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Adsorption and Performance of Chiral Cinchona Alkaloid Modifiers over Pd/C Catalyst for Enantioselective Hydrogenation of α-Phenylcinnamic Acids

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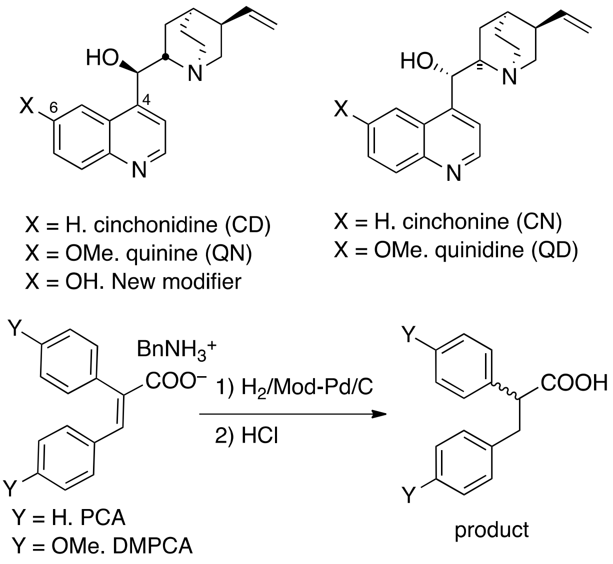
Abstract

The enantioselective hydrogenation reactions of α-phenylcinnamic acid (PCA) and 4,4'-dimethoxy α-phenylcinnamic acid (DMPCA) were carried out over chiral cinchona alkaloid-modified Pd/C. Two sets of the modifiers were employed to get deeper insights into the effects of relative adsorption strength between the modifier and the substrate on the enantioselectivity; cinchonidine (CD)/cinchonine (CN) and quinine (QN)/quinidine (QD). The performances of the two sets of modifiers were compared by systematically varying the modifier concentration over a wide range. It was clearly substantiated that the origin of the low selectivity observed with QN/QD at an ordinary concentration is primarily due to its weak adsorption strength on Pd metal surface, which originates from the steric hindrance of the methoxy substituent at C6. A new modifier, 6-hydroxy CD, was found to exhibit a performance comparable to that of CD, implying that the steric hindrance of 6-methxy group of QN/QD is much more influential than the electronic effects.



Scheme 1. Enantioselective hydrogenation over chiral cinchona alkaloid-modified Pd/C

1. Introduction

Precious metals, especially Pt and Pd, can be effective asymmetric hydrogenation catalysts when their surfaces are modified with proper chiral organic molecules.[1] The modifier molecules adsorbed onto the metal surface generate enantio-differentiating ability as well as covering the achiral catalytic active sites, thereby controlling the reaction enantioselectivity. Cinchonidine (CD)-modified Pd is such an example; numerous researchers have attempted to increase the performance of this catalyst system, yielding 82% ee of the (*S*)-product in the hydrogenation of 2,3-(*E*)-diphenylpropenoic acid (α-phenylcinnamic acid, PCA) over Pd/C in the presence of benzylamine (BnNH$_2$) (Scheme 1).[2] In highly selective reactions, the modifier should suitably cover the catalyst surface as much as possible while maintaining the ability of the metal surface to adsorb the substrate. Accordingly, this situation could be achieved in a dynamic adsorption equilibrium among the modifier, the substrate (or substrate-BnNH$_2$ salt), and hydrogen. In our previous report, we have shown that the difference between CD and cinchonine (CN, 54% ee of the (*R*)-product) as a modifier is attributable to different intrinsic stereocontrollability and catalytic activity of the modified sites and not to the adsorption strength of the modifiers.[3] We have also shown that ligand acceleration is a key to yield a high product ee;[3,4] thus, the modifier adsorbed onto the Pd surface serves as a co-catalyst in the enantio-differentiating hydrogenation catalysis.

Here we describe another series of cinchona alkaloids: quinine (QN) and quinidine (QD), which are the 6-methoxy analogues of CD and CN, respectively. Despite its structural similarity to CD/CN, QN/QD is known to be a poor chiral modifier (ee < 20%, PCA hydrogenation over Pd/TiO$_2$).[5]

The low selectivity with QN/QD was ascribed to weak adsorption of QN/QD due to an unfavorable adsorption mode: a parallel adsorption mode of the 4-substituted quinoline unit of CD/CN to the Pd surface (Figure 1a), in contrast to a tilted adsorption mode of the 4,6-disubstututed quinoline unit of QN/QD where the quinoline nitrogen faced the Pd surface (Figure 1b).[6-8] Parallel adsorption of the modifier over Pd metal surface may be a critical factor in the enantio-differentiation ability of the chiral modifier to catalyse asymmetric hydrogenation reaction under balanced competitive adsorption, but the details of this mechanism are still unknown. In the

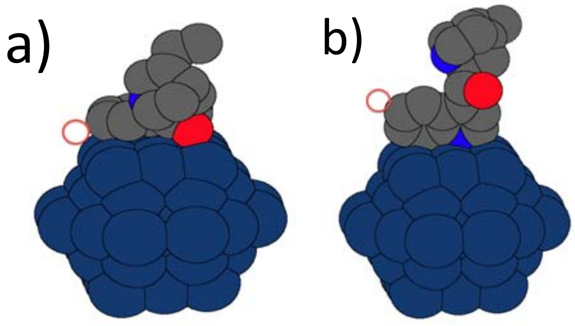


Figure 1. Adsorption model of CD on Pd/C with 76% dispersion; CD on Pd$_{55}$ in parallel (a) and tilted (b) configurations. The lower part of the particle should be buried below the active carbon. An approximate position of 6-X group is shown as a red circle.

present study, we systematically varied the cinchona alkaloid modifier concentration over a wide range to obtain deeper insights into the adsorption and performance of the modifier (CD/CN and QN/QD) in the enantioselective hydrogenation of the substrate (PCA and 4,4'-dimethoxy α-phenylcinnamic acid, DMPCA) over Pd/C. It was clearly demonstrated that the origin of the low selectivity observed with QN/QD is due to its weak adsorption strength on Pd metal surface, which originates from the steric hindrance of the 6-methoxy substituent. Figure 1 illustrates the Pd/C catalyst in our reaction system containing small Pd metal particles with an average diameter of 1.4 nm.[9]

2. Experimental

All chemicals were purchased from commercial sources and purified via distillation when necessary. 6-hydroxy CD (6-OH-CD in Scheme 1) was prepared from QN via de-methylation (55% yield). The enantioselective hydrogenation reactions of PCA and DMPCA were carried out over chiral modified Pd/C as follows.[4,9] A stirring suspension of 5% Pd/C (43 mg as a 50% content, wet form, STD-type supplied by N.E. Chemcat) and 5 ml of 2.5 % H_2O-containing dioxane was heated under 10^5 Pa of hydrogen at 353 K for 30 min. After cooling to 296 K, a solution of modifier (0.0015−12 mg) in the solvent (1 mL) was added. After 30 min, 0.5 mmol of the substrate acid in the solvent (4 mL) and then benzylamine ($BnNH_2$, 55 μL) was added. The Pd/substrate molar ratio was 10/500 (in μmol in 10 mL of polar wet dioxane). The reaction temperature and pressure were 296 K and 10^5 Pa of hydrogen, respectively. The catalytic activity was calculated from the rate of hydrogen consumption at 25% conversion. The hydrogen consumption continued for 1-3 h. After additional 2 h, a 2 M HCl aqueous solution (1 mL) was added to the solution, followed by filtration of the reaction mixture to remove the catalyst. The filtrate was extracted with ethyl acetate (2 mL) and washed with water (2 mL) .The extract was analyzed by HPLC with a chiral column (Daicel OJ-3 for PCA and AD-3 for DMPCA). The enantioselectivity is expressed as the enantiomeric excess (ee) of the (*S*)-product,

$$\%ee = 100 \times ([S] - [R])/([S] + [R]),$$

where [*S*] and [*R*] represent the concentrations of (*S*)- and (*R*)-enantiomers, respectively.

3. Results and Discussion

The product ee values are shown in Figures 2 and 3 as a function of the modifier concentration expressed in logarithm, log [modifier], for the hydrogenation of PCA and DMPCA, respectively. The ee values are low when the concentration (or amount) of the modifier is insufficient and are saturated when the concentration is higher than required.[3] The modifier concentration in our previous regular experiments was fixed at 2 mM,[2-4] which is indicated by a dotted line in Figs.2 and 3. On the basis of the metal dispersion (0.76)[9] of Pd/C used and an estimated Pd metal surface area occupied by the modifiers (ca. 10 Pd atoms per modifier), the amount of modifier (2 mM) is greater than 50 times the requirement for a monolayer formation. Although possible adsorption of the modifier on the support renders exact evaluation of the adsorption amount of the modifier on Pd metal surface difficult, the observed sigmoidal curves are well described by a simple Langmuir–Hinshelwood reaction mechanism assuming competitive adsorption of the modifier and substrate.[4]

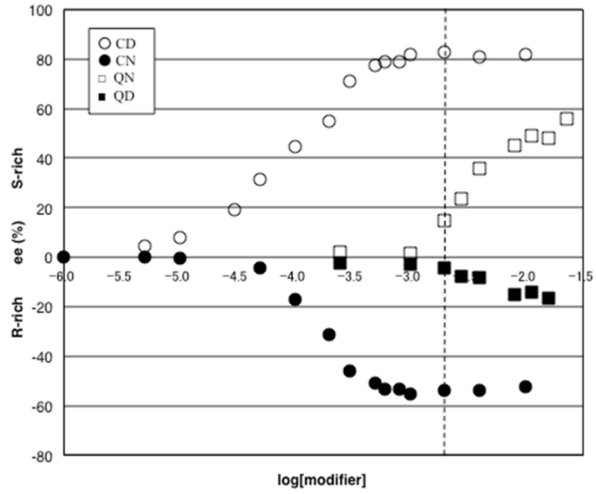


Figure 2. Product ee (%) as a function of the modifier concentration as expressed in logarithm for the hydrogenation of PCA on Pd/C. The modifiers used were (○) CD, (●) CN, (□) QN, and (■) QD. The results with CD and CN were recalculated from reference 3 for comparison.

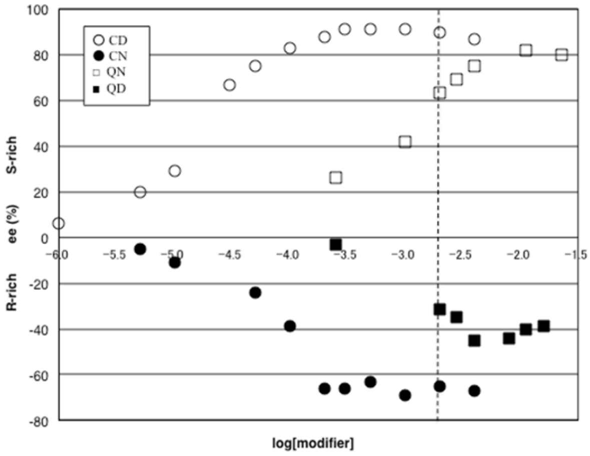


Figure 3. Product ee (%) as a function of the modifier concentration as expressed in logarithm for the hydrogenation of DMPCA on Pd/C. The modifiers used were (○) CD, (●) CN, (□) QN, and (■) QD.

As shown in Fig.2, the enantioselectivity in the hydrogenation of PCA over CD-modified Pd/C becomes apparent as low as around 3×10^{-3} mM of CD (log [CD] = -5.5). The ee value increases with the amount of the modifier and reaches a plateau value (82 %ee of the (*S*)-product) around 2 mM of CD (or log [CD] = -2.7), the optimum surface coverage of CD on Pd metal surface where adsorbed PCA effectively forms interaction intermediates with adsorbed CD in a dynamic equilibrium and thus the hydrogenation of PCA on unmodified sites is minimized. The ee value in the PCA hydrogenation over CN-modified Pd/C obviously shows a mirror image correlation of the CD-modified Pd/C, although the maximum ee value (54%ee of the (*R*)-product) attained around 2 mM of CN is lower than that on the CD-modified catalyst. It is considered that both CD and CN are adsorbed on Pd metal surface in a parallel geometry via aromatic π-bonding of the quinoline moiety and thereby the adsorption energies of the diastereomers are very similar. Actually, Meemken et al. found by ATR-IR with Pd/TiO_2 that π-bonded CD was formed on Pd metal surface, in particular, in the coexistence of CD and BA.[8] In addition, Hahn et al. showed by DFT calculations with Pt(111) that the adsorption energy of CN was very close to that of CD.[10] The mirror image correlation between CD- and CN-modified Pd/C in Fig.2 prompts us to conclude that the higher enantioselectivity of the CD-modified catalyst is not ascribed to a higher surface coverage of CD than CN, but to a higher enantio-differentiating ability of adsorbed CD. It is suggested that the absolute configurations at C8 and C9 of CD/CN primarily elucidate the enantiomer distribution.

Figure 2 shows the ee values as a function of the modifier concentration for the PCA hydrogenation over QN- and QD-modified Pd/C. With QN-modified Pd/C, enantioselectivity becomes observable only at a concentration higher than 1 mM (log[QN] = -3.0) and increases to 56%ee of the (*S*)-product as the QN concentration increases to 30 mM (log[QN] = -1.6). A plateau or maximum ee value was not attained because of experimental limitations. With PCA hydrogenation over QD-modified Pd/C, a mirror image correlation of the QN-modified Pd/C is observed, although the ee value is very limited (17 %ee of the (*R*)-product). At the regularly employed concentration (2 mM), QN and QD resulted in very low ee values (15% and 5%, respectively, with Pd/C), in agreement with the literature.[2] It is suggested from Fig.2 that these ee values on QN/QD-modified Pd/C could be improved further if higher modifier concentrations were achieved. The mirror image correlation with QN/QD-modified Pd/C in Fig.2 shows that the adsorption strength of the diastereomers on Pd metal surface are very close each other and that the different ee values attained are attributable to slightly different interaction modes between the modifier and the substrate. It is considered that the diastereomers, QN and QD, are adsorbed on Pd surface in a tilted configuration via the N-lone pair of the quinoline moiety with very close adsorption energies.

Comparing the ee value-modifier concentration mirror image correlations in Fig.2 for the PCA hydrogenation over CD/CN- and QN/QD-modified Pd/C, it is evident that the latter set of modifiers generates enantio-differentiating ability and reaches the plateau ee value at much higher modifier concentrations than the former set of modifiers. It is considered that this difference is resulted from the different adsorption strength of the modifier between the two sets of the modifiers. CD/CN is more strongly adsorbed on Pd surface with a parallel geometry via π-electrons of the quinoline moiety than QN/QD with a tilted configuration via the N-lone pair of the quinoline moiety due to steric hindrance of 6-methoxy group. In a dynamic adsorption equilibrium among the modifier, the substrate, and hydrogen during the reaction, stronger adsorption of the modifier results in a higher surface coverage of adsorbed modifier to generate a higher enantio-differentiating ability through more abundant interactions with the substrate, PCA, as well as resulting in more extensive suppression of the hydrogenation on unmodified sites or hydrogenation without interactions with the modifier. Another difference among the two sets of the modifiers is the maximum ee values attained. It is considered that the parallel adsorption of CD/CN via π-bonding of the quinoline moiety provides more favorable configurations for enantio-differentiation in PCA-modifier interaction intermediates than the tilted configuration of QN/QD.

Figure 3 presents the dependences of the ee values on the modifier concentration in the enantioselective hydrogenation of DMPCA over the two sets of CD/CN- and QN/QD-modified Pd/C. As shown in Fig.2 for the hydrogenation of PCA, two sets of mirror image correlations are observed. Assuming a dynamic equilibrium in competitive adsorption among the modifier, the substrate, and hydrogen, these results lead us to conclude again the similarity of the adsorption energies between CD and CN and between QN and QD, with the former set of the modifiers being more strongly adsorbed than the latter one. However, there are noticeable differences between PCA and DMPCA in the modifier concentrations where the enantioselectivity becomes apparent and the maximum ee values are attained; the enantioselectivity with DMPCA is detected as low as 10^{-2}-10^{-3} mM (log [modifier] = -6 ~ -5) of CD/CN, 10 times lower concentration than PCA and the maximum ee value is observed around 0.5 mM (log [CD/CN] = -3.3) in contrast to 2 mM with PCA. The maximum ee value with DMPCA is attained around 10 mM (log [modifier] = -2) of QN/QD, while at > 30 mM with PCA. These findings are interpreted by assuming weaker adsorption strength of DMPCA on Pd/C than that of PCA due to steric hindrance of the methoxy groups. It is considered that the weakened adsorption strength of DMPCA induces more preferential interactions with adsorbed chiral cinchona modifiers compared with Pd metal surface. It is noted that the electron releasing effects from the methoxy groups of DMPCA enhance the hydrogen bond interactions between the modifier and the substrate,[5] thereby resulting in the higher enantioselectivity of DMPCA compared to PCA, as suggested by Szöllösi.[11]

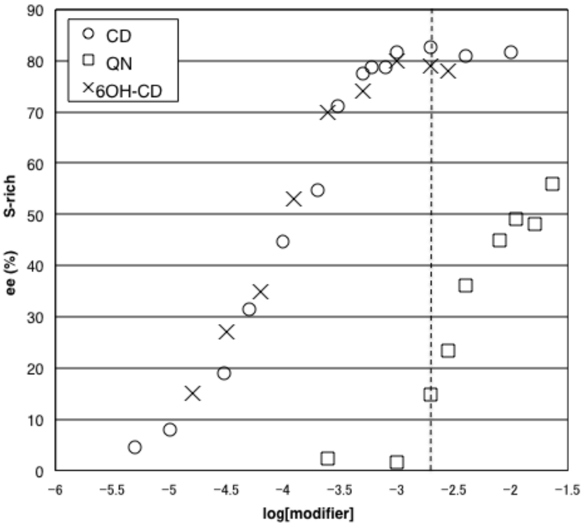


Figure 4. Product ee (%) as a function of the log of the modifier concentration for the hydrogenation of PCA on Pd/C. The modifiers used were (x) 6-hydorxy CD, (○) CD, and (□) QN. The results with CD were recalculated from reference 3 for comparison.

Another significant difference between PCA (Fig.2) and DMPCA (Fig.3) resides in the maximum ee values achieved; the maximum ee values of DMPCA are considerably higher than those of PCA with all the modifiers examined here. It is noted, in particular, that the ever highest ee values of 82% ee and 42% ee are achieved for QN and QD, respectively, with the enantioselective hydrogenation of DMPCA over QN/QD-modified Pd metal catalysts. On the basis of these results, we presume that QN exhibits a high intrinsic stereo-controllability close to that of CD; however, the low adsorption constant of QN is a decisive drawback. The adsorption constant of QN/QD in common logarithm (log K) should be lower approximately by 1.2–1.5 than that of CD/CN, assuming relatively weak adsorption of the modifiers (i.e., QN/QD should exhibit a ca. 1/20–1/30 times smaller adsorption constant).

During a further study on how the 6-methoxy group of QN/QD hinders the modifier from parallel adsorption via the quinoline ring, we found in the present study a new suitable modifier, 6-hydroxy CD (6-OH-CD in Scheme 1), which was prepared from QN via de-methylation. The performance (ee) in the enantioselective hydrogenation of PCA over 6-OH-CD is compared with CD and QN (or 6-CH_3O-CD) in Figure 4. The initial reaction rates relative to that over unmodified Pd/C are also compared in Figure 5 with CD- and CN- modified Pd/C. It is apparent that the properties of 6-OH-CD are very similar to or even almost the same as CD with respect to both the enantioselectivity and ligand acceleration effects.[4] Thus, it is revealed that the hydroxy-substitution at C6 of CD does not affect the properties of CD as a modifier. Since 6-CH_3O and 6-OH substituents have similarity in the electronic effects, a slight steric difference between OH- and CH_3O-groups results in the profound difference in the performance, presumably, due to the adsorption configuration of the modifier; 6-CH_3O substituent prefers the tilted adsorption (Figure 1b), while 6-OH substituent still favors the parallel adsorption (Figure 1a). It is also deduced that the electronic effects of 6-CH_3O substituent do not affect the interaction mode and strength with the substrate (PCA).

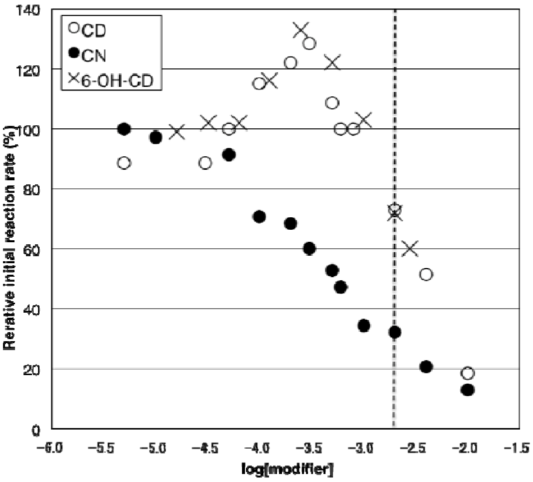


Figure 5. Initial hydrogenation rate (mmol/g·h) as a function of the log of the modifier concentration for the hydrogenation of PCA over Pd/C. The modifiers used were (x) 6-hydorxy CD, (○) CD, and (●) CN. The reaction rates are normalized with respect to the rates over the unmodified Pd/C. The results with CD and CN were recalculated from reference 3 for comparison.

4. Conclusion

In the present study, the performances of the two sets of modifiers, CD/CN and QN/QD, in the enantioselective hydrogenation reactions of PCA and DMPCA over Pd/C were compared by systematically varying the modifier concentration over a wide range. It was clearly demonstrated that the origin of the low selectivity observed with QN/QD is due to its weak adsorption strength on Pd metal surface, which originates from the steric hindrance of the methoxy substituent at C6. It is estimated that the adsorption constant of QN/QD in common logarithm (log K) is lower by 1.2–1.5 than that of CD/CN. The new modifier 6-OH-CD was found, for the first time, to exhibit a performance comparable to that of CD, indicating that the steric hindrance of 6-methxy group of QN/QD is much more influential than the electronic effects. The design of an aromatic anchor is possible to control the modifier adsorption over Pd catalysts.

References

1. a) D. Y. Murzin, P. Maki-Arela, E. Tukoniitty, T. Salmi, *Catal. Rev*. **2005**, 47, 175-256. b) E. Klabunovskii, G. V. Smith, A. Zsigmond, in Heterogeneous Enantioselective Hydrogenation, Springer, Dordrecht, **2006**, Chapters 4 and 5. c) M. Heitbaum, F. Glorius, I. Escher, *Angew. Chem. Int. Ed.* **2006**, 45, 4732-4762. d) T. Mallat, E. Orglmeister, A. Baiker, *Chem. Rev*. **2007**, 107, 4863-4890. e) T. Sugimura, in Handbook of Asymmetric Heterogeneous Catalysis, ed. by K. Ding, Y. Uozumi, Wiley-VCH, Verlagsgesellschaft, **2008**. pp. 357-382. f) F. Zaera, Acc. *Chem. Res*., **2009**, 42, 1152-1160.
2. a) Y. Nitta, J. Watanabe, T. Okuyama, T. Sugimura, *J. Catal*. **2005**, 236, 164-167. b) T. Sugimura, T. Uchida, J. Watanabe, T. Kubota, Y. Okamoto, T. Misaki, T. Okuyama, *J. Catal*. **2009**, 262, 57-64.
3. T. Sugimura, H. Ogawa, *Chem. Lett*. **2010**, 39, 232-234.
4. H. Ogawa, T. Mameda, T. Misaki, Y. Okamoto, T. Sugimura, *Chem. Lett*., **2013**, 42, 813-815.
5. Y. Nitta, A. Shibata, *Chem. Lett*. **1998**, 161-162.
6. W. R. Huck, T. Mallat, A. Baiker, *Catal. Lett*. **2003**, 87, 241-247.
7. G. Szöllösi, K. Balásik, M. Bartók, *Appl. Catal. A: Gen*., **2007**, 319, 193-201.
8. F. Meemken, N. Maeda, K. Hungerbühler, A. Baiker, *ACS Catal*. **2012**, 2, 464-467.
9. T. Y. Kim, T. Uchida, H. Ogawa, Y. Nitta, T. Okuyama, T. Sugimura, S. Hirayama, T. Honma, M. Sugiura, T. Kubota, Y. Okamoto, *Top. Catal*. **2010**, 53, 116-122.
10. K. P. Hahn, A. P. Seitsonen, A. Baiker, *Phys. Chem. Chem. Phys*., **2015**, 17, 27615-27629.
11. Szöllösi, G., *Catal. Lett*., **2012**, 142, 345-351

Graphical Abstract

<Title>

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<Authors' names>

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<Summary>

The enantioselective hydrogenations of PCA and DMPCA were carried out over chiral cinchona alkaloid-modified Pd/C by varying the modifier concentration over a wide range. The low selectivity with QN/QD relative to CD/CN is primarily attributable to its weak adsorption strength on Pd metal surface. A new modifier, 6-hydroxy CD, was found to exhibit a performance comparable to that of CD.

<Diagram>