

Palladium-catalyzed carbonylation of arylmethyl halides: efficient synthesis of arylacetic acid and esters

Ray V. H. Jones,^a W. Edward Lindsell,^{b,*} Daniel D. Palmer,^b
Peter N. Preston^{b,*} and Alan J. Whitton^a

^a*Syngenta, Earls Road, Grangemouth, Stirlingshire FK3 8XG, UK*

^b*Department of Chemistry, Heriot-Watt University, Riccarton, Edinburgh EH14 4AS, UK*

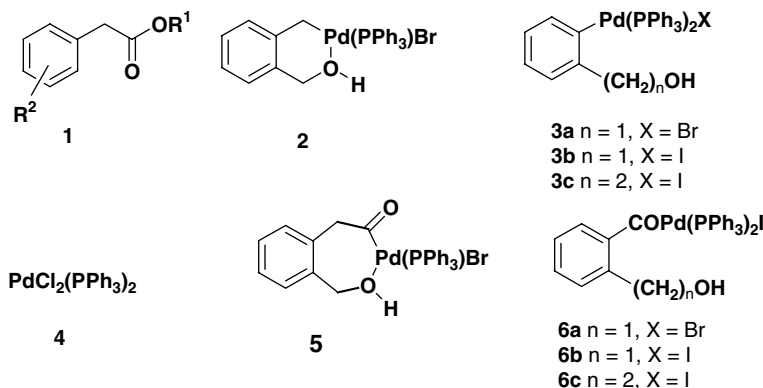
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Abstract—Organopalladium complexes derived from 2-(bromomethyl)benzenemethanol, 2-bromo- and iodobenzenemethanols and 2-iodobenzenethanol are efficient catalysts for the reaction of carbon monoxide and arylmethyl halides leading to arylacetic acids and esters.

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Phenylacetic acid (**1**, R¹ = R² = H) and its derivatives (e.g., **1**, R¹ = H; R² = alkyl, etc.), including related esters (e.g., **1**, R¹ = alkyl; R² = H, alkyl, etc.), are important industrial chemical intermediates. ‘Classical’ syntheses of arylacetic acids include the industrially important stoichiometric reaction of arylmethyl halides with metal cyanides to form analogous nitriles which are subsequently hydrolysed,¹ the (modified) Willgerodt–Kindler reaction (e.g., PhCOMe/S/*p*-toluenesulfonic acid/morpholine → PhCH₂CO₂H)² and the carboxylation of benzyl sodium.³ There is a continuing interest in cleaner syntheses of arylacetic acids (or esters)

through the reaction of carbon monoxide with arylmethyl halides catalyzed by organometallic compounds of rhodium,^{4–6} palladium^{1,8–10} and cobalt¹ in aqueous or alcoholic media. A drawback of published Pd-mediated reactions, however, is the requirement for relatively high working temperatures and pressures, for example, for synthesis of PhCH₂CO₂H or PhCH₂CO₂R from PhCH₂X (X = Cl or Br) and CO: R = Et, X = Cl, Br [cat. PdCl₂(PPh₃)₂], zeolite, 100 °C, 30 atm;⁷ R = H, X = Cl, [cat. PdCl₂], 130–150 °C, 30 atm;⁸ R = H, X = Br, [cat. PdCl₂(COD)], PNS, 130 °C, 5–10 atm;⁹ R = H, X = Cl [cat. Pd(OAc)₂], BINAS, 70–80 °C,



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* Corresponding authors. Tel.: +44 (0) 131 451 8035 (W.E.L./P.N.P.); fax: +44 (0) 131 451 3180 (W.E.L.); e-mail addresses: w.e.lindsell@hw.ac.uk; p.n.preston@hw.ac.uk

Table 1. Palladium-catalyzed carbonylation^a of arylmethyl halides in methanol

Substrate	Catalyst	Temp (°C)	Products ^b (%)		Unreacted starting material (%)
			ArCH ₂ CO ₂ Me	ArCH ₂ OMe	
PhCH ₂ Cl	2	55	99	0	0
PhCH ₂ Br	2	35	99	0	0
PhCH ₂ Br	4	55	74	11	15
4-MeC ₆ H ₄ CH ₂ Br	2	34	93	7	0
4-MeC ₆ H ₄ CH ₂ Br	4	50	59	36	5

^a See Ref. 13 for the general experimental procedure.

^b Products from reactions catalyzed by **2** are contaminated by 1,4-dihydro-3*H*-2-benzopyran-3-one (3-isochromanone) derived from the catalyst (cf. Ref. 11).

Table 2. Palladium-catalyzed carbonylation^a of benzyl halides in an aqueous (biphasic) medium

Substrate	Catalyst	Temp. (°C)	Products ^b (%)		Unreacted starting material (%)
			PhCH ₂ CO ₂ H	PhCH ₂ CO ₂ CH ₂ Ph	
PhCH ₂ Cl	2	61	91	4	5
PhCH ₂ Cl	4	71	60	9	30
PhCH ₂ Br	2	50	51	45	4
PhCH ₂ Br	4	53	65	32	1

^a See Ref. 14 for the general experimental procedure.

^b Products from reactions catalyzed by **2** are contaminated by 1,4-dihydro-3*H*-2-benzopyran-3-one (3-isochromanone) derived from the catalyst (cf. Ref. 11).

20 atm;¹ R = H, X = Cl, [cat. PdCl₂(PPh₃)₂], *n*-Bu₄NI, 95 °C, 5 atm.¹⁰ Also, the formation of by-products is observed in certain cases [e.g., PhCH₂OCH₂Ph, cf. Ref. 7; PhCH₂CO₂Ph cf. Ref. 9]; see also examples from the present work described below.

In this letter, we describe the use of new catalysts for this type of transformation in which lower temperatures and low pressures (1–4 bar) of carbon monoxide are employed; yields are almost quantitative and the formation of by-products is generally avoided. Catalysts **2**¹¹, **3a**,¹¹ **3b**¹² and **3c**¹¹ are equally effective and were initially evaluated in methanol solution for the syntheses of methyl arylacetates in comparison with [PdCl₂(PPh₃)₂] **4** under 3.45 bar CO pressure (e.g., see Table 1 for use of **2**). Catalyst **2** mediates almost quantitative conversion of benzyl chloride or bromide into methyl phenylacetate by comparison with the use of [PdCl₂(PPh₃)₂]; the latter catalyst requires higher working temperatures, effects lower conversions and by-products are formed. Catalyst **2** is also efficient for the 3.45 bar CO pressure carbonylation of benzyl chloride in an aqueous (biphasic) system, but benzyl bromide is an unsatisfactory substrate with the formation of benzyl phenylacetate being a competing pathway (see Table 2).

Experiments were then conducted at atmospheric pressure in a glass vessel fitted with a coarse sinter and a gas inlet. Carbon monoxide was introduced to generate a fine stream of bubbles such that additional stirring was unnecessary. Using methanol as solvent, the carbonylation of benzyl bromide afforded methyl phenylacetate quantitatively [catalyst **2** (5 mol %), *i*-PrNEt₂ (1.1 mol equiv), Ph₃P (10 mol %), 60 °C, 2 h]. Almost immediately the colourless mixture became deep orange and

gradually afforded a homogeneous pale yellow solution; formation of Pd-black was not observed. The transformation (PhCH₂Br → PhCH₂CO₂Me) was also achieved quantitatively using catalysts **3a–c** under identical conditions to those described above using **2**. Furthermore, all four catalysts (**2**, **3a–c**) proved to be equally efficient for the carbonylation of a series of benzyl halide derivatives [viz: XC₆H₄CH₂Br; X = 2-Br; 2-CH₂Br {affording C₆H₄(CO₂Me)₂}; 2-NO₂; 4-Me; and 2-(bromomethyl)naphthalene]. In general, the desired methyl esters were formed in quantitative yields except for one example [viz. 2-(bromomethyl)naphthalene using catalyst **3c** gave an 88% yield of the ester but also two by-products, [2-C₁₀H₇CH₂OMe (4%) and 2-C₁₀H₇CHO (4%)].

We have recently shown that compounds **2**, **3a,b** and **3c** react rapidly with carbon monoxide to form labile acyl complexes (probably **5**, **6a,b** and **6c**, respectively) with short lifetimes (ca. 0.5 h) in solution at ambient temperature.¹¹ It is probable that complexes **2**, **3a,b** and **3c** are ‘pre-catalysts’, serving to generate active catalytic species through the acyl intermediates (**5**, **6a,b** and **6c**) under relatively mild conditions.

The high yields and selectivity achievable with catalysts **2**, **3a–c** together with the use of low pressures (1–4 bar) of carbon monoxide provide incentives for investigation of industrial-scale syntheses of phenylacetic acid and derived esters through this route.

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13. General experimental procedure using low CO pressure (Table 1): PhCH₂Br (44.4 mmol), *i*-PrNEt₂ (88.8 mmol), PPh₃ (0.88 mmol), catalyst **2** (0.42 mmol) and methanol were charged to a Parr autoclave. The reaction was conducted under CO pressure (3.45 bar) at 35 °C (CO uptake began at 28 °C) for 2 h. The product, a homogeneous orange liquor, was shown (GC) to contain PhCH₂CO₂Me (99%) with no evidence for the formation of PhCH₂OMe. The major product was isolated by evaporating the solvents under reduced pressure and eluting the ester by flash chromatography (silica gel, Et₂O eluent); the product was identified (¹H NMR, IR, and GC–MS) by comparison with an authentic sample. For a comparative experiment with [PdCl₂(Ph₃P)₂], the above procedure was repeated with the temperature adjusted in the light of onset of CO uptake.
14. General experimental procedure (Table 2). The reactions were performed as outlined in Ref. 13 with methanol solvent replaced by a biphasic mixture (1:1 by volume) of water and 2-methyl-2-butanol.