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pure **1a** was obtained from diastereomerically pure **2a** which was obtained by recrystallization of **2a** from ethanol, or further optical resolutions of the resolved **1a** with (*R*)-BINOL.¹¹ The absolute configuration of **1a** was determined as the *S* configuration on the nitrogen atom by a single crystal X-ray diffraction (Figure 1).¹²

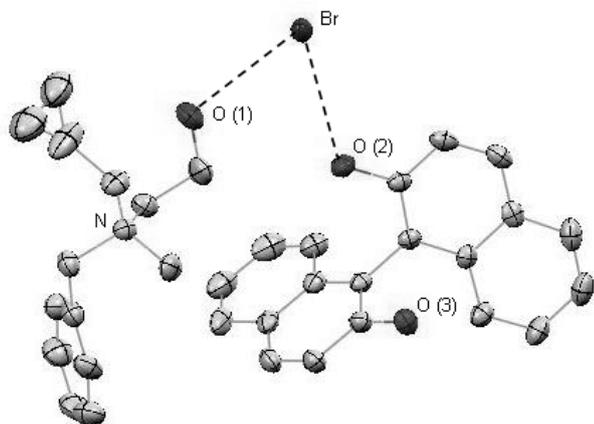
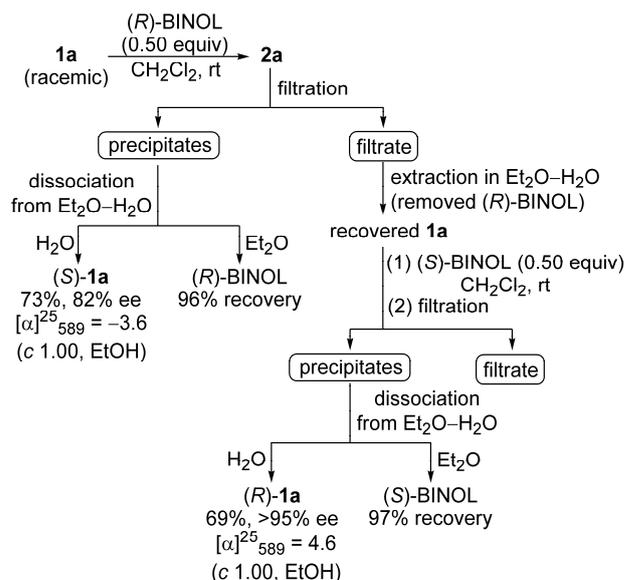


Figure 1. Molecular Structure of a 1:1 Complex **2a** (hydrogen and solvent atoms are omitted for cleanly)

The crystal structure of complex **2a** reveals that the bromide ion acts (or serves) as a bridge between the hydroxyl group of tetraalkylammonium cation of (*S*)-**1a** and one hydroxyl group of (*R*)-BINOL.^{13,14} Similar types of intermolecular hydrogen bonds have been reported in previous studies on tetraalkylammonium salt–phenol complexation.⁵

Interestingly enough, the present resolution method allows us to obtain the both enantiomers of **1a** from the single racemic sample as depicted in Scheme 2. The filtrate obtained after the 1st optical resolution was concentrated under reduced pressure and the residue was dissolved in a mixture of diethyl ether and water. Extractive separation of the aqueous solution gave the recovered ammonium salt **1a** and the salt was treated with (*S*)-BINOL in dichloromethane to resolve the other enantiomer. Significantly enough, the other enantiomer (*R*)-**1a** was obtained also in high enantio-purity (>95% ee).

The scope of substrates was further explored as shown in Table 1. Enantio-enriched *N*-chiral tetraalkylammonium salts **1b–1f** were obtained in the same way as described above. Unfortunately, the determination of ee-values for **1b–1f** by HPLC analysis using chiral column were unsuccessful. Thus, the ee of the salts obtained by the single resolution were determined by the specific rotation values ($[\alpha]_{589}^{25}$) based on the highest specific rotation values obtained by 3 times optical resolutions.¹⁵ No precipitations were observed in using *N*-cinnamyl derivative **1g**.



Scheme 2. Separation of the Both Enantiomers of **1a** by Complexation with (*R*)- or (*S*)-BINOL

Table 1. Optical Resolution of Various Types of Tetraalkylammonium Salts **1**

entry	Ar	R	yield ^b (%)	$[\alpha]_{589}^{25}$ ^c (c 1.00, EtOH)	ee ^d (%)
1	2-Me-Ph	H	b 64	-5.3	83
2	2-F-Ph	H	c 52	-5.3	83
3	4-F-Ph	H	d 37	-3.9	89
4	2-Br-Ph	H	e 48	-3.8	84
5	Ph	Me	f 58	-5.2	>95
6	Ph	Ph	g 0 ^e	–	–

^a Configurations were determined by the analogy with (*S*)-**1a**. ^b Isolated yield. ^c Include ca. ± 0.2 errors. ^d Determined by the specific rotations based on the highest specific rotations obtained by 3 times optical resolutions. The results include ca. $\pm 5\%$ errors. ^e Not precipitated.

In conclusion, we report that the first preparative method for a nitrogen-centered chirality was successfully demonstrated by optical resolution of *N*-chiral β -hydroxy-tetraalkylammonium salts **1**. This work is likely to stimulate advanced idea in the rapidly developing asymmetric chemistry of *N*-centered chiral molecules. The further applications for organic synthesis are in progress in our laboratory.

Acknowledgments

This work was supported by Grant-in-Aid for Young Scientists (17750034) from the Ministry of Education, Culture, Sports, Science and Technology, Japan and Award in Synthetic Organic Chemistry, Japan and UNION TOOL Scholarship Foundation.

References and notes

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2. Recently, the absolute configuration was determined by a single crystal X-ray diffraction, see: Torbeev, V. Y.; Lyssenko, K. A.; Kharybin, O. N.; Antipin, M. Y.; Kostyanovsky, R. G. *J. Phys. Chem. B* **2003**, *107*, 13523–13531.
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5. Previous papers have shown that BINOL and some of quaternary ammonium salts form 1:1 complexes. These studies were applied for optical resolution of *rac*-BINOL. (a) Ha, W.; Shan, Z. *Tetrahedron: Asymmetry* **2006**, *17*, 854–859; (b) Toda, F.; Yoshizawa, K.; Hyoda, S.; Toyota, S.; Chatziefthimiou, S.; Mavridis, I. M. *Org. Biomol. Chem.* **2004**, *2*, 449–451; (c) Wang, Y.; Sun, J.; Ding, K. *Tetrahedron* **2000**, *56*, 4447–4451; (d) Toda, F.; Tanaka, K.; Stein, Z.; Goldberg, I. *J. Org. Chem.* **1994**, *59*, 5748–5751; (e) Tanaka, K.; Okada, T.; Toda, F. *Angew Chem. Int. Ed. Engl.* **1993**, *32*, 1147–1148.
6. Prepared from *N*-methylaminoethanol in 3 steps. [(i) benzoyl chloride, NaHCO₃, THF, rt; (ii) LiAlH₄, THF, 0 °C to rt; (iii) allyl bromide, rt]. For more details, see the Supplementary material.
7. Use of ethanol as solvent provided the comparable result.
8. The ¹H NMR spectra of **2a** in deuterated solvents (ex. dimethylsulfoxide-*d*₆, acetone-*d*₆, and acetonitrile-*d*₃) did not show any diastereomerically separated peaks.
9. **1a** was stable for several days in a freezer without racemization.
10. The specific analysis condition (eluent system) of **1a** was found by the analysis request to Daicel Chemical Industries, Ltd. CPI Company, Chiral Separation Service.
11. Further optical resolution of (*S*)-**1a** (82% ee) with (*R*)-BINOL (0.85 equiv) in dichloromethane improved the enantiopurity to 93–95% ee. After one more optical resolution of the resolved (*S*)-**1a**, the enantiopurity was improved to >95% ee (determined by HPLC analysis).
12. CCDC-640938 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.
13. Use of a chloride salt as substrate provided the corresponding 1:1 complex with the similar yield and selectivity, but an iodide salt did not.
14. By our preliminary studies, it was found that a β-hydroxy group of ammonium salt is necessary for complexation with BINOL.
15. The highest specific rotation values was obtained by 3 times optical resolutions; **1b**: [α]²⁵₅₈₉ = –6.4 (c 1.00, EtOH), **1c**: [α]²⁵₅₈₉ = –6.4 (c 1.00, EtOH), **1d**: [α]²⁵₅₈₉ = –4.4 (c 1.00, EtOH), **1e**: [α]²⁵₅₈₉ = –4.5 (c 1.00, EtOH), **1f**: [α]²⁵₅₈₉ = –5.2 (c 1.00, EtOH). For more details, see the Supplementary material.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at XXX.