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Synthesis and chiral recognition ability of *O*-phenyl ethylphosphonothioic acid with a conformationally flexible phenoxy group for CH/π interaction

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Abstract—Enantiopure *O*-phenyl ethylphosphonothioic acid **1** was easily obtained by the enantioseparation of racemic **1**, which was prepared from commercially available phosphorothioic trichloride in four steps. Enantiopure **1** was found to show an excellent chiral recognition ability for various 1-arylethylamine derivatives during the diastereomeric salt formation. In particular, enantiopure **1** was able to recognize the chirality of *o*- and *m*-substituted 1-arylethylamine derivatives, of which the chirality is generally difficult to establish by conventional resolving agents. X-ray crystallographic analyses of the less-soluble diastereomeric salts revealed that the conformation of the phenoxy group in enantiopure **1** could change in the diastereomeric salt crystals and that the excellent chiral recognition ability of enantiopure **1** resulted from the effective CH/π interaction of the phenoxy phenyl group.
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1. Introduction

Chiral phosphorus (*P*-chiral) compounds have been attracting increasing interest due to their unique properties arising from the coordinative/functional group itself being chiral. Some enantiopure phosphorus compounds have been widely used as chiral solvating agents[1] and chiral ligands[2] in solution, and chiral recognition and induction mechanisms have been discussed on the basis of ^{1}H NMR data. However, to date there is only one report for the study on the mechanism of chiral recognition by *P*-chiral compounds in solution, inferred from the results of X-ray crystallographic analyses.[3] On the other hand, we have previously reported that *P*-chiral compounds could recognize the chirality of substrates in the crystalline state, as well as in solution; *O*-alkyl phenylphosphonothioic acids showed a superior chiral recognition ability for various racemic primary amines during diastereomeric salt formation.[4] X-ray crystallographic studies on the less- and more-soluble diastereomeric salts revealed that for the chiral recognition of racemic primary amines with *O*-alkyl phenylphosphonothioic acids, there were two obviously different mechanisms from the viewpoint of hydrogen-bonding networks constructed in the less-soluble diastereomeric salts; chiral recognitions through the formation of a cluster-like hydrogen-bonding network and a columnar hydrogen-bonding network. Moreover, the phenyl group of *O*-alkyl phenylphosphonothioic acids was found to play an important role in chiral recognition of the racemic primary amines to cause a dramatic change of the chiral recognition mechanism. These results gave valuable information for the elucidation of the mechanism of chiral recognition by *P*-chiral compounds, not only in the crystalline state, but also in solutions.

This first success in chiral recognition by *O*-alkyl phenylphosphonothioic acids during diastereomeric salt formation prompted us to develop another new chiral phosphonothioic acid, which could recognize the chirality of a wide variety of racemic primary amines. We designed enantiopure *O*-phenyl ethylphosphonothioic acid with the expectation that the phenoxy group, which is conformationally flexible, would change its conformation depending on the shape of target 1-phenylethylamine derivatives to realize close packing of the component molecules in diastereomeric salt crystals with the aid of the efficient CH/π

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interaction(s) between the phenoxy phenyl group and the phenyl group in the target amines.

Herein, we report the synthesis and chiral recognition ability of enantiopure *O*-phenyl ethylphosphonothioic acid, as well as a chiral recognition mechanism on the basis of X-ray crystallographic analyses.

2. Results and discussion

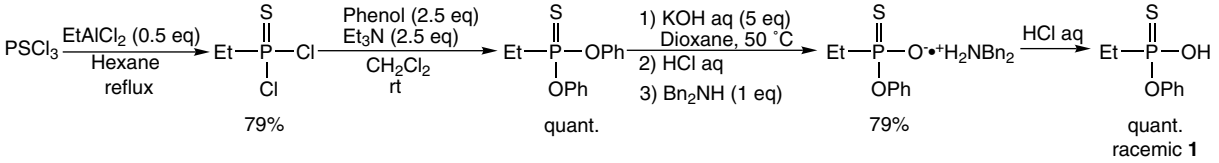
2.1. Synthesis of enantiopure *O*-phenyl ethylphosphonothioic acid 1

Racemic *O*-phenyl ethylphosphonothioic acid **1** was synthesized from commercially available phosphorothioic trichloride in four steps, according to the procedures described for the synthesis of nucleic acid derivatives[5] (Scheme 1). Phosphorothioic trichloride was allowed to react with 0.5 equiv of ethylaluminum dichloride in hexane at reflux to give crude ethylphosphonothioic dichloride in 79% yield based on the ethylaluminum dichloride used (40% yield based on phosphorothioic trichloride used). However, the distillation of crude ethylphosphonothioic dichloride resulted in a very low yield (20%), due to its thermal instability. Therefore, crude ethylphosphonothioic dichloride was used for the following step without further purification. The reaction of crude ethylphosphonothioic dichloride with 2.5 equiv of phenol in the presence of triethylamine (2.5 equiv) at room temperature afforded crude *O*,*O*′-diphenyl ethylphosphonothioate in quantitative yield, which was hydrolyzed by treatment with 4 M aqueous KOH solution in dioxane at 50 °C to give crude racemic **1** with satisfactory purity for the following enantioseparation; chemically pure **1** was easily obtained upon crystallizing the salt with dibenzylamine, followed by treatment of the salt with hydrochloric acid.

The enantioseparation of racemic **1** was attempted by using commercially available resolving agents such as enantiopure 1-phenylethylamine (PEA), *erythro*-2-amino-1,2-diphenylethanol (ADPE), and norephedrine (NE). The results are summarized in Table 1. Among the resolving agents examined, PEA was found to be the most suitable for the enantioseparation of racemic **1** from the viewpoints of yield of the diastereomeric salt and the enantiomeric excess of **1** incorporated in the salt. Then, we adopted enantiopure PEA for the enantioseparation of **1** on a large scale. As a result, enantiopure (*Rp*)-**1** was obtained in 53% yield (based on a half amount of racemic **1** used), when (*R*)-PEA was used as the resolving agent in the first stage (Scheme 2). The absolute configuration of **1** in the diastereomerically pure salt thus obtained was determined to be *Rp* in relation to that of (*R*)-PEA on the basis of the X-ray crystallographic analysis of the salt (Fig. 1). The antipode, (*Sp*)-**1**, was obtained in 73% by the enantioseparation of (*Sp*)-enriched **1**, recovered from the mother liquor, with (*S*)-PEA.

2.2. Chiral recognition ability of enantiopure *O*-phenyl ethylphosphonothioic acid 1

The chiral recognition ability of enantiopure *O*-phenyl ethylphosphonothioic acid **1** was examined for various racemic 1-phenylethylamine derivatives. As shown in Table 2, enantiopure **1** showed excellent chiral recognition ability for most of the racemic amines examined; only upon crystallizing the diastereomeric salts, the enantiomeric excesses of the amines incorporated in the corresponding diastereomeric salts and the efficiencies (the yield of the diastereomeric salt × the enantiomeric excess of the amine) exceeded 85% and 0.63, respectively, except in the case of amine **2f** (entry 6). However, the efficiency (0.53) for **2f** was even acceptable from the general viewpoint of chiral recognition during diastereomeric salt formation. It is noteworthy that enantiopure **1** effectively recognized the

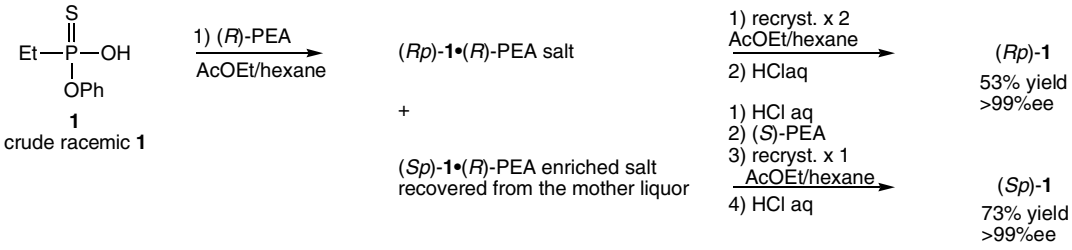


Scheme 1. Synthesis of racemic **1**.

Table 1. Enantioseparation of racemic **1** with basic resolving agents

Entry	Resolving agent	Amount of solvent[a] (mL) AcOEt/hexane	Temperature (°C)	Yield (%)[b]	ee (%)[c]
1	(*R*)-PEA[d]	1.0/0.0	rt	47	>99 (*Rp*)
2	(*R*)-PEA[d]	0.8/0.2	rt	62	98 (*Rp*)
3	(1*R*,2*S*)-ADPE[e]	1.0/1.5	rt	41	64 (*Rp*)
4	(1*S*,2*R*)-NE[f]	1.2/2.6	−10	37	95 (*Sp*)

[a] Amount of the solvent normalized to a 1 mmol scale.
[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] 1-Phenylethylamine.
[e] 2-Amino-1,2-diphenylethanol.
[f] Norephedrine.



Scheme 2. Synthesis of enantiopure **1**.

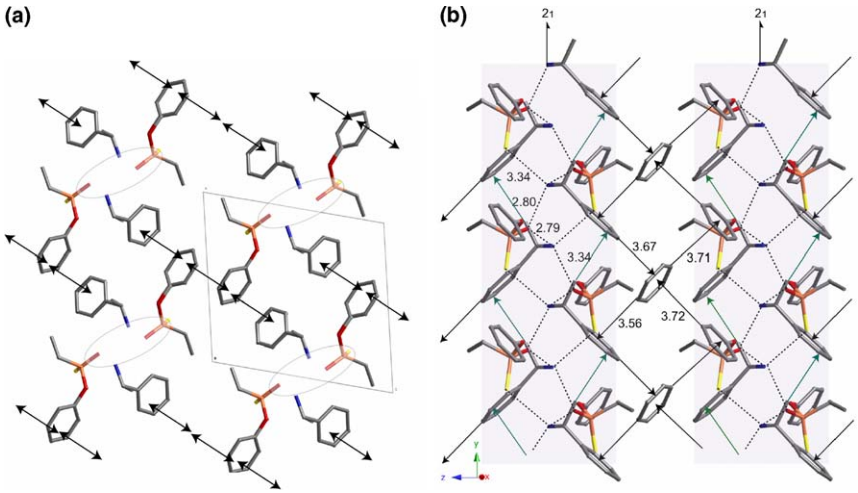


Figure 1. Crystal structure of the less-soluble (*Rp*)-**1**·(*R*)-**2a** salt: (a) top view and (b) side view. The gray circles indicate hydrogen-bonding networks. The dotted lines, black arrows, and green arrows show hydrogen bonds, inter-columnar T-shaped CH(sp^2)/π interactions, and intra-columnar CH(sp^3)/π interaction, respectively. The bond distances are in Angstroms.

Table 2. Enantioseparation of 1-phenylethylamine derivatives with enantiopure **1**

2a: R = H
2b: R = *o*-Me
2c: R = *o*-Br
2d: R = *m*-Me
2e: R = *m*-Br
2f: R = *p*-Me
2g: R = *p*-Br
2h: R = *p*-Cl
2i: R = *p*-F
2j: R = *p*-Et

Entry	Racemic amine	Amount of solvent[a] (mL) AcOEt/hexane	Yield (%)[b]	ee (%)[c]	Efficiency[d]
1[e]	**2a**	0.4/0.1	82	97 (*R*)[f]	0.80
2[g]	**2b**	3.9/0	84	97 (*S*)	0.82
3[g]	**2c**	5.0/0	80	>99 (*S*)	0.80
4[e]	**2d**	1.2/7.3	76	96 (*R*)	0.73
5[g]	**2e**	1.9/4.8	65	97 (*S*)	0.63
6[e]	**2f**	0.6/0.9	79	67 (*R*)	0.53
7[g]	**2g**	0.5/0	86	88 (*S*)	0.76
8[e]	**2h**	4.6/1.3	75	87 (*R*)	0.65
9[g]	**2i**	0.5/0	69	94 (*S*)	0.65
10[g]	**2j**	0.6/5.6	91	85 (*S*)	0.78

[a] Amount of the solvent normalized to a 1 mmol scale.
[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] (*Rp*)-**1** was used.
[f] Absolute configuration of the major enantiomer, which was determined by an X-ray crystallographic analysis and/or deduced on the basis of the elution order in the HPLC analysis.
[g] (*Sp*)-**1** was used.

chirality of *o*- and *m*-substituted amines **2b–e** (entries 2–5), which is usually difficult to distinguish by conventional carboxylic acid-type resolving agents due to the steric repulsion between the substituent and a columnar

hydrogen-bonding network consisting of ammonium cations and carboxylate anions.[6] It should be also noted that in all cases the absolute configurations of the amines **2a**–**j** majorly incorporated in the less-soluble diastereomeric salts are the same with respect to the absolute configuration of enantiopure **1** used, indicating that the chirality of amines **2a**–**j** was recognized by enantiopure **1** through the same mechanism.

2.3. Mechanism of chiral recognition by enantiopure *O*-phenyl ethylphosphonothioic acid 1

In order to clarify the chiral recognition mechanism by enantiopure *O*-phenyl ethylphosphonothioic acid **1**, we performed the X-ray crystallographic analyses of the less-soluble diastereomeric salts. Single crystals of the less-soluble diastereomeric salts of (*R*)-PEA **2a**, (*S*)-1-(2-methylphenyl)ethylamine **2b**, and (*S*)-1-(4-fluorophenyl)ethylamine **2i** with (*Rp*)- or (*Sp*)-**1** suitable for X-ray crystallographic analyses were obtained. The crystal structures are shown in Figures 1–3, respectively.

In all of the diastereomeric salt crystals, a columnar hydrogen-bonding network with a 2-fold screw axis in the center (2_1 column), which consists of the ammonium cations and phosphonothioate anions, is commonly formed. The bond lengths and angles are close to each other in the three salt crystals. Moreover, the networks are very similar to those

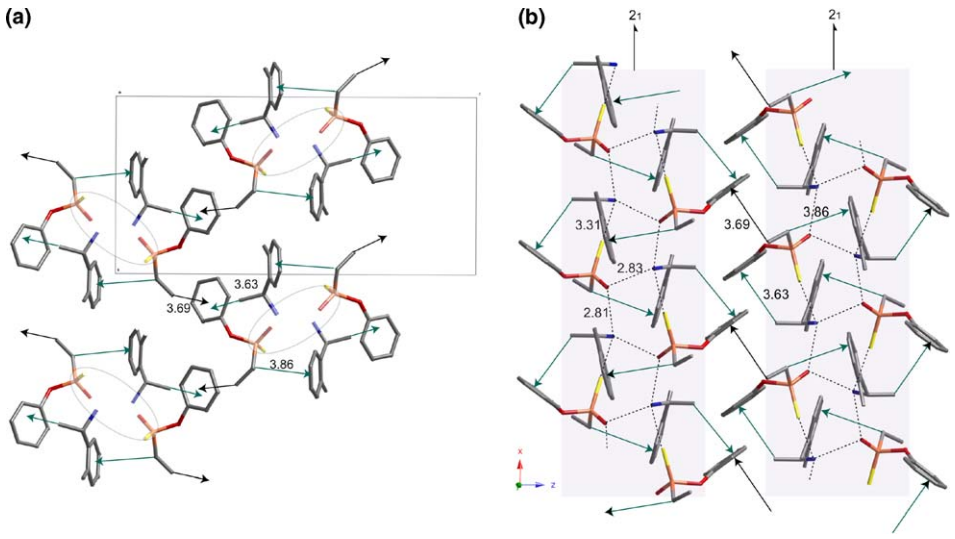


Figure 2. Crystal structure of the less-soluble (*Sp*)-**1**·(*S*)-**2b** salt: (a) top view and (b) side view. The gray circles indicate hydrogen-bonding networks. The dotted lines, black arrows, and green arrows show hydrogen bonds, inter-columnar CH(sp^3)/π interaction, and intra-columnar CH(sp^3)/π interaction, respectively. The bond distances are in Angstroms.

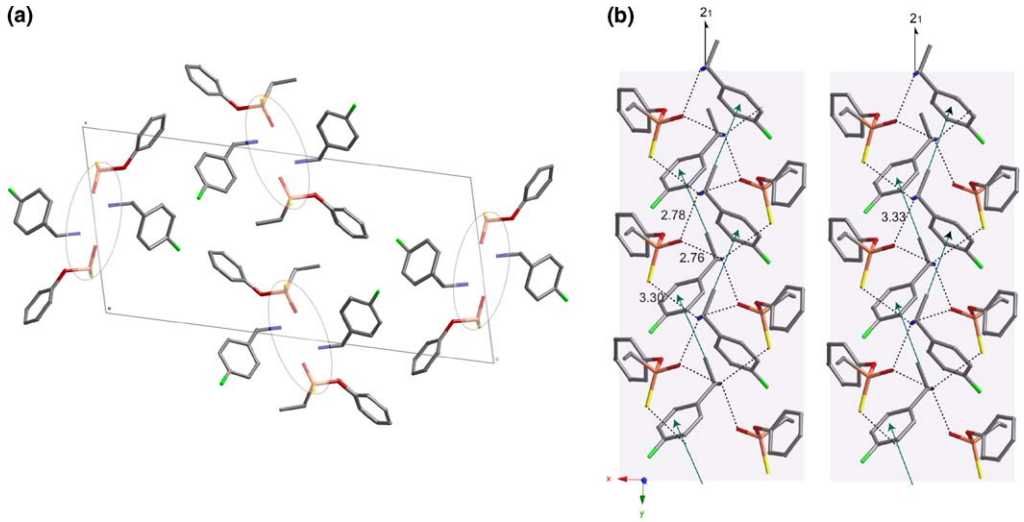


Figure 3. Crystal structure of the less-soluble (*Sp*)-**1**·(*S*)-**2e** salt: (a) top view and (b) side view. The gray circles indicate hydrogen-bonding networks. The dotted lines and green arrows show hydrogen bonds and intra-columnar CH(sp^3)/π interactions, respectively. The bond distances are in Angstroms.

in the salt crystals of chiral primary amines with *O*-ethyl phenylphosphonothioic acids[4a] and with mandelic acid derivatives.[6] However, the packing modes of the 2_1 columns for the three salt crystals are slightly different from each other and are inevitably different from those for the salt crystals with *O*-ethyl phenylphosphonothioic acid and with mandelic acid derivatives from the viewpoint of CH/π interaction.

The packing of 2_1 columns in the less-soluble diastereomeric (*Rp*)-**1**·(*R*)-**2a** salt crystal is quite effective, because three kinds of T-shaped inter-columnar CH(sp^2)/π interactions exist; one column contacts with the neighboring columns by six kinds of CH(sp^2)/π interactions (Fig. 1a). The side view of the columns indicates that intra-columnar CH(sp^3)/π interaction also exists between the methyl group at the α-position of the **2a** molecule and the phenyl group of the **2a** molecule in the neighboring unit cell along the *b*-axis (Fig. 1b). The distances for the inter-columnar CH(sp^2)/π interactions and the intra-columnar CH(sp^3)/π interaction are relatively short; 3.56–3.72 and 3.34 Å, respectively. The angles for the inter-columnar CH(sp^2)/π interactions are between 85° and 91° to achieve almost complete T-shaped contacts, which have been suggested to be energetically favorable.[7] Thus, the crystal structure of the less-soluble diastereomeric (*Rp*)-**1**·(*R*)-**2a** salt strongly indicates that the salt crystal is effectively stabilized not only by the formation of a helical hydrogen-bonding network but also by multiple CH/π interactions.

The packing mode of 2_1 columns in the less-soluble diastereomeric (*Sp*)-**1**·(*S*)-**2b** salt crystal is obviously less favorable, compared with that in the (*Rp*)-**1**·(*R*)-**2a** salt crystal. As shown in Figure 2a, there is only one inter-columnar CH(sp^3)/π interaction in the salt crystal. The top view of the columns shows that the conformation of the phenyl group of (*S*)-**2b** in the (*Sp*)-**1**·(*S*)-**2b** salt crystal is largely different from that in the (*Rp*)-**1**·(*R*)-**2a** salt crystal; the phenyl group of (*S*)-**2b** is located perpendicular to the neighboring phenyl group of the (*Sp*)-**1** molecules to avoid repulsion between the methyl group at the *o*-position in the (*S*)-**2b** molecule and the phenyl group of the (*Sp*)-**1** molecule. On the other hand, intra-columnar CH(sp^3)/π interaction increases in number (Fig. 2b), compared with that in the (*Rp*)-**1**·(*R*)-**2a** salt crystal. The methylene group of the (*Sp*)-**1** molecule interacts with the perpendicularly located phenyl group of the (*S*)-**2b** molecule at a general distance of 3.86 Å. Moreover, the methyl group of the (*S*)-**2b** molecule interacts with the neighboring phenyl group of the (*Sp*)-**1** molecule at a relatively short distance of 3.63 Å. The formation of these interactions results from the tunability of the conformation of the phenoxy group in (*Sp*)-**1** owing to the freely rotatable C–O–P bond. Thus, the crystal structure of the less-soluble (*Sp*)-**1**·(*S*)-**2b** salt crystal revealed that (*Sp*)-**1** can flexibly change its conformation, depending on a target amine, to stabilize the salt crystal more effectively through the formation of intra-columnar CH(sp^3)/π interactions instead of inter-columnar CH/π interaction(s).

Different from the above two cases, there exists no inter-columnar CH/π interaction in the less-soluble diastereomeric (*Sp*)-**1**·(*S*)-**2e** salt crystal as shown in Figure 3a. This phenomenon would arise from the relatively long molecular length of (*S*)-**2e**, compared to those of **2a** and **2b**, and is consistent with the general tendency that a large difference in molecular length between a resolving agent and a target molecule is disadvantageous for the packing of columns or sheets in a diastereomeric salt crystal.[8] However, in the (*Sp*)-**1**·(*S*)-**2e** salt crystal, there is only one highly effective CH(sp^3)/π interaction between the methyl group at the α-position of the **2e** molecule and the phenyl group of the **2e** molecule in the neighboring unit cell along the *b*-axis at a very short distance of 3.33 Å, which is almost the same as those for CH(sp^2)/π interactions, to stabilize the column. Such short intra-columnar CH(sp^3)/π interactions have never been reported for the crystals of the less-soluble diastereomeric salts with enantiopure phosphonothioic acids and with enantiopure carboxylic acids, as far as we know.[9] The formation of the strong intra-columnar CH(sp^3)/π interaction would arise from the conformational flexibility of the phenoxy group in enantiopure **1**.

A less effective packing of columns might result in lower efficiency of the enantioseparation of the *p*-substituted amines (entries 6–10), compared with that of the *o*- and *m*-substituted amines. However, moderate to excellent chiral recognition by enantiopure **1** in a range of 67–94% enantiomeric excesses was achieved as a result of the formation of strong intra-columnar CH(sp^3)/π interaction, to reinforce the hydrogen-bonded column in the crystals.

3. Conclusion

A novel resolving agent, enantiopure *O*-phenyl ethylphosphonothioic acid **1**, was synthesized by a method applicable to a large-scale preparation. The chiral recognition ability of enantiopure **1** was moderate to excellent for various 1-phenylethylamine derivatives; the efficiencies were in a range of 0.53–0.82. The X-ray crystallographic analyses of the less-soluble diastereomeric salts revealed that the high performance of enantiopure **1** in the enantioseparation resulted from the formation of inter-columnar CH(sp^2)/π, inter-columnar CH(sp^3)/π and/or intra-columnar CH(sp^3)/π interaction. The CH/π interaction site of enantiopure **1**, which can easily change its conformation in salt crystals, played an important role in decreasing the dependency on the shape of target amines and made the chiral recognition ability of enantiopure **1** moderate to excellent for a variety of racemic 1-phenylethylamine derivatives.

4. Experimental

4.1. General

Solvents were purified, dried, and stored according to standard procedures. TLC analyses were performed using Merck pre-coated silica gel plates (Art. 5715). Column chromatography was carried out using silica gel 60

(0.063–0.200 mm). Phosphorothioic trichloride was purchased from Aldrich Co. Melting points were measured using a Laboratory Devices Mel-Temp and are uncorrected. IR spectra were recorded on a JASCO FT/IR-480 Plus spectrophotometer. Optical rotations were recorded on a JASCO DIP-360 in a 1-cm cell. ^{1}H (300 MHz) and ^{31}P NMR (121 MHz) spectra were measured on a Varian MERCURY 300 instrument. Chemical shifts (δ) are reported as parts per million relative to internal tetramethylsilane for ^{1}H NMR and to external 85% H_3PO_4 for ^{31}P NMR; the coupling constants are in Hertz. HPLC analyses were performed on a Daicel CHIRALCEL OJ-H for **2b** and OD-H for **2d**, and Daicel CROWNPAK CR (+) for **2a**, **2c**, and **2e**–**j**. Intensity data for the X-ray crystallographic analyses were collected by an imaging plate (IP) instrument using a Mo X-ray source.

4.2. Ethylphosphonothioic dichloride

To a solution of phosphorothioic trichloride (10 mL, 100 mmol) in dry hexane (10 mL), 1 M ethylaluminum dichloride in dry hexane (50 mL, 50 mmol) was added at 0 °C under an argon atmosphere. After being refluxed for 8 h, the reaction mixture was cooled to 0 °C, and H_2O/1,4-dioxane (5 mL/15 mL) and H_2O (80 mL) were successively added to the mixture. The organic layer was separated, successively washed with H_2O (2×150 mL) and brine (150 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude ethylphosphonothioic dichloride (6.47 g, 39.6 mmol, 79%) with satisfactory purity for the following reaction as a colorless oil. IR (NaCl): ν 3000–2850, 1720, 1455, 1380, 1030, 1010, 775, 745, 675, 645 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (dt, $J_{P-H} = 32$ Hz, $J_{H-H} = 8$ Hz, 3H), 2.81 (dq, $J_{P-H} = 12$ Hz, $J_{H-H} = 8$ Hz, 2H). ^{31}P NMR (121 MHz, $CDCl_3$): δ 95.13.

4.3. *O*,*O*′-Diphenyl ethylphosphonothioate

To a solution of crude ethylphosphonothioic dichloride (4.98 g, 31 mmol) in dichloromethane (15 mL) was added dropwise a mixture of phenol (7.19 g, 76 mmol) and triethylamine (11 mL, 76 mmol) in dichloromethane (25 mL) at 0 °C under an argon atmosphere, and the mixture was stirred at rt for 3 h. After removal of unreacted triethylamine and dichloromethane under reduced pressure, dichloromethane (80 mL) was added to the residue. The resultant solution was successively washed with H_2O (3×80 mL) and brine (80 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude *O*,*O*′-diphenyl ethylphosphonothioate (8.57 g, 31 mmol, quant.) with satisfactory purity for the following reaction as a colorless oil.

For an elemental analysis, an aliquot of the crude product was purified by silica gel chromatography. IR (NaCl): ν 2979, 2939, 1592, 1489, 1455, 1211, 1189, 1161, 918, 798, 688 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (dt, $J_{P-H} = 23$ Hz, $J_{H-H} = 8$ Hz, 3H), 2.36 (dq, $J_{P-H} = 15$ Hz, $J_{H-H} = 8$ Hz, 2H), 7.11–7.36 (m, 10H). ^{31}P NMR (121 MHz, $CDCl_3$): δ 98.62. HRMS (EI): m/z calcd for $C_{14}H_{15}O_2PS$ 278.0530, found 278.0538.

4.4. Racemic *O*-phenyl ethylphosphonothioic acid racemic 1

A solution of crude *O*,*O*′-diphenyl ethylphosphonothioate (8.78 g, 32 mmol) in a mixture of 4 M aqueous KOH solution (40 mL) and 1,4-dioxane (180 mL) was stirred at 50 °C for 6 h. The solution was concentrated under reduced pressure to remove 1,4-dioxane and then extracted with dichloromethane (2×150 mL). The aqueous layer was neutralized with 3 M aqueous HCl solution and extracted with dichloromethane (8×150 mL). The aqueous layer was then acidified with 3 M aqueous HCl solution (30 mL) and extracted with dichloromethane (9×100 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude racemic **1** (6.49 g, 32 mmol, quant.) with satisfactory purity for the following enantioseparation as a colorless oil. For the isolation of the chemically pure **1**, an aliquot of the crude product was purified by the formation of the salt with dibenzylamine. A mixture of crude racemic **1** (643 mg, 3.2 mmol) and dibenzylamine (622 mg, 3.2 mmol) was allowed to crystallize from AcOEt/hexane (3.5 mL/10.5 mL) to give the corresponding salt, which was decomposed upon treatment with 1 M aqueous HCl solution (20 mL) to afford pure racemic **1** (506 mg, 2.5 mmol, 79%) as a colorless oil. IR (NaCl): ν 3000–2900, 2880, 1590, 1485, 1455, 1200, 1160, 920, 780, 685 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (dt, $J_{P-H} = 23$ Hz, $J_{H-H} = 8$ Hz, 3H), 2.20 (dq, $J_{P-H} = 16$ Hz, $J_{H-H} = 8$ Hz, 2H), 7.17–7.22 (m, 3H), 7.32–7.37 (m, 2H). ^{31}P NMR (121 MHz, $CDCl_3$): δ 94.62.

4.5. (*Rp*)-*O*-Phenyl ethylphosphonothioic acid (*Rp*)-1

To a solution of crude racemic **1** (3.73 g, 18.5 mmol) in a mixture of ethyl acetate/hexane (7 mL/1.75 mL), (*R*)-1-phenylethylamine (PEA; 2.24 g, 18.5 mmol) was added, after which the mixture was stirred at reflux for 30 min. The mixture was cooled to rt with stirring and then left for standing at −10 °C for 12 h. The deposited salt was collected by filtration using a membrane filter (T050A047A, ADVANTEC). The salt, which was obtained, was recrystallized twice from ethyl acetate/hexane (15 mL/2 mL and then 15 mL/2.4 mL) to afford diastereopure (*Rp*)-**1**·(*R*)-PEA salt (1.59 g, 4.9 mmol, 53% based on a half amount of racemic **1** used). Mp: 142.5–145.5 °C. IR (KBr): ν 3000–2900, 1588, 1523, 1484, 1205, 1082, 911, 884, 777, 761, 711, 596, 505 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (dt, $J_{P-H} = 23$ Hz, $J_{H-H} = 8$ Hz, 3H), 2.20 (dq, $J_{P-H} = 16$ Hz, $J_{H-H} = 8$ Hz, 2H), 7.17–7.22 (m, 3H), 7.32–7.37 (m, 2H). ^{31}P NMR (121 MHz, $CDCl_3$): δ 82.61.

To the diastereomeric salt thus obtained was added 1 M aqueous KOH solution (80 mL), and the solution was extracted with dichloromethane (5×80 mL). The aqueous layer was acidified with 3 M aqueous HCl solution (50 mL) and then extracted with dichloromethane (6×90 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford enantiopure (*Rp*)-**1** (992 mg, 4.9 mmol, 53% based on a half amount of racemic PEA used) as a yellow oil. The enantiomeric excess of (*Rp*)-**1** thus obtained was determined by HPLC analysis (Daicel CHIRALCEL

OJ-RH; eluent, $HClO_4$ (pH 2)/CH_3CN = 8:2; flow rate, 0.5 mL/min; t_1 (*Rp*-isomer) = 24 min, t_2 (*Sp*-isomer) = 34 min; enantiomeric excess, >99%). $[\alpha]_D^{20} = -9.9$ (*c* 1.23, MeOH). IR (NaCl): *v* 3000–2850, 1592, 1490, 1456, 1200, 1163, 919, 779, 689 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (dt, $J_{P-H} = 23$ Hz, $J_{H-H} = 8$ Hz, 3H), 2.19 (dq, $J_{P-H} = 16$ Hz, $J_{H-H} = 8$ Hz, 2H), 7.17–7.22 (m, 3H), 7.32–7.37 (m, 2H). ^{31}P NMR (121 MHz, $CDCl_3$): δ 94.62. Anal. Calcd for $C_8H_{11}O_2PS$: C, 47.52; H, 5.48. Found: C, 47.28; H, 5.70.

4.6. (*Sp*)-*O*-Phenyl ethylphosphonothioic acid (*Sp*)-1

After concentration of the mother liquor of the initial crystallization in the above procedure, 1 M aqueous KOH solution (50 mL) was added to the residue, and the solution extracted with dichloromethane (3 × 50 mL). The aqueous layer was acidified (pH = 1) with 3 M aqueous HCl solution and then extracted with dichloromethane (3 × 50 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (*Sp*)-enriched **1** (2.47 g, 12.2 mmol). To a solution of (*Sp*)-enriched **1** thus obtained in a mixture of ethyl acetate/hexane (12 mL/2 mL), (*S*)-PEA (1.48 g, 12.2 mmol) was added, and the mixture stirred at reflux for 2 h. After being slowly cooled to rt, the mixture was stirred overnight at rt, and the precipitated crystalline powder collected by filtration. The obtained salt was recrystallized once from ethyl acetate/hexane (22.5 mL/3.8 mL) to afford diastereopure (*Sp*)-**1**·(*S*)-PEA salt (2.11 g, 6.5 mmol, 71% based on a half amount of racemic **1** initially used) (mp: 142.5–145.5 °C). To the diastereomeric salt thus obtained, 1 M aqueous KOH solution (80 mL) was added, and the solution was extracted with dichloromethane (4 × 100 mL). The aqueous layer was acidified with 3 M aqueous HCl solution (70 mL) and then extracted with dichloromethane (5 × 100 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford enantiopure (*Sp*)-**1** (1.32 g, 6.5 mmol, 71% based on a half amount of racemic PEA initially used) as a yellow oil. $[\alpha]_D^{19} = +9.4$ (*c* 2.40, MeOH). The IR, ^1H NMR, and ^{31}P NMR were identical with those of enantiopure (*Rp*)-**1**.

4.7. Preparation of racemic amines

Racemic amines were prepared by the reductive amination of the corresponding ketones according to the procedures described in the literature.[10] To a solution of ketone (30 mmol) in methanol (50 mL), ammonium acetate (300 mmol) and sodium cyanoborohydride (30 mmol) were added at rt. After being stirred for 1 week, 3 M aqueous HCl solution (50 mL) was added dropwise to the reaction mixture. The resulting mixture was concentrated to remove methanol and washed with dichloromethane (3 × 80 mL), and then the aqueous solution was basified (pH = 12) with 3 M aqueous KOH solution (70 mL). The liberated amine was extracted with dichloromethane (3 × 80 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by distillation under reduced pressure.

4.8. General procedure for the enantioseparation of 1-phenylethylamine derivatives with enantiopure 1

To a solution of enantiopure **1** in a mixture of ethyl acetate/hexane (composition, see Tables 1 and 2), 1 equiv of a racemic amine were added. The mixture was stirred under reflux for 2 h, slowly cooled to rt with stirring, and then stirred for 3 h at rt. The precipitated crystalline powder was collected by filtration using a membrane filter (T050A047A, ADVANTEC) and dried under reduced pressure.

4.9. Preparation of single crystals for X-ray crystallography

4.9.1. General procedure for the preparation of single crystals. Single crystals for X-ray crystallographic analyses were prepared by the slow evaporation of the solvents from saturated ethyl acetate/hexane solutions.

4.9.2. Crystal data for (*Rp*)-1·(*R*)-2a salt. $FW = 323.39$, monoclinic, space group $P2_1$, $a = 11.094(11)$, $b = 6.785(5)$, $c = 12.011(2)$ Å, $\beta = 102.921(8)$, $V = 881.2(2)$ $Å^3$, $Z = 2$, $R = 0.0460$, $Rw = 0.0620$. (CCDC 294558). Mp: 142.5–145.5 °C (decomp.).

4.9.3. Crystal data for (*Sp*)-1·(*S*)-2b salt. $FW = 337.42$, orthorhombic, space group $P2_12_12_1$, $a = 7.573(2)$, $b = 10.790(5)$, $c = 21.930(13)$ Å, $V = 1792.0(1)$ $Å^3$, $Z = 4$, $R = 0.0480$, $Rw = 0.0610$. (CCDC 294559). Mp: 167.0–171.5 °C (decomp.).

4.9.4. Crystal data for (*Sp*)-1·(*S*)-2e salt. $FW = 341.38$, monoclinic, space group $P2_1$, $a = 11.591(10)$, $b = 6.683(5)$, $c = 24.156(3)$ Å, $\beta = 104.550(4)$, $V = 1811.2(3)$ $Å^3$, $Z = 4$, $R = 0.0470$, $Rw = 0.0550$. (CCDC 294560). Mp: 143.0–146.0 °C (decomp.).

References

1. (a) Li, K. Y.; Zhou, Z. H.; Chan, A. S. C.; Tang, C. C. *Heteroatom Chem.* **2002**, *1*, 93; (b) Lacour, J.; Vial, L.; Bernardinelli, G. *Org. Lett.* **2002**, *14*, 2309; (c) Omelaficzuk, J.; Mikolajczyk, M. *Tetrahedron: Asymmetry* **1999**, *7*, 2687.
2. (a) Shi, M.; Zhang, W. *Tetrahedron: Asymmetry* **2004**, *15*, 167; (b) Shi, M.; Zhang, W. *Tetrahedron: Asymmetry* **2003**, *14*, 3407; (c) Wang, C.-J.; Shi, M. *J. Org. Chem.* **2003**, *68*, 6229; (d) Wang, C.-J.; Shi, M. *Eur. J. Org. Chem.* **2003**, 2823; (e) Shi, M.; Sui, W.-S. *Tetrahedron: Asymmetry* **2000**, *11*, 835; (f) Shi, M.; Sui, W.-S. *Chirality* **2000**, *12*, 574; (g) Shi, M.; Sui, W.-S. *Tetrahedron: Asymmetry* **2000**, *11*, 773; (h) Shi, M.; Sui, W.-S. *Tetrahedron: Asymmetry* **1999**, *10*, 3319; (i) Bienewald, F.; Ricard, L.; Mercier, F.; Mathey, F. *Tetrahedron: Asymmetry* **1999**, *10*, 4701.
3. Besli, S.; Coles, S. J.; Davies, D. B.; Eaton, R. J.; Hursthouse, M. B.; Kilic, A.; Shaw, R. A.; Yenilmez, C. G.; Yesilot, S. *J. Am. Chem. Soc.* **2003**, *16*, 4943.
4. (a) Kobayashi, Y.; Morisawa, F.; Saigo, K. *J. Org. Chem.* **2006**, *71*, 606; (b) Kobayashi, Y.; Morisawa, F.; Saigo, K. *Org. Lett.* **2004**, *23*, 4227.
5. (a) Mikolajczyk, M.; Midura, W. H.; Schmutzler, R.; Schiebel, H.-M.; Schulze, P. *New J. Chem.* **2001**, *25*, 1073; (b) Maier, L. *Helv. Chim. Acta* **1964**, *47*, 27.

6. (a) Kinbara, K. *Synlett* **2005**, *5*, 732; (b) Kinbara, K.; Saigo, K. In *Topics in Stereochemistry*; Denmark, S. C., Ed.; Wiley & Sons: New York, 2003; Chapter 4.
7. (a) Kobayashi, Y.; Saigo, K. *J. Am. Chem. Soc.* **2005**, *127*, 15054; (b) Tsuzuki, S.; Honda, K.; Uchimaru, T.; Mikami, M.; Tanabe, K. *J. Am. Chem. Soc.* **2000**, *122*, 3746.
8. (a) Kinbara, K.; Harada, Y.; Saigo, K. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1339; (b) Kinbara, K.; Sakai, K.; Hashimoto, Y.; Nohira, H.; Saigo, K. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2615.
9. (a) Kobayashi, Y.; Kurasawa, T.; Kinbara, K.; Saigo, K. *J. Org. Chem.* **2004**, *69*, 7436; (b) Kinbara, K.; Kobayashi, Y.; Saigo, K. *J. Chem. Soc., Perkin Trans. 2* **2000**, 111.
10. Bordh, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.