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Enantiopure *O*-Substituted Phenylphosphonothioic Acids: Chiral Recognition Ability during Salt Crystallization and Chiral Recognition Mechanism

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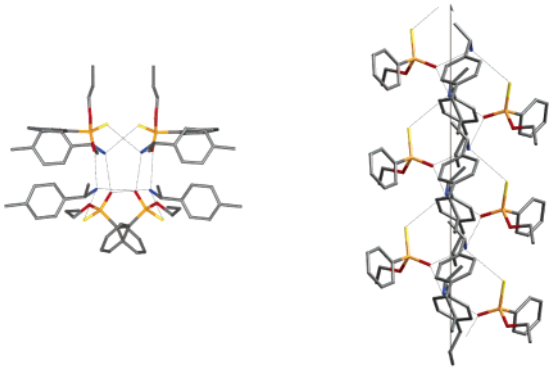

The chiral recognition ability of enantiopure *O*-methyl, *O*-ethyl, *O*-propyl, and *O*-phenyl phenylphosphonothioic acids (**1a**−**d**) for various kinds of racemic amines during salt crystallization and the chiral recognition mechanism were thoroughly investigated. The chiral recognition abilities of enantiopure **1a**−**d** for a wide variety of racemic amines varied in a range of 6 to >99% enantiomeric selectivity. Deposited less-soluble diastereomeric salts were classified into two categories, prism- and needle-type crystals; the prism-type crystals were composed of a globular molecular cluster, while there existed a 2_1 column in the needle-type crystals. In contrast to a general observation of a similar 2_1 column in the less-soluble diastereomeric salt crystals of chiral primary amines with chiral carboxylic acids, the globular molecular cluster is a very unique hydrogen-bonding motif that has never been constructed in diastereomeric salt crystals. Excellent chiral recognition was always achieved when the less-soluble diastereomeric salts were prism-type crystals. Significant correlations were found between the degree of the chiral recognition with **1a**−**d**, the crystal shape of the less-soluble diastereomeric salts, and the hydrogen-bonding motif (molecular cluster/2_1 column). The chiral recognition mechanisms via the molecular cluster and the 2_1 column formations are discussed in detail on the basis of X-ray crystallographic analyses.

Introduction

The method based on the chiral recognition of a racemate with a chirality-recognizable enantiopure reagent (resolving agent) during salt crystallization, so-called the enantioseparation of a racemate via the diastereomeric salt formation, is one of the most promising methods for obtaining enantiopure compounds.[1] Although a great number of successful results for the chiral recognition of racemates by such a method have been reported so far,[1−3] the selection of a resolving agent suitable for a target racemate is crucial even at present; there is no

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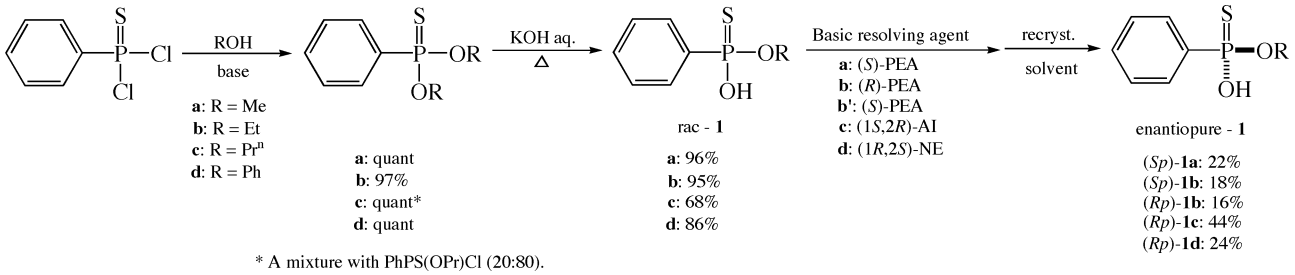
SCHEME 1. Synthesis of Enantiopure 1a−d



* A mixture with PhPS(OPr)Cl (20:80).

method for the prediction of the difference in solubility/stability between a pair of diastereomeric salt crystals of a racemate with a resolving agent, on which success in chiral recognition strongly depends. An effective solution to conquering such a situation is to clarify not only the chiral recognition ability of a resolving agent for a series of racemates but also the mechanism of the chiral recognition from a crystallographic point of view. On the basis of this consideration, we have systematically studied the chiral recognition abilities of enantiopure arylglycolic acids for various racemic primary amines and those of enantiopure 2-aminoarylenecyclopentanols for racemic carboxylic acids during salt crystallization and tried to elucidate the chiral recognition mechanism on the basis of X-ray crystallography.[3] The crystallographic analyses revealed that there were mainly three kinds of interactions for the stabilization of diastereomeric salts and that the difference in stability between less- and more-soluble diastereomeric salts largely depended on the existence and/or magnitude of the three interactions: (i) the hydrogen-bonding interaction between carboxylate anions and ammonium cations to form a helical hydrogen-bonding network (2_1 column), (ii) the CH/π interaction(s) between aryl groups in the anions/cations to allow the T-shape arrangement of the aryl groups, and (iii) the van der Waals interaction to achieve the close packing of the hydrogen-bonding columns. Among them, the hydrogen-bonding interaction is the primary concern because the other interactions can contribute to the stabilization as a result of the formation of the hydrogen-bonding column. Therefore, the understanding of the hydrogen-bonding network, formed in less-soluble diastereomeric salts, is the most important for the elucidation of the mechanism for the chiral recognition of racemates with a resolving agent during salt crystallization.

Compounds containing chiral phosphorus atom(s) (*P*-chiral) are well-known for affording a diastereomeric circumstance upon interacting with chiral substrates, and the *P*-chiral compounds are used for the determination of the enantiomeric excesses of the substrates in solutions by ^{1}H and ^{31}P NMR spectroscopies.[4] Despite the high potential for chiral recognition in solutions, the chiral recognition ability of *P*-chiral compounds during salt crystallization is still unknown. Recently, we have shown the superior chiral recognition ability of enantiopure *O*-ethyl phenylphosphonothioic acid for racemic 1-phenylethylamine (PEA) derivatives during salt crystallization and briefly reported a plausible chiral recognition mechanism.[5] The X-ray crystallographic analyses of the less-soluble diastereomeric salts revealed that the phosphonothioic acid and the amine formed a globular molecular cluster in which there existed a closed hydrogen-bonding network at the center. This hydrogen-bonding motif is very rare and is largely different from an infinitely hydrogen-bonded 2_1 column in less-soluble diastereomeric salts, deposited during the chiral recognition of racemic primary amines with conventional acidic resolving agents such as mandelic acid and its derivatives, 2-naphthylglycolic acid, 10-camphorsulfonic acid, 1-phenylethanesulfonic acid, and so on.

In this paper we report, in detail, the chiral recognition ability of *O*-methyl, *O*-ethyl, *O*-propyl, and *O*-phenyl phenylphosphonothioic acids for racemic primary amines during salt crystallization as well as the mechanism for chiral recognition.

Results and Discussion

Synthesis of Enantiopure *O*-Methyl, *O*-Ethyl, *O*-Propyl, and *O*-Phenyl Phenylphosphonothioic Acids (1a−d). Racemic *O*-methyl, *O*-ethyl, *O*-propyl, and *O*-phenyl phenylphosphonothioic acids (rac-**1a**−**d**) were successfully synthesized from phenylphosphonothioic dichloride in 96, 92, 68, and 86% total yields, respectively, according to the procedures described in the literature,[6−12] with some modifications (Scheme 1). The enantioseparations were carried out by using (*R*)-PEA for **1a**,[8] (*S*)- and (*R*)-PEA for **1b**,[10] (1*S*,2*R*)-2-amino-1-indanol (AI) for **1c**, and (1*R*,2*S*)-norephedrine (NE) for **1d** as resolving agents,

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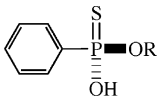
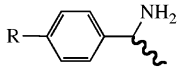
TABLE 1. Chiral Recognition of Racemic PEA Derivatives 2a−c with Enantiopure 1a−d during Salt Crystallization and Crystal Shape and Hydrogen-Bonding Pattern of the Less-Soluble Salts



a:R = Me
b:R = Et
c:R = Pr^n
d:R = Ph

1



a: R = H
b: R = Me
c: R = OMe

2

entry	acid	amine	solvent[a] (mL) ether/AcOEt/hexane/*i*-Pr_2O	yield[b] (%)	ee[c] (%)	efficiency[d]	absolute configuration[e]		crystal shape[f]	HB pattern[g]
1	**1a**	**2a**	1.4:0:0:0	96	46	0.44	S_p	*S*	needle	2_1 column[h]
2		**2b**	1.3:0:0.9:2.6	61	97	0.59	S_p	*R*	prism	n.d.[i]
3		**2c**	2.8:0:0:1.4	65	47	0.30	S_p	*S*	needle	n.d.[i]
4	**1b**	**2a**	2.7:0:0:0	78	98	0.76	S_p	*R*	prism	cluster[j]
5		**2b**	1.5:0.5:0:0	52	>99	0.51	S_p	*R*	prism	cluster[j]
6		**2c**	1.4:0:0:0	45	>99	0.45	R_p	*S*	prism	n.d.[i]
7	**1c**	**2a**	0:0:5.9:0	69	95	0.66	R_p	*R*	prism	n.d.[i]
8		**2b**	0:0:2.2:0	50	91	0.46	R_p	*S*	prism	cluster[j]
9		**2c**	0:0:3.5:1.9	46	95	0.44	R_p	*S*	prism	n.d.[i]
10	**1d**	**2a**	0:1.3:13.4:0	68	68	0.46	R_p	*R*	needle	2_1 column[h]
11		**2b**	0:1.8:13.4:0	63	66	0.42	R_p	*R*	needle	n.d.[i]
12		**2c**	0:5.3:0:0[k]	75	83	0.62	R_p	*R*	needle	n.d.[i]

[a] Amount of the solvent used in the enantioseparation (mL/1 mmol). [b] Yield of the crystallized diastereomeric salt based on a half amount of the racemic amine. [c] Enantiomeric excess (ee) of the liberated amine, which was determined by a HPLC analysis. [d] Efficiency is the product of the yield and the ee. [e] Absolute configuration: The former is the absolute configuration of enantiopure **1** used in the enantioseparation, and the latter is the absolute configuration of the major enantiomer of the incorporated amine. The absolute configuration was determined by an X-ray crystallographic analysis or on the basis of the elution order in a HPLC analysis upon comparing with that of the same amine, of which the absolute configuration had been determined by an X-ray crystallographic analysis so far. [f] Crystal shape of the less-soluble salt. [g] Hydrogen-bonding pattern observed in the less-soluble salt, which was determined by an X-ray crystallographic analysis. [h] Columnar hydrogen-bonding network with a two-fold screw axis. [i] Could not be determined. [j] Molecular cluster consisting of four acid molecules and four amine molecules. [k] Acetone in the amount of 3.6 mL was added.

respectively, to give enantiopure **1a**−**d** in 16−44% yields (based on a half amount of the racemic phosphonothioic acid used).

The stabilities of **1a**−**d** were largely different from each other. The phosphonothioic acids **1b** and **1c** were stable enough to be reused as resolving agents several times while maintaining their enantiomeric excesses over 99%, while **1a** gradually decomposed to contaminate *O*-methyl phenylphosphonic acid (ca. 2%) and phenylphosphonothioic acid (ca. 7%) upon standing at rt for 2 weeks even under an argon atmosphere, and a part of **1d** was transformed to phenylphosphonothioic acid (ca. 15%) after 3 weeks.

Comparison of the Chiral Recognition Abilities of 1a−d. At first we examined the chiral recognition abilities of the phosphonothioic acids **1a**−**d** for racemic PEA (**2a**) and its *p*-substituted derivatives **2b** and **2c** during salt crystallization under the same conditions, other than the solvent, to compare the abilities of **1a**−**d** with each other. The precipitates (the less-soluble diastereomeric salt), deposited upon stirring a solution of equimolar amounts of **1** and **2** at rt, were collected by filtration, washed with hexane, and dried under reduced pressure. The composition and amount of the solvent were adjusted so as to control the yield of the precipitates to be as close as possible to a range of 50−90% (based on a half amount of the racemate used). To determine the chiral recognition ability of **1**, the precipitates were treated with an aqueous alkaline solution, and the enantiomeric excess of the amine liberated was analyzed with chiral HPLC.

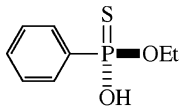
As shown in Table 1, the chiral recognition efficiencies (the yield of the precipitates based on a half amount of the racemic amine **2** used times the enantiomeric excess of the amine incorporated in the precipitates) with **1a**−**d** were moderate to excellent, not depending on the *O*-substituent. However, **1b** gave better results than did **1a**, **1c**, and **1d** from the viewpoint of the enantiomeric excesses of the amines **2a**−**c** incorporated in the deposited salts; in all cases where **1b** was applied, the enantiomeric excesses of the amines **2a**−**c** reached almost the stage of perfection. Thus, the chiral recognition ability of **1b** was found to be superior compared with those of **1a**, **1c**, and **1d**.

Chiral Recognition Ability of 1b for Racemic Amines. Because the phosphonothioic acid **1b** showed an excellent recognition ability for PEA and two *p*-substituted derivatives during salt crystallization, we next examined the chiral recognition ability of **1b** for a wide variety of *p*-substituted PEA derivatives as well as for *m*- and *o*-substituted PEA derivatives. To compare the results with each other, the salt crystallization and analysis were performed under the same conditions as those mentioned above, other than the solvent. The results are summarized in Table 2.

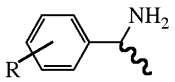
The diastereomeric pairs (the less-soluble and more-soluble diastereomeric salts) of the racemic *m*- and *o*-substituted PEA derivatives **2l**−**n** with **1b** had very low crystallinity or gave no crystals (Table 2, entries 9−11), although the less-soluble diastereomeric salt of 1-(*o*-methoxyphenyl)ethylamine (**2o**) with **1b** exceptionally deposited with a diastereomeric purity of 67% (Table 2, entry 12). These results indicate that **1b** is rather unsuitable for the chiral recognition of *m*- and *o*-substituted PEA derivatives during salt crystallization. In contrast, **1b** showed a moderate to excellent chiral recognition ability for a variety of racemic *p*-substituted PEA derivatives during salt crystallization; **1b** could recognize the chirality of the amines **2d**−**i** (Table 2, entries 1−6) as well as that of the amines **2a**−**c** (Table 1, entries 4−6).

There was some substituent dependence observed for the chiral recognition with **1b**; namely, the enantiomeric excesses of the amines, **2**, in the less-soluble diastereomeric salts had the tendency to decrease gradually as the size of the substituent became large: >99−95% for **2a**−**f** (Table 1, entries 4−6, and Table 2, entries 1−3), 90% for **2g** (Table 2, entry 4), and 73−31% for **2h** and **2i** (Table 2, entries 5 and 6). Similar dependence was also observed when the PEA derivatives had an electron-

TABLE 2. Chiral Recognition of Racemic PEA Derivatives 2d−o with Enantiopure 1b during Salt Crystallization and Crystal Shape and Hydrogen-Bonding Pattern of the Less-Soluble Salts



1b



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entry	amine R		solvent[a] (mL) ether/AcOEt/hexane	yield[b] (%)	ee[c] (%)	efficiency[d]	absolute configuration[e]		crystal shape[f]	HB pattern[g]
1	*p*-F	**2d**	1.4:0:0	84	96	0.81	S_p	*R*	prism	cluster[h]
2	*p*-Cl	**2e**	1.5:0.5:0	84	>99	0.83	S_p	*R*	prism	cluster[h]
3	*p*-Br	**2f**	1.5:0.5:0	83	95	0.79	S_p	*R*	prism	cluster[h]
4	*p*-Et	**2g**	0.3:0:2.7	60	90	0.54	R_p	*S*	needle/prism[i]	2_1 column[j]/n.d.[k]
5	*p*-Pr[i]	**2h**	0.5:0:7.2	97	31	0.30	R_p	*R*	needle/prism[i]	2_1 column[j]/n.d.[k]
6	*p*-Pr	**2i**	0.3:0:2.7	87	73	0.64	R_p	*S*	needle	2_1 column
7	*p*-NO_2	**2j**	2.7:0:0.3	79	16	0.13	S_p	n.d.[k]	n.d.[k]	n.d.[k]
8	*p*-CN	**2k**	1.4:0:0	48	12	0.06	S_p	n.d.[k]	n.d.[k]	n.d.[k]
9	*m*-Me	**2l**	0.2:0:0	*l*			R_p			
10	*m*-OMe	**2m**	0.2:0:0	*l*			R_p			
11	*o*-Me	**2n**	0.2:0:0	*l*			R_p			
12	*o*-OMe	**2o**	0.7:0:16.2	68	67	0.46	S_p	*R*	needle	2_1 column

[a] Amount of the solvent used in the enantioseparation (mL/1 mmol). [b] Yield of the crystallized diastereomeric salt based on a half amount of the racemic amine used. [c] Enantiomeric excess (ee) of the liberated amine, which was determined by a HPLC analysis. [d] Efficiency is the product of the yield and the ee. [e] Absolute configuration: The former is the absolute configuration of enantiopure **1b** used in the enantioseparation, and the latter is the absolute configuration of the major enantiomer of the incorporated amine. The absolute configuration was determined by an X-ray crystallographic analysis or on the basis of the elution order in a HPLC analysis upon comparing with that of the same amine, of which the absolute configuration had been determined by an X-ray crystallographic analysis so far. [f] Crystal shape of the less-soluble salt. [g] Hydrogen-bonding pattern observed in the less-soluble salt, which was determined by an X-ray crystallographic analysis. [h] Molecular cluster consisting of four acid molecules and four amine molecules. [i] Two kinds of crystals were formed under the same conditions as a result of polymorphism. [j] Columnar hydrogen-bonding network with a two-fold screw axis. [k] Could not be determined. [l] Could not crystallize.

withdrawing substituent at the *p*-position. The enantiomeric excesses of *p*-halo derivatives **2d**−**f** were highly satisfactory (Table 2, entries 1−3), while those of the *p*-nitro and *p*-cyano derivatives **2j** and **2k** were very low (Table 2, entries 7 and 8). These results clearly indicate that the degree of the chiral recognition with **1b** depends on the size/length of the substituent at the *p*-position of **2** rather than on its electronic nature. The dependence would arise from the general tendency that molecules pack as closely as possible in crystals, for which the relative molecular size/length would be the primary concern in the cases of two-component (acid and amine) crystals.

These successful results of the chiral recognition of *p*-substituted PEA derivatives **2a**−**f** with the phosphonothioic acid **1b** during salt crystallization prompted us to determine the chiral recognition ability of **1b** for other racemic primary amines such as 1-arylalkylamines, aliphatic amines, and 1,2-amino alcohols. The results are shown in Table 3.

The phosphonothioic acid **1b** did not show any chiral recognition ability for 1-(1-naphthyl)ethylamine (**3**) and 1-(2-naphthyl)ethylamine (**4**) (entries 1 and 2) during salt formation, probably a result of the mismatch of the molecular size/length of **3** and **4** with that of **1b**; the molecular size/length of the amines is obviously larger/longer than that of **1b**. In contrast, **1b** could recognize the chirality of 1-phenyl-2-methylpropylamine (**5**) with an excellent chiral recognition efficiency of 0.85 (entry 3), even though the isopropyl group in **5** is larger than the methyl group of **2a**. Moreover, moderate to excellent chiral recognition was also achieved for more than half of the amines we examined (entries 4−13). It is noteworthy that **1b** showed an excellent chiral recognition ability for the aliphatic amines and the 1,2-amino alcohols **6**, **7**, **12**, and **13** (entries 4, 5, 10, and 11), of which the chirality is generally difficult to recognize by conventional resolving agents.

The present results concerning the chiral recognition with **1b** strongly suggest that enantiopure *O*-substituted phosphonothioic acids are new promising candidates of widely applicable resolving agents with high performance.

Mechanism of Chiral Recognition Elucidated on the Basis of X-ray Crystallographic Study. To elucidate the mechanism for the chiral recognition with the phosphonothioic acid **1b** during salt crystallization, the X-ray crystallographic analyses of the deposited less-soluble salts would be indispensable. However, the deposited salts were not crystals but were powders because the salt crystallization in the present study had to be carried out upon stirring a solution. We then tried to recrystallize the deposited powders and also to obtain single crystals suitable for X-ray crystallography. The X-ray diffraction patterns of the crystals obtained by recrystallization were identical with those of the deposited powders (see Supporting Information), indicating that the hydrogen-bonding networks and crystal packing modes in the crystals are identical with those in the powders, respectively. Therefore, we carried out the microscopic analyses of the crystals for the comparison of their crystal shapes as well as the X-ray crystallographic analyses of the single crystals.

The microscopic analyses of the crystals of the less-soluble diastereomeric salts with **1b** gave valuable information for the chiral recognition mechanism during salt crystallization. The crystals of the less-soluble diastereomeric salts were classified into two categories on the basis of the crystal shapes, prism- and needle-type crystals, as shown in Figure 1; prism-type crystals have never been observed in the less-soluble diastereomeric salt crystals of chiral primary amines with chiral acids as far as we know, although needle-type crystals are the same as those commonly obtained from the less-soluble diastereomeric salts of chiral primary amines with enantiopure carboxylic acids. This observation strongly suggests that the chiral recognition mechanisms through which the prism- and needle-type crystals formed are different from each other. The crystal shapes of the less-soluble salts with **1b** are listed in Tables 1−3.

TABLE 3. Chiral Recognition of Other Racemic Amines 3−15 with 1b during Salt Crystallization and the Crystal Shape and Hydrogen-Bonding Pattern of the Less-Soluble Salts

entry	amine		solvent[a] (mL) ether/AcOEt/hexane	yield (%)[b]	ee (%)[c]	efficiency[d]	absolute configuration[e]		crystal shape[f]	HB pattern[g]
1		**3**	0.5 / 0 / 5.1	43	6	0.03	S_p	R	needle	2_1 column[h]
2		**4**	13.5 / 0 / 0.3	93	91	0.85	R_p	S	needle	2_1 column[h]
3		**5**	6.7 / 0 / 0	68	59	0.40	R_p	R	needle	2_1 column[h]
4		**6**	1.4 / 0 / 4.0	60	84	0.50	R_p	n.d.[i]	needle	n.d.[i]
5		**7**	1.0 / 0 / 4.1	35	21	0.07	R_p	n.d.[i]	needle	n.d.[i]
6		**8**	4.0 / 0.7 / 0	60	96	0.58	R_p	n.d.[i]	needle	n.d.[i]
7		**9**	4.0 / 2.7 / 1.4	55	30	0.17	R_p	(1*S*,2*R*)	needle	2_1 column[h]
8		**10**	0 / 3.6 / 0	72	>99	0.71	S_p	S	needle	n.d.[i]
9		**11**	2.8 / 0 / 0	75	>99	0.74	S_p	R	needle	n.d.[i]
10		**12**	6.8 / 0 / 0	39	63	0.25	R_p	n.d.[i]	needle	n.d.[i]

[a] Amount of the solvent used in the enantioseparation (mL/1 mmol). [b] Yield of the crystallized diastereomeric salt based on a half amount of the racemic amine used. [c] Enantiomeric excess (ee) of the liberated amine, which was determined by a HPLC analysis. [d] Efficiency is the product of the yield and the ee. [e] Absolute configuration: The former is the absolute configuration of enantiopure **1b** used in the enantioseparation, and the latter is the absolute configuration of the major enantiomer of the incorporated amine. The absolute configuration was determined by an X-ray crystallographic analysis or on the basis of the elution order in a HPLC analysis upon comparing with that of the same amine, of which the absolute configuration had been determined by an X-ray crystallographic analysis so far. [f] Crystal shape of the less-soluble salt. [g] Hydrogen-bonding pattern observed in the less-soluble salt, which was determined by an X-ray crystallographic analysis. [h] Columnar hydrogen-bonding network with a twofold screw axis. [i] Could not be determined.

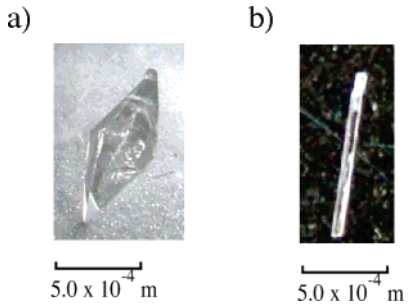

FIGURE 1. Crystal shapes of the less-soluble salts with enantiopure **1**; (a) prism- and (b) needle-type crystals.

Tables 1−3 indicate that there is high correlation between the crystal shape and the degree of the chiral recognition with **1b**. In the case of prism-type crystals, the enantiomeric excesses of the amines, recovered from the less-soluble diastereomeric salts with **1b**, are over 95% (Table 1, entries 4−6, and Table 2, entries 1−3), while the enantiomeric excesses are widely spread from 6 to >99% for the case of needle-type crystals (Table 2, entries 6 and 12, and Table 3). Among the less-soluble diastereomeric salts of *p*-substituted PEA derivatives **2** with **1b**, the salt of the amine with a relatively small substituent tends to form a prism-type crystal, while that with a relatively large substituent has a tendency to give a needle-type crystal. Moreover, in the cases of the salts of **2g** and **2h** with **1b** (Table 2, entries 4 and 5), prism- or needle-type crystals were deposited in a similar probability under the same conditions for the recrystallization, most likely a result of polymorphism. This phenomenon would be reasonably explained in terms of the medium size of the *p*-substituents.

These results strongly indicate that excellent chiral recognition is achieved in the cases of prism-type crystals, while the degree is generally low to moderate in the cases of needle-type crystals. It is noteworthy that there was a large difference in the physical properties of the less- and more-soluble diastereomeric salts, which largely contributed to the achievement of excellent chiral recognition with **1b** when prism-type crystals were obtained; the less-soluble salts deposited as crystalline powders, while the more-soluble salts were always oils.

To make the correlation more clear, we next tried the X-ray crystallographic analyses of the less-soluble diastereomeric salts with **1b**, belonging to the prism and needle forms, respectively. Among the less-soluble salts with **1b**, prepared in the present study, we could obtain the single crystals of the less-soluble diastereomeric salts of **2a**, **2b**, **2e**, and **2f** in a prism form and **2g**, **2h**, **2i**, **2o**, **3**, **5**, **6**, and **11** in a needle form, which were suitable for X-ray crystallographic analyses. As a result, in the needle-type less-soluble salt crystals there commonly exists a columnar hydrogen-bonding network that consists of hydrogen bonds between the oxygen/sulfur atoms of the phosphonothioate anions and the ammonium hydrogen atoms of the ammonium cations with a two-fold screw axis in the center, a so-called 2_1 column. The pattern of the columnar hydrogen-bonding network is almost the same as that generally observed in the less-soluble diastereomeric salts of chiral primary amines with chiral carboxylic acids, which afford needle crystals.[3] In contrast, all of the prism-type less-soluble salts have a hydrogen-bonding pattern quite different from that in the needle-type crystals; a globular molecular cluster is constructed from four phosphonothioate molecules and four ammonium molecules. In the molecular cluster, hydrophilic hydrogen-bonding sites are located at the center, and hydrophobic groups are positioned at the surface of the molecular cluster. Three kinds of T-shaped CH/π interactions[13] exist to stabilize the molecular cluster. Moreover, other CH/π interactions as well as van der Waals

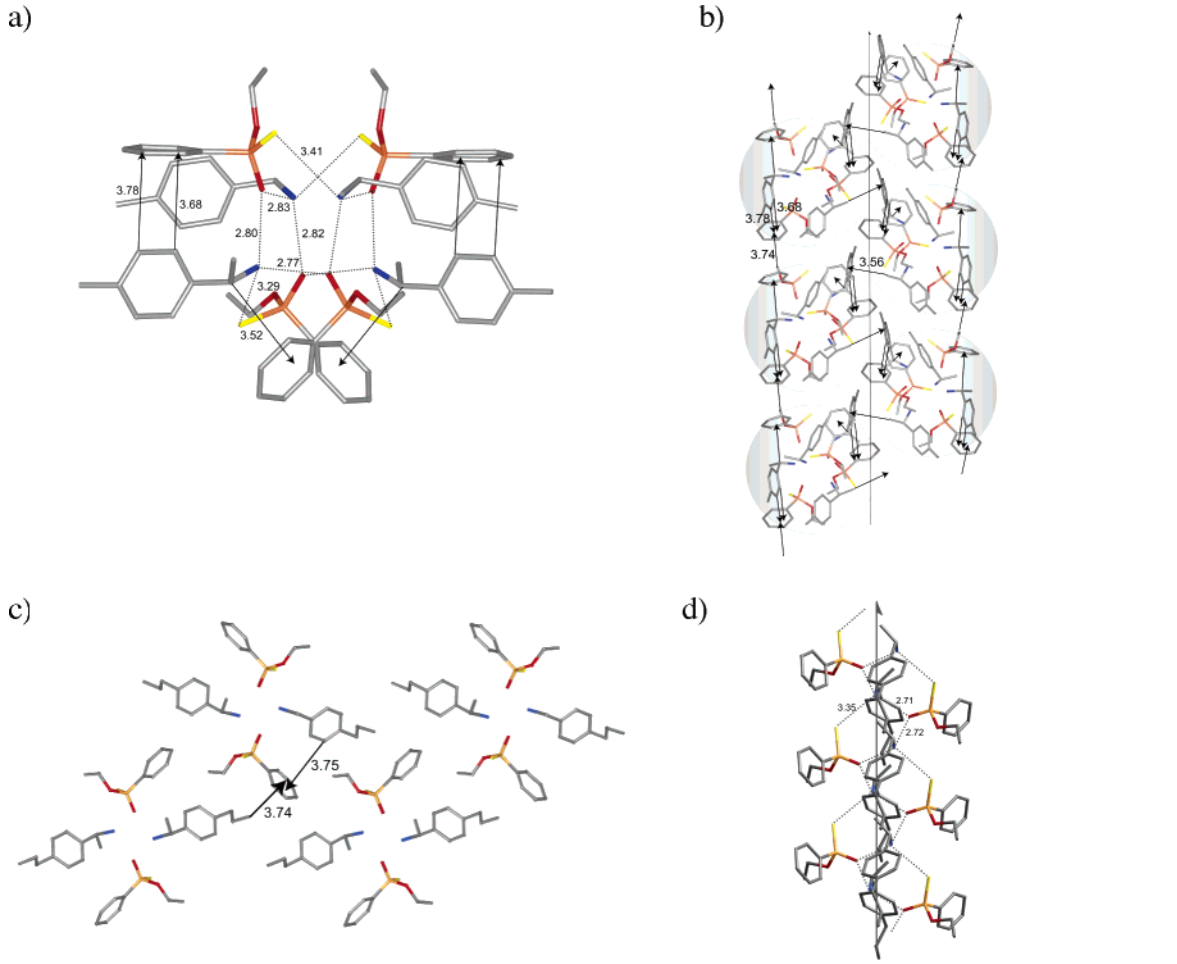

FIGURE 2. Typical examples of hydrogen-bonding networks observed in the less-soluble salts with enantiopure **1b**; (a) globular molecular cluster in the (S_p)-**1b**·(*R*)-**2b** salt, (b) its one-dimensional arrangement along with the two-fold screw axis, (c) 2_1 columns in the (R_p)-**1b**·(*S*)-**2f** salt, and (d) the side view of the column. Hydrogen atoms are omitted for clarity. Hydrogen bonds and CH/π interactions are shown by dotted lines and arrows, respectively. The bond distances are in angstroms.

interaction contributes to the close packing of the molecular clusters to form a three-dimensional crystal, although the interactions are rather weak. The hydrogen-bonding patterns, determined by X-ray crystallography, are listed in Tables 1−3, and Figure 2 shows the typical hydrogen-bonding patterns of the globular molecular cluster and the 2_1 column.

From Tables 1−3, high correlation is observed between the crystal shape of the less-soluble diastereomeric salts with **1b** and their hydrogen-bonding pattern determined by X-ray crystallography; as far as we examined, without any exception, the prism-type crystals consist of a molecular cluster, whereas there exists a 2_1 column in the needle-type crystals. This result suggests that the hydrogen-bonding patterns, which could not be determined by X-ray crystallography in the present study, can be deduced on the basis of the crystal shapes.

Thus, in the chiral recognition of racemic primary amines with **1b**, high correlations were found between the degree of chiral recognition with **1b**, the crystal shape of the corresponding less-soluble diastereomeric salts, and the hydrogen-bonding pattern in the salt crystals.

Figure 3 shows the crystal structure of the less-soluble (R_p)-**1b**·(1*S*,2*R*)-**11**·H_2O salt. In the crystal there exists a 2_1 column that is also composed of hydrogen bonds between the phosphonothioate anions and the ammonium cations. Moreover, water molecules do play a very important role in the salt crystal; the water molecule acts as a proton donor and also as a proton acceptor to form hydrogen bonds with the hydroxy group of

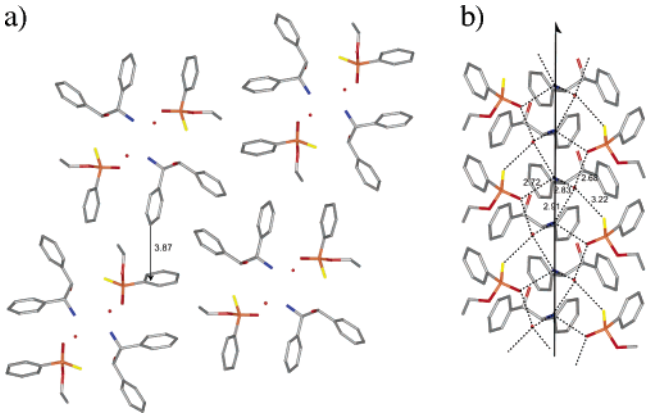

FIGURE 3. Crystal structure of the less-soluble (R_p)-**1b**·(1*S*,2*R*)-**11**·H_2O salt; (a) top view of the 2_1 columns and (b) side view of the 2_1 column. Hydrogen atoms are omitted for clarity. Hydrogen bonds and CH/π interactions are shown by dotted lines and arrows, respectively. The bond distances are in angstroms. Gray circles indicate hydrogen-bonding networks.

(13) Nishio, M.; Hirota, M.; Umezawa, Y. *The CH/π interaction. Evidence, Nature and Consequences*; Wiley-VCH: New York, 1998.

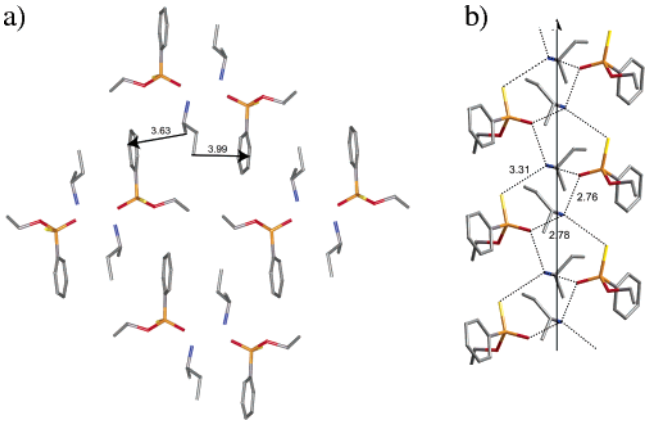

FIGURE 4. Crystal structure of the less-soluble (R_p)-**1b**·(*R*)-**6** salt; (a) top view of the 2_1 columns and (b) side view of the 2_1 column. Hydrogen atoms are omitted for clarity. Hydrogen bonds and CH/π interactions are shown by dotted lines and arrows, respectively. The bond distances are in angstroms.

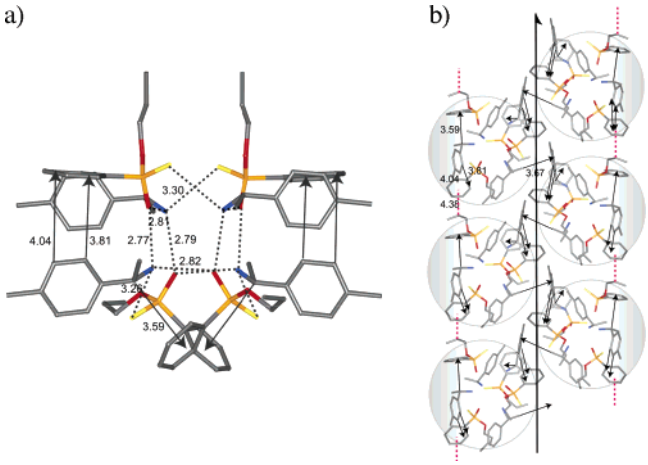

FIGURE 5. Crystal structure of the less-soluble (R_p)-**1c**·(*S*)-**2b** salt; (a) globular molecular cluster and (b) one-dimensional arrangement along with the two-fold screw axis. Hydrogen atoms are omitted for clarity. Hydrogen bonds, CH/π interactions, and weak CH/π interactions are shown in dotted lines, arrows, and red dotted lines, respectively. The bond distances are in angstroms.

11 and the sulfur atom of **1b**, which strongly reinforces the 2_1 column. The gauche conformation of the two phenyl groups of **11** and the packing mode of the columns are very similar to those in the less-soluble diastereomeric salts of chiral carboxylic acids with enantiopure **11**.[3f] On the other hand, the chiral recognition efficiency was highly improved when **10** was applied in the place of **11** as a target racemic amine. This improvement would arise from the more effective hydrogen-bonding interactions between the phosphonothioate anions of **1b**, the ammonium cations of **10**, and the water molecules in the 2_1 column and/or the more sufficient close packing of the columns, as was observed in the less-soluble diastereomeric salts of the chiral carboxylic acids with enantiopure **10**.[3d]

Because all of the less-soluble diastereomeric salts of the aliphatic amines **6**−**8** and the aliphatic amino alcohols **12**−**14** with enantiopure **1b** gave needle-type crystals, we anticipated that a 2_1 column was commonly formed in the crystals. However, it was very hard to obtain their single crystals with good quality for X-ray crystallography, other than the less-soluble (R_p)-**1b**·(*R*)-**6** salt. Thus, we could carry out only the X-ray crystallographic analysis of the (R_p)-**1b**·(*R*)-**6** salt (Figure 4). As we predicted, a 2_1 column was formed by hydrogen bonds between the phosphonothioate anions and the ammonium cations. The molecular arrangement shows that CH(sp^3)/π interactions between the phenyl groups of the **1b** molecules and the methyl groups of **6** contribute to the reinforcement of the 2_1 column and to the close packing of the columns, respectively. It is noteworthy that the distance between the carbon at the 1-position of **6** and the phenyl group of **1b** in the neighboring column is very short (3.63 Å) to play a very significant role in the close packing of the columns.

General relationships were observed between the degree of chiral recognition, the crystal shape of the less-soluble diastereomeric crystal, and the hydrogen-bonding pattern in the chiral recognition of **2a**−**c** with enantiopure **1a**, **1c**, and **1d** as well as with **1b**. From the prism-type less-soluble salts, the amines with a high enantiomeric excess were recovered, **2b** with an enantiomeric excess of 97% from the salt with **1a** (Table 1, entry 2) and **2a**−**c** with an enantiomeric excess of 91−95% from the salts with **1c** (Table 1, entries 7−9). In contrast, the enantiomeric excesses of the amines **2a**−**c** recovered from the needle-type less-soluble salts varied from 46−83% (Table 1, entries 1, 3, and 10−12). To clarify the mechanism for the chiral recognition of **2a**−**c** with **1a**, **1c**, and **1d**, we carried out X-ray crystallographic analyses for several kinds of the less-soluble diastereomeric salts. As a result, high correlation between the crystal shape and the hydrogen-bonding pattern was also realized, as was observed in the cases with **1b**; a globular molecular cluster is formed in the prism-type less-soluble (R_p)-**1c**·(*S*)-**2b** salt, whereas there exists a 2_1 column in the needle-type less-soluble (S_p)-**1a**·(*S*)-**2a** and (R_p)-**1d**·(*R*)-**2a** salts.

The crystal structure of the prism-type (R_p)-**1c**·(*S*)-**2b** salt is shown in Figure 5. The hydrogen-bonding pattern and the packing mode are quite similar to those of the prism-type salts with **1b**. The hydrogen-bonding sites are located at the center of a closed globular molecular cluster, and there are four kinds of CH/π interactions, three of which stabilize the molecular cluster with the other contributing to the close packing of the molecular clusters. Although the propyl group of **1c** does not have any interaction in the molecular cluster, the propyl group contributes to make the molecular cluster globular and to stabilize the packing of the molecular clusters along a two-fold screw axis; although the C···C distance is rather long (4.38 Å), the propyl group of **1c** weakly interacts with the phenyl group of **2b** in the neighboring molecular cluster, as was observed in the prism-type less-soluble salt with **1b** (Figures 2b and 5b). These analyses indicate that the packing mode itself is one of the most important factors to realize a globular molecular cluster, even when the key interaction is weak.

Figure 6 shows the crystal structures of the less-soluble (R_p)-**1d**·(*R*)-**2a** and more-soluble (R_p)-**1d**·(*S*)-**2a** salts. In both salt crystals, a 2_1 column is formed by hydrogen bonds between the phosphonothioate anions and the ammonium cations, and their columnar hydrogen-bonding networks are very similar to each other. However, the packing modes of the 2_1 columns are obviously different from each other. In the less-soluble (R_p)-**1d**·(*R*)-**2a** salt there are four kinds of CH/π interactions between the phenyl groups of **1d** and **2a** to stabilize the column (one kind) and to closely pack the columns (three kinds), while only one kind of CH/π interaction is observed for the stabilization of the column in the more-soluble (R_p)-**1d**·(*S*)-**2a** salt. These crystal structures suggest that the stability/solubility difference

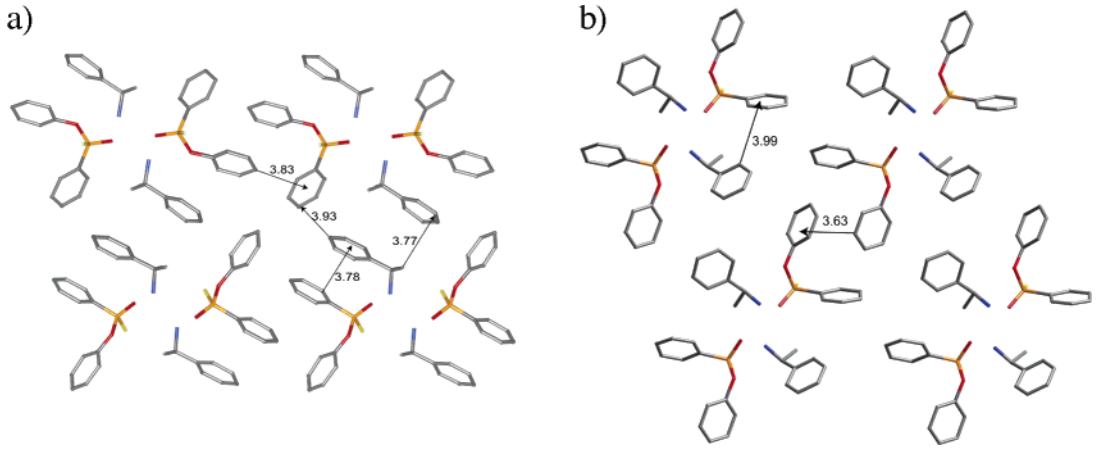

FIGURE 6. Top view of the 2_1 columns; (a) the less-soluble (R_p)-**1d**·(*R*)-**2a** salt and (b) the more-soluble (R_p)-**1d**·(*S*)-**2a** salt. Hydrogen atoms are omitted for clarity. Gray circles indicate the hydrogen-bonding networks. Hydrogen bonds and CH/π interactions are shown in dotted lines and arrows, respectively. The bond distances are in angstroms.

between the less- and the more-soluble diastereomeric crystals is mainly caused by the difference in the number of CH/π interactions contributing to the stabilization of the packing of the columns.

As shown in Figures 2 and 5, the *O*-substituents of **1b** and **1c** play an important role for the formation of a globular molecular cluster. Moreover, when the ethyl/propyl group in **1b** and **1c** is replaced by a methyl group (corresponds to **1a**), the distance between the substituent and the phenyl group in the neighboring molecular cluster would be too long to achieve similar interaction between the molecular clusters, even if the formation of the molecular cluster is supposed. As a result, some of the less-soluble salts with **1a** would have to deposit in a more stable infinite form, like a needle-type crystal. On the other hand, when the *O*-substituent is a phenyl group (corresponds to **1d**), the globular molecular cluster might no longer be formed as a result of the steric hindrance between the phenyl groups in the phosphonothioate anions and/or the ammonium cations which would result in the deposit of a crystal with a 2_1 column. These mean that the formation and packing of globular molecular clusters is sensitive not only to the shape of the amines **2** but also to the *O*-substituent of the phosphonothioic acids **1a**−**d**.

Conclusion

Racemic *O*-substituted phenylphosphonothioic acids **1a**−**d** were synthesized from phenylphosphonothioic dichloride, and the enantiopure forms were obtained very easily via enantioseparations of the racemic acids. Among the enantiopure phosphonothioic acids, *O*-ethyl phenylphosphonothioic acid (**1b**) showed chiral recognition ability better than did *O*-methyl, *O*-propyl, and *O*-phenyl phenylphosphonothioic acids (**1a**, **1c**, and **1d**) for several kinds of racemic amines in salt crystallization. A systematic study on the chiral recognition ability of **1b** during salt crystallization revealed that **1b** showed very high performance in the chiral recognition of various racemic amines. The microscopic and X-ray crystallographic analyses of the deposited (less-soluble diastereomeric) salts with **1a**−**d** revealed that the crystal shapes of the less-soluble diastereomeric salts could be classified into two categories, prism- and needle-type crystals, and that there were two independent chiral recognition mechanisms, namely, chiral recognitions through the formation of a globular molecular cluster and through the formation of a 2_1 column, of which the cluster formation is the first example in the chiral recognition during salt crystallization. Moreover, high correlations were elucidated between the degree of the chiral recognition with **1a**−**d**, the crystal shape of the less-soluble diastereomeric salts, and the hydrogen-bonding pattern in the salts, which depended on the relative molecular size/length of **1a**−**d** and the target racemic amines; prism-type crystals consisted of a globular molecular cluster without any exception and gave always very excellent results in chiral recognition, whereas needle-type crystals were composed of a 2_1 column, and the chiral recognitions varied from poor to excellent.

Experimental Section

Synthesis of Enantiopure 1a. To a solution of commercially available phenylthiophosphonoic dichloride (25.00 g, 0.12 mol) was slowly added a mixture of sodium methoxide (16.00 g, 0.30 mol) in MeOH (24 mL) over a period of 1.5 h, and the mixture was stirred at rt for 3 h. After removal of the solvent under reduced pressure, the residue was dissolved in C_6H_6 (300 mL) and washed with H_2O (3 × 300 mL), and the combined aqueous layers were extracted with C_6H_6 (3 × 1000 mL). The combined organic layers were washed with saturated aq NaCl (300 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude *O*,*O*′-dimethyl phenylphosphonothioate (24.10 g, 0.12 mol, quantitative) as an oily substance. IR (NaCl) 1438, 1123, 1024, 796, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 6H), 7.46−7.55 (m, 3H), 7.86−7.94 (m, 2H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 92.11.

A solution of crude *O*,*O*′-dimethyl phenylphosphonothioate (24.10 g, 0.12 mol) in a mixture of 12 M aq KOH (10 mL) and MeOH (150 mL) was stirred at 80 °C for 24 h. The solution was concentrated under reduced pressure to remove MeOH and extracted with CH_2Cl_2 (3 × 200 mL). The aqueous layer was acidified with 3 M aq HCl (400 mL), and the acidic aqueous solution was extracted with CH_2Cl_2 (3 × 200 mL). The combined extracts were washed with saturated aq NaCl (300 mL), dried over anhydrous Na_2SO_4, and filtered. The concentration of the organic solution under reduced pressure gave crude racemic *O*-methyl phenylphosphonothioic acid (rac-**1a**; 21.60 g, 0.12 mol, 96%) with satisfactory purity for the following enantioseparation as an oily substance. IR (NaCl) 3150, 2460, 2440, 1380, 1050, 980, 780, 730, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 3H), 7.42−7.57 (m, 3H), 7.86−7.94 (m, 2H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 83.57.

To a solution of rac-**1a** (21.64 g, 0.12 mol) in a mixture of Et_2O (230 mL) and AcOEt (70 mL) was added (*S*)-PEA (9.75 g, 0.08

mol), and the mixture was stirred at rt for 6 h. The deposited powder was collected by filtration using a membrane filter (T050A047A, Advantec) and recrystallized five times from AcOEt/hexane (1:3, 200 mL; 1:1, 80 mL; 2:3, 50 mL; 1:2, 60 mL; and then 5:1, 20 mL) to give the diastereopure (S_p)-**1a**·(*S*)-PEA salt (3.94 g, 13 mmol, 22%) as a white powder. To the diastereopure salt thus obtained was added 3 M aq HCl (500 mL), and the mixture was stirred for 1 h and extracted with CH_2Cl_2 (3 × 500 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford enantiopure (S_p)-*O*-methyl phenylphosphonothioic acid ((S_p)-**1a**; 2.40 g, 13 mmol, quantitative) as an oily substance. The enantiomeric excess of (S_p)-**1a** thus obtained was determined by a HPLC analysis (Daicel CHIRALCEL OJ-RH; eluent, $HClO_4$ (pH 2)/CH_3CN = 90:10; flow rate, 0.5 mL/min; t_1 (the S_p isomer) = 31 min, t_2 (the R_p isomer = 36 min); enantiomeric excess, >99%). (S_p)-**1a**·(*S*)-PEA salt: mp 148.5−149.0 °C. (S_p)-**1a**:[11] $[\alpha]^{25}_D = -23.5°$ (*c* 0.36, EtOH; lit. $[\alpha]^{24}_D = -21.0°$ (neat));[8] IR (NaCl) 3150, 2460, 2440, 1380, 1050, 980, 780, 730, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 3H), 7.42−7.57 (m, 3H), 7.86−7.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.91, 128.50, 130.82, 132.54; ^{31}P NMR (121 MHz, $CDCl_3$) δ 83.57.

Synthesis of Enantiopure 1b. To a solution of phenylthiophosphonoic dichloride (50.00 g, 0.24 mol) in C_6H_6 (300 mL) heated at 40 °C was slowly added a mixture of triethylamine (53.40 g, 0.53 mol) and EtOH (24.20 g, 0.53 mol) over a period of 3 h, and the mixture was stirred at 60 °C for 3.5 h. After removal of unreacted triethylamine and EtOH under reduced pressure, the solution was washed with H_2O (3 × 300 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude *O*,*O*′-diethyl phenylphosphonothioate (53.10 g, 0.23 mol, 97%) as an oily substance. IR (NaCl) 1440, 1120, 1020, 750, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, J = 7.0 Hz, 6H), 4.11 (q, J = 7.0 Hz, 4H), 7.45−7.51 (m, 3H), 7.87−7.94 (m, 2H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 87.54.

A solution of crude *O*,*O*′-diethyl phenylphosphonothioate (53.10 g, 0.23 mol) in a mixture of 5 M aq NaOH (200 mL) and EtOH (50 mL) was stirred at 80 °C for 18 h. The solution was concentrated under reduced pressure to remove EtOH and then extracted with CH_2Cl_2 (3 × 100 mL). The aqueous layer was acidified with 3 M aq HCl (500 mL), and then the acidic aqueous solution was extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with saturated aq NaCl (300 mL) and dried over anhydrous Na_2SO_4. The concentration of the organic solution under reduced pressure gave crude racemic *O*-ethyl phenylphosphonothioic acid (rac-**1b**; 44.30 g, 0.22 mol, 95%) with satisfactory purity for the following enantioseparation as an oily substance. IR (NaCl) 3000, 2380, 1440, 1120, 1020, 760, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, J = 7.0 Hz, 3H), 4.19 (q, J = 7.0 Hz, 2H), 7.43−7.52 (m, 3H), 7.88−7.96 (m, 2H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 81.64.

To a solution of rac-**1b** (6.07 g, 30 mmol) in Et_2O (70 mL) was added (*R*)-PEA (3.64 g, 30 mmol), and the mixture was stirred at rt for 6 h. The deposited solid was collected by filtration using a membrane filter (T050A047A, Advantec) and recrystallized six times from AcOEt (50, 30, 15, 25, 30, and then 40 mL) to give the diastereopure (S_p)-**1b**·(*R*)-PEA salt (0.88 g, 2.7 mmol, 18%) as a white powder. To the diastereopure salt thus obtained was added 1 M aq HCl (100 mL), and the mixture was stirred for 1 h and extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford enantiopure (S_p)-**1b** (0.54 g, 2.7 mmol, quantitative) as an oily substance. The enantiomeric excess of (S_p)-**1b** thus obtained was determined by a HPLC analysis (Daicel CHIRALCEL OJ-RH; eluent, $HClO_4$ (pH 2); flow rate, 0.5 mL/min; t_1 (S_p isomer) = 24 min, t_2 (R_p isomer) = 29 min; enantiopurity, >99%). (S_p)-**1b**·(*R*)-PEA salt: mp 134.0−134.5 °C. (S_p)-**1b**:[11] $[\alpha]^{20}_D = -15°$ (*c* 3.0, EtOH; lit. $[\alpha]_D = -15.2°$);[9] IR (NaCl) 3000, 2380, 1440, 1120, 1020, 760, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, J = 7.0 Hz, 3H), 4.19 (q, J = 7.0 Hz, 2H), 7.43−7.52 (m, 3H), 7.88−7.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.10, 62.77, 128.32, 130.59, 132.24; ^{31}P NMR (121 MHz, $CDCl_3$) δ 81.64.

The mother liquor of the enantioseparation mentioned above was basified with 1 M NaOH (50 mL), and the (*R*)-PEA that was liberated was extracted with CH_2Cl_2 (3 × 100 mL). After the aqueous solution was acidified with 1 M HCl (100 mL), (R_p)-enriched **1b** was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give (R_p)-enriched **1b** (3.36 g, 17 mmol, 96%) as an oily substance. To a solution of (R_p)-enriched **1b** (3.36 g, 17 mmol) in Et_2O (50 mL) was added (*S*)-PEA (2.02 g, 17 mmol), and the mixture was stirred at rt for 6 h. The deposited solid was collected by filtration using a membrane filter (T050A047A, Advantec) and recrystallized six times from AcOEt (50, 25, 35, 40, 40, and then 40 mL) to give the diastereopure (R_p)-**1b**·(*S*)-PEA salt (0.85 g, 2.6 mmol, 16%) as a white powder. To the diastereopure salt thus obtained was added 1 M aq HCl (100 mL), and the mixture was stirred for 1 h and extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford enantiopure (R_p)-**1b** (0.51 g, 2.5 mmol, 96%) as an oily substance. (R_p)-**1b**·(*S*)-PEA salt: mp 134.0−134.5 °C. (R_p)-**1b**: $[\alpha]^{20}_D = +15°$ (*c* 1.5, EtOH; lit. $[\alpha]_D = +15.1°$).[9] The IR, ^1H NMR, ^{13}C NMR, and ^{31}P NMR were identical with those of (R_p)-**1b**.

Synthesis of Enantiopure 1c. To a solution of phenylthiophosphonoic dichloride (8.00 g, 38 mmol) in benzene (15 mL) were successively added triethylamine (4.25 g, 42 mmol) and 1-propanol (25.24 g, 0.42 mol) drop by drop, and the mixture was stirred at 40 °C overnight. After removal of the unreacted 1-propanol under reduced pressure, the solution was washed with H_2O (2 × 300 mL) and the combined aqueous layers were extracted with C_6H_6 (3 × 300 mL). The combined organic layers were washed with aq NaCl (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude mixture of *O*,*O*′-dipropyl phenylphosphonothioate and *O*-propyl phenylthiophosphonic chloride (9.09 g, 20:80 on the basis of the ^{31}P NMR integrations, quantitative) as an oily substance.

O,*O*′-Dipropyl phenylphosphonothioate and *O*-propyl phenylthiophosphonic chloride could be separated by the preparative TLC of an aliquot of the mixture.

O,*O*′-Dipropyl phenylphosphonothioate: IR (NaCl) 1462, 1122, 1058, 1009, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, J = 7.4 Hz, 6H), 1.63−1.75 (m, 4H), 4.02 (t, J = 7.8 Hz, 4H), 7.42−7.53 (m, 3H), 7.87−7.95 (m, 2H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 87.43.

O-Propyl phenylthiophosphonic chloride: IR (NaCl) 1463, 1377, 1140, 1060, 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J = 7.1 Hz, 3H), 1.64−1.75 (m, 2H), 4.10 (t, J = 6.6 Hz, 2H), 7.39−7.54 (m, 3H), 7.83−7.95 (m, 2H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 76.91.

A solution of the crude mixture of *O*,*O*′-dipropyl phenylphosphonothioate and *O*-propyl phenylthiophosphonic chloride (9.09 g, 38 mmol) thus obtained in a mixture of 7 M KOH (8 mL) and 1-propanol (55 mL) was stirred at 100 °C overnight. The solution was concentrated under reduced pressure to remove 1-propanol and extracted with CH_2Cl_2 (3 × 200 mL). The aqueous layer was acidified with 3 M aq HCl (400 mL), and the acidic aqueous solution was extracted with CH_2Cl_2 (3 × 200 mL). The combined extracts were washed with saturated aq NaCl (100 mL) and then dried over anhydrous Na_2SO_4. The concentration of the organic solution under reduced pressure gave crude racemic *O*-propyl phenylphosphonothioic acid (rac-**1c**; 5.63 g, 26 mmol, 68%) with satisfactory purity for the following enantioseparation as an oily substance. IR (NaCl) 2980, 2350, 1440, 1380, 1120, 990, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J = 7.5 Hz, 3H), 1.68−

1.76 (m, 2H), 4.06 (t, J = 7.5 Hz, 2H), 7.46−7.52 (m, 3H), 7.89−7.96 (m, 2H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 82.13.

To a solution of rac-**1c** (4.10 g, 19 mmol) in Et_2O (60 mL) was added (1*S*,2*R*)-AI (2.80 g, 19 mmol), and the mixture was stirred at rt for 6 h. The deposited solid was collected by filtration using a membrane filter (T050A047A, Advantec) and recrystallized once from AcOEt/hexane (2:1, 160 mL) to give the diastereopure (R_p)-**1c·**(1*S*,2*R*)-AI salt (1.51 g, 4 mmol, 44%) as a white powder. To the diastereopure salt thus obtained was added 1 M aq HCl (300 mL), and the mixture was stirred for 1 h at 0 °C and extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford enantiopure (R_p)-*O*-propyl phenylphosphonothioic acid ((R_p)-**1c**; 0.86 g, 4 mmol, quantitative) as an oily substance. The enantiomeric excess of (R_p)-**1c** thus obtained was determined by a HPLC analysis (Daicel CHIRALCEL OJ-RH; eluent, $HClO_4$ (pH 2)/CH_3CN = 8:2; flow rate, 0.5 mL/min; t_1 (S_p isomer) = 28 min, t_2 (R_p isomer) = 34 min; enantiomeric excess, >99%). (R_p)-**1c·**(1*S*,2*R*)-AI salt: mp 163.5−164.0 °C. (R_p)-**1c**: $[\alpha]^{20}_D$ = +8° (*c* 0.6, EtOH); IR (NaCl) 2980, 2350, 1440, 1380, 1120, 990, 730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J = 7.5 Hz, 3H), 1.68−1.76 (m, 2H), 4.06 (t, J = 7.5 Hz, 2H), 7.46−7.52 (m, 3H), 7.89−7.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.31, 23.74, 68.33, 128.45, 130.76, 132.40; ^{31}P NMR (121 MHz, $CDCl_3$) δ 82.13. Anal. Calcd for $C_9H_{13}O_2PS$: C, 49.99; H, 6.06. Found: C, 49.82; H, 6.00.

Synthesis of Enantiopure 1d. To a solution of phenylthiophosphonoic dichloride (20.00 g, 95 mmol) in CH_2Cl_2 (40 mL) was slowly added a mixture of triethylamine (19.20 g, 190 mmol) and phenol (17.90 g, 190 mmol) in CH_2Cl_2 (60 mL) over a period of 1 h, and the mixture was stirred at 40 °C for 4 h. After removal of the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2 (300 mL). The CH_2Cl_2 solution was washed with H_2O (3 × 300 mL), and the combined aqueous layers were extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were washed with aq NaCl (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude *O*,*O*′-diphenyl phenylphosphonothioate (30.96 g, 95 mmol, quantitative) as an oily substance. IR (NaCl) 1459, 1376, 1119, 721 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09−7.20 (m, 2H), 7.26−7.31 (m, 8H), 7.51−7.63 (m, 3H), 8.09−8.16 (m, 2H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 83.64.

A solution of crude *O*,*O*′-diphenyl phenylphosphonothioate (30.96 g, 95 mmol) in a mixture of 5 M aq KOH (50 mL) and dioxane (300 mL) was stirred at 45 °C for 8 h. The solution was concentrated under reduced pressure to remove dioxane, and the aqueous solution was extracted with CH_2Cl_2 (3 × 200 mL). The aqueous layer was acidified with 3 M aq HCl (400 mL), and the acidic aqueous solution was extracted with CH_2Cl_2 (3 × 200 mL). The combined extracts were washed with saturated aq NaCl (100 mL) and dried over anhydrous Na_2SO_4. The concentration of the organic solution under reduced pressure gave crude racemic *O*-phenyl phenylphosphonothioic acid (rac-**1d**; 20.54 g, 82 mmol, 86%) with satisfactory purity for the following enantioseparation as an oily substance. IR (NaCl) 3180, 2380, 1590, 1490, 1230, 730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13−7.19 (m, 3H), 7.26−7.33 (m, 2H), 7.48−7.60 (m, 3H), 7.98−8.05 (m, 2H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 80.53.

To a solution of rac-**1d** (9.50 g, 38 mmol) in AcOEt/hexane (1:1, 40 mL) was added (1*R*,2*S*)-NE (3.48 g, 23 mmol), and the mixture was refluxed for 10 h. Then the solution was slowly cooled to rt to give a white solid mass. The solid mass was collected by filtration using a membrane filter (T050A047A, Advantec) and recrystallized three times from THF/hexane (3:1, 20 mL; 3:1, 10 mL; 3:1, 5 mL) to give the diastereopure (R_p)-**1d·**(1*R*,2*S*)-NE salt (1.82 g, 4.5 mmol, 24%) as a white powder. To the diastereopure salt thus obtained was added 1 M aq HCl (200 mL), and the mixture was stirred for 1 h and extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford enantiopure (R_p)-*O*-phenyl phenylphosphonothioic acid ((R_p)-**1d**; 1.12 g, 4.5 mmol, quantitative) as an oily substance. The enantiomeric excess of (R_p)-**1d** thus obtained was determined by a HPLC analysis (Daicel CHIRALCEL OJ-RH; eluent, $HClO_4$ (pH 2)/CH_3CN = 9:1; flow rate, 0.5 mL/min; t_1 (S_p isomer) = 33 min, t_2 (R_p isomer) = 39 min; enantiomeric excess, >99%). (R_p)-**1d·**(1*R*,2*S*)-NE salt: mp 155.5−156.0 °C. (R_p)-**1d**: $[\alpha]^{20}_D$ = +34° (*c* 0.5, EtOH); IR (NaCl) 3180, 2380, 1590, 1490, 1230, 730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13−7.19 (m, 3H), 7.26−7.33 (m, 2H), 7.48−7.60 (m, 3H), 7.98−8.05 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 121.83, 125.39, 128.49, 129.57, 130.50, 132.72; ^{31}P NMR (121 MHz, $CDCl_3$) δ 80.53.

An elemental analysis was performed on the salt of **1d** with (1*R*,2*S*)-NE as a result of the instability of **1d**. Anal. Calcd for $C_{21}H_{24}NO_3PS$: C, 62.83; H, 6.03; N, 3.49. Found: C, 62.61; H, 6.06; N, 3.30.

Typical Procedure for the Enantioseparation of Racemic Amines with Enantiopure 1a−d. To a solution of **1b** (168 mg, 0.83 mmol) in Et_2O (1 mL) was added a solution of racemic PEA (**2a**; 100 mg, 0.83 mmol) in Et_2O (1 mL), and the mixture was stirred at rt for 6 h. The deposited powder was collected by filtration, washed with hexane, and dried under reduced pressure to give the corresponding diastereomeric salt (104 mg, 0.32 mmol, 78% based on a half amount of **2a** used). The salt was dissolved in 1 M aq KOH (100 mL), and the aqueous solution was extracted with chloroform (3 × 100 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give enantio-enriched PEA (39 mg, 0.32 mmol).

The enantiomeric excesses of the amines were determined by HPLC analyses on a Daicel Chiralcel CrownPak CR(+) for **2a**−**g**,**j**,**k**,**o**, **10**, **11**, **12**, and **13**, on a Daicel Chiralcel OD-H for **2h**,**i**, **5**, **6**, **7**, and **8**, on a Daicel Chiralcel OJ-RH for **3**, and on a Daicel Chiralcel AD for **14**.

Supporting Information Available: General methods. X-ray diffraction charts of the less-soluble **1a·2a**, **1b·2a**, **1b·2f**, and **1b·2o** salts deposited in the enantioseparation and obtained under diffusion conditions. ^{1}H and ^{31}P NMR spectra of (S_p)-**1a**, (S_p)-**1b**, (R_p)-**1c**, and (R_p)-**1d**. CIF files for the crystals of (S_p)-**1b·**(*R*)-**2g**, (R_p)-**1b·**(*R*)-**2h**, (R_p)-**1b·**(*S*)-**2i**, (S_p)-**1b·**(*R*)-**2o**, (S_p)-**1b·**(*R*)-**3**, (R_p)-**1b·**(*S*)-**5**, (R_p)-**1b·**(*R*)-**6**, (R_p)-**1b·**(1*S*,2*R*)-**11·**H_2O, (R_p)-**1c·**(*S*)-**2b**, (R_p)-**1d·**(*R*)-**2a**, and (R_p)-**1d·**(*S*)-**2a** salts. This material is available free of charge via the Internet at http://pubs.acs.org.

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