Enantioselective hydrogenation of ethyl-2-oxo-4-phenylbutyrate on cinchonidine-modified Pt/γ-Al_2O_3 catalyst using a fixed-bed reactor

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Enantioselective hydrogenation of ethyl-2-oxo-4-phenylbutyrate (EOPB) on a cinchonidine-modified Pt/γ-Al_2O_3 catalyst was carried out using a fixed-bed reactor to obtain the chiral product, (R)-(+)-ethyl-2-hydroxy-4-phenylbutyrate ((R)-(+)-EHPB). About 95% conversion and 68% ee of the (R)-(+)-EHPB were obtained for the cinchonidine-modified Pt/γ-Al_2O_3 catalyst in a continuous-flow reaction system with a fixed-bed reactor. It is observed that the ee of (R)-(+)-EHPB strongly depends on the different solvent and hydrogen pressure. The competitive adsorption between the solvent and reactant molecule plays an important role in determining the ee value of (R)-(+)-EHPB. This study also shows that a compact adsorption of chiral modifiers on the platinum surface is beneficial to the higher enantioselectivity.

KEY WORDS: cinchonidine-modified Pt/γ-Al_2O_3; enantioselective hydrogenation; fixed-bed reactor; heterogeneous catalyst; competitive adsorption

1. Introduction

The enantioselective hydrogenation of α-ketoesters and related compounds on cinchonidine-modified Pt/γ-Al_2O_3 catalysts, reported first by Orito *et al.* [1], is of great scientific interest [2]. In the last decade, several research groups have extensively studied this system in a batch reactor, with respect to many system parameters, kinetic and mechanistic investigations [3–5]. Under optimized reaction conditions, up to 95% ee value can be achieved for chiral hydrogenation of ethyl pyruvate [6]. Recently, new progresses of studies on interaction between the modifiers and reactants [7], and the co-adsorption of the alkaloid with a strong co-adsorbate, for instance, oxygen of air dissolved in reactants and solvents [8] have been made. Lately, the effect of cinchonine and α-isocinchonine concentration on the enantioselective hydrogenation of ethyl pyruvate to (S)-ethyl lactate, and their stability or transformation in the reaction mixture were minutely studied by electrospray ionization mass spectrometry (ESI-MS) [9].

Several researches have shown that the saturation of the quinoline moiety of cinchonidine is detrimental to the adsorption and hence to the efficiency of the modifier [10,11], and that reusing the chirally modified catalysts is still problematic. Only by addition of a fresh modifier at the beginning of each hydrogenation cycle [12,13] or by feeding cinchonidine permanently in continuous use [14] can the enantioselectivity be maintained. The latest study shows that long-term stability of the Pt/γ-Al_2O_3 catalyst modified with cinchonidine can be achieved by stopping the reduction of ethyl pyruvate at a conversion of approximately 70%. Under the reaction conditions the destruction of the chiral modifier by hydrogenation may be prevented and the chirally modified catalyst is long-term stable [11].

Blaser and coworkers [15] have studied the enantio- and chemoselective hydrogenation of several 2,4-diketo acid derivatives in a batch reactor, to the corresponding 2-hydroxy compounds, for example, (R)-2-hydroxy-4-phenyl butyric acid ethyl ester (or named as (R)-(+)-ethyl-2-hydroxy-4-phenylbutyrate, (R)-(+)-EHPB). An ee value up to 86% and enrichment to > 98% ee in several cases were possible by a single crystallization.

Although so many developments have been gained about this system, studies on enantioselective hydrogenation with heterogeneous catalysts in a fixed-bed reactor have been rarely reported [14,16,17]. It is obvious that the separation, handling and reuse of the heterogeneous catalyst become very efficient when the fixed-bed reactor is used and it will be promising to industrialize the asymmetric catalysis with heterogeneous catalysts. In this paper we report the enantioselective hydrogenation of ethyl-2-oxo-4-phenylbutyrate (EOPB) (scheme 1) on a cinchonidine-modified Pt/γ-Al_2O_3 catalyst with a fixed-bed reactor and intend to synthesize enantiomerically pure (R)-(+)-EHPB, a building block for the synthesis of several commercially important A.C.E. inhibitors [18,19].

Up to 95% of conversion and about 68% ee of the (R)-(+)-EHPB were achieved using the fixed-bed reactor, demonstrating the possibility for the enantioselective hydrogenation on a heterogeneous catalyst in a continuous fixed-bed reactor. This study also shows that a compact adsorption of the chiral modifier on the catalyst surface is very important for the high enantioselectivity and that the coadsorption of solvent molecule and chiral modifier is helpful for improving the enantioselectivity.

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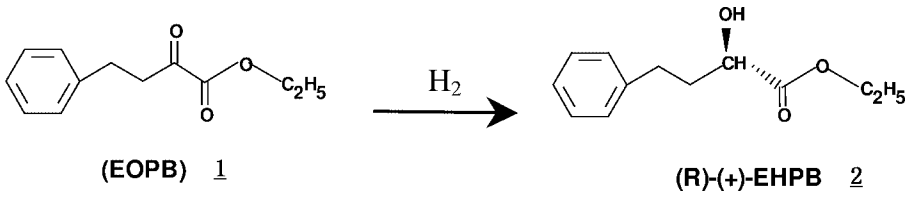

(EOPB) 1 (R)-(+)-EHPB 2

Scheme 1. Enantioselective hydrogenation of EOPB on the cinchonidine-modified Pt/γ-Al_2O_3 catalyst to the corresponding (R)-(+)-EHPB.

2. Experimental

The reaction was performed using a specially designed reaction system with a fixed-bed reactor, as demonstrated in [16]. The reaction system is adapted to a wide range of pressure, and liquid phase reactants can be fed by a high-pressure pump.

2.1. Catalyst preparation

The 5.0 wt% Pt/γ-Al_2O_3 catalyst was prepared by impregnating the support γ-Al_2O_3 with H_2PtCl_6 solution and stirring for 4 h, followed by slowly drying at 120 °C for 16 h. The reduction was carried out in Na(HCOO) solution, and then the reduced catalyst was dried at 120 °C for 24 h. Before use, the catalyst was pretreated in hydrogen at 400 °C for 2 h [20]. EOPB (Aldrich, minimum purity >97%) and cinchonidine (Acros, minimum purity >98%) were used as received.

2.2. Chiral modification of the Pt/γ-Al_2O_3 catalyst and the reaction process

2.2.1. Procedure 1 (preadsorption procedure)

The chiral catalyst was generated by impregnating the Pt/γ-Al_2O_3 catalyst, which was redued and pretreated, with cinchonidine–ethanol solution (40 ml, 2.6×10^{-2} M) overnight (referred to as the preadsorption procedure). After the chiral modification, the catalyst was transferred to the fixed-bed reactor (a 100 mm-long stainless-steel column with inner diameter 6 mm). The reaction was performed at room temperature under different hydrogen pressures and with different solvents. In a standard experiment, 0.5 g 5.0 wt% Pt/γ-Al_2O_3 catalyst was used for each time. The mixture of EOPB and solvent (ethanol, acetic acid or toluene) was introduced into the catalyst bed by a high-pressure pump, and the volume ratio of EOPB to solvent was 1 : 2. The hydrogen flow was kept constant by a balanced valve and monitored by a flowmeter. Constant pressure was maintained by a pressure-stabilized valve. The products were collected every one hour and the conversion of EOPB and ee of (R)-(+)-EHPB were analyzed by GC using a chiral column (30 m, capillary β-cyclodextrin, 140 °C).

2.2.2. Procedure 2 (in situ adsorption procedure)

The Pt/γ-Al_2O_3 catalyst, which was reduced and pretreated, was directly transferred to the fixed-bed reactor. Then the mixture containing the reactant material EOPB, solvent and chiral modifier, cinchonidine, of which the concentration was also 2.6×10^{-2} M, was introduced into the catalyst bed by a high-pressure pump. Other reaction conditions were adopted, as mentioned above. This procedure was referred to as *in situ* adsorption procedure.

Table 1
The highest ee of (R)-(+)-EHPB and conversion of EOPB at the same time obtained from the enantioselective hydrogenation of EOPB on the cinchonidine-premodified Pt/γ-Al_2O_3 catalyst using a fixed-bed reactor with different solvents under different hydrogen pressures.[a]

Hydrogen pressure (MPa)	Solvent					
	Ethanol		Acetic acid		Toluene	
	Conv. (%)	ee (%)	Conv. (%)	ee (%)	Conv. (%)	ee (%)
2.3	99.6	38.6	95.6	64.4	100	45.5
4.5	95.1	35.5	97.7	58.1	97.8	65.3
6.0	99.2	22.7	99.4	57.7	99.4	68.4

[a] Solvent 1.2 ml/h, EOPB 0.6 ml/h, H_2 3.6 l/h.

3. Results and discussion

Table 1 gives the best results for the enantioselective hydrogenation of EOPB to synthesize the (R)-(+)-EHPB catalyzed by the cinchonidine-premodified Pt/γ-Al_2O_3 catalyst under different reaction conditions. The conversion of EOPB is up to 95% with different solvents (ethanol, acetic acid or toluene) under different hydrogen pressures. However, the ee of (R)-(+)-EHPB is changed dramatically with different solvents and with different hydrogen pressures. The highest ee of (R)-(+)-EHPB of about 68% was obtained for the enantioselective hydrogenation of EOPB on cinchonidine-premodified Pt/γ-Al_2O_3 when toluene was employed as solvent under the hydrogen pressure of 6.0 MPa.

Figures 1–3 show the change trends of the conversion of EOPB and ee value of (R)-(+)-EHPB *vs.* reaction time during the preadsorption process with different solvents under different hydrogen pressures. The about 95% conversion of EOPB can be kept in steady level with reaction time for at least 9 h with different solvents (ethanol, acetic acid or toluene) under different hydrogen pressures. However, the ee of (R)-(+)-EHPB dropped considerably with time-on-stream, and is changed dramatically with different solvents and hydrogen pressures. At the initial stage of the reaction, the ee of (R)-(+)-EHPB is always higher than those achieved at the end of the reaction. The common phenomenon that the ee values of (R)-(+)-EHPB dropped considerably with time-on-stream, could be explained in terms of the wash-out

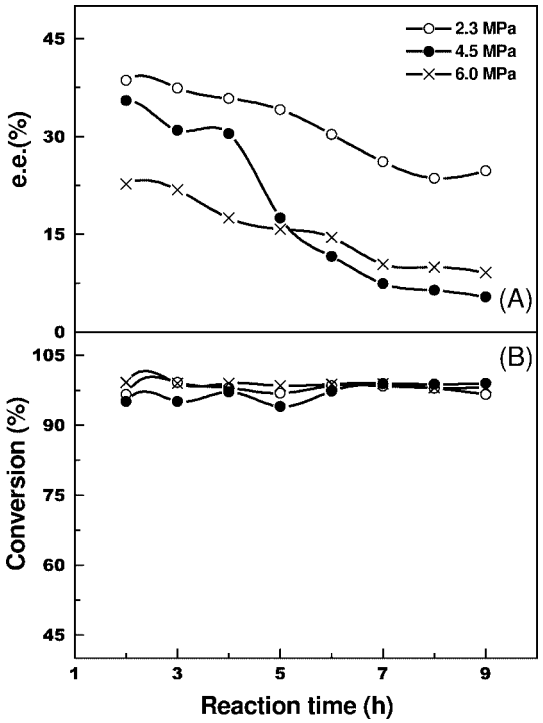

Figure 1. Conversion of EOPB (B) and ee value of (R)-(+)-EHPB (A) *vs.* reaction time under different hydrogen pressures when ethanol was used as solvent. Ethanol 1.2 ml/h, EOPB 0.6 ml/h, H_2 3.6 l/h.

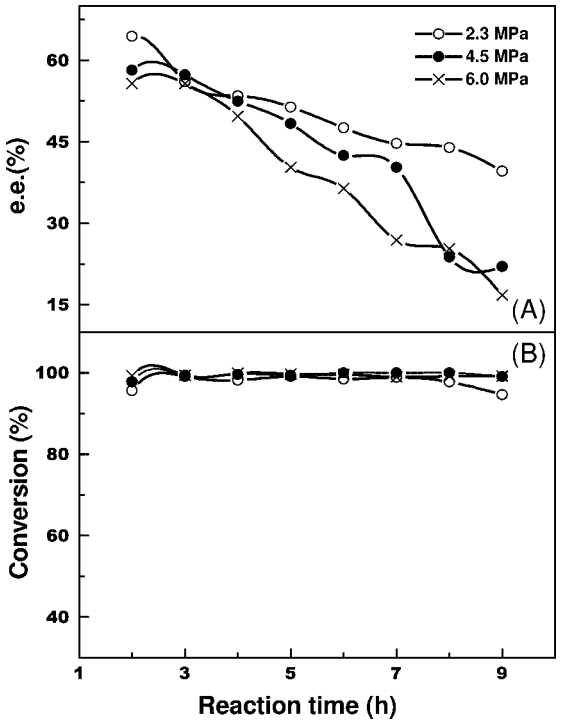

Figure 2. Conversion of EOPB (B) and ee value of (R)-(+)-EHPB (A) *vs.* reaction time under different hydrogen pressures when acetic acid was used as solvent. Acetic acid 1.2 ml/h, EOPB 0.6 ml/h, H_2 3.6 l/h.

of the chiral modifier, cinchonidine, by the reactant–solvent flow with time-on-stream [17]. Similar results were obtained for the enantioselective hydrogenation of ethyl pyruvate on the same catalyst with a fixed-bed reactor [16] in a previous study.

The ee of (R)-(+)-EHPB was increased with the hydrogen pressure when toluene was employed as solvent. ee values obtained under the hydrogen pressure of 4.5 MPa are much higher that those of 2.3 MPa, and the highest ee of (R)-(+)-EHPB are 65.3% and 45.5% under the hydrogen pressure of 4.5 and 2.3 MPa, respectively. A further increase of hydrogen pressure to 6.0 MPa makes the ee values slightly higher than those of 4.5 MPa, *i.e.*, from 65.3 to 68.4% (see table 1 and figure 3). Whereas, when ethanol or acetic acid was used as solvent the ee of (R)-(+)-EHPB is decreased when the hydrogen pressure goes up. When ethanol was used as solvent the highest ee were 38.6, 35.5 and 22.7% under the hydrogen pressures of 2.3, 4.5 and 6.0 MPa, respectively. While the highest ee values were 64.4, 58.1 and 57.7% under the hydrogen pressures of 2.3, 4.5 and 6.0 MPa, respectively, when acetic acid was the solvent (see table 1 and figures 1 and 2). Moreover, ee values obtained with toluene as solvent are higher than those obtained with the other two solvents (ethanol and acetic acid).

The fact that the highest ee was obtained under high hydrogen pressure when toluene was used as solvent indicates that the competitive adsorption between the solvent and reactant molecules plays an important role in the enantioselective hydrogenation. Because toluene can strongly adsorb on the naked platinum surface, which is unmodified by the

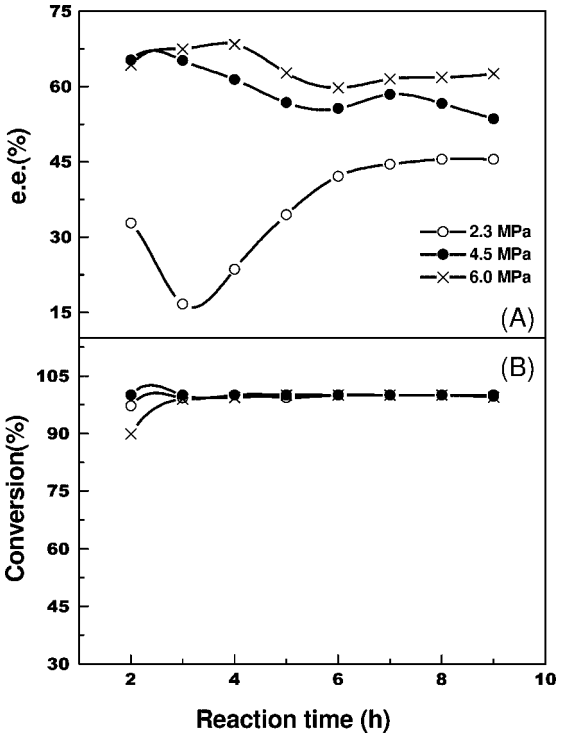

Figure 3. Conversion of EOPB and ee value (B) of (R)-(+)-EHPB (A) *vs.* reaction time under different hydrogen pressures when toluene was used as solvent. Toluene 1.2 ml/h, EOPB: 0.6 ml/h, H_2 3.6 l/h.

chiral modifiers, the enantioselectivity can be increased considerably when toluene is used as the solvent. We believe that the adsorption of solvent on the naked platinum surface

will be helpful for increasing the enantioselectivity because the coadsorbed solvent molecules block the active sites on which racemic products are formed.

The solvent weakly adsorbed on the naked platinum surface, *i.e.*, ethanol or acetic acid, may be easily replaced by adsorbed reactants under higher hydrogen pressure due to the competitive adsorption; as a result, the ee value is decreased when hydrogen pressure is augmented. However, the strongly adsorbed solvent molecules, *i.e.*, toluene will still occupy the naked platinum surface even under higher hydrogen pressure. The ee values are increased with the higher hydrogen pressure, because the enantioselective hydrogenation reaction on the platinum sites modified by cinchonidine is much faster than that on the rest unmodified sites [21]. The reason for the high ee value when acetic acid is used as solvent might be that the quinuclidine N atom of cinchonidine will be easily protonated in the presence of acetic acid, leading to the higher ee value [3,6].

Another possible explanation for the fact that ee values are decreased under higher hydrogen pressure when using a polar solvent, may be that the chiral surface modifiers would be hydrogenated under higher hydrogen pressure, so that they would be removed from the catalyst surface and the optimal surface coverage to form the (R)-(+)-EHPB is problematic when the surface concentration is too low [10]. As a result, lower ee values were achieved due to the competitive adsorption between polar solvent and reactant molecule, and the removal of the chiral modifiers from the catalyst surface by hydrogenation.

The effect of chiral modification procedure on the ee of (R)-(+)-EHPB was also investigated in detail. The ee value obtained for the Pt/γ-Al_2O_3 catalyst after modification by procedure 2 (*in situ* adsorption) is always lower than that by procedure 1 (preadsorption). For example, the highest ee of (R)-(+)-EHPB was only 45% for the Pt/γ-Al_2O_3 catalyst modified by procedure 2 under the hydrogen pressure of 2.3 MPa when acetic acid is used as solvent, while the ee value can be up to 64.4% for the Pt/γ-Al_2O_3 catalyst modified by procedure 1 under the same reaction condition. The enantioselectivity obtained for the catalyst modified by procedure 2 is much lower than that obtained for the cinchonidine-premodified Pt/γ-Al_2O_3 catalyst, indicating that long-time adsorption, *i.e.*, the preadsorption procedure, would lead to the compact adsorption of cinchonidine on the surface of the catalyst, resulting in higher ee values. It takes time for the loosely adsorbed cinchonidine to rearrange or to self-assemble on the surface in order to form the compact array on the catalyst surface. The compact array of chiral modifier on the Pt surface may form more enantioselective sites and decrease the possibility for racemic production.

4. Summary

By using a fixed-bed reactor, a conversion of more than 95% and an ee of about 68% were obtained for the enantioselective hydrogenation of EOPB on the cinchonidine-modified Pt/γ-Al_2O_3 catalyst by preadsorption of the chiral modifier. This result verifies the possibility for the synthesis of pharmaceutical precursors by using a heterogeneous catalyst and a fixed-bed reactor. The ee of (R)-(+)-EHPB strongly depends on the employed solvent and hydrogen pressure. When toluene was used as solvent under a hydrogen pressure of 6.0 MPa, the highest ee of (R)-(+)-EHPB of about 68% was achieved. The competitive adsorption between the solvent and reactant molecules plays an important role in determining the ee of (R)-(+)-EHPB. The coadsorption of solvent molecule and chiral modifier can help to improve the enantioselectivity by blocking the chirally unmodified surface. In addition, the enantioselectivity is significantly improved when chiral modifiers adsorbed compactly on the catalyst surface. This may provide important clues for a better understanding of the interaction between the chiral modifier, platinum surface and the reactants.

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