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Enantiopure *tert*-butyl(phenyl)phosphine oxide. Chirality-recognition ability and mechanism

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ABSTRACT

When enantiopure *tert*-butyl(phenyl)phosphine oxide **1** was used as a resolving agent, it showed an acceptable to good chirality-recognition ability for several kinds of racemic carboxylic acids **2**. A study on a chirality-recognition mechanism based on X-ray crystallographic analyses of the diastereomeric complexes of **2** with **1** revealed that the complex crystals consisted of helical columns and that **1** was not responsible for the formation of the helical column and occupied a void between the columns; although **1** interacted with **2** via a hydrogen bond to primarily form a pair with **2**, the complex crystals were mainly stabilized by the accumulation of weak interactions, such as CH/π, π/π and CH···O interactions, between **1**/**1**, **1**/**2** and **2**/**2.**

1. Introduction

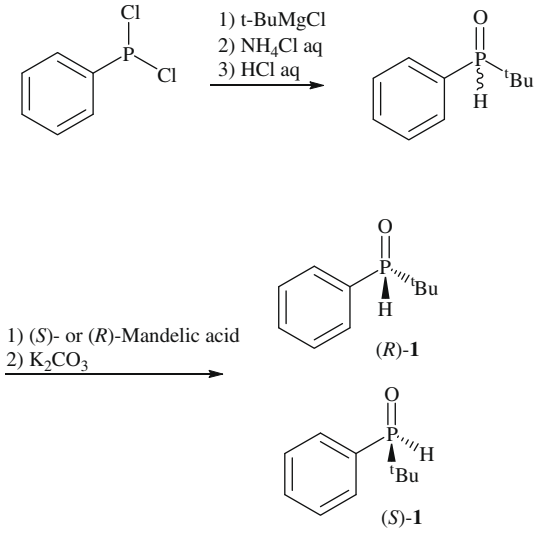
The separation of enantiomers from a racemate by diastereomeric salt formation with an enantiopure resolving agent is one of attractive methods for obtaining its enantiopure form due to some advantages such as its simplicity of operation, recyclability of the chiral source and applicability on an industrial scale.[1] Over the last two decades, we have been developing new resolving agents for carboxylic acids and amino alcohols, and studying chirality-recognition mechanisms by analyzing the difference in stability/solubility between pairs of less- and more-soluble diastereomeric salts on the basis of their X-ray crystallographic analyses.[2] Recently, we have reported that enantiopure *O*-alkyl arylphosphonothioic acids showed excellent chirality-recognition ability for racemic amines and amino alcohols, and that one of a pair of the corresponding diastereomeric salts had a unique crystal structure, which arose from a chiral phosphorus atom in phosphonothioic acids.[3] These results prompted us to apply other enantiopure compounds with a chiral phosphorus atom to the enantioseparation of racemates. On the other hand, Drabowicz et al. have reported that enantiomers of a chiral phosphine oxide could be separated with an enantiopure carboxylic acid via crystallization.[4] This means that phosphine oxides are able to form crystalline complexes with carboxylic acids.

Herein, we report the chirality-recognition ability of *tert*-butyl(phenyl)phosphine oxide for racemic carboxylic acids and the chirality-recognition mechanism elucidated on the basis of the X-ray crystallographic analyses of crystalline complexes.

2. Results and discussion

Enantiopure *tert*-butyl(phenyl)phosphine oxide **1** can be easily synthesized by the method reported by Drabowicz et al. in a large scale (Scheme 1).[4]

As shown in Table 1, (*R*)-**1** could recognize the chirality of the racemic 2-phenylalkanoic acids **2a–c** to an acceptable extent (entries 1–3). It is noteworthy that the ee of **2b** with a substituent relatively longer than that of **2a** is satisfactory although the yield is



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

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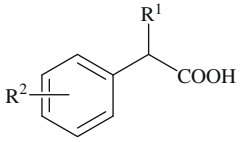
Table 1
Chirality-recognition ability of (*R*)-**1**



2a : R^1 = Me, R^2 = H
2b : R^1 = Pr, R^2 = H
2c : R^1 = iPr, R^2 = H
2d : R^1 = OH, R^2 = H
2e : R^1 = OH, R^2 = *p*-Cl
2f : R^1 = CH_2OH, R^2 = H
2g : R^1 = OMe, R^2 = H

Entry	Racemic acid	Solvent[a] and temperature ether/hexane (mL); (°C)	Yield[b] (%)	ee[c] (%)	Resolution efficiency[d] (%)
1	**2a**	1/0.7; −20	78	37 (*S*)	29
2	**2b**	1/0.6; −20	25	75	19
3	**2c**	1/1; −20	87	25	22
4	**2d**	1/0; 4	74	85 (*R*)	63
5	**2e**	0.5/0.2; 4	71	45 (*R*)	32
6	**2f**	1/0; 4	74	45 (*S*)	33
7	**2g**	0.5/0.4; −20	Oil	—	—

[a] The amount(s) of the solvent(s) used in the enantioseparation is normalized for a 1-mmol scale.
[b] The yield of the crystallized diastereomeric salt is based on a half amount of the racemic acid used.
[c] The enantiomeric excess (ee) of the liberated acid, which was determined by an HPLC analysis. The sign in the parentheses is the absolute configuration of the amine.
[d] The efficiency is the product of the yield and the ee.

rather low. Such a high ee for a chiral carboxylic acid with a long substituent is very rare in enantioseparation with conventional basic resolving agents such as enantiopure amines and amino alcohols. The phosphine oxide (*R*)-**1** also showed a moderate to good chirality-recognition ability for 2- and 3-hydroxycarboxylic acids **2d**–**f** (entries 4–6). In contrast, the chirality of the *O*-methylmandelic acid **2g** could not be recognized by (*R*)-**1** (entry 7). These results strongly suggest that the hydroxy group plays an important role in the chirality recognition with (*R*)-**1**.

In order to elucidate the origin of the chirality-recognition ability shown by the phosphine oxide (*R*)-**1**, we performed X-ray crystallographic analyses of the crystalline complexes of (*R*)-**1** with the carboxylic acids **2a**,**d**,**e**,**f**.[5]

Figure 1 shows the crystal structure of the less-soluble (*R*)-**1**·(*S*)-**2a** salt. The crystal consists of columns not with a hydrogen-bonding network but with a CH/π-interacting network. The column is constructed from units, which contain two (*R*)-**1** molecules and two (*S*)-**2f** molecules. The unit is effectively stabilized by three kinds of CH/π interactions between the phenyl hydrogen atom of a (*R*)-**1** molecule and the phenyl group of a (*S*)-**2a** molecule (2 × 3.506 Å), between the phenyl hydrogen atom of a (*S*)-**2a** molecule and the phenyl group of a (*R*)-**1** molecule (2 × 3.602 Å), and between the *tert*-butyl hydrogen atom of a (*R*)-**1** molecule and the phenyl group of a (*S*)-**2a** molecule (2 × 3.724 Å) to form one-dimensional columns. Moreover, a hydrogen bond exists between the oxygen atom of the (*R*)-**1** molecule and the hydroxy hydrogen atom of the (*S*)-**2a** molecule (2.539 Å) to reinforce the column. The columns assemble only by van der Waals interaction to form the crystal. This crystal structure is very unique from the viewpoint of the main force for the stabilization of diastereomeric crystals; in contrast to the general aspect that the units of diastereomeric crystals consisting of amines and carboxylic acids are commonly stabilized by several kinds of hydrogen-bonding interactions, CH/π interactions rather weaker than hydrogen-bonding interaction play a central role for the stabilization of the present unit. Although we could not solve the crystal structure of the more-soluble (*R*)-**1**·(*R*)-**2a** salt, the stabilization of the (*R*)-**1**·(*S*)-**2a** salt by rather weak CH/π interactions might result in the low resolution efficiency and in the requirement of a low temperature for the crystallization.

Contrary to the less-soluble (*R*)-**1**·(*S*)-**2a** salt crystal, there is a columnar hydrogen-bonding network in the less-soluble (*R*)-**1**·(*R*)-**2d** salt crystal (Fig. 2). The α-hydroxy hydrogen atom of a (*R*)-**2d** molecule interacts with the carboxylic carbonyl oxygen atom of another (*R*)-**2d** molecule in two different modes (2.842 Å and 2.899 Å) to form a helical hydrogen-bonding network. Moreover, (*R*)-**1** is attached on the surface of the network by a hydrogen bond between the carboxylic hydroxy hydrogen atom of a (*R*)-**2d** molecule and the oxygen atom of a (*R*)-**1** molecule (2.530 Å and 2.544 Å). The hydrogen-bonded structure seemed to be unstable due to the minimum number of hydrogen bonds for the construction of the column. However, between the columns there exist three kinds of intercolumnar CH/π interactions (2 × 3.679 Å, 2 × 3.709 Å, and 2 × 3.744 Å) and one kind of intercolumnar π/π interaction (2 × 3.501 Å). These efficient intercolumnar interactions would stabilize the crystal.

The columns in the more-soluble (*R*)-**1**·(*S*)-**2d** salt crystal (Fig. 3) bind with each other by four kinds of intercolumnar CH/π interactions (2 × 3.850 Å, 2 × 3.848 Å, 2 × 3.222 Å, 2 × 3.227 Å), which would contribute to the stabilization of the crystal in an extent similar to those in the less-soluble (*R*)-**1**·(*R*)-**2d** salt crystal. However, the hydrogen bonds, which afford a helical hydrogen-bonding network, are obviously longer than those in (*R*)-**1**·(*R*)-**2d**; 3.160 Å for the hydrogen bond between the α-hydroxy hydrogen atom of a (*S*)-**2d** molecule and the carboxylic carbonyl oxygen atom of another (*S*)-**2d** molecule, and 2.729 Å/2.739 Å for the hydrogen bond between the carboxylic hydroxy hydrogen atom of a (*S*)-**2d** molecule and the oxygen atom of a (*R*)-**1** molecule. These molecular arrangements indicate that the (*R*)-**1**·(*S*)-**2d** salt crystal is much less stable than the (*R*)-**1**·(*R*)-**2d** salt crystal. As a result, the

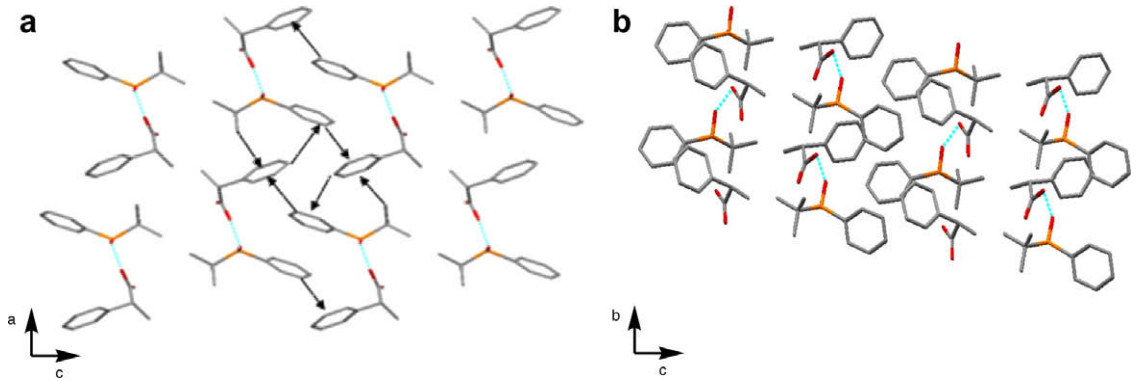


Figure 1. Crystal structure of the less-soluble (*R*)-**1**·(*S*)-**2a** salt; (a) top view and (b) side view. The dotted lines and arrows indicate hydrogen bonds and CH/π interactions, respectively.

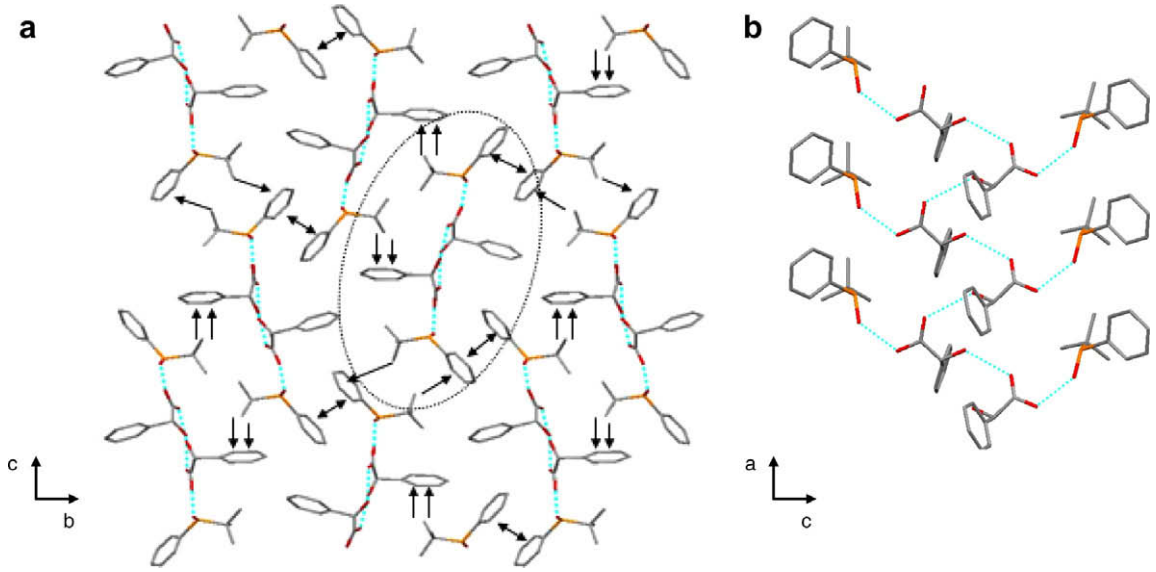


Figure 2. Crystal structure of the less-soluble (*R*)-**1**·(*R*)-**2d** salt; (a) top view and (b) side view. The circle indicates a column. The dotted lines, arrows and double arrows indicate hydrogen bonds and CH/π interactions, and π/π interactions, respectively.

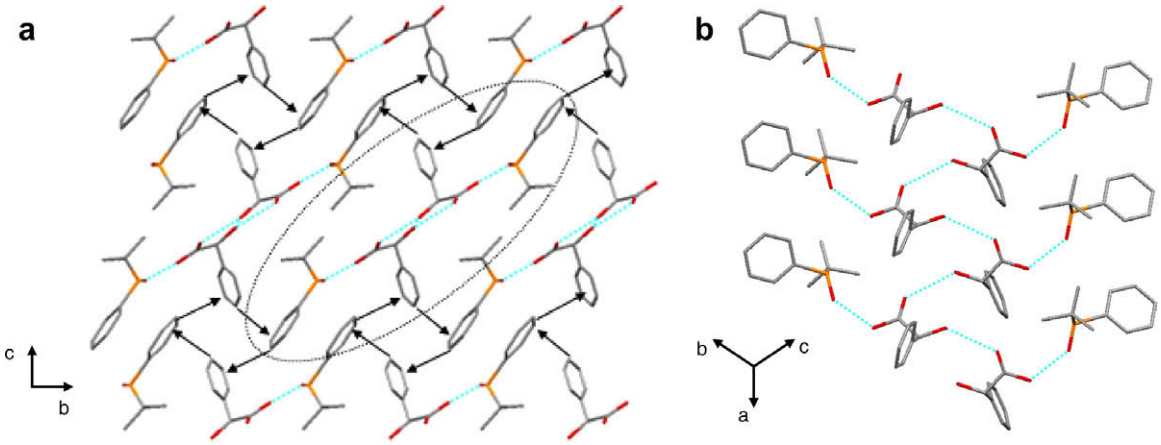


Figure 3. Crystal structure of the more-soluble (*R*)-**1**·(*R*)-**2d** salt; (a) top view and (b) side view. The circle indicates a column. The dotted lines and arrows indicate hydrogen bonds and CH/π interactions, respectively.

difference in solubility between the (*R*)-**1**·(*S*)-**2d** and (*R*)-**1**·(*R*)-**2d** salt crystals becomes very large, thus achieving the good resolution efficiency.

The crystal structure of the less-soluble (*R*)-**1**·(*R*)-**2e** salt seems to be rather complicated (Fig. 4). However, the crystal is fundamentally constructed from a columnar hydrogen-bonding network; there exist hydrogen bonds between the α-hydroxy hydrogen atom of a (*R*)-**2e** molecule and the carboxylic carbonyl oxygen atom of another (*R*)-**2e** molecule (2.853 Å), and between the carboxylic hydroxy hydrogen atom of a (*R*)-**2e** molecule and the oxygen atom of a (*R*)-**1** molecule (2.548 Å). Moreover, in the hydrogen-bonding network there are three kinds of CH···O interactions between the phenyl hydrogen atom of a (*R*)-**2e** molecule and the carboxylic carbonyl oxygen atom of another (*R*)-**2e** molecule, between the benzyl hydrogen atom of a (*R*)-**2e** molecule and the α-hydroxy oxygen atom of another (*R*)-**2e** molecule, and between the *tert*-butyl hydrogen atom of a (*R*)-**1** molecule and the oxygen atom of another (*R*)-**1** molecule; according to the definition of Desiraju, they are [D = 3.487 Å, d = 2.568 Å, θ = 162.90°], [D = 3.146 Å, d = 2.683 Å, θ = 108.42°] and [D = 3.526 Å, d = 2.591 Å, θ = 159.72°], respectively.[6] These interactions reinforce the columnar structure. The columns bind with each other by ten kinds of intercolumnar CH/π interactions (2 × 3.524 Å, 2 × 3.469 Å, 2 × 3.680 Å, 2 × 3.488 Å, 2 × 3.470 Å, 2 × 3.524 Å, 2 × 3.500 Å, 2 × 3.855 Å, 2 × 3.500 Å and 2 × 3.855 Å). In addition, there exist two intercolumnar halogen/π interactions (3.336 Å) to make the crystal stable.

In the less-soluble (*R*)-**1**·(*S*)-**2f** salt crystal, there exists a columnar hydrogen-bonding network (Fig. 5); the β-hydroxy hydrogen atom of a (*S*)-**2f** molecule interacts with the carboxylic carbonyl oxygen atom of another (*S*)-**2g** (2.833 Å), and the carboxylic hydroxy hydrogen atom interacts with the oxygen atom of a (*R*)-**1** molecule (2.530 Å). Moreover, there are two kinds of CH···O interactions between the benzyl hydrogen atom of a (*S*)-**2g** molecule and the β-hydroxy oxygen atom of another (*S*)-**2g** molecule, and between the phenyl hydrogen atom of a (*S*)-**2g** molecule and the carboxylic carbonyl oxygen atom of another (*S*)-**2g** molecule (D = 3.250 Å, d = 2.472 Å, θ = 137.73° and D = 3.431 Å, d = 2.459 Å, θ = 172.27°, respectively). There are also four kinds of intercolumnar CH/π inter-

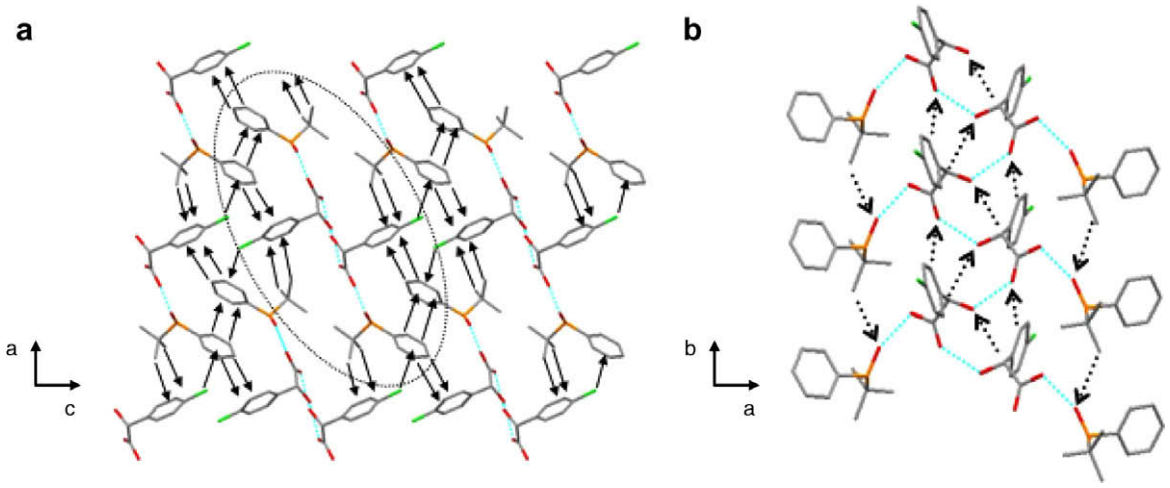


Figure 4. Crystal structure of the less-soluble (*R*)-**1**·(*S*)-**2e** salt; (a) top view and (b) side view. The circle indicates a column. The dotted lines, arrows and dotted arrows indicate hydrogen bonds, CH/π interactions, and CH···O interactions, respectively.

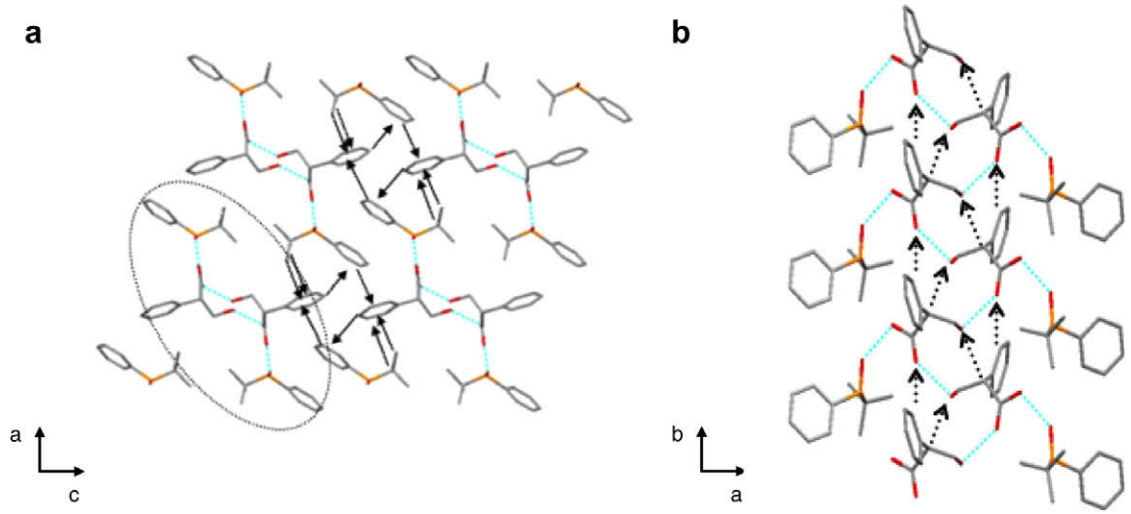


Figure 5. Crystal structure of the less-soluble (*R*)-**1**·(*S*)-**2f** salt; (a) top view and (b) side view. The circle indicates a column. The dotted lines, arrows and dotted arrows indicate hydrogen bonds, CH/π interactions, and CH···O interactions, respectively.

actions (2 × 3.840 Å, 2 × 3.748 Å, and 2 × 3.493 Å, 2 × 3.509 Å) to make the crystal packing tight.

3. Conclusion

Enantiopure *tert*-butyl(phenyl)phosphine oxide (*R*)-**1** showed an acceptable to good chirality-recognition ability for racemic carboxylic acids **2** to give crystalline (*R*)-**1**·enantio-enriched **2** complexes. The crystal structures of the crystalline complexes were determined by X-ray crystallography and revealed that (*R*)-**1** molecules in the complexes are not responsible for the formation of a columnar hydrogen-bonding network, which is commonly observed in complexes (salts) consisting of amines/amino alcohols and carboxylic acids. The role of the (*R*)-**1** molecule is to occupy a void between helical columns, which were formed by CH/π and π/π interactions between the components or single kind of hydrogen-bonding interaction between carboxylic acid molecules. Moreover, the columns were bound with each other by CH/π, π/π and/or CH···O interaction. Thus, CH/π, π/π and CH···O interactions were found to play a significant role in the stabilization of the present complexes.

4. Experimental

4.1. General

HPLC analyses were performed on a Daicel Chiralcel column using a Jasco PU-2080i pump, a Jasco PU-2075 UV detector and a Hitachi D-2500 Chromato-Integrator.

4.2. A general procedure for the enantioseparation of racemic arylcarboxylic acids (2) with (*Rp*)-1

A mixture of enantiopure **1** and racemic **2** (1 equiv) in Et_2O or Et_2O/hexane was stirred at 4 °C or −20 °C for 12 h (see Table 1). The deposited salt was collected by filtration using a membrane filter (T050A047A, ADVANTEC). The yield of the salt was evaluated on the basis of a half amount of racemic **2**. A portion of the salt thus obtained was treated with small amounts of 1 M aqueous KOH solution and Et_2O. Then, the aqueous layer was acidified to pH 2 with a concentrated HCl solution and extracted twice with small amounts of CH_2Cl_2. The cumulated CH_2Cl_2 solution was concentrated under reduced pressure to give a sample for the determination of the ee

of **2** by a HPLC analysis. In the cases of **2d**–**f**, they were converted to the corresponding methyl esters by treatment with $TMSCHN_2$ in a mixture of toluene and MeOH (1 mL/0.5 mL). Compound **2a**: Daicel Chiralcel OJ-RH, $HClO_4$ aq (pH 2)/MeCN = 70:30 (v/v), flow rate 0.3 mL/min, rt, detected at 254 nm. Compound **2b**: Daicel Chiralcel OD-RH, $HClO_4$ aq (pH 2)/MeCN = 70:30 (v/v), flow rate 0.5 mL/min, rt, detected at 254 nm. Compound **2c**: Daicel Chiralcel OJ-RH, $HClO_4$ aq (pH 2)/MeCN = 70:30 (v/v), flow rate 0.5 mL/min, rt, detected at 254 nm. Compound **2d** methyl ester: Daicel Chiralcel AS-H, hexane/*i*-PrOH = 90:10 (v/v), flow rate 0.5 mL/min, rt, detected at 254 nm. Compound **2e** methyl ester: Daicel Chiralcel OD-H, hexane/*i*-PrOH = 95:5 (v/v), flow rate 0.5 mL/min, rt, detected at 254 nm. Compound **2f** methyl ester: Daicel Chiralcel OD, hexane/*i*-PrOH = 95:5 (v/v), flow rate 0.5 mL/min, rt, detected at 254 nm.

4.3. X-ray crystallographic analyses

X-ray crystallographic data were corrected on a Rigaku/MSC Mercury diffractometer with graphite monochromated Mo Kα radiation. The distance for the CH/π interaction corresponds to the shortest distance from the carbon atom to the aromatic plane, while the distance for the π/π interaction corresponds to the shortest distance between the two aromatic planes.

The less-soluble (*R*)-**1**·(*S*)-**2a** salt: CCDC 748064. Crystal data: $C_{19}H_{25}O_3P$, M = 332.37, monoclinic, space group $P2_1$, a = 10.60(2) Å, b = 6.271(13) Å, c = 13.93(3) Å, V = 919.063 Å^3, Z = 2, Dc = 1.201 Mg m^{-3}, R = 0.1097.

The less-soluble (*R*)-**1**·(*R*)-**2d** salt: CCDC 748065. Crystal data: $C_{18}H_{23}O_4P$, M = 334.35, orthorhombic, space group $P2_12_12_1$, a = 6.106(4) Å, b = 21.855(13) Å, c = 26.964(15) Å, V = 3598.25 Å^3, Z = 8, Dc = 1.234 Mg m^{-3}, R = 0.0812.

The more-soluble (*R*)-**1**·(*S*)-**2d** salt: CCDC 748066. Crystal data: $C_{18}H_{23}O_4P$, M = 334.35, triclinic, space group $P1$, a = 6.196(4) Å, b = 10.477(7) Å, c = 13.401 Å, V = 862.979 Å^3, Z = 2, Dc = 1.287 Mg m^{-3}, R = 0.0591.

The less-soluble (*R*)-**1**·(*S*)-**2e** salt: CCDC 748067. Crystal data: $C_{18}H_{22}ClO_4P$, M = 368.79, monoclinic, space group $P2_1$, a = 11.235(11) Å, b = 6.133(5) Å, c = 13.576(12) Å, V = 927.116 Å^3, Z = 2, Dc = 1.321 Mg m^{-3}, R = 0.0448.

The less-soluble (*R*)-**1**·(*S*)-**2f** salt: CCDC 748068. Crystal data: $C_{19}H_{25}O_4P$, M = 348.37, monoclinic, space group $P2_1$, a = 10.520(5) Å, b = 6.306(3) Å, c = 14.908(7) Å, V = 944.795 Å^3, Z = 2, Dc = 1.225 Mg m^{-3}, R = 0.0431.

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