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Letter

Carbonylation reactions
7. Regioselective synthesis of 2-arylpropionic acids by catalytic carbonylation of styrene derivatives in the presence of palladium compounds: the critical role of the counter anion

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Abstract

The regioselectivity of alkoxycarbonylation of 1-arylethanols catalysed by Pd/acid systems is very sensitive to the nature of the counter anion of the acid: chloride anion favours branched products while tetrafluoroborate and sulfonates anions favour linear products, the latter ones enhancing also product yields. Alkoxycarbonylation of styrenes is also sensitive to the nature of the counter anion. © 1999 Elsevier Science B.V. All rights reserved.

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Carbonylation of allyl ethers in the presence of the catalytic system $[(\eta^3\text{-}C_3H_5)PdCl]_2/HCl$ was shown to proceed smoothly with the formal insertion of carbon monoxide into the allylic bond to provide only the corresponding terminal esters [1,2]. Our aim was to transpose such a system to benzylic substrates, and to achieve high regioselectivities for either linear or branched esters (Scheme 1). We have shown that carbonylation of 1-phenylethyl esters and ethers (e.g., **1a**, **1b**) proceeds under relatively mild conditions with a catalytic system made of $PdCl_2(PPh_3)_2$ and $HBF_4 \cdot OEt_2$ [3]. Although the yields are moderate, the regioselectivity for the linear isomer is good. Optimisation of the process by changing the benzylic derivative (1-phenylethanol **1c** instead of **1a** or **1b**) and reaction conditions leads to an increase in the yield of carbonylation products up to 65%, with the same regioselectivity: 20% of the branched products **2** and 80% of the linear ones **3**. In the case of allyl ethers, we noticed that proton and chloride ions are essential to obtain esters, although the additional presence of weakly coordinating anions like BF_4^- increases the reaction

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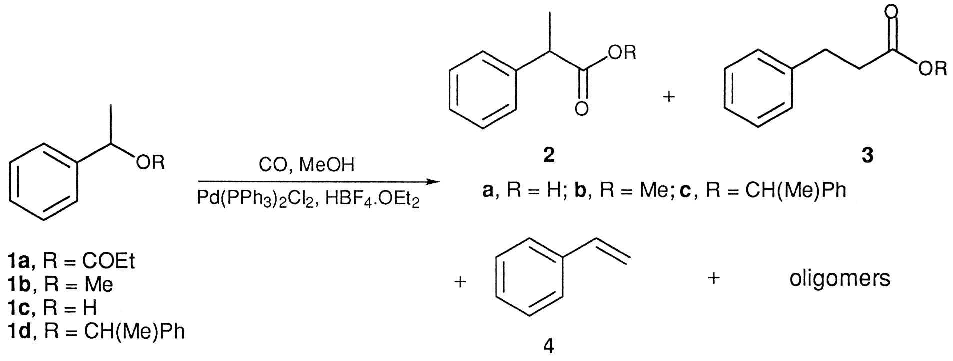


Scheme 1.

rate [4]. This observation prompted us to examine the nature of the counter anion of the acid used as co-catalyst in the carbonylation of **1c** and to extend this study to styrene. We report here on the critical role of this counter anion on product selectivities and activities which is not identical for both substrates.

Carbonylation of **1c** only occurs in the presence of phosphine complexes of palladium(II) which can be generated in situ. However, under the standard reaction conditions used (**1c**: MeOH:$HBF_4 \cdot OEt_2$:[Pd] = 50:50:5:0.5, $p_{CO} = 50$ bar, $T = 90°C$, $t = 6$ h), only triarylphosphines (e.g., PPh_3, P(*m*-tol)$_3$) are efficient ancillary ligands for the carbonylation reaction. Alkylphosphines (e.g., PCy_3, PBz_3), diphosphines (e.g., DPPE, DPPB), phosphites (e.g., $P(OEt)_3$, $P(OPh)_3$) induce the production of **1b** and styrene oligomers. In the absence of methanol, the reaction proceeds with a low yield of **2** (3%, **2a**:**2c** = 63:37) and **3** (8%, **3a**:**3c** = 76:24), the major product being oligomers (72%). The presence of methanol depress the formation of oligomers (9%) and provides **2** (5%, **2a**:**2b**:**2c** = 14:80:6) and **3** (20%, **3a**:**3b**:**3c** = 13:83:4) in addition to **1b** (61%). The reaction also occurs in water and ethanol with the same regioselectivity (**2**:**3** ~ 20:80). Increasing the amount of methanol favours the formation of **1c**. Addition of solvents leads to variable trends: toluene provides a similar yield of carbonylation products (21%) but improves the regioselectivity for the linear ones (**2**:**3** = 10:90); dichloromethane has no effect on yield but sharply decreases the formation of oligomers. However, coordinating solvents like tetrahydrofurane or dimethylacetamide strongly disfavour the carbonylation process: the substrate is almost quantitatively converted to **1b**. Finally, examination of the effects of temperature and pressure shows that an optimal set for these parameters could be achieved. Low temperatures favours the formation of **1b**; conversely, high temperatures increase the amount of oligomers. The optimal temperatures lie in the range 90–110°C. At 90°C, an increase of carbon monoxide pressure up to 50 bar improves the yield of **2** and **3** mostly at the expense of oligomers, but higher pressures reduce these yields, owing to competition for coordination on the palladium centre.

As reported for the carbonylation of **1a**, the presence of tetrafluoroboric acid is essential [3]. No reaction occurs in the absence of $HBF_4 \cdot OEt_2$. As shown in Table 1, an increase of the amount of acid leads first to an increase of the yields of **2** and **3**, but competition between the palladium-based carbonylation and the proton-based oligomerisation process favours then the oligomerisation process. However, combining higher amounts of catalyst and co-catalyst with longer reaction time enhances the yield of carbonylation products, therefore indicating that **1b** can be converted into **2** and **3**.

Table 1
Carbonylation of 1-phenylethanol **1c**: influence of tetrafluoroboric acid concentration

Run	**1c**	Amount (mmol)		Reaction time (h)	Conv. (%)	Product yields (%)			Selectivity (%)
		[Pd]	$HBF_4 \cdot OEt_2$			**2 + 3**	**1b**	Oligomers	**2**/(**2 + 3**)
1	50	0.5	5	6	97	24	67	4	19
2	50	0.5	10	6	99	47	1	50	21
3	50	0.5	20	6	99	9	–	90	23
4	25	0.5	5	6	98	49	13	33	22
5	12.5	0.5	5	6	99	20	6	72	21
6	50	1	5	6	94	26	58	7	15
7	50	0.25	5	6	96	25	56	11	19
8	50	0.125	5	6	97	14	56	22	21
9	50	1	10	24	99	64	2	32	21

Reaction conditions: [Pd] = $PdCl_2(PPh_3)_2$; [**1c**]:[MeOH] = 1:1; CH_2Cl_2 = 10 ml; p_{CO} = 50 bar; T = 90°C.

Similar results are observed with the use of $BF_3 \cdot OEt_2$ and Ph_3CBF_4 as acid sources since they are generating the same counter anion (Table 2) in the presence of methanol. It has been reported that addition of $SnCl_2$ to dichloroplatinum [5,6] or palladium complexes [7] increases the regioselectivity for the linear acid or ester in olefin carbonylation owing to the formation of a trichlorostannyl ligand. In the present case, addition of tin(II) chloride only changes the distribution between **1b** and oligomers (run 12). Sulfonic acids leads to a dramatic change in catalytic activity for carbonylation (runs 13, 14). Although trifluoromethane sulfonic acid is still producing significant amounts of oligomers, the combined yields of **2** and **3** are now 65%. The use of *p*-toluene sulfonic acid gives similar yields but its lower acidity limits the formation of oligomers: **1b** is obtained instead. However, in both cases carbonylation products selectivities are the same as with tetrafluoboric acid. Monitoring the reaction by GC indicates that an induction period is necessary for the formation of the catalytically active species. In the early stages of the reaction **1b** and **1d** are produced and are significantly converted into **2** and **3** after 3 h, the consumption of **1d** being faster. The methyl esters **2b**, **3b** are formed first, the acids and 1-phenylethyl esters appearing after 2–3 h. Small amounts of styrene are produced but not accumulated due to their consumption for carbonylation and/or oligomerisation.

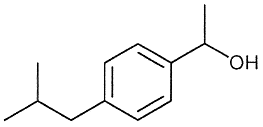
Finally, it should be pointed out that under the same conditions, HCl, which has been

Table 2
Carbonylation of 1-phenylethanol **1c**: influence of acids and additives

Run	Acid	Additive (mmol)	Conv. (%)	Product yields (%)			Selectivity (%)
				2 + 3	**1b**	Oligomers	**2**/(**2 + 3**)
1	$HBF_4 \cdot OEt_2$	–	97	24	67	4	19
10	$BF_3 \cdot OEt_2$	–	96	24	63	2	16
11	Ph_3CBF_4	–	97	22	66	7	20
12	$HBF_4 \cdot OEt_2$	$SnCl_2$ (1.2)	99	18	29	48	22
13	CF_3SO_3H	–	99	65	2	26	21
14	*p*-TsOH	–	98	62	28	4	22
15	HCl	–	61	6	49	1	73
16	*p*-TsOH	LiCl (5)	90	10	72	6	50

Reaction conditions: [Pd] = 0.5 mmol; [**1c**] = [MeOH] = 50 mmol; [acid] = 5 mmol; CH_2Cl_2 = 10 ml; p_{CO} = 50 bar; T = 90°C; t = 6 h.

claimed to be a co-catalyst for the carbonylation of 1-(4-*i*-butylphenyl)ethanol **5** into the branched carboxylic acid [8] leads to a low conversion of **1c** but with the expected regioselectivity (run 15). It is noteworthy that addition of lithium chloride to *p*-toluene sulfonic acid depletes both activity (compared to *p*-TsOH) and regioselectivity (compared to HCl) (Scheme 2).



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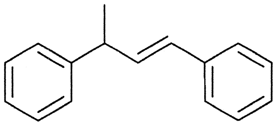

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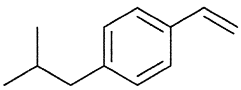

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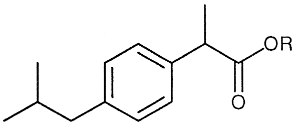

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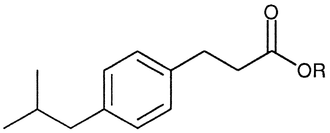

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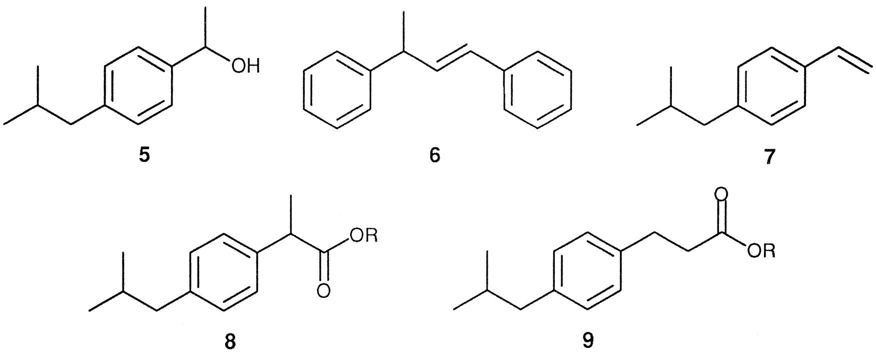
a, R = H; **b**, R = Me; **c**, R = Et



a, R = H; **b**, R = Me; **c**, R = Et

Scheme 2.

Table 3
Carbonylation of arylethenes

Run	Substrate	[Pd] (mmol)	Acid	ROH (ml)	Conv. (%)	Products (yield %)	Selectivity (%) (**2**/(**2** + **3**) or **8**/(**8** + **9**))
17[a]	**4**	0.5	$HBF_4 \cdot OEt_2$	MeOH (2)	100	**2** + **3** (11)	44
18	**4**	0.25	$BF_3 \cdot OEt_2$	MeOH (40)	98	**2** + **3** (90)	46
19	**4**	0.25	$BF_3 \cdot OEt_2$	EtOH (40)	98	**2** + **3** (92)	82
20	**7**	0.125	$BF_3 \cdot OEt_2$	MeOH (20)	97	**8** + **9** (70)	74
21	**7**	0.07	$BF_3 \cdot OEt_2$	MeOH (10)	97	**8** + **9** (54)	85
22[a]	**5**	0.5	TsOH[b]	MeOH (2)[c]	99	**8** + **9** (60)	43

Reaction conditions: [Pd] = $PdCl_2(PPh_3)_2$; [Substrate]:[Pd] = 100; [Pd]:[acid] = 5; p_{CO} = 50 bar; T = 90°C; t = 18 h.

[a] t = 6 h.

[b] [TsOH] = 5 mmol.

[c] CH_2Cl_2 = 10 ml.

The observation of trace amounts of styrene in the course of the reaction may explain the formation of the oligomers, the first one being characterised as *trans*-1,3-diphenyl-but-1-ene **6**, but it may also intervene in the carbonylation process. In fact, the carbonylation of styrene has been reported in the case of palladium with various phosphines, diphosphines [9–16] and hydrogenophosphates [17]. In practically all the examples reported, a source of proton is required (i.e., HCl, F_3CCO_2H, $BF_3 \cdot OEt_2$–ROH). Table 3 indicates that the regioselectivity for carbonylation swings from **3** to **2**. Changing the nature of the acid co-catalyst and the amount of alcohol improves the yields of **2** and **3**. Moreover, ethanol provides a higher regioselectivity for **2**. A similar reaction occurs with 4-*i*-butylstyrene **7**, the precursor of ibuprofene **8a**: the regioselectivity is again improved by comparison with the one observed for 1-(4-*i*-butylphenyl)ethanol (run 22).

In conclusion, we have shown that regioselectivity in carbonylation of 1-phenylethanol, 1-(4-*i*-butylphenyl)ethanol, styrene and 4-*i*-butylstyrene is very sensitive to the nature of the counter anion of the acid used as co-catalyst. Under similar reaction conditions, coordinating anions like chloride favours the formation of branched acids, but with low activity; weakly coordinating anions favours the formation of linear acids, but may enhance activity. These observations suggest that the reaction mechanisms for carbonylation of these aryl alcohols and olefins are different. Work is in progress to develop more selective and active catalytic systems and to provide mechanistic information.

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