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Density Functional Studies on Palladium-Catalyzed Suzuki–Miyaura Cross-Coupling Reactions Assisted by N- or P-Chelating Ligands

Yi-Luen Huang, Chia-Ming Weng, and Fung-E. Hong*[a]

Abstract: DFT studies with the B3LYP functional have been carried out on the Suzuki–Miyaura cross-coupling reactions of phenyl chloride and phenylboronic acid catalyzed by palladium complexes with N- or P-chelating ligands. The full catalytic cycle, from the addition of reactants to the catalyst to the release of the cross-coupled product from the complexed intermediate, has been examined. The stages within the cycle, such as oxidative addition, transmetalation, and reductive elimination, were validated by linking the mechanistically relevant intermediates and transition states. Various derivatives of diimine, diphosphine, and diamine were considered as potential model ligands. The catalytic reaction employing diimine as the chelating ligand has been verified as the one with the most energetically feasible route.

Keywords: cross-coupling · density functional calculations · N ligands · P ligands · palladium

Introduction

In the past few decades the Suzuki–Miyaura cross-coupling reaction has probably been the most frequently employed method of carbon–carbon bond formation. The reaction involves a coupling process between an aryl halide (or triflate) and an organoborate catalyzed by a palladium complex in basic medium.[1] Since its disclosure in the 1990s, the reaction has been extensively investigated by both experimental and computational chemists. To understand the reaction mechanism more thoroughly, a comprehensive knowledge of the reaction pathway is essential. Unfortunately, conventional experimental methods do not always provide unambiguous evidence concerning the reaction mechanism. Computational quantum techniques are now regarded as a promising alternative or at least as a valuable tool capable of providing information complementary to that obtained experimentally.[2,3] In the past few years, DFT methods with greater computational efficiency than conventional Hartree–Fock ab initio methods have been widely employed to study the characteristics of transition-metal complexes. The method has gradually received warm acceptance among both theoretical and experimental chemists.[4] Recently, Sakaki,[5] Thiel,[6] Maseras[7] and their co-workers published computational studies on the full cycle of the Suzuki–Miyaura cross-coupling reaction catalyzed by diphosphine palladium complexes. However, these studies were focused on rather specific substrates: the first on the coupling of iodobenzene with diborane, the second on the coupling of carboxylic acid anhydrides with arylboronic acids, and the last on the coupling of aryl bromides with arylboronic acids. Notably, Thiel and co-workers surmised that there are several interconnected catalytic pathways that may contribute to the overall catalytic turnover.[6]

A modified mechanism involving [Pd^0(L^L)] (L^L = chelating ligand) as the catalytic precursor was shown to accommodate the probable reaction route for the Suzuki–Miyaura reaction catalyzed by a palladium complex with a chelating ligand (Scheme 1). As shown, the mechanism is basically composed of three consecutive elementary steps: a) The oxidative addition of aryl chloride to [Pd^{0}L$_2$], b) transmetalation, involving the exchange of chloride for an aryl group, and c) the reductive elimination of diaryl from the Pd^{II} complex.

The oxidative addition and reductive elimination steps are two frequently observed processes in transition-metal-complex-catalyzed reactions.[8] Consequently, these two processes have been thoroughly studied both by experimental[9] and computational[8b,10] methods, and hence, they are quite well

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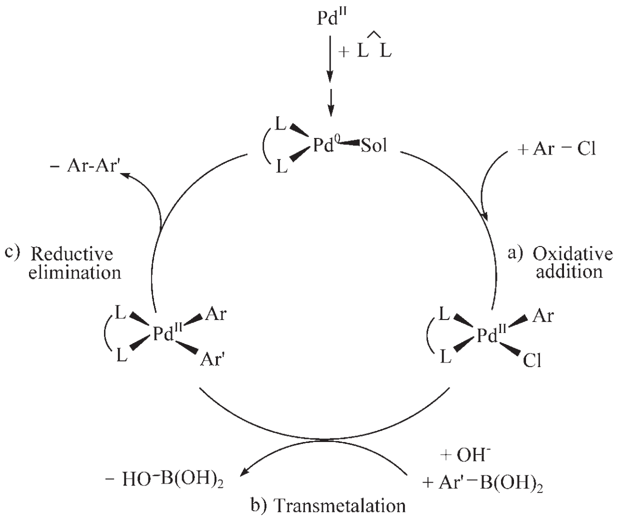
[a] Y.-L. Huang, C.-M. Weng, Prof. F.-E. Hong
Department of Chemistry
National Chung Hsing University
Taichung 40227 (Taiwan)
Fax: (+886) 4-2286-2547
E-mail: fehong@dragon.nchu.edu.tw

Supporting Information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. It contains selected Cartesian coordinates for the optimized geometries and energies determined at the B3LYP level of theory (LANL2DZ for palladium and the 6-31G(d) basis set for the other atoms).

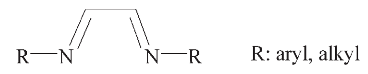


Scheme 1. A modified catalytic cycle for the Suzuki–Miyaura cross-coupling reaction catalyzed by a palladium complex with a chelating ligand. L^L: bidentate ligand, Sol: solvent.

understood. It is generally accepted that the ligands involved in both processes have to be positioned in a *cis* arrangement. In contrast, transmetalation is a more complicated and less studied step in cross-coupling reactions. Experimental evidence for this process is difficult to gather because of the complexity involved in the isolation and characterization of key intermediates.[11] Nevertheless, some progress has been made recently.[12] In the past few years, several computational studies of the transmetalation step of cross-coupling reactions, such as the Suzuki–Miyaura,[5,6,13] Stille,[14] and other coupling reactions,[15] have been carried out by using DFT methods.

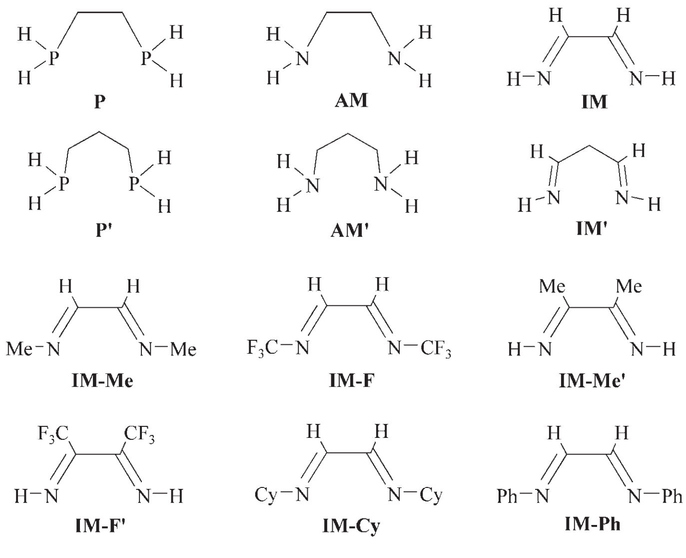
As the choice of ligand is one of the most critical factors affecting a cross-coupling reaction, much effort has been devoted to a search for a more efficient and affordable ligand. For many years phosphines were the most commonly employed ligands for the Suzuki–Miyaura reaction. However, these ligands are either air/moisture-sensitive or expensive, which places strict limits on their synthetic applications. Additionally, phosphines are not environmentally friendly. In contrast, most of the N,O- or N,N-bidentate ligands are less expensive, easily accessible, and air/thermally stable. Moreover, the complexation of palladium with a ligand of this type is straightforward, and complexes are found to be suitable for the Suzuki–Miyaura cross-coupling reactions. Thereby, the practice of employing these N,O- or N,N-bidentate-ligated palladium complexes as catalyst precursors in Suzuki–Miyaura cross-coupling reactions is of interest to many.

Recently, N-heterocyclic carbenes (NHC) have been introduced as potentially effective ligands in transition-metal-assisted cross-coupling reactions.[16] Milstein and co-workers reported an imine-cyclometalated Pd^{II} complex that was able to act as a catalyst precursor in both the Suzuki[17] and Heck[18] reactions. Unfortunately, this system requires a high reaction temperature and leads to only moderate yields. More recently, Nolan and co-workers pioneered the use of a well-known family of N,N-bidentate ligands, the diazabutadienes, in the Suzuki–Miyaura cross-coupling reaction.[19] Ligands containing the 1,4-diaza-1,3-butadiene skeleton, R-diimines (DAB-R), are shown in Scheme 2. The chelating nature of these ligands also enhances the stability of the complexed metal compound. The investigation showed that the [Pd(OAc)$_2$]/DAB-R system, a typical N,N-bidentate-complexed palladium compound, is exceptionally efficient for unactivated and sterically encumbered substrates as well as for activated aryl chlorides.[20]



Scheme 2.

Based on the encouraging results from the previous experiments, the idea of employing diimines as potential chelating ligands in Suzuki–Miyaura reactions seemed worthy of further exploration. However, to the best of our knowledge, only a few experimental studies of palladium-catalyzed Suzuki–Miyaura cross-coupling reactions assisted by diimine ligands, not to mention theoretical studies, have been reported.[21] In this work, a comprehensive computational examination of the full Suzuki–Miyaura catalytic cycle, the coupling between aryl chlorides and arylboronic acids catalyzed by diimine-ligated palladium complexes, is presented. For computing efficiency, PhCl (**1**) and PhB(OH)$_2$ (**2**) were selected as the model substrates. For comparison, palladium complexes with several other bidentate ligands (L^L) were selected as catalyst precursors, and these catalytic cycles were also examined. The ligand-chelated palladium complexes are regarded as 14-electron species in which the coordinated ligands are either mono- or bidentate.[22] The bidentate ligands (L^L) used in this work are depicted in Scheme 3. To keep the model as general as pos-



Scheme 3.

sible, a nonsubstituted diimine **IM** (HN=CH−CH=NH) was chosen as the first target ligand to be studied. In this work bidentate ligands were selected over monodentate ones for two reasons: 1) A chelating ligand provides both kinetic and thermodynamic stability for the active species and 2) it forces other ligands to be in *cis* positions with respect to each other, thus facilitating further reactions. We note that some of the trifluoromethyl derivatives are unstable or extremely difficult to synthesize.[23] Therefore, the proposed bidentate ligands, such as **IM-F** and **IM-F′**, are merely represented here as model ligands. The hydroxide anion (OH^-) was chosen as a vital base because of its simplicity and ability to provide excellent results. The purpose of this work was to find out how factors such as the number of backbone carbon atoms and the nature of substituents on the diimine, diphosphine, and diamine ligands might affect the efficiency of the catalytic cycle.

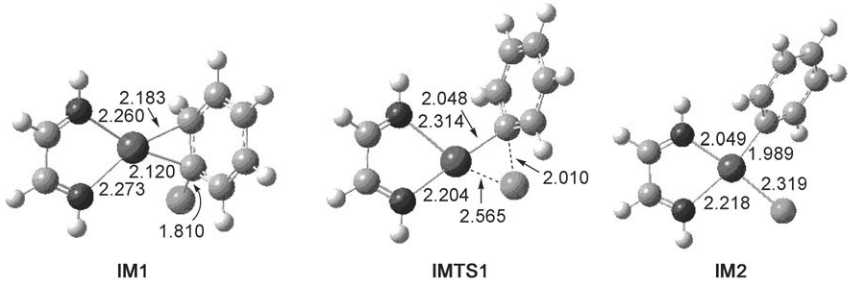
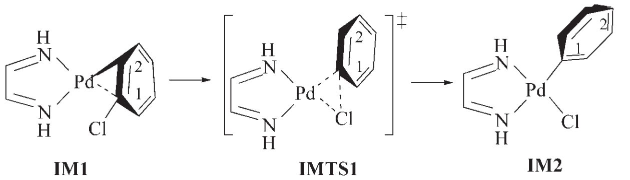


Figure 1. Geometries of selected structures in the oxidative addition step. Distances are in Å.

Results and Discussion

The state-of-the-art DFT method has repeatedly proved itself to be a useful tool to provide reliable results in studies of catalytic reactions mediated by transition metals.[3,4] This method at the B3LYP level was used to examine the validity of the proposed routes for the mechanism of the Suzuki–Miyaura cross-coupling reaction with diimine, diphosphine, and diamine ligands. To make the computations feasible, the simplest possible model compounds, namely **1** and **2**, were selected to represent all of the potential reaction participants. Three steps in the mechanism, that is, oxidative addition, transmetalation, and reductive elimination, were examined. Herein, the abbreviations used for the species involved in the reaction are as follows: **TS** for transition state, **IM** for diimine, **AM** for diamine, and **P** for the diphosphine ligand.

The oxidative addition process: As shown in Scheme 4, the approach of **1** towards the active catalyst [Pd(η^2-*N*,*N*-HN=CH−CH=NH)] leads to the breaking of the $Cl{-}C_{phenyl}$ bond and eventually to the formation of Pd−Cl and $Pd{-}C_{phenyl}$ bonds. Interestingly, a π-bonded intermediate **IM1** is first formed between the palladium complex and a double bond of **1** followed by the formation of a three-membered-ring transition state **IMTS1**. In due course, the Cl and Ph groups are forced to assume *cis* positions in the intermediate **IM2** ([Pd(Cl)(**IM**)(Ph)], Figure 1). This process leads to an increase in the palladium oxidation state from 0 to +2.



Scheme 4.

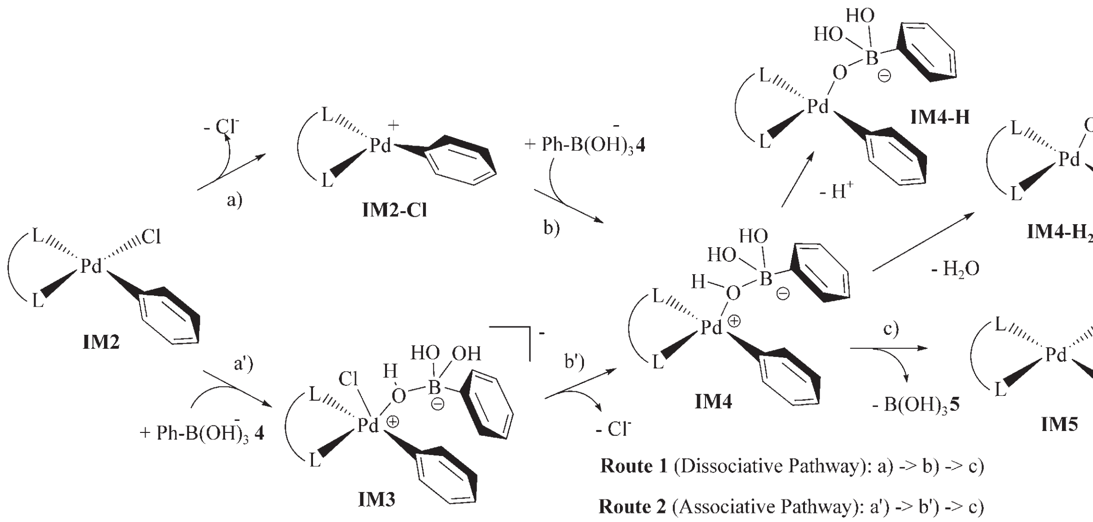
As shown in Figure 1, the initial approach between the reactants produces intermediate **IM1** in which the phenyl group is η^2-coordinated to the metal center through the C1 and C2 atoms with Pd−C distances of 2.120 and 2.183 Å, respectively. In **IMTS1**, the angle between the N-Pd-N and Cl-Pd-C1 planes is 46.9°. These two planes are clearly not parallel to each other, in agreement with the results of previous computational studies.[10a,24] In **IM2**, the Cl-Pd-C1 angle is 92.7°, which is much larger than that in **IMTS1**. This is an exothermic process, by around 22.6 $kcal\,mol^{-1}$, with an activation energy of around 9.1 $kcal\,mol^{-1}$ (Table 1).

Table 1. Energies for the oxidative addition process with various ligands relative to the reactants.

Entry	Ligand (L^L)	Energy [$kcal\,mol^{-1}$] Transition state[a]	Product
1	**P**	14.1 (241*i*)	−13.3
2	**AM**	11.9 (165*i*)	−26.3
3	**IM**	9.1 (184*i*)	−22.6
4[b]	**P′**	17.6 (246*i*)	−12.1
5	**AM′**	11.9 (132*i*)	−29.8
6	**IM′**	10.2 (162*i*)	−28.3
7	**IM-Me**	10.1 (172*i*)	−23.6
8	**IM-F**	9.0 (217*i*)	−12.5
9	**IM-Me′**	9.7 (173*i*)	−24.8
10	**IM-F′**	8.6 (205*i*)	−17.9
11	**IM-Cy**	10.5 (161*i*)	−24.5
12	**IM-Ph**	10.5 (191*i*)	−19.7

[a] Imaginary frequencies are given in parentheses. [b] In the initial approach, phenyl chloride is η^2-coordinated to the palladium metal through the C2 and C3 atoms.

For comparison, the oxidative addition processes for various related ligands (Scheme 3) were investigated. In all cases the calculated structures were similar in terms of the geometries of the metal centers. The activation and reaction energies are shown in Table 1. Note that the activation energies in the case of α- or β-diimine ligands are lower than



Scheme 5.

those for diphosphines and diamines (entries 1–6). They are around 9.1 and 10.2 kcal mol^{-1} for entries 3 and 6, respectively. For a chelating diphosphine ligand, the ring size of the palladium complex affects the activation energy greatly. It is around 14.1 kcal mol^{-1} for a five-membered-ring complex (Table 1, entry 1), however, it increases to around 17.6 kcal mol^{-1} on addition of an extra methylene unit into the backbone of the ligand (Table 1, entry 4). This observation is in good agreement with previous studies of reactions catalyzed by diphosphine-chelated palladium complexes.[15a] Those studies showed that the number of backbone carbon atoms is crucial for the activation energy of the oxidative addition. In contrast, the ring size does not affect the activation energies much in the case of the diimine ligands (Table 1, entry 2 vs. 5; entry 3 vs. 6). Next, the possible effects of introducing electron-donating or -withdrawing substituents into the diimine ligand **IM** on the activation energy were examined (Table 1, entries 7–12). Diimines with electron-withdrawing substituents, particularly trifluoromethyl groups, lower the activation energies of the oxidative addition process (entries 8 and 10).

Transmetalation: Transmetalation is the process in which the organic group of the organoboronic acid migrates to the palladium complex. Compared with other steps in the catalytic cycle, this process is definitely unique, and it is the critical step in cross-coupling reactions. It has also been the most ambiguous and least understood step in the whole catalytic cycle. Fortunately, the mechanistic details have gradually been revealed by recent computational studies.[5,6,14b,15b,c] Although those studies were focused primarily on systems with two phosphine ligands *trans* to each other,[5,13] a recent report by Thiel and co-workers deals with a *cis*-arranged $[Pd\{CH_3C(=O)\}(OAc)(PMe_3)_2]$ complex as the initial species.[6]

Transmetalation with phenylborate, $PhB(OH)_3^-$ (4): Two probable pathways for the transmetalation process are shown in Scheme 5. The pathways described herein are Route 1, which is referred to as a dissociative pathway, and Route 2, which is an associative pathway. As shown in Scheme 5, Route 1 is composed of three consecutive elementary reactions: a) The dissociation of the chloride anion from **IM2**, b) the addition of $PhB(OH)_3^-$ (**4**), which is generated from **2** and the hydroxide anion, to the highly unsaturated palladium complex **IM2-Cl**, and c) the dissociation of boric acid from **IM4** along with the formation of biaryl palladium complex **IM5**. In Route 1, the first step (a) is a highly endothermic process by 123.9 and 135.1 kcal mol^{-1}, respectively, for the reactions employing **P** and **IM** as ligands (Table 2). Evidently, Route 1 is not a thermodynamically feasible pathway, and henceforth, is ruled out as the initial elementary transmetalation reaction. Similarly, Route 2 is also composed of three consecutive elementary reactions:

Table 2. Relative energies (ΔE, ΔE^{+}), enthalpies (ΔH, ΔH^{+}), and free energies (ΔG, ΔG^{+}) for the transmetalation step.

Pathway	Ligand	ΔE [kcal mol^{-1}]	ΔH [kcal mol^{-1}]	ΔG [kcal mol^{-1}]
a	**IM**	135.1	135.7	126.2
	P	123.9	124.1	116.5
a′	**IM**	−28.1	−28.1	−15.4
	P	−21.6	−21.8	−8.8
b′	**IM**	36.4	36.8	28.0
	P	30.6	31.1	23.3
c	**IM**	−21.2	−20.9	−22.9
	P	−15.6	−15.1	−17.3
Pathway	Ligand	ΔE^{+} [kcal mol^{-1}]	ΔH^{+} [kcal mol^{-1}]	ΔG^{+} [kcal mol^{-1}]
c	**IM**	18.5	18.4	19.8
	P	21.6	21.6	23.0

a′) The addition of **4** to **IM2** through a hydroxy group leads to the formation of a pentacoordinated palladium complex **IM3**, b′) the dissociation of chloride from **IM3** with the formation of a tetracoordinated complex **IM4**, and c) the dissociation of $B(OH)_3$ from **IM4** along with the formation of **IM5**. In a basic medium, it is also possible that deprotonation or dehydration of **IM4** takes place to lead to **IM4-H** or **IM4-H$_2$O**, respectively.

The geometries of some selected structures participating in the transmetalation step are shown in Figure 2. The first two steps on the reaction profile correspond to the substitution of the halide by the organoborate species **4** in the coordination sphere of the catalyst. In the newly formed intermediate **IM4**, the OH group bridges the palladium and boron atoms at distances of 2.039 and 1.617 Å, respectively. In the transition state **IMTS4**, the distances for the Pd–C bond being formed and the B–C bond being broken are 2.190 and 2.678 Å, respectively. In **IMTS4**, $B(OH)_3$ acts as a bridging ligand across the Pd–C bond. The framework of the transition state might also be regarded as a three-membered ring comprised of palladium, carbon, and boron atoms. The last elementary reaction of this process is the formation of **IM5**, a generally accepted intermediate in the catalytic cycle formed as a result of the transmetalation process (see Scheme 1).

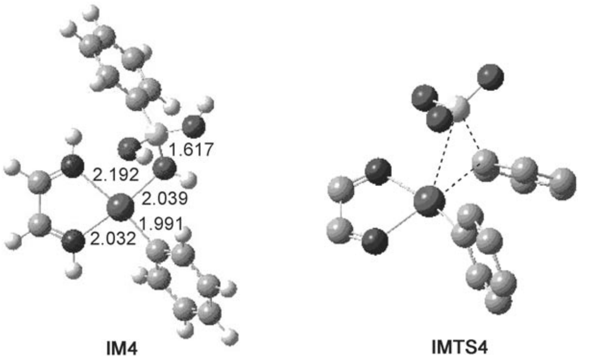


Figure 2. Geometries of selected structures in the transmetalation step. Distances are in Å. The hydrogen atoms in **IMFS4** have been omitted for clarity.

The relative energies of several selected structures are presented in Table 2. As shown, the energy of the initial complex **IM3** is 28.1 kcal mol^{-1} lower than that of the reactant **IM2**. Yet the energy of the intermediate **IM4** is 36.4 kcal mol^{-1} higher than that of the previous intermediate **IM3**. It is the removal of Cl^- from **IM3** that is responsible for this large value. Therefore, the overall reaction energy for the substitution of the chloride ligand by the organoborate species (from **IM2** to **IM4**) is 8.3 kcal mol^{-1}. From **IM4** to **IM5**, rearrangement of fragments around palladium takes place. Thus, the phenyl group from the organoborate starts to transfer to the palladium inner coordination sphere. The phenyl group interacts with the metal center in **IMTS4**, which has partially replaced the hydroxy group. Eventually, in **IM5** the C–B bond is broken and a new C–Pd bond is formed. The energy of the transition state **IMTS4** is 18.5 kcal mol^{-1} higher than that of the previous intermediate **IM4**. For this intramolecular exchange, the energy difference between **IM4** and **IM5** is −21.2 kcal mol^{-1}. The latter is regarded as an intermediate complex that exists between the transmetalation and the reductive elimination processes. At this point, none of the hydroxy groups are directly bonded to the palladium atom.

The transmetalation process with the **P** ligand was also examined. As expected, the geometries of some of the key structures calculated with the **P** ligand are not much different from the previous ones calculated with the **IM** ligand. Compared with the **IM** ligand, the relative energies of transmetalation with the **P** ligand are apparently higher. The relative energy of the initial complex **P3** is 21.6 kcal mol^{-1} lower than that of the reactant **P2**. The intermediate **P4** is 30.6 kcal mol^{-1} higher than the previous intermediate **P3**. The reaction energy for the substitution of the chloride ligand by the organoborate (from **P2** to **P4**) is 9.0 kcal mol^{-1}. The energy of this transition state **PTS4** is 21.6 kcal mol^{-1} higher than that of the previous intermediate **P4**. For this intramolecular exchange, the energy difference between **P4** and **P5** is −15.6 kcal mol^{-1}.

Based on these observations, it is worth noting that transmetalation proceeds through a three-center transition state **IMTS4** rather than the widely accepted four-center transition state.[25] The relatively diffuse orbitals of boron, compared with those of carbon, make the formation of the apparently highly strained three-membered ring in **IMTS4** possible. In addition, the transmetalation process does not proceed in a single step, but rather consists of several consecutive steps.

The activation and reaction energies of the transmetalation steps of the four representative ligands, **P**, **IM**, **IM-F**, and **IM-Me**, were calculated and the results are listed in Table 3. A similar trend to that observed in the case of the oxidative addition process is observed. Again, the diimine with electron-withdrawing substituents, **IM-F**, has the effect of reducing the activation energy of the transmetalation step (Table 3, entry 4).

Table 3. Energies for the transmetalation process with various ligands relative to the reactants.

Entry	Ligand (L^L)	Energy [kcal mol^{-1}]	
		Transition state[a]	Product
1	**P**	21.6 (272*i*)	−15.6
2	**IM**	18.5 (231*i*)	−21.2
3	**IM-Me**	23.4 (224*i*)	−18.9
4	**IM-F**	17.0 (328*i*)	−22.5

[a] Imaginary frequencies are given in parentheses.

For comparison, the effect of solvent upon the dissociative pathway of Route 1(a) was evaluated. The calculations were carried out by using Tomasi's polarized continuum model (PCM) model and CCl_4, the dielectric constant of which is

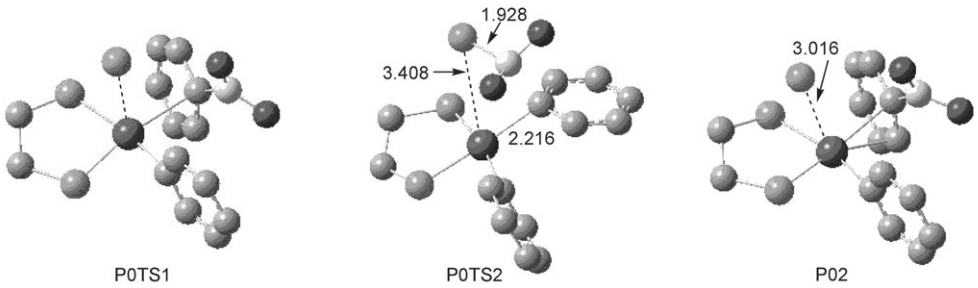


Figure 3. Geometries of some selected structures in the transmetalation process in the absence of base. Distances are in Å. Hydrogen atoms have been omitted for clarity.

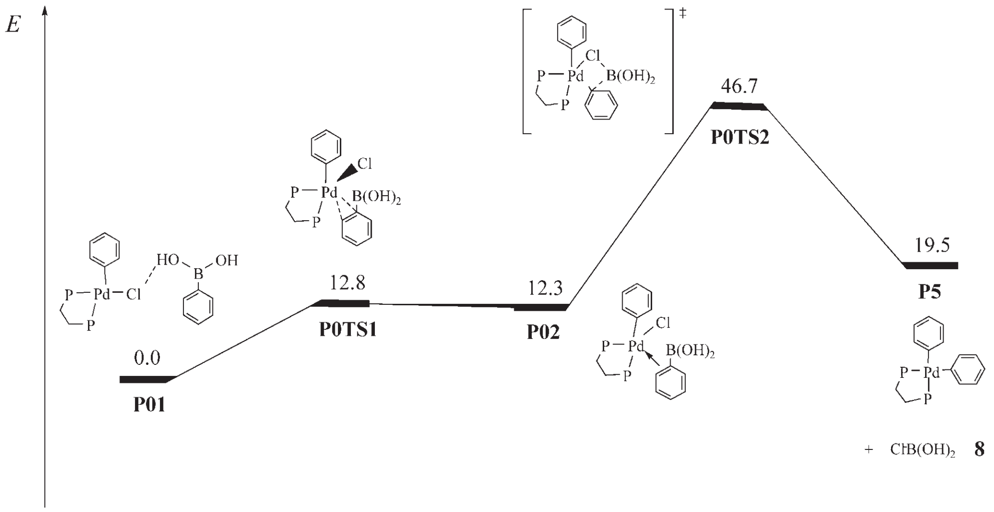
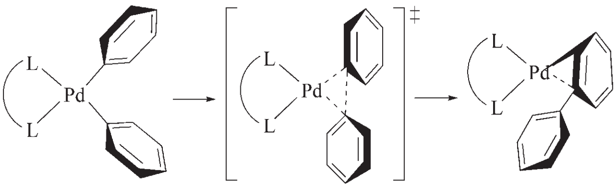


Figure 4. Energy profile for the base-free transmetalation process.

similar to that of dioxane, as the solvent.[26] Indeed, a significant reduction in the activation energy, from 135.1 to 70.7 kcal mol^{-1}, was observed. Nevertheless, it is still an unfavorable pathway compared with Route 2.

Transmetalation in the absence of base: As has already been revealed, the presence of base in the Suzuki reaction is crucial.[27] Recently, some theoretical studies on the transmetalation step of the Suzuki–Miyaura reaction in the absence of base were published.[13] In this section the transmetalation process between **2** and **P2** in the absence of base is analyzed. This process takes place in two steps: 1) The coordination of **2** to **P2** through a double bond and 2) the transfer of chloride from palladium to the boron center and that of the phenyl group from boron to palladium. The geometries of the structures most relevant to this process are presented in Figure 3 and the energy profile of this transmetalation process is presented in Figure 4. The energies of all of the structures calculated are given relative to **P01**. A significant structural change is observed in the last step, **P02**→**P0TS2**→**P5**. It leads to the formation of **P5** and a side product, $ClB(OH)_2$ (**8**). The activation energy for the process **P02**→**P0TS2** is 34.4 kcal mol^{-1}. The overall reaction is endothermic by 19.5 kcal mol^{-1}. In fact, the energy profile for the overall reaction shows that the most energetic transition state is 46.7 kcal mol^{-1} above the initial reactants. This indicates that the transmetalation between the palladium chloride complex and phenylboronic acid alone is an energy-demanding process. This observation is consistent with the previous experimental results and theoretical findings that show the reaction rate is intolerably slow in the absence of the appropriate base owing to a high energy barrier.

Reductive elimination process: The reductive elimination process is the last step in the whole catalytic cycle. At the end of this cycle, the coupled product Ar–Ar′ (**6**) is released from the intermediate [Pd(Ar)(Ar′)(L^L)] and the zerovalent active species [Pd(L^L)] is regenerated. In this process, a C–C bond between two phenyl groups is formed and two Pd–C$_{phenyl}$ bonds are broken. As a result, the oxidation state of the palladium metal decreases from +2 to 0. As shown in Scheme 6, the reductive elimination process requires the palladium complex, in this case **IM5**, to possess two *cis*-positioned, σ-coordinated phenyl moieties. The elimination proceeds from **IM5** through the transition state **IMTS5** to the intermediate **IM6** (Figure 5). In this process, the two σ-coordinated phenyl groups become an η^2-coordinated biphenyl molecule. The C–C distance of interest grad-



Scheme 6.

ually decreases from 2.857 Å in **IM5** to 1.953 Å in the transition state **IMTS5**, and eventually to 1.496 Å in **IM6**. The immediate product from the reductive elimination process is **IM6**, which is an η^2-biphenyl-coordinated palladium complex. The presence of this kind of intermediate after reductive elimination has already been reported.[10c,28] In this complex, the calculated Pd–C distances are 2.191 and 2.233 Å. The last step of the reductive elimination process is the complete release of the biphenyl product from the metal to regenerate the active species [Pd(L^L)], which is then ready to participate in another catalytic cycle. This reductive elimination requires 13.2 kcal mol^{-1} to overcome the energy barrier (**IM5**→**IMTS5**) and the overall reaction is exothermic by 14.6 kcal mol^{-1} (Figure 6).

For comparison, the reductive elimination steps were investigated with various ligands (Scheme 3). The geometries of their complexes with palladium are all similar in the reductive elimination process. The activation and reaction energies are presented in Table 4. For the benchmark **IM**

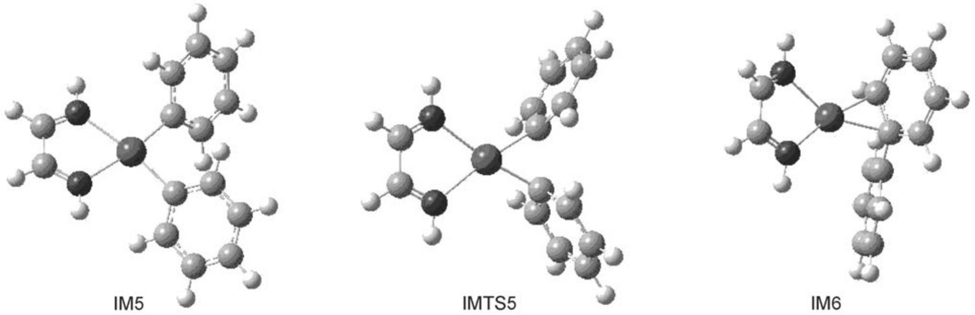


Figure 5. Geometries of selected structures in the reductive elimination step. Distances are in Å.

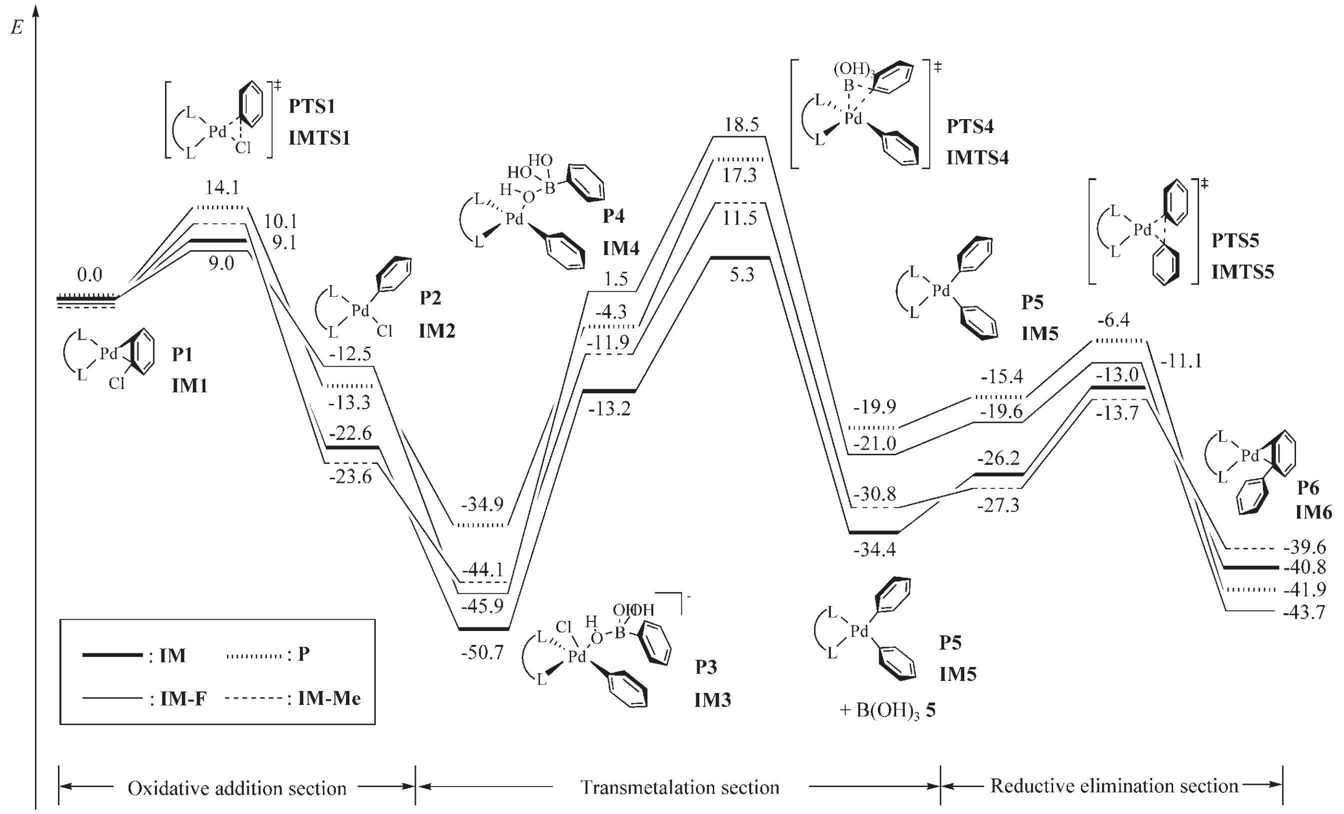


Figure 6. Energy profiles for the three major steps in the Suzuki–Miyaura cross-coupling reactions assisted by diimine and diphosphine ligands.

Table 4. Energies for the reductive elimination process with various ligands related to the reactants

Entry	Ligand (L^L)	Energy [kcal mol^{-1}]	
		Transition state[a]	Product
1	**P**	9.0 (309*i*)	−26.5
2	**AM**	15.7 (330*i*)	−9.4
3	**IM**	13.2 (329*i*)	−14.6
4	**P′**	10.1 (313*i*)	−27.9
5	**AM′**	17.7 (332*i*)	−6.6
6	**IM′**	16.6 (327*i*)	−9.0
7	**IM-Me**	13.6 (323*i*)	−12.3
8	**IM-F**	8.5 (315*i*)	−24.0
9	**IM-Me′**	14.4 (325*i*)	−12.3
10	**IM-F′**	10.9 (314*i*)	−20.2
11	**IM-Cy**	13.7 (322*i*)	−11.3
12	**IM-Ph**	10.4 (316*i*)	−15.8

[a] Imaginary frequencies are given in parentheses.

ligand, the activation energy is 13.2 kcal mol^{-1} and the energy release is 14.6 kcal mol^{-1}, as shown in Table 4, entry 3. Contrary to the oxidative addition step, in the reductive elimination process the activation energies for the α- and β-diimine ligands are higher than those for the diphosphine ligands (Table 4, entry 3 vs. 1; entry 6 vs. 4). It was also found that the activation energy for the β-diimine ligand is higher than that for the α-diimine ligand (Table 4, entry 2 vs. 5). Clearly, the activation energy of the reductive elimination process depends critically on the number of carbon atoms in the backbone of the bidentate ligand, which is in good agreement with the previously known fact that a five-membered ring chelated metal complex is much more stable than a six-membered ring complex.[15a] The effect of substitution of the NH hydrogen atoms of the diimine ligand on the elimination process was also examined (Table 4, entries 7–12). Replacement by an electron-withdrawing substituent, trifluoromethyl, reduces the activation energy (Table 4, entries 8 and 10).

The energy profile of the full catalytic cycle: The mechanism of the full catalytic cycle includes three major steps: oxidative addition, transmetalation, and reductive elimination. Two categories of full catalytic cycles for the Suzuki–Miyaura cross-coupling reaction employing diimine and diphosphine as the chelating ligands were examined and compared. The corresponding energy profiles for the three major steps are depicted in Figure 6. They are referred to as the IM Route and the P Route. In general, the potential energy of each species on the P Route is higher than that of the corresponding species on the IM Route. Based on these results, the diimine-like ligands represent a new category of promising chelating ligands for the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction. For comparison, the effects of electron-donating and -withdrawing substituents on the diimine ligands, such as **IM-F** and **IM-Me**, were also examined. It was shown that the activation energy of the oxidative addition process is lower for a strong electron-withdrawing group, such as CF_3, on the diimine, whereas it is higher for an electron-donating group, such as CH_3. By the same token, the activation energy of the reductive elimination process is lower for the former substituent on diimine and higher for the latter. In conclusion, the best ligand of those studied is **IM-F**. As we are well aware of the difficulty in the preparation of **IM-F**-like diimines, this work merely provides a preliminary theoretical background for future study.

Conclusion

Several plausible catalytic cycles of the Suzuki–Miyaura cross-coupling reaction between phenylboronic acid and phenyl chloride with three different categories of model ligands, namely, diimines, diamines, and diphosphines, have been examined mechanistically and energetically. As illustrated, the reaction employing diimine as the ligand is more favorable than those with diamine or diphosphine. In the case of diimine, the effect of electron-donating and -withdrawing substituents on the activation energy was probed. For diimines with electron-withdrawing substituents, particularly trifluoromethyl groups, the effect was to lower the activation energy. In the oxidative addition step, the activation energies with different ligands increase in the order **IM** < **AM** < **P**. In contrast, in the reductive elimination step, the activation energies are in the reverse order (**IM** > **P**), although the activation energy with **AM** is the largest. The reaction pathway of the transmetalation process in the absence of base was also investigated. The significant energy barrier found for this route indicates that the presence of base is a necessity for the reaction to proceed at a reasonable rate. This study provides a preliminary computational background to the diimine-assisted palladium-catalyzed Suzuki–Miyaura cross-coupling reaction. Further investigations into the role of the counterion (OAc^- or Cl^-) in this catalytic reaction are in progress.

Computational Methods

All calculations were carried out by using the Gaussian 03 package with a tight criterion (10^{-8} hartree) as the default for the self-consistent (SCF) convergence.[29] The molecular geometries were fully optimized with the hybrid B3LYP-DFT method under C_1 symmetry by using Becke's three-parameter exchange functional[30] and the Lee–Yang–Parr correlation functional.[31] LANL2DZ, including the double-ζ basis sets for the valence and outermost core orbitals, combined with pseudopotentials were used for the palladium atom[32,33] and the 6-31G(d) basis sets for the other atoms. All the stationary points found were characterized by harmonic vibrational frequency analysis as minima (number of imaginary frequency $N_{\mathrm{imag}}=0$) or transition states ($N_{\mathrm{imag}}=1$). To determine the transition-state geometries, intrinsic reaction coordinate (IRC)[34] analyses were performed following the geometry optimization to ensure the transition-state structures are smoothly connected by two proximal minima along the reaction coordinate. Stability analyses[35] were performed to determine whether the Kohn–Sham (KS) solutions are stable with respect to variations that break spin and spatial symmetry. The relative total energies, ΔE, were evaluated at 0 K and the enthalpies, ΔH, and free energies, ΔG^0, are given for 298 K.

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