

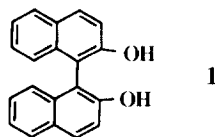
## An Efficient and Practical Direct Resolution of Racemic 1,1'-Bi-2-naphthol to Both of Its Pure Enantiomers.

Qiao-Sheng Hu, Dilrukshi Vitharana, and Lin Pu\*

Department of Chemistry, North Dakota State University, Fargo, ND 58105

**Abstract:** An efficient and practical method to directly resolve racemic 1,1'-bi-2-naphthol, *rac*-**1**, into optically pure R and S-**1** has been developed by modification of a N-benzylcinchonidinium chloride resolution procedure. In a typical experiment, 60 g of *rac*-**1** is resolved to give 22.5 g of R-**1** (75%, >99% ee) and 21 g of S-**1** (70%, >99% ee). The chiral resolving agent, (8S, 9R)-(-)-N-benzylcinchonidinium chloride, **2**, is recovered in 80% yield.

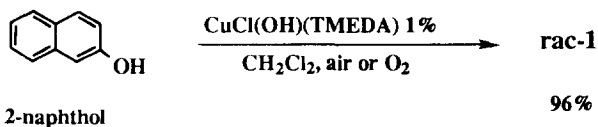
Because of the restricted rotation of the two naphthalene rings in a 1,1'-binaphthyl compound, this class of molecules is chiral. 1,1'-Bi-2-naphthol, **1**, and its derivatives have served as a very important chirality source for many chemical processes.<sup>1</sup> Complexes of these molecules with Lewis acids are used as asymmetric catalysts



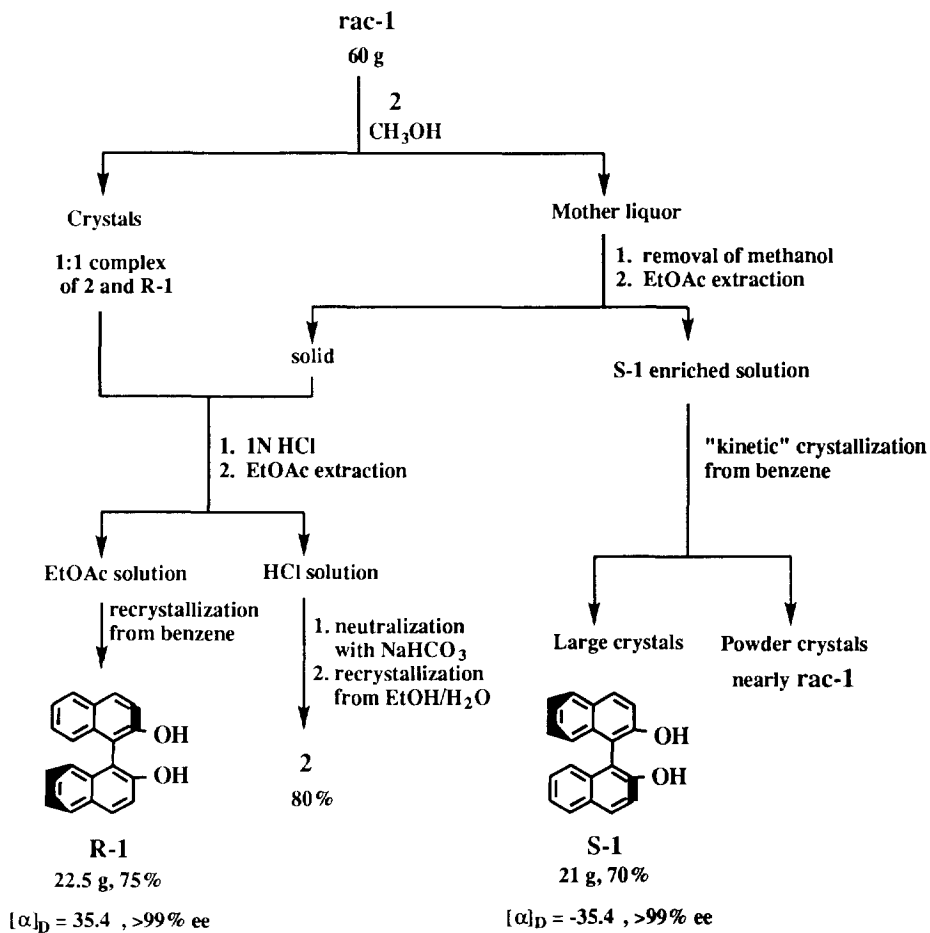
for a number of organic reactions such as the Diels-Alder reaction,<sup>2</sup> the Michael addition<sup>3</sup> and the aldol reactions.<sup>4</sup> Optically active binaphthyl derivatives have been applied in host-guest chemistry, molecular recognition and enantioselective chromatography separation.<sup>5,6</sup> Derivatives of **1** have also been used in polymerization processes to control the stereochemistry of polymer structures.<sup>7</sup> However, in spite of the outstanding asymmetric differentiation properties of the unique binaphthyl structures, the practical application of binaphthyl molecules has been limited due to the expense of optically pure **1**.

In recent years, continuous progress has been made in the preparation of **1** in its optically pure form.<sup>8</sup> The most practical method developed to date is through the direct resolution of racemic **1**, *rac*-**1**, by co-crystallization with chiral reagents.<sup>8c-j</sup> However, all of the reported direct resolutions of *rac*-**1** only lead to one pure enantiomer, either R or S, due to the difficulty involved in the isolation of the other enantiomer from the remaining mixture. This has greatly reduced the efficiency of the optical resolution. Herein, our detailed experiment to directly resolve *rac*-**1** into both of its pure enantiomers by modifying a N-benzylcinchonidinium chloride resolution method is described.

*Rac*-**1** can be synthesized in high yield from an inexpensive starting material, 2-naphthol, in the presence of a copper(II) catalyst in air.<sup>9</sup> In our laboratory, this process has been utilized to prepare *rac*-**1** in 50~60 g scale. The resolution of *rac*-**1** using (8S, 9R)-(-)-N-benzylcinchonidinium chloride, **2**, has been reported

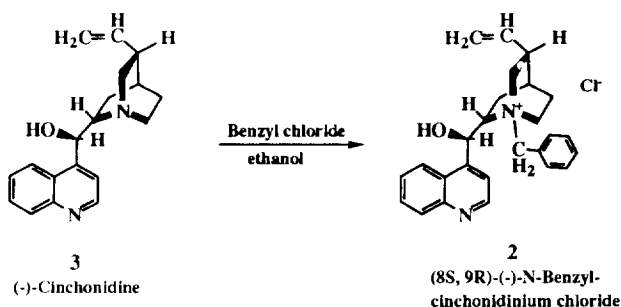


recently by Toda *et al.* to give optically pure R-1.<sup>8i,j</sup> We have modified this procedure to obtain both pure R and S-1 in large scale (Scheme 1).



Scheme 1. The direct resolution of rac-1.

The chiral resolving agent 2 was synthesized in one step from the reaction of (-)-cinchonidine, 3, an inexpensive chiral base, with benzyl chloride,<sup>10</sup> and was used to resolve rac-1. Both 2 and 3 are commercially



available. A methanol solution (1.2 L) of **2** (44.4 g, 105.5 mmol) and rac-**1** (60 g, 210 mmol) was prepared and kept at room temperature. After 6 h, a 1:1 complex of **2** and R-**1** crystallized out. The crystals were collected by filtration, and treated with 1N HCl (500 mL) to liberate R-**1**. After extraction of the HCl solution with ethyl acetate (3 x 250 mL), optically pure R-**1** was obtained by removal of ethyl acetate and recrystallization from benzene (18 g, >99% ee,  $[\alpha]_{\text{D}} = 35.4$  ( $c = 1.0$ , THF)). The methanol solution of the **2**+**1** mother liquor was evaporated under vacuum to yield a solid residue which was extracted with ethyl acetate (2 x 200 mL) to give a S-**1** enriched solution and a solid containing a **2**:R-**1** complex. Following the same procedure described above, the **2**:R-**1** complex was converted to R-**1** (4.5 g, >99% ee,  $[\alpha]_{\text{D}} = 35.4$  ( $c = 1.0$ , THF)). The combined yield of optically pure R-**1** is 75% (22.5 g). The S-**1** enriched ethyl acetate solution was evaporated under vacuum to give S-**1** with 84% ee (31.5 g,  $[\alpha]_{\text{D}} = -29.8$  ( $c = 1.0$ , THF)), a eutectic mixture of R and S-**1**.<sup>8k</sup> In order to obtain pure S-**1**, a "kinetic" crystallization method was adopted.<sup>8k</sup> The eutectic mixture was dissolved in benzene (315 g) and set at room temperature. After 6 h, large crystals (several cubic millimeters) were formed and collected by filtration. Optical rotation measurements showed that the large size crystals were optically pure S-**1** (16 g, >99% ee,  $[\alpha]_{\text{D}} = -35.2$  ( $c = 1.0$ , THF)). The benzene mother liquor after filtration of the large crystals was set at room temperature for a few hours, the powder-like crystals of nearly rac-**1** were observed. The powder-like crystals were removed by filtration and the solution was concentrated by distillation of 150 mL benzene. After the remaining solution was kept at room temperature for 6 h, additional large crystals of S-**1** were obtained (5 g, >99% ee,  $[\alpha]_{\text{D}} = -35.4$  ( $c = 1.0$ , THF)). The combined yield of optically pure S-**1** is 70% (21 g).

The chiral resolving agent, **2**, was recovered. Neutralization of the combined HCl extracts with sodium bicarbonate led to a white precipitate which was collected by filtration. Recrystallization from ethanol/water gave the crystals of **2** in 80% yield (35.6 g, >99% ee,  $[\alpha]_{\text{D}} = -179.6$  ( $c = 1.0$ , H<sub>2</sub>O)).

In summary, we have demonstrated for the first time that both enantiomers of **1** can be obtained in optically pure form from the direct resolution of rac-**1**. The copper(II) catalyzed synthesis of rac-**1** coupled with this optical resolution method makes optically pure **1** readily available in large quantity from an inexpensive starting material, 2-naphthol, and a recoverable chiral resolving agent, **2**.

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