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Computational Characterization of a Complete Palladium-Catalyzed Cross-Coupling Process: The Associative Transmetalation in the Stille Reaction

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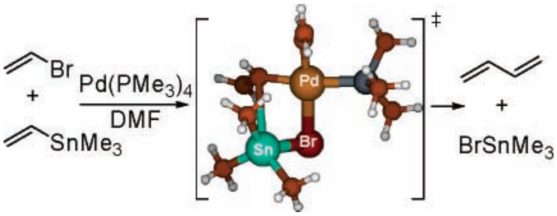
ABSTRACT



The species presumably involved in the associative ligand substitution mechanism for the Stille cross coupling of vinyl bromide and trimethylvinyl stannane with Pd(PMe$_3$)$_2$/PMe$_3$ as catalysts in DMF (as ligand and solvent) have been structurally and energetically characterized. The cyclic four-coordinate transition state for the rate-determining transmetalation step explains the retention of configuration in the Stille coupling of chiral nonracemic alkyl stannanes.

Metal-catalyzed cross-coupling processes,[1] in particular, the Stille and Suzuki reactions, are powerful synthetic methods for C−C bond formation because of their high selectivity, functional group tolerance, and mildness of the reaction conditions. However, the choice of reaction conditions (i.e., palladium source, additives, solvents, halide or pseudohalide, ligands, the "copper cocatalyst", etc.) is still rather empirical. Accounting for those variables, multifaceted reaction mechanisms (more comprehensive than the classical oxidative addition, transmetalation, and reductive elimination) are emerging.[2] Casado and Espinet proposed two associative mechanisms for the transmetalation step of the Stille reaction to comply with the reaction rates in the coupling of aryltriflates and tributyl vinylstannane and with the stereochemical outcome in the coupling of some chiral nonracemic alkyl stannanes.[3] The associative mechanism that proceeds through a cyclic transition state (or intermediate)[3] resulting in the replacement of a ligand by the stannane-transferring substituent was favored over the alternative open transition state for the coupling of X-bridging electrophiles and stannanes.

In this communication, we wish to report that the proposed associative transmetalation mechanism in the Stille coupling is supported by DFT[4] computations (B3LYP)[5] and to

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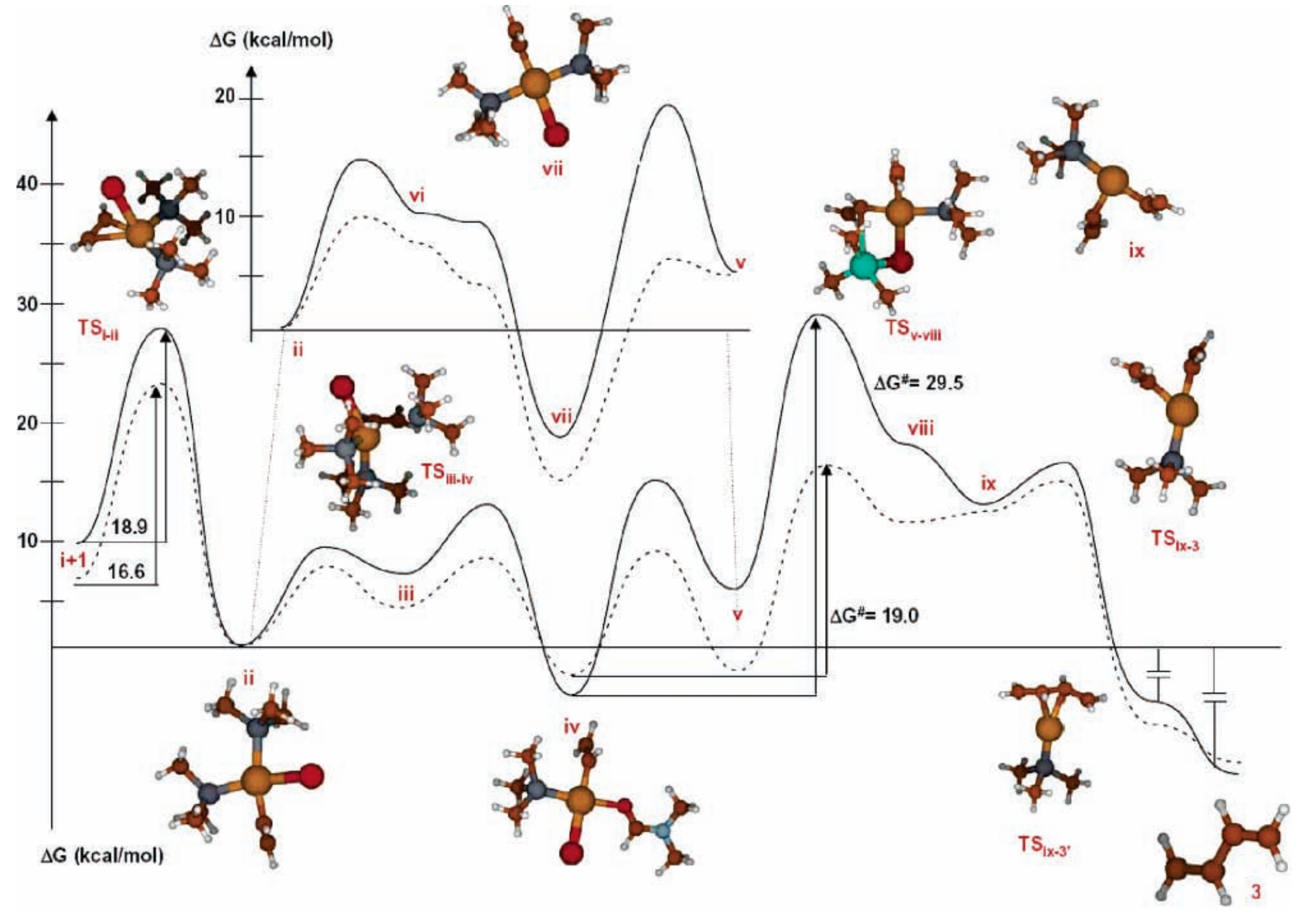

Figure 1. Computed reaction free-energy profiles in the gas phase (solid line) and in solvent (CH_3CN, COSMO; dotted line) for the catalytic cycle of Scheme 1 with L = PMe_3 (top) and L = DMF (bottom). The free energy of activation for the rate-determining steps is labeled as $\Delta G^{\ddagger}$.

characterize an associative ligand substitution as well as a cyclic species as the highest-energy transition state in the complete catalytic cycle. As a model reaction, we computed the Stille coupling of vinyl bromide **1** and trimethyl vinylstannane **2** catalyzed by $Pd(PMe_3)_2/PMe_3$ in DMF as solvent (Figure 1) using density functional theory calculations[6] (6-31G* basis set for C, H, and P, in conjunction with the Stuttgart/Dresden relativistic-effective core potentials for Pd, Sn, and Br).[7] Donating solvents (DMF) as Pd ligands were also included in the study because they might replace labile phosphine ligands to generate a more electrophilic Pd with increased reactivity toward transmetalation.[8] The energy profile of Scheme 1 is shown in Figure 1. Table 1 contains, for an easier evaluation of the reaction profile, the electronic energy, the electronic energy plus the zero-point vibrational energy (zpve) correction, and the free-energy differences (ΔG) for all species, taking complex **ii** as a reference.

The oxidative addition of palladium to the C−Br bond[9] is a concerted step with a large energy barrier (18.9 kcal/

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(5) Computational details, the geometries of the transition states, and products in this study are gathered in the Supporting Information.

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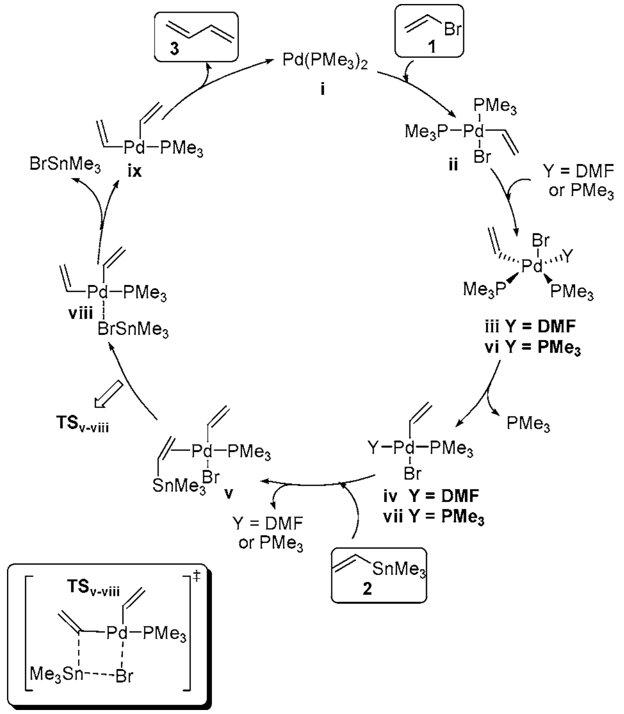
Scheme 1. Catalytic Cycle for the Associative Stille Cross-Coupling Reaction through a Cyclic Transmetalation Transition State



mol). The double bond of vinyl bromide **1** coordinates first to Pd to give a η^2-complex, in a three-centered transition state, **TS**$_{\mathbf{i-ii}}$, characterized by 1.90 and 2.40 Å distances between the Pd and the unsaturated carbon atoms (proximal and distal) and by 2.88 and 2.49 Å distances for the Pd−Br and C−Br bond lengths. Square planar complex **ii** having a cis arrangement[10] is then formed, in an overall exothermic process (the energy difference between **i** + **1** and **ii** is 9.8 kcal/mol).

Table 1. Thermodynamic Data (in kcal/mol) of the Catalytic Cycle of Scheme 1 (Gas Phase) Relative to Structure **ii**[a]

structure	electronic energy	electronic energy + zpve	ΔG
i + **1**	25.3	23.8	9.8
TS$_{\mathbf{i-ii}}$	32.0	30.2	28.7
ii	0.0	0.0	0.0
TS$_{\mathbf{ii-iii}}$	−4.1	−3.0	8.0
iii, Y = DMF	−5.0	−3.3	6.9
TS$_{\mathbf{iii-iv}}$	3.3	3.6	12.5
iv, Y = DMF	−1.9	−1.9	−4.8
TS$_{\mathbf{iv-v}}$	6.9	7.1	15.6
v	4.7	4.7	4.3
TS$_{\mathbf{v-viii}}$	25.9	24.9	24.7
viii	21.8	20.5	17.1
ix	29.9	27.8	12.6
TS1$_{\mathbf{ix-i}}$	32.7	30.6	16.7
TS2$_{\mathbf{ix-i}}$	−10.1	−10.1	−23.4
TS$_{\mathbf{ii-vi}}$	2.0	2.8	15.4
vi, Y = PMe$_3$	−5.4	−2.8	10.2
TS$_{\mathbf{vi-vii}}$	−2.9	−2.6	9.4
vii, Y = PMe$_3$	−10.9	−11.0	−11.3
TS$_{\mathbf{vii-v}}$	7.0	7.4	19.1

[a] Calculated at the B3LYP/6-31G*-SDD level.

A solvent- or ligand-assisted topomerization through a five-coordinated complex (Y = DMF, **iii**; Y = PMe$_3$, **vi**) with square pyramidal geometry was found to provide a low energy pathway for the conversion of Pd(PMe$_3$)$_2$(vinyl)Br *cis*-**ii** into *trans*-**iv** (or **vii**).[11]

The bromine occupies the apical position (Pd−Br distances of 3.85 Å in **iii** and 3.10 Å in **vi**) stabilizing the complex by electrostatic interaction along the z-axis, where the electron density is lower.[12] The trans square planar complexes **iv** and **vii** are formed by trans-ligand release from these transition-state structures.[13] The overall cis−trans isomerization process is exothermic (4.8 kcal/mol for **ii**−**iv**; 11.3 kcal/mol for **ii**−**vii**). The solvato complex **iv** is less stable than the corresponding phosphine analogue **vii**. This ground-state destabilization and the higher electrophilicity of **iv** for subsequent attachment of the stannane nucleophile combine to provide a reaction path of lower energy for the solvato complex.

Casado and Espinet depicted an L-for-R S$_E$ transmetalation at the Pd center with X ligands capable of acting as bridging groups in which ligand substitution and formation of a cyclic species occurred in concert via a five-coordinate transition state (or intermediate) at Pd.[3] However, at least for alkenyl stannanes,[14] computations support a stepwise process in which associative ligand substitution precedes the formation of a cyclic transition state. Thus, η^2-coordination of trimethyl vinylstannane **2** to the *trans*-Pd complexes **iv** and **vii** facilitates substitution of the phosphine or solvato ligands via a transition state (**TS**$_{\mathbf{iv-v}}$ and **TS**$_{\mathbf{vii-v}}$) with a geometry that shows features of a trigonal bipyramid. The apical positions are occupied by the bromine and vinyl substituents. Coordination of stannane **2** is against an energy barrier of 20.4 and 30.4 kcal/mol, respectively, whereas the energy difference between **iv** or **vii** and **v** amounts to 9.2 and 15.6 kcal/mol, respectively.

The *cyclic four-coordinate* transition state **TS**$_{\mathbf{v-viii}}$ (Figure 1) with a bridging Br ligand was characterized next. The Br−Pd, Br−Sn, and C$_{sp^2}$−Sn bond distances are 2.71, 2.79, and 3.23 Å, respectively. Inspection of the vibrational normal mode associated with the imaginary frequency of **TS**$_{\mathbf{v-viii}}$ reveals that the Me$_3$Sn is shifting between the vinyl and Br groups.[15] The entire process from intermediate **iv** is endothermic; an energy difference between **v** and **viii** of 12.8 kcal/

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(14) Among other modifications, we explored the transition structures for the series of halogens (Cl, Br, I) with restrained distances and angles of the key bonds. When unconstrained after minimization, the ring opens and the dihedral flips, keeping an X−Sn distance that increases with the size of the halogen. In addition, adding a ligand to palladium on **TS**$_{\mathbf{v-viii}}$ leads to unstable structures which points to the reluctance of Pd to engage in bipyramidal geometries with two of the ligands in a four-membered ring.

mol was computed, and reaching **TS$_{\mathbf{v-viii}}$** requires us to surmount an energy barrier of 20.4 kcal/mol. Last, the intermediate **viii** eliminates trimethyltin bromide **4**, affording a three-coordinate (T-shaped) palladium complex **ix** stabilized by 4.5 kcal/mol. The activation barrier for transmetalation is 29.5 kcal/mol for the solvato complex and 36.0 kcal/mol for the phosphine analogue.

The rapid elimination of butadiene **3** from the three-coordinate cis 14e$^-$ intermediate **ix** is a highly exothermic step (>40.1 kcal/mol),[16] occurring in a stepwise manner. Two transition structures were found: Y-shaped **TS$_{\mathbf{ix-3}}$** located only 4.1 kcal/mol above **ix** (C−C bond distance of 2.17 Å) and **TS$_{\mathbf{ix-3'}}$** located further downhill corresponding to the η^2-coordination of the diene **3** to the Pd complex prior to its release (C−C bond distance of 1.46 Å).[17]

Solvation energies were considered using the PCM and COSMO models. Both THF and CH_3CN provided the same general trends: all structures are stabilized with the exception of the square planar complexes **ii** and **iv** (L = DMF). Stabilization is particularly significant for the transition structures and intermediates in the pathway between **iv/vii** and **viii**. Consequently, the slight destabilization of the trans square planar solvato complex **iv** and the stabilization of **TS$_{\mathbf{v-viii}}$** translate into an energetically more favorable mechanism having an energy of activation of only 19.0 kcal/mol.[18] The 16.6 kcal/mol activation energy computed in CH_3CN for the oxidative addition indicates that for other substrates and/or reaction conditions this step might become rate determining.

In summary, although the palladium-catalyzed coupling of organic electrophiles with stannanes (Stille reaction) shows complex mechanistic features, a complete structural and energetic description of one of the postulated variants of the catalytic cycle has been achieved.[19] Although the ongoing theoretical treatment of the entire mechanistic manifold (open associative transmetalation vs dissociative mechanism) for the Stille reaction awaits completion, the results presented here indicate that the ligand substitution during the transmetalation step via a cyclic transition state, proceeding with retention of configuration, is indeed feasible. We found that solvent as a ligand plays a role by not only lowering the activation energy of the rate-determining transmetalation step but also favoring the isomerization of *cis*-$Pd(PMe_3)_2RBr$ **ii** to *trans*-$PdY(PMe_3)RBr$ (Y = PMe_3 **vii** or DMF **iv**) via five-coordinate Pd species after the oxidative addition. Moreover, depiction of the reaction course for the oxidative addition and the reductive elimination steps is of value because these are common not only to other cross-coupling reactions but also to other processes catalyzed by palladium as well (i.e., the oxidative addition in the Heck reaction).

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Supporting Information Available: Computational details, solvent reaction profiles, compound structures, and energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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