

The Enantioface-differentiating Hydrogenation of the C=O Double Bond with Asymmetrically Modified Raney Nickel. XXXVIII. The Hydrogenation of Methyl Ketones to Optically Active Secondary Alcohols

Tsutomu OSAWA* and Tadao HARADA

Institute for Protein Research, Osaka University, Yamada-oka, Suita, Osaka 565

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The enantioface-differentiating (asymmetric) hydrogenation of various methyl ketones ($R\text{-COCH}_3$) was carried out over the Raney nickel catalyst modified with (*R,R*)-tartaric acid and sodium bromide. The presence of an appreciable amount of carboxylic acid in the reaction system was indispensable for a high optical yield. The highest optical yield (74%) was obtained in the hydrogenation of 3,3-dimethyl-2-butanone in the presence of pivalic acid.

The development of a facile method for the preparation of optically active compounds is one of the important tasks in synthetic organic chemistry. Enantioface-differentiating (asymmetric) catalysts could be useful for a large-scale production of optically active compounds, because the reaction produces a large amount of optically active compounds from a catalytic amount of the optically active substance employed for the preparation of the catalyst.

Many attempts have been carried out to prepare optically active secondary alcohols *via* the hydrogenation of prochiral ketones over enantioface-differentiating catalysts. Several catalysts have been reported to give good optical yields in the enantioface-differentiating hydrogenation of ketones carrying polar groups or unsaturated groups.^{1–4} However, no efficient catalysts have been reported for the enantioface-differentiating hydrogenation of alkyl ketones. As far as we know, the highest optical yield (43%) was attained in the hydrogenation of 3,3-dimethyl-2-butanone using an optically active phosphine-rhodium complex catalyst.⁵

As has been reported preliminarily, the Raney nickel modified with tartaric acid (TA) and sodium bromide (TA-NaBr-MRNi) is an excellent catalyst for the enantioface-differentiating hydrogenation of 2-octanone.⁶ This paper will describe a successful attempt to obtain a high optical yield in the hydrogenation of 2-octanone and the application of MRNi to the hydrogenation of various methyl ketones.

Results and Discussion

It was well documented that the enantioface-differentiating hydrogenation of β -keto esters over TA-NaBr-MRNi proceeded to give an optical yield of more than 80%.⁷ When the optimum conditions for the hydrogenation of β -keto esters were applied to the hydrogenation of 2-hexanone, about 30% of the optical yield was obtained.⁸ This result strongly suggested that MRNi was a promising enantioface-differentiating catalyst for the hydrogenation of alkyl ketones as well as β -keto esters. However, under the same conditions as above, the hydrogenation of 2-octanone gave only a poor optical yield. Since the structural difference between 2-hexanone and 2-octanone is not significant, it was expected that the change in the reaction conditions would improve the optical yield of the hydrogenation of 2-octanone. The optical yield of the

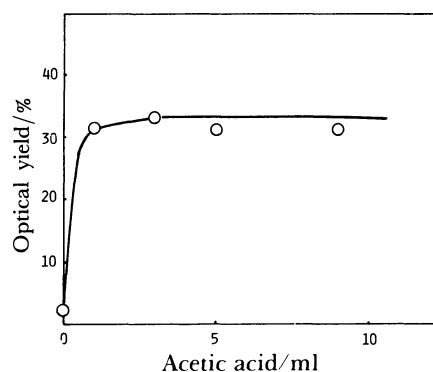


Fig. 1. The relation between the optical yield and the amount of acetic acid in the reaction system. Catalyst; RNi modified with TA (2 g) and NaBr (4 g).

hydrogenation of methyl acetoacetate (MAA) was known to be affected by the presence of carboxylic acid in the reaction system as an additive.^{9,10} Thus, the effects of additives on the hydrogenation of 2-octanone were first examined. As is shown in Fig. 1, the addition of a small amount of acetic acid to the reaction system steeply increased the optical yield. Around 30% of the optical yield was obtained by the addition of 1 ml (0.02 mol) of acetic acid to 10 ml (0.064 mol) of the substrate. However, no further increase in the optical yield was observed when more than 1 ml of acetic acid was added. In order to find a more efficient substance than acetic acid, the reaction was carried out in the presence of various additives. The results are listed in Table 1. Among the compounds examined, α -branched carboxylic acids gave the best results. The best result was obtained by the use of pivalic acid. No other classes of compounds, such as hydroxy acid, alcohol, amine, and sulfonic acid, functioned as effective additives. Figure 2 shows the relationship between the amount of pivalic acid in the reaction system and the optical yield. The optical yield increased with the increase in the amount of pivalic acid until it reached a constant value. The maximum optical yield was obtained when more than 12 ml (0.11 mol) of pivalic acid was added to 10 ml (0.064 mol) of 2-octanone. The results showed that the use of a proper amount of α -branched carboxylic acid was important in obtaining a high optical yield.

In the second step, the effects of the modification variables of the nickel catalysts on the optical yields were examined, because the optical yield was also known to be affected significantly by the modification

TABLE 1. EFFECTS OF THE ADDITIVES ON THE OPTICAL YIELD

Additives	Amount	$[\alpha]_D^{20}/^\circ$	Optical yield/%
None	—	+0.22	2
Acetic acid	3 ml	+3.2	33
Propionic acid	12 ml	+4.2	43
Hexanoic acid	13 ml	+4.2	43
Lauric acid	21 g	+3.9	40
Stearic acid	9 g	+2.9	29
Isobutyric acid	15 ml	+5.6	57
Pivalic acid	18 ml	+6.2	63
2, 2-Dimethylhexanoic acid	23 g	+5.7	58
Diphenylacetic acid	10 g	+4.1	42
Tartaric acid	10 mg	+0.11	1
3-Hydroxybutyric acid	0.01 g	+0.28	3
	11 g	— ¹⁾	— ¹⁾
2, 2-Dimethyl-1-propanol	9 g	+0.26	3
Triethylamine	15 ml	+0.88	9
<i>p</i> -Toluenesulfonic acid	7 g	— ¹⁾	— ¹⁾

Modifying solution: (*R, R*)-TA (2 g) and NaBr (4 g) in 200 ml of H₂O. 1) No hydrogen uptake.

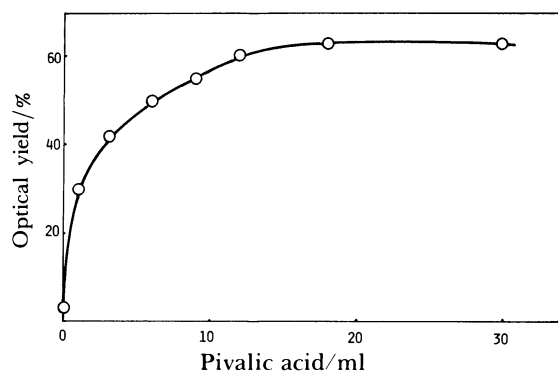


Fig. 2. The relation between the optical yield and the amount of pivalic acid in the reaction system. Catalyst; RNi modified with TA (2 g) and NaBr (4 g).

variables. Figure 3 shows the relationship between the amount of NaBr used for the preparation of MRNi and the optical yield. The optical yield increased with the increase in the amount of NaBr to reach a plateau. The constant value was obtained by the addition to TA of more than twice as much NaBr by weight.

Besides NaBr, various inorganic salts were used for the preparation of MRNi. None of the inorganic salts

was found to be more effective than NaBr, as is shown in Table 2.

The modifying pH and the temperature were found to be important factors governing the optical yield of the reaction, like the hydrogenation of MAA.⁷⁾ The dependences of the optical yields on the modifying pH and the temperature are listed in Table 3. So far as we

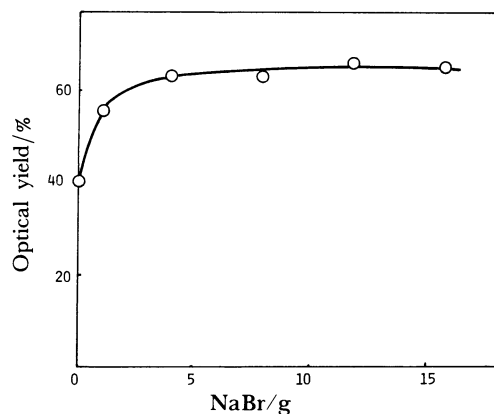


Fig. 3. The relation between the optical yield and the amount of NaBr in modifying solution. Additive; Pivalic acid (18 ml).

TABLE 2. HYDROGENATION OF 2-OCTANONE OVER TA-INORGANIC SALT-MRNi

Inorganic salt in the modifying solution(g)	Reaction		Optical yield/%
	Time	Conversion/%	
None	20 h	83	29
NaBr(14)	20 h	100	51
NaCl(16)	20 h	100	47
NaF(1.5)	20 h	100	29
NaI(0.002)	3 d	70	27
NaH ₂ PO ₄ (2)	5 d	100	4
Na ₂ SO ₄ (16)	20 h	100	31
NaNO ₃ (0.2)	3 d	100	32
LiBr(4) ¹⁾	3 d	90	14
KBr(4) ²⁾	4 d	87	7
NH ₄ Br(4) ³⁾	7 d	84	6

Modifying solution: (*R, R*)-TA (2 g) and an appropriate amount of inorganic salt in 200 ml of H₂O. Additive; Hexanoic acid (13 ml). 1) Modifying pH was adjusted with 1 mol dm⁻³ LiOH. 2) Modifying pH was adjusted with 1 mol dm⁻³ KOH. 3) Modifying pH was adjusted with 14 mol dm⁻³ NH₄OH.

TABLE 3. DEPENDENCE OF OPTICAL YIELD ON THE MODIFYING TEMPERATURE AND MODIFYING pH

Modifying temperature/°C	Modifying pH	Optical Yield/%
100	2.5	37
100	3.2	63
100	5	46
0	3.2	16
50	3.2	28

Modifying solution: TA (2g) and NaBr (8g) in 200 ml of H₂O. Additive: Pivalic acid (18ml).

TABLE 4. HYDROGENATION OF METHYL KETONES (R-CO-CH₃) OVER (R, R)-TA-NaBr-MRNi

R-	$[\alpha]_D^{20}/^\circ$	Optical yield/%	Configuration of the product
CH ₃ CH ₂ -	+6.8	49	S
CH ₃ (CH ₂) ₂ -	+8.7	63	S
CH ₃ (CH ₂) ₃ -	+7.6	66	S
CH ₃ (CH ₂) ₄ -	+6.8	66	S
CH ₃ (CH ₂) ₅ -	+6.4	66	S
CH ₃ (CH ₂) ₇ -	+5.1	58	S
CH ₃ (CH ₂) ₁₀ -	+4.7	65	S
(CH ₃) ₂ CH- ⁽¹⁾	+3.0	63	S
(CH ₃) ₃ C- ⁽¹⁾	+5.7	74	S
C ₆ H ₅ (CH ₂) ₂ -	+8.2	58	S

Modifying solution: (R, R)-TA (2g) and NaBr (12g) in 200 ml of H₂O. Additive: Pivalic acid (18ml). 1) MRNi was prepared from 19g of the RNi alloy.

examined, the modification at pH 3.2, and 100°C gave the best result.

The enantioface-differentiating hydrogenations of various kinds of methyl ketones were carried out under the optimum reaction conditions for the hydrogenation of 2-octanone. The results are shown in Table 4. Unbranched methyl ketones, except for 2-butanone and 4-phenyl-2-butanone, were hydrogenated in an optical yield of around 65%. 2-Butanone and 4-phenyl-2-butanone were hydrogenated in rather low optical yields. From the comparison of the optical yields of the hydrogenation of 2-butanone, 3-methyl-2-butanone, and 3,3-dimethyl-2-butanone, it appears that there is a tendency for methyl ketones with α -alkyl substituents to be hydrogenated in higher optical yields than unbranched ones. The highest optical yield (74%) was obtained in the hydrogenation of 3,3-dimethyl-2-butanone.

Experimental

The analytical and preparative GLC of the products were carried out with a Shimadzu GC-6A gas chromatograph. The optical rotations were measured with a Perkin Elmer 241 polarimeter. The ¹H-NMR and IR spectra were taken with a JEOL-FX200 instrument and a Shimadzu IR 27G spectrometer respectively.

Materials. All the chemicals except for those described below were obtained from commercial sources and were used without further purification.

Tetrahydrofuran. Commercial tetrahydrofuran was dried over NaH overnight and then distilled.

Racemic 3-Hydroxybutyric Acid. This was prepared by the alkali hydrolysis of methyl 3-hydroxybutyrate which had been obtained by the hydrogenation of MAA.

2,2-Dimethylhexanoic Acid. This compound was prepared by the procedure of Pfeffer *et al.*¹¹⁾

Catalyst. Unless otherwise stated in the text, the catalyst was prepared in the following manner: a 3.8-g portion of the Raney nickel alloy (Ni:Al=42:58) was added, portion by portion, to 40 ml of a 20% aqueous NaOH solution, and then the mixture was allowed to stand at 100°C for 1 h. After the subsequent removal of the alkaline solution by decantation, the catalyst was washed 30 times with a 30-ml portion of deionized water. The resulting catalyst was modified for 1 h at 100°C with 200 ml of an 1.0% aqueous solution of (R,R)-TA containing the stated amount of inorganic salt, the pH of which had been adjusted to 3.2 with 1 mol dm⁻³ NaOH. After the removal of the modifying solution, the catalyst was washed successively with a 20-ml portion of water, two 100-ml portions of methanol, and two 30-ml portions of anhydrous tetrahydrofuran.

Hydrogenation of Methyl Ketones. A mixture of methyl ketone (10 ml) dissolved in anhydrous tetrahydrofuran (20 ml) and a stated amount of an additive was subjected to hydrogenation under an initial hydrogen pressure of 90 kg/cm². Hydrogenation was carried out in a 100 ml autoclave at 100°C. After the removal of the catalyst by decantation and the evaporation of the solvent, the product was dissolved in 100 ml of ether and washed with a saturated aqueous solution of K₂CO₃ to remove the carboxylic acid. The ether solution was then dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. As for 2-hexanol, 2-heptanol, 2-octanol, 2-decanol, 2-tridecanol, and 4-phenyl-2-butanol, simple distillations gave hydrogenated products with chemical purities of more than 98% (GLC analyses: at 130°C, 5% Tween 80 on Shimalite W; at 100–220°C, 2% OV-17 on Chromosorb W). In the cases of 2-butanol, 2-pentanol, 3-methyl-2-butanol, and 3,3-dimethyl-2-butanol, the products were contaminated by the solvent (tetrahydrofuran) through the simple distillation. Some of the products were further purified by preparative GLC (at 100°C for 2-butanol, 130°C for 2-pentanol and 3,3-dimethyl-2-butanol, 20% PEG-20M Chromosorb W; at 125°C, 15% UCON 50HB-2000 on Chromosorb W for 3-methyl-2-butanol) and subjected to analyses of the chemical and optical purities. These products showed chemical purities of more than 98% in the GLC analyses (at 130°C, 5% Tween 80 on Shimalite W; at 100–220°C, 2% OV-17 on Chromosorb W). The ¹H-NMR spectra of the products were consistent with their structures: IR (neat) 3350–3400 cm⁻¹ (OH).

Determination of Optical Yield. The optical yields of the hydrogenation of methyl ketones were estimated from the specific rotations of the pure enantiomers: (S)-2-butanol, $[\alpha]_D^{20}+13.87^\circ$ (neat);¹²⁾ (S)-2-pentanol, $[\alpha]_D^{20}+13.70^\circ$ (neat);¹²⁾ (S)-2-hexanol, $[\alpha]_D^{20}+11.57^\circ$ (neat);¹²⁾ (S)-2-heptanol, $[\alpha]_D^{20}+10.32^\circ$ (neat);¹²⁾ (S)-2-octanol, $[\alpha]_D^{20}+9.76^\circ$ (neat);¹²⁾ (S)-2-decanol, $[\alpha]_D^{20}+8.68^\circ$ (neat);¹²⁾ (S)-2-tridecanol, $[\alpha]_D^{20}+7.22^\circ$ (neat);¹²⁾ (S)-3-methyl-2-butanol, $[\alpha]_D^{20}+4.85^\circ$ (neat);¹³⁾ (S)-3,3-dimethyl-2-butanol, $[\alpha]_D^{20}+7.71^\circ$ (neat);¹⁴⁾ (S)-4-phenyl-2-butanol, $[\alpha]_D^{20}+14.23^\circ$ (neat).¹⁴⁾

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References

- 1) T. Hayashi and M. Kumada, *Acc. Chem. Res.*, **15**, 395 (1982).
 - 2) K. Ito, T. Harada, and A. Tai, *Bull. Chem. Soc. Jpn.*, **53**, 3367 (1980); A. Tai, K. Ito, and T. Harada, *ibid.*, **54**, 223 (1981).
 - 3) S. Murakami, T. Harada, and A. Tai, *Bull. Chem. Soc. Jpn.*, **53**, 1356 (1980).
 - 4) Y. Hiraki, K. Ito, T. Harada, and A. Tai, *Chem. Lett.*, **1981**, 131.
 - 5) T. Hayashi, T. Mise, and M. Kumada, *Tetrahedron Lett.*, **1976**, 4351.
 - 6) T. Osawa and T. Harada, *Chem. Lett.*, **1982**, 315.
 - 7) T. Harada, M. Yamamoto, S. Onaka, M. Imaida, H. Ozaki, A. Tai, and Y. Izumi, *Bull. Chem. Soc. Jpn.*, **54**, 2323 (1981); M. Nakahata, M. Imaida, H. Ozaki, T. Harada, and A. Tai, *ibid.*, **55**, 2186 (1982); A. Tai, T. Harada, Y. Hiraki, and S. Murakami, *ibid.*, **56**, 1414 (1983).
 - 8) A. Tai, T. Harada, Y. Hiraki, and S. Murakami, *Bull. Chem. Soc. Jpn.*, **56**, 1414 (1983).
 - 9) Y. Izumi, *Angew. Chem., Int. Ed. Engl.*, **10**, 871 (1971).
 - 10) Y. Orito, S. Niwa, and S. Imai, *Yuki Gosei Kagaku Kyokai Shi*, **35**, 672, 753 (1977).
 - 11) P. E. Pfeffer, L. S. Silbert, and J. M. Chirinko, Jr., *J. Org. Chem.*, **37**, 451 (1972).
 - 12) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911).
 - 13) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **101**, 621 (1912).
 - 14) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **105**, 1115 (1914).
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