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Asymmetric hydrogenation of acetophenone catalyzed by cinchonidine stabilized Ir/SiO_2

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ABSTRACT

A series of silica (SiO_2) supported iridium catalysts stabilized by cinchona alkaloids was prepared and applied in the heterogeneous asymmetric hydrogenation of acetophenone. Cinchona alkaloids exhibited a marked ability to stabilize and disperse the Ir particles. In the presence of (1*S*,2*S*)-diphenylethylenediamine ((1*S*,2*S*)-DPEN)) as chiral modifier, the cinchonidine (CD) stabilized catalyst 5%Ir/2CD-SiO_2 exhibited excellent catalytic performance in the asymmetric hydrogenation of acetophenone in MeOH. Under the optimum conditions, the ee value of (*R*)-phenylethanol achieved 79.8% and no other product was produced, a higher enantioselectivity than that reported up to now for acetophenone hydrogenation catalyzed by the supported metal catalysts modified by chiral reagents. In particular, a synergistic effect between (1*S*,2*S*)-DPEN and CD was observed, which significantly accelerated the reaction rate and enhanced the enantioselectivity. The catalyst can be reused several times without a significant loss of activity and enantioselectivity.

1. Introduction

Asymmetric hydrogenation of prochiral ketones is a major route to chiral alcohols which are especially important in the synthesis of biologically active compounds [1,2]. Heterogeneous asymmetric catalysis has become a rapidly growing field since stereoselective reactions over supported metal catalysts have obvious advantages, especially in the easy separation and reuse of catalyst [3]. So far, it is a pity that the enantioselectivity is still low for the heterogeneous asymmetric hydrogenation of simple aromatic ketones. For example, in the asymmetric hydrogenation of acetophenone, an enantioselectivity of 22% enantiomeric excess (ee) was reported over (*S*)-proline-modified Pd/C catalyst [4], 20% ee over cinchona-modified Pt/C catalyst [5], 24% ee over chiral organotin-modified Pt- and Rh-based catalysts [6,7], and recently 60.5% ee was obtained over Ru/γ-Al_2O_3 in the presence of phosphine and (1*S*,2*S*)-diphenylethylenediamine ((1*S*,2*S*)-DPEN) [8]. The introduction of ligands as metal particles stabilizers is an efficient method for improving the catalytic performance of the supported metal catalysts [9,10]. Phosphines were frequently used as the stabilizer for the supported metal catalysts and resulted in up to 77–88% ee [11,12], but they are generally air sensitive. The nitrogen-containing ligands such as diamines and β-amino alcohols are more stable and easy to handle, but show poor enantioselectivity in the asymmetric transfer hydrogenation of acetophenone [13,14]. Therefore, the investigation into the asymmetric hydrogenation of simple aromatic ketones with supported metal catalysts is still a challenge. We previously reported that cinchona alkaloids are good stabilizer for the supported Rh catalyst in the heterogeneous asymmetric hydrogenation of ethyl pyruvate [15]. With these in mind, we explored the behavior of Ir/SiO_2 catalysts with cinchona alkaloids as stabilizer and the (1*S*,2*S*)-DPEN as chiral modifier for asymmetric hydrogenation of acetophenone. The effect of cinchona alkaloids on silica supported iridium catalysts was investigated in detail, and a synergistic effect between (1*S*,2*S*)-DPEN and cinchonidine (CD) was also discussed.

2. Experimental

2.1. Materials and instruments

Acetophenone, CD, quinine (QN) (>98% Acros) and hydrogen (99.99%) were used as received. *O*-methylcinchonidine (MeOCD) and *O*-acetylcinchonidine (AcOCD) were prepared according to literature procedures [16,17]. SiO_2 (the average pore size is 4.5 nm, SBET = 135.9 m^2/g), $H_2IrCl_6{\cdot}6H_2O$ (Ir 30 wt% in water), (1*S*,2*S*)-DPEN and other reagents were all of analytical grade. Transmission electron microscopy (TEM) images were obtained with a JEM-1200

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microscope at 80 kV. X-ray photoelectron spectroscopy (XPS) was performed by a Kratos XAM800 with a constant pass energy mode and non-monochromatic Mg Kα X-ray radiation ($h\nu$ = 1253.6 eV). The determination of conversion and ee value was performed on GC with an FID detector and a β-DEXTM120 capillary column (30 m × 0.25 mm, 0.25 μm film).

2.2. Preparation of catalyst

$H_2IrCl_6 \cdot 6H_2O$ (0.33 mmol), given amount of CD ($n \times 0.33$ mmol, n is the molar ratio of CD to Ir, n = 1, 2, 3, 4), SiO_2 (1.0 g) and 15 mL ethanol were mixed in an autoclave. After the mixture was stirred at room temperature for 1 h, hydrogen was introduced up to 3.0 MPa and the resulting mixture was stirred at 100 °C for another 5 h. After the mixture was cooled to room temperature, the solid was filtered and washed with 5 mL × 5 mL ethanol. Then, the solid was dried under vacuum at 50 °C for 1 h to give the catalyst Ir/nCD-SiO_2. The iridium content of all catalysts was 5 wt% as determined by inductively coupled plasma (ICP) experiments. Other catalysts stabilized by cinchona alkaloids were also prepared by a similar method.

2.3. Hydrogenation of acetophenone

The hydrogenation was performed in a 60 mL stainless autoclave with magnetic stirrer. A typical procedure for an asymmetric hydrogenation of acetophenone (Scheme 1) is as follows: the catalyst, (1*S*,2*S*)-DPEN, LiOH, MeOH and acetophenone were added to the autoclave, followed by a purge with hydrogen three times. Hydrogen was introduced to the desired pressure. The mixture was stirred at predetermined temperature for a given time. After the pressure was released, the products were separated and subjected to the analysis of the conversion and enantioselectivity by GC. Phenylethanol was the only hydrogenated product, and no byproducts were detected; the conversion is the chemical yield of phenylethanol. The ee value was calculated from the equation: ee (%) = $100 \times (S - R)/(S + R)$.

3. Results and discussion

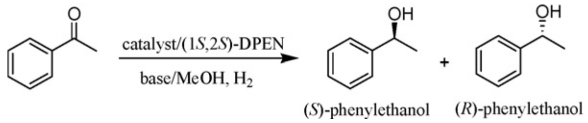
3.1. Characterization of catalysts

The typical TEM images of SiO_2 supported iridium catalysts with CD as stabilizer (Fig. 1a, 5%Ir/2CD-SiO_2) and without any stabilizer (Fig. 1b, 5%Ir/SiO_2) are shown in Fig. 1. The Ir particles (dark spots) can be clearly seen on the surface of SiO_2. Obviously, a remarkable growth in size of Ir particles in the catalyst 5%Ir/SiO_2 was observed. That is, the presence of CD was favorable for the dispersion and stability of the Ir particles.

The XPS spectrum of the catalyst 5%Ir/2CD-SiO_2 shows the Ir 4f binding energies at 60.3 and 63.3 eV, indicating that Ir^{4+} has been reduced to approximate Ir^0 (4f binding energies at 60.2 and 63.2 eV) (Fig. 2).

3.2. Effect of different stabilizers

According to the literature [15,18,19], the stabilizer is needed for an efficient catalyst in the heterogeneous asymmetric hydrogenation of carbonyl compounds. In order to improve the catalytic performance of Ir/SiO_2, cinchona alkaloids were chosen as stabilizer for the catalyst of Ir/SiO_2 on account of their good performance in the heterogeneous asymmetric hydrogenation of ethyl pyruvate catalyzed by supported Rh [15]. As shown in Table 1, in the presence of (1*S*,2*S*)-DPEN as chiral modifier, the activity and enantioselectivity of the catalysts stabilized by cinchona alkaloids (CD, CN, QN, MeOCD and AcOCD) were superior to those of the catalyst without stabilizer; the conversion of acetophenone increased from 5.0% to 82.0–100% and the enantioselectivity from 30.0% ee to 62.2–71.1% ee. From the TEM figures, it is obvious that the Ir particles on the support surface disperse very well in the presence of CD as stabilizer (Fig. 1a), and that the aggregation of Ir particles occurs easily in the absence of stabilizer (Fig. 1b). Among the used stabilizers, the CD stabilized catalyst shows the best catalytic performance, the ee



Scheme 1. Asymmetric hydrogenation of acetophenone.

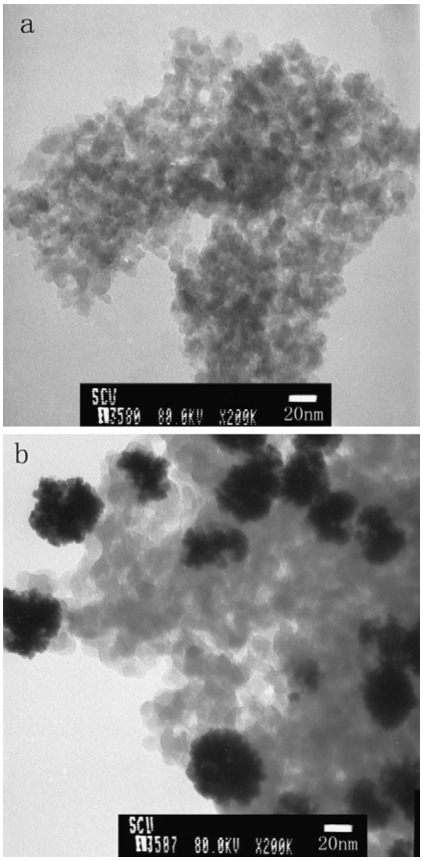


Fig. 1. TEM figures for the catalysts: (a) 5%Ir/2CD-SiO_2 and (b) 5%Ir/SiO_2.

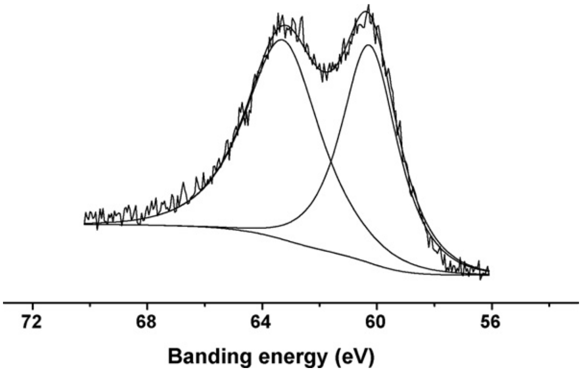
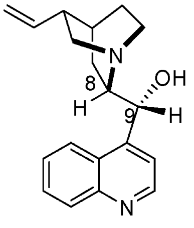
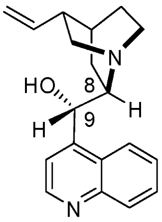


Fig. 2. XPS spectrum for 5%Ir/2CD-SiO_2.

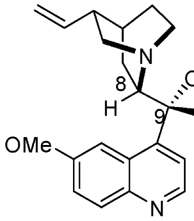
Table 1
The conversion and enantioselectivity of acetophenone catalyzed by cinchona alkaloids stabilized Ir/SiO_2.



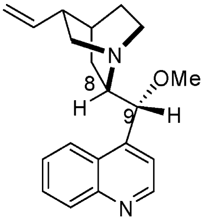
CD



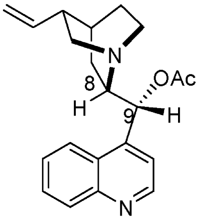
CN



QN



MeOCD



AcOCD

Entry	Catalyst (stabilizer)	Conversion (%)	ee (%)	Configuration
1	5%Ir/SiO_2 (no)	5.0	30.0	*R*
2	5%Ir/2CD-SiO_2 (CD)	87.2	71.1	*R*
3	5%Ir/2CN-SiO_2 (CN)	82.0	70.5	*R*
4	5%Ir/2QN-SiO_2 (QN)	83.0	66.1	*R*
5	5%Ir/2MeOCD-SiO_2 (MeOCD)	100	62.2	*R*
6	5%Ir/2AcOCD-SiO_2 (AcOCD)	100	64.0	*R*
7[a]	5%Ir/2CD-SiO_2 (CD)	86.9	70.9	*S*
8[a]	5%Ir/2CN-SiO_2 (CN)	80.6	69.9	*S*

Reaction conditions: acetophenone/Ir/(1*S*,2*S*)-DPEN = 163:1:2 (molar ratio); acetophenone: 0.85 mmol; MeOH: 2 mL; [LiOH]: 0.35 mol/L; P_{H_2} : 3.0 MPa; *T*: 323 K; *t*: 3 h.

[a] Modifier: (1*R*,2*R*)-DPEN.

value of the product achieving 71.1% (Table 1, entry 2). When QN, MeOCD and AcOCD were used as stabilizer, their steric effect (CN, CD < QN < MeOCD, AcOCD) had an adverse influence on the transition state with an (*R*)-configuration, and the ee values were lower than when either CD or CN was used as stabilizer (Table 1, entries 4–6). Interestingly, in the presence of (1*S*,2*S*)-DPEN as chiral modifier, a similar ee value was obtained with the (*R*)-configuration product when either CN or CD was used as stabilizer, although they are of the opposite configuration (Table 1, entries 2 and 3); in the presence of (1*R*,2*R*)-DPEN as chiral modifier, the same results were obtained with the (*S*)-configuration (Table 1, entries 7 and 8). This phenomenon is unlike the asymmetric hydrogenation of acetophenone catalyzed by Ru-diphosphine-diamine, where the combination of the (*S*)-diphosphine and the (*S*,*S*)-diamine (or *R*/*R*,*R* combination) plays very important role in the activity and enantioselectivity. However, in this catalytic system the configuration of the stabilizer seems to not vital to the activity and enantioselectivity, and only the configuration of chiral diamine determines the configuration of the product.

3.3. *Effect of CD and (1S,2S)-DPEN*

To further study the function of stabilizer, the effect of molar ratio of CD/Ir was investigated. The results are listed in Table 2. Among these CD stabilized catalysts, the catalyst 5%Ir/2CD-SiO_2 exhibited the best performance. The results suggest that the optimum steric environment of the active centre for asymmetric hydrogenation of acetophenone on the surface of the catalyst was formed when the molar ratio of CD/Ir was in an appropriate range [20,21]. In the presence of lower molar ratios of CD/Ir, Ir particles could not disperse well on the support. On the other hand, at higher molar ratios of CD/Ir, a portion of Ir surface would be covered by excess stabilizer CD, which blocked the coordination of (1*S*,2*S*)-DPEN to Ir, resulting in a disadvantage to the enantioselectivity.

Similarly to the results in the literature [5,22], CD was not an efficient chiral modifier for the asymmetric hydrogenation of acetophenone in this catalytic system. In the absence of (1*S*,2*S*)-DPEN, both the conversion and enantioselectivity were very low for the asymmetric hydrogenation of acetophenone catalyzed by 5%Ir/2CD-SiO_2, namely only 19.9% conversion and 12.6% ee, respectively (Table 3, entry 1). It is worth noting that there is a synergistic effect between (1*S*,2*S*)-DPEN and CD of accelerating the activity and enhancing the enantioselectivity. When (1*S*,2*S*)-DPEN was added into the catalytic system, a marked increase in the activity and enantioselectivity was observed.

The synergistic effect between (1*S*,2*S*)-DPEN and CD has also been investigated by varying the amount of (1*S*,2*S*)-DPEN (Table 3, entries 2–5). The best result was obtained when the molar ratio of (1*S*,2*S*)-DPEN/CD reached 1, corresponding to a (1*S*,2*S*)-DPEN/Ir molar ratio of 2. However, this was only a nominal value related to total amount of (1*S*,2*S*)-DPEN and CD present in the reaction and no conclusion could be drawn concerning the actual molar ratio of (1*S*,2*S*)-DPEN/CD on the Ir surface. The synergistic effect between modifier and stabilizer maybe provides valuable information on the reaction mechanism, and is currently being studied.

3.4. *Effect of base*

It is well known that the base is necessary to the asymmetric hydrogenation of aromatic ketones [8,11]. In this system, the basic additive plays a significant role in obtaining a high conversion and ee value. As shown in Table 4, the catalytic activity was

Table 2
Effect of molar ratio CD to Ir.

Entry	Catalyst	Conversion (%)	ee (%)	Configuration
1	5%Ir/1CD-SiO_2	85.6	64.7	*R*
2	5%Ir/1.5CD-SiO_2	82.8	69.3	*R*
3	5%Ir/2CD-SiO_2	87.2	71.1	*R*
4	5%Ir/3CD-SiO_2	100	65.0	*R*
5	5%Ir/4CD-SiO_2	100	62.8	*R*

Reaction conditions were the same as those in Table 1.

Table 3
Effect of molar ratio of (1*S*,2*S*)-DPEN to CD.

Entry	(1*S*,2*S*)-DPEN/CD (mol/mol)	Conversion (%)	ee (%)	Configuration
1	0	19.9	12.6	*R*
2	0.5/1	88.4	65.8	*R*
3	1/1	87.2	71.1	*R*
4	1.5/1	84.3	66.1	*R*
5	2/1	80.0	62.9	*R*

Reaction conditions were the same as those in Table 1.

Table 4
Effect of different bases on asymmetric hydrogenation of acetophenone.

Entry	Base	Concentration (mol/L)	Conversion (%)	ee (%)	Configuration
1	LiOH	0	12.1	27.2	*R*
2	LiOH	0.08	59.6	60.5	*R*
3	LiOH	0.17	78.5	70.2	*R*
4	LiOH	0.35	87.2	71.1	*R*
5	LiOH	0.5	92.4	66.0	*R*
6	NaOH	0.17	92.6	66.0	*R*
7	KOH	0.17	75.3	57.5	*R*
8	Li_2CO_3	0.17	80.9	68.3	*R*

Reaction conditions were the same as those in Table 1.

improved distinctly when the base was added, and the conversion depended on the base concentration. The ee value increased sharply when the concentration of LiOH increased from 0 to 0.17 mol/L, and 71.1% ee was obtained at 0.35 mol/L of LiOH. Upon further increase in LiOH concentration, the ee value decreased slightly (Table 4, entries 1–5). Notably, all alkaline bases, typically LiOH and Li_2CO_3, enhanced the activity and enantioselectivity. It is suggested that not only the basicity would affect the reaction activity and enantioselectivity but also the alkali metal cation plays an important role in the reaction to influence the enantioselectivity. According to the mechanism catalyzed by Ru-diphosphine-diamine proposed by Hartmann and Chen [23], the alkali metal cation was π-bonding to the aryl group, and thus the alkali metal cation radii must be suitable for the specific bonding site. It can explain why LiOH and Li_2CO_3 gave the high ee values in this system with Ir as active metal.

3.5. Effect of solvent

The results of the solvent effect on the asymmetric hydrogenation of acetophneone catalyzed by CD stabilized iridium catalyst (5%Ir/2CD-SiO_2) have been summarized in Table 5. Among chosen alcohol solvents, there is a roughly linear correlation between the enantioselectivity and the polarity of solvent. With the polarity of solvent increased, the ee value increased but the conversion decreased (Table 5, entries 1–4). Methanol is the most suitable choice for the enantioselectivity. This is contrast to the supported Ru catalyzed asymmetric hydrogenation of acetophenone, where 2-propanol was the best choice of solvent [11,24]. It seems that the solvent not only improves the mobility of the reactants but also influences a possible combination between the metal-stabilizer and modifier-substrate [25].

3.6. Effect of temperature

The effect of temperature on the asymmetric hydrogenation of acetophenone is shown in Fig. 3. The conversion increased sharply with increasing temperature from 278 to 323 K, and then decreased slightly at 333 K. The enantioselectivity increased with the increase in temperature below 283 K, the ee value presented a maximum of 79.8% at 283 K, and then decreased gradually with the increase in temperature from 283 to 333 K. The same phenomenon was also reported in the literature [8,15,26,27]. This could be attributed to the substrate adsorption mode on the iridium surface changing and the energy difference between transition states of two enantiomers becoming smaller with increasing temperature.

Table 5
Effect of different solvents on asymmetric hydrogenation of acetophenone.

Entry	Solvents	Conversion (%)	ee (%)	Configuration
1	MeOH	87.2	71.1	*R*
2	EtOH	99.7	52.1	*R*
3	*n*-PrOH	99.4	37.2	*R*
4	*i*-PrOH	100	22.3	*R*

Reaction conditions were the same as those in Table 1.

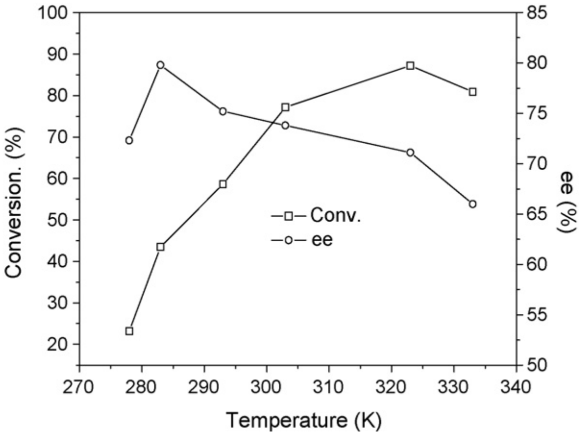


Fig. 3. Effect of temperature on asymmetric hydrogenation of acetophenone. Reaction conditions were the same as those in Table 1.

3.7. Recycling of catalyst

To explore whether the reactions occur heterogeneously on the surface of the supported catalyst or homogeneously in the reaction solution, the recycling of the catalyst has been investigated. After the first run, the reaction mixture was centrifuged, and the catalyst was separated from the liquid mixture by decantation. The catalyst was washed three times with methanol and then reused in the next run. As seen in Fig. 4, the catalyst could be reused seven times without a significant loss of activity and enantioselectivity under the same reaction conditions. It is worth noting that the modifier should be added again with substrate together in the recycling because it was soluble in organic solution and left in the solution after the reaction. The same result was observed in the literature [8,11]. However, no reaction occurred in the filtrated liquid phase mixed with fresh acetophenone under the same reaction conditions. The leaching of Ir from 5%Ir/2CD-SiO_2 into the solution was determined by ICP; only 0.1% Ir was detected in the liquid phase after the first hydrogenation of acetophenone. Others test experiments gave results similar to our recently reported ones [12]. These results indicate that the reaction was really carried out heteroge-

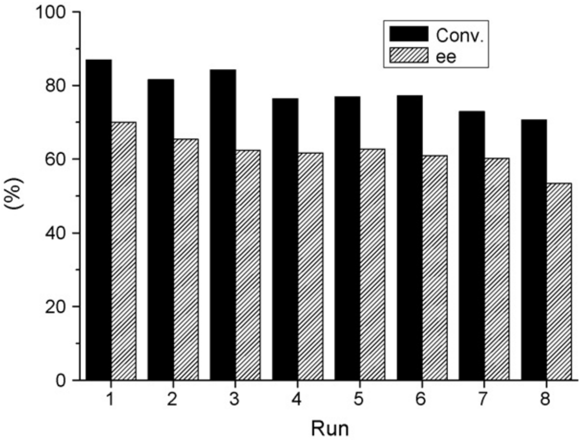


Fig. 4. The recycling of the catalyst. Reaction conditions were the same as those in Table 1, except 0.17 mol/L LiOH and 1×10^{-6} mol (1*S*,2*S*)-DPEN were added in every run.

neously on the surface of the catalyst, but not homogeneously in the liquid phase.

4. Conclusion

Supported Ir catalysts using cinchona alkaloids as stabilizer and (1*S*,2*S*)-DPEN as chiral modifier were firstly prepared by a simple method, and exhibited excellent enantioselectivity for the heterogeneous asymmetric hydrogenation of acetophenone. The results show a potential application of the supported Ir catalyst in the heterogeneous asymmetric hydrogenation. Particularly, compared with the catalyst using phosphine as stabilizer, cinchona alkaloids stabilized catalysts exhibit a unique feature. A synergistic effect between (1*S*,2*S*)-DPEN and CD significantly accelerates the reaction rate and enhances the enantioselectivity. The catalyst 5%Ir/2CD-SiO_2 could be reused several times without a significant loss of the activity and enantioselectivity.

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