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Halogen-Bonding Interaction Stabilizing Cluster-type Diastereomeric Salt Crystals

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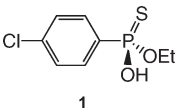
ABSTRACT: *O*-Ethyl 4-chlorophenylphosphonothioic acid (**1**) was newly synthesized and applied as a chiral selector for the enantioseparation of racemic 1-(4-halophenyl)ethylamines (halo = F, Cl, Br, I; **2a**−**d**) through diastereomeric salt formation. The phosphonothioic acid **1** showed an excellent chirality-recognition ability for the fluorinated and iodinated amines **2a** and **2d** with the dramatic switch of the absolute configuration of the enantio-enriched isomers in the deposited salts from *R* for the amine **2a** to *S* for the amine **2d**. The X-ray crystallographic analyses of the four pairs of diastereomeric salts revealed that halogen-bonding interaction in the salt crystals plays a very important role for the switch.

Introduction

In the middle of 1960s, Schmidt and his co-workers have pointed out that short Cl···Cl contact, the so-called chloro effect, plays an important role in controlling the photodimerization reaction of *trans*-cinnamic acid derivatives.[1] On the basis of a statistical study on a database of crystals having Cl···Cl contact(s), Desiraju and Parthasarathy have proposed that the short Cl···Cl contact is originated from specific attractive intermolecular force between the chlorine atoms.[2] In contrast, Price et al. have suggested by means of theoretical calculations that short Cl···Cl contact is caused by anisotropic repulsion between the chlorine atoms, depending on the C−Cl···Cl angle.[3] Although the physical origin of short Cl···Cl contact is still controversy at present, it has been generally accepted that short contact frequently exists between halogen atoms and between a carbon-bonded halogen atom and an electronegative atom in molecular crystals. For such intermolecular interactions, the terms of "halogen-bonding interaction" is introduced, which was named after very popular terms of hydrogen-bonding interaction.[4] Halogen-bonding interaction has been attracting much attention in many fields, especially in the crystal engineering of organic and organometallic compounds; from the viewpoint of the construction of molecular assemblies utilizing nonbonding interactions, halogen-bonding interaction is doubtlessly one of the major forces to control molecular arrangement and packing in organic and organometallic crystals today.[5]

On the other hand, we have recently found that there are two types of crystals, column-type and cluster-type crystals, for the diastereomeric salts of racemic 1-phenylethylamine derivatives with enantiopure *O*-ethyl phenylphosphonothioic acid and its analogues.[6] The column-type crystals are composed of 2_1 columns with an infinite helical hydrogen-bonding network, while the cluster-type crystals consist of clusters with a finite globular hydrogen-bonding network. As far as we examined by X-ray crystallography, one of a pair of the diastereomeric salts (less- and more-soluble salts) was either a column-type crystal or a cluster-type crystal. Although column-type crystals are commonly observed in both less- and more-soluble diastereomeric salts of racemic amines with enantiopure monocarboxylic acids and in those of racemic monocarboxylic acids with enantiopure amines/amino alcohols, no cluster-type crystal has been reported for diastereomeric salts until our discovery.[6a] Clusters in the cluster-type crystals are commonly composed of four amine molecules and four acid molecules to form a globular hydrogen-bonding network in the center of the clusters. The alkyl and aryl groups of the amine and phosphonothioic acid molecules surround the surface of the clusters to make them hydrophobic. As a result, in the cluster-type crystals, clusters bind with each other by relatively weak interactions such as van der Waals and CH/π interactions, which would mainly determine the stability of the crystals. On the basis of these results, we considered that upon introducing a halogen atom on both of the phenyl groups of racemic 1-phenylethylamine and the enantiopure phosphonothioic acid, the more tight packing of clusters would be realized by halogen-bonding interaction as well as van der Waals and CH/π interactions. Herein, we report the synthesis and application of enantiopure *O*-ethyl 4-chlorophenylphosphonothioic acid (**1**) and the role of halogen-bonding interaction in the stabilization of the corresponding diastereomeric salts.



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Experimental Section

General Procedure. NMR spectra were recorded on a Varian Mercury 300 instrument. IR spectra were recorded on a Jasco FT/IR-480 instrument. HPLC analyses were performed on a Daicel Chiralcel column using a Jasco PU-2080i pump, a Jasco PU-2075 UV detector, and a Hitachi D-2500 Chromato-Integrator. Melting points were measured using a Yamato Scientific MP-21.

Racemic amines **2** were synthesized according to the procedure previously reported.[7]

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Synthesis of Racemic *O*-Ethyl 4-Chlorophenylphosphonothioic Acid (Racemic 1). To a solution of 1-bromo-4-chlorobenzene (19.9 g, 104 mmol) in dry Et_2O (150 mL) was added dropwise 1.6 M butyllithium in hexane (65.0 mL, 104 mmol) at −78 °C under argon atmosphere, and the mixture was stirred at 0 °C for 40 min. Commercially available diethoxyphosphonothioyl chloride (12.6 mL, 80 mmol) in dry ether (50 mL) was then added dropwise to the mixture at −78 °C. The reaction mixture was stirred at rt for 1.5 h and then cooled with an ice bath, and H_2O (30 mL) was slowly added to the mixture. After removal of the solvent under reduced pressure, saturated ammonium chloride solution (120 mL) was added to the residue, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude *O*,*O*′-diethyl 4-chlorophenylphosphonothioate (22.4 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, J_{H-H} = 7 Hz, 6H), 4.11 (m, 4H), 7.36 (m, 2H), 7.84 (m, 2H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 85.12.

A solution of crude *O*,*O*′-diethyl 4-chlorophenylphosphonothioate (22.4 g) thus obtained in a mixture of 8 M aqueous KOH solution (160 mL) and EtOH (160 mL) was refluxed for 20 h. After removal of most EtOH under reduced pressure, 12 M aqueous HCl solution (120 mL) was slowly added to the mixture at 0 °C. The resultant solution was extracted with CH_2Cl_2 (7 × 80 mL), and then the combined organic layers were extracted with 1 M aqueous KOH solution (3 × 100 mL). The combined aqueous solutions were further acidified with 5 M aqueous HCl solution (120 mL) and extracted with CH_2Cl_2 (4 × 80 mL). Then, the combined extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude racemic *O*-ethyl 4-chlorophenylphosphonothioic acid (14.3 g).

A mixture of the crude *O*-ethyl 4-chlorophenylphosphonothioic acid (14.3 g) and dicyclohexylamine (10.9 g, 60 mmol) in $CHCl_3$ (65 mL) was refluxed to give a clear solution, and then the solution was gradually cooled to rt to give chemically pure dicyclohexylammonium *O*-ethyl 4-chlorophenylphosphonothioate (20.4 g) as a white solid. The second crop from chloroform/hexane (20 mL/10 mL) and the third crop from chloroform/hexane (15 mL/15 mL) were 2.33 and 0.31 g, respectively. The total yield was 23.04 g (55 mmol, 53% from 1-bromo-4-chlorobenzene used).

Mp 190.5−191.0 °C. IR (KBr) 2945, 2857, 1577, 1450, 1386, 1122, 1083, 1042, 928, 751, 646 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (m, 6H), 1.21 (t, J_{H-H} = 7 Hz, 3H), 1.61 (m, 10H), 2.04 (d, J_{H-H} = 11 Hz, 4H), 2.96 (br, 2H), 3.72 (m, 1H), 4.02 (m, 1H), 7.34 (m, 2H), 7.85 (m, 2H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 65.57.

The salt (20.7 g, 48 mmol) was decomposed with 1 M aqueous KOH solution (200 mL), and the aqueous solution was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with 1 M aqueous KOH solution (100 mL). To the combined alkaline solutions was added 3 M aqueous HCl solution (150 mL), and the mixture was extracted with CH_2Cl_2 (4 × 80 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give chemically pure racemic **1** (11.8 g, 47 mmol, 98%) as a brown oil.

IR (neat) 2983, 1584, 1482, 1390, 1089, 1032, 959, 759 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, J_{H-H} = 7 Hz, 3H), 4.17 (dq, J_{P-H} = 9 Hz, J_{H-H} = 7 Hz, 2H), 6.14 (br, 1H), 7.44 (m, 2H), 7.84 (m, 2H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 78.87.

Synthesis of Enantiopure 1. To a solution of racemic **1** (12.5 g, 53 mmol) in AcOEt (300 mL) was added (1*S*,2*R*)-(−)-1-amino-2-indanol (**AI**; 5.49 g, 37 mmol, 0.7 equiv), and the mixture was refluxed for 2 h, gradually cooled down to −10 °C with stirring, and then stirred at the temperature for 3 h. The deposited salt was collected by filtration using a membrane filter (T050A047A, ADVANTEC). The salt was recrystallized three times from AcOEt (200 mL each) to afford diastereopure (*R*)-**1**·(1*S*,2*R*)-**AI** (5.81 g, 15 mmol, 57% yield based on a half amount of racemic **1** used).

Mp 189.5−190.0 °C. IR (KBr) 3536, 3119, 2970, 2900, 2630, 1526, 1479, 1385, 1123, 1074, 1036, 941, 821, 752, 643, 627 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.05 (t, J_{H-H} = 7 Hz, 3H), 2.93 (dd, J_{H-H} = 16 Hz, 4 Hz, 1H), 3.11 (dd, J_{H-H} = 16 Hz, 6 Hz, 1H), 3.68 (m, 2H), 4.58 (m, 2H), 5.91 (br, 1H), 7.30 (m, 6H), 7.52 (d, J_{H-H} = 7 Hz, 1H), 7.72 (dd, J_{H-H} = 12 Hz, 7 Hz, 1H), 8.34 (br, 3H); ^{31}P NMR (121 MHz, DMSO-d_6) δ 64.86.

To the diastereomeric salt thus obtained was added 1 M aqueous KOH solution (100 mL), and the solution was extracted with Et_2O (4 × 50 mL). The aqueous layer was acidified with 3 M aqueous HCl solution (40 mL) and then extracted with Et_2O (4 × 50 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford enantiopure **1** (3.42 g, 14 mmol, 55% yield based on a half amount of racemic **1** used) as a colorless oil. The enantiomeric excess (ee) of **1** thus obtained was determined by a HPLC analysis after **1** was converted into the corresponding *S*-methyl ester with trimethylsilyldiazomethane (Daicel Chiralcel OD-H; eluent, hexane/2-propanol = 98:2; flow rate, 1.0 mL/min; t_1 [(*R*)-isomer] = 18 min, t_2 [(*S*)-isomer] = 22 min; ee, >99%).

$[\alpha]_D^{21}$ = +7.7° (*c*5.3, MeOH); IR (neat) 2984, 1584, 1482, 1390, 1124, 1089, 1034, 961, 759 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, J_{H-H} = 7 Hz, 3H), 4.20 (dq, J_{P-H} = 10 Hz, J_{H-H} = 7 Hz, 2H), 7.43 (m, 2H), 7.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.50, 133.58, 132.16, 132.00, 128.56, 128.35, 62.76, 16.07; ^{31}P NMR (121 MHz, $CDCl_3$) δ 78.75.

Anal. calcd for $C_8H_{10}ClO_2PS$: C, 40.60; H, 4.26. Found: C, 40.57; H, 4.21.

A General Procedure for the Enantioseparation of Racemic 1-(4-Halophenyl)ethylamines (2) with (*R*)-1. A mixture of enantiopure **1** and racemic **2** (1 equiv) in Et_2O or Et_2O/hexane (see Table 1) was stirred at rt for 4 h. The deposited salt was collected by filtration using a membrane filter (T050A047A, ADVANTEC). The yield of the salt was evaluated on the basis of a half amount of racemic **2**. A portion of the salt thus obtained was treated with small amounts of 1 M aqueous KOH solution and Et_2O, and the ethereal layer was concentrated under reduced pressure to give a sample for the determination of the ee of **2** by a HPLC analysis (Daicel Crownpak CR(+); eluent, $HClO_4$ aq. (pH 2) for **2a**, **2b**, $HClO_4$ aq. (pH 2)/MeOH = (95/5) for **2c** and $HClO_4$ aq. (pH 2)/MeOH = (98/15) for **2d**).

Preparation of the Single Crystals of the (*R*)-1·2 Salts. The single crystals of the (*R*)-**1**·**2** salts were prepared by a vapor diffusion method. A small vial containing a solution of the (*R*)-**1**·**2** salt (15 mg), which was obtained from (*R*)-**1** and individually prepared enantiopure (*R*)- or (*S*)-**2**,[7] in ethyl acetate (3 mL) was placed in a loosely sealed vial containing hexane (3 mL) to gradually bring into vapor-equilibrium.

X-ray Crystallographic Analyses of the Diastereopure (*R*)-1·2 Salts. X-ray data were collected on a Mac Science DIP2000 or RIGAKU Mercury CCD system diffractometer using Mo X-ray. The camera length, which is the distance between the sample and the detector, was varied from 70 to 80 mm, depending on the sample. Crystal structures were solved and refined using the SIR 92[8] or SHELX97[9] program. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were placed in calculated positions refined using idealized geometries and assigned fixed isotropic displacement parameters.

Results and Discussion

Synthesis and Absolute Configuration of Enantiopure *O*-Ethyl 4-Chlorophenylphosphonothioic Acid (1). Racemic *O*-ethyl 4-chlorophenylphosphonothioic acid (racemic **1**) could be easily prepared from commercially available 1-bromo-4-chlorobenzene in 52% total yield through lithiation, condensation, hydrolysis, ammonium salt formation, and decomposition of the salt, as shown in Scheme 1. In order to enantioseparate racemic **1**, we tried to use enantiopure 1-phenylethylamine (**PEA**), *erythro*-2-amino-1,2-diphenylethanol (**ADPE**), and *cis*-1-amino-2-indanol (**AI**). Among them, **AI** gave a crystalline salt with **1** upon stirring the mixture in ether, whereas **PEA** and **ADPE** gave no crystal under similar conditions; **1** with >99% ee was obtained in 55% yield (based on a half amount of racemic **1** used) by applying (1*S*,2*R*)-**AI** as a resolving agent.

The elution order of the enantiomers of 1-(4-fluorophenyl)ethylamine (**2a**) in a chiral HPLC analysis has been

correlated with their absolute configurations, as we previously reported.[7] On the basis of the correlation, the absolute configuration of **2a**, preferentially incorporated in the less-soluble diastereomeric salt, was deduced to be *R*. On the other hand, the X-ray crystallographic analysis of the less-soluble salt crystal revealed that the absolute configuration of enantiopure **1** used was *R* (Figure 1).

Chirality-Recognition Ability of *O*-Ethyl (*R*)-4-Chlorophenylphosphonothioic acid ((*R*)-1) for Racemic 1-(4-Halophenyl)ethylamines (2). The results of the enantioseparation of racemic 1-(4-halophenyl)ethylamines (halo = F, Cl, Br, I; **2a**−**d**) with *O*-ethyl (*R*)-4-chlorophenylphosphonothioic acid ((*R*)-**1**) are summarized in Table 1. The phosphonothioic acid (*R*)-**1** showed an excellent chirality-recognition ability for **2a** and **2d**.

The extent of chirality recognition by a selector via the diastereomeric salt formation is known to strongly depend on the difference in solubility between a pair of diastereomeric salt crystals (less- and more-soluble crystals); with increasing the difference, the ee value of a target acid/amine in a salt deposited should become larger, while the ee value should gradually reach to zero with decreasing the difference. From such a point of view, the present results are of interest; although the amines **2b** and **2c** were not enriched (12% ee and 0% ee, respectively), the amines **2a** and **2d** were highly enriched (92% ee and 88% ee, respectively) with the dramatic switch of the absolute configuration of the enantio-enriched isomers from *R* for the amine **2a** to *S* for the amine **2d**. These results suggest that the (*R*)-**1**·(*R*)-**2a** crystal is much less soluble than the (*R*)-**1**·(*S*)-**2a** crystal, while the (*R*)-**1**·(*R*)-**2d** crystal is much more soluble than the (*R*)-**1**·(*S*)-**2d** crystal, and that the solubilities of the (*R*)-**1**·(*R*)-**2b** and (*R*)-**1**·(*R*)-**2c** crystals are comparable to those of the (*R*)-**1**·(*S*)-**2b** and (*R*)-**1**·(*S*)-**2c** crystals, respectively.

Factors for the Stabilization of the (*R*)-1·(*R*)-2 and (*R*)-1·(*S*)-2 Crystals. In order to understand the difference in stability between the (*R*)-**1**·**2** crystals, we carried out X-ray

Scheme 1. Synthesis of Racemic 1

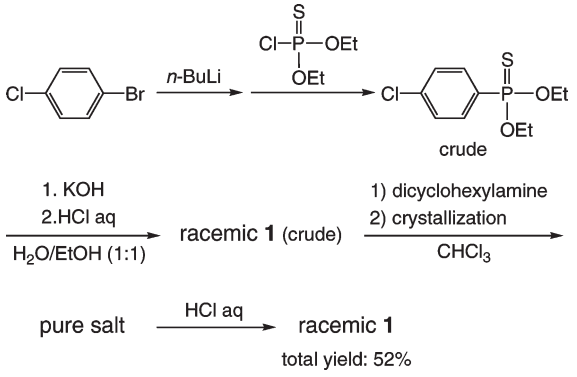
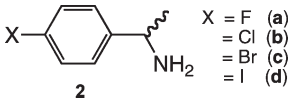


Table 1. Enantioseparation of Racemic 2 by (*R*)-1



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amine	yield (%)	ee (%)[a]	solvent for crystallization[b] Et_2O/hexane (mL/mL)
2a	64	92 (*R*)	3.2/26.0
2b	87	12 (*R*)	1.6/0
2c	98	0	1.6/0
2d	58	88 (*S*)	3.2/1.6

[a] The sign in the parentheses is the absolute configuration of the amine. [b] Normalized for a 1-mmol scale.

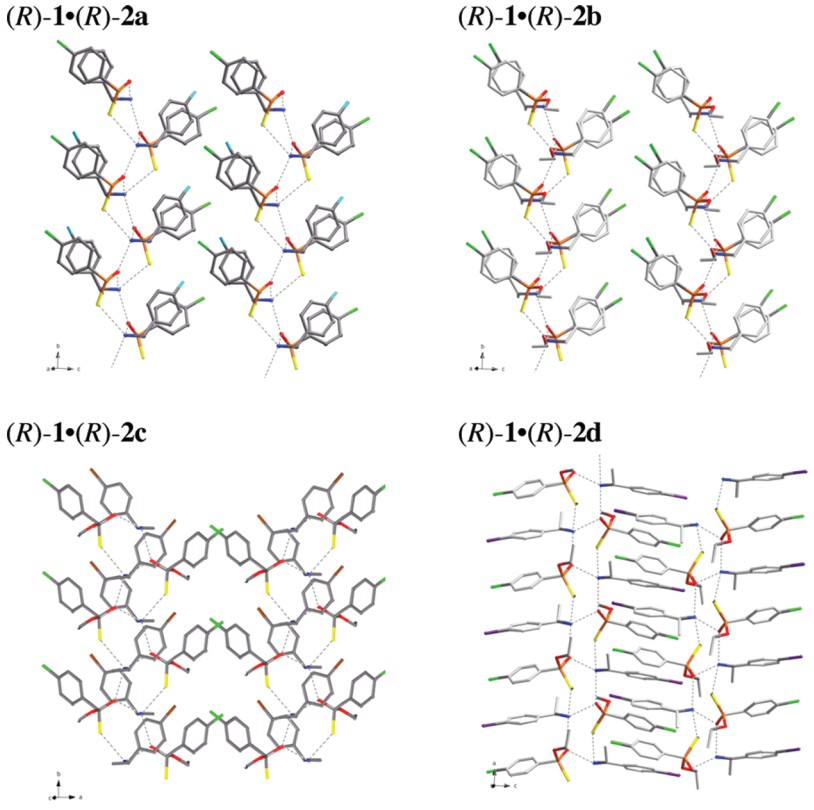

Figure 1. Crystal structures of (*R*)-**1**·(*R*)-**2** salts. Dotted lines indicate hydrogen bonds.

Table 2. Crystal Data for (*R*)-1·(*R*)-2 and (*R*)-1·(*S*)-2 Salt Crystals

	(*Rp*)-**1**·(*R*)-**2a**	(*Rp*)-**1**·(*R*)-**2b**	(*Rp*)-**1**·(*R*)-**2c**	(*Rp*)-**1**·(*R*)-**2d**
formula	$C_{16}H_{20}ClFNO_2PS$	$C_{16}H_{20}Cl_2NO_2PS$	$C_{16}H_{20}ClBrNO_2PS$	$C_{16}H_{20}ClINO_2PS$
formula weight	375.82	392.28	436.73	483.73
crystal system	monoclinic	monoclinic	monoclinic	orthorhombic
space group	*C*2	*C*2	*C*2	$P2_12_12_1$
a/Å	22.30(3)	22.328(2)	26.89(2)	7.633(3)
b/Å	7.399(10)	7.4350(5)	7.463(4)	11.733(5)
c/Å	11.91(2)	13.167(2)	21.551(12)	21.156(9)
α/°	90	90	90	90
β/°	108.738(6)	112.634(3)	115.103(2)	90
γ/°	90	90	90	90
V/Å^3	1860.1(44)	2017.5(3)	3917.0(36)	1894.8(14)
Z	4	4	4	4
crystal habit	needle	needle	needle	needle
density/g cm^{-3}	1.342	1.291	1.481	1.696
temperature/K	103	273	103	103
reflns collected	4788	1965	17119	4998
reflns used in refinement	3599	1180	14721	4937
GOF	1.309	1.028	0.892	1.118
R	0.0650	0.0500	0.0380	0.0301
R_w	0.0800	0.0570	0.0520	0.0762
	(*Rp*)-**1**·(*S*)-**2a**	(*Rp*)-**1**·(*S*)-**2b**	(*Rp*)-**1**·(*S*)-**2c**	(*Rp*)-**1**·(*S*)-**2d**
formula	$C_{16}H_{20}ClFNO_2PS$	$C_{16}H_{20}Cl_2NO_2PS$	$C_{16}H_{20}ClBrNO_2PS$	$C_{16}H_{20}ClINO_2PS$
formula weight	375.82	392.28	436.73	483.73
crystal system	monoclinic	tetragonal	tetragonal	triclinic
space group	$P2_1$	$P4_12_12$	$P4_12_12$	*P*1
a/Å	13.209(5)	13.4500(4)	13.4890(5)	12.788(3)
b/Å	21.994(8)	13.4500(4)	13.4890(5)	13.069(3)
c/Å	13.600(5)	45.1410(13)	45.241(2)	25.533(6)
α/°	90	90	90	80.684(9)
β/°	106.645(2)	90	90	75.203(8)
γ/°	90	90	90	80.957(9)
V/Å^3	3785.5(23)	8166.1(4)	8231.7(4)	4041.0(17)
Z	8	16	16	8
crystal habit	prism	prism	prism	prism
density/g cm^{-3}	1.319	1.224	1.362	1.590
temperature/K	103	296	103	103
reflns collected	32915	3635	3644	27641
reflns used in refinement	23629	3304	2681	24930
GOF	0.857	1.055	1.046	1.309
R	0.0490	0.0460	0.0510	0.0538
R_w	0.0610	0.0600	0.0590	0.0841

crystallographic analyses for all of the (*R*)-**1**·**2** salts. The crystal data are listed in Table 2.

As shown in Figures 1 and 2, the (*R*)-**1**·(*R*)-**2** crystals are commonly column-type, while all of the (*R*)-**1**·(*S*)-**2** crystals are cluster-type. The distances of hydrogen bonds in the columnar hydrogen-bonding networks of the (*R*)-**1**·(*R*)-**2** crystals are similar to each other (Table 3), suggesting that the hydrogen-bonding interactions in the (*R*)-**1**·(*R*)-**2** crystals would similarly contribute to the stabilization of the crystals. Moreover, the case of the (*R*)-**1**·(*S*)-**2** crystals would be the same.

Although a column largely penetrates to the neighboring column in the case of the (*R*)-**1**·(*R*)-**2d** crystal, most likely in order to avoid the formation of large voids, the molecular arrangements in the (*R*)-**1**·(*R*)-**2** crystals resemble each other, indicative of the similar contribution of van der Waals and CH/π interactions to the stabilization of the crystals. Moreover, there is no remarkable short contact, less than the sum of the van der Waals radii, between the halogen atoms. As a result of the similar contribution of hydrogen-bonding, van der Waals, and CH/π interactions, the (*R*)-**1**·(*R*)-**2** crystals might have similar stability to each other. This estimation is strongly supported by the fact that the (*R*)-**1**·(*R*)-**2** crystals have almost the same melting point as shown in Figure 3.

In sharp contrast, in the (*R*)-**1**·(*S*)-**2b**−**d** crystals, distinct halogen-bonding interaction between clusters is observed, although there is no halogen-bonding interaction in the (*R*)-**1**·(*S*)-**2a** crystal (Figure 2).

Intercluster Cl···Cl (acid−amine) contact is observed in the (*R*)-**1**·(*S*)-**2b** crystal; the distance (3.45 Å) is 0.07 Å shorter than the sum of van der Waals radii. In a similar manner, in the (*R*)-**1**·(*S*)-**2c** crystal, an intercluster Cl···Br (acid−amine) contact of 3.46 Å exists, which is 0.15 Å shorter than the sum of the van der Waals radii. Moreover, in the case of the (*R*)-**1**·(*S*)-**2d** crystal, two kinds of halogen-bonding interactions are observed, intercluster Cl···Cl (acid−acid) and I···I (amine−amine) contacts; the mode of the halogen-bonding interactions is different from those in the (*R*)-**1**·(*S*)-**2b**,**c** crystals, probably due to the difference in packing mode of clusters between the (*R*)-**1**·(*S*)-**2d** crystal and the (*R*)-**1**·(*S*)-**2b**,**c** crystals. The Cl···Cl and I···I distances (3.28 and 3.90 Å) are 0.24 and 0.38 Å shorter than the sums of the van der Waals radii, respectively. These crystal structures strongly indicate that the stability of the (*R*)-**1**·(*S*)-**2** crystals is highly dependent on the intercluster halogen-bonding interaction, because the contributions of hydrogen-bonding interactions in the crystals are similar to each other as mentioned above; the stability should be in an order of the (*R*)-**1**·(*S*)-**2a** crystal < the (*R*)-**1**·(*S*)-**2b** crystal < the (*R*)-**1**·(*S*)-**2c** crystal < the (*R*)-**1**·(*S*)-**2d** crystal. This

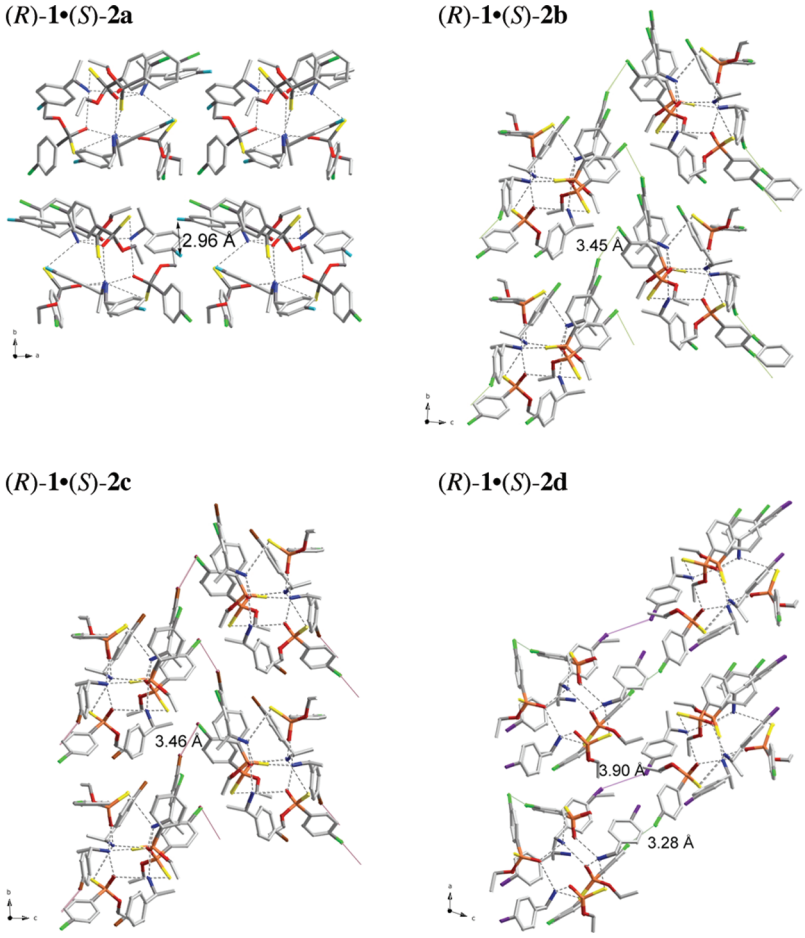

Figure 2. Crystal structures of (*R*)-**1**·(*S*)-**2** salts. Dotted lines indicate hydrogen bonds. Values are distances between neighboring halogen atoms indicated by solid lines.

Table 3. Distances of Hydrogen Bonds in (*R*)-1·(*R*)-2 and (*R*)-1·(*S*)-2 Salt Crystals

crystals	N···O (Å)	N···S (Å)
(*R*)-**1**·(*R*)-**2a**	2.774, 2.767	3.301
(*R*)-**1**·(*S*)-**2a**	2.740, 2.763	3.332
(*R*)-**1**·(*R*)-**2b**	2.777,2.810	3.295
(*R*)-**1**·(*S*)-**2b**	2.781, 2.825	3.260
(*R*)-**1**·(*R*)-**2c**	2.777, 2.742	3.278
(*R*)-**1**·(*S*)-**2c**	2.713, 2.736	3.386
(*R*)-**1**·(*R*)-**2d**	2.761, 2.814	3.286
(*R*)-**1**·(*S*)-**2d**	2.793, 2.793	3.313

order is highly consistent with that of their melting points as shown in Figure 3.

Explanation for the Dramatic Switch of the Absolute Configuration of the Amines Incorporated in the Less-Soluble Diastereomeric (*R*)-1·2 salts. Cylindrical assembly of organic molecules is known to possibly prevent the formation of large voids between the molecules in crystals owing to efficient van der Waals and CH/π interactions,[10] suggesting that the aggregation of cylindrical assemblies would be more favorable than that of spherical assemblies for the creation of stable organic crystals. This means that the column-type crystals should be more stable than the cluster-type crystals. As a result, the stability of the (*R*)-**1**·(*R*)-**2a** crystal is higher than that of the (*R*)-**1**·(*S*)-**2a** crystal. In contrast, the (*R*)-**1**·(*S*)-**2d** crystal becomes more stable than the (*R*)-**1**·(*R*)-**2d** crystal, owing to the contribution of strong halogen-bonding interactions other than van der Waals and CH/π interactions to the stabilization of the (*R*)-**1**·(*S*)-**2d** crystal.

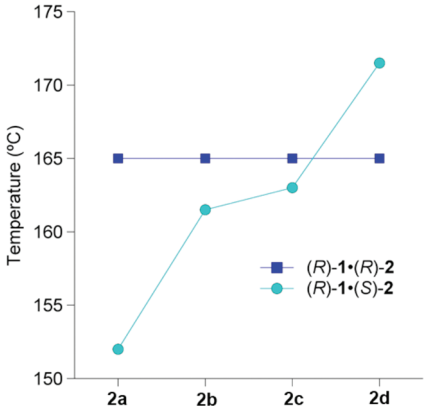

Figure 3. Melting points of (*R*)-**1**·(*R*)-**2** (blue) and (*R*)-**1**·(*S*)-**2** (green) salt crystals.

On the other hand, it is widely accepted that among a pair of diastereomeric salt crystals, a crystal with higher stability is less soluble. Therefore, the (*R*)-**1**·(*R*)-**2a** and (*R*)-**1**·(*S*)-**2d** crystals should be less soluble than the (*R*)-**1**·(*S*)-**2a** and (*R*)-**1**·(*R*)-**2d** crystals, respectively, to cause the switch of the major isomer incorporated in the deposited salts from the *R*-isomer for the amine **2a** to the *S*-isomer for the amine **2d**.

The relative stability/solubility of the (*R*)-**1**·(*R*)-**2** and (*R*)-**1**·(*S*)-**2** crystals fully reflects the ee of the amine incorporated in the salts deposited (Table 1).

Conclusion

We have examined the chirality-recognition ability of newly synthesized *O*-ethyl 4-chlorophenylphosphonothioic acid (**1**) for racemic 1-(4-halophenyl)ethylamines (halo = F, Cl, Br, I; **2a**−**d**). The phosphonothioic acid **1** excellently recognized the chirality of the amines **2a** and **2d**; the absolute configuration of the enantio-enriched isomer in the salt with **2a** was *R*, while that with **2d** was *S*. The switch of the absolute configuration of the preferred isomer could be explained on the basis of the crystal structures of the four pairs of diastereomeric salts determined by X-ray crystallography; among the column-type and cluster-type salt crystals, which were commonly formed for each pair of the diastereomeric salts, the stability of the former was almost the same, while the stability of the latter increased in an order of (*R*)-**1**·(*S*)-**2a** < (*R*)-**1**·(*S*)-**2b** < (*R*)-**1**·(*S*)-**2c** < (*R*)-**1**·(*S*)-**2d**, owing to the strong dependence of the stability on the effectiveness of halogen-bonding interaction. As a result, the stability/solubility of (*R*)-**1**·(*S*)-**2d** became higher than those of (*R*)-**1**·(*R*)-**2d**, although the stability/solubility of (*R*)-**1**·(*R*)-**2a** were higher than those of (*R*)-**1**·(*S*)-**2a**.

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Supporting Information Available: X-ray crystallographic information files (CIF) for diastereopure (*R*)-**1**·**2** salts. This material is available free of charge via the Internet at http://pubs.acs.org.

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