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An efficient optical resolution of nitrogen-centered chiral β-hydroxy-tetraalkylammonium salts via complexation with (*R*)-BINOL

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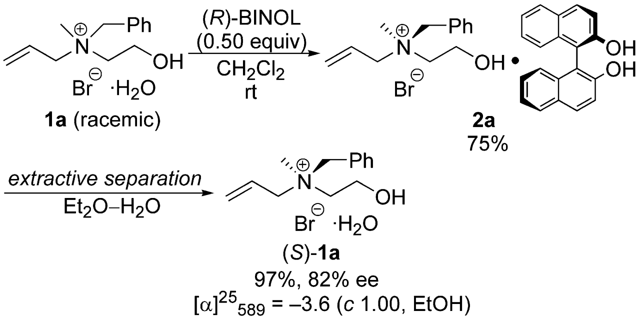
Abstract—The optical resolution of nitrogen-centered chiral β-hydroxy-tetraalkylammonium bromides is demonstrated by using chiral BINOL as a complexing agent. Determination of the enantiopurities and absolute configurations of the resolved *N*-chiral tetraalkylammonium salts are described.

While asymmetric synthesis of carbon-centered chiral molecules has rapidly been advanced, the chemistry of N-centered chiral tetraalkylammonium salts still remains largely unexplored mainly due to the severely limited accessibility thereof. In 1899, Pope et al. reported the first preparation of enantio-enriched N-centered chiral tetraalkylammonium salt via fractional crystallization of its (+)-champhorsulfonate followed by anion exchange.[1] However, the enantio-purity and absolute configuration of the enantiomer was not determined.[2] Since then, only a few examples of *N*-chiral enantiomers derived from amine *N*-oxides have been reported,[3] whereas there have been some examples of diastereoselective quaternarization of C-centered chiral tertiary amines to afford the *C*- and *N*-chiral diastereomers in the enantio-enriched forms.[4] The direct optical resolution of racemic N-centered chiral tetraalkylammonium salts has never been achieved.

During the course of our continuing studies on asymmetric Stevens rearrangements,[4a] we needed *N*-chiral *N*-allylic quaternary ammonium salts (Stevens substrates) as the enantio-enriched forms. Thus, we were interested in optical resolution via complexation with enantio-pure (*R*)-2,2′-dihydroxy-1,1′-binaphthol [(*R*)-BINOL] in view of the recent publications concerning the unique complexation of some tetraalkylammonium salts with BINOL.[5] Now we wish to report the efficient optical resolution of N-centered chiral β-hydroxy-tetraalkylammonium salts **1** using (*R*)-BINOL as the complexing agent (Scheme 1).

First, we carried out the optical resolution of *N*-allyl-*N*-benzyl-*N*-(2-hydroxyethyl)-*N*-methylammonium bromide monohydrate (**1a**)[6] by complexation with (*R*)-BINOL. When a mixture of **1a** (1.0 equiv) and (*R*)-BINOL (0.50 equiv) in dichloromethane[7] was stirred at room temperature for 24 h, a 1:1 complex (**2a**) of **1a** with (*R*)-BINOL was precipitated.[8] The complex **2a** was isolated by filtration in 75% yield [determined from the amount of (*R*)-BINOL] as colorless crystals, then complex **2a** was dissolved in a mixture of diethyl ether and



Scheme 1. Optical resolution of N-centered chiral β-hydroxy-tetraalkylammonium salt **1a** by diastereoselective complexation with (*R*)-BINOL.

Keywords: Ammonium salts; Optical resolution; Complexation; Diastereoselectivity; Nitrogen.

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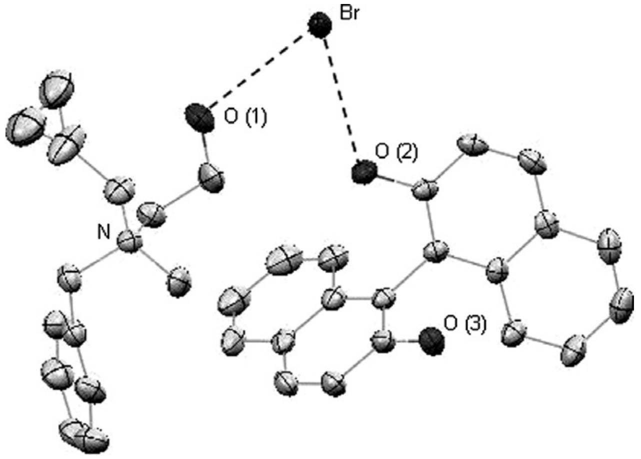
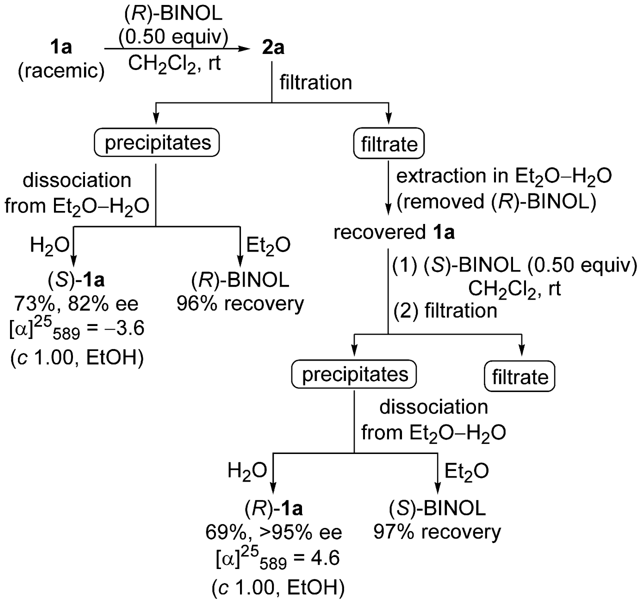


Figure 1. Molecular structure of a 1:1 complex **2a** (hydrogen and solvent atoms are omitted for cleanly).

water. By extractive separation, enantio-enriched **1a** was obtained in 97% yield from the aqueous solution by evaporation of water.[9] The (*R*)-BINOL was recovered from the diethyl ether solution (96% recovery from **2a**). The enantiomer excess (ee) of the resolved **1a** was determined to be 82% ee by chiral HPLC analysis [Daicel Chiralpak AD–H column, *n*-hexane/ethanol/trifluoroacetic acid/diethylamine = 90:10:0.1:0.1 as eluent, flow rate = 0.50 mL/min, t_R = 23.0 min for (*S*)-**1a** and 25.9 min for (*R*)-**1a**].[10] The enantiomerically 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 (Fig. 1).[12]

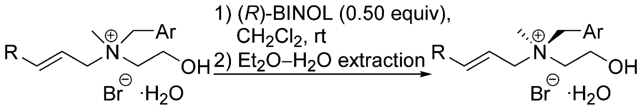
The crystal structure of complex **2a** reveals that the bromide ion acts (or serves) as a bridge between the hydroxyl group of tetraalkylammonium cation of (*S*)-**1a** and one hydroxyl group of (*R*)-BINOL.[13,14] Similar types of intermolecular hydrogen bonds have been reported in previous studies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



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**



1b-1g (*S*)-**1b-1g**[a]

Entry	Ar	R		Yield[b] (%)	$[\alpha]^{25}_{589}$ [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. ±5% errors.
[e] Not precipitated.

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 ($[\alpha]^{25}_{589}$) based on the highest specific rotation values obtained by 3 times optical resolutions.[15] No precipitations were observed in using *N*-cinnamyl derivative **1g**.

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

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.078.

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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, see: (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, $NaHCO_3$, THF, rt; (ii) $LiAlH_4$, THF, 0 °C to rt; (iii) allyl bromide, rt]. For more details, see the Supplementary data.
7. Use of ethanol as solvent provided the comparable result.
8. The ^1H NMR spectra of **2a** in deuterated solvents (e.g., dimethylsulfoxide-d_6, acetone-d_6, and acetonitrile-d_3) did not show any diastereomerically separated peaks.
9. Compound **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 enantio-purity to 93–95% ee. After one more optical resolution of the resolved (*S*)-**1a**, the enantio-purity was improved to >95% ee (determined by HPLC analysis).
12. CCDC-640938 contains the supplementary crystallographic data for this Letter. 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 were obtained by 3 times optical resolutions; **1b**: $[\alpha]^{25}_{589}$ −6.4 (*c* 1.00, EtOH), **1c**: $[\alpha]^{25}_{589}$ −6.4 (*c* 1.00, EtOH), **1d**: $[\alpha]^{25}_{589}$ −4.4 (*c* 1.00, EtOH), **1e**: $[\alpha]^{25}_{589}$ −4.5 (*c* 1.00, EtOH), **1f**: $[\alpha]^{25}_{589}$ −5.2 (*c* 1.00, EtOH). For more details, see the Supplementary data.