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SYNTHESIS AND STEREOCHEMISTRY OF NOVEL RIGID NITROXIDE BIRADICALS BASED ON PARAMAGNETIC PYRROLIDINE CORE

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Abstract – We have synthesized new chiral racemic nitroxide biradical compounds *cis*-**2** and *trans*-**2** and determined their stereochemistry by X-ray crystallographic analyses.

In 2004, we reported the preparation of prototypic paramagnetic all-organic rod-like liquid crystalline (LC) compounds **1**, which i) contain a chiral cyclic-nitroxide unit as the magnetic spin (S=1/2) and electric dipole (*ca.* 3 Debye) sources in the mesogen core, ii) show chiral or achiral LC phases over wide temperature ranges, and iii) can exhibit unique magnetic and electric properties in the LC state.[1-9] Particularly noteworthy is the fact that the cyclic-nitroxide structure, 2,2,5,5-tetrasubstituted pyrrolidin-1-yloxy (PROXYL) group, is thermally stable enough for repeated heating and cooling cycles below 150 °C in the air. Thus, this type of PROXYL group has turned out to serve as the robust spin and electric dipole sources for elaborating paramagnetic all-organic functional materials usable below 150 °C. In order to improve the magnetic and electric properties of LC compounds **1**, we have designed the new nitroxide biradical compounds **2** which are expected to serve as the synthetic intermediates for the preparation of unprecedented all-organic biradical LC compounds (Chart 1). Here we report the highly stereoselective synthesis and stereochemistry of racemic *cis*-**2** and *trans*-**2**.

The synthetic route for racemic *cis*-(R^*,R^*)-**2** and *trans*-(R^*,R^*)-**2** is summarized in Scheme 1. We have elaborated a facile one-step transformation of 1,4-cyclohexanedione dioxime[10] to 1,4-dinitrocyclohexane

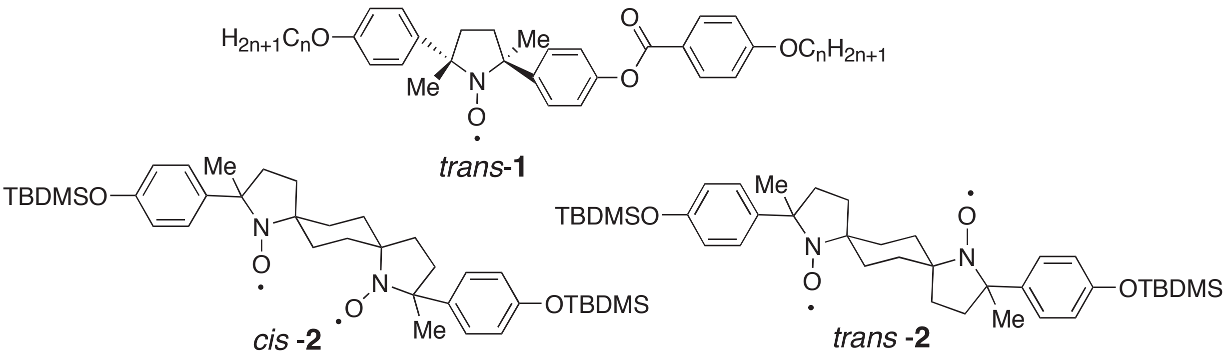
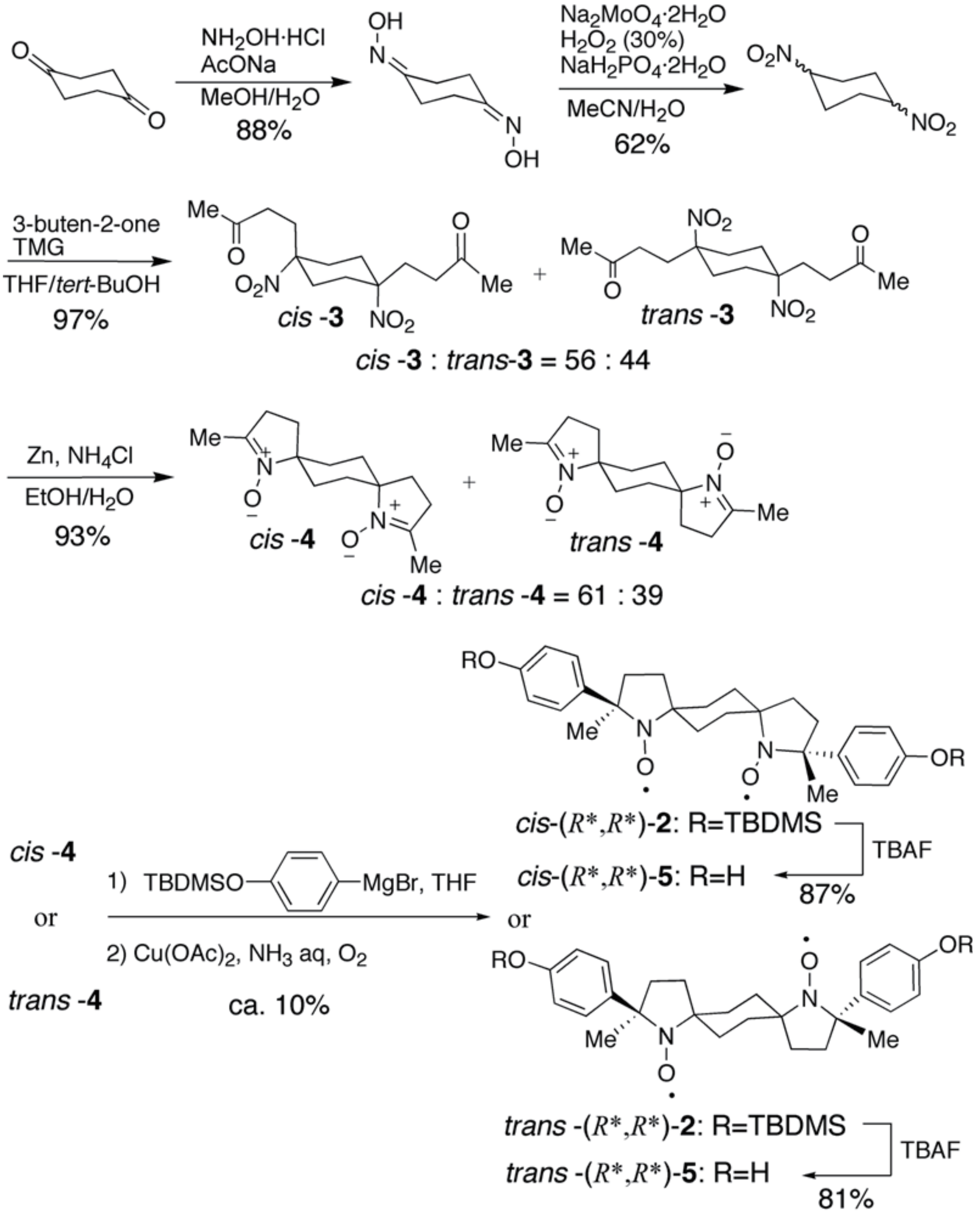


Chart 1. Monoradical compounds **1** and biradical compounds **2**



Scheme 1. Preparation of racemic *cis*-(*R**,*R**)-**2** and *trans*-(*R**,*R**)-**2**

(62% yield) by applying Na_2MoO_4/H_2O_2 oxidizing system in a phosphate buffer solution at pH = 6.5, based on an original patent.[11] The subsequent Michael addition of the obtained dinitro compound to 3-buten-2-one gave a mixture (56:44) of *cis*-**3** and *trans*-**3** in 97% yield, from which each product was isolated by silica gel column chromatography with considerable efforts. The stereochemistry of *cis*-**3** and *trans*-**3** was unequivocally established by X-ray crystallographic analysis (Figure 1 and Table 1). Synthetically, instead of separating *cis*-**3** and *trans*-**3**, the mixture of *cis*-**3** and *trans*-**3** was subjected to zinc reduction to give a mixture (61:39) of *cis*-**4** and *trans*-**4** in 93% yield, from which each dinitrone stereoisomer was easily isolated by silica gel column chromatography. Then hygroscopic *cis*-**4** or *trans*-**4** was reacted with a large excess of 4-(*tert*-butyldimethylsilyloxy)phenylmagnesium bromide in THF, followed by oxidation with $Cu(OAc)_2$ and O_2, to give racemic *cis*-(*R**,*R**)-**2** or *trans*-(*R**,*R**)-**2** with high stereoselectivity, respectively, in *ca*. 10% yield; this yield was comparable to those of analogous reactions.[1-9,12-15] Their stereochemistry was again assigned by X-ray crystallographic analysis of the desilylated compound *cis*-(*R**,*R**)-**5** or *trans*-(*R**,*R**)-**2**; although the result of the latter structure solution was preliminary and unsatisfactory because of the low quality of the single crystal used, we could confirm the stereochemistry somehow (Figure 1 and Table 1). The possible stereoisomer of *cis*-(*R**,*S**)-**2** or *trans*-(*R**,*S**)-**2** could not be isolated due to the negligible formation.

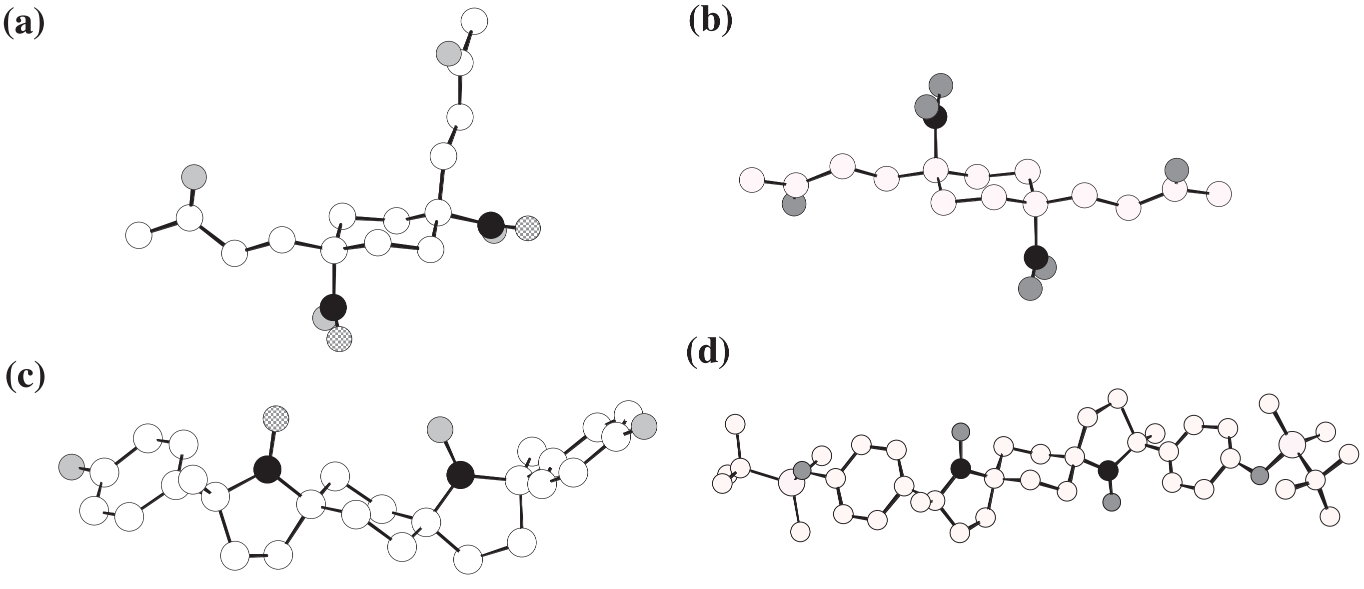


Figure 1. Molecular structures of (a) *cis*-**3**, (b) *trans*-**3**, (c) *cis*-(*R**,*R**)-**5**, and (d) *trans*-(*R**,*R**)-**2** determined by X-ray crystallographic analysis. Carbon, silicon, nitrogen, and oxygen atoms are denoted by small white, large white, black, and gray circles, respectively. Hydrogen atoms are omitted for clarity.

Table 1. Crystallographic data of *cis*-**3**, *trans*-**3**, *cis*-(R^*,R^*)-**5**, and *trans*-(R^*,R^*)-2

	cis-**3**	*trans*-**3**	*cis*-(R^*,R^*)-**5**	*trans*-(R^*,R^*)-**2a**[a]
Empirical Formula	$C_{14}H_{22}O_6N_2$	$C_{14}H_{22}O_6N_2$	$C_{26}H_{32}O_4N_2$	$C_{26}H_{32}O_4N_2$
Formula Weight	314.34	314.34	436.55	436.55
Crystal Color, Habit	colorless, needle	colorless, block	yellow, block	Yellow, block
Crystal Dimensions (mm)	0.40 X 0.40 X 0.30	0.50 X 0.50 X 0.40	0.15 X 0.15 X 0.10	0.10 X 0.10 X 0.10
Crystal System	monoclinic	triclinic	orthorhombic	triclinic
Lattice Parameters				
a (Å)	6.0065(11)	6.1523(11)	18.1861(8)	6.48(2)
b (Å)	24.785(5)	7.6063(15)	8.5527(3)	10.85(5)
c (Å)	10.523(2)	9.4013(13)	14.9691(9)	25.08(7)
α (deg)		64.602(5)		84.35(14)
β (deg)	90.926(6)	82.665(5)		82.02(9)
γ (deg)		76.561(5)		79.16(15)
V (Å^3)	1566.3(6)	386.35(12)	2328.31(19)	1709.3(112)
Space Group	$P2_1$/n (#14)	P-1 (#2)	Pna2_1 (#33)	P-1 (#2)
Z value	4	1	4	2
R value	0.041	0.050	0.069	0.146
R_w value	0.137	0.135	0.152	0.350

[a] Preliminary result due to the low quality of the single crystal.

In summary, we have successfully obtained the hitherto-unknown nitroxide biradical compounds **2** and **5** with high stereoselectivity. These biradical compounds could serve as a key intermediate for the preparation of unprecedented all-organic biradical LC materials, which are expected to show strong magnetic interactions in the LC state[6-8] or to be used as a real LC biradical spin probe.[16-20]

EXPERIMENTAL

General. Unless otherwise noted, solvents and reagents were reagent grade and used without further purification. THF which is used for electron paramagnetic resonance (EPR) spectroscopy, Michael addition, or Grignard reactions was distilled from sodium/benzophenone ketyl under argon. Melting points were determined by micro melting point apparatus (Yanako MP-500F). IR spectra were recorded with SHIMADZU IRPrestige-21. NMR spectra were recorded with a JEOL JNM-EX 270 and JEOL JNM-A500. EPR spectra were recorded with a JEOL FE1XG. Magnetizations were recorded with QUANTUM DESIGN MPMS-2 and MPMS-5S.

Synthesis.

1,4-Cyclohexanedione dioxime: To a stirred solution of 1,4-cyclohexanedione (16.80 g, 0.150 mol) in MeOH (130 mL) was added dropwise a solution of $NH_2OH \cdot HCl$ (35.0 g, 0.503 mol) and $NaOAc \cdot 3H_2O$ (66.6 g, 0.497 mol) in water (120 mL) over 35 min. The mixture was refluxed for 15 h. The resulting precipitate was filtrated and washed with a cold 1:1 mixture of MeOH and water (4×20 ml). After drying in vacuum, 18.72 g (88%) of 1,4-cyclohexanedioxime was obtained. Mp: 201.6-202.8 ^{o}C (ref.[10], 196 °C). ^{1}H NMR (270 MHz, DMSO-d_6) δ 10.35 (s, 2H), 2.40 (m, 8H).

1,4-Dinitrocyclohexane: To a solution of $NaH_2PO_4 \cdot 2H_2O$ (8.43 g, 54.0 mmol) in water (15 mL) was added aqueous 2*N* NaOH to adjust the pH to 6.5. Then 1,4-cyclohexanedione dioxime (2.13 g, 15.0 mmol) and $Na_2MoO_4 \cdot 2H_2O$ (7.26 g, 30.0 mmol) was added to this solution. The mixture was diluted with CH_3CN (45 ml) and aqueous H_2O_2 (30%, 5.10 g, 45.0 mmol) was dropwise added over 30 min. The reaction mixture was stirred at 50 ^{o}C for 2 h. MeCN was evaporated and the resulting aqueous suspension was acidified with aqueous 2*N* HCl to pH 5. The precipitate was filtered, washed with water, and dried in vacuum. 1,4-Dinitrocyclohexane (1.63 g, 9.36 mmol, 62%) was obtained as a pale-brown powder. Mp (a mixture of *cis*- and *trans*- isomers): 86.4-88.5 ^{o}C. ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.49 (m 2H), 2.44 (m, 4H), 2.09 (m, 4H). IR (KBr) 2974, 1562, 1549, 1458, 1387, 1350, 1304, 1231, 910, 893, 772. This IR spectrum was consistent with that of the sample prepared by MCPBA oxidation of 1,4-cyclohexanone dioxime.[21]

1,4-Bis(3-oxobutyl)-1,4-dinitrocyclohexane (3): To a solution of 1,4-dinitrocyclohexane (4.00 g, 23.0 mmol) and freshly distilled methyl vinyl ketone (4.28 mL, 52.9 mmol) in a mixture of *tert*-BuOH (25 mL) and THF (40 mL) was added dropwise 1,1,3,3-tetramethylguanidine (TMG) (0.727 mL, 5.75 mmol) with such a rate that reaction temperature does not exceed 35-40 ^{o}C. The mixture was stirred at room temperature for 16 h. Et_2O (400 mL) was added. After stirring for 15 min, the precipitate was filtered and washed with Et_2O. Drying in vacuum gave **3** (6.28 g, 20.0 mmol, 87%) as a white powder. The filtrate was evaporated to dryness. The residue was again triturated with Et_2O (30 mL) and filtered to give additional **3** (0.710 g, 2.26 mmol, 10%).

Separation of two stereoisomers: Compound **3** (400 mg) was subjected to flash column chromatography (silica gel, $CHCl_3$) to give *trans*–**3** (151 mg) in the first fractions and *cis*-**3** (196 mg) in the second fractions.

trans-**3**: Mp 195.6-196.9 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.56 (d, J = 11 Hz, 4H), 2.41 (t, J = 7.8 Hz, 4H), 2.14 (s, 6H), 2.06 (t, J = 7.8 Hz, 4H), 1.57 (d, J = 11 Hz, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.9, 30.0, 34.6, 37.1, 89.3, 205.6. IR (KBr): 2974, 2935, 2873, 1716, 1541, 1438, 1375, 1355, 1171, 966, 820.

Anal. Calcd for $C_{14}H_{22}N_2O_6$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.36; H, 7.04; N, 8.62. The single crystal for X-ray crystallographic analysis was obtained from $CHCl_3$/EtOAc.

cis-**3**: Mp 160.1-161.8 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 2.42 (t, J = 7.5 Hz, 4H), 2.31 (m, 4H), 2.19 (t, J = 7.5 Hz, 4H), 2.16 (s, 6H), 1.92 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 30.0, 30.01, 37.4, 88.7, 205.9. IR (KBr): 2974, 2943, 2878, 1712, 1545, 1530, 1431, 1367, 1352, 1170, 972, 797. Anal. Calcd for $C_{14}H_{22}N_2O_6$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.23; H, 7.14; N, 8.94. The single crystal for X-ray crystallographic analysis was obtained from DMF.

2,10-Dimethyl-1,9-diaza-dispiro[4.2.4.2]tetradeca-1,9-diene 1,9-dioxide (4): To a stirred suspension of **3** (3.14 g, 10.00 mmol), NH_4Cl (1.07 g, 20 mmol) in a mixture of water (20 mL) and EtOH (20 mL) was added zinc powder (5.20 g, 80.0 mmol) in small portions over 30 min at such a rate that the reaction temperature did not exceed 10 °C. Then, the mixture was stirred at room temperature for 16 h. The precipitate was filtered through celite and the residual zinc and zinc oxide was thoroughly washed with aqueous MeOH (50%, 10 mL) four times and then with MeOH (10 mL) four times. The combined filtrate was evaporated to dryness and the residue was dissolved in $CHCl_3$ (75 mL) by heating. After cooling to 40 °C, anhydrous Na_2SO_4 was added and the mixture was filtered and evaporated. After drying in vacuum, bisnitrone **4** (2.33 g, 9.32 mmol, 93%) was obtained as a pale white powder.

Separation of two isomers: Bisnitrone **4** (1.26 g) was subjected to flash column chromatography (silica gel, $CHCl_3$:MeOH 10/1-8/2) to give *trans*-**4** (376 mg) in the first fractions and *cis*-**4** (588 mg) in the second fractions. Both *trans* and *cis* isomers were so hygroscopic that the elemental analysis was infeasible.

trans-**4**: Mp 215.6-216.8 °C (dec.). ^1H NMR (500 MHz, $CDCl_3$) δ 2.63 (t, J = 7.5 Hz, 4H), 2.33 (d, J = 9.0 Hz, 4H) 2.17 (t, J = 7.5 Hz, 4H), 2.05 (s, 6H), 1.60 (d, J = 9.0 Hz, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.0, 27.9, 29.2, 29.9, 75.6, 142.1. IR (KBr): 3536-3289, 2935, 2875, 1659, 1622, 1452, 1258, 1204, 711.

cis-**4**: Mp 165.5-166.6 °C (dec.). ^1H NMR (500 MHz, $CDCl_3$) δ 2.79 (m, 4H), 2.59 (t, J = 7.3 Hz, 4H), 2.04 (s, 6H), 1.97 (t, J = 7.3 Hz, 4H), 1.52 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.1, 29.3, 31.2, 31.3, 73.6, 141.5. IR (KBr): 3468-3206, 2926, 2866, 1676, 1662, 1624, 1614, 1449, 1439, 1257, 1193, 711.

Compounds **2**: To a suspension of *cis*-**4** or *trans*-**4** (0.500 g. 2.00 mmol) in THF (10 mL) was added dropwise 4-(*tert*-butyldimethylsilyloxy)phenylmagnesium bromide (8.00 mmol) in THF (10 mL) under argon at -78 °C. The reaction mixture was slowly warmed to 25 °C, stirred for 1 day, and poured into saturated aqueous NH_4Cl (20 mL). The aqueous phase was extracted with Et_2O (3 x 30 mL). The combined organic phase was dried over $MgSO_4$ and concentrated in vacuo. To the residue dissolved in MeOH (5 mL) was added conc. aqueous NH_3 (2 mL) and $Cu(OAc)_2{\cdot}H_2O$ (0.160 g, 8.01 mmol). Oxygen was bubbled through the solution until its color became dark blue. After the solvent was evaporated, the residue was dissolved in saturated aqueous $NaHCO_3$ (20 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phase was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexane:Et_2O 8/2) to give of racemic *cis*-(*R**,*R**)-**2** (147 mg, 0.22 mmol, 11%) or *trans*-(*R**,*R**)-**2** (122 mg, 0.18 mmol, 9.2%) as a yellow solid.

(±)-*cis*-(*R**,*R**)-**2**: Mp 195.8- 197.9 °C (dec.). EPR (THF): $g = 2.0062$. IR (KBr): 2953, 2930, 2859, 1608, 1508, 1261, 1178, 1012, 920, 839, 804, 781. Anal. Calcd for $C_{38}H_{80}N_2O_4Si_2$: C, 68.63; H, 9.09; N, 4.21. Found: C, 68.67; H, 9.05; N, 4.28.

(±)-*trans*-(*R**,*R**)-**2**: Mp 198.1-201.0 °C (dec.). EPR (THF): $g = 2.0065$. IR (KBr): 2962, 2940, 2859, 1608, 1508, 1260, 1182, 1011, 924, 839, 808, 779. Anal. Calcd for $C_{38}H_{80}N_2O_4Si_2$: C, 68.63; H, 9.09; N, 4.21. Found: C, 68.80; H, 8.74; N, 4.28. The single crystal for X-ray crystallographic analysis was obtained from MeOH.

Compound **5:** To racemic *cis*-(*R**,*R**)-**2** or *trans*-(*R**,*R**)-**2** (100 mg, 0.150 mmol) dissolved in THF (5mL) was added TBAF (0.6 mL of 1 M THF solution) at 0 °C. After stirring for 1 h, the reaction mixture was poured into saturated aqueous NH_4Cl (20 mL), and the aqueous phase was extracted with Et_2O (3 x 30 mL). The combined organic phase was dried over $MgSO_4$, and concentrated in vacuo. Flash column chromatography (silica gel, CH_2Cl_2:Et_2O 8/2~7/3) of the residue gave racemic *cis*-(*R**,*R**)-**5** (57 mg, 87%) or *trans*-(*R**,*R**)-**5** (53 mg, 81%).

(±)-*cis*-(*R**,*R**)-**5**: Mp 195.1-196.3 °C (dec.). EPR (THF): $g = 2.0062$. IR (KBr): 3367, 2974, 2924, 2862, 1508, 1244, 1180, 833, 812. Anal. Calcd for $C_{26}H_{32}N_2O_4$: C, 71.53; H, 7.39; N, 6.42. Found: C, 71.41; H, 7.22; N, 6.49. The single crystal for X-ray crystallographic analysis was obtained from Et_2O.

(±)-*trans*-(*R**,*R**)-**5**: Mp 235.3-236.9 °C (dec.). EPR (THF): $g = 2.0066$. IR (KBr): 3368, 2954, 2930, 2858, 1508, 1261, 1179, 920,839, 804, 781. Anal. Calcd for $C_{26}H_{32}N_2O_4$: C, 71.53; H, 7.39; N, 6.42. Found: C, 71.27; H, 7.54; N, 6.32.

Crystallography. The X-ray crystallographic data were collected at 133, 113, 173, and 173 K, for *cis*-**3**, *trans*-**3**, *cis*-(*R**,*R**)-**5**, and *trans*-(*R**,*R**)-**2**, respectively, in a Rigaku RAXIS RAPID imaging plate. The crystal structures were solved by direct methods and refined by full-matrix least squares. All non-hydrogen atoms were refined anisotropically. All of the crystallographic calculations were performed by using the CrystalStructure software package. The summary of the fundamental crystal data for the structure determination is given in Table 1. The experimental details including data collection, data reduction, and structure solution and refinement as well as the atomic coordinates and Biso/Beq, anisotropic displacement parameters have been deposited in the Supporting Information. CCDC-742694, 742695, and 742912 contain the supplementary crystallographic data for *cis*-**3**, *trans*-**3**, and *cis*-(*R**,*R**)-**5** in this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk).

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