Supporting Information

Cp*Ir Complex-Catalyzed *N*-Heterocyclization of Primary Amines with Diols: A New Catalytic System for Environmentally Benign Synthesis of Cyclic Amines

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Experimental Section:

General: All reactions and manipulations were carried out under an atmosphere of argon by means of standard Schlenk techniques. ¹H- and ¹³C-NMR spectra were recorded on JEOL A-500 and EX-270 spectrometers. Gas chromatography (GC) analyses were performed on a Shimadzu GC-14A gas chromatograph with a capillary column (Shimadzu CBP1-M25-025) and on a GL-Sciences GC353B gas chromatograph with a chiral capillary column (CP-Chirasil-Dex-CB). High-performance liquid chromatography (HPLC) analyses were performed with a TOSOH model CCPS pumping system and a TOSOH UV-8020 ultraviolet detector and a chiral column (Daicel CHIRALCEL OD-H). Optical

rotations were measured with a JASCO DIP-1000 polarimeter. Column chromatography was carried out by using Wako-gel C-200. Solvents were dried by using standard procedures and distilled prior to use. The catalyst $[\text{Cp}^*\text{IrCl}_2]_2$ was prepared according to the literature method.¹ 2-Phenyl-1,4-butanediol, 1-phenyl-1,5-pentanediol, and 2-(2-hydroxyethyl)benzyl alcohol were prepared by reduction of phenylsuccinic acid, 4-benzoylbutyric acid, and homophthalic acid with excess (4 equiv.) lithium aluminum hydride, respectively, according to the literature procedure.² All reagents, unless otherwise stated, are commercially available and were used as received.

General procedure for the synthesis of *N*-benzylpiperidine under various conditions shown in Table 1: Under an atmosphere of argon in a heavy-walled glass reactor, benzylamine (2.0 or 3.0 mmol), 1,5-pentanediol (2.0 mmol), $[\text{Cp}^*\text{IrCl}_2]_2$ (0.010 mmol, 1.0%Ir), base (0.020 mmol, 1.0%), and toluene (1.0 mL) were placed. The reactor was sealed, and the mixture was stirred at 90 or 110 °C for 17 h. The yield of *N*-benzylpiperidine was determined by GC analysis using undecane as an internal standard.

General procedure for the N-heterocyclization of primary amines with a variety of diols shown in Table 2: Under an atmosphere of argon in a heavy-walled glass reactor, amine (3.0 mmol), diol (2.0 mmol), $[\text{Cp}^*\text{IrCl}_2]_2$ (1.0 - 5.0%Ir), base (same equivalent to the iridium catalyst), and toluene (1.0 mL) were placed. The reactor was sealed, and the mixture was stirred at 110 °C for 17 h. After evaporation of the solvent, the products were isolated by column chromatography. The products were identified by spectral comparison with literature data.

¹ Ball, R. G.; Graham, W. A. G.; Heinekey, D. M.; Hoyano, J. K.; McMaster, A. D.; Mattson, B. M.; Michel, S. T. *Inorg. Chem.* **1990**, *29*, 2023.

² Padwa, A.; Gasdaska, J. R.; Haffmanns, G.; Rebello, H. *J. Org. Chem.* **1987**, *52*, 1027.

Shim, S. C.; Huh, K. T.; Park, W. H. <i>Tetrahedron</i> , 1986 , 42, 259.
Tillack, A.; Rudloff, I.; Beller, M. <i>Eur. J. Org. Chem.</i> , 2001 , 523.
Dickson, R. S.; Bowen, J.; Campi, E. M.; Jackson, W. R.; Jonasson, C. A. M.; McGrath, F. J.; Paslow, D. J.; Polas, A.; Renton, P.; Gladiali, S. <i>J. Mol. Catal. A: Chem.</i> 1999 , 150, 133.
Boga, C.; Manescalchi, F.; Savoia, D. <i>Tetrahedron</i> , 1994 , 50, 4709.
Pearson, W. H.; Fang, W. <i>J. Org. Chem.</i> , 1995 , 60, 4960.
Roussi, G.; Zhang, J. <i>Tetrahedron</i> , 1991 , 47, 5161.
Hattori, K.; Yamamoto, H. <i>Tetrahedron</i> , 1993 , 49, 1749.
Watanabe, Y.; Shim, S. C.; Uchida, H.; Mitsudo, T.; Takegami, Y. <i>Tetrahedron</i> , 1979 , 35, 1433.
Perrio-Huard, C.; Aubert, C.; Lasne, M.-C. <i>J. Chem. Soc., Perkin Trans. 1</i> , 2000 , 311.
Cooper, M. S.; Fairhurst, R. A.; Heaney, H.; Papageorgiou, G.; Wilkins, R. F. <i>Tetrahedron</i> , 1989 , 45, 1155.
Ishikawa, T.; Uedo, E.; Tani, R.; Saito, S. <i>J. Org. Chem.</i> , 2001 , 66, 186.
Wolfe, J. P.; Buchwald, S. L. <i>J. Org. Chem.</i> , 1997 , 62, 1264.
Shim, S. C.; Huh, K. T.; Park, W. H. <i>Tetrahedron</i> , 1986 , 42, 259.
Fisher, G. B.; Fuller, J. C.; Harrison, J.; Alvarez, S. G.; Burkhardt, E. R.; Goralski, C. T.; Singaram, B. <i>J. Org. Chem.</i> , 1994 , 59, 6378.

^1H NMR (500 MHz, CDCl_3): δ 1.79 (m, 4H), 2.50 (m, 4H), 3.61 (s, 2H), 7.22-7.34 (m, 5H). ^{13}C NMR (125.7 MHz, CDCl_3): δ 23.4 (CH_2), 54.2 (CH_2), 60.8 (CH_2), 126.8 (CH), 128.2 (CH), 128.9 (CH), 139.4 (C).

^1H NMR (270 MHz, CDCl_3): δ 1.40 (m, 2H), 1.54 (m, 4H), 2.34 (m, 4H), 3.43 (s, 2H), 7.18-7.33 (m, 5H). ^{13}C NMR (67.8 MHz, CDCl_3): δ 24.5 (CH_2), 26.1 (CH_2), 54.5 (CH_2), 63.9 (CH_2), 126.7 (CH), 127.9 (CH), 129.1 (CH), 138.5 (C).

^1H NMR (270 MHz, CDCl_3): δ 1.60 (br, 8H), 2.58 (br, 4H), 3.61 (s, 2H), 7.16-7.33 (m, 5H). ^{13}C NMR (67.8 MHz, CDCl_3): δ 27.1 (CH_2), 28.3 (CH_2), 55.5 (CH_2), 62.7 (CH_2), 126.5 (CH), 127.9 (CH), 128.5 (CH), 139.9 (C).

^1H NMR (270 MHz, CDCl_3): δ 0.95 (d, $J = 6$ Hz, 3H, trans isomer), 1.03 (d, $J = 6$ Hz, 3H, cis isomer), 1.30- 2.00 (m), 2.56 (m, 2H, cis isomer), 3.02 (m, 2H, trans isomer), 3.65 (AB q, 2H, trans isomer), 3.71 (s, 2H, cis isomer), 7.17-7.37 (m). ^{13}C NMR (125.7 MHz, CDCl_3): δ 17.0 (CH_3 , trans isomer), 20.6 (CH_3 , cis isomer), 30.9 (CH_2 , trans isomer), 31.2 (CH_2 , cis isomer), 51.6 (CH_2 , trans isomer), 54.9 (CH , trans isomer), 55.1 (CH_2 , cis isomer), 59.6 (CH , cis isomer), 126.4 (CH , trans isomer), 126.5 (CH , cis isomer), 127.8 (CH , cis isomer), 128.0 (CH , trans isomer), 128.4 (CH , trans isomer), 129.2 (CH , cis isomer), 139.3 (C, cis isomer), 140.8 (C, trans isomer).

^1H NMR (500 MHz, CDCl_3): δ 1.16 (d, $J = 6$ Hz, 3H), 1.23-1.66 (m, 6H), 1.94 (m, 1H), 2.30 (m, 1H), 2.73 (m, 1H), 3.19 (d, $J = 13$ Hz, 1H), 3.99 (d, $J = 13$ Hz, 1H), 7.20-7.33 (m, 5H). ^{13}C NMR (125.7 MHz, CDCl_3): δ 19.5 (CH_3), 24.0 (CH_2), 26.0 (CH_2), 34.7 (CH_2), 52.1 (CH_2), 56.3 (CH), 58.5 (CH_2), 126.6 (CH), 128.0 (CH), 129.1 (CH), 139.5 (C).

^1H NMR (270 MHz, CDCl_3): δ 1.89 (m, 1H), 2.31 (m, 1H), 2.49 (dd, $J = 9, 8$ Hz, 1H), 2.66 (m, 1H), 2.80 (m, 1H), 3.01 (dd, $J = 9, 8$ Hz, 1H), 3.34 (m, 1H), 3.65 (s, 2H), 7.13-7.36 (m, 10H). ^{13}C NMR (67.8 MHz, CDCl_3): δ 33.3 (CH_2), 43.2 (CH), 54.4 (CH_2), 60.4 (CH_2), 62.1 (CH_2), 125.7 (CH), 126.6 (CH), 127.0 (CH), 127.9 (CH), 128.1 (CH), 128.4 (CH), 139.0 (C), 145.3 (C).

¹H NMR (270 MHz, CDCl₃): δ 1.20-1.96 (m, 7H), 2.78 (d, J = 14 Hz, 1H), 2.96 (d, J = 11 Hz, 1H), 3.09 (dd, J = 11, 3 Hz, 1H), 3.76 (d, J = 14 Hz, 1H), 7.14-7.46 (m, 10H). ¹³C NMR (67.8 MHz, CDCl₃): δ 25.3 (CH₂), 26.1 (CH₂), 37.1 (CH₂), 53.4 (CH₂), 59.8 (CH₂), 69.2 (CH), 126.4 (CH), 126.7 (CH), 127.3 (CH), 127.9 (CH), 128.4 (CH), 128.5 (CH), 139.7 (C), 145.6 (C).

^1H NMR (500 MHz, CDCl_3): δ 3.92 (s, 2H), 3.95 (s, 4H), 7.18-7.42 (m, 9H). ^{13}C NMR (125.7 MHz, CDCl_3): δ 58.9 (CH_2), 60.3 (CH_2), 122.3 (CH), 126.7 (CH), 127.2 (CH), 128.4 (CH), 128.8 (CH), 138.9 (C), 140.0 (C).

^1H NMR (500 MHz, CDCl_3): δ 2.73 (t, $J = 6$ Hz, 2H), 2.89 (t, $J = 6$ Hz, 2H), 3.62 (s, 2H), 3.67 (s, 2H), 6.96-7.40 (m, 9H). ^{13}C NMR (125.7 MHz, CDCl_3): δ 29.1 (CH_2), 50.6 (CH_2), 56.1 (CH_2), 62.8 (CH_2), 125.5 (CH), 126.0 (CH), 126.6 (CH), 127.1 (CH), 128.3 (CH), 128.7 (CH), 129.0 (CH), 134.4 (C), 134.9 (C), 138.4 (C).

¹H NMR (500 MHz, CDCl₃): δ 2.40 (t, J = 4 Hz, 4H), 3.42 (s, 2H), 3.68 (t, J = 4 Hz, 4H), 3.77 (s, 3H), 6.83-6.86 (m, 2H), 7.20-7.23 (m, 2H). ¹³C NMR (125.7 MHz, CDCl₃): δ 53.4 (CH₂), 55.0 (CH₃), 62.7 (CH₂), 66.8 (CH₂), 113.5 (CH), 129.6 (C), 130.2 (CH), 158.6 (C).

^1H NMR (270 MHz, CDCl_3): δ 1.97 (m, 4H), 3.25 (m, 4H), 6.53-7.24 (m, 5H). ^{13}C NMR (67.8 MHz, CDCl_3): δ 25.5 (CH_2), 47.5 (CH_2), 111.5 (CH), 115.2 (CH), 128.9 (CH), 147.8 (C).

^1H NMR (270 MHz, CDCl_3): δ 1.95 (m, 4H), 3.20 (m, 4H), 3.74 (s, 3H), 6.49-6.56 (m, 2H), 6.80-6.87 (m, 2H). ^{13}C NMR (67.8 MHz, CDCl_3): δ 25.4 (CH_2), 48.2 (CH_2), 56.0 (CH_3), 112.5 (CH), 114.9 (CH), 143.1 (C), 150.6 (C).

^1H NMR (270 MHz, CDCl_3): δ 1.78 (m, 4H), 2.54 (m, 4H), 2.63-2.85 (m, 4H), 7.12-7.28 (m, 5H). ^{13}C NMR (67.8 MHz, CDCl_3): d 23.3 (CH_2), 35.7 (CH_2), 54.0 (CH_2), 58.2 (CH_2), 125.6 (CH), 128.0 (CH), 128.2 (CH), 140.1 (C).

^1H NMR (270 MHz, CDCl_3): δ 0.88 (t, $J = 7$ Hz, 3H), 1.28 (br, 10H), 1.51 (br, 2H), 1.77 (m, 4H), 2.38-2.50 (m, 6H). ^{13}C NMR (67.8 MHz, CDCl_3): δ 14.2 (CH_3), 22.7 (CH_2), 23.5 (CH_2), 27.8 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.6 (CH_2), 31.9 (CH_2), 54.3 (CH_2), 56.8 (CH_2).

Procedure for the asymmetric synthesis of (*S*)-phenylpiperidine shown in Scheme 1: Under an atmosphere of argon in a heavy-walled glass reactor, (*R*)-1-phenylethylamine (99%ee) (1.0 mmol), 1-phenyl-1,5-pentanediol (1.0 mmol), [Cp*IrCl₂]₂ (3.0%Ir), KOAc (6.0%), and toluene (0.1 mL) were placed. The reactor was sealed, and the mixture was stirred at 100 °C for 17 h. The yields of *N*-(1-phenylethyl)-2-phenylpiperidines **4** and **5** were determined by GC analysis using undecane as an internal standard. The enantiomeric excesses of **4** and **5** were determined by chiral GC analysis.

data for [*N*-(*R*)-(1-phenylethyl)-(*S*)-2-phenylpiperidine] (**4**, major isomer): ¹H NMR(500 MHz, CDCl₃): δ 1.18 (d, 3H, *J* = 7 Hz), 1.30 - 1.39 (m, 1H), 1.44 - 1.52(m, 1H), 1.55 - 1.56(m, 1H), 1.63 - 1.71(m, 1H), 1.76 - 1.79(m, 2H), 2.22 (td, 1H, *J* = 12, 3 Hz), 2.56 (d, 1H, *J* = 12 Hz), 3.50 (dd, 1H, *J* = 11, 3 Hz), 3.83 (q, 1H, *J* = 7 Hz), 7.16 - 7.24 (m, 2H), 7.27 - 7.33 (m, 4H), 7.43 - 7.48 (m, 4H). ¹³C NMR (125.7 MHz, CDCl₃): δ 8.1 (CH₃), 25.6 (CH₂), 26.3 (CH₂), 37.2 (CH₂), 45.1 (CH₂), 54.9 (CH), 65.6 (CH), 126.0 (CH), 126.9 (CH), 127.49 (CH), 127.52 (CH), 127.7 (CH), 128.5 (CH), 144.7 (C), 145.2 (C). Anal. Calcd for C₁₉H₂₃N: C, 85.99; H, 8.74; N, 5.28. Found: C, 85.82; H, 8.76; N, 5.23.

data for [*N*-(*R*)-(1-phenylethyl)-(*R*)-2-phenylpiperidine] (**5**, minor isomer): ¹H NMR(500 MHz, CDCl₃): δ 1.07 - 1.19 (m, 1H), 1.36 (d, 3H, *J* = 7 Hz), 1.45 - 1.65 (m, 5H), 1.74 (td, 1H, *J* = 12, 2 Hz), 3.11 (m, 2H), 3.94 (q, 1H *J* = 7 Hz), 7.01 - 7.03 (m, 2H), 7.21 - 7.31 (m, 4H), 7.36 - 7.43 (m, 4H). ¹³C NMR(125.7 MHz, CDCl₃): δ 18.5 (CH₃), 25.1 (CH₂), 26.3 (CH₂), 38.2 (CH₂), 45.8 (CH₂), 56.6 (CH), 65.8 (CH), 126.61 (CH), 126.65 (CH), 127.4 (CH), 127.6 (CH), 128.5 (CH), 128.9 (CH), 138.7 (C), 146.1 (C).

A crude mixture of **4** and **5** (filtered through a pad of silica-gel after the reaction above), Pd on carbon (10%Pd) (270 mg), ethanol (3.5 mL), and 6N HCl_{aq} (0.35 mL) were placed in a flask. The atmosphere was changed to hydrogen, and the mixture was stirred for 14.5 h at 65 °C. After filtration, the yield of 2-phenylpiperidine was determined by GC analysis using decane as an internal standard. The enantiomeric excesses of 2-phenylpiperidine was determined by chiral HPLC analysis. The product

2-phenylpiperidine was identified by spectral comparison with literature data.³

Optical rotation was measured and determined to be levorotatory $\{[\alpha]_{\text{D}}^{28} -37.3 (c\ 0.31, \text{CH}_2\text{Cl}_2)\}$. In the literature, the optical rotation of (*R*)-2-phenylpiperidine has been reported to be dextrorotatory $\{[\alpha]_{\text{D}}^{23} +48.4 (c\ 0.31, \text{CH}_2\text{Cl}_2),^3 [\alpha]_{\text{D}}^{20} +50.0 (c\ 0.31, \text{CH}_2\text{Cl}_2)\}^4$. Thus, it is evident that the present *N*-heterocyclization reaction afforded the (*S*)-2-phenylpiperidine.

data for 2-phenylpiperidine: ¹H NMR (270 MHz, CDCl₃): δ 1.48-1.90 (m, 6H), 2.79 (m, 1H), 3.19 (d, *J* = 11 Hz, 1H), 3.58 (d, *J* = 11 Hz, 1H), 7.20-7.38 (m, 5H). ¹³C NMR (125.7 MHz, CDCl₃): δ 25.4 (CH₂), 25.9 (CH₂), 35.0 (CH₂), 47.8 (CH₂), 62.4 (CH), 126.6 (CH), 127.0 (CH), 128.4 (CH), 145.6 (C).

³ Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952.

⁴ Davis, F. A.; Chao, B.; Fang, T.; Szewczyk, J. M. *Org. Lett.* **2000**, *2*, 1041.