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ENANTIOMERIC RESOLUTION OF RACEMIC C_2-SYMMETRIC *TRANS*-2,5-DIMETHYL-2,5-DIPHENYLPYRROLIDINE AND *TRANS*-2,5-DIMETHYL-2,5-BIS(3-HYDROXYPHENYL)PYRROLIDINE BY A DIASTEREOMER METHOD

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Abstract – The racemic samples of C_2-symmetric *trans*-2,5-dimethyl-2,5-diphenylpyrrolidine (*trans*-**2a**) and *trans*-2,5-dimethyl-2,5-bis(3-hydroxyphenyl)pyrrolidine (*trans*-**2b**) have been resolved by the diastereomer method using D- or L-tartaric acid as the resolving agent. The enantiomerically enriched *trans*-**2a** and *trans*-**2b** could be oxidized with Oxone® to give *trans*-2,5-dimethyl-2,5-diphenylpyrrolidine-1-oxy (*trans*-**1a**) and *trans*-2,5-dimethyl-2,5-bis(3-hydroxyphenyl)pyrrolidine-1-oxy (*trans*-**1b**), respectively.

Recently, the enantiomerically enriched *trans*-**1a** skeleton has been found to serve as the excellent core source of all-organic chiral paramagnetic liquid crystals (*trans*-**3**), which i) can show ferroelectric and ferromagnetic properties owing to the large electric dipole moment ($\mu \approx 3$ Debye) and the magnetic moment of a nitroxyl group under the applied electric and magnetic fields, respectively (Chart 1),[1-6] and ii) can be used as a real chiral liquid crystalline spin-probe or spin-label to observe the dynamic behavior of diamagnetic or paramagnetic liquid crystals, respectively, by electron paramagnetic resonance (EPR) spectroscopy.[1,7] Meanwhile, it is expected that enantiomerically enriched *trans*-**2a**, a reduced form of *trans*-**1a**, and its dihydroxy-substituted derivatives *trans*-**2b** and *trans*-**2c** may serve as i) a chiral resolving agent or a chiral host compound for enantiomeric resolution of acidic or neutral racemic samples, respectively and ii) a chiral amine catalyst or a chiral lithium amide precursor for enantioselective deprotonation (Chart 1).[8]

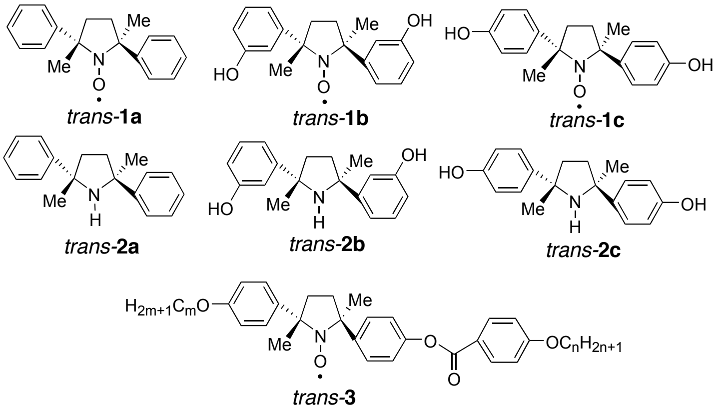
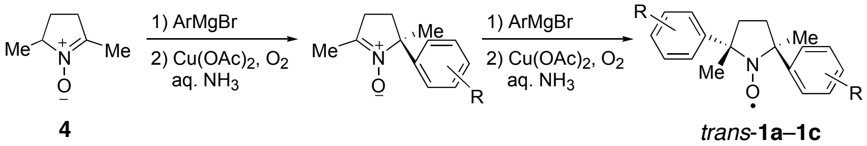


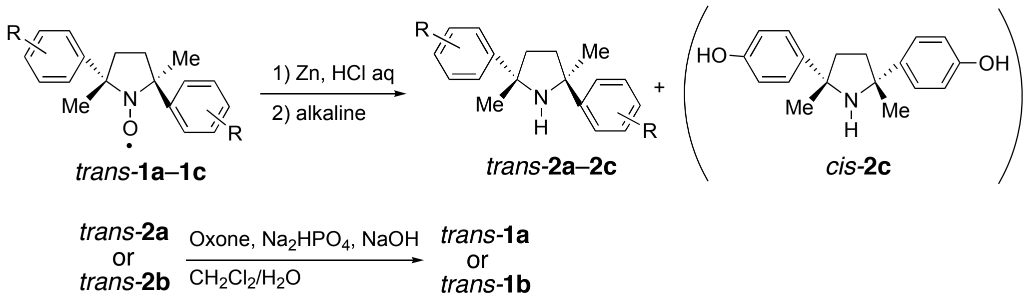
Chart 1. Pyrrolidine-1-oxys *trans*-**1a**–**1c** and pyrrolidines *trans*-**2a**–**2c**.

Although the pyrrolidine *trans*-**2a** was obtained by the reduction of the pyrrolidine-1-oxy *trans*-**1a** under acidic conditions,[9] the synthesis of enantiomerically enriched *trans*-**1a** is not an easy task because the procedure involves the time-consuming and less-efficient yeast reduction of 2,5-hexanedione, giving only (2*S*,5*S*)-**1a**.[10] In contrast, since the racemic *trans*-**1a**–**1c** are easily available from **4**, which is obtained from nitroethane and 3-buten-2-one, and the corresponding Grignard reagent (Scheme 1),[11-13] the enantiomeric resolution of racemic *trans*-**2a**–**2c** derived from racemic *trans*-**1a**–**1c** seems more appropriate to obtain both (2*S*,5*S*)- and (2*R*,5*R*)-**2a**–**2c** in large quantity. Thus far, only racemic *trans*-**1a** was resolved by using a semipreparative chiral HPLC column.[11] Here we report the successful enantiomeric resolution of racemic *trans*-**2a** and *trans*-**2b** by the diastereomer method using D- or L-tartaric acid.

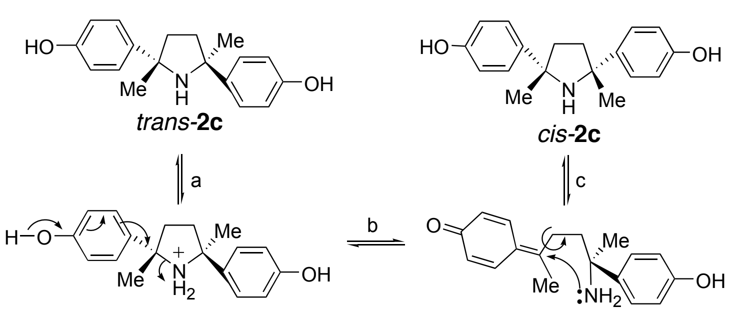


Scheme 1. Preparation of pyrrolidine-1-oxys *trans*-**1a**–**1c**.

First, the racemic *trans*-**1a**–**1c** were treated with zinc powder in aqueous hydrochloric acid, followed by alkaline work-up.[9] *Trans*-**1a** and *trans*-**1b** were smoothly converted to *trans*-**2a** and *trans*-**2b** in 97 and 84 % yields, respectively (Scheme 2), whereas *trans*-**1c** underwent unexpected epimerization under the acidic conditions to give a 45:55 mixture of *trans*-**2c** and *cis*-**2c**. Since a similar epimerization had been found to occur for *trans*-**1c** by a radical mechanism,[14] *trans*-**2c** which was once formed by reduction with zinc is most likely to undergo the subsequent epimerization by a proton-mediated mechanism shown in Scheme 3. Therefore, we investigated the enantiomeric resolution of racemic *trans*-**2a** and *trans*-**2b**.



Scheme 2. Interconversion between pyrrolidine-1-oxys (*trans*-**1**) and pyrrolidines (*trans*-**2**).



Scheme 3. Mechanism of epimerization of *trans*-**2c** under acidic conditions. a: protonation, b: pyrrolidine rind cleavage and formation of the quinoid intermediate, c: free rotation of the quinoid moiety and ring closure.

Next, we searched the suitable resolving agent and solvent for the enantiomeric resolution by the diastereomer method of racemic *trans*-**2a** and *trans*-**2b**. As the candidates of the resolving agent and solvent, four commercially-available carboxylic acids such as (–)-mandelic acid, L-(+)-tartaric acid, (–)-dibenzoyl-L-tartaric acid monohydrate, and D-camphoric acid, and eight typical solvents such as Et_2O, acetone, MeOH, EtOH, 1-PrOH, 2-PrOH, THF, 1,4-dioxane, and their mixture were examined. To a saturated solution of racemic *trans*-**2a** or *trans*-**2b** was added a saturated solution of one molar equiv of the chiral resolving acid and then a small amount of hexane (diisopropylether in the case of MeOH) to prepare a supersaturated solution. The resulting deposited diastereomeric salts were collected and hydrolyzed with aqueous ammonia to give the free amine. The *ee* values of the recovered amine were compared in Table 1. Consequently, diastereomeric salts were deposited when acetone, EtOH, 2-PrOH, or Et_2O was employed for (±)-*trans*-**2a**, while the use of acetone, 2-PrOH, or Et_2O resulted in the deposition of the salt for (±)-*trans*-**2b**. The best *ee* values, 68.3 and 47.4% *ee*, were obtained for (±)-*trans*-**2a** in EtOH and for (±)-*trans*-**2b** in acetone, respectively, as far as one molar equiv of L-(+)-tartaric acid was used.

The absolute configuration of the excess enantiomer existing in *trans*-**2a** resolved with L-(+)-tartaric acid in EtOH was determined to be 2*R*,5*R* by comparison with the reported specific rotation of (2*S*,5*S*)-**2a**,[9] while that in *trans*-**2b** resolved similarly in acetone was also assigned to be 2*R*,5*R* by comparing with the HPLC data of the (2*S*,5*S*)-**2b** obtained by reduction of (2*S*,5*S*)-**1b** synthesized from (*R*)-**4** (Figure 1).[9,10]

Table 1. Formation of diastereomeric salts and the *ee* values of resolved *trans*-**2a** and *trans*-**2b**.

solvent	compound (±)-*trans*	(–)-dibenzoyl-L-tartaric acid *ee* (%)	L-(+)-tartaric acid *ee* (%)	D-camphoric acid *ee* (%)	(–)-mandelic acid *ee* (%)
Acetone	**2a**	0.1 (2S,5S)[a]	**7.9** (2R,5R)[a]	–[b]	–[b]
	2b	–[b]	**47.4** (2R,5R)[a]	–[b]	–[b]
EtOH	**2a**	–[b]	**68.3** (2R,5R)[a]	–[b]	–[b]
	2b	–[b]	–[b]	–[b]	–[b]
2-PrOH	**2a**	–[b]	10.9 (2S,5S)[a]	–[b]	–[b]
	2b	1.0% (2R,5R)[a]	–[b]	–[b]	–[b]
Et_2O	**2a**	6.0 (2*S*,5*S*)[a]	10.4 (2R,5R)[a]	–[b]	–[b]
	2b	0.4 (2S,5S)[a]	1.5 (2R,5R)[a]	1.9% (2S,5S)[a]	2.6% (2S,5S)[a]

[a] Excess enantiomer. Ee determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralcel OJ, 0.46 cm x 25 cm), a mixture of hexane and 2-propanol (85:15) as the mobile phase at a flow rate of 0.5 mL/min after hydrolysis with aq. NH_3 to give the free amine.

[b] Diastereomeric crystals were not deposited.

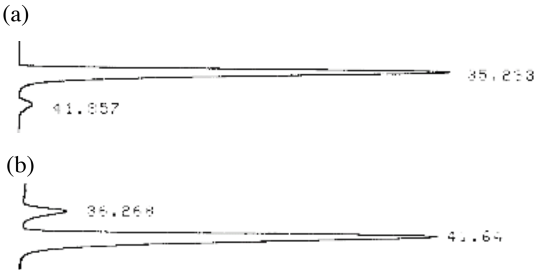


Figure 1. Determination of the absolute configuration of the resolved *trans*-**2b** by HPLC analysis using Daicel Chiralcel OJ; (a) 2*R*,5*R*-enriched *trans*-**2b** (94.3% *ee*) resolved with L-(+)-tartaric acid in acetone and (b) 2*S*,5*S*-enriched *trans*-**2b** (88.6% *ee*) synthesized from *R*-enriched **4**.

To improve the *ee* value of 2*R*,5*R*-enriched *trans*-**2a**, optimization of the molar ratio of L-(+)-tartaric acid to (±)-*trans*-**2a** was attempted. As far as EtOH was used, the use of one molar equiv of the resolving agent was the best choice, giving 2*R*,5*R*-enriched *trans*-**2a** of 68.3% *ee* with 32.9% recovery based on the original quantity of (±)-*trans*-**2a**. Although acetone did not seem to be an appropriate solvent for the resolution of (±)-*trans*-**2a** (Table 1), contrary to expectation, the best *ee* value (91.5% *ee*) with the recovery of 16.0% of 2*R*,5*R*-enriched *trans*-**2a** was obtained when 0.25 molar equiv of L-(+)-tartaric acid was used in acetone. The diastereomeric salt was determined to be composed of a 1:1 mixture of *trans*-**2a** and L-(+)-tartaric acid by ^1H NMR analysis, although the crystal structure was not obtained due to the inaccessibility of the single crystal of the salt.

Similarly, the molar ratio of L-(+)-tartaric acid to (±)-*trans*-**2b** was optimized (Table 2). In this case, the use of a 3:1 ratio of L-(+)-tartaric acid to (±)- *trans*-**2b** gave the best results, 94.3% *ee* and 51.4% recovery of (2*R*,5*R*)-enriched *trans*-**2b**. Although the crystal structure was not obtained due to the inaccessibility of the single crystal of the salt, the ^1H NMR study indicated that the diastereomeric salt consisted of a 1:1

mixture of *trans*-**2b** and L-(+)-tartaric acid, too. These results indicate the existence of a fairly large equilibrium constant in the acid-base reaction between L-(+)-tartaric acid and (±)-*trans*-**2b** in acetone as well as the relatively large difference in the stability or solubility between the resulting two diastereomeric crystals; the crystal of the salt consisting of L-(+)-tartaric acid and (2*R*,5*R*)-*trans*-**2b** is more stable than that of the other one. Furthermore, by repeating recrystallization of the obtained diastereomeric crystals from acetone once, the *ee* value of (2*R*,5*R*)-*trans*-**2b** improved from 94.3% *ee* to almost 100% and the overall recovery was 12.2%.

Table 2. Optimization of the ratio of L-(+)-tartaric acid to (±)-*trans*-**2b** in acetone.

L-(+)-tartaric acid : (±)-*trans*-**2b**	(2*R*,5*R*)-*trans*-**2b** revovery (%)[a]	*ee* (%)[b]
1 : 4	–[c]	61.1
1 : 2	41.8	83.6
1 : 1	52.1	83.1
3 : 1	51.4	94.3
6 : 1	–[c]	82.6
12 : 1	–[c]	75.6

[a] Based on the original quantity of (±)-*trans*-**2b**.

[b] Determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralcel OJ, 0.46 cm x 25 cm), a mixture of hexane and 2-propanol (85:15) as the mobile phase at a flow rate of 0.5 mL/min after hydrolysis with aq. NH_3 to give free *trans*-**2b**.

[c] Undetermined.

Likewise, enantiomeric resolution of (±)-*trans*-**2a** and (±)-*trans*-**2b** using D-(–)-tartaric acid was achieved to give 2*S*,5*S*-enriched *trans*-**2a** and *trans*-**2b**, respectively. Finally, the resolved (2*R*,5*R*)-*trans*-**2a** of 65.0% *ee* and (2*R*,5*R*)-*trans*-**2b** of 90.3% *ee* could be reoxidized with Oxone® to give (2*R*,5*R*)-*trans*-**1a** of 45.8% *ee* and (2*R*,5*R*)-*trans*-**1b** of 87.0% *ee* in 71.6% and 61.6% yield, respectively, after purification by silica gel column chromatography (Scheme 2).[9]

In summary, the enantiomeric resolution of racemic samples of C_2-symmetric pyrrolidines *trans*-**2a** and *trans*-**2b** has been accomplished by the diastereomer method using C_2-symmetric D- or L-tartaric acid as the resolving agent. This resolution procedure would be applicable to a variety of functionalized *trans*-2,5-dimethyl-2,5-diphenylpyrrolidine derivatives.

EXPERIMENTAL

To a vigorously stirred zinc powder (36 mmol) in an aqueous 2 N HCl solution (32 mL) was added the racemic *trans*-**1b** (1.22 g, 4.1 mmol) at 110°C, and the mixture was stirred under reflux for 2 h. After cooling, the reaction mixture was made basic to litmus with aqueous 25% NH_3 solution (48 mL) and extracted with Et_2O. The organic phase was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to give *trans*-**2b** as a white powder (1.01 g, 3.4 mmol, 84 % yield).

(±)-*trans*-**2b**: ^{1}H-NMR(DMSO-d_6) δ1.23 (s,6H) , 1.95-1.99 (m, 2H), 2.14-2.18 (m, 2H), 6.51-6.53 (m, 2H), 6.93-6.92 (m, 2H), 6.95-6.96 (m, 2H), 7.01-7.05 (t, 2H); ^{13}C NMR(DMSO-d_6): δ 23.1, 31.4, 57.3, 104.3, 104.6, 108.4, 120.8, 144.7, 148.9. IR (KBr): 3652, 3311, 2960, 1585, 1370, 704. Anal. Calcd for $C_{18}H_{23}NO_3$ (**2b**·H_2O): C, 71.73; H, 7.69; N, 4.65. Found: C, 71.65; H, 7.39; N, 4.63. Mp 130.1°C (DSC analysis).

To a solution of (±)-*trans*-**2b** (23.5 mg, 0.080 mmol) in acetone (0.3 mL) was added a solution of D-(−)-tartaric acid (36.0 mg, 0.24 mmol) in acetone (2.4 mL) and the mixture was allowed to stand for 12 h at 25°C. The resulting fine powder (20.7 mg) composed of the salt (1:1 ratio) was collected and hydrolyzed with aqueous 25% NH_3 solution (0.1 mL), and the aqueous mixture was extracted with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated to give (2*R*,5*R*)-*trans*-**2b** as a white powder (12.3 mg, 0.041 mmol, 94.3% *ee*, 52 % yield).

(2*R*,5*R*)-*trans*-**2b** (97.5% *ee*): $[\alpha]^{21}_D$ +92.8 (c 0.134, THF).

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