Chinese Chemical Letters Vol. 14, No. 11, pp 1101 – 1104, 2003 1101
http://www.imm.ac.cn/journal/ccl.html

Asymmetric Hydrogenation Synthesis of (S)-(+)-2-(6′-methoxyl-2-naphthyl) propionic Acid by Cinchona Modified Pd(0)-α-FeOOH Catalyst

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Abstract: Asymmetric hydrogenation of (6-methoxyl-2-naphthyl)-2-acrylic acid catalyzed by cinchona modified Pd(0)-α-FeOOH was reported and ee's of (S)-(+)-2-(6′-methoxyl-2-naphthyl) propionic acid ((S)-(+)-naproxen) up to 98% was achieved firstly.

Keywords: Asymmetric hydrogenation, catalyze, cinchona, Pd(0)-α-FeOOH, (S)-(+)-naproxen.

During the past decades enormous progress was made in asymmetric catalytic synthesis, an well-known example is BINAP[1], the chiral hydrogenation synthesis of S-(+)-naproxen catalyzed by BINAP-Ru dicarboxylate complexes provides excellent enantioselectivity (up to 99% ee) and good chemical yield (92%), however the pressures is relatively high (135-150 atm) and the (S)-BINAP-Ru(III) complex is very expensive. This problem may present a practical limitation. In recent years new methodologies have also been studied such as asymmetric methylation of 2-arylacetic acids, asymmetric hydroformylation/ hydrocarboxylation of the appropriate styrene derivatives, asymmetric alkylation of appropriate aromatic compounds. Unfortunately, the optical yields in these latter cases[2] are far from excellent.

(6-Methoxyl-2-naphthyl)-2-acrylic acids constitute an important class of substrates for this reaction because the resulting α-aryl-2-propanic acids are a variety of commercially important non-steroidal anti-inflammatory agents[3,4]. Because of the current commercial important of the well-known anti-inflammatory drug naproxen and its derivatives, we chose (6-methoxyl-2-naphthyl)-2-acrylic acid as precursor for our initial studies. Here we report our initial findings on asymmetric hydrogenation of (6-methoxyl-2-naphthyl)-2-acrylic acid catalyzed by cinchona modified Pd-α-FeOOH (CN-Pd-α-FeOOH) and ee's (enantiomeric excesses) up to 98% have been achieved. It is a thrust work to widen the type of enantioselective hydrogenation of Pt/Al_2O_3 or Pd/Al_2O_3 modified by cinchona[5]. Asymmetric hydrogenation of the substrate carried out according to Scheme 1, gave the corresponding 2-naphthylpropionic acid with high enantioselectivity.

The effect of the S/C (substrate/ catalyst molar ratio) and reaction time on enantiomeric excesses was investigated and the results were summarized in **Table 1**.

Remarkably, the highly enantioselective catalyst CN-Pd-α-FeOOH exhibits very high activity in asymmetric hydrogenation of (6-methoxyl-2-naphthyl)-2-acrylic acid

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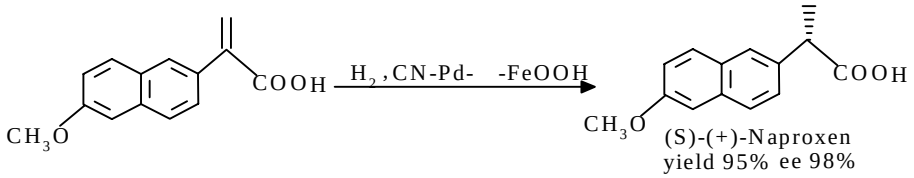
Scheme 1



(**Table 1**,entry 1-6), the catalytic activities as high as 650 turnover number/ h (780 total) have been measured for the hydrogenation using 0.4% mol α-FeOOH and 0.1% mol of Pd. Using this catalyst, the naproxen has been prepared in an optically pure form for the first time and the hydrogenated product was obtained with excellent ee (98%) and good conversion (95%) in 3 h (**Table 1**, entry 4).

Table 1 Asymmetric hydrogenation of (6-methoxyl-2-naphthyl)-2-acrylic acid [a]

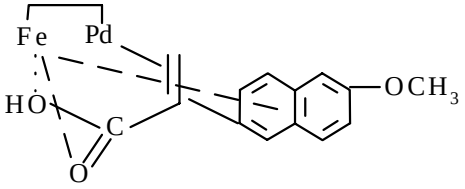
Entry	S/C	Time (h)	Conv. [b] (%)	ee [c] (%)
1	50	3	92	91
2	100	3	92	94
3	150	2	93	95
4	150	3	95	98
5	150	5	94	96
6	200	3	92	90
7 [d]	150	3	86	96
8 [e]	150	3	90	92

a. Hydrogenations were carried out under the following reaction conditions: H_2 =1 atm, room temperature; b. Bases on GC analysis and ^{1}HNMR; c. The enantiomeric excesses (ee% = (|[R]-[S] |)×100/([R]+[S])) were determined by specific rotation and were supported by ^{1}H and ^{13}C NMR measurements in the presence of tris(3-hoptfluoro propyhydroxymethox)-D-camphorate europium(III) [Eu(hfc)$_3$] as chiral reagent. The absolution configurations of the products were determined by comparison with the known, published directions of rotation[4]; d. Substrate: Ibuprofen; e.Substrate: Flurbuprofen.

To demonstrate the feasibility of this new approach, we noted that maybe (6-methoxyl-2-naphthyl)-2-acrylic acid is a typical substrate with functionalized olefin which have a high binding affinity with Pd and the oxygen atom in carbonyl group binds strongly to Lewis acid center Fe and also in the same reaction conditions, the naphthyl ring and carboxyl oxygen atom which with high electronic density taking proper orientation can bonded with Fe through electrostatic interaction. A multipoint interaction between catalyst and substrate have been formed and could effectively control the proximity and proper orientation and conformation rigidity of the substrate (**Figure 1**), high enantioselectivity should be achieved in this catalysis system.

In theory, the free energy difference($\Delta\Delta G$) in the first irreversible step involving diastereometric transition states determines the enantiomeric excess of a reaction. At room temperature, a $\Delta\Delta G$ of 3 kcal/mol will give essentially enantiomerically pure product. The control of enantioselectivity through multipoint interactions has a great advantage because most of these proposed interactions are quite strong (>3 kcal/mol) that resulting in a preferred pathway to form one enantiomer, highly selective asymmetric catalysis can be achieved.

Figure 1 Possible multipoint interactions between catalyst and substrate



Even though the enantioselectivity of our system has been optimized only for the (S)-naproxen, we briefly investigated the selectivity in a number of other substrates by cinchona modified Pd-α-FeOOH catalysis(**Table 1**, entries 7-8). In each case, the conversion and the enantioselectivity are unprecedented, and the remarkable catalytic activity of cinchona modified Pd-α-FeOOH catalyst has been confirmed.

Further studies on the asymmetric hydrogenation and applications of this catalyst in other reactions will be reported in due course.

Experimental

General methods and materials

The Pd and Fe contents in the catalysts were obtained by inductively coupled plasma atomic emission spectroscopy (AES) using ICP/6500 from Perkin-Elmer Inc. The crystallinity of the sample was determined by powder X-ray diffraction (XRD) using a scanning diffractometer of D/MAX-RA with Ni-filtered CuKa radiation (λ =1.5418 Å). A scan speed of 2^o/min was used comparing with the intensity of the reflection pattern to that of pure sample. The surface area and pore size distribution of the samples were determined by N_2 adsorption-desorption at -197℃ on previously degassed samples at RT and 10^{-7} atm pressure for BET surface area and meso-micropore analysis, macropore analysis was obtained by Hg intrusion, the pore size distribution of the samples was calculated in accordance with the BJH method.

Preparation of the Pd-α-FeOOH catalyst

The Pd-α-FeOOH catalyst with the ratio of Pd/Fe=1/4 in molar was prepared by the following procedure: Into 30 mL water solution of $PdCl_2$ (1.17 mmol, 0.208 g), the $Fe(Ac)_3$ precursors (4.70 mmol, 1.095 g) were added to 20 mL of HCHO (30%, m/m), then 20 mL of 20% NaOH solution were dropped in and pH was adjusted to ≥10.0 under stirring for 1 h, the solid were separated and washed with water (3×20 mL), dried *in vacuo* at 100°C (80 mmHg), finally the sample were calcined at 280°C for 3 h. The hydrogenations were performed in an atmospheric bath reactor at 25℃.

Asymmetric Hydrogenation of (6-methoxyl-2-naphthyl)-2-acrylic acid

Hydrogenations were carried out under the following reaction conditions: H_2 =1 atm, room temperature. The conversion was evaluated bases on GC analysis and ^{1}HNMR measurement. The absolution configurations of the products were determined by

comparison with the known, published directions of rotation[4]. Other reaction condition is the same as our previous paper[6].

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Received 16 September, 2002