Associative Transmetalation in the Stille Cross-Coupling Reaction to Form Dienes: Theoretical Insights into the Open Pathway

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The open transmetalation mechanism for the Stille cross-coupling of vinylbromide and vinyl triflate with trimethylvinylstannane catalyzed by $Pd(PMe_3)_2$ as well as the roles of a coordinating solvent molecule (DMF) and additive (LiCl) have been theoretically studied using density functional theory (DFT). The cyclic mechanism seems to be favored for vinyl bromides. In contrast, the open alternative is likely followed by triflates. An oxidative addition mechanism involving a rearrangement of the triflate group on the $Pd(PMe_3)_2(\eta^2$-vinyl triflate) complex has been characterized. The open transmetalation pathway for vinyl triflate involves the more electrophilic palladium species generated by the substitution of the triflate by a ligand Y (PMe_3, DMF) on the oxidative addition intermediate. Moreover, LiCl as additive is shown to favor the oxidative addition step of triflates by forming an anionic trivalent species, $[Pd(PMe_3)_2Cl]^-$. The square-planar *trans*-$[Pd(PMe_3)_2(vinyl)Cl]$ complex generated by reaction with vinyl triflate corresponds formally to the product of direct oxidative addition of vinyl chloride to $Pd(PMe_3)_2$, which then would follow the cyclic transmetalation pathway.

Introduction

Recent developments on ligands and additives have enormously broadened the scope of the palladium-catalyzed cross-coupling reactions in organic synthesis.[1]

Besides the traditional, more reactive, unsaturated iodides, bromides, and triflates, other electrophiles such as aryl chlorides and sulfonates and even electrophiles attached to Csp[3] centers can be efficiently coupled to a range of organometallic nucleophiles (stannanes, boron, zinc, and silicon compounds) nowadays. Under special conditions,[3] also heteroatoms have entered the list of coupling partners, forming C−Het bonds.

Regarding additives, among the different variants of the palladium-catalyzed cross-coupling processes, Stille, Suzuki, Negishi, Hiyama, Kumada, Sonogashira, etc.,[2] it is undoubtedly the Stille reaction that has benefited most from their rate acceleration effects.[4,5] In addition to the early reports on the beneficial role of copper salts,[6] other empirical observations have confirmed the increase in reaction rates achieved by modified ligands in polar coordinating solvents[7] or by certain salts[8] (such as LiCl,[9] NaF,[10] and phosphinates[11]). Some of these effects occasionally work synergistically (for example, the combination of NaF and copper salts),[10] which further complicates the interpretation of the results in terms of the possible reaction pathways and the nature of the species involved. Furthermore, the contrasting stereochemical results obtained with chiral stannanes (retention[12] or inversion[13] of configuration depending upon the reaction conditions) add another level of complexity and altogether call for a reinterpretation of the commonly accepted reaction mechanism.[4,5]

Reflection on these issues and accumulating kinetic data prompted Espinet and Casado[14] to discard an earlier mechanistic proposal by Farina[7] that assumed, previous to the stannane coordination, the dissociation of a phosphine from the oxidative addition intermediate to afford a 14-electron T-shaped palladium species. Two alternative mechanisms for the transmetalation (the putative rate-determining and stereochemically relevant step), both associative in nature, gained acceptance instead. These two pathways can operate under different sets of reaction conditions and depend on the nature of the electrophilic coupling partner.[14] The *cyclic pathway* proceeds through a cyclic transition state **TS**(**A**) (Figure 1) with a bridging electrophile (therefore, it will be more favorable for halides) and involves the replacement of a ligand by the incoming stannane that adds (if applicable) with retention of configuration. The *open pathway* is characterized

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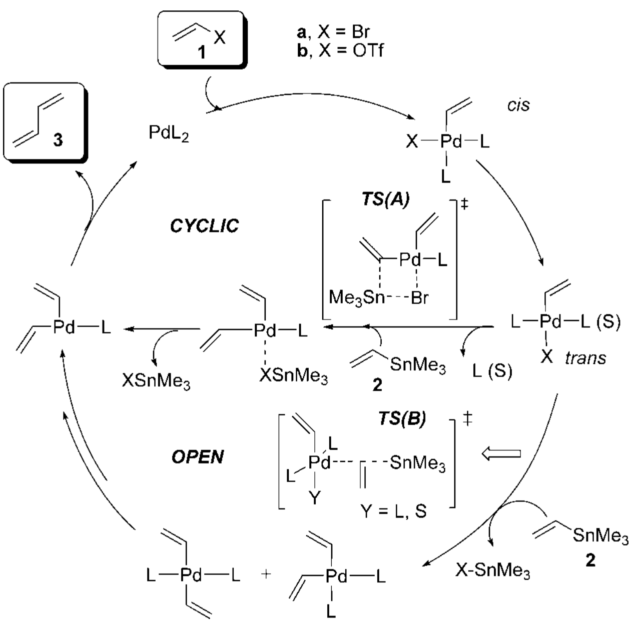

Figure 1. Schematic overview of the cyclic and open pathways involved in the transmetalation step of the Stille reaction, which affords butadiene **3** from vinyl bromide **1a**/vinyl triflate **1b** and trimethylvinylstannane **2**, catalyzed by Pd(PMe$_3$)$_2$ (L = PMe$_3$ and S = DMF).

by its cationic nature and was considered to be the favored path for pseudohalides (triflates). It starts with the departure of the leaving group X, followed by the association of either excess ligand (L) or coordinating solvent (S). A key associative trigonal bipyramidal transition state with 18 electrons, **TS**(**B**), was proposed for this open transmetalation. Its stereochemical outcome for chiral, nonracemic, stannane-bearing Csp^3 atoms would then be inversion of configuration.

We have recently reported a DFT study on the complete catalytic cycle for the model Stille cross-coupling reaction of trimethylvinylstannane (**2**) and vinyl bromide (**1a**) to afford butadiene (**3**) along the cyclic transmetalation pathway (Figure 1, top).[15] Our results supported the accessibility of this associative reaction path and characterized a cyclic transition state **TS**(**A**). The transmetalation from the *trans*-[PdL$_2$(vinyl)Br] complex was found to occur in two discrete steps: first, η^2-coordination of the stannane assisted by ligand dissociation to afford a tetracoordinated palladium species, and second a rearrangement directly resulting in a tricoordinated PdL(vinyl)$_2$ intermediate with *cis* geometry, thus highly prone to reductive elimination.[15] Similar cyclic transition states have been reported for the transmetalation step in the Stille coupling of alkynyl−alkynyl[16] and alkenyl−aryl[17] fragments, and the role of the halide (Cl, Br, or I) in the second step of the cyclic transmetalation mechanism has also been discussed.[18]

Espinet et al.[17] have recently analyzed the competition between open and cyclic mechanisms in the formation of styrene by Stille coupling of bromobenzene or phenyl triflate and trimethylvinylstannane. In this study, the nature of both the electrophile and the solvent appeared to be crucial in the determination of the reaction mechanism. It was predicted that aryl triflates would follow the open mechanism, whereas bromides would react via the cyclic alternative. It was also proposed that in the presence of coordinating solvents aryl bromides could eventually follow the open path, but the corresponding calculations were not carried out, despite the fact that these coordinating solvents (DMF, DMA, NMP) are commonly used in the usual experimental settings[5] and our previous studies[15] have shown that the mixed complexes *trans*-[PdL(DMF)(vinyl)Br] are the most likely catalytic species when using phosphines (or arsines) in polar coordinating solvents (DMF), as experimentally observed by Amatore and Jutand.[19]

Thus, in order to rationalize and expand these findings in a more general frame, we set out to perform a comprehensive study of the open transmetalation mechanism that results in butadiene (**3**) starting from trimethylvinylstannane (**2**) and either vinyl bromide (**1a**) or vinyl triflate (**1b**) as electrophiles (Figure 1, bottom). PMe$_3$ was selected as the palladium ligand in the starting PdL$_2$ catalyst that affords the *trans*-[PdL$_2$(vinyl)X] complex upon oxidative addition, a step that has already been discussed for vinyl bromide (**1a**).[15]

In this endeavor, we also addressed several aspects of the open mechanism that had not been previously considered: (i) the mechanism of the ligand-assisted dissociation of the X group (Br or OTf) from *trans*-[PdL$_2$(vinyl)X] prior to the coordination of the stannane to afford [PdL$_3$(vinyl)]$^+$; (ii) the incorporation of a solvent molecule (DMF) as an explicit ligand on palladium to afford [PdL$_2$(DMF)(vinyl)]$^+$ and other solvent-ligated species along the catalytic cycle; (iii) the role of LiCl in the oxidative addition of alkenyl triflates.[13,8,5]

After the description of these variants of the open transmetalation pathway, a comparison will be made with the competing cyclic transmetalation[15] in order to better define the most likely mechanism for the Stille reaction of alkenyl bromides under each set of conditions.

Computational Details

All calculations in this study have been performed using the Gaussian03 suite of programs.[20] To include electron correlation at a reasonable computational cost, density functional theory (DFT)[21] has been used. The Becke three-parameter exchange functional with the nonlocal correlation functional of Lee, Yang, and Parr (B3LYP)[22] was chosen. Given the complexity of the structures and transition states, the 6-31G* basis set for C, H, and P in conjunction with the Stuttgart/Dresden relativistic effective core potentials for Pd, Sn, and Br was adopted to compute the geometries, energies, and normal mode vibrational frequencies of all the stationary points. To check the basis dependence of the studied properties, some of the structures were also optimized with the 6-311G*/SDD basis set, and only very minor differences were found at the cost of a 3-fold more demanding CPU-time requirement. No symmetry constraints were imposed during the structural optimizations. The stationary points were characterized by means of harmonic analysis, and for all the transition structures, the vibration related to the imaginary frequency corresponds to the nuclear motion along the

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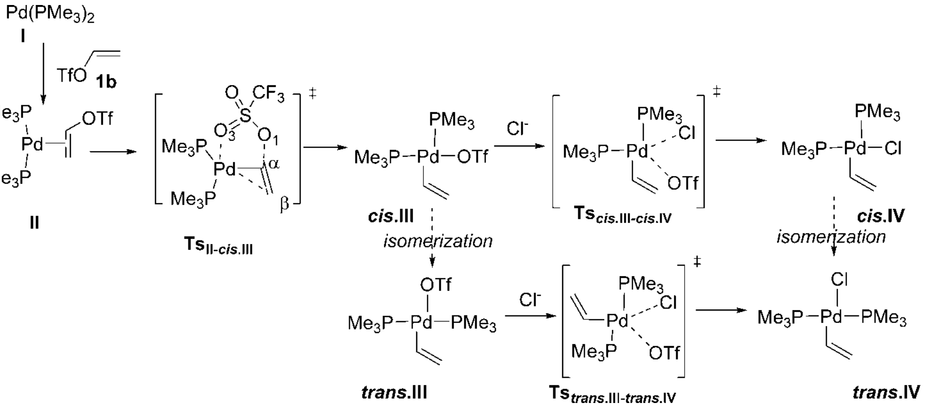
Scheme 1. Oxidative Addition of Vinyl Triflate 1b to $Pd(PMe_3)_2$ (I) and the Dissociation of Triflate Assisted by Chloride (dashed lines indicate noncomputed (but feasible) isomerization steps)



reaction coordinate under study. The effect of the solvent (THF and CH_3CN) was initially taken into account for some of the structures (see Supporting Information) through single-point calculations at each optimized geometry using a SCRF model with a spherical cavity, only keeping the dipole term of the multipolar expansion (Onsager model),[23] and also using the polarized continuum model (PCM) at 298.15 K.[24] However, for the reasons indicated below, we will limit our discussion of the open mechanism to the gas-phase computations.

From the outset we were aware of the difficulties inherent to the computation of free energy values for the dissociation of ligands that produce charged species. As acknowledged by other authors,[25,26] this is mainly due to the large entropy effects in dissociation processes in the gas phase and the overestimation of the solvation energy of the resulting charged species. Moreover, the energy values for dissociation processes are quite sensitive to the computational method used. Maseras et al. carried out computations of ligand (PH_3) and bromide dissociation from a series of palladium complexes.[25] Very large differences in the dissociation energies were found with a solvent of high polarity and high dielectric constant (H_2O) relative to the potential energies of the SCF part of the QM calculations. Other authors[26] have suggested the use of a modified free energy correction considering only the vibrational contribution to entropy, but we decided not to follow this approach since this simplification considers that the solvent constrains all the vibrations, not only the movements of the separated fragments, and also because the increase in entropy is primarily due to the translational and rotational components.

In view of these limitations, we opted to treat all the substrates as ideal gases and to consider the translation, rotation, and vibration contributions to the free energy. Also, as a result, no solvent effects are considered in the discussion, since the available continuum methods cannot treat rigorously the solvation of charged species (inclusion of solvent in the calculations provided inconsistent values, listed in the Supporting Information, for the transition states and minima), and only gas-phase energies will be discussed and compared where appropriate.

Results

In this section we will describe in detail the structures involved in the oxidative addition and open transmetalation mechanisms for the Stille coupling of vinyl bromide and vinyl triflate with vinylstannane and their relevant thermodynamic information. The effect of chloride ion as an additive is studied in subsection 1, for the oxidative addition of vinyl triflate to $Pd(PMe_3)_2$, and its consequences in the preference for a cyclic or open transmetalation explored. Subsection 2, dealing with the open transmetalation mechanism, is in turn divided in three parts corresponding with the three steps into which it can be divided: formation of a cationic species, through bromide or triflate displacement by a solvent or ligand molecule, replacement of ligand or solvent by the stannane, and transmetalation. In subsection 2, care is taken to consider all the different possible arrangements of ligands around the palladium center, the exchange reactions that can take place, and their stereochemical consequences both for the mechanism and for the resultant products.

1. Oxidative Addition of Vinyl Bromide (1a) and Vinyl Triflate (1b) to $Pd(PMe_3)_2$.

The mechanistic features of the oxidative addition of $Pd(PMe_3)_3$ to vinyl bromide (**1a**) have already been discussed in depth.[15] However, no theoretical studies on the reactivity of alkenyl triflates with palladium complexes have been carried out, despite their being common coupling partners in Stille reactions. Since Stille cross-coupling reactions of triflates and stannanes are sensitive to the presence of LiCl[8,13] (in some cases, they *take place only in the presence of chloride* anion), attention will be also paid to the role of this additive during the process.

We found that vinyl triflate (**1b**) first coordinates to the 14-e^- species $Pd(PMe_3)_2$ (**I**) (Scheme 1), and the resulting η^2-coordinated complex **II** (which is 1.4 kcal/mol more stable than the initial **I**) is then converted into the square-planar 16-e^- species *cis*-[$Pd(PMe_3)_2$(vinyl)(OTf)] (***cis*-III**) through a five-coordinated transition state $\mathbf{Ts_{II\text{-}\mathit{cis}\text{-}III}}$. The imaginary frequency of $\mathbf{Ts_{II\text{-}\mathit{cis}\text{-}III}}$ corresponds to the simultaneous breaking of the $C\beta{-}Pd$ and the $C\alpha{-}O_1$ bonds and the formation of the $O_3{-}Pd$ bond (Figure 2), a rearrangement that requires overcoming an energy barrier of 19.9 kcal/mol. The main geometric features of $\mathbf{Ts_{II\text{-}\mathit{cis}\text{-}III}}$ (Figure 2) are the distances between Pd and both unsaturated carbon atoms (2.81 and 2.36 Å to the distal $C\beta$ and to the proximal $C\alpha$, respectively) and the $O_3{-}Pd$ distance (2.91 Å). The formation of square-planar complex ***cis*-III** is exergonic (the free energy difference is −13.3 kcal/mol) relative to **II**.

The effect of chloride in the mechanism is controversial; Scott and Stille first reported that these palladium(II) species [PdL_2(vinyl)(OTf)] resulting from the oxidative addition of alkenyl triflates to Pd(0) complexes were not stable and that the role of the added lithium chloride was to allow the formation

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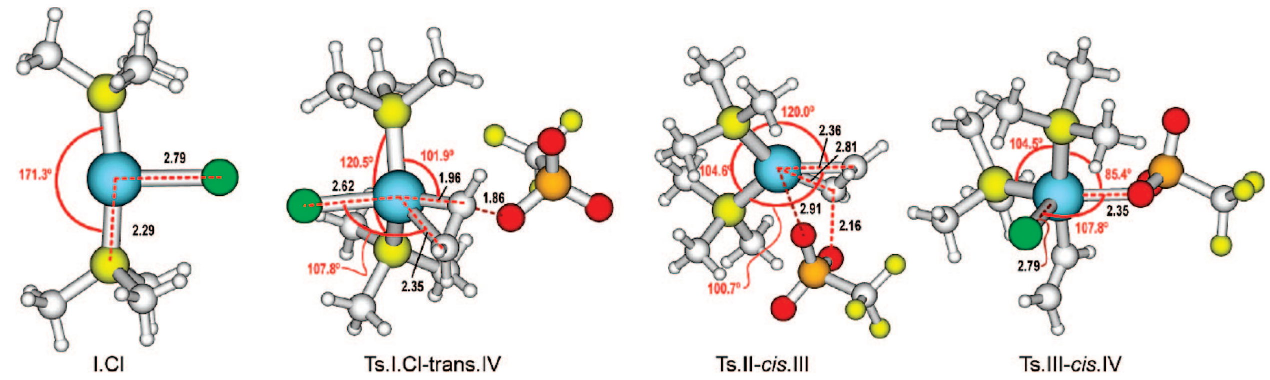

Figure 2. Optimized geometries (B3LYP/6-31G*-SDD) for the minimum **I·Cl** and the transition states $\mathbf{Ts}_{\mathbf{I\cdot Cl}-\mathit{trans}\text{-}\mathbf{IV}}$, $\mathbf{Ts}_{\mathbf{II}-\mathit{cis}\text{-}\mathbf{III}}$ and $\mathbf{Ts}_{\mathit{cis}\text{-}\mathbf{III}-\mathit{cis}\text{-}\mathbf{IV}}$ characterized along the oxidative addition of vinyl triflate **1b**.

Scheme 2. Oxidative Addition of Vinyl Triflate 1b to $[Pd(PMe_3)_2Cl]^-$, I·Cl

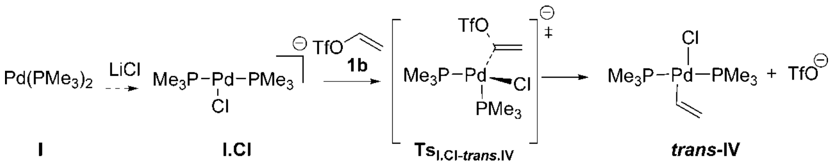

Table 1. Thermodynamic Data (in kcal/mol) for (a) the Oxidative Addition of Vinyl Triflate (1b) to $Pd(PMe_3)_2$ (I) and the Steps Proposed to Account for the Effect of Chloride Ion, (b) the Formation of the Cationic Palladium Species V $[Pd(PMe_3)_3(vinyl)]^+$ and $[Pd(PMe_3)_2(vinyl)(DMF)]^+$ from *trans*-III via Ligand- or Solvent-Assisted Dissociation and for the Association of Stannane 2, and (c) the Dissociation of Y from the Cationic Palladium Complex V·Y (Y = PMe_3 or DMF)

oxidative addition of **1b** (a)		formation of **V** (b)		dissociation of Y (c)	
structure	ΔG^a	structure	ΔG^b	structure	ΔG^c
I + **1b** + Cl^-	1.4	***trans*-III·Br**	0.0	**V·PMe_3**	0.0
II + Cl^-	0.0	$\mathbf{Ts}_{\mathbf{III\cdot Br-V\text{-}PMe3}}$	20.9	$\mathbf{Ts\text{-}L}_{\mathbf{V}-\mathit{trans}\text{-}\mathbf{VI}}$	24.1
$\mathbf{Ts}_{\mathbf{II}-\mathit{cis}\text{-}\mathbf{III}}$ + Cl^-	19.9	**V·PMe_3**	19.2	***trans*-VI·PMe_3**	12.9
***cis*-III** + Cl^-	−13.3	***trans*-III·Br**	0.0	**V·DMF**	0.0
$\mathbf{Ts}_{\mathit{cis}\text{-}\mathbf{III}-\mathit{cis}\text{-}\mathbf{IV}}$	−9.5	$\mathbf{Ts}_{\mathbf{III\text{-}Br-V\cdot DMF}}$	13.5	$\mathbf{Ts\text{-}S}_{\mathbf{V}-\mathit{trans}\text{-}\mathbf{VI}}$	23.3
***cis*-IV** + TfO^-	−26.1	**V·DMF**	17.1	***trans*-VI·PMe_3**	20.2
***trans*-III** + Cl^-	−20.3	***trans*-III·OTf**	0.0	**V·PMe_3**	0.0
$\mathbf{Ts}_{\mathit{trans}\text{-}\mathbf{III}-\mathit{trans}\text{-}\mathbf{IV}}$	−19.9	$\mathbf{Ts}_{\mathbf{III\cdot OTf-V\cdot PMe3}}$	17.1	$\mathbf{Ts\text{-}L}_{\mathbf{V}-\mathit{cis}\text{-}\mathbf{VI}}$	28.7
***trans*-IV** + TfO^-	−33.3	**V·PMe_3**	11.5	***cis*-VI·PMe_3**	19.6
I·Cl + **1b**	15.3			**V·DMF**	0.0
$\mathbf{Ts}_{\mathbf{I\cdot Cl}-\mathit{trans}\text{-}\mathbf{IV}}$	16.5			$\mathbf{Ts\text{-}S}_{\mathbf{V}-\mathit{cis}\text{-}\mathbf{VI}}$	26.2

[a] Relative to **II** + Cl. [b] Relative to ***trans*-III·Br** and ***trans*-III·OTf**. [c] Relative to **V·PMe_3** and **V·DMF**.

of a more stable PdL_2(vinyl)Cl complex.[9] Piers questioned these results based on his experimental findings,[28] and later, Farina and Krishnan reported the opposite in a kinetic study for the coupling of alkenyl triflates and tributylvinylstannane: LiCl was not necessary for the coupling of alkenyl triflates, and its presence retarded the coupling.[7] The added LiCl (3 equiv) also slowed down the coupling if excess palladium ligand was present. A parallel study established that the coupling of aryl triflates was indeed accelerated by LiCl.[29]

Aiming to shed some light on this debate, we considered a mechanistic dual role of the chloride ion on the oxidative addition of vinyl triflate to $Pd(PMe_3)_2$: (1) to assist the dissociation of triflate[9] from the $[Pd(PMe_3)_2(vinyl)(OTf)]$ species **III** with *cis* or *trans* geometry (Scheme 1); (2) to promote the formation of the anionic[29] trivalent palladium species $[Pd(PMe_3)_2Cl]^-$ (**I·Cl**) (Scheme 2) prior to the oxidative addition of vinyl triflate. A neutral square-planar palladium complex **IV** would be formed as the end result in both mechanistic variants.

The coordination of chloride to $[Pd(PMe_3)_2(vinyl)(OTf)]$ (***cis*-III**) assists the dissociation of the triflate ligand via a transition state ($\mathbf{Ts}_{\mathit{cis}\text{-}\mathbf{III}-\mathit{cis}\text{-}\mathbf{IV}}$) with a geometry that shows features of a trigonal bipyramid (Figure 2). The apical positions are occupied by a phosphine (Pd−P, 2.42 Å) and the vinyl substituent (Pd−C, 2.02 Å), whereas Cl (Pd−Cl, 2.79 Å), TfO (Pd−O, 2.35 Å), and the second phosphine (Pd−P, 2.27 Å) are placed on the equatorial plane. Coordination of chloride to $[Pd(PMe_3)_2(vinyl)(OTf)]$ (***cis*-III**) is an easy step (energy barrier of 3.8 kcal/mol), whereas the energy difference between the square-planar complexes ***cis*-III** and ***cis*-IV** is 12.8 kcal/mol, in favor of the latter (Table 1).

A similar sequence could occur for the palladium complex ***trans*-III** obtained by isomerization of the four-coordinate ***cis*-III** (Scheme 1). These isomerization reactions have been shown to proceed readily via a trigonal-bipyramidal transition state induced by free phosphine or via alternative mechanisms.[15,17] The dissociation of the triflate anion from ***trans*-III** assisted by chloride involves a transition state virtually identical to the one previously described, but the energy difference between ***trans*-III** and $\mathbf{Ts}_{\mathit{trans}\text{-}\mathbf{III}-\mathit{trans}\text{-}\mathbf{IV}}$ is reduced to 0.4 kcal/mol. Complex ***trans*-IV** could also have originated from *cis*-$[Pd(PMe_3)_2$

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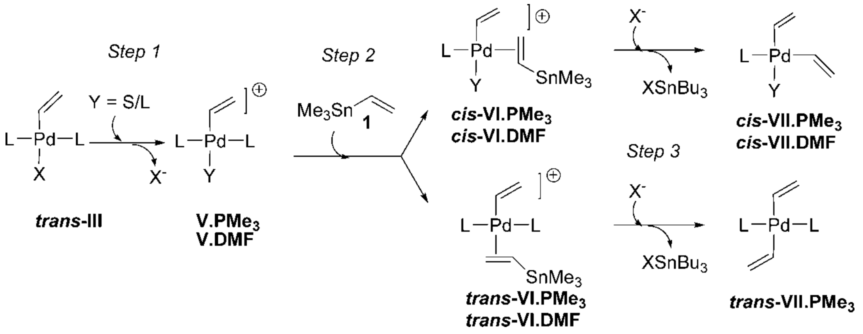
Scheme 3. Transmetalation Steps Proposed for the Open Mechanism of the Stille Coupling of Vinyl Bromide/Vinyl Triflate 1 and Trimethylvinylstannane (2) Starting from *trans*-III



(vinyl)Cl], ***cis*-IV**, via an isomerization that we have already described for the *cis*-[Pd(PMe$_3$)$_2$(vinyl)Br] analogue.[15]

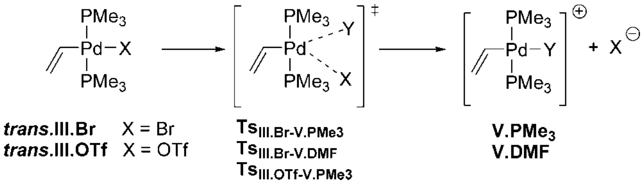
In the second mechanism explored for the effect of chloride (Scheme 2), the tricoordinate anionic complex [Pd(PMe$_2$)$_3$Cl]$^-$ (**I·Cl**) is an intermediate in the reaction of chloride ion with Pd(PMe$_3$)$_2$ (**I**) prior to reaction with vinyl triflate **1b**. **I·Cl** adopts a symmetrical structure with P—Pd and Cl—Pd bond distances of 2.29 and 2.79 Å, respectively, and P—Pd—P and P—Pd—Cl angles of 171.3° and 94.3°, respectively (Figure 2). The reactivity of these tricoordinated anionic species [PdL$_2$X]$^-$ in the oxidative addition of aryl halides has been documented elsewhere.[30,31]

Strikingly, no five-coordinate anionic intermediate species [Pd(PMe$_3$)$_2$(vinyl)(OTf)Cl]$^-$ of the type suggested for aryl triflates could be located for the oxidative addition of vinyl triflate **1b** to **I·Cl**.[32] We found instead that this step resembles a substitution reaction at the vinyl carbon, a process that is favored by the good leaving ability of triflate,[33] and is characterized by a negligeable energy barrier (1.2 kcal/mol). In the corresponding transition state (**Ts**$_{\text{I-Cl}-trans\text{-IV}}$ in Figure 2), featuring Pd—Cα, Pd—Cl, and Cα—O bond distances of 1.96, 2.62, and 1.86 Å, respectively, in a quasi-tetrahedral geometry, the Cα—Pd bond is formed in concert with the release of the TfO$^-$ group.

Since the resultant product, ***trans*-IV**, would also be the intermediate obtained from direct oxidative addition of vinyl chloride to **I** and subsequent *cis—trans* isomerization, we can assume that the most likely course for its transmetalation with stannanes would be the cyclic path. A DFT study of the halogen effect on this step showed that the overall transmetalation activation energies decrease in the order Cl < Br < I.[18] The rates of transmetalation of tributylvinylstannane with isolated *trans*-[Pd(AsPh$_3$)$_2$(Ar)X] complexes also showed the higher reactivity of chlorides.[14,35]

2. Open Transmetalation Mechanism. We only describe the open transmetalation mechanism for the processes starting from *trans*-[Pd(PMe$_3$)$_2$(vinyl)X] (***trans*-III**), since we deem unlikely the dissociation of chloride from complex *trans*-[Pd(PMe$_3$)$_2$(vinyl)Cl] (***trans*-IV**) to afford a cationic species. The open transmetalation was thus found to proceed through three discrete steps, as shown in Scheme 3. Step 1 involves the formation of a cationic species [Pd(PMe$_3$)$_2$(vinyl)Y]$^+$ (**V**) by associative ligand- or solvent-assisted displacement of X from ***trans*-III** (where X = OTf or Br and Y is either PMe$_3$ or DMF). Step 2 encompasses the subsequent replacement of one palladium ligand by the stannane to give **VI**, and step 3 is the proper transmetalation, which is thought to have the features of an S$_N$2 substitution where the vinyl group on tin is replaced by the entering halide.

Scheme 4. Dissociation of the Electrophile X from *trans*-III Assisted by the Association of Y (PMe₃ or DMF)



The second step can potentially afford two isomeric cationic complexes (***cis*-VI** or ***trans*-VI**) depending on the relative arrangement, *cis* or *trans*, of the vinyl ligands on **VI** (Scheme 3), and this duality is conserved after displacement of stannane by the halide in **VI**, which affords the neutral square-planar palladium species ***cis*-VII** or ***trans*-VII**. The rate of formation of butadiene from these complexes is expected to be different: whereas a fast reductive elimination of unsaturated ligands is anticipated from ***cis*-VII**, ***trans*-VII**, given the geometric requirement for a *cis* arrangement of the alkenyl groups in the elimination, would need an additional costly isomerization step and, as a result, be more reluctant to eliminate.[5]

2a. Step 1: Formation of a Cationic Species. The first step involves the substitution of the anionic ligand X (bromide, triflate in the absence of LiCl) by L or S (PMe$_3$ or DMF in our studies). Triflate is considered a poorly coordinating anionic ligand; in the absence of chloride salts, the alternative cyclic transmetalation step would be disfavored due to the nonbridging and highly dissociative nature of triflate complexes. Nevertheless, when triflate is replaced by chloride, the catalytic cycle for ***trans*-IV** will be similar to that of the corresponding bromide, with a transmetalation step most likely of cyclic and associative nature.[18]

The favored transmetalation path will depend on the nature of X. The nonbridging and highly dissociative nature of triflate in these complexes does not favor a cyclic transition state for this step. However, in the presence of chloride salts, ***trans*-IV** is formed, so a transmetalation step analogous to that found when X = Br, cyclic and associative, is expected.[18]

For ***trans*-III** the substitution mechanism proceeds through an 18-e$^-$ trigonal-bipyramidal transition state (Scheme 4). For bromides, the cationic [Pd(PMe$_3$)$_2$(vinyl)Y]$^+$ (Y = PMe$_3$ or DMF) species **V** is formed in an overall endergonic process

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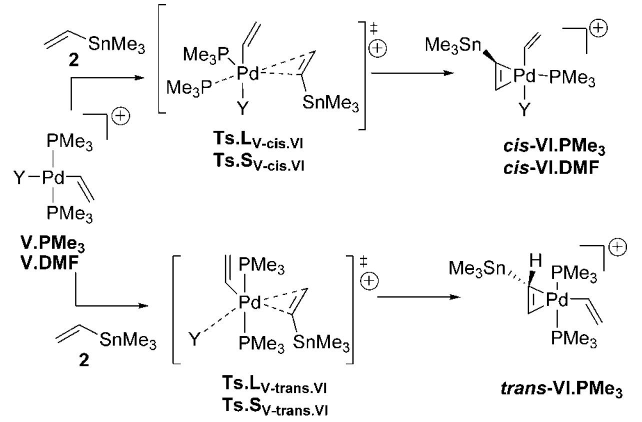
(19.2 kcal/mol for Y = PMe_3 and X = Br; 17.1 kcal/mol for Y = DMF and X = Br). The corresponding transition states **Ts**$_{\mathbf{III\text{-}Br-V\cdot PMe_3}}$ and **Ts**$_{\mathbf{III\text{-}Br\cdot V}}$ are characterized by Br−Pd bond distances of 2.86 and 3.00 Å and angles between the apical ligands ($Me_3P-Pd-PMe_3$) of 161.8° and 173.4°, respectively. With activation energies of 20.9 and 13.5 kcal/mol (Table 1) for these two transition states, the substitution of anionic bromide by neutral DMF would be favored by 7.4 kcal/mol relative to that of PMe_3 on the formation of the cationic species **V**. The greater steric congestion around pentacoordinate palladium in the transition state with an associating PMe_3 can explain the energetic as well as the geometric differences relative to DMF as ligand. Intermediate $[Pd(PMe_3)_2(DMF)(vinyl)]^+$ (**V·DMF**) is expected to exhibit a higher electrophilicity than $[Pd(PMe_3)_3(vinyl)]^+$ (**V·PMe$_3$**) for the subsequent association of the incoming stannane nucleophile along the transmetalation step.[5]

The displacement of triflate on palladium assisted by PMe_3, on the other hand, is 3.8 kcal less costly than that of bromide, which reflects the poorer coordinating ability of the former. *trans*-$[Pd(PMe_3)_2(vinyl)(OTf)]$ (**III·OTf**) is converted into the cationic complex $[Pd(PMe_3)_3(vinyl)]^+$ (**V·PMe$_3$**) through an energy barrier of 17.1 kcal/mol, corresponding to the transition state **Ts**$_{\mathbf{III\text{-}OTf-V\cdot PMe_3}}$ with trigonal bipyramidal geometry, $Pd-PMe_3$ and Pd−OTf bond distances of 2.81 and 2.44 Å, and a $Me_3P-Pd-PMe_3$ dihedral of 164.8°. Despite our efforts, we were unable to characterize a transition state for the dissociation of triflate assisted by DMF, but we surmise that the same trend would apply as for bromides (Table 1), and energies of activation below 10 kcal/mol are anticipated for this step.

The cationic complexes $[Pd(PMe_3)_3(vinyl)]^+$ (**V·PMe$_3$**) and $[Pd(PMe_3)_2(vinyl)(DMF)]^+$ (**V·DMF**) display a square-planar geometry, with $Me_3P-Pd-PMe_3$ bond angles of 96.4° and 101.3°, smaller in the former due to the greater steric effect exerted by the phosphine.

Scheme 5. Geometries Resulting from the Alternative Coordination of Trimethylvinylstannane (2) to the Cationic Palladium Complexes V·Y (Y = PMe$_3$ or DMF) That Are Responsible for the Divergent Stereochemical Outcome of the Open Transmetalation Step of the Stille Coupling



In the three cases examined the substitution processes are endergonic (Table 1). Comparison of their activation energies appears to confirm that the dissociation of an anionic ligand along the open transmetalation mechanism is feasible for triflates and even for bromides when a coordinating solvent (DMF) can act as a ligand.[35]

2b. Step 2: Displacement of One Ligand by the Stannane at the Palladium Center. The substitution of one palladium ligand by the stannane **2** in the cationic species **V·PMe$_3$** or **V·DMF** can follow two different approximations characterized by which group is on the apical positions in the transition state. The stereochemical consequence of these two alternative orientations of the incoming stannane is the formation of square-planar complexes **VI** with either *cis* or *trans* arrangements of the vinyl groups upon departure of ligand Y (Scheme 5).

***trans* Addition.** η^2-Coordination of trimethylvinylstannane (**2**) to the cationic palladium complexes **V·PMe$_3$** and **V·DMF** facilitates substitution of the ligands via the pentacoordinated transition states **Ts-L**$_{\mathbf{V-}\boldsymbol{trans}\mathbf{\text{-}VI}}$ and **Ts-S**$_{\mathbf{V-}\boldsymbol{trans}\mathbf{\text{-}VI}}$ (Figure 3). Phosphines occupy the apical positions of the trigonal bipyramid, whereas the vinyl group, the η^2-coordinated stannane, and Y (PMe_3 or DMF) rest on the equatorial plane. The bond distances between palladium and the incoming vinyl carbons are respectively 2.84 Å (Pd−Cα) and 2.75 Å (Pd−Cβ) for **Ts-L**$_{\mathbf{V-}\boldsymbol{trans}\mathbf{\text{-}VI}}$ (Y = PMe_3) and 3.01 Å (Pd−Cα) and 2.70 Å (Pd−Cβ) for **Ts-S**$_{\mathbf{V-}\boldsymbol{trans}\mathbf{\text{-}VI}}$ (Y = DMF). The energy barriers for these processes are 23.3 kcal/mol for **Ts-S**$_{\mathbf{V-}\boldsymbol{trans}\mathbf{\text{-}VI}}$ and 24.1 kcal/mol for **Ts-L**$_{\mathbf{V-}\boldsymbol{trans}\mathbf{\text{-}VI}}$ (Table 1). Both reactions are endergonic, and square-planar complexes **VI·PMe$_3$** (see Figure 4) lie at 12.9 and 20.2 kcal/mol starting from **V·PMe$_3$** or **V·DMF**, respectively.

***cis* Addition.** For the alternative *cis* orientation only the substitution of PMe_3 at palladium by the stannane is feasible through a similar transition state. Transition structure **Ts-S**$_{\mathbf{V-}\boldsymbol{cis}\mathbf{\text{-}VI}}$ (Figure 3) features a trigonal bipyramid in which the apical positions are ocuppied by the vinyl group and Y (PMe_3 or DMF). In this case, the coordination of the stannane to the Pd complexes **V·DMF** and **V·PMe$_3$** is more costly, and energy barriers of 26.2 kcal/mol for **Ts-S**$_{\mathbf{V-}\boldsymbol{cis}\mathbf{\text{-}VI}}$ and 28.7 kcal/mol for **Ts-L**$_{\mathbf{V-}\boldsymbol{cis}\mathbf{\text{-}VI}}$ were computed. The reaction energies for this step are 15.2 kcal/mol between **V·DMF** and ***cis*-VI·DMF** and 19.6 kcal/mol between **V·PMe$_3$** and ***cis*-VI·PMe$_3$**. The Pd−Cα and Pd−Cβ bond distances in these trigonal bipyramids are 2.55 and 2.65 Å for **Ts-L**$_{\mathbf{V-}\boldsymbol{cis}\mathbf{\text{-}VI}}$ and 2.31 and 2.38 Å for **Ts-S**$_{\mathbf{V-}\boldsymbol{cis}\mathbf{\text{-}VI}}$,

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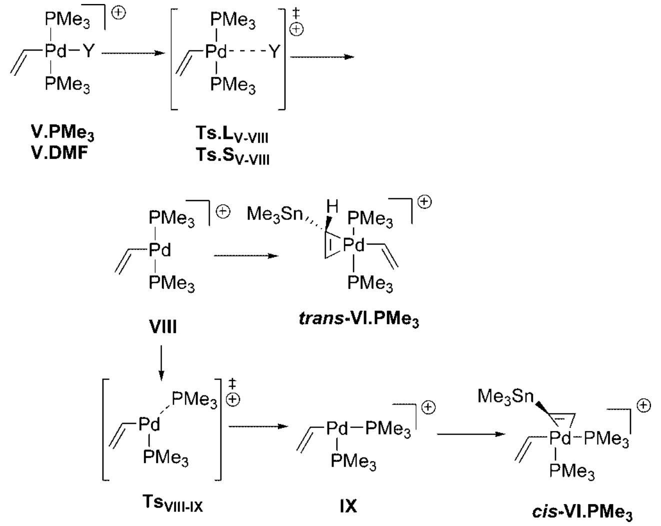
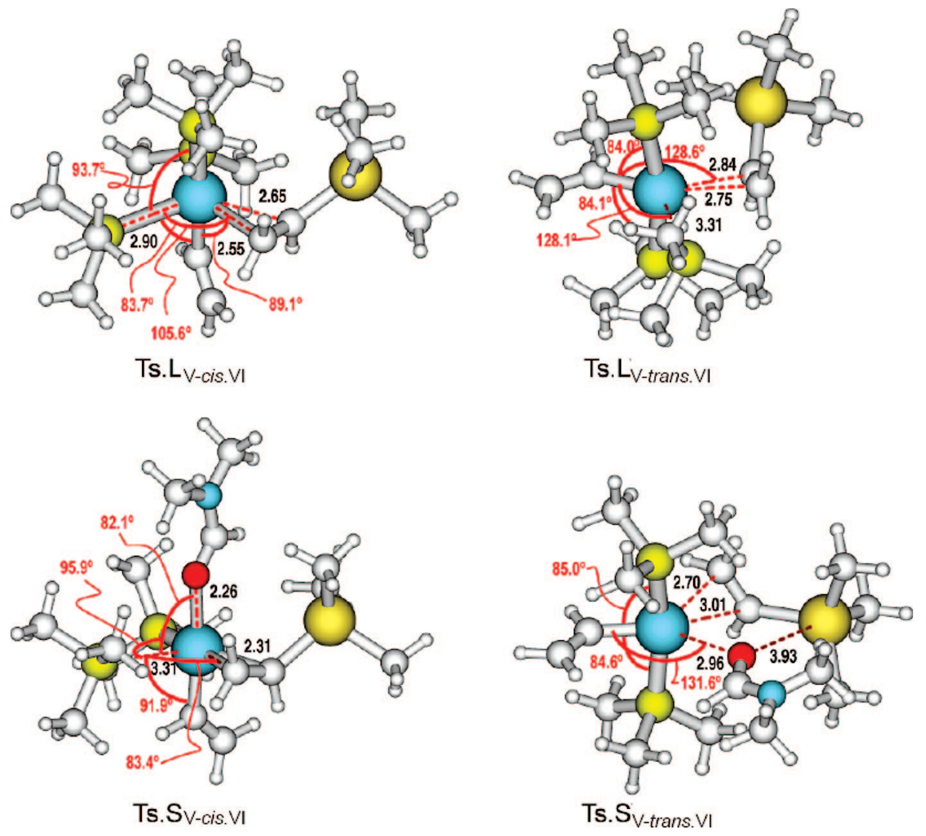
(36) For comparison, isomerization of the neutral *cis* to the *trans* complexes via association of DMF or PMe_3 (ref 15) is more favorable (on the order of 5 to 9 kcal/mol).

(37) We also explored the alternative pathway in which the dissociation of a ligand Y from $[PdL_2(vinyl)(Y)]^+$ precedes stannane coordination. This pathway could become highly competitive provided that the coordination of trimethylvinylstannane to the cationic trivalent palladium species is not penalized. Our inability to locate a transition state corresponding to the association of the vinylstannane nucleophile further attests to the greater reactivity of the tricoordinate dissociated species with *trans* and *cis* geometries $[Pd(PMe_3)_2(vinyl)]^+$ (**VIII/IX**).

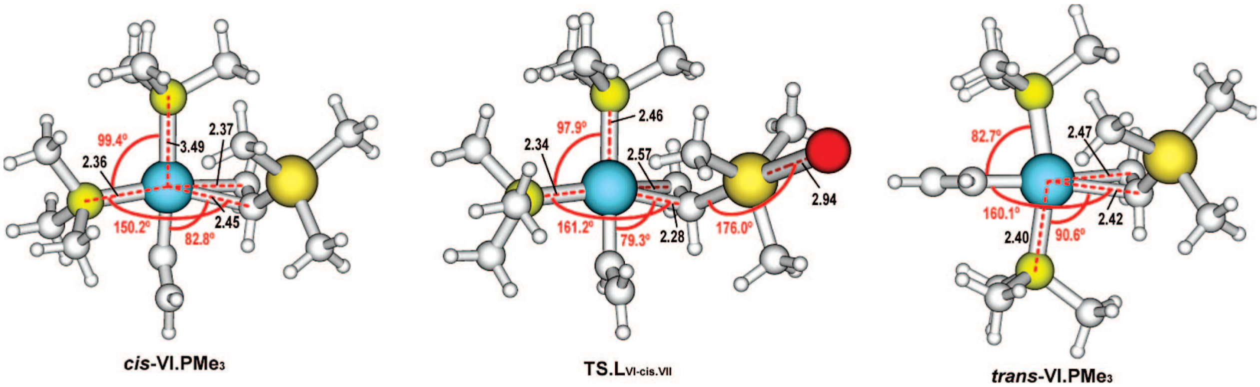




Ts.L$_{V\text{-}cis.VI}$ Ts.L$_{V\text{-}trans.VI}$

Ts.S$_{V\text{-}cis.VI}$ Ts.S$_{V\text{-}trans.VI}$

Figure 3. Optimized geometries (B3LYP/6-31G*-SDD) for the transition states **Ts-L**$_{\mathbf{V-}cis\mathbf{-VI}}$, **Ts-L**$_{\mathbf{V-}trans\mathbf{-VI}}$, **Ts-S**$_{\mathbf{V-}cis\mathbf{-VI}}$, and **Ts-S**$_{\mathbf{V-}trans\mathbf{-VI}}$ corresponding to the stannane coordination and ligand dissociation of the open transmetalation mechanism leading to the *cis* and *trans* arrangement of vinyl groups in **VI**.



***cis*-VI.PMe$_3$** **TS.L$_{VI\text{-}cis.VII}$** ***trans*-VI.PMe$_3$**

Figure 4. Optimized geometries (B3LYP/6-31G*-SDD) for the minima ***cis*-VI·PMe$_3$**, **Ts-L**$_{\mathbf{VI-}cis\mathbf{-VII}}$, and ***trans*-VI·PMe$_3$** characterized along the open transmetalation mechanism leading to the *cis* and *trans* arrangement of vinyl groups around palladium upon stannane coordination and ligand dissociation.[37]

considerably shorter than those of the alternative *trans* approximation (see Figure 3). This difference might reflect the greater accesibility of palladium to the incoming stannane in a more retarded transition state. The *cis* aproximation is more costly (4.6 kcal/mol) than its *trans* counterpart for complexes with the same substituents on palladium (Y = PMe$_3$).

2c. Step 3: Transmetalation. The mechanism proposed for this step (Scheme 6) has the features of an S$_N$2 substitution of the vinyl group by the nucleophile at the Sn center in **VI·Y**, a process that affords isomeric species [Pd(PMe$_3$)(vinyl)$_2$Y] **VII** (Y = PMe$_3$ or DMF) with *cis* or *trans* geometries, depending on the geometry of the starting **VI·Y** isomer. Consistent with this assumption, a trigonal bipyramid around the Sn center, in which the entering (Br$^-$) and the leaving group (ethylene) occupy the apical positions while the methyl groups sit in the equatorial plane, was found as a transition state. The forming Sn−Br and breaking Sn−Cα bonds evolve simultaneously, whereas the vinyl ligand changes from η^2- to η^1-coordination at palladium. The main geometric features of **Ts-L**$_{\mathbf{VI-}cis\mathbf{-VII}}$ (L = PMe$_3$) are the Pd−Cα and Pd−Cβ bond distances of 2.28 and 2.58 Å (2.30 and 2.73 Å for **Ts-L**$_{\mathbf{VI-}trans\mathbf{-VII}}$), reflecting the change in coordination of the stannane, and the Sn−Cα and Sn−Br distances of 2.45 and 2.94 Å, respectively (2.48 and 2.92 Å for **Ts-L**$_{\mathbf{VI-}trans\mathbf{-VII}}$).

The energy barrier for this S$_N$2 substitution process on tin is the same (3.9 kcal/mol, Table 2) for either the ***trans*-VI·PMe$_3$** or the ***cis*-VI·PMe$_3$** complexes. As a result of the formation of new bonds, these reactions are highly exothermic (−32.1 kcal/mol for ***trans*-VII·PMe$_3$** and −35.7 kcal/mol for ***cis*-VII·PMe$_3$**).

Scheme 6. S$_N$2 Reaction on Tin, the Final Event of the Transmetalation Step along the Open Mechanism of the Stille Reaction

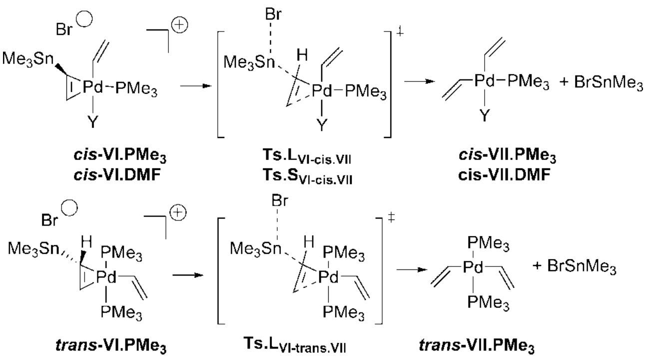


Table 2. Thermodynamic Data (in kcal/mol) for the Last Step of the Open Transmetalation Mechanism by S$_N$2 Reaction at Tin

structure	ΔG
***trans*-VI·PMe$_3$**	0.0
Ts-L$_{\mathrm{VI}-trans\text{-}\mathrm{VII}}$	3.9
***trans*-VII·PMe$_3$**	−32.1
***cis*-VI·PMe$_3$**	0.0
Ts-L$_{\mathrm{VI}-cis\text{-}\mathrm{VII}}$	3.9
***cis*-VII·PMe$_3$**	−35.7
***cis*-VI·DMF**	0.0
Ts-S$_{\mathrm{VI}-cis\text{-}\mathrm{VII}}$	5.6
***cis*-VII·DMF**	−25.3

When starting from ***cis*-VI·DMF**, the activation energy for this step (5.6 kcal/mol) is found to be 1.7 kcal/mol higher than that of ***cis*-VI·PMe$_3$**, perhaps as a consequence of the greater electrophilicity of Pd in the former. The process is also exergonic (−25.3 kcal/mol), and the transition state is geometrically similar to its PMe$_3$ analogue with Pd−Cα, Pd−Cβ, Sn−Cα, and Sn−Br distances of 2.23, 2.68, 2.46, and 2.96 Å, respectively.

Discussion

As stated in the Introduction, accumulating evidence on the kinetics and stereoselectivity of the Stille reaction has led to a reformulation of the traditional reaction mechanism.[4] The current proposal includes a dual catalytic cycle of associative nature characterized by either the cyclic or the open nature of the transition states involved in the crucial transmetalation step.[5] Species corresponding to intermediates of the transmetalation variants have been characterized by electrospray ionization mass spectrometry (EIMS).[38]

The mechanistic duality (open vs cyclic) is further complicated by the alternative associative vs dissociative paths, the occurrence of PdL$_2$RX or PdL(S)RX species in the presence of coordinating solvents, and the generation of *cis*- and *trans*-[PdL$_2$R$_2$] complexes after transmetalation via the open mechanism. At present the relevance of some of these variants to the catalytic cycle and the nature of the transition states can be assessed only with computational tools.

Thus, as a continuation of our theoretical studies of the cyclic transmetalation,[15] we carried out a similar comprehensive survey of the open variant of the Stille reaction in order to establish the boundaries of the mechanistic duality. Since the open transmetalation mechanism was considered to be favored for pseudohalides (triflates),[5] we explicitly considered these electrophiles in this work. The important role of added chloride anions in the oxidative addition of vinyl triflates, widely documented in the literature, has also been addressed.

Stille Cross-Coupling of Vinyl Bromides: Open vs Cyclic Transmetalation Mechanism. To allow comparison with previously reported results,[15] the mechanistic duality in the Stille coupling of vinyl bromide (**1a**) and trimethylvinylstannane (**2**) will be discussed starting from the stable *trans*-[Pd(PMe$_3$)$_2$(vinyl)X] complex **III** formed upon oxidative addition of **1** to Pd(PMe$_3$)$_2$ (**I**) and *cis*−*trans* isomerization.

The energy required for ligand dissociation, assisted by the association of PMe$_3$ or DMF in *trans*-[Pd(PMe$_3$)$_2$(vinyl)Br] (**III·Br**), is 20.9 and 13.5 kcal/mol, respectively. The association of the coordinating solvent is favored by 7.4 kcal/mol, which confirms that coordinating solvents with high dielectric constant greatly facilitate the formation of cationic species [PdL$_2$R(DMF)]$^+$Br$^-$.

The computed energy values for the dissociation of halide in *trans*-[Pd(PMe$_3$)$_2$(vinyl)Br] assisted by DMF indicate that the experimental conditions might in effect dictate the composition of the cationic complex. In general, [PdL$_3$(vinyl)]$^+$X$^-$ complexes are expected to be more stable than their [PdL$_2$(vinyl)(S)]$^+$X$^-$ counterparts in the presence of excess ligand (the usual experimental setting) and should be the predominant species in noncoordinating solvents or in solvents of moderate coordination ability toward palladium (THF). However, when using a coordinating solvent of high dielectric constant, such as DMF (or NMP), the predominant species are expected to be [PdL$_2$(vinyl)(S)]$^+$X$^-$, as our computations show. Experimental evidence for the formation of cationic species *trans*-[PdL$_2$(aryl)(S)]$^+$X$^-$ by ligand- or solvent-assisted substitution on *trans*-[PdL$_2$RX] complexes has already been disclosed.[14b]They are presumably more reactive than the neutral precursors because of their higher electrophilicity.

The proper open transmetalation mechanism starts from the cationic species *trans*-[Pd(PMe$_3$)$_2$(vinyl)(Y)]$^+$ **V**. It is comprised of two discrete steps: first the substitution of a palladium ligand by the incoming vinylstannane nucleophile, and second the S$_N$2-type displacement by the halide of the vinyl ligand at the tin center. Furthermore, in mixed complexes [Pd(PMe$_3$)$_2$(vinyl)(DMF)]$^+$ **V** both L and S could be exchanged by the stannane. To further complicate the analysis, two different trajectories are possible for the first step, and the result of the distinct three-dimensional arrangements is the generation of *cis* and *trans* isomers of the final palladium complex.

Values greater than 24 kcal/mol were computed for the R-for-Y ligand substitution step, with the exchange of coordinated solvent by the stannane approaching in a *trans* orientation being the most favored (ca. 1 kcal/mol lower than the PMe$_3$ substitution of the same geometry). The activation energy for the substitution of PMe$_3$ on the *cis* isomers is much higher (2.1 and 4.6 kcal/mol relative to the most favorable path).

Finally, the energy barrier corresponding to the elimination of the XSnMe$_3$ group via an S$_N$2 reaction on species **VI·Y** is very small compared to that for the association of the stannane (3.9 kcal/mol for both geometries of **V·PMe$_3$** and 5.6 kcal/mol for *cis*-**VI·DMF**).

Therefore, the analysis of the energy profiles for the open transmetalation mechanism of the Stille reaction of vinyl bromide **1a** and trimethylvinylstannane **2** catalyzed by Pd(PMe$_3$)$_2$ (**I**) reveals the likely occurrence of two alternative paths of similar energy, leading to the *trans* or the *cis* square-planar palladium species [Pd(PMe$_3$)$_2$(vinyl)$_2$] (**VII**), a conclusion in full agreement with the results reported for the related coupling of aryl bromides.[17,39] Experimentally, two competitive

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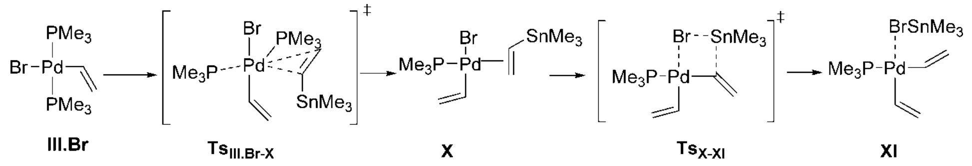
[38] Santos, L. S.; Rosso, G. B.; Pilli, R. A.; Eberlin, M. N. *J. Org. Chem.* **2007**, *72*, 5809.

Scheme 7. Transmetalation Step for the Stille Cross-Coupling Reaction between *trans*-[Pd(PMe$_3$)$_2$(vinyl)Br] (III·Br) and Trimethylvinylstannane (2) via the Cyclic Associative Mechanism[41]



pathways for the transmetalation have been observed: a fast path that leads to the product through the *cis* intermediate and a slower one that proceeds through a *trans* intermediate that can be observed in some particular experimental settings.[14b] In fact, species of general structure ***trans*-VII** can be detected in the transmetalation of aryl triflate palladium pincer complexes with 2-furyltin derivatives.[40]

How does this open transmetalation pathway compare to the cyclic alternative? Within the limitations of the used methods to accurately describe dissociation processes that yield charged species, and the uncertainties inherent to the use of continuum models for the study of solvent effects, we can provide only qualitative guidelines comparing the two processes in the gas phase.

Scheme 7 summarizes our previous results for the cyclic transmetalation via an associative ligand substitution mechanism, including the characterization of a cyclic species as the highest energy transition state in the complete catalytic cycle.[15] In that paper, we showed that the cyclic transmetalation of *trans*-[Pd(PMe$_3$)$_2$(vinyl)Br] (**III·Br**) occurs in two steps: (1) η^2-coordination of the stannane assisted by the ligand dissociation to afford a tetracoordinated palladium intermediate [Pd(PMe$_3$)(vinyl)(η^2-vinylstannane)Br] (**X**) in a fast pre-equilibrium; (2) a rate-determining rearrangement to afford directly intermediate **XI**, which then eliminates trimethyltin bromide to afford the T-coordinated complex [Pd(PMe$_3$)(vinyl)$_2$] with *cis* geometry.

Figure 5 depicts the reaction profiles in gas phase for the cyclic and open transmetalation mechanisms proposed for the Stille cross-coupling of trimethylvinylstannane (**2**), starting from the oxidative addition intermediate **III·Br**. To allow for comparison of the energies, the departing bromide has been arbitrarily placed at a nonbonding distance of the cationic palladium species of the open mechanism, and the energy of the separated ion pair was thus recalculated. Although the computed values are different from those listed in the tables, the relative values are the same. The highest energy barrier for the cyclic mechanism corresponds to the formation of the cyclic four-coordinated transition state (29.4 kcal/mol). The *cis*- and *trans*-geometric variants of the open transmetalation mechanism show rate-determining steps for the stannane coordination and S$_N$2 displacement at tin, respectively. Both are nevertheless considerably higher in energy (more than 10 kcal/mol in the gas phase) than the cyclic alternative. The effect of solvent will most likely affect the values considerably in both pathways, but a much greater reduction would be required for bromides to render the open mechanism competitive relative to the cyclic alternative.

Regardless of the mechanism followed, the results of the computations are in agreement with the kinetic rate law (order one on Pd and Sn, order minus one in L), consistent with a fast pre-equilibrium involving stannane association with ligand substitution.[14]

Stille Coupling of Alkenyl Triflates. Alkenyl triflates are valuable electrophiles in palladium-catalyzed reactions.[4,42] The most comprehensive kinetic studies on the oxidative addition of vinyl triflates to Pd(0) complexes in solution (DMF) are due to Jutand and Négri.[43] They found that the oxidative addition of vinyl triflate to Pd(PPh$_3$)$_4$ is a fast event in a coordinating solvent ($t_{1/2}$ = 4 s) that affords the moderately stable (ca. 30 min at 25 °C) cationic complex [Pd(PPh$_3$)$_2$(η^1-vinyl)(DMF)]$^+$(TfO)$^-$, a species characterized by conductivity measurements, ESI-MS, and ^{31}P NMR spectroscopy. Kinetic

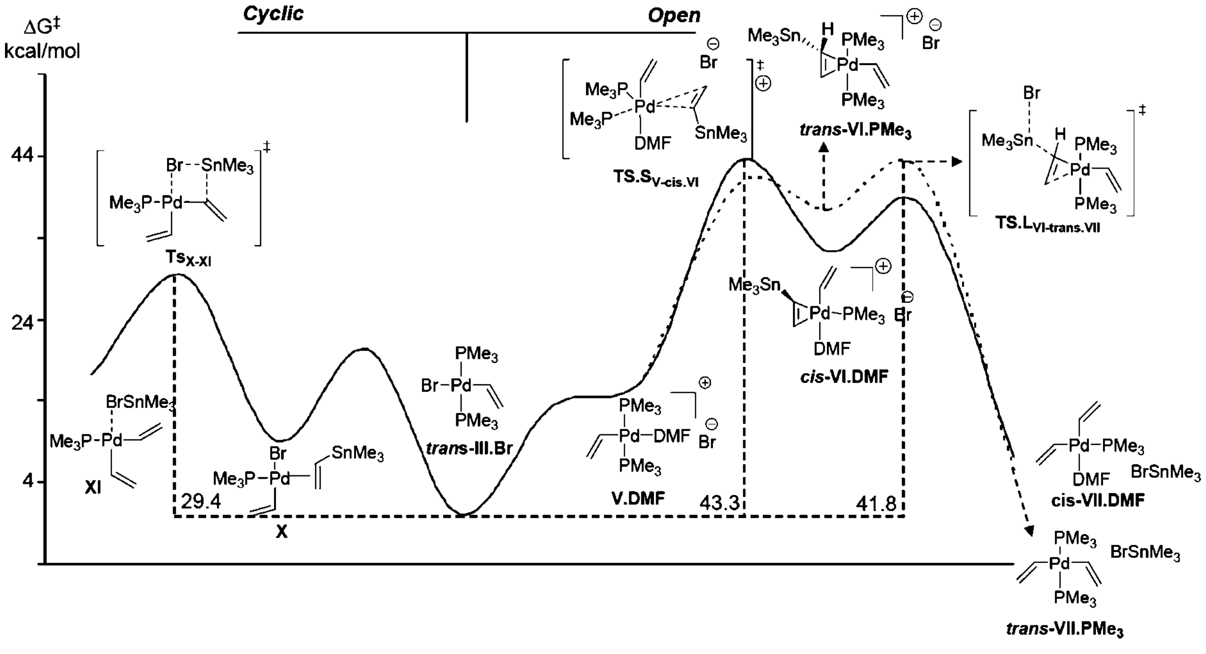


Figure 5. Comparison of the energy profiles in the gas phase for the open and cyclic transmetalation mechanisms of the Stille coupling reaction of vinyl bromide (**1a**) and trimethylvinylstannane (**2**) catalyzed by Pd(PMe$_3$)$_2$, starting from ***trans*-III·Br**.

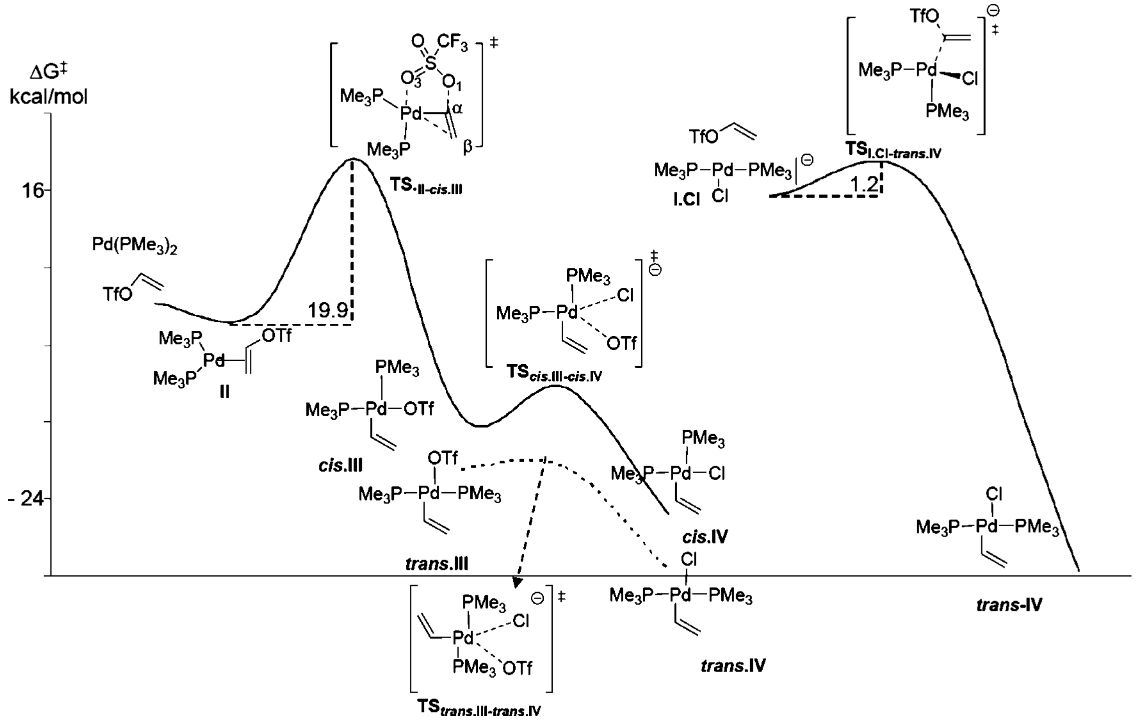


Figure 6. Energy profile for the oxidative addition of vinyl triflate (**1b**) to Pd(PMe$_3$)$_2$ (**I**) and the effect of LiCl.

analysis of this system led to the conclusion that [Pd(PPh$_3$)$_2$(η^2-vinyl-OTf)] would be transiently formed and obey steady-state kinetics, whereas the intermediate neutral [Pd(PPh$_3$)$_2$(η^1-vinyl)(OTf)] species would dissociate triflate assisted by solvent to afford cationic [Pd(PPh$_3$)$_2$(η^1-vinyl)(DMF)]$^+$(TfO)$^-$ at a higher rate than it is formed. The comparison between the oxidative addition steps of vinyl triflate and vinyl bromide allowed them to estimate that the former is ca. 10^4 times more reactive. This is in contrast to the comparable reactivity of phenyl triflate and phenyl bromide with Pd(PPh$_3$)$_4$ in DMF.[43]

We characterized the gas-phase transition state **Ts$_{\text{II}-\textit{cis}\text{-III}}$** for the oxidative addition of vinyl triflate to the 14-e$^-$ starting complex Pd(PPh$_3$)$_2$ (**I**) involving a −O−Pd-C−O−S− rearrangement after formation of the η^2-(vinyl triflate)-coordinated complex **II**, which required 19.9 kcal/mol (cf., 18.9 kcal/mol for vinyl bromide[15b]).

Our computation of the energy required for ligand dissociation in *trans*-[Pd(PMe$_3$)$_2$(vinyl)(OTf)] assisted by the association of another phosphine ligand afforded a value of 17.1 kcal/mol. The energy needed for the dissociation of triflate assisted by PMe$_3$ is 3.8 kcal/mol lower than that needed for its bromide counterpart. This value is expected to decrease considerably when DMF replaces the triflate via the same mechanism, although we could not locate the corresponding transition structure. Therefore, as predicted in ref 43, DMF as a coordinating solvent with a high dielectric constant greatly facilitates the formation of the highly reactive cationic species [PdL$_2$R(DMF)]$^+$ when triflates are used Along the same line, Espinet et al. also found that the displacement of triflate by PH$_3$ and THF in *trans*-Pd(PH$_3$)$_2$(phenyl)OTf is much easier than that of bromide, requiring for their model system 0.7 and 4.8 kcal/mol, respectively (SCF energies).[17]

As stated in the Introduction and in the Results section, the effect of added LiCl on the Stille cross-coupling of alkenyl triflates has been much debated. We computed a mechanism in which the added chloride would displace the leaving triflate by trapping the Pd(II) cationic intermediate as [Pd(PPh$_3$)$_2$(η^1-vinyl)Cl], which will then proceed through a neutral pathway.[44] This mechanistic proposal is supported by the detection and characterization of such neutral complexes ([Pd(PPh$_3$)$_2$(η^1-vinyl)Cl]) in oxidative addition reactions of triflates performed

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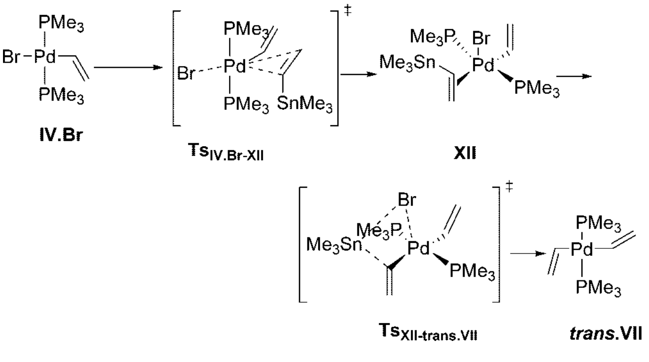
(39) Espinet, Ujaque, et al.[17] found that the *cis* trajectory is more stable than the *trans* by 1.6 kcal/mol using the less bulky PH$_3$. Our data show that the opposite is true in the gas phase, but including solvent effects the preferences might be reversed.

(40) Cotter, W. D.; Barbour, L.; McNamara, K. L.; Hechter, R.; Lachicotte, R. J. *J. Am. Chem. Soc.* **1998**, *120*, 11016.

(41) The pentacoordinated Pd species with trigonal-bipyramidal geometry initially proposed as transition state of the cyclic concerted process[14] could also be located only when the stannane, the vinyl, and the bromide ligands were placed on the equatorial plane of the bipyramid. Starting from the [Pd(PMe$_3$)$_2$(η^2-vinylstannane)(η^1-vinyl)Br] intermediate **XII** with square-pyramidal geometry, transition structure **Ts$_{\text{XII}-\textit{trans}\text{-VII}}$** was located, yielding the *trans*-square-planar complex ***trans*-VII** upon transmetalation. The overall activation barrier for the transmetalation via *a cyclic five-coordinated mechanism* was found to be considerably higher (56.1 kcal/mol in the gas phase from **III·Br**) than that corresponding to the formation of the *cyclic four-coordinate mechanism* previously characterized (36.0 kcal/mol in the gas phase).[15]



(42) Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47.

(43) Jutand, A.; Negri, S. *Organometallics* **2003**, *22*, 4229.

(44) The same role for LiCl in Heck reactions of alkenyltosylates has been suggested (Hansen, A. L.; Ebran, J.-P.; Ahlquist, M.; Norrby, P.-O.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3349).

in the presence of chloride ions.[45] As Goossen et al. before,[47] we could not confirm the formation of the anionic five-coordinate Pd(II) species $[Pd(PPh_3)_2(\eta^1\text{-vinyl})(OTf)Cl]^-$ proposed by Amatore.[29,46]

In addition, we also considered the mechanistic alternative in which the same neutral species $[Pd(PPh_3)_2(\eta^1\text{-vinyl})Cl]$ (**IV**) would be obtained by oxidative addition of vinyl triflate (**1b**) to the anionic trivalent Pd complex $[Pd(PMe_3)_2Cl]^-$ (**I·Cl**). The formation of these chloropalladium(0) anionic complexes[19] and their persistence, even in the presence of solvent molecules, has been experimentally demonstrated.[30] The trivalent complex $[Pd(PMe_3)_2Cl]^-$ has also been the object of many computational studies. At the B3LYP/6-31G*+LACVP* level it was found to display an imaginary frequency corresponding to the out-of-plane bending of the chloride, while a tighter optimization (LACVP*) revealed that the complex dissociated to a dicoordinated neutral $Pd(PMe_3)_2$ complex with Cl^- attached by "hydrogen bonds" to the C−H bonds of the methyl groups.[30] Recently, Thiel described the analogous $[Pd(PMe_3)_2(OAc)]^-$ complex as a stable local minimum (BP86/6-31G*+LANL2DZ) with a distorted structure.[31] As depicted in Figure 6, our results show that the "Jutand-type"[29] anionic Pd(0) species **I·Cl** provides a highly favorable oxidative addition path, with an almost barrierless replacement of triflate by the nucleophilic Pd(0) via a substitution reaction.

Other computational studies concur with the finding that the anionic pathway for the oxidative addition to $[Pd(PMe_3)_2(OAc)]^-$ is energetically more favorable than the neutral one,[47] the highest free energy barrier of this oxidative addition sequence being significantly lower than that of the neutral pathway.[31,47,48]

Notably, Hartwig found that the accelerating effect of added bromide on the coupling of aryl tosylates was the result of a combined effect of the medium and formation of a more reactive anionic Pd(0) species[50] after exchange of a phosphine by bromide. The irreversible oxidative addition of aryl tosylates to anionic Pd(0) occurs concurrently with the irreversible oxidative addition of the electrophile followed by the exchange of bromide by tosylate. Since the computational findings confirm the experimental results indicating that the oxidative addition of vinyl triflates does not appear to be rate-determining, the accelerating effect of the chloride ion[51] on the oxidative addition should be only moderate for the highly reactive alkenyl triflates. Another role suggested for the neutral complexes $[Pd(PPh_3)_2(\eta^1\text{-vinyl})Cl]$ is to sequester the cationic precursor and prevent its decomposition to vinylphosphonium salts.[43]

Besides originating from addition of vinyl triflate to an anionic, tricoordinate palladium complex, intermediate **IV** could also be viewed as the product of the direct oxidative addition of vinyl chloride to $Pd(PMe_3)_2$. Chlorides are generally the least reactive halogenated electrophiles in cross-coupling reactions and require the use of bulky[34] or bidentate phosphines[47] to enter similar catalytic processes, so it is hypothesized that the oxidative addition of these halides is rate-determining. From the energy values of Figure 6, we can show that **IV** would be energetically affordable from triflates in the presence of LiCl, thus circumventing the unfavorable direct oxidative addition of alkenyl(aryl) chlorides to palladium complexes with common phosphines. Intermediate **IV** is therefore proposed to enter the transmetalation step with stannanes following the cyclic mechanism. According to DFT calculations, the reactivity of common halides in this step is higher for chlorides (Cl > Br > I),[18] something that Espinet et al.[14,35] have confirmed at the bench, reporting that the transmetalation of tributylvinylstannane with isolated *trans*-$[Pd(AsPh_3)_2(Ar)X]$ takes place more rapidly with chlorides. The computed role of Cl^- is thus consistent with the assumption that a more electronegative leaving ligand assists the transmetalation process by making the Pd(II) more electropositive and thus facilitating the nucleophilic attack of the vinylstannane.

Conclusions

Our computations support the current understanding of the Stille reaction as a complex multifarious mechanism that is subject to diverse effects upong changes of substrates, palladium ligands, solvents, and additives. It is clear from the results that the nature of the electrophile plays a dominant role in determining the transmetalation mechanism (cyclic vs open) of the Stille reaction.

The open mechanism for the transmetalation step seems to be favored for electrophilic palladium species, formed by the substitution of an anionic ligand X (X = pseudohalide) by a ligand Y (Y = coordinating solvent or phosphine), whereas the cyclic mechanism is favored for X = halide, thus confirming the proposal of Casado and Expinet.[14]

For vinyl triflate we also computed two variants of the oxidative addition mechanism, trying to shed some light on the role of added chloride anion: the mechanism going through the anionic trivalent species was computed to be virtually barrierless and proceed via a nucleophilic displacement at the vinyl carbon, while the anionic ligand exchange step, originating from the direct oxidative addition of vinyl triflate via a rearrangement of the sulfonate group, takes place via a pentacoordinated transition state instead. Regardless of the exact mechanism for the oxidative addition of triflates to Pd(0) complexes, our results indicate that the chloride anion affords a neutral square-planar palladium species that is formally the product of direct oxidative addition of alkenyl chlorides to $Pd(PMe_3)_2$. Thus the added chloride anion drives the expected

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(45) (a) Jutand, A.; Mosleh, A. *Organometallics* **1995**, *14*, 1810. (b) Jutand, A.; Hii, K. K.; Thornton-Pett, M.; Brown, J. M. *Organometallics* **1999**, *18*, 5367.

(46) For an X-ray structure of a pentacoordinate Pd(II) complex, see: Bröring, M.; Brandt, C. D. *Chem. Commun.* **2003**, 2156.

(47) (a) Goossen, L. J.; Koley, D.; Hermann, H.; Thiel, W. *Chem. Commun.* **2004**, 2141. (b) Goossen, L. J.; Koley, D.; Hermann, H. L.; Thiel, W. *J. Am. Chem. Soc.* **2005**, *127*, 11102.

(48) In a more recent study (Kozuch, S. ; Amatore, C.; Jutand, A.; Shaik, S. *Organometallics* **2005**, *24*, 2319),the relevance of the anionic intermediates in catalytic cycles was examined in the light of the energetic span (i.e., the energy difference between the summit and trough of the catalytic cycle). The trivalent anionic $[Pd(PR_3)_2Cl]^-$ complex proved to be superior to the neutral one on substitution reactions with thiolates. A dual catalytic role was proposed, first stabilizing the transition state for oxidative addition, and second "destabilizing" the nucleophilic addition product using RS^- as nucleophile. During oxidative addition, the chloride anion keeps a small P−Pd−P angle, a property of certain chelating diphosphines that has been found beneficial for the cross-coupling reactions of unreactive electrophiles.[49] The coordination of ArCl to the $[Pd(PR_3)_2Cl]^-$ species induces the dissociation of the chloride, another proof of the reluctance of Pd to form pentacoordinated complexes.[45]

(49) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741.

(50) (a) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 8704. (b) Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, *23*, 194.

(51) Complexes coordinating one phosphine and one anion $[Pd(t\text{-}Bu_3P)Cl]^-$ have also been proposed as the major species in catalytic cycles (Fristrup, P.; Jensen, T.; Hoppe, J.; Norrby, P-O. *Chem.−Eur. J.* **2006**, *12*, 5352). The barrier to oxidative addition of ArCl correlates with σ^-, which suggests that the mechanism is best described as an S_N Ar type.[52]

(52) Ahlquist, M.; Norrby, P.-O. *Organometallics* **2007**, *26*, 550.

transmetalation step from the open one with triflates to the cyclic mechanism in the presence of the additive.

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Supporting Information Available: File containing Cartesian coordinates and total energy for all computed structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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