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Subtle Balance of Ligand Steric Effects in Stille Transmetalation

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Abstract: Experimental results have previously suggested that the transmetalation step in the Stille reaction is hindered at one extreme by very bulky ligands L on the PdL_2 catalyst, yet at the other extreme, transmetalation is also found to be slow for small ligands. Our aim in this paper is to resolve this dilemma using computational chemistry and to show which ligand is best and why. With the use of density functional theory we show that the reason why L = P^tBu_3 retards transmetalation is because the bulky ligand hinders the coordination of the organostannane. On the other hand a small ligand such as L = PMe_3 leads to the formation of a very stable intermediate in the catalytic cycle which then requires a large activation energy for the transmetalation to proceed. The L = PPh_3 ligand appears to provide just the right balance in that it can readily coordinate the organostannane but avoids forming the very stable intermediate, and is thus the ligand of choice. L = PPh_2Me is predicted to be the next best option, but L = $PPhMe_2$ is too small and forms an intermediate whose stability prevents further reaction in the transmetalation step. Our calculations are also able to account for the accelerating role of CsF in the transmetalation step of the Stille reaction. Finally, this work demonstrates the importance of taking into account the steric properties of the full ligand in theoretical studies of such reactions, rather than using small model phosphines.

Introduction

Pd-catalyzed cross coupling reactions have attracted many experimentalists[1] and theoreticians[2] due to their potential applications in organic synthesis. Stille reactions,[3−5] the coupling of organic electrophiles (ArX) with organostannanes ($RSnR'_3$), have been established to have several advantages over the many approaches known for the cross coupling reactions: organostannane reagents are stable against air and moisture and the Stille processes show remarkable compatibility with functional groups. A detailed understanding of the way that steric factors in the Pd catalyst[6] can affect the rate of the Stille reaction is an important goal in order to continue to improve the applicability of this valuable reaction.

The mechanism of the Stille cross-coupling reaction has been extensively studied experimentally[7] and theoretically[7g,8] The well-accepted mechanism for the reaction comprises three successive fundamental steps: (1) oxidative addition,[9] (2) transmetalation, and (3) reductive elimination (Scheme 1). Two different pathways are proposed for the transmetalation step:

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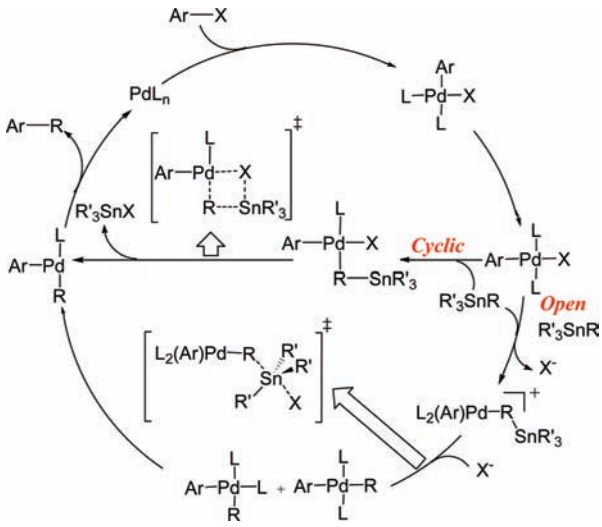
Scheme 1



open and cyclic.[7a,b,8d] An S_E2 mechanism was established for the cyclic pathway in which the SnR_3 group is bridging between the Pd-bound X and R ligands. The cyclic pathway is favorable for X = halides and proceeds with retention of configuration. In the open pathway, the transmetalation process takes place via the replacement of X by $RSnR'_3$ followed by an S_N2 substitution reaction. The open pathway is favorable for weakly coordinated ligands such as X = triflate and proceeds with inversion of configuration.

Recently, Fu and co-workers introduced Pd/P^{t}Bu$_3$ as a powerful catalyst for the Stille reaction of the aryl chlorides.[10] However, they found that under normal Stille reaction conditions the product yield was very low, and they proposed that this was due to a retarded transmetalation step. Since one might have expected[7a,d,8c] a fast transmetalation process in the presence of the Cl leaving group used by Fu, this result suggests that the reason for retarding the transmetalation step in this case is related to the presence of the sterically demanding phosphine ligand P^{t}Bu$_3$. However, Fu's conclusion appears to contradict the experimental findings of Farina and Krishnan who have shown that bulky phosphine ligands assist the transmetalation process.[11] In order to resolve the question of how the bulkiness of the ancillary ligand P^{t}Bu$_3$ introduces additional energy loading on the catalytic Stille reactions, we have theoretically studied the mechanism of the cross-coupling reaction between (vinyl)SnBu$_3$ and PhCl catalyzed by Pd(P^{t}Bu$_3$)$_2$. We have also studied the same reaction using sterically less demanding phosphine ligands PPh$_3$, PPh$_2$Me, PPhMe$_2$, and PMe$_3$ to gain a better understanding of the role of the steric effect of P^{t}Bu$_3$ on the catalytic reaction.

In the study by Fu and co-workers, they found that the addition of CsF greatly accelerated the rate of the cross coupling reaction and they proposed that it was the transmetalation step which was being affected. In this paper we will also address how the addition of CsF affects the mechanism of transmetalation.

To date, in all the theoretical studies of Pd-catalyzed Stille reaction,[7g,8] the experimentally used phosphine ligands are modeled by PH$_3$ or PMe$_3$. The main scope of the present theoretical paper is to evaluate in detail the role of the real phosphine ligands on the mechanism of the transmetalation step of the Stille reaction.

Computational Detail

Gaussian 03[12] was used to fully optimize all of the structures reported in this paper at the B3LYP level[13−15] of density functional theory. The effective core potentials of Hay and Wadt with double-ζ valence basis sets (LanL2DZ)[16−18] were chosen to describe Pd, Sn, Cs, Cl, and P. The 6-31G(d) basis set was used for other atoms.[19] Polarization functions were also added for Pd ($\zeta_f = 1.472$), Sn ($\zeta_d = 0.180$), Cs ($\zeta_d = 0.306$), Cl ($\zeta_d = 0.640$), and P ($\zeta_d = 0.387$).[20,21] This basis set combination will be referred to as BS1. Frequency calculations were carried out at the same level of theory for structural optimization. To further refine the energies obtained from the B3LYP/BS1 calculations, we carried out single-point energy calculations for all of the structures with a larger basis set (BS2): LANL2augmented:6-311+G(2d,p) basis set, incorporating the LANL2 effective core potential, a large LANL2TZ+(3f) basis set on Pd, a large LANL2TZ+(3d) basis set on Cs and Sn (see the Supporting Information) and the 6-311+G(2d,p) basis set on other atoms. To estimate the corresponding Gibbs free energies, ΔG, the entropy corrections were calculated at the B3LYP/BS1 level and added to the B3LYP/BS2 potential energies. We have used the B3LYP/BS2//B3LYP/BS1 energies throughout the paper unless otherwise stated.

To evaluate the solvent effect, we employed CPCM[22] single-point calculations using BS1 on gas phase optimized geometries. Dioxane was used as the solvent, corresponding to that used in the experiment. The relative potential and Gibbs free energies in the solvent were calculated using the following equations:

$$\Delta E_{solv} = \Delta E(\mathrm{BS2}) + \Delta E_{solv}(\mathrm{BS1}) - \Delta E(\mathrm{BS1})$$

$$\Delta G_{solv} = \Delta G + \Delta E_{solv}(\mathrm{BS1}) - \Delta E(\mathrm{BS1})$$

where ΔE_{solv}(BS1) and ΔE(BS1) are the relative potential energies calculated with BS1 in dioxane and the gas phase, respectively. ΔE(BS2) denotes the relative potential energies obtained by the single-point energy calculations with basis set BS2 at the geometry optimization with BS1.

Results and Discussion

Mechanism of Pd/P^{t}Bu$_3$-Catalyzed Stille Cross Coupling of PhCl. This section is intended to set the scene for the subsequent discussions concerning the effects of varying the ligand bulk, CsF addition, and solvent. The catalytic reaction starts with the oxidative addition of PhCl to Pd(0) as outlined in Scheme 1. The oxidative addition of PhCl has been confirmed to occur

(9) A study carried out by Casado and Espinet on the oxidative addition reaction of ArX to Pd(PPh$_3$)$_4$ has shown that a *cis*-(PPh$_3$)2Pd(Ar)(X) is formed first and then the cis-isomer isomerizes to the thermodynamically more stable trans-isomer (see Scheme 1). Casado, A. L.; Espinet, P. *Organometallics* **1998**, *17*, 954.

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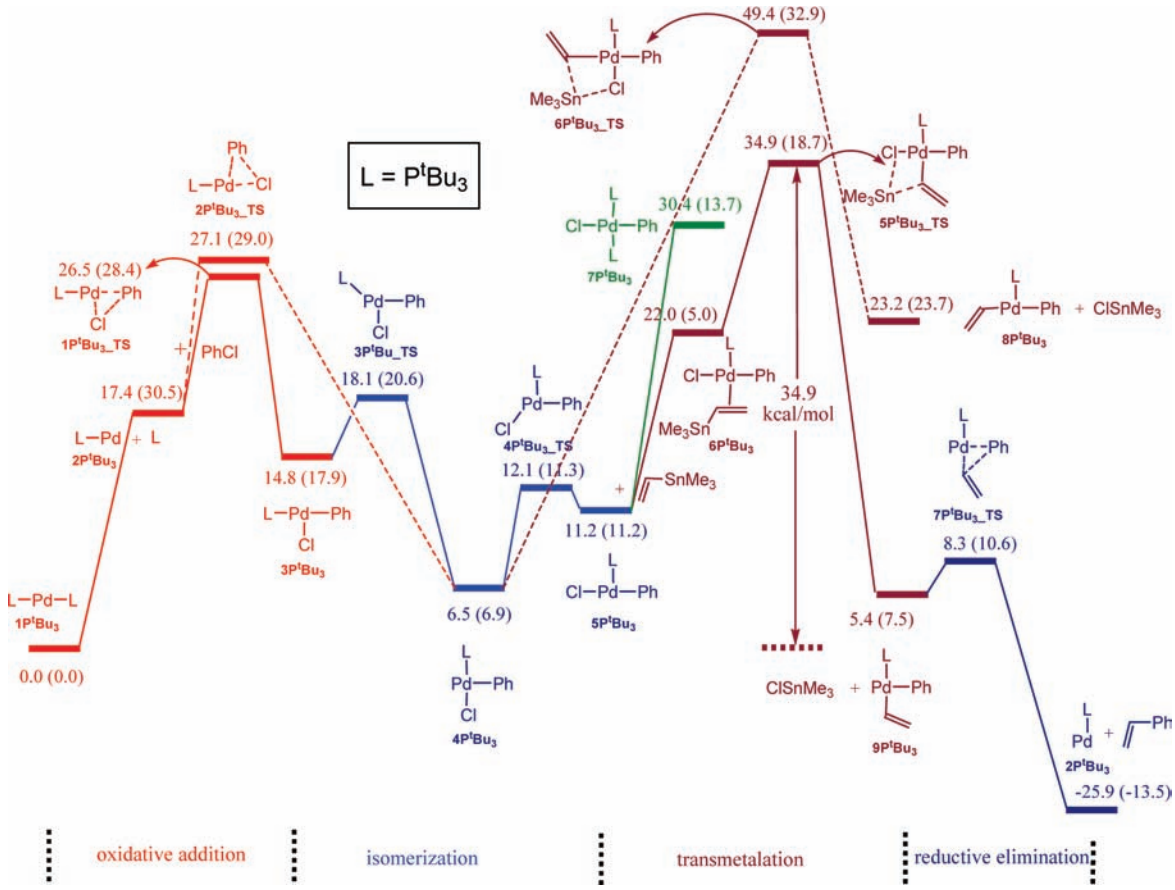

Figure 1. Energy profile calculated for the whole catalytic cycle of the Stille cross coupling reaction of PhCl catalyzed by PdL_2 where $L = P^tBu_3$. The relative free energies and potential energies (in parentheses) obtained from the B3LYP/BS2//B3LYP/BS1 calculations are given in kcal/mol.

through a monophosphine pathway in which $Pd(P^tBu_3)_2$ dissociates a P^tBu_3 ligand and then the resultant $Pd(P^tBu_3)$ intermediate undergoes the oxidative addition reaction.[23,24] The PhCl oxidative addition can proceed along two different pathways. One pathway leads to the formation of **3P^{t}Bu$_3$** via transition state **1P^{t}Bu$_3$_TS** and the other to the formation of **4P^{t}Bu$_3$** via transition state **2P^{t}Bu$_3$_TS** (Figure 1). **1P^{t}Bu$_3$_TS** is only 0.6 kcal/mol lower in energy than **2P^{t}Bu$_3$_TS**. It appears that, in **1P^{t}Bu$_3$_TS**, the existence of the σ donor P^tBu_3 ligand in the trans position to Ph facilitates the charge transfer from metal to the π^* and σ^* orbitals of Ph−Cl, slightly lowering the barrier for the formation of **3P^{t}Bu$_3$**. In contrast, the T-shaped intermediate **3P^{t}Bu$_3$** is found to lie 8.3 kcal/mol above the T-shaped intermediate **4P^{t}Bu$_3$**, a result attributed to the trans arrangement of the two strongly trans-influencing ligands P^tBu_3 and Ph in **3P^{t}Bu$_3$**. The kinetic intermediate **3P^{t}Bu$_3$** can also isomerize to **4P^{t}Bu$_3$** by moving L through the Y-shaped transition state **3P^{t}Bu$_3$_TS**. The activation barrier for the isomerization of **3P^{t}Bu$_3$** to **4P^{t}Bu$_3$** is calculated to be very low (3.3 kcal/mol). **4P^{t}Bu$_3$** is also able to undergo an isomerization reaction via the transition state **4P^{t}Bu$_3$_TS** by overcoming a barrier of 5.6 kcal/mol to reach **5P^{t}Bu$_3$**. **5P^{t}Bu$_3$** is less stable than **4P^{t}Bu$_3$** mainly due to steric effects; the bulky P^tBu_3 ligand in **5P^{t}Bu$_3$** is placed in a more crowded environment (vide infra). The higher stability calculated for **4P^{t}Bu$_3$** as compared to **3P^{t}Bu$_3$** and **5P^{t}Bu$_3$** is further supported by experimental data reported by Hartwig and co-workers. They found that the oxidative addition of ArX to $Pd(P^tBu_3)_2$ gives the arylpalladium halide complex $(P^tBu_3)Pd(Ar)(X)$ with Ar being *trans* to the vacant coordination site.[25] It is generally believed that the vacant coordination site in such systems is occupied by an agostic interaction with a γ−C-H bond on the P^tBu_3 ligand.[25] The H−Pd and C−H distances in **4P^{t}Bu$_3$** are calculated as 2.507 and 1.099 Å, respectively, suggesting a weak γ-agostic interaction.

As stated above, in the presence of an electronegative leaving group such as chloride, the transmetalation step proceeds preferentially via a cyclic pathway instead of an open pathway.[26] Therefore, the next step is surmised to be the coordination of (vinyl)$SnMe_3$ to Pd. $SnMe_3$ is used to model $SnBu_3$ frequently used in the experiment. The intermediates **4P^{t}Bu$_3$** and **5P^{t}Bu$_3$** having a vacant site in the cis position to Cl are expected to be the active reactant species for the transmetalation reaction. The (vinyl)$SnMe_3$ binds weakly to Pd in **5P^{t}Bu$_3$** to form the π-complex **6P^{t}Bu$_3$**, because of the steric hindrance of the P^tBu_3 group. The steric effect exerted by P^tBu_3 also causes the adduct between (vinyl)$SnMe_3$ and **4P^{t}Bu$_3$** not to correspond to a local minimum on the potential energy surface (PES). The coordination of (vinyl)$SnMe_3$ to Pd in **5P^{t}Bu$_3$** is an endergonic process

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because of the dominant contribution of the negative entropic term to the Gibbs free energy. The coordination of P^tBu_3 to Pd in **5P^{t}Bu$_3$** to form **7P^{t}Bu$_3$** is found to be even more endergonic (by 19.2 kcal/mol), highlighting the fact that palladium(II) complexes possessing a sterically hindered phosphine ligand such as P^tBu_3 are very reluctant to accept a fourth external ligand.[25,27]

The transmetalation process involves $SnMe_3$ migration from the π-bonded (vinyl)$SnMe_3$ group to the Cl ligand via a four-membered-ring transition state. No Me_3SnCl adducts are found as intermediates after the transmetalation transition state and the reaction forms the separated (P^tBu_3)Pd(Ph)(vinyl) and Me_3SnCl. The activation barriers and reaction energies for the transmetalation steps starting from **4P^{t}Bu$_3$** and **6P^{t}Bu$_3$** are presented in Figure 1. The results clearly show that the barrier for the conversion of **4P^{t}Bu$_3$** → **8P^{t}Bu$_3$** is about 14.5 kcal/mol higher than of the **6P^{t}Bu$_3$** → **9P^{t}Bu$_3$**. **9P^{t}Bu$_3$** is also 17.8 kcal/mol more stable than **8P^{t}Bu$_3$**. The product-like character of the transmetalation transition state, a result previously demonstrated by us,[8c] explains the greater stability of **5P^{t}Bu$_3$_TS** as compared to **6P^{t}Bu$_3$_TS**. In simple terms, the stabilities of **5P^{t}Bu$_3$_TS** and **6P^{t}Bu$_3$_TS** correlate well with those of **9P^{t}Bu$_3$** and **8P^{t}Bu$_3$**, respectively. The instability of **8P^{t}Bu$_3$** versus **9P^{t}Bu$_3$** is easily interpreted in terms of the trans arrangement of the two very strong trans-influencing ligands, Ph and vinyl, in **8P^{t}Bu$_3$**. Thus, the further consideration of the **4P^{t}Bu$_3$** → **6P^{t}Bu$_3$_TS** → **8P^{t}Bu$_3$** pathway can be ignored in the mechanistic study for energetic reasons. In the final step, Ph-vinyl is reductively eliminated from **9P^{t}Bu$_3$** with an energy barrier of 2.9 kcal/mol.

To summarize this section, the overall catalytic process for the cross coupling reaction is exergonic by −25.9 kcal/mol. Our calculations show that the maximum barrier height (34.9 kcal/mol[28] for the transition state **5P^{t}Bu$_3$_TS**) along the reaction pathway occurs for the transmetalation step. This result is in accord with experiment, which reports transmetalation is the rate-determining step for the Pd/P^tBu_3-catalyzed Stille cross coupling reaction of PhCl. These results further support the mechanism outlined in Scheme 1 and show that the sterically hindered P^tBu_3 ligand impedes transmetalation through a decrease in the tendency of the (P^tBu_3)Pd(Ph)(Cl) species to coordinate (vinyl)$SnMe_3$.

Steric Effect of the Phosphine Ligands on the Mechanism of the Stille Reaction. For the purpose of comparison, we also studied the Stille coupling reaction of PhCl catalyzed by $Pd(PPh_3)_2$ and $Pd(PMe_3)_2$.[29] However, it is necessary to mention that $Pd(PPh_3)_2$ and $Pd(PMe_3)_2$ are not the active species to oxidatively add PhCl to Pd(0) because they are reluctant to form the catalytically active monophosphine Pd(0) complexes.[24a] This is most likely due to the greater tendency of PdL_2 in solution, where L = PPh_3 and PMe_3, to become three coordinate (PdL_3) instead of mono coordinate (PdL).[29] Nevertheless, the relevant calculations provide a basis for comparison and verification of the phosphine steric effect on the catalytic reaction rate, especially on the transmetalation step. Phosphine cone angles have been proposed as quantitative measures of steric effects. The cone angles calculated by Tolman for P^tBu_3, PPh_3, and PMe_3 are 182, 145, and 118°, respectively, suggesting that the steric character of PR_3 should vary as follows: $P^tBu_3 > PPh_3 > PMe_3$.[30]

The energy profiles with PPh_3 (Figure 2) and PMe_3 (Figure 3) resemble that shown in Figure 1. As mentioned above, the first step of the catalytic reaction is proposed to be the oxidative addition of PhCl to $Pd(PPh_3)$/$PdPMe_3$ preceded by a phosphine dissociation from $Pd(PPh_3)_2$/$Pd(PMe_3)_2$. The ligand dissociations of phosphine from **1P^{t}Bu$_3$**, **1PPh$_3$**, and **1PMe$_3$** were calculated as 30.5, 30.5, and 32.1 kcal/mol, respectively (Figures 1−3). The similar values calculated for the phosphine dissociation energies can be attributed to the comparable electronic properties of all of the phosphine ligands since the steric repulsions in **1L**, where L = P^tBu_3, PPh_3, and PMe_3, are minimized by the low coordination numbers around Pd.

The computed activation barriers to the oxidative addition of PhCl to PdL_2 for L = P^tBu_3, PPh_3, and PMe_3 are 26.5, 26.3, and 31.2 kcal/mol, respectively. In comparison, the activation barrier heights for the oxidative addition reaction of PhCl to PdL are nearly independent of the type of L (the barriers for L = P^tBu_3, PPh_3, and PMe_3 are 9.1, 10.4, 10.1 kcal/mol, respectively). Therefore, the higher activation barrier for the reaction of **1PMe$_3$** + PhCl → **3PMe$_3$** + PMe_3, when compared to the analogues reactions involving the other phosphines, can be ascribed to the slightly stronger binding of PMe_3 to Pd in **1PMe$_3$**, mainly due to the electronic effects. A similar explanation has also been proposed in recent years by Liu and co-workers.[24c]

The influence of the nature of the phosphine ligands on the endergonicity of the oxidative addition reaction of **1L** + PhCl → **3L** + L is not considerable. In contrast, the heat of the reaction of **1L** + PhCl → **4L** + L is slightly affected by the steric bulkiness of the phosphine ligands (see Figures 1−3). The phosphine dissociation energies calculated in the Pd(II) complexes **4L** are 36.7 kcal/mol for **4P^{t}Bu$_3$**, 37.1 kcal/mol for **4PPh$_3$**, and 41.1 kcal/mol for **4PMe$_3$**. It follows from these results that the steric repulsion between the ligands should be small in the intermediate **4L**.

The relative stability of **5L** versus **4L** mainly depends on the steric hindrance provided by phosphines. The presence of bulkier phosphine ligands increases the instability of **5L** relative to **4L**. The steric effect is more significant in **5L** than in **4L** because in **5L** the phosphine ligand is cis to both the Ph and Cl ligands. The Cl−Pd−Ph angle is calculated to be smallest in **5P^{t}Bu$_3$** (144.0°) and greatest in **5PMe$_3$** (172.0°), indicating that the bulkier phosphine ligands force the Ph and Cl groups closer together (Figure 4).

(27) Even small coordinating solvents such as DMF and MeCN are not able to strongly bind to Pd in (P^tBu_3)Pd(Ar)(Cl) and to thermodynamically produce four coordinate complexes (see Table 1). For example, the ΔE and ΔG calculated for the coordination of MeCN to $4P^tBu_3$ based on the reaction outlined in Scheme 2 are 4.4 and 15.1 kcal/mol. The large positive value calculated for ΔG suggests that (P^tBu_3)Pd(Ar)(Cl) is reluctant to accept MeCN as the fourth ligand. A similar conclusion was also drawn by Espinet, Lledós and co-workers in a study on the THF coordination ability toward (P^tBu_3)Pd(Ar)(Br) (see ref 25b). They found a large positive value of ΔG for the THF coordination process, according to which they suggested a higher stability of (P^tBu_3)Pd(Ar)(Br) over (P^tBu_3)Pd(Ar)(Br)(THF).

(28) The free energy barrier in solution should be a few kcal/mol smaller than in the gas phase because in solution the rotational and translational motions are suppressed. (a) Tamura, H.; Yamasaki, H.; Sato, H.; Sakaki, S. *J. Am. Chem. Soc.* **2003**, *125*, 16114. (b) Sumimoto, M.; Iwane, N.; Takahama, T.; Sakaki, S. *J. Am. Chem. Soc.* **2004**, *126*, 10457. (c) Sakaki, S.; Takayama, T.; Sumimoto, M.; Sugimoto, M. *J. Am. Chem. Soc.* **2004**, *126*, 3332. (d) Braga, A. A. C.; Ujaque, G.; Maseras, F. *Organometallics* **2006**, *25*, 3647.

(29) Amatore, C.; Pflüger, F. *Organometallics* **1990**, *9*, 2276.

(30) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.

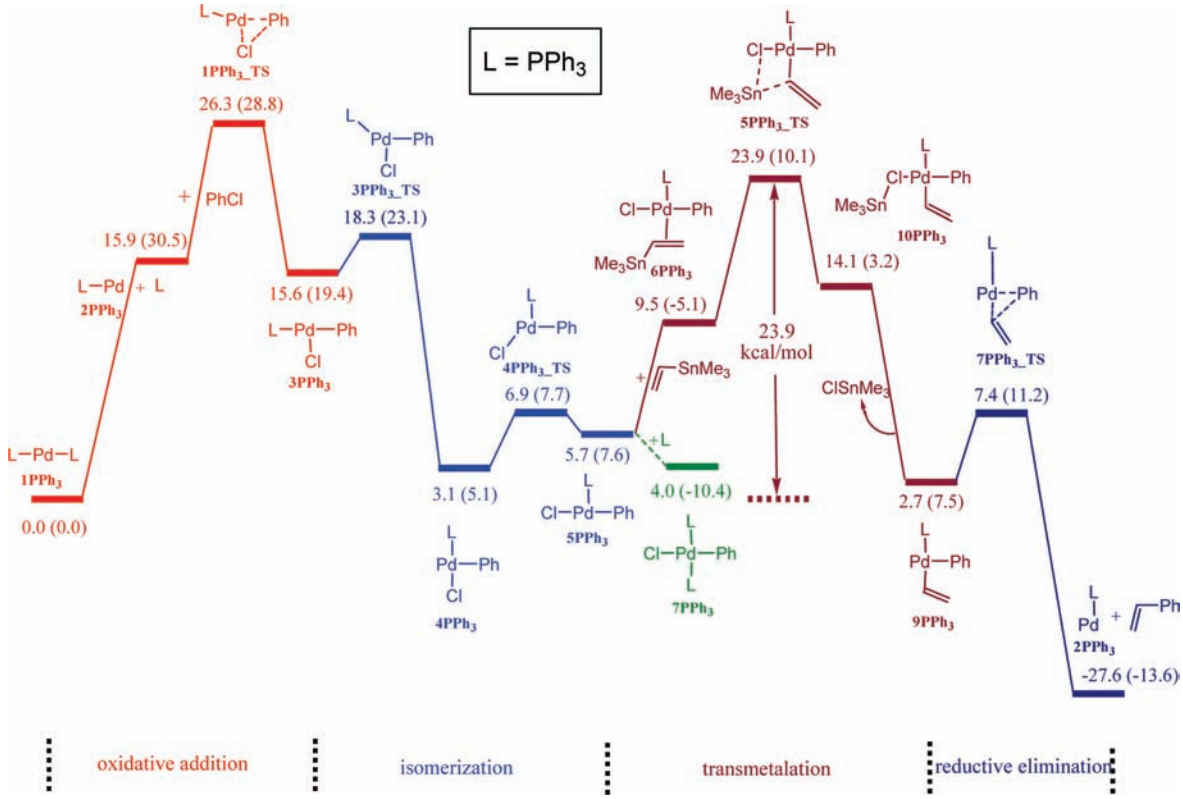


Figure 2. Energy profile calculated for the whole catalytic cycle of the Stille cross coupling reaction of PhCl catalyzed by PdL_2 where L = PPh_3. The relative free energies and potential energies (in parentheses) obtained from the B3LYP/BS2//B3LYP/BS1 calculations are given in kcal/mol. Experimentally, the oxidative addition of PhCl to Pd(0) with the phosphine ligands PPh_3 is expected to be more difficult than what is predicted here because $Pd(PPh_3)_2$ tends to be mainly three coordinate rather than mono coordinate.

In analogy to the oxidative addition process, the barrier to the reductive elimination of Ph-vinyl from **9L**[31] is nearly insensitive to the bulkiness of the L ligand (Figures 1−3). This result demonstrates that the steric repulsion between the L and Ph ligands is very small in the intermediate **9L**.

In contrast to the oxidative addition and reductive elimination processes, the overall activation barrier of the transmetalation process is strongly reliant on the bulkiness of the phosphine ligands (Figures 1−3). The lowest activation barrier is observed for L = PPh_3 with an activation free energy of 23.9 kcal/mol (Figure 2). Due to the formation of the stable intermediate **7PMe$_3$**, the transmetalation process for the case of L = PMe_3 is the most energy demanding with an activation free energy of 35.8 kcal/mol (the energy difference between **7PMe$_3$** and **5PMe$_3$_TS** in Figure 3).

For the case of L = P^tBu_3, the coordination of (vinyl)$SnMe_3$ to Pd weakens considerably the Pd-L interaction as indicated by an increase in the Pd-L distance (0.228 Å) on going from **5P^{t}Bu$_3$** to **6P^{t}Bu$_3$** (Figure 4). Indeed, the π-complexation of (vinyl)$SnMe_3$ widens the Cl−Pd−Ph angle from 144.0° in **5P^{t}Bu$_3$** to 168.1° in **6P^{t}Bu$_3$**, increasing the repulsive interaction between the P^tBu_3 ligand and the Cl and Ph ligands, subsequently making the reaction of **5P^{t}Bu$_3$** + (vinyl)$SnMe_3$ → **6P^{t}Bu$_3$** very endergonic. P^tBu_3 binding to Pd to form **7P^{t}Bu$_3$** is an even more endergonic process since the P^tBu_3 is sterically much more demanding than (vinyl)$SnMe_3$. Thus, as discussed above, the reluctance of **5P^{t}Bu$_3$** to coordinate to (vinyl)$SnMe_3$ results in an increase in the transmetalation barrier.

Replacement of P^tBu_3 by a less bulky PPh_3 group leads to the stabilization of the **6L** and **7L** intermediates relative to the initial reactants. The stabilization is even greater for **7L** compared to **6L**; **7PPh$_3$**[32] is now 5.0 kcal/mol lower in energy than **6PPh$_3$**. The Cl−Pd−Ph angle in **5PPh$_3$** is 161.0° showing that the vacant coordination site in **5PPh$_3$** is more available for binding an incoming ligand than in **5P^{t}Bu$_3$**. The Pd−P bond lengthening on going from **5L** to **6L** is less pronounced for L = PPh_3 (0.125 Å) than for L = P^tBu_3 (0.228 Å) (Figure 4). These results indicate that the less sterically demanding PPh_3 ligand enhances the binding capability of the Pd metal center in **5PPh$_3$**, which in turn reduces the transmetalation barrier. This reduction brings the transmetalation barrier down to 23.9 kcal/mol and causes the oxidative addition reaction to be rate determining step (Figure 2).

Compared to **5P^{t}Bu$_3$** and **5PPh$_3$**, both the phosphine and stannane ligands bind more strongly to **5PMe$_3$** (Figure 3) because the steric effect of phosphine in **5PMe$_3$** is negligible.

(31) We are aware of the fact that the Ph-vinyl reductive elimination occurs preferentially through four coordinate complexes when L is not a very bulky ligand (see below reference). To simplify the comparison between the energy profiles given in Figures 1−3, we have restricted our analysis solely to the reductive elimination reaction from three coordinate complexes. This choice does not affect the conclusions drawn, because the Ph-vinyl reductive elimination reaction from a Pd(II) complex is very fast: Brown, J. M.; Cooley, N. A. *Chem. Rev.* **1988**, *88*, 1031.

(32) Although the reaction of 1PPh_3+ PhCl → 7PPh_3 is an exothermic process (ΔE =−10.4 kcal/mol), inclusion of the entropic effect causes this process to be endergonic (ΔG = 4.0 kcal/mol). We believe that the entropic contribution associated with the formation of 7PPh_3 is overestimated in the calculation (see ref 28 for the further information). In other words, the actual contribution of the entropic term to the Gibbs free energy should be less negative than what is calculated here. Therefore, it is expected that if the oxidative addition reaction of PhCl to $Pd(PPh_3)_2$ occurs, the product is most likely to be four coordinated.

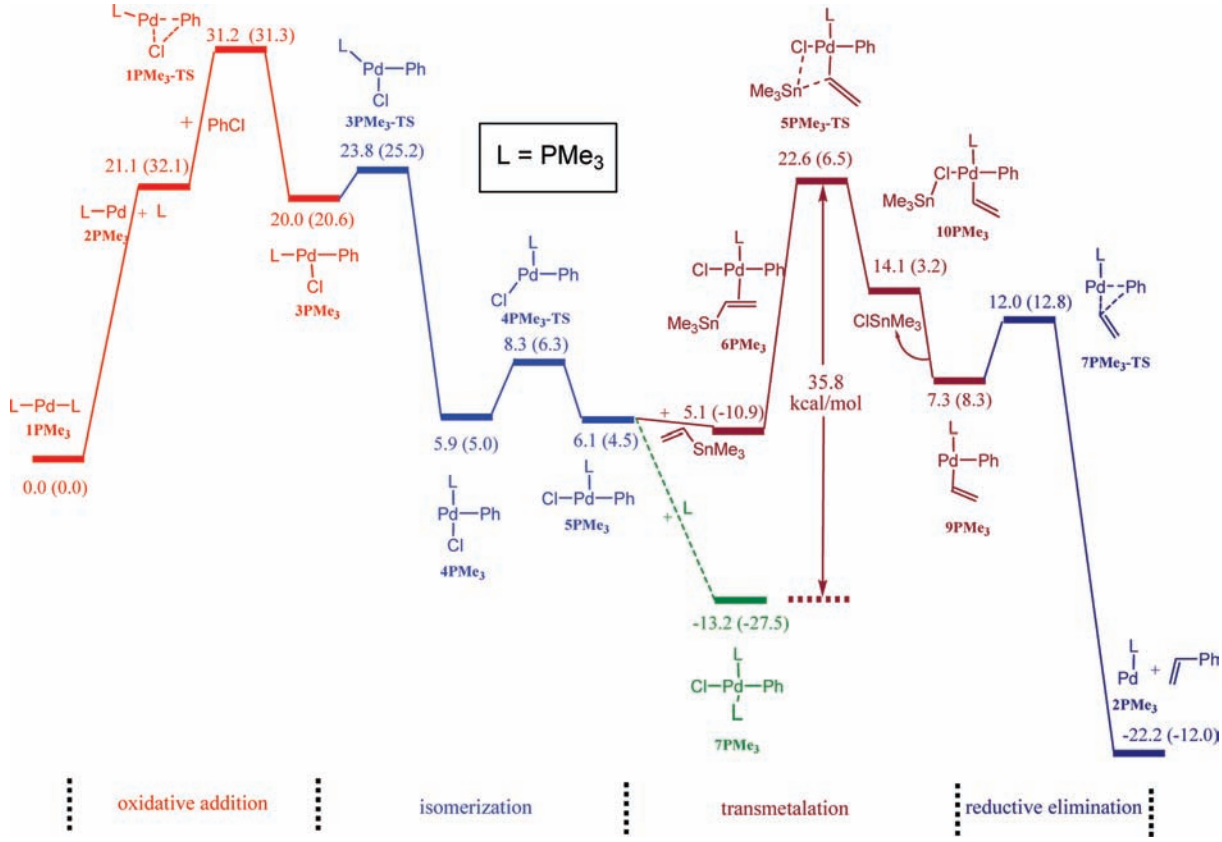


Figure 3. Energy profile calculated for the whole catalytic cycle of the Stille cross coupling reaction of PhCl catalyzed by PdL_2 where L = PMe_3. The relative free energies and potential energies (in parentheses) obtained from the B3LYP/BS2//B3LYP/BS1 calculations are given in kcal/mol. Experimentally, the oxidative addition of PhCl to Pd(0) with the phosphine ligands PMe_3 is expected to be more difficult than what is predicted here because $Pd(PMe_3)_2$ tends to be mainly three coordinate rather than mono coordinate.

The Pd−P bond in **6PMe$_3$** is much stronger than in **6P^{t}Bu$_3$** and **6PPh$_3$** as evidenced from the shorter Pd−P bond in **6PMe$_3$** (Figure 4) as well as the calculated Pd−P bond dissociation energies. The Pd−P bond energies are computed as 18.1, 26.9, and 36.6 kcal/mol in **6P^{t}Bu$_3$**, **6PPh$_3$**, **6PMe$_3$**, respectively. The formation of **7PMe$_3$** is, however, energetically much more favorable than formation of **6PMe$_3$**, mainly due to the stronger Pd-PMe_3 bond. **7PMe$_3$** acts as a moderate thermodynamic sink thereby making it difficult for the (vinyl)$SnMe_3$-for-PMe_3 substitution reaction to proceed. As a result, the large endergonicity predicted for the substitution reaction of a PMe_3 in **7PMe$_3$** by (vinyl)$SnMe_3$ (18.3 kcal/mol) is the main reason why a relatively high barrier for the transmetalation process of L = PMe_3 (35.8 kcal/mol) is estimated.[33]

In summary, the above theoretical analysis shows that in the cross-coupling reactions it is necessary to use L with a steric bulk which gives the right balance between coordination of the L and (vinyl)$SnMe_3$ ligands. L = PMe_3 gives very strong coordination of phosphine while L = P^{t}Bu$_3$ gives very weak coordination of (vinyl)$SnMe_3$. L = PPh_3 seems to fit somewhere in the middle and provides the optimum balance, leading to a moderate activation barrier for the transmetalation process. This is the reason why, in many of the Stille cross coupling reactions, PPh_3 is employed as a ligand. It also becomes obvious from our calculations that, in theoretical studies, if the steric effect introduced by the phosphines is significant, using PMe_3 as a model for PPh_3 does not provide accurate results. This argument finds further support from other studies which investigated the steric effect of phosphine ligands on the mechanism of R-R reductive elimination from Pd(II) complexes. Those studies indicated that replacing the PMe_3 ligands with PPh_3 facilitates the reductive elimination process.[34]

Steric Effect of the Phosphine Ligands on the Ease of the Reaction of 6L → 9L + ClSnMe$_3$. From inspection of Figures 1−3, one can also find that the energy gap between **6_L** and **5L_TS** lowers as L becomes more bulky, 12.9, 14.4, and 17.5 kcal/mol for L = P^{t}Bu$_3$, PPh_3, and PMe_3, respectively. It is well-known that the barrier height for the reaction of LPd(vinyl$SnMe_3$)(Ph)X → LPd(vinyl)(Ph) + $SnMe_3$X is affected by the electron donating ability of L; the stronger the σ-donor phosphine ligands, the higher the activation barrier.[8c] It is expected that the trans arrangement of the vinyl and L ligands in **5L_TS** (a product-like transition structure), when L is a strong σ-donor ligand, weakens the Pd-L bond more effectively, enhancing the activation barrier (vinyl is a strong trans influencing ligand). As described above, if L is sterically more demanding, it binds to Pd more weakly in a four coordinate complex. A positive correlation is also expected between the

(33) Although the strong coordination of (vinyl)$SnMe_3$ brings 5PMe$_3$−TS energetically below 1PMe$_3$−TS (Figure 3), the transmetalation reaction is still the rate determining step. In other words, our calculations predict a lower activation barrier for the transmetalation than the oxidative addition (about 4.6 kcal/mol), because the (vinyl)SnMe3-for-PMe_3 substitution reaction is highly endergonic.

(34) (a) Ananikov, V. P.; Musaev, D. G.; Morokuma, K. *Eur. J. Inorg. Chem.* **2007**, 5390. (b) Pérez-Rodríguez, M.; Braga, A. A. C.; Garcia-Melchor, M.; Pérez-Temprano, M. H.; Casares, J. A.; Ujaque, G.; Lera, A. R.; de; Alvarez, R.; Maseras, F.; Espinet, P. *J. Am. Chem. Soc.* **2009**, *131*, 3650. (c) Ariafard, A.; Yates, B. F. *J. Organomet. Chem.* **2009**, *694*, 2075.

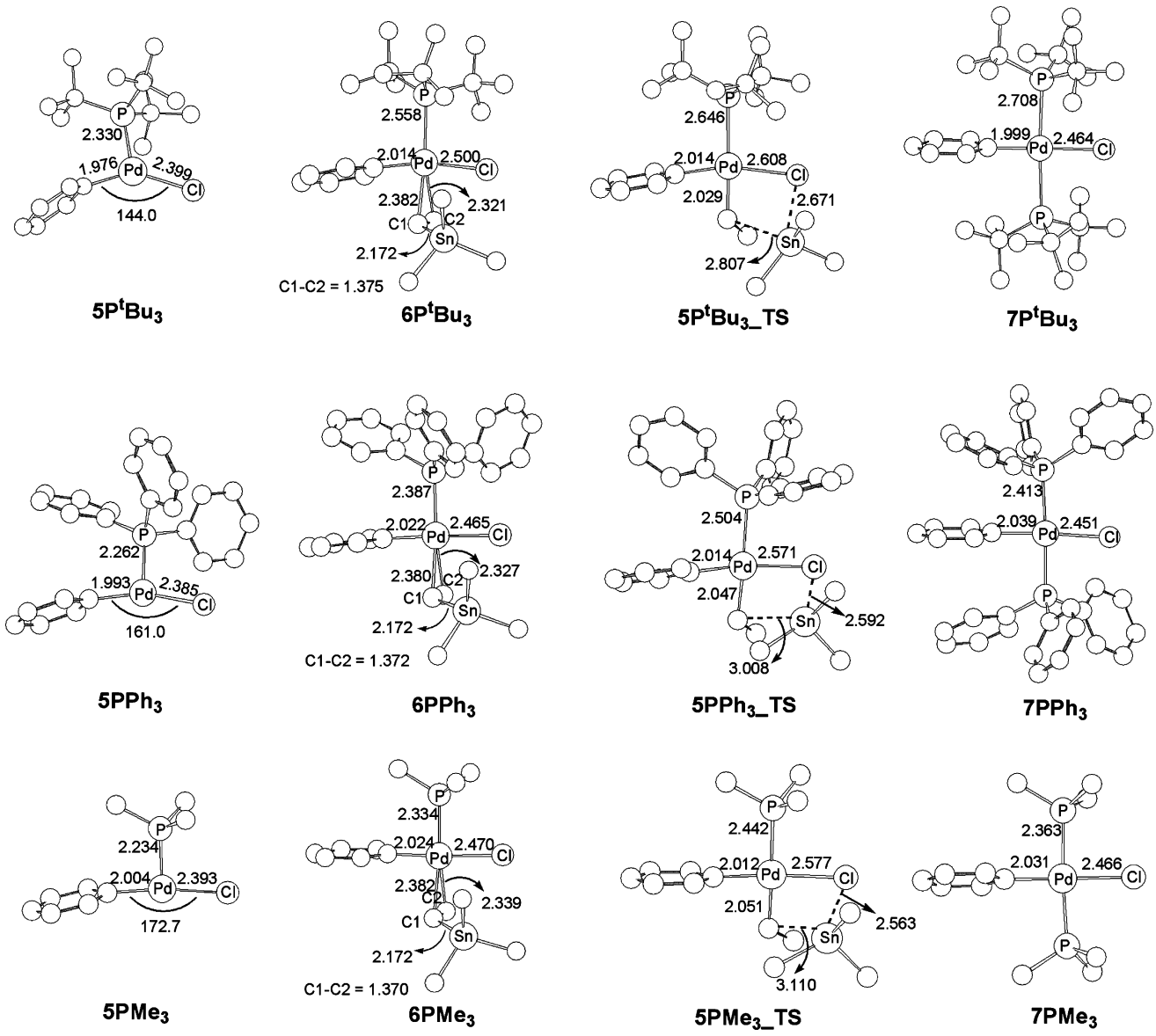


Figure 4. Optimized structures with selected structural parameters (bond length in Å and bond angle in °) for **5L**, **6L**, **5L_TS**, and **7L** where L = P^{t}Bu$_3$, PPh$_3$, and PMe$_3$. All hydrogen atoms have been omitted for the sake of clarity.

Table 1. Energetic Changes for the Binding of Solvents (Dioxane, DMF, and MeCN) and Phosphines Based on the Reactions Designed in Scheme 2[a]

L	$\Delta E_L(1)$	$\Delta E_L(2)$	$\Delta E_{dioxane}(1)$	$\Delta E_{dioxane}(2)$	$\Delta E_{DMF}(1)$	$\Delta E_{DMF}(2)$	$\Delta E_{MeCN}(1)$	$\Delta E_{MeCN}(2)$
P^{t}Bu$_3$	*b*	30.4 (13.7)	22.2 (8.1)	20.5 (6.6)	15.1 (2.1)	20.6 (7.3)	15.1 (4.4)	15.2 (3.8)
PPh$_3$	15.3 (0.0)	4.0 (−10.4)	11.2 (−1.3)	12.1 (−0.7)	3.7 (−7.9)	5.9 (−6.2)	6.3 (−4.2)	4.0 (−6.3)
PMe$_3$	0.2 (−15.5)	−13.4 (−27.1)	9.4 (−4.0)	7.0 (−6.4)	5.6 (−7.5)	1.4 (−11.9)	4.9 (−6.2)	1.1 (−9.9)

[a] The relative free energies and potential energies (in parentheses) obtained from the B3LYP/BS2//B3LYP/BS1 calculations are given in kcal/mol. [b] The *cis*-(P^{t}Bu$_3$)$_2$Pd(Ph)(Cl) isomer is not a minimum on the potential energy surface.

Pd−L bond strength and the σ-donating ability of L.[35] Therefore, the easier conversion of **6L** → **8L** for the bulkier systems can be rationalized in terms of the decreased σ-donating ability of L in **5L_TS**.

(35) We have recently shown that the contribution of the phosphine-to-Pd σ-donation to the strength of Pd-phosphine bonding in Pd(II) complexes is much more important than of the Pd-to-phosphine π-back bonding (see below reference). It is thus reasonable to expect a positive correlation between the ó-donating ability of phosphines and the Pd-phosphine bond energies: Fazaeli, R.; Ariafard, A.; Jamshidi, S.; Tabatabaie, E. S.; Pishro, K. A. *J. Organomet. Chem.* **2007**, *692*, 3984.

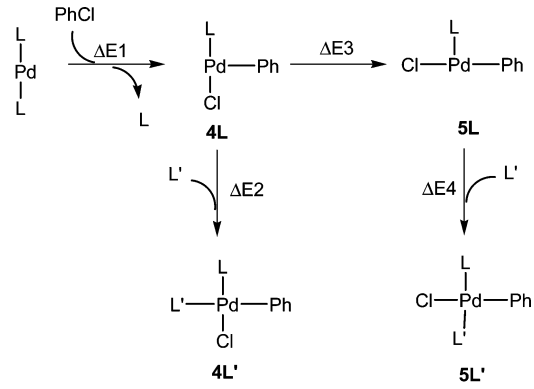
Explicit Addition of Coordinating Solvents. In solution, the coordinating solvents can react with the complexes **4L** and **5L** to form the four coordinate solvated complexes shown in Scheme 2. It is expected that a very strong coordination of solvent retards the transmetalation process. Table 1 compares the energetics of the formation of solvated complexes, where the solvents are dioxane, dimethylformamide (DMF), and MeCN, with the cis and trans phosphine complexes $(L)_2Pd(Ph)(Cl)$ based on the reactions shown in Scheme 2. Several trends are obvious from Table 1. First, the bulkiness of

Table 2. Calculated Free and Potential Energies (In Parentheses) for **4L**, **5L**, **6L**, **7L**, and **5L_TS** Relative to **1L**, where L = PPh_2Me and $PPhMe_2$, in the Stille Reaction of PhCl[a]

L	1L	4L	5L	6L	7L	5L_TS	calculated barrier for the transmetalation
PPh_2Me	0.0 (0.0)	6.2 (5.9)	6.3 (6.1)	9.5 (−7.6)	−4.7 (−21.0)	23.6 (7.9)	28.3 (28.9)
$PPhMe_2$	0.0 (0.0)	5.8 (5.7)	5.4 (4.7)	6.1 (−9.6)	−10.1 (−25.3)	23.3 (7.2)	34.4 (34.9)

[a] All relative energies are obtained from the B3LYP/BS2//B3LYP/BS1 calculations and are given in kcal/mol.

Scheme 2



$$\Delta E_{L'}(1) = \Delta E1 + \Delta E2$$

$$\Delta E_{L'}(2) = \Delta E1 + \Delta E3 + \Delta E4$$

L strongly influences the Pd-solvent binding energies. A less bulky phosphine ligand enhances the solvent coordination. Second, for a given L, the trans $(L)_2Pd(Ph)(Cl)$ complex is more stable than the cis complex. Third, for the cases of L = PPh_3 and PMe_3 the formation of the solvated complexes is energetically less favorable than the formation of the trans complex $L_2Pd(Ph)(Cl)$ while for the case of L = P^tBu_3 the solvent coordination is more preferred. Fourth, the positive values of the Gibbs free energies for the solvent complexes suggest that none of them would be thermodynamically stable. Fifth, for a given L, MeCN and DMF bind more tightly than the sterically more demanding dioxane. From these trends, it is therefore concluded that the inclusion of coordinating solvents should not significantly affect the transmetalation barriers predicted in Figures 1−3.

Transmetalation for the Cases of L = PPh_2Me and $PPhMe_2$. Further fine-tuning of L can be carried out by considering ligands such as L = PPh_2Me and $PPhMe_2$. The steric effect of the phosphine ligands increases in the order $PPhMe_2 < PPh_2Me < PPh_3$. The relative energies for some selected intermediates and **5L_TS** where L = PPh_2Me and $PPhMe_2$ are presented in Table 2. The transmetalation barriers for both cases are higher than for L = PPh_3 because the (vinyl)$SnMe_3$-for-L substitution reactions for L = $PPhMe_2$ (16.2 kcal/mol) and PPh_2Me (14.2 kcal/mol) are much more energy demanding than for L = PPh_3 (5.5 kcal/mol). This result finds further support from experimental findings of Farina[11] who has shown that reactivity of Pd(II)/PPh_3 toward transmetalation is much higher than Pd(II)/PPh_2Me.

The barrier from **6 L** for *L* = PPh_2Me (14.1 kcal/mol) is larger than for *L* = $PPhMe_2$ (17.2 kcal/mol) because in **6PPh$_2$Me** the phosphine ligand binds more strongly. The Pd−P bond dissociation energy for **6PPh$_2$Me** and **6PPhMe$_2$** is calculated to be 30.8 and 34.7 kcal/mol, respectively.

Solvent Effect on Transmetalation of (vinyl)$SnMe_3$ with (P^tBu_3)Pd(Ph)(Cl). The solvent effect on the transmetalation step was studied using the CPCM model with dioxane as the solvent.

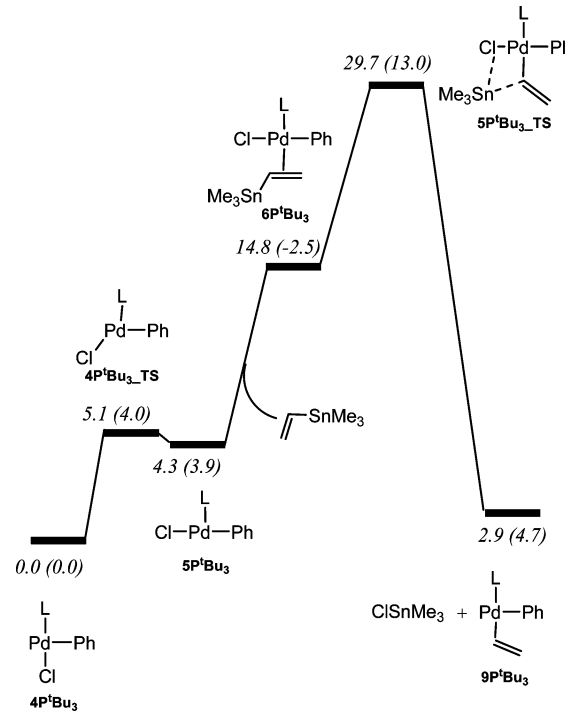


Figure 5. Solvent effect on the potential energy profiles calculated for the transmetalation of **4P^{t}Bu$_3$** with (vinyl)$SnMe_3$ with the use of dioxane as solvent. The relative potential energies (ΔE_{solv}) (in parentheses) and free energies (ΔG_{solv}) obtained from the B3LYP/BS2//B3LYP/BS1 calculations with inclusion of the solvent effect are given in kcal/mol.

A potential energy surface similar to that in the gas phase was obtained in dioxane (Figure 5). Our calculations show that the solvent effect for this reaction is very small; the incorporation of solvent effects changes the activation barrier of transmetalation from 28.4 (11.9) kcal/mol in the gas phase to 29.7 (13.0) kcal/mol in the solvent phase.

Accelerating Role of CsF in the Transmetalation Reaction between (vinyl)$SnMe_3$ and (P^tBu_3)Pd(vinyl)(Ph). Our results confirm that transmetalation is the rate determining step in the Stille cross-coupling reaction catalyzed by $Pd(P^tBu_3)_2$. As mentioned above, Fu and co-workers[10b] showed that the addition of CsF increases the reactivity of stannane reagents toward the transmetalation. With consideration of the explicit solvent effect, our calculations predict that the ionic pair CsF is mainly dissociated in solution (for further information see the Supporting Information). We propose two variants for the transmetalation reaction in the presence of the fluoride anion.[36] The first case (case A) involves the reaction of F^- with the complex (P^tBu_3)Pd(Cl)(Ph) followed by the dissociation of chloride. In such a case, the transmetalation occurs between the fluoro

(36) These two variants are very similar to those explored by Sakaki and coworkers in a study on the role of the fluoride anion in the transmetalation acceleration between vinylsilane and $(PMe_3)_2Pd(I)(Ph)$: Sugiyama, A.; Ohnishi, Y.-y.; Nakaoka, M.; Nakao, Y.; Sato, H.; Sakaki, S.; Nakao, Y.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 12975.

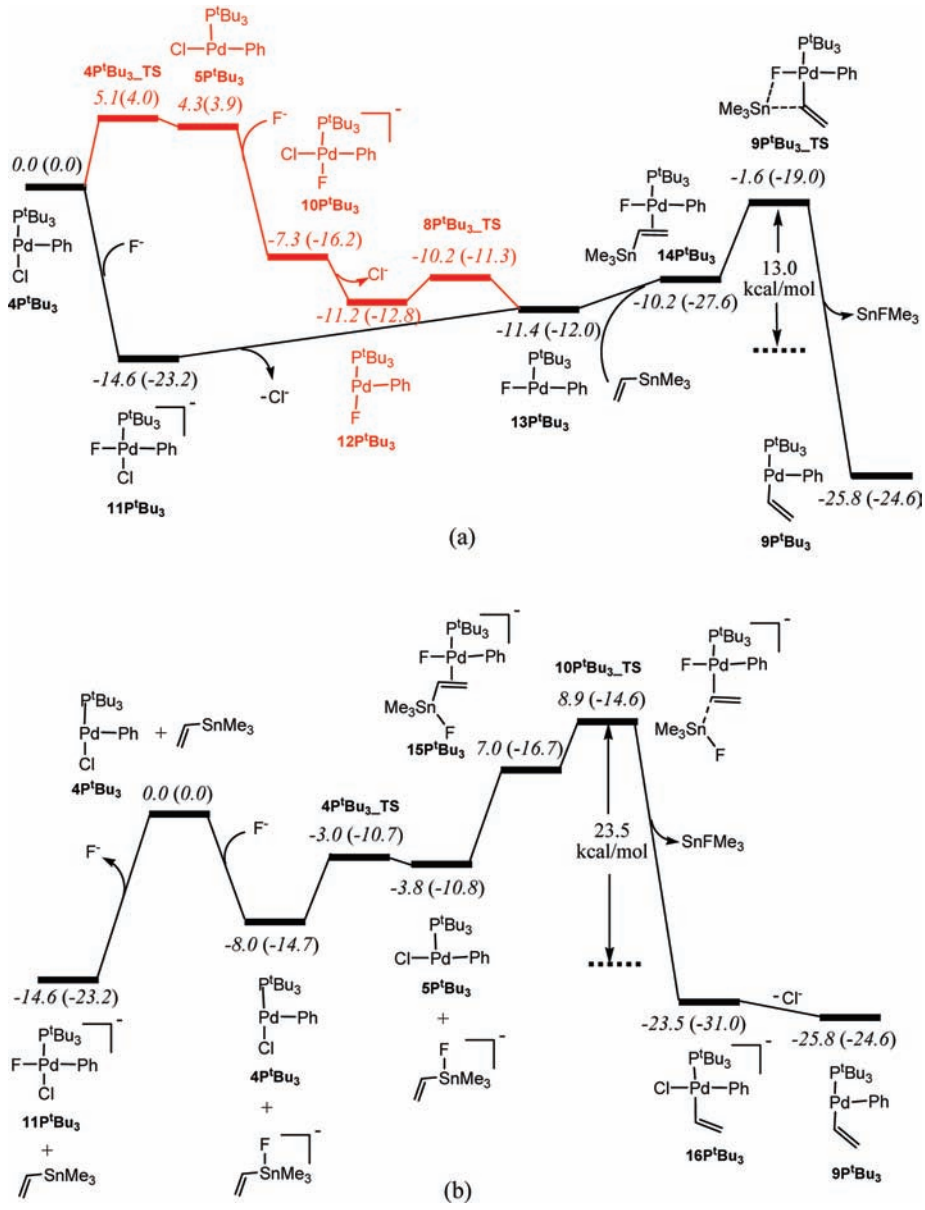


Figure 6. Solvent effect on the potential energy profiles calculated for the transmetalation of **4P^{t}Bu$_3$** with (vinyl)SnMe$_3$ with the use of dioxane as solvent in the presence of F$^-$ for (a) case A and (b) case B. The relative potential energies (ΔE_{solv}) (in parentheses) and free energies (ΔG_{solv}) obtained from the B3LYP/BS2//B3LYP/BS1 calculations with inclusion of the solvent effect are given in kcal/mol.

complex (P^{t}Bu$_3$)Pd(F)(Ph) and (vinyl)SnMe$_3$ (Figure 6a). The second case (case B) is promoted by the reaction of fluoride with (vinyl)SnMe$_3$ to give the anionic species [(vinyl)Sn(Me)$_3$(F)]$^-$. This anion then binds to **5P^{t}Bu$_3$** and undergoes the transmetalation reaction through breaking of the vinyl−Sn(Me)$_3$(F) bond (Figure 6b). Comparing Figures 5 and 6, we can see that the inclusion of the fluoride anion decreases the transmetalation barrier and increases the exergonicity of the reaction. Since charge separation occurs during the course of the transmetalation accelerated by fluoride, solvent effects are very important. Therefore, the solvent effect on the potential and Gibbs free energies is included in the reaction energy profiles shown in Figure 6. To investigate the fluoride effect, the relative potential (ΔE_{solv}) and Gibbs free energies (ΔG_{solv}) in Figure 6 were obtained from the gas-phase energies by incorporating the solvation energies from single-point calculations (see Computational Detail for further explanation).

Case A. As can be seen from Figure 6a, the addition of F$^-$ to **4P^{t}Bu$_3$** and **5P^{t}Bu$_3$** yields **11P^{t}Bu$_3$** and **10P^{t}Bu$_3$**, respectively. The reaction of F$^-$ with **4P^{t}Bu$_3$** is more exergonic than with **5P^{t}Bu$_3$**. The much higher stability of **11P^{t}Bu$_3$** versus **10P^{t}Bu$_3$** can be understood in terms of the steric repulsive interaction between P^{t}Bu$_3$ and the halide group cis to P^{t}Bu$_3$. The larger size of the Cl ligand in **10P^{t}Bu$_3$** results in stronger repulsion and hence destabilization of **10P^{t}Bu$_3$** relative to **11P^{t}Bu$_3$**. This argument is supported through the comparison of the energetics calculated for **10PMe$_3$** and **11PMe$_3$**. Since PMe$_3$ is sterically much less demanding than P^{t}Bu$_3$, **10PMe$_3$** lies only 0.5 kcal/mol above **11PMe$_3$**.

The active precursor species for transmetalation is **13P^{t}Bu$_3$** which is generated from **10P^{t}Bu$_3$** or **11P^{t}Bu$_3$** by the loss of the Cl$^-$ ligand. The chloride dissociation from **10P^{t}Bu$_3$** and **11P^{t}Bu$_3$** gives **12P^{t}Bu$_3$** and **13P^{t}Bu$_3$**, respectively. **13P^{t}Bu$_3$** has a comparable stability as **12P^{t}Bu$_3$** because the steric repulsion

between P^tBu_3 and F^- in **13P^{t}Bu$_3$** is not significant. **11P^{t}Bu$_3$** is moderately stable with respect to decomposition into Cl^- and **13P^{t}Bu$_3$**. **10P^{t}Bu$_3$** is easily dissociated into Cl^- and **12P^{t}Bu$_3$** and then **12P^{t}Bu$_3$** undergoes an intramolecular rearrangement via the low energy transition state **8P^{t}Bu$_3$_TS** to produce **13P^{t}Bu$_3$**. We think that the preference for the formation of **12P^{t}Bu$_3$** over **4P^{t}Bu$_3$** comes from the stronger Pd−F bond (94.0 kcal/mol) in **12P^{t}Bu$_3$** as compared to the Pd−Cl bond (79.4 kcal/mol) in **4P^{t}Bu$_3$** (the heterolytic Pd-X bond dissociation energies were calculated at the B3LYP/BS2//B3LYP/BS1 level). A similar explanation was recently proposed by Sakaki and coworkers in a study on the role of fluoride anion in the transmetalation process between vinylsilane and palladium(II)-vinyl complex.[36]

13P^{t}Bu$_3$ then coordinates (vinyl)$SnMe_3$ to give the π-complex **14P^{t}Bu$_3$**. Our calculations (provided in the Supporting Information) also show that dioxane (solvent) and P^tBu_3 act as poor ligands and thus can be easily replaced by (vinyl)$SnMe_3$. The π-complexation energy of (vinyl)$SnMe_3$ in **14P^{t}Bu$_3$**(−15.6 kcal/mol, Figure 6a) is far larger than in **6P^{t}Bu$_3$** (−6.4 kcal/mol, Figure 5). This finding can be rationalized on the basis of the steric repulsion between the halide group and (vinyl)$SnMe_3$ being smaller in **14P^{t}Bu$_3$** (Figure 6) than in **6P^{t}Bu$_3$**. Indeed, the vacant coordination site in **13P^{t}Bu$_3$** is more available for binding than in **5P^{t}Bu$_3$**; the P−Pd−F angle of 160.3° in **13P^{t}Bu$_3$** is much wider than the P−Pd−Cl angle of 144.0° in **5P^{t}Bu$_3$**. A similar reasoning was also used by us to explain the trend in the π-complexation energy of (vinyl)$SnMe_3$ in the model complexes (PH_3)(vinyl$SnMe_3$)Pd(X)(Ph) where X = Cl, Br, I.[8c]

Starting from **14P^{t}Bu$_3$**, the transmetalation reaction through the transition state **9P^{t}Bu$_3$_TS** leads to the formation of $FSnMe_3$ and **9P^{t}Bu$_3$**. Comparison of the energy profiles given in Figures 6a and 5 shows that the transmetalation of **14P^{t}Bu$_3$** is both kinetically and thermodynamically favored over the transmetalation of **6P^{t}Bu$_3$**. This is in consistent with the Bell-Evans-Polanyi principle[37] in which more exothermic reactions have lower lying transition states. Indeed, fluoride as a leaving group facilitates the transmetalation by forming the strong Sn−F bond (for further information, see the Supporting Information).

These results demonstrate that the transmetalation of (vinyl)-$SnMe_3$ with (P^tBu_3)Pd(X)(Ph) is much easier when using fluoride as a leaving group than when using chloride. The factors contributing to the decrease (by 19.9 kcal/mol) in the overall transmetalation barrier from the case of *X* = F to Cl are as follows: (i) the sterically less demanding nature of fluoride, (ii) the stronger coordination of (vinyl)$SnMe_3$ to (P^tBu_3)Pd(F)(Ph), and (iii) the more facile transmetalation process for the case of fluoride.

Case B. As mentioned above, case **B** starts with the coordination of F^- to the Sn center of (vinyl)$SnMe_3$ to give [(vinyl)(F)-$SnMe_3$]$^-$. This reaction is however less exergonic than the reaction of F^- with **4P^{t}Bu$_3$** (Figure 6b). The Gibbs free energy for the reaction of F^- with (vinyl)$SnMe_3$ is calculated to be −8.0 kcal/mol. The corresponding reaction can then proceed via the formation of **15P^{t}Bu$_3$** preceded by the isomerization of **4P^{t}Bu$_3$** to **5P^{t}Bu$_3$**. The binding of [(vinyl)(F)$SnMe_3$]$^-$ to **5P^{t}Bu$_3$** is an endergonic process. The transmetalation reaction from **15P^{t}Bu$_3$** via transition state **10P^{t}Bu$_3$_TS** to **16P^{t}Bu$_3$**is highly exergonic (30.5 kcal/mol) with a low free energy barrier of 1.9 kcal/mol. The high exergonicity and the low activation free energy for the reaction of **15P^{t}Bu$_3$**→ **16P^{t}Bu$_3$** + $FSnMe_3$ suggest an earlier transition structure for **10P^{t}Bu$_3$_TS** than for **5P^{t}Bu$_3$_TS** (Figures 4 and 6). The Sn−C1 distance in **10P^{t}Bu$_3$_TS** is 0.274 Å shorter than in **5P^{t}Bu$_3$_TS** while the Pd−C1 distance in **10P^{t}Bu$_3$_TS** is 0.242 Å longer. In the final step, Cl^- is easily eliminated from **16P^{t}Bu$_3$** and forms **9P^{t}Bu$_3$**.

Our overall results for case **B** confirm that the accelerating effect of F^- occurs because the hypervalent Sn interacts with the fluoride ion forming a trigonal bipyramid around the Sn atom, weakening the Sn-vinyl bond and consequently facilitating the transmetalation process.[38] However, according to our calculations, the potential energy surface for case **A** is calculated to be kinetically more favorable than case **B**. Thus, the lowest energy path for the transmetalation of (P^tBu_3)Pd(Cl)(Ph) in the presence of F^- would involve the mechanism outlined in Figure 6a.

Conclusions

Density functional theory calculations have been used to study the steric effects of the phosphine ligands on the mechanism of the Stille cross coupling reaction. In summary, the following conclusions can be made based on the calculation results:

(1) The steric properties of L have a profound effect on the transmetalation step.

(2) The transmetalation step, where a very bulky ancillary ligand such as P^tBu_3 is in use, has a considerable activation barrier because it is very difficult for the three coordinate complex **5L** to coordinate to (vinyl)$SnMe_3$.

(3) The transmetalation step, where a nonbulky ancillary ligand such as PMe_3 is in use, has a considerable activation barrier because **7L** acts as a dead-end trap on the potential energy surface, thereby making it difficult for the **7L** + (vinyl)$SnMe_3$ → **6L** + L substitution reaction to proceed.

(4) The transmetalation step, where a moderately bulky ancillary ligand such as PPh_3 is in use, has a moderate activation barrier. Indeed, using PPh_3 provides the right balance between the energy required for the coordination of the L and (vinyl)-$SnMe_3$ ligands, consequently facilitating the transmetalation process.

(5) The stability of four coordinate Pd complexes is very sensitive to the bulkiness of the phosphine ligand(s). The same is to some extent true for the three coordinate Pd complexes when the phosphine ligand is trans to the vacant coordination site.

(6) In the four coordinate complexes, the bulkier the phosphine ligands, the weaker the σ-donating ability of L (as evidenced from the Pd-L bond energies), and the smaller the energy gap between **6L** and **5L_TS**.

(7) The addition of F^- increases the reactivity of stannane reagents toward the transmetalation. In such a case, F^- interacts with the complex (P^tBu_3)Pd(Cl)(Ph) to give [(P^tBu_3)Pd(Cl)-(Ph)(F)]$^-$. This reaction further proceeds via the dissociation of chloride followed by transmetalation between the fluoro complex (P^tBu_3)Pd(F)(Ph) and (vinyl)$SnMe_3$.

(8) In theoretical studies of the transmetalation step in which steric effects play an important role, it is not sufficient to use PMe_3 as a model for the larger phosphines.

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(37) (a) Bell, R. P. *Proc. R. Soc. London, Ser. A* **1936**, *154*, 414. (b) Evans, M. G.; Polanyi, M. *J. Chem. Soc., Faraday Trans.* **1936**, *32*, 1340.

(38) The Sn−C bond distance in 15P^{t}Bu$_3$ is 0.259 Å longer than that in 6P^{t}Bu$_3$ confirming the Sn−C bond weakening in 12P^{t}Bu$_3$.

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Supporting Information Available: Tables giving Cartesian coordinates, potential, and Gibbs free energies for all the calculated structures, complete ref 12, and BS2 for Pd, Cs, and Sn. This material is available free of charge via the Internet at http://pubs.acs.org.

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