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Research Note

Activation-temperature dependence in enantioselective hydrogenation of unsaturated carboxylic acids over cinchonidine-modified Pd/C catalysts

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Abstract

The enantioselective hydrogenation of α,β-unsaturated acids catalyzed by cinchonidine-modified Pd/C was found to be highly dependent on the pretreatment temperature of the catalyst. An asymmetric yield as high as 92% was achieved in the hydrogenation of (E)-2,3-di(4-methoxyphenyl)propenoic acid using a conventional 5%Pd/C catalyst activated in situ at elevated temperatures before modification with cinchonidine.

Keywords: Enantioselectivity; Hydrogenation; Unsaturated carboxylic acid; Palladium catalyst; Cinchonidine; Activation temperature

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1. Introduction

The enantioselective hydrogenation of prochiral compounds with heterogeneous catalysts remains a challenging subject. So far, two types of catalysts—cinchona-modified platinum and tartaric acid-modified nickel—have been developed to convert ketones to the corresponding chiral alcohols at 97–98% enantiomeric excess (ee) [1]. Concerning the hydrogenation of prochiral olefins, cinchona-modified palladium (CM-Pd) catalysts have been shown to be effective [2–9], although their enantioselectivities are still moderate. At present, the highest ee measured was 94% in the hydrogenation of a pyrone derivative, which was achieved only under the condition of a very low (2/1) substrate/modifier ratio [10].

As for the hydrogenation of α,β-unsaturated carboxylic acids, (E)-2,3-diphenylpropenoic acid [α-phenylcinnamic acid (**1**)], one of the well-studied substrates, gives the highest enantioselectivity (71–72% ee) with a 5%Pd/TiO_2 catalyst prepared by a precipitation–deposition method with a non-porous titania [4,11,12]. Recently, we showed that the best ee improved to 82% in the hydrogenation of (E)-2,3-di(4-methoxyphenyl)propenoic acid (**2**) as a result of an approach designing the substrate structure to enhance the substrate–modifier interaction [13]. We also found that even a commercially available Pd/C catalyst could bring about a relatively high ee, up to 71%, when used under optimized conditions, although we previously reported that catalysts prepared with porous support materials were unfavorable for this kind of reaction [14]. Further improved ee of the hydrogenation of α,β-unsaturated carboxylic acids using conventional catalysts would be very useful, because it is handy and economical and also can avoid the difficulties in reproducibility expected in the reaction with the precipitated Pd/TiO_2 catalysts. In the present study we investigated the effect of the activation process of a commercially available Pd/C on the catalytic performance in enantioselective hydrogenations of **1** and **2** (Scheme 1).

2. Experimental

A carbon-supported Pd catalyst (5%Pd/C, STD type; N.E. CHEMCAT Co.) was mainly used in this study, with some other Pd/C catalysts used for comparison. Substrate **1** (Aldrich; 98%) was purified by recrystallization from an acetone solution, and substrate **2** was synthesized from p-anisaldehyde and p-methoxyphenylacetic acid by the Perkin reaction [15] and characterized by NMR. Solvents (Wako Pure Chemical; special grade), cinchonidine (CD) (Wako Pure Chemical; 99%),

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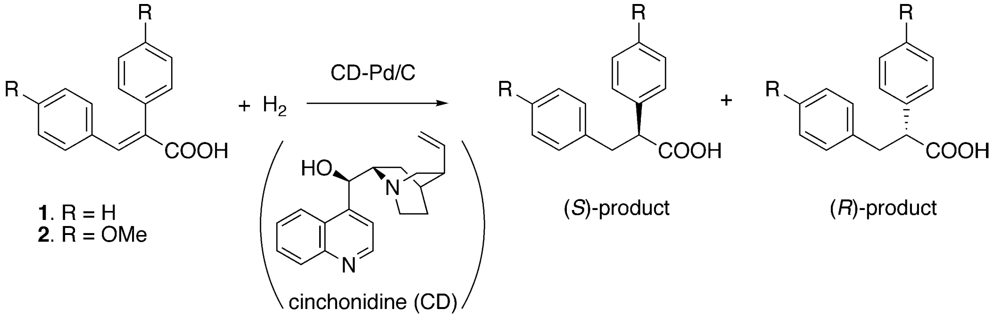

Scheme 1.

and benzylamine (BA) (Wako Pure Chemical; 98%) were used as received.

The hydrogenation was carried out in a magnetically stirred (1200 rpm) 50-ml glass reactor at room temperature (296 K) in 1,4-dioxane containing 2.5% (v/v) of water under an atmospheric pressure of hydrogen. Two types of in situ procedures for the catalyst activation were used. Procedure A is similar to that used in our previous study [13,14]; the catalyst (0.02 g) and CD (0.02 mmol) were prereduced by stirring for 30 min in 5 ml of solvent under an H_2 atmosphere. In procedure B, the catalyst was pretreated without the modifier for 30 min with stirring in 5 ml of solvent in an H_2 atmosphere before the modification with CD (0.02 mmol in 1 ml of solvent added) for an additional 30 min. Then 0.5 mmol of a substrate in 5 ml (4 ml in procedure B) of the solvent and BA (0.3 mmol unless otherwise noted) as an effective additive [8,11] were injected successively to the mixture, and the stirring was started. After the hydrogen uptake finished, the reaction mixture was neutralized with a diluted HCl solution, extracted with ethyl acetate, and analyzed by HPLC on a chiral column (Daicel Chiralcel OJ-H and Chiralpak AD, for the products from **1** and **2**, respectively). The enantiomeric excess (ee, %) of the *S* isomers was calculated according to ee (%) $= 100 \times (S - R)/(S + R)$. The catalytic activities are expressed by the initial reaction rates (r_0) estimated from the hydrogen uptake at 20% conversion.

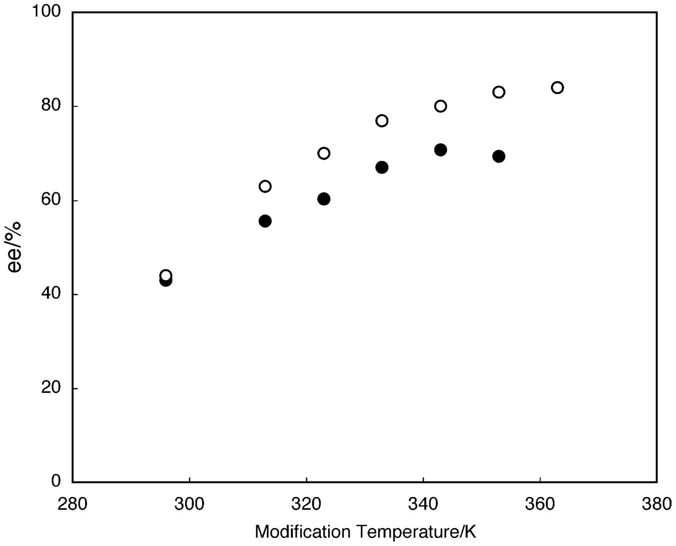

Fig. 1. Modification temperature dependence of the enantioselectivity in the hydrogenations of **1** (●) and **2** (○) with 5%Pd/C (STD) activated by procedure A. Reaction temperature, 296 K.

3. Results and discussion

Preliminary experiments, using 5%Pd/C (STD) as received, showed that the product ee in the reaction of **2** increased significantly with increasing temperature of modification and subsequent hydrogenation reaction, although higher reaction temperatures were reported to be unfavorable in the reactions of **1** with Pd/TiO_2 [4] and of an aliphatic acid with Pd/Al_2O_3 [5]. Therefore, to determine whether or not the temperature effect observed earlier comes from the modification process, a series of experiments with the Pd/C (STD) activated by procedure A were carried out by changing only the modification temperature while keeping the reaction temperature constant at 296 K. As shown in Fig. 1, the product ee for the reactions of both **1** and **2** increased markedly with increasing modification temperature, although the ee values obtained with the catalyst modified at room temperature were only 43% for the reaction of **1** and 44% for the reaction of **2**, both of which are much lower than those reported previously with an eggshell-type catalyst, Pd/C (AER) (59 and 71%), and with Pd/TiO_2 (68 and 82%) under the same reaction conditions. At the same time, the effect of the substrate structure [13] became clear under elevated modification temperatures. The ee values obtained here with the conventional Pd/C (STD) catalysts modified at 343–363 K were already on the same level as those reported with the best catalysts (Pd/TiO_2) reported so far [11–13]; the highest ee values attained were 71% in the reaction of **1** and 84% in the reaction of **2**. The reaction rate also increased to some extent with increasing modification temperature even though the reaction temperature was kept constant (296 K). When the modification procedures were carried out under N_2 atmosphere at 353 K (30 min) and then under H_2 at 296 K (30 min), increased ee was not obtained (43 and 45% ee), whereas the reaction rates decreased considerably. These observations suggest that the improvement in ee induced by the increased modification temperature is attributable to a preferable change in Pd surface in the presence of hydrogen. It seems reasonable to expect such a change in the Pd surface (e.g., the removal of surface contaminations) during the modification process under an H_2 atmosphere, especially at elevated temperatures. The temperature effect observed here is consistent with the fact that the solubility of hydrogen increases moderately with increasing temperature

Table 1
Effect of pretreatment temperature on the hydrogenation of **2** with 5%Pd/C (STD)[a] activated by procedure B

Entry	Pretreatment[b] (K)	ee (%)	Initial rate ($\text{mmol g}^{-1}\,\text{h}^{-1}$)
1	None	44	22
2	296	65	25
3	333	86	30
4	353	89	32
5	363	87	31
6[c]	353	86	33
7[d]	323	84	29

[a] Reaction conditions: 20 mg catalyst, 10 ml solvent, 0.02 mmol CD, modification and reaction temperature 296 K, 0.5 mmol substrate, 0.3 mmol benzylamine, 1200 rpm.

[b] Stirred in solvent for 30 min under an atmospheric pressure of H_2.

[c] Modified at 353 K instead of 296 K.

[d] Catalyst was reduced in an H_2 stream of 8 $\text{dm}^3\,\text{h}^{-1}$.

of the solvent under our experimental conditions [18]. In the Pt-cinchona system for the hydrogenation of α-ketoesters, the catalyst pretreatment and modification atmosphere had variable effects on catalytic performance [1,16,17], although the pretreatments in H_2 were carried out only at room temperature.

As for the effect of the reaction temperature, higher temperatures were again confirmed to be unfavorable. When the reaction was carried out at the same elevated temperature as the modification temperature, a considerable drop in ee was observed. For example, in the hydrogenation of **1** with the catalyst modified at 333 K, the ee values were 67% for the reaction at 296 K and 58% for the reaction at 333 K.

If the effect of modification temperature shown in Fig. 1 means a favorable change, such as purification only of Pd surface with H_2, then a similar temperature effect would be observed in an activation process without CD addition. We examined the effect of pretreatment temperature on the performance of Pd/C (STD), activated in situ without CD (procedure B), keeping the subsequent modification and reaction temperatures constant at 296 K. The catalyst was stirred in the solvent at different temperatures for 30 min under an atmospheric pressure of H_2 before the modification with CD. Table 1 lists the selected results for the reaction of **2**. A further increase in ee up to 89% was achieved by in situ pretreatment of the catalyst under an H_2 atmosphere, indicating the importance of the pretreatment temperature rather than the modification temperature. When the catalyst pretreated at 353 K was subsequently modified also at 353 K, a slightly lower ee (86%) was obtained, demonstrating that modification at an elevated temperature usually is not effective; procedure B is better than procedure A. This could be explained by the partial hydrogenation of the quinoline ring of CD, which inhibits the effective adsorption of CD and leads to a loss of enantio-differentiating ability, as expected on the basis of earlier observations [17,19,20].

The positive effect of the reductive pretreatment of metal catalysts or catalyst precursors, usually at much higher temperatures, is well known in hydrogenation reactions. There are several possible explanations for this, including purification of metal surface (removal of oxygen and contaminations), reduction of residual metal salts, and changes in the size or morphology of metal particles [17]. When a Pd/TiO_2 catalyst precursor was reduced in a hydrogen stream at elevated temperatures up to 473 K, a considerable increase in enantioselectivity and decrease in activity were observed in the hydrogenation of **1**, probably because of the surface purification and decreased Pd dispersion [12]. However, few studies have been reported on the effect of in situ prereduction in a solvent and on the reduction temperature dependence for CM-Pd and CM-Pt systems. Because the changes in size or morphology of Pd particles are difficult to attain under the in situ reduction conditions used here, the considerable increases in ee and rate shown in Fig. 1 and Table 1 are attributable to the purification of Pd surface with H_2, which may lead to suitable adsorption of the modifier and substrate molecules interacting with each other [21]. Actually, the prereduction of Pd/C (STD) at 323 K in a hydrogen stream of 8 dm^3/h for 1 h resulted in an ee (84%) comparable to that of the catalysts prereduced in situ. It is noteworthy that the performance of the CM-Pd catalysts is effectively improved by a simple in situ pretreatment in H_2 without CD at elevated temperatures (procedure B).

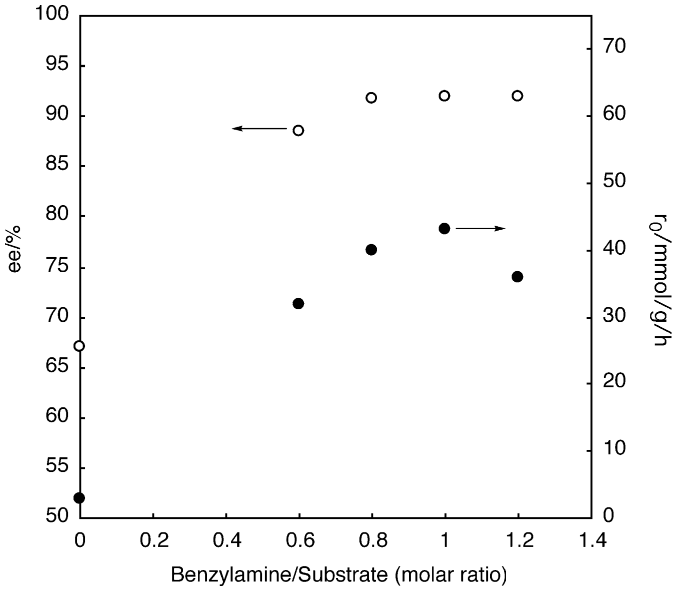

Fig. 2. Effect of benzylamine addition on ee (○) and activity (●) in the hydrogenation of **2** with 5%Pd/C (STD) activated at 353 K by procedure B. Temperature for modification and reaction, 296 K.

As a result of further optimization of the reaction conditions, an additional increase in ee up to 92% was achieved for the reaction of **2** with the Pd/C (STD) catalyst by adding larger amounts of BA to the reaction mixture under otherwise similar conditions (Fig. 2). Adding BA to the reaction mixture preferentially accelerated the selective reaction on modified sites as a result of the efficient desorption of the hydrogenated molecules from the modified sites [11]. Therefore, the amount of BA added does not affect the results obtained here, that is, the positive effect of in situ prereduction and its temperature dependency. Similar tendencies were observed in the reactions without BA. The ee of 92% is the highest achieved in the hy-

Table 2
Enantioselective hydrogenation of **1** and **2** with various Pd/C catalysts activated by procedure B under the best conditions[a]

Catalyst	Type	Substrate **1**		Substrate **2**	
		ee (%)	Initial rate (mmol g^{-1} h^{-1})	ee (%)	Initial rate (mmol g^{-1} h^{-1})
5%Pd/C[b]	STD	79	93	92	43
5%Pd/C[b]	AER (eggshell)	81	102	92	60
10%Pd/C[b]	PE (eggshell)	81	154	91	74
5%Pd/C[b]	BNA	60	17	44	4
5%Pd/C[c]	5R38H (eggshell)	77	41	91	30
5%Pd/C[c]	5R90 (intermediate)	74	27	84	14
5%Pd/C[c]	LR385 (uniform)	25	5	14	2

[a] Catalysts were pre-reduced in the solvent and H_2 atmosphere at 353 K for 30 min. Reaction conditions are the same as in Table 1 except the amount of BA (0.5 mmol) added to the reaction mixture.

[b] Catalysts donated by N.E. CHEMCAT Co.

[c] Catalysts donated by Johnson Matthey Plc.

drogenation of α,β-unsaturated carboxylic acids with heterogeneous catalysts. The fact that such a high ee can be obtained with a commercially available conventional Pd/C catalyst is not only practically useful, but also means that the use of highly porous materials, such as charcoal, is not always detrimental to catalyst preparation for this reaction. This is probably because most of the selective Pd sites, modified with CD, are located on the exterior surface of the support, and the nonselective Pd sites located in micropores of the support, if any, are inaccessible for the bulky substrate, making the contribution to the overall reaction negligible [14].

Table 2 compares the enantioselectivity and activity of different types of Pd/C catalysts obtained in the reactions carried out under the best conditions described earlier for Pd/C (STD), that is, in situ pretreatment in H_2 at 353 K (30 min) followed by the modification (30 min) and the reaction, both at room temperature. The last three catalysts listed in Table 2 (5R38H, 5R90, and LR385), all obtained from the same source, had differing locations of Pd metal within the pore structure of charcoal: eggshell, intermediate, and uniform types, respectively [22]. They exhibited behavior similar to that reported previously for the hydrogenation of **1** [14]. Although details on the nature of the other commercial Pd/C catalysts are not known, similarly high ees were obtained for eggshell-type Pd/C catalysts, whereas the reaction rate differs depending on the available Pd surface area of each catalyst. The best ees were 81% in the hydrogenation of **1** and 92% in the hydrogenation of **2**. In contrast, the 5%Pd/C catalysts with uniform distribution of Pd throughout the support structure exhibited much lower selectivities and only negligible activities. These findings are in good agreement with our previous observations that the Pd metal particles located in micropores of the support are unfavorable in this reaction; eggshell-type catalysts with Pd metal located on the exterior surface of the support are preferable when porous materials are used as the support [14]. Further studies are needed to gain insight into the influence of the nature and structure of each Pd/C catalyst.

4. Conclusions

The enantioselective hydrogenation of α,β-unsaturated acids, **1** and **2**, catalyzed by CD-modified Pd/C was found to be highly dependent on the in situ prereduction temperature. The enantioselectivity and activity increased with increasing temperature of the in situ pretreatment in H_2 atmosphere before the modification with CD. The in situ reduction of the catalyst at around 360 K was found to be the most effective. The purification of Pd surface in H_2 was suggested to be essential for the improvement of ee. Asymmetric yields $>90\%$ were achieved for the first time in the enantioselective hydrogenation of α,β-unsaturated acids with heterogeneous catalysts.

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