Conversion Dependence of Enantioselective Hydrogenation of (*E*)-α-Phenylcinnamic Acid on Cinchonidine-Modified Pd/TiO_2 Catalyst

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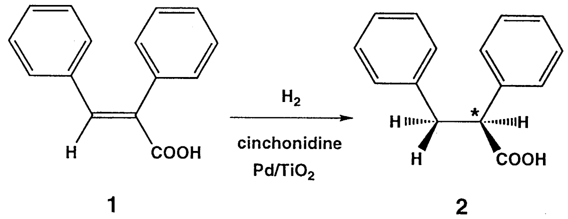
The enantioselectivity of a cinchonidine-modified Pd/TiO_2 catalyst varied with the extent of conversion in the hydrogenation of (*E*)-α-phenylcinnamic acid. The incremental enantioselectivity reached a maximum at an early stage of the reaction. Under optimized reaction conditions, optical yields of up to 72%e.e. of (*S*)-(+)-2,3-diphenylpropionic acid were obtained at 100% conversion.

Enantioselective hydrogenation of prochiral C=C bonds using heterogeneous chiral catalysts is a challenging subject.[1] Recently, palladium-catalyzed enantioselective hydrogenation of α,β-unsaturated ketones and acids has received increasing attention.[2-4] In the previous study, we reported that (*E*)-α-phenylcinnamic acid (**1**) was hydrogenated to yield (*S*)-(+)-2,3-diphenylpropionic acid (**2**) on cinchonidine-modified Pd/TiO_2 catalysts with much higher optical yields of 44-58%[5-7] than those reported for a Pd/C catalyst.[8] However, re-use of the catalyst separated from the reaction mixture resulted in an almost complete loss of the enantioselectivity, unless the modifier was added freshly. This finding suggests that the adsorption of cinchonidine on the catalyst surface is relatively weak.[9] Therefore, we examined here the effect of conversion on the optical yields of **2**, in order to obtain some insight into the stability of the adsorbed modifier, and to improve the enantioselectivity of this catalyst.



1 **2**

The 5 wt%Pd/TiO_2 catalyst was prepared by a deposition-precipitation method at 348 K with an aqueous suspension of $PdCl_2$ and TiO_2 (JRC-TIO-3, Catalysis Society of Japan) and with Na_2CO_3 as the precipitant. The catalyst precursor was dried at 383 K for 20 h and reduced before use by heating at 473 K in a hydrogen flow of 8 dm^3/h for 1 h. The hydrogenation reactions were carried out in a mixed solvent of *N,N*-dimethylformamide and water (9:1 in volume) at 298 K under an atmospheric pressure of hydrogen unless otherwise stated. Cinchonidine was added to the suspension of the reduced catalyst and hydrogenated by stirring for 20 min under a hydrogen atmosphere prior to the addition of the substrate **1**. The products were isolated from the reaction mixture according to the procedure described before,[5] converted to the methyl esters by the reaction with $CH_3OH/BF_3 \cdot CH_3OH$, and analyzed by HPLC equipped with a chiral detector (OR-990, JASCO) on a chiral column (CHIRALCEL OJ-R, DAICEL). The optical yield was expressed as the enantiomeric excess (e.e.) of **2**:

$$\text{e.e.}(\%) = 100 \times (S-R)/(S+R).$$

The initial hydrogenation rate (r_0) was measured at 20% conversion based on the hydrogen uptake.

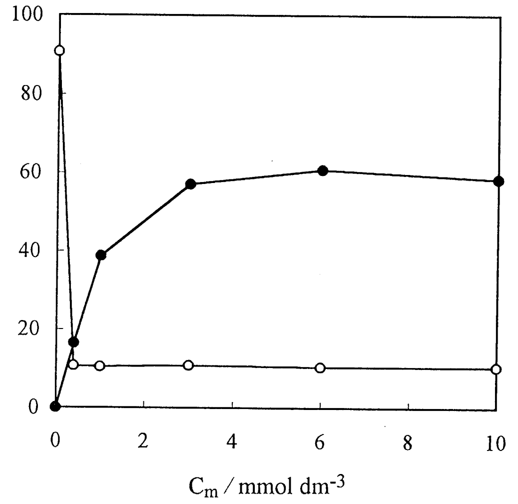


Figure 1. Influence of the concentration of cinchonidine (C_m) on the e.e. (●) and the initial hydrogenation rate, r_0 (○). Reaction conditions: catalyst 0.06 g, substrate 2 mmol (C_s = 0.2 mol/dm^3), solvent 10 cm^3, temperature 298 K, hydrogen pressure 0.1 MPa.

Figure 1 shows the effects of the cinchonidine concentration (C_m mmol/dm^3) on the e.e. of the final product and the initial rate of hydrogenation. There is a smooth increase in the e.e. with increasing C_m before reaching the maximum level of e.e. at around C_m = 3, where the modifier is present in 1.5 mol% with respect to the substrate. On the other hand, the initial rate of the hydrogenation drops rapidly upon addition of much smaller amount of the modifier, *i.e.*, less than 0.2 mol% with respect to the substrate, and remains constant with increasing C_m. Quite similar dependences of the e.e. and the reaction rate on the modifier concentration were reported for the hydrogenation of isophorone with a modified Pd/C catalyst.[2] These observations suggest that modification of the catalyst surface occurs also in this catalytic system, similarly to the Pt/cinchona system for the hydrogenation of α-ketoesters.[4] During the course of the hydrogenation with a relatively small amount of the modifier (0.4-1.0 mmol/dm^3), however, we observed a slight increase in the hydrogenation rate with increasing extent of conversion. This suggests that the modifier molecules, once-adsorbed, gradually desorb from the Pd surface in the presence of the reactant molecules, which will lead to a decrease in the enantioselectivity of the catalyst with increasing conversion.

As shown in Figure 2, decreases in the e.e. with increasing conversions were observed for both reactions with high and low concentrations of the modifier. The relatively low e.e. at the beginning of the reactions can be explained by the instability of the modified surface before the steady state is reached.[10] Since the e.e. value, measured by withdrawing a sample at a reaction time, is a cumulated optical yield of **2** produced up to that point, the incremental enantioselectivity e.e.$_{(inc)}$ was calculated to obtain the information of the working state of the catalyst.[4,9] The e.e.$_{(inc)}$ means the real enantioselectivity between two points of measurements and is given as follows:

$$\text{e.e.}_{(inc)} = [c_i \times (\text{e.e.})_i - c_{i-1} \times (\text{e.e.})_{i-1}] \,/\, (c_i - c_{i-1})$$

where c_i is the conversion and $(\text{e.e.})_i$ is the e.e., both measured at the ith point. As can be seen from Figure 2a, the e.e.$_{(inc)}$ reached up to 80% at the conversion of around 20%. However, a rapid decrease in the e.e.$_{(inc)}$ with increasing conversion was observed especially when C_m was low (Figure 2b), supporting the idea that the modifier molecules gradually desorb from the catalyst surface during the reaction, as a result of the competitive adsorption of the substrate and the modifier. The competitive adsorption of the product seems to be negligible because the decrease in the e.e.$_{(inc)}$ becomes less significant at higher conversions, *i.e.*, at higher concentrations of the product.[9] The solvent effect, reported previously,[6] is also in harmony with these findings; a solvent with a relatively poor solubility of the modifier and a high solubility of the substrate seems preferable.

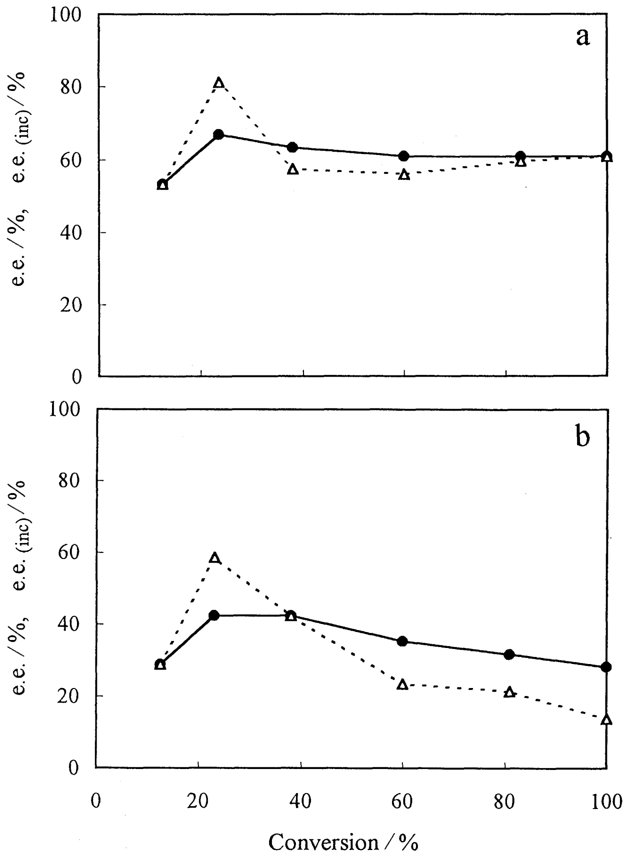


Figure 2. Conversion dependence of the optical yield, e.e.(●) and the incremental enantioselectivity, e.e.$_{(inc)}$ (△) in the reactions with (a) a relatively high concentration of cinchonidine ($C_m = 6$ mmol/dm^3) and (b) a low concentration of cinchonidine ($C_m = 0.6$ mmol/dm^3). Reaction conditions as for Figure 1.

Table 1. Best optical yields obtained in the hydrogenation of (*E*)-α-phenylcinnamic acid with a cinchonidine-modified 5wt%Pd/TiO$_2$ catalyst[a]

Entry	C_m[b] mmol dm^{-3}	C_s[c] mol dm^{-3}	T[d] K	P[e] MPa	e.e.[f] %
1	6.0	0.2	298	0.1	61
2	6.0	0.2	283	0.1	65
3	6.0	0.02	283	0.1	72
4	6.0	0.03	298	0.1	69
5	6.0	0.2	298	0.5	59

[a] Reaction conditions; catalyst: 0.06 g, solvent: 10 cm^3 of 90% *N,N*-dimethylformamide. [b] Concentration of cinchonidine. [c] Concentration of **1**. [d] Reaction temperature. [e] Hydrogen pressure. [f] Optical yield of **2** at 100% conversion.

Taking into account the adsorption equilibrium and assuming the competitive adsorption of the modifier and the substrate, we tried to suppress the desorption of the modifier by carrying out the reactions with a higher concentration of the modifier and a lower concentration of the substrate, and at a lower temperature. Table 1 lists the best results of the optimization. Up to now, 72% e.e. is the highest optical yield in the enantioselective hydrogenation of C=C bonds with heterogeneous catalysts to the best of the authors' knowledge. An increase in the hydrogen pressure was found unfavorable. This is probably because hydrogen, as a reactant, also competes with the modifier on the catalyst surface. The detailed effects of the reaction conditions and the solvents will be reported elsewhere. For further improvement of this catalyst system, it seems promising to keep the modifier adsorbed strongly on the catalyst surface. Studies on this point are now in progress.

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