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The effect of the substrate structure on the stereoselectivity in an asymmetric hydrogenation of unsaturated carboxylic acids over cinchonidine-modified palladium catalyst

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Abstract—An enantiomeric ratio of 10:1 (82% ee) was achieved for the first time in the hydrogenation of α,β-unsaturated acids with heterogeneous catalysts by designing the substrate structure to enhance the interaction with the catalyst, and to increase the intrinsic stereoselectivity.
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1. Introduction

Asymmetric syntheses using heterogeneous catalysts have a principal advantage in their productivity, although their stereoselectivities are not high and can even be negligible with the exception of some hydrogenation reactions. So far, two types of catalysts, cinchona-modified platinum and tartaric acid-modified nickel, have been developed to convert ketones to the corresponding chiral alcohols in 97–98% enantiomeric excesses (ee).[1] A candidate following these two catalysts is the cinchona-modified palladium (CM-Pd), which has been shown to be effective in the hydrogenation of prochiral olefins.[2,3] CM-Pd is different from the other two catalysts with regards to the effect of the chiral modifier on the catalytic activity; the modification decreases the hydrogenation rate 10-fold, and thus the imperfect modification of the catalyst surface directly results in low product ee's due to the rapid and nonselective hydrogenation over unmodified sites of the Pd surface. During the study to increase the fraction and activity of the modified sites, it was found that the optimized reaction conditions as well as the preparation method of suitable CM-Pd are much different among the substrates, suggesting that the mechanism of chiral recognition is dependent on the types of substrates. The highest ee currently achieved was 94% in the hydrogenation of a pyrone derivative under the extreme conditions of a very low substrate/modifier ratio.[4]

α-Phenylcinnamic acid **1** is one of the well-studied substrates giving relatively high enantioselectivities up to 72% ee under optimized conditions,[5,6] dissimilar to the conditions for aliphatic α,β-unsaturated acids as well as for pyrone derivatives. For the hydrogenation of **1**, the modified fraction (α) to all active sites on the Pd surface is regarded already close to unity, when the Pd catalyst was prepared with nonporous support, for example, Pd/TiO$_2$, is used in a very polar aqueous solvent.[7] Therefore, further improvement of the product ee may only be achieved by increasing the stereoselectivity of the modified sites, the so called intrinsic stereoselectivity, factor-*i*.[8] Factor-*i* reflects the probability of enantiodiscrimination induced by modifier molecules on the catalyst surface in their interaction with substrate molecules. Previous studies suggest that the interactions occur at the two protons of N$^+$H and OH of the protonated cinchonidine with the conjugate base of **1** as an acceptor of the two hydrogen bonds.[9] If this model properly expresses the enantiodiscrimination, a stronger interaction is expected between a substrate having a more electron-rich π-system and cinchonidine to increase factor-*i*, and thus, to lead to an improved product ee. With these considerations in mind, we designed substrates **2–4** to have *p*-methoxy substituent(s) at α- and/or β-phenyl group(s), and examine their enantioselective hydrogenations.

2. Results and discussion

Substrates **2–4** in Scheme 1 were synthesized from the corresponding aromatic aldehydes and derivatives of

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1. $R^1 = R^2 = H$
2. $R^1 = OMe, R^2 = H$
3. $R^1 = H, R^2 = OMe$
4. $R^1 = R^2 = OMe$
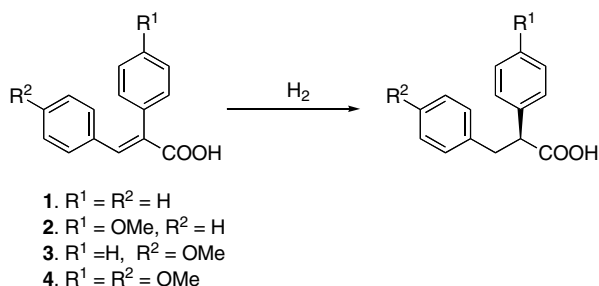
Scheme 1.

phenylacetic acid by a Perkin reaction[10] and characterized by NMR. A 5 wt % Pd/C catalyst AER (N. E. CHEMCAT, egg-shell type) was employed to examine the effects of substrate structure, because the use of such a commercially available catalyst generally shows high reproducibility. The hydrogenation was carried out in a polar solvent under standard conditions.[11] After the hydrogen uptake was finished, the products were isolated from the reaction mixture and analyzed by HPLC on a chiral column (Chiralpak AD, Daicel). The catalytic activities are expressed by the initial reaction rates (r_m) calculated from the hydrogen uptake at 20% conversion. The initial rates with the unmodified catalyst were also measured (r_u) for comparison.

The introduction of a methoxy group at the *para*-position of the α- or β-phenyl group of **1** resulted in notable improvements in ee as shown in Table 1 (**2** and **3**). Interestingly, this preferable effect of a methoxy group was observed both for α- and β-substitutions to the same degree. The β-aryl group is conjugated with the unsaturated acid, while the α-aryl group is almost perpendicular to the main π-system.[12] Hence, the α- and β-methoxy substitutions may enhance the interactions between the substrate and the cinchonidine molecules by different mechanisms. In fact, the effects of these methoxy substitutions are additive, giving 66% ee of the hydrogenation product for **4** having both α- and β-methoxy substituents.[13]

The product ee, obtained in the reactions with heterogeneous catalysts, depends on both the modified fraction (α) and the factor-*i*, while the contribution of the unmodified fraction ($1 - \alpha$) becomes larger with an increasing reactivity ratio of unmodified sites to modified sites, which can be evaluated from the reactivity ratio of r_u/r_m. The improvement in the ee observed for substrates **2**–**4** is attributable to the increase in factor-*i*, because the contribution from the unmodified sites on

Table 1. Hydrogenation of **1**–**4** with cinchonidine-modified and unmodified Pd/C catalyst[a]

Substrate	R^1 (α)	R^2 (β)	Ee (%)	r_m	r_u	r_u/r_m
1	H	H	52	39	330	8.5
2	OMe	H	59	18	160	8.9
3	H	OMe	59	15	130	8.7
4	OMe	OMe	66	11	110	10

[a] r_m and r_u (mmol g^{-1} h^{-1}) are the initial reaction rates with CM-Pd/C and with unmodified Pd/C, respectively.

Table 2. Hydrogenation of **1**–**4** in the presence of benzylamine[a]

Substrate	Pd/C				Pd/TiO$_2$	
	Ee (%)	r_m	r_u	r_u/r_m	Ee (%)	r_m
1	59	78	110	1.4	68	36
2	63	60	100	1.7	72	32
3	67	60	72	1.2	80	30
4	71	41	54	1.3	82	12

[a] 0.3 mmol (0.6 equiv) of benzylamine was added to the reaction mixture.

CM-Pd was even larger for **2**–**4** than **1** as deduced from the values of r_u/r_m.

If the methoxy substitution induces an increase in factor-*i*, application of the known technique to reduce the contribution from the unmodified sites could attain a further increase in ee. A promising way is to use amine additives. The presence of benzylamine in the reaction mixture is known to decrease the reaction rate on the unmodified sites and to accelerate the reaction on the modified sites.[6] In fact, the catalytic activity ratios r_u/r_m for **1**–**4** become much smaller as a result of larger r_m and smaller r_u values on the addition of benzylamine (Table 2). This additive effect must bring about a further increment of the product ee for all the substrates, in spite of the expected decrease in α as a result of competitive adsorption of the benzylamine and cinchonidine.[14] Here, the preferable effect of the *p*-methoxy substituent was again observed, although the model of substrate-modifier interaction in the presence of amine would be different. The best ee of 71% for **4** is on the same level of the highest results recorded in the literature for the enantioselective hydrogenation of α,β-unsaturated acids.

Our final approach of this study was to employ 5 wt % Pd/TiO$_2$ prepared with a nonporous titania, the best catalyst reported so far and expected to have the least proportion of the unmodified sites ($\alpha \approx 1$), at the sacrifice of catalytic activity due to the lower dispersion of Pd.[15] The product ee was improved for all the substrates, and 82% ee was achieved in the reaction of **4**. This is 10% higher than the best value reported with **1**, and is the highest in the enantioselective hydrogenation of C=C bonds in α,β-unsaturated acids with heterogeneous catalysts.

3. Conclusion

We have achieved the relative rate of over 10 for the enantiomeric formation in the heterogeneous catalysis for the hydrogenation of α,β-unsaturated carboxylic acids. The success of our substrate design to enhance the substrate-modifier interaction suggests a mechanism of the enantiodiscrimination, which may further improve factor-*i* and, accordingly, the ee of the product.

Acknowledgements

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11. The hydrogenation was carried out in a magnetically stirred 50 mL glass reactor at room temperature (22–24 °C) under an atmospheric pressure of hydrogen. The catalyst (0.02 g) and cinchonidine (0.02 mmol) were pre-reduced by stirring for 30 min in 10 mL of 1,4-dioxane containing 2.5% (v/v) of water. Then 0.5 mmol of a substrate was introduced to the mixture. Benzylamine (0.6 equiv) was further added when necessary.
12. The dihedral angles for **1** and its conjugate base calculated at the AM-1 level are 78.1° and 86.3°, respectively.
13. Absolute stereochemistries of the new compounds obtained by the hydrogenation of **2**–**4** are assigned as *S* by their CD spectra.
14. The addition of benzylamine prior to the substrate introduction causes a considerable decrease in the product ee, which suggests that cinchonidine is partly desorbed from Pd surface as a result of competitive adsorption of benzylamine.
15. The 5 wt % Pd/TiO$_2$ catalyst was prepared by a precipitation-deposition method with PdCl$_2$ and a nonporous titania (JRC-TIO-3, Catalysis Society of Japan) and by heating in a hydrogen flow at 473 K for 1 h immediately before use according to the procedure described previously. Nitta, Y.; Kubota, T.; Okamoto, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2635.