



Diastereoselective arylation of L-proline derivatives at the 5-position

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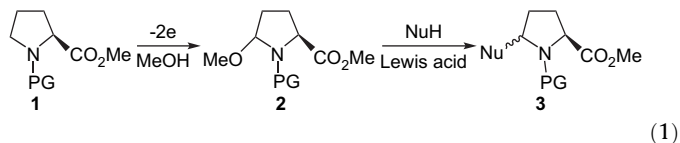
ABSTRACT

Diastereoselective introduction of nucleophiles into L-proline derivatives at the 5-position was achieved with suitable selection of N-protecting group. N-Methoxycarbonylated or benzyloxycarbonylated L-proline derivatives reacted with arene to give cis-arylated products. On the other hand, N-benzyolated L-proline derivative preferentially gave trans-arylated product, which could be easily transformed into optically active C₂-symmetrical pyrrolidine derivative. Such derivative **5** worked well as an organic activator in the asymmetric reduction of aromatic imines by Cl₃SiH.

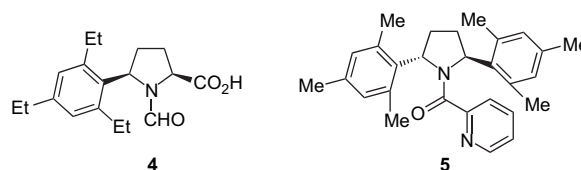
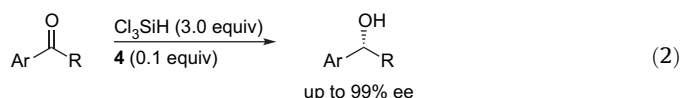
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1. Introduction

Optically active 2,5-disubstituted pyrrolidines are key intermediates for preparation of pharmaceuticals or natural products¹ as well as organocatalysts for asymmetric reactions.² Electrochemical oxidation of L-proline derivatives **1** is a useful tool for their synthesis (Eq. 1).³



Recently, we have reported that cis-5-arylated N-formyl-L-proline **4** worked well as an organic activator in the enantioselective reduction of ketones with Cl₃SiH⁵ in high enantioselectivities (Eq. 2). However, it was difficult to prepare **4** for practical use because diastereoselectivity in arylation reaction of **2a** (PG=CHO) was very low. We wish herein to report diastereoselective introduction of nucleophiles into L-proline derivatives at the 5-position. In addition, synthesis of compound **4** and C₂-symmetrical pyrrolidine derivative **5** derived from cis- and trans-arylated products, and its application to asymmetric reduction of aromatic imines with Cl₃SiH⁶ are presented.



2. Results and discussion

2.1. Diastereoselective introduction of nucleophiles into L-proline derivatives at the 5-position

First, we investigated introduction of trimethylbenzene and triethylbenzene into 5-methoxylated L-proline derivatives **2a–d**⁷ protected with various N-acyl groups in the presence of Lewis acids (Eq. 3). The results are shown in Table 1. N-Formylated proline **2a** gave the corresponding arylated product **3a** as a diastereomeric mixture (cis/trans=43:57, entry 1),⁴ while N-methoxycarbonylated **2b** and N-benzyloxycarbonylated **2c** gave compounds **3b** and **3c** as a single isomer (cis/trans=100:0, entries 2 and 3). In the case of N-benzyolated **2d**, trans-**3d**⁸ was mainly obtained along with small amount of cis-**3d** (cis/trans=11:89, entry 4). Using SnCl₄ instead of TiCl₄ did not affect the diastereoselectivity though the former had relatively poor yield (entry 5). Triethylbenzene as a nucleophile

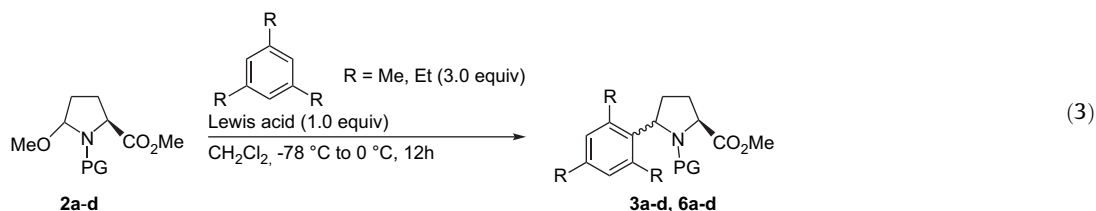
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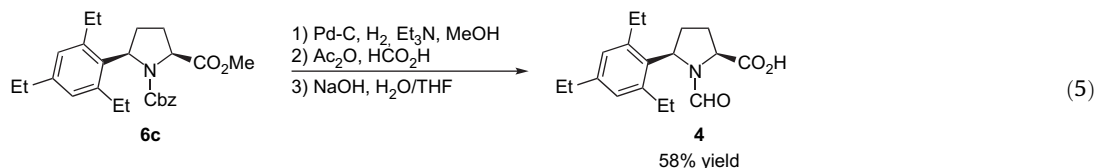
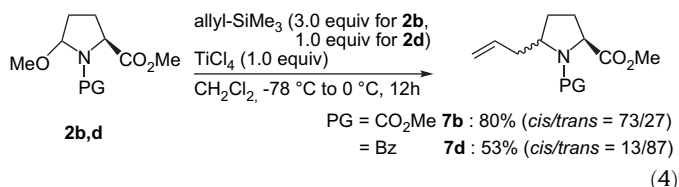
Table 1
Arylation of proline derivative **2a–d** at the 5-position

Entry	PG		Lewis acid	R	Yield (%)	cis/trans	
1	CHO	2a	TiCl ₄	Me	3a	61	43:57
2	CO ₂ Me	2b	TiCl ₄	Me	3b	51	100:0
3	Cbz	2c	TiCl ₄	Me	3c	68	100:0
4	Bz	2d	TiCl ₄	Me	3d	65	11:89
5	Bz	2d	SnCl ₄	Me	3d	43	11:89
6	CHO	2a	SnCl ₄	Et	6a	71	52:48
7	CO ₂ Me	2b	SnCl ₄	Et	6b	55	100:0
8	Cbz	2c	SnCl ₄	Et	6c	36	100:0
9	Cbz	2c	TiCl ₄	Et	6c	31	100:0
10	Bz	2d	SnCl ₄	Et	6d	0	—

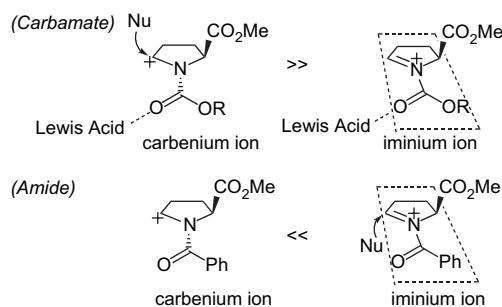
gave similar results to that of trimethylbenzene (entries 6–9), but in the case of *N*-benzoylated proline **2d** did not afford 5-arylated product **6d** (entry 10).



Allylation of 5-methoxylated L-proline derivatives **2b** and **2d** showed similar tendency to their arylation (Eq. 4). That is, *N*-methoxycarbonylated **2b** mainly gave cis-allylated proline **7b** (cis/trans=73:27),^{7c} while *N*-benzoylated proline **2d** preferentially changed into trans-allylated proline **7d** (cis/trans=13:87).⁹



Key intermediates in these reactions are carbenium and iminium ions illustrated in Scheme 1. Since the carbonyl group of carbamates (PG=CO₂Me or Cbz) can coordinate to Lewis acid, carbenium ion will be preferable to iminium ion. On the other hand, carbonyl group of amide (PG=Bz) might not coordinate to Lewis acid. Therefore, the iminium ion will be predominantly generated. The cis-selectivity in the carbenium ion intermediate is illustrated in Scheme 1 (Carbamate) in which PG (CO₂Me or Cbz) is oriented in trans position with respect to 2-CO₂Me substituent. Nucleophiles may approach the intermediate preferentially from the trans direction with respect to PG.^{7c} The trans-selectivity in the iminium ion intermediate is illustrated in Scheme 1 (Amide) in which Bz and iminium groups exist on the same plane. Nucleophiles can approach the intermediate preferentially from the trans direction with respect to 2-CO₂Me substituent.



Scheme 1. Plausible stereochemical course.

2.2. Synthesis of an organic activator **4** and C₂-symmetrical pyrrolidine derivative **5**

An organic activator **4** for the enantioselective reduction of ketones was synthesized from **6c** after hydrogenation, *N*-formylation followed by alkaline hydrolysis in 58% yield (Eq. 5).¹⁰

C₂-symmetrical pyrrolidine derivative **5** was prepared from *N*-benzoylated proline **3d** as follows (Scheme 2): alkaline hydrolysis of **3d** followed by recrystallization from CHCl₃/hexane afforded carboxylic acid **8** in 54% yield as a single isomer (cis/trans=0:100). Electrochemical decarboxylative methoxylation¹¹ of **8** in methanol afforded methoxylated compound **9**, which reacted with mesitylene in the presence of TiCl₄ to exclusively afford

trans-2,5-biarylated pyrrolidine **10** in high yield. By reduction of *N*-benzoyl group of **10**, successive deprotection of *N*-benzyl group of **11**, and *N*-picolonylation of **12**, desired pyrrolidine **5** was obtained in good yield.

2.3. Asymmetric reduction of aromatic imines catalyzed by **5** with Cl₃SiH

Catalytic activation of Cl₃SiH with compound **5** was applicable to asymmetric reduction of aromatic imines **13a–f** (Eq. 6). The results are summarized in Table 2, which also shows the results of asymmetric reduction using **15**^{6c} for comparison. In all cases, compound **5** could play the role of an activator to afford (*S*)-amines **14a–f**⁶ with good yield and enantioselectivity comparable to that of **15** (entries 1–6).

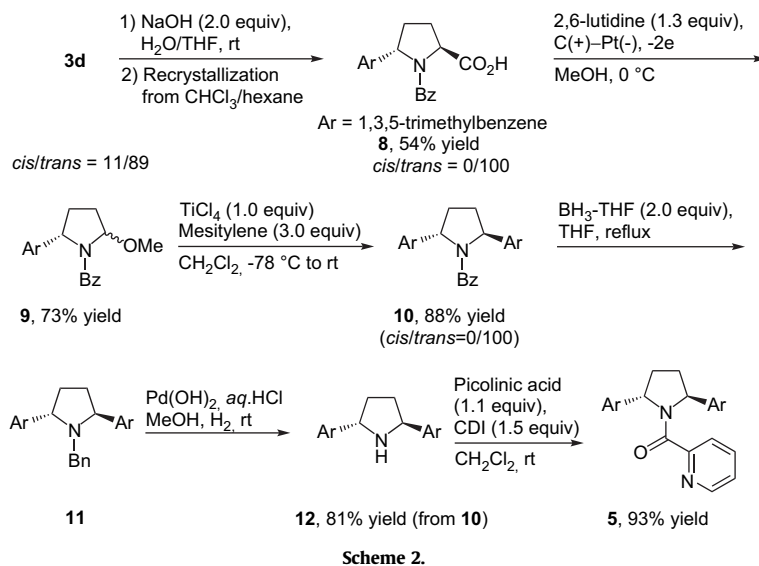
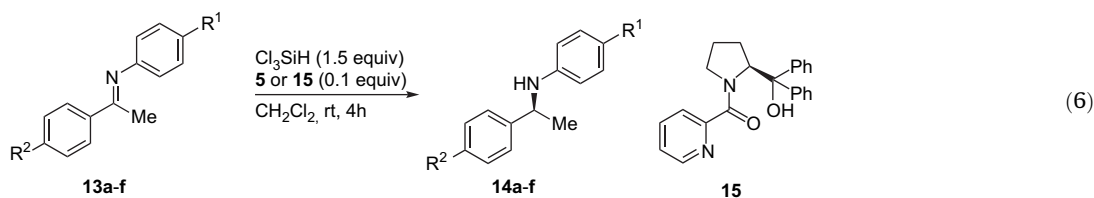


Table 2
 Asymmetric reduction of imines **13a–f**

Entry	Imine	R ¹	R ²	(S)-Amine	Activator 5		Activator 15	
					Yield (%)	ee ^a (%)	Yield (%)	ee ^a (%)
1	13a	H	H	14a	92	77	86	73
2	13b	H	OMe	14b	84	78	90	71
3	13c	OMe	H	14c	87	76	90	75
4	13d	H	Cl	14d	88	73	73	71
5	13e	H	Ac	14e	60	64	24	67
6	13f	H	NO ₂	14f	74	85	84	73

^a Determined by HPLC.



3. Conclusion

We have accomplished diastereoselective introduction of nucleophiles into L-proline derivatives at the 5-position. *N*-Methoxycarbonylated or *N*-benzyloxycarbonylated L-proline **2b** or **2c** was exclusively transformed into *cis*-arylated products **3b,c** or **6b,c**, while *N*-benzoylated L-proline derivative **2d** mainly gave *trans*-arylated product **3d**. C₂-symmetrical pyrrolidine derivative **5** derived from **3d** worked well as an organic activator in the reduction of aromatic imines to the corresponding optically active amines with high enantioselectivity by Cl₃SiH.

4. Experimental section

4.1. General

Electrochemical reactions were carried out using DC Power Supply (GP 050-2) of Takasago Seisakusho, Inc. ¹H NMR spectra were measured on a Varian Gemini 300 and 400 spectrometer with TMS as an internal standard. ¹³C NMR spectra were measured on a Varian Gemini 400 spectrometer with TMS as an internal

standard. IR spectra were obtained on a Shimadzu FTIR-8100A. Mass spectra were obtained on a JEOL JMS-DX 303 instrument. Elemental analyses were performed on Perkin Elmer 2400II.

All reagents and solvents were used as supplied without further purification.

4.2. Methyl *N*-protected 5-methoxy-L-prolinates **2a–d**

N-Protected 5-methoxy-L-prolinates **2a**,^{7c} **2b**,^{7a} **2c**,^{7d} and **2d**^{7b} were known compounds.

4.3. General procedure for arylation or allylation of methyl *N*-protected-5-methoxy-L-prolinate **2a–d**

Under an argon atmosphere, TiCl₄ (55 μL, 0.5 mmol) was added dropwise to the solution of **2a** (109 mg, 0.5 mmol) and 1,3,5-trimethylbenzene (209 μL, 1.5 mmol) in CH₂Cl₂ (5 mL) at –78 °C. The resulting mixture was stirred for 12 h and allowed to stand until it warmed to room temperature. The solution was poured in ice water (10 mL) and extracted with CHCl₃ (10 mL×3). The combined organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt=10:1) to afford **3a** as a colorless oil (93 mg, 61%). Arylation with 1,3,5-triethylbenzene and allylation with allyltrimethylsilane were carried out according to this same procedure.

4.3.1. Methyl *cis*-*N*-formyl-5-(2,4,6-trimethylphenyl)-L-prolinate (*cis*-**3a**)⁴

Colorless oil; ¹H NMR (300 MHz, CDCl₃) δ 7.85 (s, 1H), 6.88 (s, 2H), 5.04 and 5.06 (d, *J*=11.0 Hz, 1H), 4.53 (t, *J*=5.4 Hz, 1H), 3.80 (s, 3H), 2.55–1.95 (m, 13H).

4.3.2. Methyl *trans*-*N*-formyl-5-(2,4,6-trimethylphenyl)-*L*-prolinate (*trans*-**3a**)⁴

Colorless oil; ¹H NMR (300 MHz, CDCl₃) δ 7.81 (s, 1H), 6.85 (s, 2H), 5.37 (t, *J*=8.0 Hz, 1H), 4.56 (t, *J*=7.5 Hz, 1H), 3.75 (s, 3H), 2.42–1.99 (m, 13H).

4.3.3. Methyl *N*-methoxycarbonyl-5-(2,4,6-trimethylphenyl)-*L*-prolinate (**3b**)

Colorless crystal; mp 48–50 °C; [α]_D²⁷ –49.1 (c 1.0, CHCl₃); IR (neat) ν =2953, 1754, 1701, 1612, 1447, 1348, 1198, 1123, 1078, 851, 781 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 6.80 (s, 2H), 5.10 (t, *J*=9.0 Hz, 1H), 4.59–4.51 (m, 1H), 3.78 (s, 3H), 3.55 (s, 3H), 2.44–2.07 (m, 13H); ¹³C NMR (100 MHz, CDCl₃) δ 172.5, 157.1, 135.8, 135.6, 133.1, 130.0, 60.4, 52.6, 51.9, 30.2, 27.9, 20.5; HR-El(+)*m/z* calcd for C₁₇H₂₃NO₄ [M]⁺ 305.1627, found 305.1623.

4.3.4. Methyl *N*-benzyloxycarbonyl-5-(2,4,6-trimethylphenyl)-*L*-prolinate (**3c**)

Colorless oil; [α]_D²⁷ –49.6 (c 1.0, CHCl₃); IR (neat) ν =2960, 1753, 1701, 1456, 1338, 1197, 1174, 1120, 851, 735 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 7.35–7.10 (m, 5H), 6.79 (s, 2H), 5.15–4.90 (m, 3H), 4.63–4.55 (m, 1H), 3.74 (s, 3H), 2.45–2.05 (m, 13H); ¹³C NMR (100 MHz, CDCl₃) δ 172.5, 156.4, 135.8, 135.7, 133.2, 131.3, 130.1, 129.3, 128.2, 127.9, 127.8, 127.4, 127.2, 67.0, 60.4, 52.0, 30.4, 27.8, 20.6, 20.5; HR-El(+)*m/z* calcd for C₂₃H₂₇NO₄ [M]⁺ 381.1940, found 381.1938.

4.3.5. Methyl *trans*-*N*-benzoyl-5-(2,4,6-trimethylphenyl)-*L*-prolinate (**3d**)

Colorless crystal; mp 112–114 °C; [α]_D¹⁸ –133.5 (c 1.0, CHCl₃); IR (neat) ν =2953, 1755, 1745, 1659, 1641, 1632, 1580, 1444, 1414, 1279, 1202, 1175, 1127, 1028, 853 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) (cis/trans=11:89) δ 7.50–7.00 (m, 5H), 6.80 (br s, 0.11H), 6.64 (s, 0.89H), 6.60 (br s, 0.11H), 6.39 (s, 0.89H), 5.64 (t, *J*=8.7 Hz, 0.11H), 5.40 (t, *J*=8.7 Hz, 0.89H), 4.77 (t, *J*=9.0 Hz, 1H), 3.83–3.76 (m, 3H), 2.58–1.95 (m, 13H); ¹³C NMR (100 MHz, CDCl₃) δ 170.8, 169.5, 134.3, 133.3, 132.1, 129.6, 127.2, 127.0, 125.4, 123.5, 59.3, 58.0, 50.3, 30.4, 26.8, 18.4, 18.3; HR-El(+)*m/z* calcd for C₂₂H₂₅NO₃ [M]⁺ 351.1834, found 351.1832. HPLC: Daicel Chiralcel OJ-H column, *n*-hexane/isopropanol=20:1, wavelength: 254 nm, flow rate: 1.0 ml/min, retention time: 19.1 min (*cis*-**3d**), 23.3 min (*trans*-**3d**).

4.3.6. Methyl *cis*-*N*-formyl-5-(2,4,6-triethylphenyl)-*L*-prolinate (*cis*-**6a**)⁴

Colorless oil; ¹H NMR (300 MHz, CDCl₃) δ 7.87 (s, 1H), 7.10–6.82 (br s, 2H), 5.03 and 5.01 (d, *J*=12.0 Hz, 1H), 4.58–4.50 (m, 1H), 3.80 (s, 3H), 2.95–2.05 (m, 10H), 1.30–1.10 (m, 9H).

4.3.7. Methyl *trans*-*N*-formyl-5-(2,4,6-triethylphenyl)-*L*-prolinate (*trans*-**6a**)⁴

Colorless oil; ¹H NMR (300 MHz, CDCl₃) δ 7.79 (s, 1H), 6.99 (s, 1H), 6.88 (s, 1H), 5.34 and 5.33 (d, *J*=9.9 Hz, 1H), 4.62 (t, *J*=7.8 Hz, 1H), 3.80 (s, 3H), 2.74 (q, *J*=7.8 Hz, 2H), 2.65–2.40 (m, 5H), 2.38–2.01 (m, 3H), 1.30–1.10 (m, 9H).

4.3.8. Methyl *trans*-*N*-methoxycarbonyl-5-(2,4,6-triethylphenyl)-*L*-prolinate (**6b**)

Colorless oil; [α]_D²⁸ –41.3 (c 1.1, CHCl₃); IR (neat) ν =2963, 1755, 1709, 1445, 1348, 1198, 1150, 1125, 1080, 874, 781 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 6.86 (m, 2H), 5.10 (t, *J*=8.7 Hz, 1H), 4.60–4.50 (m, 1H), 3.80–3.50 (m, 6H), 2.80–2.11 (m, 10H), 1.30–1.10 (m, 9H); ¹³C NMR (100 MHz, CDCl₃) (a mixture of rotamers) δ 172.8, 157.1, 142.5, 142.1, 141.9, 141.7, 132.0, 127.0, 125.5, 60.5, 59.8, 52.1, 51.8, 32.6, 28.2, 28.0, 26.5, 25.6, 24.9, 24.7, 15.9, 15.5, 15.4, 15.2,

14.8; HR-El(+)*m/z* calcd for C₂₀H₂₉NO₄ [M]⁺ 347.2097, found 347.2081.

4.3.9. Methyl *trans*-*N*-benzyloxycarbonyl-5-(2,4,6-triethylphenyl)-*L*-prolinate (**6c**)

Colorless oil; [α]_D²⁸ –42.3 (c 1.0, CHCl₃); IR (neat) ν =2965, 1755, 1705, 1408, 1339, 1198, 1175, 1080, 696 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 7.40–6.80 (m, 7H), 5.20–4.80 (m, 3H), 4.60–4.50 (m, 1H), 3.77 (s, 3H), 3.10–1.95 (m, 10H), 1.32–0.86 (m, 9H); ¹³C NMR (100 MHz, CDCl₃) (a mixture of rotamers) δ 172.6, 156.7, 142.4, 142.3, 142.1, 135.7, 132.3, 128.1, 127.9, 127.7, 127.4, 126.5, 67.0, 61.0, 60.8, 59.9, 57.7, 52.2, 52.1, 33.3, 32.7, 28.9, 28.2, 27.8, 27.5, 27.1, 26.3, 25.1, 25.0, 24.8, 15.9, 15.7, 15.4, 15.3, 15.2; HR-El(+)*m/z* calcd for C₂₆H₃₃NO₄ [M]⁺ 423.2410, found 423.2394.

4.3.10. Methyl *N*-methoxycarbonyl-5-allyl-*L*-prolinate (**7b**)^{7c}

¹H NMR (400 MHz, CDCl₃) (cis/trans=73:27) δ 5.83–5.65 (m, 1H), 5.12–5.03 (m, 2H), 4.40–4.27 (m, 1H), 4.15–3.91 (m, 1H), 3.77–3.63 (m, 6H), 2.80–2.42 (m, 1H), 2.25–1.72 (m, 5H).

4.3.11. Methyl *N*-benzoyl-5-allyl-*L*-prolinate (**7d**)

Colorless oil; [α]_D²⁰ –26.9 (c 1.0 CHCl₃); IR (neat) ν =2977, 2953, 1750, 1644, 1603, 1446, 1410, 1277, 1203, 1174, 1076 cm^{–1}; ¹H NMR (400 MHz, CDCl₃) (cis/trans=13:87) δ 7.53–7.28 (m, 5H), 5.97–5.80 (m, 0.5H), 5.55–5.38 (m, 0.5H), 5.16–4.72 (m, 2H), 4.44–4.17 (m, 1H), 3.96 (br s, 0.5H), 3.77–3.60 (m, 3H), 3.06 (br s, 0.5H), 2.23–1.18 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) (cis/trans=13:87, a mixture of rotamers) δ 173.0, 171.5, 134.7, 133.5, 129.7, 128.3, 128.2, 126.7, 126.5, 118.1, 117.6, 62.1, 59.6, 59.3, 58.9, 52.2, 39.1, 38.4, 37.7, 28.9, 28.5, 26.8; HR-FAB(+)*m/z* calcd for C₁₆H₂₀NO₃ [M+H]⁺ 274.1443, found 274.1444.

4.4. Synthesis of *cis*-*N*-formyl-5-(2,4,6-triethylphenyl)-*L*-proline (**4**)

Pd–C (5%, 30 mg) was added to the solution of **6c** (2.0 mmol, 847 mg) and triethylamine (279 μ L, 2.0 mmol) in MeOH (5.0 mL). The mixture was then stirred under 1 atm of H₂ for 12 h. Upon completion of reaction, the mixture was then filtered through Celite and solvent was removed in vacuo to obtain methyl *cis*-5-(2,4,6-triethylphenyl)-*L*-prolinate, which was used for next reaction without further purification. Colorless oil; [α]_D²⁸ +13.4 (c 1.1, CHCl₃); IR (neat) ν =3350, 2963, 1734, 1458, 1210, 874, 669 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 6.89 (s, 2H), 4.57 (t, *J*=8.7 Hz, 1H), 3.87 (t, *J*=7.8 Hz, 1H), 3.76 (s, 3H), 2.90–2.50 (m, 6H), 2.35–2.00 (m, 4H), 1.78 (br s, 1H), 1.23 (t, *J*=7.5 Hz, 9H); HR-El(+)*m/z* calcd for C₁₈H₂₇NO₂ [M]⁺ 289.2042, found 289.2027.

Under an argon atmosphere, acetic anhydride (2.0 mL) was added dropwise to a solution of methyl *cis*-5-(2,4,6-triethylphenyl)-*L*-prolinate in formic acid (6.0 mL) and stirred at room temperature for 9 h. Upon completion of reaction, the solvent was removed under reduced pressure, then the residue was purified by silica gel column chromatography (*n*-hexane/AcOEt=3:1) to afford methyl *cis*-*N*-formyl-5-(2,4,6-triethylphenyl)-*L*-prolinate⁴ as a colorless crystals (372 mg, 58% for two steps). Then, aqueous 1 M NaOH (2.0 mL) was added to the stirred solution of methyl *cis*-*N*-formyl-5-(2,4,6-triethylphenyl)-*L*-prolinate (1.0 mmol, 317 mg) in MeOH (4.0 mL), and the solution was stirred at room temperature for 12 h. The solution was neutralized with 3% aqueous HCl, and then MeOH was evaporated. The residue was diluted with brine, extracted with AcOEt, and dried over MgSO₄. Removal of the solvent afforded compound **4**⁴ (303 mg, quant.) as colorless crystals. Mp 132–133 °C; [α]_D²⁵ –135.5 (c 0.5, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.96 (s, 1H), 6.98 (s, 1H), 6.89 (s, 1H), 5.21 and 5.19 (d, *J*=11.0 Hz, 1H), 4.75 (q, *J*=9.3 Hz, 1H), 2.90 and 2.88 (d, *J*=10 Hz, 1H), 2.85–2.05 (m, 9H), 1.30–1.10 (m, 9H).

4.5. Synthesis of *N*-picolinoyl (2*S*,5*S*)-[2,5-bis-(2,4,6-trimethylphenyl)]pyrrolidine (5)

4.5.1. *trans*-*N*-Benzoyl-5-(2,4,6-trimethylphenyl)-*L*-proline (8)

NaOH (12.9 mmol, 516 mg) was added to the stirred solution of **3d** (6.5 mmol, 2.27 g) in THF/H₂O=1:1 (60 mL), and the solution was stirred at room temperature for 4 h. The solution was then neutralized with 10% aqueous HCl, and extracted with AcOEt (150 mL×3), and dried over MgSO₄. After removal of the solvent and recrystallization from CHCl₃/hexane, compound **8** was obtained as colorless crystals (1.27 g, 58%). Mp 204–207 °C; $[\alpha]_D^{25}$ –82.3 (c 0.3, CHCl₃); IR (neat) ν =3640, 1727, 1642, 1620, 1445, 1354, 1123 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 7.20–7.00 (m, 5H), 6.66 (s, 1H), 6.41 (s, 1H), 5.38 (t, *J*=8.4 Hz, 1H), 4.83 (t, *J*=7.8 Hz, 1H), 4.20 (br s, 1H), 2.58–1.90 (m, 13H); ¹³C NMR (100 MHz, CDCl₃) (a mixture of rotamers) δ 176.1, 171.4, 136.2, 136.0, 135.7, 135.1, 134.5, 134.1, 134.0, 131.2, 130.2, 129.2, 128.9, 128.1, 127.6, 127.4, 125.6, 63.1, 61.4, 60.3, 59.4, 32.3, 31.0, 29.9, 28.6, 20.6, 20.4, 20.3; HR-El(+) *m/z* calcd for C₂₁H₂₃NO₃ [M]⁺ 337.1678, found 337.1674. EA calcd for C₂₁H₂₃NO₃: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.41; H, 6.92; N, 3.93.

4.5.2. *N*-Benzoyl-2-methoxy-(5*S*)-(2,4,6-trimethylphenyl)-pyrrolidine (9)

Anodic oxidation of **8** was carried out using graphite cathode (10 cm×5 cm) and platinum anode (12 cm×5 cm) in an undivided beaker-type cell. **8** (29.4 mmol, 9.9 g), and 2,6-lutidine (38.2 mmol, 4.5 mL) was added into MeOH (200 mL). After passing through 2.0 F/mol of electricity at constant voltage (18 V) at 0 °C, MeOH was evaporated, then the residue was poured in water, and extracted with AcOEt (200 mL×3). The combined organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt=3:1) to afford **9** (6.9 g, 73% yield) as colorless oil. $[\alpha]_D^{25}$ +17.8 (c 1.0, CHCl₃); IR (neat) ν =2732, 1765, 1727, 1692, 1642, 1613, 1582, 1547, 1503, 1468 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 7.83 (br s, 2H), 7.37 (br s, 3H), 6.77 (s, 2H), 5.23 (br s, 1H), 4.72 (br s, 1H), 3.14 (s, 3H), 2.60–2.03 (m, 13H); ¹³C NMR (100 MHz, CDCl₃) (a mixture of diastereomers and rotamers) δ 171.3, 169.2, 135.8, 133.8, 133.4, 132.6, 132.0, 130.7, 129.7, 129.5, 127.8, 126.5, 125.9, 125.6, 125.2, 123.2, 92.7, 90.0, 60.2, 58.1, 54.5, 31.5, 31.1, 30.6, 28.6, 20.6, 20.5; HR-El(+) *m/z* calcd for C₂₁H₂₅NO₂ [M]⁺ 323.1885, found 323.1866.

4.5.3. *N*-Benzoyl-(2*S*,5*S*)-[2,5-bis-(2,4,6-trimethylphenyl)]-pyrrolidine (10)

Under an argon atmosphere, TiCl₄ (140 μ L, 1.0 mmol) was added dropwise to the solution of **9** (313 mg, 0.97 mmol) and 1,3,5-trimethylbenzene (400 μ L, 2.9 mmol) in CH₂Cl₂ (10 mL) at –78 °C. The resulting mixture was stirred for 24 h and allowed to stand until it warmed to room temperature. The solution was poured in ice water (10 mL) and extracted with CHCl₃ (10 mL×3). The combined organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt=10:1) to afford **10** (351 mg, 88%) as colorless crystals. Mp 184–187 °C; $[\alpha]_D^{25}$ +24.9 (c 0.5, CHCl₃); IR (neat) ν =2963, 1738, 1632, 1580, 1483, 1408, 1348, 1240, 1102, 849, 795 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 7.20–7.00 (m, 5H), 6.85 (s, 1H), 6.81 (s, 1H), 6.60 (s, 1H), 6.35 (s, 1H), 5.65–5.59 (m, 2H), 2.61–2.20 (m, 22H); ¹³C NMR (100 MHz, CDCl₃) (a mixture of rotamers) δ 169.7, 137.3, 136.8, 136.0, 135.8, 134.9, 134.6, 134.5, 133.6, 131.2, 131.0, 129.3, 129.2, 128.8, 127.1, 126.2, 60.3, 60.0, 32.4, 30.2, 21.2, 20.7, 20.6, 20.4, 20.1; HR-El(+) *m/z* calcd for C₂₉H₃₃NO [M]⁺ 411.2562, found 411.2560. HPLC: Daicel Chiralcel OD-H column, *n*-hexane/ethanol=30:1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 8.9 min for (2*R*,5*R*)-**10**, 11.9 min for

(2*S*,5*S*)-**10**. EA calcd for C₂₉H₃₃NO: C, 84.63; H, 8.08; N, 3.40. Found: C, 84.43; H, 8.15; N, 3.02.

4.5.4. *N*-Benzyl-(2*S*,5*S*)-[2,5-bis-(2,4,6-trimethylphenyl)]-pyrrolidine (11)

BH₃/THF (1.03 M, 17.4 mL, 18.0 mmol) was added to the solution of **10** (3.6 g, 8.7 mmol) in THF (70 mL) and refluxed at 80 °C for 17 h. The solution was poured in water (100 mL) and extracted with AcOEt (100 mL×3). The combined organic layer was dried over MgSO₄ and the solvent removed in vacuo to obtain **11** (3.45 g, quant.), which was used for next reaction without further purification. Colorless crystal; mp 109–110 °C; $[\alpha]_D^{25}$ –124.5 (c 1.0, CHCl₃); IR (neat) ν =2947, 1611, 1480, 1372, 1312, 1213, 1188, 1165, 1105, 1075, 1028, 851, 741, 700 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 7.00–6.89 (m, 3H), 6.78 (s, 2H), 6.63 (s, 2H), 6.38 (dd, *J*=2.1, 7.8 Hz, 2H), 4.95 (t, *J*=7.2 Hz, 2H), 3.37 (q, *J*=12.9 Hz, 2H), 2.41–2.11 (m, 22H); ¹³C NMR (100 MHz, CDCl₃) δ 140.9, 138.8, 136.9, 136.3, 135.8, 131.2, 129.5, 129.2, 127.3, 125.9, 60.9, 51.7, 31.0, 21.5, 20.9; HR-El(+) *m/z* calcd for C₂₉H₃₅N [M]⁺ 397.2769, found 397.2766.

4.5.5. (2*S*,5*S*)-[2,5-Bis-(2,4,6-trimethylphenyl)]pyrrolidine (12)

Pd(OH)₂ (20%, 80 mg, 0.12 mmol) was added to the solution of **11** (228 mg, 0.57 mmol) and three drops of concentrated aqueous HCl in MeOH (5.0 mL). The mixture was then stirred under 1 atm of H₂ for 3 h. Upon completion of reaction, the mixture was then filtered through Celite and solvent was removed in vacuo. The residue was poured into saturated aqueous NaHCO₃ (10 mL) and extracted with CHCl₃ (20 mL×3). The combined organic layer was dried over MgSO₄ and the solvent removed in vacuo to afford **12** (142 mg, 81% from **10**), which was used for next reaction without further purification. Colorless oil; $[\alpha]_D^{25}$ –107.1 (c 0.5, CHCl₃); IR (neat) ν =2951, 1611, 1462, 1084, 849 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 6.81 (s, 4H), 5.04 (t, *J*=7.2 Hz, 2H), 2.46 (s, 12H), 2.23 (s, 6H), 2.13–2.08 (m, 4H), 1.68 (br s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 134.8, 134.2, 133.5, 128.2, 56.4, 31.0, 18.7, 18.6; HR-El(+) *m/z* calcd for C₂₂H₂₉N [M]⁺ 307.2300, found 307.2281.

4.5.6. *N*-Picolinoyl-(2*S*,5*S*)-[2,5-bis-(2,4,6-trimethylphenyl)]-pyrrolidine (5)

A solution of picolinic acid (68.9 mg, 0.55 mmol) and CDI (122 mg, 0.75 mmol) in CH₂Cl₂ (2.5 mL) was stirred at 0 °C for 30 min. Then, a solution of **12** (153 mg, 0.50 mmol) in CH₂Cl₂ (2.5 mL) was added at 0 °C, and the mixture was stirred at room temperature for 24 h. The solution was poured into saturated aqueous NaHCO₃ (10 mL) and extracted with AcOEt (20 mL×3). The combined organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt=5:1) to afford **5** (192 mg, 93% yield) as colorless crystals. Mp 73–74 °C; $[\alpha]_D^{25}$ +6.8 (c 0.3, CHCl₃); IR (neat) ν =2963, 1738, 1639, 1503, 1443, 1408, 1356, 1287, 1242, 1183, 1107, 851 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 8.30 (d, *J*=4.2 Hz, 1H), 7.32–7.26 (m, 2H), 6.91 (t, *J*=4.8 Hz, 1H), 6.85 (s, 1H), 6.79 (s, 1H), 6.53 (s, 1H), 6.40 (s, 1H), 6.03 (t, *J*=7.2 Hz, 1H), 5.67 (t, *J*=7.2 Hz, 1H), 2.63–2.02 (m, 22H); ¹³C NMR (100 MHz, CDCl₃) (a mixture of rotamers) δ 167.1, 154.4, 146.7, 136.1, 135.9, 135.7, 135.5, 135.4, 134.6, 134.5, 133.9, 131.1, 130.7, 129.0, 128.6, 123.7, 122.5, 60.0, 59.8, 32.2, 29.9, 21.0, 20.6, 20.5, 20.3, 19.9; HR-El(+) *m/z* calcd for C₂₈H₃₂N₂O [M]⁺ 412.2515, found 412.2506. EA calcd for C₂₈H₃₂N₂O: C, 81.51; H, 7.82; N, 6.79. Found: C, 81.21; H, 7.84; N, 6.54.

4.6. General procedure for asymmetric reduction of imines **13a–f**

Cl₃SiH (0.45 mmol) was added into a solution of imine **13a** (0.3 mmol) and compound **5** (0.03 mmol) in CH₂Cl₂ (1.5 mL), and the mixture was stirred at room temperature for 4 h. The mixture

was then poured into saturated aqueous NaHCO₃ (10 mL) and extracted with CHCl₃ (10 mL×3). The combined organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography to afford amine **14a** (159 mg, 77% yield).

4.6.1. (S)-N-Phenyl-N-(1-phenylethyl)amine (**14a**)^{6b}

HPLC: Daicel Chiralcel OD-H column, *n*-hexane/isopropanol/diethylamine=10:1:0.01, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 7.2 min for (S)-**14a**, 8.6 min for (R)-**14a**.

4.6.2. (S)-N-[1-(4-Methoxyphenyl)ethyl]-N-phenylamine (**14b**)^{6b}

HPLC: Daicel Chiralcel OD-H column, *n*-hexane/isopropanol=99:1, wavelength: 254 nm, flow rate: 0.7 mL/min, retention time: 13.1 min for (S)-**14b**, 14.4 min for (R)-**14b**.

4.6.3. (S)-N-(4-Methoxyphenyl)-N-(1-phenylethyl)amine (**14c**)^{6b}

HPLC: Daicel Chiralcel OD-H column, *n*-hexane/isopropanol=99:1, wavelength: 254 nm, flow rate: 0.7 mL/min, retention time: 17.5 min for (S)-**14c**, 19.3 min for (R)-**14c**.

4.6.4. (S)-N-[1-(4-Chlorophenyl)ethyl]-N-phenylamine (**14d**)^{6c}

HPLC: Daicel Chiralcel OD-H column, *n*-hexane/isopropanol=95:5, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 9.0 min for (S)-**14d**, 10.8 min for (R)-**14d**.

4.6.5. (S)-N-[1-(4-Acetylphenyl)ethyl]-N-phenylamine (**14e**)

Pale yellow oil; $[\alpha]_D^{25}$ –18.8 (c 0.7, CHCl₃); IR (neat) ν =3390, 3054, 2980, 2926, 2869, 1678, 1603, 1506, 1429, 1360, 1320, 1269, 1210, 1181, 1144, 1015, 1015, 959 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 7.92 (d, *J*=8.7 Hz, 2H), 7.47 (d, *J*=8.7 Hz, 2H), 7.08 (t, *J*=6.9 Hz, 2H), 6.65 (t, *J*=6.3 Hz, 1H), 6.47 (d, *J*=7.8 Hz, 2H), 4.53 (q, *J*=8.2 Hz, 1H), 4.08 (br s, 1H), 2.58 (s, 3H), 1.53 (d, *J*=6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 197.7, 151.0, 146.8, 136.0, 129.2, 129.1, 128.9, 126.0, 113.2, 53.4, 26.6, 24.9; HR-ESI(+) *m/z* calcd for C₁₆H₁₇NO [M]⁺ 239.1310, found 239.1287. HPLC: Daicel Chiralcel OD-H column, *n*-hexane/isopropanol=5:1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 11.1 min for (S)-**14e**, 13.2 min for (R)-**14e**.

4.6.6. (S)-N-[1-(4-Nitrophenyl)ethyl]-N-phenylamine (**14f**)^{6b}

HPLC: Daicel Chiralcel OD-H column, *n*-hexane/isopropanol=95:5, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 33.5 min for (S)-**14f**, 38.0 min for (R)-**14f**.

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References and notes

- (a) Pichon, M.; Figadère, B. *Tetrahedron: Asymmetry* **1996**, 7, 927–964; (b) Brenneman, J. B.; Machauer, R.; Martin, S. F. *Tetrahedron* **2004**, 60, 7301–7314; (c) Esseveldt, B. C. J.; Vervoort, P. W. H.; van Delft, F. L.; Rutjes, P. J. T. J. *Org. Chem.* **2005**, 70, 1791–1795; (d) Davis, F. A.; Song, M.; Augustine, A. J. *Org. Chem.* **2005**, 71, 2779–2786.
- (a) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. J. *Am. Chem. Soc.* **2004**, 126, 4790–4791; (b) Simonini, V.; Benaglia, M.; Pignataro, L.; Guizzetti, S.; Celentano, G. *Synlett* **2008**, 1061–1065.
- (a) Shono, T.; Matsumura, Y.; Tsubata, K. J. *Am. Chem. Soc.* **1981**, 103, 1172–1176; (b) Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K. J. *Org. Chem.* **1986**, 51, 2590–2592; (c) Dhiman, H.; Vanucci-Bacqué, C.; Hamon, L.; Lhommet, G. *Eur. J. Org. Chem.* **1998**, 9, 1955–1963; (d) Kim, S.; Hayashi, K.; Kitano, Y.; Tada, M.; Chiba, K. *Org. Lett.* **2002**, 4, 3735–3737; (e) Onomura, O.; Ishida, Y.; Maki, T.; Minato, D.; Demizu, Y.; Matsumura, Y. *Electrochemistry* **2006**, 74, 645–648.
- Matsumura, Y.; Ogura, K.; Kouchi, Y.; Iwasaki, F.; Onomura, O. *Org. Lett.* **2006**, 8, 3789–3792.
- Iwasaki, F.; Onomura, O.; Mishima, K.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **1999**, 40, 7507–7511.
- (a) Iwasaki, F.; Onomura, O.; Mishima, K.; Kanematsu, T.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **2001**, 42, 2525–2527; (b) Malkov, A. V.; Mariani, A.; MacDougall, K. N.; Kočovský, P. *Org. Lett.* **2004**, 6, 2253–2266; (c) Onomura, O.; Kouchi, Y.; Iwasaki, F.; Matsumura, Y. *Tetrahedron Lett.* **2006**, 47, 3751–3754; (d) Malkov, A. V.; Stewart Liddon, A. J. P.; Ramirez-López, P.; Bendová, L.; Haigh, D.; Kočovský, P. *Angew. Chem., Int. Ed.* **2006**, 45, 1432–1435; (e) Wang, Z.; Wei, S.; Wang, C.; Sun, J. *Tetrahedron: Asymmetry* **2007**, 18, 705–709.
- (a) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.; Kanazawa, T.; Aoki, T. J. *Am. Chem. Soc.* **1982**, 104, 6697–6703; (b) Shono, T.; Matsumura, Y.; Kanazawa, T.; Habuka, M.; Uchida, K.; Toyoda, K. J. *Chem. Res., Synop.* **1984**, 320–321; *J. Chem. Res., Miniprint* **1984**, 2873–2889; (c) Shono, T.; Fujita, T.; Matsumura, Y. *Chem. Lett.* **1991**, 81–84; (d) Célime, C.; Dhiman, H.; Lhommet, G. *Tetrahedron* **1998**, 54, 10457–10468.
- Stereoconfiguration of **trans-3d** was determined by the X-ray analysis. Crystallographic data for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 686483. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK; fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.
- After hydrogenation of **7d**, its stereoconfiguration was determined by comparison with authentic sample, see: Cossy, J.; Cécile, D.; Pardo, D. G. *Synlett* **1997**, 905–906.
- Deprotection of **6b** with Me₃SiI led to epimerization at the 5-position.
- (a) Iwasaki, T.; Horikawa, H.; Matsumoto, K.; Miyoshi, M. J. *Org. Chem.* **1979**, 44, 1552–1554; (b) Matsumura, Y.; Wanyoike, G. N.; Onomura, O.; Maki, T. *Electrochim. Acta* **2003**, 48, 2957–2966.