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Highly stereoselective synthesis of C_2-chiral and *meso* nitroxides from an optically active pyrrolidine

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Abstract

Starting from (2*R*,5*R*)-2,5-bis(methoxymethyl)pyrrolidine **1**, hydroxylamine *cis*-**3** was synthesized with high stereoselectivity by successive oxidation and addition of PhMgBr. By using PhLi, *trans* (C_2-chiral) pyrrolidine nitroxide *trans*-**7** was obtained from nitrone **5** derived from hydroxylamine **3**. The *cis* (*meso*) counterpart *cis*-**7** was produced along with *trans*-**7** when PhMgBr was employed in place of PhLi. Moreover, *cis*-**7** was also obtained selectively by using PhLi and Et_2AlCl with nitrone **5**. The change of stereochemical bias observed when EtMgBr and/or nitrone **10** bearing an ethyl group were employed is also discussed.

1. Introduction

Optically active nitroxides have been employed as chiral catalysts or reagents in the field of asymmetric synthesis, including oxidations of alcohols, trapping prochiral carbon radicals, and living polymerization.[1] They were also synthesized as the key components of paramagnetic chiral liquid crystals.[2] In particular, C_2-chiral nitroxides attract much attention because of their potential ability for excellent stereoregulation. Several C_2-chiral nitroxides have been prepared and they have been recently well reviewed by Braslau.[3] We now describe the synthesis of a new homochiral pyrrolidine nitroxide starting from an optically active pyrrolidine **1** bearing two symmetrically substituted methoxymethyl groups. Although our synthetic strategy is based fundamentally upon the reported procedure for the *trans* dimethyl analogue by Einhorn,[4] we achieved highly stereoselective syntheses of both the optically active *trans* (C_2-chiral) and the *cis* (*meso*) products. Recently, Braslau reported the synthesis of racemic *trans*-isoindoline nitroxide and the *cis* counterpart from an amine through a hydroxynitrone and from a phthalimide, respectively.[3]

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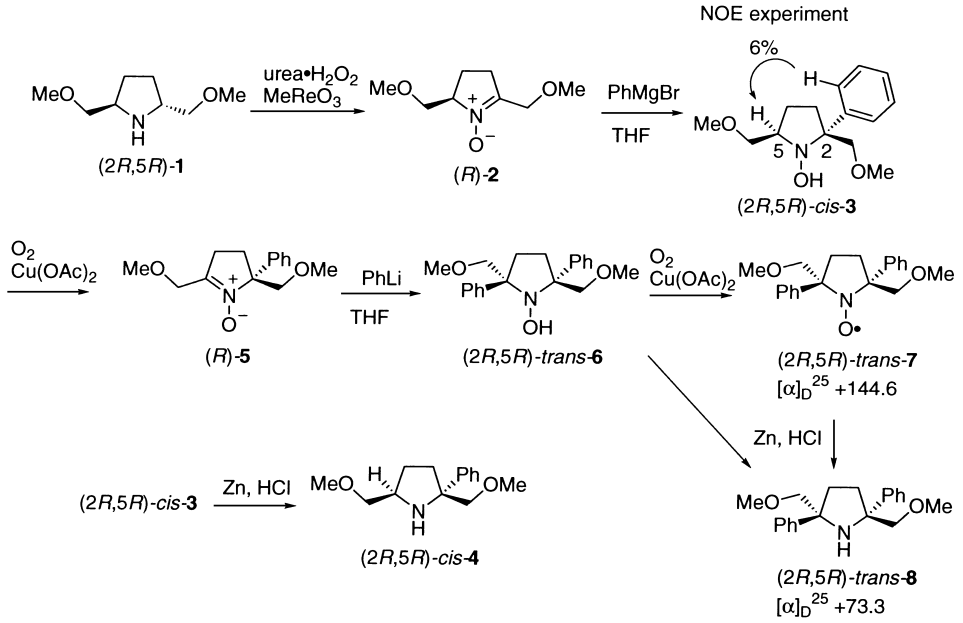
2. Results and discussion

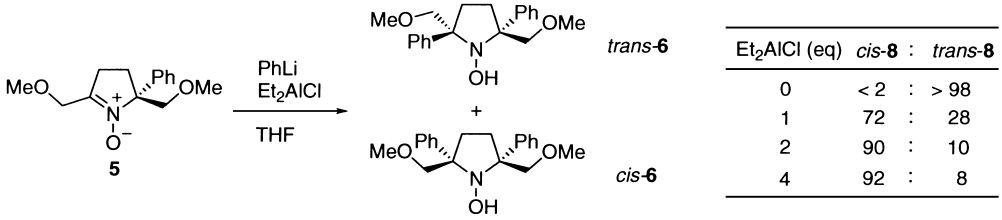
Oxidation of (2*R*,5*R*)-2,5-bis(methoxymethyl)pyrrolidine[5] **1** with $MeReO_3$/urea·H_2O_2 gave nitrone **2**.[6] Without purification, it was converted to hydroxylamine *cis*-**3** by the action of PhMgBr in THF (Scheme 1). In order to assess the *cis*/*trans* ratio of **3**, an aliquot of **3** was reduced with Zn/HCl to give pyrrolidine *cis*-**4**. The GC–MS analysis showed that *cis*-**4** contained a small amount (< 5%) of the *trans* counterpart. This contamination might lower the ee of nitrone **5** and therefore the ee of nitroxide *trans*-**7**. However, it proved not to be a problem because the ee of *trans*-**7** was easily increased by recrystallization. Hydroxylamine *cis*-**3** can be purified by silica gel column chromatography, but *cis*-**3** should not be purified because it was susceptible to air oxidation to nitrone **5**. The *cis* geometry of phenyl group to hydrogen atom at position 5 in hydroxylamine *cis*-**3** was proved by the NOE experiment as depicted in Scheme 1. Accordingly, the 2*R* configuration of *cis*-**3** was assigned based on the 5*R* configuration which was not affected by the oxidation and the Grignard reaction. The stereochemistry of the addition agrees with the model presented by Keana (Scheme 3, model A) that an organometallic reagent attacks the pyrrolidine nitrone from the less hindered site.[7] Hydoxylamine *cis*-**3** was oxidized with air in the presence of Cu(II) ion to nitrone **5** which was treated with two equivalent amounts of PhLi in THF to give hydroxylamine *trans*-**6**. This hydroxylamine was also susceptible to air oxidation and often contained a trace amount of nitroxide **7** which interfered with the NMR measurement for the unambiguous assignment of the configuration of *trans*-**6**. Without purification, *trans*-**6** was converted to nitroxide *trans*-**7** by air oxidation in the presence of Cu(II) ion. Nitroxide *trans*-**7** was obtained in an overall yield of 19% from amine **1** after silica gel chromatography followed by recrystallization from hexane. The ee of *trans*-**7** proved to be > 98% by chiral HPLC analysis on Chiralcel OD-H. A portion of nitroxide *trans*-**7** was converted to amine *trans*-**8** in order to carry out the unambiguous structure confirmation by the NMR measurement.



Scheme 1. Synthesis of C_2-chiral pyrrolidine nitroxide

In order to assess the stereoselectivity of PhLi attack on nitrone **5**, a portion of crude hydroxylamine **6** was reduced with Zn/HCl to give amine **8**. It was shown by the GC–MS measurement that the *trans* content of **8** was >98%. When PhMgBr was used in place of PhLi, the content of the *trans* form decreased to 67% in contrast to the high *trans* selectivity reported with the nitrone having Me group.[4] From the hydroxylamine thus obtained, nitroxide *cis*-**7** and amine *cis*-**8** were also prepared. The *cis* (*meso*) configuration of these compounds was established based on the observation that their specific rotations were essentially zero while the *trans* (chiral) counterparts *trans*-**7** and *trans*-**8** had significant values. Finally, the single crystal X-ray structure of nitroxide *trans*-**7** unambiguously established the *trans* geometry.

As to nitrones bearing ether functions, the change of stereochemistry in addition reactions of organometallics has been reported when Lewis acids are added into the reaction mixture.[8] In particular, Et_2AlCl was reported to change the stereochemistry significantly.[8c] In this context, we examined the effect of Et_2AlCl and found that the stereochemical bias of the addition of PhLi to nitrone **5** was reversed by the additive (Scheme 2). The *cis* content increased to 72% when the reaction was conducted with an equimolar amount of Et_2AlCl and the value finally reached 92% with 4 equivalents of the Lewis acid. These values were also determined by the GC–MS analysis of amine **8**. The addition of Et_2AlCl did not change the *cis*/*trans* ratio in the reaction by PhMgBr.

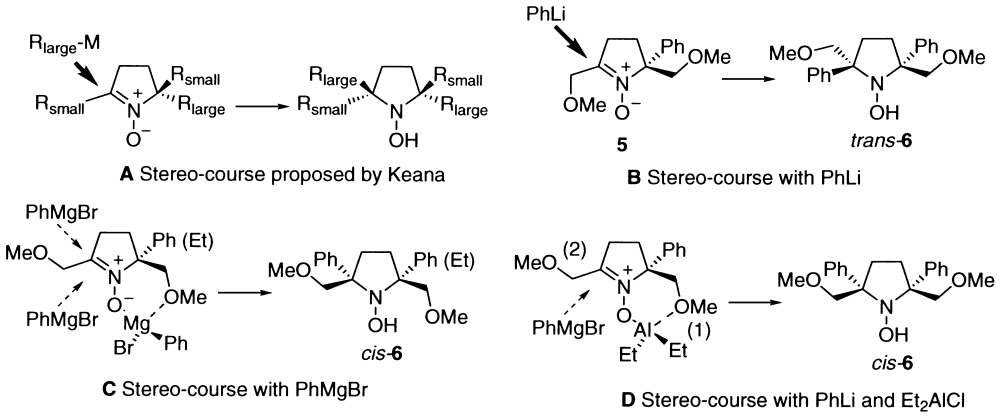


Et_2AlCl (eq)	*cis*-**8** :	*trans*-**8**
0	< 2 :	> 98
1	72 :	28
2	90 :	10
4	92 :	8

Scheme 2. Inversion of *cis*/*trans* selectivity with Et_2AlCl

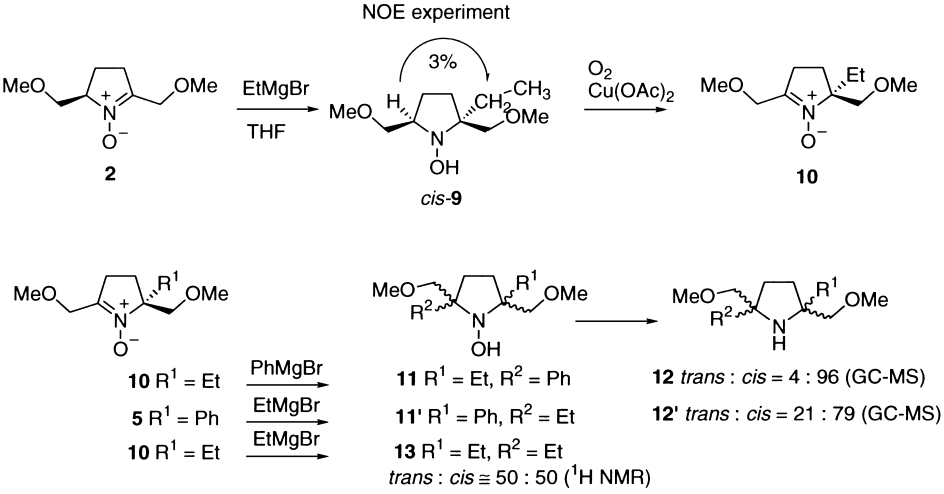
In previous reports,[8] the chelation of the Lewis acids with two oxygen atoms of nitrone and ether functions is proposed. Accordingly, the change of the steric course is ascribed to the change of the nitrone conformation generated by the chelate formation. In the present synthesis of hydroxylamine *trans*-**6**, when Et_2AlCl is absent, it is rational that PhLi attacked from the opposite direction of the phenyl group in the pyrrolidine ring because the phenyl group can be considered to be larger than the methoxymethyl group as depicted in Scheme 3 (model B).

When the Lewis acid coordinates to oxygen atom (1) in methoxymethyl group, the upper side in Scheme 3 becomes more crowded (model D). That is, the chelating methoxymethyl group is considered to be larger than the phenyl group in the pyrrolidine ring. Consequently, PhLi attacks from the same direction of the phenyl group in the ring to yield *cis*-**6**. An NMR titration experiment indicated that the Lewis acid coordinated to both the two ether oxygen atoms (1) and (2) in nitrone **5**. The other chelation structure formed with oxygen atom (2) and nitrone oxygen atom is considered not to affect the stereochemistry of the reaction. This estimation agrees with the fact that the *cis* selectivity was improved when Et_2AlCl dosage increased. The above chelation model also rationalizes the lower *trans* selective addition of PhMgBr to nitrone **5** (model C). As to the nitrone bearing ether functions, the similar chelation model has been proposed in which a molecule of the Grignard reagent coordinates to the oxygen atoms in the nitrone and another molecule of the Grignard reagent attacks on the nitrone from the less hindered side.[9]



Scheme 3. Direction of PhLi attack on nitrone

Next, we aimed to clarify the stereochemistry of the addition reaction to the nitrone bearing Et group which is considered to be less bulky than the methoxymethyl group. We examined the reaction with EtMgBr and found that the yields were comparable with those using PhMgBr (Scheme 4) although the lithium counterpart did not give the desired compounds. We here designate the isomers as *trans*- and *cis*-form which have the two methoxymethyl groups on the opposite side and on the same side of the pyrrolidine ring, respectively, regardless of the spatial relation of the other substituents. The stereochemical bias in the reaction between nitrone **2** and EtMgBr was almost same as the reaction with PhMgBr. That is, hydroxylamine *cis*-**9** was obtained as the major isomer (96%) whose geometry was proved by the NOE experiment as depicted in Scheme 4. The addition of PhMgBr to nitrone **10** gave hydroxylamine *cis*-**11** as the major product. The *cis*/*trans* ratio was also determined by GC–MS after converting it to amine **12**. The geometry of **12** was also assessed by the NOE experiment where the correlation between Ph and Et groups was observed. This result is consistent with model C in Scheme 3 because the Et group becomes much smaller than the methoxymethyl group coordinated with PhMgBr. On the other hand, EtMgBr



Scheme 4. Comparison of Et and Ph groups on Grignard reagents attack

attacked less selectively on nitrone **5** bearing a Ph group to give hydroxylamine **11′**. Although hydroxylamines **11** and **11′** as well as amines **12** and **12′** are depicted differently in Scheme 4, they are identical compounds and their *cis*/*trans* ratios are different. When nitrone **10** with an Et group was treated with EtMgBr, a ca. 50:50 mixture of *cis* and *trans* isomers of hyroxylamine **13** was obtained whose ratio was assessed by its ^{1}H NMR. It can be concluded that only the organometallic reagent bearing the bulky Ph group discriminates the bulkiness of the substituents at the opposite site of the pyrrolidine ring.

3. Experimental

3.1. General

All mp's were measured on a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with a JEOL alpha-500 (at 500 MHz to ^{1}H, 126 MHz to ^{13}C) and a JEOL-JNM-EX-270 (at 270 MHz to ^{1}H, 68 MHz to ^{13}C). *J* Values are given in hertz. IR spectra were recorded with a SHIMADZU FTIR-8600PC. ESR spectra were recorded with a JEOL JES-FE1XG. Optical rotation was measured with a JASCO DIP-1000 (with a 1 dm cell). HRMS were done with a JEOL JMS-DX-300. HPLC analyses were run on a JASCO 880-PU chromatographic system with an 875-UV detector (280 nm). GC–MS analyses were done on a SHIMADZU GCMS-QP5050A. Reactions with organometallics were conducted under argon atmosphere. The elemental analyses were performed by Kyoto University elemental analysis center.

3.2. (R)-3,4-Dihydro-2,5-bis(methoxymethyl)-2H-pyrrole 1-oxide **2**

A mixture of $MeReO_3$ (73 mg, 0.29 mmol), urea·H_2O_2 complex (10.7 g, 112 mmol) in MeOH (50 mL) was stirred at room temperature for 10 min and then cooled to 0°C. (2*R*,5*R*)-2,5-Bis(methoxymethyl)pyrrolidine **1** (2.30 g, 14.4 mmol) in MeOH (20 mL) was then added dropwise to this reaction mixture. After stirring at 0°C for 1 h and at room temperature for 12 h, the mixture was evaporated. The yellowish solid residue was washed with $CHCl_3$ (50 mL). The filtrate was concentrated to give **2** as a yellow oil (2.34 g) which was employed for the next step without purification. Compound **2**: $[\alpha]_D^{25} = +4.3$ (*c* 1.1, $CHCl_3$); δ_H (270 MHz, $CDCl_3$) 2.22 (dd, *J* 3.8, 11.3, 2H), 2.6–2.9 (m, 2H), 3.37 (s, 3H), 3.39 (s, 3H), 3.45–3.6 (m, 1H), 4.0–4.2 (m, 2H), 4.38 (s, 2H); δ_C (68 MHz, $CDCl_3$) 20.0, 28.3, 59.2, 59.3, 66.9, 70.4, 73.1, 146.5; ν_{max} (neat)/cm^{-1} 2827, 1661, 1117, 910.

3.3. (2R,5R)-1-Hydroxy-2,5-bis(methoxymethyl)-2-phenylpyrrolidine cis-**3**

A solution of PhBr (4.28 g, 27 mmol) in anhydrous THF (4 mL) was added to a suspension of Mg turnings (0.66 g, 28 mg-atom) in anhydrous THF (16 mL). This mixture was refluxed for 1 h to give PhMgBr solution. This solution was cooled at –78°C, and a solution of nitrone **2** (2.33 g, 14 mmol) in THF (14 mL) was added dropwise to it. The temperature was raised slowly to room temperature, and stirring was maintained overnight. The reaction mixture was then poured into a saturated NH_4Cl solution (30 mL). The mixture was extracted with $CHCl_3$ (30 mL×3). The combined organic extracts were dried over anhydrous $MgSO_4$, and the solvent was removed

under reduced pressure. The *cis*, *trans* mixture (3.36 g, *cis*:*trans* ≅20:1) was obtained. Pure *cis*-**3** (2.95 g, 81% overall yield from **1**) was obtained by silica gel column chromatography (75% EtOAc in hexane). *cis*-**3**: $R_f = 0.7$ (75% EtOAc in hexane); $[\alpha]_D^{25} = -4.7$ (*c* 1.4, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.7–1.8 (m, 1H), 1.9–2.1 (m, 1H), 2.1–2.2 (m, 1H), 2.3–2.4 (m, 1H), 3.0–3.1 (m, 1H), 3.32 (s, 3H), 3.34 (s, 3H), 3.4–3.6 (m, 2H), 3.7–4.0 (m, 2H), 7.2–7.5 (m, 5H); δ_C (126 MHz, $CDCl_3$) 23.8, 30.0, 59.0, 59.4, 63.6, 72.8, 74.4, 78.2, 125.4, 127.2, 127.8, 128.2, 139.0; ν_{max} (neat)/cm^{-1} 3377, 2826, 1113; HRFABMS, *m*/*z* found 252.1608 $(M+H)^+$, calcd for $C_{14}H_{21}NO_3$ 252.1601 $(M+H)^+$.

3.4. (R)-3,4-Dihydro-2,5-bis(methoxymethyl)-2-phenyl-2H-pyrrole 1-oxide 5

To a solution of hydroxylamine *cis*-**3** (1.71 g, 6.8 mmol) in methanol (8 mL), NH_4OH (28%, 1.7 mL) and $Cu(OAc)_2 \cdot H_2O$ (207 mg, 1.1 mmol) were added. Air was bubbled into the solution until a persistent deep blue color was observed (5 min). After evaporation, saturated $NaHCO_3$ (20 mL) was added to the residue. The mixture was extracted with $CHCl_3$ (20 mL×3). The combined extracts were dried over anhydrous $MgSO_4$ and evaporation gave **5** as an oil (0.49 g) which was employed for the next step without further purification. Compound **5**: $[\alpha]_D^{25} = +85.9$ (*c* 1.0, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 2.1–2.4 (m, 2H), 2.5–3.0 (m, 2H), 3.41 (s, 3H), 3.44 (s, 3H), 3.6–4.3 (m, 2H), 4.5 (br s, 2H), 7.2–7.5 (m, 5H); δ_C (126 MHz, $CDCl_3$) 26.1, 28.7, 59.2, 59.3, 67.1, 73.6, 83.0, 125.6, 127.9, 128.5, 139.1, 146.8; ν_{max} (neat)/cm^{-1} 2823, 1732, 1600, 1117.

3.5. (2R,5R)-2,5-Bis(methoxymethyl)-2,5-diphenylpyrrolidin-1-oxy radical trans-7

To a solution of PhLi in cyclohexane–diethyl ether (0.86 M, 14 mL, 12 mmol) and THF (10 mL), nitrone **5** (1.51 g, 6.0 mmol) in THF (20 mL) was added dropwise at –78°C. The temperature was raised slowly to room temperature, and stirring was maintained overnight. The reaction mixture was then poured into saturated NH_4Cl (30 mL). The mixture was extracted with $CHCl_3$ (30 mL×3). The combined organic extracts were dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to give *trans*-**6** (2.22 g). To a solution of *trans*-**6** (2.22 g) in methanol (30 mL), NH_4OH (28%, 2 mL) and $Cu(OAc)_2 \cdot H_2O$ (226 mg, 1.13 mmol) were added. Air was bubbled into the solution until a persistent deep blue color was observed (5 min). After evaporation, saturated $NaHCO_3$ (40 mL) was added to the residue. The mixture was extracted with $CHCl_3$ (30 mL×3). The combined extracts were dried over anhydrous $MgSO_4$ and evaporation gave crude *trans*-**7** (2.15 g). Pure *trans*-**7** (0.33 g, overall yield of 19% from **1**) was obtained by silica gel column chromatography (10% EtOAc in hexane) followed by recrystallization from hexane. *trans*-**7**: $R_f = 0.5$ (10% EtOAc in hexane); mp 134–136°C; $[\alpha]_D^{25}$ +144.6 (*c* 1.5, $CHCl_3$); >98% ee by chiral HPLC [Chiralcel OD-H (4 mm×25 cm), flow rate 0.5 mL/min, 280 nm], retention time/min 24.8 [(*R*,*R*)-*trans*-**7**], 27.5 [(*S*,*S*)-*trans*-**7**]; ν_{max} (film)/cm^{-1} 2893, 1452, 1103; HRFABMS, *m*/*z* found 326.1755 (M^+), calcd for $C_{20}H_{24}NO_3$ 326.1757 (M^+). Anal. found: C, 73.31; H, 7.40; N, 4.21; calcd for $C_{26}H_{24}NO_3$: C, 73.59; H, 7.41; N, 4.29; ESR (toluene) 3 lines, $a_N = 13.90$ G, $g = 2.006$.

3.6. cis-2,5-Bis(methoxymethyl)-2,5-diphenylpyrrolidin-1-oxy radical cis-7

To a solution of Grignard reagent obtained from PhBr (0.30 g, 1.9 mmol), Mg turnings (46 mg, 1.9 mg-atom) and anhydrous THF (4 mL), nitrone **5** (0.24 g, 0.96 mmol) in THF (6 mL) was added dropwise at –78°C. The same work-up as described above gave *cis*-**6** (0.36 g). From *cis*-**6**

(0.36 g), crude *cis*-**7** (0.36 g) was obtained according to the same procedure for *trans*-**7**. On silica gel column chromatography (10% EtOAc in hexane), *cis*-**7** (28 mg, overall yield of 7% from **1**) eluted after *trans*-**7** (56 mg, overall yield of 14% from **1**). *cis*-**7**: $R_f = 0.3$ (10% EtOAc in hexane); mp 49–51°C; $[\alpha]_D^{25} = 0.0$ (*c* 1.0, $CHCl_3$); ν_{max} (Nujol)/cm^{-1} 1111, 698; HRFABMS, *m*/*z* found 326.1742 (M^+), calcd for $C_{20}H_{24}NO_3$ 326.1757 (M^+). Anal. found: C, 73.47; H, 7.31; N, 4.05; calcd for $C_{26}H_{24}NO_3$: C, 73.59; H, 7.41; N, 4.29; ESR (toluene) 3 lines, $a_N = 13.81$ G, $g = 2.007$.

3.7. (2R,5R)-2,5-Bis(methoxymethyl)-2,5-diphenylpyrrolidine trans-**8**

A mixture of nitroxide *trans*-**7** (72 mg), water (19 mL), concentrated HCl (5 mL) and Zn powder (100 mg, 1.6 mg-atom) was refluxed under vigorous stirring until the yellow color of the nitroxide had disappeared (1 h). After cooling, the mixture was made alkaline (pH > 12) with NaOH (5%, 50 mL) and then extracted with ether (30 mL×3). The combined extracts were dried over anhydrous $MgSO_4$ and evaporated to afford *trans*-**8** (72 mg, 100%). An analytical sample was obtained by silica gel column chromatography (10% EtOAc in hexane). *trans*-**8**: $[\alpha]_D^{25} = +73.3$ (*c* 0.87, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.3–1.9 (br s, 1H), 2.1–2.2 (m, 2H), 2.2–2.4 (m, 2H), 3.14 (s, 6H), 3.25–3.36 (m, 4H), 7.2–7.3 (m, 2H), 7.3–7.4 (m, 4H), 7.5–7.6 (m, 4H); δ_C (126 MHz, $CDCl_3$) 35.4, 59.2, 68.5, 80.7, 126.3, 126.4, 127.9, 147.7; ν_{max} (neat)/cm^{-1} 3319, 2883, 1447, 1111; HRFABMS, *m*/*z* found 312.1971 $(M+H)^+$, calcd for $C_{20}H_{26}NO_2$ 312.1965 $(M+H)^+$.

3.8. cis-2,5-Bis(methoxymethyl)-2,5-diphenylpyrrolidine cis-**8**

From *cis*-**7** (46 mg), *cis*-**8** (44 mg, 100%) was obtained by the same procedure for *trans*-**8**. An analytical sample was obtained by silica gel column chromatography (10% EtOAc in hexane). *cis*-**8**: $[\alpha]_D^{25} = 0.0$ (*c* 1.0, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.26 (s, 1H), 1.9–2.1 (m, 2H), 2.2–2.3 (m, 2H), 3.33 (s, 6H), 3.50 (s, 4H), 7.0–7.65 (m, 10H); δ_C (126 MHz, $CDCl_3$) 34.9, 59.3, 68.4, 80.5, 126.0, 126.7, 127.6, 147.6; ν_{max} (neat)/cm^{-1} 3348, 3323, 2882, 1445, 1109; HRFABMS, *m*/*z* found 312.1969 $(M+H)^+$, calcd for $C_{20}H_{26}NO_2$ 312.1965 $(M+H)^+$.

3.9. (2R*,5S*)-1-Hydroxy-2-ethyl-2,5-bis(methoxymethyl)pyrrolidine cis-**9**

From **1** (550 mg), *cis*-**9** (548 mg, 78%) was obtained by the same procedure for *cis*-**3** where EtMgBr was employed in place of PhMgBr. *cis*-**9**: δ_H (500 MHz, $CDCl_3$) 0.9 (t, *J* 7.5, 3H), 1.4–1.5 (m, 3H), 1.6–1.7 (m, 1H), 1.8–1.9 (m, 1H), 1.9–2.0 (m, 1H), 3.2–3.3 (m, 1H), 3.28 (d, *J* 9.5, 1H), 3.35 (s, 3H), 3.37 (s, 3H), 3.43 (dd, *J* 5.5, 9.3, 1H), 3.44 (d, *J* 9.5, 1H), 3.55 (dd, *J* 5.5, 9.3, 1H); δ_C (126 MHz, $CDCl_3$) 9.1, 20.1, 22.8, 27.1, 59.2, 59.3, 63.5, 68.9, 75.7, 77.8.

3.10. (2R*,5R*)-2-Ethyl-2,5-bis(methoxymethyl)-5-phenylpyrrolidine cis-**12**

From *cis*-**9** (105 mg), *cis*-**12** (37 mg, 27%) was obtained through **10** by the same procedure for *cis*-**8**. *cis*-**12**: δ_H (500 MHz, $CDCl_3$) 0.8 (t, *J* 7.5, 3H), 1.4–1.5 (m, 2H), 1.5–1.6 (m, 1H), 1.7–1.8 (m, 1H), 2.0–2.1 (m, 1H), 2.1–2.2 (br, 1H), 2.2–2.3 (m, 1H), 3.25 (d, *J* 9.0, 1H), 3.26 (s, 3H), 3.32 (d, *J* 9.0, 3H), 3.3–3.4 (m, 2H), 3.39 (s, 3H), 7.1–7.2 (m, 1H), 7.2–7.3 (m, 2H), 7.5–7.6 (m, 2H); δ_C (126 MHz, $CDCl_3$) 9.0, 31.4, 33.2, 34.6, 59.2, 59.2, 65.1, 68.3, 77.8, 80.5, 126.2, 126.4, 126.6, 127.7, 147.7; HRFABMS (the corresponding nitroxide radical), *m*/*z* found 278.1754 (M^+), calcd for $C_{16}H_{24}NO_3$ 278.1757.

3.11. General procedure for determination of stereoselectivity of reactions yielding hydroxylamines **3**, **6**, **11**, and **13** — determination of cis/trans ratio of amines **4**, **8**, and **12**

The reactions of nitrones with organometallics, PhMgBr, PhLi or EtMgBr, were conducted as described in the synthesis of *cis*-**3**. As to the reaction with Et_2AlCl, it was added to the solution of nitrones before the addition of organometallics. The *cis*/*trans* ratio of hydroxylamine **13** was assessed by its ^1H NMR. A portion of hydroxylamines **3**, **6**, and **11** were reduced to amines **4**, **8**, and **12**, respectively, by the procedure described in *trans*-**8**. The crude products were analyzed by GC–MS to determine the *cis*/*trans* ratio [column: DB-5MS (J & W, 30 m×0.25 mm), initial temperature 50°C for 5 min, increasing rate 10°C/min for 20 min, final temperature 250°C, flow rate 1.7 mL/min]. Retention time/min 19.86 (*cis*-**4**), 19.92 (*trans*-**4**), 25.15 (*cis*-**8**), 25.18 (*trans*-**8**), 14.02 (*trans*-**12**), 14.13 (*cis*-**12**).

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