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Resolution of α-methylbenzylamine via diastereomeric salt formation using the naturally based reagent *N*-tosyl-(*S*)-phenylalanine together with a solvent switch technique

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ABSTRACT

The resolution of (*RS*)-α-methylbenzylamine **1** with the naturally based reagent *N*-tosyl-(*S*)-phenylalanine **2** via the diastereomeric salt formation method together with the solvent switch technique has been investigated. In various alcoholic solvents with a wide ε range, the less-soluble salt was (*S*)-**1**·(*S*)-**2**, while (*R*)-**1**·(*S*)-**2** was obtained when dioxane was used as a resolving solvent system. The highest enantiomeric purities of (*S*)-**1** and (*R*)-**1** were obtained from 2-PrOH and dioxane/MeOH, respectively. The X-ray single-crystal analysis showed that both (*S*)-**1**·(*S*)-**2** and (*R*)-**1**·(*S*)-**2** crystals form a hydrogen-bonding network; however, (*R*)-**1**·(*S*)-**2** contains dioxane molecules without incorporation in the hydrogen-bonding network. The drastic effect of dioxane on the present system is interpreted as space filling.

1. Introduction

The reliable preparation of enantiomerically pure compounds is important in areas such as the pharmaceutical and food industries. Among the various new and attractive techniques now available for preparing enantiopure compounds, resolution via diastereomeric salt formation is still a useful technique on an industrial scale because it is generally simple and clean, and laboratory-level data can be easily reproduced on a larger scale.[1] The commercialization of chiral drugs in single-enantiomer dosage forms has grown dramatically in recent years. It has been estimated that more than half of the chiral drugs on the pharmaceutical market are produced by the diastereomeric salt formation method using enantiomerically pure resolving agents.[2]

The general importance of chiral amines is well recognized, and α-methylbenzylamine **1** (Fig. 1) is well known as a simple, yet powerful chiral adjuvant.[3] Enantiomerically pure **1** and its derivatives have important applications as effective chiral adjuvants in the resolution of racemates, and as ligands in asymmetric (or disymmetric) catalysts.[4] Currently, **1** is being used as a chiral auxiliary and as a chiral base.

It is notable that several stereoselective synthesis methods for **1** have already been reported.[5,6] Catalytic synthesis is one of these methods and is potentially a course of action for obtaining enantiopure **1**. However, disadvantages such as the high cost and the multiple steps required by these methods must be considered.

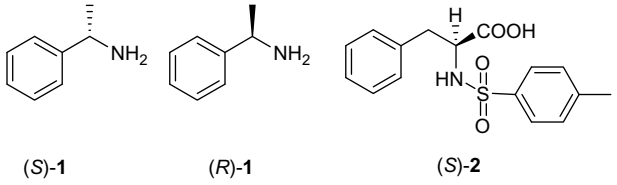

Figure 1. Chemical structures of α-methylbenzylamine and *N*-tosyl-(*S*)-phenylalanine.

Direct resolution via diastereomeric salt formation is the most convenient method for producing a pure enantiomer, although tedious separation processes of the corresponding salts are sometimes required. Tartaric acid,[7] (*S*)-carbamalactic acid,[8] and mandelic acid[9] seem to be efficient for the resolution of racemic **1**. However, the resolution of two enantiomers using a single resolving agent has not been reported thus far.

Recent papers by Sakai et al. show that the solvent dependence of the diastereomeric salt formation method allows the efficient resolution of two enantiomers using a single resolving agent.[10–12] They called this technique 'dielectrically controlled resolution' or the 'solvent switch method', and demonstrated its relationship with the dielectric constant.[10–12] It is industrially economical and effective to use natural resolving agents, which are usually available as a single enantiomer.[13] Further it is academically interesting

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to elucidate the solvent effects on enantioselectivity. Herein, we report a novel and drastic solvent dependence for the resolution of (*R*)- and (*S*)-**1** using naturally based *N*-tosyl-(*S*)-phenylalanine **2** (Fig. 1).

2. Results and discussion

2.1. Solvent dependence

To resolve **1**, the naturally based recrystallizable resolving agent (*S*)-**2** was selected in place of a number of other commercially available acidic resolving agents such as tartaric acid, (*S*)-carbamalactic acid, mandelic acid, or some of their derivatives. The flexible structure of (*S*)-**2** is expected to be a favorable factor for the solvent switch technique.[14] To date, no resolution work on **1** with **2** has been reported. In addition, considering the following statement that 'a resolving agent should have a similar or longer molecular length than the racemic target compound',[9] we chose **2** because its bent structure appeared to fit this criterion.[10,11,14] It was also found that **2** can be easily recovered.

To examine the solvent or polarity dependency of (*RS*)-**1**·(*S*)-**2**, the effects of four alcohols and water as a resolving solvent on the resolution were initially studied together with the dielectric constant (ε = 17–78) as an index (Table 1, entries 1–3, 7, and 17). The results showed that (*S*)-**1** was selectively resolved as the less-soluble salt. The enantiomeric purity of (*S*)-**1** varied depending on the solvent polarity or ε, showing moderate to low enantiomeric purity. Therefore, the enantiomeric purity and even the configuration of resolved **1** could be controlled using a mixed solvent of alcohols and water, as shown by Sakai et al.[10–12]

Based on these results, the alcohol–water solvent systems, which give a homogeneous clear solution at ambient temperature, were taken into account. All solvent systems gave crystalline precipitates, and the results of a single crystallization in each solvent are summarized in Table 1. In the whole ε range studied, (*S*)-**1** selectivity was again observed, but the enantiomeric excess was largely affected by the solvent polarity, that is, the enantiomeric excess of **1** in the salt was controlled by adjusting the water content in an alcohol. The enantiomeric purity was determined by chiral high-performance liquid chromatography (HPLC) analysis after acetylation of (*S*)-**1** liberated from the precipitated salt.

For the solvent systems shown in Table 1, a rather simple trend of the enantiomeric purity change was observed. As shown in Figure 2, the enantiomeric excess of (*S*)-**1** in the less-soluble diastereomeric salt was dependent on the solvent ε, that is, the lower ε is, the higher the enantiomeric purity of (*S*)-**1** becomes. The highest enantiomeric purity of the (*S*)-**1** enantiomer was achieved using 100% 2-PrOH (ε = 18.0) as the resolving solvent (Table 1, entry 2).

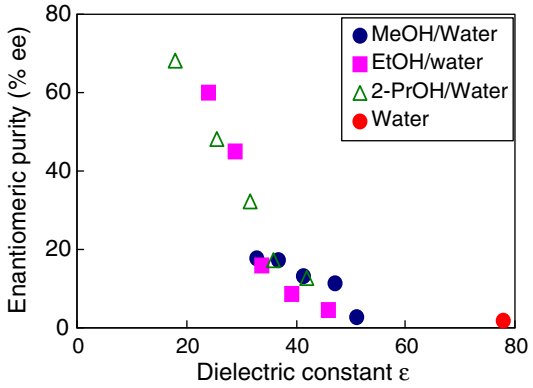

Figure 2. Relationship between the enantiomeric purity of resolved (*S*)-**1** and the solvent dielectric constant of the resolving solvent.

In order to observe the solvent effect on the (*R*)-**1** selectivity and at a lower ε range, less polar alcohols and other solvents were examined and dioxane was found to be effective in producing the (*R*)-**1**-rich diastereomeric salt. Thus, resolution conditions were optimized using various mixed solvents of dioxane–alcohol and dioxane–water; the results are summarized in Table 2.

For all the solvent systems investigated ($8.7 < \varepsilon < 23.7$), (*R*)-**1**·(*S*)-**2** was found to be the less-soluble diastereomeric salt showing the drastic effect of dioxane. The highest enantiomeric purity of the (*R*)-**1** enantiomer was provided in moderate efficiency as the less-soluble diastereomeric salt through resolution using dioxane/MeOH (50:50 w/w; ε = 17.5) as the resolving solvent (Table 2, entry 13). As described later, the (*R*)-**1**·(*S*)-**2** salt was found to contain dioxane molecules as (*R*)-**1**·(*S*)-**2**·dioxane.

Table 1
Resolution of (*RS*)-**1** with (*S*)-**2** in various alcohol–water solvents[a]

Entry	Solvent	Dielectric constant[b] (ε)	Solvent/(*RS*)-**1** ratio (v/w)	Yield[c] (%)	Enantiomeric purity[d] (% ee)	Resolution efficiency[e] (*E*, %)	Absolute configuration
1	100% *n*-BuOH	17.0	40.0	61.6	48.3	29.8	(*S*)
2	100% 2-PrOH	18.0	35.0	69.8	68.4	47.7	(*S*)
3	100% EtOH	24.0	28.0	45.7	59.8	27.3	(*S*)
4	90% 2-PrOH	25.7	25.0	64.4	48.3	31.1	(*S*)
5	90% EtOH	29.0	17.0	54.2	44.9	24.3	(*S*)
6	80% 2-PrOH	31.5	13.0	49.3	32.4	16.0	(*S*)
7	100% MeOH	33.0	10.0	50.5	17.9	9.0	(*S*)
8	80% EtOH	33.9	9.0	44.0	15.7	6.9	(*S*)
9	70% 2-PrOH	36.0	7.5	46.8	17.5	8.2	(*S*)
10	90% MeOH	36.9	8.0	45.3	17.5	7.9	(*S*)
11	70% EtOH	39.1	6.0	48.5	8.6	4.2	(*S*)
12	80% MeOH	41.5	7.5	45.8	13.2	6.1	(*S*)
13	60% 2-PrOH	42.0	6.5	47.7	12.6	6.0	(*S*)
14	60% EtOH	46.0	5.0	52.6	4.5	2.3	(*S*)
15	70% MeOH	47.0	6.0	52.1	11.3	5.9	(*S*)
16	60% MeOH	51.0	5.0	50.6	2.7	1.4	(*S*)
17	H_2O	78.0	5.4	50.7	1.9	1.0	(*S*)

[a] Resolving agent (*S*)-**2**/(*RS*)-**1** = 1.0 (molar ratio).
[b] Dielectric constant (ε) for a mixed solvent is the weighted average value calculated from those of pure solvents.[15]
[c] Yield calculated based on half the amount of (*RS*)-**1**.
[d] Determined by chiral HPLC analysis (HPLC conditions-column: Chiralpak AD-H (Daicel Chemical Ind. Ltd), eluent: 10% 2-propanol in hexane, flow rate: 0.5 mL/min).
[e] Resolution efficiency (*E*, %) = yield (%) × enantiomeric purity (% ee)/100.

Table 2
Resolution of (*RS*)-**1** with (*S*)-**2** in various mixed solvents[a]

Entry	Solvent (w/w)	Dielectric constant[b] (ε)	Solvent/(*RS*)-**1** ratio (v/w)	Yield[c] (%)	Enantiomeric purity[d] (% ee)	Resolution efficiency[e] (*E*, %)	Absolute configuration
1	Dioxane/MeOH (80:20)	8.2	57.1	53.2	13.1	7.0	(*R*)
2	Dioxane/EtOH (70:30)	8.6	53.8	60.4	46.7	28.2	(*R*)
3	Dioxane/H_2O (90:10)	9.6	15.4	68.6	47.6	32.7	(*R*)
4	Dioxane/2-PrOH (50:50)	10.0	35.7	59.3	15.3	9.1	(*R*)
5	Dioxane/EtOH (60:40)	10.8	37.5	62.7	33.4	20.9	(*R*)
6	Dioxane/MeOH (70:30)	11.3	33.3	57.6	13.8	8.0	(*R*)
7	Dioxane/EtOH (50:50)	13.0	25.0	63.3	36.3	23.0	(*R*)
8	Dioxane/2-PrOH (30:70)	13.2	25.4	74.0	29.5	21.8	(*R*)
9	Dioxane/MeOH (60:40)	14.4	21.1	58.2	16.4	9.5	(*R*)
10	Dioxane/EtOH (40:60)	15.2	22.7	70.6	31.8	22.5	(*R*)
11	Dioxane/H_2O (80:20)	17.2	12.4	65.4	6.0	3.9	(*R*)
12	Dioxane/EtOH (30:70)	17.4	16.7	54.9	29.4	16.1	(*R*)
13	Dioxane/MeOH (50:50)	17.5	17.9	67.2	53.1	35.7	(*R*)
14	Dioxane/MeOH (40:60)	20.6	15.7	66.7	43.1	29.8	(*R*)
15	Dioxane/MeOH (30:70)	23.7	14.3	62.8	38.5	24.2	(*R*)

[a] Resolving agent (*S*)-**2**/(*RS*)-**1** = 1.0 (molar ratio).
[b] Dielectric constant (ε) for a mixed solvent is the weighted average value calculated from those of pure solvents.[15]
[c] Yield calculated based on half the amount of (*RS*)-**1**.
[d] Determined by chiral HPLC analysis (HPLC conditions-column: Chiralpak AD-H (Daicel Chemical Ind. Ltd), eluent: 10% 2-propanol in hexane, flow rate: 0.5 mL/min).
[e] Resolution efficiency (*E*, %) = yield (%) × enantiomeric purity (% ee)/100.

The trends of the enantiomeric purity changes are shown in Figure 3. This figure indicates that the enantiomeric excess of (*R*)-**1** in the less-soluble diastereomeric salt was also largely dependent on the resolving solvent. However, in contrast to Figure 2, the marked scattering and rather complex solvent dependency of the enantiomeric purity were the important observations, as shown in Figure 3. Also, the plot for each solvent system showed no simple trends. Figure 3 shows that the effect or contribution of dioxane was not largely affected by an alcoholic solvent or ε, but was directly related to the (*R*)-**1**·(*S*)-**2** salt.

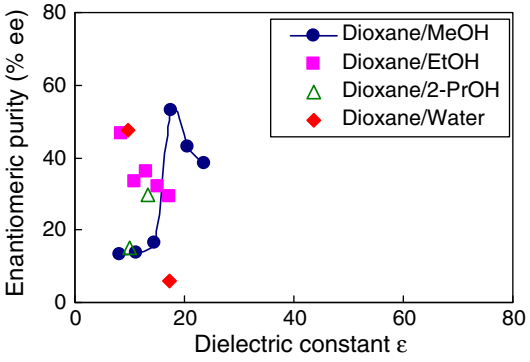

Figure 3. Relationship between the enantiomeric purity of resolved (*R*)-**1** and the solvent dielectric constant of the resolving solvent.

These results clearly indicate that the resolving solvent plays very distinctive roles, not only in polarity, but also structurally in the chiral molecular recognition between molecules **1** and **2**, that is, the resolution of (*S*)-**1** is dependent on the solvent polarity, whereas this is not the case for (*R*)-**1** selectivity. The shape or size of dioxane is likely to be a crucial factor, the elucidation of which requires the crystal structure analysis of the diastereomeric salts.

2.2. X-ray crystal structure

As resolution is the result of crystal growth from an appropriate solution, crystal structure analysis could provide information on molecular structures in the solution and the solvent effect. For this purpose, it is interesting and useful to study and compare the crystal structures of the diastereomeric salts. The structures of the salts (*S*)-**1**·(*S*)-**2** and (*R*)-**1**·(*S*)-**2** determined by X-ray single-crystal analysis are shown in Figures 4–6, respectively.

The X-ray analysis showed that both diastereomeric salts (*R*)-**1**·(*S*)-**2** and (*S*)-**1**·(*S*)-**2** form a hydrogen-bonding layer in the network of $P2_1$, as previously observed.[9,13,14,16,17] At the same time,

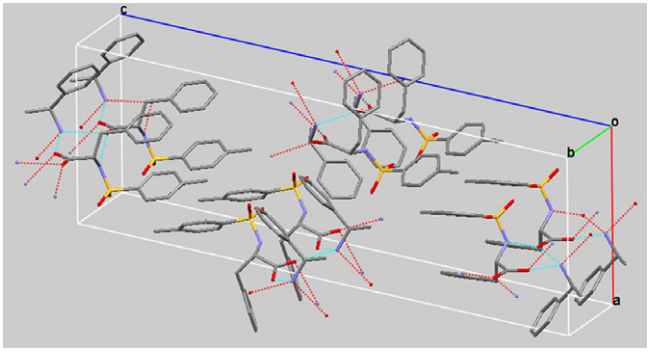

Figure 4. Crystal packing of (*S*)-**1**·(*S*)-**2**.

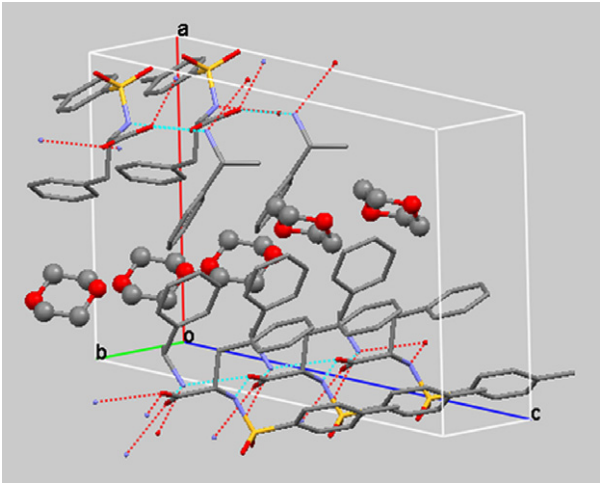

Figure 5. Crystal packing of (*R*)-**1**·(*S*)-**2**·dioxane.

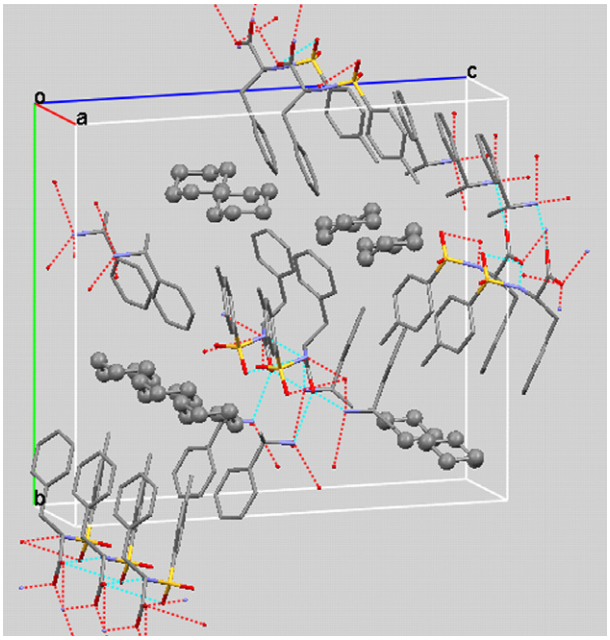

Figure 6. Crystal structure of (*R*)-**1**·(*S*)-**2**·cyclohexane.

a clear difference exists in the structures: (*R*)-**1**·(*S*)-**2** contains dioxane (Fig. 5), while (*S*)-**1**·(*S*)-**2** has no solvent molecules (Fig. 4). This is the same feature observed in the previous systems,[10–14] that is, one of the diastereomeric salt crystals contains solvent molecules. However, this is the first example in which the solvent is not protic. In addition, it was found that the solvent was not incorporated in the hydrogen-bonding network despite the fact that dioxane can be a hydrogen bond acceptor.

Considering the effect observed in the resolution, the role of dioxane is expected to be space filling in the crystal structure. Again, this is the first case observed for the systems resolved by the solvent switch technique. The markedly different schemes observed in the two crystal structures and those observed previously[10–14] indicate that the resolving solvent significantly affects the chiral discrimination processes, not only by its hydrogen bonding ability but also by its shape or size.

If the role of dioxane is simply space filling, it could be replaced with other solvents with similar size and shape. The (*R*)-**1**·(*S*)-**2** salt was recrystallized from cyclohexane/2-PrOH (50:50 w/w) and the single-crystal formed was analyzed. As observed in Figure 6, the crystal structure contained cyclohexane and was quite similar to that obtained from dioxane/2-PrOH (50:50 w/w). This result strongly supports the second effect of the resolving solvent for the solvent switch technique and the drastic effect of dioxane (Table 2).

2.3. Roles of solvent

It is well known that the composition or polarity of the resolving solvent is an important factor for resolution in the diastereomeric salt formation method because the efficiency changes depend on the resolving solvent system. Based on the present results, the resolving solvent seems to discriminate the enantiomers of a target racemate from the following two aspects: (1) polar factor for changing or adjusting the conformation of the salt. Depending on the solvent polarity, the conformation and stability or solubility of the salt change, leading to changes in crystallization and salt composition; and (2) stabilizing factor of the salt crystal as part of the hydrogen-bonding network[10–14] or as a space filler. Although the shape and size of hydrogen-bonding solvents also affect the crystallization, aprotic solvents can be included in the crystal structure, as shown for dioxane and cyclohexane in the present study. Therefore, appropriate solvent choice is possible not only as a hydrogen-bonding component, but also as a space filler under polarity control in the solvent switch technique.

3. Conclusion

Solvent control of the resolution of α-methylbenzylamine **1** was studied using *N*-tosyl-(*S*)-phenylalanine (*S*)-**2**, that is, by the solvent switch technique. The enantiomer and the enantiomeric purity of **1** in the less-soluble diastereomeric salt varied, largely depending on the composition of the resolving solvent. The configuration was inversed only by the incorporation of dioxane solvent molecules, as observed in some previous cases. However, it was demonstrated for the first time that the solvent molecules did not contribute to the hydrogen-bonding network, as determined by X-ray crystal analysis. The present data showed two types of solvent effects: (1) a polarity factor and (2) a stabilization factor through hydrogen bonding reported previously or the shape and/or size effect observed in the present study.

4. Experimental

4.1. General

The measurement of ^{1}H nuclear magnetic resonance (NMR) spectra was performed on Bruker AC300P and AC200 spectrometers (Molecular Analysis and Life Science (MALS) Center, Saitama University). Infrared spectra were recorded on a JASCO Fourier transform infrared 400 spectrometer. Melting temperatures were determined on the Mel-Temp melting point apparatus (Laboratory Devices) and are uncorrected. HPLC was performed using a JASCO Intelligent HPLC system 900 equipped with a JASCO CD-1594 detector.

Racemic and enantiomerically pure (*R*)- and (*S*)-α-methylbenzylamine **1** of >99% purity were kindly supplied by Yamakawa Chemical Industry Co. *N*-Tosyl-(*S*)-phenylalanine **2** prepared by tosylation of (*S*)-phenylalanine (>99.0%) obtained from Kanto Chemical Co., Inc. gave satisfactory analytical and spectroscopic data.[18]

4.2. Resolution procedure

The general experimental procedure (i.e., preparation of the diastereomeric salt) was as follows. A mixture of (*RS*)-**1** (121 mg, 1.0 mmol), *N*-tosyl-(*S*)-phenylalanine **2** (319 mg, 1.0 mmol), and the solvent (required amount as shown in the tables) was heated to produce a clear solution. The solution was then cooled to room temperature to grow less-soluble salt crystals. The crystals were filtered off and washed with the respective solvent to afford the crude and less-soluble diastereomeric salt (*S*)-**1**·(*S*)-**2** or (*R*)-**1**·(*S*)-**2**. Experimental results of the resolution of (*RS*)-**1** with enantiopure (*S*)-**2** from alcohol, water, alcohol–water, and various mixed solvents are summarized in Tables 1 and 2.

4.2.1. Compound (*S*)-1·(*S*)-2

Pure (*S*)-**1**·(*S*)-**2** was prepared to determine its properties as follows: in MeOH (10 mL), (*S*)-**1** (121 mg, 1.0 mmol) and (*S*)-**2** (319 mg, 1.0 mmol) were dissolved and the solvent was removed under reduced pressure to afford the salt. $[\alpha]_D^{27} = +50.5$ (*c* 0.107, MeOH); mp 156–158 °C; IR (KBr) cm^{-1}: 3300–2400, 1566, 1446, 1404, 1373, 1330, 1171, 1153, 1088, 949, 868, 816, 768, 752,

700, 660, 567, 547; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.47–6.99 (m, 14H), 5.66 (br, 4H), 4.22–4.11 (m, 1H), 3.80–3.65 (m, 1H), 2.96 (dd, J = 13.6, 5.2 Hz, 1H), 2.68 (dd, J = 13.6, 7.3 Hz, 1H), 2.34 (s, 3H), 1.42 (d, J = 6.6 Hz, 3H).

4.2.2. (*R*)-1·(*S*)-2·Dioxane[19]

Pure (*R*)-**1**·(*S*)-**2**·dioxane was prepared to determine its properties as follows: in dioxane/H_2O (9:1 w:w) (3 mL), (*R*)-**1** (70 mg, 0.58 mmol) and (*S*)-**2** (184 mg, 0.58 mmol) were dissolved and recrystallized to obtain the salt (212 mg, 0.48 mmol, 83.1%) $[\alpha]_D^{23} = +20.7$ (*c* 1.0, MeOH); mp 144–145 °C; IR (KBr) cm^{-1}: 3200–2300, 1568, 1533, 1455, 1392, 1329, 1160, 1119, 1088, 952, 874, 814, 755, 701, 667, 559; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.49 (d, J = 8.4 Hz, 2H), 7.38–7.23 (m, 5H), 7.18–7.02 (m, 7H), 4.3–3.8 (br, 4H), 4.05 (m, 1H), 3.84 (m, 1H), 3.74 (s, 8H), 3.02 (dd, J = 13.8, 5.2 Hz, 1H), 2.79 (dd, J = 13.8, 7.2 Hz, 1H), 2.35 (s, 3H), 1.43 (d, J = 6.8 Hz, 3H).

4.2.3. Compound (*R*)-1·(*S*)-2

Pure (*R*)-**1**·(*S*)-**2** was prepared to determine its properties as follows: in MeOH (10 mL), (*R*)-**1** (121 mg, 1.0 mmol) and (*S*)-**2** (319 mg, 1.0 mmol) were dissolved, and the solvent was removed under reduced pressure to afford the salt. $[\alpha]_D^{27} = +78.5$ (*c* 0.107, MeOH); mp 136–138 °C; IR (KBr) cm^{-1}: 3300–2400, 1606, 1569, 1533, 1497, 1391, 1333, 1292, 1163, 1088, 945, 862, 812, 746, 698, 665, 559; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.77 (br, 4H), 7.44–6.95 (m, 14H), 4.10–3.92 (m, 1H), 3.73 (m, 1H), 2.92 (dd, J = 13.6, 4.9 Hz, 1H), 2.65 (dd, J = 13.6, 6.9 Hz, 1H), 2.33 (s, 3H), 1.41 (d, J = 6.6 Hz, 3H).

4.3. Enantiomeric purity determination

The less-soluble diastereomeric salts (*S*)-**1**·(*S*)-**2** and (*R*)-**1**·(*S*)-**2** were acetylated to determine the enantiomeric purity of **1**. A typical experimental procedure was as follows. To a stirred solution of the salt (94 mg, 0.21 mmol) in dry tetrahydrofuran (THF) was added Et_3N (54 mg, 0.53 mmol) in dry THF at room temperature under a nitrogen atmosphere. Acetic anhydride (26 mg, 0.26 mmol) in dry THF was added dropwise to the mixture, which was stirred for 10 h at the same temperature. The reaction mixture solvent was removed under reduced pressure. The residue was dissolved in EtOAc and then washed with saturated aqueous $NaHCO_3$: brine, and dried with anhydrous Na_2SO_4. After concentration under reduced pressure, the residue was purified by preparative silica gel thin layer chromatography (TLC) (EtOAc) to afford a white solid residue (31 mg, 0.19 mmol, 89.7%).

The enantiomeric purity of resolved **1** was determined on its acetylated derivative by chiral HPLC analysis performed using CHIRALCEL AD-H (Daicel Chemical Ind. Ltd; ∅ 4.6 mm × 250 mm; detection: UV 254 nm; flow rate: 0.5 mL/min; eluent: 10% 2-PrOH in hexane).

When **1** was liberated from the diastereomeric salt, **2** was easily recovered as follows. $CHCl_3$ was added to the diastereomeric salt and treated with 1 N NaOH aq to extract **1**. The alkaline aqueous solution was acidified with 3 N HCl aq and extracted with $CHCl_3$ to obtain **2**. Then, the organic layer was dried with anhydrous Na_2SO_4, concentrated, and the residue was recrystallized from EtOH. In this procedure, **2** was recovered at >85% efficiency.

4.3.1. (*S*)-*N*-(1-Phenylethyl)acetamide

$[\alpha]_D^{24} = -170.0$ (*c* 0.106, MeOH, T = 24.0 °C); mp 102–104 °C; IR (KBr) cm^{-1}: 3265, 3070, 2980, 1643, 1556, 1491, 1450, 1375, 1302, 1286, 756, 742, 704, 621, 534; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36–7.23 (m, 5H), 5.76 (br, 1H), 5.13 (quint, J = 7.2 Hz, 1H), 1.98 (s, 3H), 1.49 (d, J = 6.6 Hz, 3H).

4.3.2. (*R*)-*N*-(1-Phenylethyl)acetamide

$[\alpha]_D^{25} = +171.9$ (*c* 0.104, MeOH, T = 25.0 °C); mp 103–104 °C; IR (KBr) cm^{-1}: 3265, 3070, 2972, 1643, 1556, 1491, 1450, 1375, 1302, 1286, 1217, 1138, 1099, 1070, 1028, 1003, 955, 908, 756, 742, 704, 648, 621, 586, 534, 502; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36–7.22 (m, 5H), 5.95 (br, 1H), 5.11 (quint, J = 7.2 Hz, 1H), 1.96 (s, 3H), 1.47 (d, J = 7.0 Hz, 3H).

4.4. Specific rotation measurement

The salt solution (10 mL) was prepared at 0.1 g/100 mL (*c* 0.1) with a solvent and incubated in a thermostated bath at 24.0–25.0 °C for 1 h. The optical rotation was measured by the Na D line using a water-jacketed cell at the same temperature.

4.5. Crystal structure analysis of (*S*)-1·(*S*)-2 and (*R*)-1·(*S*)-2

Single crystals of (*S*)-**1**·(*S*)-**2** were prepared from the pure diastereomeric salt by slow evaporation of the solvent from 2-PrOH solution, while those of (*R*)-**1**·(*S*)-**2** were prepared from dioxane/50% 2-PrOH and cyclohexane/50% 2-PrOH solution. X-ray intensities were measured up to $2\theta_{max} = 55.0°$ using graphite-monochromated Mo Kα radiation (λ = 0.71069 Å, Bruker SMART APEX, MALS). The crystal structure was determined by a direct method with SHELXS97 and refined by the full-matrix least-squares method using SHELXL97.[20]

4.5.1. Compound (*S*)-1·(*S*)-2

$C_{24}H_{28}N_2O_4S$; formula weight, 440.54; monoclinic; $P2_1$; a = 11.371(2) Å, b = 5.8653(12) Å, c = 33.222(7) Å, β = 92.99(3)°, V = 2212.7(8) Å^3 (123(2) K), Z = 4, D_{calcd} = 1.322 g cm^{-3}, μ (Mo Kα) = 0.180 mm^{-1}, R = 0.0449 and Rw = 0.1075 for 15,659 observed reflections with $I > 2\sigma$ from 9440 unique reflections. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center: Deposition number CCDC-690721.

4.5.2. (*R*)-1·(*S*)-2·Dioxane

$C_{28}H_{36}N_2O_6S$; formula weight, 528.65; monoclinic; $P2_1$, a = 12.508(3) Å, b = 6.0891(12) Å, c = 17.680(4) Å, β = 97.13(3)°, V = 1336.1(5) Å^3 (123(2) K), Z = 2, D_{calcd} = 1.314 g cm^{-3}, μ (Mo Kα) = 0.166 mm^{-1}, R = 0.0418 and Rw = 0.1234 for 9308 observed reflections with $I > 2\sigma$ from 5746 unique reflections. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center: Deposition number CCDC-690723.

4.5.3. (*R*)-1·(*S*)-2·Cyclohexane

$C_{30}H_{40}N_2O_4S$; formula weight, 524.70; orthorhombic; $P2_12_12_1$; a = 6.1824(12) Å, b = 20.039(4) Å, c = 22.350(5) Å, V = 2768.9(10) Å^3 (123(2) K), Z = 4, D_{calcd} = 1.259 g cm^{-3}, μ (Mo Kα) = 0.155 mm^{-1}, R = 0.1033 and Rw = 0.2139 for 19,187 observed reflections with $I > 2\sigma$ from 6331 unique reflections. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center: Deposition number CCDC-690722.

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