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Regioselective Synthesis of 2-Arylpropionic Esters by Palladium-Catalyzed Hydroesterification of Styrene Derivatives in Molten Salt Media

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Abstract:. The palladium-catalyzed hydroesterification of styrene derivatives is performed in a two-phase system composed of 1-*n*-butyl-3-methylimidazoliumtetrafluoroborate salt (ionic phase) and isopropanol/cyclohexane (organic phase). Very high regioselectivities in 2-arylpropionic esters (≥99.5%) are obtained using a catalytic system composed of $PdCl_2(PhCN)_2$, (+)-neomenthyldiphenylphosphine (NMDPP) and *p*-toluenesulfonic acid under mild reaction conditions (10 atm and 70°C). © 1998 Elsevier Science Ltd. All rights reserved.

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Transition metal-catalyzed carbonylation of organic substrates represents a very important process in organic synthesis. Indeed, carbon monoxide can be directly introduced into unsatured substrates to produce organic molecules such as aldehydes, ketones, esters, amides, and other carbonyl-containing funcionalities.[1] Although many transitions metals are effective catalysts for the carbonylation, palladium complexes are the most widely employed.[1,2] In this respect, palladium-catalyzed carbonylation of styrene derivatives in the presence of alcohols (hydroesterification) affords 2-arylpropionic esters , which are precursors for the most important class of non-steroidal antiinflammatory agents.[3] In homogeneous media, this reaction can be carried out with very good regioselectivities using a catalytic system composed of $Pd(OAc)_2$-PPh_3-TsOH (up to 96% in branched ester under 20 atm at room temperature)[4] or a $PdCl_2$-$CuCl_2$-chiral phosphine[5] (only trace of linear ester under 50 atm at 80°C)[5b]. On the other hand, the development of two-phase catalysis processes, in which the catalytic system can be separated from the products and recycled, is an important step towards safer and more environmentally processes.[6] Although the hydroformylation of olefins has been carried out successfully in two-phase systems,[2] little attention has been devoted to two-phase hydrocarboxylation or hydroesterification of olefins. Among them, catalytic systems composed by a water-soluble palladium complex of trisulfonated triphenylphosphine as the catalyst and a Bronsted acid as the promoter in water/toluene[7] or water/β-cyclodextrin[8] have been successfully employed. We[9] and others[10] have recently introduced the immobilization of homogeneous organometallic catalysts by the use of molten salts. In most cases, the transition metal complexes are soluble in the ionic liquids and the organic substrates are non-miscible. In this paper, we reported our first results concerning regioselective palladium-catalyzed carbonylation of styrene derivatives in a system

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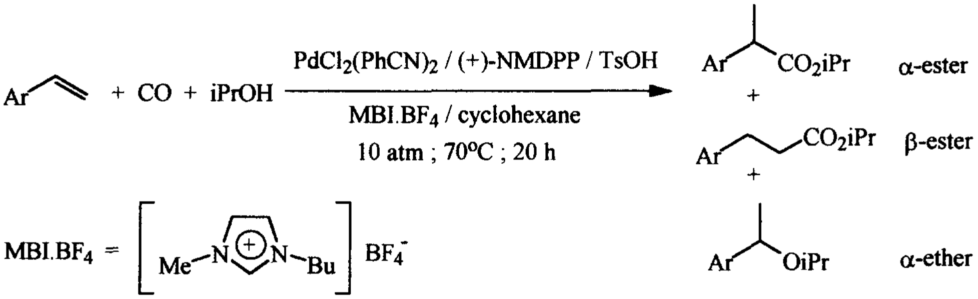
constituted of 1-*n*-butyl-3-methylimidazoliumtetrafluoroborate salt (ionic phase) and isopropanol/cyclohexane (organic phase) (Eq 1).

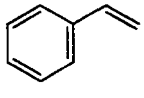
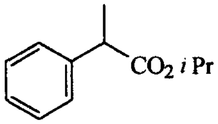
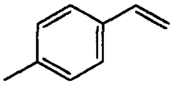
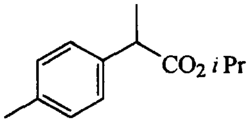
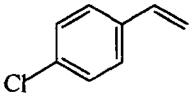
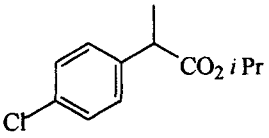
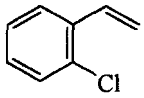
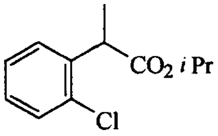
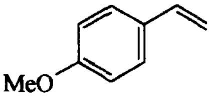
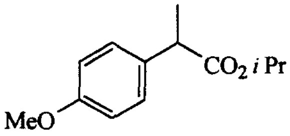
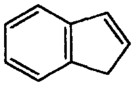
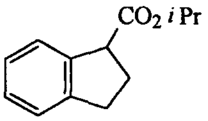
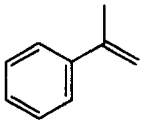
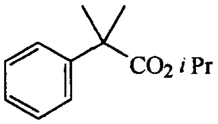


(1)

Among the various reaction conditions investigated we found that the carbonylation of styrene proceeds under 10 atm of CO at 70°C for 20 h to give isopropyl 2-phenylpropionate in good yield (89%) and very high regioselectivity (ratio α : β = 99.5 : 0.5). [11] In addition to the carbonylation products, the only by-product detected by GC-MS was the 1-isopropoxy-1-phenylethane (1%). This ether was formed from the acid-catalyzed reaction between the styrene and isopropanol. The choice of phosphine ligand is critical to achieve high regioselectivities. For instance, using triphenylphosphine instead of (+)-NMDPP under the same reaction conditions induced a decrease in regioselectivity to 80%. On the other hand, using triphenylphosphine, the regioselectivity can be improved with higher pressures of carbon monoxide (94% at 30 bar), but remains below the regioselectivity obtained with (+)-NMDPP operating at 10 bar. Cyclohexyldiphenylphosphine ($CyPPh_2$) and menthyldiphenylphosphine (MDPP) gave excellent regioselectivities in hydroesterification of 6-methoxy-2-naphthylethene[12], but in our system the use of $CyPPh_2$, that is less hindered than (+)-NMDPP, lowered the regioselectivity to 89%. Nevertheless, when we have used highly hindered phosphine, such as tri-*o*-tolylphosphine, cause the system to become completely inactive. These results show the importance of steric properties of phosphine ligand on the control of regioselectivity and activity. It should be noted that although a chiral phosphine ligand is used, the degree of asymmetric induction observed was very low (<5%). $Pd(dba)_2$ (dba = dibenzylideneacetone), NMDPP and trifluoroacetic acid have previously been used in the asymmetric hydroesterification of styrene.[13] The best results (52% e.e.; α : β = 94 : 6) have been obtained at low conversions and 1 atm of CO, but the authors observed a remarkable decreasing in the asymmetric induction by increasing the carbon monoxide pressure.

In order to investigate the scope of this reaction, various substituted substrates have been employed as in the hydroesterification reaction under the same conditions described for styrene (Table 1). It is worth noting that all the substrates were carbonylated affording the corresponding α-esters in a regioselectivity equal or superior to 99.5%. *p*-Methylstyrene (entry 2) and *p*-chlorostyrene (entry 3) were carbonylated with high yields. Lower activity was observed for *o*-chlorostyrene (entry 4) probably due to the steric effect of the chloride atom at the ortho position. This effect was more pronounced in the case of indene (entry 6) and especially of α-methylstyrene (entry 7). The *p*-vinylanisol (entry 5) was almost completely consumed but only 22% of formed products were 2-(p-methoxyphenyl)propionic ester. In this case, we observed a higher yield of the corresponding ether (entry 5). The substantial ether formation observed with the *p*-vinylanisol could be explained by the resonance effect of the electron-donating methoxy group that stabilizes carbocation intermediate. The ether product was also formed for reactions using an olefin-containing electron-donating group at the phenyl ring (entries 2 and 6) or at benzylic carbon (entry 7), but not in the case of olefins containing electron-withdrawing groups (entries 3 and 4).

Table 1. Hydroesterification of Styrene Derivatives in Organic Solvent/Molten Salt Two-phases System Catalyzed by Palladium-(+)-Neomenthyldiphenylphosphine.

Entry	Styrene derivative	Conv. (%)[a]	α–Ester	Yield (%)	α : β	α-Ether (%)
1		89		89	99.5 : 0.5	1
2		90		76 (68)	> 99.5 : 0.5	2
3		83		71 (71)	> 99.5 : 0.5	-
4		60		60 (58)	> 99.5 : 0.5	-
5		97		22	> 99.5 : 0.5	8
6		9		9	-	1
7		< 1		< 1	-	4

a) Reaction conditions were the same as for styrene.[11] b) Conversions and yields were determined by GC and GC-MS. Isolated yields are shown in parentheses. Spectroscopic data (^1H and ^{13}C NMR, IR and GC-MS) for all products are in agreement with the given structures.

Similar results were observed for the hydroesterification of styrene in the absence of the molten salt (homogeneous media). However, in the presence of the molten salt the 2-arylpropionic esters are easily separated from the ionic catalytic solution by simple decantation. Unfortunately, this solution could not be recycled since the palladium catalyst is partially or totally decomposed after the catalytic reaction. In order to demonstrate the role of the molten salt and to avoid decomposition of palladium catalyst the reaction was carried out at low conversion (<35% after 3 h). Under theses conditions, atomic absorption analysis of the organic phase and the ionic phase indicated that more than 95% of the Pd was still retained into ionic phase, as already observed for other reactions catalyzed by Pd compounds immobilized in ionic liquids.[9b,c] It is also worth mentioning that the recovered ionic solution obtained at low conversions was reused giving 60% conversion of styrene after 20 h.[14]

In conclusion, we have demonstrated that palladium-based catalyst associated with (+)-NMDPP and immobilized in 1-*n*-butyl-3-methylimidazoliumtetrafluoroborate is highly efficient for the regioselective hydroesterification of styrene-derivatives under mild reaction conditions. Our protocol is able to carry out the reaction under lower CO pressure than those used in homogeneous systems with similar[5b, 12] or higher[4] regioselectivities. This method allows the selective preparation of a variety of 2-arylpropionic esters, precursors for non-steroidal antiinflammatory drugs. We are currently investigating palladium-based catalytic systems that might be reused at high conversions.

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11. Hydroesterification procedure: The PdCl$_2$(PhCN)$_2$ (0.05 mmol), (+)-neomenthyldiphenylphosphine (NMDPP, 0.1 mmol), *p*-toluenesulfonic acid(0.25 mmol), 1-*n*-butyl-3-methylimidazoliumtetrafluoroborate (4 mL), cyclohexane (12 mL), isopropanol (8 mL) and styrene-derivative (4.5 mmol) were placed in a 100 mL-stainless steel autoclave under argon. The reactor was pressurized with 10 atm of CO and the reaction mixture was stirred at 70° C during 20 hours. After cooling and releasing the excess of carbon monoxide the organic phase, (upper phase) was separated by decantation and analyzed by GC or distilled to afford the 2-arylpropionic ester.

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14. Despite the styrene solution was added to the ionic solution under argon, some metallic palladium was observed after the organic solution giving lower the activity compared to entry 1 (table 1).