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Direct enantioseparation of diarylmethylamines with an *ortho*-hydroxy group via diastereomeric salt formation and their application to the enantioselective addition reaction of diethylzinc

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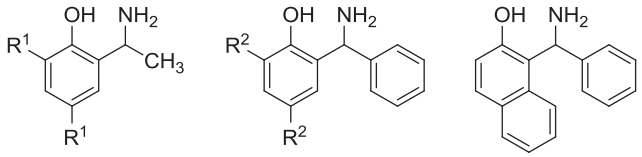
ABSTRACT

Two chiral diarylmethylamines with a phenolic hydroxy group at their *ortho* positions (**1c** and **1d**) were synthesized, and their direct enantioseparation via diastereomeric salt formation was investigated. Crystallographic analyses of the diastereomeric salts involving **1c** were conducted: water molecules incorporated in the space played an important role in chiral recognition. Enantiopure **1** were applied for the enantioselective addition of diethylzinc to benzaldehyde. Ligand (*R*)-**1d** afforded the product in very high yield (96%) and enantiopurity (92% ee). Not only the phenyl group on the stereogenic center of (*R*)-**1d** but also its bulky *tert*-butyl group is important for chiral induction.

1. Introduction

Enantiopure aminoalcohols are important chiral building blocks, which have been widely applied as chiral ligands,[1] organocatalysts,[2] and resolving agents for carboxylic acids.[3] Thus far, various enantiopure aliphatic aminoalcohols have been reported as they are predominantly derivatized from naturally occurring chiral sources.[4] In contrast, enantiopure *ortho*-(aminomethyl)phenols (*o*-APs), which represent a category of 1,3-aminoalcohols with a phenolic hydroxy group, have not been extensively examined. Because of their rigid backbone and the acidic hydroxy group, *o*-APs are unique, potential candidates for asymmetric reactions[5] and models for proton-coupled electron transfer.[6] In addition, *o*-AP is a substructure of salan compounds, which are extensively investigated as powerful ligands.[7]

Previously, we have reported the synthesis and enantioseparation of 2-(1-aminoethyl)phenols (**1a** and **1b**), which are chiral *o*-APs with a simple structure based on 1-phenylethylamine.[8] Resolution of enantiomers via diastereomeric salt formation with an acidic resolving agent is one of the most useful methods for preparing enantiopure amines.[9] Despite the intramolecular hydrogen bond between an amino group and an *ortho*-hydroxy group in the native form of **1**, salt formation is possible for several carboxylic acids, and the hydroxy group plays an important role in chiral recognition by the formation of OH ⋯ O and CH ⋯ O hydrogen bonds.[8]



1a: R^1 = H
1b: R^1 = ^{t}Bu

1c: R^2 = H
1d: R^2 = ^{t}Bu

Betti base

For systematically investigating chiral *o*-APs, herein, we focused on *o*-APs with two phenyl groups on the stereogenic center. Such a diarylmethylamine skeleton is an important substructure found in biologically active compounds.[10] In addition, the Betti base, a type of an *o*-AP based on a diarylmethylamine, is well known to be applied for asymmetric synthesis as well as a chiral auxiliary.[11] This suggests that other *o*-APs based on diarylmethylamine are potentially useful as chiral auxiliaries. As the initial target diarylmethylamine-based simple *o*-APs, 2-[amino(phenyl)methyl]

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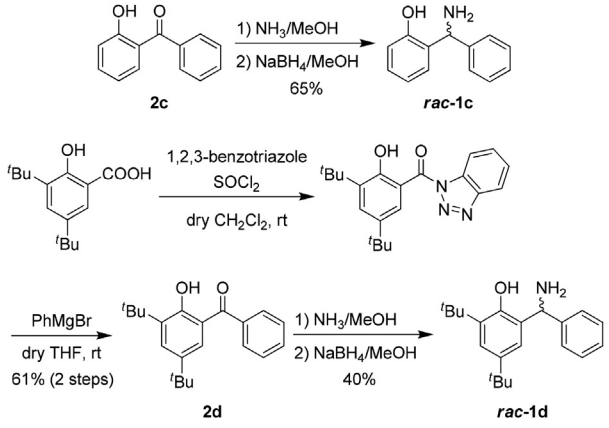
phenols (**1c** and **1d**), were selected, where a methyl group on the stereogenic centers of **1a** and **1b** is replaced by a phenyl group. The sterically demanding phenyl groups of **1c** is expected to enhance molecular recognition ability, as well as the bulky *tert*-butyl groups of **1d** contribute to high chiral induction ability. Herein, **1c** and **1d** were synthesized, followed by their direct enantioseparation via diastereomeric salt formation to obtain their enantiopure forms. The mechanism of chiral recognition was discussed on the basis of X-ray crystallographic analysis of their less-soluble salts; finally, their potential as a chiral ligand was demonstrated for the asymmetric addition of Et_2Zn to benzaldehyde.

2. Results and discussion

2.1. Synthesis of racemic substrates (*rac*-1c and *rac*-1d) and resolution of their enantiomers

For accessing enantiopure **1c** and **1d**, we first synthesized their racemic forms, followed by resolution of their enantiomers via diastereomeric salt formation. Although asymmetric hydrogenation transfer of the corresponding imine has been reported to afford enantio-enriched **1c**, a chiral Brönsted acid catalyst with a complicated structure is necessary, and **1c** is not obtained in an enantiopure form.[12] Scheme 1 shows the synthesis of *rac*-**1c** and *rac*-**1d**, where the one-pot reductive amination of the corresponding ketones **2** was adopted.[8] Ketone **2d** was prepared from 3,5-di-*tert*-butylsalicylic acid by amidation, followed by the Grignard reaction according to a previously published study.[13] The yields were moderate probably caused by the steric hindrance around the carbonyl group, and the products were characterized by ^{1}H NMR, ^{13}C NMR, IR spectra, and elemental analysis.



Scheme 1. Synthesis of *rac*-**1c** and *rac*-**1d**.

Fig. 1 shows the X-ray crystallographic structure of *rac*-**1d** after its recrystallization from EtOH. Both enantiomers of **1d** were crystallized together in the $Pna2_1$ space group, and an intramolecular hydrogen bond was observed between the hydroxy hydrogen atom and the nitrogen atom (the N ⋯ O distance was as short as 2.65 Å, and the O–H ⋯ N angle was 151°), which was also observed for *rac*-**1b**.[8]

Fig. 2 shows the eight commercially available acidic resolving agents **3**–**10**, which were used for testing the enantioseparation of *rac*-**1c** and *rac*-**1d**. Equimolar amounts of racemic *o*-AP and each resolving agent were mixed and recrystallized from an aqueous ethanol solution (Table 1). Among the tested resolving agents, L-mandelic acid (**3**), L-pyroglutamic acid (**5**), and (+)-10-camphorsulfonic acid (**7**) did not afford crystalline salts with both

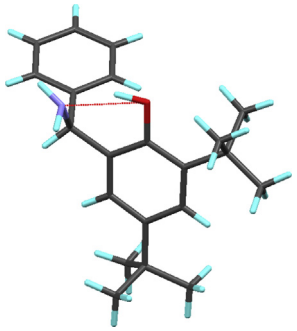


Fig. 1. Crystal structure of *rac*-**1d**. Dotted line represents the hydrogen bond.

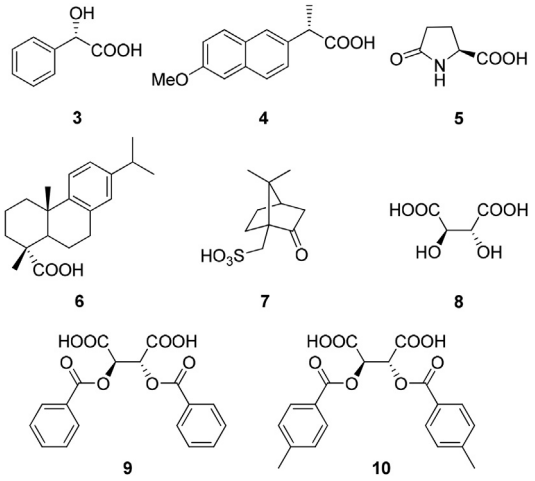


Fig. 2. Acidic resolving agents used in this study.

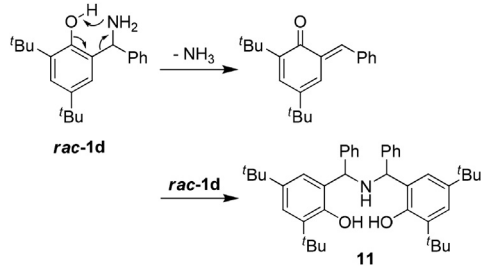
1c and **1d**, probably because these resolving agents have lower molecular weight, or are not significantly functionalized. On the other hand, highly functionalized L-tartaric acid (**8**) afforded a crystalline salt with **1c**; however, it did not exhibit any ability for chiral recognition. For the resolution of *rac*-**1c**, (*S*)-naproxen (**4**), dehydroabietic acid (**6**), and dibenzoyl-L-tartaric acid (**9**) afforded moderate efficiencies. Two former acids afforded (*R*)-**1c** salt as a less-soluble salt; on the other hand, antipode (*S*)-**1c** was preferentially deposited by salt formation with **9**. To our surprise, di-(*p*-toluoyl)-L-tartaric acid (**10**), which is structurally related to **9**, afforded a crystalline salt with **1c** but resulted in only a racemic form. Although **9** and **10** are divalent carboxylic acids, the molar ratio of **1c** and **9**/**10** in the precipitated solid was 1:1, as estimated from ^{1}H NMR analysis.

In contrast, *rac*-**1d** was separated with good efficiencies by **9** or **10**, while others were not useful. During the resolution of *rac*-**1d**, some insoluble material (**11**) was obtained, which was produced by the bimolecular condensation of *rac*-**1d** at refluxing temperature. Fig. S1 shows the X-ray crystallographic structure of **11**. Scheme 2 shows the plausible reaction mechanism, and such a reaction previously reported for simple 2-(aminomethyl)phenol has been found to proceed via an *ortho*-quinone methide intermediate.[14] After insoluble **11** was filtered, from ^{1}H NMR analysis, the composition ratio of **1d** and **9** in the precipitated solid was approximately **1d**:**9**=3:2. The IR spectra and powder X-ray diffraction patterns were compared; **1d** or **9** was not found to be included in the precipitate, and a new solid phase was produced (Fig. S2). The molar amount of **9** was less than that of **1d** probably because **9** is a divalent carboxylic acid, and a part of the carboxyl groups is not ionized.

Table 1
Enantioseparation of racemic **1c** and **1d** with acidic resolving agents in 50% aqueous EtOH[a]

rac-**1c**						*rac*-**1d**					
Entry	Resolving agent	Solvent (L/mol)	Yield[b] (%)	ee[c] (%)	Eff.[d]	Entry	Resolving agent	Solvent (L/mol)	Yield[b] (%)	ee[c] (%)	Eff.[d]
1	**3**	7.5	Not crystallized		—	9[e]	**3**	172.5	Not crystallized		—
2	**4**	17.5	90	38(*R*)	0.34	10[e]	**4**	30	Not crystallized		—
3	**5**	2.5	Not crystallized		—	11[f]	**5**	2.5	Not crystallized		—
4	**6**	50	75	50(*R*)	0.38	12[g]	**6**	33.8	Not crystallized		—
5	**7**	2.5	Not crystallized		—	13	**7**	12.5	Not crystallized		—
6	**8**	5.0	77	4(*R*)	0.03	14[e]	**8**	38.8	Not crystallized		—
7	**9**	10.0	70	54(*S*)	0.38	15[h]	**9**	37.5	74	43(*R*)	0.32
8	**10**	60	32	*rac.*	0	16[i]	**10**	28.8	43	64(*R*)	0.31

The bold letters correspond to the compound numbers shown in Fig. 2.
[a] Each resolving agent (0.4 mmol) and *rac*-**1** (0.4 mmol) were used.
[b] Yield based on half of the amount of *rac*-**1**.
[c] Ee was determined by HPLC analysis.
[d] Eff.=Yield (%)×Ee (%)/10,000.
[e] 87% EtOH was used as the solvent.
[f] EtOH was used as the solvent.
[g] 65% EtOH was used as the solvent.
[h] The insoluble solid (31.8 mg) was removed before crystallization.
[i] The insoluble solid (16.2 mg) was removed before crystallization.



Scheme 2. Plausible reaction mechanism for the bimolecular condensation of *rac*-**1d** to afford **11**.

During the systematic investigation of the acidic resolving agents for **1a**–**1d**, **4** was found to be effective for the resolution of **1a** and **1c**, which lacked *tert*-butyl groups on the phenol ring. In contrast, bulkier *o*-APs **1b**–**1d** could be separated by salt formation with **9**, which is also rather bulky because of the twisted conformation of the two phenyl groups.[15] A size complementarity should be present between **1** and the suitable resolving agents although the absolute configurations of **1c** and **1d** in the less-soluble salts with **9** were not consistent.

2.2. Optimization of resolution conditions

After examining the resolving agents, the resolution conditions were optimized. Several solvents, such as MeOH, EtOH, and their mixtures with H_2O, were tested for the resolution of *rac*-**1c** with the three potential resolving agents **4**, **6**, and **9** (Table 2). When the resolution with **4** was conducted from H_2O, the resolution efficiency significantly decreased, and marginal chiral recognition was observed (Entry 1). With the addition of alcohol, the results were improved, and 50% EtOH afforded the (*R*)-**1c** salt in the highest efficiency (Entry 3). Notably, the salt of antipode (*S*)-**1c** was slightly preferred from recrystallization using EtOH (Entry 4), implying that the addition of water results in a different chiral recognition mechanism with **4**. In the resolution of *rac*-**1c** with **6**, although EtOH did not afford crystalline materials, both 67% MeOH and 50% EtOH afforded (*R*)-**1c** salts with an equally high efficiency (Entries 5 and 6, respectively). However, it was not convenient for practical use because significant amounts of the recrystallization solvent was necessary, caused by the low solubility of the **1c**·**6** salt.

Table 2
Enantioseparation of *rac*-**1c** with **4**, **6**, and **9** from various solvents[a]

Entry	Resolving agent	Solvent (L/mol)	Yield[b] (%)	Ee[c] (%)	Eff.[d]
1	**4**	H_2O (112.5)	79	3(*S*)	0.02
2	**4**	50% MeOH (7.5)	127	12(*R*)	0.15
3	**4**	50% EtOH (10.0)	90	38(*R*)	0.34
4	**4**	EtOH (5.0)	99	17(*S*)	0.17
5	**6**	67% MeOH (75.0)	42	87(*R*)	0.36
6	**6**	50% EtOH (50.0)	75	50(*R*)	0.38
7	**6**	EtOH (5.0)	Not crystallized		—
8	**9**	H_2O (75.0)	102	19(*S*)	0.19
9	**9**	50% MeOH (10.0)	139	24(*S*)	0.33
10	**9**	50% EtOH (17.5)	70	54(*S*)	0.38
11	**9**	EtOH (5.0)	33	95(*S*)	0.31

[a] Each resolving agent (0.4 mmol) and *rac*-**1c** (0.4 mmol) were used.
[b] Yield was based on the half of the salt amount.
[c] Ee was determined by HPLC analysis.
[d] Eff.=Yield (%)×Ee (%)/10,000.

Similarly, resolution with **9** demonstrated that the (*S*)-**1c** salt is deposited from all solvents, and 50% EtOH afforded the best efficiency (as high as 0.38; entry 10). Regardless of the resolving agents, equally high efficiencies were achieved by recrystallization from 50% EtOH. Considering the values of resolution efficiencies and the amount of the required solvent, the optimized condition for the resolution of *rac*-**1c** was recrystallization with **9** from a 50% aqueous EtOH solution.

For optimizing the resolution conditions of *rac*-**1d**, the amount of the resolving agent and solvent was investigated with the

Table 3
Optimization of the resolution conditions of *rac*-**1d** with **9**[a]

Entry	Initial molar ratio **1d**:**9**	Solvent (L/mol)[b]	Yield[c] (%)	Molar ratio[d] (**1d**:**9**)	Ee[e] (%)	Eff.[f]
1	1:0.25	50% EtOH (60.0)	47	Only **1d**	*rac.*	0
2	1:0.5	50% EtOH (45.0)	122	2:1	7(*R*)	0.09
3	1:1	50% EtOH (37.5)	74	3:2	43(*R*)	0.32
4	1:2	50% EtOH (32.5)	86	3:2	68(*R*)	0.58
5	1:1	70% EtOH (15.0)	72	3:2	68(*R*)	0.49
6	1:1	90% EtOH (10.0)	24	3:2	75(*R*)	0.18
7	1:2	70% EtOH (10.0)	80	1:0.9	67(*R*)	0.54

[a] *Rac*-**1d** (0.4 mmol) were used.
[b] The amount of the solvent based on the amount of *rac*-**1d** is shown within the parenthesis.
[c] Yield was based on half of the amount of *rac*-**1d**.
[d] Molar ratio of **1d** and **9** in the precipitates was determined by ^{1}H NMR analysis.
[e] Ee was determined by HPLC analysis.
[f] Eff.=Yield (%)×Ee (%)/10,000.

matched resolving agent **9** (Table 3). When the initial amount of **9** was decreased to *rac*-**1d**:**9**=1:0.5, the precipitated solid had the same composition as the initial ratio; however, the resolution efficiency of **1d** drastically decreased to 0.09 (Entry 2). With further decrease in the initial feed of **9** to *rac*-**1d**:**9**=1:0.25, only *rac*-**1d** was obtained without salt formation (Entry 1). In contrast, when the initial amount of **9** was increased to *rac*-**1d**:**9**=1:2, the efficiency was improved to 0.58 while maintaining a molar ratio as **1d**:**9**=3:2 in the precipitate (Entry 4). Changing the EtOH concentration in the recrystallization solvents resulted in only lower yields and efficiencies of **1d** (Entries 5 and 6). When a 1:2 mixture of *rac*-**1d** and **9** was recrystallized from 70% EtOH, a precipitate containing more **9** was obtained, while the efficiency was similar with that obtained from the recrystallization from 50% EtOH (Entry 7). From these investigations, the optimized resolution of *rac*-**1d** was conducted with 2 molar equivalents of **9** by recrystallization from a 50% aqueous EtOH solution (Entry 4).

2.3. Crystallographic analyses of the less-soluble salts of (*R*)-1c·4 and (*S*)-1c·9

For elucidating the mechanism of successful resolution of **1c** and **1d**, we conducted the crystallographic analysis of their less-soluble salts. Although suitable single crystals of **1d**·**9** were not obtained, analysis of the less-soluble salt of **1c** formed with **4** was successfully performed (Fig. 3). The salt was observed to consist of (*R*)-**1c**, **4**, and water molecules in a ratio of (*R*)-**1c**:**4**:H_2O=2:2:1. In the hemihydrated (*R*)-**1c**·**4**·0.5H_2O salt crystals, the molecules formed a columnar hydrogen-bonding network along the *b* axis, and the water molecules occupied the center of the columnar structure to tightly combine (*R*)-**1c** and **4** by hydrogen bonds (Fig. 3a). The phenolic hydroxy group of (*R*)-**1c** formed hydrogen bonds not only with the carboxylate oxygen atom of **4** but also with an ammonium nitrogen atom within the molecule. A similar structure was also observed for (*S*)-**1a**·**4**·0.5H_2O, while the absolute configuration of **1** was opposite.[8] It is probable that the bulky and rigid phenyl group of **1c**, instead of the methyl group of **1a**, changed its molecular orientation. The (*R*)-selective chiral recognition with **4** was attributed to the fixation of the phenyl group of (*R*)-**1c** by the edge-to-face-type CH/π interaction between the *meta*-CH of the phenyl group of (*R*)-**1c** and the naphthalene ring of **4** (The C ⋯ π-plane distance was 3.48 Å as indicated by the arrows in Fig. 3b).

Fig. 4 shows the crystal structure of the less-soluble salt of **1c** and **9** prepared from an aqueous EtOH solution. The salt was also shown to be hydrated and composed of (*S*)-**1c**:**9**:H_2O=1:1:3, which was consistent with its partial weight loss up to 90 °C from TGA results (Fig. S3). While **9** is a divalent carboxylic acid, one of the carboxyl groups of **9** was ionized, and the other was neutral. The molecules were arranged along a 2-fold screw axis (*b* axis) by intricate hydrogen bonds, affording a one-dimensional columnar structure (Fig. 4a). Bulky substituents of (*S*)-**1c** and **9** left a rather large space inside the columnar structure, which was occupied by 3 equiv of water molecules (w1–w3), which played an important role in the chiral recognition of **1c**. The hydroxy group of (*S*)-**1c** was hydrogen-bonded with the carboxylate oxygen atom of **9**, a water molecule (w2), as well as an intramolecular ammonium hydrogen atom. In addition, the phenyl group of (*S*)-**1c** was fixed with a CH/π interaction between the *para*-CH of (*S*)-**1c** and the phenyl ring of **9** (The C ⋯ π-plane distance was 3.64 Å as indicated by the arrows in Fig. 4a). Such interactions fixed the position of the ammonium, phenol, and phenyl groups, thereby allowing for (*S*)-**1c** to be accommodated in the asymmetric space. Resolving agent **10**, which is structurally similar to **9**, afforded a good-quality crystal with *rac*-**1c** although it did not exhibit any ability for chiral recognition (Table 1, entry 8). Fig. S4 shows the crystal structure. A similar columnar hydrogen-bonding network was formed from equimolar **1c** and

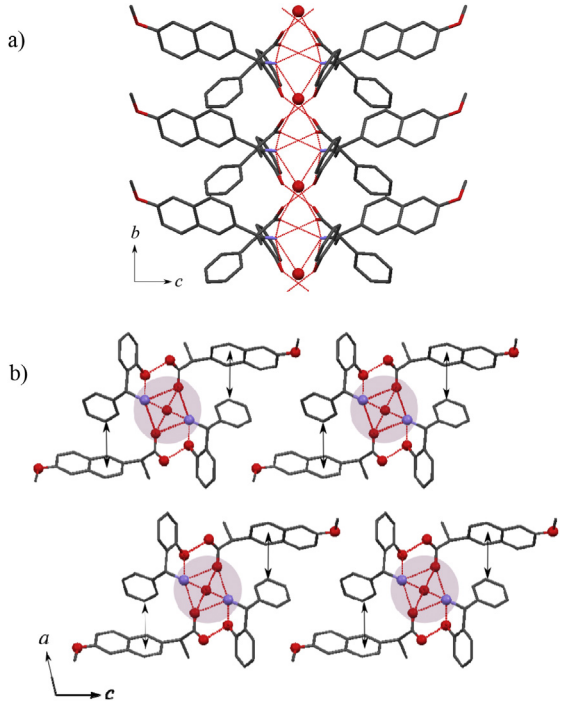


Fig. 3. Crystal structure of (*R*)-**1c**·**4**·0.5H_2O. (a) Side view of the columnar structure. Red balls represent the oxygen atoms of water. (b) Top view of the columnar structures. Hydrogen atoms are omitted for clarity. Dotted lines and arrows represent hydrogen bonds and CH/π interactions, respectively.

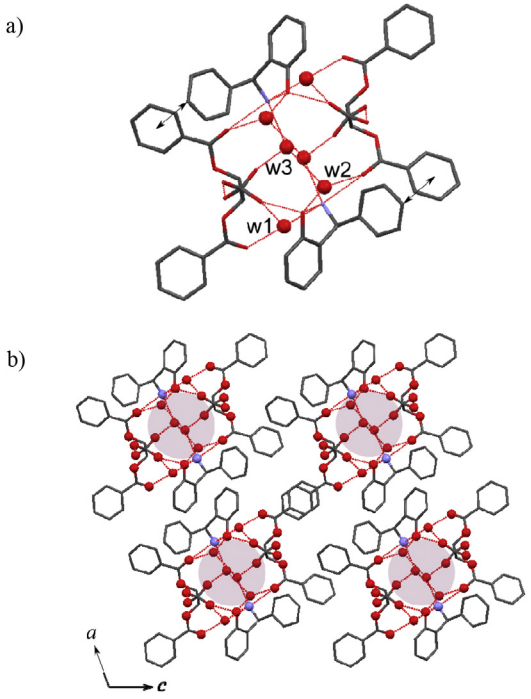


Fig. 4. Crystal structure of (*S*)-**1c**·**9**·3H_2O. (a) Top view of a columnar structure. Red balls represent the oxygen atoms of water (w1–w3). (b) Top view of the four columnar structures viewed from the *b* axis. Hydrogen atoms are omitted for clarity. Dotted lines and arrows represent hydrogen bonds and CH/π interactions, respectively.

10; however, both enantiomers of **1c** were equally incorporated in the same position in a disordered manner without any hydration. Only an additional methyl group on the phenyl groups of **9** changed the molecular packing and hydration state, which resulted in the unsuccessful resolution of *rac*-**1c** with **10**.

2.4. Preparation of enantiopure 1c and 1d

According to the optimized resolution conditions stated above, we attempted to prepare enantiopure **1c** and **1d** by the repeated recrystallization of their less-soluble salts with **9** from 50% EtOH. Scheme 3 shows the resolution of *rac*-**1c** and *rac*-**1d**, and Table 4 shows the detailed yields and ee values. The highest resolution efficiency up to 0.71 was achieved after recrystallization was conducted two times (Entry 2), and the highly enantio-enriched (*S*)-**1c** (97% ee) was obtained with 42% yield after recrystallization was conducted five times (Entry 5). Finally, the salt of enantiopure (*S*)-**1c** with 99% ee was prepared after conducting recrystallization seven times (Entry 7). The enantio-enriched (*R*)-**1c** (55% ee) was recovered from the mother liquors of the two initial recrystallization steps and combined with resolving agent **4**, which afforded a less-soluble salt with (*R*)-**1c**. The **1c**·**4** salt was recrystallized two times from 50% EtOH, affording enantiopure (*R*)-**1c** salt in 42% yield (Entry 9). By using two commercially available resolving agents **9** and **4**, both enantiomers of **1c** could be obtained in moderate-to-good efficiencies.

A similar experiment was conducted for **1d** with **9** (2 equiv), and enantiopure (*R*)-**1d** was obtained in 30% yield after recrystallization was conducted three times (Entries 10–12). The molar ratio of **1d** and **9** in the precipitates was constant (**1d**:**9**=3:2) during the repeated recrystallization steps, indicating that this salt is a thermodynamically stable composition of the less-soluble (*R*)-**1d**·**9** salt although the detailed structural information is not clear. Thus, this resolution method is confirmed for applications to large-scale production of enantiopure *o*-APs.

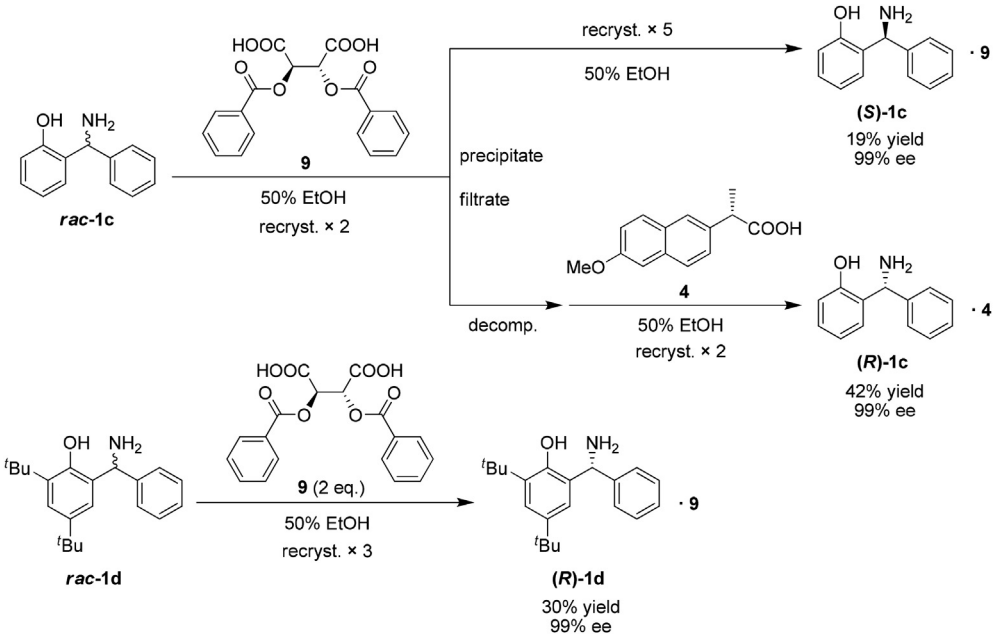
2.5. Asymmetric addition of Et_2Zn to benzaldehyde catalyzed by enantiopure *o*-APs

Chiral 1,3-aminoalcohols are potential ligands for asymmetric reactions. Several chiral *o*-APs have been applied to the asymmetric addition reaction of Et_2Zn to aldehydes.[16] For examining the chiral induction ability of enantiopure **1a**-**d**, they were tested as ligands for the enantioselective addition of Et_2Zn to benzaldehyde (Table 5). With (*S*)-**1a** and (*S*)-**1c** (10 mol %), the product (*R*)-1-phenyl-1-propanol was obtained in low yields, and only marginal chiral induction was observed (Entries 1 and 3, respectively). On the other hand, (*R*)-**1b** afforded the (*S*)-isomer of the product with moderate yield and good enantioselectivity (Entry 2). Furthermore, (*R*)-**1d** drastically improved the results, and the (*S*)-isomer of the alcohol was obtained in very high yield (96%) and ee value (92% ee). The results were compared, and the bulky *tert*-butyl group attached close to the hydroxy group of **1** plays an important role in the induction of chirality, which is

Table 4
Repeated recrystallization of the salts of **1c**·**9**, **1c**·**4**, and **1d**·**9** from 50% EtOH

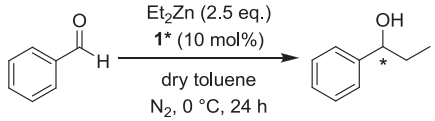
Entry	Salt	Solvent (L/mol)[a]	Yield[b] (%)	Ee[c] (%)	Eff.[d]
1[e]	**1c**·**9** (1st)	100	123	47(*S*)	0.58
2	**1c**·**9** (2nd)	65	92	77(*S*)	0.71
3	**1c**·**9** (3rd)	100	70	85(*S*)	0.60
4	**1c**·**9** (4th)	75	55	93(*S*)	0.51
5	**1c**·**9** (5th)	60	42	97(*S*)	0.41
6	**1c**·**9** (6th)	85	30	98(*S*)	0.30
7	**1c**·**9** (7th)	60	19	99(*S*)	0.19
8[f]	**1c**·**4** (1st)	90	59	97(*R*)	0.57
9	**1c**·**4** (2nd)	70	42	99(*R*)	0.42
10[g]	**1d**·**9** (1st)	90	94[h]	69(*R*)	0.65
11	**1d**·**9** (2nd)	120	51	97(*R*)	0.49
12	**1d**·**9** (3rd)	75	30	99(*R*)	0.30

[a] Amount of the solvent based on the amount of *rac*-**1** is shown.
[b] Yield was based on half of the amount of *rac*-**1**.
[c] Ee was determined by HPLC analysis.
[d] Eff.=Yield (%)×Ee (%)/10,000.
[e] *Rac*-**1c** (10.0 mmol) and **9** (10.0 mmol) were used.
[f] (*R*)-**1c** (55% ee, 6.18 mmol) and **4** (6.18 mmol) were used.
[g] *Rac*-**1d** (2.57 mmol) and **9** (5.14 mmol) were used.
[h] The insoluble solid (32.8 mg) was removed before crystallization.



Scheme 3. Preparation of enantiopure (*S*)-**1c**, (*R*)-**1c**, and (*R*)-**1d** by repeated recrystallization of the diastereomeric salts.

Table 5
Enantioselective addition of Et_2Zn to benzaldehyde catalyzed by enantiopure *o*-AP ligands **1a-d**[a]



Entry	Chiral ligand	Yield[b] (%)	Ee[c] (%)
1	(*S*)-**1a**	26	13(*R*)
2	(*R*)-**1b**	54	75(*S*)
3	(*S*)-**1c**	6	39(*R*)
4	(*R*)-**1d**	96	92(*S*)

[a] All reactions were conducted under N_2 with benzaldehyde (1 mmol), Et_2Zn (0.77 M hexane solution), and dry toluene as the solvent in the presence of enantiopure **1** (10 mol %) at 0 °C for 24 h.
[b] Isolated yield was based on benzaldehyde.
[c] Ee was determined by HPLC analysis.

consistent with the transition state model proposed in our previous study.[16c] The bulky substituents on the stereogenic center also positively affected the chiral induction of this type of a reaction, albeit to a lesser extent.

3. Conclusion

In this study, two *ortho*-(aminomethyl)phenols (*o*-APs, **1c** and **1d**) were synthesized, and their enantioseparation via diastereomeric salt formation was carried out. The successful enantioseparation of *rac*-**1c** was conducted with (*S*)-naproxen (**4**) or dibenzoyl-L-tartaric acid (**9**) by recrystallization from 50% aqueous EtOH, which preferentially afforded (*R*)-**1c** or (*S*)-**1c**, respectively. When a 1:2 mixture of *rac*-**1d** and **9** was recrystallized from the same solvent, (*R*)-**1d** was obtained with the highest resolution efficiency. The X-ray crystallographic analysis of the less-soluble diastereomeric salts of (*R*)-**1c**·**4** and (*S*)-**1c**·**9** showed that a columnar hydrogen-bonding network was formed from **1c** and the resolving agent, as well as water molecules. The water molecules incorporated in the salt crystals with hydrogen bonds played an important role in the chiral recognition of **1c**. Enantiopure **1c** and **1d** were successfully prepared by the repeated recrystallization of the diastereomeric salts, and (*R*)-**1d** exhibited high ability for chiral induction in the asymmetric addition of Et_2Zn to benzaldehyde. The further application of these *o*-APs to other asymmetric reactions is underway.

4. Experimental section

4.1. Materials and general methods

All commercially available reagents were used as received unless noted. Benzaldehyde was distilled under reduced pressure before use. Dried dichloromethane, toluene and tetrahydrofuran were prepared by distillation. All ^1H and ^{13}C NMR spectra were recorded on Bruker Avance 300, 400 or 500 MHz spectrometer. IR spectra were measured on a JASCO FT/IR-460 spectrometer as KBr pellets. Melting points were recorded on a MEL-TEMP apparatus and reported uncorrected. TG-DTA analysis was performed on a SII EXSTAR 6000 system at a heating rate of 10 °C min^{-1}. Enantiomeric excesses were determined by HPLC analyses with a Daicel Chiralcel OD-3 column with detection at 254 nm. Powder X-ray diffractions were obtained with a Rigaku RINT UltimaIII diffractometer using graphite-monochromated Cu-Kα radiation. Optical rotations were measured with a JASCO DIP-370 polarimeter.

4.2. Synthesis of *rac*-2-[amino(phenyl)methyl]phenol (*rac*-1c)[17]

2c (5.00 g, 25.2 mmol) was dissolved in dry MeOH (300 mL) and gaseous ammonia was introduced to the solution at 0 °C. Then the solution was stirred at room temperature for 20 h. The solvent was removed under reduced pressure and the residue was dissolved in dry MeOH (200 mL). $NaBH_4$ (7.63 g, 202 mmol) was added portionwise to the mixture at 0 °C and the mixture was stirred at room temperature for 42 h. After the reaction mixture was acidified by addition of 1N HClaq, MeOH was removed under reduced pressure. The residual solution was basified by addition of $NaHCO_3$ until the pH became 8–9. The resulting mixture was extracted with $CHCl_3$ (50 mL×3) and the organic phase was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (hexane/EtOAc=10:1) to give *rac*-**1c** (3.26 g, 16.4 mmol, 65%) as pale yellow solid. Mp: 101–102 °C. ^1H MNR (500 MHz, $CDCl_3$): δ 7.38–7.28 (m, 5H), 7.18–7.13 (m, 1H), 6.90–6.87 (m, 1H), 6.80–6.69 (m, 2H), 5.31 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.9, 143.2, 129.0, 128.9, 128.6, 127.8, 126.9, 126.3, 119.1, 117.4, 60.0. IR (KBr): ν_{max}=3350, 3294, 2581, 1589, 1457, 1272, 1155, 1074, 998, 755, 695, 647, 608, 574, 526 cm^{-1}.

4.3. Synthesis of *rac*-2-[amino(phenyl)methyl]-4,6-di-*tert*-butylphenol (*rac*-1d)

To the solution of 1,2,3-benzotriazole (4.29 g, 36.0 mmol) in dry CH_2Cl_2 (15 mL), thionyl chloride (1.0 mL) was added dropwise under a N_2 atmosphere. After 45 min, 3,5-di-*tert*-butylsalicylic acid (3.01 g, 12.0 mmol) dissolved in dry CH_2Cl_2 (15 mL) was added dropwise and the mixture was stirred at room temperature for 22 h. The solid was filtered off and the solvent was removed under reduced pressure. To the residue was added hexane and the mixture was filtered. From the filtrate, the solvent was removed under reduced pressure. The crude product (4.20 g) was used for the next reaction without further purification.

A solution of bromobenzene (3.0 mL, 30 mmol) in dry THF (10 mL) was added dropwise to magnesium turning (0.736 g, 30.3 mmol) in dry THF (20 mL) under a N_2 atmosphere. After the addition of bromobenzene, the reaction mixture was stirred at room temperature for 5 h to prepare Grignard reagent. The solution of this Grignard reagent was slowly added to the solution of amide (4.20 g) in dry THF (80 mL) and the mixture was stirred at room temperature for three days. After the reaction was quenched by the addition of saturated NH_4Claq at 0 °C, the mixture was extracted with $CHCl_3$ (50 mL×3) and the organic phase was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (hexane/EtOAc=10:1) to afford ketone **2d** (2.29 g, 7.36 mmol, 61%) as yellow solid. Mp: 60.5–61.0 °C (lit.[13] mp 60–62 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 12.69 (s, 1H), 7.69–7.64 (m, 2H), 7.60–7.54 (m, 2H), 7.52–7.46 (m, 2H), 7.42 (d, 1H, *J*=2.4 Hz), 1.48 (s, 9H), 1.24 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.5, 160.7, 139.8, 138.7, 137.9, 131.6, 131.2, 129.2, 128.2, 127.8, 118.2, 35.2, 34.2, 31.3, 29.4. IR (KBr): ν_{max}=2962, 1616, 1596, 1574, 1435, 1337, 1281, 1242, 1179, 1156, 991, 817, 775, 719, 695, 671, 625 cm^{-1}.

2d (5.30 g, 17.1 mmol) was dissolved in dry MeOH (350 mL) and the gaseous ammonia was introduced to the solution at 0 °C. The solution was allowed to warm to room temperature and stirred for a day. The solvent was removed under reduced pressure and the residue was dissolved in dry MeOH (350 mL). $NaBH_4$ (7.95 g, 210 mmol) was added portionwise to the mixture at 0 °C and stirred at room temperature for four days. After the reaction mixture was acidified by addition of 1N HClaq, MeOH was removed under reduced pressure. The mixture was basified by addition of

$NaHCO_3$ until the pH became 8–9. The resulting mixture was extracted with $CHCl_3$ (100 mL×3) and the organic phase was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (hexane/EtOAc=10:1). Further recrystallization from ethanol gave *rac*-**1d** (2.12 g, 6.81 mmol, 40%) as colorless needle-shaped crystals. Mp: 113–114 °C. ^{1}H MNR (400 MHz, $CDCl_3$): δ 11.6 (br, 1H), 7.41–7.32 (m, 4H), 7.31–7.26 (m, 1H), 7.22 (d, 1H, J=2.4 Hz), 6.64 (d, 1H, J=2.4 Hz), 5.31 (s, 1H), 2.24 (br, 2H), 1.44 (s, 9H), 1.19 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 143.4, 140.2, 136.7, 128.8, 127.6, 127.0, 125.5, 123.4, 123.2, 60.6, 35.1, 34.1, 31.6, 29.7. IR (KBr): ν_{max}=3378, 3290, 2956, 1573, 1478, 1440, 1362, 1252, 1231, 1203, 961, 903, 878, 754, 703, 649 cm^{-1}. Elemental analysis: calcd for $C_{21}H_{29}NO$: C 80.98%, H 9.38%, N 4.51%; found: C 80.81%, H 9.54%, N 4.39%.

4.4. General procedure for the diastereomeric resolution of *rac*-1

The mixture of **1** (0.4 mmol) and each resolving agent (0.4 mmol) were dissolved in MeOH. After concentration, the diastereomeric salts were recrystallized from an appropriate solvent. When **1d** was used, some insoluble solid **11** was filtered off before cooling. The precipitated salt was collected by filtration and dried under reduced pressure. The yield was calculated based on a half amount of *rac*-**1** initially used. A part of the salt was added in 1N NaOHaq and extracted with EtOAc. The organic phase was dried over anhydrous Na_2SO_4. After removal of the solvent, **1** was obtained as a solid. The enantiomeric excess was determined by an HPLC analysis (**1c**: Daicel ChiralPak OD-3, hexane/2-propanol=9:1, 0.8 mL min^{-1}, t_r(*S*)=23.9 min; t_r(*R*)=43.8 min, **1d**: ChiralPak OD-3, hexane/2-propanol=9:1, 1.0 mL min^{-1}, t_r(*S*)=7.7 min; t_r(*R*)=12.5 min).

11: Mp: 189–191 °C (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 2H), 7.34–7.20 (m, 12H), 6.86 (d, 2H, J=2.4 Hz), 4.87 (d, 2H, J=5.6 Hz), 3.19 (t, 1H, J=6.4 Hz), 1.44 (s, 18H), 1.27 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 141.9, 141.2, 136.8, 128.8, 127.6, 127.6, 125.3, 124.7, 123.3, 63.5, 34.9, 34.3, 31.7, 29.9. IR (KBr): ν_{max}=3507, 2959, 2869, 1604, 1479, 1447, 1391, 1362, 1240, 1201, 1161, 1123, 881, 825, 756, 700 cm^{-1}. MS (MALDI-TOF, matrix; dithranol): m/z calcd for $[M+H]^+$: 606.43, found: 606.49.

4.5. Preparation of enantiopure 1c and 1d

The mixture of **1c** (2.00 g, 10.0 mmol) and **9** (3.60 g, 10.0 mmol) was dissolved in MeOH. After removal of the solvent, the salt was recrystallized seven times from 50% EtOH to afford diastereopure salt (*S*)-**1c**·**9** (0.54 g, 0.96 mmol, 19%) as colorless crystals. The filtrates of the first and second recrystallization were collected and the solvent was removed. The salt was decomposed to recover enantio-enriched (*R*)-**1c** (1.23 g, 6.17 mmol, 55 %ee), which was mixed with an equimolar amount of **4** (1.42 g, 6.18 mmol). The salt **1c**·**4** was recrystallized from 50% EtOH twice to afford diastereopure salt (*R*)-**1c**·**4** (1.12 g, 2.6 mmol, 42%) as colorless crystals. The salts were decomposed to afford enantiopure **1c** quantitatively. Similarly, recrystallization of the salt between **1d** (0.80 g, 2.57 mmol) and **9** (1.84 g, 5.14 mmol) from 50% EtOH three times afforded diastereopure (*R*)-**1d**·**9** (210 mg, 0.49 mmol, 30%) as a white solid. The composition ratio of the solid was **1d**:**9**=3:2 and (*R*)-**1d** was quantitatively recovered by decomposition of the salt.

(*S*)-**1c**·**9**: Mp: 174–175 °C (decomp.). IR (KBr): ν_{max}=3509, 3164, 1715, 1602, 1499, 1461, 1335, 1270, 1119, 761, 715, 617, 566, 514 cm^{-1}. $[\alpha]_D^{22}$=−70.7 (*c* 1.0, EtOH). (*R*)-**1c**·**4**: Mp: 127.5–129.0 °C. IR (KBr): ν_{max}=3060, 1606, 1558, 1462, 1386, 1363, 1269, 1229, 1031, 856, 814, 757, 695 cm^{-1}. $[\alpha]_D^{22}$=−1.6 (*c* 1.0, EtOH). (*S*)-**1c**: Mp: 88.5–90.0 °C. IR (KBr): ν_{max}=3343, 3281, 2572, 1595, 1455, 1407, 1276, 1251, 1094, 1006, 804, 762, 729, 700, 610 cm^{-1}. $[\alpha]_D^{22}$=55.9 (*c* 0.8, EtOH). (*R*)-**1c**: Mp: 87.8–89.5 °C. IR (KBr): ν_{max}=3343, 3281, 2575, 1596, 1454, 1407, 1276, 1251, 1006, 762, 700, 61s0 cm^{-1}. $[\alpha]_D^{22}$=−47.0 (*c* 1.0, EtOH). (*R*)-**1d**·**9**: Mp: 176.5–178.0 °C. IR (KBr): ν_{max}=3429, 2959, 1717, 1624, 1479, 1453, 1267, 1117, 713 cm^{-1}. $[\alpha]_D^{22}$=−49.0 (*c* 1.0, EtOH). (*R*)-**1d**: Mp: 105.0–107.0 °C. IR (KBr): ν_{max}=3295, 2957, 1600, 1480, 1442, 1361, 1251, 1231, 973, 883, 756, 698 cm^{-1}. $[\alpha]_D^{22}$=−77.0 (*c* 1.0, EtOH).

4.6. Asymmetric addition reaction of diethylzinc to benzaldehyde catalyzed by enantiopure 1

To a solution of **1** (0.1 mmol) in dry toluene (1.5 mL) was added Et_2Zn (0.77 Mhexane solution, 3.25 mL, 2.50 mmol) dropwise at 0 °C under N_2 atmosphere, and the mixture was stirred for 30 min. A solution of benzaldehyde (106 mg, 1.00 mmol) in dry toluene (2.0 mL) was added dropwise to the mixture and the reaction mixture was stirred for 24 h at 0 °C. The reaction was quenched by the addition of 1N HClaq (5 mL) and water (20 mL). The aqueous layer was extracted with EtOAc (20 mL×3). The extracts was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by preparative scale TLC (hexane/EtOAc=7:3) and its enantiopurity was determined by an HPLC analysis (Daicel ChiralPak OD-3, hexane/2-propanol=9:1, 1.0 mL min^{-1}, t_r(*R*)=11.8 min; t_r(*S*)=13.4 min).

4.7. Single crystal X-ray analyses

X-ray crystallographic data were collected on a Bruker Smart APEX II diffractometer with graphite monochromated Mo-Kα radiation. The structures were solved by a direct method using SIR 2004 and refined by SHELXL-2013 program.[18] Crystal data for *rac*-**1d**: C21H29NO, M=311.45, orthorhombic, a=17.203(3), b=18.271(3), c=5.9332(9) Å, V=1864.9(5) Å^3, T=150 K, space group $Pna2_1$, Z=4, 8584 reflections measured, 3093 independent reflections (R_{int}=0.1168), The final R_1 was 0.0634 (I>2σ(I)) and $wR(F_2)$ was 0.1677 (I>2σ(I)), CCDC: 1435690. Crystal data for (*R*)-**1c**·**4**·0.5H_2O: C27H28NO4.5, M=438.50, monoclinic, a=26.870(6), b=5.4794(13), c=15.955(4) Å, β=102.335(3) °, V=2294.9(9) Å^3, T=200 K, space group $C2$, Z=4, 5512 reflections measured, 3765 independent reflections (R_{int}=0.1244), The final R_1 was 0.0608 (I>2σ(I)) and $wR(F_2)$ was 0.1367 (I>2σ(I)), CCDC: 1435691. Crystal data for (*S*)-**1c**·**9**·3H_2O: C31H33NO12, M=611.58, monoclinic, a=12.908(2), b=7.7688(12), c=15.594(3) Å, β=109.440(2)°, V=1474.7(4) Å^3, T=150 K, space group $P2_1$, Z=2, 7042 reflections measured, 4957 independent reflections (R_{int}=0.0712), The final R_1 was 0.0551 (I>2σ(I)) and $wR(F_2)$ was 0.1254 (I>2σ(I)), CCDC: 1435692. Detailed data is summarized in the Supplementary data (Table S1). Crystallographic data for the structures in this paper can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supplementary data

Supplementary data (Crystal structure of **11** (Fig. S1), powder XRD patterns of the compounds (Fig. S2), TGA chart of (*S*)-**1c**·**9** (Fig. S3), crystal structure of **1c**·**10** (Fig. S4), summary of crystallographic data (Table S1), copies of ^{1}H NMR, ^{13}C NMR, and IR spectra of the reported compounds) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.01.034.

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