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PAPER

Enantioseparation of 1-arylethanols *via* a supramolecular chiral host consisting of *N*-(2-naphthoyl)-L-aspartic acid and an achiral diamine†

Koichi Kodama,* Ayaka Kanno, Eriko Sekine and Takuji Hirose*

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A supramolecular chiral host consisting of *N*-(2-naphthoyl)-L-aspartic acid (L-**1**) and *meso*-1,2-diphenylethylenediamine (**2**) is effective in enantioseparation of 1-arylethanols (up to 96% ee with 100% inclusion ratio). Here we report three different methods to prepare the inclusion crystals and discuss the chiral recognition mechanism on the basis of X-ray crystallography results.

Introduction

Enantiomeric separation *via* diastereomeric salt formation is simple and easily scaled up, making it one of the most useful and practical methods of preparing optically active compounds.[1] However, this method cannot be directly applied to neutral compounds such as alcohols and sulfoxides because of their weaker intermolecular interaction sites. Instead, host–guest inclusion complexation has been found to be a useful alternative and is therefore gaining popularity.[2] Diastereomeric inclusion crystals are formed by selective incorporation of one guest enantiomer into asymmetric voids created by chiral host compounds and no strong interactions between host and guest molecules are essential to obtain inclusion crystals. A further advantage is that several methods have already been developed to prepare inclusion crystals: i) crystallization from the host/guest solution, ii) suspension of host/guest in a solvent, and iii) direct mixing and cogrinding of host/guest compounds.[3] However, for highly enantioselective inclusion complexation, appropriate design of the chiral host compound is essential and the key factor is the extent of host complementarity to one enantiomer of the guest compound. Consequently, the best host compound for the purpose will depend on the structure of the guest. In other words, a new host compound must be designed and synthesized in an enantiopure form for each target racemate.

This disadvantage has led to increased attention on the use of supramolecular chiral hosts, comprising several different types of molecules, because simple replacement of their components allows modification of inclusion and recognition sites to match different target racemates.[4] Recently, the carboxylic acid/primary amine combination has been often used to construct supramolecular materials because of the strong ionic hydrogen bonds between them.[5] We previously reported that acid–base supramolecular chiral host systems composed of dibenzoyl-L-tartaric acid and some achiral diamines are effective in enantioselective inclusion of chiral benzylic and aliphatic alcohols.[6] It is noteworthy that L-tartaric acid is an easily available chiral source and its chiral recognition ability can be successfully controlled by changing the achiral diamine.

In this study, we focused on expanding the utility of these systems by using natural amino acids as the chiral components. They are quite common and inexpensive chiral sources and also have more structural variety than tartaric acid. In addition to their wide commercial availability, they are easy to derivatize into both acidic and basic compounds by an appropriate modification of the amino and carboxyl groups, respectively. Moreover, it has been reported that several dipeptides derived from α-amino acids can be applied to enantioselective inclusion of alcohols and sulfoxides.[7]

We selected *N*-acylated L-aspartic acid, a chiral dicarboxylic acid, because of its simple structure and synthetic accessibility. The target guest compounds selected were 1-arylalkanols because they can act as both hydrogen-bonding donors and acceptors. In the preliminary screening of the host systems, four achiral diamines including those employed in our previous study were tested.[6] All the tested diamines have simple and symmetrical structures to avoid complicated polymorphs. In addition, they have rigid aromatic rings to give appropriate cavities. Fortunately, it was found that the combination of *N*-(2-naphthoyl)-L-aspartic acid (L-**1**) and *meso*-1,2-diphenylethylenediamine (**2**) was a good candidate for enantioselective inclusion of 1-arylethanols. Compound **2** is an achiral *meso*-form of a diamine with two stereogenic centers. Here we report the chiral recognition ability of L-**1**·**2** in three different techniques: crystallization (Method A), re-precipitation (Method B), and suspension (Method C). In order to understand the chiral recognition

Graduate School of Science and Engineering, Saitama University, 255 Shimo-Okubo, Sakura-ku, Saitama 338-8570, Japan. E-mail: kodama@mail.saitama-u.ac.jp; Fax: +81-48-858-9548; Tel: +81-48-858-9548

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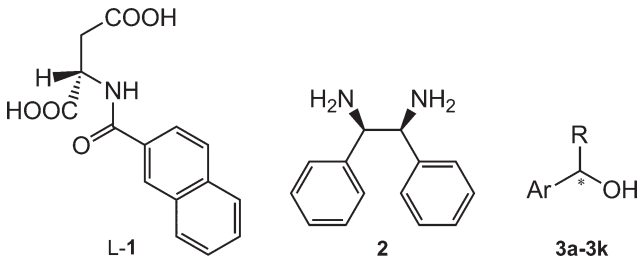
mechanism, crystallographic analyses of the ternary inclusion crystals were carried out. On the basis of the results, we discuss the effects of the hydrogen-bonding networks, molecular packing mode, and the structures of the guest compounds.



Results and discussion

Enantioselective inclusion of 1-arylalkanols by L-1·2 *via* crystallization (Method A)

In this method, equimolar amounts of L-**1** and **2** were dissolved in an aqueous acetonitrile solution of racemic **3**, followed by crystallization of the inclusion complexes. The results in Table 1 clearly show that the (*R*)-enantiomer of each guest was preferentially incorporated but the efficiency depended on the structure of the alcohols: the chiral host efficiently included (*R*)-**3a** of 88% ee in 83% yield with 100% inclusion ratio as a L-**1** : **2** : **3a** = 1 : 1 : 1 complex (entry 1). For the positional isomers of 1-(methylphenyl)ethanols, a drastic decrease in enantiomeric excess to 28% (in 90% yield) was observed for the *ortho*-isomer **3b** (entry 2), whereas the highest enantioselectivity (91% ee) with 100% inclusion was obtained for the *meta*-isomer **3c** (entry 3). The good results for 1-(3-chlorophenyl)ethanol (**3d**) suggest that substituents such as methyl and chloro groups are acceptable at the *meta*-position of a phenyl group but not at the *ortho*-position. For the *para*-isomer **3e**, a moderate yield and selectivity (76% ee in 85% yield) was achieved (entry 5).

The greater the length of the alkyl group at the *para*-position of the phenyl group, the lower was the enantiomeric excess, although the yield and the inclusion ratio remained high (entries 5–7). This result suggests the supramolecular host has some adaptability with regard to the molecular sizes of the *para*-substituted 1-phenylethanol derivatives. The comparably higher inclusion ratios and selectivities for the 1-arylethanols with halogen groups at the *para*-position indicate that the electron-withdrawing effect of the substituents had little influence on the inclusion phenomenon. That is, the inclusion efficiency was mainly determined by the size and shape of the guest compounds (entries 8 and 9).

However, as seen in entry 10, bulky alkyl group at the stereogenic center of the target arylalkanol drastically hampered the formation of inclusion crystals. This means the void around the stereogenic center of incorporated **3** is small and less flexible. A bulky alcohol, 1-(2-naphthyl)ethanol (**3k**), suffered a low inclusion ratio and selectivity, probably because the 2-naphthyl group was too large for inclusion and chiral recognition by L-**1**·**2**. Despite the limitations shown above, various 1-phenylethanols were included by L-**1**·**2** in a highly efficient and enantioselective manner, and in particular the combination was found to be suitable for *meta*- and *para*-substituted 1-phenylethanols.

Enantioselective inclusion of 1-arylethanols by L-1·2 *via* re-precipitation (Method B) and suspension (Method C)

As stated above, several methods have been used to prepare inclusion crystals and they can afford different results. Method A (crystallization) is the most reliable and commonly used strategy; however, it is usually time-consuming (usually takes more than 3 days to obtain the inclusion crystals) and requires a large amount of solvent. To further examine the applicability of the present host system and improve the enantioselectivities for **3**, Methods B and C were also tested to prepare inclusion crystals L-**1**·**2**·**3** and the results compared for four 1-arylethanols; the results are summarized in Table 2. In these methods, the host was suspended in hexane and the pre-organized crystals may have played some role in preventing the inclusion of the undesired enantiomer.

As seen in Method A, **3a–c** and **3e** were included by L-**1**·**2** using Methods B and C, although the inclusion ratio was slightly lower. Furthermore, as in Method A, (*R*)-enantiomers of **3a**, **3c**, and **3e** were predominantly selected. Furthermore, improved enantioselectivity was observed for **3e** in both Method B and Method C (93% and 96% ee, respectively). The powder XRD patterns of L-**1**·**2**·**3a** prepared by the three methods were almost identical, which indicated that the structures of the inclusion

Table 1 Enantioselective inclusion of 1-arylalkanols by inclusion complexation with L-**1**·**2** using Method A

Entry	1-Arylalkanol	R	Ar	Yield[a] (%)	Inclusion ratio[b] (%)	ee[c] (%)
1	**3a**	Me	Ph	83	100	88 (*R*)
2	**3b**	Me	*o*-MePh	85	90	28 (*R*)
3	**3c**	Me	*m*-MePh	83	100	91 (*R*)
4	**3d**	Me	*m*-ClPh	90	100	81 (*R*)
5	**3e**	Me	*p*-MePh	85	100	76 (*R*)
6	**3f**	Me	*p*-EtPh	90	100	72 (*R*)
7	**3g**	Me	*p*-^{n}PrPh	94	100	64 (*R*)
8	**3h**	Me	*p*-FPh	94	90	74 (*R*)
9	**3i**	Me	*p*-ClPh	88	100	85 (*R*)
10	**3j**	Et	Ph	Not crystallized		
11	**3k**	Me	2-Naphthyl	77	60	13 (*R*)

[a] Yield was determined on the basis of molar ratio of L-**1**·**2** salt. [b] Inclusion ratio of **3** was determined by ^{1}H NMR. [c] Enantiomeric excess was determined by HPLC analysis.

Table 2 Comparison of the three methods for enantioselective inclusion of 1-arylethanols

			Method A (Crystallization)			Method B (Re-precipitation)			Method C (Suspension)		
Entry	1-Arylethanol	Ar	Yield[a] (%)	Inc.[b] (%)	Ee[c] (%)	Yield[a] (%)	Inc.[b] (%)	Ee[c] (%)	Yield[a] (%)	Inc.[b] (%)	Ee[c] (%)
1	**3a**	Ph	83	100	88 (*R*)	89	90	92 (*R*)	82	95	88 (*R*)
2	**3b**	*o*-MePh	85	90	28 (*R*)	22[d]	50[d]	*rac*.	87	65	30 (*R*)
3	**3c**	*m*-MePh	83	100	91 (*R*)	90	90	91 (*R*)	90	90	91 (*R*)
4	**3e**	*p*-MePh	85	100	76 (*R*)	90	100	93 (*R*)	85	100	96 (*R*)

[a] Yield was determined on the basis of the molar amount of L-**1**·**2**. [b] Inclusion ratio was determined by ^{1}H NMR. [c] Enantiomeric excess was determined by HPLC analysis. [d] Yield and inclusion ratio were determined on the basis of the molar amount of **2**.

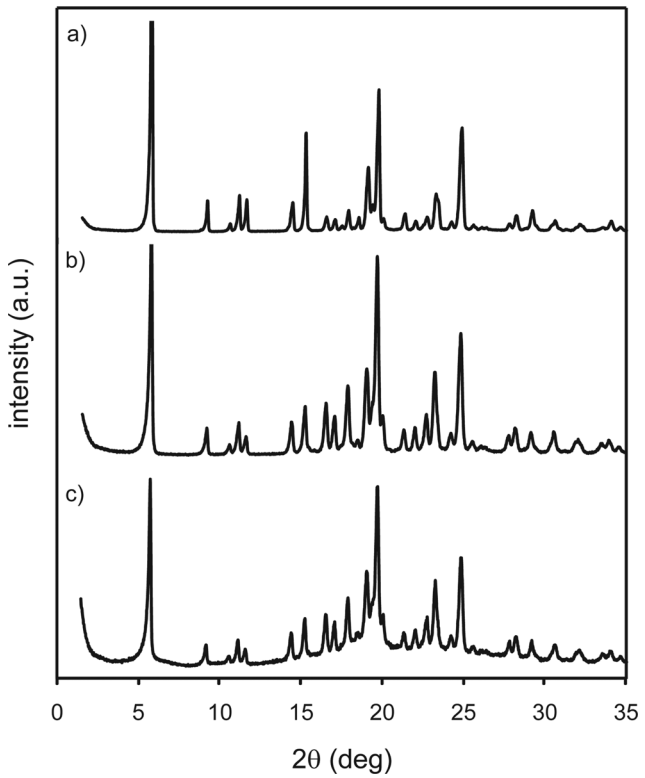


Fig. 1 Powder XRD patterns of the inclusion crystals L-**1**·**2**·**3a** obtained by a) crystallization (Method A), b) re-precipitation (Method B), and c) suspension (Method C).

crystals and their chiral recognition mechanisms were similar (Fig. 1). Therefore, the higher enantioselectivities in Methods B and C could probably be attributed to greater effectiveness of pre-organized and suspended hosts in the preferential inclusion of (*R*)-enantiomers from a dilute guest solution. However, both methods afforded unacceptably low inclusion ratios and/or enantioselectivities for **3b** (entry 2). Considering the fact that Method A was not effective either, the steric hindrance of the *ortho*-methyl group seems have strongly affected the inclusion process in Methods B and Method C as well. In fact, ^{1}H NMR analysis indicated that the molar ratio of the precipitate obtained by Method B was L-**1** : **2** : **3b** = 3.3 : 1 : 0.5, suggesting that the precipitate was a mixture of the expected inclusion crystals and the uncomplexed host compounds.

Next, we applied Method B to a large-scale preparation of enantioenriched **3a**. The mixture of L-**1** and **2** (4.71 mmol) was suspended in hexane in the presence of *rac*-**3a**. The resultant inclusion crystal was filtered and heated under reduced pressure to afford (*R*)-enriched **3a** (2.56 mmol, 95% ee) in high yield and enantiopurity. Thus, it has been shown that this method is readily applicable to the preparative-scale enantioseparation of **3**.

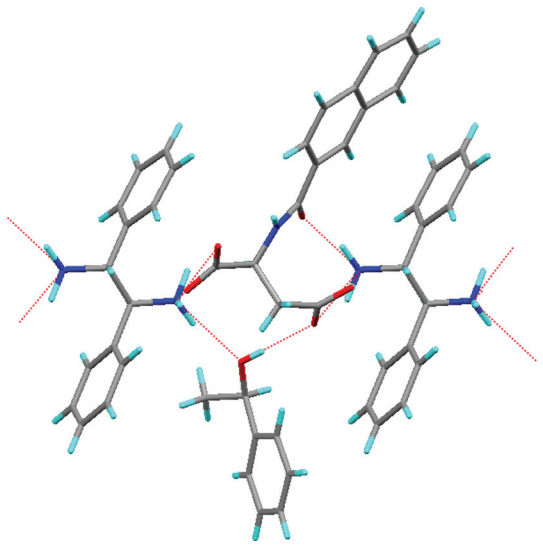


Fig. 2 Crystal structure of L-**1**·**2**·(*R*)-**3a** (1 : 1 : 1, enantiomeric excess of (*R*)-**3a** was 84%) viewed from the *ac* plane. The hydrogen bonds are shown by dashed lines.

Crystallographic analyses of the ternary inclusion crystals L-1·2·3

To examine the chiral recognition mechanism of **3** in detail, crystallographic analyses of the inclusion crystals L-**1**·**2**·**3** prepared by Method A were carried out. Single crystals suitable for the analysis were fortunately obtained from aqueous acetonitrile solution of L-**1**·**2** in the presence of racemic **3a** or **3e**.

For both guest compounds, it was confirmed that the inclusion crystals consisted of a 1 : 1 : 1 mixture of L-**1**, **2**, and **3**. In addition, only (*R*)-isomers of **3** were incorporated, which is in accordance with the results of the inclusion experiments. Fig. 2 shows the hydrogen bonds between the three components of the L-**1**·**2**·(*R*)-**3a** inclusion crystals. There are two kinds of hydrogen bonds in the host, that is, between L-**1** and **2**: one is between carboxylate oxygens of L-**1** and ammonium nitrogens of **2** and the other is between an amide oxygen of L-**1** and an ammonium nitrogen of **2**. They constitute a 2D sheet-like hydrogen-bonding

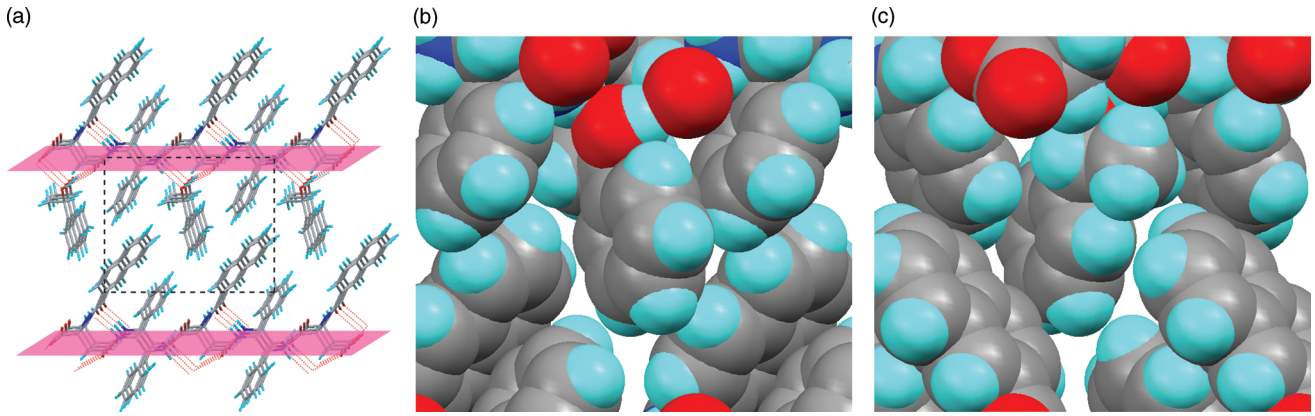


Fig. 3 Crystal structure of L-**1**·**2**·(*R*)-**3a** (1 : 1 : 1; 84% ee for (*R*)-**3a**). (a) Perspective view of the inclusion crystal. (b) Enlarged anterior view of dashed square in (a). (c) Enlarged posterior view of dashed square in (a).

network along the *ac* plane (Fig. 3a). The guest molecules (*R*)-**3a** are sandwiched between the two 2D-sheet structures of the host. There are two hydrogen bonds involving the hydroxy group of (*R*)-**3a** and the host: one is with a carboxylate oxygen of L-**1** and the other is with an ammonium nitrogen of **2**. There are no additional weak intermolecular interactions such as π–π or CH–π interactions.[8]

In the solid state, the conformation of **2** was fixed by the interactions with L-**1** and the desymmetrized molecules **2** efficiently afforded an asymmetric environment around them. As seen in the space-filling models in Fig. 3b and 3c, the guest molecule (*R*)-**3a** is located in the void created by two phenyl groups of **2** and two naphthyl groups of L-**1**. During the inclusion process of **3**, the hydroxyl group of **3** is first captured by the two aforementioned hydrogen bonds between the hosts. Thereafter, the phenyl group, methyl group, and the hydrogen atom seem to be arranged to fill the asymmetric void according to their sizes.

Comparing the crystal structures of L-**1**·**2**·(*R*)-**3a** and L-**1**·**2**·(*R*)-**3e** (Fig. 4), it is apparent that the 2D sheet-like hydrogen-bonding networks and the molecular arrangements are almost identical, but the distance between the two networks increases from 14.904 Å for L-**1**·**2**·(*R*)-**3a** to 15.456 Å for L-**1**·**2**·(*R*)-**3e** because the methyl group of (*R*)-**3e** is oriented perpendicular to the sheet structures. Thus, it may be concluded that because the hydrogen-bonding networks are almost identical, similar yields and inclusion ratios were obtained for **3a** and **3e** (entries 1 and 5 in Table 1). This high flexibility between the two sheet structures may explain the high adaptability for *para*-substituted 1-phenylethanols **3e–i**. Moreover, it appears that the enantioselectivities were gradually lowered because the *para*-substituted, longer guests **3e–g** increased the network distance, which reduced the molecular packing density, allowing the incorporation of the unfavored enantiomers.

The remarkably lower inclusion ratios and enantioselectivities for **3b** and **3j** can be attributed to the insufficient flexibility of the void around the stereogenic center of **3** along the direction parallel to the sheet structures.

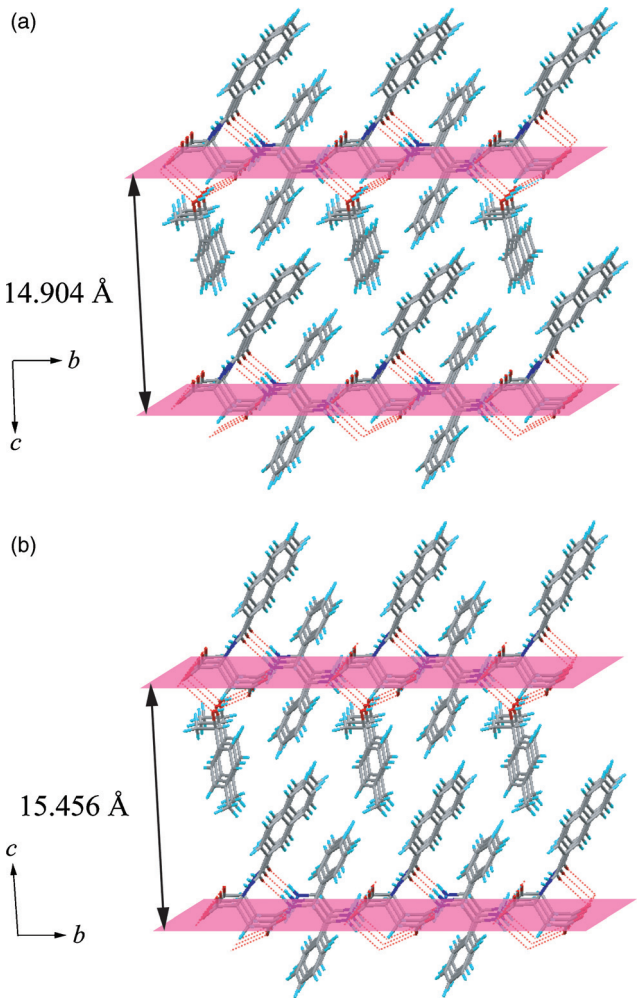


Fig. 4 Comparison of the crystal structures of (a) L-**1**·**2**·(*R*)-**3a** and (b) L-**1**·**2**·(*R*)-**3e**.

Conclusions

We have demonstrated that the combination of *N*-(2-naphthoyl)-L-aspartic acid (L-**1**) and *meso*-1,2-diphenylethylenediamine (**2**) can successfully serve as a supramolecular chiral host for enantioselective inclusion of (*R*)-1-arylethanols (**3**). The inclusion crystals could be prepared by all three different methods, but re-precipitation and suspension, in particular, afforded higher selectivity for (*R*)-**3e** (up to 96% ee). The suspension method was

successfully applied to a practical scale enantioseparation. X-Ray crystallographic analyses revealed that 2D sheet-like hydrogen-bonding networks formed in L-**1**·**2**, and **3** was incorporated in the asymmetric voids between two sheet structures. The chiral recognition mechanism can be explained by the matching between the (*R*)-isomer of **3** and the flexibility of the asymmetric voids.

These host components are easily accessible from commercially available compounds, allowing various host combinations to be prepared without elaborate synthesis. The development of other potential supramolecular host systems from chiral amino acids is currently under investigation.

Experimental

Materials and general methods

Diamine **2** was synthesized according to the literature.[9] All the 1-arylalkanols except for **3a** were prepared by reduction of the corresponding ketones. ^{1}H NMR spectra of the inclusion crystals in $CDCl_3/CD_3OD$ were recorded on a Bruker AVANCE 300 or AVANCE 500 spectrometer. IR spectra were measured on a JASCO FT/IR-460 spectrometer by the KBr method at room temperature. Melting points were measured on a MEL-TEMP apparatus and reported uncorrected. Optical rotation was measured by a JASCO DIP-370 polarimeter with a Hg lamp and interference filter at 435 nm. Mass spectra were obtained using a Bruker autoflex III matrix-assisted laser desorption ionization mass spectrometer. Enantiomeric excesses and absolute configurations of the alcohols were determined by HPLC analyses with a Daicel Chiralcel OB-H, OD-3, or OJ column with detection at 254 nm. Powder X-ray diffractions were obtained with a Rigaku RINT UltimaIII diffractometer using graphite-monochromated Cu-Kα radiation at room temperature. Single crystals for the X-ray diffraction analysis were prepared by slow evaporation of a solution of L-**1**·**2** in the presence of racemic **3**.

Synthesis

***N*-(2-Naphthoyl)-L-aspartic acid (L-1).** A solution of 2-naphthoyl chloride (9.9 g, 52 mmol, 1.5 equiv.) in Et_2O (45 ml) was added to a solution of L-aspartic acid (4.6 g, 35 mmol) in 4 N NaOH *aq.* (43 ml) at 0 °C. The resulting biphasic mixture was vigorously stirred at room temperature overnight. The Et_2O layer was then discarded and the basic aqueous layer was washed with Et_2O (2 × 30 ml). Then the aqueous phase was acidified at 0 °C with conc. HCl soln. to pH 1. The precipitated product was collected and dissolved in a minimum amount of methanol and water was carefully added until the solution became slightly cloudy. The mixture was heated to afford a clear solution and allowed to cool to obtain colorless needle crystals (3.5 g, 12 mmol, 35% yield). Mp: 172.7–173.3 °C. $[\alpha]_{435}^{23}$ −2.70 (*c* 1.0 in MeOH). ^{1}H NMR (300 MHz, CD_3OD) δ 8.40 (s, 1H), 7.99–7.87 (m, 4H), 7.62–7.53 (m, 2H), 5.01 (dd, J_1 = 7.0 Hz, J_2 = 5.6 Hz, 1H), 3.04 (dd, J_1 = 16.7 Hz, J_2 = 5.6 Hz, 1H), 2.95 (dd, J_1 = 16.7 Hz, J_2 = 7.0 Hz, 1H). ^{13}C NMR (125 MHz, CD_3OD) δ 175.1, 175.0, 170.9, 137.3, 134.9, 133.3, 130.9, 130.2, 129.9, 129.8, 129.7, 128.8, 125.8, 51.9, 37.7. IR (KBr) 3277, 3064 (br), 1738, 1704, 1634, 1537, 1409, 1250 cm^{-1}. MS (MALDI-TOF, matrix; dithranol): *m*/*z* calcd for $[M + H]^+$; 288.09 found 288.00, $[M + Na]^+$; 310.07 found 310.00. Elemental analysis: Found: C, 62.90; H, 4.55; N, 4.58. Calc. for $C_{15}H_{13}NO_5$: C, 62.72; H, 4.56; N, 4.88%.

1,2-Diphenyl-*N*-phenylmethylene-*N*′-benzoyl-1,2-diaminoethane.[9] A mixture of benzaldehyde (76.2 ml, 754 mmol) and ammonium acetate (165 g) was heated to 120 °C and stirred at this temperature for 3 h. After cooling to room temperature, the precipitate was collected, washed with water and hot ethanol to obtain a white solid (39 g, 97 mmol, 52% yield).

Mp: 262.5–263.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.85 (d, J = 9.6 Hz, 1H), 8.00 (s, 1H), 7.62–7.10 (m, 20H), 5.61 (t, J = 9.6 Hz, 1H), 4.79 (d, J = 9.6 Hz, 1H). IR (KBr): 3381, 1636, 1523 cm^{-1}.

***meso*-1,2-Diphenylethylenediamine (2).**[9] A mixture of 1,2-diphenyl-*N*-phenylmethylene-*N*′-benzoyl-1,2-diaminoethane (37.9 g, 93.5 mmol), 98 ml of conc. H_2SO_4, and 303 ml of water was refluxed for 24 h, then the solid materials were filtered off. The resultant acidic aqueous solution was basified with 6 N NaOH aq. The light yellow precipitate was filtered and recrystallized from hexane to obtain yellow needle-like crystals (10.7 g, 50.4 mmol, 54% yield). Mp: 122.3–123.2 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 7.42–7.27 (m, 10H), 4.01 (s, 2H). IR (KBr) 3346, 3274 (br), 1592, 1493, 1452, 915, 699 cm^{-1}.

General procedures for the preparation of inclusion crystals

The inclusion crystals were prepared according to the following three methods.

Method A (crystallization method): A H_2O–CH_3CN solution of L-**1** (66 μmol), **2** (66 μmol), and **3** (1.32 mmol) was left standing at ambient temperature until the solvent had evaporated to afford the inclusion compound. The crystals were washed with hexane and collected.

Method B (re-precipitation method): To a solution of **2** (66 μmol) and **3** (1.32 mmol) in hexane (5 mL), L-**1** (66 μmol) was added in solid form and the mixture was stirred at rt for one day. Usually L-**1** appeared to dissolve slowly and re-precipitate quickly as the inclusion compound. (It is expected that the partially-organized salt formed a suspension to recognize and include the guest molecules.)

Method C (suspension method): L-**1**·**2** salt was prepared by concentration of the methanol solution containing equimolar amounts of their mixture in advance. To the suspension of L-**1**·**2** salt (66 μmol) in hexane (5 mL), **3** (1.32 mmol) was added and stirred at rt for one day to obtain the inclusion compound. (It is expected that the host components are pre-organized before inclusion of guest molecules.)

Large scale preparation of the enantio-enriched 1-phenylethanol by re-precipitation method

According to Method B described above, L-**1** (1.35 g, 4.71 mmol) was added to a hexane solution of **2** (1.00 g, 4.71 mmol) and **3a** (11.5 g, 94.2 mmol), and the mixture was stirred at rt for a day. The precipitated white solid (2.21 g) was filtered and washed with hexane followed by characterization by

^{1}H NMR analysis (L-**1** : **2** : **3a** = 1.5 : 1 : 1). The solid obtained was heated at 100–140 °C under reduced pressure (10 mmHg) to give (*R*)-**3a** (0.312 g, 2.56 mmol, 95% ee) as a colorless oil.

The conditions of HPLC analyses for enantiomer separations of the alcohols

Absolute configuration of the alcohols was determined by comparison of the HPLC elution order with that of the literature data.[4d,6,10]

1-Phenylethanol (3a).[6] Determination of the ee by HPLC analysis: Chiralcel OD-3, *n*-hexane/2-propanol (95 : 5), 0.8 mL min^{-1}; t_r (*S*) = 13.7 min; t_r (*R*) = 11.3 min.

1-(2-Methylphenyl)ethanol (3b).[6] Determination of the ee by HPLC analysis: Chiralcel OB-H, *n*-hexane/2-propanol (95 : 5), 0.8 mL min^{-1}; t_r (*S*) = 17.4 min; t_r (*R*) = 22.7 min.

1-(3-Methylphenyl)ethanol (3c).[6] Determination of the ee by HPLC analysis: Chiralcel OB-H, *n*-hexane/2-propanol (98 : 2), 0.8 mL min^{-1}; t_r (*S*) = 17.9 min; t_r (*R*) = 28.3 min.

1-(3-Chlorophenyl)ethanol (3d).[10] Determination of the ee by HPLC analysis: Chiralcel OB-H, *n*-hexane/2-propanol (98 : 2), 0.8 mL min^{-1}; t_r (*S*) = 23.9 min; t_r (*R*) = 31.3 min.

1-(4-Methylphenyl)ethanol (3e).[6] Determination of the ee by HPLC analysis: Chiralcel OJ, *n*-hexane/2-propanol (98 : 2), 0.8 mL min^{-1}; t_r (*S*) = 25.7 min; t_r (*R*) = 29.2 min.

1-(4-Ethylphenyl)ethanol (3f).[4d] Determination of the ee by HPLC analysis: Chiralcel OD-3, *n*-hexane/2-propanol (99 : 1), 0.8 mL min^{-1}; t_r (*S*) = 30.9 min; t_r (*R*) = 27.4 min.

1-(4-Propylphenyl)ethanol (3g).[4d] Determination of the ee by HPLC analysis: Chiralcel OD-3, *n*-hexane/2-propanol (98 : 2), 1.0 mL min^{-1}; t_r (*S*) = 16.3 min; t_r (*R*) = 13.7 min.

1-(4-Fluorophenyl)ethanol (3h).[6] **3h** was derivatized to its acetyl ester to determine enantiomeric excess by HPLC analysis: Chiralcel OJ, *n*-hexane/2-propanol (98 : 2), 0.8 mL min^{-1}; t_r (*S*) = 17.4 min; t_r (*R*) = 14.5 min.

1-(4-Chlorophenyl)ethanol (3i).[6] Determination of the ee by HPLC analysis: Chiralcel OD-3, *n*-hexane/2-propanol (98 : 2), 0.8 mL min^{-1}; t_r (*S*) = 22.2 min; t_r (*R*) = 24.1 min.

1-(2-Naphthyl)ethanol (3k).[4d] Determination of the ee by HPLC analysis: Chiralcel OB-H, *n*-hexane/2-propanol (93 : 7), 0.5 mL min^{-1}; t_r (*S*) = 26.8 min; t_r (*R*) = 30.8 min.

Single crystal X-ray analyses of the inclusion crystals

X-Ray crystallographic data were collected on a Bruker Smart APEX II diffractometer with graphite monochromated Mo-Kα radiation. The structures were solved by a direct method using SIR 97[11] and refined by SHELXL-97 programs.[12] Crystal data for L-**1**·**2**·**3a**: $C_{37}H_{39}N_3O_6$, M = 621.71, triclinic, a = 5.7098(9), b = 9.5517(15), c = 14.904(2) Å, α = 87.425(2), β = 89.606(2), γ = 82.942(2)°, V = 805.9(2) Å^3, T = 100 K, space group *P*1, Z = 1, 3862 reflections measured, 3236 independent reflections (R_{int} = 0.1402). The final R_1 was 0.0587 ($I > 2\sigma(I)$) and wR (F_2) was 0.1544 ($I > 2\sigma(I)$). Crystal data for L-**1**·**2**·**3e**: $C_{38}H_{41}N_3O_6$, M = 635.74, triclinic, a = 5.660(2), b = 9.583(4), c = 15.456(6) Å, α = 94.113(5), β = 92.683(5), γ = 96.361(5)°, V = 829.8(5) Å^3, T = 100 K, space group *P*1, Z = 1, 3764 reflections measured, 3208 independent reflections (R_{int} = 0.1348). The final R_1 was 0.0863 ($I > 2\sigma(I)$) and wR (F_2) was 0.2314 ($I > 2\sigma(I)$).†

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