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Resolution of nitrogen-centered chiral tetraalkylammonium salts: application to [1,2] Stevens rearrangements with *N*-to-*C* chirality transmission

Eiji Tayama *, Seijun Otoyama, Hiroyuki Tanaka

Department of Chemistry, Faculty of Science, Niigata University, Niigata 950-2181, Japan

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ABSTRACT

The resolution of *N*-chiral, amino acid-derived quaternary ammonium salts is demonstrated by using chiral BINOL as a complexing agent. Determination of the enantiopurities and absolute configurations of the resolved *N*-chiral tetraalkylammonium salts are described. The [1,2] Stevens rearrangement of *N*-chiral ammonium salts is shown to proceed with *N*-to-*C* chirality transmission to afford optically active 3-substituted morpholin-2-one derivatives.

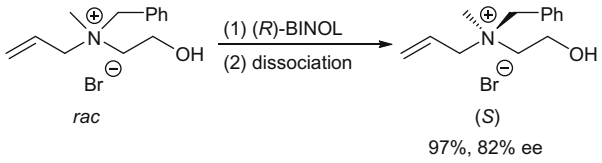
1. Introduction

The asymmetric Stevens rearrangement[1] of ammonium ylides, in which chirality is transmitted from a nitrogen to a carbon center, is a potentially interesting transformation for organic synthesis; however, preparative methods for nitrogen-centered chiral (*N*-chiral) tetraalkylammonium salts have been limited. The diastereoselective quaternarization of tertiary amines bearing a stereogenic carbon (e.g., L-proline derivatives) to prepare enantio-enriched *C*- and *N*-chiral diastereomers is known as a common preparative method.[2] Another method, the resolution of *N*-chiral tetraalkylammonium salts by fractional crystallization, was reported by Pope,[3] Jones,[4] and Torbeev.[5] However, these methods have limited practical value because they cannot be applied to several types of *N*-chiral tetraalkylammonium salts.

Recently, we described the efficient and direct resolution of racemic, *N*-centered chiral tetraalkylammonium salts by complexation with (*R*)-1,1′-bi-2-naphthol (BINOL) (Scheme 1).[6] Herein, we report that *N*-chiral tetraalkylammonium salts resolved by this method undergo asymmetric [1,2] Stevens rearrangements to afford optically active rearrangement products via *N*-to-*C* chirality transmission.

2. Results and discussion

First, we attempted the resolution of the *N*-racemic, amino acid-derived tetraalkylammonium salt **1**, which we hoped to subject to a base-induced [1,2] Stevens rearrangement (Table 1). A solution of *N*-benzyl-*N*-(*tert*-butoxycarbonylmethyl)-*N*-(2-hydroxyethyl)-*N*-methylammonium bromide **1a** (1.0 equiv) in dichloromethane was



Scheme 1. Previously reported resolution of nitrogen-centered chiral tetraalkylammonium salts.

treated with (*S*)-BINOL (0.50 equiv) at room temperature for 24 h. Unfortunately, no precipitation was observed, and the resolution of **1a** consequently failed (entry 1). However, treatment of its chloride salt **1b** under the same conditions afforded the corresponding 1:1 complex **2b** as colorless crystals. The complex **2b** was isolated by filtration in 90% yield, as determined from the amount of (*S*)-BINOL (entry 2). Then, complex **2b** was dissociated in a mixture of diethyl ether and water. Following extractive separation and the evaporation of solvent, enantio-enriched **1b** was obtained in 84% yield from the aqueous solution. The enantiomeric excess (ee) of resolved **1b** was determined to be 89% ee by a comparison of the specific rotation $\{[\alpha]_{589}^{23} = +17.0$ (*c* 1.00, EtOH)$\}$ with the highest value of specific rotation $\{[\alpha]_{589}^{23} = +19.1\}$ obtained after three resolutions as the standard value (details: see Section 4).

To define the scope and limitations of the present resolution method, we prepared a series of substrates **1c**–**1l** and carried out their resolution by complexation with (*S*)-BINOL (entries 3–12). Enantio-enriched *N*-(2-methylbenzyl)ammonium bromide **1c** was obtained in lower yield with excellent selectivity (entry 3, 45% yield, 94% ee) because the corresponding 1:1 complex **2c** proved somewhat soluble in dichloromethane, however, its chloride salt **1d** was obtained in good yield with almost perfect selectivity (entry 4, 79% yield, 98% ee). *N*-(2-Methoxybenzyl)- **1e**, **1f,** and *N*-[2-(trifluoromethyl)benzyl]- **1g** derivatives were also resolved by the same general procedure with similar enantioselectivities

* Corresponding author. Tel./fax: +81 25 262 7741.
E-mail address: tayama@chem.sc.niigata-u.ac.jp (E. Tayama).

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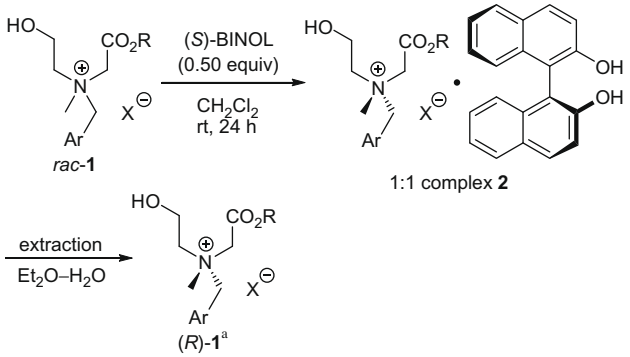
Table 1
Resolution of *N*-centered chiral tetraalkylammonium salt **1** by diastereoselective complexation with (*S*)-BINOL



Entry	Ar	R	X		Yield (%)[b]		ee (%)
					2	**1** (two steps)	**1**
1	Ph	*t*-Bu	Br	**a**	0[c]	—	—
2	Ph	*t*-Bu	Cl	**b**	90	84	89[d]
3	2-Me–Ph	*t*-Bu	Br	**c**	49	45	94[e]
4	2-Me–Ph	*t*-Bu	Cl	**d**	84	79	98[e]
5	2-MeO–Ph	*t*-Bu	Br	**e**	76	72	79[e]
6	2-MeO–Ph	*t*-Bu	Cl	**f**	69	66	93[e]
7	2-CF_3–Ph	*t*-Bu	Br	**g**	85	77	80[e]
8	4-Me–Ph	*t*-Bu	Br	**h**	0[c]	—	—
9	4-Me–Ph	*t*-Bu	Cl	**i**	0[c]	—	—
10	4-CF_3–Ph	*t*-Bu	Br	**j**	0[c]	—	—
11	4-CF_3–Ph	*t*-Bu	Cl	**k**	0[c]	—	—
12	2-Me–Ph	Me	Br	**l**	82	77	81[d] (*R*)[f]

[a] Tentatively assigned configuration determined by analogy with (*R*)-**1l**.
[b] Isolated yield. Determined from the amount of (*S*)-BINOL.
[c] Not precipitated.
[d] Determined by specific rotation, using the highest specific rotation obtained after three resolutions as the standard value. The results include ca. ±5% errors.
[e] Determined by HPLC analysis.
[f] The absolute configuration was determined by a single crystal X-ray diffraction.

(entries 5–7). The ee of the resolved **1c**–**1g** could be determined by chiral HPLC analysis (Daicel Chiralcel OD-H column, *n*-hexane/ethanol/trifluoroacetic acid/diethylamine = 95:5:0.1:0.1 as eluent). No precipitations were observed using 4-substituted tetraalkylammonium salts **1h**–**1k** (entries 8–11). Methyl ester derivative **1l** could also be resolved under the same resolution conditions (entry 12, 77% yield, 81% ee). The yield of **1l** was better than the *tert*-butyl derivative **1c** (entry 3, 45% yield) because the 1:1 complex **2l** proved to be less soluble in dichloromethane than **2c**. The absolute configuration of **1l** was determined as (*R*) on the nitrogen atom by a single crystal X-ray diffraction (Fig. 1).[7]

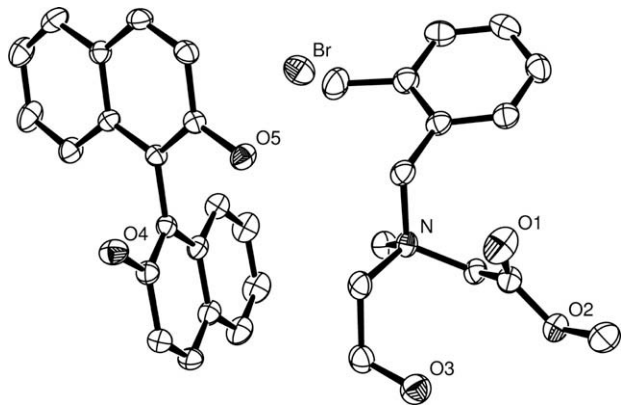
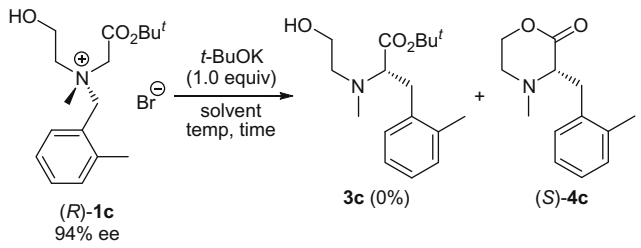


Figure 1. Molecular structure of the 1:1 complex **2l** (hydrogen atoms are omitted for clarity).

Next, we carried out the [1,2] Stevens rearrangement of the resolved *N*-chiral tetraalkylammonium salt (*R*)-**1c**. In preliminary experiments, we found that the use of potassium *tert*-butoxide as a base afforded the rearrangement product in reasonable yields.[8] Treatment of (*R*)-**1c** (94% ee) with potassium *tert*-butoxide (1.0 equiv) in THF at −20 °C for 6 h gave (*S*)-4-methyl-3-(2-methylbenzyl)morpholin-2-one **4c** in 41% yield as the corresponding [1,2] Stevens rearrangement product (Table 2, entry 1). The non-lactonized derivative **3c** could not be detected. The enantiopurity of **4c** was determined to be 48% ee by chiral HPLC analysis; thus, the efficiency of *N*-to-*C* chirality transmission from (*R*)-**1c** to **4c** was 51% (94% ee to 48% ee). The absolute configuration of **4c** was assigned as (*S*) by comparison with an (*S*)-authentic sample.[9]

Table 2
Asymmetric [1,2] Stevens rearrangement of (*R*)-**1c** with *N*-to-*C* chirality transmission



Entry	Solvent	Temp, time (°C, h)	Yield of **4c**[a] (%)	ee[b,c] (%)
1	THF	−20, 6	41	48 (51)
2	CH_2Cl_2–THF (10:1)	−20, 6	55	52 (55)
3	CH_2Cl_2–THF (10:1)	−30, 6	57	55 (59)
4	CH_3CN–THF (10:1)	−30, 6	62	60 (64)
5	CH_3CN–THF (10:1)	−40, 15	22	67 (71)

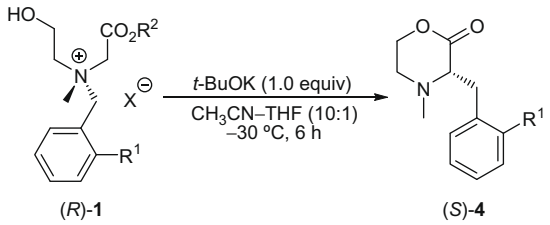
[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] The parentheses are the rate of *N*-to-*C* chirality transmission.

To improve the yield of (*S*)-**4c** and the transmission of *N*-to-*C* chirality during the [1,2] Stevens rearrangement, we examined the reactions of (*R*)-**1c** under different conditions. When the reaction was carried out in dichloromethane–THF[10] (10:1) as a solvent at −20 or −30 °C, (*S*)-**4c** was obtained with better yields and selectivities (entry 2: 55% yield, 52% ee; entry 3: 57% yield, 55% ee). The use of acetonitrile–THF (10:1) as a solvent afforded (*S*)-**4c** with moderate yield and chirality transmission (entry 4: 62% yield, 60% ee).[11] Using the same solvent blend at a lower temperature (−40 °C), the rate of *N*-to-*C* chirality transmission reached over 70% (entry 5); however, the reaction proceeded very slowly. The rearrangement product (*S*)-**4c** was obtained in only 22% yield, but with 67% ee (71% *N*-to-*C* chirality transmission). Although the solvent effect is presently unclear, it was reported that the rate of chirality transmission in the [1,2] Stevens rearrangement is changeable by a variety of solvents.[12]

With the optimized conditions in hand (Table 2, entry 4), we carried out the rearrangement of other *N*-chiral tetraalkylammonium salts (*R*)-**1** (Table 3). The rearrangement of *N*-benzyl ammonium chloride (*R*)-**1b** (entry 1, >95% ee) gave (*S*)-**4b** in lower yield (39%) with a similar level of *N*-to-*C* chirality transmission (56%). The reaction of (*R*)-**1d**, **1e**, **1f,** or the methyl ester derivative (*R*)-**1l** afforded the corresponding rearrangement products (*S*)-**4** with similar levels of chirality transmission (entries 2–5, 45–65%), respectively. The absolute configurations of the rearrangement products **4** were assigned by analogy with (*S*)-**4c**.

While an exact mechanism cannot be advanced at present, it is safe to say that in the reaction from (*R*)-**1** to (*S*)-**4**, the lactonization

Table 3
Rearrangement of *N*-chiral tetraalkylammonium salts (*R*)-**1**

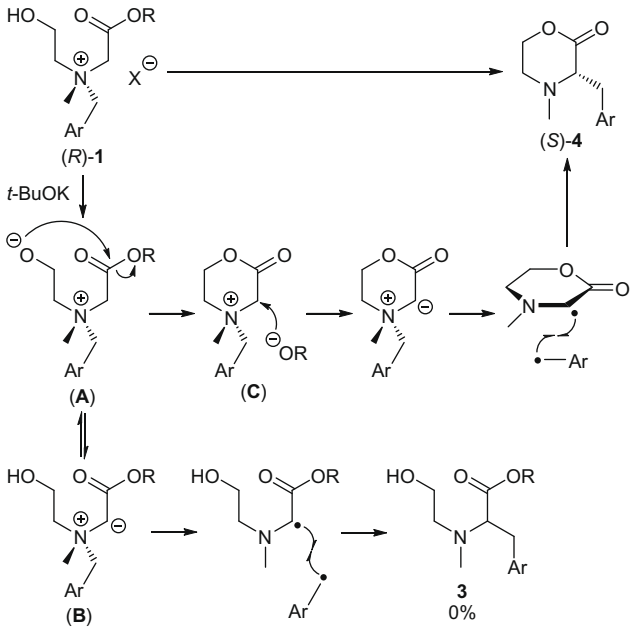


(*R*)-**1** (*S*)-**4**

Entry	R^1	R^2	X		ee of (*R*)-**1** (%)	Yield[a] (%)	ee[b,c] (%)
1	H	*t*-Bu	Cl	**b**	>95	39	56 (56)
2	Me	*t*-Bu	Cl	**d**	98	76	44 (45)
3	OMe	*t*-Bu	Br	**e**	79	52	50 (63)
4	OMe	*t*-Bu	Cl	**f**	93	53	49 (53)
5	Me	Me	Br	**l**	>95	60	65 (65)

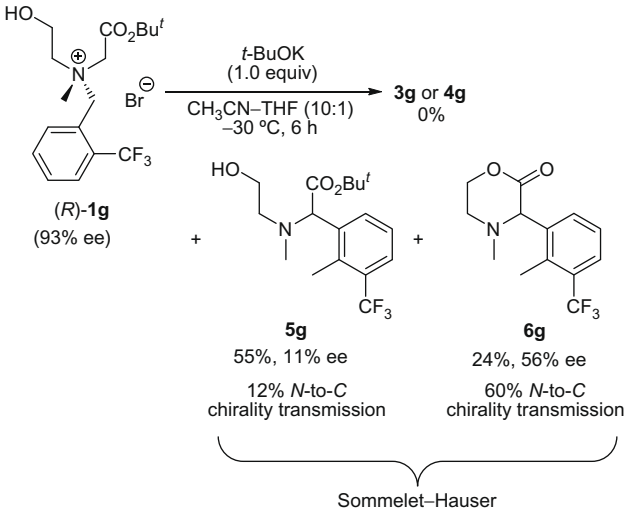
[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] The parentheses are the rate of *N*-to-*C* chirality transmission.

of **1** proceeds first to form the corresponding cyclic ammonium salt **C** (Scheme 2). Treatment of (*R*)-**1** with potassium *tert*-butoxide affords an equilibrium mixture of alkoxide **A** and ylide **B**. The alkoxide **A** is easily lactonized to the corresponding cyclic ammonium salt **C** because the ester carbonyl of **1** is activated toward the nucleophilic attack by an α-electron-withdrawing substituent (ammonium cation). Then, the [1,2] Stevens rearrangement with *N*-to-*C* chirality transmission proceeds via radical cleavage and recombination to afford the 3-substituted morpholin-2-one (*S*)-**4**. If the rearrangement proceeded without lactonization of **A**, the product **3** derived by [1,2] rearrangement of linear ammonium ylide **B** should be formed; however, any detectable amount of **3** was not obtained.



Scheme 2. Rearrangement of *N*-chiral tetraalkylammonium salts (*R*)-**1**.

On the other hand, in the reaction of *N*-2-(trifluoromethyl)benzyl derivative (*R*)-**1g** (93% ee),[13] the [1,2] Stevens products **3g** and **4g** were not obtained. Instead, the Sommelet–Hauser rearrangement proceeded to exclusively afford **5g** and **6g** in 79% combined yield (Scheme 3).[14] The non-lactonized derivative **5e** was obtained as the major product without chirality transmission (55%, 11% ee) along with lactone **6g** with moderate chirality transmission (24%, 56% ee).[15] The Sommelet–Hauser rearrangement from the corresponding linear ammonium ylide might proceed more smoothly than lactonization because of the concerted [2,3] sigmatropic process.



Scheme 3. Sommelet–Hauser rearrangement of (*R*)-**1g**.

3. Conclusion

In conclusion, we have reported the resolution of *N*-chiral, amino acid-derived quaternary ammonium salts using chiral BINOL as a complexing agent. The resulting products undergo a [1,2] Stevens rearrangement with *N*-to-*C* chirality transmission to afford the optically active 3-substituted morpholin-2-one analogues. This work is likely to stimulate further advances in the rapidly developing asymmetric chemistry of *N*-centered chiral molecules.

4. Experimental

4.1. General

Infrared (IR) spectra were recorded on a HITACHI Infrared Spectrometer Model 270–30. ^{1}H and ^{13}C NMR spectra were measured on a JEOL 270 MHz (^{1}H: 270 MHz, ^{13}C: 68 MHz) spectrometer. Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Specific rotations were recorded on a JASCO Polarimeter P-1010. Elemental analyses were recorded on a Yanaco CHN Corder MT-3. For thin layer chromatography (TLC) analysis throughout this work, Merck TLC plates (Silica Gel 60F_{254}) were used. The products were purified by preparative column chromatography on silica gel (Silica Gel 60N, spherical neutral, KANTO Chemical Co., Inc., Japan). (*S*)-BINOL was purified by recrystallization from ethanol. A 1.0 M THF solution of potassium *tert*-butoxide was purchased from Aldrich, and fresh bottles were used for as many reactions as possible.

4.2. Resolutions and reactions

4.2.1. Representative procedure for the resolution of *N*-chiral tetraalkylammonium salt 1c

To a solution of **1c** (2.13 g, 5.56 mmol) in dichloromethane (5.6 mL) was added (*S*)-BINOL (795 mg, 2.78 mmol), and the mixture was stirred for 24 h at room temperature. The precipitate

was isolated by filtration and washed with a small amount of the mother liquid. The solid was dried under reduced pressure to afford the corresponding 1:1 complex **2c** as colorless crystals [901 mg, 49% yield from the amount of (*S*)-BINOL]. The 1:1 complex **2c** (901 mg, 1.36 mmol) was dissolved in small amounts of methanol, and the solution was transferred to a separatory funnel. Diethyl ether (ca. 20 mL) and water (ca. 20 mL) were added to the separatory funnel, and it was shaken at room temperature. The two phases were then separated. From the diethyl ether solution, (*S*)-BINOL was recovered as colorless crystals (369 mg, 95% recovery) after solvent evaporation. From the aqueous solution, wet (*R*)-**1c** was obtained after evaporation. The wet (*R*)-**1c** was dissolved in dichloromethane and dried over sodium sulfate. Evaporation of the solvent gave (*R*)-**1c** as a white solid (480 mg, 45% yield from racemic **1c**). The enantiomeric excess (ee) was determined to be 94% ee by HPLC analysis [Daicel Chiralcel OD-H column, *n*-hexane/ethanol/trifluoroacetic acid/diethylamine = 95:5:0.1:0.1 as eluent, flow rate = 0.50 mL/min, t_R = 20.9 min for the (*S*)-**1c** and 23.7 min for (*R*)-**1c**].

4.2.2. (*R*)-*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(2-hydroxyethyl)-*N*-methyl-*N*-(2-methylbenzyl)ammonium bromide, 0.5 hydrate (*R*)-1c

White solid; $[\alpha]_{589}^{26} = +13.3$ (*c* 1.00, EtOH); 94% ee (determined by HPLC); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.57 (1H, d, *J* = 7.3 Hz, Ar-H), 7.44–7.20 (3H, m, Ar-H), 5.22 (2H, s, CH_2COO), 5.09 (1H, br, OH), 4.62 (1H, d, *J* = 17.3 Hz, CH_2Ar), 4.54 (1H, d, *J* = 17.3 Hz, CH_2Ar), 4.30–4.04 (3H, m, CH_2CH_2OH), 3.86–3.68 (1H, m, CH_2CH_2OH), 3.43 (3H, s, NCH_3), 2.55 (3H, s, $ArCH_3$), 1.51 (9H, s, *t*-Bu); ^{13}C NMR (68 MHz, $CDCl_3$) δ 164.1, 140.3, 134.5, 131.9, 130.8, 126.4, 125.3, 84.9, 65.0, 62.3, 59.2, 55.5, 48.7, 27.8, 20.5; IR (film) 3272, 2960, 1734, 1602, 1454, 1392, 1368, 1240, 1148, 1088, 832, 724 cm^{-1}; Anal. Calcd for $C_{17}H_{29}BrNO_{3.5}$: C, 53.27; H, 7.63; N, 3.65. Found: C, 53.57; H, 7.48; N, 3.59.

4.2.3. Resolution of 1b, 1d, 1e, 1f, 1g, and 1l

Resolutions of **1b**, **1d**, **1e**, **1f**, **1g**, and **1l** were carried out using the procedure described for **1c**. The ee for (*R*)-**1b** and (*R*)-**1l** were determined by specific rotation, using the highest specific rotations obtained after three optical resolutions as standard values. These procedures are described in detail within the next section. The ee of (*R*)-**1d**, (*R*)-**1e**, (*R*)-**1f**, and (*R*)-**1g** were determined by HPLC analysis.

4.2.4. Determination of the highest specific rotation of (*R*)-1b and (*R*)-1l

The highest specific rotation of (*R*)-**1b** was obtained after three successive resolutions. Initially resolved (*R*)-**1b** {$[\alpha]_{589}^{23} = +17.0$ (*c* 1.00, EtOH)} was subjected to second and third resolution under similar conditions [1.0 equiv of (*S*)-BINOL was used in the second and third resolutions]. After a second resolution, (*R*)-**1b** was obtained in 78% yield, and the specific rotation value was $[\alpha]_{589}^{24} = +18.9$. After a third resolution, (*R*)-**1b** was obtained in 94% yield, and the specific rotation value was $[\alpha]_{589}^{23} = +19.1$. This highest specific rotation value was assigned as an enantiopure (*R*)-**1b**. The ee of (*R*)-**1b** includes ca. ±5% error. The highest specific rotation of (*R*)-**1l** was obtained through largely identical procedures, with $[\alpha]_{589}^{22} = +8.3$ (*c* 1.00, EtOH) after one resolution, $[\alpha]_{589}^{22} = +10.1$ after a second resolution, and $[\alpha]_{589}^{24} = +10.3$ after a third resolution.

4.2.5. (*R*)-*N*-Benzyl-*N*-(*tert*-butoxycarbonylmethyl)-*N*-(2-hydroxyethyl)-*N*-methylammonium chloride, monohydrate (*R*)-1b

White solid; $[\alpha]_{589}^{23} = +17.0$ (*c* 1.00, EtOH); 89% ee (determined by specific rotation, using triply-resolved material to give a standard specific rotation, $[\alpha]_{589}^{23} = +19.1$ with ca. ±5% error); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.63 (2H, d, *J* = 7.6 Hz, Ph), 7.54–7.39 (3H, m, Ph), 5.95 (1H, s, OH), 5.30 (1H, d, *J* = 12.4 Hz, CH_2COO), 5.17 (1H, d, *J* = 12.4 Hz, CH_2COO), 4.65 (1H, d, *J* = 17.4 Hz, CH_2Ph), 4.56 (1H, d, *J* = 17.4 Hz, CH_2Ph), 4.19 (2H, s, CH_2CH_2OH), 4.04–3.70 (2H, m, CH_2CH_2OH), 3.48 (3H, s, NCH_3), 1.48 (9H, s, *t*-Bu); ^{13}C NMR (68 MHz, $CDCl_3$) δ 164.0, 133.2, 130.6, 129.1, 126.9, 84.8, 66.9, 62.5, 58.8, 55.6, 48.8, 27.8; IR (film) 3204, 2960, 1732, 1628, 1452, 1392, 1368, 1240, 1146, 1086, 882, 834, 700 cm^{-1}; Anal. Calcd for $C_{16}H_{28}ClNO_4$: C, 57.56; H, 8.45; N, 4.20. Found: C, 57.40; H, 8.16; N, 4.16.

4.2.6. (*R*)-*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(2-hydroxyethyl)-*N*-methyl-*N*-(2-methylbenzyl)ammonium chloride, 1.5 hydrate (*R*)-1d

White solid; $[\alpha]_{589}^{24} = +17.5$ (*c* 1.00, EtOH); 98% ee [determined by HPLC analysis: Daicel Chiralcel OD-H column, *n*-hexane/ethanol/trifluoroacetic acid/diethylamine = 95:5:0.1:0.1 as eluent, flow rate = 0.50 mL/min, t_R = 28.6 min for the (*S*)-**1d** and 32.4 min for (*R*)-**1d**]; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.56 (1H, d, *J* = 7.6 Hz, Ar-H), 7.44–7.23 (3H, m, Ar-H), 5.93 (1H, br, OH), 5.25 (1H, d, *J* = 13.5 Hz, CH_2COO), 5.19 (1H, d, *J* = 13.5 Hz, CH_2COO), 4.74 (2H, s, CH_2Ar), 4.30–4.05 (3H, m, CH_2CH_2OH), 3.77–3.62 (1H, m, CH_2CH_2OH), 3.44 (3H, s, NCH_3), 2.56 (3H, s, $ArCH_3$), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (68 MHz, $CDCl_3$) δ 164.3, 140.3, 134.5, 131.9, 130.7, 126.3, 125.5, 84.8, 64.9, 62.3, 59.1, 55.6, 48.5, 27.8, 20.4; IR (film) 3232, 2964, 1726, 1448, 1368, 1236, 1146, 834, 722 cm^{-1}; Anal. Calcd for $C_{17}H_{31}ClNO_{4.5}$: C, 57.21; H, 8.76; N, 3.92. Found: C, 57.22; H, 8.63; N, 3.62.

4.2.7. (*R*)-*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(2-hydroxyethyl)-*N*-(2-methoxybenzyl)-*N*-methylammonium bromide, 0.5 hydrate (*R*)-1e

White solid; $[\alpha]_{589}^{26} = +4.2$ (*c* 1.00, EtOH); 79% ee [determined by HPLC analysis: Daicel Chiralcel OD-H column, *n*-hexane/ethanol/trifluoroacetic acid/diethylamine = 95:5:0.1:0.1 as eluent, flow rate = 0.50 mL/min, t_R = 17.1 min for the (*S*)-**1e** and 22.7 min for (*R*)-**1e**]; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.66 (1H, dd, *J* = 7.6, 1.8 Hz, Ar-H), 7.49 (1H, ddd, *J* = 8.4, 7.6, 1.8 Hz, Ar-H), 7.05 (1H, dd, *J* = 7.6, 7.6 Hz, Ar-H), 7.00 (1H, d, *J* = 8.4 Hz, Ar-H), 5.27–4.93 (1H, br, OH), 5.14 (1H, d, *J* = 12.4 Hz, CH_2COO), 5.02 (1H, d, *J* = 12.4 Hz, CH_2COO), 4.51 (1H, d, *J* = 17.1 Hz, CH_2Ar), 4.43 (1H, d, *J* = 17.1 Hz, CH_2Ar), 4.30–4.13 (2H, m, CH_2CH_2OH), 4.13–3.99 (1H, m, CH_2CH_2OH), 3.99–3.78 (1H, m, CH_2CH_2OH), 3.89 (3H, s, OCH_3), 3.40 (3H, s, NCH_3), 1.52 (9H, s, *t*-Bu); ^{13}C NMR (68 MHz, $CDCl_3$) δ 163.8, 158.7, 135.6, 132.8, 121.1, 115.1, 111.6, 84.7, 63.2, 62.3, 59.1, 55.7, 55.6, 49.4, 27.9; IR (film) 3268, 2956, 1734, 1600, 1458, 1392, 1368, 1246, 1148, 1086, 1018, 836, 724 cm^{-1}; Anal. Calcd for $C_{17}H_{29}BrNO_{4.5}$: C, 51.13; H, 7.32; N, 3.51. Found: C, 51.20; H, 7.21; N, 3.54.

4.2.8. (*R*)-*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(2-hydroxyethyl)-*N*-(2-methoxybenzyl)-*N*-methylammonium chloride, 1.5 hydrate (*R*)-1f

White solid; $[\alpha]_{589}^{23} = +12.6$ (*c* 1.00, EtOH); 93% ee [determined by HPLC analysis: Daicel Chiralcel OD-H column, *n*-hexane/ethanol/trifluoroacetic acid/diethylamine = 96.5:3.5:0.1:0.1 as eluent, flow rate = 0.50 mL/min, t_R = 63.4 min for the (*S*)-**1f** and 74.4 min for (*R*)-**1f**]; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.63 (1H, dd, *J* = 7.6, 1.6 Hz, Ar-H), 7.49 (1H, ddd, *J* = 8.6, 7.6, 1.6 Hz, Ar-H), 7.06 (1H, dd, *J* = 7.6, 7.6 Hz, Ar-H), 7.00 (1H, d, *J* = 8.6 Hz, Ar-H), 5.12 (1H, d, *J* = 12.4 Hz, CH_2COO), 4.99 (1H, d, *J* = 12.4 Hz, CH_2COO), 4.54 (1H, d, *J* = 17.4 Hz, CH_2Ar), 4.46 (1H, d, *J* = 17.4 Hz, CH_2Ar), 4.27–4.11 (2H, m, CH_2CH_2OH), 4.11–3.97 (1H, m, CH_2CH_2OH), 3.94–3.73 (1H, m, CH_2CH_2OH), 3.89 (3H, s, OCH_3), 3.39 (3H, s, NCH_3), 2.28 (1H, br, OH), 1.52 (9H, s, *t*-Bu); ^{13}C NMR (68 MHz, $CDCl_3$) δ 164.0, 158.7, 135.7, 132.8, 121.2, 115.3, 111.5, 84.6, 63.4, 62.3, 59.1,

55.8, 55.7, 49.4, 27.9; IR (film) 3336, 2968, 1726, 1600, 1440, 1366, 1238, 1146, 1018, 832, 724 cm^{-1}; Anal. Calcd for $C_{17}H_{31}ClNO_{5.5}$: C, 54.76; H, 8.38; N, 3.76. Found: C, 54.71; H, 8.31; N, 3.48.

4.2.9. (*R*)-*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(2-hydroxyethyl)-*N*-methyl-*N*-[2-(trifluoromethyl)benzyl]ammonium bromide (*R*)-1g

White solid; $[\alpha]_{589}^{25} = +6.2$ (*c* 1.00, EtOH); 80% ee [determined by HPLC analysis: Daicel Chiralcel OD-H column, *n*-hexane/ethanol/trifluoroacetic acid/diethylamine = 95:5:0.1:0.1 as eluent, flow rate = 0.50 mL/min, t_R = 17.9 min for the (*S*)-**1g** and 21.5 min for (*R*)-**1g**]; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.15 (1H, d, *J* = 7.6 Hz, Ar-H), 7.84 (1H, d, *J* = 7.6 Hz, Ar-H), 7.76 (1H, dd, *J* = 7.6, 7.6 Hz, Ar-H), 7.68 (1H, dd, *J* = 7.6, 7.6 Hz, Ar-H), 5.51 (1H, d, *J* = 13.6 Hz, CH_2COO), 5.41 (1H, dd, *J* = 13.6 Hz, CH_2COO), 5.05 (1H, br, OH), 4.85 (1H, d, *J* = 17.0 Hz, CH_2Ar), 4.61 (1H, d, *J* = 17.0 Hz, CH_2Ar), 4.35–4.11 (3H, m, CH_2CH_2OH), 3.75–3.60 (1H, m, CH_2CH_2OH), 3.49 (3H, s, NCH_3), 1.52 (9H, s, *t*-Bu); ^{13}C NMR (68 MHz, $CDCl_3$) δ 163.3, 136.8, 132.4, 131.2, 131.0 (q, *J* = 30 Hz), 127.7 (q, *J* = 5 Hz), 124.6, 123.5 (q, *J* = 275 Hz), 85.0, 63.4, 63.1, 60.2, 55.3, 49.4, 27.6; IR (film) 3300, 2960, 1732, 1602, 1580, 1450, 1392, 1368, 1300, 1242, 1146, 1120, 1036, 894, 832, 724 cm^{-1}; Anal. Calcd for $C_{17}H_{25}BrF_3NO_3$: C, 47.67; H, 5.88; N, 3.27. Found: C, 47.69; H, 6.09; N, 3.22.

4.2.10. (*R*)-*N*-(2-Hydroxyethyl)-*N*-(methoxycarbonylmethyl)-*N*-methyl-*N*-(2-methylbenzyl)ammonium bromide, 0.5 hydrate (*R*)-1l

White solid; 8:2 mixture of rotamers; $[\alpha]_{589}^{22} = +8.3$ (*c* 1.00, EtOH); 81% ee (determined by specific rotation, using triply-resolved material to give a standard specific rotation with ca. ±5% error); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.74 (0.2H, d, *J* = 7.4 Hz, Ar-H), 7.58 (0.8H, d, *J* = 7.4 Hz, Ar-H), 7.45–7.23 (3H, m, Ar-H), 5.52 (0.2H, d, *J* = 13.1 Hz, CH_2COO), 5.44 (0.2H, d, *J* = 13.1 Hz, CH_2COO), 5.26 (1.6H, s, CH_2COO), 5.14 (0.8H, d, *J* = 17.4 Hz, CH_2Ar), 5.03 (0.8H, d, *J* = 17.4 Hz, CH_2Ar), 4.97–4.49 (1.4H, m, CH_2Ar and OH), 4.42–4.03 (3H, m, CH_2CH_2OH), 3.79 (3H, s, OCH_3 or NCH_3), 3.69–3.55 (1H, m, CH_2CH_2OH), 3.52 (0.6H, s, OCH_3 or NCH_3), 3.46 (2.4H, s, OCH_3 or NCH_3), 2.63 (0.6H, s, $ArCH_3$), 2.56 (2.4H, s, $ArCH_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 165.2 (0.8C), 160.4 (0.2C), 140.0 (0.2C), 139.9 (0.8C), 134.3 (0.2C), 134.1 (0.8C), 131.6 (0.2C), 131.5 (0.8C), 130.8 (0.2C), 130.5 (0.8C), 126.2 (0.2C), 126.1 (0.8C), 124.8 (0.8C), 123.8 (0.2C), 66.0 (0.2C), 64.8 (0.8C), 62.4 (0.2C), 61.5 (0.8C), 58.9 (0.8C), 58.5 (0.2C), 54.9 (1.0C), 53.7 (0.2C), 52.6 (0.8C), 48.1 (0.8C), 47.4 (0.2C), 20.2 (0.2C), 20.1 (0.8C); IR (film) 3280, 2948, 1742, 1602, 1438, 1262, 1222, 1086, 1000, 886, 722 cm^{-1}; Anal. Calcd for $C_{14}H_{23}BrNO_{3.5}$: C, 49.28; H, 6.79; N, 4.10. Found: C, 49.12; H, 6.56; N, 4.04.

4.2.11. Determination of the absolute configuration of 1l

The absolute configuration of **1l** was determined as (*R*) on the nitrogen atom by a single crystal X-ray diffraction of a 1:1 complex **2l** (Fig. 1). Recrystallization of **2l** from methanol–diethyl ether gave a single crystal which was suitable for crystallographic analysis.[7] Crystal data of **2l**: $C_{34}H_{36}BrNO_5$, *MW* = 618.57; *monoclinic*; space group $P2_1$ (#4); *a* = 9.1803(2) Å, *b* = 13.3010(4) Å, *c* = 12.6018(4) Å, β = 101.267(2)°; *V* = 1509.11(8) Å^3; *Z* = 2; D_{calcd} = 1.361 g/cm^3; μ = 14.08 cm^{-1}; $2\theta_{max}$ = 60.1°; *T* = 296 K; R_1 ($I > 2\sigma(I)$) = 0.045; wR_2 (all data) = 0.102; GOF = 1.16 for 8210 reflections and 370 parameters. The absolute structure was determined based on Flack parameter, 0.001(7), refined using 3823 Friedel pairs.

4.2.12. Representative procedure for the rearrangement of *N*-chiral tetraalkylammonium salt (*R*)-1c

A solution of (*R*)-**1c** (58.6 mg, 0.153 mmol, 94% ee) in acetonitrile (1.5 mL) was cooled to −30 °C and treated with a 1.0 M THF solution of potassium *tert*-butoxide (0.15 mL, 0.15 mmol). The mixture was stirred for 6 h at the same temperature under an argon atmosphere. The resulting mixture was added to a stirred, ice-cold solution of saturated aqueous ammonium chloride, and the mixture was extracted with ether. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine, dried over sodium sulfate, and concentrated. Purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 1:1 as eluent) gave **4c** (20.7 mg, 62% yield) as a colorless oil. The ee was determined to be 60% ee by HPLC analysis [Daicel Chiralpak AD-H column, *n*-hexane/ethanol = 95:5 as eluent, flow rate = 0.50 mL/min, t_R = 20.9 min for the (*S*)-isomer and 27.6 min for (*R*)-isomer].

4.2.13. (*S*)-4-Methyl-3-(2-methylbenzyl)morpholin-2-one (*S*)-4c and (*S*)-4l

Colorless oil; $[\alpha]_{589}^{22} = +4.0$ (*c* 1.00, EtOH); 60% ee (determined by HPLC); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.34–7.08 (4H, m, Ar-H), 4.23 (1H, ddd, *J* = 10.9, 3.0, 3.0 Hz, 6-H), 4.11 (1H, ddd, *J* = 10.9, 10.2, 3.0 Hz, 6-H), 3.45 (1H, dd, *J* = 5.8, 4.9 Hz, 3-H), 3.22 (1H, dd, *J* = 14.5, 4.9 Hz, CH_2Ar), 3.14 (1H, dd, *J* = 14.5, 5.8 Hz, CH_2Ar), 2.89 (1H, ddd, *J* = 12.9, 3.0, 3.0 Hz, 5-H), 2.64 (1H, ddd, *J* = 12.9, 10.2, 3.0 Hz, 5-H), 2.37 (3H, s, NCH_3 or $ArCH_3$), 2.31 (3H, s, NCH_3 or $ArCH_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 170.5, 136.9, 136.1, 130.11, 130.07, 126.5, 125.6, 67.22, 67.16, 50.3, 43.5, 34.5, 19.8; IR (film) 2940, 2848, 2788, 1726, 1488, 1452, 1402, 1368, 1334, 1288, 1184, 1146, 1056, 932, 740 cm^{-1}; Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.12; H, 7.84; N, 6.46.

4.2.14. (*S*)-3-Benzyl-4-methylmorpholin-2-one (*S*)-4b

Colorless oil; $[\alpha]_{589}^{25} = +6.1$ (*c* 1.00, EtOH); 56% ee [determined by HPLC analysis: Daicel Chiralpak AD–H column, *n*-hexane/ethanol = 95:5 as eluent, flow rate = 0.50 mL/min, t_R = 20.4 min for the (*S*)-**4b** and 28.4 min for (*R*)-**4b**]; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.35–7.17 (5H, m, Ph), 4.13 (1H, ddd, *J* = 10.8, 2.7, 2.7 Hz, 6-H), 3.96 (1H, ddd, *J* = 10.8, 10.8, 2.7 Hz, 6-H), 3.38 (1H, dd, *J* = 4.6, 4.3 Hz, 3-H), 3.26 (1H, dd, *J* = 14.3, 4.3 Hz, CH_2Ph), 3.13 (1H, dd, *J* = 14.3, 4.6 Hz, CH_2Ph), 2.82 (1H, ddd, *J* = 12.6, 2.7, 2.7 Hz, 5-H), 2.63 (1H, ddd, *J* = 12.6, 10.8, 2.7 Hz, 5-H), 2.42 (3H, s, NCH_3); ^{13}C NMR (68 MHz, $CDCl_3$) δ 170.1, 137.4, 129.9, 128.0, 126.5, 68.0, 67.4, 50.6, 43.1, 36.4; IR (film) 3020, 2944, 2844, 2788, 1726, 1600, 1490, 1450, 1402, 1368, 1334, 1290, 1180, 1144, 1056, 934, 746, 696 cm^{-1}; Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.92; H, 7.31; N, 6.79.

4.2.15. (*S*)-3-(2-Methoxybenzyl)-4-methylmorpholin-2-one (*S*)-4e and (*S*)-4f

Colorless oil; $[\alpha]_{589}^{25} = +12.0$ (*c* 1.00, EtOH); 50% ee [determined by HPLC analysis: Daicel Chiralpak AD–H column, *n*-hexane/ethanol = 95:5 as eluent, flow rate = 0.50 mL/min, t_R = 25.8 min for the (*S*)-isomer and 31.0 min for (*R*)-isomer]; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.28–7.16 (2H, m, Ar-H), 6.93–6.81 (2H, m, Ar-H), 4.30–4.15 (2H, m, 6-H), 3.81 (3H, s, OCH_3), 3.41–3.24 (2H, m, 3-H and CH_2Ar), 3.18 (1H, dd, *J* = 14.2, 6.6 Hz, CH_2Ar), 2.83 (1H, ddd, *J* = 12.8, 3.0, 3.0 Hz, 5-H), 2.61 (1H, ddd, *J* = 12.8, 8.4, 5.0 Hz, 5-H), 2.33 (3H, s, NCH_3); ^{13}C NMR (68 MHz, $CDCl_3$) δ 170.6, 157.7, 131.0, 127.7, 126.2, 120.2, 110.0, 67.3, 66.3, 54.8, 50.5, 43.1, 31.9; IR (film) 2940, 2828, 2784, 1722, 1598, 1584, 1488, 1452, 1402, 1334, 1290, 1238, 1182, 1146, 1110, 1026, 932, 804, 746 cm^{-1}; Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.15; H, 7.41; N, 5.92.

4.2.16. 2-[*N*-(2-Hydroxyethyl)-*N*-methylamino]-2-[2-methyl-3-(trifluoromethyl)phenyl]acetic acid *tert*-butyl ester 5g

Colorless oil; $[\alpha]_{589}^{23} = +5.8$ (*c* 1.00, EtOH); 11% ee [determined by HPLC analysis: Daicel Chiralpak AD-H column, *n*-hexane/isopropanol =

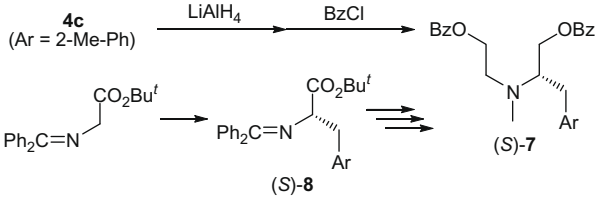
99.5:0.5 as eluent, flow rate = 0.50 mL/min, t_R = 39.3 min for the minor isomer and 46.0 min for the major isomer]; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.62 (1H, d, J = 7.6 Hz, Ar-H), 7.61 (1H, d, J = 7.6 Hz, Ar-H), 7.29 (1H, dd, J = 7.6, 7.6 Hz, Ar-H), 4.53 (1H, s, NCH-COO), 3.68–3.46 (2H, br, NCH_2CH_2OH), 2.84–2.58 (3H, m, NCH_2CH_2OH), 2.52 (3H, s, NCH_3 or $ArCH_3$), 2.30 (3H, s, NCH_3 or $ArCH_3$), 1.41 (9H, s, *t*-Bu); ^{13}C NMR (68 MHz, $CDCl_3$) δ 171.0, 137.4, 136.1, 131.7, 129.7 (q, J = 29 Hz), 125.6, 125.5 (q, J = 5 Hz), 124.4 (q, J = 274 Hz), 81.9, 68.8, 58.7, 55.6, 38.3, 27.8, 14.7; IR (film) 3436, 2964, 2872, 2796, 1722, 1588, 1450, 1390, 1366, 1308, 1248, 1204, 1120, 1022, 946, 784, 722 cm^{-1}; Anal. Calcd for $C_{17}H_{24}F_3NO_3$: C, 58.78; H, 6.96; N, 4.03. Found: C, 59.05; H, 6.93; N, 4.00.

4.2.17. *N*-(2-Hydroxyethyl)-*N*-methyl-3-[2-(trifluoromethyl)-phenyl]morpholin-2-one 6g

Colorless oil; $[\alpha]_{589}^{23} = +42.3$ (c 1.00, EtOH); 56% ee [determined by HPLC analysis: Daicel Chiralpak AS-H column, *n*-hexane/ethanol = 90:10 as eluent, flow rate = 0.50 mL/min, t_R = 14.3 min for the minor isomer and 16.5 min for the major isomer]; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.62 (1H, d, J = 7.8 Hz, Ar-H), 7.56 (1H, d, J = 7.8 Hz, Ar-H), 7.28 (1H, dd, J = 7.8, 7.8 Hz, Ar-H), 4.70 (1H, ddd, J = 11.9, 11.0, 3.2 Hz, 6-H), 4.45 (1H, ddd, J = 11.0, 3.2, 1.4 Hz, 6-H), 4.13 (1H, s, 3-H), 3.03 (1H, ddd, J = 12.8, 3.2, 1.4 Hz, 5-H), 2.78 (1H, ddd, J = 12.8, 11.9, 3.2 Hz, 5-H), 2.53 (3H, s, NCH_3), 2.13 (3H, s, $ArCH_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 167.9, 137.9, 136.3, 133.6, 130.0 (q, J = 29 Hz), 126.0 (q, J = 5 Hz), 125.7, 124.5 (q, J = 275 Hz), 70.5, 68.2, 51.4, 43.5, 15.3; IR (film) 2948, 2900, 2840, 2792, 2708, 1722, 1636, 1586, 1450, 1404, 1366, 1306, 1104, 1024, 928, 884, 840, 794, 724 cm^{-1}; Anal. Calcd for $C_{13}H_{14}F_3NO_2$: C, 57.14; H, 5.16; N, 5.13. Found: C, 57.30; H, 5.21; N, 5.00.

4.2.18. Determination of the absolute configuration of [1,2] Stevens rearrangement product 4

The (*S*)-configuration of **4** was assigned as follows. The [1,2] Stevens rearrangement product **4c** was converted to the corresponding dibenzoyl derivative **7**; this compound was then chromatographically correlated with the (*S*)-authentic sample (*S*)-**7**. Compound (*S*)-**7** was prepared from Schiff-base protected glycine *tert*-butyl ester via phase-transfer catalyzed asymmetric alkylation using (*R*, *R*)-bis(2-naphthyl)-NAS bromide (Maruoka catalyst).[16] The configurations of **4b**, **4d**, **4e**, **4f**, and **4l** were determined by analogy with **4c**.



4.2.18.1. Preparation of dibenzoyl derivative 7 from 4c. A solution of **4c** (41 mg, 0.19 mmol) in THF (1.0 mL) was added to a suspension of lithium aluminum hydride (9 mg, 0.24 mmol) in THF (1.1 mL) at 0 °C and the mixture was stirred at room temperature for 2 h. The resulting mixture was diluted with diethyl ether and the reaction was quenched with water (9 μL), 15% aqueous sodium hydroxide solution (9 μL), and water (27 μL) at 0 °C. The mixture was stirred for 1 h at room temperature and filtered through a pad of Celite. The residual solids in the flask and/or on the pad of Celite were washed with hot ethanol and filtered. The filtrate was concentrated and the residue was dissolved in dichloromethane (1.5 ml). Triethylamine (0.11 mL, 0.79 mmol), 4-dimethylaminopyridine (DMAP) (2 mg, 0.02 mmol), and benzoyl chloride (44 μL, 0.38 mmol) were added to the solution at 0 °C. After stirring for 2 h at room temperature, the resulting mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine, dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 5:1 as eluent) to afford *N*-(2-benzoyloxyethyl)-*N*-[2-benzoyloxy-1-(2-methylbenzyl)]ethylmethylamine **7** (54 mg, 66% yield) as a colorless oil. The ee was determined to be 60% ee by chiral HPLC analysis [Daicel Chiralcel OD-H, hexane/isopropanol = 90:10, 0.50 mL/min, t_R = 15.1 min for the (*S*)-isomer and 18.3 min for the (*R*)-isomer]. The absolute configuration of **7** thus obtained was determined to be (*S*) by comparison with the (*S*)-authentic sample (*S*)-**7**.

4.2.18.2. Preparation of the authentic sample of (S)-7. (Step 1) To a mixture of *tert*-butyl 2-(diphenylmethyleneamino)acetate (89 mg, 0.30 mmol), 2-methylbenzyl bromide (48 μL, 0.36 mmol), (*R*,*R*)-bis(2-naphthyl)-NAS bromide (Maruoka catalyst)[16] (5 mg, 0.006 mmol) in toluene (1.5 mL) was added 50 wt % potassium hydroxide aqueous solution (1 mL) at 0 °C under an air atmosphere. The mixture was stirred for 1 h at the same temperature and quenched with saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate and the combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 7:1–5:1 as eluent) to obtain (*S*)-*tert*-butyl 2-(diphenylmethyleneamino)-3-(2-methylphenyl)propanoate (*S*)-**8** (112 mg, 93% yield) as a colorless oil. The ee was determined to be 94% ee by chiral HPLC analysis [Daicel Chiralcel OD-H, hexane/ethanol = 99.5:0.5, 0.50 mL/min, t_R = 12.2 min for the (*R*)-isomer and 15.4 min for the (*S*)-isomer]. The absolute configuration was assigned as (*S*) by analogy with the previous examples of (*R*,*R*)-bis(2-naphthyl)-NAS bromide-catalyzed asymmetric alkylation of Schiff-base protected glycine *tert*-butyl ester. (Step 2) A solution of (*S*)-**8** (163 mg, 0.41 mmol) in THF (2 mL) was treated with a 10 wt % citric acid aqueous solution (2 mL) and stirred for 2 h at room temperature. The resulting mixture was diluted with diethyl ether and extracted with a 10 wt % citric acid aqueous solution (two times). The combined aqueous extracts were treated with a 15 wt % sodium hydroxide aqueous solution and extracted with diethyl ether (three times). The combined ethereal extracts were washed with brine, dried over sodium sulfate, and concentrated. The residual oil was dissolved in methanol (1 ml) and treated with diisopropylethylamine (61 μL, 0.35 mmol) and methyl bromoacetate (30 μL, 0.32 mmol) at room temperature. After stirring for 4 h at the same temperature, the resulting mixture was diluted with saturated aqueous sodium hydrogen carbonate. The mixture was extracted with diethyl ether and the combined extracts were washed with brine. The organic layer was dried over sodium sulfate and evaporated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 2:1–1:1 as eluent) to obtain *tert*-butyl 2-(2-methoxy-2-oxoethylamino)-3-(2-methylphenyl)propanoate **10** (41 mg, 42% yield) as a colorless oil. (Step 3) A mixture of **10** (41 mg, 0.13 mmol), palladium on carbon (loading: 10 wt %, 7 mg), and 37 wt % formaldehyde aqueous solution (0.10 mL) in ethanol (1.3 mL) was stirred for 12 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue (44 mg) was dissolved in THF (1.3 mL) and the solution was added to a suspension of lithium aluminum hydride (25 mg, 0.66 mmol) in THF (1.3 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 2 h. The resulting mixture was diluted with diethyl ether and quenched with water (25 μL), 15% aqueous sodium hydroxide solution (25 μL), and water (75 μL) at 0 °C. The mixture was stirred for 2 h at room temperature and filtered through a pad

of Celite. The residual solids in the flask and/or on the pad of Celite were washed with hot ethanol and filtered. The filtrate was concentrated and the residue (27 mg) was dissolved in dichloromethane (1.3 mL). Triethylamine (91 μL, 0.65 mmol), 4-dimethylamino-pyridine (DMAP) (2 mg, 0.02 mmol), and benzoyl chloride (36 μL, 0.31 mmol) were added to the solution at 0 °C. After stirring for 1 h at 0 °C and 2.5 h at room temperature, the resulting mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 5:1–3:1 as eluent) to afford (*S*)-**7** (32 mg, 57% yield) as a colorless oil. The ee was determined to be 94% ee by chiral HPLC analysis [Daicel Chiralcel OD-H, hexane/isopropanol = 90:10, 0.50 mL/min, t_R = 14.9 min for the (*S*)-isomer and 19.1 min for the (*R*)-isomer]: $[\alpha]_{589}^{23} = 4.8$ (*c* 1.00, EtOH); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.05–7.91 (4H, m, Ar-H), 7.57–7.46 (2H, m, Ar-H), 7.43–7.31 (4H, m, Ar-H), 7.19–7.00 (4H, m, Ar-H), 4.49 (1H, dd, *J* = 11.7, 7.4 Hz, NCHC*H*$_2$O), 4.33 (2H, t, *J* = 5.7 Hz, NCH$_2$C*H*$_2$O), 4.28 (1H, dd, *J* = 11.7, 4.6 Hz, NCHC*H*$_2$O), 3.36–3.22 (1H, m, NC*H*CH$_2$O), 3.04 (2H, t, *J* = 5.7 Hz, NC*H*$_2$CH$_2$O), 2.92 (1H, dd, *J* = 13.6, 5.5 Hz, CH$_2$Ar), 2.76 (1H, dd, *J* = 13.6, 8.2 Hz, CH$_2$Ar), 2.55 (3H, s, NCH$_3$), 2.32 (3H, s, ArCH$_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 166.4, 166.3, 137.3, 135.9, 132.8, 132.7, 130.3, 130.1, 130.0, 129.9, 129.4 (4C), 128.3 (2C), 128.2 (2C), 126.3, 125.9, 63.9, 63.4, 62.9, 53.1, 37.9, 32.3, 19.4; IR (film) 3056, 2944, 1710, 1598, 1582, 1448, 1368, 1310, 1266, 1172, 1110, 1066, 1024, 968, 704 cm^{-1}; Anal. Calcd for $C_{27}H_{29}NO_4$: C, 75.15; H, 6.77; N, 3.25. Found: C, 75.43; H, 6.97; N, 3.23.

4.3. Preparation of substrates

4.3.1. *N*-(*tert*-Butoxycarbonylmethyl)-*N*-(2-hydroxyethyl)-*N*-methyl-*N*-(2-methylbenzyl)ammonium bromide, 0.5 hydrate 1c

(Step 1) A mixture of *N*-methylethanolamine (0.92 mL, 11.5 mmol), *tert*-butyl bromoacetate (1.48 mL, 10.0 mmol), and triethylamine (1.39 mL, 10.0 mmol) in methanol (20 mL) was stirred for 4 h at room temperature. The resulting mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel (dichloromethane/methanol = 10:1 as eluent) to afford *N*-(*tert*-butoxycarbonylmethyl)-*N*-(2-hydroxyethyl)methyl-amine **11** (1.78 g, 94% yield) as a colorless oil. (Step 2) A mixture of **11** (261 mg, 1.38 mmol) and 2-methylbenzyl bromide (0.22 mL, 1.6 mmol) in acetonitrile (2.7 mL) was stirred for 48 h at room temperature. The resulting mixture was concentrated by evaporation and the residue was purified by chromatography on silica gel (dichloromethane/methanol = 10:1–5:1 as eluent) to afford **1c** (507 mg, 96% yield) as a white solid.

4.3.2. *N*-Benzyl-*N*-(*tert*-butoxycarbonylmethyl)-*N*-(2-hydroxyethyl)-*N*-methylammonium bromide 1a

Prepared in 94% yield (two steps) by the same procedures with **1c** using benzyl bromide instead of 2-methylbenzyl bromide in step 2: white solid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.67–7.59 (2H, m, Ph), 7.55–7.41 (3H, m, Ph), 5.30 (1H, d, *J* = 12.7 Hz, CH$_2$COO), 5.16 (1H, d, *J* = 12.7 Hz, CH$_2$COO), 5.10 (1H, t, *J* = 5.1 Hz, OH), 4.57 (1H, d, *J* = 17.1 Hz, CH$_2$Ph), 4.49 (1H, d, *J* = 17.1 Hz, CH$_2$Ph), 4.29–4.16 (2H, m, C*H*$_2$CH$_2$OH), 4.05–3.84 (2H, m, CH$_2$C*H*$_2$OH), 3.49 (3H, s, NCH$_3$), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (68 MHz, $CDCl_3$) δ 164.0, 133.3, 130.8, 129.2, 126.7, 85.0, 67.0, 62.5, 58.9, 55.5, 49.0, 27.8; IR (film) 3280, 2968, 1734, 1622, 1452, 1392, 1368, 1240, 1148, 1086, 898, 834, 702 cm^{-1}; Anal. Calcd for $C_{16}H_{26}BrNO_3$: C, 53.34; H, 7.27; N, 3.89. Found: C, 53.52; H, 7.57; N, 3.73.

4.3.3. *N*-Benzyl-*N*-(*tert*-butoxycarbonylmethyl)-*N*-(2-hydroxyethyl)-*N*-methylammonium chloride, monohydrate 1b

Prepared in 95% yield (two steps) by similar procedures with **1c**. In step 2, the reaction was carried out without solvent using an excess amount of benzyl chloride (5 equiv) instead of 2-methylbenzyl bromide.

4.3.4. *N*-(*tert*-Butoxycarbonylmethyl)-*N*-(2-hydroxyethyl)-*N*-methyl-*N*-(2-methylbenzyl)ammonium chloride, 1.5 hydrate 1d

Prepared in 84% yield (two steps) by similar procedures with **1c**. In step 2, the reaction was carried out without solvent using an excess amount of 2-methylbenzyl chloride (1.5 equiv) instead of 2-methylbenzyl bromide.

4.3.5. *N*-(*tert*-Butoxycarbonylmethyl)-*N*-(2-hydroxyethyl)-*N*-(2-methoxybenzyl)-*N*-methylammonium bromide, 0.5 hydrate 1e

(Step 1) A mixture of ethanolamine (604 μL, 10.0 mmol) and *o*-anisaldehyde (1.22 mL, 10.0 mmol) in trimethyl orthoformate (15 mL) was stirred for 18 h at room temperature. The resulting mixture was concentrated and the residue was dissolved in methanol (10 mL). The solution was treated with sodium borohydride (378 mg, 10.0 mmol) at 0 °C and stirred for 4 h at room temperature. The solution was diluted with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel (dichloromethane/methanol = 10:1–3:1 as eluent) to afford *N*-(2-hydroxyethyl)-*N*-(2-methoxylbenzyl)amine **12** (1.81 g, quant.) as a colorless oil. (Step 2) A mixture of **12** (1.81 g, 10.0 mmol), 37 wt % formaldehyde aqueous solution (1.1 mL, 14 mmol), and formic acid (0.52 mL, 14 mmol) was heated at 100 °C for 2 h. The resulting mixture was cooled to room temperature, diluted with water, and treated with saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate and the combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine. The organic layer was dried over sodium sulfate and concentrated. Purification of the residue by chromatography on silica gel (dichloromethane/methanol = 10:1 as eluent) gave *N*-(2-hydroxyethyl)-*N*-(2-methoxylbenzyl)methylamine **13** (1.67 g, 86% yield) as a colorless oil. (Step 3) A mixture of **13** (750 mg, 3.84 mmol) and bromoacetic acid *tert*-butyl ester (0.85 mL, 5.8 mmol) in acetonitrile (7.7 mL) was stirred for 48 h at room temperature. The resulting mixture was concentrated by evaporation and the residue was purified by chromatography on silica gel (dichloromethane/methanol = 10:1–5:1 as eluent) to afford **1e** (1.15 g, 75% yield) as a white solid.

4.3.6. *N*-(*tert*-Butoxycarbonylmethyl)-*N*-(2-hydroxyethyl)-*N*-(2-methoxybenzyl)-*N*-methylammonium chloride, 1.5 hydrate 1f

Prepared in 81% yield (two steps) by similar procedures with **1c**. In step 2, the reaction was carried out without solvent using excess amount of 2-methoxybenzyl chloride (1.5 equiv) instead of 2-methylbenzyl bromide.

4.3.7. *N*-(*tert*-Butoxycarbonylmethyl)-*N*-(2-hydroxyethyl)-*N*-methyl-*N*-[2-(trifluoromethyl)benzyl] ammonium bromide 1g

Prepared in 88% yield (two steps) by the same procedures with **1c** using 2-(trifluoromethyl)benzyl bromide instead of 2-methylbenzyl bromide in step 2.

4.3.8. *N*-(*tert*-Butoxycarbonylmethyl)-*N*-(2-hydroxyethyl)-*N*-methyl-*N*-(4-methylbenzyl)ammonium bromide 1h

(Step 1) A mixture of *N*-methylethanolamine (0.18 mL, 2.2 mmol) and sodium hydrogen carbonate (0.50 g, 6.0 mmol) in THF (4 mL) was treated with *p*-toluoyl chloride (0.26 mL, 2.0 mmol) at 0 °C and the mixture was stirred for 2 h at room

temperature. The resulting mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was dissolved in THF (2.0 mL) and the solution was added to a suspension of lithium aluminum hydride (114 mg, 3.0 mmol) in THF (4 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 3 h. The resulting mixture was diluted with diethyl ether and quenched with water (0.11 mL), 15% aqueous sodium hydroxide solution (0.11 mL), and water (0.33 mL) at 0 °C. The mixture was stirred for 1 h at room temperature and filtered through a pad of Celite. The filtrate was concentrated and the residue was purified by chromatography on silica gel (dichloromethane/methanol = 10:1 as eluent) to afford *N*-(2-hydroxyethyl)-*N*-(4-methylbenzyl)methylamine **14** (319 mg, 89% yield) as a colorless oil. (Step 2) A mixture of **14** (305 mg, 1.70 mmol) and bromoacetic acid *tert*-butyl ester (0.30 mL, 2.0 mmol) in acetonitrile (3.4 mL) was stirred for 48 h at room temperature. The resulting mixture was concentrated by evaporation and the residue was purified by chromatography on silica gel (dichloromethane/methanol = 10:1–7:1 as eluent) to afford **1h** (606 mg, 95% yield) as a white solid: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.48 (2H, d, J = 8.0 Hz, Ar-H), 7.25 (2H, d, J = 8.0 Hz, Ar-H), 5.30–4.95 (1H, br, OH), 5.21 (1H, d, J = 12.6 Hz, CH_2COO), 5.08 (1H, d, J = 12.6 Hz, CH_2COO), 4.46 (2H, s, CH_2Ar), 4.21 (2H, t, J = 4.2 Hz, CH_2CH_2OH), 3.98 (1H, dt, J = 13.9, 4.2 Hz, CH_2CH_2OH), 3.88 (1H, dt, J = 13.9, 4.2 Hz, CH_2CH_2OH), 3.46 (3H, s, NCH_3), 2.38 (3H, s, $ArCH_3$), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (68 MHz, $CDCl_3$) δ 164.0, 141.1, 133.1, 129.9, 123.6, 84.9, 66.9, 62.4, 58.7, 55.6, 48.9, 27.8, 21.2; IR (film) 3272, 2952, 1728, 1610, 1448, 1390, 1368, 1240, 1148, 1082, 802, 722 cm^{-1}; Anal. Calcd for $C_{17}H_{28}BrNO_3$: C, 54.55; H, 7.54; N, 3.74. Found: C, 54.28; H, 7.70; N, 3.55.

4.3.9. *N*-(*tert*-Butoxycarbonylmethyl)-*N*-(2-hydroxyethyl)-*N*-methyl-*N*-(4-methylbenzyl)ammonium chloride, monohydrate 1i

Prepared in 78% yield (two steps) by similar procedures with **1c**. In step 2, the reaction was carried out without solvent using excess amount of 4-methylbenzyl chloride (1.5 equiv) instead of 2-methylbenzyl bromide: white solid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.48 (2H, d, J = 7.8 Hz, Ar-H), 7.24 (2H, d, J = 7.8 Hz, Ar-H), 6.40–5.50 (1H, br, OH), 5.21 (1H, d, J = 12.6 Hz, CH_2COO), 5.09 (1H, d, J = 12.6 Hz, CH_2COO), 4.51 (2H, s, CH_2Ar), 4.18 (2H, s, CH_2CH_2OH), 4.02–3.78 (2H, m, CH_2CH_2OH), 3.45 (3H, s, NCH_3), 2.38 (3H, s, $ArCH_3$), 1.49 (9H, s, *t*-Bu); ^{13}C NMR (68 MHz, $CDCl_3$) δ 164.1 141.0, 133.1, 129.8, 123.8, 84.7, 66.9, 62.5, 58.7, 55.7, 48.8, 27.8, 21.1; IR (film) 3256, 2964, 1726, 1612, 1388, 1366, 1234, 1146, 802, 722 cm^{-1}; Anal. Calcd for $C_{17}H_{30}ClNO_4$: C, 58.69; H, 8.69; N, 4.03. Found: C, 58.87; H, 8.74; N, 3.73.

4.3.10. *N*-(*tert*-Butoxycarbonylmethyl)-*N*-(2-hydroxyethyl)-*N*-methyl-*N*-(4-trifluoromethylbenzyl)ammonium bromide, monohydrate 1j

Prepared in 99% yield (two steps) by the same procedures with **1c** using 4-(trifluoromethyl)benzyl bromide instead of 2-methylbenzyl bromide in step 2: white solid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.91 (2H, d, J = 7.8 Hz, Ar-H), 7.72 (2H, d, J = 7.8 Hz, Ar-H), 5.44 (1H, d, J = 12.4 Hz, CH_2COO), 5.36 (1H, d, J = 12.4 Hz, CH_2COO), 5.10 (1H, br, OH), 4.56 (1H, d, J = 17.1 Hz, CH_2Ar), 4.41 (1H, d, J = 17.1 Hz, CH_2Ar), 4.22 (2H, s, CH_2CH_2OH), 4.10–3.87 (2H, m, CH_2CH_2OH), 3.52 (3H, s, NCH_3), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (68 MHz, $CDCl_3$) δ 163.7, 134.0, 132.7 (q, J = 33 Hz), 130.7, 126.0, 123.3 (q, J = 273 Hz), 85.3, 65.7, 62.7, 59.2, 55.5, 49.1, 27.8; IR (film) 3272, 2964, 1728, 1616, 1454, 1418, 1392, 1368, 1320, 1242, 1148, 1066, 1018, 822, 722 cm^{-1}; Anal. Calcd for $C_{17}H_{27}BrF_3NO_4$: C, 45.75; H, 6.10; N, 3.14. Found: C, 45.88; H, 5.81; N, 3.27.

4.3.11. *N*-(*tert*-Butoxycarbonylmethyl)-*N*-(2-hydroxyethyl)-*N*-methyl-*N*-(4-trifluoromethylbenzyl)ammonium chloride, monohydrate 1k

Prepared in 86% yield (two steps) by similar procedures with **1c**. In step 2, the reaction was carried out without solvent using an excess amount of 4-(trifluoromethyl)benzyl chloride (1.5 equiv) instead of 2-methylbenzyl bromide: white solid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.89 (2H, d, J = 8.0 Hz, Ar-H), 7.71 (2H, d, J = 8.0 Hz, Ar-H), 5.93 (1H, br, OH), 5.48 (1H, d, J = 12.3 Hz, CH_2COO), 5.38 (1H, d, J = 12.3 Hz, CH_2COO), 4.74 (1H, d, J = 17.1 Hz, CH_2Ar), 4.56 (1H, d, J = 17.1 Hz, CH_2Ar), 4.20 (2H, s, CH_2CH_2OH), 4.03–3.80 (2H, m, CH_2CH_2OH), 3.50 (3H, s, NCH_3), 1.48 (9H, s, *t*-Bu); ^{13}C NMR (68 MHz, $CDCl_3$) δ 164.0, 134.1, 132.8 (q, J = 33 Hz), 131.0 (q, J = 1 Hz), 126.0 (q, J = 3 Hz), 123.4 (q, J = 273 Hz), 85.3, 65.9, 62.7, 59.2, 55.7, 49.1, 27.8; IR (film) 3220, 2968, 1728, 1390, 1368, 1320, 1238, 1124, 1066, 824, 724 cm^{-1}; Anal. Calcd for $C_{17}H_{27}ClF_3NO_4$: C, 50.81; H, 6.77; N, 3.49. Found: C, 50.89; H, 6.93; N, 3.35.

4.3.12. *N*-(2-Hydroxyethyl)-*N*-(methoxycarbonylmethyl)-*N*-methyl-*N*-(2-methylbenzyl)ammonium bromide, 0.5 hydrate 1l

(Step 1) 2-Methylbenzyl bromide (0.27 mL, 2.0 mmol) was added to a solution of *N*-methylethanolamine (0.46 mL, 5.7 mmol) in methanol (4 mL) at 0 °C and the mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated and diluted with water. The mixture was extracted with ether and the combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel (dichloromethane/methanol = 10:1–5:1 as eluent) to afford *N*-(2-hydroxyethyl)-*N*-(2-methylbenzyl)methylamine **15** as a colorless oil (308 mg, 86% yield). (Step 2) A mixture of **15** (300 mg, 1.67 mmol) and methyl bromoacetate (0.19 mL, 2.0 mmol) in acetonitrile (3.3 mL) was stirred for 48 h at room temperature. The resulting mixture was concentrated by evaporation and the residue was purified by chromatography on silica gel (dichloromethane/methanol = 10:1–5:1 as eluent) to afford **1l** as a white solid (489 mg, 86% yield).

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8. We attempted to use inorganic bases such as KOH or CsOH to improve the rate of *N*-to-*C* chirality transmission, as described by our previous report (Ref.[2b]); however, the yield and ee of the product **4c** were lowered.
9. The compound **4c** was converted to the *O*,*O*-dibenzoyl protected amino diol **7** by $LiAlH_4$ reduction and dibenzoylation; this material was then chromatographically correlated with the (*S*)-authentic sample. The compound (*S*)-**7** was prepared from Schiff-base protected glycine *tert*-butyl ester via phase transfer catalyzed asymmetric alkylation. Details: see Section 4.2.18.
10. THF was added as a 1.0 M THF solution of *t*-BuOK.
11. When the product (*S*)-**4c** (60% ee) was treated with *t*-BuOK (0.2 equiv) in CH_3CN–THF (10:1) at −30 °C for 30 min, (*S*)-**4c** was recovered in 74% yield without racemization (60% ee). Use of excess amount of *t*-BuOK (over 1.0 equiv) in the rearrangement of (*R*)-**1c** decreased the chemical yield.
12. (a) Ollis, W. D.; Rey, M.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1009; (b) Ollis, W. D.; Rey, M.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1975**, 543.
13. Preparation: Treatment of (*R*)-**1g** (80% ee) with (*S*)-BINOL (1.0 equiv) in dichloromethane afforded the 1:1 complex **2g**. Adduct **2g** was recrystallized from dichloromethane–hexane; then the crystals were dissociated in diethyl ether–water to give (*R*)-**1g** (93% ee).
14. Recently, our group reported that an electron-withdrawing group on *N*-benzylic substituent enhanced the rate of Sommelet–Hauser rearrangement: (a) Tayama, E.; Orihara, K.; Kimura, H. *Org. Biomol. Chem.* **2008**, *6*, 3673; (b) Tayama, E.; Kimura, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 8869.
15. The absolute configurations of **5g** and **6g** were not determined.
16. (a) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139; (b) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519.