Highly active supported palladium catalyst for the regioselective synthesis of 2-arylpropionic acids by carbonylation

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

Homogeneous Catalysis Division, National Chemical Laboratory, Pune- 411 008, India. E-mail: rvc@ems.ncl.res.in

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A catalyst system consisting of supported palladium in the presence of phosphine ligands, TsOH and LiCl catalyses the carbonylation of 1-arylethanols to 2-arylpropionic acids with significantly improved activity and regioselectivity; the catalyst can be recycled with no loss in activity and selecivity.

Carbonylation of 1-arylethanols is of great interest since it provides an environmentally benign route[1] for the synthesis of anti-inflammatory drugs such as Ibuprofen, Naproxen *etc*. The importance of this route can be clearly demonstrated from the commercialisation of an Ibuprofen process at Texas in 1992 by Hoechst Celanese Corporation based on the carbonylation of 1-(4-isobutylphenyl)ethanol using a palladium complex catalyst.[2] The desired high selectivity (> 98%) for Ibuprofen was achieved only at very high pressures[3] (16–34 MPa). This homogeneous palladium catalyst system gave lower TOF† (50–100 h^{-1}) and selectivity (< 68%) at lower pressures (~ 6.8 MPa).[4] Additives such as $CuCl_2$ were reported to improve the selectivity under similar conditions.[5] In another study, a biphasic catalyst with a water soluble palladium complex[6] has been reported but in this case also, very low reaction rates (TOF = 2.3 h^{-1}) and lower Ibuprofen selectivity (70%) were observed.

Here we report, for the first time, highly active and selective supported palladium and platinum catalyst systems for the synthesis of 2-arylpropionic acids from the corresponding 1-arylethanols. Supported palladium combined with PPh_3, LiCl and TsOH provides very high TOF (3375 h^{-1}) and more importantly high selectivity (99.5%) for 2-arylpropionic acids at lower pressures (5.4 MPa). The activity as well as the selectivity was substantially higher compared to previous reports under identical conditions. The catalyst was recycled four times with no loss in activity and selectivity, attaining a total TON of 55,000. These results indicate that this new catalyst system (Pd-C/PPh_3/TsOH/LiCl) is highly efficient and provides significant improvement over the current state of the art for the synthesis of 2-arylpropionic acids.

In a typical experiment, the supported catalyst,‡ the substrate, the phosphine ligand, LiCl, TsOH, H_2O and the solvent (methyl ethyl ketone) were charged into a stirred pressure reactor and the reaction was carried out at 5.4 MPa of CO partial pressure at 115 °C under 1100 rpm for a specified time. The reaction mixture was analysed by gas chromatography§ and the products were further characterized by GC-MS and NMR.

Typical results for the carbonylation of 1-(4-isobutylphenyl)-ethanol (*p*-IBPE) using different catalysts, supports, promoters and ligands are presented in Table 1. Pt/C provided comparatively lower activity than Pd/C. Other supports such as γ-alumina and H-ZSM-5 were also useful. Different acid and halide sources were checked and were found to not significantly effect the catalytic activity. The nature of the phosphine ligand has a strong influence on the catalytic activity, as evidenced from Table 1. No reaction was observed with diphos ligands such as dppb, unlike the catalyst system reported by Ali *et al.* for the carbonylation of olefins.[7]

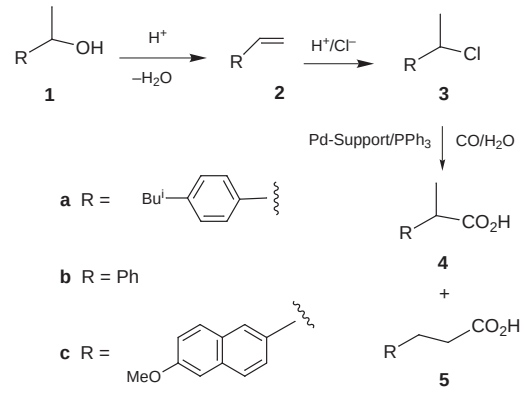
It was important to understand whether the reaction occurs heterogeneously or homogeneously (by soluble complexes of Pd formed *in situ*). For this purpose, liquid phase reaction samples were withdrawn during reaction and also after the end of the reaction (on cooling of the contents). The analysis of the liquid phase, after the reaction, for Pd content by atomic absorption spectroscopy showed < 0.1 ppm of Pd in solution, but the sample withdrawn under the reaction conditions showed significant leaching of Pd (1.5 ppm Pd). This indicates that the reaction is more likely to be homogeneously catalysed and the enhanced activity and selectivity is due to the combination of Pd with PPh_3 and promoters like TsOH, and LiCl. At the same time, readsorption of Pd onto the support after the reaction facilitates repeated recycling. Thus, the proposed catalyst system offers significant advantages, not only with respect to activity and selectivity, but also to catalyst recycling.

Intermediate sampling for the carbonylation of *p*-IBPE showed that the reaction proceeds through the formation of 4-isobutylstyrene and 1-(4-isobutylphenyl)ethyl chloride as the intermediates. Here the question was, which intermediate is undergoing carbonylation? To make this point clear, the carbonylation of 4-isobutylstyrene was performed in the absence of LiCl. The reaction was found to be very slow (TOF = 300 h^{-1}) with very poor Ibuprofen selectivity (65%). But in

Table 1 Carbonylation of 1-(4-isobutylphenyl)ethanol (*p*-IBPE) to give Ibuprofen using supported palladium and platinum catalysts[a]

Catalyst	Ligand	*t*/h	Conversion (%)	Selectivity (%)	TOF/h^{-1}
1% Pd/C	PPh_3	4.2	96	99.2	3375
1% Pd/γ-alumina	PPh_3	5.5	92	99.5	2475
1% Pd/H-ZSM-5	PPh_3	5.8	90	99.0	2285
1% Pt/C	PPh_3	24	90	99.2	550
Pd metal[b]	PPh_3	8	97	99.3	90
1% Pd/C	P(*p*-Tol)$_3$	4.5	94	98.5	3062
1% Pd/C	P(*p*-FPh)$_3$	5.9	95	99.5	2384
1% Pd/C	P(Cy)$_3$	24	50	99.5	308
1% Pd/C[c]	PPh_3	8	91	99.0	1676
1% Pd/C[d]	PPh_3	6	93	98.5	2272

[a] *Conditions:* *p*-IBPE (14.04 mmol), catalyst (10 mg), phosphine (0.1908 mmol), TsOH (5.6052 mmol), LiCl (5.6052 mmol), H_2O (67 mmol), methyl ethyl ketone (21 ml), P_{CO} = 5.4 MPa, T = 115 °C. [b] Pd metal (2 mg). [c] HCl (5.6052 mmol) instead of TsOH and LiCl. [d] Bu_4NCl instead of LiCl.



Scheme 1

Table 2 Synthesis of 2-arylpropionic acids by carbonylation[a]

Substrate	*t*/h	Conversion (%)	Selectivity (%)	TOF/h^{-1}
1a	4.2	96	99.2	3375
2a	4	92	99.1	3400
3a	4	90	99.3	3300
1b	13	90	98	1010
2b	4.6	92	98	2900
1c	24	90	99	552

[a] *Conditions:* Substrate (14.04 mmol), catalyst (10 mg), phosphine (0.1908 mmol), TsOH (5.6052 mmol), LiCl (5.6052 mmol), H_2O (67 mmol), methyl ethyl ketone (21 ml), P_{CO} = 5.4 MPa, T = 115 °C.

the presence of LiCl the catalytic activity and Ibuprofen selectivity were the same as that of *p*-IBPE carbonylation. Under similar conditions, 1-(4-isobutylphenyl)ethyl chloride also showed the same catalytic activity and selectivity behaviour. This indicates that in the presence of LiCl, the major reaction pathway is the carbonylation of the chloro derivative, as shown in Scheme 1.

The catalyst system was also applicable for the carbonylation of various 1-arylethanols and their corresponding olefin and chloro analogues, as demonstrated in Table 2. In all cases, high TOF and 2-arylpropionic acid selectivity were achieved.

In summary, in the presence of phosphines, TsOH and LiCl, with supported palladium and platinum as the catalyst systems, the carbonylation of 1-arylethanols to 2-arylpropionic acids occurs with high activity and regioselectivity with efficient recycling of the catalyst.

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Notes and references

† TOF = Turn over frequency = number of moles of Ibuprofen produced per mole of metal per hour.

‡ The catalysts were prepared by wet impregnation of the chloride salts of the metals followed by reduction using formaldehyde (for carbon) or sodium formate (for alumina and H-ZSM-5).

§ Analysis of the components was by GC (FFAP capillary column 25 m × 0.2 mm, FID)

1 R. A. Sheldon, *Chem. Ind.*, 1992, 903; C. B. Dartt and M. E. Davis, *Ind. Eng. Chem. Res*., 1994, **33**, 2887.
2 J. N. Armor, *Appl. Catal*., 1991, **78**,141.
3 V. Elango, D. G. Kenneth, M. M. Alan, M. N. Graham, Z. G. Edward and S. B. Lee, EP 400 892, 1990.
4 A. Seayad, A. A. Kelkar and R. V. Chaudhari, *Stud. Surf. Sci. Catal*., 1998, **113**, 883.
5 E. J. Jang, K. H. Lee, J. S. Lee and Y. G. Kim, *J. Mol. Catal. A: Chem.*, 1999, **138**, 25.
6 G. Papadogianakis, L. Maat and R. A. Sheldon, *J. Chem. Technol. Biotechnol*., 1997, **70**, 83; G. Papadogianakis, G. Verspui, L. Maat and R. A. Sheldon, *Catal. Lett.*, 1997, **47**, 43.
7 B. E. Ali, G. Vasapollo and H. Alper, *J. Org. Chem.*, 1993, **58**, 4739.

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