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Catalytic carbonylation of α-(6-methoxyl-2-naphthyl)ethanol to methyl esters of naproxen using $PdCl_2$–$CuCl_2$–PPh_3–acid catalyst system

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Abstract

α-(6-Methoxyl-2-naphthyl)ethanol was carbonylated into methyl ester of α-(6-methoxyl-2-naphthyl)propionic acid (Naproxen) in up to 100% yield and 100% selectivity using $PdCl_2$–$CuCl_2$–PPh_3–*p*-Ts catalyst system without any halogen promoter or other extreme condition.

Keywords: Carbonylation; α-(6-Methoxyl-2-naphthyl)ethanol; Methyl esters of Naproxen; $PdCl_2$–$CuCl_2$–PPh_3–acid catalyst system

The transition metal complex catalyzed carbonylation of olefins with carbon monoxide and alcohol is of great interest for the synthesis of industrially valuable carboxylic esters such as linear fatty acid esters and 2-aryl-propionic acid esters [1–3]. The carbonylation reaction of vinyl aromatics leads itself to the synthesis of intermediates towards nonsteroidal antiinfammatory agents which are functionalized 2-aryl-propionic acids [4–7], but the satisfactory yields have not been obtained. In some cases, it is difficult to obtain olefins from corresponding alcohol or other compounds. Therefore, in place of the olefins, it is desirable to use the corresponding hydroxylic compounds as substrates for carbonylation. The study of carbonylation of alcohols to acids have been reported [8–12], such as α-(6-methoxyl-2-naphthyl)ethanol was carbonylated to Naproxen using $Pd(PPh_3)_2$/HCl catalytic system [8], and 1-(4′-isobutylphenyl)ethanol was also carbonylated to Ibuprofen using the same catalytic system [9,10]. But both carbonylation reactions of the alcohols took place in hydrogen chloride media which is seriously corrosive for the autoclave and may deactivate the catalyst. The carbonylation of *tert*-butyl alcohol to esters of *iso*-valeric acid using Pd–PPh_3–*p*-Ts catalyst system was reported in our previous papers [13–15].

In this work the catalytic system obtained in situ from $PdCl_2$, $CuCl_2$, PPh_3, and *p*-toluenesulfonic acid (*p*-Ts) promotes a highly selective formation of methyl esters of Naproxen from α-(6-methoxyl-2-naphthyl)ethanol, carbon monoxide and methanol in 1,4-dioxane without any halogen, and the results of the carbonylation of α-(6-methoxyl-2-naphthyl)ethanol and other similar alcohols to various esters catalyzed by this catalyst system are presented in this paper.

The reaction of carbonylation of the α-(6-methoxyl-2-naphthyl)ethanol to methyl ester of Naproxen is shown in Eq. (1), and the side reaction in Eq. (2) and Eq (3).

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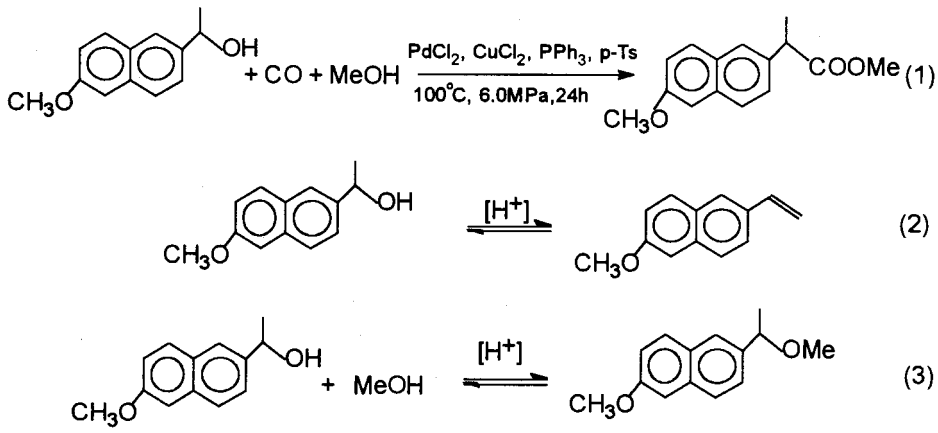


This reaction was strongly influenced by the amount of *p*-Ts, the results are listed in Table 1. Under the reported experimental conditions high yield and selectivity are obtained when *p*-Ts/Pd (mol/mol) = 13.1. These results suggest that the starting α-(6-methoxyl-2-naphthyl)ethanol undergoes a reversible reaction in Eq. (2), that is, in the presence of certain amounts of *p*-Ts, α-(6-methoxyl-2-naphthyl)ethanol is dehydrated to 2-vinyl-6-methoxynaphthalene which is carbonylated to the esters of Naproxen by $PdCl_2$–$CuCl_2$–PPh_3.

Various palladium compounds are widely used as carbonylation catalysts. When the dioxane was used as solvent and the molar ratio of *p*-Ts to Pd was 13.1, the effect of the Pd(II) catalyst precursors on the carbonylation of α-(6-methoxyl-2-naphthyl)ethanol was investigated and the results were listed in Table 2. Under these conditions high yield was obtained only when the palladium chloride is used as precursors in combination with six equivalents of PPh_3, and mild yield was obtained using Pd/C as precursors. When the amount of PPh_3 was reduced at half, the yield and selectivity were also reduced nearly at half. This result showed that molar ratio of P to Pd must surpass 3, otherwise poor yields were obtained.

The reaction in Eq. (1) is also influenced by the nature of the solvents and the results are listed in Table 3. It can be seen from Table 3 that the highest yields of methyl esters of Naproxen were obtained when the solvents with suitable polarization were used, such as

Table 1
The effect of the amount of *p*-Ts on carbonylation of α-(6-methoxyl-2-naphthyl)ethanol

No.	*p*-Ts/Pd (mol/mol)	Conversion of alcohol (mol%)	Yield (mol%)[a]			Selectivity to ester (%)
			Ester	Ether	Olefin	
1	7.5	~100	66.7	17.9	15.4	66.7
2	9.9	96.3	77.0	4.8	14.5	80.0
3	13.1	~100	~100	0	0	~100
4	15.0	~100	78.6	5.2	16.4	78.6

Reaction conditions: $PdCl_2$, 0.08 mmol; $CuCl_2$, 0.185 mmol; PPh_3, 0.50 mmol; pressure, 6.0 MPa; temp. 100°C; reaction time, 24 h; α-(6-methoxyl-2-naphthyl) ethanol, 0.80 g; methanol, 0.5 ml; 1,4-dioxane, 6.0 ml.
[a] Yield based on the starting alcohol.

Table 2
Carbonylation of α-(6-methoxyl-2-naphthyl)ethanol using different palladium precursors

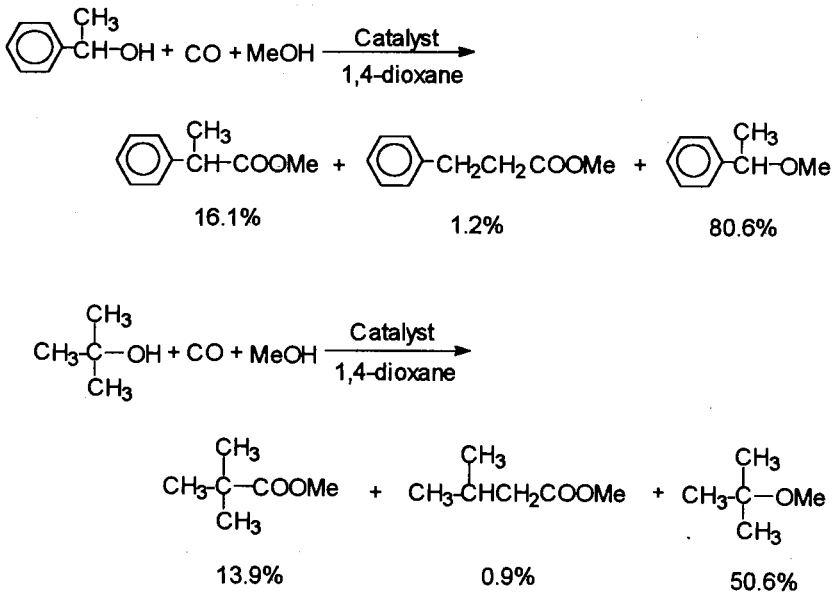
No.	Catalyst precursor (0.08 mmol)	Conversion of alcohol (mol%)	Yield (mol%)			Selectivity to ester (%)
			Ester	Ether	Olefin	
1	$PdCl_2$	~100	~100	0	0	~100
2	$Pd_3(dba)_2^a$	~100	95.0	0	5.0	95.0
3	$Pd(OAc)_2$	95.7	85.0	3.1	7.6	89.6
4	Pd/C	81.7	69.1	0	12.6	84.6
5	$PdCl_2^b$	90.3	45.9	5.2	39.2	50.8

Reaction conditions are the same as in Table 1, except that *p*-Ts/Pd = 13.1 and catalyst precursor varied.
[a] dba: dibenzylideneacetone.
[b] PPh_3, 0.25 mmol.

Table 3
Catalytic carbonylation of α-(6-methoxyl-2-naphthyl)ethanol in different solvents

No.	Solvent (5 ml)	Conversion of alcohol (mol%)	Yield (mol%)			Selectivity to ester (%)
			Ester	Ether	Olefin	
1	Benzene	~100	64.5	22.9	12.6	64.5
2	Toluene	~100	86.8	13.2		86.8
3	1,4-dioxane	~100	~100	0	0	~100
4	THF	~100	65.5	11.2	23.3	65.5
5	Anisole	~100	~100	0	0	~100
6	Dimethoxyethane	~100	~100	0	0	~100
7	Dioxane[a]	89.0	77.6	4.5	11.4	87.2

Reaction conditions are the same as in Table 1, except that p-Ts/Pd = 13.1 and solvent varied.
[a] Ethanol was used instead of methanol.



Scheme 1. Carbonylation of two kinds of alcohols in dioxane, namely α-phenyl ethanol and *tert*-butyl alcohol.

1,4-dioxane, 1,2-dimethoxyethane and anisole, which give nearly 100% yields of ester. But the yields of ester were not as high when the solvent's polarization was too large and too small. For example, when the ethanol was used instead of methanol, the yield of ester was only 77.6% because of the smaller polarization of ethanol. This phenomena can be explained by the fact that the first step of this catalytic reaction is the dehydration of α-(6-methoxyl-2-naphthyl)ethanol to 2-vinyl-6-methoxynaphthalene, then 2-vinyl-6-methoxynaphthalene is carbonylated to the esters of Naproxen. In the first step, the larger polarization of solvent is more favorable to the dehydration. But in the second step, the smaller polarization of solvent is more favorable to the hydroesterification [9]. Therefore, the solvents with suitable polarization are required for this catalytic reaction.

Other tertiary and secondary alcohols were also carbonylated by $PdCl_2$–$CuCl_2$–PPh_3–p-Ts catalytic system. We have investigated the carbonylation of two kinds of alcohols in dioxane: α-phenyl ethanol and *tert*-butyl alcohol. The results are listed in Scheme 1 (reaction conditions were the same as in Table 1, except that p-Ts/Pd = 13.1, yields are calculated based on the starting alcohols). It can be seen from Scheme 1 that the reaction activity of α-phenyl ethanol is lower than that of α-(6-methoxyl-2-naphthyl) ethanol. A possible explanation is that α-phenyl ethanol easily undergo etherification, and the ether is too stable to produce styrene. In addition, two isomers of the product (b/n = 13.4) were obtained when α-phenyl ethanol was carbonylated by this catalyst. This result is just the same as the carbonylation of styrene using $PdCl_2$–$CuCl_2$–PPh_3 catalyst system [9]. *tert*-Butyl alcohol can be also carbonylated by this kind of catalyst and poor yield of ester was obtained. The main product is methyl 2,2-dimethylpropionate.

In conclusion, esters of Naproxen can be obtained in good yields with excellent regiochemical selectivity by the carbonylation of α-(6-methoxyl-2-naphthyl)ethanol

with palladium chloride, copper chloride and *p*-toluenesulfonic acid in the presence of triphenylphosphine ligand. Other similar alcohols can also be carbonylated by the same catalytic system.

Acknowledgements

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