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Studies of co-modifier and carboxylic acid for the enantio-differentiating hydrogenation of 2-octanone over a tartaric acid in situ modified nickel catalyst

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ABSTRACT

The effects of a co-modifier and carboxylic acid on the hydrogenation rate and the enantio-differentiating ability (e.d.a.) were studied for the hydrogenation of 2-octanone and methyl acetoacetate over a tartaric acid modified reduced nickel catalyst. For the hydrogenation of 2-octanone, tartaric acid, pivalic acid, and Na^+ were necessary for the appearance of the predominant e.d.a. Sodium pivalate, instead of the typical co-modifier, NaBr, was appropriate for the in situ modification of reduced nickel. The use of sodium pivalate resulted in a higher hydrogenation rate and e.d.a.

1. Introduction

Producing optically active compounds is a key step for synthesizing pharmaceuticals and agrochemicals. Many strategies, such as enantio-selective homogeneous catalysts (organometallic complexes, enzymes, or organocatalysts) [1–6] and enantio-selective solid catalysts [7–12], have been used and widely studied. The enantio-selective solid catalysts are some of the promising solutions especially for saving energy and resources, because solid catalysts have the advantages of easy preparation, easy separation from the reaction mixture, and easy reuse.

A tartaric acid–NaBr-modified nickel catalyst is one of the successful enantio-differentiating solid catalysts for the hydrogenation of β-ketoesters [13] and 2-alkanones [14,15]. This catalyst is a unique solid catalyst for attaining up to an 85% enantio-differentiating ability (e.d.a.) for the hydrogenation of various 2-alkanones, for example, 80% for the hydrogenation of 2-octanone, 85% for 3,3-dimethyl-2-butanone, and 72% for 2-butanone [16,17].

The catalyst is prepared by the modification of an activated nickel catalyst. The modification of the catalyst (adsorption of tartaric acid and co-modifier on nickel catalyst) can be performed by two methods, one is a pre-modification and the other is an in situ modification. The pre-modified nickel catalyst is prepared in a different vessel from the reactor before hydrogenation of the substrate. An activated nickel catalyst is soaked in an aqueous solution of tartaric acid (modifier) and a co-modifier (typically NaBr) at pH 3.2 and 373 K [18]. The pH of the modification solution is adjusted with NaOH solution before the modification. On the other hand, the in situ modification is carried out in a reactor during the initial stage of the hydrogenation [19–21]. Tartaric acid and the co-modifier are added to the reaction media.

It was reported that the addition of a carboxylic acid, such as pivalic acid, to the reaction media was required for attaining a high e.d.a. for the enantio-differentiating hydrogenation of 2-alkanones over a tartaric acid–NaBr-modified nickel catalyst [16]. During the course of our studies on the role of the pivalic acid, we reported the effect of the addition of pivalic acid on the e.d.a. and the hydrogenation rate during the hydrogenation of 2-octanone over an in situ modified catalyst. We proposed the following two points [22]: (i) the pivalic acid increases the e.d.a. of the in situ modified nickel catalyst not only by the specific acceleration of the hydrogenation on the enantio-differentiating sites, but also by the improvement of the intrinsic e.d.a. of the adsorbed tartaric acid, and (ii) the appearance of the enantio-differentiating ability would need NaBr as a co-modifier as well as tartaric acid (modifier) and pivalic acid (additive).

In the present study, in order to investigate the role of the co-modifier on the enantio-differentiating hydrogenation of 2-octanone, the effect of the addition of a co-modifier on the e.d.a. and the hydrogenation rate was investigated using an in situ modified

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reduced nickel catalyst. As the in situ modification does not need a pH adjustment of the modification solution with NaOH solution, it is appropriate for investigating the effect of the co-modifier, such as NaBr, on the hydrogenation rate and the e.d.a. For the activated nickel catalyst, this study used a reduced nickel prepared by the reduction of nickel oxide in a hydrogen stream, because reduced nickel has little Na^+ on its surface, while Raney nickel adsorbs lots of Na^+ on its surface during the development of the Ni–Al alloy using a NaOH solution.

2. Experimental

All the chemicals, except sodium pivalate, were used as received. Sodium pivalate was obtained by the neutralization of pivalic acid with NaOH solution. The GLC measurements for determining the conversion and 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 rotation was done using a JASCO DIP-1000 polarimeter. The hydrogenation was carried out in a stirred autoclave produced by OM Lab-Tech Co., Ltd. (Tochigi, Japan). In this study, two types of autoclaves (No. 1 and No. 2) were used. The heating systems in these autoclaves were different from each other.

2.1. Reduced nickel catalyst

Nickel oxide (Wako Pure Chemical Industries, Ltd., lot CEL7157, for the hydrogenation of 2-octanone) calcined at 1373 K for 6 h or nickel oxide (Wako Pure Chemical Industries, Ltd., lot LDQ3413, for the hydrogenation of methyl acetoacetate) was reduced at 623 K in a hydrogen stream (40 cm^3 min^{-1}) for 1 h to produce a reduced nickel catalyst.

2.2. Enantio-differentiating hydrogenation of 2-octanone over a reduced nickel

2-Octanone (2.5 g) was hydrogenated using the reduced nickel catalyst (2.0 g) in THF (10 cm^3). The modification was carried out using an in situ-modification method [22]. (*R*,*R*)-Tartaric acid and a co-modifier, NaBr or sodium pivalate (the amounts are stated in the text) were added to the reaction mixture. For the addition of NaBr, the NaBr was first dissolved in 25 mm^3 of distilled water, because the solubility of NaBr in the reaction mixture is low. The hydrogenation was carried out in a stirred autoclave (No. 1) at the initial hydrogen pressure of 9 MPa and at 373 K with a stirring rate of 1370 r.p.m. The hydrogen pressure in the reactor was recorded by a PC every 1 min. The hydrogenation rate was expressed by the amount of hydrogen consumption during the reaction after the temperature of the autoclave reached the reaction temperature (373 K). After the reaction was completed, the reaction solution was separated by decantation from the catalyst, the hydrogenated product was dissolved in ether, then washed with a saturated aqueous solution of K_2CO_3. The ether solution was then dried over anhydrous Na_2SO_4 and concentrated in vacuo. A simple distillation was carried out to obtain the hydrogenated product. The conversion was determined by GLC analyses (5% Thermon 1000 on Chromosorb W at 383 K).

2.3. Enantio-differentiating hydrogenation of methyl acetoacetate over a reduced nickel

Methyl acetoacetate (5.0 g) was hydrogenated using the reduced nickel catalyst (0.5 g) in THF (10 cm^3) containing acetic acid (0.1 g). (*R*,*R*)-Tartaric acid and NaBr (the amounts are stated in the text) were then added to the reaction mixture. The hydrogenation was carried out in a stirred autoclave (No. 1 or No. 2) at the initial hydrogen pressure of 9 MPa and at 373 K with a stirring rate of 1370 r.p.m. A simple distillation was then carried out to obtain the hydrogenated product. The conversion was determined by GLC analyses (5% Thermon 1000 on Chromosorb W at 383 K).

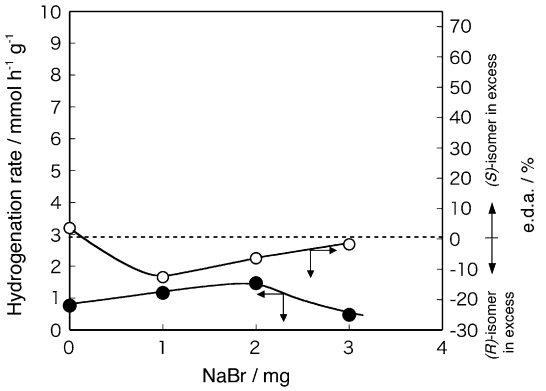

Fig. 1. Enantio-differentiating hydrogenation of 2-octanone over a modified reduced nickel catalyst in the absence of pivalic acid. (○) e.d.a., (●) hydrogenation rate. Modifier: 1.3 mg of tartaric acid and NaBr.

2.4. Determination of e.d.a.

The e.d.a. of the modified catalyst was expressed using the optical purity of the hydrogenated product determined by polarimetry or the enantiomer excess determined by GLC.

$$\text{Optical purity (\%)} = \frac{[\alpha]_D^{20} \text{ of the hydrogenated product}}{[\alpha]_D^{20} \text{ of optically pure alcohol}} \times 100$$

The $[\alpha]_D^{20}$ of the hydrogenated product was calculated using the following values. Specific gravity: 2-octanol; d_{20} = 0.8202, methyl 3-hydroxybuturate; d_{20} = 1.058. Specific optical rotation $[\alpha]_D^{20}$ of the optically pure enantiomers: (*S*)-2-octanol; $[\alpha]_D^{20} = +9.76^\circ$ (neat) [23], (*R*)-methyl 3-hydroxybuturate; $[\alpha]_D^{20} = -22.95^\circ$ (neat) [18]. When the purity of the product after distillation was less than 100% (in the case of the low conversion), the e.d.a. was evaluated by the 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 (CP Chirasil DEX-CB (0.25 mm × 25 m) at 373 K). The e.e. was calculated from the peak integration of the corresponding enantiomers. In the present paper, for the results of the hydrogenation of 2-octanone and methyl acetoacetate, the e.d.a. with a positive sign indicates the (*S*)-isomer in excess in the product while the negative sign indicates the (*R*)-isomer in excess.

3. Results and discussion

3.1. Effects of the addition of NaBr on the hydrogenation rate and e.d.a.

Fig. 1 shows the effect of the amount of NaBr on the e.d.a. and the hydrogenation rate without the addition of pivalic acid to the reaction media. In the absence of pivalic acid, the hydrogenated product of the (*S*)-isomer in excess (4% e.e.) was attained without the addition of NaBr. The production of the (*R*)-isomer was increased by the addition of NaBr. The hydrogenation rate was also increased with the increase in the amount of NaBr up to 2 mg. Fig. 2 shows the effect of the amount of NaBr on the e.d.a. and the hydrogenation rate with the addition of 5.1 g pivalic acid (50 mmol) to the reaction media. In the presence of pivalic acid, no addition of NaBr produced the

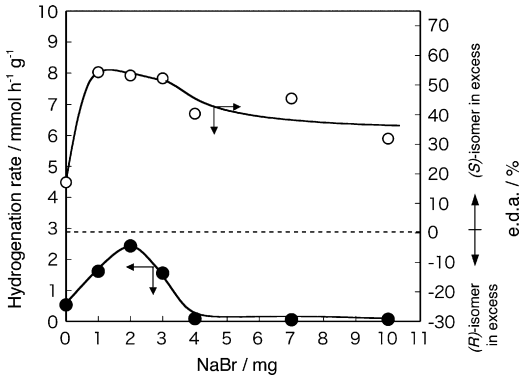

Fig. 2. Enantio-differentiating hydrogenation of 2-octanone over a modified reduced nickel catalyst in the presence of pivalic acid. (○) e.d.a., (●) hydrogenation rate. Modifier: 1.3 mg of tartaric acid and NaBr.

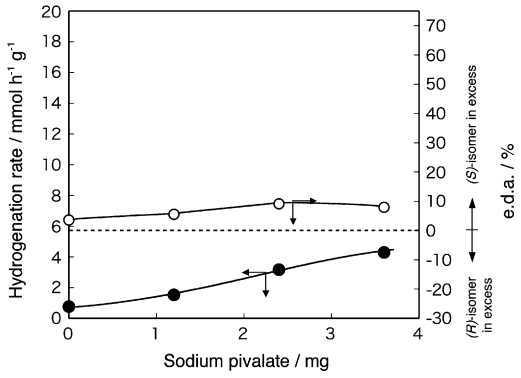

Fig. 4. Enantio-differentiating hydrogenation of 2-octanone over a modified reduced nickel catalyst in the absence of pivalic acid. (○) e.d.a., (●) hydrogenation rate. Modifier: 1.3 mg of tartaric acid and sodium pivalate.

low e.d.a. of 17%. However, the addition of 1 mg of NaBr resulted in a significant increase in the e.d.a., while the further addition of NaBr gradually decreased it. The preferential configuration of the product was (*S*) irrespective of the amount of NaBr. Although the hydrogenation was slow without NaBr, the hydrogenation rate increased with the increase in the amount of NaBr up to 2 mg. The addition of more than 2 mg NaBr resulted in a decreased hydrogenation rate. These results in Figs. 1 and 2 support our previous proposal that for the hydrogenation of 2-octanone, the appearance of the e.d.a. would require a "nickel catalyst modified with both tartaric acid and NaBr" and "pivalic acid in the reaction media" [22]. This study revealed that the combination of the appropriate amount of tartaric acid, NaBr and pivalic acid increased the hydrogenation rate. The results for the hydrogenation of 2-octanone were significantly different from the enantio-differentiating hydrogenation of methyl acetoacetate (Fig. 3(a) and (b)). That is, for the enantio-differentiating hydrogenation of methyl acetoacetate over tartaric acid in situ modified reduced nickel, even in the absence of the carboxylic acid, such as acetic acid in the reaction media (Fig. 3(a)), a moderate e.d.a. (54%, (*R*)-isomer in excess) was obtained without NaBr. In the presence of acetic acid (Fig. 3(b)), effects of the amount of NaBr on the e.d.a. and the hydrogenation rate were similar to those in the absence of acetic acid. Concerning the role of NaBr in the hydrogenation of methyl acetoacetate in the absence of acetic acid, we proposed that NaBr would have the following two roles, i.e., Na^+ activates the enantio-differentiating sites through the interaction with tartaric acid, and Br^- deactivates both the enantio-differentiating sites and non-enantio-differentiating sites. The e.d.a. values and the hydrogenation rate would be determined by the combination of these effects of Na^+ and Br^- [24]. It was revealed that these effects were observed both in the hydrogenation of methyl acetoacetate and 2-octanone, except that (*S*)-isomer in excess was obtained for the hydrogenation of 2-octanone in the presence of pivalic acid.

3.2. Effects of the addition of sodium pivalate on the hydrogenation rate and e.d.a.

It was mentioned in Section 3.1 that NaBr, as well as pivalic acid, were mandatory for the appearance of the predominant e.d.a. for the hydrogenation of 2-octanone over the TA in situ modified reduced nickel catalyst. In order to clarify the effects of the Na^+ in the reaction media on the e.d.a. and the hydrogenation rate, sodium pivalate was employed instead of the NaBr for the investigation of the effects of the amount of Na^+ on the e.d.a. and the hydrogenation rate. Fig. 4 shows the effects of the amount of sodium pivalate on the e.d.a. and the hydrogenation rate in the absence of pivalic acid. The e.d.a. was 4–9% ((*S*)-isomer in excess) irrespective of the amount of sodium pivalate. The hydrogenation rate increased with an increase in the amount of sodium pivalate. Fig. 5 shows the effects of the amount of sodium pivalate on the e.d.a. and the hydrogenation rate when 5.1 g (50 mmol) of pivalic acid was added to the reaction media. The addition of 1.2 mg of sodium pivalate resulted in a significant increase in the e.d.a. (62% at the hydrogenation temperature of 373 K) and almost a constant e.d.a. with the further addition of sodium pivalate. The hydrogenation rate increased as well with an increase in the amount of sodium pivalate. As the addition of sodium pivalate as the co-modifier resulted in a 60%

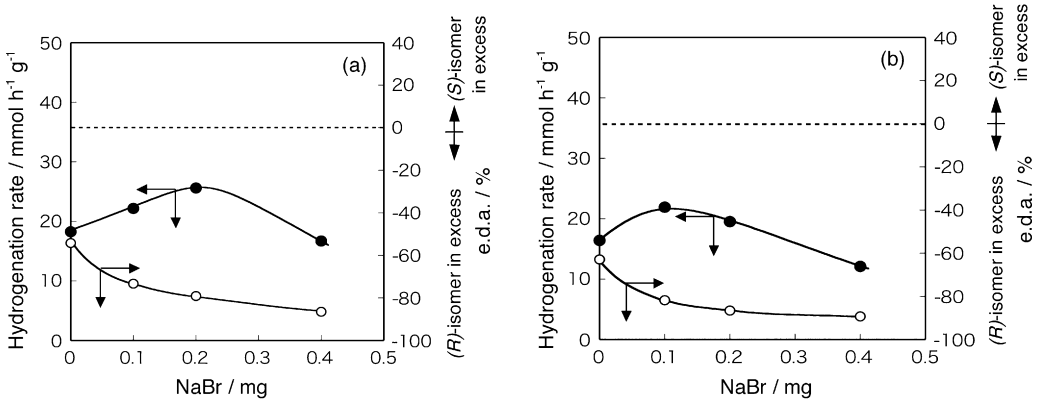

Fig. 3. Enantio-differentiating hydrogenation of methyl acetoacetate over a tartaric acid–NaBr-modified nickel catalyst: (a): in the absence of acetic acid [22] using autoclave No. 2 and (b): in the presence of acetic acid (0.1 g) using autoclave No. 1. (○) e.d.a., (●) hydrogenation rate. Reduced nickel catalyst: 0.33 g, modifier: 2.5 mg of tartaric acid and NaBr.

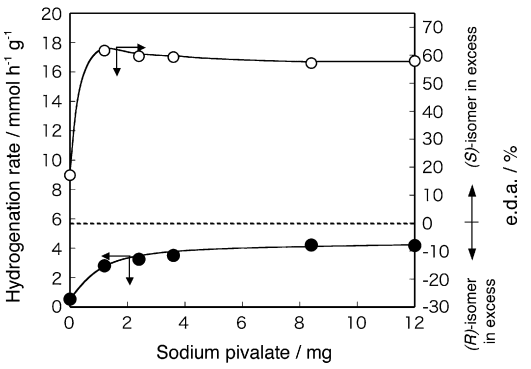

Fig. 5. Enantio-differentiating hydrogenation of 2-octanone over a modified reduced nickel catalyst in the presence of pivalic acid (5.1 g). (○) e.d.a., (●) hydrogenation rate. Modifier: 1.3 mg of tartaric acid and sodium pivalate.

e.d.a., it would be concluded that not Br^-, but Na^+ was important for the increased e.d.a. Comparing the effects of NaBr (Fig. 2) and those of sodium pivalate (Fig. 5), the addition of sodium pivalate resulted in a higher e.d.a. and a higher hydrogenation rate than those of NaBr. Furthermore, the excess addition of sodium pivalate did not lead to a decreased e.d.a. and hydrogenation rate. Based on these results, it was revealed that sodium pivalate is a more appropriate co-modifier than NaBr for the hydrogenation of 2-octanone over the tartaric acid-modified reduced nickel catalyst. Br^- is considered to produce an increase in the e.d.a. by deactivation of the non-enantio-differentiating sites (where racemic products are produced) [25]. As the area of the non-enantio-differentiating sites of the reduced nickel catalyst would be smaller than that of the Raney nickel catalyst [25], the increase in the e.d.a. by the adsorption of Br^- was low for the reduced nickel. Fig. 6 shows the effects of the addition of sodium pivalate on the e.d.a. and the hydrogenation rate when 1.3 g (12.7 mmol) of pivalic acid was added. The e.d.a. significantly increased with 1.2 mg of sodium pivalate and slightly decreased with the further addition of sodium pivalate. The hydrogenation rate was significantly increased with the addition of 1.2 mg sodium pivalate, then gradually increased with the addition of more than 1.2 mg. The hydrogenation rate values in Fig. 6 (pivalic acid: 1.3 g) were greater than those in Fig. 5 (pivalic acid: 5.1 g). As the 2-octanone would be competitively adsorbed on the nickel surface versus pivalic acid, the presence of a lower amount of pivalic acid produced a higher hydrogenation rate. The characteristics of the changes in the e.d.a. and the hydrogenation rate in Fig. 6 were similar to those in Fig. 5. However, the maximum e.d.a. of 42% was attained with 1.3 g of pivalic acid, while 62% with the addition of 5.1 g of pivalic acid. The e.d.a. value depended significantly on the amount of pivalic acid, not on the amount of sodium pivalate. The

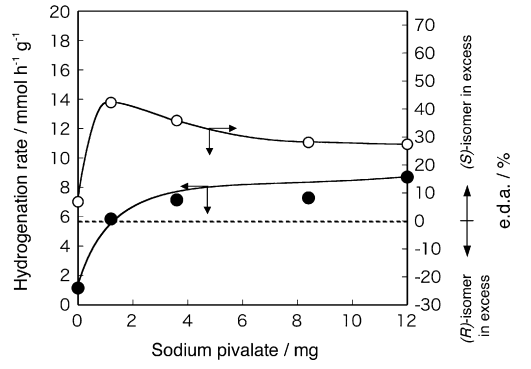

Fig. 6. Enantio-differentiating hydrogenation of 2-octanone over a modified reduced nickel catalyst in the presence of pivalic acid (1.3 g). (○) e.d.a., (●) hydrogenation rate. Modifier: 1.3 mg of tartaric acid and sodium pivalate.

amount of 1.2 mg (9.7×10^{-6} mol) of sodium pivalate and 1.3 mg (8.7×10^{-6} mol) of tartaric acid are on the same order. As these values correspond to about 1/2000 of the amount of 2-octanone (2.5 g (1.95×10^{-2} mol)) and to about 1/5000 of the amount of pivalic acid (5.1 g (5.0×10^{-2} mol)), sodium pivalate added to the reaction media would have an interaction with tartaric acid on the surface. Based on the fact that the pK_{a1} of tartaric acid (2.93) is smaller than that of pivalic acid (5.01), it would be reasonable to assume that sodium ions from sodium pivalate formed the sodium salt of tartaric acid. For the enantio-differentiating hydrogenation of 2-octanone, the appearance of the predominant e.d.a. and the increase in the hydrogenation rate would be realized by the interaction between "the complex of pivalic acid and 2-octanone" and "the sodium salts of tartaric acid". When tartaric acid does not form its sodium salt, the interaction between the "tartaric acid" and "2-octanone-pivalic acid complex" would not be appropriate for the effective enantio-differentiation. Effective formation of "2-octanone-pivalic acid complex" would be realized by the addition of about twice the moles of pivalic acid to 2-octanone.

4. Conclusion

The effects of a co-modifier and carboxylic acid on the hydrogenation rate and the enantio-differentiating ability were studied for the hydrogenation of 2-octanone and methyl acetoacetate over a tartaric acid modified reduced nickel catalyst. For the hydrogenation of 2-octanone, tartaric acid, pivalic acid, and Na^+ were necessary for the appearance of the predominant e.d.a. The appearance of the e.d.a. and the increase in the hydrogenation rate would be realized by the interaction between "the complex of pivalic acid and 2-octanone" and "the sodium salts of tartaric acid". Sodium pivalate, instead of the typical co-modifier, NaBr, was appropriate for the in situ modification of reduced nickel. The use of sodium pivalate resulted in a higher hydrogenation rate and e.d.a. than the use of NaBr. The 62% e.d.a. attained by the hydrogenation in the presence of sodium pivalate at 373 K was lower than 80% e.d.a. attained by the hydrogenation at 323 K over the tartaric acid–NaBr-pre-modified nickel [26]. The effects of the hydrogenation temperature on the e.d.a. for the hydrogenation of 2-octanone using sodium pivalate are under way.

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