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Enantio-differentiating hydrogenation of methyl acetoacetate over reduced nickel catalysts pre-modified in methanol

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The enantio-differentiating hydrogenation of methyl acetoacetate was carried out over a (*R,R*)-tartaric acid-NaBr-modified reduced Ni catalyst. Reduced Ni was pre-modified in a methanol solution of tartaric acid and NaBr. It was revealed that the pre-treatment of methanol by molecular sieves was essential for attaining the high enantio-differentiating ability of 80–90% and high durability during repeated uses of the recovered catalyst.

KEY WORDS: pre-modified nickel catalyst; methanol; tartaric acid; enantio-differentiating; hydrogenation.

1. Introduction

Production of optically active compounds is a key issue for the synthetic organic chemistry, especially in the fields of pharmaceuticals and agrochemicals. Many feasible strategies for designing the catalysts for this purpose have been proposed. The development of heterogeneous enantio-differentiating catalysts is one of the most promising solutions for this purpose. Heterogeneous enantio-differentiating catalysts have several advantages, that is, i) easy preparation, ii) easy separation from the reaction mixture, and iii) easy reuse. Therefore, although enantio-differentiating homogeneous catalysts, such as organometallic complexes, have made a great success for attaining high enantioselectivities, it is preferable to switch them to the heterogeneous ones. Heterogenization of enantio-differentiating homogeneous catalysts have been widely studied for integrating the advantages of homogeneous catalysts with those of heterogeneous ones, and some heterogenized catalysts exihibited high enantioselectivities [1–3]. Enantio-differentiating solid catalysts, which are prepared by the modification of the solid carrying an intrinsic catalytic activity, are another choice. A tartaric acid-NaBr-modified Ni catalyst is one of the most successful enantio-differentiating solid catalysts. This catalyst produces optically active alcohols for the enantio-differentiating hydrogenation of various β-functionalized ketones and 2-alkanones. The enantio-differentiating ability (e.d.a.) of this catalyst reaches 80–98% [4–5] for β-ketoesters and 72–85% for 2-alkanones [6]. The catalyst has been prepared by the pre-modification of a Ni catalyst in an aqueous modification solution [7–13]. That is, an activated Ni catalyst, such as Raney Ni, supported Ni, Ni powder prepared by the reduction of Ni oxide (reduced Ni), or fine Ni powder, is soaked in an aqueous solution of tartaric acid and NaBr (pH of the solution is adjusted to 3.2 by NaOH solution) at 373 K for 1 h. Although the modification of Raney Ni in an aqueous solution attained a high e.d.a., the durability of the e.d.a. is very low [4] and the modification produces an aqueous waste containing Ni ions [8].

Several groups have reported the modification of Ni in an organic solvent. Bostellaar *et al.* reported that pre-modified Ni/SiO_2 in the methanol solution of tartaric acid showed the e.d.a. of 14–17% for the hydrogenation of methyl acetoacetate [14]. They also demonstrated that the alkali ions were not indispensable for attaining the e.d.a. of the tartaric acid-modified Ni catalyst because the e.d.a. of the pre-modified Ni/SiO_2 prepared in a methanolic solution was not zero. Keane reported that the enantio-differentiating hydrogenation of methyl acetoacetate over the tartaric acid-pre-modified Ni/SiO_2, modified in a solution of methanol, ethanol, or 1-butanol, gave the e.d.a. of 26–36% [15]. They demonstrated that the e.d.a. of the catalyst modified in alcohol was higher than that modified in an aqueous solution and that this was attributed to the higher concentration of tartaric acid adsorbed on the catalyst surface modified in alcohol. They also reported that the amount of Ni leached into the modification solvent was significantly decreased when alcohols were used as the modification solvent compared with modification in water.

In this study, we carried out the modification of the reduced nickel in methanol under atmospheric pressure. The effects of the pre-treatment of methanol by molecular sieves on the e.d.a. of the resulting catalyst and its durability for repeated use of the recovered catalyst were examined.

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2. Experimental

Two kinds of methanols were used in this study; Methanol A: Commercial methanol obtained from Wako Pure Chemical Ind., Ltd. (99 + %), and Methanol B: Commercial anhydrous methanol obtained from Sigma-Aldrich (99.8%, $H_2O < 0.002\%$). Racemic Na 2-ethylhexanoate was obtained by the neutralization of racemic 2-ethylhexanoic acid using a NaOH solution. The GLC measurement for determining the conversion and the enantiomer excess (e.e.) were carried out using a Hitachi 263–30 gas chromatograph and a Shimadzu GC-18A gas chromatograph, respectively. The measurement of the optical rotations was carried out using a JASCO DIP-1000 polarimeter. The amounts of alkali ions in the methanol were measured by an ion chromatograph using a Metrohm 761 Compact IC.

2.1. Reduced nickel catalyst

Nickel oxide (1.5 g) (Wako Pure Chemical Ind., Ltd., lot LDQ3413) was reduced at 623 K in a hydrogen stream for 1 h.

2.2. Treatment of the commercial methanol by molecular sieves

Molecular sieves 3A 1/16 (Wako Pure Chemical Ind., Ltd.) were treated at 473 K for 5 h to dry them. One third of the molecular sieves by volume was added to Methanol A and stored overnight. The resulting methanol was used for the experiments without distillation.

2.3. Modification of the reduced nickel.

The reduced Ni was modified by a pre-modification method. The reduced Ni was immersed in the methanol solution (118 cm^3) containing (*R,R*)-tartaric acid (1.18 g), NaBr (18 mg (0.17 mmol)), and if necessary, Na 2-ethylhexanoate (20 mg (0.12 mmol)) at 273 K for 1 h. After the modification, the catalyst was washed with methanol (two 25 cm^3 portions) and THF (two 8 cm^3 portions). The same kind of methanol was used for the modification and for the washing of the catalyst.

2.4. Enantio-differentiating hydrogenation of methyl acetoacetate.

The reaction mixture of methyl acetoacetate (5.0 g), THF (10 cm^3) and acetic acid (0.1 g) was subjected to hydrogenation over the modified reduced nickel catalyst. The hydrogenation was carried out at 373 K and the initial hydrogen pressure was 9 MPa. Conversion was determined by GLC analyses (5% Thermon 1000 on Chromosorb W at 383 K).

2.5. Determination of e.d.a.

The e.d.a. of the modified catalyst was evaluated using the optical purity of the hydrogenated product determined by polarimetry.

$$\text{e.d.a. }(\%) = ([\alpha]_D^{20} \text{ of methyl 3-hydroxybutyrate } /[\alpha]_D^{20} \text{ of pure enantiomer}) \times 100$$

The specific optical rotation $[\alpha]_D$ of the optically pure (R)-methyl 3-hydroxybutyrate is$[\alpha]_D^{20} = -22.95$ (neat) [8]. When the purity of the methyl 3-hydroxybutyrate after distillation was less than 100% (in the case of the low conversion), the e.d.a. was evaluated by the enantiomer excess (e.e.) determined by GLC. Acetylation of the sample was carried out using acetyl chloride and pyridine. A portion of the acetylated sample was subjected to the analysis using a chiral capillary gas chromatograph equipped with a CP Chirasil DEX-CB (0.25 mm × 25 m). The e.e. was calculated from the peak integration of the corresponding enantiomers.

2.6. Quantitative analyses of Na^+ and K^+ in methanol

The amounts of Na^+ and K^+ in the methanol used for the modification solvent were determined by an ion chromatograph equipped with a Shodex IC YK-421 (4.6 mm ID × 125 mm). The eluent: 4 mmol dm^{-3} H_3PO_4.

3. Results and discussion

In order to investigate the modification in an organic solvent, methanol was used in the present study, because both tartaric acid and NaBr were soluble in methanol. Modification of the reduced Ni in the methanolic solution of tartaric acid and NaBr was carried out using the commercial Methanol A as received or the Methanol A pre-treated by molecular sieves 3A. The results of the enantio-differentiating hydrogenation of methyl acetoacetate are shown in Figure 1. The e.d.a. and its durability were very low when the catalyst was prepared using Methanol A as received. On the contrary, the use of the pre-treated Methanol A by molecular sieves significantly increased the e.d.a. and its durability. A high e.d.a. of 80–90% and a high durability during the repeated uses of the recovered catalyst were attained. To clarify the reason for this phenomenon, the effect of a water impurity in methanol as a modification solvent was examined. Figure 2 shows the results using commercial anhydrous methanol (Methanol B: $H_2O < 0.002\%$). The use of Methanol B attained the e.d.a. of 28% in the first run, however, the e.d.a decreased to 3% in the 4th run. These results suggest that the effects of the pre-treatment of Methanol A by molecular sieves are not explained only based on the water in Methanol A. As the composition of the

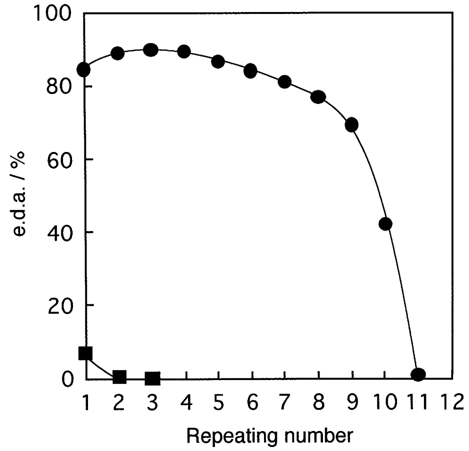

Figure 1. Enantio-differentiating hydrogenation of methyl acetoacetate over modified Ni prepared using Methanol A. ■: modified Ni prepared in Methanol A. ●: modified Ni prepared in Methanol A treated by molecular sieves 3A.

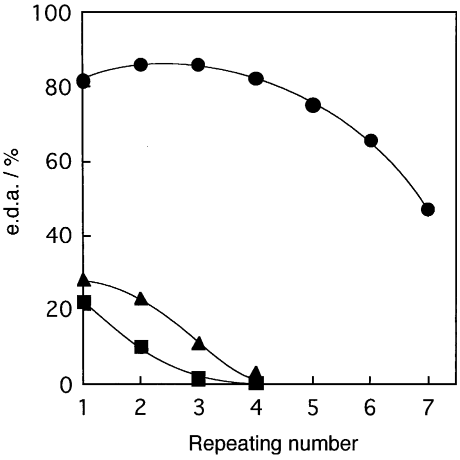

Figure 2. Effect of Na^+ on the enantio-differentiating hydrogenation of methyl acetoacetate over modified Ni. ▲: modified Ni prepared in Methanol B as received. ■: modified Ni prepared in Methanol A containing Na 2-ethylhexanoate. ●: modified Ni prepared in Methanol B containing Na 2-ethylhexanoate.

Table 1

The amount of alkali ions in methanol used as the modification solvent

Methanol	Na^+ / mg dm^{-3}	K^+ / mg dm^{-3}
Methanol A as received	0.005	0.02
Methanol A treated with molecular sieves 3A	15.3	7.1
Methanol B as received	0.60	0.02

molecular sieves 3A used in this experiment is $K_9Na_3[(AlO_2)_12(SiO_2)_12]$, alkali ions in the molecular sieves could be leached into the solvent and they could contribute to the increase in the e.d.a. and its durability. The importance of Na^+ for attaining a high e.d.a. has been reported for the hydrogenation of methyl acetoacetate and 2-octanone [6]. Table 1 shows the amounts of Na^+ and K^+ in Methanol A and Methanol B. Methanol A as received has almost no Na^+ or K^+. Methanol B as received has 0.6 mg dm^{-3} of Na^+ (0.003 mmol Na^+ in 118 ml of modification solution). The treatment of Methanol A by molecular sieves resulted in the leaching of Na^+ and K^+ into the methanol. The leached amount of Na^+ (15.3 mg dm^{-3} Na^+ corresponds to 0.08 mmol Na^+ in 118 ml of modification solution) was greater than that of K^+ (7.1 mg dm^{-3} K^+ corresponds to 0.02 mmol K^+ in 118 ml of modification solution). In order to confirm the effect of Na^+ in the modification solution on the e.d.a., the addition of racemic Na 2-ethylhexanoate to Methanols A and B was carried out. Although NaBr is one source of Na^+ for this experiment, racemic Na 2-ethylhexanoate was used for the further addition of Na^+ to the modification solution. It has been reported that the excess addition of NaBr to the modification solution causes a decrease in the e.d.a. [4]. It has also been reported that the addition of Na 2-ethylhexanonate to the reaction media increased or maintained the e.d.a. level and its durability for the methyl acetoacetate [16] and 2-octanone [17]. The results of the effects of the addition of Na 2-ethylhexanoate to Methanols A and B are shown in Fig. 2. In the case of Methanol A, the e.d.a. of 22% was attained in the first run, but it was lost in the 4th run. The value of the e.d.a. was significantly higher than the results using the as received Methanol A shown in Fig. 1, however, much lower than the results obtained using Methanol A pre-treated with molecular sieves. On the other hand, when Na 2-ethylhexanoate was added to Methanol B, the e.d.a. and its durability were significantly improved in comparison with the results using Methanol B as received. Based on these results, for the pre-modification in methanol, both the content of water and the amount of Na^+ in the methanol significantly affected the e.d.a. and its durability during the repeated use of the recovered catalyst for the enantio-differentiating hydrogenation of methyl acetoacetate. The presence of water would be detrimental or would affect the optimal concentration of the modifier in methanol for attaining a high e.d.a. and its durability. Concerning Na^+ in methanol, an appropriate amount of Na^+ in methanol would be essential for attaining a high e.d.a. and better durability. The pre-treatment of methanol by molecular sieves supplies Na^+ to the solvent as well as drying it, and hence, the procedure is preferable as the modification solvent for the preparation of the tartaric acid-NaBr-modified Ni catalyst.

4. Conclusion

The enantio-differentiating hydrogenation of methyl acetoacetate was carried out over a tartaric acid-NaBr-pre-modified reduced nickel catalyst. The Ni catalyst was modified in a methanol solution of the modifier. A high enantio-differentiating ability of 80–90% and a high durability during the repeated use of the recovered catalyst were attained when methanol was pre-treated with molecular sieves 3A. It was revealed that Na^+ ions were leached into the methanol from the molecular sieves during the drying process. The treatment of methanol by molecular sieves supplies Na^+ to the solvent as well as drying it and is appropriate for the pretreatment of the modification solvent (methanol) for the preparation of the tartaric acid-NaBr-modified Ni catalyst.

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