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Computational Perspective on Pd-Catalyzed C−C Cross-Coupling Reaction Mechanisms

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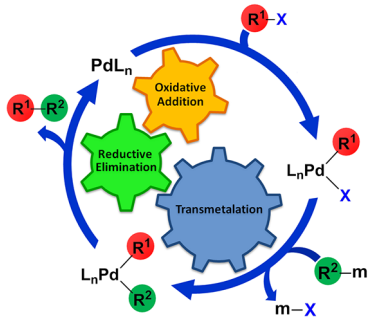
CONSPECTUS

Palladium-catalyzed C−C cross-coupling reactions (Suzuki−Miyaura, Negishi, Stille, Sonogashira, etc.) are among the most useful reactions in modern organic synthesis because of their wide scope and selectivity under mild conditions. The many steps involved and the availability of competing pathways with similar energy barriers cause the mechanism to be quite complicated. In addition, the short-lived intermediates are difficult to detect, making it challenging to fully characterize the mechanism of these reactions using purely experimental techniques. Therefore, computational chemistry has proven crucial for elucidating the mechanism and shaping our current understanding of these processes. This mechanistic elucidation provides an opportunity to further expand these reactions to new substrates and to refine the selectivity of these reactions.



During the past decade, we have applied computational chemistry, mostly using density functional theory (DFT), to the study of the mechanism of C−C cross-coupling reactions. This Account summarizes the results of our work, as well as significant contributions from others. Apart from a few studies on the general features of the catalytic cycles that have highlighted the existence of manifold competing pathways, most studies have focused on a specific reaction step, leading to the analysis of the oxidative addition, transmetalation, and reductive elimination steps of these processes. In oxidative addition, computational studies have clarified the connection between coordination number and selectivity. For transmetalation, computation has increased the understanding of different issues for the various named reactions: the role of the base in the Suzuki−Miyaura cross-coupling, the factors distinguishing the cyclic and open mechanisms in the Stille reaction, the identity of the active intermediates in the Negishi cross-coupling, and the different mechanistic alternatives in the Sonogashira reaction. We have also studied the closely related direct arylation process and highlighted the role of an external base as proton abstractor. Finally, we have also rationalized the effect of ligand substitution on the reductive elimination process.

Computational chemistry has improved our understanding of palladium-catalyzed cross-coupling processes, allowing us to identify the mechanistic complexity of these reactions and, in a few selected cases, to fully clarify their mechanisms. Modern computational tools can deal with systems of the size and complexity involved in cross-coupling and have a continuing role in solving specific problems in this field.

Introduction

Catalyzed C−C cross-coupling reactions are among the most important and useful reactions in organic synthesis and organometallic chemistry, because they allow the selective formation of C−C bonds under mild conditions and are a primary tool for the synthesis of large variety of complex compounds from readily accessible reactants.[1] Three of their main developers, Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki, were awarded with the Nobel Prize in Chemistry in 2010 for their work in this field. These reactions consist in the carbon−carbon bond formation between an organic electrophile, R^1−X, and an organometallic nucleophile, R^2−m, in the presence of a catalyst [M] (Scheme 1). C−C cross-coupling reactions are often classified depending on the metal or

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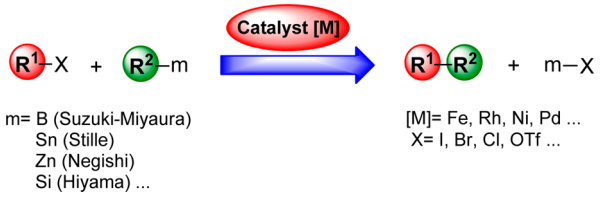
SCHEME 1. General Scheme for C–C Cross-Coupling Reactions



semimetal present in the nucleophile. For instance, Suzuki–Miyaura[2] is boron-mediated, Stille[3] reaction tin-mediated, Negishi[4] reaction, zinc-mediated, etc. The catalysts most widely employed are transition metal complexes from groups 8–10, especially complexes of palladium.

Despite the wide use of cross-coupling reactions, their application has been often based on a trial-and-error approach, because mechanistic knowledge has been difficult to acquire from pure experimental techniques. These are multistep processes with many intermediates involved, and competing equilibria are often present. The ever increasing computational power and the development of more efficient theoretical algorithms have allowed computational chemistry to enter to this field in the past decade, with significant contributions in terms of mechanistic clarification. In 2008, this journal[5] dedicated a special issue to recent developments in cross-coupling reactions regarding several topics: the class of ligands used, the nature of metal catalysts, the types of the bonds formed (e.g., C–C, C–N), the kind of reactants used, etc. In this Account, we cover the research on the reaction mechanism for the most known Pd-catalyzed C–C cross-coupling reactions from a computational perspective. These contributions have been collected in a number of reviews,[6−8] which we are summarizing and updating in this Account, with particular emphasis on our work in the field.

General Catalytic Cycle

It is generally accepted that cross-coupling reactions follow a catalytic cycle consisting of three main steps (Figure 1): oxidative addition, transmetalation, and reductive elimination. There are, however, relatively few computational studies that have attempted to compute the full catalytic cycle. The main reason is highlighted by our work dealing with the full catalytic cycle for the Suzuki–Miyaura reaction, where we showed the existence of a manifold of similar energy pathways, with no clear general preference for one of them.[9−11] In particular, we showed that both mono- and bis-ligated catalysts could lead in principle to efficient catalytic cycles. Other works on the full catalytic cycle have been also

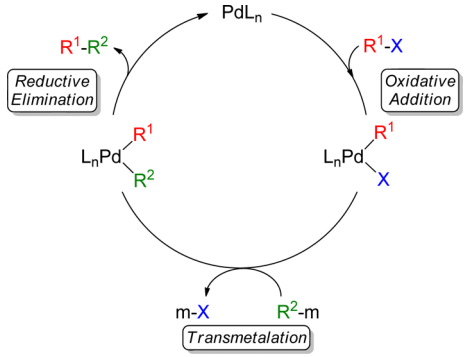


FIGURE 1. General catalytic cycle for Pd-catalyzed C–C cross-coupling reactions.

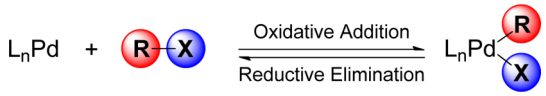
published. The effect of changes in the nature of the phosphine ligands over the different steps in the Suzuki–Miyaura reaction was analyzed by Harvey et al.[12] by means of steric and electronic descriptors in conjunction with DFT methods. The combination of the steric and electronic effects resulted in the following order in the transmetalation energy barriers with the different phosphine ligands: $P(CF_3)_3 < PPh_3 < PMe_3 < P(t\text{-}Bu_3)$. The effect of some of these ligands (i.e., PMe_3, PPh_3, and $P(t\text{-}Bu_3)$) was also theoretically investigated by Kozuch and Martin for the Suzuki–Miyaura coupling of Ph–Br and $PhB(OH)_3^-$ catalyzed by $[PdL_n]$ complexes.[13] The full catalytic cycle for the Negishi Csp^3–Csp^3 coupling between Et–Br and EtZnBr catalyzed by monoligated NHC–Pd (NHC = N-heterocyclic carbene) complexes was also investigated by Organ et al.,[14] with focus on the role of the NHC ligand. The full catalytic cycle of a selective Heck reaction has been computationally analyzed.[15]

Despite the fact that the three-step mechanism is generally accepted, each of these main steps has different possibilities and can be quite subtle and specific for each reaction. The following sections describe the knowledge gained on each of the three fundamental steps from computational chemistry. The section devoted to transmetalation will be the longest one because it is the characteristic reaction step for the different cross-coupling reactions.

The Oxidative Addition Step

In the oxidative addition step, the bond between the organic R group and the heteroatom X breaks, and two new bonds are formed with the metal, which increases its oxidation state by two units (Scheme 2). These reactions can be reversible, but the equilibrium is expected to be displaced toward the oxidative addition product when ligands with strong electron-donating abilities (that stabilize higher oxidation states of the metal) are employed. The oxidative

SCHEME 2. General Scheme for the Oxidative Addition Reaction



addition has been postulated to be rate-limiting in a number of cross-coupling reactions.[16,17]

For this step, two main mechanisms have been proposed (Figure 2). The *concerted* pathway entails the simultaneous formation of the Pd−C and Pd−X bonds in the transition state, which leads to retention of configuration at a stereogenic carbon atom in the case of chiral electrophiles R−X. The second pathway is an associative bimolecular process that consists of two steps: first, the carbon is attacked by the metal and the anion X^- is expelled giving rise to a cationic species; subsequently, both charged species combine to yield the product. This second mechanism has been labeled as S_N2 by analogy with the organic chemistry substitution reaction and gives rise to the inversion of configuration if a stereogenic carbon center is involved.

The oxidative addition of Ph−X (X = Cl, Br, or I) to Pd(0) complexes with bidentate phosphines [Pd(PP)] (PP = 1,2-bis-(dimethylphosphino)ethane or (P)-2,2′-bis(dimethylphosphino)-1,1′-biphenyl) in THF solution was theoretically investigated by Senn and Ziegler.[18] Interestingly, the authors could not locate in solution the concerted transition state reported for the gas phase. Instead, the dissociation of the halide and its subsequent recombination with the cationic phenyl complex (i.e., S_N2 mechanism) was found to be a facile process in solution. For other Pd complexes, however, the concerted transition state has been recently located in a polar solvent described by means of both an implicit and a combined implicit/explicit solvation model.[19]

Several authors have claimed that anionic Pd species can be involved in the oxidative addition step when anionic additives are present in the reaction medium. Jutand and co-workers[20] provided a significant amount of experimental evidence suggesting an anionic form for the catalyst, $[Pd(Cl)(L)_n]^-$, while Thiel and co-workers explored the reaction of $[Pd(OAc)(PMe_3)_2]^-$ with Ph−I.[21] The participation of the anionic or neutral form of catalyst as active species has been recently found to be significantly affected by the solvent polarity, especially when both species can coexist and compete.[22]

The bisligated form of the catalyst $[Pd(L)_2]$ has been postulated in most experimental proposals, but the monoligated form [Pd(L)] can be also envisaged. In fact, in the cases where oxidative addition to both of them has been computed,

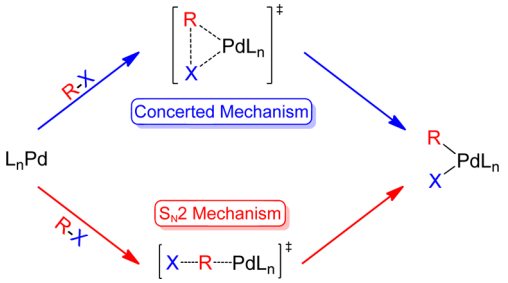


FIGURE 2. Proposed reaction mechanisms for the oxidative addition reaction.

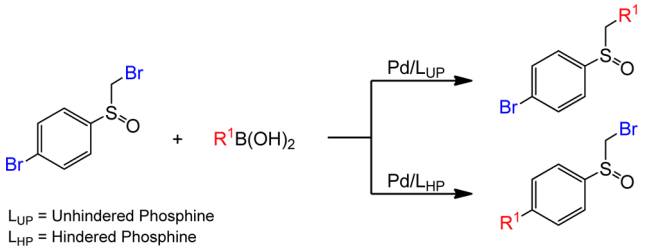


FIGURE 3. Competition experiments for the selective Pd-catalyzed Suzuki−Miyaura reaction of α-bromosulfoxides.

it has been found that the barrier is systematically lower for the monoligated system[9,23−25] and that the prevalence of one or the other in the catalytic cycle depends on the ligand dissociation energy from the metal complex.

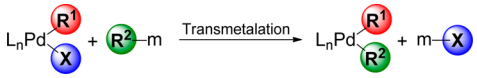
A representative example of successful application of calculations to mechanistic clarification is provided by our study on the relationship between the phosphine nature and selectivity in the Suzuki−Miyaura reactions shown in Figure 3.[26] The less hindered phosphine, PPh_3 in our calculations, is associated with a bisligated form of the catalyst, which favors a S_N2 mechanism and activation of the α-bromosulfoxide side. The more hindered phosphine, P(1-napthyl)$_3$ in our calculations, is associated with the monoligated form of the catalyst, which promotes a concerted mechanism and activation of the bromoaryl moiety. A similar connection between selectivity and coordination number was also identified by Schoenebeck and Houk on the competition between oxidative addition of Ph−Cl and Ph−OTf bonds.[27]

The Transmetalation Step

Transmetalation is the most characteristic step of C−C cross-coupling reactions. This is the reaction stage where the organic group R^2 bound to an electropositive group m is transferred to the catalyst, as shown in Scheme 3.

The mechanism for the transmetalation process is expected to show differences depending on the particular

SCHEME 3. General Scheme for the Transmetalation Reaction



cross-coupling reactions since they differ in the nucleophile used. Therefore, in the following four subsections, we present an overview of the reported computational studies on the transmetalation process for the Suzuki–Miyaura, Stille, Negishi, and Sonogashira coupling reactions, as well as on the closely related direct arylation.

Suzuki–Miyaura Reaction. The Suzuki–Miyaura reaction is one of the most used synthetic methods for the construction of biaryls and substituted aromatic moieties.[2] This reaction takes place between an organic halide (or triflate), R^1–X, and a boronic acid, R^2–$B(OH)_2$, in the presence of a base (Scheme 4).

The role of the external base in the reaction was initially not clear, and several proposals had been made.[28] In particular, two main roles for this species were proposed (Figure 4): either the base binds first to the boronic acid to form the organoboronate species (pathway A), or the base substitutes first the leaving group X in the coordination sphere of the catalyst (pathway B). We evaluated theoretically these two pathways as well as a direct mechanism in the absence of a base (pathway 0) for a model system, using *trans*-[Pd(CH_2=CH-)(Br)(PH_3)$_2$], CH_2=CH–$B(OH)_2$, and OH^- species as reactants.[29] In the absence of the base (pathway 0), the reaction was found to be highly endothermic (ca. 32 kcal·mol^{-1}) and has a very high energy barrier (ca. 44 kcal·mol^{-1}). These results agree with the experimental fact that the reaction does not proceed without addition of a base.

For pathway A, transmetalation was found to be a multistep process resulting in complex *trans*-[Pd(CH_2=CH)$_2$(PH_3)$_2$], organoboronic acid $B(OH)_3$, and free halide Br^-. The calculated energy difference between the lowest and highest energy points was around 20 kcal·mol^{-1}, therefore becoming a suitable pathway explaining the role of the base. Our exploration of pathway B was not so successful using such a model system; we were unable to locate a transition state for the direct replacement of the halide by the hydroxyl group in the bisphosphine complex. The optimization attempts led either to binding of OH^- to a phosphine center or to replacement of one of the phosphines by OH^- in the metal coordination sphere. Hence, it was concluded that the main catalytic cycle should proceed through pathway A, which has low energy barriers and no obvious undesired products. These computational results were found to remain qualitatively

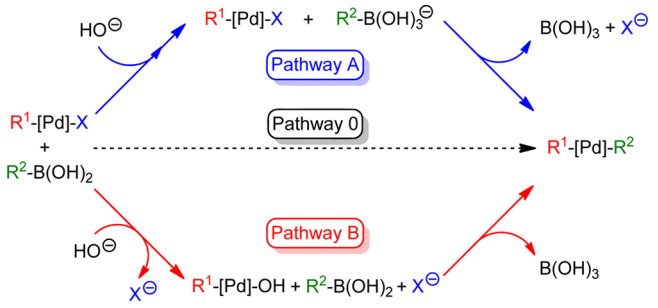
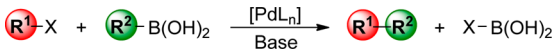


FIGURE 4. Roles proposed for the external base in the transmetalation step of Suzuki–Miyaura reaction.

SCHEME 4. General Scheme for the Pd-Catalyzed Suzuki–Miyaura Reaction



valid when the PH_3 ligands were replaced by PPh_3 and when vinyl groups were replaced by phenyl groups.[10] This proposal has been recently questioned, because pathway B has been postulated to be preferred in at least some cases.[30–33] Ongoing calculations in our groups on extended models suggest that both pathways may be competitive.

A recurrent issue in the Suzuki–Miyaura reaction is related to the number of phosphine ligands (one or two) in the Pd catalytic species, and this issue affects also the transmetalation step, as shown in studies on the full catalytic cycle.[9] The role of monophosphine complexes was also discussed by Thiel and co-workers in the palladium-catalyzed Suzuki–Miyaura reaction of acetic anhydride with phenylboronic acid.[34]

Stille Reaction. The Stille reaction is the second most broadly studied C–C cross-coupling reaction.[35] In this case, the reaction takes place between an organic halide (or triflate) R^1–X and a stannane R^2–SnR_3, as shown in Scheme 5. In contrast to the Suzuki–Miyaura reaction, no base is required for the Stille reaction to take place.

For the transmetalation process involved in the Stille reaction, two main mechanisms dubbed as *cyclic mechanism* and *open mechanism* (Figure 5) have been proposed to account for the reported experimental evidence.[35] One of the main contributions of computational chemistry has been the clarification of the competition between the two mechanisms. DFT studies in our group,[36] followed closely in time by those of Álvarez et al.,[37] proved that the open mechanism will prevail whenever two ancillary ligands, usually phosphines or arsines, remain attached to palladium in the key transition state, while the cyclic mechanism will dominate when one ligand is released during the process.

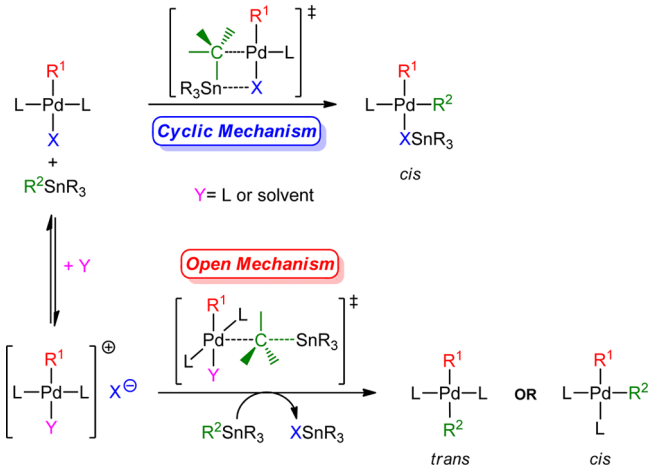
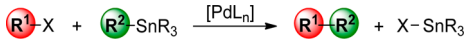


FIGURE 5. Proposed mechanisms for the transmetalation step in the Stille reaction: cyclic (top) and open (bottom) mechanisms.

SCHEME 5. General Scheme for the Pd-Catalyzed Stille Reaction

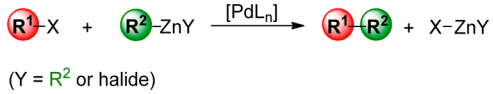


Therefore, any feature favoring phosphine dissociation, such as bulky phosphines, will favor the cyclic mechanism. The open mechanism will be favored by features favoring dissociation of the X group, because this will render phosphine dissociation more difficult. This is favored by the presence of good leaving groups (i.e., triflate) or polar solvents. The theoretical evaluation of the open mechanism showed that the highest energy barrier in this mechanism corresponds to the substitution of the L (or Y) ligand by the stannane.

The cyclic mechanism has been studied in more detail. The process has been shown to proceed in two steps: associative ligand substitution followed by the transmetalation reaction through a cyclic transition state (Figure 5). This cyclic transition state was found to have the highest energy barrier within the overall cyclic mechanism, thus becoming the rate-limiting step. The accelerating effect of CsF additives was examined by Ariafard and Yates for the transmetalation through the cyclic mechanism between (vinyl)$SnMe_3$ and [Pd(Ph)(Cl)$(L)_n$] (L = P(*t*-Bu)$_3$, PPh_3, PPh_2Me, $PPhMe_2$, and PMe_3).[38] The enhanced reactivity with this additive was proven to be associated with the formation of the more reactive [Pd(Ph)(F)(L)] intermediate. In a recent work in collaboration with the experimental group of Espinet, we have found that gold cocatalysts can accelerate Stille transmetalations of bulky organic groups by effectively reducing steric crowding in the key transition states.[39]

Negishi Reaction. The Negishi reaction is a reliable cross-coupling process that can be applied to every possible

SCHEME 6. General Scheme for the Pd-Catalyzed Negishi Reaction



combination of carbon type (sp, sp^2, or sp^3) and that tolerates many different functional groups at the reagents. This reaction takes place between an organic halide (or triflate), R^1–X, and an organozinc compound, as shown in Scheme 6.

The main role of computational chemistry in the study of the Negishi reaction has been to collaborate in the identification of the active organozinc species that undergoes transmetalation and the role of the experimentally observed palladium intermediates in the reaction pathway. The organozinc reactant is usually introduced in the form ZnR_2 or ZnRX, but this species can participate in a variety of chemical equilibria prior to transmetalation because of the preference of zinc for coordination number four and its affinity for halide anions. Thus, the presence of species such as $ZnRXS_2$ (S = solvent) cannot be ruled out a priori. The nature of the active species may affect the reaction rate, the role of additives, and the eventual observation of side products.

The first experimental studies on the mechanism of the transmetalation step in the Negishi coupling were reported by Espinet et al.[40] for the transmetalation reaction between *trans*-[Pd(Rf)(Cl)$(PPh_3)_2$] (Rf = 3,5-dichloro-2,4,6-trifluorophenyl) and the organozinc reagents $ZnMe_2$ and ZnMeCl in THF. Later on, we reported in a joint investigation a combined experimental and theoretical study on the mechanism of the transmetalation reaction between ZnMeCl and *trans*-[Pd(Me)(Cl)-$(PMePh_2)_2$] in THF.[41] The mechanistic conclusions are summarized in Figure 6. The transmetalation may follow two competitive pathways: one producing the dimethylated complex *trans*-[Pd$(Me)_2(PMePh_2)_2$], which is kinetically preferred but unproductive for coupling, and the other, about 1 order of magnitude slower, that affords the complex *cis*-[Pd$(Me)_2$-$(PMePh_2)_2$] from which coupling will eventually take place, although at a much slower rate. Furthermore, the rate of the direct *trans*-to-*cis* isomerization was found to be very low compared with the indirect isomerization via retrotransmetalation.

We also investigated the reaction between *trans*-[Pd(Me)-(Cl)$(PMePh_2)_2$] and $ZnMe_2$ in THF,[42] which was much faster than that with ZnMeCl. This rate acceleration was explained by the presence of a minute amount of the nonobserved catalytic intermediate *trans*-[Pd(Me)$(PMePh_2)_2$(THF)]$^+$, which opens a faster reaction pathway. Transmetalation involving zinc out of a traditional cross-coupling context has been also computationally explored.[43]

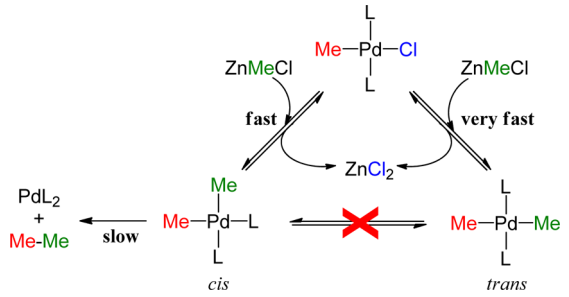
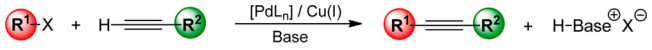


FIGURE 6. Mechanistic proposal for the Negishi transmetalation between ZnMeCl and *trans*-[Pd(Me)(Cl)($PMePh_2$)$_2$].

SCHEME 7. General Scheme for the Pd-Catalyzed Sonogashira Reaction

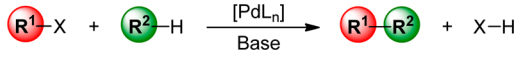


R^1= aryl, hetaryl, alkenyl, alkyl, SiR_3
R^2= aryl, hetaryl, vinyl
X= I, Br, Cl, OTf

Sonogashira Reaction. The Sonogashira reaction is a widely used method for preparing arylalkynes and conjugated enynes.[44] The general Sonogashira protocol for the reaction of terminal alkynes with aryl or alkenyl halides (or triflates) involves a Pd(0)/Cu(I) catalytic system and at least a stoichiometric amount of a base (Scheme 7). The presence of a Cu(I) salt is generally believed to facilitate the transfer of the alkynyl group to the Pd catalyst by the *in situ* generation of a copper acetylide species and the subsequent transmetalation of this group to Pd. In some cases, however, Cu(I) salts have been shown to have an inhibitory effect in the Sonogashira reaction.[45,46] In recent years, many efforts have been devoted to develop reaction procedures working in the absence of copper salts; these strategies are commonly referred as *copper-free Sonogashira reaction*. Computational studies have mainly focused on the mechanism of this copper-free process.

The Sonogashira transmetalation has been recently shown to proceed through the so-called deprotonation mechanism (Figure 7).[47] An external base is required to deprotonate the terminal alkyne, transforming into an alkynyl ready to undergo reductive elimination with the other R group attached to the metal. This mechanism is known to entail ligand exchange in the metal coordination sphere, and the nature of these ligand exchanges has been clarified by calculations.[48] Depending on the order of these ligand exchanges and the deprotonation, two different alternatives had been proposed from the experimental work, labeled as *cationic* and *anionic* (Figure 7). In our theoretical evaluation of the reaction mechanisms, we could identify a third reaction

SCHEME 8. General Scheme for the Pd-Catalyzed Direct Arylation Reaction



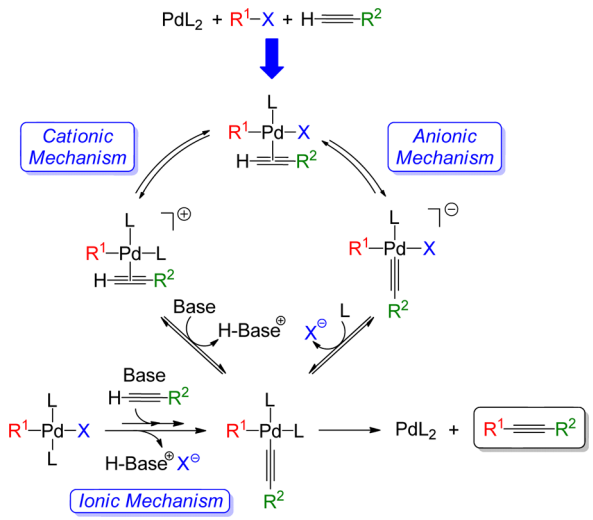


FIGURE 7. Cationic and anionic alternatives for the transmetalation step in the Pd-catalyzed Sonogashira reaction via deprotonation mechanism.

pathway that we labeled as *ionic mechanism*. In this mechanism the base has two roles: substituting the halide in the coordination sphere of the catalyst and helping the formation of acetylide species by subtracting the proton. Our theoretical results showed that this mechanism is competitive with the cationic and anionic alternatives and that may lead to higher reaction rates with alkynes bearing electron-withdrawing groups, in agreement with experiments.

Direct Arylation. Direct arylation is a reaction formally similar to cross-coupling, with the key difference that one of the carbons involved in the process is bound not to a heteroatom but to hydrogen (Scheme 8). This turns this reaction into a very powerful method for the synthesis of aryl–aryl bonds, since it allows skipping the introduction of the electropositive heteroatom as required in cross-coupling reactions.[49] Direct arylation is often considered as a different process from cross-coupling, but we have decided to include it in this Account because of their mechanistic similarities.

From a computational point of view, the key issue is the nature of the metalation step, where the R^2 group moves from a R^2–H bond to a M–R^2 bond. The metalation in palladium-catalyzed arylation involves the metal in its divalent state. It has been applied in ring closure reactions[50] and intermolecular arylation.[51] Calculations have shown that the reaction proceeds without direct interaction between the metal and the proton. The hydrogen atom is captured by

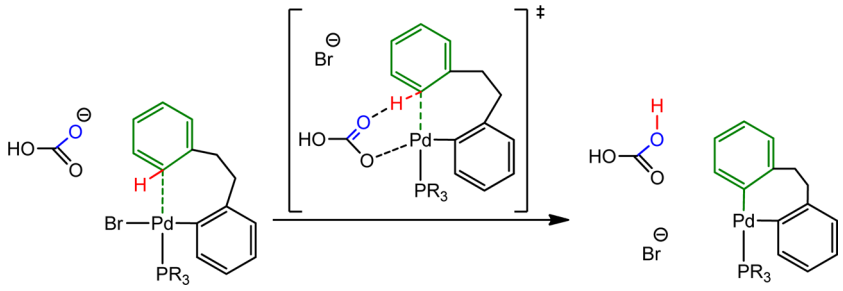


FIGURE 8. Transition state for the metalation step in the Pd-catalyzed direct arylation assisted by HCO_3^-.

a base (e.g., carbonate, hydrogenocarbonate), with simultaneous formal generation of a carbanion that binds to the metal center. A typical transition state is shown in Figure 8. The mechanism has been labeled as concerted metalation−deprotonation (CMD).[51] Similar mechanisms have been found to operate in ruthenium-catalyzed[52] and in iridium-catalyzed processes.[53,54]

This mechanism is to a certain extent surprising because a relatively weak base such as carbonate is able to take away an arylic proton, which has a very low acidity. The presence of the metal in this case is crucial to stabilize the development of a negative charge in the carbon center, as proven by the structure of the transition states, where the metal−carbon bond is almost completely formed.

The Reductive Elimination Step

In order to complete the catalytic cycle, the reductive elimination step after the transmetalation process is needed. This step consists of the coupling of the two organic groups, R^1 and R^2, in *cis* position (Figure 9). In the case in which the complex resulting from transmetalation has the R^1 and R^2 groups *trans* to each other, a *trans* to *cis* isomerization reaction previous to the reductive elimination is required. The generally accepted mechanism for this step is concerted and features a cyclic three-coordinated transition state that results in the final C−C coupling and the concomitant regeneration of the catalytic species, $[PdL_2]$ (Figure 9). The reductive elimination is usually irreversible.

Although the general problem of reductive elimination of H−H and C−H bonds was among the first topics analyzed in the computational study of transition metal complexes,[55] its direct connection with cross-coupling was not explored in detail until the work by Ananikov, Musaev, and Morokuma[56] on *cis*-$[Pd(R^1)(R^2)(PH_3)_2]$ complexes (R^1,R^2 = Me, vinyl, Ph, ethynyl). They found that the barriers increase in the order vinyl < Ph < ethynyl < Me. The effect of the bite angle in the case of diphosphine ligands was also analyzed by Bo et al.[57]

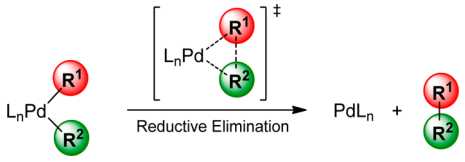


FIGURE 9. Generally accepted mechanism for the reductive elimination step.

In collaboration with Espinet and Álvarez et al.,[58] we reported a combined experimental and theoretical study on the C−C coupling from complexes *cis*-$[Pd(R)_2(PMe_3)(L)]$. This work allowed us to characterize the effect of the ancillary ligand L on the reaction barrier. The barrier was shown to increase in the order maleic anhydride < "empty" < ethylene < $PMe_3 \approx$ MeCN. For four-coordinate complexes, the barrier decreases with the increasing π-acceptor ability of L; thus additives with strong π-accepting abilities will accelerate the reaction. The barrier for the three-coordinate complex (L = "empty") is lower than that for most four-coordinate systems, and because of that, weakly coordinating ligands will dissociate prior to reductive elimination. We completed this study with an analysis of reductive elimination in *cis*-$[Pd(\eta^1\text{-allyl})_2(PMe_3)(L)]$,[59] where we found the $C_{sp^2}-C'_{sp^2}$ elimination to be the most favored one, in agreement with previous experimental results.

Concluding Remarks

Cross-coupling is a complex and diverse multistep catalytic process, and because of this, it is difficult to fully characterize the mechanism from pure experimental techniques. Computational chemistry has proven to be a powerful tool in this context and has helped to shape our current understanding of the mechanism. The collaboration between experiment and theory has led to the construction of a general scheme where seemingly contradictory results can be explained, a framework that is already making its way into textbooks. Much of this knowledge has been gained from calculations on model systems. However, calculations themselves have proven that in many cases competitive pathways exist with

close energy barriers. The choice of a particular pathway will then depend on the particular reaction conditions (e.g., ligands, substrates, solvent). Most major mechanistic problems in C−C cross-coupling seem to be already solved, but there is still a role for computational chemistry. Challenges remain in the study of particular systems to further expand the scope of these fascinating reactions, and there is always the intriguing possibility of discovering new reagents for transmetalation. Computational Chemistry is now sufficiently mature to assist experimental chemistry in these future developments.

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FOOTNOTES

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