

Enantioselective Hydrogenation of (*E*)- $\alpha$ -Phenylcinnamic Acid over Cinchonidine-Modified Palladium Catalysts

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Prochiral (*E*)- $\alpha$ -phenylcinnamic acid was hydrogenated enantioselectively over alumina- and titania-supported Pd catalysts modified with cinchonidine giving optical yields of 36.9% and 44.4%, respectively, in favor of (*S*)-(+)-2,3-diphenylpropionic acid. The influence of solvent on the optical yield was significant ; a water containing solvent gave the best result.

Enantioselective hydrogenation using chiral heterogeneous catalysts has attracted much attention and some catalytic systems have been studied systematically. There are two families of synthetically useful catalytic systems: tartaric acid-modified Ni catalysts for enantioselective hydrogenation of  $\beta$ -ketoesters<sup>1)</sup> and cinchona alkaloids-modified platinum catalysts for  $\alpha$ -ketoesters.<sup>2)</sup> As for the enantioselective hydrogenation of prochiral C=C bonds, there is no preparatively useful, heterogeneous catalytic system reported until now.<sup>3)</sup>

Recently, Bartok et al.<sup>4)</sup> studied the hydrogenation of substituted cinnamic acids containing a prochiral C=C bond and their salts over a Raney-Ni catalyst modified with tartaric acid. They reported that the hydrogenation of the Na salt of (*E*)- $\alpha$ -phenylcinnamic acid (**1**) gave the highest optical yield of 17% whereas the hydrogenation of the acid gave only a low optical yield of 0.21%. In an earlier report, Perez et al.<sup>5)</sup> showed that **1** was enantioselectively hydrogenated to (*S*)-2,3-diphenylpropionic acid (**2**) with an optical yield of 30.5% over a 5wt% Pd/C catalyst modified with cinchonidine. These findings suggest that cinchona alkaloids-modified catalyst systems are more favorable than tartaric acid-modified systems for the substrate **1** to display enantioselectivity. As it is well known that the preparation variables of the modified catalysts as well as the reaction conditions have significant influence on the enantioselectivity, we examined the effects of some preparation variables of Pd catalysts and the solvent used for the reaction.

Supported 5wt% Pd catalysts were prepared by impregnation to incipient wetness (*i*) using an aqueous solution of Pd(NH<sub>3</sub>)<sub>4</sub>Cl<sub>2</sub> or by a precipitation method (*p*) at 348 K with aqueous solutions of PdCl<sub>2</sub> and Na<sub>2</sub>CO<sub>3</sub>. Support materials used are Al<sub>2</sub>O<sub>3</sub>(JRC-ALO-4, Catalysis Society of Japan), TiO<sub>2</sub>(JRC-TIO-3, Catalysis Society of Japan), SiO<sub>2</sub>(Silica gel No.1, Nacalai tesqu), and activated carbon(HC-42, Tsurumicoal). The catalyst precursors were dried at 383 K for 20 h and reduced just before use by stirring in a solvent under an atomospheric pressure of hydrogen at 298 K for 1 h unless otherwise stated. The impregnated precursors were calcined at 773 K for 3 h prior to the hydrogen reduction. Two commercial 5wt% Pd/C catalysts were also used for comparison.

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The hydrogenation was carried out at 298 K under an atmospheric pressure or 1 MPa of hydrogen in autoclave using a magnetic stirring system of 1200 rpm. The substrate **1** (5 mmol) was hydrogenated in a solvent (25 cm<sup>3</sup>) in the presence of 0.15 g of a Pd catalyst and 0.15 mmol of cinchonidine.

After the hydrogen uptake finished, the catalyst was removed from the solution and the product was isolated according to the procedure described in the literatures<sup>4,5)</sup> as follows. After evaporating off the solvent, the solid residue was dissolved in a mixture of 10 cm<sup>3</sup> ethyl acetate and 15 cm<sup>3</sup> 0.6 N HCl. The ethyl acetate phase was washed twice with distilled water and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, the ethyl acetate was evaporated off in vacuo. The optical yield (OY) was calculated from the optical activity at 293 K for a 10 g/100 cm<sup>3</sup> acetone solution of the product and the specific rotation of **2**:  $[\alpha]_D^{20}=133.7^\circ(c: 0.535, \text{acetone})$ .<sup>6)</sup>

In spite of the good results given in reference (5) with a Pd/C catalyst, our preliminary experiments showed that Pd/C catalysts, both commercial and prepared by impregnation, exhibit very low hydrogenation activities. This is probably attributable to the difference in the method of catalyst preparation, although Perez et al.<sup>5)</sup> did not describe the preparation details of their Pd/C catalyst.

Table 1 lists the hydrogenation results in various solvents over a Pd/Al<sub>2</sub>O<sub>3</sub> catalyst prepared by the impregnation method. The influence of the solvent on the optical yield of **2** was significant. A mixed solvent of ethyl acetate and 95% ethanol, employed previously in reference (5) without any explanation, gave the highest optical yield especially under a low hydrogen pressure (entry 8). Ethyl acetate only or pure ethanol, however, did not give as high optical yield as the mixed solvent. This finding led us to examine the influence of water contained in ethanol. As shown in Fig. 1, the water content ( $C_w$ ) in the mixed solvent (ethyl acetate : ethanol : water = 60 : 40 -  $C_w$  :  $C_w$ ) strongly affected the OY and slightly increased the activity; 10–15% water gave the best result. The positive effect of water on this reaction is in good contrast with the hydrogenation of  $\beta$ -keto esters on tartaric acid-modified Ni catalysts.<sup>1)</sup> Blaser and Jalett reported the influence of the polarity of solvent on the enantioselectivity of cinchonidine-modified Pt catalysts for the hydrogenation of  $\alpha$ -keto esters and acids.<sup>7)</sup> Further studies are needed to explain the solvent effects satisfactorily.

Table 2 compares the enantioselectivity and activity of various Pd catalysts prepared by two different methods. The catalysts prepared by a precipitation method have higher activities than those prepared by an

Table 1. Solvent effect on the enantioselective hydrogenation<sup>a)</sup> of (*E*)- $\alpha$ -phenylcinnamic acid over a 5wt%Pd/Al<sub>2</sub>O<sub>3</sub>(*i*) catalyst

No.	Solvent	H <sub>2</sub> pressure/MPa	OY <sup>b)</sup> /%
1	Methanol	1.0	12.1
2	Ethanol	1.0	8.1
3	2-Propanol	1.0	8.2
4	Ethyl acetate	1.0	1.6
5	Tetrahydrofuran	1.0	9.3
6	Mixed solvent <sup>c)</sup>	1.0	12.1
7	Methanol	0.1	14.4
8	Mixed solvent <sup>c)</sup>	0.1	17.5

a) Hydrogenation: 5 mmol of substrate in 25 cm<sup>3</sup> solvent, at 298 K.

b) Optical yield of (*S*)-2,3-diphenylpropionic acid.

c) Ethyl acetate(15 cm<sup>3</sup>) + 95% Ethanol(10 cm<sup>3</sup>) ;  $C_w = 2 \text{ vol\%}$ .

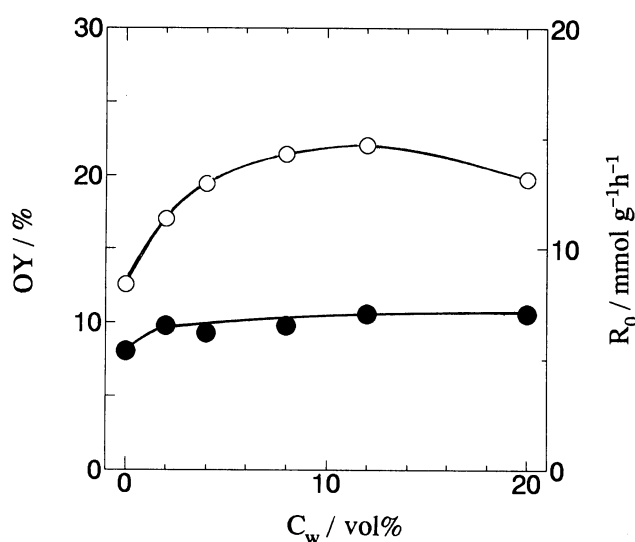


Fig. 1. Effect of water in mixed solvent on the enantioselectivity and activity of 5wt%Pd/Al<sub>2</sub>O<sub>3</sub> (*i*) catalyst.  
○: Optical yield of (*S*)-2,3-diphenylpropionic acid, ●: initial hydrogenation rate ( $R_0$ ).

impregnation method. This is probably because of the detrimental effects of remaining chlorine in the impregnated catalysts. The effects of support materials were also significant both on the selectivity and activity. Alumina- and titania-supported catalysts seem to be most favorable.

Published data on enantioselective catalysts for the hydrogenation of keto esters indicate that the improvement in the crystallinity of metal are beneficial for obtaining higher enantioselectivity.<sup>7-9)</sup> Therefore, Pd/Al<sub>2</sub>O<sub>3</sub> and Pd/TiO<sub>2</sub> catalysts were reduced by heating in a hydrogen stream at higher temperatures for 1h in order to increase the crystallite size of Pd, and used for the hydrogenation under the best reaction conditions described above. As shown in Table 3, the high-temperature reduction of the catalysts prepared by the

Table 2. Effects of support and preparation method on the enantioselectivity of 5wt%Pd/Support catalysts<sup>a)</sup>

No.	Support	Preparation method	OY <sup>b)</sup> /%	$R_0$ <sup>c)</sup> /mmol g <sup>-1</sup> h <sup>-1</sup>
1	SiO <sub>2</sub>	impregnation ( <i>i</i> )	18.1	1.6
2	Al <sub>2</sub> O <sub>3</sub>	impregnation ( <i>i</i> )	17.5	6.6
3	TiO <sub>2</sub>	impregnation ( <i>i</i> )	20.9	6.1
4	C	<i>d</i> )	14.4	1.1
5	C	<i>e</i> )	21.3	0.8
6	SiO <sub>2</sub>	Precipitation ( <i>p</i> )	17.0	16.2
7	Al <sub>2</sub> O <sub>3</sub>	Precipitation ( <i>p</i> )	21.0	20.0
8	TiO <sub>2</sub>	Precipitation ( <i>p</i> )	18.8	41.1
9	C	Precipitation ( <i>p</i> )	10.1	7.3

*a)* Hydrogenation: 5 mmol of (*E*)- $\alpha$ -phenylcinnamic acid in 25 cm<sup>3</sup> of mixed solvent (see Table 1), at 298 K under 0.1 MPa of H<sub>2</sub>. *b)* Optical yield of (*S*)-2,3-diphenylpropionic acid. *c)* Initial hydrogenation rate.

*d)* A commercial Pd/C catalyst obtained from Nacalai Tesqu, Inc. *e)* A commercial Pd/C catalyst obtained from Wako Pure Chemical Ind.

Table 3. The enantioselectivity of 5wt%Pd/Al<sub>2</sub>O<sub>3</sub> and 5wt%Pd/TiO<sub>2</sub> catalysts reduced at higher temperatures<sup>a)</sup>

No.	Catalyst	Reduction conditions	OY <sup>b)</sup> /%	R <sub>0</sub> <sup>c)</sup> /mmol g <sup>-1</sup> h <sup>-1</sup>
1	Pd/Al <sub>2</sub> O <sub>3</sub> (i)	298 K, 1 h	22.1	7.0
2	Pd/Al <sub>2</sub> O <sub>3</sub> (i)	573 K, 1 h	25.7	27.0
3	Pd/TiO <sub>2</sub> (i)	573 K, 1 h	22.3	3.0
4	Pd/Al <sub>2</sub> O <sub>3</sub> (p)	473 K, 1 h	31.3	23.8
5	Pd/Al <sub>2</sub> O <sub>3</sub> (p)	573 K, 1 h	36.9	29.2
6	Pd/Al <sub>2</sub> O <sub>3</sub> (p)	673 K, 1 h	33.5	19.5
7	Pd/TiO <sub>2</sub> (p)	473 K, 1 h	44.4	23.6
8	Pd/TiO <sub>2</sub> (p)	573 K, 1 h	42.4	28.1
9	Pd/TiO <sub>2</sub> (p)	673 K, 1 h	39.6	19.2

a) Hydrogenation: 5 mmol of (*E*)- $\alpha$ -phenylcinnamic acid in 25 cm<sup>3</sup> of a mixed solvent (ethyl acetate : ethanol : water = 15 : 7 : 3), at 298 K under 0.1 MPa of hydrogen.

b) Optical yield of (*S*)-2,3-diphenylpropionic acid. c) Initial hydrogenation rate.

precipitation method resulted in markedly increased optical yields keeping the high reaction activities of the original catalysts. The Pd/TiO<sub>2</sub>(p) catalyst reduced at 473 K gave the highest optical yield (44.4%) of **2** in the data reported with heterogeneous catalysts so far.<sup>3)</sup>

The favorable or unfavorable effects of water, residual chlorine, and the crystallite size of Pd may be related to the adsorption and interaction modes of the substrate and the modifier on Pd surface. Further studies on the preparation of enantioselective Pd catalysts and on the effects of reaction variables are currently underway in order to increase the optical yield of **2** and also for the hydrogenation of various compounds with the prochiral C=C double bond.

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