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Synthesis and chiral recognition ability of *O*-ethyl (2-naphthyl)phosphonothioic acid

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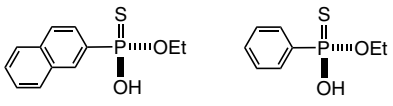
Abstract—Enantiopure *O*-ethyl (2-naphthyl)phosphonothioic acid **1** was designed on the model of *O*-ethyl phenylphosphonothioic acid, based on the fact that the chiral recognition abilities of enantiopure mandelic acid and *cis*-1-aminoindan-2-ol were improved upon by replacing their phenyl/phenylene groups with naphthyl/naphthylene groups, respectively. Enantiopure **1** was easily obtained by the enantioseparation of racemic **1**, which was easily synthesized from commercially available 2-bromonaphthalene and diethoxyphosphonothioic chloride, with enantiopure 1-phenylethylamine. Enantiopure **1** showed an excellent chiral recognition ability for several 1-arylethylamine derivatives during the diastereomeric salt formation. The effect of the enlarged aromatic part of **1** is discussed on the basis of X-ray crystallographic analyses.

1. Introduction

Recently, we have reported the superior chiral recognition ability of *O*-alkyl phenylphosphonothioic acids during diastereomeric salt formation in the enantioseparations of various types of 1-phenylethylamine derivatives; a systematic study on the chiral recognition abilities of enantiopure *O*-methyl, *O*-ethyl, and *O*-propyl phenylphosphonothioic acids revealed that *O*-ethyl phenylphosphonothioic acid **2** was the most effective with a wide applicability.[1,2] X-ray crystallographic studies showed that the excellent chiral recognition ability of **2** was caused by the formation of globular clusters in the less-soluble diastereomeric salts, of which the stacking was highly stabilized by the efficient CH/π interaction between the phenyl group in a cluster and the ethyl group in the neighboring cluster. The formation of the globular clusters in the less-soluble salt always led to excellent chiral recognition with **2**, which resulted in >99–91% enantiomeric excesses (ee) for the amines incorporated in the less-soluble salts. These results suggest that the phenyl and *O*-alkyl groups in **2** play an important role in the realization of the high chiral recognition ability.

On the other hand, the chiral recognition abilities of enantiopure mandelic acid and 1-aminoindan-2-ol have been improved by changing the aromatic parts from the phenyl/phenylene groups to naphthyl/naphthylene groups, respectively (2-naphthylglycolic acid[3] and 1-aminobenz[*f*]indan-2-ol[4]). The effect of the enlargement of the aromatic parts led to a dramatic improvement with respect to the chiral recognition abilities for *p*-substituted 1-phenylethylamine derivatives and *p*-substituted 2-phenylpropanoic acid derivatives with a long molecular length, respectively. Moreover, from a crystallographic point of view, the naphthyl and naphthylene groups commonly provided very effective CH/π interaction sites to stabilize the less-soluble diastereomeric salts.

On the basis of these results, we designed *O*-ethyl (2-naphthyl)phosphonothioic acid **1**, which has a naphthyl group, for more effective CH/π interaction than the phenyl group in the prototype of *O*-ethyl phenylphosphonothioic acid **2**. Herein, we report the synthesis and chiral recognition ability of enantiopure **1** as well as the chiral recognition mechanism based on the X-ray crystallographic analyses of the corresponding less-soluble diastereomeric salts.



1 **2**

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2. Results and discussion

2.1. Synthesis of enantiopure *O*-ethyl (2-naphthyl)-phosphonothioic acid 1

Racemic *O*-ethyl (2-naphthyl)phosphonothioic acid **1** was synthesized from commercially available 2-bromonaphthalene and diethoxyphosphonothioic chloride, as shown in Scheme 1. 2-Bromonaphthalene was treated with 1 equiv of *n*-BuLi in ether and then allowed to react with diethoxyphosphonothioic chloride to give crude *O*,*O*′-diethyl (2-naphthyl)phosphonothioate, which was hydrolyzed with 8 M aqueous KOH solution to afford crude racemic **1**.[5] Crude racemic **1** was purified upon crystallizing the salt with dicyclohexylamine from $CHCl_3$, followed by decomposition of the salt, to give chemically pure racemic **1** (78% total yield based on diethoxyphosphonothioic chloride used).[5]

Enantiopure **1** was obtained by the enantioseparation of racemic **1** with enantiopure 1-phenylethylamine (PEA) by stirring in ether. The diastereo-enriched salt of **1** with (*R*)-PEA was recrystallized once from acetone, and the diastereopure salt thus obtained was decomposed with 2 M aqueous HCl solution to give enantiopure (*Sp*)-**1**, the absolute configuration of which was determined on the basis of the X-ray crystallographic analysis of the diastereopure salt, in 77% total yield (based on a half amount of racemic **1** used).[6] The antipode (*Rp*)-**1** was obtained in 77% total yield by the enantioseparation of (*Rp*)-enriched **1**, recovered from the mother liquor, with (*S*)-PEA, followed by similar recrystallization and decomposition.[6]

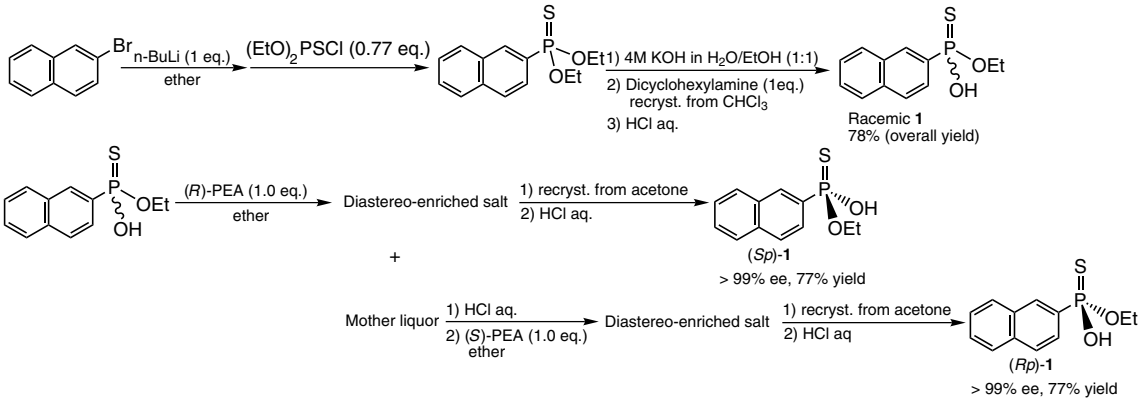
2.2. Chiral recognition ability of enantiopure *O*-ethyl (2-naphthyl)phosphonothioic acid 1

The enantioseparation of 1-phenylethylamine derivatives **3** with enantiopure *O*-ethyl (2-naphthyl)phosphonothioic acid **1** was carried out as follows: the ether solution of a 1-phenylethylamine derivative and 1 equiv of **1** was stirred for more than 4 h at room temperature. The crystalline powder deposited (diastereo-enriched salt) was collected by filtration, washed with hexane, and dried under reduced pressure. The salt was decomposed with 1 M aqueous KOH solution to yield the enantio-enriched amine (Table 1). As can be seen from Table 1, **1** showed excellent chiral recognition ability in the enantioseparations of *p*-substituted 1-phenylethylamine derivatives (entries 4–8). The ees of the amines incorporated in the diastereo-enriched salts were in a high range of 86–99%, which are only a little less than those achieved with *O*-ethyl phenylphosphonothioic acid **2** (96–>99%),[1,2] although the yields were rather low due to the high solubility of the diastereomeric salts in ether, making control of the amount of ether difficult; subsequently, the efficiencies (the yield × the enantiomeric excess) were lowered considerably. It is noteworthy that the enantioseparations of *m*-methyl and *p*-nitro substituted amines with **1** (entries 3 and 8) were highly improved, compared with those with **2** (not crystallized and 16% ee/0.13 efficiency, respectively[1,2]). These results indicate that **1** and **2** are complementary for the enantioseparation of 1-phenylethylamine derivatives.

There were two crystal shapes for the less-soluble diastereomeric salts of **3** with **1**; we observed a high correlation between the crystal shapes and the results of the enantioseparations. In the cases of the prism-type crystals (entries 5–7) high chiral recognitions were achieved (91–99% ee), while the chiral recognition ability varied in the range of 56–93% ee in the cases of needle-type crystals (entries 1, 3, 4 and 8). Since a similar correlation has been found in the enantioseparation with enantiopure *O*-alkyl phenylphosphonothioic acids,[1,2] the correlation was considered to be a general phenomenon in the enantioseparation with enantiopure arylphosphonothioic acids.

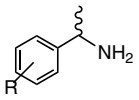
2.3. Mechanism of the chiral recognition with enantiopure *O*-ethyl (2-naphthyl)phosphonothioic acid 1

In the next stage, in order to clarify the chiral recognition mechanism, we carried out an X-ray crystallographic analysis for one of the prism-type crystals (entry 6). Figure 1 shows the crystal structure of the less-soluble diastereomeric salt of (*S*)-1-(4-chlorophenyl)ethylamine **3f** with *O*-ethyl (*Rp*)-(2-naphthyl)phosphonothioic acid (*Rp*)-**1**.[7] A molecular aggregate, which consists of four (*Rp*)-**1** molecules and four (*S*)-**3f** molecules, was formed with a closed hydrogen-bonding network, which is almost the same as



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

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



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3a: R = H **3b**: R = *o*-Me **3c**: R = *m*-Me **3d**: R = *p*-Me **3e**: R = *p*-F **3f**: R = *p*-Cl **3g**: R = *p*-Br **3h**: R = *p*-NO_2

Entry	Amine	Amount of ether[a] (mL)	Yield[b] (%)	ee[c] (%)	Absolute configuration[d]	Efficiency[e]	Crystal shape[f]
1[g]	**3a**	4.0	100	56	*R*	0.56	Needle
2[h]	**3b**	0.7	n.c.[i]	—	—	—	—
3[h]	**3c**	0.8	61	93	*S*	0.56	Needle
4[h]	**3d**	4.0	63	86	*S*	0.54	Needle
5[h]	**3e**	1.0	42	91	*S*	0.38	Prism
6[h]	**3f**	0.8	58	99	*S*	0.57	Prism
7[h]	**3g**	0.8	67	96	*S*	0.64	Prism
8[h]	**3h**	0.8	75	90	n.d.[j]	0.68	Needle

[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] Absolute configuration of the major enantiomer, which was determined by X-ray crystallographic analysis and/or deduced on the basis of the elution order in the HPLC analysis.
[e] Efficiency is the product of the yield and the ee.
[f] Crystal shape of less-soluble salt.
[g] (*Sp*)-**1** was used.
[h] (*Rp*)-**1** was used.
[i] Not crystallized.
[j] Not determined.

that in the globular cluster formed in the salt of (*R*)-**3f** with *O*-ethyl (*Sp*)-phenylphosphonothioic acid (*Sp*)-**2**.[1,2] However, the shape of the aggregate of the (*Rp*)-**1**·(*S*)-**3f** salt is fairly different from that of the globular cluster of the (*Sp*)-**2**·(*R*)-**3f** salt. The top view of the aggregate of the (*Rp*)-**1**·(*S*)-**3f** salt reveals that the naphthyl group of **1** is located at the outer part of the aggregate. As a result, the CH(sp^2)/π interactions between (*Rp*)-**1** molecules and (*S*)-**3f** molecules in the aggregate of the (*Rp*)-**1**·(*S*)-**3f** salt is less in number than those in the globular cluster of the (*Sp*)-**2**·(*R*)-**3f** salt, contrary to our expectation. Moreover, the packing of the aggregates is not sufficient, because the naphthyl groups stick out from the aggregates to form a cavity between the aggregates (Fig. 1c); the density of the (*Rp*)-**1**·(*S*)-**3f** salt is smaller than that of the (*Sp*)-**2**·(*R*)-**3f** salt (1.223 and 1.446 g/cm^3, respectively). Thus, the (*Rp*)-**1**·(*S*)-**3f** salt has some disadvantages, compared with the (*Sp*)-**2**·(*R*)-**3f** salt, with regards to effective interaction and close packing. However, (*Rp*)-**1** showed a high chiral recognition ability, when the resultant less-soluble diastereomeric salts were prism-type crystals. These results indicate that the formation of an aggregate/cluster, consisting of four phosphonothioic acid molecules and four 1-phenylethylamine derivative molecules, is very important for achieving efficient chiral recognition.

In order to clarify the chiral recognition mechanism through the formation of needle-type crystals, we tried to

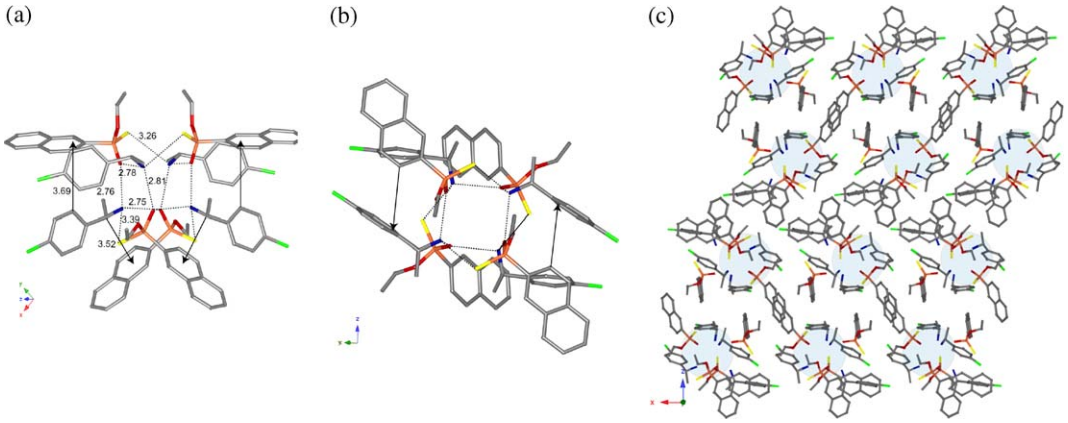

Figure 1. Crystal structure of the less-soluble (*Rp*)-**1**·(*S*)-**3f** salt; (a) side view of the aggregate, (b) top view of the aggregate, and (c) packing mode of the aggregates. The pale blue circles indicate the closed hydrogen-bonding networks. The dotted lines and arrows show hydrogen bonds and CH/π interactions, respectively. The bond distances are in angstrom.

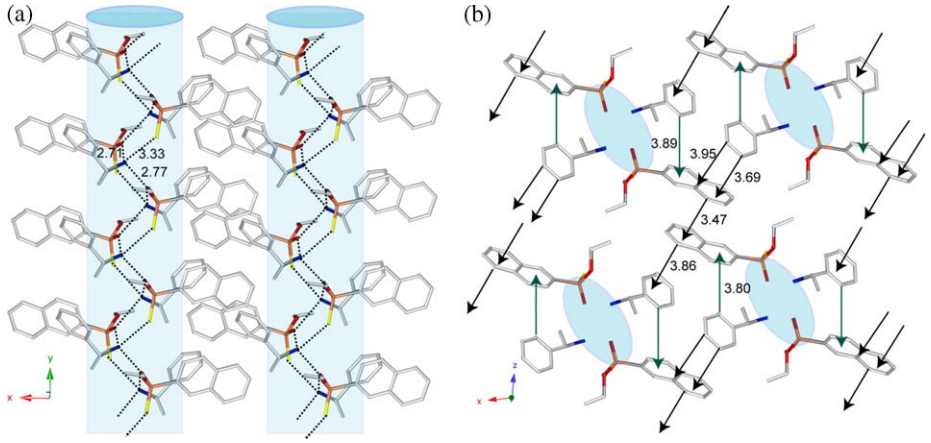

Figure 2. Crystal structure of the less-soluble (*Sp*)-**1**·(*R*)-**3a** salt; (a) columnar hydrogen-bonding network and (b) packing mode of the columns with CH/π interactions. The pale blue circles indicate the closed hydrogen-bonding networks. The dotted lines, black arrow, and green arrow show hydrogen bonds, inter-columnar CH(sp^2)/π interactions, and intra-columnar CH(sp^2)/π interactions, respectively. The bond distances are in angstroms.

prepare single crystals of the less-soluble diastereomeric salts (*Sp*)-**1**·(*R*)-**3a**, (*Sp*)-**1**·(*R*)-**3c**, and (*Sp*)-**1**·(*R*)-**3h** for X-ray crystallographic analyses. Among them, the single crystal of the (*Sp*)-**1**·(*R*)-**3a** salt was solely obtained, and its crystal structure could be solved (Fig. 2).[8] There exists a columnar hydrogen-bonding network, consisting of the phosphonothioate anions and the ammonium cations, as was observed in the needle-type less-soluble diastereomeric salts with *O*-alkyl phenylphosphonothioic acids.[1,2] The top view of the column indicates that intra-columnar CH(sp^2)/π interaction reinforces the one-dimensional hydrogen-bonding column. Furthermore, the packing of the columns is sufficiently stabilized by four kinds of inter-columnar CH(sp^2)/π interactions. From a crystallographic point of view, the *m*- and *p*-substituted phenylethylamines **3c** and **3h** would be able to make a similar conformation, because the substituents at the *m*- and *p*-positions have no serious influence on the stability of the crystals owing to relatively low occupancy for the spaces around the hydrogen-bonding network and between the columns. This X-ray crystallographic analysis indicates that the enlargement of the aromatic part in *O*-alkyl arylphosphonothioic acids is favorable for the chiral recognition via the formation of a columnar hydrogen-bonding network, as was found in the chiral recognition with enantiopure 2-naphthylglycolic acid[3] and 1-aminobenz[*f*]indan-2-ol.[4]

3. Conclusion

Enantiopure *O*-ethyl (2-naphthyl)phosphonothioic acid **1** was prepared from racemic **1**, which was synthesized from 2-bromonaphthalene and diethoxyphosphonothioic chloride, through enantioseparation with enantiopure 1-phenylethylamine. Enantiopure **1** showed an excellent chiral recognition ability for racemic 1-phenylethylamine derivatives; the ees were 91–99% in the cases of prism-type less-soluble diastereomeric salts and were 56–93% in the cases of needle-type less-soluble salts. The X-ray crystallographic analyses revealed that the enlarged aromatic part in **1**, compared with that in *O*-ethyl phenylphosphonothioic acid **2**, played a significant role in the chiral recognition via the formation of a columnar hydrogen-bonding network to stabilize the packing of the columns with efficient CH/π interactions, but was not so effective for the stabilization of the aggregates consisting of four (2-naphthyl)phosphonothioic acid molecules and four 1-phenylethylamine derivative molecules.

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5. A typical procedure: To a solution of 2-bromonaphthalene (16.2 g, 78 mmol) in dry ether (120 mL) was added dropwise 1.6 M butyllithium in hexane (49.4 mL, 78 mmol) at −78 °C under an argon atmosphere, and the mixture stirred at 0 °C for 20 min. Diethoxyphosphonothioic chloride (9.41 mL, 60 mmol) in dry ether (50 mL) was then added dropwise to the mixture at −78 °C. The reaction mixture was stirred at rt for 1.5 h and then cooled with an ice bath, after which H_2O (30 mL) was slowly added to the mixture. After removal of the solvent under reduced pressure, 1 M aqueous HCl solution (100 mL) was added, and the aqueous layer extracted with ether (8 × 80 mL). Then the combined extracts were successively washed with 1 M aqueous HCl solution (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude *O*,*O*-diethyl 2-naphthylphosphonothioate. A solution of crude *O*,*O*-diethyl 2-naphthylphosphonothioate in a mixture of 8 M aqueous KOH solution (120 mL) and ethanol (120 mL) was refluxed for 12 h. After removal of ethanol under reduced pressure, 12 M aqueous HCl solution (60 mL) was added to the residue. The resultant solution was extracted with CH_2Cl_2 (1 × 200 mL, and then 3 × 100 mL). The aqueous solution was acidified with 12 M aqueous HCl solution (50 mL) and extracted with dichloromethane (9 × 100 mL). The combined extracts were washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude

racemic *O*-ethyl (2-naphthyl)phosphonothioic acid (13.8 g, 55 mmol) as a colorless oil. Crude *O*-ethyl (2-naphthyl)phosphonothioic acid (13.8 g, 55 mmol) was purified via salt crystallization with dicyclohexylamine (10.0 mL, 55 mmol) from $CHCl_3$ (120 mL). Decomposition of the corresponding salt by 3 M aqueous HCl solution (150 mL), followed by extraction with CH_2Cl_2 (4×80 mL) and concentration under reduced pressure, gave chemically pure racemic **1** (11.84 g, 47 mmol) in 78% overall yield (on the basis of diethoxyphosphonothioic chloride used).

6. A typical procedure: To a solution of racemic **1** (9.08 g, 36 mmol) in ether (50 mL) was added (*R*)-1-phenylethylamine (PEA; 4.36 g, 36 mmol), and the mixture stirred at rt for 4 h. The deposited salt was collected by filtration using a membrane filter (T050A047A, ADVANTEC). The salt was recrystallized once from acetone (90 mL) to afford the diastereopure salt (*Sp*)-**1**·(*R*)-PEA (5.30 g, 14 mmol, 79% based on a half amount of racemic **1** used). To the diastereomeric salt thus obtained was added 1 M aqueous KOH solution (50 mL), and the solution extracted with CH_2Cl_2 (3×50 mL). The aqueous layer was acidified with 2 M aqueous HCl solution (30 mL) and then extracted with CH_2Cl_2 (4×50 mL). The combined extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford enantiopure (*Sp*)-**1** (3.51 g, 14 mmol, 77% based on a half amount of racemic **1** used) as a yellow oil. The enantiomeric excess of (*Sp*)-**1** thus obtained was determined by HPLC analysis after (*Sp*)-**1** was converted into the corresponding (*S*)-methyl ester with diazomethane (Daicel CHIRALCEL OD-H; eluent, hexane/2-propanol = 98:2; flow rate, 1.0 mL/min; t_1 [(*Rp*)-isomer] = 36 min, t_2 [(*Sp*)-isomer] = 42 min; enantiomeric excess, >99%). $[\alpha]_D^{21} = +10.1$ (*c* 5.4, MeOH). IR (NaCl): *v* 3600–3300, 3056, 2982, 1627, 1093, 1031, 957, 779, 746, 677 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (t, $J_{H-H} = 7$ Hz, 3H), 4.20 (dq, $J_{P-H} = 7$ Hz, $J_{H-H} = 7$ Hz, 2H), 6.14 (br, 1H), 7.51–7.62 (m, 2H), 7.83–7.89 (m, 4H), 8.49 (d, $J_{H-H} = 18$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.10, 62.77, 125.39, 126.81, 127.68, 128.15, 129.05, 129.66, 131.68, 132.05, 132.58, 134.73. ^{31}P NMR (121 MHz, $CDCl_3$): δ80.15. After concentration of the mother liquor of the first crystallization in the above procedure, 1 M aqueous KOH solution (50 mL) was added to the residue, and the solution was extracted with CH_2Cl_2 (5×50 mL). The aqueous layer was acidified with 3 M aqueous HCl solution and then extracted with CH_2Cl_2 (4×50 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (*Rp*)-enriched **1** (4.98 g, 19.7 mmol). To a solution of (*Rp*)-enriched **1** in ether (25 mL) was added (*S*)-PEA(2.39 g, 19.7 mmol), and the mixture was stirred at rt for 2 h. The deposited salt was collected by filtration using a membrane filter (T050A047A, ADVANTEC). The salt obtained was recrystallized once from acetone (100 mL) to afford the diastereopure salt (*Rp*)-**1**·(*S*)-PEA (5.34 g, 14 mmol, 79% based on a half amount of racemic **1** used). To the diastereomeric salt thus obtained was added 1 M aqueous KOH solution (50 mL), and the solution extracted with CH_2Cl_2 (4×50 mL). The aqueous layer was acidified with 3 M aqueous HCl solution (110 mL) and then extracted with CH_2Cl_2 (5×60 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure to afford enantiopure (*Rp*)-**1** (3.51 g, 14 mmol, 77% based on half the amount of racemic **1** used) as a yellow oil. $[\alpha]_D^{17} = -9.7$ (*c* 4.8, MeOH). The IR, ^1H NMR, ^{13}C NMR, and ^{31}P NMR were identical with those of (*Sp*)-**1**.

7. Crystal data of the less-soluble (*Rp*)-**1**·(*S*)-**3f** salt: FW = 407.89, tetragonal, space group $P4_32_12$, $a = 13.725(0)$, $c = 47.049(11)$ Å, $V = 8862.9(2)$ Å^3, $Z = 16$, $R = 0.0510$, $Rw = 0.0600$ (CCDC 605590).
8. Crystal data of the less-soluble (*Sp*)-**1**·(*R*)-**3a** salt: FW = 373.45, orthorhombic, space group $P2_1$, $a = 12.542(9)$, $b = 6.309(3)$, $c = 13.222(13)$ Å, $\beta = 103.437(3)$, $V = 1017.58(13)$ Å^3, $Z = 2$, $R = 0.0430$, $Rw = 0.0510$ (CCDC 605588).