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Solvent-induced chirality switching in the enantioseparation of regioisomeric hydroxyphenylpropionic acids via diastereomeric salt formation with (1*R*,2*S*)-2-amino-1,2-diphenylethanol

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ABSTRACT

The enantioseparation of three hydroxyphenylpropionic acid isomers via diastereomeric salt formation with (1*R*,2*S*)-2-amino-1,2-diphenylethanol has been demonstrated. The racemates of all three acid isomers were successfully separated with high efficiency (0.56–0.84) after single crystallization. For 2-hydroxy-3-phenylpropionic acid **4**, the configuration of the less-soluble salt was controlled by the crystallization solvent: the (*R*)-**4** salt was crystallized from water, while 2-propanol afforded the (*S*)-**4** salt. The chiral recognition mechanism of the three acids was discussed based on the crystal structures of the diastereomeric salts.

1. Introduction

Among several methods available for the preparation of enantiopure compounds, enantioseparation of a racemate via diastereomeric salt formation with an enantiopure resolving agent is one of the most reliable and often used methods.[1] One advantage of this method is that the enantiopurity may be improved by repeated recrystallization of the less-soluble diastereomeric salt. However, the corresponding more-soluble diastereomeric salt is difficult to purify, and therefore, additional operations, such as decomposition of the salt followed by its re-formation with another resolving agent, are necessary to obtain the other enantiomer.[2]

On the other hand, it has been reported that the absolute configuration of the preferably deposited diastereomeric salt changed dependent on the dielectric constant of the crystallization solvents in several cases. This dielectrically controlled resolution (DCR) method is advantageous because both enantiomers of the target compound can be accessed in a small number of operations using only one enantiomer of the resolving agent.[3] Previously we have reported the same phenomenon in the enantioseparation of racemic mandelic acid (MA) via diastereomeric salt formation with enantiopure (1*R*,2*S*)-2-amino-1,2-diphenylethanol.[4] In contrast to the DCR method, the configuration of the less-soluble salt was mainly determined by the size and shape of the solvent molecules. Crystallization from short-chain alcohols (MeOH, EtOH, *i*-PrOH, *t*-BuOH) afforded (*S*)-MA·(1*R*,2*S*)-2-amino-1,2-diphenylethanol salt crystals while (*R*)-MA·(1*R*,2*S*)-2-amino-1,2-diphenylethanol salt was obtained from a solution of longer alcohols (*n*-PrOH, *i*-BuOH, *s*-BuOH, *n*-BuOH).[5] This solvent-induced chirality switching phenomenon with 2-amino-1,2-diphenylethanol was also observed during the enantioseparation of 3-hydroxy-2-phenylpropionic acid **1** (tropic acid), which has one additional methylene group between the stereogenic center and hydroxy group of mandelic acid.[6] X-ray crystallographic analysis of these salts showed that incorporation of the solvent alcohol molecules in the diastereomeric salt during crystallization played a key role in changing their solubilities. Only a subtle structural modification of the target racemate can often change the molecular packing in the crystalline state and the enantioseparation result, however, the solvent-induced chirality switching method was applicable to *rac*-**1** as well as mandelic acid.

Enantiopure hydroxycarboxylic acids are key compounds for asymmetric synthesis[7] and production of pharmaceuticals.[8] To expand the substrate scope to other carboxylic acids, herein we investigated the enantioseparation of the other three regioisomers of hydroxyphenylpropionic acids **2**–**4** with (1*R*,2*S*)-2-amino-1,2-diphenylethanol and have elucidated the mechanism of chiral recognition based on their crystal structures.

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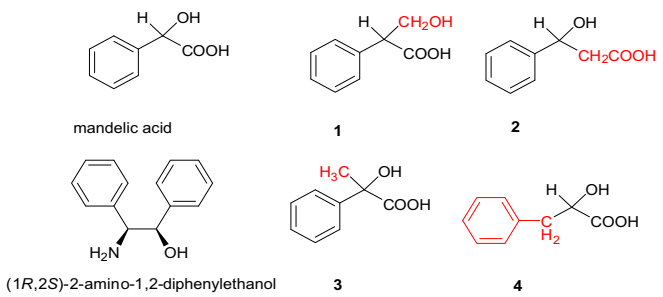

2. Results and discussion

Optically active 3-hydroxy-3-phenylpropionic acid **2**, which has a methylene group between the carboxy group and the stereogenic center of mandelic acid, has been applied to the stereoselective synthesis of chiral drugs such as (*S*)-dapoxetine.[9] Its enantioseparation is not easy due to the flexible methylene group but has been achieved by diastereomeric salt formation with morphine, a highly toxic alkaloid.[10]

Racemic **2** was synthesized from ethyl benzoylacetate according to a reported method and purified by recrystallization from toluene.[11] The salt of *rac*-**2** and (1*R*,2*S*)-2-amino-1,2-diphenylethanol was prepared in advance by evaporation of the methanol solution of their equimolar mixture. The salt was recrystallized once from various solvents and the deposited solid was filtered and dried before characterization by ^{1}H NMR spectroscopy. Part of the salt was decomposed and the enantiopurity of recovered **2** was determined by HPLC analysis after derivatization to its methyl ester. The results are summarized in Table 1. Seven types of solvents with different polarities were tested and all of them preferentially afforded the (*S*)-**2**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol salt. No chirality switching was observed, which was in accordance with the fact that none of the tested solvents was included in the precipitated salt crystals, although the presence of water was unknown (entry 1). It is noteworthy that the resolution efficiency (=yield × ee) was as high as 0.5; the less polar THF and 1,4-dioxane afforded the highest efficiencies (entries 6 and 7), while (*S*)-**2** was obtained with the highest enantiopurity by recrystallization from 50% EtOH (entry 2). According to this method, enantiopure (*S*)-**2** was prepared after repeated recrystallization of the initial salt (4 times) from 50% EtOH (27% overall yield, >99% ee).

While the solvent-induced chirality switching method was not achieved with **2**, X-ray crystallographic analyses of the diastereomeric salts were performed in order to elucidate the mechanism of chiral recognition of **2**. The structure of the less-soluble (*S*)-**2**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol salt prepared from its ethanol solution is shown in Figure 1. As suggested from the ^{1}H NMR result mentioned above, no solvent was included and a 1:1 salt of (*S*)-**2** and (1*R*,2*S*)-2-amino-1,2-diphenylethanol was formed. A columnar hydrogen-bonding network was constructed with a 2-fold screw axis, which is similar to previously reported (*S*)-**1**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol salt.[6] The space group of the crystal was $P2_1$ and the neighboring columns were packed in parallel. In addition to the charge-assisted hydrogen bonds between the ammonium group of (1*R*,2*S*)-2-amino-1,2-diphenylethanol and the carboxylate group of (*S*)-**2**, the molecules were combined by hydrogen bonds between the hydroxy groups of (*S*)-**2** and (1*R*,2*S*)-2-amino-1,2-diphenylethanol to reinforce the columnar network.

Furthermore, there are two CH/π interactions to fix the substituents of (*S*)-**2**. One is between the *para*-CH of (*S*)-**2** and the phenyl ring of (1*R*,2*S*)-2-amino-1,2-diphenylethanol of the neighboring column (the C···π-plane and CH···π-plane distances were 3.67 and 2.74 Å, respectively) and the other is the intracolumnar interaction between the methylene hydrogen atom and the phenyl ring of (*S*)-**2** (the C···π-plane and CH···π-plane distances were 3.61 and 3.00 Å, respectively).[12] These CH/π interactions probably played an important role to fix the substituents of (*S*)-**2** and recognize the chirality. The bulky phenyl group of **2** is one-carbon more remote from the carboxylate group than in mandelic acid, and the resulting flexibility allowed dense molecular packing without incorporation of the solvent molecules to form a stable salt.

In order to examine the structure of the corresponding more-soluble (*R*)-**2**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol salt, its antipode (*S*)-**2**·(1*S*,2*R*)-2-amino-1,2-diphenylethanol salt was prepared from enantiopure (*S*)-**2** and commercially available (1*S*,2*R*)-2-amino-1,2-diphenylethanol. The structure of the salt crystallized from aqueous ethanol solution is shown in Figure 2. The columnar hydrogen-bonding network was constructed from (*S*)-**2** and (1*S*,2*R*)-2-amino-1,2-diphenylethanol, which was similar to the less-soluble (*S*)-**2**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol salt. However, a water molecule was embedded in the center of the columnar structure to afford the (*S*)-**2**·(1*S*,2*R*)-2-amino-1,2-diphenylethanol·0.5H_2O salt. Moreover, two CH/π interactions were present in the same parts as was the less-soluble (*S*)-**2**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol salt. Although the two diastereomeric salts have similar molecular orientations, the space group of the hemihydrated more-soluble salt crystal was *C*2 and the structure appeared to be less symmetrical. Preferential crystallization of (*S*)-**2**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol salt during enantioseparation in aqueous solvents probably resulted from this subtle difference.

When the more-soluble (*S*)-**2**·(1*S*,2*R*)-2-amino-1,2-diphenylethanol salt was recrystallized from 1,4-dioxane, a crystal with a

Table 1
Enantioseparation of *rac*-**2** with (1*R*,2*S*)-2-amino-1,2-diphenylethanol[a]

Entry	Solvent (L/mol)	Solvent inclusion[b] (%)	Yield[c] (%)	Ee[d] (%)	Eff.[e]
1	H_2O (21)	–	80	68 (*S*)	0.54
2	50% EtOH (11)	Not included	47	83 (*S*)	0.39
3	EtOH (9)	Not included	95	58 (*S*)	0.55
4	2-PrOH (13)	Not included	61	68 (*S*)	0.42
5	Acetone (10)	Not included	59	74 (*S*)	0.44
6	THF (17)	Not included	78	72 (*S*)	0.56
7	1,4-Dioxane (20)	Trace	100	56 (*S*)	0.56

[a] *rac*-**2** and (1*R*,2*S*)-2-amino-1,2-diphenylethanol (1.0 mmol) were used.
[b] The solvent inclusion was determined by ^{1}H NMR analysis.
[c] Yield is based on the half of the salt amount.
[d] Ee was determined by HPLC analysis after derivatization to its methyl ester.
[e] Eff. = Yield (%) × Ee (%)/10,000.

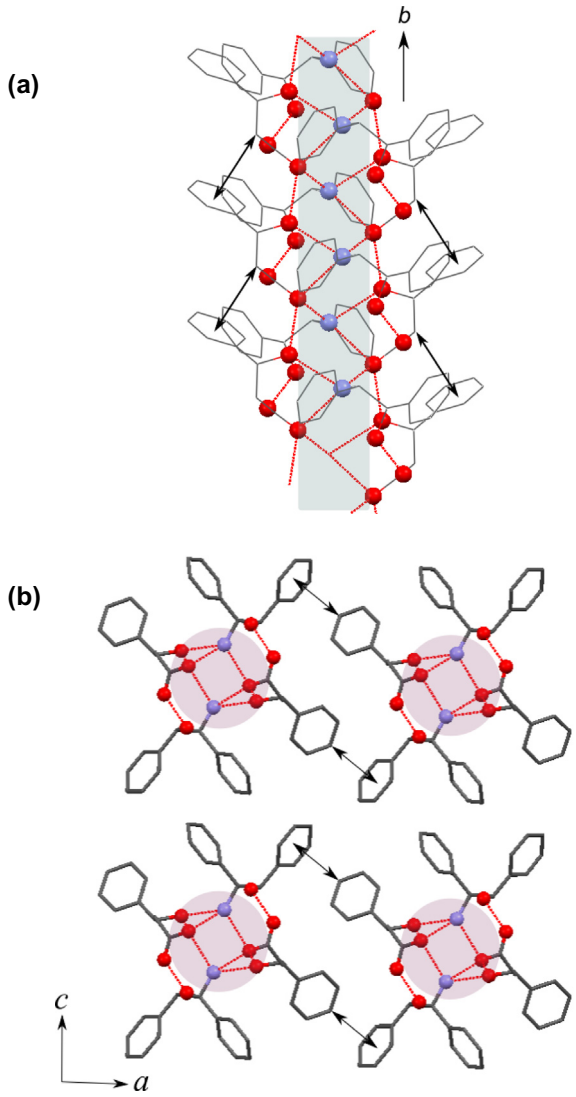

Figure 1. Crystal structure of the (*S*)-**2**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol salt. (a) Side view of the columnar structure. (b) Top view of the columnar structures. Oxygen atom and nitrogen atoms are presented with red and blue balls. The dotted lines and arrows show hydrogen bonds and CH/π interactions, respectively.

different composition was obtained (Fig. 3). The space group was $P2_12_12_1$ and columnar networks were constructed from (*S*)-**2** and (1*S*,2*R*)-2-amino-1,2-diphenylethanol. It should be noted that an equimolar amount of 1,4-dioxane was incorporated in the salt crystal. The dioxane molecule was captured by the formation of a hydrogen bond with a hydroxy group of (*S*)-**2**. An intercolumnar CH/π interaction between the methylene group of dioxane and the phenyl group of (*S*)-**2** also contributed to the fixation of the dioxane molecule. The trace amount of dioxane in the solid precipitated during enantioseparation (Table 1, entry 7) can be attributed to its inclusion in the more-soluble salt. In our systematic investigation of chirality switching in the enantioseparation of aromatic hydroxycarboxylic acids with 2-amino-1,2-diphenylethanol, this is the first example wherein a non-solvated diastereomeric salt is less soluble than the solvated form of the other diastereomeric salt. It appears that the incorporation of the solvent should increase the stability of (*R*)-**2**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol salt; however, it is not significant enough to switch the enantioselectivity of **2**.

A similar procedure was applied to 2-hydroxy-2-phenylpropionic acid **3** (atrolactic acid) which contains a quaternary stereogenic carbon and is important in pharmaceuticals. Several examples of its enantioseparation by diastereomeric salt formation with basic resolving agents have already been reported.[13] Among them, (1*R*,2*S*)-2-amino-1,2-diphenylethanol was reported to give highly enantioenriched (*R*)-**3** by recrystallization from methanol while details on the solvent effects and crystal structures of the salt were unknown.[14] Racemic **3** was synthesized from ethyl benzoylformate by a Grignard reaction followed by saponification, according to a reported method.[15] The results of the enantioseparation of **3** with various solvents are shown in Table 2. All of the tested solvents, as well as methanol, consistently afforded (*R*)-**3**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol as the less-soluble salt without inclusion of the solvent molecules. The resolution efficiencies were high regardless of the solvent and the best result of 0.72 was achieved by recrystallization from ethanol. Single crystals of the less-soluble salt were grown from its ethanol solution and the structure is shown in Figure 4. The (*R*)-**3**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol salt was non-solvated and the hydrogen-bonded columnar structure was constructed. The space group was $P2_12_12_1$ and the neighboring columns were packed efficiently in

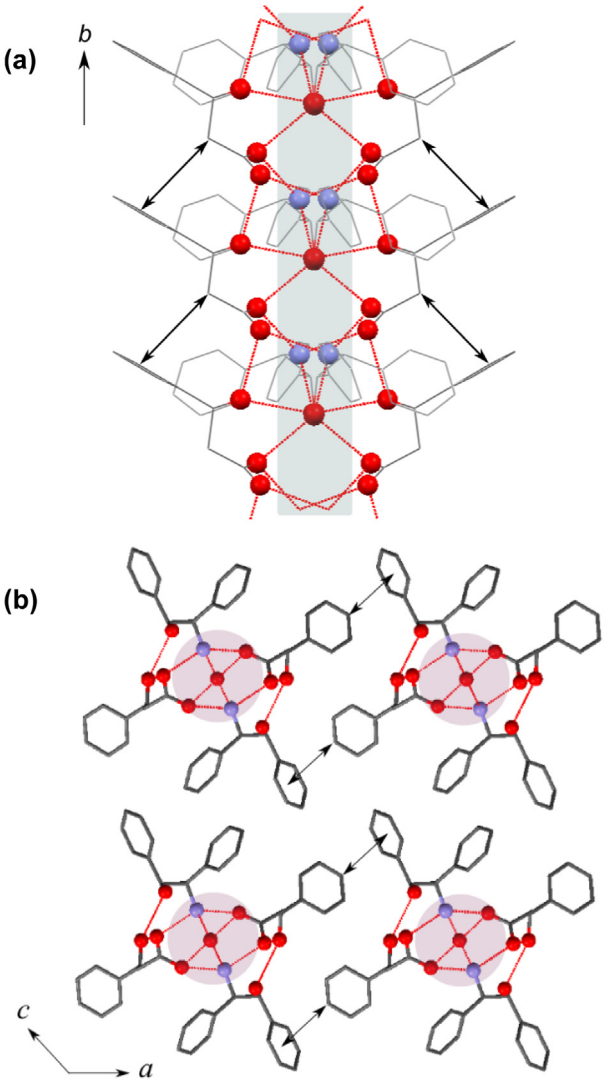

Figure 2. Crystal structure of the (*S*)-**2**·(1*S*,2*R*)-2-amino-1,2-diphenylethanol·0.5H_2O salt. (a) Side view of the columnar structure. (b) Top view of the columnar structures. Oxygen atom and nitrogen atoms are presented with red and blue balls. The dotted lines and arrows show hydrogen bonds and CH/π interactions, respectively.

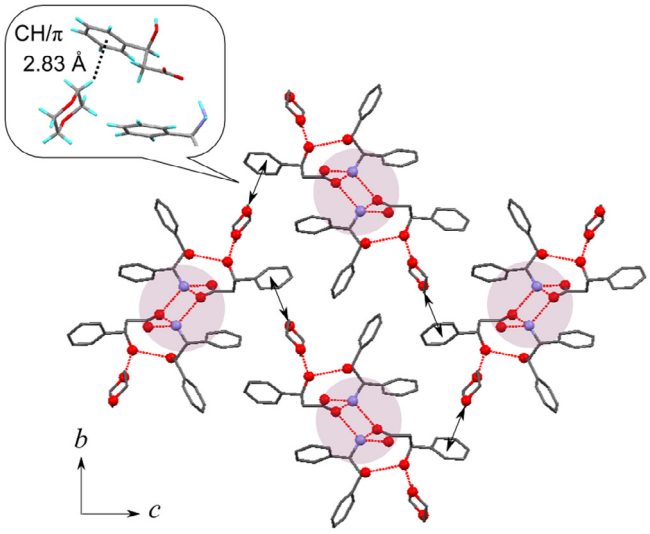

Figure 3. Crystal structure of the (*S*)-**2**·(1*S*,2*R*)-2-amino-1,2-diphenylethanol·1,4-dioxane salt. Oxygen atom and nitrogen atoms are presented with red and blue balls. The dotted lines and arrows show hydrogen bonds and CH/π interactions, respectively.

an anti-parallel fashion. The presence of a methyl group on the stereogenic center of **3**, instead of a hydrogen atom as in mandelic acid drastically facilitated molecular packing without inclusion of solvent molecules. Although the structural information of the corresponding more-soluble (*S*)-**3**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol salt is missing, the dense molecular packing in (*R*)-**3**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol salt resulted in the highly efficient enantioseparation of **3**.

Finally, (1*R*,2*S*)-2-amino-1,2-diphenylethanol was applied as a resolving agent for the enantioseparation of 2-hydroxy-3-phenylpropionic acid **4**. The chemical enantioseparation of racemic **4** has been reported with some resolving agents such as L-phenylglycinol or dehydroabietylamine.[16] The results are summarized in Table 3. Crystallization from water or methanol afforded the (*R*)-**4**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol salt, while aqueous alcohols, 2-propanol, and 1,4-dioxane preferentially afforded the (*S*)-**4**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol salt. Solvent-induced chirality switching was achieved and both diastereomeric salts were obtained with quite high efficiencies, up to 0.75 for the (*R*)-salt from water and 0.84 for the (*S*)-salt from 2-propanol (entries 1 and 6). It is noteworthy that the switching in the stereochemistry appeared to be independent of the dielectric constant of the crystallization solvents and almost enantiopure (*R*)-**4** was obtained by a single crystallization from water. It was suggested from ^{1}H NMR and thermogravimetric analysis (TGA) that the crystallization solvents were incorporated in the deposited salts and the salt/solvent ratio was 1:2 for water and 1:1 for 2-propanol, respectively. Both salts showed a weight decrease during 70–100 °C before decomposition above 180 °C (Fig. 5). These included solvent molecules should stabilize each diastereomeric salt to change their relative solubilities. Crystallization from 50% methanol or 50% ethanol also preferentially afforded the *S*-salt despite the low ratio of the included solvent (entries 2 and 4). This is probably due to the gradual desorption of the included alcohols from the salt under ambient conditions.

During the crystallization from 50% methanol (entry 2), a white powdery solid precipitated soon after cooling and several days later, a small amount of colorless needle-like crystals appeared from the solution. The two solids were manually separated after filtration and their HPLC analysis showed that the former powdery solid was the (*S*)-**4** rich salt (73% yield, 75%ee) whereas the latter crystalline solid was the (*R*)-**4**-rich salt (2% yield, 75%ee). The X-ray structural analysis of the latter needle-like crystal showed that the salt was hydrated and (*R*)-**4**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol·2H_2O was formed (Fig. 6), which was in accordance with the TGA result mentioned above. In contrast to the other salt crystals, (*R*)-**4** and (1*R*,2*S*)-2-amino-1,2-diphenylethanol were arranged to form a sheet-like hydrogen-bonding network, together with two water molecules (w1 and w2). The occurrence of such a sheet-like network rather than a columnar one is attributable to the increased hydrophilic region by the incorporation of water molecules and the remote hydrophobic phenyl group of **4** in comparison with other acids.[17] The space group was $P2_1$ and the

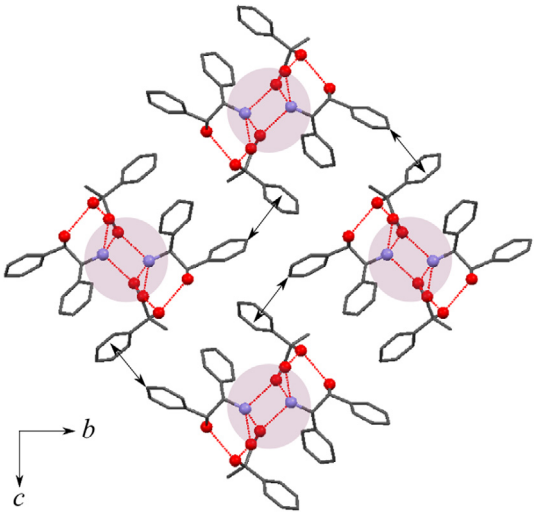

Figure 4. Crystal structure of (*R*)-**3**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol salt. Oxygen atom and nitrogen atoms are presented with red and blue balls. The dotted lines and arrows show hydrogen bonds and CH/π interactions, respectively.

Table 2
Enantioseparation of *rac*-**3** with (1*R*,2*S*)-2-amino-1,2-diphenylethanol[a]

Entry	Solvent (L/mol)	Solvent inclusion[b] (%)	Yield[c] (%)	Ee[d] (%)	Eff.[e]
1	H_2O (19)	–	75	90 (*R*)	0.67
2	MeOH (4)	Not included	37	92 (*R*)	0.34
3	50% EtOH (6)	Not included	54	85 (*R*)	0.46
4	EtOH (10)	Not included	81	89 (*R*)	0.72
5	THF (9)	Not included	32	92 (*R*)	0.29
6	1,4-Dioxane (7)	Not included	39	79 (*R*)	0.31

[a] *rac*-**3** and (1*R*,2*S*)-2-amino-1,2-diphenylethanol (1.0 mmol) were used.
[b] The solvent inclusion was determined by ^{1}H NMR analysis.
[c] Yield is based on the half of the salt amount.
[d] Ee was determined by HPLC analysis after derivatization to its methyl ester.
[e] Eff. = Yield (%) × Ee (%)/10,000.

Table 3
Enantioseparation of *rac*-**4** with (1*R*,2*S*)-2-amino-1,2-diphenylethanol[a]

Entry	Solvent (L/mol)	Solvent inclusion[b] (%)	Yield[c] (%)	Ee[d] (%)	Eff.[e]
1	H_2O (13)	200	77	98 (*R*)	0.75
2	50% MeOH (14)	Not included	75	71 (*S*)	0.54
3	MeOH (1.5)	Not included	66	69 (*R*)	0.46
4	50% EtOH (15)	20	58	95 (*S*)	0.55
5	EtOH (9)	15	96	9 (*S*)	0.09
6	2-PrOH (25)	100	92	91 (*S*)	0.84
7	1,4-Dioxane (1.5)	50	86	37 (*S*)	0.32

[a] *rac*-**4** and (1*R*,2*S*)-2-amino-1,2-diphenylethanol (1.0 mmol) were used.
[b] The solvent inclusion was determined by ^{1}H NMR analysis.
[c] Yield is based on the half of the salt amount.
[d] Ee was determined by HPLC analysis after derivatization to its methyl ester.
[e] Eff. = Yield (%) × Ee (%)/10,000.

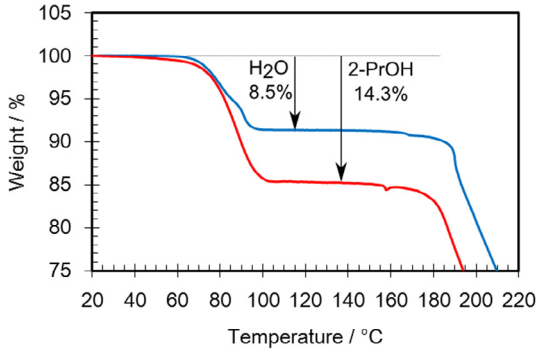

Figure 5. TGA charts of **4**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol salt crystallized from water (blue) and 2-propanol (red). Heating rate was 10 °C/min.

neighboring sheets were stacked in an antiparallel arrangement. The rough surface of the sheet structure could be unfavorable for efficient stacking, which resulted in delayed crystallization of the (*R*)-**4**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol·2H_2O salt. The melting points of both diastereomeric salts indicated that the (*R*)-**4**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol salt (159–161 °C) is thermodynamically more stable than the (*S*)-**4**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol salt (148–150 °C). Crystallization from methanol (entry 3) preferentially afforded the *R*-salt probably due to high solubility and delayed crystallization of the salt. Unfortunately, recrystallization of the (*S*)-**4**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol salt from various alcohols afforded only a powdery solid and the detailed structural information is unknown. However, it was clarified that the incorporation of the crystallization solvents induced chirality switching in the enantioseparation of **4**.

3. Conclusion

We have shown that three regioisomers of hydroxyphenylpropionic acid **2**–**4** were successfully enantioseparated via diastereomeric salt formation with (1*R*,2*S*)-2-amino-1,2-diphenylethanol. During the enantioseparation of 3-hydroxy-3-phenylpropionic acid **2**, the (*S*)-**2** salt was consistently obtained and the chirality switching phenomenon was not induced despite the incorporation of the crystallization solvents in the salt crystals. The salt of (*R*)-2-hydroxy-2-phenylpropionic acid **3** was obtained with high efficiency (up to 0.72), regardless of the solvents. On the other hand, both enantiomers of 2-hydroxy-3-phenylpropionic acid **4** were obtained with high efficiencies (0.84 and 0.75) by a single crystallization of the *rac*-**4**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol salt from water and 2-propanol, respectively. The mechanism of their efficient enantioseparation and the relationship with the chirality switching have been explained based on the crystallographic analysis of the salts. Herein we have expanded upon the scope of the chirality switching method, which contributes to the production of all four isomers of hydroxyphenylpropionic acid in an enantiopure form.

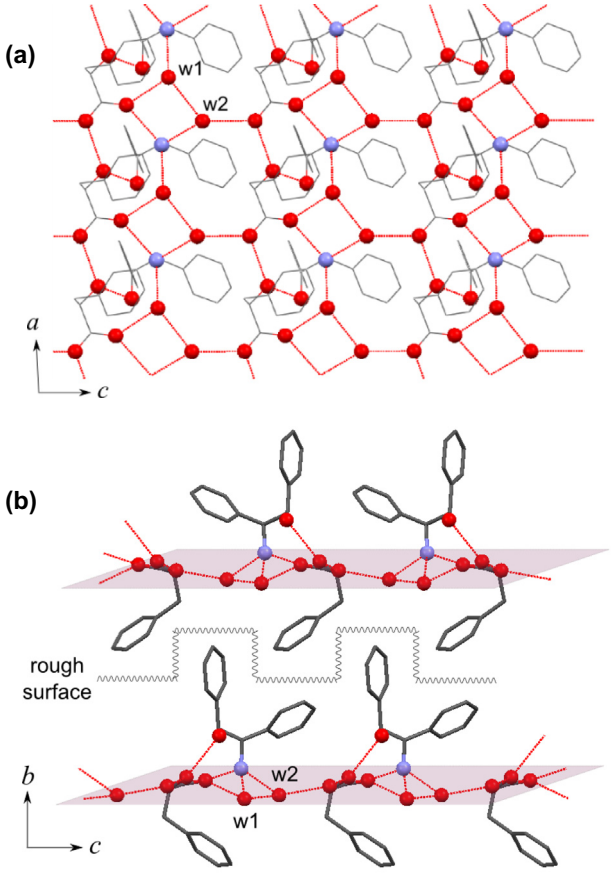

Figure 6. Crystal structure of (*R*)-**4**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol·2H_2O salt. (a) Viewed from the *b* axis. The water molecules (w1 and w2) assisted the structure. (b) Viewed from the *a* axis. Sheet-like hydrogen-bonding networks are presented as shaded. Oxygen atom and nitrogen atoms are presented with red and blue balls. The dotted lines and arrows show hydrogen bonds.

4. Experimental

4.1. General

All commercially available reagents were used as received unless noted. Dried solvents were prepared by distillation before use. Racemic hydroxycarboxylic acids **2** and **3** were synthesized

according to the literatures. All ^{1}H NMR spectra were recorded on Bruker Avance 300 MHz spectrometer. IR spectra were measured on a JASCO FT/IR-460 spectrometer as KBr pellets. Melting points were recorded on a MEL-TEMP apparatus and reported uncorrected. TG-DTA analysis was performed on a SII EXSTAR 6000 system at a heating rate of 10 °C·min^{-1}. Enantiomeric excesses were determined by HPLC analyses with a Daicel Chiralcel OD-3 column with detection at 254 nm. Optical rotations were measured with a JASCO DIP-370 polarimeter.

4.2. Procedure for the enantioseparation of carboxylic acids (2–4) via diastereomeric salt formation with (1*R*,2*S*)-2-amino-1,2-diphenylethanol

Equimolar amounts (1 mmol) of the racemic carboxylic acid and (1*R*,2*S*)-2-amino-1,2-diphenylethanol were dissolved in methanol. After concentration of the solution, the white solid was dissolved in an appropriate solvent by heating and cooled to ambient temperature to recrystallize the salt. The precipitated solid was filtered and dried overnight. The yield of the salt was calculated based on the ^{1}H NMR data considering the amount of included solvent. A part of the salt was decomposed by addition of 1 M aqueous hydrochloric acid solution and the aqueous layer was extracted with diethyl ether. After drying over anhydrous sodium sulfate, the organic layer was concentrated to obtain carboxylic acids as a white solid. The liberated acids were quantitatively derivatized to their methyl esters by the reaction with trimethylsilyldiazomethane in methanol/toluene to determine the enantiomeric excess values by chiral HPLC analysis. The absolute configuration was assigned by comparison of the elution order in HPLC with literature data.

Methyl ester of **2**: Daicel Chiralcel OD-3, hexane/2-propanol = 90:10, 1.0 mL/min; $t_r(S)$ = 10.4 min, $t_r(R)$ = 16.6 min.[18] Methyl ester of **3**: Daicel Chiralcel OD-3, hexane/2-propanol = 99:1, 1.0 mL/min; $t_r(S)$ = 16.4 min, $t_r(R)$ = 18.2 min.[19] Methyl ester of **4**: Daicel Chiralcel OD-3, hexane/2-propanol = 99:1, 1.0 mL/min; $t_r(R)$ = 36.0 min, $t_r(S)$ = 39.0 min.[20]

The diastereomeric salts for the measurements of the physical and spectroscopic data were prepared by evaporation of the solutions containing equimolar amounts of enantiopure (or racemic) carboxylic acids and enantiopure 2-amino-1,2-diphenylethanol in methanol. *rac*-**2**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol: Mp: 173–175 °C. IR (KBr): ν_{max} = 3246, 2918, 1574, 1496, 1454, 1393, 1206, 1050, 766 cm^{-1}. $[\alpha]_D^{18}$ = −75.7 (*c* 1.00, methanol). (*S*)-**2**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol: Mp: 177–179 °C. IR (KBr): ν_{max} = 3450, 2888, 1574, 1493, 1389, 1207, 1046, 761 cm^{-1}. $[\alpha]_D^{18}$ = −97.7 (*c* 0.94, methanol). (*S*)-**2**·(1*S*,2*R*)-2-amino-1,2-diphenylethanol: Mp: 149–150 °C. IR (KBr): ν_{max} = 3241, 3033, 1634, 1568, 1454, 1387, 1211, 1082 cm^{-1}. $[\alpha]_D^{18}$ = +33.6 (*c* 0.81, methanol).

rac-**3**·(1*R*,2*S*)-2-Amino-1,2-diphenylethanol: Mp: 155–157 °C. IR (KBr): ν_{max} = 3377, 3033, 1560, 1453, 1393, 1333, 1281, 1209, 1149, 1099, 768, 737, 699, 654, 569 cm^{-1}. $[\alpha]_D^{20}$ = −79.6 (c 1.00, methanol). (*S*)-**3**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol: Mp: 163–165 °C. IR (KBr): ν_{max} = 3388, 3034, 1560, 1495, 1454, 1389, 1336, 1209, 1149, 1056, 699, 655, 569 cm^{-1}. $[\alpha]_D^{20}$ = −61.9 (*c* 1.00, methanol). (*S*)-**3**·(1*S*,2*R*)-2-amino-1,2-diphenylethanol: Mp: 176–177 °C. IR (KBr): ν_{max} = 3473, 3366, 2925, 1623, 1542, 1451, 1404, 1381, 1102, 1048, 706, 698, 578 cm^{-1}. $[\alpha]_D^{20}$ = +106.5 (*c* 1.00, methanol).

rac-**4**·(1*R*,2*S*)-2-Amino-1,2-diphenylethanol: Mp: 142–143 °C. IR (KBr): ν_{max} = 3032, 2917, 1566, 1454, 1409, 1204, 1085, 767, 698 cm^{-1}. $[\alpha]_D^{18}$ = −77.5 (*c* 0.99, methanol). (*S*)-**4**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol: Mp: 148–150 °C. IR (KBr): ν_{max} = 3032, 2910, 1568, 1454, 1408, 1204, 1086, 767, 704, 570 cm^{-1}. $[\alpha]_D^{18}$ = −99.2 (*c* 1.00, methanol). (*S*)-**4**·(1*S*,2*R*)-2-amino-1,2-diphenylethanol: Mp: 159–161 °C. IR (KBr): ν_{max} = 3281, 3033, 2926, 1615, 1562, 1453, 1407, 772, 700, 570 cm^{-1}. $[\alpha]_D^{18}$ = +50.5 (*c* 1.00, methanol).

4.3. Single crystal X-ray analysis

Single crystals of the diastereomeric salts suitable for X-ray diffraction analysis were prepared by recrystallization or slow evaporation of the solvent from their solutions. X-ray crystallographic data were collected on a Bruker Smart APEX II diffractometer with a graphite monochromated Mo Kα radiation. The structures were solved by a direct method SIR 2004 and refined by SHELXL-2013 programs.[21] Detailed data is summarized in the Supporting Information (Table S1). Crystallographic data for the structures in this paper (CCDC 1519789–1519793) 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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A. Supplementary data

Supplementary data (detailed experimental procedures, summary of crystallographic data (Table S1), a copy of ^{1}H NMR spectrum of (*S*)-**4**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol·2-propanol salt (Fig. S1), and TGA charts of **4**·(1*R*,2*S*)-2-amino-1,2-diphenylethanol salts (Figs. S2 and S3)) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2017.02.011.

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