

Chirality Enrichment through the Heterorecognition of Enantiomers in an Achiral Coordination Host**

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The enrichment of the enantiomeric excess (*ee*) of chiral compounds without adding any external chirality source is an attractive challenge in organic chemistry not only from the viewpoint of scientific interest but also for a practical application in the production of chiral compounds.^[1] Recrystallization has been used for a long time as a convenient method for the enrichment of the chirality of compounds with low *ee* values.^[2] However, this traditional method is applicable only to crystalline compounds in which the solids have no racemic solid-solution properties. Herein, we report chirality enrichment by the bimolecular heterorecognition of enantiomers in a synthetic host.^[3] The host employed is the bowl-shaped coordination compound **1** that self-assembles from [Pd(en)(NO₃)₂] (en = ethylenediamine) and the tris(3-pyridyl)triazine ligand (Figure 1).^[4,5] Treatment of an aqueous

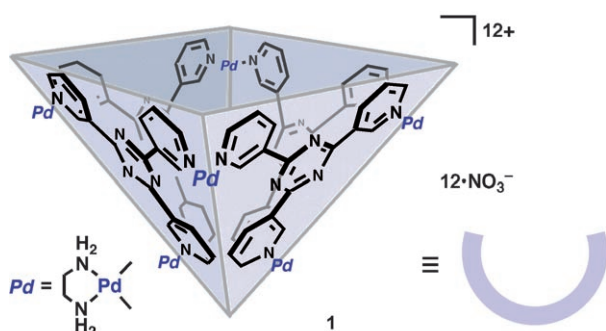


Figure 1. The structure of the bowl-shaped coordination cage **1**.

solution of the host with, for example, an organic solution of 1,1'-bi-2-naphthol (**2**) of low *ee* value results in the racemic pair of **2** being selectively recognized by the host, with enantiomerically enriched **2** left in the organic phase. Throughout the overall process, the substrates are handled

only in solutions and no source of chirality is added. Homo- and heterorecognition of enantiomers has been described for catalytic species involved in asymmetric amplification reactions, where the enantiomers are not separated.^[6]

When a solution of (*S*)-**2** at 50% *ee* (20.0 μmol) in hexane (1.0 mL) was stirred with a solution of cage **1** (5.0 μmol) in D₂O (1.0 mL) at room temperature for one day (Figure 2a), the room-temperature ¹H NMR spectrum of the aqueous phase showed broad signals arising from both host **1** and guest **2** (Figure 2b).^[7,8] The signals became very sharp at 5 °C, thus indicating a freezing of the dynamic motion of the host and/or the guest at this temperature (Figure 2c). The set of signals

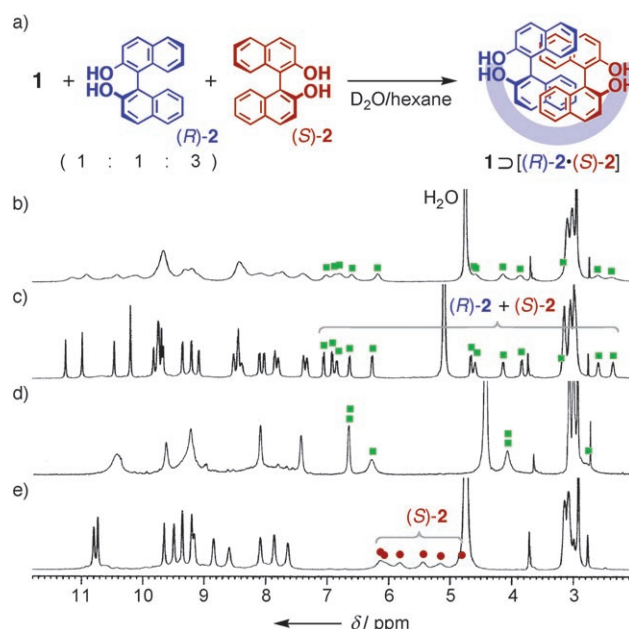


Figure 2. a) Bimolecular heterorecognition of enantiomers (*R*)-**2** and (*S*)-**2** within bowl-shaped host **1**. ¹H NMR spectra (500 MHz, D₂O) of the **1**⊃[(*R*)-**2**⋅(*S*)-**2**] complex at b) RT, c) 5 °C, and d) 50 °C, and e) of the **1**⊃(*S*)-**2** complex at RT.

arising from the host–guest complex frozen in either enantiomeric form was observed for both guest **2** and the triazine ligand of **1**: namely, twelve signals for **2** (δ = 7.1–2.4 ppm) and twenty four signals for the ligand (δ = 11.3–7.4 ppm).^[7] The ratios of the integrals for the signals revealed the formation of a 1:2 host–guest complex. This observation is explained only by assuming the pairwise selective recognition of *R* and *S* enantiomers of **2** and a slow exchange of the enantiomers in the cavity (Figure 3). Thus, interconversion between enantiomeric complexes **A** and **B** is very slow as a consequence of

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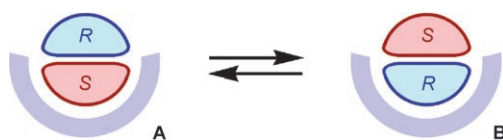


Figure 3. Interconversion between enantiomeric complexes A and B.

efficient host–guest interactions, thereby resulting in the two sets of signals for the guest. At the same time, the symmetry of the host is reduced from C_{2v} to C_2 , thus resulting in diastereomeric relationships between any two adjacent ligands in host **1**. Heating the solution at 50 °C resulted in the exchange process of Figure 3 becoming rapid and only one set of signals was observed for both the host and the guest (Figure 2d).

An important feature in this host–guest complexation is that, despite the use of an *S*-rich guest (50 % *ee*), a 1:1 racemic pair was selectively recognized in the cavity to give the $1 \supset [(R)\text{-}2 \cdot (S)\text{-}2]$ complex, as evident from the integral ratios in the NMR spectrum. To confirm the racemic heterorecognition of the enantiomers, the aqueous phase was separated and guest **2** bound in **1** was extracted from the aqueous solution with CHCl_3 . Analysis of the extracts by HPLC on a chiral stationary phase revealed only 9 % *ee* for enclathrated **2**. This result indicates that heterorecognized complex $1 \supset [(R)\text{-}2 \cdot (S)\text{-}2]$ is much more stable than the homorecognized complex $1 \supset (S)\text{-}2$. For comparison, $1 \supset (S)\text{-}2$ was prepared by treating optically pure (*S*)-**2** with **1**. The NMR spectrum of $1 \supset (S)\text{-}2$ showed neither very large upfield shifts of the signals corresponding to the guest, nor clear desymmetrization of the host, thus implying the presence of only relatively weak host–guest interactions (Figure 2e).

The efficient bimolecular heterorecognition of the enantiomers of **2** afforded a significant enrichment of the chirality of free **2**. After removal of the aqueous phase, the free **2** was recovered from the hexane solution as a water-insoluble solid. The *ee* value of the recovered **2** was shown to be 81 % *ee*. It is particularly interesting that the asymmetric enhancement from 50 to 81 % *ee* was achieved in a solution without using any other chiral source.

Hydroxy groups at the 2- and 2'-positions of **2** are essential for the bimolecular heterorecognition. Chirality enrichment was not observed when 2,2'-dimethyl-1,1'-binaphthyl (**2'**) was employed because of the formation of only a 1:1 host–guest complex. This feature suggests that the OH groups of **2** in the $1 \supset [(R)\text{-}2 \cdot (S)\text{-}2]$ complex are exposed outside the host, thus stabilizing the complex through hydrophilic contact with water at the opening. Similar to **2**, 1,1'-binaphthyl-2,2'-diamine (**3**, 50 % *ee*) afforded the complex $1 \supset [(R)\text{-}3 \cdot (S)\text{-}3]$.^[7] The *ee* value of recovered **3** from the complex was only 17 % *ee*, while that of free **3** was enriched to 72 % *ee*.

Finally, we examined the optical resolution of a racemic compound by the pairwise selective bimolecular recognition.^[9] A solution of racemic octahydro-2,2'-binaphthol (*rac*-**4**, 10.0 μmol) in hexane (1.0 mL) was treated with (*R*)-**2** (5.0 μmol) in an aqueous solution (1.0 mL) of **1** (5.0 μmol) in the expectation of obtaining the coenclathration complex $1 \supset [(R)\text{-}2 \cdot (S)\text{-}4]$. After five hours at room temperature, the

NMR spectrum of the aqueous phase showed the formation of a host–guest complex with a stoichiometry of $1 \cdot [(R)\text{-}2] \cdot (S)\text{-}4$ (Figure 4). This stoichiometry strongly suggested the

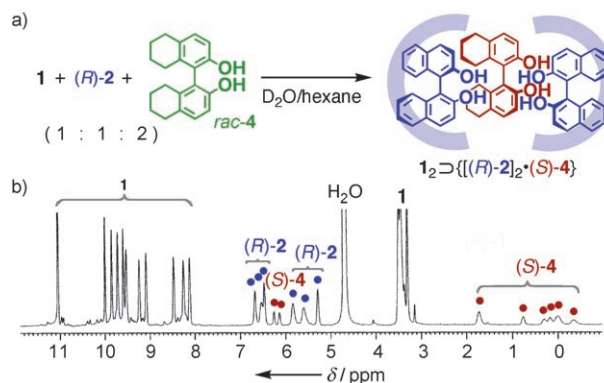


Figure 4. a) Hetero-bimolecular recognition of (*S*)-**4** by (*R*)-**2** within host **1**. b) The ^1H NMR spectrum (500 MHz, D_2O , 80 °C) of the complex $1_2 \supset [(R)\text{-}2]_2 \cdot (S)\text{-}4$.

formation of encapsulation complex $1_2 \supset [(R)\text{-}2]_2 \cdot (S)\text{-}4$, where a dimeric capsule of **1** accommodates two (*R*)-**2** molecules and one molecule of **4**.^[7,10] Most probably, (*S*)-**4** is sandwiched and stabilized by two (*R*)-**2** molecules in the dimeric capsule of **1**. This proposed aggregation structure was suggested by the fact that the signals of (*R*)-**2** were highly shifted upfield because of stacking interactions with the framework of **1**, whereas those of **4** were shifted less upfield. Thus, complexed **4** was recovered from the aqueous phase and analyzed by HPLC on a chiral stationary phase. The configuration was confirmed to be *S* and the *ee* value was as high as 87 % *ee*.

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