

Enantio-differentiating hydrogenation of prochiral ketones over modified nickel

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Abstract

This article reviews the enantio-differentiating hydrogenation of prochiral ketones over a asymmetrically modified catalyst, focusing on the hydrogenation of simple prochiral alkanones. The parameters affecting catalytic activity and enantio-differentiating ability are considerable in number, and each parameter should be optimized in order to attain a high-performance enantio-differentiating catalyst. Optimization of the parameters and the mode of enantio-differentiation are discussed and compared with the enantio-differentiating hydrogenation of β -ketoesters.

Keywords: Alkanone; Enantio-differentiation; Heterogenous catalyst; Hydrogenation; Asymmetric modification

1. Introduction

Enantio-differentiating (e.d.) hydrogenation of prochiral ketones has been studied for many years over heterogeneous catalysts [1], homogeneous catalysts [2] and enzymes (bio-catalysts) [3]. Although various substrates have been employed in those catalytic systems, substrates giving high optical yields were limited to those able to undergo two or more interactions between substrate and catalyst. For example, regarding homogeneous catalysts, 2,2'-bis(diarylphosphino)-1,1'-binaphthyl (BINAP)-rare metal catalysts hydrogenated methyl α -acetoaminocinnamic acid, α,β - or β,γ -unsaturated carboxylic acids, hydroxylated or acetoxylated unsaturated acids and simple ketones with aromatic or unsaturated group in high

optical yield [4,5]. Regarding the heterogeneous catalysts, only two systems, (i) a tartaric acid-modified nickel (TA-MNi) catalyst [6] and (ii) a cinchona-modified platinum catalyst [7], have been intensively studied and reached an industrial applicable level. The TA-MNi catalyst hydrogenated various β -functionalized ketones and the cinchona-modified platinum catalyst hydrogenated α -functionalized ketones in high optical yield. The development strategy for an effective e.d. hydrogenation catalyst for such substrates has already been established, and some of the homogeneous catalysts have attained almost a perfect optical yield. However, e.d. hydrogenation of substrates not carrying a polar group or unsaturated group other than an unsaturated bond to be hydrogenated, for example, simple prochiral alkanones, has not yet been successfully achieved with various homogeneous and heterogeneous reaction systems

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including catalytic and stoichiometric reactions. The reason is that it is difficult to construct a reaction site which effectively recognizes the two alkyl groups attached to the prochiral center.

As a challenging subject, we have attempted the e.d. hydrogenation of simple alkanones with a heterogeneous catalyst in the hope that a solid surface would effectively participate in the construction of the site to differentiate two alkyl groups on the prochiral center. For this purpose, we employed an asymmetrically modified nickel (MNi) catalyst based on some clues found in the course of studies on the e.d. hydrogenation of β -ketoesters over MNi.

MNi was first invented by Izumi et al. in 1963 [8]. They modified Raney nickel (RNi) with a mono sodium salt of glutamic acid and hydrogenated methyl acetoacetate (MAA) in 15% optical yield. After that, MNi has been systematically studied by Izumi and his research group. Over 90% optical yield has now been attained in the MAA hydrogenation. From the 1970s to the 1980s, MNi was also studied by Yasumori [9], Nitta and Imanaka [10], Klabunovskii [11] and Sachtler [12] independently. Recently Webb [13] and Brunner [14] reported their studies on MNi. As well as the intensive examination of the preparation conditions and reaction conditions aiming at a high optical yield, the studies of obtaining reaction parameters in liquid [15,16] and gas phase [17,18] hydrogenation and the investigation of the catalyst surface by spectroscopy [19–21] were performed.

MNi can be prepared easily by soaking an activated nickel catalyst in an aqueous solution of an optically active compound. It offers both activated hydrogen generated from H_2 by the metal surface and an asymmetric environment organized by the optically active compound adsorbed on the catalyst surface. These two functions cooperatively work to produce optically active compounds. That is, MNi recognizes the *re*- and *si*-faces of the substrates, and dissociated hydrogen preferentially attacks one enantioface of the substrate to produce one enantiomer of the alcohol (Fig. 1).

Detailed reviews of the e.d. hydrogenation of MAA over modified nickel catalysts have already been published [6,22–24]; therefore, in this overview, development of e.d. hydrogenation of alkanones

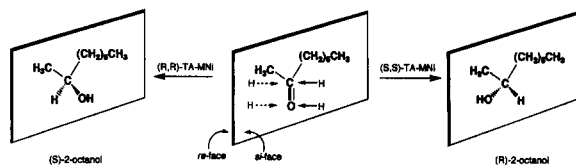


Fig. 1. Enantioface-differentiating hydrogenation of 2-octanone.

will be mainly discussed in contrast to that of MAA.

2. Enantio-differentiating hydrogenation of 2-alkanones

2.1. Enantio-differentiating hydrogenation of 2-alkanones under the conventional conditions for MAA

In the course of the studies on e.d. hydrogenation of 2-alkanones, we first attempted the hydrogenations under the representative conditions for MAA. A Ni–Al alloy (Ni:Al=42:58) was digested with NaOH solution at 100°C for 1 h. Then the catalyst was washed with a small portion of water. The Raney nickel catalyst (RNi) thus obtained was soaked in a solution containing (*R,R*)-tartaric acid and NaBr at 100°C for 1 h. This modification solution had been adjusted to pH 3.2 with NaOH solution before modification. The catalyst was then washed with water, methanol and the reaction solvent. When 2-hexanone was hydrogenated using the catalyst thus obtained, a low optical yield of 28% was attained [25]. This fact suggests that TA on the Ni surface cannot differentiate effectively between methyl and butyl groups and that the catalyst and hydrogenation conditions for MAA cannot be simply applied to the hydrogenation of 2-alkanones. Tai et al. already proposed the mode of enantio-differentiation of MAA hydrogenation with this catalyst (Fig. 2) [25]. This model suggests that hydrogen bonds between the two hydroxyl groups in TA and the two carbonyl groups in MAA are essential for attaining a high optical yield. However, 2-alkanones have only one carbonyl group that can interact with TA on the surface of the catalyst. If this model applies to the hydrogenation of 2-alkanones, the substrates would approach the

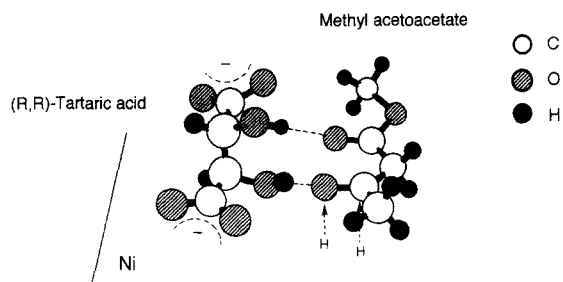


Fig. 2. Stereochemical model of the hydrogenation of methyl acetoacetate over (R,R)-TA-MNi.

catalyst surface facing the *si*- and *re*-faces in a similar proportion (Fig. 3).

2.2. Factors controlling the optical yield

In order to develop effective e.d. catalysts for alkanones, we have fully investigated the factors controlling the optical yield. Fig. 4 describes the general factors controlling the optical yield of e.d. hydrogenation. This catalyst can be prepared very easily, but the number of factors controlling the optical yield of the reaction is considerable. All the processes of the e.d. hydrogenation consist of three processes, that is, (i) a catalyst preparation process, (ii) a modification process and (iii) a hydrogenation process. These processes have preparation variables for activated nickel as a base catalyst for MNi, modification variables for the activated nickel catalyst and reaction variables of the hydrogenation process, respectively. All these factors should be optimized for each substrate. In order to attain a high optical yield in the

hydrogenation of 2-alkanones, catalyst preparation conditions and hydrogenation conditions have been fully investigated using 2-octanone as the standard substrate.

Because preliminary experiments showed that the additive to the reaction system enormously affected the optical yield in the 2-octanone hydrogenation, we will discuss this subject first.

2.2.1. Additives to the reaction system

In the hydrogenation of MAA, a small amount of acetic acid in the reaction media slightly increased the optical yield [22,26]. Taking this fact into account, the effects of the addition of acetic acid on optical yield in the 2-octanone hydrogenation was investigated (Fig. 5) [27]. Without the addition of acetic acid, only a 2% optical yield was attained. However, the addition of acetic acid was so effective that addition of more than 1 ml of acetic acid corresponding to 10 ml of substrate enhanced the optical yield to over 30%. As the third component in the reaction system affecting the optical yield, the effects of various kinds of additives on the optical yield were examined in the hydrogenation of 2-octanone (Table 1). Among them, carboxylic acids were found to be most effective in enhancing the optical yield in the 2-octanone hydrogenation. The addition of triethylamine slightly increased the optical yield, but that of alcohol did not increase the optical yield. Carboxylic acids with branching at the α -position, such as isobutyric acid or pivalic acid, enormously increased the optical yield. However, an α -branched carboxylic acid with bulkier alkyl groups (1-adamantanecarboxylic acid

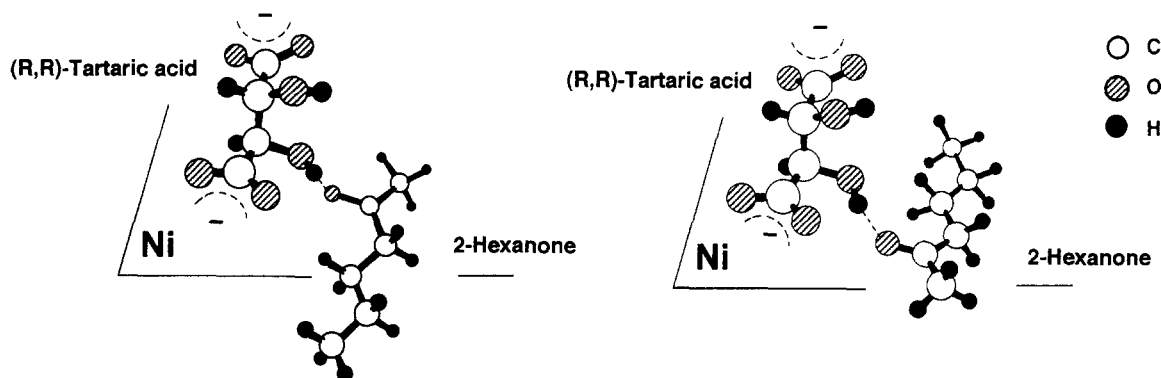


Fig. 3. Enantio-differentiating hydrogenation of 2-hexanone under conventional conditions for methyl acetoacetate.

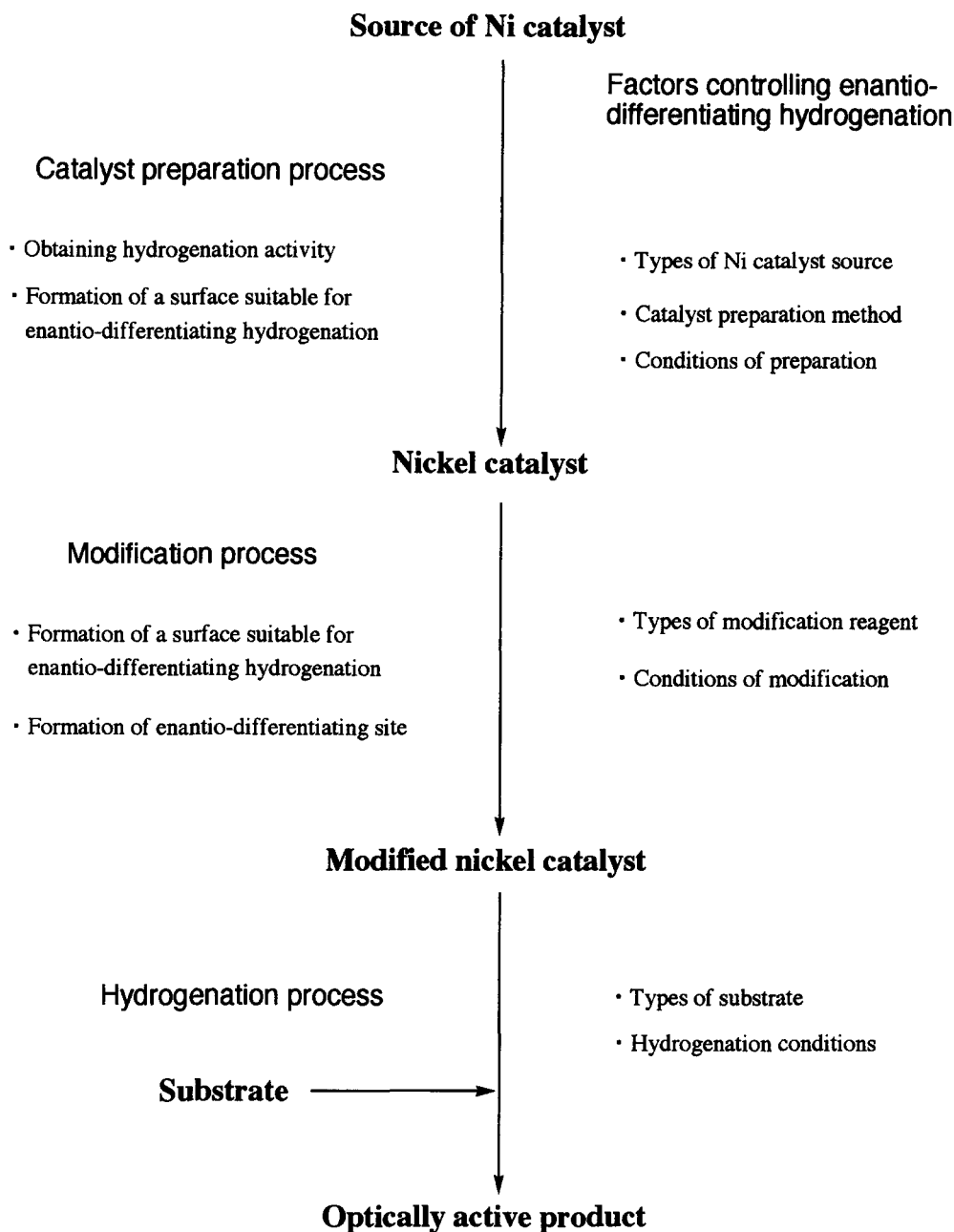


Fig. 4. Factors controlling optical yield of e.d. hydrogenation.

or 1-methyl-1-cyclohexanecarboxylic acid) was not as effective as pivalic acid. Hydroxyl acid did not increase the optical yield, and the addition of a large amount retarded the hydrogenation activity of the catalyst. The stereochemistry of the acid had no effect

on the optical yield (racemic or optically pure 2-ethylhexanoic acid). Fig. 6 shows the effects of the amount of pivalic acid, which was the most effective for enhancing the optical yield [27]. The optical yield steeply increased with a slight addition of pivalic acid.

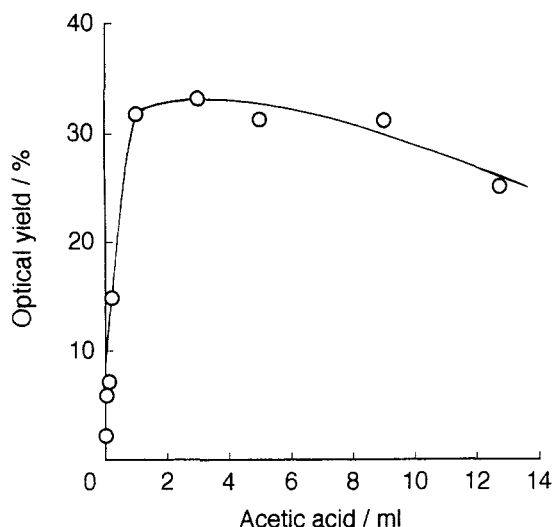


Fig. 5. The relation between the optical yield and the amount of acetic acid in the hydrogenation of 2-octanone. Catalyst: RNi (1.6 g) modified with 200 ml of aqueous solution containing (*R,R*)-TA (2 g) and NaBr (4 g) at pH 3.2, 100°C, for 1 h; Reaction mixture: 2-octanone (8.2 g), THF (20 ml) and acetic acid; Hydrogenation temperature: 100°C.

Table 1

Effects of the additives in the reaction media on optical yield in the 2-octanone hydrogenation

Carboxylic acid	Amount (mol)	Optical yield (%)
None	—	2 ^a
Acetic acid	0.05	33 ^a
Propionic acid	0.16	43 ^a
Hexanoic acid	0.11	43 ^a
Isobutyric acid	0.16	57 ^a
Pivalic acid	0.11	60 ^a
1-Adamantanecarboxylic acid	0.11	49
1-Methyl-1-cyclohexanecarboxylic acid	0.11	53
(<i>R/S</i>)-2-ethylhexanoic acid	0.11	50
(<i>S</i>)-2-ethylhexanoic acid	0.11	51
(<i>R</i>)-2-ethylhexanoic acid	0.11	55
Tartaric acid	0.0001	1 ^a
3-Hydroxybutyric acid	0.0001	3 ^a
2,2-Dimethyl-1-propanol	0.11	3 ^a
Triethylamine	0.11	9 ^a

^aData from Ref. [27]

Catalyst: RNi (1.6 g) modified with 200 ml of aqueous solution containing (*R,R*)-TA (2 g) and NaBr (4 g) at pH 3.2, 100°C, for 1 h; Reaction mixture: 2-octanone (8.2 g), THF (20 ml) and the additives; Hydrogenation temperature: 100°C.

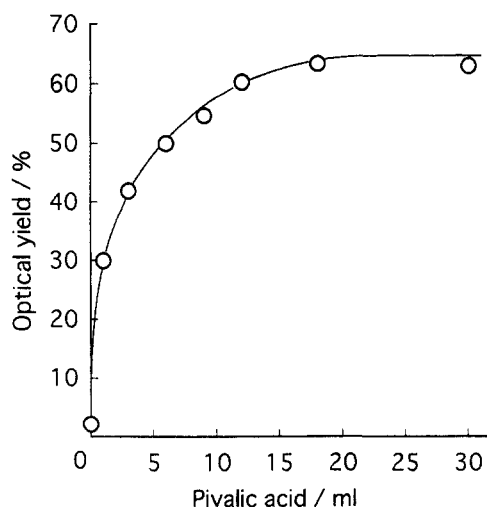


Fig. 6. The relation between the optical yield and the amount of pivalic acid in the hydrogenation of 2-octanone. Catalyst: RNi (1.6 g) modified with 200 ml of aqueous solution containing (*R,R*)-TA (2 g) and NaBr (4 g) at pH 3.2, 100°C, for 1 h; Reaction mixture: 2-octanone (8.2 g), THF (20 ml) and pivalic acid; Hydrogenation temperature: 100°C.

Addition of pivalic acid at about twice the molar concentration of the substrate was necessary for attaining a high optical yield.

2.2.2. Catalyst preparation process

In the catalyst preparation process, the precursor of the catalyst obtains the hydrogenation activity and the surface suitable for e.d. hydrogenation. There are hundreds of methods for obtaining metallic nickel catalysts for the hydrogenation. Among them, only limited types of nickels can be utilized as a base catalyst of MNi. As a result of extensive screening carried out for the e.d. hydrogenation of MAA, the nickel materials suitable for the base of MNi are the following four types: Raney nickel (RNi) [28–30], nickel black obtained by the hydrogenolysis of pure nickel oxide or nickel carbonate (HNi) [31–33], commercial Ni powder [14] or fine nickel powder obtained by the condensation of nickel vapor in vacuum (FNiP) [34], and silica-supported nickel obtained by the hydrogenolysis of nickel carbonate deposited on silica (Ni/SiO₂) [13,35,36]. With the above mentioned types, the catalysts made up of a larger mean crystallite size of nickel tend to give an MNi of higher e.d. ability [33].

Table 2

Hydrogenation of 2-octanone over various kinds of MRNi

Modification condition			e.d.a. (%)	Configuration of the product
Modification reagent	pH	Temperature (°C)		
(<i>R,R</i>)-tartaric acid	3.2	100	38 ^a	<i>S</i>
(<i>S</i>)-malic acid	3.2	100	10 ^a	<i>R</i>
(<i>S</i>)-glyceric acid	3.2	100	0.1 ^b	<i>S</i>
(<i>S</i>)-mandelic acid	3.2	100	0.1	<i>R</i>
(<i>S</i>)-2-hydroxyoctanoic acid	3.2	100	0.1 ^b	<i>R</i>
(<i>S</i>)-2-hydroxy-4-methylvaleric acid	3.2	100	0.5	<i>R</i>
(<i>S</i>)-aspartic acid	5	0	0	—
(<i>S</i>)-glutamic acid	5	0	1 ^a	<i>R</i>
(2 <i>S</i> ,3 <i>R</i>)-threonine	5	0	0.6	<i>S</i>
(<i>S</i>)-leucine	5	0	0.3 ^a	<i>S</i>

^aData from Ref. [34].^bData from Ref. [37].

Reaction mixture: 2-octanone (8.2 g), THF (20 ml) and pivalic acid (10.9 g); Hydrogenation temperature: 100°C.

The same tendency was found in the screening with the e.d. hydrogenation of 2-octanone. In this case, RNi was found to be more favorable for its high hydrogenation activity and e.d. ability. RNi catalyst prepared at a high leaching temperature with low aluminum content showed high e.d.a. in the hydrogenation of 2-alkanones as well as that of MAA.

2.2.3. Modification process

This process is for the formation of an e.d. site on the surface as well as for conditioning the catalyst surface to obtain a suitable surface for e.d. hydrogenation. The types of modification reagent and the conditions of modification are definite factors in controlling the e.d.a. of MNi.

2.2.3.1. Modification reagents. In the early studies of e.d. hydrogenation of MAA, over one hundred modification reagents including hydroxy acids and their derivatives, amino acids and their derivatives, and peptides were examined [22]. As a result, tartaric acid proved to be the best modification reagent showing a high e.d.a. No modification reagent better than TA has been discovered yet in the MAA hydrogenation. For the hydrogenation of 2-octanone, various hydroxy acids and amino acids were examined as the modification reagents (Table 2). A dihydroxy-dicarboxylic acid, such as tartaric acid, gave the highest e.d.a. A monohydroxy-dicarboxylic acid gave a moderate

e.d.a. A dihydroxy-monocarboxylic acid, monohydroxy-monocarboxylic acid and an amino acid gave negligible e.d.a. Tartaric acid was revealed to be the best modification reagent in the hydrogenation of 2-octanone as well as that of MAA.

2.2.3.2. Supplementary modification reagents.

Inorganic salts in the modification solution are known to enhance the e.d.a. of unsupported [28] and supported [38,39] modified Ni catalysts in the MAA hydrogenation. Table 3 shows the effects of the inorganic salts on the e.d.a. of a tartaric acid-modified

Table 3

Enantio-differentiating hydrogenation of 2-octanone over TA-inorganic salt-MRNi

Inorganic salt	Amount (g)	e.d.a. (%)
None	—	29
NaBr	14	51
NaCl	16	47
NaF	1.5	29
NaI	0.002	27
Na ₂ SO ₄	16	31
NaNO ₃	0.2	32
LiBr	4	14
KBr	4	7
NH ₄ Br	4	6

Catalyst: RNi (1.6 g) modified with 200 ml of aqueous solution containing (*R,R*)-TA (2 g) and inorganic salt at pH 3.2, 100°C, for 1 h; Reaction mixture: 2-octanone (8.2 g), THF (20 ml) and hexanoic acid (12.1 g); Hydrogenation temperature: 100°C.

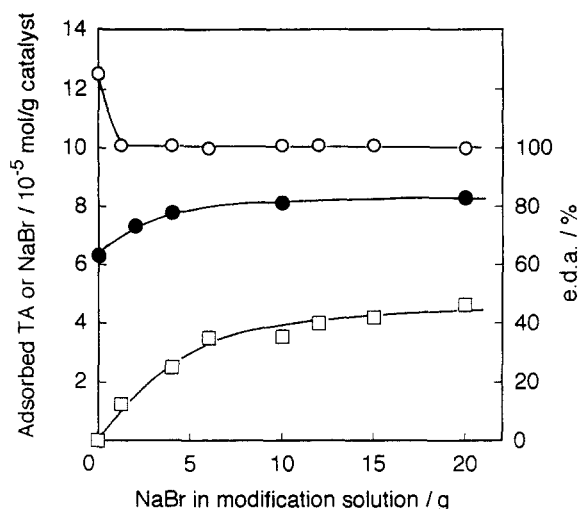


Fig. 7. Effects of the amount of NaBr in the modification solution on the amount of adsorbed TA or Br⁻ and e.d.a. of the catalyst (○: adsorbed TA, □: adsorbed Br⁻, ●: e.d.a.). Catalyst: RNi-A (1 g) (RNi was treated with 1% TA solution at pH 3.2, 100°C for 1 h and after that, the catalyst was treated with 1 M NaOH at 100°C for 1 h) modified with 100 ml of aqueous solution containing (*R,R*)-TA (1 g) and NaBr at pH 5.0, 0°C, for 1 h. The e.d.a. was represented by the optical yield of the hydrogenation of MAA (11.5 ml) in the mixture of methyl propionate (23 ml) and acetic acid (0.2 ml).

RNi (TA-MRNi) catalyst in the 2-octanone hydrogenation. [27] Although the absence of inorganic salts in the modification solution resulted in an e.d.a. of only 29%, addition of NaBr enhanced it to 51%. The addition of sodium salts generally increased the optical yield, but lithium, potassium, or ammonium salts, on the contrary, decreased the optical yield. We proposed that NaBr deactivated the non-enantio-differentiating site to reduce the production of racemic products.

2.2.3.3. Enantio-differentiating site and non-enantio-differentiating site. When the catalyst was modified with the solution containing TA and NaBr, both TA and Br⁻ were adsorbed on the surface of the catalyst. Fig. 7 indicates the effects of the amount of NaBr in the modification solution on the amount of adsorbed TA and Br⁻ and on the e.d.a. of the catalyst in the hydrogenation of MAA [40]. The amount of adsorbed Br⁻ was increased with an increase in the amount of NaBr in the modification solution. The amount of TA steeply decreased with a small addition of NaBr and remained constant with further addition. The value of

e.d.a. of the catalyst was increased with an increase in the amount of adsorbed Br⁻. These results suggest that there are two types of surfaces on the catalyst [41]: (i) the site with affinity for TA where e.d. hydrogenation takes place (enantio-differentiating site (e.d. site)); (ii) the site without affinity for TA where racemic products are produced (non-enantio-differentiating site (non-e.d. site)). In the modification with the solution containing TA and NaBr, Br⁻ would be assumed to be preferentially adsorbed on the non-e.d. site and inhibit the production of the racemate. This would result in enhancement of the e.d.a. of the catalyst. With this hypothesis, the e.d.a. of the catalyst would be represented by the intrinsic e.d.a. of the modification reagent and the ratio of optically active compound produced on the e.d. site (*E*) to the racemate produced on the non-e.d. site (*N*). The value of the e.d.a. is expressed by the following equation:

$$\text{e.d.a. of the catalyst} = iE/(N + E),$$

where *i* represents the intrinsic e.d.a. of the modification reagent.

Fig. 8 shows the effects of the amount of NaBr on e.d.a. in the hydrogenation of 2-octanone over modified RNi [27]. The value of the e.d.a. was increased with an increase in the amount of NaBr. This tendency

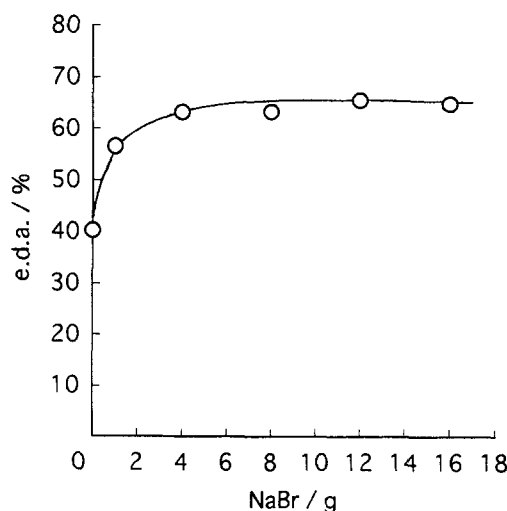


Fig. 8. The effect of the amount of NaBr on e.d.a. in the 2-octanone hydrogenation. Catalyst: RNi (1.6 g) modified with 200 ml of aqueous solution containing (*R,R*)-TA (2 g) and NaBr at pH 3.2, 100°C, for 1 h; Reaction mixture: 2-octanone (8.2 g), THF (20 ml) and pivalic acid (16.3 g); Hydrogenation temperature: 100°C.

is the same as that in the hydrogenation of MAA over modified RNi; therefore, the role of NaBr in the hydrogenation of 2-octanone would be as a blocking reagent for the non-e.d. site as well as in the case of MAA.

The effect of NaBr was also investigated in the hydrogenation over supported-Ni catalyst. Although Bostelarr and Sachtler admitted the e.d.a. enhancement effect of NaBr, they interpreted the effects of NaBr as a change in the intrinsic enantio-selectivity of the product-determining surface complex [42]. Keane et al. [24] demonstrated that the addition of NaBr increased the e.d.a. even when a thiophene-poisoned catalyst was used and that the NaBr could not be simply regarded as a site-blocking agent.

2.2.4. Method of eliminating non-enantio-differentiating site from the catalyst surface

Based on our hypothesis, positive elimination of the non-e.d. site from the surface would enhance the e.d.a. of the catalyst.

2.2.4.1. Chemical removal of non-e.d. site. In order to eliminate the non-e.d. site, it is known that chemical removal of non-e.d. sites by acid treatment is effective. Fig. 9 shows the effects of modification pH on e.d.a.

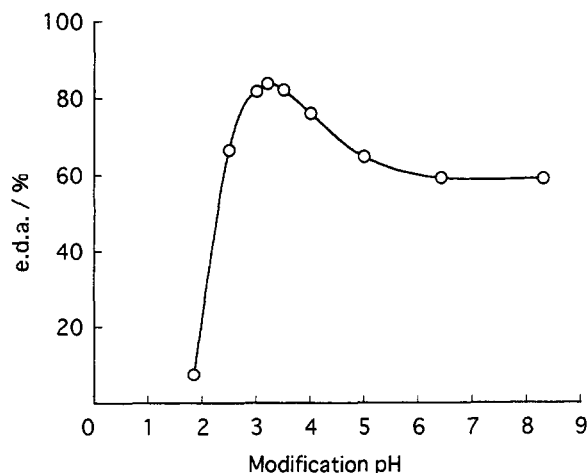


Fig. 9. Effects of the modification pH on e.d.a. in the MAA hydrogenation. Catalyst: RNi (0.8 g) modified with 100 ml of aqueous solution containing (*R,R*)-TA (1 g) and NaBr (10 g) at 100°C for 1 h; Reaction mixture: MAA (11.5 ml), methyl propionate (23 ml) and acetic acid (0.2 ml); Hydrogenation temperature: 100°C.

Table 4

Effects of various modification conditions on e.d.a. of TA–NaBr–MRNi

Modification					e.d.a. (%)
TA/g	NaBr/g	pH	Temp. (°C)	Time (h)	
0.5	4.5	3.2	98	1	84
0.5	4.5	3.2	125	1	89
3.0	60.0	3.2	98	1	87
3.0	54.0	3.2	98	4	90
3.0	165.0	3.1	98	8	91

RNi: 0.42 g. Reaction mixture: MAA (5 g), THF (5 ml) and 1-adamantanecarboxylic acid (0.3 g); Hydrogenation temperature: 100°C.

of the catalyst in the MAA hydrogenation [43]. In the modification of RNi with TA and NaBr, the e.d.a. of the catalyst was varied by the modification pH; 3.2 was the optimal value. Existence of the optimal pH would be interpreted based on the idea that the modification process involves two functions: (i) Adsorption of TA on the catalyst surface. The adsorption species of TA was varied according to the modification pH and the effective species for the e.d. is a mono- and/or di- sodium salt [6]. These species are adsorbed from solutions of pH 3.2 and over. (ii) Conditioning of the surface of the catalyst. TA modification at high temperature is a corrosion process. The value of the pH determines to what extent the surface is corroded. The optimal pH of the modification would be determined by the combination of individual optimal pH of these two functions. Because the acid treatment at high temperature effectively eliminated aluminum and its derivatives from the surface [43], part of the non-e.d. site would be formed by aluminum or its derivatives. Table 4 shows the effects of the conditions of modification on the e.d.a. of TA–NaBr–MRNi. When the catalyst was modified substantially (large amount of TA and NaBr or longer hours), the e.d.a. was enhanced to reach the maximal value of 91% in the MAA hydrogenation [44]. Effect of acid treatment was also observed over the modified supported-Ni [13,36] and modified fine nickel powder [45]. As these catalysts have no aluminum or its derivatives, acid treatment would also remove the non-e.d. site made of disordered or amorphous nickel domain. Hoek et al. proposed that higher modification temperature (acid treatment at high temperature) gave higher optical

yield because high temperature modification solution would effectively pull Ni atoms out of the Ni lattice to produce Ni tartrate complex for making enantio-selective site [36]. Keane et al. demonstrated that the relation between optical yield and modification temperature depended on the initial TA concentration in the modification solution [13]. In the hydrogenation of 2-alkanones over modified RNi [27], the relation between modification pH and e.d.a. of the catalyst has the same tendency as in the MAA hydrogenation. The same area would function as the non-e.d. site in the 2-alkanone hydrogenation.

2.2.4.2. Physical removal of non-e.d. site. Recently, we developed another method of eliminating the non-e.d. site during the preparation process of TA–NaBr–MRNi. The aluminum-enriched disordered nickel domain, which would offer a non-e.d. site through modification, was found to be removed by ultrasonic irradiation prior to the modification process [46]. Ultrasonication of RNi enhanced the e.d.a. from 80% to 86% in the MAA hydrogenation. Hydrogenation activity was also increased. The effect of the treatment of ultrasonic irradiation on supported-Ni catalyst and the hydrogenation of 2-alkanones over MNi prepared by the ultrasonicated RNi have not been investigated yet.

2.2.5. Hydrogenation process

In the hydrogenation process, additives in the reaction system greatly influenced the optical yield as already mentioned in Section 2.2.1. Other than that, hydrogenation temperature was the key factor in attaining a high optical yield in the 2-alkanone hydrogenations. In the hydrogenation over TA–NaBr–MRNi, the effects of the hydrogenation temperature on optical yield were revealed to depend on the types of substrates. In the hydrogenation of MAA, changing the reaction temperature (60–120°C) in high-pressure liquid-phase hydrogenation did not affect the optical yield (Fig. 10) [47]. However, in the hydrogenation of 2-octanone, it was revealed that the optical yield greatly depended on the hydrogenation temperature. The optimal temperature was about 50–60°C and the optical yield reached 80% (Fig. 11) [48].

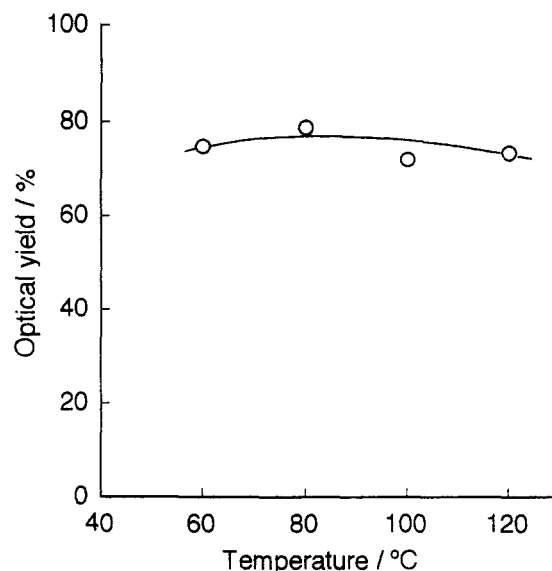


Fig. 10. Effects of hydrogenation temperature on optical yield in the hydrogenation of MAA. Catalyst: RNi (1.6 g) modified with 200 ml of aqueous solution containing (*R,R*)-TA (2 g) and NaBr (12 g) at pH 3.2, 100°C, for 1 h; Reaction mixture: MAA (10.8 g) and THF (20 ml).

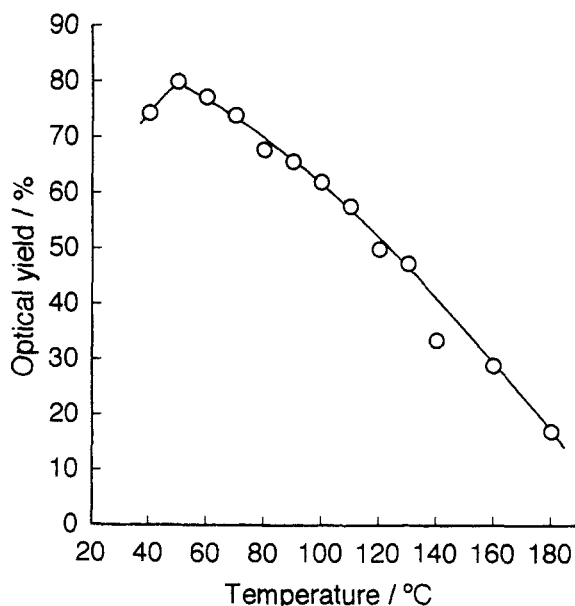


Fig. 11. Effects of hydrogenation temperature on optical yield in the hydrogenation of 2-octanone. Catalyst: RNi (1.6 g) modified with 200 ml of aqueous solution containing (*R,R*)-TA (2 g) and NaBr (12 g) at pH 3.2, 100°C, for 1 h; Reaction mixture: 2-octanone (8.2 g), THF (20 ml) and pivalic acid (16.3 g).

Table 5
Enantio-differentiating hydrogenation of 2-alkanones over (R,R)-TA–NaBr–MRNi

Substrate	Modification and hydrogenation condition	Optical yield (%)			Configuration of the product
		100°C ^a	60°C ^a	50°C ^a	
CH ₃ –CO–CH ₂ CH ₃	A	49	63	—	S
CH ₃ –CO–(CH ₂) ₃ CH ₃	A	66	80	—	S
CH ₃ –CO–(CH ₂) ₄ CH ₃	A	66	71	—	S
CH ₃ –CO–(CH ₂) ₅ CH ₃	A	66	80	—	S
CH ₃ –CO–(CH ₂) ₇ CH ₃	A	58	76	—	S
CH ₃ –CO–(CH ₂) ₁₀ CH ₃	A	65	75	—	S
CH ₃ –CO–CH(CH ₃) ₂	A	63	85 ^b	—	S
CH ₃ –CO–C(CH ₃) ₃	A	74	—	—	S
CH ₃ –CO–CH ₂ CH ₃	B	—	—	72	S

^aHydrogenation temperature

^bData from Ref. [50].

A: RNi prepared from 1.9 g of RNi alloy, TA 1 g and NaBr 6 g in 100 ml of H₂O, pH 3.2, 100°C, 1 h; Substrate: 5 ml, pivalic acid: 8.1 g, THF: 10 ml; B: RNi prepared from 10 g of RNi alloy, TA 4 g and NaBr 61.4 g in 400 ml of H₂O, pH 3.2, 100°C, 1 h; Substrate: 5 ml, pivalic acid: 18 g, THF: 20 ml.

2.3. Enantio-differentiating hydrogenation of various 2-alkanones

Table 5 shows the e.d. hydrogenation of various 2-alkanones using the optimal conditions for 2-octanone (Condition A) [34]. Around 80% optical yield was attained in the various 2-alkanone hydrogenations at 60°C. The maximum optical yield of 85% was achieved in the hydrogenation of 3,3-dimethyl-2-butanone. On all substrates, hydrogenations at lower temperature (60°C) gave a higher optical yield compared with those at 100°C. Substrates having α -branching of alkyl group(s) tended to give a higher optical yield than straight chain substrates. When each condition (catalyst preparation and hydrogenation conditions) was optimized for the hydrogenation of 2-butanone (Condition B), the optical yield reached 72% which corresponds to a 10% increment in optical yield compared with the standard conditions for 2-octanone [49]. This means that this catalyst can differentiate between the methyl and ethyl groups to a high degree.

As described in this chapter, we succeeded in providing a TA–MNi catalyst with the ability to differentiate between the two alkyl groups in 2-alkanones through a detailed investigation of preparation conditions of the catalysts and hydrogenation conditions.

2.4. Preparation of optically pure 2-alkanols by preferential recrystallization

Although optical yields of around 80% were attained in the e.d. hydrogenation of 2-alkanones, the present method was not satisfactory for the practical preparation of optically pure 2-alkanols. To utilize this convenient TA–NaBr–MRNi system for obtaining optically pure 2-alkanols, optical enrichment of the reaction products by preferential recrystallization was investigated. Hydrogenation products were converted to crystalline esters with phthalic or 3,5-dinitrobenzoic acid, and the resulting esters were subjected to optical enrichment by recrystallization (Table 6) [34]. Optically pure crystals were obtained by three or four successive recrystallizations. The yields of optically pure 2-alkanols based on 2-alkanones were 21–56%. A convenient procedure for obtaining optically pure 2-alkanols was thus achieved by the combination of e.d. hydrogenation of 2-alkanones and optical enrichment of the hydrogenation products by recrystallization of the crystalline derivatives.

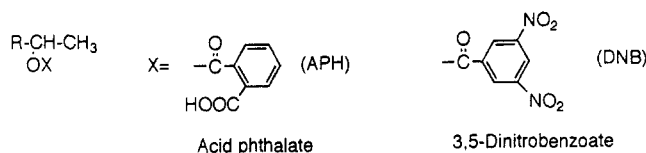
2.5. Investigation of the mechanism of enantio-differentiating hydrogenation of 2-alkanones

Considering the fact that a large amount of carboxylic acid added to the reaction system is essential

Table 6
Preparation of optically pure 2-alkanols from the hydrogenation products

Hydrogenation product (Optical purity (%))	Crystalline derivative, X	Solvent for recrystallization	Optically pure crystals, $[\alpha]_D^{20}$	Optically pure (S)-2-alkanol	
				$[\alpha]_D^{20}$	Yield/% ^a
2-Hexanol (80)	DNB	Methanol	+35.8 (c=5.1, CHCl ₃)	+12.1 (neat)	23
2-Heptanol (71)	APH	Hexane	+48.7 (c=2.7, EtOH)	+10.5 (neat)	21
2-Octanol (77)	APH	Acetonitrile	+47.0 (c=6.0, EtOH)	+9.8 (neat)	37
2-Decanol (76)	DNB	Ethanol	+32.6 (c=4.6, CHCl ₃)	+8.7 (neat)	28
2-Tridecanol (75)	DNB	Ethanol	+29.0 (c=5.1, CHCl ₃)	+8.9 (c=5, C ₆ H ₆)	56

Crystalline derivatives:



^aOverall chemical yield from 2-alkanone to optically pure (S)-2-alkanol.

for attaining high optical yield, investigation of the role of carboxylic acid is the key issue in clarifying the mechanism of the e.d. process of 2-alkanones.

2.5.1. Interaction between substrate, modification reagent and carboxylic acid added to the reaction system

Table 7 shows the relation between the structure of the modification reagents and optical yield in the hydrogenation of 2-octanone [37,50]. When hydrogenation was carried out without pivalic acid, a low optical yield was attained irrespective of the structure of the modification reagents. When pivalic acid was added to the reaction system, the optical yield varied according to the structure of the modification reagents. A detailed study of the structure of the modification reagent should reveal the indispensable functional groups in the modification reagent and the means of mutual interaction between modification reagent and pivalic acid. Modification reagents leading to the highest optical yield are those that have a carbon skeleton of tartaric acid with two carboxyl groups and two hydroxyl groups. Substitution of one or two of the hydroxyl or carboxyl groups decreased the optical yield. These results demonstrate that tartaric acid on the surface would fix pivalic acid by hydrogen bonds between the carboxyl and/or

hydroxyl groups in tartaric acid and the carboxyl group in pivalic acid. Because pivaloyl tartaric acid showed a low optical yield, the combination of the pivaloyl group with the hydroxyl group in tartaric acid by a covalent bond is not suitable for attaining a high optical yield. Pivalic acid should interact with a hydroxyl group and a carboxyl group in tartaric acid through non-covalent bonds. The formation of the pivalic acid–tartaric acid complex on the catalyst was essential to improve the intrinsic e.d. ability of tartaric acid.

The hydrogenation of substrates with various structures was carried out under the same reaction conditions (Table 8) [37,50]. Almost the same optical yields were attained for a series of straight chain 2-alkanones. The effects of the branched methyl group of substrates on the optical yield depend on the position of the branching. With branching at the α , β , or γ -positions of the carbonyl group, the optical yield increased by 25%, 10% and 10%, respectively, compared with the corresponding straight chain substrates. However, branching at the δ -position resulted in no increase in optical yield. These results indicate that steric interaction of the *t*-butyl group in the fixed pivalic acid can affect the neighboring parts of the carbonyl group (C_α , C_β and C_γ) in the substrate. The δ -position of the substrate would have no interaction with the fixed pivalic acid.

Table 7

Effect of the structure of modification reagent on optical yield in the hydrogenation of 2-octanone.

Modification reagent	Optical yield (%) (configuration)		Modification reagent	Optical yield (%) (configuration)	
	Absence of PA*	Presence of PA*		Absence of PA*	Presence of PA*
$\begin{array}{c} \text{COOH} \\ \\ \text{H}-\text{C}-\text{OH} \\ \\ \text{HO}-\text{C}-\text{H} \\ \\ \text{COOH} \end{array}$	3 (S)	38 (S)	$\begin{array}{c} \text{COOH} \\ \\ \text{H}-\text{C}-\text{O}-\text{C}-\text{C}(\text{CH}_3)_3 \\ \quad \parallel \\ \text{HO}-\text{C}-\text{H} \quad \text{O} \\ \\ \text{COOH} \end{array}$	2 (S)	0.8 (S)
(R,R)-tartaric acid			O-pivaloyl-(R,R)-tartaric acid		
$\begin{array}{c} \text{COOH} \\ \\ \text{H}-\text{C}-\text{OH} \\ \\ \text{HO}-\text{C}-\text{CH}_3 \\ \\ \text{COOH} \end{array}$	0.3 (S)	30 (S)	$\begin{array}{c} \text{COOH} \\ \\ \text{H}-\text{C}-\text{OCH}_3 \\ \\ \text{H}_3\text{CO}-\text{C}-\text{H} \\ \\ \text{COOH} \end{array}$	1 (S)	2 (S)
(R*,R*)(+)-2-methyltartaric acid			(R,R)-2,3-dimethoxysuccinic acid		
$\begin{array}{c} \text{COOH} \\ \\ \text{HO}-\text{C}-\text{H} \\ \\ \text{H}-\text{C}-\text{H} \\ \\ \text{COOH} \end{array}$	1 (R)	10 (R)	$\begin{array}{c} \text{COOH} \\ \\ \text{HO}-\text{C}-\text{H} \\ \\ \text{H}-\text{C}-\text{OH} \\ \\ \text{H} \end{array}$	0.2 (S)	0.1 (S)
(S)-malic acid			(S)-glyceric acid		
$\begin{array}{c} \text{COOH} \\ \\ \text{H}-\text{C}-\text{OCH}_3 \\ \\ \text{HO}-\text{C}-\text{H} \\ \\ \text{COOH} \end{array}$	2 (S)	8 (S)	$\begin{array}{c} \text{COOH} \\ \\ \text{HO}-\text{C}-\text{H} \\ \\ (\text{CH}_2)_5 \\ \\ \text{CH}_3 \end{array}$	1 (R)	0.1 (R)
(R,R)-3-methoxymalic acid			(S)-2-hydroxyoctanoic acid		

Catalyst: RNi (1.6 g) modified with 200 ml of aqueous solution containing modification reagent (0.013 mol) at pH 3.2, 100°C, for 1 h; Reaction mixture: 2-octanone (8 g), THF (20 ml) and pivalic acid (PA 0 or 10.8 g); Hydrogenation temperature: 100°C.

2.5.2. Mode of enantio-differentiation

The mode of enantio-differentiation in the hydrogenation of 2-alkanones can be visualized based on the interaction among (R,R)-tartaric acid, pivalic acid and the substrate (Fig. 12). Orientation of tartaric acid and 2-alkanone on the surface follows our earlier model for the hydrogenation of MAA [51]. The conformation of tartaric acid is based on the X-ray and neutron diffraction analyses of the metal salts of tartaric acid [52,53] and the optimized structure obtained from the calculation at semiempirical level [54]. In this stereochemical model, one of the hydroxyl groups of tartaric acid comes close to the catalyst surface (site 1) and the second one is somewhat remote from the surface

(site 2). Tartaric acid forms an associative complex with pivalic acid through a hydrogen bond (site 2). The carbonyl group of 2-alkanone is fixed at site 1 by a hydrogen bond under the steric effect between the alkyl group of the substrate and the *t*-butyl group of pivalic acid. Because a large amount of pivalic acid is present in the system, pivalic acid exists as a homo dimer, hetero dimer with tartaric acid, and also exists around the hydrophilic groups in tartaric acid. Among all these interactions, the important linkages for the effective enantio-differentiation are those described in Fig. 12. The tartaric acid–pivalic acid linkage in Fig. 12 is expected to form only when a significant amount of pivalic acid is added to the reaction system.

Table 8
Effects of the substrate structures on optical yield

Substrate $\begin{array}{c} \text{(R-C-CH}_3\text{)} \\ \parallel \\ \text{O} \end{array}$	Optical yield (%)	Substrate $\begin{array}{c} \text{(R-C-CH}_3\text{)} \\ \parallel \\ \text{O} \end{array}$	Optical yield (%)
$\text{CH}_3\text{CH}_2\text{-}$	59	$\begin{array}{c} \text{CH}_3\text{-CH-} \\ \\ \text{CH}_3 \end{array}$	85
$\text{CH}_3\text{CH}_2\text{CH}_2\text{-}$	64	$\begin{array}{c} \text{CH}_3\text{-CH-CH}_2\text{-} \\ \\ \text{CH}_3 \end{array}$	75
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{-}$	65	$\begin{array}{c} \text{CH}_3\text{-CH-CH}_2\text{CH}_2\text{-} \\ \\ \text{CH}_3 \end{array}$	77
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{-}$	67	$\begin{array}{c} \text{CH}_3\text{-CH-CH}_2\text{CH}_2\text{CH}_2\text{-} \\ \\ \text{CH}_3 \end{array}$	66

Catalyst: RNi (1.6 g) modified with 200 ml of aqueous solution containing (*R,R*)-TA (2 g) and NaBr (12 g) at pH 3.2, 100°C, for 1 h; Reaction mixture: 2-alkanone (8 g), THF (20 ml) and pivalic acid (16.2 g); Hydrogenation temperature: 60°C.

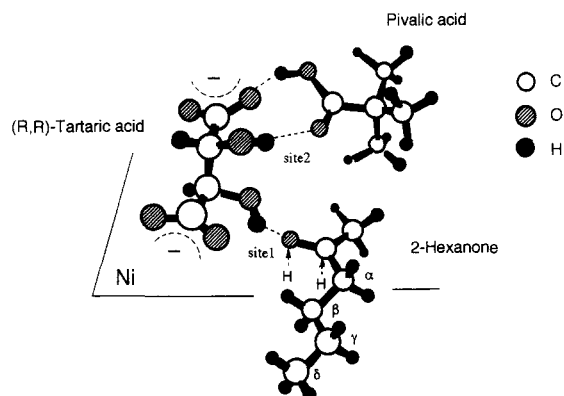


Fig. 12. Mode of enantio-differentiation of the hydrogenation of 2-hexanone.

This is why a large amount of pivalic acid is required to attain a high optical yield. The tartaric acid–pivalic acid complex would efficiently recognize the structure of the C–CO–C α –C β –C γ site in 2-alkanone by expelling the bulky alkyl group of the substrate to the opposite side of pivalic acid. Consequently, a *re*-face attack of hydrogen is carried out to give the (*S*)-alcohol in excess. Reverse orientation in which 2-alkanone is fixed at site 2 and pivalic acid forms a complex with TA at site 1 could be possible. However, in this case, hydrogenation would not occur because the carbonyl group is so far from the catalyst surface.

Although there has been no research except by our group on the mode of e.d. hydrogenation of 2-alkanones over MNi, several researchers have proposed their mechanisms for the e.d. hydrogenation of MAA over TA-modified metals. Yasumori proposed an alternative interaction between MAA and TA adsorbed on the catalyst surface [55]. Klabunovskii et al. also proposed an interaction between acetylacetone and TA on the metal atoms in the edge or corner positions in a Ni/Cu alloy catalyst [11]. Hoek and Sachter proposed that the Na–Ni–tartrate complex was the enantio-selective site, but they did not present the structure of this complex [36]. Recently, Keane and Webb demonstrated that nickel tartrate itself had both enantio-selectivity and hydrogenation activity and that metallic nickel was not an essential component of the enantio-selective catalyst [56].

2.6. Effects of sodium ions in the system

Because the reaction mixture of the 2-alkanone hydrogenation contains a large amount of pivalic acid, the surface component would be readily removed during the hydrogenation. It was revealed that especially sodium ions on the catalyst surface were readily removed by the treatment with a mixture of 2-alkanone, THF and pivalic acid for 1 h (original amount of 2.8×10^{-5} mol/g cat was reduced to 0.7×10^{-5} mol/g

Table 9
Effects of added sodium ions on optical yields in the hydrogenation of 2-alkanones over MRNi-T

Catalyst ^a	Substrate	Sodium pivalate (mg)	Optical yield (%)
A	2-Octanone	0	9
		0.5	21
		3	61
		20	60
B	3-Methyl-2-butanone	0	3
		20	68
C	2-Decanone	0	13
		20	63

^a MRNi-T was prepared by the treatment of TA-NaBr-MRNi with the mixture of 2-octanone (A), 3-methyl-2-butanone (B), or 2-decanone (C) and pivalic acid in THF; TA-NaBr-MRNi: RNi (1.6 g) was modified with 200 ml of aqueous solution containing (*R,R*)-TA (2 g) and NaBr (12 g) at pH 3.2, 100°C, for 1 h; Reaction mixture: 2-alkanone (8 g), THF (20 ml) and pivalic acid (16.3 g); Hydrogenation temperature: 100°C.

cat; the catalyst with very little Na⁺ after such treatment was called TA-NaBr-MRNi-T [57]. When various 2-alkanone hydrogenations were carried out over TA-NaBr-MRNi-T with a freshly prepared reaction mixture, a low optical yield below 10% was

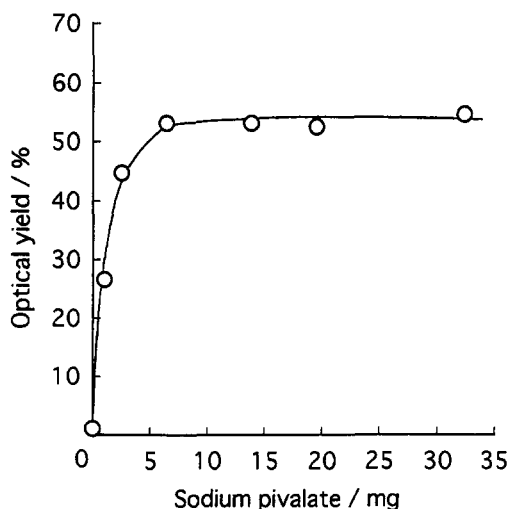


Fig. 13. The effect of the amount of sodium pivalate in the reaction system on optical yield over TA-modified fine nickel powder. Catalyst: fine nickel powder (1.6 g) modified with 200 ml of aqueous solution containing (*R,R*)-TA (16 mg) at 0°C for 1 h; Reaction mixture: 2-octanone (6 g), THF (16 ml), pivalic acid (19.5 g) and sodium pivalate; Hydrogenation temperature: 100°C.

obtained. However, when Na⁺ was added as sodium pivalate to the reaction media, the intrinsic e.d.a. of the catalyst was recovered (Table 9) [57]. Fig. 13 shows the relationship between the amount of sodium pivalate and optical yield over the TA-modified fine nickel powder [34]. Without the addition of sodium pivalate, a negligible optical yield was obtained. However, a very small amount of sodium pivalate greatly increased the optical yield. Considering the fact that this catalyst prepared from fine nickel powder has no Na⁺ on the surface, sodium ion is another essential factor for attaining a high optical yield in the 2-alkanone hydrogenations. From a practical point of view, a sodium-free TA-modified nickel catalyst requires sodium ions in the system, but a conventional TA-NaBr-MRNi (with about 2.8×10^{-5} mol of Na⁺/g cat) originally has adequate Na⁺ in the system and no further addition of Na⁺ is needed.

3. Extension of applicable substrates for modified nickel catalyst

3.1. Enantio-differentiating hydrogenation of δ -, ϵ -ketoesters

Because an optical yield over 90% was achieved in the e.d. hydrogenation of prochiral ketones with the functional group at the β -position of the carbonyl group and around 80% in the 2-alkanone hydrogenations, we then attempted the extension of substrate specificity (meaning specificity for a substrate giving a high optical yield) of this catalyst. The hydrogenation of δ -ketoesters under the conventional MAA hydrogenation conditions resulted in production of racemic alcohols [25]. However, when δ -ketoesters were regarded as the analogs of 2-alkanones (i.e., pivalic acid was added to the reaction system), around 60% optical yield was attained [58]. ϵ -Ketoesters were also hydrogenated to around 60% optical yield in the presence of pivalic acid [59].

3.2. Enantio-differentiating hydrogenation of 3-alkanones

In the hydrogenation of 3-alkanones, the catalyst should differentiate a smaller difference between the two carbon chains attached to the carbonyl group than

that in the 2-alkanones. It is expected that TA–NaBr–MnI would be utilized with various kinds of substrates when it gains greater ability for differentiating alkyl groups. For the hydrogenation of 3-alkanones, TA–NaBr–MnI prepared from fine nickel powder was much better than conventional TA–NaBr–MRNi with respect to reproducibility and e.d.a. [60]. Furthermore, the effect of hydrogenation temperature on optical yield was different from that in the case of 2-alkanones. The optimal hydrogenation temperature was about 100°C in the hydrogenation of 3-alkanones [60] but about 50–60°C in that of 2-alkanones. The highest optical yield attained now in the hydrogenation of 3-octanone is 44% [61]. The rather low optical yield of about 40% supports our estimate that the differentiation between ethyl and other alkyl groups is much more difficult than that between methyl and other alkyl groups. In the hydrogenation of 3-alkanones, further detailed investigations are required for attaining high optical yields comparable to that in the hydrogenation of 2-alkanones.

4. Summary

The parameters affecting the performance of an e.d. catalyst (catalytic activity and e.d.a.) are considerable in number and too many to be readily optimized. However, once the parameters are optimized, heterogeneous catalytic systems are preferable to homogeneous or enzymatic systems because of the easy handling and separation, which are suitable for industrial application. Attaining a high optical yield in the hydrogenation of alkanones, which have one interaction site with a modification reagent on the catalyst surface, was achieved by a fully detailed investigation of catalyst preparation variables and hydrogenation variables. TA–NaBr–MnI should be a promising catalyst for the various substrates, when it can be optimized for the individual substrate.

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