C–C Coupling

The Mechanisms of the Stille Reaction

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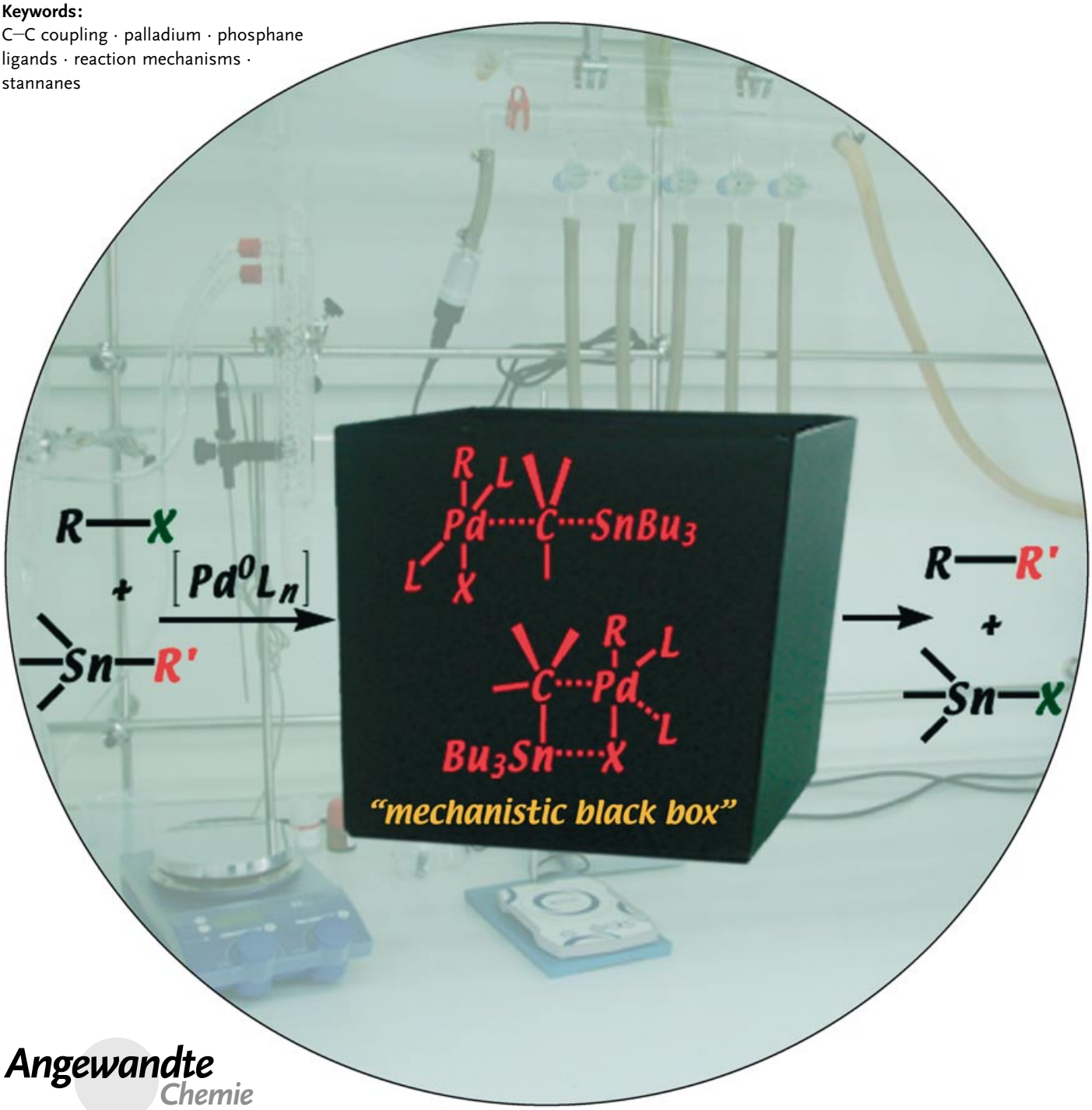

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Eighteen years ago in Angewandte Chemie John K. Stille reviewed a novel methodology, which eventually became known by his name, for the coupling of organostannanes with organic electrophiles. Since then that seed has blossomed into a multifaceted methodology full of hidden possibilities to explore, discover, and enjoy. Very recent modifications are making synthetic wishes come true that were only dreamed of a few years ago. Moreover, as important advances are being made in the understanding of the mechanistic details of the process, it is becoming increasingly possible to apply this essential reaction and its new variants in a less empirical way. The purpose of this Review is to give a critical account of this progress.

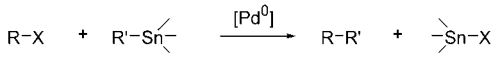
From the Contents

> *"Why with the time do I not glance asideTo new-found methods...?"*
> W. Shakespeare, Sonnet LXXVI

1. Introduction

1.1. Palladium-Catalyzed Cross-Coupling Reactions

The Stille reaction has established itself as one of the two most general and most selective palladium-catalyzed cross-coupling reactions (Scheme 1),[1–3] along with the Suzuki



Scheme 1. The Stille coupling.

cross-coupling of organoboron compounds.[4] The first examples of the coupling of organostannanes with organic electrophiles were disclosed during the period 1976–1977 by the research groups of Eaborn[5] and Kosugi,[6,7] but it was the extensive synthetic and mechanistic work carried out by Stille and co-workers from 1978[8] that made this reaction a standard method in organic synthesis.[9]

The Stille and Suzuki reactions rank today amongst the more general transformations in organic synthesis.[10] For the synthesis of complex molecules,[11] the Stille coupling is usually superior, displaying high selectivity and broad scope. Its tolerance towards most functional groups makes the Stille coupling particularly effective for transformations of highly functionalized molecules. In fact it has been applied successfully to the construction of a variety of ring systems bearing sensitive functional groups.[12] Notable examples are the syntheses of dynemicin A by Danishefsky and co-workers[13] and rapamycin by Nicolaou and co-workers,[14] in which double couplings are used for the formation of two C–C bonds are formed in a single step.

The Stille reaction is related to other cross-coupling reactions based transmetalations of a variety of hard or soft organometallic nucleophiles.[15] Besides the two prominent members already mentioned, the family of palladium-catalyzed cross-coupling reactions includes the Hiyama,[16–18] Sonogashira,[19] Kumada,[20] and Negishi reactions,[21] and related reactions.[22,23] Cross-coupling reactions are also somewhat related to the Heck reaction (the alkenylation of organic electrophiles).[24] However, although the first step in both processes is identical (activation of the organic electrophile by oxidative addition to Pd), there is no transmetalation step in the Heck reaction, in which the C–C bond is formed through an insertion step, followed by a β-hydride elimination to form the substituted alkene product.

1.2. Original Mechanistic Proposal

In his influential Review of 1986,[1] Stille proposed a mechanism for the Stille reaction based primarily on data obtained from the coupling of benzoyl chloride with tributyl(phenyl)stannane.[1] In the generalized mechanism, the active catalytic species was assumed to be a $[PdL_2]$ ($L = PPh_3$) complex, which reacts with the organic electrophile R–X to

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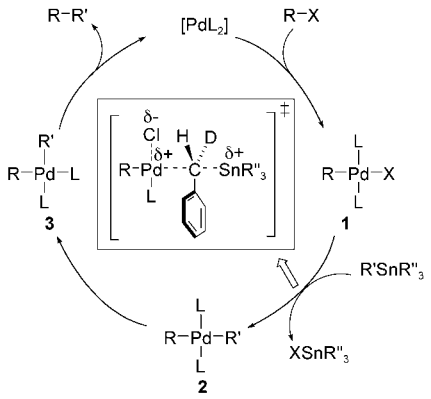
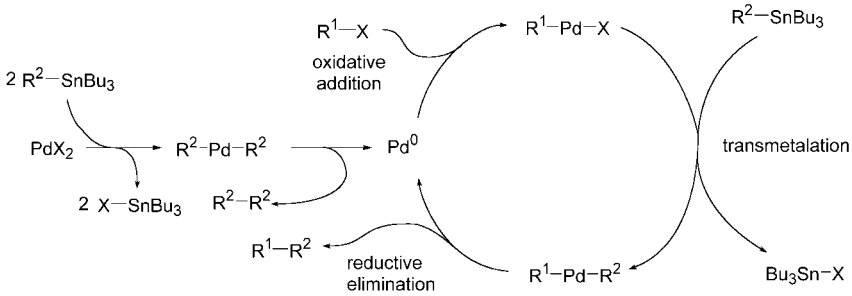


Scheme 2. The original proposal for the mechanism of the Stille reaction.

form complex **1** (Scheme 2). The latter complex was the only observable species in the catalytic cycle, even in the presence of excess organostannane, which demonstrated that the slow step was the transmetalation reaction with the organostannane. The transmetalation was believed to lead to complex **2**. A *trans* to *cis* isomerization to give **3**, thought to be very fast, was then required for the reductive elimination to give the organic product R–R′.

In that Review, Stille considered that the oxidative-addition and reductive-elimination sequences were reasonably well understood, whereas the transmetalation step was much less so.[1] He pointed out that the existing data for the transmetalation supported an electrophilic cleavage of the Sn–C bond (S_E2), with the Pd^{II} complex **1** acting as the electrophile. (Looking at the reaction from the point of view of the metal undergoing the attack, this is a nucleophilic attack (S_N2), which is convenient to have in mind to see the relationship with the ligand substitution reactions discussed later). From his studies on the $[Pd(CH_2Ph)Cl(PPh_3)_2]$-catalyzed coupling of benzoyl chloride with (*S*)-$PhCHDSnBu_3$, which took place "certainly with more than 65% net inversion",[1] Stille proposed for the S_E2 transmetalation step the open transition state shown in the center of Scheme 2. This early mechanistic interpretation of the Stille reaction has been very fruitful in the hands of Farina and co-workers, who have been able to improve the practical application of the reaction considerably by using different ligands L from the commonly used triphenylphosphane, such as trifurylphosphane[25,26] and triphenylarsane.[27–29]

Interestingly, although the mechanism in Scheme 2 was proposed by Stille as a working model,[1] it seems to have been taken for granted. Moreover, it is not unusual for some details shown clearly in Scheme 2 to be oversimplified in papers and reviews focused on the synthetic applications of the Stille reaction, and to be systematically overlooked by practitioners of the process. For example, Scheme 3 shows a simplified catalytic cycle as published in a recent thorough and valuable synthesis-focused review. This scheme is more detailed than average in that it offers details about the formation of Pd^0 from a Pd^{II} precursor.[7] However, as is often the case in books and articles, it fails to provide any information about the geometry at the Pd center in the complexes or about the ligands; only the fragments arising from the two organic reagents are depicted. Thus, the need for a *trans–cis* isomerization step to give **3**, preceding the coupling step, is omitted. In our view, neglect of the coordination sphere of the palladium center can be detrimental to a more rational application of the process.



Scheme 3. A recent simplified representation of the Pd-catalyzed coupling of stannanes with organic electrophiles.

Although the use of the Stille coupling in synthesis is frequently empirical, the achievements are remarkable. The

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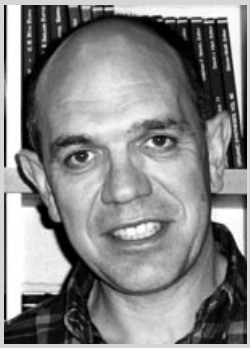

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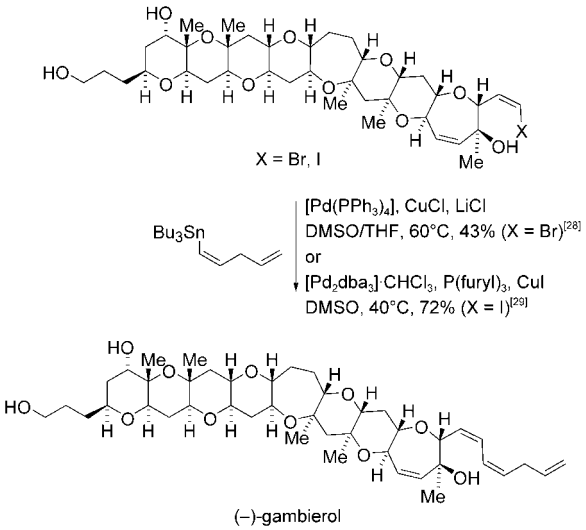
recent syntheses of gambierol by the groups of Sasaki[30] and Yamamoto[31] illustrate the advanced state of the art in this field. Both syntheses take advantage of the Stille coupling reaction to construct the *Z*,*Z* 1,3-diene functionality in the last step (Scheme 4), whereby it is not necessary to protect the hydroxy groups. These selective couplings were achieved under quite different conditions (see conditions in Scheme 4),[32] but in both cases the addition of a Cu^I salt was required to facilitate the transmetalation.[33]



Scheme 4. The Stille coupling in the synthesis of (−)-gambierol.

The success of the coupling reactions depicted in Scheme 4 relies on recent work aimed at improving the transmetalation step, which has been deemed as the rate-determining step in the coupling cycle. Thus, the addition of CuI or the use of $P(furyl)_3$ in place of PPh_3 is meant to facilitate the dissociation of one ligand and the formation of a [PdRXL] or [PdRXL(S)] intermediate ((S) = solvent molecule) prior to the formation of the putative transition state shown in Scheme 2.[25–27]

There are many indications that the original mechanistic model needs revision and completion. For example, both inversion[34] and retention[35] of the configuration of alkyl stannanes with a stereogenic C^α center have been observed. These results need to be accommodated in the mechanistic model. Similar stereoselectivity was found in the coupling of silanes.[36] Furthermore, it is not clear that the *trans–cis* isomerization of $[PdR_2L_2]$ complexes is always fast.[37] Actually, some isomerization reactions studied for isolated $[PdR_2L_2]$ complexes are slow,[38] or even extremely slow.[39] Therefore, intermediates of the type *trans*-$[PdRR'L_2]$ (**2** in Scheme 2) might be expected to be quite long-lived, but they have never been detected under catalytic conditions.[40] The effects of additives, such as Cu^I halides and alkaline salts, and the influence of the organic electrophile and the solvent are not yet well understood.

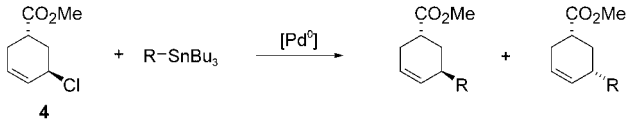
The purpose of this Review is to present a more complete and complex mechanistic picture of the reaction, including the interpretation of new experimental findings. It is hoped that this will help to emphasize the capital importance of the coordination sphere of the metal center, and will offer some hints for a more rational selection of reaction conditions. Selectivity, scope,[1,9] and other synthetic aspects of the reaction[41,42] that have already been covered in recent reviews are not dealt with in detail. Herein the different steps are discussed as they occur in the catalytic cycle. However, since the different factors that influence the course of the reaction are difficult to separate, this order is interrupted occasionally.

2. The Oxidative Addition

2.1. Inversion versus Retention

The oxidative addition of organic electrophiles (halides, sulfonates, and related compounds)[43] to Pd^0 is the first step in cross-coupling and Heck reactions.[24] The oxidative addition of $C(sp^3)$–X to Pd^0 complexes $[PdL_4]$ (L = phosphane) is usually an associative bimolecular process (S_N2 reaction). The leaving anion then adds to the metal center to give the product. The expected inversion at stereogenic centers was confirmed by the studies of Stille on the oxidative addition of chiral benzyl derivatives to Pd^0 coordinated to phosphane ligands.[50,51]

The stereochemical course of the oxidative addition of allyl halides depends on the nature of the solvent and the metal-bound ligands. Thus, the coupling of **4** with $RSnBu_3$ occurred with overall retention of configuration when the reactions were performed in benzene with a Pd^0 complex made in situ from $[Pd(\eta^3\text{-}C_3H_5)Cl]$ and maleic anhydride (Scheme 5). The configuration of the product is a conse-



R = Ph:	benzene	96	4
	MeCN	0	100
R = vinyl:	benzene	92	8
	MeCN	0	100

Scheme 5. The effect of the polarity of the solvent on stereoselective coupling reactions.

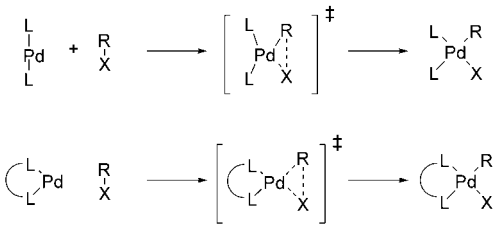
quence of the oxidative addition step, which occurs with complete or predominant retention of configuration in less coordinating solvents, such as benzene, CH_2Cl_2, THF, or acetone.[44,45] However, complete or nearly complete inversion was observed in more polar, coordinating solvents, such as MeCN or DMSO.[44] The results of theoretical studies on the oxidative addition of CH_3Cl to ligand-free Pd^0 support a three-center transition state involving the Pd atom and the C–Cl bond, which should lead to retention of configuration at a stereogenic carbon atom.[46] Oxidative addition in a *syn* sense has also been reported for related substrates.[47] However, with $[Pd(PPh_3)_4]$ the usual inversion of configuration in the oxidative addition was observed.[44,48,49]

Much work has been carried out on the mechanisms of the oxidative addition of aryl and alkenyl halides and triflates (electrophiles $C(sp^2)$–X), the most common organic electro-

philes in the Stille reaction.[50,51] These studies have shown that this transformation is not as simple as it appears in simplified general mechanistic schemes.[1]

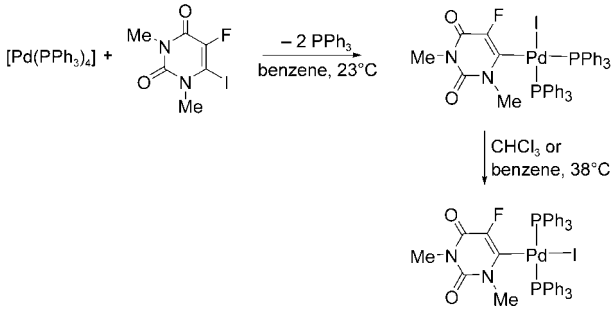
2.2. cis *Complexes in the Oxidative Addition*

As the intermediates observed in the catalytic cycle of the Stille reaction are *trans*-[PdRXL$_2$] complexes, this led to the widespread belief that these complexes are the primary products of the oxidative addition. However, the mechanism of the oxidative addition (at least for the most common electrophiles C(sp^2)–X) has been proposed to proceed by a concerted interaction of a reactive [PdL$_2$] or [Pd(L-L)] (L-L = diphosphane) species with R–X in a three-center transition state. This process should lead to *cis*-[PdRXL$_2$] complexes (Scheme 6). In the case of complexes with monodentate phosphane ligands, the initially formed *cis*-[PdRXL$_2$] complexes can isomerize to form the more stable *trans*-[PdRXL$_2$] complexes.



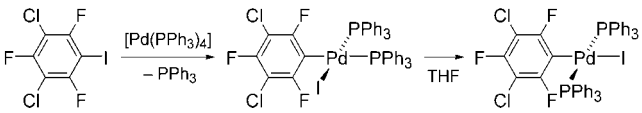
Scheme 6. Formation of *cis* complexes by oxidative addition to [PdL$_2$] or [Pd(L-L)] (L-L = diphosphane).

In fact *cis* complexes are observed to result from the oxidative addition reaction in a few cases with C(sp^2) electrophiles. The reaction of an iodouracil with [Pd(PPh$_3$)$_4$] leads initially to a *cis* Pd^{II} complex, which subsequently isomerizes to the more stable *trans* complex (Scheme 7).[52] A few other *cis* complexes have also been reported as the kinetic products of oxidative addition to Pd.[53]



Scheme 7. Formation of a stable *cis* complex through oxidative addition.

The *cis–trans* isomerization process has been analyzed in detail for the complex formed by the oxidative addition of C$_6$Cl$_2$F$_3$I to [Pd(PPh$_3$)$_4$] (Scheme 8).[54] It takes place by four major parallel pathways. The two main pathways involve direct and solvent-assisted associative replacement of PPh$_3$ by an iodo ligand of a second palladium complex, thus leading to the mono-iodo-bridged intermediate *cis*-[Pd(C$_6$Cl$_2$F$_3$)I(PPh$_3$)(μ-I)–{Pd}], which then rearranges to *trans*-[Pd(C$_6$Cl$_2$F$_3$)I(PPh$_3$)(μ-I)–{Pd}]. The two minor routes involve Berry pseudorotations on pentacoordinated species.



Scheme 8. Model reaction for the *cis–trans* isomerization.

It is quite general that complexes with a phosphane ligand and an R group in a *trans* relationship (usually the kinetic product of the oxidative addition) are unstable, as a result of the mutual destabilizing effect associated with the high *trans* influence of these ligands. Often they isomerize to the *cis* product (the thermodynamic product). The destabilizing interaction between pairs of ligands (in this case a phosphane ligand and a *trans* C-donor ligand) in Pd^{II} complexes has been named transphobia,[55] an effect that results in the enhanced kinetic reactivity of such complexes in ligand substitution reactions.[56]

A recent study on the oxidative addition of a series of aryl iodides with different Hammet parameters to [Pd(PPh$_3$)$_4$] confirmed that in all cases the oxidative addition step initially gives *cis*-[PdArI(PPh$_3$)$_2$].[57] These *cis* complexes undergo isomerization to *trans*-[PdArI(PPh$_3$)$_2$] at very different rates, and sometimes extremely fast. When the isomerization is too fast, the putative initial product of the oxidative addition, *cis*-[PdArI(PPh$_3$)$_2$], can not be observed. Under the standard reaction conditions for the Stille coupling, the isomerization of the initial *cis* complex to the thermodynamically favored *trans* isomer appears to be very fast relative to the transmetalation. Thus, for most *practical* purposes the intermediates *cis*-[PdRXL$_2$] need not be considered.

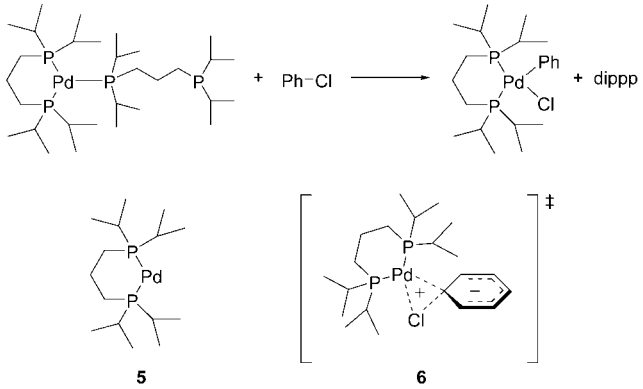
2.3. *Regioselectivity of the Oxidative Addition.*

The regioselectivity of the oxidative addition has not yet been systematically investigated. However, it was reported recently that the coupling of *p*-BrC$_6$H$_4$CH$_2$Br with tributyl(vinyl)tin catalyzed by *cis*-[PdBr(*N*-succinimido)(PPh$_3$)$_2$] yields a mixture of *p*-BrC$_6$H$_4$CH$_2$CH=CH$_2$ (84%) and *p*-CH$_2$=CHC$_6$H$_4$CH$_2$Br (7%). This selectivity must be traced back to the oxidative addition step.[58] Another example of regioselectivity, which is induced by the addition of copper salts, is discussed in Section 7.

2.4. *The Role of Bidentate Ligands*

The results of an early study on the mechanism of the oxidative addition of aryl iodides to [PdL$_2$] were consistent with an aromatic nucleophilic substitution.[59] Accordingly, electron-withdrawing substituents on aryl electrophiles lead

to rate acceleration.[60] Similar conclusions were drawn by Portnoy and Milstein for the oxidative addition of aryl chlorides to $[Pd(L\text{-}L)_2]$ (Scheme 9).[61] In this study, the kinetic data suggested that the oxidative addition was



Scheme 9. Oxidative addition of chlorobenzene to $[Pd(dippp)_2]$ (dippp = 1,3-bis(diisopropylphosphanyl)propane).

preceded by a ligand dissociation to form the 14-electron complex **5**. On the other hand, the results of a Hammett study and the activation parameters for the oxidative addition supported the charged transition state **6** (Scheme 9). It was also found that on increasing the bite angle of the ligand by exchanging 1,3-bis(diisopropropylphosphanyl)propane for 1,4-bis(diisopropropylphosphanyl)butane, the rate of the oxidative addition decreased.[61,62] Note that these diphosphanes have bulky substituents, and ligands of this type have some unusual features (see Section 2.7).

2.5. Oxidative Addition with $[Pd_2(dba)_3]$

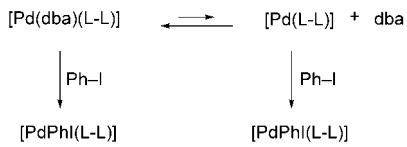
Complexes $[Pd_2(dba)_3]\cdot(S)$ (dba = dibenzylideneacetone, (S) = dba or solvent molecule)[63,64] have been used as source of Pd^0 in palladium-catalyzed reactions.[10] Early work by Roundhill and co-workers suggested that the dba ligands are not completely substituted in the reactions of $[Pd_2(dba)_3]\cdot(S)$ with P,N bidentate ligands under mild conditions.[65] The equilibrium established upon the addition of different phosphanes and diphosphanes has been studied in detail by Amatore, Jutand, and co-workers.[66–68]

On the basis of ^{31}P NMR spectroscopy and voltammetric studies it was suggested that upon the mixing of $[Pd_2(dba)_3]$ and PPh_3, $[Pd(dba)(PPh_3)_2]$ is formed in equilibrium with $[Pd(PPh_3)_3]$ (Scheme 10).[65,67b,69] The equilibrium constant of $K_0 = 0.14$ determined in THF indicates that dba is a better ligand for PPh_3 than $[Pd(PPh_3)_2]$. In monomeric $[Pd(dba)L_2]$ complexes dba coordinates to the palladium center as a monodentate, two-electron-donor ligand. Similar equilibria were found for tri-2-furylphosphane (TFP)[70] and triphenylarsane.[71,72] $[Pd(dba)(AsPh_3)_2]$ was found to be more stable than analogous phosphane complexes $[Pd(dba)L_2]$ (L = PPh_3 or TFP).

Scheme 10. Ligand-exchange equilibrium in the system $[Pd_2(dba)_3]/PPh_3$.

Interestingly, the oxidative addition of PhI to a 1:2 $[Pd_2(dba)_3]/PPh_3$ mixture proceeds at an overall rate approximately 10 times lower than for $[Pd(PPh_3)_4]$. A similar effect was observed in the oxidative addition of PhI to $[Pd(PPh_3)_4]$ or to the anionic complex $[Pd(OAc)(PPh_3)_3]^-$ in the presence of an alkene (styrene, methyl acrylate),[73] as well as in the Heck reaction of PhOTf and methyl acrylate catalyzed by $[Pd_2(dba)_3]$/dppf (dppf = 1,1′-bis(diphenylphosphanyl)ferrocene).[74] In coupling reactions with alkenyl stannanes catalyzed by $[Pd_2(dba)_3]/AsPh_3$, η^2-coordination of the alkene[75] slows down the oxidative addition because the concentration of the active complex $[Pd(AsPh_3)_2]$ or $[Pd(AsPh_3)_2(S)]$ decreases.[71]

Amatore, Jutand, and co-workers compared the effect of the ligands diop (diop = 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphanyl)butan), dppf, and binap (binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl) on the oxidative addition of iodobenzene (Scheme 11), and observed the



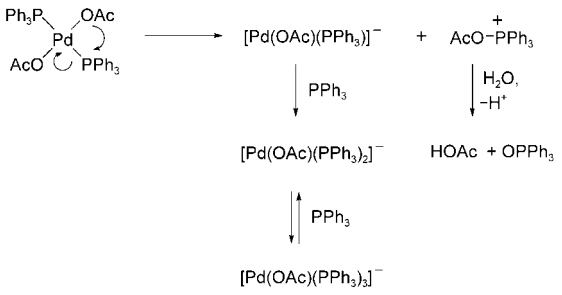
Scheme 11. Oxidative addition of iodobenzene to [Pd(dba)(L-L)] and [Pd(L-L)].

slowest oxidative addition with binap, which is the ligand with the smallest bite angle.[76,77] This result is opposite to that previously observed by Milstein and Portnoy.[61] However, Portnoy and Milstein used ligands of very different basicity to those used by Amatore and Jutand.[78] All the systems with bidentate ligands investigated are less reactive than $[Pd_2(dba)_3]+2\,PPh_3$. Coordinatively saturated $[Pd(L\text{-}L)_2]$ complexes were found to be unreactive in the oxidative addition with iodobenzene.[76]

2.6. The Role of Anionic Ligands

In a series of studies combining electrochemistry and ^{31}P NMR spectroscopy, Amatore and Jutand established the important role played by anionic ligands in oxidative addition reactions.[79] They concluded that in the presence of acetate or chloride anions, tricoordinated anionic complexes $[Pd(OAc)L_2]^-$ or $[PdClL_2]^-$ are the actual species that undergo oxidative addition, rather than the neutral $[PdL_2]$ complex usually postulated (see below). These anions will be present in the reaction mixture whenever Pd^{II} salts (e.g. $Pd(OAc)_2$) or complexes (e.g. $[PdCl_2L_2]$; L = MeCN, PhCN, PPh_3, etc.) are used as the catalyst precursor.

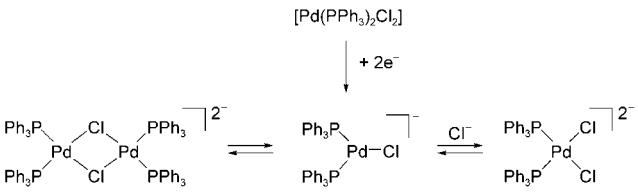
Mixtures of $Pd(OAc)_2$ and PPh_3 rapidly lead to $[Pd(OAc)_2(PPh_3)_2]$,[80,81] which undergoes slow intramolecular reduction to form a Pd^0 complex (Scheme 12). This reduction is facilitated by electron-withdrawing substituents



Scheme 12. Formation of Pd^0 species in the system $Pd(OAc)_2/PPh_3$.

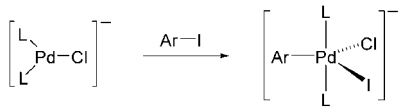
at the *para* position of the aryl groups on the phosphane.[81,82] Even in the presence of excess PPh_3, anionic Pd^0 complexes with acetate as a ligand are formed. The anionic complex $[Pd(OAc)(PPh_3)_2]^-$ is the reactive species undergoing oxidative addition.[83] The reaction of $Pd(OAc)_2$ with diphosphanes can be more complex. Thus, with dppe (dppe = 1,2-bis(diphenylphosphanyl)ethane) $[Pd(dppe)_2](OAc)_2$ is formed as the kinetic product, which slowly undergoes conversion into the thermodynamically favored monochelate $[Pd(OAc)_2(dppe)]$. In the presence of 2 equivalents of dppp (dppp = 1,3-bis(diphenylphosphanyl)propane), water, and a base (NEt_3), the hemioxide of dppp and the stable anionic complex $[Pd(OAc)(dppp)]^-$ are formed.[84] In this instance, the oxidative addition of PhI is mechanistically complex, as both dimeric and monomeric Pd^0 complexes ligated by AcO^- can be involved as reactive species.[85]

Many cross-coupling reactions are carried out with catalysts generated from $[PdCl_2L_2]$ or similar complexes. In the presence of chloride ions, anionic Pd^0 complexes are also formed.[86,87] For example, the reduction of $[PdCl_2(PPh_3)_2]$ in THF affords three anionic complexes, including one dimer (Scheme 13).[88,89]



Scheme 13. Pd^0 complexes that form during the reduction of $[PdCl_2(PPh_3)]$.

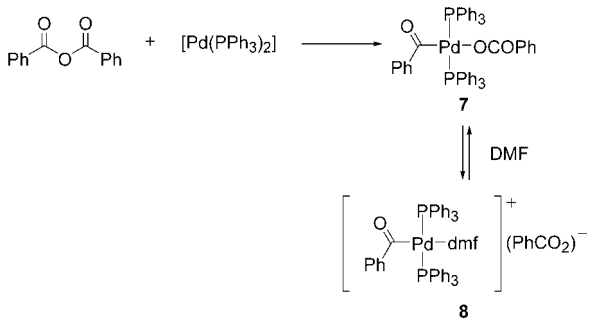
Under the usual conditions, the major Pd^0 complex generated by the reduction of $[PdX_2(PPh_3)_2]$ is $[PdX(PPh_3)_2]^-$, with the order of stabilization of the halide X^- on the anionic Pd^0 species: $I^- > Br^- > Cl^-$.[89] The oxidative addition reaction of PhI to $[PdCl(PPh_3)_2]^-$ affords *trans*-$[PdPhI(PPh_3)_2]$ as expected. However, after shorter reaction times an intermediate anionic species was detected, which was proposed to be the 18-electron complex $[PdPhClI(PPh_3)_2]^-$ (Scheme 14).[90] It was also proposed that this pentacoordinated intermediate was involved in the transmetalation reaction, but this view seems to have found little echo.[90] Related anionic $[PdAr(PPh_3)_2]^-$ species have



Scheme 14. Oxidative addition to $[PdClL_2]^-$ (L = PPh_3) proceeds via a five-coordinate intermediate.

also been postulated as key intermediates in the palladium-catalyzed homocoupling of aryl halides.[91]

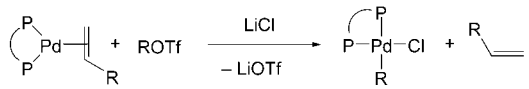
The oxidative addition of benzoic anhydride to $[Pd(PPh_3)_4]$ was proposed by Jutand et al.[92] to follow a pathway similar to that observed earlier for aryl halides and triflates (Scheme 15).[69,93] The reaction of benzoic anhydride



Scheme 15. Solvolysis equilibrium following the oxidative addition of benzoic anhydride to $[Pd(PPh_3)_2]$. DMF = *N*,*N*-dimethylformamide.

with $[Pd(PPh_3)_2]$ yields a *trans* complex **7**, in agreement with previous results of Grushin and Alper,[94] and Yamamoto and co-workers.[95] Complex **7** is in equilibrium with the cationic complex **8**, which results from benzoate displacement by the solvent DMF.

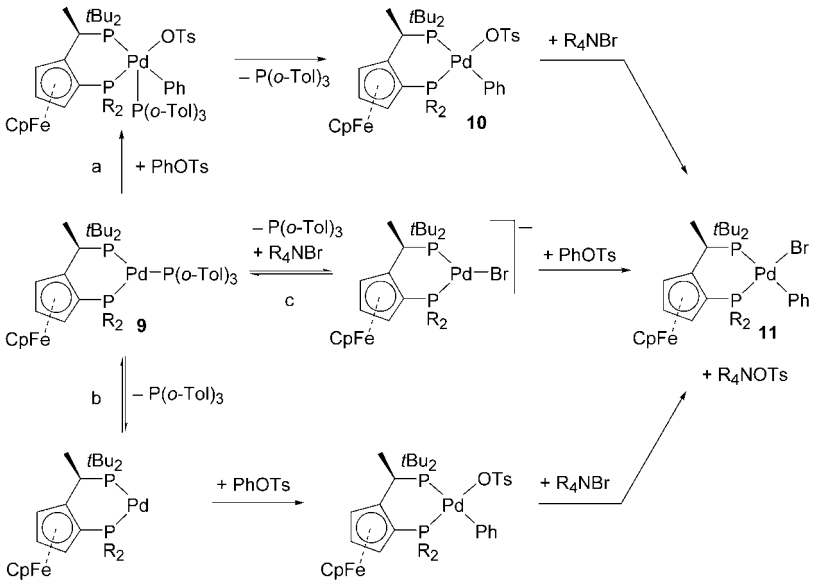
The oxidative addition of C_6F_5OTf to $[PdL_4]$ complexes proceeds well for L = PPh_3, but requires the addition of LiCl for L = $AsPh_3$. Thus, for L = $AsPh_3$ the oxidative addition becomes rate determining in the absence of an added halide, and the Stille coupling is hindered.[96] Similarly, the oxidative addition of C_6F_5OTf to complexes [Pd(dppe)(olefin)] extremely slow, but can be accelerated very efficiently by adding LiCl, which promotes the ready formation of [PdRCl(dppe)] (Scheme 16).[97]



Scheme 16. Oxidative addition of ROTf in the presence of LiCl. P–P = dppe.

A recent study showed that the oxidative addition of alkenyl triflates to $[Pd(PPh_3)_4]$ in DMF gives $[Pd(\eta^1\text{-alkenyl})(PPh_3)_2(dmf)](TfO)$ under stoichiometric conditions (Tf = trifluoromethanesulfonyl).[98] The following reactivity order was established: alkenyl–OTf ≫ vinyl–Br > PhBr and vinyl–OTf ≫ PhOTf.

Roy and Hartwig studied in detail the oxidative addition of aryl tosylates to the Pd^0 complex **9** (Scheme 17).[99] The

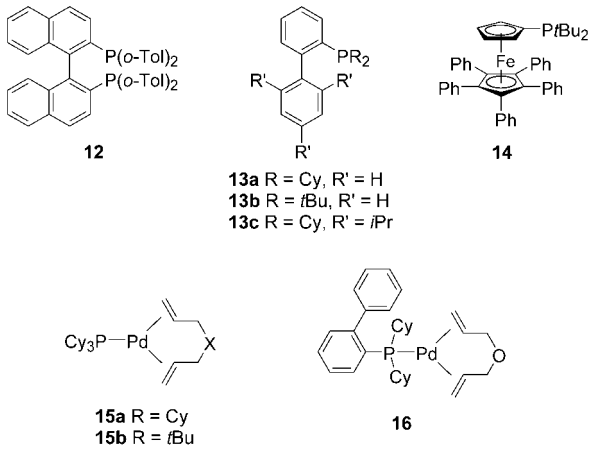


Scheme 17. Oxidative addition of PhOTs in the presence of R_4NBr. Tol = tolyl, Ts = *p*-toluenesulfonyl.

The research groups of Buchwald and Hartwig also demonstrated the activity of a variety of sterically hindered chelating phosphanes in palladium-catalyzed transformations. In particular, the amination and etherification of aryl electrophiles,[105] as well as processes for the arylation of ketones and malonates,[106–108] benefit greatly from the use of ligands such as **12**.[109] Other bulky bidentate ferrocenyl diphosphanes allow Kumada and amination reactions with unactivated aryl tosylates at room temperature (see Scheme 17).[99] Bulky P,O chelating ligands also facilitate Suzuki coupling reactions of a wide variety of aryl boronic acids and aryl chlorides, bromides, and iodides.[110,111]

Monodentate bulky phosphane ligands also promote the coupling of less reactive substrates under relatively mild conditions. This accelerating effect on the oxidative addition had already been demonstrated in

results offer new views on the role of added salts. The reaction in benzene of **9** with aryl tosylates at room temperature affords the isolable complex **10**, which reacts fast with $(n\text{-}C_8H_{17})_4NBr$ to give **11**. The oxidative addition of the tosylate is faster if R_4NBr is present from the beginning and gives **11**. The reaction shows positive kinetic order in PhOTs, inverse order in $P(o\text{-Tol})_3$, and positive order in the bromide, thus eliminating path a. In the absence of the bromide, the kinetics are consistent with path b. Taken alone, the acceleration of the reaction by the bromide might be considered to support path c, in accordance with the related results of Amatore and Jutand. However, an even higher acceleration was found in the presence of Bu_4NPF_6 or in polar solvents. This was interpreted to imply that in this case the acceleration by R_4NBr is due to the creation of a more polar medium and not to the direct coordination of this ion to Pd^0.[99]



2.7. Cross-Coupling Reactions in the Presence of Bulky Phosphanes

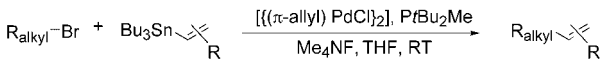
In the last few years the use of bulky phosphanes has revolutionized the scope of cross-coupling reactions, particularly for the coupling of less reactive organic substrates, such as aryl chlorides[100,101] and alkyl electrophiles.[102] Since bulky phosphanes make a big difference in the oxidative addition step, they are treated in this section.

Aryl chlorides usually react more sluggishly in cross-coupling reactions than the corresponding bromides, iodides, and triflates, as a result of their reluctance to undergo oxidative addition to Pd^0.[103] Early on it was noted that the use of sterically hindered, chelating ligands could help to overcome this problem. Thus, Milstein and co-workers reported that $[Pd(dippp)_2]$ (Scheme 9) was an efficient catalyst for carbonylation, formylation, and Heck reactions of aryl chlorides.[61,104]

the context of the formation of η^3-allyl palladium complexes.[112] Particularly useful for the activation of aryl chlorides are palladium complexes of the bulky phosphane $P(t\text{Bu})_3$,[113–117] which is readily available.[118] Even bulkier phosphanes, such as $P(1\text{-Ad})t\text{Bu}_2$ (Ad = adamantyl), have also been used in the palladium-catalyzed arylation of malonates and cyanoesters.[119] The biphenylphosphanes **13** (Cy = cyclohexyl) were employed by Buchwald and co-workers in the palladium-catalyzed reaction of amines with aryl bromides, chlorides, and triflates,[120] and in Suzuki coupling reactions.[120a,121] In particular, ligand **13c** was found to be extremely effective in the Suzuki coupling and enolate arylation of aryl arene sulfonates.[122] Ligand **14** has been used for Suzuki coupling reactions and C–N or C–O bond-forming reactions.[123] Beller and co-workers showed that a series of [Pd(1,6-diene)L] (L = phosphane) complexes, such as **15** and **16**, catalyze efficiently the Suzuki coupling of aryl chlorides with phenylboronic acid.[124,125] The [Pd(1,6-diene)L] complexes were found to be more effective catalysts

for these reactions than mixtures of the phosphanes and $Pd(OAc)_2$ or $[Pd_2(dba)_3]$.[126]

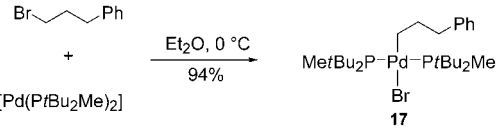
The Stille coupling at room temperature of alkenyl stannanes with alkyl bromides that possess β hydrogen atoms is also possible with similar catalysts (Scheme 18),[127]



Scheme 18. Stille coupling of alkyl electrophiles catalyzed by a palladium complex with the bulky, monodentate phosphane ligand $PtBu_2Me$.

although it was necessary to add a fluoride salt to promote the reactivity of the stannane. With the diaminophosphane ligand $PCy(pyrrolidinyl)_2$ the reaction can be extended to the coupling of aryl stannanes.[128]

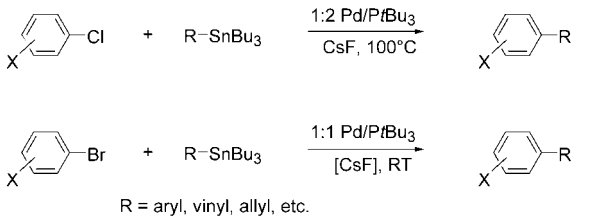
In reactions with $Pd/PtBu_2Me$, the complex that undergoes oxidative addition by the alkyl halide is $[Pd(PtBu_2Me)_2]$, and the activation parameters correspond to an S_N2 process with a large negative activation entropy.[129] Consequently, the oxidative addition is very sensitive to steric hindrance on the alkyl halide. The product of the oxidative addition of an alkyl bromide to the active complex $[Pd(PtBu_2Me)_2]$ has been isolated and structurally characterized (Scheme 19):[130] The



Scheme 19. Oxidative addition to give the structurally characterized product **17**.

complex **17** was formed readily at 0 °C and was found to react with o-$TolB(OH)_2$ at room temperature to give the coupling product. Alkyl electrophiles also couple with other organometallic reagents.[131]

The $Pd/PtBu_3$ system is also useful in the Stille reaction with aryl electrophiles (Scheme 20).[132] Thus, the coupling of

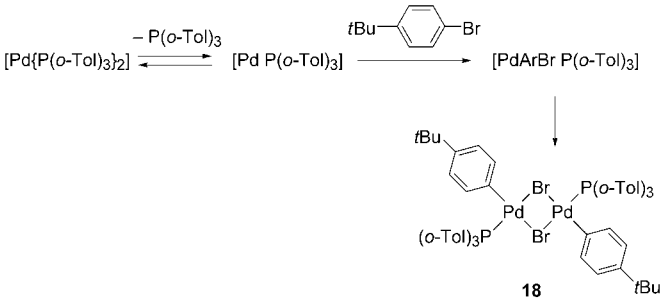


Scheme 20. CsF can have an activating effect in the coupling of aryl chlorides and aryl bromides with stannanes.

aryl chlorides with organostannanes can be performed at 100 °C, and in some cases even at room temperature, with a catalyst prepared from $[Pd_2(dba)_3]/PtBu_3$ (1:2) or with $[Pd(P(tBu)_3)_2]$. CsF was used to activate the stannane. It is suggested that the fluoride anion coordinates to tin to afford a pentacoordinated tin species with enhanced reactivity towards transmetalation.[133] Aryl bromides could also be coupled at room temperature, although in this case a 1:1 ratio of phosphane to Pd was necessary. In the coupling of aryl bromides, CsF was only required with less reactive organostannanes. Again, aryl chlorides underwent coupling more readily than aryl triflates. Preliminary mechanistic studies suggested that a palladium monophosphane complex [PdL] is the active catalyst in the cross-coupling of aryl halides.[132]

Although, as usual, aryl iodides undergo oxidative addition more rapidly than aryl bromides, the rate-limiting transmetalation of the resulting $[PdArI(PtBu_3)]$ complex is slower than the transmetalation of $[PdArBr(PtBu_3)]$.[132] Similar conclusions were reached for Suzuki reactions catalyzed by $Pd(OAc)_2/PPh_3$.[134]

Hartwig and co-workers proposed that the oxidative addition of an aryl bromide to $[Pd\{P(o\text{-}Tol)_3\}_2]$ involved prior dissociation of a phosphane ligand to give the 12-electron complex $[Pd\{P(o\text{-}Tol)_3\}]$ (Scheme 21).[135–137] In a related

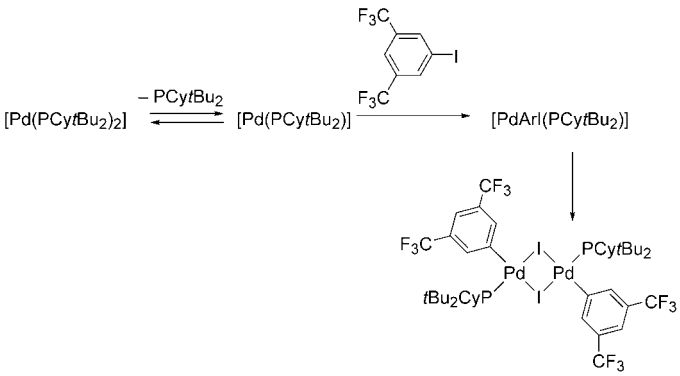


Scheme 21. Predissociation of a $P(o\text{-}Tol)_3$ ligand before the oxidative addition of an aryl bromide.

system it was concluded from kinetic measurements that the oxidative addition of ArBr to $[Pd(PtBu_3)]$ is faster than coordination of a new $PtBu_3$ ligand to the highly uncoordinated $[Pd(PtBu_3)]$ intermediate.[138] The addition of $PtBu_3$ to dimeric complexes of type **18** promotes the reductive elimination with formation of ArX. This process was proposed to involve irreversible dissociative ligand substitution (a very unusual mechanism, presumably induced by the steric properties of the ligands involved) and cleavage to the monomers, prior to reductive elimination.[139]

The thermodynamics of the reductive elimination from $[PdArX(PtBu_3)]$ complexes parallels the strengths of the Ar–X bonds (Cl > Br > I) and is most favorable for X = Cl.[138] However, the kinetic trend is the opposite, and the reductive elimination of ArCl is actually the slowest. It was suggested that the stability of the transition state depends critically on the softness of the halide.

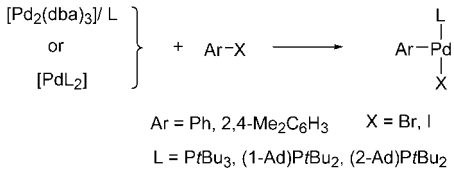
Brown, Jutand, and co-workers reported that $[Pd(PCy_3)_2]$ reacts with PhOTf by an associative mechanism.[140] The reaction of PhI with $[Pd(PCy_3)_2]$ or $[Pd(PCy_2tBu)_2]$ also proceeds associatively. In contrast, $[Pd(PCytBu_2)_2]$ (Scheme 22) and $[Pd(PtBu_3)_2]$, with bulkier phosphane ligands, behave like $[Pd\{P(o\text{-}Tol)_3\}_2]$, which requires ligand dissociation to a [PdL] complex prior to oxidative addition.



Scheme 22. Predissociation of a PCy*t*Bu$_2$ ligand before the oxidative addition of an aryl iodide. Cy = cyclohexyl.

X-ray crystal-structure analysis of [Pd{P(*o*-Tol)$_3$}$_2$][135] and [Pd(PPh*t*Bu$_2$)$_2$][141] showed that they have linear or near-linear geometries. However, the [PdL$_2$] complex with the ligand **13b** differs from these complexes and displays an unusual P1-Pd-P2 angle of 154.82(4)° and η^1-π coordination of the *ortho* carbon atom of the unsubstituted phenyl ring of the ligand to the Pd center.[142]

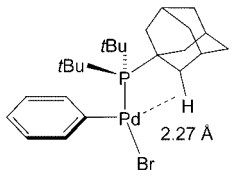
Hartwig and co-workers also reported the isolation of so-called tricoordinated, T-shaped, Pd^{II} complexes resulting from the oxidative addition of Ar–X to [PdL$_2$] or [Pd(dba)L] complexes bearing very bulky phosphane ligands (Scheme 23).[143] The resulting species are *cis* complexes with



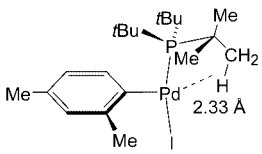
Scheme 23. The oxidative addition of Ar–X to Pd complexes with bulky phosphane ligands leads to apparently three-coordinate products. Ad = adamantyl.

an apparently open coordination site *trans* to the aryl group.[55,56]

Two of these apparently three-coordinate complexes, [PdPhBr{P(1-Ad)*t*Bu$_2$}] (**19**) and [Pd(2,4-Me$_2$C$_6$H$_3$)I(P*t*Bu$_3$)] (**20**), were structurally characterized. In both complexes there are agostic interactions between the Pd center and the C–H bonds of the phosphane.[143] Therefore, it would be more correct to consider them as four-coordinate distorted square-planar Pd^{II} complexes. However, the intrinsic weakness of the agostic bond is an important difference with respect to regular tetracoordinated complexes.



19
P-Pd-Br angle = 162.6°



20
P-Pd-I angle = 164.6°

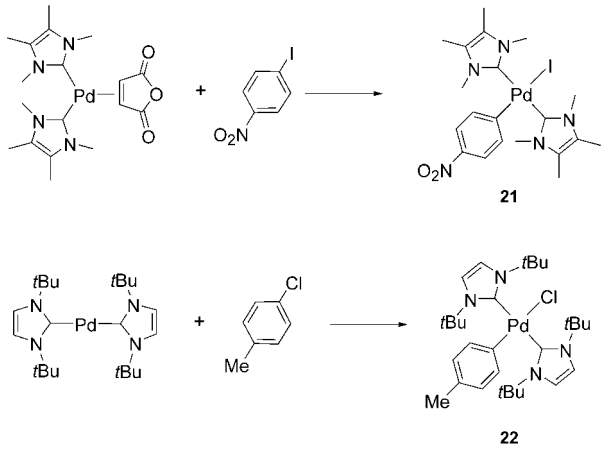
Recently, Blackmond, Buchwald, and co-workers carried out kinetic studies by using reaction calorimetry under synthetically relevant conditions to study the mechanism of the amination of bromobenzene with primary and secondary amines. The catalysts were [Pd$_2$(dba)$_3$]/binap mixtures, as well as preformed [Pd(binap)(dba)], [Pd(*p*-Tol)Br(binap)], and [Pd(binap)$_2$] complexes.[144] The significant induction period observed for the reaction was attributed to the slow activation of the catalytic precursor, resulting in an increase in the concentration of active species within the catalytic cycle. It was also confirmed that [Pd(binap)$_2$] does not play a direct catalytic role.[76] Both a pathway involving oxidative addition of the aryl halide to [Pd(binap)] as the first step and a pathway initiated by addition of the amine to the catalyst were proposed.

In a more radical approach in the quest for coordinatively unsaturated palladium catalysts "ligandless conditions" are used,[145–149] based on the pioneering work of Beletskaya and co-workers.[150] Thus, in the absence of phosphanes and other common ligands, palladium nanoparticles are formed.[151] Details of the mechanism in the context of Stille reactions under these conditions are lacking,[152] although the results of studies on a Heck reaction under very similar conditions are available.[153]

2.8. Heterocyclic Carbenes as Ligands

N-Heterocyclic carbenes have demonstrated their utility as ligands in a variety of cross-coupling reactions, including the Stille reaction.[154–157] Recent mechanistic work has shown that the oxidative addition of aryl halides to [PdL$_2$] (L = heterocyclic carbene = NHC) furnishes the expected *trans* square planar complexes (e.g. **21** and **22**, Scheme 24).[158–160]

Very bulky *N*-heterocyclic carbene ligands lead to substantial rate increases,[161] which might be attributed to the inhibition of dimer formation[162] and enhancement of the rate

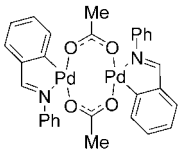


Scheme 24. Oxidative addition of aryl halides to Pd complexes with sterically demanding N-heterocyclic ligands.

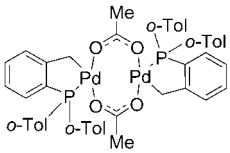
of the reductive elimination step.[157] In the context of the catalytic amination of aryl chlorides, the oxidative addition to $[PdL_2]$ (L = NHC) has been shown to be rate determining.[163] The oxidative addition proceeded dissociatively and the expected acceleration by electron-withdrawing substituents on the aryl chloride was observed.

2.9. Palladacycles as Catalysts

Many palladacycles have been described as active catalysts for cross-coupling and related reactions.[164–172] Strong evidence has been accumulated that indicates that the palladacycles actually act as a reservoir for Pd^{II}, which must undergo reduction to Pd^0 to enter the catalytic cycle.[169–171,173] Thus, in a detailed study of a Heck reaction with the palladacycles **23** and **24** as precatalysts, Blackmond, Pfaltz,



23



24

and co-workers concluded that the resting state of the catalyst within the catalytic cycle was the product of oxidative addition $[PdRXL_2]$. The majority of the palladium remained outside the catalytic cycle as the dimer $[(\mu\text{-}X)_2Pd_2R_2L_2]$, which is in equilibrium with $[PdRXL_2]$.[173]

3. The Transmetalation

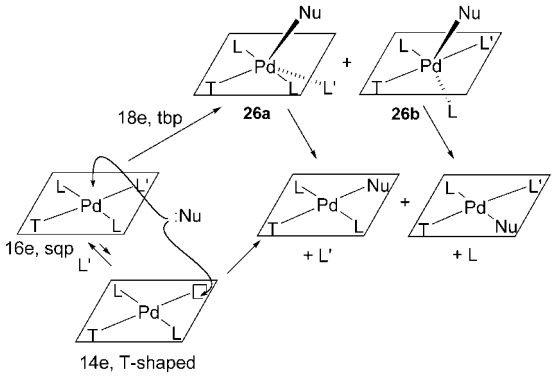
3.1. The Intricate Step That Makes the Difference

All Pd-catalyzed cross-coupling processes have in common a sequence that, starting with Pd^0, involves oxidative addition, transmetalation, and reductive elimination steps (as well as isomerization steps when needed). One of the reasons for the popularity of the Stille reaction in modern organic synthesis is the fact that trialkyl organotin species are readily available, quite air and moisture stable, and tolerate many functional groups.[1,9,174] These properties are mostly due to the low polarity of the Sn–C bond. In this respect, the Stille reaction differs from others with more polar organometallic reagents (e.g. Grignard reagents in the Kumada reaction[175] or zinc derivatives in the Negishi reaction) and is more similar to those in which boron (Suzuki coupling) or silicon (Hiyama coupling) derivatives are used. It can be assumed that the polarity of the organometallic nucleophile is important in determining the mechanism of the transmetalation, and some similarities are expected for the all processes involving nucleophiles with M–C bonds of moderate polarity. Consequently, insight gained into the transmetalation step of the Stille reaction has the added value that it may be relevant to the Suzuki and Hiyama coupling reactions.

The mechanisms proposed for the transmetalation should be able to explain satisfactorily the experimental observations. Improvements in the ability to detect intermediates and in kinetic studies have led to an increasingly complex mechanistic picture. Each variable in the reaction (the electrophile, the nucleophile, the ancillary ligands, the solvent, and the presence of additives) seems to be able to produce dramatic changes in the process.

3.2. The Transmetalation: A Ligand Substitution at Pd^{II}

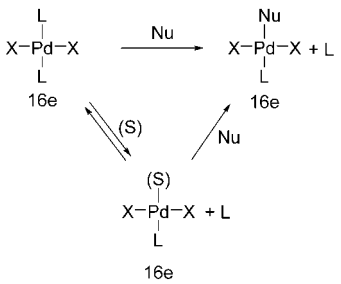
Some background mechanistic comments on palladium are pertinent before we proceed to review the studies on transmetalation. It is interesting to realize from the beginning that the very nature of the transmetalation is that of a ligand substitution on a Pd^{II} complex.[176] These complexes are usually tetracoordinated square-planar 16-electron species and can undergo ligand-substitution processes by the two pathways depicted in Scheme 25.[177,178] The dissociative path-



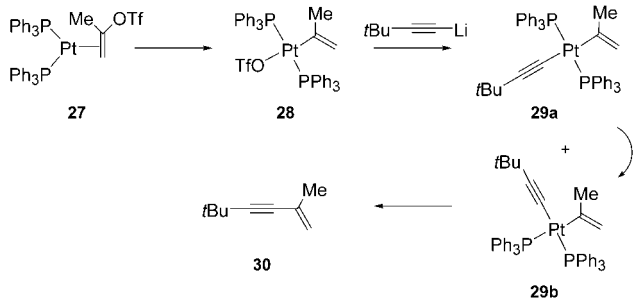
Scheme 25. Possible reaction pathways for the transmetalation.

way involves a 14-electron T-shaped intermediate **25**, and the position at which the substitution occurs is determined by the ligand with the highest *trans* influence, which weakens the bond *trans* to it and determines the dissociation equilibrium. The associative pathway goes through an 18-electron trigonal bipyramidal complex **26** as an intermediate or transition state, and the position at which the substitution occurs is determined by the ligand with the highest *trans* effect, which determines the lowest-energy transition state. In both pathways the substituted ligand is eventually released. It is frequently said, cursorily, that the ligand has dissociated, but this expression should be avoided because it can lead to confusion with a dissociative pathway.

Often the associative mechanism includes two parallel pathways: direct substitution and solvent-assisted substitution (Scheme 26). The two pathways contribute to the rate of substitution, and the reaction kinetics become more complex. Note that in the solvent-assisted pathway both the substitution of L for (S) and that of (S) for Nu are associative. Note also that a coordinating solvent is simply a ligand and contributes two electrons to the complex. Thus, a [PdRXL(S)]



Scheme 26. Direct and solvent-assisted substitution of L by Nu. (S) = solvent molecule.



Scheme 27. Transmetalation and coupling in a Pt model system. Tf = trifluoromethanesulfonyl.

complex is a 16-electron species. Olefins, adventitious water, and agostic bonds can play a similar role as ligands.

In the frequently used halo-bridged $[PdR_2(\mu\text{-}X)_2L_2]$ complexes the dissociative mechanism should involve direct cleavage of the bridges, whereas an associative cleavage involves associative substitution of the bridging ligand at one Pd atom by the entering ligand. The bridging X is then transformed into a terminal X ligand.

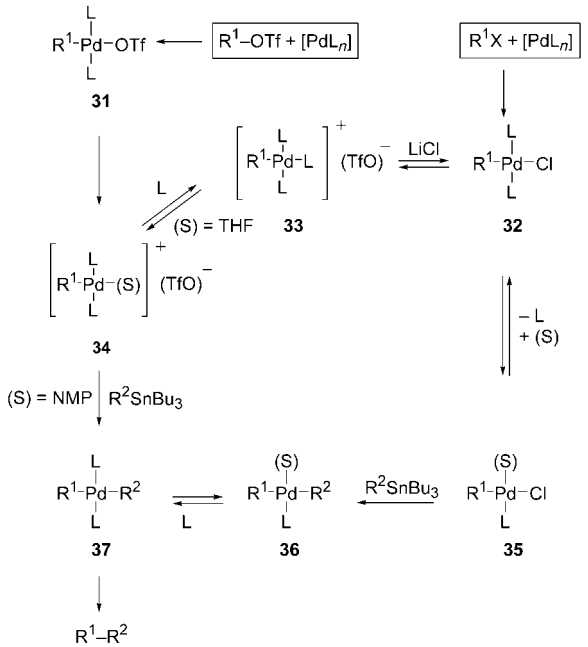
Although dissociative mechanisms apparently play a role in isomerization, β-H elimination, reductive elimination, and other processes involving Pd^{II} complexes (three-coordinate species were "observed" in kinetic studies on the rotation of some fluoroaryl compounds),[179] they are a rarity in ligand substitutions.[180] There is convincing support for dissociative ligand substitution in the case of relatively electron-rich platinum complexes $[PtR_2L_2]$ (with fairly good σ donors R),[181,182] but all ligand substitutions on the more electrophilic $[PdRXL_2]$ complexes seem to follow an associative pathway.[183]

These background comments on ligand substitution should in principle hold for the transmetalation with stannanes, in which the role of the nucleophile is played by the carbon atom undergoing transmetalation (in the case of alkynyl, vinyl, or aryl stannanes the π-electron density can facilitate the initial coordination). The differences are that stannanes are weak nucleophiles relative to typical two-electron ligands, and that the transmetalation with stannanes requires formal heterolytic cleavage of a C–Sn bond and release of R_3Sn^+.

3.3. Landmarks in the Study of the Transmetalation Mechanisms

The results of early mechanistic work aimed at ascertaining key aspects of cross-coupling and Heck reactions were in agreement with the original proposal advanced by Stille. A model study carried out by Stang et al. on the coupling of alkynes with vinyl triflates in the presence of $[Pt(PPh_3)_4]$ showed that the oxidative addition proceeded by the rate-determining formation of the (η^2-alkene)Pt complex **27**.[184] The reaction of **28** with lithium *tert*-butylacetylide (Li/Pt transmetalation) afforded a 4:1 mixture of *trans* and *cis* Pt^{II} complexes **29a** and **29b**, respectively (Scheme 27).[185,186] It was suggested that the *trans* and the *cis* isomer were in equilibrium with one another through ligand dissociation via T-shaped intermediates, and that reductive elimination from the *cis* isomer led to the enyne product **30**. Although some of the complexes in Scheme 27 are likely intermediate types in the Stille reaction, it should be kept in mind that Pd and Pt can be very different kinetically, and that the nucleophilicity of lithium organometallic compounds is very different from that of tin organometallic compounds.

The initial kinetic studies by Farina and others on the overall catalytic cycle of the Stille reaction, for which the transmetalation was assumed to be rate determining, confirmed that the reactions with organic halides (usually iodides, R^1I) showed a first-order dependence on [Sn] and [Pd], and an inverse dependence on [L].[29,27,187] These results were interpreted in terms of a dissociative preequilibrium of *trans*-$[PdR^1XL_2]$ to form $[PdR^1XL]$, which can be represented indistinctly as such or as a "solvent-stabilized" complex $[PdR^1XL(S)]$ (e.g. **35**, Scheme 28). This intermediate should undergo transmetalation to exchange X for R^2 and give the intermediate **36**. It is not clear why the subsequent coordination of L and coupling from that *trans* complex was proposed, since the complex needs to isomerize to the *cis* isomer before

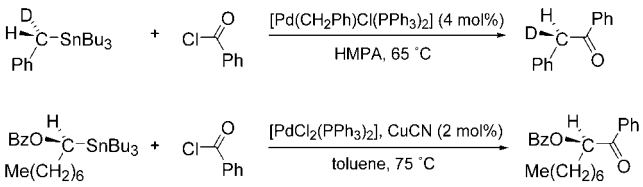


Scheme 28. Course of the transmetalation of halo and triflato complexes with R^2SnBu_3.

the coupling product can form. Based on the observed inverse dependence on the concentration of the ligand, Farina and co-workers proposed the use of less coordinating ligands ($AsPh_3$, $P(furyl)_3$) to facilitate the transmetalation step, a strategy that has had a very positive impact on synthesis.

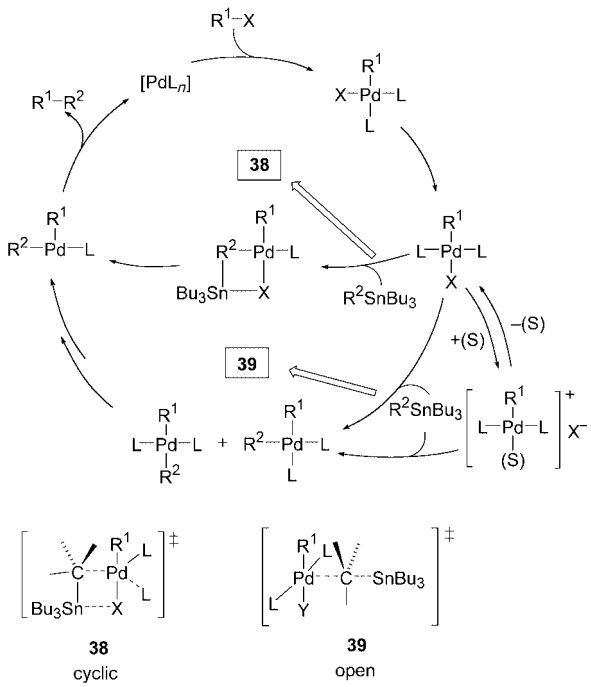
Farina and Roth also noted that reactions with organic triflates show some distinct characteristics, and proposed for them a different pathway (Scheme 28).[29] In this case the triflato complex **31** formed upon oxidative addition would react to give a cationic solvento complex **34** by substitution of the triflate group by a molecule of a coordinating solvent (e.g. *N*-methyl-2-pyrrolidinone (NMP)). The failure of organic triflates to react in less coordinating solvents (e.g. THF) was attributed to the instability of the triflato complex. This problem could be overcome by adding LiCl. This additive was proposed to transform the triflato complex into the chloro complex **32**, which then enters the catalytic cycle discussed above for organic halide complexes. Although some of these proposals have since been shown not to be fully correct, the use of LiCl often has a positive effect.

The studies mentioned so far did not provide a detailed picture of how the interaction between the palladium complex and the stannane brings about transmetalation. It is also clear that these mechanistic proposals can not accommodate the fact that the transmetalation of chiral stannanes can take place with retention or with inversion of configuration. There are two reports in the literature that provide stereochemical information on the transmetalated carbon center: Stille and Labadie found the reaction to proceed with predominant inversion of configuration (Scheme 29, top),[34] whereas Falk and co-workers reported complete retention of configuration in a related process (Scheme 29, bottom).[35]



Scheme 29. Inversion (top) and retention (bottom) of the configuration at the α carbon atom in the Stille coupling. HMPA = hexamethyl phosphoramide. Bz = benzoyl.

The need to explain the different stereochemical outcome of the reactions in Scheme 29 and consideration of quantitative results on transmetalation rates led to the proposal by Espinet and Casado of a dual catalytic cycle with two different transition states, one cyclic and one open, **38** and **39**, respectively (Scheme 30).[96,188] The upper cycle in Scheme 30 depicts the cyclic transmetalation as an associative process assisted by the formation of a Pd–X–Sn second bridge. This mechanism leads to the exchange of L (and not X) for R^2, forces retention (and not inversion) of the configuration at C^{α}, and leads to a *cis* (rather than a *trans*) $[PdR^1R^2L_2]$ complex, from which coupling is immediate. All these features differ from the previous proposals.



Scheme 30. Catalytic cycles for the transmetalation with the cyclic and open transition states **38** and **39**, respectively. Y = (S) or X, (S) = L or solvent molecule.

The lower cycle includes and expands on open mechanisms. It is not excluded that open mechanisms can also operate on halide-containing complexes (leading to the replacement of any of the ligand on palladium), provided that a sufficiently electrophilic complex (e.g. a solvento complex) or a sufficiently nucleophilic stannane (e.g. an alkynyl stannane) makes the rate of such a process competitive. This is further elaborated below.

These studies also revealed clearly that, although the transmetalation is often rate determining, this is not always the case. In some instances it is the oxidative addition[96] or the reductive elimination[97] that controls the rate of the reaction.

The general representation $[PdR^1XL_2]$ (Scheme 30) stands for neutral compounds with a potentially bridging X ligand (to assist Pd–X–Sn formation), including chelate complexes $[PdR^1X(L\text{-}L)]$ (in which case the complex is necessarily *cis*), $[PdR^1XL(S)]$ (formed by the substitution of one ligand L by a solvent or water molecule (S)), $[PdR^1X(L\text{-}H_{agostic})]$, and other species.

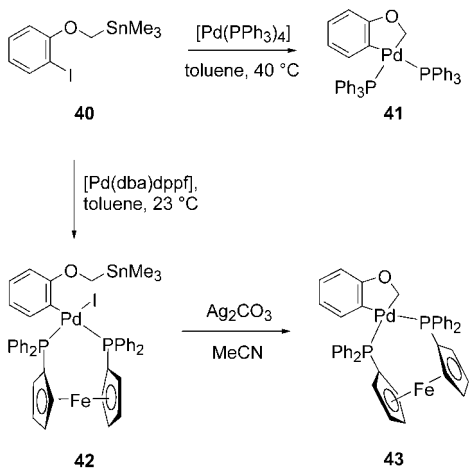
The actual Pd species in solution can be different from those introduced initially as a catalyst or formed directly in the oxidative addition, as discussed below. Studies have shown the formation of cationic complexes by the replacement of coordinated OTf groups or halides with ligands or coordinating solvent molecules,[96] neutral solvento complexes by the replacement of one or more ligands with coordinating solvent molecules,[96,176] and dimers by the replacement of weakly coordinating ligands with the terminal halide of the monomer.[176] It is difficult to ascertain which species undergoes faster transmetalation even by kinetic studies, because the kinetic equations show similar dependences on the concentration of the reagents. Whereas in some cases it

seems clear that the associative transmetalation occurs on the dominant $[PdR^1XL_2]$ complex,[188] Amatore, Jutand, and co-workers showed in a nice study that in certain other cases the reaction mainly proceeds by associative substitution on the solvento complex $[PdR^1XL(S)]$ ((S) *trans* to L), even when the concentration of this solvento complex is kept very low through the addition of L.[189] However, a substitution of (S) for R^2 (as in the modern Scheme 30) rather than of X for R^2 (as in Schemes 2 and 28) is still proposed.

Thus, Scheme 30 is fairly comprehensive, and most experimental observations, including the stereochemical outcome of the transmetalation can be rationalized satisfactorily within this framework (retention of configuration implies a cyclic pathway, inversion an open pathway). A different mechanism is proposed for a few exceptional cases (see Section 6).

3.4. Isolation of the Transmetalation Step

There have been a number of observations made and studies carried out on the transmetalation as an isolated step, in instances in which the reductive elimination is slow. Thus, Echavarren and co-workers studied an intramolecular version of the transmetalation step with systems **40**, which undergo oxidative addition to $[Pd(PPh_3)_4]$ followed by transmetalation to form palladacycles **41** (Scheme 31).[190] These are stable species that do not undergo reductive elimination because of the high ring strain of the four-membered heterocyclic ring that would form.

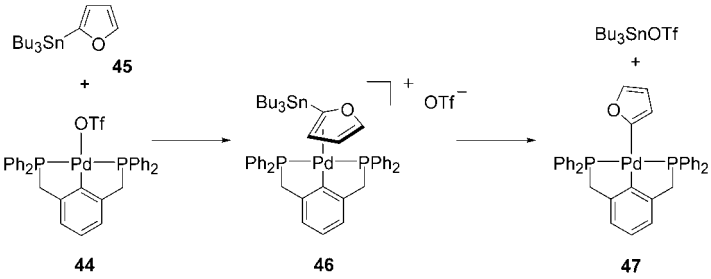


Scheme 31. Stable cyclic transmetalation products: **41** and **43**.

Intermediate **42** was isolated from the oxidative addition of **40** to the complex [Pd(dba)dppf]. Presumably, the chelating dppf ligand disfavors a cyclic transmetalation (Section 3.6). However, a smooth transmetalation was observed in the presence of Ag_2CO_3 to form palladacycle **43**.[190b] Under these conditions, the formation of a cationic acetonitrile complex upon extraction of the iodide with the silver salt might facilitate transmetalation through an open transition state.

The concept outlined in Scheme 31 was also extended to the study of the transmetalation of silanes (the key step of the Hiyama cross-coupling reaction) isolated from the oxidative addition and reductive elimination steps,[191] and to the related transmetalation of stannanes with Pt^{II}.[192]

The reaction between the pincer triflato complex **44** and 2-tributylstannyl furan (**45**) led to transmetalation product **47** as a stable compound (Scheme 32).[193,194] When the reaction



Scheme 32. The transmetalation of the stannyl furan **45** with the pincer complex **44** afford the stable product **47**.

was performed at low temperature, an intermediate cationic complex **46** was observed, with the furan ligand η^2-coordinated to the palladium center. Intermediate **46** is a model for the transmetalation of vinyl stannanes. Transmetalation intermediates [Pd(aryl)(heteroaryl)] have been detected by electrospray mass spectrometry in the Suzuki coupling of bromopyridines with aryl boronic acids.[195]

Under certain conditions, the transmetalation of tributyl(vinyl)stannane with $[Pd(C_6Cl_2F_3)(PPh_3)_3]BF_4$ (**48**, Figure 1) gives rise to significant concentrations of the

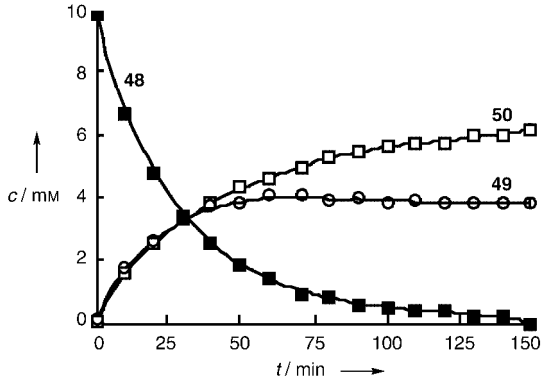
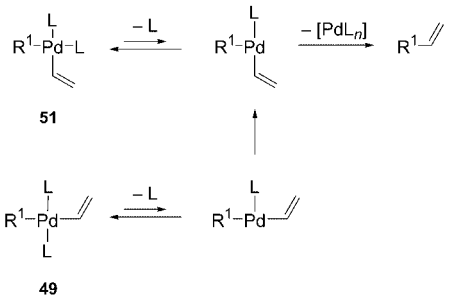


Figure 1. Concentration profiles of the reaction between $[PdR^1(PPh_3)_3]BF_4$ (**48**) and $Bu_3SnCH{=}CH_2$ in CH_2Cl_2, as determined by ^{19}F NMR spectroscopy; *trans*-$[PdR^1(CH{=}CH_2)L_2]$ (**49**) and the coupling product $R^1{-}CH{=}CH_2$ (**50**) were observed. ($R^1 = C_6Cl_2F_3$).

intermediate *trans*-$[PdR^1(CH{=}CH_2)L_2]$ (**49**), which has a noticeably long lifetime (even at 50 °C) but eventually generates the coupling product $R^1{-}CH{=}CH_2$ (**50**; $R^1 = C_6Cl_2F_3$).[96] Complex **49** is the result of a *trans* transmetalation via an open transition state. There is also, in competition, a *cis* transmetalation via an open transition state, which leads to

substitution of the PPh_3 ligand *cis* to the R^1 group in $[PdR^1L_3]^+$ to give a putative intermediate *cis*-$[PdR^1(CH{=}CH_2)(PPh_3)_2]$. (The same competition can be found with iodide instead of a stannane as the nucleophile, which affords a kinetic mixture of *cis*- and *trans*-$[PdR^1I(PPh_3)_2]$; this establishes a perfect correlation between a typical ligand substitution and an open transmetalation.) Complex *cis*-$[PdR^1(CH{=}CH_2)(PPh_3)_2]$ couples immediately and was not observed directly, but could be inferred kinetically from its effect on the rate of formation of the coupling product **50**, which is initially much faster than could be expected from the (very slow) decomposition of the *trans* complex **49** alone.

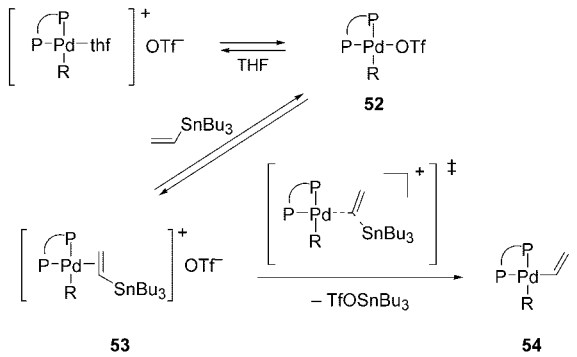
Assuming that the coupling takes place from a *cis* three-coordinate species (Scheme 33), the proposed *cis* intermediate **51** needs only to undergo the dissociation of L (if even



Scheme 33. Different pathways for the reductive elimination of *cis* and *trans* vinyl palladium complexes **51** and **49**, respectively. Three-coordinate *trans* complexes must isomerize to the corresponding *cis* complex before elimination of the product can occur.

that) for the coupling to occur. The *trans* isomer **49** must undergo isomerization into a three-coordinate species, which has been shown to be the highest barrier towards coupling in closely related complexes. Consequently, the *cis* complex produces the coupling product much faster than the *trans* isomer[196] and is not observed.

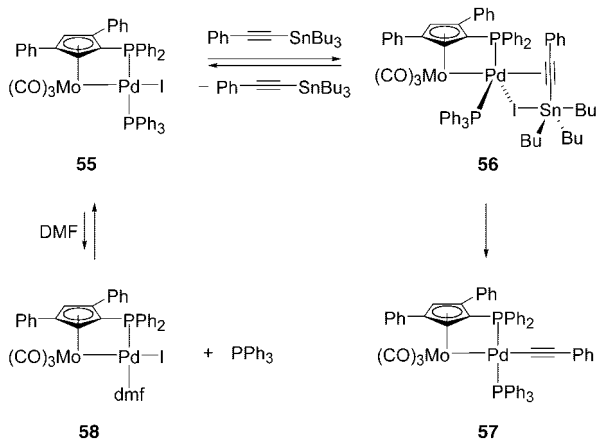
The reductive elimination is also slow when allyl groups (see Section 5.2)[197] or chelating ligands are involved (as in **52**, Scheme 34), enabling the observation of *cis* transmetalation products. Thus, by using dppe as the ligand, Espinet and co-workers observed the key intermediates in the catalytic cycle



Scheme 34. The mechanism of the transmetalation can be investigated by using chelate complexes.

for the coupling of an aryl triflate with tributyl(vinyl)stannane,[97] including the transmetalation product $[PdR(CH{=}CH_2)(dppe)]$ (**54**). The reaction proceeds as outlined in Scheme 34 via an S_E(open) transmetalation on complex **53**.

Lo Sterzo and co-workers detected spectroscopically the pentacoordinated palladium complex **56** in the transmetalation of complex **55** with an alkynyl stannanes (Scheme 35).[198]



Scheme 35. Complex **56** as a model for the transition state of the cyclic transmetalation.

This reaction is an example of palladium-catalyzed metal–carbon bond formation.[198–201] Complex **56** is a model of the transition state for the cyclic transmetalation and was shown to evolve to give **57** by first eliminating PPh_3.

Complex **55** exchanged a PPh_3 ligand in DMF to form complex **58** and the corresponding iodo-bridged palladium dimer (Scheme 35).[198] The involvement of this complex in a parallel transmetalation with the organostannane is another example of the competition of open and cyclic mechanisms.[198]

3.5. Proposals for Dissociative Mechanisms

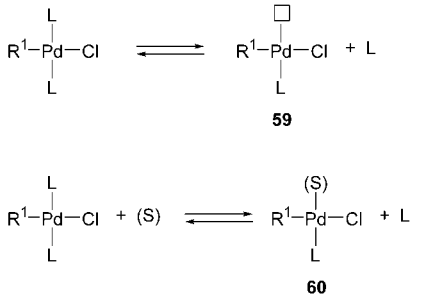
As stated above, the fact that the addition of a neutral ligand L retards the coupling[28,187] was initially taken as an indication that the dissociation of L from **32** (see Scheme 28) was a key step in the transmetalation. However, as discussed in Section 3.3, it is unlikely that transmetalations at Pd should proceed through true dissociative mechanisms involving 14-electron Pd intermediates.

Although supposed evidence for the involvement and observation of a 14-electron T-shaped complex, $[PdPhI(AsPh_3)]$, was reported,[71] a reexamination of the issue revealed that the species observed differed depending on the solvent and whether or not excess ligand was present.[176] At a Pd/$AsPh_3$ ratio of 1:2 in $CHCl_3$ the species initially thought to be T-shaped was actually the dimeric complex $[Pd_2Ph_2(\mu\text{-}I)_2(AsPh_3)_2]$.[176] In the more coordinating solvent DMF, the species detected was in fact the 16-electron tetracoordinated complex $[PdPhI(AsPh_3)(dmf)]$. In a later publication the authors of the original report reexamined thoroughly their system and acknowledged this reinterpreta-

tion.[189] The reformulation of the nature of these complexes also affects some earlier definitions of "$[ArPd(PPh_3)_2]^+$" complexes with triflate as the counterion.[93] In coordinating solvents these complexes are most likely the solvent-coordinated (rather than "solvated") complexes $[ArPd(PPh_3)_2(S)](TfO)$ ((S) = dmf), whereas in THF an equilibrium between $[ArPd(PPh_3)_2(S)](TfO)$ and $[ArPd(PPh_3)_2(TfO)]$ would exist, as found in related cases.[96] In less coordinating solvents, such as toluene, or in the solid state, these complexes should exist as covalent triflato derivatives $[PdAr(TfO)(PPh_3)_2]$, rather than as ion pairs.

The rate equations for dissociative transmetalation on $[PdR^1XL]$ (formed by the fast dissociation of L), on $[PdR^1XL(S)]$ (formed by a fast associative ligand substitution preequilibrium) with replacement of (S), and for associative transmetalation on $[PdR^1X(L)_2]$ with replacement of L display similar qualitative concentration dependence (Scheme 30).[176,188] Only with complete quantitative data would it be possible to decide whether the value of the concentration of $[PdR^1XL(S)]$ that would mathematically account for the reaction rate observed is a plausible value or not.

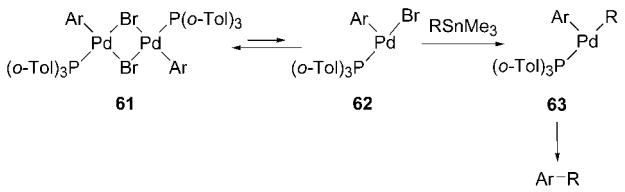
In the publication in which these issues were reexamined it was noted that ligand substitutions at Pd^{II} are usually associative (via pentacoordinated intermediates) and that the S_N2 transmetalation, whether through an open or a cyclic mechanism, is not an exception, except, perhaps, in special cases.[176] Since the concentration of the three-coordinate species is negligible in conventional systems, the transmetalation must involve associative displacement of one ligand (L, (S), or X) by the entering R^2 from R^2SnR_3. Thus, independent of the formulation of the complexes in the original literature, we regard herein those processes described as *dissociative* in the literature as *solvent-assisted associative*, and the dissociation equilibria to give three-coordinate species **59** (Scheme 36, top) as solvolysis reactions to give solvento



Scheme 36. Three-coordinate intermediates **59** and four-coordinate solvento complexes **60**.

four-coordinate complexes **60** (Scheme 36, bottom). The corresponding literature will be discussed in Sections 4.4 and 4.5 on associative transmetalation.

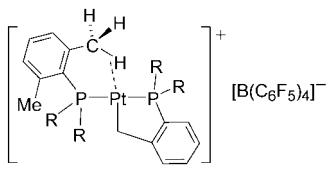
There are, however, a few possible exceptions. The best candidate for a true observation of transmetalation at a T-shaped 14-electron complex is the report by Louie and Hartwig on the behavior of **61** (Scheme 37).[187] This complex



Scheme 37. Apparently three-coordinate intermediates such as **62** can be stabilized through agostic interactions. Ar = *p*-Tol.

undergoes stoichiometric transmetalation with organotin aryl, thiolate, and amide compounds. Hartwig found that the transmetalation rate depends on the square root of the concentration of the dimer,[187] which is consistent with a dissociation of the dimer. Therefore, T-shaped monomers **62** were proposed to react with the organostannane to form **63**, from which the coupled product Ar–R forms.

The properties of complex **61** were rather unique at that time: The addition of $P(o\text{-Tol})_3$ does not lead to cleavage of this complex nor to retardation of the transmetalation (retardation is usually observed for catalysts with conventional ligands), thus showing that the formation of $[PdArBr\{P(o\text{-Tol})_3\}_2]$ is severely hindered. The monomer formed is unlikely to be $[PdArBr\{P(o\text{-Tol})_3\}(S)]$, as the solvent (toluene) is noncoordinanting. However, another possibility for the stabilization of the monomer as a 16-electron complex was not considered in the original publication: the formation of an agostic complex. It is plausible that the monomeric species **62** might be stabilized by an agostic interaction involving the empty orbital on Pd and the electron pair of the C–H bond of a methyl group. Since this intermediate is not observed spectroscopically because of its very low concentration, this hypothesis can not be proven, but the recent X-ray crystal structures of apparently three-coordinate Pd complexes with bulky phosphane ligands (complexes **19** and **20**) indeed reveal the existence of agostic interactions at the "vacant" coordination site.[143] A recent example from platinum chemistry also illustrates that apparently three-coordinate aryl Pt^{II} complexes **64a** and **64b** are in fact square planar complexes stabilized through an agostic interaction with one of the methyl groups of the phosphane ligand.[202]



64a R = Ph
64b R = Cy

Since it was recognized that complexes with bulky ligands can catalyze the Stille and other coupling reactions with less active organic nucleophiles, such as chlorides or triflates (see Section 2.6), the number of examples of such complexes has increased.[203,204] From a practical point of view, a formally 16-electron agostic complex, with very high nucleophilicity and

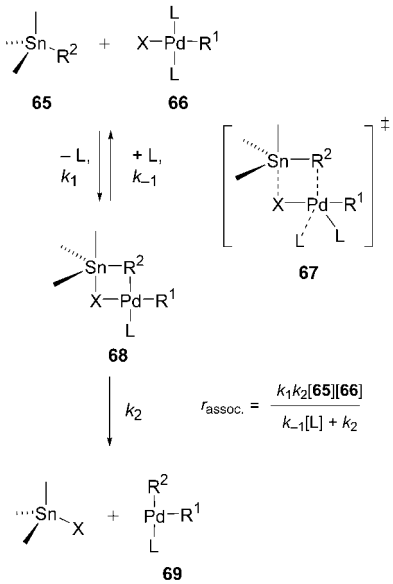
reactivity, is probably the stabilized intermediate that is functionally most similar to a T-shaped 14-electron species. Ligands that produce these agostic interactions might be considered an extreme case of hemilabile ligands. Because of the very poor donation from the agostic bond, these complexes have a highly electrophilic metal center.

In practice complexes stabilized by agostic bonds may be functionally equivalent to three-coordinate complexes. True T-shaped three-coordinate complexes were characterized recently in the solid state for electron-rich Pd complexes bonded to a very basic bulky phosphane, an amido group, and an aryl or thienyl group. The examples include one case of the coexistence of three-coordinate and agostic-bond-stabilized square-planar-coordinated isomers in the same crystal, thus showing the proximity in stability of the two systems and the extremely weak nature of agostic bonds to electron-rich centers.[205]

3.6. The Cyclic Associative Transmetalation

In the mechanistic proposals of Stille and Farina (Schemes 2 and 28, respectively) it was assumed that the transmetalation involved a preequilibrium to release one ligand, which explained the inverse dependence of the rate of reaction on the concentration of L.[1,29] It was also thought, in analogy with transmetalation reactions of organometallic compounds of main-group elements, that the *trans* geometry of the starting complex *trans*-$[PdR^1XL_2]$ was preserved in the reaction to give a *trans*-$[PdR^1R^2L_2]$ complex.[206] Since it is well established that the reductive elimination of R^1–R^2 occurs from *cis* derivatives,[1] a fast *trans* to *cis* isomerization is needed (Scheme 2).

The observed inverse dependence on the ligand concentration was recently found to be perfectly compatible with the rate expression for an associative mechanism (Scheme 38).[188]



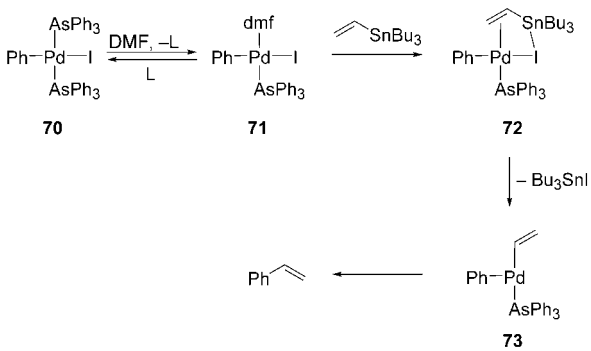
Scheme 38. The cyclic associative transmetalation.

This result led to the proposal of an additional transmetalation pathway via the cyclic structure **67**.

Importantly, this transmetalation pathway involves an associative substitution of L for R^2 via the bridged intermediate **68**[207,208] to give directly the complex **69** with R^1 and R^2 in a *cis* rather than a *trans* arrangement from which the coupled product will eliminate immediately. Moreover, the mechanism in Scheme 38 accounts for the retention of the configuration at C^α observed in some reactions,[35] which is difficult to account for by any other mechanism. Similar activated complexes have been proposed by Hatanaka and Hiyama for the palladium-catalyzed coupling of organosilicon compounds with the aid of fluoride ions.[36]

In coordinating solvents this mechanism can operate on $[PdR^1XL_2]$ or $[PdR^1XL(S)]$ complexes. Since these complexes obey rate laws with qualitatively similar kinetic dependence on the reagents, detailed studies are needed to distinguish between these possibilities. For the coupling in THF of 3,5-dichloro-2,4,6-trifluoro-1-iodobenzene ($C_6Cl_2F_3I$) and tributyl(vinyl)tin catalyzed by *trans*-$[Pd(C_6Cl_2F_3)I(AsPh_3)_2]$, the coupling rate observed would require the formation of 12% *trans*-$[Pd(C_6Cl_2F_3)I(AsPh_3)(thf)]$ if the transmetalation took place on this intermediate. At such a high concentration this complex could not escape detection by ^{19}F NMR spectroscopy. Since only *trans*-$[Pd(C_6Cl_2F_3)I(AsPh_3)_2]$ was observed, any kinetically relevant participation by *trans*-$[Pd(C_6Cl_2F_3)I(AsPh_3)(thf)]$ was excluded. The transmetalation takes place in this case on *trans*-$[Pd(C_6Cl_2F_3)X(AsPh_3)_2]$, and the rate increases with increasing electrophilicity of the metal center in the order $X = I < Br < Cl$.[188]

In contrast, in the coupling of PhI with tributyl(vinyl)tin in the presence of $[Pd(dba)(AsPh_3)_2]$ in DMF,[189] the species on which the transmetalation takes place is not *trans*-$[PdPhI(AsPh_3)_2]$ (**70**), but *trans*-$[PdPhI(AsPh_3)(dmf)]$ (**71**; Scheme 39). The alkenyl stannane then substitutes the dmf ligand to form **72**, which evolves to the transmetalation product **73**. An elegant kinetic study showed that even in the presence of excess $AsPh_3$ (when the concentration of **71** is very low) the associative transmetalation still mainly takes place on the solvento complex. Although the authors state that these findings confirm Farina's proposal for reactions in THF, in fact the sequence of reaction that they propose involves the substitution of a neutral ligand for R, as proposed



Scheme 39. An example of the influence of the solvent on the transmetalation.

by Espinet, rather than a substitution of I for R as proposed by Farina. Moreover, it is clear that under the conditions of Farina (PhI, $(CH_2{=}CH)SnBu_3$, and $AsPh_3$ in THF) the substitution does not occur on *trans*-[PdPhI($AsPh_3$)(thf)]. As calculated by Casado and Espinet, the rate of reaction observed should require 40% solvolysis to *trans*-[PdPhI($AsPh_3$)(thf)], which is not observed.[29,188] The complexes detected experimentally in a solution of *trans*-[PdPhI$(AsPh_3)_2$] in THF, in the absence of added $AsPh_3$, are [PdPhI$(AsPh_3)_2$] and $[Pd_2Ph_2(\mu\text{-}I)_2(AsPh_3)_2]$,[176] whereas those observed in DMF are [PdPhI$(AsPh_3)_2$] and [PdPhI($AsPh_3$)(dmf)].[176,189] These observations emphasize the important influence of the solvent on the transmetalation mechanism, and serve as a warning on the risk of giving conclusions drawn for a particular system universal value.

In summary, although the operation of a cyclic mechanism with exchange of L for R^2 (or (S) for R^2) now seems to be well established, it is also clear that the exact complex undergoing the transmetalation can change as a function of the solvent, R^1, L, and X.

3.7. The Open Associative Transmetalation

Until recently open transmetalation pathways were the only mechanisms considered in the literature (although within the misconception of dissociation). Most reactions probably do proceed by open mechanisms (but associatively), which explains the fact that the transmetalation step can be very fast in the absence of any potential bridging ligand, and that inversion at the α carbon atom sometimes occurs.[34]

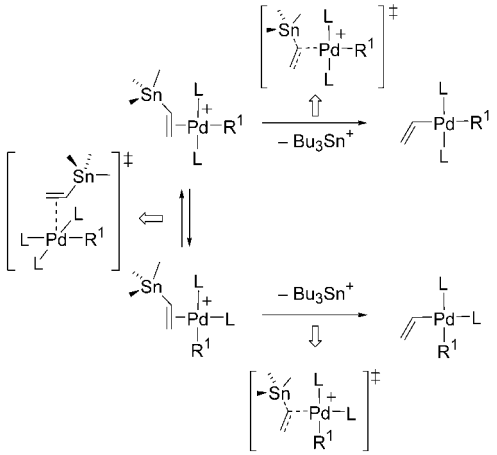
The main products of the oxidative addition of ArOTf to $[PdL_n]$ complexes are not neutral complexes $[PdAr(OTf)L_2]$, but cationic complexes $[PdAr(S)L_2](OTf)$, with a molecule of solvent (e.g. THF, DMF) or water coordinated to the palladium center.[93,96,209] Simplified representations, such as $[PdAr(PPh_3)_2]^+$, which ignore the coordination of the solvent, have most often been formuated.

For the coupling of organostannanes with vinyl[210] and aryl triflates,[211,212] LiCl has been used as an additive. Iodide salts have also been shown to promote other coupling reactions with aryl triflates.[213] Farina and co-workers found both accelerating and retarding effects for added LiCl,[27,29] depending on the solvent (NMP or THF), the organic triflate (R^1 = aryl or vinyl), and the neutral ancillary ligand (L = $AsPh_3$ or PPh_3). Based on results for related platinum systems,[184] it was postulated that the intermediates formed upon the oxidative addition of organic triflates to Pd^0 in the absence of LiCl are cationic complexes, such as $[PdR^1(S)L_2]^+$ and $[PdR^1L_3]^+$. The solvento complexes could be the active species in the subsequent transmetalation step.[28] In solvents such as THF, in which these species were inactive, the neutral complex $[PdR^1ClL_2]$ would be formed in the presence of LiCl, and the reaction would continue from this point by ligand "dissociation", transmetalation to a *trans* complex, and coupling (Scheme 28).[29]

This proposal is not correct, and the coupling of aryl triflates is mechanistically more complex.[96,97] Thus, the addition of LiCl favors the coupling of C_6F_5I with stannanes catalyzed by $[Pd(AsPh_3)_4]$ in THF.[96] In this case, LiCl promotes the very slow rate-determining oxidative addition of the aryl triflate by converting $[Pd(AsPh_3)_4]$ into more electron rich $[PdCl_n(AsPh_3)_m]^{n-}$ complexes, which give *trans*-$[PdRClL_2]$ as the product of the oxidative addition. In contrast, with the more nucleophilic $[Pd(PPh_3)_4]$, the Stille coupling is retarded by the addition of LiCl. In this case, the oxidative addition takes place readily in the absence of LiCl. In the presence of chloride ions the complex *trans*-$[PdRClL_2]$ is formed rapidly. In their absence *trans*-$[PdR(OTf)(PPh_3)_2]$ and $[PdR(PPh_3)_3]^+$, which undergo transmetalation faster, are formed. Therefore, the overall process is retarded in the presence of LiCl.[96] The recent proposal of Roy and Hartwig that the acceleration of the oxidative addition step by LiX is due in some cases to an increase in the polarity of the reaction medium may explain why this promoter is not needed in polar solvents.[99]

In general, the transmetalation in the absence of LiCl occurs on *trans*-$[PdR^1(OTf)L_2]$, $[PdR^1L_3]^+$, or *trans*-$[PdR^1L_2(S)]^+$. Studies of the transmetalation of $[PdR^1L_3]^+$ as an isolated step (Section 3.4, Figure 1) showed that the transmetalation gives rise to a significant concentration of the intermediate *trans*-$[PdR^1(CH{=}CH_2)L_2]$. *cis*-$[PdR^1(CH{=}CH_2)L_2]$ is also formed, but is not detected because of its high reactivity. The *trans* complexes have a long lifetime in solution, whereas the *cis* complexes undergo coupling very rapidly and are not observed, unless they are stabilized by chelating ligands. These results reveal competitive *cis* and *trans* ligand substitution in palladium complexes (both via open transition states), in proportions controlled by the different *trans* effects of the ligands (see Section 3.4). The process is illustrated for a cationic $[PdR^1L_3]^+$ complex and a vinyl stannane in Scheme 40. Similar results were obtained for *trans*-$[PdR^1(OTf)L_2]$,[96] as well as in the coupling of an aryl triflate with tributyl(vinyl)tin with dppe as the ligand (see Scheme 34).[97]

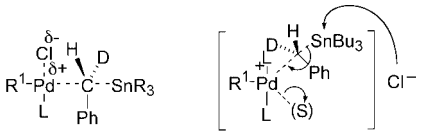
In the case of alkyl stannanes and other derivatives with sp^3-configured α carbon atoms, the transmetalation leads to inversion of configuration. As the nucleophilicity of the α carbon atoms of alkyl stannanes is very low, an efficient



Scheme 40. Formation pathways of the complexes *cis*- and *trans*-$[PdR^1(CH{=}CH_2)L_2]$ in the transmetalation with a vinyl stannane.

transmetalation will probably require a highly electrophilic metal center. A cationic complex $[PdR^1L_2(S)]^+$ would therefore be expected to be a more favorable intermediate than the neutral $[PdClR^1L(S)]$ ((S) = hmpa) initially suggested by Stille for the transformation shown in Scheme 29 (top).[34] In fact, in strongly coordinating and solvating HMPA the complexes $[PdR^1XL^2]$ (X = Cl, Br, I) are fully converted into $[PdR^1L_2(hmpa)]X$.[96]

Thus, solvents exert a very important influence on the transmetalation and can displace both neutral and anionic ligands, including halides. This behavior has very important stereochemical consequences, as the contradictory stereochemical results reported in the literature (Scheme 29) can now be understood. Thus, Falck and co-workers reported 98% retention of configuration in the coupling of chiral stannanes bearing an α-alkoxy substituent with acyl chlorides in toluene.[35] These conditions should strongly favor reaction via a cyclic transition state, because the transmetalation will take place on *trans*-$[Pd(acyl)Cl(PPh_3)_2]$.[96] Labadie and Stille found ≥65% inversion in the coupling of a chiral benzylic stannane with an acyl chloride in the highly polar solvent HMPA.[34] These conditions should favor reaction via an open transition state, which is probably **75**, arising from attack on $[Pd(acyl)(PPh_3)_2(hmpa)]^+$, rather than the neutral form **74** proposed by Stille.[96] Interestingly, the latter result shows that



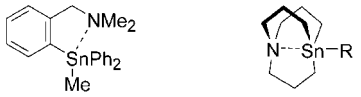
the S_E2(open) mechanism may be preferred even in the presence of a halide, provided that the solvent used is polar enough to provide good stabilization of the polar transition state **75**. This may explain the early observation of a significant rate acceleration in the presence of coordinating polar solvents, such as HMPA.[1]

In summary, the S_E(open) transmetalation mechanism is the only possible pathway in the absence of bridging ligands, but it can also operate in the presence of such ligands under appropriate conditions. It implies overall replacement of X for R^2 or L for R^2 at the Pd center, with competitive formation of *cis* and *trans* intermediates, and leads to inversion of configuration at the α carbon atom. This mechanism should be favored by the use of polar, coordinating, nonbridging solvents and for nonbridging anionic ligands that are readily cleaved.

3.8. Enhancement of Stannane Nucleophilicity by Additives

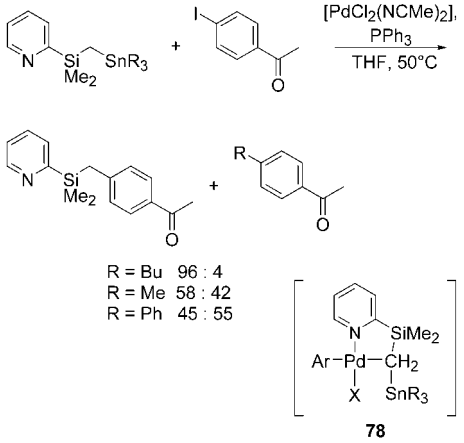
As mentioned in Section 2.6, fluoride additives enhance the reactivity of organostannanes.[132,133,214] Hydroxide ions[215] have a similar effect. Hydroxo ligands also play a major role in the transmetalation step of the Suzuki coupling reaction[4,216] and in other catalytic transformations of organoboranes.[217]

Particularly effective is the coordination of the nitrogen atom in benzyl amines such as **76**[218] and stannatrane derivatives **77**,[219–221] which allows the selective transfer of



the R group in Stille coupling reactions. The activation of stannanes by fluoride ions is particularly effective[133] and can be carried out in situ for the coupling of certain monoorganostannanes with alkenyl and aryl triflates.[133d]

The selective transfer of a substituted alkyl group in $RSnMe_3$ is difficult. Thus, in the palladium-catalyzed coupling of $Me_3SiCH_2SnMe_3$ with aryl triflates, the methyl group is transferred selectively.[211a] However, Yoshida and co-workers have demonstrated that when the silane is substituted with a 2-pyridyl ring (2-Py), selective transfer of the silylmethyl group takes place (Scheme 41).[222] A new concept is involved



Scheme 41. Selective transfer of a silylmethyl group. Taking into account the 2-$pyMe_2SiCH_2$/R ratio of 1:3 on the organotin reagent, the relative ratios for the transfer of the two groups are 99:1 (R = Bu), 81:19 (R = Me), and 71:29 (R = Ph).

in this selective coupling, as the coordination of the pyridyl nitrogen atom to the tin center should favor the transfer of R, whereas coordination to the palladium(II) center should favor the intramolecular transmetalation via an S_E2(cyclic) intermediate **78**.

Although not strictly an additive, it is very likely that in many cases the solvent acts as a ligand for the stannane in solution, enhancing its nucleophilicity. This behavior can also contribute to the rate acceleration observed in the presence of solvents such as HMPA.[1] Although no detailed study has been carried out specifically on this important aspect, recent theoretical calculations on the transmetalation of $[Pd(C{\equiv}CH)Br(PH_3)_2]$ with tetraethynylstannane in the presence of

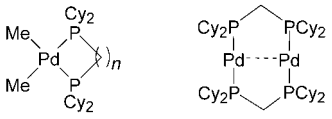
ammonia as a nucleophilic assistant support the hypothesis that coordination expansion at tin plays an important role in facilitating the transmetalation.[223]

4. The Reductive Elimination

An excellent review on reductive elimination is available. For this reason only a few examples are discussed herein.[224]

4.1. The Effect of Bidentate Ligands

As stated above, the formation of T-shaped intermediates [PdRR′L] greatly accelerates the reductive elimination of [PdRR′(L)$_2$] complexes.[40] The same is true for complexes bearing bidentate diphosphane ligands.[37,38,40] The reductive elimination of a series of complexes [PdMe$_2$(L-L)] (**79**, L-L = Cy$_2$P(CH$_2$)$_n$PCy$_2$; $n = 1$–4) revealed that only Cy$_2$PCH$_2$PCy$_2$,



79a–d **80**

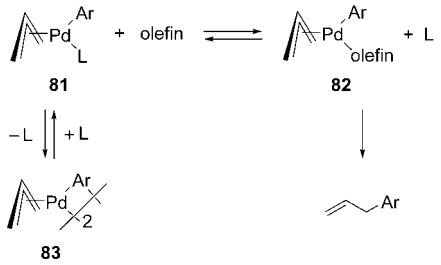
the ligand with the smallest bite angle, leads to a smooth elimination of ethane. Reductive elimination from these complexes is probably preceded by the dissociation of one of the diphosphane arms to form a T-shaped intermediate.[225] The resulting Pd^0 complex [Pd(L-L)] undergoes dimerization to form complex **80**. The complexes with more stable chelates ($n = 2$–4) do not eliminate ethane under mild conditions.

On the other hand, the fastest elimination for a series of complexes [PdMe$_2$(L-L)] with L-L = dppp, dppf, and 1,1′-bis(diphenylphosphanyl)ruthenocene (dppr) was observed with the ligand with the largest bite angle.[226,227] This effect on the reductive elimination was also found by Hayashi et al.[228] and van Leeuwen and co-workers[229] in the palladium-catalyzed cross-coupling reaction of Grignard reagents with aryl halides. In this process, the highest initial turnover frequencies were observed with ligands with large bite angles.

4.2. Coupling with Allylic Electrophiles: The Slow Reductive Elimination

The rate-determining step in the coupling of aryl halides or triflates with aryl or alkenyl stannanes can either be the transmetalation or the oxidative addition, depending on the exact reaction conditions.[97,188] On the other hand, in the coupling of allylic electrophiles, the reductive elimination step might become rate determining, since the C–C coupling is slower for allyl–R than for aryl–aryl or vinyl–aryl coupling.[224]

In fact, Schwartz and co-workers have shown that the coupling of allylic halides with allylic organometallic reagents does not proceed unless an electron-withdrawing olefin, such as maleic anhydride, is added.[230,231] The reductive elimination in allyl aryl palladium complexes of type **81** was studied by Kurosawa and co-workers (Scheme 42), who also noted



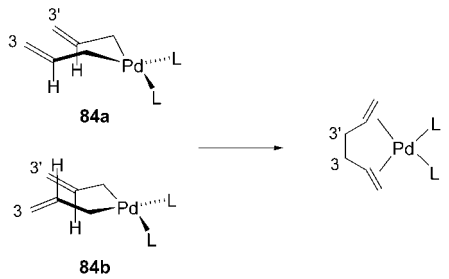
Scheme 42. Electron-poor olefins accelerate the reductive elimination of allylic arenes through the formation of complexes such as **82**.

this promoting effect of olefins with electron-withdrawing substituents.[232] Kinetic studies supported by theoretical work suggest that the reductive elimination occurs from an η^3-allyl palladium complex **82** with a coordinated olefin. This species was detected by NMR spectroscopy at low temperature.[232d] These results have been used to improve some catalytic coupling reactions by adding olefins with electron-withdrawing substituents (often maleic anhydride).[230,233,234]

It is remarkable that palladium-catalyzed coupling reactions of allyl halides with aryl stannanes are more efficient than the stoichiometric allyl–aryl reductive coupling on isolated allyl aryl palladium complexes. The stoichiometric transmetalation of η^3-allyl palladium complexes with an aryl stannane (Ar = C$_6$F$_5$) gives allyl aryl palladium complexes **81** and **82** (Scheme 42).[197] Reductive elimination from these complexes does not occur in the absence of additives. For an efficient coupling, the coordination of a promoter of reductive elimination, such as 1,4-benzoquinone or another electron-withdrawing olefin, is needed. Under catalytic conditions, the allyl electrophile itself acts as the electron-withdrawing olefin,[197] which explains why the catalytic coupling proceeds fairly well despite the resistance of complexes **81** or **83** to reductive elimination.

The coupling of allyl stannanes with allyl carboxylates[235,236] or allyl bromides[237,238] allows the synthesis of 1,5-dienes.[239] Bis(η^3-allyl) palladium complexes do not show any tendency to undergo reductive elimination.[240,241] In the presence of phosphane ligands, η^1-allyl η^3-allyl palladium complexes are formed,[242,243] which can decompose to form dinuclear Pd^I derivatives.[244] On the other hand, the addition of diphosphanes leads to bis(η^1-allyl) palladium diphosphane complexes,[245] which undergo smooth reductive elimination at low temperatures.[246]

That the most favorable pathway for the reductive elimination involves bis(η^1-allyl) palladium complexes bearing two phosphane ligands is supported by calculations (Scheme 43).[247] Interestingly, regardless of whether the allyl moieties are in a *syn* (**84a**) or an *anti* (**84b**) arrangement, the formation of a C3–C3′ bond ($E_a = 11.1$ and 8.5 kcal mol^{-1}, respectively, for L = PH$_3$) is favored significantly over the

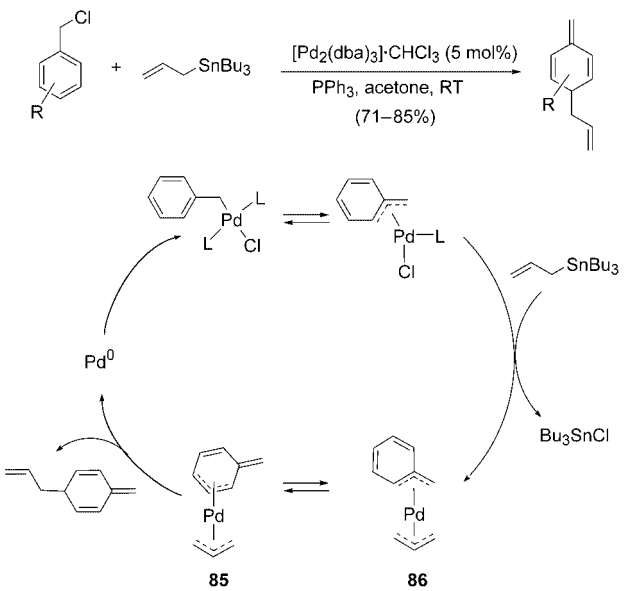


Scheme 43. Favored 3,3′ coupling of two allyl ligands.

formation of a C1–C1′ or a C1–C3′ bond ($E_a = 20.9$ and 22.8 kcal mol^{-1}, respectively).

4.3. Allyl–Benzyl Coupling

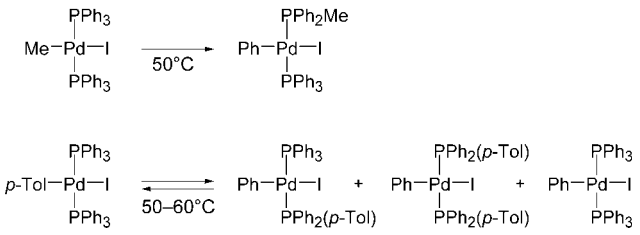
The recently discovered coupling of allyl stannanes with benzyl chlorides, resulting in the dearomatization of the aryl ring, is synthetically and mechanistically remarkable (Scheme 44).[248] Although the mechanism of this transformation has not been studied, the overall process probably involves isomerization of an η^3-allyl η^3-benzyl palladium complex **85** to give **86**, which could undergo reductive elimination to form the dearomatized product.[248]



Scheme 44. Mechanism of the dearomatizing coupling of benzyl chlorides with allyltributylstannane.

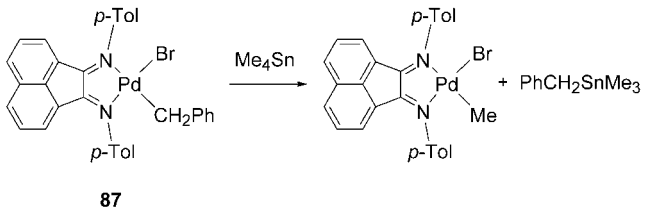
5. Scrambling of Substituents and Homocoupling

The exchange of R groups between the palladium center and the phosphane can take place under very mild conditions.[249–251] Investigations into the Me/Ph and the Ar/Ph exchange led to contradictory mechanistic results. In the first study (Scheme 45, top),[249] the rate was not affected by added PPh_3. However, in the second example (Scheme 45, bottom), the rearrangement was almost completely inhibited by PPh_3.[250] This contradiction was addressed by Novak and co-workers,[252] who showed that the aryl–aryl exchange reaction of $[PdArL_2X]$ proceeds first through a reductive elimination to form a phosphonium salt, followed by the oxidative addition of a different phosphorous–carbon bond.[253,254] Homocoupling processes resulting from an intermolecular Ar/Ar exchange between different Pd^{II} complexes have also been documented.[39b,255–257]



Scheme 45. Exchange of organic groups between the Pd center and the phosphane ligand.

Occasionally, instead of the expected transmetalation, the organostannane may undergo exchange reactions with the organic group in the oxidative-addition product, a process that can result in the formation of homocoupled derivatives.[256,258] This process has been studied by van Asselt and Elsevier with complexes such as **87** containing rigid bidentate nitrogen ligands (Scheme 46).[259]



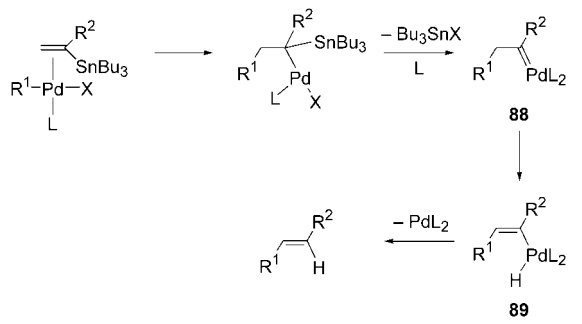
Scheme 46. Exchange of organic groups between the Pd complex **87** and tetramethyltin.

6. Unorthodox Mechanisms

Although the classical mechanistic sequence for the Stille coupling reaction (oxidative addition, transmetalation, reductive elimination) is reasonably reliable, some significant exceptions are known.

6.1. Reactions via Palladium Carbenes

Sterically hindered alkenyl stannanes might react by a different mechanism, which results in the formation of cine-substitution products.[260] Mechanistic studies carried out by Busacca et al.[260c] and Farina and Hossain[260d] suggest the participation of palladium carbenes **88** as intermediates,[261] which are formed by a Heck-type reaction involving olefin insertion and elimination of Bu_3SnX (Scheme 47). β-Hydride



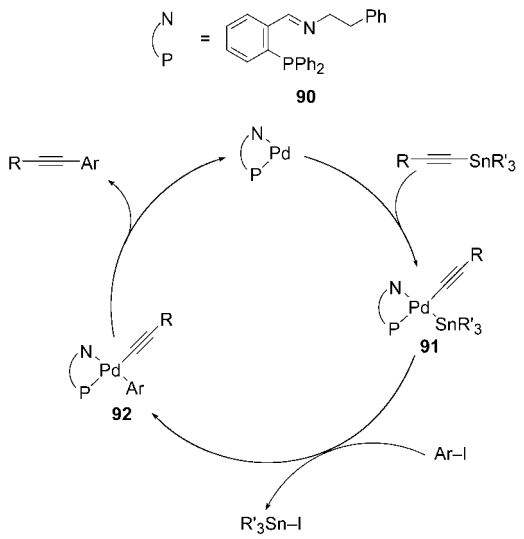
Scheme 47. Synthesis of 1,2-disubstituted alkenes via the palladium complex **88**.

elimination of the intermediate carbenes[262] gives complexes **89**, which undergo reductive elimination to form 1,2-disubstituted alkenes as the final products.

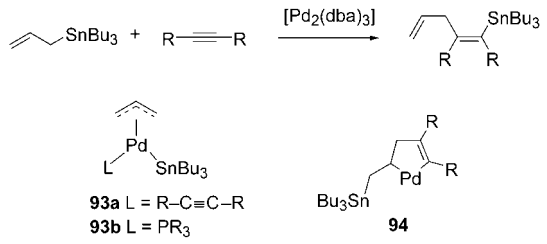
6.2. Reactions Initiated by the Oxidative Addition of Stannanes to Pd^0

The oxidative addition of some types of stannanes to Pd^0 complexes also appears to be an alternative pathway to the classical Stille sequence. Thus, Shirakawa et al. found that alkynyl stannanes react with certain Pd^0 complexes by oxidative addition.[263] Whereas aryl iodides react with alkynyl stannanes by the usual Stille pathway in the presence of Pd^0 complexes bearing phosphane ligands, the reaction proceeds via the complex **91** in the presence of a Pd^0 complex with the ligand **90** (Scheme 48).[263,264] Subsequent reaction with the aryl iodide was proposed to give **92**, which undergoes reductive elimination to form the C–C bond.

Allyl stannanes add to Pd^0 complexes to give η^3-allyl palladium complexes **93** (Scheme 49), which react with alkynes to afford allylstannylated derivatives.[265] An intramolecular version of this reaction has also been developed.[266]



Scheme 48. Example of a mechanism involving oxidative addition of the organotin reagent to a Pd^0 complex.



Scheme 49. Addition of allyltributylstannane to alkynes.

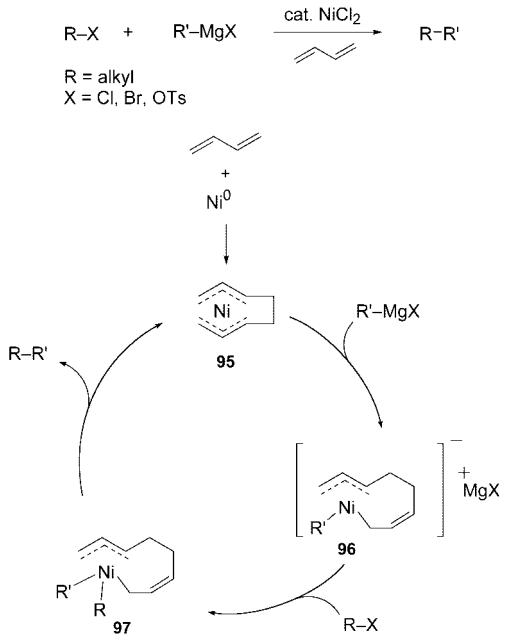
Complexes **93b** have also been proposed as intermediates in the Pd^0-catalyzed carboxylation of allyl stannanes with CO_2.[267] Similar complexes are probably formed by the transmetalation of η^3-allyl palladium complexes with hexamethyldistannane.[268]

For the allylstannylation reaction, an alternative process involving an oxidative cyclometalation to form a palladacyclopentene complex **94** seems less likely on the basis of recent theoretical calculations, which support the smooth oxidative addition of allyl stannanes to Pd^0.[266]

6.3. A New Catalytic Cycle Based on Pd^{II}/Pd^{IV}?

Although a Pd^{II}/Pd^{IV} catalytic cycle has not yet been proposed for the Stille reaction, there are hints that this possibility should be kept in mind when considering mechanisms of Pd-catalyzed coupling processes. There is strong evidence for the formation of Pd^{IV} intermediates by the oxidative addition of alkyl halides to Pd^{II} complexes.[269] Other d^8 organometallic compounds, such as $[IrCl(CO)L_2]$ (Vaska-type complexes) and certain Pt^{II} complexes, react readily with alkyl halides.[270,271] However, electrophiles $C(sp^2)$–X, such as aryl halides, are much less reactive in the oxidative addition to Pd^{II} complexes, and the formation of Pd^{IV} species from these electrophiles is therefore less likely. Indeed, there is no experimental evidence for such a process in the organometallic chemistry of Pd^{II} complexes,[272,273] although Pd^{IV} complexes $[PdArX_3(L\text{-}L)]$ ($Ar = C_6F_5$; X = Cl, Br), obtained by the oxidative addition of X_2 to [PdArX(L-L)], are known.[274]

The nickel-catalyzed coupling of alkyl halides and tosylates with Grignard reagents discovered by Kambe and coworkers is probably a genuine example of a coupling reaction under M^{II}/M^{IV} catalysis with a Group 10 metal (Scheme 50).[275] The active nickel complex is generated in situ by reaction of $NiCl_2$ and the Grignard reagent in the presence of 1,3-butadiene or isoprene. Although reduction of $NiCl_2$ by the Grignard reagent undoubtedly takes place under the reaction conditions, it was demonstrated that Ni^0 complexes are not the active catalysts. The requirement of a diene suggests that a bis(η^3-allyl) nickel(II) complex **95** is formed by oxidative dimerization,[276] and that **95** reacts subsequently with the Grignard reagent to form **96**. The oxidative addition of the alkyl halide or tosylate to the electron-rich complex **96** would then give a Ni^{IV} complex **97**. Reductive elimination should lead to the formation of the C–C bond and regeneration of the active Ni^{II} complex.



Scheme 50. The proposed catalytic cycle proceeds via Ni^{II} intermediates **95** and **96**, and Ni^{IV} intermediates **97**.

7. Copper Effects

A remarkable phenomenon in Stille coupling reactions is the effect of the addition of CuI or other Cu^{I} salts, which accelerate couplings catalyzed by $[PdL_4]$ with variable success.[27,29,35,277–281] This so-called "copper effect" was first studied by the research groups of Farina and Liebeskind.[282] Assuming a predissociation mechanism for the transmetalation, they concluded that the role of CuI in systems with "strong" ligands, such as PPh_3, was to scavenge free ligand. It was also suggested that for "soft ligands" (such as $AsPh_3$) ligand dissociation from Pd^{II} is not a problem, and therefore the addition of CuI leads to minimal rate acceleration.

The "copper effect" can be rationalized within the new framework of the associative mechanism. Accordingly, CuI does not promote the dissociation of L from *trans*-$[PdR^1IL_2]$, but it captures part of the neutral ligand L released during the oxidation of $[PdL_4]$ to *trans*-$[PdR^1IL_2]$, the species that actually undergoes the transmetalation. Thus, the effect of CuI is to mitigate the "autoretardation" by free L of the rate-determining associative transmetalation.[283] The effect is strong for PPh_3 and weak for $AsPh_3$ for two reasons: 1) The autoretardation is much more effective for $L = PPh_3$ (Figure 2), and 2) CuI is a more effective scavenger of PPh_3 than of $AsPh_3$.

In their initial study, Farina, Liebeskind and co-workers[282] proposed that in very polar solvents another phenomenon, a Sn/Cu transmetalation, was taking place. Thus, organocopper species were participating in the reaction.[284] An effective coupling system was later developed based on this proposal. Piers and Wong demonstrated that the intramolecular coupling of alkenyl iodides with alkenyl stannanes can be carried out in the presence of a stoichiometric amount

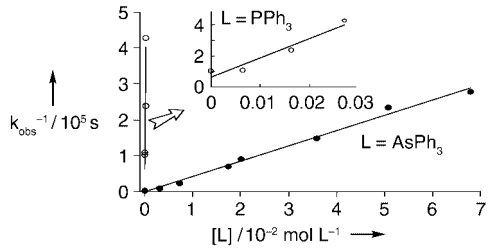
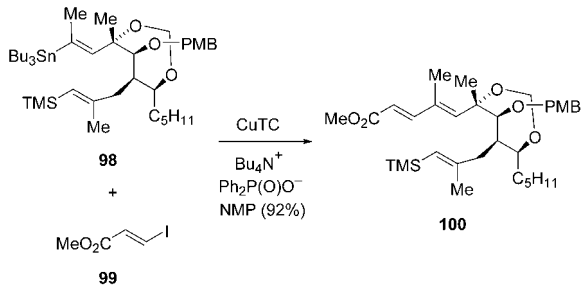


Figure 2. Inhibition by added L of the coupling of $C_6Cl_2F_3I$ with $Bu_3SnCH{=}CH_2$ catalyzed by *trans*-$[PdC_6Cl_2F_3)IL_2]$, represented as k_{obs}^{-1} versus [L]. $[C_6Cl_2F_3I] = [Bu_3SnCH{=}CH_2] = 0.2$ mol L^{-1}, THF, 322.6 K.

of CuCl.[285,286] Better results were later obtained with other Cu^{I} salts under catalytic conditions.[287–291] As an illustration, the cross-coupling of **98** and methyl (*E*)-β-iodoacrylate (**99**) promoted by copper(I) thiophene-2-carboxylate (CuTC) furnished **100** (Scheme 51), an intermediate in the synthesis of

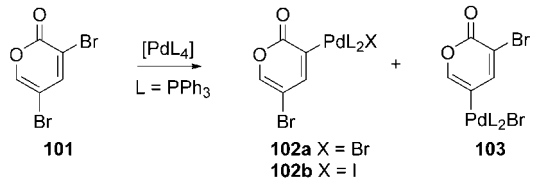


Scheme 51. Copper-catalyzed coupling of the alkenyl stannane **98** with the alkenyl iodide **99**. PMB = 4-methoxybenzyl, TMS = trimethylsilyl.

formamicinone.[292] Recently, the Stille coupling of heteroaromatic thioethers as the electrophiles was achieved in the presence of CuBr[293] or copper(I) 3-methylsalicylate.[294]

Finally, a new effect of the addition of copper salts was noted recently: The regioselectivity of Stille coupling reactions of 3,5-dibromo-2-pyrone (**101**) changes in the presence of CuI in DMF as the solvent, leading to the Pd^{II} complex **103** (Table 1).[295]

Table 1: Regioselectivity of the coupling of **101** in the presence and absence of CuI, in toluene and DMF.



Entry	Conditions	102/103
1	toluene, 100 °C	100:0
2	toluene, 100 °C, CuI (1 equiv)	100:0
3	DMF, 50 °C	100:0
4	DMF, 50 °C, CuI (1 equiv)	30:70

8. Summary and Outlook

Recent studies on the mechanism of the Stille reaction are uncovering a complex picture (Scheme 30), rich in possibilities. Each step can be rate determining, depending on the reaction variables. However, it is now better understood how each step can be accelerated. The transmetalation appears particularly complex, as it can operate on different Pd^{II} species in solution. These species change depending on the solvent, the reagents, and the catalyst. The nucleophilicity of the tin reagent can also be influenced by the solvent or by additives. The use of complexes with sterically demanding ligands as catalysts has recently made it possible to carry out the reaction with electrophiles that were unreactive when conventional ligands were used. Finally, a unified view seems to be emerging for transmetalations to palladium, whether with organotin compounds (Stille coupling), fluoride-activated silanes (Hiyama coupling), or other nucleophilic organometallic compounds: Some reactions occur with retention of configuration at the carbon atom that is transmetalated and probably proceed by an S_E2(cyclic) substitution of L for R at the Pd center. Other reactions occur with inversion of configuration by an S_E2(open) mechanism. This behavior, common to tin and silicon organometallic compounds, strongly suggests that under appropriate conditions similar dual reaction pathways might be found in reactions involving other organometallic reagents with the less electropositive metals, such as the Suzuki coupling.

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