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PCP-Bis(phosphinite) pincer complexes: new homogeneous catalysts for α-arylation of ketones

Fátima Churruca, Raul SanMartin,* Imanol Tellitu and Esther Domínguez*

Kimika Organikoa II Saila, Zientzia eta Teknologia Fakultatea, Euskal Herriko Unibertsitatea, PO Box 644, 48080 Bilbao, Spain

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Abstract—Two new *p*-alkoxycarbonylated palladium bis(phosphinite) PCP pincer complexes are easily prepared and for the first time evaluated as homogeneous catalysts in α-arylation of ketone enolates. Apart from the total absence of phenyl–aryl exchange by-products and significantly low catalyst loadings, the general α-arylation protocols described in this letter feature not only a broad applicability to a range of ketones and aryl bromides with marked electronic and steric differences but also the possibility to generate mono-diarylated products.
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Metal complexes based on pincer framework are an appealing target because of their unique balance of stability versus reactivity, which can provide enhanced reactivity and catalytic performances.[1] In particular there has been an increased interest in the use of PCP pincer complexes in homogeneous catalysis due to their excellent moisture-, air- and temperature-stability.[2] In the last years, the demand for a cleaner, environmentally friendlier chemistry has led to the development of new heterogeneous catalytic systems[3] and, in our opinion, PCP pincer-type complexes would constitute excellent candidates for such task.

Consequently, and as part of our ongoing research on the development of pincer-type heterogeneous catalysts,[4] we planned to transform homogeneous bis(phosphinite) PCP-pincer palladacycles[5] into heterogeneous catalysts by anchoring conveniently modified complexes to an insoluble support.[6] For that purpose, we devised the preparation of suitable functionalized *para*-ethoxycarbonylated palladacycles **1**, which would be subsequently submitted to several coupling reactions in order to ensure their catalytic activity before the heterogenization step. Phosphinite PCP pincer complexes, which appear to combine in one molecule the advantages of palladacycles and a modulation of catalyst properties by phosphinite ligands, have been proved to be highly active in a number of C–C bond-forming reactions.[5,7] No ketone α-arylation has been described employing the latter phosphinite complexes, and, to the best of our knowledge, the use of pincer-type palladacycles in α-arylation of ketone enolates has not been investigated so far.[8] In this context, considering our experience in palladium-catalyzed arylations of ketones[9] it seemed likely to us that phosphinite pincer complexes could act as homogeneous catalysts for such an important transformation.[10]

The successful application of bis(phosphinite) PCP-pincer palladacycles **1** in the firstly reported α-arylation of ketones performed by pincer-type catalysts is disclosed in this letter.

New alkoxycarbonylated complexes **1a** and **1b** were easily prepared from commercially available ethyl 3,5-dihydroxybenzoate **2** by a one-pot phosphorylation/palladation sequence, according to procedures similar to those described in the literature (Scheme 1).[5] Thus, reaction of the resorcinol derivative **2** with the appropriate chlorophosphine afforded the corresponding air- and moisture-sensitive diphosphinite ligands,[11] which were subsequently treated with the suitable palladium source [$PdCl_2(COD)$ or $Pd(OCOCF_3)_2$] to yield target palladium complexes **1a** and **1b**.[12]

As mentioned above, the catalytic activity of **1a**–**b** in several C–C bond-forming reactions was initially tested

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* Corresponding authors. Tel.: +34 9460 15435; fax: +34 9460 12748 (R.S.); e-mail: raul.sanmartin@ehu.es

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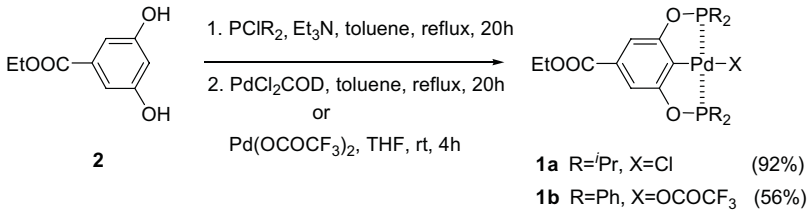


Scheme 1.

by a series of preliminary studies,[13] showing excellent catalytic properties in Heck, Suzuki and Sonogashira cross-coupling reactions, as shown in Scheme 2.

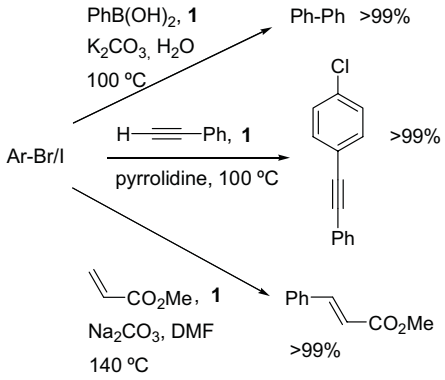
Encouraged by these results, we then focussed our attention to the application of so promising catalysts to the α-arylation of ketone enolates, the main issue of the present research.

On the basis of our experience in ketone α-arylation reactions, we considered that deoxybenzoins could be challenging substrates to accomplish initial arylation assays due to their steric hindrance at the α-position of the carbonyl group. Our reported conditions for the arylation of deoxybenzoins with $Pd(OAc)_2$ (Cs_2CO_3 as base in DMF)[9a] were initially applied to the α-phenylation of phenyl benzyl ketone replacing $Pd(OAc)_2$ with catalysts **1a**–**b**. The corresponding triarylethanone **3a** was obtained in good yields employing relatively low loadings (0.1 mol %) of both catalysts **1a** and **1b** (Table 1, entry 1). Moreover, the latter procedure was extended to a series of deoxybenzoins and bromoarenes affording target triarylethanones **3a**–**f** in high yields (entries 1–6). It is noteworthy that not only the coupling of electron-poor or neutral but also of electron-rich ketones and bromoarenes was effectively achieved.[15] In addition to the generality of the latest procedure regardless the electronic nature of the coupling partners, the excellent yields obtained with substituted aryl bromides relied on the total absence of by-products derived from phenyl–aryl exchange side reaction.[16]

In a similar fashion the selective monoarylation of symmetrical dialkyl ketone, cyclohexanone, with several aryl bromides was performed as shown in Table 1 (entries 7–9). Once the effectiveness of phosphinite palladacycles **1a**–**b** to arylate sterically hindered aryl alkyl ketones had been established (Table 1, entries 1–6), their ability to catalyze selective mono- or/and diarylation reactions of less hindered substrates was explored.[17] Accordingly, a careful search and development of experimental reaction conditions was performed with acetophenone and bromobenzene as substrates. The most remarkable results are shown in Table 1. Regioselective quantitative α-monoarylation of acetophenone was successfully accomplished with **1a** in the presence of either Cs_2CO_3 or K_3PO_4 in toluene at 130 °C (entries 10–11). Nevertheless, when using **1b**, a slightly better outcome was achieved with K_3PO_4 as base. Considering the shorter reaction times required by the latter procedure, it was elected to expand its scope by application to different substrates. A series of deoxybenzoins **5a**–**f** were thus prepared from the corresponding acetophenones and aryl bromides in good yields (entries 12–16), thus confirming the efficacy of pincer complexes **1** in such a controlled α-monoarylation. Moreover, selective diarylation of acetophenone was also attained under the latter reaction conditions after a reasonable increase of the amount of aryl bromide, base and reaction temperature (entry 17).[18] The application of the so-optimized diarylation procedure to different acetophenones and to 1-indanone afforded successfully target triarylethanones **3g**–**i** and **6** (entries 18–21).

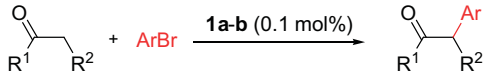
In view of the results summarized in Table 1, phosphinite pincer-type complexes **1a**–**b** have shown to be highly effective catalysts for the α-arylation of aryl and alkyl ketones. Despite the higher efficacy of the complex **1a** in α-monoarylation of acetophenones, in general there is no clear trend regarding catalytic activity between both phosphinite catalysts, providing target aryl ketones in similar yields.

If these results are compared with our previous works using the homogeneous $Pd(OAc)_2/PPh_3$ system or heterogeneous FibreCat™ catalysts,[9a–c] the procedures now introduced have led to higher overall yields for both activated and deactivated aryl bromides even decreasing the catalyst amounts from 2–5% to 0.1% (turnover numbers of 800–1000). It should be pointed out that, although some authors have reported higher TON values, it has been only for particular cases of monoarylation reactions, where in addition considerably longer reaction times were needed.[17,19] Therefore, we consider that the protocol presented in this letter constitutes a reliable methodology of general applicability for the α-arylation of ketone enolates.



Scheme 2.

Table 1. Ketone α-arylation catalyzed by PCP palladium pincer complexes **1a**–**b**[a,14]



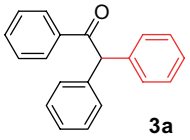
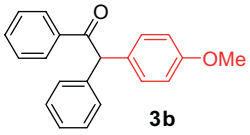
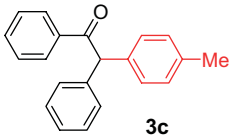
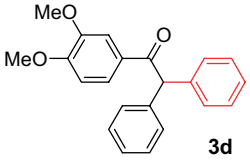
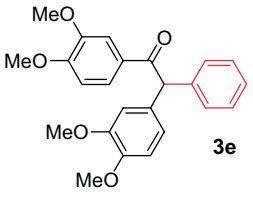
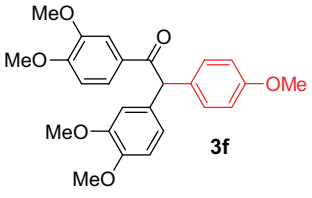
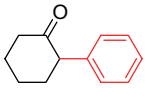
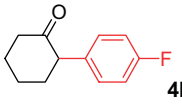
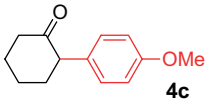
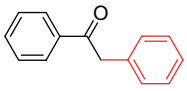
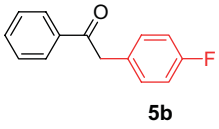
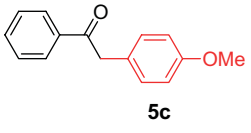
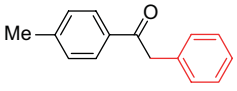
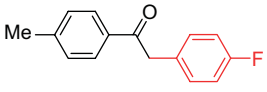
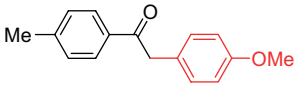
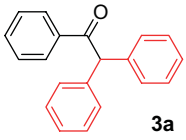
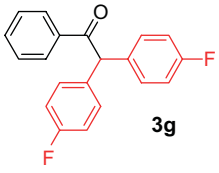
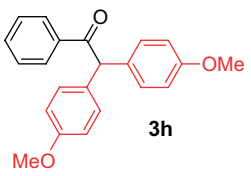
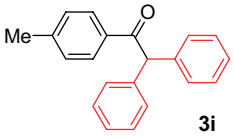
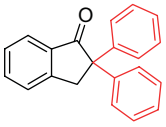
Entry	Product	Method	Yield (%)[b] 1a	1b
1	 **3a**	A	78	84
2	 **3b**	A	95	96
3	 **3c**	A	88	96
4	 **3d**	A[c]	92	95
5	 **3e**	A[c]	93	92
6	 **3f**	A[c]	95	91
7	 **4a**	A[c]	88	83[d]
8	 **4b**	A[c]	85	86[d]
9	 **4c**	A[c]	80	78[d]

Table 1 (*continued*)

Entry	Product	Method	Yield (%)[b] 1a	1b
10	 **5a**	B	>99	94
11		C	>99	88
12	 **5b**	B	>99	94
13	 **5c**	B	>99	93
14	 **5d**	B	>99	90
15	 **5e**	B	>99	91
16	 **5f**	B	>99	90
17	 **3a**	D	87	88
18	 **3g**	D	84	85
19	 **3h**	D	86	88

(*continued on next page*)

Table 1 (*continued*)

Entry	Product	Method	Yield (%)[b]	
			1a	**1b**
20	 **3i**	D	84	86
21	 **6**	D	89	89

[a] Method A: ketone (0.5 mmol), aryl bromide (0.5 mmol), Cs_2CO_3 (1.2 mmol), **1** (0.1 mol %), DMF (1 mL), 153 °C, 60 min. Method B: ketone (0.5 mmol), aryl bromide (0.5 mmol), K_3PO_4 (1.2 mmol), **1** (0.1 mol %), toluene (1 mL), 130 °C, 75 min. Method C: ketone (0.5 mmol), aryl bromide (0.5 mmol), Cs_2CO_3 (1.2 mmol), **1** (0.1 mol %), toluene (1 mL), 130 °C, 2 h. Method D: ketone (0.5 mmol), aryl bromide (1.05 mmol), K_3PO_4 (1.35 mmol), **1** (0.1 mol %), *o*-xylene (1 mL), 153 °C, 22 h.

[b] Determined by NMR on the basis of the amount of starting ketone. Bis(ethylene glycol) dimethyl ether was used as the internal standard.

[c] 75 min.

[d] Phenyl benzyl ketone was used as the internal standard.

In conclusion, PCP-bis(phosphinite) pincer complexes have proved to be not only highly active Heck, Suzuki and Sonogashira catalysts but also effective catalytic systems in ketone α-arylation reactions. The different procedures developed have allowed both regioselective monoarylation and diarylation of hindered and unhindered ketone enolates with a wide range of aryl bromides of dissimilar electronic activation. Future research is directed towards the immobilization of such powerful catalysts onto an insoluble support in order to get an easy recovery and reuse.

Acknowledgements

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11. NMR spectroscopy showed the products to be greater than 90% pure. *1,3-Bis(diisopropylphosphinito)-5-ethylbenzoate*. Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12–1.25 (27H, m, CH_3), 1.91–2.01 (4H, m, CH), 4.22 (2H, q, J 7.1 Hz, CH_2), 6.65 (1H, s, H2), 6.98 (2H, s, H4, H6). ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.23 (CH_3CH_2), 14.85, 16.05 (CH_3CH), 25.33 (m, CH), 60.63 (CH_2), 107.71 (m, C2), 108.14 (m, C4, C6), 131.86 (C5), 158.26 (m, C1, C3), 166.88 (CO). ^{31}P NMR (202 MHz, $CDCl_3$) δ 149.56. *1,3-Bis(diphenylphosphinito)-5-ethylbenzoate*. Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (3H, t, J 7.1 Hz, CH_3), 4.34 (2H, q, J 7.1 Hz, CH_2), 7.22 (1H, s, H2), 7.25 (2H, s, H4, H6), 7.36–7.41 (12H, m, H3′, H4′), 7.81–7.88 (8H, m, H2′). ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.88 (CH_3), 60.30 (CH_2), 107.59 (m, C2), 107.94 (m, C4, C6), 128.55 (m, C3′), 130.31 (m, C2′), 132.49 (C4′), 133.40 (C1′), 133.68 (C5), 158.15 (m, C1, C3), 166.54 (CO). ^{31}P NMR (202 MHz, $CDCl_3$) δ 112.62.
12. Compound **2a**: white solid, mp 130–130.5 °C (EtOAc). FTIR (neat film): 1713 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25–1.42 (27H, m, CH_3), 2.48 (4H, hep, J

7.2 Hz, CH), 4.32 (2H, q, *J* 7.1 Hz, CH_2), 7.22 (2H, s, H4, H6). ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.25 (CH_3CH_2), 16.57, 17.11 (CH_3CH), 28.76 (m, CH), 60.90 (CH_2), 107.08 (m, C4, C6), 130.74 (C5), 136.22 (m, C2), 165.88 (m, C1, C3), 166.11 (CO). ^{31}P NMR (202 MHz, $CDCl_3$) δ 188.52. Anal. Calcd for $C_{21}H_{35}ClO_4P_2Pd$: C, 45.42; H, 6.35. Found: C, 45.46; H, 6.33. Compound **2b**. white solid: mp 245.5–246 °C (EtOAc). FTIR (neat film): 1715 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.36 (3H, t, *J* 7.1 Hz, CH_3), 4.33 (2H, q, *J* 7.1 Hz, CH_2), 7.38 (2H, s, H4, H6), 7.47–7.60 (12H, m, H3′, H4′), 7.81–7.88 (8H, m, H2′). ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.23 (CH_3), 61.12 (CH_2), 108.34 (m, C4, C6), 116.2 (q, *J* 290.8 Hz, CF_3), 128.92 (m, C3′), 131.80 (m, C2′), 132.31 (C4′), 132.69 (C1′), 133.11 (C5), 133.52 (m, C2), 161.3 (q, *J* 35.9 Hz, $COCF_3$), 164.43 (m, C1, C3), 165.77 (COO). ^{31}P NMR (202 MHz, $CDCl_3$) δ 145.57. Anal. Calcd for $C_{35}H_{27}F_3O_6P_2Pd$: C, 54.67; H, 3.54. Found: C, 54.65; H, 3.58.

13. For these preliminary assays with phosphinite PCP catalysts, the reaction conditions were those employed in our previous work on NCN pincer catalysts. Accordingly, the amount of catalysts **1** employed in the three cases (Suzuki, Sonogashira and Heck couplings) was 10^{-1} mol % Pd. See Ref. 4 for more details. For a significant application of a related palladacycle to Heck reaction, see: Miyazaki, F.; Yamaguchi, K.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 7379–7383.
14. General procedure (Method A): A dry 5-mL round bottom flask was charged with the aryl bromide (0.5 mmol), ketone (0.5 mmol), catalyst **2** (0.0005 mmol Pd), Cs_2CO_3 (1.2 mmol) and dry DMF (1 mL). The mixture was stirred at 153 °C under argon for 1 h. After cooling, water (10 mL) was added, and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated in vacuo. The residue was dissolved in $CDCl_3$ and analyzed by ^1H NMR and ^{13}C NMR (using bis(ethylene glycol) dimethyl ether as an internal standard). For Methods B, C and D see Table 1. Selected examples: *2,2-Bis(4-fluorophenyl)-1-phenylethanone* **3g**:[9c] ^1H NMR (250 MHz, $CDCl_3$) δ 6.00 (1H, s), 7.02 (4H, ddd, *J* 8.7, 8.3, 1.9 Hz), 7.29 (4H, ddd, *J* 8.7, 5.5, 2.4 Hz), 7.39–7.45 (2H, m), 7.53 (1H, dddd, *J* 7.5, 7.1, 2.4, 1.6 Hz), 7.95–7.99 (2H, m). *1,2-Bis(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)ethanone* **3f**:[9c] ^1H NMR (250 MHz, $CDCl_3$) δ 3.73 (3H, s), 3.79 (3H, s), 3.81 (3H, s), 3.85 (3H, s), 3.86 (3H, s), 5.91 (1H, s), 6.78–6.85 (6H, m), 7.16 (2H, d, *J* 8.3 Hz), 7.57 (1H, s), 7.63 (1H, d, *J* 8.3 Hz). *1-(3,4-Dimethoxyphenyl)-2,2-diphenylethanone* **3d**:[20a] ^1H NMR (250 MHz, $CDCl_3$) δ 3.87 (3H, s), 3.90 (3H, s), 6.02 (1H, s), 6.82 (1H, d, *J* 8.3 Hz), 7.22–7.35 (10H, m), 7.58 (1H, s), 7.64 (1H, d, *J* 8.3 Hz). *2-(4-Fluorophenyl)-1-(4-methylphenyl)ethanone* **5e**:[20b] ^1H NMR (250 MHz, $CDCl_3$) δ 2.41 (3H, s), 4.23 (2H, s), 7.01 (2H, dd, *J* 8,7, 8,3 Hz), 7.21 (2H, dd, *J* 8.7, 5.5 Hz), 7.26 (2H, d, *J* 8.3 Hz), 7.80 (2H, d, *J* 8.3 Hz).
15. The yields of α-arylation of ketone enolates are generally lower for electron-rich coupling partners than for neutral or electron-deficient ones. (a) Palucki, M.; Buchwald, S. L. *J. Am. Soc. Chem.* **1997**, *119*, 11108–11109; (b) Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 4053–4056.
16. Phenyl migration or the phenyl/aryl exchange between an aryl halide/triflate and the phenyl group of PPh_3 is well documented and becomes a deleterious side-process in palladium-catalyzed arylation reactions. See Ref. 9b.
17. Several authors have reported arylations of such substrates, but in most cases featuring a lack of control of the reaction towards selective mono- or diarylation processes. See Ref. 15a. See also: Ehrentraut, A.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 209–217.
18. It should be taken into account that in addition to the higher amounts of bromobenzene (2.1 equiv) and base (2.7 equiv) needed for the diarylation reaction, the insertion of the second aryl group implies the arylation of a hindered ketone as deoxybenzoin requiring relatively higher temperatures.
19. (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Soc. Chem.* **1999**, *121*, 1473–1478; (b) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Soc. Chem.* **2000**, *122*, 1360–1370.
20. (a) Alesso, E. N.; Tombari, D. G.; Ibanez, A. F.; Bonafede, J. D.; Moltrasio, G. Y.; Aguirre, J. M. *An. Asoc. Quim. Argent.* **1987**, *75*, 393–401; (b) Kim, C. K.; Lee, I. *Bull. Korean Chem. Soc.* **1997**, *18*, 395–401.