

## Highly Durable Enantio-Differentiating Nickel Catalyst for Repeated Use for the Hydrogenation of Methyl Acetoacetate

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(Received February 5, 2001; CL-010100)

The enantio-differentiating hydrogenation of methyl acetoacetate was repeated 30 times over a fine Ni powder catalyst while modifiers (optically active tartaric acid and NaBr) were directly added to the reaction media only in the first run. Over 80% optical yields were attained for the repeated runs. The addition of sodium 2-ethylhexanoate increased the optical yields in the subsequent runs. The very simple and highly durable enantio-differentiating nickel catalyst for repeated use was developed by an in situ modification.

The tartaric acid-NaBr-modified Raney Ni catalyst (TA-NaBr-MRNi) is one of the most successful heterogeneous enantio-selective catalysts for producing optically active compounds. TA-NaBr-MRNi can be prepared by pre-modification before hydrogenation, that is, immersing RNi in an aqueous solution of TA and NaBr at pH 3.2. The resulting MRNi hydrogenates  $\beta$ -ketoesters in the high optical yields of 80–98%.<sup>1,2</sup> The heterogeneous enantio-selective catalyst can produce large amounts of optically active compounds using a small amount of an optically active modifier. Repeated use of the modified Ni catalyst would have a great advantage in further minimizing the starting optically active modifiers and waste of the modification solution.

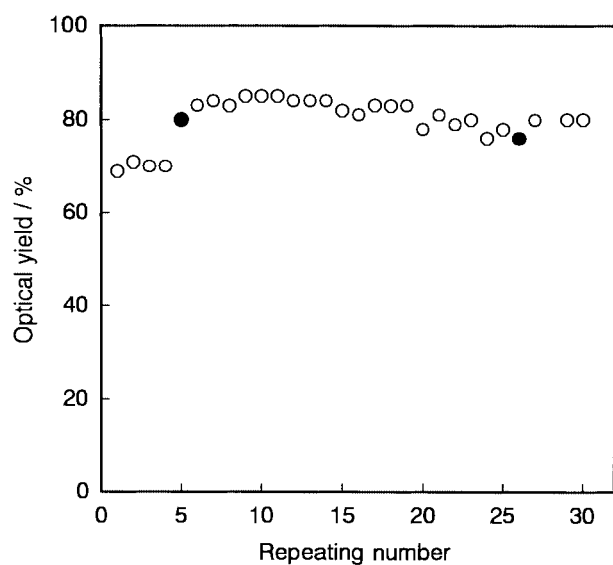
The studies of the repeated use of the enantio-differentiating heterogeneous catalysts were performed with cinchona-modified Pt catalysts and with TA-modified Ni catalysts. Böhmer et al. reported that Pt/zeolite modified with cinchonidine was an effective catalyst for long-term use with the addition of the modifier during each run of the hydrogenation. However, the decrease in the enantiomer excess of the product and, especially, the decrease in the hydrogenation rate were inevitable.<sup>3</sup> Tai et al. demonstrated that the repeated use of the conventional TA-NaBr-MRNi resulted in a drastic decrease in the enantio-differentiating ability and hydrogenation activity after the second run of the catalyst while the silicone-embedded catalyst kept its initial enantio-differentiating ability and hydrogenation ability even after the 27th repeated uses.<sup>4</sup> However, the enantio-differentiating ability of the silicone embedded catalyst was about 10% lower than that of TA-NaBr-MRNi. Tai et al. also demonstrated that the amine-treated TA-NaBr-MRNi maintained about 80% of the initial optical yield after the 10th run in the repeated trials.<sup>5,6</sup>

Recently, we reported that the in situ modification (TA and NaBr were directly added to the reaction media) was applied to the enantio-differentiating hydrogenation of methyl acetoacetate with about an 80% optical yield using the fine Ni powder catalyst.<sup>7</sup> In the present communication, we show a highly durable catalyst for the enantio-differentiating hydrogenation of methyl acetoacetate using a fine Ni powder prepared by an in

situ modification.

The typical experimental procedure is as follows. Fine Ni powder (0.5 g) (Vacuum Metallurgical Co., Ltd., Chiba, Japan) was treated in a hydrogen stream at 280 °C for 0.5 h. Methyl acetoacetate (5 g) was hydrogenated with the activated fine Ni powder in a mixture of THF (10 mL) and acetic acid (0.1 g). (*R,R*)-TA (0.1 g) and NaBr (2 mg) were added to the reaction mixture only in the first run. NaBr was added as an aqueous solution of 50  $\mu$ L distilled water. The hydrogenation was carried out in a 30 mL glass tube in a 100 mL stainless steel autoclave at the initial hydrogen pressure of 9 MPa and at 100 °C. After the reaction was completed, the reaction media was separated by decantation from the catalyst and then subjected to distillation. The optical purity of the methyl 3-hydroxybutyrate was determined by polarimetry. It was calculated using the value of  $[\alpha]_D^{20} = -22.95$  (neat) for the optically pure (*R*)-methyl 3-hydroxybutyrate. For the repeated use of the catalyst, the catalyst remaining in the glass tube was washed three times with THF (3  $\times$  10 mL) and then used for the next run under the same reaction conditions except for TA and NaBr. In the present study, sodium 2-ethylhexanoate (5 mg in 50  $\mu$ L THF) was added to the reaction media (methyl acetoacetate, THF, and acetic acid) in the 5th and 26th runs. The hydrogenation was completed within 5 h for the first run, and within 2 h for the runs from 2 to 30. No decrease in the hydrogenation activity was observed under the present experimental conditions during the repeated runs.

Figure 1 shows the results on the optical yield in the repeated runs of the catalyst. In the runs from the first to the 4th, the optical yields were maintained at about 70%. When racemic sodium 2-ethylhexanoate was added to the reaction media in the 5th run, the optical yield increased to 80%. In runs 6 to 23, 80 to 85% optical yields were obtained. In runs 24 to 26, 76 to 78% optical yields were attained. The addition of sodium 2-ethylhexanoate to the reaction media in the 26th run recovered the optical yield of 80% for the 27th run. These runs show a remarkable durability of the catalyst for the enantio-differentiating hydrogenation. The addition of only 0.1 g of (*R,R*)-TA to the reaction media involving the fine Ni powder (0.5 g) in the first run gave optically active methyl 3-hydroxybutyrate for 30 runs. The addition of sodium 2-ethylhexanoate increased the optical yield of the reaction. As we demonstrated that sodium ions were important for the effective enantio-differentiation,<sup>8</sup> the effect of the sodium ions on the optical yield was confirmed again in the repeated runs of the catalyst prepared by the in situ modification. For the practical procedure of the enantio-differentiating hydrogenation of methyl acetoacetate, the addition of TA, NaBr, and sodium 2-ethylhexanoate in the first run would be more appropriate for attaining high optical yields from the first run.



**Figure 1.** Durability of the catalyst for the enantio-differentiating hydrogenation of methyl acetoacetate solid circle; addition of sodium 2-ethylhexanoate to the reaction media.

Further investigations on the difference between the *in situ* modification method and the conventional modification method, and the role of NaBr and sodium 2-ethylhexanoate in the *in situ* modification are currently underway in our laboratory.

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