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C_2-SYMMETRIC PYRROLIDINE-BASED CHIRAL AMMONIUM SALTS AS A PHASE-TRANSFER CATALYST

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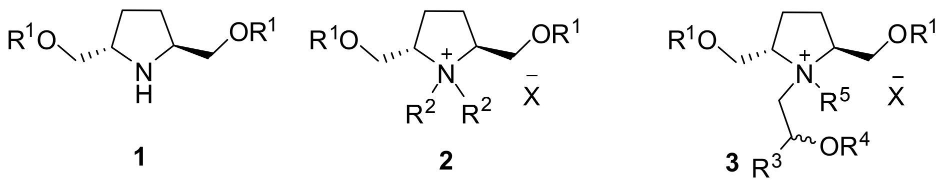
Abstract – Chiral pyrrolidinium salts having substituents at the α, α' positions were synthesized to develop a chiral phase-transfer catalyst which have more simplified structure. The catalytic function of these synthesized catalysts was evaluated using asymmetric benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester, and α,α'-disubstituded pyrrolidinium salts having an alkyl chain with a hydroxyl group at a chiral center were found to afford moderate enantioselectivity.

Phase-transfer catalytic asymmetric reaction has been extensively investigated in the last two decades, because it is operationally simple, environmentally benign, and carried out under mild conditions.[1] Since Dolling and co-workers reported an enantioselective alkylation of active methylene compounds with cinchona alkaloid-derived phase-transfer catalyst (PTC) in 1984,[2] numerous novel PTCs and the asymmetric reaction using a PTC have been reported.[3] Among the catalysts developed, *N*-spiroquaternary ammonium salts, which are derived from 1,1'-binaphthol, and cinchona alkaloid-derived ammonium salts are major ones. We have been investigating asymmetric reaction with PTC and reported several new reactions.[4] PTC used in the reactions, however, is expensive and required many steps to be synthesized. Thus we next studied on the development of a PTC which has a simple structure. In this paper we describe the synthesis of chiral pyrrolidine-based quaternary ammonium salts[5] and its evaluation for PTC.

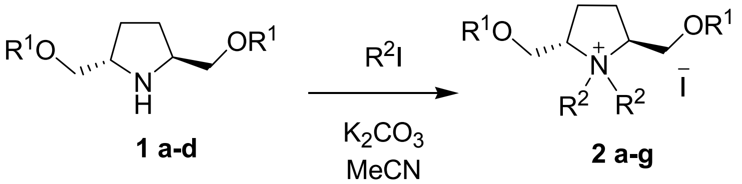
The chiral PTC investigated were α,α'-disubstituted pyrrolidinium salts with stereogenic centers that are adjacent to the quaternary ammonium nitrogen (Figure 1). α,α'-Disubstituted pyrrolidines **1**, the precursors of the quaternary ammonium salts, were prepared according to a literature[6] method from adipic



1 **2** **3**

Figure 1

acid, and both of the enantiomers could be prepared. The chiral pyrrolidinium salts **2** were prepared by the alkylation of **1** with some kinds of alkyl halides in the presence of K_2CO_3 (Table 1).



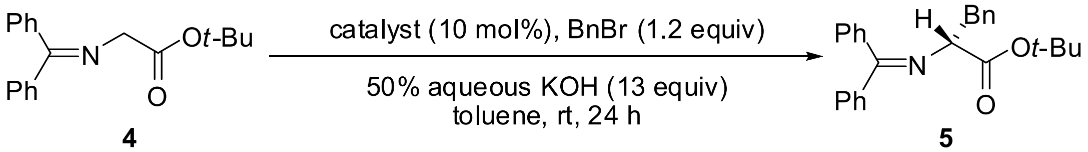
1 a-d **2 a-g**

a: R^1= Me
b: R^1= Pr
c: R^1= Bn
d: R^1= TBS

Table 1

	compound **2**		yield of **2**
	R^1	R^2	(%)
a	Me	Me	39
b	Me	allyl	90
c	Me	Bu	16
d	Me	hexyl	11
e	Pr	Me	87
f	Bn	Me	74
g	TBS	Me	88

Catalytic activities of the obtained quaternary ammonium salts were evaluated in the asymmetric benzylation of glycinate Sciff base **4** (Table 2). Although the synthesized pyrrolidinium salts were



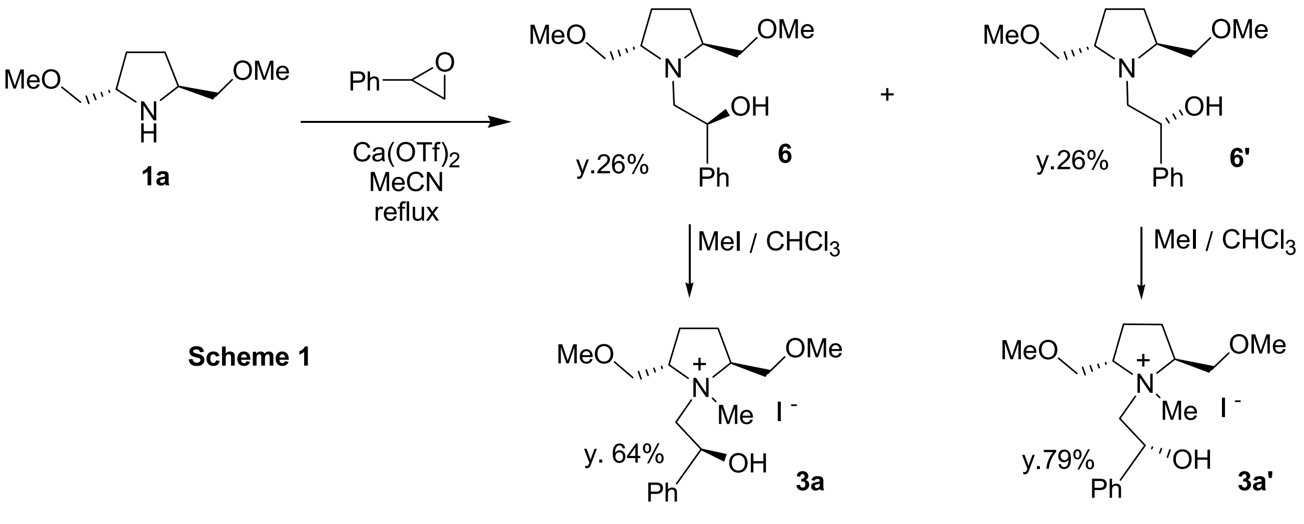
4 **5**

Table 2. Benzylation of glycine Schiff base **4** using catalyst **2a-g**.

Entry	Catalyst	R^1	R^2	Yield (%)[a]	Ee (%)[b]
1	**2a**	Me	Me	25	24
2	**2b**	Me	ally	31	14
3	**2c**	Me	Bu	46	21
4	**2d**	Me	hexyl	51	11
5	**2e**	Pr	Me	44	0
6	**2f**	Bn	Me	43	2
7	**2g**	TBS	Me	41	11

[a] Determined by ^{1}H NMR using mesitylene as an internal standard.

[b] Determined by HPLC analysis using a chiralcel OJ-H after hydrolysis of **5.**



Scheme 1

found to exhibit catalytic activity, the reaction was slow with low enantioselectivity. The results showed that more lipophilic derivatives gave better yield, but less selectivity. Thus, it was considered that another chiral element and functional group which can interact with the substrate were necessary to improve the enantioselectivity. We then attempted to introduce a hydroxyl group to the alkyl chain at β-position of ammonium nitrogen to produce the third chiral center. Pyrrolidine **1** was allowed to react with styrene oxide in the presence of $Ca(OTf)_2$[7] to give tertiary amine **6** as a mixture of diastereomer. They were separated by a column chromatography, and then alkylated with methyl iodide to give

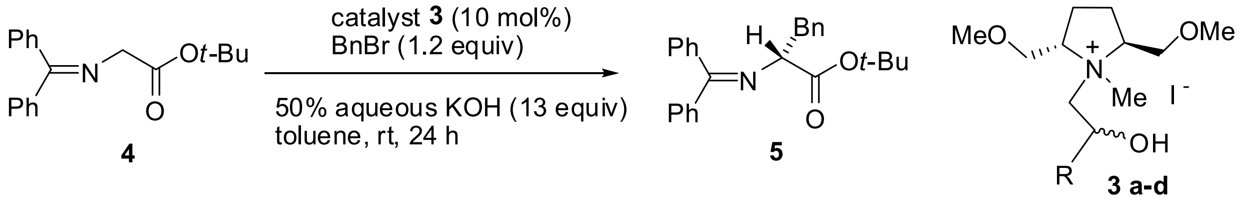


Table 3. Benzylation of glycine Schiff base **4** using catalyst **3a-d**.

Entry	Catalyst	R	Temp.	Yield (%)[a]	Ee (%)[b]
1	**3a**	phenyl	rt	42	22
2	**3a**	phenyl	0 °C	36	46
3	**3a'**	phenyl	rt	44	4
4	**3a'**	phenyl	0 °C	28	3
5	**3b**	butyl	rt	61	8
6	**3b**	butyl	0 °C	55	16
7	**3c**	*p*-fluorophenyl	rt	49	16
8	**3c**	*p*-fluorophenyl	0 °C	20	26
9	**3d**	2-naphthyl	rt	40	24
10	**3d**	2-naphthyl	0 °C	26	28

[a] Determined by ^1H NMR using mesitylene as an internal standard.

[b] Determined by HPLC analysis using a chiralcel OJ-H after hydrolysis of **5**.

quaternary ammonium salts **3a** and **3a'** (Scheme 1). The absolute configuration of the obtained ammonium salts at the chiral center having hydroxyl group were correlated by comparison of the NMR data with that of ammonium salt synthesized by the reaction with (*S*)-styrene oxide. The other pyrrolidinium salts **3b-d** were prepared in the same way, and their activity as a chiral catalyst was examined (Table 3). Among the newly synthesized catalysts, **3a** gave moderate enantioselectivity in the reaction of glycine imine **4** with benzyl bromide at 0 ºC (Table 3, entry 2). When the epimer of **3a** at the chiral center bearing hydroxyl group (**3a'**) was used as a catalyst, the enantioselectivity became low.

We next investigated the counter anion effect of catalyst **3a** on the present reaction (Table 4). Catalysts **3aa** and **3ab** were synthesized by the reaction of **6** with Meerwein reagent and methyl trifluoromethanesulfonate respectively. When tetrafluoroborate catalyst **3aa** with a hard counter anion was used, the reaction was accelerated to raise the yield up to 66%.

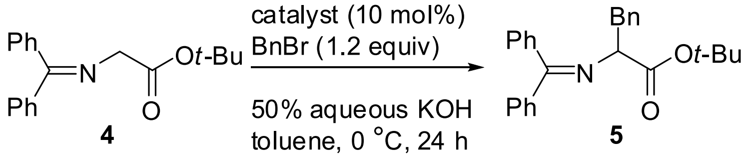


Table 4

Entry	Catalyst	Counter anion	Yield(%)[a]	Ee(%)[b]
1	**3a**	I^-	36	46
2	**3aa**	BF_4^-	66	41
3	**3ab**	TfO^-	30	36

[a] Determined by ^1H NMR using mesitylene as an internal standard.

[b] Determined by HPLC analysis using a chiralcel OJ-H after hydrolysis of **5**.

In Figure 2, a plausible ion pair model of matched case is shown. Our results and previously reported ion pair model[8] suggest that more stable (*E*)-enolate forms ion pair with PTC by both ionic and hydrogen bonding interaction. Benzyl bromide is thought to preferentially approach from sterically less hindered *Re* face of the enolate to give the product having *R* configuration.

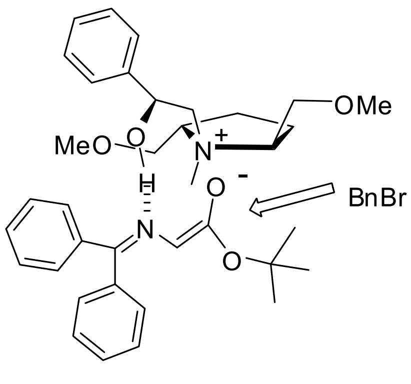


Figure 2

In conclusion, we have synthesized quaternary ammonium salts that have C_2 symmetric pyrrolidine skeleton and as a whole simple structure compared to the chiral PTCs reported so far. These ammonium salts were shown to act as a PTC in the alkylation of glycinate imine and afford moderate yield and enantioselectivity. The results claimed that it might be possible to develop much simpler PTCs compared to conventional ones in the future. These possibilities have been studied in our laboratory.

EXPERIMENTAL

General. Unless otherwise specified, reagents were purchased from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a 500 MHz (125 MHz for ^{13}C) or a 400 MHz (100 MHz for ^{13}C) spectrometer. All melting points are uncorrected. TLC was carried out on a Merck Kieselgel 60 PF 254 or Fuji silysia NH-TLC. Column chromatography was performed using Merck Kieselgel 60 (0.063–0.200 mm) or Fuji silysia NH silica gel (Chromatorex, 100-210 mesh).

Starting material

(2*S*,5*S*)-Bismethoxymethylpyrrolidine (**1a**) was prepared according to a reported procedure.[6]

Synthesis of 2, 5-bis(alkoxymethyl)pyrrolidine 1b-d.

(2*S*,5*S*)-2,5-Bis(propoxymethyl)pyrrolidine (1b).

To a solution of (2*S*,5*S*)-2,5-bis(hydroxymethyl)-1-((*S*)-1-phenylethyl)pyrrolidine[6] (30 mg, 0.13 mmol) in THF (1.5 mL) was added NaH in oil (60%) (26 mg, 0.65 mmol), and the solution was stirred for 30 min at rt under Ar atmosphere. Then allyl iodide (58 µL, 0.64 mmol) was added, and the mixture was stirred for 3 h at rt. After water (4.0 mL) was added, the mixture was extracted with CH_2Cl_2 (12 mL x 3). The combined extracts were dried over anhydrous $MgSO_4$, and concentrated by evaporation. The residue was purified by column chromatography on silica gel (AcOEt: hexane = 1: 3 as eluent) to give (2*S*,5*S*)-2,5-bis(allyloxymethyl)-1-((*S*)-1-phenylethyl)pyrrolidine (35 mg, 0.11 mmol) in 85% yield. Thus prepared (2*S*,5*S*)-2,5-bis(allyloxymethyl)-1-((*S*)-1-phenylethyl)pyrrolidine (240 mg, 0.76 mmol) was dissolved in MeOH (8.0 mL) and $Pd(OH)_2$ (81 mg, 0.08 mmol) was added. The mixture was stirred under H_2 atmosphere for 20h at rt and filtered. The filtrate was evaporated to give **1b** (162 mg, 0.75 mmol) in 99% yield: a colorless oil; ^{1}H-NMR ($CDCl_3$) δ 0.91 (6H, t, *J* = 7.2 Hz), 1.41-1.46 (2H, m), 1.58 (4H, sxt, *J* = 7.2 Hz), 1.85-1.98 (2H, m), 2.40 (1H, bs), 3.28-3.45 (10H, m); ^{13}C-NMR ($CDCl_3$) δ 10.1, 22.4, 27.4, 56.4, 72.4, 73.8; HR-FAB MS: Calcd for $C_{12}H_{26}NO_2$ $[M+H]^+$: 216.1964, Found 216.1948.

(2*S*,5*S*)-2,5-Bis(benzyloxymethyl)pyrrolidine (1c).

To a solution of (2*S*,5*S*)-*N*-boc-2,5-bis(hydroxymethyl)pyrrolidine[9] (45 mg, 0.19 mmol) in THF (2.0 mL) was added NaH in oil (60%) (39 mg, 0.97 mmol), and the solution was stirred for 30 min at rt. Then benzyl bromide (120 µL, 0.97 mmol) and TBAI (7.0 mg, 0.02 mmol) were added, and the mixtue was stirred for 16 h at rt under Ar atmosphere. After water (4.0 mL) was added, the mixture was extracted with CH_2Cl_2 (12 mL x 3). The combined extracts were dried over anhydrous $MgSO_4$, and concentrated by evaporation. The residue was purified by column chromatography on silica gel (AcOEt: hexane = 1: 5 as eluent) to give (2*S*,5*S*)-*N*-benzyl-2,5-bis(benzyloxymethyl)pyrrolidine (52 mg, 0.13 mmol) in 68% yield. Thus obtained (2*S*,5*S*)-*N*-benzyl-2,5-bis(benzyloxymethyl)pyrrolidine (52 mg, 0.13 mmol) was dissolved in MeOH (1.5 mL) and $Pd(OH)_2$ (14 mg, 0.01 mmol) was added. The mixture was stirred under H_2 atmosphere for 3h at rt and filtered. The filtrate was evaporated to give **1c** (32 mg, 0.10 mmol) in 79% yield: a colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.41-1.50 (2H, m), 1.86-1.92 (2H, m), 2.25 (1H, bs), 3.33-3.45 (6H, m), 4.50 (2H, d, *J* = 6.0 Hz), 4.53 (2H, d, *J* = 6.0 Hz), 7.26-7.34 (10H, m); ^{13}C-NMR ($CDCl_3$) δ 27.86, 56.89, 73.17, 73.81, 127.56, 127.67, 128.36, 138.41.

(2*S*,5*S*)-2,5-Bis[*tert*-butyl(dimethyl)silyloxymethyl]pyrrolidine (1d).

To a solution of (2*S*,5*S*)-2,5-bis(hydroxymethyl)-1-((*S*)-1-phenylethyl)pyrrolidine (30 mg, 0.13 mmol) in DMF (1.5 mL) were added TBSCl (46 mg, 0.31 mmol) and imidazole (43 mg, 0.64 mmol), and the solution was stirred for 12 h at rt under Ar atmosphere. After water (4.0 mL) was added, the mixture was extracted with CH_2Cl_2 (12 mL x 3). The combined extracts were dried over anhydrous $MgSO_4$, and concentrated by evaporation. The residue was purified by column chromatography on silica gel (AcOEt: hexane = 1: 10 as eluent) to give (2*S*,5*S*)-2,5-bis[*tert*-butyl(dimethyl)silyloxymethyl]pyrrolidine (48 mg, 0.10 mmol) in 80% yield. Thus prepared (2*S*,5*S*)-2,5-bis-[*tert*-butyl(dimethyl)-silyloxymethyl]pyrrolidine (292 mg, 0.63 mmol) was dissolved in MeOH (7.0 mL) and $Pd(OH)_2$ (70 mg, 0.06 mmol) was added. The mixture was stirred under H_2 atmosphere for 1 h at rt and filtered. The filtrate was evaporated to give **1d** (226 mg, 0.62 mmol) in 99% yield: a colorless oil; ^{1}H-NMR ($CDCl_3$) δ 0.05 (12H, s), 0.88 (18H, s), 1.39-1.45 (2H, m), 1.78-1.83 (2H, m), 3.23-3.40 (2H, m), 3.46-3.53 (4H, m); ^{13}C-NMR ($CDCl_3$) δ -4.8, 18.8, 26.5, 27.8, 59.6, 66.6; HR-FAB MS: Calcd for $C_{18}H_{42}NO_2Si_2$ $[M+H]^+$: 360.2754, Found 360.2767.

Synthesis of *N*,*N*'-dialkyl-2,5-bis(alkoxymethyl)pyrrolidinium iodide 2a-g.

(2*S*,5*S*)-*N*,*N'*-Dimethyl-2,5-bis(methoxymethyl)pyrrolidinium iodide (2a).

To a solution of **1a** (107 mg, 0.67 mmol) in MeCN (4.0 mL) were added MeI (420 μL, 6.7 mmol) and K_2CO_3 (370 mg, 2.68 mmol). The mixture was stirred for 3 h at rt under Ar atmosphere. After water was added, the mixture was extracted with CH_2Cl_2 (15 mL x 3). The combined extracts were dried over anhydrous $MgSO_4$. Evaporation of the solvent gave **2a** (82 mg, 0.26 mmol) in 39% yield: brown oil; ^{1}H-NMR (CD_3OD) δ 1.99-2.05 (2H, m), 2.25-2.30 (2H, m), 3.19 (6H, s), 3.41 (6H, s), 3.70-3.75 (2H, m), 3.78-3.83 (2H, m), 3.97-4.03 (2H, m); ^{13}C-NMR (CD_3OD) δ 25.5, 49.8, 59.4, 70.8, 77.9; HR-FAB MS: Calcd for $C_{10}H_{22}NO_2$ $[M-I^-]^+$: 188.1597. Found 188.1663.

(2*S*,5*S*)-*N*,*N'*-Diallyl-2,5-bis(methoxymethyl)pyrrolidinium iodide (2b).

2b was prepared in a manner similar to that described for the preparation of **2a** using allyl iodide instead of methyl iodide (90% yield): brownish needles; mp 132 °C ($CHCl_3$/AcOEt); ^{1}H-NMR(CD_3OD) δ 2.10-2.16 (2H, m), 2.22-2.32 (2H, m), 3.40 (6H, s), 3.76-3.83 (4H, m), 4.11-4.23 (4H, m), 4,25-4.33 (2H, m), 5.61 (2H, d, *J* = 10.4 Hz), 5.72 (2H, d, *J* = 16.8 Hz), 6.17-6.26 (2H, m); ^{13}C-NMR (CD_3OD) δ 26.3, 60.1, 62.9, 71.6, 76.4, 127.8, 129.0; HR-FAB MS: Calcd for $C_{14}H_{26}NO_2$ $[M-I^-]^+$: 240.1964, Found 240.1997. Anal. Calcd for $C_{14}H_{26}INO_2$: C, 45.78; H, 7.14; N, 3.81. Found: C, 45.63; H, 7.15; N, 3.68.

(2*S*,5*S*)-*N*,*N'*-Dibutyl-2,5-bis(methoxymethyl)pyrrolidinium iodide (2c).

2c was prepared in a manner similar to that described for the preparation of **2a** using 1-iodobutane instead of methyl iodide and the reaction mixture was refluxed for 20 h. After extraction, obtained residue was purified by column chromatography on silica gel (AcOEt: MeOH = 10: 1 as eluent) to give **2c** (16% yield): pale-yellow oil; ^{1}H-NMR (CDCl$_3$) δ 1.01 (6H, t, J = 7.2 Hz), 1.40-1.44 (4H, m), 1.67-1.82 (4H, m), 2.08-2.12 (2H, m), 2.26-2.34 (2H, m), 3.23 (2H, dt, J = 4.0 Hz, 12.8 Hz), 3.32 (6H, s), 3.57 (2H, dt, J = 4.4 Hz, 12.8Hz), 3.69 (2H, d, J = 12 Hz), 3.75 (2H, dd, J = 6 Hz, 12 Hz), 4.38 (2H, d, J = 5.6 Hz); ^{13}C-NMR (CDCl$_3$) δ: 13.8, 20.3, 25.0, 26.3, 57.8, 59.3, 70.6, 75.5; HR-FAB MS: Calcd for $C_{16}H_{34}NO_2$ $[M-I^-]^+$: 272.2590, Found 272.2620.

(2*S*,5*S*)-*N*,*N'*-Dihexyl-2,5-bis(methoxymethyl)pyrrolidinium iodide (2d).

2d was prepared in a manner similar to that described for the preparation of **2c** using 1-iodohexane instead of 1-iodobutane (11% yield): pale-yellow oil; ^{1}H-NMR (CDCl$_3$) δ 0.91 (6H, t, J = 6.8 Hz), 1.25-1.35 (12H, m), 1.75-1.84 (6H, m), 2.14-2.18 (2H, m), 2,32-2.36 (2H, m), 3.27 (2H, dt, J = 4.8 Hz, 12.8 Hz), 3.40 (6H, s), 3.64 (2H, dt, J = 4.8 Hz, 12.8 Hz), 3.72-3.84 (2H, m), 4.42-4.49 (2H, m); ^{13}C-NMR(CDCl$_3$) δ 14.3, 22.8, 24.7, 25.3, 27.0, 31.7, 58.4, 59.7, 70.9, 75.9; HR-FAB MS: Calcd for $C_{20}H_{42}NO_2$ $[M-I^-]^+$: 328.3153, Found 329.3200.

(2*S*,5*S*)-*N*,*N'*-Dimethyl-2,5-bis(propoxymethyl)pyrrolidinium iodide (2e).

2e was prepared in a manner similar to that described for the preparation of **2a** using **1b** as a starting material (87% yield): brown oil; ^{1}H-NMR (CDCl$_3$) δ 0.93 (6H, t, J = 7.6 Hz), 1.60 (4H, sxt, J = 7.6 Hz), 2.03-2.18 (2H, m), 2.32-2.40 (2H, m), 3.42 (6H, s), 3.39-3.51 (4H, m), 3.74-3.79 (2H, m), 3.93-3.96 (2H, m), 4.34-4.37 (2H, m); ^{13}C-NMR (CDCl$_3$) δ 10.7, 22.7, 24.7, 49.2, 68.6, 73.5, 76.2; HR-FAB MS: Calcd for $C_{14}H_{30}NO_2$ $[M-I^-]^+$: 244.2277, Found 244.2300.

(2*S*,5*S*)-*N*,*N'*-Dimethyl-2,5-bis(benzyloxymethyl)pyrrolidinium iodide (2f).

2f was prepared in a manner similar to that described for the preparation of **2a** using **1c** as a starting material (74% yield): brown oil; ^{1}H-NMR (CDCl$_3$) δ 2.00-2.10 (2H, m), 2.18-2.30 (2H, m), 3.37 (6H, s), 3.75-3.81 (2H, m), 3.91-3.99 (2H, m), 4.37-4.39 (2H, m), 4.53 (2H, d, J = 12.0 Hz), 4.58 (2H, d, J = 12.0 Hz), 7.28-7.37 (10H, m); ^{13}C-NMR (CDCl$_3$) δ 24.6, 49.1, 67.7, 73.8, 76.0, 128.1, 128.5, 128.8, 136.4; HR-FAB MS: Calcd for $C_{22}H_{30}NO_2$ $[M-I^-]^+$: 340.2277, Found 340.2305.

(2*S*,5*S*)-*N*,*N'*-Dimethyl-2,5-bis[*tert*-butyl(dimethyl)silyloxymethyl]pyrrolidinium iodide (2g).

2g was prepared in a manner similar to that described for the preparation of **2a** using **1d** as a starting material (88% yield): colorless crystals; mp 274 °C; ^{1}H-NMR (CDCl$_3$) δ 0.14 (12H, s), 0.90 (18H, s), 2.02-2.09 (2H, m), 2.27-2.42 (2H, m), 3.47 (6H, m), 3.89 (2H, dd, J = 5.8, 13.4 Hz), 4.16 (2H, dd, J = 2.2, 13.4 Hz), 4.31-4.38 (2H, m); ^{13}C-NMR (CDCl$_3$) δ -5.7, 17.9, 24.2, 25,6, 49.0, 61.6, 77.4; HR-FAB MS: Calcd for $C_{20}H_{46}NO_2Si_2$ $[M-I^-]^+$: 388.3067, Found 388.3102. Anal. Calcd for $C_{20}H_{46}INO_2Si_2$: C, 46.58; H, 8.99; N, 2.72. Found: C, 46.37; H, 9.07; N, 2.58.

Synthesis of 1-(2-hydroxy-2-phenylethyl)[(2*S*,5*S*)-2,5-bis(methoxymethyl)]pyrrolidine (6).

To a solution of **1a** (160 mg, 1.0 mmol) in MeCN (6 mL) were added styrene oxide (57 μL, 0.5 mmol) and $Ca(OTf)_2$ (17 mg, 0.1 mmol). The solution was heated and refluxed for 3 d. After cooled to rt, sat.$NaHCO_3$ aqueous solution (10 mL) was added and extracted with CH_2Cl_2 (15 mL x3). The combined extracts were dried over anhydrous $MgSO_4$, and concentrated by evaporation. The residue was purified by column chromatography on NH-silica gel (AcOEt: hexane = 1: 5 as eluent) to give **6 (**more polar isomer) (35 mg, 0.13 mmol) and **6'** (less polar isomer) (36 mg, 0.13 mmol).

1-[(*S*)-2-Hydroxy-2-phenylethyl][(2*S*,5*S*)-2,5-bis(methoxymethyl)]pyrrolidine (6): Colorless oil; $[\alpha]^{25}_D$ -84.2 (*c* 2.39, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.59-1.66 (2H, m), 1.94-1.97 (2H, m), 2.88 (1H, dd, *J* = 4.0, 13.2 Hz), 2.95 (1H, dd, *J* = 8.8, 13.2 Hz), 3.14-3.20 (2H, m), 3.32 (6H, s), 3.28-3.38 (4H, m), 4.27 (1H, bs), 4.65 (1H, dd, *J* = 3.6, 8.4 Hz), 7.23-7.39 (5H, m); ^{13}C-NMR ($CDCl_3$) δ 27.4, 57.7, 59.0, 62.9, 72.1, 74.5, 125.7, 127.1, 128.2, 143.3; HR-FAB MS: Calcd for $C_{16}H_{26}NO_3$ $[M+H]^+$: 280.1913, Found 280.1927. The NMR data were in agreement with those of product prepared with (*S*)-styrene oxide.

1-[(*R*)-2-Hydroxy-2-phenylethyl][(2*S*,5*S*)-2,5-bis(methoxymethyl)]pyrrolidine (6'): Colorless oil; $[\alpha]^{25}_D$ -5.20 (*c* 2.38, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.64-1.69 (2H, m), 1.95-1.99 (2H, m), 2.65 (1H, dd, *J* = 11.2, 13.2 Hz), 3.13 (1H, dd, *J* = 2.8, 13.2 Hz), 3.32-3.47 (6H, m), 3.36 (6H, s), 4.73 (1H, dd, *J* = 2.8 Hz, 10.8 Hz), 7.24-7.23 (1H, m), 7.32-7.40 (4H, m); ^{13}C-NMR ($CDCl_3$) δ 27.3, 56.0, 59.0, 59.7, 70.0, 74.4, 125.8, 127.2, 128.2, 142.7; HR-FAB MS: Calcd for $C_{16}H_{26}NO_3$ $[M+H]^+$: 280.1913, Found 280.1944.

General procedure for the synthesis of pyrrolidinium iodide 3.

To a solution of **6** (35 mg, 0.13 mmol) in $CHCl_3$ (1.0 mL) was added MeI (2.0 mL), and the solution was refluxed for 3d. The mixture was evaporated and the residue was purified by column chromatography on NH-silica gel (AcOEt: MeOH = 9: 1 as eluent) to give **3a** (35 mg 0.083 mmol) in 67 % yield.

1-[(*S*)-2-Hydroxy-2-phenylethyl]-1-methyl-[(2*S*,5*S*)-2,5-bis(methoxymethyl)]pyrrolidinium iodide (3a).

pale-yellow oil; $[\alpha]^{25}_D$ +21.4 (*c* 0.51, MeOH); ^{1}H-NMR ($CDCl_3$) δ 1.97 (1H, m), 2.07 (1H, m), 2.24 (1H, m), 2.45 (1H, m), 3.34 (3H, s), 3.38 (3H, s), 3.48 (3H, s), 3.34-3.53 (2H, m), 3.70-3.95 (3H, m), 4.25-4.40 (3H, m), 4.99 (1H, bs), 5.61 (1H, dd, *J* = 11.6, 2.8 Hz), 7.24-7.39 (3H, m), 7.52 (2H, d, *J* = 7.6 Hz); ^{13}C-NMR ($CDCl_3$) δ 24.2, 25.2, 46.0, 59.9, 60.0, 64.1, 67.0, 70.6, 72.5, 75.3, 126.8, 128.7, 129.3, 141.1; HR-FAB MS: Calcd for $C_{17}H_{28}NO_3$ $[M-I^-]^+$: 294.2069, Found 294.2044.

1-[(*R*)-2-Hydroxy-2-phenylethyl]-1-methyl-[(2*S*,5*S*)-2,5-bis(methoxymethyl)]pyrrolidinium iodide (3a').

79% yield; pale-yellow oil; $[\alpha]^{25}_D$ -5.20 (*c* 2.19, MeOH); ^{1}H-NMR ($CDCl_3$) δ 1.94 (1H, m), 2.09 (1H, m), 2.29 (1H, m), 2.44 (1H, m), 3.36 (3H, s), 3.39 (3H, s), 3.51 (3H, s), 3.28-3.51 (2H, m), 3.62-3.69 (2H, m), 3.80-3.99 (3H, m), 4.44 (1H, m), 4.85 (1H, m), 5.77 (1H, m), 7.29-7.39 (3H, m), 7.49 (2H, d, *J* = 7.2 Hz); ^{13}C-NMR ($CDCl_3$) δ: 24.0, 24.3, 47.0, 59.42, 59.46, 64.4, 67.6, 70.1, 70.8, 73.8, 126.2, 128.3, 128.9, 141.0; HR-FAB MS: Calcd for $C_{17}H_{28}NO_3$ $[M+H]^+$: 294.2069, Found 294.2068.

1-(2-Hydroxyhexyl)-1-methyl-[(2*S*,5*S*)-2,5-bis(methoxymethyl)]pyrrolidinium iodide (3b).

Diastereomer prepared from less polar 1-(2-hydroxyhexyl)[(2*S*,5*S*)-2,5-bis(methoxymethyl)]pyrrolidine: 14% yield from **1a**; pale-yellow oil; ^{1}H-NMR ($CDCl_3$) δ 0.91 (3H, t, *J* = 7.2 Hz), 1.26-1.67 (6H, m), 1.96-2.14 (2H, m), 2.29 (1H, m), 2.44 (1H, m), 3.11 (1H, d, *J* = 13.6 Hz), 3.40 (6H, s), 3.42 (3H, s), 3.58-3.75 (4H, m), 3.96 (1H, d, *J* = 12.4 Hz), 4.38-4.45 (2H, m), 4.59 (1H, m), 4.91 (1H, m); ^{13}C-NMR ($CDCl_3$) δ 14.0, 22.6, 24.0, 24.3, 27.4, 36.1, 59.4, 59.5, 63.5, 65.4, 70.1, 71.0, 73.6, 76.5, 76.8; HR-FAB MS: Calcd for $C_{15}H_{32}NO_3$ $[M-I^-]^+$: 274.2382, Found 274.2405.

Diastereomer prepared from more polar 1-(2-hydroxyhexyl)[(2*S*,5*S*)-2,5-bis(methoxymethyl)]pyrrolidine: 5% yield from **1a**; pale-yellow oil; ^{1}H-NMR ($CDCl_3$) δ 0.91 (3H, t, *J* = 7.2 Hz), 1.26-1.51 (6H, m), 1.90 (1H, m), 2.09 (1H, m), 2.29 (1H, m), 2.40(1H, m), 3.29-3.46 (2H, m), 3.39 (3H, s), 3.40 (6H, s), 3.55 (1H, m), 3.71 (1H, d, *J* = 13.6 Hz), 3.70-3.80 (2H, m), 4.26 (1H, d, *J* = 12.0 Hz), 4.35 (1H, m), 4.41-4.51 (2H, m); HR-FAB MS: Calcd for $C_{15}H_{32}NO_3$ $[M-I^-]^+$: 274.2382, Found 274.2379.

1-[2-Hydroxy-2-(4-fluorophenyl)ethyl]-1-methyl-[(2*S*,5*S*)-2,5-bis(methoxymethyl)]pyrrolidinium iodide (3c).

Diastereomer prepared from less polar 1-[2-hydroxy-2-(4-fluorophenyl)ethyl][(2*S*,5*S*)-2,5-bis(methoxymethyl)]pyrrolidine: 29% yield from **1a**; pale-yellow oil; $[\alpha]^{25}_{D}$ -50.142 (*c* 2.24, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 2.02-2.12 (2H, m), 2.25-2.49 (2H, m), 3.30 (3H, s), 3.39 (3H, s), 3.53 (3H, s), 3.60-3.69 (2H, m), 3.75-3.84 (2H, m), 4.01 (1H, d, *J* = 12.8 Hz), 4.44 (1H, m), 4.70 (1H, bs), 4.88 (1H, m), 4,93 (1H, d, *J* = 6.4 Hz), 5.83 (1H, m), 7.02-7.06 (2H, t, *J* = 8.4 Hz), 7.53-7.56 (2H, dd, *J* = 5.2 Hz, 8.4 Hz); ^{13}C-NMR ($CDCl_3$) δ 23.9, 24.2, 46.9, 59.4, 59.5, 64.2, 66.9, 69.9, 70.8, 73.7, 76.9, 115.6 (d, J_{C-F} = 21.4 Hz), 128.2 (d, J_{C-F} = 8.3 Hz), 136.8, 162.5 (d, J_{C-F} = 246.2 Hz) ; HR-FAB MS: Calcd for $C_{17}H_{27}FNO_3$ $[M-I^-]^+$: 312.1975, Found 312.1979.

Diastereomer prepared from more polar 1-[2-hydroxy-2-(4-fluorophenyl)ethyl][(2*S*,5*S*)-2,5-bis-(methoxymethyl)]pyrrolidine: 31% yield from **1a**; pale-yellow oil; $[\alpha]^{25}_{D}$ +4.19(*c* 1.96, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.90-2.04 (1H, m), 2.05-2.19 (1H, m), 2.29 (1H, m), 2.43 (1H, m), 3.35 (3H, s), 3.39 (3H, s), 3.50 (3H, s), 3.53 (1H, bs), 3.75 (1H, m), 3.85-3.95 (2H, m), 4.24-4.28 (1H, m), 4.35 (1H, d, *J* = 12.4 Hz), 4.41 (1H, m), 5.01 (1H, d, *J* = 6.4 Hz), 5.65 (1H, m), 7.02-7.07 (2H, t, *J* = 8.8 Hz), 7.52-7.55 (2H, dd, *J* = 5.6 Hz, 8.4 Hz); ^{13}C-NMR ($CDCl_3$) δ 23.6, 24.6, 45.5, 59.4, 59.5, 63.3, 65.7, 69.9, 72.0, 74.8, 77.2, 115.5 (d, J_{C-F} = 21.4 Hz), 128.0 (d, J_{C-F} = 8.3 Hz), 136.3, 161.2 (d, J_{C-F} = 244.5 Hz); HR-FAB MS: Calcd for $C_{17}H_{27}FNO_3$ $[M-I^-]^+$: 312.1975, Found 312.1991.

1-[2-Hydroxy-2-(naphth-2-yl)ethyl]-1-methyl-[(2*S*,5*S*)-2,5-bis(methoxymethyl)]pyrrolidinium iodide

(3d).

Diastereomer prepared from less polar 1-[2-hydroxy-2-(nathth-2-yl)ethyl][(2*S*,5*S*)-2,5-bis-(methoxymethyl)]pyrrolidine: 36% yield from **1a**; pale-yellow oil; $[\alpha]^{25}_{D}$ +12.3 (*c* 1.46, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.88-2.02 (2H, m), 2.21 (1H, m), 2.35 (1H, m), 3.19 (3H, s), 3.33 (3H, s), 3.35 (1H, m), 3.47 (3H, s), 3.51-3.58 (2H, m), 3.74-3.91 (3H, m), 4.33 (1H, m), 4.82 (1H, m), 5.00 (1H, d, *J* = 6.4 Hz), 5.90 (1H, m), 7.41-7.46 (2H, m), 7.57 (1H, dd, *J* = 1.6 Hz, 8.8 Hz), 7.75-7.77 (2H, m), 7.84 (1H, m), 8.03 (1H, s); ^{13}C-NMR ($CDCl_3$) δ 23.9, 24.2, 46.9, 59.28, 59.33, 64.1, 67.6, 69.8, 70.7, 73.6, 76.8, 124.0, 125.4, 126.2, 126.3, 127.5, 128.1, 128.6, 133.0, 133.1, 138.3; HR-FAB MS: Calcd for $C_{21}H_{30}NO_3$ $[M-I^-]^+$: 344.2226, Found 344.2219.

Diastereomer prepared from more polar 1-[2-hydroxy-2-(nathth-2-yl)ethyl][(2*S*,5*S*)-2,5-bis-(methoxymethyl)]pyrrolidine: 29% yield from **1a**; pale-yellow oil; $[\alpha]^{25}_{D}$ -61.0 (*c* 2.67, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.75-2.01 (2H, m), 2.11-2.42 (2H, m), 3.25 (3H, s), 3.27 (3H, s), 3.39 (1H, m), 3.44 (3H, s), 3.64 (1H, m), 3.73 (1H, m), 3.92 (1H, d, *J* = 13.6 Hz), 4.20-4.35 (3H, m), 5.06 (1H, d, *J* = 5.6 Hz), 5.72 (1H, m), 5.98 (1H, bs), 7.40-7.42 (2H, m), 7.51 (1H, d, *J* = 8.8 Hz), 7.75-7.80 (3H, m), 7.98 (1H, s); ^{13}C-NMR ($CDCl_3$) δ 24.1, 25.2, 42.0, 59.9, 60.0, 67.1, 67.5, 70.7, 71.5, 72.5, 77.9, 124.5, 125.9, 126.8, 126.9, 128.2, 128.7, 129.1, 133.6, 133.8, 138.4; HR-FAB MS: Calcd for $C_{21}H_{30}NO_3$ $[M-I^-]^+$: 344.2226, Found 344.2223.

1-[(*S*)-2-Hydroxy-2-phenylethyl]-1-methyl-[(2*S*,5*S*)-2,5-bis(methoxymethyl)]pyrrolidinium tetrafluoroborate (3aa).

To a solution of **6** (79 mg, 0.28 mmol) in $CHCl_3$ (7.0 mL) was added trimethyloxonium tetrafluoroborate (20 mg, 0.14 mmol) under Ar atmosphere, and the solution was stirred at rt for 4h. After MeOH (2.0 mL) was added, the solution was concentrated by evaporation. The residue was purified by column chromatography on NH-silica gel (AcOEt: MeOH = 9: 1 as eluent) to give **3aa** (37 mg 0.10 mmol) in 73% yield: colorless oil; $[\alpha]^{25}_{D}$ +3.10 (*c* 0.87, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.89 (1H, m), 2.07 (1H, m), 2.27 (1H, m), 2.41 (1H, m), 3.25 (3H, s), 3.33 (3H, s), 3.34 (3H, s), 3.38 (1H, m), 3.52 (1H, d, *J* = 8.8 Hz), 3.63 (1H, d, *J* = 12.0 Hz), 3.66-3.88 (2H, m), 4.14-4.16 (2H, m), 4.25-4.28 (2H, m), 4.28 (1H, s), 5.37 (1H, dd, *J* = 11.8, 3.4 Hz), 7.30-7.44 (5H, m); ^{13}C-NMR ($CDCl_3$) δ 23.3, 24.4, 43.7, 59.1, 59.4, 63.6, 68.0, 69.7, 71.8, 74.6, 77.2, 126.0, 128.4, 128.9, 140.5; HR-FAB MS: Calcd for $C_{17}H_{28}NO_3$ $[M-BF_4^-]^+$: 294.2069, Found 294.2082.

1-[(*S*)-2-Hydroxy-2-phenylethyl]-1-methyl-[(2*S*,5*S*)-2,5-bis(methoxymethyl)]pyrrolidinium trifluoromethanesulfonate (3ab).

To a solution of **6** (124 mg, 0.44 mmol) in $CHCl_3$ (3.0 mL) was added methyl trifluoromethanesulfonate (145 mg, 0.88 mmol) under Ar atmosphere, and the solution was stirred at rt for 3 h. The solution was concentrated by evaporation and the residue was purified by column chromatography on NH-silica gel

(AcOEt: MeOH = 9: 1 as eluent) to give **3ab** (106 mg 0.24 mmol) in 54% yield: brown oil; $[\alpha]^{25}_D$ +6.40 (*c* 0.55, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.88-1.93 (1H, m), 2.05-2.10 (1H, m), 2.25-2.31 (1H, m), 2.38-2.44 (1H, m), 3.23 (3H, s), 3.32 (3H, s), 3.33 (3H, s), 3.21-3.39 (2H, m), 3.47-3.66 (2H, m), 3.71-3.95 (2H, m), 4.07-4.19 (2H, m), 4.20-4.26 (2H, m), 5.42 (1H, dd, *J* = 2.8 Hz, 11.2 Hz), 7.30-7.33 (1H, m), 7.36-7.40 (2H, m), 7.43-7.45 (2H, m); ^{13}C-NMR ($CDCl_3$) δ 23.4, 24.4, 43.9, 59.1, 59.4, 63.7, 67.8, 69.8, 71.8, 74.6, 77.2, 120.4 (q, $J_{C\text{-}F}$ = 317.8 Hz), 126.0, 128.4, 128.9, 140.5; HR-FAB MS: Calcd for $C_{17}H_{28}NO_3$ $[M\text{-}TfO^-]^+$: 294.2069, Found 294.2082.

General procedure for the catalytic asymmetric benzylation of *tert*-butyl glycinate benzophenone Schiff base.

To a solution of *t*-butyl *N*-(diphenylmethylene)glycinate (**5**) (50 mg, 0.17 mmol), BnBr 24 μL (0.20 mmol), and catalyst (10 mol%) in toluene (1.5 mL) was added 50% aq. KOH solution (0.41 mL). The solution was stirred at rt or 0 °C for 24 h. After H_2O was added, the mixture was extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were dried over $MgSO_4$ and concentrated. The yield of **5** was calculated by ^{1}H NMR using mesitylene as an internal standard.[10] Then the obtained mixture was dissolved in THF (1.0 mL) and 0.5 M aqueous citric acid solution (1.0 mL) was added. The mixture was stirred at rt for 3 h. After H_2O (4.0 mL) was added, the aqueous solution was washed with Et_2O (10 mL x 2), then basified with sat.$NaHCO_3$ aqueous solution. The solution was extracted with CH_2Cl_2 (10 mL x 4) and dried over anhydrous $MgSO_4$. After evaporation, *tert*-butyl phenylalaninate was obtained as a single product, and the enantiomeric excess was determined by HPLC analysis (Daicel Chiralcel OJ-H, hexane: *i*-PrOH = 100: 1, flow rate = 0.5 mL/min, retention time; 21.2 min (*R* isomer) and 23.8 min (*S* isomer)).

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REFERENCES

1. a) E. V. Dehmlow and S. S. Dehmlow, *Phase Transfer Catalysis*, 3rd ed.; VCH: Weinheim, 1993; b) C. M. Stark, C. L. Liotta, and M. Halpern, *Phase-Transfer Catalysis*; Chapman and Hall: New York, 1994; c) R. A. Jones, *Quaternary Ammonium Salts: Their use in Phase Transfer Catalysis*; Academic Press: San Diego, 2001.
2. U.-H. Dolling, P. Davis, and E. J. J. Grabowski, *J. Am. Chem. Soc.*, 1984, **106**, 446.
3. For reviews: a) T. Ooi and K. Maruoka, *Angew. Chem. Int. Ed.*, 2007, **46**, 4222; b) M. J. O'Donnel, *Acc. Chem. Res.*, 2004, **37**, 506; c) B. Lygo and B. I. Andrews, *Acc. Chem. Res.*, 2004, **37**, 518; d) K.

Maruoka and T. Ooi, *Chem. Rev.*, 2003, **103**, 3013.

4. a) K. Nagata, D. Sano, and T. Itoh, *Synlett*, 2007, 547; b) D. Sano, K. Nagata, and T. Itoh, *Org. Lett.*, 2008, **10**, 1593; c) K. Nagata, D. Sano, Y. Shimizu, M. Miyazaki, T. Kanemitsu, and T. Itoh, *Tetrahedron: Asymmetry*, 2009, **20**, 2530.
5. Three reactions in which a chiral pyrrolidinium salt was used as a PTC were reported: a) B. Lygo, B. Allbutt, and S. R. James, *Tetrahedron Lett.*, 2003, **44**, 5629; b) S. Arai, R. Tsuji, and A. Nishida, *Tetrahedron Lett.*, 2002, **43**, 9535; c) M. Shi, K. Kazuta, Y. Satoh, and Y. Masaki, *Chem. Pharm. Bull.*, 1994, **42**, 2625.
6. Y. Yamamoto, J. Hoshino, Y. Fujimoto, J. Ohmoto, and S. Sawada, *Synthesis*, 1993, 298.
7. a) G. N. Grover, W. E. Kowtoniuk, and D. K. MacFarland, *Tetrahedron Lett.*, 2006, **47**, 57; b) I. Cepanec, M. Litvic, H. Mikuldas, A. Bartolincic, and V. Vinkovic, *Tetrahedron*, 2003, **59**, 2435.
8. N. Mase, T. Ohno, N. Hoshikawa, K. Ohishi, H. Morimoto, H. Yoda, and K. Takebe, *Tetrahedron Lett.*, 2003, **44**, 4073.
9. B. H. Kim, H. B. Lee, J. K. Hwang, and Y. G. Kim, *Tetrahedron: Asymmetry*, 2005, **16**, 1215.
10. *N*-(Diphenylmethylene)glycine was produced as a side product, and no starting material was detected.