Palladium Catalysts

Monoligated Palladium Species as Catalysts in Cross-Coupling Reactions

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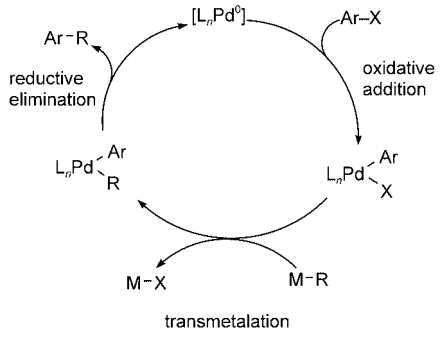
Palladium-mediated cross-coupling reactions are attractive organometallic transformations for the generation of C–C, C–N, C–O, and C–S bonds. Despite being widely employed in small-scale syntheses, cross-coupling reactions have not found important industrial applications because until recently, only reactive aryl bromides and iodides could be used as substrates. These substrates are generally more expensive and less widely available than their chloride counterparts. Over the past few years, new catalytic systems with the ability to activate unreactive and sterically hindered aryl chlorides have been developed. The new catalysts are based on palladium complexes that contain electron-rich and bulky phosphine or carbene ligands. The enhanced reactivity observed with these new systems has been attributed to the formation of unsaturated and reactive [PdL] species which can readily undergo oxidative addition reactions with ArX to yield [Pd(Ar)X(L)].

1. Introduction

Palladium-mediated cross-coupling reactions to form C–C, C–N, C–O, and C–S bonds are among the most powerful organometallic transformations employed in organic synthesis. These reactions are generally thought to proceed through a mechanism that involves three distinctive steps (see Scheme 1). First, an aryl halide reacts with the palladium(0) center through an oxidative addition reaction. This is followed by a transmetalation reaction to yield a palladium(II) complex that contains the two moieties to be coupled. The final step is the reductive elimination of the product with the concomitant regeneration of the active palladium(0) catalyst. In this mechanism, the nature of the aryl halide substrate is very important in the determination of the rate-limiting step. For example, for aryl chlorides and unactivated aryl bromides, it is often found that the oxidative addition is the rate-limiting step.

Initially, cross-coupling reactions had an important limitation: only reactive aryl bromides and iodides could be used as substrates. However, as aryl chlorides are more widely available and generally less expensive than their bromide and iodide counterparts, there has been a growing interest to find catalytic systems that can successfully catalyze cross-coupling reactions with these substrates. The past few years have seen important advances in this direction, with part of this success owed to the development of new palladium complexes which contain electron-rich and bulky ligands (namely phosphines and carbenes) that improve their catalytic activity in coupling



Scheme 1. General mechanism for cross-coupling reactions.

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reactions. The enhanced reactivity observed with these new systems has been attributed to the formation of unsaturated [PdL] species, which can readily undergo oxidative addition reactions to yield [Pd(Ar)X(L)].

Herein we present the most important advances that have been made over the past few years in the development of catalytic systems that use bulky and electron-rich ligands for cross-coupling reactions. As several excellent reviews[1–16] and books[17,18] on palladium-catalyzed coupling reactions have already been published, we limit our discussion to examples in which monoligated palladium species have been implicated in the catalytic process.

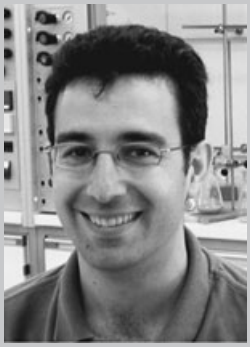
2. Palladium Catalysts Supported by Bulky and Electron-Rich Ligands

2.1. Phosphines

Several groups have established that the combination of bulky and electron-rich phosphines with different sources of palladium generate species that show high catalytic activity in cross-coupling reactions. In 1998, Nishiyama and co-workers showed that mixtures of $P t Bu_3$ and either $Pd(OAc)_2$ or $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone) had unusually high activities in amination reactions.[19] The same year, Littke and Fu reported that a mixture which contained $[Pd_2(dba)_3]$ and $P t Bu_3$ was highly active as a catalyst for the Suzuki coupling reaction of a broad spectrum of aryl halides.[20] A more detailed study by Fu and co-workers, in which the catalytic properties of palladium complexes with different phosphines as ligands were compared by using different aryl halides as substrates, gave further insight into the catalytic mechanism.[21] In these studies, it was shown that a mixture of $[Pd_2(dba)_3]$ and $P t Bu_3$ catalyzed the Suzuki cross-coupling of vinyl and aryl halides (including chloride) with arylboronic acids, whereas $Pd(OAc)_2$ in the presence of PCy_3 (Cy = cyclohexyl) generated a good catalyst for the cross-coupling reaction of vinyl and aryl triflates with arylboronic acids. The system with $P t Bu_3$ showed high selectivity with the order of reactivity $I > Br > Cl \gg OTf$. Interestingly, it was shown that the optimal palladium/phosphine ratio for high catalytic activity was between 1 and 1.5, which suggested that a monophosphine–palladium complex may be the catalytically active species. It was observed that $[Pd(P t Bu_3)_2]$ was a very poor catalyst for the Suzuki coupling of 3-chloropyridine and *o*-tolylboronic acid (7% conversion). However, addition of the phosphine-free species $[Pd_2(dba)_3]$ to $[Pd(P t Bu_3)_2]$ to generate the $[Pd(P t Bu_3)]$ species produced an important increase in activity (91% conversion).

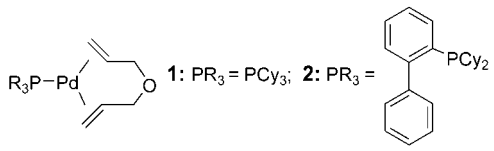
These studies were followed by various reports which showed that other types of cross-coupling reactions occur readily in the presence of a range of palladium sources and bulky phosphine ligands. Littke and Fu also demonstrated that a mixture of $[Pd_2(dba)_3]$ and $P t Bu_3$ yields a general catalyst system for Stille cross-coupling[22] and Heck reactions.[23] Hartwig and co-workers, on the other hand, reported that this palladium/phosphine combination produces an excellent catalyst for the arylation of ketones and malonates.[24,25] They also studied in detail the formation of C–N bonds catalyzed by palladium in the presence of bulky and electron-rich phosphines such as $P t Bu_3$, PCy_3, $PAd(t Bu_2)$ (Ad = 1-adamantyl), and $(Ph_5Fc)P t Bu_2$ (Q-phos; Fc = ferrocenyl).[26–28] In most cases, standard palladium sources such as $[Pd_2(dba)_3]$ and $Pd(OAc)_2$ were employed to generate the catalytic species in the presence of the corresponding phosphine. Further studies by Hartwig and co-workers showed that the previously reported palladium(I) dimer $[Pd_2(\mu\text{-}Br)_2(P t Bu_3)_2]$[29,30] could be used as a novel single-source precatalyst for cross-coupling reactions.[31] Unparalleled rates for amination and Suzuki–Miyaura cross-coupling reactions of aryl chlorides and bromides were observed with this complex. The high reactivity of this compound was attributed to the formation of the monoligated species $[Pd(P t Bu_3)]$ by either a disproportionation reaction or by the direct reduction of the dipalladium complex in the presence of the substrate and a base.

Beller and co-workers reported an efficient catalytic system for cross-coupling reactions based on the sterically demanding phosphine, $PAd_2(n Bu)$.[32] A mixture of $Pd(OAc)_2$ and this phosphine generates catalysts for the amination of aryl chlorides, the Suzuki coupling of aryl halides and boronic acids, and the α-arylation of ketones. In these reports, a detailed comparison of the activity of several catalytic systems was carried out that highlighted the influence of the supporting phosphine, the palladium/phosphine ratio, and the quantity (mol%) of the catalyst in the corresponding cross-coupling reactions. Furthermore, Beller and co-workers isolated the monophosphine–palladium(0) complexes **1** and **2** (see Scheme 2) which were used as efficient catalysts for Suzuki cross-coupling reactions.[33] The effectiveness of these complexes as catalysts is directly related to their ability to



Ramón Vilar, born in Mexico City in 1969, completed his PhD (1996) on the synthesis and catalytic properties of palladium cluster compounds in the group of Prof. D. M. P. Mingos at Imperial College London. He remained at Imperial College as a lecturer and was appointed Senior Lecturer in 2003. Since April 2004, he is an ICREA Research Professor at the Institute of Chemical Research of Catalonia (ICIQ). His current research interests include the organometallic chemistry of palladium and supramolecular chemistry of metal complexes.

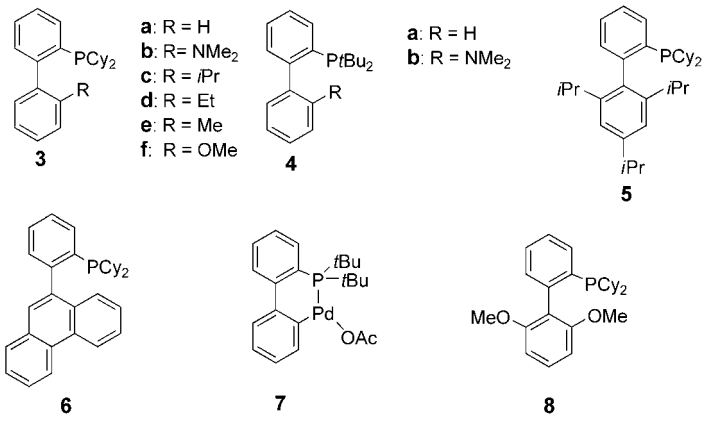
Ute Christmann, born in Peine (Germany), studied chemistry at the University of Hamburg. After completing her diploma with Prof. D. Rehder, she started her PhD (2002) in the group of Dr. R. Vilar at Imperial College, London (currently at ICIQ, Tarragona). Her research interests include the activation of small molecules by palladium(I) dimers and organometallic catalysis.



Scheme 2. Monophosphine–palladium complexes.

liberate the coordinated diene to generate the corresponding 12-electron species [PdL].

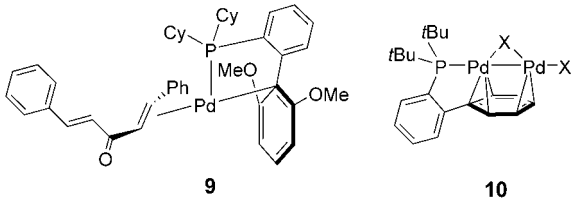
In the late 1990's, Buchwald and co-workers reported an important set of phosphines which proved to be excellent supporting ligands for the palladium-catalyzed formation of C–C, C–N, and C–O bonds with substrates such as aryl chlorides and bromides (see Scheme 3).[34–36] The effective-



Scheme 3. Buchwald's biaryl phosphine ligands and a cyclometallated palladium complex, **7**, of one such ligand (see References [6, 37]).

ness of these systems was attributed to a combination of electronic and steric properties of the ligands that favor both the oxidative addition and reductive elimination steps in the catalytic cycle. The formation of monoligated palladium species with biaryl phosphines was also invoked to be responsible for the rapid oxidative addition of the aryl halide substrates to the palladium(0) center. More recently, Buchwald's group reported a second generation of phosphines (see **5** and **8** in Scheme 3) with improved activities that demonstrate the generality of the catalyst system for a wide range of cross-coupling reactions.[37] As part of these studies, it was shown that the source of palladium and the phosphine/palladium ratio had an important impact on the catalytic performance of the system.

Besides the use of common palladium sources such as $Pd(OAc)_2$ and $[Pd_2(dba)_3]$, a single-component precatalyst based on a cyclometallated biaryl phosphine **7** was reported as a convenient air- and moisture-stable complex for aryl amination reactions.[38] It has been suggested that the biaryl group in Buchwald's phosphines may contribute to the stabilization of monophosphine–palladium complexes by establishing π interactions with the palladium(0) center. This is supported by the recent isolation of the complexes [Pd(dba)(L)] (where L = **4a**, **6**, or **8**) in which there is indeed a π interaction between the metal center and the aromatic system of the biaryl group (see **9**, Scheme 4).[39–41] The ability of this type of phosphine to stabilize unusual coordinations around metal centers can also be seen in the palladium dinuclear complex **10** in which $PtBu_2(bph)$ (bph = biphenyl)

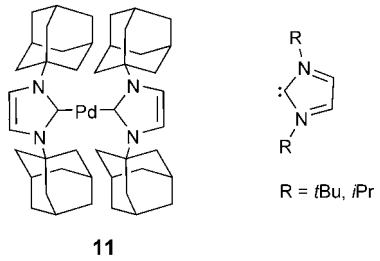


Scheme 4. Representation of a monometallic palladium(0) complex and a dinuclear palladium(I) compound with the π interactions between the metal center and the corresponding biaryl phosphine shown. X = Br, Cl.

bridges the two palladium centers through a μ_2-η^3:η^3-coordinated phenyl group (see Scheme 4).[41] This species catalyzed the amination reaction of aryl chlorides and bromides. The system is phosphine-deficient, thus it is likely that $[Pd\{PtBu_2(bph)\}]$ species are generated and these act as the true catalysts.

2.2. N-Heterocyclic Carbenes

Palladium complexes of N-heterocyclic carbenes (NHCs) can also be used as catalysts to activate aryl chlorides for cross-coupling reactions. For this type of reaction to occur at low temperatures and with reasonable yields, sterically demanding NHCs need to be employed (see Scheme 5). Some of these bulky ligands were successfully prepared and used in catalytic coupling reactions by the groups of Herrmann,[42] Beller,[43] Nolan,[44–46] Glorius,[47] and Cloke.[48]

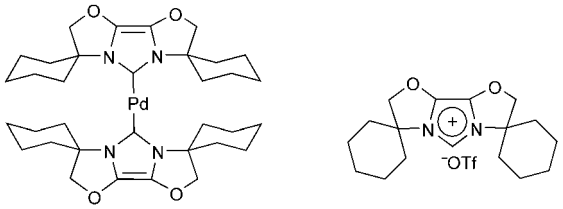


Scheme 5. General N-heterocyclic carbenes (NHC) that are commonly used as ligands in cross-coupling reactions and a palladium(0) homoleptic NHC complex **11**.

The ratios of ligand/palladium, the steric bulk of the ligand, and the source of palladium were shown to be very important in defining the catalytic activity of the system. Furthermore, mechanistic studies suggested that monoligated palladium(0) complexes are implicated in the catalysis. Herrmann and co-workers reported that homoleptic palladium complexes $[Pd(NHC)_2]$ are good catalysts for the Suzuki

coupling of aryl chlorides.[49] The activity of this type of complex is highly dependent on the steric bulk of the carbene ligand. In particular, the complex $[Pd(NHC)_2]$ **11**, in which the NHC is the very sterically demanding 1,3-bisadamantylimidazolin-2-ylidene (see Scheme 5), proved to be an excellent catalyst for the Suzuki coupling of aryl chlorides at ambient temperature.

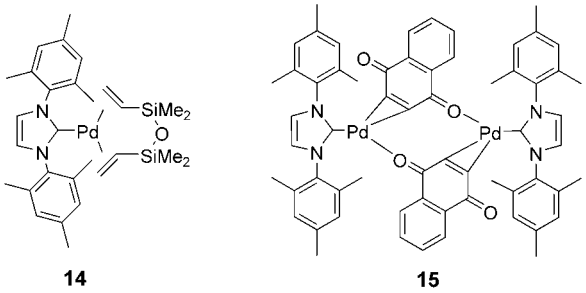
More recently, Glorius and co-workers reported the new homoleptic palladium complex **12**, which comprised the sterically demanding but flexible NHC ligand derived from **13** (see Scheme 6).[47] In contrast to the complexes described by Herrmann,[49] complex **12** proved to be catalytically inactive in the Suzuki coupling reaction at room temperature. However, a catalyst prepared from $Pd(OAc)_2$ and only one equivalent of the imidazolium salt **13** showed excellent catalytic activity for Suzuki cross-coupling reactions of aryl chlorides and even of sterically demanding substrates at room temperature. The authors attributed the high activity of this catalyst system to the formation of monoligated palladium–carbene complexes.



12 13

Scheme 6. Palladium(0) complex **12** with a geometrically flexible N-heterocyclic carbene ligand derived from the imidazolium salt **13**. OTf = trifluoromethylsulfonyl.

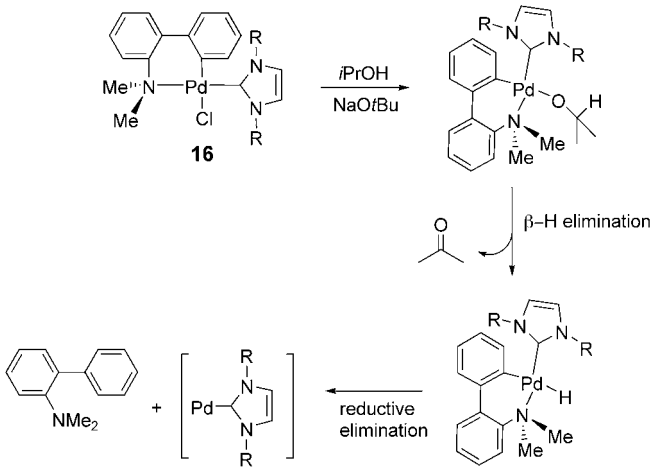
The potential role played by monoligated palladium–carbene complexes in cross-coupling reactions has also been studied by Beller and co-workers, who reported that the monocarbene–palladium(0) complexes **14** and **15** (see Scheme 7) act as good catalysts for Heck reactions of aryl chlorides (above 140 °C).[43] It was suggested that these complexes can generate the active 12-electron [PdL] species under the catalytic conditions. Interestingly, compound **14** has shown remarkable productivities and selectivities for the telomerization of 1,3-dienes with alcohols.[50,51] The good catalytic properties of this complex were attributed to the presence of unsaturated [PdL] species.



14 15

Scheme 7. Monocarbene–palladium(0) complexes.

Nolan and co-workers reported that the monocarbene–palladium(II) complex **16** (see Scheme 8) generated good catalytic species for Suzuki–Miyaura coupling reactions and Heck reactions of sterically hindered aryl chlorides at room temperature.[44,52] The isolation and identification of the organic fragments liberated in the initial steps of these reactions led the authors to propose a mechanism in which [Pd(NHC)] species, which act as the true catalysts, were generated (see Scheme 8).



Scheme 8. Representation of the reaction pathway to produce a catalytically active palladium(0)–monocarbene complex from **16**. R = 2,6-diisopropylphenyl.

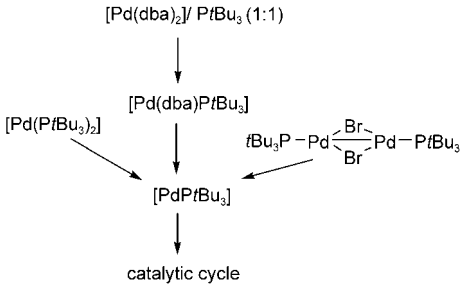
3. Mechanistic Studies

The experimental evidence described in the previous sections indicates that palladium in the presence of bulky and electron-rich ligands (either phosphines or carbenes) yields active catalytic systems for a wide range of cross-coupling reactions. The experimental observations also indicate that the source of palladium and the ratio of palladium/ligand employed have a great impact on the catalytic activity of the corresponding system. Some detailed mechanistic studies have now appeared which support the important catalytic role that monoligated palladium complexes play in cross-coupling reactions. To understand the mechanism of action of the catalytic species (and to optimize consequently conditions to enhance their catalytic properties), it is important to consider the different steps involved in the process. First, the generation of the catalytically active species from the corresponding palladium precursor needs to be considered; this step has demonstrated to be rate-limiting in several cases. After the "true" catalyst is generated, the oxidative addition of the aryl halide to the palladium(0) center takes place (which is favored by electron-rich ligands). Following a transmetalation reaction, the final step is the reductive elimination of the product,

the rate of which is usually increased by the coordination of bulky ligands to the palladium center. Furthermore, the mechanism of the catalysis can also be significantly influenced by the nature of the base added to the system.

3.1. Formation of Catalytically Active Species from Palladium Precursors

It is first necessary to address the step in which the catalytically active species are generated from the corresponding palladium precursors. Several authors have shown that even when the same phosphine or carbene ligand is used in a particular reaction, the source of palladium employed has an important influence on the catalytic rates. For example, Hartwig and co-workers recently published a study on the palladium-catalyzed amination of five-membered heterocyclic halides in which various combinations of palladium precursors and P*t*Bu$_3$ were tested as catalysts for the reaction of 3-bromothiophene with *N*-methylaniline (see Scheme 9).[28] The fastest reactions were observed with the



Scheme 9. Scheme showing the different potential routes employed by Hartwig and co-workers to generate the catalytically active [Pd(P*t*Bu$_3$)] species.[28]

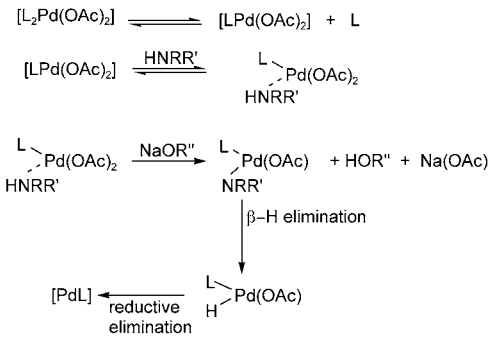
palladium(I) dimer [Pd$_2$(μ-Br)$_2$(P*t*Bu$_3$)$_2$], whereas those conducted with [Pd(P*t*Bu$_3$)$_2$] were very slow. If [Pd(dba)$_2$] was added to the latter, the reaction was faster than with the homoleptic diphosphine compound. Interestingly, the rate of reactions catalyzed by 1:1 mixtures of [Pd(dba)$_2$] and P*t*Bu$_3$ depended on the mixing time: Catalytic reactions conducted after allowing [Pd(dba)$_2$] and P*t*Bu$_3$ to mix for five minutes proceeded approximately three times faster than those conducted after mixing the two components for one hour. Note: the formation of [Pd(P*t*Bu$_3$)$_2$] from [Pd(dba)$_2$] and P*t*Bu$_3$ takes approximately one hour. These investigations strongly suggest that the efficiency of the formation of the monophosphine complex [Pd(P*t*Bu$_3$)] controls the rates of the amination reaction.

Analogous observations were reported by Littke and Fu, who used P*t*Bu$_3$ in palladium-catalyzed C–C bond formation,[4] by Glorius and co-workers, who used bulky carbenes as supporting ligands,[47] and by Buchwald and co-workers, who used (biphenyl)phosphines in C–N and C–C bond-forming reactions.[6,40,53,54] In these reports, the ability of the system to generate monoligated [PdL] species was proposed to be very important in the rate of catalysis.

Strieter, Blackmond, and Buchwald recently reported that the bulkiness of the phosphine group controls not only the catalytic activity of palladium complexes in amination reactions, but also the rate of the activation of the catalyst.[53] They used reaction calorimetry to study the amination of *p*-chlorotoluene with morpholine in the presence of catalytic systems, which comprised mixtures of Pd(OAc)$_2$ and different biaryl phosphines. With the trisubstituted isopropyl biaryl phosphine **5** (see Scheme 3), higher initial rates were observed relative to those observed with the less sterically demanding P*t*Bu$_2$(bph) phosphine (**4a**). In an additional experiment, the reactivities of the catalyst systems with the *ortho*-substituted biaryl phosphines **3c**–**3e** were compared with the reactivity of the trisubstituted biaryl phosphine **5**. Across the series **5**, **3c, 3d**, and **3e**, a 10-fold difference in the reaction rate was observed, and the highest activity was shown for the bulkier phosphine **5**.

In these studies, it was also demonstrated that the amine has an important effect on the activation of the catalyst. When the catalyst system derived from **3c**–**3e** was preincubated with the amine, although the initial rate was increased in comparison to the corresponding system without preincubation, the subsequent reactions displayed a decrease in the rate. In contrast, the preincubation of the phosphine **5** with the amine did not seem to influence the initial rates of consecutive reactions. This implicates the amine in the activation of the catalyst and indicates that the less bulky ligands **3c**–**3e** require longer exposure to the amine to reach a steady-state concentration of the active catalyst.

The sensitivity of the activation of the catalyst to the size of the phosphine suggests that dissociation of the phosphine from a diphosphine–palladium(II) species takes place. On the basis of the results described above, Strieter, Blackmond, and Buchwald proposed a mechanism in which monophosphine–palladium species are formed by the dissociation of [PdX$_2$(PR$_3$)$_2$] (see Scheme 10).[53] Slow dissociation (observed



Scheme 10. Mechanism for the generation of [PdL] catalytically active species (L = biaryl phosphine) proposed by Strieter, Blackmond, and Buchwald on the basis of calorimetric studies (see Reference [53]).

for the less bulky phosphines) of the palladium(II) complexes resulted in slower activation of the catalyst. This clearly indicates the important relationship between the steady-state concentration of the palladium catalysts and the size of the supporting phosphine.

3.2. The Oxidative Addition Step

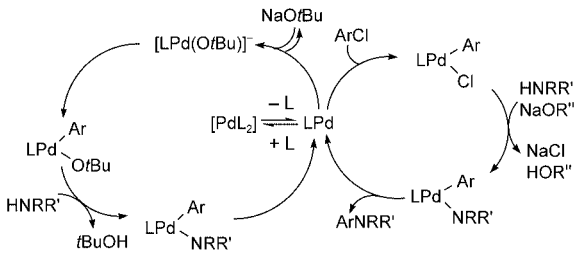
Several studies have been carried out to establish the effect of different ligands on the oxidative addition step of the catalytic cycle. Sterically demanding ligands have the ability to stabilize low-coordination palladium complexes (in particular monoligated species) which, owing to their low electron count, are more reactive. On the other hand, electron-donating ligands generate an electron-rich metal complex which undergoes faster oxidative addition reactions.

In a series of papers published in the mid 1990's, Hartwig and co-workers proposed monoligated palladium species as important intermediates in the catalytic amination of aryl halides using P(*o*-tolyl)$_3$ as a supporting ligand.[55] The oxidative addition of various aryl halides to [Pd{P(*o*-tolyl)$_3$}$_2$] generated the palladium(II) dimer [Pd$_2$Ar$_2$(μ-X)$_2${P(*o*-tolyl)$_3$}$_2$] where only one phosphine per palladium was present. Kinetic data demonstrated that this dimetallic compound was formed by oxidative addition to the monoligated species [Pd{P(*o*-tolyl)$_3$}] through a dissociative mechanism.[56–58]

More recently, Brown and co-workers[59] showed the mechanism of oxidative addition to [Pd(PR$_3$)$_2$] complexes to be highly sensitive to the bulkiness of PR$_3$ (where PR$_3$ = PCy$_n$*t*Bu$_{3-n}$, n = 0, 1, 2, 3). Complexes with PR$_3$ = P*t*Bu$_3$ or PCy*t*Bu$_2$ undergo oxidative addition with aryl halides by a dissociative mechanism, whereas [Pd(PR$_3$)$_2$] complexes with the less bulky phosphines PCy$_2$*t*Bu and PCy$_3$ follow an associative mechanism. The dissociative mechanism for the bulkier phosphines has been substantiated by the recent isolation by Hartwig and co-workers of a series of tricoordinated palladium(II) compounds with general formula [Pd(Ph)X(PR$_3$)] (PR$_3$ = PAd*t*Bu$_2$, P*t*Bu$_3$, or (Ph$_5$Fc)P*t*Bu$_2$; X = Br, I, or OTf).[60,61] These complexes were obtained in good yields by treating the phenyl halides with either [Pd(PR$_3$)$_2$] or with mixtures of [Pd(dba)$_2$] and one equivalent of the corresponding phosphine. This suggests that the tricoordinated products are formed through oxidative addition of the phenyl halide to monophosphine–palladium(0) complexes. The rates of oxidative addition reactions to generate the [Pd(Ph)X(PR$_3$)] complexes correlate well with the catalytic rates observed for the corresponding systems in cross-coupling reactions.

The X-ray crystal structures of [Pd(Ph)X(PR$_3$)] revealed that these species have a T-shaped monomeric geometry with the phenyl ring located in a position *trans* to the open coordination site of the metal. The structural characterization also showed weak agostic interactions between the palladium center and a C–H bond from a ligand—this was suggested to be the interaction that stabilizes the unusual geometry of these complexes. More recently, the palladium(II) complexes [Pd(*p*-anisyl)(NAr$_2$)(PR$_3$)] (PR$_3$ = (Ph$_5$Fc)P*t*Bu$_2$, FcP*t*Bu$_2$; Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$) were reported and their crystal structures revealed the absence of agostic interactions although they also have T-shaped geometries around the palladium center.[62] In the context of palladium-catalyzed coupling reactions, these tricoordinated species are very important because they demonstrate the possibility to obtain monophosphine complexes in which both of the substrates to be coupled are attached to the metal center.[63]

In 2001, Hartwig and co-workers proposed that the catalytic reaction of aryl chlorides with amines in the presence of alkoxide bases occurs by two concurrent mechanisms (see Scheme 11).[64] In one of these mechanisms, the alkoxide base



Scheme 11. Proposed concurrent catalytic cycles for the amination of aryl halides; the left-hand cycle depicts the anionic path.[64]

participates directly in the oxidative addition step to generate a monophosphine anionic active species.[65] This proposed mechanism could explain the observation that several cross-coupling reactions with the same aryl halide substrate and catalyst system required different conditions and reaction times. This is also consistent with the experimental observation that the amination of aryl halides with weak or strong bases require very different temperatures and catalyst loadings.

Despite the increasing interest in the use of palladium–NHC complexes as catalysts in cross-coupling reactions (see Section 2.2), their mechanism of action remains unclear. To gain a better understanding of this process, Caddick, Cloke, and co-workers carried out mechanistic investigations into the catalytic amination of aryl chlorides using [Pd(NHC)$_2$] (where NHC = *cyclo*-C{N(*t*Bu)CH}$_2$).[48] Their studies indicated that the oxidative addition of the aryl chloride is the rate-limiting step, and that the reaction takes place through a dissociative mechanism—as also observed with palladium complexes that contain bulky phosphines. Variable-temperature NMR spectroscopy experiments showed the dissociation of [Pd(Ar)Cl(NHC)$_2$] into the monoligated [Pd(Ar)Cl(NHC)] complex upon heating. Under conditions typical of catalytic amination, it was proposed that this dissociation of the complex into monocarbene–palladium species is the rate-determining step.

3.3. Reductive Elimination of the Final Product

The final step in the catalytic cycle corresponds to the reductive elimination of the coupled product from the metal center (see Scheme 1). It is generally accepted that this step is faster when palladium is coordinated to electron-withdrawing and sterically demanding ligands. It has also been shown that for very bulky ligands, the steric properties dominate over the electronic properties and even electron-donating ligands (such as the phosphines and carbenes discussed so far) accelerate the reductive elimination reaction. Although there are several studies which discuss the reductive elimination step of "classical" cross-coupling catalysts, only a few reports

have appeared in which this process is analyzed for catalyst systems with bulky and electron-rich ligands that favor monoligated palladium species. This is probably because the reductive elimination step is rarely rate-limiting when these bulky ligands are used.

The reductive elimination of different organic partners to generate C–C, C–N, C–O, and C–S bonds can proceed through different mechanistic pathways.[66–68] The supporting ligands, the ability of the metal complex to dissociate, and the nature of the substrates to be coupled have an important influence on which of the paths is followed. Three-coordinated palladium(II) complexes have often been postulated as the intermediate species that form the coupled product by reductive elimination. Until recently, the implication of such species was postulated mainly from kinetic and computational data. Early kinetic studies by Stille and Loare on C–C bond-forming reactions already suggested that the dissociation of a phosphine group from the palladium(II) complex was required prior to the reductive elimination step.[67] More recently, it was suggested that three-coordinated palladium(II) complexes (with bulky biaryl phosphines) are involved in the formation of diaryl ethers.[34,69] Although the exact mechanism of the reductive elimination step in these reactions is still unknown, Buchwald and co-workers proposed some hypotheses and found that for electron-deficient aryl halides, the most likely mechanism for the reductive elimination involves the transfer of a phenolate group from palladium to the *ipso*-carbon atom of the aryl halide. This intermediate is then converted into the diaryl ether to regenerate the palladium(0) species. In contrast, for electron-rich and electronically neutral aryl halides, the most likely mechanism involves a three-centered transition state.

The importance of three-coordinated palladium(II) intermediates in the reductive elimination step has been recently confirmed by Hartwig and co-workers, who reported the first fully characterized three-coordinated aryl–palladium amido complexes (see Section 3.2).[62] The reaction of 2-thienyl bromide with $[Pd(P\mathit{t}Bu_3)_2]$ in the presence of $KNAr_2$ yielded $[Pd(thienyl)(NAr_2)(P\mathit{t}Bu_3)]$, which was isolated and structurally characterized (analogous complexes with $(Ph_5Fc)P\mathit{t}Bu_2$ and $FcP\mathit{t}Bu_2$ were prepared by treating $[Pd(Ar)Br(PR_3)]$ with $KNAr_2$). Upon heating these complexes in toluene, reductive elimination reactions took place and the corresponding amine was formed. The rate of reductive elimination from the three-coordinated palladium complex $[Pd(p\text{-anisyl})(NAr_2)(P\mathit{t}Bu_3)]$ was compared with the rate of the analogous reaction from the four-coordinated complex $[Pd(p\text{-anisyl})(NAr_2)(dppf)]$ (dppf = 1,1′-bis(diphenylphosphino)ferrocene). The three-coordinated complex underwent reductive elimination at −10 °C to form the triarylamine product in 91% yield and with a half-life of 10 minutes. In contrast, the four-coordinated complex eliminated the triarylamine with a half-time of 55 minutes at 75 °C. These results strongly point toward three-coordinated palladium complex intermediates in the reductive elimination step of the catalytic cycle.

Hartwig and co-workers also recently presented a detailed mechanistic study of the reductive elimination of aryl halides from the dimeric arylpalladium(II) halide complexes $[Pd_2Ar_2(\mu\text{-}X)_2\{P(o\text{-tolyl})_3\}_2]$ (X = Cl, Br, I) upon addition of the hindered alkylphosphines $P\mathit{t}Bu_3$.[72] As stated earlier, it is generally accepted that reductive elimination is faster for complexes with weakly electron-withdrawing ligands because these ligands can remove some electron density from the metal center to generate favorable conditions for the reduction. Consequently, it would be expected that electron-rich phosphines such as $P\mathit{t}Bu_3$ would not favor the reductive elimination step. However, this recent study showed that coordination of $P\mathit{t}Bu_3$ to the palladium center induces reductive elimination of the aryl halide and indicates that the steric properties of this phosphine override its electronic effects.This is an important observation in the context of cross-coupling reactions as it suggests that $P\mathit{t}Bu_3$ indeed has a unique combination of steric and electronic properties to favor both the oxidative addition of the aryl halide (owing to its highly electron-donating properties) and the reductive elimination of the coupled product (owing to its steric bulk).

4. Conclusions and Outlook

The past few years have seen important advances in the development of highly-active catalysts to carry out cross-coupling reactions with unreactive and sterically hindered aryl halide substrates (with particular emphasis on aryl chlorides). To develop these new catalytic systems, a series of sterically demanding and electron-rich phosphine and N-heterocyclic carbene ligands have been employed. As shown throughout this review, there is increasing evidence to suggest that the ability of these ligands to stabilize monoligated palladium species is responsible for their enhanced reactivity. The generation of the catalytically active [PdL] species and the oxidative addition of the aryl halide onto the palladium(0) center are generally considered the rate-limiting steps. The steric bulk of the ligands discussed here has proved to be very important in the stabilization of the unsaturated [PdL] species, which is needed to initiate the catalytic cycle. Also, the electron-rich properties of the ligands favor the oxidative addition of the aryl halide onto the palladium(0) center even when the substrate is sterically hindered and unreactive. Besides their implication in cross-coupling reactions, unsaturated [PdL] complexes have also been invoked as the catalytically active species in some highly selective and efficient telomerization reactions.

The success of the systems described here provides a good basis for a more rational approach to the design and development of new catalytic systems for cross-coupling reactions. Important structure–activity relationships have been already established which open possibilities for the design of more-active and general catalytic systems. An important challenge remains the search for catalytic systems that not only activate unreactive aryl halides but also C–H bonds. Furthermore, the knowledge that has already been generated should stimulate the investigation of other organometallic transformations that could benefit from these ligand/metal systems.

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