Enantioface-Differentiating (Asymmetric) Hydrogenation of β-Ketoester with Modified Raney Nickel Catalyst (MRNi). XXXI. A Comparative Study of Reaction Rates and Optical Yields

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Enantioface-differentiating hydrogenations of methyl acetoacetate over (*S*)-alanine-, (*S*)-2-aminobutyric acid, (*S*)-valine-, (*S*)-leucine-, (*S*)-malic acid-, and (*R,R*)-tartaric acid-MRNi were carried out under atmospheric pressure of hydrogen and the effects of the modifying reagent on the rates of the formation of enantiomer, v_S and v_R, were investigated. The rates of hydrogenation, $v=v_S+v_R$, were the same for all the amino acid-MRNi and also for all the hydroxy dicarboxylic acid-MRNi. However, the v_R/v_S ratios were different. These results are explained in terms of the independence of the rate-determining and enantioface-differentiating steps in the reaction pathway of hydrogenation. The rate-determining step of hydrogenation was shown to be the hydrogen addition to the adsorbed substrate, while the enantioface-differentiating step was expected to occur prior to the rate-determining step.

Modified Raney nickel catalyst (MRNi) is the most intensively studied catalyst for the enantioface-differentiating hydrogenation of the C=O double bond.[1]

As reported in the preceding paper,[2] the features of the hydrogenation of methyl acetoacetate (MAA) to methyl 3-hydroxybutyrate (MHB) over MRNi have been summarized as follows. 1) The Arrhenius plots with respect to the initial rate of hydrogenation over various MRNi were parallel to one another and the resulting apparent activation energies were 10.5±0.5 kcal/mol in all cases. That is, the reaction mechanism of the rate-determining step was not influenced by the modifying reagent. 2) The rate of hydrogenation followed the equation: $v=k[\mathrm{MAA}]^{0.2-0.3}$. Taking the value of activation energy into consideration, the rate-determining step of hydrogenation was supposed to be the hydrogen addition to the adsorbed substrate (surface reaction). 3) The initial rate of hydrogenation linearly increased with the decrease in the amount of modifying reagent adsorbed on the catalyst, and the amounts of adsorption were found to be similar in so far as the structures of the modifying reagents were homologous. However, there was no systematic relation between the rate and the optical yield. Thus the roles of the modifying reagent were divided into two independent functions: one is to regulate the rate of reaction by occupying a part of the active sites of the catalyst and the other is to make the catalyst differentiate the enantioface of the substrate. We have pointed out[2] that these features of the enantio-differentiating reaction are not explained by the simple kinetic controlled enantio-differentiation usually claimed in the literature[3] and have proposed that the enantio-differentiation should take place elsewhere than in the rate-determining step. Recently, many experimental results favoring our proposal have been reported in the reaction with chiral homogeneous catalyst[4] and the proposal has gradually become general. In this report, the validity of our previous proposal in the reaction with MRNi will be verified on the basis of the detailed studies of the relations between the rate and the optical yield.

Results

Raney nickel catalyst suited for the kinetic studies was prepared by a newly developed method and was modified with α-amino acid or α-hydroxy acid under the conditions reported before.[5]

The resulting time courses of the hydrogenation and optical yields at 20% of conversion are shown in Fig. 1 (α-amino acid-MRNi) and Fig. 2 (α-hydroxy dicarboxylic acid).

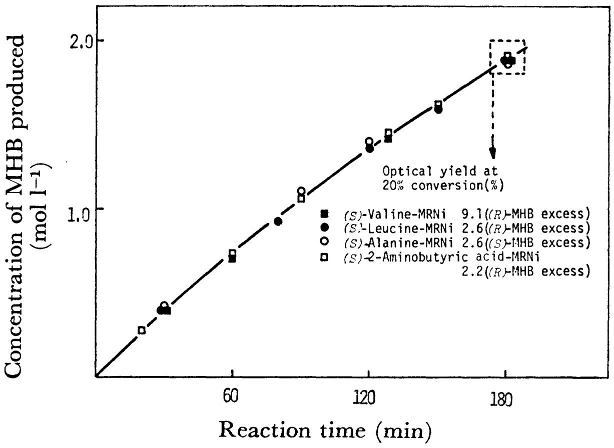


Fig. 1. Time courses of hydrogenation with α-amino acid MRNi.

All the plots in Fig. 1 overlapped one another, that is, all kinetic features of the hydrogenations with α-amino acid-MRNi appeared to be identical. On the other hand, the optical yields were intrinsic to each catalyst. As found in Fig. 2, similar results were obtained in the hydrogenations with α-hydroxy dicarboxylic acid-MRNi.

Figures 3 and 4 show the time courses of (*S*)- and (*R*)-MHB formations calculated from the optical yield of the product with α-amino acid-MRNi ((*S*)-valine and (*S*)-leucine) and α-hydroxy dicarboxylic acid-MRNi ((*S*)-malic acid and (*R,R*)-tartaric acid) respectively.

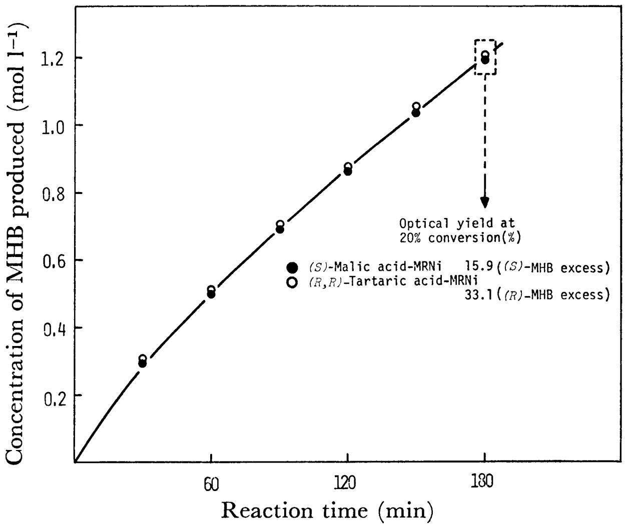


Fig. 2. Time courses of hydrogenation with α-hydroxy dicarboxylic acid-MRNi.

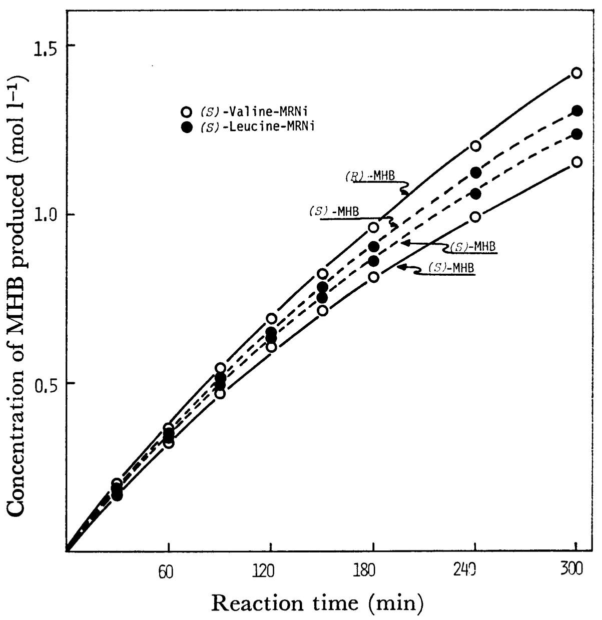


Fig. 3. Time courses of (*S*)- and (*R*)-MHB formation.

The rates of formations of *S*- and *R*-isomers, v_R and v_S, were determined graphically from the figures. The results are listed in Table 1.

From all these data, it became evident that the overall rates, $v=v_R+v_S$, at each reaction time were identical where the modifying reagents were of homologous structure, despite the difference in the rates of formation of each enantiomer, v_R and v_S, with respect to each catalyst.

The rate law of the hydrogenations with MRNi was determined in the usual manner. Initial rates, v_0, at different initial concentrations of MAA, [MAA], were determined by independent experiments. As shown in Fig. 5, plots of $1/v_0$ against 1/[MAA] gave straight lines and the plots corresponding to valine- and leucine-MRNi overlapped each other. Thus, the rates of the hydrogenations with α-amino acid-MRNi and α-hydroxy dicarboxylic acid-MRNi were found to follow the equation

$$v_0 = \beta^\circ[\mathrm{MAA}]/(1+\alpha^\circ[\mathrm{MAA}]) \qquad (1)$$

and the following relations were expected to hold between valine- and leucine-MRNi:

$$\alpha^\circ_{(\mathrm{valine})} = \alpha^\circ_{(\mathrm{leucine})}, \quad \beta^\circ_{(\mathrm{valine})} = \beta^\circ_{(\mathrm{leucine})}. \qquad (2)$$

The rates, v, determined in a single experiment (shown in Table 1), however, gradually deviated from the relations shown in Eq. 1 with increase of the conversion, owing to the decay of the catalyst.

Since all the α-amino acid-MRNi gave the same initial rates, as expected from Fig. 1, Eq. 2 was expected to hold among all the α-amino acid-MRNi examined. The relations $\alpha^\circ_{(\mathrm{malic\ acid})}=\alpha^\circ_{(\mathrm{tartaric\ acid})}$ and $\beta^\circ_{(\mathrm{maric\ acid})}=\beta^\circ_{(\mathrm{tartaric\ acid})}$ were also expected to hold between malic acid- and tartaric acid-MRNi.

TABLE 1. THE RATES OF THE FORMATIONS OF (*S*)- AND (*R*)-MHB

Catalyst (Reaction temp)		Reaction time (min)							
		30	60	90	120	150	180	240	300
(*S*)-Valine-MRNi	v_R (mol l^{-1} min^{-1}) × 10^3	6.15	5.90	5.32	4.81	4.51	4.33	3.73	3.62
(70 °C)	v_S	5.75	5.11	4.59	4.00	3.38	3.16	2.81	2.55
	v	11.90	11.01	9.91	8.81	7.89	7.49	6.54	6.17
	$(\lvert v_R-v_S\rvert/v)\times 10^2$	3.4	7.2	7.4	9.2	14.3	15.6	14.1	17.3
(*S*)-Leucine-MRNi	v_R (mol l^{-1} min^{-1}) × 10^3	6.01	5.37	5.10	4.55	4.24	4.00	3.42	3.21
(70 °C)	v_S	5.77	5.26	4.89	4.35	3.96	3.58	3.13	2.90
	v	11.78	10.63	9.90	8.90	8.20	7.58	6.55	6.11
	$(\lvert v_R-v_S\rvert/v)\times 10^2$	2.0	1.0	1.2	2.3	3.4	5.5	4.4	5.1
(*S*)-Malic acid-MRNi	v_R (mol l^{-1} min^{-1}) × 10^3	4.54	3.77	3.54	3.38	3.28	3.11	2.87	2.77
(60 °C)	v_S	3.98	2.99	2.54	2.51	2.38	2.27	1.94	1.63
	v	8.52	6.76	6.08	5.89	5.66	5.38	4.81	4.40
	$(\lvert v_R-v_S\rvert/v)\times 10^2$	6.6	11.5	16.4	14.8	15.9	15.6	19.3	25.9
(*R*,*R*)-Tartaric acid-MRNi	v_R (mol l^{-1} min^{-1}) × 10^3	5.16	4.52	4.18	4.01	3.94	3.63	3.47	3.32
(60 °C)	v_S	3.36	2.35	2.05	1.94	1.84	1.68	1.52	1.60
	v	8.52	6.87	6.23	5.95	5.78	5.31	4.99	4.93
	$(\lvert v_R-v_S\rvert/v)\times 10^2$	21.1	31.6	34.2	34.8	36.3	36.7	39.1	34.7

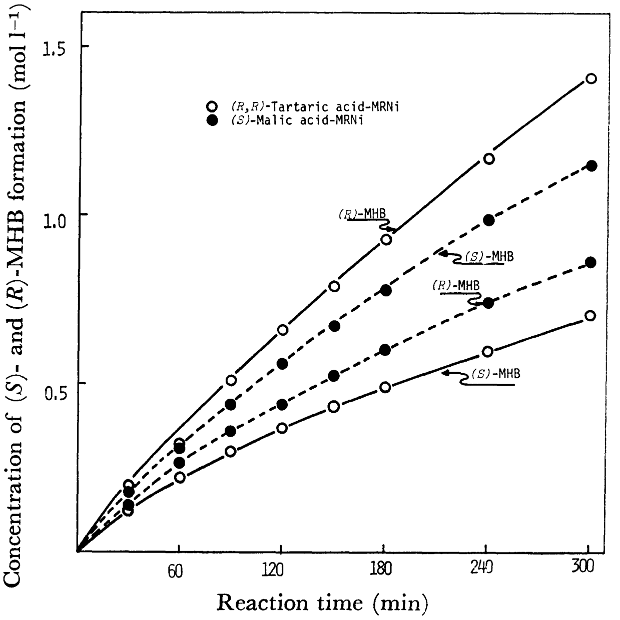
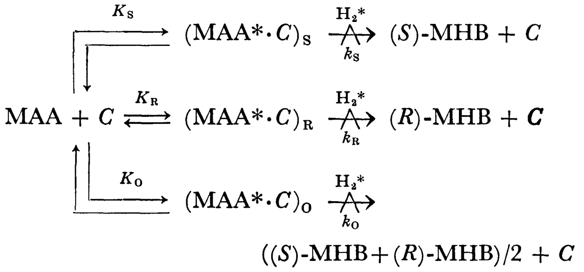


Fig. 4. Time courses of (*S*)- and (*R*)-MHB formation.

The relations mentioned above are also applicable to the values α and β at any reaction times, because the overlapping of the time courses shown in Figs. 1 and 2 indicated that all kinetic constants at each reaction time possess the same value within the same class of MRNi.

Discussions

The rate law shown in Eq. 1 can be derived from the following reaction Scheme, in which the adsorption of MAA to the modified and unmodified parts of catalyst is in competition and each adsorbed species is convertible with the others under the pre-equilibrium condition:



$$\begin{aligned} \mathrm{MAA} + C &\xrightarrow{K_S} (\mathrm{MAA}^*\cdot C)_S \xrightarrow[k_S]{H_2^*} (S)\text{-MHB} + C \\ \mathrm{MAA} + C &\underset{}{\overset{K_R}{\rightleftarrows}} (\mathrm{MAA}^*\cdot C)_R \xrightarrow[k_R]{H_2^*} (R)\text{-MHB} + C \\ \mathrm{MAA} + C &\xrightarrow{K_O} (\mathrm{MAA}^*\cdot C)_O \xrightarrow[k_O]{H_2^*} ((S)\text{-MHB}+(R)\text{-MHB})/2 + C \end{aligned} \tag{3}$$

C: Amount of adsorption site of MAA in given weight of catalyst.

K_S and K_R: Adsorption constants of MAA to be hydrogenated to (*S*)- and (*R*)-MHB under the influence of the modifying reagent.

K_O: Adsorption constant of MAA which did not interact with the modifying reagent.

k_S and k_R: Rate constants of the formations of (*S*)- and (*R*)-MHB from the (MAA*·*C*) interacted with the modifying reagent.

k_O: Rate constant of the formation of racemic MHB from the (MAA*·*C*) which did not interact with the modifying reagent.

Since the adsorption of hydrogen and MAA was not competitive[6] and all reactions were carried out under the same hydrogen pressure, the concentration of active hydrogen on the catalyst, [H_2^*], would be constant under the experimental conditions.

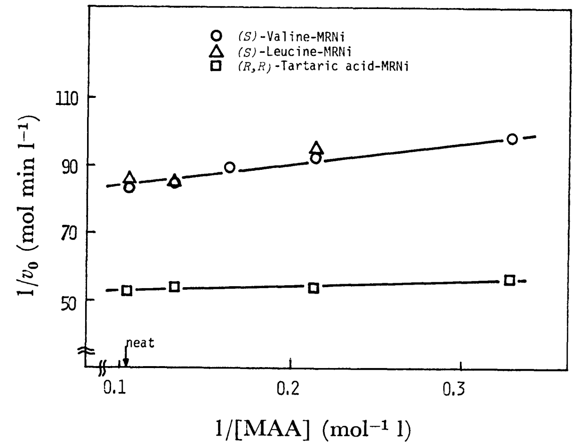


Fig. 5. Relation between initial rate (v_0) and initial concentration of substrate ([MHB]).

The rate of the reaction can be reduced to

$$v_R = \frac{(k_OK_O/2+k_SK_S)[\mathrm{MAA}]C[\mathrm{H}^*]}{1+(K_O+K_S+K_R)[\mathrm{MAA}]}, \tag{4}$$

$$v_S = \frac{(k_OK_O/2+k_RK_R)[\mathrm{MAA}]C[\mathrm{H}^*]}{1+(K_O+K_S+K_R)[\mathrm{MAA}]}, \tag{5}$$

$$v = \frac{(k_OK_O+k_SK_S+k_RK_R)[\mathrm{MAA}]C[\mathrm{H}^*]}{1+(K_O+K_S+K_R)[\mathrm{MAA}]}. \tag{6}$$

When Eq. 6 was compared with Eq. 1, the following relations were deduced:

$$\alpha = K_R + K_S + K_O, \tag{7}$$

$$\beta = (k_RK_R+k_SK_S+k_OK_O)\cdot C\cdot[\mathrm{H}^*]. \tag{8}$$

If we simply assume that the enantio-differentiation takes place only at the rate-determining step of the hydrogenation and does not depend on the relative amounts of adsorption species, [MAA*·C]$_R$, [MAA*·C]$_S$, and [MAA*·C]$_S$, the rates of formation of enantiomers, v_R and v_S should be proportional to ($k_S+k_O/2$) and ($k_R+k_O/2$). When the common adsorption constant of MAA is expressed by K, the relation $\beta=(k_O+k_R+k_S)$-$K\cdot C\cdot[\mathrm{H}^*]$ is expected to hold. In such a case, k_O is a common value for all the modified catalysts, while k_R and k_S should be independent values with respect to each catalyst. Therefore, the catalysts with different v_R and v_S values no longer give the same β value.

Thus this assumption would not be adequate to elucidate the present experimental results that the same class of MRNi gave the same β value but different v_R and v_S values.

The alternative assumption that the rates of formation of enantiomers are related to the amounts of [MAA*·C]$_R$, [MAA*·C]$_O$, and [MAA*·C]$_S$ but not related to k_S, k_R, and k_O, leads to the equation

$$\beta = k(K_S+K_R+K_O)\cdot C\cdot[\mathrm{H}^*]. \tag{9}$$

Here, k is the common rate constant of the all adsorption species ($k=k_R=k_S=k_O$).

From the linear relation between the rate of hydrogenation and the amount of the adsorbed modifying reagent on the catalyst,[2] it is expected that the modifying reagent makes the adsorption site of MAA change by occupying the adsorption site as a simple competitive adsorption species, but the exsistence of the modifying reagent on the catalyst does not affect the equilibrium constant between MAA and vacant adsorption sites. It has also been confirmed that the same class of modifying reagent was adsorbed on the catalyst in the same amount. Therefore, the same adsorption sites of MAA and C, and the same adsorption constants, K, are expected in the same class of MRNi. Hence the total amounts of the adsorbed MAA, that is $[\mathrm{MAA}^*\cdot C]_\mathrm{S}+[\mathrm{MAA}^*\cdot C]_\mathrm{R}+[\mathrm{MAA}^*\cdot C]_\mathrm{O}$, are the same for the same class of MRNi and only the molar fractions of the adsorption species, γ_S, γ_R, and γ_O, are determined by the chiral influence of the modifying reagent. Under these conditions, β can be reduced to

$$\beta = (K_\mathrm{O}+K_\mathrm{R}+K_\mathrm{S})\cdot C\cdot[\mathrm{H}^*] = (\gamma_\mathrm{O}+\gamma_\mathrm{R}+\gamma_\mathrm{S})\cdot K\cdot C\cdot[\mathrm{H}^*]$$
$$= K\cdot C\cdot[\mathrm{H}^*] = \alpha\cdot C\cdot[\mathrm{H}^*],$$

where K is an adsorption constant of MAA and γ_O, γ_R, and γ_S are fraction coefficients of the adsorbed MAA. In this manner, the experimental result that the same class of MRNi gave the same β and α was justified.

Although the kinetic studies do not give any direct indications of the relations, $k_\mathrm{O}=k_\mathrm{S}=k_\mathrm{R}=k$ and $K_\mathrm{O}+K_\mathrm{R}+K_\mathrm{S}=(\gamma_\mathrm{O}+\gamma_\mathrm{R}+\gamma_\mathrm{S})K$, the present experimental results can only be rationalized without conflicting with the kinetic law under the assumption that the ratios of formation of enantiomers are determined by γ_O, γ_R, and γ_S. The function of the modifying reagent can be reduced to interacting with the substrate on the catalyst; such interaction results in the disproportionate formations of the diastereomeric adsorption species. The conclusion of the present studies is that the ratio of formation of enantiomers depends principally on the term, $(\gamma_\mathrm{O}/2+\gamma_\mathrm{R})/(\gamma_\mathrm{O}/2+\gamma_\mathrm{S})$, and that the enantioface-differentiating step occurs before the rate-determining step.

Another important finding of this study is that $|v_\mathrm{R}-v_\mathrm{S}|/v$ increased with the progress of the decay of the catalytic activity, as shown in Table 1. This may be caused by either the specific inactivation of the catalytic site at which the modifying reagent is absent and R- and S-isomers are produced at equal rates (decrease of γ_O), or the change of the adsorption mode of the modifying reagent with the change of the surface of the catalyst by the decay of the catalyst. Further detailed studies on this line are underway.

Experimental

Preparation of Modified Raney Nickel Catalyst. Into an alkaline solution (52 g of sodium hydroxide in 260 ml of water) whose temperature has been adjusted to 19 °C, 19.5 g of well-pulverized Raney alloy (Ni 42%, Al 58%, Kawaken Finechemical Co.) was added in portions at such a rate that the temperature of the mixture was maintained at 19±1 °C with vigorous shaking and cooling on an ice bath. It took 18 min to complete the addition of the alloy. The resulting suspension of Raney nickel was kept at 75—78 °C for 45 min, then allowed to stand at room temperature for 1.5—3 h. After the removal of the alkaline solution by decantation, the Raney nickel (RNi) was washed with eight 300 ml-portions of deionized water.

The modification of RNi was carried out in a 1% solution of modifying reagent. The pH of the modifying solution was adjusted to 5.1 for tartaric acid and malic acid with sodium hydroxide, and to an isoelectric point for each monoamino monocarboxylic acid.

Into 400 ml of the modifying solution, a 2.4 g-portion of the catalyst was immersed at 0 °C for 15 min. During that time, the solution was gently stirred for a few seconds every 5 min. After the removal of the solution, the catalyst was washed with a 40 ml-portion of water and three 200 ml-portions of methanol.

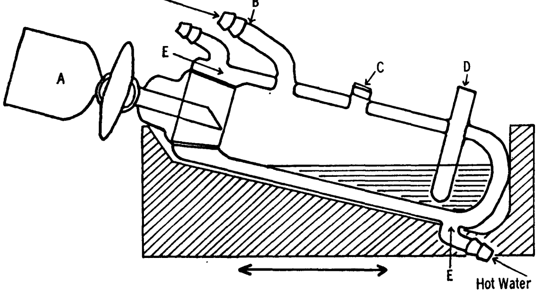


Fig. 6. Frask for hydrogenation.

Hydrogenation. The liquid-phase hydrogenation under atmospheric pressure was carried out with a specially designed 400 ml flask having a liquid inlet funnel (A), a gas inlet side-tube (B), a serum capped hole for sampling (C), a case for the thermometer (D), and a heating jacket with hot water (Fig. 6). Into the flask which had been filled with hydrogen and connected with a graduated hydrogen reservoir through the side-tube B, the modified catalyst suspended in 70 ml of

TABLE 2. THE TIME COURSE OF THE HYDROGENATION

Reaction time (min)	Hydrogen uptake (ml)					
	Reaction temp 70 °C				Reaction temp 60 °C	
	Ala-MRNi	But-MRNi[a]	Val-MRNi	Leu-MRNi	Tar-MRNi[b]	Mal-MRNi[c]
0	0	0	0	0	0	0
30	710	684	649	674	529	507
60	1364	1240	1240	1250	898	860
90	1931	1855	1781	1790	1228	1187
120	2415	2380	2345	2345	1538	1493
150	2872	2866	2814	2804	1835	1785
180	3218	3315	3278	3236	2115	2066

a) 2-Aminobutyric acid. b) Tartaric acid. c) Malic acid.

MAA (or solution of MAA in MHB) was introduced. The flask was fixed to a reciprocating shaker and the jacket was connected with a hot water circulation system. The heating and shaking of the reaction mixture were started simultaneously. The hydrogen uptake was followed by measurement taken every 10 min. The hydrogen uptake of each catalyst is listed in Table 2; from this the concentration of MHB at each stage was calculated. The concentration of MHB thus calculated matched with that determined by GLPC. The plots of time against concentration of MHB in the reaction mixture are shown in the text (Figs. 1 and 2).

Determination of Optical Yield. The optical yield was determined from the optical purity of the MHB dissolved in MAA. After the removal of the catalyst from the reaction mixture by filtration, the filtrate was distilled under reduced pressure. The optical rotation and the ratio, MAA/MHB, in the distillate were determined by means of polarimetry (Perkin-Elmer Model 241 Polarimeter with a 1 dm cell) at 20 °C and GLPC (Shimadzu GC-3HA, 300×0.5 cm stainless-steel column packed with PEG 20 M (20%) on Chromosorb W) at 100 °C respectively. The optical purity of MHB was determined by means of a calibration chart prepared by the plotting of α_D against the concentrations of MHB of different optical purities in MAA.

Time Course of the Formations of (S)- and (R)-MHB. The hydrogenation was carried out in the apparatus described above. A 2 ml portion of the reaction mixture was taken out through the serum capped sampling hole, using an injection syringe, at the times shown in Figs. 3 and 4. The concentration of MAA and the optical rotation of each sample were determined by the procedures mentioned above.

The plots of time against concentrations of (*S*)-and (*R*)-MHB are shown in the text (Figs. 4 and 5).

Initial Rates of Hydrogenation. The hydrogenations of MAA diluted with DL-MHB ranging in concentration from 1.86 to 9.29 (neat) mol/l were carried out at 70 °C. The initial rates of each experiment was determined graphically from the plot of hydrogen uptake against reaction time.

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