Enantioselective Hydrogenation of (*E*)-α-Phenylcinnamic Acid on Pd/TiO_2 Catalyst Modified by Cinchona Alkaloids : Effect of Modifier Structure

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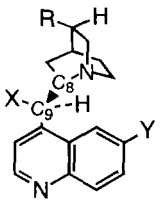
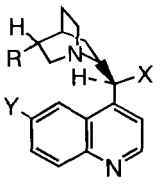
The effect of modifier structure on enantioselectivity and activity in the hydrogenation of (*E*)-α-phenylcinnamic acid with cinchona-modified Pd/TiO_2 catalyst has been found to be in contrast to the hydrogenation of α-ketoesters with modified platinum catalysts. It is suggested that the interaction of the hydroxyl group at C9 of cinchonidine with the carboxyl group in the substrate is crucial to induce a high enantioselectivity.

The enantioselective hydrogenation of C=C bonds using modified heterogeneous catalysts is still a challenging subject.[1] Recently, palladium-catalyzed enantioselective hydrogenation of α,β-unsaturated acids and ketones has received increasing attention.[2-7] In the previous study, we reported that (*E*)-α-phenylcinnamic acid (**1**) was hydrogenated to yield preferentially the *S*-enantiomer of 2,3-diphenylpropionic acid (**2**) on a cinchonidine-modified Pd/TiO_2 catalyst with an enantiomeric excess of 72% under optimal conditions.[8] In order to obtain further improvement of the enantioselectivity, it seems necessary to study the interaction between the modifier and the substrate and to understand the mechanism of the enantiodifferentiation in this reaction. Therefore, we have examined the influence of the modifier structure on the activity and enantioselectivity in the hydrogenation of **1** on a modified 5 wt%Pd/TiO_2 catalyst.

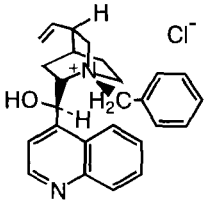
The 5 wt%Pd/TiO_2 catalyst was prepared by a precipitation-deposition method according to the procedures described previously.[8,9] Modifiers (**3-10**, shown below) and **1** were used as received. Methyl ester and Na salt of **1** were prepared according to literature procedures and used for comparison.



3: Cinchonidine X = OH, Y = H, R = $CHCH_2$



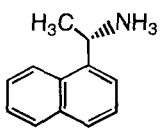
4 : Cinchonine



9 : *N*-Benzylcinchonidinium chloride

5 : Quinine **6** : Quinidine X = OH, Y = OCH_3, R = $CHCH_2$

7 : Norcinchol X = OH, Y = H, R = CH_2OH



8 : *O*-Methylhydrocinchonidine X = OCH_3, Y = H, R = CH_2CH_3

10 : (*S*)-1-(1-Naphthyl)-ethylamine

The hydrogenation reactions were carried out in methanol or in a mixed solvent of *N,N*-dimethylformamide (DMF) and water (9:1 in volume) at 298 K under an atmospheric pressure of hydrogen. Modifier was added to the suspension of the reduced catalyst and stirred for 20 min under a hydrogen atmosphere prior to the addition of the substrate. The hydrogenation products were analyzed after esterification with $CH_3OH/BF_3{\cdot}CH_3OH$ followed by HPLC on a chiral column (CHIRALCEL OJ-R, DAICEL). The enantioselectivity is 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.

Results obtained for the reactions with various cinchona alkaloids (**3-9**) and a related compound (**10**) are summarized in Table 1. With each modifier, the sense of chiral induction was the same for both solvents, although the use of methanol resulted in higher activity and lower selectivity as we reported before.[10] Cinchonidine (**3**) (acting as 10,11-dihydrocinchonidine in the hydrogenation) was confirmed to be the best modifier. Most cinchona alkaloids (**5, 7, 9**) with the same absolute configuration as **3** produced preferentially the *S*-enantiomer, and cinchonine (**4**) produced preferentially the *R*-enantiomer. This suggests that the absolute configurations at C8 and C9 primarily determine the product distribution as in the case of the

Table 1. Effect of modifier structure on the enantioselective hydrogenation of (*E*)-α-phenylcinnamic acid [a]

Entry	Modifier [b]	Solvent	r_0 [c] mmol $h^{-1}g^{-1}$	e.e. [d] %	Major enantiomer
1	**3**	MeOH	36	49	*S*
2	**4**	MeOH	21	28	*R*
3	**5**	MeOH	17	10	*S*
4	**6**	MeOH	18	1	*S*
5	**7**	MeOH	34	42	*S*
6	**8**	MeOH	20	12	*R*
7	**9**	MeOH	19	31	*S*
8 [e]	**10**	MeOH	47	12	*R*
9	**3**	90%DMF	10	61	*S*
10	**4**	90%DMF	8	29	*R*
11	**5**	90%DMF	7	5	*S*
12	**6**	90%DMF	9	4	*S*
13	**7**	90%DMF	8	50	*S*
14	**8**	90%DMF	8	18	*R*
15	**9**	90%DMF	18	57	*S*
16 [e]	**10**	90%DMF	11	4	*S*

[a] Reaction conditions; catalyst: 0.02 g, solvent: 10 cm^3, substrate: 1 mmol, modifier: 0.02 mmol, H_2: 0.1 MPa, reaction temperature: 298 K. [b] **3**: Cinchonidine, **4**: Cinchonine, **5**: Quinine, **6**: Quinidine, **7**: Norcinchol, **8**: *O*-Methylhydrocinchonidine, **9**: *N*-Benzylcinchonidinium chloride, **10**: (*S*)-1-(1-Naphthyl)-ethylamine. [c] Initial reaction rate. [d] Optical yield of **2** at full conversion. [e] Modifier: 0.04 mmol.

hydrogenation of α-ketoesters on cinchona-modified Pt catalysts.[7,11] Quinidine (**6**) with the same configuration as **4**, however, led to the *S*-enantiomer with low e.e. values, as reported by Perez *et al.* with a Pd/C catalyst.[12] The low efficiency of **5** and **6** is probably explained by the steric constraints between the methoxy group of the modifier and the phenyl group of the substrate. It is noteworthy that the introduction of methoxy group to C9 of cinchonidine has decisive influence both on sign and size of the optical induction (entries 6 and 14) while the alkylation of the nitrogen atom in the quinuclidine ring has only a minor effect (entries 7 and 15). These findings are in contrast to the well studied hydrogenation of ethyl pyruvate with cinchona-modified Pt catalysts where the introduction of methoxy group leads to the highest optical yield and the alkylation of the nitrogen atom to complete loss of enantioselectivity.[11] A simple modifier **10** was found not as effective as in the hydrogenation of ethyl pyruvate on Pt.[13]

Concerning the interaction between the modifier and the substrate, one hydrogen bonding between the tertiary nitrogen of the modifier and the oxygen at the α-carbonyl group of the substrate has been proposed for the Pt system.[13] The difference between Pd and Pt systems in the effects of modifier structure strongly suggests that the cinchonidine molecule adsorbed on Pd interacts with substrate **1** *via* two hydrogen bonds as shown in Figure 1, and that the interaction with OH group at C9 has

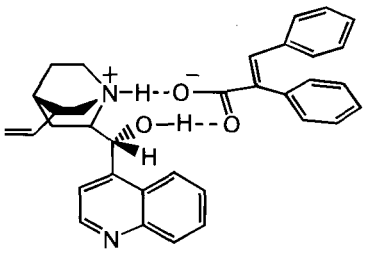


Figure 1. A possible interaction between cinchonidine and (*E*)-α-phenylcinnamic acid adsorbed on Pd surface.

crucial influence on the optical induction. The substitution of OH group at C9 to OCH_3 will remarkably weaken the interaction between the modifier and the substrate, and lead to less controlled orientation of the adsorbed substrate on Pd surface, which explains the results shown in Table 1.

The combined effects of **3** and **8** or **9** have been examined to have information on the adsorption strength of the interacting species. As shown in Figure 2, only a small amount of **3** added to **8** took over the governing role in the optical induction while the mixture of **3** and **9** only showed average effect, indicating that the adsorption of the substrate interacting with **8** is weaker than that interacting with **3** or **9**. This supports the importance of the hydrogen bond using the OH group at C9 of the modifier.

The esterification of the carboxyl group of **1** resulted in complete loss of enantioselectivity while the hydrogenation of the Na salt of **1** gave *S*-enantiomer with *ca.* 10%e.e. in 90%DMF. These observations also support the interaction model shown in Figure 1. We have shown that the polarity of the solvent influences the selectivity of this catalytic system.[10]

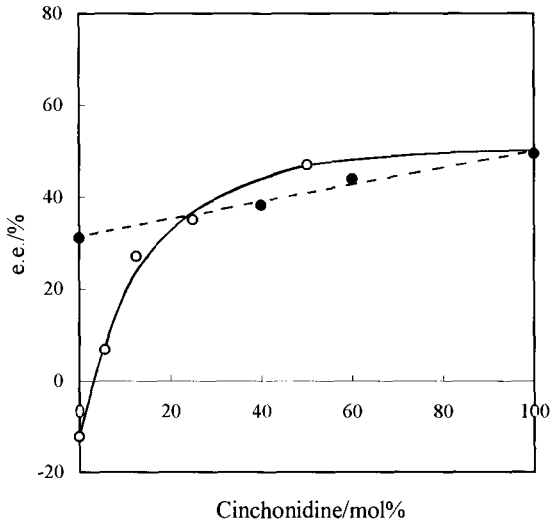


Figure 2. Influence of mixed modifiers on the optical induction in the hydrogenation of (*E*)-α-phenylcinnamic acid.
Modifiers: *O*-methylhydrocinchonidine (**8**) and cinchonidine (○), and *N*-benzylcinchonidinium chloride (**9**) and cinchonidine (●).
Solvent: methanol. Other reaction conditions as for Table 1.

Therefore, the interaction with solvent should also be considered. Studies on this point are currently under way.

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