Almost Perfect Enantio-differentiating Hydrogenation of Methyl 3-Cyclopropyl-3-oxopropanoate over Tartaric Acid Modified Raney Nickel Catalyst

Satoshi Nakagawa, Takashi Sugimura, and Akira Tai*
Faculty of Science, Himeji Institute of Technology, Kanaji, Kamigori, Hyogo 678-12

(Received May 12, 1997; CL-970354)

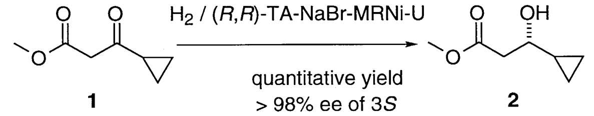
Almost perfect enantio-differentiating hydrogenation was achieved by asymmetrically modified heterogeneous catalyst. The hydrogenation of methyl 3-cyclopropyl-3-oxopropanoate over tartaric acid modified Raney nickel gave methyl 3-cyclopropyl-3-hydroxypropanoate in more than 98% of optical purity.

Tartaric acid modified Raney nickel (TA-MRNi) is a classical asymmetrically modified heterogeneous metal catalyst developed by Izumi in 1963.[1,2] Because of its simple preparation process, excellent hydrogenation activity, and clean reaction product, TA-MRNi has long been considered to be a promising catalyst for enantio-differentiating hydrogenation but the improvement of optical yield (OY) of this system required long term efforts. The important characteristics of TA-MRNi found thereafter[3-5] can be postulated that the crystalline nickel in the catalyst functioned as an enantio-differentiating reaction site (*E*-site), while the mechanically and chemically unstable disordered nickel part contaminated with aluminum (*N*-site) spoiled the OY of the system by producing a racemic product. The OY of the product could schematically be expressed as eq. 1 where factor-*i* is the enantio-differentiating ability of the *E*-site (OY of *E*-site catalyzed product) provided by the interaction between the substrate and tartaric acid.

$$OY(\%) = i \times \frac{E}{E+N} \qquad (1)$$

The latest TA-MRNi employed in this study was prepared by the following procedure: 1) Refining and cleaning of Raney nickel (W-1 type) by ultrasound irradiation in water (RNi-U). 2) Asymmetric modification of the resulting RNi-U with an acidic aqueous solution of tartaric acid and NaBr (pH adjusted to 3.2 with NaOH) at 100 °C for 1 h. With this preparation, the elimination of the unfavorable part (*N*-site) from the entire MRNi was effectively carried out by the mechanical cleaning, acid corrosion, and selective poisoning with NaBr. The resulting TA-NaBr-MRNi-U showed excellent enantio-differentiating ability as well as high hydrogenation activity, which enabled us to carry out the hydrogenation at relatively low temperature.[6] With this catalyst, the hydrogenation of a series of β-ketoesters (R–$COCH_2COOCH_3$) was carried out at 100° C and 60 °C. The resulting OYs were in the order; R = methyl (86% at 100 °C, 86% at 60 °C) << ethyl (91% at 100 °C, 94% at 60 °C) < isopropyl (88% at 100 °C, 96% at 60 °C) = neopentyl (84% at 100 °C, 96% at 60 °C). The substrates giving higher OYs always resulted in a higher increment of OY with a lower reaction temperature. The results indicated that factor-*i* in eq. 1 could be controlled by the reaction temperature as well as the steric factor of the substrate.[7]

The essential requirements for the asymmetric catalysis system are the excellent OY as well as that the resulting optically active reaction product should be useful as a chiral synthon. To satisfy these two requirements, we designed methyl 3-cyclopropyl-3-oxopropanoate (**1**). That is, the cyclopropyl group in this compound is between the ethyl and isopropyl group in steric bulkiness and can survive under the hydrogenation over a Ni catalyst, and that in the resulting methyl 3-cyclopropyl-3-hydroxypropanoate (**2**) can convert to various functional groups by ring opening based on the well documented cyclopropane chemistry.[8] As a result, we encountered with the best substrate so far as examined for the enantio-differentiating hydrogenation of the TA-MRNi system.



(2)

The hydrogenation of **1** with (*R*,*R*)-TA-NaBr-MRNi-U was carried out as follows; the substrate (4 g) in THF (10 cm^3) with acetic acid (0.2 cm^3) was shaken under a hydrogen pressure of 100 bar (10^7 Pa) with 0.9 g of catalyst. The reaction proceeded smoothly and completed within 48 h giving (+)-**2**[9] in a quantitative chemical yield. The configuration of (+)-**2** was determined to be *S* by chemical transformation to (*S*)-(-)-methyl 3-hydroxy-4-methylpentanoate[10] by the ring opening over PtO_2 with H_2. A portion of the reaction mixture was treated with an excess amount of (*S*)-MTPACl and the resulting MTPA ester was subject to chiral capillary GLC analysis under the conditions of baseline separation (CP-Chirasil DEX-CB, 25 m, 0.25 mm i.d., 145 °C). The OY was calculated from the peak integration of corresponding enantiomers as OY (%) = $|[R]-[S]|/([R]+[S]) \times 100$. The OY of the product was also determined by a chiral micelle capillary electrophoresis as *p*-toluate.[11] The both results well matched each other. The OY of the reaction was 96% at 100 °C and more than 98% at 60 °C. The reproducibility of the OY in three separate runs at 60 °C was 98.1%, 98.3%, and 98.6% .

As a matter of course, the hydrogenation of **1** over (*S*,*S*)-TA-NaBr-MRNi-U gave (*R*)-(-)-**2** in 98.0% OY.

The OY of the present reaction means that more than 99% of the substrate is attacked by hydrogen from the one side of its enantio-faces under the rigorous control of the tartaric acid on the nickel surface. When eq. 1 is taken into account, it is expected that the active site of TA-NaBr-MRNi-U is almost freed from *N*-site and factor-*i* on *E*-site is close to 100%. The asymmetric heterogeneous metal catalyst developed in early stage could not gave sufficient OYs and it has long been believed that rigorous stereo control on the metal surface would be difficult because the reaction sites on the metal surface are not uniform. By achieving a more than 98% OY in the hydrogenation of a well designed β-

ketoester with the latest MRNi, we now realized that the insufficient OY in the asymmetric heterogeneous catalysis is not due to the inherent problem of the catalyst itself but due to the insufficient tuning of the reaction system.

We thank Dr. Y. Izumi, professor emeritus Osaka University, for his encouragement and useful private information about his early studies, and Professors T. Harada of Ryukoku University and T. Osawa of Toyama University for their helpful discussions. We also thank Professors K. Otsuka, S. Terabe and Mr. Y. Tanaka of Himeji Institute of Technology for their help to determine the OY by electrophoresis.

References

1 Y. Izumi, M. Imaida, H. Fukawa, and S. Akabori, *Bull. Chem. Soc. Jpn.*, **36**, 155–160 (1963).

2 Y. Izumi, *Angew. Chem., Int. Ed. Enl.*, **10**, 871–881 (1971).

3 Y. Izumi, *Adv. Catal.*, **32**, 215–271 (1983).

4 W. M. H. Sachtler, in "Catalysis of Organic Reaction", ed by R. L. Augustine, p. 189–206 (Marcel Decker, New York, 1985).

5 A. Tai and T. Harada, in "Tailored Metal Catalysts", ed by Y. Iwasawa, p. 265–324 (D. Reidel, Dordrecht, 1986).

6 A. Tai, T. Kikukawa, T. Sugimura, Y. Inoue, S. Abe, T. Osawa, and T. Harada, *Bull. Chem. Soc. Jpn.*, **67**, 2473–2477 (1994).

7 T. Sugimura, T. Osawa, S. Nakagawa, T. Harada, and A. Tai, in "Studies in Surface Science and Catalyst **101** (11th International Congress on Catalysis)", ed by J. W. Hightower, 231–240 (Elsevier, Amsterdam, 1996).

8 "The Chemistry of the Cyclopropyl Group", Vols. 1 and 2, ed by Z. Rappoport, (John Wiley, Chichester, 1987).

9 Optical rotation of the sample obtained in the best OY (98.6%): $[\alpha]_D^{20} = +11.0°$ (neat).

10 T. Sugimura, M. Yoshikawa, T. Yoneda, and A. Tai, *Bull. Chem. Soc. Jpn.* **63**, 1080–1082 (1990).

11 Y. Tanaka, M. Yanagawa, and S. Terabe, *J. High Resol. Chromatogr.,* **19,** 421–433 (1996).