Molecular Recognition

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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 $[Pd(en)(NO_3)_2]$ (en = ethylenediamine) and the tris(3-pyridyl)triazine ligand (Figure 1).[4,5] Treatment of an aqueous

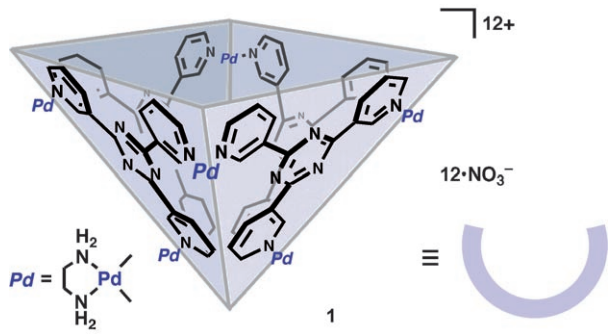

Figure 1. The structure of the bowl-shaped coordination cage **1**.

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 enanitiomers 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 D_2O (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

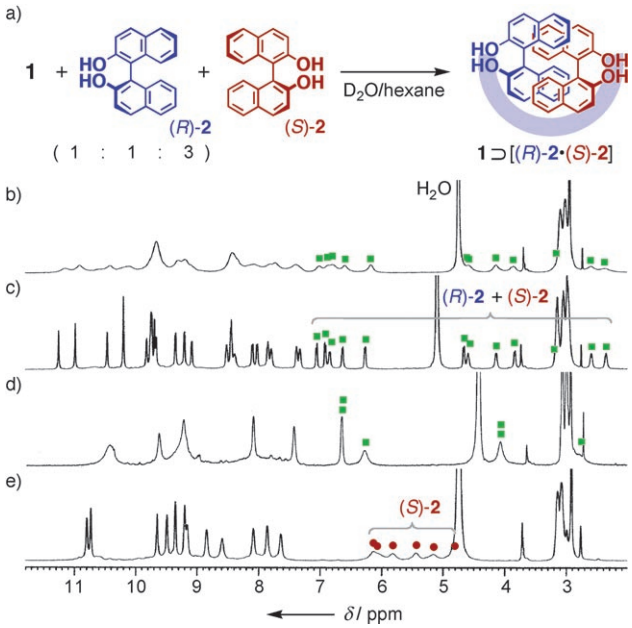

Figure 2. a) Bimolecular heterorecognition of enantiomers (*R*)-**2** and (*S*)-**2** within bowl-shaped host **1**. ^1H NMR spectra (500 MHz, D_2O) of the **1**⊃[(*R*)-**2**·(*S*)-**2**] complex at b) RT, c) 5 °C, and d) 50 °C, and e) of the **1**⊃(*S*)-**2** complex at RT.

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** ($\delta = 7.1$–2.4 ppm) and twenty four signals for the ligand ($\delta = 11.3$–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 enantiometric complexes **A** and **B** is very slow as a consequence of

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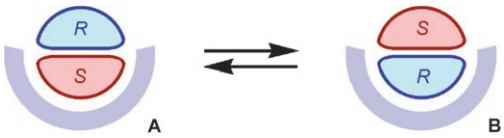

Figure 3. Interconversion between enantiometric complexes **A** and **B**.

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 2 d).

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**⊃[(*R*)-**2**·(*S*)-**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**⊃[(*R*)-**2**·(*S*)-**2**] is much more stable than the homorecognized complex **1**⊃(*S*)-**2**. For comparison, **1**⊃(*S*)-**2** was prepared by treating optically pure (*S*)-**2** with **1**. The NMR spectrum of **1**⊃(*S*)-**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 2 e).

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**⊃[(*R*)-**2**·(*S*)-**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**⊃[(*R*)-**3**·(*S*)-**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**⊃[(*R*)-**2**·(*S*)-**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**·[(*R*)-**2**]·(**4**)$_{0.5}$ (Figure 4). This stoichiometry strongly suggested the

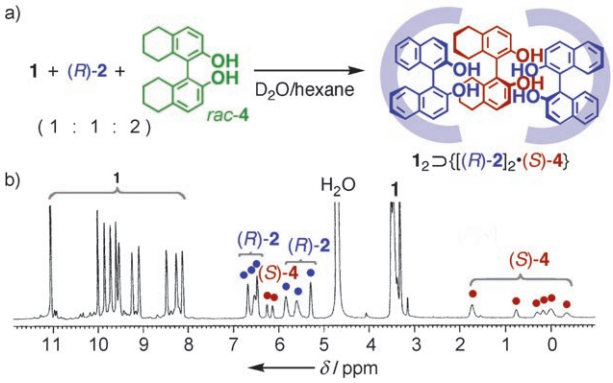

Figure 4. a) Hetero-bimolecular recognition of (*S*)-**4** by (*R*)-**2** within host **1**. b) The ^{1}H NMR spectrum (500 MHz, D_2O, 80 °C) of the complex **1**$_2$⊃{[(*R*)-**2**]$_2$·(*S*)-**4**}.

formation of encapsulation complex **1**$_2$⊃{[(*R*)-**2**]$_2$·**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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