A Substrate Specific Chiral Modifier Activation on Enantio-differentiating Hydrogenation over Tartaric Acid-Modified Raney Nickel

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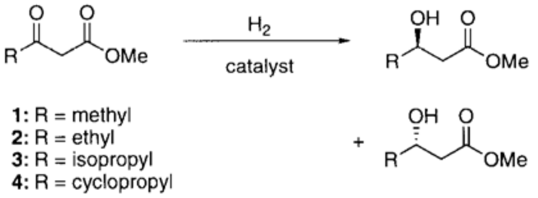
A comparative study of the reactivities of the hydrogenation of β-ketoesters over tartaric acid-modified and unmodified Raney nickels indicated that a substrate specific activation by the tartaric acid modification is the reason for the almost perfect enantio-differentiation in the reaction of methyl 3-cyclopropyl-3-oxopropanoate (**4**).

Tartaric acid-modified Raney nickel (MRNi) is a heterogeneous catalyst developed for the enantio-differentiating hydrogenation of ketones.[1] Using the latest MRNi catalyst[2] under optimized conditions,[3] we achieved more than 98% optical yield during the hydrogenation of **4**.[4] Although this almost perfect enantio-differentiation was found during studies of a substrate design based on the models,[3] the enantiomers production of over 100 to 1 ratio was beyond our expectation. In this communication, we would like to report that the high enantio-differentiation of **4** is due to the substrate specific activation of the catalysis by the TA-modification.



Scheme 1.

Considering the heterogeneity of the active sites on the MRNi surface, the enantiomeric excess (%ee) of the product is schematically expressed as

$$\%\mathrm{ee} = iE / (N + E) \qquad (1)$$

where E and N are the product amounts on the enantio- and non-enantio-differentiating, respectively, sites of MRNi and factor-i is the %ee of the E-site catalysis. The extended stereochemical model[3] indicates that the bulkiness at the γ-position of the β-ketoester affects factor-i, and the hydrogenation of a bulkier substrate has a lager factor-i resulting in a higher ee as far as the hydrogenation smoothly proceeds at 60 °C. Since the steric bulkiness of a cyclopropyl group in **4** is similar to or even smaller than an isopropyl group in **3**, it was difficult to understand the high ee of **4** by the structural bulkiness for controlling factor-i. Thus, the remaining possibility will be the difference in $E/(E+N)$ between **4** and the other β-ketoesters. In the latest catalyst of MRNi,[2] the proportion of the N-site on the MRNi catalysis is expected to be very small, but is still unknown whether or not it is negligible. To evaluate the difference in the contribution of the N-site catalysis on the hydrogenation of **4** and the other β-ketoesters, comparative studies of the reactivities were carried out with chiral MRNi's having different N/E ratios and achiral catalysts.

The catalysts employed in this study were as follows; as achiral catalysts, RNi (ultrasound irradiated W1 type Raney nickel prepared from the Ni/Al alloy of 42/58 supplied by Kawaken Fine Chemical Co.) and NaBr-modified RNi (NaBr-MRNi), and as chiral catalysts, tartaric acid-modified RNi (TA-MRNi) and tartaric acid-NaBr-modified RNi (TA-NaBr-MRNi). The modifications were carried out in aqueous solution at 100 °C for 1 h. The pH was adjusted to 3.2 before the modification when TA was used as the modifier. The β-ketoesters, **1**–**3** having a different bulkiness at the γ-position and **4**, were employed as the hydrogenation substrates. Each substrate (6.8 mmol) in 10 ml of THF with a trace amount of acetic acid was hydrogenated with 0.4 g of catalyst under 10^7 Pa of initial hydrogen pressure at 60 °C in a 100 ml autoclave reciprocating shaking. The %ee's of the products from **1**–**4** by using TA-NaBr-MRNi are 86, 94, 96, and >98, respectively, at 100% conversion.[4] The runs for the reactivity studies were carried out under the same conditions as above except for the addition of methyl hexanoate (2%) in the reaction system as an internal standard, and the reactions were stopped at specific times (method A). Conversions of the reactants were determined by GLC analysis (TC-WAX, 60 m x 0.25 mm i.d., 120 °C).

The conversions for **1** and **3** using TA-NaBr-MRNi as a function of the hydrogenation time are shown in Figure 1. Since nearly linear relations between the conversion and reaction time were found up to 4 h even for **1** having the highest reactivity, the reactivity of each substrate could be roughly estimated by the conversion at 4 h.

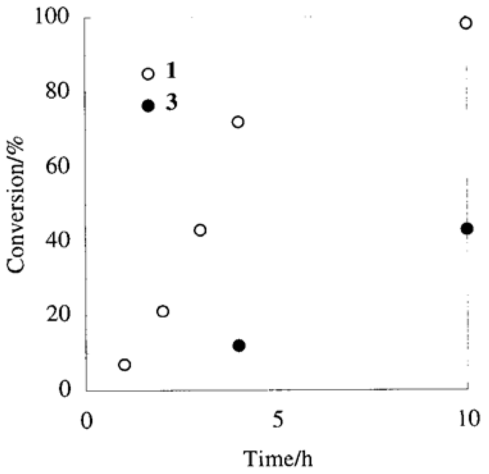


Figure 1. Conversion of **1** and **3** as a function of the hydrogenation time

Table 1. Conversion (%) of β-ketoesters **1**–**4** at 4 h over MRNi prepared with varied modifiers

Entry	Method[a]	Catalyst	**1**	**2**	**3**	**4**	Relative reactivity of **1** : **2** : **3** : **4**
1	A	TA-NaBr-MRNi	71	45	13	45	1 : 0.63 : 0.19 : 0.63
2	A	NaBr-MRNi	47	23	6	9	1 : 0.49 : 0.13 : 0.19
3	B	TA-NaBr-MRNi	73	48	10	42	1 : 0.65 : 0.14 : 0.57
4	B	TA-MRNi	76	53	16	37	1 : 0.70 : 0.21 : 0.49
5	B	NaBr-MRNi	48	23	7	7	1 : 0.49 : 0.14 : 0.15
6	B	RNi	65	36	13	13	1 : 0.55 : 0.20 : 0.20

[a] method A: The substrates were hydrogenated, separately. method B: A mixture of the four substrates were hydrogenated.

When the substrates **1–4** were hydrogenated with NaBr-MRNi of the achiral catalyst, the relative reactivity estimated from the conversions was reasonably understood as the reverse order of the bulkiness (Table 1, entry 2). TA-NaBr-MRNi of the chiral catalyst has a higher activity than NaBr-MRNi for all substrates (entry 1). The relative reactivity of **1–3** was similar to that with the achiral catalyst, but the hydrogenation of **4** was obviously faster, and the reactivity was almost the same as that of **2** with a less bulkiness. The hydrogenation of a mixture of the four substrates (1.7 mmol each) was also carried out with RNi, NaBr-MRNi, TA-MRNi, and TA-NaBr-MRNi (method B). As shown in entry 3, the conversions with TA-NaBr-MRNi well matched with the corresponding runs by method A (entry 1). The results of methods A and B with NaBr-MRNi were also well consistent with each other (entries 2 and 5). These results indicated that the occupation of catalytic sites at the adsorption step was even among the substrates employed, and that the difference in the conversions of each substrate depended on the rate of the surface reaction at the catalytic sites.[5] TA-MRNi is known to have a more contribution of the N-site than TA-NaBr-MRNi due to the lack of a deactivation effect of NaBr to the N-site.[5,6] With TA-MRNi (entry 4), the activation effect by the TA-modification was somewhat lower than that of TA-NaBr-MRNi, but the difference between **3** and **4** was still obvious, whereas negligible with RNi of the achiral catalyst (entry 6). From these results, a higher reactivity for **4** in the enantio-differentiating hydrogenation was expected to result from a substrate specific activation on the *E*-site catalysis, and eventually gave higher ee of the product as a result of the high *E*/*N* ratio.

In conclusion, a substrate specific chiral modifier activation was observed for the first time in the MRNi system, which was considered to be the origin of the high ee for the hydrogenation of **4**. Although the mechanism of this activation is still unknown and the contributions of the factor-*i* and *E*(*E*+*N*) are not clearly distinguished from each other, the present data provide a clue for further advanced understanding of the MRNi system.

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6 The hydrogenation of **1–4** over TA-MRNi with 100% conversion resulted in 59, 77, 76, and 85%ee, respectively.