

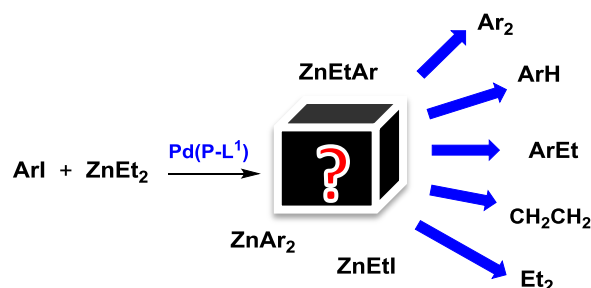
Experimental Study of the Mechanism of the Pd-catalyzed Aryl-alkyl Negishi Coupling using Hybrid Phosphine-Electron Withdrawing Olefin Ligands

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Negishi cross-coupling, β -H elimination, palladium, hybrid phosphine, electron withdrawing olefin, diethyl zinc

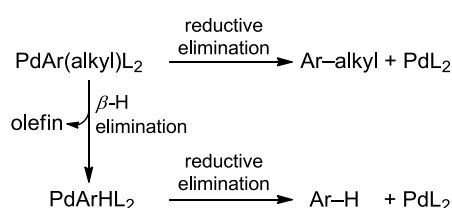
ABSTRACT: A detailed study of the Negishi cross-coupling reaction of ArI (Ar = 2-C₆H₄CO₂Et) and ZnEt₂ with palladium catalysts containing conventional phosphines versus one using a chelating hybrid phosphine-electron withdrawing olefin (P-EWO) ligand reveals that for conventional phosphines (e.g. PPh₃) β -H elimination from intermediate [PdArEt(PPh₃)₂] 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 β -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 [PdEt₂(P-EWO)] and ZnArEt are more effective at early stages of the reactions, and less effective when the ethylating agent becomes poorer in ZnEt₂ and richer in ZnEtX (X= I), as the reaction goes by. Careful analysis 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, sp², or sp³) and is compatible with many functional groups present in the reagents.¹ 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 β -H elimination on a Pd-alkyl intermediate, a well-known process in Pd chemistry.² In this mechanistic hypothesis the relative rates of transmetalation and reductive elimination versus β -H elimination should be crucial for the formation of the Ar-alkyl (cross coupling) versus Ar-H (reduction) product (Scheme 1).

Scheme 1. Cross coupling versus reduction

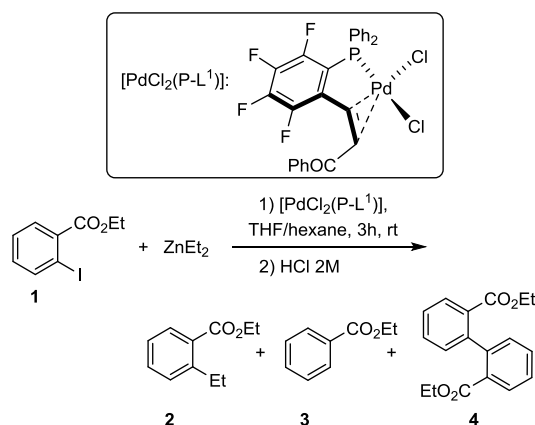


A few years ago Lei *et al.*³ reported an efficient Pd-catalyzed Negishi-coupling of aryl halides with dialkylzinc reagents (including primary and secondary alkyl nucleophiles containing β hydrogen atoms), using the hybrid phosphine/olefin ligand PPh₂(2-RC₆H₄)

(R = CH=CHCOPh). The selectivity towards C-C cross-coupling products decreased substantially, and important proportions of ArH were formed with other ligands not having the electron withdrawing olefin fragment (EWO). 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 β -H elimination by the EWO ligand.

Similar results were reported recently by our group using the related phosphine/olefin PPh₂(2-RC₆F₄) ligand in Scheme 2 (R = CH=CHCOPh), nicknamed P-L¹, and other PPh₂(2-RC₆F₄) ligands with R groups different from EWO. The former phosphine was by far the most effective one for cross coupling.⁴

Scheme 2. Pd-catalyzed Negishi coupling under study



Our previous results fit well the hypothesis that the origin of the improved selectivity toward the cross-coupling product using $\text{PR}_2(\text{EWO})$ ligands (EWO = electron-withdrawing olefin) is the smaller activation energy for the reductive elimination step upon coordination of the EWO fragment, as expected from our previous study of EWO as promoters of C–C coupling.⁵ We also noted that there is no indication in favor of the literature proposal that $\text{PR}_2(\text{EWO})$ protects the complexes against β -H elimination as the source of C–H reductive elimination. If that were the cause, one should expect higher protection against β -H elimination in palladium complexes with two strong PR_3 ligands (e.g. $\text{PdCl}_2(\text{PPh}_3)_2$) than by those with one hemilabile $\text{PR}_2(\text{EWO})$ chelating ligand (e.g. P-L^1),⁴ 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_2 from the usual value 2.5 to 0.65 produced a notable increase of **2**/**3** (Ar–Et/Ar–H) selectivity towards 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 β -H elimination in the formation of the undesired reduction product **3**, and to better understand the effect of the ZnEt_2/ArI ratio on the reaction outcome, by way of an anatomical analysis of the process at different stages and in different conditions.

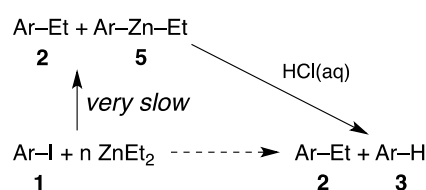
RESULTS AND DISCUSSION

The reactions of **1** and ZnEt_2 under different conditions were carried out in Schlenk tube under argon in THF/hexane at 293 K unless otherwise stated, and were ^1H checked before and after hydrolysis. For short, from now on Ar stands for $\text{C}_6\text{H}_4\text{CO}_2\text{Et}$.⁶

1.- Reactions in the absence of Pd-catalyst. This reactivity was studied for two different $\text{ZnEt}_2/\mathbf{1}$ ratios: 0.65, and 2.5. For $\text{ZnEt}_2/\mathbf{1} = 0.65$, the reaction was very slow and only 15% conversion of **1** was observed (by ^1H NMR) after 12 h reaction. The cross coupling product ArEt (**2**) and ZnArEt (**5**) were produced in approx. 1.1:1 ratio. The resonances assigned to **5** were confirmed by comparison with ZnArEt prepared independently by treatment of **1** with $\text{MgBr}^i\text{Pr}\cdot\text{LiCl}$ and ZnEt_2 .

For $\text{ZnEt}_2/\mathbf{1} = 2.5$ 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 $\text{H}_2\text{C}=\text{CH}_2$ was detected.⁷ At longer reaction times, the formation of ZnAr_2 (**6**) was also observed as somewhat broadened signals.⁸ After hydrolysis and work up of the reaction mixture, an oily residue was isolated. Its ^1H 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 .

Scheme 3. Reaction products before and after hydrolysis for the non-catalyzed reaction



2.- Reactions in the presence of a Pd-catalyst with $\text{PR}_2(\text{EWO})$ ligand P-L^1 . As in section 1, this reactivity was studied for two $\text{ZnEt}_2/\mathbf{1}$ ratios: 0.65 and 2.5. For $\text{ZnEt}_2/\mathbf{1} = 2.5$, the reactions of **1** and ZnEt_2 with 5% of $[\text{PdCl}_2(\text{P-L}^1)]$ as catalyst produced almost complete conversion of **1** (> 95%) in 5 min.⁹ Since the non-catalyzed reaction is much slower, the products observed can be assigned to the catalyzed pathway only. Before hydrolysis (Figure 1a), the ^1H NMR spectrum 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.⁸ Small amounts of the reduction product ArH (**3**, 1.5%), the homocoupling product ArAr (**4**, 1.3%), and CH_2CH_2 were also detected.

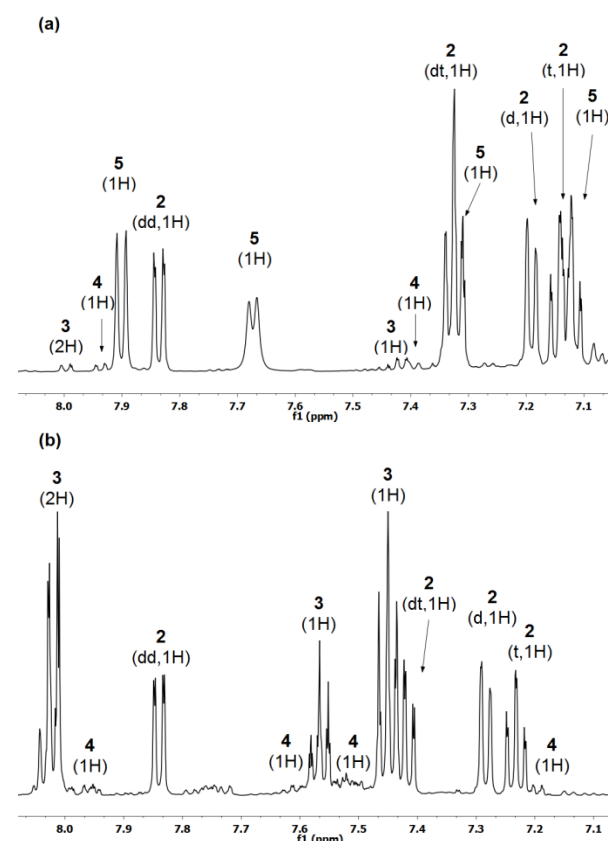
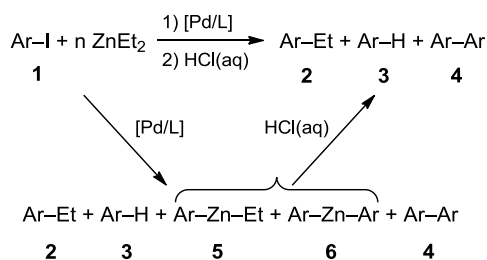


Figure 1. ^1H NMR spectrum (aryl region) (a) before and (b) after hydrolysis of the reaction mixture of **1** and ZnEt_2 (1:2.5 ratio) using $[\text{PdCl}_2(\text{P-L}^1)]$ as catalyst.¹⁰

After hydrolysis (Figure 1b) all **5** produces **3**, as in the non-catalyzed reaction. Assuming that ethylene might be the byproduct of β -H elimination, this would indicate that only a very small proportion (that observed before hydrolysis) of the reduction product **3** could be generated by β -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_2O for the hydrolysis; then the reduction 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 ^1H signals of **3** ca. $\delta = 8.03$ (2 H for ArH; 1H+1D for ArD). The formation of ArD was also confirmed by mass-spectrometry.

For $\text{ZnEt}_2/\mathbf{1} = 0.65$, the reaction showed different proportions of the products. Before hydrolysis (Figure 2), the ^1H 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 non-observed **5**

Scheme 4. Reaction products before and after hydrolysis for the Pd-catalyzed reaction



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 $\text{ZnEt}_2/\mathbf{1} = 2.5$, 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 $\text{ZnEt}_2/\mathbf{1} = 0.65$ and $\text{ZnCl}_2/\mathbf{1} = 1.85$ (this amounts to $\text{Zn}/\mathbf{1} = 2.5$) revealed a much slower reaction which, after 3 h, still contained 21% of unreacted starting material **1**, 75.5% of cross-coupling product **2**, 3.5% of homocoupling product **4**, and total absence of reduction product.

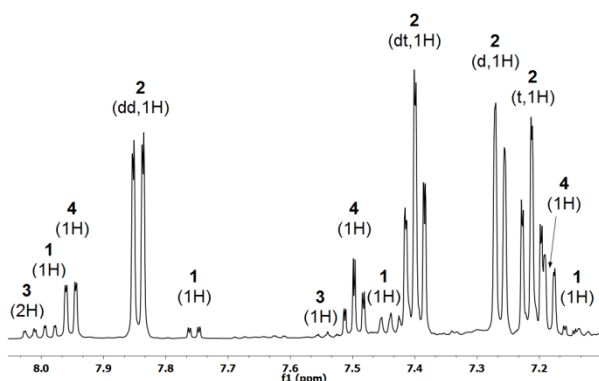


Figure 2. ^1H NMR spectrum (aryl region) *before* hydrolysis of the reaction mixture of **1** and ZnEt_2 (1:0.65 ratio) using $[\text{PdCl}_2(\text{P-L}^1)]$ as catalyst.

3.- Reactions in the presence of a Pd-catalyst with a phosphine ligand that do not contain an EWO group. For this study, the catalyst $[\text{PdCl}_2(\text{PPh}_2(\text{6-HC}_6\text{F}_4))_2]$ 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 $\beta\text{-H}$ elimination process is active. Using 5% of $[\text{PdCl}_2(\text{PPh}_3)_2]$ as catalyst, the amount of ArH (**3**) observed *before* hydrolysis (hence formed by $\beta\text{-H}$ 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 $\text{PR}_2(\text{EWO})$, and the $\beta\text{-H}$ elimination process to give PdArHL_2 , followed by Ar-H coupling, becomes competitive.

4.- The 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 ^1H 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 $\text{ZnEt}_2/\mathbf{1} = 2.5$ and THF-d_8 as solvent. The ^1H 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 approximate molar ratio $\text{BuH}:\text{EtH}:\text{CH}_2\text{CH}_2 = 6:1:0.7$.

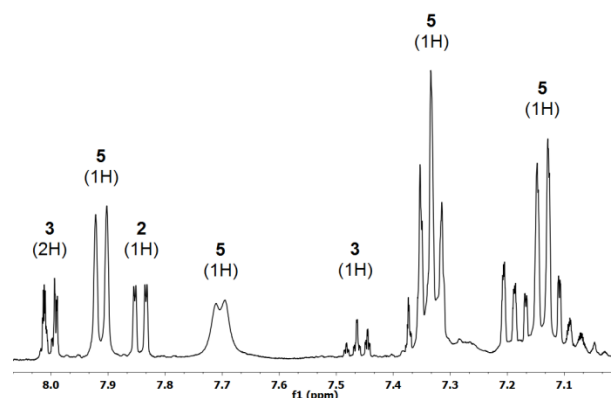
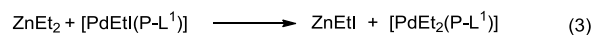
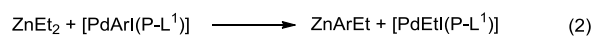
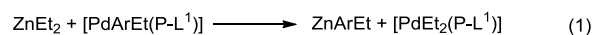


Figure 3. ^1H NMR spectrum *before* hydrolysis (Ar region) of the reaction products using $\text{PPh}_2(\text{6-HC}_6\text{F}_4)$ as ligand.

Obviously butane comes from homocoupling on $\text{PdEt}_2(\text{P-L}^1)$, and ethylene+ethane from $\beta\text{-H}$ elimination followed by Et-H reductive elimination on intermediate $\text{PdEtH}(\text{P-L}^1)$. However, there is 30% of EtH in excess on the amount expected from the ethylene produced, which should be assigned to ZnEt_2 hydrolysis by water in the deuterated solvent.¹¹ 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 $\beta\text{-H}$ elimination by about half to one order of magnitude. The efficiency of formation of the $\text{PdEt}_2(\text{P-L}^1)$ 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 $\beta\text{-H}$ 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; CH_2CH_2 : 12.9. This illustrates that much of the initial ZnEt_2 reagent is wasted in the formation of butane and ethane+ethylene from $\text{PdEt}_2(\text{P-L}^1)$. 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.



The major difference between the experiment in Figure 1 (Schlenk experiment; ArEt: 100; ArH: 3.2; ArAr: 2.9; CH_2CH_2 : 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 Fig. 1 compared to 12.9 in Fig. 4), confirming that gasses had been swept away. As explained above, the majority of ethane and ethylene comes from a $\text{PdEt}_2(\text{P-L}^1)$ intermediate, and only very little (as many moles as ArH observed *before* hydrolysis) comes from $\beta\text{-H}$ elimination followed by Ar-H coupling on $[\text{PdArEt}(\text{P-L}^1)]$. Since adventitious water has been eliminated at the beginning of the catalysis by reaction with ZnEt_2 , it is reasonable to assume that the amount of ArH formed *before* hydrolysis measures the proportion of $\beta\text{-H}$ elimination occurring on $[\text{PdArEt}(\text{P-L}^1)]$. In practice this represents only a very small part of the total ArH observed *after* hydrolysis.

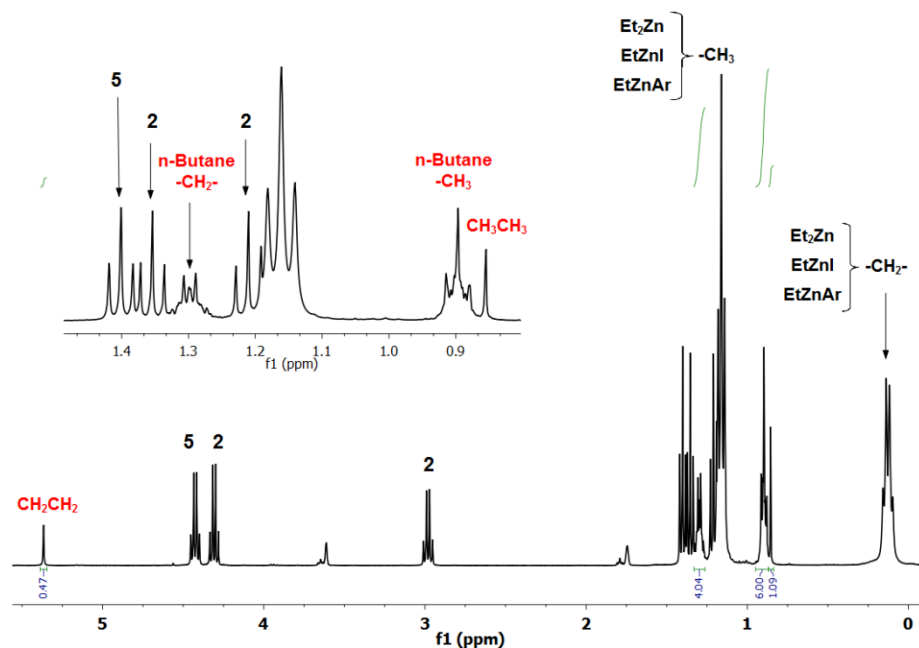


Figure 4. ^1H NMR spectrum *before* hydrolysis of the reaction mixture of **1** and ZnEt_2 (1:2.5 ratio) in THF-d_8 using $[\text{PdCl}_2(\text{P-L}^1)]$ as catalyst.

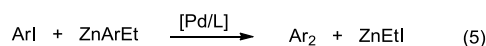
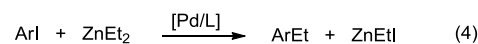
5.- The effect of the ZnEt_2/ArI ratio on the reactions using a Pd catalyst with P-L^1 . From the previous results it is clear that the competitive formation of *cross-coupling* ArEt , *homocoupling* ArAr , and most of *reduction* ArH products is independent of the $\beta\text{-H}$ elimination process, 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 on the oxidative addition product $[\text{PdArI}(\text{P-L}^1)]$ the formation of ArEt requires a $[\text{PdArEt}(\text{P-L}^1)]$ intermediate; ArH should arise from a Zn-Ar intermediate by hydrolysis; and ArAr should come from coupling on a $[\text{PdAr}_2(\text{P-L}^1)]$ 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 $[\text{PdEt}_2(\text{P-L}^1)]$ intermediate. Considering only the most direct transmetalations for the sake of simplicity,^{12,13,14,15} and a simple representation of the Zn derivatives in solution, some considerations can be made. For this, it is interesting to remind that it is known that the activation energy for C-C coupling decays in the order $\text{sp}^3\text{-sp}^3 > \text{sp}^3\text{-sp}^2 > \text{sp}^2\text{-sp}^2$.^{5,16}

At the very start of the reaction, the only Ar activated for coupling corresponds to the oxidative addition product $[\text{PdArI}(\text{P-L}^1)]$, 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_2) is terribly high. This means that the fast exchange in Eq. 1 quickly converts $[\text{PdArI}(\text{P-L}^1)]$ into $[\text{PdEt}_2(\text{P-L}^1)]$, 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 $\beta\text{-H}$ 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 ZnEtI (Eq. 4). Finally the formation of Ar-Ar homocoupling converts one molecule of ZnArEt in ZnEtI (Eq. 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.

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 $\text{ZnEt}_2/\mathbf{1} = 0.65$ 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 $\text{Ar-Et}/\text{Ar-H}$ ratios *after* hydrolysis are observed than in the reaction with $\text{ZnEt}_2/\mathbf{1} = 2.5$, as commented above.

The reaction using $\text{ZnEt}_2/\mathbf{1} = 0.65$ and $\text{ZnCl}_2/\mathbf{1} = 1.85$ would represent a later stage of the process, when the reagents are poorer in Et and richer in Ar . Then, the strong nucleophile ZnEt_2 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 $[\text{PdAr}_2(\text{P-L}^1)]$, associated to the fastest Ar-Ar coupling starts to produce biaryl homocoupling very competitively, as observed.

6.- Improving the $\text{Ar-Et}/\text{Ar-H}$ selectivity. Taking into consideration the factors disturbing the Ar-Et selectivity, discussed

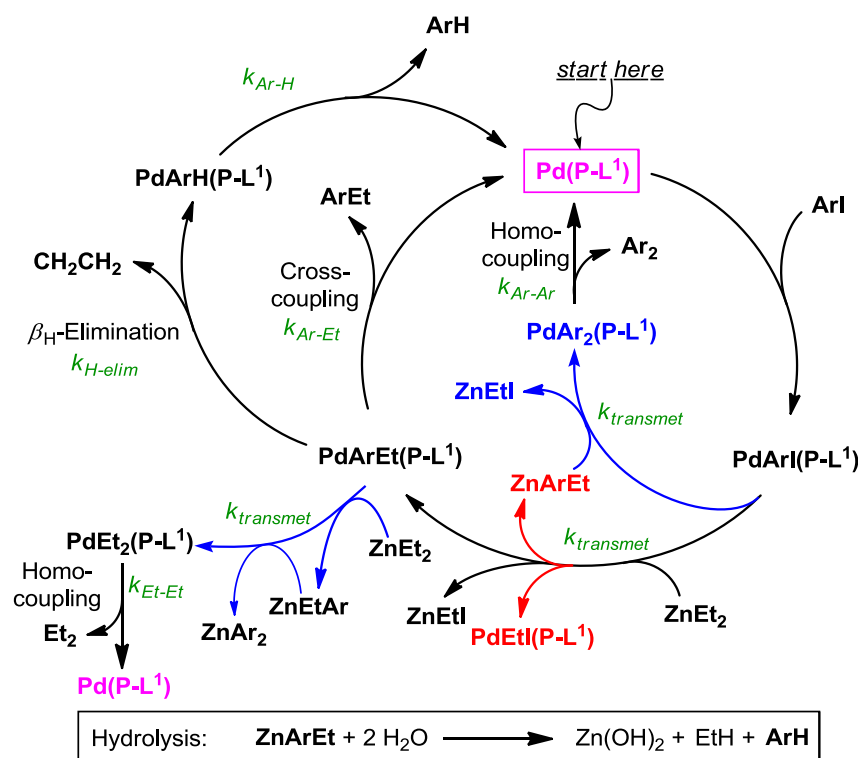
above, we should be able to find a set of conditions where the ethylation of Pd will be better controlled in order to avoid double ethylation. Should this be controlled efficiently, there will not be accumulation of $ZnArEt$, which is the source of ArH hydrolysis product.

As we have mentioned in last section, $ZnEtI$ or $ZnEtCl$ are less nucleophilic than $ZnEt_2$ and exchanges bringing Ar from Pd to Zn are less efficient.¹³ 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 $ZnEt_2$ (for $ZnEt_2/1 = 2.5$), with 5% of $[PdCl_2(P-L^1)]$ as catalyst produced complete conversion of **1** leading, after hydrolysis: $ArEt$: 46.2%; ArH : 52.6%; $ArAr$: 1.2%. Under the same conditions, using $ZnEtCl$ instead of $ZnEt_2$ ($ZnEtCl/1 = 2.5$), much higher cross coupling product selectivity is observed: $ArEt$: 93.9%; $Ar-H$: 6.1%, $Ar-Ar$: 0.0%.

CONCLUSION

All these results can be fit and summarized in the catalytic cycle proposed in Scheme 5, where the relatively slow β -H elimination followed by C-H reductive elimination is not competitive when a $PR_2(EWO)$ 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.

Scheme 5. Proposed mechanisms associated to the Pd-catalyzed Ar-Et coupling and their byproducts. The indicated rate constants are only relative. However, k_{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.



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 a solvent purification system SPS PS-MD-5 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.⁴ Solutions of $ZnEt_2$ 1.0 M in dry hexane were prepared from commercial salt-free liquid $ZnEt_2$ (Sigma-Aldrich Zn wt. $\geq 52.0\%$).¹⁷ Solutions of $ZnEtCl$ were prepared by asymmetric rearrangement of $ZnEt_2$ and $ZnCl_2$. All other reagents were commercially available and used as received.

¹H, ¹⁹F and ³¹P{¹H} spectra were recorded on a Bruker AV-400 or a Varian Inova 500 spectrometer. Chemical shifts (in δ units, parts per million)

were referenced to the residual solvent signal, to $CFCl_3$ and to 85% H_3PO_4 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 Perkin Elmer 2400B CHN analyzer.

$[PdCl_2(PPh_2(6-HC_6F_4))_2]$. Phosphine $PPh_2(6-HC_6F_4)$ (50.9 mg, 0.152 mmol) was added to a solution of $[PdCl_2(NCMe)_2]$ 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 at vacuum. (59.2 mg, 92%). ¹H NMR (400.13 MHz, δ , $CDCl_3$): 7.86–7.76 (m, 8H), 7.58–7.52 (m, 4H), 7.51–7.45 (m, 8H), 6.59 (m, 2H) ¹⁹F NMR (376.46 MHz, δ , $CDCl_3$): –120.16 (m, 2F), –137.56 (m, 2F), –149.76 (m, 2F), –153.29 (m, 2F). ³¹P{¹H} NMR (161.97 MHz, δ ,

CDCl₃): 1.7.76 (dd, $J_{P-F} = 7.0, 7.0$ Hz, 2P). Anal. Calcd for C₃₆H₂₂Cl₂F₈P₂D: 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 weighted and put into an oven-dried 10 mL Schlenk, which was evacuated and refilled with argon. Ethyl 2-iodobenzoate (50.8 μ L, 0.3 mmol) was added by micro syringe and Schlenk was sealed. Finally, a previously prepared solution of ZnEt₂ (0.75 mL, 1.0 M in hexane) in 0.25 mL of THF was added slowly with a gentle stirring of the mixture, which turns immediately into 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).

Ethyl 2-ethylbenzoate (2). ¹H NMR (400.13 MHz, δ , CDCl₃): 7.84 (dd, $J = 7.7$ Hz, 1.4 Hz, H^a), 7.42 (ddd, $J = 7.7, 7.7, 1.4$ Hz, H^b), 7.24 (ddd, $J = 7.7, 7.7, 1.5$ Hz, H^c), 7.27 (dm, $J = 7.7$ Hz, H^d), 4.36 (q, $J = 7.1$ Hz, CH₂ from COOEt), 2.97 (q, $J = 7.5$ Hz, CH₂ from Et) 1.39 (t, $J = 7.1$ Hz, CH₃ from COOEt) 1.24 (t, $J = 7.1$ Hz, CH₃ from Et).

Ethylbenzoate (3). ¹H NMR (400.13 MHz, δ , CDCl₃): 8.05 (m, H^a + H^b), 7.55 (tt, $J = 7.4, 1.3$ Hz, H^c), 7.44 (m, H^d + H^e), 4.38 (q, $J = 7.1$ Hz, CH₂ from COOEt), 1.40 (t, $J = 7.1$ Hz, CH₃ from COOEt).

Diethyl biphenyl 2,2'-dicarboxylate (4). ¹H NMR (400.13 MHz, δ , CDCl₃): 8.01 (ddd, $J = 7.7, 1.4, 0.4$ Hz, H^a), 7.52 (ddd, $J = 7.7, 7.7, 1.4$ Hz, H^b), 7.43 (ddd, $J = 7.7, 7.7, 1.4$ Hz, H^c), 7.21 (dm, $J = 7.7$ Hz, H^d), 4.04 (q, $J = 7.1$ Hz, CH₂ from COOEt), 0.98 (t, $J = 7.1$ Hz, CH₃ from COOEt).

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Notes

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- (6) The Ar–Et/Ar–H/Ar–Ar ratios of the products observed in these reactions follow the same trends reported previously,⁴ 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 than in long time manipulations of ZnEt₂ traces of ethylene can be observed. We suspect that it can be related to catalysis by traces of metals. In such case the slow “non-catalyzed” 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 in this work. ¹H NMR experiments prove that the broadening is due to exchange of the Et groups between **5**, ZnEtI and ZnEt₂, and the exchange of the Ar groups between **5** and **6**.
- (9) Note that [PdCl₂(P–L¹)] is in fact a precatalyst that has to be transformed into [Pd(P–L¹)] to enter the catalytic cycle. This requires double ethylation to [PdEt₂(P–L¹)], and reductive elimination producing butane. For 5% of Pd catalyst, 5% of ZnEt₂ (or 10% of ZnEtCl, when this is the ethylating agent) will be consumed in this pre-catalytic process.
- (10) Observed shifts are due to different solvent-mixtures polarities. While before hydrolysis there was a mixture THF/Hexane 3:1, after hydrolysis solvent was only THF.
- (11) By checking the ¹H NMR spectrum of the preformed solution of ZnEt₂ in THF-d₈ 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 references 13–15). Only some examples (Eqs. 1–2) are shown.
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- (17) This procedure of preparation of solutions of ZnEt₂ in hexane was used in order to prevent the presence of significant amounts of salt byproducts, which is difficult to avoid when ZnEt₂ is prepared *in situ* from ZnX₂ 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.

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