Supporting information

A domino copper-catalyzed C-N and C-O cross-coupling for the conversion of primary amides into benzoxazoles

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General. The solvents used were purified by distillation over the drying agents indicated and were transferred under Ar: tetrahydrofuran (THF) (Na), CH$_2$Cl$_2$ (P$_4$O$_{10}$), MeCN, Et$_3$N, pyridine, NMP, hexamethylphosphoramide (HMPA), tetramethylethylenediamine (CaH$_2$), dimethylformamide (DMF) (dibutyltin dilaurate/Desmodur), MeOH, EtOH (Mg), and toluene (Na/K). For flash chromatography, Merck silica gel 60 (230–400 mesh) was used. For NMR, spectra were recorded on a DPX 300 or AV 400 spectrometer (Bruker) in the solvents indicated; chemical shifts (δ) are given in parts per million relative to tetramethylsilane, and coupling constants (J) are given in hertz. For IR, a Nicolet FT-7199 spectrometer or Perkin-Elmer Fourier transform-IR Diamant Spectrum One (ATR) was used; wavenumbers (ν) are given in cm$^{-1}$. For MS [electron ionization (EI)], a FinniganMAT 8200 (70 eV) was used, and for high-resolution MS (HRMS), a Finnigan MAT 95 was used. All commercially available compounds were used as received.

General procedure I for the cyclization of 2-bromobenzamides (Scheme 3):
2-Bromobenzamide (1.0 mmol), K$_2$CO$_3$ (276 mg, 2.0 mmol) and CuI (10 mg, 0.05 mmol) were weighed into a vial under air. The vial was evacuated and filled with argon, followed by the addition of N,N’-dimethylethylenediamine (11 μL, 0.1 mmol) and toluene (3 mL). The vial was sealed and the reaction mixture stirred at 110 °C for 24 h. After cooling to rt the reaction mixture was poured into 25% aqueous NH$_4$OH, extracted with EtOAc, dried over Na$_2$SO$_4$, filtered and
concentrated. Chromatography over silica gel yielded the benzoxazole. NMR, IR, MS and HRMS were in agreement with published data.

2-Methylbenzoxazole (4a): The general procedure I was followed, using N-2-bromophenyl-acetamide (3a) (215 mg, 1.0 mmol). Chromatography (EtOAc/hexane = 1/20) yielded 4a (109 mg, 81%) as a light red oil.

2-(1,1-Dimethylethyl)benzoxazole (4b): The general procedure I was followed, using N-(2-bromophenyl)-(1,1-dimethylethyl)amide (3b) (215 mg, 1.0 mmol). Chromatography (EtOAc/hexane = 1/20) yielded 4b (166 mg, 94%) as a light yellow oil.

2-Phenylbenzoxazole (4c): The general procedure I was followed, using N-(2-bromophenyl)-benzamide (3c) (276 mg, 1.0 mmol). Chromatography (EtOAc/hexane = 1/20) yielded 4c (194 mg, 98%) as a white powder.

General procedure II for the synthesis of benzoxazoles (Tables 1 and 2):
1,2-Dibromobenzene (120 µL, 1.0 mmol), benzamide (133 mg, 1.1 mmol), K₂CO₃ (414 mg, 3.0 mmol) and CuI (10 mg, 0.05 mmol) were weighed into a vial under air. The vial was evacuated and filled with argon, followed by the addition of N,N'-dimethylethylenediamine (11 µL, 0.1 mmol) and toluene (3 mL). The vial was sealed and the reaction mixture stirred at 110 °C for 24 h. After cooling to ambient temperature the reaction mixture was poured into 25% aqueous NH₄OH, extracted with EtOAc, dried over Na₂SO₄, filtered and concentrated. Chromatography over silica gel (EtOAc/hexane = 1/10) yielded 4c (176 mg, 90%) as a white powder. NMR, IR, MS and HRMS were in agreement with published data.

2-Phenylbenzoxazole (4c) (table 1, entry 2): A 100 mL roundbottom flask was charged with benzamide (2.66 g, 22 mmol), K₂CO₃ (8.28 g, 60 mmol), CuI (180 mg, 1.0 mmol) and three times evacuated and backfilled with argon. Toluene (60 mL), N,N'-dimethylethylenediamine (220 µL, 2.0 mmol) and 1,2-dibromobenzene (2.4 mL, 20 mmol) were added. The reaction mixture was stirred at 110 °C for 24 h. Aqueous workup with 25% NH₄OH and EtOAc, followed by chromatography yielded 4c (3.72 g, 95%) as a light brown solid.

2-Phenyl-[1,3]dioxolo[4',5':4,5]benzo[1,2-d]oxazol (4d) (table 1, entry 3): The general procedure II was followed, using 5,6-dibromo-1,3-benzodioxole (286 mg, 1.0 mmol), benzamide (133 mg, 1.1 mmol), K₂CO₃ (414 mg, 3.0 mmol), CuI (10 mg, 0.05 mmol) and N,N'-dimethylethylenediamine
(11 µL, 0.1 mmol). Chromatography (EtOAc/hexane = 1/12) yielded 4d (212 mg, 88%) as a white solid.

R_f = 0.43 (EtOAc/hexane = 1/4); IR (KBr) 3105, 3038, 2894, 2871, 2777, 1556, 1498, 1461, 1447, 1332, 1311, 1296, 1275, 1148, 1058, 1043, 1019, 928, 848, 829, 788, 771, 690 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.17-8.12 (m, 2H), 7.51 - 7.45 (m, 3H), 7.15 (s, 1H), 7.05 (s, 1H), 6.02 (s, 2H).

¹³C NMR (75 MHz, CDCl₃) δ 162.5, 146.3, 145.7, 145.6, 136.0, 130.8, 128.8, 127.3, 126.9, 101.6, 99.4, 92.5; MS (EI), m/z (%) 239 (100), 153 (9), 105 (6), 77 (5), 53 (7), 50 (6); HRMS (EI) calcd for C₁₄H₉NO₃: 239.0582 found 239.0583.

2-Phenylbenzoxazole (4c) (table 1, entry 5):¹ The general procedure II was followed, using 1,2-diiodobenzene (123 µL, 1.0 mmol), benzamide (133 mg, 1.1 mmol), K₂CO₃ (600 mg, 4.3 mmol), CuI (20 mg, 0.1 mmol) and N,N’-dimethylethylenediamine (22 µL, 0.2 mmol). Chromatography (EtOAc/hexane = 1/10) yielded 4c (174 mg, 89%) as an off white powder.

2-Phenylbenzoxazole (4c) (table 1, entry 8):¹ The general procedure II was followed, using 2-bromochlorobenzene (117 µL, 1.0 mmol), benzamide (133 mg, 1.1 mmol), K₂CO₃ (600 mg, 4.3 mmol), CuI (20 mg, 0.1 mmol) and N,N’-dimethylethylenediamine (22 µL, 0.2 mmol). Chromatography (EtOAc/hexane = 1/10) yielded 4c (185 mg, 95%) as a white powder.

2-Phenyl-oxazolo[5,4-b]pyridine (4e) (table 1, entry 9):² The general procedure II was followed, using 3-bromo-2-chloropyridine (192 mg, 1.0 mmol), benzamide (133 mg, 1.1 mmol), K₂CO₃ (414 mg, 3.0 mmol), CuI (10 mg, 0.05 mmol) and N,N’-dimethylethylenediamine (11 µL, 0.1 mmol). Chromatography (EtOAc/hexane = 3/7) yielded 4e (151 mg, 77%) as a white solid.

R_f = 0.44 (EtOAc/hexane = 2/3); IR (KBr) 3064, 1618, 1605, 1545, 1483, 1451, 1403, 1292, 1233, 1059, 918, 815, 798, 770, 704, 686 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.31 (dd, 1H, J = 4.9, 1.5 Hz), 8.27-8.22 (m, 2H), 8.02 (dd, 1H, J = 7.9, 1.5 Hz), 7.54-7.47 (m, 3H), 7.30 (dd, 1H, J = 7.9, 4.9 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 163.0, 159.8, 144.6, 133.9, 132.2, 129.0, 128.2, 127.8, 126.5, 121.0; MS (EI), m/z (%) 196 (100), 168 (43), 140 (6), 103 (6), 84 (5), 77 (10), 51 (6), 38 (12); HRMS (EI) calcd for C₁₂H₈N₂O: 198.0637 found 196.0639.

Comparison of the NMR data of 4e with the data of the regioisomer 4p, independently synthesized by us from 2-amino-3-hydroxypyridine (4p):¹³C NMR (75 MHz, CDCl₃) δ 165.6, 156.3, 146.6, 143.0, 132.4, 129.0, 128.0, 126.4, 120.0, 118.1), allowed the assignment of the regiochemistry of 4e.³
4-Chloro-2-phenylbenzoxazole (4f) (table 1, entry 10): The general procedure II was followed, using 1-bromo-2,6-dichlorobenzene (227 mg, 1.0 mmol), benzamide (133 mg, 1.1 mmol), K$_2$CO$_3$ (600 mg, 4.3 mmol), Cul (20 mg, 0.1 mmol) and N,N’-dimethylethylenediamine (22 µL, 0.2 mmol). Chromatography (triethylamine/hexane = 0.1/20 to 0.1/10) yielded 4f (172 mg, 75%) as a white solid. R$_f$ = 0.55 (EtOAc/hexane = 1/4); IR (KBr) 3083, 1614, 1597, 1552, 1489, 1471, 1418, 1347, 1245, 1186, 1060, 1024, 955, 922, 864, 784, 750, 702, 686, 642 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) d 8.34-8.25 (m, 2H), 7.57 -7.25 (m, 4H), 7.38 -7.45 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) d 163.6, 151.3, 140.0, 131.9, 128.8, 127.9, 126.5, 125.4, 124.8, 124.6, 109.1; MS (EI), m/z (%) 229 (100), 201 (12), 77 (16), 63 (19), 51 (5); HRMS (EI) calcd for C$_{13}$H$_8$ClNO: 229.0294 found 229.0298.

2-Phenyl-5-trifluoromethyl-benzoxazole (4g) (table 1, entry 11): The general procedure II was followed, using 3-bromo-4-chlorobenzotrifluoride (149 µL, 1.0 mmol), benzamide (133 mg, 1.1 mmol), K$_2$CO$_3$ (600 mg, 4.3 mmol), Cul (20 mg, 0.1 mmol) and N,N’-dimethylethylenediamine (22 µL, 0.2 mmol). Chromatography (EtOAc/hexane = 1/10) yielded 4g (154 mg, 59%) as a white solid. The regiochemistry of this compound was assigned by analogy to 4e, 4f and 4h only. R$_f$ = 0.57 (EtOAc/hexane = 1/4); IR (KBr) 3071, 3039, 1630, 1559, 1490, 1451, 1440, 1332, 1276, 1230, 1203, 1167, 1153, 1130, 1114, 1051, 1024, 932, 878, 826, 707, 675 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) d 8.28-8.23 (m, 2H), 8.71 (m, 1H), 7.70 -7.50 (m, 5H); $^{13}$C NMR (75 MHz, CDCl$_3$) d 164.7, 152.5, 142.3, 132.2, 129.0, 127.9, 127.4 (q, J$_{CF}$ = 216 Hz), 127.4 (q, J$_{CF}$ = 27 Hz), 122.3 (q, J$_{CF}$ = 4 Hz), 117.6 (q, J$_{CF}$ = 4 Hz), 111.0; MS (EI), m/z (%) 263 (100), 235 (11), 132 (6), 77 (10), HRMS (EI) calcd for C$_{14}$H$_8$F$_3$NO: 263.0558 found 263.0558.

5-Chloro-2-phenylbenzoxazole (4h) (table 1, entry 12):$^4$ The general procedure II was followed, using 2-bromo-1,4-dichlorobenzene (227 mg, 1.0 mmol), benzamide (133 mg, 1.1 mmol), K$_2$CO$_3$ (600 mg, 4.3 mmol), Cul (20 mg, 0.1 mmol) and N,N’-dimethylethylenediamine (22 µL, 0.2 mmol). Chromatography (triethylamine/hexane = 0.1/10) yielded 4h (166 mg, 72%) as a white solid.

2-(2-Fluorophenyl)benzoxazole (4i) (table 2, entry 1): The general procedure II was followed, using 1,2-dibromobenzene (120 µL, 1.0 mmol), 2-fluorobenzamide (152 mg, mmol), K$_2$CO$_3$ (414 mg, 3.0
mmol), CuI (10 mg, 0.05 mmol) and N,N’-dimethylethylenediamine (10 µL, 0.1 mmol). Chromatography (EtOAc/hexane = 1/10) yielded 4i (183 mg, 86%) as white solid. 

R_f = 0.52 (EtOAc/hexane = 1/4); IR (KBr) 3320, 3062, 1654, 1623, 1585, 1543, 1497, 1451, 1313, 1247, 1228, 1197, 1111, 1027, 834, 796, 775, 760, 746 cm^{-1}; ^1H NMR (300 MHz, CDCl_3) δ 8.21 (m, 1H), 7.83 (m, 1H), 7.58 (m, 1H), 7.52-7.43 (m, 1H), 7.35 (m, 2H), 7.30-7.20 (m, 2H); 13C NMR (75 MHz, CDCl_3) δ 160.7 (d, J_{CF} = 258 Hz), 159.3 (d, J_{CF} = 5 Hz), 150.4, 141.7, 133.0 (d, J_{CF} = 8 Hz), 130.4 (d, J_{CF} = 1 Hz), 125.4, 124.6, 124.4 (d, J_{CF} = 4 Hz), 120.3, 116.9 (d, J_{CF} = 21 Hz), 115.4 (d, J_{CF} = 10 Hz), 110.6; MS (EI), m/z (%) 213 (100), 185 (14), 123 (5), 92 (7), 63 (17); HRMS (EI) calcd for C_{13}H_{8}FNO: 213.0590, found 213.0592.

2-(4-Aminophenyl)benzoxazole (4j) (table 2, entry 2):^5 The general procedure II was followed, using 1,2-dibromobenzene (120 µL, 1.0 mmol), 4-aminobenzamide (153 mg, 1.1 mmol), K_2CO_3 (414 mg, 3.0 mmol), CuI (10 mg, 0.05 mmol) and N,N’-dimethylethylenediamine (11 µL, 0.1 mmol). Chromatography (EtOAc/hexane = 1/10) yielded 4j (142 mg, 67%) as a brown solid.

2-(4-Methoxy)benzoxazole (4k) (table 2, entry 3):^6 The general procedure II was followed, using 1,2-dibromobenzene (120 µL, 1.0 mmol), 4-methoxybenzamide (169 mg, 1.1 mmol), K_2CO_3 (414 mg, 3.0 mmol), CuI (10 mg, 0.05 mmol) and N,N’-dimethylethylenediamine (11 µL, 0.1 mmol). Chromatography (EtOAc/hexane = 1/11) yielded 4k (161 mg, 72%) as an off white powder.

2-(3-Pyridinyl)benzoxazole (4l) (table 2, entry 4):^4 The general procedure II was followed, using 1,2-dibromobenzene (120 µL, 1.0 mmol), nicotinamide (134 mg, 1.1 mmol), K_2CO_3 (414 mg, 3.0 mmol), CuI (10 mg, 0.05 mmol) and N,N’-dimethylethylenediamine (11 µL, 0.1 mmol). Chromatography (EtOAc/hexane = 1/10) yielded 4l (152 mg, 78%) as an off white powder.

2-(2-Styryl)benzoxazole (4m) (table 2, entry 5):^6 The general procedure II was followed, using 1,2-dibromobenzene (120 µL, 1.0 mmol), cinnamamide (166 mg, mmol), K_2CO_3 (414 mg, 3.0 mmol), CuI (10 mg, 0.05 mmol) and N,N’-dimethylethylenediamine (11 µL, 0.1 mmol). Chromatography (EtOAc/hexane = 1/10) yielded 4m (170 mg, 77%) as an off white powder.

2-tert-Butylbenzoxazole (4b) (table 2, entry 6):^1 The general procedure II was followed, using 1,2-dibromobenzene (120 µL, 1.0 mmol), pivalamide (113 mg, mmol), K_2CO_3 (414 mg, 3.0 mmol), CuI (10 mg, 0.05 mmol) and N,N’-dimethylethylenediamine (11 µL, 0.1 mmol). Chromatography (EtOAc/hexane = 1/10) yielded 4b (161 mg, 92%) as a light red liquid.
2-iso-Propylbenzoxazole (4n) (table 2, entry 7): 5 The general procedure II was followed, using 1,2-dibromobenzene (120 µL, 1.0 mmol), isobutyramide (96 mg, 1.1 mmol), K$_2$CO$_3$ (414 mg, 3.0 mmol), CuI (10 mg, 0.05 mmol) and N,N'-dimethylethylenediamine (11 µL, 0.1 mmol). Chromatography (EtOAc/hexane = 1/10) yielded 4n (110 mg, 68%) as a light red liquid.

2-Propylbenzoxazole (4o) (table 2, entry 8): 7 The general procedure II was followed, using 1,2-dibromobenzene (120 µL, 1.0 mmol), butyramide (96 mg, 1.1 mmol), K$_2$CO$_3$ (600 mg, 4.3 mmol), CuI (10 mg, 0.1 mmol) and N,N'-dimethylethylenediamine (22 µL, 0.2 mmol). Chromatography (EtOAc/hexane = 1/10) yielded 4o (110 mg, 68%) as a light yellow liquid.

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2 a) C. Flouzant, G. Guillaumet, Synthesis 1990, 64; b) A. Couture, P. Grandclaudon, Heterocycles 1984, 22, 1383.