# ORGANOMETALLICS-

# Experimental Study of the Mechanism of the Palladium-Catalyzed Aryl–Alkyl Negishi Coupling Using Hybrid Phosphine–Electron-Withdrawing Olefin Ligands

Estefanía Gioria, Jesús M. Martínez-Ilarduya,\* and Pablo Espinet\*

IU CINQUIMA/Química Inorgánica, Universidad de Valladolid, 47011, Valladolid, Spain

**ABSTRACT:** A detailed study of the Negishi cross-coupling reaction of ArI (Ar =  $2 \cdot C_6 H_4 CO_2 Et$ ) and ZnEt<sub>2</sub> with palladium catalysts containing conventional phosphines versus one using a chelating hybrid phosphine–electron-withdrawing olefin (P-EWO) ligand reveals that for conventional phosphines (e.g., PPh<sub>3</sub>)  $\beta$ -H elimination from intermediate [PdArEt(PPh<sub>3</sub>)<sub>2</sub>] is competitive with Ar–Et reductive elimination and is responsible for part of the undesired reduction product ArH. In contrast, with the EWO phosphine, the  $\beta$ -H elimination from intermediate [PdArEt(P-EWO)] is slow compared to the fast Ar–Et reductive elimination, and the undesired reduction



product ArH observed proceeds in this case of hydrolysis of ZnArEt, formed in transmetalations where Ar is transferred from Pd to Zn. The rate of these transmetalations is comparable to the rate of reductive eliminations. Consequently, undesired transmetalations affording  $[PdEt_2(P-EWO)]$  and ZnArEt are more effective at early stages of the reactions and less effective when the ethylating agent becomes poorer in ZnEt<sub>2</sub> and richer in ZnEtX (X = I), as the reaction proceeds. Careful analysis of the experiments reveals the detailed changing evolution of the reaction, not only providing the main features of the catalytic cycle but also deducing how the reagents in the system change with time and what the effects on the products of these changes are.

# INTRODUCTION

The Negishi reaction is a cross-coupling process widely used in organic synthesis that can be applied to every possible combination of carbon type (sp, sp<sup>2</sup>, or sp<sup>3</sup>) and is compatible with many functional groups present in the reagents.<sup>1</sup> However, where alkyl groups are involved, the efficiency of the process is often lowered because of the formation of high percentages of undesired C–H side-products along with the desired C–C cross-coupling product. This complication has been routinely attributed to competitive  $\beta$ -H elimination on a Pd–alkyl intermediate, a well-known process in Pd chemistry.<sup>2</sup> In this mechanistic hypothesis the relative rates of transmetalation and reductive elimination versus  $\beta$ -H elimination should be crucial for the formation of the Ar–alkyl (cross-coupling) versus Ar–H (reduction) product (Scheme 1).

A few years ago Lei et al.<sup>3</sup> reported an efficient Pd-catalyzed Negishi coupling of aryl halides with dialkylzinc reagents (including primary and secondary alkyl nucleophiles containing  $\beta$ -hydrogen atoms), using the hybrid phosphine/olefin ligand





PPh<sub>2</sub>(2-RC<sub>6</sub>H<sub>4</sub>) (R = CH=CHCOPh). The selectivity toward C–C cross-coupling products decreased substantially, and important proportions of ArH were formed with other ligands not having the electron-withdrawing olefin (EWO) fragment. Thus, the success of the reaction could be attributed to enhancement of the cross-coupling reductive elimination rate favored by the ligand and/or to protection versus the undesired  $\beta$ -H elimination by the EWO ligand.

Similar results were reported recently by our group using the related phosphine/olefin  $PPh_2(2-RC_6F_4)$  ligand in Scheme 2 (R = CH=CHCOPh), nicknamed P-L<sup>1</sup>, and other  $PPh_2(2-RC_6F_4)$  ligands with R groups different from EWO. The former phosphine was by far the most effective one for cross-coupling.<sup>4</sup>

Our previous results fit well the hypothesis that the origin of the improved selectivity toward the cross-coupling product using PR<sub>2</sub>(EWO) ligands is the smaller activation energy for the reductive elimination step upon coordination of the EWO fragment, as expected from our previous study of EWOs as promoters of C–C coupling.<sup>5</sup> We also noted that there is no indication in favor of the literature proposal that PR<sub>2</sub>(EWO) protects the complexes against  $\beta$ -H elimination as the source of C–H reductive elimination. If that were the cause, one should expect higher protection against  $\beta$ -H elimination in palladium complexes with two strong PR<sub>3</sub> ligands (e.g., PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>) than by those with one hemilabile PR<sub>2</sub>(EWO) chelating ligand

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### Scheme 2. Pd-Catalyzed Negishi Coupling under Study



(e.g., P-L<sup>1</sup>),<sup>4</sup> but in fact the opposite effect (more reduction) is observed. An additional and synthetically interesting observation in our previous study was that diminishing the Zn:1 proportion of ZnEt<sub>2</sub> from the usual value of 2.5 to 0.65 produced a notable increase of 2/3 (Ar–Et/Ar–H) selectivity toward the coupling product (97/3, instead of 90/10), although with formation of some homocoupling biphenyl product (4).

With the precedents above, in this paper we undertake further studies of the coupling in Scheme 2 to definitely confirm or discard the involvement of  $\beta$ -H elimination in the formation of the undesired reduction product 3 and to better understand the effect of the ZnEt<sub>2</sub>/ArI ratio on the reaction outcome, by way of an anatomical analysis of the process at different stages and in different conditions.

#### RESULTS AND DISCUSSION

The reactions of 1 and ZnEt<sub>2</sub> under different conditions were carried out in a Schlenk tube under argon in THF/hexane at 293 K unless otherwise stated and were <sup>1</sup>H NMR checked before and after hydrolysis. For short, from now on Ar stands for  $C_6H_4CO_2Et.^6$ 

1. Reactions in the Absence of Pd-Catalyst. This reactivity was studied for two different  $ZnEt_2/1$  ratios: 0.65 and 2.5. For  $ZnEt_2/1 = 0.65$ , the reaction was very slow, and only 15% conversion of 1 was observed (by <sup>1</sup>H NMR) after 12 h reaction. The cross-coupling products ArEt (2) and ZnArEt (5) were produced in approximately 1.1:1 ratio. The resonances assigned to 5 were confirmed by comparison with ZnArEt prepared independently by treatment of 1 with MgBr<sup>i</sup>Pr·LiCl and ZnEt<sub>2</sub>.

For  $ZnEt_2/1 = 2.5$  the reaction was faster (although still very slow compared to the Pd-catalyzed reaction), and conversion of 1 after 12 h was 60%; the products 2 and 5 were obtained in 1:2.8 molar ratio. In addition, a very small amount of  $H_2C=$  $CH_2$  was detected.<sup>7</sup> At longer reaction times, the formation of ZnAr<sub>2</sub> (6) was also observed as somewhat broadened signals.<sup>8</sup> After hydrolysis and workup of the reaction mixture, an oily residue was isolated. Its <sup>1</sup>H NMR spectrum showed a 1:2:3 mixture, in a ratio very close to the 1:2:5 ratio observed in the spectrum before hydrolysis. Therefore, it is obvious that, in these conditions, the so-called reduction product 3 is a hydrolysis product of 5 (Scheme 3). In other words, although slowly in this case, the reduction product ArH is formed from its precursor ZnArEt.

2. Reactions in the Presence of a Pd-Catalyst with PR<sub>2</sub>(EWO) Ligand P-L<sup>1</sup>. As in section 1, this reactivity was

Scheme 3. Reaction Products before and after Hydrolysis for the Noncatalyzed Reaction



studied for two ZnEt<sub>2</sub>/1 ratios: 0.65 and 2.5. For ZnEt<sub>2</sub>/1 = 2.5, the reactions of 1 and ZnEt<sub>2</sub> with 5% [PdCl<sub>2</sub>(P-L<sup>1</sup>)] as catalyst produced almost complete conversion of 1 (>95%) in 5 min.<sup>9</sup> Since the noncatalyzed reaction is much slower, the products observed can be assigned to the catalyzed pathway only. *Before* hydrolysis (Figure 1a), the <sup>1</sup>H NMR spectrum



**Figure 1.** <sup>1</sup>H NMR spectrum (aryl region) (a) *before* and (b) *after* hydrolysis of the reaction mixture of **1** and  $ZnEt_2$  (1:2.5 ratio) using [PdCl<sub>2</sub>(P-L<sup>1</sup>)] as catalyst.<sup>10</sup>

shows signals of ArEt (2, 45.9% molar of Ar-containing products) and ZnArEt (5, 51.3%) as the main products, with the signals due to ZnArEt slightly broadened as discussed above.<sup>8</sup> Small amounts of the reduction product ArH (3, 1.5%), the homocoupling product ArAr (4, 1.3%), and  $CH_2CH_2$  were also detected.

After hydrolysis (Figure 1b) all 5 produces 3, as in the noncatalyzed reaction. Assuming that ethylene might be the byproduct of  $\beta$ -H elimination, this would indicate that only a very small proportion (that observed before hydrolysis) of the reduction product 3 could be generated by  $\beta$ -H elimination from a Pd-Et intermediate. Hence, the vast majority of 3 formed in the catalyzed reaction, if not all, comes from hydrolysis of 5 (Scheme 4). The catalyzed reaction was also studied using D<sub>2</sub>O for the hydrolysis; then the reduction

Scheme 4. Reaction Products before and after Hydrolysis for the Pd-Catalyzed Reaction



product observed was ArD instead of ArH, as expected from hydrolysis of Zn–Ar derivatives. This was confirmed by the lowering to half-intensity of the <sup>1</sup>H signals of **3** ca.  $\delta$  = 8.03 (2H for ArH; 1H+1D for ArD). The formation of ArD was also confirmed by mass spectrometry.



**Figure 2.** <sup>1</sup>H NMR spectrum (aryl region) *before* hydrolysis of the reaction mixture of **1** and ZnEt<sub>2</sub> (1:0.65 ratio) using  $[PdCl_2(P-L^1)]$  as catalyst.

For  $ZnEt_2/1 = 0.65$ , the reaction showed different proportions of the products. Before hydrolysis (Figure 2), the <sup>1</sup>H NMR spectrum showed the cross-coupling product **2** as the main one (83.3%). The second most abundant product was the homocoupling biphenyl 4 (10.8%), while neither 5 nor 6 was detected. The nonobserved 5 must have been transiently formed, since its intermediacy is necessary to explain the formation of 4 (see below). A small amount of the starting material 1 (4.2%), showing that the reaction is slower than with  $ZnEt_2/1 = 2.5$ , and the reduction product 3 (1.7%) were also detected. No aromatic Zn products susceptible to hydrolysis were observed, since they have been consumed in the higher formation of the Ar-Ar homocoupling product 4. In line with this observation, an experiment using  $ZnEt_2/1 = 0.65$  and  $ZnCl_2/1 = 1.85$  (this amounts to Zn/1 = 2.5) revealed a much slower reaction, which, after 3 h, still contained 21% unreacted starting material 1, 75.5% cross-coupling product 2, 3.5% homocoupling product 4, and a total absence of reduction product.

3. Reactions in the Presence of a Pd-Catalyst with a Phosphine Ligand That Does Not Contain an EWO Group. For this study, the catalyst  $[PdCl_2(PPh_2(6-HC_6F_4))_2]$  was chosen. The reaction of 1 and  $ZnEt_2$  (1:2.5 ratio) using 5% of catalyst gave, *before* hydrolysis, a mixture of products 2:3:5 = 1:0.5:2.2 (Figure 3), proving that in this case the  $\beta$ -H elimination process is active. Using 5% of  $[PdCl_2(PPh_3)_2]$  as



**Figure 3.** <sup>1</sup>H NMR spectrum *before* hydrolysis (Ar region) of the reaction products using  $PPh_2(6-HC_6F_4)$  as ligand.

catalyst, the amount of ArH (3) observed before hydrolysis (hence formed by  $\beta$ -H elimination) was even more abundant. This is consistent with the interpretation that reductive elimination of Ar–Et is considerably slower with conventional phosphines than with PR<sub>2</sub>(EWO), and the  $\beta$ -H elimination process to give PdArHL<sub>2</sub>, followed by Ar–H coupling, becomes competitive.

**4. Fate of Pd–Et Intermediates.** Under our normal reaction conditions some gaseous products (EtH, ethylene, or butane) could be totally or partially swept away and some <sup>1</sup>H NMR signals are overlapped with those of the reaction solvent. In order to get information on them, the Pd-catalyzed reaction was carried out in a sealed NMR tube, using  $\text{ZnEt}_2/1 = 2.5$  and  $\text{THF-}d_8$  as solvent. The <sup>1</sup>H NMR spectrum of the reaction products *before* hydrolysis is shown in Figure 4. In addition to Et-containing Zn products, which are averaged by fast exchange, giving only a triplet and a quadruplet in the spectrum, signals of butane, ethane, and ethylene are observed in the approximate molar ratio Et<sub>2</sub>:EtH:CH<sub>2</sub>CH<sub>2</sub> = 6:1:0.7.

Obviously butane comes from homocoupling on  $PdEt_2(P-L^1)$ , and ethylene+ethane from  $\beta$ -H elimination followed by Et–H reductive elimination on intermediate  $PdEtH(P-L^1)$ . However, there is a 30% excess of EtH in the amount expected from the ethylene produced, which should be assigned to  $ZnEt_2$  hydrolysis by water in the deuterated solvent.<sup>11</sup> Since this hydrolysis occurs at the beginning of the reaction, the solvent can be considered dry for the rest of the processes observed. The butane:ethylene ratio is about 8.5:1; assuming that Et–H coupling is faster than Et–Et coupling, this ratio suggests that Et–Et coupling is faster than  $\beta$ -H elimination by about 0.5 to 1 order of magnitude. The efficiency of formation of the  $PdEt_2(P-L^1)$  intermediate means that the exchanges in eqs 1–3 are very fast. As a matter of fact, all the Pd-catalyzed transmetalations look very fast, as compared to  $\beta$ -H elimination.

The relative contents of some relevant compounds formed in this last reaction (Figure 4), setting ArEt as 100 and expressed in molar ratios, are ArEt, 100; ArH, 3.8; ArAr, 2.7; Et–Et, 105.5; and  $CH_2CH_2$ , 12.9. This illustrates that much of the initial ZnEt<sub>2</sub> reagent is wasted in the formation of butane and ethane+ethylene from  $PdEt_2(P-L^1)$ . The formation of this Pd complex requires a double transmetalation of Et to Pd or, in other words, the kind of exchanges shown in eq 1 or eqs 2 + 3.

Since these exchanges are efficacious, this suggests that they are at least comparable in rate to the reductive elimination processes.

$$ZnEt_{2} + [PdArEt(P-L^{l})] \rightarrow ZnArEt + [PdEt_{2}(P-L^{l})]$$
(1)



Figure 4. <sup>1</sup>H NMR spectrum before hydrolysis of the reaction mixture of 1 and  $\text{ZnEt}_2$  (1:2.5 ratio) in THF- $d_8$  using [PdCl<sub>2</sub>(P-L<sup>1</sup>)] as catalyst.

 $ZnEt_{2} + [PdArl(P-L^{1})] \rightarrow ZnArEt + [PdEtl(P-L^{1})]$ (2)

$$ZnEt_{2} + [PdEtl(P-L^{l})] \rightarrow ZnEtl + [PdEt_{2}(P-L^{l})]$$
(3)

The major difference between the experiment in Figure 1 (Schlenk experiment; ArEt. 100; ArH. 3.2; ArAr. 2.9; CH<sub>2</sub>CH<sub>2</sub>. 1.5) and that in Figure 4 (NMR tube experiment) is that the amount of ethylene is much less in the former one (only 1.5 relative to ArEt in Figure 1 compared to 12.9 in Figure 4), confirming that gases had been swept away. As explained above, the majority of ethane and ethylene comes from a  $PdEt_2(P-L^1)$ intermediate, and only very little (as many moles as ArH observed before hydrolysis) comes from  $\beta$ -H elimination followed by Ar-H coupling on  $[PdArEt(P-L^1)]$ . Since adventitious water has been eliminated at the beginning of the catalysis by reaction with ZnEt<sub>2</sub>, it is reasonable to assume that the amount of ArH formed before hydrolysis measures the proportion of  $\beta$ -H elimination occurring on [PdArEt(P-L<sup>1</sup>)]. In practice this represents only a very small part of the total ArH observed after hydrolysis.

5. Effect of the ZnEt<sub>2</sub>/Arl Ratio on the Reactions Using a Pd-Catalyst with P-L<sup>1</sup>. From the previous results it is clear that the competitive formation of *cross-coupling* ArEt, *homocoupling* ArAr, and most of the *reduction* ArH products is independent of the  $\beta$ -H elimination process, which has only a modest incidence because of its relative slowness. The formation and proportions of Ar-containing products can be basically discussed in the scenario of the Pd/Zn transmetalations and the reductive elimination processes on Pd. In spite of the complexity of the system, some simple considerations can be made to explain satisfactorily the point under discussion in this section and the behavior of the system in general.

For the aryl products, starting with the oxidative addition product  $[PdArI(P-L^1)]$  the formation of ArEt requires a  $[PdArEt(P-L^1)]$  intermediate; ArH should arise from a Zn– Ar intermediate by hydrolysis, and ArAr should come from coupling on a  $[PdAr_2(P-L^1)]$  intermediate, which in turn requires a transmetalation of a second aryl to Pd, coming from a Zn–Ar intermediate. For the ethyl products we have already discussed that they proceed from a  $[{\rm PdEt}_2({\rm P-L}^1)]$  intermediate. Considering only the most direct transmetalations for the sake of simplicity,  $^{12-15}$  and a simple representation of the Zn derivatives in solution, some considerations can be made. For this, it is interesting to note that it is known that the activation energy for C–C coupling decays in the order  $sp^3-sp^3>sp^3-sp^2>sp^2-sp^2.^{5,16}$ 

At the very start of the reaction, the only Ar activated for coupling corresponds to the oxidative addition product [PdArI(P-L<sup>1</sup>)], which is in small concentration (the concentration of the catalyst). In comparison, the concentration of active Et (in the form of the highly nucleophilic ZnEt<sub>2</sub>) is terribly high. This means that the fast exchange in eq 1 quickly converts [PdArI(P-L<sup>1</sup>)] into [PdEt<sub>2</sub>(P-L<sup>1</sup>)], from which butane and ethane+ethylene are produced. In other words, at this early point the faster coupling Ar–Et is prevented because the Ar group on Pd is quickly substituted by Et in a fast exchange and only Et–Et coupling (or  $\beta$ -H elimination) is feasible.

The reacting conditions change as the process continues. Every time that an activation of ArI occurs, one Ar and one I are introduced in the system. In the case of Et-Et coupling, each coupling consumes two molecules of  $ZnEt_2$  and produces one molecule of ZnEtI and one molecule of ZnArEt (eq 2 + eq 3). Similarly, if Ar-Et cross-coupling occurs, this spends one molecule of  $ZnEt_2$  and produces one molecule of  $ZnEt_1$  (eq 4). Finally the formation of Ar-Ar homocoupling converts one molecule of ZnArEt into ZnEtI (eq 5).

$$\operatorname{Arl} + \operatorname{ZnEt}_{2} \xrightarrow{[\operatorname{Pd}/\operatorname{L}]} \operatorname{ArEt} + \operatorname{ZnEtl}$$
(4)

Arl + ZnArEt 
$$\xrightarrow{[Pd/L]}$$
 Ar<sub>2</sub> + ZnEtl (5)

The effect is devastating for  $ZnEt_2$  at the early steps of the process, when mostly Et-Et coupling occurs because of the Ar scarcity: the concentration of  $ZnEt_2$  drops and starts to be replaced by the less nucleophilic ZnEtI and by growing ZnArEt. As the availability of active Ar groups increases, the production of the faster Ar–Et cross-coupling and, at a later stage, Ar–Ar homocoupling should become more and more probable.

Scheme 5. Proposed Mechanisms Associated with the Pd-Catalyzed Ar-Et Coupling and Their Byproducts<sup>a</sup>



<sup>a</sup>The indicated rate constants are only relative. However,  $k_{\text{H-elim}}$  is clearly slower than the others (for the complexes with a P-(EWO) ligand). The different transmetalations are competitive with the reductive eliminations, and the concentrations of the intermediates are determinant for their actual rates.

Can we support experimentally this evolution of the reaction with time? The reaction is too fast, even at low temperature, to be efficiently monitored by NMR. However, as reported in section 2 we have carried out two studies that are essentially reproducing two advanced stages of the reaction. The reaction using  $\text{ZnEt}_2/1 = 0.65$  mimics an advanced stage where the huge initial excess of Et on Ar has been attenuated. This should lower the probability of eqs 1 and 2, decrease from the very beginning the production of  $[\text{PdEt}_2(\text{P-L}^1)]$ , and consistently diminish the production of ZnArEt (which eventually gives ArH after hydrolysis); additionally, the probability of  $[\text{PdArEt}-(\text{P-L}^1)]$  leading to fast formation of ArEt increases. Consistently, better Ar–Et/Ar–H ratios *after* hydrolysis are observed than in the reaction with ZnEt<sub>2</sub>/1 = 2.5, as commented on above.

The reaction using  $\text{ZnEt}_2/1 = 0.65$  and  $\text{ZnCl}_2/1 = 1.85$ would represent a later stage of the process, when the reagents are poorer in Et and richer in Ar. Then, the strong nucleophile ZnEt<sub>2</sub> is almost absent (Schlenk-type equilibrium), the less nucleophilic ZnEtI (or ZnEtCl) is the ethylating agent, and (in the case of reaction in Figure 2) there is also accumulation of ZnArEt. In these conditions, the higher probability of [PdAr<sub>2</sub>(P-L<sup>1</sup>)], associated with the fastest Ar–Ar coupling, starts to produce biaryl homocoupling very competitively, as observed.

**6.** Improving the Ar–Et/Ar–H Selectivity. Taking into consideration the factors disturbing the Ar–Et selectivity, discussed above, we should be able to find a set of conditions where the ethylation of Pd will be better controlled in order to avoid double ethylation. Should this be controlled efficiently, there will not be accumulation of ZnArEt, which is the source of ArH hydrolysis product.

As we have mentioned in the last section, ZnEtI or ZnEtCl is less nucleophilic than ZnEt<sub>2</sub> and exchanges bringing Ar from Pd to Zn are less efficient.<sup>13</sup> Therefore, they should be better candidates for a controlled ethylation, even when the reaction time should be longer, as we know from section 2. Not attempting to be exhaustive in this respect, the following examples of catalysis support this proposal to increase the proportion of the cross-coupling product ArEt (2): The reaction of 1 and ZnEt<sub>2</sub> (for ZnEt<sub>2</sub>/1 = 2.5) with 5% of [PdCl<sub>2</sub>(P-L<sup>1</sup>)] as catalyst produced complete conversion of 1, leading, after hydrolysis, to ArEt, 46.2%; ArH, 52.6%; and ArAr, 1.2%. Under the same conditions, using ZnEtCl instead of ZnEt<sub>2</sub> (ZnEtCl/1 = 2.5), much higher cross-coupling product selectivity is observed: Ar-Et, 93.9%; Ar–H, 6.1%, and Ar–Ar, 0.0%.

# CONCLUSION

All these results can be fit and summarized in the catalytic cycle proposed in Scheme 5, where the relatively slow  $\beta$ -H elimination followed by C–H reductive elimination is not competitive when a PR<sub>2</sub>(EWO) ligand is used, but operates for conventional ligands. The Pd-catalyzed transmetalations and the reductive eliminations are of comparable rates, and for this reason the overall reaction rate depends on the concentration and abundance of highly nucleophilic organozinc reagents and not only on the reductive elimination rate constant to the different coupling products. At early stages, the reaction produces large amounts of butane, ethane, and ethylene. The course of the reaction produces aryl–zinc intermediates via secondary transmetalations. These are the origin of the reduction product ArH by hydrolysis and also allow for the formation of ArAr homocoupling via secondary transmetalations. The proportion of products can be understood as a function of the rates of the different processes involved, as discussed above.

# EXPERIMENTAL SECTION

**General Methods.** All the manipulations were performed under an atmosphere of argon using standard Schlenk techniques unless otherwise stated. Solvents were dried using an SPS PS-MD-5 solvent purification system or distilled from appropriate drying agents under nitrogen, prior to use. The compounds  $[PdCl_2(P-L^1)]$  and  $[PdCl_2(PPh_3)_2]$  were prepared by literature methods.<sup>4</sup> Solutions of ZnEt<sub>2</sub> 1.0 M in dry hexane were prepared from commercial salt-free liquid ZnEt<sub>2</sub> (Sigma-Aldrich Zn wt  $\geq$  52.0%).<sup>17</sup> Solutions of ZnEtCl were prepared by asymmetrization rearrangement of ZnEt<sub>2</sub> and ZnCl<sub>2</sub>. All other reagents were commercially available and used as received.

<sup>1</sup>H, <sup>19</sup>F, and <sup>31</sup>P{<sup>1</sup>H} spectra were recorded on a Bruker AV-400 or a Varian Inova 500 spectrometer. Chemicals shifts (in  $\delta$  units, parts per million) were referenced to the residual solvent signal, to CFCl<sub>3</sub>, and to 85% H<sub>3</sub>PO<sub>4</sub>, respectively. The spectral data were recorded at 293 K unless otherwise noted. GC-mass spectra were recorded on a Thermo Scientific Focus DSQII system. Elemental analyses were performed on a PerkinElmer 2400B CHN analyzer.

[PdCl<sub>2</sub>(PPh<sub>2</sub>(6-HC<sub>6</sub>F<sub>4</sub>))<sub>2</sub>]. Phosphine PPh<sub>2</sub>(6-HC<sub>6</sub>F<sub>4</sub>) (50.9 mg, 0.152 mmol) was added to a solution of [PdCl<sub>2</sub>(NCMe)<sub>2</sub>] in 4 mL of THF (phosphine:Pd molar ratio = 2:1). The reaction mixture was stirred for 2 h at RT. The volatiles were evaporated. A pale yellow solid was obtained, washed with pentane, and dried under vacuum (59.2 mg, 92%). <sup>1</sup>H NMR (400.13 MHz,  $\delta$ , CDCl<sub>3</sub>): 7.86–7.76 (m, 8H), 7.58–7.52 (m, 4H), 7.51–7.45 (m, 8H), 6.59 (m, 2H). <sup>19</sup>F NMR (376.46 MHz,  $\delta$ , CDCl<sub>3</sub>): -120.16 (m, 2F), -137.56 (m, 2F), -149.76 (m, 2F), -153.29 (m, 2F). <sup>31</sup>P{<sup>1</sup>H} NMR (161.97 MHz,  $\delta$ , CDCl<sub>3</sub>): 17.76 (dd, *J*<sub>P-F</sub> = 7.0, 7.0 Hz, 2P). Anal. Calcd for C<sub>36</sub>H<sub>22</sub>Cl<sub>2</sub>F<sub>8</sub>P<sub>2</sub>Pd: C, 51.12; H, 2.62. Found: C, 50.93; H, 2.86.

**General Procedure for the Catalysis.** Preformed palladium complex (0.015 mmol) was weighed and put into an oven-dried 10 mL Schlenk, which was evacuated and refilled with argon. Ethyl 2-iodobenzoate (50.8  $\mu$ L, 0.3 mmol) was added by microsyringe, and the Schlenk was sealed. Finally, a solution of ZnEt<sub>2</sub> (0.75 mL, 1.0 M in hexane) in 0.25 mL of THF was added slowly with gentle stirring of the mixture, which turned immediately to dark brown. After 3 h a sample was taken and checked by NMR (*before* hydrolysis spectrum). The sample was hydrolyzed with a 2 M solution of HCl, extracted with diethyl ether, dried with magnesium sulfate, and filtered through silica gel. This final solution was checked by GC-MS and NMR (*after* hydrolysis spectrum). For the experiment in THF-*d*<sub>8</sub> liquid ZnEt<sub>2</sub> was directly used to avoid the presence of hexane.

**Ethyl 2-Ethylbenzoate (2).** <sup>1</sup>H NMR (400.13 MHz, δ, CDCl<sub>3</sub>): 7.84 (dd, J = 7.7 Hz, 1.4 Hz, H<sup>6</sup>), 7.42 (ddd, J = 7.7, 7.7, 1.4 Hz, H<sup>4</sup>), 7.24 (ddd, J = 7.7, 7.7, 1.5 Hz, H<sup>5</sup>), 7.27 (dm, J = 7.7 Hz, H<sup>3</sup>), 4.36 (q, J = 7.1 Hz, CH<sub>2</sub> from COOEt), 2.97 (q, J = 7.5 Hz, CH<sub>2</sub> from Et) 1.39 (t, J = 7.1 Hz, CH<sub>3</sub> from COOEt) 1.24 (t, J = 7.5 Hz, CH<sub>3</sub> from Et).

**Ethylbenzoate (3).** <sup>1</sup>H NMR (400.13 MHz,  $\delta$ , CDCl<sub>3</sub>): 8.05 (m, H<sup>6</sup> + H<sup>2</sup>), 7.55 (tt, J = 7.4, 1.3 Hz, H<sup>4</sup>), 7.44 (m, H<sup>5</sup> + H<sup>3</sup>), 4.38 (q, J = 7.1 Hz, CH<sub>2</sub> from COOEt), 1.40 (t, J = 7.1 Hz, CH<sub>3</sub> from COOEt).

**Diethyl Biphenyl 2,2'-Dicarboxylate (4).** <sup>1</sup>H NMR (400.13 MHz,  $\delta$ , CDCl<sub>3</sub>): 8.01 (ddd, J = 7.7, 1.4, 0.4 Hz, H<sup>6</sup>), 7.52 (ddd, J = 7.7, 7.7, 1.4 Hz, H<sup>4</sup>), 7.43 (ddd, J = 7.7, 7.7, 1.4 Hz, H<sup>5</sup>), 7.21 (dm, J = 7.7 Hz, H<sup>3</sup>), 4.04 (q, J = 7.1 Hz, CH<sub>2</sub> from COOEt), 0.98 (t, J = 7.1 Hz, CH<sub>3</sub> from COOEt).

### AUTHOR INFORMATION

#### Corresponding Authors

\*E-mail: jmi@qi.uva.es.

\*E-mail: espinet@qi.uva.es.

#### Notes

The authors declare no competing financial interest.

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#### REFERENCES

 (1) (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. (c) Negishi, E.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. Aldrichim. Acta 2005, 38, 71–88.
 (d) Negishi, E. Bull. Chem. Soc. Jpn. 2007, 80, 233–257. (e) Phapale, V. B.; Cárdenas, D. J. Chem. Soc. Rev. 2009, 38, 1598–1607.

(2) (a) Davidson, P. J.; Lappert, M. F.; Pearce, R. Chem. Rev. 1976, 76, 219-242. (b) Zaera, F. Chem. Rev. 1995, 95, 2651-2693.
(c) Cárdenas, D. J. Angew. Chem., Int. Ed. 2003, 42, 384-387.
(d) Espinet, P.; Albéniz, A. C. In Current Methods in Inorganic Chemistry; Fundamentals of Molecular Catalysis; Kurosawa, H., Yamamoto, A., Eds.; Elservier: Amsterdam, 2003; Vol. 3, Chapter 6, p 300.

(3) (a) Luo, X.; Zhang, H.; Duan, H.; Liu, Q.; Zhu, L.; Zhang, T.; Lei, A. Org. Lett. 2007, 9, 4571–4574. (b) Zhang, H.; Luo, X.; Wongkhan, K.; Duan, H.; Li, Q.; Zhu, L.; Wang, J.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B.; Lei, A. Chem.–Eur. J. 2009, 15, 3823– 3829.

(4) Gioria, E.; Martínez-Ilarduya, J. M.; García-Cuadrado, D.; Miguel, J. A.; Genov, M.; Espinet, P. Organometallics **2013**, *32*, 4255–4261.

(5) 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.

(6) The Ar–Et/Ar–H/Ar–Ar ratios of the products observed in these reactions follow the same trends reported previously,<sup>4</sup> although there are quantitative differences probably due to the use of preformed catalyst and to the faster reaction rates produced by the higher concentrations of reagents employed here. In fact the reaction rates of the competing processes discussed below have different concentration dependence, and the proportion of products changes with the concentration or with the mixture of solvents. These are kept identical within this study.

(7) It is not unusual that in long-time manipulations of  $ZnEt_2$  traces of ethylene can be observed. We suspect that it can be related to catalysis by traces of metals. In such case the slow "noncatalyzed" reaction would in fact be a catalyzed one with very little catalyst.

(8) Some broadening is observed for the signals of **5** and **6** in all the spectra commented on in this work. <sup>1</sup>H NMR experiments prove that the broadening is due to exchange of the Et groups between **5**, ZnEtI, and ZnEt<sub>2</sub> and the exchange of the Ar groups between **5** and **6**.

(9) Note that  $[PdCl_2(P-L^1)]$  is in fact a precatalyst that has to be transformed into  $[Pd(P-L^1)]$  to enter the catalytic cycle. This requires double ethylation to  $[PdEt_2(P-L^1)]$  and reductive elimination producing butane. For 5% of Pd-catalyst, 5% of ZnEt<sub>2</sub> (or 10% of ZnEtCl, when this is the ethylating agent) will be consumed in this precatalytic process.

(10) Observed shifts are due to different solvent-mixture polarities. While *before* hydrolysis there was a 3:1 mixture of THF/hexane, *after* hydrolysis the solvent was only THF.

(11) By checking the <sup>1</sup>H NMR spectrum of the preformed solution of  $\text{ZnEt}_2$  in THF-*d*<sub>8</sub> it was confirmed that it contained about 53 ppm of ethane.

(12) Note that other Pd/Zn transmetalations (secondary transmetalations) can occur, as we and others have studied thoroughly in other papers (see refs 13–15). Only some examples (eqs 1 and 2) are shown.

(13) (a) Casares, J. A.; Espinet, P.; Fuentes, B.; Salas, G. J. Am. Chem. Soc. 2007, 129, 3508-3509. (b) Fuentes, B.; García-Melchor, M.; Lledós, A.; Maseras, F.; Casares, J. A.; Ujaque, G.; Espinet, P. *Chem.– Eur. J.* **2010**, *16*, 8596–8599. (c) García-Melchor, M.; Fuentes, B.; Lledós, A.; Casares, J. A.; Ujaque, G.; Espinet, P. *J. Am. Chem. Soc.* **2011**, *133*, 13519–13526.

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

(15) (a) Liu, Q.; Lan, Y.; Liu, J.; Li, G.; Wu, Y.-D.; Lei, A. J. Am. Chem. Soc. 2009, 131, 10201–10210. (b) Jin, L.; Lei, A. Org. Biomol. Chem. 2012, 10, 6817–6825.

(16) Ananikov, V. P.; Musaev, D. G.; Morokuma, K. Organometallics 2005, 24, 715–723.

(17) This procedure of preparation of solutions of ZnEt<sub>2</sub> in hexane was used in order to prevent the presence of significant amounts of salt byproducts, which is difficult to avoid when ZnEt<sub>2</sub> is prepared *in situ* from ZnX<sub>2</sub> and EtLi or EtMgX. The presence of these salts can produce dramatic differences in reactivity, as studied carefully by Organ's group and others. See, for instance: (a) McCann, L. C.; Organ, M. G. *Angew. Chem., Int. Ed.* **2014**, *53*, 4386–4389 and references therein. (b) McCann, L. C.; Hunter, H. N.; Clyburne, J. A. C.; Organ, M. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 7024–7027. (c) Hunter, H. N.; Hadei, N.; Blagojevic, V.; Patschinski, P.; Achonduh, G. T.; Avola, S.; Bohme, D. K.; Organ, M. G. *Chem.— Eur. J.* **2011**, *17*, 7845–7851. (d) Côté, A.; Charette, A. B. J. Am. Chem. Soc. **2008**, *130*, 2771–2773.