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Structural requirements for substrate in highly enantioselective hydrogenation over the cinchonidine-modified Pd/C

Takashi Sugimura [a,*], Takayuki Uchida [a], Junya Watanabe [a], Takeshi Kubota [b], Yasuaki Okamoto [b], Tomonori Misaki [a], Tadashi Okuyama [a]

[a] Graduate School of Material Science, Himeji Institute of Technology, University of Hyogo, Kohto, Kamigori, Hyogo 678-1297, Japan
[b] Department of Material Science, Shimane University, 1060 Nishikawatsu, Matsue 6908504, Japan

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ABSTRACT

Relationship between substrate structure and enantioselectivity is studied for the asymmetric hydrogenation of 42 different (*E*)-α,β-disubstituted acrylic acids (propenoic acids) over cinchonidine-modified Pd/C. The β-phenyl group is indispensable for high enantioselectivity of α-phenylcinnamic acid (2,3-diphenylpropenoic acid, 81% ee), and substitution on this group affects markedly the selectivity. The high ee up to 92% was achieved by the β-*p*-alkoxyphenyl substitution, and the selectivity is ascribed mainly to stronger interaction of the substrate with the chiral modifier on the catalyst surface. In contrast, substitution on the α-phenyl group does not affect notably the enantioselectivity (80–82% ee) or even the α-phenyl group itself is not indispensable but replaceable with a properly bulky group for the high enantioselectivity.

1. Introduction

Alkaloid-modified palladium is a unique heterogeneous catalyst that can perform enantioselective hydrogenation of prochiral olefins [1–3]. The enantioselectivity of the catalyst largely depends on the chiral modifier employed, and cinchonidine (CD) and cinchonine (CN) are so far the best modifiers that show opposite stereoselectivities to each other [4–8]. Choice of palladium catalyst as a base catalyst for the modification is another important factor. For the hydrogenation of a representative substrate, α-phenylcinnamic acid (PCA), a 5% Pd/TiO_2 prepared from a certain titania is so far the best palladium catalyst to give 72% ee of the product [9], when it is modified with CD in a polar solvent, such as water-containing (wet) DMF or wet dioxane (Scheme 1). Low metal dispersion with a larger Pd particle size is believed to be an essential factor to induce the good stereoselectivity [10].

Palladium-on-carbon (Pd/C) is a popular catalyst, but stereoselectivity of the hydrogenation is known to be poor in the range of 20–50% ee when it is used with the CD modifier [4,11]. However, we have recently found that pretreatment under hydrogen at 80 °C prior to the modification results in notable improvement in the product ee, and the best ee value of 81% was obtained for the hydrogenation of PCA with a certain ready-made Pd/C, in spite of the high metal dispersion [12]. It was also reported more recently that a hydrogen-pretreated Pd/Al_2O_3 at 250 °C was a suitable catalyst to give 73% ee (80% ee at 0 °C) [13]. The newly introduced catalysts are noteworthy because the reproducible stereoselectivities are obtained with commercially available catalysts, and any skillful technique is no longer required for the catalyst preparation. With these catalysts in hand, high-throughput screening of the CD-modified catalysis system became possible.

Several years ago, we have started a project to explore relationship between the substrate structure and the enantioselectivity, and found that the *p*-methoxy substitution of PCA brings about improvement in the product ee [14]. When the improved catalyst prepared from Pd/C was employed, the ee reached 92% with *p*,*p*′-dimethoxyphenylcinnamic acid (DMPCA) [12]. A report dealing with the effects of methoxy substitution has recently been published also by others [13]. In the present report, we would like to present the results with PCA and its 41 analogues as hydrogenation substrates to explore the electronic and steric requirements to give the high ee [15]. Mechanisms for the stereoselective hydrogenation will be discussed.

2. Experimental

STD-type 5% Pd/C was supplied from N.E. Chemcat in a wet form (51%, w/w), the metal surface area of which is given as 339 $m^2\,g^{-1}$, corresponding to metal dispersion of 76%. Our own evaluation showed the dispersion is 66%, on the basis of the CO

* Corresponding author. Fax: +81 791 58 0115.
E-mail address: sugimura@sci.u-hydogo.ac.jp (T. Sugimura).

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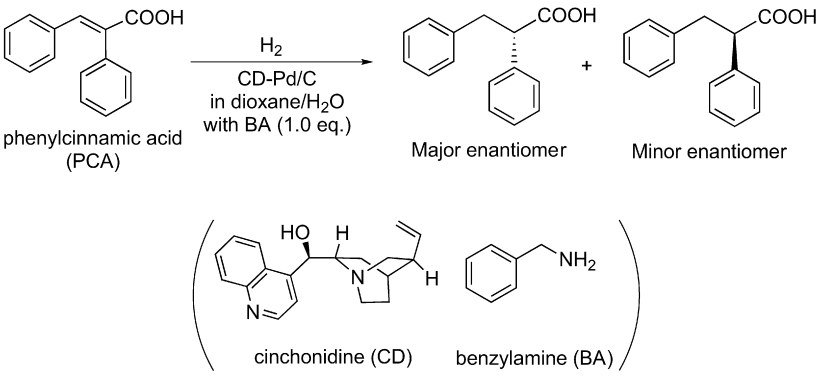


Scheme 1. Enantioselective hydrogenation of PCA over CD-modified Pd/C.

adsorption capacity obtained by a pulse technique assuming a CO/Pd ratio of 1:2 (for the catalyst pretreated with hydrogen at 200 °C) [16]. AER-type 5% Pd/C and 5% Pd/Al_2O_3 (Engelhard 40692) were also obtained from N.E. Chemcat (dispersion determined by the producers = 67% and 19%, respectively). 5% Pd/TiO_2 was made by the reported procedure (dispersion = 26%) [10]. Phenyl- and methylcinnamic acids were used after recrystallization from acetone, but tiglic acid was used as received. α-Aryl substrates were prepared by the Perkin reaction, and α-alkyl substrates were prepared by the aldol condensation or the Reformatsky reaction. 1-Acenaphthylene and 9-phenanthrene carboxylic acids were prepared from the corresponding bromides via the Grignard reaction. Details of preparation and characterization of new compounds are given in the supplementary material.

Most hydrogenations were carried out with the STD-type 5% Pd/C catalyst after the pretreatment as follows [12]. In a 50 ml glass reactor with a small septum port, Pd/C (20 mg in dry form) and 5 ml of 2.5% (v/v) wet dioxane were placed. Hydrogen of atmospheric pressure was charged to the flask, and the mixture was heated at 80 °C for 30 min under stirring (1200 rpm). The suspension was cooled to 23 °C, and a solution of cinchonidine (6 mg, 0.02 mmol) in the wet dioxane (1 ml) was added. After stirring for 30 min, a solution of a substrate (0.5 mmol, 100–150 mg) in the wet dioxane (4 ml) was added, followed by addition of benzylamine (BA, 55 μl, 0.5 mmol) [17]. The same hydrogenations were also performed in the absence of BA. Hydrogenations over other catalysts were performed under the same conditions except for the pretreatment.

The reactivity of each substrate was roughly evaluated by the initial hydrogenation rates (r, mol g^{-1} h^{-1}) calculated from the hydrogen uptake around 25% conversion. After the hydrogen uptake was complete, the reaction was continued for additional 2 h, and 2 M HCl (1 ml) was added to the solution. The mixture was filtered with a small amount of ethyl acetate to remove the catalyst. It was confirmed in every run that the product was completely dissolved in the solution prior to filtration, and that no detectable product remained in the filtered solid. The filtrate was extracted with ethyl acetate (5 ml) and then washed with water (5 ml × 2). The extract was analyzed by ^{1}H NMR (600 Hz) in $CDCl_3$ to confirm the completion of hydrogenation, and by HPLC with a chiral column (OJ-H, AD, or QD, Daicel, 25 cm × 4.6 mm) to determine the enantiomer ratio of the product. The enantiomer excess (ee) value was calculated from the ratio according to % ee = $100 \times |S - R|/(S + R)$. The analysis conditions and the retention time for each compound are given in the supplementary material.

The absolute stereochemistry was determined by the optical rotations for stereochemically known compounds; the products from PCA, B-4, E-1, E-2, E-4, F-1, F-2, and F-3 (Fig. 1). The other products are assumed to have the same stereochemistry among the series of the substrates, deduced from their optical rotations. The ee values determined by the different chiral columns or by the repeated runs were in agreement with one another (±0.5%).

Precise hydrogenation rates were determined by ^{1}H NMR as follows. In a 50 ml glass reactor with a small septum port, Pd/C (10 mg) in 2.5 ml of 2.5% (v/v) wet dioxane was heated at 80 °C for 30 min, and after cooling to 23 °C, a solution of cinchonidine (3 mg, 0.02 mmol) in the wet dioxane (0.5 ml) was added. After stirring for 30 min, a solution of a substrate or a mixture of two substrates (0.5 mmol in total) in the wet dioxane (1 ml) and then ethanolamine (0.5 mmol) were added. A portion of the reaction mixture was taken out 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. The ee value at the end of reaction was determined by the HPLC.

3. Results

Unsaturated carboxylic acids employed for the substrates of hydrogenation are classified in seven groups A–G, as illustrated in Fig. 1. Groups A–C include methyl-, methoxy-, and trifluoromethyl-(fluoro-) substituted analogues, respectively. Group D is higher analogues of DMPCA (B-6) and a naphthyl analogue (D-4). Group E is α-alkyl analogues, while Group F is β-alkyl analogues. Group G includes other types of substrates. The catalyst employed for the modification was the pretreated Pd/C, the best catalyst for the PCA hydrogenation [12]. The hydrogenation was carried out in a water-containing dioxane (2.5%) at 23 °C under the atmospheric pressure of hydrogen. Since added amine is known to give better product ee [17], benzylamine (BA) was added to the reaction mixture. Fig. 2 shows the effect of the amount of BA for five selected substrates, PCA, B-4, DMPCA, C-3, and E-4. The effects of added BA reach close to the maximum for all the substrates around 0.6 molar ratio (equivalent) to the substrate both in the product ee and in the hydrogenation rate, but additional BA induces some further change in ee, depending on the substrate. To compare the results with different substrates under the common reaction conditions, hydrogenation was performed at 1.0 equivalent of BA. Except for Group G, the substrate was consumed completely, and no side products were detected by ^{1}H NMR. The values shown under each substrate in Fig. 1 are the ee value of the hydrogenation product and the initial reaction rate (r, mol g^{-1} h^{-1}) in the presence of BA.

The hydrogenations were also performed in the absence of BA for all the substrates. Fig. 3 illustrates the ee values obtained in the reactions with BA vs. without BA for the substrates of Groups A–E (see the supplementary material for the effects on the rate). In the absence of BA, hydrogenations of some substrates were very slow, which can be a reason for the low ee values due to the loss in the catalyst performance during long reaction time. The slow reaction must be due to the low solubility of the substrate acid in

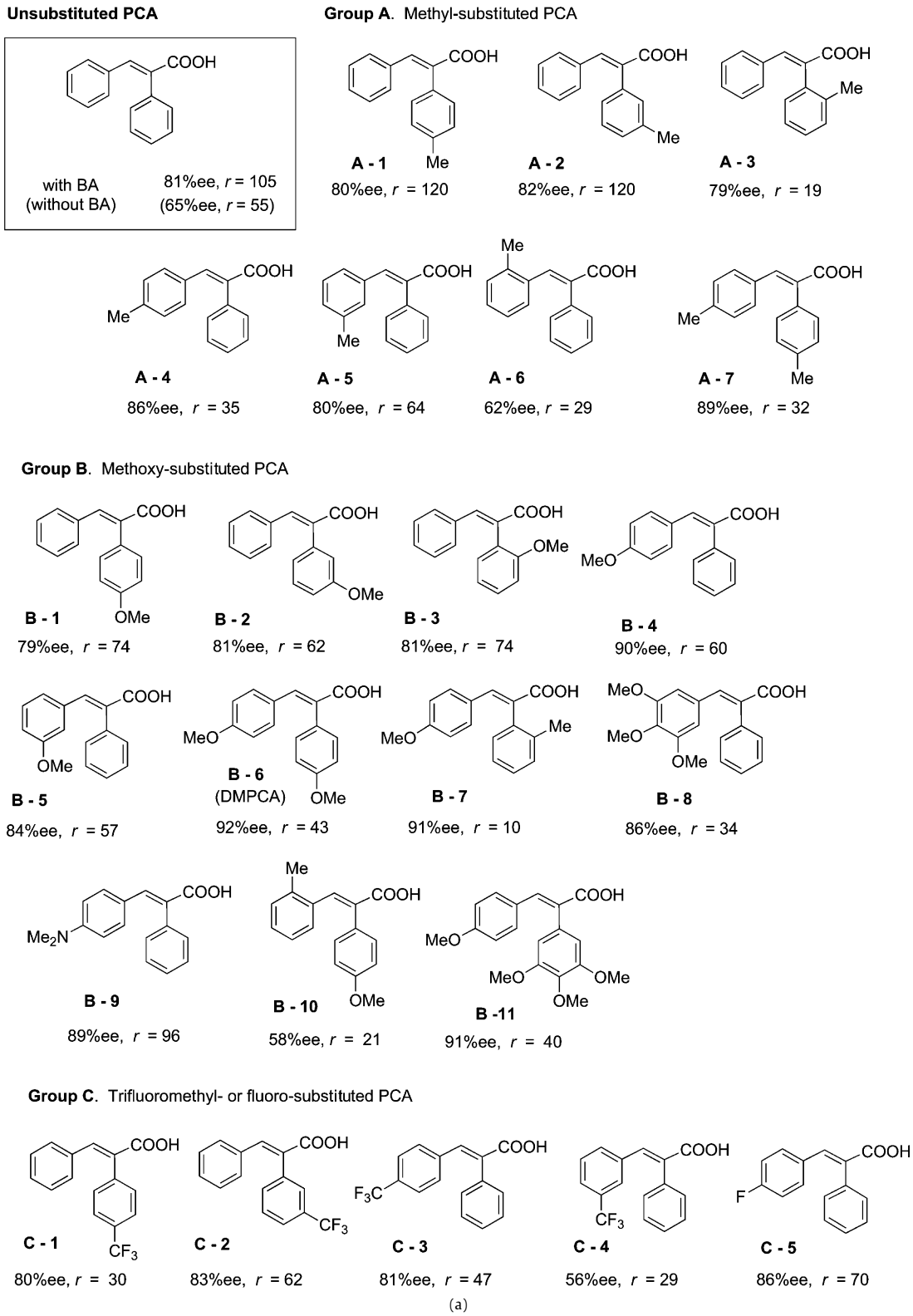
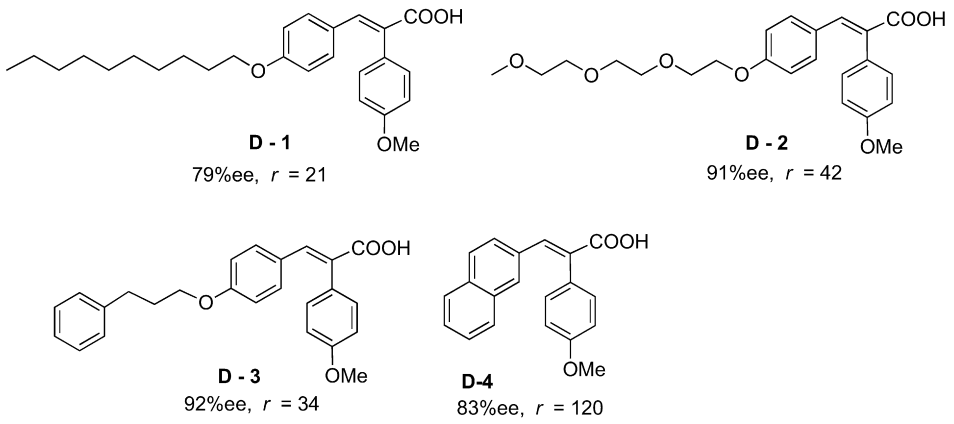


Fig. 1. Substrate structures in Groups A–G and the values of the product ee and the initial rate (mmol g^{-1} h^{-1}, determined by the H_2 uptake) of their hydrogenation in the presence of BA.

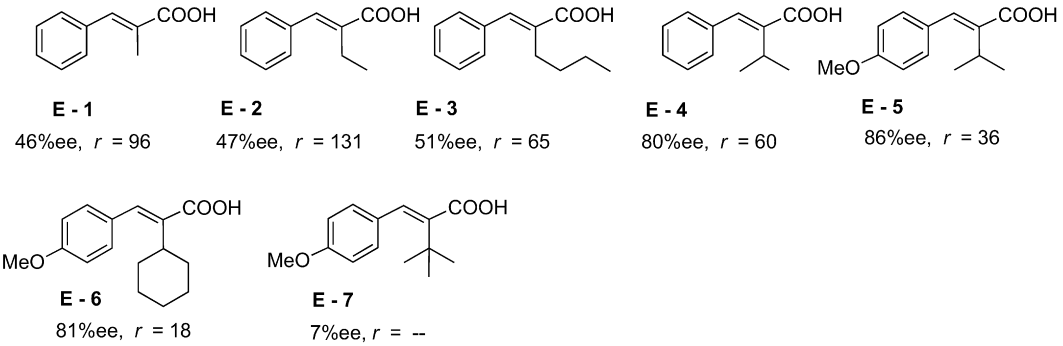
the reaction solvent. A representative substrate is D-4, which gives 41% ee at the slow initial rate of $r = 8$ in the absence of BA, while the ee is high 83% in the presence of BA ($r = 92$). Except for these poor substrates, the BA addition was found to increase the product ee by 1.2–1.5 times (15–25%) for most of the substrates.

Under the present conditions, the reference substrate PCA resulted in 81% ee in the presence of BA (65% ee in the absence of BA) as shown in Fig. 1. As seen in the results for Group A, effects of the methyl substitution are not large, but some improvement was observed in the product ee. The substitution on the α-phenyl

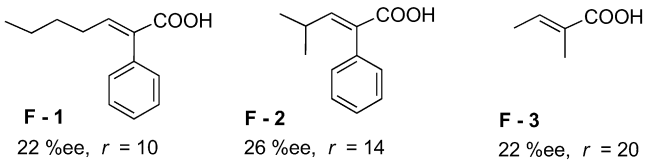
Group D. Larger analogues of PCA



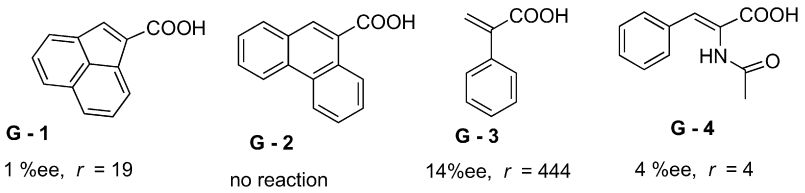
Group E. α-Alkyl analogues



Group F. β-Alkyl analogues



Group G. Other analogues of PCA

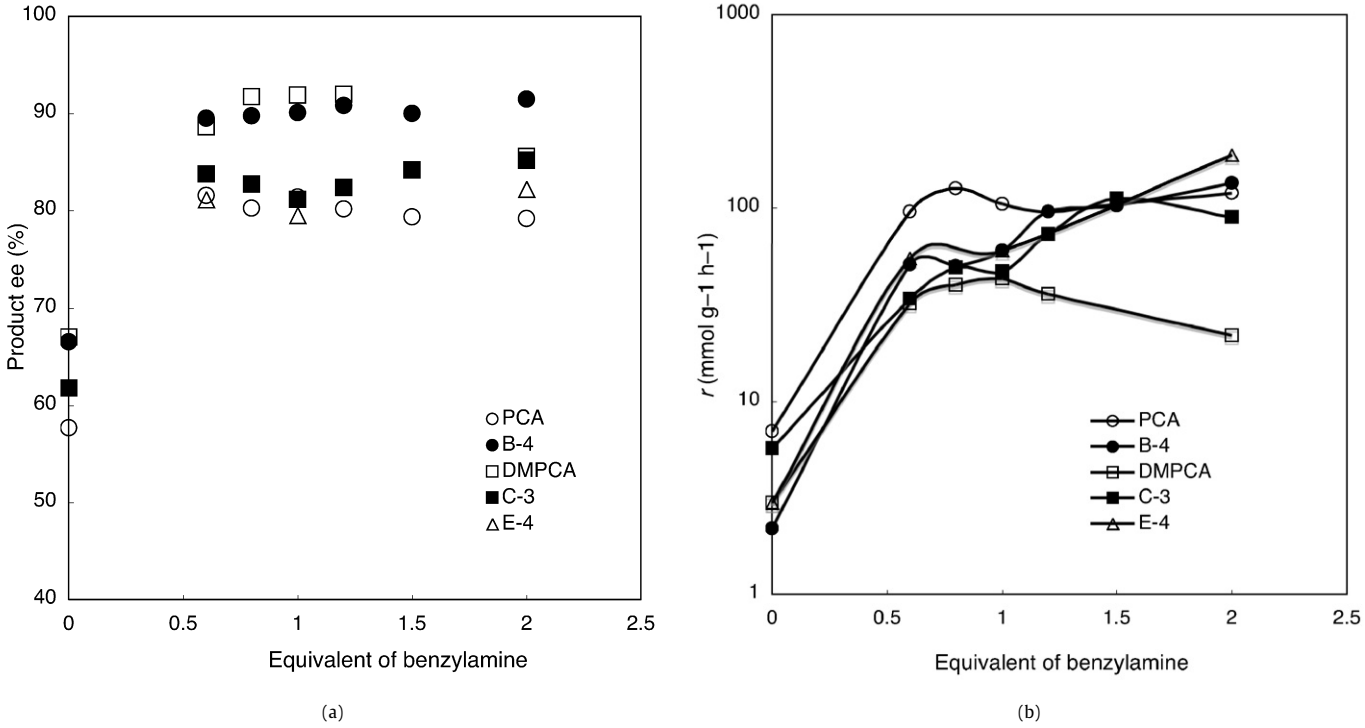


(b)

Fig. 1. (*continued*)

group (A-1 to A-3) does not affect much the stereoselectivity, but only decrease in the hydrogenation rate was observed by the *o*-substitution. In contrast, that on the β-phenyl group affects the product ee depending on the position; *p*-methyl gives higher ee of 86%, and *o*-methyl gives lower ee of 62%, while *m*-methyl does not affect the ee (A-4 to A-6). Among the methyl-substituted substrates studied so far, the p,p'-dimethyl-substituted substrate A-7 gives the best result of 89% ee.

Methoxy substitution on the α-phenyl affects little the enantioselectivity at any positions (B-1 to B-3), while the effects of the substitution on the β-phenyl are different depending on the positions; *p*-methoxy-substitution results in a notable improvement (B-4, 90% ee), while the substitution at the *m*-position does not lead to a higher enantioselectivity (B-5). These substituent effects are well consistent with the reported results with Pd/Al_2O_3, except for B-3 [13]. The *p*-methoxy-substitution is still effective with additional substitutions (B-6 to B-8 and B-12). Dimethylamino group is a stronger donor than methoxy, but the substitution at the β-*p*-position does not result in further improvement (B-9). DMPCA (B-6) is, so far, the simplest analogue to give the best ee of 92%. In



(a) (b)

Fig. 2. Effects of the amount of added BA for the hydrogenation of five representative substrates (a) on the product ee and (b) on the initial hydrogenation rate (mmol g^{-1} h^{-1}) determined by the H_2 uptake.

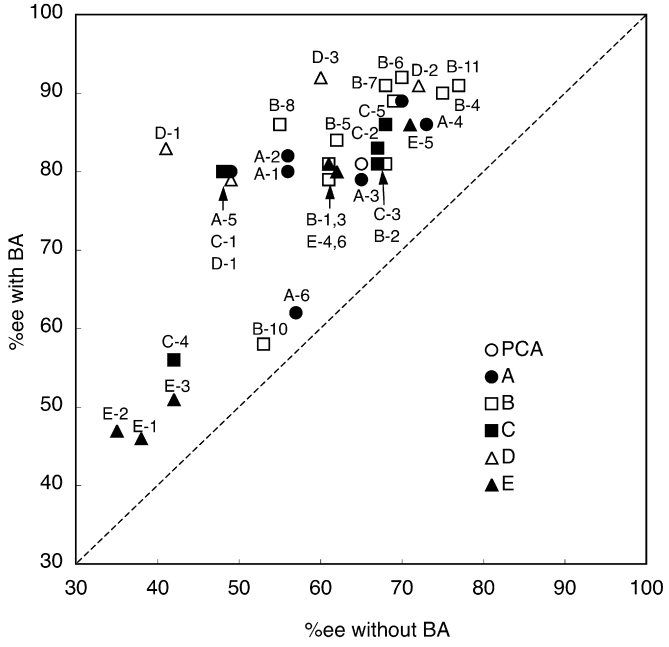


Fig. 3. Plots of the product ee for substrates of Groups A–E in the presence vs. absence of BA.

Group C, trifluoromethyl (CF_3) substitution at the α-phenyl does not show any obvious effects (C-1, C-2). On the β-phenyl, p-CF_3 (C-3) does not affect the product ee, but m-CF_3 shows negative effects to give 56% ee (C-4). Notable improvement to give 86% ee is observed with the β-p-fluoro group (C-5), which is electron-withdrawing but also electron-donating in a conjugative sense.

Comparing with DMPCA, some loss in the product ee is observed with a lipophilic analogue D-1 (79% ee), but the other two analogues give similar ee to DMPCA irrespective of the alkoxy structure (D-2: 91% ee and D-3: 92% ee). The lower ee with D-1 may not indicate an essential structural drawback but can be due to the low solubility under the present reaction conditions. Naphthyl group should be adsorbed more strongly than phenyl group on the palladium surface, but this nature does not bring about any notable effects on the product ee (D-4 vs. B-2).

The hydrogenation of commercially available E-1 under the present conditions gives 46% ee of the same stereochemistry as the product of PCA. The product ee is lower than that of PCA, but still higher than the reported values for E-1 using other palladium catalysts [4,18,19]. Chain elongation increasing the lipophilicity of the α-substituent as E-2 and E-3 results in a slight improvement in the product ee. In contrast, substitution by the sterically bulky isopropyl group yields the product in higher stereoselectivity to give 80% ee in combination with β-phenyl (E-4) and 86% ee with β-p-methoxyphenyl (E-5). Cyclohexyl group may be too bulky and the reaction of E-6 gives lower 81% ee at a slower reaction rate. Hydrogenation of E-7 carrying a tBu group was so slow that it took five days to complete the reaction.

In the reverse, the β-aryl group is indispensable to perform sufficient stereocontrol under the present conditions. As shown in Group F, both normal (F-1) and branched (F-2) β-alkyl substrates react slowly and do not induce notable stereocontrol, as does a conventional aliphatic example of tiglic acid (F-3). It should be noted that the stereochemistries of the products from F-1 and F-2 determined by the optical rotations are reverse of those of PCA and its analogues of Groups A–E, but are the same as those of aliphatic substrates represented by tiglic acid [18,20].

When both α- and β-aryl groups in the substrate are fixed to be coplanar with the olefinic bond as in G-1 and G-2, enantioselectivity is lost (G-1) or the hydrogenation itself is interrupted (G-2). Lack of the β-substituent results in poorer enantioselectivity (G-3). Application of the present hydrogenation system to N-acetyldehydrophenylalanine (G-4) was unsuccessful.

To disclose the role of the electron-donating group at the p-position of the β-phenyl ring, properties of DMPCA during the hydrogenation are compared with those of unsubstituted PCA. As

Table 1
Structure dependency on the product ee with various catalysts.[a]

Catalyst	% D_M[b]	D (nm)[c]	Additive	PCA			DMPCA		
				% ee	r_m and r_u	(r_m/r_u)[d]	% ee	r_m and r_u	(r_m/r_u)[d]
5% Pd/Al_2O_3	19	5.8	BA	39	9/74	(0.12)	58	4/21	(0.18)
			–	35	15/120	(0.12)	55	5/74	(0.07)
5% Pd/C (STD)	76	1.5	BA	46	40/96	(0.42)	65	24/5	(0.47)
			–	43	12/250	(0.05)	56	8/150	(0.05)
5% Pd/C (AER)	67	1.7	BA	59	78/110	(0.74)	72	32/62	(0.47)
			–	52	39/360	(0.11)	66	11/240	(0.05)
5% Pd/TiO_2	52	2.1	BA	71	33/58	(0.57)	82	12/–	
			–	59	7/110	(0.06)	70	11/–	
5% Pd/C (STD)	76	1.5	BA	81	105/240	(0.44)	92	43/60	(0.72)
(pretreated)			–	65	55/340	(0.16)	69	12/120	(0.10)

[a] The hydrogenation was performed in a 2.5% water-containing dioxane on a 0.5 mmol scale with 23 mg of Pd catalyst and 6 mg (20 μmol) of cinchonidine at 23 °C in the presence or absence of benzylamine (BA, 1 equiv.).
[b] Degree of palladium dispersion calculated from the metal surface.
[c] Mean particle size of palladium estimated form the metal dispersion.
[d] r_m and r_u (mmol g^{-1} h^{-1}) are the initial reaction rates determined by the H_2 uptake with CD-Pd/C and with unmodified Pd/C, respectively.

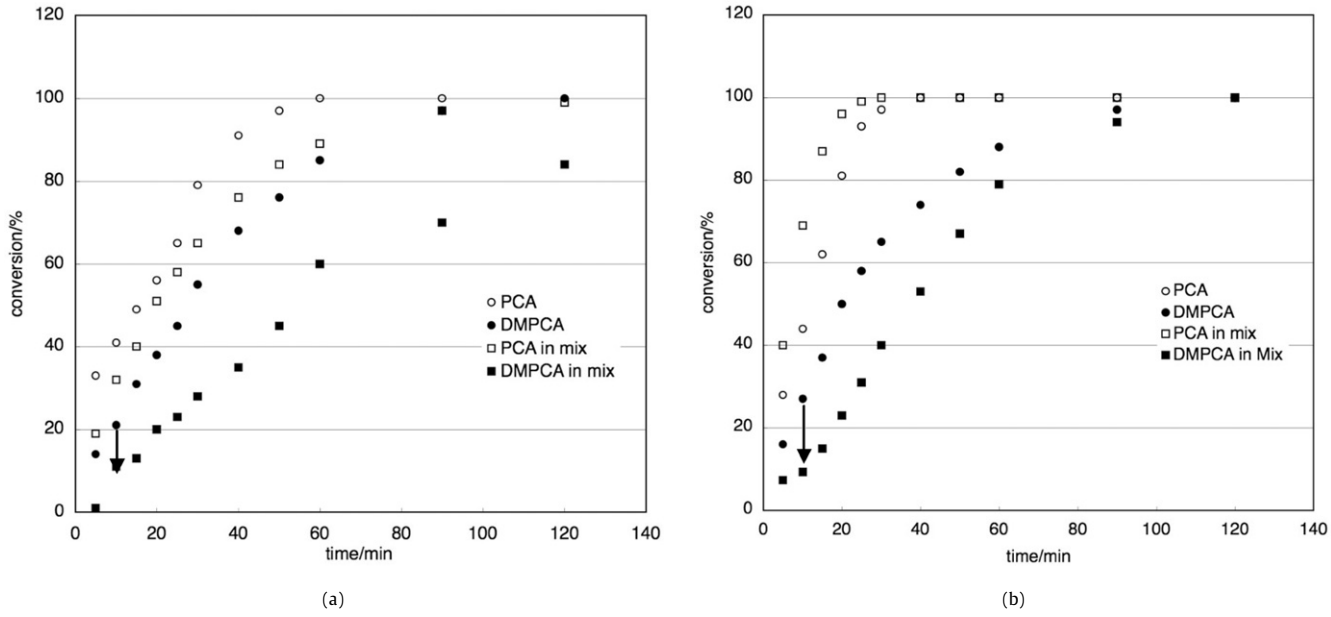


Fig. 4. Reaction conversion of PCA and DMPCA in the presence of ethanolamine over (a) CD-modified catalyst and (b) unmodified catalyst. The hydrogenation was carried out with an individual substrate (shown by circles) and with a 1-to-1 mixture of the substrates (shown by squares).

shown in Table 1, DMPCA always gives better product ee than PCA using palladium catalysts supported on different supports [21]. Improvement of the enantioselectivity by added BA was observed for the both substrates, and with different catalysts. Effects of the CD-modification on the hydrogenation rate are always negative, irrespective of the substrate, as seen in r_m/r_u values (<1), which are obviously larger in the presence of BA. The r_m/r_u value is also larger for good palladium catalysts, but detailed comparison of the r_m/r_u values needs more accurate kinetic study. Comparing the two substrates, DMPCA tends to have larger r_m/r_u values than PCA in the presence of BA, while the differences are smaller in the absence of BA. Under the best conditions (line 9 in Table 1), the r_m/r_u values are 0.44 for PCA and 0.72 for DMPCA.

Precise kinetic studies with PCA and DMPCA were performed by monitoring the reaction by ^1H NMR. Ethanolamine ($pK_{BH+} = 9.50$ in aqueous solution) was employed in place of BA ($pK_{BH+} = 9.34$) to avoid precipitation of the product salt during the reaction. The substrate/catalyst ratio was doubled from the original procedure. Fig. 4a illustrates conversion profiles of hydrogenation of PCA and DMPCA over the CD-modified catalyst in individual reactions as well as in the reactions with a 1-to-1 mixture of the two substrates (one half in concentration of each substrate). Fig. 4b also illustrates similar profiles with the CD-unmodified catalyst. By mixing the two substrates, the hydrogenation of DMPCA is suppressed by the co-existing PCA, and becomes faster as the consumption of PCA proceeds. This suppression phenomenon is larger with the unmodified catalyst (Fig. 4b) than that with the CD-modified catalyst (Fig. 4a). The extent of suppression is seen in Table 2, where the reaction rates obtained from the data of initial regions (10–40% conversion) are given. Since PCA is consumed in a short time with a 1:1 mixture, the same experiment was also performed with a mixture of PCA and DMPCA in 5:1 ratio to emphasize the suppression effect by PCA (see the supplementary material for the conversion profiles). As a matter of fact, the tendency observed with the 1:1 mixture becomes obvious, and the hydrogenation of DMPCA with the CD-modified catalyst becomes even faster than that with the unmodified catalyst in the presence of a sufficient amount of PCA (Table 2, entry 3, $r_m/r_u > 1$). The ee values at the end of reaction are not affected by the change in the reaction conditions or by mixing the two substrates. The r_m/r_u values determined from the hydrogen consumption rate given in Table 2 are 0.56 for PCA and 0.81 for DMPCA.

Table 2
The hydrogenation rate (mmol g^{-1} h^{-1}, determined by ^1H NMR) of PCA and DMPCA in the presence of ethanolamine.

Entry		PCA			DMPCA		
		CD-modified	Unmodified	r_m/r_u	CD-modified	Unmodified	r_m/r_u
1	Separate experiment	21 (82%)[a]	37	0.56	17 (92%)[a]	22	0.81
2	1:1 mixture	17 (81%)[a]	35	0.48	4.8 (92%)[a]	6.8	0.7
3	5:1 mixture	12	23	0.53	2.3	1.2	1.9

[a] The product ee values determined by HPLC after the complete conversion.

4. Discussion

The enantioselectivities observed for the hydrogenation of 42 different α,β-unsaturated carboxylic acids are summarized as follows. The α-phenyl group is not electronically important but is necessary only as a steric fence; the α-phenyl group must be twisted from the olefinic plane of PCA. This non-planarity should work to differentiate the enantioface of the olefin. This presumption is supported by the high enantioselectivity with the substrates having a properly bulky α-alkyl substituent (E-4 and 5) and the low enantioselectivity with the coplanar α-aryl substrate (G-1).

In contrast, the β-aromatic group is indispensable for the stereoselectivity and its electronic effect is large. The β-aryl group can directly interact with the palladium catalyst surface during the hydrogenation of the olefinic part, and the interaction can be a reason for the big difference in selectivities between the β-aryl and β-alkyl substrates. However, the effect of different β-aryl groups cannot be simply attributable to change in the direct interaction, because the *m*-substituted substrate does not show the same effect as the *p*-substituted one. This presumption is confirmed by the results with Group D, where the β-aryl substrates expected to have different adsorption ability do not show different stereoselectivity.

A key to obtain the high stereoselectivity is a conjugative electron-donating substituent on the β-phenyl group of PCA, represented by DMPCA. The conjugative electron-donating group at the *p*-position causes stronger through-conjugation with the carboxylic acid via the aromatic and olefinic π bonds, which makes flatter conformation of the whole β-arene–olefin–carboxylic acid conjugation system. In the reverse, β-*o*-methyl substituent interferes with the flat conformation for steric reasons, and thus, the low ee values are obtained with A-6 and B-10. The conjugation with an electron-donating group also causes reduction of acidity of the substrate. The lower acidity makes the carboxylate anion more basic, and then ionic interaction between the *N*-protonated CD of the chiral modifier and the carboxylate anion of the substrate becomes stronger. The stronger CD–substrate interaction is experimentally supported by the results of the competitive hydrogenation given in Table 2. That is, adsorption of DMPCA on the catalyst is weaker than PCA, but the difference between the substrates is smaller when the catalyst is modified by CD. Thus, CD–DMPCA interaction must be stronger than CD–PCA interaction.

Fig. 5 illustrates four geometries of the carboxylate adsorbed by the aid of the chiral CD on catalyst surface by Newman projection through CO–C_α bond (views from CD), where the geometry 5a leads to the major enantiomer, while 5b–5d give the minor enantiomer. Selection of 5a can be achieved when C_α cannot get close to the Pd surface, but C_β can. 5b has just opposite tendency to 5a. The minor enantiomer formation cannot effectively be suppressed if the olefin and the carboxylate are not coplanar as shown in Fig. 5c, or the primary chiral recognition at the carboxylate is looser as shown in Fig. 5d. This model is compatible with the structural requirements for the substrate experimentally observed to obtain the high enantioselectivity; coplanar arene group at the β-position, bulkiness at the α-position, the flat conformation of the whole conjugation system, and the stronger conjugate base (carboxylate).

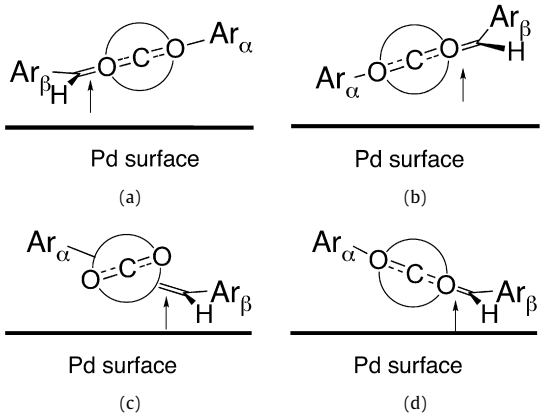


Fig. 5. Newman projections of the substrate looking from the chiral amine adsorbed on the Pd surface to give (a) a major enantiomer and (b–d) a minor enantiomer, the latter of which is caused by (b) misidentification of α-aryl as the olefin part, (c) loss of the conformational planarity, or (d) lack of the stereo recognition of the carboxyl group.

In general, chiral modification of a heterogeneous catalyst is not uniform, but some unmodified sites remain active to produce racemic product. Thus, the ee value is not only governed by the stereodifferentiating ability of the chiral modifier. A simplified model to express the product ee with consideration of the catalyst uniformity is given as % ee = factor-i $\times$ $E/(E+N)$, where E is contribution from enantioselective site (E-site) by the aid of the chiral modifier and N is that from non-enantioselective site (N-site) performed on remaining unmodified surface [22]. The contribution from the E-site in the total reaction is expressed as $E/(E+N)$. The other factor is factor-i, which is the intrinsic stereocontrollability of the chiral modifier on the catalyst and is equal to an ee value produced specifically at the E-site. Here, the stronger modifier-substrate interaction can induce both the higher $E/(E+N)$ and the larger factor-i.

Among the reactions using the same catalyst, relative magnitudes of the E-site contribution, $E/(E+N)$, can be evaluated by the kinetic parameters, r_m and r_u [23]. If the hydrogenation rate over the unmodified catalyst (r_u) represents the catalytic activity of the unmodified site (N-site) on the CD-modified catalyst, changes in a ratio of r_u/r_m parallel changes in the $N/(E+N)$ value. The most reliable r_m and r_u values to discuss the substrate structure effect are those in entry 1 of Table 2. The r_u/r_m values of 1.79 for PCA and 1.23 for DMPCA indicate that contribution of the N-site catalysis in DMPCA is smaller than PCA by 0.7 times. Since the N-site catalysis in the reaction with DMPCA is in a range of 0–8% (= 100% − % ee), the N-site catalysis with PCA is calculated to be in a range of 0–11%, which means the factor-i of PCA is less than 92% (<0.82/0.89) [23]. As a result, the ee improvement by the β-*p*-donor substitution on PCA must induce the larger factor-i by the stronger substrate–modifier interaction.

5. Conclusion

We have studied the hydrogenation of a range of analogous substrates originating from PCA, and found that α,β-unsaturated

acids having a properly bulky α-substituent and an electron-donating β-aryl group are suitable substrates for the enantioselective hydrogenation over the CD-modified palladium catalyst. This substrate design is effective irrespective of the type of the palladium catalyst and the reaction conditions. The electron-donating β-aryl group with the p-alkoxy substitution realized improvement of the product ee up to 92%. Stronger interaction between the chiral modifier CD and such a substrate was experimentally supported.

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Supplementary material

The online version of this article contains additional supplementary material.

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