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Heterocomplexation of a Chiral Dipeptide and Quantitative Enantiomeric Enrichment of Nonracemic 1,1′-Bi-2-naphthol

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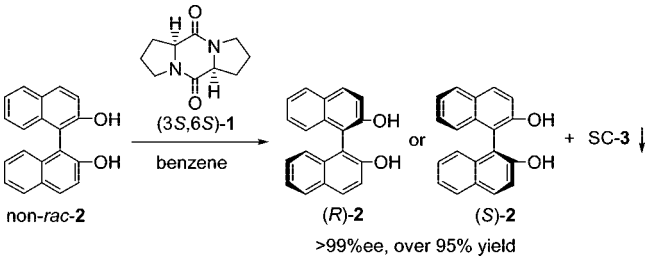

Heterocomplexation of a chiral host to a racemic guest has been discovered. A cyclic dipeptide generated from (*S*)-proline alkyl ester undergoes an achiroselective complexation to both the enantiomers of racemic BINOL in benzene to yield a crystalline heterocomplex bearing the solvent molecules. However, complexation crystallization does not occur between the diptide and either enantiomer of BINOL under similar conditions. The difference in complexation behavior has been successfully applied in the enantiomeric enrichment of nonracemic BINOLs, and almost quantitative separation of the excess enantiomer from racemic BINOL was achieved.

Chiral discrimination of a chiral host to a racemic guest is one of the most important forms of molecular recognition. In the molecular recognition, the chiral host stereoselectively interacts with one enantiomer of the racemic guest, leading to chiral separation of the racemic compound. This chiral recognition has been developed into an effective method for preparing optically active organic materials.[1] However, simultaneous complexation of a chiral host to two enantiomers of a racemic guest has never been observed to date, though heterorecognition of an achiral host to a racemic guest has been recently reported.[2] In an attempt to prepare an enantiopure diol via enantioselective complexation of a chiral tricyclic dipeptide host (3*S*,6*S*)-**1** (Figure 1) to an axially chiral guest racemic 1,1′-bi-2-naphthol (*rac*-**2**), we unexpectedly observed an achiroselective complexation crystallization of the dipeptide to the two enantiomers of *rac*-**2**. Further investigation found that no complexation crystallization occurred between (3*S*,6*S*)-**1** and enantiopure (*R*)- or (*S*)-1,1′-bi-2-naphthol [(*R*)-**2** or (*S*)-**2**] under similar conditions. This difference in complexation behaviors naturally aroused our interest in the enrichment of the excess enantiomer in (*R*)-**2** or (*S*)-**2** with lower ee via the heterocomplexation strategy. We successfully applied the strategy and realized almost quantitative separation of the excess enantiomer from the racemate. We herein report the novel enrichment of the excess enantiomer in nonracemic 1,1′-bi-2-naphthols (non-*rac*-**2**).

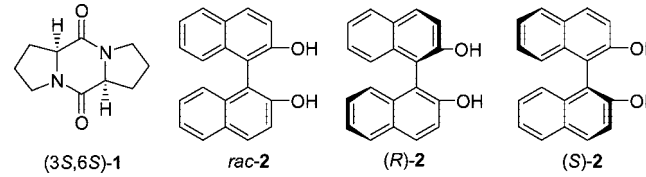

FIGURE 1. Cyclic tricyclic dipeptide (3*S*,6*S*)-**1** and 1,1′-bi-2-naphthol.

The tricyclic dipeptide (3*S*,6*S*)-**1**[3] generated from (*S*)-proline methyl ester was allowed to mix with *rac*-**2** in benzene with heating until the solids dissolved completely, followed by reflux for an additional 1 h, and then cooled to ambient temperature to give a colorless crystalline material SC-**3**[4] with $[\alpha]_D^{25} = -18.3°$ ($c = 1$, THF). The ^{1}H NMR spectrum of SC-**3** clearly indicates that it is a 1:2:3 complex consisting of the dipeptide, 1,1′-bi-2-naphthol, and benzene, and the dipeptide retains its configuration under the solution NMR condition. However, decomplexation of SC-**3** yielded almost quantitative *rac*-**2**, meaning that two opposite configurational 1,1′-bi-2-naphthol molecules are included in the complex. This fact reveals that an achiroselective complexation of (3*S*,6*S*)-**1** to both the enantiomers of *rac*-**2** occurs in this system.

Single crystal X-ray diffraction analysis[5] of SC-**3** further confirmed the composition of the complex (Figure 2 on left). In the crystal, it can be observed that both OH groups of each 1,1′-bi-2-naphthol molecule are involved in H-bonds with neighboring carbonyl groups of the dipeptides, and that each peptide carbonyl group is hydrogen-bonded with two 1,1′-bi-2-naphthols having different chirality, namely, each

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(4) When the molar ration of racemic 1,1′-bi-2-naphthol and (3*S*,6*S*)-**1** is higher than 2:1, a co-precipitation of the complex and racemic 1,1′-bi-2-naphthol occurred. The co-precipitate was treated by recrystallization in benzene to offer pure complex SC-**3**.

(5) Final atomic coordinates of the crystal, along with lists of anisotropic thermal parameters, hydrogen coordinates, bond lengths, and bond angles, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-287999. Data can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: (+44) 1223−336−033. E-mail: deposit@ccdc.cam.cn. Web: http//www.ccdc.cam.ac.uk).

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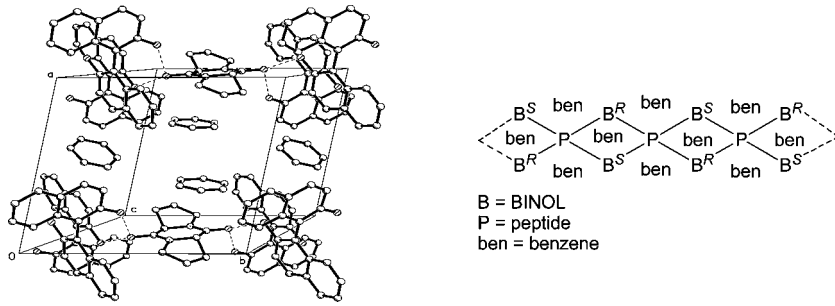

FIGURE 2. (Left) Molecular packing diagram of the complex SC-**3** (hydrogen bonds are shown as dotted lines). (Right) Chain structure of SC-**3**.

SCHEME 1. Enrichment of Non-*rac*-2 via Hetereocamplexation of (3*S*,6*S*)-1

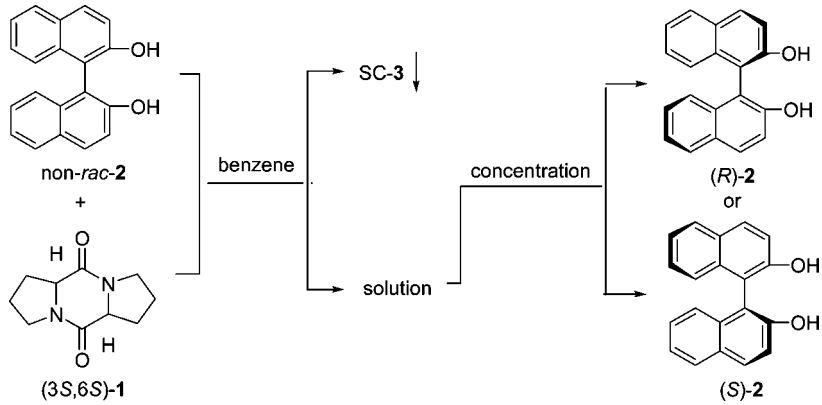

TABLE 1. Enantiomeric Enrichment of Non-Racemic BINOLs by Heterocomplexation of (3*S*,6*S*)-1

entry	nonrac-2[a]	yield of SC-3 (%)	yield of the enantiomer enriched (%)[b]	$[\alpha]_D$ of the enantiomer enriched (THF, c 1)	ee of the enantiomer enriched (%)[c]
1	80% ee (*R*)-2	96	96	$[\alpha]_D^{25} = +35.6$	>99
2	80% ee (*S*)-2	98	97	$[\alpha]_D^{25} = -35.4$	>99
3	50% ee (*S*)-2	97	96	$[\alpha]_D^{25} = -35.6$	>99
4	20% ee (*S*)-2	98	95	$[\alpha]_D^{25} = -35.5$	>99

[a] Nonracemic BINOLs were made up by mixing of rac-2 with an appropriate amount of enantiopure (R)- or (S)-2. [b] Yield of optically active BINOL is calculated based on the sum of two or three crops by crystallization. [c] Ee of optically active BINOL is obtained based on chiral HPLC determination and the specific rotation.

peptide C═O group actually accepted two H-bonds, and the OH···O distances are 2.014 and 2.149 Å, respectively, and in one H-bond, the three atoms are nearly collinear with a bond angle of 178°. This molecular assembly results in the formation of an infinite chain, where each link is composed of the peptide molecules doubly bridged by two BINOL molecules, and the solvent molecules (benzenes) are locked between the chains to form a more stable three-dimensional network (Figure 2 on right). To the best of our knowledge, this interesting supramolecular construction has never been observed before.

In contrast to the above, enantiopure (*R*)-**2** or (*S*)-**2** can not undergo complexation crystallization with (3*S*,6*S*)-**1** under similar condition.

The strikingly different complexation behavior of *rac*-**2** from enantiopure (*R*)-**2** or (*S*)-**2** was applied to enrich the excess enantiomer in 1,1′-bi-2-naphthols with lower ee (Scheme 1). For a non-*rac*-**2**, the amount of the *rac*-**2** included can be readily calculated based on the ee value of the non-*rac*-**2**, thus the appropriate (3*S*,6*S*)-**1** loading requested for the formation of a 1:2 complex with the *rac*-**2** can be determined. When a stoichiometric (3*S*,6*S*)-**1** was added to a benzene solution of the non-*rac*-**2**, refluxed, and then cooled, the *rac*-**2** contained in the non-*rac*-**2** precipitated from the solution as a crystalline complex (SC-**3**). The benzene solution removed from the crystals was concentrated to give massy transparent crystals[6] of enantiopure (*R*)-**2** or (*S*)-**2**. Some results obtained by the heterocomplexation enrichment were summarized in Table 1. It may be seen that efficient separation of the excess enantiomer from *rac*-**2** is realized.

Theoretically, this enrichment method is suitable for any enantiomerically impure 1,1′-bi-2-naphthol; however, in consideration of preparative efficiency, it is more suitable for nonracemic 1,1′-bi-2-naphthols with medium or higher enantiomeric purity.[7]

(6) We early observed that enantiopure (*R*)- or (*S*)-BINOL has different crystalline behavior from racemic BINOL in benzene or toluene. In both the solvents, enantiopure (*R*)- or (*S*)-BINOL is isolated as a massy colorless transparent crystal, whereas racemic BINOL is obtained as a light, white needle. However, in Et_2O, they are isolated as a massy colorless transparent crystal. Therefore, benzene and toluene are selected as solvent for the enrichment of the excessive enantiomer in nonracemic BINOL.

(7) Our enrichment is more suitable for the (*R*)- or (*S*)-BINOLs in higher than 50% ee. That is because the (*R*)- and (*S*)-BINOLs with low ee include high ratio of racemic BINOL, whereas racemic BINOL has low solubility in benzene even under reflux condition. Thus, a great amount of the solvent, bulky equipment, and long time are required for their dissolution. On the other hand, it is low efficiency to obtain relative small amount of enantiopure (*R*)- or (*S*)-BINOL by evaporation of plentiful low-concentration solution.

In addition, it is noteworthy that the heterocomplex SC-**3** is easily dissociated by a H_2O-CH_3COOEt mixture, from which (3*S*,6*S*)-**1** and *rac*-**2** can be recovered almost quantitatively for reuse.

Enantiomerically pure (*R*)-**2** and (*S*)-**2** have been widely used in asymmetric synthesis,[8] supramolecular chemistry,[9] chiral separation[10] and preparation of a variety of chiral materials.[11] However, most of the reported preparations for them cannot directly offer high-yieldingly enantiopure products, and further purification or enrichment is generally required. It must be pointed out that the known purifications, including chiral[12a,b] or achiral stationary phase chromatography,[12c] fractional crystallization,[12d−f] "kinetic" crystallization[12g] and chiral discrimination of bovine serum albumin,[12h,i] often are not satisfied in cost or in efficiency. Our enrichment possesses some remarkable advantages, such as simple procedure, stoichiometric separation, lower cost and higher efficiency.

In summary, an achiroselective complexation of chiral host (3*S*,6*S*)-**1** to racemic guest *rac*-**2** has been discovered, and the heterocomplexation has been successfully applied to enantiomeric enrichment of a wide range of nonracemic 1,1′-bi-2-naphthols, where stoichiometric separation of the excess enantiomer from the racemate is realized.

Experimental Section

Representative Procedure for the Enrichment of the Excessive Enantiomer in a Nonracemic 1,1′-Bi-2-naphthol. A mixture of (3*S*,6*S*)-**1** (0.1 g, 0.515 mmol) and 80% ee (*S*)-1,1′-bi-2-naphthol (1.44 g, 5.035 mmol) was refluxed in benzene (15 mL) for 1.5 h. The resulting solution was cooled to rt and stood for 24 h to isolate a white solid. The solid was filtered, washed with benzene, collected, and then dried under reduced pressure to weigh 0.495 g, mp 170−172 °C, $[\alpha]_D^{20} = -18.6$ (*c* 1, in THF), 98% yield (calcd based on a 1:2:3 complex consisting of the dipeptide, 1,1′-bi-2-naphthol and benzene). IR (KBr, cm^{-1}): 3358, 3224, 1623. ^1H NMR ($DCCl_3$, 300 MHz): 1.85−2.33 (m, 8H); 3.49−3.54 (dd, $J = 9.0$ Hz, $J = 6.0$ Hz, 4H); 4.13 (t, $J = 8.1$ Hz, 2H); 5.18 (s, 4H); 7.15 (d, $J = 8.1$ Hz, 4H); 7.40−7.28 (m, 30 H); 7.90 (d, $J = 7.2$ Hz, 4H), 7.98 (d, $J = 9.3$ Hz, 4H). The benzene mother liquor removed from the solid was concentrated and slowly cooled to furnish massy transparent crystals of enantiopure (*S*)-**2** (1.102 g), mp 208−210, 96% yield, $[\alpha]_D^{20} = -35.6$ (*c* 1, in THF). >99% ee.

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Supporting Information Available: The preparative procedure of (3*S*,6*S*)-**1** and the IR, ^1H NMR spectra, crystal structure and CIF for SC-**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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