Enantioface-differentiating (Asymmetric) Hydrogenation of Keto Ester with Modified Nickel Catalyst. XXXII. Structural Requirements of Modifying Reagent and Substrate

Shinji Okamoto, Tadao Harada, and Akira Tai*
Division of Organic Chemistry, Institute for Protein Research, Osaka University, Suita, Osaka 565
(Received March 29, 1979)

The enantioface-differentiating hydrogenation of α-, β-, γ-, and δ-keto esters over α-, β-, and γ-amino acid-MRNi has been conducted. The optimum enantio-differentiating power of α-amino acid-MRNi has been found in the hydrogenation of the β-keto ester and that of β-amino acid-MRNi found in the hydrogenation of the γ-keto ester. The results have been explained in terms of the intermolecular recognition between substrate and modifying reagent through the functional groups.

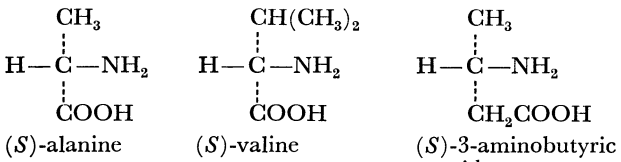
Asymmetrically modified nickel catalysts (MNi) provide attractive catalysts for the enantioface-differentiating hydrogenation of prochiral unsaturated compounds because of their simplicity and wide applicability.

The modifying reagents which have high enantio-differentiating power with one type of substrate do not necessarily do so with another substrates.[1] Therefore, the choice of modifying reagent suited to each type of substrate is the most important criteria for preparing an effective catalyst. In general, α-amino acid- or α-hydroxy acid-MRNi show good enantio-differentiating power with β-keto esters but not with α- and γ-keto esters. In a preceding paper which dealt with the hydrogenation of β-keto esters with tartaric acid-MNi, it was shown that the intermolecular hydrogen bond between substrate and the modifying reagent were one of the most important factors governing the optical yield of the reaction.[2] On this basis, the effect of the structural relation between the modifying reagent and the substrate on the enantio-differentiating power of the modified catalyst has been investigated by monitoring the optical yields of the hydrogenations of α-, β-, γ-, and δ-keto esters over α-, β-, and γ-amino acid-MRNi.

Results and Discussion

The substrates and the modifying reagents used in this study are as follows;

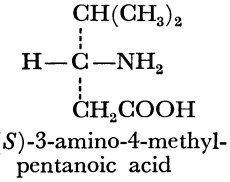
Modifying reagents



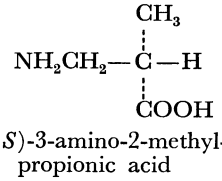
(*S*)-alanine (I)

(*S*)-valine (II)

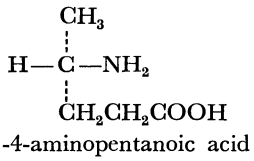
(*S*)-3-aminobutyric acid (III)



(*S*)-3-amino-4-methylpentanoic acid (IV)



(*S*)-3-amino-2-methylpropionic acid (V)



(*S*)-4-aminopentanoic acid (VI)

Substrates

$CH_3CO(CH_2)_nCOOCH_3$	$n=0$	methyl pyruvate (**1**)
	$n=1$	methyl acetoacetate (**2**)
	$n=2$	methyl 4-oxopentanoate (**3**)
	$n=3$	methyl 5-oxohexanoate (**4**)

The modification of Raney nickel was conducted as previously reported.[3]

The hydrogenation of each substrate was performed in an autoclave at 100 kg/cm² of initial hydrogen pressure at 60 °C. The optical yields of the reactions are summarized in Table 1.

In the hydrogenation of various keto esters over α-amino acid-MRNi the maximum optical yield was obtained with methyl acetoacetate as shown in Fig. 1. Methyl 4-oxopentanoate gave the optimum optical yield on hydrogenation with a β-amino acid-MRNi (Fig 2). In the β-amino acid-MRNi, III and IV, in which the chiral center is at the β-position of the carboxyl group and V in which the chiral center is at the α-position of the carboxyl group, the same trend in enantio-differentiating power with change in substrate was observed.

From a geometrical point of view, it is thought that the positions of the $-NH_2$ and $-COOH$ groups in the modifying reagent and those of the $-CO-$ and $-COOCH_3$ groups in the substrate are the most important factors in the optical yield of hydrogenation, *i.e.*, a reasonable optical yield is only attained when the substrate can make a stabilized complex with the modifying reagent involving more than two pairs of interaction through functional groups as indicated above.

As shown in Fig. 2, with a structural fit between the substrate and the modifying reagent, the optical yield is not influenced by the position of the chiral center.

In the case of the γ-amino acid-MRNi, no significant enantio-differentiating power was observed in all substrates examined ($n=0$ to 3). The low optical

Table 1. Hydrogenation of keto esters with Raney nickel catalyst modified with α-, β-, and γ-amino acid

Substrate $CH_3(CH_2)_nCO_2CH_3$	Optical yield(%) and configuration of enantiomer produced in excess modifying reagent					
	α-amino acid		β-amino acid			γ-amino acid
	I	II	III	IV	V	VI
1 (n=0)	0	0.3(S)	0.6(R)	0.4(R)	0.2(S)	0.9(R)
2 (n=1)	1.6(R)	8.9(R)	1.1(R)	3.8(R)	2.4(R)	0.1(S)
3 (n=2)	0.4(R)	2.8(R)	7.4(S)	7.5(S)	4.8(S)	0
4 (n=3)	0.1(R)	0	0.4(R)	0.1(R)	0.2(R)	0.1(S)

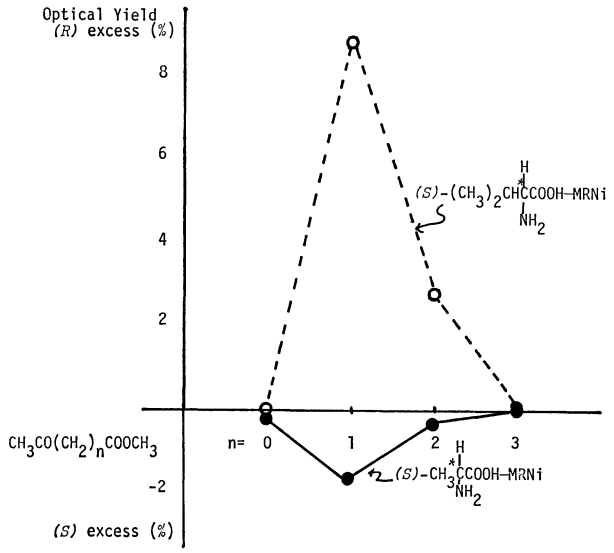


Fig. 1. Optical yield of the hydrogenation of $CH_3C(=O)-(CH_2)_n-COOCH_3$ (n=0—3) with α-amino acid–MRNi.

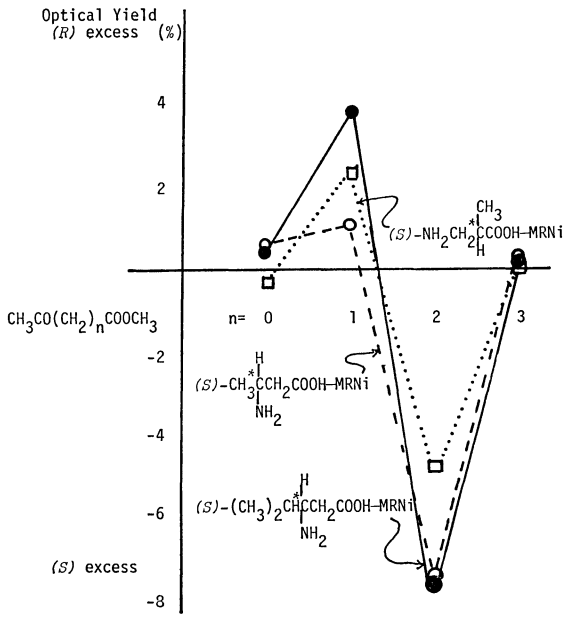


Fig. 2. Optical yield of the hydrogenation of $CH_3C(=O)-(CH_2)_n-COOCH_3$ (n=0—3) with β-amino acid–MRNi.

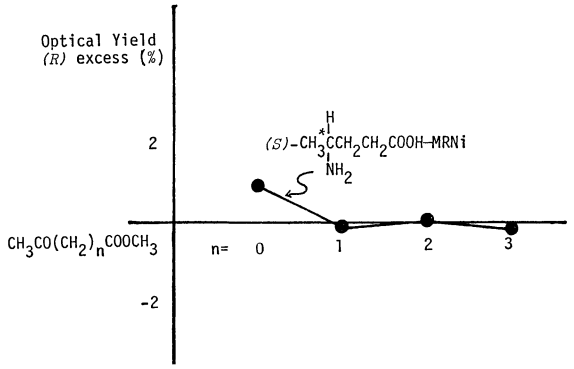


Fig. 3. Optical yield of the hydrogenation of $CH_3C(=O)-(CH_2)_n-COOCH_3$ (n=0—3) with γ-amino acid–MRNi.

yields in the reactions with the γ-amino acid–MRNi, even in the case of the δ-keto ester, may be ascribed to the lack of rigid intermolecular interaction due to the flexible nature of the molecules. Thus, the formation of rigid interaction between the substrate and the modifying reagent is the most important factor in obtaining a reasonable optical yield in this reaction system.

No special models demonstrating the mode of differentiation between the direction of enantioface-differentiation and absolute configuration of the modifying reagent, were derive from the present data. The structural requirement between the substrate and the modifying reagent provides, however, useful information as to the design of effective catalysts for enantio-differentiating reactions.

Experimental

Gas chromatographic analysis was conducted with a Shimadzu GC-4APF apparatus using a 300×0.5 cm glass column packed with neopentyl glycol succinate (5%) on Chromosorb W. Optical rotation was measured with a Perkin Elmer 241 polarimeter at 589 nm. NMR and IR spectra were measured on Hitachi R-24 and Shimadzu IR-27G spectrometers respectively.

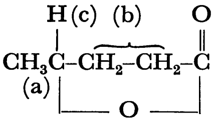
Modified Raney Nickel Catalyst. The Raney nickel

catalyst was prepared as reported before.[3] A portion of the Raney nickel (0.1 g) was added to a 1% aqueous solution of the modifying reagent (20 ml). The mixture was allowed to stand with occasional shaking at 0 °C for 15 min. After decantation, the catalyst was washed with a portion of water (1 ml) and three portions of methanol (3×10 ml).

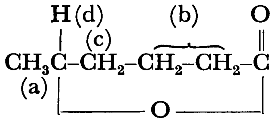
Hydrogenation and Optical Yield. Into a 10 ml flask equiped with a small gas inlet tube, was introduced the modified catalyst (0.1 g) suspended in the substrate (0.028 mol). The flask was placed in an autoclave and the hydrogenation conducted under hydrogen (90 kg/cm²) at 60 °C until no more consumption of hydrogen was observed. After filtration of the catalyst, the filtrate was distilled under reduced pressure. GLC analysis of each distillate indicated that the hydrogenation was complete.

Methyl lactate, bp 60—61 °C/35 mmHg† and methyl 3-hydroxybutyrate bp 61—62 °C/12 mmHg were obtained almost quantitatively from methyl pyruvate and methyl acetoacetate respectively.

A mixture of methyl 4-hydroxypentanoate and 4-pentanolide, and a mixture of methyl 5-hydroxyhexanoate and 5-hexanolide were obtained from methyl 5-oxopentanoate and methyl 5-oxohexanoate respectively. The optical yields of the hydrogenations of methyl pyruvate and methyl acetoacetate were calculated from the optical rotation of the products based on the values of $[\alpha]_D^{20}$ −8.25° (neat) for methyl (*S*)-lactate[4] and $[\alpha]_D^{20}$ −22.95° (neat) for methyl (*R*)-3-hydroxybutyrate.[5] The hydrogenation product of methyl 5-oxopentanoate was refluxed with Amberlyst 15 in benzene for 3 h to give 4-pentanolide bp 88—84 °C/13 mmHg.

NMR for  : δ, 1.42, d, 3H, (a); 1.6—2.6, m, 4H, (b); 4.68, m, 1H, (c). The optical yield of the hydrogenation was indirectly evaluated from the optical rotation of 4-pentanolide derived from the hydrogenation product based on the value of $[\alpha]_D^{22}$ −35.1±1° (*c* 4.018, dioxane) for (*S*)-5-pentanolide.[6]

The hydrogenation product of methyl 5-oxohexanoate was also converted to 5-hexanolide (bp 97—99 °C/12 mmHg)

NMR for  : δ 1.41, d, 3H, (a), 1.6—2.8, m, 4H, (b), 2.5, m, 2H, (c), 4.5, m, 1H, (d), by the same method as above. The optical yield of the hydrogenation was indirectly determined from the optical rotation of 5-hexanolide thus obtained based on $[\alpha]_D^{20}$ −51.4° (c=4, ethanol) for (*S*)-5-hexanolide.[7]

Modifying Reagents. *(S)-3-Aminobutyric Acid (III)*: This compound was obtained by the optical resolution of ethyl (*RS*)-3-aminobutyrate with (*R,R*)-tartaric acid in methanol and saponification of the resolved ester. From ethyl (*RS*)-3-aminobutyrate (131 g), optically pure (+)-(*S*)-III (7.5 g) was obtained. $[\alpha]_D^{23}$ +37.0° (*c* 0.5, H_2O) (lit, $[\alpha]_D^{19}$ 38.8° (*c* 0.8, H_2O)).[8] Mp 221 °C. Found: C, 46.69; H, 8.99; N, 13.60%. Calcd for $C_4H_9O_2N$: C, 46.59; H, 8.80; N, 13.58%.

(S)-3-Amino-4-methylpentanoic Acid (IV): (*S*)-Valine was converted to (+)-methyl (*S*)-3-phthalimido-4-methylpentanoate (VII) by the reported method.[9] To a solution of hydrazine hydrate (90%, 13 g) in a mixture of water (100 ml) and methanol (200 ml), VII (32 g) was added and the mixture maintained at room temperature for one week. After removal of the methanol from the reaction mixture and acidification of the residue with hydrochloric acid to pH 4, the precipitate was removed. Condensation of the filtrate to dryness gave crude 3-amino-4-methylpentanoic acid hydrazide as an oil. The oil was refluxed with 2M†† hydrochloric acid (300 ml) for 4 h and the resulting solution concentrated to dryness to give 3-amino-4-methylpentanoic acid hydrochloride. The crude amino acid hydrochloride was charged on to a column of IR 120B (H^+ type) and eluted with 0.2 M aqueous ammonia. Evaporation of water from the eluate gave crude crystals of IV. Recrystallization from a mixture of methanol and ether yielded (*S*)-(+)-IV (6 g). Mp 212 °C, $[\alpha]_D^{23}$ +52.3° (*c* 0.6, H_2O), (lit, $[\alpha]_D^{24}$ −39.2° (*c* 0.51, H_2O) for (*R*)-(−)-IV.[11] Found: C, 54.66; H, 10.09; N, 10.49%. Calcd for $C_6H_{13}O_2N$: C, 54.94; H, 9.99; N, 10.68%.

(S)-3-Amino-2-methylpropionic Acid (V): This compound was obtained by the Hoffman degradation of (*S*)-3-carbamoyl-2-methylpropionic acid (VIII) ($[\alpha]_D^{23}$ −22° (*c* 2, ethanol)) which was prepared from (*E*)-3-carbamoylmethacrylic acid.[10] To a solution of KOBr prepared from bromine (12 g) and 10% aqueous potassium hydroxide (400 ml), VIII was added (9.8 g). The mixture was maintained at 55 °C for 1 h and then cooled to 0 °C. The solution was acidified to pH 2 with hydrochloric acid and concentrated to dryness. The residue was extracted with three portions of ethanol (3×30 ml) and the combined extracts condensed to dryness to give crude crystals of 3-amino-2-methylpropionic acid hydrochloride. The hydrochloride was dissolved in water (200 ml) and passed through a column of Dowex-50. The amino acid loaded on the resin was eluted with 0.2 M aqueous ammonia. Evaporation of water from the eluate gave crystals of V. Recrystallization from a mixture of methanol and ethanol gave (*S*)-(+)-V (5.3 g), mp 194—5 °C, $[\alpha]_D^{21}$ +15.4° (*c* 5, H_2O), (lit, (*R*)-(−)-V, $[\alpha]_D^{26}$ −15.4° (*c* 1, H_2O).[11] Found: C, 46.06; H, 9.10; N, 13.31%. Calcd for $C_4H_9NO_2$: C, 46.59; H, 8.80; N, 13.58%.

(S)-(+)-4-Aminopentanoic Acid (VI): This compound was obtained by the optical resolution of 4-(benzoylamino)-pentanoic acid with quinine and saponification of the resolved acylamino acid.[12] 4-(Benzoylamino)pentanoic acid (65 g) gave (*S*)-(+)-VI (2.7 g) as crystals, mp 205 °C, $[\alpha]_D^{23}$ +12.1° (*c* 10, H_2O) (lit, $[\alpha]_D^{20}$ +12.0° (*c* 10, H_2O)).[8] Found: C, 50.88; H, 9.69; N, 11.57%. Calcd for $C_5H_{11}NO_2$: C, 51.26; H, 9.46; N, 11.96%.

Substrate. *Methyl Pyruvate (1)*: This was obtained from silver pyruvate (190 g) and methyl iodide (164 g) by a conventional procedure (yield 70%), bp 61—63 °C/13 mmHg. GLC (80 °C) showed a single peak. The IR spectrum (neat) was identical with that from an authentic sample.

Methyl Acetoacetate (2): The commercial product (Nihon-gosei Co.) was used without further purification.

Methyl 4-Oxopentanoate (3): This compound was obtained by the esterification of 4-oxopentanoic acid with methanol in the presence of Amberlyst 15 (yield 90%). GLC (130 °C) showed 98% purity. H^1 NMR (CCl_4) and IR spectra were consistent with the structure of **3**. Elementary analysis was conducted as the 2,4-dinitrophenylhydrazone of **3**. Found: C, 48.19; H, 4.97; N, 17.30%. Calcd for $C_{13}H_{16}O_6N_4$; C, 48.15; H, 4.97; N, 17.28%.

Methyl 5-Oxohexanoate (4): 5-Oxohexanoic acid was obtained from methyl acetoacetate and methyl acrylate (yield 68%).[13] The esterification of the acid with methanol

† 1 mmHg=133.3 Pa.

†† 1 M=1 mol dm⁻³.

in the presence of Amberlyst 15 gave **4** (yield 90%). Bp 96 °C/15 mmHg. GLC analysis (130 °C) showed a single peak. Elemental analysis was conducted as the 2,4-dinitrophenylhydrazone of **4**. Found: C, 48.19; H, 4.97; N, 17.30%. Calcd for $C_{13}H_{16}O_6N_4$: C, 48.15; H, 4.97; N, 17.28%.

The authors would like to thank Professor Yoshiharu Izumi for his helpful suggestions and discussions. Thanks are also due to Mrs A. Kobatake for the elemental analyses. The present work was partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Education.

References

1) Y. Izumi, M. Imaida, T. Harada, T. Tanabe, S. Yajima, and T. Ninomiya, *Bull. Chem. Soc. Jpn.*, **42**, 241 (1969); Y. Izumi, *Angew. Chem. Int. Ed. Engl.*, **10**, 871 (1971).
2) A. Tai, H. Watanabe, and T. Harada, *Bull. Chem. Soc. Jpn.*, **52**, 1468 (1979).
3) H. Ozaki, A. Tai, S. Kobatake, H. Watanabe, and Y. Izumi, *Bull. Chem. Soc. Jpn.*, **51**, 3559 (1978).
4) T. Purdie and J. C. Irvine, *J. Chem. Soc.*, **75**, 484 (1899).
5) T. Harada and Y. Izumi, *Chem. Lett.*, **1978**, 1195.
6) H. Minato, *Chem. Pharm. Bull.*, **9**, 625 (1961).
7) R. Kuhn and D. Jerchel, *Ber.*, **76**, 413 (1943).
8) K. Balenovic, D. Cerar, and Z. Funks, *J. Chem. Soc.*, **1952**, 3316.
9) K. Balenovic and D. Dvornik, *J. Chem. Soc.*, **1962**, 1386.
10) R. Adams and D. Fles, *J. Am. Chem. Soc.*, **81**, 4946 (1959).
11) Y. Kakimoto and M. D. Armstrong, *J. Biol. Chem.*, **236**, 3283 (1961).
12) E. Fischer and R. Groh, *Ann. Chem.*, **383**, 363 (1911).
13) N. F. Albertson, *J. Am. Chem. Soc.*, **70**, 669 (1948).