Supporting Information

Synthesis and Palladium Catalyzed Coupling Reactions of Enantiopure *p*-Bromophenyl Methyl Sulfoximine

*Gae Young Cho, Hiroaki Okamura, and Carsten Bolm**

Institut für Organische Chemie der RWTH Aachen
Professor-Pirlet-Str. 1, D-52056 Aachen, Germany

* To whom the correspondence should be addressed. Fax: (Int.) +49 241 809 2391. Phone: (Int.) +49 241 809 4675. E-mail: Carsten.Bolm@oc.rwth-aachen.de

Table of Contents

- General
- Synthesis of (*S*)- and *rac-p*-bromophenyl methyl sulfoximine [(*S*)-**2** and *rac*-**2**, respectively]
- Representative procedures for the palladium-catalyzed couplings
- Full experimental details and analytical data for all new compounds
- References

General. Unless otherwise specified, all reagents were purchased from commercial suppliers and used without further purification. Toluene was distilled from sodium benzophenone ketyl radical under argon, CH₂Cl₂ from CaH₂. All other solvents were reagent grade and used as received. Unless otherwise noted all reactions were carried out under argon using standard Schlenk and vacuum line techniques. ¹H and ¹³C NMR (400 and 100 MHz, respectively) spectra were recorded in CDCl₃. Chemical shifts are given in ppm and spin-spin coupling constants, *J*, are given in Hz. Some depicted spectra contain solvent residues. Those have been removed prior to elemental analyses. IR spectra were recorded as KBr pellets. Melting Points were measured in open glass capillaries and are uncorrected. Optical rotation were determined at 25 °C using HPLC-grade solvents. *O*-Mesitylenesulfonylhydroxylamine

(MSH)¹ and (*S*)-*p*-bromophenyl methyl sulfoxide² were prepared according to literature protocols.

(*S*)-*p*-Bromophenyl methyl sulfoximine [(*S*)-2]. *O*-(Mesitylsulfonyl)acetohydroxamate (24 g, 84.2 mmol) was dissolved in dioxane (41 mL). The reaction mixture was cooled to 0 °C and perchloric acid (70% aq., 41 mL) was slowly added to the mixture under vigorous stirring. After 10 min ice water (200 mL) and dichloromethane were added sequentially, and the organic phase was separated. (*S*)-*p*-Bromophenyl methyl sulfoxide (6.24 g, 28.5 mmol) was added to the organic phase at room temperature. After 2 d the reaction mixture was poured into a cold aqueous solution of NaOH (10%, 200 mL), stirred for 10 min, and extracted with dichloromethane. The combined extracts were washed with HCl (10%). Sulfoximine **2** was isolated by neutralizing the acidic aqueous layer with Na₂CO₃ (solid) and extracting it with dichloromethane. After concentration in vacuo (using a rotary evaporation), (*S*)-*p*-bromophenyl methylsulfoximine [(*S*)-2] was obtained in 86% yield (5.73 g) as a solid with ≥99% ee. Mp. 105-106 °C; [α]_D –13.0 (*c* 1.07, MeOH); ¹H NMR (CDCl₃, 400 MHz) δ 7.83-7.79 (m, 2H), 7.63-7.60 (m, 2H), 3.04 (s, 3H), 2.74 (s, br, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 142.5, 132.3, 129.2, 128.0, 46.0; IR (neat, cm⁻¹) 3304, 3081, 1915, 1219; MS (EI, *m/z*) 233 (M⁺); Anal. Calcd for C₇H₈BrNOS: C, 35.91; H, 3.44; N, 5.98. Found: C, 35.56; H, 3.54; N, 5.90. The enantiomer ratio was determined by HPLC using a chiral column (250 x 4.6 mm Chiralcel OJ column, 0.5 mL/min, 85:15 heptane/2-propanol); *t*_R = 44 min (*S*) and *t*_R = 71 min (*R*).

Preparation of racemic *p*-bromophenyl methyl sulfoximine (*rac*-2). To a solution of *p*-bromophenylthioanisole (16.9 g, 83.3 mmol) and acetic acid (20 mL), aqueous H₂O₂ (35%, 124 mmol) was slowly added at –5 °C. The reaction mixture was then warmed to room temperature and stirred overnight. An aqueous solution of NaOH (12 N, 30 mL) was added at 0 °C and the resulting mixture was extracted with dichloromethane several times. The combined organic layers were dried (MgSO₄) and concentrated affording pure *p*-bromophenyl methyl sulfoxide (15.9 g) as a white solid in 86% yield. In the subsequent imination reaction this product was used without further purification.

p-Bromophenyl methyl sulfoxide (10.8 g, 49.5 mmol) and sodium azide (3.5 g, 54.3 mmol) were dissolved in chloroform (55 mL). The mixture was cooled to 0 °C and concentrated sulfuric acid (23 g) was slowly added over 15 min. The reaction mixture was then warmed to room temperature and stirred overnight. Subsequently, ice water was added until the salts

were dissolved completely. The aqueous layer was extracted with chloroform, neutralized with an aqueous solution of NaOH (16 N), and extracted with dichloromethane. Drying of the organic phase (MgSO₄) followed by its concentration in vacuo afforded *p*-bromophenyl methyl sulfoximine (6.4 g) as a white solid in 56% yield.

Preparation of (*S,S*)-7. Boc-Phe-OH (1.6 g, 6 mmol) was dissolved in dichloromethane (50 mL), and after sequential addition of DCC (1.3 g, 6.3 mmol), HOBT (854 mg, 6.3 mmol) and (*S*)-*p*-bromophenyl methyl sulfoximine [(*S*)-2] at room temperature the reaction mixture was stirred overnight. After DCC urea was filtered out, the reaction mixture was concentrated and the product was purified by column chromatography (SiO₂, 3:2 = hexane:ethyl acetate) to give (*S,S*)-7 (2.4 g) as a white solid in 96% yield. Mp. 163-165 °C; [α]_D -40.2 (*c* 1.03, MeOH); ¹H NMR (CDCl₃, 400 MHz) δ 7.71-7.65 (m, 4H), 7.30-7.20 (m, 5H), 5.14 (d, 1H, *J* = 7.1 Hz), 4.60-4.55 (m, 1H) 3.31 (s, 3H), 3.23-3.08 (m, 2H), 1.42 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 179.9, 155.3, 137.3, 137.1, 132.9, 129.7, 129.4, 128.7, 128.3, 126.6, 79.4, 57.4, 44.0, 38.5, 28.3; IR (neat, cm⁻¹) 2984, 1648, 1507, 1217; MS (CI, *m/z*) 481 (MH⁺); HRMS of [M]⁺ Calcd. 480.0719; found 480.0718.

Preparation of (*S*)-8. To a solution of sulfoximine (*S*)-2 (2 g, 8.6 mmol) in dry THF (25 mL) was added NaH (478.8 mg, 12 mmol, 60% in mineral oil) at room temperature under argon, followed by di-*tert*-butyl-dicarbonate (3.7 g, 17 mmol). The reaction mixture was then stirred at room temperature overnight and subsequently quenched with a saturated solution of NH₄Cl. The aqueous layer was extracted with dichloromethane several times, and the combined organic extracts were then dried (MgSO₄) and concentrated. Purification by column chromatography (SiO₂, 1:2 = hexane:ethyl acetate) gave (*S*)-8 (2.1 g) as a white solid in 74% yield. Mp. 116-117 °C; [α]_D -76.8 (*c* 1.01, MeOH); ¹H NMR (CDCl₃, 400 MHz) δ 7.86-7.81 (m, 2H), 7.76-7.72 (m, 2H), 3.23 (s, 3H), 1.39 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 157.4, 137.8, 132.9, 129.1, 128.9, 80.9, 44.6, 28.0; IR (neat, cm⁻¹) 3090, 2933, 1388, 1272; MS (CI, *m/z*) 334 (MH⁺); Anal. Calcd for C₁₂H₁₆BrNO₃S: C, 43.12; H, 4.83; N, 4.19. Found: C, 42.96; H, 4.78; N, 4.00.

General Procedure (GP 1) for the Palladium-Catalyzed Amination of (*S,S*)-7 and *rac*-8. A solution of (*S,S*)-7 (96 mg, 0.2 mmol) or *rac*-8 (100 mg, 0.3 mmol), amine (1.2 equiv), potassium carbonate or cesium carbonate (1.4 equiv), tris(dibenzylideneacetone)dipalladium (0) or palladium acetate (II) (2 mol%) and *rac*-BINAP (1.5 equiv/Pd) in toluene (0.2 M) was

heated to reflux under argon until the starting material completely disappeared (TLC analysis). After cooling to room temperature, aq. HCl (1 N, ca. 20 mL) and ethyl acetate (ca. 30 mL) were added, and the organic phase was separated, dried (MgSO₄), and concentrated. The product was purified by column chromatography (SiO₂).

Synthesis of (*S,S*)-9a**.** Following GP 1 using (*S,S*)-**7**, benzylamine, K₂CO₃, *rac*-BINAP and Pd₂(dba)₃ gave 89.2 mg (88%) of (*S,S*)-**9a** as a colorless oil (and as a single isomer): [α]_D –32.4 (*c* 1.01, MeOH); ¹H NMR (CDCl₃, 400 MHz) δ 7.55 (d, 2H, *J* = 8.8 Hz), 7.38–7.15 (m, 10H), 6.62 (d, 2H, *J* = 8.8 Hz), 5.20 (d, 1H, *J* = 8.0 Hz), 5.02 (s, br, 1H), 4.55 (dd, 1H, *J* = 5.8, 13.2 Hz), 4.38 (s, br, 2H), 3.27 (s, 3H), 3.24–3.07 (m, 2H), 1.40 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 179.7, 155.2, 152.4, 137.6, 137.2, 129.7, 129.1, 128.8, 128.1, 127.7, 127.2, 126.4, 123.8, 112.2, 79.1, 57.4, 47.4, 44.5, 38.7, 28.3; IR (neat, cm^{–1}) 3376, 2978, 1706, 1596; MS (CI, *m/z*) 508 (MH⁺); Anal. Calcd for C₂₈H₃₃N₃O₄S: C, 66.25; H, 6.55; N, 8.28. Found: C, 66.03; H, 6.59; N, 8.22.

Synthesis of **9b.** Following GP 1 using (*S,S*)-**7**, morpholine, Cs₂CO₃, *rac*-BINAP and Pd(OAc)₂ gave 89.3 mg (92%) of **9b** as a colorless oil and as a mixture of diastereomers: ¹H NMR (CDCl₃, 400 MHz) δ 7.70–7.64 (m, 2H), 7.29–7.18 (m, 5H), 6.94–6.89 (m, 2H), 5.25–5.17 (m, 1H), 4.58–4.56 (m, 1H), 3.87–3.83 (m, 4H), 3.33–3.29 (m, 4H), 3.24–3.07 (m, 5H), 1.41 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 179.8/179.7, 155.2, 154.4, 137.4/137.3, 129.7/129.6, 128.9, 128.1, 126.4, 126.1, 114.0, 79.1, 66.3, 57.5, 47.4, 44.4, 39.1/38.7 28.4 (signal pairs of diastereomers are indicated by /); IR (neat, cm^{–1}) 3424, 2974, 1707, 1363; MS (CI, *m/z*) 488 (MH⁺); HRMS of [M–C₄H₉O]⁺: Calcd. 414.1529; found 414.1529.

Synthesis of (*S,S*)-9c**.** Following GP 1 using (*S,S*)-**7**, aniline, K₂CO₃, *rac*-BINAP and Pd₂(dba)₃ gave 94.6 mg (92%) of (*S,S*)-**9c** as a yellow oil and as a single isomer: [α]_D –36.27 (*c* 0.91, MeOH); ¹H NMR (CDCl₃, 400 MHz) δ 7.68 (d, 2H, *J* = 8.7 Hz), 7.43–7.38 (m, 2H), 7.37–7.14 (m, 8H), 7.03(m, 2H, *J* = 8.9 Hz), 6.54 (s, br, 1H), 5.23 (d, 1H, *J* = 7.9 Hz), 4.62–4.60 (m, 1H), 3.54 (s, 3H), 3.30–3.11(m, 2H), 1.45(s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 179.9, 155.3, 149.5, 139.9, 137.2, 129.7, 129.6, 129.1, 128.2, 126.5, 126.1, 124.1, 121.5, 114.7, 79.2, 57.5, 44.6, 38.7, 28.3; IR (neat, cm^{–1}) 3335, 2928, 1882, 1584; MS (CI, *m/z*) 494 (MH⁺); Anal. Calcd for C₂₇H₃₁N₃O₄S: C, 65.70; H, 6.33; N, 8.51. Found: C, 65.74; H, 6.63; N, 8.27.

^1H and ^{13}C NMR data of compound (*S,R*)-**9c**: ^1H NMR (CDCl_3 , 400 MHz) δ 7.60-7.57 (m, 2H), 7.38-7.09 (m, 8H), 7.00-6.95 (m, 2H), 6.57 (s, br, 1H), 5.22 (d, 1H, $J = 7.4$ Hz), 4.61-4.54 (m, 1H), 3.23-3.17 (m, 5H), 1.40 (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 179.9, 155.2, 149.5, 139.9, 137.3, 129.6, 129.6, 129.1, 128.2, 126.5, 125.9, 124.0, 121.4, 114.7, 79.2, 57.5, 44.6, 39.0, 28.3.

Synthesis of (*S,S,S*)-9d**.** Following GP 1 using (*S,S*)-**7**, (*S*)-*S*-methyl-*S*-phenyl sulfoximine [(*S*)-**1**], K_2CO_3 , *rac*-BINAP and $\text{Pd}(\text{OAc})_2$ gave 113.3 mg (99%) of (*S,S,S*)-**9d** as a white solid and as a single isomer. Mp. 70-72 °C; $[\alpha]_D$ 75.43 (c 1.19, MeOH); ^1H NMR (CDCl_3 , 400 MHz) δ 7.96-7.90 (m, 2H), 7.69-7.65 (m, 1H), 7.61-7.52 (m, 4H), 7.20-7.12 (m, 5H), 7.08-7.05 (m, 2H), 5.16 (d, 1H, $J = 7.7$ Hz), 4.55-4.51 (m, 1H), 3.29 (s, 3H), 3.26 (s, 3H), 3.19-3.05 (m, 2H), 1.39 (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 179.7, 155.2, 151.2, 138.4, 137.2, 134.0, 130.0, 129.7, 129.4, 128.5, 128.4, 128.1, 126.4, 123.1, 79.2, 57.4, 46.5, 44.3, 38.7, 28.4; IR (neat, cm^{-1}) 3422, 2923, 1711, 1450; MS (CI, m/z) 556 (MH^+); Anal. Calcd for $\text{C}_{28}\text{H}_{33}\text{N}_3\text{O}_5\text{S}_2 \cdot \text{H}_2\text{O}$: C, 58.62; H, 6.15; N, 7.32. Found: C, 58.67; H, 6.10; N, 6.92.

Synthesis of **9e.** Following GP 1 using (*S,S*)-**7**, *tert*-butyl carbazate, K_2CO_3 , *rac*-BINAP and $\text{Pd}_2(\text{dba})_3$ gave 77.5 mg (73%) of **9e** as a white solid and as a mixture of diastereomers (ca. 1:1). ^1H NMR (CDCl_3 , 400 MHz) δ 7.86-7.82 (m, 2H), 7.75-7.70 (m, 2H), 7.30-7.21 (m, 5H), 5.22-5.16 (m, 1H), 4.58-4.57 (m, 1H), 3.33-3.10 (m, 5H), 1.57/1.56 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 179.8, 154.0, 148.1, 137.3, 137.1, 129.6, 129.5, 128.1, 127.4, 126.4, 122.0, 83.4, 79.2, 57.6/57.5, 44.2/44.2, 39.1/38.7, 28.4, 28.3 (signal pairs of diastereomers are indicated by /; in the aromatic region those pairs can not reliably be assigned); IR (neat, cm^{-1}) 3349, 2979, 1707, 1494; MS (CI, m/z) 533 (MH^+); HRMS of $[\text{M}]^+$: Calcd. 532.2356; found 532.2356.

Synthesis of *rac*-9f**.** Following GP 1 using *rac*-**8**, benzylamine, Cs_2CO_3 , *rac*-BINAP and $\text{Pd}_2(\text{dba})_3$ gave 101.0 mg (94%) of *rac*-**9f** as a white solid. Mp. 162-163 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 7.70 (d, 2H, $J = 8.8$ Hz), 7.38-7.28 (m, 5H), 6.67 (d, 2H, $J = 8.8$ Hz), 4.39 (s, 2H), 3.19 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 157.8, 152.0, 137.6, 129.3, 128.8, 128.6, 124.2, 112.1, 79.9, 47.4, 45.3, 28.0; IR (neat, cm^{-1}) 3303, 2963, 1669, 1261; MS (EI, m/z) 360 (M^+); Anal. Calcd for $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_3\text{S}$: C, 63.31; H, 6.71; N, 7.77. Found: C, 63.23; H, 6.57; N, 7.66.

Synthesis of *rac*-9g. Following GP 1 using *rac*-8, morpholine, Cs₂CO₃, *rac*-BINAP and Pd(OAc)₂ gave 80.4 mg (79%) of *rac*-9g as a white solid. Mp. 187 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.82-7.77 (m, 2H), 6.96-6.93 (m, 2H), 3.86-3.83 (m, 4H), 3.32-3.29 (m, 4H), 3.20 (s, 3H), 1.40 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 157.9, 154.4, 129.0, 126.3, 114.0, 80.1, 66.4, 47.3, 45.2, 28.0; IR (neat, cm⁻¹) 3447, 2966, 1656, 1287; MS (EI, m/z) 340 (M⁺); Anal. Calcd for C₁₆H₂₄N₂O₄S: C, 56.45; H, 7.11; N, 8.23. Found: C, 56.83; H, 7.28; N, 8.14.

Synthesis of *rac*-9h. Following GP 1 using *rac*-8, aniline, Cs₂CO₃, *rac*-BINAP and Pd₂(dba)₃ gave 99.1 mg (96%) of *rac*-9h as a white solid. Mp. 182 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.73 (d, 2H, *J* = 9.1 Hz), 7.71-7.32 (m, 2H), 7.19-7.16 (m, 2H), 7.12-7.08 (m, 1H), 7.01 (d, 2H, *J* = 9.1 Hz), 3.20 (s, 3H), 1.41 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 157.9, 149.1, 140.0, 129.5, 129.2, 126.5, 123.8, 121.2, 114.8, 80.3, 45.4, 28.2; IR (neat, cm⁻¹) 3324, 1587, 1499, 1287; MS (EI, m/z) 346 (M⁺); HRMS of [M]⁺: Calcd. 346.1351; found 346.1351.

Synthesis of *rac*-9i. Following GP 1 using *rac*-8, *n*-butylamine, Cs₂CO₃, *rac*-BINAP and Pd₂(dba)₃ gave 79.2 mg (81%) of *rac*-9i as a white solid. Mp. 99-100 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.67 (d, 2H, *J* = 9.1 Hz), 6.59 (d, 2H, *J* = 8.8 Hz), 4.41 (s, br, 1H), 3.18 (s, 3H), 3.16-3.12 (m, 2H), 1.64-1.55 (m, 2H), 1.46-1.37 (m, 2H), 1.40 (s, 9H), 1.34 (t, 3H, *J* = 7.1 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 157.8, 152.4, 129.1, 123.3, 111.8, 79.9, 45.5, 43.0, 31.2, 28.1, 20.2, 13.8; IR (neat, cm⁻¹) 3333, 2955, 1676, 1281; MS (EI, m/z) 326 (M⁺); HRMS of [M]⁺: Calcd. 326.1664; found 326.1665.

Synthesis of 9j. Following GP 1 using *rac*-8, *rac*-*S*-methyl-*S*-phenyl sulfoximine (*rac*-1), Cs₂CO₃, *rac*-BINAP and Pd(OAc)₂ gave 87.6 mg (72%) of 9j as a white solid and as a mixture of diastereomers. Mp. 156-158 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.95-7.92 (m, 2H), 7.69-7.52 (m, 5H), 7.12-7.07 (m, 2H), 3.30/3.29 (s, 3H), 3.18/3.17 (s, 3H), 1.34/1.31 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 157.6, 151.2, 138.3, 129.8, 128.6, 128.4, 123.2, 80.2, 46.5, 45.0/44.9, 28.0 (signal pairs of diastereomers are indicated by /; one C_{aryl} signal could not be assigned); IR (neat, cm⁻¹) 3443, 2926, 1684, 1275; MS (EI, m/z) 408 (M⁺); HRMS of [M]⁺: Calcd. 408.1178; found 408.117.

General Procedure (GP 2) for Palladium-Catalyzed Suzuki Coupling of (*S,S*)-7 and *rac*-8. To a mixture of (*S,S*)-7 (96 mg, 0.2 mmol) or *rac*-8 (100 mg, 0.3 mmol) and Pd(PPh₃)₄ (2 mol%) in acetonitrile (3 mL) was added the aryl boronic acid (1.2 equiv), followed by K₂CO₃

(1.5 equiv) in H₂O (1 mL). The mixture was heated to reflux until the starting material was completely consumed (TLC analysis). After cooling to room temperature, the reaction mixture was partitioned between ethyl acetate and brine. The organic phase was separated, dried (MgSO₄) and concentrated. The product was purified by column chromatography (SiO₂).

Synthesis of 11a. Following GP 2 using (*S,S*)-**7** and 4-biphenylboronic acid gave 89.5 mg (78%) of **11a** as a white solid and as a mixture of diastereomers (> 10:1). ¹H NMR (CDCl₃, 400 MHz) δ 7.83 (d, 2H, *J* = 8.5 Hz), 7.73-7.71 (m, 2H), 7.67-7.56 (m, 6H), 7.42-7.38 (m, 2H), 7.34-7.29 (m, 1H), 7.23-7.13 (m, 5H), 5.12 (d, 1H, *J* = 7.7 Hz), 4.57-4.52 (m, 1H), 3.30/3.24 (s, 3H), 3.21-3.04 (m, 2H), 1.35 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 179.9, 155.3, 146.5, 141.7, 140.1, 137.6, 137.2, 136.7, 129.7, 128.9, 128.2, 128.0, 127.8, 127.7, 127.0, 126.5, 79.3, 57.4, 44.1, 38.6, 28.3 (signal pairs of diastereomers are indicated by /; two C_{aryl} signals could not be assigned); IR (neat, cm⁻¹) 3375, 2928, 1648, 1501; MS (CI, *m/z*) 555 (MH⁺); Anal. Calcd for C₃₃H₃₄N₂O₄S: C, 71.45; H, 6.18; N, 5.05. Found: C, 71.67; H, 6.18; N, 4.75.

Synthesis of (*S,S*)-11b. Following GP 2 using (*S,S*)-**7** and 4-methoxyphenylboronic acid gave 94.9 mg (90%) of (*S,S*)-**11b** as a white solid and as a single isomer. Mp. 124-125 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.86 (d, 2H, *J* = 8.4 Hz), 7.74-7.69 (m, 2H), 7.59-7.54 (m, 2H), 7.32-7.20 (m, 5H), 7.04-7.00 (m, 2H), 5.19 (d, 1H, *J* = 7.9 Hz), 4.65-4.59 (m, 1H), 3.88 (s, 3H), 3.37 (s, 3H), 3.28-3.10 (m, 2H), 1.43 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 179.9, 160.3, 155.3, 146.6, 137.2, 135.8, 131.2, 129.7, 128.5, 128.2, 127.7, 127.6, 126.5, 114.6, 79.3, 57.4, 55.4, 44.1, 38.1, 28.3; IR (neat, cm⁻¹) 3385, 2929, 1519, 1249; MS (CI, *m/z*) 509 (MH⁺); HRMS of [M-C₄H₅O]⁺: Calcd. 435.1379; found 435.1379.

Synthesis of 11c. Following GP 2 using (*S,S*)-**7** and 2,5-dimethylphenylboronic acid gave 76.1 mg (75%) of **11c** as a white solid and as a mixture of diastereomers (8:1). ¹H NMR (CDCl₃, 400 MHz) δ 7.92 (d, 2H, *J* = 8.4 Hz), 7.40-7.35 (m, 2H), 7.31-7.20 (m, 6H), 7.16-7.13 (m, 2H), 5.21 (d, 1H, *J* = 7.9 Hz), 4.68-4.61 (m, 1H), 3.44/3.37 (s, 3H), 3.30-3.13 (m, 2H), 2.02/2.01 (s, 6H), 1.43 (s, 9H) (signal pairs of diastereomers are indicated by /); ¹³C NMR (CDCl₃, 100 MHz) δ 179.9, 155.3, 147.6, 139.5, 137.2, 136.6, 135.4, 130.4, 129.7, 128.2, 128.0, 127.6, 127.4, 126.5, 79.3, 57.5, 44.1, 38.6, 28.3, 20.8; IR (neat, cm⁻¹) 3428,

2928, 1711, 1364; MS (CI, m/z) 507 (MH⁺); HRMS of [M]⁺: Calcd. 506.2239; found 506.2239.

Synthesis of 11d. Following GP 2 using (*S,S*)-**7** and 4-acetylphenylboronic acid gave 75.4 mg (70%) of **11d** as a white solid and as a mixture of diastereomers (>10:1). ¹H NMR (CDCl₃, 400 MHz) δ 8.09-8.05 (m, 2H), 7.91 (d, 2H, *J* = 8.2 Hz), 7.79-7.75 (m, 2H), 7.71-7.67 (m, 2H), 7.30-7.19 (m, 5H), 5.17 (d, 1H, *J* = 7.7 Hz), 4.63-4.56 (m, 1H), 3.36/3.30 (s, 3H) 3.26-3.08 (m, 2H), 2.64 (s, 3H), 1.41 (s, 9H) (signal pairs of diastereomers are indicated by /); ¹³C NMR (CDCl₃, 100 MHz) δ 197.4, 180.0, 155.3, 145.6, 143.3, 137.7, 137.1, 137.0, 129.7, 129.1, 128.4, 128.2, 127.9, 127.6, 126.6, 79.3, 57.4, 44.1, 38.6, 28.3, 26.7; IR (neat, cm⁻¹) 3378, 2925, 1685, 1516; MS (CI, m/z) 521 (MH⁺); HRMS of [M-C₄H₉O]⁺: Calcd. 447.1379; found 447.1379.

Synthesis of rac-11e. Following GP 2 using *rac*-**8** and using 4-biphenylboronic acid gave 115.0 mg (95%) of *rac*-**11e** as a white solid. Mp. 196 °C; ¹H NMR (CDCl₃, 400 MHz) δ 8.07-8.03 (m, 2H), 7.86-7.82 (m, 2H), 7.74-7.62 (m, 6H), 7.51-7.45 (m, 2H), 7.44-7.36 (m, 1H), 3.29 (s, 3H), 1.42 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 157.7, 146.2, 141.6, 140.1, 137.7, 137.2, 128.9, 128.0, 127.9, 127.8, 127.7, 127.7, 127.0, 80.6, 44.8, 28.0; IR (neat, cm⁻¹) 3418, 2977, 1664, 1283; MS (EI, m/z) 407 (M⁺); Anal. Calcd for C₂₄H₂₅NO₃S: C, 70.73; H, 6.18; N, 3.44. Found: C, 70.95; H, 6.29; N, 3.31.

Synthesis of rac-11f. Following GP 2 using *rac*-**8** and 4-methoxyphenylboronic acid gave 97.5 mg (90%) of *rac*-**11f** as a white solid. Mp. 135 °C; ¹H NMR (CDCl₃, 400 MHz) δ 8.01-7.98 (m, 2H), 7.76-7.73 (m, 2H), 7.58-7.54 (m, 2H), 7.02-6.99 (m, 2H), 3.87 (s, 3H), 3.26 (s, 3H), 1.39 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 160.2, 157.7, 146.3, 136.3, 131.3, 128.5, 127.9, 127.6, 114.5, 80.6, 55.4, 44.9, 28.0; IR (neat, cm⁻¹) 3381, 2973, 1697, 1604; MS (CI, m/z) 362 (MH⁺); Anal. Calcd for C₁₉H₂₃NO₄S: C, 63.13; H, 6.41; N, 3.88. Found: C, 62.81; H, 6.53; N, 3.67.

Synthesis of rac-11g. Following GP 2 using *rac*-**8** and 2,5-dimethylphenylboronic acid gave 99.7 mg (93%) of *rac*-**11g** as a colorless oil. ¹H NMR (CDCl₃, 400 MHz) δ 8.00-7.96 (m, 2H), 7.35-7.31 (m, 2H), 7.19-7.12 (m, 1H), 7.07-7.05 (m, 2H), 3.27 (s, 3H), 2.0 (s, 6H), 1.33 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 157.4, 147.3, 139.6, 137.2, 135.4, 130.4, 127.9, 127.6, 127.6, 80.6, 44.6, 28.0, 20.7; IR (neat, cm⁻¹) 3462, 2975, 1695, 1367; MS (CI, m/z) 360

(MH⁺); Anal. Calcd for C₂₀H₂₅NO₃S: C, 66.82; H, 7.01; N, 3.90. Found: C, 66.52; H, 7.15; N, 3.82.

Synthesis of *rac*-11h. Following GP 2 using *rac*-8 and 4-acetylphenylboronic acid gave 107.7 mg (97%) of *rac*-11h as a solid. Mp. 135 °C; ¹H NMR (CDCl₃, 400 MHz) δ 8.09-8.06 (m, 4H), 7.84-7.81 (m, 2H), 7.72-7.70 (m, 2H), 3.28 (s, 3H), 2.66 (s, 3H), 1.41 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 197.4, 157.6, 145.2, 143.2, 138.1, 136.8, 129.0, 128.4, 128.0, 127.5, 80.6, 44.7, 27.9, 26.6; IR (neat, cm⁻¹) 3443, 2979, 1674, 1603; MS (CI, m/z) 374 (MH⁺); Anal. Calcd for C₂₀H₂₃NO₄S: C, 64.32; H, 6.21; N, 3.75. Found: C, 64.34; H, 6.33; N, 3.61.

General Procedure (GP 3) for Palladium-Catalyzed Stille Coupling of (*S,S*)-7 and *rac*-8.

Under argon (*S,S*)-7 (96 mg, 0.2 mmol) or *rac*-8 (100 mg, 0.3 mmol), Pd₂(dba)₃ (1 mol%) and *rac*-BINAP (2.2 mol%) were dissolved in toluene (2 mL). After adding the stannane (1.2 equiv), the mixture was heated to reflux until the starting material was completely consumed (TLC analysis). The solution was concentrated in vacuo, and the resulting product was isolated by column chromatography (SiO₂).

Synthesis of (*S,S*)-12a. Following GP 3 using (*S,S*)-7 and tributyl(vinyl)tin gave 86.4 mg (97%) of (*S,S*)-12a as a white solid and as a single isomer. Mp. 153-154 °C; [α]_D -41.42 (*c* 1.26, MeOH); ¹H NMR (CDCl₃, 400 MHz) δ 7.78 (d, 2H, *J* = 8.2 Hz), 7.56 (d, 2H, *J* = 8.5 Hz), 7.29-7.20 (m, 5H), 6.76 (dd, 1H, *J* = 11.0, 17.6 Hz), 5.92 (d, 1H, *J* = 17.6 Hz), 5.48 (d, 1H, *J* = 11.0 Hz), 5.16 (d, 1H, *J* = 7.4 Hz), 4.61-4.56 (m, 1H), 3.33 (s, 3H), 3.25-3.08 (m, 2H), 1.41 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 179.9, 155.3, 143.2, 137.2, 136.9, 135.0, 129.7, 128.2, 127.5, 127.1, 126.5, 118.4, 79.2, 57.4, 44.1, 38.6, 28.4; IR (neat, cm⁻¹) 3384, 2930, 1623, 1525; MS (CI, m/z) 429 (MH⁺); Anal. Calcd for C₂₃H₂₈N₂O₄S: C, 64.46; H, 6.59; N, 6.54. Found: C, 64.33; H, 6.70; N, 6.48.

Synthesis of (*S,S*)-12b. Following GP 3 using (*S,S*)-7 and tributylphenyltin gave 97.4 mg (98%) of (*S,S*)-12b as a white solid and as a single isomer. Mp. 126-127 °C; [α]_D -36.63 (*c* 1.43, MeOH); ¹H NMR (CDCl₃, 400 MHz) δ 7.82 (d, 2H, *J* = 8.4 Hz), 7.70-7.66 (m, 2H), 7.55-7.51 (m, 2H), 7.46-7.35 (m, 3H), 7.24-7.13 (m, 5H), 5.11 (d, 1H, *J* = 7.7 Hz), 4.57-4.51 (m, 1H), 3.30 (s, 3H), 3.20-3.03 (m, 2H), 1.14 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 180.0, 155.3, 147.1, 138.9, 137.2, 136.7, 129.7, 129.1, 128.8, 128.2, 127.7, 127.4, 126.5, 79.3, 57.4, 44.1, 38.6, 28.3 (one signal could not be detected); IR (neat, cm⁻¹) 3428, 2927, 1693, 1364;

MS (CI, m/z) 479 (MH^+); Anal. Calcd for $C_{27}H_{30}N_2O_4S$: C, 67.76; H, 6.32; N, 5.85. Found: C, 67.92; H, 6.65; N, 5.64.

Synthesis of (*S,S*)-12c. Following GP 3 using (*S,S*)-7 and tributyl(1-ethoxyvinyl)tin gave 85.3 mg (87%) of (*S,S*)-12c as a colorless oil. $[\alpha]_D -40.96$ (c 1.10, MeOH); 1H NMR ($CDCl_3$, 400 MHz) δ 7.84-7.78 (m, 4H), 7.32-7.22 (m, 5H), 5.19 (d, 1H, $J = 7.7$ Hz), 4.81 (d, 1H, $J = 3.0$ Hz), 4.64-4.58 (m, 1H), 4.40 (d, 1H, $J = 3.0$ Hz), 3.97 (dd, 2H, $J = 7.1, 14.0$ Hz), 3.35 (s, 3H), 3.28-3.10 (m, 2H), 1.49-1.39 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.9, 157.8, 155.2, 142.2, 137.4, 137.1, 129.7, 128.2, 127.0, 126.5, 126.4, 85.0, 79.2, 63.7, 57.4, 41.0, 38.6, 28.3, 14.6; IR (neat, cm^{-1}) 3371, 2930, 1681, 1628, 1530; MS (EI, m/z) 472 (M^+); Anal. Calcd for $C_{25}H_{32}N_2O_5S$: C, 63.54; H, 6.82; N, 5.93. Found: C, 63.55; H, 6.43; N, 5.82.

Synthesis of (*S,S*)-12d. Following GP 3 using (*S,S*)-7 and tributyl(phenylethynyl)tin gave 89.5 mg (86%) of (*S,S*)-12d as a white solid and as a single isomer. Mp. 160-161 °C; $[\alpha]_D 13.75$ (c 1.88, MeOH); 1H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, 2H, $J = 8.4$ Hz), 7.70-7.65 (m, 2H), 7.58-7.57 (m, 2H), 7.42-7.37 (m, 3H), 7.32-7.21 (m, 5H), 5.17 (d, 1H, $J = 7.9$ Hz), 4.61-4.59 (m, 1H), 3.35 (s, 3H), 3.26-3.09 (m, 2H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.0, 155.2, 137.2, 137.1, 132.4, 131.8, 129.7, 129.5, 129.2, 128.5, 128.2, 127.2, 126.5, 122.1, 93.8, 87.4, 79.3, 57.4, 44.0, 38.6, 28.3; IR (neat, cm^{-1}) 3377, 2926, 2219, 1696; MS (CI, m/z) 503 (MH^+); Anal. Calcd for $C_{29}H_{30}N_2O_4S$: C, 69.30; H, 6.02; N, 5.57. Found: C, 69.35; H, 6.26; N, 5.32.

Synthesis of (*S,S*)-12e. Following GP 3 using (*S,S*)-7 and allyltributyltin gave 83.5 mg (91%) of (*S,S*)-12e as a white solid and as a single isomer. Mp. 135 °C; $[\alpha]_D -38.40$ (c 1.88, MeOH); 1H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, 2H, $J = 7.9$ Hz), 7.40-7.39 (m, 2H), 7.29-7.20 (m, 5H), 6.01-5.87 (m, 1H), 5.19-5.10 (m, 3H), 4.60-4.57 (m, 1H), 3.48 (d, 2H, $J = 6.7$ Hz), 3.33 (s, 3H), 3.24-3.07 (m, 2H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.9, 155.3, 146.9, 137.1, 135.8, 135.4, 129.7, 129.6, 128.1, 127.2, 126.4, 117.3, 79.2, 57.4, 44.1, 40.0, 38.7, 28.4; IR (neat, cm^{-1}) 3382, 2927, 1681, 1527; MS (EI, m/z) 442 (M^+); HRMS of $[M]^+$: Calcd. 442.1926; found 442.1926. The product proved to be very unstable, and rapid decomposition occurred.

Synthesis of *rac*-12f. Following GP 3 using *rac*-8 and tributyl(vinyl)tin gave 82.3 mg (98%) of *rac*-12f as a white solid. Mp. 112-113 °C; 1H NMR ($CDCl_3$, 400 MHz) δ 7.93-7.89 (m,

2H), 7.60-7.57 (m, 2H), 6.76 (dd, 1H, $J = 11.0, 17.6$ Hz), 5.55 (d, 1H, $J = 17.6$ Hz), 5.46 (d, 1H, $J = 11.0$ Hz), 3.22 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 157.4, 142.8, 137.0, 135.0, 127.7, 127.1, 118.1, 80.6, 44.8, 28.1; IR (neat, cm^{-1}) 3445, 2932, 1666, 1274; MS (CI, m/z) 282 (MH^+); HRMS of $[\text{M}-\text{C}_4\text{H}_9\text{O}]^+$: Calcd. 208.0432; found 208.0433.

Synthesis of *rac*-12g. Following GP 3 using *rac*-8 and tributylphenyltin gave 95.0 mg (96%) of *rac*-12g as a white solid. Mp. 128-129 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 8.05-8.02 (m, 2H), 7.81-7.78 (m, 2H), 7.63-7.60 (m, 2H), 7.52-7.42 (m, 3H), 3.28 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 157.4, 146.7, 138.9, 137.1, 129.0, 128.6, 128.2, 127.8, 127.3, 80.6, 44.9, 28.1; IR (neat, cm^{-1}) 2979, 1662, 1591, 1284; MS (CI, m/z) 332 (MH^+); Anal. Calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_3\text{S}$: C, 65.23; H, 6.39; N, 4.23. Found: C, 65.42; H, 6.71; N, 4.08.

Synthesis of *rac*-12h. Following GP 3 using *rac*-8 and tributyl(phenylethynyl)tin gave 99.4 mg (94%) of *rac*-12i as a white solid. Mp. 125 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 7.96-7.93 (m, 2H), 7.74-7.70 (m, 2H), 7.56-7.53 (m, 2H), 7.39-7.36 (m, 3H), 3.25 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 157.3, 137.8, 132.4, 131.7, 129.2, 129.1, 128.4, 127.3, 93.6, 87.5, 80.7, 44.7, 28.1; IR (neat, cm^{-1}) 3440, 1665, 1389, 1287; MS (CI, m/z) 356 (MH^+); Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_3\text{S}$: C, 67.58; H, 5.95; N, 3.94. Found: C, 67.80; H, 5.85; N, 3.95.

Synthesis of *rac*-12i. Following GP 3 using *rac*-8 and allyltributyltin gave 78.8 mg (89%) of *rac*-12j as a white solid. Mp. 66 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 7.88 (d, 2H, $J = 8.4$ Hz), 7.40 (d, 2H, $J = 8.4$ Hz), 6.00-5.87 (m, 1H), 5.16-5.09 (m, 2H), 3.48 (d, 2H, $J = 6.7$ Hz), 3.22 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 157.6, 146.7, 136.3, 135.6, 129.8, 127.5, 117.3, 80.5, 44.8, 39.9, 28.0; IR (neat, cm^{-1}) 3450, 3019, 2979, 2929, 1665; MS (CI, m/z) 296 (MH^+); Anal. Calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_3\text{S}$: C, 60.99; H, 7.17; N, 4.74. Found: C, 60.80; H, 7.39; N, 4.50.

Synthesis of (*S,S*)-14 To a solution of TFA (1 mL) and dichloromethane (3 mL) was added (*S*)-9g (668 mg, 2 mmol), and the mixture was stirred at room temperature for 1 h. After the addition of H_2O (30 mL) the aqueous phase was neutralized with NaHCO_3 (solid) and extracted with dichloromethane several times. The combined organic layers were dried (MgSO_4) and concentrated under reduced pressure. Without further purification, the crude product was dissolved in dichloromethane (20 mL) under argon and the resulting solution was cooled to 0 °C. Then, DCC (433 mg, 2.1 mmol), HOBT (284 mg, 2.1 mmol) and N-Boc-Val-

OH (434 mg, 2 mmol) were added and the reaction mixture was stirred over night. DCC urea was filtered off (celite), and the reaction mixture was concentrated. After column chromatography (SiO₂) (*S,S*)-**14** (771 mg) was obtained as a colorless oil in 88% yield. ¹H NMR (CDCl₃, 400 MHz) δ 7.81 (d, 2H, *J* = 9.2 Hz), 6.94 (d, 2H, *J* = 9.2 Hz), 5.19 (d, 1H, *J* = 9.2 Hz), 4.24 (dd, 1H, *J* = 4.0, 8.9 Hz), 3.87-3.83 (m, 4H), 3.34-3.30 (m, 7H), 2.27 (m, 1H), 1.44 (s, 9H), 0.97 (d, 3H, *J* = 6.9 Hz), 0.84 (d, 3H, *J* = 6.9 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 180.7, 156.0, 154.5, 128.9, 126.1, 113.9, 79.0, 66.4, 61.4, 47.3, 44.6, 28.4, 19.6; IR (neat, cm⁻¹) 3426, 2969, 1711, 1593; MS (CI, *m/z*) 440 (MH⁺); HRMS of [M-C₉H₁₈NO₂]⁺: Calcd. 267.0803; found 267.0804.

Synthesis of (*S,S,S*)-15**.**³ To a solution of cyclohexyl(isopropyl)amine (70 μL, 0.42 mmol) in THF (500 μL) at 0 °C under argon was added *n*-BuLi (15% in hexane, 0.42 mmol). The reaction mixture was stirred for 30 min at 0 °C and then cooled at -78 °C. A solution of (*S,S*)-**14** (50 mg, 0.1 mmol) and THF (500 μL) was added dropwise at this temperature. After stirring for 30 min at -78 °C, dried CO₂ was bubbled through the solution for 10 min. The cooling bath was removed and the gas flow reduced. After 10 min the gas flow stopped, and the reaction mixture was warmed to room temperature. Under vigorous stirring water was added. The organic phase was separated and the aqueous phase extracted once with diethyl ether. The organic phases were discarded and to the aqueous phase NH₄Cl (solid) was added until a precipitate formed. The suspension was extracted with dichloromethane several times, the dichloromethane phase dried (MgSO₄), and the solvent removed under reduced pressure at room temperature (without heating!). After drying (and without further purification) the resulting crude product was dissolved in dichloromethane (1 mL) at 0 °C, and DMAP (1.8 mg, 0.01 mmol) and H-Val-OBn•Tos (38 mg, 0.1 mmol) were added under argon. After cooling to -12 °C, a solution of EEDQ (31 mg, 0.1 mmol) and dichloromethane (1 mL) was added, the reaction mixture was slowly warmed to room temperature and stirred over night. After evaporating the solvent under reduced pressure, purification by column chromatography (SiO₂) gave (*S,S,S*)-**15** (40.8 mg) as a colorless oil in 55% yield. [α]_D -31.1 (*c* 1.54, MeOH); ¹H NMR (CDCl₃, 400 MHz) δ 7.79 (d, 2H, *J* = 9.2 Hz), 7.38-7.32 (m, 5H), 6.87 (d, 2H, *J* = 9.2 Hz), 5.27-5.15 (m, 3H), 4.51-4.29 (m, 4H), 3.85-3.81 (m, 4H), 3.32-3.16 (m, 4H), 2.35-2.20 (m, 2H), 1.45 (s, 9H), 1.01-0.86 (m, 12H); ¹³C NMR (CDCl₃, 100 MHz) δ 181.5, 171.1, 160.4, 154.9, 135.4, 129.9, 128.7, 128.4, 123.3, 113.7, 79.2, 67.1, 66.4, 61.9, 61.7, 58.0, 47.1, 31.5, 31.1, 28.4, 19.7, 19.1, 17.7, 17.1; IR (neat, cm⁻¹) 3354, 2967, 1713, 1505; MS (CI, *m/z*)

673 (MH^+); Anal. Calcd for $\text{C}_{34}\text{H}_{48}\text{N}_4\text{O}_8\text{S}$: C, 60.69; H, 7.19; N, 8.33. Found: C, 61.03; H, 7.53; N, 8.33.

References

1. (a) Tamura, Y.; Minamikawa, J.; Sumoto, K.; Fujii, S.; Ikeda, M. *J. Org. Chem.* **1973**, *38*, 1239. (b) Johnson, C. R.; Kirchhoff, R. A.; Corkins, H. G. *J. Org. Chem.* **1974**, *39*, 2458. (c) Tamura, Y.; Matushima, H.; Minamikawa, J.; Ikeda, M.; Sumoto, K. *Tetrahedron* **1975**, *31*, 3035.
2. Capozzi, M. A. M.; Cardellicchio, C.; Naso, F.; Spina, G.; Tortorella, P. *J. Org. Chem.* **2001**, *66*, 5933.
3. Bolm, C.; Moll, G.; Kahmann, J. D. *Chem. Eur. J.* **2001**, *7*, 1118.