

Palladium-Catalyzed Diorganozinc Conjugate Additions to Enones: Preparative and Computational Studies

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Keywords: C-C coupling / Homogeneous catalysis / Palladium / Conjugate additions / Reaction mechanisms

The Pd-catalyzed conjugate addition of diorganozinc reagents to α , β -unsaturated carbonyl compounds has been applied to a variety of enone substrates, both cyclic and acyclic, encompassing various combinations of aryl and alkyl substitution, in combination with diorganozinc reagents incorporating alkyl (Me, linear and branched) or Ph groups. While both Pd⁰ and Pd^{II} complexes have been found to be competent precatalysts, reaction yields are strongly dependent on

Introduction

Metal-catalyzed organozinc conjugate additions to α,β unsaturated carbonyl derivatives^[1–5] offer an alternative to the classical use of organocuprate reagents.^[6] In particular, the corresponding palladium-catalyzed processes^[7,8] present advantages in cases where formation of 1,2 adducts is a competing side-reaction. Although precise mechanistic information is lacking, these reactions are thought to be Pd⁰catalyzed processes proceeding through η^3 -palladium complexes related to **3**, which then undergo reductive elimination to a zinc enolate **4** (Scheme 1).^[7,9]

Formation of intermediate **3** would presumably involve oxidative addition and transmetalation steps related to those suggested to take place in other $\text{Et}_2\text{Zn}/\text{Pd}^0$ -promoted coupling processes involving allylic and propargylic alcohol derivatives^[10–16] and, very particularly, in the Lewis-acid-induced, Pd⁰-catalyzed, organometal conjugate additions to enones.^[17–22] As a result, in the transformation $1 \rightarrow 3$, R₂Zn would be expected to play a dual role as Lewis acid and transmetalating agent. On the other hand, some ambiguity is brought to this mechanistic picture by the fact that these reactions customarily employ Pd^{II} starting complexes, which are expected to first undergo reduction with R₂Zn to

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- Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201201519.

the relative amounts of Pd to phosphane ligand. Thus, a 1:1 Pd/P ratio is well tolerated, but going to Pd/P = 1:2 leads to poor conversions and yields. A calculated Pd⁰-mediated pathway involving an unusual oxidative addition step with simultaneous transmetalation, followed by reductive elimination, has been found to be compatible with the observed phosphane effect.



Scheme 1. Suggested mechanism for palladium-catalyzed $R_2 Zn$ conjugate additions.

generate the active Pd⁰ catalytic species.^[7] Reduction of PdX₂ is likely to involve intermediate RPdX complexes, and the participation of these species could provide an alternative mechanistic interpretation for formation of 2 by carbopalladation of the C-C double bond of 1. In fact, this is the pathway believed to be followed by the related Pd-catalyzed diorganozinc additions to oxabicyclic alkenes.^[23-27] Better understanding of the mechanistic details of the $1 \rightarrow 2$ transformation would be desirable, as it involves Pd– Zn transmetalation processes which are common to other important synthetic reactions.^[28] With this aim we have compared the efficiency of this reaction as a function of the oxidation state of Pd (Pd^{II} or Pd⁰) in the starting precatalyst complex, and we have also examined the effect of added phosphane ligands. Additionally, we have explored a possible reaction pathway computationally. So far, this reaction had been mainly applied to enal substrates, with enones only represented by two independent examples, both of them on acyclic substrates with Et₂Zn as the coupling

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agent.^[7,8] As a result, we have centered our study on the use of enones, with the further aim of extending the scope of this chemistry to a wider range of such substrates in reactions with diorganozinc reagents.

Results and Discussion

The results of reactions of (*E*)-non-3-en-2-one (**5a**) with Et_2Zn in THF, in the presence of various palladium catalysts, are collected in Table 1. Reaction conditions parallel those reported in the literature for similar reactions^[7] with an initial mixing at -78 °C, followed by warming to 0 or

Table 1. Effect of palladium catalyst and phosphanes on the addition of $\rm Et_2Zn$ to enone ${\bf 5a}.^{[a]}$

r	о-С ₅ Н ₁₁ 5а	Et ₂ Zn Pd complex/L THF –78 °C to T		<i>n</i> -C ₅ H ₁₁ 6a		
Entry	Pd complex	L	Pd/P ratio	Т	t	Yield of 6a
				[°C]	[h]	[%]
1	_			0	20	[b]
2	Pd(OAc) ₂			0	4	55
3	$Pd(O_2CCF_3)_2$			0	7	85
4	PdCl ₂			0	22	77
5 ^[c]	Pd(PPh ₃) ₄			25	25	<10
6 ^[c]	$Pd_2(dba)_3$			25	20	77
7 ^[d]	Pd(OAc) ₂	PPh_3	1:1	0	7	70
8 ^[d]	$Pd(OAc)_2$	PPh_3	1:2	0, 25	7, 23	<10
9	$Pd(OAc)_2$	$P(nBu)_3$	1:1	0	24	73
10	Pd(OAc) ₂	$P(nBu)_3$	1:2	0	22	20
11 ^[d]	$Pd(O_2CCF_3)_2$	PPh_3	1:1	0	23	63
12	$Pd(O_2CCF_3)_2$	PPh_3	1:2	0	28	<20
13	$Pd_2(dba)_3$	PPh ₃	1:1	25	25	44
14	$Pd_2(dba)_3$	PPh_3	1:2	25	25	<10

[a] Reaction conditions: Unless otherwise indicated, palladium complex (5 mol-%), E_2Zn (1.5 equiv.), **5a** (0.1 M), THF, -78 °C to *T* (final temperature), under Ar. [b] Recovered starting material. [c] The initial mixing temperature was 25 °C. [d] $E_{t_2}Zn$ (2 equiv.).

Table 2. Palladium-catalyzed conjugate additions of R₂Zn to enones 5.^[a]

		$R^2 \xrightarrow{O} R^1 \text{ or}$ 5a–d	0 5e	$\begin{array}{c} R_2 Zn \\ Pd \text{ catalyst} \\ \hline \\ \hline \\ THF \\ -78 ^{\circ}C \text{ to } T \end{array} R^{2}$	R O R ¹ or 6a–g	O R 6h-j	
Entry	5	\mathbb{R}^1	\mathbb{R}^2	R ₂ Zn	<i>Т</i> [°С]	<i>t</i> [h]	6, yield [%]
1	5a	Me	<i>n</i> -C ₅ H ₁₁	Et ₂ Zn	0	7	6a , 85
2	5a	Me	$n - C_5 H_{11}$	Me ₂ Zn	0, 25	8, 19	6b , 78
3	5a	Me	$n-C_5H_{11}$	Cy_2Zn	0	1	6c, 65
4	5a	Me	$n-C_5H_{11}$	Ph_2Zn	0	1	6d , 84
5	5b	Me	Ph	Et_2Zn	0	20	6e , 73
6	5c	Ph	Me	Et_2Zn	0	3	6f , 73
7 ^[b]	5d	Ph	Ph	Et_2Zn	25	2.5	6g , 62
8	5e	Ph	Ph	Et_2Zn	0	5	6h , 91
9	5e	Ph	Ph	Cy_2Zn	0	1	6i , 80
10	5e	Ph	Ph	Ph_2Zn	0	1	6 j, 85

[a] Reaction conditions: Unless otherwise indicated, $Pd(O_2CCF_3)_2$ (5 mol-%), Et_2Zn (1.5 equiv.), **5** (0.1 M), THF, -78 °C to *T* (final temperature), under Ar; Cy = cyclohexyl. [b] Reaction run with $Pd_2(dba)_3$.

25 °C, depending on the precatalyst. Reactions at lower temperatures were sluggish and low yielding.

As shown in Table 1, the reaction is efficiently promoted by several Pd^{II} complexes (Entries 2-4). It is significant that $Pd_2(dba)_3$, a Pd^0 catalyst, also worked well (Entry 6). The implication of this observation is that Pd⁰ is likely to be the type of species ultimately responsible for the catalytic activity, and that the steps broadly delineated in Scheme 1 are also likely to be operating. In contrast, however, a phosphane-ligated Pd complex displayed sluggish reactivity and gave a low yield of product 6a (Entry 5). As will be discussed below, our results suggest that the failure of Pd(PPh₃)₄ to catalyze the reaction efficiently is likely to be related to the number of phosphane ligands available for complexation with Pd. Additionally, in the foregoing mechanistic scenario,^[7] Entries 2–4 require reduction of PdX₂ with Et₂Zn to yield Pd⁰, and this process generates Lewisacidic ZnX₂, which could in turn participate in the activation of the carbonyl group of the enone substrate. This could perhaps explain the higher temperature required by the Pd^0 catalyst (Entry 6), where ZnX_2 is not formed and only the less acidic Et₂Zn is available for activation.

The effect of phosphanes was evaluated by using PPh₃ and P(*n*Bu)₃ (entries 7–14). It was found that a 1:1 Pd/P ratio was well tolerated, leading in all cases to acceptable yields, albeit variably depending on the catalyst. An increase in reaction times was also noticed in the case of Pd^{II} precatalysts relative to the phosphane-free conditions (Entries 1–6). However, a ratio of Pd/P = 1:2 led to sluggish reactions and a considerable drop in the isolated yields, consistent with the failure of Pd(PPh₃)₄ to catalyze the reaction efficiently. Additionally, these results are in line with reports from Ogoshi and Kurosawa on the inhibitory effect of phosphanes in the palladium-catalyzed conjugate addition of AlMe₃ to benzylideneacetone, due to slow transmetalation between AlMe₃ and (η^3 -allyl)(PPh₃)₂ complexes generated by oxidative addition of the enone to Pd⁰.^[17]



The results of Pd-catalyzed conjugate additions to enones **5** by using various diorganozinc reagents are collected in Table 2. Dialkylzinc reagents with methyl and branched alkyl groups were all suitable, and the presence of an aryl group was also successful (Ph₂Zn). As for the enone substrate, both aryl and alkyl groups were well tolerated as carbonyl substituents (\mathbb{R}^1), as well as at the terminal alkene position (\mathbb{R}^2) (Entries 1–7), and a cyclic enone also participated effectively (Entries 8–10). While palladium trifluoroacetate was a convenient catalyst precursor in most cases, chalcone underwent substantial degradation with this complex, and Pd₂(dba)₃ was used in that particular case (Entry 7).

Mechanistic Considerations

The use of $Pd_2(dba)_3$ as an effective catalyst points towards a Pd⁰-based reaction mechanism, possibly involving oxidative addition of the enone to Pd⁰, transmetalation and reductive elimination steps.^[7,17,29] Whereas the alternative carbopalladation pathway could in principle be possible by starting with Pd^{II} complexes,^[23] the lack of reactivity of related substrates such as α,β -unsaturated esters, α,β -unsaturated amides or α,β -unsaturated nitriles^[7] or the complete absence of Heck-type side-products in these reactions would be difficult to justify in that scenario. We have checked for formation of these and other side-products, that could arise after a carbopalladation step, by running reactions of 5a with relative ratios of Pd^{II}/Et₂Zn, which were higher than required by our standard conditions (Table 3). The amount of Pd complex was always kept high (20 mol-% relative to 5a) to facilitate detection of small amounts of those side-products. Not surprisingly, under those conditions, which are partially deprived of Et₂Zn, incomplete reactions ensued. Significantly, however, the only detectable side-product was the reduction product 7a. This was likely formed as a result of competitive hydropalladation of the starting enone with an HPdX complex originated from Pd^{II}

Table 3. Effect of Pd^{II}/Et_2Zn relative amounts on the reactions of enone 5a.^[a]



[a] Reaction conditions: Pd(OAc)₂ (20 mol-%), P(nBu)₃ (20 mol-%), Et₂Zn (n equiv.), **5a** (0.1 M), THF, -78 to 0 °C, under Ar.

and $Et_2Zn^{[30]}$ by transmetalation/ β -hydride elimination along the reduction pathway eventually leading to Pd⁰. Therefore, this result is also suggestive of Pd⁰ being involved as the actual catalytic species.

Similarly consistent with a Pd⁰-mediated pathway is the above-mentioned effect of phosphanes in these reactions. Phosphanes could retard the reaction by acting on any of the two steps presumably involved in the formation of zinc enolate 4 (Scheme 1). Thus, transmetalation between AlMe₃ and $(\eta^3-\text{allyl})(\text{PPh}_3)_n$ complexes derived from benzylideneacetone and Pd^0 was reported as being slow when n =2, but fast formation of the product formally resulting from conjugate addition of AlMe₃ to the enone (presumably involving transmetalation and reductive elimination steps) was observed when n = 1.^[17] Additionally, the rate of reductive elimination has been reported to be higher for mono(phosphane) relative to bis(phosphane) complexes.^[31] Taking all of these observations together, it is likely that similar phosphane-derived effects could also be operating in the transmetalation/reductive elimination steps leading to 4 (Scheme 1). Alternatively, we noticed that a phosphanedependent reductive elimination may also be involved in the initial $Pd^{II} \rightarrow Pd^0$ reduction, and that the additional pathway for reduction, involving β -H elimination, is a process requiring a vacant position in the Pd coordination sphere, and therefore also sensitive to the amount of available phosphane. However, it is unlikely that a slow reduction of Pd^{II} to Pd⁰ would be the only source of the observed phosphane effect, since this is observed also in the reaction catalyzed by Pd₂(dba)₃, where Pd reduction is not involved (Table 1, Entries 13 and 14).[32]

A model reaction between acrolein and Me₂Zn has been studied computationally to specifically check the viability of a pathway leading to species of type 3 by oxidative addition and transmetalation steps (Scheme 1). We have additionally probed the possibility of inhibition of that pathway with the addition of phosphane ligands, using PMe₃ as a simplified model for the experimentally used $P(nBu)_3$ ligand. A further simplification in the computational model has involved the use of a single diorganozinc species acting both as transmetalating agent and Lewis acid. This has resulted in complexes I as the starting point in our computational investigation (Scheme 2 and Figure 1). In support of the viability of such intermediates, the participation of related dimetallic species with a Pd–Zn bond has been suggested in other coupling reactions involving transmetalations between Pd and Zn complexes,^[33–38] and the crystal structures of complexes with a Pd-Zn covalent bond have also been reported.^[39,40]

By starting from I (I_{1L} or I_{2L}), oxidative addition of acrolein to Pd⁰ takes place with *simultaneous transfer of an Me* group from Zn to Pd and formation of II, a dimetallic complex featuring a zinc enolate and an η^1 -palladium moiety. This kind of oxidative addition/transmetalation step has been previously suggested in the literature to participate in Ni⁰-catalyzed enone couplings^[42] and reductions^[43] mediated by Et₂Zn. From II, reductive elimination leads directly to zinc enolate III. In the bis(phosphane) pathway

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Scheme 2. Computed pathways for Pd(PMe₃)₂-mediated conjugate addition of Me₂Zn to acrolein (L = PMe₃; S = OMe₂).



Figure 1. Reaction free energy profiles for oxidative addition/transmetalation and reductive elimination steps computed in THF (wB97XD/6-31G*/PCM).^[41]

(Scheme 2a and 2L pathway in Figure 1) both steps proceed through relatively-high-energy transition states (TS) (18.8 and 39.4 kcal/mol above I_{2L} , respectively), whereas the corresponding mono(phosphane) pathway (Scheme 2b and 1L pathway in Figure 1) results in a significant decrease in the energy for both the oxidative addition and reductive elimination steps (TS 11.4 and 24.4 kcal/mol above I_{1L} , respectively; Figure 1). This is consistent with the detrimental effect noticed for a 1:2 Pd/P ratio. Interestingly, in the mono-(phosphane) pathway, the key oxidative addition/transmetalation step is predicted to be a relatively-low-energy process, whereas reductive elimination would provide the rate-determining TS in both pathways.

Conclusions

The Pd-catalyzed conjugate addition of diorganozinc reagents to α , β -unsaturated carbonyl compounds has been extended to the use of both cyclic and acyclic enone sub-

strates encompassing various combinations of aryl and alkyl substitution, in combination with diorganozinc reagents incorporating alkyl (Me, linear and branched) or Ph groups. Both Pd⁰ and Pd^{II} complexes have been found to be useful precatalysts, implying that the latter are probably first reduced by R₂Zn to Pd⁰. Whereas the reaction proceeds efficiently in the absence of added ligands, the use of phosphanes in a 1:1 Pd/P ratio is well tolerated and even found to be advantageous, depending on the particular catalyst. However, increasing the amount of phosphane to a 1:2 Pd/P ratio is clearly detrimental in terms of yields and reactivity. Calculations have revealed the possibility of a reaction pathway where an α , β -unsaturated carbonyl derivative coordinated to both Pd⁰ and R₂Zn undergoes oxidative addition to Pd⁰ with simultaneous transmetalation from Zn to Pd. Reductive elimination would then lead to the final addition product. The calculated effect of the Pd/P ratio on the activation energies on this pathway is consistent with experimental observations.^[44]

Experimental Section

General: Solvents were dried according to published methods and distilled before use. All other reagents were commercial compounds of the highest purity available. All reactions were carried out under argon. Analytical thin layer chromatography (TLC) was performed on aluminium plates with Merck Kieselgel 60F254 and visualised by UV irradiation (254 nm) or by staining with an ethanolic solution of phosphomolybdic acid. Flash column chromatography was carried out by using Merck Kieselgel 60 (230-400 mesh) under pressure. For ESI mass spectra, an APEX III FT-ICR MS (Bruker Daltonics, Billerica, MA), equipped with a 7 T actively shielded magnet was used, and ions were generated by using an Apollo API electrospray ionization (ESI) source, with a voltage between 1800 and 2200 V (to optimize ionisation efficiency) applied to the needle, and a counter voltage of 450 V applied to the capillary. Samples for ESI mass spectra were prepared by adding a spray solution of 70:29.9:0.1 (v/v/v) CH₃OH/water/formic acid to a solution of the sample at a v/v ratio of 1-5% to give the best signal-to-noise ratio. High-resolution mass spectra were taken with a VG Autospec instrument. ¹H NMR spectra were recorded in CDCl₃ at ambient temperature with a Bruker AMX-400 spectrometer at 400.13 MHz



with residual protic solvent as the internal reference (CDCl₃: $\delta_{\rm H}$ = 7.26); chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are given in Hertz [Hz]. The proton spectra are reported as follows: δ (multiplicity, J, number of protons, assignment). ¹³C NMR spectra were recorded at ambient temperature with the same spectrometer at 100.62 MHz, with the central peak of the solvent (CDCl₃: $\delta_{\rm C}$ = 77.0) as the internal reference. DEPT135 measurements were used to aid in the assignment of signals in the ¹³C NMR spectra.

Procedure for Conjugate Addition of Organozinc Reagents to α,β-Unsaturated Ketones by Using a Pd^{II} Precatalyst: In a typical experiment, to a cooled (-78 °C) solution of a Pd^{II} complex (5 mol-%) in THF (7 mL) was added a solution of a phosphane ligand (5 or 10 mol-%, where appropriate; see Table 1) and the corresponding enone (1 mmol) in THF (3 mL). After 10 min, a solution of the organozinc reagent (1.5 mmol) was added dropwise to the stirred solution, and the reaction mixture was stirred under the indicated conditions of temperature and time (Tables 1 and 2). The resulting mixture was poured into a cooled (0 °C) saturated aqueous solution of NH₄Cl (10 mL), and the layers were separated. The aqueous layer was extracted with Et₂O (3×), the combined organic layers were dried (Na₂SO₄), and the solvent was evaporated. The residue was purified by column chromatography (silica gel; hexane/EtOAc) to afford a colourless oil in all cases.

Procedure for Reactions with Pd₂(dba)₃: In a typical experiment, to a stirred solution of an enone (1 mmol) in THF (10 mL) were added Pd₂(dba)₃ (5 mol-%), a phosphane ligand (20 or 40 mol-%, Pd/P = 1:1 or 1:2, respectively, where appropriate; see Table 1) and a solution of Et₂Zn (1.5 mmol, 1 M in hexane) dropwise at room temperature. The reaction mixture was stirred for the indicated time (Tables 1 and 2), and the products were then isolated and purified as described above.

Procedure for Conjugate Addition of Et₂Zn to (*E*)-Non-3-en-2-one by Using Pd(PPh₃)₄: To a solution of (*E*)-non-3-en-2-one (1 mmol) in THF (10 mL) were added Pd(PPh₃)₄ (5 mol-%) and a solution of Et₂Zn (1.5 mmol, 1 M in hexane) dropwise at room temperature. The reaction mixture was stirred for 25 h, and the product was then isolated and purified as described above.

Procedure for Conjugate Additions to 5a by Using Different Relative Ratios of $Pd(OAc)_2/Et_2Zn$: See Table 3. To a cooled (-78 °C) solution of $Pd(OAc)_2$ (0.2 mmol) in THF (10 mL) were added $P(nBu)_3$ (0.2 mmol) and 5a (1 mmol). After 10 min, Et_2Zn (0.4–2.0 mmol) was added dropwise to the stirred solution, and the reaction mixture was stirred at 0 °C for 6.5 h. The products were isolated and purified as described in the procedures above.

By applying the procedures described above, compounds 6a-j and 7a were prepared. Compounds $6a,^{[45]}6b,^{[45]}6d,^{[46]}6e,^{[45]}6f,^{[47]}6g,^{[48]}6h,^{[49]}6i,^{[50]}6j^{[51]}$ and $7a^{[52]}$ had been described previously, and the samples prepared here presented spectroscopic data that match those described in the literature for the same compounds.

4-Cyclohexylnonan-2-one (6c): According to the procedure for conjugate addition of organozinc reagents to enones by using a Pd^{II} precatalyst, the reaction of **5a** (0.03 mL, 0.18 mmol), Pd-(O₂CCF₃)₂ (3 mg, 0.0091 mmol) and Cy₂Zn (0.68 mL, 0.4 m in Et₂O, 0.27 mmol) in THF (1.8 mL) afforded, after purification by column chromatography (silica gel; hexane/EtOAc, 97:3), a viscous oil (0.026 g, 65%) identified as **6c**. ¹H NMR (400.13 MHz, CDCl₃): $\delta = 2.41$ (dd, ²J_{H,H} = 16.1 Hz, ³J_{H,H} = 5.9 Hz, 1 H, 3-H), 2.23 (dd, ²J_{H,H} = 16.1 Hz, ³J_{H,H} = 7.3 Hz, 1 H, 3-H), 2.13 [s, 3 H, C(O)-CH₃], 1.8 (m, 1 H, 4-H), 1.8-1.5 (m, 6 H, 3 CH₂), 1.4-1.0 (m, 13 H, CH, 6 CH₂), 0.87 (t, ³J_{H,H} = 7.0 Hz, 3 H, CH₃) ppm. ¹³C NMR

 $\begin{array}{l} (100.62 \ MHz, \ CDCl_3): \delta = 209.7 \ (s), 46.1 \ (t), 40.5 \ (d), 39.2 \ (d), 32.2 \\ (t), 31.4 \ (t), 30.3 \ (q), 30.2 \ (t), 29.2 \ (t), 27.1 \ (t), 26.8 \ (t), 26.7 \ (t, 2 \ C), \\ 22.6 \ (t), 14.1 \ (q) \ ppm. \ HRMS \ (ESI^+): \ calcd. \ for \ C_{15}H_{29}O \\ [M + H]^+ \ 225.2219; \ found \ 225.2213. \ IR \ (NaCl): \ \tilde{\nu} = 2925 \ (s, \ C-H), \\ 2853 \ (s, \ C-H), \ 1717 \ (s, \ C=O), \ 1449 \ (w), \ 1356 \ (w) \ cm^{-1}. \end{array}$

Supporting Information (see footnote on the first page of this article): Cartesian coordinates and energies (in hartrees) for all calculated structures. Copies of 1 H and 13 C NMR spectra for **6c**.

Acknowledgments

We thank the Spanish Ministerio de Economía y Competitividad (Grants CTQ2008-06647 and CTQ2009-14186, FEDER) for financial support.

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Received: November 13, 2012 Published Online: March 13, 2013