

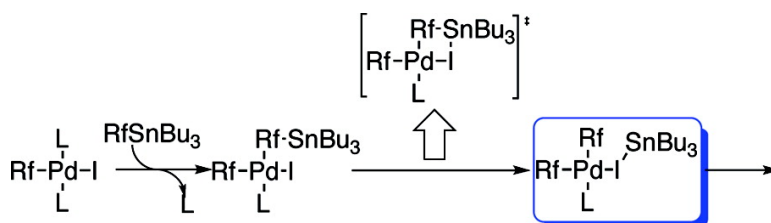
Communication

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 Study of the Reversal of the Transmetalation Step**

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Observation of a Hidden Intermediate in the Stille Reaction. Study of the Reversal of the Transmetalation Step

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Among the palladium-catalyzed cross-coupling processes, the Migita–Stille reaction is perhaps the most deeply studied experimentally. The accepted mechanism can follow the open or cyclic pathways shown in Scheme 1. A comprehensive account of the mechanistic studies was published in 2004.¹ Further mechanistic studies,^{2–4} including detailed theoretical (DFT) calculations,^{5,6} have been published recently.

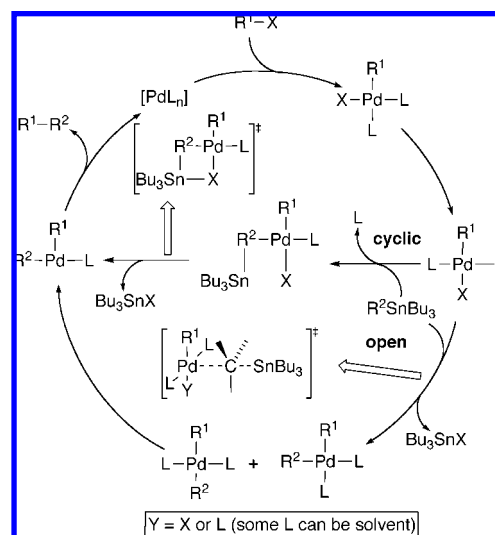
The steps preceding the transmetalation have been experimentally confirmed by observation of intermediates. Of the two intermediates produced by transmetalation in an *open* mechanism (lower part of Scheme 1), *trans*-[PdR¹R²L₂] (for which the reductive elimination is rate-determining) was observed by NMR, whereas *cis*-[PdR¹R²L₂] (for which the reductive elimination is faster than transmetalation) was unambiguously deduced kinetically.^{7,8} However, for the *cyclic* mechanism (upper part of Scheme 1), the transmetalation is usually rate-determining⁹ since the *cis* arrangement of the R¹ and R² substituents obtained from the transmetalation makes their coupling fast. This has precluded so far the observation of any putative transmetalated intermediate that would further support experimentally the proposed *cyclic* mechanism.

Our recent DFT calculations for the catalyzed coupling of PhBr and Sn(vinyl)Me₃ suggest that the formation of the intermediate *cis*-[PdR¹R²L₂] from the starting reagents is thermodynamically disfavored, so a successful coupling requires an easy irreversible R¹–R² reductive elimination to pull the reaction forward.⁵ Moreover, a post-transmetalation intermediate with I-SnBu₃ acting as a I donor ligand, [PdR¹R²(AsPh₃)(ISnBu₃)] (**II**), was predicted. The detection of this intermediate would provide strong experimental support to the cyclic mechanism since this intermediate does not appear in the open mechanism.

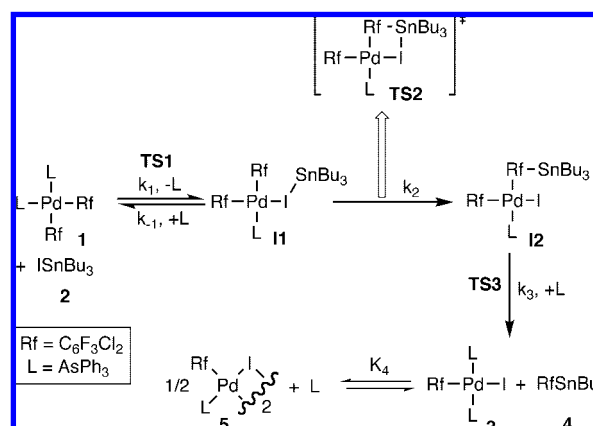
A reaction of XSnBu₃ with a *cis*-[PdR¹R²L₂] complex reluctant to reductively eliminate R¹–R² might behave (obeying the microscopic reversibility principle) as the reverse of the Stille reaction, to give *trans*-[PdR¹XL₂] and R²SnBu₃. This reverse reaction should allow for study of the hidden post-transmetalation steps in the cyclic mechanism; since in the retro-transmetalation¹⁰ sense the intermediate **II** precedes the transmetalation step, which is the highest barrier for the process, it might become observable. *cis*-[PdRf₂(AsPh₃)₂] (R¹ = R² = Rf = 3,5-C₆Cl₂F₃), **1**,¹¹ a stable compound that additionally offers easy monitoring of the reactions by ¹⁹F NMR,¹² was chosen to study the retro-transmetalation of the Stille reaction (Scheme 2).

The reaction of **1** and ISnBu₃ (**2**) in THF at 323 K yielded a mixture of *trans*-[PdRfI(AsPh₃)₂] (**3**) and RfSnBu₃ (**4**) (Scheme 2). Minor side reactions (some decomposition to Pd(0) or formation of some *trans*-[PdRf₂(AsPh₃)₂], which does not undergo retro-

Scheme 1



Scheme 2



transmetalation) were irrelevant for the kinetic study of the retro-transmetalation process, as they were observed only at times larger than those used in the kinetic study. The other species detected by ¹⁹F NMR were the pursued intermediate [PdRf₂(AsPh₃)(ISnBu₃)] (**II**) and the dimer [Pd₂Rf₂(μ-I)₂(AsPh₃)₂] (**5**), already reported.¹³ In an independent study, the fast equilibrium **3** + **4** = ¹/₂ **5** + L was fully characterized (K₄(323 K) = 3.7 × 10⁻⁵ mol L⁻¹; ΔH⁰ = 19.4 ± 2.0 kcal mol⁻¹; ΔS⁰ = 39.7 ± 6.2 cal K⁻¹ mol⁻¹).¹⁴ These values are important for the retro-transmetalation kinetics since the AsPh₃ released modifies the rate of transmetalation. Moreover, due to the high ΔS⁰ value, **5** is not observed in the NMR spectra at room or lower temperatures. The relevance of these

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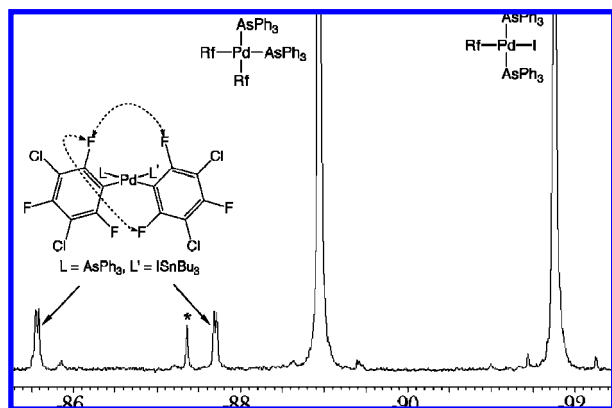
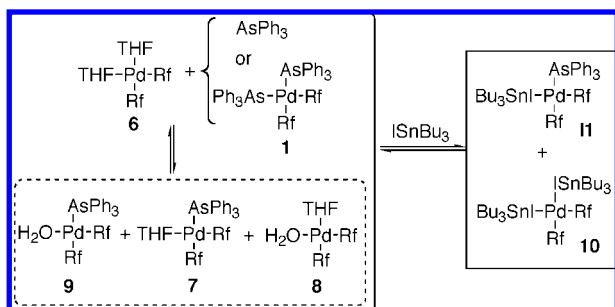


Figure 1. ^{19}F NMR spectrum (F_{ortho} range) of the reaction in Scheme 2, recorded at 230 K, showing the signals of intermediate **II** and a schematic representation of the through-space ^{19}F – ^{19}F coupling (dotted curves in the structure). The signal * belongs to *trans*- $[\text{PdRf}_2(\text{AsPh}_3)_2]$. ^{13}C satellites are observed for the very intense signals of *cis*- $[\text{PdRf}_2(\text{AsPh}_3)_2]$ and *trans*- $[\text{PdRfI}_2(\text{AsPh}_3)_2]$.

Scheme 3



dimeric species in the Stille reaction, usually carried out at reflux, has been noticed before.^{13,15–17}

The predicted intermediate $[\text{PdRf}_2(\text{AsPh}_3)(\text{ISnBu}_3)]$ (**II**) could be unambiguously detected in the course of the kinetic experiments below 283 K, as a deceptively simple pair of doublets of an AA'BB' spin system, due to the through-space J coupling of *ortho*-fluorine atoms of the nonequivalent perhaloaryl groups in conditions of slow rotation of the fluoroaryl group about the C–Pd bond (Figure 1). Irradiation of one of the signals simplifies the other to a sharp singlet, while at 323 K the signals appear as broad triplets. This spectroscopic and dynamic behavior has been reported in depth for other $[\text{PdRf}_2\text{L}^1\text{L}^2]$ complexes.^{12,18,19}

The identity of **II** was confirmed independently. Attempts to prepare $[\text{PdRf}_2(\text{AsPh}_3)(\text{THF})]$ (Scheme 3) as a possible precursor for **II** afforded a complex mixture of **1** and **6–9** in THF,^{18,20} which were easily identified. The addition to this mixture of a large excess of ISnBu_3 gave, as major species, *cis*- $[\text{PdRf}_2(\text{AsPh}_3)_2]$ (**1**), *cis*- $[\text{PdRf}_2(\text{ISnBu}_3)_2]$ (**10**), and $[\text{PdRf}_2(\text{AsPh}_3)(\text{ISnBu}_3)]$ (**II**). In addition to the ^{19}F NMR spectra, the ^{119}Sn NMR spectrum confirmed three Sn-containing species, appearing at 63.2 ppm (m) (the most intense, ISnBu_3 , in excess in solution), 39.7 (**II**), and 104.6 ppm (**10**).

The activation parameters for the formation of **II** were determined by an Eyring study using ^{19}F NMR (at 376.50 MHz) in the range of 225–270 K. Fortunately, at these temperatures, the slow transmetalation step is not observed within the time of experiment. The study afforded for **TS1** the following values: $\Delta H^\ddagger = 15.0 \pm 1.1 \text{ kcal mol}^{-1}$; $\Delta S^\ddagger = -17.4 \pm 4.5 \text{ cal K}^{-1} \text{ mol}^{-1}$. The negative value for ΔS^\ddagger supports an associative substitution of AsPh_3 by

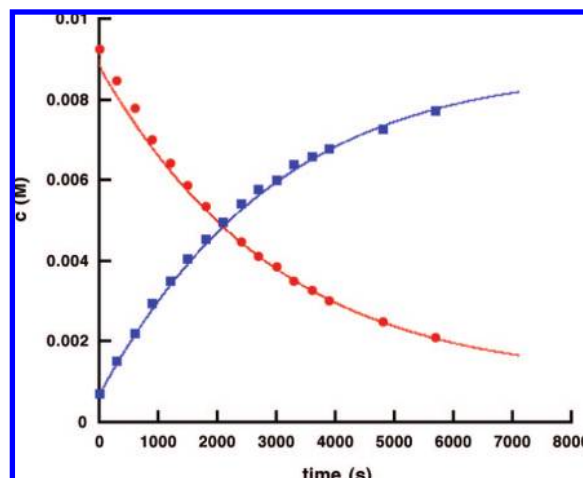


Figure 2. Observed concentrations as a function of time of (●) the palladium reactant **1**; (■) the trans product **3** (corrected for the formation of dimer **4**). Solid lines are the best fit using Gepasi.

ISnBu_3 . These values were used to calculate ΔG^\ddagger for the pre-equilibrium at other temperatures.

In an independent study, ΔG^\ddagger for the transmetalation (**TS2**) was determined at 323 K by monitoring the variations of concentrations of **1** and **3** during the retro-transmetalation reaction. At this temperature, the concentration of **II** reached a maximum very quickly and then kept steady until the final steps of the reaction. The data of eleven runs were fit to the multistep kinetic model proposed in Scheme 2, by nonlinear least-squares (NLLS) regression, using the program Gepasi.²¹ The experimental values for the equilibrium constants K_1 ($K_1 = k_1/k_{-1}$; see Scheme 1) and K_4 were entered into the adjust program. Figure 2 shows the results of a typical run (consumption of reactant and formation of trans product as a function of time) and the curves of the Gepasi fit. Luckily, it was found that the value of k_2 was little sensitive to the value assumed for k_3 (which could not be determined experimentally). Thus, although the Gibbs energy of **TS3** could not be assigned, a reliable value of $\Delta G^\ddagger(323 \text{ K}) = 26.5 \text{ kcal/mol}$ ($k_2 = 5.28 \times 10^{-3} \text{ s}^{-1}$) was calculated for **TS2**.

DFT calculations were carried out on a model where AsH_3 and ISnMe_3 are used instead of AsPh_3 and ISnBu_3 (the computational details are given in the Supporting Information). The calculated $\Delta E(\text{gas})$ and $\Delta E(\text{solvent, THF})$ values for the whole reaction are depicted in Figure 3, along with the experimental ΔG values determined in THF, so that calculated and experimental results can be directly compared. Note that the experimental data only reach to **TS2** since, beyond that point, only the formation of **3** + **4** is experimentally observed, along with the formation of dimer **5**. In agreement with the calculated ΔE^0 values of 7–8 kcal/mol for the retro-transmetalation equilibrium $\mathbf{1} + \mathbf{2} = \mathbf{3} + \mathbf{4}$ (including in **3** the amount corresponding to its dimerization to **5**), the retro-transmetalation reaction is completely shifted to the right, that is, to the formation of the Stille reagents, as observed by ^{19}F NMR.

For intermediate **II** and for **TS2** (Figure 4), the total number of particles does not change with respect to the starting system (in each case, taking into account the molecule of ligand released, the exchange is two particles for two particles), and a moderate entropic contribution is expected. Consistent with this prediction, the respective experimental values of their Gibbs energies lie between those calculated for E in the gas phase and in solvent. This

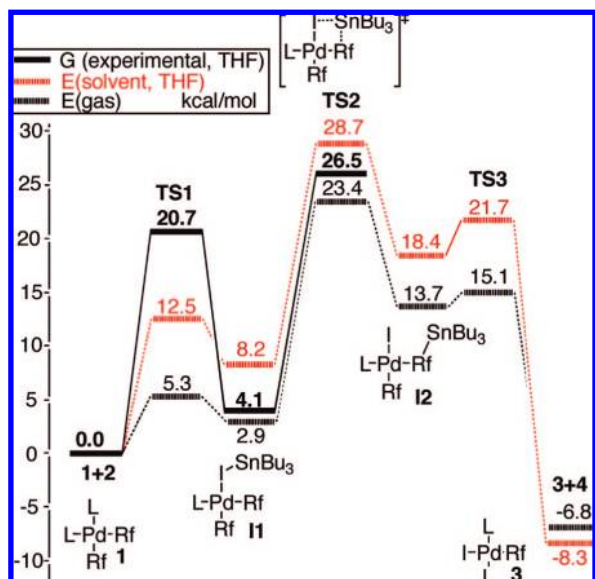


Figure 3. Profile of the retro-transmetalation reaction **1** + **2**, showing the experimental values in THF and the calculated values $\Delta E(\text{gas})$ and $\Delta E(\text{solvent})$ in kcal/mol. The calculated structure of the detected intermediate **II** is also shown.

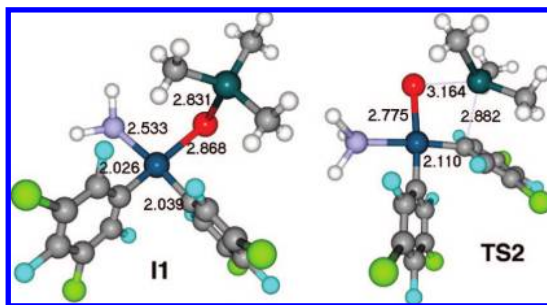


Figure 4. Calculated geometry (DFT) for the observed intermediate **II**, and for the transmetalation transition state **TS2**. Other calculated geometries are given in the Supporting Information.

coincidence supports the idea that the calculated values give a reasonable estimation of the system as far as entropy changes are small.

In contrast, the E values calculated for **TS1** are noticeably lower than the experimental Gibbs energy value, but the calculated $E_{\text{TS1}}(\text{solvent, THF})$ value (12.5 kcal/mol) is not far from the experimental ΔH^\ddagger value (15.0 ± 1.1 kcal/mol). As discussed above, the experimental data point to an associative transition state (hence with a considerable entropic contribution). Interestingly, a correction for entropy of about 8–10 kcal/mol to the $E_{\text{TS1}}(\text{solvent, THF})$ value would bring the calculation very close to the $\Delta G^\ddagger_{\text{TS1}}$ value obtained experimentally (20.7 kcal/mol).²² Thus, in spite of some deviations, arising from the simplification of the system using a calculation model with smaller ligands, the estimation of $E(\text{solvent})$ and the crude correction for entropy (based only in the number of particles) behave remarkably well and should possibly be reliable enough to

assign associative versus dissociative processes in other cases where only ΔG^\ddagger values were experimentally available.

In summary, an intermediate of the type $\text{cis-}[\text{PdR}^1\text{R}^2\text{L}(\text{ISnBu}_3)]$, which was proposed to be the result of a cyclic transmetalation but had never been detected in the direct reaction, has been spectroscopically observed in a retro-transmetalation reaction. The formation of this intermediate is a strong experimental support for the occurrence of cyclic mechanisms in some Migita–Stille reactions.

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Supporting Information Available: Details of syntheses, characterization of the complexes, kinetic experiments, and DFT calculations including calculated structures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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