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Enantio-differentiating hydrogenation of methyl acetoacetate over modified Raney nickel catalysts prepared by two-step modifications

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Two-step modifications of the Raney nickel were examined for the enantio-differentiating hydrogenation of methyl acetoacetate. Among the two-step modifications attempted in this study, the combination of 'pre-modification with disodium tartrate and NaBr in water' and '*in-situ* modification with tartaric acid' resulted in the highest optical yield (84%). This modification process is a greener process than the conventional one carried out under weakly acidic conditions, because this process generated almost no Ni^{2+} ions. The pre-modification with the tartrate and NaBr preferentially eliminated Al^{3+} from the Raney nickel surface.

KEY WORDS: tartaric acid-sodium bromide-modified Raney nickel; *in-situ* modification; pre-modification; two-step modification; enantio-differentiating hydrogenation.

1. Introduction

The study of the enantio-differentiating reaction using a homogeneous or heterogeneous catalyst is one of the most active areas in fine chemical synthesis [1,2]. Some homogeneous enantio-differentiating catalysts with the BINAP ligand(s) provide significant results for the enantiomer excess (e.e.) of products [3]. In addition, the investigation of heterogenized catalysts prepared from homogeneous enantio-differentiating catalysts has been attracting increasing attention as advances in clean technology and green chemistry [4]. Generally, heterogeneous enantio-differentiating catalysts possess several advantages over homogeneous ones, such as easy separation, easy regeneration, and long service life. Heterogeneous enantio-differentiating catalysts are expected to play an increasing important role in the development of greener processes and products. Nevertheless, the successful uses of heterogeneous catalysts for the production of enantiomerically pure compounds are rare. Among the enantio-differentiating heterogeneous catalysts, Ni catalysts modified with tartaric acid and sodium bromide (TA–NaBr–MNi) and cinchona-modified Pt or Pd catalysts have already reached the industrial applicable level [1,5,6].

The conventional TA–NaBr–MNi catalysts can be easily prepared by immersion of the activated Ni powder in an aqueous solution of TA and NaBr under weakly acidic and high-temperature conditions (pre-modification method) [6,7]. During the pre-modification process, the nickel powder is partially oxidized to Ni^{2+} ions and the ions are then dissolved into the modification solution [7]. The nickel ions possess some toxicity to people or the environment. Thus, the waste solution containing Ni^{2+} can cause environmental problems when this catalyst is used on an industrial scale. The prevention of toxic waste generation is one of the most important subjects of green chemistry [8].

Some novel modification methods for Ni catalysts were developed to prevent the formation of Ni^{2+} by us [9,10]. First, we devised the *in-situ* modification method, in which small amounts of TA and NaBr are directly added to the reaction mixture to modify the Ni catalyst before the hydrogenation of a substrate. The Ni^{2+} generated by the *in-situ* modification was negligible. The *in-situ* modification of the reduced Ni catalyst with TA and NaBr results in a greater than 80% e.e. during the hydrogenation of methyl acetoacetate. The e.e. values attained by the *in-situ* modification of the reduced Ni or fine Ni powder are similar to those attained by the pre-modified reduced Ni, and the enantio-differentiating ability (e.d.a.) of the *in-situ* modified reduced Ni is durable during repeated use of the recovered catalyst [10]. Moreover, we reported that the pre-modification of the reduced nickel catalyst in a tetrahydrofuran (THF) solution of tartaric acid and NaBr under high pressure hydrogen resulted in a negligible Ni^{2+} formation and the resulting pre-modified catalyst exhibited a high e.d.a. for the hydrogenation of methyl acetoacetate (e.e.: close to 90%) [11].

The Raney nickel (RNi) is widely used for the pre-modification with TA and NaBr due to the easy

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preparation from a Ni/Al alloy, the high hydrogenation activity, and the high e.d.a. of the pre-modified RNi (80–90% e.e. in the hydrogenation of methyl acetoacetate) [5,6,12]. However, when the best *in-situ* modification variables for the reduced Ni were employed, the resulting *in-situ* modified RNi exhibited only a low e.d.a. (36% e.e.) [9]. We have been continuing our studies to develop a novel modification method for the RNi, and recently succeeded in developing some novel modification methods for this catalyst. The methods cause practically no oxidation of Ni^0 to Ni^{2+} and significantly improve the e.d.a. of the *in-situ* modified RNi. In this paper, we describe our approach leading to the novel modification methods for the RNi.

2. Experimental

The GLC measurements of the hydrogenated products were carried out using a Shimadzu GC 15A (CBP-20, 25 m, 373 K). The optical rotations were measured by a Perkin-Elmer 241 polarimeter.

2.1. Combination of pre-modification and in-situ-modification

2.1.1. Enantio-differentiating hydrogenation over MRNi-PI(1)

MRNi-PI(1): A Ni–Al alloy (3.0 g, Ni:Al = 41:59, Kawaken Fine Chemical, Saitama, Japan) was leached with 100 cm^3 of a 12% NaOH aqueous solution at 371 K for 1 h. The catalyst was washed 15 times with 30 cm^3 portions of deionized water, and then a 25-cm^3 portion of methanol. The catalyst was pre-modified using a 25-cm^3 aliquot of methanol containing NaBr (the amount of NaBr is stated in the text). The suspension was then allowed to stand at room temperature for 20 min. The resulting NaBr-pre-modified RNi was washed with a 15-cm^3 portion of THF, and placed in a 30-cm^3 autoclave with a mixture of methyl acetoacetate (5.0 g), THF (5.0 cm^3) and tartaric acid (TA, the amount of TA is stated in the text). The methyl acetoacetate was hydrogenated at 373 K at the initial hydrogen pressure of 10 MPa. The hydrogenation product, methyl 3-hydroxybutyrate, was collected by a single distillation in vacuo. The hydrogenation yields were evaluated by GLC. The e.d.a. value is expressed by the optical purity of the produced methyl 3-hydroxybutyrate. The specific optical rotation of the optically pure (*R*)-methyl 3-hydroxybutyrate is −22.95° (Na D line, at 293 K, neat) [6].

2.1.2. Enantio-differentiating hydrogenation over MRNi-PI(2)

The RNi was prepared according to the procedure mentioned in section 2.1.1. The catalyst was washed 15 times with 30 cm^3 portions of deionized water. The RNi was pre-modified with an aqueous solution containing sodium tartrate (the amount is stated in the text) and NaBr (the amount is stated in the text) at 371 K (the modification time is stated in the text). After washing with a 20-cm^3 portion of deionized water, a 20-cm^3 portion of methanol and a 20-cm^3 portion of THF, the catalyst was placed in a 30-cm^3 autoclave with a mixture of methyl acetoacetate (5.0 g), TA (the amount is stated in the text), and THF (10 cm^3). The hydrogenation of methyl acetoacetate and evaluation of the e.d.a. were carried out according to the procedure mentioned above.

2.2. Combination of NaBr-pre-modification in methanol and TA-pre-modification in THF: Enantio-differentiating hydrogenation over MRNi-PP

The RNi was prepared according to the procedure mentioned in 2.1.1. The catalyst was washed 15 times with 30 cm^3 portions of deionized water, and then a 25-cm^3 portion of a 0.4% (g/ml) NaBr-methanol solution. The catalyst was pre-modified using a 10-cm^3 portion of a 0.4% (g/ml) NaBr-methanol solution under 10 MPa hydrogen (the temperature and the time for the modification are stated in the text). The resulting NaBr-pre-modified RNi was washed with two 10-cm^3 portions of THF, and pre-modified with TA using a mixture of THF (7.0 cm^3) and TA (0.15 g) under 10 MPa hydrogen (the temperature: 373 K, the time: 1 h). The pre-modification with NaBr or TA was carried out in a 30-cm^3 autoclave. After the pre-modification with TA, methyl acetoacetate was added to the mixture of the MRNi-PP, THF, and TA. The hydrogenation of methyl acetoacetate and evaluation of the e.d.a. were carried out according to the procedure mentioned in 2.1.1.

2.3. Determination of Ni^{2+} and Al^{3+} in the modification solution

The amounts of Ni^{2+} and Al^{3+}, dissolved in the pre-modification solutions during the preparation of MRNi-PI and MRNi-PP, were determined by the EDTA titration method [7].

3. Results and discussion

3.1. Combination of pre-modification and in-situ-modification

When the RNi was *in-situ* modified with TA and NaBr, the resulting MRNi exhibited only a less than 40% e.d.a. under the optimal modification conditions for the reduced Ni and the fine Ni powder [9]. It will be necessary to optimize the modification variables to obtain the *in-situ* modified RNi with an excellent e.d.a. For the *in-situ* modification with TA and NaBr, the NaBr was dissolved in a small amount of H_2O, because NaBr was almost totally insoluble in the reaction media, THF. It can be assumed that the H_2O in the reaction media decreases the e.d.a. of the modified catalyst because the substrate, methyl acetoacetate, forms hydrogen bond(s) with the H_2O instead of the TA adsorbed on the catalyst surface. The formation of hydrogen bonds between the substrate and TA has been proposed to be indispensable for the efficient enantio-differentiation over TA-NaBr-MRNi [6]. In the present study, we carried out the *in-situ*-modification using only TA. We pre-modified the RNi with 'NaBr in methanol' or 'disodium tartrate and NaBr in water', prior to the *in-situ*-modification with TA. The catalyst prepared by the combination of the pre-modification and *in-situ*-modification is abbreviated MRNi-PI.

3.1.1. *Enantio-differentiating hydrogenation over MRNi-PI(1)*

The RNi was pre-modified with NaBr in methanol, and then *in-situ* modified with TA in the reaction media. The resulting catalyst is termed MRNi-PI(1). For this type of catalyst, the pre-modification was carried out at room temperature. Figure 1 shows the relation between the amount of NaBr in the methanol and the e.d.a. of the catalyst. The e.d.a. of MRNi-PI(1) was less than 30% when the RNi was pre-modified with 0.05 g of NaBr. More than 0.1 g of NaBr in the modification solution (25 cm^3) was necessary to attain the maximum e.d.a. (around 50%). Figure 2 shows the relation between the amount of TA for the *in-situ* modification and the e.d.a. of the resulting MRNi-PI(1). The NaBr pre-modified RNi for this experiment was prepared using 0.1 g of NaBr in 25 cm^3 of methanol. The *in-situ* modification using 0.3 g of TA resulted in the maximum e.d.a. The modification with < 0.3 g of TA would provide the surface area where neither TA nor NaBr is adsorbed. This type of area (non-enantio-differentiating sites) produces a racemic product, and the e.d.a. decreases with a decrease in the TA adsorption. However, the excess TA on the catalyst surface would also decrease the e.d.a., because it would block the smooth progress of the hydrogenation of methyl acetoacetate to the optically active methyl 3-hydroxybutyrate over the TA-adsorbed area (enantio-differentiating sites). It was found that the combination of 0.1 g NaBr for the pre-modification and 0.3 g TA for the *in-situ* modification was optimal for the preparation of MRNi-PI(1).

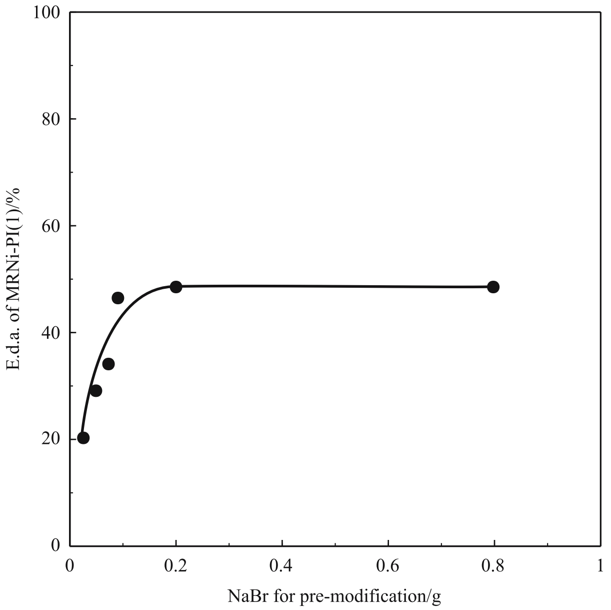

Figure 1. Relationship between the amount of NaBr in pre-modification solution and e.d.a. of MRNi-PI(1). Amount of TA needed for the *in-situ*-modification: 0.3 g.

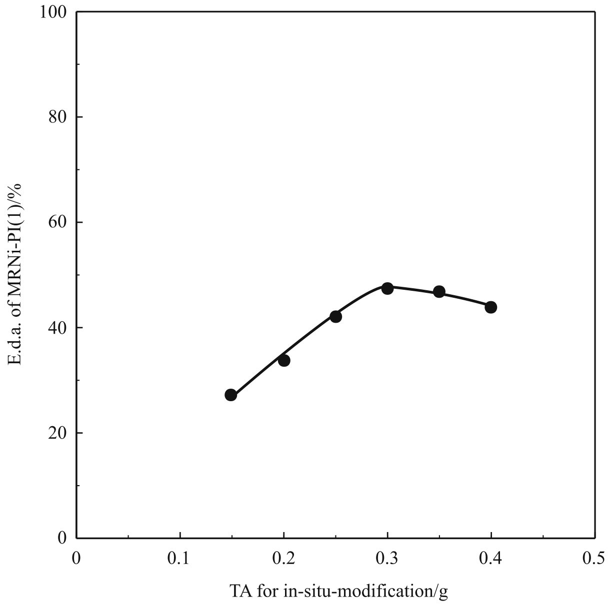

Figure 2. Relationship between amount of TA for *in-situ*-modification and e.d.a. of MRNi-PI(2). Amount of NaBr in the pre-modification solution: 0.1 g.

3.1.2. *Enantio-differentiating hydrogenation over MRNi-PI(2)*

The RNi was pre-modified with disodium tartrate and NaBr in an aqueous solution, and then *in-situ* modified with TA in the reaction media. This is termed MRNi-PI(2). The pre-modification was carried out at 371 K. Table 1 shows the relation between the amounts of disodium tartrate dihydrate and NaBr dissolved in the pre-modification solution and the e.d.a. of the resulting MRNi-PI(2). The pre-modification with disodium tartrate and NaBr in an aqueous solution or the *in-situ*-modification with TA alone was not sufficient for the preparation of MRNi with a > 70% e.d.a. (entries 1 and 2). The combination of the pre-modification and the *in-situ*-modification resulted in a > 70% e.d.a. (entry 3). In order to attain around an 80% e.d.a., large amounts of disodium tartrate and NaBr were required for the pre-modification. The highest e.d.a. of MRNi-PI(2) was similar to that for the conventional TA-NaBr-MRNi.

Table 1
Enantio-differentiating hydrogenation of methyl acetoacetate over MRNi-PI(2)

Entry	Pre-modification				*In-situ*-modification	MRNi-PI(2)
	Na_2 tartrate●$2H_2O$/g	NaBr/g	H_2O/ml	Time/h	TA/g	e.d.a/%
1	0	0	0	0	0.1	7
2	5	15	50	6	0	13
3	5	15	50	6	0.1	72
4	3	6	50	18	0.1	71
5	3	9	50	18	0.1	75
6	3	30	50	18	0.1	75
7	5	15	50	18	0.1	77
8	10	30	50	18	0.1	79
9	20	60	100	18	0.1	81
10	20	60	100	18	0.2	84

3.2. *Combination of NaBr-pre-modification in methanol and TA-pre-modification in THF: Enantio-differentiating hydrogenation over MRNi-PP*

We demonstrated for the pre-modification with TA and NaBr in THF that the e.d.a. of close to 90% was attained with the reduced Ni when the modification was carried out at 373 K under 9 MPa hydrogen [11]. This fact suggested that the pre-modification with TA and NaBr in an organic solvent(s) under high pressure H_2 promises to be an efficient modification method for the RNi. As a modification solvent for NaBr, we employed methanol. The esterification of TA was predicted during the modification in methanol. Thus, THF was employed for the TA-pre-modification. The RNi prepared by the successive pre-modifications with NaBr in methanol and with TA in THF is abbreviated MRNi-PP. Table 2 shows the effect of the NaBr-pre-modification variables (the temperature and the H_2 pressure) on the e.d.a. of MRNi-PP. The e.d.a. of MRNi-PP reached 70% when the RNi was pre-modified with NaBr at 373 K under 10 MPa hydrogen for 60 min. Figure 3 shows the relation between the temperature for the NaBr-pre-modification and the e.d.a. of the resulting MRNi-PP (the modification time: 60 min). The pre-modification with NaBr at 383 K under 10 MPa hydrogen resulted in the maximum e.d.a. (73%), and the modification at above 383 K resulted in a rather lower e.d.a. Figure 4 shows the relation between the time for the NaBr-pre-modification and the e.d.a. of the MRNi-PP (the modification temperature: 383 K). It can be seen that 60 min is sufficient for the pre-modification with NaBr.

Table 2
Enantio-differentiating hydrogenation of methyl acetoacetate over MRNi-PP

Entry	NaBr-pre-modification		MRNi-PP
	Temperature/K	H_2 pressure/Mpa	e.d.a/%
1	333	0.1	58
2	373	0.1	39
3	333	10	60
4	373	10	70

3.3. *Ni^{2+} and Al^{3+} eliminated from the RNi during the pre-modification process*

During the conventional pre-modification process using an aqueous solution of TA and NaBr under weakly acidic conditions at 373 K, more than 100 mg of Ni^{2+} and nearly 30 mg of Al^{3+} are eliminated from the RNi into the modification solution [7]. Table 3 shows the amounts of Ni^{2+} and Al^{3+} ions contained in the recovered pre-modification solutions used for the preparation of MRNi-PI(1), MRNi-PI(2) and MRNi-PP. It is clear that the pre-modification with NaBr in methanol, disodium tartrate and NaBr in water, or TA in THF

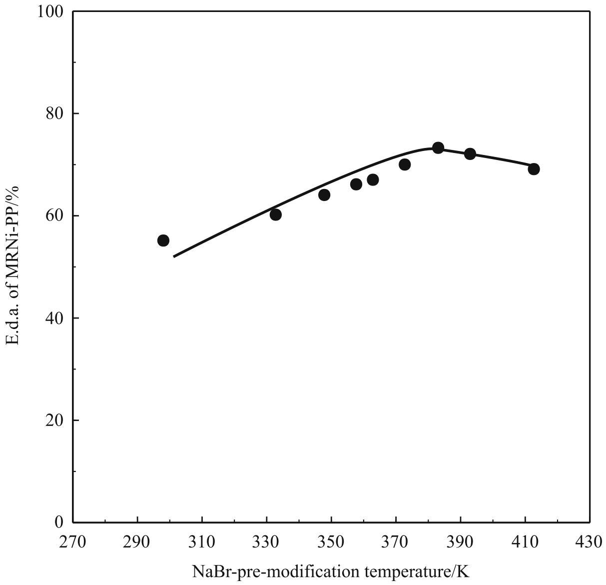

Figure 3. Relationship between the temperature for the NaBr-pre-modification and e.d.a. of MRNi-PP.

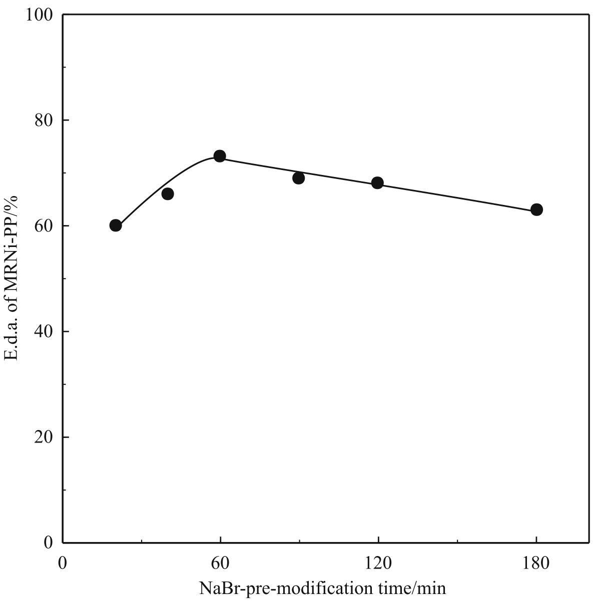

Figure 4. Relationship between time required for NaBr-pre-modification and e.d.a. of MRNi-PP.

Table 3
Amounts of Ni^{2+} and Al^{3+} ions in the recovered pre-modification solution

Entry	Catalyst	Recovered pre-modification solution	
		Ni^{2+}/mg	Al^{3+}/mg
1	MRNi-PI(1)[a]	0	0
2	MRNi-PI(2)[b]	0	5–8[d]
3	MRNi-PP[c]	0	0

[a] Pre-modified with NaBr (0.1 g) in methanol (25 cm^3).

[b] Pre-modified with disodium tartrate dihydrate (5 g) and NaBr (15 g) in water (50 cm^3) for 6 h.

[c] Pre-modified with NaBr and then with TA, at 373 K for 1 h.

[d] The presence of large amounts of the tartrate in the modification solution restricted a clear color change in the indicator (Cu-PAN).

generated only a negligible amount of Ni^{2+} ions compared to the ions generated during the conventional pre-modification. Taking into account the fact that nickel ions possess some toxicity, the novel modification methods for MRNi-PI and MRNi-PP have an advantage from the viewpoint of green chemistry.

Based on the amounts of Al^{3+} in the recovered modification solutions, it can be claimed that the pre-modification with disodium tartrate and NaBr in water is a useful method for the preferential elimination of Al^{3+} from the RNi surface to afford a surface with a lower Al^{3+} content. It has been proposed that there are non-enantio-differentiating sites in the region containing substantial amounts of contaminants such as residual Al^0 and Al^{3+} [7,13]. This proposal leads to the idea that MRNi-PI(2) has more enantio-differentiating sites than the other MRNi's. This may be one reason why MRNi-PI(2) exhibits a higher e.d.a. than MRNi-PI(1) and MRNi-PP.

4. Conclusion

The RNi was modified with TA and NaBr in two steps. MRNi-PI(1): the RNi was first pre-modified with a methanol solution of NaBr, and then *in-situ* modified with TA. MRNi-PI(2): the RNi was pre-modified with disodium tartrate and NaBr in water, and then *in-situ* modified with TA. MRNi-PP: the RNi was first pre-modified with NaBr in methanol under high pressure H_2, and then pre-modified with TA in THF under the high pressure H_2. Among them, MRNi-PI(2) exhibited the highest e.d.a. (84%) for the hydrogenation of methyl acetoacetate. MRNi-PI(2) was expected to have more enantio-differentiating sites on the surface than MRNi-PI(1) and MRNi-PP.

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