

Over 98% Optical Yield Achieved by a Heterogeneous Catalysis. Substrate Design and Analysis of Enantio-Differentiating Factors of Tartaric Acid-Modified Raney Nickel Hydrogenation

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Tartaric acid-modified Raney nickel (TA-MRNi) is a chiral heterogeneous catalyst for the hydrogenation of prochiral ketones. An optical yield (OY) of 86% with methyl acetoacetate (**1**) as a substrate was improved to 94–96% by employing β-keto esters having a proper bulkiness at the γ-position. The γ-bulkiness effect contributes to a high intrinsic enantio-differentiating ability (factor-*i*) of the TA-MRNi catalysis. Through the study, we found the best substrate, γ-cyclopropyl-β-keto ester, the hydrogenation of which resulted in 98.6% OY. This further improvement in the OY was ascribed to a smaller contribution of non-enantio-differentiating hydrogenation (N-site catalysis) due to the substrate-specific activation of the enantio-differentiating hydrogenation by the chiral modifier. The OY of the hydrogenation of **1** was analyzed by comparing with well-behaved β-keto esters, and the contribution of the factor-*i* and the N-site to the OY value was evaluated to deduce the origin of the enantiodifferentiation.

An enantio-differentiating (asymmetric) reaction using a heterogeneous catalyst (solid catalyst) was first disclosed in 1956 using silk-supported palladium, which catalyzes the hydrogenation of a C=N bond to result in chiral amino acids in 6–35% optical yield (OY).[1] Many efforts were devoted thereafter to obtain higher OY using various heterogeneous catalyses, and have resulted in only two reaction systems to give one enantiomer produced over 10-times faster than the other ($>$ 82% OY). The Orito system, first reported in 1979, used cinchona-modified palladium for the hydrogenation of α-keto esters to result in 80–89% OY.[2] By modifying this system, two groups have achieved high OYs during the last decade,[3] where the highest OY of 97.6% indicates an 82-times faster production of one enantiomer than the other. The success of this system is mainly due to several hundred-fold activation of the catalysis by the chiral modifier. The other system developed by Izumi and co-workers uses tartaric acid-modified Raney nickel (TA-MRNi) for the enantio-differentiating hydrogenation of prochiral ketones,[4] where they employed methyl acetoacetate (**1**) as a simple β-keto ester substrate for the survey of a proper chiral modifier for Raney nickel catalysts, and found the best modifier, tartaric acid (TA).[5] By using a combination of nickel (base catalyst), TA (chiral modifier) and **1** (substrate), the catalysis system has been investigated in detail by many research groups to improve the OY;[6,7] the OY had reached 80–91%, and 86% OY using our catalyst.[8]

The OY of the TA-MRNi system as well as other heterogeneous catalyses can be expressed in terms of the intrinsic enantio-differentiating ability of the catalyst (factor-*i*) and the heterogeneity of the catalyst surface. The chiral catalyst has an enantio-differentiating region (E-site) to give an optically active product in some enantiomeric excess, that is factor-*i*, while the other region produces a racemic product without perturbation from the chiral source (non-enantio-differentiating region = N-site). Thus, the overall OY can be expressed as

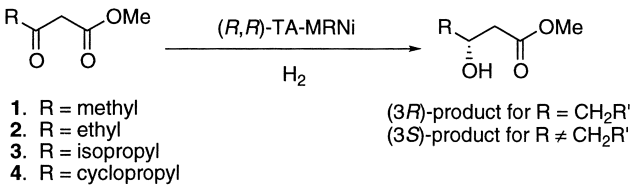
$$\%\mathrm{OY} = 100\times(\text{factor-}i)\times E/(E + N) \quad (1)$$

where E and N are relative contributions of the E- and N-site catalyses, respectively.

N-site catalysis is an inherent problem in enantio-differentiating heterogeneous catalyses due to a difficulty in making a uniform chiral catalyst surface. Although the origin of the lowering OY was not known, most of the studies on the TA-MRNi system had been intended to remove the N-site so as to increase the value of $E/(E + N)$. However, through studies with various keto esters we have come to believe that factor-*i* should be considered as being the reason for the low OY with **1**, and have proposed an extended-stereochemical model, which expresses the mechanism controlling the factor-*i*.[9] This model was suggested to us as a working hypothesis to improve the OY of the TA-MRNi system. That is, the OY with **1** would be increased with increasing factor-*i* when the γ-position is bulky. Based on this substrate design, we have reported 96% OY with methyl 4-methyl-3-oxopentanoate (**3**), the highest OY of a heterogeneous catalysis at that time.[9]

The present report describes our efforts to improve the OY of the TA-MRNi system by designing the substrate and by tuning the reaction conditions based on the extended stereochemical model. The study resulted in a group of substrates, including **3**, giving 94–96% OY, and methyl 3-cyclopropyl-3-oxopropanoate (**4**) and its analogues, resulting in over 98% OY, the first example of over a 100-times faster production of one enantiomer against the antipode by a heterogeneous catalysis.[10] With this almost perfect enantio-differentiation as a clue, the OY control factors, factor-*i* and $E/(E + N)$, were separated,

and then a black box of the TA-MRNi system has been disclosed (Scheme 1).



Scheme 1.

Results and Discussion

Steric and Hydrophobic Effects at the γ-Position of the Substrate. TA-MRNi prepared from the ultrasonicated W-1 type Raney nickel has a minimum amount of the N-region as well as high hydrogenation activity,[8] which made it possible for us to use a variety of β-keto esters, not only at 100 °C of the commonly used temperature, but also at 60 °C. The hydrogenation of the β-keto esters (R-$COCH_2COOMe$) listed in Table 1 at 60 and 100 °C gave essentially pure β-hydroxy esters only by filtration and concentration of the reaction mixture (except for entries 14 and 15). The OY values were calculated from the ratios of the enantiomers determined by GLC analysis, and are summarized in Table 1. Improved Taft's steric constants, $-E_s^*$ for the *R* groups[11] are also given.

Among the substrates having a linear alkyl chain at the γ-position (entries 2–7), **2**, having an ethyl group, gave the highest OY of 94% at 60 °C. The OY gradually diminished according to the extension of the alkyl chain. Different from **1**, they showed a temperature dependency of ca. 3% increment in the OY from 100 to 60 °C. The results indicate that **1**, a commonly employed standard substrate, is not the best substrate for the TA-MRNi system; regarding the temperature dependency, **1** is an exception among the β-keto esters. From these findings, the common expertise in the TA-MRNi system, that the OY with a β-keto ester does not depend on the temperature,[12] has been corrected (except for **1** itself). The OY was affected even by a change in the partial structure of the substrate remote from the reaction site, and thus the enantioface differentiation of the β-keto esters by TA-MRNi does not simply depend on the structure around the reaction site, but on the whole substrate structure. A similar temperature dependency among entries 2–7 indicates that their enantio-differentiating modes are essentially the same, and some other factors, such as the unfavorable interaction between the hydrophobic alkyl chain and the hydrophilic nickel surface, slightly affect the adsorption mode of the substrate and diminish the enantio-differentiating ability of TA-MRNi.

Table 1. Optical Yields (%OY) of Hydrogenation of Methyl β-Keto Esters (R–$COCH_2COOMe$) over TA-MRNi at 100 and 60 °C, and Improved Taft's Steric Constants ($-E_s^*$)

Entry	R	$-E_s^*$ [a]	100 °C	60 °C
1	Me (**1**)	0	86[b]	86[b]
2	Et (**2**)	0.08	91[b]	94[b]
3	*n*-C_3H_7	0.36	90	93
4	*n*-C_4H_9	0.39	88	91
5	*n*-C_6H_{13}	—	87[b]	90[b]
6	*n*-C_7H_{15}	—	87	89
7	*n*-C_9H_{19}	—	83	86
8	Iso-C_3H_7 (**3**)	0.36	88[b]	96[b]
9	Cyclo-C_4H_7	0.06	—	94
10	Cyclo-C_5H_9	0.51	90	95
11	Cyclo-C_6H_{11}	0.71	88	94
12	Iso-C_4H_9	0.93	—	93
13	Neo-C_5H_{11}	1.84	84	96
14	Et_2CH	1.98	—	—[c]
15	*t*-C_4H_9	4.22	—[d]	—

a) Ref. 11. b) Ref. 9. c) 20% Conversion after 4 days (82% OY). d) No reaction after 2 days.

As expected from the extended stereochemical model and the results of the former report (entry 8),[9] the bulkiness at the γ-position induced both a larger temperature dependency and a higher OY at 60 °C. Substrates having a branch at the γ-position (entries 8–11) resulted in a moderately high OY at 100 °C, but the OY increased and reached a higher level of 94–96% at 60 °C. When the δ-position was branched (entry 12), the OY at 60 °C became lower, 93%, but again a 96% OY was obtained when the δ-substituent was sufficiently bulky as a *t*-butyl group (entry 13).

Although the substrate design using the γ-steric effect efficiently improved the OY up to 96%, this could not be extended to a further improvement of the OY. When the γ-position was too bulky like a *t*-butyl group (entry 15), the hydrogenation did not proceed at all at 100 °C or even at 120 °C after 2 days. Among the γ-mono-branched substrates, the (1-ethyl)propyl analogue is also an unsuitable substrate resulting in a slow and sluggish hydrogenation (20% conversion at 60 °C after 4 days, entry 14). Although proper bulkiness at the γ-position in a Taft's steric constant ($-Es^*$) is in the range of 0.06–1.9, there is a notable non-linearity between the OY and the $-Es^*$ value. A part of this inconsistency may be due to the hydrophobicity of the substituent group, e.g. isopropyl vs cyclohexyl, but a main part should be attributed to the speciality of molecular recognition on the surface; the adsorption and reactions on the surface are strictly regulated by geometrical demands.

A study of this series produced a group of the substrates, resulting in an enantiomer production ratio of 32–49. The γ-steric effect should affect factor-*i*, but not $E/(E + N)$, based on the extended stereochemical model, which was supported by a kinetic study, which is discussed later.

Further Increment of the OY toward over 98%. Since most chiral pharmaceuticals require starting materials having over 98% optical purity, an enantio-differentiating reaction becomes profitable when it can result in over 98% OY as well as over 98% chemical yield. Hence, an enantiomer production ratio of > 100 is a goal for studies for improving the OY of the TA-MRNi system. Since a system resulting in 96% OY was already in hand, $>$ 98% OY can be achieved by reducing the antipode production (or racemic production) by less than half. During a further survey of a suitable substrate for TA-MRNi system, we obtained methyl 3-cyclopropyl-3-oxopropanoate (**4**). The cyclopropyl group in **4** is similar to the isopropyl group in **3** regarding the steric bulkiness and hydrophobicity. It was also expected that the cyclopropyl group survives the hydrogenation conditions with TA-MRNi, while the resulting

product can be converted to more valuable optically active compounds through cleavage of the cyclopropane ring.

The hydrogenation of **4** proceeded smoothly up to 100% conversion, and none of the side reactions, like isomerization or hydrogenation of the cyclopropane unit, were detected. When the reaction was carried out at 100 °C, the minor enantiomer produced was only 2%, and thus the OY was as high as 96%. The high OY at 100 °C indicates the speciality of **4** among the γ-branched substrates. At 60 °C, the produced antipode was diminished to be less than 1%. Judging from seven repeated runs and the GLC integration errors, the amount of the antipode was determined to be in a range of 0.6–0.8%. The calculated OY of 98.6 $\pm$ 0.2% is concluded to be $>$ 98% (or 99%). The absolute structure of the product was determined by a chemical correlation with (3*S*)-methyl 3-hydroxy-4-methylpentanoate by a PtO_2-catalyzed hydrogenation of the product.

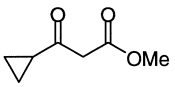
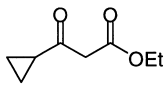
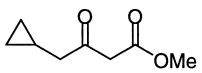
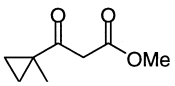
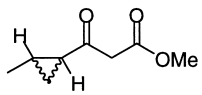
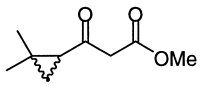
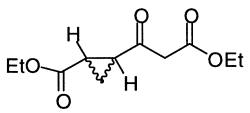
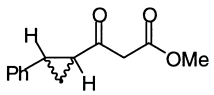
Here, we achieved the TA-MRNi system producing the optical active product needless of purification or optically enrichment as a chiral synthon. The further increment of the OY in **4** from **3** is not reasonably understood based on the γ-steric effect or the hydrophobicity. Based on a kinetic study, the difference is attributed to a smaller contribution of the N-site catalysis producing an unfavorable racemic product, but not to an increase of the factor-*i*.

Hydrogenation of a Family of Cyclopropyl β-Keto Esters. The high performance of the TA-MRNi system with **4** at 60 °C (Table 2, entry 1) was continued at a lower reaction temperature of 40 °C, where completion of the reaction took a longer time of 78 h, but again the product of $>$ 98% OY was obtained in a quantitative yield (entry 2). The use of TA-MRNi prepared with (*S*,*S*)-tartaric acid instead of the (*R*,*R*)-modifier resulted in the antipode in the same OY (entry 3). The use of ethyl ester instead of methyl of **4** also resulted in over 98% OY (entry 4).

Although the introduction of a cyclopropyl group into the substrate produced a fruitful result, the existence of other functional groups as well as a proper steric bulkiness is still a preferential factor in controlling the OY. The substrates of entries 5 and 6 are analogues of those of entries 12 and 15 in Table 1, respectively. The moderate OY in entry 5 (91%) suggests that a cyclopropyl group should be placed at the vicinal position of the ketone to receive an extra benefit. The (1-methyl)cyclopropyl group in entry 6 did not completely interrupt the hydrogenation, though its steric bulkiness is similar to that of the *t*-butyl group, and thus the cyclopropane at the γ-position was suggested to have a function to promote hydrogenation of the ketone at the β-position.

Chiral derivatives of **4** having substituent(s) at the 2-position of the cyclopropyl unit, shown in entries 7–10, were employed as racemic mixtures. The hydrogenation of each enantiomer of them gives diastereomeric alcohols, and thus, stereo-differentiations of those substrates in TA-MRNi catalysis can be evaluated by the ratios of the diastereomers, which were converted to the OY as an expedient (Table 2, entries 7–10). The methyl substitution in the trans form slightly affected the OY, the degree of which depended on the stereochemistry of the substrate (entry 7). When the substitution was *gem*-dimethyl, the hydrogenation became very sluggish (entry 8), which again indicates

Table 2. Enantio- and Diastereodifferentiation of 3-Cyclopropyl-3-oxopropanoate and Its Analogues at 60 °C

Entry	Substrate	%OY
1		$>$ 98
2		$>$ 98[a]
3		$>$ 98[b]
4		$>$ 98
5		91
6		94[c]
7[d]		$>$ 98 and 97
8[d]		50 and 50[e]
9[d]		94 and 39
10[d]		71 and 62[f]

a) Hydrogenation temperature = 40 °C.
b) (*S*,*S*)-TA-MRNi as catalyst.
c) 93% Conversion after 69 h.
d) Employed substrates are racemic mixtures. The values of the OY for each enantiomer of the substrate were calculated as %de.
e) 29% Conversion after 30 h.
f) 44% Conversion after 67 h.

the limit of the proper bulkiness of the substrate. The ester or phenyl substitution reduced the OY drastically, but differently, between the isomers. The moderately high OY of 94% in the hydrogenation of one of the ester-substituted enantiomers (entry 9) indicates that an extra ester group demands a certain geometrical placement to reduce the stereo-differentiating ability of TA-MRNi.

Kinetic Study to Evaluate the Contribution of the N-Site Catalysis From the present survey of suitable substrates for the TA-MRNi catalysis, we found two groups of β-keto esters, one giving 94–96% OY and the other accessible to 98% OY. If the extended stereochemical model explaining the γ-steric effect is appropriate, the OY differences among **1**–**3** are due to factor-*i*, and the difference between **3** and **4** should be attributable to the other remaining factor, $E/(E + N)$. The contribution of the N-site catalysis in the total hydrogenation of the TA-MRNi system is difficult to determine by physicochemical

Table 3. Conversion (%) of β-Keto Esters **1**–**4** at 4 h over MRNi Prepared by Varied Modifiers and Calculated Relative Reactivities

Entry	Method[a)]	Catalyst modifier [b)]	**1**	**2**	**3**	**4**	Relative reactivity of **1**:**2**:**3**:**4**
1	A	TA-NaBr	71	45	13	45	1:0.63:0.19:0.63
2	A	NaBr	47	23	6	9	1:0.49:0.13:0.19
3	B	TA-NaBr	73	48	10	42	1:0.65:0.14:0.57
4	B′	TA-NaBr	63	—	7	—	1: — :0.12: —
5	B″	TA-NaBr	67	—	12	—	1: — :0.18: —
6	B	TA	76	53	16	37	1:0.70:0.21:0.49
7	B	MA-NaBr	18	8	2	4	1:0.45:0.11:0.20
8	B	NaBr	48	23	7	7	1:0.49:0.14:0.15
9	B	SA-NaBr	19	8	2	2	1:0.39:0.11:0.10
10	B	none	65	36	13	13	1:0.55:0.20:0.20

a) method A: The substrates (17 mmol/1 g of catalyst) were hydrogenated, separately. method B: A mixture of the four substrates (4.25 mmol each/1 g of catalyst) were hydrogenated. method B′: A mixture of the two substrates (8.5 mmol each/ 1 g of catalyst). method B″: A mixture of the two substrates (4.25 mmol of **1** and 12.75 mmol of **3**/1 g of catalyst).
b) TA: tartaric acid, MA: malic acid, SA: succinic acid.

methods, but we established a reasonable system to estimate the value of $E/(E + N)$. The hydrogenation rates over TA-MRNi with β-keto esters are considered to be approximately equal to the rate over the E-site catalysis, since the lowest OY is as high as 86%, and thus most of the hydrogenation should proceed through the E-site catalysis. As a representative model for the N-site catalysis, we employed achiral catalysts prepared without any chiral modifiers. The achiral catalysis proceeds with no perturbation from the chiral modifier (tartaric acid) and, thus, the hydrogenation rate over the achiral catalyst can mimic the N-site catalysis rate in the TA-MRNi system.

The four representative substrates **1**–**4** (17 mmol/1 g catalyst, method A) were hydrogenated for 4 h at 60 °C (10^7 Pa) with TA-MRNi (modified with TA and NaBr) and with its achiral counter catalyst (modified only with NaBr). From the observed reaction conversions, relative reactivities of **2**–**4** in reference to **1** were roughly estimated, as listed in Table 3 (entries 1 and 2). Although the hydrogenation rates were varied with the substrates and the catalysts employed, the relative reactivities of **1**–**3** are similar between the chiral and achiral catalyses if the higher conversion of **1** in entry 1 (71%) is considered to be a factor to increase the apparent relative reactivities of **2** and **3**. In contrast, the hydrogenation of **4** was much faster over the chiral catalyst (entry 1) than that over the achiral catalyst (entry 2). As for the similar reactivities of **3** and **4** in the achiral catalysis, it can be reasonably understood from the similarity in their steric bulkiness; the hydrogenation of **4** is concluded to be accelerated by the tartaric acid modification.

The substrate-specific activation of the hydrogenation of **4** by the chiral modifier can be induced by two possible mechanisms: the larger adsorption constant for **4** onto the TA-MRNi surface and the faster surface reaction of the adsorbed **4** with hydrogen. When the substrates are hydrogenated at a common adsorption site, the hydrogenation rates for the coexisting substrates are affected by each other, the degree of which depends on the adsorption constants of the substrates. In method B, a mixture of substrates **1**–**4** in an equimolar amount (4.25 mmol/g each) was hydrogenated under the same hydrogenation conditions while keeping the total molar amount of the substrates per catalyst (17 mmol/g) constant. As shown in Table 3, both the chiral and achiral catalyses showed conversions independent of the existence of the other substrates (entries 1 vs 3 and 2 vs 8). The similar results between methods A and B indicate that the adsorption site of **1**–**4** is common, and evenly co-occupied in both the chiral and achiral catalyses. Thus, the substrate-specific activation for **4** can be concluded to be a faster reaction of the adsorbed **4** on the TA-MRNi surface. Other chiral and achiral catalyses using method B and its variations (methods B′ and B″) show a similar tendency, and support the above conclusion. The malic acid-modified catalyst has a smaller enantio-differentiating ability than TA-MRNi (60% OY with **1**). Interrelated to the lower enantio-differentiating ability, the degree of the substrate-specific activation of **4** by a malic acid-modification is smaller than that with TA-MRNi (entry 7, see the difference between **3** and **4**).

More detailed kinetic experiments were examined using an autoclave fitted with an outlet to remove the sample during hydrogenation under high pressure. A mixture of four substrates, **1**–**4**, was hydrogenated over the chiral TA-MRNi catalyst (TA and NaBr-modified nickel) and the achiral counter catalyst (NaBr-modified nickel) at 50, 60, 70, 80, and 100 °C; the conversions were determined by GLC at one-hour intervals. The conversions at 60 °C as a function of the reaction time are shown in Figs. 1 and 2. The initial reaction rates as a specific rate of the reaction (r_m, mmol g^{-1} h^{-1}) were obtained by curve fitting using data below the 20% conversion (Table 4). Since some of the conversions at 80 and 100 °C were already over 20%, even in the initial 1 h, accurate values of r_m could not be obtained.

From the r_m values for each substrate, the ratios of the chiral and achiral catalysis (shown as C/A in Table 4) were calculated. The C/A value represents the ratio of the E-site catalysis to the N-site catalysis. When the contribution ratio of the E-site and N-site catalyses in the hydrogenation of **1** is defined as a reference at each temperature, the relative contribution of the E-site for other substrates can be calculated, the values of which are summarized in Table 5.

The calculated values, 1.2–1.3 and 1.1–1.3, for **2** and **3** indi-

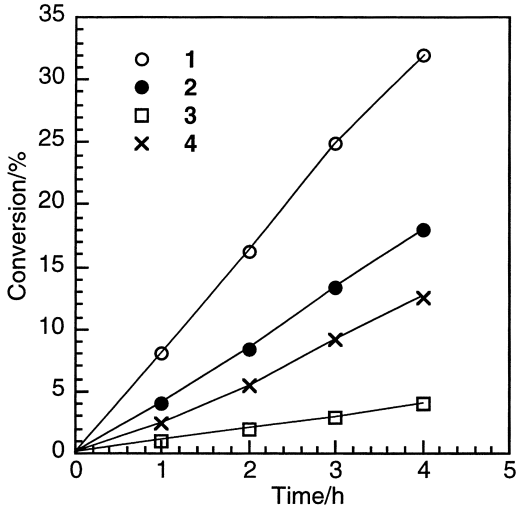


Fig. 1. Reaction conversion with the chiral (TA and NaBr-modified) catalyst at 60 °C.

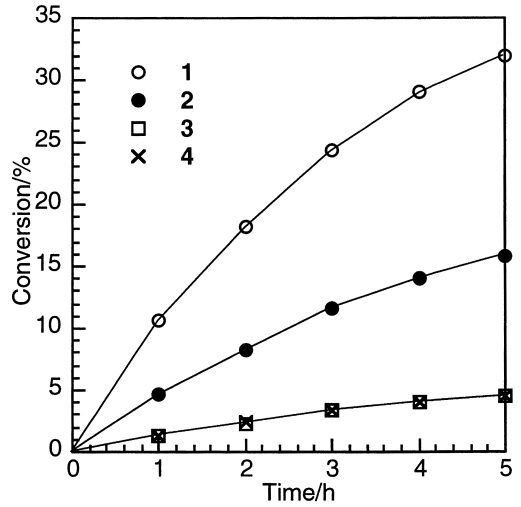


Fig. 2. Reaction conversion with the achiral (NaBr-modified) catalyst at 60 °C.

cate that the effects of the tartaric acid-modification to the hydrogenation rates are approximately equal to that for **1**. Similar kinetic effects among the hydrogenations of **1**–**3** due to the tartaric acid modification imply that the $E/(E + N)$ values in their TA-MRNi hydrogenations are almost unchanged and, thus, the differences in the OY among them arise from the factor-*i*. This result is consistent with the expectation from our working hypothesis based on the extended stereochemical model.

In contrast, the values for **4** indicate that the activation of the hydrogenation by the tartaric acid modification is 3.0–3.6 fold. The activation of 3-fold at 60 °C, estimated by the preliminary experiments. was refined to be 3.4. The substrate-specific activation for **4** indicates increment of the contribution of the E-site catalysis over the N-site catalysis; thus, the $E/(E + N)$ value is larger and closer to unity than those for other substrates. The 3.4-fold activation of the E-site catalysis for **4** reduces the contribution of the N-site catalysis for **1** by 1/3.4 and that for **3** by 1/3.1. By this calculation, 4% formation of a racemic product from **3** is reduced to be 1.3% by activation with **4**, the value of which well simulates the actual racemic production in the hydrogenation of **4** (1.2–1.6%). Thus, the imperfect OY for both **3** and **4**, and the improvement of the OY from **3** to **4** mostly originated from the contribution of the N-site catalysis, and the values of factor-*i* for both **3** and **4** were calculated to be almost unity. This result is consistent with an earlier expectation; the factor-*i* values for **3** and **4** should be approximately equal due to the similarity in their steric bulkiness and hydrophobicity.

Table 4. Calculated Specific Rate (r_m, mmol g^{-1} h^{-1}) of the Chiral and Achiral Catalysis with the Substrates **1**–**4** at Various Temperatures, and the Rate Ratio of the Chiral and Achiral Catalyses (= C/A) [a)]

Temp/°C	Catalyst	**1**	**2**	**3**	**4**
50	Chiral	0.065	0.033	0.008	0.022
	Achiral	0.080	0.034	0.009	0.009
	Ratio of C/A	**0.81**	**0.97**	**0.9**	**2.4**
60	Chiral	0.146	0.080	0.018	0.056
	Achiral	0.176	0.073	0.020	0.020
	Ratio of C/A	**0.83**	**1.1**	**0.9**	**2.8**
70	Chiral	0.248	0.159	0.043	0.121
	Achiral	0.30	0.143	0.038	0.041
	Ratio of C/A	**0.83**	**1.1**	**1.1**	**3.0**
80	Chiral	(0.4)	(0.3)	0.085	0.219
	Achiral	(0.4)	0.157	0.072	0.079
	Ratio of C/A	**—**	**—**	**1.2**	**3.6**
100	Chiral	(0.7)	(0.6)	(0.2)	(0.5)
	Achiral	(0.6)	(0.4)	0.12	0.13

a) The values in parentheses are estimated from data over 20% conversions.

Table 5. Calculated Relative E-site Contribution of the Hydrogenation of **2**–**4** Normalized with **1**

Temp/ °C	**2**	**3**	**4**
50	1.2	1.1	3.0
60	1.3	1.1	3.4
70	1.3	1.3	3.6

Separation of the Factor-*i* and E/N Ratio in the Hydrogenation of 1. The remaining task for the TA-MRNi/β-keto ester system regarding the OY should be an improvement of the OY for acetoacetate esters (86% OY for **1**, methyl ester), since the products of optically active 3-hydroxybutanoates are industrially important chiral building blocks.[13] The contribution of the N-site catalysis to the hydrogenation of **1** at 60 °C was calculated to be 4–5% (4% of **3** × 1.1 of its relative contribution of the E-site = 4.4%). Thus, factor-*i* for **1** was evaluated to be 0.90 (0.86/(1–0.044)). This analysis shows direction toward a further improvement of the OY for **1**. By optimizing the base catalyst or the modification conditions, the N-site catalysis will be reduced, but the expected maximum improvement in the OY is only 4–5%. On the other hand, any variation of the reaction conditions as well as the choice of the chiral modifier affects factor-*i*; such an investigation has a potential to improve the OY by 9–10%. The best MRNi for **1** in the OY, though it has poorer activity, is the deep modified catalyst,

which was reported to give 91% OY,[14] the value of which is consistent with our analysis and indicates that the deep modified catalyst has no more N-sites.

Summary. In this report, we presented an achievement of over 98% OY by fine tuning the TA-MRNi system, and we have proved that a heterogeneous catalysis can perform strictly controlled enantio-differentiation. Together with 100% conversion, a quantitative yield, and easy recovery and re-use of the catalyst, the TA-MRNi system will become a promising process for a large-scale production of sufficiently optically pure alcohols.

Experimental

General. All of the substrates and the hydrogenation products were characterized by ^{1}H NMR using a JEOL EXcaliber-400 spectrometer, and IR with a JASCO IR-88 spectrometer. The optical rotations were measured with a Perkin-Elmer 243B polarimeter. Analytical GLC was concluded on a Shimadzu GC17A. Deionized water for preparating the catalyst was obtained from Kanto Chemicals, Co., Ltd. All solvents were purified by distillation with proper drying agents.

Substrates. Methyl 3-oxobutanoate (**1**), methyl 3-oxopentanoate (**2**), methyl 3-oxohexanoate, methyl 3-oxoheptanoate, and methyl 4,4-dimethyl-3-oxopentanoate were obtained from commercial sources. Methyl 3-oxononanoate, methyl 3-oxodecanoate, methyl 3-oxododecanoate, methyl 4-methyl-3-oxopentanoate (**3**), methyl 3-cyclohexyl-3-oxopropanoate, methyl 5-methyl-3-oxohexanoate, methyl 5,5-dimethyl-3-oxohexanoate, and methyl 3-cyclopropyl-3-oxopropanoate (**4**) were prepared from Meldrum's acid by the reported methods.[15,16] The other substrates were obtained by applying reported methods.[17,18]

Catalysts. All of the catalysts were prepared from Raney nickel prepared by the W-1 type development of the Ni–Al alloy (42/58, Kawaken Fine Chemicals, Ltd. Japan), followed by washing three times with ultrasonic irradiation in deionized water. The modification was performed by heating the Raney nickel in a solution including the modifiers at 100 °C for 1 h. For preparing 0.4 g of TA-MRNi, a solution of (*R*,*R*)-tartaric acid (0.5 g) and NaBr (5 g) in water (50 mL) was employed after adjusting the pH with NaOH at 3.2. See the Ref. 8 for details of this catalyst. The other catalysts were obtained by the same procedure, except for the use of other acids (pH 3.2) or without using an acid (no pH adjustment).

Preparative Hydrogenation. In a 100 mL autoclave (i.d. 36 mm × 100 mm), (*R*,*R*)-TA-NaBr-MRNi (0.4 g) and a solution of the substrate (1.5 g) in THF (10 mL) were placed. Hydrogen was charged into the autoclave under an initial pressure of ca. 10^7 Pa (100 ± 1 kg cm^{-2}), and the autoclave was heated to 60 ± 1 or 100 ± 1 °C under reciprocating shaking until the end of the hydrogen uptake. The autoclave was cooled and the excess hydrogen was released from it. The products were obtained by filtration and concentration of the reaction mixture, and were essentially chemically pure, judged by ^{1}H NMR, except for the several sluggish reactions mentioned in the text. Enantiomeric ratios of the products were determined by GLC equipped with a CP-Chirasil DEX CB capillary column (25 m, 0.25 mm id, GL Science, Japan, flow rate: 30 cm/s). As for authentic samples of the GLC analysis, racemic alcohols were prepared by reduction of the substrates with $NaBH_4$ in methanol. The absolute configurations of the hydrogenation products were determined by optical rotation and by a chemical correlation in several key reactions.

Methyl 3-Oxobutanoate (1). The hydrogenation of **1** was carried out at 100 °C for 4 h or at 60 °C for 31 h to give (*R*)-methyl 3-hydroxybutanoate.[19] An analytical sample was subjected to the chiral GLC after acetylation with Ac_2O/pyridine. The retention times of the GLC (90 °C) were 5.5 min for (*S*) and 12 min for (*R*). Distillation of the product gave a colorless oil, $[\alpha]_D^{20} = -19.7°$ (neat) for the product at 100 °C, lit.[19] −22.95° (neat, 100% ee).

Methyl 3-Oxopentanoate (2) The hydrogenation of **2** was carried out at 100 °C for 18 h or at 60 °C for 34 h to give (*R*)-methyl 3-hydroxypentanoate.[20,21,22] The retention times of the GLC (80 °C) were 10.2 min for (*S*) and 10.4 min for (*R*). The calculated OY values were 91.4% (at 100 °C) and 94.2% (at 60 °C). Filtration of the mixture through a silica-gel column gave a colorless oil, $[\alpha]_D^{20} = -16.0°$ (neat) for the product at 60 °C, lit.[21] −10.19° (neat, 55% ee).

Methyl 3-Oxohexanoate. The hydrogenation of methyl 3-oxohexanoate was carried out at 100 °C for 29 h or at 60 °C for 45 h to give (*R*)-methyl 3-hydroxyhexanoate.[23] The retention times of the GLC (90 °C) were 8.4 min for (*S*) and 8.6 min for (*R*). The calculated OY values were 89.9% (at 100 °C) and 92.5% (at 60 °C). Filtration of the mixture through a silica-gel column gave a colorless oil, $[\alpha]_D^{20} = -9.0°$ (neat) for the product at 60 °C, lit.[23] for antipode +13.8° (*c* 3.5, $CHCl_3$, 56% ee).

Methyl 3-Oxoheptanoate. The hydrogenation of methyl 3-oxoheptanoate was carried out at 100 °C for 31 h or at 60 °C for 67 h to give (*R*)-methyl 3-hydroxyheptanoate.[24] The retention times of the GLC (100 °C) were 12.6 min for (*S*) and 12.9 min for (*R*). The calculated OY values were 88.4% (at 100 °C) and 91.2% (at 60 °C). Filtration of the mixture through a silica-gel column gave a colorless oil, $[\alpha]_D^{20} = -7.6°$ (neat) for the product at 60 °C, lit.[24] for antipode, +26.2° (*c* 1.5, $CHCl_3$, 99.5% ee).

Methyl 3-Oxononanoate. The hydrogenation of methyl 3-oxononanoate was carried out at 100 °C for 36 h or at 60 °C for 52 h to give (*R*)-methyl 3-hydroxynonanoate. The retention times of the GLC (130 °C) were 9.1 min for (*S*) and 9.3 min for (*R*). The calculated OY values were 86.8% (at 100 °C) and 90.2% (at 60 °C). Filtration of the mixture through a silica-gel column gave a colorless oil, $[\alpha]_D^{20} = -5.5°$ (neat) for the product at 60 °C; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 6.8 Hz, 3H), 1.21–1.57 (m, 10H), 2.40 (dd, J = 16.4, 9.0 Hz, 1H), 2.51 (dd, J = 16.4, 3.2 Hz, 1H), 2.89 (brs, 1H), 3.71 (s, 3H), 3.98 (m, 1H).

Methyl 3-Oxodecanoate. The hydrogenation of methyl 3-oxodecanoate was carried out at 100 °C for 24 h or at 60 °C for 66 h to give (*R*)-methyl 3-hydroxydecanoate.[16, 21] The retention times of the GLC (140 °C) were 9.3 min for (*S*) and 9.5 min for (*R*). The calculated OY values were 87.4% (at 100 °C) and 89.0% (at 60 °C). Filtration of the mixture through a silica-gel column gave a colorless oil, $[\alpha]_D^{20} = -4.5°$ (neat) for the product at 60 °C; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 6.7 Hz, 3H), 1.18–1.57 (m, 12H), 2.40 (dd, J = 16.4, 9.0 Hz, 1H), 2.51 (dd, J = 16.4, 3.2 Hz, 1H), 3.70 (s, 3H), 4.00 (m, 1H).

Methyl 3-Oxododecanoate. The hydrogenation of methyl 3-oxododecanoate was carried out at 100 °C for 24 h or at 60 °C for 69 h to give (*R*)-methyl 3-hydroxydodecanoate.[16] The retention times of the GLC (155 °C) were 11.7 min for (*S*) and 12.0 min for (*R*). The calculated OY values were 83.1% (at 100 °C) and 86.4% (at 60 °C). Filtration of the mixture through a silica-gel column gave a colorless oil, $[\alpha]_D^{20} = -1.0°$ (*c* 1.2, MeOH) for the product at 60 °C; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 6.6 Hz), 1.25–1.57 (m, 16H), 2.40 (dd, J = 16.4, 9.0 Hz, 1H), 2.51 (dd, J = 16.4, 3.2 Hz, 1H), 3.70 (s, 3H), 3.99 (m, 1H).

Methyl 4-Methyl-3-oxopentanoate (3). The hydrogenation of **3** was carried out at 100 °C for 55 h or at 60 °C for 71 h to give (*S*)-methyl 3-hydroxy-4-methylpentanoate.[20,22,23] The retention times of the GLC (80 °C) were 17.2 min for (*R*) and 17.5 min for (*S*). The calculated OY values were 87.9% (at 100 °C) and 95.9% (at 60 °C). Filtration of the mixture through a silica-gel column gave a colorless oil, $[\alpha]_D^{20} = -26.5°$ (neat) for the product at 60 °C, lit.[23] for antipode +14.8° (*c* 1.2, EtOH, 52% ee).

Methyl 3-Cyclobutyl-3-oxopropanoate. The hydrogenation of methyl 3-cyclobutyl-3-oxopropanoate was carried out at 60 °C for 72 h to give (*S*)-methyl 3-cyclobutyl-3-hydroxypropanoate. An analytical sample was subjected to the chiral GLC after acetylation with Ac_2O/pyridine. The retention times of the GLC (100 °C) were 20.4 min for (*S*) and 22.0 min for (*R*). The calculated OY value was 94.0%. Filtration of the mixture through a silica-gel column gave a colorless oil, $[\alpha]_D^{20} = +2.1°$ (neat); ^{1}H NMR ($CDCl_3$) δ 1.71–2.06 (m, 7H), 2.26 (dd, J = 16.2, 9.3 Hz, 1H), 2.41 (dd, J = 16.2, 2.9 Hz, 1H), 2.29 (m, 1H), 3.68 (s, 3H), 3.72 (m, 1H), 3.90 (m, 1H).

Methyl 3-Cyclpentyl-3-oxopropanoate. The hydrogenation of methyl 3-cyclpentyl-3-oxopropanoate was carried out at 100 °C for 60 h or at 60 °C for 72 h to give (*S*)-methyl 3-cyclopentyl-3-hydroxypropanoate. An analytical sample was subjected to the chiral GLC after acetylation with Ac_2O/pyridine. Retention times of the GLC (110 °C): 23.1 min for (*S*) and 24.5 min for (*R*). The calculated OY values were 89.7% (at 100 °C) and 95.2% (at 60 °C). Filtration of the mixture through a silica-gel column gave a colorless oil: $[\alpha]_D^{20} = -9.6°$ (neat) for the product at 60 °C; ^{1}H NMR ($CDCl_3$) δ 1.14–1.94 (m, 9H), 2.41 (dd, J = 16.4, 9.5 Hz, 1H), 2.55 (dd, J = 16.4, 2.7 Hz, 1H), 3.70 (s, 3H), 3.79 (m, 1H).

Methyl 3-Cyclohexyl-3-oxopropanoate. The hydrogenation of methyl 3-cyclohexyl-3-oxopropanoate was carried out at 100 °C for 60 h or at 60 °C for 75 h to give (*S*)-methyl 3-cyclohexyl-3-hydroxypropanoate.[20,24] An analytical sample was subjected to the chiral GLC after acetylation with Ac_2O/pyridine. The retention times of the GLC (135 °C) were 13.4 min for (*S*) and 14.1 min for (*R*). The calculated OY values were 87.6% (at 100 °C) and 94.0% (at 60 °C). Filtration of the mixture through a silica-gel column gave a colorless oil, $[\alpha]_D^{20} = -21.2°$ (neat) for the product at 60 °C, lit.[24] for antipode, +32.1° (*c* 1.4, $CHCl_3$, 99.7% ee).

Methyl 5-Methyl-3-oxohexanoate. The hydrogenation of methyl 5-methyl-3-oxohexanoate was carried out at 60 °C for 76 h to give (*R*)-methyl 3-hydroxy-5-methylhexanoate.[24] The conversion of the hydrogenation was 71%. The retention times of the GLC (100 °C) were 10.2 min for (*S*) and 10.6 min for (*R*). The calculated OY values were 92.8%. The product was separated by a silica-gel chromatography to give a colorless oil, $[\alpha]_D^{20} = +5.1°$ (*c* 0.9, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 6.4 Hz, 6H), 1.13–1.22 (m, 2H), 1.72–1.83 (m, 1H), 2.38 (dd, J = 16.4, 8.8 Hz, 1H), 2.49 (dd, J = 16.4, 3.8 Hz, 1H), 3.71 (s, 3H), 4.08 (m, 1H).

Methyl 5,5-Dimetyl-3-oxohexanoate. The hydrogenation of methyl 5,5-dimetyl-3-oxohexanoate was carried out at 100 °C for 55 h or at 60 °C for 82 h to give (*R*)-methyl 3-hydroxy-5,5-dimethylhexanoate. The retention times of the GLC (110 °C) were 7.3 min for (*S*) and 7.6 min for (*R*). The calculated OY values were 84.4% (at 100 °C) and 96.0% (at 60 °C). The optical rotation of this product was not determined. ^{1}H NMR ($CDCl_3$) δ 0.98 (s, 9H), 1.41–1.52 (m, 2H), 2.38 (dd, J = 16.4, 8.8 Hz, 1H), 2.49 (dd, J = 16.4, 3.8 Hz, 1H), 3.71 (s, 3H), 4.16 (m, 1H).

Methyl 4-Ethyl-3-oxohexanoate. The hydrogenation of methyl 4-ethyl-3-oxohexanoate was carried out at 60 °C for 4 days to give (*S*)-methyl 4-ethyl-3-hydroxyhexanoate. The conversion of the hydrogenation was 20%. An analytical sample was subjected to the chiral GLC after acetylation with Ac_2O/pyridine. The retention times of the GLC (100 °C) were 16.7 min for (*S*) and 17.3 min for (*R*). The calculated OY value was 82.1%. ^{1}H NMR (racemic form, $CDCl_3$) δ 0.82–0.87 (m, 6H), 1.35–1.39 (m, 4H), 2.40 (dd, J = 16.6, 8.6 Hz, 1H), 2.47 (dd, J = 16.6, 3.8 Hz, 1H), 3.65 (s, 3H), 4.01 (m, 1H).

Methyl 3-Cyclopropyl-3-oxopropanoate (4). The hydrogenation of **4** was carried out at 100 °C for 24 h or at 60 °C for 44 h to give (*S*)-methyl 3-cyclopropyl-3-hydroxypropanoate.[25] An analytical sample was subjected to the chiral GLC after acylation with (*S*)-MTPA chloride/pyridine. The retention times of the GLC (145 °C) were 42.0 min for (*S*) and 42.7 min for (*R*). The calculated OY values were 95.9% (at 100 °C) and 98.6% (at 60 °C). Filtration of the mixture through a silica-gel column gave a colorless oil, $[\alpha]_D^{20} = +11.0°$ (neat) for the product at 60 °C; ^{1}H NMR ($CDCl_3$) δ 0.21 (m, 1H), 0.39 (m, 1H), 0.46–0.58 (m, 2H), 0.94 (m, 1H), 2.56 (dd, J = 16.0, 7.8 Hz, 1H), 2.62 (dd, J = 16.0, 4.2 Hz, 1H), 3.31 (m, 1H) 3.70 (s, 3H).

The absolute configuration of the product was determined to be (*S*) by a chemical correlation. When the product from **4** was hydrogenated over PtO_2 under H_2 (1 kg cm^{-2}, rt, in acetic acid), (*S*)-methyl 3-hydroxy-4-methylpentanoate was obtained in a quantitative yield.

Ethyl 3-Cyclopropyl-3-oxopropanoate. The hydrogenation of ethyl 3-cyclopropyl-3-oxopropanoate was carried out at 60 °C for 73 h to give (*S*)-ethyl 3-cyclopropyl-3-hydroxypropanoate. An analytical sample was subjected to the chiral GLC after acetylation with Ac_2O/pyridine. The retention times of the GLC (100 °C) were 16.3 min for (*R*) and 16.6 min for (*S*). The calculated OY value was 98.2%. Filtration of the mixture through a silica-gel column gave a colorless oil, $[\alpha]_D^{20} = +8.5°$ (neat); ^{1}H NMR ($CDCl_3$) δ 0.21 (m, 1H), 0.38 (m, 1H), 0.46–0.57 (m, 2H), 0.94 (m, 1H), 1.27 (t, J = 6.0 Hz, 3H), 2.57 (dd, J = 16.0, 8.0 Hz, 1H), 2.64 (dd, J = 16.0, 3.9 Hz, 1H), 2.84 (brs, 1H), 3.30 (m, 1H), 4.16 (q, J = 6.0 Hz, 2H).

Methyl 4-Cyclopropyl-3-oxobutanoate. The hydrogenation of methyl 4-cyclopropyl-3-oxobutanoate was carried out at 60 °C for 53 h to give (*R*)-methyl 4-cyclopropyl-3-hydroxybutanoate. An analytical sample was subjected to the chiral GLC after acylation with (*S*)-MTPA chloride/pyridine. The retention times of the GLC (170 °C) were 17.7 min for (*R*) and 18.2 min for (*S*). The calculated OY value was 91.3%. The optical rotation of this product was not determined. ^{1}H NMR ($CDCl_3$) δ 0.03–0.11 (m, 2H), 0.44–0.47 (m, 2H), 0.70–0.76 (m, 1H), 1.24–1.31 (m, 1H), 1.49–1.56 (m, 1H), 2.45 (dd, J = 16.0, 8.0 Hz, 1H), 2.59 (dd, J = 16.0, 3.9 Hz, 1H), 3.69 (s, 3H), 4.07–4.13 (m, 1H).

Methyl 3-(1-Methylcyclopropyl)-3-oxopropanoate. The hydrogenation of methyl 3-(1-methylcyclopropyl)-3-oxopropanoate was carried out at 60 °C for 69 h to give (*S*)-methyl 3-hydroxy-3-(1-methylcyclopropyl)propanoate. The conversion was determined by ^{1}H NMR to be 93%. An analytical sample was subjected to the chiral GLC after acetylation with Ac_2O/pyridine. The retention times of the GLC (100 °C): 13.0 min for (*R*) and 13.2 min for (*S*). The calculated OY was 94.3%. ^{1}H NMR in racemic form ($CDCl_3$) δ 0.27–0.30 (m, 1H), 0.33–0.40 (m, 2H), 0.47–0.50 (m, 1H), 1.03 (s, 3H), 2.52 (dd, J = 16.0, 3.9 Hz, 1H), 2.58 (dd, J = 16.0, 9.3 Hz, 1H), 3.33–3.36 (m, 1H), 3.69 (s, 3H).

Methyl 3-[(1*RS*,2*RS*)-2-Methylcyclopropyl]-3-oxopropanoate. The hydrogenation of methyl 3-[(1*RS*,2*RS*)-2-methylcyclopropyl]-3-oxopropanoate was carried out at 60 °C for 28 h to give

(3*S*)-methyl 3-hydroxy-3-[(1*RS*,2*RS*)-2-methylcyclopropyl]propanoate. An analytical sample was subjected to the chiral GLC after acetylation with Ac_2O/pyridine. Enantiomeric pairs were assigned using the reduction product with $NaBH_4$. The retention times of the GLC (115 °C) for one pair of enantiomers were 11.8 and 12.5 min, and the other ones were 12.7 and 13.4 min. The compositions of the hydrogenation products were 49.0, 0.9, 49.7, and 0.4% (in order of the retention times). The two major products were empirically assigned to be (3*S*). Thus, the diastereomeric excesses at the 3-position were 98.3 and 96.5%. Filtration of the mixture through a silica-gel column gave a colorless oil (a mixture of the diastereomers): ^{1}H NMR ($CDCl_3$) δ 0.20–0.78 (m, 4H), 1.00 and 1.03 (d, J = 4.0 Hz, 3H), 2.05–2.62 (m, 2H), 3.29–3.35 (m, 1H), 3.68 and 3.68 (s, 3H).

Methyl 3-[(1*RS*)-2,2-Dimethylcyclopropyl]-3-oxopropanoate. The hydrogenation of methyl 3-[(1*RS*)-2,2-dimethylcyclopropyl]-3-oxopropanoate was carried out at 60 °C for 30 h to give (3*S*)-methyl 3-[(1*RS*)-2,2-dimethylcyclopropyl]-3-hydroxypropanoate. The conversion was determined by ^{1}H NMR to be 29%. An analytical sample was subjected to the chiral GLC after acetylation with Ac_2O/pyridine. Enantiomeric pairs were assigned using the reduction product with $NaBH_4$. The retention times of the GLC (100 °C) of one pair of enantiomers were 36.6 and 37.8 min, and the other ones were 39.8 and 41.5 min. The compositions of the hydrogenation products were 42.8, 10.7, 32.1, and 14.5% (in order of the retention times). The two major products were empirically assigned to be (3*S*). Thus, the diastereomeric excesses at the 3-position were 50.0 and 50.0%. Filtration of the mixture through a silica-gel column gave a colorless oil (mixture of the diastereomers): ^{1}H NMR ($CDCl_3$) δ 0.03–0.06 (m, 1H), 0.43–0.46 (m, 1H), 0.69–0.75 (m, 1H), 0.88 and 0.90 (s, 3H), 1.02–1.05 (s, 3H), 2.55–2.60 (m, 2H), 3.52–3.61 (m, 1H), 3.68 and 3.69 (s, 3H).

Ethyl 3-[(1*RS*,2*RS*)-2-Ethoxycarbonylcyclopropyl]-3-oxopropanoate. The hydrogenation of ethyl 3-[(1*RS*,2*RS*)-2-ethoxycarbonylcyclopropyl]-3-oxopropanoate was carried out at 60 °C for 28 h to give (3*S*)-ethyl 3-[(1*RS*,2*RS*)-2-ethoxycarbonylcyclopropyl]-3-hydroxypropanoate. An analytical sample was subjected to the chiral GLC after acylation with butanoic anhydride/pyridine. Enantiomeric pairs were assigned using the reduction product with $NaBH_4$. The retention times of the GLC (120 °C) for one pair of enantiomers were 130.3 and 133.3 min, and the other ones were 136.1 and 146.6 min. The compositions of the hydrogenation products were 52.7, 13.9, 31.7, and 1.7% (in order of the retention times). The two major products were empirically assigned to be (3*S*). Thus, the diastereomeric excesses at the 3-position were 93.9 and 38.9%. Filtration of the mixture through a silica-gel column gave a colorless oil (a mixture of the diastereomers), ^{1}H NMR ($CDCl_3$) δ 0.88 and 1.01 (m, 1H), 1.12–1.17 and 1.52–1.57 (m, 2H), 1.20–1.28 (m, 6H), 1.61 and 1.67 (m, 1H), 2.51–2.63 (m, 2H), 3.60 and 3.70 (m, 1H), 4.06–4.19 (m, 4H).

Methyl 3-Oxo-3-[(1*RS*,2*RS*)-2-phenylcyclopropyl]propanoate. The hydrogenation of methyl 3-oxo-3-[(1*RS*,2*RS*)-2-phenylcyclopropyl]propanoate was carried out at 60 °C for 67 h to give (3*S*)-methyl 3-hydroxy-3-[(1*RS*,2*RS*)-2-phenylcyclopropyl]-propanoate. The conversion of **7** was determined by ^{1}H NMR to be 44%. An analytical sample was subjected to the chiral GLC after acetylation with Ac_2O/pyridine. Enantiomeric pairs were assigned using the reduction product with $NaBH_4$. The retention times of the GLC (170 °C) for one pair of enantiomers were 26.5 and 27.3 min, and the other ones were 28.3 and 29.0 min. The compositions of the hydrogenation mixture were 45.6, 9.0, 37.8, and 7.6% (in order of the retention times). The two major products were empirically assigned to be (3*S*). Thus, the diastereomeric excesses at the 3-position were 71.4 and 61.5%. Filtration of the mixture through a silica-gel column gave a colorless oil (a mixture of the diastereomers), ^{1}H NMR ($CDCl_3$) δ 0.90–0.99 (m, 1H), 1.22–1.31 (m, 1H), 1.96–2.02 (m, 1H), 2.35–2.48 (m, 1H), 2.58–2.68 (m, 1H), 3.69 and 3.70 (s, 3H), 3.97–4.04 (m, 1H), 7.04–7.29 (m, 5H).

Reaction Conversion by the Method A. In a 100 mL autoclave were placed a catalyst (0.4 g), a substrate (6.8 mmol), acetic acid (0.05 mL), and methyl hexanoate (ca. 50 mg) as an internal standard in THF (10 mL). Hydrogen was charged into the autoclave under an initial pressure of ca. 10^7 Pa. The autoclave was heated to 60 °C before starting to shake. After the shaking had continued for 4 h, the reaction mixture was cooled to room temperature, and filtered to remove the catalyst. An analytical sample was directly subjected to the GLC equipped with a TC-WAX capillary column (120 °C). The retention times of the four products were 13.7 min for **1**, 17.7 min for **2**, 20.1 min for **3** and 43.1 min for **4**, and that of the internal standard was 6.6 min.

Reaction Conversion by the Method B. Into a 100 mL autoclave were placed a catalyst (0.4 g), a mixture of four substrates **1**–**4** (1.7 mmol × 4), acetic acid (0.05 mL), methyl hexanoate (ca. 50 mg) as an internal standard, and THF (10 mL). The reaction conditions and analytical method were the same as those for the method A.

Kinetic Study of the Hydrogenation. The same procedure as method B was adapted, except for the use of 40 mL of THF and varied reaction temperatures (50–100 °C). An experiment at 100 °C was carried out with 0.08 g of the catalyst. The hydrogenation was started with shaking after the temperature became constant. Analytical samples were taken out every hour through a side tube connected to the autoclave. The sample was analyzed under the same conditions as in methods A and B.

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