Importance of Product Desorption in Enantioselective Hydrogenation of (*E*)-α-Phenylcinnamic Acid with a Cinchonidine-Modified Pd/TiO_2 Catalyst: Effect of Additives

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Addition of amines, especially benzylamine, to the reaction mixture of (*E*)-α-phenylcinnamic acid with a cinchonidine-modified palladium catalyst resulted in much enhanced activities and fairly increased enantioselectivities. The preferential acceleration of the selective reaction is attributable to the effective desorption, assisted by the added base, of the hydrogenated molecules from the modified sites.

The enantioselective hydrogenation of C=C double bonds in α,β-unsaturated acids is known to be catalyzed by palladium catalysts modified with cinchona alkaloids.[1-3] The highest enantiomeric excess (e.e.) reported until now, however, is 72% at the most, which was obtained in the hydrogenation of (*E*)-α-phenylcinnamic acid (**1**) to 2,3-diphenylpropionic acid (**2**) with a cinchonidine-modified 5 wt% Pd/TiO_2 catalyst under optimized reaction conditions.[4] The difficulty in obtaining high e.e. in this reaction is considered to arise from the fact that the hydrogenation on unmodified sites is about ten times faster than that on modified sites,[4] in contrast to the hydrogenation of α-ketoesters with cinchona-modified Pt catalysts.[1] This idea is consistent with the finding that a small proportion of Pd metal particles, located in micropores of the support and so left unmodified, leads to a considerable decrease of the overall enantioselectivity in this reaction.[5] Therefore, the kinetic acceleration of the reaction on modified sites, as well as the deactivation of unmodified sites, seems to be promising in order to improve the enantioselectivity. With these considerations in mind, the effect of additives has been studied for the hydrogenation of **1** on a cinchonidine-modified Pd/TiO_2 catalyst.

The 5wt%Pd/TiO_2 catalyst was prepared by a precipitation-deposition method with $PdCl_2$ and nonporous TiO_2 (JRC-TIO-3, Catalysis Society of Japan), and reduced at 473 K for 1 h in a hydrogen flow immediately before use.[4,6] The hydrogenation of **1** (1 mmol) was carried out at 298 K under an atmospheric pressure of hydrogen usually in 10 cm^3 of 1,4-dioxane containing 2.5vol% of water. Amines and other additives were introduced to the reaction mixture just after the addition of the substrate. After the hydrogen uptake finished, the products were isolated from the reaction mixture and washed with dilute HCl to remove added amines and the modifier. Detailed procedures of product analysis are the same as described in our previous papers.[6,7] The enantioselectivity is expressed as an enantiomeric excess (e.e.) of (*S*)-(+)-**2** at full conversion:

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

Initial hydrogenation rates (r_0) were evaluated from the rates of hydrogen uptake at 20% conversion.

Table 1. The effect of additives on the enantioselective hydrogenation of (*E*)-α-phenylcinnamic acid with a cinchonidine-modified 5 wt% Pd/TiO_2 catalyst [a]

Entry	Additive	Amount mmol	Solvent[b]	r_0[c] mmol $g^{-1}h^{-1}$	e.e.[d] %
1	None	---	A	7	59
2	Acetic acid	0.5	A	11	57
3	Ammonia	0.5	A	21	64
4	Diethylamine	0.5	A	32	63
5	Triethylamine	0.5	A	30	65
6	Butylamine	0.5	A	28	60
7	*t*-Butylamine	0.5	A	17	62
8	Aniline	0.5	A	9	57
9	Benzylamine	0.1	A	21	64
10	Benzylamine	0.3	A	33	67
11	Benzylamine	0.5	A	33	71 (81)[e]
12	Benzylamine	0.7	A	34	68 (86)[e]
13	Benzylamine	1.0	A	32	71 (92)[e]
14	Sodium hydroxide	0.5	A	39	45
15	None	---	B	27	48
16	Benzylamine	0.5	B	44	60
17	None	---	C	4	60
18	Benzylamine	0.5	C	10	69

[a] Reaction conditions; catalyst: 20 mg, solvent: 10 cm^3, substrate: 1 mmol, modifier: cinchonidine 0.02 mmol, H_2: 0.1 MPa, reaction temperature: 298 K, stirring speed: 1200 rpm. [b] Solvent; A: 1,4-dioxane + water (2.5 vol%), B: methanol, C: DMF + water (2.5 vol%). [c] Initial reaction rate. [d] Enantiomeric excess of (*S*)-(+)-2,3-diphenylpropionic acid at full conversion. [e] The e.e. value for the product contained only in the filtrate.

Table 1 lists selected results of the effects of additives on the activity (r_0) and the enantioselectivity (e.e.). Acetic acid was found to have rather a detrimental effect on e.e., although it is one of the well-known effective additives for the enantioselective hydrogenation of α-ketoesters with cinchona-modified Pt catalysts[1] and also for the reaction of ketones with tartaric acid-modified Raney-Ni catalysts.[8] This result seems quite reasonable because the added acid will interfere the acid-base interaction of the substrate acid with the modifier.[7] On the other hand, the addition of an amine remarkably increased the activity in almost all cases examined, and some amines also increased the enantioselectivity. Aniline was not effective probably because of the comparatively low basicity. The addition of benzylamine (0.5 to 1.0 molar equivalent to the substrate) was found to be most effective. It is noteworthy that nearly the highest enantioselectivity (71%e.e.) and about five times higher activity were observed under these standard, *i.e.*, not optimized, reaction conditions. In our previous paper,[4] we reported that the highest e.e. (72%e.e.) was achieved in a mixed solvent of *N*,*N*-dimethylformamide (DMF) and water (10 vol%) under relatively extreme conditions, *i.e.*, with three times higher concentration of the modifier, with much lower concentration of the substrate, and under a lower reaction temperature (283 K) than those employed in this study. Sodium hydroxide also much increased the activity of the modified catalyst but markedly decreased the enantioselectivity. This means that the addition of a strong base is rather detrimental, possibly because it makes the modifier desorb from the catalyst surface.

These results indicate that the reaction on modified sites must be preferentially accelerated in the presence of additives such as benzylamine. The initial activity of the unmodified catalyst was rather decreased to about half of the original activity by the addition of benzylamine (0.5 mmol). This is attributable to a poisoning effect of the adsorbed amine or to the apparently lowered concentration of the substrate as a result of the salt formation with the added amine. On the other hand, the reaction rate on modified sites will not be affected so much by the substrate concentration, because the substrate molecules may be adsorbed more strongly on modified sites than on unmodified sites, interacting with the modifier. Therefore, the increase in the enantioselectivity in the presence of amines could be explained in terms of the substrate concentration. Actually, we have observed that the lower concentration of **1** is preferable for the enantioselectivity.[4] However, the greatly enhanced activity observed in the presence of amines cannot be explained by the substrate concentration. A plausible explanation for the preferential activation of the modified sites is, therefore, that the added amine with suitable basicity promotes the desorption of the hydrogenated molecule which is still interacting with the modifier on the catalyst surface,[7] as a result of the acid-base interaction between the added amine and the product. In other words, the rate-determining step for the reaction on modified sites is supposed to be the step of product desorption, being different from that for the reaction on unmodified sites. The importance of the product desorption from modified sites was also suggested by the finding that too slow stirring is unfavorable for the enantioselectivity, in spite of the preferable effect of the lowered concentration of hydrogen in the solution.[4] The favorable effect of water, added to the solvents employed here and in our previous studies,[3,9] could be explained similarly; a small amount of water could behave as a base. However, other factors, such as solubilities of reactants and modifier, should be examined in detail to clarify the effect of solvents and water.

Since the product desorption must be also affected by the product concentration in the solution especially at the final stage of the reaction, the effect of the product concentration has been examined by adding racemic **2** to the reaction mixture simultaneously with the introduction of the substrate. As shown in Figure 1, the previous addition of **2** decreased both the activity and e.e. of the fresh product to some extent. Taking into account the much higher activity of unmodified sites, this result shows that the reaction on modified sites is relatively suppressed by the addition of **2**. Accordingly, the favorable effect of added amines could be also attributed to the apparently lowered concentration of the product in the solution, which will be caused by the adduct formation between the amines and the product. In other words, the role of amines can be explained not only by the acceleration of the product desorption from modified sites through acid-base interaction, as mentioned above, but also in terms of the adsorption-desorption equilibrium, especially at the final stage of the reaction. Further kinetic studies are now in progress to reveal the role of amines as well as the effect of solvents on this reaction.

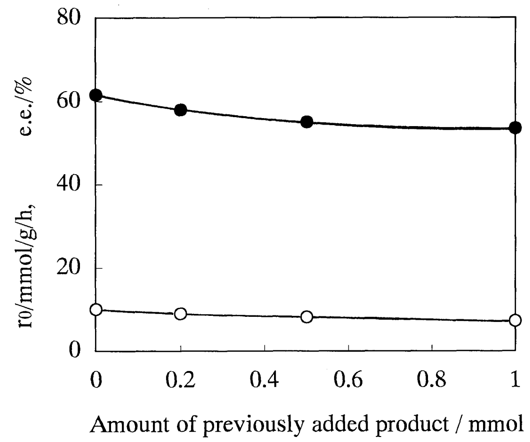

Figure 1. Effect of the previously added racemic product on the enantioselective hydrogenation of (*E*)-α -phenylcinnamic acid. Reaction conditions as for Table l. ○: Initial hydrogenation rate, ●: Enantiomeric excess of the freshly obtained product.

The remarkable effect of the added benzylamine was observed in all the solvents examined. In the best solvent used here, *i.e.*, 1,4-dioxane containing 2.5 vol% water, the solubility of the salt of benzylamine with **2** is much lower than that of the amine salt with **1**. It was observed, therefore, that the salt of benzylamine with the product began to precipitate as the reaction proceeded. Moreover, it has been confirmed that the solubility of the salt of benzylamine with racemic **2** is lower than that of the salt with individual enantiomers of **2**. Consequently, much higher e.e. values, 81-92% (entries 11-13 in Table 1), were observed for the products contained only in the filtrates of the final reaction mixtures before decomposing the precipitated amine salt. Similar but apparently opposite phenomena are well known as the preferential crystallization used for the optical resolution of racemic amines.[10] The adsorption-desorption equilibrium, mentioned above, will favor the enantioselectivity especially when an insoluble amine salt of **2** is formed as in the case of benzylamine.

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