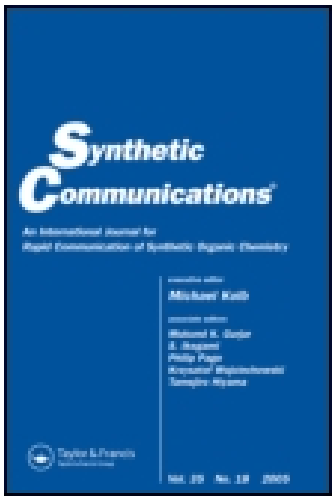

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New Synthesis of Optically Active α-Arylpropanoic Acid: The Asymmetric Hydrogenation of Atropic Acid over Cinchona-Modified Pd/Fe_2O_3 Catalysts

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New Synthesis of Optically Active α-Arylpropanoic Acid: The Asymmetric Hydrogenation of Atropic Acid over Cinchona-Modified Pd/Fe_2O_3 Catalysts

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ABSTRACT

The first satisfactory application of the heterogeneous cinchona-modified Pd/Fe_2O_3 catalyst system in the synthesis of optically active α-arylpropanoic acid, namely, the highly enantioselective (up to 87% ee) hydrogenation of atropic acid to *S*-(+)-naproxen is described.

Key Words: α-Arylpropanoic acid; Cinchona; Catalyst; S-(+)-Naproxen.

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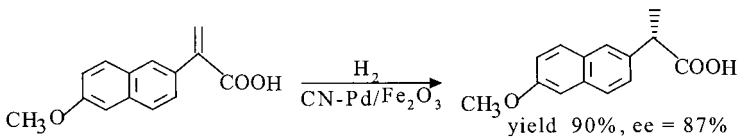
The increasing use of chiral compounds has raised the profile of asymmetric synthesis, in particular the environmentally more friendly heterogeneous enantioselective hydrogenations.[1,2] One of them, the industrially useful chiral catalysts based on 2,2′-*bis*(diarylphosphino)-1,1′-binaphthyl (BINAP) ruthenium system, was found to be effective in the hydrogenation of unsaturated carboxylic acids to optically active saturated carboxylic acids. The chiral hydrogenation in the synthesis of *S*-(+)-naproxen provides excellent enantioselectivity (up to 99% ee) and chemical yield (92%) by using BINAP-Ru dicarboxylate complexes,[3] but the relatively high pressures (135–150 atm) 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 are far from excellent.

To widen the cinchonidine-Pt-Al_2O_3 catalyzed hydrogenation,[4–6] here we report our initial findings on enantioselective hydrogenation of atropic acid in the presence of cinchona-modified Pd/Fe_2O_3. The enantioselectivity of this reaction has been optimized by change the preparation method of an easily cinchona-modified Pd/Fe_2O_3 catalyst system, and good optical yield was obtained. Atropic acids are an important class of substrates for this reaction because the resulting α-arylpropanoic acids are a variety of commercially important non-steroidal anti-inflammatory agents. Because of its current commercial importance, we chose atropic acid as substrates for our initial studies. In sharp contrast to the well-known hydrogenation catalyzed by (*S*)-BINAP–Ru(III) complex,[1,4] the asymmetric hydrogenation of atropic acid over cinchona-modified Pd/Fe_2O_3 (CN-Pd/Fe_2O_3) carried out according to the Sch. 1 show, gave the corresponding (*S*)-(+)-naproxen with unprecedented enantioselectivity.

Atropic acid itself has already been reduced to the corresponding optically active compounds by chiral phosphine rhodium complexes,[7]



Scheme 1.

ruthenium[3] or enzymatic resolutions.[8] Although each method is satifactory, in cost or simplicity they cannot be compared to the cinchona-modified Pd-catalyzed hydrogenations.

Note that Fe_2O_3 is inactive for the reaction and Pd and Pd/Fe_2O_3 exhibit relative high active but no chiral product produced, the cinchona-modified Pd/Fe_2O_3 catalyst show both active and enantioselective in the heterogeneous hydrogenation, indicating that cinchona is the origin of asymmetric induction for the asymmetric hydrogenation of atropic acid.

Taking into account the fact that the different preparation methods of the catalysts have been applied, it was necessary to find the most suitable strategy to prepare the efficiency catalyst.

In our experiment three preparation methods were adopted and the results with or without CN cinchona-modified are listed in Table 1. The synthetic methods are as follows: catalyst(I) was prepared by simply mixing Pd and Fe_2O_3. Catalyst(II) was prepared by using $PdCl_2$ instead of Pd, reduced by HCHO in the mixture of Fe_2O_3 and NaOH. Using $Fe(Ac)_3{\cdot}6H_2O$ and $PdCl_2$ as starting material, catalyst(III) was prepared by co-precipitation from the mixture solution of starting material. For catalyst(I), the Pd active center is just on the surface of Fe_2O_3 and no or little interaction can be formed between Pd and Fe or O atom, results in the ee of the hydrogenation product is less than 3% (Table 1, Entry 3). In the second methodology much Pd is ''dispersed'' on the surface of Fe_2O_3 and exist a little interaction of Pd with Fe or O atom, the ee of the product is up to 10% (Table 1, Entry 4). For catalyst(III) the ee's up to 15% (Table 1, Entry 5). When modified with CN, the reaction rates and the optical yield are greatly increased (Table 1, Entries 6–8).

For the model reaction, the influence of substrate, solvent, and modifier concentration were also investigated. According to the ee data the enantioselectivity seems to be strongly solvent dependent. It was found that the application of CN provides the higher optical yields in methanol. In our opinion this significant solvent dependence is a result of the weaker absorption of atropic acids in the case of benzene (6π electrons vs. 2π electrons). While using methanol the substrate can form an ester with the solvent as pointed out for atropic acid. However, the increase is more pronounced in benzene than in methanol, for which only a slight increase was observed.

The reaction rates of the modified and the unmodified system were compared in methanol. The modified reaction all take place at higher rates than the unmodified one as Table 1 show, indicating a

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Table 1. Preparation methods and solvent effect on asymmetric hydrogenation.

Entry	Catalyst	Product	Solvent	Rate (mol $g^{-1}min^{-1}$)	ee (%)	Yield (%)
1	Fe_2O_3	*S*-(+)-naproxen	Methanol	0	0	0
2	Pd	*S*-(+)-naproxen	Methanol	0.13	0	36
3	$Pd/Fe_2O_3(I)$	*S*-(+)-naproxen	Methanol	0.22	≤ 3	50
4	$Pd/Fe_2O_3(II)$	*S*-(+)-naproxen	Methanol	0.25	10	52
5	$Pd/Fe_2O_3(III)$	*S*-(+)-naproxen	Methanol	0.37	15	63
6	$CN\text{-}Pd/Fe_2O_3(I)$	*S*-(+)-naproxen	Methanol	0.65	16	74
7	$CN\text{-}Pd/Fe_2O_3(II)$	*S*-(+)-naproxen	Methanol	0.71	63	86
8	$CN\text{-}Pd/Fe_2O_3(III)$	*S*-(+)-naproxen	Methanol	0.82	87	90
9	$CN\text{-}Pd/Fe_2O_3(III)$	*S*-(+)-naproxen	Benzene	0.76	73	88
10	$CN\text{-}Pd/Fe_2O_3(III)$	Ibuprofen	Methanol	0.85	86	90
11	$CN\text{-}Pd/Fe_2O_3(III)$	Ibuprofen	Benzene	0.76	76	81
12	$CN\text{-}Pd/Fe_2O_3(III)$	Flurbiprofen	Methanol	0.88	87	91
13	$CN\text{-}Pd/Fe_2O_3(III)$	Flurbiprofen	Benzene	0.81	85	83

ligand accelerated mechanism. As a result, the highest enantioselectivity was obtained at the highest reaction rate (Table 1, Entry 8). However, explaining the roles of geometrical and electronic factors is not possible at this level of the study.

Figure 1 shows the dependence of ee and rates on the modifier concentration. Both curves had a similar shape and could be modeled with a simple kinetic model assuming reversible but strong absorption of the modifier on the Pd surface. As expected, the ee values are rather low at low modifier concentration, it is probably because the modifier is hydrogenated and thereby made ineffective during the course of the reaction.

In this way, both ibuprofen and flurbiprofen can be prepared in excellent optical purity (Table 1, Entry 10,12), and no further optimization is needed.

The present study provides the first experimental proof that atropic acid can be hydrogenated with excellent optical yields over cinchona-modified Pd catalysts. Since the synthetic importance of *S*-(+)-naproxen as useful anti-inflammatory agents is well-known, this new, environmentally friendly method for their preparation may even widen their applications.

In conclusion, the cinchona-modified Pd/Fe_2O_3 catalytic system was found to be effective in the enantioselective hydrogenation of atropic acids, providing the opportunity to still widen the practical applications and potential of this unique and important catalytic system.

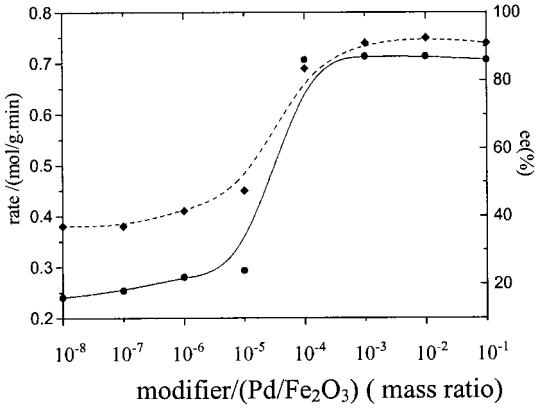

Figure 1. Enantiomeric excess and rates vs. modifier concentration: cinchona-modified 5% Pd/Fe_2O_3 (30 mg) catalyst(III) system at 20°C ((◆) rate, (●) ee value).

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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 CuK α radiation ($\lambda = 1.5418$ Å). A scan speed of 2°/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°C on previously degassed samples at RT and 10^{-4} torr 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 Pd/Fe_2O_3 Catalyst

The preparation of Pd/Fe_2O_3 catalyst (Pd/Fe = 1/4, mol/mol) follows[7] and described below.

Catalyst(I): The quantities of Pd (2.35 mmol, 0.2488 g) and Fe_2O_3 (4.70 mmol, 0.7511 g) were mixed carefully and dried at 200°C/2 h.

Catalyst(II): Into 30 cm^3 water solution of $PdCl_2$ (2.35 mmol, 0.416 g), Fe_2O_3(4.70 mmol, 0.525 g) were suspended and 20 cm^3 of HCHO (30%, m/m) was dropped in then 20 cm^3 of 20% NaOH solution were added and stirred for about 30 min, the solid were filtered and washed with water (3×20 cm^3), dried at 100°C in vacuo (80 mmHg), finally the sample were roasted at 280°C in air for 3 h after cooled before use.

Catalyst(III): Into 50 cm^3 water solution of $PdCl_2$ (2.35 mmol, 0.416 g), and $Fe(Ac)_3 \cdot 6H_2O$ (9.4 mmol, 3.206 g), 20 cm^3 of HCHO (30%, m/m) were dropped in with stirring, then 50 cm^3 of 20% NaOH solution were added and stirred for about 30 min, the solid were filtered and washed with demineral water (3×30 cm^3), dried at 100°C in vacuo (80 mm Hg), finally the sample were roasted at 280°C in air for 3 h after cooled before use.

The physical characteristics of the catalysts along with their compositions are shown in Table 2, which shows that the surface areas and pore volumes are increased in the catalyst in comparison with the

Table 2. Physical characteristics of the Pd/Fe_2O_3 catalysts.

Catalysts	Fe Content ($g/g_{cat.}$)	Pd Content ($g/g_{cat.}$)	S_{BET} (m^2/g)	V_p ($cm^3/g_{cat.}$)	XRD Peak
Pd	0	0.05	150	0.08	Pd
Fe_2O_3	0.08	0	260	0.35	Fe_2O_3
Catalyst(I)	0.0547	0.0259	280	0.50	Pd/Fe_2O_3
Catalyst(II)	0.0547	0.0259	265	0.56	Pd/Fe_2O_3
Catalyst(III)	0.0548	0.0258	360	0.58	Pd/Fe_2O_3

corresponding Pd(0) or Fe_2O_3. The XRD pattern of Pd/Fe_2O_3 catalyst shows peaks arising from metallic Pd(0) and Fe_2O_3.

Asymmetric Hydrogenation of Atropic Acid by Pd/Fe_2O_3 Catalysts

In a typical reaction, a solution of atropic acid (0.228 g, 1.0 mmol) in 10 mL methanol and Pd/Fe_2O_3 (0.085 g, contains Pd, 0.0003 mmol) were added to a 50 mL three-neck flask fitted with an inert gas inlet and reflux condenser, then H_2 (10 Kg/cm^2, 25°C) was introduced and the reaction mixture was analyzed by GC and HPLC after 4 h. The ee value of the product was determined (on a sample filtered through silica gel; ether/hexane) by HPLC using Daicel Chiralcel column: 10% ether/hexane, 2 mL/min, 25°C. The ee values were reproducible to within 1%. The eluting enantiomer was determined to be *S* isomer by comparison with pure sample (Ref. [5]. M.p. 155°C, $[\alpha]_D^{25} = +65°$, $c = 1$, $CHCl_3$).

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