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

Osamu Onomura,* Peter G. Kirira, Toshimitsu Tanaka, Shinsuke Tsukada, Yoshihiro Matsumura, Yosuke Demizu

Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan

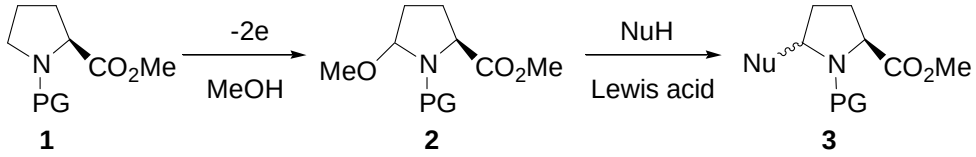
Abstract- Diastereoselective introduction of nucleophiles into L-proline derivatives at the 5-position was achieved with suitable selection of *N*-protecting group. *N*-Methoxycarbonylated or benzyloxycarbonylated L-proline derivatives reacted with arene to give *cis*-arylated products. On the other hand, *N*-benzoylated L-proline derivative preferentially gave *trans*-arylated product which could be easily transformed into optically active C_2-symmetrical pyrrolidine derivative. Such derivative **5**, worked well as an organic activator in the asymmetric reduction of aromatic imines by Cl_3SiH.

Keywords: Diastereoselective; Organocatalysis; Asymmetric reduction of imines; C_2-Symmetrical pyrrolidine; Proline derivative

1. Introduction

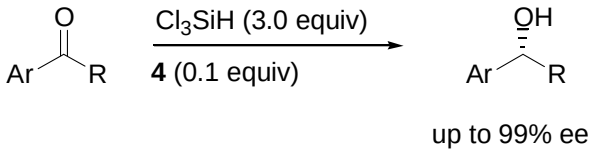
Optically active 2,5-disubstituted pyrrolidines are key intermediates for preparation of pharmaceuticals or natural products[1] as well as organocatalysts for asymmetric reactions.[2] Electrochemical oxidation of L-proline derivatives **1** is a useful tool for their synthesis (Eq. 1).[3]

*Corresponding author, Tel +81-95-819-2429, Fax +81-95-819-2476, E-mail: onomura@nagasaki-u.ac.jp

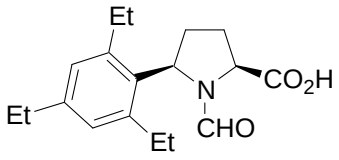


(1)

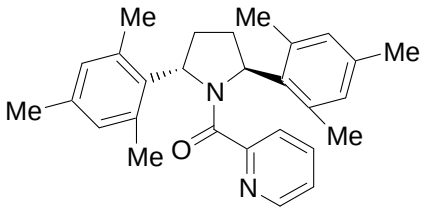
Recently, we have reported that *cis*-5-arylated *N*-formyl-L-proline **4**[4] worked well as an organic activator in the enantioselective reduction of ketones with Cl_3SiH[5] in high enantioselectivities (Eq. 2). However, it was difficult to prepare **4** for practical use because diastereoselectivity 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 C_2-symmetrical pyrrolidine derivative **5** derived from *cis*- and *trans*-arylated products, and its application to asymmetric reduction of aromatic imines with Cl_3SiH[6] are presented.



(2)



4



5

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 diastereomer 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*-benzoylated **2d**, *trans*-**3d**[8] was mainly obtained along with small amount of *cis*-**3d** (*cis*/*trans* = 11/89, entry 4). Using $SnCl_4$ instead of $TiCl_4$ did not affect the diastereoselectivity though the former had relatively poor yield (entry 5). Triethylbenzene as a nucleophile 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).

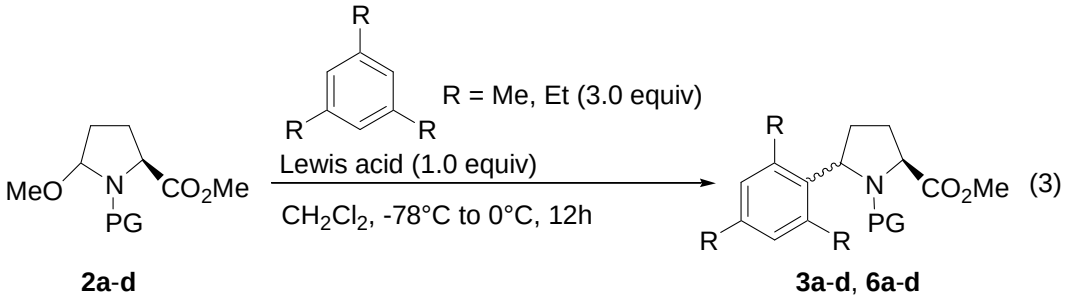
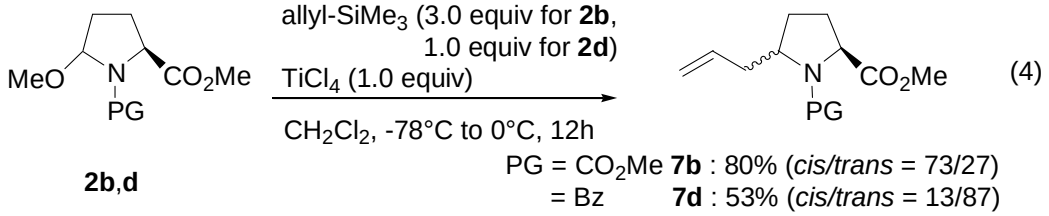


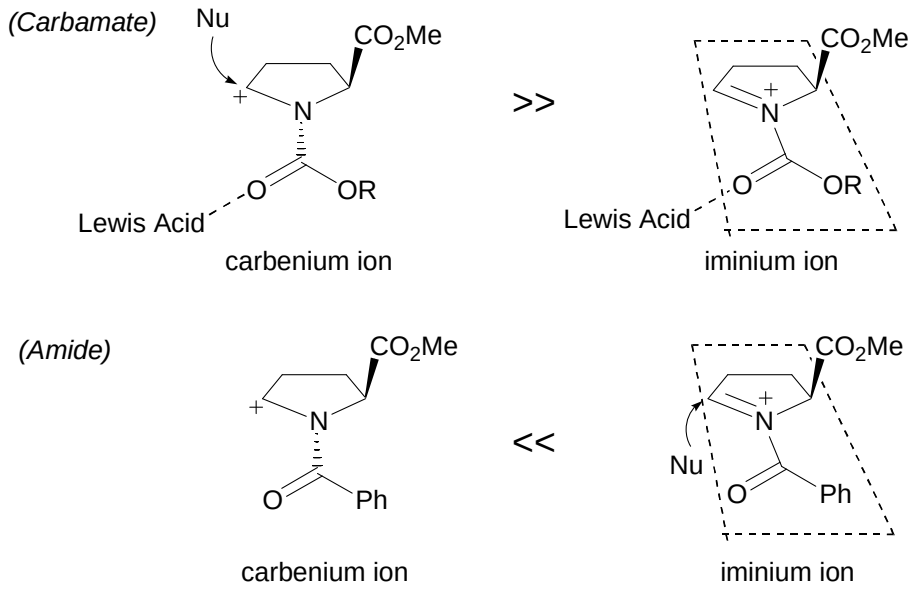
Table 1. Arylation of proline derivative **2a-d** at the 5-position

Entry	PG		Lewis acid	R	Yield (%)	*cis*/*trans*
1	CHO	**2a**	$TiCl_4$	Me	**3a** 61	43/57
2	CO_2Me	**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_2Me	**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	-

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]



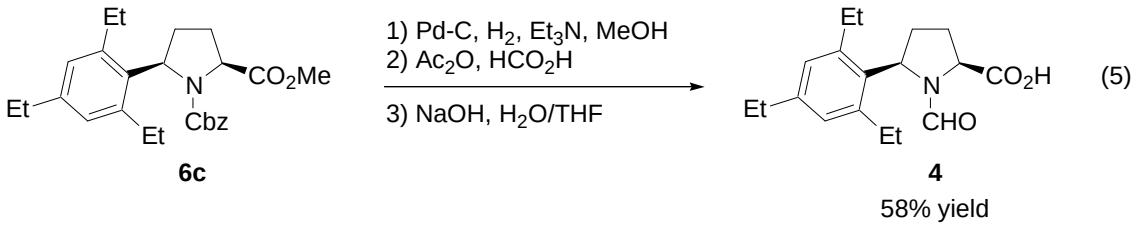
Key intermediates in these reactions are carbenium and iminium ions illustrated in Scheme 1. Since the carbonyl group of carbamates (PG= CO_2Me or Cbz) can coordinate to Lewis acid, carbenium ion will be preferable to iminium ion. On the other hand, carbonyl group of amide (PG=Bz) might not coordinate 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 (CO_2Me or Cbz) is oriented in *trans* position with respect to 2-CO_2Me substituent. Nucleophiles may approach the intermediate preferentially from the *trans* direction with respect to PG.[7c] The *trans*-selectivity (PG=Bz) 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-CO_2Me substituent.



Scheme 1. Plausible stereochemical course.

*2.2. Synthesis of an organic activator **4** and C_2-symmetrical pyrrolidine derivative **5***

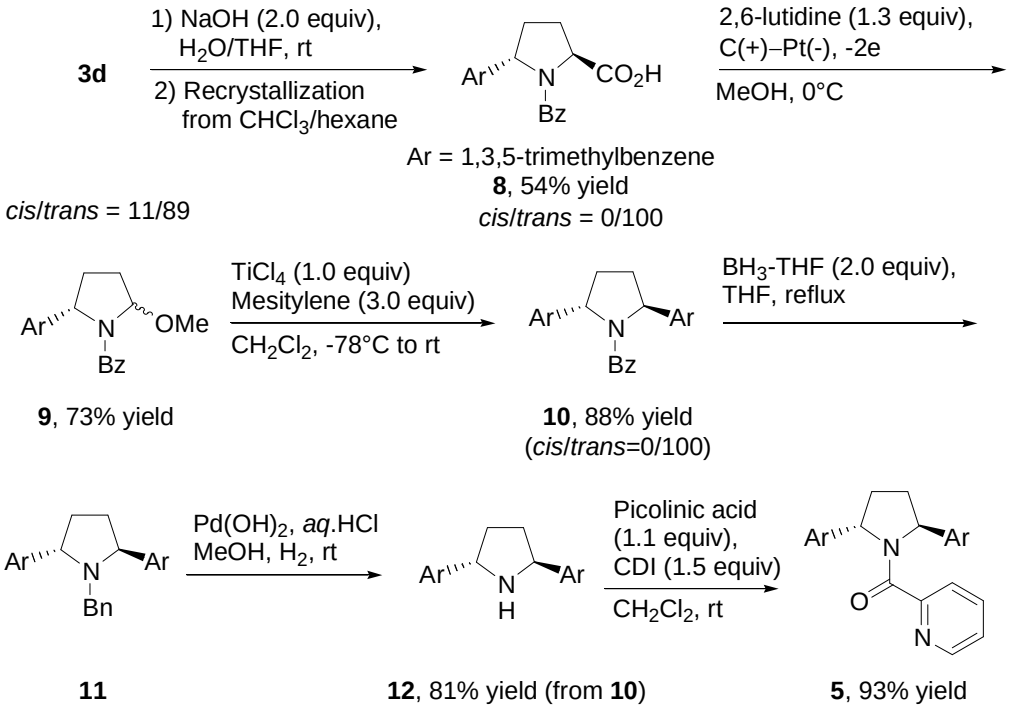
An organic activator **4** for the enantioselective reduction of ketones was synthesized from **6c** after hydrogenation, *N*-formylation followed by alkaline hydrolysis in 58% yield (Eq. 5).[10]



(5)

C_2-Symmetrical pyrrolidine derivative **5** was prepared from *N*-benzoylated proline **3d** as follows (Scheme 2); Alkaline hydrolysis of **3d** followed by recrystallization from $CHCl_3$/hexane afforded carboxylic acid **8** in 54% yield as a single isomer (*cis*/*trans* = 0/100). Electrochemical decarboxylative methoxylation[11] of **8** in methanol afforded methoxylated compound **9**, which reacted with mesitylene in the presence of $TiCl_4$ to

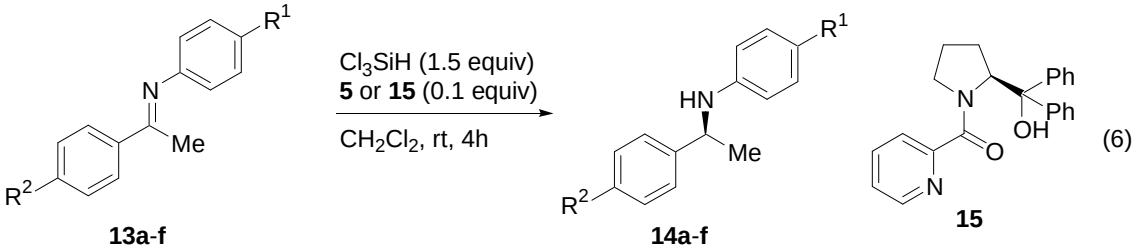
exclusively afford *trans*-2,5-biarylated pyrrolidine **10** in high yield. By reduction of *N*-benzoyl group of **10**, successive deprotection of *N*-benzyl group of **11**, and *N*-picolynoylation of **12**, desired pyrrolidine **5** was obtained in enough yield.



Scheme 2

*2.3. Asymmetric reduction of aromatic imines catalyzed by **5** with Cl_3SiH*

Catalytic activation of Cl_3SiH 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 just like that of **15** (entries 1-6).



(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** were exclusively transformed into *cis*-arylated products **3b**,**c** or **6b**,**c**, while *N*-benzoylated L-proline derivative **2d** mainly gave *trans*-arylated product **3d**. C_2-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 Cl_3SiH.

4. Experimental Section

4.1. General

Electrochemical reactions were carried out using DC Power Supply (GP 050-2) of Takasago Seisakusho, Inc. ^{1}H NMR spectra were measured on a Varian Gemini 300 and 400 spectrometer with TMS as an internal standard. ^{13}C 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-prolinate ***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, $TiCl_4$ (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 CH_2Cl_2 (5 mL) at -78^{o}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 $CHCl_3$ (10 mL x 3). The combined organic layer was dried over $MgSO_4$ 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; ^{1}H NMR (300 MHz, $CDCl_3$) 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; ^{1}H NMR (300 MHz, $CDCl_3$) 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^{o}C; $[\alpha]^{27}_{D}$ -49.1 (*c*=1.0, $CHCl_3$); IR (neat) ν = 2953, 1754, 1701, 1612, 1447, 1348, 1198, 1123, 1078, 851, 781 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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-EI(+) *m/z* calcd for $C_{17}H_{23}NO_4$ $[M]^+$ 305.1627, found 305.1623.

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

Colorless oil; $[\alpha]_D$ ^{27} -49.6 (*c*=1.0, $CHCl_3$); IR (neat) ν = 2960, 1753, 1701, 1456, 1338, 1197, 1174, 1120, 851, 735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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-EI(+) *m/z* calcd for $C_{23}H_{27}NO_4$ $[M]^+$ 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 ^{o}C; $[\alpha]_D^{18}$-133.5 (*c*=1.0, $CHCl_3$); IR (neat) ν = 2953, 1755, 1745, 1659, 1641, 1632, 1580, 1444, 1414, 1279, 1202, 1175, 1127, 1028, 853 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) (*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); ^{13}C NMR (100 MHz, $CDCl_3$) 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-EI(+) *m/z* calcd for $C_{22}H_{25}NO_3$ $[M]^+$ 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; ^{1}H NMR (300 MHz, $CDCl_3$) 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; ^{1}H NMR (300 MHz, $CDCl_3$) 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; $[\alpha]_D^{28}$ -41.3 (*c*=1.1, $CHCl_3$); IR (neat) ν = 2963, 1755, 1709, 1445, 1348, 1198, 1150, 1125, 1080, 874, 781 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) (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-EI(+) *m/z* calcd for $C_{20}H_{29}NO_4$ $[M]^+$ 347.2097, found 347.2081.

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

Colorless oil; $[\alpha]_D^{28}$ -42.3 (*c*=1.0, $CHCl_3$); IR (neat) ν = 2965, 1755, 1705, 1408, 1339, 1198, 1175, 1080, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) (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-EI(+) *m/z* calcd for $C_{26}H_{33}NO_4$ $[M]^+$ 423.2410, found 423.2394.

*4.3.10. Methyl N-methoxycarbonyl-5-allyl-L-prolinate (**7b**)*[7c]

^{1}H NMR (400 MHz, $CDCl_3$) (*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; $[\alpha]_D^{20}$ -26.9 (*c*=1.0 $CHCl_3$); IR (neat) ν = 2977, 2953, 1750, 1644, 1603, 1446, 1410, 1277, 1203, 1174, 1076 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (*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); ^{13}C NMR (100 MHz, $CDCl_3$) (*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 $C_{16}H_{20}NO_3$ $[M+H]^+$ 274.1443 found 274.1444.

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

5% Pd-C (30 mg) was added to the solution of **6c** (2.0 mmol, 847 mg) and triethylamine (279 μL, 2.0 mmol) in MeOH (5.0 mL). The mixture was then stirred under 1 atm of H_2 for 12 h. Upon completion of reaction the mixture was then filtered through celite and solvent 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; $[\alpha]^{28}_D$ +13.4 (*c*=1.1, $CHCl_3$); IR (neat) ν = 3350, 2963, 1734, 1458, 1210, 874, 669 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 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-EI(+) *m/z* calcd for $C_{18}H_{27}NO_2$ $[M]^+$ 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-prolinate[4] as a colorless crystal (372 mg, 58 % for 2 steps). Then, aqueous 1M 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 $MgSO_4$. Removal of the solvent afforded compound **4**[4] (303 mg, quant.) as colorless crystals. Mp 132-133 ^oC; $[\alpha]_D^{25}$ -135.5 (*c*=0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 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 (2S,5S)-[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/H_2O = 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 x 3), and dried over $MgSO_4$. After removal of the solvent and recrystallization from $CHCl_3$/hexane, compound **8** was obtained as colorless crystals (1.27 g, 58%). Mp 204-207^{o}C; $[\alpha]_D^{19}$ -82.3 (*c*=0.3, $CHCl_3$), IR (neat) ν = 3640, 1727, 1642, 1620, 1445, 1354, 1123 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (100MHz, $CDCl_3$) (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; EA calcd for $C_{21}H_{23}NO_3$: C 74.75, H 6.87, N 4.15: found C 74.41, H 6.92, N 3.93; HR-EI(+) *m/z* calcd for $C_{21}H_{23}NO_3$ $[M]^+$ 337.1678, found 337.1674.

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

Anodic oxidation of **8** was carried out using graphite cathode (10 cm x 5 cm) and platinum anode (12 cm x 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) were 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 x 3). The combined organic layer was dried over $MgSO_4$ and 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. $[\alpha]_D^{24}$ +17.8 (*c*=1.0, $CHCl_3$); IR (neat) ν = 2732, 1765, 1727, 1692, 1642, 1613, 1582, 1547, 1503, 1468 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) (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-EI(+) *m/z* calcd for $C_{21}H_{25}NO_2$ $[M]^+$ 323.1885, found 323.1866.

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

Under an argon atmosphere, $TiCl_4$ (140 μL, 1.0 mmol) was added dropwise to the solution of **9** (313 mg, 0.97 mmol) and 1,3,5-trimethylbenzene (400 μL, 2.9 mmol) in CH_2Cl_2 (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 $CHCl_3$ (10 mL x 3). The combined organic layer was dried over

$MgSO_4$ 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; $[\alpha]_D^{22}$ +24.9 (*c*=0.5, $CHCl_3$); IR (neat) ν = 2963, 1738, 1632, 1580, 1483, 1408, 1348, 1240, 1102, 849, 795 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) (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; EA calcd for $C_{29}H_{33}NO$: C 84.63, H 8.08, N 3.40: found C 84.43, H 8.15, N 3.02; HR-EI(+) *m/z* calcd for $C_{29}H_{33}NO$ $[M]^+$ 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**.

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

1.03 M BH_3-THF (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 x 3). The combined organic layer was dried over $MgSO_4$ and 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; $[\alpha]_D^{23}$ -124.5 (*c*=1.0, $CHCl_3$); IR (neat) ν = 2947, 1611, 1480, 1372, 1312, 1213, 1188, 1165, 1105, 1075, 1028, 851, 741, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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-EI(+) *m/z* calcd for $C_{29}H_{35}N$ $[M]^+$ 397.2769, found 397.2766.

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

20% $Pd(OH)_2$ (80 mg, 0.12 mmol) was added to the solution of **11** (228 mg, 0.57 mmol) and 3 drops of concentrated aqueous HCl in MeOH (5.0 mL). The mixture was then stirred under 1 atm of H_2 for 3 h. Upon completion of reaction the mixture was then filtered through celite and solvent removed in vacuo. The residue was poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with $CHCl_3$ (20 mL x 3). The combined organic layer was dried over $MgSO_4$ and solvent removed in vacuo to afford **12** (142 mg, 81% from **10**), which was used for next reaction without further purification. Colorless oil; $[\alpha]_D^{22}$ -107.1 (*c*=0.5, $CHCl_3$); IR (neat) ν = 2951, 1611, 1462, 1084, 849 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8, 134.2, 133.5, 128.2, 56.4, 31.0, 18.7, 18.6; HR-EI(+) *m/z* calcd for $C_{22}H_{29}N$ $[M]^+$ 307.2300, found 307.2281.

*4.5.6. N-Picolinoyl-(2S,5S)-[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 CH_2Cl_2 (2.5 mL) was stirred at 0°C for 30 min. Then, a solution of **12** (153 mg, 0.50 mmol) in CH_2Cl_2 (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 $NaHCO_3$ (10 mL) and extracted with AcOEt (20 mL x 3). The combined organic layer was dried over $MgSO_4$ and 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; $[\alpha]_D^{20}$ +6.8 (*c*=0.3, $CHCl_3$), IR (neat) 2963, 1738, 1639, 1503, 1443, 1408, 1356, 1287, 1242, 1183, 1107, 851 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) (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; EA calcd for $C_{28}H_{32}N_2O$: C 81.51, H 7.82, N 6.79: found C 81.21, H 7.84, N 6.54; HR-EI(+) *m/z* calcd for $C_{28}H_{32}N_2O$ $[M]^+$ 412.2515, found 412.2506.

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

Cl_3SiH (0.45 mmol) was added into a solution of imines **13a** (0.3 mmol) and compound **5** (0.03 mmol) in CH_2Cl_2 (1.5 mL), and the mixture was stirred at room temperature for 4 h. The mixture was then poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with $CHCl_3$ (10 mL x 3). The combined organic layer was dried over $MgSO_4$ and 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-Methoxylphenyl)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. (**14c**) (S)-N-(4-Methoxylphenyl)-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*)-**12c**, 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*)-**12d**, 10.8 min for (*R*)-**14d**.

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

Pale yellow oil; $[\alpha]_D^{27}$ -18.8 (*c*=0.7, $CHCl_3$), IR (neat) 3390, 3054, 2980, 2926, 2869, 1678, 1603, 1506, 1429, 1360, 1320, 1269, 1210, 1181, 1144, 1015, 1015, 959 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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-EI(+) *m/z* calcd for $C_{16}H_{17}NO$ $[M]^+$ 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**.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research (C) (19550109) from Japan Society for the Promotion of Science, and a Grant-in-Aid for Young Scientists (B) (19790017) from the Ministry of Education, Science, Sports and Culture, Japan.

References and notes

1. (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.
2. (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.
3. (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) Dhimane, 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.

4. Matsumura, Y.; Ogura, K.; Kouchi, Y.; Iwasaki, F.; Onomura, O. *Org. Lett.* **2006**, *8*, 3789-3792.
5. Iwasaki, F.; Onomura, O.; Mishima, K.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **1999**, *40*, 7507-7511.
6. (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.; Ramírez-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.
7. (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. (S).* **1984**, 320-321; *J. Chem. Res. (M).* **1984**, 2873-2889. (c) Shono, T.; Fujita, T.; Matsumura, Y. *Chem. Lett.* **1991**, 81-84. (d) Célimène, C.; Dhimane, H.; Lhommet, G. *Tetrahedron* **1998**, *54*, 10457-10468.
8. 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.

9. 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.
10. Deprotection of **6b** with Me_3SiI led to epimerization at the 5-position.
11. (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.