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Direct enantioseparation of axially chiral 1,1'-biaryl-2,2'-diols using amidine-based resolving agents†

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Amidine-based optically active resolving agents for enantiomer separation of axially chiral 1,1'-biaryl-2,2'-diols have been developed. A strongly basic amidine bearing no substituents on its nitrogen atoms enables the formation of their diastereomeric salts upon being mixed with weakly acidic phenol derivatives. Enantiopure 1,1'-biaryl-2,2'-diols can be obtained in high yields after only one crystallization of their salts with the chiral amidine derived from dehydroabietic acid. X-ray crystallography revealed that the amidine moiety forms a salt with the phenol group and additional intermolecular NH/ π interactions contribute to the efficient chiral recognition process.

Introduction

Among the various methods used for the industrial production of optically pure chiral compounds, optical resolution of a racemate into its enantiomers *via* diastereomeric salt formation, followed by recrystallization, is one of the most reliable and economical methods reported to date.¹ Various chiral carboxylic acids and amines have been developed as acidic and basic resolving agents for this purpose. However, this method is sometimes not applicable to weak acids and bases because they cannot form their corresponding diastereomeric salts. To overcome this problem, chiral sulfonic acids and phosphoric acids have been developed as acidic resolving agents for the enantioseparation of weakly basic amines due to their strong acidities.² On the other hand, strongly basic resolving agents used for the separation of weak acids are limited.

Amidines have been comprehensively demonstrated to be stronger Brønsted bases than conventional amines. Several chiral amidines have been developed and applied as N-chelating ligands,³ asymmetric organocatalysts,⁴ and in the kinetic resolution of alcohols.⁵ Recently, chiral supramolecular structures constructed *via* salt formation using chiral amidines and carboxylic acids have been reported.⁶ Their robust supramolecular assembly has been attributed to the strong charge-assisted hydrogen bonds formed during the salt formation process. It is expected that such strongly basic chiral amidines can be applied toward the enantioseparation of weakly acidic compounds *via* diastereomeric salt formation.

The atropisomers of 1,1'-biaryl-2,2'-diols (**1**) are an important class of compounds with weakly acidic phenol moieties. Functionalized chiral biaryl derivatives can be applied as ligands in asymmetric synthesis,⁷ dopants for nematic liquid crystals to induce a helical arrangement, *etc.*⁸ Dobashi reported the NMR-based chiral recognition of 1,1'-binaphthyl-2,2'-diol (BINOL, **1a**) using a twisted chiral bisamidine.⁹ Enantiopure **1a** is useful not only as a chiral ligand in catalytic asymmetric reactions, but as a starting material for the synthesis of various chiral auxiliaries, such as BINAP.¹⁰ Although various methods to access enantiopure **1a** have been reported including enantioselective oxidative coupling, enzymatic resolution, chemical resolution of its diastereomers with chiral auxiliaries,¹⁰ and complexation with chiral reagents,¹¹ the practical enantioseparation of **1** from its racemate is still challenging.

In this paper, we report the efficient enantioseparation of **1** *via* diastereomeric salt formation using chiral amidine-based resolving agents (**2**).

Results and discussion

Enantioseparation of **1a** by *N,N'*-disubstituted chiral amidine (**2a**)

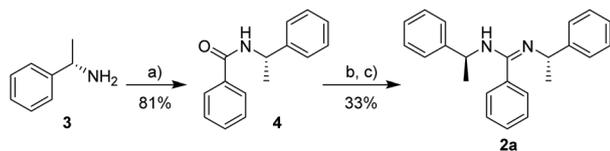
We selected *N,N'*-disubstituted chiral amidine **2a** as a resolving agent because resolving agents bearing aromatic groups generally result in dense molecular packing during the formation of their salt crystals. Amidine **2a** in its optically active form has been previously reported and was easily synthesized from commercially available (*S*)-1-phenylethylamine (**3**) (Scheme 1).¹¹ As previously reported, the IR spectrum of **2a** in solid state exhibits an absorption band at 1637 cm⁻¹, corresponding to the C=N stretching vibrations.

Sterically demanding **1a** was selected as the first target axially chiral phenol. Equimolar amounts of *rac*-**1a** and **2a** were mixed and crystallized from toluene to give colorless crystals. Analysis

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† Electronic supplementary information (ESI) available: Fig. S1–S4 and Table S1, experimental detail, copies of ¹H, ¹³C NMR, and IR spectra, HPLC chromatograms. CCDC 2057487–2057489. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ra03546k





Scheme 1 Synthesis of chiral amidine **2a**. Reagents and conditions: (a) PhCOCl, NaOH, H₂O, 0 °C to rt; (b) (COCl)₂, 2,6-lutidine, dry CH₂Cl₂, 0 °C to rt; (c) **3**, reflux.

of the ¹H NMR spectrum shows that the resulting crystals consisted of both **1a** and **2a** (84% yield based on half the amount of **1a** used; molar ratio **1a** : **2a** = 1.8 : 1). The complex of **1a** and **2a** was decomposed and **1a** was isolated *via* extraction. The enantiopurity of **1a** was determined using chiral HPLC analysis, which was as high as 81% ee, and (*S*)-**1a** was found to be preferentially crystallized with **2a**.

Platelet crystals suitable for X-ray crystallographic analysis were obtained during the crystallization step and it was found that **2a** and **1a** were co-crystallized with a molar ratio of (*S*)-**1a** : **2a** = 2 : 1 (Fig. 1). There are two independent (*S*)-**1a** molecules in the asymmetric unit cell. The **2a** molecule was in the form of its protonated amidinium cation with an (*E,E*) configuration, which forms two hydrogen bonds with (*S*)-**1a**. The two N–H hydrogen atoms were combined with the same phenolate oxygen atom in (*S*)-**1a** to give the salt. Only one molecule of (*S*)-**1a** was ionized and the other (*S*)-**1a** molecule was not charged

(Fig. 1a). The neutral (*S*)-**1a** molecule was incorporated by the formation of a hydrogen bond with the ionized (*S*)-**1a** molecule and these three molecules assemble to form an aggregate. All the naphthalene planes of (*S*)-**1a** were fixed by CH/π interactions with the neighboring aromatic CH of **2a**, which should result in the good chiral recognition of the (*S*)-isomer of **1a** (Fig. 1b).

Unfortunately, this complex formation process was not always reproducible and occasionally **1a** was crystallized alone under the same conditions. The IR spectrum of a mixture of **1a** and **2a** in methanol showed that the absorption band at 1637 cm⁻¹, corresponding to **2a**, was unchanged upon the addition of **1a**, which indicates no obvious salt formation (Fig. S1†). This can be attributed to the steric hindrance of the bulky chiral substituents of **2a** around the amidine hydrogen-bonding site, which prevents salt formation with **1a**.

Synthesis of *N*-non-substituted chiral amidines (**2b** and **2c**)

In order to prepare salts with phenols more reliably, a series of chiral amidines without any substituents on their nitrogen atoms were designed. Such non-substituted amidines may be better candidates as resolving agents because of their reduced steric hindrance and increased number of hydrogen atoms available to form hydrogen bonds. Non-substituted amidines have been applied as ligands to detect carboxylic acids and inhibitors¹³ and recently used to construct supramolecular hydrogen-bonded organic frameworks (HOFs) by combining with carboxylic acids or sulfonic acids. Such salt-type HOFs with large and permanent porosities have been applied in selective gas absorption, enzyme encapsulation, *etc.*¹⁴ However, chiral non-substituted amidines are very rare with only a few examples have been reported.¹⁵

Benzamidine, which is one of the simplest non-substituted amidines was studied as a model compound in our preliminary experiments to examine the salt formation ability of non-substituted amidines with phenols. When benzamidine was mixed with 4-nitrophenol, the resulting IR spectrum showed that the absorption peak at 1637 cm⁻¹, corresponding to benzamidine, was shifted to 1654 cm⁻¹, which suggested the formation of the amidinium salt, although a mixture of 4-nitrophenol and **2a** showed no such a shift in the absorption peak (Fig. S2†). The 1 : 1 salt formed between benzamidine and 4-nitrophenol was also confirmed using X-ray crystallography (Fig. S3†).

One general and convenient synthetic route toward non-substituted amidines is to start from their corresponding carboxylic acids by way of their nitrile derivatives.¹⁶ In addition, the amidine functional group should be close to the asymmetric center to enhance the chiral recognition ability. Based on these concepts, non-substituted chiral amidine **2b** derived from (*S*)-naproxen (**5**) was designed. Compound **5** is a commercially available chiral carboxylic acid, which has been used as an acidic resolving agent as well as a non-steroidal anti-inflammatory drug.¹⁷ Amidine **2b** was synthesized from enantiopure **5** *via* nitrile derivative **7** (Scheme 2). Nitrile **7** was converted into its corresponding *N*-hydroxyamidine (**8**), followed by

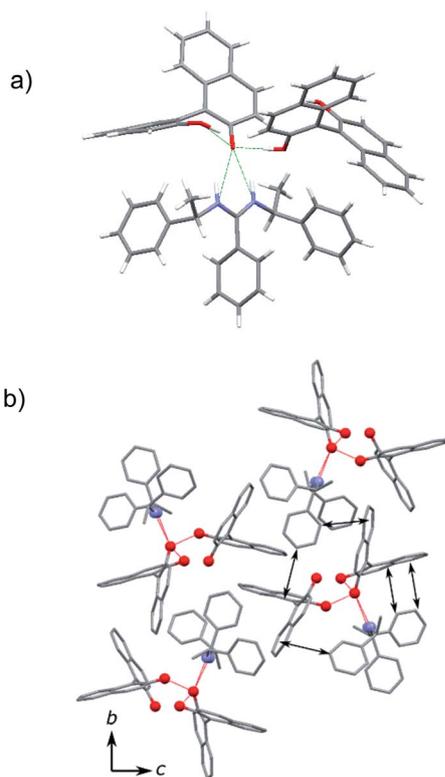
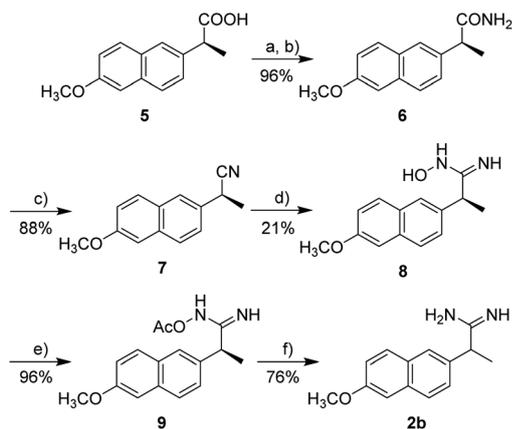


Fig. 1 Crystal structure of **2a**·2(*S*)-**1a**. The oxygen and nitrogen atoms are represented using red and blue spheres. The dotted lines represent the hydrogen bonds. The arrows represent the CH/π interactions.

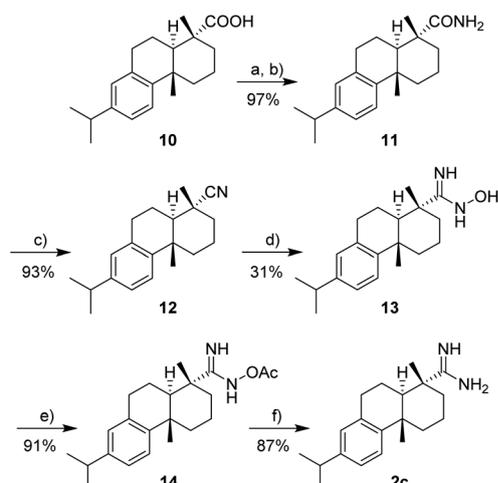




Scheme 2 Synthesis of chiral amidine **2b**. Reagents and conditions: (a) $(\text{COCl})_2$, 0 to 40 °C; (b) 28% NH_3 (aq.), toluene, 0 °C to rt; (c) PPh_3 , Et_3N , CCl_4 , dry CH_2Cl_2 , reflux; (d) $\text{NH}_2\text{OH}\cdot\text{HCl}$, Et_3N , dry EtOH, dry DMF, 80 °C; (e) Ac_2O , pyridine, THF, 0 °C to rt; (f) H_2 (1 atm), cat. Pd/C, EtOH, rt.

O-acetylation and hydrogenolysis to afford desired non-substituted amidine (**2b**). However, it was found that the enantiopurity of the intermediate **8** decreased to 51% ee and **2b** showed no optical activity. This suggests that the base used during the synthesis induced partial racemization due to the abstraction of the acidic hydrogen atom on the stereogenic center and the strong basicity of the amidine itself caused complete racemization of **2b**.

To avoid racemization, dehydroabietic acid (**10**) bearing a quaternary stereogenic center was selected as the starting chiral carboxylic acid. Carboxylic acid **10** is an abundant natural acid obtained from rosin, which has been used as a chiral source because of its rigid and hydrophobic nature.¹⁸ Non-substituted chiral amidine **2c** was successfully prepared in



Scheme 3 Synthesis of chiral amidine **2c**. Reagents and conditions: (a) $(\text{COCl})_2$, cat. DMF, dry CH_2Cl_2 , 0 °C to reflux; (b) 28% NH_3 (aq.), toluene, 0 °C to rt; (c) PPh_3 , Et_3N , CCl_4 , dry CH_2Cl_2 , reflux; (d) $\text{NH}_2\text{OH}\cdot\text{HCl}$, Et_3N , dry EtOH, reflux; (e) Ac_2O , pyridine, THF, 0 °C to rt; (f) H_2 (1 atm), cat. Pd/C, EtOH, rt.

moderate-to-high yield using a similar synthetic route *via* nitrile **12** (Scheme 3). The high stereochemical purity of **2c** was confirmed by its narrow melting point range, ^1H NMR analysis, and specific optical rotation.¹⁹ The IR spectrum of a mixture of **2c** and **1a** showed that the absorption peak corresponding to the $\text{C}=\text{N}$ stretching vibration at 1634 cm^{-1} derived from **2c** disappears and a new peak at 1673 cm^{-1} appeared, which indicates that the amidinium salt of **2c** was formed upon mixing with **1a** (Fig. S4).[†]

Enantioseparation of **1** by *N*-non-substituted chiral amidine (**2c**)

The enantioseparation of *rac*-**1a** with **2c** *via* diastereomeric salt formation was investigated (Table 1). Crystallization of a mixture of equimolar amounts of *rac*-**1a** and **2c** from toluene afforded the 1 : 1 salt of **1a** and **2c** in high yield (88%) and the enantiopurity of **1a** was as high as 97% for the (*R*)-isomer (entry 1). Using ethyl acetate as the solvent further increased the yield up to 94% and pure (*R*)-**1a** salt was obtained by only one crystallization step (entry 2). Ethanol, a more polar solvent, also afforded the salt of enantiopure (*R*)-**1a**, albeit in lower yield (entry 3). As a control experiment, dehydroabietylamine, which is a primary amine with the same chiral skeleton as **2c**, was mixed with *rac*-**1a** and recrystallized from toluene. However only **1a** was precipitated, which clearly suggests that the amidine functional group of **2c** was essential for enantioselective salt formation with (*R*)-**1a**.

Prompted by this result, the scope for the enantioseparation of other axially chiral 1,1'-biaryl-2,2'-diols was investigated (Table 1). Binaphthalene-based diol **1b** bearing two bromine atoms also afforded a 1 : 1 salt with **2c**. However, only racemic **1b** was obtained from the salt and the enantioseparation was

Table 1 Enantioseparation of racemic 1,1'-biaryl-2,2'-diols (**1a–1c**) and monophenol (**15**) *via* diastereomeric salt formation with **2c**^a

Entry	Phenol	Solvent (mL)	Yield ^b (%)	ee ^c (%)
1	1a	Toluene (8.5)	88	97(<i>R</i>)
2	1a	AcOEt (29.5)	94	>99(<i>R</i>)
3	1a	EtOH (15.5)	34	>99(<i>R</i>)
4	1b	Toluene (4.0)	66	<i>Rac</i>
5	1b	Toluene/AcOEt (1.5/0.15)	Not crystallized	—
6	1c	Toluene	Gelated	—
7	1c	AcOEt (4.5)	58	>99(<i>R</i>)
8	1c	EtOH (0.6)	30	80(<i>R</i>)
9	15	Toluene/hexane (0.2/0.6)	Not crystallized	—

^a *Rac*-**1** and **2c** (0.25 mmol) were used. ^b The yield is based on half the amount of the initial salt. ^c The ee was determined using HPLC analysis. The absolute configuration of the major enantiomer is shown in the parentheses.



not successful (entry 4). On the other hand, 6,6'-dimethyl-2,2'-biphenol (**1c**), which is one of the simplest axially chiral biphenols, was crystallized with **2c** from ethyl acetate to afford pure (*R*)-**1c** salt in a good yield (entry 7). Crystallization from ethanol again decreased the separation efficiency, which was attributed to the polar solvent reducing the efficiency of hydrogen bond formation and decreasing the rate of salt formation (entry 8). A previously reported method for the enantioseparation of **1c** requires its derivatization into a phosphoric acid derivative, followed by diastereomeric salt formation with cinchonidine, a toxic alkaloid amine.²⁰ To the best of our knowledge, this is the first example of a simple and direct enantiomeric separation of *rac*-**1c** using crystallization. On the other hand, the salt of **2c** with monophenol **15** bearing another aliphatic hydroxy group on the asymmetric center was not crystallized (entry 9). This result indicates that the two phenolic hydroxy groups in 1,1'-biaryl-2,2'-diols cooperatively interact with the amidine moiety in **2c** to form their corresponding salts.

A needle-like crystal was obtained from an ethanol solution of a mixture of (*R*)-**1a** and **2c**, which was subjected to X-ray crystallography (Fig. 2). The 1 : 1 salt was formed between (*R*)-**1a** and **2c**, and one hydroxy group in (*R*)-**1a** was ionized. The two amidinium hydrogen atoms in the (*Z*)-configuration of **2c** form hydrogen bonds with the oxygen atoms of two molecules of **1a**. The two oxygen atoms are combined *via* a OH–O hydrogen bond. The other two amidinium hydrogen atoms in the (*E*)-configuration form cationic NH– π interactions with the naphthalene rings in **1a** (Fig. 2a).²¹ Two (*R*)-**1a** molecules are tightly

fixed by these intermolecular interactions with **2c** and they are helically arranged to construct a one-dimensional hydrogen-bonding network along the *a*-axis (Fig. 2b). Because both **1a** and **2c** are not flexible molecules, the efficient packing of the naphthalene moieties in **1a** and the large hydrocarbon moiety in **2c** also contribute to the highly stereoselective crystallization of one diastereomeric salt **2c**·(*R*)-**1a**.

Conclusions

Chiral amidines have been developed for the enantioseparation of weakly acidic phenol derivatives *via* diastereomeric salt formation. Atropisomers of axially chiral 1,1'-binaphthyl-2,2'-diol (**1a**) and 6,6'-dimethyl-2,2'-biphenol (**1c**) have been separated in high yield and with high enantiopurity using a non-substituted chiral amidine (**2c**) derived from dehydroabiatic acid (**10**), a commercially available chiral source. IR spectra and X-ray crystallography has shown that hydrogen bonds and additional NH– π interactions with the amidinium group played an important role in the chiral recognition process. Based on the reliable amidinium-phenolate salt formation, further design of chiral amidines as resolving agents will expand the scope for enantioseparation of different chiral phenols, which is now under investigation.

Experimental

General and materials

All the ¹H and ¹³C NMR spectra were measured using 300, 400, or 500 MHz spectrometers. IR spectra were reported in reciprocal centimeters. Melting points are uncorrected. Optical rotation values were measured with a polarimeter. All commercially available reagents and solvents were purchased and used as received unless noted. Dry THF was freshly distilled from sodium under a nitrogen atmosphere. Dry CH₂Cl₂ and dry CCl₄ were distilled after drying over CaCl₂ and stored with 4 Å molecular sieves under a nitrogen atmosphere. Dry triethylamine was distilled after drying over KOH and stored with KOH under a nitrogen atmosphere. Dry toluene was distilled from sodium under a nitrogen atmosphere and stored with sodium under a nitrogen atmosphere. Dry EtOH was distilled from sodium under a nitrogen atmosphere and stored with molecular sieves 4 Å under a nitrogen atmosphere. Dehydroabiatic acid (**10**) was supplied from Arakawa Chemical Ind, Ltd. and purified by repeated recrystallization of its salt with 2-aminoethanol.²² The enantiomeric excess of the compounds was determined by chiral HPLC analysis (Daicel Chiralcel OD-3 column 4.6 × 250 mm or Chiralpak AS-3 column 2.1 × 250 mm) with UV detection at 254 nm.

(*S*)-*N*-(1-Phenylethyl)benzamide (**4**)^{12b}

To a vigorously stirred mixture of (*S*)-1-phenylethylamine (**3**) (2.81 g, 23.2 mmol) and NaOH (1.29 g, 32.2 mmol) in H₂O (25 mL) was added dropwise benzoylchloride (3.62 g, 25.8 mmol) over 10 min at 0 °C. After the suspension was stirred for 2 h at room temperature, the white precipitate was filtered, washed

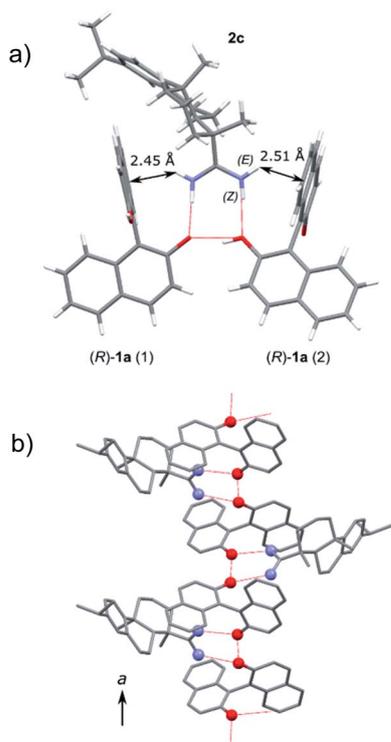


Fig. 2 Crystal structure of **2c**·(*R*)-**1a**. The oxygen and nitrogen atoms are represented using red and blue spheres. The dotted lines represent the hydrogen bonds. The arrows represent the NH/ π interactions.



several times with H₂O and then dried *in vacuo*. The desired product **4** (4.24 g, 18.8 mmol, 81%) was obtained as a white solid. Mp: 118.5–120.3 °C. $[\alpha]_{\text{D}}^{17} = +7.2^{\circ}$ (*c* 0.251, MeOH). ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.84–7.70 (m, 2H), 7.58–7.22 (m, 8H), 6.42–6.18 (br, 1H), 5.44–5.26 (m, 1H), 1.62 (d, *J* = 6.9 Hz, 3H). IR (KBr): ν (cm⁻¹) 3451, 3331, 1634, 1523, 1490, 1319, 758, 700.

(*S,S*)-*N,N'*-Bis(1-phenylethyl)benzamidine (**2a**)^{12b}

A solution of **4** (0.903 g, 4.01 mmol) and 2,6-lutidine (0.647 g, 6.04 mmol) in dry CH₂Cl₂ (10 mL) was cooled to 0 °C. Oxalyl chloride (0.543 g, 4.28 mmol) diluted with dry CH₂Cl₂ (5 mL) was slowly added to the solution over 30 min. Stirring was continued at 0 °C for 30 min, and the solution was allowed to warm to room temperature and stirred for 30 min. **3** (0.490 g, 4.04 mmol) diluted with dry CH₂Cl₂ (5 mL) was slowly added to the solution over 30 min at room temperature. The reaction mixture was refluxed for 24 h, and then concentrated under reduced pressure. The residue was dissolved in AcOEt (20 mL) and extracted with 1 N HCl aq. (10 mL × 15). The aqueous phase was basified with 6 N NaOH aq. and extracted with CHCl₃ (5 mL × 5). The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was suspended in hexane, and the resulting solid was collected by filtration. The crude product (0.530 g) was recrystallized from EtOH (0.8 mL) and the desired product **2a** (0.441 g, 1.34 mmol, 33%) was obtained as colorless crystals. Mp: 124.3–125.0 °C. $[\alpha]_{\text{D}}^{24} = -48.5^{\circ}$ (*c* 1.00, CHCl₃). ¹H NMR (300 MHz, DMSO-*d*₆): δ (ppm) 7.52–6.72 (m, 15H), 6.70–6.56 (m, 1H), 5.26–5.02 (m, 1H), 4.12–3.96 (m, 1H), 1.49 (d, *J* = 7.2 Hz, 3H), 1.17 (d, *J* = 6.3 Hz, 3H). IR (KBr): ν (cm⁻¹) 3060, 2955, 2877, 1637, 1599, 1494, 1484, 1451, 1361, 1349, 1309, 1268, 1142, 1090, 766, 699.

(*S*)-2-(6-Methoxy-2-naphthyl)propionamide (**6**)²³

Oxalyl chloride (3.0 mL) and DMF (3 drops) were added to (*S*)-2-(6-methoxy-2-naphthyl)propanoic acid (**5**) (2.32 g, 10.1 mmol) under a nitrogen atmosphere at 0 °C, and the resulting solution was refluxed for 2 h. After the excess of oxalyl chloride was distilled off, dry toluene (20 mL) and 28% NH₃ aq. (4 mL) were added at 0 °C. After the resulting suspension was stirred at room temperature for 1 h, the white precipitate formed was filtered, washed several times with H₂O and then dried *in vacuo*. The desired product **6** (2.21 g, 9.63 mmol, 96%, >99% ee) was obtained as a white solid, which was used for next step without further purification. Mp: 177.0–179.0 °C. $[\alpha]_{\text{D}}^{22} = +33.3^{\circ}$ (*c* 0.195, MeOH). ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.80–7.66 (m, 3H), 7.44–7.34 (m, 1H), 7.20–7.08 (m, 2H), 3.92 (s, 3H), 3.74 (q, *J* = 7.2 Hz, 1H), 1.61 (d, *J* = 7.2 Hz, 3H). IR (KBr): ν (cm⁻¹) 3348, 3195, 2983, 2898, 1660, 1606, 1505, 1486, 1461, 1403, 1309, 1267, 1228, 1217, 1173, 1114, 1027, 927, 894, 854, 814. HPLC analysis (Daicel Chiralcel OD-3, hexane/2-propanol = 80 : 20, 1.0 mL min⁻¹, 254 nm UV detector; *t*_r(*S*) = 10.3 min, *t*_r(*R*) = 16.4 min).

(*S*)-2-(6-Methoxy-2-naphthyl)propionitrile (**7**)²⁴

To a stirred solution of **6** (0.300 g, 1.31 mmol) in dry CH₂Cl₂ (15 mL), PPh₃ (0.420 g, 1.60 mmol), dry triethylamine (0.161 g, 1.59 mmol) and dry CCl₄ (0.246 g, 1.60 mmol) were added under a nitrogen atmosphere. The solution was refluxed for 20 h. After the reaction was quenched with H₂O, the organic layer was separated, washed with 1 N HCl aq., dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude product (0.875 g) was purified by silica gel column chromatography (eluent: CHCl₃). The desired product **7** (0.244 g, 1.15 mmol, 88%, >99% ee) was obtained as a pale yellow solid. Mp: 98.7–100.0 °C. $[\alpha]_{\text{D}}^{17} = -28.9^{\circ}$ (*c* 1.00, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.84–7.68 (m, 3H), 7.46–7.34 (m, 1H), 7.22–7.08 (m, 2H), 4.04 (q, *J* = 7.2 Hz, 1H), 3.93 (s, 3H), 1.72 (d, *J* = 7.2 Hz, 3H). IR (KBr): ν (cm⁻¹) 3065, 3020, 2992, 2963, 2942, 2905, 2840, 2240, 1916, 1777, 1712, 1632, 1604, 1506, 1483, 1448, 1419, 1393, 1376, 1356, 1260, 1214, 1188, 1165, 1085, 1024, 960, 927, 891, 856. HPLC analysis (Daicel Chiralpak AS-3, hexane/2-propanol = 99.5 : 0.5, 0.3 mL min⁻¹, 254 nm UV detector; *t*_r(*S*) = 34.6 min, *t*_r(*R*) = 41.2 min).

(*S*)-*N*-Hydroxy-2-(6-methoxy-2-naphthyl)propionamidine (**8**)

To a stirred solution of **7** (1.14 g, 5.40 mmol) in dry EtOH (3 mL) and dry DMF (3 mL), H₂NOH·HCl (1.13 g, 16.3 mmol) and dry triethylamine (1.65 g, 16.3 mmol) were added, and then the solution was refluxed under a nitrogen atmosphere for 10 h. After cooling to room temperature, the solution was concentrated under reduced pressure. The residue was dissolved in AcOEt (40 mL) and washed with H₂O/sat. NaCl aq. = 1/1. The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude product (0.893 g) was purified by silica gel column chromatography (eluent: CHCl₃/MeOH = 30/1, v/v). The desired product **8** (0.272 g, 1.11 mmol, 21%, 51% ee) was obtained as a white solid. Mp: 142.0–143.5 °C (21% ee). $[\alpha]_{\text{D}}^{18} = -10.5^{\circ}$ (*c* 0.506, MeOH) (21% ee). ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.80–7.64 (m, 3H), 7.46–7.36 (m, 1H), 7.20–7.04 (m, 2H), 4.50–4.26 (br, 2H), 3.92 (s, 3H), 3.76 (q, *J* = 7.2 Hz, 1H), 1.58 (d, *J* = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 157.7, 156.6, 136.9, 133.8, 129.2, 128.9, 127.5, 126.2, 125.6, 119.1, 105.7, 55.3, 41.8, 18.0. IR (KBr): ν (cm⁻¹) 3479, 3372, 3268, 3055, 2976, 2936, 1663, 1637, 1607, 1586, 1505, 1486, 1460, 1449, 1418, 1390, 1266, 1231, 1216, 1192, 1174, 1160, 1124, 1078, 1026, 921, 889, 849. HPLC analysis (Daicel Chiralcel OD-3, hexane/2-propanol = 80 : 20, 1.0 mL min⁻¹, 254 nm UV detector; *t*_r(*S*) = 10.5 min, *t*_r(*R*) = 13.1 min).

(*S*)-*N*-Acetoxy-2-(6-methoxy-2-naphthyl)propionamidine (**9**)

To a stirred solution of **8** (0.267 g, 1.10 mmol) in THF (5 mL), pyridine (0.111 g, 1.40 mmol) and acetic anhydride (0.135 g, 1.32 mmol) were added at 0 °C, and then the solution was stirred at room temperature for 1 h. After the solvent was distilled off, the residue was dissolved in CHCl₃ (50 mL), and washed with 1 N HCl aq., sat. NaHCO₃ aq. and sat. NaCl aq. The organic phase was dried over anhydrous Na₂SO₄, filtered and



concentrated under reduced pressure. The desired product **9** (0.301 g, 1.05 mmol, 96%, 51% ee) was obtained as a white solid, which was used for next step without further purification. Mp: 105.0–108.0 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.80–7.68 (m, 3H), 7.50–7.38 (m, 1H), 7.22–7.08 (m, 2H), 4.66–4.42 (br, 2H), 4.04–3.84 (m, 4H), 2.19 (s, 3H), 1.67 (d, *J* = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 168.8, 160.3, 157.9, 135.4, 133.9, 129.2, 128.9, 127.6, 126.2, 125.5, 119.3, 105.7, 55.4, 41.3, 19.9, 17.7. IR (KBr): ν (cm⁻¹) 3449, 3332, 3196, 3060, 2962, 2936, 2841, 1744, 1627, 1505, 1486, 1464, 1439, 1418, 1392, 1371, 1266, 1227, 1173, 1119, 1027, 1010, 957, 927, 885, 855, 814. HPLC analysis (Daicel Chiralcel OD-3, hexane/2-propanol = 80 : 20, 1.0 mL min⁻¹, 254 nm UV detector; *t_r*(*S*) = 13.8 min, *t_r*(*R*) = 30.7 min).

2-(6-Methoxy-2-naphthyl)propionamidine (**2b**)

A suspension of **9** (0.720 g, 2.51 mmol) and 10% Pd-C (0.173 g) in EtOH (30 mL) was stirred under a hydrogen atmosphere at room temperature for 2 h. The solid was filtered off and the filtrate was concentrated under reduced pressure. The residue (0.752 g) was recrystallized from MeOH (8.5 mL) to give the acetate salt of the product as a solid. The separated filtrate was concentrated under reduced pressure and the residue was recrystallized from EtOH/H₂O (4 mL/0.5 mL). The combined solid was dissolved in CHCl₃ (30 mL) and 1 N NaOH aq. (20 mL) was added. The aqueous layer was separated and extracted with CHCl₃ (15 mL × 5). The combined organic layer was washed with sat. NaCl aq., dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The desired product **2b** (0.597 g, 2.07 mmol, 83%, racemic) was obtained as a white solid. Mp: 125.0–129.0 °C. $[\alpha]_D^{25} = 0^\circ$ (*c* 1.00, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.80–7.62 (m, 3H), 7.40–7.30 (m, 1H), 7.22–7.04 (m, 2H), 3.92 (s, 3H), 3.73 (q, *J* = 7.2 Hz, 1H), 1.58 (d, *J* = 7.2 Hz, 3H). IR (KBr): ν (cm⁻¹) 3321, 3163, 2966, 1684, 1635, 1606, 1505, 1485, 1455, 1436, 1392, 1264, 1216, 1163, 1030, 927, 891, 853.

Dehydroabietyl amide (**11**)²⁵

To a stirred solution of dehydroabietic acid (**10**) (2.01 g, 6.09 mmol) in dry CH₂Cl₂ (3 mL), DMF (3 drops) and oxalyl chloride (1.5 mL) were added under a nitrogen atmosphere at 0 °C, and the solution was refluxed for 2 h. After the volatile components were distilled off, dry toluene (10 mL) and 28% NH₃ aq. (3 mL) were added at 0 °C. The resulting suspension was stirred at room temperature for 2 h, and then was added to AcOEt (100 mL) and H₂O (50 mL). The organic layer was separated and washed with sat. NaHCO₃ aq. and sat. NaCl aq. The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The desired product **11** (1.95 g, 6.50 mmol, 97%) was obtained as a pale yellow solid, which was used for next step without further purification. Mp: 153.0–156.0 °C. $[\alpha]_D^{25} = +41.1^\circ$ (*c* 1.00, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.22–7.12 (m, 1H), 7.04–6.96 (m, 1H), 6.90–6.82 (m, 1H), 5.90–5.60 (br, 1H), 5.50–5.20 (br, 1H), 2.96–2.85 (m, 2H), 2.85–2.73 (m, 1H), 2.39–2.25 (m, 1H), 2.16–2.04 (m, 1H), 1.90–1.40 (m, 7H), 1.29 (s, 3H), 1.26–1.14 (m, 9H). IR (KBr): ν

(cm⁻¹) 3428, 3328, 2927, 2867, 1629, 1575, 1498, 1456, 1383, 1362, 1085, 1036, 905, 883, 822.

Dehydroabietyl cyanide (**12**)²⁶

To a stirred solution of **11** (5.49 g, 18.3 mmol) in dry CH₂Cl₂ (100 mL), PPh₃ (7.20 g, 27.4 mmol), dry triethylamine (2.78 g, 27.4 mmol) and dry CCl₄ (4.23 g, 27.5 mmol) were added under a nitrogen atmosphere. The solution was refluxed for 17 h. After the reaction was quenched with H₂O, the organic layer was separated, washed with 1 N HCl aq., dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude product (14.8 g) was purified by silica gel column chromatography (eluent: hexane/CHCl₃ = 1/1, v/v). The desired product **12** (4.77 g, 16.9 mmol, 93%) was obtained as a white solid. Mp: 77.0–80.0 °C. $[\alpha]_D^{26} = +37.0^\circ$ (*c* 1.00, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.20–7.10 (m, 1H), 7.06–6.92 (m, 1H), 6.92–6.86 (m, 1H), 3.10–2.92 (m, 2H), 2.92–2.70 (m, 1H), 2.40–2.24 (m, 1H), 2.14–1.66 (m, 8H), 1.42 (s, 3H), 1.22 (d, *J* = 6.9 Hz, 6H), 1.18 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 146.2, 145.4, 134.2, 127.0, 126.6, 124.2, 124.0, 46.8, 37.5, 37.4, 37.3, 37.2, 33.5, 29.8, 25.2, 23.9, 21.7, 18.9, 17.7. IR (KBr): ν (cm⁻¹) 3010, 2930, 2930, 2863, 2225, 1612, 1496, 1458, 1419, 1383, 889, 819. MS (MALDI-TOF) *m/z* calcd for C₂₀H₂₇N + Na⁺: 304.204 [M + Na]⁺; found: 304.245.

N-Hydroxy-dehydroabietyl amidine (**13**)

To a stirred solution of **12** (4.76 g, 16.9 mmol) in dry EtOH (35 mL), H₂NOH·HCl (5.89 g, 84.8 mmol) and dry triethylamine (8.58 g, 84.8 mmol) were added, and then the solution was refluxed under a nitrogen atmosphere for 28 h. After cooling to room temperature, the solution was concentrated under reduced pressure. The residue was dissolved in AcOEt (100 mL) and washed with H₂O and sat. NaCl aq. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude product (5.76 g) was purified by silica gel column chromatography (eluent: hexane/AcOEt = 2/1, v/v). The desired product **13** (1.66 g, 5.29 mmol, 31%) was obtained as a white solid. Mp: 89.7–91.7 °C. $[\alpha]_D^{24} = +86.2^\circ$ (*c* 1.00, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.22–7.12 (m, 1H), 7.04–6.94 (m, 1H), 6.94–6.84 (m, 1H), 4.80–4.48 (br, 2H), 2.98–2.74 (m, 3H), 2.45–2.28 (m, 1H), 2.00–1.56 (m, 8H), 1.34–1.18 (m, 12H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 160.0, 147.2, 145.9, 134.8, 127.0, 124.0, 123.9, 46.3, 42.8, 38.3, 37.5, 37.4, 33.5, 30.0, 25.5, 24.0, 20.1, 18.7, 16.0. IR (KBr): ν (cm⁻¹) 3500, 3399, 3255, 2930, 1651, 1575, 1497, 1457, 1382, 1362, 1230, 1197, 1173, 1140, 1074, 923, 822. MS (MALDI-TOF) *m/z* calcd for C₂₀H₃₀N₂O + H⁺: 315.244 [M + H]⁺; found: 315.242.

N-Acetoxy-dehydroabietyl amidine (**14**)

To a stirred solution of **13** (1.64 g, 5.21 mmol) in THF (44 mL), pyridine (0.503 g, 6.36 mmol) and acetic anhydride (0.638 g, 6.25 mmol) were added at 0 °C, and then the solution was stirred at room temperature for 1 h. After the solvent was distilled off, the residue was dissolved in CHCl₃ (50 mL), and washed with 1 N HCl aq., sat. NaHCO₃ aq. and sat. NaCl aq. The organic layer was dried over anhydrous Na₂SO₄, filtered and



concentrated under reduced pressure. The desired product **14** (1.69 g, 4.73 mmol, 91%) was obtained as a white solid, which was used for next step without further purification. Mp: 125.8–127.8 °C. $[\alpha]_D^{24} = +66.6^\circ$ (c 1.00, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.24–7.12 (m, 1H), 7.06–6.98 (m, 1H), 6.92–6.86 (m, 1H), 4.86–4.64 (br, 2H), 2.98–2.74 (m, 3H), 2.44–2.28 (m, 1H), 2.20 (s, 3H), 1.98–1.62 (m, 8H), 1.31 (s, 3H), 1.26 (s, 3H), 1.22 (d, *J* = 6.9 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 169.7, 163.5, 147.0, 145.9, 134.6, 127.0, 124.0, 124.0, 46.4, 43.5, 38.1, 37.9, 37.4, 33.5, 30.0, 25.5, 24.0, 20.4, 20.2, 18.6, 16.0. IR (KBr): ν (cm⁻¹) 3501, 3378, 2957, 2869, 1743, 1626, 1582, 1497, 1459, 1384, 1364, 1231, 1008, 939, 882, 822. MS (MALDI-TOF) *m/z* calcd for C₂₂H₃₂N₂O₂ + Na⁺: 379.236 [M + Na]⁺; found: 379.217.

Dehydroabietyl amidine (**2c**)

A suspension of **14** (1.68 g, 4.72 mmol) and 10% Pd-C (0.614 g) in EtOH (60 mL) was stirred under a hydrogen atmosphere at room temperature for 1 day. Pd-C was filtered off and the filtrate was concentrated under reduced pressure. The residue was suspended in hexane, and the resulting solid was collected by filtration. The residue (1.44 g) was dissolved in CHCl₃ (30 mL) and sat. NaHCO₃ aq. (70 mL) was added. The aqueous layer was extracted with CHCl₃ (15 mL × 3). The combined organic layer was washed with sat. NaCl aq., dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The desired product **2c** (1.22 g, 4.09 mmol, 87%) was obtained as a white solid. Mp: 76.7–79.7 °C. $[\alpha]_D^{25} = +54.7^\circ$ (c 1.00, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.24–7.12 (m, 1H), 7.08–6.96 (m, 1H), 6.94–6.84 (m, 1H), 3.00–2.76 (m, 3H), 2.44–2.30 (m, 1H), 1.92–1.38 (m, 8H), 1.27, (s, 3H), 1.25 (s, 3H), 1.22 (d, *J* = 7.2, 6H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 174.8, 147.0, 146.0, 134.5, 127.0, 124.1, 124.0, 46.8, 45.6, 38.2, 38.1, 37.3, 33.5, 29.9, 25.3, 24.0, 20.5, 19.0, 16.8. IR (KBr): ν (cm⁻¹) 3345, 2958, 2869, 1634, 1577, 1497, 1459, 1382, 1363, 1201, 1171, 822. MS (MALDI-TOF) *m/z* calcd for C₂₀H₃₀N₂ + H⁺: 299.249 [M + H]⁺; found: 299.241.

(*Rac*)-6,6'-dibromo-1,1'-bi-2-naphthol (**1b**)²⁷

Rac-1,1'-bi-2-naphthol (**1a**) (1.00 g, 3.49 mmol) was dissolved in dry CH₂Cl₂ (40 mL) under a nitrogen atmosphere. After the mixture was cooled to -10 °C, bromine (1.51 g, 9.45 mmol) diluted with CH₂Cl₂ (4 mL) was added dropwise over 30 min and the solution was stirred for an additional 2.5 h. After the solution was gradually warmed to room temperature and stirred for another 1 h, the reaction was quenched with sat. Na₂SO₃ aq. (25 mL). The aqueous phase was extracted with CHCl₃ (15 mL × 3) and the combined organic phase was washed with sat. NaCl aq. dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The crude product (1.59 g) was recrystallized from toluene/heptane (7 mL/5 mL) and the desired product **1b** (1.11 g, 2.51 mmol, 72%) was obtained as colorless needles. Mp: 206.0–207.0 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 8.06 (d, *J* = 1.8 Hz, 2H), 7.90 (d, *J* = 9.0 Hz, 2H), 7.46–7.32 (m, 4H), 6.97 (d, *J* = 9.0 Hz, 2H), 5.00 (s, 2H). IR (KBr): ν (cm⁻¹) 3451, 2952, 1612, 1586, 1502, 1466, 1407, 1382, 1350, 1319, 1268, 1216, 1162, 1145, 1125, 1066, 951, 930, 876, 811.

(*Rac*)-6,6'-dimethyl-2,2'-bisphenol (**1c**)²⁸

To a solution of 4,6-di-*tert*-butyl-4-methylphenol (1.01 g, 4.60 mmol) in CH₂Cl₂ (9 mL), CuCl (45.5 mg, 0.460 mmol) and *N,N,N',N'*-tetramethylethylenediamine (80.1 mg, 0.689 mmol) were added. The suspension was stirred under air at room temperature for 8 h. After addition of H₂O (20 mL) to the reaction mixture, the whole was extracted with CHCl₃ (10 mL × 3). The organic phase was washed with sat. NaCl aq. and dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude product (1.19 g) was purified by silica gel column chromatography (eluent: hexane/CHCl₃ = 1/1, v/v) to afford (*rac*)-3,3',5,5'-tetra-*tert*-butyl-6,6'-dimethyl-2,2'-bisphenol (0.594 g, 1.35 mmol, 59%) as a white solid. Mp: 244.0–245.3 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.39 (s, 2H), 4.80 (s, 2H), 2.00 (s, 6H), 1.42 (s, 18H), 1.40 (s, 18H). IR (KBr): ν (cm⁻¹) 3504, 2991, 2959, 2909, 2871, 1560, 1470, 1414, 1395, 1362, 1332, 1280, 1254, 1233, 1196, 1167, 1116, 1033, 927.

To a solution of (*rac*)-3,3',5,5'-tetra-*tert*-butyl-6,6'-dimethyl-2,2'-bisphenol (0.303 g, 0.691 mmol) in dry toluene (5 mL) was added AlCl₃ (39.2 mg, 0.294 mmol) in small portions at 0 °C under a nitrogen atmosphere. The suspension was stirred at 50 °C for 18 h, and AlCl₃ (99.3 mg, 0.745 mmol) was added to the suspension at 0 °C. The suspension was stirred at 50 °C for 3 h, and AlCl₃ (58.8 mg, 0.441 mmol) was added to the suspension at 0 °C. The suspension was stirred at 50 °C for 3 h, and AlCl₃ (58.4 mg, 0.438 mmol) was added to the suspension at 0 °C. After the suspension was stirred at 50 °C for 13 h, the suspension was cooled to 0 °C and carefully quenched by addition of H₂O (14 mL) and 3 N HCl aq. (56 mL). The organic phase was separated and the aqueous phase was extracted with Et₂O (10 mL × 3). The combined organic phase was extracted with 3 N NaOH aq. (10 mL × 3). The aqueous phase was acidified with 6 N HCl aq. and extracted with Et₂O (10 mL × 3). The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The desired product **1c** (0.145 g, 0.677 mmol, 98%) was obtained as a white solid. Mp: 159.7–162.7 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.32–7.18 (m, 2H), 7.00–6.86 (m, 4H), 4.66 (s, 2H), 2.01 (s, 6H). IR (KBr): ν (cm⁻¹) 3464, 3413, 3034, 2973, 2915, 1605, 1575, 1465, 1378, 1335, 1281, 1261, 1180, 1090, 1025, 1006, 947, 883.

(*Rac*)-1-[hydroxy(phenyl)methyl]-2-naphthol (**1d**)²⁹

To a stirred suspension of Mg turnings (0.304 g, 12.5 mmol) in dry THF (4 mL) under a nitrogen atmosphere was added dropwise a solution of bromobenzene (1.96 g, 12.5 mmol) in dry THF (9 mL) over 1.5 h at room temperature. After formation of the Grignard reagent has started, the suspension was stirred at room temperature for 30 min, and then refluxed for 1 h. After cooling with an ice bath, 2-hydroxy-1-naphthaldehyde (0.861 g, 5.00 mmol), which was dissolved in dry THF (5.5 mL), was added dropwise to the mixture over 30 min and the suspension was stirred for 2 h at room temperature. The reaction was quenched with sat. NH₄Cl aq. (5 mL) and H₂O (15 mL) and the whole was extracted with CHCl₃ (10 mL × 3). The organic phase was washed with sat. NaCl aq., dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude



product was purified by silica gel column chromatography (eluent: hexane/AcOEt = 4/1, v/v). The desired product **1d** (1.23 g, 4.91 mmol, 98%) was obtained as a white solid. Mp: 118.5–120.3 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 9.21 (s, 1H), 7.82–7.62 (m, 3H), 7.50–7.12 (m, 8H), 6.82 (d, *J* = 2.6 Hz, 1H), 2.92 (d, *J* = 2.6 Hz, 1H). IR (KBr): ν (cm⁻¹) 3363, 3029, 1625, 1602, 1521, 1469, 1455, 1411, 1326, 1265, 1226, 1154, 1065, 1011, 939, 830.

Enantiomer separation of phenols (**1**) with chiral amidines (**2**)

Equimolar amounts of **2** and *rac*-**1** (0.250 mmol) were dissolved in MeOH or CHCl₃, and the solution was concentrated under reduced pressure to give a salt. An appropriate solvent was added to the salt with heating until a homogeneous solution was formed. The solution was gradually cooled to room temperature and left at the temperature for several days to induce crystallization. The salt **1**·**2** was collected by filtration and dried *in vacuo* at room temperature. The yield was calculated based on a half amount of *rac*-**1** initially used. A part of the salt was dissolved in ethyl acetate, and the organic phase was washed with 1 N HCl aq. to remove **2**. The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel preparative TLC to give **1**. The enantiomeric excess of **1** was determined by chiral HPLC analysis. **1a** (column: Chiralcel OD-3, eluent: 2-propanol/hexane = 1/9, flow rate: 0.5 mL min⁻¹, detection: 254 nm, *t_r*(S) = 29.0 min, *t_r*(R) = 30.7 min). **1b** (column: Chiralcel OD-3, eluent: 2-propanol/hexane = 1/9, flow rate: 1.0 mL min⁻¹, detection: 254 nm, *t_r*(1st) = 15.6 min, *t_r*(2nd) = 35.0 min). **1c** (column: Chiralcel OD-3, eluent: 2-propanol/hexane = 1/9, flow rate: 0.5 mL min⁻¹, detection: 254 nm, *t_r*(S) = 17.6 min, *t_r*(R) = 32.1 min).

X-ray crystallographic analysis

Single crystals suitable for X-ray diffraction analysis were prepared by slow evaporation of the saturated solutions of the salt. X-ray crystallographic data were collected on a Bruker Smart APEX II diffractometer with graphite monochromated Mo Kα radiation. Data collections were carried out at 150 K. The structures were solved by a direct method (SIR 2014) and refined by SHELXL-2013 or SHELXL-2018 programs.³⁰ Crystallographic information files have been deposited with the Cambridge Structural Database. Deposition number 2057487–2057489 contains the supplementary crystallographic data for this paper.†

Conflicts of interest

There are no conflicts to declare.

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