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Facile Asymmetric Synthesis of α-Amino Acids Employing Chiral Ligand-Mediated Asymmetric Addition Reactions of Phenyllithium with Imines

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We dedicate this paper for the memory of the late Professor Toshiro Ibuka, Graduate School of Pharmaceutical Sciences, Kyoto University

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Abstract—A three-step methodology involving an external chiral ligand-mediated asymmetric addition of phenyllithium to an anisidine imine, oxidative removal of *N*-PMP group, and finally oxidative conversion of the phenyl group to a carboxyl group provides a facile synthesis of optically pure α-amino acid derivatives bearing a bulky α-substituent.

Introduction

We have been involved in an asymmetric addition reaction of organolithium reagents with imines using an external chiral ligand as a stereocontroller.[1,2] Especially, 1,2-addition reaction[3] of phenyllithium with pivalaldehyde anisidine imine **2a** (R=*t*-Bu, PMP=*p*-MeOPh) was mediated by chiral dimethoxydiphenylethane **1** to give the corresponding secondary amine **3a** in high enantioselectivity.[4] Either enantiomer of **3** is available since both enantiomers of **1** are readily available by asymmetric dihydroxylation of stilbene followed by methylation.[3] Combined with our related projects aimed at applications of asymmetric reactions to the synthesis of biologically important compounds,[5] oxidative conversion of the phenyl group of **3a** to a carboxyl group without racemization provides a new synthetic route to optically active *tert*-leucine.[6,7] It is generally known that a bulky side chain of α-amino acid residue around the active site of the peptide greatly influences the activity.[8] It is also important to note that an optically pure α-amino acid is a versatile chiral source for the synthesis of a chiral auxiliary.[9] Therefore, natural and unnatural α-amino acids have been one of the targets for asymmetric synthesis.[10,11] Recently, North has disclosed an elegant asymmetric synthesis of α-amino acids based on external chiral ligand-mediated asymmetric addition of an organolithium to *N*-trimethylsilylimine and subsequent oxidative conversion of the olefin moiety to a carboxyl group. However, it was very disappointing for us to read that oxidative removal of the *N*-PMP group was unsuccessful.[12] We describe herein a three-step asymmetric synthesis of α-amino acid derivatives **5** bearing a bulky α-substituent by employing the asymmetric addition reaction of phenyllithium with anisidine imines **2** and successful oxidative removal of *N*-PMP group (Fig. 1).

Asymmetric addition reactions of phenyllithium with imine 2

The starting imines **2** were prepared in nearly quantitative yields by condensation of the corresponding aldehydes with *p*-anisidine in the presence of magnesium sulfate. The addition reaction of 2 equiv. of phenyllithium with **2a** (R=*t*-Bu) was mediated by 2.6 equiv. (1.3 equiv. against

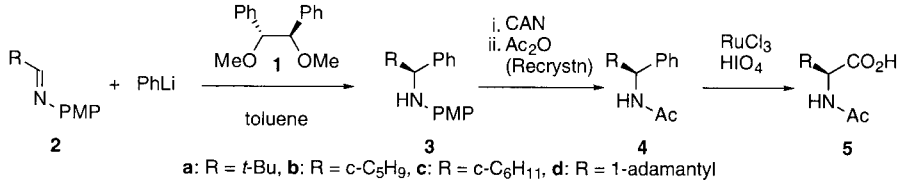

Figure 1. Three-step asymmetric synthesis of optically pure *N*-actyl α-amino acids.

Keywords: alkylation; asymmetric synthesis; oxidation; amino acid.

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Table 1. Asymmetric reactions of phenyllithium with imine **2** giving **3** mediated by the ligand **1** (2 equiv. of phenyllithium were used)

Entry	**2**	R	**1** (equiv.)[a]	Temp (°C)	Time (h)	Yield (%)	ee (%)	*R*/*S*
1	**a**	*t*-Bu	1.3	−45	0.7	95	90	*S*
2	**b**	*c*-C_5H_9	1.3	−45	1	84	76	*S*
3	**c**	*c*-C_6H_{11}	1.3	−45	1	77	80	*S*
4	**d**	1-adamantyl	1.3	−45	1	98	89	*S*

[a] The equivalency against phenyllithium.

phenyllithium) of a chiral diether ligand (*R*,*R*)-**1**. The reaction was conducted in toluene at −45°C for 0.7 h to afford (*S*)-**3a** in 95% isolated yield after purification by silica gel column chromatography. The enantioselectivity was determined to be 90% by chiral stationary phase HPLC.[13] The specific rotation of **3a**[4] and its conversion to *N*-acetyl L-*tert*-leucine determined (*S*)-absolute configuration. The chiral ligand **1** was recovered for reuse in nearly quantitative yield. The asymmetric addition of phenyllithium was also examined with **2b**–**d** to afford (*S*)-**3b**–**d** in 76–89% ee and 77–98% yield (Table 1, entries 2–4).

The sense of enantiofacial differentiation in the addition reaction of phenyllithium with **2** under the control by **1** was same in all reactions examined here. Phenyllithium attacks the imines from the *re*-face to give (*S*)-**3**. The degree of enantioselectivity is related to the bulkiness of the α-substituent (R) of the imine **2**. The tertiary substituents, *t*-butyl and 1-adamantyl groups (**2a** and **2d**), induced 90% ee and 89% ee, respectively (entries 1 and 4). Smaller secondary *c*-pentyl and *c*-hexyl groups (**2b** and **2c**) gave 76% ee and 80% ee, respectively (entries 2 and 3).

Catalytic addition reactions using 0.15 equiv. (against phenyllithium) of **1** at −45°C did not proceed smoothly, but proceeded at 0°C for 1–1.5 h to give **3** in 69–97% yield (Table 2). The enantioselectivity was maintained in the range of 31–58% ee. The lower enantioselectivity is attributable to the reaction of phenyllithium without influence of **1** at 0°C.

Enantiofacial differentiation of imine 2

Enantiofacial differentiation of the imine **2** was reasonably predictable by analyzing two coordinated structures **A**, **A′** and **B**, **B′** (Fig. 2). The chiral ligand **1** forms a chelated complex with phenyllithium, in which two methyl groups on the ether oxygen atoms are placed up and down faces of the five-membered chelate due to steric reason avoiding repulsion between methyl groups and adjacent phenyl groups. Coordination of imine nitrogen to the lithium is the initial event for the reaction taking place. The structure **A** represents a four-centered mechanism,[14] in which the nucleophilic phenyl group attacks the imine from the *re*-face giving the product amine having the absolute configuration identical with that observed. The presentation **A′** indicates the positional relationship of the approaching imine and chelated phenyllithium. On the other hand, the structure **B**, giving the antipode, suffers from severe steric repulsion between PMP and R groups of the imine and the methyl groups of the ligand **1**. The steric interaction between PMP and methyl groups is the primary steric factor, because the PMP group is nearer to the stereocontrolling methyl group than the R group.

Analysis based on the structures **A** and **B** indicates that **B** is much destabilized by the bulky R group of the imine, in other words, **A** is much more favorable than **B**. Thus, the observed higher selectivity of **3a** (R=*t*-Bu) and **3d** (R= 1-adamantyl) having tertiary α-substituent than those of **3b** (R=*c*-pentyl) and **3c** (R=*c*-hexyl) having secondary group is reasonably predictable.

One-flask conversion of *N*-PMP group to *N*-acetyl group

We have previously reported that oxidative removal of the *N*-PMP group in **3** required a prior acylation of amine nitrogen (**6**) for ease of hydrolytic elimination of quinone **9** from the oxidation product **7** (Fig. 3).[4] However, attempted CAN oxidation of **6a** (R=*t*-Bu) gave **4a** in only 29% yield. Since CAN oxidation of the *N*-PMP group of **3** undergoes readily to form quinone derivative **8**, subsequent hydrolysis and acylation should form **4**. Without acylation, resulting amine should attack to quinone **9** to form a 1,4-conjugate addition product. The process from **3** to **4** via **8** can be carried out in one-flask.

Successive treatment of **3a** (90% ee) with 2 equiv. of CAN in aqueous acetonitrile at 0°C for 0.5 h and at rt for further 2 h, and then with 10 equiv. of acetic anhydride and sodium hydroxide at rt for 2 h provided *N*-acetylamine **4a** in 78% yield without detectable racemization. Enantioenrichment by recrystallization of **4a** of 90% ee from ethanol gave optically pure **4a** in 55% overall yield.

Under the same one-flask procedure, the removal of PMP

Table 2. Catalytic asymmetric reactions of phenyllithium with imine **2** mediated by 0.15 equiv. of **1** (2 equiv. of phenyllithium were used)

Entry	**2**	R	**1** (equiv.)[a]	Temp (°C)	Time (h)	Yield (%)	ee (%)	*R*/*S*
1	**a**	*t*-Bu	0.15	0	1	85	58	*S*
2	**b**	*c*-C_5H_9	0.15	0	1.5	79	31	*S*
3	**c**	*c*-C_6H_{11}	0.15	0	1.5	69	53	*S*
4	**d**	1-adamantyl	0.15	0	1	97	43	*S*

[a] The equivalency against phenyllithium.

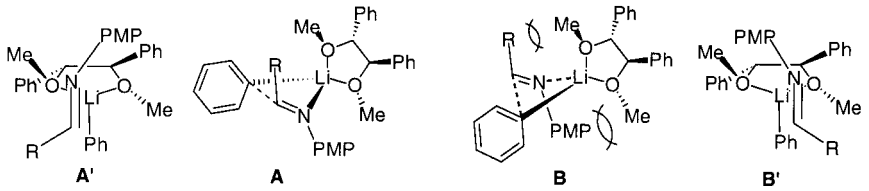

Figure 2. Models for favorable (**A**, **A′**) and disfavorable (**B**, **B′**) structures.

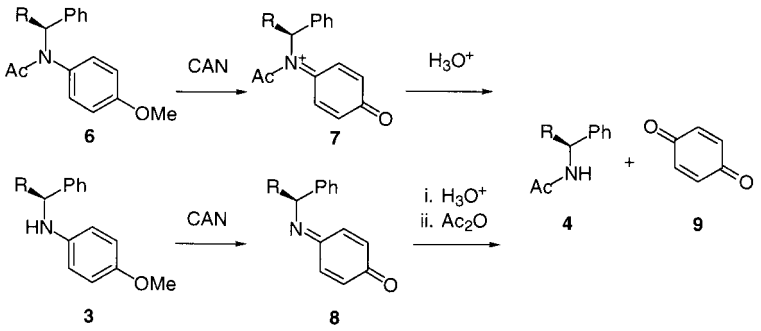

Figure 3. One-flask conversion of **3** to **4** by oxidative removal of *N*-PMP and acetylation.

group followed by acetylation of **3b–d** obtained using 1.3 equiv. of **1** was carried out without any racemization to give **4b–d** in 64, 69, and 86% yields, respectively. Enantioenrichment of *N*-acetylamines by recrystallization gave optically pure *N*-acetylamines **4**.

Synthesis of *N*-acetyl amino acids by conversion of a phenyl group to a carboxyl group

Finally, conversion of the phenyl group of optically pure **4a** to a carboxyl group was conducted under modified-Sharpless conditions,[15] $RuCl_3$–HIO_4 in aqueous acetonitrile-CCl_4 at rt for 48 h, to afford optically pure *N*-acetyl-*tert*-leucine (*S*)-**5a**[16] in 53% recrystallization yield. Optically pure *tert*-leucine is easily available from **5a** by acid hydrolysis.[17] Likewise, conversion of **4b–d** was carried out under the same oxidative conditions for **4a** to give optically pure *N*-acetyl amino acids **5b–d** in 40, 53, and 25% recrystallization yields. Optically pure (*S*)-1-adamantylglycine hydrochloride was obtained by acid hydrolysis of **5d** in 34% recrystallization yield.

Conclusion

The three-step methodology provided optically pure *N*-acetyl α-amino acids **5** bearing bulky α-substituent from the *p*-anisidine imines **2**. The enantiofacial differentiation is predictable by analyzing a coordination model. Since both enantiomers of **1** are available by asymmetric dihydroxylation,[3] the present synthesis provides either enantiomer of optically pure α-amino acids.

Experimental[18]

2,2-Dimethylpropylidene-4-methoxyphenylamine (2a). (R=*t*-Bu): Prepared as described before.[4]

Cyclopentylmethylene-4-methoxyphenylamine (2b). (R=*c*-C_5H_9): A mixture of cyclopentanecarboxaldehyde (1.77 g, 18 mmol), 4-methoxyaniline (1.85 g, 15 mmol) and magnesium sulfate (3.61 g) in ether ((30 mL) was stirred at 0°C for 0.5 h. Filtration through a pad of potassium carbonate followed by concentration gave **2b** (3.03 g, quant) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, TMS) δ: 1.6–1.8 (6H, m, CH_2), 1.9–2.0 (2H, m, CH_2), 2.83 (1H, m, CH), 3.80 (3H, s, OMe), 6.86 and 7.03 (each 2H, dd, *J*=8.6, 2.8 Hz, ArH), 7.75 (1H, d, *J*=6.1 Hz, =CH). ^{13}C NMR ($CDCl_3$, TMS) δ: 25.7, 30.2, 46.0, 55.4, 114.1, 121.7, 145.1, 157.6, 168.2. IR (neat): 1650 cm^{-1}. MS *m/z*: 203 (M^+). HRMS Calcd for $C_{13}H_{17}NO$: 203.1310. Found: 203.1315.

Cyclohexylmethylene-4-methoxyphenylamine (2c). (R=*c*-C_6H_{11}): A mixture of cyclohexanecarboxaldehyde (1.23 g, 10 mmol), 4-methoxyaniline (1.23 g, 10 mmol) and magnesium sulfate (2.41 g) in chloroform (10 mL) was stirred at rt for 2 h. Filtration through a pad of potassium carbonate followed by concentration gave **2c** (2.20 g, quant) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, TMS) δ: 1.2–1.4 (5H, m, CH_2), 1.7–1.9 (5H, m, CH_2), 2.34 (1H, m, CH), 3.80 (3H, s, OMe), 6.86 and 7.01 (each 2H, dd, *J*=8.6, 2.8 Hz, ArH), 7.71 (1H, d, *J*=5.2 Hz, =CH). ^{13}C NMR ($CDCl_3$, TMS) δ: 25.4, 25.9, 29.5, 44.0, 55.3, 114.1, 121.6, 145.3, 157.6, 168.4. IR (neat): 1650 cm^{-1}. MS *m/z*: 217 (M^+). Anal. Calcd for $C_{14}H_{19}NO$: C 77.38, H 8.81, N 6.45. Found: C 77.21, H 8.98, N 6.46.

1-Adamantylmethylene 4-methoxyphenylamine (2d). (R=1-adamantyl): A mixture of 1-adamantanecarboxaldehyde (12.1 g, 74 mmol), 4-methoxyaniline (8.24 g, 67 mmol) and magnesium sulfate (17.7 g) in ether (150 mL) was stirred at 0°C for 4 h. Filtration through a pad of potassium carbonate followed by concentration and recrystallization from EtOH gave **2d** (9.80 g, 54%) as a pale yellow powder of mp 89–90°C. ^{1}H NMR ($CDCl_3$, TMS) δ: 1.7–1.8 (12H, m, CH_2), 2.0–2.1 (3H, m, CH), 3.79 (3H, s, OMe), 6.85 and 6.99 (each 2H, dd, *J*=8.6, 2.6 Hz, ArH), 7.54 (1H, s, =CH). ^{13}C NMR ($CDCl_3$, TMS) δ: 28.0, 36.8, 38.7, 39.3, 55.4, 114.1, 121.7, 145.9, 157.5, 171.6. IR

(nujol): 1650 cm^{-1}. MS *m/z*: 269 (M^+). Anal. Calcd for $C_{18}H_{23}NO$: C 80.26, H 8.61, N 5.20. Found: C 79.97, H 8.49, N 5.11.

Asymmetric addition reaction of phenyllithium with an imine 2a. (−)-(*S*)-2,2-Dimethyl-1-phenylpropyl-4-methoxyphenylamine (3a). (R=*t*-Bu): A solution of phenyllithium (13.5 mL, 20 mmol) in a mixture of cyclohexane and diethyl ether was added to a mixture of **2a** (1.91 g, 10 mmol) and **1** (6.30 g, 26 mmol) in toluene (200 mL) at −45°C over a period of 10 min. The mixture was stirred at −45°C for 0.7 h and was quenched with water (100 mL). The organic layer was separated. The aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, and then dried over K_2CO_3. Concentration and column chromatography (ether–hexane) gave (*S*)-**3a** (2.55 g, 95%) as a pale yellow solid of mp 67–70°C. $[\alpha]_{435}^{20}$ −52.7 (*c* 1.51, EtOH). ^{1}H NMR ($CDCl_3$, TMS) δ: 0.98 (9H, s, 3 x Me), 3.66 (3H, s, OMe), 3.96 (1H, s, CH), 4.00 (1H, brs, NH), 6.43 and 6.64 (each 2H, dd, *J*=8.8, 3.1 Hz, ArH), 7.2–7.3 (5H, m, ArH). ^{13}C NMR ($CDCl_3$, TMS) δ: 27.1, 34.9, 55.7, 68.1, 114.3, 114.7, 126.7, 127.6, 128.5, 141.4, 142.2, 151.7. IR (nujol): 3400 cm^{-1}. MS *m/z*: 269 (M^+). Anal. Calcd for $C_{18}H_{23}NO$: C 80.26, H 8.61, N 5.20. Found: C 80.41, H 8.78, N 5.20.

Ee was determined to be 90% by chiral stationary phase HPLC analysis (Daicel Chiralcel OJ, hexane–*i*-PrOH (100:1), 254 nm, 0.5 mL/min, 33.6 min (minor enantiomer), 39.3 min (major enantiomer)).

(−)-(*S*)-Cyclopentylphenylmethyl-4-methoxyphenylamine (3b). (R=*c*-C_5H_9): Purified by column chromatography (hexane–AcOEt) in 84% yield. A pale yellow oil of $[\alpha]_{435}^{20}$=−96.7 (*c* 1.54, EtOH). ^{1}H NMR ($CDCl_3$, TMS) δ: 1.3 –1.9 (8H, m, CH_2), 2.11 (1H, m, CH), 3.63 (3H, s, OMe), 3.92 (1H, brs, NH), 3.98 (1H, d, *J*=8.0 Hz, CH), 6.44 and 6.64 (each 2H, dd, *J*=8.7, 2.9 Hz, ArH), 7.1–7.3 (5H, m, ArH). ^{13}C NMR ($CDCl_3$, TMS) δ: 25.27, 25.33, 30.1, 30.2, 47.9, 55.8, 64.1, 114.5, 114.8, 126.8, 127.1, 128.4, 142.1, 144.3, 151.8. IR (neat): 3400 cm^{-1}. MS *m/z*: 281 (M^+). Anal. Calcd for $C_{19}H_{23}NO$: C 81.10, H 8.24, N 4.98. Found: C 80.85, H 8.26, N 4.80.

Ee was determined to be 76% by chiral stationary phase HPLC analysis (Daicel Chiralpak AS, hexane–*i*-PrOH (30:1), 0.5 mL/min, 254 nm, 12.3 min (minor enantiomer), 18.0 min (major enantiomer)).

(−)-(*S*)-Cyclohexylphenylmethyl-4-methoxyphenylamine (3c). (R=*c*-C_6H_{11}): Purified by column chromatography (hexane–AcOEt) in 77% yield. A pale yellow oil of $[\alpha]_{435}^{20}$=−70.1 (*c* 1.59, EtOH). ^{1}H NMR ($CDCl_3$, TMS) δ: 1.0–1.3 (5H, m, CH_2), 1.5–1.9 (6H, m, CH_2), 3.67 (3H, s, OMe), 3.89 (1H, brs, NH), 4.03 (1H, d, *J*=6.4 Hz, CH), 6.44 and 6.66 (each 2H, dd, *J*=8.4, 3.1 Hz, ArH), 7.2–7.3 (5H, m, ArH). ^{13}C NMR ($CDCl_3$, TMS) δ: 26.30, 26.34, 26.4, 29.4, 30.1, 44.9, 55.6, 64.2, 114.2, 114.7, 126.6, 127.2, 128.1, 142.1, 142.8, 151.6. IR (neat): 3400 cm^{-1}. MS *m/z*: 295 (M^+). Anal. Calcd for $C_{20}H_{25}NO$: C 81.31, H 8.53, N 4.74. Found: C 81.18, H 8.64, N 4.45.

Ee was determined to be 80% by chiral stationary phase HPLC analysis (Daicel Chiralcel OJ, hexane–*i*-PrOH (25:1), 254 nm, 1 mL/min, 14.7 min (minor enantiomer), 36.0 min (major enantiomer)).

(−)-(*S*)-*N*-[(1-Adamantyl)phenylmethyl]-4-methoxyphenylamine (3d). (R=1-adamantyl): Purified by column chromatography (hexane–AcOEt) in 98% yield. A pale yellow oil of $[\alpha]_{435}^{20}$=−34.9 (*c* 1.72, EtOH). ^{1}H NMR ($CDCl_3$, TMS) δ: 1.4–1.7 (12H, m, CH_2), 1.9–2.0 (3H, m, CH), 3.65 (3H, s, OMe), 3.79 (1H, s, CH), 4.07 (1H, brs, NH), 6.43 and 6.63 (each 2H, dd, *J*=8.6, 3.1 Hz, ArH), 7.2–7.3 (5H, m, ArH). ^{13}C NMR ($CDCl_3$, TMS) δ: 28.4, 36.5, 36.9, 39.3, 55.7, 68.9, 114.2, 114.7, 126.6, 127.5, 128.7, 140.5, 142.3, 151.5. IR (neat): 3410 cm^{-1}. MS *m/z*: 347 (M^+). Anal. Calcd for $C_{24}H_{29}NO$: C 82.95, H 8.41, N 4.03. Found: C 82.86, H 8.15, N 3.81.

One-flask procedure for CAN oxidation followed by acetylation. (−)-(*S*)-*N*-(2,2-Dimethyl-1-phenylpropyl)-acetamide (4a). (R=*t*-Bu): Cerium(IV) diammonium nitrate (CAN) (18.4 g, 32 mmol) was added at once to a solution of **3a** (4.27 g, 16 mmol, 90% ee) in a mixture of acetonitrile (64 mL) and water (32 mL) at 0°C. The mixture was stirred at 0°C for 0.5 h and at rt for 2 h, and then was added successively by 10% aqueous sodium hydroxide (30 mL) and acetic anhydride (16.2 g, 160 mmol) at 0°C. After stirring for 1 h at 0°C, the mixture was filtered through a Celite pad. The aqueous layer was extracted with AcOEt. The combined organic layers were washed with satd sodium bicarbonate, 10% aqueous sodium sulfite, and brine, and then dried over magnesium sulfate. Concentration and column chromatography (hexane–AcOEt) gave **4a** of 90% ee (2.55 g, 78%) as a solid. Recrystallization from ethanol gave optically pure **4a** (1.82 g, 56%) as colorless cubes of constant mp 177–177.5°C. $[\alpha]_D^{28}$=−92.0 (*c* 2.05, EtOH). ^{1}H NMR ($CDCl_3$, TMS) δ: 0.92 (9H, s, 3×Me), 2.01 (3H, s, CH_3CO), 4.83 (1H, d, *J*=9.5 Hz, CH), 6.04 (1H, brd, *J*=9.5 Hz, NH), 7.2–7.3 (5H, m, ArH). ^{13}C NMR ($CDCl_3$, TMS) δ: 23.5, 26.7, 34.8, 61.5, 127.0, 127.7, 128.1, 140.1, 169.2. IR (nujol): 3300, 1640 cm^{-1}. MS *m/z*: 205 (M^+). Anal. Calcd for $C_{13}H_{19}NO$: C 76.06, H 9.33. Found: C 75.83, H 9.44.

Ee was determined to be over 99% by chiral stationary phase HPLC analysis (Daicel Chiralpak AS, hexane–*i*-PrOH (19:1), 254 nm, 0.5 mL/min, 32.7 min (minor enantiomer), 36.7 min (major enantiomer)).

(−)-(*S*)-*N*-(Cyclopentylphenylmethyl)acetamide (4b). (R=*c*-C_5H_9): Purified by column chromatography (hexane–AcOEt) in 64% yield as a solid. Recrystallization from AcOEt gave optically pure **4b** as colorless cubes of constant mp 145–145.5°C in 27% overall yield. $[\alpha]_D^{25}$=−118 (*c* 2.00, EtOH). ^{1}H NMR ($CDCl_3$, TMS) δ: 1.1–1.2 (1H, m, CH_2), 1.4–1.8 (7H, m, CH_2), 2.25 (1H, m, CH), 1.97 (3H, s, CH_3CO), 4.79 (1H, dd, *J*=9.5, 9.5 Hz, CH), 5.82 (1H, brd, *J*=9.5 Hz, NH), 7.2–7.3 (5H, m, ArH). ^{13}C NMR ($CDCl_3$, TMS) δ: 23.4, 25.21, 25.25, 29.9, 30.2, 45.4, 57.9, 127.0, 127.1, 128.4, 142.6, 169.1. IR (nujol): 1650 cm^{-1}. MS *m/z*: 217 (M^+). Anal. Calcd for $C_{14}H_{19}NO$: C 77.38, H 8.81, N 6.45. Found: C 77.44, H 8.70, N 6.41.

Ee was determined to be over 99% by chiral stationary

phase HPLC analysis (Daicel Chiralpak AS, hexane–*i*-PrOH (10:1), 254 nm, 1 mL/min, 18.3 min (major enantiomer), 30.8 min (minor enantiomer)).

(−)-(*S*)-*N*-(Cyclohexylphenylmethyl)acetamide (4c). (R=*c*-C_6H_{11}):[19] Purified by column chromatography (hexane–AcOEt) in 69% yield as a colorless powder of mp 127°C. $[\alpha]_D^{21}=-75.0$ (*c* 2.14, MeOH). ^{1}H NMR ($CDCl_3$, TMS) δ: 0.9–1.2 (4H, m, CH_2), 1.4–1.5 (1H, m, CH_2), 1.6–1.9 (6H, m, CH_2, CH), 1.99 (3H, s, CH_3CO), 4.77 (1H, dd, *J*=8.6, 8.6 Hz, CH), 5.69 (1H, brd, *J*=8.6 Hz, NH), 7.2–7.3 (5H, m, ArH). ^{13}C NMR ($CDCl_3$, TMS) δ: 23.4, 25.95, 26.02, 26.2, 29.4, 30.1, 43.0, 58.4, 127.0, 128.4, 141.5, 169.2. IR (nujol): 1650 cm^{-1}. MS *m/z*: 231 (M^+). HRMS Calcd for $C_{15}H_{22}NO$ (M^++1): 232.1701. Found: 232.1695.

Ee was determined to be 80% by chiral stationary phase HPLC analysis (Daicel Chiralpak AS, hexane–*i*-PrOH (10:1), 254 nm, 1 mL/min, 15.9 min (major enantiomer), 38.3 min (minor enantiomer)).

(−)-(*S*)-*N*-[(1-Adamantyl)phenylmethyl]acetamide (4d). (R=1-adamantyl): Purified by column chromatography (hexane–AcOEt) in 86% yield as a solid of mp 195–205°C. Recrystallization from benzene gave optically pure **4d** as colorless needles of constant mp 202–203°C in 51% overall yield. $[\alpha]_D^{25}=-28.4$ (*c* 1.60, EtOH). ^{1}H NMR ($CDCl_3$, TMS) δ: 1.4–1.5 (3H, m, CH_2), 1.5–1.7 (9H, m, CH_2), 1.9–2.0 (3H, m, CH), 2.02 (3H, s, CH_3CO), 4.66 (1H, d, *J*=9.5 Hz, CH), 6.02 (1H, brd, *J*=9.5 Hz, NH), 7.1–7.2 (2H, m, ArH), 7.2–7.3 (3H, m, ArH). ^{13}C NMR ($CDCl_3$, TMS) δ: 23.4, 28.1, 36.2, 36.7, 38.8, 62.4, 126.8, 127.6, 128.3, 139.0, 169.5. IR (nujol): 1640 cm^{-1}. MS *m/z*: 283 (M^+). Anal. Calcd for $C_{19}H_{25}NO$: C 80.52, H 8.89, N 4.94. Found: C 80.76, H 8.68, N 4.65.

Ee was determined to be over 99% by chiral stationary phase HPLC analysis (Daicel Chiralpak OD-H, hexane–*i*-PrOH (20:1), 254 nm, 1 mL/min, 12.1 min (minor enantiomer), 27.2 min (major enantiomer)).

Procedure for oxidation of phenyl group to carboxylic group. (−)-(*S*)-*N*-Acetyl-*tert*-leucine (5a). (R=*t*-Bu)[16]: A mixture of **4a** (616 mg, 3.0 mmol, >99% ee), ruthenium trichloride hydrate (38 mg, 0.15 mmol) and periodic acid (13.7 g, 60 mmol) in a mixture of carbon tetrachloride (6 mL), acetonitrile (6 mL) and water (9 mL) was stirred at rt for 2 d. The mixture was extracted with AcOEt. The organic layer was washed with brine and then dried over magnesium sulfate. Concentration followed by recrystallization from aqueous EtOH gave **5a** (276 mg, 53%) as colorless cubes of dp 233–234°C. $[\alpha]_D^{26}=-3.4$ (*c* 2.00, EtOH). ^{1}H NMR (CD_3OD) δ: 1.02 (9H, s, 3×Me), 2.00 (3H, s, CH_3CO), 4.28 (1H, s, CH). ^{13}C NMR (CD_3OD) δ: 22.3, 27.1, 34.7, 62.2, 173.3, 174.2. IR (nujol): 3350, 1700, 1620 cm^{-1}. MS (CI) *m/z*: 174 (M^++1). Anal. Calcd for $C_8H_{15}NO_3$: C 55.47, H 8.73. N 8.09. Found: C 55.47, H 8.43, N 7.83.

(−)-(*S*)-Acetylaminocyclopentylacetic acid (5b). (R=*c*-C_5H_9):[20] Purified by recrystallization from AcOEt in 40% yield as colorless needles of mp 173–175°C. $[\alpha]_D^{25}=-6.1$ (*c* 0.38, EtOH). ^{1}H NMR (DMSO-d_6) δ: 1.3–1.4 (2H, m, CH_2), 1.5–1.7 (6H, m, CH_2), 1.91 (3H, s, CH_3CO), 2.20 (1H, m, CH), 4.15 (1H, dd, *J*=7.9, 7.9 Hz, CH), 8.14 (1H, d, *J*=7.9 Hz, NH), 12.5 (1H, s, CO_2H). ^{13}C NMR (DMSO-d_6) δ: 22.3, 24.5, 24.8, 28.5, 28.7, 41.1, 55.4, 169.3, 173.5. IR (nujol): 1700, 1620 cm^{-1}. MS (CI) *m/z*: 186 (M^++1). HRMS Calcd for $C_9H_{16}NO_3$ (M^++1): 186.1130. Found: 186.1135.

(+)-(*S*)-Acetylaminocyclohexylacetic acid (5c). (R=*c*-C_6H_{11}):[21] Purified by recrystallization from EtOH in 53% yield as colorless needles of constant mp 208–210°C. $[\alpha]_D^{20}=+23.1$ (*c* 1.09, MeOH). ^{1}H NMR (DMSO-d_6) δ: 1.0–1.3 (5H, m, CH_2), 1.6–1.8 (6H, m, CH_2, CH), 1.92 (3H, s, CH_3CO), 4.17 (1H, dd, *J*=6.4, 8.2 Hz, CH), 8.03 (1H, d, *J*=8.2 Hz, NH), 12.5 (1H, brs, CO_2H). ^{13}C NMR (DMSO-d_6) δ: 22.3, 25.5, 25.6, 28.0, 29.2, 56.7, 169.3, 173.1. IR (nujol): 1710, 1620 cm^{-1}. MS (CI) *m/z*: 200 (M^++1). Anal. Calcd for $C_{10}H_{17}NO_3$: C 60.28, H 8.60. N 7.03. Found: C 60.02, H 8.33, N 6.79.

(+)-(*S*)-Acetylaminotricyclo[3.3.1.1^{0,0}]dec-2-ylacetic acid (5d). (R=1-adamantyl): Purified by recrystallization from MeOH in 25% yield as colorless cubes of constant mp 234–240°C. A mixture of 10:7 rotamers by PMR. $[\alpha]_D^{25}=+38.3$ (*c* 1.03, MeOH). ^{1}H NMR (CD_3OD) δ: major rotamer: 1.6–2.3 (15H, m, CH_2), 2.012 (3H, s, Ac), 4.24 (1H, s, CH); minor rotamer: 1.6–2.3 (15H, m, CH_2), 2.006 (3H, s, CH_3CO), 4.14 (1H, s, CH). ^{13}C NMR (CD_3OD) δ: 22.3, 22.4, 29.8, 32.7, 35.7, 36.7, 37.8, 38.0, 38.1, 39.8, 40.8, 62.0, 63.0, 68.7, 173.1, 173.3, 173.7. IR (nujol): 1710, 1655 cm^{-1}. MS (CI) *m/z*: 252 (M^++1). HRMS Calcd for $C_{14}H_{22}NO_3$ (M^++1): 252.1600. Found: 252.1596.

(+)-(*S*)-1-Adamantylglycine hydrochloride.[22] A suspension of **5d** (80 mg, 0.32 mmol, >99% ee) in 7 M aqueous HCl (3 mL) was refluxed for 1 h to give a pale yellow solution. Concentration and recrystallization from MeOH–AcOEt (1:10) gave (+)-(*S*)-1-adamantylglycine hydrochloride (27 mg) in 34% yield as colorless powder of mp 236–241°C. $[\alpha]_D^{25}=+18.0$ (*c* 0.50, MeOH). ^{1}H NMR (D_2O) δ: 1.4–2.2 (15H, m, CH_2, CH), 3.57 (1H, s, CH). IR (nujol): 1740 cm^{-1}. MS (CI) *m/z*: 210 (M^++1). HRMS Calcd for $C_{12}H_{20}NO_2$ (M^++1): 210.1494. Found: 210.1501. Melting point and specific rotation were identical with those reported.

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References

1. For excellent reviews, see: (a) Denmark, S. E.; Nicaise, O. J.-C. *J. Chem. Soc., Chem. Commun.* **1996**, 999–1004. (b) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895–1946. (c) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407–1438. For leading references, see: (a) Itsuno, S.; Yanaka, H.; Hachisuka, C.; Ito, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1341–1342. (b) Katritzky, A. R.; Harris, P. A. *Tetrahedron: Asymmetry* **1992**, *3*, 437–442.

(c) Soai, K.; Hatanaka, T.; Miyazawa, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1097–1098. (d) Ukaji, Y.; Hatanaka, T.; Ahmed, A.; Inomata, K. *Chemistry Lett.* **1993**, 1313–1316. (e) Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C. *J. Am. Chem. Soc.* **1994**, *116*, 8797–8798. (f) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **1996**, *118*, 8489–8490.

2. (a) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 6681–6684. (b) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1991**, *32*, 3095–3098. (c) Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1603–1606. (d) Inoue, I.; Shindo, M.; Koga, K.; Kanai, M.; Tomioka, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2527–2533. (e) Taniyama, D.; Kanai, M.; Iida, A.; Tomioka, K. *Heterocycles* **1997**, *46*, 165–168. (f) Taniyama, D.; Kanai, M.; Iida, A.; Tomioka, K. *Chem. Pharm. Bull. 1997*, *45*, 1705–1707.

3. For 1,4-conjugate addition reactions of organolithiums with α,β-unsaturated imines, see: (a) Shindo, M.; Koga, K.; Tomioka, K. *J. Am. Chem. Soc.* **1992**, *114*, 8732–8733. (b) Shindo, M.; Koga, K.; Tomioka, K. *J. Org. Chem.* **1998**, *63*, 9351–9357.

4. Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron* **1994**, *50*, 4429–4438.

5. (a) Tomioka, K.; Satoh, M.; Taniyama, D.; Kanai, M.; Iida, A. *Heterocycles* **1998**, *47*, 77–80. (b) Taniyama, D.; Hasegawa, M.; Tomioka, K. *Tetrahedron: Asymmetry* **1999**, *10*, 221–223.

6. Efficient use of the phenyl group as the carboxyl synthon in the total synthesis of mugineic acid has been reported. Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1993**, *49*, 8211–8222.

7. *tert*-Leucine has been the target of chemical and enzymatic asymmetric synthesis. (a) Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 1906–1908. (b) Kunz, H.; Pfrengle, W. *Tetrahedron* **1988**, *44*, 5487–5494. (c) Grabley, S.; Keller, R.; Schlingmann, M. EP 0141223, 1987. (d) Steglich, W.; Frauendorfer, E.; Weygand, F. *Chem. Ber.* **1971**, *104*, 687–690.

8. Josien, H.; Lavielle, S.; Brunissen, A.; Saffroy, M.; Torrens, Y.; Beaujouan, J.-C.; Glowinski, J.; Chassaing, G. *J. Med. Chem.* **1994**, *37*, 1586–1601.

9. Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, Wiley: New York, 1995.

10. For excellent reviews, see: (a) Cativiela, C.; Diaz-De-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599. (b) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: New York, 1989.

11. For recent impressive reports on asymmetric synthesis of amino acids, see: (a) Ohtake, H.; Imada, Y.; Murahashi, S. *J. Org. Chem.* **1999**, *64*, 3790–3791. (b) Moody, C. J.; Gallagher, P. T.; Lightfoot, A. P.; Slawin, A. M. Z. *J. Org. Chem.* **1999**, *64*, 4419–4425. (c) Cardillo, G.; Gentilucci, L.; Tolomelli, A.; Tomasini, C. *Tetrahedron* **1999**, *55*, 6231–6242. (d) Davis, F. A.; McCoull, W. *J. Org. Chem.* **1999**, *64*, 3396–3397. (e) Tunge, J. A.; Gately, D. A.; Norton, J. R. *J. Am. Chem. Soc.* **1999**, *121*, 4520–4521. (f) Fondekar, K. Pai; Volk, F.-J.; Frahm, A. W. *Tetrahedron: Asymmetry* **1999**, *10*, 727–735. (g) Camps, P.; Perez, F.; Soldevilla, N.; Borrego, M. A. *Tetrahedron: Asymmetry* **1999**, *10*, 493–509. (h) Jew, S.-S.; Cha, K.-H.; Kang, S.-D.; Woo, Y.-H.; Kim, H.-O.; Park, H.-G. *Heterocycles* **1999**, *50*, 677–680. (i) Cundy, D. J.; Donohue, A. C.; McCarthy, T. D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 559–568. (j) Chinchilla, R.; Galindo, N.; Najera, C. *Synthesis* **1999**, 704–717. (k) Lygo, B. *Tetrahedron Lett.* **1999**, *40*, 1389–1392. Kim, B. J.; Park, Y. S.; Beak, P. *J. Org. Chem.* **1999**, *64*, 1705–1708. (l) Muller, P.; Imogai, H. *Tetrahedron: Asymmetry* **1999**, *9*, 4419–4428. (m) Guillena, G.; Najera, C. *Tetrahedron: Asymmetry* **1999**, *9*, 3935–3938. (n) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12–13. (o) Seebach, D.; Boog, A.; Schweizer, W. B. *Eur. J. Org. Chem.* **1999**, 335–360. (p) Linderman, R. J.; Binet, S.; Petrich, S. R. *J. Org. Chem.* **1999**, *64*, 336–337. (q) Bull, S. D.; Davies, S. G.; O'Shea, M. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3657–3658. (r) O'Donnell, M. J.; Delgado, F.; Hostettler, C.; Schwesinger, R. *Tetrahedron Lett.* **1998**, *39*, 8775–8778. (s) Giraud, L.; Renaud, P. *J. Org. Chem.* **1998**, *63*, 9162–9163. (t) Meyer, L.; Poirier, J.-M.; Duhamel, P.; Duhamel, L. *J. Org. Chem.* **1998**, *63*, 8094–8095.

12. Gittins (née Jones), C. A.; North, M. *Tetrahedron: Asymmetry* **1997**, *8*, 3789–3799.

13. Ee was accurately determined to be 90% by changing chiral column described here instead of 87% reported previously (Ref. [4]).

14. A six-membered mechanism is a possible alternative to the four-centered one, because usually 2 equiv. of phenyllithium was required for completion of the reaction. The six-membered mechanism provides the same prediction of the enantiofacial differentiation.

15. Nuñez, M. T.; Martín, V. S. *J. Org. Chem.* **1990**, *55*, 1928–1932.

16. Barker, J.; Cook, S. L.; Lasterra-Sánchez, M. E.; Thomas, S. E. *J. Chem. Soc., Chem. Commun.* **1992**, 830–832.

17. Bommarius, A. S.; Schwarm, M.; Stingl, K.; Kottenhahn, M.; Huthmacher, K.; Drauz, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2851–2888.

18. The reaction was monitored by tlc. Purification was carried out using silica gel column chromatography unless otherwise noted. ^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) were measured in $CDCl_3$ unless otherwise noted. Chemical shift (δ) was presented in ppm relative to internal tetramethylsilane. Coupling constant value (*J*) was presented in Hz. Mass spectra were measured by EI mode unless otherwise noted.

19. Ghislandi, V.; Vercesi, D. *Il Farmaco-Ed. Sc.* **1971**, *26*, 474–486.

20. Eisler, K.; Rudinger, J.; Sorm, F. *Coll. Czech. Chem. Commun.* **1966**, *31*, 4563–4580.

21. Beller, M.; Eckert, M.; Geissler, H.; Napierski, B.; Rebenstock, H.-P.; Holla, E. W. *Chem. Eur. J.* **1998**, *4*, 935–941.

22. Gálvez, N.; Morena-Mañas, M.; Vallribera, A.; Molins, E.; Cabrero, A. *Tetrahedron Lett.* **1996**, *37*, 6197–6200.