1
Mechanistic Aspects of Metal-Catalyzed C,C- and C,X-Bond Forming Reactions

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1.1
Mechanisms of Cross-Coupling Reactions

Cross-coupling reactions comprise a group of transformations for the formation of C–C bonds based on the transmetallation of nucleophilic organometallic compounds with organic electrophiles in the presence of late-transition metals as catalysts [1]. In most cases, cross-coupling reactions are based on palladium(0) catalysis [2–7], although nickel catalysts were actually involved in the initial discovery of cross-coupling methods by Kumada *et al.* [8] and are currently receiving renewed attention [9]. These transformations were later extended to the use of heteronucleophiles, such as amines, alcohols, and thiols, for the formation of C-X bonds.

The first palladium-catalyzed cross-coupling reactions of organostannanes were reported in the 1976–1978 period by the groups of Eaborn [10], Kosugi *et al.* [11], and Stille [12]. This transformation is usually known as the *Stille coupling* [13–17] and, together with the Suzuki–Miyaura cross-coupling of organoboron compounds [18–21], has been established as the most general and selective palladium-catalyzed cross-coupling reaction [1, 22–24] (Scheme 1.1). Synthetically, the Stille reaction takes prevalence over the Suzuki–Miyaura coupling in substrates bearing a stannane and a boronic ester as reactive sites [25]. Mechanistically, these reactions are closely related to other transmetallation-based cross-couplings of organometallic nucleophiles [26] such as the Negishi [27, 28], Hiyama [29, 30], Sonogashira [31, 32], Kumada (or Kumada–Corriu), and other related couplings [33–36].

The first thorough mechanistic studies centered on the Stille reaction [13, 14]. Although some important differences exist between this reaction and related cross-couplings, the main mechanistic conclusions that arose from work done on this reaction pertain to other related cross-couplings proceeding through Pd(0)/Pd(II) catalytic cycles. Although nickel, copper, iron, cobalt, and occasionally platinum have also been used as catalysts for cross-coupling processes, most of the detailed mechanistic studies concern palladium chemistry. Cross-coupling reactions share important mechanistic details with the Heck alkenylation of organic electrophiles [37, 38]. Indeed, the 2009 Nobel Prize for chemistry recognized both the Heck

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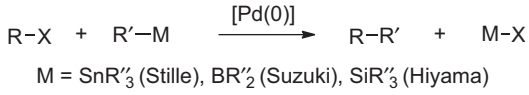


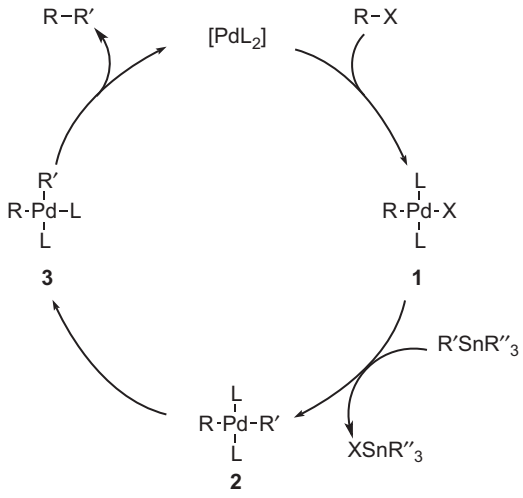
Scheme 1.1 Representative palladium-catalyzed cross-coupling reactions.

and cross-coupling reactions as the most important contributions from palladium organometallic chemistry inorganic synthesis [39].

In this chapter, we update our previous review on this topic [22], centering most of the discussion on palladium-catalyzed transformations, although the most significant mechanistic aspects of other cross-couplings are also included. To keep the length of the review within reasonable limits, the coverage is not exhaustive, although key references are provided for all important aspects. The mechanism of the palladium-catalyzed direct arylation of arenes, which is a practical alternative to cross-coupling methods for the formation of biaryls [40–51], is not covered in this review.

1.1.1 The Earlier Mechanistic Proposal: The Stille Reaction

The extensive synthetic and mechanistic work carried out by Stille [12, 13] established this reaction as a mature synthetic method for organic synthesis [40, 52, 53]. In the first comprehensive mechanistic proposal, a $[PdL_2]$ ($L = PPh_3$) complex was proposed to react with the organic electrophile R-X to form complex **1** (Scheme 1.2). Complex **1** was the only observable species in the catalytic cycle, even in the presence of excess organostannane, which demonstrated that the slow step is the



Scheme 1.2 The original proposal for the mechanism of the Stille reaction.

transmetallation reaction with the organostannane. This transmetallation was believed to give rise directly to the Pd(II) complex **2**. Then, a trans-to-cis isomerization would give complex **3**, from which the reductive elimination immediately ensued to afford the final coupling product R–R′.

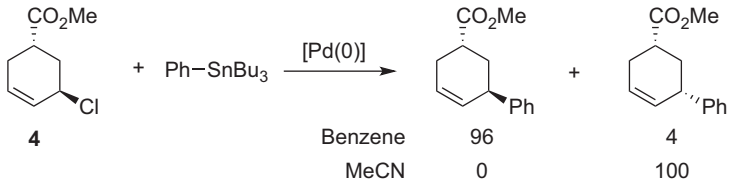
This mechanistic interpretation of the Stille reaction has been the base for the formulation of the mechanisms of other cross-coupling reactions. Model studies on the coupling of alkynes with vinyl triflates with $[Pt(PPh_3)_4]$ were in overall agreement with that proposal [54], although involvement of cationic complexes in the transmetallation step was strongly suggested by this work. Farina [55] and Brown [56] also found that the intermediates formed upon oxidative addition of organic triflates to Pd(0) are cationic complexes such as $[PdR^1(S)L_2]^+$ and $[PdR^1L_3]^+$.

Although these studies shed light on the transmetallation step, this transformation was initially mechanistically obscure. Thus, for example, either inversion [57] or retention [58] of the configuration of alkylstannanes has been found. Inversion has also been observed in other processes as a result of an S_N2 oxidative addition process [59, 60]. In addition, theoretical studies and experimental results were in contradiction with several aspects of the mechanistic model of Scheme 1.2. In effect, intermediates of the type *trans*-$[PdR^1R^2L_2]$ (**2**) [61] might be expected to be quite long-lived, as trans-to-cis isomerizations in this type of complexes are not facile processes [62–64].

1.1.2 The Oxidative Addition

The oxidative addition of organic electrophiles (halides, sulfonates, and related activated compounds) to palladium(0) is the first step in the cross-coupling and Heck reactions. Much work has been done on the mechanisms of the oxidative addition reactions of aryl and alkenyl halides and triflates ($C(sp^2)$-X electrophiles) [65], the most common organic electrophiles in cross-coupling reactions.

The oxidative addition of $C(sp^3)$-X electrophiles to Pd(0) complexes PdL_4 (L = phosphine) takes place usually by an associative bimolecular process (S_N2 reaction). The anion then adds to the metal to give the product. However, the reaction of allylic electrophiles is more complex, because, in addition, S_N2' substitutions are conceivable pathways. The coupling of the trans-configurated allylic chloride **4** with $PhSnBu_3$ proceeded with overall retention of configuration when the reaction was performed in benzene with a Pd(0) complex made *in situ* from $[Pd(\eta^3\text{-}C_3H_5)Cl]$ and maleic anhydride, while clean inversion was observed in polar, coordinating solvents (Scheme 1.3) [66]. The observed configuration is a consequence of the oxidative addition step. This reaction proceeds with complete or predominant retention in noncoordinating solvents [66, 67], which is in agreement with theoretical studies on the oxidative addition of CH_3X to Pd(0) [68]. On the other hand, in coordinating solvents such as MeCN or DMSO, complete or nearly complete inversion was observed [66]. Syn oxidative addition has also been observed in related substrates [69]. However, the usual inversion of configuration in the oxidative addition was observed with $[Pd(PPh_3)_4]$ [66, 70].



Scheme 1.3 Retention or inversion of configuration in the oxidative addition as a function of solvent polarity.

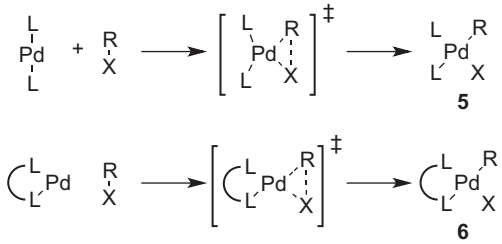
Allylic fluorides react with sodium dimethyl malonate (the Tsuji–Trost reaction) to form initially tight ion pairs [71]. Interestingly, the reaction does not follow the normal double-inversion mechanism, which has been explained by the competitive reaction of the intermediate ion pair with neutral $[PdL_2]$.

An earlier study on the mechanism of the oxidative addition of aryl iodides to $[PdL_2]$ was consistent with an aromatic nucleophilic substitution [72]. Accordingly, electron-withdrawing substituents on aryl electrophiles lead to rate acceleration [73, 74]. In general, increasing the bite angle of bidentate ligands leads to a decrease in the rate of the oxidative addition [74, 75]. However, the opposite effect has also been observed [76], although in this case ligands of very different basicity were considered [77].

Contrary to the general thought that palladium-catalyzed couplings of alkenyl halides are always stereoretentive; the Suzuki–Miyaura coupling of (*Z*)-alkenyl halides with boronic acids can give significant amounts of coupled products with (*E*)-configuration [78]. The best stereoretention was achieved with $[Pd(P(o\text{-Tol})_3)_2]$ as the catalyst.

1.1.2.1 *Cis*-Complexes in the Oxidative Addition

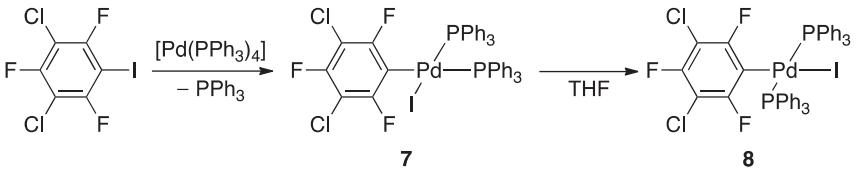
The intermediates that are usually observed after the oxidative addition are *trans*-$[PdRXL_2]$ complexes (**2**, Scheme 1.2), an observation which has led to the general proposal that these complexes are the primary products of the reaction. However, the oxidative addition for the most common C(sp^2)-X electrophiles proceeds by a concerted interaction of a reactive $[PdL_2]$ or [Pd(L-L)] (L-L = diphosphine) species with the substrate R-X via a three-center transition state that should necessarily lead to *cis*-$[PdRXL_2]$ complexes (Scheme 1.4). In the *cis*-isomers, a destabilizing



Scheme 1.4 Oxidative additions of C(sp^2)-X electrophiles to Pd(0).

interaction exists between the mutually trans-positioned phosphorus donor and aryl ligands [79]. Therefore, in the case of complexes with monodentate phosphines, the initially formed *cis*-[PdRXL2] (**5**) complexes undergo isomerization to form the more stable *trans*-[PdRXL2] complexes [80]. Such isomerization is obviously not possible for complexes **6** with cis-coordinating bidentate phosphines.

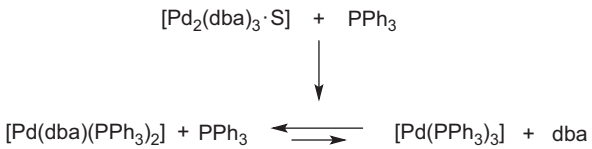
The isomerization process was analyzed in detail by the group of Espinet [81] in the case of complex **7**, formed by the oxidative addition of $C_6Cl_2F_3I$ to $[Pd(PPh_3)]_4$ (Scheme 1.5). The isomerization of *cis*-**7** to *trans*-**8** is a rather complex process that can take place by four major competitive pathways. Two of these pathways involve associative replacements of PPh_3 by an iodide ligand of a second palladium complex. Two additional routes involve two consecutive Berry pseudorotations on pentacoordinated species formed by coordination of the solvent tetrahydrofuran (THF) [81].



Scheme 1.5 Cis-to-trans isomerization of a primary oxidative addition product.

1.1.2.2 **The Role of Alkene and Anionic Ligands**

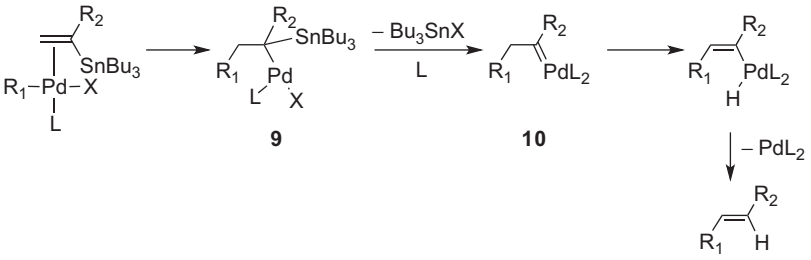
The complex $[Pd_2(dba)_3 \cdot S]$ (dba, dibenzylideneacetone; S = dba or solvent molecule)[1] [82] has been used as a source of Pd(0) in many palladium-catalyzed reactions [23]. Early work by Roundhill [83], and subsequent detailed studies by Amatore and Jutand [76, 84–86], established that the dba ligands are not completely substituted in the reactions of $[Pd_2(dba)_3 \cdot S]$ with phosphines under mild conditions. With PPh_3, mixtures of $[Pd(PPh_3)_3]$ in equilibrium with $[Pd(dba)(PPh_3)_2]$ are formed (Scheme 1.6) [83, 87]. As a result, starting from $[Pd_2(dba)_3]$ and 2 equiv. of PPh_3, the oxidative addition of PhI proceeds at an overall rate that is about 10 times less than that starting from $[Pd(PPh_3)_4]$. Similar equilibria were found for other ligands [88, 89].



Scheme 1.6 Equilibrium resulting from $[Pd_2(dba)_3 \cdot S]$ and PPh_3.

1) The rates of oxidative addition starting from complexes $[Pd_2(dba)_3 \cdot dba]$ or $[Pd_2(dba)_3 \cdot S]$ are probably different, as the excess of dba may retard that reaction. We refer to these complexes as $[Pd_2(dba)_3]$.

The double bond of certain sterically encumbered alkenylstannanes can undergo insertion into the oxidative addition intermediates leading to products of cine substitution (Scheme 1.7) [90]. Mechanistic studies suggest the involvement of palladium carbenes **10** as intermediates, which are formed by evolution of intermediates **9** [90c,d].



Scheme 1.7 Insertion of the double bond of alkenylstannanes into the oxidative addition intermediates.

Anionic ligands play a very significant role in oxidative and transmetallation addition reactions [91, 92]. Thus, for example, Amatore and Jutand [93, 94] concluded that in the presence of acetate, the tricoordinated anionic species $[PdL_2(OAc)]^-$ are the effective complexes in oxidative addition [94], instead of the usually postulated neutral $[PdL_2]$ complex. In the presence of halide anions, anionic complexes are also formed [95–97]. In general, the following order of stabilization of the anionic Pd(0) species is observed: $I^- > Br^- > Cl^-$ [98].

1.1.2.3 Cross-Couplings in the Presence of Bulky Phosphines

It may be risky to raise mechanistic conclusions on qualitative observations regarding rate accelerations upon changes on any reaction variable in complex catalytic processes such as cross-coupling reactions. Nevertheless, some interesting hints can be obtained from work aimed at developing new conditions for the coupling of the less reactive organic substrates such as aryl chlorides [99, 100] and alkyl electrophiles [101].

Aryl chlorides react more sluggishly in cross-coupling reactions than bromides, iodides, and triflates because of their aversion toward oxidative addition to Pd(0) [102]. Initially, the focus was on the development of sterically encumbered, chelating ligands to activate these substrates. Thus, Milstein [74, 103] reported that $[Pd(dippp)_2]$ (dippp, 1,3-bis(diisopropylphosphino)propane) was an efficient catalyst for the carbonylation, formylation, and Heck reactions of aryl chlorides. The groups of Hartwig and Buchwald also demonstrated the importance of a variety of sterically congested, chelating ferrocenyl- or biphenylphosphines in palladium-catalyzed transformations. In particular, the amination and etherification of aryl electrophiles [104], as well as the ketone and malonate arylation processes [105–108], benefit greatly from the use of this type of ligands.

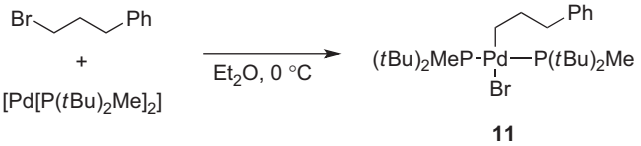
Relatively simple, bulky monodentate phosphines that form [PdL] or [PdL_2] complexes, promote the coupling of the less reactive substrates under relatively mild conditions [109, 110]. This accelerating effect on the oxidative addition was demonstrated in the context of the formation of (η^3-allyl)palladium complexes [111]. Particularly useful for the activation of aryl chlorides are palladium complexes of the bulky phosphine P(tBu)$_3$ [109, 112–115]. Bulkier phosphines such as (1-Ad)P(tBu)$_2$ (Ad, adamantyl) have been used in the palladium-catalyzed arylation of malonates and cyanoesters [116]. The related bulky phosphine P(tBu)$_2$(o-biphenyl) and many variations on this theme have been developed by Buchwald as ligands for the palladium-catalyzed reaction of amines with aryl bromides, chlorides, and triflates [117–119] and in the Suzuki–Miyaura coupling reactions [117a, 120]. Bulky, monodentate phosphines are also the ligands of choice for the coupling of organotrifluoroborates [121].

Highly reactive palladium catalysts based on this type of bulky biphenylphosphines can be readily generated from phenylethylamine-derived palladacycles [122] or, even more conveniently, from biarylamine-derived precatalysts [123]. Complexes PdL_2 can also be conveniently prepared *in situ* by the reaction of Pd(η^3-1-PhC_3H_4)(η^5-C_5H_5) with tertiary phosphines L [124].

Coordinatively, unsaturated [(1,6-diene)PdL] (L = phosphine) complexes are also efficient catalysts for the Suzuki–Miyaura coupling of aryl chlorides with phenylboronic acid [125, 126].

Fu reported that the complex [Pd(PCy_3)$_2$] (Cy, cyclohexyl), formed *in situ* from [$Pd(OAc)_2$] and PCy_3, catalyzes the room-temperature coupling of primary alkyl bromides that possess β-hydrogens with alkyl-BBN (BBN, 9-borabicyclo[3.3.1]nonane) [127, 128]. A similar complex, formed from [$Pd_2(dba)_3$] and PCy_3 (1 : 2 ratio of Pd to phosphine), allowed couplings of primary alkyl chlorides that possess β-hydrogens with alkylboranes [129]. The complex [Pd(PCy_3)$_2$] and the related complexes with other monodentate bulky phosphines are catalysts for the Kumada coupling of alkyl chlorides [130].

For the coupling of primary alkyl tosylates, the bulkier phosphine P(tBu)$_2$Me gave the best results [131]. As expected, the oxidative addition of an alkyl tosylate to Pd(0) results in predominant inversion of configuration, while the transmetallation occurs with retention [131]. The complex [Pd(P(tBu)$_2$Me)$_2$] is also a catalyst for the room-temperature coupling of primary alkyl bromides that possess β-hydrogens with boronic acids [132]. Complex **11**, the oxidative addition product of an alkyl bromide to [Pd(P(tBu)$_2$Me)$_2$], has been isolated and structurally characterized [132]



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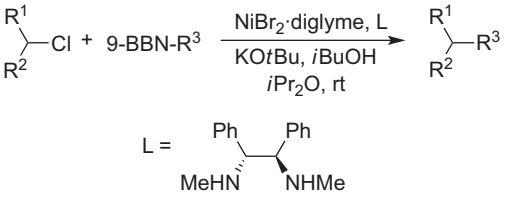
Scheme 1.8 Oxidative addition of a primary alkyl bromide to the palladium complex [Pd(P(tBu)$_2$Me)$_2$].

(Scheme 1.8). The Stille coupling of alkenylstannanes with alkyl bromides that possess β-hydrogens is possible at room temperature, with $[Pd(P(tBu)_2Me)_2]$ as the catalyst [133]. In this case, the addition of fluoride was required to enhance the reactivity of the stannane.

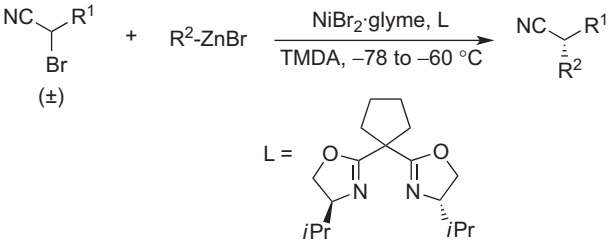
Interestingly, while with isolated $[Pd(P(tBu)_3)_2]$ high temperatures are required for the activation of aryl halides in the Suzuki–Miyaura coupling [134], as well as the amination [113d] and Heck reaction [112], the complex that results from the reaction between $[Pd_2(dba)_3 \cdot dba]$ and 1 equiv. of $P(tBu)_3$ allows performing these reactions at room temperature [105d, 112, 135–137]. Under these conditions, aryl chlorides are coupled in preference to aryl triflates [135]. The less bulky PCy_3 could be used for the Suzuki–Miyaura reaction of aryl triflates. Related bulky phosphines also allow performing the Suzuki–Miyaura couplings under relatively mild conditions [118].

Secondary alkyl halides are a much more challenging class of electrophiles for cross-coupling reactions [138]. The use of nickel catalysts allows coupling of these substrates with organoboranes in the presence of a 1,2-diamine ligand (Scheme 1.9) [139]. Similar results have been obtained in the Negishi couplings with nickel catalysts [140].



Scheme 1.9 Cross-coupling of a secondary alkyl halide with an organoborane reagent catalyzed by $NiBr_2 \cdot$diglyme.

Interestingly, the use of nickel catalysts with chiral ligands allows performing the stereoconvergent Suzuki–Miyaura or Negishi cross-couplings of racemic electrophiles with organometallic nucleophiles. Thus, the stereoconvergent cross-coupling of racemic α-halonitriles has been achieved by nickel-catalyzed Negishi arylations and alkenylations (Scheme 1.10) [141]. For this reaction and the

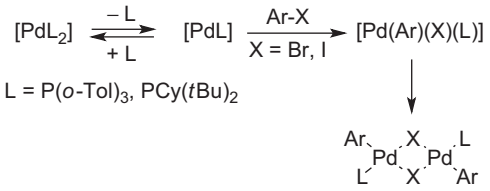


Scheme 1.10 Ni-catalyzed stereoconvergent reaction of a racemic α-halonitrile.

other related nickel-catalyzed Negishi, Hiyama, and Suzuki–Miyaura reactions of unactivated secondary alkyl halides, radical intermediates may be involved [140, 142–144].

All the experimental evidence points to the involvement of Ni(I)–Ni(III) catalytic cycles in Ni-catalyzed Kumada-type and related couplings [144a,b,c –146]. A theoretical study on the Ni-catalyzed cross-coupling of unactivated secondary alkyl halides with alkylboranes confirms that the reaction proceeds through a catalytic cycle involving a Ni(I)–Ni(III) transformation [144c]. This catalytic cycle involves a rate-determining transmetallation of [Ni(L)Br] with K[B(Me)$_2$(Et)(O*i*Bu)] to form [Ni(L)Et], followed by the oxidative addition of *i*PrBr with [Ni(L)Et] by bromine abstraction and radical recombination to give [Ni(L)(*i*Pr)(Et)Br]. The C–C reductive elimination of [Ni(L)(*i*Pr)(Et)Br] leads to [Ni(L)Br] and the coupled product. On the other hand, the oxidative addition of *t*BuBr generates a *t*Bu radical and singlet [Ni(L)(Et)Br], which equilibrates to the triplet [Ni(L)(Et)Br] through facile spin crossover, which raises significantly the overall activation barrier of the reductive elimination. This explains why tertiary halides are not reactive in the title cross-coupling [144c].

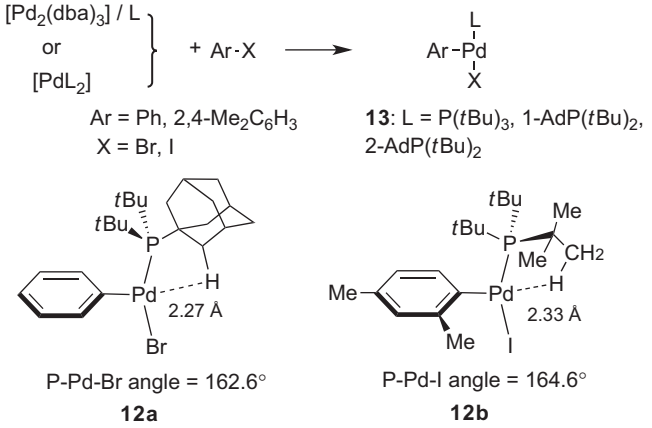
The Pd/P(*t*Bu)$_3$ system was also applied for the Stille reaction with aryl electrophiles using CsF as the activator for the stannane [147]. Mechanistic work suggested that a palladium monophosphine complex [PdL] is the active catalyst in the cross-coupling of aryl halides [135, 136]. Accordingly, Hartwig [147–149] proposed that the oxidative addition of an aryl bromide to the complex [Pd(P(*o*-Tol)$_3$)$_2$] involved prior dissociation of a phosphine ligand giving a 12e-complex [Pd(P(*o*-Tol)$_3$)] (Scheme 1.11). Addition of a second equivalent of ligand then leads to the dimeric complexes. This process involves the dissociative ligand substitution and cleavage to the monomers, before the reductive elimination [150].



Scheme 1.11 Oxidative addition from [PdL$_2$] complexes with very bulky monodentate phosphines.

Brown *et al*. [151] reported that [Pd(PCy$_3$)$_2$] reacts with PhOTf according to an associative mechanism. Reaction of PhI with [Pd(PCy$_3$)$_2$] or [Pd(PCy$_2$(*t*Bu))$_2$] also proceeded associatively. In contrast, complexes [Pd(P(*t*Bu)$_3$)$_2$] or [Pd(PCy(*t*Bu))$_2$] with bulkier phosphines behaved like [Pd(P(*o*-Tol)$_3$)$_2$].

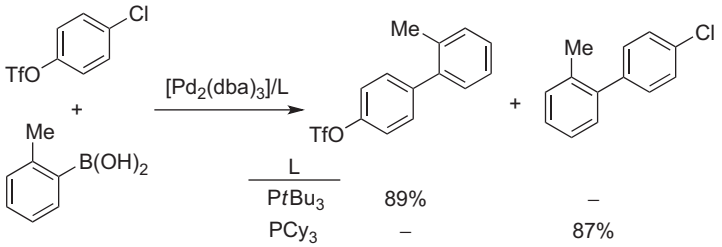
Hartwig [152] also reported the isolation of formally tricoordinated, T-shaped, Pd(II) complexes **12** in the oxidative addition of ArX to [PdL$_2$] or [Pd(dba)L], bearing very bulky phosphines (Scheme 1.12). Two of these complexes **12a**,**b** showed agostic interactions with C–H bonds of the phosphine resembling distorted square-planar



Scheme 1.12 Formation of tricoordinated Pd(II) complexes from $[PdL_2]$ with very bulky monodentate phosphines.

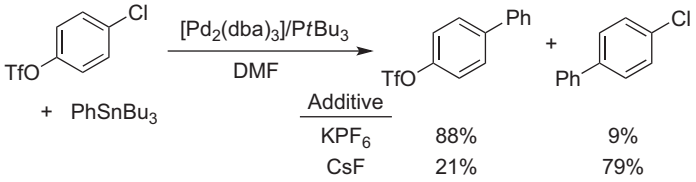
Pd(II) complexes. A related platinum complex shows a seemingly three-coordinate Pt(II) core [153], although the metal is actually stabilized by an agostic interaction with one of the methyl groups of the phosphine ligand.

The Suzuki–Miyaura cross-coupling of 4-chlorophenyl triflate led regioselectively to different products using PCy_3 or $PtBu_3$ as the ligands for Pd(0) (Scheme 1.13) [135, 151, 152, 154, 155]. The oxidative addition of the C–Cl bond is promoted selectively by $[PdP(tBu)_3]$, formed *in situ* from $[Pd_2(dba)_3]$ and $P(tBu)_3$ [135], whereas reaction through the triflate occurs with $[Pd(PCy_3)]$ [156]. The reason for this regiocontrol was rationalized by computation analyzing the bond dissociation energies (BDEs) [157]. On the basis of this analysis, monocoordinated palladium species preferentially react with the C–Cl bond, which is easier to distort and, therefore, would be of higher reactivity than the C–OTf bond. On the other hand, the most nucleophilic species, PdL_2, reacts through a more distorted transition state with the C–OTf bond, which is the site of lowest LUMO (lowest unoccupied molecular orbital) energy.



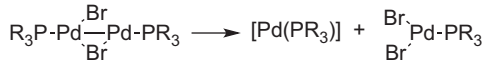
Scheme 1.13 The Suzuki–Miyaura cross-coupling of 4-chlorophenyl triflate leading regioselectively to different products using PCy_3 or $PtBu_3$ as the ligands for Pd(0).

4-Bromophenyl triflate reacted in the Stille coupling with vinyl tributylstannane through the Ar–Br bond in the absence of additives, whereas in the presence of LiCl, the Ar–OTf bond was selectively activated [158]. In the Kumada couplings, bulky monophosphine palladium catalysts favor the reaction of bromides over triflates, while a chelating diaryldiphosphine activates the bromide [159]. The Negishi coupling occurred at the triflate site [155]. Theoretical studies and experimental results using $[Pd_2(dba)_3]/PtBu_3$ as the catalytic system and 4-chlorophenyl triflate as the substrate provided strong support of a change in the catalytically active species in polar solvents depending on the additives (Scheme 1.14) [160]. Calculations show a preference for the oxidative addition of the Ar–Cl bond to $[Pd(P(tBu)_3)_2]$, although in the presence of CsF, activation of the Ar–OTf bond is observed. These results suggest that the active species under such conditions in polar solvents is $[Pd(P(tBu)_3)_2F]^-$ in agreement with the proposals of Amatore and Jutand of anionic palladium as the active catalytic species [91, 92], in line with conclusions by Hartwig [161].



Scheme 1.14 The Stille cross-coupling of 4-chlorophenyl triflate leading regioselectively to different products using KPF_6 or CsF as additives.

In support of the involvement of $[Pd(PR_3)]$ in the oxidative addition, Pd(I) dimers **13a,b** have been found to catalyze the room-temperature amination and the Suzuki–Miyaura couplings of aryl chlorides and bromides (Scheme 1.15) [162]. These palladium dimers decompose to form the palladium dibromide $[Pd(PR_3)Br_2]$ and a highly reactive Pd(0) complex $[Pd(PR_3)]$ [162, 163].



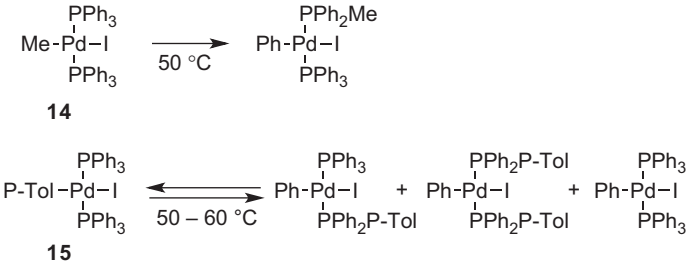
13a $PR_3 = P(1\text{-Ad})(t\,Bu)_2$
13b $PR_3 = P(tBu)_3$

Scheme 1.15 Formation of highly reactive [PdL] complexes from Pd(I) dimers.

The highly reactive catalyst $[PdPtBu_3]$ can be generated by fast 1 : 1 micromixing of $[Pd(OAc)_2]$ and $PtBu_3$ and can be quickly transferred to the reaction vessel using a flow system to perform the Suzuki–Miyaura couplings [164].

In the quest for coordinatively unsaturated palladium catalysts, the more radical approach uses "ligandless conditions" [165, 166] following the work pioneered by Beletskaya [38b, 167]. However, the mechanism of cross-coupling reactions under these conditions is not known [168].

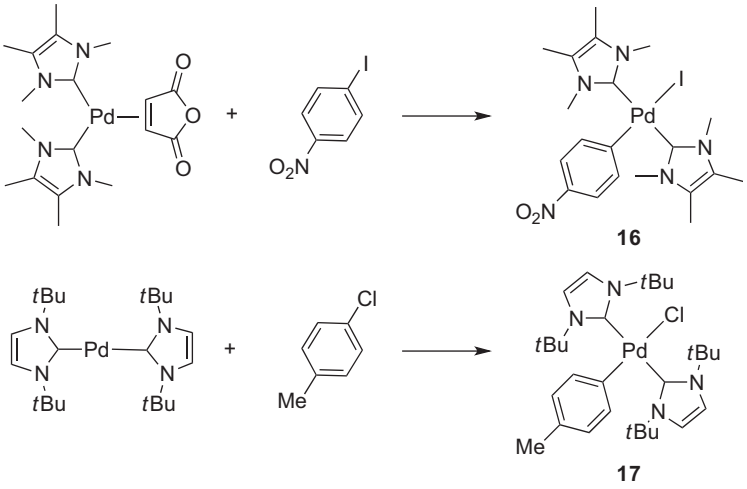
1.1.2.3.1 **Scrambling with the Phosphine** Exchange between R residues on palladium and the phosphine ligand can take place under very mild conditions (Scheme 1.16), which may lead to homocoupling [169–171]. In a study with complexes such as **14** [169], the rate was not affected by the added Ph_3. However, the rearrangement of arylpalladium(II) complexes **15** was nearly completely inhibited by Ph_3 [170]. The contradiction has been addressed by Novak [172], who demonstrated that the aryl–aryl interchange reaction of $[PdArL_2X]$ proceeds first through a reductive elimination to form a phosphonium salt followed by an oxidative addition of a different phosphorus–carbon bond. The interchange and phosphonium salt formation reactions alike are facilitated by the predissociation of either phosphine or iodide.



Scheme 1.16 Scrambling of alkyl/aryl iodide residues with those on the phosphine ligands.

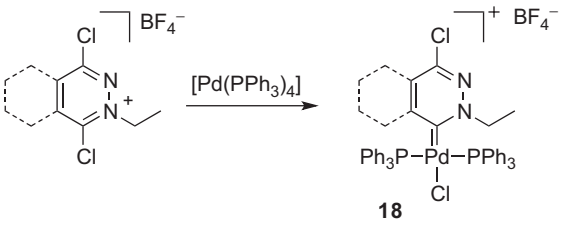
1.1.2.4 **N-Heterocyclic Carbenes as Ligands**

N-heterocyclic carbenes (NHCs) have demonstrated their utility as ligands in a variety of cross-coupling reactions [173–176]. The oxidative addition of aryl halides to $[PdL_2]$ (L = N-heterocyclic carbene) has been shown to furnish the expected *trans*-square-planar complexes such as **16** and **17** (Scheme 1.17) [177, 178].



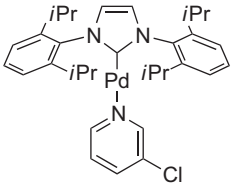
Scheme 1.17 Oxidative addition products with N-heterocyclic carbenes as ligands.

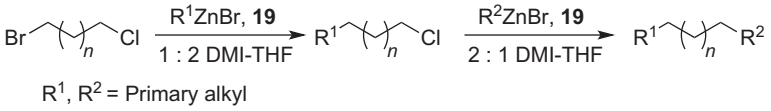
Interestingly, NHC–palladium(II) complexes **18** with unconventional pyridazine- and phthalazine-derived carbene ligands can be directly obtained by oxidative addition of pyridazinium or phthalazinium salts to [Pd(PPh_3)$_4$] (Scheme 1.18) [179].



Scheme 1.18 Oxidative addition of pyridazinium or phthalazinium salts to [Pd(PPh_3)$_4$].

Interestingly, while selective couplings through the more reactive alkyl bromides over alkyl chlorides can be achieved by performing the Kumada couplings at low temperature [180], similar selectivities can also be obtained by playing with the solvent in the Negishi couplings [181]. Thus, using a 1 : 2 ratio of DMI to THF (DMI, dimethylimidazolidinone) and NHC-Pd complex **19** as the catalyst [182], the coupling through the bromide was carried out at room temperature, while increasing the polarity of the medium allowed performing the coupling through the chloride (Scheme 1.19). Related palladium complexes with bulkier NHC ligands allow for the selective coupling of secondary zinc reagents with aryl halides and triflates by favoring the reductive elimination that competes with the β-hydride elimination [183].

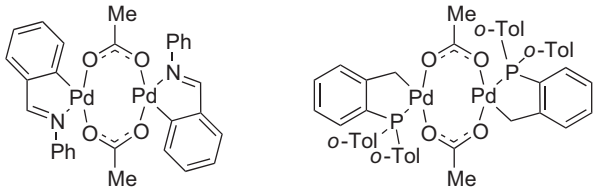




Scheme 1.19 The selective Negishi couplings through the more reactive alkyl bromide over alkyl chloride by playing with the solvent.

1.1.2.5 **Palladacycles as Catalysts**

Many palladacycles have also been described as useful catalysts for cross-coupling and the related reactions [184–192]. However, strong evidence has been accumulated indicating that the palladacycles merely act as a reservoir of Pd(II), which requires reduction to Pd(0) to enter into the catalytic cycle [189, 190, 193]. Thus, in a



20 **21**

Figure 1.1 Palladacycles used in the Heck reaction.

detailed study of the Heck reaction catalyzed by palladacycles **20** and **21** (Figure 1.1), Pfaltz and Blackmond [193] concluded that the resting state of the catalyst within the catalytic cycle was a Pd(II) intermediate derived from oxidative addition, while the majority of Pd remained outside the catalytic cycle as a dimer in equilibrium with the oxidative addition species.

Palladium nanoparticles and other heterogeneous catalysts are often invoked as catalysts in cross-coupling processes [194, 195]. Direct evidence in support of an oxidative-addition-promoted leaching mechanism has been recently obtained in the Suzuki–Miyaura reactions with nanoparticle catalysts, suggesting that true surface catalysis remains largely unknown with these heterogeneous catalysts [196].

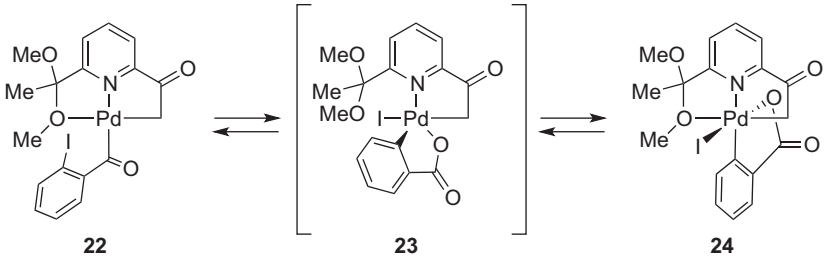
1.1.2.6 **Involvement of Pd(IV) in Catalytic Cycles**

Formation of Pd(IV) intermediates by oxidative addition of alkyl halides to Pd(II) complexes [197, 198] and in other oxidative processes [199] is a well-known process. However, C(sp^2)-X electrophiles, such as aryl halides, are much less reactive in the oxidative addition to Pd(II) complexes, and therefore, the formation of Pd(IV) species from these electrophiles is less likely. The hypothetical mechanism for the Heck reaction based on Pd(II)/Pd(IV) has been analyzed computationally [200].

Reaction of [Ph_2I]OTf with Pd(II) and Pt(II) gives metal(IV) species by formal transfer of Ph^+ to the metal center [201, 202]. Intramolecular oxidative additions of C–C bonds to Pt(II) to form hexacoordinated Pt(IV) complexes is also known [203].

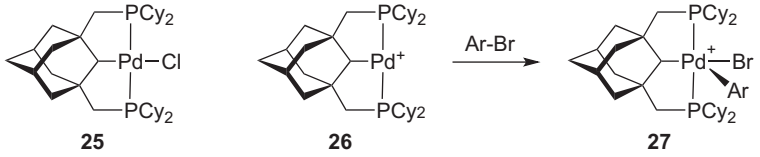
The first direct, clear-cut experimental evidence for the formation of Pd(IV) species by oxidative addition of an aryl iodide to Pd(II) was provided by the group of Vicente [204] (Scheme 1.20). The oxidative addition occurs intramolecularly on a palladacycle **22** with a particularly electron-rich Pd(II) center to form **24** via intermediate **23.** Although Pd(IV) complexes related to **24** can undergo insertion reactions with styrene and alkyl acrylates in a Heck process, the catalytic cycle involved is probably not particularly pertinent to most Heck catalytic Heck reactions [204b].

A Pd(IV) intermediate has also been proposed in the Negishi coupling using the pincer-Pd(II) complex **25** as catalyst [205]. Experimental and computational results suggested that a T-shaped 14e pincer complex **26** was the key intermediate, which undergoes oxidative addition with aryl bromides to yield the pentacoordinated



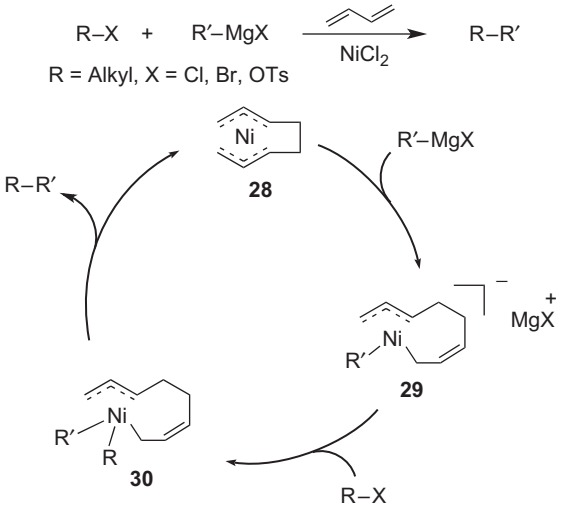
Scheme 1.20 First experimental evidence for the formation of Pd(IV) species by the oxidative addition of an aryl iodide to **22**.

Pd(IV) aryl bromide complex **27** (Scheme 1.21). Subsequent transmetallation of **27** with $Zn(Ar')_2$ followed by reductive elimination gives the coupling products.



Scheme 1.21 Proposed pincer-Pd(II) **25** and **26** intermediates that undergo oxidative addition.

A genuine coupling based on a group 10 M(II)/M(IV) catalysis is probably involved in the nickel-catalyzed coupling of alkyl halides and tosylates with the Grignard reagents discovered by Kambe (Scheme 1.22) [206]. A similar system has

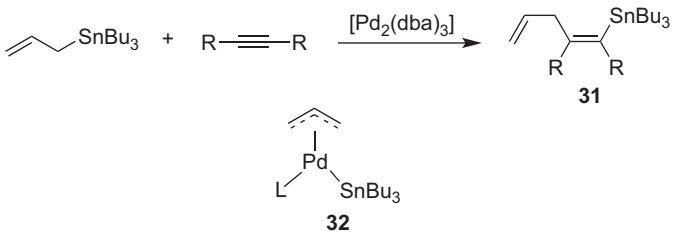


Scheme 1.22 Ni-catalyzed coupling of alkyl halides and tosylates with the Grignard reagents.

been developed for the catalytic C–C-bond-forming reaction using nonactivated alkyl fluorides by coupling of the alkyl Grignard reagents with $CuCl_2$ or $NiCl_2$ as the catalysts [206b]. In this system, a bis(η^3-allyl)nickel(II) complex **28** formed by an oxidative dimerization of butadiene is involved in the catalytic cycle (Scheme 1.22). The oxidative addition of the alkyl halide or tosylate to the electron-rich intermediate **29** probably forms the Ni(IV) complex **30**, which leads to the C–C bond formation by reductive elimination.

1.1.2.7 Oxidative Addition of Stannanes to Pd(0)

Oxidative addition of certain stannanes to Pd(0) complexes is also possible. Thus, alkynylstannanes have been shown to react with Pd(0) complexes [207, 208]. In addition, the Pd(0)-catalyzed reaction of allylstannanes with alkynes has been found to afford allylstannylation products **31** (Scheme 1.23) [209]. A likely mechanism involves oxidative addition of the allylstannanes to Pd(0) to give (η^3-allyl)palladium complexes **32** (L = alkyne) (Scheme 1.23). In this transformation, the usually nucleophilic allylstannanes behave as electrophiles. Complexes of type **32** are probably formed by transmetallation of (η^3-allyl)palladium complexes with hexamethylditin [210]. An oxidative addition to form complexes **32** has been proposed in the Pd(0)-catalyzed carboxylation of allylstannanes with CO_2 [211]. Although complexes **32** have not been isolated as stable species, work on the intramolecular reaction of allylstannanes with alkynes and theoretical calculations give support to the formation of these complexes by the oxidative addition of allylstannanes to Pd(0) [212].

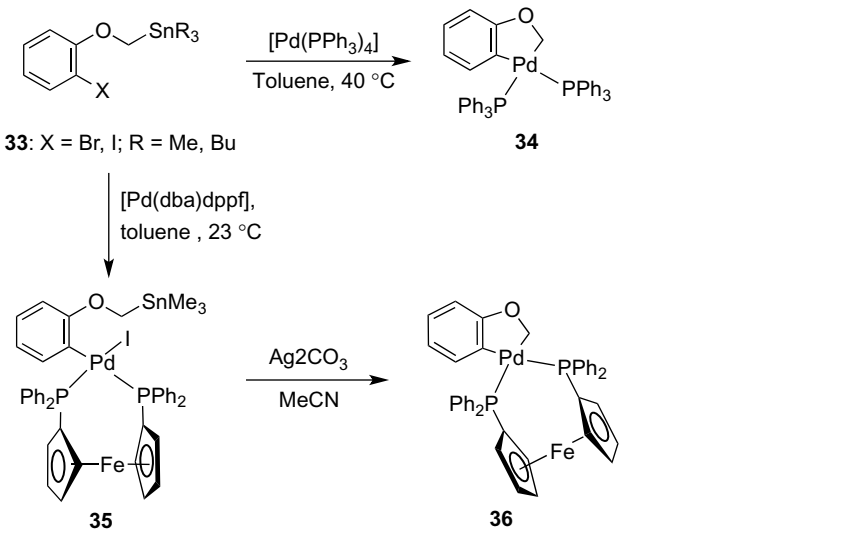


Scheme 1.23 Allylstannylation of alkynes by oxidative addition of allylstannanes to Pd(0).

1.1.3 The Transmetallation in the Stille Reaction

1.1.3.1 Isolation of the Transmetallation Step

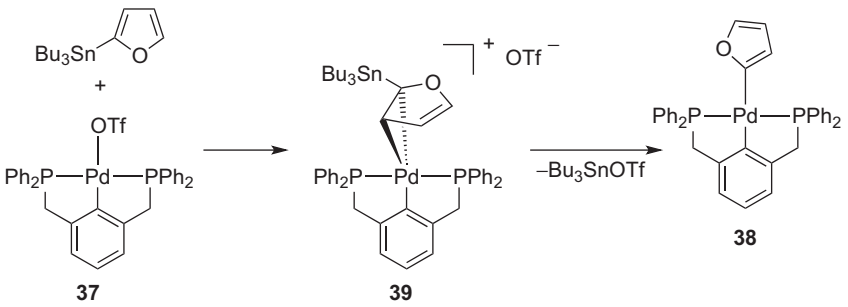
The transmetallation step was studied for an intramolecular case with systems **33** (X = Br, I), which undergo oxidative addition to $[Pd(PPh_3)_4]$ to give intermediate complexes that suffered transmetallation to form palladacycles **34** that do not undergo reductive elimination because of the high ring strain of the expected four-membered-ring heterocycles [213] (Scheme 1.24). The product of oxidative



Scheme 1.24 Isolation of transmetallation intermediates in the Stille reaction.

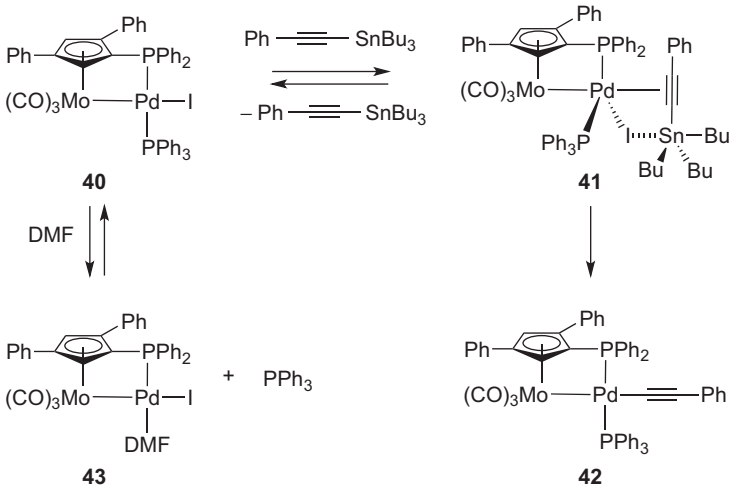
addition **35** was isolated presumably because the sterically demanding dppf (bis(1,1′-diphenylphosphino)ferrocene) ligand prevents the necessary alignment of the Pd–I and C–Sn bonds in the transition state of the transmetallation. However, smooth transmetallation was achieved by formation of the carbonate by reaction with Ag_2CO_3 to form palladacycle **36**, presumably through an open transition state [213b]. Similar systems were used in a study on the transmetallation of silanes with Pd(II) [214] and stannanes with Pt(II) [215].

The reaction of pincer triflato complex **37** with 2-(tributylstannyl)furan allowed isolating the transmetallation product **38** as a stable compound (Scheme 1.25) [216]. Furthermore, by performing the reaction at low temperature, intermediate **39** was observed in which the furan is η^2-coordinated to the palladium center.



Scheme 1.25 Isolation of a η^2-furyl palladium(II) complex in a transmetallation reaction.

In a study on the transmetallation of the bimetallic complex **40** with alkynylstannanes, a different precoordinated palladium intermediate **41** was observed, which evolved to the alkynyl-Pd(II) complex **42** (Scheme 1.26) [217, 218].

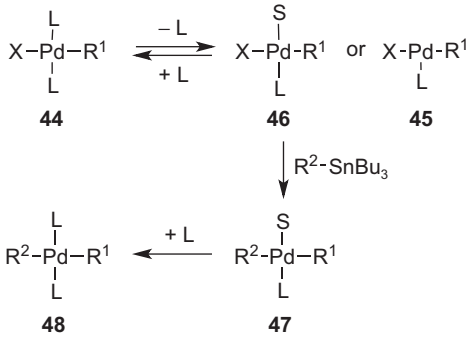


Scheme 1.26 Transmetallation intermediates in the palladium-catalyzed metal–carbon bond formation.

1.1.3.2 **Dissociative Mechanistic Proposals**

It has been shown that the addition of a neutral ligand L retards the coupling [219, 220]. In addition, ligands such as trifurylphosphine [221, 222] and triphenylarsine [55, 220, 223], which are of lower donicity than PPh_3, have a beneficial effect in the Stille reaction. These results have been taken as an indication that ligand dissociation is a key step in the transmetallation.

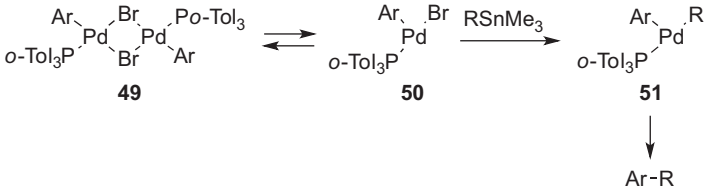
Thus, the simplified mechanism in Scheme 1.27, involving a dissociative X-for-R^2 substitution (X = I, Br) with preservation of the configuration at Pd, was



Scheme 1.27 Mechanistic scheme for the dissociative transmetallation in the Stille reaction.

proposed for vinyl- and arylstannanes. It was assumed that **44** cannot undergo transmetallation, probably because it is too electron rich, and ligand dissociation occurs prior to the transmetallation to form coordinatively unsaturated **45** or, more likely, **46**, with a coordinated solvent molecule. The more electrophilic complex **46** would then be involved in the transmetallation with stannane to give **47**, which could then afford the trans-configured complex **48**.

Although the preceding interpretation has been disputed (Sections 1.1.3.3 and 1.1.3.4), a dissociative transmetallation probably takes place with complexes bearing very bulky ligands. Thus, Hartwig found that for the transmetallation of dimers [PdArBr{P(*o*-Tol)3}]2 **49** [149], the rate depended on the square root of the concentration of dimer (Scheme 1.28). This is consistent with a dissociative mechanism, in which T-shaped monomers **50** [219] react with the organostannane, presumably through **51**, to give the coupled product Ar-R.



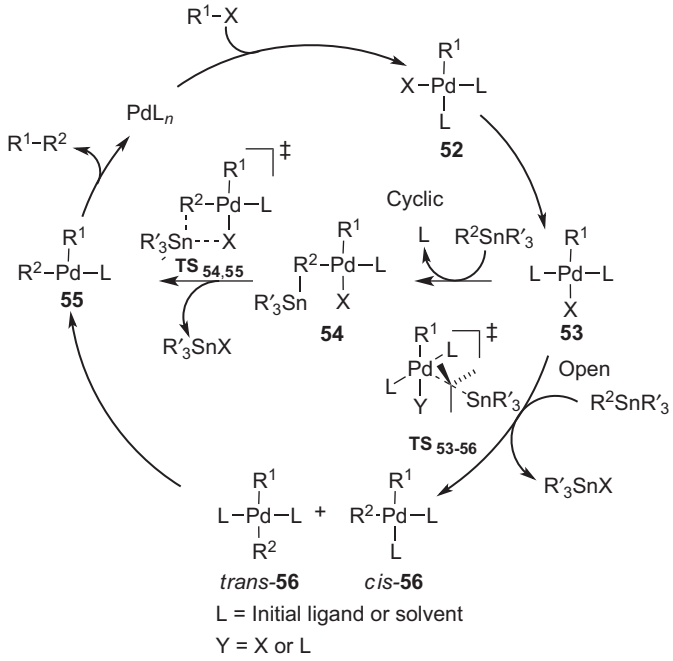
Scheme 1.28 Transmetallation of T-shaped Pd(II) complexes with organostannanes.

1.1.3.3 Cyclic and Open Associative Transmetallation

The proposals for a dissociative transmetallation assume that the trans configuration of complex **44** to give a *trans*-[$PdR^1R^2L_2$] complex **48** is preserved (Scheme 1.27). As the reductive elimination of R^1-R^2 is well established to occur on cis-configured derivatives, a fast isomerization of *trans*- to *cis*-[$PdR^1R^2L_2$] needs to be postulated (Scheme 1.29). An important additional problem with mechanisms based on ligand dissociation is that this type of substitution is rare for Pd(II) [224].

Kinetic studies on the palladium-catalyzed coupling of substrates such as 1-iodo-3,5-dichlorotrifluorobenzene with vinyl- or (4-methoxyphenyl)tributyltin carried out by the group of Espinet [225–228] led to a comprehensive proposal for the mechanisms of the Stille reaction that includes both open and cyclic transmetallation steps (Scheme 1.29). The transmetallation in the cyclic mechanism involves an associative substitution (L for R^2) through intermediate **54** and transition state $\mathbf{TS_{54,55}}$ to give directly a *cis*-R^1/R^2 complex 55, from which the coupled product will immediately lead to the formation of R^1-R^2 by reductive elimination. A post-transmetallation intermediate *cis*-[$PdR^1R^2L(ISnBu_3)$] in the cyclic mechanism was spectroscopically detected [229].

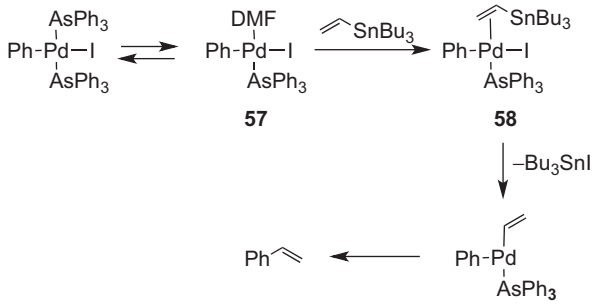
The proposal in Scheme 1.29 explains the observed dependence on L and produces immediately the cis arrangement needed for fast R^1-R^2 coupling. The known inverse relationship between ligand donor ability and transmetallation rate [14, 52, 219, 220] supports the dissociative model because ligands of modest donicity



Scheme 1.29 Mechanism of the Stille reaction based on an open/cyclic associative transmetallation.

(such as $AsPh_3$) would be more easily displaced in an associative substitution process.

The coupling of iodobenzene and vinyltributylstannane with $[Pd(dba)(AsPh_3)_2]$ in dimethylformamide (DMF) was examined by Amatore and Jutand (Scheme 1.30) [89, 230]. In this study, the transmetallation was proposed to occur on intermediate **58**, formed by consecutive ligand substitutions via **57**.



Scheme 1.30 Coordination to Pd(II) for the selective alkenyl transmetallation.

The open transition state operates in cases where no bridging groups are available on the coordination sphere of Pd(II) to produce a cyclic intermediate [227]. The

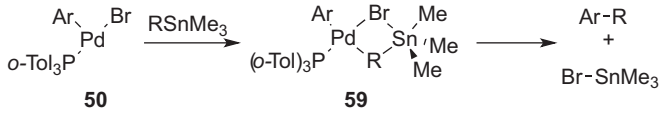
S_E(open) transmetallation mechanism, proceeding through transition state $\mathbf{TS_{53-56}}$ (Scheme 1.30), is the only possible path in the absence of bridging ligands, but it can also operate in the presence of the ligands. It implies X-for-R^2 or L-for-R^2 replacement at the Pd center, leading competitively to cis and trans arrangements to give complexes **56a,b** and produces inversion of configuration at the α-carbon transferred from the stannane. This mechanism is favored by the use of polar, coordinating solvents, lacking bridging ability. It might also operate in the presence of an excess of L and with easily leaving anionic ligands lacking bridging ability, in which case transmetallation proceeds from cationic complexes. This mechanism also occurs in the coupling of aryl triflates with vinyltributylstannane in the presence of dppe (bis(1,2-diphenylphosphino)ethane) as the ligand [228].

The fact that the transmetallation step in the Stille reaction can follow two different paths, S_E2(cyclic) and S_E2(open), has important stereochemical consequences, as this transformation determines the stereochemical outcome of the overall coupling reaction with C(sp^2)-X electrophiles. Therefore, retention of the configuration would be expected for an S_E2(cyclic) pathway, while an S_E2(open) mechanism would result in overall inversion of configuration. This clarifies the contradictory stereochemical results reported in the literature. Thus, Falck [58] reported 98% retention of configuration in the coupling of chiral α-alkoxystannanes with acyl chlorides in toluene, which would proceed along a cyclic pathway. On the other hand, Labadie and Stille [57] found inversion (≥65%) in the coupling of a chiral benzylic stannane to an acyl chloride in HMPA (hexamethylphosphoric triamide). In the last example, the use of a highly polar and coordinating solvent favors the open pathway, even in the presence of a potentially bridging chloride ligand.

This comprehensive mechanistic proposal advanced by the group of Espinet [231] was supported theoretically. This study shows that both transmetallations with alkenylstannanes occur in two steps. First, a ligand substitution takes place, followed by an intramolecular transmetallation. In the cyclic mechanism, this second step requires the highest activation energy. In the open process, the transmetallation occurs by an S_N2 reaction at the tin center with the X^- as the incoming group and the alkenyl as the leaving group. In this case, in contrast to the cyclic mechanism, the first step has the highest energy barrier in the process.

An in-depth study of the Stille reaction of alkynylstannanes with aryl iodides reveals the high complexity of many cross-coupling processes, in which the often ignored isomerization reactions can compete with the oxidative addition or the transmetallation as the slow steps in the overall process [232]. The effect of ligands as well as that of fluoride anion in the Stille reaction has been studied in detail computationally within this overall mechanistic scenario [233].

However, when very bulky ligands are used, a dissociative mechanism probably operates through T-shaped intermediates such as **50** (Scheme 1.31) [149, 219]; these intermediates may then evolve by S_E2 (cyclic) transmetallation with the organostannane via **59**.



Scheme 1.31 Transmetallation from T-shaped Pd(II) complex **50**.

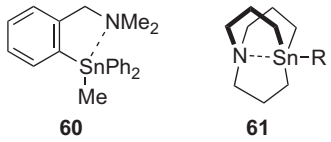
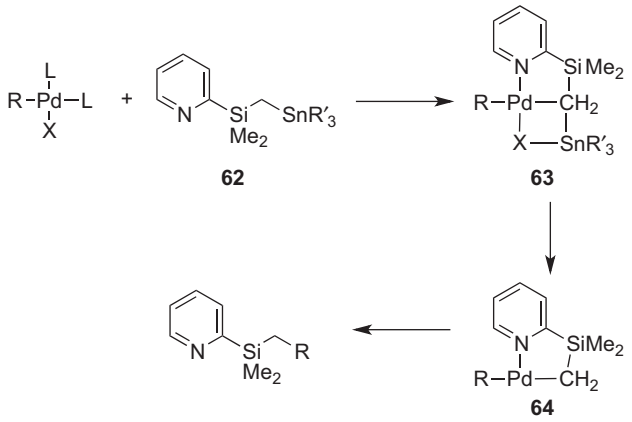


Figure 1.2 Internal coordination to tin favors transmetallation to Pd(II).

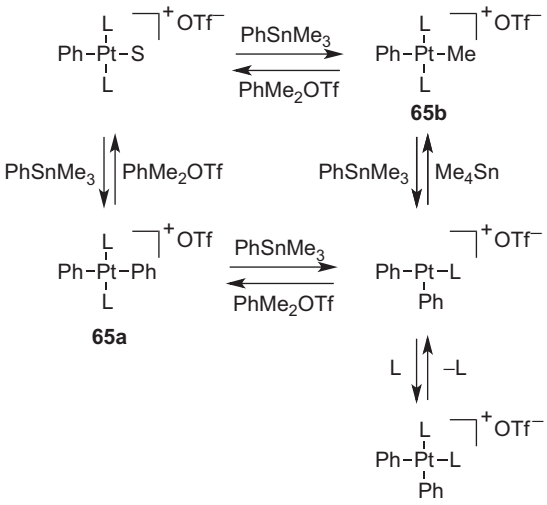
The open-associative mechanism probably operates in the Stille reaction carried out in the presence of additives such as fluoride [147] and hydroxide anion [234]. Similarly, coordination of tin to the nitrogen of benzylamines **60** [235] and stannatrane derivatives **61** [236, 237] (Figure 1.2) presumably leads to transmetallation by an S_E2(open) mechanism.

A different type of coordination is involved in a system developed by Yoshida for the selective transfer of the $Me_3SiCH_2^-$ group from **62** (Scheme 1.32) [238]. In this case, coordination of the pyridine nitrogen to Pd(II) as shown in **63** favors the intramolecular transmetallation through an S_E2(cyclic) intermediate. However, a trans-to-cis isomerization is now required for the reductive elimination of complex **64**.



Scheme 1.32 Coordination to Pd(II) for the selective alkyl transmetallation.

In a model study for the Stille reaction using platinum instead of palladium, the transmetallation reaction between *trans*-[PtPh(OTf)(PMe_2Ph)$_2$] and $PhSnMe_3$ was found to give simultaneously *trans*-[$PtPh_2(PMe_2Ph)_2$] and *cis*-[$PtPh_2(PMe_2Ph)_2$]



Scheme 1.33 Transmetallation reaction between *trans*-[PtPh(OTf)$(PMe_2Ph)_2$] and $PhSnMe_3$ gives both *trans*-[$PtPh_2(PMe_2Ph)_2$] and *cis*-[$PtPh_2(PMe_2Ph)_2$].

(Scheme 1.33) [239]. In THF, the intermediate *trans*-[PtPhMe$(PMe_2Ph)_2$] was also detected in the pathway involving the formation of *cis*-[$PtPh_2(PMe_2Ph)_2$]. In this mechanism, the initial attack takes place trans to the phenyl ligand leading to **64a,b**. Interestingly, the stannanes actually function as catalysts for the cis–trans isomerization.

1.1.3.4 **The Copper Effect**

An interesting phenomenon in the Stille couplings is the acceleration observed upon the addition of Cu(I) salts [52, 55, 58, 240–245].

Farina and Liebeskind [242] initially suggested that in highly polar solvents, a Sn/Cu transmetallation could take place, leading to the *in situ* formation of organocopper species, a proposal that later developed into effective coupling systems. Thus, Piers demonstrated that the intramolecular coupling of alkenyl iodides with alkenylstannanes can be carried out using CuCl in stoichiometric quantities [246, 247]. A new procedure of broad scope for the Stille reaction has been developed using both CuI and CsF as additives [248].

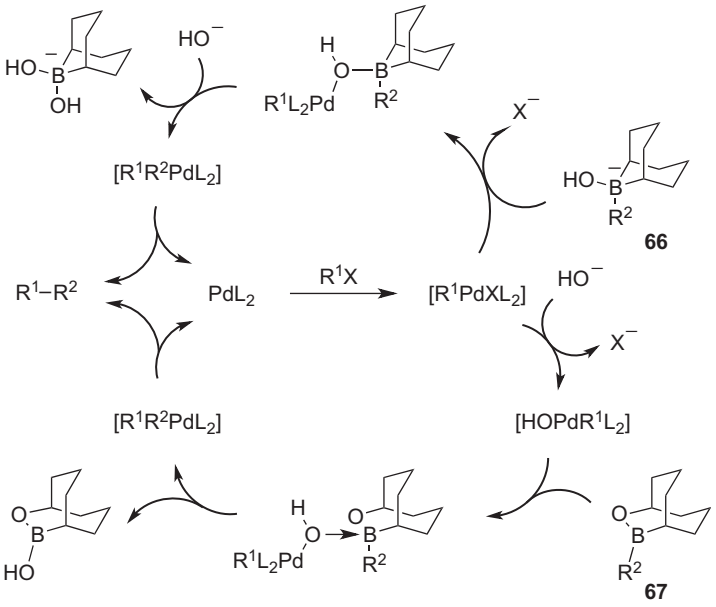
This copper effect was rationalized by Espinet within the framework provided by the associative mechanism. Accordingly, Cu(I) captures part of the free neutral ligand L released during the oxidative addition of [PdL_4] that yields the species actually undergoing transmetallation, *trans*-[PdR^1IL_2]. Therefore, Cu(I) would mitigate the "autoretardation" produced by the presence of free L on the rate-determining associative transmetallation [249].

Better results were later obtained using other Cu(I) salts, which allow the reaction to proceed under catalytic conditions [58b, 250–256].

Oxidation of the Pd(0) catalyst [$Pd(PtBu_3)_2$] to dinuclear Pd(I) complexes takes place in the presence of Cu(I) and Ag(I) salts [257]. For the Suzuki–Miyaura cross-coupling reactions with ArCl, the effect of oxidants depends on the anion. If X = I (i.e., CuI), the highly stable dinuclear complex [{$(PtBu_3)PdI\}_2$] is formed, which leads to slow transformations in cross-couplings. However, when X = Br, a more active precatalyst [{$(PtBu_3)PdBr\}_2$] is formed, which leads to [$PdPtBu_3$], a highly reactive species in the oxidative addition. In the case of Sonogashira couplings, the Pd(I) complexes react with the alkynes leading to products of polymerization, which explains the inhibitory effect of Cu salts in reactions with ArCl. Alternative cycles involving bimetallic Pd(I) were also suggested in this study [257]. The highly selective Pd-catalyzed C_{sp}–C_{sp} Sonogashira coupling of bromoalkynes has been achieved with very low loadings of palladium nanoparticles generated from $Pd(OAc)_2$ and tetrabutylammonium bromide, in the presence of CuI and iPr_2NH [258].

1.1.3.5 Transmetallation in the Suzuki–Miyaura Reaction

Owing to the low nucleophilicity of the borane reagents (compared with organostannanes, for example), the Suzuki–Miyaura, reaction in order to take place, requires the addition of a base. Stronger bases such as NaOH, TlOH, and NaOMe perform well in THF/H_2O solvent systems, whereas weaker bases such as K_2CO_3 and K_3PO_4 are usually more successful in DMF. The base is involved in several steps of the catalytic cycle, most notably in the transmetallation process. Soderquist [259] performed detailed mechanistic studies on the coupling of trialkylboranes and alkoxy(dialkyl)boranes with aryl and alkenyl electrophiles (Scheme 1.34).



Scheme 1.34 Catalytic cycles for the coupling of trialkylboranes (top) and alkoxy derivatives (bottom).

This study allowed determining the stereochemistry of the transmetallation step [259, 260] and the role of the base in the catalytic cycle. The main role of the base is to generate a more reactive boranate **66** by coordination of hydroxide to boron, which will react with the intermediate R-Pd(II)-X complex. On the other hand, in the case of the alkoxyboranes **67**, the base also reacts with the intermediate R-Pd(II)-X derivatives to form the more reactive R-Pd(II)-OH species (Scheme 1.34).

A detailed study of the transmetallation in the Suzuki–Miyaura reaction by the group of Amatore and Jutand shows that hydroxide [261] and fluoride anions [262] form the key *trans*-$[ArPdX(L)_2]$ complexes that react with the boronic acid in a rate-determining transmetallation. In addition, the anions promote the reductive elimination. Conversely, the anions disfavor the reaction by formation of nonreactive anionic $[Ar'B(OH)_{3-n}X_n]^-$ ($n = 1–3$). Countercations M^+ (Na^+, K^+, and Cs^+) of anionic bases in the palladium-catalyzed Suzuki–Miyaura reactions decelerate the transmetallation step in the following decreasing reactivity order: nBu$_4$NOH > KOH > CsOH > NaOH; this is due to the complexation of the hydroxy ligand in $[ArPd(OH)(PPh_3)_2]$ by M^+[263].

The two main mechanistic proposals for the role of the base in the transmetallation step of the Suzuki–Miyaura cross-coupling reaction, first attack at the palladium complex or at the boronic acid, were studied computationally by the group of Maseras [264]. These calculations were fully consistent with the experimental data and strongly suggested that the main pathway for the Suzuki–Miyaura catalytic cycle starts with the attack of the base on the organoboronic acid. The transmetallation can actually proceed by dissociative or associative mechanisms depending on the different nature of the ligands and other experimental conditions [265]. A theoretical study of the full catalytic cycle of the Suzuki–Miyaura coupling between bromobenzene and $PhB(OH)_2$ was carried out depending on the ligand in $[PdL_2]$ complexes and demonstrated that electron-poor ligands such as $P(CF_3)_2$ greatly facilitated the transmetallation step [266]. A theoretical study of the Suzuki–Miyaura reaction using diimine palladium complexes has also been reported [267].

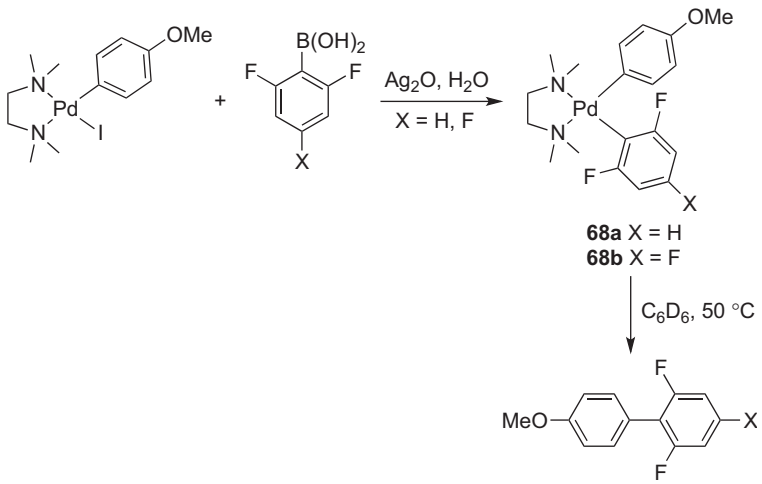
Several intermediates in the Suzuki–Miyaura coupling of bromopyridines with arylboronic acids have been identified by *in situ* analysis of the reaction by electrospray ionization mass spectrometry (ESI-MS) [268]. Interestingly, monitoring the coupling by ESI-MS demonstrates that, at the end of the reaction, there is an accumulation of binuclear Pd(0)-Pd(II) halide clusters, which are still catalytically active [269].

Chiral secondary boronic esters react with aryl iodides in the palladium-catalyzed Suzuki–Miyaura couplings with high retention of configuration, as expected in a transmetallation proceeding through a four-membered transition state [270, 271]. The cross-coupling of secondary organotrifluoroborates is also a stereospecific process that occurs with complete retention of the configuration [272]. In contrast, cross-coupling of potassium β-trifluoroboratoamides and α-(acylamino)alkylboronic esters proceeds with inversion of configuration as a result

of the presence of a strongly coordinating group that binds to the boronate during the transmetallation [273, 274].

Base-free C–C couplings of organoboron reagents have been carried out starting from perfluoroalkenes and fluorinated arenes [275]. In this reaction, the transmetallation occurred directly between the fluoride [$RPdL_2F$] and the organoboron compound. The first [$RPdL_2F$] complexes were reported by Grushin [276, 277] formed by reaction of organopalladium hydroxides with $Et_3N(HF)_3$ in the presence of free phosphine or by reaction of [$RPdL_2I$] with AgF. Related platinum fluoride complexes had been prepared before by reaction of liquid HF with [$Pt(PR_2Ph)_4$] complexes [278]. Fluoroarenes were also coupled with arylboronates using a Ni(0)/NHC catalyst [275]. Benzylic fluorides undergo the Suzuki–Miyaura coupling, presumably through intermediates of the type [$RPdL_2F$] [279].

Transmetallation products between arylboronic acids and platinum(II) halides or palladium(II) halides were isolated and characterized spectroscopically as well as by X-ray diffraction [280]. As expected, the reductive elimination of *cis*-diarylpalladium(II) complex **68a** was considerably faster than that of **68b** with a more electron-deficient fluorinated aryl ring (Scheme 1.35) [280a]. However, a kinetic study of the transmetallation between para-substituted arylboronic acids and cationic [$Pd(Ph)(PPh_3)(dppe)]BF_4$ showed a small negative ρ value (−0.54) [281]. It is interesting that the Hammett analysis of the palladium-catalyzed allyl–aryl coupling using aryl silicate derivatives revealed that the reaction is facilitated by electron-withdrawing groups on the arylsiloxane [282]. This result is consistent with either the transmetallation or the reductive elimination being the rate-determining step.



Scheme 1.35 Reductive elimination of *cis*-diarylpalladium(II) complexes **68a,b**.

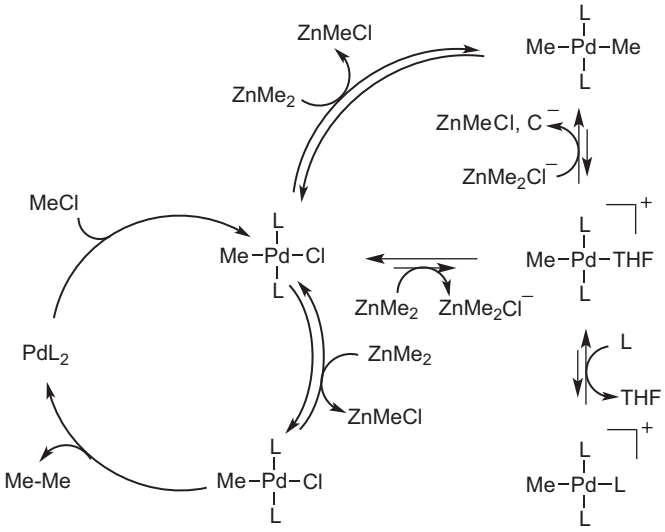
The transmetallation in the γ-selective Suzuki–Miyaura coupling between potassium allyltrifluoroborates with haloarenes is rate-determining and was shown

to occur on $[Pd(Ar)(L\text{-}L)]^+$ through an S_E2' (open) transition state according to experimental and theoretical studies [283].

Complexes of other metals have recently been found to catalyze the Suzuki-type reactions. Thus, platinum complexes catalyze the coupling between arylboronic acids and aryl halides [215], and $[Ni(PCy_3)_2Cl_2]$ is effective in the cross-coupling of arylboronic acids and aryl tosylates [284]. In this case, the usual mechanism involving oxidative addition of the aryl tosylate to $[Ni(PCy_3)_2]$, followed by transmetallation and reductive elimination, has been proposed. The study of the effects of the substituents on the electrophile and the boronic acid indicates that transmetallation is the rate-determining step. The mechanism of the Pd-catalyzed homocoupling of arylboronic acids has also been studied [285].

1.1.3.6 **Transmetallation in the Negishi Reaction**

The transmetallation step in a palladium-catalyzed Negishi reaction is a complex transformation that has been investigated combining experimental and theoretical studies (Scheme 1.36) [286]. The reaction between *trans*-$[PdMeCl(PMePh_2)_2]$ and $ZnMe_2$ in THF shows that in the absence of added phosphine, an ionic intermediate $[PdMe(PMePh_2)_2(THF)]^+$ leads to an ionic transmetallation pathway. In contrast, an excess of phosphine retards the reaction because of the formation of a highly stable cationic complex with three phosphines $[PdMe(PMePh_2)_3]^+$. The ionic pathway via cationic complexes with one weak ligand is faster than the concerted pathways via neutral intermediates.

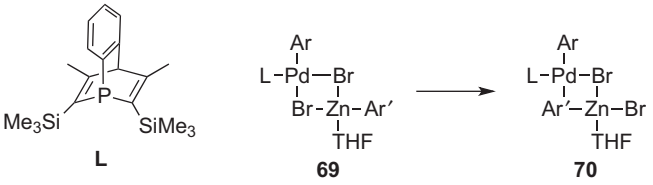


Scheme 1.36 Transmetallation in the Negishi reaction in the presence/absence of added phosphine.

This work demonstrated the existence of some competitive transmetallation pathways in the Negishi coupling reaction that had not been invoked before [286b].

Another experimental and theoretical investigation of the palladium-catalyzed Negishi coupling also showed the importance of a secondary transmetallation reaction between the intermediate $[PdAr^1Ar^2(L)_2]$ and the organozinc reagent Ar^2-ZnX to form $[Pd(Ar^2)_2(L)_2]$ and Ar^1ZnCl [287, 288]. The possible involvement of Pd-Zn species of type L_2Pd-ZnRX(S) in the Negishi coupling has been examined computationally [289].

A cyclic associative transmetallation of **69** to **70** through a low-energy transition state was proposed based on density functional theory (DFT) calculations for the Negishi coupling using $[\{Pd(allyl)Cl\}_2]$ and a bulky monodentate phosphabarrelene ligand (Scheme 1.37) [290].



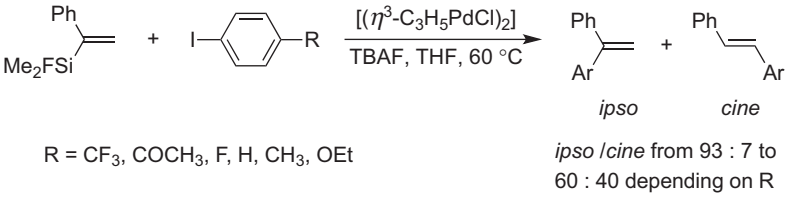
Scheme 1.37 Transmetallation of **69** to **70**.

Transmetallation has been demonstrated to be the rate-limiting step in the Sonogashira coupling reaction [291]. The transmetallation is also rate-determining in the nickel-catalyzed reaction between arylzinc reagents and α-chloro carbonyl compounds that proceeds via ArNi(II)R intermediates [292].

1.1.3.7 **Transmetallation in the Hiyama Reaction**

The lower reactivity of the Si–C bond requires the use of activating reagents to enhance the reactivity of silanes and to promote the Si-Pd transmetallations. Fluoride is the common additive, although other nucleophiles such as hydroxide, metal oxides, and alkoxides are also effective [30, 293, 294]. Fluoride converts the starting silanes into pentacoordinate fluorosilicates, which are the actual transmetallation reagents.

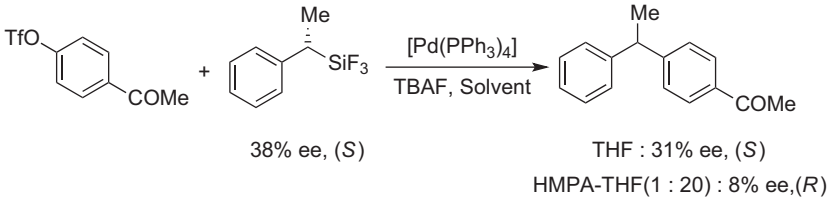
Transmetallation of alkenylsilanes takes place with retention of the double bond configuration, as in other cross-coupling reactions [295]. Owing to the lower transmetallation rate, competing 1,2-insertion of the alkene in the intermediate organopalladium complex (as a Heck type reaction) may take place, which affects the regioselectivity of the Hiyama reaction in some cases (Scheme 1.38) [296]. This



Scheme 1.38 The Hiyama reaction involving alkene insertion (as a Heck type reaction) before transmetallation.

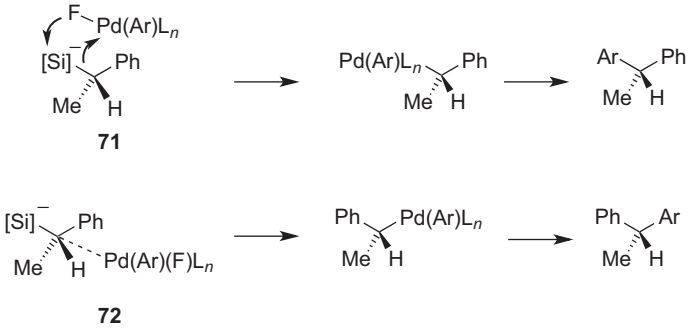
results in cine substitution, a process also observed in the Stille coupling reactions of some hindered alkenylstannanes [90].

Hiyama studied the stereoselectivity of alkyl transmetallation in the $[Pd(PPh_3)_4]$-catalyzed reaction of aryl triflates with enantiomerically enriched (*S*)-1-phenylethyltrifluorosilane in the presence of TBAF (tetrabutylammonium fluoride) [297]. At 50 °C, there was retention of the configuration, but at higher temperatures, a linear decrease in the degree of retention took place and finally, inversion was observed above 75 °C. A significant solvent effect was also observed. Thus, the reaction in THF resulted in retention. On the other hand, inversion was found in HMPA-THF (1 : 20) (Scheme 1.39).



Scheme 1.39 Solvent effect on the stereoselectivity of Si-Pd alkyl transmetallation.

The retention of configuration at low temperatures in THF can be explained assuming a fluorine-bridged S_E2(cyclic) transition state (**71**), analogous to that proposed for the Stille reaction formed from a pentacoordinate silicate (Scheme 1.40).



Scheme 1.40 Formation of arylpalladium amide complexes from alkoxy and hydroxy derivatives.

In polar solvents or at higher temperatures, the fluorine-silicon bridge would be cleaved to switch the transition-state model to the S_E2(open) (**72**), thus resulting in inversion. On the other hand, open and cyclic S_E2' mechanisms have been proposed to justify the observed stereochemistry in the γ-selective cross-coupling of allylsilanes [298]. Allylic silanolates undergo the palladium-catalyzed Hiyama cross-coupling with aromatic bromides with excellent stereoselectivity through a syn SE' transmetallation [299].

1.1.3.8 Couplings Catalyzed by Copper and Gold

Couplings with organocopper complexes under stoichiometric conditions are well established [300]. A copper-catalyzed coupling between arylboronates and primary alkyl halides or tosylates has also been developed using CuI and Li*O*t*Bu* [301]. Preliminary mechanistic studies exclude the involvement of a radical mechanism in this process, whereas the tBuO$^-$ anion was proposed to facilitate the transmetallation by coordinating with the boron atom. The related copper-catalyzed coupling of Grignard reagents with alkyl halides or tosylates proceeds by an S_N2 mechanism [180, 206b, 302].

The Kumada-type couplings catalyzed by copper probably involve Cu(I)/Cu(III) redox catalytic cycles [180, 206, 303–305]. Indeed, the oxidative addition of aryl halides to copper(I) to form well-characterized aryl-Cu(III) complexes has recently been reported [306].

Gold(I) was considered as a surrogate of palladium(0) in cross-coupling reactions, as both share the same d^{10} configuration [307]. There have been indeed some claims to this type of role for gold(I) in the Sonogashira-type [307–309] and the Suzuki coupling reactions [310, 311] via the usual d^{10} to d^8 redox pathway characteristic of palladium [312]. However, these claims have been disputed, and it now seems clear that at least in some cases the catalytic role is played by either small amounts of palladium contaminants [313–316] or gold nanoparticles [317, 318]. Although the minimal size of the reactive gold clusters is not known, recent results show that bisphosphine-ligated small gold clusters $[Au_3L_5]^+$ and $[Au_3L_6]^+$ react in the gas phase with iodobenzene by C–I bond activation [319].

The complex [AuCl(tht)] (tht, tetrahydrothiophene) can be used instead of Cu(I) as cocatalyst in the Sonogashira reactions catalyzed by $[PdCl_2(PPh_3)_2]$, although this Au(I) complex is inactive in the absence of palladium [320]. Gold and palladium have also been used as catalysts in the Sonogashira reactions of arenediazonium salts [321].

Additional examples of Au(I)/Pd(II) transmetallation have been reported [322], and palladium has been found essential to catalyze couplings involving organogold(I) compounds [314]. Complexes $[AuR(PPh_3)]$ also react with aryl and allyl electrophiles in cross-coupling reactions in the presence of palladium [323, 324] or nickel catalyst [325].

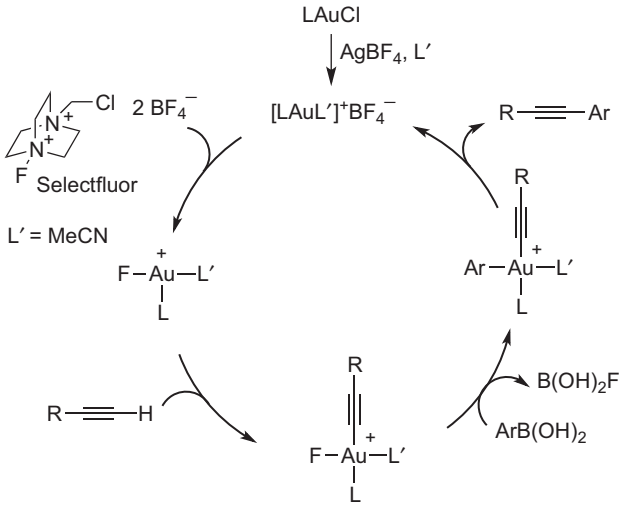
Arylgold(I) complexes $[AuAr(PPh_3)]$ react with terminal alkynes in the presence of $Pd(OAc)_2$ at room temperature in the presence of oxygen to form the corresponding coupling products [326]. This variant of the Sonogashira coupling, in which palladium(0) is oxidized by O_2 to palladium(II), most likely proceeds by transmetallation of the intermediate Pd(II) acetylides with the Au(I) aryl complex.

The oxidative addition of ArX to $[AuX(PPh_3)]$ would give Au(III) complexes $[AuArX_2(PPh_3)]$. However, the oxidative addition of aryl halide ArX to a Au(I) complex [AuXL] is unknown. Indeed, methylgold(I) complexes $[AuMePR_3]$ ($PR_3 = PMe_3$, PMe_2Ph, $PMePh_2$, PPh_3) behave as ordinary S_N2-type nucleophiles reacting slowly with alkyl iodides, with the expected order of reactivity: $CH_3I > EtI > i$PrI [327]. [IMesAuPh] (IMes, 1,3-di(2,4,6-trimethyl-phenyl) imidazol-2-ylidene) reacts with MeI (110 °C) or MeOTf (room temperature) to

form toluene, biphenyl, and ethane following an oxidative addition process [328]. On the other hand, reaction of [IMesAuPh] with PhI at 110 °C gives only biphenyl by a process that could involve the formation of gold nanoparticles.

It is important to note that other mechanisms could compete with other types of substrates. Thus, a radical mechanism is involved in the reaction between [$AuMePR_3$] and CF_3I [329], and disulfides undergo oxidative addition reactions with Au(I) dithiolate complexes [330]. Interestingly, it has been reported that relatively weak Si–Si bonds undergo oxidative addition to Au(I), and this has been found to be a favorable process [331].

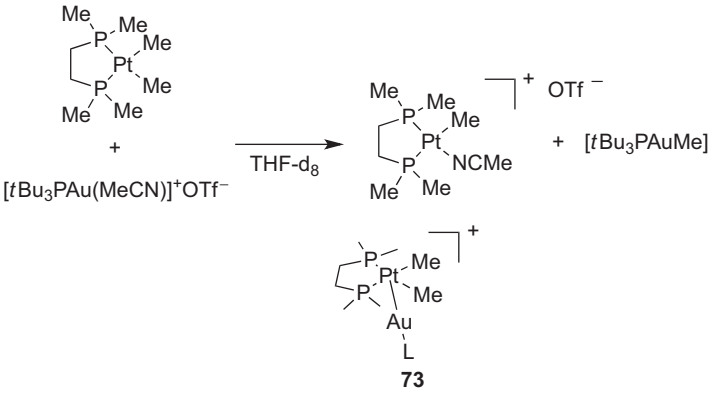
However, it has been demonstrated that in the presence of highly electrophilic reagents such as selectfluor, Au(I) can be oxidized to Au(III), thus allowing to complete the catalytic cycles based on gold [332–336]. A Sonogashira coupling has been developed through a Au(I)/Au(III) catalytic cycle (Scheme 1.41) [337]. In this transformation, the arylboronic acids were proposed to transmetallate with alkylgold(III) fluoride intermediates. Boronic acids $RB(OH)_2$ can also react with [AuXL] complexes by transmetallation to form [AuRL] complexes [338]. On the basis of the homocoupling of arylsilanes observed in gold-catalyzed oxidative additions to alkenes [339], a gold-catalyzed direct arylation was developed by treating arylsilanes with electron-deficient arenes using [$Au(PPh_3)OTs$] as the catalyst and $PhI(OAc)_2$ as the stoichiometric oxidant [340]. An oxidative cross-coupling between [$ArAuPPh_3$] complexes and electron-rich iodoarenes in the presence of PhI(OH)OTs has been recently developed for the synthesis of biaryls [341].



Scheme 1.41 The Sonogashira coupling thorough a Au(I)/Au(III) catalytic cycle in the presence of selectfluor.

Gold(I) complexes [AuR(L)] (L = tetrahydrothiophene) efficiently catalyze the isomerization of *trans*-[$Pd(R)_2(L)_2$] to *cis*-[$Pd(R)_2(L)_2$] via intermediates with Pd–Au bonds [342, 343]. The transmetallation between Pt(II) and Au(I) in the gas phase

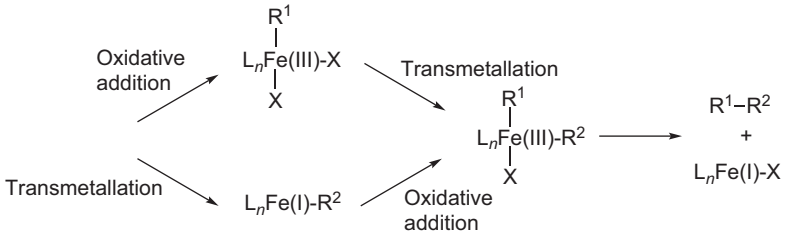
and in solution was found to proceed through related bimetallic intermediates of type **73** (Scheme 1.42) [344].



Scheme 1.42 Isomerization of *trans*-$[Pd(R)_2(L)_2]$ to *cis*-$[Pd(R)_2(L)_2]$ via intermediates with Pd–Au bonds.

1.1.3.9 **Couplings Catalyzed by Iron and Cobalt**

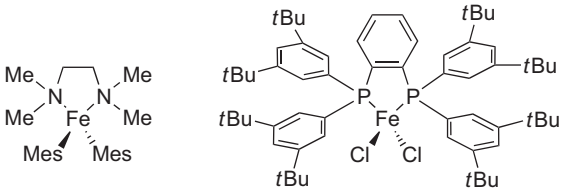
Iron catalysts have also been used for a variety of coupling reactions, although an in-depth knowledge of the mechanisms of these reactions is still lacking (Scheme 1.43) [345, 346].



Scheme 1.43 Proposed Fe-catalyzed coupling mechanisms.

It has been established that Fe(II) complexes such as **74** and **75** are active catalysts in iron-catalyzed cross-couplings of alkyl halides (Figure 1.3) [347, 348]. The couplings probably involve a Fe(I)–Fe(III) cycle, in which radical intermediates in the coupling step can be excluded, although they might be involved in the oxidative addition step [349, 350].

Cobalt catalysis has also received increased attention [351, 352]. Cobalt-catalyzed heterobiaryl coupling reactions between aryl chlorides and arylmagnesium halides take place with low loadings of $Co(acac)_3$ as the precatalyst under mild conditions [353]. Kinetic studies indicate that the active catalyst is an arylcobaltate(I) species.



74 **75**

Figure 1.3 Active catalysis in iron-catalyzed cross-couplings of alkyl halides.

1.1.4 Reductive Elimination

A theoretical study on the reductive elimination square-planar phosphine complexes *cis*-[$Pd(CH_3)_2L_2$] and *cis*-[$Pd(CH_3)(Cl)L_2$] shows that the activation energies depend on the σ-donating ability of L [354]. For bulky phosphine ligands, the steric effect is also significant.

Formation of T-shaped intermediates from square-planar complexes greatly accelerates the reductive elimination of [$Pd(L)_2RR'$] complexes [61].

The key C–C coupling in *cis*-[$PdR_2(PR'_3)_2$] complexes can occur directly, or on tetracoordinated intermediates *cis*-[$PdR_2(PR'_3)L$] formed by ligand substitution with addition of L, or on tricoordinated intermediates [$PdR_2(PR'_3)$] formed by phosphine dissociation [355]. Alkenes with electron-withdrawing substituents act as coupling promoters because the formation of a coupling intermediate *cis*-[$PdMe_2(PR_3)$(alkene)] can reduce the activation energy for the reductive elimination by up to 15 kcal mol^{-1}. However, this type of ligands disfavors the oxidative addition. Bulkier phosphines favor dissociative couplings leading to tricoordinated intermediates. This is particularly significant in the case of the more difficult alkyl–alkyl couplings.

The reductive elimination of a series of [$Pd(L\text{-}L)Me_2$] complexes revealed that only complex **76a** with $Cy_2PCH_2PCy_2$, with the smallest bite angle, leads to a smooth elimination of ethane, while complexes **76b**,**d**, with more stable chelates, do not eliminate ethane under mild conditions (Scheme 1.44) [61–63]. The reductive elimination from these complexes is most probably preceded by dissociation of one of the diphosphine arms to form a T-shaped intermediate [356]. The resulting Pd(0) complex [Pd(L-L)] undergoes dimerization to form complex **77**.

76a-d: n = 1–4 **77**

Scheme 1.44 Reductive elimination of ethane from dimethylpalladium complexes with diphosphine ligands **76a–d**.

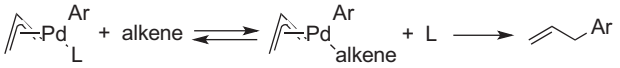
On the other hand, for a series of [Pd(L-L)Me_2] with L-L = dppp (bis(1,3-diphenylphosphino)propane), dppf, and dppr (1,1′-bis(diphenylphosphino)ruthenocene), the fastest elimination was observed for the ligand with the largest bite angle [357, 358]. This effect on the reductive elimination was also found by Hayashi *et al.* [359] and van Leeuwen [360] in the palladium-catalyzed cross-coupling reaction of Grignard reagents with aryl halides.

An ESI-MS/MS study by CID (collision-induced dissociation) of the Suzuki–Miyaura reaction with palladium-diene catalysts showed that in this system, the reductive elimination step determines the rate of the whole process [361].

The rate-determining step in the coupling of aryl halides or triflates with aryl- or alkenylstannanes can be either the transmetallation or the oxidative addition, depending on the exact circumstances of the reaction [225, 227]. On the other hand, in the coupling of allylic electrophiles, the reductive elimination step might become rate-determining. Schwartz *et al.* [362, 363] have shown that the coupling of allylic halides and allylic organometallics does not proceed unless electron-deficient alkenes such as maleic anhydride are used. Kurosawa [364] also noted the promoting effect of electron deficiency on reductive elimination.

A new Pd(0)-catalyzed carboiodination reaction of alkenes with aryl iodides, which generates a C–C and a C–I bond, involves a rate-determining reductive elimination step to form the C(sp^3)–I bond, which is facilitated by bulky monophosphine ligands by preventing the formation of tetracoordinated intermediates [365].

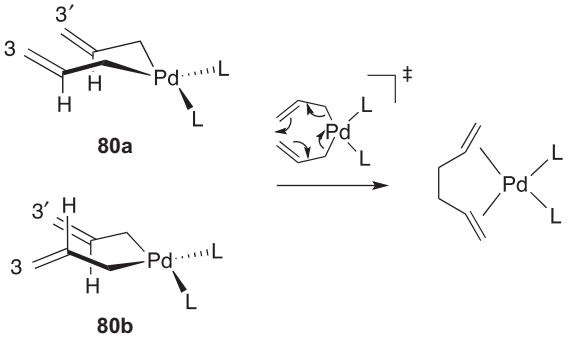
Transmetallation of (η^3-allyl)palladium complexes with arylstannanes gives aryl–allylpalladium complexes **78** (Scheme 1.45) [366]. The reductive elimination from these complexes is slow and controls the reaction outcome. In order to produce an efficient coupling, the coordination of *p*-benzoquinone or other electron-deficient alkenes to form **79** promotes the reductive elimination. Under catalytic conditions, the allyl electrophile acts as the electron-deficient alkene itself [366].



78 **79**

Scheme 1.45 Transmetallation of (η^3-allyl)palladium complexes with arylstannanes.

Bis(η^3-allyl)palladium complexes are not productive intermediates in the coupling of allylstannanes with allyl carboxylates or halides [367], as these complexes do not show any tendency to undergo reductive elimination [368, 369]. In the presence of phosphine ligands, (η^1-allyl)(η^3-allyl)palladium complexes are formed [370–372]. On the other hand, addition of diphosphines gives bis(η^1-allyl)palladium diphosphine complexes [373], which undergo smooth reductive elimination at low temperatures [374]. Calculations also support that the most favorable pathway for the reductive elimination involves bis(η^1-allyl)palladium complexes bearing two phosphine ligands (Scheme 1.46) [375, 376]. Interestingly, formation of a bond between C3 and C3′ of the allyl moieties in **80** to form 1,5-hexadiene is significantly preferred (Scheme 1.46), regardless of the syn or anti arrangement of both the allyl moieties, compared with the formation of C1–C1′ or C1–C3′ bond. This type of

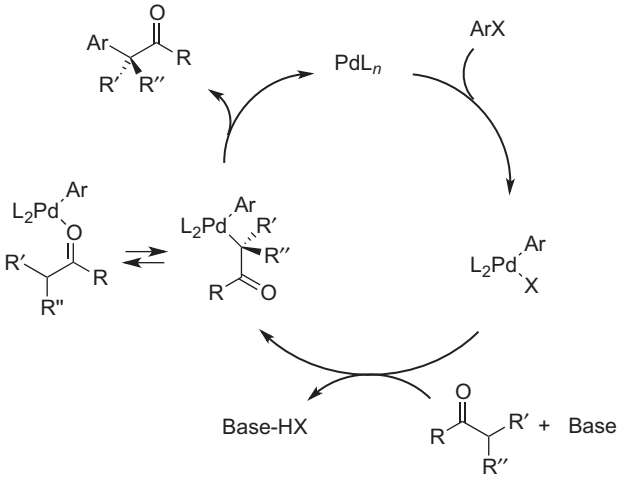


Scheme 1.46 Formation of a bond between C3 and C3′ of allyls **80**.

reductive elimination has also been found in other palladium- or nickel-catalyzed allyl–allyl couplings [377].

1.2
Palladium-Catalyzed α-Arylation of Carbonyl Compounds and Nitriles

The palladium-catalyzed α-arylation of ketones has become a useful and general synthetic method [106]. Initial studies required preformed zinc [378] or tin enolates [379]. On the other hand, Ni-mediated [380] or Ni-catalyzed couplings are also known. A great development of the reaction has occurred since 1997 based on the use of new catalysts with electron-rich alkylphosphines and NHCs as ligands [173, 381]. The reactions resemble cross-coupling processes in which the enolates behave as the nucleophilic organometallic reagents (Scheme 1.47).



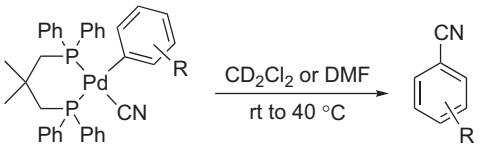
Scheme 1.47 Proposed mechanism for the palladium-catalyzed α-arylation of carbonyl compounds.

The reductive elimination step has been studied on isolated Pd complexes containing both an aryl group and an enolate as ligands. A suitable choice of phosphine is necessary to afford the complexes stable enough to be isolable and sufficiently reactive to undergo reductive elimination. In the case of ketone–enolate complexes, both C- and O-bound species are formed depending on the type of ketone and the phosphine ligand. Reductive elimination rates of complexes for a series of 1,2-bis(diphenylphosphino)benzene (dppBz) arylpalladium complexes with different C-enolate ligands parallel the nucleophilicity of the R group.

As far as the influence of the phosphine ligand in the catalyzed reactions is concerned, $P(t\mathrm{Bu})_3$ is effective in most cases. The rate of the reductive elimination of enolate complexes containing this and other bulky phosphines is faster, and the scope of many couplings catalyzed by complexes with these ligands is broader. Recently, it has been found that a catalytic quantity of phenol causes a remarkable increase in the efficiency of ketone enolate arylation [382].

Formation of a Cy_3P-Pd-L (L = NHC) has been proposed as the catalytically active species in the aryl amination and α-arylation of ketones by Nolan in a system starting from a palladacycle containing an NHC [383].

Arylpalladium(II) cyanide complexes have been isolated and have undergone reductive elimination of arylnitriles (Scheme 1.48) [384]. This reductive elimination is accelerated by electron-donating substituents on the aryl ligand.



Scheme 1.48 Reductive elimination from arylpalladium(II) cyanide complexes.

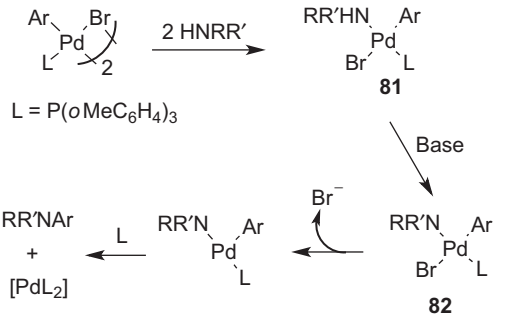
Copper-catalyzed arylation of malonates [385] and other activated methylene compounds (malononitrile, ethyl cyanoacetate) [386] have also been reported. It is likely that the catalytically active species is a Cu(I) enolate.

1.3 Formation of C–X (X = N, O, S) Bonds in Metal-Catalyzed Reactions

Pd(II) complexes formed by oxidative addition of organic electrophiles to Pd(0) may react with amines, alcohols, or thiols in the presence of a base to give the corresponding key amido, alkoxide, or sulfide complexes. These complexes undergo reductive elimination to afford the new C-X (X = O, N, S) bond in the final organic product [104, 387] and the palladium(0) species is regenerated. The palladium-catalyzed cyanation of aryl halides [388] is probably mechanistically related to these reactions.

The mechanism for the formation of the C-Pd-X complexes depends on the type of nucleophile. When amines play this role, two different mechanisms may be

involved in the formation of amido species from oxidative addition complexes. Thus, amine-containing arylpalladium complexes **81** formed by ligand substitution or by cleavage of dimeric species react with the base to give organopalladium-amido derivatives **82**, which then suffer reductive elimination to give the arylamines (Scheme 1.49) [147, 389].

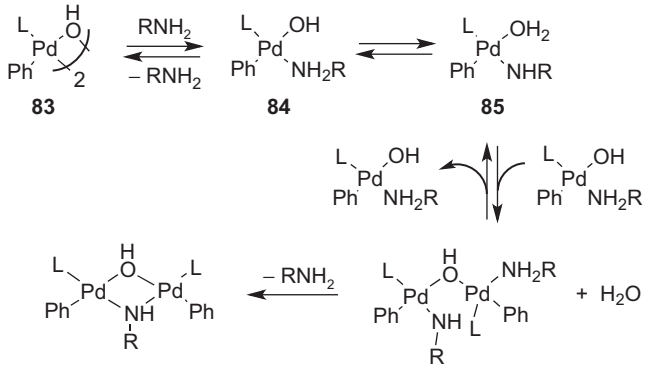


Scheme 1.49 Formation of arylpalladium amide complexes from amine precursors and subsequent reductive elimination.

The base used is not innocent in the catalytic cycle. Hartwig and Shekhar [390] studied the effects of the anions on the rates of amination reactions catalyzed by $Pd(PtBu_3)_2$. Chloroarenes bearing electron-neutral and electron-donating substituents were independent of the concentration of bulky bases, but were dependent on the concentration of less sterically demanding or weaker bases. This fact is explained by the simultaneous oxidative addition to $[Pd(PtBu_3)]$ and $[(PtBu_3)Pd(OR)]^-$ observed. On the contrary, electron-poor chloroarenes and bromoarenes are independent of the concentration of the base. Thus, both the concentration and the type of base used are dependent on the electronic properties of the haloarenes.

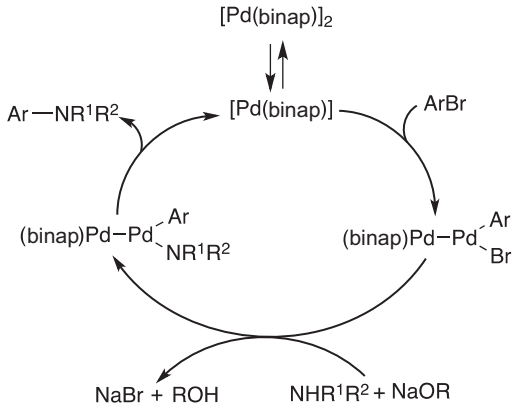
Alternatively, alkoxides or silylamides may first coordinate with the palladium precursor to form an intermediate that might react with the amine to form the required amido-aryl intermediate. Extensive kinetic studies on stoichiometric reaction models support a mechanism in which the amine cleaves the dimeric hydroxy complex **83** to give an amine intermediate **84**, which would suffer intramolecular proton transfer to give **85** (Scheme 1.50) [391]. A similar process is proposed for a dppf derivative [392].

Detailed kinetic studies have been carried out by the groups of Hartwig, Blackmond, and Buchwald under synthetically relevant conditions to study the mechanism of the amination of an aryl bromide with primary and secondary amines using Pd complexes of binap (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), among others [393]. Different mechanisms were proposed for this reaction, and a final reevaluation of the mechanism was made in collaboration between the three aforementioned groups [393c].



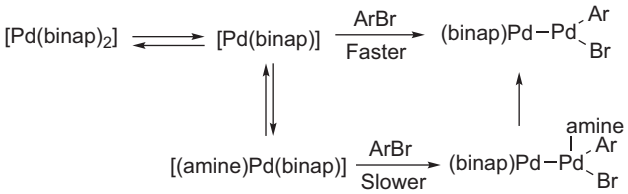
Scheme 1.50 Formation of arylpalladium amide complexes from hydroxy and alkoxy derivatives.

The bromoarene is oxidatively added to the [Pd(binap)], and the resulting complex reacts with the corresponding amine and base to furnish the parent amido complex **86**, which undergoes reductive elimination and leads to the new compound, recycling the Pd species (Scheme 1.51). The occurrence of a significant induction period observed during the reactions conducted with [Pd(binap)$_2$] as catalyst, when free binap is not added, confirms that the bis-ligand complex [Pd(binap)$_2$] lies off the catalytic cycle [393]. The kinetic study revealed a zero order in amine, first order in bromoarene, and inverse first order in added ligand.



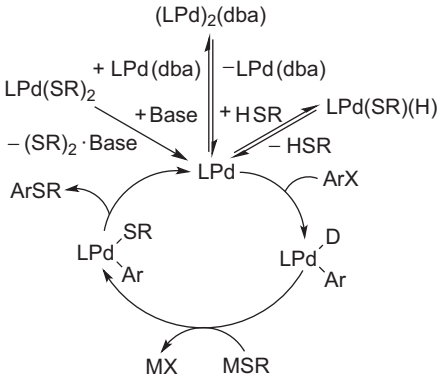
Scheme 1.51 Proposed mechanism for the Pd-binap-mediated amination of bromobenzene.

The proposed mechanism excludes the pathway that involves the amine as a ligand on a palladium(0) complex in the oxidative addition process. A conclusive contribution of Hartwig shows that the oxidative addition of the aryl halide to the amine complex is slower than that to the [Pd(binap)] (Scheme 1.52) [394].



Scheme 1.52 Oxidative addition of an aryl bromide to Pd(binap) versus Pd(binap) (amine).

An extensive mechanistic study of the coupling of aryl halides and thiols catalyzed by alkylbisphosphine complexes of palladium was also carried out (Scheme 1.53) [394]. Hartwig and coworkers stated that the resting states of the reaction depend on the palladium source used in the beginning. The resting state for the reaction catalyzed by $Pd(OAc)_2$/L is $LPd(SR_2)$, while for Pd(L)(X)(Ar), it is LPd(SR)(H) and for $Pd(dba)_2$/L, it is $(LPd)_2(dba)$. In the last case, only the aryl halide is needed to undergo oxidative addition, in contrast to the other two cases, in which a base is required. All the mentioned resting states lie off the catalytic cycle [395]. No heating is required to couple aryl chlorides with thiols using complexes ligated by CyPF-*t*Bu. The reaction proceeds by way of the catalytic cycle shown in Scheme 1.53.



Scheme 1.53 Proposed mechanism for the palladium-catalyzed coupling of aryl halides with thiols.

1.3.1
Reductive Elimination to Generate C–N, C–O, and C–S Bonds from Organopalladium(II) Complexes

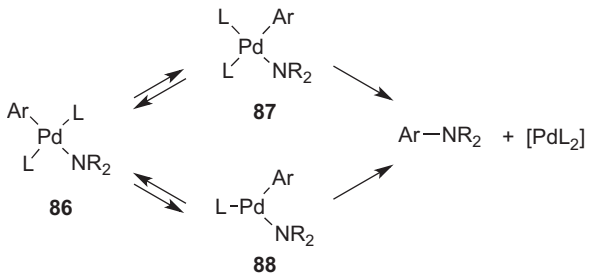
Reductive elimination of amine and ethers is the key bond-forming step in the catalytic amination and etheration reactions. Kinetic studies on stoichiometric reactions from isolated amido and alkoxyorganopalladium complexes have shed

light on the mechanism by identifying the actual species involved and the factors controlling this process. The concerted pathway that palladium(II) follows in the reductive elimination step, as well as the nonpronounced π effects in the square-planar and T-shaped palladium(II) complexes, makes it possible to propose different trends along the chapter by varying the substrates [396].

Different sets of experiments have made it possible to compare the rates for reductive elimination from arylpalladium amido, alkoxy and thiolato complexes bearing similar substituents on the heteroatom, following the trend: C–S > C–N > C–O [397]. Although the thiolate ligand is less basic than an amido ligand, it is much more polarizable. The rate of reductive elimination is controlled by the polarizability of the heteroatom, which is of the same importance as the overall electron-donating ability.

The most extensively studied of these reactions is the reductive elimination with the formation of C–N bonds from amido arylpalladium complexes [397a, 398]. Both monomeric and dimeric species have been studied. In the case of monomeric complexes, some differences occur depending on the nature (mono- or bidentate) of the coordinating phosphines.

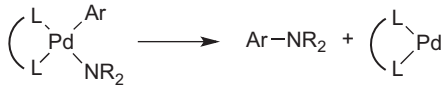
Thus, the reductive eliminations from *trans*-bis(triphenylphosphine) amido-aryl complexes **86** showed first-order kinetics demonstrating that the reductive elimination takes place from monomeric species (Scheme 1.54). The dependence of the reaction rate on the concentration of added PPh_3 is compatible with two competing mechanisms, one involving C–N bond formation to a *cis*-16-electron species **87** formed by isomerization of the trans derivative. The other mechanism involves initial reversible phosphine dissociation to give a 14-electron three-coordinate intermediate **88** that would undergo C–N bond formation (Scheme 1.54). Dimeric monophosphine complexes follow a dissociative pathway to give three-coordinate amido monomers, which suffer reductive elimination. The formation of the 14-electron intermediates can be reversible or irreversible depending on the type of amine.



Scheme 1.54 Possible competing pathways for the C–N reductive elimination from monodentate phosphine complexes.

Amidoorganopalladium complexes containing bidentate phosphines have the cis configuration necessary to undergo the reductive elimination. The zero-order dependence on the concentration of the added ligand is consistent with

a direct concerted formation of the amine from the square-planar complexes **89** (Scheme 1.55).



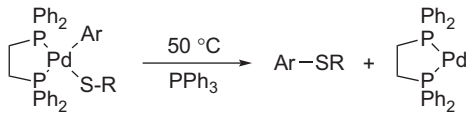
89

Scheme 1.55 C–N reductive elimination from dppf complexes.

The influence on the reductive elimination of the substituents on both the amido and the R ligands has been studied on the dppf model derivatives, as it seems to be a one-step process. The relative rates for elimination of different amido groups is alkylamido > arylamido > diarylamido [397a, 399, 400]. This trend implies that the more nucleophilic the amido ligand is, the faster the reductive elimination takes place. The chemistry of the parent amido complexes is different – they do not undergo reductive elimination when ligated to the bisphosphines dppf and binap. However, they undergo reductive elimination when ligated to CyPF-*t*Bu, but more slowly than the corresponding alkylamido and arylamino analogs [401].

On the other hand, the presence of substituents on the aryl group also affects the reductive elimination rate. Electron-poor arylpalladium complexes eliminate faster than the ones bearing electron-donating substituents. The electronic properties of the aryl groups involve both inductive and resonance effects, although the prior effect is smaller [397a, 402]. The resonance effects result from interaction of the metal center with the arene π-system and the resulting η^2-arene is the initial product of the reductive elimination process [358a].

A similar behavior is observed for the reductive elimination to form C–S bonds from aryl sulfide palladium complexes **90** (Scheme 1.56). However, in this case, the rates of reductive elimination are less sensitive to the electronic properties of the substituents of the thiolato ligands compared to the amido ones.



90

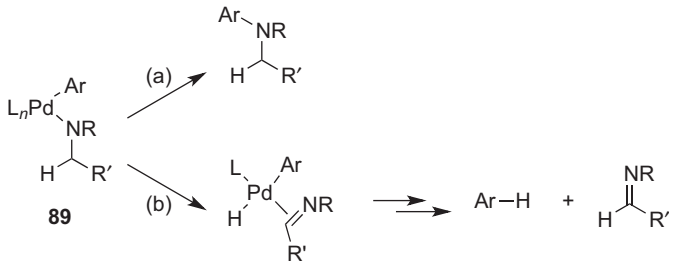
Scheme 1.56 Reductive elimination to form C–S bonds.

Ancillary ligands are not innocent in the rates of reductive elimination. Experiments conducted by varying the electronic properties of the ligands in an aryl amidopalladium complex show that reductive elimination is faster with less electron-donating ligands [400]. Bulky ligands enhance the rate of reductive elimination as well [397a]. In palladium(II) square complexes, steric effects prevail over electronic effects.

In the case of unsymmetrical ancillary ligands, the effect of the orientation of the electron donors can be as large as the effect of changes to the overall electron density on the metal [400].

The formation of ethers by reductive elimination from alkoxyorganopalladium complexes faces some difficulties because of the lower nucleophilicity of the alkoxides compared with metal amides. The choice of suitable phosphine ligands is crucial for this type of reactions. Bulky aryldialkylphosphines allow the reactions of aryl chlorides, bromides, and triflates with a variety of isolated alkoxides [403] or, more interestingly, phenols and base [404], regardless of the substitution of the aryl groups. Intermediate alkoxy organopalladium complexes have been proposed to form by transmetallation from alkali metal alkoxides to organopalladium derivatives. The rate of the reductive elimination from these intermediates is significantly lower than the corresponding rate to form C–N bonds. Two possibilities exist for the intimate mechanism of the elimination: the occurrence of a three-center transition state or an initial attack of the alkoxide on the aryl ipso carbon followed by elimination of the metal complex. The three-coordinated intermediate is favored when a sterically demanding ligand with a single donor atom is present [397b]. The second mechanism would be more probable in the case of aryl electrophiles containing electron-withdrawing groups. It has been proposed that bulkier ligands are necessary to destabilize the ground state of the intermediate [L_nPd(OR)Ar] complex, forcing the palladium-bound aryl and alkoxide groups together. As in the case of alkylpalladium and amidopalladium complexes, tricoordinated species reductively eliminate faster than the tetracoordinated ones [405].

As it happens in the case of C–C cross-coupling reactions, β-hydrogen elimination is a competing pathway in the palladium-catalyzed amination and etheration reactions. The conversion of the organic electrophiles to amines or ethers depends on the reductive elimination being faster than β-hydrogen elimination from amido or alkoxy intermediates. The extension of the undesired β-hydrogen elimination in C–N couplings has been studied on stoichiometric elimination reactions from amidoarylpalladium complexes **89** (Scheme 1.57). The C–N β-hydrogen elimination has been proposed to take place also from amino complexes in some cases [406].



Scheme 1.57 Competitive pathways in the evolution of amidoorganopalladium complexes: (a) reductive elimination and (b) β-hydrogen elimination.

The amount of the final β-hydrogen elimination products (arenes) produced depends on several factors [393a]. Thus, electron-withdrawing groups on the aryl ring increase the rate of the reductive elimination and minimize the formation of the arene. As it is observed for the etheration reactions, bulkier monophosphines enhance the rate of the C–N reductive elimination. In the case of bidentate phosphines, the results are more difficult to rationalize. Thus, electron-poor derivatives of dppf give more arene than dppf itself, albeit a more deficient metal center is supposed to suffer an easier reductive elimination. Ligands with smaller bite angles give less β-hydrogen elimination products, in contrast to the observed dependence for C–C reductive eliminations. Detailed studies have been performed on amide [407] and alkoxide [408] Ir(I) square-planar complexes, as well as on Rh iminyl complexes [409], which indicate that reversible phosphine dissociation takes place before the β-hydrogen elimination for both amide and alkoxy complexes.

Since the first coupling of amines with aryl halides in the presence of a base, the synthesis of new catalysts in all those years has been a trial-and-error art. First reactions were carried out with the so-called first-generation catalysts, which consisted of a palladium(II) source and P(*o*-Tol)$_3$ as the ligand [422, 423]. Years later, palladium complexes of bidentate phosphines, such as binap or dppf, allowed couplings with primary amines and other nucleophiles [424–427]. The ''third generation'' relied on catalysts containing sterically encumbered monodentate ligands [387b, 428, 429] as well as hindered NHC ligands [174] that are able to couple aryl bromides and chlorides to secondary and primary amines, including weak nitrogen nucleophiles [387b]. Palladium complexes bearing hindered alkyl bisphosphines or N-heterocyclic carbene ligands complete the ''fourth-generation'' catalysts, which have accomplished couplings of primary amines with high selectivity for monoarylation and high turnover numbers [118, 162, 430, 431], couplings with aryl chlorides with high turnover numbers [430, 432–434], the coupling of aryl halides with ammonia to form primary aromatic amines [435, 436], and the coupling of heteroaromatic halides with high turnover numbers [432, 433, 437]. Lewis acids have been shown to accelerate the reductive elimination of the hetereoaryl amido complexes [438].

Some of the most relevant ''fourth-generation'' catalysts are shown in Figure 1.4. The high steric demand of the ligands, in addition to their particular electronic properties, makes these new-generation catalysts highly selective and efficient for the amination reactions.

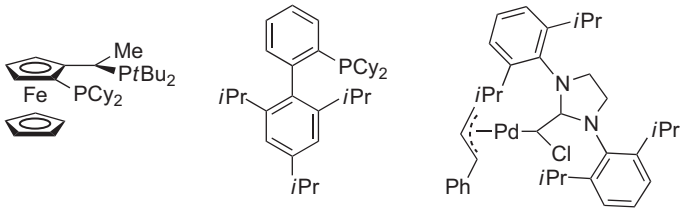


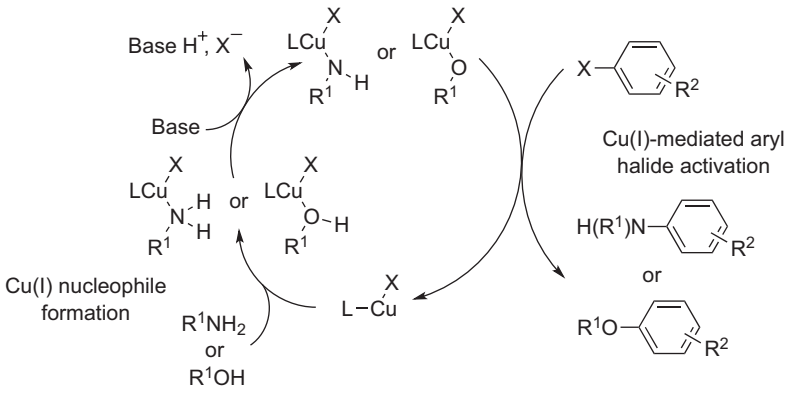
Figure 1.4 ''Fourth-generation'' catalysts for the amination of aryl halides.

1.3.2
Nickel- and Copper-Catalyzed Formation of C–X Bonds

Other metal salts and complexes also catalyze the formation of C–N, C–O, and C–S bonds from organic electrophiles. Thus, a mixture of $[Ni(COD)_2]$ and a bidentate phosphine catalyzes the formation of aryl ethers from aryl halides and alkoxides [410]. In some cases, the reactions occur under milder conditions and with higher yields than when catalyzed by Pd complexes.

Copper has also been used to couple aryl halides with amines, alcohols, or thiols in the presence of a ligand [411, 412]. Chelating N^N, N^O, and O^O ligands [413–421] are crucial in these C–X bond-forming reactions.

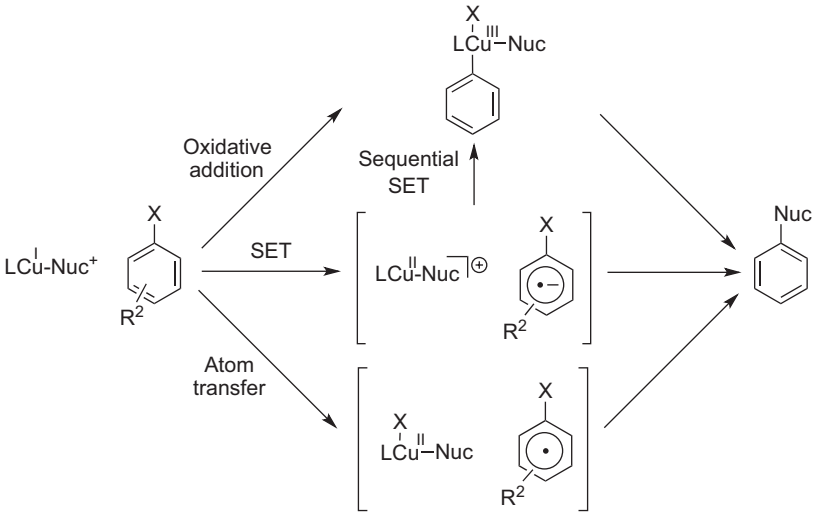
In general, the C–N or C–O coupling between an aryl halide and a nucleophile catalyzed by copper occurs in two sequential stages: the formation of the nucleophile and the activation of the aryl halide by the Cu(I)-nucleophile complex [439] (Scheme 1.58).



Scheme 1.58 Proposed mechanism for the Cu-catalyzed coupling of aryl halides with heteroatom nucleophiles.

Different experimental [440] and theoretical studies [441] have been carried out to examine the formation of the Cu(I)-nucleophile, which is highly dependent on the chelating ligand concentration. The succeeding stage only occurs in the presence of intermediate ligand concentrations. However, the mechanism for the activation of the aryl halide to the corresponding nucleophile complex, which is the rate-determining step, is not yet clear. The most commonly accepted mechanism consists of the oxidative addition of the electrophile leading to the corresponding Cu(III) complex, followed by reductive elimination. A single-electron transfer (SET) has also been postulated, involving a radical anion intermediate and a Cu(II) species. This radical could evolve to another SET step leading to the aforementioned

Cu(III) complex, or directly forming the new C–X bond by an $S_{RN}1$ mechanism. An atom transfer mechanism has also been proposed (Scheme 1.59).



Scheme 1.59 Proposed mechanisms for the Cu(I)-mediated activation of an aryl halide.

Copper(0) precatalysts with 1,10-phenanthroline ligands lead to copper(I) species after activation of PhI by electron transfer, while copper(II) precursors give copper(I) species by reaction of N- or O-nucleophiles in the presence of a base [442]. In the case of a 1,3-diketonate ligand, key complexes are generated by reaction of copper(I) with the N- or O-nucleophiles in the presence of a base, forming anionic Cu(I) species. They undergo oxidative addition to aryl iodides via intermediate complexes formed by halogen bonding between the substrate and the negatively charged N or O atom of the anionic Cu(I) species.

Stahl [443] has demonstrated that reductive elimination of isolated Cu(III)–aryl species occurs rapidly, rendering the corresponding N-arylated products. Nevertheless, this fact does not rule out the presence of other mechanisms. The presence of free aryl radicals and Cu(II) intermediates has been argued [439c]. Theoretical and experimental work indicate that arylation may occur via SET or iodine atom transfer (IAT), depending on the electron-donating abilities of the ligand [444], with β-diketonate ligands favoring an SET mechanism and phenanthroline ligands promoting the reaction via IAT processes. The SET mechanism has been the recently demonstrated in an Ullman C–N coupling via a photoinduced step proceeding through a radical pathway [445].

Orthogonal selectivity in copper catalysts was found in the N- or O-arylations of aminoalcohols [446]. Further detailed mechanistic studies stated that the selectivity arises from the activation of the aryl halide and not from the formation of the nucleophile complex [444]. The most plausible mechanisms for the activation of the aryls are a SET or an IAT, depending on the electron donation by the ligand

and the nature of the nucleophile. Labile β-diketonate Cu(I) species, which are likely the active catalysts for the copper-catalyzed C–C coupling, have been recently observed by operando IR spectroscopic techniques and *in situ* X-ray absorption near-edge structure/extended X-ray absorption fine structure (XANES/EXAFS) [447].

Buchwald [448] reported an example of an orthogonal chemoselectivity between Pd- and Cu-catalyst systems in the cross-coupling of unprotected oxindoles. The selectivity was explained with the rates of reductive elimination in the C–C-bond-forming step catalyzed by Pd and the rapid aryl activation from diamine-Cu(I)-amidate complex.

1.4 Summary and Outlook

The original proposal for cross-coupling reactions has evolved considerably. On the basis of studies on the Stille, Suzuki–Miyaura, Negishi, and Hiyama couplings, a clearer mechanistic picture has emerged. Although these transformations follow essentially the same steps, significant differences exist with regard to the rate-determining step(s) that depend on the nature of the electrophile, the nucleophile, the ligands on palladium, the presence of additives, and the nature of the solvent.

Most of the sound mechanistic work has been done on processes that involve palladium catalysts. In addition, mechanistic studies are needed to fully understand the more recently developed reactions for the formation of C–C and C–X bonds with nickel, copper, iron, and cobalt catalysts.

List of Abbreviations

Ad	Adamantyl
BBN	9-Borabicyclo[3.3.1]nonane
binap	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
Cy	Cyclohexyl
dba	Dibenzylideneacetone
dippp	1,3-Bis(diisopropylphosphino)propane
dppBz	1,2-Bis(diphenylphosphino)benzene
dppe	Bis(1,2-diphenylphosphino)ethane
dppf	Bis(1,1′-diphenylphosphino)ferrocene
dppp	Bis(1,3-diphenylphosphino)propane
dppr	Bis(1,1′-diphenylphosphino)ruthenocene
HMPA	Hexamethylphosphoric triamide
TBAF	Tetrabutylammonium fluoride
TMEDA	*N,N,N′,N′*-Tetramethylethylenediamine
tfp	Tri-(2-furyl)phosphine

References

1. Johansson Seechurn, C.C.C., Kitching, M.O., Colacot, T.J., and Snieckus, V. (2012) *Angew. Chem. Int. Ed.*, **51**, 5062–5085.
2. Li, H., Johansson Seechurn, C.C.C., and Colacot, T.J. (2012) *ACS Catal.*, **2**, 1147–1164.
3. Ming So, C. and Kwong, F.Y. (2011) *Chem. Soc. Rev.*, **40**, 4963–4972.
4. Fortman, G.C. and Nolan, S.P. (2011) *Chem. Soc. Rev.*, **40**, 5151–5169.
5. Sellars, J.D. and Steel, P.G. (2011) *Chem. Soc. Rev.*, **40**, 5170–5180.
6. Jana, R., Pathak, T.P., and Sigman, M.S. (2011) *Chem. Rev.*, **111**, 1417–1492.
7. McGlacken, G.P. and Fairlamb, I.J.S. (2009) *Eur. J. Org. Chem.*, 4011–4029.
8. (a) Tamao, K., Sumitani, K., and Kumada, M. (1972) *J. Am. Chem. Soc.*, **94**, 4374–4376; (b) Corriu, R.J.P. and Masse, J.P. (1972) *J. Chem. Soc., Chem. Commun.*, 144; (c) Tamao, K. (2002) *J. Organomet. Chem.*, **653**, 23–26.
9. Yamaguchi, J., Muto, K., and Itami, K. (2013) *Eur. J. Org. Chem.*, 19–30.
10. Azarian, D., Dua, S.S., Eaborn, C., and Walton, D.R.M. (1976) *J. Organomet. Chem.*, **117**, C55–C75.
11. (a) Kosugi, M., Sasazawa, K., Shimizu, Y., and Migita, T. (1977) *Chem. Lett.*, 301–302; (b) Kosugi, M., Shimizu, Y., and Migita, T. (1977) *Chem. Lett.*, 1423–1424; (c) Kosugi, M. and Fugami, K. (2002) *J. Organomet. Chem.*, **653**, 50–53.
12. Milstein, D. and Stille, J.K. (1978) *J. Am. Chem. Soc.*, **100**, 3636–3638.
13. Stille, J.K. (1986) *Angew. Chem., Int. Ed. Engl.*, **25**, 508–524.
14. Farina, V. (1995) in *Comprehensive Organometallic Chemistry II*, Vol. 12 Chapter 3.4 (eds E.W. Abel, F.G.A. Stone, and G. Wilkinson), Pergamon, Oxford, pp. 161–240.
15. (a) Mitchell, T.N. (1998) in *Metal-Catalyzed Cross-Coupling Reactions* (eds F. Diederich and P.J. Stang) Chapter 4, Wiley-VCH Verlag GmbH, Weinheim, pp. 167–202; (b) Mitchell, T.N. (1992) *Synthesis*, 803–815.
16. Espinet, P. and Echavarren, A.M. (2004) *Angew. Chem. Int. Ed.*, **43**, 4704–4734.
17. Pitaval, A. and Echavarren, A.M. (2013) *Science of Synthesis: Cross Coupling and Heck-Type Reactions*, Vol. 1 Chapter 1.3.1, Thieme, Stuttgart.
18. (a) Miyaura, N. and Suzuki, A. (1995) *Chem. Rev.*, **95**, 2457–2483; (b) Suzuki, A. (1998) in *Metal-Catalyzed Cross-Coupling Reactions* (eds F. Diederich and P.J. Stang) Chapter 2, Wiley-VCH Verlag GmbH, Weinheim, pp. 49–97; (c) Chemler, S.R., Trauner, D., and Danishefsky, S.J. (2001) *Angew. Chem. Int. Ed.*, **40**, 4544–4568.
19. Suzuki, A. (2011) *Angew. Chem. Int. Ed.*, **50**, 6722–6737.
20. Rossi, R., Bellina, F., and Less, M. (2012) *Adv. Synth. Catal.*, **352**, 1181–1255.
21. Bonin, H., Fouquet, E., and Felpin, F.-X. (2011) *Adv. Synth. Catal.*, **353**, 3063–3084.
22. Echavarren, A.M. and Cárdenas, D.J. (2004) in *Metal-Catalyzed Cross-Coupling Reactions* (eds A. de Meijere and F. Diederich) Chapter 1, Wiley-VCH Verlag GmbH, Weinheim, pp. 1–40.
23. Tsuji, J. (1995) *Palladium Reagents and Catalysts*, John Wiley & Sons, Ltd, Chichester.
24. Nicolaou, K.C., Bulger, P.G., and Sarlah, D. (2005) *Angew. Chem. Int. Ed.*, **44**, 4442–4489.
25. Linshoeft, J., Heinrich, A.C.J., Segler, S.A.W., Gates, P.J., and Staubitz, A. (2012) *Org. Lett.*, **14**, 5644–5647.
26. Negishi, E.-I. (2002) *J. Organomet. Chem.*, **653**, 34–40.
27. Negishi, E. (2007) *Bull. Chem. Soc. Jpn.*, **80**, 233–257.
28. Phapale, V.B. and Cárdenas, D.J. (2009) *Chem. Soc. Rev.*, **38**, 1598–1607.
29. (a) Hiyama, T. and Hatanaka, Y. (1994) *Pure Appl. Chem.*, **66**, 1471–1478; (b) Hatanaka, Y. and Hiyama, T. (1991) *Synlett*, 845–853; (c) Hiyama, T. (1998) in *Metal-Catalyzed Cross-Coupling Reactions* (eds F. Diederich and P.J. Stang) Chapter 10, Wiley-VCH Verlag GmbH, Weinheim, pp. 421–454.

30. (a) Denmark, S.E. and Sweis, R.F. (2002) *Acc. Chem. Res.*, **35**, 835–846; (b) Denmark, S.E. and Sweis, R.F. (2004) in *Metal-Catalyzed Cross-Coupling Reactions*, (eds A. de Meijere and F. Diederich) Vol. 1 chapter 4, Wiley-VCH Verlag Gmbh, Weinheim, pp. 163–216. (c) Denmark, S.E. and Regens, C.S. (2008) *Acc. Chem. Res.*, **41**, 1486–1499.
31. (a) Sonogashira, K. (1998) in *Metal-Catalyzed Cross-Coupling Reactions* (eds F. Diederich and P.J. Stang) Chapter 5, Wiley-VCH Verlag GmbH, Weinheim, pp. 203–229; (b) Tykwinski, R.R. (2003) *Angew. Chem. Int. Ed.*, **42**, 1566–1568.
32. (a) Chinchilla, R. and Nájera, C. (2011) *Chem. Soc. Rev.*, **40**, 5084–5121; (b) Jenny, N.M., Mayor, M., and Eaton, T.R. (2011) *Eur. J. Org. Chem.*, **26**, 4965–4983; (c) Schilz, M. and Plenio, H. (2012) *J. Org. Chem.*, **77**, 2798–2807.
33. (a) Yamamura, M., Moritani, I., and Murahashi, S.I. (1975) *J. Organomet. Chem.*, **91**, C39–C42; (b) Fauvarque, J.F. and Jutand, A. (1976) *Bull. Soc. Chim. Fr.*, 765–770; (c) Sekiya, A. and Ishikawa, N. (1976) *J. Organomet. Chem.*, **118**, 349–354.
34. Negishi, E. (1982) *Acc. Chem. Res.*, **15**, 340–348.
35. Groll, K., Blümke, T.D., Unsinn, A., Haas, D., and Knochel, P. (2012) *Angew. Chem. Int. Ed.*, **51**, 11157–11161.
36. (a) Fürstner, A. and Leitner, A. (2002) *Angew. Chem. Int. Ed.*, **41**, 609–612; (b) Fürstner, A., Leitner, A., Méndez, M., and Krause, H. (2002) *J. Am. Chem. Soc.*, **124**, 13856–13863.
37. (a) Heck, R.F. (1982) *Org. React.*, **27**, 345–390; (b) Heck, R.F. (1991) in *Comprehensive Organic Synthesis*, Vol. 4 Chapter 4.3 (ed. B.M. Trost), Pergamon, Oxford, pp. 833–863.
38. (a) de Meijere, A. and Meyer, F.E. (1994) *Angew. Chem., Int. Ed. Engl.*, **33**, 2379–2411; (b) Beletskaya, I.P. and Cheprakov, A.V. (2000) *Chem. Rev.*, **100**, 3009–3066; (c) Bräse, S. and de Meijere, A. (1998) in *Metal-Catalyzed Cross-Coupling Reactions* (eds F. Diederich and P.J. Stang) Chapter 3, Wiley-VCH Verlag GmbH, Weinheim, pp. 99–166; (d) Link, J.T. and Overman, L.E. (1998) in *Metal-Catalyzed Cross-Coupling Reactions* (eds F. Diederich and P.J. Stang) Chapter 6, Wiley-VCH Verlag GmbH, Weinheim, pp. 231–269; (e) Bräse, S. and de Meijere, A. (2004) in *Metal-Catalyzed Cross-Coupling Reactions*, (eds A. de Meijere and F. Diederich) chapter 5, Wiley-VCH Verlag Gmbh, Weinheim, pp. 217–315.
39. Echavarren, A.M. (2010) *ChemCatChem*, **2**, 1331–1332.
40. Hassan, J., Sévignon, M., Gozzi, C., Schulz, E., and Lemaire, M. (2002) *Chem. Rev.*, **102**, 1359–1470.
41. Bringmann, G., Tasler, S., Pfeifer, R.-M., and Breuning, M. (2002) *J. Organomet. Chem.*, **661**, 49–65.
42. (a) Campeau, L.-C. and Fagnou, K. (2006) *Chem. Commun.*, 1253–1264; (b) Campeau, L.-C., Stuart, D.R., and Fagnou, K. (2007) *Aldrichim. Acta*, **40**, 35–41.
43. Alberico, D., Scott, M.E., and Lautens, M. (2007) *Chem. Rev.*, **107**, 174–238.
44. Pascual, S., de Mendoza, P., and Echavarren, A.M. (2007) *Org. Biol. Chem.*, **5**, 2727–2734.
45. (a) Catellani, M., Motti, E., Della Ca', N., and Ferraccioli, R. (2007) *Eur. J. Org. Chem.*, **25**, 4153–4165; (b) Chiusoli, G.P., Catellani, M., Costa, M., Motti, E., Della Ca', N., and Maestri, G. (2010) *Coord. Chem. Rev.*, **254**, 456–469.
46. Li, B.-J., Yang, S.-D., and Shi, Z.-J. (2008) *Synlett*, **7**, 949–957.
47. de Mendoza, P. and Echavarren, A.M. (2008) in *Modern Arylation Methods* (ed. L. Achermann) Chapter 11, Wiley-VCH Verlag GmbH, Weinheim, pp. 363–399.
48. Ackermann, L., Vicente, R., and Kapdi, A.R. (2009) *Angew. Chem. Int. Ed.*, **48**, 9792–9826.
49. Chen, X., Engle, K.M., Wang, D.-H., and Yu, J.-Q. (2009) *Angew. Chem. Int. Ed.*, **48**, 5094–5115.
50. McGlacken, G.P. and Bateman, L.M. (2009) *Chem. Soc. Rev.*, **38**, 2447–2464.

51. Livendahl, M. and Echavarren, A.M. (2010) *Isr. J. Chem.*, **5–6**, 630–651.
52. Farina, V., Krishnamurthy, V., and Scott, W.K. (1997) *Org. React.*, **50**, 1–676.
53. Pascual, S. and Echavarren, A.M. (2008) in *Tin Chemistry–Fundamentals Frontiers, and Applications* (eds A.G. Davies, M. Gielen, K.H. Pannell, and E.R.T.K. Tiekink) Chapter 5.4, Wiley-VCH Verlag GmbH, Weinheim, pp. 579–606.
54. (a) Stang, P.J., Kowalski, M.H., Schiavelli, M.D., and Longford, D. (1989) *J. Am. Chem. Soc.*, **111**, 3347–3356; (b) Stang, P.J. and Kowalski, M.H. (1989) *J. Am. Chem. Soc.*, **111**, 3356–3362.
55. (a) Farina, V. and Roth, G.P. (1996) *Adv. Met.-Org. Chem.*, **5**, 1–53; (b) Farina, V. (1996) *Pure Appl. Chem.*, **68**, 73–78.
56. Brown, J.M. and Hii, K.K. (1996) *Angew. Chem., Int. Ed. Engl.*, **35**, 657–659.
57. Labadie, J.W. and Stille, J.K. (1983) *J. Am. Chem. Soc.*, **105**, 6129–6137.
58. (a) Ye, J., Bhatt, R.K., and Falck, J.R. (1994) *J. Am. Chem. Soc.*, **116**, 1–5; (b) Ye, J., Bhatt, R.K., and Falck, J.R. (1993) *Tetrahedron Lett.*, **34**, 8007–8010.
59. He, A. and Falck, J.R. (2010) *J. Am. Chem. Soc.*, **132**, 2524–2525.
60. Pudasaini, B. and Janesko, B.G. (2012) *Organometallics*, **31**, 4610–4618.
61. Gillie, A. and Stille, J.K. (1980) *J. Am. Chem. Soc.*, **102**, 4933–4941.
62. Tatsumi, K., Hoffmann, R., Yamamoto, A., and Stille, J.K. (1981) *Bull. Chem. Soc. Jpn.*, **54**, 1857–1867.
63. Ozawa, F., Ito, T., Nakamura, Y., and Yamamoto, A. (1981) *Bull. Chem. Soc. Jpn.*, **54**, 1868–1880.
64. (a) Minniti, D. (1994) *Inorg. Chem.*, **33**, 2631–2634; (b) Casado, A.L., Casares, J.A., and Espinet, P. (1997) *Organometallics*, **16**, 5730–5736.
65. (a) Stille, J.K. (1985) in *The Chemistry of the Metal-Carbon Bond*, Vol. 2 Chapter 9 (eds F.R. Hartley and S. Patai), John Wiley & Sons, Ltd, Chichester, pp. 625–787; (b) Stille, J.K. and Lau, K.S.Y. (1977) *Acc. Chem. Res.*, **10**, 434–442.
66. (a) Kurosawa, H., Ogoshi, S., Kawasaki, Y., Murai, S., Miyoshi, M., and Ikeda, I. (1990) *J. Am. Chem. Soc.*, **112**, 2813–2814; (b) Kurosawa, H., Kajimura, H., Ogoshi, S., Yoneda, H., Miki, K., Kasai, N., Murai, S., and Ikeda, I. (1992) *J. Am. Chem. Soc.*, **114**, 8417–8424.
67. Vitagliano, A., Åkermark, B., and Hansson, S. (1991) *Organometallics*, **10**, 2592–2599.
68. Diefenbach, A. and Bickelhaupt, F.M. (2001) *J. Chem. Phys.*, **115**, 4030–4040.
69. Stary, I. and Kocovsky, P. (1989) *J. Am. Chem. Soc.*, **111**, 4981–4982.
70. Amatore, C., Gamez, S., Jutand, A., Meyer, G., Moreno-Mañas, M., Morral, L., and Pleixats, R. (2000) *Chem.—Eur. J.*, **6**, 3372–3376.
71. Hazari, A., Gouverneur, V., and Brown, J.M. (2009) *Angew. Chem. Int. Ed.*, **48**, 1296–1299.
72. Fauvarque, J.-F., Pflüger, F., and Troupel, M. (1981) *J. Organomet. Chem.*, **208**, 419–427.
73. Jutand, A. and Moshleh, A. (1995) *Organometallics*, **14**, 1810–1817.
74. (a) Portnoy, M. and Milstein, D. (1993) *Organometallics*, **12**, 1655–1664; (b) Portnoy, M. and Milstein, D. (1993) *Organometallics*, **12**, 1665–1673.
75. A review on the effect of ligand bite angles on organometallic reactions: van Leeuwen, P.W.N.M., Kamer, P.C.J., Reek, J.N.H., and Dierker, P. (2000) *Chem. Rev.*, **100**, 2741–2769.
76. Amatore, C., Broeker, G., Jutand, A., and Khalil, F. (1997) *J. Am. Chem. Soc.*, **119**, 5176–5185.
77. In the oxidative addition of allyl acetates to [Pd(L,L)], the following order was observed: dppb> dppf> PPh_3:Amatore, C., Gamez, S., and Jutand, A. (2001) *Chem.—Eur. J.*, **7**, 1273–1280.
78. Lu, G.-P., Voigtritter, K.R., Cai, C., and Lipshutz, B.H. (2012) *J. Org. Chem.*, **77**, 3700–3703.
79. Vicente, J., Arcas, A., Bautista, D., and Jones, P.G. (1997) *Organometallics*, **16**, 2127–2138.

80. Urata, H., Tanaka, M., and Fuchikami, T. (1987) *Chem. Lett.*, 751–754.

81. Casado, A.L. and Espinet, P. (1998) *Organometallics*, **17**, 954–959.

82. (a) Very often, this complex is described as $[Pd(dba)_2]$. However, this is a dimetallic complex of formula $[Pd_2(dba)_3 \cdot dba]$: Takahashi, Y., Ito, T., Sakai, S., and Ishii, Y. (1970) *J. Chem. Soc., Chem. Commun.*, 1065–1066; (b) After recrystallization, the solvates $[Pd_2(dba)_3 \cdot (S)]$ (S = CH_2Cl_2, $CHCl_3$, benzene, toluene) are obtained: Ukai, T., Kawazura, H., Ishii, Y., Bonnet, J.J., and Ibers, J.A. (1974) *J. Organomet. Chem.*, **65**, 253–266; (c) Mazza, M.C. and Pierpont, C.G. (1973) *J. Chem. Soc., Chem. Commun.*, 207; (d) Mazza, M.C. and Pierpont, C.G. (1974) *Inorg. Chem.*, **13**, 1891–1895; (e) See also: Echavarren, A.M. and Stille, J.K. (1988) *J. Organomet. Chem.*, **356**, C35–C37; (f) Tris(dibenzylideneacetone)palladium(0), $[Pd(dba)_3]$, has been prepared by heating $[Pd(dba)_2]$ with excess dba in benzene:Mazza, M.C. and Pierpont, C.G. (1973) *Inorg. Chem.*, **12**, 2955–2959.

83. Park, S., Hidden, D., Rheingold, A.L., and Roundhill, D.M. (1986) *Organometallics*, **5**, 1305–1311.

84. Amatore, C. and Jutand, A. (1998) *Coord. Chem. Rev.*, **178–180**, 511–528.

85. Amatore, C., Jutand, A., and Meyer, G. (1998) *Inorg. Chim. Acta*, **273**, 76–84.

86. Sørensen, H.S., Larsen, J., Rasmussen, B.S., Laursen, B., Hansen, S.G., Skrydstrup, T., Amatore, C., and Jutand, A. (2002) *Organometallics*, **21**, 5243–5253.

87. Amatore, C., Jutand, A., Khalil, F., M'Barki, M.A., and Mottier, L. (1993) *Organometallics*, **12**, 3168–3178.

88. Amatore, C., Jutand, A., Meyer, G., Atmani, H., Khalil, F., and Chahdi, F.O. (1998) *Organometallics*, **17**, 2958–2964.

89. Amatore, C., Bucaille, A., Fuxa, A., Jutand, A., Meyer, G., and Ndedi Ntepe, A. (2001) *Chem.—Eur. J.*, **7**, 2134–2142.

90. (a) Stork, G. and Isaacs, R.C.A. (1990) *J. Am. Chem. Soc.*, **112**, 7399–7400; (b) Busacca, C.A., Swestock, J., Johnson, R.E., Bailey, T.R., Musza, L., and Rodger, C.A. (1994) *J. Org. Chem.*, **59**, 7553–7556; (c) Farina, V. and Hossain, M.A. (1996) *Tetrahedron Lett.*, **37**, 6997–7000; (d) Choshi, T., Yamada, S., Nobuhiro, J., Mihara, Y., Sugino, E., and Hibino, S. (1998) *Heterocycles*, **48**, 11–14; (e) Flohr, A. (1998) *Tetrahedron Lett.*, **39**, 5177–5180; (f) Shen, W. and Wang, L. (1999) *J. Org. Chem.*, **64**, 8873–8879.

91. (a) Amatore, C., Azzabi, M., and Jutand, A. (1991) *J. Am. Chem. Soc.*, **113**, 1670–1677; (b) Amatore, C. and Jutand, A. (2000) *Acc. Chem. Res.*, **33**, 314–321; (c) Jutand, A. (2003) *Eur. J. Inorg. Chem.*, 2017–2040; (d) Kozuch, S., Shaik, S., Jutand, A., and Amatore, A. (2004) *Chem.—Eur. J.*, **10**, 3072–3080; (e) Kozuch, S. and Shaik, S. (2006) *J. Am. Chem. Soc.*, **128**, 3355–3365.

92. Amatore, C., Jutand, A., and Suarez, A. (1993) *J. Am. Chem. Soc.*, **115**, 9531–9541.

93. Amatore, C., Jutand, A., and M'Barki, M.A. (1992) *Organometallics*, **11**, 3009–3013.

94. Amatore, C., Carré, E., Jutand, A., M'Barki, M.A., and Meyer, G. (1995) *Organometallics*, **14**, 5605–5614.

95. Neghishi, E.-I., Takahashi, T., and Akiyoshi, K. (1986) *J. Chem. Soc., Chem. Commun.*, 1338–1339.

96. Reetz, M.T., Lohmer, G., and Schwickardi, R. (1998) *Angew. Chem., Int. Ed. Engl.*, **37**, 481–483.

97. Amatore, C., Azzabi, M., and Jutand, A. (1989) *J. Organomet. Chem.*, **363**, C41–C45.

98. Amatore, C., Azzabi, M., and Jutand, A. (1991) *J. Am. Chem. Soc.*, **113**, 8375–8384.

99. Littke, A.F. and Fu, G.C. (2002) *Angew. Chem. Int. Ed.*, **41**, 4176–4211.

100. The Stille coupling of activated aryl fluorides proceeds with $[Pd(PPh_3)_4]$ as the catalyst: Kim, Y.M. and Yu, S. (2003) *J. Am. Chem. Soc.*, **125**, 1696–1697.

101. (a) Cárdenas, D.J. (1999) *Angew. Chem. Int. Ed.*, **38**, 3018–3020; (b) Cárdenas, D.J. (2003) *Angew. Chem. Int. Ed.*, **42**, 384–387.

102. Grushin, V.V. and Alper, H. (1994) *Chem. Rev.*, **94**, 1047–1062.

103. (a) Ben-David, Y., Portnoy, M., and Milstein, D. (1989) *J. Am. Chem. Soc.*, **111**, 8742–8743; (b) Ben-David, Y., Portnoy, M., and Milstein, D. (1989) *J. Chem. Soc., Chem. Commun.*, 1816–1817; (c) Ben-David, Y., Portnoy, M., Gozin, M., and Milstein, D. (1992) *Organometallics*, **11**, 1995–1996.

104. (a) Hartwig, J.F. (1998) *Angew. Chem., Int. Ed. Engl.*, **37**, 2046–2067; (b) Muci, A.R. and Buchwald, S.L. (2002) *Top. Curr. Chem.*, **219**, 131–209; (c) Prim, D., Champagne, J.-M., Joseph, D., and Andrioletti, B. (2002) *Tetrahedron*, **58**, 2041–2075.

105. (a) Hamann, B.C. and Hartwig, J.F. (1997) *J. Am. Chem. Soc.*, **119**, 12382–12383; (b) Hamann, B.C. and Hartwig, J.F. (1998) *J. Am. Chem. Soc.*, **120**, 7369–7370; (c) Hamann, B.C. and Hartwig, J.F. (1998) *J. Am. Chem. Soc.*, **120**, 3694–3703; (d) Kawatsura, M. and Hartwig, J.F. (1999) *J. Am. Chem. Soc.*, **121**, 1473–1478.

106. Culkin, D.A. and Hartwig, J.F. (2003) *Acc. Chem. Res.*, **36**, 234–245.

107. (a) Palucki, M. and Buchwald, S.L. (1997) *J. Am. Chem. Soc.*, **119**, 11108–11109; (b) Åhman, J., Wolfe, J.P., Troutman, M.V., Palucki, M., and Buchwald, S.L. (1998) *J. Am. Chem. Soc.*, **120**, 1918–1919.

108. Martin, R. and Buchwald, S.L. (2008) *Acc. Chem. Res.*, **41**, 1461–1473.

109. Christmann, U. and Vilar, R. (2005) *Angew. Chem. Int. Ed.*, **44**, 366–374.

110. Fleckensteinab, C.A. and Plenio, H. (2010) *Chem. Soc. Rev.*, **39**, 694–711.

111. (a) Yamamoto, T., Saito, O., and Yamamoto, A. (1981) *J. Am. Chem. Soc.*, **103**, 5600–5602; (b) Yamamoto, T., Akimoto, M., and Yamamoto, A. (1983) *Chem. Lett.*, 1725–1726; (c) Yamamoto, T., Akimoto, M., Saito, O., and Yamamoto, A. (1986) *Organometallics*, **5**, 1559–1567.

112. Heck reactions: (a) Litke, A.F. and Fu, G.C. (1999) *J. Org. Chem.*, **64**, 10–11; (b) Litke, A.F. and Fu, G.C. (2001) *J. Am. Chem. Soc.*, **123**, 6989–7000.

113. Amination of aryl bromides and chlorides with $[Pd(P(tBu)_3)_2]$: (a) Nishiyama, M., Yamamoto, T., and Koie, Y. (1998) *Tetrahedron Lett.*, **39**, 617–620; (b) Yamamoto, T., Nishiyama, M., and Koie, Y. (1998) *Tetrahedron Lett.*, **39**, 2367–2370; (c) Hartwig, J.F., Kawatsura, M., Hauck, S.I., Shaughnessy, K.H., and Alcazar-Roman, L.M. (1999) *J. Org. Chem.*, **64**, 5575–5580; (d) Kuwano, R., Utsunomiya, M., and Hartwig, J.F. (2002) *J. Org. Chem.*, **67**, 6479–6486; (e) Sonogashira coupling: Böhm, V.P.W. and Herrmann, W.A. (2000) *Eur. J. Org. Chem.*, 3679–3681.

114. Other related phosphines for activation of aryl chlorides: (a) Li, G.Y. (2002) *J. Org. Chem.*, **67**, 3643–3650; (b) Li, G.Y., Zheng, G., and Noonan, A.F. (2001) *J. Org. Chem.*, **66**, 8677–8688; (c) Li, G.Y. (2001) *Angew. Chem. Int. Ed.*, **40**, 1513–1516; (d) Zapf, A., Ehrentraut, A., and Beller, M. (2000) *Angew. Chem. Int. Ed.*, **39**, 4153–4155; (e) Liu, S.-Y., Choi, M.J., and Fu, G.C. (2001) *Chem. Commun.*, 2408–2409; (f) Urgaonkar, S., Nagarajan, M., and Verkade, J.G. (2002) *Tetrahedron Lett.*, **43**, 8921–8924.

115. Netherton, M.R. and Fu, G.C. (2001) *Org. Lett.*, **3**, 4295–4298.

116. (a) Stauffer, S.R., Beare, N.A., Stambuli, J.P., and Hartwig, J.F. (2001) *J. Am. Chem. Soc.*, **123**, 4641–4642; (b) Beare, N.A. and Hartwig, J.F. (2002) *J. Org. Chem.*, **67**, 541–555.

117. (a) Old, D.W., Wolfe, J.P., and Buchwald, S.L. (1998) *J. Am. Chem. Soc.*, **120**, 9722–9723; (b) Wolfe, J.P. and Buchwald, S.L. (1999) *Angew. Chem. Int. Ed.*, **38**, 2413–2416; (c) Harris, M.C. and Buchwald, S.L. (2000) *J. Org. Chem.*, **65**, 5327–5333.

118. Kataoka, N., Shelby, Q., Stambuli, J.P., and Hartwig, J.F. (2002) *J. Org. Chem.*, **67**, 5553–5566.

119. Bei, X., Crevier, T., Guram, A.S., Jandeleit, B., Powers, T.S., Turner, H.W., Uno, T., and Weinberg, W.H. (1999) *Tetrahedron Lett.*, **40**, 3855–3858.

120. Wolfe, J.P., Singer, R.A., Yang, B.H., and Buchwald, S.L. (1999) *J. Am. Chem. Soc.*, **121**, 9550–9561.

121. Molander, G.A. and Canturk, B. (2009) *Angew. Chem. Int. Ed.*, **48**, 9240–9261.

122. Biscoe, M.R., Fors, B.P., and Buchwald, S.L. (2008) *J. Am. Chem. Soc.*, **130**, 6686–6687.

123. (a) Kinzel, T., Zhang, Y., and Buchwald, S.L. (2010) *J. Am. Chem. Soc.*, **132**, 14073–14075; (b) Bruno, N.C., Tudge, M.T., and Buchwald, S.L. (2013) *Chem. Sci.*, **4**, 916–920.

124. (a) Norton, D.M., Mitchell, E.A., Botros, N.R., Jessop, P.G., and Baird, M.C. (2009) *J. Org. Chem.*, **74**, 6674–6680; (b) Fraser, A.W., Besaw, J.E., Hull, L.E., and Baird, M.C. (2012) *Organometallics*, **31**, 2470–2475; (c) Fraser, A.W., Jaksic, B.E., Batcup, R., Sarsons, C.D., Woolman, M., and Baird, M.C. (2013) *Organometallics*, **32**, 9–11.

125. Gómez Andreu, M., Zapf, A., and Beller, M. (2000) *Chem. Commun.*, 2475–2476.

126. (a) Cortès, J., Moreno-Mañas, M., and Pleixats, R. (2000) *Eur. J. Org. Chem.*, 239–243; (b) Llobet, A., Masllorens, E., Moreno-Mañas, M., Pla-Quintana, A., Rodríguez, M., and Roglans, A. (2002) *Tetrahedron Lett.*, **43**, 1425–1428; (c) Moreno-Mañas, M., Pleixats, R., and Serra-Muns, A. (2006) *Synlett*, 3001–3004; (d) Serra-Muns, A., Jutand, A., Moreno-Mañas, M., and Pleixats, R. (2008) *Organometallics*, **27**, 2411–2427.

127. Netherton, M.R., Dai, M.R.C., Neuschütz, K., and Fu, G.C. (2001) *J. Am. Chem. Soc.*, **123**, 10099–10100.

128. Fu, G.C. (2008) *Acc. Chem. Res.*, **41**, 1555–1564.

129. Kirchhoff, J.H., Dai, C., and Fu, G.C. (2002) *Angew. Chem. Int. Ed.*, **41**, 1945–1947.

130. Frisch, A.C., Shaikh, N., Zapf, A., and Beller, M. (2002) *Angew. Chem. Int. Ed.*, **41**, 4056–4059.

131. Netherton, M.R. and Fu, G.C. (2002) *Angew. Chem. Int. Ed.*, **41**, 3910–3912.

132. Kirchhoff, J.H., Netherton, M.R., Hills, I.D., and Fu, G.C. (2002) *J. Am. Chem. Soc.*, **124**, 13662–13663.

133. Menzel, K. and Fu, G.C. (2003) *J. Am. Chem. Soc.*, **125**, 3718–3719.

134. Alcazar-Roman, L.M. and Hartwig, J.F. (2001) *J. Am. Chem. Soc.*, **123**, 12905–12906.

135. Litke, A.F. and Fu, G.C. (2000) *J. Am. Chem. Soc.*, **122**, 4020–4028.

136. (a) Littke, A.F. and Fu, G.C. (1999) *Angew. Chem. Int. Ed.*, **38**, 2411–2413; (b) Littke, A.F. and Fu, G.C. (1998) *Angew. Chem., Int. Ed. Engl.*, **37**, 3387–3388.

137. Grasa, G.A., Viciu, M.S., Huang, J., and Nolan, S.P. (2001) *J. Org. Chem.*, **66**, 7729–7737.

138. Rudolph, A. and Lautens, M. (2009) *Angew. Chem. Int. Ed.*, **48**, 2656–2670.

139. Lu, Z. and Fu, G.C. (2010) *Angew. Chem. Int. Ed.*, **49**, 6676–6678.

140. (a) González-Bobes, F. and Fu, G.C. (2006) *J. Am. Chem. Soc.*, **128**, 5360–5361; (b) Smith, S.W. and Fu, G.C. (2008) *Angew. Chem. Int. Ed.*, **47**, 9334–9336.

141. Choi, J. and Fu, G.C. (2012) *J. Am. Chem. Soc.*, **134**, 9102–9105.

142. (a) Zhou, J. and Fu, G.C. (2004) *J. Am. Chem. Soc.*, **126**, 1340–1341; (b) Powell, D.A. and Fu, G.C. (2004) *J. Am. Chem. Soc.*, **126**, 7788–7789; (c) Zultanski, S.L. and Fu, G.C. (2011) *J. Am. Chem. Soc.*, **133**, 15362–15364.

143. Powell, D.A., Maki, T., and Fu, G.C. (2005) *J. Am. Chem. Soc.*, **127**, 510–511.

144. (a) Jones, G.D., Martin, J.L., McFarland, C., Allen, O.R., Hall, R.E., Haley, A.D., Brandon, R.J., Konovalova, T., Desrochers, P.J., Pulay, P., and Vicic, D.A. (2006) *J. Am. Chem. Soc.*, **128**, 13175–13183; (b) Phapale, V.B., Buñuel, E., García-Iglesias, M., and Cárdenas, D.J. (2007) *Angew. Chem. Int. Ed.*, **46**, 8790–8795; (c) Lin, X. and Phillips, D.L. (2008) *J. Org. Chem.*, **73**, 3680–3688.

145. (a) Hu, X.L. (2011) *Chem. Sci.*, **2**, 1867–1886; (b) Vechorkin, O., Csok, Z., Scopelliti, R., and Hu, X.L. (2009) *Chem.—Eur. J.*, **15**, 3889–3899; (c) Vechorkin, O., Proust, V., and Hu, X.L. (2009) *J. Am. Chem. Soc.*, **131**, 9756–9766.

146. Phapale, V.B., Guisán-Ceinos, M., Buñuel, E., and Cárdenas, D.J. (2009) *Chem.—Eur. J.*, **15**, 12681–12688.

147. Paul, F., Patt, J., and Hartwig, J.F. (1995) *Organometallics*, **14**, 3030–3039.

148. Paul, F., Patt, J., and Hartwig, J.F. (1994) *J. Am. Chem. Soc.*, **116**, 5969–5970.

149. Hartwig, J.F. and Paul, F. (1995) *J. Am. Chem. Soc.*, **117**, 5373–5374.

150. Roy, A.H. and Hartwig, J.F. (2001) *J. Am. Chem. Soc.*, **123**, 1232–1233.

151. Galardon, E., Ramdeehul, S., Brown, J.M., Cowley, A., Hii, K.K., and Jutand, A. (2002) *Angew. Chem. Int. Ed.*, **41**, 1760–1763.

152. Stambuli, J.P., Bühl, M., and Hartwig, J.F. (2002) *J. Am. Chem. Soc.*, **124**, 9346–9347.

153. Baratta, W., Stoccoro, S., Doppiu, A., Hertweck, E., Zucca, A., and Rigo, P. (2003) *Angew. Chem. Int. Ed.*, **42**, 105–108.

154. (a) Stambuli, J.P., Incarvito, C.D., Buehl, M., and Hartwig, J.F. (2004) *J. Am. Chem. Soc.*, **126**, 1184–1194; (b) Yamashita, M. and Hartwig, J.F. (2004) *J. Am. Chem. Soc.*, **126**, 5344–5345.

155. Espino, G., Kurbangalieva, A., and Brown, J.M. (2007) *Chem. Commun.*, 1742–1744.

156. Barrios-Landeros, F., Carrow, B.P., and Hartwig, J.F. (2009) *J. Am. Chem. Soc.*, **131**, 8141–8154.

157. Schoenebeck, F. and Houk, K.N. (2010) *J. Am. Chem. Soc.*, **132**, 2496–2497.

158. Echavarren, A.M. and Stille, J.K. (1987) *J. Am. Chem. Soc.*, **109**, 5478–5486.

159. Kamikawa, T. and Hayashi, T. (1997) *Tetrahedron Lett.*, **38**, 7087–7090.

160. Proutiere, F. and Schoenebeck, F. (2011) *Angew. Chem. Int. Ed.*, **50**, 8192–8195.

161. Roy, A.H. and Hartwig, J.F. (2004) *Organometallics*, **23**, 194–202.

162. Stambuli, J.P., Kuwano, R., and Hartwig, J.F. (2002) *Angew. Chem. Int. Ed.*, **41**, 4746–4748.

163. Paton, R.S. and Brown, J.M. (2012) *Angew. Chem. Int. Ed.*, **51**, 10448–10450.

164. Nagaki, A., Takabayashi, N., Moriwaki, Y., and Yoshida, J. (2012) *Chem.—Eur. J.*, **18**, 11871–11875.

165. Mori, Y. and Seki, M. (2003) *J. Org. Chem.*, **68**, 1571–1574.

166. Choudary, B.M., Madhi, S., Chowdari, N.S., Kantam, M.L., and Sreedhar, B. (2002) *J. Am. Chem. Soc.*, **124**, 14127–14136.

167. Beletskaya, I.P. (1982) *J. Organomet. Chem.*, **250**, 551–564.

168. For a leading reference on the mechanism of the Heck reaction with palladium metal: Le Bars, J., Specht, U., Bradley, J.S., and Blackmond, D.G. (1999) *Langmuir*, **15**, 7621–7625.

169. Morita, D.K., Stille, J.K., and Norton, J.R. (1995) *J. Am. Chem. Soc.*, **117**, 8576–8581.

170. Kong, K.-C. and Cheng, C.-H. (1991) *J. Am. Chem. Soc.*, **113**, 6313–6315.

171. Segelstein, B.E., Butler, T.W., and Chenard, B.L. (1995) *J. Org. Chem.*, **60**, 12–13.

172. Goodson, F.E., Wallow, T.I., and Novak, B.M. (1997) *J. Am. Chem. Soc.*, **119**, 12441–12453.

173. Herrmann, W.A. (2002) *Angew. Chem. Int. Ed.*, **41**, 1290–1309.

174. (a) Marion, N. and Nolan, S.P. (2008) *Acc. Chem. Res.*, **41**, 1440–1449; (b) Díez-González, S., Marion, N., and Nolan, S.P. (2009) *Chem. Rev.*, **109**, 3612–3676.

175. Dröge, T. and Glorius, F. (2010) *Angew. Chem. Int. Ed.*, **49**, 6940–6952.

176. Valente, C., Çalimsiz, S., Hoi, K.H., Mallik, D., Sayah, M., and Organ, M.G. (2012) *Angew. Chem. Int. Ed.*, **51**, 3314–3332.

177. (a) McGuinness, D.S., Green, M.J., Cavell, K.J., Skelton, B.W., and White, A.H. (1998) *J. Organomet. Chem.*, **565**, 165–178; (b) McGuinness, D.S., Cavell, K.J., Skelton, B.W., and White, A.H. (1999) *Organometallics*, **18**, 1596–1605.

178. (a) Caddick, S., Cloke, F.G.N., Hitchcock, P.B., Leonard, J., Lewis, A.K.D.K., McKerrecher, D., and Titcomb, L.R. (2002) *Organometallics*, **21**, 4318–4319; (b) Marshall, W.J. and Grushin, V.V. (2003) *Organometallics*, **22**, 1591–1593.

179. Guo, T., Dechert, S., Meyer, S., and Meyer, F. (2012) *Organometallics*, **31**, 8537–8543.

180. Terao, J., Todo, H., Begum, S.A., Kuniyasu, H., and Kambe, N. (2007) *Angew. Chem. Int. Ed.*, **46**, 2086–2089.

181. Hadei, N., Achonduh, G.T., Valente, C., O'Brien, C.J., and Organ, M.G. (2011) *Angew. Chem. Int. Ed.*, **50**, 3896–3899.

182. (a) Organ, M.G., Chass, G.A., Fang, D., Hopkinson, A.C., and Valente, C. (2008) *Synthesis*, 2776–2797; (b) Valente, C., Belowich, M.E., Hadei, N., and Organ, M.G. (2010) *Eur. J. Org. Chem.*, 4343–4354.

183. Pompeo, M., Froese, R.D.J., Hadei, N., and Organ, M.G. (2012) *Angew. Chem. Int. Ed.*, **51**, 11354–11357.

184. Dupont, J., Pfeffer, M., and Spencer, J. (2001) *Eur. J. Inorg. Chem.*, 1917–1927.

185. (a) Bedford, R.B. and Cazin, C.S.J. (2001) *Chem. Commun.*, 1540–1541; (b) Bedford, R.B., Cazin, C.S.J., and Hazelwood, S.L. (2002) *Angew. Chem. Int. Ed.*, **41**, 4120–4122; (c) Bedford, R.B., Cazin, C.S.J., Coles, S.J., Gelbrich, T., Horton, P.N., Hursthouse, M.B., and Light, M.E. (2003) *Organometallics*, **22**, 987–999.

186. Schnyder, A., Indolese, A.F., Studer, M., and Blaser, H.-U. (2002) *Angew. Chem. Int. Ed.*, **41**, 3668–3671.

187. (a) Alonso, D.A., Nájera, C., and Pacheco, M.C. (2000) *Org. Lett.*, **2**, 1823–1826; (b) Alonso, D.A., Nájera, C., and Pacheco, M.C. (2002) *J. Org. Chem.*, **67**, 5588–5594; (c) Alonso, D.A., Nájera, C., and Pacheco, M.C. (2002) *Adv. Synth. Catal.*, **344**, 172–183; (d) Botella, L. and Nájera, C. (2002) *Angew. Chem. Int. Ed.*, **41**, 179–181.

188. (a) Beller, M., Fischer, H., Herrmann, W.A., Öfele, K., and Brossmer, C. (1995) *Angew. Chem., Int. Ed. Engl.*, **34**, 1848–1849; (b) Gibson, S., Foster, D.F., Eastham, G.R., Tooze, R.P., and Cole-Hamilton, D.J. (2001) *Chem. Commun.*, 779–780; (c) Albisson, D.A., Bedford, R.B., Lawrence, S.E., and Scully, P.N. (1998) *Chem. Commun.*, 2095–2096; (d) Bedford, R.B. and Welch, S.L. (2001) *Chem. Commun.*, 129–130; (e) Bedford, R.B., Draper, S.M., Scully, P.N., and Welch, S.L. (2000) *New J. Chem.*, 745–746; (f) Zim, D., Gruber, A.S., Ebeling, G., Dupont, J., and Monteiro, A.L. (2000) *Org. Lett.*, **2**, 2881–2884; (g) Weissman, H. and Milstein, D. (1999) *Chem. Commun.*, 1901–1902.

189. Beletskaya, I.P., Kashin, A.N., Karlstedt, N.B., Mitin, A.V., Cheprakov, A.V., and Kazankov, G.M. (2001) *J. Organomet. Chem.*, **622**, 89–96.

190. Muñoz, M.P., Martín-Matute, B., Fernández-Rivas, C., Cárdenas, D.J., and Echavarren, A.M. (2001) *Adv. Synth. Catal.*, **343**, 338–342.

191. Consorti, C.S., Zanini, M.L., Leal, S., Ebeling, G., and Dupont, J. (2003) *Org. Lett.*, **5**, 983–986.

192. Rocaboy, C. and Gladysz, J.A. (2003) *New J. Chem.*, **27**, 39–49.

193. (a) Rosner, T., Le Bars, J., Pfaltz, A., and Blackmond, D.G. (2001) *J. Am. Chem. Soc.*, **123**, 1848–1855; (b) Rosner, T., Pfaltz, A., and Blackmond, D.G. (2001) *J. Am. Chem. Soc.*, **123**, 4621–4622.

194. Moreno-Mañas, M. and Pleixats, R. (2003) *Acc. Chem. Res.*, **36**, 638–643.

195. Phan, N.T.S., Van Der Sluys, M., and Jones, C.W. (2006) *Adv. Synth. Catal.*, **348**, 609–679.

196. Niu, Z., Peng, Q., Zhuang, Z., He, W., and Li, Y. (2012) *Chem.—Eur. J.*, **18**, 9813–9817.

197. (a) Canty, A.J. (1992) *Acc. Chem. Res.*, **25**, 83–90; (b) Canty, A.J. (1993) *Platinum Met. Rev.*, **37**, 2–7.

198. Catellani, M., Frignani, F., and Rangoni, A. (1997) *Angew. Chem. Int. Ed.*, **36**, 119–122.

199. Hickman, A.J. and Sanford, M.S. (2012) *Nature*, **484**, 177–185.

200. Sundermann, A., Uzan, O., and Martin, J.M.L. (2001) *Chem.—Eur. J.*, **7**, 1703–1711.

201. (a) Bayler, A., Canty, A.J., Ryan, J.H., Skelton, B.W., and White, A.H. (2000) *Inorg. Chem. Commun.*, **3**, 575–578; (b) Canty, A.J. and Rodemann, T. (2003) *Inorg. Chem. Commun.*, **6**, 1382; (c) Canty, A.J., Patel, J., Rodeman, T., Ryan, J.H., Skelton, B.W., and White, A.H. (2004) *Organometallics*, **23**, 3466–3473.

202. (a) Kalyani, D., Deprez, N.R., Desai, L.V., and Sanford, M.S. (2005) *J. Am. Chem. Soc.*, **127**, 7330–7331; (b) Dick, A.R., Kampf, J.W., and Sanford, M.S. (2005) *J. Am. Chem. Soc.*, **127**, 12790–12791.

203. Calvet, T., Crespo, M., Font-Bardía, M., Jansat, S., and Martínez, M. (2012) *Organometallics*, **31**, 4367–4373.

204. (a) Vicente, J., Arcas, A., Juliá-Hernández, F.F., and Bautista, D. (2011) *Angew. Chem. Int. Ed.*, **50**, 6896–6899; (b) Juliá-Hernández, F., Arcas, A., and Vicente, J. (2012) *Chem.—Eur. J.*, **18**, 7780–7786.

205. Gerber, R., Blacque, O., and Frech, C.M. (2011) *Dalton Trans.*, **40**, 8996–9003; Correction: 2011 *Dalton Trans.*, **40**, 12939.

206. (a) Terao, J., Watanabe, H., Ikumi, A., Kuniyasu, H., and Kambe, N. (2002) *J. Am. Chem. Soc.*, **124**, 4222–4223; (b) Terao, J., Ikumi, A., Kuniyasu, H., and Kambe, N. (2003) *J. Am. Chem. Soc.*, **125**, 5646–5647.

207. (a) Shirakawa, E., Yoshida, H., and Hiyama, T. (1997) *Tetrahedron Lett.*, **38**, 5177–5180; (b) Shirakawa, E. and Hiyama, T. (1999) *J. Organomet. Chem.*, **576**, 169–178; (c) Shirakawa, E., Yoshida, H., Kurahashi, T., Nakao, Y., and Hiyama, T. (1998) *J. Am. Chem. Soc.*, **120**, 2975–2976; (d) Yoshida, H., Shirakawa, E., Kurahashi, T., Nakao, Y., and Hiyama, T. (2000) *Organometallics*, **19**, 5671–5678; (e) Shirakawa, E., Murota, Y., Nakao, Y., and Hiyama, T. (1997) *Synlett*, 1143–1144; (f) Shirakawa, E., Nakao, Y., Murota, Y., and Hiyama, T. (2003) *J. Organomet. Chem.*, **670**, 132–136.

208. Matsubara, T. and Hirao, K. (2002) *Organometallics*, **21**, 4482–4489.

209. (a) Shirakawa, E., Yamasaki, K., Yoshida, H., and Hiyama, T. (1999) *J. Am. Chem. Soc.*, **121**, 10221–10222; (b) Shirakawa, E., Yoshida, H., Nakao, Y., and Hiyama, T. (2000) *Org. Lett.*, **2**, 2209–2211.

210. (a) Bumagin, N.A., Kasatkin, A.N., and Beletskaya, I.P. (1984) *Izv. Akad. Nauk SSSR Ser. Khim. (Engl. Transl.)*, 588–594; (b) Wallner, O.A. and Szabó, K.J. (2002) *Org. Lett.*, **4**, 1563–1566.

211. Shi, M. and Nicholas, K.M. (1997) *J. Am. Chem. Soc.*, **119**, 5057–5058.

212. Martín-Matute, B., Buñuel, E., Cárdenas, D.J., Méndez, M., Nieto-Oberhuber, C., and Echavarren, A.M. (2003) *J. Organomet. Chem.*, **687**, 410–419.

213. (a) Cárdenas, D.J., Mateo, C., and Echavarren, A.M. (1994) *Angew. Chem., Int. Ed. Engl.*, **33**, 2445–2447; (b) Mateo, C., Cárdenas, D.J., Fernández-Rivas, C., and Echavarren, A.M. (1996) *Chem.—Eur. J.*, **2**, 1596–1606.

214. Mateo, C., Fernández-Rivas, C., Echavarren, A.M., and Cárdenas, D.J. (1997) *Organometallics*, **16**, 1997–1999.

215. Platinum catalysts in Suzuki-type reactions: Bedford, R.B., Hazelwood, S.L., and Albisson, D.A. (2002) *Organometallics*, **21**, 2599–2600.

216. Cotter, W.D., Barbour, L., McNamara, K.L., Hechter, R., and Lachicotte, R.J. (1998) *J. Am. Chem. Soc.*, **120**, 11016–11017.

217. Ricci, A., Angelucci, A., Bassetti, M., and Lo Sterzo, C. (2002) *J. Am. Chem. Soc.*, **124**, 1060–1071.

218. (a) Spadoni, L., Lo Sterzo, C., Crescenzi, R., and Frachey, G. (1995) *Organometallics*, **14**, 3149–3151; (b) Cianfriglia, P., Narducci, V., Lo Sterzo, C., Viola, E., Bocelli, G., and Kodenkandath, T.A. (1996) *Organometallics*, **15**, 5220–5230; (c) Tollis, S., Narducci, V., Cianfriglia, P., Lo Sterzo, C., and Viola, E. (1998) *Organometallics*, **17**, 2388–2390; (d) Angelucci, F., Ricci, A., Lo Sterzo, C., Masi, D., Bianchini, C., and Bocelli, G. (2002) *Organometallics*, **21**, 3001–3008.

219. Louie, J. and Hartwig, J.F. (1995) *J. Am. Chem. Soc.*, **117**, 11598–11599.

220. Farina, V. and Krishnan, B. (1991) *J. Am. Chem. Soc.*, **113**, 9585–9595.

221. Farina, V., Baker, S.R., Benigni, D.A., and Sapino, C. (1988) *Tetrahedron Lett.*, **29**, 5739–5742.

222. Review on 2-furylphosphanes: Andersen, N.G. and Keay, B.A. (2001) *Chem. Rev.*, **101**, 997–1030.

223. Farina, V., Krishnan, B., Marshall, D.R., and Roth, G.P. (1993) *J. Org. Chem.*, **58**, 5434–5444.

224. Cross, R.J. (1989) *Adv. Inorg. Chem.*, **34**, 219–292.

225. Casado, A.L. and Espinet, P. (1998) *J. Am. Chem. Soc.*, **120**, 8978–8985.

226. Casares, J.A., Espinet, P., and Salas, G. (2002) *Chem.—Eur. J.*, **8**, 4843–4853.

227. Casado, A.L., Espinet, P., and Gallego, A.M. (2000) *J. Am. Chem. Soc.*, **122**, 11771–11782.

228. Casado, A.L., Espinet, P., Gallego, A.M., and Martínez-Ilarduya, J.M. (2001) *Chem. Commun.*, 339–340.

229. Pérez-Temprano, M.H., Nova, A., Casares, J.A., and Espinet, P. (2008) *J. Am. Chem. Soc.*, **130**, 10518–10520.

230. Amatore, C., Bahsoun, A.A., Jutand, A., Meyer, G., Ndedi Ntepe, A., and Ricard, L. (2003) *J. Am. Chem. Soc.*, **125**, 4212–4222.

231. Nova, A., Ujaque, G., Maseras, F., Lledós, A., and Espinet, P. (2006) *J. Am. Chem. Soc.*, **128**, 14571–14578.

232. Pérez-Temprano, M.H., Gallego, A.M., Casares, J.A., and Espinet, P. (2011) *Organometallics*, **30**, 611–617.

233. Ariafard, A. and Yates, B.F. (2009) *J. Am. Chem. Soc.*, **131**, 13981–13991.

234. (a) Roshchin, A.I., Bumagin, N.A., and Beletskaya, I.P. (1995) *Tetrahedron Lett.*, **36**, 125–128; (b) Rai, R., Aubrecht, K.B., and Collum, D.B. (1995) *Tetrahedron Lett.*, **36**, 3111–3114.

235. (a) Brown, J.M., Pearson, M., Jastrzebski, J.T.B.H., and van Koten, G. (1992) *J. Chem. Soc., Chem. Commun.*, 1440–1441; (b) Fouquet, E., Pereyre, M., and Rodriguez, A.L. (1997) *J. Org. Chem.*, **62**, 5242–5243.

236. Vedejs, E., Haigt, A.R., and Moss, W.O. (1992) *J. Am. Chem. Soc.*, **114**, 6556–6558.

237. (a) Jensen, M.S., Yang, C., Hsiao, Y., Rivera, N., Wells, K.M., Chung, J.Y.L., Yasuda, N., Hughes, D.L., and Reider, P.J. (2000) *Org. Lett.*, **2**, 1081–1084; (b) Sebahar, H.L., Yoshida, K., and Hegedus, L.S. (2002) *J. Org. Chem.*, **67**, 3788–3795; (c) Intramolecular coordination by an amine also facilitates the transmetallation of less reactive organobismuth compounds with aryl bromides: Shimada, S., Yamazaki, O., Tanaka, T., Rao, M.L.N., Suzuki, Y., and Tanaka, M. (2003) *Angew. Chem. Int. Ed.*, **42**, 1845–1848.

238. Itami, K., Kamei, T., and Yoshida, J. (2001) *J. Am. Chem. Soc.*, **123**, 8773–8779.

239. Nilsson, P., Puxty, G., and Wendt, O.F. (2006) *Organometallics*, **25**, 1285–1292.

240. (a) Liebeskind, L.S. and Fengl, R.W. (1990) *J. Org. Chem.*, **55**, 5359–5364; (b) Liebeskind, L.S. and Riesinger, S.W. (1993) *J. Org. Chem.*, **58**, 408–413.

241. Gómez-Bengoa, E. and Echavarren, A.M. (1991) *J. Org. Chem.*, **56**, 3497–3501.

242. Farina, V., Kapadia, S., Krishnan, B., Wang, C., and Liebeskind, L.S. (1994) *J. Org. Chem.*, **59**, 5905–5911.

243. Saá, J.M. and Martorell, G. (1993) *J. Org. Chem.*, **58**, 1963–1966.

244. Mazzola, R.D., Giese, S., Benson, C.L., and West, F.G. (2004) *J. Org. Chem.*, **69**, 220–223.

245. Wang, M. and Lin, Z. (2010) *Organometallics*, **29**, 3077–3084.

246. Piers, E. and Wong, T. (1993) *J. Org. Chem.*, **58**, 3609–3610.

247. Takeda, T., Matsunaga, K.I., Kabasawa, Y., and Fukiwara, T. (1995) *Chem. Lett.*, 771–772.

248. Mee, S.P.H., Lee, V., and Baldwin, J.E. (2004) *Angew. Chem. Int. Ed.*, **43**, 1132–1136.

249. Casado, A.L. and Espinet, P. (2003) *Organometallics*, **22**, 1305–1309.

250. Falck, J.R., Bahtt, R.K., and Ye, J. (1995) *J. Am. Chem. Soc.*, **117**, 5973–5982.

251. Linderman, R.J. and Siedlecki, J.M. (1996) *J. Org. Chem.*, **61**, 6492–6493.

252. (a) Allred, G.D. and Liebeskind, L.S. (1996) *J. Am. Chem. Soc.*, **118**, 2748–2749; (b) Zhang, S., Zhang, D., and Liebeskind, L.S. (1997) *J. Org. Chem.*, **62**, 2312–2313.

253. Coupling catalyzed by Cu(I) or Mn(II): Kang, S.-K., Kim, J.-S., and Choi, S.-C. (1997) *J. Org. Chem.*, **62**, 4208–4209.

254. Savall, B.M., Blanchard, N., and Roush, W.R. (2003) *Org. Lett.*, **5**, 377–379.

255. Alphonse, F.-A., Suzenet, F., Keromnes, A., Lebret, B., and Guillaumet, G. (2003) *Org. Lett.*, **5**, 803–805.

256. Egi, M. and Liebeskind, L.S. (2003) *Org. Lett.*, **5**, 801–802.

257. Aufiero, M., Proutiere, F., and Schoenebeck, F. (2012) *Angew. Chem. Int. Ed.*, **51**, 7226–7230.

258. Weng, Y., Cheng, B., He, C., and Lei, A. (2012) *Angew. Chem. Int. Ed.*, **51**, 9547–9551.

259. Matos, K. and Soderquist, J.A. (1998) *J. Org. Chem.*, **63**, 461–470.

260. Ridgway, B.H. and Woerpel, K.A. (1998) *J. Org. Chem.*, **63**, 458–460.

261. Amatore, C., Jutand, A., and Le Duc, G. (2011) *Chem.—Eur. J.*, **17**, 2492–2503.

262. Amatore, C., Jutand, A., and Le Duc, G. (2011) *Angew. Chem. Int. Ed.*, **51**, 1379–1382.

263. Amatore, C., Jutand, A., and Le Duc, G. (2012) *Chem.—Eur. J.*, **18**, 6616–6625.

264. Braga, A.A.C., Morgon, N.H., Ujaque, G., and Maseras, F. (2005) *J. Am. Chem. Soc.*, **127**, 9298–9307.

265. Braga, A.A.C., Ujaque, G., and Maseras, F. (2006) *Organometallics*, **25**, 3647–3658.

266. Jover, J., Fey, N., Purdie, M., Lloyd-Jones, F.C., and Harvey, J.N. (2010) *J. Mol. Catal. A*, **324**, 39–47.

267. Weng, C.-M. and Hong, F.-E. (2011) *Dalton Trans.*, **40**, 6458–6468.

268. Aliprantis, A.O. and Canary, J.W. (1994) *J. Am. Chem. Soc.*, **116**, 6985–6986.

269. Agrawal, D., Schröder, D., and Frech, C.M. (2011) *Organometallics*, **30**, 3579–3587.

270. Imao, D., Glasspoole, B.W., Laberge, V.S., and Crudden, C.M. (2009) *J. Am. Chem. Soc.*, **131**, 5024–5025.

271. Ohmura, T., Awano, T., and Suginome, M. (2010) *J. Am. Chem. Soc.*, **132**, 13191–13193.

272. Molander, G.A. and Wisniewski, S.R. (2012) *J. Am. Chem. Soc.*, **134**, 16856–16868.

273. Sandrock, D.L., Jean-Gerard, L., Chen, C.-Y., Dreher, S.D., and Molander, G.A. (2010) *J. Am. Chem. Soc.*, **132**, 17108–17110.

274. Awano, T., Ohmura, T., and Suginome, M. (2011) *J. Am. Chem. Soc.*, **133**, 20738–20741.

275. Ohashi, M., Saijo, H., Shibata, M., and Ogoshi, S. (2013) *Eur. J. Org. Chem.*, **2013**, 443–447.

276. Grushin, V.V. (2002) *Chem.—Eur. J.*, **8**, 1006–1014.

277. Pagenkopf, B.L. and Carreira, E.M. (1999) *Chem.—Eur. J.*, **5**, 3437–3442.

278. Kemmitt, R.D.W., Peacock, R.D., and Stocks, J. (1971) *J. Chem. Soc. A*, 846–849.

279. Blessley, G., Holden, P., Walker, M., Brown, J.M., and Gouverneur, V. (2012) *Org. Lett.*, **14**, 2754–2757.

280. (a) Osakada, K., Onodera, H., and Nishihara, Y. (2005) *Organometallics*, **24**, 190–192; (b) Pantcheva, I., Nishihara, Y., and Osakada, K. (2005) *Organometallics*, **24**, 3815; (c) Pantcheva, I. and Osakada, K. (2006) *Organometallics*, **25**, 1735; (d) Suzaki, Y. and Osakada, K. (2006) *Organometallics*, **25**, 3251.

281. Nishikata, T., Yamamoto, Y., and Miyaura, N. (2004) *Organometallics*, **23**, 4317–4324.

282. Shukla, K.H. and DeShong, P. (2008) *J. Org. Chem.*, **73**, 6283–6291.

283. Yamamoto, Y., Takada, S., Miyaura, N., Iyama, T., and Tachikawa, H. (2009) *Organometallics*, **28**, 152–160.

284. Zim, D., Lando, V.R., Dupont, J., and Monteiro, A.L. (2001) *Org. Lett.*, **3**, 3049–3051.

285. Moreno-Mañas, M., Pérez, M., and Pleixats, R. (1996) *J. Org. Chem.*, **61**, 2346–2351.

286. (a) Casares, J.A., Espinet, P., Fuentes, B., and Salas, G. (2007) *J. Am. Chem. Soc.*, **129**, 3508–3509; (b) García-Melchor, M., Fuentes, B., Lledós, A., Casares, J.A., Ujaque, G., and Espinet, P. (2011) *J. Am. Chem. Soc.*, **133**, 13519–13526.

287. Liu, Q., Lan, Y., Liu, J., Li, G., Wu, Y.-D., and Lei, A. (2009) *J. Am. Chem. Soc.*, **131**, 10201–10210.

288. Jina, L. and Lei, A. (2012) *Org. Biomol. Chem.*, **10**, 6817–6825.

289. González-Pérez, A.B., Álvarez, R., Nieto Faza, O., de Lera, Á.R., and Aurrecoechea, J.M. (2012) *Organometallics*, **31**, 2053–2058.

290. Ribagnac, P., Blug, M., Villa-Uribe, J., Le Goff, X.-F., Gosmini, C., and Mézailles, N. (2011) *Chem.—Eur. J.*, **17**, 14389–14393.

291. He, C., Ke, J., Xu, H., and Lei, A. (2013) *Angew. Chem. Int. Ed.*, **52**, 1527–1530.

292. Jin, L., Xin, J., Huang, Z., He, J., and Lei, A. (2010) *J. Am. Chem. Soc.*, **132**, 9607–9609.

293. Hirabayashi, K., Kawashima, J., Nishihara, Y., Mori, A., and Hiyama, T. (1999) *Org. Lett.*, **1**, 299–302.

294. (a) Denmark, S.E. and Sweis, R.F. (2001) *J. Am. Chem. Soc.*, **123**, 6439–6440; (b) Denmark, S.E. and Sweis, R.F. (2004) *J. Am. Chem. Soc.*, **126**, 4876–4882; (c) Denmark, S.E., Smith, R.C., Chang, W.-T.T., and Muhuhi, J.M. (2009) *J. Am. Chem. Soc.*, **131**, 3104–3118.

295. Hatanaka, Y. and Hiyama, T. (1989) *J. Org. Chem.*, **54**, 268–270.

296. Hatanaka, Y., Goda, K., and Hiyama, T. (1994) *J. Organomet. Chem.*, **465**, 97–100.

297. Hatanaka, Y. and Hiyama, T. (1990) *J. Am. Chem. Soc.*, **112**, 7793–7794.

298. Hatanaka, Y., Goda, G., and Hiyama, T. (1994) *Tetrahedron Lett.*, **35**, 1279–1282.

299. (a) Denmark, S.E. and Werner, N.S. (2008) *J. Am. Chem. Soc.*, **130**, 16382–16393; (b) Denmark, S.E. and Werner, N.S. (2010) *J. Am. Chem. Soc.*, **132**, 3612–3620.

300. Yoshikai, N. and Nakamura, E. (2012) *Chem. Rev.*, **112**, 2339–2372.

301. Yang, C.-T., Zhang, Z.-Q., Liu, Y.-C., and Liu, L. (2011) *Angew. Chem. Int. Ed.*, **50**, 3904–3907.

302. Yang, C.-T., Zhang, Z.-Q., Liang, J., Liu, J.-H., Lu, X.-Y., Chen, H.-H., and Liu, L. (2012) *J. Am. Chem. Soc.*, **134**, 11124–11127.

303. Casitas, A., Canta, M., Sola, M., Costas, M., and Ribas, X. (2011) *J. Am. Chem. Soc.*, **133**, 19386–19392.

304. Ren, P., Stern, L.-A., and Hu, X. (2012) *Angew. Chem. Int. Ed.*, **51**, 9110–9113.

305. Shen, R., Iwasaki, T., Terao, J., and Kambe, N. (2012) *Chem. Commun.*, **48**, 9313–9315.

306. Casitas, A., King, A.E., Parella, T., Costas, M., Stahl, S.S., and Ribas, X. (2010) *Chem. Sci.*, **1**, 326–330.

307. (a) González-Arellano, C., Abad, A., Corma, A., Garcia, H., Iglesias, M., and Sánchez, F. (2007) *Angew. Chem. Int. Ed.*, **46**, 1536–1538; (b) Corma, A., González-Arellano, C., Iglesias, M., Pérez-Ferreras, S., and Sánchez, F. (2007) *Synlett*, 1771–1774; (c) González-Arellano, C., Corma, A., Iglesias, M., and Sánchez, F. (2008) *Eur. J. Inorg. Chem.*, 1107–1115.

308. Li, P., Wang, L., Wang, M., and You, F. (2008) *Eur. J. Org. Chem.*, 5946–5951.

309. de Souza, O.M.A., Bittar, M.S., Mendes, L.V.P., Michele, C., and da Silva, F. (2008) *Synlett*, 1777–1780.

310. Han, J., Liu, Y., and Guo, R. (2009) *J. Am. Chem. Soc.*, **131**, 2060–2061.

311. (a) Carrettin, S., Corma, A., Iglesias, M., and Sánchez, F. (2005) *Appl. Catal. A*, **291**, 247–252; (b) González-Arellano, C., Corma, A., Iglesias, M., and Sánchez, F. (2006) *J. Catal.*, **238**, 497–501; (c) Corma, A., Gutiérrez-Puebla, E., Iglesias, M., Monge, A., Pérez-Ferreras, S., and Sánchez, F. (2006) *Adv. Synth. Catal.*, **348**, 1899–1907; (d) Debono, N., Iglesias, M., and Sánchez, F. (2007) *Adv. Synth. Catal.*, **349**, 2470–2476.

312. Plenio, H. (2008) *Angew. Chem. Int. Ed.*, **47**, 6954–6956.

313. (a) Lauterbach, T., Livendahl, M., Rosellón, A., Espinet, P., and Echavarren, A.M. (2010) *Org. Lett.*, **12**, 3006–3009; (b) Livendahl, M., Espinet, P., and Echavarren, A.M. (2011) *Platinum Met. Rev.*, **55**, 216–218; (c) Livendahl, M. and Echavarren, A.M. (2012) *Chem. Today.*, **30**, 19–21.

314. (a) Hashmi, A.S.K., Lothschütz, C., Döpp, R., Rudolph, M., Ramamurthi, T.D., and Rominger, F. (2009) *Angew. Chem. Int. Ed.*, **48**, 8243–8246; (b) Hashmi, A.S.K., Döpp, R., Lothschütz, C., Rudolph, M., Riedel, D., and Rominger, F. (2010) *Adv. Synth. Catal.*, **352**, 1307–1314; (c) Hashmi, A.S.K., Lothschütz, C., Döpp, R., Ackermann, M., Becker, J.D.B., Rudolph, M., Scholz, C., and Rominger, F. (2012) *Adv. Synth. Catal.*, **354**, 133–147.

315. Suzuki coupling proceeds with very low palladium(0) loadings: Arvela, R.K., Leadbeater, N.E., Sangi, M.S., Williams, V.A., Granados, P., and Singer, R.D. (2005) *J. Org. Chem.*, **70**, 161–168.

316. Review on the topic of trace metal impurities in catalysis: Thome, I., Nijs,

A., and Bolm, C. (2012) *Chem. Soc. Rev.*, **41**, 979–987.
317. Corma, A., Juárez, R., Boronat, M., Sánchez, F., Iglesias, M., and García, H. (2010) *Chem. Commun.*, **47**, 1446–1448.
318. Stratakis, M. and García, H. (2012) *Chem. Rev.*, **102**, 4469–4506.
319. Robinson, P.S.D., Khairallah, G.N., da Silva, G., Lioe, H., and O'Hair, R.A.J. (2012) *Angew. Chem. Int. Ed.*, **51**, 3812–3817.
320. Jones, L.A., Sanz, S., and Laguna, M. (2007) *Catal. Today*, **122**, 403–406.
321. (a) Panda, B. and Sarkar, T.K. (2010) *Tetrahedron Lett.*, **51**, 301–305; (b) Panda, B. and Sarkar, T.K. (2010) *Chem. Commun.*, **46**, 3131–3133.
322. (a) Hirner, J.J., Shi, Y., and Blum, S.A. (2011) *Acc. Chem. Res.*, **44**, 603–613; (b) Rothe, K.A. and Blum, S.A. (2011) *Organometallics*, **30**, 4811–4813.
323. Peña-López, M., Ayán-Varela, M., Sarandeses, L.A., and Pérez Sestelo, J. (2010) *Chem.—Eur. J.*, **16**, 9905–9909.
324. Peña-López, M., Ayán-Varela, M., Sarandeses, L.A., and Pérez Sestelo, J. (2012) *Org. Biomol. Chem.*, **10**, 1686–1694.
325. Hirner, J.J. and Blum, S.A. (2011) *Organometallics*, **30**, 1299–1302.
326. Pankajakshan, S. and Loh, T.-P. (2011) *Chem. Asian J.*, **9**, 2291–2295.
327. (a) Tamaki, A. and Kochi, J.K. (1972) *J. Organomet. Chem.*, **40**, C81–C84; (b) Tamaki, A. and Kochi, J.K. (1973) *J. Chem. Soc., Dalton Trans.*, 2620–2626; (c) Johnson, A. and Puddephatt, R.J. (1973) *Inorg. Nucl. Chem. Lett.*, **9**, 1175–1177; (d) Tamaki, A. and Kochi, J.K. (1974) *J. Organomet. Chem.*, **64**, 411–425; (e) Johnson, A. and Puddephatt, R.J. (1975) *J. Organomet. Chem.*, **85**, 115–121.
328. Johnson, M.T., van Rensburg, J.M.J., Axelsson, M., Ahlquist, M.S.G., and Wendt, O.F. (2011) *Chem. Sci.*, **2**, 2373–2377.
329. Johnson, A. and Puddephatt, R.J. (1976) *J. Chem. Soc., Dalton Trans.*, 1360–1363.
330. Bachman, R.E., Bodolosky-Bettis, S.A., Pyle, C.J., and Gray, M.A. (2008) *J. Am. Chem. Soc.*, **130**, 14303–14310.
331. Gualco, P., Ladeira, S., Miqueu, K., Amgoune, A., and Bourissou, D. (2011) *Angew. Chem. Int. Ed.*, **50**, 8320–8324.
332. (a) Zhang, G., Peng, Y., Cui, L., and Zhang, L. (2009) *Angew. Chem. Int. Ed.*, **48**, 3112–3115; (b) Peng, Y., Cui, L., Zhang, G., and Zhang, L. (2009) *J. Am. Chem. Soc.*, **131**, 5062–5063.
333. (a) Melhado, A.D., Brenzovich, W.E., Lackner, A.D., and Toste, F.D. (2010) *J. Am. Chem. Soc.*, **132**, 8885–8887; (b) Mankad, N.P. and Toste, F.D. (2010) *J. Am. Chem. Soc.*, **132**, 12859–12861.
334. Hopkinson, N.N., Gee, A.D., and Gouverneur, V. (2011) *Chem.—Eur. J.*, **17**, 8248–8262.
335. de Haro, T. and Nevado, C. (2010) *J. Am. Chem. Soc.*, **132**, 1512–1513.
336. (a) Brand, P., Charpentier, J., and Waser, J. (2009) *Angew. Chem. Int. Ed.*, **48**, 9346–9349; (b) Brand, J.P. and Waser, J. (2010) *Angew. Chem. Int. Ed.*, **49**, 7304–7307; (c) Brand, J.P., Chevalley, C., and Waser, J. (2011) *Beilstein J. Org. Chem.*, **7**, 565–569; (d) Brand, J.P. and Waser, J. (2012) *Org. Lett.*, **14**, 744–747.
337. Qian, D. and Zhang, J. (2011) *Beilstein J. Org. Chem.*, **7**, 808–812.
338. (a) Partyka, D.V., Zeller, M., Hunter, A.D., and Gray, T.G. (2006) *Angew. Chem. Int. Ed.*, **45**, 8188–8191; (b) Partyka, D.V., Updegraff, J.B., Zeller, M., Hunter, A.D., and Gray, T.G. (2009) *Organometallics*, **28**, 1666–1674.
339. (a) Ball, L.T., Green, M., Lloyd-Jones, G.C., and Russell, C.A. (2010) *Org. Lett.*, **12**, 4724–4727; (b) Ball, L.T., Lloyd-Jones, G.C., and Russell, C.A. (2012) *Chem.—Eur. J.*, **18**, 2931–2937.
340. Ball, L.T., Lloyd-Jones, G.C., and Russell, C.A. (2012) *Science*, **337**, 1644–1648.
341. Cambeiro, X.C., Boorman, T.C., Lu, P., and Larrosa, I. (2013) *Angew. Chem. Int. Ed.*, **52**, 1781–1784.
342. Casado, A.L. and Espinet, P. (1998) *Organometallics*, **17**, 3677–3683.
343. Review on bimetallic intermediates:Pérez-Temprano, M.H., Casares, J.A., and Espinet, P. (2012) *Chem.—Eur. J.*, **18**, 1864–1884.

344. Serra, D., Moret, M.-E., and Chen, P. (2011) *J. Am. Chem. Soc.*, **133**, 8914–8926.

345. (a) Sherry, B.D. and Fürstner, A. (2008) *Acc. Chem. Res.*, **41**, 1500–1511; (b) Fürstner, A. (2009) *Angew. Chem. Int. Ed.*, **48**, 1364–1367.

346. (a) Bedford, R.B., Betham, M., Bruce, D.W., Danopoulos, A.A., Frost, R.M., and Hird, M. (2006) *J. Org. Chem.*, **71**, 1104–1110; (b) Adams, C.J., Bedford, R.B., Carter, E., Gower, N.J., Haddow, M.F., Harvey, J.N., Huwe, M., Cartes, M.Á., Mansell, S.M., Mendoza, C., Murphy, D.M., Neeve, E.C., and Nunn, J. (2012) *J. Am. Chem. Soc.*, **134**, 10333–10336; (c) Bedford, R.B., Carter, E., Cogswell, P.M., Gower, N.J., Haddow, M.F., Harvey, J.N., Murphy, D.M., Neeve, E.C., and Nunn, J. (2013) *Angew. Chem. Int. Ed.*, **52**, 1285–1288.

347. Noda, D., Sunada, Y., Hatakeyama, T., Nakamura, M., and Nagashima, H. (2009) *J. Am. Chem. Soc.*, **131**, 6078–6079.

348. Hatakeyama, T., Okada, Y., Yoshimoto, Y., and Nakamura, M. (2011) *Angew. Chem. Int. Ed.*, **50**, 10973–10976.

349. (a) Hedström, A., Bollmann, U., Bravidor, J., and Norrby, P.-O. (2011) *Chem.—Eur. J.*, **17**, 11991–11993; (b) Kleimark, J., Larsson, P.-F., Emamy, P., Hedström, A., and Norrby, P.-O. (2012) *Adv. Synth. Catal.*, **354**, 448–456.

350. Guisán-Ceinos, M., Tato, F., Buñuel, E., Calle, P., and Cárdenas, D.J. (2013) *Chem. Sci.*, **4**, 1098–1104.

351. (a) Gosmini, C., Bégouin, J.-M., and Moncomble, A. (2008) *Chem. Commun.*, 3221–3233; (b) Gosmini, C. and Moncomble, A. (2010) *Isr. J. Chem.*, **50**, 568–576.

352. Cahiez, G. and Moyeux, A. (2010) *Chem. Rev.*, **110**, 1435–1462.

353. Gülak, S., Stepanek, O., Malberg, J., Rad, B.R., Kotora, M., Wolf, R., and von Wangelin, A.J. (2013) *Chem. Sci.*, **4**, 776–784.

354. Sajith, P.K. and Suresh, C.H. (2011) *Inorg. Chem.*, **50**, 8085–8093.

355. Pérez-Rodríguez, M., Braga, A.A.C., Garcia-Melchor, M., Pérez-Temprano, M.H., Casares, J.A., Ujaque, G., de Lera, A.R., Álvarez, R., Maseras, F., and Espinet, P. (2009) *J. Am. Chem. Soc.*, **131**, 3650–3657.

356. Dierkes, P. and van Leeuwen, P.W.N.M. (1999) *J. Chem. Soc., Dalton Trans.*, 1519–1530.

357. (a) Brown, J.M. and Guiry, P.J. (1994) *Inorg. Chim. Acta*, **220**, 249–259; (b) Calhorda, M.J., Brown, J.M., and Cooley, N.A. (1991) *Organometallics*, **10**, 1431–1438.

358. The same effect has been observed in other reductive eliminations: (a) Mann, G., Barañano, D., Hartwig, J.F., Rheingold, A.L., and Guzei, I.A. (1998) *J. Am. Chem. Soc.*, **120**, 9205–9219; (b) Marcone, J.E. and Moloy, K.G. (1998) *J. Am. Chem. Soc.*, **120**, 8527–8528.

359. Hayashi, T., Konishi, M., Kobori, Y., Kumada, M., Higuchi, T., and Hirotsu, K. (1984) *J. Am. Chem. Soc.*, **106**, 158–163.

360. Kranenburg, M., Kamer, P.C.J., and van Leeuwen, P.W.N.M. (1998) *Eur. J. Inorg. Chem.*, **1998**, 155–157.

361. He, X., Zhang, S., Guo, Y., Wang, H., and Lin, G. (2012) *Organometallics*, **31**, 2945–2948.

362. (a) Goliaszewski, A. and Schwartz, J. (1985) *Organometallics*, **4**, 417–419; (b) Goliaszewski, A. and Schwartz, J. (1984) *J. Am. Chem. Soc.*, **106**, 5028–5030; (c) Temple, J.S., Riediker, M., and Schwartz, J. (1982) *J. Am. Chem. Soc.*, **104**, 1310–1315; (d) Goliaszewski, A. and Schwartz, J. (1985) *Tetrahedron*, **41**, 5779–5789.

363. Bertani, R., Berton, A., Carturan, G., and Campostrini, R. (1988) *J. Organomet. Chem.*, **349**, 263–268.

364. (a) Numata, S. and Kurosawa, H. (1977) *J. Organomet. Chem.*, **131**, 301–308; (b) Kurosawa, H., Shiba, K., Hirako, K., Kakiuchi, K., and Ikeda, I. (1994) *J. Chem. Soc., Chem. Commun.*, 1099–1100; (c) Kurosawa, H., Emoto, M., and Kawasaki, Y. (1988) *J. Organomet. Chem.*, **346**, 137–146; (d) Kurosawa, H., Emoto, M., Ohnishi, H., Miki, K., Kasai, N., Tatsumi, K., and Nakamura, A. (1987) *J. Am. Chem. Soc.*, **109**, 6333–6340.

365. (a) Newman, S.G. and Lautens, M. (2011) *J. Am. Chem. Soc.*, **133**, 1778–1780; (b) Lan, Y., Liu, P.,

Newman, S.G., Lautens, M., and Houk, K.N. (2012) *Chem. Sci.*, **3**, 1987–1995.
366. Albéniz, A.C., Espinet, P., and Martínez-Ruiz, B. (2001) *Chem.—Eur. J.*, **7**, 2481–2489.
367. Méndez, M. and Echavarren, A.M. (2002) *Eur. J. Org. Chem.*, 15–28.
368. Nakamura, H., Aoyagi, K., Shim, J.-G., and Yamamoto, Y. (2001) *J. Am. Chem. Soc.*, **123**, 372–377.
369. Szabó, K.J. (2000) *Chem.—Eur. J.*, 4413–4421.
370. Henc, B., Jolly, P.W., Salz, R., Stobbe, S., Wilke, G., Benn, R., Mynott, R., Seevogel, K., Goddard, R., and Kruger, C. (1980) *J. Organomet. Chem.*, **191**, 449–475.
371. Kuhn, O. and Mayr, H. (1999) *Angew. Chem. Int. Ed.*, **38**, 343–346.
372. Krause, J., Goddard, R., Mynott, R., and Pörschke, K.-R. (2001) *Organometallics*, **20**, 1992–1999.
373. Jolly, P.W. (1985) *Angew. Chem., Int. Ed. Engl.*, **24**, 283–295.
374. Krause, J., Bonrath, W., and Pörschke, K.-R. (1992) *Organometallics*, **11**, 1158–1167.
375. Méndez, M., Cuerva, J.M., Gómez-Bengoa, E., Cárdenas, D.J., and Echavarren, A.M. (2002) *Chem.—Eur. J.*, **8**, 3620–3628.
376. Pérez-Rodríguez, M., Braga, A.A.C., de Lera, A.R., Maseras, F., Álvarez, R., and Espinet, P. (2010) *Organometallics*, **29**, 4983–4991.
377. (a) Sieber, J.D., Liu, S., and Morken, J.P. (2007) *J. Am. Chem. Soc.*, **129**, 2214–2215; (b) Zhang, P. and Morken, J.P. (2009) *J. Am. Chem. Soc.*, **131**, 12550–12551; (c) Zhang, P., Brozek, L.A., and Morken, J.P. (2010) *J. Am. Chem. Soc.*, **132**, 10686–10688; (d) Brozek, L.A., Ardolino, M.J., and Morken, J.P. (2011) *J. Am. Chem. Soc.*, **133**, 16778–16781.
378. Fauvarque, J.F. and Jutand, A. (1979) *J. Organomet. Chem.*, **177**, 273–281.
379. (a) Galarini, R., Musco, A., Pontellini, R., and Santi, R. (1992) *J. Mol. Catal.*, **72**, L11–L13; (b) Kuwajima, I. and Nakamura, E.-I. (1985) *Acc. Chem. Res.*, **18**, 181–187; (c) Kosugi, M., Hagiwara, I., Sumiya, T., and Migita, T. (1984) *Bull. Chem. Soc. Jpn.*, **57**, 242–246.
380. Semmelhack, M.F., Stauffer, R.D., and Rogerson, T.D. (1973) *Tetrahedron Lett.*, **14**, 4519–4522.
381. Miura, M. and Nomura, M. (2002) *Top. Curr. Chem.*, **219**, 211–241.
382. Rutherford, J.L., Rainka, M.P., and Buchwald, S.L. (2002) *J. Am. Chem. Soc.*, **124**, 15168–15169.
383. Viciu, M.S., Kelly, R.A., Stevens, E.D., Naud, F., Studer, M., and Nolan, S.P. (2003) *Org. Lett.*, **5**, 1479–1482.
384. Klinkenberg, J.L. and Hartwig, J.F. (2012) *J. Am. Chem. Soc.*, **134**, 5758–5761.
385. (a) Hennessy, E.J. and Buchwald, S.L. (2002) *Org. Lett.*, **4**, 269–272; (b) Konopelski, J.P., Hottenroth, J.M., Oltra, H.M., Véliz, E.A., and Yang, Z.-C. (1996) *Synlett*, 609–611; (c) Hang, H.C., Drotleff, E., Elliott, G.I., Ritsema, T.A., and Konopelski, J.P. (1999) *Synthesis*, 398–400.
386. Okuro, K., Feruune, M., Miura, M., and Nomura, M. (1993) *J. Org. Chem.*, **58**, 7606–7607.
387. Hartwig, J.F. (2008) *Acc. Chem. Res.*, **41**, 1534–1544.
388. (a) Anderson, B.A., Bell, E.C., Ginah, F.O., Harn, N.K., Pagh, L.M., and Wepsiec, J.P. (1998) *J. Org. Chem.*, **63**, 8224–8228; (b) Sundermeier, M., Zapf, A., and Beller, M. (2003) *Angew. Chem. Int. Ed.*, **42**, 1661–1664; (c) Mechanistic studies indicate that the amine (TMEDA) co-catalyst prevents deactivation of Pd(0) complexes by cyanide ions: Sundermeier, M., Zapf, A., Mutyala, S., Baumann, W., Sans, J., Weiss, S., and Beller, M. (2003) *Chem.—Eur. J.*, **9**, 1828–1836; (d) Ushkov, A.V. and Grushin, V.V. (2010) *J. Am. Chem. Soc.*, **133**, 10999–11005.
389. Widenhoefer, R.A. and Buchwald, S.L. (1996) *Organometallics*, **15**, 2755–2763.
390. Shekhar, S. and Hartwig, J.F. (2007) *Organometallics*, **26**, 340–351.
391. Mann, G. and Hartwig, J.F. (1996) *J. Am. Chem. Soc.*, **118**, 13109–13110.
392. Singh, U.K., Strieter, E.R., Blackmond, D.G., and Buchwald, S.L. (2003) *J. Am. Chem. Soc.*, **124**, 14104–14114.
393. (a) Alcazar-Roman, L.M., Hartwig, J.F., Rheingold, A.L., Liable-Sands, L.M., and Guzei, I.A. (2000) *J. Am. Chem.*

Soc., **122**, 4618–4630; (b) Yin, J. and Buchwald, S.L. (2002) *J. Am. Chem. Soc.*, **124**, 6043–6048; (c) Shekhar, S., Ryberg, P., Hartwig, J.F., Mathew, J.S., Blackmon, D.G., Stieter, E.R., and Buchwald, S.L. (2006) *J. Am. Chem. Soc.*, **128**, 3584–3591.

394. Shekhar, S., Ryberg, P., and Hartwig, J.F. (2006) *Org. Lett.*, **8**, 851–854.

395. Alvaro, E. and Hartwig, J.F. (2009) *J. Am. Chem. Soc.*, **131**, 7858–7868.

396. Harwig, J.F. (2007) *Inorg. Chem.*, **46**, 1936–1947.

397. (a) Driver, M.S. and Hartwig, J.F. (1997) *J. Am. Chem. Soc.*, **119**, 8232–8245; (b) Mann, G., Shelby, Q., Roy, A.H., and Hartwig, J.F. (2003) *Organometallics*, **22**, 2775–2789; (c) Fujita, K.I., Yamashita, M., Puschmann, F., Alvarez-Falcon, M.M., Incarvito, C.D., and Hartwig, J.F. (2006) *J. Am. Chem. Soc.*, **128**, 9044–9045.

398. Villanueva, L.A., Abboud, K.A., and Boncellam, J.M. (1994) *Organometallics*, **13**, 3921–3931.

399. Driver, M.S. and Hartwig, J.F. (1995) *J. Am. Chem. Soc.*, **117**, 4708–4709.

400. Yamashita, M., Cuevas Vicario, J.V., and Hartwig, J.F. (2003) *J. Am. Chem. Soc.*, **25**, 16347–16360.

401. Klinkenberg, J.L. and Hartwig, J.F. (2010) *J. Am. Chem. Soc.*, **132**, 11830–11833.

402. Barañano, D. and Hartwig, J.F. (1995) *J. Am. Chem. Soc.*, **117**, 2937–2938.

403. (a) Shelby, Q., Kataoka, N., Mann, G., and Hartwig, J.F. (2000) *J. Am. Chem. Soc.*, **122**, 10718–10719; (b) Mann, G., Incarvito, C., Rheingold, A.L., and Hartwig, J.F. (1999) *J. Am. Chem. Soc.*, **121**, 3224–3225.

404. (a) Aranyos, A., Old, D.W., Koyimori, A., Wolfe, J.P., Sadighi, J.P., and Buchwald, S.L. (1999) *J. Am. Chem. Soc.*, **121**, 4369–4378; (b) Torraca, K.E., Huang, X., Parrish, C.A., and Buchwald, S.L. (2001) *J. Am. Chem. Soc.*, **123**, 10770–10771; (c) Kuwabe, S., Torraca, K.E., and Buchwald, S.L. (2001) *J. Am. Chem. Soc.*, **123**, 12202–12206; (d) Harkal, S., Kumar, K., Michalik, D., Zapf, A., Jackstell, R., Rataboul, F., Riermeier, T., Monsees, A., and Beller, M. (2005) *Tetrahedron Lett.*, **46**, 3237–3240; (e) Burgos, C.H., Barder, T.E., Huang, X., and Buchwald, S.L. (2006) *Angew. Chem. Int. Ed.*, **118**, 4321–4326; (f) Hu, T., Schulz, T., Torborg, C., Chen, X., Wang, J., Beller, M., and Huang, J. (2009) *Chem. Commun.*, 7330–7332; (g) Wu, X., Fors, B.P., and Buchwald, S.L. (2011) *Angew. Chem. Int. Ed.*, **50**, 9943–9947.

405. Stambuli, J.P., Weng, Z., Incarvito, C.D., and Hartwig, J.F. (2007) *Angew. Chem. Int. Ed.*, **46**, 7674–7677.

406. Beletskaya, I.P., Bessmertnykh, A.L., and Guilard, R. (1999) *Tetrahedron Lett.*, **40**, 6393–6397.

407. Hartwig, J.F. (1996) *J. Am. Chem. Soc.*, **118**, 7010–7011.

408. Zhao, J., Hesslink, H., and Hartwig, J.F. (2001) *J. Am. Chem. Soc.*, **123**, 7220–7227.

409. Zhao, P. and Hartwig, J.F. (2005) *J. Am. Chem. Soc.*, **127**, 11618–11619.

410. Mann, G. and Hartwig, J.F. (1997) *J. Org. Chem.*, **62**, 5413–5418.

411. Ley, S.V. and Thomas, A.W. (2003) *Angew. Chem. Int. Ed.*, **42**, 5400–5449.

412. Beletskaya, I.P. and Cheprakov, A.V. (2004) *Coord. Chem. Rev.*, **248**, 2337–2364.

413. (a) Gujadhur, R.K., Bates, C.G., and Venkataraman, D. (2001) *Org. Lett.*, **3**, 4315–4317; (b) Goodbrand, H.B. and Hu, N.X. (1999) *J. Org. Chem.*, **64**, 670–674; (c) Kiyomori, A., Marcoux, J.-F., and Buchwald, S.L. (1999) *Tetrahedron Lett.*, **40**, 2657–2660.

414. (a) Klapars, A., Huang, X., and Buchwald, S.L. (2002) *J. Am. Chem. Soc.*, **124**, 7421–7428; (b) Antilla, J.C., Klapars, A., and Buchwald, S.L. (2002) *J. Am. Chem. Soc.*, **124**, 11684–11688; (c) Maiti, D. and Buchwald, S.L. (2010) *J. Org. Chem.*, **75**, 1791–1794.

415. Ma, D., Zhang, Y., Yao, J., Wu, S., and Tao, F. (1998) *J. Am. Chem. Soc.*, **120**, 12459–12467.

416. (a) Cristau, H.-J., Cellier, P.P., Spindler, J.-F., and Taillefer, M. (2004) *Chem.—Eur. J.*, **10**, 5607–5622; (b) Cristau, H.-J., Cellier, P.P., Spindler, J.-F., and Taillefer, M. (2004) *Eur. J. Org. Chem.*, 695–709; (c) Cristau, H.-J., Cellier, P.P., Ouali, A., Spindler, J.-F.,

and Taillefer, M. (2006) *Adv. Synth. Catal.*, **348**, 499–505; (d) Cristau, H.-J., Cellier, P.P., Hamada, S., Spindler, J.-F., and Taillefer, M. (2004) *Org. Lett.*, **6**, 913–916; (e) Ouali, A., Taillefer, M., Spindler, J.-F., and Jutand, A. (2007) *Organometallics*, **26**, 65–74; (f) Ouali, A., Spindler, J.-F., Jutand, A., and Taillefer, M. (2007) *Adv. Synth. Catal.*, **349**, 1906–1916.

417. Yang, C.-T., Fu, Y., Huang, Y.-B., Yi, J., Guo, Q.-X., and Liu, L. (2009) *Angew. Chem. Int. Ed.*, **48**, 7398–7401.

418. Larsson, P.-F., Correa, A., Carril, M., Norrby, P.-O., and Bolm, C. (2009) *Angew. Chem. Int. Ed.*, **48**, 5691–5693.

419. Zaho, D., Wu, N., Zhang, S., Xi, P., Su, X., Lan, J., and You, J. (2009) *Angew. Chem. Int. Ed.*, **48**, 8729–8732.

420. (a) Yang, D. and Fu, H. (2010) *Chem.—Eur. J.*, **16**, 2366–2370; (b) Jing, L., Wei, J., Zhou, L., Huang, Z., Li, Z., and Zhou, X. (2010) *Chem. Commun.*, **46**, 4767–4769; (c) Maurer, S., Liu, W., Zhang, X., Jiang, Y., and Ma, D. (2010) *Synlett*, 976–978; (e) Paul, R., Ali, M.A., and Punniyamurthy, T. (2010) *Synthesis*, **24**, 4268–4272; (f) Yang, K., Li, Z., Wang, Z., Yao, Z., and Jiang, S. (2011) *Org. Lett.*, **13**, 4340–4343.

421. (a) de Lange, B., Lambers-Verstappen, M.H., Schmieder-van de Vondervoort, L., Sereinig, N., de Rijk, R., de Vries, A.H.M., and de Vries, J.G. (2006) *Synlett*, 3105–3109; (b) Shafir, A. and Buchwald, S.L. (2006) *J. Am. Chem. Soc.*, **128**, 8742–8743.

422. Guram, A.S., Rennels, R.A., and Buchwald, S.L. (1995) *Angew. Chem., Int. Ed. Engl.*, **34**, 1348–1350.

423. Louie, J. and Hartwig, J.F. (1995) *Tetrahedron Lett.*, **36**, 3609–3612.

424. Wolfe, J.P., Wagaw, S., and Buchwald, S.L. (1996) *J. Am. Chem. Soc.*, **118**, 7215–7216.

425. Driver, S.M. and Hartwig, J.F. (1996) *J. Am. Chem. Soc.*, **118**, 7217–7218.

426. Wolfe, J.P. and Buchwald, S.L. (2000) *J. Org. Chem.*, **65**, 1144–1157.

427. Platon, M., Cui, L., Mom, S., Richard, P., Saeys, M., and Hierso, J.-C. (2011) *Adv. Synth. Catal.*, **353**, 3403–3414.

428. Wolfe, J.P., Wawgaw, S., Marcoux, J.-F., and Buchwald, S.L. (1998) *Acc. Chem. Res.*, **31**, 805–818.

429. Harkal, S., Rataboul, F., Zapf, A., Fuhrmann, C., Riermeier, T., Monsees, A., and Beller, M. (2004) *Adv. Synth. Catal.*, **346**, 1742–1748.

430. Shen, Q., Shekhar, S., Stambuli, J.P., and Hartwig, J.F. (2004) *Angew. Chem. Int. Ed.*, **44**, 1371–1375.

431. Hoi, K.H., Çalimsiz, S., Froese, R.D.J., Hopkinson, A.C., and Organ, M.G. (2012) *Chem.—Eur. J.*, **18**, 145–151.

432. Shen, Q., Ogata, T., and Hartwig, J.F. (2008) *J. Am. Chem. Soc.*, **130**, 6586–6596.

433. Wolfe, J.P., Tomori, H., Sadighi, J.P., Yin, J.J., and Buchwald, S.L. (2000) *J. Org. Chem.*, **65**, 1158–1178.

434. Marion, N., Navarro, O., Mei, J., Stevens, E.D., Scott, N.M., and Nolan, S.P. (2006) *J. Am. Chem. Soc.*, **128**, 4101–4111.

435. Shen, Q. and Hartwig, J.F. (2006) *J. Am. Chem. Soc.*, **128**, 10028–10029.

436. Surry, D.S. and Buchwald, S.L. (2007) *J. Am. Chem. Soc.*, **129**, 10354–10355.

437. Anderson, K.W., Tundel, R.E., Ikawa, T., Altman, R.A., and Buchwald, S.L. (2006) *Angew. Chem. Int. Ed.*, **45**, 6523–6527.

438. Shen, Q. and Hartwig, J.F. (2007) *J. Am. Chem. Soc.*, **129**, 7734–7735.

439. Strieter, E.R., Bhayana, B., and Buchwald, S.L. (2009) *J. Am. Chem. Soc.*, **131**, 78–88.

440. (a) Strieter, E.R., Blackmond, D.G., and Buchwald, S.L. (2005) *J. Am. Chem. Soc.*, **127**, 4120–4121; (b) Tye, J.W., Weng, Z., Johns, A.M., Incarvito, C.D., and Hartwig, J.F. (2008) *J. Am. Chem. Soc.*, **130**, 9971–9983; (c) Tye, J.W., Weng, Z., Giri, R., and Hartwig, J.F. (2010) *Angew. Chem. Int. Ed.*, **49**, 2185–2189; (d) Giri, R. and Hartwig, J.F. (2010) *J. Am. Chem. Soc.*, **132**, 15860–15863; (e) Yu, H.-Z., Jiang, Y.-Y., Fu, Y., and Liu, L. (2010) *J. Am. Chem. Soc.*, **132**, 18078–18091.

441. Zhang, S.-L., Liu, L., Fu, Y., and Guo, Q.-X. (2007) *Organometallics*, **26**, 4546–4554.

442. Lefèvre, G., Franc, G., Tlili, A., Adamo, C., Taillefer, M., Ciofini, I., and Jutand, A. (2012) *Organometallics*, **31**, 7694–7707.
443. Huffman, L.M. and Stahl, S.S. (2008) *J. Am. Chem. Soc.*, **130**, 9196–9197.
444. Jones, G.O., Liu, P., Houk, K.N., and Buchwald, S.L. (2010) *J. Am. Chem. Soc.*, **132**, 6205–6213.
445. Creutz, S.E., Lotito, K.J., Fu, G.C., and Peters, J.C. (2012) *Science*, **338**, 647–650.
446. Shafir, A., Lichtor, P.A., and Buchwald, S.L. (2007) *J. Am. Chem. Soc.*, **129**, 3490–3491.
447. He, C., Zhang, G., Ke, J., Zhang, H., Miller, J.T., Kropf, A.J., and Lei, A. (2013) *J. Am. Chem. Soc.*, **135**, 488–493
448. Altman, R.A., Hyde, A.M., Huang, X., and Buchwald, S.L. (2008) *J. Am. Chem. Soc.*, **130**, 9613–9620.