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

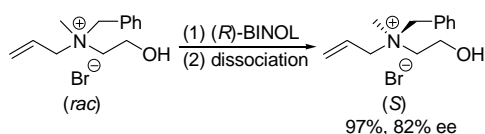
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Abstract—The optical resolution of *N*-chiral, amino acid-derived quaternary ammonium salts is demonstrated by using chiral BINOL as a complexing agent. Determination of the enantiopurities and absolute configurations of the resolved *N*-chiral tetraalkylammonium 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. © 2013 Elsevier Science. All rights reserved

1. Introduction

The asymmetric Stevens rearrangement¹ 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. Diastereoselective quaternarization of tertiary amines bearing a chiral 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 optical resolution of *N*-chiral tetraalkylammonium salts by fractional crystallization—was reported by Pope,³ Jones⁴ and Torbeev.⁵ However, these methods have limited practical value because they cannot be applied to several types of *N*-chiral tetraalkylammonium salts.



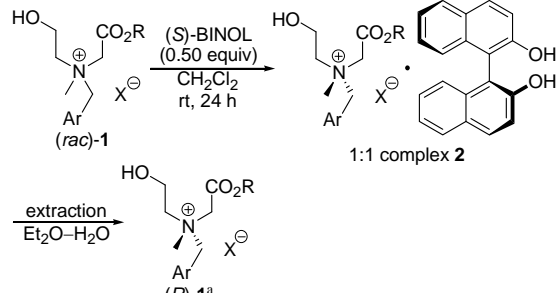
Scheme 1. Previously reported optical resolution of nitrogen-centered chiral tetraalkylammonium salts

Recently, we described the efficient and direct optical resolution of racemic, *N*-centered chiral tetraalkylammonium salts by complexation with (*R*)-1,1'-bi-2-naphthol (BINOL) (Scheme 1).⁶ We now 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 optical 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 treated with (*S*)-BINOL (0.50 equiv) at room temperature for 24 h. Unfortunately, no precipitation was observed, and the optical 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, the 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 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 optical resolutions as the standard value (Details: see experimental section).

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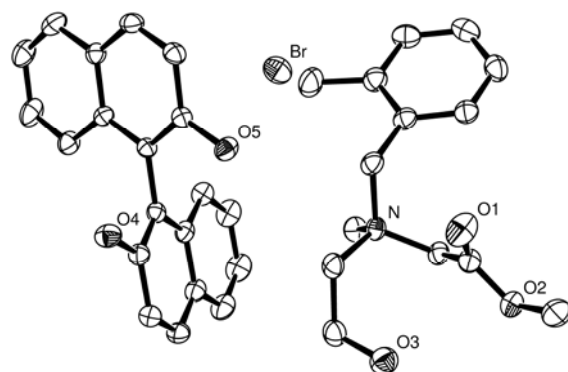
Table 1. Optical resolution of *N*-centered chiral tetraalkylammonium salt **1** by diastereoselective complexation with (*S*)-BINOL


entry	Ar	R	X		yield (%) ^b	ee (%)
					2	1 (2 steps)
1	Ph	<i>t</i> -Bu	Br	a	0 ^c	—
2	Ph	<i>t</i> -Bu	Cl	b	90	84
3	2-Me-Ph	<i>t</i> -Bu	Br	c	49	45
4	2-Me-Ph	<i>t</i> -Bu	Cl	d	84	79
5	2-MeO-Ph	<i>t</i> -Bu	Br	e	76	72
6	2-MeO-Ph	<i>t</i> -Bu	Cl	f	69	66
7	2-CF ₃ -Ph	<i>t</i> -Bu	Br	g	85	77
8	4-Me-Ph	<i>t</i> -Bu	Br	h	0 ^c	—
9	4-Me-Ph	<i>t</i> -Bu	Cl	i	0 ^c	—
10	4-CF ₃ -Ph	<i>t</i> -Bu	Br	j	0 ^c	—
11	4-CF ₃ -Ph	<i>t</i> -Bu	Cl	k	0 ^c	—
12	2-Me-Ph	Me	Br	l	82	77

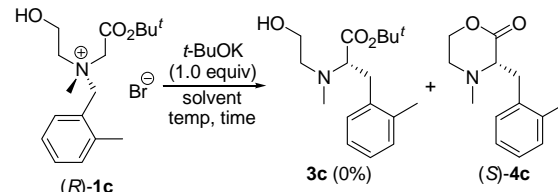
^a Tentatively assigned configuration determined by analogy with (*R*)-**11**.^b Isolated yield. Determined from the amount of (*S*)-BINOL. ^c Not precipitated. ^d Determined by specific rotation, using the highest specific rotation obtained after three optical resolutions as the standard value. The results include ca. ±5% errors. ^e Determined by HPLC analysis. ^f The absolute configuration was determined by a single crystal X-ray diffraction.

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 (entries 5–7). The ee of 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 (Figure 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 (*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 ₂ Cl ₂ –THF (10:1)	−20, 6	55	52 (55)
3	CH ₂ Cl ₂ –THF (10:1)	−30, 6	57	55 (59)
4	CH ₃ CN–THF (10:1)	−30, 6	62	60 (64)
5	CH ₃ CN–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–

THF¹⁰ (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). 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). Though the solvent effect is presently unclear, however, it was reported that the rate of chirality transmission in [1,2] Stevens rearrangement is changeable by a variety of solvents.¹²

With optimized conditions in hand (Table 2, entry 4), we carried out the rearrangement of other *N*-chiral tetraalkylammonium salts (*R*)-**1**. 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 the 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**.

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

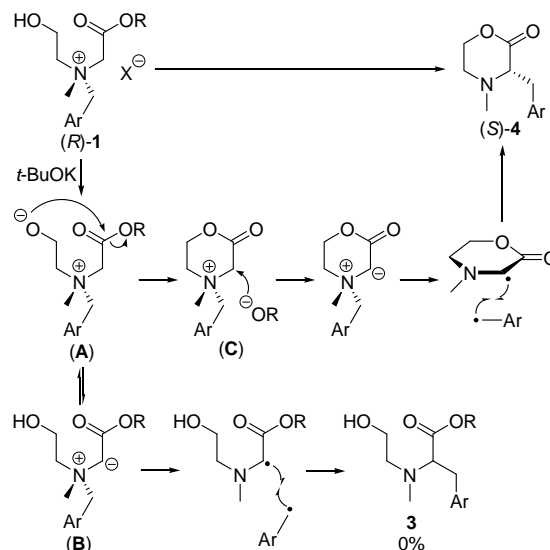
Reaction scheme showing the conversion of **(R)-1** to **(S)-4** using $t\text{-BuOK}$ (1.0 equiv) in $\text{CH}_3\text{CN-THF}$ (10:1) at -30°C for 6 h.

entry	R ¹	R ²	X		ee of (<i>R</i>)- 1 (%)	yield ^a (%)	ee ^{b,c} (%)
1	H	<i>t</i> -Bu	Cl	b	>95	39	56 (56)
2	Me	<i>t</i> -Bu	Cl	d	98	76	44 (45)
3	OMe	<i>t</i> -Bu	Br	e	79	52	50 (63)
4	OMe	<i>t</i> -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.

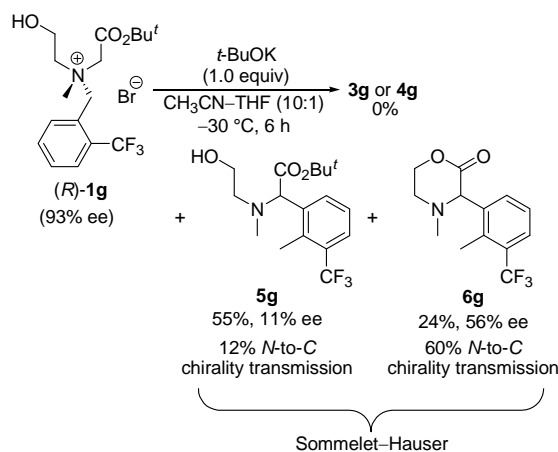
While an exact mechanism cannot be advanced at present, it is safe to say that in the reaction from (*R*)-**1** to (*S*)-**4**, the lactonization of **1** proceeds first to form the corresponding cyclic ammonium salt **C** (Scheme 2). Treatment of (*R*)-**1** with potassium *tert*-butoxide affords an 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 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, Sommelet–Hauser rearrangement proceeded exclusively to 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 concerted [2,3] sigmatropic process.



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

3. Conclusion

In conclusion, we report the optical resolution of *N*-chiral, amino acid-derived quaternary ammonium salts using chiral BINOL as a complexing agent. The resulting products undergo the [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*-centred chiral molecules.

4. Experimental

4.1. General

Infrared (IR) spectra were recorded on a HITACHI Infrared Spectrometer Model 270–30. ^1H and ^{13}C NMR spectra were measured on a JEOL 270 MHz (^1H : 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 60F₂₅₄) 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 1.0M 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 optical 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 amount 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); ^1H 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, $\text{CH}_2\text{CH}_2\text{OH}$), 3.86–3.68 (1H, m, $\text{CH}_2\text{CH}_2\text{OH}$), 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 $\text{C}_{17}\text{H}_{29}\text{BrNO}_{3.5}$: C, 53.27; H, 7.63; N, 3.65. Found: C, 53.57; H, 7.48; N, 3.59.

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

Optical 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 optical resolutions. Initially resolved (*R*)-**1b** $\{[\alpha]_{589}^{23} = +17.0$ (*c* 1.00, EtOH) $\}$ was subjected to second and third optical resolutions under similar conditions [1.0 equiv of (*S*)-BINOL was used in the second and third resolutions.]. After a second optical resolution, (*R*)-**1b** was obtained in 78% yield, and the specific rotation value was $[\alpha]_{589}^{24} = +18.9$. After a third optical 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 enantio-pure (*R*)-**1b**. The ee of (*R*)-**1b** includes ca. $\pm 5\%$ 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. $\pm 5\%$ error); ^1H 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, $\text{CH}_2\text{CH}_2\text{OH}$), 4.04–3.70 (2H, m, $\text{CH}_2\text{CH}_2\text{OH}$), 3.48 (3H, s,

NCH₃), 1.48 (9H, s, *t*-Bu); ¹³C NMR (68 MHz, CDCl₃) 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 C₁₆H₂₈ClNO₄: 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; [α]_D²⁴₅₈₉ = +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]; ¹H NMR (270 MHz, CDCl₃) 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, CH₂COO), 5.19 (1H, d, *J* = 13.5 Hz, CH₂COO), 4.74 (2H, s, CH₂Ar), 4.30-4.05 (3H, m, CH₂CH₂OH), 3.77-3.62 (1H, m, CH₂CH₂OH), 3.44 (3H, s, NCH₃), 2.56 (3H, s, ArCH₃), 1.50 (9H, s, *t*-Bu); ¹³C NMR (68 MHz, CDCl₃) 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 C₁₇H₃₁ClNO_{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; [α]_D²⁶₅₈₉ = +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]; ¹H NMR (270 MHz, CDCl₃) 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, CH₂COO), 5.02 (1H, d, *J* = 12.4 Hz, CH₂COO), 4.51 (1H, d, *J* = 17.1 Hz, CH₂Ar), 4.43 (1H, d, *J* = 17.1 Hz, CH₂Ar), 4.30-4.13 (2H, m, CH₂CH₂OH), 4.13-3.99 (1H, m, CH₂CH₂OH), 3.99-3.78 (1H, m, CH₂CH₂OH), 3.89 (3H, s, OCH₃), 3.40 (3H, s, NCH₃), 1.52 (9H, s, *t*-Bu); ¹³C NMR (68 MHz, CDCl₃) 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 C₁₇H₂₉BrNO_{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; [α]_D²³₅₈₉ = +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]; ¹H NMR (270 MHz, CDCl₃) 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, CH₂COO), 4.99 (1H, d, *J* = 12.4 Hz, CH₂COO), 4.54 (1H, d, *J* = 17.4 Hz, CH₂Ar), 4.46 (1H, d, *J* = 17.4 Hz, CH₂Ar), 4.27-4.11 (2H, m, CH₂CH₂OH), 4.11-3.97 (1H, m, CH₂CH₂OH), 3.94-3.73 (1H, m, CH₂CH₂OH), 3.89 (3H, s, OCH₃), 3.39 (3H, s, NCH₃), 2.28 (1H, br, OH), 1.52 (9H, s, *t*-Bu); ¹³C NMR (68 MHz, CDCl₃) 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 C₁₇H₃₁ClNO_{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; [α]_D²⁵₅₈₉ = +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]; ¹H NMR (270 MHz, CDCl₃) 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, CH₂COO), 5.41 (1H, dd, *J* = 13.6 Hz, CH₂COO), 5.05 (1H, br, OH), 4.85 (1H, d, *J* = 17.0 Hz, CH₂Ar), 4.61 (1H, d, *J* = 17.0 Hz, CH₂Ar), 4.35-4.11 (3H, m, CH₂CH₂OH), 3.75-3.60 (1H, m, CH₂CH₂OH), 3.49 (3H, s, NCH₃), 1.52 (9H, s, *t*-Bu); ¹³C NMR (68 MHz, CDCl₃) 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 C₁₇H₂₅BrF₃NO₃: 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*)-1i]

White solid; 8:2 mixture of rotamers; [α]_D²²₅₈₉ = +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); ¹H NMR (270 MHz, CDCl₃) 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, CH₂COO), 5.44 (0.2H, d, *J* = 13.1 Hz, CH₂COO), 5.26 (1.6H, s, CH₂COO), 5.14 (0.8H, d, *J* = 17.4 Hz, CH₂Ar), 5.03 (0.8H, d, *J* = 17.4 Hz, CH₂Ar), 4.97-4.49 (1.4H, m, CH₂Ar and OH), 4.42-4.03 (3H, m, CH₂CH₂OH), 3.79 (3H, s, OCH₃ or NCH₃), 3.69-3.55 (1H, m, CH₂CH₂OH), 3.52 (0.6H, s, OCH₃ or NCH₃), 3.46 (2.4H, s, OCH₃ or NCH₃), 2.63 (0.6H, s, ArCH₃), 2.56 (2.4H, s, ArCH₃); ¹³C NMR (68 MHz, CDCl₃) 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 C₁₄H₂₃BrNO_{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 **11**

The absolute configuration of **11** was determined as *R* on the nitrogen atom by a single crystal X-ray diffraction of a 1:1 complex **21** (Figure 1). Recrystallization of **21** from methanol–diethyl ether gave a single crystal which was suitable for crystallographic analysis.⁷ Crystal data of **21**: C₃₄H₃₆BrNO₅, *MW* = 618.57; *monoclinic*; space group *P*2₁ (#4); *a* = 9.1803(2) Å, *b* = 13.3010(4) Å, *c* = 12.6018(4) Å, β = 101.267(2)°; *V* = 1509.11(8) Å³; *Z* = 2; *D*_{calcd} = 1.361 g/cm³; μ = 14.08 cm⁻¹; $2\theta_{\max}$ = 60.1°; *T* = 296 K; *R*₁ (*I* > 2σ(*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; $[\alpha]^{25}_{589} = +4.0$ (*c* 1.00, EtOH); 60% ee (determined by HPLC); ¹H NMR (270 MHz, CDCl₃) 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, CH₂Ar), 3.14 (1H, dd, *J* = 14.5, 5.8 Hz, CH₂Ar), 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, NCH₃ or ArCH₃), 2.31 (3H, s, NCH₃ or ArCH₃); ¹³C NMR (68 MHz, CDCl₃) 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 C₁₃H₁₇NO₂: 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; $[\alpha]^{25}_{589} = +6.1$ (*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**]; ¹H NMR (270 MHz, CDCl₃) 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, CH₂Ph), 3.13 (1H, dd, *J*

= 14.3, 4.6 Hz, CH₂Ph), 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, NCH₃); ¹³C NMR (68 MHz, CDCl₃) 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 C₁₂H₁₅NO₂: 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; $[\alpha]^{25}_{589} = +12.0$ (*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]; ¹H NMR (270 MHz, CDCl₃) 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, OCH₃), 3.41–3.24 (2H, m, 3-H and CH₂Ar), 3.18 (1H, dd, *J* = 14.2, 6.6 Hz, CH₂Ar), 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, NCH₃); ¹³C NMR (68 MHz, CDCl₃) 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 C₁₃H₁₇NO₃: 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; $[\alpha]^{23}_{589} = +5.8$ (*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]; ¹H NMR (270 MHz, CDCl₃) 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, NCHCOO), 3.68–3.46 (2H, br, NCH₂CH₂OH), 2.84–2.58 (3H, m, NCH₂CH₂OH), 2.52 (3H, s, NCH₃ or ArCH₃), 2.30 (3H, s, NCH₃ or ArCH₃), 1.41 (9H, s, *t*-Bu); ¹³C NMR (68 MHz, CDCl₃) 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 C₁₇H₂₄F₃NO₃: C, 58.78; H, 6.96; N, 4.03. Found: C, 59.05; H, 6.93; N, 4.00.

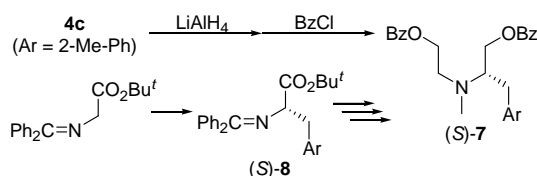
4.2.17. *N*-(2-Hydroxyethyl)-*N*-methyl-3-[2-(trifluoromethyl)phenyl]morpholin-2-one (**6g**)

Colorless oil; $[\alpha]^{23}_{589} = +42.3$ (*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]; ¹H NMR (270 MHz, CDCl₃) 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, NCH₃), 2.13 (3H, s, ArCH₃); ¹³C NMR (68 MHz, CDCl₃) 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 C₁₃H₁₄F₃NO₂: 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**. The compound (*S*)-**7** was prepared from Schiff-base protected glycine *tert*-butyl ester via phase-transfer catalysed asymmetric alkylation using (*R,R*)-bis(2-naphthyl)-NAS bromide (Maruoka catalyst).¹⁶ 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 aluminium 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 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)]ethylmethanamine **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 (*S*)-**7**

(Step 1) To a mixture of *tert*-butyl 2-(diphenylmethyleamino)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 to 5:1 as eluent) to obtain (*S*)-*tert*-butyl 2-(diphenylmethyleamino)-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 catalysed 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 (2 times). The combined aqueous extracts were treated with a 15 wt.% sodium hydroxide aqueous solution and extracted with diethyl ether (3 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 to 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 aluminium 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 μ L, 0.65 mmol), 4-dimethylamino-pyridine (DMAP) (2 mg, 0.02 mmol), and benzoyl chloride (36 μ L, 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 to 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); ^1H 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, NCHCH_2O), 4.33 (2H, t, J = 5.7 Hz, $\text{NCH}_2\text{CH}_2\text{O}$), 4.28 (1H, dd, J = 11.7, 4.6 Hz, NCHCH_2O), 3.36-3.22 (1H, m, NCHCH_2O), 3.04 (2H, t, J = 5.7 Hz, $\text{NCH}_2\text{CH}_2\text{O}$), 2.92 (1H, dd, J = 13.6, 5.5 Hz, CH_2Ar), 2.76 (1H, dd, J = 13.6, 8.2 Hz, CH_2Ar), 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 $\text{C}_{27}\text{H}_{29}\text{NO}_4$: 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)methylamine (**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 to 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 (2 steps) by the same procedures with **1c** using benzyl bromide instead of 2-methylbenzyl bromide in step 2: white solid; ^1H 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_2COO), 5.16 (1H, d, J = 12.7 Hz, CH_2COO), 5.10 (1H, t, J = 5.1 Hz, OH), 4.57 (1H, d, J = 17.1 Hz, CH_2Ph), 4.49 (1H, d, J = 17.1 Hz, CH_2Ph), 4.29-4.16 (2H, m, $\text{CH}_2\text{CH}_2\text{OH}$), 4.05-3.84 (2H, m, $\text{CH}_2\text{CH}_2\text{OH}$), 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 $\text{C}_{16}\text{H}_{26}\text{BrNO}_3$: 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 (2 steps) by the similar procedures with **1c**. In step 2, the reaction was carried out without solvent using 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 (2 steps) by the similar procedures with **1c**. In step 2, the reaction was carried out without solvent using 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 μ L, 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 to 3:1 as eluent) to afford *N*-(2-hydroxyethyl)-*N*-(2-methoxybenzyl)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-methoxybenzyl)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 to 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 (2 steps) by the 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 (2 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 aluminium 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 to 7:1 as eluent) to afford **1h** (606 mg, 95% yield) as a white solid: ¹H NMR (270 MHz, CDCl₃) 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, CH₂COO), 5.08 (1H, d, *J* = 12.6 Hz, CH₂COO), 4.46 (2H, s, CH₂Ar), 4.21 (2H, t, *J* = 4.2 Hz,

CH₂CH₂OH), 3.98 (1H, dt, *J* = 13.9, 4.2 Hz, CH₂CH₂OH), 3.88 (1H, dt, *J* = 13.9, 4.2 Hz, CH₂CH₂OH), 3.46 (3H, s, NCH₃), 2.38 (3H, s, ArCH₃), 1.50 (9H, s, *t*-Bu); ¹³C NMR (68 MHz, CDCl₃) 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 C₁₇H₂₈BrNO₃: 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 (2 steps) by the 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; ¹H NMR (270 MHz, CDCl₃) 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, CH₂COO), 5.09 (1H, d, *J* = 12.6 Hz, CH₂COO), 4.51 (2H, s, CH₂Ar), 4.18 (2H, s, CH₂CH₂OH), 4.02-3.78 (2H, m, CH₂CH₂OH), 3.45 (3H, s, NCH₃), 2.38 (3H, s, ArCH₃), 1.49 (9H, s, *t*-Bu); ¹³C NMR (68 MHz, CDCl₃) 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 C₁₇H₃₀ClNO₄: 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 (2 steps) by the same procedures with **1c** using 4-(trifluoromethyl)benzyl bromide instead of 2-methylbenzyl bromide in step 2: white solid; ¹H NMR (270 MHz, CDCl₃) 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, CH₂COO), 5.36 (1H, d, *J* = 12.4 Hz, CH₂COO), 5.10 (1H, br, OH), 4.56 (1H, d, *J* = 17.1 Hz, CH₂Ar), 4.41 (1H, d, *J* = 17.1 Hz, CH₂Ar), 4.22 (2H, s, CH₂CH₂OH), 4.10-3.87 (2H, m, CH₂CH₂OH), 3.52 (3H, s, NCH₃), 1.50 (9H, s, *t*-Bu); ¹³C NMR (68 MHz, CDCl₃) 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 C₁₇H₂₇BrF₃NO₄: 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 (2 steps) by the similar procedures with **1c**. In step 2, the reaction was carried out without solvent using excess amount of 4-(trifluoromethyl)benzyl chloride (1.5 equiv) instead of 2-methylbenzyl bromide: white solid; ¹H NMR (270 MHz, CDCl₃) 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, CH₂COO), 5.38 (1H, d, *J* = 12.3 Hz, CH₂COO), 4.74 (1H, d, *J* = 17.1 Hz, CH₂Ar), 4.56 (1H, d, *J* = 17.1 Hz, CH₂Ar),

4.20 (2H, s, $\text{CH}_2\text{CH}_2\text{OH}$), 4.03–3.80 (2H, m, $\text{CH}_2\text{CH}_2\text{OH}$), 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 $\text{C}_{17}\text{H}_{27}\text{ClF}_3\text{NO}_4$: 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 (**11**)

(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 to 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 to 5:1 as eluent) to afford **11** as a white solid (489 mg, 86% yield).

Acknowledgments

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- CCDC-735959 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- 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.
- 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 catalysed asymmetric alkylation. Details: see, experimental section (4.2.18).
- THF was added as a 1.0 M THF solution of *t*-BuOK.
- 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.
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- 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).
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