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Enantioselective hydrogenation of ethyl pyruvate catalyzed by alumina support rhodium modified with quinine

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Abstract—Alumina supported rhodium catalyst using cinchonidine as a stabilizer exhibited excellent performance in the asymmetric hydrogenation of ethyl pyruvate with the addition of quinine. Quinine as a chiral modifier can not only induce the enantioselectivity, but also greatly accelerate the reaction. Under the optimum conditions: 293 K, 7.0 MPa of hydrogen pressure and 4.6×10^{-3} mol/L of quinine concentration in THF, TOF of Rh/2(cinchonidine)-γ-Al_2O_3 as catalyst and ee value of (*R*)-ethyl lactate can achieve 894 h^{-1} and 71.6% ee, respectively.

1. Introduction

The asymmetric hydrogenation of a prochiral ketone is an important approach to obtain optically active alcohols and its investigation has received more and more attention in the recent years.[1,2] Homogeneous catalysis is a main method for preparing chiral alcohols, however, the separation of a chiral catalyst from products is difficult and thus the application of this method is limited. Heterogeneous catalysis could overcome the problem and would become rapidly growing field.[3,4] One of the best known heterogeneous asymmetric reactions is the enantioselective hydrogenation of α-ketoesters catalyzed by an alumina supported platinum cluster using cinchona alkaloid as modified. It has been studied extensively by Orito et al.[5] Baiker et al.,[6,7] Blaser et al.,[8] Wells et al.[9] and Augustine et al.[10] and some interesting progress being obtained. In the hydrogenation of methyl or ethyl pyruvate catalyzed by cinchonidine modified Pt/γ-Al_2O_3, an enantiomeric excess (ee) of 95% could be achieved.[8,11,12] Bonnemann and Braun[13] synthesized several Pt colloidal clusters with dihydrocinchonidine and examined their enantioselectivities in the hydrogenation of ethyl pyruvate. An ee of 80% of the product could be achieved. When other transition metals such as Ru, Rh, Pd and Ir were used as the active element in the supported catalyst, the enantioselectivity decreased greatly. For example, the ee value was only 20–30% in hydrogenation of ethyl pyruvate using Rh/γ-Al_2O_3 as catalyst and cinchonidine as chiral modifier. In order to improve the catalytic performance some new methods for preparing the supported nanocluster catalysts were studied in our group.[14–17] γ-Al_2O_3 supported Rh nanocluster catalyst, which was prepared by a new method and was stabilized by polyvinylpyrrolidone (PVP) and modified by cinchonidine, exhibited high activity and middle enantioselectivity (65%, ee) in the hydrogenation of ethyl pyruvate. However, it was found that the aggregation of nanoparticles occurred easily in the preparation process and would influence the metal dispersion on the support surface. Herein we report a further improved preparation method by using cinchonidine as the stabilizer and quinine as the modifier. These Rh/γ-Al_2O_3 catalysts displayed better enantioselectivities in the asymmetric hydrogenation of ethyl pyruvate. The effect of the modification and reaction conditions on the hydrogenation are also discussed.

2. Results and discussion

2.1. Acceleration and chiral induction of quinine

The effect of the chiral modifier on the activity and enantioselectivity of Rh/2(cinchonidine)-γ-Al_2O_3 in

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asymmetric hydrogenation of ethyl pyruvate was investigated with the results shown in Figure 1. When cinchonidine was used as a stabilizer in the catalyst preparation, the catalytic activity and enantioselectivity of Rh/2(cinchonidine)-γ-Al_2O_3 were very low in the absence of quinine. With the addition of quinine, the catalyst activities and enantioselectivity increased greatly. When the quinine concentration was increased to 4.6×10^{-3} mol/L, TOF and ee value of product achieved 894 h^{-1} and 71.6%, respectively. Upon further increase of quinine concentration, the TOF and ee decreased slightly. The data indicated that not only could quinine accelerate the reaction, but it also had a stronger chiral induction effect for preferential formation of (*R*)-ethyl lactate in comparison to when just cinchonidine was used as the stabilizer and chiral modifier.[17] Under the optimum concentration of quinine there was a maximum of TOF and ee. If the concentration of quinine was excessively high, a portion of the metal active centres of the catalyst could be covered, resulting in a decrease in activity and enantioselectivity also.

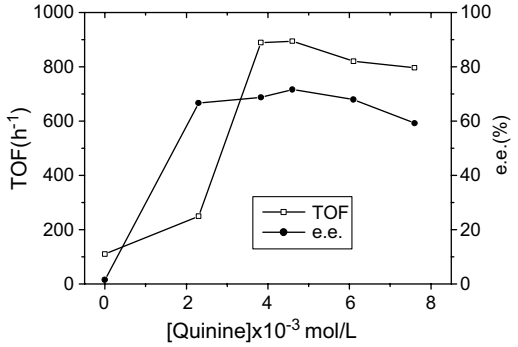

Figure 1. The effect of quinine concentration on the enantioselective hydrogenation. Reaction conditions: catalyst Rh/2(cinchonidine)-γ-Al_2O_3 (containing 1.0×10^{-3} mmol rhodium): THF (2.0 mL), ethyl pyruvate (1.0 mmol), P_{H2} = 7.0 MPa, T = 293 K, reaction time 1 h.

2.2. Effect of Rh/cinchonidine ratio

Four catalysts with different molar ratios of Rh/cinchonidine (Rh/1(cinchonidine)-γ-Al_2O_3, Rh/2(cinchonidine)-γ-Al_2O_3, Rh/4(cinchonidine)-γ-Al_2O_3 and Rh/8(cinchonidine)-γ-Al_2O_3) prepared and their catalytic performances were examined under the standard reaction conditions. The data in Table 1 show the obvious differences of their catalytic activities and enantioselectivities in the asymmetric hydrogenation of ethyl pyruvate. Among the four catalysts, the performance of Rh/2(cinchonidine)-γ-Al_2O_3 was the best. The results suggest that when the ratio of Rh/cinchonidine was in an appropriate range, the optimum configuration of the active centre on the surface of catalyst would form.[18,19] If the molar ratio of Rh/cinchonidine was larger than 2, a portion of rhodium surface would be covered and thus the catalytic activity and enantioselectivity would decrease. Therefore, the catalytic performance of Rh/2(cinchonidine)-γ-Al_2O_3 was investigated in detail under different reaction conditions.

2.3. Chiral induction comparison of cinchonidine and quinine

The comparison of the catalytic activity and enantioselectivity of Rh/2(cinchonidine)-γ-Al_2O_3 and Rh/2(quinine)-γ-Al_2O_3 in Table 2 indicated that cinchonidine and quinine could almost play the same stabilization role in the catalyst preparation. However, when they were used as the chiral modifier, quinine exhibited the better chiral induction. The ee of the products in ethyl pyruvate hydrogenation was 5–6% higher for quinine than that for cinchonidine. The results show that the catalytic activity of Rh/γ-Al_2O_3 was not sensitive enough for the composition and structure of the stabilizer, which was used in the preparation of catalyst, because the main function of stabilizer was to avoid metal nanoparticle aggregation and to keep their high dispersion on the support surface. However, when cinchonidine and quinine were used as the chiral modifier in the asymmetric hydrogenation, their composition and structure were key factors for the enantioselectivity. Thus the delicate difference between cinchonidine and quinine was displayed in the reaction process. It is possible that the steric effect of the methoxy group in quinine exerted a favourable influence on the transition state with an (*R*)-configuration. The difference of the cinchona modification from the report in the literature[17] was ascribed to the different preparation method of two

Table 1. The effect of molar ratio of rhodium to cinchonidine

Catalyst	Mole conversion (%)	TOF (h^{-1})	Ee (%)	Configuration
Rh/1(cinchonidine)-γ-Al_2O_3	76.0	715	60.3	*R*
Rh/2(cinchonidine)-γ-Al_2O_3	95.0	894	71.6	*R*
Rh/4(cinchonidine)-γ-Al_2O_3	61.2	576	59.7	*R*
Rh/8(cinchonidine)-γ-Al_2O_3	59.3	558	59.0	*R*

Reaction conditions are the same as those listed in Figure 1, except Rh/*n*(cinchonidine)-γ-Al_2O_3.

Table 2. Modification comparison of cinchonidine and quinine

Catalyst	Modifier	Mole conversion (%)	TOF (h^{-1})	Ee (%)	Configuration
Rh/2(cinchonidine)-γ-Al_2O_3	Quinine	95.0	894	71.6	*R*
Rh/2(cinchonidine)-γ-Al_2O_3	Cinchonidine	96.6	909	65.2	*R*
Rh/2(quinine)-γ-Al_2O_3	Quinine	92.6	871	67.2	*R*
Rh/2(quinine)-γ-Al_2O_3	Cinchonidine	93.2	877	62.0	*R*

Reaction conditions are the same as those listed in Figure 1.

catalysts and the different properties of both supports, γ-Al_2O_3 and TS-1.

2.4. Effect of solvent

The effect of the solvent property on the behaviours of γ-Al_2O_3 supported rhodium catalyst (Rh/2(cinchonidine)-γ-Al_2O_3) is listed in Table 3. The results indicate that there is no clear correlation between the catalytic performance of Rh/2(cinchonidine)-γ-Al_2O_3 and the solvent polarity. This is different from the conventionally supported platinum/cinchonidine catalyst, whose activity and enantioselectivity were generally better in polar solvents than those in apolar ones.[3,20] This might be ascribed to the different interactions between the solvent and the modified rhodium cluster. Toluene and alcohol were not suitable solvents for the reaction. The reaction was fast but the enantioselectivity was very low in water. Among the solvents investigated, tetrahydrofuran was the most suitable for the reaction, in which the TOF and ee were 894 h^{-1} and 71.6%, respectively. This is in agreement with our previous reports.[14,17]

Table 3. Effect of solvent on the activity and enantioselectivity

Solvent	Dielectric constant	TOF (h^{-1})	Ee (%)	Configuration
Toluene	2.38	134	14.4	*R*
Tetrahydrofuran	7.60	894	71.6	*R*
Ethanol	24.3	213	18.7	*R*
Methanol	33.6	241	23.7	*R*
H_2O	80.4	604	3.2	*R*

Reaction conditions are the same as those listed in Figure 1, except quinine concentration is 4.6×10^{-3} mol/L.

2.5. Effect of hydrogen pressure and temperature

The effect of hydrogen pressure on the asymmetric hydrogenation of ethyl pyruvate is shown in Figure 2. It was observed that the TOF and ee values increased initially when increasing hydrogen pressure. The increase of hydrogen pressure was favourable for the formation of dihydroquinine, which could promote the effect of chiral induction. The fact that TOF and ee values reduced upon further increase of hydrogen pressure, suggested that the competitive adsorption of hydrogen on the metal surface would influence the access of the substrate.[21] At the same time, a too high hydrogen pressure could cause further hydrogenation of the quinoline ring of the dihydroquinine, which would weaken the dihydroquinine chiral induction and its adsorption on a metal surface.[22,23]

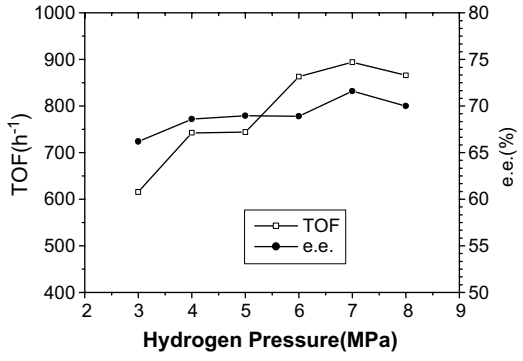

Figure 2. The effect of hydrogen pressure. Reaction conditions are the same as those listed in Figure 1, except quinine concentration is 4.6×10^{-3} mol/L.

The effect of temperature on the catalytic behaviours is shown in Figure 3. The data showed that the conversion increased drastically when increasing the temperature from 0 °C to 20 °C, while enantioselectivity rose slightly. When the temperature was over 20 °C, the enantioselectivity of the product decreased gradually from 71.6% ee at 20 °C to 56.5% ee at 60 °C, although the catalytic activity did not obviously change. This phenomena[16] could be attributed to the substrate adsorption mode on rhodium surface changing and the energy difference between transition states of two enantiomers becoming smaller with increasing temperature.

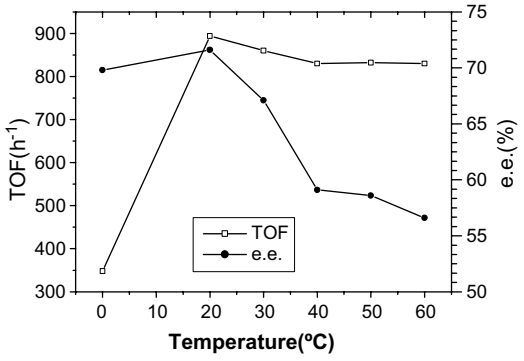

Figure 3. The effect of temperature. Reaction conditions are the same as those listed in Figure 1, except quinine concentration is 4.6×10^{-3} mol/L.

3. Experimental

3.1. Materials

Ethyl pyruvate, quinine and cinchonidine were used as received from Acros without further purification. THF was treated by sodium metal and distilled before use. $RhCl_3 \cdot 3H_2O$ and other reagents are of analytical grade. The purity of hydrogen was 99.99%. The specific surface areas of γ-Al_2O_3 were 154 m^2/g.

3.2. Preparation of Rh/*n*(cinchonidine)-γ-Al_2O_3 catalyst

γ-Al_2O_3 (1.0 g), suitable amount of cinchonidine ($n \times 10^{-2}$ mmol, n = 5, 10, 20, 40) and a mixed solvent of 50 mL (containing ethanol, *i*-propanol, distilled water and formic acid, their volume ratio = 11:11:2:1) were added into a round flask of 100 mL and stirred for 16 h at room temperature. Then $RhCl_3 \cdot 3H_2O$ (5.0×10^{-2} mmol) was introduced and continually stirred for 1 h. After the solution was refluxed at 100–120 °C for 3–5 h, γ-Al_2O_3 supported rhodium catalyst

was filtrated and washed with distilled water several times. The Rh/*n*(cinchonidine)-γ-Al_2O_3 (here *n* is molar ratio of cinchonidine/Rh, $n = 1, 2, 4, 8$) catalysts were dried under vacuum at 50 °C for 8 h. The rhodium content of all catalysts was 0.5 wt %. Rh/2(quinine)-γ-Al_2O_3 catalyst was also prepared by a similar method (here the molar ratio of quinine/Rh is 2).

3.3. Catalytic hydrogenation

The reaction was performed in a 60 mL stainless autoclave with a glass linear and magnetic stirrer. The catalyst (20 mg, containing 1×10^{-3} mmol rhodium), quinine or cinchonidine (4.6×10^{-3} mol/L) and solvent (2.0 mL) were added into the autoclave and then hydrogen introduced up to 5.0 MPa. After the solution was stirred for 1 h at 298 K, ethyl pyruvate (1.0 mmol) was added into the autoclave and purged with hydrogen several times. The reaction was carried out under the designed conditions for a desired period of time. The products were determined by GC960 with FID detector and β-DEX^{TM}120 chiral capillary column (30 m × 0.25 mm, 0.25 μm film) at 80 °C.

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