Preparation of Cinchonidine-Modified Palladium Catalysts for the Enantioselective Hydrogenation of (*E*)-*α*-Phenylcinnamic Acid

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The enantioselective hydrogenation of the C=C double bond in (*E*)-*α*-phenylcinnamic acid has been studied with different supported Pd catalysts prepared by a precipitation-deposition method and modified with cinchonidine. The influences of the support materials and the texture, Pd loadings, precipitation procedures, and reduction conditions on the hydrogenation activity and enantioselectivity are described. The texture of the supports has a decisive influence on the behavior of the resulting catalysts, especially when it is pre-reduced at elevated temperatures. Nonporous titania with a relatively small specific surface area was found to be the most suitable. The use of a large excess amount of precipitant resulted in an increase in the amount of residual Na and in a drastic decrease in the amount of residual Cl, leading to a remarkable increase in the activity. The elimination of both the residual Na and Cl from the catalyst precursor was found to be preferable for the enantioselectivity. A considerable increase in the enantioselectivity was observed when a 5wt%Pd/TiO_2 catalyst, prepared with nonporous titania, was reduced in a hydrogen flow at elevated temperatures up to 473 K. The influences of the surface area of nonporous supports, Pd loadings, and reduction conditions strongly suggest that the enantioselectivity of the modified Pd/TiO_2 catalysts depends on the Pd dispersion; a relatively low dispersion around 0.2—0.3 was found to be optimal.

Enantioselective hydrogenation using heterogeneous catalysts has attracted much attention and some catalytic systems have been systematically investigated. The most efficient enantioselective heterogeneous catalytic systems to date are the tartaric acid-modified Ni catalysts for the hydrogenation of *β*-keto esters and the cinchona alkaloids-modified Pt catalysts for the hydrogenation of *α*-keto esters.[1] These systems have been extensively studied and reported to provide the highest optical yields, up to 98.6%ee[2] and 97.6%ee,[3] for the hydrogenations of methyl 3-cyclopropyl-3-oxopropanoate and methyl pyruvate, respectively. As for heterogeneous catalysts for the enantioselective hydrogenation of C=C double bonds, the results of recent studies on *α*, *β*-unsaturated acids and ketones have shown that palladium is the superior metal, although the attained selectivity is still too low for efficient synthesis.[4—8] Enantiomeric excesses (ee) of up to 72%, 52%, and 47% have been reported for the hydrogenations of (*E*)-*α*-phenylcinnamic acid (**1**) with a Pd/TiO_2 catalyst,[5] (*E*)-2-methyl-2-pentenoic acid with a Pd/Al_2O_3 catalyst,[6] and tiglic acid also with a Pd/Al_2O_3 catalyst,[8] respectively, all modified with cinchonidine (**CD**). Isophorone, an *α*, *β*-unsaturated ketone, has been hydrogenated to give 55%ee by using a Pd black catalyst modified with a vinca-type alkaloid, (−)-dihydroapovincaminic acid ethyl ester ((−)-DHVIN).[9] On the other hand, the Ni and Pt catalyst systems, used for the enantioselective hydrogenation of C=O double bonds, were shown to be far less effective for the hydrogenation of C=C double bonds.[1,10]

Since an optical yield of 30.5% of (*S*)-(+)-2,3-diphenylpropionic acid (**2**) was reported in the hydrogenation of **1** with a **CD**-modified 5wt%Pd/C catalyst,[11] we have investigated the influence of process variables to optimize the catalyst preparation and reaction conditions for this reaction.[5,12—17] Greatly increased optical yields of up to 72%ee were obtained with a 5wt%Pd/TiO_2 catalyst, prepared by a precipitation-deposition method using nonporous titania and reduced in a hydrogen flow at 473 K just before use, in reactions carried out in water-containing solvents of *N*,*N*-dimethylformamide (DMF)[5] and 1,4-dioxane[17] under mild reaction conditions. However, the optimal conditions for the catalyst preparation as well as for the hydrogenation reaction have not really been established; different optimal conditions have been reported in the literature for different substrates.[5—9] Moreover, little has been known about the effect of the structural properties of the Pd catalysts.

In preparing Pd catalysts, we have found that the use of a support material having appreciable amounts of both acidic and basic sites with a moderate specific surface area, e.g., a particular kind of titania, seems to be favorable.[14] Furthermore, the distribution of Pd metal particles in the pores of the supports was found to have a decisive influence on the catalytic behavior of supported Pd catalysts.[16] We have suggested that Pd metal particles, located in the micropores of the support, will be inaccessible to the bulky molecules of the modifier and substrate, and especially to the modifier-substrate complex, and would lead to a lowered ee in this reaction. Thus, nonporous ultra fine materials were thought to be preferable as supports. On the other hand, little is known so far about the influence of the structure of Pd metal surface, such as Pd dispersion. The effect of the residual Cl in the catalyst also remains to be clarified.

With respect to the effect of metal dispersion, it has been reported that, in general, high metal dispersions are detrimental for obtaining high enantioselectivities in the hydrogenation of C=O double bonds.[18,19] In our previous reports on the hydrogenation of methyl acetoacetate with tartaric acid-modified Ni catalysts,[20—23] we showed that the enantioselectivity increases with increasing crystallite size of Ni under otherwise fixed conditions. This tendency was explained by the increased fraction of surface Ni atoms in regular crystal faces for larger metal particles; the probability of obtaining large surface ensembles of Ni atoms, where the modifier and the reactant can adsorb in a stereochemically defined arrangement, may be higher for the larger metal particles. Similar results were reported for the hydrogenation of ethyl pyruvate with **CD**-modified Pt/Al_2O_3 catalysts.[24—26] Blaser et al.[26] have concluded that platinum dispersion is the most important catalyst parameter; in order to obtain high optical yields the Pt dispersion should be lower than 0.2. From the effect of catalyst dispersion it was speculated that a flat arrangement of the Pt atoms should be favorable. The adsorption of the modifier, **CD**, was thought to be with the quinoline part, probably parallel to the catalyst surface, and the adsorption of the substrate to be anchored on the same face with **CD**.[4] On the contrary, Zuo et al.[3,27] have recently reported that the reaction is less structure sensitive; better enantioselectivity was achieved over polymer-stabilized small Pt clusters. They have suggested a possibility of the enantioface recognition, even working for the limited surface of the smaller Pt particles. Therefore, also in the hydrogenation of C=C double bonds with **CD**-modified Pd catalyst, studies on the correlation between enantioselectivity and Pd metal dispersion will be helpful for understanding the mechanism of enantioface-differentiation and for the improvement of the selectivity of this catalytic system. For studies on the effect of metal dispersion, it is important to use catalysts prepared with nonporous supports, in order to minimize the effect of pore diffusion, as mentioned above.[16] Surface contaminants, which may affect the adsorption of **CD**, must also be eliminated as thoroughly as possible.

Here, we describe the influence of the preparation parameters, such as the support texture, Pd loading, precipitation conditions, and pretreatment conditions, on the catalytic performance of **CD**-modified Pd catalysts in the enantioselective hydrogenation of **1**, before discussing the effects of metal dispersion and the residual Cl content.

Experimental

Supported Pd catalysts (0.5—20wt%Pd/TiO_2, 5wt%Pd/SiO_2, 5wt%Pd/Al_2O_3, and 5wt%Pd/ZrO_2) were prepared by a precipitation-deposition method. The procedure for a standard 5wt%Pd/TiO_2 catalyst is as follows. An aqueous $PdCl_2$ solution previously acidified with hydrochloric acid was added to a suspension of titania (JRC-TIO-3, Catalysis Society of Japan) and gently stirred for 15 min at 348 K. An eight-times excess amount of Na_2CO_3 solution was added dropwise to the suspension under vigorous stirring. After aging for 15 min under gentle stirring at the same temperature, the precipitate was filtered, washed twice with 50 cm^3 each of distilled water, and dried in air at 383 K for 20 h. The dried catalyst (0.02 g) was reduced immediately before use by heating at 473 K for 1 h in a hydrogen flow of 8 dm^3/h, unless otherwise noted. Different precipitation and pretreatment conditions were employed. A commercial Pd black catalyst (Wako Pure Chemical, 9.3 m^2/g) was used for a comparison. The degree of Pd dispersion (D_M) was estimated from the surface area of Pd metal determined by a CO chemisorption measurement at 323 K, assuming the CO/Pd ratio of 1 : 2.

The freshly reduced catalyst was modified with **CD** (0.02 mmol) by stirring for 20 min in 10 cm^3 of a solvent under the same conditions as used for the hydrogenation reaction, prior to the addition of the substrate. Two kinds of mixed solvent were used: solvent A, *N,N*-dimethylformamide and water (10 vol%); solvent B, 1,4-dioxane and water (2.5 vol%). These solvents were shown to give similar performance of the standard Pd/TiO_2 catalyst under the optimal reaction conditions.[28] Cinchonidine (Wako Pure Chemical, 99%) and (*E*)-α-phenylcinnamic acid (Aldrich, 98%) were used as received. The hydrogenation of **1** (1 mmol) was carried out at 298 K under an atmospheric pressure of hydrogen and an agitation speed of 1200 rpm. After the hydrogen uptake finished, the catalyst was filtered off. Water was added to the filtrate and the mixture was extracted by methyl propionate. The organic phase was washed with dilute HCl and then with distilled water, before drying over Na_2SO_4. After filtration, methyl propionate was evaporated off in vacuo to give a crude product. The resulting product was esterified with $CH_3OH/BF_3\cdot CH_3OH$, and analyzed by HPLC on a chiral column (CHIRALCEL OJ-R, DAICEL). The enantioselectivity is expressed as the enantiomeric excess (ee) of *S*-(+)-**2** at full conversion: ee (%) = $100\times(S-R)/(S+R)$. The initial hydrogenation rate (r_0) was evaluated from the rate of hydrogen uptake at 20% conversion where the effect of the contaminant (stilbene, less than 2 wt% of the substrate) can be neglected.

Results

Preliminary experiments showed that supported Pd catalysts prepared by a precipitation-deposition method have much higher activities in the enantioselective hydrogenation of **1** than those prepared by an impregnation method.[12] The use of $PdCl_2$ as the starting salt of palladium was also found to be preferable. Therefore, we report here on the effects of other preparation variables on the performance of Pd catalysts prepared by a precipitation-deposition method with $PdCl_2$.

Influence of Support Texture. In a previous paper,[16] we showed that the textural properties of support materials have a decisive influence on the behavior of **CD**-modified Pd catalysts in the enantioselective hydrogenation of **1**. Both the activity and the enantioselectivity of 5wt%Pd/SiO_2 catalysts, prepared by an impregnation method and reduced in situ at 298 K, increased with increasing average pore diameter of SiO_2 employed. It was suggested that Pd metal particles located only in the pores, large enough for the bulky molecules of both the modifier and the substrate or for the substrate-modifier complex[15] to diffuse through, can behave as selective sites. Palladium metal particles in smaller pores are difficult to modify, and behave as nonselective sites, while those in much smaller pores, inaccessible even to the substrate molecules, lead to a lowered total activity of the catalyst. This idea was supported by the result of the reduction temperature dependence measured with another series of Pd/SiO_2 catalysts, prepared by a precipitation-deposition method with different silica gels having different pore structures. As shown in Fig. 1, the catalysts reduced at 298 K showed similar ee values, irrespective of the difference in the support texture, while a striking difference was observed in their behaviors when these catalysts were reduced at elevated temperatures. The enantioselectivity of the catalyst supported on a nonporous silica (silica-1, Fluka Cab-osil M-5) was increased by reduction at higher temperatures up to 573 K. Heat treatments of the other two catalysts resulted in losses of the enantioselectivity, to a small extent for the catalyst supported on a wide-pore silica (silica-2, Fuji Silysia Chemical FL60D), and to a large extent for that supported on a silica having micropores (silica-3, Wakogel C-200), both accompanying great decreases in the activity. The latter catalyst almost completely lost its enantioselectivity and activity after reduction at 473 K. These observations can be explained similarly to those with the impregnated catalysts mentioned above. Most of the Pd species, precipitated and deposited only on the exterior surface of the support, can be selective sites after low-temperature reduction, while Pd metal particles sintered by a heat treatment would narrow the pores and hinder the diffusion of bulky molecules, thereby lowering the selectivity as well as the activity. The detrimental effects of Pd metal particles located in micropores were also observed in the behavior of commercial Pd/C catalysts.[16] An eggshell-type catalyst with Pd metal particles located on the exterior surface of charcoal exhibited much higher ee than those with Pd located deeper within the pore structure and with Pd evenly dispersed throughout the support structure. Therefore, nonporous ultra-fine materials seem to be suitable as a support of Pd catalysts for this reaction.

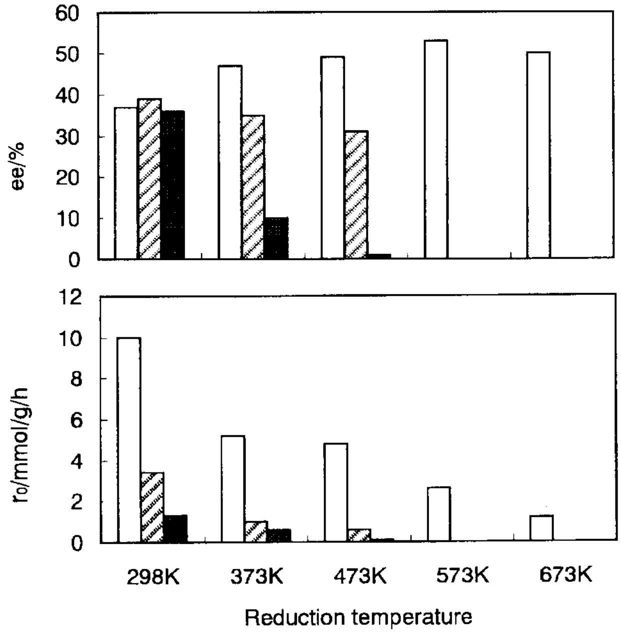

Fig. 1. Effect of pre-reduction temperature on activity (r_0) and enantioselectivity (ee) of 5wt%Pd/SiO_2 catalysts prepared by a precipitation-deposition method with different silica gels having different support textures. Reaction conditions as for Table 1. □: Pd/silica-1, ▨:Pd/silica-2, ■:Pd/silica-3.

In order to confirm the importance of the support texture, we prepared 5wt%Pd-supported catalysts using different kinds of supports with different textural properties. Their catalytic performances in the enantioselective hydrogenation of **1** were compared after being reduced at 473 K for 1 h. As listed in Table 1, the catalysts prepared with nonporous silica, alumina, and titania exhibited higher enantioselectivities and activities than those prepared with respective porous materials of these supports. Among the four kinds of nonporous supports examined, titania was found to be the best, as already expected in our earlier report.[14] It is noteworthy that not

Table 1. Influence of Support Texture on Catalytic Performance of 5wt%Pd-Supported Catalysts in the Enantioselective Hydrogenation of (*E*)-α-Phenylcinnamic Acid [a]

Support	$Sa^{b)}$	Texture	$D_M^{c)}$	$ee^{d)}$	$r_0^{e)}$
	$m^2\,g^{-1}$			%	$mmol\,g^{-1}\,h^{-1}$
SiO_2 (Fluka Cab-osil M-5)	197	nonporous		49.1	6.0
SiO_2 (Fuji Silysia Chemical FL60D)	300	10 nm pore		30.7	0.6
Al_2O_3 (Sumitomo Chemical AMS-12)	42	nonporous		48.5	3.0
Al_2O_3 (Sumitomo Chemical A-26)	4	wide pore		31.1	0.8
ZrO_2 (JRC-ZRO-1)	15	nonporous		46.7	9.5
ZrO_2 (Nippon Shokubai NS-0Y)	25	nonporous		47.7	12.7
TiO_2 (Ishihara Sangyo TTN-55(N))	39	nonporous	0.25	59.7	24
TiO_2 (JRC-TIO-3)	40	nonporous	0.26	62.0	19
TiO_2 (Ishihara Sangyo ST-21)	65	~ nonporous	0.26	55.0	15
TiO_2 (HyCOM-1)[f]	140	~ nonporous	0.31	43.3	14
TiO_2 (Ishihara Sangyo ST-01)	319	porous	0.40	29.4	9

a) Reaction conditions; catalyst: 0.02 g, solvent: 10 cm^3 of B (2.5 vol% H_2O in 1,4-dioxane), substrate (**1**): 1 mmol, modifier (**CD**): 0.02 mmol, H_2: 0.1 MPa, reaction temperature: 298 K. b) Specific surface area of support. c) Degree of Pd dispersion estimated from CO uptake. d) Enantiomeric excess of **2** at full conversion. e) Initial hydrogenation rate. f) A microcrystalline anatase titania synthesized by hydrothermal crystallization in organic media.[29]

only the reaction rate, but also the ee value, varies depending on the surface area of the nonporous titania; the smaller is the surface area of titania, the higher is the enantioselectivity of the catalyst. This strongly suggests that lower Pd dispersion is preferable for enantioselectivity.

Effect of Reduction Temperature. As shown above for the SiO_2-supported Pd catalysts, catalytic performance is strongly influenced by the reduction conditions of the catalysts. For catalysts prepared with nonporous SiO_2 (silica-1), reduction at elevated temperatures resulted in higher selectivities, although the specific activity decreased with increasing reduction temperature, which was an expected result of sintering.[16] The standard catalyst, 5wt%Pd/TiO_2 prepared with nonporous titania (JRC-TIO-3), showed a similar dependence on the reduction temperature, as shown in Fig. 2, while the optimal temperature for ee was around 473 K, lower than that for the Pd/SiO_2 (silica-1) catalyst.

The heat treatment of catalysts would bring about the removal of surface contaminations as well as the sintering of metal particles, leading to an increase in the enantioselectivity of the modified catalyst. The detrimental effect of surface contaminations, remaining after low-temperature reduction, has been suggested from the results of adsorption measurements for the modifier; the amount of **CD** adsorbed per unit surface area of Pd metal was greatly increased by reduction at 473 K for all of the catalysts examined.[14] Since an increase in the amount of adsorbed **CD** is known to result in a great decrease in the hydrogenation rate of **1**,[5] the observed decrease in the activity as a result of the heat treatment can also be attributed to the removal of surface contaminations. Therefore, the effect of the reduction temperature is not necessarily explained only in terms of Pd dispersion in the catalyst.

Effect of Pd Loading. In order to vary the Pd dispersion, a series of Pd/TiO_2 catalysts with different Pd loadings were prepared under otherwise standard conditions using a nonporous titania (JRC-TIO-3) as the support. The results of the hydrogenation with these catalysts are given in Table 2 together with the result on a Pd black catalyst. The Pd dispersion decreased from 0.72 to 0.14 with increasing Pd loading from 0.5 to 20 wt% in the catalyst. Both the activity and enantioselectivity increased with increasing Pd loading up to 5 wt%. A similar dependence of the catalytic performance on the metal loading was reported for the hydrogenation of ethyl pyruvate with a series of **CD**-modified Pt/Al_2O_3 catalysts.[24—26] It is noteworthy that higher Pd loadings than 10 wt% were quite unfavorable for the hydrogenation of **1**, in contrast to the results on **CD**-modified Pt systems. Drastic decreases both in ee and the specific activity (r_{Pd}) were observed for those catalysts with Pd dispersions lower than 0.2. The optimal Pd dispersion seems to be around 0.2—0.3.

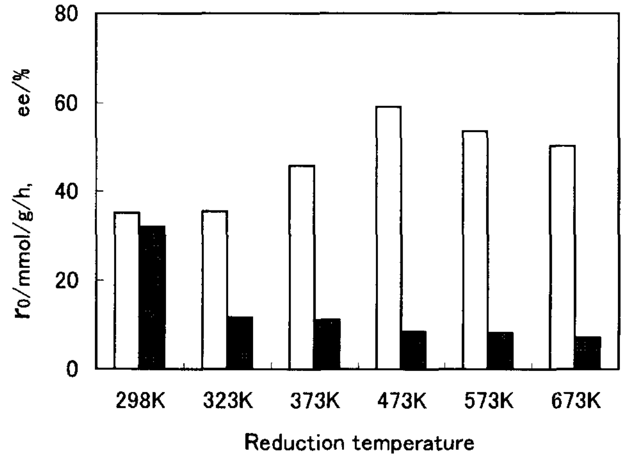

Fig. 2. Effect of pre-reduction temperature on activity (r_0, ■) and enantioselectivity (ee, □) of 5wt%Pd/TiO_2 catalyst prepared with a nonporous titania. Reaction conditions as for Table 2.

Table 2. Effect of Pd Loading in Pd/TiO_2 Catalysts on Catalytic Performance in the Enantioselective Hydrogenation of (*E*)-α-Phenylcinnamic Acid [a)]

Pd loading wt%	$D_M^{b)}$	ee[c)] %	$r_0^{d)}$ mmol g^{-1} h^{-1}	$r_{Pd}^{e)}$ mmol m^{-2} h^{-1}
0.5	0.72	39.5	2.4	1.8
1.0	0.47	45.0	3.5	2.0
2.0	0.41	54.5	5.3	1.8
2.5	0.35	58.8	8.1	2.5
5.0	0.26	58.6	14.6	3.0
10	0.19	58.2	9.8	1.4
20	0.14	17.3	3.0	0.3
Pd black[f)]	0.02	8.0	0.6	0.1

a) Reaction conditions; solvent: 10 cm^3 of A (10 vol% H_2O in DMF), others as for Table 1. b) Degree of Pd dispersion estimated from CO uptake. c) Enantiomeric excess of **2** at full conversion. d) Initial hydrogenation rate per gram of catalyst. e) Initial hydrogenation rate per unit surface area of Pd metal. f) Wako Pure Chemical, 9.3 m^2 g^{-1}.

Effect of Precipitation Conditions. In the early stage of our studies on this Pd catalyst system, we noticed that the catalytic properties, especially the activity, varied considerably depending on the batch of the catalyst preparation. In particular, the precipitation conditions, such as the amount of alkali precipitant, seemed to be important. Also, in the preparation of supported Ni catalysts used for the enantioselective hydrogenation of β-keto esters, the precipitation parameters had a decisive influence on the enantioselectivity.[30] Besides, it is well known that the use of chlorine-containing precursors is beneficial for modified catalyst systems.[25,31,32] Since we prepare the Pd catalysts from $PdCl_2$, the precipitation and washing conditions may affect the chlorine contents in the resulting catalysts.[33] Therefore, we examined the influence of these preparation conditions on the behavior of resulting catalysts in the enantioselective hydrogenation of **1** using otherwise-standard 5wt%Pd/TiO_2 catalysts. From the results given in Table 3, it is clear that an increase in the amount of added precipitant results in a remarkable decrease in the amount of residual Cl and an increase in that of Na in the catalysts before reduction, being accompanied with a significant increase in the activity of the reduced catalysts. Repeated washing with distilled water led to decreases in both the Cl and Na contents in the catalysts, while wash-

Table 3. Influence of Preparation Conditions of 5wt%Pd/TiO_2 Catalysts on Catalytic Performance in the Enantioselective Hydrogenation of (*E*)-α-Phenylcinnamic Acid [a)]

Precipitation	Alkali[b)]	Washing	Na[c)]	Cl[c)]	$D_M^{d)}$	ee[e)]	$r_0^{f)}$
Temp/K	*f*	times	wt%	wt%		%	mmol g^{-1} h^{-1}
348	1	2	0.09	0.48	0.24	55.8	5
348	3	2	0.19	0.41	0.22	61.6	11
348	8	2	0.26	0.04	0.26	62.0	19
348	18	2	0.33	0.02	0.26	59.7	23
348	18	0	1.5	0.51	0.18	53.5	11
348	8	4	0.23	0.03	0.26	61.2	24
348	8	2[g)]	1.0	0.03	0.18	56.1	31
293	2	2	0.10	0.41		55.3	4
293	8	2	0.31	0.05		61.0	19

a) Reaction conditions as for Table 1. b) Molar ratio of added Na_2CO_3 to $PdCl_2$. c) Amounts remaining in the catalyst precursor before reduction. d) Degree of Pd dispersion estimated from CO uptake. e) Enantiomeric excess of **2** at full conversion. f) Initial hydrogenation rate. g) Washed with a 0.1 mol/dm^3 Na_2CO_3 aqueous solution instead of distilled water.

ing with an alkaline solution led to a great decrease only in the Cl content; both procedures are again accompanied with an increase in the activity of the reduced catalysts. From these observations, the significant variation in the activity is attributable to changes in both the Na and Cl contents; the residual Na and Cl exhibit favorable and unfavorable effects, respectively, on the activity in this reaction. As for the enantioselectivity, smaller amounts of residual Na and Cl seem to be preferable, although the effects of both species on ee are not very obvious. After all, catalysts should be prepared with a large excess amount of precipitant and washed repeatedly with water, in order to remove both of the residual Na and Cl as thoroughly as possible and to improve the performance of the modified catalyst.

The precipitation temperature seems to have little influence on both the activity and the enantioselectivity of the resulting catalysts. Precipitation at ambient temperatures is, however, not recommended because of the poor reproducibility; the precipitation reaction tends to be incomplete, and thus the Pd loading becomes uncertain.

Discussion

The enantioselective hydrogenation of carbonyl groups with modified Ni and Pt catalysts has been reported to be structure sensitive. The enantioselectivities obtained in the reactions of β-keto esters with tartaric acid-modified Ni catalysts[20—23] and of α-keto esters with cinchonidine-modified Pt catalysts[24—26] are known to increase with increasing crystallite size of Ni and Pt, respectively, under otherwize fixed conditions. However, other factors, such as support texture, contaminants, and morphology of the catalysts, tend to make the dispersion dependence ambiguous. Since some of our Pd catalysts, used here for the enantioselective hydrogenation of **1**, were prepared by using nonporous titania and reduced at a relatively high temperature, the results are thought to be appropriate for assessing the Pd dispersion dependence.

In Fig. 3, the ee values are plotted against the Pd dispersions for selected Pd/TiO_2 catalysts in Tables 1, 2, and 3, i.e., for those prepared with nonporous titania under standard conditions and reduced at 473 K. It is clear that this reaction is mildly structure sensitive in the dispersion range higher than 0.2; lower Pd dispersion is favorable similarly to the tendencies observed in Pt and Ni systems for the enantioselective hydrogenation of carbonyl groups of α- and β-keto esters, respectively. However, it is noteworthy that ee suddenly decreases with decreasing dispersion of Pd in the range lower than 0.2, in accord with the tendency observed in the hydrogenation of **1** with Pd catalysts modified with a bulky vinca-type alkaloid,[9] and in a great contrast to the tendency reported for the Pt and Ni systems as mentioned above.

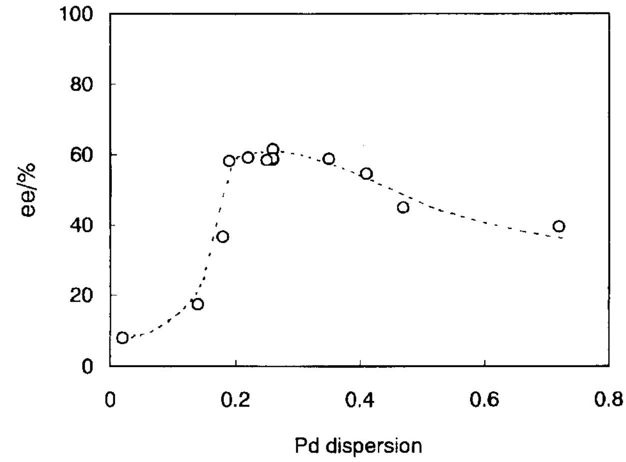

Fig. 3. Correlation between Pd dispersion and the enantioselectivity of cinchonidine-modified Pd/TiO_2 catalysts in the hydrogenation of (*E*)-α-phenylcinnamic acid. Reaction conditions as for Table 2.

It is reasonable to suppose that well-crystallized particles with large ensembles of regularly arranged Pd atoms in the surface generally have a better chance to adsorb the large molecules of both **CD** and **1**, interacting with each other in a proper conformation, which may lead to a high enantioselectivity. When the interaction between an adsorbed modifier and the substrate is relatively weak or flexible, as in the case of the tartaric acid-modified Ni system, the adsorption of the interacting molecules on the metal surface should be tight enough for effective enantioface differentiation.[18] With the **CD**-modified Pt system, one hydrogen bonding between the tertiary nitrogen of the modifier and the oxygen at the α-carbonyl group of the substrate has been proposed.[34] In the case of the enantioselective hydrogenation of **1** with **CD**-modified Pd catalysts, the basic **CD** molecule is supposed to interact with the acidic substrate molecule rigidly enough via two hydrogen bondings.[15] The steric constraint of the modifier-substrate complex interacting with Pd surface is also large enough for the bulky species to adsorb with a controlled orientation, i.e., with the quinoline ring of CD parallel to the metal surface. Therefore, the role which the metal surface plays in the stage of enantioface differentiation would not be as important as in the cases of modified Ni and Pt systems. Thus, the slight difference between the Pd and Pt systems in the dependence on metal dispersion in the range higher than 0.2, i.e., a relatively mild dependence of Pd system, could be attributed to the differences in the adsorption and interaction modes between the modifier, substrate and metal surface.

The strikingly different behavior of Pd catalysts with very low dispersion in the enantioselective hydrogenation of **1** could also be explained in terms of the adsorption mode of the intermediate complex on the Pd surface. It is conceivable that the overly tight adsorption of **CD** on large Pd atom ensembles hinders the C=C double bond of **1** to approach the Pd surface and to be hydrogenated, which would lead to a lowered activity and selectivity. In other words, the rigid interaction between **CD** and **1** cannot be preserved when **CD** is adsorbed tightly on a flat surface of a large Pd ensemble. When the substrate is relatively small and does not have such a bulky substituent around the C=C bond as **1** has, the low Pd dispersion would cause little problem. This may be the case in the hydrogenation of isophorone with Pd catalysts modified with a vinca-type alkaloid, where ee increased with decreasing Pd dispersion and a Pd black catalyst exhibited the highest enantioselctivity.[9] Also, in the hydrogenation of isophorone with **CD**-modified Pd catalysts, Tungler et al. reported that a Pd black catalyst ($D_M = 0.1$) gave a higher ee than a Pd/C catalyst ($D_M = 0.5$).[35] The substituent groups around the C=O bonds of methyl and ethyl pyruvates, the substrates used in the Pt-cinchona system, are much less bulky than those of **1** used in this study. Thus, the difference in the steric hindrance between the modifier-substrate complex and the Pd surface can be a reason for the different behaviors of the Pt and Pd systems in the dispersion dependence. Concerning the adsorption mode of the modifier-substrate complex, Borszeky et al. have proposed an arrangement of a **CD**-unsaturated acid dimer adduct on an ideal flat Pd surface, and indicated that the adsorption of a **CD** : acid 1 : 1 adduct on the Pd surface is sterically hindered.[8,36] Therefore, the adsorption mode or the configuration of the **CD-1** complex could change depending on the Pd dispersion, as suggested for the adsorption of the **CD**-methyl pyruvate complex on Pt surfaces.[27]

Treatments of catalysts with halogen compounds are known to affect the dispersion of noble metal particles. The presence of residual chlorine in Pt and Pd catalysts during the reduction process was reported to inhibit the growth of metal particles,[37,38] rather than to promote it as observed in the preparation of Ni and Co catalysts.[31,39] Actually, as shown in Table 3, the Pd dispersion was scarcely affected by the Cl content in the precursor, while a precursor with a large amount of residual Na resulted in a catalyst with relatively low Pd dispersion. Therefore, the unfavorable effect of residual Cl on the activity cannot be explained by a change in the Pd dispersion during the heat treatment. Rather, the effect of the adsorbed Cl still remaining on the catalyst surface after the reduction process seems to be responsible for the low activity. As for the influence on the enantioselectivity, the presence of residual Cl exhibited no distinct effect on ee, in contrast to the favorable promoter action of the Cl ion in the hydrogenation of α-keto esters with enantioselective Pt and Ir catalysts.[25,32] On the other hand, the presence of a relatively large amount of residual Na in the catalyst precursor gave superior activity, but inferior enantioselectivity to the resulting catalyst. This is in harmony with our previous observation that the addition of NaOH to the reaction mixture considerably increases the activity, but decreases the selectivity of the enantioselective hydrogenation of **1** with the standard catalyst.[17]

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