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The First Asymmetric Carbonylation of 1-(6'-Methoxy-2'-naphthyl)ethanol to the Methyl Ester of (*S*)-Naproxen

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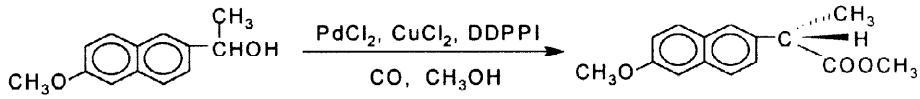
Abstract: 1-(6'-Methoxy-2'-naphthyl)ethanol is asymmetrically carbonylated to the methyl ester of (*S*)-naproxen in a $PdCl_2$-$CuCl_2$-DDPPI (DDPPI: 1,4:3,6-dianhydro-2,5-dideoxy-2,5-bis(diphenylphosphino)-*L*-iditol) catalytic system with a chemical yield of 90% and an optical yield of 81% e.e.. The reaction was carried out in ethyl methyl ketone under 100°C and 8 MPa of CO for 24-48h.

Synthesis of (*S*)-naproxen through homogeneous catalytic processes has received considerable attention in recent years[1]. Asymmetric hydrogenation process of 2-(6'-methoxy-2'-naphthyl)acrylic acid is effective. chiral ruthenium and rhodium complexes have been used to give an optical yield more than 95% e.e. at a conversion of 100%[2]. Asymmetric hydroesterification of olefins is also effective. Catalyzed by $PdCl_2$-$CuCl_2$-BNPPA, 2-vinyl-6-methoxynaphthalene was asymmetrically hydroesterified to (*S*)-naproxen with an optical yield of 85%[3]. It is worth noting that 2-(6'-methoxy-2'-naphthyl) acrylic acid and 2-vinyl-6-methoxynaphthalene are not commercially available.



1 **2**

Scheme 1.

We therefore propose an asymmetric carbonylation process in which methyl ester of (*S*)-naproxen (**2**) is prepared from 1-(6'-methoxy-2'-naphthyl)ethanol (**1**) (as shown in Scheme 1). The alcohol **1** can be easily obtained from the industrial intermediate, 6-methoxy-2-acetylnaphthalene, over a 5wt% Pd/C catalyst at a conversion of 100% in THF.

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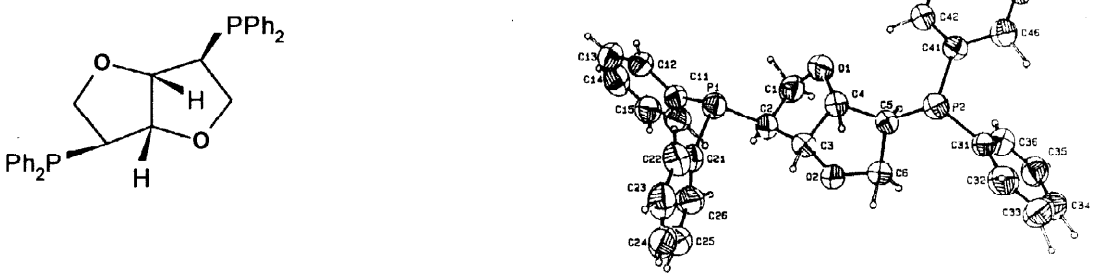
The reaction conditions were optimized and some of the results are listed in Table 1.

The steric and electronic properties of chiral phosphine ligands exert a dramatic influence on the catalytic activity and selectivity of this reaction. DDPPI (1,4:3,6-dianhydro-2,5-dideoxy-2,5-bis(diphenylphosphino)-*L*-iditol) has four chiral carbon centers, two of them, connected to phosphorus atoms, are in S forms[4]. Crystal X-ray diffraction analysis shows that DDPPI has a rigid frame and a strong steric hindrance (Scheme 2)[5]. The distance between P1-P2 is 6.24 Å. These features lead to a non-chelating character and are responsible for the highly chiral induction of some reactions. DDPPI was found very effective in the asymmetric hydroesterification of styrene in our previous work(99.3 % e.e.)[6]. Application of this ligand to the asymmetric carbonylation of alcohol **1** also gives good results(Table 1).



Scheme 2

Both the ratio of DDPPI/Pd and acidity of the acids used have a significant influence on the chemical and optical yields. As shown in Table 1, 90% chemical yield and 76% optical yield are obtained with the ratio of DDPPI/Pd = 1.5/1 in the presence of p-toluenesulfonic acid (p-TsOH)(Run No.2). Higher ratio (DDPPI/Pd = 3/1) can enhance the optical yield to 81% e.e. but decrease the chemical yield to 54% (Run No.3). CF_3COOH has a negative influence on the optical yield and is corrosive to the autoclave (Run No.7).

Solvents play a prominent role in the reaction course. Dioxane and tetrahydrofuran are effective, but methyl ethyl ketone is the optimum. A weak coordination of the solvents with palladium may be involved.

Cocatalyst $CuCl_2$ has a positive influence on the regio- and enantioselectivities of the reaction (Run No.5 and 6).

Under these reaction conditions, a trace amount of the normal product (methyl 3-(6'-methoxy-2'-nathphyl)propanoate) is detected.

For a typical procedure, $PdCl_2$, $CuCl_2$, **1**, p-TsOH, DDPPI, CH_3OH, methyl ethyl ketone were added into a 20 ml autoclave. Under the conditions of 8 MPa CO and 100 ℃, the reaction was maintained for 24-48 h. Yield of the methyl ester **2** was determined by GC analysis based on the starting alcohol **1**. Optical yield was

determined by ^{1}H NMR with chemical shifting reagent ($Eu(hfc)_3$) after column separation of the crude product (gel silica, 200-300 mesh, n-hexane/ethyl acetate = 10/1). The methyl ester of (*S*)-naproxen can be hydrolyzed into (*S*)-naproxen if desired.

Table 1. Asymmetric Carbonylation of 1-(6'-Methoxy-2'-naphthyl)ethanol to Methyl Ester of (*S*)-Naproxen Catalyzed by $PdCl_2$-$CuCl_2$-DDPPI System

Run No.	Acids	**1**/Pd/Cu/DDPPI (mol)	b / n [1]	Yield of **2** % [1]	Optical purity of **2** % e.e [2]
1	p-TsOH	50/1/2/1	90/10	85	56
2	p-TsOH	50/1/2/1.5	96/4	90	75
3	p-TsOH	50/1/2/3	99/1	54	81
4	p-TsOH	100/1/2/1.5	90/10	70	60
5	p-TsOH	50/1/0/1.5	85/15	81	42
6	p-TsOH	50/1/4/1.5	97/3	90	77
7	CF_3COOH	50/1/2/1.5	82/18	93	11

Reaction conditions: **1**, 2.0 mmol; p-TsOH or CF_3COOH, 0.4 mmol; methyl ethyl ketone, 5.0 ml; time, 40h; temperature, 100 ℃; CO, 8 MPa.

[1] Determined by GC analysis.

[2] Determined by ^{1}H NMR with chemical shifting reagent ($Eu(hfc)_3$). Configuration was determined by the signs of optical rotation.

b: Methyl ester of (*S*)- naproxen (The branched product)

n: The normal product

Palladium(II) complexes with chiral phosphine ligands are important precursors in asymmetric carbonylation reactions[7]. The mechanism of olefin hydrocarboxylations is well-known[8]; nevertheless, the mechanism of α-aryl ethanol carbonylations is still not clear. We are trying to prepare Pd-Cu-DDPPI complex under the reaction conditions to gain more insight into the reaction mechanism. The experiment is in progress.

In summary, the asymmetric carbonylation of 1-(6'-methoxy-2'-naphthyl)ethanol to methyl ester of (*S*)-naproxen catalyzed by $PdCl_2$-$CuCl_2$-DDPPI system is stereoselective and regioselective at high chemical yields.

REFERENCES AND NOTES

1. Sonawane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kulkarni D. G. *Tetrahedron: Asymmetry* 1992, 3(2), 163.

2. a) Ohta, T.; Takaya, H.; Kitamura, K.; Nagai, K.; Noyori, R. *J. Org. Chem.* 1987, 52, 3174.

b) Manimaran, T.; Wu, T.-C.; Klobucar, W. D.; Kolich, C. H.; Stahly, G. P. *Organometallics*1993, 12, 1467.

3. Stille, J. K.; Parrinello, G. *J. Am. Chem. Soc.* 1987, 52, 3174.

4. Bakos, J.; Heil, B.; Marko, L. *J. Organomet. Chem.* 1983, 253, 249.

5. Crystal structure data for DDPPI($C_{30}H_{28}O_2P_2$): F(000)=1016, orthorhombic space group $P2_12_12_1$, a=9.460(8) Å, b=14.822(5) Å, c=18.424(6) Å,V=2583(2) $Å^3$, Z=4.

6. Zhou, H.-Y.; Hou, J.-G.; Cheng, J.; Lu, S.-J.; Fu, H.-X.; Wang, H.-Q. *J. Oganomet. Chem.* 1997, 543, 227.

7. a) Alper, H.; Hamel, N. *J. Am. Chem. Soc.* 1990, 112, 2803.

b) Wehman, P.; van Donge, H.M.A.; Hagos, A.; Kamer, P.C.J.; van Leeuwen, P.W.N.M. *J. Organomet. Chem.* 1997, 535, 183.

8. Noyori, R. *Asymmetric Catalysis In Organic Synthesis*; John Wiley & Sons, Inc.: New York, 1994; pp. 167.