Enantioselective, Palladium-Catalyzed α -Arylation of *N*-Boc-pyrrolidine

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General

All reagents were used directly from a commercial source without any further purification. Solvents were found to contain 50 ppm water or less via Kf titration. *sec*-BuLi was titrated against *N*-pivaloyl-*o*-toluamide before use. ZnCl₂ was purchased as a 1 M solution on Et₂O and used directly. All reactions were performed under a nitrogen atmosphere using glassware stored at ambient temperature and humidity. Flash column chromatography was performed with Silica gel 60 (0.04-0.063 mm particle size). Thin layer chromatography was performed with Silica Gel 60 F₂₅₄ precoated plates (2.5x7.5 cm, 250 um thickness). ¹H and ¹³C NMR spectra were recorded on a Bruker Avance DRX 500 using an internal deuterium lock. Unless otherwise indicated, samples were acquired using CDCl₃ as solvent at -20 °C to sharpen the resonance signals for characterization. Chemical shifts are quoted in parts per million (ppm) and referenced to the solvent signal (CHCl₃ and CDCl₃ for ¹H and ¹³C, respectively). ¹³C NMR spectra were recorded with composite pulse (Waltz16) proton decoupling. Chemical ionization and high resolution mass spectra were acquired on a Micromass QTOF Ultima API US mass spectrometer using electrospray ionization in the positive ion mode. Optical rotations were recorded at 20 °C on a Perkin Elmer 241 Polarimeter using a cell length of 1.0 dm. [α]_D was calculated according to the following equation:

$$[\alpha]_D = \alpha_{(\text{observed})} / (d * c)$$

where *d* refers to the cell length in decimeters and *c* refers to the concentration in g/mL.

Chiral stationary phase HPLC was performed on a Agilent Series 1100 HPLC using a Chiralpak AD-H column (0.3x150 mm, 5 um) with Heptane and *i*-PrOH as eluents. Signals were recorded at both 210 nm and 250 nm.

General Procedure: Asymmetric deprotonation/transmetalation/Negishi coupling

To a solution of *N*-Boc-pyrrolidine **1** (1.0 mL, 5.7 mmol) and (-)-sparteine (1.3 mL, 5.7 mmol) in MTBE (12 mL) at -78 °C was added *s*-BuLi (1.2 M in cyclohexane, 4.8 mL, 5.7 mmol) dropwise, keeping the temperature below -68 °C. The resulting solution was aged for 3 h at -74 °C. A solution of ZnCl₂ (1 M in Et₂O, 3.4 mL, 3.4 mmol) was added to the reaction dropwise with rapid stirring, keeping the temperature below -68 °C. The resulting light suspension was aged at -74 °C for 30 minutes and then warmed to 20 °C. The resulting homogeneous solution was aged for 30 minutes at 20 °C, and then was charged with arylbromide (4.75 mmol) followed by Pd(OAc)₂ (51 mg, 0.23 mmol), and *t*Bu₃P-HBF₄ (83 mg, 0.285 mmol) in one portion. The mixture, which precipitated zinc salts during the course of the reaction, was aged overnight in a water bath at 20 °C. To facilitate the filtration, 350 µL of NH₄OH was added, and the mixture was aged for 1h. The resulting slurry was filtered over Celite and washed with 60 mL MTBE. The filtrate was washed with 50 mL of 1 M HCl and then twice with 50 mL deionized water. The organic layer was dried over sodium sulfate, filtered, and concentrated. Purification of products was accomplished by flash chromatography.

***N*-Boc-(*R*)-2-phenylpyrrolidine (4a).** Prepared according to the general procedure on 4.75 mmol scale. Purification by flash chromatography (80:20 CH₂Cl₂:Hexanes to 90:10 CH₂Cl₂:Hexanes) provided **4a** (962 mg, 82% yield) as a crystalline white solid. mp=61.9-62.7 °C; [α]_D= +85.3 (*c*=0.019, acetone); ¹H NMR (499.87 MHz, CDCl₃, -20 °C) 1:2.2 ratio amide bond rotamers: δ 7.32-7.29 (om, 2H), 7.22 (m, 1H), 7.17 (m, 2H), 4.96 (dd, *J*=8.0, 2.8 Hz, 0.3H), 4.75 (dd, *J*=8.0, 4.8 Hz, 0.7H), 3.67-3.58 (om, 1.7H), 3.49 (dt, *J*=10.3, 8.0 Hz, 0.3H), 2.36-2.22 (om, 1H), 1.96-1.77 (om, 3H), 1.45 (s, 2.8H), 1.16 (s, 6.2H); ¹³C NMR (125.69 MHz, CDCl₃, -20 °C) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis (): δ 154.70 (154.60), 145.10 (144.00), (128.47) 128.17, (126.66) 126.54, 125.56 (125.31), (79.38) 79.26, 61.30 (60.60), (47.38) 47.12, 36.13 (34.95), (28.56) 28.16, (23.40) 23.25; Exact mass calculated for C₁₅H₂₁NO₂+H requires *m/z* 248.1651, found *m/z* 248.1655.

Separation of enantiomers was accomplished using chiral HPLC: Chiralpak AD-H (99:1 Heptane:*i*PrOH, 0.5 mL/min), (*R*)-**4a** 10.8 min, (*S*)-**4a** 11.4 min.

N-Boc-(*R*)-2-(4-fluorophenyl)pyrrolidine (4b). Prepared according to the general procedure on 4.75 mmol scale. Purification by flash chromatography (85:10:5 CH₂Cl₂:Hexanes:MTBE) provided **4b** (945 mg, 75% yield) as a solid. mp=68.2-69.2 °C; [α]_D= +75.7 (*c*=0.021, acetone); ¹H NMR (499.87 MHz, CDCl₃, -20 °C) 1:1.9 ratio amide bond rotamers: δ 7.14-7.10 (om, 2H), 6.99-6.95 (om, 2H), 4.90 (dd, *J*=8.0, 2.8 Hz, 0.3H), 4.72 (dd, *J*=8.0, 5.2 Hz, 0.7H), 3.64-3.55 (om, 1.7H), 3.47 (dt, *J*=10.7, 7.6 Hz, 0.3H), 2.34-2.20 (om, 1H), 1.93-1.71 (om, 3H), 1.43 (s, 3H), 1.16 (s, 6H); ¹³C NMR (125.69 MHz, CDCl₃, -20 °C) rotameric mixture, resonances for minor rotamer are enclosed in brackets []: δ [161.58 (d, *J*=243.6 Hz)] 161.46 (d, *J*=243.6 Hz), 154.61-both rotamers, 140.87 (d, *J*=3.1 Hz) [139.75 (d, *J*=3.1 Hz)], 127.03 (d, *J*=8.0 Hz) [126.81 (d, *J*=8.0 Hz)], [115.26 (d, *J*=21.5 Hz)] 114.95 (d, *J*=21.5 Hz)], [79.53] 79.38, 60.69 [60.08], [47.38] 47.09, 36.20 [35.04], [28.53] 28.18, [23.41] 23.23; Exact mass calculated for C₁₅H₂₀FNO₂+H requires *m/z* 266.1556, found *m/z* 266.1558. Separation of enantiomers was accomplished using chiral HPLC: Chiralpak AD-H (99:1 Heptane:*i*PrOH, 0.5 mL/min), (*R*)-**4b** 11.1 min, (*S*)-**4b** 12.6 min.

N-Boc-(*R*)-2-(4-dimethylaminophenyl)pyrrolidine (4c). Prepared according to the general procedure on 4.75 mmol scale. Purification by flash chromatography (70:30 Hexanes:EtOAc) provided **4c** (1.08 g, 78% yield) as a solid. mp=79.9-80.8 °C; [α]_D= +107 (*c*=0.018, acetone); ¹H NMR (499.87 MHz, CDCl₃, -20 °C) 1:2.1 ratio amide bond rotamers: δ 7.07 (d, *J*=8.3 Hz, 0.7 H), 7.05 (d, *J*=8.7 Hz, 1.3 H), 6.72-6.68 (om, 2H), 4.88 (dd, *J*=8.0, 2.8 Hz, 0.3H), 4.71 (dd, *J*=8.0, 4.4 Hz, 0.7H), 3.64-3.54 (om, 1.7H), 3.46 (m, 0.3H), 2.94 (s, 4H), 2.91 (s, 2H), 2.30-2.17 (om, 1H), 1.95-1.88 (om, 1H), 1.86-1.76 (om, 2H), 1.45 (s, 3H), 1.21 (s, 6H); ¹³C NMR (125.69 MHz, CDCl₃, -20 °C) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis (): δ 154.90 (154.57), (149.49) 149.31, 133.08 (132.15), 126.44 (126.12), (112.90) 112.37, (79.11) 79.09, 60.66 (60.05), (47.30) 46.95, (41.06) 41.01, 36.04 (34.95), (28.60) 28.28, (23.49) 23.17; Exact mass calculated for C₁₇H₂₆N₂O₂+H

requires m/z 291.2073, found m/z 291.2071. Separation of enantiomers was accomplished using chiral HPLC: Chiralpak AD-H (95:5 Heptane:*i*PrOH, 1.0 mL/min), (*R*)-**4c** 3.4 min, (*S*)-**4c** 3.7 min.

***N*-Boc-(*R*)-2-(4-carboxymethylphenyl)pyrrolidine (4d).**

Prepared according to the general procedure on 4.75 mmol scale. Purification by flash chromatography (75:25 Hexanes:EtOAc) provided **4d** (1.18 g, 81% yield) as a solid. mp=80.3-81.2 °C; $[\alpha]_D^{25}$ +98.6 (c =0.022, acetone); ^1H NMR (499.87 MHz, CDCl_3 , -20 °C) 1:2.3 ratio amide bond rotamers: δ 7.96 (d, J =8.0 Hz, 2H), 7.24-7.22 (om, 2H), 4.95 (dd, J =8.0, 3.2 Hz, 0.3H), 4.77 (dd, J =8.0, 5.2 Hz, 0.7H), 3.89 (s, 2.1H), 3.87 (s, 0.9H), 3.66-3.58 (om, 1.7H), 3.50 (dt, J =10.7, 8.0 Hz, 0.3H), 2.38-2.25 (om, 1H), 1.94-1.73 (om, 3H), 1.42 (s, 2.8H), 1.12 (s, 6.2H); ^{13}C NMR (125.69 MHz, CDCl_3 , -20 °C) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis (): δ 167.21-both rotamers, (154.58) 154.50, 150.68 (149.62), (129.94) 129.66, (128.37) 128.29, 125.57 (125.40), (79.68) 79.57, 61.19 (60.64), 52.36 (52.30), (47.46) 47.18, 36.04 (34.90), (28.51) 28.15, (23.59) 23.38 ; Exact mass calculated for $\text{C}_{17}\text{H}_{23}\text{NO}_4+\text{H}$ requires m/z 306.1705, found m/z 306.1708. Separation of enantiomers was accomplished using chiral HPLC: Chiralpak AD-H (95:5 Heptane:*i*PrOH, 1.0 mL/min), (*R*)-**4d** 5.1 min, (*S*)-**4d** 5.7 min.

***N*-Boc-(*R*)-2-(4-methanesulfonylphenyl)pyrrolidine (4e).**

Prepared according to the general procedure on 4.75 mmol scale. Purification by flash chromatography (60:40 Hexanes:EtOAc) provided **4e** (1.34 g, 87% yield) as a solid. mp=100.6-101.0 °C; $[\alpha]_D^{25}$ +94.8 (c =0.018, acetone); ^1H NMR (499.87 MHz, CDCl_3 , -20 °C) 1:1.1 ratio amide bond rotamers: δ 7.86 (d, 8.3 Hz, 1H), 7.85 (d, J =8.3 Hz, 1H), 7.36 (d, J =8.3 Hz, 2H), 4.96 (dd, J =8.0, 3.2 Hz, 0.5H), 4.82 (dd, J =8.0, 4.8 Hz, 0.5H), 3.65-3.58 (om, 1.5H), 3.51 (dt, J =10.7, 8.0 Hz, 0.5H), 3.06 (s, 1.6H), 3.02 (s, 1.4H), 2.40-2.28 (om, 1H) 1.90-1.70 (om, 3H), 1.42 (s, 4.2H), 1.13 (s, 4.8H); ^{13}C NMR (125.69 MHz, CDCl_3 , -20 °C) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis (): δ (154.64) 154.33, 151.77 (150.79), 138.32 (138.29), (127.83) 127.49, 126.44 (126.27), (79.95) 79.78, 60.96 (60.51), (47.51) 47.15, (44.70) 44.68,

35.98 (34.91), 28.46 (28.14), (23.54) 23.25; Exact mass calculated for $C_{16}H_{23}NO_4S+H$ requires m/z 326.1426, found m/z 326.1426. Separation of enantiomers was accomplished using chiral HPLC: Chiralpak AD-H (90:10 Heptane:*i*PrOH, 1.0 mL/min), (*R*)-**4e** 8.3 min, (*S*)-**4e** 9.7 min.

N-Boc-(*R*)-2-(4-cyanophenyl)pyrrolidine (4f). Prepared according to the general procedure on 4.75 mmol scale. Purification by flash chromatography (70:30 Hexanes:EtOAc) provided **4f** (1.03 g, 80% yield) as a solid. mp=121.2-122.0 °C; $[\alpha]_D = +151$ ($c=0.016$, acetone); 1H NMR (499.87 MHz, $CDCl_3$, -20 °C) 1:1.6 ratio amide bond rotamers: δ 7.59 (om, 2H), 7.27 (om, 2H), 4.92 (dd, $J=8.0, 3.2$ Hz, 0.4H) 4.76 (dd, $J=7.6, 5.6$ Hz, 0.6H), 3.65-3.56 (om, 1.6H), 3.50 (dt, $J=10.3, 7.6$ Hz, 0.4H), 2.39-2.27 (om, 1H), 1.90-1.70 (om, 3H), 1.41 (s, 3.5H), 1.23 (s, 5.5H); ^{13}C NMR (125.69 MHz, $CDCl_3$, -20 °C) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis (): δ (154.56) 154.28, 150.86 (149.80), (132.47) 132.23, 126.29 (126.14), (119.31) 119.22, (110.20) 110.14, (79.89) 79.74, 61.12 (60.60), (47.48) 47.18, 35.98 (34.84), (28.45) 28.11, (23.60) 23.34; Exact mass calculated for $C_{16}H_{20}N_2O_2+H$ requires m/z 273.1603, found m/z 273.1611. Separation of enantiomers was accomplished using chiral HPLC: Chiralpak AD-H (95:5 Heptane:*i*PrOH, 1.0 mL/min), (*R*)-**4f** 5.4 min, (*S*)-**4f** 6.9 min.

N-Boc-(*R*)-2-(4-aminophenyl)pyrrolidine (4g). Prepared according to the general procedure on 4.75 mmol scale. Purification by flash chromatography (55:45 Hexanes:EtOAc) provided **4g** (872 mg, 70% yield) as a solid. mp=170.4-171.6 °C; $[\alpha]_D = +104$ ($c=0.016$, acetone); 1H NMR (499.87 MHz, $CDCl_3$, -20 °C) 1:2.2 ratio amide bond rotamers: δ 6.97-6.93 (om, 2H), 6.63 (m, 2H), 4.84 (dd, $J=8.0, 2.9$ Hz, 0.3H), 4.65 (dd, $J=8.0, 4.8$ Hz, 0.7H), 3.67 (br s, 2H), 3.62-3.53 (om, 1.7H), 3.44 (m, 0.3H), 2.29-2.15 (om, 1H), 1.93-1.73 (om, 3H), 1.43 (s, 3H), 1.19 (s, 6H); ^{13}C NMR (125.69 MHz, $CDCl_3$, -20 °C) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis (): δ 154.81 (154.55), (144.94) 144.79, 135.20 (134.18), 126.57 (126.31), (115.27) 114.92, (79.18) 79.12, 60.76 (60.13), 47.28 (46.97), 36.12 (34.99), (28.56) 28.23, 23.41 (23.16); Exact mass calculated for $C_{15}H_{22}N_2O_2+H$ requires m/z

263.1760, found m/z 263.1763. Separation of enantiomers was accomplished using chiral HPLC: Chiralpak AD-H (90:10 Heptane:*i*PrOH, 1.0 mL/min), (*R*)-**4g** 6.3 min, (*S*)-**4g** 6.8 min.

N-Boc-(*R*)-2-(2-methylphenyl)pyrrolidine (4h). Prepared according to the general procedure on 4.75 mmol scale. Purification by flash chromatography (85:10:5 CH₂Cl₂:Hexanes:MTBE) provided **4h** (881 mg, 71% yield) as an oil. [α]_D = +121 (c =0.017, acetone); ¹H NMR (499.87 MHz, CDCl₃, -20 °C) 1:1.9 ratio amide bond rotamers: δ 7.17-7.11 (om, 3H), 7.08 (m, 0.7H), 7.04 (d, J =7.2 Hz, 0.3H), 5.13 (dd, J =8.3, 1.6 Hz, 0.3H), 4.96 (dd, J =8.0, 4.4 Hz, 0.7H), 3.72-3.59 (om, 1.7H), 3.49 (dt, J =10.3, 8.0 Hz, 0.3H), 2.35 (s, 1H), 2.33 (s, 2H), 2.34-2.20 (om, 1H), 1.99-1.83 (om, 2H), 1.75-1.66 (om, 1H), 1.46 (s, 3H), 1.41 (s, 6H); ¹³C NMR (125.69 MHz, CDCl₃, -20 °C) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis (): δ 154.51 (154.47), 143.20 (141.74), (134.16) 133.96, (130.64) 129.98, (126.59) 126.33, 125.96 (125.88), 124.40 (123.89), (79.30) 79.10, (58.00) 57.94, (47.39) 47.07, 34.09 (32.72), (28.56) 28.09, 23.16 (23.08), 19.54 (19.48); Exact mass calculated for C₁₆H₂₃NO₂+H requires m/z 262.1807, found m/z 262.1805. Separation of enantiomers was accomplished using chiral HPLC: Chiralpak AD-H (99:1 Heptane:*i*PrOH, 0.5 mL/min), (*R*)-**4h** 9.4 min, (*S*)-**4h** 10.1 min.

N-Boc-(*R*)-2-(2-methoxyphenyl)pyrrolidine (4i). Prepared according to the general procedure on 4.75 mmol scale. Purification by flash chromatography (85:10:5 CH₂Cl₂:Hexanes:MTBE) provided **4i** (949 mg, 72% yield) as an oil. [α]_D = +109 (c =0.017, acetone); ¹H NMR (499.87 MHz, CDCl₃, -20 °C) 1:1.6 ratio amide bond rotamers: δ 7.22-7.18 (om, 1H), 7.05 (dd, J =7.6, 1.6 Hz, 0.6H), 7.01 (dd, J =7.6, 1.6 Hz, 0.4H), 6.91-6.88 (om, 1H), 6.84 (t, J =7.6 Hz, 1H), 5.24 (dd, J =8.3, 1.6 Hz, 0.4H), 5.09 (dd, J =8.3, 3.6 Hz, 0.6H), 3.82 (s, 1.9H), 3.80 (s, 1.1H), 3.68-3.60 (om, 1H), 3.55 (dt, J =10.7, 7.6 Hz, 0.6H), 3.44 (m, 0.4H), 2.30-2.14 (om, 1H), 1.85-1.72 (om, 3H), 1.46 (s, 3.6 H), 1.18 (s, 5.4H); ¹³C NMR (125.69 MHz, CDCl₃, -20 °C) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis (): δ (155.98) 155.94, 154.70 (154.42), 132.56 (131.51), 127.67 (127.44), 125.85 (125.15), (120.08) 120.05,

(110.12) 109.90, (79.22) 79.00, 55.98 (55.90), 55.35 (55.22), (47.23) 46.85, 33.78 (32.70), (28.57) 28.17, (23.18) 23.05; Exact mass calculated for $C_{16}H_{23}NO_3+H$ requires m/z 278.1756, found m/z 278.1758. Separation of enantiomers was accomplished using chiral HPLC: Chiralpak AD-H (99:1 Heptane:*i*PrOH, 0.5 mL/min), (*R*)-**4i** 15.2 min, (*S*)-**4i** 13.0 min.

***N*-Boc-(*R*)-2-(3-acetylphenyl)pyrrolidine (**4j**).** Prepared according to the general procedure on 4.75 mmol scale. Purification by flash chromatography (70:30 Hexanes:EtOAc) provided **4j** (1.07 g, 78% yield) as an oil. $[\alpha]_D^{25} = +133$ ($c=0.013$, acetone); 1H NMR (499.87 MHz, $CDCl_3$, $-20^\circ C$) 1:1.6 ratio amide bond rotamers: δ 7.82-7.77 (om, 1H), 7.76 (br s, 1H), 7.41-7.36 (om, 2H), 4.95 (dd, $J=8.0, 3.2$ Hz, 0.4H), 4.79 (dd, $J=8.0, 5.2$ Hz, 0.6H), 3.66-3.60 (om, 1.6H), 3.50 (dt, $J=10.7, 8.0$ Hz, 0.4H), 2.60 (s, 1.9H), 2.59 (s, 1.1H), 2.38-2.26 (om, 1H), 1.93-1.73 (om, 3H), 1.42 (s, 3.6H), 1.12 (s, 5.6H); ^{13}C NMR (125.69 MHz, $CDCl_3$, $-20^\circ C$) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis (): δ (198.72) 198.60, (154.66) 154.56, 145.78 (144.76), (137.01) 136.79, 130.41 (130.36), (128.84) 128.58, (127.11) 126.96, 125.44 (124.96), (79.68) 79.49, 61.13 (60.53), (47.50) 47.20, 36.16 (35.01), (28.50) 28.16, 27.08-both rotamers, (23.52) 23.36; Exact mass calculated for $C_{17}H_{23}NO_3+H$ requires m/z 290.1756, found m/z 290.1755. Separation of enantiomers was accomplished using chiral HPLC: Chiralpak AD-H (95:5 Heptane:*i*PrOH, 1.0 mL/min), (*R*)-**4j** 6.0 min, (*S*)-**4j** 6.5 min.

***N*-Boc-(*R*)-2-(5-*N*-Boc-indolyl)pyrrolidine (**4k**).** Prepared according to the general procedure on 4.75 mmol scale. Purification by flash chromatography (50:45:5 CH_2Cl_2 :Hexanes:MTBE) provided **4k** (1.49 g, 81% yield) as a solid. mp=139.6-140.1 $^\circ C$; $[\alpha]_D^{25} = +84.6$ ($c=0.014$, acetone); 1H NMR (499.87 MHz, $DMSO-d_6$, $+90^\circ C$): δ 7.99 (d, $J=8.3$ Hz, 1H), 7.61 (d, $J=3.6$ Hz, 1H), 7.38 (d, $J=1.2$ Hz, 1H), 7.15 (dd, $J=8.3, 1.2$ Hz, 1H), 6.64 (d, $J=3.6$ Hz, 1H), 4.88 (dd, $J=8.0, 3.6$ Hz, 1H), 3.59-3.50 (om, 2H), 2.32 (dq, $J=11.9, 7.6$ Hz, 1H), 1.92-1.75 (om, 3H), 1.65 (s, 9H), 1.24 (br s, 9H); ^{13}C NMR (125.69 MHz, $DMSO-d_6$, $+90^\circ C$): δ 153.16, 148.65, 139.02, 133.12, 129.73, 125.63, 121.51, 117.15, 113.77, 106.84, 83.17, 77.61, 60.19,

46.44, 34.80 (br), 27.56, 27.30, 22.40; Exact mass calculated for $C_{22}H_{30}N_2O_4+H$ requires m/z 387.2284, found m/z 387.2284. Separation of enantiomers was accomplished using chiral HPLC: Chiralpak AD-H (95:5 Heptane:*i*PrOH, 1.0 mL/min), (*R*)-**4k** 3.3 min, (*S*)-**4k** 3.6 min.

N-Boc-(*R*)-2-(4-indolyl)pyrrolidine (4l). Prepared according to the general procedure on 4.75 mmol scale. Purification by flash chromatography (75:25 Hexanes:EtOAc) provided **4l** (1.05 g, 77% yield) as a solid. mp=149.8-151.0 °C; $[\alpha]_D = +82.6$ ($c=0.012$, acetone); 1H NMR (499.87 MHz, $CDCl_3$, -20 °C) 1:1.7 ratio amide bond rotamers: δ 8.96 (s, 0.6H), 8.85 (s, 0.4H), 7.26 (d, $J=8.3$ Hz, 0.6H), 7.20 (d, $J=8.3$ Hz, 0.4H), 7.12 (t, $J=8.0$ Hz, 0.6H), 7.11 (t, $J=8.0$ Hz, 0.4H), 7.08 (t, $J=2.8$ Hz, 0.6H), 7.06 (t, $J=2.8$ Hz, 0.4H), 6.88 (d, $J=7.6$ Hz, 0.6H), 6.85 (d, $J=7.6$ Hz, 0.4H), 6.50 (t, $J=2.0$ Hz, 0.6H), 6.48 (t, $J=2.0$ Hz, 0.4H), 5.45 (dd, $J=8.0, 2.0$ Hz, 0.4H), 5.21 (dd, $J=7.6, 4.8$ Hz, 0.6H), 3.79-3.65 (om, 1.6H), 3.56 (m, 0.4H), 2.40-2.26 (om, 1H), 2.06-1.85 (om, 3H), 1.52 (s, 3.3H), 1.08 (s, 5.7H); ^{13}C NMR (125.69 MHz, $CDCl_3$, -20 °C) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis (): δ 155.14 (154.81), 136.09 (136.01), 135.88 (134.91), (124.77) 124.57, (124.15) 124.12, (121.54) 121.36, 115.85 (114.86), (110.07) 109.75, 100.05-both rotamers, (79.45) 79.20, 60.02 (59.08), (47.28) 46.99, 34.47 (33.25), (28.65) 28.13, (23.63) 23.52; Exact mass calculated for $C_{17}H_{22}N_2O_2+H$ requires m/z 287.1760, found m/z 287.1761. Separation of enantiomers was accomplished using chiral HPLC: Chiralpak AD-H (90:10 Heptane:*i*PrOH, 0.7 mL/min), (*R*)-**4l** 22.7 min, (*S*)-**4l** 23.4 min.

N-Boc-(*R*)-2-(3-pyridyl)pyrrolidine (4m). Prepared according to the general procedure on 10 mmol scale. Purification by flash chromatography (60:40 Hexanes:EtOAc) provided **4m** (1.48 g, 60% yield as an oil. $[\alpha]_D = +83.6$ ($c=0.0155$, CH_2Cl_2); 1H NMR (499.87 MHz, $CDCl_3$, -20 °C) 1:1.8 ratio amide bond rotamers: δ 8.44-8.41 (om, 2H), 7.48-7.45 (om, 1H), 7.23-7.20 (om, 1H), 4.91 (dd, $J=8.3, 3.2$ Hz, 0.4H), 4.73 (dd, $J=8.0, 5.2$ Hz, 0.6H), 3.58 (t, $J=6.8$ Hz, 1.2H), 3.55 (m, 0.4H), 3.46 (dd, $J=10.7, 8.0$ Hz, 0.4H), 2.36-2.23 (om, 1H), 1.91-1.71 (om, 3H), 1.39 (s, 3.3H), 1.12 (s, 5.7H); ^{13}C NMR (125.69 MHz, $CDCl_3$, -20 °C) rotameric mixture, resonances for

minor rotamer are enclosed in parenthesis (): δ (154.51) 154.34, 148.03 (147.87), 147.66 (147.09), 140.34 (139.37), (133.43) 133.15, (123.54) 123.35, (79.77) 79.67, 59.06 (58.61), (47.30) 47.08, 35.95 (34.67), (28.44) 28.11, (23.44) 23.32; Exact mass calculated for $C_{14}H_{20}N_2O_2+H$ requires m/z 249.1603, found m/z 249.1606. Separation of enantiomers was accomplished using chiral HPLC: Chiralpak AD-H (isocratic 80:20 Heptane:*i*PrOH, 0.7 mL/min), (*R*)-**4m** 3.77 min, (*S*)-**4m** 3.45 min.

***N*-Boc-(2*R*,5*R*)-diphenylpyrrolidine (5).** Prepared according to the general procedure on 4.75 mmol scale. Purification by flash chromatography (90:10 Hexanes:EtOAc) provided **5** (875 mg, 57% yield) as a solid. mp=139.4-139.5 °C; $[\alpha]_D= +133$ ($c=0.010$, acetone); 1H NMR (499.87 MHz, $CDCl_3$, -20 °C): δ 7.40-7.35 (om, 4H), 7.30-7.25 (om, 6H), 5.36 (d, $J=7.6$ Hz, 1H), 5.19 (d, $J=7.6$ Hz, 1H), 2.48 (m, 2H), 1.75 (m, 2H), 1.16 (s, 9H); ^{13}C NMR (125.69 MHz, $CDCl_3$, -20 °C): δ 154.16, 145.13, 143.78, 128.62, 128.28, 126.86, 128.68, 125.35, 125.20, 79.61, 62.27, 61.53, 32.00, 31.51, 28.11; Exact mass calculated for $C_{21}H_{25}NO_2+H$ requires m/z 324.1964, found m/z 324.1969.