Glyoxal Bis-hydrazones: A New Family of Nitrogen Ligands for Asymmetric Catalysis

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Electronic Supplementary Information (ESI)

General Experimental Procedures: Melting points were determined using a metal block and are uncorrected. Optical rotations were measured at room temperature. ^{1}H and ^{13}C-NMR spectra were obtained in $CDCl_3$ as the solvent with either TMS (0.00 ppm ^{1}H, 0.00 ppm ^{13}C) or CDCl3 (7.26 ppm, 77.00 ppm 13C) as an internal reference. FT-IR spectra were recorded for KBr pellets or films. EI-mass spectra were recorded at 70 eV, using an ionizing current of 100 □A, an accelerating voltage of 4kV, and a resolution of 1000 or 10000 (10% valley definition). The reactions were monitored by TLC. Purification of the products was carried out by chromatography (silica gel). The light petroleum ether used had boiling range 40-65 ºC.

(2S, 5*S*)-1-amino-2,5-diphenylpyrrolidine 7: To a stirred, cooled (-20 °C) solution of MsCl (8 mL, 106 mmol) in CH_2Cl_2 (100 mL) was added dropwise a solution of (1*R*,4*R*)-1,4-diphenyl-1,4-butanediol[1] (10 g, 41.2 mmol) and Et_3N (7.4 mL, 124 mmol) in CH_2Cl_2 (100 mL). After stirring for 90 min. at –20 °C, satd. NH_4Cl (20 mL) was added, the organic layer was concentrated to a volume of 40 mL, diluted with AcOEt

[1] Aldous, D. J.; Dutton, W. M.; Steel, P. G. *Tetrahedron: Asymmetry* **2000**, *11*, 2455.

(150 mL), and washed with a 1:2:1 mixture of water, brine and satd. $NaHCO_3$ (4 × 100 mL) and satd. $NaHCO_3$ (2 × 100 mL). The organic layer was concentrated to a volume of 30 mL, cooled to 0 °C, and n-hexane (200 mL) was added dropwise to yield the product as white crystals. This material was suspended in isopropanol (40 mL), and hydrazine monohydrate (840 mmol, 20 eq.) was then added. After vigorous stirring for 4 days at 4 °C, the reaction was diluted with Et_2O (150 mL) and washed with satd. $NaHCO_3$ (2 × 50 mL) and brine (50 mL). The aqueous layer was extracted with Et_2O, and the combined organic layer was dried ($MgSO_4$) and concentrated to yield (*R*,*R*)-1-amino-2,5diphenylpirrolidine as an oil (92%). $[\alpha]^{20}_D$ +122.5 (*c* 0.36, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.02-2.07 (m, 2H), 2.44-2.52 (m, 2H), 4.10 (dd, *J* = 5.7, 4.2 Hz, 2H), 7.27-7.38 (m, 10H). ^{13}C NMR (75MHz, $CDCl_3$): δ 30.8, 69.6, 127.7, 128.7, 128.8, 141,6. Anal Calcd. for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61. Found: C, 80.78; H, 7.59.

(2S, 6*S*)-1-amino-2,6-diphenylpyperidine 8: Following the method described above for hydrazine **7**, but starting from (1*R*,5*R*)-1,5-diphenyl-1,5-pentanediol,[1] hydrazine **8** was obtained in 91% yield: $[\alpha]_D^{20}$ +74.5 (*c* 0.94, $CHCl_3$).); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.86-1.96 (m, 2H), 2.02-2.12 (m, 2H), 2.83 (br. s, 2H), 4.23 (dd, *J* = 6.4, 4.8 Hz, 2H), 7.22-7.48 (m,10H); ^{3}C NMR (100 MHz, $CDCl_3$): δ 19.3, 30.4, 65.6, 127.0, 128.4, 128.5, 142.8. Anal Calcd. for $C_{17}H_{20}N_2$: C, 80.91; H, 7.82; N,11.07. Found: C, C, 80.91; H, 7.99, N, 11.10.

Glyoxal bis-hydrazone 9

A solution of hydrazine **7** (19.4 mmol) and dry glyoxal[2] (9.24 mmol) was stirred in methanol (6 mL) at room temperature. After 1 hour, the mixture was filtered to afford **9** (54%) as a white powder. Flash chromatography (8:1 *n*-hexane/EtOAc + 1% Et_3N) of the mother liquors afforded an additional amount of product (14%). m.p. 193-194 °C; $[\alpha]_D^{20}$ -392.8 (*c* 1.05, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.63-1.71 (m, 4H), 2.40-2.51 (m, 4H), 4.48 (d, *J* = 6.8 Hz, 4H), 6.48 (s, 2H), 7.11-7.31 (m, 20H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.0, 64.8, 126.1, 126.7, 128.4, 133.3, 143,7. Anal calcd. for $C_{34}H_{34}N_4$: C, 81.89; H, 6.87; N, 11.24; found: C, 81.68 H, 6.67; N, 11.18.

Glyoxal bis-hydrazone 10

Following the procedure described above for bis-hydrazone **9**, but starting from hydrazine **8**, bis-hydrazone **10** (52%) was obtained as a white powder: M.p. 196-197 °C; $[\alpha]_D^{20}$ –251.1 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.45-1.51 (m, 4H), 1.91-2.03 (m, 8H), 4.83 (t, *J* = 5.5 Hz, 4H), 6.89 (s, 2H), 7.16-7.28 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.6, 60.7, 136.2, 126.3, 127.6, 128.1, 142,1. Anal calcd. for $C_{36}H_{38}N_4$: C, 82.09; H, 7.27; N, 10.64; found: C, 81.99 H, 7.32; N, 10.82.

General procedure for Diels-Alder cycloadditions:. A mixture $Cu(OTf)_2$ (0.04 mmol), **9** or *ent*-**9** (0.044 mmol), **1** (0.44 mmol), and activated 4Å molecular sieves (15 mg) was heated *in vacuo* at 50 °C for 20 min. The mixture was cooled to rt, solved in dry CH_2Cl_2 (0.5 mL), and cooled (Table 1). Freshly distilled diene **2**, **11-14** (2.20 mmol) was added and the mixture was stirred until consumption of **1** (tlc). Column

[2] G. Sheikhnejad, A. Brank, J. K. Christman, A. Goddard, E. Alvarez, H. Ford, Jr., V. E. Marquez, C. J. Marasco, J. R. Sufrin, M. O'Gara, X. Cheng *J. Mol. Biol.* **1999**, *285*, 2021.

chromatography (2:1 *n*-hexane/EtOAc) afforded recovered **9** (75-80%) and cycloadduct **6**, **15-18**. Compounds (*R*)-**6**,[3] (*R*)-**15**,[4] **16,**[5] and **18**[6] were characterized and identified by comparison with literature data. Characterization data for compound **17**: 92% ee by HPLC (Chiralpak AD, 2-propanol:hexane 10:90, 1.0 mL/min, 25 °C), *S*,*S* isomer 9.62 min, *R*,*R* isomer 10.85 min; $[\alpha]_D^{25}$ +51.0 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.38 (t, *J* = 7.8Hz, 2H), 4.0 (t, *J* = 7.8 Hz, 2H), 3.73-3.59 (m, 1H), 2.29-1.81 (m, 6H), 1.59 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176,9, 153.5, 125.6, 124.0, 62.2, 43.1, 39.3, 33.7, 31.4, 26.5, 19.3, 19.1. HRMS *m/z* calcd. for $C_{12}H_{17}NO_3$ 223.1208, found 223.1210.

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[4] Owens, T. D.; Hollander, F. J.; Oliver, A. G.; Ellman J. A. *J. Am. Chem. Soc.* **2001**, *123*, 1539.
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[6] Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D..; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7559.