Studies of the effect of pivalic acid on the hydrogenation rate and the enantio-differentiating ability for the hydrogenation of 2-octanone over a tartaric acid-NaBr-modified nickel catalyst

Tsutomu Osawa,[a],* Yuki Nakagawa,[a] Tadao Harada,[b] and Osamu Takayasu[a]

[a]*Faculty of Science, University of Toyama, Toyama, 930-8555, Japan*
[b]*Faculty of Science and Technology, Ryukoku University, Otsu, 520-2194, Japan*

The effects of the addition of pivalic acid to the reaction media on the hydrogenation rate and the enantio-differentiating ability (e.d.a.) for the hydrogenation of 2-octanone were studied over an (R,R)-tartaric acid-NaBr-in-situ-modified nickel catalyst. It was revealed that the modification with both tartaric acid and NaBr was necessary for increasing the e.d.a. by the addition of pivalic acid to the reaction media. The role of pivalic acid in the enantio-differentiating hydrogenation of 2-octanone was different from that of acetic acid in the hydrogenation of methyl acetoacetate.

KEY WORDS: 2-octanone; enantio-differentiating; hydrogenation rate; pivalic acid; tartaric acid; nickel catalyst.

1. Introduction

Producing optically active compounds is the key technology for pharmaceutical and agrochemical industries. For this purpose, many strategies, such as enantio-selective homogeneous catalysts (organometallic complexes or enzymes) [1–3], enantio-selective heterogenized catalysts [4–5], and enantio-selective solid catalysts [6–8], have been used and widely studied. The enantio-selective solid catalysts are some of the most promising solutions especially in our current society for saving energy and resources, because solid catalysts have the advantages of easy preparation, easy separation from the reaction mixture, and easy reuse. For developing such catalysts, their applicability to various reactions is also an important issue. The enantio-differentiating hydrogenation of simple alkanones is one of the difficult reactions with respect to attaining a high enantio-selectivity and a high hydrogenation activity [9].

A tartaric acid-NaBr-modified nickel catalyst is one of the successful enantio-differentiating solid catalysts for the hydrogenation of β-ketoesters [10] and 2-alkanones. This catalyst is a unique solid catalyst for attaining up to an 85% enantio-differentiating ability (e.d.a.) for the hydrogenation of 2-alkanones, for example, 80% for the hydrogenation of 2-octanone, 85% for 3,3-dimethyl-2-butanone, and 72% for 2-butanone [11]. For the enantio-differentiating hydrogenation over the tartaric acid-NaBr-modified nickel, it was reported that the addition of carboxylic acid to the reaction media increased the e.d.a. [12–14]. For the hydrogenation of methyl acetoacetate, we recently reported that by using an in-situ modification, the role of the acetic acid for increasing the e.d.a. was attributed to the specific acceleration of the hydrogenation rate on the enantio-differentiating sites, where optically active compounds are produced with the aid of tartaric acid [15]. The in-situ-modification is a powerful method for kinetic investigations, because the effect of the modifier adsorption on the hydrogenation rate can be measured without a change in the nickel surface during the modification [15]. On the other hand, for the hydrogenation of 2-alkanones, a few reports concerning the role of pivalic acid have been published, while the addition of pivalic acid to the reaction media is mandatory for the appearance of the enantio-selectivity. We proposed that the complex of tartaric acid, 2-octanone, pivalic acid, and Na$^+$ would be important for an effective enantio-differentiation [16,17].

In this study, during the course of the investigations of the role of pivalic acid for the enantio-differentiating hydrogenation of 2-octanone, the effects of the pivalic acid on the hydrogenation rate and the e.d.a. were examined using an in-situ-modification method. The results were compared with those for methyl acetoacetate.

2. Experimental

The GLC measurement for determining the conversion and enantiomer excess (e.e.) were carried out using a Hitachi 263–30 gas chromatograph and a Shimadzu

*To whom correspondence should be addressed.
 E-mail: osawa@sci.u-toyama.ac.jp

GC-18A gas chromatograph, respectively. The measurement of the optical rotation was carried out using a JASCO DIP-1000 polarimeter.

2.1. Reduced nickel catalyst

Nickel oxide (Wako Pure Chemical Industries, Ltd., lot CEL7157) was calcined at 1373 K for 6 h. The resulting nickel oxide was then 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 (2.3 g) in THF (10 cm^3). The modification was carried out using an in-situ-modification method [15]. (R,R)-tartaric acid and NaBr (the amounts were stated in the text) were added to the reaction mixture. As the solubility of the NaBr in the reaction mixture was low, NaBr was dissolved in 25 mm^3 of distilled water. The hydrogenation was carried out in a stirred autoclave 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 one minute. 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, then the hydrogenated product was dissolved in ether and washed with a saturated aqueous solution of K$_2$CO$_3$. The ether solution was then dried over anhydrous Na$_2$SO$_4$ 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. 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.

$$\text{Optical purity}/\% = ([\alpha]_D^{20} \text{ of 2-octanol}/[\alpha]_D^{20}$$
$$\text{of optically pure 2-octanol}) \times 100$$

The $[\alpha]_D^{20}$ of 2-octanol was calculated using its specific gravity; $d_{20} = 0.8202$. The specific optical rotation $[\alpha]_D^{20}$ of the optically pure (S)-2-octanol is $[\alpha]_D^{20} = + 9.76°$ (neat) [18]. When the purity of 2-octanol 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.

3. Results and discussion

In the preliminary experiment, it was revealed that the hydrogenation rate and e.d.a. decreased during the repeated use of the catalyst, when the catalyst was modified with tartaric acid and NaBr. Therefore, the hydrogenation rate and e.d.a. in the first run were measured and used for the discussion in this paper.

Figure 1 shows the effect of the amount of pivalic acid on the hydrogenation rate and the e.d.a. for the hydrogenation of 2-octanone over a nickel catalyst which was in-situ-modified with tartaric acid. The hydrogenation rate was almost constant irrespective of the amount of pivalic acid in the reaction media. The low e.d.a. of 4% was attained when no pivalic acid was added, but the e.d.a. gradually increased with the increase in the amount of pivalic acid. However, only a 17% e.d.a. was attained by the addition of 50 mmol pivalic acid. 2-Octanol with an excess of the (S)-enantiomer was obtained in the presence or absence of the pivalic acid. Figure 2 shows the effect of the amount of pivalic acid on the hydrogenation rate and the e.d.a., when nickel was in-situ modified with both tartaric acid and NaBr. The hydrogenation rates were higher than those obtained by the nickel modified with tartaric acid (figure 1). The rate increased till 12 mmol of pivalic acid, but beyond this amount, the rate gradually decreased. Concerning the e.d.a., a 13% (R)-alcohol excess was attained without pivalic acid. The configuration of the excess alcohol was changed to (S) by the addition of a small amount of pivalic acid, and the e.d.a.
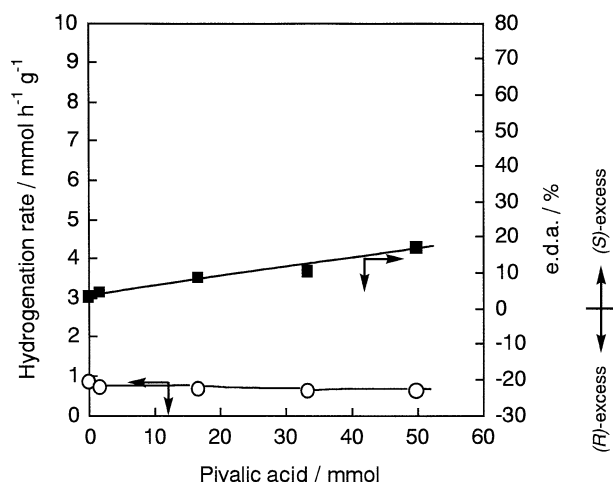

Figure 1. Effect of the amount of pivalic acid on the hydrogenation rate and e.d.a. over tartaric acid-modified nickel; ○: Hydrogenation rate, ■: e.d.a; Modifying reagent: tartaric acid (1.3 mg).
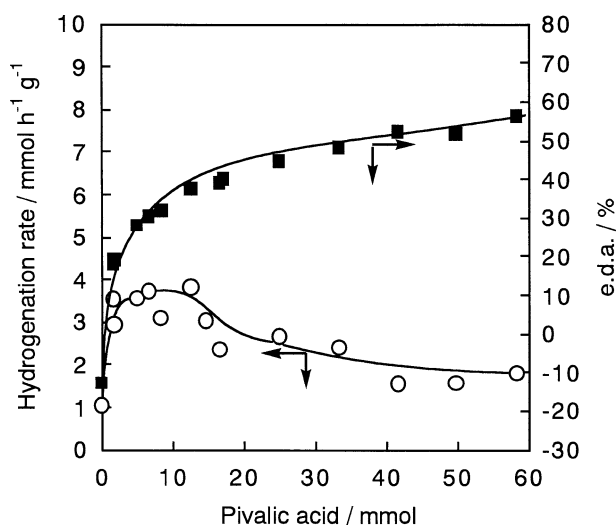
Figure 2. Effect of the amount of pivalic acid on the hydrogenation rate and e.d.a. over tartaric acid-NaBr-modified nickel; ○: Hydrogenation rate, ■: e.d.a; Modifying reagent: tartaric acid (1.3 mg) and NaBr (1.0 mg).

increased with an increase in the amount of pivalic acid. About a 60% e.d.a. was attained by the addition of 58 mmol of pivalic acid for the 373 K hydrogenation. Figure 3 shows the relation between the amount of pivalic acid and the hydrogenation rate over the nickel catalyst in-situ-modified with NaBr. The rate was slightly affected by the amount of pivalic acid added to the reaction media.

From the results shown in figures 1 to 3, the modification with both tartaric acid and NaBr was necessary for increasing the hydrogenation rate and e.d.a. by the
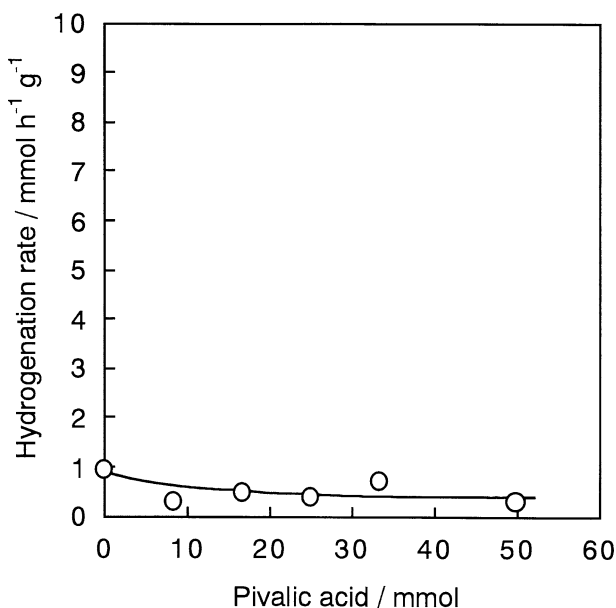

Figure 3. Effect of the amount of pivalic acid on the hydrogenation rate and e.d.a. over NaBr-modified nickel; ○: Hydrogenation rate; Modifying reagent: NaBr (1.0 mg).

addition of pivalic acid to the reaction media. These results were completely different from those obtained by the enantio-differentiating hydrogenation of methyl acetoacetate. For the hydrogenation of methyl acetoacetate, when the nickel catalyst was in-situ-modified with only tartaric acid (not with tartaric acid and NaBr), the hydrogenation rate and e.d.a. increased with the addition of acetic acid (e.d.a. increased from 40% to 70% with an increase in the amount of acetic acid from 0 to 0.5 g) [15]. The results of the present study indicate that NaBr as well as tartaric acid play an important role in the enantio-differentiating process during the hydrogenation of 2-octanone. Considering the fact that the addition of Na^+ (sodium 2-ethylhexanoate) to the reaction media in every other run is necessary to maintain the e.d.a. for the repeated use of the catalyst for the enantio-differentiating hydrogenation of 2-octanone [19], Na^+ in NaBr plays a crucial role during the e-nantio-differentiation. The role of pivalic acid for the enantio-differentiating hydrogenation of 2-octanone would be different from the role of acetic acid for the hydrogenation of methyl acetoacetate. For the hydrogenation of methyl acetoacetate, the features of the dependence of the hydrogenation rate and e.d.a. on the amount of acetic acid were similar, and the increase in the hydrogenation rate of the enantio-differentiating sites (e.d.-sites) by the addition of acetic acid resulted in the increased e.d.a. [15]. On the contrary, for hydrogenation of 2-octanone, the dependence feature of the hydrogenation rate on the amount of pivalic acid was different from that of the e.d.a. on the amount of pivalic acid (figure 2). The e.d.a. increased with the addition of up to 60 mmol of pivalic acid, while the hydrogenation rate first increased then decreased beyond 12 mmol of pivalic acid. These results indicate that the increase in the production of the (*S*)-alcohol compared to that of the (*R*)-alcohol (the absolute configuration changed from (*R*) to (*S*) and then the e.d.a. increased) by the addition of pivalic acid would be attributed not only to the contribution of the acceleration of the hydrogenation rate of the e.d.-site, but to the contribution of the pivalic acid to control the enantio-differentiation mode of 2-octanone during the enantio-differentiating process.

Based on these results, it was concluded that the role of pivalic acid added to the reaction media for the hydrogenation of 2-octanone would be different from the role of acetic acid for the hydrogenation of methyl acetoacetate. The differentiation of the enantio-face of 2-octanone would be performed in the following manner. In the absence of pivalic acid, the effective enantio-differentiation was not carried out; the e.d.a. was low and the absolute configuration of the excess enantiomer depended on the presence of NaBr. In the presence of pivalic acid, the formation of a complex, which consisted of tartaric acid, 2-octanone, pivalic acid, and Na^+, would increase the hydrogenation rate on the

e.d.-sites and that the complex would play an important role in the effective enantio-differentiation. The addition of more than 12 mmol of pivalic acid to 20 mmol of the substrate would decrease the hydrogenation rate due to the competitive adsorption of pivalic acid on the catalyst surface. In the range of these pivalic acid amounts, the effect of controlling the enantio-differentiation mode of the substrate by pivalic acid mainly contributed to the increased e.d.a.

References

[1] H.U. Blaser and E. Schmidt, *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions (Chemistry)* (John Wiley & Sons, New York, 2004).

[2] H.U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner and M. Studer, Adv. Syn. Catal. 345 (2003) 103 and references therein.

[3] J.M. Thomas and R. Raja, J. Organomet. Chem. 689 (2004) 4110and references therein..

[4] I.F.J. Vankelecom, and P.A. Jacobs, Chiral Catalyst Immobilization and Recycling, eds. D.E. De Vos, I.F.J. Vankelecom, and P.A. Jacobs, Wiley-VCH (2000) 19 and references therein.

[5] U. Kragl and T. Dwars, Trends in Biotechnology 19 (2001) 442 and references therein.

[6] T. Mallat, and A. Baiker, In Fine Chemicals Through Heterogeneous Catalysis, eds. R.A. Sheldon, and H. van Bekkum, Wiley-VCH, (2001) 449–460 and references therein.

[7] D.Y. Murzin, P. Mäki-Arvela, E. Toukoniitty and T. Salmi, Catal. Rev. Sci. Eng. 47 (2005) 175 and references therein.

[8] T. Osawa, T. Harada and O. Takayasu, Curr. Org. Chem. 10 (2006) 1513and references therein.

[9] A. López-Martínez and M.A. Keane, J. Mol. Catal. A: Chem. 153 (2000) 257 and references therein.

[10] A. Tai, and T. Sugimura, Chiral Catalyst Immobilization and Recycling, eds. D.E. De Vos, I.F.J. Vankelecom, and P.A. Jacobs, Wiley-VCH (2000) 173 and references therein.

[11] T. Osawa and T. Harada, A. Tai, Catal. Today 37 (1997) 465.

[12] Y. Orito, S. Niwa and S. Imai, Yukigoseikagaku 35 (1977) 672.

[13] A. Tai and T. Harada, Tailored Metal Catalysts, ed. Y. Iwasawa, Reidel, Dordrecht, (1986) 265.

[14] T. Osawa and T. Harada, Bull. Chem. Soc. Jpn. 57 (1984) 1518.

[15] T. Osawa, M. Ando, S. Sakai, T. Harada and O. Takayasu, Catal. Lett. 105 (2005) 41.

[16] T. Osawa, T. Harada and A. Tai, J. Mol. Catal. 87 (1994) 333.

[17] T. Osawa, T. Harada and O. Takayasu, Topics Catal. 13 (2000) 115.

[18] R.H. Pickard and J. Kenyon, J. Chem. Soc. 99 (1911) 45.

[19] T. Osawa, K. Sawada, T. Harada and O. Takayasu, Appl. Catal. A: Gen. 264 (2004) 33.