

A convenient synthesis of phenylpropanoic acids: the palladium catalyzed hydrocarboxylation of styrene derivatives in a two-phase system

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Abstract

Biphasic hydrocarboxylation of various styrene derivatives can be achieved in high yields and selectivities in biphasic medium by using a water-soluble palladium/triphenylphosphine trisulfonate catalyst. The results are interpreted from the steric and electronic properties of substituent groups and from the solubilities of substrates in the aqueous phases. © 1999 Elsevier Science B.V. All rights reserved.

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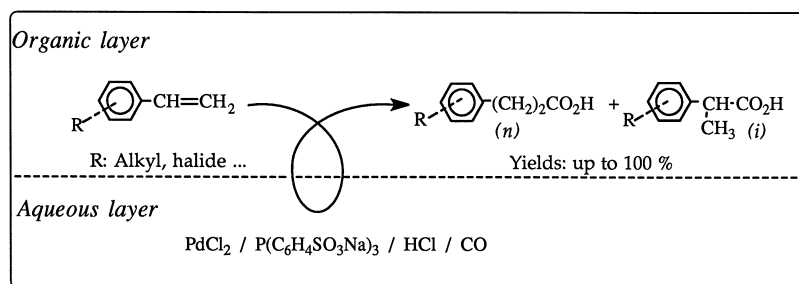
1. Introduction

Hydrocarboxylation of alkenes to carboxylic acids in the presence of carbon monoxide and water appears as an economically and environmentally attractive process for the carboxylic acids synthesis [1,2]. For instance, the hydrocarboxylation of 4-isobutylstyrene is of potential industrial interest as it may offer, provided it is highly chemoselective, a new alternative to produce α -(4-isobutylphenyl)propionic acid, a large volume nonsteroidal antiinflammatory

drug. Although the chemo-, regio-, and atomselectivity of hydrocarboxylation reactions are generally very high [3–6], no industrial application has been reported and the synthetic value of this reaction remains so far unexploited. This is mainly due to a tedious work-up of the reaction crude and to the difficult separation of the catalyst from products.

In this context, we have recently described a new catalytic system to carry out the hydrocarboxylation of styrene [7]. This system consists of a water soluble palladium complex of trisulfonated triphenylphosphine as catalyst and a Bronsted acid as promoter dissolved in an aqueous solution. In the present paper, we wish to report that this approach is efficient for a wide

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Scheme 1. Hydrocarboxylation of various styrene derivatives in a two-phase system.

variety of styrene derivatives and that the catalytic system can be easily recovered by simple separation of the aqueous layer from the organic layer (Scheme 1).

2. Experimental

2.1. Materials and apparatus

Palladium chloride and styrene derivatives were purchased from Strem, Aldrich and Acros in their highest purity and used without further purification. Trisodium tris(*m*-sulfonatophenyl)phosphine (TPPTS) was synthesized as reported by Gärtner et al. [8,9]. The purity of the TPPTS was carefully controlled. In particular, ^{31}P solution NMR indicated that the product was a mixture of TPPTS (ca. 98%) and its oxide (ca. 2%). Carbon monoxide was used directly from cylinders (> 99.9% pure; Air Liquide). Distilled deionized water was used in all the experiments. All the catalytic reactions were performed under nitrogen using standard Schlenk techniques. All the solvents and liquid reagents were degassed by bubbling nitrogen for 15 min before each use or by two freeze–pump–thaw cycles before use.

All the hydrocarboxylation experiments were carried out in a 100 ml stainless steel autoclave. The autoclave supplied by Autoclave Engineer was equipped with arrangements for automatic temperature control, pressure regulation, and variable stirred speed. A safety rupture disk was also fitted to the reactor. Gas liquid chromatography analyses were carried out on a Chrompack

9001 apparatus equipped with a CP Sil 5-CB column (25 m \times 0.32 mm).

2.2. Catalytic runs

In a typical experiment, PdCl_2 (0.25 mmol), TPPTS (1.5 mmol) and HCl (1 mmol) were dissolved in 35 ml of water. The resulting aqueous solution and an organic phase composed of substrate (12.5 mmol), toluene (35 ml) and cumene (1.2 mmol—GC internal standard) were charged under N_2 into a 100 ml stainless steel autoclave, then heated at 100°C , and pressurized with 40 atm of CO. The pressure was kept constant throughout the whole reaction by using a gas reservoir along with a pressure regulator. The reaction was monitored by quantitative gas chromatographic analysis. Products were identified by comparison of retention times and spectral properties with authentic samples.

2.3. Recycling experiments

The first batch was carried out as described above. After total conversion of styrene (GLC analysis), the autoclave was cooled to room temperature and the carbon monoxide pressure was evacuated. After a 10 min time of decantation, the bulk organic solution was then removed under the carbon monoxide atmosphere, leaving the aqueous phase in the bottom of the reactor. The latter was washed with toluene (30 ml), and a new reaction mixture containing styrene (12.5 mmol), toluene (35 ml) and cumene (1.2 mmol—GC internal standard) was

introduced. The second batch was carried out using the same procedure as described above. The overall recycling procedure was then repeated.

3. Results and discussion

In order to get a better insight into the scope and the limitation of our approach, hydrocarboxylation of pyridine and styrene derivatives with various substituents groups have been investigated. (Table 1). Obviously, several general remarks emerge from the results presented in Table 1.

(1) The hydrocarboxylation rates are dependent on the water solubility of styrene derivatives. The best results in terms of activity have been obtained with partially water-soluble substrates such as 4-acetoxystyrene and styrene (entries 1 and 13). For less soluble organic

reactant, high yields can also be obtained but high reaction times are required. For instance, with 4-trifluoromethylstyrene which is 14 times less soluble in water than styrene, the acids yield was 60% and 95% after 20 h and 96 h of reaction, respectively (entry 12). As expected for biphasic system [11], these results suggest that the rate determining step is the mass transfer between aqueous and organic layers. Although the results are not presented in Table 1, it is noteworthy that the catalytic activity can be significantly enhanced with these substrates by using a co-solvent like acetonitrile. For example, some amounts of acetonitrile in the aqueous phase (20 wt.%) allowed to increase by a factor of about five the initial activity for the hydrocarboxylation of 4-trifluoromethylstyrene and the acids yield reached 100% after 20 h.

(2) The hydrocarboxylation rates decrease with increasing steric hindrance of the reacting double bond. Indeed, despite their similar water

Table 1
Palladium catalyzed hydrocarboxylation of various styrene and pyridine derivatives in two-phase system^a

Entry	Styrene and pyridine derivatives	Water solubility ^b (mol/l × 10 ⁴)	Initial activity ^c	Acids yield ^d		n/i ratio ^e
				3 h	20 h	
1	styrene	11	25	88	100(95) ^f	0.8
2	2-methylstyrene	2.8	9	42	100(96) ^f	2.8
3	3-methylstyrene	2.8	16	63	100	1
4	4-methylstyrene	3.1	16	60	100(97) ^f	0.7
5	2,4-dimethylstyrene	0.8	3.5	19	100	2.6
6	2,4,6-trimethylstyrene	0.1	0.1	2	12	18
7	α-methylstyrene	2.6	1	5	32	(-) ^g
8	β-methylstyrene	2.7	< 0.1	1	5	(-) ^h
9	4-chlorostyrene	4.6	7	45	98	0.7
10	4-bromostyrene	2.5	3.4	22	70	0.7
11	4-fluorostyrene	13.2	15	63	100(95) ^f	0.9
12	4-trifluoromethylstyrene	0.8	2.5	15	60	1
13	4-acetoxystyrene	17	36	100(96) ^f	(-)	0.6
14	4-vinylpyridine	(-) ^h	< 1	3	3	(-) ^h
15	3-vinylpyridine	(-) ^h	< 1	5	6	(-) ^h
16	2-vinylpyridine	(-) ^h	< 1	1	2	(-) ^h

^a Conditions: see typical experiment.

^b Calculated according to Ref. [10].

^c Initially converted olefin per mol of palladium per hour.

^d (mol acids)/(mol converted olefin) × 100.

^e Normal to branched carboxylic acid ratio.

^f Isolated yield.

^g The branched acid was not detected.

^h Not determined.

solubility, the reactivity of 2-methylstyrene, α -methylstyrene and β -methylstyrene relative to 4-methylstyrene is decreased by a factor of about 2, 16 and 160, respectively (entries 2,4,7,8). As numerous reactions like hydrogenation and hydroformylation [12], these results show that steric effect is a predominant factor in palladium-catalyzed hydrocarboxylation.

(3) The normal to branched acids ratio is not sensitive to the electronic properties (electron-withdrawing or electron-donor group) of the aromatic ring substituents but rather again to steric hindrance of the α -carbon atom of the double bond. This ratio increases with increasing steric hindrance of the α -carbon atom. As a matter of fact, a methyl group in the 2-position on the ring has a larger effect on the acids ratio than one in the 3- or 4-position (entries 2 to 4). With 2,4,6-trimethylstyrene, this trend is still more marked due to the two methyl groups in 2 and 6 position and the n/i acid ratio reached 18 (entry 6). Interestingly, hydrocarboxylation of α -methylstyrene gives only the linear acid, probably because the steric hindrance is especially large with this substrate (entry 7).

(4) Electron-withdrawing groups on the aromatic ring impede the substrate reactivity. So, despite their lower water solubility, 4-methylstyrene and styrene reacted about twice faster than 4-chloro and 4-fluorostyrene, respectively (compare entries 4,9 and 1,11). This behaviour could be due to the weaker coordinating ability of the double bond or to the more difficult insertion of carbon monoxide into the palladium-alkyl bond.

(5) The presence of nitrogen atom on the aromatic ring affected strongly the activity and the stability of the catalytic system. Indeed, with these substrates, acids yield did not exceed 6% and formation of metallic palladium at the phase boundary is rapidly observed (entries 14 to 16). The lack of stability and reactivity with pyridine derivatives is not yet totally clear and a more detailed investigation with the aim to clarify the crucial role played by the pyridine nitrogen atom is now underway in our laboratory.

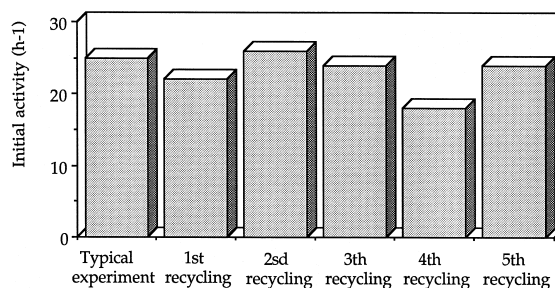


Fig. 1. Recycling of the catalytic system. PdCl₂ (0.25 mmol), TPPTS (1.5 mmol), HCl (1 mmol), water (35 ml), styrene (12.5 mmol), toluene (35 ml), cumene (1.2 mmol), T : 100°C, P (CO): 40 atm. Recycling experiments were carried out under CO atmosphere.

An important aspect of our approach is the possibility to separate easily the catalyst from the reaction medium and to recycle it in further experiments. Fig. 1 illustrates some of the results we obtained in such experiments with styrene like olefin.

No significant decrease in catalytic activity was observed between the recycling experiments. This suggests no leaching of palladium into the organic phase occurred in our experimental conditions. Moreover, as the phase separation between organic and aqueous phases is fast and excellent (< 1 min; formation of stable emulsion was not observed), all conditions for a quantitative and easy recycling are collected.

4. Conclusion

This work demonstrates that the catalytic system tolerates a wide range of functionalities for the styrene and that high yields in phenylpropionic acids can be obtained when the steric hindrance of the reacting double bond is weak. Advantages of such processes over conventional methods include simplicity in work-up of the reaction and the quantitative recovery of the catalytic system. Experiments to perform asymmetric catalytic hydrocarboxylation in biphasic medium are currently under way.

Acknowledgements

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