A palladium complex catalyst for the regioselective hydrocarboxylation of 4-methylstyrene

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Abstract

With a homogeneous catalyst system of $PdCl_2$–$CuCl_2$–PPh_3 dissolved in a polar solvent, highly regioselective hydrocarboxylation of 4-methylstyrene to the branched α-(4-methylphenyl) propionic acid has been achieved. Effects of additives (mineral acids and O_2) and reaction conditions (amounts of catalyst components, reaction temperature, pressure and solvents) have been studied. Compared with the previous results of hydrocarboalkoxylation of 4-methyl-styrene to the ester by the same catalyst, the hydrocarboxylation required severer reaction conditions and the presence of a polar solvent that could solubilize water. Efficient hydrocarboxylation was achieved only after fine adjustments of the reaction conditions and addition of a halogen compound. And the addition of HCl improved the reaction rate significantly. This improvement was due to the effect of chlorine, not the effect of the proton. The addition of oxygen reduced reaction rates by oxidizing carbon monoxide and PPh_3.

Keywords: Alkylstyrene; Hydrocarboxylation; Palladium complex; Additive effects; Regioselectivity

1. Introduction

In our previous study of hydrocarboalkoxylation of 4-methylstyrene with CO and methanol [1], it was found that a catalyst system of $PdCl_2$–$CuCl_2$–PPh_3 dissolved in a nonpolar solvent provided a nearly regiospecific conversion to the branched α-(4-methylphenyl) propionic acid ester at high rates at 373 K and 41 bar of CO. Effects of catalyst components and reaction conditions were studied. Incidentally, the

catalyst components were same as claimed in a recent patent [2] for the synthesis of α-(4-iso-butylphenyl) propionic acid (commonly called ibuprofen which is a large volume, nonsteroidal anti-inflammatory drug) by hydrocarboxylation of 4-isobutylstyrene with CO and water. Hence, as an extension of the previous study, we applied the same catalyst system for hydrocarboxylation of 4-methylstyrene, our model compound of 4-isobutylstyrene. The hydrocarboxylation is a direct method of acid synthesis that could save one step of ester hydrolysis in the synthesis of ibuprofen. Effects of additives (mineral acids and O_2) and reaction conditions

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(amounts of catalyst components, reaction temperature, pressure and solvents) have been studied.

Palladium-catalyzed hydrocarboxylation and hydrocarboalkoxylation of olefins or alcohols have been the subject of extensive recent studies [3–19]. Besides a palladium complex, the reaction requires various promoters to achieve desired activity, selectivity and stability of the catalyst. The hydrocarboxylation with CO and water generally requires more harsh reaction conditions than the hydrocarboalkoxylation with CO and a primary alcohol.

2. Experimental

A 300 ml stirred autoclave with Hastelloy C walls (Parr Co.) was used as a batch reactor that was enclosed in an electric furnace. A thermocouple and a PID temperature controller monitored and controlled reaction temperature. In most runs, 50 mmol of 4-methylstyrene, 0.5 mmol of $PdCl_2$ and 1 g of t-butyl-benzene (an internal standard for gas chromatographic analysis) were used as the standard reaction mixture and the amounts of other components were varied in order to investigate their effects. In a typical run, 4-methylstyrene, t-butylbenzene and HCl were dissolved in 80 ml of tetrahydrofuran (THF) together with H_2O and then $PdCl_2$, $CuCl_2$ and PPh_3 were charged into the reactor. The reactor was flushed three times with 3 bar of CO and then pressurized to the reaction condition (mostly 41–45 bar). Then the reactor was heated to a desired reaction temperature (mostly 373 K) in 20 min and the time when the temperature was reached was taken to be the start of the reaction. The reaction product was sampled during the reaction and analyzed by a gas chromatograph (Varian) equipped with a FID detector and a cross linked poly(diphenyl dimethyl siloxane) capillary column. The identification of GC peaks was done by GC-MS (Shimazu) analysis.

3. Results and discussion

In the hydrocarboxylation of 4-methylstyrene, two major products were formed. One was the branched α-(4-methylphenyl) propionic acid, $H_3CC_6H_4CH$ (COOH)(CH_3) and the other was its linear form, $H_3CC_6H_4CH_2CH_2COOH$. The formation of other products was negligible.

We started hydrocarboxylation of 4-methylstyrene with the catalyst system and the reaction conditions that were employed and optimized for hydrocarboalkoxylation of the same substrate in our previous study [1]. Thus, at 373 K and 41 bar of CO and with 4.5 ml of H_2O (5 mol of H_2O per 1 mol of 4-methylstyrene), the $PdCl_2$–$CuCl_2$–PPh_3 catalyst in mol ratio of 1:2:4 dissolved in 70 ml of THF gave 29% conversion of 4-methylstyrene and 85% selectivity to branched α-(4-methylphenyl) propionic acid in 6 h. The conversion and the selectivity were improved as reaction temperature and pressure increased. Thus it appeared that the hydrocarboxylation with CO and water generally required severer reaction conditions than the hydrocarboalkoxylation with CO and methanol. However, efficient hydrocarboxylation under mild conditions was achieved after fine adjustments of the reaction conditions and the addition of HCl as discussed below.

Fig. 1 shows the effect of the reaction temperature on the conversion and the selectivity of hydrocarboxylation under the optimized conditions (45 bar, $PdCl_2/CuCl_2/PPh_3 = 1/3/4$, H_2O/4-methylstyrene = 10) and with the addition of 0.5 ml HCl in 2 h. Thus, 100% conversion of 4-methylstyrene and 93% selectivity to the branched acid were obtained at 373 K in 2 h. This performance is similar to the best results obtained in the hydrocarboalkoxylation. Both conversion and selectivity were deteriorated as the reaction temperature was further decreased.

The content of water in the reaction mixture had a profound effect as shown in Fig. 2. When 5 mol of water was used per mol of 4-methylstyrene, the conversion of 4-methylstyrene was only 25%. As the ratio increased, the conversion
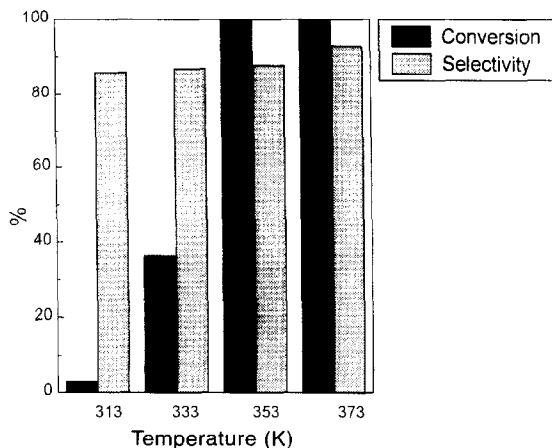
Fig. 1. The effect of reaction temperature on the conversion of 4-methylstyrene and the selectivity to the branched α-(4-methylphenyl) propionic acid: Pressure = 45 bar, time = 2 h, PPh_3/$PdCl_2$ = 4, $CuCl_2$/$PdCl_2$ = 3, HCl = 0.5 ml, H_2O = 9 ml (H_2O/4-methylstyrene = 10. mol/mol).

showed a maximum at about 10 and then rapidly decreased. Selectivity to branched acid also showed a maximum at the H_2O/reactant molar ratio of 10, yet the variation in selectivity was mush less than that in the conversion. Similar effect of water has been reported by Alper et al. [15] in the same reaction with $PdCl_2$–$CuCl_2$–HCl in THF. As pointed out by Fenton [9], a two-phase system would exist at high water levels and it would reduce the effective concen-
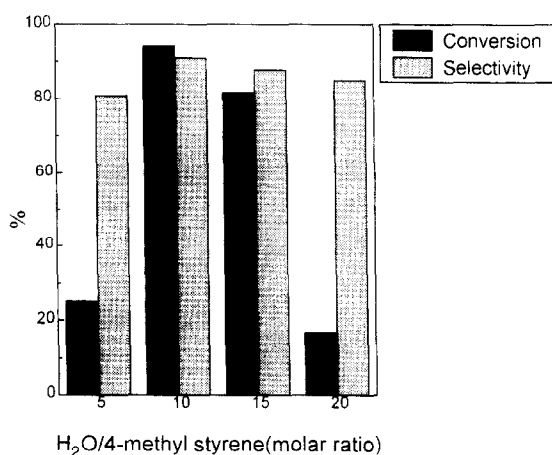

Fig. 2. The effect of H_2O on the conversion of 4-methylstyrene and the selectivity to the branched α-(4-methylphenyl) propionic acid: Temperature = 373 K, pressure = 41 bar, time = 4 h, HCl = 0, PPh_3/$PdCl_2$ = 4, $CuCl_2$/$PdCl_2$ = 2.
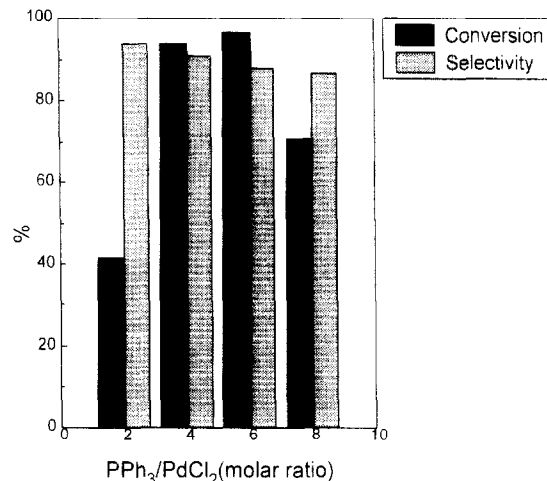

Fig. 3. The effect of triphenylphosphine on the conversion of 4-methylstyrene and the selectivity to the branched α-(4-methylphenyl) propionic acid: Temperature = 373 K, pressure = 41 bar, time = 4 h, HCl = 0, $CuCl_2$/$PdCl_2$ = 2, H_2O = 9 ml (H_2O/4-methylstyrene = 10, mol/mol).

tration of water in the olefin-rich phase. On the other hand, a certain excess amount of water would be required to obtain high reaction rates as a reactant or as a desirable ligand to palladium [8].

In Fig. 3, the significant influence of PPh_3 on the reaction was examined. When PPh_3 was absent, the reaction rate was extremely slow, giving only 6% conversion in 2 h, although the reaction condition was slightly different. In the presence of PPh_3, the conversion showed a maximum at PPh_3/$PdCl_2$ molar ratio of 4–6 and then reduced as PPh_3 was further added. The selectivity to branched acid did not change appreciably with the amount of PPh_3. PPh_3 is the most widely employed ligand for homogeneous metal catalysts, especially for Pd, and this monodentate phophine ligand gives high values of regioselectivity to branched carboxylic acid [11]. One of its important roles is to stabilize molecular Pd species (most frequently zero valent species) and thus to prevent the formation of inactive bulk Pd particles [20]. In this case of Pd–PPh_3 system, the effect of increasing amounts of PPh_3 upon the reaction rate (or the conversion of the reactant) is usually flattened
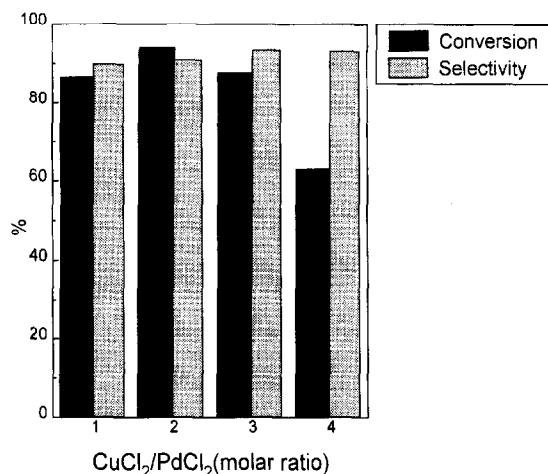
Fig. 4. The effect of $CuCl_2$ on the conversion of 4-methylstyrene and the selectivity to the branched α-(4-methylphenyl) propionic acid: Temperature = 373 K, pressure = 41 bar, time = 4 h, HCl = 0, $PPh_3/PdCl_2$ = 4, H_2O = 9 ml(H_2O/4-methylstyrene = 10, mol/mol).
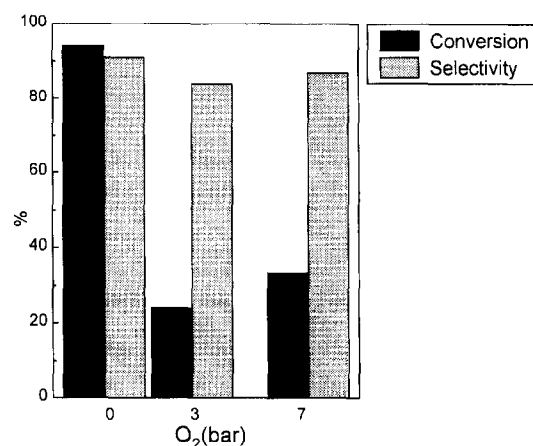

Fig. 5. The effect of O_2 on the conversion of 4-methylstyrene and the selectivity to the branched α-(4-methylphenyl) propionic acid: Temperature = 373 K, pressure = 41 bar, time = 4 h, HCl = 0, $PPh_3/PdCl_2$ = 4, $CuCl_2/PdCl_2$ = 2, H_2O = 9 ml(H_2O/4-methylstyrene = 10, mol/mol).

out above a certain concentration [21]. The presence of a maximum in the present $PdCl_2$–$CuCl_2$–PPh_3 catalyst system suggests that a redox cycle between Pd(0) and Pd(II) is operating with the participation of $CuCl_2$. Thus, Pd(0) stabilized by PPh_3 should be reoxidized to become active Pd(II) and too much PPh_3 would retard this step.

The role of $CuCl_2$ in a reaction catalyzed by $PdCl_2$ is known to reoxidize Pd(0) to active Pd(II). In our previous work of hydrocarboalkoxylation of 4-methylstyrene [1], the most significant effect of $CuCl_2$ in Pd complex was the improved selectivity of the branched isomer. The role of $CuCl_2$ in the preferred formation of branched esters is not understood. Its effect in hydrocarboxylation is shown in Fig. 4. In general, the effect of different amounts of $CuCl_2$ was not great at $CuCl_2/PdCl_2$ mol ratios of 1–3.

The addition of oxygen was reported to promote the hydrocarboxylation in the presence of $PdCl_2$–$CuCl_2$–HCl catalysts by Alper and coworkers [15–19]. Its effect in the present system is shown in Fig. 5. The addition of O_2 in the gas phase reduced the conversion from 94% (without O_2) to 24% (3 bar O_2) and to 33% (7

bar O_2). This observation could be explained by two reasons. First, an aqueous solution of $PdCl_2$–$CuCl_2$ was a known catalyst system that could oxidize CO to CO_2 at room temperature [22–26]. This was indicated by the unusually large pressure drop that we observed in the early stage of the reaction when O_2 was added. Second, PPh_3 was oxidized to triphenylphosphene oxide (TPPO). As shown in Fig. 6a, the reaction mixture without O_2 addition showed one peak at 30 ppm in ^{31}P NMR, which
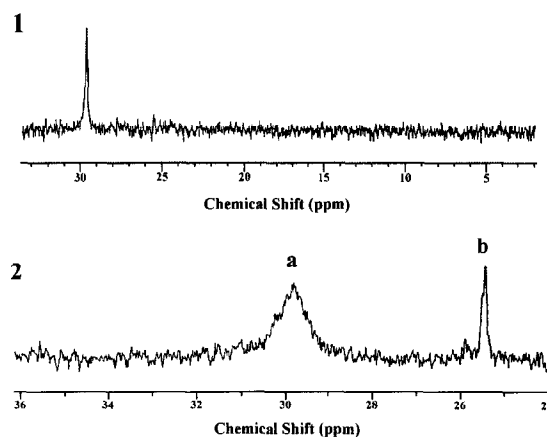

Fig. 6. ^{31}P NMR spectra for the reaction mixture after the reaction without O_2 (1) and with O_2 (2). The peak at 30 ppm (a) could be assigned to be PPh_3 and that at 25.4 ppm, PPh_3 oxide (b).
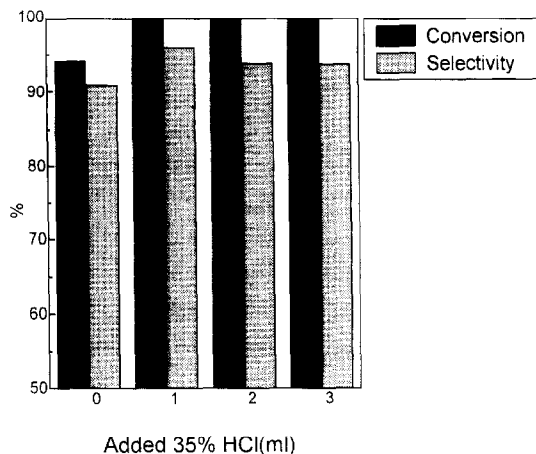
Fig. 7. The effect of added 35% HCl on the conversion of 4-methylstyrene and the selectivity to the branched α-(4-methylphenyl) propionic acid: Temperature = 373 K, pressure = 41 bar, time = 4 h, $PPh_3/PdCl_2 = 4$, $CuCl_2/PdCl_2 = 2$, $H_2O = 9$ ml (H_2O/4-methylstyrene = 10, mol/mol).

Fig. 8. The effect of different acids on the conversion of 4-methylstyrene and the selectivity to the branched α-(4-methylphenyl) propionic acid: Temperature = 373 K, pressure = 41 bar, time = 2 h, $PPh_3/PdCl_2 = 4$, $CuCl_2/PdCl_2 = 3$, 4-methylstyrene/acid = 6.85/0.5 vol/vol.

was originated from PPh_3. When O_2 was added, an additional sharp peak appeared at 25.4 ppm as shown in Fig. 6b that could be assigned to TPPO. The presence of TPPO was also confirmed by GC–MS analysis. The oxidation of PPh_3 was catalyzed by Pd complexes [27–29]. Having far less electron donating ability than PPh_3, TPPO is believed to be ineffective as a ligand for Pd [20].

HCl has also been reported as an absolutely necessary promoter in hydrocarboxylation [8,15–19,30], although, in hydrocarboalkoxylation, its addition resulted in the formation of undesired ether [1]. The effect of HCl is shown in Fig. 7. Significant improvement in the conversion and slight increase in the selectivity were achieved by addition of HCl. The best result (96% yield in 4 h) was obtained when $HCl/PdCl_2$ mol ratio of 20 (1 ml of 35% solution) was employed. The role of HCl in hydrocarboxylation is not well understood and there are two views. One emphasizes the role of Cl ion as an anionic ligand [8] and the other proposes that acidity of proton is important. To clarify this point, other mineral acids were tested. Fig. 8 shows that only HCl has a promotional effect. The conversion was slightly re-
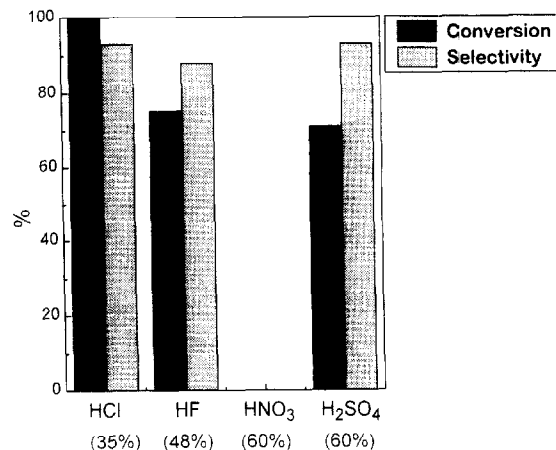
duced by the addition of HF or H_2SO_4 and the reaction stopped completely by the addition of HNO_3. In the case of HNO_3, some poisoning effect of NO_3^- ion exceeded other positive effects. Hence, the proton did not play a major role in hydrocarboxylation.

In Fig. 9, the results of several experiments are presented to investigate the effect of chlorine in more detail. Under the identical condi-
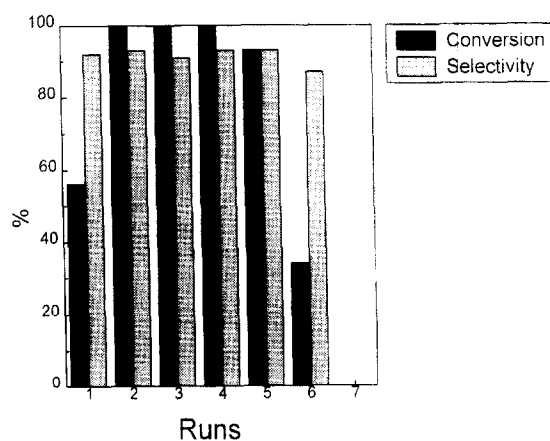

Fig. 9. The effect of catalyst components to show the effect of chlorine: (1) $PdCl_2$–$CuCl_2$, (2) $PdCl_2$–HCl–$CuCl_2$, (3) $PdCl_2$–TAC–CuCl, (4) $Pd(acetate)_2$–HCl–$CuCl_2$, (5) $Pd(acetate)_2$–TAC–$CuCl_2$, (6) $Pd(acetate)_2$–$CuCl_2$, (7) $Pd(acetate)_2$, TAC = tetrabutylammonium chloride.

tions (373 K, 45 bar, 2 mmol of PPh_3 and 2 h of reaction), the catalyst components were varied. Without any added chlorine source, the basic catalyst of $PdCl_2$–$CuCl_2$ yielded a conversion of 55% and a selectivity of 92%. When 0.5 ml of HCl was added, the conversion reached 100%. As HCl was replaced with 5 mmol of tetrabutylammonium chloride $N(C_4H_9)_4Cl$, the same 100% conversion was achieved. Since $N(C_4H_9)_4Cl$ does not contain a proton source, the result could be taken as another evidence that chlorine is responsible for the effect of HCl addition. When $PdCl_2$ was replaced with $Pd(OCOCH_3)_2$, the effect was small if HCl or $N(C_4H_9)_4Cl$ was added. Without HCl and $N(C_4H_9)_4Cl$, the conversion was significantly low in $Pd(OCOCH_3)$–$CuCl_2$ system. And $Pd(OCOCH_3)$ alone was completely inactive. The addition of HCl, thus, appears to provide chlorine that serves as a ligand of an active Pd catalyst complex. It has been suggested that the role of chlorine is to stabilize a divalent Pd complex [8]. The complex could be unstable in the presence of CO unless sufficient amount of Cl is provided because divalent Pd would be reduced by CO to Pd metal which is inactive in the reaction.
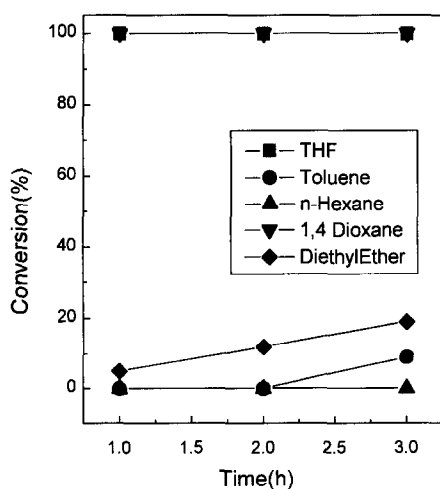

Fig. 10. Conversion of 4-methylstyrene with different solvents: Temperature = 373 K, pressure = 45 bar, HCl = 0.5 ml, $PPh_3/PdCl_2 = 4$, $CuCl_2/PdCl_2 = 3$, $H_2O = 9$ ml (H_2O/4-methylstyrene = 10, mol/mol).

The effect of solvents is shown in Fig. 10. Among the tested solvents, THF, 1,4-dioxane and methylethylketone showed good results. Nonpolar solvents such as n-hexane, toluene and diethylether were not effective. The effectiveness of solvent correlates well with the solubility of water, i.e., THF ~ 1,4-dioxane (miscible with water) > methylethylketone (27.5% soluble) > diethylether (slightly soluble) > toluene (very slightly soluble) > n-hexane (insoluble). Since the reaction occurs in the organic solvent, high solubility of water that is one of the reactants is required for an efficient reaction. The amount of the employed solvent did not make much difference on the conversion and selectivity.

4. Conclusions

As a result of the study, it has been found that a homogeneous catalyst system of $PdCl_2$–$CuCl_2$–PPh_3–HCl dissolved in a highly water-soluble solvent accomplishes almost regiospecific hydrocarboxylation of 4-methylstyrene, a model reactant of 4-isobutylstyrene, to the branched α-(4-methylphenyl) propionic acid. In the reactions, choices of a solvent, the molar ratio of $PPh_3/PdCl_2$, H_2O/4-methylstyrene and the addition of Cl are main factors contributing to the optimal performance of the catalyst system. Compared with the previous results of hydrocarboalkoxylation of 4-methylstyrene to the ester by the same catalyst, the hydrocarboxylation requires severer reaction conditions and the presence of a polar solvent that could solubilize water. The promotional effect of HCl addition is due to the effect of Cl, not of the proton. The addition of oxygen reduces the reaction rates by oxidizing carbon monoxide and PPh_3.

Acknowledgements

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