

Supplementary Material

Iterative organometallic addition to chiral hydroxylated cyclic nitrones: Highly stereoselective syntheses of α,α' - and α,α -substituted hydroxypyrrrolidines

Andrea Goti,^{*,†} Stefano Cicchi,[†] Vanni Mannucci,^{†,‡} Francesca Cardona,[†] Francesco Guarna,[†] Pedro Merino^{*,‡} and Tomas Tejero,[‡]

[†]*Dipartimento di Chimica Organica “Ugo Schiff”, Università di Firenze, via della Lastruccia 13, I-50019 Sesto Fiorentino (FI), Italy. E-mail: andrea.goti@unifi.it*

[‡]*Departamento de Química Orgánica, ICMA, Facultad de Ciencias, Universidad de Zaragoza-CSIC, E-50009 Zaragoza, Aragon, Spain. E-mail: pmerino@posta.unizar.es*

Experimental details and characterization data for the preparation of all compounds.

General Comments. The reaction flasks and other glass equipment were heated in an oven at 130 °C overnight and assembled in a stream of Ar. All reactions were monitored by TLC on silica gel 60 F₂₅₄; the position of the spots was detected with 254 nm UV light or by spraying with 5% ethanolic phosphomolybdic acid, iodine or 2.5% ethanolic *p*-anisaldehyde solution. *R*_f values refer to TLC on 0.25-mm silica gel plates (Merck F₂₅₄) with the same eluent used for separation of the compound by flash column chromatography. Preparative centrifugally accelerated radial thin-layer chromatography (radial chromatography) was performed with a Chromatotron® Model 7924 T (Harrison Research, Palo Alto, CA, USA); the rotors (1 or 2 mm layer thickness) were coated with silica gel Merck grade type 7749, TLC grade, with binder and fluorescence indicator (Aldrich 34,644-6) and the eluting solvents were delivered by the pump at a flow-rate of 0.5-1.5 mL min⁻¹. Preparative flash column chromatography was performed on columns of silica gel (40-60 microns). Melting points were measured with an RCH Kofler apparatus and are uncorrected. ¹H and ¹³C NMR spectra were recorded on a Varian Gemini (¹H, 200 MHz), a Varian Unity (¹H, 300 MHz), or Avance Bruker (¹H, 400 MHz) instruments. Chemical shifts are reported in ppm (δ) relative to the solvent used. Optical rotations were carried out with a Jasco DIP-370 polarimeter or a Perkin-Elmer 241 polarimeter. Elemental analysis was performed on a Perkin Elmer 240B microanalyzer or on a Perkin-Elmer 2400 instrument.

(2S,3S,4S)-3,4-Di-*tert*-butoxy-2-phenyl-*N*-hydroxypyrrrolidine (8). To a well-stirred solution of nitrone (*ent*)-1 (0.8 g, 3.49 mmol) in THF (25 mL) was added dropwise under argon atmosphere a 3.0 M ethereal solution of PhMgBr (2.91 mL, 8.73 mmol). When the addition is complete the reaction mixture is stirred at ambient temperature for

an additional 1 h at which time the reaction is quenched with a saturated aq solution of NaHCO₃. The organic layer is separated and the aqueous layer is extracted twice with Et₂O. The combined organic extracts were dried (MgSO₄), filtered and the solvent evaporated under reduced pressure to give the crude product. The NMR analysis of the crude product showed the presence of only one diastereomer to the limit of detectability. Purification by radial chromatography (Hexane/EtOAc, 5:1) gave pure **8** (1.07 g, 100%) as a white solid. Mp 75 °C. $[\alpha]_D^{20} = +62$ (*c* 1.0, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 7.47-7.32 (2H, m), 7.31-7.18 (3H, m), 5.6 (1H, bs), 3.98 (1H, ddd, *J* = 7.3, 3.9, 2.4 Hz), 3.77 (1H, dd, *J* = 8.3, 3.9 Hz), 3.57 (1H, d, *J* = 8.3 Hz), 3.37 (1H, dd, *J* = 10.3, 8.3 Hz), 3.20 (1H, dd, *J* = 10.3, 7.3 Hz), 1.20 (9H, s), 0.85 (9H, s). ¹³C NMR (75 MHz, CDCl₃) δ 139.6, 128.5, 128.1, 127.3, 83.5, 77.5, 75.3, 74.1, 73.8, 64.4, 28.7, 28.6. Anal Calcd. for C₁₈H₂₉NO₃: C, 70.32; H, 9.51; N 4.56. Found: C, 70.39; H, 9.51; N, 4.70.

(3S,4S,5R)-3,4-Di-*tert*-butoxy-5-phenyl-1-pyrroline N-oxide (9) and (3S,4S)-3,4-Di-*tert*-butoxy-2-phenyl-1-pyrroline N-oxide (10). Manganese (II) oxide (0.325 g, 3.52 mmol) was added in portions to an ice-cooled solution of **8** (0.9 g, 2.93 mmol) in CH₂Cl₂ (25 mL). The reaction was stirred for an additional 4 h at 0 °C. The solution was then filtered through Na₂SO₄ and concentrated under reduced pressure. The NMR analysis of the crude product revealed the presence of the two regioisomeric nitrones **9** and **10** in a 1.5:1 ratio, respectively. The crude product was purified by flash chromatography (hexane/EtOAc, 1:1) to give the pure products.

9: oil; (0.45 g, 42%); R_f = 0.14; $[\alpha]_D^{20} = -10$ (*c* 1.0, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 7.44-7.28 (5H, m), 6.93 (1H, t, *J* = 1.9 Hz), 4.64 (1H, d, *J* = 2.4 Hz), 4.55 (1H, t, *J* = 1.9 Hz), 4.08 (1H, t, *J* = 2.4 Hz), 1.23 (9H, s), 1.06 (9H, s). ¹³C NMR (75 MHz, CDCl₃) δ 135.0, 134.7, 128.8, 128.5, 84.2, 81.6, 78.1, 75.1, 74.9, 28.6, 28.3. Anal Calcd. for C₁₈H₂₇NO₃: C, 70.79; H, 8.91; N 4.59. Found: C, 70.85; H, 8.82; N, 4.48.

10: white solid; mp: 146-147 °C; (0.31 g, 29%); R_f = 0.25; $[\alpha]_D^{20} = -14$ (*c* 1.0, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 8.14-8.09 (2H, m), 7.39-7.30 (3H, m), 4.67 (1H, s), 4.49 (1H, dd, *J* = 14.2, 4.9 Hz), 4.00 (1H, d, *J* = 5.3 Hz), 3.83 (1H, d, *J* = 14.2 Hz), 1.19 (9H, s), 1.17 (9H, s). ¹³C NMR (75 MHz, CDCl₃) δ 140.7, 129.7, 128.4, 128.1, 128.0, 81.5, 75.1, 74.6, 70.9, 70.7, 28.9, 28.6. Anal Calcd. for C₁₈H₂₇NO₃: C, 70.79; H, 8.91; N 4.59. Found: C, 71.31; H, 9.05; N, 4.36.

(2S,3S,4S,5S)-3,4-Di-*tert*-butoxy-2-phenyl-5-[(2-trimethylsilyl)ethynyl]-*N*-hydroxypyrrolidine (12). To a solution of trimethylsilyl acetylene (0.58 mL, 4.02 mmol) in dry THF (10 mL) at -10 °C was added *n*-butyllithium (2.63 mL, 1.6 M in hexanes, 4.02 mmol). This solution was stirred for 15 min and then cooled to -80 °C. A cold (-80 °C) solution of nitrone **9** (0.25 g, 0.82 mmol) in THF (15 mL) was then quickly added with a cannula over a period of 15 min. The solution turned yellow and orange as the addition progressed. Stirring at -80 °C was continued for additional 15 min until all the nitrone was consumed (TLC). The reaction was quenched with saturated NH₄Cl (2 mL) and the result allowed to warm to room temperature. The reaction mixture was partitioned between Et₂O (25 mL) and saturated aqueous NH₄Cl (50 mL) and then shaken vigorously. The layers were separated and the aqueous layer was further extracted with Et₂O (3x25 mL). The organic extracts were combined, washed with brine, dried (MgSO₄) and filtered. The solvent was removed under reduced pressure to give a colorless oil (only one product was detected by NMR). The crude product was purified by radial chromatography (hexane/EtOAc, 5:1) to give the hydroxylamine **12** (0.248 g, 100%) as a clear oil. $[\alpha]_D^{20} = +48$ (*c* 1.0, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 7.38-7.35 (2H, m), 7.27-7.18 (3H, m), 5.10 (1H, br), 4.17 (1H, d, *J* = 2.0), 3.97 (1H, dd, *J* = 4.4, 2.0 Hz), 3.84 (1H, d, *J* = 8.3 Hz), 3.66 (1H, dd, *J* = 7.8, 3.9 Hz), 1.22 (9H, s), 0.80 (9H, s), 0.18 (3H, s). ¹³C NMR (75 MHz, CDCl₃) δ 138.7, 128.4, 128.1, 127.5, 100.8, 93.3, 82.2, 82.1, 74.5, 74.1, 73.8, 64.9, 28.6, 28.4, -0.1. Anal Calcd. for C₂₃H₃₇NO₃Si: C, 68.44; H, 9.24; N 3.47. Found: C, 68.59; H, 9.36; N, 3.29.

(2*R*,3*S*,4*S*)-3,4-Di-*tert*-butoxy-2-methyl-*N*-hydroxypyrrolidine (15). To a well-stirred solution of nitrone **1** (1.5 g, 6.55 mmol) in dry Et₂O (60 mL) was added dropwise under N₂ atmosphere a 3.0 M ethereal solution of MeMgBr (2.4 ml, 7.2 mmol). The reaction mixture is stirred at ambient temperature for 2 h at which time the reaction is quenched with a saturated aq solution of NaHCO₃ (15 mL). The organic layer is separated and the aqueous layer is extracted with Et₂O (3x20 mL). The combined organic extracts were dried (Na₂SO₄), filtered and the solvent evaporated under reduced pressure to give **15** (1.55 g, 100%) as an analytically pure white solid. Mp: 63-65 °C. $[\alpha]_D^{20} = -50.4$ (*c* 0.80, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 3.89 (1H, dt, *J* = 3.0, 6.5 Hz), 3.54 (1H, dd, *J* = 6.7, 3.4 Hz), 3.23 (1H, dd, *J* = 10.9, 2.4 Hz), 3.09 (1H, dd, *J* = 10.8, 7.2 Hz), 2.66 (1H, quintet, *J* = 6.7 Hz), 1.57 (3H, d, *J* = 6.6 Hz), 1.25 (9H, s), 1.19 (9H, s). ¹³C

NMR (50 MHz, CDCl_3) δ 81.3, 74.9, 73.2, 72.9, 66.7, 63.5, 27.9 (6C), 15.0. Anal Calcd. for $\text{C}_{13}\text{H}_{27}\text{NO}_3$: C, 63.64; H, 11.09; N, 5.71. Found: C, 63.58; H, 11.08; N, 5.89.

(3*R*,4*R*,5*R*)-3,4-Di-*tert*-butoxy-5-methyl-1-pyrroline *N*-oxide (16) and (3*R*,4*R*)-3,4-di-*tert*-butoxy-2-methyl-1-pyrroline *N*-oxide (17). Manganese (II) oxide (344 mg, 3.96 mmol) was added in portions to an ice-cooled solution of **15** (810 mg, 3.3 mmol) in CH_2Cl_2 (15 mL). The ice bath was removed and the reaction was stirred for an additional 18 h at rt. The solution was then filtered through Na_2SO_4 and concentrated under reduced pressure to give a crude yellow oil (quantitative yield). The NMR analysis of the crude product revealed the presence of the two regioisomeric nitrones **16** and **17** in a 2.3:1 ratio, respectively. A portion of the crude product (100 mg) was purified by flash chromatography (EtOAc/MeOH 50:1, then 30:1) to give samples of the pure nitrones **16** (R_f 0.53, EtOAc/MeOH 50:1) as an oil and **17** (R_f 0.31) as a solid.

16: $[\alpha]_D^{20} = -91.2$ (*c* 1.6, CHCl_3). ^1H NMR (200 MHz, CDCl_3) δ 6.83 (1H, d, *J* = 1.5 Hz), 4.46 (1H, d, *J* = 1.5 Hz), 3.81 (1H, d, *J* = 2.9 Hz), 3.76-3.69 (1H, qd, *J* = 6.6, 2.9 Hz), 1.57 (3H, d, *J* = 6.6 Hz), 1.25 (9H, s), 1.18 (9H, s). ^{13}C NMR (50 MHz, CDCl_3) δ 133.7, 80.0, 77.8, 75.6, 74.7, 74.6, 28.5 (3C), 28.2 (3C), 16.4. Anal Calcd. for $\text{C}_{13}\text{H}_{25}\text{NO}_3$: C, 64.16; H, 10.36; N, 5.76. Found: C, 64.05; H, 10.71; N, 5.89.

17: Mp: 83-86 °C. $[\alpha]_D^{20} = -35.8$ (*c* 3.7, CHCl_3). ^1H NMR (200 MHz, CDCl_3) δ 4.54-4.46 (1H, m), 4.28-4.12 (1H, m), 4.06-3.98 (1H, m), 3.80-3.66 (1H, m), 2.00 (3H, s), 1.25 (9H, s), 1.19 (9H, s). ^{13}C NMR (50 MHz, CDCl_3) δ 103.5, 81.1, 78.6, 74.2, 74.1, 67.7, 28.6 (3C), 28.5 (3C), 16.1. Anal Calcd. for $\text{C}_{13}\text{H}_{25}\text{NO}_3$: C, 64.16; H, 10.36; N, 5.76. Found: C, 64.02; H, 10.46; N, 5.26.

(2*R*,3*R*,4*R*,5*R*)-3,4-Di-*tert*-butoxy-2-methyl-5-(4-methoxyphenyl)-*N*-hydroxypyrrolidine (19) and (2*R*,3*R*,4*R*)-3,4-Di-*tert*-butoxy-2-(4-methoxyphenyl)-2-methyl-*N*-hydroxypyrrolidine (20). To a well-stirred solution of nitrones **16** and **17** (2.3:1 ratio, 50 mg, 0.21 mmol) in dry Et_2O (3 mL) was added dropwise at rt under N_2 atmosphere a 0.5 M THF solution of *p*-methoxyphenylmagnesium bromide (**18**, 0.44 mL, 0.22 mmol). When the addition is complete the reaction mixture is stirred at ambient temperature for an additional 2 h at which time the reaction is quenched with a saturated aq solution of NaHCO_3 (5 mL). The organic layer is separated and the aqueous layer is extracted with Et_2O (3x5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent evaporated under reduced pressure to give the crude product (51 mg, 73% yield). The NMR analysis of the crude product showed the

presence of the two hydroxylamines **19** and **20** in a 2.3:1 ratio. Purification by flash column chromatography (petroleum ether/EtOAc 8:1, then 6:1) gave pure **20** (R_f 0.32, petroleum ether/EtOAc 6:1, 10 mg, 14%) and **19** (R_f 0.21, petroleum ether/EtOAc 6:1, 35 mg, 50%), both as white solid compounds.

19: mp: 130-132 °C. $[\alpha]_D^{20} = -25.3$ (c 0.65, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 7.28-7.24 (2H, m), 6.84-6.80 (2H, m), 3.91 (1H, d, J = 5.9 Hz), 3.86 (1H, dd, J = 5.9, 2.3 Hz), 3.79 (3H, s), 3.66 (1H, t, J = 2.3 Hz), 3.40 (1H, dd, J = 6.7, 2.6 Hz), 1.31 (3H, d, J = 6.7 Hz), 1.25 (9H, s), 0.97 (9H, s). ^{13}C NMR (50 MHz, CDCl_3) δ 158.1, 131.0, 129.5 (2C), 112.7 (2C), 82.8, 81.7, 73.5, 73.2 (2C), 65.3, 54.5, 28.2 (6C), 10.1. Anal Calcd. for $\text{C}_{20}\text{H}_{33}\text{NO}_4$: C, 68.34; H, 9.46; N, 3.99. Found: C, 68.07; H, 9.50; N, 4.08.

20: mp: 108-110 °C. ^1H NMR (200 MHz, CDCl_3) δ 7.54-7.49 (2H, m), 6.88-6.84 (2H, m), 3.81 (3H, s), 3.77-3.72 (2H, m), 3.36-3.30 (2H, m), 1.40 (3H, s), 1.21 (9H, s), 0.83 (9H, s). ^{13}C NMR (50 MHz, CDCl_3) δ 158.7, 130.1, 127.6 (2C), 113.6 (2C), 83.5, 81.4, 75.1, 74.5, 68.0, 55.0, 49.5, 28.7 (3C), 28.6 (3C), 11.5. Anal Calcd. for $\text{C}_{20}\text{H}_{33}\text{NO}_4$: C, 68.34; H, 9.46; N, 3.99. Found: C, 68.13; H, 9.45; N, 4.11.

(2*R*,3*R*,4*R*,5*R*)-3,4-Dihydroxy-1,2-dimethyl-5-(4-methoxyphenyl)pyrrolidine ((-)-Codonopsinine, **14).** Methyl iodide (276 μL , 4.42 mmol) was added to a solution of **19** (120 mg, 0.34 mmol) in MeOH (5 mL) cooled into an ice bath. The solution was then heated at rt and stirred 20 h. Removal of the solvent and excess reagent under reduced pressure afforded the methylpyrrolidinium salt (150 mg) which was used for the next step without purification. The obtained salt was then dissolved in MeOH (5 mL), after which sat. NH_4Cl solution (9 mL), Zn dust (107 mg, 1.64 mmol), and catalytic In dust (8 mg, 0.072 mmol) were added. The resulting mixture was refluxed until all the starting salt was reacted (1.5 h, TLC control). After removal of the solvent under reduced pressure, the residue was treated with a sat. Na_2CO_3 solution (8 mL), extracted with Et_2O (3x10 mL) and dried over Na_2SO_4 . Concentration and removal of the solvent under reduced pressure afforded the protected codonopsinine [(2*R*,3*R*,4*R*,5*R*)-3,4-di-*tert*-butoxy-5-(4-methoxyphenyl)-1,2-dimethylpirrolydine] (90 mg, 76% from **19**), pure enough to be used for the final deprotection step. ^1H NMR (200 MHz, CDCl_3) δ 7.34-7.30 (2H, m), 6.90-6.86 (2H, m), 3.88 (1H, dd, J = 5.1, 2.2 Hz), 3.83 (3H, s), 3.62 (1H, t, J = 3.0 Hz), 3.48 (1H, d, J = 5.1 Hz), 3.21 (1H, qd, J = 6.6, 5.1 Hz), 2.82 (3H, s), 1.15 (3H, d, J = 6.6 Hz), 1.28 (9H, s), 0.98 (9H, s). ^{13}C NMR (50 MHz, CDCl_3) δ 158.0,

132.0, 129.0 (2C), 112.0 (2C), 86.5, 84.1, 73.0 (2C), 72.9, 63.8, 54.5, 34.5 (3C), 28.3 (3C), 10.1.

The diprotected codonopsinine (48 mg, 0.13 mmol) was dissolved in trifluoroacetic acid (2.5 mL) at 0 °C. After removal of the ice bath, the solution was stirred at rt 15 h. The crude oil obtained after removal of TFA under reduced pressure was dissolved in MeOH (2 mL) and was stirred 15 h in the presence of Ambersep 900-OH. The mixture was then filtered over Celite and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography, eluent CHCl₃/MeOH 4:1. The product collected with *R*_f 0.23 was then eluted with a 5% NH₃ solution (40 ml) from a DOWEX 50WX8 resin. (–)-Codonopsinine (**14**) (25 mg, 78%) was collected as a white solid after removal of the solvent under reduced pressure, with spectral and analytical properties in agreement with the literature.

14: mp: 166 °C. [α]_D²⁰ = -7.2 (c 0.1, MeOH) [lit.¹ mp: 169-170 °C; [α]_D²⁰ = -8.8 (c 0.1, MeOH)]. ¹H NMR (200 MHz, pyridine-*d*₅) δ 7.37-7.33 (2H, m), 6.62-6.58 (2H, m), 4.47 (1H, dd, *J* = 7.3, 4.4 Hz), 4.13 (1H, t, *J* = 4.4 Hz), 4.05 (1H, d, *J* = 7.3 Hz), 3.46 (1H, qd, *J* = 4.4, 7.3 Hz), 3.28 (3H, s), 1.97 (3H, s), 1.11 (3H, d, *J* = 7.3 Hz).²

(2S,3S)-3-tert-Butoxy-2-phenyl-N-hydroxypyrrolidine (21). To a well-stirred solution of nitrone **2** (0.1 g, 0.64 mmol) in THF (10 mL) was added dropwise under argon atmosphere a 3.0 M ethereal solution of PhMgBr (0.46 mL, 1.38 mmol). When the addition is complete the reaction mixture is stirred at ambient temperature for an additional 1 h at which time the reaction is quenched with a saturated aq solution of NaHCO₃. The organic layer is separated and the aqueous layer is extracted twice with Et₂O. The combined organic extracts were dried (MgSO₄), filtered and the solvent evaporated under reduced pressure to give the crude product. The NMR analysis of the crude product showed the presence of only one diastereomer to the limit of detectability. Purification by radial chromatography (Hexane/EtOAc, 4:1) gave pure **21** (0.143 g, 95%) as a white solid; mp: 68-69 °C; [α]_D²⁰ = -13 (c 1.0, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 7.32-7.28 (2H, m), 7.25-7.16 (3H, m), 6.03 (1H, br), 3.82 (1H, dt, *J* = 8.3, 3.9 Hz), 3.51 (1H, d, *J* = 7.8), 3.25 (1H, td, *J* = 8.3, 2.0 Hz), 3.05 (1H, q, *J* = 9.6 Hz), 2.20-2.00 (1H, m), 1.81-1.66 (1H, m), 0.88 (9H, s). ¹³C NMR (75 MHz, CDCl₃) δ 139.0, 128.0, 127.0, 78.5, 75.5, 73.5, 56.3, 31.5, 28.0. Anal Calcd. for C₁₄H₂₁NO₂: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.23; H, 9.10; N, 5.82.

(3S)-3-*tert*-Butoxy-2-phenyl-1-pyrroline N-oxide (22). Manganese (II) oxide (0.090 g, 1 mmol) was added in portions to an ice-cooled solution of **21** (0.149 g, 0.63 mmol) in CH₂Cl₂ (10 mL). The reaction was stirred for an additional 8 h at 0 °C. The solution was then filtered through Na₂SO₄ and concentrated under reduced pressure. The NMR analysis of the crude product revealed the presence of only regioisomer **22**. The crude product was purified by radial chromatography (EtOAc) to give pure **22** as a white solid; mp: 82 °C; [α]_D²⁰ = -1 (c 1.0, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 8.14-8.08 (2H, m), 7.31-7.18 (3H, m), 5.07 (1H, dt, J = 6.9, 2.2 Hz), 4.18 (1H, dddd, J = 15.8, 8.8, 6.9, 2.2 Hz), 3.83 (1H, ddd, J = 14.0, 9.2, 4.8 Hz), 2.33-2.17 (1H, m), 1.98-1.85 (1H, m), 1.09 (9H, s). ¹³C NMR (75 MHz, CDCl₃) δ 141.2, 129.7, 128.0 (2C), 126.8, 73.8, 62.7, 30.9, 28.8, 28.5. Anal Calcd. for C₁₄H₁₉NO₂: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.90; H, 8.40; N, 5.89.

Addition of trimethylsilyl cyanide to nitrone 22. To a solution of nitrone **22** (0.233 g, 1 mmol) in THF (10 mL) was added dropwise a 1.0 M solution of Et₂AlCl in hexanes (1 mL, 1 mmol). The resulting mixture was stirred for 5 min at ambient temperature and then cooled to -20 °C, at which time trimethylsilyl cyanide (0.100 g, 1 mmol) was added. After stirring for 2 h, the solvent was rotatory evaporated. The residue was taken up into 5% methanolic citric acid (10 mL) and the resulting mixture was stirred for 1 h, at which time saturated aqueous sodium bicarbonate (25 mL) was added. The reaction mixture was extracted with dichloromethane (3×15 mL) and the combined organic extracts were dried (MgSO₄) and evaporated to give the crude mixture of hydroxylamines **23** and **24** (see Table 1, entry 3), which was purified by radial chromatography.

Addition of diethylaluminium cyanide to nitrone 22. To a cooled (-20 °C) solution of nitrone **22** (0.233 g, 1 mmol) in THF (10 mL) was added diethylaluminium cyanide (0.333 g, 3 mmol). The resulting solution was stirred at ambient temperature for 2 h, at which time the reaction mixture was quenched by the addition of saturated aqueous sodium bicarbonate (15 mL). The resulting mixture was stirred for additional 5 min at ambient temperature and then extracted with CH₂Cl₂ (3×15 mL). The combined organic extracts were dried (MgSO₄) and evaporated to give the crude mixture of hydroxylamines **23** and **24** (see Table 1, entry 7). Separation of the diastereomers was performed by radial chromatography with a Chromatotron®.

(2R,3S)-3-tert-Butoxy-2-cyano-2-phenyl-N-hydroxypyrrolidine (23). Oil; $[\alpha]_D^{20} = +144$ (*c* 0.20, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 7.64-7.57 (2H, m), 7.44-7.33 (2H, m), 4.9 (1H, br), 4.24 (1H, dd, *J* = 7.8, 2.9 Hz), 3.60 (1H, td, *J* = 9.3, 1.9 Hz), 3.18 (1H, q, *J* = 9.3 Hz), 2.64-2.51 (1H, m), 1.98-1.84 (1H, m), 0.75 (9H, s). ^{13}C NMR (75 MHz, CDCl_3) δ 133.5, 128.8, 128.8, 127.8, 117.8, 75.6, 75.0, 72.6, 52.3, 31.4, 27.5. Anal Calcd. for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.20; H, 7.83; N, 10.49.

(2S,3S)-3-tert-Butoxy-2-cyano-2-phenyl-1-pyrroline N-oxide (24). White solid; mp: 143-145 °C; $[\alpha]_D^{20} = -10$ (*c* 0.25, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 7.68-7.58 (2H, m), 7.45-7.35 (3H, m), 4.75 (1H, br), 3.90 (1H, dd, *J* = 6.8, 1.9), 3.59 (1H, td, *J* = 9.3, 2.4 Hz), 3.54 (1H, td, *J* = 9.3, 3.4 Hz), 2.37-2.15 (1H, m), 2.14-1.94 (1H, m), 0.90 (9H, s). ^{13}C NMR (75 MHz, CDCl_3) δ 135.6, 128.8, 128.6, 126.5, 115.6, 78.1, 74.6, 53.4, 29.9, 29.7, 28.0. Anal Calcd. for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.12; H, 7.64; N, 10.68.

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