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Substrate adsorption on the cinchonidine-modified Pd/C during the enantio-differentiating hydrogenation as a vital stereocontrol factor

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ABSTRACT

Two regioisomeric α-phenyl-β-pyridylacrylic acids were hydrogenated with cinchonidine (CD)-modified Pd/C. The low ee obtained was attributed to the strong adsorption of the substrate, which caused desorption of CD from the catalyst surface. The ee was improved at the low substrate/CD ratio up to 82% for the 4-pyridyl isomer. The unmodified site in the CD-modified Pd catalyst was experimentally proved to be variable depending on the relative adsorption strength between the substrate and CD. At the low substrate/CD ratio, the ee with the 3-pyridyl isomer was also improved, but the highest ee was only 45%. The difference between the isomers suggests that the strong adsorption of the substrate on the metal surface may interrupt the interaction between CD and the substrate.

1. Introduction

Cinchonidine (CD)-modified palladium is an asymmetric heterogeneous catalyst effective for the enantioselective hydrogenation of olefins [1–6]. The olefins applicable to this catalysis are classified in α,β-unsaturated acid and α-pyrone derivative [7], and the former substrates are divided into aliphatic [8,9] and aromatic ones. Phenylcinnamic acid (PCA) is a representative example of the aromatic α,β-unsaturated acid, and shows high performance both in the enantioselectivity and the catalytic activities. By intensive studies searching for suitable palladium catalyst for the hydrogenation of PCA [10], some types of commercial Pd/C were found to show sufficient enantioselectivity when they are used after the 80 °C pretreatment (under H_2 in the reaction solvent) [11]. The improvement on the catalyst is attributable to conversion of the unmodifiable region, which produces racemic product, to the modifiable one. The unmodifiable region should remain small in the latest CD-modified catalyst, but is highly active compared with the modified region [12]. With the easily available pretreated Pd/C in hand, the substrate structure–enantioselectivity relationship has been investigated [13–15]. Among the derivatives of PCA, the β-*p*-alkoxyphenyl analogues, represented by *p*,*p*′-dimethoxy PCA (DMPCA), were found to provide higher ee (enantiomer excess) up to 92% than PCA itself (81%ee) (Scheme 1). It was also found that the hydrogenation of DMPCA becomes slower when PCA coexists in the reaction media, while the hydrogenation of PCA is not affected by the coexisting DMPCA. The degree of suppression is larger with the unmodified catalyst than with the modified catalyst, suggesting that DMPCA is adsorbed on the catalysts more weakly than PCA, and the difference in the adsorption strength is larger on the unmodified catalyst than on the modified catalyst. The observed properties seemed to indicate that the contribution of the unmodified region in the CD-modified catalyst is smaller for the hydrogenation of DMPCA than that of PCA, and the smaller contribution of the unmodified region results in increase in the ee.

The above finding presented in the last report [13] is very important since the stereocontrol factors in an asymmetric heterogeneous catalysis are keys to improve the catalyst to attain high selectivity and to develop a new reaction system. However, the factors are still difficult to identify: the product ee is governed by the intrinsic stereocontrollability of the chiral modifier and by the contribution from the unmodified region [16], but each factor is difficult of quantify. To obtain more information on the roles of the substrate adsorption in the stereocontrol mechanism, two regioisomeric β-pyridyl analogues, (*E*)-α-phenyl-β-(4-pyridyl)acrylic acid (4-Py) and (*E*)-α-phenyl-β-(3-pyridyl)acrylic acid (3-Py), were studied since they are expected to show stronger adsorption tendency than PCA [17]. The structures of 4-Py and 3-Py and their *N*-oxide analogues are shown in Scheme 1. A new refined stereocontrol mechanism to explain the substrate structure–enantioselectivity relationship will

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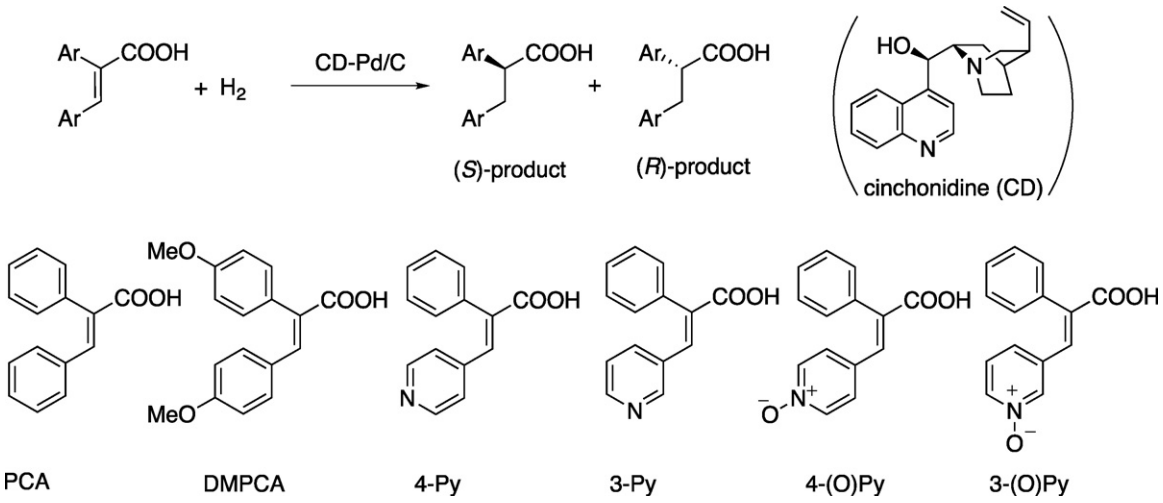

Scheme 1. Enantioselective hydrogenation using CD-modified Pd/C and the substrates for the present study.

be proposed on the basis of the observations on behavior of the two substrates.

2. Experimental

2.1. Materials

STD-type 5% Pd/C was supplied from N.E. CHEMCAT in the wet form (catalyst content = 51%, w/w), the metal surface area of which is given as 339 $m^2\ g^{-1}$, corresponding to metal dispersion of 76%. 5% Pd/Al_2O_3 (Engelhard 40692) was also obtained from N.E. CHEMCAT (dispersion = 19%). 4-Py and 3-Py were prepared by the Perkin reaction [18]. The *N*-oxide analogues were prepared from 4-Py and 3-Py by the treatment with hydrogen peroxide (30%, 1.3 equivalents) in acetic acid at 80 °C (24 h) [19]. Phenylcinnamic acids were used after recrystallization from acetone.

2.2. Hydrogenation [13]

In a 50 ml glass reactor with a small septum port, Pd/C (43 mg) and 2.5% (v/v) water-containing dioxane (4 ml, wet dioxane hereafter) were placed. Hydrogen of atmospheric pressure was charged to the flask, and the mixture was heated at 353 K for 30 min under stirring (1200 rpm). The suspension was cooled to 296 K, and a solution of cinchonidine (6 mg, 0.02 mmol) in wet dioxane (1 ml) was added. After stirring for 30 min, a solution of a substrate (0.5 mmol) in wet dioxane (5 ml) was added, followed by addition of benzylamine (55 μl, 0.5 mmol). The reactivity of the substrate was roughly evaluated by the initial hydrogenation rates (r/mol $g^{-1}\ h^{-1}$) calculated from the hydrogen uptake around the 25% conversion. After the hydrogen uptake finished (3–5 h), the mixture was filtered, concentrated under vacuum, and confirmed the completion of the hydrogenation by ^{1}H NMR (600 Hz) in $CDCl_3$.

Optical rotation was measured by a Perkin-Elmer 241 polarimeter for selected runs. In the case of the *N*-oxide, the saturated product was further hydrogenated in methanol (2 ml) with Pd/C (40 mg) for 4 h to reduce at the remaining *N*-oxide part. The optically active saturated acids obtained were converted to the corresponding methyl esters by the treatment of methanol (1 ml) and sulfuric acid (1 drop) at 343 K for 24 h. The enantiomer ratio was determined by HPLC with a chiral column; Chiralpak AD (Daicel, 25 cm × 4.6 mm) eluted with 2% 2-propanol in hexane (1 ml/min) for 4-Py, Rt = 30.0 min (*S*-isomer) and 31.7 min (*R*-isomer), and Chiralpak AS-H eluted with 1% 2-propanol in hexane for 3-Py, Rt = 33.0 min (*S*-isomer) and 40.4 min (*R*-isomer). The enantiomer excess (ee) value was calculated from the ratio according to %ee = 100 × |*S*–*R*|/(*S* + *R*).

2.3. Kinetic study by the competitive hydrogenation

In a 50 ml glass reactor with a small septum port, Pd/C (10 mg, dry basis) in wet dioxane (2.5 ml) was heated at 353 K for 30 min, and after cooling to 296 K, a solution of cinchonidine (3 mg, 0.01 mmol) in wet dioxane (1 ml) was added. After stirring for 30 min, a solution of a mixture of the two substrates (0.25 mmol each) in wet dioxane (4 ml) and then ethanolamine (30 μl) were added. A portion (0.2 ml) of the reaction mixture was taken out in every 10 min via a syringe during the hydrogenation and subjected to ^{1}H NMR analysis (600 MHz, $CDCl_3$) to determine the reaction conversion of each substrate.

3. Results

3.1. Enantioselective hydrogenation

Table 1 summarizes the results of the hydrogenation of 4-Py and 3-Py with different palladium catalysts under the standard conditions. The results for 4-(O)Py and 3-(O)Py are shown in entries 4 and 8, and those for the reference substrates are given in entries 9–14. The hydrogenation of 4-Py with the 80 °C-pretreated Pd/C gave moderately high 56%ee, while that of 3-Py gave lower ee of 22% (entries 1 and 5). The hydrogenation of 4-(O)Py and 3-(O)Py gave the corresponding saturated acids accompanied with some by-products of over reduction at the *N*-oxide group (<30% deduced from the ^{1}H NMR in d_6-DMSO), and the reaction mixture was analyzed as the pyridyl products after the complete reduction. As shown in Table 1, the product ee was not affected much by the introduction of the *N*-oxide group, but only the hydrogenation became slower. Stereochemistries of the products are estimated to be *S*, the same as PCA and DMPCA deduced from the sign of optical rotations. With 4-Py, the product ee much depended on the catalyst used, similarly to those with PCA and DMPCA, while 3-Py showed low ee with the small dependency.

3.2. Competitive hydrogenation with PCA

The relative strength of the substrate adsorption was estimated by the competitive hydrogenation using a one-to-one mixture of

Table 1
Results of enantioselective hydrogenation of 4-Py and 3-Py with different Pd catalysts[a].

Entry	Substrate	Catalyst	Ee%	r/mmol h^{-1} g^{-1}	$[\alpha]_D^{20}$ (c, solvent)	^{1}H NMR ($CDCl_3$, 600 MHz); ^{13}C NMR ($CDCl_3$, 150 MHz); HRMS of the product
1	4-Py	Pretreated Pd/C	56	52	+35.2(0.9, CH_2Cl_2)	^{1}H NMR δ 8.43 (d, J = 6.2 Hz, 2H), 7.31–7.25 (m, 5H), 7.01 (d, J = 6.2 Hz, 2H), 3.82 (t, J = 7.7 Hz, 1H), 3.6 (s, 1H), 3.38 (q, J = 8.25 Hz, 1H), 3.00 (q, J = 7.56 Hz, 1H); ^{13}C NMR δ 173.25, 149.76, 147.89, 137.78, 128.82, 127.83, 127.71, 124.23, 52.36, 52.20, 38.89; (ESI+) m/z (M+Na$^+$) calcd for 241.1103 obsd. 241.1100
2	4-Py	Untreated Pd/C	46	44		
3	4-Py	Pd/Al_2O_3	37	23		
4	4-(O)Py	Pretreated Pd/C	53	12		
5	3-Py	Pretreated Pd/C	22	18	+23.7(0.9, CH_2Cl_2)	^{1}H NMR δ 8.41–8.40 (m, 1H), 8.36 (d, J = 2.1 Hz, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.31–7.25 (m, 5H), 7.13 (q, J = 4.8 Hz, 1H), 3.79 (t, J = 8.3 Hz, 1H), 3.6 (s, 1H), 3.38 (q, J = 8.25 Hz, 1H), 3.01 (q, J = 6.9 Hz, 1H); ^{13}C NMR δ 173.36, 150.34, 147.92, 137.87, 136.44, 134.37, 128.81, 127.90, 127.67, 123.19, 53.15, 52.16, 36.86; (ESI+) m/z (M+Na$^+$) calcd for 241.1103 obsd. 241.1126.
6	3-Py	Untreated Pd/C	24	8		
7	3-Py	Pd/Al_2O_3	16	10		
8	3-(O)Py	Pretreated Pd/C	24	8		
9	PCA	Pretreated Pd/C	81	105	+104.3(0.5, acetone)	
10	PCA	Untreated Pd/C	65	55		
11	PCA	Pd/Al_2O_3	39	8		
12	DMPCA	Pretreated Pd/C	92	43	+115(1.1, acetone)	
13	DMPCA	Untreated Pd/C	77	26		
14	DMPCA	Pd/Al_2O_3	58	4		

[a] The results with PCA and DMPCA (entries 9–12) are quoted from Ref. [6], but the reexamination gave the same results.

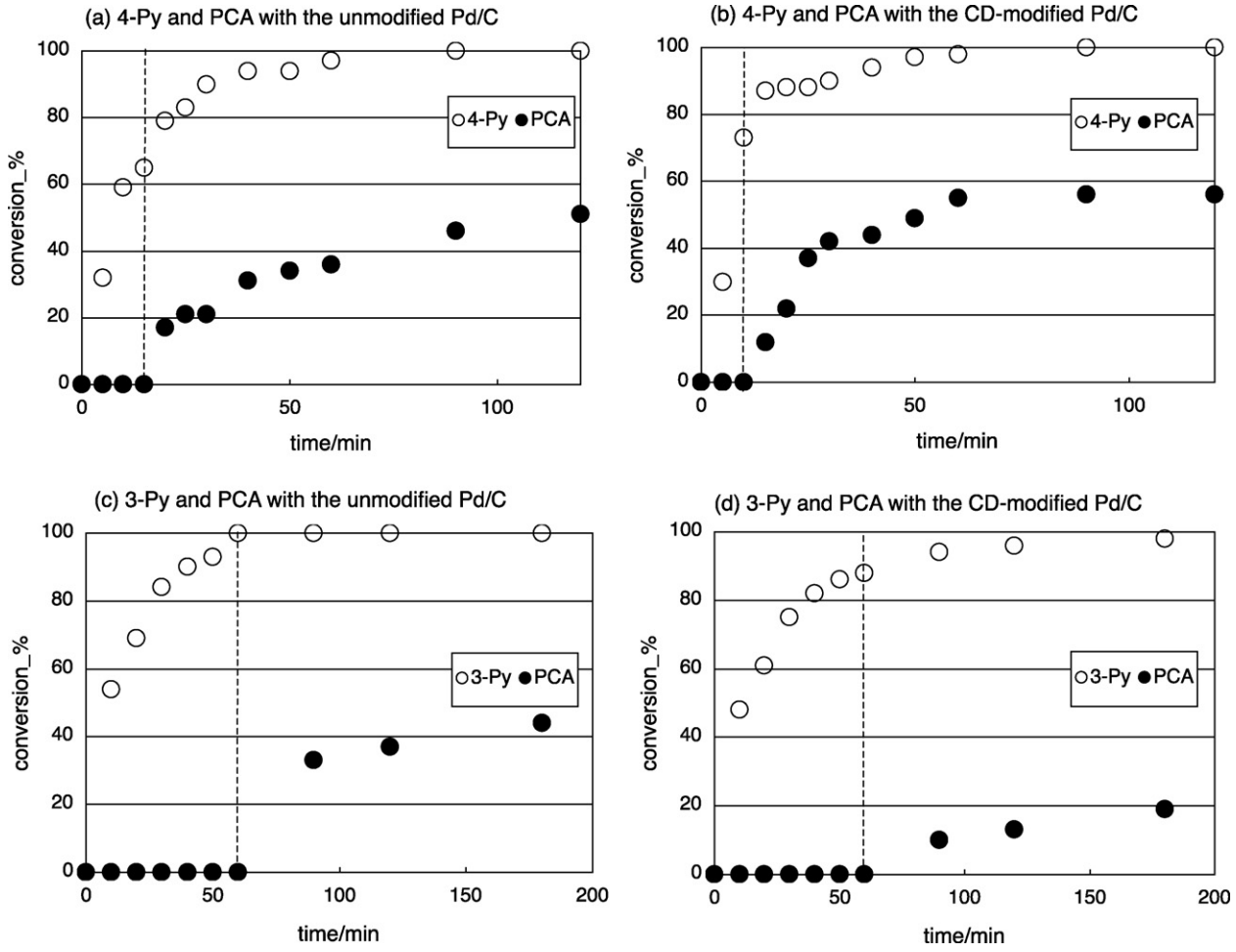

Fig. 1. The conversions during the hydrogenation of a mixture of PCA and 4-Py (a and b) and PCA and 4-Py (c and d) with unmodified (a and c) and modified catalyst (b and d).

PCA and one of the pyridyl substrates. The adsorption of the substrate over the unmodified Pd/C is assumed to represent that on the palladium surface and that over the CD-modified Pd/C is to represent the adsorption under the influence of the CD. The hydrogenation was performed in the presence of ethanolamine instead of benzylamine, because the use of benzylamine often gives precipitates during the hydrogenation, but ethanolamine does not [13]. Fig. 1a and b shows the conversions of 4-Py and PCA for the reaction with their mixture over the unmodified and modified Pd/C. Evidently, 4-Py suppresses the hydrogenation of PCA, and the reaction of PCA starts only after consumption of the most part of 4-Py (ca. 80%). The suppression of the PCA hydrogenation must be due to the strong adsorption of 4-Py that excludes PCA from the reaction site on the catalyst. The imperfect conversion of PCA is attributable to the catalyst deactivation caused by the product from 4-Py.

The same reactions except for the use of 3-Py instead of 4-Py gave the results shown in Fig. 1c and d. The suppression effect is still stronger, and the hydrogenation of PCA stars only after >90% conversion of 3-Py.

3.3. Improvement of enantioselectivity

Since the pyridyl substrates showed the strong adsorption onto the palladium metal surface, it was assumed that the substrate adsorption is competitive with the CD adsorption and decrease in the adsorbed CD is a reason for the low ee. With this working hypothesis, the effect of the substrate/CD ratio on the ee was examined. Starting from the standard conditions, substrate concentration [S] = 50 mM, CD concentration [CD] = 2 mM ([S]/[CD] = 25), and S/Pd = 50 (substrate/total palladium in mol), the hydrogenation was examined with different CD concentrations. The results with 4-Py and 3-Py are given in Fig. 2. When the CD concentration was reduced to half, the ee values became low to be 52% for 4-Py and 15% for 3-Py. Oppositely, the ee values increased up to 76% for 4-Py and 45% for 3-Py ([S]/[CD] = 5) with increasing the CD concentration. Since CD could not dissolve in wet dioxane more than 10 mM, the substrate concentration was reduced to half ([S]/[CD] = 2.5). Under these particular conditions, 4-Py gave 82%ee (r = 74), the same value as the hydrogenation of PCA. The hydrogenation of 3-Py did not result in further improvement under these conditions (42%ee, r = 17).

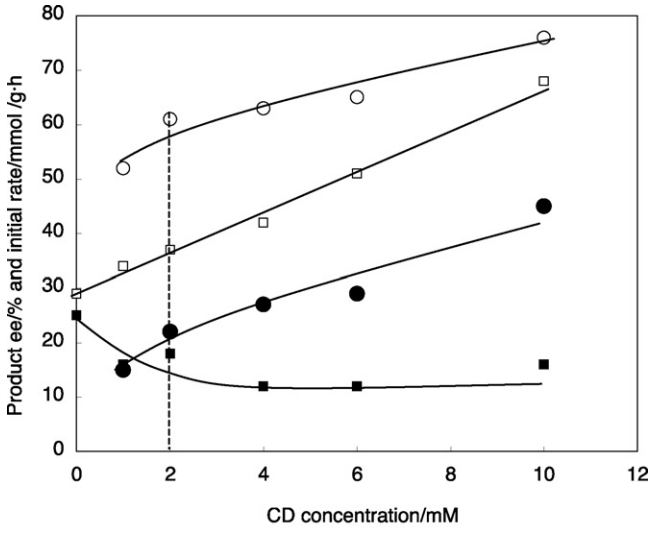

Fig. 2. Ee (open circles) and the initial rate (open squares) for the hydrogenation of 4-Py with different CD concentration (standard conditions = 2 mM). Closed circles and squares indicate the results with 3-Py.

4. Discussion

Acidities of the substrate carboxylic acid will be discussed first since the acidity directly reflects on the strength of the ionic interaction between the adsorbed CD protonated at the quinuclidine part and the conjugate base (carboxylate) of the substrate. Pyridyl groups are electron withdrawing compared with phenyl, and 4-pyridyl is stronger than 3-pyidyl [20]. Thus, the order of the substrate acidity should be 4-Py > 3-Py > PCA > DMPCA, but the order of the product ee showed different order, 3-Py < 4-Py < PCA < DMPCA. The electron withdrawing power of the pyridyl groups is enhanced by conversion to the *N*-oxide analogues, but in fact, did not affect the ee value. It is concluded that the acidity is not a main factor governing the difference between PCA and the β-pyridyl substrates, but another factor, the most probably adsorption, makes the difference.

The adsorption strengths of the substrates estimated from the results of the competitive hydrogenation are summarized to decease in the order, 3-Py > 4-Py ≫ PCA > DMPCA, which corresponds to the increasing order of the product ee. Unfortunately, the differences between the modified and unmodified catalysts are unclear. This information was used to evaluate the activity ratio of the modified/unmodified regions [14], but was found to be less important for the pyridyl substrates (vide infra). The high ee under the low [S]/[CD] conditions must mean that the substrate adsorption is so strong that CD on the metal surface is desorbed to result in increase of the racemic production under the standard conditions. Since the nitrogen atoms in 4-Py and 3-Py should play a major role in enhancing the substrate adsorption, geometry of the adsorption on the metal surface must be different between the two substrates, and this may be an origin of the large difference in the product ee, 82% for 4-Py vs. 45% for 3-Py.

Another apparent difference between 4-Py and 3-Py is on the hydrogenation rate; hydrogenation of 4-Py accelerated with increasing concentration of CD, while that of 3-Py decelerated to some constant rate. Since the rate acceleration of 4-Py accompanies the ee increment, the acceleration must induced by the interaction of 4-Py with the CD on the surface. This rate profile is contrasting to that with PCA, where the rate with unmodified Pd/C (r = 240) was decreased (r = 105) by the CD modification (2 mM) [13]. Increment of the CD amount for the hydrogenation of PCA is known not to result in the higher ee, but only cause decrease in the rate [21]. We also confirmed this behavior with the Pd/C (4 mM of CD for the PCA hydrogenation gave 81%ee, r = 72).

The difference among PCA, 4-Py and 3-Py in their rate properties is explainable by the difference in the adsorption strength and geometry that are controlled by the position of the nitrogen atom in the pyridyl group. Under the hydrogenation conditions prior to the addition of the substrate, CD should cover the most part of the active metal surface. For the hydrogenation of PCA, the reaction needs adsorption of PCA by pushing out or by replacing the CD on the surface. The PCA adsorption must be enhanced by the interaction with CD, but this effect could not overcome the deceleration effect by the competitive adsorption with CD because the CD adsorption is much stronger than the PCA adsorption. As the results, the hydrogenation rate becomes slower by increasing the CD concentration. In the case of 4-Py, the adsorption ability of 4-Py is so strong that CD is easily replaced by 4-Py. Since the interaction between CD and 4-Py enhances the hydrogenation rate, the increase in the adsorbed CD by increasing its concentration accelerates the hydrogenation. In the case of 3-Py, the adsorption on the metal surface is still strong. The adsorbed 3-Py should have different geometry from the adsorbed 4-Py, and the strongly regulated geometry of 3-Py by attachment to the metal surface may not fit the geometry for interaction with the CD on the metal surface. For any reasons, the weakened interaction could not result in rate acceleration nor the high ee.

5. Conclusion

The adsorption of the substrate was confidentially confirmed to be a key stereocontrol factor in the enantioselective hydrogenation with the CD-modified Pd catalyst. The strongly absorbable substrates are not suitable as the substrate for the CD-modified Pd/C because of the two reasons; desorption of the CD by the competitive adsorption, and interference of the CD–substrate interaction by the geometrical requirement. The first drawback could be overcome by the reaction conditions at high [S]/[CD] ratio, but the second drawback could not sufficiently be addressed with the present modifier. For the strongly adsorbable substrates, the unmodified site on the CD-modified Pd/C is not stationary, but changeable depending on the substrates. Although the adsorption strengths of PCA and DMPCA are much weaker than 4-Py and 3-Py, the higher ee with DMPCA than with PCA may also be attributable to the less competitive adsorption with CD.

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