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Solvent-Induced Reversed Stereoselectivity in Reciprocal Resolutions of Mandelic Acid and *erythro*-2-Amino-1,2-diphenylethanol

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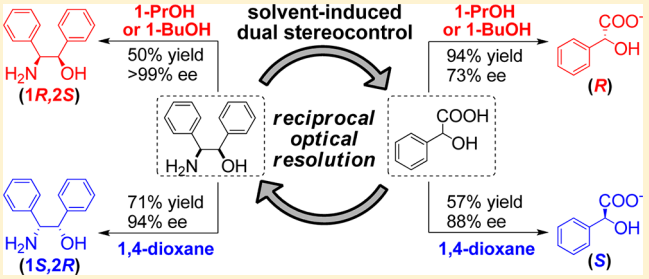
Supporting Information

ABSTRACT: Solvent-induced chirality switching in reciprocal optical resolution between mandelic acid (**1**) and *erythro*-2-amino-1,2-diphenylethanol (**2**) has been demonstrated. The stereochemistry of the deposited salts was controlled by changing the crystallization solvent from 1-PrOH or 1-BuOH to 1,4-dioxane. It was revealed from ^{1}H NMR spectra, thermogravimetric analysis, and X-ray crystallography of the salts that an equimolar amount of the crystallization solvent was incorporated in each diastereomeric salt. On the basis of the crystal structures, it was found that both the hydrogen-bonding ability and the size of the solvent molecule played an important role. Differences in the formed hydrogen-bonding networks (columnar or sheetlike structure) and their packing manner were found to be crucial for the reversed stereoselectivity. Furthermore, pseudopolymorphic salt crystals that incorporated 1,4-dioxane were obtained during the enantioseparation of racemic **2**, and their solid-state properties were examined by measurement of their IR spectra. This solvent-induced dual stereocontrol technique was successfully applied to the successive resolution process, eliminating the need to change the resolving agent for access to both enantiomers of **1** and **2**.



INTRODUCTION

Enantiopure compounds are extremely valuable in both academic and industrial fields as they are key intermediates in the synthesis of functional compounds and materials. In the pharmaceutical industry in particular, the demand for single enantiomers has been steadily increasing over the last two decades.[1] One commonly used method for obtaining enantiopure acids and amines is optical resolution via diastereomeric salt formation with a chiral resolving agent.[2] Although it is many years since this technique was first described, it remains the dominant approach in manufacturing pharmaceutical products that contain chiral centers. This methodology has the advantage of operational simplicity with standard equipment and facilities. Recently, a modified version, termed Dutch resolution, was reported to give improved results, working by the application of a mixture of a small number of structurally related compounds as resolving agents.[3]

However, a major issue associated with diastereomeric resolution is achieving the optimal conditions, with selection of a suitable resolving agent being the most significant factor. A screening process is generally required in order to identify potential resolving agents that crystallize to form a salt with a target racemate in a specific solvent. Further optimization to achieve preferential crystallization of one diastereomeric salt (the less-soluble salt) is then necessary, with conditions such as solvent, crystallization temperature, and amount of resolving agent needing to be screened. The purity of this salt can be improved by repeated recrystallization, with its subsequent decomposition affording the pure enantiomer. When the other enantiomer of a target racemate is sought, it is common to recover the residual mother liquor and use the antipode of the initial resolving agent to produce the other less-soluble diastereomeric salt. These are labor-intensive and time-consuming processes, making them economically unfavorable.

The solvent has been recognized as being one of the crucial factors involved in the process of optical resolution. The particular solvent used affects the incidence and efficiency of the crystallization, and even the stereochemistry, of the less-soluble diastereomeric salt. A number of reports have been published that demonstrate the important role that solvents play in the isolation of both enantiomers.[4] The key role of the resolving solvent is mostly regarded to be its ability to solubilize the two diastereomeric salts to differing degrees. On the other hand, the more qualitative feature of its ability to reverse the chirality, has been generally overlooked to date.[2,5]

In 2004, Sakai et al. recognized the significance of such a solvent effect and proposed a strategic method called dielectrically controlled resolution (DCR). By employing this technique, both enantiomers of a target molecule could be obtained using a single enantiomer of the resolving agent under controlling the permittivity of the solvent.[6a,b] This method-

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Table 1. Diastereomeric Resolution of (±)-1 with Enantiopure (−)-2

				1			
entry	solvent	ε	yield[a] (%)	$[\alpha]_D$[b] (deg)	OP[c] (%ee)	resolution efficiency[d]	less-soluble salt
1	EtOH	24	12	95.2	62	7	(+)-**1**·(−)-**2**
2	1-PrOH	22	54	−139.6	90	48	(−)-**1**·(−)-**2**
3	1-BuOH	17	94	−112.0	73	68	(−)-**1**·(−)-**2**
4	1,4-dioxane	2	57	135.8	88	50	(+)-**1**·(−)-**2**

[a]Yield of the less-soluble diastereomeric salt. See the Experimental Section. [b]Specific rotation values of resolved **1**. Solvent: H_2O, *c* 0.8, 20 °C. [c]Optical purity calculated from the specific rotation value based on the literature.[13] $[\alpha]_D$ ± 153.5° (*c* 1, H_2O). [d]Resolution efficiency = yield (%) × OP (%ee)/100.

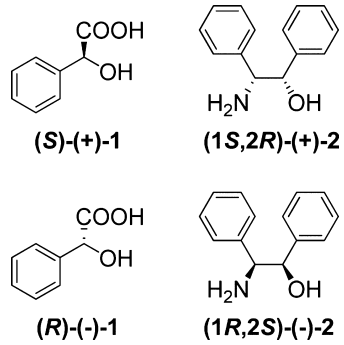
ology saves a great deal of time and effort as it removes the need to change the resolving agent to obtain the second target molecule, and it is especially attractive in the cases where only one enantiomer is available as a resolving agent because owing to their derivation from natural chiral sources.[6] A key factor of the DCR method lies in control of the hydration of one of the diastereomeric salt pair, aided by hydrogen-bond formation.

This methodology was particularly interesting for its uniqueness, in addition to its expected merit in industrial applications, and prompted us to further investigate novel systems. In our previous studies, as well as a hydrogen-bond forming effect,[7a] a space-filling effect[7b,c] of organic solvent molecules was demonstrated. In the resolution of α-methylbenzylamine (MBA) with *N*-(*p*-toluenesulfonyl)-(*S*)-phenylalanine (TPA), (*S*)-MBA·(*S*)-TPA crystallized as the less-soluble salt from aqueous alcohol. On the other hand, the (*R*)-MBA·(*S*)-TPA salt was obtained from a mixture of 2-PrOH/1,4-dioxane or 2-PrOH/cyclohexane.[7b,c] The latter salt contained an equimolar amount of the 1,4-dioxane or cyclohexane molecules, with no hydrogen bonds contributing to the structure; that is, the solvent molecules worked only as a space filler. To the best of our knowledge, such a phenomenon has not been reported to date. However, the efficiency of resolving each enantiomer was not satisfactory using this method. It is noteworthy that these chirality switching systems are based on the structural change of only *one* diastereomeric salt induced by solvent incorporation. This is disadvantageous from the viewpoint of obtaining both enantiomers in high-resolution efficiency.

In this work, we present a diastereomeric resolution system involving mandelic acid (**1**) and *erythro*-2-amino-1,2-diphenylethanol (**2**), which shows chirality switching induced by solvent incorporation into *both* diastereomeric salts, as well as *reciprocal* resolution. The structural features of the solvent molecules and the crystal packing are discussed on the basis of comparison of the crystallographic data of the diastereomeric salts. The potential of this stereocontrol technique is also demonstrated by the successive resolution of **1** and **2**.

RESULTS AND DISCUSSION

Optical Resolution of Mandelic Acid (1) with Enantiopure *erythro*-2-Amino-1,2-diphenylethanol (2) via Diastereomeric Salt Formation. Enantiopure **2** has been applied as a chiral auxiliary,[8] an organic fluorescent material,[9] and in supramolecular gel formation.[10] Furthermore, **2** has been previously reported to be a suitable resolving agent for various 2-arylalkanoic acids.[11] However, resolution of α-hydroxycarboxylic acids has not been frequently reported.[12] In the present study, an equimolar amount of (−)-**2** and (±)-**1** were mixed to form the diastereomeric salts. In order to study the effects of the solvent, three alcohols, EtOH, 1-PrOH, and 1-BuOH, as well as 1,4-dioxane, were examined as the fractional crystallization solvent of (±)-**1**·(−)-**2**. The deposited salt was filtered and decomposed by addition of an aqueous NaOH solution. After (−)-**2** was recovered by extraction, the aqueous solution was acidified, and optically active **1** was extracted. The optical purity of resolved **1** was determined by comparison of its specific rotation value with literature data.[13] The results of the optical resolution are summarized in Table 1, along with the permittivity of each solvent.



It was observed that the resolving solvent significantly affected the resolution. In the cases of EtOH and 1,4-dioxane, (+)-**1**·(−)-**2** was obtained as the less-soluble salt (Table 1, entries 1 and 4), whereas for 1-PrOH and 1-BuOH, (−)-**1**·(−)-**2** was obtained preferentially (entries 2 and 3). The present system is therefore a novel example in which both enantiomers can be obtained using a single enantiomer of a resolving agent by solvent switching. While the result using EtOH was not satisfactory, (+)-**1** was obtained in high yield and purity by crystallization from 1,4-dioxane. On the other hand, remarkably high optical purity of (−)-**1** (90% ee) was achieved from 1-PrOH, while its resolution efficiency was higher for 1-BuOH. From these results, the permittivity of the solvents cannot be regarded as a determining parameter for reversed stereoselectivity, although resolution using a combination of different solvents to control the permittivity was not examined.[14]

The composition of the precipitated salts was estimated from the measured ^{1}H NMR spectra, and it was suggested that the salts contained solvent molecules (molar ratio of solvent to **1**·(−)-**2** was 0.8−1.0), and crystallized as a **1**·(−)-**2**·solvent salt, with the exception of that obtained from EtOH. Such an inclusion of solvents could change the solubility of the diastereomeric salt crystals, resulting in the switching of chirality. It is known that EtOH can be also incorporated into the salts; however, in the present case, only a small amount of EtOH was detected in the ^{1}H NMR analysis, probably due to its desorption, even at ambient temperature.[15]

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Table 2. Diastereomeric Resolution of (±)-2 with Enantiopure (−)-1

				2			
entry	solvent	ε	yield[a] (%)	$[\alpha]_D$[b] (deg)	OP[c] (%ee)	resolution efficiency[d]	less-soluble salt
1	1-PrOH	22	50	−8.5	>99	50	(−)-**1**·(−)-**2**
2	1-BuOH	17	93	−6.1	44	40	(−)-**1**·(−)-**2**
3	1,4-dioxane	2	71[e]	7.8	94	66	(−)-**1**·(+)-**2**

[a]Yields of the less-soluble diastereomeric salt. See the Experimental Section. [b]Specific rotation values of resolved **2**. Solvent: EtOH, *c* 0.6, 20 °C. [c]Optical purity determined by chiral HPLC analysis of the 2-oxazolidinone derivative. (Chiralcel OJ-3 column, 4.6 mm × 250 mm; 2-PrOH/hexane = 3:7 v/v). [d]Resolution efficiency = yield (%) × OP (%ee)/100. [e]Calculated based on half the amount of (±)-**2**.

The thermal stability of the incorporation of solvent molecules in the diastereomeric salts was examined using thermogravimetric analysis (TGA). Heating of the three salts of **1**·(−)-**2** obtained by recrystallization from 1-PrOH, 1-BuOH, and 1,4-dioxane showed a gradual weight loss at 80−120 °C, which mostly corresponded to the amounts of included solvents estimated from ^{1}H NMR measurements (Supporting Information, Figure S1). These results indicate that the interactions responsible for the incorporation of the solvent molecules were comparable for all of the solvents, even though they gave rise to reversed enantioselectivity.

Optical Resolution of *erythro*-2-Amino-1,2-diphenylethanol (2) with Enantiopure Mandelic acid (1) via Diastereomeric Salt Formation. Considering the impact of solvent on enantioselectivity in the resolution of (±)-**1** with (−)-**2**, its *reciprocal* resolution was next examined, with (−)-**1** used as the resolving agent and (±)-**2** used as the target racemic substrate. It is known that reciprocal resolution is not always successful because it is not enantiomeric with the original resolution system.[2] The diastereomeric resolution of racemic **2** with enantiopure **1** in EtOH has been previously shown to be unsuccessful, with both salts being deposited.[15] On consideration of the results shown in Table 1, 1-PrOH, 1-BuOH, and 1,4-dioxane were examined as fractional crystallization solvents (Table 2). As the specific rotation value of enantiopure **2** was very small, the optical purity of resolved **2** was determined by chiral high-performance liquid chromatography (HPLC) analysis of its 2-oxazolidinone derivative.[16] The solvent dependency of the enantioselectivity was found to correspond well with the original resolution shown in Table 1; (−)-**2** was efficiently obtained from 1-PrOH and 1-BuOH (entries 1 and 2), and (+)-**2** was obtained from 1,4-dioxane, with higher efficiency (entry 3). It was observed in the ^{1}H NMR spectra that the deposited salts from 1-PrOH and 1-BuOH were a 1:1 mixture of (−)-**1**·**2** and the solvent, which was the same as was observed in the original resolution. However, the composition of the salt obtained from 1,4-dioxane was estimated to be (−)-**1**/**2**/solvent = 2:1:1.8 from the ^{1}H NMR analysis. This result indicates that the crystallized salt was different from that obtained in the original resolution, in spite of the same solvent being used for the crystallization. Although the molar ratio was different, high efficiency for (+)-**2** was still achieved by crystallization from 1,4-dioxane, and facile solvent-induced stereocontrol was possible.

Comparison of the Crystal Structures of the Diastereomeric Salts (−)-1·(−)-2 and (+)-1·(−)-2. In order to elucidate the mechanism of the reversed enantioselectivity in the reciprocal resolutions of **1** and **2** that were dependent on the crystallization solvents, we carried out X-ray crystallographic analysis of both diastereomeric salts. The structures of the more-soluble (−)-**1**·(−)-**2** salt and less-soluble (+)-**1**·(−)-**2** salts prepared from EtOH solution are shown in Figure 1. As suggested in previous literature,[15] both salts incorporated EtOH molecules, with compositions of **1**·(−)-**2**/EtOH = 1:1.

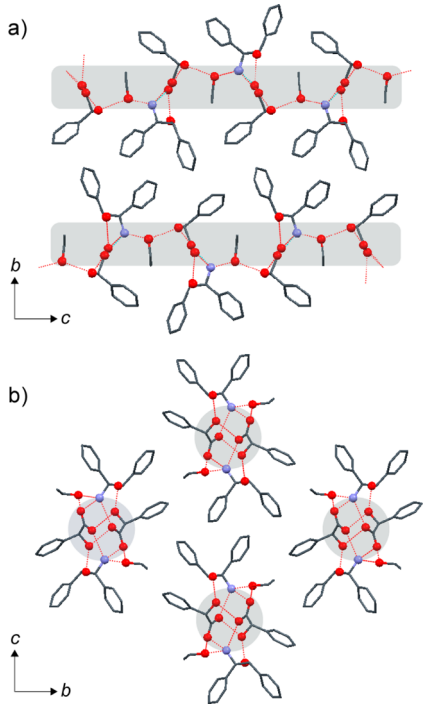

Figure 1. Crystal structures of the diastereomeric salts of **1** with (−)-**2** crystallized from EtOH. (a) (−)-**1**·(−)-**2**·EtOH (more-soluble salt) viewed from the *a* axis. (b) (+)-**1**·(−)-**2**·EtOH (less-soluble salt) viewed from the *a* axis. Hydrogen atoms are omitted for clarity. The dotted lines and shadows represent hydrogen bonds and hydrogen-bonding networks, respectively.

In both diastereomeric salt crystals, **1** and **2** formed charge-assisted hydrogen bonds, producing hydrogen-bonding supramolecular networks. In addition, the EtOH molecules were included by formation of hydrogen bonds, thereby reinforcing the networks. However, the particular type of network for each diastereomer was totally different. In the (−)-**1**·(−)-**2**·EtOH salt, (−)-**1** and (−)-**2** formed one-dimensional (1D) hydrogen-bonding ladderlike networks, linked together by EtOH molecules to afford a two-dimensional (2D) sheetlike structure (Figure 1a). The hydroxy group of each EtOH molecule formed two hydrogen bonds to link a hydroxy oxygen atom of (−)-**1** and an ammonium nitrogen atom of (−)-**2**. On the other hand, in the (+)-**1**·(−)-**2**·EtOH salt crystal, 1D columnar hydrogen-bonding networks with a 2-fold screw axis were constructed (Figure 1b). Channel-like cavities were formed along the column, and the EtOH molecules were incorporated within the channels via the formation of two hydrogen bonds,

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one with a carboxylate group of (+)-**1** and the other with an ammonium group of (−)-**2**. Formation of such a 1D columnar structure is often observed in salts consisting of carboxylic acids and enantiopure **2** when crystallized from alcoholic solvents. In addition, there have been a number of reports regarding solvent alcohol molecules being included in the channels of columnar structures.[9,11] We have previously successfully applied such an inclusion phenomenon to the efficient enantioseparation of various alcohols and sulfoxides.[17] Such a high ability of the salts of **2** to incorporate solvent molecules could be due to the two bulky and rigid aromatic rings of **2** positioned in a *gauche* conformation.[18]

The low efficiency of the optical resolution in EtOH demonstrated that the (−)-**1**·(−)-**2** salt was slightly more soluble than the (+)-**1**·(−)-**2** salt, while the two diastereomeric salts had similar stabilities. From a comparison of these crystal structures, it appears that the (+)-**1**·(−)-**2**·EtOH salt was preferable from the viewpoint of the stability of the 1D networks. In this case, the molecules were related by the 2_1-screw symmetry and combined more tightly, while the (−)-**1**·(−)-**2**·EtOH salt formed less symmetrical 1D ladderlike networks. However, the latter is preferable due to the higher dimensionality of the hydrogen-bonding network connected by EtOH molecules. It is indicated that the opposite influence of these two factors resulted in the comparable stability of the two diastereomeric salts and low resolution efficiency.

When optical resolution was carried out in 1-BuOH or 1-PrOH, (−)-**1**·(−)-**2** was precipitated as the less-soluble salt with high efficiency. The structures of both diastereomeric salts prepared from 1-BuOH are shown in Figure 2. It was found that 1-BuOH was included in these crystals, with compositions of **1**·(−)-**2**/1-BuOH = 1:1. Unlike the salts that incorporated EtOH, similar 1D columnar hydrogen-bonding networks were constructed in both diastereomeric salt crystals, with 1-BuOH embedded in the channels of the columns. However, there are several differences between the two diastereomeric salts. First, the orientations of **1** in the columnar structure were different, and therefore, 1-BuOH molecules became associated by hydrogen bonds in a different fashion. The hydroxy group of 1-BuOH formed hydrogen bonds with an ammonium group of (−)-**2** and a hydroxy group of (−)-**1** in the (−)-**1**·(−)-**2**·1-BuOH crystal (Figure 2a). On the other hand, 1-BuOH was captured by an ammonium group of (−)-**2** and a carboxylate group of (+)-**1** in the (+)-**1**·(−)-**2**·1-BuOH crystal (Figure 2b). Second, the manner of column packing was found to be different. All of the columnar structures were uniform and arranged in a highly symmetrical fashion (space group: $P2_12_12_1$) in the (−)-**1**·(−)-**2**·1-BuOH crystal. However, the more-soluble salt crystal, (+)-**1**·(−)-**2**·1-BuOH, was composed of two kinds of columns with slightly different molecular orientations, which should be unfavorable from the viewpoint of the lower symmetry. In addition, the columns were packed in a less symmetrical $P2_1$ space group. Less dense molecular packing in (+)-**1**·(−)-**2**·1-BuOH was suggested by the crystal densities, which were 1.239 and 1.207 for the less and more soluble diastereomers, respectively. These disadvantages would result in the lower stability of the (+)-**1**·(−)-**2**·1-BuOH salt, and as a result, improved resolution efficiency.

The crystal structures of the diastereomeric salts prepared from 1-PrOH are shown in Figure 3. The stoichiometry was the same as for the cases of the other alcohols, with **1**·(−)-**2**/1-PrOH = 1:1 found for both salt crystals. In the two diastereomeric salts, the molecules were arranged in the form

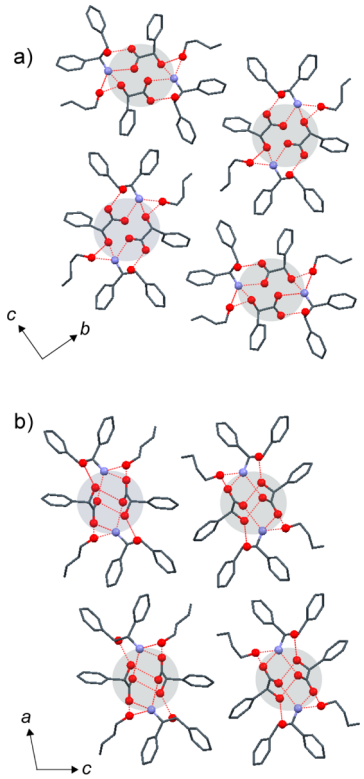

Figure 2. Crystal structures of the diastereomeric salts of **1** and (−)-**2** crystallized from 1-BuOH. (a) (−)-**1**·(−)-**2**·1-BuOH (less-soluble salt) viewed from the *a* axis. (b) (+)-**1**·(−)-**2**·1-BuOH (more-soluble salt) viewed from the *b* axis. Hydrogen atoms are omitted for clarity. The dotted lines and shadows represent hydrogen bonds and hydrogen-bonding networks, respectively.

of 1D columnar structures; however, the situation was different from the case of **1**·(−)-**2**·1-BuOH, with both crystallized in the same space group $P2_12_12_1$. The crystal structure of the less-soluble (−)-**1**·(−)-**2**·1-PrOH salt was observed to be almost the same as that of the (−)-**1**·(−)-**2**·1-BuOH crystal (Figure 3a), whereas the structure of the more-soluble (+)-**1**·(−)-**2**·1-PrOH was very similar to that of (+)-**1**·(−)-**2**·EtOH (Figure 3b). The positions of the 1-PrOH molecules included in the more-soluble salt could not be accurately determined owing to the structural disorder, which was probably due to the shape of the channel being unsuitable for the inclusion of 1-PrOH. Comparison of the densities of both salt crystals demonstrated that (+)-**1**·(−)-**2**·1-PrOH was less dense than (−)-**1**·(−)-**2**·1-PrOH (1.216 and 1.237, respectively). These differences indicated that (+)-**1**·(−)-**2**·1-PrOH was less stable than (−)-**1**·(−)-**2**·1-PrOH, which led to the predominant precipitation of the (−)-**1**·(−)-**2**·1-PrOH salt during the optical resolution.

The three linear aliphatic alcohols were each incorporated via two hydrogen bonds in both diastereomeric salts. In the case of (+)-**1**·(−)-**2**, columnar hydrogen-bonding networks were commonly constructed. However, by increasing the alkyl chain length of the solvent, from EtOH to 1-PrOH and 1-BuOH, it appears that the molecule became too long to be settled in the channel, with symmetrical packing of the resulting columns prevented for the (+)-**1**·(−)-**2**·1-BuOH salt. On the other hand, the molecular arrangement of the (−)-**1**·(−)-**2** salt changed from ladderlike to a columnar structure on increasing the alkyl chain length, with dense packing of columns achieved

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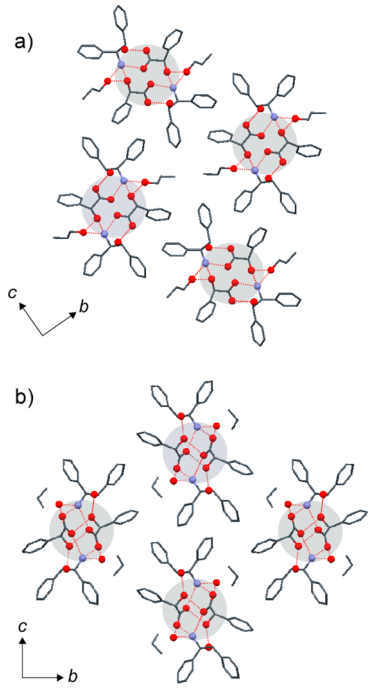

Figure 3. Crystal structures of the diastereomeric salts of **1** with (−)-**2** crystallized from 1-PrOH. (a) (−)-**1**·(−)-**2**·1-PrOH (less-soluble salt) viewed from the *a* axis. (b) (+)-**1**·(−)-**2**·1-PrOH (more-soluble salt) viewed from the *b* axis. Hydrogen atoms are omitted for clarity. The dotted lines and shadows represent hydrogen bonds and hydrogen-bonding networks, respectively.

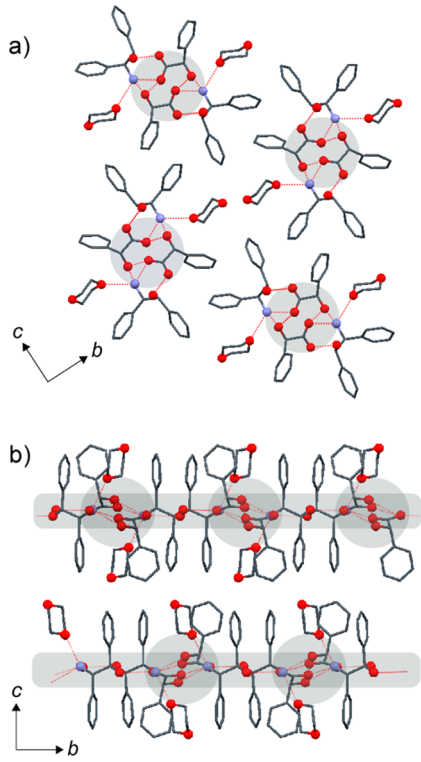

Figure 4. Crystal structures of the diastereomeric salts of **1** with (−)-**2** crystallized from 1,4-dioxane. (a) (−)-**1**·(−)-**2**·1,4-dioxane (more-soluble salt) viewed from the *a* axis. (b) (+)-**1**·(−)-**2**·1,4-dioxane (less-soluble salt) viewed from the *a* axis. Hydrogen atoms are omitted for clarity. The dotted lines and shadows represent hydrogen bonds and hydrogen-bonding networks, respectively.

by effectively filling the channels between the columns with the solvent molecules. Such an influence of the molecular length of alcohols was further supported by the fact that (+)-**1**·(−)-**2** crystallized from 2-PrOH afforded a solvated (+)-**1**·(−)-**2**·2-PrOH crystal, in which the molecular arrangement was very similar to that of the (+)-**1**·(−)-**2**·EtOH crystal (Supporting Information, Figure S2). Because the effective molecular lengths of EtOH and 2-PrOH are comparable, it is probable that the manner of packing in the columnar structures was mainly determined by molecular length of the solvent alcohols. A similar effect of the molecular length of the alcohols on the packing of columnar structures was also observed in our previous study.[17c]

Finally, the structures of both diastereomeric salts prepared from 1,4-dioxane solution of the 1:1 mixture of **1** and (−)-**2** are shown in Figure 4. As suggested from the ^{1}H NMR spectra, both salts included 1,4-dioxane molecules, with their composition identified as being **1**·(−)-**2**/1,4-dioxane = 1:1. The more-soluble (−)-**1**·(−)-**2**·1,4-dioxane salt formed 1D columnar structures, packed in a $P2_12_12_1$ space group (Figure 4a). The molecular arrangement was almost the same as those of the less-soluble (−)-**1**·(−)-**2**·1-PrOH and (−)-**1**·(−)-**2**·1-BuOH salts. The intercolumnar channels were occupied with 1,4-dioxane molecules that were connected by one hydrogen bond between an ether oxygen atom of 1,4-dioxane and an ammonium group of (−)-**2**. The density of the crystal was as large as 1.309, and it was suggested that the molecules were tightly packed and the salt crystal was relatively stable. The solubility of the salt crystallized from 1,4-dioxane was found to be lower than those of 1-PrOH or 1-BuOH. On the other hand, a rather different structure was observed for the less-soluble (+)-**1**·(−)-**2**·1,4-dioxane salt crystal (Figure 4b). Symmetric 1D columnar structures with a 2-fold screw axis were formed, and the conformation of (+)-**1** was fixed by a bifurcated hydrogen bond involving an ammonium hydrogen atom of (−)-**2** interacting with both a hydroxy oxygen atom and a carboxylate oxygen atom of (+)-**1**. The two phenyl groups of (−)-**2** were present in a *trans* conformation, and a hydroxy group of (−)-**2** faced outward from the columns. The hydroxy hydrogen atom of (−)-**2** formed a hydrogen bond with the carboxylate oxygen atom of (+)-**1** in the neighboring column, and the columns were tightly connected to give a 2D sheetlike hydrogen-bonding network with a void space. The 1,4-dioxane molecules were incorporated in the void by formation of a hydrogen bond between an ether oxygen atom of 1,4-dioxane and an ammonium group of (−)-**2**. The molecular length of 1,4-dioxane was comparable with the size of the void space; therefore, it appeared that 1,4-dioxane was appropriate for filling the void. In addition, the resulting fairly planar surface of the 2D sheet-like networks contributed to efficient van der Waals packing. All of these factors presumably resulted in the high stability of the (+)-**1**·(−)-**2**·1,4-dioxane salt, and the resulting high-resolution efficiency with reversed stereoselectivity compared to the cases where alcohols were applied as the solvent.

Furthermore, during the optical resolution of **2** with enantiopure (−)-**1** in 1,4-dioxane, the precipitated crystals consisted of (−)-**1** and **2** in a molar ratio of 2:1, with high stereoselectivity for (+)-**2** still achieved. In order to elucidate the detailed mechanism, a single crystal was prepared from a 1,4-dioxane solution of a 2:1 mixture of (+)-**1** and (−)-**2**, and its structure is shown in Figure 5. The obtained crystal was

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Table 3. Successive Resolution of (±)-1 with (−)-2 by the Solvent Switch Method[a]

first resolution (±)-**1** from 1-BuOH				second resolution (+)-enriched **1** from 1,4-dioxane			
yield[b] (%)	$[\alpha]_D$[c] (deg)	OP[d] (%ee)	resolution efficiency[e]	yield[b] (%)	$[\alpha]_D$[c] (deg)	OP[d] (%ee)	resolution efficiency[e]
70	−136.7	89	62	71	116.6	75	53

[a](±)-**1**/(−)-**2** = 1.0. [b]Yield of the less-soluble salt. [c]Specific rotation of resolved **1**. Solvent: H_2O, *c* 0.8, 25 °C. [d]Optical purity calculated from the specific rotation value based on the literature; $[\alpha]_D$ ± 153.5° (*c* 1, H_2O). [e]Resolution efficiency = yield (%) × OP(%)/100.

Table 4. Successive Resolution of (±)-2 with (−)-1 by the Solvent Switch Method[a]

first resolution (±)-**2** from 1-BuOH				second resolution (+)-enriched **2** from 1,4-dioxane			
yield[b] (%)	$[\alpha]_D$[c] (deg)	OP[d] (%ee)	resolution efficiency[e]	yield[b,f] (%)	$[\alpha]_D$[c] (deg)	OP[d] (%ee)	resolution efficiency[e]
93	−6.1	44	40	40	7.8	95	37

[a](±)-**2**/(−)-**1** = 1.0. [b]Yield of the less-soluble salt. [c]Specific rotation of resolved **2**. Solvent: EtOH, *c* 0.6, 20 °C. [d]Optical purity determined by chiral HPLC for the 2-oxazolidinone derivative. [e]Resolution efficiency = yield (%) × OP(%)/100. [f]Calculated based on half the amount of (±)-**2**.

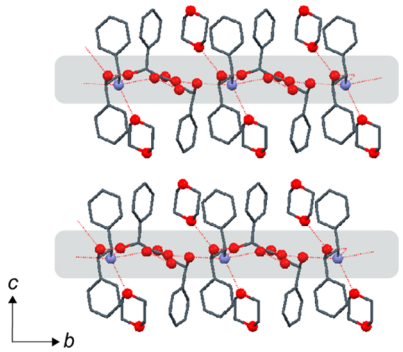

Figure 5. Crystal structure of 2((+)-**1**)·(−)-**2**·2(1,4-dioxane) viewed from the *a* axis. Hydrogen atoms are omitted for clarity. The dotted lines and shadows represent hydrogen bonds and hydrogen-bonding networks, respectively.

found to be a pseudopolymorph of the (+)-**1**·(−)-**2**·1,4-dioxane mentioned above, with a composition of (+)-**1**/(−)-**2**/1,4-dioxane = 2:1:2. The molecular arrangement of 2((+)-**1**)·(−)-**2**·2(1,4-dioxane) was apparently similar to that of (+)-**1**·(−)-**2**·1,4-dioxane, with the two phenyl groups of (−)-**2** present in the *trans* position, and 2D sheetlike hydrogen-bonding networks constructed. One of the two molecules of (+)-**1** formed charge-assisted hydrogen bonds with (−)-**2**, and the resultant 1D ladderlike hydrogen-bonding networks were combined with the other neutral (+)-**1** molecules. Two 1,4-dioxane molecules were also independently included, filling the void space. One formed a hydrogen bond with an ammonium hydrogen atom of (−)-**2**, while the other interacted with a hydroxy hydrogen atom of (−)-**2**. Though they crystallized in a less symmetric space group (*P*1), it appeared that the efficient packing of the planar 2D networks made this pseudopolymorphic crystal stable enough to precipitate preferentially. The solid-state behavior of the salts was further elucidated by measurement of their IR spectra (Supporting Information, Figure S3). The salt, 2((+)-**1**)·(−)-**2**·2(1,4-dioxane), showed an absorption band at 1719 cm^{-1}, derived from the C=O stretching vibration of neutral **1**. This absorption band disappeared on cogrinding of this salt with another equivalent of (−)-**2** in the presence of a few drops of 1,4-dioxane. The spectrum of the resultant solid was consistent with that of (+)-**1**·(−)-**2**·1,4-dioxane, which suggested that the 1:1 salt formation was enhanced by grinding. There have been some reports on similar liquid-assisted cogrinding being useful for controlling the polymorphic forms of cocrystals or salts.[19] One possible reason for such a polymorphism in our reciprocal resolution system is the difference in the amount of (−)-**1** (or (+)-**1**) and (+)-**2** (or (−)-**2**) during crystallization. In the resolution of (±)-**2** using (−)-**1**, two equivalents of (−)-**1** for every (+)-**2** were present, while a half amount of (+)-**1** to (−)-**2** was present in the original resolution involving (±)-**1**.

Successive Resolution of 1 and 2 by Solvent Switching. The present data and the aforementioned high utility of **1** and **2** prompted us to successively resolve both enantiomers of each compound by solvent switching, using a previously reported method.[6b] Successive resolution of (±)-**1** with (−)-**2** was first examined. As can be seen in Table 1, the less-soluble diastereomeric salts changed from (+)-**1**·(−)-**2** to (−)-**1**·(−)-**2** by selecting 1-BuOH for the first resolution and 1,4-dioxane for the second resolution.

After the (−)-**1**·(−)-**2**·1-BuOH salt was collected by filtration in the first resolution, the (+)-**1**·(−)-**2** enriched salt was recovered by condensation of the mother liquor. The residue was crystallized from 1,4-dioxane to obtain (+)-**1**·(−)-**2**·1,4-dioxane as the second crop. Although the procedure was not optimized, the results shown in Table 3 corresponded well to those in Table 1. In addition, as a reciprocal resolution system, resolution of (±)-**2** with (−)-**1** was performed. Considering that resolution from 1,4-dioxane produced the nonstoichiometric salt, as seen in Table 2, 1-BuOH was selected as the first resolving solvent, with good results obtained, as summarized in Table 4.

CONCLUSION

In conclusion, we have demonstrated highly efficient reciprocal optical resolution between mandelic acid, **1**, and *erythro*-2-amino-1,2-diphenylethanol, **2**. The stereoselectivity was dramatically switched by changing the crystallization solvent from 1,4-dioxane to 1-PrOH or 1-BuOH, while EtOH gave disappointing results. The technique was applied to the successive resolution without the requirement for a change in resolving agent, and both enantiomers of **1** combined with **2** were obtained efficiently. Crystallographic analysis of the diastereomeric salts showed that they generally incorporated the crystallization solvent, affording inclusion crystals with different compositions and structures. Differences in the hydrogen-bonding networks and their packing manner were found to be crucial for the solvent-dependent switching of stereoselectivity in the diastereomeric resolution. This is the first example of a solvent switching system where the stabilities of both diastereomers are altered by incorporation of solvent

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molecules. The insight obtained from this study will potentially contribute to clarification of the mechanisms of solvent switching. Further application of this method to other hydroxycarboxylic acids or aminoalcohols is now under investigation.

EXPERIMENTAL SECTION

Resolution of (±)-Mandelic Acid ((±)-1) by *erythro*-(1*R*,2*S*)-(−)-2-Amino-1,2-diphenylethanol ((−)-2) from EtOH. To (±)-**1** (0.5310 g, 3.49 mmol) in MeOH (5 mL) was added (−)-**2** (0.7414 g, 3.47 mmol) in MeOH (15 mL). After concentration, the resulting diastereomeric salts (1.3251 g) were recrystallized from EtOH (12 mL) and filtered to obtain needlelike crystals (0.7225 g). The crystals were recrystallized once from 90% EtOH (10 mL) to afford the less-soluble (+)-**1**·(−)-**2** salt (0.0795 g, 12%; $[\alpha]_D^{18}$ = −55.6° (*c* 0.97, MeOH); mp 147−150 °C). The apparent yield was calculated assuming the salt composition was 1:1 for **1**/(−)-**2**.

The salt was dissolved in H_2O (5 mL) and decomposed by addition of 1 M aqueous NaOH (5 mL), followed by extraction with Et_2O. The aqueous layer was acidified by addition of 1 M aqueous HCl (8 mL) and extracted with Et_2O. After drying over anhydrous Na_2SO_4, the organic layer was concentrated to obtain (+)-**1** (0.0256 g, 9.6%). From the measurement of the specific rotation, the optical purity was calculated to be 62% ee ($[\alpha]_D^{25}$ = 95.2° (*c* 0.51, H_2O)).

Resolution of (±)-Mandelic Acid ((±)-1) by *erythro*-(1*R*,2*S*)-(−)-2-Amino-1,2-diphenylethanol ((−)-2) from 1-PrOH. The diastereomeric salts of (±)-**1** (0.5003 g, 3.28 mmol) and (−)-**2** (0.7025 g, 3.29 mmol) were recrystallized from 1-PrOH (60 mL) to obtain needlelike crystals (0.5739 g). Further recrystallization of the crystals from 1-PrOH (35 mL) afforded the less-soluble (−)-**1**·(−)-**2** salt (0.3686 g, 54%; $[\alpha]_D^{18}$ = −114.0° (*c* 0.97, MeOH); mp 146−151 °C). The apparent yield was calculated based on the ^{1}H NMR data, which indicated a ratio of (−)-**1**·(−)-**2**/1-PrOH = 1:0.8. Decomposition of the salt (0.2468 g) afforded (−)-**1** (0.0783 g, 46%) in 90% ee ($[\alpha]_D^{20}$ = −139.6° (*c* 0.78, H_2O)).

Resolution of (±)-Mandelic Acid ((±)-1) by *erythro*-(1*R*,2*S*)-(−)-2-Amino-1,2-diphenylethanol ((−)-2) from 1-BuOH. The diastereomeric salts of (±)-**1** (0.5926 g, 3.89 mmol) and (−)-**2** (0.8325 g, 3.90 mmol) were recrystallized from 1-BuOH (70 mL) to obtain needlelike crystals (1.1238 g). Recrystallization of the crystals from 1-BuOH (50 mL) afforded the less-soluble (−)-**1**·(−)-**2** salt (0.8063 g, 94%; $[\alpha]_D^{20}$ = −101.3° (*c* 1.0, MeOH); mp 149−154 °C). The apparent yield was calculated based on the ^{1}H NMR data, which indicated a ratio of (−)-**1**·(−)-**2**/1-BuOH = 1:0.94. Decomposition of the crystals (0.2562 g) afforded (−)-**1** (0.0786 g, 83%) in 73% ee ($[\alpha]_D^{21}$ = −112.0° (*c* 0.78, H_2O)).

Resolution of (±)-Mandelic Acid ((±)-1) by *erythro*-(1*R*,2*S*)-(−)-2-Amino-1,2-diphenylethanol ((−)-2) from 1,4-Dioxane. The diastereomeric salts of (±)-**1** (0.5961 g, 3.91 mmol) and (−)-**2** (0.8393 g, 3.93 mmol) were recrystallized from 1,4-dioxane (100 mL) to obtain platelike crystals (0.6530 g). Further recrystallization from 1,4-dioxane (20 mL) afforded the less-soluble (+)-**1**·(−)-**2** salt crystals (0.5072 g, 57%; $[\alpha]_D^{20}$ = −43.4° (*c* 1.0, MeOH); mp 149−154 °C). The apparent yield was calculated based on the ^{1}H NMR data, which indicated a ratio of (+)-**1**·(−)-**2**/1,4-dioxane = 1:1. Decomposition of the crystals (0.2481 g) afforded (+)-**1** (0.0775 g, 53%) in 88% ee ($[\alpha]_D^{22}$ = 135.8° (*c* 0.77, H_2O)).

Successive Resolution of (±)-Mandelic Acid ((±)-1) by *erythro*-(1*R*,2*S*)-(−)-2-Amino-1,2-diphenylethanol ((−)-2) by Solvent Switch between 1-BuOH and 1,4-Dioxane. The diastereomeric salts of (±)-**1** (0.5406 g, 3.55 mmol) and (−)-**2** (0.7546 g, 3.53 mmol) were recrystallized from 1-BuOH (90 mL) to obtain needlelike crystals (0.7538 g). Further recrystallization from 1-BuOH (40 mL) afforded the less-soluble (−)-**1**·(−)-**2** salt crystals (0.5473 g, 70%; $[\alpha]_D^{24}$ = −103.7° (*c* 1.0, MeOH); mp 157−159 °C). The apparent yield was calculated based on the ^{1}H NMR data, which indicated a ratio of (−)-**1**·(−)-**2**/1-BuOH = 1:1. Decomposition of the crystals (0.2535 g) afforded (−)-**1** (0.0748 g, 59%) in 89% ee ($[\alpha]_D^{27}$ = −136.7° (*c* 0.74, H_2O)).

The white solid (0.7291 g) recovered from the filtrate was recrystallized from 1,4-dioxane (30 mL) to obtain the less-soluble (+)-**1**·(−)-**2** salt as platelet crystals (0.5693 g, 71%; $[\alpha]_D^{24}$ = −44.9° (*c* 1.0, MeOH); mp 147−152 °C). The apparent yield was calculated based on the ^{1}H NMR data, which indicated a ratio of (+)-**1**·(−)-**2**/1,4-dioxane = 1:1. Decomposition of the crystals (0.2572 g) afforded (+)-**1** (0.0800 g, 65%) in 75% ee ($[\alpha]_D^{25}$ = 116.6° (*c* 0.80, H_2O)).

Resolution of (±)-*erythro*-2-Amino-1,2-diphenylethanol ((±)-2) by (−)-Mandelic Acid ((−)-1) from 1-PrOH. The diastereomeric salts of (±)-**2** (0.2927 g, 1.37 mmol) and (−)-**1** (0.2119 g, 1.39 mmol) were recrystallized from 1-PrOH (20 mL) to obtain needlelike crystals (0.1867 g). Further recrystallization from 1-PrOH (5 mL) afforded the less-soluble (−)-**1**·(−)-**2** salt (0.1420 g, 50%; $[\alpha]_D^{23}$ = −115.6° (*c* 1.0, MeOH); mp 157−159 °C). The apparent yield was calculated based on the ^{1}H NMR data, which indicated a ratio of (−)-**1**·(−)-**2**/1-PrOH = 1:0.8.

The salt crystals were dissolved in H_2O at 60 °C and decomposed by addition of 28% aqueous ammonia (0.2 mL) to precipitate (−)-**2** (0.0621 g, 42%) ($[\alpha]_D^{24}$ = −8.5° (*c* 0.48, EtOH)).

The optical purity of (−)-**2** was determined to be greater than 99% ee by chiral HPLC analysis of its oxazolidinone derivative, which was prepared by reaction with triphosgene (Chiralcel OJ-3, 4.6 mm × 250 mm; eluent: 2-PrOH/hexane = 3:7 v:v; flow rate: 0.5 mL min^{-1}; detection wavelength: 254 nm; retention time: derivative of (+)-**2**, 14 min, derivative of (−)-**2**, 20 min).

Resolution of (±)-*erythro*-2-Amino-1,2-diphenylethanol ((±)-2) by (−)-Mandelic Acid ((−)-1) from 1-BuOH. The diastereomeric salts of (±)-**2** (0.2912 g, 1.36 mmol) and (−)-**1** (0.2094 g, 1.37 mmol) were recrystallized from 1-BuOH (25 mL) to obtain needlelike crystals (0.3599 g), and the filtrate was concentrated to obtain a white solid (0.2136 g). Recrystallization of the crystals from 1-BuOH (10 mL) afforded the less-soluble (−)-**1**·(−)-**2** salt (0.2787 g, 93%; $[\alpha]_D^{20}$ = −87.8° (*c* 1.0, MeOH); mp 141−149 °C). The apparent yield was calculated based on the ^{1}H NMR data, which indicated a ratio of (−)-**1**·(−)-**2**/1-BuOH = 1:1. Decomposition of the crystals (0.2062 g) afforded (−)-**2** (0.0621 g, 57%) in 44% ee ($[\alpha]_D^{20}$ = −6.1° (*c* 0.6, EtOH)).

Resolution of (±)-*erythro*-2-Amino-1,2-diphenylethanol ((±)-2) by (−)-Mandelic Acid ((−)-1) from 1,4-Dioxane. The diastereomeric salts of (±)-**2** (0.3030 g, 1.42 mmol) and (−)-**1** (0.2159 g, 1.41 mmol) were recrystallized from 1,4-dioxane (30 mL) to obtain platelike crystals (0.3855 g, 91%; $[\alpha]_D^{16}$ = −12.7° (*c* 0.9, MeOH); mp 109−114 °C). The apparent yield was calculated based on the ^{1}H NMR data, which indicated a ratio of (−)-**1**/(+)-**2**/1,4-dioxane = 2:1:1.8. Decomposition of the salt crystals (0.3855 g) afforded (+)-**2** (0.1107 g, 72%) in 94% ee ($[\alpha]_D^{21}$ = 7.8° (*c* 0.6, EtOH)).

Successive Resolution of (±)-*erythro*-2-Amino-1,2-diphenylethanol ((±)-2) by (−)-Mandelic Acid ((−)-1) by Solvent Switch between 1-BuOH and 1,4-Dioxane. The white solid (0.2136 g) obtained from the mother liquor after resolution of (±)-**2** by (−)-**1** from 1-BuOH was recrystallized from 1,4-dioxane (20 mL) to obtain the less-soluble (−)-**1**·(+)-**2** salt crystals as platelets (0.1755 g, 40%; $[\alpha]_D^{20}$ = 31.4° (*c* 1.0, MeOH); mp 157−160 °C). The apparent yield was calculated based on the ^{1}H NMR data, which indicated a ratio of (−)-**1**/(+)-**2**/1,4-dioxane = 1.8:1:1.8. Decomposition of the crystals (0.1755 g) afforded (+)-**2** (0.0575 g, 39%) in 95% ee ($[\alpha]_D^{19}$ = 7.8° (*c* 0.57, EtOH)).

Single-Crystal X-ray Analyses of the Solvated Diastereomeric Salt Crystals. Single crystals suitable for X-ray diffraction analysis were successfully prepared by slow evaporation of the saturated solutions of pure diastereomeric salts, except for (+)-**1**·(−)-**2**·EtOH. The single crystal of (+)-**1**·(−)-**2**·EtOH was obtained during optical resolution of (±)-**1** with (−)-**2**. X-ray crystallographic data were collected using a CCD diffractometer with graphite monochromated Mo Kα radiation. Data collections were carried out at low temperature (150 K). The structures were solved by a direct methods SIR 97[20] and refined by SHELXL-97 programs.[21] Crystallographic information files have been deposited with the Cambridge

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Structural Database. Crystallographic parameters and CCDC numbers are summarized in Table S1 in the Supporting Information.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Summary of crystallographic data; additional figures including TGA and IR spectra of the diastereometric salts and the crystal structure of (+)-**1**·(−)-**2**·**2**-PrOH; and X-ray crystallographic data (in CIF format) of the salt crystals. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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