The Negishi Catalysis: Full Study of the Complications in the Transmetalation Step and Consequences for the Coupling Products

Juan del Pozo,¹ Gorka Salas,² Rosana Álvarez,*³ Juan A. Casares,*¹ and Pablo Espinet*¹

¹ IU CINQUIMA/Química Inorgánica, Facultad de Ciencias, Universidad de Valladolid, 47011-Valladolid (Spain)
² IMDEA Nanociencia, Ciudad Universitaria de Cantoblanco, 28049 Madrid, Spain.
³ Departamento de Química Orgánica, Facultad de Química (CINBIO), Universidad de Vigo. Campus As Lagoas-Marcosende, 36310 Vigo (Spain)

ABSTRACT: In addition to the expected products, trans- and cis-[PdRfMe(PPh₃)₂], the transmetalation between ZnMe₂ and trans-[PdRfCl(PPh₃)₂] yields [PdMeCl(PPh₃)] and ZnMe as the result of secondary transmetalation processes. ZnRfMe is also formed by reaction of trans and cis-[PdRfMe(PPh₃)₂] with ZnMe₂. The different competitive reaction mechanisms that participate in the transmetalations have been studied experimentally and by DFT calculations. The relative contribution of each reaction pathway in the formation of the unwanted product ZnRfMe has been measured. The effect of excess ligand (PPh₃) on the several transmetalations has been established.

INTRODUCTION

The Negishi reaction is a powerful process for the formation of C-C bonds. In fact, it is the reaction of choice for couplings involving sp³ carbons, due to the high reactivity of organozinc reagents. The coupling of alkyl groups from organoboron and organotin organometallics is usually very sluggish unless highly nucleophilic activators are used to facilitate the transmetalation step. In sharp contrast, organozincs have been shown to transmetalate to Pd at temperatures as low as −60 °C, which allows for remarkably facile coupling of alkyl groups, even secondary ones. As for other palladium catalyzed couplings of organic electrophiles (R’X) and nucleophiles (MR’), the reaction pursues the selective formation of R’−R”; but frequently homocoupling by-products, presumably formed via undesired transmetalations, contaminate the result. In 1994 van Aselt and Elsevier showed that these homo-coupling products could arise from undesired reactions that exchange the organic group in the nucleophile by another organic group at the palladium, rather than by the halogen (Scheme 1a). Thus, in the reaction of [PdBzBr(ArBIAN)] (Bz = benzyl; Ar-BIAN = bis(arylimino)acenaphthene) with ZnTolCl they found that the exchange produced the observable Bz/Tol intermediate [PdTolBr(ArBIAN)], which after subsequent Br/Tol transmetalation led to [MeC₆H₄] as the main reaction product.

A second report, this time involving C(sp³) in the coupling, came some years later from our group, when we found that the transmetalation of trans-[PdRfCl(PPh₃)₂] (1) (Rf = 3,5-dichloro-2,4,6-trifluorophenyl) with ZnMe₂ or with ZnMeCl produced, in addition to the two expected palladium complexes trans-[PdRfMe(PPh₃)₂] (2) and cis-[PdRfMe(PPh₃)₂] (3), large amounts of ZnRfMe, ZnRfCl, and [PdMe₂(PPh₃)] (4). Following our observation Lei et al. reported the formation of undesired aryl exchanges between zinc and palladium (Scheme 1b), as well as the formation of homocoupling biaryl’s, in the Pd catalyzed coupling of ArI with ZnArCl. They suggested that the Ar⁺-Ar² to Ar⁺-Ar² ratio found in the products was the result of the kinetic competition between reductive elimination and aryl exchange reaction rates on a [PdAr⁺Ar²(dpff)] intermediate.

Scheme 1. Previous results

In Negishi syntheses, where halides are always present (introduced in the initial oxidative addition step of ArX to Pd⁰), the study of the undesired reactions shown in Scheme 1 (equations a and b) is obscured by the interference of re-
trotransmetalation reactions (Scheme 1c). A good starting point to analyze these complicated systems is to dissect the study starting on the reactivity of complexes [PdArClL₂] with ZnR₃ derivatives, which provides a particular scenario where halides (hence reactions a and b in Scheme 1) are absent. These complexes are well known intermediates in cross-coupling reactions. The reductive elimination of two sp² carbons from cis-[PdArClL₂] is usually fast, but in instances that disfavor reductive elimination (e.g. electron withdrawing groups in the carbon fragments, or large steric hindrance), the undesired transmetalations shown in Scheme 1a-c can become a serious competition to the expected Ar–Ar coupling.

Furthermore, the reductive elimination step in coupling reactions involving sp³ carbon atoms is usually slow, and when seeking for Ar–alkyl couplings reactions these undesired transmetalations may become an efficient via to undesired Ar–Ar products. Moreover, we have recently shown that there are cis/trans isomerization reactions of [PdRR′L₂] complexes (R = Me; R′ = Me or 3,5-dichloro-2,4,6-trifluorophenyl (RF)) that are mechanistically associated to transmetalations because they share a common intermediate. This further complicates the reaction scheme during the cross-coupling reaction. From a positive point of view, all these model systems with high coupling barriers to the desired product create a landscape where the undesired side processes can be more easily studied.

Herein we report kinetic experiments and DFT computational studies to understand the complications disturbing the desired ideal Negishi process, by examining the reactivity of [PdMeArL₂] (cis and trans, Ar = C₆F₅, C₆F₅Cl₂) complexes with ZnMe₂ and other secondary transmetalations. The computational studies provide features of the structures participating in the transmetalations, stereochemistry at palladium, additional intermediates or transition states that cannot be kinetically deduced, structural details of the exchange process, etc. The graphical presentation of the process is made in a unified manner, so the reaction profiles will contain experimental and calculated values for comparison but, obviously, not every calculated structure has a measured experimental energy. For instance, energies of species after the rate determining state cannot be experimentally measured.

Results and discussion

In the Negishi process (also in others) we can define two categories of transmetalation, depending on the groups undergoing exchange: i) primary transmetalations, in which an R group on Zn is exchanged for an X group (usually a halide) on Pd (X for carbon exchange); ii) secondary transmetalations, meaning transmetalations that exchange two R fragments between Pd and Zn (carbon for carbon exchange). Other possible combinations as transmetalations where an X group on Zn were exchanged for an R group on Pd are usually thermodynamically unfavorable.

The first step in the PdL₄-catalyzed (L = PPh₃) Negishi coupling of RX (X = halide) with ZnMe₂ is the oxidative addition of RX to PdL₄, producing [PdRXL₂] (1, RF = C₆F₅Cl₂). Then, in the transmetalation step, only the exchanges involving non-identical groups are synthetically relevant and observable by NMR, in addition to the isomerization of the Pd complexes. With these conditions, the most relevant exchanges of different groups (taken in both senses of the equilibrium) are shown in Chart 1.

$$\text{PdRL} \rightarrow \text{Zn} \rightarrow \text{Pd} \rightarrow \text{Zn}$$

Chart 1. Primary and secondary transmetalations (cis/trans isomers not specified for simplicity).

The only desired transmetalation (X for Me) is the primary transmetalation in Eq. 1, leading to [PdRMeL₂], which is the complex precursor of the cross-coupling product. However, an undesired secondary transmetalation (RF for Me) can take place with the same reagents (Equation 2), leading to [PdMeXL₂]. Another possible undesired secondary transmetalation (Eq. 3) consumes [PdRMeL₂] to produce undesired PdMe₂L₂, a potential source of Me–Me homocoupling. Equations 1, 2, and 3 produce previously inexistd Pd complexes or Zn reagents that are a potential source of new primary transmetalations, now undesired, as shown in Eq. 4 (forming a potential source of RF–RF homocoupling), and Eq. 5 (along with Eq. 3, forming a potential source of Me–Me homocoupling).

To organize the discussion we are considering the exchanges in three sections.

1.- Analysis of the primary Cl/Me transmetalation exchange on trans-[PdRCl(PPh₃)₂] (1) with ZnMe₂, complicated by secondary Rf/Me transmetalations.

Some time ago we reported that the transmetalation reaction between trans-[PdRCl(PPh₃)₂] (1) and ZnMe₂, run at 25°C in THF with a 20:1 excess of ZnMe₂, produces trans and cis-[PdRMe(PPh₃)₂] (2 and 3, respectively) and ZnMeCl, but also a large amount of the exchange products ZnRMe and [PdMe₂(PPh₃)] (Scheme 2).

![Scheme 2](image-url)

We have studied here the effect of an excess of ligand in that system. Figure 1 plots the disappearance of 1, and the formation of the different products, in the reaction of trans-[PdRCl(PPh₃)₂] (1) with a fixed excess of ZnMe₂ (Zn:pd = 10:1), in solutions with increasing amount of PPh₃.

The data in Figure 1 show that the rate of consumption of 1 depends on [PPh₃]⁻¹, meaning that, as in many other transmetalation processes with other nucleophiles, the first
2. Analysis of the secondary Rf/Me transmetalation exchanges on trans- and cis-[PdRfMe(PPh3)2] with ZnMe2. The reactions of trans- and cis-[PdMeRf(PPh3)2] (2 and 3, respectively) with ZnMe2 in THF were studied at 298°K, monitoring the Rf/Me exchange by 19F and 31P NMR. When a large excess of ZnMe2 was employed (as it is the conditions of Negishi cross-coupling reactions), the transmetalation equilibrium was shifted towards the formation of the ZnRfMe. Under these conditions the isomerization trans to cis-[PdMe2(PPh3)2] is very fast, so eventually both isomers, cis- and trans-[PdRfMe(PPh3)2], are transformed into cis-[PdMe2(PPh3)2], which is the thermodynamically highly favored isomer (Scheme 3).

![Figure 1](image)

**Figure 1.** Experimental concentration versus time plots for the transmetalation reaction of trans-[PdRfCl(PPh3)2] with ZnMe2 under different concentrations of PPh3. Traces of (a) trans-[PdRfCl(PPh3)2] (1), (b) cis-[PdRfMe(PPh3)2] (3), (c) trans-[PdRfMe(PPh3)2] (2) and (d) ZnRfMe. Note the different scale for the concentrations of cis-[PdRfMeL2] (Figure 1b). The data have been obtained by integration of 19F NMR spectra.

Regarding the formation of cis-[PdRfMe(PPh3)2] (3) and ZnRfMe, interpretation of the data is less clear cut: their experimental kinetic orders are 0.2 and 0.3 respectively, suggesting that these species are involved in several reactions that have different dependence on the concentration of PPh3. We have shown in a previous study that the isomerization of 3 to 2 is phosphine dependent and can be catalyzed by ZnMe2. For ZnRfMe the situation is even more complex since ZnRfMe is formed by two ways: (i) through the secondary transmetalations between 2 or 3 and ZnMe2; and (ii) by direct Me/Rf exchange between 1 and ZnMe2. The dependence of these processes on the concentration of PPh3 has not been established so far. There are other possible sources of ZnRfMe, such the retrotransmetalation of ZnMeCl with 2 or 3, but these are not significant under the very low concentration of ZnMeCl existing at the beginning of the reaction, consequently retrotransmetalation pathways cannot explain the high rate of formation of ZnRfMe observed at short reaction times.

Although the bizarre kinetic order for the formation of cis-[PdRfMe(PPh3)2] (3) and ZnRfMe suggests the competition of several mechanisms, it is not possible to quantify the reaction parameters unless the reactions of 2 and 3 with ZnMe2 are addressed first.

![Scheme 3](image)

**Scheme 3.** Formation of cis-[PdMe2L2] by secondary transmetalations involving complexes 2 and 3.

The reaction rates were measured in experiments with added PPh3. In these conditions the kinetic influence of reductive elimination of RF-Me or RF-Rf is negligible. The reaction orders on the concentration of PPh3 were obtained for 2 and 3 from the initial rates, and kinetic rate constants were obtained by non-linear-least-square fitting of the data. The experimental ΔG values are represented, along with the calculated ones, in the reaction profile in Figure 2.

The experimental studies for the cis isomer 3 show that the free ligand retards the formation of ZnRfMe. The process is roughly order minus one (slope ~0.9 based on initial rates of formation of ZnRfMe, see SI) with respect to the concentration of PPh3, and the rate of 10−1 versus the concentration of PPh3 added is a straight line. This is consistent with a mechanism in which the first step is the substitution of one phosphine ligand by ZnMe2, producing an intermediate [PdRfMeL2ZnMe2], prior to the transmetalation step (equations 6–8 in Chart 2). Fitting the experimental values to this model, the activation energies for the phosphine dissociation (22.4 kcal/mol) and for the RF/Me exchange (25.7 kcal/mol) were obtained for complex 3.

![Chart 2](image)

**Chart 2.** Proposed mechanism for Me/Rf exchange between Zn and Pd in the reaction of cis-[PdRfMe(PPh3)2] (3) with ZnMe2.
The proposed pathways were studied by DFT methods (wB97XD/PCM(THF)/6-31G*-SDD//B3LYP/6-31G*-SDD; Ar = Pd and L₁ = L₂ = PPh₃), and the experimental values (blue, Ar = R) for the mechanisms proposed for the secondary transmetalation (ligand dependent and independent pathways) in the reaction between cis-[PdArMe(L)₂] and ZnMe₂ (ΔG⁺ are given in kcal/mol). Obviously the calculated energy for the intermediate connecting TSI₁ and TSI₂ makes its formation slower than its disappearance, so it cannot be observed experimentally.

Starting with cis-[PdArMe(L)₂] (3) and following the ligand substitution pathway in Figure 2, the calculations propose first a very weak interaction between ZnMe₂, which was commented on in a previous paper and has no kinetic significance. In the transition state TSI₁ the Zn-Me bond acts as incoming ligand releasing one PPh₃ (L₁) from the palladium, while the zinc takes electron density from the RF-Pd bond, affording intermediate I₁, with the exchanging Me involved in a 3c-2e bond. The second substitution takes place so that the incoming ligand is PPh₃ and the leaving ligand is the RF–Zn bond (TSI₂). The activation energy for these transition states (19.5 and 22.7 kcal/mol, respectively) fit very well with the experimental values obtained (22.4 and 25.7 kcal/mol, respectively). Note that this pathway produces cis to trans isomerization of the PPh₃ ligands yielding trans-[PdMe₂L₄], but the ZnMe₂ catalyzed isomerization to cis-[PdMe₂L₄] is fast.

The putative reaction without ligand substitution for cis-[PdArMe(L)₂] was also studied by DFT (Figure 2, ligand-independent mechanism) and consists in a rather common associative exchange of Me and RF via a double-bridge (with Pd–Zn bond participation). The PPh₃ ligands remain cis throughout the process. The participation of this pathways looks unimportant since it shows a much higher activation energy (30.3 kcal/mol).

The reaction of trans-[PdRfMe(PPh₃)] with ZnMe₂ was studied under the same experimental conditions. In this case the dependence of the reaction rate on the concentration of PPh₃ was very small (the experimental order of the secondary transmetalation reaction is -0.3). This suggests the participation of two competitive pathways, one independent of the phosphine concentration and another (slower but not negligible) dependent (Scheme 4). The experimental data fit well to this kinetic model, although the system contains too many variables to be fully resolved.

Scheme 4. RF/Me secondary transmetalation on trans-[PdRfMe(PPh₃)].

Figure 3 shows the DFT profiles starting with trans-[PdArMe(L)₂] (2) and ZnMe₂ for both mechanisms (ligand substitution and no-ligand-dependent mechanisms). The ligand substitution pathway that takes place in one single step (ligand-independent), is again an associative exchange of Me and RF via a double-bridged transition state TSI₆. The calculated activation energy is ΔG⁺ = 26.4 kcal/mol (experimental, 23.7 kcal/mol). As for the cis complex, there is no PPh₃ isomerization in this pathway.

The higher efficiency of the direct RF/Me exchange in the trans complex 2, confirming lower activation energy than for the cis complex 3, is due to the large trans-influence of the Me group, which induces electron density into the Ar group.
making the bridge where it participates in **TSI6** less electron deficient, consequently stabilizing this transition state. Although the product of transmetalation through this pathway is **trans**-[PdMe\(_2\)L\(_2\)], in the reaction conditions it isomerizes fast to **cis**-[PdMe\(_2\)L\(_2\)] as already discussed.

![Figure 3](image)

**Figure 3.** DFT profiles (wB97XD/PCM/THF/6-31G*-SDD//B3LYP/6-31G*-SDD; green Ar = Pf and L\(_1\) = L\(_2\) = PPh\(_3\); and experimental energetic values (blue, Ar = Rf) for the mechanisms proposed for the secondary transmetalation (ligand dependent and independent pathways) in the reaction between **trans**-[PdArMe(L)\(_2\)] 2 and ZnMe\(_2\) (ΔG\(^a\) are given in kcal/mol).

The phosphine-dependent pathway starting from the **trans** isomer, (Figure 3) is a double substitution process similar to that discussed above for the reaction of the **cis** isomer, and for the previously reported isomerization catalyzed by ZnMe\(_2\) of 2 to 3.\(^5\) It yields directly **cis**-[PdMe\(_2\)L\(_2\)]. The activation energy is very similar to the phosphine independent pathway and this explains the -0.3 dependence order on PPh\(_3\) concentration.

The studies in this section show that both isomers, 2 and 3, are able to suffer secondary transmetalations under the conditions in which the main reaction (primary transmetalation on 1) takes place, eventually producing **cis**-[PdMe\(_2\)L\(_2\)]. With PPh\(_3\) as ligand, the ligand-independent pathway prevails for 3, and is in competition with the ligand-dependent pathways for 2. Due to these ligand-independent pathways, the addition of excess of ligand cannot completely inhibit the secondary transmetalations. It looks that one plausible solution to suppress them might be the use of ligands that make stronger Pd-L bonds: that would inhibit their substitution by alkylzinc reagents, quenching the ligand dependent pathway. Calculations for the stronger ligand PMe\(_3\) for comparison (Table 1) show a more complex behavior.\(^6\) For complex 3 and the ligand-dependent pathway (Figure 2) the rate determining ΔG\(^a\) certainly increases from 22.7 to 23.9 kcal. mol\(^{-1}\), but this difference involves a change of transition state from **TSII** to **TSII**. In fact the large effect upon ligand change occurs in **TSII**, which changes from 19.5 to 23.9 kcal. mol\(^{-1}\). Also a significant change is produced in the competitive ligand independent pathway, for which **TSI3** changes from 30.3 to 25.7 kcal/mol, increasing its global contribution to the reaction. However, for complex 2 and the ligand-dependent pathway transition (Figure 3) a small decrease in ΔG\(^a\) from 26.7 to 24.3 kcal.mol\(^{-1}\); this time associated to only one transition state (**TSI6**), is observed, whereas the large increase (from 14.8 to 23.4 kcal.mol\(^{-1}\)) occurs in **TSI5** and is insufficient to produce an overall increase for this pathway. For this isomer the stabilization of **TSI6** (from 26.4 to 22.7 kcal/mol) in the ligand independent pathway makes of it the favorite for L = PMe\(_3\), frustrating the otherwise beneficial effect of using a strong donor ligand. Thus, how much the transition states are affected is not easy to guess when comparing the **cis** and the **trans** isomers.

**Table 1.** ΔG\(^a\) (kcal/mol) for the transition states of the pathways in the reaction between **trans** or **cis**-[PdArMe(L)\(_2\)] (2 or 3) and ZnMe\(_2\) (L = PMe\(_3\) or PPh\(_3\)).

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Somehow against our initial expectations, the transition states of the simpler ligand-independent pathway are highly stabilized for the better donor ligand PMe3 for both isomers (TSI3 and TSII) and the secondary transmetalations become more competitive, totally frustrating this solution to the problem. In fact, the transition state of the pathways we have been calling “ligand-independent” because ligand is not released, are ligand dependent through the electronic effect of the ancillary ligand on the bridges, which are less electron deficient for stronger donor ancillary ligands.

From a practical point of view the conclusion of this section is that the best way to address this problem and reduce the incidence of these undesired secondary transmetalations seems to be the use ligands that accelerate the reductive elimination.

3.- Analysis of the secondary Rf/Me transmetalation exchange on trans-[PdRfClL3] with ZnMe2.

Now, having determined independently the rates for the isomerization between 2 and 3, and for the secondary Rf/Me transmetalations in the reaction between cis- or trans-[PdRfClL3] and ZnMe2, it is possible to revisit our initial study on trans-[PdClRfL3]. Figure 4 shows the course of the transmetalation experiment of trans-[PdClRfL3] 1 and ZnMe2. In order to fit the observed results we carry out an overall kinetic simulation including the primary Cl/Me substitution and all the previous observations (Scheme 5), and taking into account the isomerization and the two profiles (ligand-dependent and no-ligand-independent mechanisms) discussed in the previous section. In these simulations the rate constants of the secondary transmetalations on 2 and 3, the 2/3 isomerization, and the reductive elimination from 3 have been taken from experimental values reported in our previous works with the same system. 

\[
\Delta G^\ominus = -272.51 \text{ kJ mol}^{-1}
\]

Figure 4. Experimental plot (B) for the transmetalation reaction of [PdRfClL3] 1 with ZnMe2, and kinetic simulations following model I (A), or model II (C). The plots are shown as concentration versus time, using as starting concentrations: [1] = 8·10^{-3}M, [ZnMe2] = 8·10^{-3}M, [PPh3] = 4·10^{-3}M.

Considering the same set of equations of model I, but adding the formation of ZnRfMe by secondary transmetalation with Rf/Me exchange from complex 1, through a ligand-dependent pathway sharing the trans-[PdClRfZnMe2L3] intermediate in model I, the overall picture (Model II) reproduces very well the formation of ZnRfMe. Thus, the early
intuition of van Asselt and Elsevier, about the origin of homo biaryl in the reaction of in the reaction of [PdBrBr:ArBIAN]) /Br = benzyl; Ar-BIAN = bis(arylimino)acenaphthene with ZnTolCl, finds full support for the cross coupling processes of sp3-sp3 carbons in which the direct reaction of ZnMe2 and trans-[PdRfCl(PPh3)2] is confirmed as the dominant transmetalation mechanism when the concentration of trans-[PdRfCl(PPh3)2] is high.

Model II was used for the least squares fitting of the set of experimental data of reactions carried out with different concentrations of PPh3, affording the kinetic rate constants for the transmetalation processes. The reaction profile and the experimental ΔG‡ values from these fittings are shown in Figure 5.

![Experimental profile for the transmetalation pathways in the reaction between trans-[PdRfCl(PPh3)2] 1 and ZnMe2. Free energies are in kcal/mol.](image)

Obviously Figure 5 cannot reflect the effect of [PPh3] on observed rates. Under low PPh3 concentration, the equilibrium leading to formation of intermediate [PdRfCl(PPh3)ZnMe2] is shifted to the right, and the transmetalation to form 2 is the fastest process. However, under moderate PPh3 concentration the transmetalation reactions to form 2 or 3 have almost the same rate.

Conclusions

This study shows that unwanted Ar/Me transmetalations leading to ZnArMe can take place on complexes trans-[PdArXL2], and also in cis and trans-[PdArMeL2]. The exchange is faster on trans-[PdArXL2], than on [PdArMeL2] complexes, but the activation energies for them, and also for the desired transmetalation (Cl/Me exchange) are not very dissimilar, so all the exchanges are accessible at room temperature. In these circumstances, the specific features of the alkyl, aryl or halide groups involved, and the ancillary ligands, can be decisive. The faster pathways for the undesired Ar/Me exchange involve ligand-dependent associative substitution of phosphine by ZnMe2 on the square-planar complexes, but direct (ligand-“independent”) exchange pathways are also accessible, at least in complexes trans-[PdArMeL2].

In catalysis, the formation of ZnArR (R = alkyl) derivatives leads to homocoupling products and should be avoided. The addition of an excess of phosphine reduces its formation rate, but also the transmetalation reaction rate. On the other hand, if the reductive elimination is slow (as this usually happens when sp3 carbons are involved) the aryl/alkyl exchange on the coupling intermediates [PdArR{	extsubscript}2] takes place at a non-negligible rate. Thus the use of ligands bearing some ability to induce faster reductive eliminations is highly desirable.

Experimental section

General Methods. All reactions were carried out under N\textsubscript{2} or Ar in THF dried using a Solvent Purification System (SPS). NMR spectra were recorded on Bruker ARX 300, AV 400 or AV 500 instruments equipped with variable-temperature probes. Chemical shifts are reported in ppm from tetramethylsilane (\textsuperscript{1}H), and CCI\textsubscript{3}F (\textsuperscript{19}F), with positive shifts downfield, at ambient probe temperature 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).[29] In the \textsuperscript{1}H and \textsuperscript{19}F NMR spectra registered in non-deuterated solvents, a coaxial tube containing acetone-d6 was used to maintain the lock \textsuperscript{1}H signal, and the chemical shifts are reported from the CCI\textsubscript{3}F signal in deuterated acetone. The compounds trans-[PdRfMe(PPh3)] (2) and cis-[PdRfMe(PPh3)] (3) were prepared as reported in the literature.\textsuperscript{[10]}

Kinetic experiments. In a standard experiment a solution of palladium complex trans-[PdRfCl(PPh3)] (1), trans-[PdRfMe(PPh3)] (2) or cis-[PdRfMe(PPh3)] (3) (10 mg, 1.13x10\textsuperscript{1} mmol) and PPh3 (0 to 6 mg; 0 to 2.3 x10\textsuperscript{1} mmol) in THF (0.40 ml) was prepared in a RMN tube and cooled to -96 °C. A solution of ZnMe2, 2M in toluene (0.20 ml, 0.40 mmol) was added plus cold THF to make 0.60 ml of a final volume. Then a coaxial capillary containing acetone-d6, was added, and the sample was placed into the NMR probe thermostated at 25 °C. The kinetic experiments were followed by \textsuperscript{31}P NMR or \textsuperscript{19}F NMR and concentration-time data were acquired by integration of the NMR signals.

The kinetic models were fit to the measured concentration vs. time by nonlinear least-squares (NLLS) regression using the program COPASI.\textsuperscript{[9]} The experimental data were arranged into the matrix, where the columns collect the time-dependent concentration profile of a particular species detected by \textsuperscript{19}F NMR. The proposed kinetic model was entered into the software program, as well as the known values for the constants measured independently, as specified below. The program produces a list of parameters (rate constants) and constructs a system of simultaneous ordinary differential equations that describe the change in concentration of each species with time. The rates constants were refined by NLLS regression until a best fit was found. The uncertainties of the fitted constants correspond to the standard deviation of the least squares fitting, given by COPASI. To calculate the kinetic constants from the obtained concentration versus time data, the initial rate method was used. Only the first points (10% of the data) were taken into account to avoid the formation of Pd\textsuperscript{4} species that alter the reaction rate

ASSOCIATED CONTENT

Electronic Supplementary Information (ESI) Available: Text, figures, tables, containing experimental and kinetic details and computational information.

7
AUTHOR INFORMATION

Corresponding Author
E-mail: espinet@qii.uva.es
E-mail: casares@qi.uva.es
E-mail: rar@uvigo.es

Notes
The authors declare no competing financial interests.

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5 The chemical reactions are reversible. The equilibrium constant, K, is the ratio of the concentrations of the products to the reactants. The equilibrium constant is given by K = [PdO][Ph][PhCl]/[PdCl][Ph2]. The equilibrium constant for the reaction is greater than one, indicating that the products are favored. The reaction is an example of a condensation reaction, which is a type of nucleophilic addition reaction. The reaction is catalyzed by a transition metal, in this case, Pd. The reaction is a synthetically useful reaction because it can be used to synthesize a variety of organic compounds. The reaction is a useful tool for organic synthesis, and it is used in a variety of applications, such as the synthesis of pharmaceuticals and polymers.

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7 The reaction is a condensation reaction, which is a type of nucleophilic addition reaction. The reaction is catalyzed by a transition metal, in this case, Pd. The reaction is a synthetically useful reaction because it can be used to synthesize a variety of organic compounds. The reaction is a useful tool for organic synthesis, and it is used in a variety of applications, such as the synthesis of pharmaceuticals and polymers.
Note, however, that the amount of 3 formed during the reaction is so small that this result does not affect the overall behavior of the disappearance of 1.

The rate of the reactions (whether with or without added PPh₃) is also very sensitive to the presence of Pd(0) (presumably Pd(PPh₃)₂), which is eager to coordinate more PPh₃ to produce [Pd(PPh₃)₃]. The consequence is that, since reductive elimination is retarded by free PPh₃, the formation of palladium(0) by reductive elimination has an autocatalytic effect on the reductive elimination. This effect would mislead the interpretation of the reaction rates measured in the absence of added PPh₃.

Although the kinetic experiments have been developed with C₆Cl₂F₃ (Rf) (which provides simple NMR spectra with more reliable integrations) and PPh₃, the DFT study was developed with a simpler model (Ar = C₆F₅(Pf) and PPh₃ as ligand). We have shown that there is no significant difference in activation energies for C₆F₅ instead of C₆Cl₂F₃.


The kinetic scheme does not presume any interaction between Zn and chlorine or any other atom in the intermediate formed by substitution of PPh₃ by ZnMe₂.

For the stronger σ-donor ligand PMePh₂ the direct (ligand-independent) substitution pathway seems to be dominant, see ref. 6.