Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 1487–1494

TETRAHEDRON: *ASYMMETRY*

DPAMPP in catalytic asymmetric reactions: enantioselective synthesis of L-homophenylalanine

Yinong Xie, Rongliang Lou, Zhi Li, Aiqiao Mi and Yaozhong Jiang*

Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu, 610041, PR China

Received 5 January 2000; accepted 6 March 2000

Abstract

L-Homophenylalanine **1**, a key intermediate of most commercially important ACE inhibitors, was prepared via catalytic asymmetric hydrogenation of (*Z*)-2-acetamido-4-phenylcrotonate **3a** with a cationic rhodium complex of (1*R*,2*S*)-DPAMPP, followed by acid-hydrolysis of the protecting groups in good yield with >99.9% enantioselectivity.

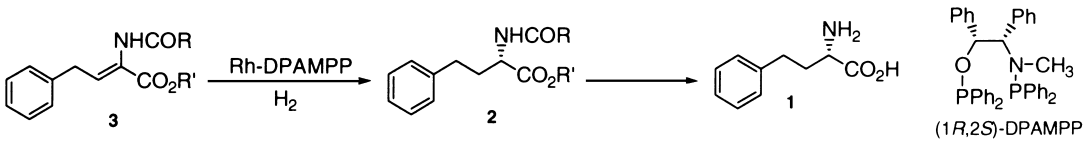
1. Introduction

Angiotensin-converting enzyme (ACE) inhibition is an effective therapy for the control of hypertension and congestive heart failure.[1] Many ACE inhibitors such as Benazepril, Enalapril and Lisinopril, that are now widely used in clinics, possess L-homophenylalanine **1** as a component. Although various synthetic methods to L-homophenylalanine **1** by traditional resolutions,[2] biocatalytic methods,[3] or stoichiometric use of chiral auxiliaries[4] have been reported, an efficient catalytic asymmetric hydrogenation procedure, a potentially more competitive route, has not been developed.

In principle, asymmetric catalytic hydrogenation of dehydroamino acids using transition metal complexes containing chiral bidentate ligands is a practical way to generate enantiomerically pure α-amino acids. In contrast to high enantioselectivities and reactivities observed with phosphine or phosphinite ligands, the utility of chiral aminophosphine–phosphinite ligands (AMPPs) has met with limited success.[5] Recently, we reported the preparation of a new aminophosphine phosphinite, DPAMPP, and its application in cationic Rh-catalyzed hydrogenation of (*Z*)-acetamidocinnamic acid and its derivatives.[6] In view of both the easy access to DPAMPP based on amino alcohol and the excellent chiral recognition ability of the Rh(I)-DPAMPP complex, and in the hope of exploring a wider utility of such a complex, we now extend our studies to develop a practical asymmetric hydrogenation method for the enantioselective synthesis of L-homophenylalanine **1** (Scheme 1).

* Corresponding author. E-mail: ulas@cioc.ac.cn

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00092-6

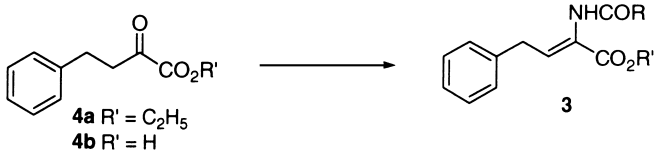


Scheme 1.

2. Results and discussion

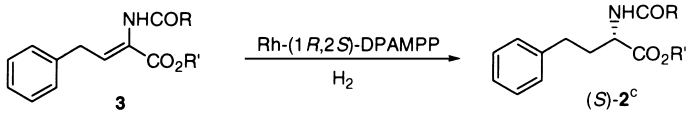
2.1. Selection of hydrogenation substrate

It is well known that substrate chelation is a critical element for the attainment of high enantioselectivities in α,β-dehydroamino acid hydrogenation.[7] In addition to the olefin to be reduced, the *N*-carbonyl oxygen acts as an indispensable secondary donor group to coordinate to the metal center. The variation of the *N*-protecting group (R of **3**) could potentially lead to higher enantioselectivities, therefore a series of (*Z*)-2-aminocrotonates **3a–g**, bearing a wide range of *N*-protecting groups, has been synthesized[8] (Scheme 2) and investigated in the cationic Rh(I)-DPAMPP-catalyzed hydrogenation. The results are summarized in Table 1.



Scheme 2.

Table 1
Influence of the *N*-protecting group in hydrogenation of (*Z*)-2-aminocrotonates **3**[a]



Entry	Substrate	R	R'	ee (%)[b]	Conv. (%)
1	(*Z*)-**3a**	CH_3	C_2H_5	95.7	100
2	(*Z*)-**3b**	C_6H_5	C_2H_5	94.6	100
3	(*Z*)-**3c**	OCH_3	C_2H_5	85.0	19
4[e]	(*Z*)-**3d**	OCH_3	H	2.9	81[d]
5	(*Z*)-**3e**	$OCH_2C_6H_5$	C_2H_5	58.4	20
6	(*Z*)-**3f**	$OCH_2CH(CH_3)_2$	C_2H_5	93.1	94
7[e]	(*Z*)-**3g**	$OC(CH_3)_3$	C_2H_5	78.1	43

[a] The reactions were carried out in MeOH under 50 atm H_2 at rt for 1 h with a ratio of S/C of 100. The catalyst was made in situ by stirring a solution of Rh precursor and (1*R*,2*S*)-DPAMPP in THF. [b] The enantiomeric excesses were determined by GC on a CP Chirasil-L-Val column.[c] The absolute configuration *S* was assigned by converting to homophenylalanine **1** and comparing the sign of the specific rotation shown with reported data[9]. [d] Determined by GC as methyl ester derivative. [e] Reaction time was 4 h.

As expected, the enantioselectivities and reactivities in the hydrogenation of substrates **3a–g** turned out to be dependent on the *N*-protecting group. Clearly, *N*-acyl groups performed uniformly superior to *N*-alkoxycarbonyl groups. For example, replacement of an *N*-acetyl group with an *N*-methoxycarbonyl group led to a dramatic decrease in both ee value and conversion rate (ee: from 95.7 to 85.0%; conversion rate: from 100 to 19%; entry 1 versus entry 3). Between the two kinds of *N*-acyl 2-aminocrotonates **3a** and **3b**, **3a** was chosen as a typical hydrogenation substrate in view of its easier access and easier deprotection in the next hydrolysis step. All further reaction optimization studies were conducted with the substrate **3a**.

2.2. Optimization studies

2.2.1. Solvent effects

Substantial solvent effects have been found in the hydrogenation of substrate **3a** (Table 2). Our preliminary hydrogenation was conducted in methanol, where the Rh(I)-(1*R*,2*S*)-DPAMPP afforded the product **2a** in 95.7% ee. Switching to a non-polar solvent such as benzene, or polar aprotic solvents such as THF, CH_2Cl_2 or acetone, a significant drop in the ee was noted. Protic solvents seem to be required for high enantioselectivities, but not for the reaction to proceed. Notably, even among the alcohol solvents, large variations were observed (entries 1–3). Methanol appears to be the most suitable solvent to perform the hydrogenation of **3a**.

Table 2
Influence of solvent in the hydrogenation of (*Z*)-2-aminocrotonates **3a**[a]

Entry	Solvent	ee (%)[b]	Conv. (%)
1	MeOH	95.7	100
2	EtOH	77.1	100
3	*i*-PrOH	83.9	100
4	THF	88.3	100
5	CH_2Cl_2	52.4	76.1
6	CH_3COCH_3	79.0	89.3
7	C_6H_6	80.2	100

[a] The reactions were carried out at rt under 50 atm H_2 for 1 h with a ratio of S/C of 100. The catalyst was made in situ by stirring a solution of Rh precursor and (1*R*,2*S*)-DPAMPP in THF. [b] The enantiomeric excesses were determined by GC on a CP Chirasil-L-Val column.

2.2.2. Hydrogen pressure and temperature effects

While the selectivities remained constant over the 3–50 atm range, the reaction rate varied to some extent (Table 3). A longer reaction time was required for a lower hydrogen pressure. On the other hand, significant temperature effects were observed (Table 4). It was clear that lower temperatures had a beneficial effect on the enantioselectivities (e.g., 95.7% ee at 10°C (entry 2) versus 70.8% ee at 50°C (entry 4)). However, dropping the temperature further did not provide any improvement in the enantioselectivities (entry 1).

2.2.3. Ligand effects

Under optimal reaction conditions with the Rh-(1*R*,2*S*)-DPAMPP catalyst (MeOH, 40 bar, 20°C, S/C = 100, 1 h), a variety of other potential ligands has been examined in the Rh-catalyzed

Table 3
Influence of pressure in the hydrogenation of (*Z*)-2-acetamidocrotonate **3a**[a]

Entry	P. (bar)	Time (h)	ee (%)[b]
1	3	5	94.6
2	20	3	95.2
3	50	1	95.7

[a] The reactions were carried out in MeOH at rt with a ratio of S/C of 100. The catalyst was made in situ by stirring a solution of Rh precursor and (1*R*,2*S*)-DPAMPP in THF. [b] The enantiomeric excesses were determined by GC on a CP Chirasil-L-Val column.

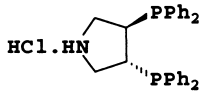
Table 4
Influence of temperature in the hydrogenation of (*Z*)-2-acetamidocrotonate **3a**[a]

Entry	Temp. (°C)	Time (h)	ee (%)[b]
1	-10	4	93.6
2	10	1	95.7
3	30	1	93.3
4	50	0.5	70.8

[a] The reactions were carried out in MeOH under 50 atm H_2 with a ratio of S/C of 100. The catalyst was made in situ by stirring a solution of Rh precursor and (1*R*,2*S*)-DPAMPP in THF. [b] The enantiomeric excesses were determined by GC on a CP Chirasil-L-Val column.

hydrogenation of **3a**. The results are listed in Table 5. Compared with Rh-DPAMPP, chiral diphosphine-Rh catalysts performed uniformly poorly with respect to rates and enantioselectivities. For example, the Rh-BINAP catalyst provided product **2a** in 100% conversion but in at most 21.8% ee (entry 2), and Rh-PPM in 14.4% ee with only 7.9% conversion (entry 5). Overall, the cationic Rh-DPAMPP system appears to be uniquely effective for carrying out the hydrogenation of (*Z*)-ethyl 2-acetamidocrotonate **3a**. In MeOH at room temperature over 1 h (*Z*)-**3a** was smoothly reduced to (*S*)-**2a** in 95.7% ee and 100% conversion. After single recrystallization from petroleum/ethyl acetate (*S*)-**2a** could be obtained in >99.9% ee.

Table 5
Influence of ligands in the hydrogenation of (*Z*)-2-acetamidocrotonate **3a**[a]

Entry	Ligand	ee (%)[b]	Conv. (%)
1	(1*R*,2*S*)-DPAMPP	95.7	100
2	(*S*)-BINAP[c]	21.8	100
3	(*S*,*S*)-DIPAMP[d]	50.8	100
4	(2*R*,4*R*)-BDPP[e]	69.4	100
5	(2*S*,4*S*)-PPM[f]	14.4	7.9
6		85.5	99

[a] The reactions were carried out in MeOH under 50 atm H_2 at rt for 1 h with a ratio of S/C of 100. The catalyst was made in situ by stirring a solution of Rh precursor and appropriate ligands in THF. [b] The enantiomeric excesses were determined by GC on a CP Chirasil-L-Val column. The absolute configuration *S* was determined by comparison of their chiral GC elution order. [c] (*S*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl. [d] (*S*,*S*)-1,2-bis[(o-methoxyphenyl)phenylphosphino]ethane. [e] (2*R*,4*R*)-2,4-bis(diphenylphosphino)pentane. [f] (2*S*,4*S*)-4-(diphenylphosphino)-2-(diphenylphosphinomethyl)pyrrolidine.

2.2.4. Hydrolysis of the protecting group

Acid and base-catalytic hydrolysis of an *N*-acyl group or *C*-ester group to provide free α-amino acids are well-documented.[10] In the case in hand, a method was required for the conversion of (*S*)-**2a** to L-homophenylalanine **1** with the retention of enantioselectivity. Since base-catalysis is usually easier to racemization, we first attempted acid-hydrolysis. Fortunately, in 3N HCl (*S*)-**2a** was readily hydrolyzed to the desired L-homophenylalanine **1** in 96% chemical yield without loss of enantiomeric purity.

3. Conclusion

In summary, the cationic Rh-DPAMPP catalyst is effective for the asymmetric hydrogenation of (*Z*)-2-acetamido-4-phenylcrotonate **3a**. This efficient enantioselective reduction step combined with facile hydrolysis of the protecting groups provides a practical protocol for the synthesis of L-homophenylalanine **1** in good yield with >99.9% ee.

4. Experimental

4.1. General procedures

All hydrogenation reactions were performed in an argon-filled glovebox. Benzene and tetrahydrofuran (THF) were distilled from sodium–benzophenone ketyl under nitrogen. All other solvents used in hydrogenation were deoxygenated by three freeze–thaw cycles prior to use. The $[Rh(COD)Cl]_2$, $AgClO_4 \cdot xH_2O$ and phosphines (*S*)-BINAP, (*S*,*S*)-DIPAMP, (2*R*,4*R*)-BDPP, (2*S*,4*S*)-PPM were purchased from the Aldrich Chemical Co. (3*R*,4*R*)-3,4-Bis(diphenylphosphino)-pyrrolidine hydrogen chloride was a gift from the Department of Applied Biology and Chemical Technology, the Hong Kong Polytechnic University.

Melting points were measured on a digital melting point apparatus and were uncorrected. IR spectra were obtained on a Nicolet 200SXV spectrometer. ^1H NMR spectra were recorded on a Bruker AC-E 300 and Bruker AC-E 200. Mass spectra were determined on a VG 7070E GC/MS/DC instrument. Elemental analysis data were recorded on a Carlo-1160 instrument. The ee and conversion values were determined by chiral GC with a Chiasil-L-Val Column. Optical rotations were measured on a Perkin–Elmer 241 polarimeter.

4.2. General procedures for asymmetric hydrogenation

The cationic Rh(I) catalyst was made in situ by stirring a solution of $[Rh(COD)Cl]_2$ (13.4 mg, 0.027 mmol) and $AgClO_4 \cdot xH_2O$ (12.5 mg, 0.06 mmol) in THF (2.2 mL) for 2 h, then 1 h after addition of appropriate ligands (0.06 mmol). A 50 mL steel autoclave was charged with a stir bar and substrate **3a**–**g** (1 mmol), followed by a degassed solvent (10 mL) and a prepared catalyst (0.01 mmol). The reaction vessel was then pressurized with hydrogen and the reduction was run under the chosen conditions. After the hydrogen was released, the reaction mixture was passed through a short SiO_2 column to remove the catalyst. The enantiomeric excess was measured by capillary GC directly without any further purification.

4.3. Characterizations of products

(*S*)-Ethyl 4-phenyl-2-acetamidobutanoate **2a**: $[\alpha]_D^{20}=+2.1$ (*c* 1.0, EtOH); mp 79–80°C; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, $J=7.2$, OCH_2CH_3), 1.98 (s, 3H, $COCH_3$), 2.29–2.11 (m, 2H, $PhCH_2CH_2$), 2.69–2.60 (m, 2H, $PhCH_2$), 4.18 (q, 2H, $J=7.2$, OCH_2CH_3), 4.66 (m, 1H, NCH), 5.60 (d, 1H, $J=6.9$, NH), 7.31–7.14 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.11 (OCH_2CH_3), 23.03 ($COCH_3$), 31.57 ($PhCH_2$), 33.93 ($PhCH_2CH_2$), 52.05 (NCH), 61.45 (OCH_2CH_3), 126.11, 128.28, 128.33, 128.42, 140.71, 169.92 (NHCO), 172.47 (CO_2); IR (KBr) 3325, 1750, 1652, 1538 cm^{-1}; MS *m*/*z* 249 (M^+, 2), 204 (11), 145 (100), 134 (28), 117 (20), 99 (60), 91 (83); anal. calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.35; H, 7.89; N, 5.54. (*S*)-Ethyl 4-phenyl-2-benzamidobutanoate **2b**: $[\alpha]_D^{20}=-16.6$ (*c* 1.0, EtOH); mp 125–127°C; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3H, $J=7.2$, OCH_2CH_3), 2.41–2.08 (m, 2H, $PhCH_2CH_2$), 2.76–2.70 (m, 2H, $PhCH_2$), 4.23 (q, 2H, $J=7.2$, OCH_2CH_3), 4.94–4.86 (m, 1H, NCH), 6.68 (d, 1H, $J=7.2$, NH), 7.31–7.19 (m, 5H, Ph), 7.52–7.42 (m, 3H, Ph), 7.74–7.71 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.17 (OCH_2CH_3), 31.69 ($PhCH_2$), 33.96 ($PhCH_2CH_2$), 52.55 (NCH), 61.59 (OCH_2CH_3), 126.14, 127.02, 128.38, 128.48, 128.51, 131.66, 133.81, 140.77, 167.01 (NHCO), 172.44 (CO_2); IR (KBr) 3330, 1746, 1640, 1522 cm^{-1}; MS *m*/*z* 207 (M^+–$PhCH{=}CH_2$, 43), 161 (30), 105 (100), 77 (41), 28 (33); anal. calcd for $C_{19}H_{21}NO_3$: C, 73.27; H, 6.80; N, 4.50. Found: C, 73.13; H, 6.88; N, 4.66. (*S*)-Ethyl 4-phenyl-2-methoxycarbonylaminobutanoate **2c**: $[\alpha]_D^{20}=-8.0$ (*c* 1.0, EtOH); mp 49–50°C; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, $J=7.1$, OCH_2CH_3), 2.26–1.86 (m, 2H, $PhCH_2CH_2$), 2.74–2.58 (m, 2H, $PhCH_2$), 3.69 (s, 3H, OCH_3), 4.17 (q, 2H, $J=7.1$, OCH_2CH_3), 4.44–4.34 (m, 1H, NCH), 5.27 (d, 1H, $J=8.0$, NH), 7.35–7.10 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.11 (OCH_2CH_3), 31.47 ($PhCH_2$), 34.27 ($PhCH_2CH_2$), 52.29 (OCH_3), 53.62 (NCH), 61.41 (OCH_2CH_3), 126.10, 128.33, 128.42, 140.66, 156.54 ($NHCO_2$), 172.39 (CO_2); IR (neat) 3339, 1726, 1531 cm^{-1}; MS *m*/*z* 233 (M^+–CH_3OH, 0.4), 161 (73), 117 (64), 91 (100), 77 (10), 28 (54); anal. calcd for $C_{14}H_{19}NO_4$: C, 63.36; H, 7.22; N, 5.28. Found: C, 63.21; H, 7.30; N, 5.26. (*S*)-4-Phenyl-2-methoxycarbonylaminobutanoic acid **2d**: $[\alpha]_D^{20}=+11.1$ (*c* 1.0, EtOH); mp 107–108°C; ^{1}H NMR (DMSO-d_6) δ 1.98–1.79 (m, 2H, $PhCH_2CH_2$), 2.67–2.57 (m, 2H, $PhCH_2$), 3.55 (s, 3H, OCH_3), 3.90–3.84 (m, 1H, NCH), 7.32–7.17 (m, 5H, Ph), 7.55 (d, 1H, $J=7.4$, NH), 12.60 (br s, 1H, CO_2H); ^{13}C NMR ($CDCl_3$) δ 31.48 ($PhCH_2$), 33.91 ($PhCH_2CH_2$), 52.54 (OCH_3), 53.44 (NCH), 126.22, 128.38, 128.48, 140.35, 156.75 ($NHCO_2$), 177.09 (CO_2H); IR (KBr) 3288, 1708, 1535 cm^{-1}; MS *m*/*z* 205 (M^+–CH_3OH, 26), 160 (12), 133 (81), 115 (61), 105 (48), 91 (100), 28 (49); anal. calcd for $C_{12}H_{15}NO_4$: C, 60.73; H, 6.38; N, 5.90. Found: C, 60.97; H, 6.55; N, 5.88. (*S*)-Ethyl 4-phenyl-2-benzoxycarbonylaminobutanoate **2e**: $[\alpha]_D^{20}=-19.3$ (*c* 1.0, EtOH); mp 64–66°C; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, $J=7.1$, OCH_2CH_3), 2.16–1.86 (m, 2H, $PhCH_2CH_2$), 2.80–2.61 (m, 2H, $PhCH_2$), 4.20 (q, 2H, $J=7.1$, OCH_2CH_3), 4.44–4.35 (m, 1H, NCH), 5.11 (s, 2H, OCH_2Ph), 5.26 (d, 1H, $J=7.4$, NH), 7.35–7.14 (m, 10H, 2×Ph); ^{13}C NMR ($CDCl_3$) δ 14.11 (OCH_2CH_3), 31.42 ($PhCH_2$), 34.30 ($PhCH_2CH_2$), 53.65 (NCH), 61.46 (OCH_2CH_3), 66.95 (OCH_2Ph), 126.12, 128.06, 128.14, 128.33, 128.42, 128.48, 136.18, 140.62, 143.69, 155.81 ($NHCO_2$), 172.22 (CO_2); IR (neat) 3330, 1730, 1520 cm^{-1}; MS *m*/*z* 250 (M^+–CH_2Ph, 3), 237 (8), 233 (6), 160 (12), 129 (8), 115 (8), 91 (100), 28 (12); anal. calcd for $C_{20}H_{23}NO_4$: C, 70.34; H, 6.79; N, 4.11. Found: C, 70.20; H, 6.83; N, 4.11. (*S*)-Ethyl 4-phenyl-2-*iso*-butoxycarbonylaminobutanoate **2f**: $[\alpha]_D^{20}=-13.0$ (*c* 1.0, EtOH); mp 58–59°C; ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 6H, $J=6.7$, $CH(CH_3)_2$), 1.27 (t, 3H, $J=7.2$, OCH_2CH_3), 2.05–1.84 (m, 2H, $PhCH_2CH_2$), 2.23–2.08 (m, 1H, $CH(CH_3)_2$), 2.75–2.63 (m, 2H, $PhCH_2$), 3.85 (d, 2H, $J=6.6$, OCH_2CH), 4.17 (q, 2H, $J=7.2$, OCH_2CH_3), 4.44–4.34 (m, 1H, NCH), 5.23 (d, 1H, $J=7.9$, NH), 7.33–7.15 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.15 (OCH_2CH_3), 18.98 ($CH(CH_3)_2$), 27.93

($CH(CH_3)_2$), 31.49 ($PhCH_2$), 34.37 ($PhCH_2CH_2$), 53.55 (NCH), 61.43 (OCH_2CH_3), 71.28 (OCH_2CH), 126.12, 128.35, 128.43, 140.71, 143.35, 156.26 ($NHCO_2$), 172.46 (CO_2); IR (KBr) 3354, 1749, 1693, 1523 cm^{-1}; MS *m/z* 307 (M^+, 0.6), 234 (12), 203 (74), 147 (54), 117 (65), 101 (47), 91 (100), 57 (97), 41 (60), 29 (100); anal. calcd for $C_{17}H_{25}NO_4$: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.40; H, 8.03; N, 4.66. (*S*)-Ethyl 4-phenyl-2-*tert*-butoxycarbonylaminobutanoate **2g**: $[\alpha]_D^{20} = -9.8$ (*c* 1.0, EtOH); mp 71–72°C; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, $J = 7.1$, OCH_2CH_3), 1.45 (s, 9H, $C(CH_3)_3$), 2.16–1.90 (m, 2H, $PhCH_2CH_2$), 2.75–2.41 (m, 2H, $PhCH_2$), 4.17 (q, 2H, $J = 7.1$, OCH_2CH_3), 4.35–4.26 (m, 1H, NCH), 5.08 (d, 1H, $J = 8.0$, NH), 7.32–7.10 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.13 (OCH_2CH_3), 28.26 ($C(CH_3)_3$), 31.57 ($PhCH_2$), 34.40 ($PhCH_2CH_2$), 53.27 (NCH), 61.26 (OCH_2CH_3), 79.77 ($C(CH_3)_3$), 126.06, 128.33, 128.40, 140.80, 143.31, 155.29 ($NHCO_2$), 172.57 (CO_2); IR (neat) 3360, 1775, 1715, 1503 cm^{-1}; MS *m/z* 307 (M^+, 0.3), 251 (1), 234 (3), 147 (100), 134 (48), 117 (28), 91 (25), 57 (87); anal. calcd for $C_{17}H_{25}NO_4$: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.24; H, 8.07; N, 4.59.

4.4. Hydrolysis of protecting group

A solution of **2a** (300 mg, 1.2 mmol, >99.9% ee) in 3N HCl (3 mL) was refluxed for 2 h. After cooling to room temperature, the mixture was neutralized to pH = 5.6 by saturated NaOAc, filtered and the cake was washed with H_2O and acetone and dried in air to give L-homophenylalanine **1** (200 mg, 96% yield, >99.9% ee) as colorless leaflets. An analytical sample was recrystallized from 50% aqueous NaOAc. $[\alpha]_D^{20} = +47.2$ (*c* 1.0, 1N HCl) [lit.[9] $[\alpha]_D^{20} = +47.5$ (*c* 1.0, 1N HCl)]; mp >250°C; ^1H NMR (D_2O+TFA) δ 2.00–1.81 (m, 2H, $PhCH_2CH_2$), 2.45–2.39 (m, 2H, $PhCH_2$), 3.71 (t, 1H, $J = 6.3$, NCH), 7.04–6.91 (m, 5H, Ph); IR (KBr) 3435, 1654, 1623, 1581 cm^{-1}; anal. calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.85; H, 7.39; N, 7.81.

4.5. Determination of enantiomeric excess

Chiral capillary GC column: Chrompack Chirasil-L-Val column. Dimensions: 25 m×0.25 mm (i.d.). Carrier gas: H_2. The racemic products were obtained by hydrogenation of substrates **3a**–**g** with 10% Pd–C. The following are the retention times for the racemic products. Ethyl 4-phenyl-2-acetamidobutanoate **2a** (capillary GC, 172°C, 0.73 kgf/cm^2, isothermal): (*R*) $t_1 = 6.45$ min, (*S*) $t_2 = 7.26$ min. Ethyl 4-phenyl-2-benzamidobutanoate **2b** (capillary GC, 201°C, 0.91 kgf/cm^2, isothermal): (*R*) $t_1 = 10.41$ min, (*S*) $t_2 = 11.19$ min. Ethyl 4-phenyl-2-methoxycarbonylaminobutanoate **2c** (capillary GC, 172°C, 0.73 kgf/cm^2, isothermal): (*R*) $t_1 = 5.36$ min, (*S*) $t_2 = 5.50$ min. Methyl 4-phenyl-2-methoxycarbonylaminobutanoate (methyl ester of **2d**) (capillary GC, 165°C, 0.70 kgf/cm^2, isothermal): (*R*) $t_1 = 6.41$ min, (*S*) $t_2 = 6.57$ min. Ethyl 4-phenyl-2-benzoxycarbonylaminobutanoate **2e** (capillary GC, 198°C, 0.91 kgf/cm^2, isothermal): (*R*) $t_1 = 15.10$ min, (*S*) $t_2 = 15.35$ min. Ethyl 4-phenyl-2-*iso*-butoxycarbonylaminobutanoate **2f** (capillary GC, 184°C, 0.82 kgf/cm^2, isothermal): (*R*) $t_1 = 6.59$ min, (*S*) $t_2 = 7.12$ min. Ethyl 4-phenyl-2-*tert*-butoxycarbonylaminobutanoate **2g** (capillary GC, 172°C, 0.73 kgf/cm^2, isothermal): (*R*) $t_1 = 6.26$ min, (*S*) $t_2 = 6.38$ min.

Chiral HPLC column: CrownPack CR (+). Particle size: 5.0 μm. Column dimensions: 150 mm (length)×4.6 mm (i.d.). Column temperature: 45°C. L-Homophenylalanine **1** (HPLC, 0.8 mL/min, MeOH:pH 1.7 $HClO_4$ = 15:85): (*R*) $t_1 = 12.28$ min, (*S*) $t_2 = 28.52$ min.

Acknowledgements

We are grateful for financial support from the National Science Foundation of China (No. 29790124).

References

1. (a) Salvetti, A. *Drugs* **1990**, *40*, 800, and references cited therein. (b) Leonetti, G.; Cuspidi, C. *Drugs* **1995**, *49*, 516.
2. (a) Miyazawa, Y.; Oishi, N.; Maehara, K. Japanese Patent, Jpn Kokai Tokkyo Koho JP 63,63,646, 1988. (b) Miyazawa, Y.; Oishi, N.; Maehara, K. Japanese Patent, Jpn Kokai Tokkyo Koho JP 63,145,256, 1988. (c) Keller, R.; Mueller, W. Eur. Pat. Appl. EP 310,012, 1989. (d) Houng, J.; Hsieh, C. US Patent 5,552,317, 1996. (e) Pugniere, M.; Domergue, N.; Castro, B.; Previero, A. *Chirality* **1994**, *6*, 472. (f) Chen, S. T.; Huang, W. H.; Wang, K. T. *Chirality* **1994**, *6*, 572.
3. (a) Bradshaw, C. W.; Wang, C. H.; Hummel, W.; Kula, M. R. *Bioorg. Chem.* **1991**, *19*, 29. (b) Asano, Y.; Yamada, A.; Kato, Y.; Yamaguchi, K.; Hibino, Y.; Hirai, K.; Kondo, K. *J. Org. Chem.* **1990**, *55*, 5567. (c) Asano, Y.; Iwasaki, G.; Kondo, S. Japanese Patent, Jpn Kokai Tokkyo Koho JP 01,47,386, 1989. (d) Fujikawa, K.; Sato, H.; Yonehara, T.; Miyata, A. Japanese Patent, Jpn Kokai Tokkyo Koho JP 03,112,409, 1991. (e) Senuma, M.; Nakamichi, K.; Nabe, K.; Nishimoto, S.; Tosa, T. *Appl. Biochem. Biotechnol.* **1989**, *22*, 141. (f) Fujikawa, K.; Sato, H.; Yonehara, T.; Miyata, A. Japanese Patent, Jpn Kokai Tokkyo Koho JP 03,112,491, 1991. (g) Nakayama, K.; Ozawa, T. Japanese Patent, Jpn Kokai Tokkyo Koho JP 02,278,585, 1990. (h) Nakayama, K.; Ozawa, T. Japanese Patent, Jpn Kokai Tokkyo Koho JP 02,119,796, 1990. (i) Nabe, K.; Nishida, Y.; Nakamichi, K.; Nishimoto, S. Japanese Patent, Jpn Kokai Tokkyo Koho JP 63,273,498, 1988. (j) Mihara, Y.; Onishi, I. Japanese Patent, Jpn Kokai Tokkyo Koho JP 06,343,483, 1994. (k) Syldatk, C.; Lehmensiek, V.; Ulrichs, G.; Bilitewski, U.; Krohn, K.; Hoeke, H.; Wagner, F. *Biotechnol. Lett.* **1992**, *14*, 99. (l) Fotheringham, I. G.; Kidman, G. E.; McArthur, B. S.; Robinson, L. E.; Scollar, M. P. *Biotechnol. Prog.* **1991**, *7*, 380.
4. (a) Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547. (b) Zhai, D.; Zhai, W.; Williams, R. M. *J. Am. Chem. Soc.* **1988**, *110*, 2501. (c) Gasanov, R. G.; II'inskaya, L. V.; Misharin, M. A.; Maleev, V. I.; Raevski, N. I.; Ikonnikov, N. S.; Orlova, S. A.; Kuzmina, N. A.; Belokon, Y. N. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3343. (d) Belokon, Y. N.; Sagyan, A. S.; Djamgaryan, S. M.; Bakhmutov, V. I.; Belikov, V. M. *Tetrahedron* **1988**, *44*, 5507.
5. (a) Cesarotti, E.; Chiesa, A.; D'Alfonso, G. *Tetrahedron Lett.* **1982**, *23*, 2995. (b) Pracejus, G.; Pracejus, H. *J. Mol. Catal.* **1984**, *24*, 227. (c) Döbler, C.; Kreuzfeld, H. J.; Pracejus, H. *J. Organometal. Chem.* **1988**, *344*, 89. (d) Krause, H. W.; Foken, H.; Pracejus, H. *New J. Chem.* **1989**, *13*, 615. (e) Döbler, C.; Schimidt, U.; Krause, H. W.; Kreuzfeld, H. J.; Michalik, M. *Tetrahedron: Asymmetry* **1995**, *6*, 385. (f) Kreuzfeld, H. J.; Schimidt, U.; Döbler, C.; Krause, H. W. *Tetrahedron: Asymmetry* **1996**, *7*, 1011. (g) Kreuzfeld, H. J.; Döbler, C. *J. Mol. Catal.* **1998**, *13*, 105.
6. (a) Mi, A. Q.; Lou, R. L.; Jiang, Y. Z.; Deng, J. G.; Qin, Y.; Fu, F. M.; Li, Z.; Hu, W. H.; Chan, A. S. C. *Synlett* **1998**, 847. (b) Mi, A. Q.; Lou, R. L.; Qin, Y.; Jiang, Y. Z.; Hu, W. H.; Chan, A. S. C. Chinese Patent Application No. 97107608.1, July 24, 1997.
7. (a) Koenig, K. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 3. (b) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518. (c) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345. (d) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106.
8. (a) (*Z*)-2-Acetamidocrotonate **3a** was prepared by reduction of oxime, derived from α-keto ester **4a**, by Fe/Ac_2O in the presence of HOAc. See: Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084. (b) All other (*Z*)-2-aminocrotonates **3b**–**g** were prepared by condensation of α-keto ester **4a** or the corresponding α-keto acid **4b** with benzamide or appropriate carbamates, following the procedure outlined by Melillo et al. with a little modification: Melillo, D. G.; Larsen, R. D.; Mathre, D. J.; Shukis, W. F.; Wood, A. W.; Colleluori, J. R. *J. Org. Chem.* **1987**, *52*, 5143.
9. Kubota, H.; Nunami, K.; Hayashi, K.; Hashimoto, Y.; Ogiku, N.; Matsuoka, Y.; Ishida, R. *Chem. Pharm. Bull. Jpn* **1992**, *40*, 1619.
10. *Protective Groups in Organic Synthesis*; Greene, T. W.; Wuts, P. G., Eds.; John Wiley & Sons: New York, 1991; Chapters 5 and 7.