SUPPORTING INFORMATION

Enantioselective Synthesis of 2-Substituted 2-Phenylethyl Amines by Lithiation-Substitution Sequences: Synthetic Development and Mechanistic Pathway

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Flash column chromatography was performed using 230-400 mesh silica gel. Analytical TLC was carried out on Merck silica gel plates with QF-254 indicator and detected by UV light or KMnO_4 solution. Preparative high-pressure liquid chromatography (HPLC) was performed on a Dynamax-60-A 8 μm silica column (Rainin Instrument Co., 25 cm x 21.4 mm i.d.) with a Knauer UV detector (254 nm). Melting points (mp) are uncorrected.

^1H and ^{13}C NMR spectra were acquired in the University of Illinois VOICE NMR Laboratory on either a Varian U400 (400 MHz ^1H , 100.6 MHz ^{13}C) spectrometer or a Varian U500 (500 MHz ^1H , 125.7 MHz ^{13}C) spectrometer. Chemical shifts (δ) are reported in ppm referenced to CDCl_3 solvent (^1H δ =7.26 ppm, ^{13}C δ =77.0 ppm), acetone solvent (^1H δ =2.05 ppm, ^{13}C δ =206.3 ppm), and DMSO solvent (^1H δ =2.50 ppm, ^{13}C δ =39.5 ppm); the following abbreviations are used to describe multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sx (sextet), sept (septet), m (multiplet), or b (broadened). Coupling constants (J) are reported in Hz.

The University of Illinois Mass Spectrometry Center performed mass spectrometry analysis. High resolution electron impact (EI) mass spectrometry was performed on a Finnigan-MAT 731 spectrometer and high resolution fast atom bombardment (FAB) spectra were obtained on a Micromass 70-SE-4F. The University of Illinois Microanalytical Service Laboratory performed elemental analyses.

***N*-(2-Phenylethyl)-isobutyramide (2)**

To a solution of CH_2Cl_2 (20 mL) and triethylamine (2.0 mL) was added phenethylamine (1.26 mL, 10.0 mmol). The solution was cooled to 0 $^\circ\text{C}$ followed by

drop-wise addition of isobutyryl chloride (1.05 mL, 10.0 mmol) in CH₂Cl₂ (10 mL). The reaction mixture was allowed to stir at room temperature for 24 hours. The solution was poured into 2M HCl (25 mL), the layers were separated and the CH₂Cl₂ layer was washed with 5% NaHCO₃ (20 mL) and dried over MgSO₄. The solvent was removed *in vacuo* to provide an off-white solid. The crude product was recrystallized from 20 mL hexane to provide pure **2** (1.59 g, 83%), mp 89-90 °C; (lit. mp 91-92 °C)¹². ¹H NMR (CDCl₃, 400 MHz): δ 1.11 (d, *J*=6.8 Hz, 6H, CH(CH₃)₂), 2.27 (sept, *J*=6.9 Hz, 1H, CH(CH₃)₂), 2.81 (t, *J*=6.8 Hz, 2H, PhCH₂CH₂N), 3.51 (q, *J*=6.5 Hz, 2H, PhCH₂CH₂N), 5.41 (bs, 1H, NH), 7.18-7.33 (m, 5H, Ar-H). ¹³C NMR (CDCl₃, 100 MHz): δ 19.44 (CH₃), 35.51 (CH), 35.56 (CH₂), 40.26 (CH₂), 126.33 (Ar-H), 128.46 (Ar-H), 128.65 (Ar-H), 138.83 (Ar), 176.70 (C=O). The spectral data are consistent with the previously reported data for this compound.¹³

(*S*)-*N*-Boc-*N*-(2-phenylbutyl)-isobutyramide (11**)**

To a flask containing (*S*)-**8** (0.084 g, 0.38 mmol) dissolved in THF (10 mL) at –78 °C was added *n*-BuLi (1.6 M, 0.25 mL, 0.42 mmol). After the solution was allowed to stir for 2 h, Boc anhydride (0.09 mL, 0.39 mmol) was added. The solution was allowed to slowly warm to room temperature and stirring was continued for 6 hours. The solution was poured into water (25 mL), the layers were separated and the aqueous layer was extracted with ether (3 x 20 mL). The ethereal layers were combined, dried (MgSO₄) and filtered. The solvent was removed *in vacuo* to provide crude (*S*)-**11**. The crude product was purified using flash chromatography (25% EtOAc/Hexane) to provide (*S*)-**11** as a mixture with unreacted Boc anhydride (97% mass balance). The oil was used in the

synthesis of (*S*)-**12** without further purification. ¹H NMR (CDCl₃, 400 MHz): δ 0.75 (t, *J*= 7.5 Hz, 3H, CH₂CH₃), 0.93 (d, *J*=6.8 Hz, 3H, CHCH₃), 1.08 (d, *J*=6.6 Hz, 3H, CHCH₃), 1.40 (s, 9H, C(CH₃)₃), 1.50 (s, BocOBoc), 1.62 (m, 2H, CH₂CH₃), 2.84 (m, 1H, PhCH), 3.45 (sept, *J*=6.7 Hz, 1H, CH(CH₃)₂), 3.85 (m, 2H, PhCHCH₂N), 7.10-7.26 (m, 5H, Ar-H).

(*S*)-*N*-Boc-2-phenyl butylamine (12)

In a 50 mL flask was dissolved KOH (0.306 g, 5.45 mmol) in H₂O (2 mL). *N*-Boc amide (*S*)-**11** (0.117 g, 0.37 mmol) was dissolved in dioxane (10 mL) and transferred to the KOH solution. The (*S*)-**11** flask was rinsed with additional dioxane (10 mL) and transferred to the KOH solution. The reaction mixture was stirred at reflux for 24 hours. The solution was poured into 5% HCl (20 mL) and then extracted with ether (3 x 15 mL). The ethereal extracts were combined and made basic with 10% KOH. The layers were separated and the aqueous layer was back extracted with ether (15 mL). The ethereal extracts were combined, dried (MgSO₄) and filtered. The solvent was removed *in vacuo* to provide (*S*)-**12** (0.082 g, 89%) as a viscous oil. ¹H NMR (CDCl₃, 400 MHz): δ 0.81 (t, *J*=7.3 Hz, 3H, CH₂CH₃), 1.40 (s, 9H, C(CH₃)₃), 1.56 (m, 1H, CHHCH₃), 1.71 (m, 1H, CHHCH₃), 2.64 (m, 1H, PhCH), 3.14 (ddd, *J*=13.2, 9.3, 4.5 Hz, 1H, PhCHCHHN), 3.54 (m, 1H, PhCHCHHN), 4.37 (bs, 1H, NH), 7.15-7.34 (m, 5H, Ar-H). ¹³C NMR (CDCl₃, 100 MHz): δ 11.86 (CH₃), 26.65 (CH₂), 28.34 (CH₃), 45.92 (CH₂), 47.86 (CH), 126.54 (Ar-H), 127.86 (Ar-H), 128.54 (Ar-H), 142.69 (Ar), 155.87 (C=O).

(*S*)-2-Phenylbutylamine (13)

In a 35 mL flask was dissolved (*S*)-**12** (0.082 g, 0.33 mmol) in CH₂Cl₂ (6 mL). To the solution was added trifluoroacetic acid (TFA) (1 M in THF, 1 mL, 1 mmol). The solution was stirred at rt for 2 h and then poured into 10% NaOH (15 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 15 mL). The combined ether layers were washed with 2M HCl. The acid layer was back extracted with ether to remove any by-products. The aqueous layer was then made basic with KOH and washed with ether (3 x 15 mL). The combined ether layers were dried (MgSO₄) and filtered. The solvent was removed *in vacuo* to provide (*S*)-**13**. The configuration of (*S*)-**13** was confirmed as (*S*) by the sign of optical rotation. $[\alpha]_D^{25} = +7.3^\circ$ (*c*=18.1 in ether), corresponding to 87:13 er; [lit. (*S*)-**13** $[\alpha]_D^{25} = +10$ (*c*=1.2 in ether)]⁷. ¹H NMR (CDCl₃, 400 MHz): δ 0.79 (t, *J*=7.3 Hz, 3H, CH₂CH₃), 1.55 (m, 1H, CHHCH₃), 1.67 (m, 1H, CHHCH₃), 2.54 (m, 1H, PhCH), 2.82 (m, 1H, PhCHCHHN), 2.83 (m, 1H, PhCHCHHN), 3.42 (bs, 2H, NH₂), 7.14-7.32 (m, 5H, Ar-H). ¹³C NMR (CDCl₃, 100 MHz): δ 11.89 (CH₃), 26.76 (CH₂), 46.75 (CH₂), 49.91 (CH), 126.73 (Ar-H), 127.95 (Ar-H), 128.65 (Ar-H), 142.31 (Ar). The spectral data are consistent with the previously reported data for this compound.¹⁴

Conversion of (2*S*)-**10** (major diastereomer) to (*S*)-**6**

In a 10 mL flask was dissolved (2*S*)-**10** (major diastereomer, 0.101 g, 0.39 mmol) in benzene (2.7 mL) and CH₂Cl₂ (1.3 mL). To this solution was added ~ 0.1 mL pyridine, followed by methyl oxalylchloride (40 μ L, 0.43 mmol). The reaction mixture was stirred at room temperature for 12 hours, poured into water (20 mL), and extracted with ether (3 x 10 mL). The ethereal extracts were combined, dried (MgSO₄) and filtered. The solvent

was removed *in vacuo* to provide the crude oxalyl derivative. The crude product was passed through a plug of silica gel (50% EtOAc/hexane) to afford the oxalyl derivative (72.7 mg, 49%) as a viscous oil. The oxalyl derivative was used in the next step without further purification. In a 5 mL flask the oxalyl derivative (72.7 mg, 0.19 mmol), tributyltin hydride (0.26 mL, 0.97 mmol), and AIBN (7.0 mg, 0.04 mmol) were dissolved in benzene (0.5 mL). The solution was stirred at reflux for 5 hours. To the reaction mixture, at room temperature, was added excess *t*-butyl bromide. After being allowed to stir at room temperature for 3 hours, saturated aqueous KF was added to the solution. The solution was diluted with ether (15 mL) after 30 minutes, the layers were separated and the aqueous layer was extracted with ether (15 mL). The combined ethereal extracts were filtered through celite to remove all precipitates. The organic layers were dried (MgSO₄), filtered, and the solvent was removed *in vacuo* to provide crude (*S*)-**6**. The crude product was purified using flash chromatography (45% EtOAc/hexane) to afford (*S*)-**6** (40.9 mg, 76%) as a viscous oil. The spectral data are consistent with the previously prepared compound. The enantiomeric ratio of (*S*)-**6** was determined to be 80:20 by CSP-HPLC on a Whelk-O column with 10% IPA/hexane mobile phase; retention times for the minor and major enantiomers were 16.3 min and 18.7 min respectively. ¹H NMR crude oxalyl derivative (CDCl₃, 400 MHz): δ 1.02 (d, *J*=6.8 Hz, 3H, CHCH₃), 1.03 (d, *J*=7.1 Hz, 3H, CHCH₃), 2.22 (sept, *J*=6.8 Hz, 1H, CH(CH₃)₂), 3.47 (td, *J*=8.4, 6.2 Hz, 1H, PhCHCH₂N), 3.65 (ddd, *J*=13.7, 7.9, 6.0 Hz, 1H, PhCHCHHN), 3.87 (m, 1H, PhCHCHHN), 3.92 (s, 3H, OCH₃), 5.60 (bs, 1H, NH), 6.01 (d, *J*=8.8 Hz, 1H, PhCHOCO), 7.01-7.21 (m, 10H, Ar-H). ¹³C NMR crude oxalyl derivative (CDCl₃, 100 MHz): δ 19.39 (CH₃), 19.49 (CH₃), 35.52 (CH), 40.96 (CH₂),

50.97 (CH₃), 53.72 (CH), 81.49 (CH), 127.06 (Ar-H), 127.50 (Ar-H), 128.28 (Ar-H), 128.46 (Ar-H), 128.52 (Ar-H), 128.66 (Ar-H), 136.85 (Ar), 137.48 (Ar), 156.48 (C=O), 157.96 (C=O), 176.86 (C=O).

Tin-lithium exchange of *rac*-5

To a stirring solution of *rac*-5 (127 mg, 0.27 mmol) in MTBE (3 mL) and THF (1 mL) was added **1** (0.14 mL, 0.59 mmol). The solution was cooled to -78°C and after addition of *sec*-BuLi (0.44 mL, 1.36 M in cyclohexane, 0.59 mmol) stirring was continued for 3 hours before chlorotrimethylsilane (38.0 μL , 0.30 mmol) was added at -78°C . The reaction was quenched with 2 mL of CH₃OH after stirring at -78°C for an additional 4 hours. Stirring was continued as the solution was allowed to warm to room temperature. The solution was poured into 5% H₃PO₄ (10 mL) and 10 mL of ether was added. The layers were separated and the aqueous layer was extracted with ether (3 x 10 mL). The combined ether layers were dried over MgSO₄ and the solvent removed *in vacuo* to afford the crude (*S*)-4. The crude product was purified using flash chromatography (30% EtOAc/Hexane) to give (*S*)-4 (47.8 mg, 67%). The spectral data are consistent with the previously prepared compound. The enantiomeric ratio of (*S*)-4 was determined to be 89:11 by CSP-HPLC on a Whelk-O column with 5% IPA/hexane mobile phase; retention times for the minor and major enantiomers were 13.9 min and 16.3 min respectively.

“Poor Man’s Hoffmann Test” of **2 at -78°C**

General procedure

To a flame-dried flask, purged with N₂, and charged with **2** (0.0956 g, 0.50 mmol) was added MTBE (6.0 mL) and THF (2.0 mL) followed by 2.3 equivalents of **1** (0.26 mL, 1.13 mmol). The solution was cooled to –78 °C in a dry ice-acetone bath and 2.1 equivalents of *sec*-BuLi (0.79 mL, 1.31 M in cyclohexane, 1.04 mmol) were added drop wise. The reaction mixture was stirred at –78 °C for 1 hour before a given amount of electrophile was added. The reaction was quenched with 2 mL of CH₃OH after stirring at –78 °C for a given amount of time. Standard work-up was performed to afford the crude product.

Reaction with excess chlorotrimethylsilane

The general procedure was followed using 1.1 equivalents of chlorotrimethylsilane (70.0 µL, 0.55 mmol). The crude product was purified using flash chromatography (40% EtOAc/Hexane) to give (*S*)-**4** (118.9 mg, 90%). The spectral data are consistent with the previously prepared compound. The enantiomeric ratio of (*S*)-**4** was determined to be 91:9 by CSP-HPLC on a Whelk-O column with 10% IPA/hexane mobile phase; retention times for the minor and major enantiomers were 8.4 min and 9.1 min respectively.

Reaction with deficient chlorotrimethylsilane

The general procedure was followed using 0.1 equivalents of chlorotrimethylsilane (6.0 µL, 0.047 mmol). The crude product was purified using flash chromatography (40% EtOAc/Hexane) to give (*S*)-**4** (12.3 mg, 9%). The spectral data are consistent with the previously prepared compound. The enantiomeric ratio of (*S*)-**4** was determined to be 85:15 by CSP-HPLC on a Whelk-O column with 10% IPA/hexane mobile phase; retention times for the minor and major enantiomers were 8.3 min and 9.1 min respectively.

“Poor Man’s Hoffmann Test” of **2 at $-100\text{ }^{\circ}\text{C}$**

General procedure

To a flame-dried flask, purged with N_2 , and charged with **2** (0.096 g, 0.50 mmol) was added MTBE (4.5 mL) and THF (1.5 mL) followed by 2.3 equivalents of **1** (0.26 mL, 1.13 mmol). The solution was cooled to either $-78\text{ }^{\circ}\text{C}$ in a dry ice-acetone bath or $-100\text{ }^{\circ}\text{C}$ in a liquid N_2 -9:1 methanol/ethanol bath and 2.2 equivalents of *sec*-BuLi (0.75-0.80 mL, 1.36-1.45 M in cyclohexene, 1.09 mmol) were added drop wise. The reaction mixture was stirred at a given temperature for 1 hour before a given amount of electrophile was added. The reaction was quenched with 2 mL of CH_3OH after stirring at $-100\text{ }^{\circ}\text{C}$ for a given amount of time. Standard work-up was performed to afford the crude product.

Lithiation at $-78\text{ }^{\circ}\text{C}$ and reaction at $-100\text{ }^{\circ}\text{C}$ with excess chlorotrimethylsilane

The general procedure was followed with lithiation at $-78\text{ }^{\circ}\text{C}$ for 1 hour followed by stirring at $-100\text{ }^{\circ}\text{C}$ for 15 minutes before addition of 1.1 equivalents of chlorotrimethylsilane (70.0 μL , 0.55 mmol). The reaction mixture was stirred for 1 hour at $-100\text{ }^{\circ}\text{C}$ before quenching with CH_3OH . The crude product was purified using flash chromatography (45% EtOAc/Hexane) to give (*S*)-**4** (104.0 mg, 79%). The spectral data are consistent with the previously prepared compound. The enantiomeric ratio of (*S*)-**4** was determined to be 94:6 by CSP-HPLC on a Whelk-O column with 5% IPA/hexane mobile phase; retention times for the minor and major enantiomers were 14.1 min and 15.4 min respectively.

Lithiation at $-78\text{ }^{\circ}\text{C}$ and reaction at $-100\text{ }^{\circ}\text{C}$ with deficient chlorotrimethylsilane

The general procedure was followed with lithiation at $-78\text{ }^{\circ}\text{C}$ for 1 hour followed by stirring at $-100\text{ }^{\circ}\text{C}$ for 10 minutes before addition of 0.1 equivalents of chlorotrimethylsilane ($6.0\text{ }\mu\text{L}$, 0.047 mmol). The reaction mixture was stirred for 10 minutes at $-100\text{ }^{\circ}\text{C}$ before quenching with CH_3OH . The crude product was purified using flash chromatography (45% EtOAc/Hexane) to give (*S*)-**4** (10.8 mg , 8%). The spectral data are consistent with the previously prepared compound. The enantiomeric ratio of (*S*)-**4** was determined to be 86:14 by CSP-HPLC on a Whelk-O column with 5% IPA/hexane mobile phase; retention times for the minor and major enantiomers were 14.8 min and 16.9 min respectively.

Lithiation at $-100\text{ }^{\circ}\text{C}$ and reaction with excess chlorotrimethylsilane

The general procedure was followed with lithiation at $-100\text{ }^{\circ}\text{C}$ for 1 hour before addition of 1.1 equivalents of chlorotrimethylsilane ($70.0\text{ }\mu\text{L}$, 0.55 mmol). The reaction mixture was stirred for 1 hour at $-100\text{ }^{\circ}\text{C}$ before quenching with CH_3OH . The crude product was purified using flash chromatography (45% EtOAc/Hexane) to give (*S*)-**4** (60.9 mg , 46%). The spectral data are consistent with the previously prepared compound. The enantiomeric ratio of (*S*)-**4** was determined to be 52:48 by CSP-HPLC on a Whelk-O column with 5% IPA/hexane mobile phase; retention times for the minor and major enantiomers were 13.6 min and 16.2 min respectively.

Lithiation at $-100\text{ }^{\circ}\text{C}$ and reaction with deficient chlorotrimethylsilane

The general procedure was followed with lithiation at $-100\text{ }^{\circ}\text{C}$ for 70 minutes before addition of 0.1 equivalents of chlorotrimethylsilane ($6.0\text{ }\mu\text{L}$, 0.047 mmol). The reaction mixture was stirred for 10 minutes at $-100\text{ }^{\circ}\text{C}$ before quenching with CH_3OH . The crude product was purified using flash chromatography (45% EtOAc/Hexane) to give (*S*)-**4**

(10.9 mg, 8%). The spectral data are consistent with the previously prepared compound. The enantiomeric ratio of (*S*)-**4** was determined to be 52:48 by CSP-HPLC on a Whelk-O column with 5% IPA/hexane mobile phase; retention times for the minor and major enantiomers were 14.6 min and 17.4 min respectively.

Reaction with excess benzyl bromide at $-78\text{ }^{\circ}\text{C}$

The general procedure was followed using 1.1 equivalents of benzyl bromide (71.0 μL , 0.60 mmol). The crude product was purified using prep-HPLC (40% EtOAc/Hexane) to give (*S*)-**6** (88.6 mg, 63%). The spectral data are consistent with the previously prepared compound. The enantiomeric ratio of (*S*)-**6** was determined to be 83:17 by CSP-HPLC on a Whelk-O column with 10% IPA/hexane mobile phase; retention times for the minor and major enantiomers were 16.3 min and 18.7 min respectively.

Reaction with deficient benzyl bromide at $-78\text{ }^{\circ}\text{C}$

The general procedure was followed using 0.1 equivalents of benzyl bromide (6.0 μL , 0.050 mmol). The crude product was purified using prep-HPLC (40% EtOAc/Hexane) to give (*S*)-**6** (7.0 mg, 5%). The spectral data are consistent with the previously prepared compound. The enantiomeric ratio of (*S*)-**6** was determined to be 82:18 by CSP-HPLC on a Whelk-O column with 10% IPA/hexane mobile phase; retention times for the minor and major enantiomers were 16.3 min and 18.7 min respectively.

Lithiation at $-78\text{ }^{\circ}\text{C}$ and reaction at $-100\text{ }^{\circ}\text{C}$ with excess benzyl bromide

The general procedure was followed with lithiation at $-78\text{ }^{\circ}\text{C}$ for 1 hour followed by stirring at $-100\text{ }^{\circ}\text{C}$ for 10 minutes before addition of 1.1 equivalents of benzyl bromide (65.0 μL , 0.55 mmol). The reaction mixture was stirred for 1 hour at $-100\text{ }^{\circ}\text{C}$ before

quenching with CH₃OH. The crude product was purified using flash chromatography (40% EtOAc/Hexane) to give (*S*)-**6** (109.3 mg, 78%). The spectral data are consistent with the previously prepared compound. The enantiomeric ratio of (*S*)-**6** was determined to be 85:15 by CSP-HPLC on a Whelk-O column with 10% IPA/hexane mobile phase; retention times for the minor and major enantiomers were 17.8 min and 20.4 min respectively.

Lithiation at –78 °C and reaction at –100 °C with deficient benzyl bromide

The general procedure was followed with lithiation at –78 °C for 1 hour followed by stirring at –100 °C for 10 minutes before addition of 0.1 equivalents of benzyl bromide (5.6 µL, 0.047 mmol). The reaction mixture was stirred for 10 minutes at –100 °C before quenching with CH₃OH. The crude product was purified using flash chromatography (40% EtOAc/Hexane) to give (*S*)-**6** (6.4 mg, 5%). The spectral data are consistent with the previously prepared compound. The enantiomeric ratio of (*S*)-**6** was determined to be 85:15 by CSP-HPLC on a Whelk-O column with 10% IPA/hexane mobile phase; retention times for the minor and major enantiomers were 18.1 min and 21.0 min respectively.

Lithiation at –100 °C and reaction with excess benzyl bromide

The general procedure was followed with lithiation at –100 °C for 1 hour before addition of 1.1 equivalents of benzyl bromide (65.0 µL, 0.55 mmol). The reaction mixture was stirred for 1 hour at –100 °C before quenching with CH₃OH. The crude product was purified using flash chromatography (40% EtOAc/Hexane) to give (*S*)-**6** (70.7 mg, 50%). The spectral data are consistent with the previously prepared compound. The enantiomeric ratio of (*S*)-**6** was determined to be 55:45 by CSP-HPLC

on a Whelk-O column with 10% IPA/hexane mobile phase; retention times for the minor and major enantiomers were 17.1 min and 20.5 min respectively.

Lithiation at $-100\text{ }^{\circ}\text{C}$ and reaction with deficient benzyl bromide

The general procedure was followed with lithiation at $-100\text{ }^{\circ}\text{C}$ for 70 minutes before addition of 0.1 equivalents of benzyl bromide (5.6 μL , 0.047 mmol). The reaction mixture was stirred for 10 minutes at $-100\text{ }^{\circ}\text{C}$ before quenching with CH_3OH . The crude product was purified using flash chromatography (40% EtOAc/Hexane) to give (*S*)-**6** (8.3 mg, 6%). The spectral data are consistent with the previously prepared compound. The enantiomeric ratio of (*S*)-**6** was determined to be 56:44 by CSP-HPLC on a Whelk-O column with 10% IPA/hexane mobile phase; retention times for the minor and major enantiomers were 18.3 min and 22.1 min respectively.

Tin-lithium exchange of (*S*)-5** from -78 ° to $-100\text{ }^{\circ}\text{C}$**

To a stirring solution of (*S*)-**5** (147 mg, 0.31 mmol) in MTBE (3 mL) and THF (1 mL) at $-78\text{ }^{\circ}\text{C}$ was added a solution of **1** (0.155 mL, 0.65 mmol) and *sec*-BuLi (0.585 mL, 1.36 M in cyclohexane, 0.65 mmol) in MTBE (3 mL) and THF (1 mL), pre-cooled to $-78\text{ }^{\circ}\text{C}$. After stirring for 1 hour, the solution was cooled to $-100\text{ }^{\circ}\text{C}$ for 1 hour and chlorotrimethylsilane (47.0 μL , 0.35 mmol) was added at $-100\text{ }^{\circ}\text{C}$. The reaction was quenched with 1 mL of CH_3OH after stirring at $-100\text{ }^{\circ}\text{C}$ for an additional 2 hours. Stirring was continued as the solution was allowed to warm to room temperature. The solution was poured into 5% H_3PO_4 (10 mL) and 10 mL of ether was added. The layers were separated and the aqueous layer was extracted with ether (3 x 10 mL). The combined ether layers were dried over MgSO_4 and the solvent removed *in vacuo* to

afford the crude (*S*)-**4**. The crude product was purified using flash chromatography (25% EtOAc/Hexane) to give (*S*)-**4** (70.9 mg, 88%). The spectral data are consistent with the previously prepared compound. The enantiomeric ratio of (*S*)-**4** was determined to be 77:23 by CSP-HPLC on a Whelk-O column with 5% IPA/hexane mobile phase; retention times for the minor and major enantiomers were 14.0 min and 16.2 min respectively.

Tin-lithium exchange of (*S*)-5** at –100 °C**

To a stirring solution of (*S*)-**5** (54 mg, 0.11 mmol) in MTBE (3 mL) and THF (1 mL) at –100 °C was added a solution of **1** (0.057 mL, 0.24 mmol) and *sec*-BuLi (0.215 mL, 1.36 M in cyclohexane, 0.24 mmol) in MTBE (3 mL) and THF (1 mL), pre-cooled to –100 °C. After stirring for 1 hour, chlorotrimethylsilane (17.0 µL, 0.13 mmol) was added at –100 °C. The reaction was quenched with 1 mL of CH₃OH after stirring at –100 °C for an additional 2 hours. Stirring was continued as the solution was allowed to warm to room temperature. The solution was poured into 5% H₃PO₄ (10 mL) and 10 mL of ether was added. The layers were separated and the aqueous layer was extracted with ether (3 x 10 mL). The combined ether layers were dried over MgSO₄ and the solvent removed *in vacuo* to afford the crude (*S*)-**4**. The crude product was purified using flash chromatography (25% EtOAc/Hexane) to give (*S*)-**4** (6.9 mg, 23%) and recovered (*S*)-**5** (28.2 mg, 53%). The spectral data are consistent with the previously prepared compounds. The enantiomeric ratio of (*S*)-**4** was determined to be 63:37 by CSP-HPLC on a Whelk-O column with 5% IPA/hexane mobile phase; retention times for the minor and major enantiomers were 14.1 min and 16.5 min respectively. The enantiomeric ratio of recovered (*S*)-**5** was determined to be 88:12 by CSP-HPLC on a Whelk-O column with

1.5% IPA/hexane mobile phase; retention times for the minor and major enantiomers were 21.2 min and 23.5 min respectively.

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