



Is amine addition vital for highly enantioselective hydrogenation of α,β -unsaturated carboxylic acid over cinchonidine-modified palladium?

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ABSTRACT

Benzylamine (BA) is a commonly employed additive for the hydrogenation of α,β -unsaturated acids over the cinchonidine-modified palladium catalyst, but the BA addition effects largely depend on the reaction solvent. In toluene, BA is not required to obtain the high enantioselectivity. Quicker desorption of the product due to weaker acidity in toluene than in a commonly used wet dioxane reasonably explains both the kinetic properties and the product selectivities.

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1. Introduction

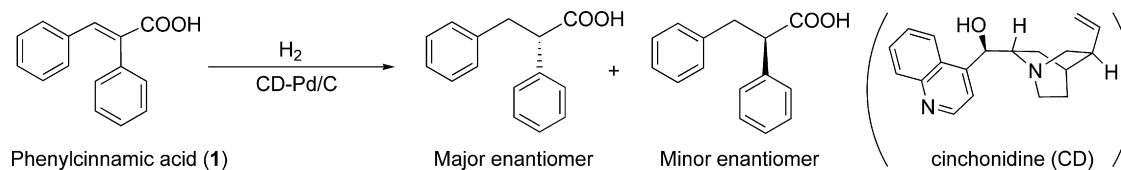
For the enantioselective hydrogenation over heterogeneous palladium catalysts, olefins are representative substrates [1]. The most studied reaction is conversion of α,β -unsaturated acids into saturated ones carrying a chiral α -carbon, the stereochemistry of which can be controlled satisfactorily with cinchonidine (CD) as a chiral surface modifier [2,3]. A possible mechanism for differentiating enantioface of the substrate originates in an acid–base interaction with CD at the quinuclidine (1-azabicyclo[2.2.2]octane) part. The enantiomeric excess (ee) of the product largely depends on the preparation method of the palladium catalyst as well as the hydrogenation conditions, but so far in all the cases, addition of amine, usually benzylamine (BA) in a stoichiometric amount (0.6–1.0 molar equivalent to the substrate), was indispensable to obtain the high product ee. The BA effects were first reported by Nitta; the presence of BA increased the product ee with accompanying increase in the reaction rate of the hydrogenation of phenylcinamic acid (**1**) (Scheme 1), and the amine effects were attributed to promotion of the product desorption from the modified catalyst surface [4]. The BA effects were observed in all the solvents examined, though they were limited to protic or water-containing solvents. Szöllösi et al. reported the same effects for the hydrogenation of different α,β -unsaturated acids, but they suggested a different mechanism for hydrogenation of itaconic acid, which

includes formation of a complex containing the three components, CD, BA and the substrate, on the basis of the rate comparison under moderate enantioselectivity (ee < 50%) [5]. Now, we assume that addition of BA is not essential for the enantioselective hydrogenation if the role played by BA is only in the product desorption from the CD-modified site as suggested by Nitta, and that the high product ee could be obtained without BA by performing the catalysis under proper conditions. In this report, we will summarize details of the results of reinvestigation aiming at an atom-economically more preferable process to minimize use of the BA additive.

2. Experimental

The CD-modified Pd catalyst was prepared from STD-type 5%Pd/C supplied by N.E. Chemcat in a wet form (51%, w/w). The metal surface area of the catalyst is $339\text{ m}^2\text{ g}^{-1}$ (metal base), corresponding to metal dispersion of 76%. Substrates **1** and **9** were obtained from commercial source, and other substrates were prepared as reported [6]. BA was used from a freshly opened bottle since an old one contained a considerable amount of *N*-benzylidene(phenyl)methanamine. Solvents were reagent grade and used as obtained. The hydrogenation procedure including the pretreatment method of Pd/C was the same as that reported [7,8]. The procedure for the hydrogenation of **1** in toluene in the absence of BA is as follows. In a 50 ml flat-bottomed glass flask with a small septum port, Pd/C (43 mg as the wet form) and a stirring bar were placed. The flask was evacuated to 13 kPa (10 Torr) for 10 min to remove the water and then was charged with hydrogen at the atmospheric pressure. Toluene (5 ml) was added to the

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Scheme 1. Enantioselective hydrogenation of phenylcinnamic acid (PCA) over CD-modified Pd/C.

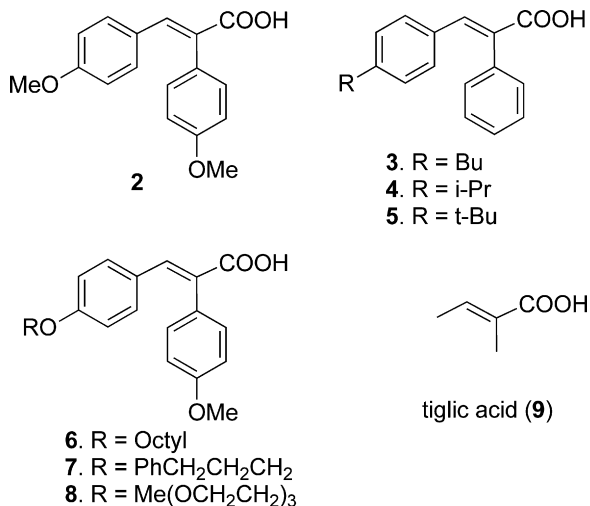


Fig. 1. Structures of the employed substrates.

flask, and the mixture was heated at 353 K for 30 min under stirring (1200 rpm). The suspension was cooled to 296 K in a temperature-controlled water bath, and a solution of CD (6 mg, 0.02 mmol) in toluene (1 ml) was added. After stirring for 30 min, a solution of **1** (112 mg, 0.5 mmol) in toluene (4 ml) was added. The catalytic activity was evaluated from the rate of hydrogen consumption at 20–25% conversion. The reaction was continued until hydrogenation was complete. To the hydrogenation mixture, 2 M HCl (1 ml) was added and the mixture was filtered to remove the catalyst. Here, it was confirmed that the product was completely dissolved in the solution, and no detectable product remained in the filtered solid. The filtrate was extracted with ethyl acetate (5 ml) and then washed with water (5 ml 2×). The extract was analyzed by ¹H NMR (600 MHz, CDCl₃) to confirm completion of the hydrogenation, and by HPLC with a chiral column (Chiracel OJ-H; Daicel), eluted with a mixture of 2-propanol/hexane/trifluoroacetic acid = 5/95/0.1 at a flow rate of 1 ml/min to determine the enantiomer ratio of the product from **1**. The standard retention times were 15.4 min for the *R*-product and 24.4 min for the *S*-product. See Ref. [6] for HPLC analysis conditions for the other products. Kinetic study was performed under the conditions similar to those used for ee determination except for use of twice more substrate (1 mmol) and at a higher temperature (323 K) to reduce experimental errors in measuring

the hydrogen uptake. IR spectra were obtained by a JASCO Ubest-50 with a solution cell having CaF₂ windows.

3. Results

The effects of BA on the product ee were first investigated for the hydrogenation of **1** using different solvents. Table 1 summarizes ee values obtained in the presence and absence of BA, the differences of which are given as Δee. The initial hydrogenation rates are in parentheses. Dielectric constants and hydrogen solubilities of the solvents studied are also given [9]. In the presence of BA, high ee values in a range of 78–83% were obtained in all the solvents so far studied. In contrast, the ee in the absence of BA depends on the solvent used. The ee values are low in wet dioxane and wet DMF as reported [4], but the ee is high in toluene and xylene to make the effect of BA unclear. Another distinctiveness of the reactions in toluene and xylene is lack of acceleration by the BA addition as seen in r_{BA}/r_{noBA} values, though the values become larger than unity under different conditions (vide infra). The polarity or hydrogen solubility of the solvent does not seem to be related with the BA effects.

Table 2 summarizes the results with substrates **1–9**, the structures of which are shown in Fig. 1. Under the optimized conditions with BA, 4,4'-dimethoxy substrate (**2**) shows higher enantioselectivity than **1**. Substrates **3–5** are analogues of **1** having different steric hindrance at the β-*p*-phenyl that should play a major role in the adsorption of the substrate [6]. Substrates **6–8** are analogues of **2** having different affinity to the solvent and the catalyst surface. Substrate **9** is an aliphatic one that is known to give higher enantioselectivity at 5 MPa than at the atmospheric pressure of hydrogen by suppressing an isomerization/hydrogenation ratio [10]. For each substrate, difference (Δee) in the effects of BA was compared between the two solvents, wet dioxane and toluene. With all the substrates, the effects of BA are clear on the reactions in wet dioxane, while the effects are not obvious in toluene; Δee's are small or even better ee was obtained in the absence of BA with several substrates. The BA effects on the rate do not change systematically according to the properties of the substrates, presumably due to the product precipitation unexpectedly occurring during the hydrogenation to deteriorate the catalyst performance.

The kinetic effect of the BA addition could not be determined precisely under the conditions of the reactions given in Table 2. Reliable values were obtained from the hydrogen uptake monitored with twice more substrate (1 mmol) and at a higher temperature

Table 1

Enantiomer excess (initial rate r /mmol g⁻¹ h⁻¹) of the product of hydrogenation of **1** in different solvents in the presence or absence of benzylamine (BA).

Solvent	ϵ_r^a	$10^4 x_2^b$	With BA	Without BA	Δee^c (r_{BA}/r_{noBA})
Wet dioxane	2.5	–	83 (72)	57 (12)	26 (6)
Ethyl acetate	6.1	3.46	78 (26)	59 (14)	19 (1.9)
MeOH	33.6	1.61	83 (36)	61 (14)	12 (1.7)
DMF	37.1	–	83 (14)	58 (8)	25 (1.8)
Toluene	2.4	3.15	78 (36)	75 (72)	3 (0.5)
<i>p</i> -Xylene	2.2	4.15	80 (33)	72 (72)	8 (0.5)

^a Dielectric constant.

^b H₂ gas solubility in mol fraction.

^c Δee = (ee with BA) – (ee without BA).

Table 2
Enantiomeric excess (initial rate $r/\text{mmol g}^{-1} \text{h}^{-1}$) of the product of hydrogenation of various substrates in the presence or absence of benzylamine in wet dioxane or toluene.

Substrate	In wet dioxane			In toluene		
	BA	Without BA	Δee^a	BA	Without BA	Δee^a
1	83 (72)	57 (12)	26	78 (36)	75 (72)	3
2	92 (43)	67 (3)	25	88 (36)	84 (11)	4
3	86 (40)	70 (15)	16	75 (57)	83 (75)	-8
4	85 (34)	50 (9)	35	63 (27)	63 (51)	0
5	81 (16)	55 (4)	26	62 (8)	65 (48)	-3
6	79 (21)	49 (10)	30	82 (19)	73 (7)	9
7	92 (34)	60 (14)	32	89 (5)	91 (17)	-2
8	91 (42)	72 (35)	19	85 (15)	86 (5)	-1
9	22 (<2)	16 (16)	6	16 (34)	21 (36)	-5
9 (5 MPa)	38	21	17	28	33	-5

^a Difference in the ee between those obtained in the presence and absence of BA.

Table 3
Initial hydrogenation rates ($\text{mmol g}^{-1} \text{h}^{-1}$) of **1** and **2** at 323 K: comparison of the results obtained in the presence/absence of BA and in wet dioxane/toluene over the modified and unmodified Pd catalyst.

Substrate	Catalyst	In wet dioxane			In toluene		
		BA	None	BA/noBA	BA	None	BA/noBA
1	Unmodified Pd	432	522	0.83	402	499	0.81
1	CD-Pd	344	120	2.9	199	172	1.2
2	Unmodified Pd	180	223	0.81	138	165	0.84
2	CD-Pd	179	12	15	180	45	4.0

(323 K), where the precipitation formation was still observed at the later stage of the reaction. The uptake profiles of hydrogen are given in Fig. 2. The reaction of **1** was performed over unmodified and CD-modified catalysts in the absence and presence of BA in wet dioxane (a). The same sets of the experiments were performed in toluene (b), and with **2** in wet dioxane (c) and in toluene (d). The hydrogenation rates given in Table 3 were determined from the initial linear part consisting of 5–7 data points ($r^2 > 0.995$). In all the experiments

with the CD-modified Pd, the BA addition accelerates the reaction ($\text{BA}/\text{noBA} > 1$), while BA decelerates the reaction with the unmodified catalyst ($\text{BA}/\text{noBA} = 0.81\text{--}0.84$). The kinetic effect of BA on the hydrogenation of **1** in wet dioxane is negative with unmodified Pd/C to result in deceleration of 0.83 time, but it becomes positive with CD-modified Pd/C to result in acceleration of 2.9 times, and thus the ratio of the modified/unmodified catalysts ($=m/u$) is 3.5. This m/u value is much larger with **2** to be 19 ($=15/0.81$). In toluene, the

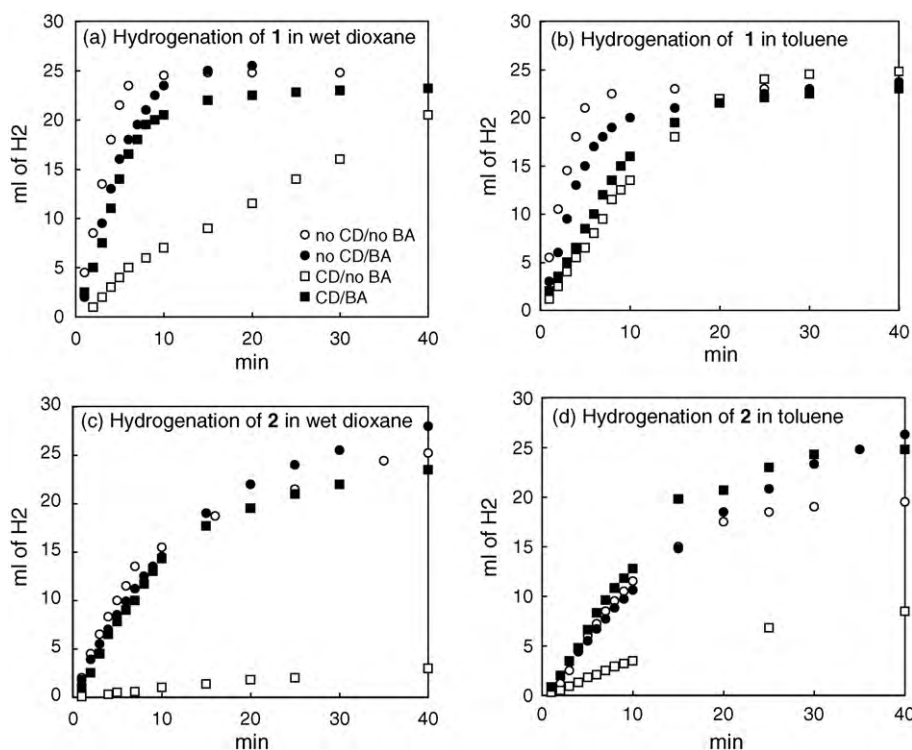


Fig. 2. Hydrogenation uptake properties of (a) **1** in wet dioxane, (b) **1** in toluene, (c) **2** in wet dioxane, and (d) **2** in toluene. Each plot indicates following conditions. Open circles: unmodified Pd/C in the absence of BA. Closed circles: unmodified Pd/C in the presence of BA. Open squares: CD-modified Pd/C in the absence of BA. Closed squares: CD-modified Pd/C in the presence of BA.

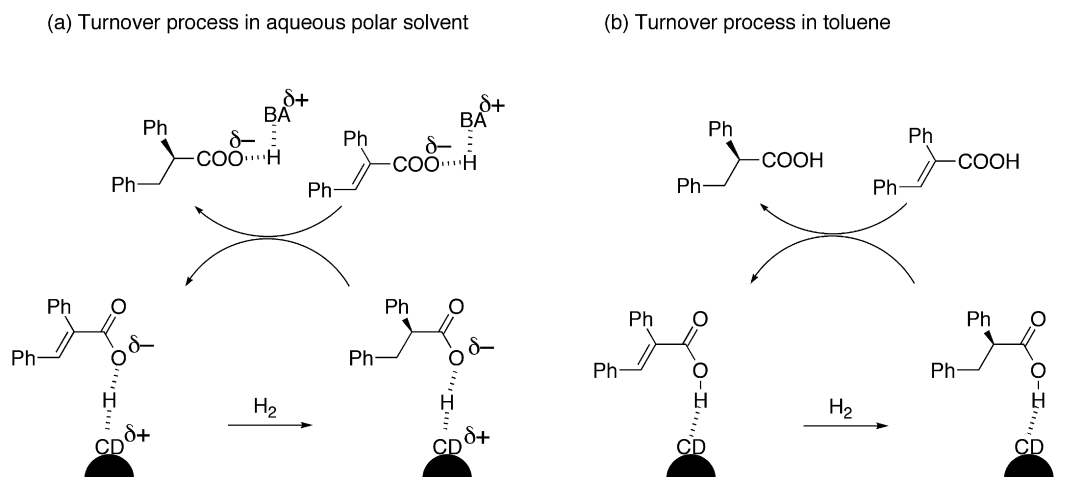


Fig. 3. Expected difference between the solvents in the turn-over mechanism.

kinetic BA effect is also positive with CD-modified Pd/C to result in acceleration, but it is much smaller than that observed in wet dioxane. As a result, the *m/u* values in toluene, 1.5 (=1.2/0.81) for **1** and 4.8 (=4.0/0.84) for **2**, are smaller than those in wet dioxane.

4. Discussion

During the reinvestigation of solvent effects on the hydrogenation of **1**, it was found that the ee values obtained without BA are sufficiently high in toluene but the BA effects are poor. In xylene, the ee was somewhat lower than in toluene, but the BA effects were similar. The poor BA effects at the high ee in toluene were also observed with other substrates having different properties. The value of 91% ee with **7** obtained without BA is on the same level of the highest ee obtained by using CD-modified Pd catalyst under the conditions optimized with BA. Since toluene has difficulty in the product solubility under the present conditions, some of the ee values obtained in toluene may be improved by tuning the reaction conditions to solubilize the product. In fact, the reaction of **1** without BA in toluene gave higher 78% ee (*r* = 70) when the substrate concentration was reduced to half that of the standard conditions.

Another notable feature observed with the toluene solvent is the kinetic effect of BA. Acceleration effect by the BA addition is evident in wet dioxane with the CD-modified Pd, while it was not observed without CD modification. This observation is in good agreement with the reported results, which gives the following explanation on the ee improvement by the BA addition [4]. The substrate is adsorbed on the CD-modified metal surface by the assistance of an acid–base interaction with CD, which makes the substrate adsorption stronger. Just after the hydrogenation step, the product is still adsorbed similarly, and the strong adsorption makes the desorption step rate-determining of the overall hydrogenation reaction. The slow catalytic cycle due to the desorption problem at the CD-modified catalyst surface will allow the background reaction to show up, which occurs at the CD-unmodified surface to produce the racemic product [6]. The observed ee values suggest that the reaction in toluene does not have a desorption problem in giving high product ee independent of the BA addition. Kinetic effects of BA in toluene are dependent on the reaction conditions, but they are much smaller than those in wet dioxane in conformity with the above explanation.

Fig. 3a shows the catalyst cycle in wet dioxane in the presence of BA, where the product is replaced by the ionic substrate more smoothly than by the neutral substrate in the desorption step. The quick catalysis cycle on the CD-modified site suppresses the rel-

ative contribution from the background reaction to increase the total product ee. The polarity of 2.5% water-containing dioxane is not high (ϵ_r = ca. 2.5), but carboxylic acid should have certain acidity due to the specific solvation. However, the degree of ionization seems to be still low as deduced from the IR spectrum of the PCA-CD salt dissolved in wet dioxane, where a sharp absorption peak corresponding to the hydrogen-bonding neutral carboxyl group was observed at 1710 cm^{-1} , while no obvious absorption for carboxylate was observed in a range of $1550\text{--}1650\text{ cm}^{-1}$.

In an aprotic solvent, acidity of the carboxylic acid becomes weak as $\text{p}K_A = 11\text{--}12$ even in very polar DMSO (12–14 in DMF), and should be much weaker in less polar toluene. In contrast, basicity of amine is not much affected; $\text{p}K_{\text{BH}} = 11.0$ for quinuclidine in water and 9.8 in DMSO [11]. Thus, interaction between carboxylic acid and tertiary amine in toluene should not be a polar acid–base salt formation, but weaker hydrogen-bonding. Hence, as illustrated in Fig. 3b, the interaction between the product and CD on Pd surface should be less ionic in toluene, and the unionized product on CD can be exchanged quickly with the neutral substrate.

5. Conclusion

By the present study, it was found that the BA addition is effective, but is not always required to obtain the high enantioselectivity in the hydrogenation of α,β -unsaturated acids over the CD-modified Pd/C. As a result, the atom-economically preferable process avoiding the use of BA could be established. From a different viewpoint, the solvent effect on the enantioselectivity is large in the absence of BA due to the background reaction.

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