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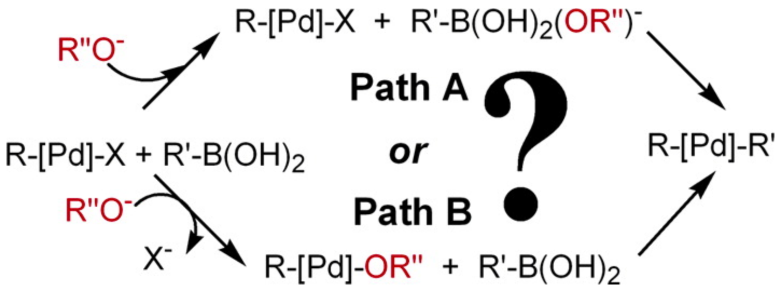

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Computational Characterization of the Role of the Base in the Suzuki−Miyaura Cross-Coupling Reaction

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Abstract: The role of the base in the transmetalation step of the Suzuki−Miyaura cross-coupling reaction is analyzed computationally by means of DFT calculations with the Becke3LYP functional. The model system studied consists of $Pd(CH{=}CH_2)(PH_3)_2Br$ as the starting catalyst complex, $CH_2{=}CHB(OH)_2$ as the organoboronic acid, and OH^- as the base. The two main mechanistic proposals, consisting of the base attacking first either the palladium complex or the organoboronic acid, are evaluated through geometry optimization of the corresponding intermediates and transition states. Supplementary calculations are carried out on the uncatalyzed reaction and on a process where the starting complex is $Pd(CH{=}CH_2)(PH_3)_2(OH)$. These calculations, considered together with available experimental data, strongly suggest that the main mechanism of transmetalation in the catalytic cycle starts with the reaction of the base and the organoboronic acid.

1. Introduction

Cross-coupling reactions are among the most powerful synthetic tools for the generation of carbon−carbon bonds.[1−4] The Suzuki−Miyaura reaction,[5,6] where palladium complexes[7] catalyze the coupling between organic halides (or triflates) and organoboronic acids (eq 1), occupies a prominent place among

$$R{-}X + R'{-}B(OH)_2 \rightarrow R{-}R' + X{-}B(OH)_2 \qquad (1)$$

them. The ability of organoboronic acids to tolerate a large variety of functional groups and reaction conditions[5] has led to the development of coupling processes involving a number of different saturated and unsaturated organic groups.[5−18] A complete mechanistic knowledge is however still lacking.[5,19,20] In particular, it is known that the reaction requires the presence of a base to take place, but its role has not been fully clarified.[20]

Cross-coupling processes are usually accepted to take place in three main steps: (I) oxidative addition, (II) transmetalation, and (III) reductive elimination (see Scheme 1).[1,2] Oxidative addition[21] and reductive elimination[22] are quite common in transition-metal-catalyzed reactions, and are reasonably well understood. Nevertheless, less is known about the transmetalation step (eq 2).[23] Moreover, in the case of the Suzuki−

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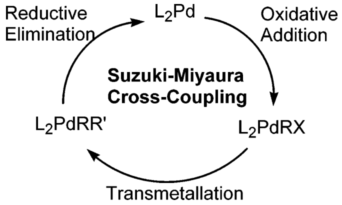
Scheme 1



Miyaura cross-coupling reaction, the transmetalation is the specific step where the base seems to be required.

$$Pd{-}X + B{-}R \rightarrow Pd{-}R + B{-}X \qquad (2)$$

Several roles have been proposed for the added base on the basis of experimental studies, though they have not been definitely established. In their initial investigations on the cross-coupling of haloalkenes and alkenylboranes, Suzuki and co-workers[5a,20,24,25] proposed a catalytic cycle adding a new step to the general one, where the base replaces the halide in the palladium complex, prior to the transmetalation process itself. Later mechanistic investigations on biaryl couplings by means of electrospray mass spectrometry were not able to locate any intermediate where the halide had been replaced by the base.[26] In another mechanistic study on the coupling of aryl halides with arylboronic acids, Smith and co-workers[27] proposed that the base binds the boronic acid, forming $[RB(OH)_3]^-$ species, with the latter becoming the reactive species. Afterward, in a very thorough work on the cross-coupling reaction of alkylboranes,[28] Matos and Soderquist proposed that the base can either replace the halide in the palladium complex or bind to the organoborane species depending on the base affinity of the latter. In their study on alkylboranes, Ridgway and Woerpel demonstrated that the reaction proceeds with retention of configuration.[29] Another mechanism has been recently proposed for the particular case of cross-coupling reactions between thiol esters and boronic acids,[30] though it is beyond the scope of this work. The mechanism of the palladium-catalyzed homocoupling of arylboronic acids has also been studied.[31]

Most of the information available about the role of the base on the transmetalation process was recently summarized by Miyaura in a very clarifying paper.[20] Two main pathways have been proposed to account for the effect of the base (Scheme 2): either the base binds the boronic acid to form the organoboronate species (path A), or the base replaces the halide in the coordination sphere of the palladium complex (path B). In addition, it has also been experimentally shown that using reactants which are able to react with the palladium catalyst to form an (oxo)palladium(II) complex (where oxo means an RO group, in which R is an organic group), this complex is able to undergo transmetalation with organoboronic acids without the addition of a base (path C).[25,32] In fact, this discovery has been sometimes used to support path B, and will also be analyzed here.

Computational chemistry is a useful tool in mechanistic analysis,[33] and in this work we present a theoretical study of the transmetalation process for the cross-coupling reaction between two vinyl groups that will serve as model compounds for the general cross-coupling reaction. The mechanisms proposed for the role of the base in the Suzuki−Miyaura cross-coupling reaction will be analyzed here. In addition, and for the sake of comparison, the mechanism without the addition of a base will also be investigated (path 0); this will also serve to account for the effect of the base speeding up the reaction rate.

The coupling reaction between diboron and iodobenzene has been recently reported by Miyaura and co-workers,[34] and theoretically studied by Sakaki et al.[35] In that study detailed and valuable information is provided about the transmetalation process, though the role of the base was not addressed; they assumed that the base replaces the halide in the coordination sphere of the catalyst. Hence, this investigation complements previous studies on the structure of the catalyst,[36] and on the mechanism of the Suzuki−Miyaura[35] and other cross-coupling reactions.[37]

2. Computational Details

Most calculations were performed at the DFT level, by means of the hybrid Becke3LYP[38] functional as implemented in Gaussian98.[39] Pd and Br atoms were described using an effective core potential (LANL2DZ) for the inner electrons,[39,40] and its associated double-ζ basis set for the outer ones. In the case of the Br atom a d-polarization function was added (exponent 0.4280).[41] The 6-31G* basis set was used for the P, B, C, O, and H atoms.[18,42] In the mechanisms where anionic species are involved, a set of diffuse functions were added for Br atoms[43] and P, O, C, and B atoms.[44] The structures of the reactants, intermediates, transition states, and products were fully optimized

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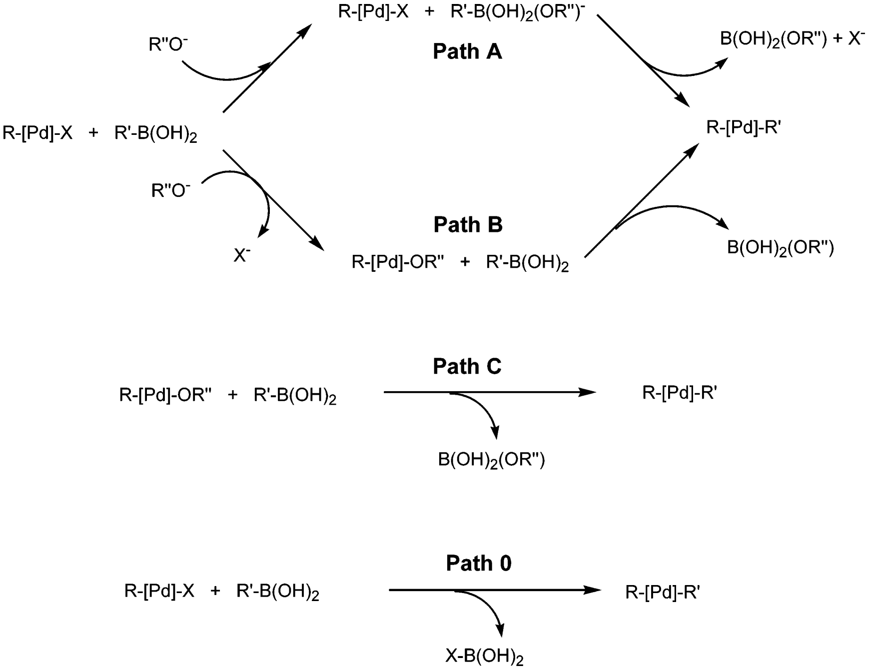
Scheme 2



without any symmetry restriction (otherwise specified in the text). Transition states were identified by having one imaginary frequency in the Hessian matrix. An additional set of calculations was carried out with the ONIOM (Becke3LYP:UFF) method[45] on a larger model where triphenylphosphine (PPh_3) was used. The QM region was the same model system of the pure DFT calculations, and the basis set was the same. For the MM region, containing the six phenyl substituents, the UFF force field was used.[46]

3. Results

The organohalide compound selected for the computational study was $CH_2{=}CHBr$, **1**, and the boronic acid was $CH_2{=}CHB(OH)_2$, **2**. The catalyst was modeled as the $Pd(PH_3)_2$, **3**, complex. The catalyst is considered to be a 14-electron Pd^0L_2 species, where L is usually a mono- or bidentate ligand;[47] we chose this as a general catalyst, though several kinds of ligands have been developed.[48] The OH^-, **4**, group was selected as the base because it is one of the most typical bases, giving excellent results. Other bases are used that also provide very good results (amines, F^-, AcO^-, etc.), but will not be analyzed here.

To check the effect of the base on the reaction, by investigating the transmetalation process for the different proposed reaction paths, we will assume for the calculations that the oxidative addition of the organic halide to the palladium catalyst gives rise to the *trans*-$Pd(CH{=}CH_2)(PH_3)_2Br$, **5**, complex. This is the intermediate that is commonly depicted in the general catalytic cycle after the initial oxidative addition step (Scheme 1).

The different mechanisms proposed for the role of the base during the reaction that have been described in the Introduction will be separately analyzed in the following subsections. In the first subsection the hypothetic mechanism that would take place for the reaction without the addition of a base is discussed. The next subsection is dedicated to analyze the mechanism where the reactive species is supposed to be $RB(OH)_3^-$, **6** (path A). The following subsection is devoted to the evaluation of the mechanism where the base directly replaces the halide in the coordination sphere of the catalyst (path B). After that, in the last subsection, the mechanism where the catalyst is an (oxo)-palladium(II) complex will be discussed.

3.1. Path 0: Direct Mechanism without the Addition of a Base. The transmetalation process between $CH_2{=}CHB(OH)_2$, **2**, and *trans*-$Pd(CH{=}CH_2)(PH_3)_2Br$, **5** (the Pd square-planar complex obtained after oxidative addition), is analyzed in this section. The transmetalation process takes place in two steps. In the first step, the organoboronic acid **2** coordinates to the Pd complex by means of the double bond through an η^2 coordination mode. The second step corresponds to the transmetalation itself, with the bromide migrating from Pd to B centers, and the double bond becoming exclusively bonded to the Pd complex as a vinyl group. Figure 1 presents the geometries of the most relevant structures for this process.

At the initial transition state, **TS01**, where the double bond is incorporated to the coordination sphere of palladium, the distances between the Pd and the incoming carbon atoms of the double bond are 2.675 and 2.682 Å, respectively. Once the square-pyramidal complex **I02** is formed, these distances become 2.479 and 2.493 Å, respectively; the Br^- occupies the apical position with a bond distance of 3.080 Å. The second step corresponds to the formation of the *trans*-$Pd(CH{=}CH_2)_2(PH_3)_2$ complex, **7**, and boronic acid **8**. In this step there is a notable atomic rearrangement, with the Br^- ligand leaving from the metal complex to become bonded to the boronic acid and the transformation of the coordinated double bond to a vinyl group. At the transition state **TS02** the forming

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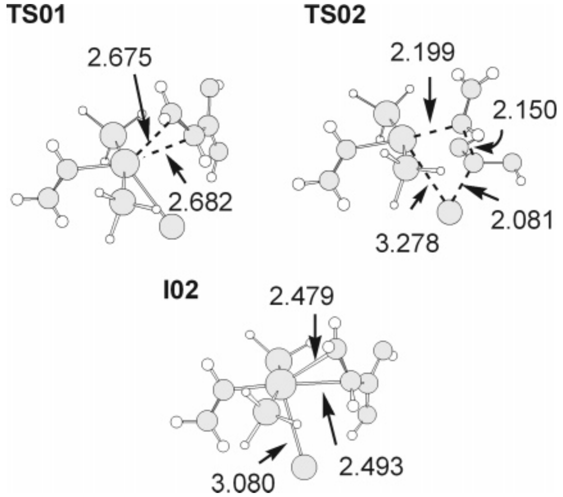

Figure 1. Geometries of selected structures for reaction path 0. Distances are in angstroms.

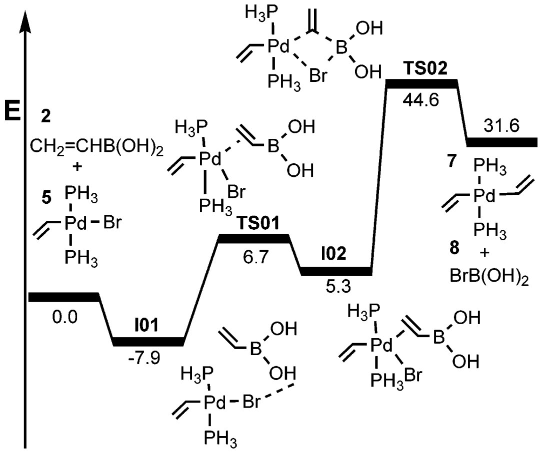

Figure 2. Energy profile for reaction path 0.

Pd−C_{vinyl} and B−Br bond distances are 2.199 and 2.081 Å, respectively, whereas the breaking Pd−Br bond distance is 3.278 Å.

The energy profile of this transmetalation process is presented in Figure 2. The energy of the initial structure, **I01**, a hydrogen-bonded complex between **2** and **5**, is −7.9 kcal/mol; all the energies will be referred to those of separated reactants. After that, the double bond of the organoboronic acid is incorporated into the Pd coordination sphere, forming a square-pyramidal complex, with the bromide ligand occupying the apical position. The energy of the transition state for this process, **TS01**, is 6.7 kcal/mol, whereas the energy of the five-coordinate intermediate **I02** is 5.3 kcal/mol. In the last step, there is a large structural rearrangement to produce products **7** and $BrB(OH)_2$, **8**; the energy of the corresponding transition state **TS02**, is 44.6 kcal/mol.

The overall reaction profile is uphill, giving an endothermic process with an energetic difference between reactants and products of 31.6 kcal/mol. The energy profile for the reaction shows a large energy barrier, having the most energetic transition state 44.6 kcal/mol above the separated reactants. This energy profile indicates that the transmetalation is too energy demanding for the reaction between the reactants themselves (**2** and **5**) to proceed; in fact, experiment shows that if a base is not added to the medium, the reaction does not take place.

3.2. Path A: Initial Formation of the Organoboronate Species. In this proposed mechanism, the base initially binds to the organoboronic acid **2** to form the corresponding organoboronate species $R{-}B(OH)_3^-$, **6**. This acid−base reaction is expected to have a low barrier in solution. However, our gas-phase calculation on $OH^- + R{-}B(OH)_2$ introduces a computational artifact in the form of a very stable intermediate with a strong hydrogen bond between the oxygen of the base and one of the protons of the boron species. This intermediate would not be that stable in solution because of the competition for hydrogen bonds of solvent molecules. To avoid this computational artifact, we repeated this calculation with $OH^- + RB(OCH_3)_2$, where the hydroxyl ligands at boron are replaced by methoxy groups to avoid the overstabilizing hydrogen bonds. In this case, there is a weak intermediate 68.4 kcal/mol below the separate reactants and 33.0 kcal/mol above the organoboronate product. The path between this intermediate and the product has a barrier of only 2.7 kcal/mol. Therefore, this second set of calculations confirms the expectation that the formation of the organoboronate species from the addition between the boronic species and the base is practically barrierless. Because of this, we will use as a starting point for this path the $R{-}B(OH)_3^-$, **6**, species in what follows.

The initial species considered for the mechanistic analysis, **IA1**, corresponds to the van der Waals complex between the *trans*-$Pd(CH{=}CH_2)(PH_3)_2Br$, **5**, complex and the organoboronate species **6**. The first step on the reaction profile corresponds to the substitution of the halide by the organoboronate species in the coordination sphere of the catalyst. This is a concerted step that proceeds through a transition state with a geometry that can be considered as a trigonal bipyramid with the two phosphines in the apical position, **TSA1**. The distances of the forming Pd−O and the breaking Pd−Br are 2.528 and 2.951 Å, respectively (see Figure 3). In the newly formed intermediate **IA2**, the OH group is bridging the Pd and B atoms with bond lengths of 2.168 and 1.645 Å, respectively.

In the next step there is an intramolecular substitution within the complex where the OH group is substituted by the alkene of the boronated ligand, both groups belonging to the boronate ligand. In this intermediate, **IA3**, the vinyl group is coordinated to the palladium through the double bond. In the transition state for this step, **TSA2**, the two forming Pd−C bond distances are 2.881 and 2.711 Å, respectively, whereas the Pd−O breaking bond distance is 2.529 Å. The latter distance, as expected, is very similar to the one found in the previous transition state, **TSA1**, for the formation of the Pd−O bond.

The last step corresponds to the formation of intermediate **7**, the commonly accepted intermediate in the general depicted cycle formed after the transmetalation process that is depicted in the general cycle (see Scheme 1). In the corresponding transition state **TSA3**, the breaking B−C distance is 2.000 Å, whereas the forming Pd−C distance is 2.250 Å. In the transition state the alkene group acts as a bridging group between the Pd and B metal centers. In this step, the alkene group changes its coordination mode with respect to the palladium from an η^2 coordination mode to a coordination through a single carbon atom, therefore becoming a vinyl group.

The energy profile is presented in Figure 4. The energy of the initial van der Waals complex, **IA1**, is 16.2 kcal/mol lower than those of the separated reactants. The next step corresponds

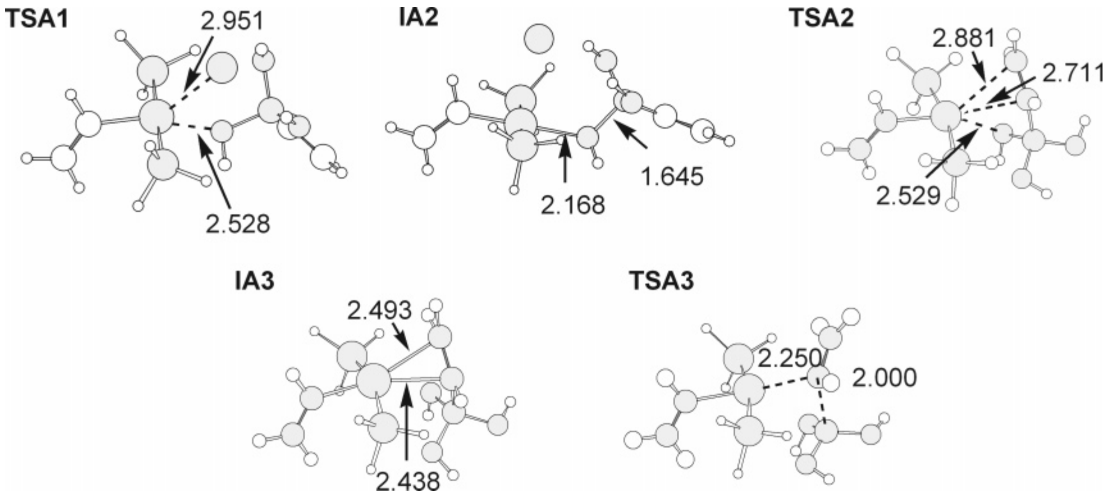

Figure 3. Geometries of selected structures for reaction path A. Distances are in angstroms.

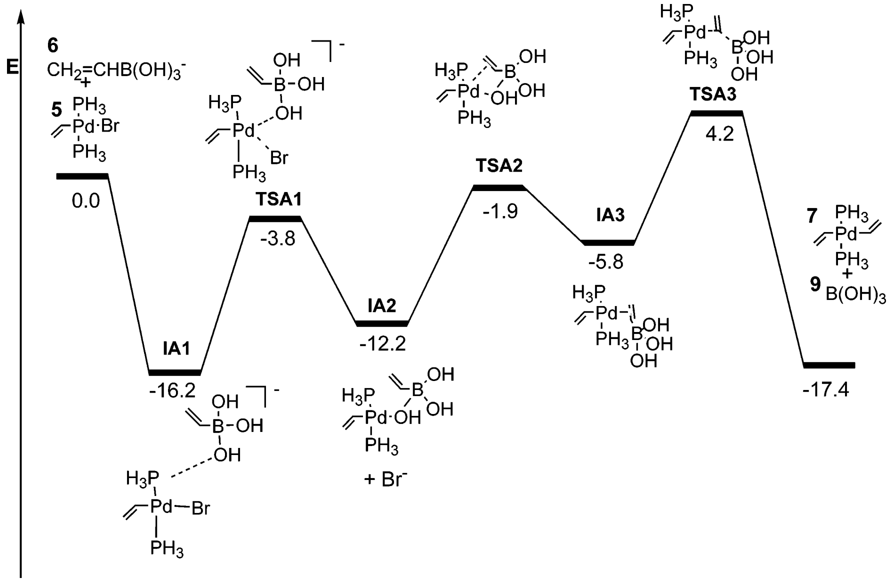

Figure 4. Energy profile for reaction path A.

to the replacement of the Br$^-$ by the [(CH$_2$═CH)B(OH)$_3$]$^-$ ligand in the coordination sphere of the palladium complex; the newly formed intermediate corresponds to the van der Waals complex between the *trans*-Pd(CH═CH$_2$)(PH$_3$)$_2$(CH═CH$_2$−B(OH)$_3$) complex and the Br$^-$ anion, **IA2**. In this intermediate the organoboronate ligand is bonded to the metal center through one of the hydroxyl groups. This intermediate, **IA2**, is 4.0 kcal/mol higher in energy than the previous intermediate, **IA1**. The energy barrier for the substitution of the bromide ligand by the organoboronate species is 12.4 kcal/mol.

Once the reaction reaches this point, the transmetalation process itself takes place, with the transfer of the vinyl group from the organoboronate to the palladium species. At first, the vinyl group replaces the hydroxyl group in the coordination sphere of the catalyst, with both groups belonging to the same organoboronate ligand. The vinyl group is coordinated to the metal center through the double bond, thus giving rise to a species with η^2 coordination, **IA3**. The energy of this intermediate is 6.4 kcal/mol above that of the previous one, **IA2**; the energy barrier for this intramolecular substitution is 10.3 kcal/mol. At this point, none of the hydroxyl groups are directly bonded to the metal center.

The last step corresponds to the formation of the *trans*-Pd(CH═CH$_2$)$_2$(PH$_3$)$_2$ complex, **7**, and the B(OH)$_3$, **9**, species. The former is considered to be the intermediate complex formed after the transmetalation and prior reductive elimination processes within the catalytic cycle. This intermediate is 11.6 kcal/mol more stable than the preceding one, **IA3**, and 17.4 kcal/mol more stable than the separated reactants. The energy barrier for this step is 10.0 kcal/mol, though its energy in the overall pathway is 4.2 kcal/mol (see Figure 4); therefore, this stationary point corresponds to the highest energy transition state of the overall transmetalation process within this mechanism. In this step, the C−B bond is broken at the same time that the vinyl group becomes bonded to the Pd through a single carbon atom.

On the basis of these results, this pathway corresponds to a feasible mechanism for the reaction. It is important to note that the boronate species is able to quite easily replace the halide in the coordination sphere of the catalyst, and the reaction occurs very smoothly (as usually required in a catalytic process), with the highest energy transition state only 4.2 kcal/mol above the separated reactants.

In addition, it is worth mentioning that contrary to the common transmetalation processes that are believed to take place through a four-center transition state,[23] with two bridging groups between both metal atoms, in this case there is only one bridging group, the vinyl group. In addition, the transmetalation process does not take place in one step, but several steps are needed.

3.3. Path B: Direct Replacement of the Halide by the Base. To evaluate the reaction mechanism where the base directly replaces the halide in the coordination sphere of the palladium complex, the corresponding reaction profile was theoretically investigated. In this mechanism, once the oxidative addition step has taken place to form *trans*-$Pd(PH_3)_2(C_2H_3)Br$, **5**, the next step should correspond to the replacement of the Br^- ligand by the OH^- group.

Despite the great effort dedicated to find and characterize the transition state for the direct replacement of the halide by a hydroxyl group, none of the attempts were successful. This result was somehow unexpected because the ligand substitution mechanism for a square-planar complex is a generally accepted mechanism going through a trigonal-bipyramidal structure.[49] Nevertheless, all the different optimizations ended up in either high-energy chemically unreasonable structures or two different complexes: one with the OH^- oxidizing one of the phosphine ligands of the palladium complex, and another with the base replacing one of the phosphine ligands of the catalyst.

The search for the transition state for the direct substitution can be illustrated by our exploration of geometries with a forced C_s symmetry. The incoming OH^- group was located in such a way that the whole structure had a mirror plane. The mirror plane contains the Pd, vinyl, Br^-, and OH^- groups, whereas both of the phosphine ligands are each on every side of the symmetry plane. Nevertheless, even performing such a calculation, forcing the C_s symmetry, it was not possible to locate a transition state for this substitution. This transition-state search provided a stationary point, though the analysis of the geometry and the imaginary frequencies (three negative eigenvalues) showed that this stationary point corresponds to the migration of the OH^- group from one of the phosphine ligands to the other one. Hence, the fact that this stationary point (forcing the C_s symmetry) does not involve the bromide ligand at all is a strong indication that the direct substitution of Br^- by OH^- does not take place, at least in the gas phase.

During the exploration of the potential energy surface for the direct substitution of Br^- by OH^-, the $Pd(CH{=}CH_2)(PH_3)(OH)Br$, **10**, complex was found. It corresponds to a complex where starting from **5** the base replaces one of the phosphine ligands. This intermediate is thermodynamically more stable than the separated reactants (by 37.3 kcal/mol), but it is not relevant for the catalytic reaction. This complex could certainly give rise, in principle, to the transmetalation process with the organoboronic acid. But if the mechanism were to go through this intermediate, the catalytic cycle could not be closed; to close the catalytic cycle, the palladium complex must get rid of the bromide ligand at some point, to restore the initial $Pd(PH_3)_2$ reactive species. Hence, we decided not to further explore the reactivity of species **10**, which moreover has been neither experimentally characterized nor proposed as a possible intermediate for the Suzuki–Miyaura cross-coupling reaction.

The other species located in the potential surface was that where the OH^- group oxidizes one of the phosphine ligands, forming the *trans*-$[Pd(CH{=}CH_2)(PH_3)(PH_3OH)Br]^-$, **IB1**, complex. In this complex, the P–O distance adopts a value of 1.916 Å (see Figure 5); the phosphorus atom adopts a trigonal-bipyramidal bonding mode, with the OH^- group occupying an apical position, and the Pd occupying an equatorial position. This species is 46.9 kcal/mol below the separated reactants. Despite its stability, the presence of an oxidized phosphorus group makes the presence of this species in the reaction cycle quite unlikely. Indeed phosphine oxidation is one of the known causes of catalyst destruction, and it seems to be already incipient in this compound.

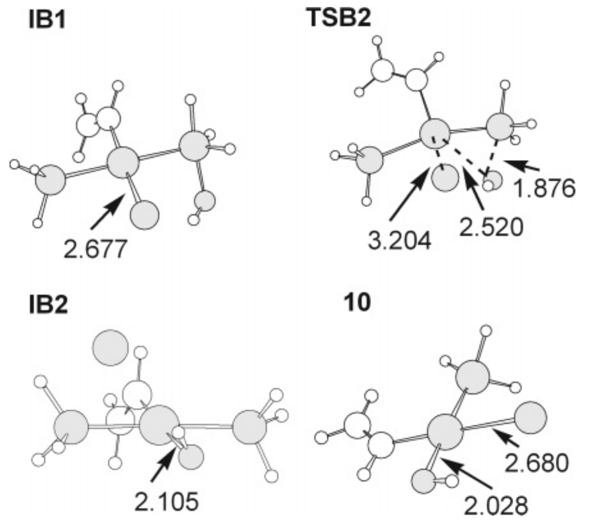

Figure 5. Geometries of selected structures associated with path B. Distances are in angstroms.

In any case, the cross-coupling process can progress from **IB1**, and we were able to locate a transition state with an energy barrier of 6.3 kcal/mol connecting this species to complex **11**, where the halide has been replaced by the base. In the transition state **TSB2**, the OH^- initially bonded to the phosphine migrates to the metal center, concomitantly with the release of the bromide ligand. The energy barrier for this process is 6.3 kcal/mol. Intermediate **IB2** is 0.5 kcal/mol above intermediate **IB1** and 46.4 kcal/mol below the reactants. We will label this alternative mechanism as B′, to emphasize that the bromide is not replaced in one step by the base, as in mechanism B. **IB2** is in fact analogous to the starting point for path C, which will be described in detail below, and from this point the transmetalation process takes place.

It is interesting to compare our computational results on mechanism B′ with experiment. Experimental results show that, in the absence of organoboron species, the addition of a base to a complex like the one formed after the oxidative addition (**5** in the studied case) leads to a complex partially hydrolyzed (which would correspond to complex **11**), and the amount of the oxidized phosphine present in the media increases significantly.[28,50] Our computed mechanism B′ is fully consistent with both observations. However, oxidation of phosphine is much smaller when the organoboron compound is present, and as a consequence, mechanism B′ has to be discarded as the main path for the catalytic cycle.

In summary, theoretical calculations do not support a mechanism where the OH^- group directly replaces the Br^- ligand in

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(49) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Mill Valley, CA, 1994.

(50) Grushin, V. V.; Alper, H. *Organometallics* **1996**, *15*, 5242.

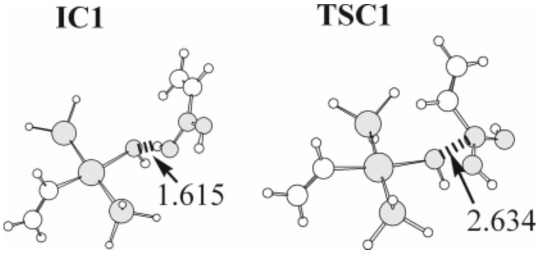


Figure 6. Geometries of selected structures for reaction path C. Distances are in angstroms.

the coordination sphere of the palladium catalyst prior the transmetalation process itself (path B); the base by itself is not able to replace the bromide ligand in the coordination sphere of the catalyst. In a recent study by Sakaki and co-workers, the transition state for the substitution of a halide (iodide in that case) by OH^- was not located either.[35] The reaction going through a pathway where the base initially binds one of the phosphine ligands, with the subsequent migration to the Pd center, along with the release of the Br^- ligand (path B′), could be an alternative way. Nevertheless, this path would produce a large amount of phosphine oxidation, which is not observed experimentally when the Suzuki−Miyaura cross-coupling takes place. Because of this, we think that the catalytic process does not go through any of these two possible paths.

3.4. Path C: Reaction from an (Oxo)palladium(II) Complex. The schematic representation of such an (oxo)palladium(II) complex is *trans*-$Pd(RO)(P)_2X$, where RO is an alkoxy group, P is a phosphine, and X is a halide. It has been experimentally proven that the reaction of this kind of complex with organoboronic acids takes place without the addition of a base on the reaction media.[20,32] For theoretical calculations the RO^- group has been modeled by an OH^- group, the simplest oxo group.

Once the (oxo)palladium(II) complex **11** is formed, usually by oxidative addition of an R′−OR group, the transmetalation process involves several steps. The first step corresponds to the formation of an intermediate, **IC2** (starting from the H-bonded complex **IC1**), where the boronic acid is bonded to the catalytic complex through the OH^- ligand. The bond distances between the B and O atoms at the transition state **TSC1** and the intermediate **IC2** are 2.634 and 1.645 Å, respectively (Figure 6). The **IC2** intermediate is equivalent to that found in path A, **IA2**, having the boron and palladium centers bonded by means of a hydroxyl group. The reaction mechanism from this point until the transmetalation process is completed is equivalent to that found for path A once the **IA2** intermediate is formed. In fact, the geometries of **IC2**, **TSC2**, **IC3**, and **TSC3** are equivalent to those found for **IA2**, **TSA2**, **IA3**, and **TSA3**, respectively. Hence, all of these geometries have already been commented on in a previous section. In addition, if their structures are equivalent, so are their relative energies.

Figure 7 shows the energy profile for the transmetalation process starting from the (oxo)palladium(II) complex **11**. The energy of the initial H-bond complex, **IC1**, is −19.2 kcal/mol, which indicates a strong H-bond interaction. The energy of the intermediate formed in the next step, **IC2**, is −15.9 kcal/mol, whereas the transition state for this step, **TSC1**, is −5.7 kcal/mol. The energies of the intermediates and transition states from **IC2** till the transmetalation process is completed are analogous to those found in path A from the **IA2** intermediate; however, the energy values are different here because they are referred to a different starting point. Hence, in the next step from the **IC2** intermediate, the double bond replaces the OH^- in the coordination sphere of the catalyst, to form intermediate **IC3**, going through **TSC2**, and their energies are −9.4 and −5.6 kcal/mol, respectively. The transition state for the last step, **TSC3**, which corresponds to the formation of products **7** and **8**, has an energy of 0.6 kcal/mol. In this case, the overall reaction is exothermic by 21.0 kcal/mol, and the most energetic transition state is only 0.6 kcal/mol above the separated reactants. Therefore, this is a plausible mechanism for the transmetalation process.

The calculated reaction profile perfectly agrees with the experimental data where the cross-coupling reaction takes place starting from an (oxo)palladium(II) complex without the addition of a base. In fact, the reaction takes place smoothly, with the highest transition state being only 0.6 kcal/mol above the separated reactants.

The initial process corresponds to the formation of the **IC2** intermediate starting from the H-bond complex **IC1**. This complex is analogous to the one formed by the substitution of the Br^- by the $R-B(OH)_3^-$ in the coordination sphere of the palladium in path A. The following steps take place analogously to the mechanism described by path A. In fact, the difference is in the initial step, where in one case the bromide is replaced by the organoboronate species to form the hydroxo complex, whereas in the other case the hydroxo complex is directly formed by oxidative addition of an R−OR′ to the $Pd(PH_3)_2$ catalyst. Therefore, this is a clear indication that the palladium complex must get rid of the bromide ligand for the reaction to occur.

4. Discussion

The role of the base in the Suzuki−Miyaura cross-coupling reaction between a palladium complex formed after the initial oxidative addition step, *trans*-$Pd(CH{=}CH_2)(PH_3)_2Br$, **5**, and an organoboronic acid, $CH_2{=}CHB(OH)_2$, **2**, has been analyzed by means of theoretical calculations. The different pathways proposed to include the base in the reaction pathway have been studied and their intermediates and transition states identified. Scheme 3 summarizes the view that emerges from our calculations. This has to be compared with Scheme 2, which presented the view preliminary to this set of calculations.

Reaction path A consists of the initial reaction between the base and the organoboronic acid to form $R-B(OH)_3^-$, **6**. The formed organoboronate species is able to easily undertake the substitution of the Br^- ligand in the coordination sphere of the *trans*-$Pd(CH{=}CH_2)(PH_3)_2Br$, **5**, complex (the complex resulting from the initial oxidative addition step). In fact, boron centers are known to exhibit high oxophilicity, and consequently, the addition of alkaline base to a solution of $R-B(OH)_2$, **2**, shows an equilibrium fairly displaced to the formation of the $R-B(OH)_3^-$, **6**, species; theoretical calculations show that this reaction is almost barrierless, and highly displaced to the formation of the organoboronate species. Moreover, the highest energy barrier found in the complete reaction pathway is quite smooth, only 4.2 kcal/mol above the separated reactants.

Therefore, given these results, this mechanism is a plausible mechanism for the Suzuki−Miyaura cross-coupling reaction, properly explaining the role of the alkaline base within the

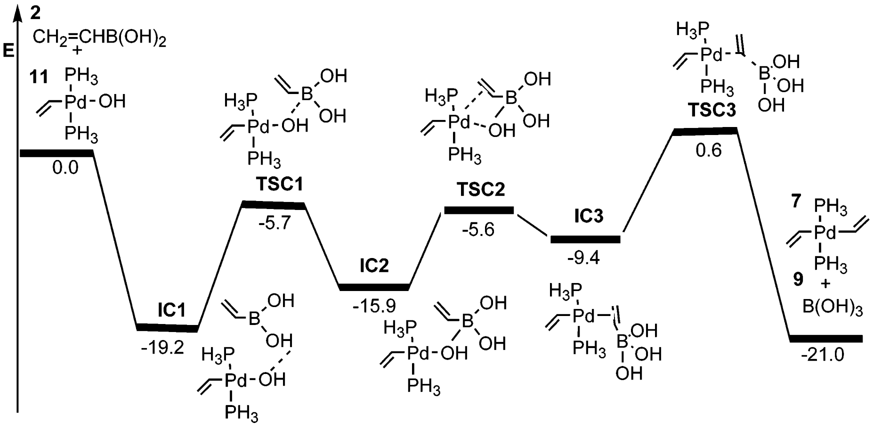
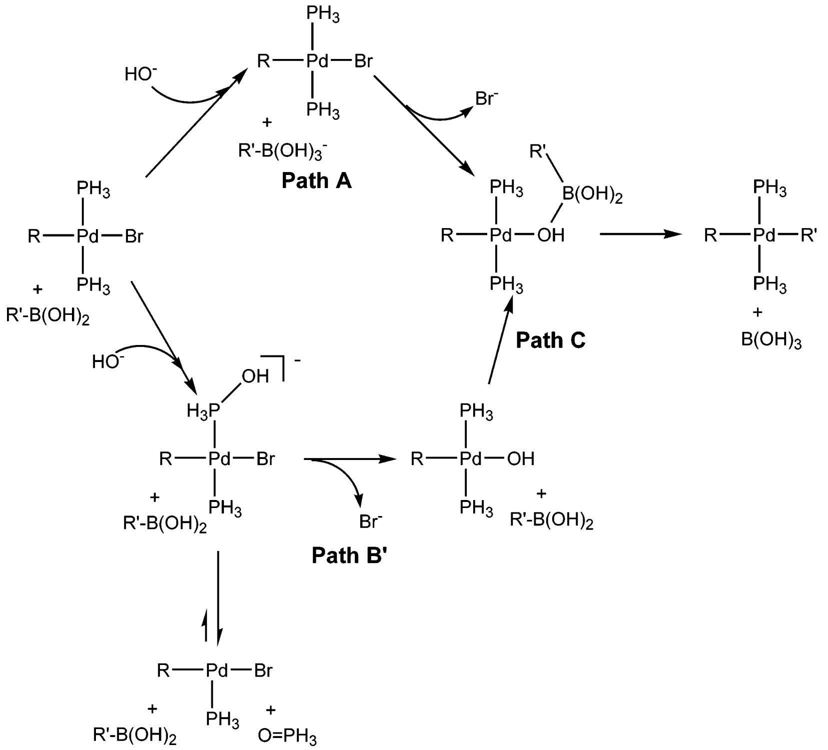


Figure 7. Energy profile for reaction path C.

Scheme 3



catalytic cycle. The major implication of this pathway is that the base does not directly react with the catalyst, but it does react with the boronic acid. These results are also in agreement with the experimental fact that organoboronic acids are unreactive toward cross-coupling reactions, whereas boronate species (R_4B^-, R_3BOR^-, etc.) are much more reactive.

The proposed reaction mechanism where the OH^- group directly replaces the Br^- ligand in the coordination sphere of the palladium catalyst was also analyzed (path B). Despite the great effort dedicated to searching for a stationary point, the transition state for the direct ligand substitution could not be located. All the different trials indicated any of the following possibilities: (i) high-energy chemically unreasonable structures, (ii) a complex where one of the phosphine ligands was replaced by the base, or (iii) a complex where one of the phosphine ligands was oxidized. Results from (i) and (ii) do not provide any insight into the mechanism proposed in pathway B because the located structures are not in the catalytic cycle; in contrast, results obtained in (iii) give rise to a conceivable mechanism for path B, which we label as B′.

In path B′, the base initially binds to one of the phosphines coordinated to the palladium center, and after that, there is a migration of the OH^- group from the phosphine to the Pd center, along with the release of the Br^- ligand. Once the reaction reaches this point, the catalyst reacts with the boronic acid, performing the transmetalation process.

Given the fact that phosphine oxidation is usually one of the sources of catalyst destruction, a mechanism that implies the initial oxidation of a phosphine ligand is dubious as the main reaction mechanism. In fact, path B′ can be related to other experimental observations. For instance, in the experimental study by Matos and Soderquist,[28] they realized that after the addition of NaOH to *trans*-$BrPdPh(PPh_3)_2$ the amount of triphenylphosphine oxide increases significantly in the mixture. This observation can be directly related to the intermediate found for pathway B′, **IB1**, where a coordinated phosphine binds the

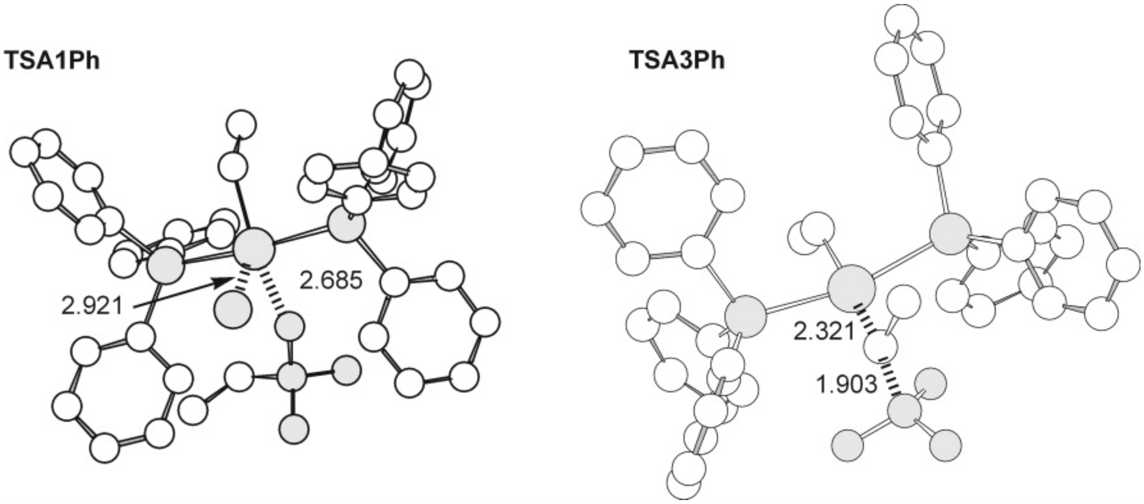


Figure 8. Geometries of selected ONIOM-calculated structures for reaction path A. Hydrogens are omitted for clarity. Distances are in angstroms.

OH^- group. From this intermediate, the reaction could evolve to form the oxidized phosphine that is experimentally observed. On the other hand, the reaction profile for path B′ is energetically accessible, and in fact, this could be the reaction pathway for those cases where the organoborane species cannot form the corresponding organoborate species.

The mechanism starting from the (oxo)palladium(II) complex (path C) has also been analyzed. The energy profile for this mechanism shows that the reaction goes quite smoothly. The highest energy transition state is only 0.6 kcal/mol above the separated reactants. The calculations agree with experimental results that show that this reaction goes easily without the need for a base. In this case, the Pd complex already has an oxo ligand in its coordination sphere, which is the one facilitating an easy bond formation with the boronic acid, therefore allowing the transmetalation process to occur. Therefore, the efficiency of path C does not support path B, because the starting point of path C is after the phosphine oxidation step that is critical for the validity of path B.

The reaction profile for the reaction without the base (path 0) has also been analyzed. This hypothetic reaction serves to confirm that the addition of a base is necessary for the reaction to proceed. The reaction profile shows that the highest energy transition state is 44.6 kcal/mol above the separated reactants. Thus, the energy barrier is too high for the reaction to occur, and this is the reason the base is required.

The ensemble of results indicates that one of the key problems of the catalytic cycle is the displacement of the bromide ligand from the metal coordination sphere. The boronic acid itself is obviously incapable of performing this replacement at a reasonable energy cost, as shown by mechanism 0. Hence, a base is therefore necessary for the process to take place. Nevertheless, OH^- is unable to directly attack the metal center (what would be path B), which does not seem oxophilic enough, and attacks first the boron (path A) or the phosphorous (path B′); only afterward the base can be transferred to palladium, where it displaces the bromide. Path B′ must be discarded as the main mechanism because it easily leads to ligand oxidation and catalyst destruction. The main catalytic cycle must thus proceed through path A, which has low-energy barriers and no obvious undesired subproducts.

5. Effect of the Phosphine Substituents

All the calculations presented above were carried out on a model system where the phosphine ligand was modeled by PH_3. This choice was motivated by the computational cost. In this section, we consider a more realistic ligand to see how it affects the qualitative picture just presented. The steric effects of the triphenylphosphine ligand, PPh_3, often used in experimental Suzuki−Miyaura systems, were introduced into the calculation through the use of the ONIOM (Becke3LYP:UFF) approach. The energetics will be discussed here, and the computed geometries are collected in the Supporting Information. The labels will be the same used above for the model systems, with the addition of **Ph** to indicate that they refer to the PPh_3 case.

The structures involved in the profiles presented in Figures 2−4 were recomputed with this new phosphine. For the structures related to the profile in Figure 2, corresponding to path 0, the relative energies for **2** + **5Ph**, **I01Ph**, **TS01Ph**, **I02Ph**, **TS02Ph**, and **7Ph** + **8** are 0.0, −12.5, 12.1, 11.2, 54.1, and 31.4 kcal/mol, respectively. These values should be compared with the corresponding values for the PH_3 model system, which were 0.0, −7.9, 6.7, 5.3, 44.6, and 31.6 kcal/mol, respectively. The differences in relative energies are in some cases remarkable, reaching a maximum of 9.5 kcal/mol between **TS02Ph** and **TS02**, but the overall qualitative picture is unchanged. Path 0 stays indeed with a prohibitively high barrier. One can also look at changes in the relative energies of the particular species. The overall endothermicity of the reaction, indicated by the relative energy of the products **7Ph** + **8** with respect to the reactants **2** + **5Ph**, is practically unchanged, 31.6 kcal/mol (vs 31.4 kcal/mol) for the model system. This is consistent with the square-planar geometry with a trans arrangement of the phosphines in both **7Ph** and **5Ph**, with little steric interaction. For most other species, such as **TS01Ph**, **I02Ph**, and **TS02Ph**, there is an increase between 5.4 and 9.5 kcal/mol in the relative energy associated with the presence of the phenyl groups. The entry of the organoboronate into the coordination sphere of the palladium introduces some steric crowding, with a subsequent increase in energy. In contrast, **I01Ph** has a lower relative energy than **I01**. This suggests some attractive long-range interaction between the phenyl susbstituents and the organoboronic acid in this initial intermediate.

The structures related to path A, presented for the model system in Figure 4, were also recomputed. The relative energies for **6** + **5Ph**, **IA1Ph**, **TSA1Ph**, **IA2Ph**, **TSA2Ph**, **IA3Ph**, **TSA3Ph**, and **7Ph** + **9** were 0.0, −13.9, −6.1, −10.1, 6.8, 1.7, 12.4, and −17.2 kcal/mol, respectively. The corresponding energies for the model system were 0.0, −16.2, −3.8, −10.1, −1.9, −5.8, 4.2, and −17.4 kcal/mol, respectively. The maximum difference in relative energies in this case is in **TSA2Ph**, which was 1.9 kcal/mol below the reactants with PH_3 and 6.8 kcal/mol above them with PPh_3. The qualitative picture is however unchanged. The overall profile goes smoothly, and the highest energy is at **TSA3Ph**, which is now 12.4 kcal/mol above the reactants. The energy difference between the reactants and products changes only by 0.2 kcal/mol. As for the intermediate species, two sets of geometries can be distinguished: **IA1Ph**, **TSA1Ph**, and **IA2Ph** and **TSA2Ph**, **IA3Ph**, and **TSA3Ph**. In the first block, the relative energies are within 2.5 kcal/mol of those for the model system, these species corresponding to the replacement of the bromide by the boronic acid. In the second block, the relative energies are ca. 8.0 kcal/mol higher than for the model system. In this second block, the vinyl group attached to the boron approaches the metal, thus inducing a larger steric crowding. Geometries, in turn, are slightly modified compared to those obtained with PH_3 as ligand (see Figure 8).

Finally, the structures in reaction C, corresponding to the profile reported in Figure 7, were recomputed. In this case, the relative energies for **2** + **11Ph**, **IC1Ph**, **TSC1Ph**, **IC2Ph**, **TSC2Ph**, **IC3Ph**, **TSC3Ph,** and **7Ph** + **9** were 0.0, −21.5, −8.7, −14.8, 2.2, −3.0, 7.7, and −21.8 kcal/mol, respectively. The associated values for the model system were 0.0, −19.2, −5.7, −15.9, −5.6, −9.4, 0.6, and −21.0 kcal/mol, respectively. The general pattern discussed above for path A is reproduced for path C. The profile is smooth, with the highest energy being at **TSC3Ph**, 7.7 kcal/mol above the reactants. The relative energies for species **IC1Ph**, **TSC1Ph**, and **IC2Ph** are very similar between the PH_3 and the PPh_3 systems, with differences being larger for **TSC2Ph**, **IC3Ph**, and **TSC3Ph**. These latter species appear after the vinyl group attached to boron approaches palladium and increases the steric pressure.

In summary, in the three recomputed profiles the consideration of the more realistic triphenylphosphine affects the energetic details, but leaves the overall trends practically unchanged. Path 0 continues to be forbidden, while both paths A and C have low barriers. We expect path B to remain forbidden, but we did not recompute it because the lack of stationary points for the exchange of bromide by hydroxyl in the model system made the calculation more complicated. The fact that the qualitative picture is unchanged by the introduction of more realistic ligands confirms the validity of the PH_3 model for this particular problem. Moreover, it also suggests that these results will continue to be valid for minor variations in the nature of both the phosphine and the substrates.

6. Conclusions

The role of the base in the cross-coupling reaction between a palladium complex and an organoboronic acid has been analyzed by means of theoretical calculations based on DFT and ONIOM methods. The resulting picture, summarized in Scheme 3, explains satisfactorily most of the available experimental evidence on the topic.

The analysis of the transmetalation process without the addition of a base shows that this reaction has an elevated energy barrier. This agrees with experimental results where the base is critical for the reaction to proceed. In light of the results obtained here, we conclude that, in the most feasible mechanism, which we have labeled as path A, the base initially reacts with the boronic acid to form a boronate species (this is an equilibrium fairly displaced to the right), and the latter species is the one that undertakes the transmetalation process with the palladium catalyst. The energy profile is quite smooth, as expected for a catalytic process.

The main alternative mechanism that had also been proposed, where the halide is directly substituted by the base in the coordination sphere of the catalyst (path B), does not seem to take place in the system we have considered. A new mechanism, B′, has been instead computationally characterized. This new mechanism goes through an intermediate that corresponds to the oxidation of one of the phosphine ligands of the catalyst. Path B′ is quite smooth from an energy point of view, but it is a dubious candidate to be the main process in the catalytic system because it would likely produce large amounts of oxidized phosphine.

The transmetalation process starting from an oxo−Pd complex (path C) has also been studied. The results show that this process takes place very smoothly, and in this case the base is not needed for the reaction to proceed, in agreement with experiment.

The current results on the Suzuki−Miyaura cross-coupling reaction of this particular system cannot be directly extrapolated to the entire variety of available cross-coupling processes, but we hope that they will provide at least a reasonable interpretation of general validity. In fact, the consideration of a more realistic phosphine ligand does not affect the overall picture of the reaction. In this sense, it seems clear that the transmetalation reaction is in all cases shown to be a multistep process. The complete reaction cycle for this and other C−C coupling reactions is under investigation in our laboratories.

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Supporting Information Available: Cartesian coordinates for all optimized structures and their absolute energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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