1356 © 1980 The Chemical Society of Japan Bull. Chem. Soc. Jpn., 53, 1356—1360 (1980) [Vol. 53, No. 5

The Enantioface-differentiating Hydrogenation of the C=O Double Bond with Asymmetrically Modified Raney Nickel. XXXIII. The Preparation of (*R*)- and (*S*)-1,3-Butanediol from 4-Hydroxy-2-butanone

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(Received July 13, 1979)

The enantioface-differentiating hydrogenation of 4-hydroxy-2-butanone (I) to 1,3-butanediol(II) was conducted with asymmetrically modified metal catalysts. Among the modified catalysts examined, Raney nickel modified with a solution containing tartaric acid and NaBr (TA–NaBr–MRNi) gave the best results with respect to the optical and chemical yields. (*R*)-II, an optical purity of 69% was obtained in a quantitative chemical yield by the use of (*R,R*)-TA–NaBr–MRNi. (*S*)-II was also obtained by the use of (*S,S*)-TA–NaBr–MRNi. A simple method for the preparation of optically pure (*S*)-and (*R*)-II from the hydrogenation product was also developed.

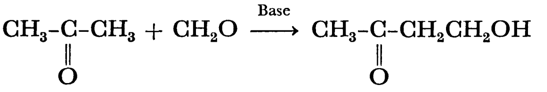
1,3-Butanediol (II) is a biologically interesting compound as a synthetic source of dietary calories[1)] and a hypoglycemic agent for diabetes.[2)]

A recent study has indicated that (*R*)- and (*S*)-II show different physiological activities.[3)] In order to make clear the relations between the absolute configuration and the biological activity of II, the development of a simple method of preparing optically active I was required.

This report will deal with our recent efforts to prepare (*S*)- and (*R*)-II by the enantioface-differentiating hydrogenation of 4-hydroxy-2-butanone (I) with an asymmetrically modified metal catalyst.

Results

The substrate of the present work was prepared from acetone and formaldehyde by a modification of Hays's method:[4)]

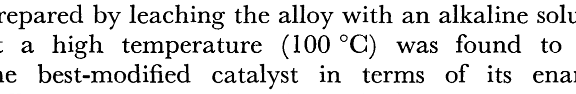


$$CH_3\text{-}\underset{\underset{O}{\|}}{C}\text{-}CH_3 + CH_2O \xrightarrow{\text{Base}} CH_3\text{-}\underset{\underset{O}{\|}}{C}\text{-}CH_2CH_2OH \qquad (1)$$

(I)

Since this reaction proceeds in a flow reactor with a short contact time, the large-scale production of the substrate is feasible.

The hydrogenation of I with various metal catalysts modified with (*R,R*)-tartaric acid easily proceeded at hydrogen pressures of 50—100 kg/cm² and at reaction temperatures of 80—140 °C to give II in good chemical yields.



$$CH_3\text{-}\underset{\underset{O}{\|}}{C}\text{-}CH_2CH_2OH \xrightarrow{H_2/cat} CH_3\text{-}\underset{\underset{OH}{|}}{CH}\text{-}CH_2CH_2OH \qquad (2)$$

(I) (II)

However, the optical yields of the reaction were generally low except for the cases of nickel catalysts (Table 1). Thus, further studies were carried out with nickel catalysts.

Among the nickel catalysts examined, Raney nickel prepared by leaching the alloy with an alkaline solution at a high temperature (100 °C) was found to give the best-modified catalyst in terms of its enantio-differentiating ability and the hydrogenating activity (Table 2). The selection of the favorable modifying reagent was carried out with the above-mentioned Raney nickel. As is shown in Table 3, tartaric acid

Table 1. Optical yield in the hydrogenation of I with a modified metal catalyst

Catalyst	Reaction temp °C	$[\alpha]^{20}_D$ of the product	Optical yield %	Chemical yield[c)] %
RNi[a)]	80	−8.27	27.3	80
RCo[a)]	100	−0.23	0.8	82
RCu[a)]	100	−0.38	1.3	80
RPd[a)]	80	−0.10	0.3	85
Reduced NiO[b)]	140	−4.7	15.9	45

a) A 1.5-g portion of Raney alloys (aluminium content: 50%) was leached with 20 ml of a 20% aqueous NaOH solution at 100 °C, and the resulting catalyst was modified with 100 ml of a 1% aq solution of (*R,R*)-tartaric acid at pH 4.0, at 85 °C. I (10 g) in 20 ml of THF and 0.2 ml of acetic acid was subjected to hydrogenation with each catalyst under a hydrogen pressure of 90 kg/cm². b) A 1-g portion of a nickel catalyst prepared from NiO[6)] was modified in the same manner as above. c) Determined by GLC.

Table 2. Effect of leaching conditions of Raney alloy on the optical yield

	Amount of leaching solution[a)] ml	Leaching temp of alloy °C	$[\alpha]^{20}_D$ of the product	Optical yield %
1	4	28	−2.88	9.8
2	4	50	−3.08	10.4
3	4	100	−4.58	15.5
4	20	100	−4.34	14.7
5	20	100	−8.69	27.3[b)]

a) A 0.3-g portion of Raney alloy was leached with a 20% aqueous NaOH solution under the conditions listed in the table. Each catalyst was modified with 20 ml of 1% tartaric acid at pH 4 at 100 °C. I (2 g) in 3 ml of THF was subjected to hydrogenation at 100 °C under a hydrogen pressure of 90 kg/cm² for 14 h. b) The hydrogenation of I was carried out under the same conditions as above except for the addition of 0.04 ml of acetic acid to the reaction mixture.

Table 3. Optical yield of the hydrogenation of I with various sorts of modified Raney nickels[a)]

	Modifying reagent	pH of modifying solution[b)]	MRNi		NaBr-treated MRNi[d)]	
			$[\alpha]^{20}_{D}$ of the product	Optical yield %	$[\alpha]^{20}_{D}$ of the product	Optical yield %
1	(*S*)-Valine	6.0	+1.88	6.3	+0.49	1.6
2	(*S*)-Proline	6.1	+0.34	1.1	—	—
3	(*S*)-Serine	5.7	+0.50	1.7	—	—
4	(*S*)-Threonine	6.5	+0.40	0.1	—	—
5	(*S*)-Aspartic acid	4	−0.18	0.6	−0.20	0.6
6	(*S*)-Glutamic acid	4	−0.65	2.2	—	—
7	(2*S*, 3*R*)-2-Amino-3-hydroxy-butanedioic acid	4	−0.45	1.6	−1.94	6.3
8	(2*S*, 3*S*)-2-Amino-3-hydroxy-butanedioic acid	4	+0.63	2.1	+2.65	8.6
9	(*R*,*R*)-Tartaric acid	4	−5.15	17.4	−15.6	50.0
10	(*R*,*R*)-2-Methyltartaric acid	4	−5.31	17.9	−17.2	55.9
11	(*S*)-Malic acid	4	+0.46	1.6	+0.29	0.9

a) A 0.3-g portion of Raney alloy was leached with 20 ml of a 20% aq NaOH solution at 100 °C. b) The pH was adjusted by the addition of NaOH to the solution of each modifying reagent. In the case of neutral amino acid, the aqueous solution was used without any pH adjustment. c) The catalyst was modified with 20 ml of an aqueous solution containing 0.2 g of each modifying reagent at 100 °C. I (2 g) in 3 ml of THF was subjected to hydrogenation with MRNi at 100 °C under H_2 pressure of 90 kg/cm^2 for 14 h. d) The catalyst was modified with 20 ml of a solution containing 1.6 g of NaBr and 0.2 g of each modifying reagent.

was one of the best modifying reagents in giving a highly enantio-differentiating catalyst.

The addition of sodium bromide to the modifying solution[5)] resulted in a great increase in the enantio-differentiating ability of the catalyst when tartaric acid was used as the modifying reagent (Table 3).

Enhancements of the enantio-differentiating ability of the catalyst were observed by the addition of various sorts of inorganic salt to the modifying solution. Among the inorganic salts examined, sodium bromide was the most effective additive for the modifying solution in giving a catalyst with a high enantio-differentiating ability (Table 4).

Table 4. Optical yield of the hydrogenation of I with TA-inorganic salt-MRNi[a)]

	Inorganic salt	Amount of salt in modifying solution[b)]	Times of modification process	$[\alpha]^{20}_{D}$ of the product	Optical yield %
1	—	—	1	−9.00	27.3
2	NaF	1.6 g	1	−8.84	29.9
3	NaCl	1.6	1	−10.92	36.9
4	NaBr	1.6	1	−17.77	59.8
5	NaBr	1.6	2	−20.80	70.2
6	NaBr	1.6	3	−20.79	70.2
7	NaI	1.6	1	—	—[c)]
8	NaI	4×10^{-4}	1	−5.3	17.7
9	$Na_2B_4O_7$	0.2	1	−5.91	20.0
10	CH_3COONa	0.2	1	−5.86	19.8
11	Na_2SO_4	1.6	1	−8.88	30.3

a) All the experimental conditions were the same as those described in Table 2. b) Into a 20-ml portion of a 1% solution of (*R*,*R*)-tartaric acid, the listed amount of each salt was dissolved. c) Hydrogenation did not proceed.

The relation between the enantio-differentiating ability of the catalyst and the concentration of sodium bromide in the modifying solution is shown in Fig. 1. The maximum enantio-differentiating ability was observed when the catalyst was modified with a solution containing 8% NaBr and 1% tartaric acid. A high concentration of sodium bromide resulted in a decrease in the enantio-differentiating ability. On the other hand, the repetition of the modification procedure under the best conditions of NaBr concentration resulted in an increase in the enantio-differentiating ability of the catalyst (Table 4, Entries 5 and 6).

Thus, the Raney nickel treated twice with a solution containing 8% NaBr and 1% tartaric acid was found to be the best enantio-differentiating hydrogenation catalyst (TA–NaBr–MRNi) for I.

The optical yield of the hydrogenation was also affected by the reaction conditions, such as the sort of solvent employed, the relative amounts of substrate,

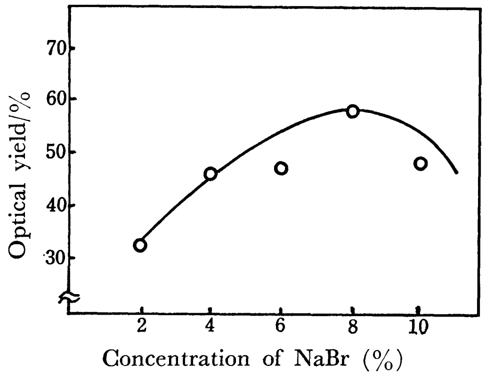


Fig. 1. The relation between optical yield and the concentration of NaBr in modifying solution.

catalyst, and solvent, and the reaction temperature.

As may be seen in Table 5, aprotic moderately polar solvents, such as THF, methyl propionate, and ethyl acetate, gave good optical yields. However, the use of methanol resulted in a poor optical yield.

As is shown in Fig. 2, the optical yields were constantly high over a wide range of the relative amounts of the catalyst, solvent, and substrate. However, the use of small amounts of a catalyst and/or a solvent resulted in poor optical yields.

The optimum optical yield was obtained at the reaction temperature of 85—100 °C (Fig. 3). This temperature was also favorable for giving a good chemical yield.

Table 5. Solvent effect on the optical yield of the reaction[a)]

Solvent	$[\alpha]^{20}_{D}$ of the product	Optical yield / %
MeOH	−10.11	34.1
AcOEt	−16.74	56.6
$EtCO_2Me$	−17.76	60.0
THF	−20.50	69.4
THF/Benzene=3/20	−17.65	59.6

a) The reaction conditions were the same as those described in Footnote a) of Table 1 except for the reaction time (14 h).

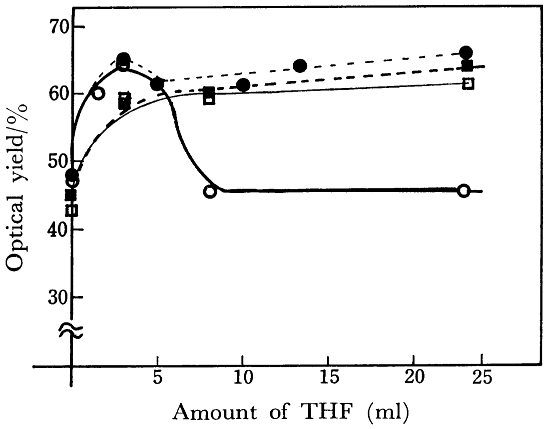


Fig. 2. The effect of the relative amounts of catalyst and solvent on the optical yield.
The substrate (2 g) was subjected to hydrogenation with the catalysts prepared from 0.3 g (-○-), 0.6 g (--●--), 0.9 g (-□-), and 1.5 g (--■--) of Raney alloy, respectively.

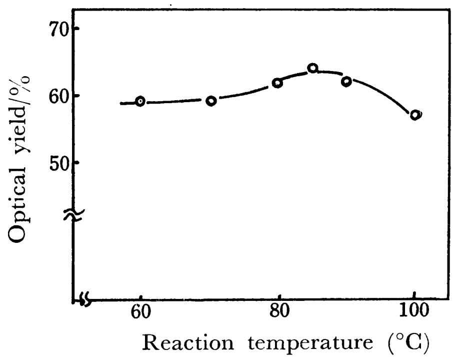


Fig. 3. The effect of reaction temperature on the optical yield.

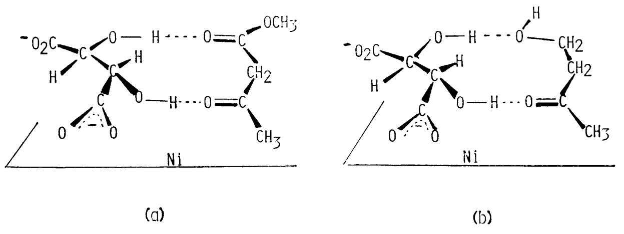
Under the conditions optimized from all the results mentioned before, (*R*)-II and (*S*)-II with an optical purity of 68—70% were obtained from I with (*R*,*R*)- and (*S*,*S*)-tartaric acid–MRNi's in almost quantitative chemical yields and with good reproducibility.

The reaction of the hydrogenation product with phenyl isocyanate gave 1,3-butanedioldicarbanilate (III) as crystals. When a saturated methanolic solution of III with an optical purity of 70% was kept in the presence of small pieces of crystals of optically pure III, optically pure III was crystallized out of the solution in a yield of 64%, based on the total weight of III. The reductive cleavage of the urethane group of optically pure III with $LiAlH_4$ gave optically pure II in a yield of 62% based on III. The overall yield of optically pure II was 40% based on I.

Discussion

From the results of the present study, the optical yield of the reaction is considered to be determined by two major factors. The first factor is the differentiating ability of the modifying reagent, which depends mostly on the intermolecular interaction between the modifying reagent and the substrate adsorbed on the catalyst. The second factor is the ratio of the enantio-differentiating area to the non-enantio-differentiating area on the surface of the catalyst.

In the course of earlier studies of the enantio-differentiating hydrogenation of the *β*-ketoester, tartaric acid–MNi was found to be the best enantio-differentiating catalyst, as in the present work.[7)] The excellent result was attributed to the formation of two-site intermolecular interaction through hydrogen bondings between tartaric acid and the *β*-ketoester (Fig. 4a) in the enantioface-differentiating process.[8)] In a similar manner, tartaric acid can make hydrogen bondings with I, the hydroxyl group of I taking the place of the ester carbonyl group of the *β*-ketoester (Fig. 4b). The fact that both I and the *β*-ketoester gave the (*R*)-enantiomer in the hydrogenation over (*R*,*R*)-tartaric acid–MNi also strongly suggests that the mode of the enantioface-differentiating process of I is identical with that of the *β*-ketoester. From these considerations, it can be concluded that a high optical yield is obtained when a well-fitting intermolecular interaction is formed



(a) (b)

Fig. 4. Schematic representation of the complex of *β*-ketoester and (*R*,*R*)-tartaric acid (a) and that of I and tartaric acid (b).

between a modifying reagent and substrate adsorbed on the catalyst.

Such protic solvents as water and alcohol in the reaction system, which can take part in hydrogen bondings with I and/or tartaric acid, interfere with the formation of the rigid interaction between I and tartaric acid. Thus, the use of a protic solvent resulted in a significant decrease in the optical yield.

The dependence of the optical yield on the leaching temperature of the Raney alloy (Table 2) is closely related to the amount of aluminium remaining in the catalyst. It is well documented that Raney nickel prepared at a low temperature contains a large amount of aluminium and shows a high hydrogenation activity. The aluminium in the catalyst is considered to be in a polymeric form of aluminium hydroxide.[9] The hydroxyl groups of tartaric acid on the catalyst and the hydroxyl group of aluminium derivatives may compete in the formation of hydrogen bondings with the substrate. Under these conditions, the formation of a rigid tartaric acid-substrate interaction is disturbed to a large extent. For these reasons, the hydrogenation at the aluminium-enriched part of the catalyst gives the racemic product predominantly. Thus, the use of a Raney nickel leached at a low temperature resulted in a significant decrease in the optical yield.

A Raney nickel leached at a high temperature still contains some of an active nickel in the aluminium-enriched part of the catalyst. Partial poisoning with suitable substances is one way to remove such an active part of the catalyst.

In general, sodium bromide is considered to be a weakly poisoning reagent of a metal catalyst. This compound is apt to be adsorbed on the highly active nickel surface in the aluminium-enriched part of the catalyst. The remarkable increase in the optical yield on the treatment of the catalyst with sodium bromide is caused by the effective blocking of the non-enantio-differentiating reaction site with sodium bromide.

Experimental

The GLC was carried out with a Shimadzu GC-4APF gas chromatograph using a 3-m, 5-mm-o.d. glass column packed with 5% Tween 80 on Shimalite W at the specified temperature.

The optical rotations were measured with a Perkin Elmer 241 polarimeter. The IR and ^{1}H-NMR spectra were taken with a Shimadzu IR-27G spectrometer and a Hitachi R-24 spectrometer respectively.

Substrate. 4-Hydroxy-2-butanone (I): This compound was obtained, by the aldol condensation of formaldehyde and acetone,[4] in a yield of 28%, based on formaldehyde; bp 56—58 °C/5 mmHg.** The GLC (130 °C) analysis of the distillate showed a 98% purity, with 2% of diacetone alcohol. The NMR and IR spectra of the product were compatible with those expected from the structure of I.

Modifying Reagent. (*R*,*R*)-Tartaric acid, (*S*,*S*)-tartaric acid, (*S*)-aspartic acid, (*S*)-glutamic acid, (*S*)-serine, (*S*)-threonine, (*S*)-valine, and (*S*)-malic acid were commercially purchased.

(2*S*,3*S*)-2-Amino-3-hydroxysuccinic acid ($[\alpha]^{20}_{D}$ 8.0° (*c* 1, 5 M HCl), lit,[7] 6.4° (*c* 1, H_2O). Anal. Found: C, 31.89; H, 4.73; N, 9.55%. Calcd for $C_4H_7O_5N$: C, 32.22; H, 4.73; N, 9.40%) and (2*S*,3*R*)-2-amino-3-hydroxysuccinic acid ($[\alpha]^{20}_{D}$ 46.5° (*c* 1, H_2O), lit,[10] 47.0° (*c* 1, H_2O). Anal. Found: C, 31.97; H, 4.71; N, 9.50%) were prepared by the previously reported method.[11]

Catalyst. Raney alloy was leached by adding it portion by portion, to a solution of NaOH under the conditions stated in the tables in the text.

The nickel catalyst was subjected to modification by soaking in the modifying solution for 1 h under the conditions stated in the table in the text.

After the removal of the modifying solution, the modified catalyst was rinsed successively with a 17-ml/(g-catalyst) portion of water, two 80-ml portions of methanol, and a 40-ml portion of the solvent used for the reaction.

Hydrogenation. Hydrogenation was carried out either in a 100-ml autoclave (the data in Tables 1 and 5 were thus obtained) or a 30-ml glass tube in the autoclave (the data in Tables 2,3 and 4 were thus obtained).

After the removal of the catalyst, the reaction prodcut was dried over anhydrous K_2CO_3 (overnight) and then distilled under reduced pressure to give II (bp 117 °C/40 mmHg). Subsequent GLC (130 °C) of the product showed a single peak at a retention time of 14 min. The IR and ^{1}H-NMR spectra of the product were identical with those of the racemic authentic sample (Wako Pure Chemical Co., Ltd.). A 1-g portion of the distillate was diluted in 10 ml of ethanol and, then the optical rotation was determined. The optical purity of the product was calculated based on the optical rotation of optically pure (*R*)-II, $[\alpha]^{20}_{D}$ −29.6° (*c* 10, EtOH).

Preparation of Optically Pure II. A mixture of II (8.8 g, $[\alpha]^{20}_{D}$ −20.7° (*c* 10, EtOH) and phenyl isocyanate (22.5 g) was heated at 100 °C for 1 h on an oil bath and then cooled to room temperature to give 30 g of crude III.

A 5-g portion of crude III was dissolved in 14 ml of boiling ethanol. The solution was cooled to room temperature and then mixed with 25 ml of hexane. The mixture was kept overnight at 5 °C. The separation of the crystals from the mixture gave 3.5 g of III ($[\alpha]^{20}_{D}$ −46.7° (*c* 5, EtOH). Three successive recrystallizations from ethanol–hexane under the same conditions as above gave 2.5 g of III ($[\alpha]^{20}_{D}$ −56.3° (*c* 5, EtOH)). Three further successive recystallizations resulted in no increase in the optical rotation.

The major portion of the crude III (25 g) was dissolved in 150 ml of methanol under reflux, after which the solution was kept at 5 °C overnight in the presence of small pieces of the crystals of III with $[\alpha]^{20}_{D}$ −56.3° (*c* 5, EtOH). The crystals were then collected and washed with a 10-ml portion of cold methanol. The crystals thus obtained amounted to 16 g. $[\alpha]^{20}_{D}$ −56.3° (*c* 5, EtOH), mp 130—131 °C. Found: C, 65.93; H, 6.15; N, 8.55%. Calcd for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53%.

To the suspension of $LiAlH_4$ (30 g) in 300 ml of dry dioxane, which has been heated at 80 °C on an oil bath, a solution of 15 g of III ($[\alpha]^{20}_{D}$ −56.3°) in 300 ml of dioxane was added, drop by drop. The reaction mixture was heated for 3 h under reflux, cooled to 5 °C on an ice bath, and then hydrolyzed with 60 ml of water. The insoluble matter was separated by filtration and washed with 30 ml of methanol. The filtrate and washings were then combined and freed of the solvent under reduced pressure at 50 °C. The residue was mixed with 50 ml of water and then washed with three 15-ml portions of benzene. After the evaporation of water from the aqueous layer under reduced pressure, the residue was dried over zeolite 3 A (overnight) and then distilled

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** 1 mmHg = 133.322 Pa.

under reduced pressure to give 2.5 g II; bp 95—98 °C/10 mmHg, $[\alpha]_D^{20}$ −29.6° (*c* 10, EtOH), $[\alpha]_D^{20}$ −31.6° (*c* 1, EtOH) lit,[11] ($[\alpha]_D^{20}$ −29° (*c* 1, EtOH). The IR and NMR spectra, and the retention time in GLC were identical with those of the authentic sample.

The authors wish to express their thanks to Professor Yoshiharu Izumi and Dr. Hiroshi Ozaki, Institute for Protein Research, Osaka University, for their helpful suggestions. The present work was supported in part by a Grant in Aid for Scientific Research from the Ministry of Education (No. 303530).

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