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The regioselective hydrocarboalkoxylation of 4-methylstyrene catalyzed by palladium complexes

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Abstract

Effects of promoters and reaction conditions have been studied on the regioselectivity of palladium complex-catalyzed hydrocarboalkoxylation of 4-methylstyrene. A catalyst system of $PdCl_2$–$CuCl_2$–PPh_3 dissolved in a nonpolar solvent provided a nearly regiospecific conversion to the branched acid ester at high rates at 100°C and 41 bar of CO pressure. The dependence of regioselectivity on employed phosphines (monodentate vs. bidentate ligands) suggested that the key catalytic species might be a palladium hydride complex rather than a carboalkoxy complex.

Keywords: Alkylstyrene; Hydrocarboalkoxylation; Palladium complex; Promoters; Regioselectivty

1. Introduction

The hydrocarboalkoxylation of alkenes with carbon monoxide and a hydrogen donor is a process of considerable industrial importance to produce carboxylic acids. When the substrate is 4-isobutylstyrene, the product is α-(4-isobutylphenyl) propionic acid (commonly called ibuprofen), a large volume, nonsteroidal anti-inflammatory drug. Current technologies to manufacture ibuprofen entail a number of mostly noncatalytic steps involving noxious reagents [1]. Hydrocarboalkoxylation of 4-isobutylstyrene could provide an efficient and environmentally benign alternative technology [2,3].

The best known carboxylation catalyst is cobalt carbonyls usually promoted with pyridine [4]. Recently, palladium complexes have received great attention because they are effective at lower pressures and selective to branched acids [5–16]. Of particular interest is a catalyst system of $PdCl_2$–$CuCl_2$–HCl–O_2 developed by Alper and coworkers [17–21]. The catalyst system was shown to be effective in the carbonylation of alkenes, amines, chloroarenes, diols, allenes, or alkenols under ambient reaction conditions.

In general, palladium-catalyzed hydrocarboalkoxylation or hydrocarboxylation requires various promoters in order to achieve the desired activity, selectivity and stability of the catalyst. The role of each promoter, however, is not well understood. In the present work, we investigate effects of promoters and reaction conditions on hydrocarboalkoxylation of 4-methylstyrene, a model compound of 4-isobutylstyrene. A particular attention was paid to the regioselectivity to

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the branched ester. For this substrate, the Alper catalyst system dissolved in tetrahydrofuran gives a branched acid yield of 58% in 18 h of reaction at atmospheric pressure and room temperature [17]. On the other hand, branched acid yields greater than 95% have been reported for styrene as the substrate and $PdCl_2(PPh_3)_2$ as the catalyst in 18 h of the reaction at 120°C and 200 bar [15,16]. With a catalyst system of $PdCl_2$–$CuCl_2$–PPh_3 dissolved in a nonpolar solvent, we achieved nearly regiospecific conversion of 4-methylstyrene to the branched acid ester in 2 h of the reaction at 100°C and 41 bar.

2. Experimental

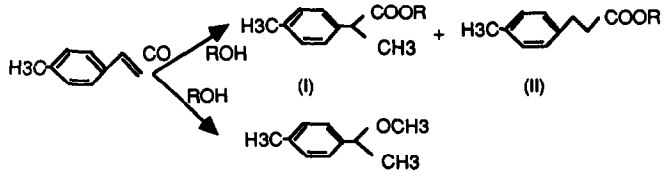
The reactions were performed in a 300 cm^3 stirred autoclave with Hastelloy C walls. The batch reactor was enclosed in an electric furnace whose temperature was monitored and controlled by a thermocouple and a PID temperature controller. In a typical run, 50 mmol of 4-methylstyrene and 0.5 mmol of $PdCl_2$ were dissolved in 70 mmol of toluene or other solvents together with methanol and some promoters (2 mmol of PPh_3 and/or 1 mmol of $CuCl_2$) and charged into the reactor. As an internal standard of gas chromatograph (GC) analysis, 1 g of t-butyl benzene was also charged with the reaction mixture. While stirring, the gas phase of the reactor was flushed three times with 0.4 MPa of CO and then pressurized to the reaction pressure (mostly 4.1 MPa). The reactor was then heated to 100°C in 20 min and the time when the temperature was reached the temperature was taken to be the start of the reaction ($t=0$). The reaction mixture was sampled during the reaction for analysis. A GC (Varian) equipped with FID detector and a crosslinked poly(diphenyl dimethyl siloxane) capillary column was employed for quantitative analysis. The identification of GC peaks was done with authentic samples and GC–MS (Shimazu) analysis.

3. Results

In all runs, three major products were formed. The branched ester of α-methyl p-tolylacetic acid (**I**) and the linear ester (**II**) are expected carbonylation products, and ether (**III**) are the products of a simple etherification between the starting olefin and alcohol without addition of CO. Hence the overall reaction can be expressed by Scheme 1.

Experimental results are summarized in Table 1. Keeping 50 mmol of 4-methylstyrene and 0.5 mmol of $PdCl_2$ constant, promoters, solvent, and some reaction conditions were varied. In Run 1, conditions similar to those of Alper et al. was applied. Thus, the reaction was carried out with the catalyst system of $PdCl_2$–$CuCl_2$–HCl at 40°C and 7 bar of oxygen in methanol. In 17 h, 60% of 4-methylstyrene converted to three products all in comparable proportions. When the temperature was increased to 100°C (Run 1A), the reaction rate increased, yet the product was mostly ether. An interesting observation was that there was a rapid initial pressure drop of the reactor, especially for Run 1A, although the conversion of 4-methylstyrene was still low. It appeared that gas phase oxidation took place. Indeed, aqueous solution of $PdCl_2$–$CuCl_2$ is a known catalyst that can oxidize CO to CO_2 at room temperature [22–25].

In Run 2, triphenyl phosphine (PPh_3) was employed as a promoter instead of $CuCl_2$. The reaction was performed at 100°C and 41 bar of



Scheme 1.

Table 1
Hydrocarboalkoxylation [a] of 4-methylstyrene with $PdCl_2$ and promoters

Run	$CuCl_2$ (mmol)	PPh_3 (mmol)	HCl (ml)	Solvent, ml	Time (h)	Conv. (%)	Selectivity (%)		
							I	II	III
1 [b]	1	–	1	MeOH, 70	17	60	35	30	35
1A [c]	1	–	1	MeOH, 70	7	72	7	2	81
2	–	2	2	MeOH, 70	1	90	6	15	79
2A [d]	–	2	2	MeOH, 70	1	90	–	–	100
2B	–	2	2	MeOH, 4 xylene, 70	2.5	90	81	7	12
2C	–	2	2	MeOH, 4 DME, 70	2	96	68	15	17
3	–	2	–	MeOH, 4 xylene, 70	2	90	85	15	–
3A	–	–	–	MeOH, 4 toluene, 70	2	4	9	–	91
3B	–	–	2	MeOH, 4 toluene, 70	2	23	5	–	95
3C	–	2 (dppr) [e]	–	MeOH, 4 toluene, 70	2	17	12	88	–
3D	–	2	–	H_2O, 4 toluene, 70	3	11	–	–	–
4	1	2	–	MeOH, 4 toluene, 70	2	99	97	1	2
4A [f]	1	2	2	MeOH, 4 toluene, 70	3	64	80	6	13

[a] Reaction was performed under the following conditions unless otherwise stated: 100°C, 41 bar of CO, and 0.5 mmol of $PdCl_2$.
[b] 40°C, 7 har of CO, and 3 bar of O_2.
[c] 100°C, 7 bar of CO, and 3 bar of O_2.
[d] Without CO.
[e] dppr = 1,3-bis(diphenylphosphino)propane.
[f] With 7 bar of O_2 added.

CO without O_2, which became the standard reaction conditions for other runs. The reaction rate increased dramatically, achieving 90% 4-methylstyrene conversion in 1 h. However, ether was the major product again. In addition, PPh_3 system seems to produce more linear isomer compared to the $CuCl_2$ system. When the reaction was run without CO (Run 2A), the same amount of 4-methylstyrene was converted exclusively to the ether. Hence, it was confirmed that CO was not involved at all in the ether formation and that the rate of carbonylation was much slower than etherification under the present condition. In an effort to suppress the ether formation, the amount of methanol was reduced to 4 ml with xylene as a solvent. As shown in Run 2B, ether formation was greatly reduced and the desired branched ester emerged as the dominant product. If solvent was replaced with polar 1,2-dimethoxyethane (DME, Run 2C), the rate increased, but the selectivity to the branched ester was substantially deteriorated.

In Run 3, HCl was omitted from the reaction solution. The formation of ether was completely suppressed. When PPh_3 was also omitted (Run 3A), the reaction was extremely slow, giving only 4% conversion in 2 h, mostly to ether. When HCl

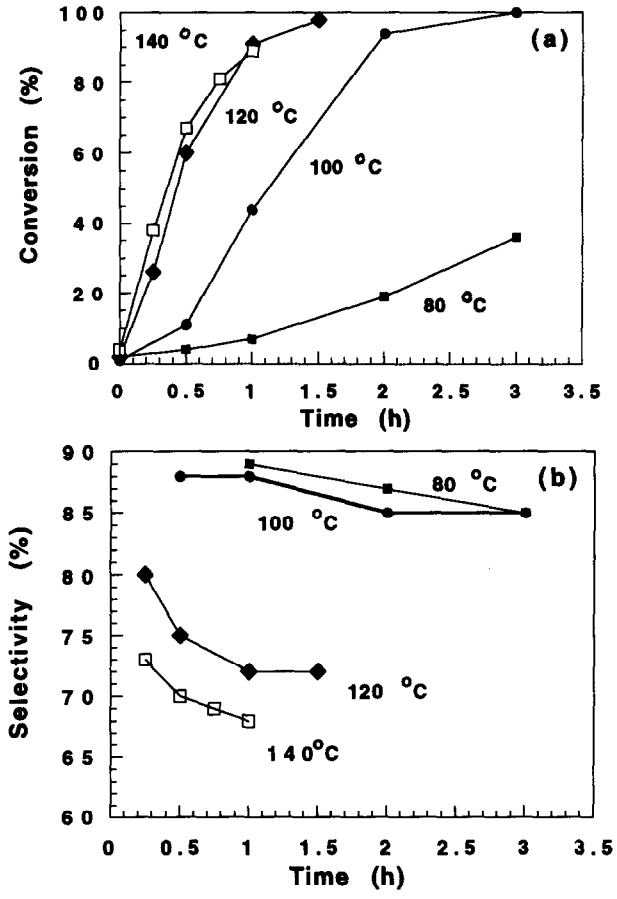


Fig. 1. Effect of reaction temperature on (a) the conversion of 4-methyl styrene and (b) selectivity to the branched ester. Reaction was performed at 41 bar of CO, and 0.5 mmol $PdCl_2$, 2 mmol PPh_3, 4 ml methanol and 70 ml of toluene.

was added again without PPh_3, conversion to the ether increased substantially. The results clearly show the role of each promoter in 4-methylstyrene conversion. The undesired side reaction, ether formation is catalyzed by an acid. The most significant role of HCl is thus that of an acid catalyst. The etherification is suppressed by reducing methanol concentration or removing HCl from the reaction system. In the carbonylation which is in competition with the etherification, the presence of PPh_3 is essential for significant rates. Without PPh_3, $PdCl_2$ catalyzes mostly etherification due to its own acidity. In order to see the effect of different phosphines, PPh_3 was replaced with 1,3-bis(diphenylphosphino)propane (dppr), a potential bidentate ligand (Run 3C). The reaction rate was reduced significantly and the linear ester became the dominant product. This dramatic change in regioselectivity between monodentate and bidentate ligands has been reported before in palladium-catalyzed hydrocarboalkoxylation of styrene [15]. In Run 3D, water was used instead of methanol in an attempt to produce the acid directly. The reaction rate was greatly reduced.

When $CuCl_2$ was added to $PdCl_2$–PPh_3 without HCl and with a small amount of methanol in xylene, our best system was found as shown in Run 4. The almost complete conversion of 4-methylstyrene in 2 h, and 97% selectivity, to the desired branched acid were achieved. Addition of O_2 and HCl to this system deteriorated the performance (Run 4A).

The effects of reaction temperature are shown in Fig. 1 for $PdCl_2$–PPh_3 catalyst system. Higher

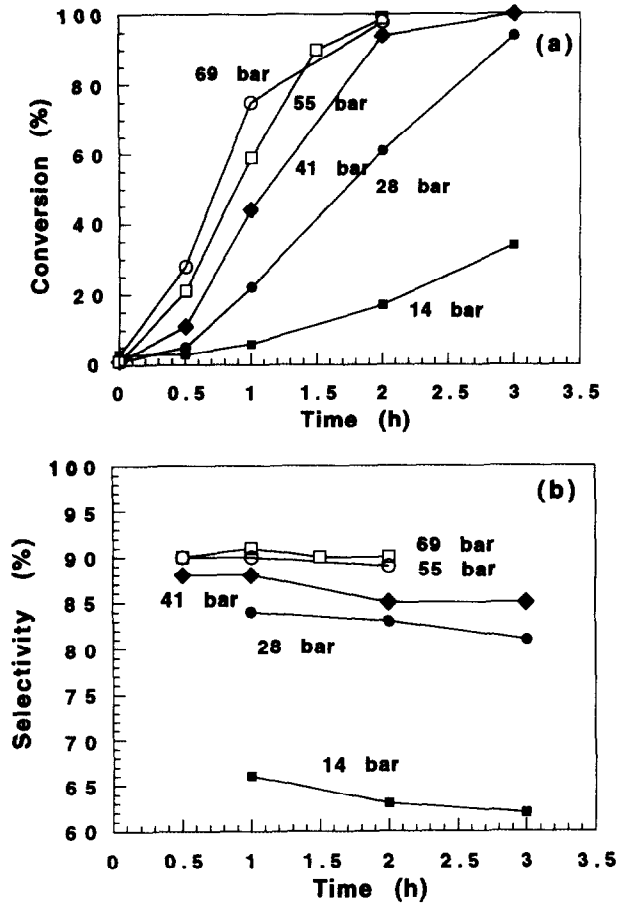
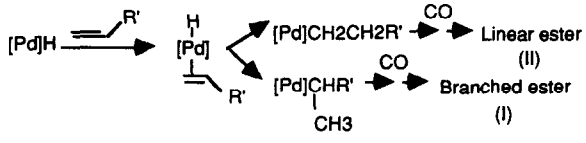


Fig. 2. Effect of CO pressure on (a) the conversion of 4-methyl styrene and (b) selectivity to the branched ester. Reaction was performed at 100°C, and 0.5 mmol $PdCl_2$, 2 mmol, 4 ml methanol and 70 ml of toluene.

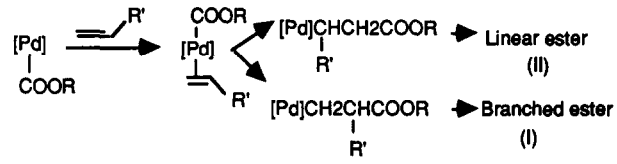
reaction temperatures yielded higher rates and lower selectivities to the branched ester. The optimal temperature appears to be 100–120°C. The reduction in selectivity was due to the preferred formation of the linear ester at high temperatures. The ether formation was negligible (max. 2%) at all temperatures. Fig. 2 shows the effects of reaction pressure. High CO pressures increased both rates and selectivities. The ether formation was negligible (Max. 3% at 14 bar) and completely disappeared above 50 bar. A pressure near 50 bar appears to be optimal because further increase brought about only small improvements in the rate and selectivity. In both experiments shown in Figs. 1 and 2, there was a slight decrease in selectivity with the reaction time.

4. Discussion

As described, it has been found that the catalyst system of $PdCl_2$–$CuCl_2$–PPh_3 in a nonpolar solvent promotes almost regiospecific hydrocarboalkoxylation of 4-methylstyrene, a model substrate for 4-isobutylstyrene which is the key intermediate in the new synthetic processes of ibuprofen. Each catalytic component and solvent had its spe-



Scheme 2.



Scheme 3.

cific role. Optimal reaction conditions were defined.

In addition to palladium, the main catalytic component for the carbonylation reaction, some promoters or additives were essential for high reaction rates. In particular, only when both PPh_3 and $CuCl_2$ were employed, the regiospecifc hydrocarboalkoxylation of 4-methylstyrene resulted. PPh_3 is the mostly widely employed ligand for homogeneous Pd catalysis [15,26]. One of its important roles is known to stabilize molecular palladium species (most frequently zero valent species), and thus to prevent the formation of inactive metal particles. $CuCl_2$ is the usual promoter which reoxidizes Pd(0) to active Pd(II) in palladium redox catalysis. It is interesting that both of them are needed here. Acidity of the reaction mixture has to be avoided and alcohol concentration should be minimized in order to prevent the formation of the ether.

The mechanism of hydrocarboalkoxylation with palladium catalysts is not well defined [27]. Depending on key palladium complex prior to olefin insertion, two major mechanisms have been proposed. One involves palladium hydride Pd–H [4,12] and the other does palladium carboalkoxy Pd–COOR [11]. The hydride mechanism as summarized below involves insertion of olefin into Pd–H bond followed by carbonylation of the resulting alkyl. The direction of olefin insertion determines whether a linear or a branched ester is formed (Scheme 2). The carboalkoxy mechanism can be summarized in the same manner (Scheme 3).

A notable difference between these two mechanisms in relation to regioselectivity is that the effect of bulky ligands in the palladium coordination sphere may be different when steric effects dominate the selectivity. As is obvious in Schemes 2 and 3, a bulky ligand would promote the selective formation of linear ester in the hydride mechanism, while branched ester formation would be preferred in the hydroalkoxy mechanism. The marked difference in selectivity between PPh_3 and dppr provides a clue to which mechanism may prevail under the present reaction conditions. Chelating dppr with its preferred *cis* ligation would make the palladium coordination sphere more crowded than monodentate PPh_3 would. Hence, the fact that dppr promotes selective formation of the linear ester might be taken as evidence for the hydride mechanism. Furthermore, a recent work [4] provided evidence that the carbomethoxy complex often observed in the reaction system was not an intermediate on the catalytic cycle, but rather a byproduct.

With PPh_3, which does not impose steric hindrance, it has been inferred that the branched palladium alkyl complex in Scheme 2 is more stable than the linear complex because the former may be stabilized by π-benzylic interaction of phenyl group with palladium, but not the latter [14]. This would result in preferential formation of the branched ester over the linear ester. The effect of $CuCl_2$ could not be understood on any steric ground. $CuCl_2$ by itself provides remarkable selectivities for branched esters under certain conditions as exemplified in the work of Alper et al. [17]. In the present work, it yields dramatic improvement of the selectivity in cooperation with PPh_3. The selectivity is also significantly affected by reaction temperature, pressure, and the polarity of solvent. Obviously, there are many factors governing the selectivity.

An interesting finding in this work is an apparent harmful effect of HCl, which has often been reported as a beneficial promoter [16,17]. The role of HCl has been proposed to cleave Pd–C

bond for the final product formation and to regenerate active catalytic Pd complex such as $PdCl_2(PPh_3)_2$ [27]. After Run 3A, we observed dark metal deposits in the reactor. When HCl was added (Run 3B), the formation of the deposits was suppressed significantly. Hence, a role of HCl could be to stabilize the palladium complex by preventing the formation of palladium particles. However, this role and acceleration of carbonylation appears to be accomplished more efficiently by PPh_3.

Acknowledgements

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