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# Enantioselective hydrogenation of $\beta$ -aryl- $\beta$ -ketoester over $\alpha$ -hydroxy acid-modified Raney nickel catalysts: competitive hydrogenation with methyl acetoacetate

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### ABSTRACT

The enantioselective hydrogenation of the aromatic  $\beta$ -ketoesters, methyl 3-phenyl-3-oxypropanoate (1) and its *p*-methoxy-analogue (2), was studied over tartaric acid-modified Raney nickel catalysts. A competitive hydrogenation approach was used to clarify the catalytic behaviors of the enantio-differentiating hydrogenation of aromatic  $\beta$ -ketoesters over tartaric acid-modified Raney nickel, malic acid-modified Raney nickel, and unmodified Raney nickel in comparison with aliphatic one, represented by methyl ace-toacetate. We found that the enantioselectivity could be elucidated by the interaction modes between the surface modifier, Ni metal surface, and the substrate as well as the keto/enol ratio of the substrate. We suggest that the moderate enantioselectivity of 1 over tartaric acid-modified Raney nickel is the result of distorted, weak two-point hydrogen bond interactions with surface tartrate due to unfavorable phenyl–Ni metal surface interactions. The *p*-methoxy group of 2 suppresses the phenyl–Ni metal surface interactions in the enantioselectivity of 2 over tartaric acid-modified Raney nickel. Ligand acceleration effects were observed with methyl acecoacetate and 2 but not with 1.

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Tetrahedron

### 1. Introduction

Enantioselective hydrogenation of prochiral ketones and olefins over chiral organic compound-modified heterogeneous metal catalysts has received extensive attention from both scientific and practical points of view, because of their easy handling, separation, and rejuvenation compared with homogeneous catalyst systems.<sup>1-</sup> One industrially feasible catalyst system is the tartaric acid-modified Raney nickel catalyst, which is an excellent enantioselective catalyst for the hydrogenation of  $\beta$ -ketoesters, represented by methyl acetoacetate.<sup>1,8–12</sup> The enantioselective hydrogenation of methyl acetoacetate reached 86% enantiomeric excess (ee) at a reaction temperature of 333–373 K.<sup>8–10,13,14</sup> Many studies have been devoted to extend the applications of tartaric acid-modified Raney nickel to a variety of prochiral aliphatic  $\beta$ -ketoesters.<sup>1,8–10</sup> However, aromatic ketones have been much less studied so far.<sup>8–10</sup> Our previous study showed that the hydrogenation of methyl 3-phenyl-3oxypropanoate 1 resulted in only 30% ee at 373 K and 52% ee at 333 K.<sup>15</sup> In contrast, the *p*-OCH<sub>3</sub>-substituted analogue of **1**, **2**, gave high selectivity (72%ee at 333 K). This significant difference

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http://dx.doi.org/10.1016/j.tetasy.2016.05.006 0957-4166/© 2016 Elsevier Ltd. All rights reserved. between the substrates prompted us to further clarify the reaction behaviors of **1** and **2**.

The origin of the enantioselectivity in the hydrogenation of  $\beta$ -ketoesters on tartaric acid-modified Raney nickel has been extensively studied using a variety of techniques.<sup>8–11,16,17</sup> The modifier is believed to play two roles in the enantioselective hydrogenation: one is as a poison against the active catalyst surface to hinder racemic hydrogenation reactions together with NaBr, a co-modifier, and another is as interaction sites for a prochiral substrate to fix a certain enantioface of the substrate toward the enantioselective hydrogenation. The optimum coverage of the modifier, tartaric acid, on the Ni metal surface was reported to be approximately 20% to form ensembles suitable for the enantioselective hydrogenation,<sup>18–20</sup> with non-selective sites being poisoned by NaBr.

The enantioselectivity of the reaction is usually evaluated by the %ee of the products, defined as

$$\% ee = ([(R)-product] - [(S)-product])/([(R)-product]) + [S-product]) \times 100,$$

as long as the hydrogenation proceeds quantitatively. We have previously proposed that %ee can be also expressed as [factor *i*] ×  $r_E/(r_E + r_N)$ , where [factor *i*] is the intrinsic %ee of the hydrogenation

on tartaric acid-modified sites and  $r_E/(r_E + r_N)$  is a contribution of tartaric acid-modified sites in the total hydrogenation ( $r_F$ : reaction rate over the modified sites and r<sub>N</sub>: reaction rate over non-modified or non-selective sites).<sup>8,9</sup> In our previous study, it was suggested that the relatively low %ee in the enantioselective hydrogenation of 1 (52%ee) over tartaric acid-modified Raney nickel, compared to that of methyl acetoacetate (86%ee), resulted from two factors; a relatively lower [factor *i*] and a relatively lower  $r_E/(r_E + r_N)$  ratio.<sup>15</sup> Recently, we showed with the enantioselective hydrogenation of methyl acetoacetate over tartaric acid-, malic acid-, and succinic acid-modified Raney nickel catalysts that molecular interactions between the chiral surface acids and the substrate determined both the enantioselectivity and the reaction rate.<sup>20</sup> It has been proposed that hydrogen bond(s) interactions between the surface chiral carboxvlate and methyl acetoacetate induce stronger adsorption of methyl acetoacetate and thereby an enhanced reaction rate (ligand acceleration) as well as an increased enantioselectivity.

Experimental techniques of the competitive hydrogenation of more than one substrate provide important information on the reaction mechanism in enantioselective hydrogenations: the relative rates of each substrate indicate the relative adsorption strength in a dynamic adsorption equilibrium<sup>21</sup> and relative contribution of the catalysis on modified sites.<sup>14</sup> In a previous study, we briefly studied the competitive hydrogenation of **1** or **2** and methyl acetoacetate over tartaric acid-modified Raney nickel, which suggested that with 1, the contribution of the catalysis on modified sites was lower than that with methyl acetoacetate, while with **2**, it was similar.<sup>15</sup> In the present study, we have extended previous study to obtain further insight into the catalytic behaviors of the enantioselective hydrogenations of aromatic β-ketoesters, represented by **1** and **2** (Scheme 1), through competitive hydrogenations with methyl acetoacetate as a reference substrate over tartaric acid- and malic acid-modified Raney nickel catalysts.



Scheme 1. Enantioselective hydrogenations of aromatic β-ketoesters 1 and 2.

### 2. Results and discussion

Since reproducible and precise kinetic information was relatively difficult to obtain by using a usual reactor with a magnetic stirrer because of diffusion limitations, enantioselective hydrogenation reactions over the tartaric acid- or malic acid-modified Raney nickel catalysts were conducted at an elevated H<sub>2</sub>-pressure (10 MPa) under reciprocation shaking (the strongest agitation technique available to our group).<sup>13-15</sup> Herein, a certain amount of the reaction sample was periodically withdrawn from the reactor while keeping the hydrogen pressure high and the conversion analysis of each sample was conducted by NMR. The sizes of the reaction solution and sampling, however, limited the numbers of the sampling and analysis (in the present study, 4 times sampling for each run). In the present study we adopted a technique of competitive hydrogenation of 1 or 2 and methyl acetoacetate, a standard substrate, to facilitate a direct comparison of the catalytic behavior of 1 or 2 with that of methyl acetoacetate under the identical reaction conditions. Equimolar amounts of methyl acetoacetate and 1 or 2 were used in the present competitive hydrogenation for the sake of simplicity.

The enantioselectivities of methyl acetoacetate, **1**, and **2** were 86, 52, and 72%ee, respectively, in separate hydrogenation reactions

over tartaric acid-modified Raney nickel catalysts. These ee values are consistent with our best ee values for these enantioselective hvdrogenations.<sup>8,15</sup> With the hydrogenation over malic acid-modified Raney nickel, the products were almost racemic for 1 and 2. A considerable decrease in the enantioselectivity to 60%ee was also observed for the hydrogenation of methyl acetoacetate over malic acid-modified Raney nickel in our previous study.<sup>20</sup> This can be rationally accounted for in terms of the hydrogen bond interaction modes between the hydroxyl groups of the modifier and the carbonyl groups of methyl acetoacetate: A two-point interaction mode between the surface bitartrate (possibly monosodium bitartrate surface species<sup>8,9</sup> in the presence of NaBr) and methyl acetoacetate for tartaric acid-modified Raney nickel to result in a high enantiodifferentiation, while a single point interaction between adsorbed bimalate and methyl acetoacetate for malic acid-modified Raney nickel to result in less selective hydrogenation. The significant decreases in the hydrogenation selectivity of **1** and **2** over malic acid-modified Raney nickel compared with tartaric acid-modified Raney nickel lead us to conclude that the enantioselective hydrogenation of the aromatic  $\beta$ -ketoesters is also controlled by the hydrogen bond interaction modes with the surface modifier: twopoint interaction modes with surface bitartrate species are much more favorable for enantio-differentiation than single point interactions with bimalate counterparts. It was found that the hydrogenation rate of methyl acetoacetate was also affected by the interactions with the surface modifier.<sup>20</sup> When unmodified Raney nickel (modified with NaBr but without the organic acid modifier) was modified with succinic acid, the hydrogenation rate of methyl acetoacetate was greatly reduced and racemic products were obtained, thus indicating that the surface modifier species poisoned Raney nickel by covering the Ni metal surface.<sup>20</sup> On the other hand, the hydrogenation rate of methyl acetoacetate was increased by replacing succinic acid with malic acid in spite of the same coverage of the surface modifier. The reaction rate was further increased by replacing malic acid with tartaric acid. On the basis of the analysis of the kinetic behaviors of the enantioselective hydrogenation of methyl acetoacetate, it was suggested that such profound ligand acceleration effects were induced by the increase in the adsorption strength of methyl acetoacetate through hydrogen bond interactions with the hydroxyl groups of the modifier.<sup>20</sup> A two-point hydrogen bond interaction model for methyl acetoacetate over tartaric acid-modified Raney nickel is illustrated in Figure 1.8

Figure 2a-c show the conversions of the substrates to the products [(*S*)- and (*R*)-enantiomers] as a function of reaction time in the competitive hydrogenations of **1** and methyl acetoacetate over unmodified Raney nickel, malic acid-modified Raney nickel, and tartaric acid-modified Raney nickel, respectively. Table 1



Figure 1. Two-points hydrogen bond interaction model for methyl acetoacetatesurface tartrate modifier.

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Figure 2. Conversions of the substrates, 1 (blue circle) and methyl acetoacetate (pink square), as a function of reaction time in the competitive hydrogenation over (a) unmodified Raney nickel, (b) malic acid-modified Raney nickel, and (c) tartaric acid-modified Raney nickel. Note that the scales of the vertical axes are altered for the sake of clarity.

Fable 1
Conversions of substrate 1 or 2 and methyl acetoacetate on modified and unmodified Raney nickel in the competitive hydrogenation

Entry	Substrate	Modifier	(	Conversion % (substrate 1 or 2/methyl acetoacetate)			
			1 h	2 h	3 h	4 h	
1	1	Tartaric acid-NaBr	1.3/0	2.4/6.9	3.4/8.8	4.4/13	
2	1	Malic acid-NaBr	7.2/0	14/0	22/6.1	34/8.1	
3	1	NaBr	97/0	100/3.8	100/95	100/99	
4	2	Tartaric acid-NaBr	0.9/13	1.5/25	2.1/38	5/52	
5	2	Malic acid-NaBr	0.6/0	0.8/1.3	1.5/5.2	2.7/8.7	
6	2	NaBr	52/42	78/76	91/90	97/98	

summarizes the conversions of **1** and methyl acetoacetate in the competitive hydrogenation. Figure 2a shows that during the first hour, only **1** is preferentially hydrogenated over unmodified Raney nickel, while leaving methyl acetoacetate intact. After almost complete consumption of **1** in 1 h of reaction time, the hydrogenation of methyl acetoacetate began at >1 h and finished after approximately 3 h of reaction time. The reaction behavior in Figure 2a is reasonably understood on the basis of a Langmuir–Hinshelwood formalism for competitive hydrogenations; assuming that the substrates and hydrogen are competitively adsorbed on the Ni surface and that the first addition of an adsorbed hydrogen atom to the adsorbed substrate molecule is the rate-determining step of the hydrogenation,<sup>20</sup> the reaction rate  $r_s$  can be expressed as

$$r_{\rm Sa} = k_{\rm a}^{\rm 0} K_{\rm Sa} C_{\rm Sa} K_{\rm H}^{1/2} P_{\rm H}^{1/2} / \left(1 + K_{\rm Sa} C_{\rm Sa} + K_{\rm Sb} C_{\rm Sb} + K_{\rm H}^{1/2} P_{\rm H}^{1/2}\right)^2 \tag{1}$$

$$r_{\rm Sb} = k_{\rm b}^{0} K_{\rm Sb} C_{\rm Sb} K_{\rm H}^{1/2} P_{\rm H}^{1/2} / \left(1 + K_{\rm Sa} C_{\rm Sa} + K_{\rm Sb} C_{\rm Sb} + K_{\rm H}^{1/2} P_{\rm H}^{1/2}\right)^{2}$$
(2)

$$r_{\rm Sa}/r_{\rm Sb} = (k_{\rm a}^0/k_{\rm b}^0)(K_{\rm Sa}/K_{\rm Sb})(C_{\rm Sa}/C_{\rm Sb})$$
(3)

where  $k^0$  is a real rate constant,  $K_S$  and  $K_H$  the adsorption constants of the substrate (a or b) and  $H_2$ ,  $C_S$  the concentration of the substrate, and P<sub>H</sub> the pressure of H<sub>2</sub>. The catalytic behavior presented in Figure 2a for the competitive hydrogenation on unmodified Raney nickel cannot be interpreted simply by the large difference in the rate constant of the hydrogenations of 1 and methyl acetoacetate. Instead, it was considered that the large difference in the adsorption constant between the substrates controls the catalytic results, i.e., when  $K_1C_1$  is much larger than  $K_{MAA}C_{MAA}$ ,  $r_1 \gg r_{MAA}$ . This is the case in Figure 2a at <2 h, i.e., the adsorption strength of 1 on unmodified Raney nickel is much greater than that of methyl acetoacetate ( $K_1 \gg K_{MAA}$  on unmodified Raney nickel) and substrate 1 plays a role as a poison with regards to the adsorption of methyl acetoacetate and thus the hydrogenation of methyl acetoacetate. Thus, the hydrogenation of 1 proceeds exclusively until almost complete consumption of 1, whereas the hydrogenation of methyl acetoacetate rapidly proceeds with a reaction time of >2 h. Figure 2a suggests that the rate constants of **1** and methyl acetoacetate are not very different to each other. It can be concluded that **1** is much more strongly adsorbed on unmodified Raney nickel than methyl acetoacetate, possibly because of the much stronger interaction of the phenyl group of **1** with Ni metal surface than the carbonyl groups of methyl acetoacetate.

Figure 2b shows that the hydrogenations of 1 and methyl acetoacetate take place simultaneously in a parallel manner on malic acid-modified Raney nickel, although **1** is hydrogenated at a higher rate than methyl acetoacetate. It is noteworthy that the reaction pattern in the competitive hydrogenation can be varied by the modification of Raney nickel with malic acid from the exclusive hydrogenation of 1 (Fig. 2a) to the parallel hydrogenations of 1 and methyl acetoacetate (Fig. 2b). It is also apparent that **1** is not simply a strong poison that hinders the adsorption of methyl acetoacetate on malic acid-modified Raney nickel, but methyl acetoacetate is competitively adsorbed with 1 and thereby the hydrogenation of methyl acetoacetate takes place in a parallel way. These findings cannot be explained only in terms of a change in the ratio of the rate constants,  $k^0$ , of **1** and methyl acetoacetate by the modification. As a result, the drastic change in the reaction pattern of the competitive hydrogenation leads us to conclude that the extent of difference in the adsorption constant, K, between 1 and methyl acetoacetate is significantly reduced by the modification of Raney nickel with chiral malic acid having one OH group. It was considered that the adsorption mode of the substrate could be significantly modified by one-point hydrogen bond interactions with a surface bimalate species (possibly monosodium bimalate species) formed by double deprotonation.<sup>20</sup> With the hydrogenation of methyl acetoacetate over malic acid-modified Raney nickel, we previously revealed that such interactions increased the adsorption strength of methyl acetoacetate compared to that on succinic acid-modified Raney nickel.<sup>20</sup> As a result, we propose that methyl acetoacetate has suitable one-point hydrogen bond interactions with surface malate species at site-1 or site-2 in the model in Figure 1, accompanying enhanced adsorption strength and a moderate enantioselectivity. On the other hand, we considered that the hydrogen bond interactions between 1 and surface malate

species were not properly developed because of its unfavorable interactions between the phenyl group of **1** and Ni metal surface, resulting in a weakened adsorption strength of 1 on malic acidmodified Raney nickel, where the phenyl group-Ni metal surface interactions are effectively hindered by the presence of the surface modifier, compared with that of 1 on unmodified Raney nickel. Thus the difference in the adsorption strength between 1 and methyl acetoacetate over malic acid-modified Raney nickel becomes much smaller than that on unmodified Raney nickel. As shown in Figure 2b, the reaction rate of **1** is still considerably higher than that of methyl acetoacetate. The preferential hydrogenation of 1 on malic acid-modified Raney nickel can be understood by assuming a stronger adsorption of **1** on the catalyst than that of methyl acetoacetate ( $K_1 > K_{MAA}$  on malic acid-modified Raney nickel) as a predominant factor because of similar chemical properties of their C=O groups to be hydrogenated.

In sharp contrast to the reaction over unmodified Ranev nickel (Fig. 2a) or malic acid-modified Raney nickel (Fig. 2b), the hydrogenation rate of methyl acetoacetate is considerably larger than that of 1 in the competitive hydrogenation over tartaric acid-modified Raney nickel, as presented in Figure 2c. It was accordingly concluded that the adsorption strength of methyl acetoacetate over tartaric acid-modified Raney nickel was greater than that of 1 ( $K_{MAA} > K_1$  on tartaric acid-modified Raney nickel). It is generally accepted as illustrated in Figure 1 that methyl acetoacetate molecules are adsorbed on tartaric acid-modified Raney nickel by forming two-point hydrogen bond interactions with a surface tartrate bicarboxylate species,<sup>8–11</sup> thus generating highly enantio-differentiating reaction intermediates. We previously suggested that the two-point interactions between methyl acetoacetate and surface tartrate species, possibly due to a very favorable configuration of methyl acetoacetate, led to high enantioselectivity as well as strong ligand acceleration effects induced by enhanced adsorption strength with respect to the reaction over succinic acid-modified Raney nickel.<sup>20</sup> It was concluded that the weaker adsorption strength of 1 on tartaric acid-modified Raney nickel compared to methyl acetoacetate is caused by weakened two-point hydrogen bond interactions distorted by unfavorable interactions between the phenyl group and Ni metal surface. The relatively low enantioselectivity of 1 on tartaric acid-modified Raney nickel may in part be due to these distorted two-point interactions, although we cannot rule out the possibility that a contribution of the hydrogenation on unmodified sites is larger with **1** than methyl acetoacetate.<sup>15</sup>

Figure 3a–c show the conversions of the substrates, **2** and methyl acetoacetate, in the competitive hydrogenation over unmodified Raney nickel, malic acid-modified Raney nickel, and tartaric acid-modified Raney nickel, respectively. The conversion values of **2** and methyl acetoacetate are summarized in Table 1. As presented in Figure 3a, methyl acetoacetate and **2** are

simultaneously hydrogenated in a parallel manner over unmodified Raney nickel with **2** being consumed at a slightly higher reaction rate. It was suggested that the adsorption strength of **2** over Ni metal surface was not very different from that of methyl acetoacetate in contrast to the much higher adsorption strength of **1** compared to methyl acetoacetate (Fig. 2a). The *p*-CH<sub>3</sub>O substituent of **2** apparently increases the  $\pi$ -electron density of the phenyl group. Thus it was expected that the adsorption strength of **2** on Ni metal surface is increased compared with that of **1**. However, this was not the case. Accordingly, we suggested that the strong phenyl group-surface Ni metal interactions observed for **1** were effectively suppressed, possibly, by the steric hindrance of the *p*-CH<sub>3</sub>O group of **2** and/or that enhanced polarity of **2** by the *p*-CH<sub>3</sub>O group decreases the adsorption strength of **2** in a polar solvent (THF) compared with that of **1**.

Figure 3b shows that methyl acetoacetate is hydrogenated more rapidly over malic acid-modified Raney nickel than 2, thus suggesting enhanced interactions of methyl acetoacetate with surface malate species compared to 2 (possibly  $K_{MAA} > K_2$  on malic acidmodified Raney nickel). It is worth noting in Figure 3c that methyl acetoacetate is much more preferentially hydrogenated than 2 over tartaric acid-modified Raney nickel (possibly  $K_{MAA} \gg K_2$  on tartaric acid-modified Raney nickel). As discussed above, it is well accepted that methyl acetoacetate interacts strongly with surface tartrate species to generate a high enantioselectivity.8-11 As a result, we considered that methyl acetoacetate forms suitable strong two-point interactions with the surface modifier, as illustrated in Figure 1, but 2 forms weaker hydrogen bond interactions at site-1 and/or site-2 possibly due to slight distortions by weak, but unfavorable phenyl group-Ni metal interactions and/or steric hindrance of the *p*-CH<sub>3</sub>O-phenyl group to the optimum configuration, accompanying a slight decrease in %ee from 86% to 72%.

Comparing the reaction behaviors in Figures 2c and 3c, it can be concluded that the relative adsorption strength of methyl acetoacetate on tartaric acid-modified Raney nickel is effectively enhanced in the presence of surface tartrate species compared with that of **1** or **2**. The two-point interactions optimized with methyl acetoacetate are estimated to be distorted by *p*-CH<sub>3</sub>O-phenyl group- and, in particular, the phenyl group-Ni metal surface interactions, this partly explaining the order of %ee, methyl acetoacetate > **2** > **1**. Electron-releasing effects from the methoxy group of **2** are expected to strengthen the hydrogen bond interactions with the modifier, thus further increasing the enantioselectivity compared to that of **1**, as suggested by Szöllösi.<sup>22</sup> It can be seen that the suitable interactions between the surface chiral tartrate species and the prochiral substrate are pivotal in the enantioselective hydrogenation of  $\beta$ -ketoesters over tartaric acid-modified Raney nickel.

There could be another possible reason for the low enantioselectivity of **1**. Most  $\beta$ -ketoesters, including methyl acetoacetate



Figure 3. Conversions of the substrates, 2 (blue circle) and methyl acetoacetate (pink square), as a function of reaction time in the competitive hydrogenation over (a) unmodified Raney nickel, (b) malic acid-modified Raney nickel, and (c) tartaric acid-modified Raney nickel. Note that the scales of the vertical axes are altered for the sake of clarity.

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and other aliphatic substrates, mainly take a keto form. On the other hand, according to the present NMR observations, the keto/ enol ratio was 83/17 in CDCl<sub>3</sub> for **1**, while 94/6 for **2**, which is as high as aliphatic  $\beta$ -ketoesters. Taking into consideration the reaction mechanism that generates the enantioselectivity, the enol-form of the  $\beta$ -ketoester contributes only to the formation of the racemic products, thus lowering the enantioselectivity of the hydrogenation of **1** over tartaric acid-modified Raney nickel.

Finally, we will discuss the ligand acceleration in the competitive hydrogenation reactions. Table 1 shows that the conversions of methyl acetoacetate over malic acid-modified Raney nickel increased in both competitive hydrogenations with 1 and 2 by replacing malic acid with tartaric acid. These observations clearly demonstrate the effects of ligand acceleration due to the enhanced adsorption strength of methyl acetoacetate induced by the change in the methyl acetoacetate-modifier interaction mode from onepoint to two-point hydrogen bonding, as aforementioned.<sup>20</sup> With 2, the increase in conversion is also observed in Table 1 by replacing malic acid with tartaric acid, clearly indicating the generation of ligand acceleration due to an enhanced adsorption strength. However, with **1** the conversions on tartaric acid-modified Raney nickel are even lower than on malic acid-modified Raney nickel in contrast to the other substrate, methyl acetoacetate or 2. It was considered that the abnormal behavior of **1** was induced by the strong phenyl-Ni metal interactions, resulting in distorted and thus weaker modifier-1 hydrogen bond interactions and a lower enantioselectivity.

### 3. Conclusions

Herein we have used a competitive hydrogenation approach to clarify the catalytic behaviors of the enantio-differentiating hydrogenation of aromatic *B*-ketoesters over tartaric acid-modified Raney nickel in comparison with aliphatic one, represented by methyl acetoacetate. We have shown that the competitive hydrogenation technique was very effective for this purpose. The relative adsorption strength of the substrate was dramatically changed by the modification of Raney nickel with tartaric acid or malic acid, clearly demonstrating the importance of the suitable interactions between the surface chiral modifier and the prochiral substrate in the enantioselective hydrogenation of  $\beta$ -ketoesters. It can be concluded that the enantioselectivity is elucidated by the interaction modes between the surface modifier, Ni metal surface, and the substrate as well as the keto/enol ratio of the substrate. We have suggested that the moderate enantioselectivity of 1 over tartaric acid-modified Raney nickel is the result of distorted twopoint hydrogen bond interactions between the surface tartrate and 1 due to unfavorable phenyl-Ni metal surface interactions. The *p*-methoxy substituent of **2** suppresses the phenyl-Ni metal surface interactions, resulting in an increase in the enantioselectivity of 2 over tartaric acid-modified Raney nickel compared with that of 1. Clear ligand acceleration effects were observed with methyl acetoacetate and **2** by replacing malic acid with tartaric acid, while no clear acceleration effects with 1.

### 4. Experimental

### 4.1. Preparation of 1

Ethyl 3-oxo-3-phenylpropanonate (5 g) in methanol (75 mL) with MeONa (0.25 g) was heated at 343 K for 24 h. After cooling, the precipitate was filtered off (mostly MeONa), partially concentrated, and subsequently purified twice via silica-gel column (25% ethyl acetate in hexane), distillation (0.7 mmHg/383 K) to give a yellow oily product **1** (3.75 g, <sup>1</sup>H NMR: (keto-form)  $\delta$  7.93

(d, J = 4.5 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.9 Hz, 2H), 3.99 (s, 2H), 3.74 (s, 3H), (enol-form)  $\delta$  7.76 (d, J = 5.6 Hz, 2H), 7.45 (t, J = 6.8 Hz, 1H), 7.4 (t, J = 5.0 Hz, 2H), 5.66 (s, 1H), 3.79 (s, 3H)).

### 4.2. Preparation of 2

To an NaH (10.4 g, used after washing with dry hexane) suspension (50 mL, THF), (MeO)<sub>2</sub>CO (15.9 g) and *p*-methoxyacetophenon (13 g) were added dropwise over 2 h. Next, KH (ca. 0.5 g) was added and the resulting mixture was stirred for 1.5 h and then quenched with AcOH (1000 mL). Extraction, distillation (423 K/1 mmHg), and subsequent purification via column chromatography gave **2** (13.18 g) as a yellow oily product (<sup>1</sup>H NMR: (keto-form)  $\delta$  7.91 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 6.9 Hz, 2H), 3.94 (s, 2H), 3.86 (s, 3H), 3.73 (s, 3H), (enol-form)  $\delta$  7.72 (d, *J* = 6.0 Hz, 2H), 6.9 (d, *J* = 6.9 Hz, 2H), 5.57 (s, 1H), 3.86 (s, 1H), 3.83 (s, 3H), 3.73 (s, 3H)).

### 4.3. Catalyst preparation and modification

Raney nickel (RNi) was prepared from a Ni/Al alloy (42/58, Kawaken Fine Chemicals, Ltd. Japan) by the W-2 type development followed by washing with water under ultrasonic irradiation.<sup>13,14</sup> An aliquot of the alloy (1.0 g) was treated in an alkaline solution of NaOH (4.5 g) in deionized water (20 mL) at 373 K for 1 h. The modification was performed to prepare tartaric acid- or malic acid-modified Raney nickel (0.4 g) by heating the RNi at 373 K for 1 h in solution, including the modifier (tartaric acid or malic acid, 6.6 mmol) and NaBr (5 g) in water (50 mL), after adjustment of the pH at 3.2 with NaOH. After the modification, the solution was removed by decantation, followed by thorough washing with water, then with methyl alcohol, and finally with tetrahydrofuran (THF) to prepare tartaric acid-modified Raney nickel. Unmodified Raney nickel denotes RNi catalysts modified with NaBr alone, hereafter.

### 4.4. Hydrogenation procedure<sup>13–15</sup>

To a 100 mL autoclave, a substrate mixture of methyl acetoacetate (2.8 mmol) and **1** (2.8 mmol) or **2** (2.8 mmol) in THF (40 mL) was placed with acetic acid (0.2 mL) and a tartaric acidor malic acid-modified Raney nickel or unmodified Raney nickel catalyst (400 mg). Hydrogen was injected (10 MPa), and the autoclave was heated to 333 K. At 293 K, shaking was started to initiate the catalytic reaction. Next, 3 mL of the product mixture were withdrawn each time from the reactor at predetermined reaction times for analysis, while keeping the hydrogen pressure high. The conversion analysis of each sample was conducted by NMR. The conversion is defined here as the conversion of the substrate to total hydrogenated products, (*S*)- and (*R*)-enantiomers.

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