

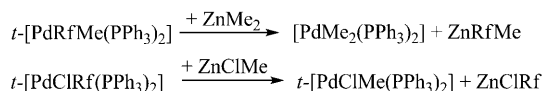
# Palladium Round Trip in the Negishi Coupling of *trans*-[PdMeCl(PMePh<sub>2</sub>)<sub>2</sub>] with ZnMeCl: An Experimental and DFT Study of the Transmetalation Step

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Compared with the detailed mechanistic knowledge of the Stille reaction,<sup>[1]</sup> little is known about the Negishi reaction.<sup>[2,3]</sup> Recently, we experimentally uncovered the complicated behavior of the transmetalation of *trans*-[PdRfCl(PPh<sub>3</sub>)<sub>2</sub>] (Rf = 3,5-dichloro-2,4,6-trifluorophenyl) with ZnMe<sub>2</sub> or ZnMeCl, showing that each methylating reagent afforded stereoselectively a different isomer (*trans* or *cis*, respectively) of the coupling intermediate [PdRfMe(PPh<sub>3</sub>)<sub>2</sub>].<sup>[4]</sup> Moreover, the study revealed the occurrence of undesired transmetalations, such as those shown in Scheme 1, which could eventually produce homocoupling products; the corresponding undesired intermediates were detected and identified by NMR spectroscopy techniques.

The formation of undesired intermediates in related reactions with aryl zinc derivatives was later observed by Lei et al.<sup>[5]</sup>

Herein, we report an experimental mechanistic study of the reaction of *trans*-[PdClMe(PMePh<sub>2</sub>)<sub>2</sub>] (**1**) with



Scheme 1.

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ZnMeCl,<sup>[6]</sup> which affords the first experimental determination of thermodynamic parameters of a Negishi transmetalation. This is complemented with a theoretical DFT study, which provides a detailed view of the reaction pathway, consistent with the experimental parameters.

The reactions of **1** with ZnMeCl were carried out (with one exception) in 1:20 ratio, simulating catalytic conditions with 5% Pd, in THF at different temperatures.

At room temperature, the only product observed was *cis*-[PdMe<sub>2</sub>(PMePh<sub>2</sub>)<sub>2</sub>] (**2**), in equilibrium with the starting material **1**. In these conditions, complex **2** undergoes slow decomposition (reductive elimination) to give ethane.<sup>[7,8]</sup>

When the reaction was monitored by <sup>31</sup>P NMR spectroscopy at 223 K (Figure 1 a), the coupling rate to give ethane became negligible and the formation of *trans*-[PdMe<sub>2</sub>(PMePh<sub>2</sub>)<sub>2</sub>] (**3**), as well as *cis*-[PdMe<sub>2</sub>(PMePh<sub>2</sub>)<sub>2</sub>] (**2**), was observed. The *trans* isomer **3** seemed to be formed first and then disappeared. The same reaction, carried out at 203 K in 1:1 ratio to get a slower rate of transformation, confirmed that **3** is formed noticeably faster than **2** (Figure 1 b). Thus, the observation of the *cis* isomer at room temperature is deceptive for the stereoselectivity of the transmetalation. Snapshots of two moments of the transmetalation reaction at 203 K, as seen by <sup>31</sup>P NMR spectroscopy, are shown in Figure 1 c.

The behavior of **3** is typical of a kinetic product of noticeably lower stability than the thermodynamic product (**2**): eventually it disappears from observation as the reaction proceeds and gets closer to the equilibrium concentrations, where the concentration of **3** is very small. In effect, during the progress of the reaction at 223 K (Figure 1 a), the concentration of **2** increases continuously; in contrast, a small accumulation of **3** is produced initially and then its concentration decreases, so that in 300 min **3** has practically disappeared. After about 10 h at 223 K, the system has reached equilibrium between the starting complex **1** and the final thermodynamic product **2** ([**1**] = 5.8 × 10<sup>-3</sup> mol l<sup>-1</sup>, [**2**] = 4.4 × 10<sup>-3</sup> mol l<sup>-1</sup>, and K<sub>eq</sub> = 2.0 × 10<sup>-2</sup>); the concentration of **3** is below the limit of NMR observation.

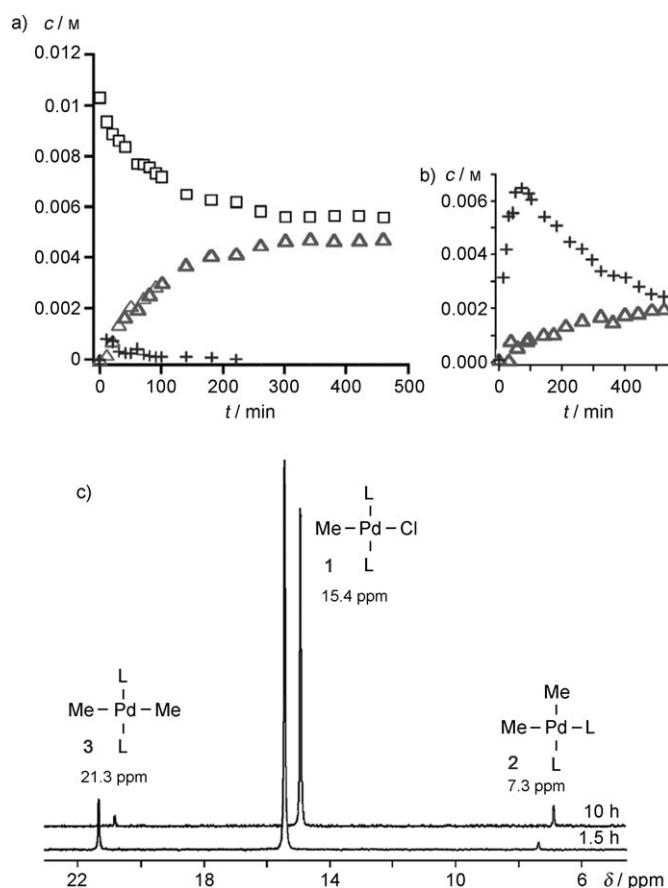


Figure 1. Concentration versus time data, obtained by  $^{31}P$  NMR spectroscopy, for the reaction of **1** ( $\square$ ) with  $ZnMeCl$  in different conditions: a) ratio 1:20, in THF at 223 K. Starting conditions:  $[Pd]=0.01 M$ ;  $[ZnMeCl]=0.20 M$ ; b) ratio 1:1, in THF at 203 K (**1** is not depicted because its abundance is above the values represented in the ordinate axis).  $\Delta$ : **2**, +: **3**. Starting conditions:  $[Pd]=0.056 M$ ;  $[ZnMeCl]=0.056 M$ ; c)  $^{31}P$  NMR spectra of the transmetalation reaction at 203 K, showing the evolution with time of the signals of **1**, **2**, and **3**.

In contrast to the transient existence of **3** in the transmetalation experiments (in fact **3** could not be observed in the experiments at room temperature), *trans*-[PdMe<sub>2</sub>(PMePh<sub>2</sub>)<sub>2</sub>] (**3**) as an isolated compound (prepared by an independent method)<sup>[8]</sup> is fairly stable: it takes 10 h in THF at 273 K for about half of it to isomerize to **2**, whereas at 223 K the **3** to **2** isomerization rate is negligible. On the other hand, the addition of  $ZnCl_2$  to a solution of **3** in THF, at 223 K, produces the instantaneous and complete transformation of **3** to **1**. In the same conditions (addition of  $ZnCl_2$ ), compound **2** is also transformed into **1** until equilibrium is reached. In other words, the transmetalations between **1** and  $ZnMeCl$  to give **2** or **3** are quickly reversible. These experiments support the interpretation of the observations shown in Figure 1 that in Negishi conditions there should be a fast isomerization between **3** and **2** by fast retrotransmetalations to **1**, in spite of the fact that direct isomerization is slow.<sup>[9]</sup>

The measured concentration versus time data of the experiments depicted in Figure 1 were fitted to the kinetic model shown in Figure 2,<sup>[10]</sup> and the transmetalation and ret-

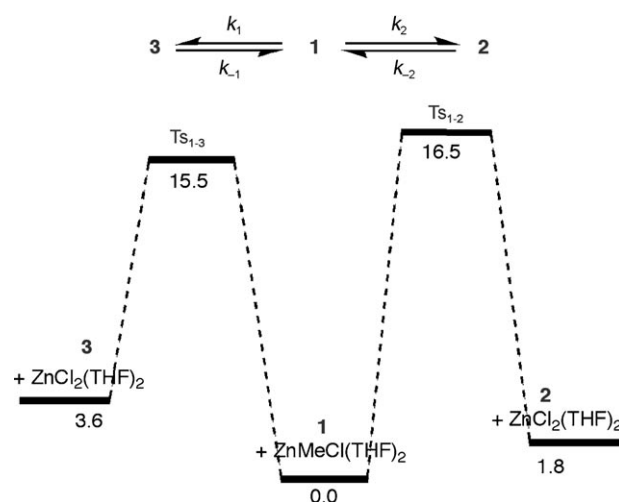
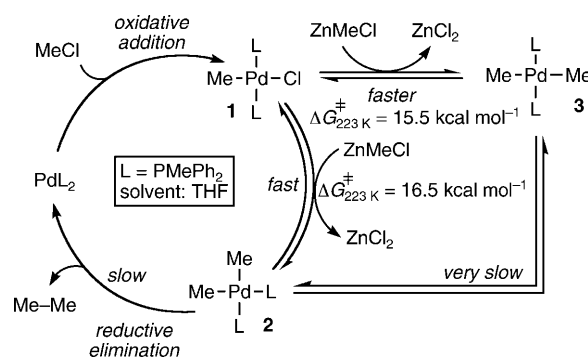


Figure 2. Kinetic model (top) and experimental  $\Delta G^\ddagger$  profile (bottom) (kcal mol<sup>-1</sup>, in THF at 223 K) of the reaction.  $k_1$  and  $k_2$  are the transmetalation rate constants, whereas  $k_{-1}$  and  $k_{-2}$  are the retrotransmetalation rate constants. Ts=transition state.

rotransmetalation rates at 223 K were calculated. From these rates, the relative  $\Delta G_{223}^\ddagger$  values for **1**, **2**, **3**, and for the transition states were obtained (for details see the Supporting Information). These thermodynamic parameters are plotted in Figure 2. Similar parameters ( $\Delta G_{203}^\ddagger(Ts_{1,2})=15.6$  kcal mol<sup>-1</sup>;  $\Delta G_{203}^\ddagger(Ts_{1,3})=14.3$  kcal mol<sup>-1</sup>) were obtained at 203 K. The values obtained indicate that the transmetalation of **1** to **3** is about 5–10 times faster than the transmetalation of **1** to **2**; the retrotransmetalations from **3** or **2** to **1** are still faster. At the same temperatures, the coupling rate for **2** to give ethane is negligible.

These quantitative results support the mechanism shown in Scheme 2. The transmetalation follows two competitive pathways: One, producing **3**, is kinetically preferred, but is unproductive for coupling. The other, about one order of magnitude slower, affords **2** from which coupling will eventually take place, although at a much slower rate. The rate of direct *cis*–*trans* isomerization (very slow even at room temperature) is negligible compared with the indirect isomerization by retrotransmetalation to **1**, catalyzed by the



Scheme 2. Simplified reaction mechanism of the Negishi coupling.

ZnCl<sub>2</sub> formed in the reaction. Thus, the slowness of the reductive elimination of **2** allows many **1**→**2** and **1**→**3** round trips to occur before the irreversible coupling takes place.

Having the experimental thermodynamic parameters in hand, we performed DFT calculations by means of the Truhlar's M06 functional to uncover the features of the transition states and other mechanistic details. There are two recent theoretical studies on Negishi reactions,<sup>[5,11]</sup> but they are on special Pd complexes that cannot give rise to *cis/trans* isomers, as observed here. One of the studies uses a chelating ligand, in which *cis-trans* isomerism is excluded; the other is on a tricoordinated complex with a bulky ligand, again excluding isomers. Hence, none of them could account for our experimental observation of two competing transmetalation products. Moreover, the two studies have overlooked the usual tetrahedral coordination of Zn, using instead linearly coordinated Zn species. This neglect of the coordination ability of the solvent gives birth to some intermediates that might perhaps exist in vacuum, but are unrealistic in coordinating solvents.

Our theoretical DFT study was undertaken by using the real molecules and realistic tetrahedral Zn species coordinated with THF;<sup>[12]</sup> moreover, the calculations were fitted to the same temperature of the experimental kinetic study (223 K). Two low-energy, concerted transmetalation pathways were found, leading to the kinetic product **3** (concerted *trans* (CT) transmetalation, Figure 3, lower  $\Delta G^\ddagger$ ) and the thermodynamic one **2** (concerted *cis* (CC) transmetalation, Figure 4, higher  $\Delta G^\ddagger$ ), respectively. The reaction starts by ligand substitution on Zn, which involves THF displacement

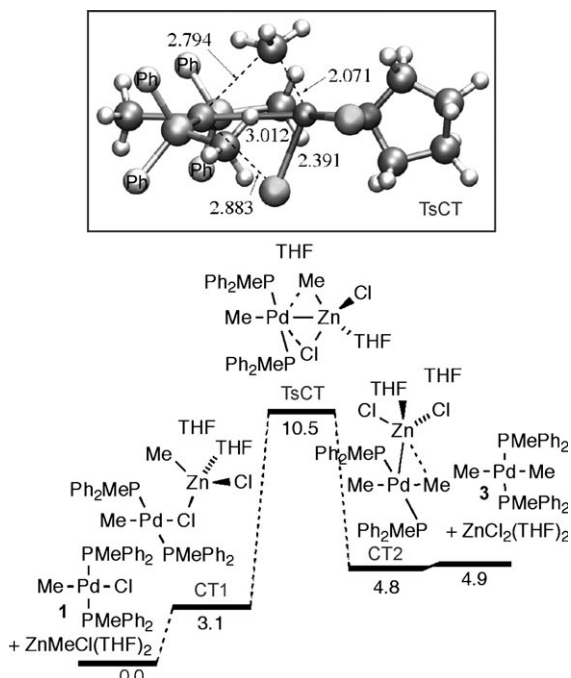


Figure 3. Energy profile for the concerted transmetalation to form the *trans* product, showing  $\Delta G_{\text{solv}}$  values obtained at 223 K (a color version of the drawing of the TsCT geometry can be found in the Supporting Information).

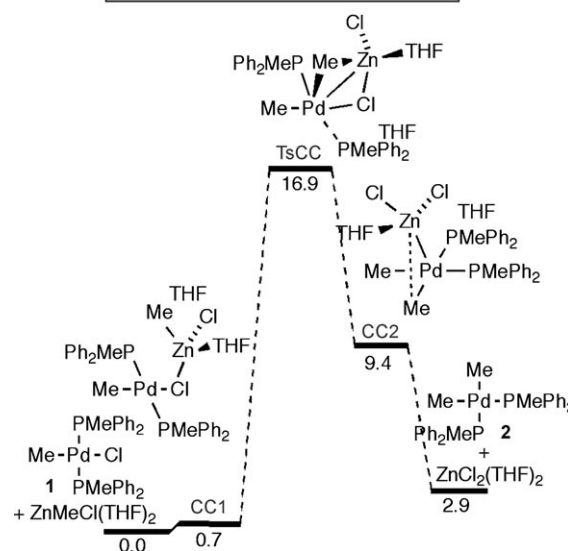
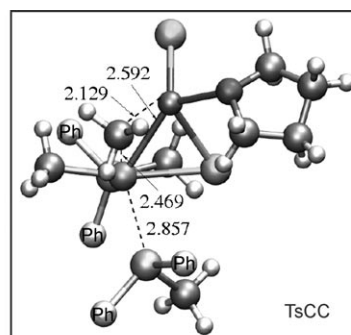
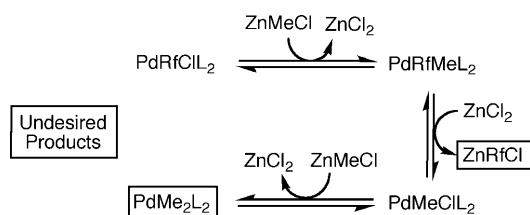


Figure 4. Energy profile for the concerted transmetalation to form the *cis* product showing the  $\Delta G_{\text{solv}}$  values obtained at 223 K (a color version of the drawing of the TsCC geometry can be found in the Supporting Information).

by the Cl atom of **1**. Each possible conformation of this intermediate leads to a different transition state. Both transmetalations involve the formation of cyclic transition states [Pd( $\mu$ -Cl)( $\mu$ -Me)Zn], which are very reminiscent of the cyclic mechanism proposed for the Stille reaction.<sup>[1,9,14,15]</sup> However, a distinct feature found in the theoretical study of the Negishi transmetalation and absent in the Stille reaction is the existence, in both transition states and in some intermediates, of Pd...Zn bond interactions between the electron-rich Pd center and the fairly positive Zn center.<sup>[13]</sup> These interactions are deemed responsible for the remarkably low energy of the transmetalation barriers with organozinc compounds as nucleophiles, compared with the noticeably higher barriers for organotin compounds.

The experimental evidence and the theoretical calculations presented herein consistently support the fast reversibility of the transmetalation reactions of Pd complexes with Zn alkyl reagents. Based on these kinetic observations, a new possibility for the formation of undesired homocoupling products can be envisaged for a catalyzed coupling  $R^1X + R^2ZnCl$  (or  $R^2_2Zn$ ), in addition to the undesired transmetalations already discussed in above. Since the transmetalations and their reverse processes are much faster than the

reductive elimination from **2**, the 2–1–3 round trip will take place many times before coupling occurs. Consequently, for the general case of reactions [PdR<sup>1</sup>ClL<sub>2</sub>] with ZnR<sup>2</sup>Cl, there are statistically many chances for new intermediates [PdR<sup>2</sup>ClL<sub>2</sub>] and ZnR<sup>1</sup>Cl to be formed through undesired retrotransmetalations from the initial intermediate [PdR<sup>1</sup>R<sup>2</sup>L<sub>2</sub>], eventually leading to R<sup>1</sup>–R<sup>1</sup> and R<sup>2</sup>–R<sup>2</sup> homocoupling side products. In fact, the compounds [PdMe<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>] and ZnRfCl, reported to be formed in the reaction of [PdRfCl(PPh<sub>3</sub>)<sub>2</sub>] with ZnMeCl,<sup>[4]</sup> are undesired retrotransmetalation products (Scheme 3). Of course the mistaken retrotransmetalation products can, in turn, enter the cycle, further complicating the problem.



Scheme 3. Formation of side products (in black boxes) from undesired retrotransmetalations.

Side products of undesired retrotransmetalations have also been observed in Stille reactions (e.g., formation of SnRfBu<sub>3</sub> from Sn(CH=CH<sub>2</sub>)Bu<sub>3</sub> and BrRf),<sup>[16]</sup> and are expected for other metal-catalyzed couplings whenever the retrotransmetalation is faster than the reductive elimination step. It is worth recalling that complexes [PdR<sup>1</sup>R<sup>2</sup>L<sub>2</sub>] can also undergo uncatalyzed rearrangements by R exchange,<sup>[17]</sup> or isomerize through a gold-catalyzed process.<sup>[18]</sup> However, these reactions take usually place at a much slower rate than the transmetalations observed herein and do not seem to be an effective source of complications in Pd-catalyzed C–C heterocoupling reactions.

## Experimental Section

**Kinetic studies:** A solution of palladium complex ( $5.15 \times 10^{-3}$  mmol) in THF (0.30 mL) was prepared in an NMR tube and cooled to  $-78^\circ\text{C}$ . A precooled solution of ZnMeCl in THF (0.09 mL 1.14 M, 0.103 mmol) was added, plus cold THF to make 0.50 mL of final volume. The sample was placed into thermostated NMR spectrometer at 223 or 203 K. The kinetic experiments were followed by <sup>31</sup>P NMR spectroscopy and concentration–time data were acquired by integration of the <sup>31</sup>P NMR signals.

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**Keywords:** C–C coupling • density functional calculations • homogeneous catalysis • kinetics • Negishi coupling

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