RSC Advances

PAPER

View Article Online
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Cite this: *RSC Adv.*, 2014, **4**, 25609

Direct enantioseparation of 1-(2-hydroxyphenyl) ethylamines *via* diastereomeric salt formation: chiral recognition mechanism based on the crystal structure†

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Received 15th January 2014
Accepted 30th May 2014

DOI: 10.1039/c4ra00414k

www.rsc.org/advances

In this study, the direct enantioseparation of unprotected 1-(2-hydroxyphenyl)ethylamines (**1a** and **1b**) *via* diastereomeric salt formation is reported. After the one-pot synthesis of racemic **1**, the screening of seven acidic chiral resolving agents showed that the extraction of (*S*)-naproxen (**6**) with dibenzoyl-L-tartaric acid (**5**) afforded the corresponding 1 : 1 diastereomeric salts that were suitable for the resolution of **1a** and **1b**. The optimization of the solvents resulted in high efficiencies for the resolution of **1a**·**6** in aqueous alcohols, which was consistent with the fact that the incorporated water molecules in the less-soluble diastereomeric salt reinforced its hydrogen-bonding network. For the efficient enantioseparation of *rac*-**1b** with **5**, the intramolecular CH···O hydrogen bond played an important role in the chiral recognition.

Introduction

Over the past two decades, various potent chiral catalysts have been developed for asymmetric synthesis to meet the increasing demand for enantiopure chiral compounds.[1] On the other hand, the enantioseparation of racemates into their enantiomers *via* classical diastereomeric salt formation is still a useful method to synthesize enantiopure compounds on an industrial scale.[2] In addition to the classical method, new methodologies such as Dutch resolution[3] and solvent-induced chirality switching[4] have been recently reported. In any case, the key to succeed in diastereomeric resolution is to find a suitable combination of chiral resolving agents that can afford a stable acid–base diastereomeric salt.

1-Phenylethylamine is one of the most useful chiral auxiliaries and basic resolving agents because both of its enantiomers are commercially available in a large quantity.[5] The derivatives of 1-phenylethylamine have been often selected for the systematic investigation of diastereomeric resolution because of its simple structure.[6] However, the enantioseparation of 1-phenylalkylamines with a hydroxy group at the *ortho* position has been rarely investigated even though they are potent chiral building blocks and chiral ligands. For example, 1-(2-hydroxyphenyl)ethylamine (**1a**) has been used for the synthesis of pharmaceutically important compounds.[7] Moreover, the enantiopure 1-(2-hydroxyphenyl)alkylamines with bulky substituents on their phenyl groups have been successfully applied as the chiral ligands for the asymmetric alkylation of aldehydes.[8] One possible problem associated with the diastereomeric resolution of 1-phenylalkylamines with a hydroxy group at the *ortho* position is the intramolecular hydrogen bond between the acidic hydroxy and the basic amino groups, resulting in the decreased basicity to prevent the diastereomeric salt formation with an acidic chiral resolving agent.[9]

Several methods have been reported to obtain *enantio*-enriched 1-(2-hydroxyphenyl)alkylamines. One successful example is the stereoselective synthesis of the enantiomers using 1-phenylethylamine or 1-phenyl-1,2-ethanediol as the chiral auxiliary.[10] Another example is the enantioseparation of its precursor, 1-(2-methoxyphenyl)alkylamine *via* diastereomeric salt formation with enantiopure mandelic acid.[11] However, the former method requires multi-step synthesis and the latter method involves the Lewis acid-mediated deprotection of the phenol group, where acid-labile substituents such as a *tert*-butyl group are not tolerable. Recently, acid-catalyzed enantioselective transfer hydrogenation of ketimines has been reported, even though it is not cost-effective for industrial application.[12] Therefore, we decided to develop a direct enantioseparation method for 1-(2-hydroxyphenyl)ethylamines **1a** and **1b** *via* diastereomeric salt formation. In addition, the chiral recognition mechanisms were elucidated from the X-ray crystallographic analysis of the less-soluble diastereomeric salts.

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† Electronic supplementary information (ESI) available: TGA chart of the salt (*S*)-**1a**·**6** (Fig. S1) and copies of ^{1}H NMR and ^{13}C NMR spectra of the compounds. CCDC 970253–970256. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ra00414k

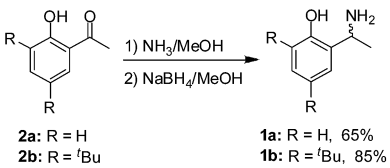
Results and discussion

Synthesis of racemic 1-(2-hydroxyphenyl)ethylamines (*rac*-1a and *rac*-1b) and their diastereomeric resolution

The synthesis of *rac*-**1a** has already been reported, however, it depended on multi-step synthesis or a detailed procedure was missing and that of *rac*-**1b** has not been reported.[13] Therefore we opted for a one-pot synthetic route by the reductive amination of the corresponding ketones (Scheme 1). To synthesize *rac*-**1a**, commercially available 2-acetylphenol (**2a**) was derivatized to the corresponding imine using methanolic ammonia solution, followed by the reduction using sodium borohydride. The reaction proceeded smoothly and afforded *rac*-**1a** in a moderate yield. The same procedure was applied to 6-acetyl-2,4-di-*tert*-butylphenol (**2b**), prepared according to the literature method,[14] to afford *rac*-**1b** in a better yield. The structure of *rac*-**1b** was further confirmed by the X-ray crystallographic analysis (Fig. 1). Both the enantiomers were crystallized together and an intramolecular hydrogen bond was observed between the hydroxy hydrogen and the nitrogen atoms, where the N···O distance was 2.61 Å and the O–H···N angle was 149°.

Though the basicity of these amines was expected to decrease because of the abovementioned intramolecular hydrogen bond, seven different acidic chiral resolving agents (**3**–**9**), as shown in Fig. 2, were screened for the diastereomeric resolution of **1a** and **1b**. The mixtures of equimolar amounts of **1** and each resolving agent were recrystallized once from ethanol or aqueous ethanol. The precipitated diastereomeric salts were partially liberated to determine the enantiopurity of **1**, and the results are shown in Table 1.

For *rac*-**1a**, most of the chiral resolving agents afforded a trace amount or no crystalline material; however, (*S*)-naproxen (**6**) and dehydroabietic acid (**9**) afforded the corresponding crystalline diastereomeric salts from a 50% aqueous ethanol solution (Table 1, entries 4 and 7). The ^{1}H NMR spectra showed that both the crystals were 1 : 1 diastereomeric salts of **1a** and the resolving agent. In addition, **1a** liberated from the precipitated salt with **6** afforded (*S*)-**1a** with a resolution efficiency as high as 0.55, whereas the diastereomeric salt with **9** resulted in only *rac*-**1a**. It appears that the chiral resolving agents with a large hydrophobic structure are suitable to afford the crystalline salts with **1a** probably due to its low molecular weight. When the same screening experiment was applied to *rac*-**1b**, two other chiral resolving agents afforded precipitates by the recrystallization from ethanol or 60% aqueous ethanol solution (Table 1, entries 10 and 12). The diastereomeric salt with dibenzoyl-L-tartaric acid (**5**) afforded *enantio*-enriched (*R*)-**1b** in a low efficiency. On the other hand, the diastereomeric salt with L-pyroglutamic acid (**7**) showed a higher resolution efficiency. Notably, *enantio*-enriched (*S*)-**1b** was obtained from the less-soluble diastereomeric salts with **7**, which was opposite to the case when **5** was used. Because only one enantiomer of **5** and **7** is available from the natural chiral source, it is advantageous that both the enantiomers of **1b** are accessible by changing the resolving agent. The ^{1}H NMR measurements showed that the molar ratio of **1b** and **5** in the precipitated diastereomeric salt was 1 : 1, where **5** is a divalent carboxylic acid.



Scheme 1 Synthesis of racemic 1-(2-hydroxyphenyl)ethylamines **1a** and **1b**.

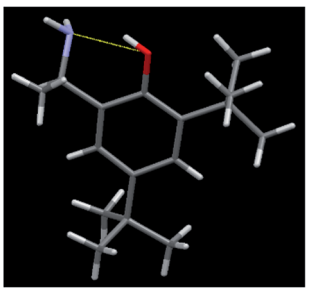


Fig. 1 Crystal structure of *rac*-**1b**. The dotted line shows a hydrogen bond between an amino nitrogen atom and a hydroxy hydrogen atom.

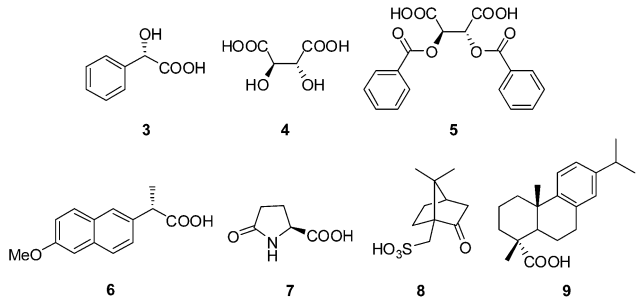


Fig. 2 Acidic chiral resolving agents used in this study.

With the potential chiral resolving agents in hand, the optimization of the crystallization solvents (MeOH, EtOH, 1-PrOH, 2-PrOH, CH_3CN, and their mixtures with H_2O) for **1a**·**6**, **1b**·**5**, and **1b**·**7** was carried out and the results are summarized in Table 2. When the recrystallization of **1a**·**6** was carried out from pure alcohols, the resolution efficiencies decreased (Table 2, entries 2–4) whereas the low solubility of **1a**·**6** prevented its recrystallization from water (Table 2, entry 1). On the other hand, the recrystallization from aqueous alcohol solutions afforded (*S*)-**1a** with better selectivities and high efficiency (Table 2, entries 5–8). The result showed that the water in the recrystallizing solvent mixture plays an important role in the efficient resolution, while additional alcohol is necessary to increase the solubility of the salt. The thermogravimetric analysis (TGA) of the diastereomeric salt (*S*)-**1a**·**6** prepared from a 50% aqueous EtOH solution showed a gradual weight loss from ~100 °C to 150 °C before melting (Fig. S1†). It shows that the salt was hydrated even though the amount of incorporated water was difficult to be determined because of the successive decomposition of the salt. On the other hand, the resolution of *rac*-**1b** using **5** or **7** from aqueous alcohols resulted in only low

Table 1 Enantioseparation of racemic 1-(2-hydroxyphenyl)ethylamines **1a** and **1b** with acidic chiral resolving agents

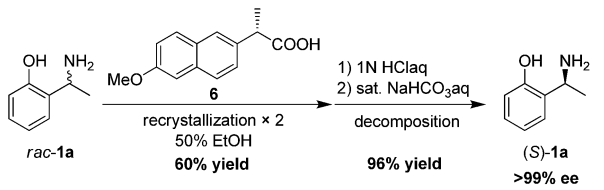
1a						**1b**					
Entry	Resolving agent	Solvent (L mol^{-1})	Yield[a] (%)	ee[b] (%)	Eff.[c]	Entry	Resolving agent	Solvent (L mol^{-1})	Yield[a] (%)	ee[b] (%)	Eff.[c]
1	**3**	50% EtOH (1.0)	Trace	—	—	8	**3**	EtOH (3.3)	Not crystallized		—
2	**4**	50% EtOH (0.8)	Not crystallized		—	9	**4**	EtOH (3.3)	Trace	—	—
3	**5**	50% EtOH (1.0)	Not crystallized		—	10	**5**	60% EtOH (8.3)	52	17(*R*)	0.09
4	**6**	50% EtOH (12.0)	97	57(*S*)	0.55	11	**6**	EtOH (7.0)	Not crystallized		—
5	**7**	50% EtOH (2.0)	Not crystallized		—	12	**7**	EtOH (8.0)	83	30(*S*)	0.25
6	**8**	—	Not crystallized		—	13	**8**	EtOH (3.3)	Not crystallized		—
7	**9**	50% EtOH (28.0)	82	*rac*	0	14	**9**	EtOH (3.3)	Not crystallized		—

[a] Yield is based on the half amount of the salt. [b] ee is determined by HPLC analysis. [c] Eff. = yield × ee.

Table 2 Enantioseparation of 1-(2-hydroxyphenyl)ethylamines **1a** and **1b** recrystallized from various solvents

Entry	**1**	Resolving agent	Solvent (L mol^{-1})	Yield[a] (%)	ee[b] (%)	Eff.[c]
1	**1a**	**6**	H_2O (60.0)	Not dissolved		—
2	**1a**	**6**	EtOH (5.0)	88	7(*R*)	0.06
3	**1a**	**6**	1-PrOH (8.0)	94	34(*S*)	0.32
4	**1a**	**6**	2-PrOH (8.0)	124	10(*S*)	0.13
5	**1a**	**6**	50% MeOH (30.0)	62	84(*S*)	0.51
6	**1a**	**6**	50% EtOH (12.0)	97	57(*S*)	0.55
7	**1a**	**6**	50% 1-PrOH (6.0)	59	65(*S*)	0.38
8	**1a**	**6**	50% 2-PrOH (6.0)	72	49(*S*)	0.35
9	**1b**	**5**	EtOH (2.7)	Not crystallized		—
10	**1b**	**5**	60% MeOH (17)	20	42(*R*)	0.08
11	**1b**	**5**	60% EtOH (8.3)	52	17(*R*)	0.09
12	**1b**	**5**	CH_3CN (18)	33	88(*R*)	0.29
13	**1b**	**7**	EtOH (8.0)	83	30(*S*)	0.25
14	**1b**	**7**	50% EtOH (3.3)	26	2(*S*)	0.01
15	**1b**	**7**	90% CH_3CN (13.3)	83	35(*S*)	0.29

[a] Yield is based on the half amount of the salt. [b] ee is determined by HPLC analysis. [c] Eff. = yield × ee.



Scheme 2 Preparation of an enantiopure (*S*)-**1a**.

efficiency (Table 2, entries 10, 11, and 14). The recrystallization of the diastereomeric salts from CH_3CN or 90% CH_3CN resulted in moderate efficiencies and the enantiomeric excess (ee) of (*R*)-**1b** resolved using **5** reached up to 88% ee, whereas **1b**·**7** afforded the antipode (*S*)-**1b** in only 35% ee (Table 2, entries 12 and 15).[15] The introduction of bulky *tert*-butyl groups on the aromatic ring of **1a** drastically changed the matched combination with chiral resolving agents to afford the corresponding crystalline diastereomeric salts and more functionalized acids have been favored for **1b**.

With the optimized condition in hand, we applied it to a resolution of *rac*-**1a** to prepare an enantiopure **1a** (Scheme 2). The diastereomeric salt of *rac*-**1a** (0.99 g) and **6** (1.68 g) was recrystallized from a 50% aqueous EtOH solution to afford (*S*)-**1a**·**6** (1.09 g, 79% yield, 91% ee). The resolution efficiency was improved up to 0.72 probably because of the decreased operational loss. Another recrystallization of the diastereomeric salts from the same solvent successfully afforded the salts (0.83 g, 60% yield, >99% ee) in a diastereomerically pure form. The overall efficiency was as high as 0.60, and it was shown that this resolution method is potentially applicable to a larger-scale production of an enantiopure **1a**.

Crystallographic analyses of the less-soluble diastereomeric salts 1a·6, 1b·7, and 1b·5

To elucidate the chiral recognition mechanism of **1a** and **1b**, X-ray crystallographic analyses of the three less-soluble salts **1a**·**6**, **1b**·**7**, and **1b**·**5** were carried out. The structure of (*S*)-**1a**·**6** is shown in Fig. 3, where the absolute configuration of **1a** was determined to be (*S*)-isomer by the comparison with that of **6**. As suggested from the TGA result, the diastereomeric salt was hydrated and the composition ratio was (*S*)-**1a** : **6** : H_2O = 2 : 2 : 1. They constructed a one-dimensional (1D) columnar hydrogen-bonding network along the *b* axis, which is an often observed motif in primary ammonium-carboxylate salts.[16] The water molecules were positioned at the center of the columnar structure to connect (*S*)-**1a** and **6** along the columnar axis by the hydrogen bonds (Fig. 3a). The participation of water to reinforce the 1D network stabilized (*S*)-**1a**·**6** salt, resulting in the high resolution efficiency in aqueous alcohols as stated above. One of the ammonium hydrogen atoms of (*S*)-**1a** formed a bifurcated hydrogen bond and shared by the intramolecular hydroxy oxygen atom (the N···O distance was 2.72 Å) to fix the aromatic group of (*S*)-**1a**. The high enantioselectivity can be explained by the favorable CH···π interaction between the CH of the methyl group of (*S*)-**1a** and the naphthalene ring of **6** (the C···π-plane distance was 3.48 Å, as indicated by the arrows in Fig. 3b), which fixed the position of the methyl group of (*S*)-**1a**.[17] Notably, the salt of **1a** and (*R*)-2-phenylpropionic acid did not crystallize under the same conditions, indicating that not only the

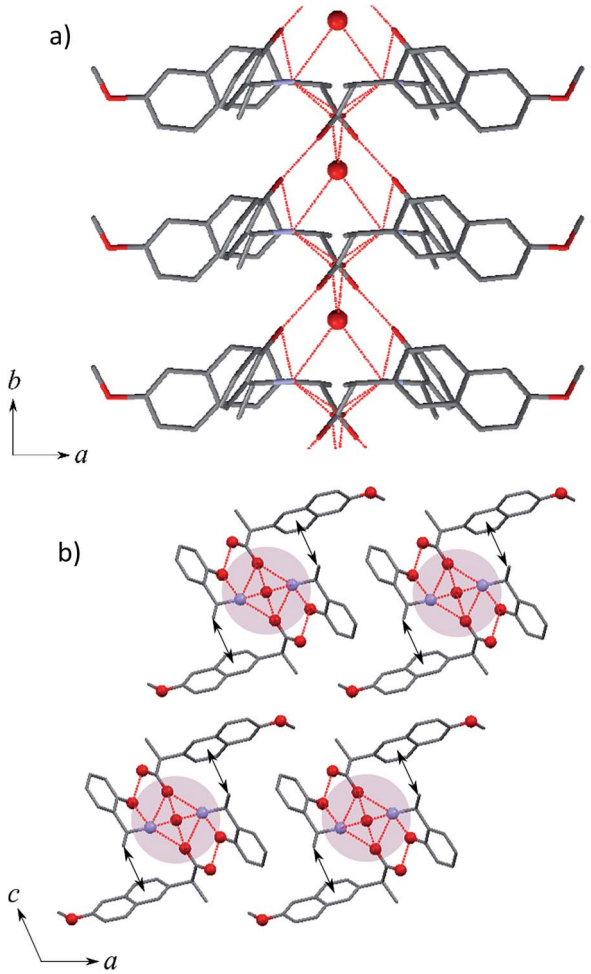


Fig. 3 Crystal structure of (*S*)-**1a**·**6**·0.5H_2O. (a) Side view of the columnar structure. Water oxygen atoms are represented with red balls. (b) Top view of the columnar structures. Hydrogen atoms are omitted for clarity. The dotted lines and arrows show hydrogen bonds and CH···π interactions, respectively.

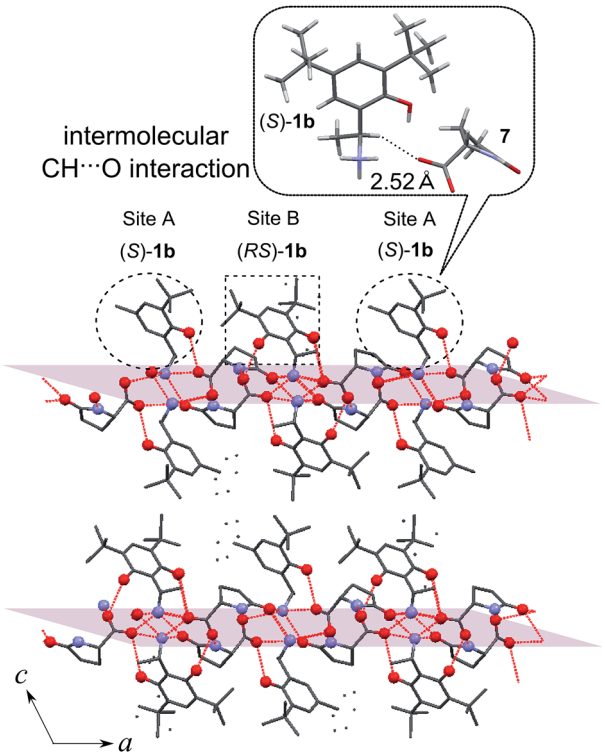


Fig. 4 Crystal structure of **1b**·**7** viewed from the *b* axis. The dotted lines show hydrogen bonds. Two hydroxy oxygen atoms of (*RS*)-**1b** are shown at site B due to rotational disorder of the phenyl group.

structure of 2-arylpropionic acid, but also the rigid and long naphthyl group of **6** contribute to the efficient packing of the molecules.

Platelet fine crystals were obtained during the resolution of *rac*-**1b** with **7**, and the crystal structure was determined. As in the case of (*S*)-**1a**·**6** salt, 1D columnar hydrogen-bonding networks were constructed from **1b** and **7** along the *b* axis, whereas no solvent molecules were incorporated. Interestingly, additional hydrogen bonds of the amide group of **7** connected the neighboring columns to form two-dimensional (2D) sheet-like networks (Fig. 4). The efficient van der Waals packing of the resultant sheets contributed to the high stability of the diastereomeric salt. In contrast to (*S*)-**1a**·**6**, the hydroxy group of **1b** interacted only with the carboxylate oxygen atom of **7** instead of involving in the intramolecular hydrogen bond. Two crystallographically independent molecules of **1b** with slightly different orientations were observed in the asymmetric unit, positioned at sites A and B, respectively. The stereoselective salt formation occurred at site A, and only (*S*)-**1b** was positioned. On the other hand, two enantiomers of **1b** existed in a disordered manner at site B, and they were not distinguished. The low enantioselectivity for (*S*)-**1b** in the resolution experiment with **7** probably reflected the sum of the selectivity at these two sites. The stereoselective incorporation of (*S*)-**1b** at site A could be attributed to the fixation of the hydrogen atom on the stereogenic center of (*S*)-**1b** as well as the ammonium and phenyl groups. The carboxylate oxygen atom of **7** that forms hydrogen bonds with the ammonium nitrogen and hydroxy oxygen atoms of (*S*)-**1b** is also close to the hydrogen atom of (*S*)-**1b**. The CH···O distance was as short as 2.52 Å, which is shorter than the sum of the van der Waals radii of hydrogen and oxygen atoms [2.80 Å = 1.20 Å (hydrogen) + 1.60 Å (oxygen)].[18] This intermolecular CH···O type hydrogen bond appears to be important for the chiral recognition of (*S*)-**1b**.

Finally, a single crystal of **1b**·**5** was prepared from a CH_3CN solution of the equimolar mixture of *rac*-**1b** and **5**, which afforded high enantioselectivity for (*R*)-**1b** (Table 2, entry 12). The crystal consisted of **5** and (*R*)-**1b** in a ratio of 1 : 1, which was in accordance with the ^{1}H NMR result of the precipitated salt (Fig. 5). The molecules arranged to construct a 1D hydrogen-bonding network along the *b* axis, which was reinforced by the intermolecular hydrogen bond between the ionized and neutral carboxyl groups of **5**. Such a motif has been also reported in other salts of substituted 1-phenylethylamines and **5**.[19] Furthermore, the hydroxy hydrogen atom of (*R*)-**1b** interacted with the ester carbonyl group of **5**. The high enantioselectivity for (*R*)-**1b** could be explained by the intramolecular CH···O type

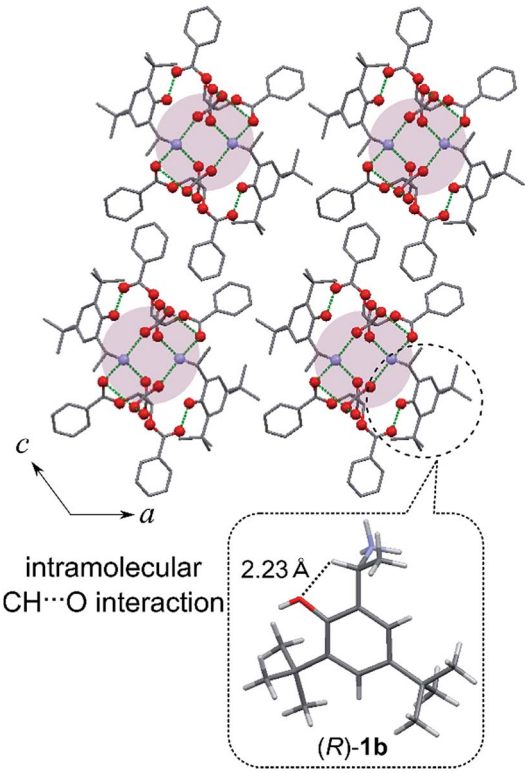


Fig. 5 Crystal structure of (*R*)-**1b**·**5** viewed from the *b* axis. The dotted lines show hydrogen bonds.

interaction; the hydrogen atom on the stereogenic center of (*R*)-**1b** was directed toward the hydroxy group within the molecule. The CH···O distance was 2.23 Å, which is much shorter than their sum of the van der Waals radii. This result indicates that the phenol moiety plays a crucial role in the fixation of not only the aromatic group on the stereogenic center, but also the hydrogen atom on the stereogenic center, resulting in the efficient chiral recognition.

Conclusions

In this study, we have carried out the direct enantioseparation of unprotected 1-(2-hydroxyphenyl)ethylamines **1a** and **1b** *via* diastereomeric salt formation. *Rac*-**1a** could be efficiently resolved with (*S*)-naproxen (**6**) by the recrystallization from an aqueous alcohol solution, whereas bulkier *rac*-**1b** was separated with more functionalized chiral resolving agent, L-pyroglutamic acid (**7**) or dibenzoyl-L-tartaric acid (**5**). The X-ray crystallographic analysis of the less-soluble diastereomeric salt showed that the incorporated water molecule reinforced the 1D hydrogen-bonding network of the crystal of (*S*)-**1a**·**6** salt. The high enantioselectivity was attributed to the CH···π interaction between (*S*)-**1a** and the large π-plane of **6**. Although the enantioselectivity of (*S*)-**1b** obtained by the resolution with **7** was not so high because of the partially disordered structure of **1b**, the intermolecular CH···O interaction between the hydrogen atom of **1b** and the carboxylate group of **7** was responsible for the chiral recognition. On the other hand, the intramolecular CH···O interaction as well as the hydrogen bond between the ester group of **5** involving the hydroxy group of (*R*)-**1b** contributed to the efficient chiral recognition for (*R*)-**1b**·**5**. Although their chiral recognition mechanisms were found to be not consistent and dependent on their molecular structures, the hydroxy group played an important role for efficient chiral recognition in each less-soluble diastereomeric salt. These insights may help to find the suitable conditions in the enantioseparation and enable to easily synthesize various enantiopure 1-(2-hydroxyphenyl)alkylamines, which can be applied for chiral building blocks and ligands. Further investigation for the strategic enantioseparation of other chiral 1-(2-hydroxyphenyl) alkylamines are now in progress.

Experimental

Materials and general methods

All commercially available reagents (**1a**, **3–9**) were used as received. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AVANCE 300 or 500 spectrometer. IR spectra were measured on a JASCO FT/IR-460 spectrometer by the KBr method at room temperature. 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} under a nitrogen atmosphere. Enantiomeric excesses were determined by HPLC analyses with a Daicel OD-3 or OJ-3 column with detection at 254 nm.

Synthesis and characterization

***rac*-1-(2-Hydroxyphenyl)ethylamine (*rac*-1a). 2a** (3.01 g, 22.1 mmol) was dissolved in an ice-cooled NH_3/MeOH solution (180 mL) and the solution was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was dissolved in MeOH (180 mL). $NaBH_4$ (4.16 g, 0.11 mol) was added portionwise to the mixture at 0 °C and stirred at room temperature overnight. After the reaction mixture was acidified by addition of 1 N HCl aq., MeOH was removed under reduced pressure. The aqueous phase was washed with $CHCl_3$ (40 mL × 6) and basified by addition of $NaHCO_3$ until the pH became 8–9. The resulting mixture was extracted with EtOAc (40 mL × 6) 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 ($CHCl_3$ to $CHCl_3$–EtOAc = 1 : 1). Further recrystallization from hexane–EtOAc = 500 : 1 (18 mL) gave *rac*-**1a** (1.97 g, 14.4 mmol, 65%) as a white solid. Mp: 85–88 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17–7.12 (m, 1H), 6.98–6.95 (m, 1H), 6.85–6.75 (m, 2H), 4.33 (q, J = 6.6 Hz, 1H), 1.48 (d, J = 6.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.6, 128.5, 128.1, 127.2, 119.0, 117.2, 51.7, 23.9. IR (KBr): ν_{max} 3344, 2979, 2488, 1594, 1455, 1353, 1291, 1039, 894, 746, 606, 563, 523 cm^{-1}.

***rac*-1-(2-Hydroxy-3,5-di-*tert*-butylphenyl)ethylamine (*rac*-1b). 2b** (5.57 g, 22.4 mmol) was dissolved in an ice-cooled NH_3/MeOH solution (150 mL) and the gaseous NH_3 was introduced to the solution for 2.5 h. After the solution was stirred at room temperature for 4 days, the solvent was removed under reduced

pressure and the residue was dissolved in MeOH (150 mL). $NaBH_4$ (4.24 g, 112 mmol) was added portionwise to the solution at 0 °C and stirred at room temperature for 5 days. After the reaction mixture was acidified by addition of HCl aq., MeOH was removed under reduced pressure and the aqueous phase was extracted with $CHCl_3$. The organic phase was washed with sat. $NaHCO_3$ aq. and 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 hexane afforded *rac*-**1b** (4.74 g, 19.0 mmol, 85%) as a colorless needle crystal. Mp: 104–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22–7.21 (m, 1H), 6.85–6.84 (m, 1H), 4.31 (q, J = 6.6 Hz, 1H), 1.49 (d, J = 6.6 Hz, 3H), 1.43 (s, 9H), 1.29 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.2, 140.2, 136.5, 127.2, 122.7, 122.0, 52.5, 35.0, 34.2, 31.7, 29.7, 23.7. IR (KBr): ν_{max} 3371, 3300, 2954, 2871, 1601, 1587, 1479, 1440, 1361, 1252, 1232, 1053, 880, 820 cm^{-1}.

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

An equimolar amounts of **1** and each resolving agent (0.5 mmol for **1a** and 0.3 mmol for **1b**) were dissolved in methanol. After concentration, the diastereomeric salts were recrystallized from an appropriate solvent and 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. (*S*)-**1a**·**6**. ^{1}H NMR (300 MHz, $CDCl_3$–CD_3OD): δ 7.72–7.69 (m, 3H), 7.46–7.43 (m, 1H), 7.17–7.11 (m, 3H), 7.02–6.99 (m, 1H), 6.83–6.77 (m, 2H), 4.32 (q, J = 6.9 Hz, 1H), 3.92 (s, 3H), 3.82 (q, J = 7.2 Hz, 1H), 1.56 (d, J = 7.2 Hz, 3H), 1.49 (d, J = 6.9 Hz, 3H). **1b**·**5**. ^{1}H NMR (300 MHz, $CDCl_3$–CD_3OD): δ 8.13 (d, J = 8.1 Hz, 4H), 7.61–7.56 (m, 2H), 7.48–7.43 (m, 4H), 7.26 (s, 1H), 6.99 (s. 1H), 5.96 (s, 2H), 4.53–4.47 (m, 1H), 1.52 (d, J = 6.3 Hz, 3H), 1.39 (s, 9H), 1.28 (s, 9H). **1b**·**7**. ^{1}H NMR (300 MHz, $CDCl_3$–CD_3OD): δ 7.28 (d, J = 2.4 Hz, 1H), 7.05 (d, J = 2.4 Hz, 1H), 4.56 (q, J = 6.9 Hz, 1H), 4.18–4.13 (m, 1H), 2.54–2.30 (m, 3H), 2.22–2.11 (m, 1H), 1.74 (d, J = 6.9 Hz, 3H), 1.43 (s, 9H), 1.30 (s, 9H).

To determine the enantiomeric excess of resolved **1a**, a small amount of the salt was added in 1 N HCl aq. and washed with $CHCl_3$, and the solution was basified by addition of $NaHCO_3$. The aqueous phase was extracted with EtOAc and dried over anhydrous Na_2SO_4. After removal of the solvent, **1a** was obtained as a solid. Resolved **1a** was quantitatively derivatized to its acetamide in the presence of acetic anhydride, of which the enantiomeric excess was determined by a HPLC analysis (Daicel ChiralPak OD-3, hexane–2-propanol = 9 : 1, 1.0 mL min^{-1}, $t_r(R)$ = 13.4 min; $t_r(S)$ = 15.3 min).

The salt of **1b** was added in 1 N NaOH aq. and extracted with EtOAc due to the low solubility of **1b** in an aqueous phase. The extract was washed with sat. $NaHCO_3$ aq., water and dried over anhydrous Na_2SO_4. After removal of the solvent, **1b** was obtained as a solid. The enantiomeric excess of resolved **1b** was determined by a HPLC analysis (Daicel ChiralPak OJ-3, hexane–2-propanol = 97 : 3, 0.5 mL min^{-1}, $t_r(S)$ = 11.8 min; $t_r(R)$ = 15.7 min). The absolute configurations were determined by comparison with the products prepared according to the literature.[10b]

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 97 (ref. 20) and refined by SHELXL-97 or SHELXL-2013 programs.[21] Crystal data for *rac*-**1b**: $C_{16}H_{27}NO$, M = 249.39, monoclinic, a = 15.4268(18), b = 9.5663(11), c = 11.1965(13) Å, β = 105.9770(10)°, V = 1588.5(3) Å^3, T = 150 K, space group $P2_1/c$, Z = 4, 2789 reflections measured, 2366 independent reflections (R_{int} = 0.1447). The final R_1 was 0.0755 ($I > 2\sigma(I)$) and w$R(F_2)$ was 0.2066 ($I > 2\sigma(I)$). Crystal data for (*S*)-**1a**·**6**·0.5H_2O: $C_{22}H_{26}NO_{4.5}$, M = 376.44, monoclinic, a = 23.818(8), b = 5.5862(18), c = 15.671(5) Å, β = 113.803(4)°, V = 1907.8(11) Å^3, T = 150 K, space group $C2$, Z = 4, 2980 reflections measured, 2690 independent reflections (R_{int} = 0.0979). The final R_1 was 0.0590 ($I > 2\sigma(I)$) and w$R(F_2)$ was 0.1577 ($I > 2\sigma(I)$). Crystal data for **1b**·**7**: $C_{21}H_{34}N_2O_4$, M = 378.50, monoclinic, a = 16.749(4), b = 8.124(2), c = 17.552(4) Å, β = 116.504(3)°, V = 2137.2(9) Å^3, T = 150 K, space group $P2_1$, Z = 4, 5394 reflections measured, 4024 independent reflections (R_{int} = 0.1078). The final R_1 was 0.0814 ($I > 2\sigma(I)$) and w$R(F_2)$ was 0.2084 ($I > 2\sigma(I)$). Crystal data for (*R*)-**1b**·**5**: $C_{34}H_{41}NO_9$, M = 607.68, monoclinic, a = 29.287(5), b = 7.6383(12), c = 18.538(4) Å, β = 126.490(4)°, V = 3333.9(10) Å^3, T = 150 K, space group $C2$, Z = 4, 5298 reflections measured, 4235 independent reflections (R_{int} = 0.1093). The final R_1 was 0.0495 ($I > 2\sigma(I)$) and w$R(F_2)$ was 0.1021 ($I > 2\sigma(I)$).†

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