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Two-Component Supramolecular Helical Architectures: Creation of Tunable Dissymmetric Cavities for the Inclusion and Chiral Recognition of the Third Components

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Abstract: The inclusion and chiral recognition of racemic arylalkanols by supramolecular helical architectures consisting of enantiopure primary amines and achiral carboxylic acids were thoroughly studied. Among the architectures examined, a supramolecular helical architecture composed of the salt of enantiopure *erythro*-2-amino-1,2-diphenylethanol (**1b**) and benzoic acid (**2a**) was found to include a wide variety of racemic arylalkanols with recognition of their chirality. The helical architecture gave a dissymmetric 1D groove in the salt crystal, and the arylalkanols were enantioselectively included in the groove. The size and shape of the groove were tunable by proper selection of the achiral carboxylic acid component. The origin of the chiral recognition with the combination **1b**/**2a** is discussed on the basis of X-ray crystallographic analyses.

Keywords: chiral resolution · host–guest systems · molecular recognition · self-assembly · supramolecular chemistry

Introduction

Supramolecular chemistry, based on the ingenious application of nonbonding interactions, has spread widely and has been drawing much attention in many fields.[1] Molecular recognition in the crystalline state by so-called host–guest complexation through nonbonding interaction(s) is one of the most fundamental and fascinating phenomena in supramolecular chemistry. Highly porous frameworks with an absorption capability and/or catalytic activity have been constructed from only organic molecules (organic zeolites),[2] as well as from metal cations and organic ligands.[3] Upon introduction of chirality to organic molecules, organic zeolites afford dissymmetric cavities that can be applied to chiral recognition, enantioselective reactions, and so on.[4] Among these, the chiral recognition of racemic guest molecules has been intensively studied, and many organic host molecules are now known to form enantioselective inclusion complexes.[5] Although such continuous efforts have enabled us to control the cavities in crystals to some extent, it is still difficult to construct proper host molecules for inclusion, in spite of the much more intricate designs of host molecules that have recently been required. A solution for such a difficult situation is the application of hydrogen-bonding interactions to the construction of host systems, because hydrogen-bonding interactions have been recognized to be fascinating among the various intermolecular interactions involved in organic crystals, owing to their strength and directionality,[6] and have been used as the most reliable tool to construct supramolecular architectures.[7]

On the other hand, a helical structure is one of the most attractive motifs for efficient chiral recognition in various fields. For example, helical covalent polymers are known to be very useful as chiral stationary phases for HPLC columns.[8] In general, similar helical structures are also constructed in the crystals of enantiomeric and diastereomeric salts consisting of chiral primary amines with achiral/chiral carboxylic acids (and also the reverse combinations). In cases of proper primary amine/carboxylic acid combinations, which result in successful enantioseparation by preferential or diastereomeric crystallization, the components are closely packed to form a supramolecular helical columnar architecture with a twofold screw axis in the enantiomeric and diastereomeric salt crystals, as we have previously reported.[9] These results strongly suggest that dissymmetric cavities for a third component would be created in the column of a supramolecular architecture when the combination of a pri-

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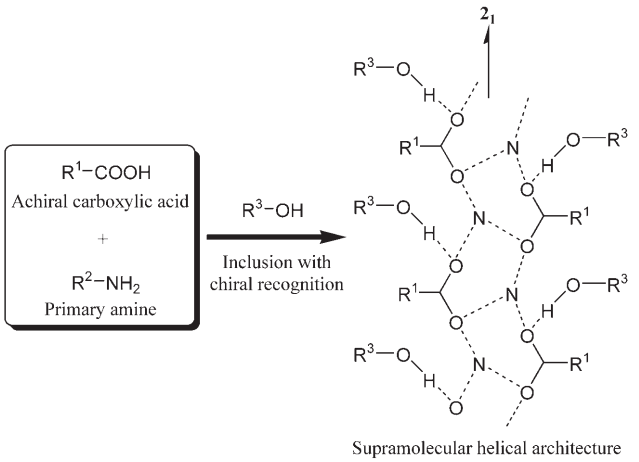
mary amine and a carboxylic acid is improper for enantioseparation and that such a supramolecular helical architecture would be easily modified because a wide variety of primary amines and carboxylic acids are available. In this case, the third chiral component molecules, having a hydrogen-donating functional group, would be incorporated into the cavities with chiral recognition upon interaction with the vacant hydrogen-accepting sites at the carboxylate oxygen atoms in the supramolecular helical column (Scheme 1).

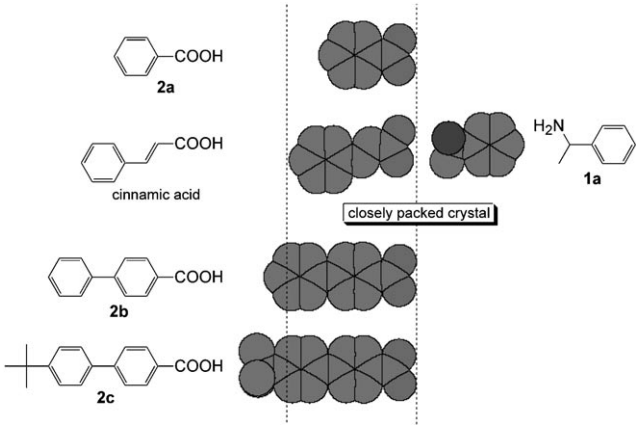


Scheme 1. Schematic hydrogen-bonding network consisting of an achiral carboxylic acid, a primary amine, and an alcohol. The dashed lines show the hydrogen bonds, which form a 2_1 column.

Studies on chiral recognition with such preorganized helical architectures in crystals are very rare despite their high potential,[10] although some highly functionalized three-component crystals have been reported.[3d,11] Recently, we have briefly reported chiral recognition with a helical architecture, composed of an enantiopure primary amine and an achiral carboxylic acid, through the cocrystallization of the two components and the third component (chiral guest) from a solution.[12] In this paper, we describe chiral recognition upon suspension of preorganized, chiral primary amine/achiral carboxylic acid supramolecular helical architectures in a solution of the third component, as well as the details of the chiral recognition by cocrystallization.

Results and Discussion

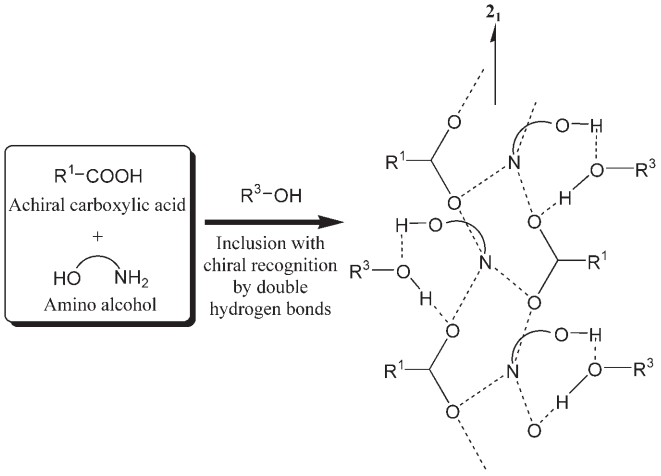
Inclusion and chiral recognition of racemic 1-phenylethanol by the combination of an enantiopure amine and an achiral carboxylic acid: To create a helical columnar architecture with unihelicity from the two components of a primary amine and a carboxylic acid, it is enough to use at least one enantiopure component.[9] Therefore, as the enantiopure component, we at first used enantiopure 1-phenylethylamine (**1a**), which is a simple aromatic primary amine and of which both enantiomers are commercially available. Since the salt of **1a** with cinnamic acid is known to give a closely packed crystal with no cavities, owing to the similarity in molecular length between **1a** and cinnamic acid,[13] benzoic acid (**2a**), 4-biphenylcarboxylic acid (**2b**), and 4-(*tert*-butylphenyl)benzoic acid (**2c**) were selected as the achiral acid components, with the expectation that the salts of **1a** with **2a–c**, for which the molecular lengths are either shorter or longer than that of cinnamic acid, would give cavities in the salt crystals (Scheme 2). Moreover, we chose 1-phenylethanol (**3a**) with a simple structure as the third chiral component (the target chiral compound), because the hydroxy and phenyl groups of **3a** would be able to interact with the vacant hydrogen-accepting site in the helical column consisting of **1a** and **2a–c** and with the phenyl groups of **1a** and **2a–c**, respectively, to stabilize the three-component crystals. As a result, crystallization of a mixture of (*R*)-**1a** and **2c** in the presence of an excess amount (20 equiv) of **3a** from water/acetonitrile gave needle-like crystals, in which **3a** was included in a ratio of 1:1:0.7–1 with an enantioselectivity of 7%, while crystallizations of (*R*)-**1a**, **2a** or **2b**, and **3a** afforded only guest-free salts.[14] The X-ray crystallographic analysis of the three-component crystal of (*R*)-**1a**·**2c**·**3a**[15] demonstrated that (*R*)-**3a** is included in a ratio of 1:1:1 and that a helical column with dissymmetric cavities is constructed from (*R*)-**1a** and **2c**. Moreover, (*R*)-**3a** molecules are located in the cavities and fixed by a hydrogen bond between the hydroxy hydrogen atom of (*R*)-**3a** and the carboxylate oxygen atom of **2c**. Thus, inclusion of the third component in an enantiopure primary amine/achiral carboxylic acid salt could be achieved, although the enantioselectivity was unsatisfactory.



Scheme 2. Relative molecular lengths of **2a–c** and cinnamic acid.

The three-component crystal (*R*)-**1a**·**2c**·(*R*)-**3a** was unstable and gradually became opaque upon standing for several hours as (*R*)-**3a** molecules were released. This instability could be explained in terms of **3a** molecules being loosely captured in the cavities by only one hydrogen bond and very weak van der Waals interactions, and it would result in a decrease of the (*R*)-**3a** ratio in the bulk crystals of (*R*)-**1a**·**2c**·(*R*)-**3a** and in a low chiral-recognition ability of (*R*)-

1a·**2c** for **3a**. On the basis of this result, we considered that the introduction of another functional group, which can interact with the hydroxy group of an alcohol, into the amine or carboxylic acid component would be efficacious in order to improve the stability of the three-component crystal. Among interactive functional groups, we selected a hydroxy group, because the hydrogen-donating ability of a hydroxy group is strong enough to form a hydrogen bond in a crystal but a hydroxy group does not retard the formation of a columnar network consisting of carboxylate anions and ammonium cations; the hydrogen-donating hydroxy group newly introduced and the vacant hydrogen-accepting site in the helical column would cooperatively fix an alcohol to stabilize a three-component crystal (Scheme 3). On the other

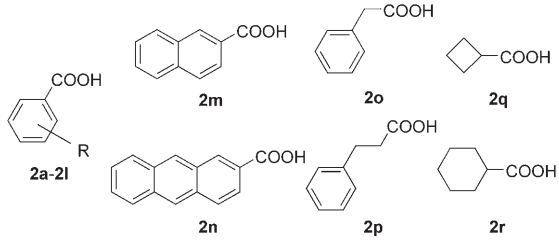


Scheme 3. Schematic hydrogen-bonding network consisting of an achiral carboxylic acid, a primary amino alcohol, and an alcohol. The dashed lines show the hydrogen bonds, which form the columns.

hand, water molecules have been found to be included in the salts of enantiopure *erythro*-2-amino-1,2-diphenylethanol (**1b**) and chiral 2-arylalkanoic acids, when the salts were crystallized from an aqueous alcohol solution. The crystal structures of the salts have revealed that water molecules are tightly captured by hydrogen bonds not only with the carboxylate oxygen atom of the carboxylic acid component but also with the hydroxy hydrogen atom of **1b**. In addition, the two phenyl groups of **1b** preferentially take a *gauche* conformation, thereby giving cavities for water molecules in the crystals.[16] These considerations and evidence prompted us to use enantiopure **1b** as the enantiopure primary amine component.

Three-component crystals were first prepared by mixing equimolar amounts of enantiopure **1b** and an achiral carboxylic acid (**2**) in the presence of an excess amount of racemic **3a**. The molar ratios in the three-component crystals and the enantioselectivity for **3a** are summarized in Table 1. As can be seen from Table 1, the salts of **1b** with unsubstituted and *p*-substituted benzoic acids **2a**–**e** were found to be favorable for the inclusion of **3a** with chiral recognition.

Table 1. Inclusion and chiral recognition of **3a** by combinations of (1*S*,2*R*)-**1b** and various achiral carboxylic acids **2**.



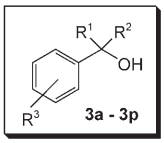
Compound	R	Inclusion ratio [%]	*ee* [%]
2a	H	100	87 (*R*)
2b	4-C_6H_5	100	63 (*R*)[a]
2c	4-(4-*t*Bu-C_6H_4)	100	61 (*R*)
2d	4-(4-HO-C_6H_4)	100	79 (*S*)[a]
2e	4-Me	100	15 (*R*)
2f	4-Cl	70	0
2g	4-Et	60	47 (*R*)
2h	4-*t*Bu	25	–[b]
2i	3-Me	10	–[b]
2j	3-Cl	70	49 (*R*)
2k	2-Me	25	–[b]
2l	2-Cl	10	–[b]
2m		40	–[b]
2n		80	61 (*R*)
2o		100	40 (*S*)
2p		60	0
2q		100	47 (*R*)
2r		100	84 (*R*)

[a] (1*R*,2*S*)-**1b** was used. [b] Not determined.

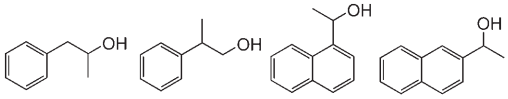
The results strongly support the validity of our strategy that certain carboxylic acid/primary amine combinations should form supramolecular helical architectures to give dissymmetric cavities in the salt crystal and that the third component molecules should be included in the cavities with recognition of their chirality. Among the salts examined, the salt of **1b** with **2a** was the most effective from the viewpoints of the inclusion and chiral-recognition abilities. Therefore, **2a** was mainly used as the achiral carboxylic acid component for further study.

Inclusion and chiral recognition of various racemic alcohols with the combination of (1*S*,2*R*)-2-amino-1,2-diphenylethanol and benzoic acid by the cocrystallization and suspension methods: By using (1*S*,2*R*)-2-amino-1,2-diphenylethanol ((1*S*,2*R*)-**1b**) and benzoic acid (**2a**) as the components of a supramolecular helical architecture, the enantioselective inclusion of 20 kinds of 1-phenylethanol derivative (**3a**–**t**) was investigated by 2 methods: 1) three-component crystals were allowed to deposit upon standing of an aqueous acetonitrile solution of enantiopure **1b**, **2a**, and **3a**–**t** in a molar ratio of 1:1:20 at room temperature (the cocrystallization method) and 2) the salt of enantiopure **1b** and **2a**, which was prepared in advance by concentration of a methanol solution of a 1:1 mixture of the 2 components, followed by drying in vacuo, was suspended in hexane containing 20 equivalents of **3a**–**t** (the suspension method). The results are listed in Table 2.

Table 2. Inclusion and chiral recognition of arylalkanols by combinations of (1*S*,2*R*)-**1b** and **2a**.



3a: R^1 = Me, R^2 = H, R^3 = H
3b: R^1 = Me, R^2 = H, R^3 = *o*-Me
3c: R^1 = Me, R^2 = H, R^3 = *m*-Me
3d: R^1 = Me, R^2 = H, R^3 = *p*-Me
3e: R^1 = Me, R^2 = H, R^3 = *p*-Et
3f: R^1 = Me, R^2 = H, R^3 = *p*-*n*Pr
3g: R^1 = Me, R^2 = H, R^3 = *o*-OMe
3h: R^1 = Me, R^2 = H, R^3 = *m*-OMe
3i: R^1 = Me, R^2 = H, R^3 = *p*-OMe
3j: R^1 = Me, R^2 = H, R^3 = *p*-F
3k: R^1 = Me, R^2 = H, R^3 = *p*-Cl
3l: R^1 = Me, R^2 = H, R^3 = 2,4-Me_2
3m: R^1 = Et, R^2 = H, R^3 = H
3n: R^1 = *n*Pr, R^2 = H, R^3 = H
3o: R^1 = *i*Pr, R^2 = H, R^3 = H
3p: R^1 = Me, R^2 = Et, R^3 = H



3q **3r** **3s** **3t**

Arylalkanol	Crystallization method		Suspension method	
	yield [%][a]	*ee* [%]	yield [%][a]	*ee* [%]
3a	91 (1.0)	87 (*R*)	89 (1.0)	84 (*R*)
3b	86 (1.0)	72 (*R*)	81 (1.0)	82 (*R*)
3c	91 (1.0)	80 (*R*)	88 (1.0)	87 (*R*)
3d	85 (1.0)	20 (*R*)	77 (1.0)	84 (*R*)
3e	85 (1.0)	80 (*R*)	86 (0.8)	78 (*R*)
3f	86 (1.0)	73 (*R*)	84 (0.9)	74 (*R*)
3g	85 (1.0)	82 (*S*)	86 (0.9)	77 (*S*)
3h	91 (1.0)	85 (*R*)	84 (0.9)	97 (*R*)
3i	97 (1.0)	67 (*S*)	72 (0.9)	70 (*S*)
3j	89 (1.0)	32 (*S*)	83 (1.0)	91 (*R*)
3k	95 (1.0)	70 (*S*)	82 (1.0)	65 (*S*)
3l	87 (1.0)	98 (*S*)	86 (1.0)	>99 (*S*)
3m	89 (1.0)	46 (*R*)	75 (0.9)	46 (*R*)
3n	98 (1.0)	60 (*R*)	88 (1.0)	72 (*R*)
3o	70 (1.0)	92 (*R*)	87 (0.8)	98 (*R*)
3p	67 (1.0)	39 (*S*)	not included	
3q	89 (1.0)	24 (*R*)	87 (1.0)	28 (*R*)
3r	93 (1.0)	32 (*R*)	88 (1.0)	28 (*R*)
3s	75 (1.0)	64 (*R*)	74 (0.9)	81 (*R*)
3t	65 (1.0)	36 (*R*)	70 (0.9)[b]	85 (*R*)

[a] The values in parentheses show the ratio of the included alcohol. [b] Benzene was used as the solvent.

In the case of the cocrystallization method, three-component crystals (1*S*,2*R*)-**1b**·**2a**·**3a–t** were commonly formed in which **3a–t** were included in a ratio of 1:1:1. Although the enantioselectivity for **3a–t** varied from 20–98%, moderate to excellent enantioselectivity (>70%) was achieved for 10 cases among the 20 examples. The helicity of the columns in a salt could be easily switched by the proper use of antipodes; for example, the combination (1*S*,2*R*)-**1b**/**2a** preferentially included (*R*)-**3a** with an enantioselectivity of 87%, while the combination (1*R*,2*S*)-**1b**/**2a** predominantly contained (*S*)-**3a** with an enantioselectivity of 86%.

The inclusion and chiral recognition of aliphatic alcohols, of which chiral recognition is more difficult due to the flexibility and fewer interaction sites of the alcohols, could be achieved by using a suitable achiral carboxylic acid component. When (1*S*,2*R*)-**1b** and **2a** were crystallized from a 2-butanol (**5a**) solution, the three-component crystal (1*S*,2*R*)-**1b**·**2a**·**5a** was formed, although the inclusion ratio of **5a** was only 1:1:0.2. In contrast, a similar experiment with the combination (1*R*,2*S*)-**1b**/**2b** afforded the three-component crystal (1*R*,2*S*)-**1b**·**2b**·**5a** in a ratio of 1:1:0.8; the inclusion ratio of **5a** was highly improved. The combination (1*R*,2*S*)-**1b**/**2b** also included 2-pentanol (**5b**) and 3-methyl-2-butanol (**5c**) in a ratio of 1:1:0.8. Although the enantioselectivities for **5a–c** were rather low, it is noteworthy that the enantioselectivity of the combination (1*R*,2*S*)-**1b**/**2b** was gradually improved with an increase in the bulkiness of the alkyl group at the α position of the alcohols (**5a**, 4% *ee*; **5b**, 27% *ee*; **5c**, 35% *ee*), probably owing to the increase of effective van der Waals interaction sites.

Upon stirring of the suspension of (1*S*,2*R*)-**1b**·**2a** in a hexane solution of **3a** for 12 h at room temperature (the suspension method), (*R*)-**3a** was included in a ratio of 1:1:1 with an enantioselectivity of 84%. The powder XRD patterns of the three-component crystals (1*S*,2*R*)-**1b**·**2a**·**3a** obtained by the suspension and cocrystallization methods were identical with each other. This means that the molecular arrangements of the acid and amine components in both crystals are the same and that the third component molecules (**3a**) are located in the dissymmetric cavities in the same manner.

This method required no special techniques and was easily applicable to a large-scale operation. The enantioselectivities by the suspension method were improved for almost all of the alcohols, compared with those obtained by the cocrystallization method; moderate to excellent enantioselectivities (>70%) were achieved for 15 cases among 20 kinds of alcohol, although the inclusion ratio of the alcohols decreased to 1:1:0.8–0.9 in some cases. In particular, the enantioselectivity for (*R*)-**3d** was highly improved from 20% by the cocrystallization method to 84% by the suspension method, and enantiopure **3l** was obtained by a single operation of the suspension method. The improvement of the chiral-recognition ability by the suspension method would arise from preorganization of the helical column consisting of (1*S*,2*R*)-**1b** and **2a**, which would exclude the retardation of crystal growth by another substance and/or the occurrence of complicated polymorphism, which is sometimes observed during crystallization. It is noteworthy that (*R*)-**3j** was predominantly included with a high enantioselectivity of 91% by the suspension method, while the antipode (*S*)-**3j** was obtained with an enantioselectivity of 32% by the cocrystallization method. This result implies that the salt with preorganized helical columns used for the suspension method acted as a nucleus for the formation of stable three-component crystals.

The inclusion ability of the combination of enantiopure **1b** and an achiral carboxylic acid was improved by adopting the proper carboxylic acid. For example, a suspension of the salt (1*S*,2*R*)-**1b**·**2a** in benzene containing 20 equivalents of 1-(4-biphenyl)ethanol (**3u**) afforded the guest-free salt. By contrast, (*R*)-**3u** was included in a ratio of 1:1:0.9 with an enantioselectivity of 58%, when the salt (1*R*,2*S*)-**1b**/**2b** was suspended in a benzene solution of **3u**. These results indicate that the salt (1*R*,2*S*)-**1b**·**2b** affords larger cavities than

the salt (1*S*,2*R*)-**1b**·**2a** and that **3u**, with an obviously long molecular length, can be efficiently accommodated in the cavities created from (1*R*,2*S*)-**1b** and **2b**, the molecular length of which is obviously longer than that of **2a**.

The included alcohols could be easily removed under reduced pressure to make the inclusion phenomenon reversible. For example, when the three-component crystal (1*S*,2*R*)-**1b**·**2a**·**3a** was heated at 80 °C under reduced pressure (approximately 0.3 mmHg), **3a** was removed from the complex to give the salt (1*S*,2*R*)-**1b**·**2a** as a white solid. The powder XRD pattern of (1*S*,2*R*)-**1b**·**2a** thus obtained showed only a weak and broad peak, which indicates that the helical column was partially destroyed by removal of the **3a** molecules. However, suspension of the resultant solid in a hexane solution of **3a** gave the three-component crystal (1*S*,2*R*)-**1b**·**2a**·**3a** again, with an enantioselectivity of 84%. Moreover, the XRD pattern of the obtained crystal was identical with that of the original three-component crystal, thereby strongly suggesting that the helical column was reconstructed. Thus, the reversible removal/inclusion of the third component molecules, which corresponds to the deconstruction/reconstruction of the helical column in the crystal, was possible by the suspension method.

The enantiopurity of the included alcohols could be improved by recrystallization. Recrystallization of the three-component crystal (1*S*,2*R*)-**1b**·**2a**·**3a** (64% *ee*) afforded the three-component crystals including (*R*)-**3a** with an enantioselectivity of 98%. As exemplified, the third components could be obtained in almost enantiopure forms.

The present results indicate that the combination of enantiopure **1b** and achiral **2a** has inclusion and chiral-recognition abilities upon cocrystallization with arylalkanols from solutions and upon suspension in solutions of arylalkanols. Moreover, the inclusion and chiral-recognition abilities were found to be fundamentally tunable upon selection of a proper achiral carboxylic acid component.

The supramolecular helical architecture of the salt (1*S*,2*R*)-**1b**·**2a** may be partially preserved to act as a preorganized template for the nucleation of the stable three-component crystals (1*S*,2*R*)-**1b**·**2a**·**3** by the suspension method, although the three-component crystals might be formed through a dissolution/crystallization process.

Structure of the three-component crystals (1*S*,2*R*)-1b·2a·3: From solutions of (1*S*,2*R*)-**1b**, **2a**, and racemic alcohols **3a**–**t**, we succeeded in obtaining single crystals of the three-component complexes for X-ray crystallographic analyses ((1*S*,2*R*)-**1b**·**2a** with **3a**, **3b**, **3e**–**g**, **3j**, **3l**, **3p**, and **3q**). They were all needlelike, colorless crystals and were stable at least for a few days. The hydrogen-bonding network of the three-component crystal (1*S*,2*R*)-**1b**·**2a**·**3a** is depicted in Figure 1 as a representative example. The molecular arrangements of (1*S*,2*R*)-**1b** and **2a** in (1*S*,2*R*)-**1b**·**2a**·**3** are found to be quite similar to each other, and a hydrogen-bonded helical column (a 2_1 column) is commonly constructed, although the refinements of the analyses are incomplete for some cases at present because of the disordered **3** molecules or the poor quality of the crystals. In each three-component crystal, a fan-shaped 1D groove is created in the hel-

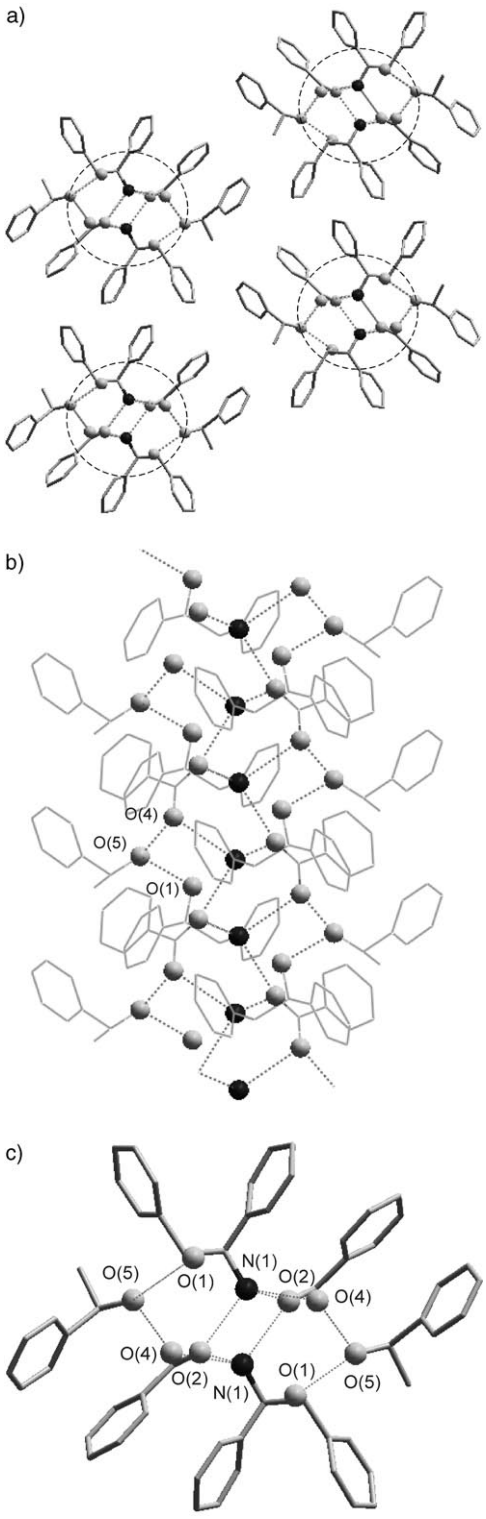


Figure 1. Crystal structure of (1*S*,2*R*)-**1b**·**2a**·(*R*)-**3a**. a) Packing of the hydrogen-bonded columns viewed down the columnar axis. b) Hydrogen-bonded columnar network. c) One columnar network viewed down the columnar axis. The dotted lines and circles show hydrogen bonds and columnar networks, respectively.

ical column, because the two phenyl groups of (1*S*,2*R*)-**1b** take a *gauche* conformation. (The torsion angles of the two benzene rings of (1*S*,2*R*)-**1b** are 54–62°.) The pivot of the fan-shaped motif is hydrogen bonded, and a pair of the motifs construct one unit of the helical column.[15] The inside of the groove is hydrophilic, while the outside is hydrophobic. The hydroxy group of an alcohol locates inside of the groove, whereas the aromatic group of the alcohol directs toward outside. Thus, the 1D groove is occupied by the alcohol molecules to form a closely packed crystal (Figure 2). These facts suggest that the inclusions of **3** with

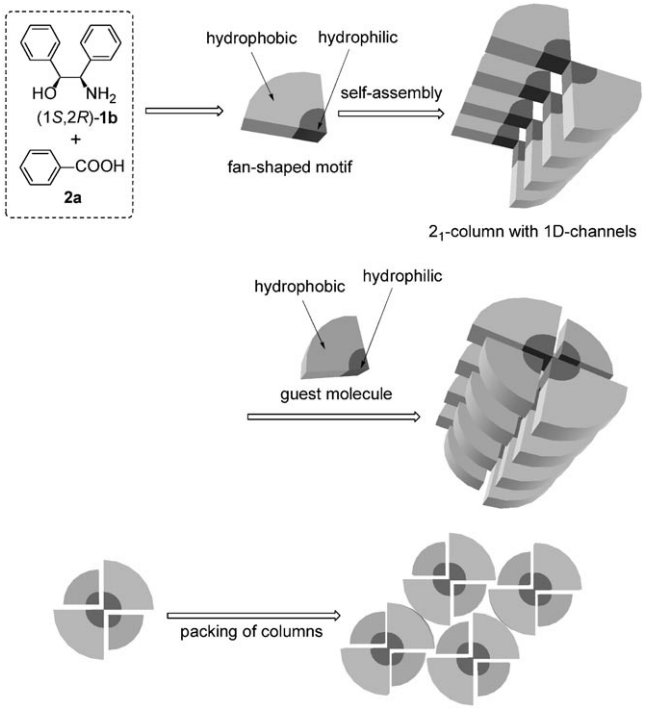


Figure 2. Schematic representations for the formation of a fan-shaped 1D groove by the self-assembly of (1*S*,2*R*)-**1b** and **2a** and the molecular arrangement of guest molecules in the groove viewed down the columnar axis.

chiral recognition occur through almost the same process. It is noteworthy that, except with **3p**, there are commonly two kinds of hydrogen bonds, between the carboxylate oxygen atom of **2a** and the hydroxy hydrogen atom of **3** and between the hydroxy hydrogen atom of (1*S*,2*R*)-**1b** and the hydroxy oxygen atom of **3** (Figure 1c), as we expected. The present stable inclusion phenomenon would be mostly attributable to these two hydrogen bonds.

In the case of **3p**, a water molecule occupies the vacant site in the helical 2_1 column with linkage through two cooperative hydrogen bonds, and **3p** interacts with the water molecule upon formation of another hydrogen bond to prevent steric repulsion between the substituent adjacent to the hydroxy group of **3p** and the helical column consisting of (1*S*,2*R*)-**1b** and **2a** (Figure 3). The fact that **3p** was not included at all by the suspension method would be explained

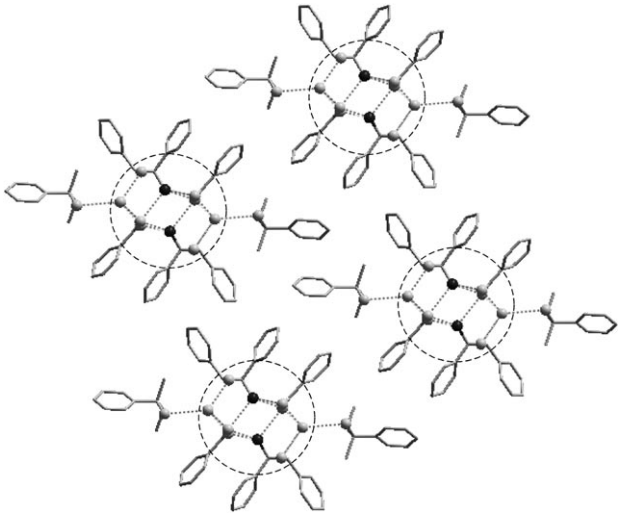


Figure 3. Crystal structure of (1*S*,2*R*)-**1b**·**2a**·(*S*)-**3p**·H_2O viewed down the columnar axis. The dotted lines and circles show hydrogen bonds and columnar networks, respectively.

in terms of the absence of water molecules in the suspension.

Origin of chiral recognition by the combination of (1*S*,2*R*)-1b/2a: Although the combination of (1*S*,2*R*)-**1b** and **2a** included (*R*)-**3q** in excess, the enantioselectivity was very low (24%) by the cocrystallization method. The structure of a single crystal prepared from (1*S*,2*R*)-**1b**, **2a**, and racemic **3q** shows that both enantiomers of **3q** occupy the hydrogen-accepting sites in the helical column with a location disorder; the space around the columnar network is too large to differentiate the methyl and benzyl groups adjacent to the hydroxy group of **3q** (Figure 4) and this results in the unselective inclusion of **3q** in the crystal.

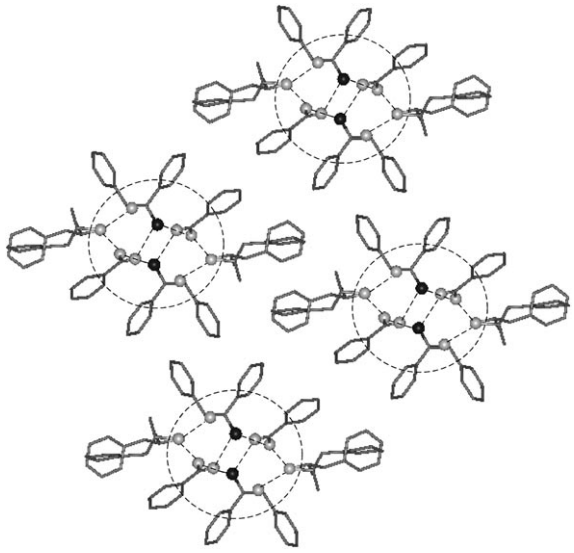


Figure 4. Crystal structure of (1*S*,2*R*)-**1b**·**2a**·**3q** viewed down the columnar axis. The dotted lines and circles show hydrogen bonds and columnar networks, respectively.

The combination of (1*S*,2*R*)-**1b** and **2a** superiorly included (*S*)-**3j** by the cocrystallization method, whereas (*R*)-**3j** was preferentially incorporated into the salt (1*S*,2*R*)-**1b**·**2a** by the suspension method. In order to explain this dramatic switch in selectivity, the crystal structures of (1*S*,2*R*)-**1b**·**2a**·(*R*)-**3j** and (1*S*,2*R*)-**1b**·**2a**·(*S*)-**3j** were solved (Figure 5). In both crystals, a helical column is constructed

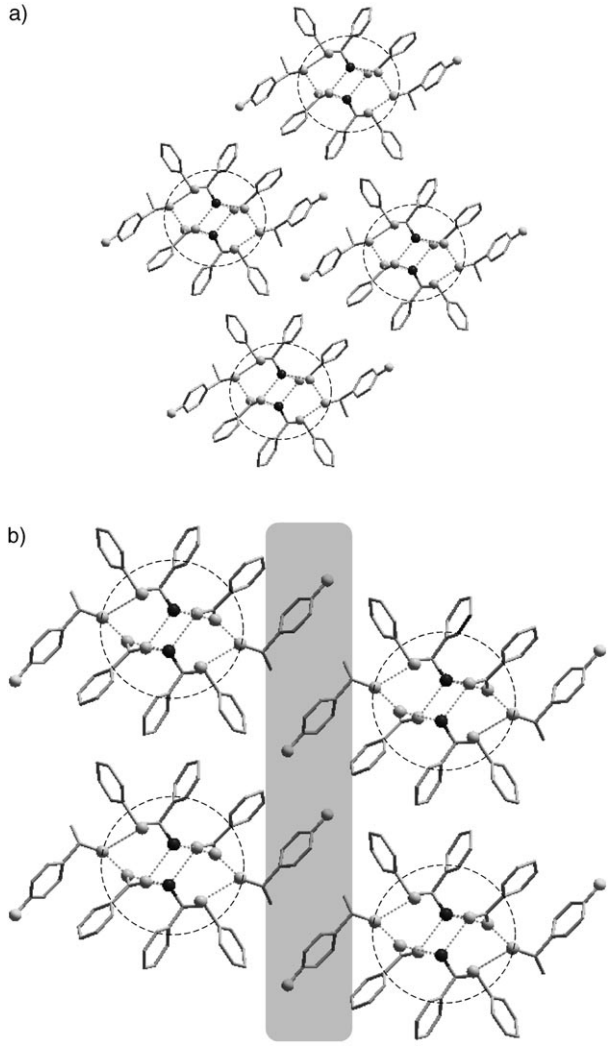


Figure 5. Crystal structures of a) (1*S*,2*R*)-**1b**·**2a**·(*R*)-**3j** and b) (1*S*,2*R*)-**1b**·**2a**·(*S*)-**3j** viewed from the columnar axis. The dotted lines and circles show hydrogen bonds and columnar networks, respectively.

from (1*S*,2*R*)-**1b** and **2a** to include **3j** in a similar manner. However, the hydrogen-bonding distances of O(**3j**)···O(**1b**) and O(**3j**)···O(**2a**) in the crystal of (1*S*,2*R*)-**1b**·**2a**·(*R*)-**3j** (2.731 and 2.674 Å) are a little shorter than those in the crystal of (1*S*,2*R*)-**1b**·**2a**·(*S*)-**3j** (2.801 and 2.702 Å), and the density of the crystalline (1*S*,2*R*)-**1b**·**2a**·(*R*)-**3j** (1.284) is slightly larger than that of the crystalline (1*S*,2*R*)-**1b**·**2a**·(*S*)-**3j** (1.238). The facts indicate that the crystal of (1*S*,2*R*)-**1b**·**2a**·(*R*)-**3j** is more stable than the crystal of (1*S*,2*R*)-**1b**·**2a**·(*S*)-**3j** from the viewpoint of the close packing of the components in the helical column. Moreover, there is no nonbonding interaction other than the van der Waals interaction between the helical columns in both crystals, although the packing mode of the columns in the crystal (1*S*,2*R*)-**1b**·**2a**·(*S*)-**3j** is different from that of (1*S*,2*R*)-**1b**·**2a**·(*R*)-**3j** and is also exceptionally different from those of the other three-component crystals, in that a layer of the phenyl groups in the third-component molecules is formed. These observations indicate that the molecular arrangement of the components in the salt (1*S*,2*R*)-**1b**·**2a** is favorable for the formation of the stable three-component crystal of (1*S*,2*R*)-**1b**·**2a**·(*R*)-**3j** and that the crystal (1*S*,2*R*)-**1b**·**2a**·(*S*)-**3j** was obtained as a metastable form due to polymorphism upon crystallization.

Single crystals of (1*S*,2*R*)-**1b**·**2a**·(*R*)-**3a** and (1*S*,2*R*)-**1b**·**2a**·(*S*)-**3a**·0.5 H_2O were prepared from mixtures of (1*S*,2*R*)-**1b**/**2a** with racemic **3a** and of (1*S*,2*R*)-**1b**/**2a** with enantiopure (*S*)-**3a**, respectively,[15] in order to explain the phenomenon that (*R*)-**3a** was preferentially included in the combination (1*S*,2*R*)-**1b**/**2a** by the cocrystallization and suspension methods. Although a helical column is formed and **3a** is included in a ratio of 1:1:1 in both crystals, the crystal (1*S*,2*R*)-**1b**·**2a**·(*S*)-**3a**·0.5 H_2O is composed of two kinds of columns. One column includes only (*S*)-**3a** molecules as guest molecules, while the other column includes (*S*)-**3a** molecules and water molecules in a ratio of 1:1:1:1. In other words, the latter column is constructed from four components and should be less stable from an entropic point of view. Moreover, the heteroaggregation of two kinds of columns in (1*S*,2*R*)-**1b**·**2a**·(*S*)-**3a**·0.5 H_2O would be unfavorable. These disadvantages for the inclusion of (*S*)-**3a** would result in the observed high enantioselectivity for (*R*)-**3a** by the cocrystallization and suspension methods.

Conclusion

In the present study, supramolecular architectures consisting of enantiopure primary amines and achiral carboxylic acids were found to be useful as host systems showing efficient inclusion and chiral-recognition abilities for racemic alcohols. In particular, the combination of enantiopure *erythro*-2-amino-1,2-diphenylethanol (**1b**) and benzoic acid (**2a**) was found to be effective for the inclusion of a variety of 1-arylalkanols (**3**) with chiral recognition. Two methods were applicable for the inclusion: 1) the cocrystallization of the salt from a solution of an alcohol, and 2) the suspension of the salt in a solution of an alcohol. The suspension method afforded better enantioselectivity than the cocrystallization method for most of the alcohols included. The size and shape of the preorganized cavities in a salt were tunable by proper selection of the achiral carboxylic acid component. The X-ray crystallographic analyses revealed that (1*S*,2*R*)-**1b** and **2a** commonly constructed a helical columnar hydrogen-bonded network (2_1 column) in the inclusion crystals and that the hydroxy group of **3**, included in the column, generally interacts with the carboxylate oxygen atom of **2a**

and the hydroxy hydrogen atom of **1b**. These double interactions resulted in the stable inclusion of molecules of **3** in the cavities. The present results indicate that various host systems with supramolecular architectures can be constructed from combinations of enantiopure/achiral primary amines and achiral/enantiopure carboxylic acids and that such multicomponent host systems could be applied to molecular recognition, asymmetric reactions, and so on.

Experimental Section

General methods: All of the alcohols except for **3a**, **3p**, and **3q** were synthesized by reduction of the corresponding carbonyl compounds and were identified by ^{1}H NMR spectroscopy. The alcohol **3p** was prepared by the Grignard reaction of acetophenone and ethylmagnesium bromide. Commercially available alcohols **3a** and **3q** were used without further purification. ^{1}H NMR spectra of the inclusion crystals in $CDCl_3/CD_3OD$ were measured with a 300 MHz NMR instrument. IR spectra were measured by the KBr method at room temperature. Powder X-ray diffraction patterns were measured by using graphite-monochromated $Cu_{K\alpha}$ radiation with a scanning rate of 0.02° min^{-1} at room temperature. Single crystals for X-ray analyses were prepared by slow evaporation of saturated solutions of the salts and alcohols in aqueous acetonitrile or aqueous alcohol.

Preparation of inclusion crystals: Each salt of an achiral carboxylic acid/enantiopure primary amine combination was prepared by concentration of a methanol solution containing equimolar amounts of a carboxylic acid and an amine, followed by drying in vacuo.

1) The cocrystallization method: The salt and a racemic alcohol (20 equiv for **3a**–**t** and a large excess for **5a**–**c**) were dissolved in water/acetonitrile (1:4 v/v) with heating, and the solution was stood at room temperature until the solvent had evaporated. The deposited crystals were collected by filtration and washed with hexane.

2) The suspension method: The salt was added to a hexane solution of a racemic alcohol (20 equiv), and the mixture was stirred at room temperature for 12 h. The resultant solid mass was collected by filtration and washed with hexane. In the cases of **3t** and **3u**, benzene was used as the solvent because of the low solubility of these compounds in hexane.

The inclusion ratios of the alcohols in the three-component crystals were estimated by ^{1}H NMR spectroscopy. The included alcohols were isolated by preparative TLC (hexane/ethyl acetate 3:2 v/v). The enantiomeric excesses of the isolated alcohols were determined, directly (**3a**–**u**) or after derivatization to form the corresponding 3,5-dinitrobenzoate derivatives (**5a**–**c**), by HPLC with a Daicel Chiralcel OB-H, OD-H, or OJ column and detection at 254 nm. The detailed conditions for the HPLC analyses are described in the Supporting Information.

Crystallographic analyses: The X-ray intensities were collected by using $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$). The crystal structures were solved by the direct method with the SIR92[17] program and refined by the full-matrix least-squares procedure for all non-hydrogen atoms anisotropically. All hydrogen atoms were generated geometrically. Assignment of the absolute configurations of the included alcohols was made through agreement with the known configurations of the participating primary amine components. CCDC-619693–619705 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[14] The alcohol **3a** was not included in (*R*)-**1a**·**2a**, probably due to the lack of sufficient difference in molecular length between **1a** and **2a**, which results in the formation of only very small cavities in the column. In the case of (*R*)-**1a**·**2b**, the crystal structure of the guest-free salt (*R*)-**1a**·**2a**[15] clearly showed that cavities are created in a helical column consisting of (*R*)-**1a** and **2a**, as we expected, but the cavities are occupied by the phenyl groups of **2b** molecules in the neighboring columns, through interpenetration to form a closely packed crystal without any other molecule. The *tert*-butyl group of **2c** obstructed the interpenetration.[15]

[15] See the Supporting Information.

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