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Carbonylation of Vinyl Aromatics: Convenient Regioselective Synthesis of 2-Arylpropanoic Acids

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

Homogeneous Catalysis Division, National Chemical Laboratory, Pune-411 008, India

rvc@ems.ncl.res.in

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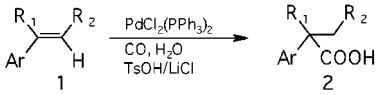
ABSTRACT



Ar = aryl; R_1, R_2 = H or CH_3

Various substituted and nonsubstituted 2-arylpropanoic acids have been synthesized in high turnovers with high regioselectivity by palladium-catalyzed carbonylation of vinyl aromatics. Both terminal and internal olefins are carbonylated, though hindered olefins are less reactive. In all the cases high yields and high selectivity are observed. Olefins with electron-withdrawing para substituents gave the highest regioselectivity in the formation of the corresponding 2-arylpropanoic acids.

2-Arylpropanoic acids are an important class of organic compounds having wide-ranging applications in pharmaceutical as well as in the fine chemical industries.[1] Carbonylation of vinyl aromatics[2] or 1-arylethanols[3] provide a convenient and environmentally benign[4] process for their production. Palladium complexes are widely used for this reaction, and the activity and selectivity are found to be sensitive to the reaction conditions employed. The desired high selectivity for the branched isomer was obtained only under high pressures of CO (16−36 MPa)[3a] or by the use of cocatalysts such as $CuCl_2$.[5] However, in most of the cases the reaction rate (20−75 h^{-1}) as well as the selectivity to 2-arylpropanoic acids (<70%) was found to be very low under moderate conditions (80−130 °C and 3.4−6.8 MPa).[6] Even though the biphasic carboxylation[7] of vinyl aromatic compounds provides easy catalyst separation, the reaction rate (1.5−25 h^{-1}) as well as the selectivity (50−70%) was quite low. Another important route to 2-arylpropanoic acids is the hydrolysis of the corresponding carboxylic acid esters, which are obtained by the hydroesterification of vinyl aromatics. These hydroesterification reactions are efficiently carried out using cationic palladium complexes,[8] which are the most active catalysts reported for such reactions. However, in this case also the high selectivity to the 2-arylpropionic acid ester is achieved only at lower temperatures, where the activity

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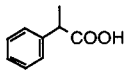
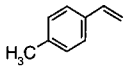
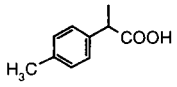
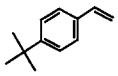
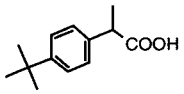
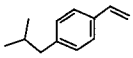
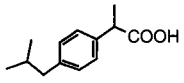
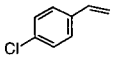
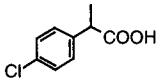
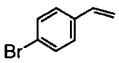
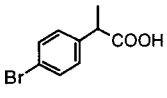
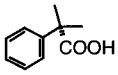
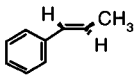
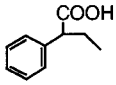
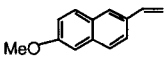
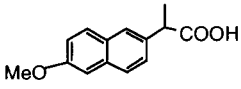
Table 1. Synthesis of 2-Arylpropanoic Acids by Palladium-Catalyzed Carbonylation of Vinyl Aromatics

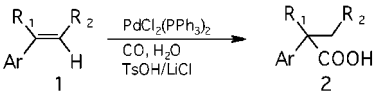
Run	Substrate 1	Time h	Conversion[a] %	TOF[b] h^{-1}	Product 2	Selectivity[a] %	Yield[c] %
1	 **1a**	0.22	99	2255	 **2a**[12]	99.3	91
2.	 **1b**	0.38	98.7	1301	 **2b**[13]	95	88
3.	 **1c**	0.29	99.2	1713	 **2c**	97.5	92
4.	 **1d**	0.4	99	1240	 **2d**[3a]	97	93
5.	 **1e**	0.4	99.6	1247	 **2e**[14]	99.8	88
6	 **1f**	0.38	98.5	1298	 **2f**	99.7	92
7	 **1g**	5.5	85	77	 **2g**	61	50
8	 **1h**	2	90	225	 **2h**	95.5	85
9	 **1i**	1.17	95	406	 **2i**[15]	97.5	89

[a] Calculated by GC analysis. [b] TOF = turnover frequency = no. of moles of substrate converted per mole of catalyst per unit time. [c] Isolated yields (the percentage yield of **2** in the isolated acid mixture was calculated from GC and NMR analysis).

of the catalyst is very low. Hence, the direct, regioselective synthesis of 2-arylpropanoic acids with high turnovers under low-pressure conditions has been a major challenge.

Here, we demonstrate the efficient regioselective synthesis of a variety of substituted and nonsubstituted 2-arylpropanoic acids (**2a**−**i**) by the palladium-catalyzed carbonylation of the corresponding vinyl aromatics (Scheme 1). Very high regioselectivity (up to 99.8%) and significantly enhanced turnover frequencies (up to 2250 h^{-1}) have been achieved under moderate reaction conditions (115 °C, 5.4 MPa) as compared to the prior reports.

Scheme 1



Ar = aryl; R_1, R_2 = H or CH_3

The catalyst system consists of the classical palladium complex $PdCl_2(PPh_3)_2$ along with *p*-toluenesulfonic acid (TsOH) and LiCl as promoters. This combination of promoters shows significant improvement in the activity and selectivity of the catalyst compared to promoters such as HCl as observed in our previous studies, on carbonylation of 1-(4-isobutylphenyl)ethanol to ibuprofen.[9] Another point to be noted is that this reaction proceeds by the formation of the corresponding 1-chloro derivative[10] as an intermediate, carbonylation of which is the major pathway for the 2-arylpropanoic acid formation. The beauty of this route is that it is applicable for terminal olefins as well as internal olefins, both providing good yields of the corresponding 2-arylpropanoic acids.

Table 1 presents the typical results of carbonylation of various vinyl aromatics to afford the corresponding 2-aryl-

(9) Manuscript submitted for publication.

(10) GC analysis of samples withdrawn at regular intervals of time from the reaction mixture showed the formation of the 1-chloro derivative as an intermediate.

propanoic acids.[11] In most of the cases high conversions and reaction rates are observed with more than 95% selectivity to the desired 2-arylpropanoic acids. The only traces of detected byproduct are the isomeric 3-arylpropanoic acids.

In the case of less hindered terminal olefins very high reaction rates and selectivity were obtained with almost complete conversion. The reaction rate was the highest for styrene (**1a**). When the reactivities of 4-substituted styrenes are compared, slight enhancement in the reaction rate can be seen for 4-methyl (**1b**) and 4-*tert*-butyl (**1c**) styrenes, which have a positive inductive effect compared to 4-chloro- (**1e**) and 4-bromostyrenes (**1f**). However, **1e** and **1f** showed very high selectivity for the 2-arylpropanoic acids. With hindered terminal olefins such as α-methylstyrene (**1g**), reaction rates were very low, with poor selectivity for 2-methyl-2-phenylpropanoic acid product (**2g**). This may be due to the steric hindrance created at the metal center, and isomerization can easily take place to decrease the strain due to steric bulk at the palladium center. Internal olefins such as *β*-methylstyrene (**1h)** also showed lower reactivity, but the regioselectivity was comparatively higher than that of α-substituted terminal olefins.

Palladium(0) complexes such as $Pd(PPh_3)_4$ and $Pd(dba)_2$ can also be used as the catalyst precursors. Since water also is a reactant, solvents which homogenize the reactants as well as catalyst components are required. We found that in this case methyl ethyl ketone (MEK) is convenient to work with, even though other polar solvents such as NMP and DMF also give similar results. In toluene, the reaction proceeds very slowly, but the selectivity remained almost the same.

In conclusion, we have demonstrated a convenient and regioselective method for the synthesis of a variety of 2-arylpropanoic acids from the corresponding vinyl aromatic compounds through carbonylation. Up to 99.8% selectivity is obtained for nonhindered terminal olefins with very high turnover frequencies ranging from 1000 to 2250 h^{-1}. Comparatively high reaction rates were also obtained for carbonylation of hindered olefins.

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(11) **Typical Procedure for the Preparation of 2-Arylpropanoic Acids by Carbonylation of Vinyl Aromatics**. The carbonylation reactions were carried out in a Parr Hastelloy C autoclave (50 mL). In a typical reaction, the substrate **1** (28.1 mmol), $PdCl_2(PPh_3)_2$ (0.056 mmol), LiCl/TsOH (5.6 mmol), water (66 mmol), and the methyl ethyl ketone (21 mL) were charged to the autoclave. The contents were flushed a few times with nitrogen followed by carbon monoxide and heated to the desired temperature. After the temperature was attained (115 °C), the autoclave was pressurized with CO (5.4 MPa) 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. The reaction was continued until the CO absorption was stopped. After the reaction, the autoclave was cooled to room temperature, CO-depressurized, and flushed with nitrogen and the reaction mixture removed. The analysis of the liquid samples was carried out using a gas chromatograph (HP 5890) using a HP-FFAP capillary column. To isolate the product, the solvent was evaporated, the residue was dissolved in toluene and was filtered to remove the precipitate. From the filtrate, the product was isolated by extraction with aqueous $NaHCO_3$ followed by acidification, re-extraction using dichloromethane, and evaporation. The products were further confirmed by IR and NMR. **2a**: IR (neat) 3500−2500 (bs), 1695 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.258 (m, 4H), 3.725 (q, 4H), 1.5 (d, 3H). **2b**: IR (neat) 3000−2600 (bs), 1700 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.409 (bs, 1H), 7.321 (d, 2H), 7.234 (d, 2H), 3.8 (q, 1H), 2.425 (s, 3H), 1.598 (d, 3H). **2c**: IR ($CHCl_3$) 3100−2600 (bs), 1700(s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.77 (bs, 1H), 7.353 (d, 2H), 7.254 (d, 2H), 3.716 (q, 1H), 1.501 (d, 3H), 1.308 (s, 9H). **2d**: IR ($CHCl_3$) 3400−2800 (bs), 1705 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3 (d, 2H), 7.125 (d, 2H), 3.75 (q, 1H), 2.5 (d, 3H), 1.85 (m, 1H), 1.515 (d, 2H) 0.945 (d, 6H). **2e**: IR (neat) 3200−2500 (bs), 1695 (bs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.83 (bs, 1H), 7.285 (d, 2H), 7.231 (d, 2H), 3.699 (q, 1H), 1.48 (d, 3H). **2f**: IR ($CHCl_3$) 3300−2600 (bs), 1700(s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.823 (bs, 1H), 7.445 (d, 2H), 7.187 (d, 2H), 3.689 (q, 1H), 1.486 (d, 3H). **2g**: IR (neat) 3500−2600 (bs), 1698 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.156 (bs, 1H), 7.604−7.278 (m, 5H), 1.706 (s, 6H). **2h**: IR (neat) 3500−2600 (bs), 1700 (bs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.245 (bs, 1H), 7.428−7.253 (m, 5H), 3.508 (t, 1H)2.159 (m, 2H), 0.952 (t, 3H). **2i**: IR ($CHCl_3$) 3500−3000 (bs), 1710 (s); ^1H NMR ($CDCl_3$), δ 7.67−7.05 (m, 6H), 5.075 (q, 1H), 3.865 (s, 3H), 1.575 (d, 3H).

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