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Highly enantioselective hydrogenation of α-Alkyl-β-arylpropenoic acids over cinchonidine-modified palladium catalyst

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Enantioselective hydrogenation of (*E*)- α-alkyl-β-arylpropenoic acids was studied over the cinchonidine-modified Pd/C under the conditions optimized for (*E*)-α,β-diarylpropenoic acids. Enantiomeric excess (ee) of the product was increased by adjusting the α-alkyl group as a properly bulky isopropyl. The ee was as high as 80% when the β-group is phenyl, and reached 86% with *p*-anisyl group. Stereoselection of those substrates is similar to that of (*E*)-α,β-diarylpropenoic acids.

KEY WORDS: asymmetric synthesis; enantioselective hydrogenation; palladium on carbon; olefin.

1. Introduction

Cinchonidine-modified palladium is a heterogeneous catalyst for enantioselective hydrogenation of prochiral olefins [1]. Since Peretz employed α,β-unsaturated acids as substrates in 1985 [2], this hydrogenation system has been mostly developed with those substrates, though some pyrone derivatives were recently found to be also good substrates [3]. Enantioselectivity of the hydrogenation is strongly affected by source of the palladium catalyst, its pretreatment conditions, solvent and additive for the reaction, hydrogenation pressure, the optimization of which to achieve the current level of the stereocontrol necessitated trial and error. According to the optimized reaction conditions, the substrates are divided into two groups; one prefers a non-polar solvent under pressured conditions and gives enantiomer I as a major product, whilst the other needs to use a polar solvent under atmospheric hydrogen and gives enantiomer II (Scheme 1). (*E*)-α,β-Dialkylpropenoic acids, represented by tiglic acid (**1**, $R_\alpha = R_\beta = Me$), belong to the first group, and their reactions yield saturated acids under moderate stereocontrol of 47–66% enantiomeric excess (ee) [4–7]. The second group is defined as (*E*)-α,β-diarylpropenoic acids, but practically phenylcinnamic acid (**2**, $R_\alpha = R_\beta = Ph$) was the only example except for our recent study [8]. The best ee with 2 has long been 72% by using a specially prepared Pd/TiO_2 [9], but was very recently renewed to 74% with a similar catalyst [10], and to 81% using the hydrogen-treated Pd/C [11].

The substrates studied in this report are (*E*)-α -alkyl-β -arylpropenoic acids; a hybrid of the two substrate classes. Before the present study, methylcinnamic acid (**3**, $R_\alpha = Me$, $R_\beta = Ph$) has been the only substrate subjected to the hydrogenation, which resulted in 14% [2] or 23% ee [5] of enantiomer II under polar conditions. The very poor selectivity compared with **2** seems to indicate that the structure of **3** is not suitable for the stereocontrolled hydrogenation. From a different viewpoint, the ee with **3** is the middle of 66% ee of enantiomer I with **1** and 81% ee of enantiomer II with **2**. Clear classification of (*E*)-α-alkyl-β-arylpropenoic acids into one of the two substrate groups [6] or another unknown group is of importance to disclose the stereocontrol mechanism of the cinchonidine-modified palladium hydrogenation as well as to extend a range of obtainable optically active products. To address both the issues, achievement of the effective control to give the high ee of the product with those substrates will provide a key.

2. Method

Substrates **1** and **3** were used as received. Substrates **4** and **5** shown in figure 1 were prepared by the cross aldol condensation [12] followed by oxidation according to the reference [13]. The other substrates **6**–**9** were prepared by the reaction of an aliphatic ester and an aromatic aldehyde with LDA [14], acetylation (methanesulfonation for **6**), and DBU treatment at 110 °C followed by hydrolysis [15]. All new compounds including hydrogenation products were identified by NMR, IR, and high-resolution mass spectra. The hydrogenation was carried out in two different ways. Reaction in the absence of benzylamine: A suspension of 5%Pd/C (20 mg, N. E. Chemcat, STD type) in a wet 1,4-dioxane (2.5% water, 5 mL) containing cinchonidine (6 mg, 0.02 mmol) was heated in a flat-bottom flask at 80 °C under atmospheric hydrogen and sufficient

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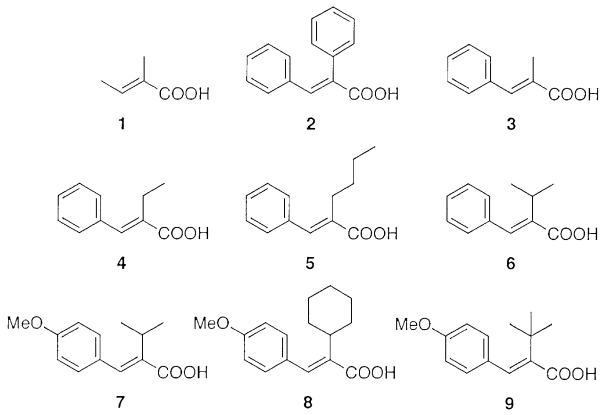


Figure 1. Structure of the substrates.

stirring (1200 rpm) for 30 min. After cooling to 23 °C, a substrate (0.5 mmol, 81−110 mg) in the solvent (4 mL) was injected to the flask in keeping the same hydrogen atmosphere. Reaction in the presence of benzylamine: 5%Pd/C (20 mg) was heated in a wet 1,4-dioxane (2.5% water, 5 mL) at 80 °C under atmospheric hydrogen for 30 min under sufficient stirring. Cinchonidine (6 mg) in the solvent (1 mL) was added to the catalyst suspension at 23 °C. After 30 min, a substrate (0.5 mmol, 81−110 mg) in the solvent (4 mL) was injected followed by benzylamine (0.5 mmol unless noted otherwise) under the same hydrogen atmosphere. The hydrogenation rate was determined from the hydrogen uptake at 20% conversion (r_0/mmol g^{-1} h^{-1}). The hydrogenations were generally performed in 8 h. After addition of 2 M HCl (0.5 mL), the mixture was filtered, extracted with ethyl acetate, and dried over sodium sulfate. The chemical yields were deduced from the ^{1}H NMR at 600 MHz. The ee value of the product was determined by a chiral GLC (CP-Chirasil DEC CB, 100 °C, as methyl esters) for **3** and **4**, or by a chiral HPLC (Chiralpak AD, Hex/IPA/TFA = 95/5/0.1) for the others. Stereochemistries of the products were assigned by the optical rotations.

3. Results

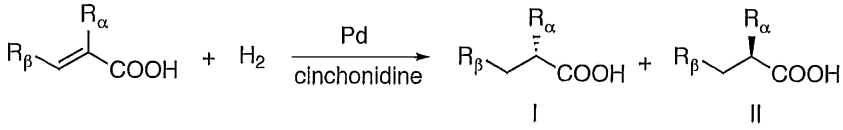
The hydrogenation proceeded smoothly until 100% conversion except for the reaction of **9**, and after the workup, chemically pure saturated acids were obtained in quantitative yields. All the β-aromatic products had levorotatory optical rotation. That is, $[\alpha]_D^{20} = -11.9$ (c 0.86, $CHCl_3$, 46% ee) from **3**, $[\alpha]_D^{20} = -18.1$ (c 1.95, CH_2Cl_2, 47% ee) from **4**, $[\alpha]_D^{20} = -9.8$ (c 1.95, CH_2Cl_2, 47% ee) from **5**, $[\alpha]_D^{20} = -42.3$ (c 1.32, $CHCl_3$, 76% ee) from **6**, $[\alpha]_D^{20} = -54.8$ (c 1.75, CH_2Cl_2, 86% ee) from **7**, $[\alpha]_D^{20} = -31.7$ (c 1.84, CH_2Cl_2, 81% ee) from **8**. Those from **3, 4** and **5** are stereochemically known compounds [16, 17], and the major enantiomers were assigned to enantiomer II. The other products were also estimated to be enantiomer II from the similarity in the substrate structure and the optical rotation. In the case of **1**, the product was dextrorotatory; $[\alpha]_D^{20} = +7.2$ (C 2.27, MeOH, 23% ee), and is enantiomer I in excess [18]. Enantiomeric excesses of the product and the initial hydrogenation rates are summarized in table 1. The hydrogenation of **3** over the hydrogen-treated Pd/C under the standard polar conditions (without benzylamine) results in 38% ee, which already exceeds the reported values with other Pd catalysts (Pd/Al_2O_3 or Pd/TiO_2). The initial hydrogenation rate of **3** (r_0 = 87) is larger than that of **2** (r_0 = 55) [11] under the same conditions. The activity ratio of **3/2** (87/55 = 1.6) is almost the same as that obtained with the cinchonidine-unmodified Pd/C; **3/2** = 1.7 (r_0 = 560 and 330, respectively). Substrates **4** and **5** carrying ethyl and butyl group at the α-position show selectivity similar to **3** to result in 35% and 42% ee, respectively. On the other hand, isopropyl-substituted **6** shows better selectivity to give 62% ee. Decrease in the hydrogenation rate due to the bulkiness at the α-position is not so large (**6/3** = 0.46).

Methoxy substitution at the *para*-position of the phenyl groups in **2** is known to bring about a higher product ee [8]. By applying the substrate design to the α-isopropyl substrate, the product ee is also further improved to 71% ee when the phenyl group in **6** is

Table 1
Hydrogenation in the absence and presence of benzylamine (BA)

	Substrate		Without BA		With BA	
	$\mathbf{R}_\alpha$ =	$\mathbf{R}_\beta$ =	ee[a, b](%)	Initial rate(mmol $g^{-1}h^{-1}$)	ee[a, b](%)	Initial rate(mmol $g^{-1}h^{-1}$)
3	Me	Ph	38	87	46	96
4	Et	Ph	35	67	47	131
5	Bu	Ph	42	65	51	65
6	i-Pr	Ph	62	40	80	60
7	i-Pr	*p*-MeOPh	71	34	86	36
8	c-Hex	*p*-MeOPh	61	20	81	18
9	t-Bu	*p*-MeOPh	–	–[b]	0	4[c]
I[d]	Me	Me	23 (17)	51 (79)	21 (9)	70 (64)

[a]Enantiomer II was produced except for the reaction of **1**, but indication of the product stereochemistry is different. That is, the products from **3**–**5** have *R*-stereochemistry, while those from **6**–**8** have *S*-stereochemistry.
[b]No reaction. [c]*20*% conversion after 5 days. [d]The values in parentheses are obtained by the reaction in toluene.



Enantiomer I: Major isomer in a non-polar media when R_a, R_b = alkyl

Enantiomer II: Major isomer in a polar media when R_a, R_b = aryl

Scheme 1. Hydrogenation of α, β-substituted propenoic acid over cinchonidine-modified Pd catalyst.

replaced with *p*-anisyl (substrate **7**). A more bulky cyclohexyl group at the α-position **(8)** decreases the product ee to 61% with accompanying large loss in the reaction rate. In the case of α-*tert*-butyl substrate **9**, the hydrogenation does not proceed at all. The hydrogenation of **1** is not sufficiently stereocontrolled with the present catalyst under atmospheric hydrogen in the polar or non-polar solvent, but gives enantiomer I in excess.

Addition of an achiral amine such as benzylamrne (BA) is known to improve the product ee in the reaction with **2** [19]. For the α-alkyl-β-aryl substrates, the BA addition (1 equivalent) to the reaction mixture generally and notably improves the product ee with increase in the hydrogenation rate. α-Methyl substrate **3** can be converted to the product in 46% ee, and the analogues bearing a longer α-alkyl group (**4** and **5**) give somewhat higher ee. The steric effects of the α-substituent and the electronic effect of the β-substituent are still effective and increase the ee to 80% with **6** and up to 86% with **7**. The hydrogenation of the more bulky substrate **5** is also improved by the addition of BA, and even **9** shows some reactivity. However, **1** is an exception and the hydrogenation is not affected positively. The amount of BA is known to affect the stereoselectivity in the hydrogenation of **2** [19], but in the case **6**, the ee was not varied much (80−82% ee) in the range of 0.6−2.0 equivalents of BA.

4. Discussion

The currently optimized catalyst and conditions for the hydrogenation of **2** was found to be effective for the hydrogenation of **3** to give the ee of up to 46%. This suggests the similarity of the stereocontrol mechanism between the substrates, though the degree of the stereocontrol with **3** is still lower than that with **2** (81%) [8]. The structural difference between alkyl and aryl groups at the α-position is not an essential factor, but the steric factor seems to be governing. This explanation is very reasonable if the comparable stereoselectivity with α-isopropyl **6** (80%) and with **2** is considered. The high product ee of 86% observed for **7** is even better than that with **2**. The results with bulkier **8** and **9** at the α-position clearly indicate that the hydrogenation rate is sensitive to the bulkiness, and there must be a proper size of the α-substituent to achieve the high stereoselectivity. Since the α-substituent is close to the catalyst surface during the hydrogenation reaction, hydrophobicity of the cyclohexyl group in **8** is also a factor to be considered. Substrate **1** of an α,β-dialkylpropenoic acid is distinctively different from the α-alkyl-β-aryl substrates not only in the stereoselectivity but also in the dependency on the additive. Thus, (*E*)-α-alkyl-β-arylpropenoic acids are confidently classified in a substrate group of (*E*)-α,β-diarylpropenoic acids. Isomerization of olefin in the substrate is observed in the hydrogenation of **1** to reduce the stereoselectivity [20], but it is not a fatal problem for the present substrates probably due to suppression of the isomerization by the conjugation with the β-aromatic group.

5. Conclusion

(*E*)-α-Alkyl-β-arylpropenoic acids are classified in the substrate group (*E*)-α,β-diarylpropenoic acids. In other words, the substrate group of (*E*)-α,β-diarylpropenoic acids does not necessitate aromatic substituent at the α-position to yield the high product ee. This finding is consistent with our preliminary expectation for the transition state of the hydrogenation that the β-phenyl group of **2** is coplanar and conjugated to the double bond, while the α-phenyl is not [8]. The classification of the substrates dealing with their structures as aliphatic acid or aromatic acid is now revised to aliphatic or β-aromatic acids. Detailed study of the substrate structure−stereoselectivity relationship is now in progress.

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