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A novel axially dissymmetric chiral ligand based on amine *N*-oxide: (*R*)- and (*S*)-3,3′-dimethyl-2,2′-biquinoline *N,N′*-dioxide

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Abstract: Novel axially dissymmetric chiral ligands (*R*)- and (*S*)-3,3′-dimethyl-2,2′-biquinoline *N,N′*-dioxide (*R*)-**1** and (*S*)-**1** were resolved *via* the hydrogen-bonding complex with (*S*)- or (*R*)-binaphthol. © 1997 Elsevier Science Ltd. All rights reserved.

The rational design and synthesis of novel chiral molecules directed towards asymmetric synthesis or asymmetric molecular recognition is one of the most important goals in modern organic chemistry. In this context, a great number of homochiral molecules containing amines, ethers, and phosphines as electron-pair donors, have been developed as asymmetric controllers.[1] Although it is well documented that amine *N*-oxides act as powerful electron-pair donors to form complexes with a variety of acceptor molecules,[2] synthetic utility of amine *N*-oxides[3] still remains to be developed. While optically active amine *N*-oxides have been synthesized in view of their structural interest, only few attempts have been reported of the application of chiral amine *N*-oxides to synthetic organic chemistry.[4] As part of our studies on axially dissymmetric chiral molecules,[5] our interest was focused on bipyridine *N,N′*-dioxide derivatives.[6] Herein we wish to describe the syntheses of (*R*)- and (*S*)-3,3′-dimethyl-2,2′-biquinoline *N,N′*-dioxide **1** (Figure 1), which are expected to function as a chiral bidentate ligands based on *N*-oxide.

(±)-**1** was prepared by mCPBA oxidation of **2**,[7] readily obtained from anthranilic acid in three steps. We were pleased to find that resolution of (±)-**1** was effected successfully *via* complexation with (*R*)- or (*S*)-binaphthol.[8,9] A hot solution of (±)-**1** and (*R*)-binaphthol in dichloromethane–hexane was cooled to room temperature to yield colorless crystals, which consist of equimolar (−)-**1** and (*R*)-binaphthol. The collected crystalline complex was separated into its components by silica gel column chromatography to give enantiomerically pure (−)-**1** in 35% yield from (±)-**1**. The enantiomerically pure (+)-**1** was obtained with the aid of (*S*)-binaphthol in the same manner as described above. Enantiomeric excesses of (+)- and (−)-**1** were determined by chiral stationary phase HPLC to be >99% ee. **1** was configurationally stable under acidic (aq.HCl–EtOH, pH 1, 70°C) or basic (aq.NaOH–EtOH,

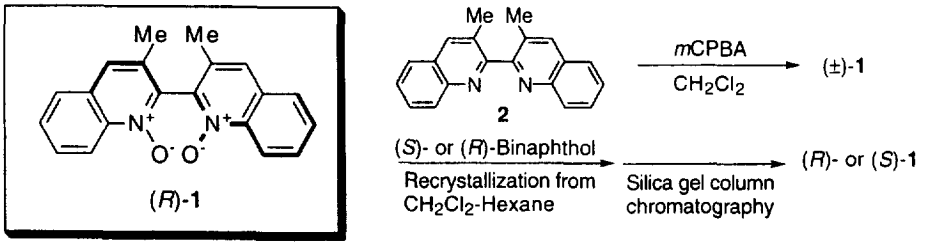

Figure 1. Synthesis of (*R*)- and (*S*)-**1**.

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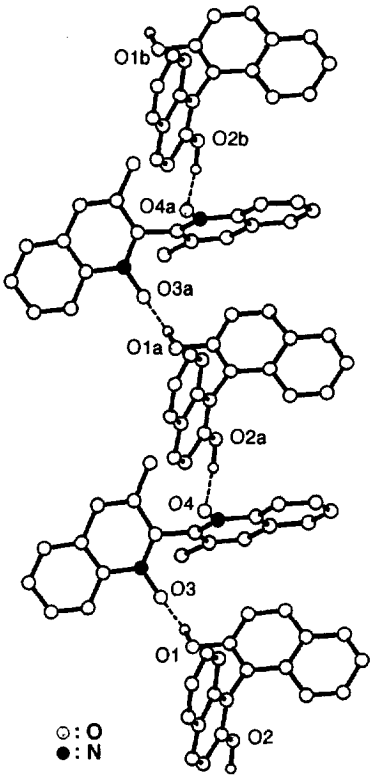

Figure 2. A part of crystal structure of the complex of (*R*)-**1** and (*S*)-binaphthol.

pH 14, 70°C) conditions. The absolute configuration of (+)-**1** was unambiguously determined to be *R* by single crystal X-ray analysis of its complex with (*S*)-binaphthol.[10] As can be seen in Figure 2, the crystal structure consists of continuous chains of tightly hydrogen-bonded species which are aligned along the *b*-axis of the crystal. The *N*-oxide moiety acts as an electron-pair donor, *i.e.* a proton acceptor, wherein the corresponding hydrogen bond (O–H···O–N) distance 1.7 Å (O1H···O3, O1aH···O3a) or 1.6 Å (O2aH–O4, O2bH···O4a) is notably shorter than that (2.6 Å) of the known *N*-oxide–binaphthol complex.[8]

These findings prompted us to test the feasibility of this system to asymmetric molecular recognition in solution, which was investigated with ^{1}H NMR (Figure 3). Upon addition of 1 mol equiv. of (*R*)-**1** to a racemic binaphthol in $CDCl_3$ (1.0 mM, 25°C), a large shift nonequivalence in phenolic protons of binaphthol was observed in which the induced downfield shifts were 0.56 ppm for (*R*)-binaphthol and only 0.09 ppm for (*S*)-binaphthol.[11] To evaluate further the potential of chirality discrimination by homochiral **1**, NMR studies with several organic acids were conducted. The signal separation obtained with mandelic acid and camphorsulfonic acid is great enough to allow one to carry out a determination of enantiomeric excess of organic acids. This is the first reported example of use of chiral amine *N*-oxides as chiral solvating agents.[12] Moreover, when (*R*)-**1** was added to the $CDCl_3$ solution of *N*-phthaloylglycine, significant signal separation ($\Delta\delta$ 0.04 and 0.12 ppm) of the prochiral methylene protons was observed, suggesting that a highly organized chiral environment might be created around the hydrogen bond center.

In summary, we have synthesized a novel homochiral diamine *N,N'*-dioxide **1** by resolution *via* hydrogen-bonding complex with binaphthol. Chiral discrimination of homochiral **1** demonstrated here shows the great potential of **1** as a chiral ligand for asymmetric synthesis or molecular recognition.

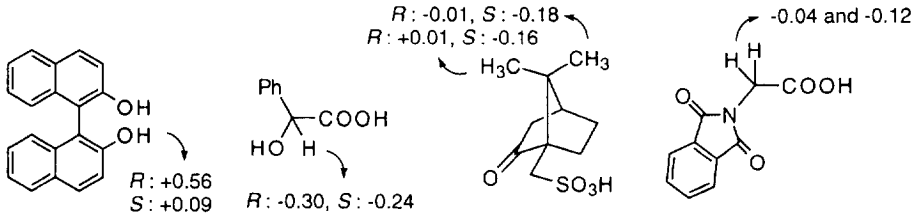

Figure 3. Δδ of some NMR signals of organic acids induced by complexation with (*R*)-**1**. Δδ (ppm, 270 MHz) were measured in $CDCl_3$ at 25°C. [(*R*)-**1**]=1.0 mM, [Substrate]=1.0 mM. The value with negative sign indicates the signal shifted upfield relative to that of acid without (*R*)-**1**.

Experimental section

Melting points were measured using a Büchi 535 melting point apparatus and were not corrected. Optical rotations were taken with a JASCO DIP-370 digital polarimeter. IR spectra were taken with a JASCO FT/IR-5300 infrared spectrometer and expressed in cm^{-1}. NMR spectra were taken with a JEOL EX-270 spectrometer. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, br, broad. MS were taken with a JEOL DX-303 mass spectrometer.

(±)-3,3′-Dimethyl-2,2′-biquinoline N,N′*-dioxide (±)-1*

m-Chloroperbenzoic acid (70%, 10 g, 40 mmol) was added portionwise to a solution of **2**[7] (5.0 g, 18 mmol) in dichloromethane (100 ml) at 0°C and the whole was stirred for 5 h at rt. The reaction mixture was washed successively with satd. $NaHCO_3$ (100 ml×3), and brine (100 ml). After drying over Na_2SO_4, the solvent was evaporated *in vacuo*. The crude product was recrystallized from ethanol (90 ml) to give (±)-**1** (3.5 g, 64%) as colorless needles. mp 270°C (dec); IR (nujol): 1335, 1210, 1086, 752; ^1H NMR (270 MHz, $CDCl_3$) δ: 2.28 (6H, s, CH_3), 7.63–7.88 (8H, m, arom.), 8.73 (2H, d, *J*=8.1 Hz, arom.); ^{13}C NMR (67MHz, $CDCl_3$) δ: 17.96 (CH_3), 120.7 (CH), 125.23 (CH), 127.39 (CH), 129.08 (CH), 129.31 (CH), 130.14 (C), 131.72 (C), 140.32 (C); MS m/z: 316 (M^+).

(R)- and (S)-3,3′-Dimethyl-2,2′-biquinoline N,N′*-dioxide (R)- and (S)-1*

n-Hexane (40 ml) was added to a hot clear solution of (±)-**1** (1.0 g, 3.2 mmol) and (*R*)-(+)-2,2′-binaphthol (850 mg, 2.9 mmol) in dichloromethane (50 ml). The whole was allowed to stand for 12 h at rt to precipitate colorless prisms (0.63 g). mp 140–142°C; $[\alpha]_D^{26}$ −58.9 (*c* 1.01, $CHCl_3$); Anal. Calcd for $C_{20}H_{16}N_2O_2 \cdot C_{20}H_{14}O_2 \cdot 1/2H_2O$: C, 78.54; H, 5.11; N, 4.58. Found C, 78.41; H, 5.16; N, 4.41. The collected complex was purified by silica gel column chromatography (eluent; 0–5% methanol in dichloromethane) to afford (*R*)-binaphthol (0.27 g) and optically pure (*S*)-(−)-**1** (0.35 g, 35%) as colorless needles. mp 247–249°C; $[\alpha]_D^{20}$ −120 (*c* 1.01, $CHCl_3$); Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found C, 76.02; H, 5.36; N, 8.72. Other spectroscopic data were identical with those of (±)-**1**. The mother liquor was concentrated *in vacuo* and the residue was purified by silica gel column chromatography to recover binaphthol and dioxide. Partially resolved dioxide thus obtained was resolved with the aid of (*S*)-(−)-2,2′-binaphthol in the similar manner described as above through hydrogen-bonding complex (mp 140–142°C; $[\alpha]_D^{24}$ +55.3 (*c* 1.11, $CHCl_3$)) to afford enantiomerically pure (*R*)-(+)-**1** (0.42 g, 42%) as colorless needles. mp 248–250°C; $[\alpha]_D^{20}$ +127 (*c* 1.02, $CHCl_3$); CD (MeOH) abs. λmax nm (mdeg); 228 (+1.4), 238 (0), 262 (−9.0); Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found C, 75.70; H, 5.17; N, 8.88. The ee's of (*R*)-(+)-**1** and (*S*)-(−)-**1** were determined by HPLC (Daicel CHIRALCEL OJ, 0.46 cmϕ × 25 cm; hexane/2-propanol=3/1, 1.0 ml/min; t_R: 17.7 min for (*S*)-(−)-**1** and 33.8 min for (*R*)-(+)-**1**).

Acknowledgements

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9. The only known optically active bipyridine *N,N'*-dioxide derivatives are obtained by the resolution *via* tartrate–chromium complex,[6a] direct chiral stationary phase HPLC,[6b] or brucine complex with additional carboxyl group on pyridine ring.[6c].
10. Crystal data: $C_{40}H_{30}N_2O_4 \cdot H_2O \cdot 1/2CH_2Cl_2$, M=663.17, Monoclinic, space group *C*2(#5); *a*=28.74(1), *b*=10.823(2), *c*=11.206(4) Å, β=99.36(2)°, *V*=3439.4099(2) Å^3, *F*(000)=1399, *Z*=4, D_c=1.281 g/cm^3, Mo–Kα radiation, λ=0.71070 Å, μ(Mo–Kα)=1.59cm^{-1}. Intensities were measured on a Rigaku RAXIS-VI diffractometer at room temperature. The final *R* value was 0.060 (R_w=0.076).
11. Titration study[12] showed *K*=280 M^{-1}, Δδmax=2.9 ppm for (*R*)-binaphthol with (*R*)-**1** and *K*=81 M^{-1}, Δδmax=1.7 ppm for (*S*)-binaphthol with (*R*)-**1**.
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