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Experimental Study of the $[ZnCl_2(THF)_2]$ Catalyzed *cis/trans*- Isomerization of $[Pd(C_6Cl_2F_3)Me(PPh_3)_2]$ and the Transmetalation of *trans*-$[PdCl(C_6Cl_2F_3)(PPh_3)_2]$ with $[ZnMeCl(THF)_2]$

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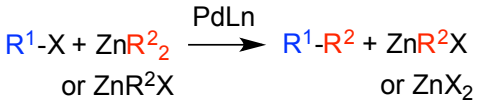
Dedicated to Prof. Maurizio Peruzzini on the occasion of his retirement.

Abstract

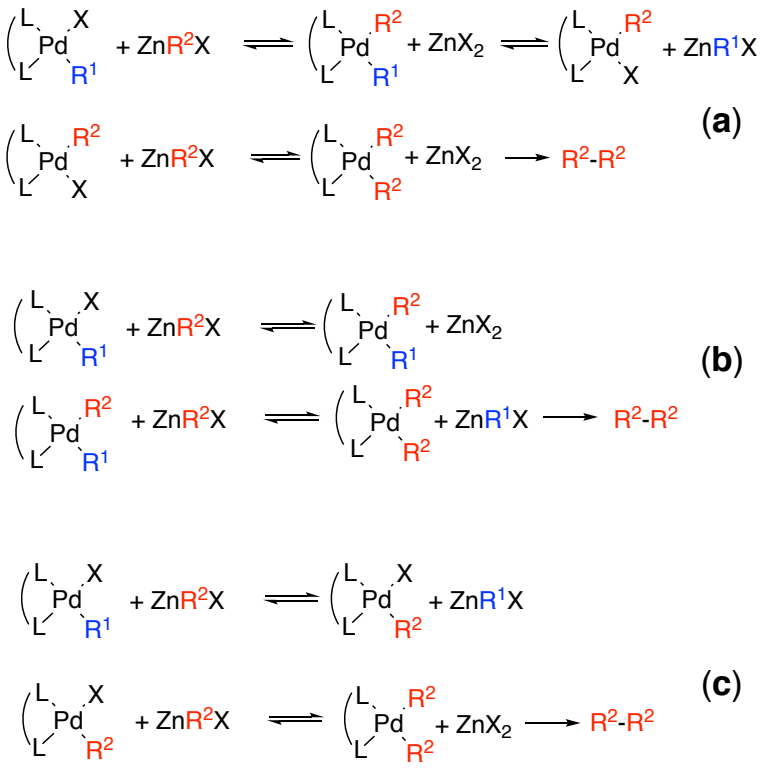
The kinetics of the transmetalation reaction between trans-$[PdCl(C_6Cl_2F_3)(PPh_3)_2]$ and $[ZnMeCl(THF)_2]$ shows a complex dependence on $[PPh_3]$ for the rate of formation of different reaction products: cis and trans-$[Pd(C_6Cl_2F_3)Me(PPh_3)_2]$, trans-$[PdClMe(PPh_3)]$ (which further reacts with $[ZnClMe(THF)_2]$), and $[Zn(C_6Cl_2F_3)Cl(THF)_2]$. To better understand the system the reactions between cis and trans-$[Pd(C_6Cl_2F_3)Me(PPh_3)_2]$ and $[ZnCl_2(THF)_2]$ (the retro-transmetalation reactions) and their kinetic dependence on $[PPh_3]$ were studied. These reactions lead to the formation of trans-$[PdClMe(PPh_3)]$ and $[Zn(C_6Cl_2F_3)Cl(THF)_2]$ as main products. Additionally, the experiments show that the isomerization of cis to trans-$[Pd(C_6Cl_2F_3)Me(PPh_3)_2]$ is catalyzed by $[ZnCl_2(THF)_2]$. In this catalyzed isomerization the concentration of PPh_3 is involved in two ways: It modulates the concentration of the organozinc $[Zn(C_6Cl_2F_3)Cl(THF)_2]$, and also it shifts a phosphine substitution equilibrium in the palladium complex, producing an anomalous dependence of the reaction rate on the concentration of this ligand.

Introduction

The Negishi reaction is a palladium or nickel catalyzed cross coupling in which an aryl halide reacts with an organozinc nucleophile (Scheme 1). The reaction is one of the most successful cross-coupling systems and its utility has been widely recognized.[1-3] Although most of the time the reaction works nicely using palladium catalysts, for specific pairs of reagents the homocoupling products are competitively formed. This happens when the transmetalation reactions, that are fast and reversible, lead to an exchange of aryls between zinc and palladium by a transmetalation / retro-transmetalation sequence or, alternatively, by the direct aryl-by-aryl exchange between palladium and zinc (Scheme 2).



Scheme 1. General scheme of the Negishi reaction.



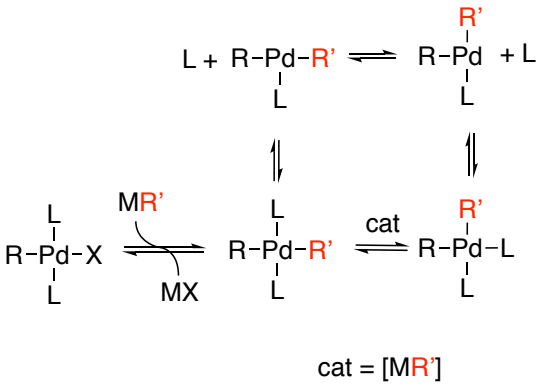
Scheme 2. Processes that lead to homocoupling products in the Negishi reaction: (a) through a transmetalation / retro-transmetalation sequence, (b) and (c) through aryl-by-aryl exchange and transmetalation reactions.

The study of the transmetalation is important because sometimes it is the rate limiting step, and because of its relevance to the selectivity of the reaction. Unfortunately, it is not an easy task, not only because the high reaction rate of this step, but also because of the difficulties regarding the speciation of zinc reagents that complicates the computational modeling of the systems.[4] First of all, the consideration or not of solvent molecules coordinated to the zinc may change the energy and the geometry of intermediate states of the reaction.[5] In addition, the organozinc species involved change during the reaction course; for instance when a diorganozinc [$ZnR_2(solv)_2$] reagents are used, the halo-organozinc [$ZnRX(solv)_2$] is produced during the reaction leading to a different transmetalation reaction.[6] The speciation also depends on reagents from which organozinc compounds are synthesized. The most effective routes to form organozinc halides and diorganozinc compounds involve transmetalation reactions between ZnX_2 and LiR or organomagnesium reagents, and the final solutions of the organozinc compound contain significant amounts of LiX or MgX_2 that can react with the organozinc reagents. [7,8,9] The coordination of anions to the organozinc species leads to anionic species "zincates", whose exact composition is not always easily established, and whose reactivity differs substantially from neutral organozinc reagents.[7-9,10-25] Finally, the halogen coordinated to the zinc in halo-organozinc reagents, (whose halogen may proceed from any of the reagents used in its synthesis), also plays a relevant role. A. Lei *et al*. carried out mechanistic studies using *in situ* IR and X-Ray

absorption spectroscopy.[26-28] They found that in phenylzinc derivatives the Zn-C bond distance increases upon changing the halide anion from chloride to bromide and to iodide and that a higher transmetalation rate occurs when organozinc with longer Zn-C bond distances are employed.

As stated above, in transmetalation reactions organozinc reagents are able to exchange their organic group for a halogen, but also for another organic group from the organopalladium complex. The first example of an aryl-for-aryl exchange was observed in 1994 on the reaction between *p*-tolylzinc chloride and the complex [PdBzBr(ArBIAN)] (Bz = benzyl; ArBIAN = bis(aryliminio)acenaphthene), reported by Elsevier et al.[29] A similar reaction takes place in the $C(sp^3)$-$C(sp^2)$ cross-coupling with alkylzinc reagents: On the study of the transmetalation of *trans*-[PdRfCl(PPh_3)$_2$] (**1**) (Rf = 3,5-dichloro-2,4,6-trifluorophenyl), with [$ZnMe_2(solv)_2$] and [ZnMeCl$(solv)_2$], we found the formation of fluoroaryl-zinc species resulting from the exchange of Rf by Me groups between metals.[6] The exchange of non-fluorinated aryls by alkylzinc is also a fast process that often hinders the analysis or the reaction products.[30] In the aryl-aryl cross coupling reaction this problem can be overcome by a judicious choice of the organozinc and haloaryl groups. In this sense A. Lei et al. analyzed the factors that produced the aryl by aryl exchange in the cross-coupling reaction of aryl iodides Ar^1X with arylzinc halides [$ZnAr^2Cl(solv)_2$], catalyzed by [$PdCl_2$(dppf)]. Depending on the substituents in the Ar^I group the reaction yields the cross-coupling product or the exchange products [$ZnAr^1X(solv)_2$] and "Ar^2PdAr^2" that eventually render the homocoupling product.[31]

When complexes with monodentate ligands, such as phosphines, are used as catalysts the stereochemistry of the transmetalation is also an issue. The transmetalation of complexes of the type [$PdXR^1L_2$] with reagents [$ZnER^2(THF)_2$] (E = halogen or R^2) in THF (THF : tetrahydrofuran) produces mixtures of *cis* and *trans*-[$PdR^2R^1L_2$].[6,32,33] This point is relevant in catalytic systems because the reductive elimination step can only take place from the *cis* isomer, thus the formation of the *trans* isomer means that a fraction of the catalyst is accumulated in a relatively inert form. The most accessible pathway for the *trans-cis* isomerization of isolated [$PdR^1R^2L_2$] complexes is through three-coordinated species [PdR^1R^2L] (scheme 3). This mechanism seems to be quite general for palladium(II) and platinum(II) organometallics.[34-38] However the catalysis is often carried out under an excess of phosphine in order to prevent the decomposition of Pd(0) intermediates, so this pathway becomes inaccessible under catalytic conditions. Fortunately for the cross-coupling reaction, organozinc, as other organometallics, catalyze the trans-cis isomerization (Scheme 3).[32,33,39-41]



Scheme 3

The lack of stereochemical selectivity in the transmetalation was discussed in experimental and computational mechanistic studies of the reaction between *trans*-[PdRClL$_2$] (R = Me or Rf, L PPh_2Me or PPh_3) and [ZnMeCl(solv)$_2$] or [ZnMe$_2$(solv)$_2$], [4,32,33,42] and is a consequence of the excellent nucleophilicity of the C-Zn bond, that allows its behavior as donor ligand instead of the phosphine ligand opening a pathway of phosphine substitution that competes with the direct substitution of the halogen. But even if the ligand L is inert to the substitution, organozinc reagents are able to find a relatively "flat" reaction surface connecting different transition states that allows the fast equilibria between intermediates that lead to different isomers. This, along with the small ΔH associated to the exchange between C-Zn and C-Pd bonds, is the reason by which organozinc catalyze the *cis-trans* isomerization of [PdR^{1}R^{2}L$_2$] complexes. The isomerization catalyzed by poor nucleophiles, such as [ZnCl$_2$(solv)$_2$] remains unproven until now, although the role of zinc halides in other steps of the Negishi reaction has been reported. [25]

In this work we study the effect of the ligand in solution on the transmetalation between *trans*-[PdRfCl(PPh_3)$_2$] (**1**) and [ZnMeCl(THF)$_2$] and on the retro-transmetalation system formed by [ZnCl$_2$(THF)$_2$] and the complexes *cis* and *trans*-[PdRfMe(PPh_3)$_2$] (**2** and **3**). We chose these systems because the Rf-Me coupling step is slow, the initial transmetalation isomers, **2** and **3**, are stable, and also because the use of fluorinated ligands provides a useful label in ^{19}F NMR spectroscopy allowing the monitoring of the reaction. [43]

Experimental

All the manipulations were performed under N_2 or Ar atmosphere, using standard Schlenk techniques unless otherwise stated. Solvents were dried using a solvent purification system SPS PS-MD-5 or distilled from appropriate drying agents under nitrogen according to literature,[44] and stored over 3 Å zeolites for a week. The residual amount of water (in the range 1-5 ppm) was measured with a Metler Toledo C20KF Karl Fischer instrument. Prior to their use, solvents were degassed by three freeze-pump-thaw cycles. NMR spectra were recorded on Bruker AV 400 or Agilent 500-MR instruments equipped with variable-temperature probes. Chemical shifts are

reported in ppm from tetramethylsilane (^{1}H and ^{13}C), CCl_3F (^{19}F), at 298 K unless otherwise stated. The temperature for the NMR probe was calibrated with an ethylene glycol standard (high temperature) and with a methanol standard (low temperature).[**¡Error! Marcador no definido.**] In the ^{19}F NMR spectra recorded in non-deuterated THF, a coaxial tube containing acetone-d_6 was used to maintain the lock to ^{2}H signal, and the chemical shifts in ^{19}F NMR are reported relative to 1,3,5-trichloro 2,4,6-trifluorobencene (δ = -115.1 ppm) as internal standard. Complexes cis-[PdRfMe(PPh_3)$_2$],[6] trans-[PdRfMe(PPh_3)$_2$],[6] tran*s*-[PdRfCl(PPh_3)$_2$],[45] cis-[$PdMe_2$(PPh_3)$_2$] and trans-[PdClMe(PPh_3)$_2$],[46] and Ag($C_6Cl_2F_3$),[47] were prepared and characterized as reported in the literature. In order to identify the chemical shift of the complex [ZnRfCl(THF)$_2$] in the absence of residual halide, a solution of [ZnRfCl(THF)$_2$] in THF was prepared reacting in THF [$ZnCl_2$(THF)$_2$] with the stoichiometric amount of Ag($C_6Cl_2F_3$). A [ZnMeCl(THF)$_2$] solution was prepared by mixing a solution of [$ZnCl_2$(THF)$_2$] (9.4 mL, 1.1 mol·L^{-1}) in THF with a solution of $ZnMe_2$ (5.0 mL, 2.0 mol· L^{-1}) in toluene, under argon. ^{1}H NMR (THF, acetone-d_6 capillary, 298 K): δ –0.65 ppm (s, 3H).

Kinetic experiments. Typical procedure.

In a standard experiment an NMR tube cooled to 193 K was charged with the palladium compound ($9.9x10^{-3}$ mmol), zinc compound (0.20 mmol), and THF until a volume of 0.60 mL. When the mixture was dissolved in the THF, a coaxial capillary containing acetone-d_6 was added and the sample was placed into the NMR probe that had been previously thermostated at 298 K. The evolution of the reaction was monitored by ^{19}F NMR spectroscopy without the use of internal standard. 128 scan spectra were recorded employing 33768 complex points using a π/8 pulse length. The delay between spectra was of 20 s so that one spectrum was recorded every five minutes. No significative variation of the overall integral values during the reaction course was noticed in the experiments. Concentration-time data were obtained by integration of the ^{19}F NMR signals corresponding to the fluorine nuclei in position *ortho* to the palladium whose chemical shirts are collected in table 1. The kinetic order was obtained by the initial rates method, and kinetic rate constants were obtained by non-linear minimum square fitting of the experimental data points to kinetic models, with the aid of the software "COPASI".[48]

Table 1. Chemical shifts (ppm) of the nuclei of $F^{2,6}$ of the organometallic compounds used for the quantification of their concentration in THF solutions.

trans-[PdRfCl(PPh_3)$_2$]	*cis*-[PdRfMe(PPh_3)$_2$]	*trans*-[PdRfMe(PPh_3)$_2$]	[ZnRfCl(THF)$_2$]	Rf–CH_3
– 91.9 (t, $^{4}J_{F-P}$ = 7 Hz)	–90.6 (d, $^{4}J_{F-P}$ = 10 Hz)	– 91.0 (t, $^{4}J_{F-P}$ = 3 Hz)	–92.1 (s)	–117.4 (s)

Results and discussion

In a previous work we have shown that, under a large excess of [ZnMeCl(THF)$_2$] that resembles catalytic conditions, the reaction between trans-[PdRfCl(PPh$_3$)$_2$] and [ZnMeCl(THF)$_2$] produces preferentially cis-[PdRfMe(PPh$_3$)$_2$] that isomerizes to the trans isomer.[6] The reaction also produces [ZnRfCl(THF)$_2$] and trans-[PdMeCl(PPh$_3$)$_2$] which further reacts with [ZnMeCl(THF)$_2$] to give cis-[PdMe$_2$(PPh$_3$)$_2$]. Figure 1 shows the typical reaction profile monitored by ^{19}F NMR of the reaction of **1** with [ZnClMe(THF)$_2$] and compares it with the same experiment in which an excess of PPh$_3$ has been added.

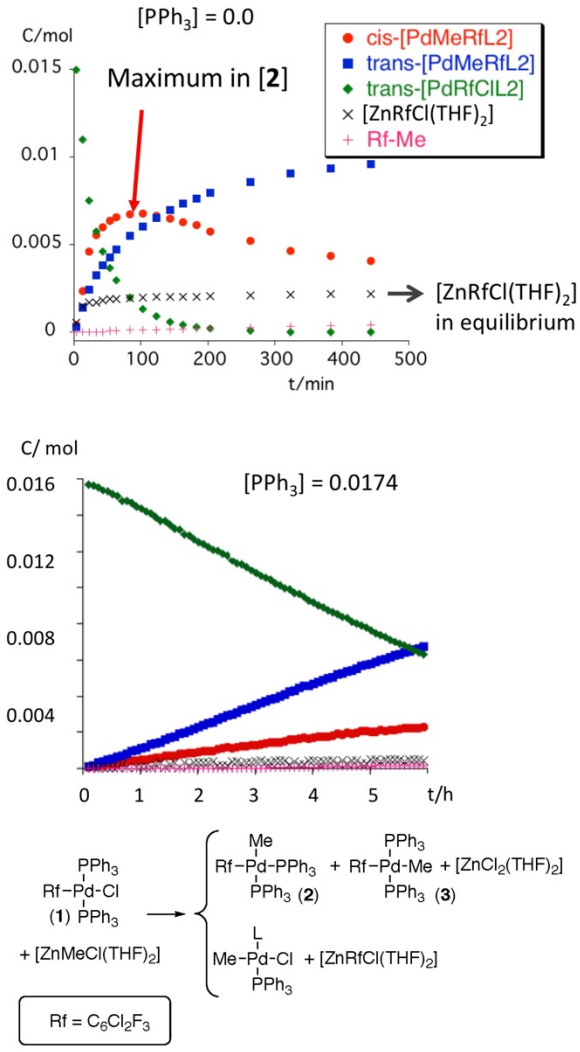


Figure 1. Concentrations time plot of the reactions between trans-[PdRfCl(PPh$_3$)$_2$] and [ZnMeCl(THF)$_2$] ([trans-[PdRfCl(PPh$_3$)$_2$] = 1.6*10^{-2} M, [ZnMeCl(THF)$_2$]$_0$ = 0.33 mol·L^{-1}). Upper plot: T = 293K, no phosphine added; lower plot T = 298K; [PPh$_3$] = 0.0174 mol·L^{-1}.

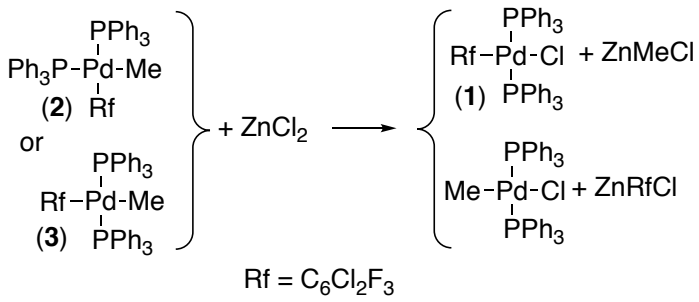
The most obvious difference between the reactions with and without added phosphine is the reaction rate. The half-life of **1** is about 30 min in the first case and about five hours in the

second. The kinetic experiments under different concentrations of PPh_3 (Table S1 in supplementary material) show that the reaction is strongly retarded by the addition of free PPh_3, the kinetic order on $[PPh_3]$ for the disappearance of trans-$[PdRfCl(PPh_3)_2]$ has been measured by the initial rates method, giving roughly a value of –1. This suggests a transmetalation mechanism that involves the substitution of a phosphine ligand by $[ZnMeCl(THF)_2]$ as first step. But there is also a significant difference in the ratio of the products of the reaction: In the absence of added phosphine $[ZnRfCl(THF)_2]$ is formed very quickly, reaching in a few minutes the equilibrium concentration that then changes slightly with the composition of the reaction mixture, the *cis* isomer **2** is formed quickly at the beginning of the reaction and the *trans* isomer **3** is formed at an slower pace, however under added PPh_3 the concentration of $[ZnRfCl(THF)_2]$ remains in "quasi steady-state" concentration, and **2** and **3** are formed in their equilibrium ratio.

The role of $[ZnRfCl(THF)_2]$ in the reaction is not clear, and several mechanisms may be invoked to explain its formation. This organozinc could be just an unwanted by-product formed by a transmetalation retro-transmetalation sequence, or it could be formed in a direct methyl-by-aryl exchange between palladium and zinc. The system includes several competitive pathways and reversible reactions and is too complex to allow the obtention of a detailed picture or quantitative values for rate constants. Additional information about the equilibria involved in this system was obtained from the study of the reverse reaction.

Retro-transmetalation experiments

The reactions between *cis*-$[PdRfMe(PPh_3)_2]$ (**2**) or *trans*-$[PdRfMe(PPh_3)_2]$ (**3**) with $[ZnCl_2(THF)_2]$ were studied. These mixtures form an exchange system in which, in addition to the known *cis/trans*-$[PdRfMe(PPh_3)_2]$ isomerization equilibrium,[41] other products are formed such as $[ZnRfCl(THF)_2]$ (**4**) and minor amounts of the *trans*-$[PdRfCl(PPh_3)_2]$ (**1**) (Scheme 4), as well as small amounts of the reductive elimination product RfMe. Transmetalation equilibria are shifted to the formation of $[PdRfMe(PPh_3)_2]$ and $[ZnCl_2(THF)_2]$, so that the reactions required a large excess of $[ZnCl_2(THF)_2]$ to be studied. The formation of the compound $[PdCl_2(PPh_3)_2]$ was not observed even under a large excess of $[ZnCl_2(THF)_2]$.



Scheme 4. Reaction between cis-$[PdRfMe(PPh_3)_2]$ (**2**) or tran*s*-$[PdRfMe(PPh_3)_2]$ (**3**) with $[ZnCl_2(THF)_2]$ in THF.

The main effect of the addition of $[ZnCl_2(THF)_2]$ to **2** or **3** is on the *cis*/*trans* isomerization rate. In Figure 2 the experimental graphics of the isomerization with $[ZnCl_2(THF)_2]$ are compared to the reaction without added $[ZnCl_2(THF)_2]$ (simulated course from experimental kinetic parameters) , showing that the isomerization from cis- to trans-$[PdRfMe(PPh_3)_2]$ is faster in the presence of $[ZnCl_2(THF)_2]$. Note that at equilibrium both complexes reach a concentration that can be measured by NMR, therefore the isomerization rate can be measured starting from either the cis or from the trans isomer. It is also clear from the graphics that, irrespectively of the chosen starting system, the fastest reaction is the formation of $[ZnRfCl(THF)_2]$. It is worth noting that an induction period was observed for the isomerization process that is coincident with the time required for the formation of the maximum amount of $[ZnRfCl(THF)_2]$.

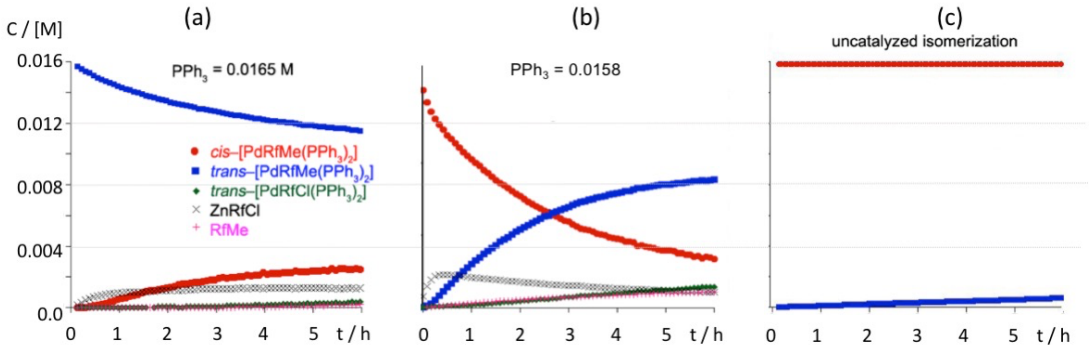


Figure 2. a) and b): experimental concentration / time plots for the reactions: a) **3** + $[ZnCl_2(THF)_2]$ ($[\mathbf{3}]_0$ = 0.0165 mol·L^{-1}, $[ZnCl_2(THF)_2]_0$ = 0.66 mol·L^{-1}, [1] and $[PPh_3]_0$ = 0.0165 mol·L^{-1}), b) **2** + $[ZnCl_2(THF)_2]$ ($[\mathbf{2}]_0$ = 0.0165 mol·L^{-1}, $[ZnCl_2(THF)_2]_0$ = 0.66 mol·L^{-1} and $[PPh_3]_0$ = 0.0158 mol·L^{-1}), and c) Simulated *cis*- to *trans*-$[PdRfMe(PPh_3)_2]$ isomerization reaction with $[PPh_3]_0$ = 0.0165 mol·L^{-1}. The simulation was done by using the data taken from Ref.[41]

The dependence of the reaction on the concentration of PPh_3 is not identical for the different species involved. Figures 3 and 4 show the concentration-time plots for the reactions between $[ZnCl_2(THF)_2]$ with cis-$[PdRfMe(PPh_3)_2]$ (**2**) (Figure 3) and $[ZnCl_2(THF)_2]$ with trans-$[PdRfMe(PPh_3)_2]$ (**3**) (Figure 4). The disappearance of the starting complex, **2** or **3** is almost insensitive to the concentration of PPh_3. However, the plots showing the formation of $[ZnRfCl(THF)_2]$ and the isomerization product on each case (**3** and **2** respectively) change noticeably with $[PPh_3]$. The formation of $[ZnRfCl(THF)_2]$ is particularly informative. Starting from **2** (Figure 3) $[ZnRfCl(THF)_2]$ is formed very fast at the beginning of the reaction, its concentration reaches a maximum and then gently declines. The initial reaction rate of formation of $ZnRfCl(THF)_2$ is not sensitive to $[PPh_3]$, and it is possible to obtain a common value of about

$1.8 \cdot 10^{-6}$ $molL^{-1}s^{-1}$ for all the experiments, however, the maximum concentration of $[ZnRfCl(THF)_2]$ increases with the concentration of phosphine.

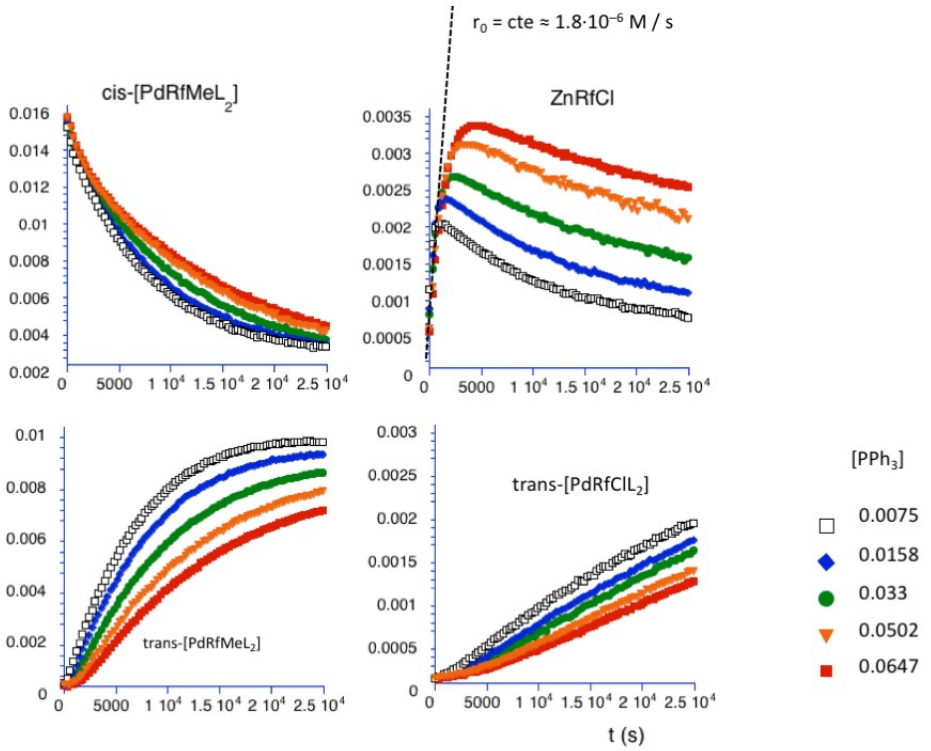


Figure 3. Concentration-time plots for the reactions between $[ZnCl_2(THF)_2]$ and cis-$[PdRfMe(PPh_3)_2]$ (**2**) at 298 K under different concentrations of PPh_3 in THF. The values on the table represent the initial concentration of PPh_3 in $molL^{-1}$. Starting conditions: $[\mathbf{2}]_0$ = 0.0160 $mol \cdot L^{-1}$, $[ZnCl_2(THF)_2]_0$ = 0.66 $mol \cdot L^{-1}$. Note that the vertical scale is different for each plot.

The same behavior is obtained starting from complex trans-$[PdRfMe(PPh_3)_2]$ (**3**) (Figure 4) although the formation of $[ZnRfCl(THF)_2]$ from the trans isomer is about one order of magnitude slower than from the cis, and as consequence of the isomerization **3** to **2**, the formation of $[ZnRfCl(THF)_2]$ do not stop as suddenly as when starting from **2**. To explain this behavior, the reactions shown in Scheme 5 were proposed.

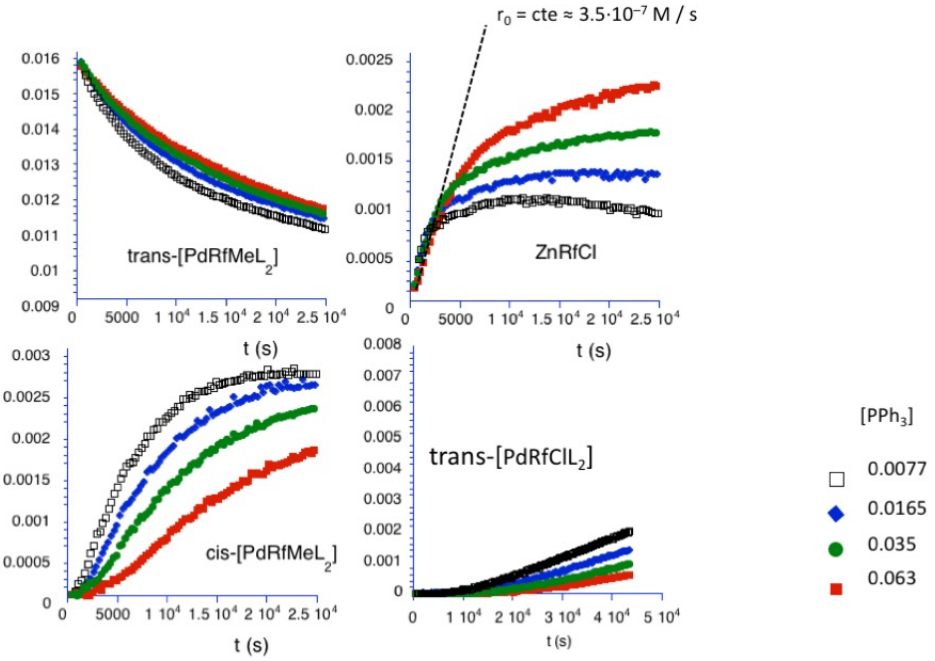
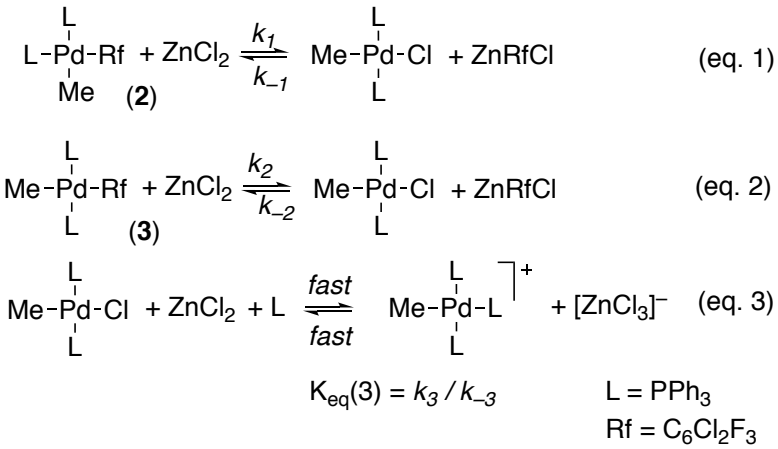


Figure 4 Concentration-time plot for the reaction between $[ZnCl_2(THF)_2]$ and trans-$[PdRfMe(PPh_3)_2]$ (**3**) at 298 K under different concentrations of PPh_3 in THF. The values on the table represent the initial concentration of PPh_3 in mol·L^{-1}. ([**3**]$_0$ = 0.0160 molL^{-1} , $[ZnCl_2(THF)_2]_0$ = 0.66 mol·L^{-1}). Note that the vertical scale is different for each plot.



Scheme 5.

The formation of cationic species $[PdMeL_3]^+$ induced by Lewis acids, such as organozinc derivatives, has been demonstrated previously,[42] and is not unexpected in the presence of a strong acid as $[ZnCl_2(THF)_2]$. In an attempt to detect the formation of $[PdMeL_3]^+$, the reaction of cis-$[PdRfMe(PPh_3)_2]$ (**2**) with $[ZnCl_2(THF)_2]$ in the presence of PPh_3 was stopped after one hour by cooling it to –20 °C. The ^{19}F spectrum shows the partial conversion of **2** to trans-$[PdRfMe(PPh_3)_2]$ (**3**), and the formation of $[ZnRfCl(THF)_2]$. Accordingly, the $^{31}P\{^1H\}$ spectrum shows the presence of **2**, **3** and also $[PdMeL_3]^+$, characterized by its AX_2 spin system, in an amount that matches the amount of $[ZnRfCl(THF)_2]$ observed in the ^{19}F NMR spectrum (Figure 5).

Thus, the reaction shown in equilibrium 3, removes [PdMeCl(PPh_3)$_2$] from the reaction medium shifting equilibria 1 and 2 to the right so that a larger amount of [ZnRfCl(THF)$_2$] is produced for higher concentrations of PPh_3.

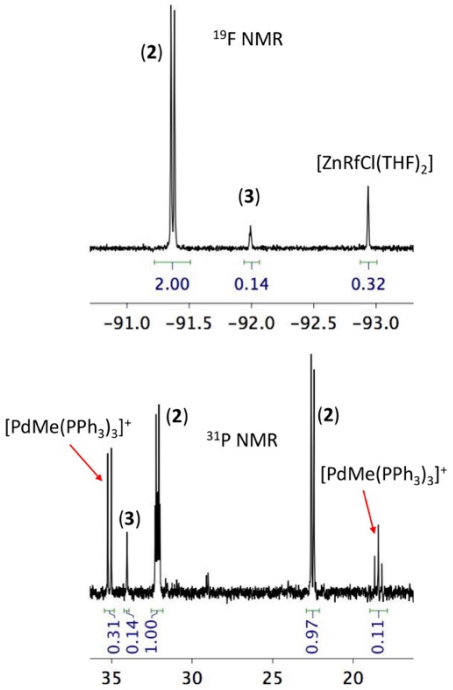
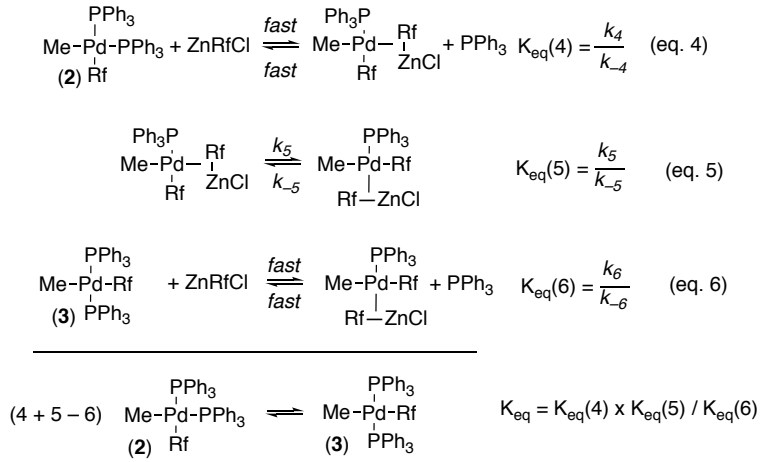


Figure 5. ^{19}F (F(2) and F(6) only) and $^{31}P\{^1H\}$ NMR of the reaction of **2** with [$ZnCl_2(THF)_2$] in the presence of PPh_3 showing the signals due to the cation $[PdMeL_3]^+$. The spectra have been recorded at –20˚C in THF.

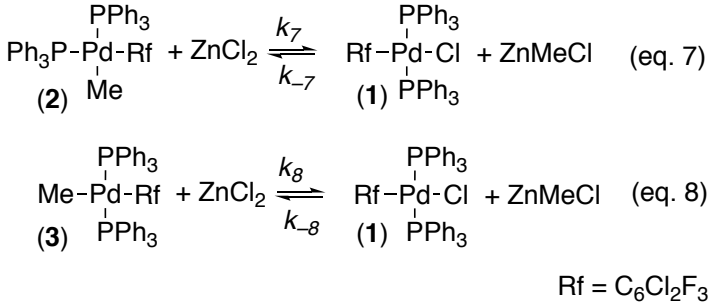
Scheme 5 also explains the increase on the isomerization rate between **2** and **3** in the presence of [$ZnCl_2(THF)_2$], that is implicit in equations 1 and 2, but does not explain satisfactorily the dependence on [PPh_3] of the isomerization rates: the formation of trans-[PdRfMe(PPh_3)$_2$] **(3)** when starting from cis-[PdRfMe(PPh_3)$_2$] (**2**) (Fig. 3) or the formation of **2** when starting from **3** (Fig. 4). The shape of these curves is a sigmoid suggesting an induction period, coincident with the formation of [ZnRfCl(THF)$_2$] (**4**). To explain this behavior another isomerization route, catalyzed by [ZnRfCl(THF)$_2$] was proposed (Scheme 6). This reaction is similar to that studied for the isomerization of **2** and **3** in the presence of $ZnMe_2$, and involves the substitution of one phosphine ligand by the incoming [ZnRfCl(THF)$_2$].[32] During this reaction the aryl group is exchanged between the organozinc and the organopalladium.



Scheme 6.

The experimental data fit nicely with this complex scheme (see supplementary information) in a wide interval of values for Keq(4), the values of k_5 and Keq(5) being dependent on this parameter. Thus, although a good qualitative interpretation of the results is possible, the obtention of a complete energy profile for the reaction system is not possible with a reasonable number of experiments.

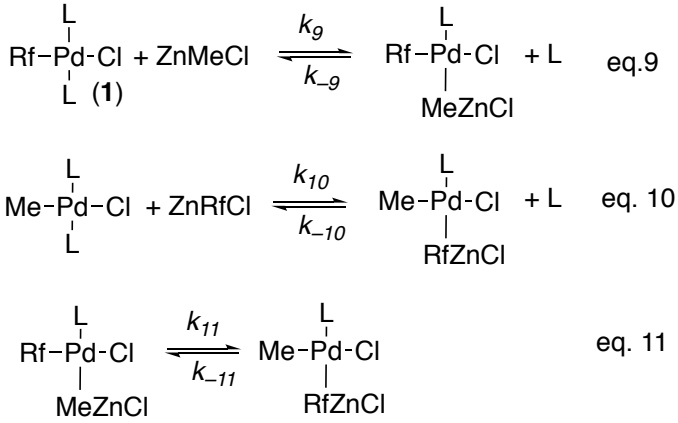
Another interesting feature of this set of experiments is the behavior of the species trans-[PdRfCl(PPh_3)$_2$] (**1**). This product is formed very slowly in both systems, either starting from **2** or from **3**, and is the product of the retro-transmetalation of **1** with [$ZnCl_2$(THF)$_2$]. Equations 7 and 8 were introduced to account for this result. A close inspection of the experiments starting from trans-[PdRfMe(PPh_3)$_2$] (**3**) in Figure 4 shows that the initial rate of formation of trans-[PdRfCl(PPh_3)$_2$] (**1**) is close to zero and that **1** is only formed when the reaction has produced a significant amount of the isomer **2**, so that k_8 is assumed to be negligible.



Scheme 7

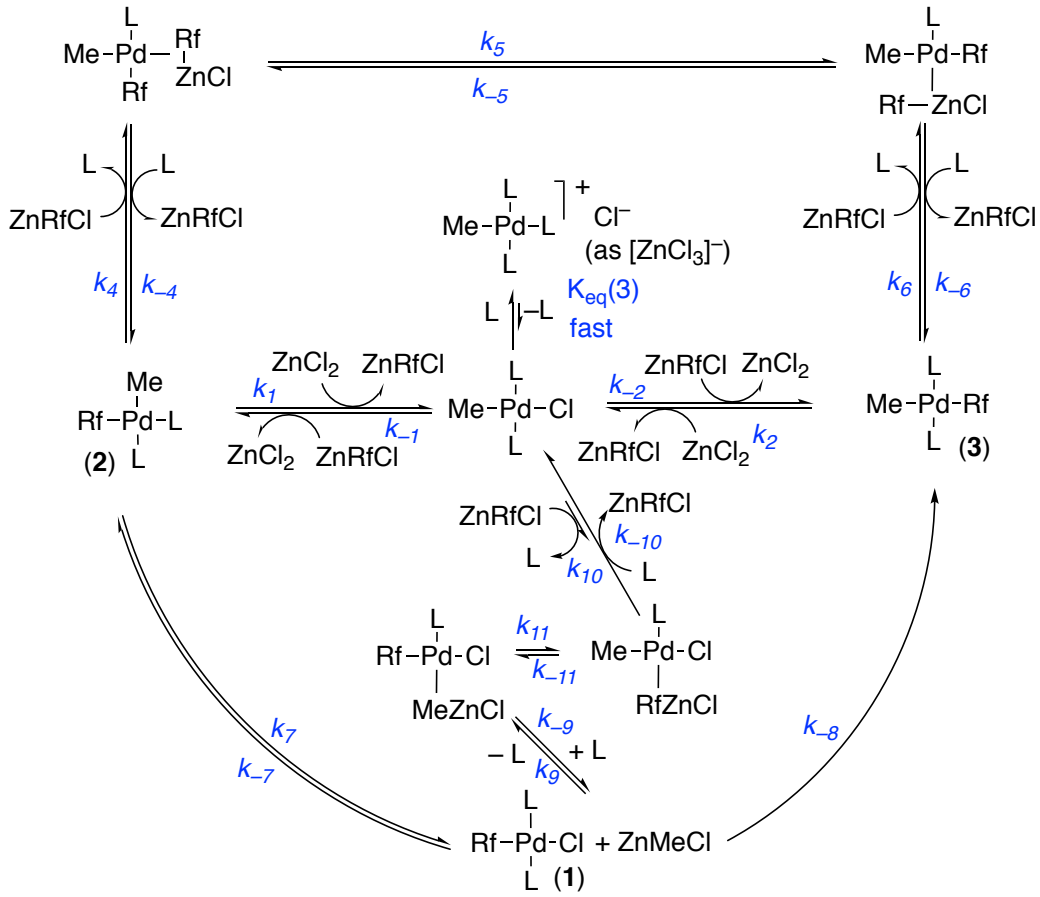
Turning back to the reaction between trans-[PdRfCl(PPh_3)$_2$] (**1**) and [ZnMeCl(THF)$_2$], the above described set of equations with their values was used to simulate the behavior of this system. Starting from **1**, the fast formation of [ZnRfCl(THF)$_2$] cannot be explained merely as result of the reactions 1 and 2, since the amount of cis and trans-[PdRfMe(PPh_3)$_2$] and of [$ZnCl_2$(THF)$_2$] at the beginning of the reaction is very small. The dependence on [PPh_3] is satisfactorily explained by

introducing a preequilibrium in which [ZnClMe(THF)$_2$] substitutes one triphenylphosphine (Scheme 8). It should be pointed out that under a large excess of [ZnMeCl(THF)$_2$], the product [PdMeCl(PPh$_3$)$_2$] reacts to produce *cis* and *trans*-[PdMe$_2$(PPh$_3$)$_2$], but these complexes also exchange the methyl groups for fluoroaryls when reacting with fluoroarylzinc derivatives, as shown previously in reactive systems with [ZnMe$_2$(THF)$_2$].[32]



Scheme 8

Finally, when the whole system is considered it is clear that the number of kinetic parameters involved (rate and equilibrium constants) is too large to allow the extraction of their actual values within the desirable statistical validity. The rates of transmetalation are affected by the concentration of PPh$_3$ because this ligand affects the equilibria in equations 4, 6, 9 and 10 involved in the transmetalation pathways, but also because the concentration of the key complex [PdClMe(PPh$_3$)$_2$] depends on the equilibrium 3. Since the actual equilibrium constant of the equation 3 (Scheme 5) in unknown, the concentration of the intermediate [PdClMe(PPh$_3$)$_2$] cannot be univocally stablished, and this affects the values of the other rate constants. Additionally, other reactions may be considered; for instance, the above mentioned transmetalation of [PdClMe(PPh$_3$)$_2$] with [ZnMeCl(THF)$_2$], which for the sake of clarity has not been included in the schemes. This reaction has been previously studied in systems with PPh$_2$Me instead of PPh$_3$ showing that the complexes react very fast to give trans and cis-[PdMe$_2$(PPh$_2$Me)], but the exact values for these rate constants on the system with PPh$_3$ are not available. In spite of these limitations, the reaction scheme depicted in Scheme 9, provides a sound qualitative interpretation of the complex system of the transmetalations related to the Negishi cross-coupling reactions.



Scheme 9

Conclusions

The study of the system formed by trans-[PdRfCl(PPh_3)$_2$], [ZnMeCl(THF)$_2$], and their products of reaction, shows some interesting features of the transmetalation reactions with organozinc derivatives and palladium complexes, such as: i) The almost complete absence of stereoselectivity of the transmetalation reaction. As shown also in previous works the transmetalation lead to the cis or to the trans isomer with a small difference on the reaction rates.[33] ii) The reaction is reversible and the equilibrium is only slightly shifted towards the products. Thus, mechanistic proposals that include transmetalation of organozinc reagents should consider this step as a reversible reaction. And iii) as shown in the studied system, the reactions of organometallic species of palladium complexes containing halides as ligands with zinc organometallics often produce the exchange of aryl or alkyl groups competitively with the exchange of the organic group for the halogen.

Additionally, this work provides information about the reactions in which zinc chloride participates, which is relevant not only because zinc halides are formed during the Neghisi reaction but also because they are occasionally used as "additives". It has been found that [$ZnCl_2$(THF)$_2$] acts on transmetalation equilibria in two ways: i) driving the aryl retro-transmetalation reaction and ii) in those reactions that are carried out in excess of ligand, ZnX_2

can divert the complex *trans*-[PdXRL$_2$] to form [PdRL$_3$]$^+$ and [ZnX$_3$]$^-$ decreasing the concentration of the reagent that primarily suffers the transmetalation, and either of these has a detrimental effect on the transmetalation kinetics. The study also shows that [ZnCl$_2$(THF)$_2$] is an efficient catalyst for the cis-trans isomerization reaction of complexes [PdRfMe(PPh$_3$)$_2$]. The isomerization occurs through the exchange of Rf fluoroaryls between the cis or trans-[PdRfMe(PPh$_3$)$_2$] complex and the organozinc [ZnRfCl(THF)$_2$] formed in situ by a transmetalation reaction.

From a kinetic point of view the transmetalation system formed by organozinc and organopalladium complexes lead to a large number of intermediates connected by low energy transition states shown in Scheme 9, although other reactions are also probably participating. This provides a qualitative understanding of the system. However the exact quantification of such a complex system is beyond the scope of the available experimental data.

ACKNOWLEDGMENTS

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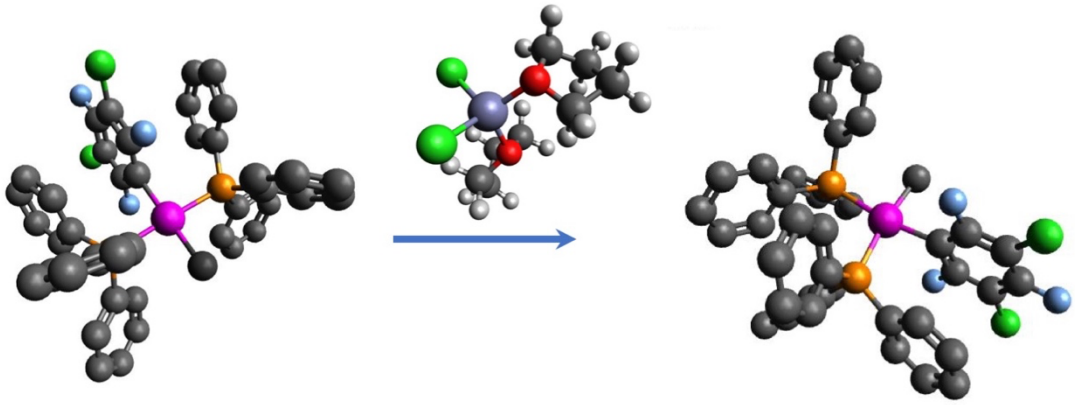
Graphical Abstract



The isomerization of cis-[Pd($C_6Cl_2F_3$)Me(PPh_3)$_2$] to its trans isomer is efficiently catalyzed by [$ZnCl_2$(THF)$_2$]. The reaction takes place through a series of transmetalation steps involving [ZnCl($C_6Cl_2F_3$)(THF)$_2$]. This reaction is part of a complex set of equilibria that describe the transmetalation pathway in systems related to the Negishi Cross-coupling reaction.

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