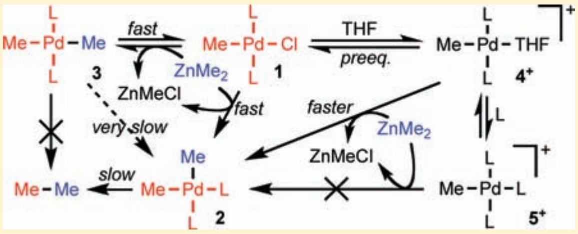
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
ARTICLE
pubs.acs.org/JACS

Cationic Intermediates in the Pd-Catalyzed Negishi Coupling. Kinetic and Density Functional Theory Study of Alternative Transmetalation Pathways in the Me–Me Coupling of $ZnMe_2$ and *trans*-$[PdMeCl(PMePh_2)_2]$

Max García-Melchor,[†] Beatriz Fuentes,[‡] Agustí Lledós,[†] Juan A. Casares,*[,‡] Gregori Ujaque,*[,†] and Pablo Espinet*[,‡]

[†]Química Física, Edifici C.n., Universitat Autònoma de Barcelona, E-08193 Bellaterra, Catalonia, Spain
[‡]IU CINQUIMA/Química Inorgánica, Facultad de Ciencias, Universidad de Valladolid, E-47071 Valladolid, Spain

S *Supporting Information*



ABSTRACT: The complexity of the transmetalation step in a Pd-catalyzed Negishi reaction has been investigated by combining experiment and theoretical calculations. The reaction between *trans*-$[PdMeCl(PMePh_2)_2]$ and $ZnMe_2$ in THF as solvent was analyzed. The results reveal some unexpected and relevant mechanistic aspects not observed for ZnMeCl as nucleophile. The operative reaction mechanism is not the same when the reaction is carried out in the presence or in the absence of an excess of phosphine in the medium. In the absence of added phosphine an ionic intermediate with THF as ligand ($[PdMe(PMePh_2)_2(THF)]^+$) opens ionic transmetalation pathways. In contrast, an excess of phosphine retards the reaction because of the formation of a very stable cationic complex with three phosphines ($[PdMe(PMePh_2)_3]^+$) that sequesters the catalyst. These ionic intermediates had never been observed or proposed in palladium Negishi systems and warn on the possible detrimental effect of an excess of good ligand (as $PMePh_2$) for the process. In contrast, the ionic pathways via cationic complexes with one solvent (or a weak ligand) can be noticeably faster and provide a more rapid reaction than the concerted pathways via neutral intermediates. Theoretical calculations on the real molecules reproduce well the experimental rate trends observed for the different mechanistic pathways.

INTRODUCTION

The Negishi reaction is a wide scope most reliable cross-coupling process that can be applied to every possible combination of carbon type (sp, sp^2, or sp^3), and tolerates many different functions in the reagents.[1−3] The reaction can be carried out using either ZnR_2 or ZnRX as the nucleophile, and the more accessible reagent is usually chosen. While the choice of organozinc does not seem to alter the cross coupling products in the Negishi coupling, the rate and mechanism of the transmetalation step might be affected. However, very little is known about this transmetalation, compared to the transmetalation mechanisms in the Stille[4−8] or Suzuki[9−12] reactions, in spite of the fact that the transmetalation between organozinc and palladium complexes is also involved in other synthetically useful processes such as the hydroalkylation of styrenes,[13] the asymmetric allylation of aryl aldehydes,[14] the coupling of propargylic benzoates and aldehydes,[15] or the double-transmetalation oxidative cross-coupling reaction.[16]

In an initial mechanistic work on the Negishi reaction we met a remarkable behavior in the transmetalation of *trans*-$[PdRfCl(PPh_3)_2]$ (Rf = 3,5-dichloro-2,4,6-trifluorophenyl) with $ZnMe_2$ or with ZnMeCl: apparently each methylating reagent afforded a different isomer (*trans* or *cis*, respectively) of the coupling intermediate $[PdRfMe(PPh_3)_2]$.[17] The study revealed also the existence of secondary undesired transmetalations (methyl by aryl exchanges, eqs 1 and 2), which could eventually produce homocoupling products. The same phenomenon had been noted by van Asselt and Elsevier,[18] and after our report was also observed by A. Lei et al. on related reactions with aryl zinc derivatives.[19]

$$\textit{trans}\text{-}[\mathrm{PdMeRf(PPh_3)_2}] + \mathrm{ZnMe_2} \longrightarrow \textit{cis}\text{-}[\mathrm{PdMe_2(PPh_3)_2}] + \mathrm{ZnMeRf} \qquad (1)$$

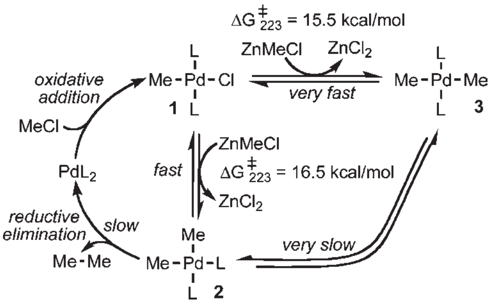
$$\textit{trans}\text{-}[\mathrm{PdRfCl(PPh_3)_2}] + \mathrm{ZnMeCl} \longrightarrow \textit{trans}\text{-}[\mathrm{PdMeCl(PPh_3)_2}] + \mathrm{ZnRfCl} \qquad (2)$$

Recently, we have published kinetic experimental and theoretical studies of the transmetalation between ZnMeCl and *trans*-$[PdMeCl(PMePh_2)_2]$.[20] That study showed that the

Received: May 9, 2011
Published: July 27, 2011

© 2011 American Chemical Society

Scheme 1. Simplified Reaction Mechanism of the Negishi Coupling with ZnMeCl



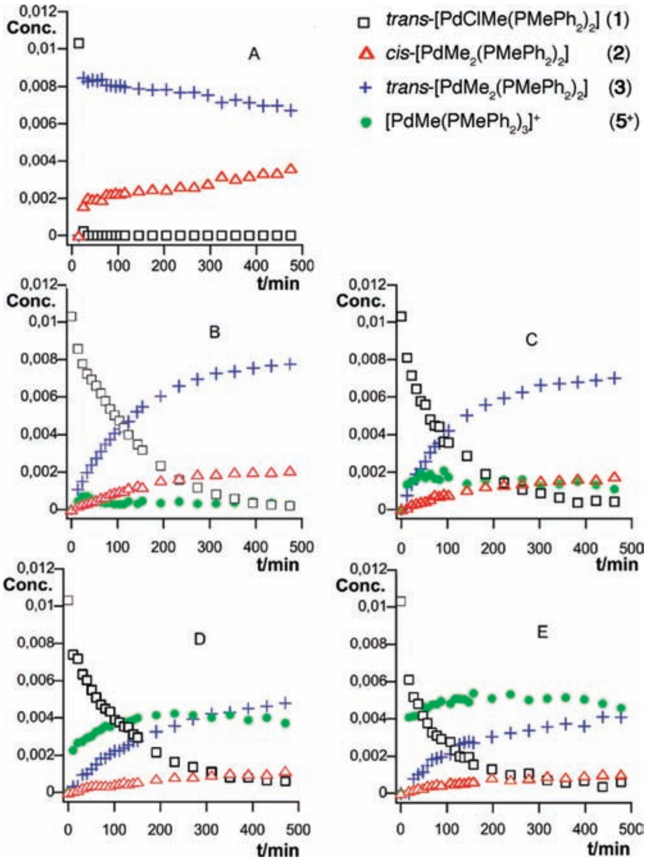
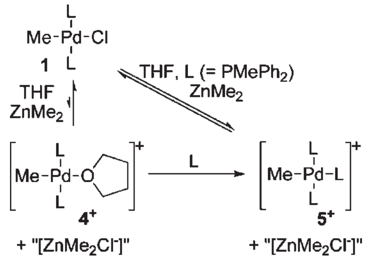


Figure 1. Concentration/time data, obtained by ^{31}P NMR, for the reaction of *trans*-[PdMeCl(PMePh$_2$)$_2$] (**1**) with ZnMe$_2$ in THF at 203 K. Starting conditions: [**1**]$_0$ = 1.0 × 10^{-2} M, [ZnMe$_2$]$_0$ = 0.21 M. Added phosphine: (**A**) [PMePh$_2$] = 0 M, (**B**) [PMePh$_2$] = 6.0 × 10^{-4} M, (**C**) [PMePh$_2$] = 2.0 × 10^{-3} M, (**D**) [PMePh$_2$] = 5.0 × 10^{-3} M, (**E**) [PMePh$_2$] = 1.0 × 10^{-2} M.

reagents (ZnMeCl + *trans*-[PdMeCl(PMePh$_2$)$_2$] (**1**)) are more stable than the products (ZnCl$_2$ + *cis*-[PdMe$_2$(PMePh$_2$)$_2$] (**2**)), and the latter are more stable than the alternative products (ZnCl$_2$ + *trans*-[PdMe$_2$(PMePh$_2$)$_2$] (**3**)). The Gibbs energy differences are such that, in catalytic conditions (using a large excess of ZnMeCl), the equilibria are shifted toward the most stable products ZnCl$_2$ + *cis*-[PdMe$_2$(PMePh$_2$)$_2$], but the kinetics of the reactions favor the faster formation of *trans*-[PdMe$_2$(PMePh$_2$)$_2$], which is seen to appear and then fade out in favor of the more stable *cis*-[PdMe$_2$(PMePh$_2$)$_2$]. It was demonstrated that the latter transformation is not a direct *trans*/*cis* isomerization, which is slow, but occurs *via* retrotransmetalation to the initial reagents followed by transmetalation to *cis*-[PdMe$_2$(PMePh$_2$)$_2$].[21] The catalytic cycle in Scheme 1 summarizes those results. No other Pd complex was observed in that study.[20]

Scheme 2



In this paper we study the transmetalation using ZnMe$_2$ as the transmetalating nucleophile. *A priori* only minor differences with the results with ZnMeCl were expected. However, this study has revealed unknown and unexpected aspects of the Negishi process.

■ RESULTS AND DISCUSSION

1. Experimental Studies. The reaction of **1** with ZnMe$_2$ (1:20 ratio simulating catalytic conditions with 5% Pd, in THF at room temperature) gives *cis*-[PdMe$_2$(PMePh$_2$)$_2$] (**2**) as the only observable product. In these conditions complex **2** slowly decomposes to give the Negishi coupling product ethane.[22,23] This behavior is in coincidence with the synthetic results observed using ZnMeCl at room temperature.[20] However, important mechanistic differences between the two Zn reagents were observed when the reactions were monitored by ^{31}P NMR at 203 K (at which temperature the coupling rate to give ethane is negligible), with and without added phosphine (Figure 1).

1.1. Occurrence of Cationic Pd Species. The first unexpected observation (Figure 1A) was that the rate of consumption of *trans*-[PdMeCl(PMePh$_2$)$_2$] (**1**) with ZnMe$_2$ seemed too high, compared to our previous study with ZnMeCl,[20] even considering that ZnMe$_2$ is a stronger nucleophile than ZnMeCl and some rate acceleration was to be expected. Addition of a small amount of PMePh$_2$ markedly decreased the rate of consumption (Figure 1B), bringing the reaction rate into the range convenient for kinetic studies by ^{31}P NMR. Interestingly, further increases in PMePh$_2$ concentration affected only slightly the rate of consumption (Figure 1C–E) and the profiles of the other curves in the graphics (these are discussed later). This behavior suggests the existence, in the initial conditions of reaction **1A**, of a minute proportion of a nonobserved catalytic intermediate that opens a much faster reaction pathway; this intermediate would be quenched by addition of just a small amount of phosphine. A most plausible intermediate is the cation *trans*-[PdMe(PMePh$_2$)$_2$(THF)]$^+$ (THF = tetrahydrofuran, **4**$^+$), formed in the presence of a large amount of ZnMe$_2$ acting as Cl$^-$ scavenger (Scheme 2). As a precedent for this proposal, the role of ZnBr$_2$ as a Lewis acid, facilitating halide abstraction from Ni complexes, was hypothesized by Buchwald et al.,[24] who found an accelerating effect of ZnBr$_2$ as cocatalyst in a process of enantioselective α-arylation of α-substituted γ-butyrolactones requiring a step of

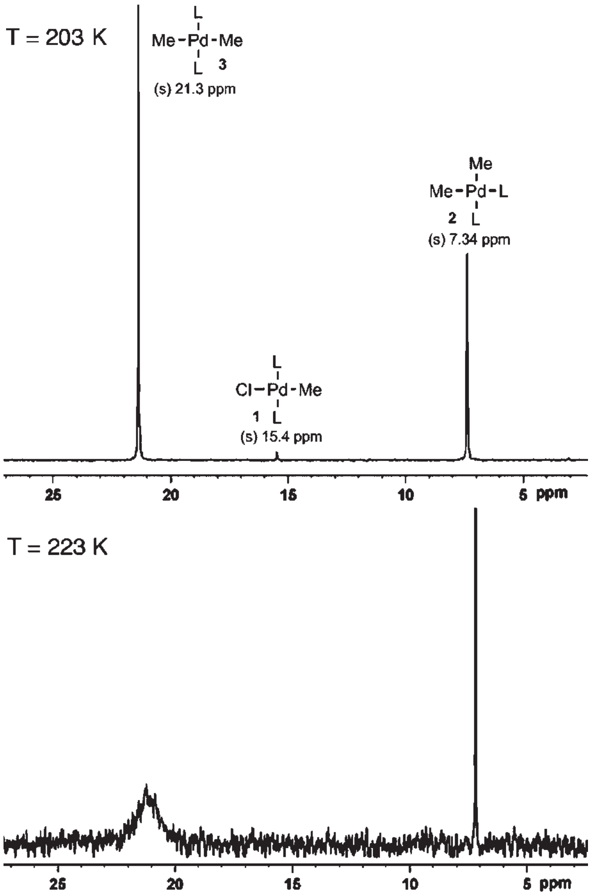


Figure 2. ^{31}P NMR of a mixture of **1**, $ZnMe_2$, and $PMePh_2$ in THF at 203 and 223 K, after 15 min, close to the end of the transmetalation. Starting conditions: $[\mathbf{1}]_0 = 0.033$ M, $[ZnMe_2]_0 = 0.16$ M, $[PMePh_2] = 0.008$ M. The coalescence of the signals at 223 K is due to exchange of coordinated and uncoordinated phosphine. The signal of the free phosphine appears at −29.5 ppm at 203 K, and is not observed at 223 K.

halide abstraction from [(*S*)-BINAP]Ni(Ar)(X), and also by Majundar and Cheng in the Ni(II)/Zn-mediated chemoselective arylation of aromatic aldehydes.[25] Actually, the formation of $[Ni(\eta^3\text{-Bz})(diphosphine)][ZnBr_3(THF)]$ complexes from $[Ni(\sigma\text{-Bz})Br(diphosphine)]$ and $ZnBr_2$ in THF has been reported by Anderson and Vicic.[26]

To the best of our knowledge this instrumental effect of $ZnMe_2$ acting as Cl^- scavenger has never been observed nor proposed in palladium Negishi systems where, probably due to the different hardness of the metal center, the behavior is somewhat different from nickel. A THF complex similar to $\mathbf{4}^+$, *trans*-$[Pd(C_6F_5)(PPh_3)_2(THF)](OTf)$, in equilibrium with *trans*-$[Pd(C_6F_5)(OTf)(PPh_3)_2]$ in THF,[6,7] has been reported, but TfO^- is a very good leaving ligand. Moreover, treating *trans*-$[PdMeCl(PMePh_2)_2]$ in THF solution at −20 °C with $AgBF_4$, to force the extraction of Cl^- (see Supporting Information for details), $[PdMe(PMePh_2)_2(THF)](BF_4)$ ($\mathbf{4}\cdot BF_4$) is formed quantitatively. When the counteranion is Cl^- an equilibrium between *trans*-$[PdMeCl(PMePh_2)_2]$ and *trans*-$[PdMeCl(PMePh_2)_2(THF)]^+$ ($\mathbf{4}^+$) seems to be established to a small extent, but only in the presence of $ZnMe_2$ as Cl^- acceptor. This accelerating effect was not detected in the reactions where the reagent was the better acceptor ZnMeCl,[20] but this has some logic: intermediate $\mathbf{4}^+$ would not be formed in solutions very rich in species containing terminal chloro donor atoms, which will coordinate palladium in preference to THF.[27]

The proposal of intermediate $\mathbf{4}^+$ was reinforced by the observation of a cationic complex ($\mathbf{5}^+$ in Scheme 2) when $PMePh_2$ was added (Figure 1B−E). It was identified as $[PdMe(PMePh_2)_3]^+$ by comparison with an authentic sample prepared independently (eq 3).

$$\mathrm{Me{-}\overset{L}{\underset{L}{Pd}}{-}Cl} \xrightarrow[-\,AgCl]{Ag(BF_4)} \left[\mathrm{Me{-}\overset{L}{\underset{L}{Pd}}{-}L}\right]^{+} BF_4^- \qquad (3)$$

L = $PMePh_2$ $\qquad$ $\mathbf{5}\cdot BF_4$

The observation of $\mathbf{5}^+$, in variable concentration depending on the amount of phosphine added, confirms unequivocally that, in the presence of added phosphine, a second cationic species, this time observable, is made available from the very beginning of the reaction, opening a plausible additional alternative transmetalation pathway. In summary, depending on the reaction conditions the transmetalation could take place on **1**, on $\mathbf{4}^+$, or on $\mathbf{5}^+$ (Scheme 2). It looks that the reaction via $\mathbf{4}^+$ is faster than on **1**, while the presence of $\mathbf{5}^+$ does not accelerate the transmetalation.

1.2. Kinetic Studies of the Transmetalation with $ZnMe_2$, without Added $PMePh_2$. The high transmetalation rate observed in Figure 1A (no added $PMePh_2$) leads to the complete transformation of the starting complex *trans*-$[PdMeCl(PMePh_2)_2]$ (**1**) into a mixture of the transmetalated products *trans*- and *cis*-$[PdMe_2(PMePh_2)_2]$ (**3** and **2**, respectively) where the *trans* isomer is very major. This takes place in about one minute, which is very fast considering that the working temperature is 203 K. Then a very slow isomerization of **3** to **2** follows.

1.3. Kinetic Studies of the Transmetalation with $ZnMe_2$ and Added $PMePh_2$. In order to observe the products involved in catalysis, these reactions were carried out at 203 K to quench the fast exchange of coordinated and uncoordinated phosphine that already occurs at 223 K (Figure 2).

The reactions in the presence of added $PMePh_2$ (Figure 1B−D) show the fast formation of the cationic species $\mathbf{5}^+$, and a much slower rate of transmetalation than without added phosphine, in agreement with the absence of $\mathbf{4}^+$. The graphics show that, as usual, *trans* isomer **3** is formed faster than *cis* isomer **2**. In order to decide whether the transmetalation takes place on **1**, on $\mathbf{5}^+$, or competitively on both species, the experimental data collection was fitted to two kinetic models: (a) supposing that the transmetalation operates only on the neutral complexes **1** (eqs 4 and 5); and (b) considering also the competitive transmetalation operating on the cationic complex $[PdMe(PMePh_2)_3]^+$ ($\mathbf{5}^+$) (eqs 6 and 7). The results are given in Tables 1 and 2. The fitting using model b affords negligible values for k^+_3; thus, the competitive transmetalation pathway *via* the trisphosphine cationic complex $\mathbf{5}^+$ can be discarded. Consistently, almost identical values are obtained for k_3 and for k_4 in models a and b. The two rate constants, with average values $k_3 \approx 2.8 \times 10^{-2}$ min^{-1}, and $k_4 \approx 6.2 \times 10^{-3}$, differ in less than 1 order of magnitude.

$$\underset{\mathbf{1}}{trans\text{-}[PdMeClL_2]} + ZnMe_2 \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \underset{\mathbf{3}}{trans\text{-}[PdMe_2L_2]} + ZnMeCl \qquad (4)$$

$$\underset{\mathbf{1}}{trans\text{-}[PdMeClL_2]} + ZnMe_2 \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} \underset{\mathbf{2}}{cis\text{-}[PdMe_2L_2]} + ZnMeCl \qquad (5)$$

$$\underset{\mathbf{1}}{trans\text{-}[PdMeClL_2]} + ZnMe_2 + L \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} \underset{\mathbf{5}^+}{[PdMeL_3]^+}[ZnMe_2Cl]^- \qquad (6)$$

Table 1. Rate Constants (min^{-1} mol^{-1}L) and $\Delta G^{\ddagger}$ values (kcal mol^{-1}) at 203 K, Using Model A^{a}

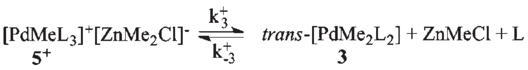
% added PMePh$_2$	k_3^{b}	$\Delta G_3^{\ddagger}$	k_4	$\Delta G_4^{\ddagger}$
6	$3.0(\pm 0.1) \times 10^{-2}$	14.80 ($\pm$0.07)	$7.5(\pm 0.2) \times 10^{-3}$	15.36 ($\pm$0.08)
20	$3.3(\pm 0.1) \times 10^{-2}$	14.77 ($\pm$0.07)	$7.7(\pm 0.2) \times 10^{-3}$	15.37 ($\pm$0.08)
50	$1.9(\pm 0.1) \times 10^{-2}$	14.99 ($\pm$0.08)	$4.1(\pm 0.1) \times 10^{-3}$	15.61 ($\pm$0.08)
100	$2.2(\pm 0.1) \times 10^{-2}$	14.93 ($\pm$0.08)	$5(\pm 1) \times 10^{-3}$	15.53 ($\pm$0.08)

[a] Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: London, 1982. The fittings were made using the values $k_5 = 9.8$ min^{-1} mol^{-1}L; $k_{-5} = 0.002$ min^{-1} mol^{-1} L for the formation of **5**$^{+}$ (eq 6). These were determined in the experiment in Figure 1E, where the experimental values to be measured for formation of **5**$^{+}$ are larger, and hence more reliable. This also applies to Table 2. [b] Standard deviations in parentheses.

Table 2. Rate Constants at 203 K, Using Model *b*^{a}

(%) added PMePh$_2$	k_3 (min^{-1} mol^{-1} L)	k_4 (min^{-1} mol^{-1} L)	$k^{+}{}_{3}$ (min^{-1})
6	$3(\pm{>}3) \times 10^{-2}$	$8(\pm{>}8) \times 10^{-3}$	$2(\pm{>}2) \times 10^{-16}$
20	$3.4(\pm 1) \times 10^{-2}$	$8(\pm 2) \times 10^{-3}$	$1(\pm{>}1) \times 10^{-4}$
50	$2.7(\pm 2) \times 10^{-2}$	$4(\pm 1.6) \times 10^{-3}$	$3(\pm{>}3) \times 10^{-15}$
100	$2(\pm{>}2) \times 10^{-2}$	$6(\pm{>}6) \times 10^{-3}$	$2(\pm{>}2) \times 10^{-16}$

[a] See note text in Table 1. Standard deviations in parentheses.



$$\underset{\mathbf{5^+}}{[\mathrm{PdMeL_3}]^+[\mathrm{ZnMe_2Cl}]^-} \underset{k_{-3}^{+}}{\overset{k_3^{+}}{\rightleftharpoons}} \underset{\mathbf{3}}{trans\text{-}[\mathrm{PdMe_2L_2}]} + \mathrm{ZnMeCl} + \mathrm{L} \qquad (7)$$

In summary, the experimental results show the following: (1) In the absence of added phosphine the observed rate is unusually fast for the transmetalation that should take place on *trans*-[PdMeCl(PMePh$_2$)$_2$],[28] and this suggests that it must be going through a nonobserved cationic intermediate **4**$^{+}$. This proposal is later supported by DFT calculations. (2) In the presence of some added phosphine the reactions go *via* *trans*-[PdMeCl(PMePh$_2$)$_2$]. The presence of a new cationic intermediate **5**$^{+}$ is kinetically of little relevance (except for the detrimental effect associated to the percentage of Pd scavenging), indicating that it is not an intermediate toward a faster reaction pathway. (3) At variance with the system using ZnMeCl, where the reaction equilibrium is displaced toward the reagents (**1** + ZnMeCl, see Figure 1),[20] in the system **1** + ZnMe$_2$ the reaction is displaced toward the products (**2** + ZnMeCl, and **3** + ZnMeCl), reflecting the higher nucleophilicity of ZnMe$_2$. Methyl for chloride exchange is an exergonic process for ZnMe$_2$ and an endergonic one for ZnMeCl, reflecting the relative stability of the Zn complexes. Since it is already known that **2** is about 2 kcal mol^{-1} more stable than **3**,[20] it follows that the reaction equilibrium with ZnMe$_2$ is strongly displaced toward **2**. (4) The transmetalation to *trans* (**3**) is clearly faster than the transmetalation to *cis* (**2**), in coincidence with the reaction with ZnMeCl.[20] (5) The subsequent isomerization of **3** to **2** is much slower than in the reaction with ZnMeCl. This was expected from our previous study, which showed that the rate of the *trans*/*cis* uncatalyzed isomerization is negligible at low temperatures, while the isomerization *via* retrotransmetalation to *trans*-[PdMeCl(PMePh$_2$)$_2$] is catalyzed by the presence of ZnCl$_2$ and, less efficiently, by ZnMeCl.[20] Additional experiments (at 223 K, in order to increase the isomerization rates) show that ZnMe$_2$ does not catalyze the isomerization: after 13 h at 223 K a solution 0.01 M of **3** and 0.21 M of ZnMe$_2$ contains only 1% of the *cis* isomer **2**; in contrast, the same experiment performed with ZnMeCl gives, after 10 min, a mixture of about 25% *cis*-[PdMe$_2$(PMePh$_2$)$_2$] and 75% *trans*-[PdMeCl(PPh$_2$Me)$_2$], reaching equilibrium (**1**:**2** ≈ 43:57) in 200 min.

2. DFT Studies of the Transmetalation. In order to support the proposals based on the experimental data and obtain a more detailed picture of the transmetalation process, all the proposed transmetalation pathways were computationally investigated by density functional theory (DFT) calculations using the M06 dispersion-corrected functional, which has been shown to provide good results for both organometallic systems and noncovalent interactions.[29] The theoretical calculations were performed on the very catalyst used for the experiments (i.e., with the real ligands). The solvent, THF, was introduced by a discrete-continuum model: two THF molecules were explicitly included in the calculations as potential ligands, and the effect of the bulk solvent was taken into account with a continuum model ($\varepsilon = 7.4257$). This methodology allowed us to consider tetrahedral Zn species coordinated with THF along the studied pathways, rather than the unrealistic linear dicoordinated Zn species often used that lead to calculated species of unlikely existence in THF solution.[30] Gibbs energies in THF solution (ΔG_{THF}) were calculated adding the gas-phase Gibbs energy corrections of the solute to the energies in solution. All the energies collected in the text are ΔG_{THF}, calculated at 203 K for further approximation to the experimental conditions.[31] With these DFT calculations we expected to reproduce the trends of energy barriers found experimentally,[32] which are the following: ionic to *trans* (PMePh$_2$) > concerted to *cis* > concerted to *trans* > ionic to *trans* (THF).

*2.1. Ionic Mechanism via an Undetectable Cationic Intermediate [PdMe(PMePh$_2$)$_2$(THF)]$^{+}$ (**4**$^{+}$).* The experimental studies suggest the formation of an undetected cationic intermediate [PdMe(PMePh$_2$)$_2$(THF)]$^{+}$ (**4**$^{+}$) (with [ZnMe$_2$Cl(THF)]$^{-}$ as the counterion), which is the one undergoing the fastest transmetalation process. The computational analysis of a plausible transmetalation *via* **4**$^{+}$ afforded the reaction profile and optimized transition state structures shown in Figure 3. The reaction pathway starts with a chloride abstraction from the initial Pd complex (**1**), assisted by a THF molecule and ZnMe$_2$ (which is in large excess). This results in the formation of **IT2** (corresponding to the proposed intermediate **4**$^{+}$ in the experimental nomenclature) through the transition state **TsIT1**.[33] Interestingly, the position of **IT2** in the Gibbs energy profile is 5.3 kcal mol^{-1} higher than the initial reactants, which makes its observation by NMR extremely unlikely.[34] Subsequently, the transmetalation takes place from **IT2** *via* **TsIT2**, yielding the last intermediate **IT3**. The latter transition state has the highest energy value (10.3 kcal mol^{-1}) within the overall reaction profile thus becoming the rate-determining step.

2.2. Concerted Mechanisms. The only operative transmetalation pathways for the transmetalation reaction with ZnMeCl involve concerted Cl for Me exchanges.[20] A similar concerted mechanism

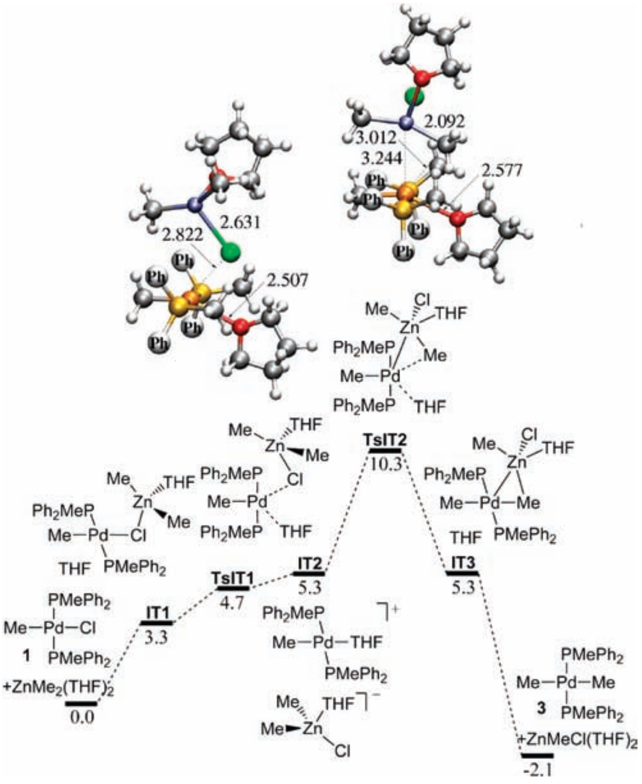


Figure 3. Gibbs energy profile in THF (in kcal mol^{-1}) calculated for the transmetalation to the trans product (**3**) via Pd ionic intermediate with THF. The optimized structures for the transition states **TsIT1** (left) and **TsIT2** (right) are shown. Phenyl rings simplified for clarity.

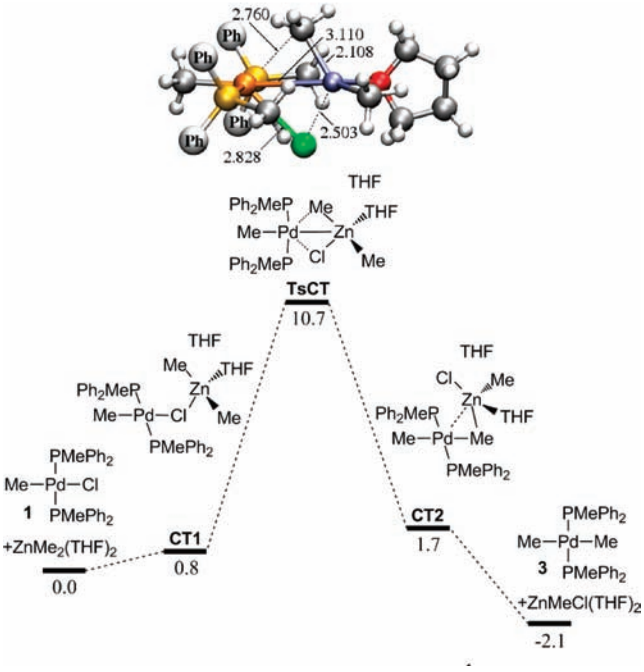


Figure 4. Gibbs energy profile in THF (in kcal mol^{-1}) calculated for the concerted transmetalation to the *trans* product (**3**). The optimized structure for the transition state **TsCT** is shown. Phenyl rings simplified for clarity.

was found for $ZnMe_2$. Figures 4 and 5 depict the Gibbs energy profiles of the concerted transmetalation pathways on *trans*-[$PdMeCl(PMePh_2)_2$] (**1**) to *trans*- and *cis*-[$PdMe_2(PMePh_2)_2$], respectively. Both mechanisms share the initial dissociation of a THF molecule from the Zn reagent with concomitant chloride coordination to Zn, yielding intermediates **CT1** and **CC1**, respectively.[35] The concerted transmetalation to the *trans* product **3** (Figure 4) takes place through one transition state (**TsCT**), with an energy barrier of 10.7 kcal mol^{-1}. At variance, the transmetalation to *cis* product **2** (Figure 5) displays two transition states of almost identical energy (**TsCC1** =11.5; **TsCC2** = 11.8 kcal mol^{-1}). **TsCC1** corresponds to the substitution of the phosphine ligand by a methyl group from the Zn reactant, giving rise to a high energy intermediate **CC2**, unobservable by NMR. In **TsCC2**, the phosphine ligand replaces the chloride group, which ends up bound to Zn.

From the calculated barriers, the concerted transmetalation to *trans* is slower than the transmetalation through the ionic intermediate 4^+, and faster than the concerted transmetalation to *cis*. On the other hand, the *cis* isomer **2** is 2.3 kcal mol^{-1} more stable than the *trans* isomer **3**.

2.3. Ionic Mechanism via a Detected Cationic Intermediate [$PdMe(PMePh_2)_3$]$^+$ (**5**$^+$). Finally, in order to unravel the observed decrease of the reaction rates for the transmetalation process with added phosphine, and further support the observation of the species [$PdMe(PMePh_2)_3$]$^+$[$ZnMe_2Cl(THF)$]$^-$ (**5**$^+$), we computed the transmetalation pathway *via* this species (Figure 6). The pathway is analogous to that going through 4^+, but very different energies are involved. The calculations indicate that intermediate **IT2** (corresponding to 5^+ in the experimental nomenclature) is very stable, as expected from its NMR observation. For the ionic pathway through 5^+ the calculated transmetalation barrier **TsIT2** increases to 15.5 kcal mol^{-1}. This is more than 3 kcal mol^{-1} higher than that calculated for the concerted processes (11.8−10.7 kcal mol^{-1}, see above), which in terms of reaction rates means more than 3 orders of magnitude slower. In other words, this pathway is clearly the most disfavored one for the Negishi transmetalation studied, in agreement with the experimental observations.

3. Comparing Theoretical and Experimental Results. The number of computational studies of transition metal catalyzed reactions has increased exponentially in recent years,[36] but only rarely are experimental energy values (especially transition barriers) available for direct comparison with the theoretical results. When they are, it is found that the quantitative matching is not always as good as hoped.[37−39] It has been stated that, at present, it cannot be excluded that good matches stem from error cancellation of different contributions to the calculated values.[38]

The experimental ΔG values derived from the kinetic experimental studies are estimated to have an error of ±0.08 kcal mol^{-1}.[40] Aiming at obtaining theoretical results to compare with the experimental values, we have used in this paper an optimum chemical model for calculations. The reactant molecules were not substituted by a simplified model: the complete catalyst with the real ligands and realistic tetracoordinated Zn species including explicitly solvent molecules were used. Moreover, a well balanced computational cost/quality method was selected by using a dispersion-corrected functional with a large basis set and including a discrete + continuum solvent scheme (the new implemented SMD solvation model) in the calculations.

Simplified experimental profiles for the concerted transmetalations to *trans* and to *cis* using $ZnMe_2$ are plotted in black in Figure 7. The values for the concerted mechanisms are the quantitative kinetic results, whereas for the ionic mechanisms the

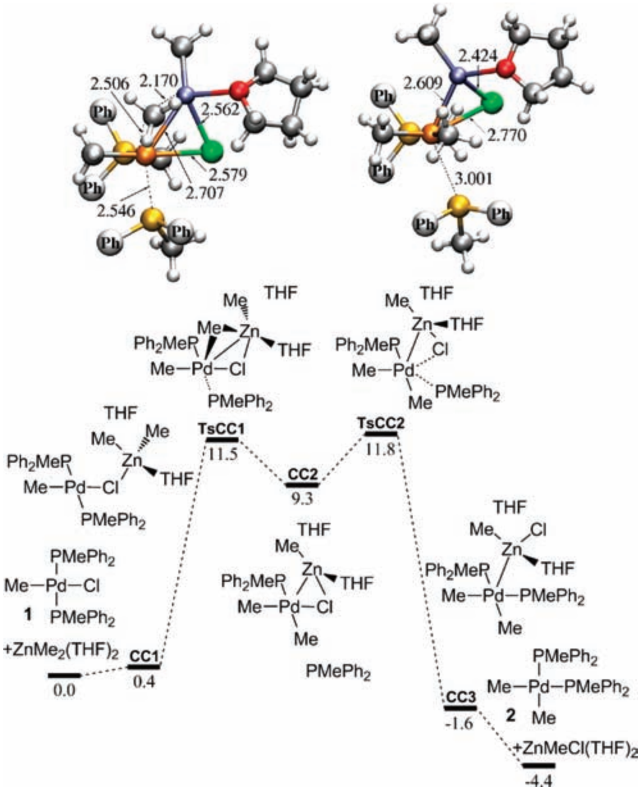


Figure 5. Gibbs energy profile in THF (in kcal mol^{-1}) calculated for the concerted transmetalation to the *cis* product (**2**). The optimized structures of the transition states **TsCC1** (left) and **TsCC2** (right) are shown.

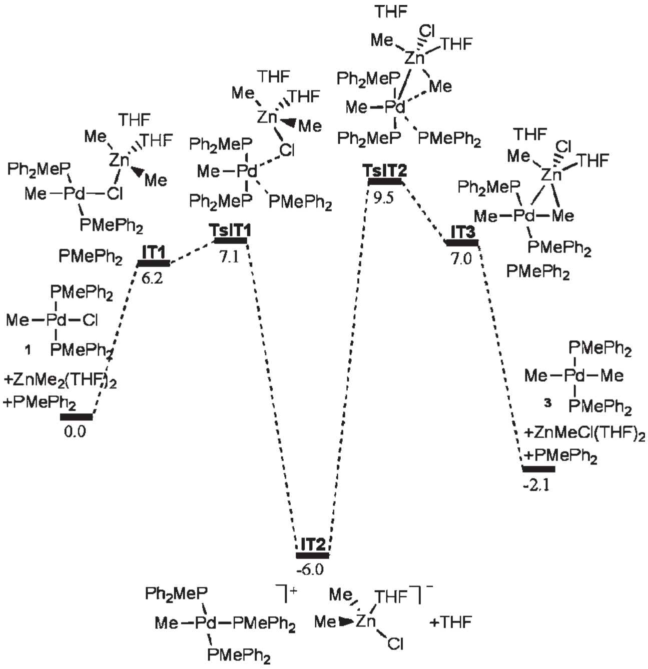


Figure 6. Gibbs energy profile in THF (in kcal mol^{-1}) calculated for the transmetalation to the *trans* product (**3**) via ionic intermediate with $PMePh_2$. Gibbs energies are given in kcal mol^{-1}. Phenyl rings simplified for clarity.

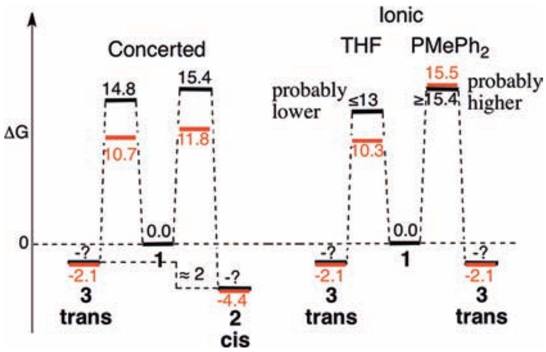
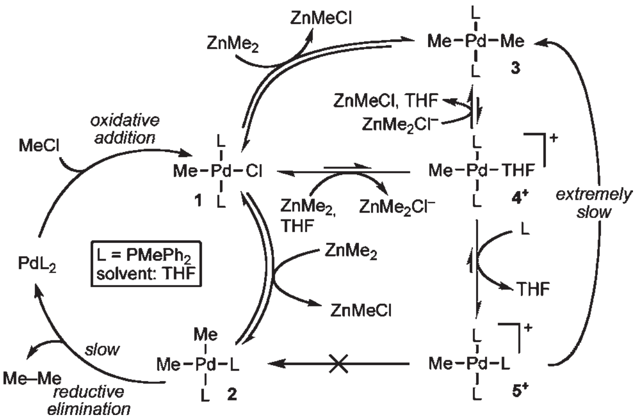


Figure 7. Comparison, for the reactions with $ZnMe_2$, of the relative Gibbs energy values at 203 K (kcal mol^{-1}) of the rate determining transition states and the products. Experimental values in black, calculated values in red.

Scheme 3. Simplified Reaction Mechanism of the Negishi Coupling with $ZnMe_2$



values plotted are the estimated maximum (for L = THF) or minimum (for L = $PMePh_2$) value compatible with the experimental observations. The data in red correspond to the computationally obtained values. First of all, it is worth noting that the calculations reproduce qualitatively the experimental observations. From the kinetic point of view, the order of the energy barriers for the transmetalation process through the different pathways is as follows: ionic to *trans* ($PMePh_2$) > concerted to *cis* > concerted to *trans* > ionic to *trans* (THF). As far the thermodynamics is concerned, the order of stability of the reagents and products in equilibrium (as represented by the Pd complex contained in the corresponding combination of compounds) is **2** (*cis*) > **3** (*trans*) > **1**.

From a strictly quantitative perspective, we can compare theoretical and experimental values only for the concerted mechanisms, for which we have specific experimental values (for the ionic mechanisms specific values could not be obtained from experiments, and only lower (for 4^+) or higher (for 5^+) limits can be estimated). On the basis of these results it seems that our theoretical calculations underestimate the reaction barriers by about 4 kcal mol^{-1}. However, the calculations nicely reproduce the energy difference between both concerted mechanisms (the difference is 0.6 kcal mol^{-1} for the experimental values and 1.1 kcal mol^{-1} for the theoretical values), which is important, and sufficient in this case to compare reaction rates and elucidate which pathway is preferred. On the other hand, the relative stability for the products **2** and **3** could not be experimentally quantified in this paper, but we had determined in a previous study that **2** is about 2.0 kcal mol^{-1} more stable than **3**.[20] In this study the calculated difference is 2.3 kcal mol^{-1}, which is a very satisfactory fit with the experiment.

CONCLUSIONS

The experimental study of the transmetalation step in a Pd-catalyzed Negishi reaction to produce Me—Me coupling using $ZnMe_2$, in THF as solvent, shows that in all cases the reactions are faster than with ZnMeCl. The concerted transmetalation to *trans* is faster than the transmetalation to *cis*, and the *trans*-to-*cis* isomerization (which is required to produce the coupling product) is slower than in the case of ZnMeCl as nucleophile, because $ZnMe_2$ is not a good isomerization catalyst.

Particularly interesting is the observation that, in addition to the expected concerted pathways previously found for ZnMeCl as nucleophile, alternative ionic mechanisms can operate, through ionic intermediates $[PdMe(PMePh_2)_2L]^+[ZnMe_2Cl(THF)]^-$ (L = THF, $PMePh_2$). For L = THF this pathway is faster than the concerted mechanisms, while for L = $PMePh_2$ this pathway is much slower than the concerted mechanisms; in fact, the corresponding intermediate $[PdMe(PMePh_2)_3]^+$ becomes a trap of part of the Pd catalyst. The observation of these ionic intermediates warns on the possible detrimental effect of using excess of good ligands (as $PMePh_2$) in the Negishi process, but is also suggestive of the possibility to use solvents or weak ligands more coordinating than THF in order to promote the existence, in higher concentration than for THF, of ionic intermediates that could still produce further acceleration of the transmetalation step. All these conclusions are summarized in Scheme 3.

Concerning the DFT results, the theoretically calculated free energy values reproduce fairly well the experimental trends (which depend on the differences of calculated values for several pathways). Nevertheless, in spite of all the computational efforts, the calculated values do not match the experimental ones. In fact, matching experimental relative Gibbs energies in solution with theoretical calculations for a complex multistep reaction system like ours is, particularly regarding Gibbs activation barriers, a harsh work, even using good chemical and methodological models. There is still a long way in front before such accuracy is reached. In particular, the computation of entropic contributions in solution and the description of the solvent effects require further improvements.[41] Any progress in this problem will need more interactive work where experiments and calculations are put and discussed together.

Finally, following the suggestion of a reviewer, it is worth putting into perspective the significance of this work. It provides proof of the existence, operation, and effects of competitive transmetalation pathways, some of which had not been invoked before but should be considered from now on when planning or discussing Negishi syntheses. The basic transmetalation scheme proposed here is expected not to change dramatically for reactions involving aryls instead of Me, although obviously the specific values and energetic barriers determining the fastest pathway will depend on each change in the reacting system (R, X, ligands, solvent). For instance, the RX reagent in a general synthesis could probably be ArX (X = Br, I or OAc, OTs, etc.) rather than MeCl, and afford as starting point for transmetalation $[PdArXL_2]$, or $[PdArL_2(solvent)]^+X^-$ in the case of weakly coordinating anions; the latter groups will undoubtedly propitiate ionic transmetalation mechanisms. In reactions with aryls, a less donating Ar group on Pd, instead of Me, is expected to be somewhat less prone to produce ionic species, whereas heavier halogens will propitiate ionic Pd intermediates better than Cl. Concerning solvents, those more coordinating solvents than THF will also be more favorable for ionic mechanisms. All these circumstances can now be considered, in the framework of our reaction scheme of competitive pathways, when planning new synthesis.

It is worth recalling that this study concerns the transmetalation step only. The oxidative addition or the reductive elimination steps are required for a successful cross coupling, but can turn out to be rate determining. This should not be overlooked.[42]

ASSOCIATED CONTENT

Ⓢ **Supporting Information.** Details of experimental studies, computational details, relative energies for all the computed structures, optimized structures, and absolute energies in gas phase and in solution. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Authors

casares@qi.uva.es; gregori@klingon.uab.es; espinet@qi.uva.es

ACKNOWLEDGMENT

We thank the Ministerio de Ciencia y Tecnología (CTQ2010-18901, CTQ2008-06866-CO2-01), Consolider Ingenio 2010 (CSD2006-0003, CSD2007-00006), and the Junta de Castilla y León (VA373A11-2 and VA281A11-2) for financial support, and for studentships to M.G.-M. (UAB PIF) and B.F. (MCyT).

REFERENCES

(1) For reviews see: (a) Negishi, E. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 233–257. (b) Negishi, E.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichimica Acta* **2005**, *38*, 71–87. (c) Phapale, V. B.; Cárdenas, D. J. *Chem. Soc. Rev.* **2009**, *38*, 1598–1607.

(2) (a) *Handbook of Organopalladium Chemistry for Organic Synthesis*, Vol. 1, part III; Negishi, E., Ed; Wiley-Interscience: New York, 2002. (b) Negishi, E.; Zeng, X.; Tan, Z.; Qian, M.; Hu, Q.; Huang, Z. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004; Chapter 15.

(3) (a) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527–12530. (b) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726–14727. (c) Tan, Z.; Negishi, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 762–765. (d) Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Bandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175–13183. (e) Jones, G. D.; McFarland, C.; Anderson, T. J.; Vicic, D. A. *Chem. Commun.* **2005**, 4211–4213.

(4) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704–4734.

(5) Casado, A. L.; Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978–8985.

(6) Casado, A. L.; Espinet, P.; Gallego, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 11771–11782.

(7) Nova, A.; Ujaque, G.; Maseras, F.; Lledós, A.; Espinet, P. *J. Am. Chem. Soc.* **2006**, *128*, 14571–14578.

(8) Pérez-Temprano, M. H.; Gallego, A. M.; Casares, J. A.; Espinet, P. *Organometallics* **2011**, *30*, 611–617.

(9) Goossen, L. J.; Koley, D.; Hermann, H. L.; Thiel, W. *J. Am. Chem. Soc.* **2005**, *127*, 11102–11114.

(10) Braga, A. A. C.; Morgon, N. H.; Ujaque, G.; Maseras, F. *J. Am. Chem. Soc.* **2005**, *127*, 9298–9307.

(11) Braga, A. A. C.; Ujaque, G.; Maseras, F. *Organometallics* **2006**, *25*, 3647–3658.

(12) Jover, J.; Fey, N.; Purdie, M.; Lloyd-Jones, G. C.; Harvey, J. N. *J. Mol. Catal. A: Chem.* **2010**, *324*, 39–47.

(13) Urkalan, K. B.; Sigman, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 18042–18043.

(14) Howell, G. P.; Minnaard, A. J.; Feringa, B. L. *Org. Biomol. Chem.* **2006**, *4*, 1278–1283.

(15) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163–3185.

(16) (a) Jin, L.; Zhao, Y.; Zhu, L.; Zhang, H.; Lei, A. *Adv. Synth. Catal.* **2009**, *351*, 630–634. (b) Chen, M.; Zheng, X.; Li, W.; He, J.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 4101–4103.

(17) Casares, J. A.; Espinet, P.; Fuentes, B.; Salas, G. *J. Am. Chem. Soc.* **2007**, *129*, 3508–3509.

(18) van Asselt, R.; Elsevier, C. J. *Organometallics* **1994**, *13*, 1972–1980.

(19) Liu, Q.; Lan, Y.; Liu, J.; Li, G.; Wu, Y. D.; Lei, A. *J. Am. Chem. Soc.* **2009**, *131*, 10201–10210.

(20) Fuentes, B.; García-Melchor, M.; Casares, J. A.; Ujaque, G.; Lledós, A.; Maseras, F.; Espinet, P. *Chem.—Eur. J.* **2010**, *16*, 8596–8599.

(21) By "retrotransmetalation" we mean the reverse of the transmetalation reaction. See: Pérez-Temprano, M. H.; Nova, A.; Casares, J. A.; Espinet, P. *J. Am. Chem. Soc.* **2008**, *130*, 10518–10519.

(22) Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4933–4941.

(23) (a) Ozawa, F.; Ito, T.; Nakamura, Y.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1868–1880. (b) Ozawa, F.; Kurihara, K.; Yamamoto, T.; Yamamoto, A. *J. Organomet. Chem.* **1985**, *279*, 233–243.

(24) (a) Spielvogel, D. J.; Davis, W. M.; Buchwald, S. L. *Organometallics* **2002**, *21*, 3833–3836. (b) Spielvogel, D. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 3500–3501.

(25) Majumdar, K. K.; Cheng, C.-H. *Org. Lett.* **2000**, *15*, 2295–2298.

(26) Anderson, T. J.; Vicic, D. A. *Organometallics* **2004**, *23*, 623–625.

(27) The exact structure of the anion represented as "[$ZnMe_2Cl^-$]" in Scheme 2 was not determined, but it is very reasonable to assume a chloro-bridged dimeric structure [$Me_2Zn(\mu\text{-}Cl)_2ZnMe_2$]$^{2-}$, which satisfies a tetrahedral coordination for Zn. This anion is not good at coordinating, and THF can compete for the vacant Pd site. In contrast, if [$ClMeZn(\mu\text{-}Cl)_2ZnMeCl$]$^{2-}$ is formed by Cl^- abstraction when using ZnMeCl, the anionic dimer produced contains terminal chlorides that will still be better coordinating than THF, and will occupy the Pd site forming Pd−Cl−Zn bridges.

(28) Although the kinetic data for this process are not so good, we estimate that the value of $\Delta G^{\ddagger}{}_{\text{transmetal}}$ for the reaction via **4**$^+$ should be at most 13.6 kcal mol^{-1} to the *trans* and 14.6 kcal mol^{-1} to the *cis*, or lower.

(29) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215–241.

(30) Weidenbruch, M.; Herrndorf, M.; Schafer, A.; Pohl, S.; Saak, W. *J. Organomet. Chem.* **1989**, *361*, 139–145.

(31) For further computational details, see Supporting Information.

(32) As discussed below, because of the difficult treatment of noncovalent interactions, matching quantitative values in transition metal containing molecules is unlikely.

(33) This transition state **TsIT1** appears 0.6 kcal mol^{-1} lower in energy than the following intermediate **IT2** in the Gibbs energy surface, indicating a very easy backward process to regenerate the reactants.

(34) A Gibbs energy difference larger than 3 kcal mol^{-1} compared to the starting materials should be sufficient to make its equilibrium concentration low enough to be nonobservable by NMR.

(35) The very small energy difference between these two intermediates (0.4 kcal mol^{-1}) is due to the different conformations of the tetrahedral Zn.

(36) Sakaki, S.; Ohnishi, Y.-Y.; Sato, H. *Chem. Rec.* **2010**, *10*, 29–45.

(37) Bartlett, K. L.; Goldberg, K. I.; Borden, W. T. *J. Am. Chem. Soc.* **2000**, *122*, 1456–1465.

(38) Sieffert, N.; Bühl, M. *Inorg. Chem.* **2009**, *48*, 4622–4624.

(39) (a) Zhao, Y.; Truhlar, D. G. *Org. Lett.* **2007**, *9*, 1967–1970. (b) Zhao, Y.; Truhlar, D. G. *J. Chem. Theory Comput.* **2009**, *5*, 324–333.

(40) At 203 K, assuming as safe estimations 10% error in the rate constant and 1 degree in the determination of T, the error in ΔG is only 0.08 kcal mol^{-1}.

(41) (a) Harvey, J. N. *Faraday Discuss.* **2010**, *145*, 487–505. (b) McMullin, C. L.; Jover, J.; Harvey, J. N.; Fey, N. *Dalton Trans.* **2010**, *39*, 10833–10836.

(42) For oxidative addition, see refs 4 and 5; for concurrence of competitive pathways and the occasional need of isomerization, see reference 8; for C−C coupling, see: Pérez-Rodríguez, M.; Braga, A. A. C.; García-Melchor, M.; Pérez-Temprano, M. H.; Casares, J. A.; Ujaque, G.; de Lera, A. R.; Álvarez, R.; Maseras, F.; Espinet, P. *J. Am. Chem. Soc.* **2009**, *131*, 3650–3657.