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A Critical Analysis of the Cyclic and Open Alternatives of the Transmetalation Step in the Stille Cross-Coupling Reaction

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Abstract: The transmetalation step of the Stille cross-coupling reaction catalyzed by PdL_2 ($L = PH_3$, AsH_3) has been analyzed by means of DFT methods for PhBr as the electrophile and $CH_2{=}CHSnMe_3$ as the nucleophile. Both experimentally proposed mechanisms (cyclic and open) were theoretically studied. For the case of the cyclic mechanism, the associative and dissociative ligand substitution alternatives were both analyzed. For the case of the open mechanism, the cis and the trans pathways were evaluated. All the reaction pathways were also studied taking into account the solvent effects by means of continuum models, for THF and PhCl as solvents. In selected cases, explicit solvent molecules were introduced to account for their potential role as ligands. Theoretical analysis indicates that the open reaction mechanism is preferred for organotriflate systems, whereas the cyclic mechanism is favored for the reaction with organohalide systems.

1. Introduction

The Stille reaction is one of the most general and selective Pd-catalyzed cross-coupling reactions,[1−5] owing in part to the easy preparation of organotin compounds, used as nucleophiles, and their tolerance toward most functional groups.[1,6,7] After the first mechanistic proposal by Stille in 1978, new suggestions have been made trying to accommodate all the experimental observations.[3,5,7] A critical review of the experimental observations and their mechanistic implications has been recently published.[3]

The reaction mechanism consists of three main steps (oxidative addition, transmetalation, and reductive elimination), as well as a cis-to-trans isomerization preceding transmetalation in the case of organic halides as electrophiles. The oxidative addition and reductive elimination are common to other catalytic coupling processes (Suzuki, Negishi, Hiyama, etc.) and are reasonably well understood, although new proposals are still being made.[8−12] The transmetalation step is expected to show differences depending on the corresponding nucleophile used (an organometallic derivative of Sn, B, Zn, Si, etc.) and is less well-known. For the Stille reaction, two mechanisms, dubbed as *cyclic* and *open*, have been recently proposed to explain the retention or, respectively, inversion of configuration in the products.

The existence of a cyclic mechanism for the reaction was proposed to account for the evidence of Stille processes with retention of configuration at the transmetalated carbon, which requires a transition state where the X and R^2 ligands are bridging the two metal atoms.[13] It was shown that the reaction is kinetically compatible with an associative substitution mechanism producing an R^2-for-L ligand substitution. A concerted mechanism where the transmetalation and the ligand substitution take place simultaneously was proposed (Scheme 1, upper pathway) on the basis of the assumption that this should increase the electrophilicity of palladium and the nucleophilicity of the stannane. However, the same qualitative kinetic dependence should be expected for a two-step exchange where a preequilibrium of substitution of a leaving ligand by the entering stannane took place first and was then followed by a rate determining transmetalation. These two associative possibilities can only be safely distinguished by theoretical calculation. Previous to these associative proposals, a dissociative substitution mechanism had been postulated, where an L ligand is

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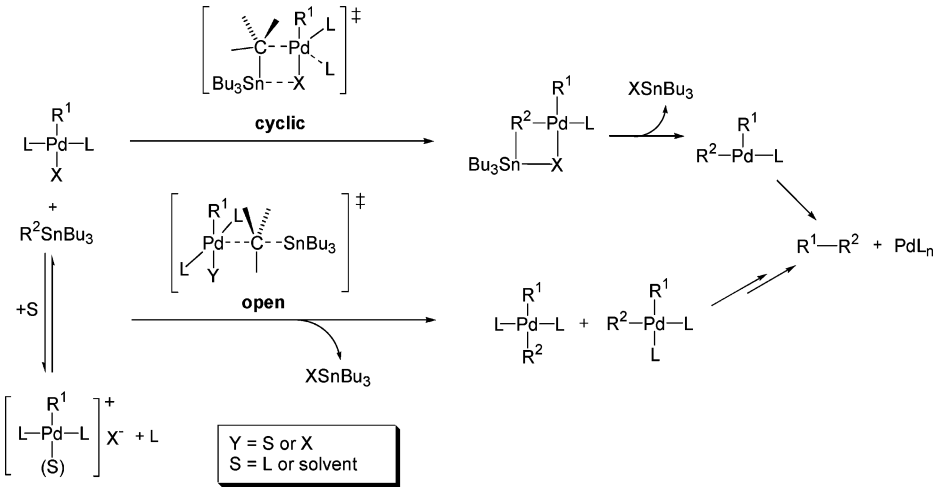
Scheme 1



dissociated to form a T-shaped intermediate, and then stannane coordination occurs.[14] However, the dissociative mechanism was found to afford a qualitatively similar rate law but to be quantitatively incompatible with the experimental data for ligands such as $AsPh_3$.[13]

The open mechanism (the only one considered in the literature until the recent inclusion of the cyclic mechanism) is proposed for cases where the product presents inversion of configuration, and can go through cis or trans geometries depending on the relative position of the two R fragments after transmetalation (Scheme 1, lower pathway).[15] This pathway seems to be more common and is expected to be favored for more electrophilic Pd centers, as in species with bad coordinating anions (like triflate) which are easily substituted by a neutral molecule, such as a coordinating solvent or the ligand that is used in excess.[15−17]

Computational chemistry is a useful tool in mechanistic analysis.[18,19] Theoretical analyses of the Stille reaction are rather scarce,[20,21] compared to the studies performed on other coupling reactions.[11,22−36] In this work we present a theoretical study of the transmetalation process for a model cross-coupling reaction between aryl electrophiles and vinyl nucleophiles, in the same conditions used for recent experimental kinetic studies,[13,15] so that calculated and experimental results are directly related.

2. Computational Details

All calculations were performed at DFT level, by means of the hybrid Becke3LYP[37−39] functional as implemented in Gaussian 03.[40] Pd, Br, P, As, and Sn atoms were described using an effective core potential (LANL2DZ) for the inner electrons,[40−42] and its associated double-ζ basis set for the more external ones. In the case of Br, P, As, Sn, and S atoms a d-polarization shell was added (exponent 0.428, 0.387, 0.303, 0.180, and 0.503 respectively).[43] The 6-31G(d) basis set was used for the C and Cl, and 6-31G for H and F atoms.[44,45] The O atoms were described by the 6-31G+(d) basis set.[46] Arsines and phosphines were modeled by PH_3 and AsH_3. Inclusion of real ligands will modify the relative energies within the energy profile, though the overall conclusions will probably remain unchanged. The structures of the reactants, intermediates, transition states, and products were fully optimized without any symmetry restriction. Transition states were identified by having one imaginary frequency in the Hessian matrix. Single point solvent calculations were performed at the optimized gas-phase geometries for all the minima and transition states, using the CPCM approach,[47,48] which is an implementation of the

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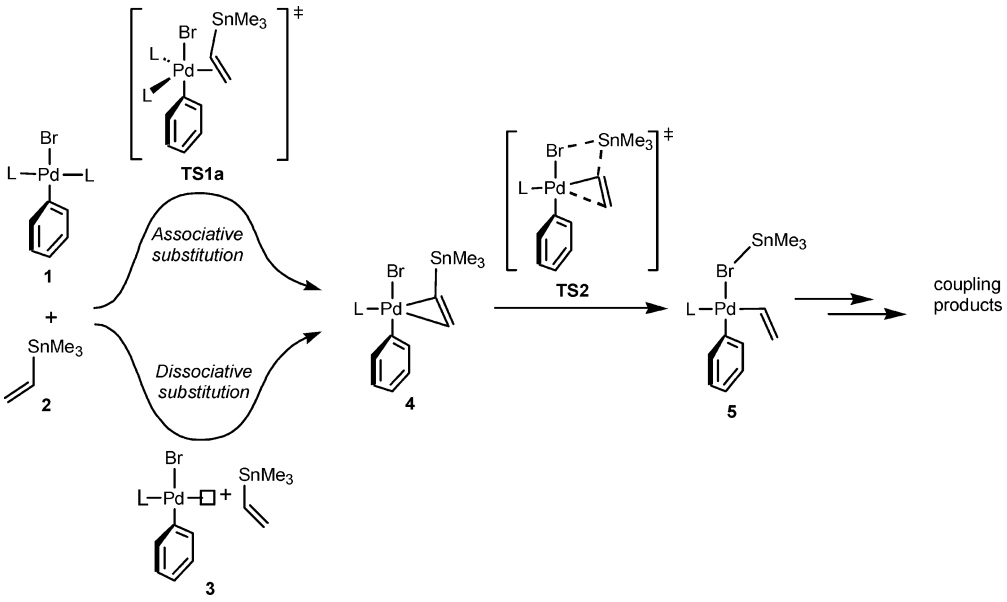
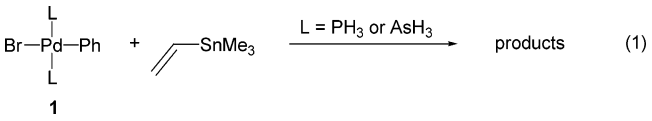
Scheme 2



conductor-likescreening solvation model (COSMO) in Gaussian 03;[49] THF (tetrahydrofurane) and PhCl (chlorobenzene), used in the kinetic experimental studies, were chosen as solvents (dielectric constant $\epsilon = 7.58$ and $\epsilon = 5.62$, respectively). The CPCM approach is not exact for the comparison of mechanisms involving charged and uncharged species but is able to provide at least a semiquantitative approach to the importance of solvent effects.

3. Results

The study of the transmetalation step for the Stille reaction was carried out for the process depicted in eq 1. The starting point for computation, *trans*-[PdPhBrL$_2$] (**1**), is generated in the catalytic cycle through oxidative addition of the organic halide (PhBr) to PdL$_2$(0), giving the cis complex, followed by fast cis to trans isomerization.[50] The stannane compound studied was (CH_2═CH)$SnMe_3$ (**2**). Two ligands with different donor ability, phosphines and arsines, were considered modeled by PH_3 and AsH_3, respectively.



3.1. The Cyclic Mechanism. The three possibilities (concerted, stepwise associative, and stepwise dissociative) were considered in the calculations for the cyclic mechanism. The cyclic structure proposed for the concerted transmetalation (Scheme 1) could not be identified as transition state, nor as a hypothetic cyclic intermediate. It was found that the transmetalation takes place in two steps. First, there is a substitution of an L ligand by the incoming vinyl to form intermediate **4**. Then the transmetalation takes place through a cyclic transition state (Scheme 2). This confirmation of a cyclic mechanism is in coincidence with the theoretical results found recently by Napolitano and co-workers for alkynyl stannanes,[20] and by Álvarez, de Lera and co-workers for alkenyl stannanes.[21] As a consequence of the two step (rather than concerted) mechanism,[13] the cyclic structure which had been initially proposed as an intermediate is in fact formed in the transition state **TS2**.

3.1.1. Substitution of an L Ligand by the Incoming Stannane. The formation of intermediate **4** involves substitution of an L ligand by the stannane and might take place either by an associative mechanism (with a five-coordinated palladium in the transition state) or by a dissociative mechanism (with a three-coordinated palladium in the transition state) where the L ligand is dissociated previous to coordination of the organotin group.

In the transition state of the associative mechanism, **TS1a**, we have considered two different alternatives, one where the organotin group replaces an L ligand (**TS1a$_L$**) and another where it replaces a solvent molecule (**TS1a$_S$**). This last hypothesis corresponds to the possibility that the substitution takes place on *trans*-[PdPhBrL(S)] (S = solvent molecule), formed previously by L exchange for a solvent molecule.[51]

A representative example of the structure of these associative transition states is included in Figure 1. **TS1a$_L$ AsH$_3$**, shows a bond breaking distance between Pd and the leaving As of 2.602 Å and distances between the metal center and carbon atoms of the incoming vinyl moiety of 2.774 (C_α) and 2.619 Å (C_β), respectively.

The relative energies of all computed associative transition states **TS1a$_L$** and **TS1a$_S$** are included in Table 1. It can be seen that they are always quite similar and low, with values between 5.7 kcal/mol (gas-phase AsH_3) and 8.8 kcal/mol (THF PH_3). The minor differences between them will not be discussed in detail, because, as it will be seen below, this is in no case the rate-limiting step in the transmetalation process.

Considering now the dissociative mechanism (Scheme 2), the formation of intermediate **4** should proceed by an initial L bond breaking process to generate a 14-electron intermediate, **3**. The

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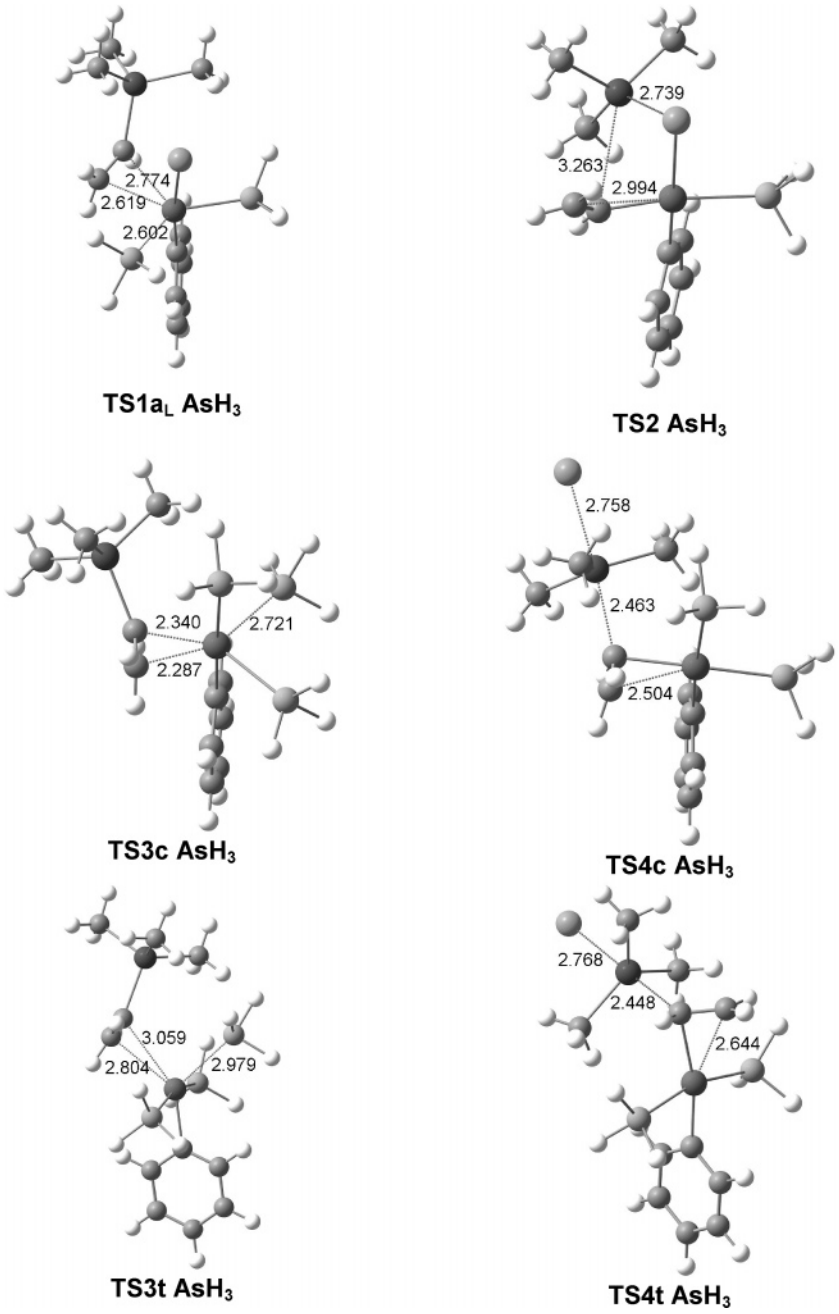


Figure 1. Geometries of the transition states for the cyclic and open mechanism for L = AsH_3.

Table 1. Energies (kcal/mol) Computed for the Cyclic Mechanism

	gas phase		THF		chlorobenzene	
cyclic L	PH_3	AsH_3	PH_3	AsH_3	PH_3	AsH_3
1 + 2	0.0	0.0	0.0	0.0	0.0	0.0
1$_S$ + 2	3.8	1.4				
3 + 2	23.2	21.0	21.8	17.8	22.3	18.5
TS1a$_L$	7.3	5.7	8.8	7.7	8.5	7.8
TS1a$_S$	7.7	5.1				
4	3.4	0.1	7.0	2.5	6.9	2.8
TS2	19.0	14.9	25.1	20.1	24.4	20.1
5	13.4	9.2	19.8	14.7	19.5	14.7

vacant coordination site generated might then be occupied by the vinyl double bond of the entering stannane. The energy for the corresponding structure, indicated as **3 + 2** in Table 1, presents values between 17.8 and 23.2 kcal/mol, always much higher than the corresponding transition states for the associative mechanism. Therefore, this substitution will take place through an associative mechanism.

3.1.2. Cyclic Transmetalation Step. Once intermediate **4** is formed, the next step should properly correspond to the transmetalation (Scheme 2). This step involves a large structural rearrangement involving migration of the $SnMe_3$ group, breaking of the Sn−C bond and formation of a new Sn−Br bond. In addition, the coordination mode of the vinyl group to the Pd center changes from η^2- to η^1-coordination. The energy of the transition state **TS2** in gas phase is 14.9 kcal/mol for L = AsH_3, that is 9.2 kcal/mol higher than **TS1a**. The inclusion of solvent in the calculation increases this energy barrier, giving the same value of 20.1 kcal/mol for THF and PhCl. This is the highest energy transition state for the cyclic mechanism. Regarding the geometry, the forming Sn−Br bond distance is 2.739 Å, whereas

Table 2. Reaction Energies (kcal/mol) for the Process $PdR^1XL_2 + Y \rightarrow [PdR^1YL_2]^+ + X^-$ [a]

entry	solvent	reaction	ΔE
1	THF	$[PdPhBr(AsH_3)_2] + AsH_3 \rightarrow [PdPh(AsH_3)_3]^+ + Br^-$	16.7
2		$[PdPhBr(PH_3)_2] + PH_3 \rightarrow [PdPh(PH_3)_3]^+ + Br^-$	14.9
3		$[PdPhBr(AsH_3)_2] + THF \rightarrow [PdPh(AsH_3)_2(THF)]^+ + Br^-$	19.0
4		$[PdPhBr(PH_3)_2] + THF \rightarrow [PdPh(PH_3)_2(THF)]^+ + Br^-$	19.0
5	PhCl	$[PdPhBr(AsH_3)_2] + AsH_3 \rightarrow [PdPh(AsH_3)_3]^+ + Br^-$	21.9
6		$[PdPhBr(PH_3)_2] + PH_3 \rightarrow [PdPh(PH_3)_3]^+ + Br^-$	19.8
7		$[PdPhBr(AsH_3)_2] + PhCl \rightarrow [PdPh(AsH_3)_2(PhCl)]^+ + Br^-$	34.1
8		$[PdPhBr(PH_3)_2] + PhCl \rightarrow [PdPh(PH_3)_2(PhCl)]^+ + Br^-$	35.0
9	THF	$[PdPh(OTf)(AsH_3)_2] + AsH_3 \rightarrow [PdPh(AsH_3)_3]^+ + OTf^-$	2.5
10		$[PdPh(OTf)(PH_3)_2] + PH_3 \rightarrow [PdPh(PH_3)_3]^+ + OTf^-$	0.7
11		$[PdPh(OTf)(AsH_3)_2] + THF \rightarrow [PdPh(AsH_3)_2(THF)]^+ + OTf^-$	4.8
12		$[PdPh(OTf)(PH_3)_2] + THF \rightarrow [PdPh(PH_3)_2(THF)]^+ + OTf^-$	4.8
13	PhCl	$[PdPh(OTf)(AsH_3)_2] + AsH_3 \rightarrow [PdPh(AsH_3)_3]^+ + OTf^-$	6.6
14		$[PdPh(OTf)(PH_3)_2] + PH_3 \rightarrow [PdPh(PH_3)_3]^+ + OTf^-$	4.7
15		$[PdPh(OTf)(AsH_3)_2] + PhCl \rightarrow [PdPh(AsH_3)_2(PhCl)]^+ + OTf^-$	18.9
16		$[PdPh(OTf)(PH_3)_2] + PhCl \rightarrow [PdPh(PH_3)_2(PhCl)]^+ + OTf^-$	20.0

[a] Solvents: THF and PhCl; X = Br and OTf; Y = L (PH_3 or AsH_3) or a solvent molecule (THF or PhCl).

the breaking Pd−C_α and Sn−C_β distances are 2.994 Å and 3.263 Å, respectively (Figure 1). For L = PH_3, similar trends are observed.

Interestingly, this mechanism affords directly an intermediate, **5**, with the vinyl and phenyl groups in a cis arrangement, therefore ready to produce the reductive elimination.

3.2. The Open Mechanism. The defining feature of the open mechanism is the absence of a cyclic species. As shown in Scheme 1, an open Pd−C−Sn−Br sequence in the transition state is the actual proposal. To force the evolution of the reaction toward the open mechanism we assumed the formation from **1** of a cationic species where the leaving X ligand (halide or triflate) has been substituted by a neutral ligand, whether an L ligand (L = phosphine or arsine) or a solvent molecule (S). Obviously this process is very costly in energy for X = Br, but not that much for triflate. Experimentally the *trans*-$[PdL_2XR]$ complexes formed after oxidative addition, in solution, are found to be in equilibrium with other species such as *trans*-$[PdL_2SR]^+$ or $[PdL_3R]^+$, depending on the reaction conditions, specially on the X group and the solvent.[15] In such cases the transmetalation is considered to occur on these cationic species, which are assumed to be generally more reactive than their neutral counterparts because of their higher electrophilicity. The relative stabilities of the ligand substitution processes involved in the open transmetalation mechanism are gathered in Table 2.

3.2.1. Formation of a Cationic Species. The substitution of the bromide ligand by a neutral group (an L ligand or a solvent molecule) to generate a cationic species was evaluated in two solvents with different coordination capacities: THF and PhCl. The reaction energies of these substitution processes are given in entries 1−8 of Table 2.

The energies associated to the substitution of the bromide by an L ligand in THF are 16.7 and 14.9 kcal/mol for arsine and phosphine (entries 1 and 2), respectively. These values are 21.9 and 19.8 kcal/mol in PhCl (entries 5 and 6), respectively. On the other hand, the substitution of Br^- by a solvent THF molecule has an energy cost of 19.0 kcal/mol for the complexes with both L ligands (entries 3 and 4, respectively). These values are 34.1 and 35.0 kcal/mol for a PhCl molecule (entries 7 and 8), showing, as expected, that THF is a much better coordinating ligand than PhCl, but worse than either AsH_3 or PH_3.

In addition to the case where X is a bromo ligand, the energies for the ligand substitution of the analogous complex where X is a triflate (OTf) were also evaluated (Table 2, entries 9−16). The displacement of triflate is as expected always much easier than that of bromide, with a cost as small as 0.7 kcal/mol in the best case (row 10). Otherwise, the facility of substitution follows the same trends resported above, PH_3 is the strongest replacing agent, followed by AsH_3 and THF, with PhCl being by far the weakest.

The next steps on the reaction mechanism (see Scheme 3) were studied starting from intermediate **8**, with three L ligands coordinated to the palladium center. In the presence of excess ligand (as it is often the experimental conditions), these complexes are usually more stable than their $[PdPhSL_2]^+$-counterparts, and are highly predominant in noncoordinating solvents or in solvents of moderate coordination ability toward palladium (e.g., THF). Note, however that this may not be the case in solvents highly polar and with good coordination ability (e.g., hexamethyl phosphoramide, see experimental results in ref 14) or in the absence of excess L.

3.2.2. R-for-L Substitution Step. Starting on the cationic intermediate **8**, the next step in the open mechanism is the replacement of one L ligand by the incoming stannane **2**, to form intermediate **9**.[52] This step may follow two different competitive pathways, depending on whether the stannane group goes cis (**TS3c**) or trans (**TS3t**) to the Ph group (Scheme 3). Then, a S_N2 substitution of the vinyl group by the bromide at the Sn center (**TS4**) will follow. Both possibilities (cis open and trans open mechanisms) were explored in gas phase and in the two solvents (THF and PhCl). The energy results are gathered in Table 3.

The transition state for the replacement of an arsine or phosphine ligand by the stannane group (**TS3**) is a five-coordinated structure, regardless of whether the cis or the trans intermediate is formed, as expected for this type of ligand substitution process. The structures **TS3c AsH_3** and **TS3t AsH_3** (Figure 1) are in this sense typical examples. Both of them are trigonal bipyramidal, differing in the arrangement of the ligands.

(52) An intermediate of type 9t has been reported as spectroscopically observed in a reversible tin-to-palladium transmetalation of 2-furyl using 2-tributylstannylfuran: Cotter, W. D.; Barbour, L. K.; McNamara, L.; Hechter, R.; Lachicotte R. J. *J. Am. Chem. Soc.* **1998**, *120*, 11016−11017.

Scheme 3

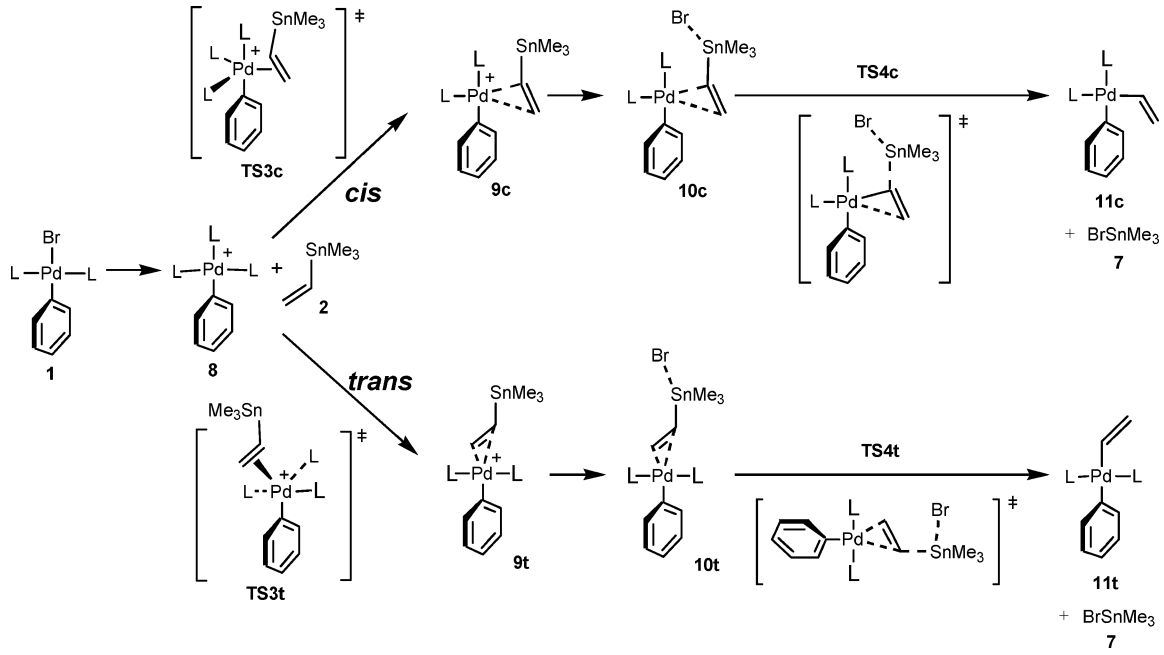


Table 3. Relative Energies (kcal/mol) Computed for Species Involved in the Open Mechanism; L = PH_3 or AsH_3

	open	gas phase		THF		chlorobenzene	
		PH_3	AsH_3	PH_3	AsH_3	PH_3	AsH_3
cis	**8** + **2** + Br	0.0	0.0	0.0	0.0	0.0	0.0
	TS3c + Br	7.2	5.3	8.3	9.2	8.0	9.1
	9c + Br + L	5.3	1.9	9.4	6.1	9.3	6.4
	10c + L	0.0	0.0	5.7	2.4	1.1	−1.9
	TS4c + L	0.1	0.9	7.9	5.3	3.5	0.9
	7 + **11c** + L	−26.1	−26.9	−6.1	−9.7	−11.2	−14.5
trans	**8** + **2** + Br	0.0	0.0	0.0	0.0	0.0	0.0
	TS3t + Br	7.2	5.8	8.9	10.5	8.7	10.7
	9t + Br + L	2.4	−0.6	5.5	3.4	5.3	3.6
	10t + L	0.0	0.0	3.2	1.4	−1.2	−2.8
	TS4t + L	0.5	0.6	5.4	4.1	0.9	−0.3
	7 + **11t** + L	−20.1	−20.2	−1.8	−3.6	−6.9	−8.5

As for bond distances, if we take **TS3c**, it can be seen that values for the forming Pd−C bonds have reasonable values as 2.340 Å (C_α) and 2.287 Å (C_β), while the distance between Pd and the leaving AsH_3 ligand is 2.721 Å, (longer than in **TS1a**).

The relative energies of the cis and trans transition states are in all cases close to each other, with the cis transition state being more stable by 1.6 kcal/mol at most.

3.2.3. Open Transmetalation Step. Once the stannane is coordinated to Pd, a S_N2 substitution of the vinyl group by the halide at the Sn center should follow (**TS4**). For this step, the difference in energy barrier between the cis and trans pathways for L = AsH_3 in gas phase is only 0.3 kcal/mol. In solvent, this difference is somewhat larger, 1.2 kcal/mol in THF, and 1.4 kcal/mol in PhCl.

The geometry observed for the transition state **TS4** (Figure 1) with L = AsH_3 is representative. It is fully consistent with a S_N2 mechanism on the Sn atom. It corresponds to a trigonal bipyramid around the Sn center with the incoming bromide and the leaving vinyl occupying axial positions. Simultaneously, the vinyl group switches from η^2- to η^1-coordination. The Sn···Br bond forming and Sn···C_α bond breaking distances are 2.758 and 2.463 Å in **TS4c** (cis mechanism), and 2.768 and 2.448 Å in **TS4t** (trans mechanism), respectively. In addition, the C_β···Pd distances are 2.504 and 2.644 Å in **TS4c** and **TS4t**, respectively (Figure 1).

4. Discussion

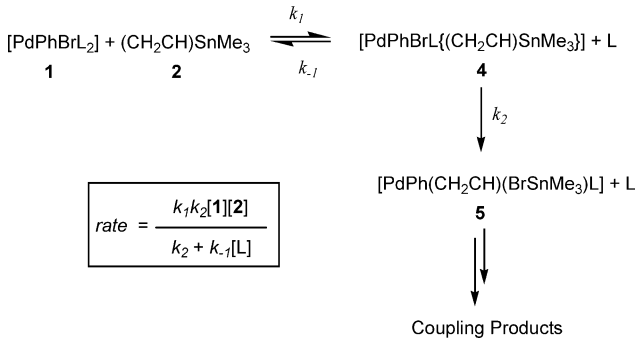
The transmetalation step for the reaction between PhBr and CH_2=$CHSnMe_3$ catalyzed by PdL_4 (L = PH_3, AsH_3) has been analyzed by means of DFT methods as a model reaction for the Stille cross-coupling. Experimental studies are available in the literature for systems with ArX (Ar = Ph, C_6F_5; X = I), $RSnMe_3$ (R = Ph, C_6H_4Me-p, CH_2=CH), and PdL_4 (L = PPh_3, $AsPh_3$).[13−17]

4.1. Cyclic Mechanism. The analysis of the cyclic mechanism shows that the transmetalation does not occur in a concerted manner (Scheme 1), but is a two-step process (Scheme 2, upper pathway). For the first step, producing L-for-stannane ligand substitution, the results of the theoretical analysis support an associative mechanism for both, phosphine and arsine ligands.[53] In effect, in gas phase the associative mechanism is around 16 kcal/mol lower than the dissociative. In solvent, the difference decreases to 12 kcal/mol, with the associative mechanism as the lowest energy one, still a difference big enough to discard dissociative substitution as a rate competing process.

It is known that associative ligand substitutions can occur directly or via solvent assisted processes. For this reason, the associative process starting from [PdPhBrL(THF)] species (where the L ligand has been previously substituted by a solvent molecule, S = THF) was also studied in gas phase. In this case the S-for-stannane substitution process has somewhat lower energy barriers than the L-for-stannane ligand substitutions process (around 2 kcal/mol) for both L ligands. However, considering the S-for-L exchange energy, the total energy required is similar for both associative mechanisms. In other words, associative substitutions on both complexes will have competitive rates and in general one or the other might

(53) Casares, J. A.; Espinet, P.; Salas, G. *Chem.−Eur. J.* **2002**, *8*, 4843−4853.

Scheme 4



predominate depending on the solvent S, the ligand L, and the ligand concentration in the medium.

This ligand substitution step is previous to the highest energy barrier step. This means that complex **4**, with the stannane coordinated as a ligand is a real intermediate, although its low concentration can keep it below the observation level in front of the higher concentration of **1**. The kinetic consequence is that the reaction from **1** to **4** should better be looked at as a fast preequilibrium. The kinetic behavior experimentally observed (order one in [Pd] and [Sn] and order minus one in [L]) is consistent with the rate expression deduced for this process (Scheme 4).

The second step, where strictly speaking the transmetalation takes place, has the highest energy barrier for the cyclic mechanism in the overall transmetalation pathway. The energy barriers for the overall process are lower for AsH_3, in agreement with the higher reaction rates observed experimentally for $AsPh_3$ as compared to PPh_3. The introduction of solvent effects does not modify importantly the reaction profile, though it is noteworthy that the overall profile increases in energy for both solvents. According to these results, the solvent represented as a continuum is not accelerating the reaction for the cyclic mechanism. On the contrary, this suggests that in order to favor the cyclic mechanism one should choose solvents with small dielectric constant. Since the open mechanism is favored when ionic species are produced, this choice of solvents will, in addition, disfavor the open mechanism.

It is important to remark that the first and the second steps are both endothermic. Therefore the transmetalation process for palladium halocomplexes is thermodynamically unfavorable, and the success of the catalysis fully depends on an efficient reductive elimination step, which will compensate for this thermodynamic deficit.

4.2. Open Mechanism. The first step for the open mechanism is the substitution of X^- by a neutral ligand L (L = phosphine or arsine) to form a cationic species $[PdRL_3]^+$. The cationic complex (**8**) is considered to be the reactive species in the catalytic cycle in the presence of excess L. Related species $[PdRL_2(S)]^+$ could be operating in coordinating solvents. The formation of the ionic complex $[PdPhL_3]Br$ by Br^- displacement with a L ligand has associated an unfavorable energy of ca. 14.9 kcal/mol for PH_3 and 16.7 kcal/mol for AsH_3 in THF, reflecting the better coordination ability of PH_3. In PhCl these values are 19.8 and 21.9 kcal/mol (Table 2). Thus, the equilibrium is very displaced to the left, in agreement with experiment,[13] but it is remarkable that moderate increase of dielectric constant in the solvent, produces a large decrease in the barrier of this first step, in fact larger than a change of ligand.

Comparison between the two solvents acting as the third ligand shows that the substitution of Br^- by a solvent molecule is much less unfavorable for THF (ca. 19.0 kcal/mol for both L ligands) than for PhCl (35.0 kcal/mol), probably because THF is a much better coordinating solvent, in addition to the solvent effect just commented.

Overall, a coordinating solvent with a high dielectric constant should greatly facilitate the process of formation of cationic species $[PdRL_2(S)]X$ and $[PdRL_3]X$, thus driving the reaction toward the open mechanism, even in cases where X^- = halide. In fact, frequent solvents of choice for the Stille reaction are MeCN, NMP (1-methyl-2-pyrrolidinone), and HMPA (hexamethylphosphoramide), which possess these properties.

As shown in Table 2, the formation of cationic species using OTf^- instead of Br^- is much less costly. Thus, the energy associated to the formation of the cationic species by substitution of OTf^- by PH_3 or AsH_3 is only 0.7 and 2.5 kcal/mol in THF, respectively (Table 2). These results indicate that significant concentrations of the cationic species, favoring an open transmetalation, will be present in the reaction medium when X is a triflate, even in solvents of moderate dielectric constant or coordination ability, as observed in the experiment for THF as solvent.[15]

After the formation of the cationic species the highest energy barrier corresponds to the substitution of the L ligand by the stannane group, **TS3**, which is therefore the step controlling the formation of cis and the trans intermediate. Considering the values found for **TS3**, the energy of the transition states for the cis and trans pathways are comparable. Including solvent effects introduces a small differentiation in favor of the cis pathway, for any combination of both L ligands and both solvents (Table 3). The energy barrier for the second step, **TS4**, which corresponds to a S_N2 reaction at the Sn center, is very moderate and somewhat lower in energy for the cis than for the trans pathway. The calculations fully agree with the experimental observation of two competitive pathways for the transmetalation, one leading fast to the coupling products (going via the nonobserved cis intermediate **11c**), and another leading more slowly to the coupling products and permitting an observation of the trans intermediate **11t** in some cases.[15]

5. Conclusions

The reaction between PhBr and CH_2=$CHSnMe_3$ catalyzed by PdL_2 (L = PH_3, AsH_3) was taken as a model reaction to analyze the transmetalation process for the Stille cross-coupling reaction by means of DFT methods. The general proposed mechanisms, the cyclic and the open mechanism, including their own variants have been studied in two solvents, THF and PhCl.

For the cyclic mechanism, a concerted pathway for the transmetalation of the alkenyl stannane was not found. Instead, a two step reaction process was characterized. The first step is the substitution of the L ligand by the stannane group (with the stannane acting as a metaloligand through the vinyl double bond), whereas the second corresponds to the transmetalation, properly speaking, where the vinyl group is transferred from the stannane to the palladium center. For the first step both ligand substitution mechanisms, the associative and dissociative, were analyzed and computational results support the associative mechanism. The second step does present a cyclic four member ring transition state and has the highest energy barrier, therefore

becoming the controlling step in the overall cyclic mechanism. The reaction profile is qualitatively similar for both L ligands, though energy barriers are lower for the catalyst with arsine ligands. Both solvents give similar qualitative and quantitative results for each of the L ligands.

The open mechanism was also computationally analyzed. In this case, the reactive species toward the stannane group is a cationic species generated by a ligand substitution of an anion X^- (bromide or triflate) for a neutral ligand (L, or a solvent molecule). This point will be more easily reached for triflate, but will demand the use of solvents with high dielectric constant and preferably coordinating in the case of bromide, to compensate the much more unfavorable formation of the ionic complex. The transmetalation process for the open mechanism also takes place in two steps. There is an initial stannane-for-L substitution (with the stannane acting as a metaloligand through the vinyl double bond), followed by a S_N2 reaction at the Sn center with the previously dissociated X^- as the incoming group and the vinyl (already coordinated to Pd) as the leaving group. In this case, conversely to the cyclic mechanism, the first step (corresponding to the stannane-for-L substitution) has the highest energy barrier within the overall profile. The analysis of the cis and the trans pathways shows that both are energetically comparable, and should be kinetically competitive, as observed experimentally. As for the L ligands, energy barriers are slightly lower for the phosphine than for the arsine ligand. In summary, the mechanism for the transmetalation process is mainly affected by the X group and the solvent, while the L ligand exerts a smaller (although kinetically significant) effect.

Finally, the success of the complete cycle remains dependent on the success of the reductive elimination step to give the coupling product since all the obtained energy profiles for the transmetalation process are endothermic. Computational studies on this last step are in progress.

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Supporting Information Available: Cartesian coordinates and absolute energies for all computed structures; geometries of the transition states for the open mechanism considering PH_3; energy profiles for the open and cyclic mechanisms in THF; complete ref 40. This material is available free of charge via the Internet at http://pubs.acs.org.

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