excess of the ligand is not required in order to prevent aggregation of the catalyst to yield bulk metal. As a consequence, an increasing number of catalytic reactions make use of nucleophilic carbenes as catalyst modifiers. Specific examples are the use of metal–carbene complexes in hydrosilylation [13], Ru-catalyzed furan synthesis [14], Ir-catalyzed hydrogenation [15], and Ru-catalyzed olefin metathesis [16].

In order to understand the ability of carbenes to act as ligands, an understanding of their electronic properties is necessary. In general, all carbenes can be viewed as neutral, six-electron species in which the carbenic carbon is divalent. The geometry of the carbon is planar and its formal hybridization is sp^2. For singlet carbenes such as NHC, the nonbonding electrons are in the p_π orbital of lower energy. The energy gap between the occupied and unoccupied orbitals is larger than 2 eV (as required for the stabilization of singlet carbenes) [17] (Fig. 2).

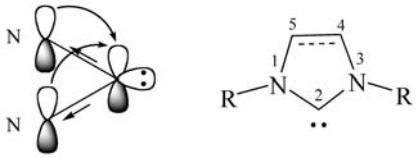


Fig. 2 Electronic stabilization of N-heterocyclic carbenes

The nature and electronic effects imparted by the substituents on the carbenic carbon have a profound effect on this energy gap. By inductive effects, electron-withdrawing groups increase the s character of the σ orbital. The effect on p_π is minimal, resulting in an increase in the gap between the two orbitals and a stabilization of the singlet ground state [18]. Mesomeric effects from the substituents have a marked interaction with p_π and less with the in-plane orbital. π-Electron-donating groups lead to a formal three-center/four-electron bonding picture that increases the energy of the out-of-plane orbital and induces a further stabilization of the singlet ground state.

The electron distribution in the two orbitals raises the question of an amphiphilic character, σ-donor doubled by π-acceptor capabilities. However, the electron pairs of the two nitrogens donate sufficient electron density into p_π to minimize π-backbonding. As a result, the NHC can be regarded as a Fischer-type carbene with usually insignificant π-backbonding. Overall, NHC nitrogens adjacent to the carbenic center act complementarily by both inductive and mesomeric effects to stabilize a singlet state. Furthermore, the NHC are prevented from dimerization by the presence of usually large neutral sub-

stituents on the nitrogens. It is interesting to note that NHC with very small methyl substituents on the nitrogens are reported to be relatively stable liquids and 1,3,4,5-tetramethylimidazol-2-ylidene is a stable crystalline material [19]. It can be concluded that the electronic stabilization induced by nitrogens is enough to prevent dimerization in most cases irrespective of the size of the substituents.

2 Synthesis of *N*-Heterocyclic Carbenes

The first isolated NHC was reported by Arduengo et al. in 1991 [12]. The synthetic protocol leading to this isolation followed a methodology developed to deprotonate the precursor imidazolium salt with sodium or potassium hydride in the presence of KO^tBu in DMSO [20]. Herrmann subsequently developed a method based on deprotonation of the corresponding salts in liquid ammonia [21]. These methods tolerate a large variety of functional groups and can be scaled up. Other synthetic approaches include reaction of imidazol-2-thiones with potassium metal [22], thermal elimination of methanol from adducts to form triazol-2-ylidene [23], and elimination of phenoxides.

Herrmann has previously emphasized the similarities between NHC and tertiary phosphines in terms of electronic properties [24]. A step forward in understanding the NHC ligand capabilities was achieved through solution calorimetric studies. The study aimed at determining the steric and electronic effects of NHC in their reaction with an electron-deficient ruthenium complex $[Cp^*RuCl]_4$ (Cp^*=pentamethylcyclopentadienyl). The ruthenium complex reacts easily with sterically demanding electron-donor ligands leading to the formation of monomeric, 16-electron $Cp^*Ru(L)Cl$ complexes. The value of ΔH is a measure of the binding properties of the ligand: the more exothermic the value the better nucleophile (strong donor) the ligand. In this study almost all NHC gave substantially higher exothermic values for ΔH than their phosphine counterparts by 25–30 kcal/mol [25]. The binding properties of NHC are profoundly affected when bulky substituents such as adamantyl are involved. The enthalpy of reaction (ΔH) between IAd (R=1-adamantyl) and $[Cp^*RuCl]_4$ is only 27.4 kcal/mol, a value indicating a more weakly binding ligand than basic phosphines such as PCy_3 and P^iPr_3. This result can be rationalized in terms of a strong steric congestion of the ligand-inhibiting metal–ligand orbital overlap.

Recently, the electronic and steric parameters of NHC ligands were analyzed in a series of nickel complexes bearing CO ligands [26]. The CO infrared frequencies are directly related to the electron density around the metal center induced by the supporting ligands, while minimizing steric congestion or effects. Electron-donating ligands provide increased electronic density on nickel, which allows for increased backdonation into π-accepting ligands such as CO. This results in the carbonyl IR frequency moving to lower cm^{-1} values. The reaction of $Ni(CO)_4$ with one equivalent of NHC led to stable complexes of

Table 1 CO infrared frequencies for $(NHC)Ni(CO)_3$ complexes

Ligand	Complex	ν_{CO} (A_1, cm^{-1}) CH_2Cl_2	ν_{CO} (E, cm^{-1}) CH_2Cl_2
IMes	$Ni(CO)_3$(IMes)	2050.7	1969.8
SIMes	$Ni(CO)_3$(SIMes)	2051.5	1970.6
IPr	$Ni(CO)_3$(IPr)	2051.5	1970.0
SIPr	$Ni(CO)_3$(SIPr)	2052.2	1971.3
ICy	$Ni(CO)_3$(ICy)	2049.6	1964.6
P^tBu_3	$Ni(CO)_3(P^tBu_3)$	2056.1	1971
P^iPr_3	$Ni(CO)_3(P^iPr_3)$	2059.2	1977
PPh_3	$Ni(CO)_3(PPh_3)$	2068.9	1990

formula $(NHC)Ni(CO)_3$. The infrared carbonyl frequency values of the complexes confirmed a better donor ability for NHC compared to the most donating tertiary phosphines (Table 1). The carbonyl infrared bands from such complexes are very close to each other as a function of NHC, and support the idea of an electronic behavior of NHC mainly induced by the presence of nitrogen atoms adjacent to the carbenic center [27].

3
Palladium Complexes of *N*-Heterocyclic Carbene

3.1
Palladium(0) Complexes of *N*-Heterocyclic Carbene

Complexes of Pd(0) enter into catalytic cycles more straightforwardly than their Pd(II) counterparts since they are primed for oxidative addition. Despite the fact that literature reports describe numerous examples of Pd(II) complexes stabilized by NHC ligands (see below), examples of (NHC)Pd(0) species are relatively scarce. The first homoleptic $Pd(NHC)_2$ complex was synthesized by a metal vapor method, but yields of the product were low and the utility of the method is strictly limited to easy to sublime NHC [28] (Fig. 3).

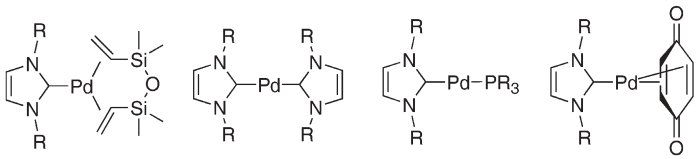
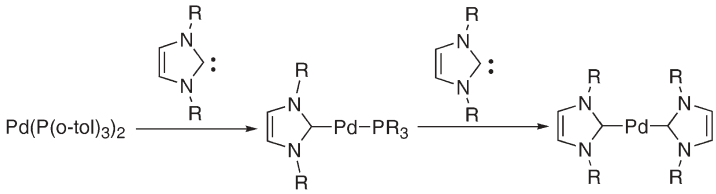


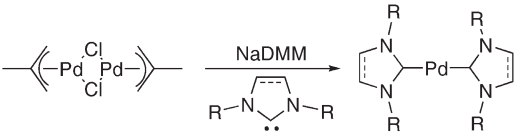
Fig. 3 Examples of NHC/Pd(0) complexes

Solution-phase synthetic procedures leading to $(NHC)_2Pd$ complexes revolve around ligand displacement reactions involving palladium centers bearing weakly coordinating ligands such as phosphines or olefins (see Scheme 1). For instance, a 14-electron species such as $Pd(P(o\text{-tolyl})_3)_2$ reacts with free NHC



Scheme 1 Synthesis of bis-NHC palladium complexes

leading first to carbene/phosphine/palladium complexes then to a bis-NHC complex by complete displacement of all phosphine ligands. The synthesis of mixed species can be achieved by mixing the bis-carbene complex with free phosphine, either $Pd(P(o\text{-tolyl})_3)_2$ or PCy_3, indicating a degree of reversibility associated with this reaction [29]. A second approach, depicted in Scheme 2, is the *in situ* reduction of Pd(II) species in the presence of NHC [30]. The electrochemical reduction of palladium(II) complexes was investigated and reported but no complexes have been isolated and characterized so far [31].



Scheme 2 Synthesis of Pd(0) complexes in the presence of reducing agents

3.2 Palladium(II) Complexes of *N*-Heterocyclic Carbene

3.2.1 Palladium(II) Complexes of *N*-Heterocyclic Carbene by the Acetate Method

Since the first applications of palladium/NHC complexes in catalysis in 1995 [32], numerous complexes have been synthesized using various methods. One of the first methods leading to palladium/NHC was the reaction of $Pd(OAc)_2$ and imidazolium salts. The carbenes are formed by an *in situ* deprotonation of the imidazolium salts by the acetate base which is built into the palladium salt precursor. In most cases the reaction requires two equivalents of the ligand per metal center and leads to bis-carbene palladium(II) salts. In only one case was the intermediate, a mixed palladium/acetate/anion complex, isolated and characterized [33]. In this system, the second acetate anion can act as a base for the deprotonation of the second imidazolium salt to form bis-carbene palladium(II) salts. The method is quite general and gives high yields of both simple and chelating NHC complexes. The methodology requires high temperature and reduced

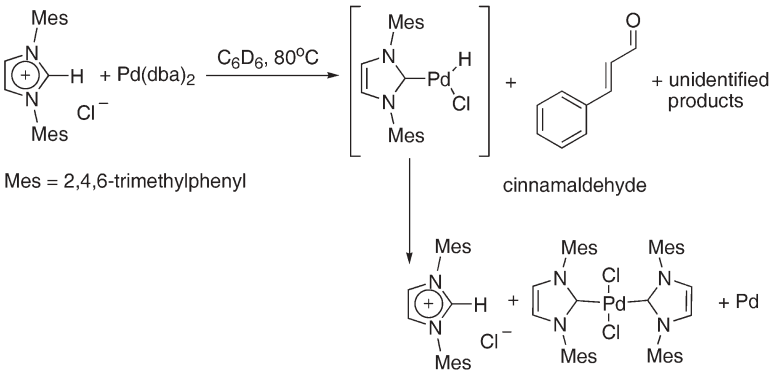
pressure to remove the acetic acid formed during the reaction. If the acetic acid is not removed the imidazolium salts can be deprotonated at the C4 position [34].

3.2.2
Palladium(II) Complexes of *N*-Heterocyclic Carbene by the Free Carbene Method

A second general method for the synthesis of Pd(II) complexes is the reaction of palladium salts with isolated or *in situ* generated NHC. The method is very versatile but requires the separate isolation of the ligand or a reliable method for deprotonation. The base or its degradative by-product should be compatible with the functional groups present as ligands or anions in the palladium precursor. A large number of complexes bearing monocarbene, bis-carbene, chelating carbene, and mixed chelating ligands having at least one carbene have been successfully synthesized using this protocol [35]. This is now a very well-established method.

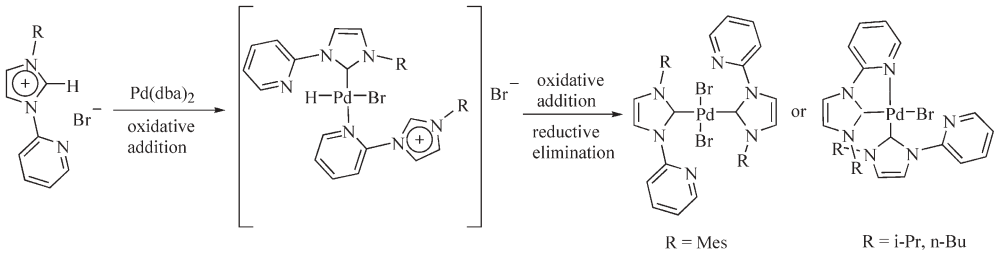
3.2.3
Palladium(II) Complexes of *N*-Heterocyclic Carbene by Oxidative Methods

The oxidative addition of imidazolium salts to palladium(0) centers was thought possible as a result of theoretical studies [36]. This mode of activation was observed in the reaction of $Pd(dba)_2$ and IMes·HCl in deuterated benzene, giving a mixture of products in which cinnamaldehyde was identified by GC–MS. This is the expected organic product resulting from elimination of the dba moiety from palladium. Furthermore, a specific upfield signal at –14.8 ppm in ^1H NMR led to the conclusion that formation of Pd–H species was possible in this manner. Unfortunately isolation and crystallographic characterization of this complex was not possible due to a rapid decomposition leading to palladium black and formation of crystalline $(IMes)_2PdCl_2$ along with IMes·HCl (Scheme 3) [37].



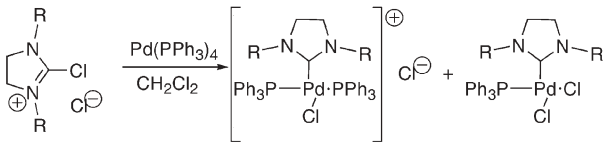
Scheme 3 Formation of palladium hydride species after oxidative addition of imidazolium salts to a Pd(0) center

In the reaction of 2-pyridine-substituted imidazolium salts with $Pd(dba)_2$ (Scheme 4), the formation of either *cis* or *trans* complexes having two carbenes per palladium center was observed [38]. No metal hydride was detected despite the fact that the ratio of metal to ligand was varied from 1:1 to 1:4. One of the proposed mechanisms for the formation of such complexes involves a double oxidative addition and elimination of H_2 from a Pd(IV) center. The transient Pd–H species is then presumably too reactive toward the second molecule of the imidazolium salt and cannot be observed. A second possible mechanism involves two oxidative steps separated by a reductive elimination from the Pd(II) center.



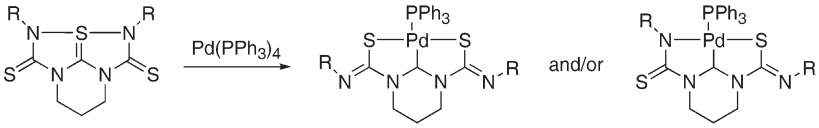
Scheme 4 Formation of palladium/bis-carbene complexes after oxidative addition of imidazolium salts to a Pd(0) center

Oxidative addition of 2-chloroimidazolium salts to electron-rich $Pd(PPh_3)_4$ has been reported by Fürstner and is illustrated in Scheme 5 [39]. The methodology led to a mixture of complexes in which the dominant products are the cationic $[(PPh_3)_2Pd(NHC)Cl]Cl$ and the neutral form $(PPh_3)Pd(NHC)Cl_2$. Other complexes have a higher propensity to expel one additional equivalent of phosphine.



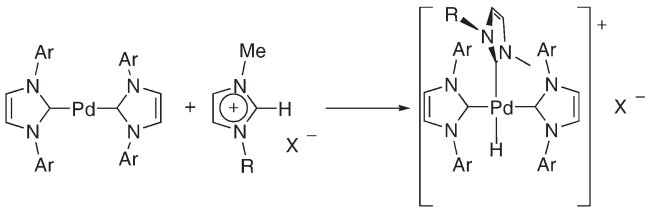
Scheme 5 Oxidative addition of imidazoliumchloroformate to an electron-rich Pd(0) center

An interesting oxidative addition reaction leading to a pincer-type complex was reported by Matsumura and Inoue et al. [40]. The protocol involves the reaction of a π-sulfurane (10-*S*-3-tetraazapentalene) with $Pd(PPh_3)_4$. The hypervalent sulfur is reduced, and at the same time one of the phosphines and Pd(0) are oxidized to triphenylphosphine sulfide and Pd(II), respectively (see Scheme 6).



Scheme 6 Pincer palladium complexes by the oxidative addition of (10-*S*-3-tetraazapentalene) to $Pd(PPh_3)_4$

Theoretical density functional calculations on the possibility of addition of imidazolium salts to electron-rich palladium centers predicted an exothermic enthalpy for such a process [36]. These results suggested that, under appropriate reaction conditions and with the use of a proper carbene precursor, this reaction should present a feasible synthetic path to carbene/palladium complexes. Only recently, the addition of the C(2)–H bond of an imidazolium salt, in the form of an ionic liquid, to a Pd(0)/NHC complex with the formation of a stable Pd–H bond has been reported [41]. These complexes bear three carbenes per metal center, the fourth coordination position being occupied by hydrogen. The isolation of these complexes has proven that the "beneficial" role of ionic liquids as solvent can lead to the formation of catalytically active palladium–carbene complexes (see Scheme 7).



Scheme 7 Oxidative addition of an ionic liquid to a homoleptic $(NHC)_2Pd$ complex

4
Palladium/NHC Complexes as Catalysts

4.1
Palladium/NHC Catalysts for Cross-Coupling Reactions

Highly promising and versatile supporting-ligand alternatives to phosphine ligands have been found in the NHC ligand family for use in cross-coupling catalysis [42]. These NHC (see Fig. 4), generally bearing bulky and/or electron-donating N-substituents, exhibit greater thermal stability than tertiary phosphines.

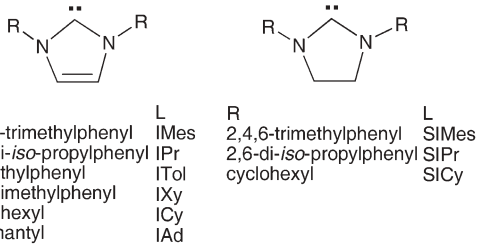
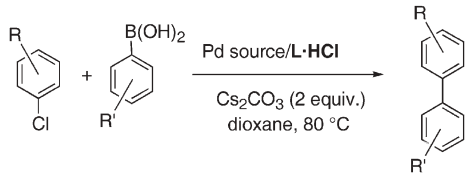


Fig. 4 Commonly used unsaturated and saturated NHC ligands

4.1.1 Suzuki–Miyaura Cross-Coupling of Aryl Halides or Pseudo-Halides with Arylboronic Acids

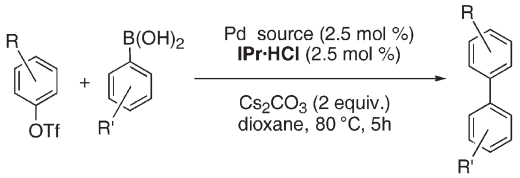
Initial research in this area focused on the use of zerovalent $Pd_2(dba)_3$ as the palladium source, the carbene IMes, and Cs_2CO_3 as base [43]. This reagent combination afforded a 59% yield in the coupling of 4-chlorotoluene with phenylboronic acid. The catalytic protocol could be simplified by the use of air-stable IMes·HCl that is deprotonated *in situ* with Cs_2CO_3; isolated yields for the Suzuki–Miyaura coupling then reached >95% (Scheme 8). Subsequently a further simplification of the catalytic system was achieved, by extension of the reaction to air-stable Pd(II) precursors [44].



Scheme 8 Suzuki cross-coupling reaction mediated by in situ generated Pd/NHC system

An activation period of 30 min was required in order to insure the reduction of Pd(II) to Pd(0) and the deprotonation of IMes·HCl. The use of NHC bearing bulky *ortho*-substituted aryl groups as N-substituents provided the highest yields in this transformation, and clearly indicated the importance of steric factors on the effectiveness of the catalytic system. The Pd/NHC system tolerates diverse electron-donating and electron-withdrawing substituents. Steric factors associated with *ortho*-substituted reagents lower the yields and reaction rates. The same catalytic protocol was applied to the cross-coupling of aryl triflates with phenylboronic acids with excellent yields (Scheme 9).

Palladium(0) complexes bearing NHC ligands have been used as active precatalysts in the Suzuki–Miyaura reaction. Homoleptic $(NHC)_2Pd$ complexes were prepared by phosphine displacement from $Pd(P(o\text{-tol})_3)_2$ with free carbene [45]. The complexes having *tert*-butyl or mesityl substituents on the nitrogen atoms of the imidazol-2-ylidene catalyzed the reaction of phenylboronic acid



Scheme 9 Cross-coupling reaction of aryl triflates and phenylboronic acids mediated by in situ generated Pd/NHC system

and 4-chlorotoluene at 80 °C. The yields varied from moderate to more than 90% depending on the nature of the substituents on the NHC ligands. Adamantyl substituents in the corresponding homoleptic complexes allow for the same coupling; however, the reaction can then be performed at room temperature, in the presence of CsF [30].

The use of a "flexible" substituent (cyclohexyl) has presumably a beneficial role in the reductive-elimination step of the catalytic cycle by increasing the steric pressure on the metal center. Most aryl chlorides including sterically demanding ones can be converted to the corresponding biaryls at room temperature using this flexible ancillary ligand (see Fig. 5) [46].

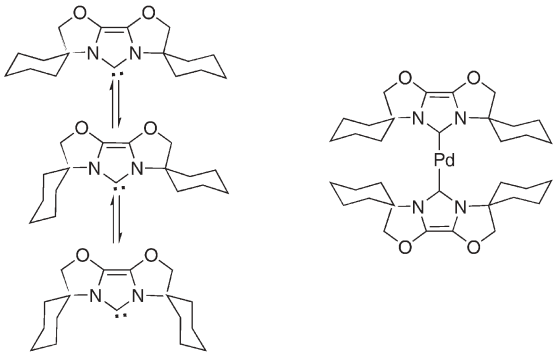
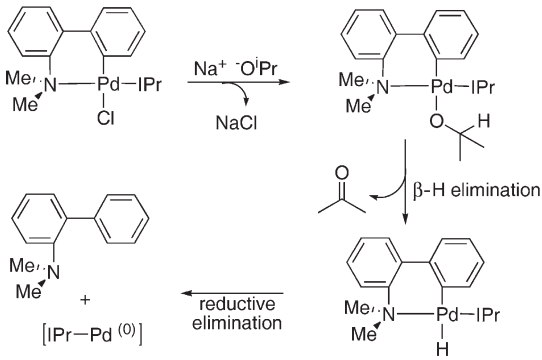


Fig. 5 Mixed phosphine/carbene ligand precursor

The most efficient of these Pd/NHC systems reported to date for the synthesis of di- and trisubstituted biaryls is based on an NHC-modified palladacycle, NaO^{t}Bu as base, and isopropanol as solvent [47]. Using this protocol, sterically hindered aryl chlorides couple with sterically hindered boronic acids at room temperature in minutes. The proposed activation of the catalyst relies on the formation of an unstable palladium hydride upon attack of ^{i}PrO$^-$ followed by β-hydrogen elimination (Scheme 10).

The active catalytic species in this situation is Pd-NHC and not Pd(NHC)$_2$ as in the previously described systems. It should also be mentioned here that the Pd(NHC)$_2$ complexes may very well act as precatalysts in these reports. In support of a species of formula Pd-NHC as active catalytic species, Hollis et al.



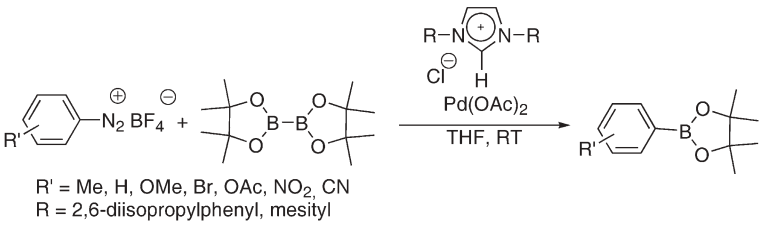
Scheme 10 Activation of NHC-stabilized palladacycle in the presence of alkoxide base

[48] recently reported on the reaction of phenyl halides and phenylboronic acid mediated by a series of chelating and monocarbene complexes of palladium. The monocarbene system gave consistently better yields of the desired product compared with the chelating counterparts when chlorobenzene was used as coupling partner.

The impressive stability of Pd/NHC complexes and their activity in cross-coupling reactions is strongly supported by the recent report of Zhao et al. [49], who developed an environmentally benign protocol for the cross-coupling of aryl bromides with phenylboronic acids in water. The catalytic system is based on a tetradentate NHC ligand.

4.1.2 Borylation of Aryl Diazonium Salts

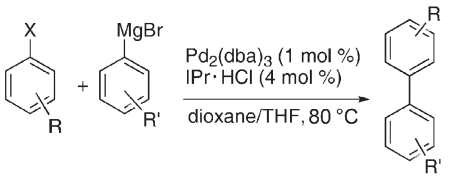
Reactive aryl diazonium salts can be efficiently borylated in the presence of $Pd(OAc)_2$ and imidazolium or dihydroimidazolium salts to form arylpinacolatoborane products [50, 51]. The reaction does not require a base and proceeds at mild or room temperature. A solvent dependence on the product distribution was observed. Solvents such as DMF, MeOH and dioxane led to a mixture of the desired product and biaryl by-product in yields as high as 28%. Sterically demanding 1,3-(2,6-diisopropylphenyl)-4,5-dihydroimidazolium chloride (SIPr · HCl) as precatalyst gave the best conversion and minimum amount of by-products. Raising the temperature to 65 °C shortens the reaction time but increases substantially the amount of undesired biaryl by-product. The reactions can be performed in the presence of alkyl, aryl, or vinyl boronates (Scheme 11). This protocol tolerates many functional groups on the aryl moiety and yields are usually excellent. However, a decrease in the reactivity was observed for hindered substrates. The active catalytic species is not unequivocally known, but the authors speculated the involvement of dimeric complexes of formula $[(NHC)PdCl_2]_2$ that can be synthesized by reaction of $Pd(OAc)_2$ with imidazolium salts.



Scheme 11 Borylation of aryl diazonium salts

4.1.3 Kumada–Tamao–Corriu Cross-Coupling of Aryl Chlorides with Aryl Grignard Reagents

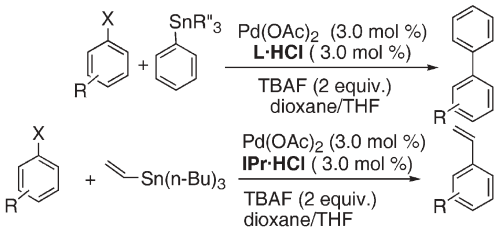
The first successful coupling involving unactivated aryl chlorides and PhMgBr Grignard reagent was reported in 1999 [52]. Optimization studies resulted in an efficient catalytic transformation mediated by $Pd_2(dba)_3$/IPr·HCl in dioxane/THF solvent mixture at 80 °C. PhMgBr (and other aryl Grignards) was utilized as a base for the deprotonation of imidazolium salts and active coupling partner. The catalytic system was tolerant of variations in the electronic nature of the substituents of the aryl Grignard and/or aryl halides. Steric congestion of both aryl Grignard and aryl halide affected drastically the conversion to the desired products (Scheme 12). Recently, Beller and coworkers reported the first Kumada reaction that involves alkyl chlorides as coupling partners [53].



Scheme 12 Cross-coupling of aryl chlorides with aryl Grignard reagent mediated by in situ generated Pd/NHC system

4.1.4 Stille Cross-Coupling of Aryl Halides with Hypervalent Organostannanes

Catalytic systems consisting of a mixture of $Pd(OAc)_2$ and IPr·HCl mediate successfully the coupling of 4-chlorotoluene and Me_3SnPh to afford the desired biaryl cross-coupling product (Scheme 13) [54]. The presence of TBAF is essential in performing the reaction as it performs a dual role: base/nucleophile to deprotonate the imidazolium salt and fluorinating agent for the tin substrate. The slow transmetalating step is accelerated by the formation of the more



Scheme 13 Cross-coupling of aryl chlorides with $Sn(^nBu)_3Ph$ or vinylstannanes mediated by in situ generated Pd/NHC system

reactive hypervalent organostannate. Electron-neutral and electron-deficient aryl bromides are coupled rapidly with $SnMe_3Ph$, $Sn(^nBu)_3Ph$, or vinylstannanes but the reactivity of electron-rich substrates is less facile. Unfortunately, the reaction is limited to aryl bromides or activated aryl chlorides. These results suggest that electron-withdrawing substituents facilitate the coupling reaction, consistent with a rate-determining oxidative addition step.

The chemical similarities between tin and silicon are obvious in cross-coupling reactions. Aryl halides and phenyltrimethoxysilane can react in the presence of 3 mol% each of $Pd(OAc)_2$ and IPr·HCl and two equivalents of TBAF in 1,4-dioxane at 80 °C to afford the desired coupling products [55]. As in the Stille reaction, the system is efficient if aryl bromides or electron-deficient aryl chlorides are used. Styrenes can be obtained in quantitative yield (with prolonged reaction times) from the reaction of aryl halides with vinyltrimethoxysilane.

4.1.5 The Heck Reaction

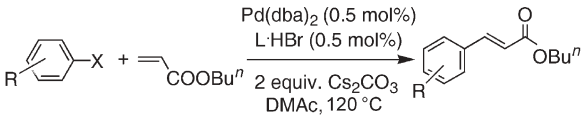
The Heck reaction was the first catalytic application examined for palladium/NHC complexes. A high degree of efficiency was observed for chelating biscarbene/palladium complexes in this transformation. The reactions involving butyl acrylate with aryl halides were efficiently mediated by such complexes at catalyst loadings as low as 10^{-4} mol%. Unactivated chlorides required, however, a catalyst loading up to 1 mol%. The impressive stability of the catalytic system under harsh reaction conditions and its reactivity profile were described as quite impressive [32, 56].

An insight into the activation of catalysts of type L_2PdX_2 (L=NHC) suggested a base-assisted reduction of Pd(II) to Pd(0). Tertiary amines, common bases in the Heck reaction, can be involved in a β-hydrogen transfer to the metal followed by elimination of HX. The mechanism can be useful in understanding the elusive catalyst activation in cross-coupling reactions [31]. Optimized reaction conditions in the presence of various reducing agents led to complete conversion of aryl iodides (and in some cased bromides) to products. The problems associated with the reduction of the metal and induction were overcome

by the use of Pd(0) complexes and ionic liquids as solvent [57]. The very attractive feature of the system is its ability to convert unactivated aryl chlorides to styrenes or cinnamic esters in excellent yields. Despite high temperatures (140 °C) and prolonged reaction times (24–48 h) no side reactions were reported.

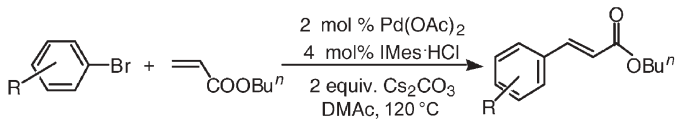
Following a recent theoretical study that suggested the suitability of mixed carbene–phosphine chelates for the Pd-catalyzed Heck reaction [58], a carbene–phosphine chelating ligand (Fig. 5) was prepared and its efficacy investigated in the cross-coupling of aryl bromides with *n*-butyl acrylate [59].

$Pd(dba)_2$ in conjunction with one equivalent of L·HBr, Cs_2CO_3, and *N*,*N*-dimethylacetamide (DMAc) at 120 °C gave excellent yields of styrenes for activated and unactivated aryl bromides (Scheme 14). The protocol was ineffective for unactivated aryl chlorides.



Scheme 14 Cross-coupling of aryl halides and acrylates mediated by in situ generated Pd/NHC system

Employing the same protocol as for the chelating NHC/phosphine system, nonchelating NHC ligands [60] gave high yields of *trans* coupling products for an array of aryl bromides (Scheme 15).

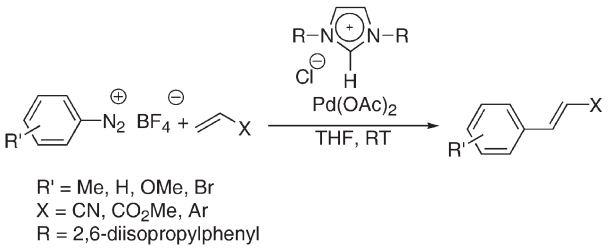


Scheme 15 Cross-coupling of aryl halides and acrylates mediated by in situ generated Pd(II)/NHC system

Tsoureas et al. [61] employed a closely related system bearing an NHC/phosphine ligand in well-defined catalysts of $LPdX_2$ formulation (X=Br, Me) or their corresponding cationic complexes. The results in the Heck coupling of aryl bromides and methyl acrylate were lower than the results using the *in situ* system. A maximum TON of 2,242 was achieved when the reaction was performed in NMP as solvent and NEt_3 as base.

Aryl diazonium salts are considered more reactive toward oxidative addition than aryl iodides. Furthermore, the presence of the anion eliminates the need for an additional base [62]. The reactions of various aryl diazonium fluoroborate salts with styrene mediated by $Pd(OAc)_2$/bis-(2,6-diisopropylimidazolium chloride) proceeds in almost all solvents at room temperature. In the opti-

mization studies THF was found to be the best solvent. The catalytic system allows the conversion of methyl acrylate, acrylonitrile, and various styrenes to the corresponding stilbenes in very good to excellent yields even at catalyst loadings as low as 0.1 mol%. Substrates having both diazonium salt and bromide react only at the diazonium position, highlighting the high activity of these substrates in C–C coupling (Scheme 16). The flexibility of the catalytic system was further illustrated by its ability to tolerate simple anilines that were converted to the corresponding diazonium salts *in situ*.



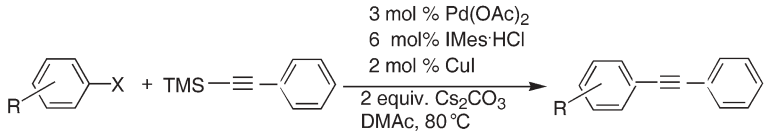
Scheme 16 Cross-coupling of aryl diazonium salts and olefins mediated by in situ generated Pd/NHC system

Recently, the high activity of palladium/NHC complexes in the Heck reaction was combined with an efficient recyclability process [63]. Bis-carbene pincer complexes of palladium(II) were immobilized on montmorillonite K-10. The catalytic activity of the heterogeneous system is similar to that displayed by their homogeneous counterparts. The stability of the catalyst was tested in the reaction of phenyl iodide and styrene. The product yield decreases from 99 to 79% after ten cycles.

Considering the importance of the Heck reaction and the studies described here, it is easy to understand why NHC have emerged as very powerful ligands in Heck reactions. Numerous studies exploring not only the nature of the ligands but also the optimized reaction conditions and the nature of the coupling partners have been conducted [64].

4.1.6 Cross-Coupling with Terminal Alkynes: the Sonogashira Reaction

The cross-coupling of aryl bromides and alkynes was found to be catalyzed by $Pd(OAc)_2$/IMes·HCl/Cs_2CO_3 in DMAc at 80 °C (Scheme 17). Undesired dimerization products were obtained when phenylacetylene was employed as the alkyne source. This side reaction was suppressed by using a more reactive substrate, 1-phenyl-2-(trimethylsilyl)acetylene [65]. Worthy of note is that high yields of coupled products were achieved under Cu-free conditions. Addition of 2 mol% CuI increased the reaction rates, most notably with deactivated or sterically encumbered aryl bromides. The catalytic system has a limited



Scheme 17 Cross-coupling of aryl halides and TMS-acetylenes mediated by in situ generated Pd/NHC system

effectiveness for the conversion of unactivated substrates such as chlorobenzene.

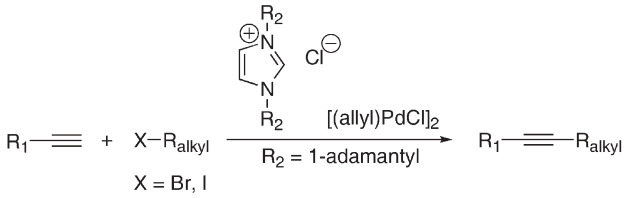
A dramatic dependence on the steric bulk of extended aromatic phenanthrylimidazol-2-ylidene ligand was observed in palladium-catalyzed Sonogashira coupling [66]. The yield of the coupling reaction of phenyl bromide and phenylacetylene increased from 17% for mesityl substituents on the imidazole nitrogens to 90% isolated yield for 2,9-dicyclohexyl-10-phenanthryl substituents. The catalytic system consists of a mixture of $Pd(PPh_3)_2Cl_2$ and KO^tBu as base in THF as solvent. Despite high yields of cross-coupling products observed for aryl bromides as partners, the system was ineffective for the conversion of aryl chlorides.

N-carbamoyl-substituted heterocyclic carbene/Pd(II) complexes in the presence of PPh_3 and CuI are reported to mediate the cross-coupling of aryl iodides with terminal alkynes at very mild temperature [67]. The system is compatible with aryl bromides; however, the temperature then required is 80 °C. In all reactions, the addition of 1 mol% of phosphine increased the yield of product. The role of the phosphine ligand is not completely understood but may facilitate the initial generation of a Pd(0) species.

Highly active immobilized palladium catalysts modified with a rigid C,N,C-pincer carbene ligand were successfully applied in the coupling of aryl halides to terminal acetylenes. The homogeneous catalyst was immobilized on three types of solids – montmorillonite K-10, bentonite A, and bentonite B – by the solvent-impregnation method. No significant differences were observed in the catalytic efficiency between the various supports. The reactivity of the system is relatively constant after as many as five cycles [68].

An interesting application of the Sonogashira reaction was recently reported by Fu and Eckhardt [69]. Alkyl electrophiles (bromides or iodides) can be efficiently coupled with terminal acetylenes when palladium/NHC complexes are used (Scheme 18). One of the most commonly encountered side reactions in palladium-mediated cross-couplings is β-hydrogen elimination. A striking difference was observed in moving from phosphine ligands (<5% product) to NHC (5–81% product) for the reaction involving *n*-nonyl bromide and 1-octyne. Optimization studies revealed the beneficial role of steric demand associated with the ligands, with a maximum yield of the product observed for R=*t*-Bu or 1-adamantyl.

The reaction tolerates a broad range of functional groups: esters, CN, Cl, aryl, vinyl, and acetals. The reaction is selective if two halides of different

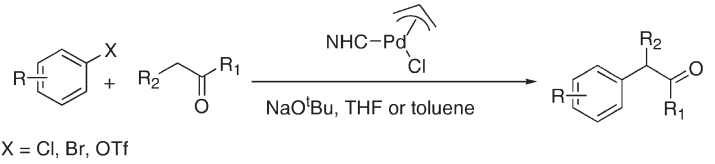


Scheme 18 Sonogashira reaction involving alkyl halides

reactivity are involved (e.g., Cl and Br). The ratio between NHC and palladium was optimized as 2:1 and the lack of available coordination sites on the metal center may explain why β-hydrogen elimination is retarded.

4.2 α-Arylation of Ketones

The cross-coupling of aryl halides and enolates is a powerful method to generate new C–C bonds and it has been extensively investigated using various palladium catalysts [70]. Extremely active NHC/Pd systems have been reported for the α-arylation of esters at room temperature [71] and for the arylation of amides [72]. Ketones that possess α-protons can be deprotonated in the presence of strong bases. α-Arylation of ketones can be performed in the presence of a catalytic amount of (NHC)Pd(allyl)Cl as catalyst and NaO^{t}Bu as base (Scheme 19).

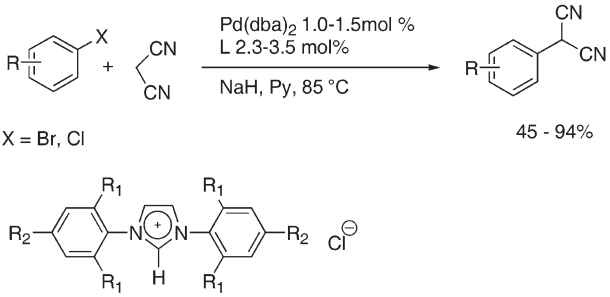


Scheme 19 α-Arylation of ketones

Hypothetically, the active catalyst is a Pd(NHC) species that oxidatively adds the aryl halides rapidly, but the presence of a free coordination site on the metal center after enolate attack makes possible undesirable side reactions such as β-hydrogen elimination. This usually results in the formation, in some cases, of dehalogenated by-products. An increase in the size of the supporting ligand decreases the susceptibility of the system toward β-hydrogen elimination. This can be accomplished simply by appropriate selection of bulky substituents on the imidazole nitrogens. In this manner the catalytic system tolerates a wide range of ketones and aryl halides. Aryl triflates are efficient partners in this reaction when the solvent is changed from THF to toluene. Mono- or multiple arylation reactions can be conducted with a proper selection of ketone and control of the base stoichiometry. This system proved extremely versatile.

4.3
Coupling of Aryl Halides and Malonitrile

The nature of the nucleophile in palladium-catalyzed coupling of aryl halides was extended to malonitrile as a practical approach to new C–C bond formation [73, 74]. The catalytic system consists of a mixture of $Pd(dba)_2$ and imidazolium salts having bulky aryl substituents on the nitrogen atoms and a ratio of metal to ligand of approximately 1:2 (Scheme 20). The reactions were performed in pyridine as solvent and NaH as base. Most aryl bromides were converted smoothly to the corresponding products in yields varying from 60 to 94%. Aryl chlorides are less reactive and usually required longer reaction times of 14–16 h. The yields were only marginally smaller than those for bromide equivalents. The catalytic system involving imidazolium salts as ligand precursors were found to be more active than the previously reported systems using phosphine ancillary ligands.



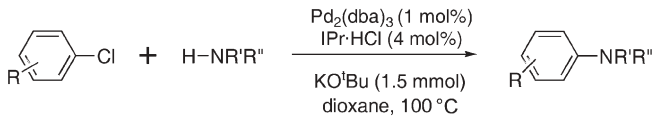
	1	2	3	4	5	6
R_1	H	Me	iPr	Me	Et	iPr
R_2	Me	H	H	Me	Et	iPr

Scheme 20 Coupling of aryl halides and malonitrile mediated by in situ generated Pd/NHC system

4.4
C–N Bond-Forming Reactions: the Hartwig–Buchwald Reaction

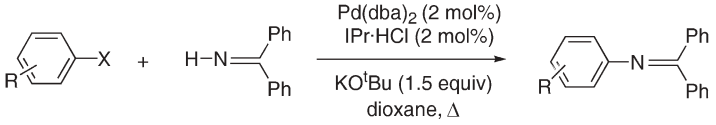
The use of bulky NHC precursor IPr·HCl in conjunction with KO^tBu as base, a palladium source, and 1,4-dioxane as solvent permits the catalytic C–N coupling of aryl iodides and bromides at room temperature and of aryl chlorides at elevated temperature. High conversions were achieved with primary and secondary, cyclic and acyclic amines with various aryl halides. 4-Chlorotoluene and *ortho*-substituted aryl halides were aminated in good to excellent yields. The effective coupling of 4-chloroanisole with sterically unhindered amines makes this one of the most effective catalytic systems to date (Scheme 21) [75].

The simple conversion of aryl halides to anilines can be achieved through the formation of benzophenone imine adducts in the reaction of benzophe-



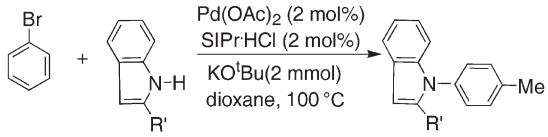
Scheme 21 Cross-coupling of aryl halides and amines mediated by in situ generated Pd/NHC system

none imine and aryl halides followed by hydrolysis (Scheme 22). Under the conditions established for catalytic aryl amination, benzophenone imine reacts readily with unactivated and *ortho*-substituted aryl chlorides in high yield at 80 °C. The reactions performed at higher temperatures or using aryl bromides were faster and led to clean formation of the desired product. Using a slightly modified catalytic protocol (SIPr · HCl) and NaO^{t}Bu as base, Hartwig reported the same conversion, albeit at room temperature [76].



Scheme 22 Cross-coupling of aryl halides and ammonia substitutes mediated by in situ generated Pd/NHC system

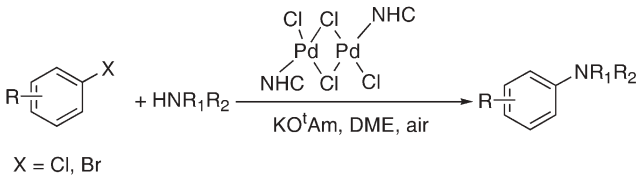
The aryl amination protocol described previously was found to be incompatible with the formation of N-aryl heterocycles such as N-arylindoles. The electron richness of heteroaromatic substrates limits the applicability of N-arylation of indoles to more reactive aryl iodides and bromides. However, good results were obtained in coupling a number of aryl bromides and indole derivatives employing a $Pd(OAc)_2$/SIPr·HCl/NaOH catalytic system. This protocol additionally overcomes a common problem in indole synthesis, namely the formation of C-arylation side products (Scheme 23).



Scheme 23 Coupling of aryl bromides and indoles mediated by in situ generated Pd/NHC system

Easily synthesized, highly active, yet air- and shelf-stable palladium complexes have added to the existing arsenal of cross-coupling catalysts. Well-defined $[(NHC)PdCl_2]_2$ complexes have been used in aryl amination of more economical and more difficult to activate aryl chlorides and amines/anilines in DME as solvent and potassium *tert*-amylate (KO^{t}Am) as base [77]. When

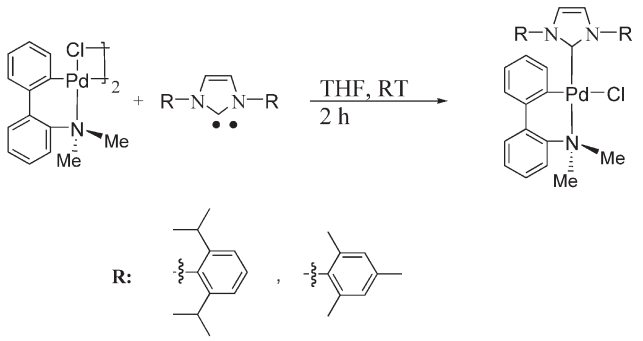
activated aryl bromides and chlorides were used, the products were obtained in just a few minutes (Scheme 24). As evidence of the robust nature of the catalyst, the amination reactions can be performed in reagent-grade solvent (without measures to exclude air or water) in air with little deleterious effect on the yield of the product or reaction time.



Scheme 24 Aryl amination reaction mediated by $[(NHC)PdCl_2]_2$

Other efficient catalysts for the aryl amination reaction include the (NHC)-Pd(allyl)Cl series that bear the same metal/ligand ratio of 1:1 and allow excellent conversions to products at temperatures as low as room temperature [78]. Alkoxide bases lacking β-hydrogens (amylates and *tert*-butoxide) have a dual action in this system as they activate the catalyst through nucleophilic attack on the palladium allyl moiety and act as an efficient base for the catalytic process. The complexes were successfully used in the key step of a *Cryptocarya* alkaloid synthesis [79].

A step forward in the design of catalysts enabling the N-arylation of amines is to eliminate the activation step (reduction of palladium(II) to palladium(0) prior to oxidative addition). One approach is to use well-defined palladium(0) complexes of $(NHC)_2Pd$ or mixed phosphine/NHC,$(R_3P)Pd(NHC)$ type [80]. These complexes are efficient catalysts for this transformation at mild temperatures. A second approach is to sidestep two required activation stages in the catalytic cycle and eliminate the need for the preactivation and the oxidative addition processes by using well-defined catalysts that are "oxidative addition" adducts such as NHC-stabilized palladacycles (Scheme 25) [81].



Scheme 25 Synthesis of NHC-stabilized palladacycle

These complexes show high catalytic activity (0.5 mol% loading) in short reaction times for the aryl amination of aryl chlorides, triflates, and bromides. Primary and secondary amines, both alkyl and aryl, are well tolerated. The mirroring of results can be emphasized if these palladacycles are compared to the (NHC)Pd(allyl)Cl systems, supporting the idea of identical active species [NHC-Pd] during the catalytic cycle. One of the limitations of these catalytic procedures or catalysts is their limited activity for the coupling of electron-rich heterocycles with aryl halides.

Novel approaches such as microwave-assisted heating were successfully applied in the aryl amination mediated by Pd/NHC complexes. The thermal stability of palladium/NHC complexes made them compatible with the high temperatures associated with the microwave protocols [82].

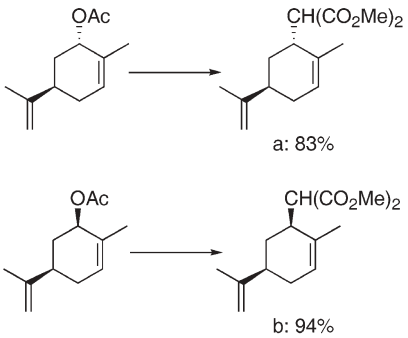
4.5 C–H Bond-Forming Reactions: the Dehalogenation of Aryl Halides

In the absence of coupling partners and operating with adequate bases, the displacement of the halide from aryl halide with hydrogen can take place easily. These aryl dehalogenations can be performed in the presence of electron-rich palladium/NHC complexes, either generated *in situ* or with preformed (NHC)Pd(allyl)Cl complexes [37, 83]. *In situ* catalytic systems were generated from imidazolium salts in the presence of a base. Metal alkoxides having β-hydrogen atoms, particularly methoxides, have proven most efficient bases for this transformation. Presumably the reaction takes place by an alkoxide attack on the arylpalladium intermediate followed by β-hydrogen transfer to the palladium center. The arylpalladium hydride reductive eliminates the dehalogenated product and regenerates Pd(0) species. The use of cyclohexanol/NaOH in conjunction with Pd/NHC for the dehalogenation of aryl halides further supports this reaction pathway. β-Hydrogen transfer from cyclohexanol led to the formation of cyclohexanone. A free coordination site on the metal center appears to be an essential requirement for this transformation. An increase in the ratio of metal to NHC to 1:2 led to a decrease in the reactivity from 96 to less than 10% in the dehalogenation of 4-chlorotoluene. This synthetic protocol was efficiently applied for the dehalogenation of both aryl chlorides and aryl bromides. The system shows high tolerance to functional groups present on the aryl moiety; however, the operating temperature is relatively high (80 °C). An improved reaction protocol uses a series of well-defined, air- and moisture-stable (NHC)Pd(allyl)Cl complexes along with NaO^tBu/2-propanol in an attempt to formulate an easy, scalable, and economical process. Aryl chlorides can be dehalogenated either under mild heating conditions (60 °C) or under microwave heating, where the reaction time is reduced to 2 min and the amount of catalyst is as low as 0.025 mol%.

4.6 Other Catalytic Reactions

4.6.1 Allylic Alkylation

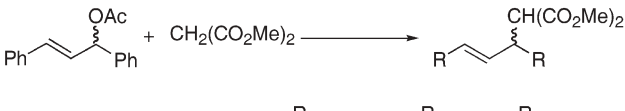
The NHC and phosphines analogy directly transfers to the use of carbene ligands in allylic alkylation. The first report along those lines came relatively recently and has made use of NHC generated *in situ* by deprotonation of the corresponding imidazolium salts with the addition of palladium salts. The standard reaction of an allyl acetate and dimethyl malonate is strongly dependent on the size of the substituents on the nitrogen atoms. Most of the imidazolium salts gave low conversion. However, sterically demanding 2,6-diisopropylphenyl was the only substituent that led to a good yield, 77%, of product after 24 h at 50 °C [84]. Optimized conditions using $Pd_2(dba)_3CHCl_3$, imidazolium salts, and Cs_2CO_3 as deprotonating base improved the yield to 100% and reduced the reaction time to 2 h (NaH as base) or 10 h (Cs_2CO_3 as base), all other parameters being held constant. The stereochemical reaction course indicated that allylic substitution proceeds via an overall retention of configuration (Scheme 26). The asymmetric allylic alkylation reaction can be performed successfully if chiral ligands such as chelating imino carbene are involved [85].

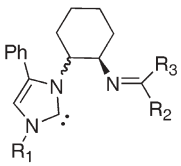


Scheme 26 The observed stereochemistry in allylic substitution reaction

Palladium complexes of the ligands presented in Table 2 are prepared via ligand transfer from silver imidazolium salts. X-ray studies of the palladium complexes revealed a rigid boatlike conformation of the six-membered metallacycle. The enantioselectivity in a standard reaction of (*E*)-1,3-diphenylprop-3-en-1-yl acetate and dimethyl malonate increases with the steric bulk of the imidazolium substituent (R_1) and decreases with the size of the imine (R_2, R_3). This trend can be explained by a reaction route involving an addition of soft nucleophile, such as malonates *trans* to the strongest σ-donor ligand, the carbene in this instance [86].

Table 2 Ligand selection in allylic alkylation reaction

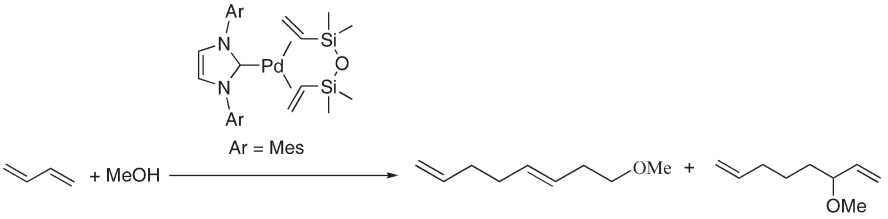




R_1	R_2	R_3
Et	Ph	H
*i*Pr	Ph	H
CH_2Ph	Ph	H
$CMe_2C(O)Ph$	Ph	H
*i*Pr	H	H
$CHPh_2$	H	H
*i*Pr	Mes	H
*i*Pr	*t*Bu	H
*i*Pr	Me	Me
CH_2Ph	Me	Me

4.6.2 Telomerization of Butadiene and Alcohols

Complexes of Pd(0) stabilized by the presence of NHC have been found to be a most efficient catalyst in the telomerization of butadiene and alcohols (Scheme 27) [87]. The design of the catalyst exploited facts already known for this reaction: (1) only one strong donor ligand is needed per palladium center, (2) steric bulk favors the elimination of the product, and (3) the presence of multiple ligands retards the reaction rate by competing with the substrates for the coordination sites of the metal. The resulting catalyst shows unprecedented reaction rates in the reaction of butadiene with methanol. Furthermore, the chemoselectivity is higher than 99% compared with a maximum of 90% when tertiary phosphines were used, and the ratio of linear to branched products is as high as 82:1 compared to 13:1 observed for phosphines as supporting ligands.



Scheme 27 Telomerization of butadiene and methanol mediated by NHC/Pd(0) complexes

An initial TON of 267,000 was achieved but recent studies show an increase in TON up to 1.5 million along with good tolerance to various alcohols and phenols. Both Pd(0) and Pd(II) complexes bearing mesityl-substituted NHC

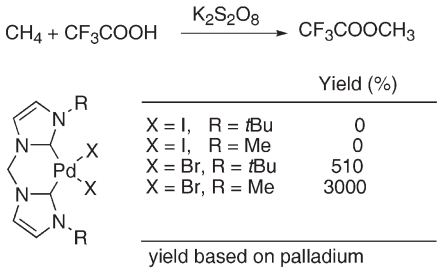
lead to similar reaction rates, supporting the idea of a common intermediate during the catalytic cycle.

4.6.3 Telomerization of Butadiene and Amines

Well-defined complexes (NHC)Pd(allyl)X (X=PF_6, BF_4) as well as the *in situ* generated cationic catalysts have been used successfully in the telomerization of butadiene in the presence of various amines acting as nucleophiles [88]. Obviously, all catalyst characteristics mentioned for telomerization of dienes and methanol are identical for cationic complexes. However, the catalyst possessing a more electrophilic center should display an increased susceptibility to nucleophilic attack. The strong coordination properties of NHC ligands prevent catalyst decomposition during the catalytic cycle. The stability of the catalyst minimizes the formation of by-products in favor of the terminal C8 telomers. Secondary amines, both cyclic and linear, led to octadienylamines in quantitative yields with a catalyst loading of 0.02–0.2 mol% at mild to room temperature. Slower reaction rates were observed when sterically demanding amines were used. Primary amines could react leading to single or double alkylation at the amine center depending on the concentration of the reactants and their steric encumbrance.

4.6.4 Methane Oxidation to Methanol

A very interesting selective oxidation of methane to methyl esters using palladium/NHC was reported recently by the Herrmann group [89]. This transformation requires harsh acidic conditions, limiting the type of supporting ligands. Previously, bidentate amine ligands were used to prevent aggregation of palladium catalysts. Using chelating carbene, the authors were able to perform the reaction in trifluoroacetic acid. The advantage of using carboxylic acids instead of strong inorganic acids is reflected in the ability to distill the product and to recover the acid after hydrolysis. One of the most appealing features of this



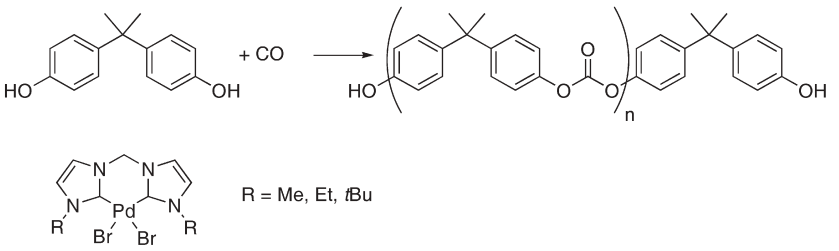
Scheme 28 Methane oxidation to methanol mediated by cationic Pd/NHC complexes

catalytic system is its extraordinary inertness in acidic medium. The carbene shows no sign of decomposition or protonation, as revealed by NMR studies. The reaction was performed in TFA/trifluoroacetic anhydride and $K_2S_2O_8$ as oxidant at temperatures varying from 80 to 100 °C (Scheme 28).

Interestingly enough, the analogous platinum complexes decompose to platinum metal under these acidic conditions. Comparative reactivity studies were performed in the presence of amine ligands but the palladium complexes showed no catalytic activity. The reactivity of palladium(II)/NHC complexes used in this reaction was found to strongly depend on the nature of the counterion. The relatively low basicity of iodide inhibits the protonation of the anion and subsequent generation of active sites on the metal center. Despite the fact that the maximum yield of 3,000% (reported relative to the amount of palladium) is still below industrial standards for usefulness, variations in the nature of the carbene ligands and reaction conditions may increase substantially the efficiency of this important transformation. This work may open new directions in the field of late transition Lewis acidic metals. The authors speculated that the catalytic activity of palladium/NHC systems could be extended to other systems of lower bond energies such as higher alkanes and arenes.

4.6.5 Polymerization of Phenols or Olefins with Carbon Monoxide Mediated by (NHC)Pd Complexes

N-heterocyclic carbene/palladium complexes were successfully used as catalysts in the copolymerization of bisphenol and carbon monoxide (Scheme 29) [90]. The NHC were chosen as supporting ligands as a result of comparisons with previously described catalytic systems based on dicationic phosphine or sterically encumbered β-diimine. The phosphine and β-diimine systems prevent chain transfer and termination processes. By analogy, it was speculated that mutually *cis*-chelating NHC, stabilized by sterically demanding aryl substituents, would help promote the copolymerization of ethylene and carbon monoxide. Unfortunately, mesityl substituents on nitrogen atoms were the only



Scheme 29 Copolymerization of ethylene and carbon monoxide mediated by cationic NHC/Pd complexes

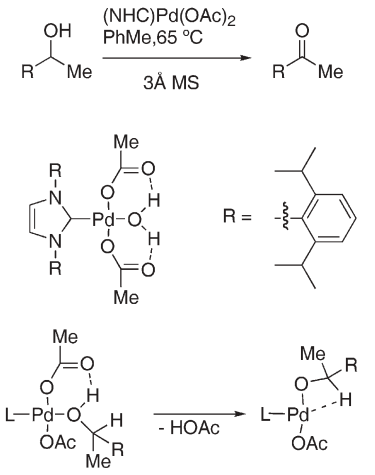
aryl groups employed for synthetic purposes. Complexes of chelating carbenes were used mostly in MeOH, to afford high molecular weight polyketone polymers. NMR studies showed no signals for double insertion of ethylene, suggesting a perfect alternation of CO and C_2H_4 building blocks. The observed TONs were less than 1,000; however, the authors speculated that a very small percentage of palladium had been activated. This assumption was supported by the very high molecular weight of the products, the lack of oligomers, and incorporation of palladium into the mass of the polymer. The complexes, both cationic and dicationic, have very limited solubility in common solvents with the exception of DMSO and MeCN. Further optimization studies should target complexes of higher solubility in medium-polarity solvents. Strong coordinating solvents inhibit the reaction, competing with the substrates for the coordination sites at the metal center. Modified protocols allowed the polymerization of CO and norbornylene [91].

4.6.6 Aerobic Oxidation of Alcohols

The ability of NHC to strongly bind to palladium centers was exploited in the aerobic oxidation of alcohols. A logical approach toward this reaction considered a number of important factors helping ligand selection and design. An excess of the ligand was usually required to prevent decomposition, and the presence of free coordination sites around the metal was required in order to accommodate the alcohol and the required base. Sigman and coworkers made use of NHC-stabilized palladium acetate as catalyst [92]. The presence of carbene ligand eliminates the requirement for excess ligand and the acetate anion acts as a built-in, masked base for the intramolecular deprotonation of the alcohol. The amount of catalyst could be as low as 0.5 mol% if a small amount of acetic acid was added to the reaction mixture. The system allowed TONs up to 1,000 and proved to accommodate a large variety of alcohols and tolerate the presence of double bonds. The products, aldehydes and ketones, were cleanly generated in quantitative yields. In some instances, the auto-oxidation of the aldehyde products under acidic conditions was observed. This inconvenient side reaction is eliminated if Bu_4NOAc is used instead of acetic acid. A spectacular feature of this system is its ability to be carried out under aerobic conditions (Scheme 30).

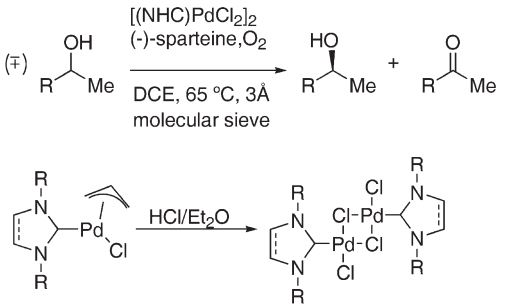
It is known that the CO_2 present in air degrades palladium catalysts in oxidative processes leading to inactive carbonate salts, and that water can hydrolyze the peroxo-palladium complex in the proposed catalytic cycle. These competitive processes seem not to affect the robustness of this catalyst system.

Preceeding this work, palladium/NHC complexes had been used in the aerobic oxidative kinetic resolution of secondary alcohols [93]. The reaction was explored as a measure of "match–mismatch" interaction between a supporting NHC ligand and an exogenous chiral base. The NHC ligands met two essential criteria: compatibility under oxidation conditions and stability toward dis-



Scheme 30 Aerobic oxidation of alcohols mediated by NHC/Pd complexes

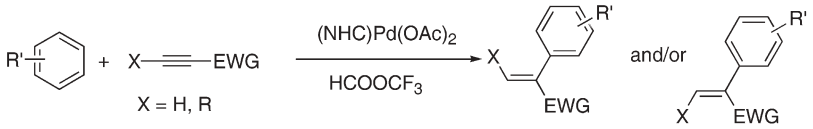
placement in the presence of the exogenous base. The enantiomeric excesses observed were up to 96% when nonchiral NHC were used but dropped to around 40% ee for chiral carbenes. When the exogenous (–)-sparteine was replaced with a nonchiral AgOAc, an enantiomeric excess of only 10% was obtained (Scheme 31).



Scheme 31 Aerobic oxidation of alcohols mediated by NHC/Pd complexes and (–)-sparteine

4.6.7 Hydroarylation of Alkynes

The stability to oxidative degradation of palladium/NHC complexes has made possible the synthesis of complexes previously unknown or much less explored. (NHC)Pd(κ-OAc)(OAc) shows a unique coordination of the acetate units that stabilizes a distorted square planar geometry around the metal center. These complexes are stable in acidic media and can activate C–H bonds of simple arenes by an electrophilic metalation mechanism (Scheme 32).



Scheme 32 Hydroarylation of alkynes mediated by $(NHC)Pd(OAc)_2$

The hydroarylation of alkynes can be performed in a catalytic manner at room temperature when a combination of $HOOCCF_3$ and CH_2Cl_2 is used as reaction medium [94]. The nature of the NHC ligand has little influence on the rate of the reaction. Arenes bearing alkyl, alkoxy, or halide substituents are competent substrates as well as various internal and terminal alkynes.

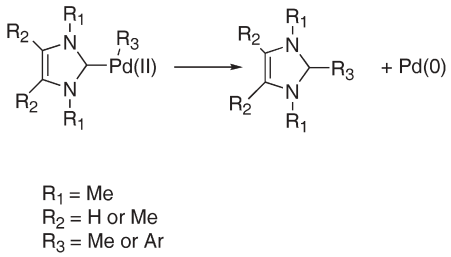
5
Catalytically Relevant Studies

5.1
Decomposition of Palladium/NHC Complexes

Palladium complexes bearing NHC ligands are generally very robust systems with impressive thermal and atmospheric stability. From this point of view, they seem to be ideal candidates for catalytic processes. However, the palladium–carbenic carbon bond can be visualized as a single bond and the usual chemistry of Pd–aryl or Pd–alkyl, such as elimination of C–C, C–H, or C–X, has been both observed and investigated from a theoretical perspective.

Cavell and coworkers observed that a number of methyl-Pd(II) complexes bearing NHC of the form $[PdMe(tmiy)L_2]BF_4$ (tmiy=1,3,4,5-tetramethylimidazolin-2-ylidene; L=various ligands, mostly phosphines) are predisposed to a facile decomposition route [95]. In this process the methyl is transferred to the carbene, leading to the formation of 1,2,3,4,5-pentamethylimidazolium tetrafluoroborate and Pd(0) species (Scheme 33).

It was found that cationic complexes have a much higher rate of decomposition compared to that of their neutral counterparts [96]. Moreover, not only



Scheme 33 Decomposition of hydrocarbyl palladium/NHC complexes

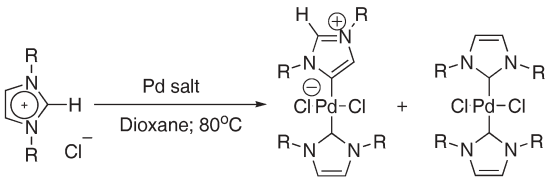
palladium alkyl complexes but also neutral aryl Pd(II) [97] and acyl palladium complexes [98] are prone to decomposition via elimination of aryl/acyl imidazolium salts. Kinetic investigations combined with density functional calculation studies supported a concerted reductive elimination of the organic group and carbene in an analogous manner to the well-known reductive elimination from Pd(II) centers. This type of decomposition is a low-energy path and does not depend on the usually high dissociation energy of the ligand [95].

The authors propose multiple ways to overcome the decomposition problems associated with palladium/NHC complexes. One of the solutions is to carry out reactions, particularly the Heck reaction, at elevated temperatures when β-hydrogen elimination and subsequent formation of the product competes successfully with the decomposition. A second way to stabilize the catalyst is to involve very large nitrogen substituents that will minimize the migration of the hydrocarbyl group. In fact, the beneficial role of bulky ligands can be observed throughout this review. A third approach to prevent catalyst decomposition is to limit the availability of *cis* coordination of the hydrocarbyl group relative to the NHC ligand. Chelating ligands bearing NHC and coordinating groups such as amines, ethers, or phosphines may lead to an increased stability. A fourth path toward high catalytic activity of NHC/Pd complexes is to force the reaction in the reverse direction working with excess ligand, for instance in ionic liquids. All of these approaches, together or separately, could substantially increase catalyst lifetime.

5.2 "Unusual" Coordination Mode of NHC Ligands

An "unusual" coordination mode of NHC is through the C5 carbon position. This coordination was first reported by Crabtree and coworkers in the reaction of $IrH_5(PPh_3)_2$ and imidazolium salts [99]. This observation was somehow intriguing since normal coordination is favored by ~20 kcal/mol compared to C5 binding and a full elucidation of the observed phenomenon is still waiting additional data. Recently an "abnormal" complex was reported in a palladium case. The reaction of $Pd(OAc)_2$ and imidazolium salts led to a mixture of products, through bis-C2 and C2,C5 coordination of the carbene ligands (Scheme 34) [100]. Compared to the previously reported Ir system in which an increase in steric factor of NHC favors atypical coordination, in the palladium case the opposite seems to prevail. ^{1}H NMR of the complex having R=Mes as substituents shows diagnostic peaks for C5 coordination: two doublets at 6.57 and 7.47 ppm. Furthermore, in ^{13}C NMR, the C5 coordinated to palladium is at 150.7 ppm compared to 175.9 ppm for the C2 of the second carbene coordinated in the normal mode. Single crystal X-ray analysis of the complex mentioned above shows almost equal distances in both situations (2.019 Å for C2-Pd and 2.021 Å for C5-Pd) consistent with a single Pd–C bond.

The reaction of Pd salts with imidazolium salts and Cs_2CO_3 as base gave solely the normal binding mode for R=Mes but insignificant conversion to



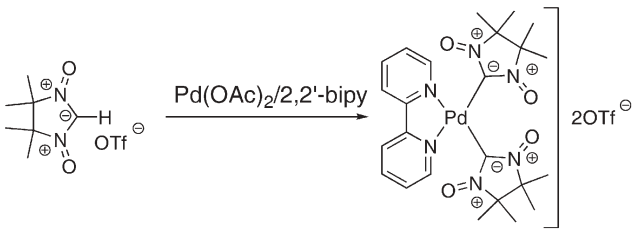
R = 2,4,6-trimethylphenyl (Mes)		
$Pd(OAc)_2$	< 1%	74%
$PdCl_2$; Cs_2CO_3	68%	< 1%
R = 2,6- diisopropylphenyl (Pr)		
$Pd(OAc)_2$	20%	43%
$PdCl_2$; Cs_2CO_3	< 1%	7%

Scheme 34 "Abnormal" coordination of NHC unit to a palladium center

products in R=i-Pr. This is the reactivity trend of $Pd(OAc)_2$ in neutral medium. This observation raises the question of a possible electrophilic metalation involved in this reaction. This unusual binding mode at the C5 position may actually be more common than initially thought, and any system where two NHC are used as ancillary ligands (especially when the catalyst is generated *in situ*) should be carefully examined for such possible bonding modes.

5.3
Unusual Carbenes: Dinitroxide Carbenes

Recently, Weiss and Kraut reported an unusual NHC in which the two substituents at the nitrogen atoms are oxygen [101]. The carbene center can be viewed as the terminus of two, mutually independent two-step π-redox systems. This electronic configuration is expected to interact with high flexibility with a metal center coordinated to the carbenic center that is predicted to act as either π-donor (Schrock-type carbene) or π-acceptor (Fischer-type carbene). The multiplicity at the carbonic center depends on the nature of the metallic fragment. The carbene could not be isolated but the authors were able to trap it in the presence of palladium salts (Scheme 35).



Scheme 35 Dinitroxide carbene palladium complex

The synthetic protocol involves the deprotonation of a nitronylnitrosonium triflate in the presence of $Pd(OAc)_2$. The structure analysis supports a singlet ground state at the coordinated carbene center. The overall electronics of this class of NHC ligands seems to contradict the general concept that Arduengo-type carbenes are σ-donors and have a minimum π-backbonding. Hopefully this example will highlight the potential versatility of NHC and will expand the range of catalytic processes mediated by such ligands.

6 Conclusions

N-heterocyclic carbenes have emerged as a new and versatile class of ligands for a large variety of metal-mediated organic transformations. Some of the advantages of these ligands are: (1) limited or insignificant toxicity, (2) powerful electron-donating properties, (3) nondissociative behavior under normal reaction conditions, and (4) impressive air, thermal, and moisture stability of many metal–NHC complexes. As mentioned, one of the most appealing characteristics of metal–NHC complexes is the nondissociative behavior of the ligand that makes its use in excess unnecessary in most catalytic processes. A better control of the number of catalytically active and available sites is easily achieved and maintained along the catalytic cycle when compared to tertiary phosphine complexes. A good understanding of the active catalytic species is particularly important for NHC involved in metal-mediated organic transformations, as excess or improper ratio of metal:ligand can have a profound negative effect on reaction rates.

In spite of this "rosy picture", no system is perfect and relatively recent studies have shown that catalysts of this type could undergo decomposition and therefore limit success of some catalytic processes. Numerous catalytic reactions can be effectively mediated by Pd/NHC complexes which, because of their simplicity of assembly and use, makes this ligand family a promising platform for further development of new catalysts. In addition to their interesting catalytic activity, their stability under normal storage conditions and activity in simple synthetic protocols could promote them as viable industrial catalysts; in one instance (telomerization of butadiene with methanol), it already has.

The chemistry of NHC and of complexes bearing NHC continues to fascinate and surprise. The synthesis of "abnormal" coordinated carbenes (C5 coordination) in a process explored for more than 8 years is just one example that encourages chemists to examine closely the exact nature of active species involved in catalytic cycles. There is no doubt that recent and future developments in this field of chemistry will separate NHC ligands from the "phosphine mimic" label placed on them at the early development stages and will confer on them a distinct role in modern catalytic chemistry [102].

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Active Pd(II) Complexes as Either Lewis Acid Catalysts or Transition Metal Catalysts

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Abstract The new frontier of asymmetric catalyses by Pd(II) complexes is reviewed. Asymmetric catalyses of carbon–carbon bond formation by Pd(II) complexes are divided into transition metal catalysis and Lewis acid catalysis. Transition metal catalyses are observed in anomalous six-membered ring formation, ene-type cyclization leading to five-membered rings, spiro cyclization, alkaloid and quinoline synthesis, Suzuki–Miyaura coupling, C–H bond activation/C–C bond formation, and Claisen rearrangement. Lewis acid catalyses take place in the carbonyl–ene reaction, hetero Diels–Alder reaction, Friedel–Crafts reaction, and aldol reaction. The specific mechanisms and deep insights into the key reaction intermediates or active organopalladium species are discussed on the basis of the new design of neutral and cationic Pd(II) complexes with chiral ligands.

Keywords Asymmetric catalysis · C–C bond formation · Chiral ligand · Lewis acid · Transition metal

Abbreviations

acac	Acetylacetonate
BIPHEP	2,2′-Bis(diphenylphosphino)-1,1′-biphenyl
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
Cy	Cyclohexyl
DABN	2,2′-Diamino-1,1′-binaphthyl
dba	Dibenzylideneacetone
DMSO	Dimethyl sulfoxide
HDA	Hetero Diels–Alder
MAP	2-(Diphenylphosphino)-2′-(*N*,*N*-dimethylamino)-1,1′-binaphthyl
MOP	2-(Diphenylphosphino)-2′-methoxy-1,1′-binaphthyl
SEGPHOS	(4,4′-Bi-1,3-benzodioxole)-5,5′-diylbis-(diphenylphosphine)
Tetraphos	2,4′,6′,2″-Tetrakis(diphenylphosphanyl)-[1,1′;3′,1″]terphenyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
Tol	Tolyl
Ts	Toluenesulfonyl
Xyl	3,5-Xylyl

1 Introduction

1.1 General Properties

In organic synthesis, modern asymmetric catalysis in particular, Pd can be more versatile [1–5] than Ni and Pt from the same group 10. The reason why Pd has become so useful is not easy to answer. However, one of the reasons stems from the favorable oxidation states of 0 and +2 (i.e., Pd(0) and Pd(II)). Pt, which is larger than Pd, can easily make coordinatively saturated octahedral Pt(IV) complexes with low catalytic activity. Ni, which is smaller than Pd, is apt to change its oxidation state to +1. Sometimes the Ni(I) complexes are not only too active as catalysts but also unstable for handling during the reactions. In turn, Pd, possessing an intermediate nature between those of Ni and Pt, has both the adequate stability and the suitable activity for a variety of catalyses.

Pd catalysts have two important dimensions: (1) as a late transition metal catalyst; and (2) as a Lewis acid catalyst. There is no need to describe the former catalysis, which is usually based on the Pd(0)–Pd(II) redox catalytic system. The latter Lewis acid catalysis, despite the "soft" metal, is based on the empty orbital of the coordinatively unsaturated 16-electron Pd(II) species.

In asymmetric catalysis, we can select a variety of commercially available achiral Pd(0) or Pd(II) precatalysts as shown in Fig. 1. Pd(0) precatalysts are always neutral species, while Pd(II) precatalysts are divided into neutral and cationic species.

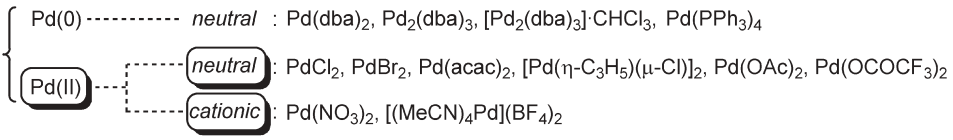
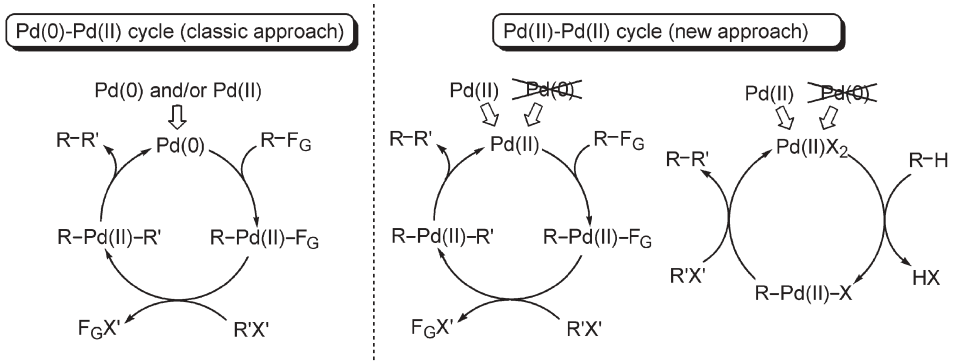


Fig. 1 Representative neutral Pd(0), neutral Pd(II), and cationic Pd(II) precatalysts

1.2 Pd(II)–Pd(II) Catalytic Cycle

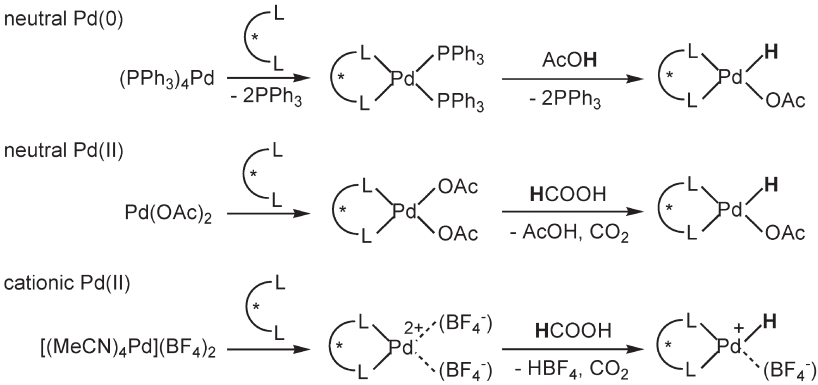
In the Pd(0)–Pd(II) catalytic system, a large part of the catalytic cycle is essentially occupied by the oxidation state of Pd(II) (Scheme 1). Once the cycle is closed, the state of Pd(0) is set in the final stage of regeneration of the initial species. However, much effort has been devoted to the development of the active chiral Pd(0) complex from Pd(0) or Pd(II) precatalysts, with scrupulous care for the deactivation to Pd metal (mirror) or Pd black. On the contrary, another solution to devise a highly active catalyst is to keep the oxidation state of +2 (i.e., Pd(II)) throughout the catalytic cycle without dropping out to Pd(0). This new approach is based on the Pd(II)–Pd(II) cycle in contrast to the



Scheme 1 Pd(0)–Pd(II) cycle and Pd(II)–Pd(II) cycle

Pd(0)–Pd(II) cycle. Lewis acid catalyses also accompany nonredox processes to maintain the favorable oxidation state of +2, particularly cationic Pd(II) rather than neutral Pd(II), to obtain the stronger Lewis acidity.

A good example of Pd(II) complexes as precatalysts is shown in Scheme 2. The H-Pd(II) species has been known as a "chemical chameleon", as a hydride not as a proton [6]. A typical method to generate Pd(II) in situ from Pd(0) precatalyst is the oxidative addition of weak acid such as AcOH. Proton (H^+) in AcOH is directly converted to a hydride (H^-) source of H-Pd(II) via oxidative addition. This method works well in the case of nonasymmetric catalysis without chiral bidentate ligands. In asymmetric catalysis, however, generation of the active catalyst by this oxidative addition method is often ineffective, because the initial achiral ligand such as dibenzylideneacetone (dba) cannot efficiently be exchanged with the corresponding chiral ligand. In contrast, from Pd(II) precatalyst, ligand exchange is so smooth as to generate the active Pd(II) species with chiral bidentate ligands. Through the ligand exchange, not an acidic proton (HCOO<u>H</u>) but a formic hydride (<u>H</u>COOH) is used as a hydride (H^-) source

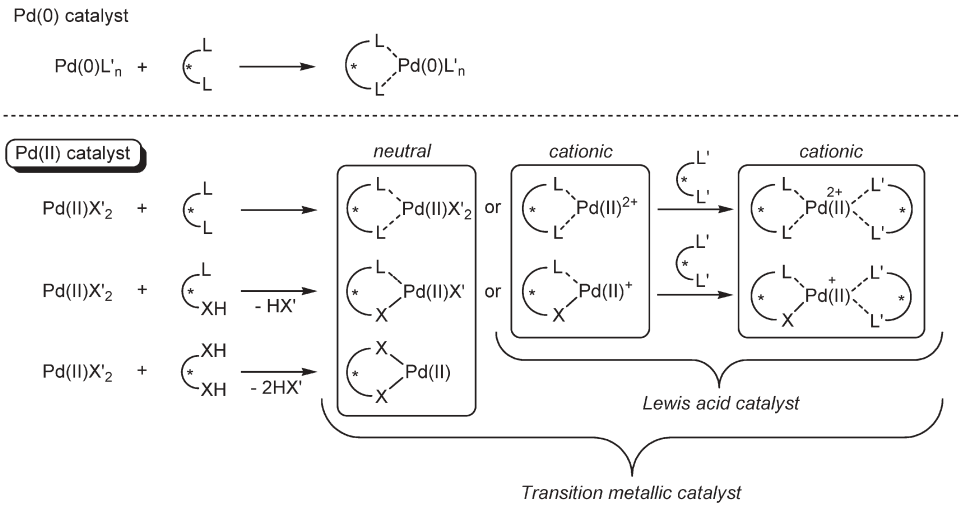


Scheme 2 Preparation of the active Pd(II) catalyst from Pd(0) and Pd(II)

of H-Pd(II). This method is useful to keep the oxidation state of +2 in the asymmetric reactions without any intervention of Pd(0).

1.3 Neutral and Cationic Chiral Pd(II) Catalysts

Chiral bidentate ligands are necessary to design the active Pd(II) catalysts. Three types of bidentate ligands exist: LL, LX, and XX types (Scheme 3). With Pd(0) precatalyst, usually neutral–neutral LL ligands have been used. In contrast, particularly with Pd(II), there is an advantage to designing LX ligands (neutral and anionic) and XX ligands (anionic and anionic) in addition to LL ligands. If the anionic part X′ (such as BF_4^- and SbF_6^-) in the Pd precatalyst is weakly coordinating, the corresponding chiral Pd(II) complexes also bear cationic character. An important advantage of the cationic complexes is that one or two vacant sites of tetracoordinate square planar geometry are available for the approach of substrates or reagents in the course of the reaction. Thus, the catalytic activity would be higher than that of neutral complexes. Coordinatively saturated neutral complexes, in which X′ such as Cl and $OCOCH_3$ fully occupy the four sites of the square planar complex, can form relatively unfavorable but highly enantiocontrolled pentacoodinate intermediates.



Scheme 3 Neutral and cationic chiral Pd(II) catalysts with bidentate ligands and Pd(0) catalysts

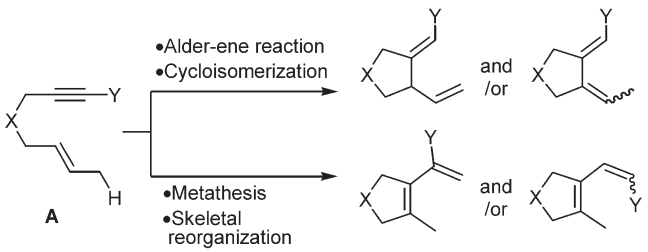
For the design of cationic Lewis acidic Pd(II) catalysts, one more equivalent of LL ligand can be introduced. Thus, the corresponding cationic Pd(II) complexes are able to bear two kinds of chiral ligands. These coordinatively saturated cationic Pd(II) complexes have high Lewis acidity, enough to catalyze asymmetric reactions.

2
Transition Metal Catalysis by Pd Complexes

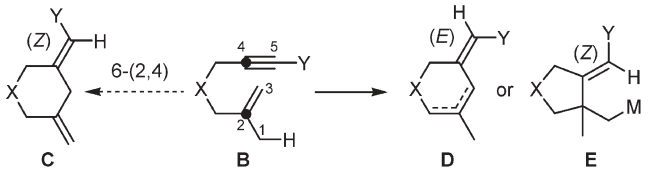
2.1
Anomalous Six-Membered Ring Formation from 1,6-Enynes

2.1.1
6-(2,4) Ene-Type Cyclization and Anomalous Carbocyclization

Transition metal-catalyzed carbocyclizations of 1,6-enynes **A** [7–11] such as cycloisomerization [12–18], metathesis [19–30], skeletal reorganization [31–34], and ene reactions [35] are useful synthetic methods leading to five-membered rings (Scheme 4). Transition metal-catalyzed carbocyclizations of 1,6-enynes basically lead only to five-membered rings. However, ene-type cyclization of 1,6-enyne **B** to provide a five-membered ring is not possible. By contrast, we challenged six-membered ring formation from 1,6-enynes of type **B** by alkyne–metal or carbonyl (Y=C=O)–Lewis acid complexation via 6-(2,4) ene-type cyclization (following [1,5]-hydrogen shift numbering) (Oppolzer's type II) (Scheme 5) [36, 37]. A six-membered ring was obtained, however, not as the expected (*Z*)-olefin **C**. Dicationic palladium-catalyzed carbocyclization of 1,6-enynes, unlike ruthenium-, rhodium- and platinum-catalyzed metatheses, leads to the (*E*)-six-membered rings (**D**), wherein water-derived hydride is involved to fix the (*E*)-olefin geometry. The mechanistic features of this anomalous carbocyclization and isolation of the chiral five-membered ring carbon-Pd (C-Pd) intermediate (**E**) as a trifluoroacetate have been discussed [38].

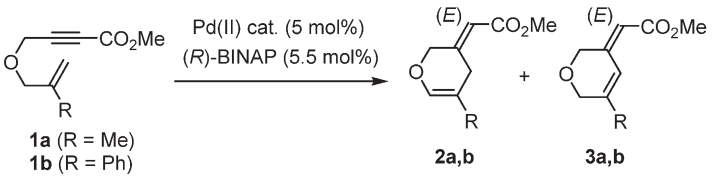


Scheme 4 Typical transition metal-catalyzed carbocyclizations



Scheme 5 6-(2,4) Ene-type cyclization and anomalous carbocyclization of 1,6-enynes

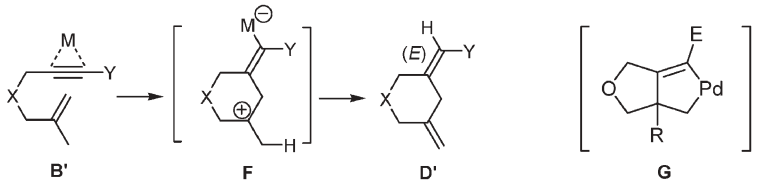
The Pd(II)-catalyzed cyclization of the enyne **1a** took place with 5 mol% of $[(MeCN)_4Pd](BF_4)_2$ or $Pd(OCOCF_3)_2$ and 5.5 mol% of diphosphine ligands such as (*R*)-BINAP in well-deaerated DMSO or benzene, respectively, to afford the six-membered ring cyclization products **2a** and **3a** (type **D**) in good yields (Scheme 6). The dicationic $[(MeCN)_4Pd](BF_4)_2$ complex in DMSO was found to be catalytically more active, affording 19% of (*E*)-**2a** and 61% of (*E*)-**3a** at lower temperature [39–41]. In sharp contrast, ruthenium ($[Ru(CO)_3Cl_3]_2$)- [42] or platinum ($PtCl_2$)-catalyzed carbocyclization led only to the five-membered ring cyclization products [43–50].



Substrate	Pd(II) cat.	Temp. [°C], Time [h]	Yield [%] of 2	3
1a	$Pd(OCOCF_3)_2/C_6D_6$	100, 15	15	53
1a	$[(MeCN)_4Pd](BF_4)_2$/DMSO	80, 24	19	61
1b	$[(MeCN)_4Pd](BF_4)_2$/DMSO	100, 24	26	55

Scheme 6 Cationic Pd(II)-catalyzed six-membered ring formation from1,6-enynes

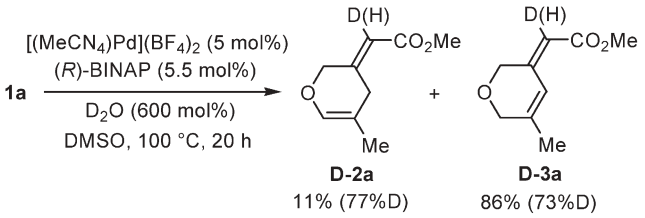
A possible triggering complex, palladacyclopropene (**B′**) (Scheme 7), could be isolated (vide infra), but did not provide the cyclization product (**D′**) under the reaction conditions used (80–100 °C). This result indicates that the alkyne–metal complex (**B′**) does not initiate the present cyclization leading to the six-membered ring product (**D′**) via the ionic intermediate (**F**).



Scheme 7 Ionic intermediates or palladacyclopentene

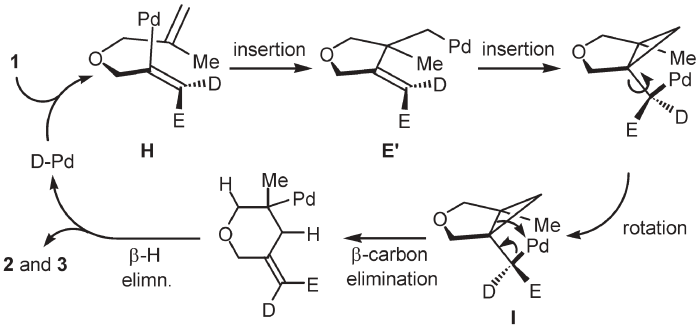
An attempted isolation of another possible intermediate, palladacyclopentene (Scheme 7, **G**), using β-phenyl substrate **1b** without β-methyl (allylic hydrogen) was totally unsuccessful, but resulted simply in the formation of the six-membered ring products **2b** and **3b** in 26 and 55% yields, respectively (Scheme 6)

There is no equilibrium between **2** and **3** under the reaction conditions employed. However, the generation of palladium hydride (H-Pd) from adventitious water and *syn* addition of H-Pd to the alkyne portion is highly likely to initiate the six-membered ring carbocyclization. Thus, cyclizations in the presence of an excess amount (600 mol%) of deuterated water (D_2O) were examined [51, 52]. Indeed, the products **D-2a** and **D-3a**, which were regiospecifically deuterated at the *exo* olefin in the α position to the ester functionality, were obtained with ~75% deuterium content (Scheme 8).



Scheme 8 Effect of water in cationic Pd(II)-catalyzed six-membered ring formation from 1,6-enynes

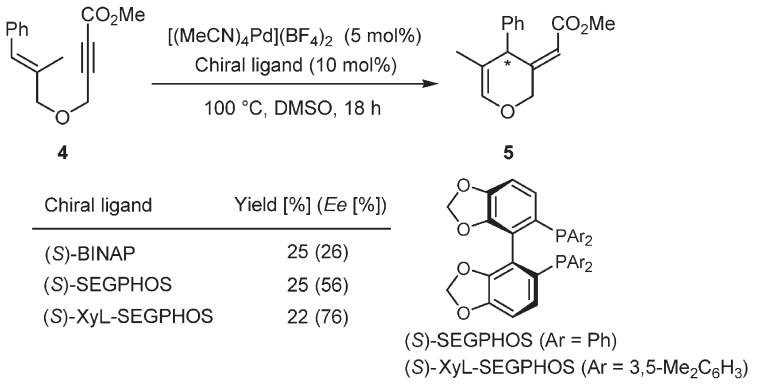
The key intermediate should be a deuterated vinylpalladium species (**H**) generated via *syn* addition of D-Pd species (Scheme 9). This vinylpalladium intermediate **H** is similar in its structure to the Negishi intermediate in the Mizoroki–Heck-type cyclization of 2-iodo-1,6-dienes to six-membered carbocycles, which proceeds with olefinic geometry inversion[53–56]. Thus, the plausible mechanism follows a D-Pd *syn* addition, β-carbon elimination, and β-H elimination mechanism effective in controlling olefin inversion via cyclopropane intermediate (**E′** and then **I**).



Scheme 9 Proposed mechanism of six-membered ring formation

2.1.2
Asymmetric Catalytic Six-Membered Ring Formation from 1,6-Enynes

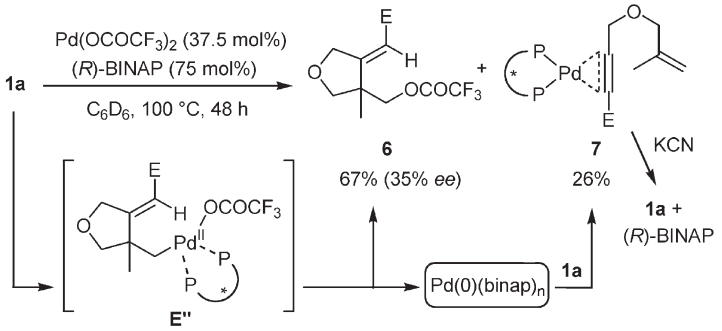
The attention is now turned to the asymmetric synthesis of six-membered rings because substrates **1** led to *achiral* products via β-H elimination although the intermediates could be enantiomerically enriched. Pd(II)/(*S*)-BINAP systems were applied to the substrate **4** with trisubstituted olefin to give the cyclized product **5** with 26% *ee* in 25% yield (Scheme 10). (*S*)-SEGPHOS was more effective than BINAP to afford **5** with 56% *ee*. Moreover, the enantioselectivity dramatically increased up to 76% *ee* by using sterically demanding (*S*)-Xyl-SEGPHOS.



Scheme 10 Asymmetric catalytic six-membered ring formation by cationic Pd(II)

2.1.3
Oxidation Leading to Five-Membered Ring Bearing Trifluoroacetate

The isolation of a proposed chiral five-membered ring carbon-Pd (C-Pd) intermediate (**E″**) is the next challenge (Scheme 11). In order to isolate this cyclized intermediate, one more equivalent of BINAP ligand was added. Oxidation of **E″**



Scheme 11 Novel oxidation of the C-Pd intermediate **E″**

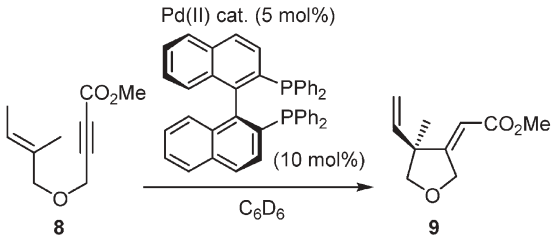
leading to trifluoroacetate **6** in an enantioenriched form (35% *ee*) was attained, presumably via the reductive elimination of BINAP-Pd(0) to give palladacyclopropene **7** (vide supra) from [–C–Pd(OCOCF$_3$)](BINAP) (**E″**). In this reaction, a proper (1:2) ratio of Pd(OCOCF$_3$)$_2$ (37.5 mol%) and (*R*)-BINAP (75 mol%) is critical to give a good isolated yield (67%) of the five-membered ring trifluoroacetate **6**, along with 26% of alkyne-Pd(BINAP) complex **7** [57, 58], thus implying a "catalytic" process of a tandem cyclization–oxidation reaction sequence. Notably, BINAP and the enyne substrate **1a** were released immediately from alkyne-Pd(BINAP) complex **7** upon addition of KCN/MeOH via ligand exchanges with CN^- at room temperature.

2.2 Ene-Type Cyclization with P,P Ligand via Five-Membered Ring Formation

2.2.1 Pd(II) vs Pd(0)

Among the many transition metal complexes, palladium complexes have been known as the classic but still the most effective catalysts for ene-type cyclizations leading to five-membered rings [59, 60]. However, the precedent examples for the enantioselective catalysis thereof are few [61–63], and hence there is a challenge to establish high levels of asymmetric induction as well as chemical yields [64].

The Pd(II)-catalyzed carbocyclization reactions of 1,6-enynes have generally been performed by Pd(OAc)$_2$ or by combined use of Pd(0) species, [Pd$_2$(dba)$_3$]·CHCl$_3$, and a weak acid such as acetic acid or trifluoroacetic acid. However, these typical palladium catalysts were ineffective for the 1,6-enyne system (**8**) in the presence of a chiral bidentate phosphine ligand, such as BINAP, exhibit-



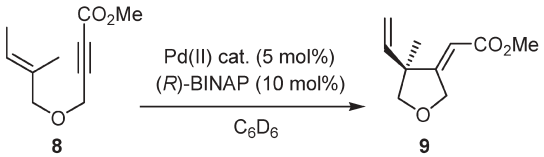
8 **9**

Pd(II) cat. (mol%)	Temp.	Yield (%)	*Ee* (%)
Pd(OAc)$_2$ (5)	100 °C, 72 h	68	11 (*S*)
[Pd$_2$(dba)$_3$]·CHCl$_3$ (2.5) / AcOH (12)	80 °C, 96 h	18	77 (*S*)
[Pd$_2$(dba)$_3$]·CHCl$_3$ (2.5) / CF$_3$CO$_2$H (12)	80 °C, 96 h	25	84 (*S*)

Scheme 12 Pd(II) catalysts from Pd(0) precatalysts for asymmetric ene-type carbocyclization

ing insufficient catalytic activity and low levels of asymmetric induction (Scheme 12).

The Pd(II)-catalyzed asymmetric cyclization of enyne **8** to 1,4-diene (*S*)-**9** was successfully achieved in a quantitative yield and with high enantioselectivity (93% *ee*) by using 5 mol% of $Pd(OCOCF_3)_2$ and 10 mol% of (*R*)-BINAP in thoroughly degassed C_6D_6 at 100 °C (Scheme 13). A remarkable solvent effect was also observed in this catalytic reaction. In a "more polar solvent" such as DMSO, the reaction was completed within a shorter period of time at lower reaction temperature, but the enantiomeric excess decreased to 72% *ee* as compared with that in the "less polar solvent" such as benzene. The dicationic Pd(II) species, $[(MeCN)_4Pd](BF_4)_2$, was found to dramatically accelerate the reaction in DMSO.



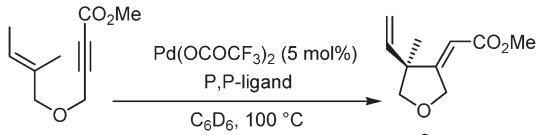
8 **9**

Pd(II) cat.	Solvent	Temp.	Yield (%)	*Ee* (%)
$Pd(OCOCF_3)_2$	C_6D_6	100 °C, 24 h	>99	93 (*S*)
$Pd(OCOCF_3)_2$	DMSO	80 °C, 16 h	>99	72 (*S*)
$[(MeCN)_4Pd](BF_4)_2$	DMSO	80 °C, 6 h	>99	73 (*S*)

Scheme 13 (*R*)-BINAP-Pd(II)-catalyzed ene-type carbocyclization of 1,6-enyne

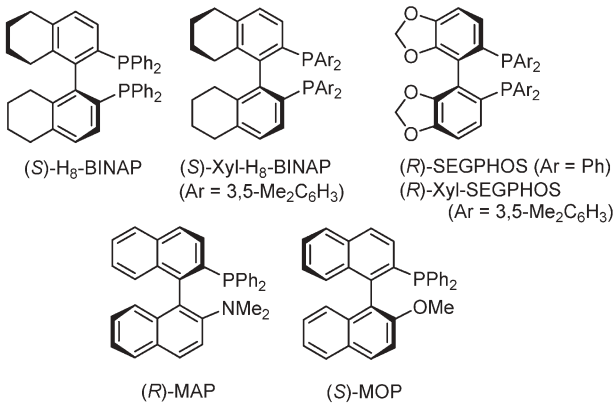
2.2.2 Neutral Pd(II) Species

Exploration of modified BINAP ligands with the $Pd(OCOCF_3)_2/C_6D_6$ system led to a remarkable improvement in the enantioselectivity (Scheme 14). In the less polar solvent ($Pd(OCOCF_3)_2/C_6D_6$ system), eventually the enantiopure product (**9**) was obtained by using (*R*)-SEGPHOS as a bidentate phosphine ligand. (*R*)-Tol-BINAP and (*S*)-H_8-BINAP ligands were also effective [65]. The sterically more demanding (*S*)-Xyl-H_8-BINAP exhibited significant lowering in enantioselectivity, presumably because its bulkiness forced it to dissociate from a Pd(II) complex during the catalysis to generate an achiral Pd(II) species. Finally, the virtually complete enantioselectivity was achieved with (*R*)-SEGPHOS to give the cyclized product **9** in quantitative yield and in an enantiopure form (>99% *ee*). Notably, chiral monophosphine ligands such as MAP [66, 67] and MOP [68] resulted in the formation of nearly racemic products. Thus, diphosphine chelation to Pd(II) was found to be necessary to achieve a high enantioselectivity.



8 9

P,P-ligand (mol%)	Reaction time [h]	Yield (%)	*Ee* (%)
(*R*)-Tol-BINAP (10)	43	>99	94 (*S*)
(*S*)-H_8-BINAP (10)	48	>99	95 (*R*)
(*S*)-Xyl-H_8-BINAP (10)	20	>99	12 (*R*)
(*R*)-SEGPHOS (10)	37	>99	>99 (*S*)
(*R*)-MAP (30)	6	>99	3 (*S*)
(*S*)-MOP (30)	9	>99	5 (*S*)



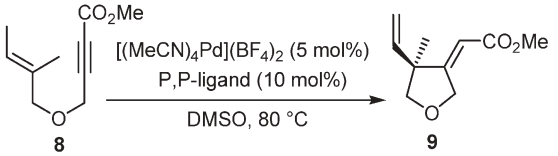
(*S*)-H_8-BINAP (*S*)-Xyl-H_8-BINAP (Ar = 3,5-$Me_2C_6H_3$) (*R*)-SEGPHOS (Ar = Ph) (*R*)-Xyl-SEGPHOS (Ar = 3,5-$Me_2C_6H_3$)

(*R*)-MAP (*S*)-MOP

Scheme 14 Ene-type carbocyclization catalyzed by $Pd(OCOCF_3)_2/C_6D_6$ with modified BINAP ligands

2.2.3 Cationic Pd(II) Species

(*R*)-SEGPHOS ligand is also effective in the polar solvent. Thus, the $[(MeCN)_4Pd](BF_4)_2$/DMSO system exhibited a higher enantioselectivity than that with the parent BINAP (Scheme 15). It is noteworthy that further improvement in the enantioselectivity was achieved by using sterically demanding (*S*)-Xyl-H_8-BINAP, in sharp contrast to the low enantioselectivity observed in the less polar solvent using the $Pd(OCOCF_3)_2/C_6D_6$ system (Scheme 14). By the combination of a SEGPHOS skeleton and a bulky xylyl substituent, (*S*)-Xyl-SEGPHOS ligand eventually established highly enantioselective catalysis (96% *ee*) in the $[(MeCN)_4Pd](BF_4)_2$/DMSO system.



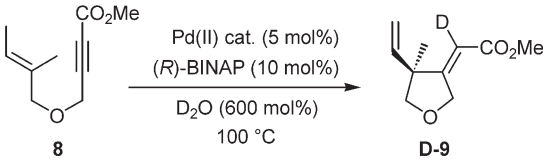
8 9

P,P-ligand	Reaction time [h]	Yield (%)	*Ee* (%)
(*R*)-SEGPHOS	6	>99	90 (*S*)
(*S*)-Xyl-H_8-BINAP	12	>99	94 (*R*)
(*S*)-Xyl-SEGPHOS	14	>99	96 (*R*)

Scheme 15 Ene-type carbocyclization catalyzed by $[(MeCN)_4Pd](BF_4)_2$/DMSO with modified BINAP ligands

2.2.4 Mechanistic Aspects with H-Pd(II) Species

The key to clarifying the catalytic cycle is to determine whether or not hydride-palladium (H-Pd) is the active species. Taking advantage of hydride exchange between D_2O and H-Pd to generate D-Pd species [69, 70], the reactions under excess D_2O (600 mol%) conditions were examined (Scheme 16). Consequently, the deuterated product at the vinylic position was obtained without diminution of catalytic activity under either polar or less polar conditions. These results indicate that the hydride(deuteride)-palladium is the active species. The possible catalytic cycle would be completed as shown in Scheme 17: the initially formed D-Pd coordinates to acetylene (**B′**), followed by D-Pd addition (**H**), insertion (cyclization) (**E**), and β-H elimination to give the product (**9**) and regenerate the H-Pd species.



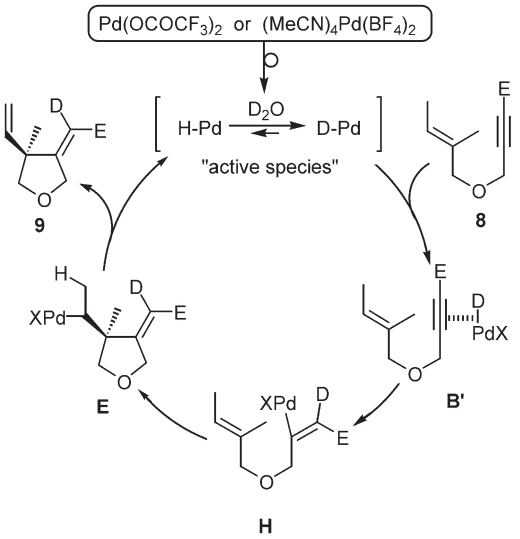
8 D-9

Pd(II) cat.	Reaction time [h]	Yield (%)	D-content (%)	*Ee* (%)
$Pd(OCOCF_3)_2/C_6D_6$	30	>99	56	93
$Pd(OCOCF_3)_2$/DMSO	24	>99	74	68
$[(MeCN)_4Pd](BF_4)_2$/DMSO	24	>99	77	65

Scheme 16 Ene-type carbocyclization in the presence of D_2O

2.2.5 Tetracoordination and Pentacoordination

It should be pointed out that the Pd(II)-catalyzed carbocyclization reveals (1) the dependence of enantioselectivity as well as catalytic activity on the solvent polarity, and (2) the independence of the enantioselectivity of the Pd(II) sources, $Pd(OCOCF_3)_2$ or $[(MeCN)_4Pd](BF_4)_2$, under the polar conditions (Scheme 17). These observations are fully rationalized on the basis of tetracoordination (**TC**) and pentacoordination (**PC**) modes [71, 72] in the intermediates (**H**) (Fig. 2).



Scheme 17 Catalytic cycle involving H(D)-Pd as the active species

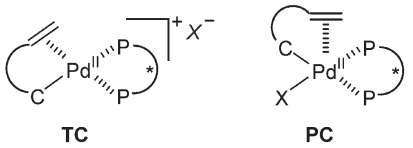


Fig. 2 Tetra- (**TC**) and pentacoordinate (**PC**) intermediates

In the polar solvent, the $[(MeCN)_4Pd](BF_4)_2$/DMSO system facilitates the generation of a cationic tetracoordinate intermediate (**TC**) due to the solvent polarity and weakly coordinating nature of BF_4^-. The same levels of enantioselectivity obtained under the polar conditions regardless of the Pd(II) sources imply that the reaction proceeded via the identical intermediate **TC** in the $Pd(OCOCF_3)_2$/DMSO system. In the polar solvent, $Pd(OCOCF_3)_2$ associatively

releases the counter anion, even CF_3COO^-, to offer one coordination site on the square planar cationic complex. The olefin moiety is able to occupy this site to give the identical tetracoordinate intermediate **TC** to that obtained in the $[(MeCN)_4Pd](BF_4)_2$/DMSO system (Fig. 2). The higher catalytic activity observed in the $[(MeCN)_4Pd](BF_4)_2$/DMSO system than in the $Pd(OCOCF_3)_2$/DMSO system (Scheme 13) is consistent with the stabilization of the cationic intermediates by the counter anion, BF_4^- vs CF_3COO^-.

In contrast, in the less polar solvent ($Pd(OCOCF_3)_2/C_6D_6$ system), the counter anion remains coordinated on the Pd(II) species. The olefin moiety is forced to coordinate to the fully occupied square planar Pd(II), generating a relatively unfavorable pentacoordinate intermediate (**PC**) as a neutral complex (Fig. 2)[73, 74]. The higher catalytic activity under the polar conditions than that under the less polar conditions is well rationalized, in that the reaction proceeded via the preferred tetracoordinate intermediate **TC**. The high enantioselectivity by using sterically demanding Xyl-BINAP analogues under the polar conditions (Scheme 15) is in sharp contrast to the low enantioselectivity under the less polar conditions (Scheme 13). The dependence of the enantioselectivity on the solvent polarity reveals strong evidence that the reaction took place via different coordination modes. Under the less polar conditions the bulky Xyl-H_8-BINAP ligand is forced to dissociate from sterically congested *five*-coordinate intermediate **PC** to generate an achiral Pd(II) species.

2.2.6 Transition States for Carbocyclizations

The high enantioselectivities are rationalized on the basis of these intermediates (Fig. 3). Under the polar conditions, the reaction took place via tetracoordinate transition states (**TC-1** and **TC-2**) to afford the cyclized products (*S*)-**9** and (*R*)-**9**, respectively. The transition state **TC-2** is relatively less favorable because of a steric repulsion between the terminal Me group of the substrate **1** and the equatorial Ph group of (*R*)-BINAP. On the other hand, the transition state **TC-1** avoids this repulsion, eventually affording (*S*)-**9** via β-H elimination. Under less polar conditions, the olefin is forced to coordinate to Pd(II) on one site of the *z*-axis to reach the five-coordinate transition states (**PC-1** and **PC-2**). The repulsive interaction between the terminal Me group of the substrate **8** and the equatorial Ph group of (*R*)-BINAP is significant in the transition state **PC-2**, giving (*R*)-**9**. The reaction entirely takes place via the transition state **PC-1** to afford (*S*)-**9**.

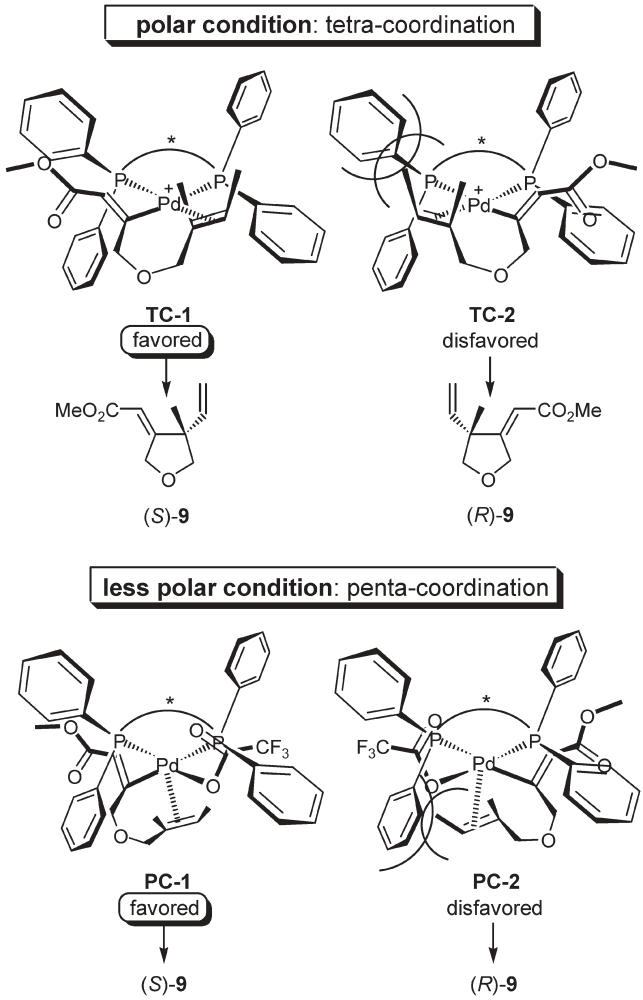
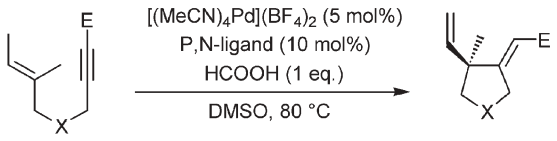


Fig. 3 Transition states for enantioselective carbocyclization catalyzed by chiral Pd(II) complexes under polar or less polar conditions

2.3 Ene-Type Cyclization with P,N Ligand via Five-Membered Ring Formation

2.3.1 Introduction of P,N Ligand

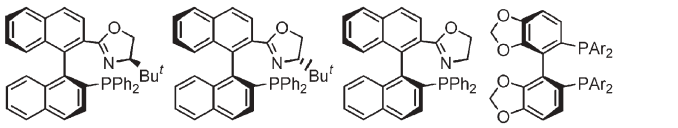
Because of the limitation of P,P ligands such as BINAPs and SEGPHOSs with enyne substrates (vide supra), bidentate C_1-symmetric P,N ligands for a variety of substrates were investigated under polar conditions ([$(MeCN)_4Pd$]$(BF_4)_2$/HCOOH/DMSO). P,N ligands **16a** and **16b** having a chiral *tert*-butyl oxazoline



10 (X = O, E = CO_2Me)
12 (X = NTs, E = CO_2Me)
14 (X = $C(CO_2Et)_2$, E = $CONMe_2$)

11
13
15

Substrate	P,N-ligand	Reaction time (h)	Yield (%)	*Ee*(%) (Config)
10	**16a**	12	>99	78 (*S*)-(+)
10	**16b**	24	92	87 (*S*)-(+)
10	**17**	18	89	41 (*S*)-(+)
12	**16a**	3	>99	93 (*S*)-(+)
12	**16b**	3	>99	92 (*S*)-(+)
12	**17**	3	>99	35 (*S*)-(+)
14	**16a**	24	42	81 (*S*)-(+)
14	**16b**	9	>99	86 (*S*)-(+)
14	**17**	24	9	50 (*S*)-(+)
12	**18**	3	>99	61 (*R*)-(-)
14	**18**	3	>99	6 (*R*)-(-)



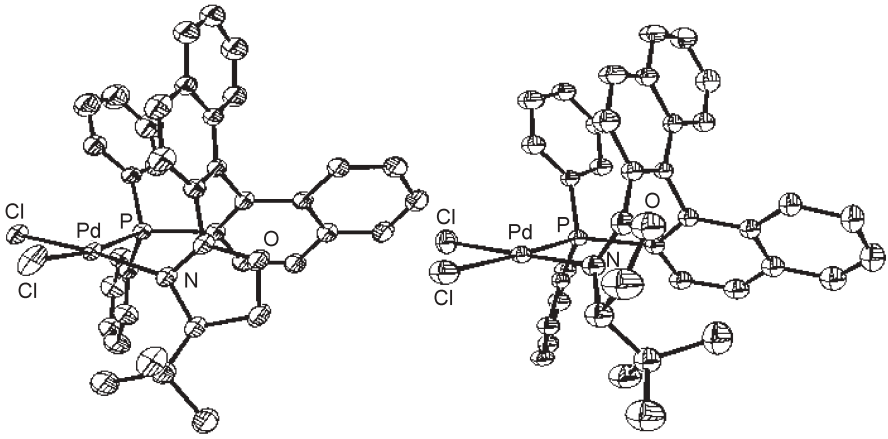
(a*S*, *R*)-**16a** (a*S*, *S*)-**16b** **17** **18** (Ar = 3,5-Me_2-C_6H_3)

Scheme 18 Enantioselective carbocyclization catalyzed by Pd(II) complexes with (a*S*)-P,P and P,N ligand

unit with binaphthyl backbone were examined (Scheme 18) [75–90]. P,N ligands **16a** and **16b** gave higher enantioselectivity (81–93% *ee*) than those obtained with C_2-symmetric P,P ligand Xyl-SEGPHOS (**18**) (6–61% *ee*: vide supra). Interestingly enough, the same (*S*)-(+) products were obtained by these two epimeric (a*S*)-P,N ligands **16a** and **16b** from all substrates (**10**, **12**, and **14**). By contrast, P,N ligand **17** having no alkyl substituent in the oxazoline unit showed poor enantiomeric excesses (35–50% *ee*). These results imply that the center of chirality (*R* or *S*) at the 4 position of the oxazolines is *not* important and that the presence of a sterically demanding substituent is necessary.

2.3.2 X-Ray Analysis of Pd(II) Complexes with P,N Ligands with Chiral Oxazoline

X-ray analyses of dichloropalladium(II) complexes (**19a, 19b**) with P,N ligands of **16a** and **16b** were examined (Fig. 4). According to the X-ray analyses of these diastereomeric Pd(II) complexes **19a** and **19b**, a general drawing of the Pd(II)



[(a*S*,*R*)-**16a**]$PdCl_2$ complex **19a** [(a*S*,*S*)-**16b**]$PdCl_2$ complex **19b**

Fig. 4 ORTEP drawings of chiral dichloropalladium(II) complexes with P,N ligands

complex is shown in Fig. 5, divided into four quadrants (from I to IV). In sharp contrast to Pd(II) complexes with P,P ligands such as BINAP [91], there is essentially no steric difference in axial and equatorial phenyl groups located in the quadrants II and III, respectively, due to the following factors: (1) little difference of the torsional angle of N–Pd–P–Ph; and (2) similar direction of phenyl ring such as face and edge rotating on the C–P bond (Fig. 4). Furthermore, the substituents R or R′ are located in quadrant IV. This is caused by a *strong twist* of the oxazoline from the Pd square planar geometry: the torsional angles of P–Pd–N–C(–O) are 72 and 79° for **19a** and **19b**, respectively.

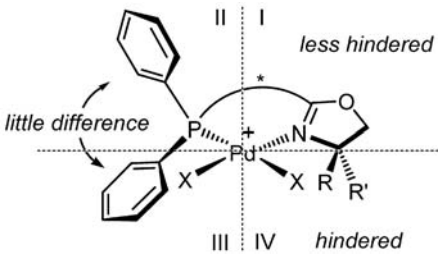


Fig. 5 Drawing of Pd(II) complexes with (a*S*)-P,N ligands

2.3.3 Transition States for the N/C *Trans* Mode

On the basis of the X-ray analyses, a more effective P,N ligand **20** having two geminal methyl groups was developed (Fig. 6). The advantage of the C_1-sym-

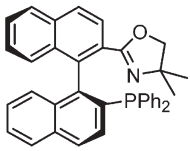


Fig. 6 *gem*-Dimethyl P,N ligand **20**

metric Pd(II) complex with the (a*S*)-P,N ligand **20** could be predicted in view of steric and electronic features (Fig. 7). Two possible (*N*/*C trans* and *cis*) modes in the tetracoordinate transition states (**TS1** and **TS2**) would afford the (*S*)-(+) products. In the *N*/*C trans* mode **TS1**, high enantioselectivities would be achieved using the P,N ligand **20** because of significant steric repulsion between the terminal Me groups of the substrate (**10**, **12**, and **14**) and the dimethyl substituents of the oxazoline unit in quadrant IV [92–94]. In contrast, lower enantioselectivity should be observed in the *N*/*C cis* mode **TS2**, since the terminal alkenyl Me group could not fully differentiate between the two Ph groups in the quadrants II and III. The (*S*)-(+) enantiomers would be obtained highly enantioselectively via Mizoroki–Heck-type C–C bond formation and β-H elimination via **TS1**, by effective differentiation with the dimethyloxazoline (quadrant I vs IV) [95–98].

The preference for the *N*/*C trans* mode is clearly illustrated by the ONIOM calculations [99–102]. The steric factor of P,N ligand **20** dominates the enantioselectivity, while the electronic factor causes the *N*/*C trans* mode. The details in the 3D geometries of **CP1** and **CP2** (X=O, aldehyde group was used instead of ester group as the models of **TS1** and **TS2**) are optimized using the ONIOM (B3LYP/631SDD: HF/321LAN) method (Fig. 7). The *N*/*C trans* mode of **CP1** is 6.3 kcal/mol lower in energy than the *N*/*C cis* mode of **CP2.** This indicates that the C–C bond formation proceeds via the transition state of the *N*/*C trans* mode **TS1**. The relative energy difference between **CP1** and **CP2** is due to the *trans* influence of the electronically asymmetric P,N ligand, which affects Pd-C1 and Pd-C2 (and Pd-C3) lengths. Since the P-coordinating unit acts as an electron acceptor and the N-coordinating unit as a donor [92], the π-coordination of the olefinic carbons C2–C3 *trans* to phosphine in **CP1** is electronically favored. The Pd–C1 bond in **CP1** (2.02 Å) is stronger than that in **CP2** (2.08 Å) by the *trans* influence of the N-coordinating unit. In contrast, the π-coordination of C2–C3 *trans* to the N-coordinating unit as a donor in **CP2** is electronically mismatched, and hence the coordination structure around the Pd center in **CP2** is distorted in comparison with the square planar structure in **CP1.** The electronic influence can be combined with the steric differentiation in the oxazoline to form **TS1** in the *N*/*C trans* mode, which can achieve the high enantioselectivity.

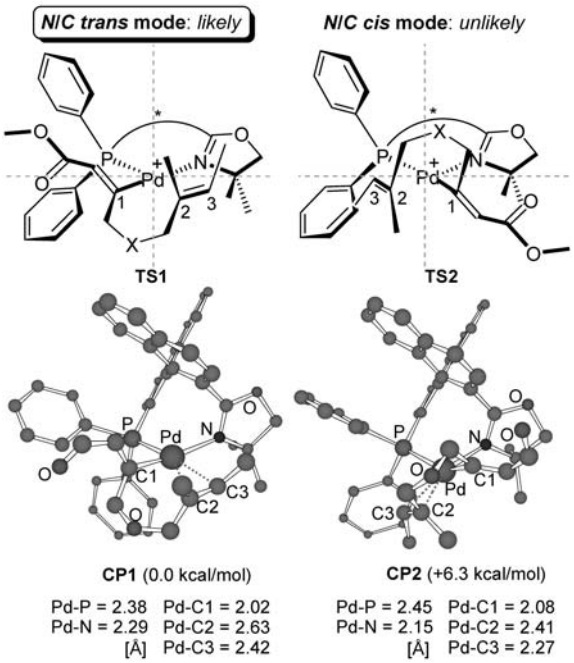
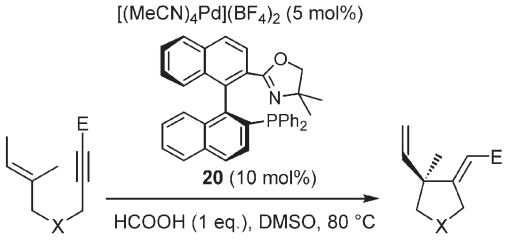


Fig. 7 Transition states for C–C bond formation by (a*S*)-P,N ligand **20**

2.3.4 P,N Ligand with Achiral *gem*-Dimethyloxazoline

The *gem*-dimethyl P,N ligand **20** (see Sect. 2.4.2) thus prepared gave the carbocyclization products (**11**, **13**, and **15**) in high enantiomeric excesses and almost quantitative yields (up to 95% *ee*, 99% yield) (Scheme 19). The key to the



Substrate	Reaction time (h)	Yield (%)	*Ee* (%) (Config.)
10 (X = O)	24	87	88 (*S*)-(+)
12 (X = NTs)	3	>99	93 (*S*)-(+)
14 (X = $C(CO_2Et)_2$)	3	>99	95 (*S*)-(+)

Scheme 19 Asymmetric carbocyclization catalyzed by Pd(II) complexes with *gem*-dimethyl P,N ligand **20**

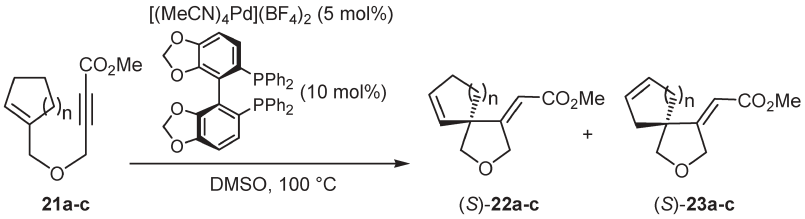
success in increasing the enantioselectivity in carbocyclization of the amide **14** in particular from 6% *ee* by Xyl-SEGPHOS **18** (vide supra) to 95% *ee* by **20** is the employment of the sterically demanding achiral *gem*-dimethyloxazoline.

2.4 Ene-Type Spiro Cyclization via Five-Membered Ring Formation

2.4.1 P,P Ligand vs P,N Ligand

The enantioselective spiro ring construction is an important issue because many natural compounds have chiral spiro centers [103, 104]. Pd catalyses of spiro cyclizations have been reported by asymmetric intramolecular Mizoroki–Heck reactions [105, 106]. In spite of a similar potential, transition metal-catalyzed ene-type carbocyclization has never been applied to asymmetric spiro cyclizations [107–110].

First, in spiro cyclizations for a variety of cyclic allyl progargyl ethers **21** under polar conditions ($[(MeCN)_4Pd](BF_4)_2$/DMSO), bidentate C_2-symmetric P,P ligand such as (*R*)-SEGPHOS was employed (Scheme 20) [111]. However, reactions were rather slow, taking 72 h for full conversion. Enantioselectivities were unexpectedly low (21–38% *ee*), although the common-membered spiro products were obtained in good to high yields. Moreover, the olefin migrations from the primary generated product **22** occurred in all cases leading to the secondary olefin regioisomer **23.**

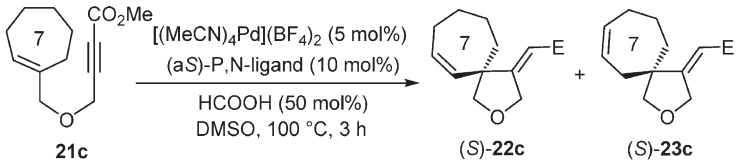


Substrate	Reaction time [h]	Yield [%] (*Ee* [%])		Total *ee* value [%]
		22	**23**	
21a (n=1)	72	35 (23)	21	23
21b (n=2)	72	20 (8)	52 (27)	21
21c (n=3)	16	0 (-)	99 (38)	38

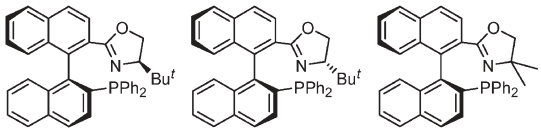
Scheme 20 Enantioselective ene-type spiro cyclization of 1,6-enyne catalyzed by cationic (*R*)-SEGPHOS-Pd(II) complexes

In sharp contrast to P,P ligand, the P,N ligands **16a** and **16b** having a *tert*-Bu oxazoline unit were found to be effective to give the spiro product **22c** with (*S*) sense in excellent yields and good enantioselectivities (over 80% *ee*) along with

olefin migrations [112] (Scheme 21). Also the (a*S*)-P,N ligand **20**, substituted by two methyl groups, provided the corresponding spiro products **22c** and **23c** with higher enantiomeric excess (total 84% *ee*) and in excellent yield. These results imply that the center of chirality (*R* or *S*) at the 4 position of the oxazoline is *not* important, but the presence of sterically demanding alkyl substituent is necessary to achieve higher enantioselectivity.



P,N-ligand	Yield [%] (*Ee* [%])		Total *ee* value [%]
	22c	**23c**	
(a*S*, *R*)-**16a**	22 (96)	77 (78)	82
(a*S*, *S*)-**16b**	32 (88)	65 (76)	80
(a*S*)-**20**	13 (88)	78 (83)	84



(a*S*, *R*)-**16a** (a*S*, *S*)-**16b** (a*S*)-**20**

Scheme 21 Enantioselective ene-type spiro cyclization of 1,6-enyne catalyzed by cationic Pd(II) complexes with chiral P,N ligand

2.4.2 X-Ray Analysis of Pd(II) Complexes Coordinated by P,N Ligand Having Achiral *gem*-Dimethyloxazoline

X-ray analyses of η^3-allyl Pd(II) complexes that are easily prepared from $[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2/AgSbF_6$ and the P,N ligand **20** were executed. The ORTEP drawings of η^3-allyl palladium complex **24** derived from **20** are shown in Fig. 8. In the Pd(II) complex **24** with the P,N ligand (a*S*)-**20**, for instance, the bond distance of Pd–P is 2.304 Å and that of Pd–N is 2.096 Å. The bite angle of P–Pd–N is 96.74°. Because other corresponding η^3-allyl Pd(II) complexes with monosubstituted P,N ligands have no significant difference in the backbone structure of the binaphthyl moiety and the phosphine part, the attention can be focused only on the oxazoline parts of these complexes (see Sect. 2.3.2).

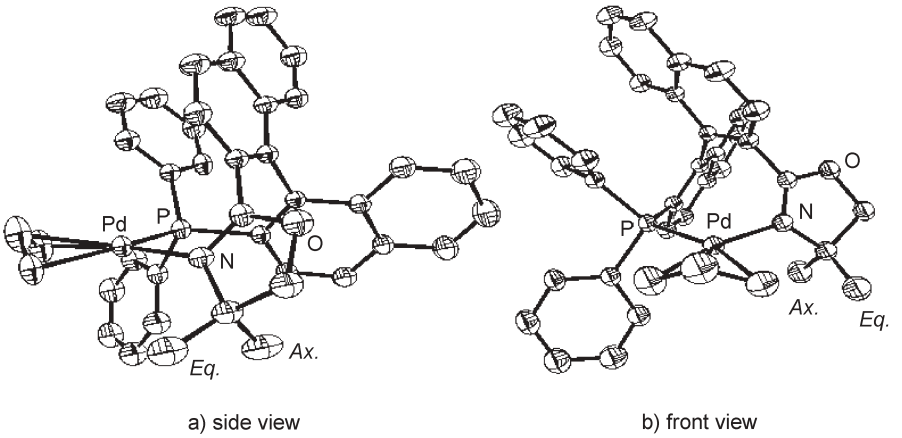
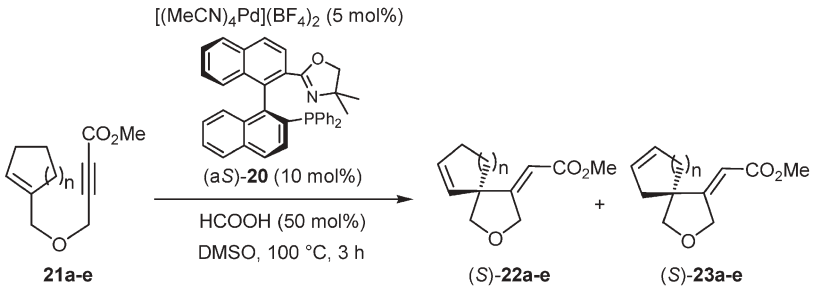


Fig. 8 ORTEP drawings of η^3-allyl Pd(II) complex **24** with P,N ligand **20**

2.4.3 Spiro Furan Synthesis

With the (a*S*)-P,N ligand **20**, substituted by two methyl groups, other spiro cyclizations leading to spiro furan compounds proceeded successfully: as a total value, 88% *ee* and 95% yield for five-membered ring **21a**, 71% *ee* and 83% yield for six-membered ring **21b** (Scheme 22) [113]. For **21a** with the P,N ligand **20**,



Substrate (Ring size)	Reaction time [h]	Yield [%] (*Ee* [%])		Total *ee* value [%]
		22	**23**	
21a (5)	3	88 (88)	7	88
21b (6)	22	63 (84)	20 (31)	71
21c (7)	3	13 (88)	78 (83)	84
21d (8)	6	33 (93)	61 (80)	84
21e (15)	11	90 (83)	0 (-)	83

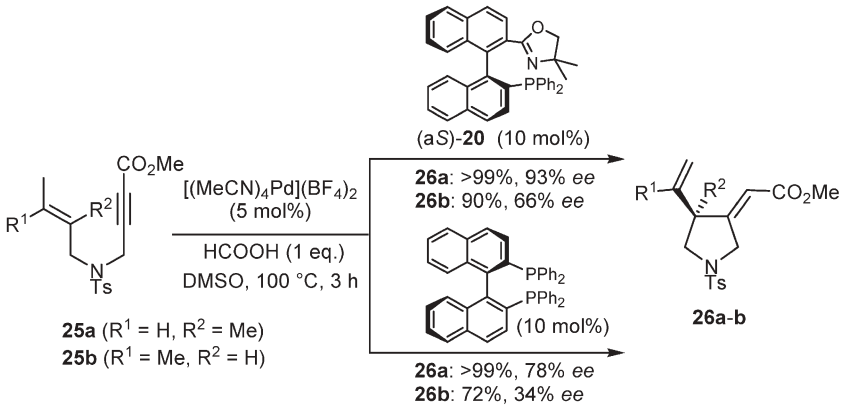
Scheme 22 Spiro cyclization of 1,6-enyne ethers catalyzed by cationic Pd(II) complexes with (a*S*)-*gem*-dimethyl P,N ligand

olefin migration was prevented, so that the enantioenriched **22a** was obtained as the major product with the isomeric **23a**. The medium eight-membered ring substrate **21d** also cyclized successfully in 94% yield and 84% *ee*. For the large 15-membered ring **21e**, spiro cyclization proceeded successfully without accompanying the olefin migration, to afford the single product **22e** in 83% *ee* and in almost quantitative yield.

2.4.4 Spiro Alkaloid Synthesis

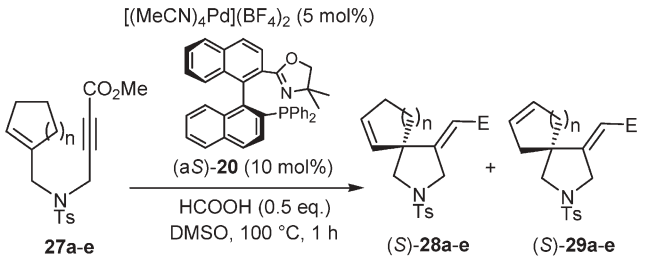
Catalytic asymmetric alkaloid synthesis remains a challenge [114], in spite of the pharmaceutical importance of kainic acid [115, 116] etc. Chiral transition metal complexes are the catalysts [117] of choice for cyclization of enynes, dienes [118, 119], or diynes [120]. With axially chiral P,N ligands having an *achiral gem*-dimethyloxazoline unit, alkaloid synthesis can be attained via ene-type cyclization [121].

For **25a**, the P,N ligand (a*S*)-**20** was effective to afford **26a** with 93% *ee* quantitatively, but (*R*)-BINAP as a P,P ligand resulted in only 78% *ee*. A big difference was seen in the cyclization of **25b**. Reaction with (*R*)-BINAP proceeded smoothly to provide the corresponding product **26b** in moderate (72%) yield with quite low enantiomeric excess (34% *ee*). However, the P,N ligand (a*S*)-**20** showed an advantage over the P,P ligand, not only in chemical yield but also in enantioselectivity (90%, 66% *ee*) (Scheme 23).



Scheme 23 Alkaloid synthesis with P,P vs P,N ligand

For the syntheses of spiro alkaloid analogues, the P,N ligand (a*S*)-**20** having geminal methyl groups was effective (Scheme 24). For the five-membered ring substrate **27a**, the P,N ligand (a*S*)-**20** provided the corresponding spiro product **28a** with high enantiomeric excess in excellent yield (96% *ee*, 90%) after reaction for 1 h at 100 °C. Even for other common rings, the spiro cyclization pro-

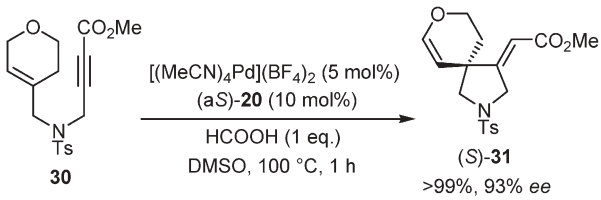


Substrate (Ring size)	Yield [%] (% *Ee*)	
	28	**29**
27a (5)	90 (96)	9 (-)
27b (6)	71 (84)	29 (35)
27c (7)	6 (95)	93 (95)
27d (8)	25 (92)	70 (91)
27e (15)	>95 (84)	0 (-)

Scheme 24 Spiro alkaloid synthesis by ene-type cyclization

ceeded smoothly, although accompanied by olefin migration products (**29a–c**). For **27b**, however, enantioenriched **28b** was the major product (84% *ee*, 71%) with the minor isomer **29b**. Surprisingly, serious olefin migration occurred in the case of **27c**, leading to the isomeric product **29c** with 95% *ee* in 93% yield. The medium-ring substrate **27d** also cyclized successfully, to afford **29d** (91% *ee*) as the major product and **28d** (92% *ee*) as the minor one. For the large ring system, the spiro cyclization of 15-membered ring **27e** proceeded successfully without olefin migration, to afford **28e** as the sole product in 84% *ee* quantitatively.

To show the special advantage of no olefin migration, the cyclization of **30** with the P,N ligand (a*S*)-**20** proceeded smoothly to give the corresponding spiro pyran **31** with 93% *ee* quantitatively (Scheme 25). The result reflects the high potential of the cationic Pd(II) complexes with the P,N ligand (a*S*)-**20** in the syntheses of heterocycles including alkaloids.



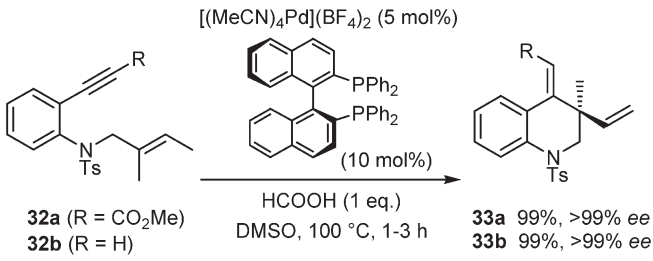
Scheme 25 Spiro alkaloid synthesis by ene-type cyclization without olefin migration

2.5 Tetrahydroquinoline Synthesis via Six-Membered Ring Formation

2.5.1 Six-Membered Ring Formation from 1,7-Enynes

Catalytic asymmetric syntheses of chiral quinoline derivatives are of great importance, since many biologically and pharmacologically active alkaloids bear this skeleton [122]. Thermal and transition metal-catalyzed syntheses of quinolines have thus been amply investigated [123–129]. For the construction of these heterocycles, using chiral Rh [130, 131] and Pd complexes as catalysts, asymmetric versions with high enantiomeric excesses have been developed [132, 133]. Despite its synthetic potential, there has been no report on transition metal-catalyzed asymmetric six-membered ring formation from 1,7-enyne, due to the difficulty of forming six-membered ring as compared with five-membered rings. Following is the first efficient asymmetric synthesis of six-membered ring quinoline derivatives bearing a quaternary carbon center or a spiro ring [134, 135], by the ene-type cyclization of 1,7-enynes catalyzed by cationic BINAP-Pd(II) complex [136].

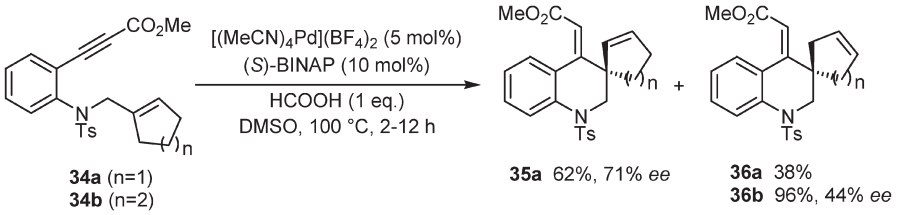
The reaction of 1,7-enynes was performed by a combination of 5 mol% of a cationic Pd(II) catalyst such as $[(MeCN)_4Pd](BF_4)_2$, 10 mol% of (*S*)-BINAP as a chiral bidentate P,P ligand, and 1 equivalent of formic acid in DMSO. Cyclization of the substrate **32** leads to tetrahydroquinoline **33** with a quaternary carbon center (Scheme 26). For **32a**, in which the terminal acetylene is functionalized by a carbomethoxy group, the cyclization gave **33a** as a *single enantiomer* in a quantitative yield within 3 h. The substrate **32b** also cyclized under the same conditions within 1 h to afford the corresponding chiral quinoline **33b** bearing an *exo*-methylene moiety. Remarkably, the presence of the highly reactive terminal acetylene does not lead to side reactions such as polymerizations. Since non-benzo-fused 1,7-enynes provide no six-membered ring products, the *ortho*-substituted benzene skeleton is essential.



Scheme 26 Quinoline synthesis via six-membered ring formation from 1,7-enynes by cationic BINAP-Pd(II)

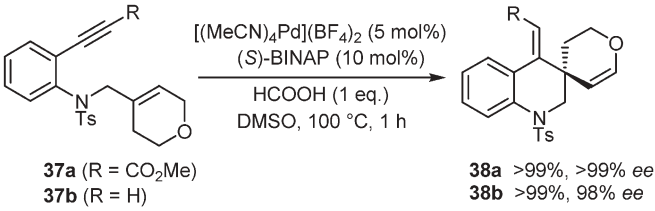
2.5.2 Spiro Tetrahydroquinoline Synthesis

The enyne substrate **34a**, which has a cyclopentene moiety, gave the desired spiro ring product **35a** but in 62% yield and 71% *ee*, along with the *achiral* olefin migration product **36a** (38% yield) (Scheme 27). The six-membered ring substrate **34b** gave completely olefin-migrated spiro quinoline **36b** as the sole product (96%) with 44% *ee*.

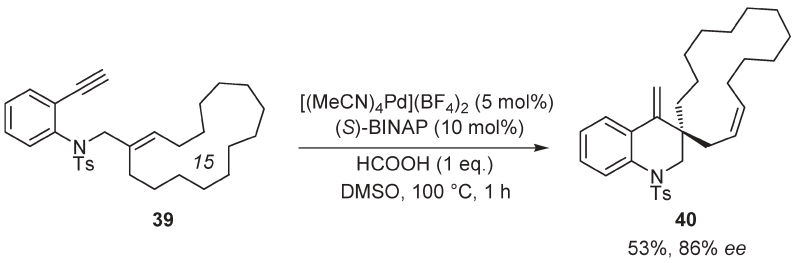


Scheme 27 Spiro quinoline synthesis by cationic BINAP-Pd(II)

In order to avoid the olefin migration which causes the decrease in enantioselectivities and to clarify the real enantioselectivity for spiro systems, transformation of substrate **37**, with a pyran as a cyclic olefin, was examined. With both functionalized and free terminal acetylenes, the cyclizations of **37a** and **37b** proceeded successfully to give **38a** and **38b**, respectively, achieving the spiro ring formation in quantitative yield and 98% *ee* (Scheme 28).



Scheme 28 Spiro pyran–quinoline synthesis by cationic BINAP-Pd(II)



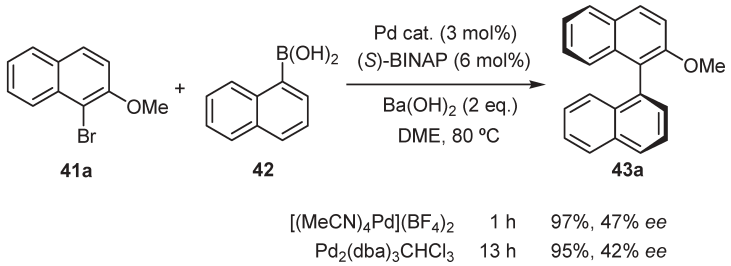
Scheme 29 Synthesis of spiro quinoline with large ring by cationic BINAP-Pd(II)

The spiro quinoline formation was applied to a large-membered ring. The substrate **39**, bearing a 15-membered ring cyclic olefin and a terminal acetylene was cyclized under the previously described conditions to give the olefin migration product **40** in a moderate yield (53%) but good enantioselectivity (86% *ee*) (Scheme 29).

2.6 Catalytic Asymmetric Suzuki–Miyaura Coupling

The practice of asymmetric synthesis is primarily based on the construction of carbon–carbon bonds and the introduction of chirality therein, mediated by chiral metal complexes (nickel and palladium, etc.)[137]. The palladium-catalyzed Suzuki–Miyaura coupling reaction [138, 139] of aryl boronates with aryl halides is one of the most useful coupling reactions in terms of the wide range of functional group applicabilities [140–142]. However, there is one serious drawback of low reactivity, namely the long period of reaction time or low catalyst turnover efficiency. An investigation has been carried out on the asymmetric Suzuki–Miyaura coupling reaction under cationic chiral Pd(II) conditions, to afford the binaphthyl coupling products within a shorter reaction time than that achieved with the generally employed neutral Pd(0) catalysts [143–147].

A typical experimental procedure is as follows: the reaction of the naphthyl halides **41a** and naphthylboronate **42** with Pd catalyst (3 mol%) and (*S*)-BINAP (6 mol%) in the presence of $Ba(OH)_2{\cdot}8H_2O$ in dimethoxyethane (DME) afforded the coupling product **43a** after column chromatographic separation (Scheme 30) [148]. A typical Pd(0) species $Pd_2(dba)_3{\cdot}CHCl_3$ with (*S*)-BINAP showed low catalytic activity. However, the cationic species, $[(MeCN)_4Pd](BF_4)_2$, showed significantly high activity to give **43a** (47% *ee*) within 1 h in an excellent yield.



Scheme 30 Cationic Pd(II) vs Pd(0) in asymmetric Suzuki–Miyaura coupling

Moreover, the combined use of [(*S*)-P,P ligand]Pd(II) (3 mol%) and the corresponding (*S*)-P,P ligand (3 mol%) was effective in increasing the enantioselectivity up to 56% *ee* from 47% *ee* just by simply mixing $[(MeCN)_4Pd](BF_4)_2$ (3 mol%) and the P,P ligand (6 mol%) (Scheme 2). Sterically demanding Pd(II)

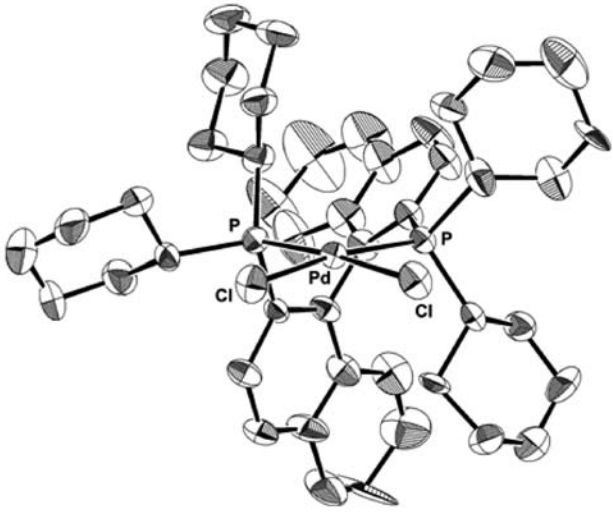
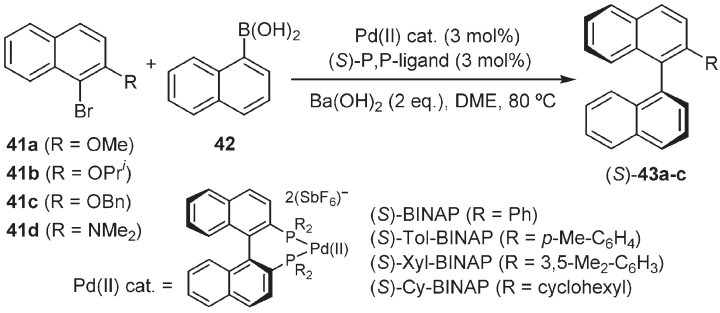


Fig. 9 ORTEP drawing of [(*S*)-Cy-BINAP]$PdCl_2$ complex **44**



Substrate	P,P-ligand	Reaction time [h]	% Yield (% *ee*)
41a	(*S*)-BINAP	0.5	91 (56)
41a	(*S*)-Tol-BINAP	1	97 (40)
41a	(*S*)-Xyl-BINAP	4	0 (-)
41a	(*S*)-Cy-BINAP	1	92 (70)
41a	(*S*)-Cy-BINAP	6 (r.t.)	17 (84)
41b	(*S*)-BINAP	0.5	99 (50)
41c	(*S*)-Cy-BINAP	4	99 (54)
41d	(*S*)-BINAP	0.5	61 (58)

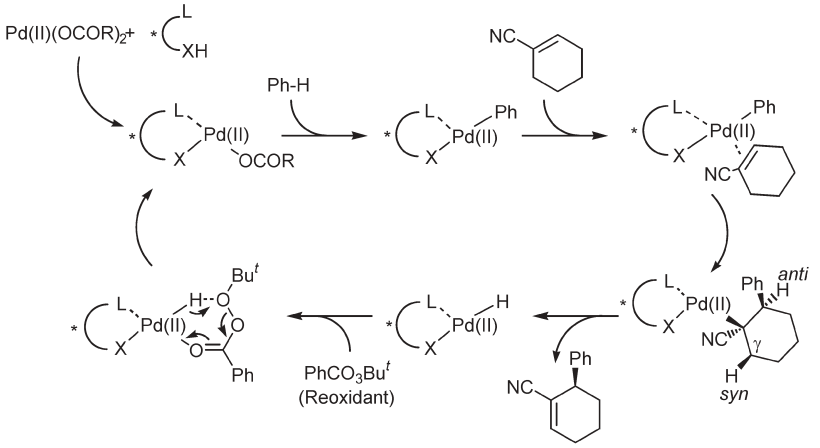
Scheme 31 Cationic Pd(II)-catalyzed asymmetric Suzuki–Miyaura coupling

complexes, such as Pd(II)/(*S*)-Tol-BINAP or Pd(II)/(*S*)-Xyl-BINAP, did not give good selectivities. However, further increase in enantioselectivity (70% *ee*) was observed with the use of (*S*)-cyclohexyl-BINAP (Cy-BINAP) instead of (*S*)-BINAP. The enantioselectivity increased up to 84% *ee* when the reaction was executed at room temperature. The high catalytic activity and enantioselectivity stem from the highly sterically demanding nature of this complex. X-ray analysis of a single crystal of [(*S*)-Cy-BINAP]$PdCl_2$ complex **44** was thus performed to show the novel C_1-symmetric field (Fig. 9) [149]. This is in sharp contrast to the C_2-symmetric field usually seen in other $PdCl_2$ complexes with BINAP analogues. Cationic Pd(II)/BINAP or Pd(II)/Cy-BINAP catalysts were effective for other substrates to afford the products quantitatively, although the selectivities were moderate (Scheme 31).

2.7 Catalytic Asymmetric C–H Bond Activation/C–C Bond Formation

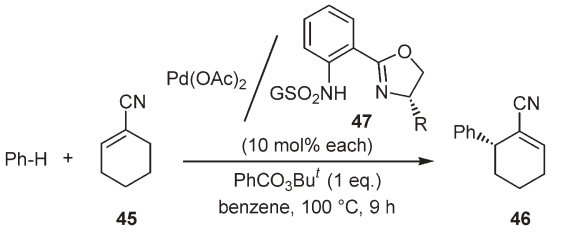
C–H bond activation and C–C bond formation are the key issues in organic synthesis [150–156]. The so-called Fujiwara–Moritani reaction has been regarded as one of the most versatile methods for activation of aromatic C–H bonds to provide a coupling product with an olefin using a catalytic amount of Pd(II) complex with an equimolar amount of a reoxidant [157–159].

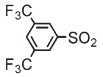
By using an LX-type ligand, the catalytic asymmetric Fujiwara–Moritani reaction of benzene with cyclic olefins can afford the chiral phenyl-substituted cyclic olefins through *syn* β-H elimination from the opposite (γ) side to the phenyl group (Scheme 32) [160].



Scheme 32 Catalytic cycle of C–H bond activation by chiral Pd(II) with LX ligand

A benzene solution of cyclohexenecarbonitrile (**45**) and 10 mol% of $Pd(OAc)_2$ with chiral sulfonylamino-oxazoline ligand **47** in the presence of one equiva-



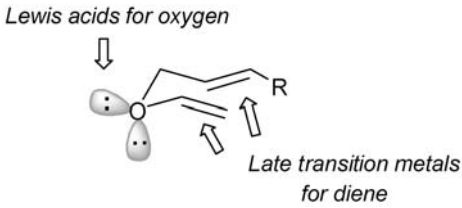
Ligand	R	GSO_2	Yield (%)	*Ee* (%)
47a	*i*-Pr	Ts	6	40
47b	*i*-Pr	CF_3SO_2	25	44
47c	*tert*-Bu	CF_3SO_2	15	47
47d	*i*-Pr	$C_4F_9SO_2$	25	42
47e	*i*-Pr		19	49

Scheme 33 C–H bond activation/C–C bond formation by chiral Pd(II) catalysts

lent of *tert*-butyl perbenzoate as a reoxidant was heated at 100 °C to afford the coupling product **46** [161] (Scheme 33). Modification of the chiral ligand **47** with an electron-withdrawing and sterically demanding highly fluorinated sulfonyl group was found to lead to an increased chemical yield and enantioselectivity (up to 49% *ee* by **47e**).

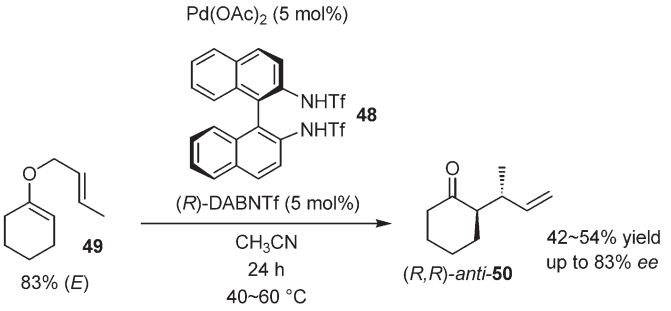
2.8 Catalytic Asymmetric Claisen Rearrangement

The Claisen rearrangement of allyl vinyl ether is one of the most important carbon–carbon bond-forming reactions in organic synthesis [162–166]. However, there are only a few examples of asymmetric catalysis for the Claisen rearrangement [167–170]. The reason is that metal catalysts for the Claisen rearrangement are generally based on the Lewis acidity, to distinguish two enantiotopic lone pairs on the oxygen of allyl vinyl ether, and that the carbonyl products are strongly complexed to these oxophilic metals (Scheme 34).



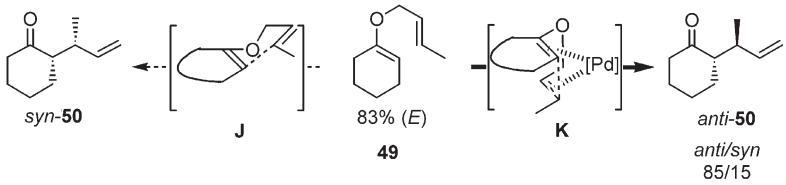
Scheme 34 Two models of the metal-catalyzed Claisen rearrangement

In contrast, the late transition metal palladium is more coordinative to soft carbon–carbon multiple bonds rather than hard oxygen. The bidentate coordination is further advantageous over the weak monodentate coordination of γ,δ-unsaturated carbonyl product to set the catalytic cycle. Recently we reported the (*R*)-DABNTf-Pd(II) complex as an effective catalyst for asymmetric Claisen rearrangement. (R)-DABNTf-Pd(II) catalyst gave the (*R*,*R*)-*anti*-**50** in 83% *ee* (Scheme 35) [171].



Scheme 35 Pd(II)-DABNTf-catalyzed Claisen rearrangement

The stereochemistry of the Claisen rearrangement is generally predicted on the basis of conformational analysis in chairlike transition states (**J**) leading to the (*E*) substrate **49** and to the *syn* product. However, in this Pd(II)-catalyzed reaction, the (*E*) substrate **49** gave *anti*-**50**. This anomalous stereoselectivity is explained by six-membered ring boat transition states (**K**) via bidentate coordination to the palladium catalyst (Scheme 36).



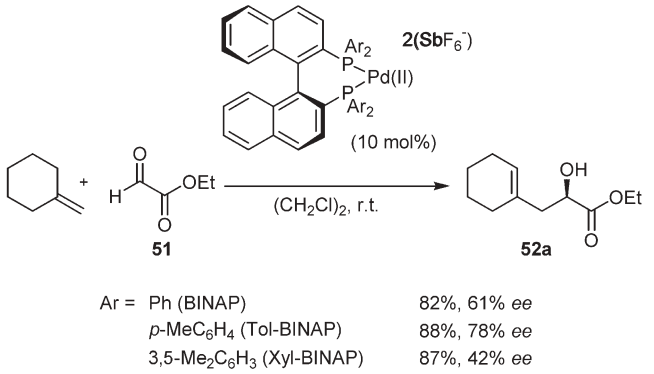
Scheme 36 The boat transition state in the Pd(II)-DABNTf-catalyzed Claisen rearrangement

3
Lewis Acid Catalysis

3.1
Catalytic Asymmetric Carbonyl–Ene Reaction

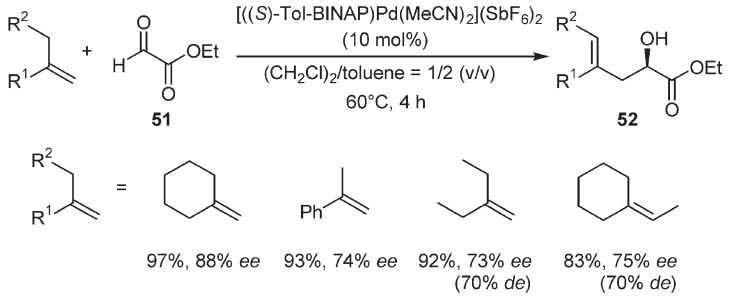
As one of the most important methodologies for carbon–carbon bond construction, asymmetric ene reactions catalyzed by chiral Lewis acids have received great attention in recent years [172–175]. An effective chiral cationic

(*S*)-BINAP-Pd(II) complex was developed for the asymmetric carbonyl–ene reaction with 1,1-disubstituted olefins and ethyl glyoxylate **51** (Scheme 37) [176]. The combination of dicationic (*S*)-BINAP-Pd(II) species with a strongly anionic ligand such as SbF_6^- could be employed as an efficient catalyst in carbonyl–ene reactions. In contrast to the BINOL-Ti-catalyzed carbonyl–ene reaction, which is restricted to 1,1-disubstituted olefins, this dicationic Pd(II) catalyst afforded the α-hydroxy esters **52** with high enantioselectivities even from trisubstituted olefins. The medium size of the (*S*)-Tol-BINAP ligand led to better enantioselectivity than the sterically less demanding (*S*)-BINAP and more bulky (*S*)-Xyl-BINAP ligands.



Scheme 37 Dicationic (*S*)-BINAP-Pd(II)-catalyzed glyoxylate–ene reaction

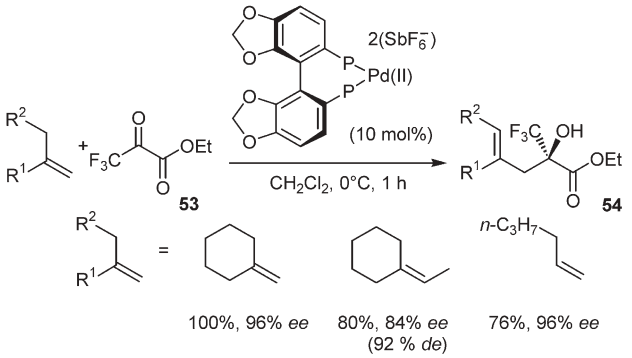
The best result of 88% *ee* was obtained in the reaction using [((*S*)-Tol-BINAP)$Pd(CH_3CN)_2$]$(SbF_6)_2$ as a catalyst and 1,2-dichloroethane/toluene (1/2 by volume) as a solvent system (Scheme 38). This catalytic system is generally applicable to other 1,1-disubstituted olefins, such as α-methylstyrene and 2-ethyl-1-butene, and furthermore to trisubstituted olefins, such as ethylidenecyclohexane.



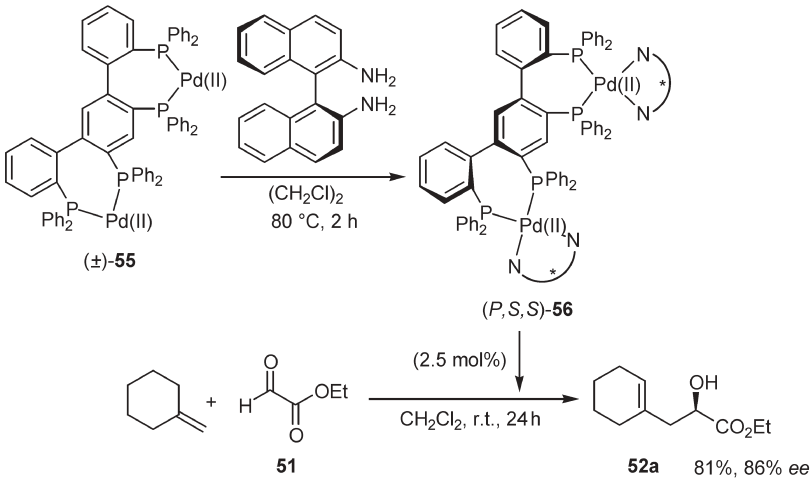
Scheme 38 Enantioselective glyoxylate–ene reaction with 1,1-disubstituted and trisubstituted olefins

The considerable difference in the enantioselectivity is shown by use of (*S*)-SEGPHOS-Pd(II) complex (Scheme 39). The increase of the enantioselectivity may arise from the structural differences between BINAP-Pd and SEGPHOS-Pd catalysts. On the basis of the X-ray structure of the dicationic BINAP-Pd(II), MeO-BIPHEP-Pd(II), and further to SEGPHOS-Pd(II), where the metal center geometry is close to square planar, it may be proposed that effective shielding by (*S*)-SEGPHOS of the most obtuse dihedral angle is the origin of the highest enantioselectivity [177]. The attack on the *si* face of the substrate **53** formyl group is prevented by the equatorial phenyl group of (*S*)-SEGPHOS, and hence the attack on the *re* face is significantly favored.

A further advanced asymmetric catalyst can be highlighted in the use of chirally flexible *tropos* ligands such as BIPHEP or tetraphos [178, 179] instead of



Scheme 39 Ene reaction catalyzed by cationic SEGPHOS-Pd(II) complex



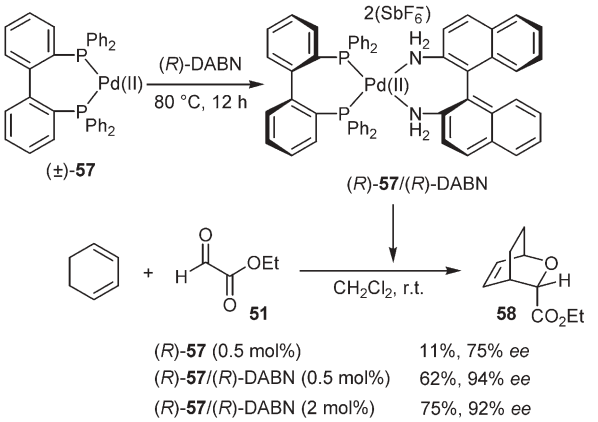
Scheme 40 Carbonyl–ene reaction catalyzed by DABN-activated cationic tetraphos-Pd(II) catalysts

atropos ligands such as BINAP. The word *atropos* consists of "*a*" meaning "not" and "*tropos*" meaning "turn" in Greek [180].

Tetraphos (2,4′,6′,2″-tetrakis(diphenylphosphinyl)-[1,1′;3′,1″]terphenyl)) (**55**) bearing a nonplanar helical structure was newly designed (Scheme 40) [181]. Complexation of (±)-**55** with two equivalents of (*S*)-DABN gave a single diastereomer (*P*,*S*,*S*)-**56** after reaction at 80 °C for 2 h. The single diastereomer (*P*,*S*,*S*)-**56** thus prepared can be used as an active chiral catalyst for the carbonyl–ene reaction of glyoxylate **51** and can generate the product in 81% yield and 86% *ee*.

3.2 Catalytic Asymmetric Hetero Diels–Alder Reaction

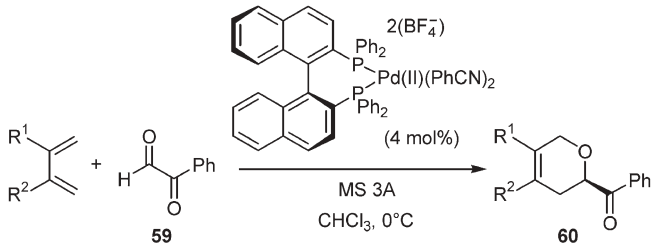
A combination of chiral metal complexes derived from the *tropos* biphenylphosphine (BIPHEP) ligand and the chiral 2,2′-diamino-1,1′-binaphthyl (DABN) as a chiral activator can also be used in a similar but more advantageous manner to the *atropos* BINAP ligand. With one equivalent of (*R*)-DABN, complexation of both enantiomers of BIPHEP-Pd and (±)-**57** takes place to afford a 1:1 ratio of a diastereomeric mixture of (*R*)-**57**/(*R*)-DABN and (*S*)-**57**/(*R*)-DABN. The diastereomeric mixture of **57**/(*R*)-DABN can exhibit *tropo* inversion of the BIPHEP-Pd moiety at 80 °C to afford favorable (*R*)-**57**/(*R*)-DABN exclusively. The single diastereomer (*R*)-**57**/(*R*)-DABN prepared via *tropo* inversion can be used as an activated chiral catalyst for the hetero Diels–Alder (HDA) reaction of glyoxylate **51**, leading to significantly higher chemical yields and enantioselectivity (Scheme 41) [182]. The efficiency of (*R*)-DABN as a chiral activator is highlighted by the higher levels of enantioselectivity and catalytic activity than those (11%, 75% *ee*) attained by using the enantiopure (*R*)-**57** without (*R*)-DABN. The chemical yield and enantioselectivity increased up to 75% and 92% *ee* by using 2 mol% of (*R*)-**57**/(*R*)-DABN catalyst.



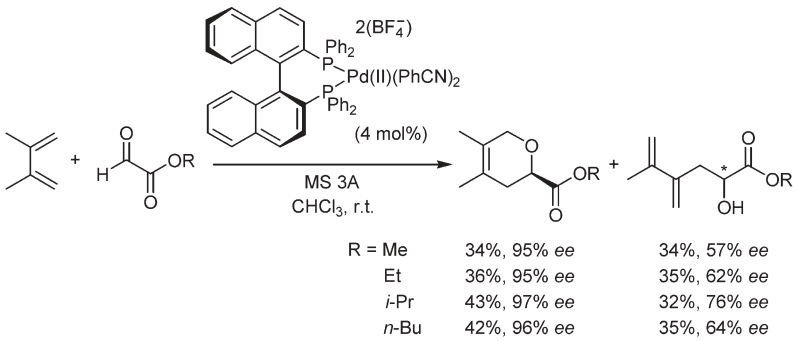
Scheme 41 HDA reaction catalyzed by DABN-activated cationic BIPHEP-Pd(II) catalysts

3.3
Carbonyl–Ene vs Hetero Diels–Alder Reaction

The cationic chiral BINAP-Pd(II) complexes are found to be catalysts for the HDA reaction of nonactivated diene with phenylglyoxal **59** (Scheme 42). The addition of MS 3A and the adoption of a lower reaction temperature improved the chemical yield and the enantioselectivity up to 66% and 99% *ee*. The metal center geometries of the chiral BINAP-Pd(II) complexes are close to square planar, and two carbonyl groups of phenylglyoxal could coordinate on the metal center. The attack on the *si* face of the formyl group is prevented by the equatorial phenyl group of the (*S*)-BINAP, and hence the attack on the *re* face is significantly favored. A bulky alkyl moiety in glyoxylate esters improved the HDA selectivity and the enantioselectivity of the ene product (Scheme 43).



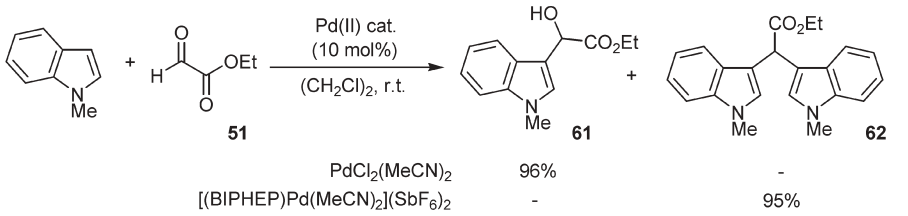
Scheme 42 HDA reaction with phenylglyoxal catalyzed by cationic BINAP-Pd(II) complexes



Scheme 43 HDA reaction with glyoxylate esters catalyzed by cationic BINAP-Pd(II) complexes

3.4
Catalytic Asymmetric Friedel–Crafts Reaction

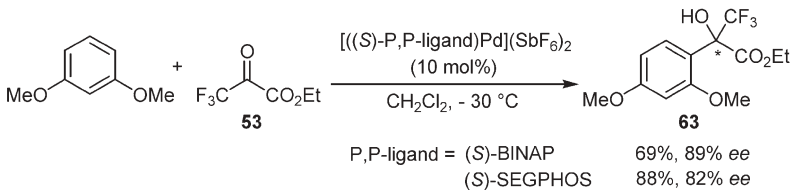
The Friedel–Crafts-type reactions of *N*-methylindole with ethyl glyoxylate **51** are catalyzed by the Lewis acidity of Pd(II) complexes [183]. Unprecedentedly,



Scheme 44 Friedel–Crafts reaction catalyzed by neutral and cationic Pd(II) complexes

both neutral and cationic Pd(II) catalysts accomplished the Friedel–Crafts-type carbon–carbon bond formations, although a dramatic changeover of the product was observed between these catalysts. The α-hydroxyindolylacetate **61** was obtained in 96% yield when the neutral $PdCl_2(MeCN)_2$ complex was used, while the diindolylacetate **62** was the sole product (95% yield) when the cationic BIPHEP-Pd(II) complex was used (Scheme 44).

The asymmetric Friedel–Crafts reaction of trifluoromethyl pyruvate **53** with aromatic compounds is catalyzed by cationic Pd(II) complexes with BINAP or SEGPHOS [184]. The reaction proceeded at –30 °C to afford the product **63** in 89% *ee* with (*S*)-BINAP and in 82% *ee* with (*S*)-SEGPHOS (Scheme 45). In sharp contrast to the situation of the carbonyl–ene reaction, the BINAP ligand provides higher enantioselectivity than the SEGPHOS ligand.

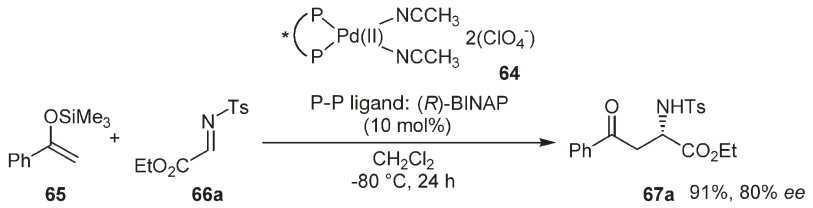


Scheme 45 Asymmetric catalytic Friedel–Crafts reaction catalyzed by cationic Pd(II) complexes

3.5 Catalytic Asymmetric Imine–Aldol Reaction

Asymmetric Mannich (imine–aldol) reactions give optically active β-amino carbonyl compounds of biological activity. There are two types of Pd-catalyzed asymmetric Mannich-type reactions: Lewis acid catalyzed and Pd–enolate reactions. These reactions proceed similarly, but the reaction mechanisms are quite different.

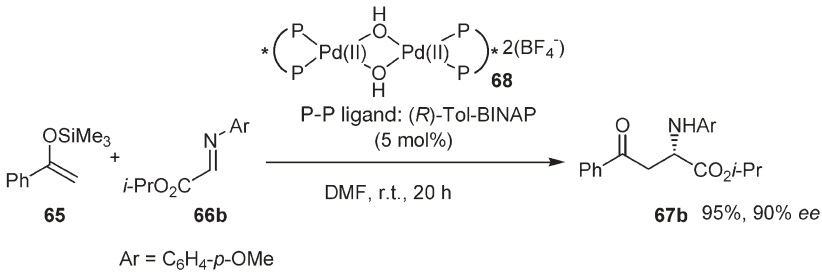
Lectka and coworkers reported a Pd(II)-catalyzed asymmetric Mannich-type reaction (Scheme 46) [185, 186]. The cationic Pd(II)/(R)-BINAP complex **64** activated imines as a Lewis acid. The activated imine was attacked by the silyl enolate **65** to give the product **67a** in high enantioselectivity (80% *ee*). This reaction needed strictly anhydrous conditions. The presence of a small amount of water



Scheme 46 Asymmetric catalytic Mannich reaction catalyzed by cationic Pd(II) complex as Lewis acid

promoted the formation of the Pd aqua complex, which decreased the catalytic activity and hence the enantioselectivity. They also examined other metal BINAP complexes such as Ag, Cu, and Ni. The best result was obtained with the Cu complex [187, 188].

In contrast, Sodeoka and coworkers reported Pd-catalyzed asymmetric Mannich-type reactions (Scheme 47) [189–191]. In this case, the Pd(II)/tol-BINAP hydroxo complex **68** did not act as a Lewis acid, but formed the chiral Pd enolate generated from the silyl enol ether **65** through transmetalation to give the product **67b** in high enantioselectivity (90% *ee*). The Pd(II)/tol-BINAP hydroxo complex **65a** is effective to suppress the generation of strong protic acid HBF_4 that catalyzed the racemic reaction.



Scheme 47 Pd(II) hydroxo complex-catalyzed asymmetric Mannich-type reaction

4 Conclusion

It has been proven that the chiral Pd(II) complexes as transition metal catalysts vs Lewis acid catalysts bring a breakthrough in the frontier of catalytic asymmetric organic synthesis. Here we discussed the key issues based on asymmetric carbon–carbon bond formations: anomalous six-membered ring formation, ene-type cyclization leading to five-membered rings, spiro cyclization, alkaloid and quinoline synthesis, Suzuki–Miyaura coupling, and C–H bond activation/C–C bond formation by transition metallic Pd(II) catalysts. On the other hand, the carbonyl–ene reaction, hetero Diels–Alder reaction, and

Friedel–Crafts reaction by Lewis acidic Pd(II) catalysts are also reported. Particularly, chiral cationic Pd(II) catalysts have great potential to go beyond catalyses with Pd(0) and/or neutral Pd(II) species. Our ongoing studies shown here are just the tip of an iceberg, and further progress in the Pd(II) history will continue with increasing acceleration.

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