Highly efficient catalyst system for the synthesis of 2-arylpropionic acids by carbonylation

A. Seayad, S. Jayasree and R.V. Chaudhari [*]

Homogeneous Catalysis Division, National Chemical Laboratory, Pune 411008, India
E-mail: rvc@ems.ncl.res.in

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Carbonylation of 1-(4-isobutylphenyl)ethanol has been studied using a homogeneous catalyst system consisting of $PdCl_2(PPh_3)_2$/TsOH/LiCl. Higher reaction rates with TOF up to 1200 h^{-1} and ibuprofen selectivity $>95\%$ have been achieved at 388 K under a CO partial pressure of 5.4 MPa. The reaction proceeds through the formation of 4-isobutylstyrene and 1-(4-isobutylphenyl)ethyl chloride as intermediates. The same catalyst system is shown to be effective for carbonylation of various α-arylethanols, vinyl aromatics and corresponding chloro derivatives.

Keywords: carbonylation, 1-(4-isobutylphenyl)ethanol, ibuprofen, naproxen, styrene, palladium, 2-arylpropionic acids

1. Introduction

2-arylpropionic acids are a class of non-steroidal anti-inflammatory drugs, ibuprofen and naproxen being the important members of this family [1]. Carbonylation technology provides an environmentally benign process for their synthesis [2]. Hoechst Celanese corporation has commercialised a process at Texas [3] in 1992 for the production of ibuprofen based on a three-step catalytic process in which carbonylation of 1-(4-isobutylphenyl)ethanol (IBPE) is the key step. The carbonylation step uses bis(triphenylphosphino)dichloro palladium as the catalyst precursor in a biphasic medium consisting of IBPE in methyl ethyl ketone (MEK) as the organic phase and 10% HCl as the aqueous phase [4]. The desired high selectivity ($>95\%$) for ibuprofen was obtained in this process at 16–35 MPa, but at lower pressures (6.8 MPa), the selectivity to ibuprofen is reported to be around 67% [5]. The turnover frequency (TOF) was found to be 50–70 h^{-1} even at high pressures (35 MPa). Recently, Sheldon et al. [6] have reported carbonylation of IBPE using water soluble palladium complexes in a biphasic system. This system also has the disadvantages of lower reaction rates (TOF $= 2.3$ h^{-1}) and lower selectivity (72%). In another study, 95–98% selectivity to ibuprofen was obtained from 4-isobutylstyrene by carboxylation using a palladium catalyst along with copper salts [7] but the reaction rates were very low (0.5–2 h^{-1}).

In most of the previous reports on carbonylation of IBPE, two-phase catalyst systems have been employed; either the catalyst and the substrate are in the organic phase with HCl promoter in the aqueous phase, or the catalyst in the aqueous phase and the substrate in the organic phase. In all these cases, lower reaction rates (0.5–60 h^{-1}) are reported and a high selectivity for ibuprofen was achieved only at very high pressure (16–35 MPa). Here, we report an efficient homogeneous palladium catalyst system for the carbonylation of IBPE to ibuprofen with significantly enhanced catalytic activity and selectivity under lower pressure conditions. Turnover frequencies (TOF) up to 1200 h^{-1} and ibuprofen (IBN) selectivities $>95\%$ have been achieved at 388 K and 5.4 MPa of CO partial pressure using a $PdCl_2(PPh_3)_2$ catalyst along with p-toluenesulphonic acid (TsOH) and lithium chloride as promoters. It is shown that the reaction proceeds through 4-isobutylstyrene (IBS) and 1-(4-isobutylphenyl)ethyl chloride (IBPCl) as intermediates. 1-(4-isobutylphenyl)ethyl chloride was confirmed to be the active substrate that undergoes carbonylation to yield ibuprofen.

2. Experimental

2.1. Preparation of IBPE

IBPE was prepared from isobutylbenzene by a two-step process which involves acylation of isobutylbenzene to p-isobutylacetophenone followed by reduction of p-isobutylacetophenone. For the acylation step, isobutylbenzene was slowly added under vigorous stirring to a solution of acetyl chloride and anhydrous $AlCl_3$ in dichloromethane at 0–5 °C. After 4–5 h of stirring, the reaction was quenched by pouring the reaction mixture to ice. The aqueous layer was re-extracted with dichloromethane and the combined organic layer was washed with saturated brine and then with saturated sodium bicarbonate. The washed dichloromethane layer was then dried using anhydrous sodium sulphate, concentrated and distilled under reduced pressure to yield p-isobutylacetophenone.

The reduction of p-isobutylacetophenone was carried out using sodium borohydride. Sodium borohydride was added

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[*] To whom correspondence should be addressed.

to a solution of p-isobutylacetophenone in methanol under ice bath. After 1 h of continuous stirring, the reaction mixture was treated with diluted HCl and extracted with dichloromethane. The dichloromethane layer was washed with brine, dried over anhydrous sodium sulphate, concentrated and vacuum distilled to yield pure p-isobutylphenylethanol.

2.2. Preparation of IBPCl

IBPCl was prepared from IBPE. A solution of IBPE in chloroform was treated with 1.2 equivalents of $SOCl_2$ under ice bath and kept for stirring at room temperature. After 10 h, the reaction was quenched by adding the reaction mixture to ice. The aqueous layer was re-extracted with chloroform and the chloroform layer was washed several times with distilled water, dried using anhydrous sodium sulphate, concentrated and vacuum distilled to yield pure IBPCl.

2.3. Preparation of IBS

IBS was prepared by the acid-catalysed dehydration of IBPE. p-toluenesulphonic acid was added to a solution of IBPE in chloroform and was vigorously stirred at 80 °C. After 2 h, the reaction mixture was cooled, washed with distilled water several times, dried, concentrated and vacuum distilled to yield pure 4-isobutylstyrene.

The carbonylation reactions were carried out in a Parr Hastelloy C autoclave (50 ml). In a typical reaction, known quantities of the substrate, catalyst, ligand, promoters, water and the solvent were charged to the autoclave. The contents were flushed few times with nitrogen followed by carbon monoxide and heated to the desired temperature. After attaining the temperature, the autoclave was pressurised with CO and the reaction was started by agitation (1000 rpm). To maintain the pressure in the reactor, CO was fed through a constant-pressure regulator from a reservoir vessel. The pressure drop in the reservoir vessel was recorded by means of a pressure transducer. Intermediate liquid samples were also taken at regular intervals of time. The reaction was continued until the CO absorption was stopped. After the reaction, the autoclave was cooled to room temperature, CO de-pressurised, flushed with nitrogen and the reaction mixture removed. The analysis of the liquid samples was carried out using a gas chromatograph (HP 5890) with a HP-FFAP capillary column. The products were further confirmed by GC-MS, NMR and IR analysis.

3. Results and discussion

In the course of our preliminary studies on the carbonylation of IBPE using $PdCl_2(PPh_3)_2$ as the catalyst and 10% aqueous HCl as a promoter, we found that 4-isobutylstyrene (IBS) and 1-(4-isobutylphenyl)ethyl chloride (IBPCl) were formed as the reaction intermediates. The possible substrate that undergoes carbonylation can be IBS or IBPCl, formation of both requires the presence of an acidic promoter. Under biphasic conditions, the solubility of HCl in the organic phase will be limited and, hence, the rate of formation of IBS and IBPCl. In order to reduce these limitations, we tried to homogenise the medium by using organic acid promoters. With p-toluenesulphonic acid (TsOH) as the promoter we obtained IBS as the major intermediate product with only traces of ibuprofen as the carbonylation product. Hence, it was assumed that the carbonylation reaction might be going through IBPCl, which can be formed from IBS. To facilitate the formation of IBPCl, lithium chloride was added as the halide promoter along with p-toluenesulphonic acid, which resulted in a dramatic enhancement in the carbonylation reaction rate (TOF of 850 h^{-1}) with high ibuprofen selectivity (>95%). A typical concentration–time profile for this reaction is shown in figure 1. It is clear from these results that immediate dehydration of IBPE to IBS occurs under the reaction conditions and concentration of IBPCl remained very low. In order to confirm the reaction pathway, individual reactions were carried out using IBS and IBPCl as substrates and the results are presented in table 1. No carbonylation product was obtained when IBS was used as the substrate in the presence of TsOH as the promoter without any added halide promoter, after 1 h of reaction. But traces of ibuprofen were obtained after 6 h of reaction. In the presence of both the acid and halide promoters (TsOH/LiCl), the rate of carbonylation of IBS was very much enhanced (TOF of 1150 h^{-1}). This clearly indicates that IBPCl is the major active substrate, which undergoes carbonylation. To further clarify this point, direct carbonylation of IBPCl was carried out. Without any added promoter the reaction was too slow (TOF = 30 h^{-1}; run 4, table 1), but on addition of excess TsOH alone, most of the IBPCl was

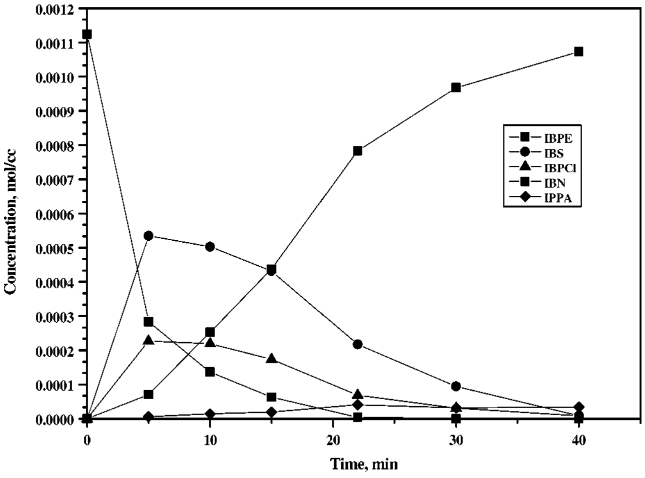


Figure 1. Concentration–time profile for the carbonylation of IBPE. Reaction conditions: IBPE, 28.1 mmol; $PdCl_2(PPh_3)_2$, 0.056 mmol; PPh_3, 0.112 mmol; TsOH, 11.2 mmol; LiCl, 11.2 mmol; water, 1.2 ml; solvent, MEK; $T = 115\,^\circ C$; $P_{CO} = 5.4$ MPa. IBN = 2-(4-isobutylphenyl)-propionic acid (ibuprofen), IPPA = 3-(4-isobutylphenyl)propionic acid.

found to be converted to IBS. To prevent the formation of IBS, the acidity of the reaction medium was lowered by reducing the TsOH concentration to catalytic amounts (TsOH/Pd = 5), which resulted in complete conversion of IBPCl to ibuprofen (95.8%), with a TOF of 125 h^{-1} (see run 5, table 1). This shows that under highly acidic conditions IBPCl undergoes dehydrohalogenation to form IBS which is not getting carbonylated in the absence of halide promoters. On addition of LiCl in equivalent amount of TsOH, the carbonylation reaction occurred with a TOF of 1120 h^{-1} (run 6, table 1). These observations confirm that the active substrate undergoing carbonylation is IBPCl, which is formed from IBPE through IBS, as schematised in scheme 1.

This catalyst system consisting of $PdCl_2(PPh_3)_2$/TsOH/LiCl is also applicable to various α-arylethanols, vinyl aromatics and corresponding chloro derivatives, as evident from table 1. In general, the vinyl aromatics and the chloro derivatives showed better reaction rates compared to their alcohol analogues. *Sec*-phenethyl alcohol (**1b**) showed very low reaction rates as compared to IBPE (**1a**). But the reaction rates of styrene (**2b**) and 4-isobutylstyrene (**2a**) were almost equal. Another interesting substrate is 1-(6-methoxynaphthyl)ethanol (**1c**) which gave naproxen, 2-(6-methoxynaphthyl)propionic acid, in good yields even though the reaction rate was comparatively lower (215 h^{-1}). In all the cases, the selectivity of the branched product was very high (95–98%).

The rate of carbonylation of IBPE was found to increase linearly with concentration of promoters (TsOH and LiCl) as well as partial pressure of CO and concentration of IBPE with ibuprofen selectivity in the range of 91–97% (table 2). In acetone as a solvent, the reaction rate was slightly higher (TOF = 1220 h^{-1}) compared to methyl ethyl ketone (TOF = 850 h^{-1}). Different acid and halide promoters were investigated, from which the TsOH/LiCl combination was found to be the best. The results are presented in table 2.

An interesting observation was that homogeneous reaction using concentrated HCl as the promoter instead of TsOH/LiCl gave only lower activity (TOF = 90 h^{-1}; run 12, table 2) even though IBPCl was formed in sufficient concentrations (see figure 2). From this we can infer that both TsOH and LiCl play important roles in the formation of active catalyst from the precursor $PdCl_2(PPh_3)_2$. To make this point clear, experiments were conducted by doubling the concentration of TsOH without increasing the amount of LiCl. This resulted in doubling the initial rate

Table 1
Carbonylation of different substrates.[a]

Sl. No.	Substrate	Time (min)	Conversion (%)	Selectivity (%) 4	5	TOF (h^{-1})
1	**1a**	35	99	96.2	3.7	850
2	**2a**[b]	360	–	traces	–	–
3	**2a**	30	99	97.0	2.8	1150
4	**3a**[c,d]	140	77	96.3	3.1	30
5	**3a**[b,c,e]	50	98	96.8	3	125
6	**3a**[f]	30	99	97.1	2.8	1120
7	**1b**	55	90	95.2	4.3	510
8[h]	**2b**	40	99	97	2.8	1220
9	**1c**	140	98	97.2	1.6	215

[a] Substrate = 28.1 mmol; $PdCl_2(PPh_3)_2$ = 0.056 mmol; water = 1.2 ml; P_{CO} = 5.4 MPa; T = 388 K; solvent = methyl ethyl ketone (MEK); TsOH/LiCl = 11.2 mmol.

[b] No LiCl.

[c] Substrate = 5.62 mmol.

[d] No promoters.

[e] TsOH/Pd = 5.

[f] Substrate = 12.78 mmol.

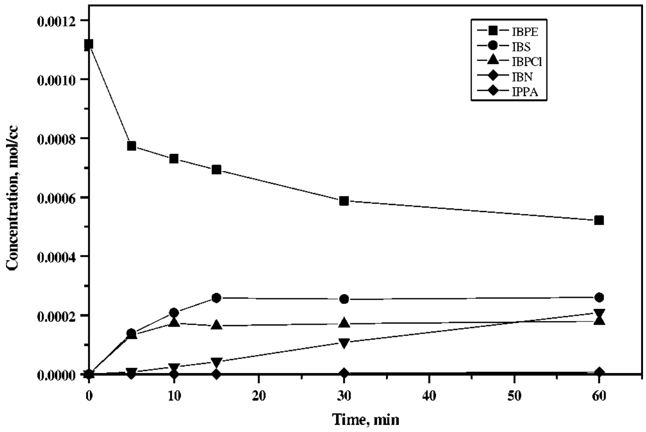
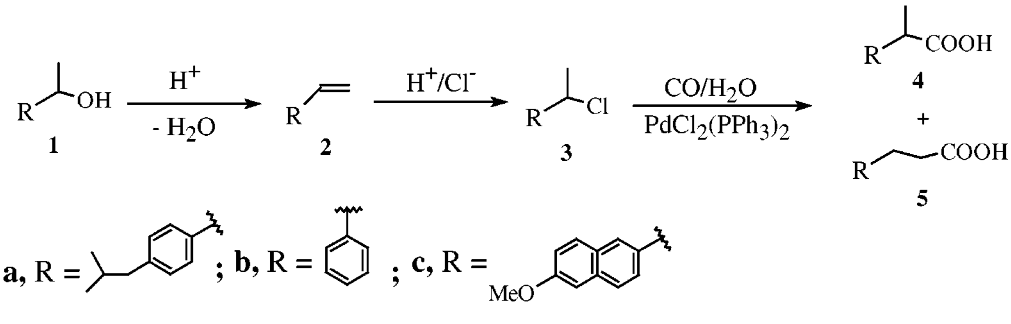


Figure 2. Concentration–time profile for the carbonylation of IBPE using HCl promoter. Reaction conditions: IBPE, 28.1 mmol; $PdCl_2(PPh_3)_2$, 0.056 mmol; PPh_3, 0.112 mmol; HCl, 5.6 mmol; water, 1.2 ml; solvent, MEK; T = 115 °C; P_{CO} = 5.4 MPa. IBN = 2-(4-isobutylphenyl)-propionic acid (ibuprofen), IPPA = 3-(4-isobutylphenyl)propionic acid.



Scheme 1.

Table 2

Catalytic carbonylation of IBPE under homogeneous conditions.[a]

Sl. No.	TsOH/LiCl (mmol)	H^+/substrate (molar ratio)	Time (min)	Conversion (%)	Selectivity (%)		TOF (h^{-1})
					4	**5**	
1	11.2	0.398	35	100	96.2	3.7	850
2	5.6	0.199	75	99.5	96.2	3.7	405
3	11.2/5.6	0.398	35	90	93.5	6	950
4	5.6/11.2	0.199	230	96	97.5	2.4	125
5	2.8	0.099	250	95	91.7	8.0	100
6[b]	11.2	0.398	30	100	97.5	2.4	1005
7[c]	11.2	0.398	110	95	88.0	11.5	256
8[d]	11.2	0.199	50	96	88.0	11.5	1120
9[e]	11.2	0.796	40	99	96.3	3.6	375
10[f]	11.2	0.398	165	97	92.5	7	177
11[g]	11.2	0.398	50	100	95.7	4.2	1210
12[h]	11.2	0.398	350	95	93.1	2.9	90
13[i]	5.6	0.199	150	97	97	2.8	205
14[j]	5.6	0.199	130	98	96	3.7	228
15[k]	5.6	0.199	135	98	96.5	3.3	223

[a] Substrate = 28.1 mmol; $PdCl_2(PPh_3)_2 = 0.056$ mmol; water = 1.2 ml; $P_{CO} = 5.4$ MPa; $T = 388$ K; solvent = methyl ethyl ketone (MEK).

[b] $P_{CO} = 7.48$ MPa.

[c] $P_{CO} = 1.36$ MPa.

[d] **1a** = 56.18 mmol.

[e] **1a** = 14.04 mmol.

[f] Methane sulphonic acid instead of TsOH.

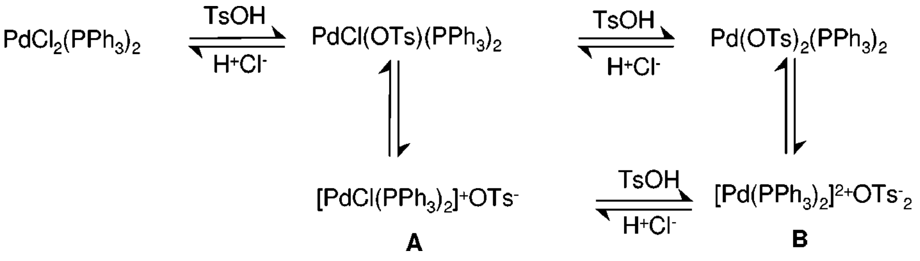
[g] Acetone instead of MEK.

[h] HCl instead of TsOH/LiCl.

[i] NaCl instead of LiCl.

[j] KCl instead of LiCl.

[k] Bu_4NH_4Cl instead of LiCl.



Scheme 2.

of the reaction (TOF = 950 h^{-1}; run 3, table 2). In this case, a major part of the catalyst was found to be precipitated to Pd metal after the reaction. In contrast, by doubling the LiCl concentration without increasing TsOH concentration, the reaction rate decreased (TOF = 125 h^{-1}; run 4, table 2), even though the effective formation of IBPCl was observed. In this case, no Pd metal precipitation was observed, but a crystalline precipitate of the catalyst precursor, $PdCl_2(PPh_3)_2$, was observed in the final reaction mixture. These observations support the possible involvement of TsOH in the formation of active catalytic species. It is well known in the literature [8] that the active catalyst in this type of reactions is the Pd(0) complex and the catalytic cycle is initiated by the oxidative addition of organic halide to the Pd(0) species. At higher OTs^- concentrations, it is possible that the chloride ligands in $PdCl_2(PPh_3)_2$ are exchanged with OTs^- ions as illustrated in scheme 2.

The weakly coordinating nature of OTs^- may facilitate easy formation of Pd(0) species from **A** or **B** compared to $PdCl_2(PPh_3)_2$, through a kind of water–gas shift reaction, as represented in equation (1):

$$\left[Pd(PPh_3)_2\right]^{2+}OTs_2^- \xrightarrow[-TsOH/CO_2]{CO/H_2O} \underset{\mathbf{C}}{HPd(OTs)(PPh_3)_2} \leftrightharpoons \underset{\mathbf{D}}{Pd(PPh_3)_2} + TsOH \tag{1}$$

Under acidic conditions, the equilibrium in equation (1) can shift towards the hydrido palladium species, **C** [9], which may be responsible for trace amount of carbonylation products in the case of isobutylstyrene even in the absence of added LiCl (run 2, table 1). The palladium hydride species, **C**, can also activate organic halides via a heterolytic addition mechanism. However, the exact nature of the active catalytic species and catalytic cycle needs further investigation.

4. Conclusions

We have shown that a homogeneous catalyst system consisting of $PdCl_2(PPh_3)_2$/TsOH/LiCl provides a highly efficient catalyst for the carbonylation of IBPE to ibuprofen. Higher reaction rates (TOF up to 1200 h^{-1}) and ibuprofen selectivity ($>95\%$) have been achieved at 388 K under a CO partial pressure of 5.4 MPa. The reaction proceeds through the formation of IBS and IBPCl as intermediates and IBPCl is confirmed as the active substrate that gets carbonylated. The same catalyst system is shown to be effective for various α-arylethanols, vinyl aromatics and corresponding chloro derivatives.

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References

[1] J.P. Rieu, A. Boucherle, H. Cousse and G. Mouzin, Tetrahedron 42 (1986) 4095.
[2] R.A. Sheldon, Chem. Ind. (1992) 903.
[3] J.N. Armor, Appl. Catal. 78 (1991) 141.
[4] V. Elango, M.A. Murphy, G.N. Mott, E.G. Zey, B.L. Smith and G.L. Moss, Eur. Patent 400 892 (1990).
[5] A. Seayad, A.A. Kelkar and R.V. Chaudhari, Stud. Surf. Sci. Catal. 113 (1998) 883.
[6] G. Papadogianakis, L. Maat and R.A. Sheldon, J. Chem. Tech. Biotechnol. 70 (1997) 83.
[7] H. Alper and N. Hamel, J. Am. Chem. Soc. 112 (1990) 2803.
[8] K.S.Y. Lau, P.K. Wong and J.K. Stille, J. Am. Chem. Soc. 98 (1976) 5832.
[9] V.N. Zudin, V.D. Chinakov, V.M. Nekipelov, V.A. Rogov, V.A. Lakholobov and Yu.I. Yermakov, J. Mol. Catal. 52 (1989) 27.