CuI Catalyzed Coupling Reaction of β-Amino Acids or Esters with Aryl Halides at Lower Temperature then Employed in the Normal Ullmann Reaction. Facile Synthesis of SB-214857

Dawei Ma*, Chengfeng Xia

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, 354 Fenglin Lu, Shanghai 200032, China

Supporting Information

General procedure for CuI catalyzed coupling reaction:

To a solution of aryl halide (1 mmol) and β-amino acid or β-amino ester (1 mmol) in 5 mL of DMF were added potassium carbonate (2.5 mmol), 0.1mL of water and CuI (0.1 mmol) under nitrogen. After the mixture was stirred at 100 ^{o}C for 24 h under nitrogen atmosphere, the cooled solution was concentrated in vacuo. The residue was dissolved in water, acidified to pH = 5, and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by chromatography eluting with 1/3 to 1/1 ethyl acetate/petroleum ether to afford the corresponding *N*-aryl b-amino acid.

(*S*)-3-Phenylamino-4-methylpentanoic acid 4a: $[\alpha]_D^{20}$ –9.4 (*c* 0.43, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 8.1, 7.6 Hz, 2H), 6.80 (br, 1H), 6.72 (d, *J* = 7.2 Hz, 1H), 6.65 (d, *J* = 8.2 Hz, 2H), 3.69 (m, 1H), 2.56 (dd, *J* = 15.2, 5.4, 1H), 2.46 (dd, *J* = 15.2, 7.5 Hz, 1H), 1.98 (m, 1H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H); MS *m/z* 208 ($M^+ + H^+$); 207 (M^+), 164, 146, 118, 104, 77; HRMS found *m/z* 207.1260 (M^+); $C_{12}H_{17}NO_2$ requires 207.1259.

(*S*)-3-(4-Methylphenyl)amino-4-methylpentanoic acid 4b: $[\alpha]_D^{20}$ –5.2 (*c* 0.38, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (br, 1H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.61 (d, *J* = 8.4 Hz, 2H), 3.65 (m, 1H), 2.54 (dd, *J* = 15.3, 5.3, 1H), 2.44 (dd, *J* = 15.3, 7.7 Hz, 1H), 2.23 (s, 3H), 1.95 (m, 1H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.7 Hz,

3H); MS *m/z* 222 ($M^+ + H^+$); 221 (M^+), 178, 162, 132, 118, 91; HRMS found *m/z* 221.1414 (M^+); $C_{13}H_{19}NO_2$ requires 221.1416.

(*S*)-3-(4-Iodophenyl)amino-4-methylpentanoic acid 4c: $[\alpha]_D^{20}$ –25.4 (*c* 0.41, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, *J* = 9.8 Hz, 2H), 6.43 (d, *J* = 9.9 Hz, 2H), 6.10 (br, 1H), 3.63 (m, 1H), 2.56 (dd, *J* = 15.3, 5.3 Hz, 1H), 2.44 (dd, *J* = 15.3, 7.5 Hz, 1H), 1.92 (m, 1H), 0.98 (d, *J* = 4.7 Hz, 3H), 0.94 (d, *J* = 5.3 Hz, 3H); MS *m/z* 333 (M^+), 290, 230, 220, 164; HRMS found *m/z* 333.0192 (M^+); $C_{12}H_{16}INO_2$ requires 333.0226.

(*S*)-3-(2-Chlorophenyl)amino-4-methylpentanoic acid 4d: $[\alpha]_D^{20}$ –11.8 (*c* 0.78, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.8 Hz, 1H), 7.11 (dd, *J* = 8.7, 7.1 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.61 (dd, *J* = 8.7, 7.5 Hz, 1H), 3.78 (m, 1H), 2.53 (m, 2H), 1.96 (m, 1H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H); MS *m/z* 241 (M^+), 200, 198, 182, 180, 140, 138; HRMS found *m/z* 241.0882 (M^+); $C_{12}H_{16}ClNO_2$ requires 241.0870.

(*S*)-3-(4-Nitrophenyl)amino-4-methylpentanoic acid 4e: $[\alpha]_D^{20}$ –67 (*c* 0.12, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 9.2 Hz, 2H), 6.57 (d, *J* = 9.2 Hz, 2H), 4.60 (br, 1H), 3.78 (m, 1H), 2.64 (dd, *J* = 15.6, 4.8, 1H), 2.50 (dd, *J* = 15.7, 7.4 Hz, 1H), 1.95 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H); MS *m/z* 252 (M^+), 209, 191, 149, 83; HRMS found *m/z* 252.1098 (M^+); $C_{12}H_{16}N_2O_4$ requires 252.1110.

(*S*)-3-(4-Acetylaminophenyl)amino-4-methylpentanoic acid 4f: $[\alpha]_D^{20}$ –11.7 (*c* 0.85, MeOH); ^1H NMR (300 MHz, CD_3COCD_3) δ 7.44 (d, *J* = 6.7 Hz, 2H),

6.75 (d, *J* = 6.6 Hz, 2H), 4.13 (m, 1H), 2.49 (dd, *J* = 15.4, 5.3, 1H), 2.37 (dd, *J* = 15.4, 8.4 Hz, 1H), 1.81 (m, 1H), 1.40 (s, 3H), 0.88 (d, *J* = 6.7 Hz, 6H); MS *m/z* 264 (M^+), 220, 202, 156, 152, 116, 109, 43; HRMS found *m/z* 264.1449 (M^+); $C_{14}H_{20}N_2O_3$ requires 264.1474.

(*S*)-3-(4-Bromophenyl)amino-4-methylpentanoic acid 4g: $[\alpha]_D^{20}$ –30.3 (*c* 0.48, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, *J* = 10.2 Hz, 2H), 6.70 (br, 1H), 6.52 (d, *J* = 10.1 Hz, 2H), 3.64 (m, 1H), 2.54 (dd, *J* = 15.2, 5.1 Hz, 1H), 2.42 (dd, *J* = 15.3, 7.6 Hz, 1H), 1.90 (m, 1H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H); MS *m/z* 285 (M^+), 244, 242, 226, 186, 184, 174, 172; HRMS found *m/z* 285.0338 (M^+); $C_{12}H_{16}BrNO_2$ requires 285.0364.

(*S*)-3-(4-Methoxylphenyl)amino-4-methylpentanoic acid 4h: $[\alpha]_D^{20}$ +17.2 (*c* 0.34, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.81 (d, *J* = 9.1 Hz, 2H), 6.74 (d, *J* = 9.2 Hz, 3H), 4.91 (br, 1H), 3.53 (m, 1H), 2.56 (, dd, *J* = 15.7, 4.4 Hz, 1H), 2.40 (dd, *J* = 15.7, 8.9 Hz, 1H), 1.97 (m, 1H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H); MS *m/z* 237 (M^+), 220, 194, 176, 149, 134, 122, 108; HRMS found *m/z* 237.1336 (M^+); $C_{13}H_{19}NO_3$ requires 237.1365.

(*S*)-3-Phenylaminobutanoic acid 4i: $[\alpha]_D^{20}$ –21.1 (*c* 0.49, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 2H), 6.80-6.66 (m, 3H), 3.93 (m, 1H), 2.67 (dd, *J* = 15.4, 5.6 Hz, 1H), 2.49 (dd, *J* = 15.4, 6.5 Hz, 1H),, 1.30 (d, *J* = 6.4 Hz, 3H); MS *m/z* 179 (M^+), 164, 120, 104, 77; HRMS found *m/z* 179.0937 (M^+); $C_{10}H_{13}NO_2$ requires 179.0946.

(*S*)-3-Phenylaminononanoic acid 4j: $[\alpha]_D^{20}$ +4.6 (*c* 0.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (m, 2H), 6.84 (m, 1H), 6.73 (m, 2H), 5.60 (br, 1H), 3.78 (m, 1H), 2.58 (m, 2H), 1.60 (m, 2H), 1.42-1.10 (m, 8H), 0.86 (t, *J* = 6.6 Hz, 3H); MS *m/z* 249 (M^+), 190, 164, 146, 129, 115, 104, 94; HRMS found *m/z* 249.1737 (M^+); $C_{15}H_{23}NO_2$ requires 249.1729.

(*S*)-3-Phenylaminohexanoic acid 4k: $[\alpha]_D^{20}$ +1.3 (*c* 0.51, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 2H), 6.78-6.67 (m, 3H), 5.02 (br, 1H), 4.15 (m, 1H), 2.57 (m, 2H), 1.62-1.35 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 3H); MS *m/z* 207 (M^+), 164, 148, 118, 104, 77; HRMS found *m/z* 207.1266 (M^+); $C_{12}H_{17}NO_2$ requires 207.1259.

(*S*)-3-Cyclohexyl-3-phenylaminopropionic acid 4l: $[\alpha]_D^{20}$ -1.3 (*c* 0.57, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (m, 2H), 6.69 (m, 3H), 6.47 (br, 1H), 3.67 (m, 1H), 2.56 (dd, *J* = 15.4, 5.2, 1H), 2.44 (dd, *J* = 15.4, 7.3 Hz, 1H), 1.77-1.54 (m, 6H), 1.25-1.02 (m, 5H); MS *m/z* 247 (M^+), 220, 188, 164, 116, 105; HRMS found *m/z* 247.1588 (M^+); $C_{15}H_{21}NO_2$ requires 247.1572.

(*R*)-3- (4-Methoxylphenyl)-3-phenylaminopropionic acid 4m: $[\alpha]_D^{20}$ +1.3 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 1H), 7.13 (m, 2H), 6.94 (m, 3H), 6.72-6.61 (m, 3H), 4.84 (m, 1H), 3.78 (s, 3H), 2.86 (s, 1H), 2.84 (d, *J* = 2.4 Hz, 1H); MS *m/z* 271 (M^+), 212, 180, 135, 121, 91; HRMS found *m/z* 271.1191 (M^+); $C_{16}H_{17}NO_3$ requires 271.1208.

***tert*-Butyl 4-iodo-3-methyl-benzoate 8.** To a solution of 4-iodo-3-methyl-benzoic acid (20.0 g, 76.3 mmol) in 200 mL *t*-butanol was added $(Boc)_2O$ (20.0 g, 92 mmol). After the solution was stirred for 10 min, DMAP (2.8 g, 23 mmol) was added

in portions with caution. The reaction mixture was stirred for another 0.5 h at room temperature. The solvent was removed in vacuo and the residue was purified by chromatography eluting with 1/40 ethyl acetate/petroleum ether to give 25.4 g (89%) of **8**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 1.8 Hz, 1H), 7.46 (dd, *J* = 8.2, 2.0 Hz, 1H), 2.48 (s, 3H), 1.60 (s, 9H); MS *m/z* 318(M^+), 262, 245.

***tert*-Butyl 4-iodo-3-methylaminomethylbenzoate 9:** A solution of *t*-butyl 4-iodo-3-methylbenzoate **8** (18.0 g, 56.6 mmol), NBS (12.1 g, 67.9 mmol) and $(PhCO)_2O$ (1.37 g, 5.7 mmol) in 100 mL of CCl_4 was refluxed for 2 days under nitrogen atmosphere. After it was cooled to room temperature, the mixture was washed with water, and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was dissolved in 50 mL THF. To this stirring solution was added dropwise to a solution of 28% CH_3NH_2 (22 mL, 198 mmol) in 100 mL of THF and 50 mL of H_2O. The reaction mixture was stirred for 1 h at room temperature before the solvent was removed under reduced pressure. The residue was dissolved with $CHCl_3$ and washed with water. After it was dried over anhydrous Na_2SO_4, the solution was concentrated and the residual oil was purified by chromatography eluting with triethylamine/ethyl acetate/petroleum ether (0.05/1/2) to give 18.3 g (93%) of **9**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 2.1 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.55 (dd, *J* = 8.2, 2.1 Hz, 1H), 3.81 (s, 2H), 2.48 (s, 3H), 1.59 (s, 9H); MS *m/z* 347 (M^+), 290, 246, 164.

(*S*)-*tert*-Butyl 3-(*N*-Fmoc-aspartate-β-methyl ester-*N*-methyl)-amino-methyl-4-iodo-benzoate 10. To a solution of *t*-butyl 4-iodo-3-methylaminomethyl-benzoate

9 (5.60 g, 16.1 mol), Fmoc (*S*)-aspartic acid β-methyl ester (5.99 g, 16.1 mmol) and HOBT (2.4 0g, 17.7 mmol) in 80 mL of anhydrous CH_2Cl_2 was added a solution of DCC (3.66 g, 17.7 mmol) in 10 mL of CH_2Cl_2. After the resultant reaction mixture was stirred for 1 h the insoluble solid was filtered off. The filtrate was washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by chromatography eluting with 1/3 ethyl acetate/petroleum ether to give 8.46 g (75%) of **10**. $[\alpha]_D^{20}$ –33.5 (*c* 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.2 Hz, 1H), 7.75 (m, 2H), 7.62-7.53 (m, 4H), 7.40 (m, 2H), 7.29 (m, 2H), 5.75 (t, *J* = 9.5 Hz, 1H), 5.18 (m, 1H), 4.77-4.60 (m, 2H), 4.41 (d, *J* = 7.1 Hz, 2H), 3.71 (s, 3H), 3.12 (s, 3H), 2.90 (m, 1H), 2.74 (m, 1H), 1.54 (s, 9H); ESI-MS *m/z* 734 ($M^+ + K^+$), 721 ($M^+ + Na^+$), 699 ($M^+ + H^+$); Anal Calcd for $C_{33}H_{35}IN_2O_7$: C: 56.74; H: 5.05; N: 4.01; I: 18.17; found: C: 56.96; H: 5.19; N: 4.01; I: 17.94.

(*S*)-2-Methoxycarbonylmethyl-4-methyl-3-exo-2,3,4,5-tetrahydro-1*H*-benzo-[*e*][1,4]diazepine-7-carboxylic acid *tert*-butyl ester 6. To a solution of amide **9** (4.24 g, 6.06 mmol) in 20 mL of *t*-BuOH was added a solution of NaOH (0.97 g, 24.2 mmol) in 10 mL of H_2O. The reaction mixture was stirred over night before it was acidified to pH = 6 by adding 1 N HCl. The solvent was removed in vacuo and the residue was dissolved with 20 mL of water. The aqueous layer was extracted with benzene, and concentrated to dryness. The residue was extracted with a mixture of methanol and chloroform in 1:1 portion. The solvent was removed and the residue was dried at 60 ^{o}C for 2 h under reduced pressure to give the corresponding amino acid. This amino acid was dissolved in 20 mL of anhydrous DMF. To this solution

were added anhydrous K_2CO_3 (1.85 g, 13.4 mmol), CuI (0.10 g, 0.54 mmol). After the resultant mixture was stirred at 90 ^oC for 2 days under nitrogen atmosphere, the solvent was evaporated in vacuo and the residue was dissolved with 20 mL of $CHCl_3$ and 10 mL of water. The mixture was acidified to pH = 5 with 1 N HCl. The organic layer was separated, and the aqueous was extracted with chloroform. The combined organic layers was washed with brine, and dried over anhydrous Na_2SO_4. After the solvent was removed the residue was treated with a solution of diazomethane in ether. The mixture was stirred over night before the solvent was evaporated. The residue was purified by chromatography eluting with 1/1 ethyl acetate/petroleum ether to give 1.41 g (67%) of **6**. $[\alpha]_D^{20}$ +267.5 (*c* 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.59 (d, *J* = 1.4 Hz, 1H), 7.21 (br s, 1H), 6.50 (d, *J* = 8.4 Hz, 1H), 5.45 (d, *J* = 16.4 Hz, 1H), 5.11 (q, *J* = 5.1Hz, 1H), 4.56 (d, *J* = 4.1 Hz, 1H), 3.75 (s, 3H), 3.04 (s, 3H), 3.00 (dd, *J* = 15.9, 7.0 Hz, 1H), 2.67 (dd, *J* = 15.9, 6.4 Hz, 1H), 1.57 (s, 9H); MS *m/z* 348 (M^+), 292, 275, 232, 219, 205, 191, 174, 162.

(*S*)-1'-(3-Methoxylcarbonylmethyl-4-methyl-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4] diazepone-7-carbonyl)-[4,4']bipiperidinyl-1-carboxylic acid *tert*-butyl ester 12. To a solution of **6** (100 mg, 0.29 mmol) in 10 mL of anhydrous CH_2Cl_2 were added 5 mL of TFA and 0.2 mL of anisole. After the mixture was stirred for 3 h at room temperature, the solvent was removed under reduced pressure. The residue was purified by chromatography to give acid, which was dissolved in 5 mL of anhydrous methylene chloride. To this solution were added amine **11** (86 mg, 0.32 mmol), HOBT (43 mg, 0.32 mmol) and EDCI (61 mg, 0.32 mmol). The reaction

mixture was stirred for 1 h at room temperature before 10 mL of methylene chloride was added to dilute the solution. The solution was washed with water, and dried over anhydrous Na_2SO_4. After the solvent was evaporated the residue was purified by chromatography eluting with 1/3 ethyl acetate/petroleum ether to give 143 mg (91%) of **12**. $[\alpha]_D^{20}$ –158 (*c* 0.28, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.6 Hz, 1H), 7.08 (s, 1H), 6.49 (d, *J* = 8.6 Hz, 1H), 5.41 (d, *J* = 16.4 Hz, 1H), 5.04 (m, 1H), 4.38 (m, 2H), 4.12 (m, 4H), 3.74 (s, 3H), 3.10 (s, 3H), 2.98 (dd, *J* = 16.0, 6.7 Hz, 1H), 2.82 (m, 2H), 2.67 (dd, *J* = 16.1, 6.0 Hz, 1H), 2.65 (m, 2H), 1.78-1.60 (m, 4H), 1.45 (s, 9H), 1.42-1.14 (m, 5H); MS *m/z* 542 (M^+), 486, 442, 369, 275, 246, 218.

SB214857. To a solution of **12** (130 mg, 0.24 mmol) in 2 mL of MeOH and 2 mL of H_2O was added NaOH (48 mg, 1.2 mmol). After the mixture was refluxed for 10 h, the cooled solution was concentrated under reduced pressure. The residue was dissolved in 5 mL of dioxane and the it was treated with 2 mL of 4 N HCl for 3 h. The solvent was removed and the residue was purified by revised phase chromatography (C_{18}) eluting with water to give 79 mg of SB214857 as a hydrochloride salt. $[\alpha]_D^{20}$ –109 (*c* 0.18, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 2H), 6.81 (d, *J* = 6.9 Hz, 1H), 5.83 (d, *J* = 16.5 Hz, 1H), 5.42 (m, 1H), 4.46 (m, 2H), 4.13 (m, 2H), 3.66 (m, 2H), 3.54 (s, 3H), 3.28-3.05 (m, 4H), 2.18 (m, 2H), 2.04 (m, 2H), 1.65-1.30 (m, 6H).