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Research Note

Increased enantioselectivity in the presence of benzylamine in the heterogeneous hydrogenation of α,β-unsaturated carboxylic acids

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Abstract

The use of one equivalent of benzylamine increased the enantioselectivity in the heterogeneous catalytic hydrogenation of α,β-unsaturated carboxylic acids over cinchonidine-modified 5% Pd/Al_2O_3 catalyst. The beneficial effect of the amine additive was dependent on substrate structure. The highest effect, a more than sixfold increase in the enantiomeric excess, was obtained in the hydrogenation of itaconic acid. This is the first report on the enantioselective hydrogenation of a prochiral α,β-unsaturated dicarboxylic acid over a supported heterogeneous metal catalyst.

Keywords: Unsaturated carboxylic acid; Enantioselective; Hydrogenation; Heterogeneous; Palladium; Cinchonidine; Itaconic acid

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1. Introduction

The enantioselective catalytic hydrogenation of α,β-unsaturated carboxylic acids (see Fig. 1) is one of the most convenient methods for the synthesis of optically pure chiral carboxylic acid building blocks for the production of pharmaceuticals, flavors, and fragrances [1–3]. The catalysts used are homogeneous metal complexes bearing chiral ligands. Extensive efforts have been devoted to the development of heterogeneous catalytic systems for this purpose. Although the heterogenization of chiral metal complexes often leads to good results [4–7], the method still has the disadvantage of requiring expensive and sensitive complexes.

A more preferable method would be the use of the combination of chiral modifiers and supported metal catalysts such as those used in the hydrogenation of α-keto or β-keto esters [8–10]. However, these catalytic systems afford only low or moderate enantiomeric excesses (ee) in the hydrogenation of unsaturated carboxylic acids [11–20]. The best results were obtained over cinchonidine (CD)-modified Pd catalysts [21,22]. Recently, achiral amine additives were shown by Nitta to improve the ee in the hydrogenation of (E)-α-phenylcinnamic acid over CD-modified Pd/TiO_2 [23,24]. Benzylamine (BA) was found to bring about the largest increase of 12%. Although remarkable variations in the ee as a function of substrate structure in the hydrogenation of α,β-unsaturated carboxylic acids were observed [25,26], the use of amine additives to increase the ee in the heterogeneous hydrogenation of other α,β-unsaturated carboxylic acids has not yet been studied. The aim of our present study was, therefore, to investigate the effect of the BA additive on enantioselectivity as a function of the α,β-unsaturated carboxylic acid structure.

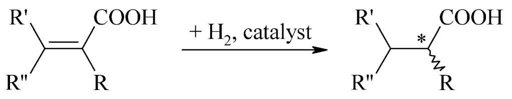

Fig. 1. Scheme of catalytic hydrogenation of α,β-unsaturated carboxylic acids.

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2. Experimental

Cinchonidine (CD) ($\geqslant$ 98%) and benzylamine (BA) ($\geqslant$ 99.5%) were purchased from Nacalai Tesque Inc. and used without purification. The substrates, tiglic acid (**1**, Wako Pure Chem. Ind.), (*E*)-2-methyl-2-pentenoic acid (**2**, Tokyo Kasei Kogyo Co.), (*E*)-α-methylcinnamic acid (**3**, Aldrich), (*E*)-α-phenylcinnamic acid (**4**, Tokyo Kasei Kogyo Co.), mesaconic acid (**5**, Tokyo Kasei Kogyo Co.), citraconic acid (**6**, Wako Pure Chem. Ind.), and itaconic acid (**7**, Wako Pure Chem. Ind.), were used as received. The high-purity, dehydrated organic solvents were Wako Pure Chem. Ind. products. An alumina-supported Pd catalyst (5% Pd/Al_2O_3, Engelhard 40692), with 0.21 metal dispersion (by TEM) and 200 m^2 BET surface area [17,18], was used as received.

Hydrogenations were carried out in a 100-ml stainless-steel Taiatsu Techno autoclave equipped with a teflon liner and mechanical stirrer. The catalyst (25 mg) was pretreated for 1 h with stirring (1000 rpm) in 10 ml of solvent under H_2 at 296 K followed by the addition of 0.05 mmol of CD, the specified amount of BA, and 1 mmol of substrate. Toluene (**1**, **2**), DMF/H_2O 9/1 (**4**), and methanol (**3**, **5**, **6**, **7**) were used as solvents based on literature data or preliminary experiments. After 1 h of reaction the catalyst was filtered, the solvent was evaporated, and the remaining solid was washed with HCl solution and dissolved in methanol. The samples were analyzed by gas chromatography (GC) on a Shimadzu GC-17A apparatus equipped with a flame ionization detector. Conversions and ee values in the reactions of **1** and **2** were determined with a HP-Chiral (30 m × 0.2 mm, J&W Scientific Inc.) capillary column. The products obtained in the hydrogenations of **3**, **4**, **5**, **6**, and **7** were transformed into the corresponding methyl esters with the use of cc. H_2SO_4 and analyzed on a CycloSil B (30 m × 0.2 mm; J&W Scientific Inc.) chiral capillary column. Products were identified by GC-MS (Agilent Techn. 6890N GC - 5973 MSD) analysis and comparison with authentic samples. The enantiomeric excess (ee%) was calculated with the formula $\text{ee\%} = 100 \times |E_1 - E_2|/(E_1 + E_2)$, where E_1 and E_2 are the concentrations of the corresponding saturated product enantiomers. The reactions were repeated at least three times; the results were reproducible within ±1%. The configuration of the enantiomers formed in excess was determined by GC by comparison with authentic samples (for **1**, **5**, **6**, and **7**) or with published data (for **2** and **4**) [12,17]. For the product formed in the hydrogenation of **3**, optical rotation measurements were used [27,28]. Optical rotations were measured on a Jasco IP-181 Digital Polarimeter. Separate experiments were carried out to determine the reaction rates in the hydrogenation of **7** in a 15-ml autoclave with 25 mg of catalyst, 3 ml of methanol as solvent, and 1 mmol of **7** under 50 bar H_2 pressure. The H_2 uptake was calculated from the drop of the pressure recorded automatically, and the initial rate of the reaction was determined at 20 ± 2% conversions.

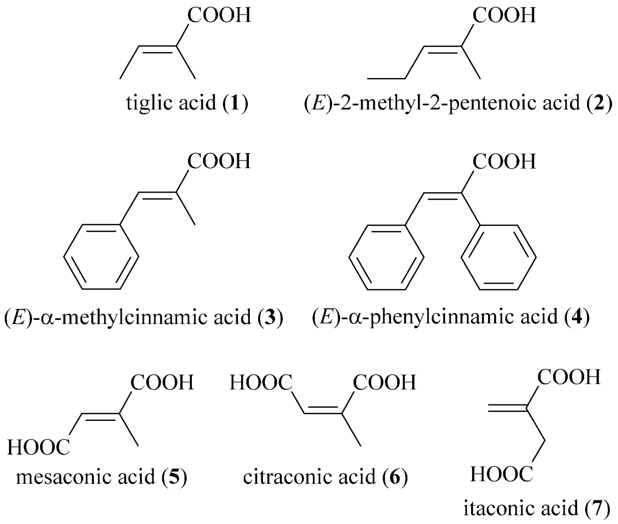

Fig. 2. Substrates tested in the enantioselective hydrogenation over CD modified Pd/Al_2O_3 catalyst in presence of benzylamine.

3. Results and discussion

It is well known that the ee of the heterogeneous catalytic enantioselective hydrogenation of α,β-unsaturated carboxylic acids over a CD-modified Pd catalyst depends on the substrate structure. Thus, the use of additives to increase the ee of the reaction may also be structure dependent. Accordingly, we have studied the effect of BA on the ee in the hydrogenation of the substrates presented in Fig. 2 over CD-modified Pd/Al_2O_3 catalyst. The results are summarized in Table 1. Under the experimental conditions used, all of the substrates with the exception of **4** were fully hydrogenated after 1 h of reaction (100% conversion) (see Table 1).

Over Pd/Al_2O_3, the addition of 1 equivalent (eq) of BA to the reaction mixture increased the ee in the hydrogenation of **4**, in accordance with Nitta's findings over Pd/TiO_2 [23,24]. Similar or even larger increases in the ee were obtained in the hydrogenation of the aliphatic monocarboxylic acids studied. In the hydrogenation of **1**, (*S*)-2-methylbutanoic acid was formed in 56% ee in the presence of 0.5 eq of BA. A further increase in the amount of BA to 1 eq, however, resulted in only a slight increase (58%). Such high ee value had never been reported for the hydrogenation of tiglic acid (compound **1**) over a supported metal catalyst. In contrast, the use of BA led to a slight decrease in the ee value in the hydrogenation of **3**.

The dicarboxylic acids tested in this study, particularly **7**, are often used as test molecules in enantioselective hydrogenations catalyzed by homogeneous chiral metal complexes [29–32]. To the best of our knowledge, the enantioselective hydrogenation of these compounds has not yet been tested over CD-modified supported Pd catalysts. In the hydrogenation of these three unsaturated dicarboxylic acids (**5**, **6**, and **7**) very low ee's, up to 10%, are obtained in the presence of CD (see Table 1). Interestingly, the hydrogenation of **5** led to the (*S*)-methylsuccinic acid in excess,

Table 1
Hydrogenation of α,β-unsaturated carboxylic acids over CD modified Pd catalyst[a]

Substrate	Amount BA (mmol)	H_2 pressure (MPa)	ee (%)	Config.[b]
1	–	5	46	(*S*)
	0.5	5	56	(*S*)
	1	5	58	(*S*)
2	–	5	52	(*S*)
	1	5	61	(*S*)
3	–	0.5	23	(*R*)
	1	0.5	20	(*R*)
4	–	0.1	52[c]	(*S*)
	1	0.1	60 (72)[d]	(*S*)
5	–	5	10	(*S*)
	1	5	Racemic	–
6	–	5	7	(*R*)
	2	1	Racemic	–
7	–	5	8	(*R*)
	1	1	26	(*R*)
	2	1	41	(*R*)
	2	5	49	(*R*)
	2	10	44	(*R*)
	8	5	23	(*R*)

[a] Reaction conditions: 25 mg catalyst, 10 mL solvent, 0.05 mmol CD, 1 mmol substrate, 1000 rpm, 296 K, 1 h. Conversions are 100% except for compound **4**.

[b] Configuration of the major enantiomer.

[c] Conversion is 60%.

[d] Reaction time is 2 h; ee of filtrate in parentheses.

whereas in the reaction of **6** and **7** an excess of the corresponding (*R*) enantiomer was obtained. It is known that the hydrogenation of both tiglic and angelic acids ((*E*)- and (*Z*)-2-methyl-2-butenoic acids) over CD-modified Pd results in the formation of the same (*S*)-2-methylbutyric acid as the major product [25,26]. Surprisingly, in the hydrogenation of the (*E*) and (*Z*) dicarboxylic acids **5** and **6**, the opposite enantiomers were formed in excess. This could be due to the orientation and steric effect of the second carboxylic acid group, leading to preferential adsorption on the opposite sides of the C=C group of the two isomers (**5** and **6**). In the hydrogenation of **7**, the mode of adsorption is identical with that of the (*E*) isomer **5**, ensuring the formation of (*R*)-methylsuccinic acid as the major enantiomer.

The presence of BA in the reaction mixture results in racemic mixtures in the hydrogenation of both **5** and **6**. Surprisingly, in the hydrogenation of **7** the addition of BA brings about highly increased ee values. The amount of the additive was crucial; the highest value was obtained with 2 eq of BA. A further increase in the amount of BA (8 eq) resulted in a decrease in the ee value. Furthermore, the H_2 pressure also affects enantioselectivity, with the highest ee obtained under 5 MPa. A further increase to 10 MPa, in contrast, led to a slightly decreased value. Thus, the highest ee of 49% was obtained with 2 eq BA under 5 MPa H_2 pressure, which represents a more than sixfold increase as compared with the ee obtained without BA as an additive. It is important to point out that this is the first report in which substantial enantioselectivity has been obtained in the hydrogenation of an unsaturated dicarboxylic acid over chirally modified heterogeneous metal catalyst. Moreover, it has been shown for the first time that the presence of an achiral additive, such as BA, may lead to a high increase in the ee (from 8 to 49%) in the heterogeneous hydrogenation of an unsaturated carboxylic acid.

Table 2
Effect of BA on the hydrogenation of **7**[a] and **4**[b] [23,24]

Substrate	Modifier (mmol)	Additive (mmol)	Initial rate (mmol h^{-1} g^{-1})	ee (%)
7	–	–	2535	–
	CD, 0.05	–	1890	6
	CD, 0.05	BA, 1	1720	20
	CD, 0.05	BA, 2	1065	46
	–	BA, 2	1245	–
4	CD, 0.02	–	7	59
	CD, 0.02	BA, 1	32	71

[a] Reaction conditions: 25 mg 5% Pd/Al_2O_3, 3 mL methanol, 1 mmol **7**, 1000 rpm, 293 K, H_2 pressure 5 MPa.

[b] Reaction conditions: 20 mg 5% Pd/TiO_2, 10 mL 1,4-dioxane (2.5 vol% water), 1 mmol **4**, 1200 rpm, 298 K, H_2 pressure 0.1 MPa [23,24].

According to Nitta, the presence of an amine during the hydrogenation of **4** promotes the desorption of the product from the modified sites of the catalyst, thereby accelerating the reaction [23,24]. However, in the hydrogenation of **4**, product desorption was found to be the rate-determining step [23,24,33], which is accelerated by the presence of BA (due to salt formation), resulting in an increased initial rate and ee of the overall reaction. In contrast, in the hydrogenation of **7** the initial rate decreased with the addition of BA, as shown in Table 2. One can see the very high reaction rates obtained in the hydrogenation of **7** as compared with those obtained in that of **4**, which may be due to the differences in the structure of the substrates and the reaction conditions (catalyst, H_2 pressure, solvent, catalyst, and substrate concentrations, etc.). An increase in the amount of BA from 1 to 2 mmol led to a further decrease in the initial rate, indicating that the possible interaction of the additive with the substrate is responsible for the increased ee, rather than surface modification or poisoning. Formation of a complex including CD, BA, and **7** could be possible. Future investigations will include a demonstration of the existence of such structures.

Finally, we point out that further optimization of the crucial reaction parameters, such as the nature and the amount of the catalyst, modifier, solvent, and amine; H_2 pressure; and temperature, may lead to a further increase in the ee. Such investigations are already in progress.

4. Conclusions

It was demonstrated that benzylamine is an effective additive for increasing the ee in the enantioselective heterogeneous catalytic hydrogenation of a range of α,β-unsaturated carboxylic acids over a CD-modified Pd catalyst, previously reported only for the hydrogenation of (E)-α-phenylcinnamic acid. Similar or even higher increases in the ee were obtained in the hydrogenation of some aliphatic substrates. A surprising sixfold increase (from 8 to 49%) in the ee was obtained in the hydrogenation of itaconic acid. This is the first report in which substantial enantioselectivity has been obtained in the hydrogenation of an α,β-unsaturated dicarboxylic acid over a chirally modified heterogeneous metal catalyst.

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