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Article

Copper-catalyzed amination of phenylboronic acids with benzofurazan 1-oxides

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ABSTRACT

CuCl/Phen can catalyze the C–N coupling between arylboronic acid and benzofurazan 1-oxide. This reaction occurred under mild and redox-neutral conditions with benzofurazan 1-oxide as an aminating reagent via ring scission, leading to a bifunctionalized aminonitrobenzene.

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1. Introduction

The C–N bond is a key linkage in most pharmaceuticals and organic functional molecules [1–6]. Traditional methods to construct C–N bonds include the Goldberg reaction [5–11], the Buchwald–Hartwig coupling [12–16], the Chan–Lam coupling [17–24], and C–H activation-amination/amidation [25–45]. Although very efficient, these methods either require the employment of functionalized arenes [46], functionalized aminating reagents [47–53], or oxidative conditions [54]. From the redox-economy aspect, the amination reaction is ideally performed under redox-neutral conditions. Moreover, it is ideal that this process allows the introduction of an amine group simultaneously with another functional group. The most straightforward strategy to realize this is probably the em-

ployment of an azacycle (Scheme 1). Upon cleavage of N–E bond, both the N and the E atoms can be incorporated, especially under redox-neutral conditions. Indeed, this difunctionalization process has been recently realized by us and others in C–H activation chemistry using anthranils [50,55–58] and azabenzonorbornadienes [59].

Although appealing, difunctionalization via scission of an azacycle requires overcome of unfavorable thermodynamics associated with scission of unstrained rings. In this respect and as a continuation of our interest in amination of nucleophiles [50,55,59], we reasoned that benzofurazan 1-oxide may function as an aminating reagent because it is known to undergo ring scission to give an *ortho* dinitrosobenzene [60,61]. On the other hand, although simple amination of phenylboronic acid has been reported using nitrosobenzene [62], either a stoichi-

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Scheme 1. Amination leading to bifunctionality.

ometric amount of copper salt or terminal reducing reagent is necessary. We now report copper-catalyzed amination of phenylboronic acid using benzofurazan 1-oxide, leading to difunctionalization under mild and redox-neutral conditions.

2. Experimental

2.1. General

All chemicals were obtained from commercial sources and were used as received unless otherwise noted. All the reactions were carried out under nitrogen atmosphere using standard Schlenk technique. The ^1H NMR spectra were recorded on a 400 or 600 MHz NMR spectrometer. The ^{13}C NMR spectra were recorded at 100 or 150 MHz. The ^{19}F NMR spectra were recorded at 565 MHz. Chemical shifts were expressed in parts per million (δ) downfield from the internal standard tetramethylsilane, and were reported as s (singlet), d (doublet), t (triplet), dd (doublet of doublet), dt (doublet of triplet), m (multiplet), br s (broad singlet), etc. The residual solvent signals were used as references and the chemical shifts were converted to the TMS scale. High resolution mass spectra were obtained on an Agilent Q-TOF 6540 spectrometer. Column chromatography was performed on silica gel (300–400 mesh) using ethyl acetate (EA)/petroleum ether (PE).

The [c][1,2,5]oxadiazole 1-oxide **1a**, **1b** and **1h** were obtained from commercial sources. The others were prepared following a published procedure [63]. Compounds **6** and **7** were prepared according to the literature report [64,65].

2.2. General procedure for the synthesis of compounds **3** and **3'**

Benzofuroxan (0.2 mmol), phenylboronic acid (0.6 mmol), CuCl (10 mol%), 1,10-phen (10 mol%) and Na_2CO_3 (2 equiv.) were charged into a Schlenk tube, to which was added anhydrous 1,4-dioxane (2 ml) under N_2 atmosphere. The reaction mixture was stirred at 60 $^\circ\text{C}$ for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using PE/EA to afford the product.

2.3. Spectral data for products

3aa. ^1H NMR (400 MHz, CDCl_3) δ 9.41 (br s, 1H), 8.12 (dd, J = 8.6, 1.4 Hz, 1H), 7.34 (t, J = 7.8 Hz, 2H), 7.31–7.25 (m, 1H), 7.22–7.12 (m, 4H), 6.70–6.67 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 143.1, 138.7, 135.7, 133.2, 129.8, 126.7, 125.7, 124.4, 117.5, 116.1. HRMS calc. for $\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_2^+$ ($M + \text{H}$) $^+$: 215.0815; found: 215.0818.

3ab. ^1H NMR (400 MHz, CDCl_3) δ 9.36 (br s, 1H), 8.09 (dd, J = 8.6, 1.5 Hz, 1H), 7.26–7.22 (m, 1H), 7.13 (m, 2H), 7.09–7.03 (m, 3H), 6.66–6.61 (m, 1H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 143.7, 135.9, 135.7, 135.7, 132.8, 130.3, 126.6, 124.8, 117.1, 116.0, 21.0. HRMS calc. for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_2^+$ ($M + \text{H}$) $^+$: 229.0972; found: 229.0974.

3ac. ^1H NMR (400 MHz, CDCl_3) δ 9.39 (br s, 1H), 8.10 (dd, J = 8.6, 1.5 Hz, 1H), 7.38–7.31 (m, 2H), 7.36–7.32 (m, 1H), 7.12–7.10 (m, 3H), 6.66–6.62 (m, 1H), 1.26 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 148.9, 143.6, 135.9, 135.7, 132.9, 126.7, 126.6, 124.3, 117.2, 116.1, 34.6, 31.4. HRMS calc. for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_2^+$ ($M + \text{H}$) $^+$: 271.1441; found: 271.1443.

3ad. ^1H NMR (400 MHz, CDCl_3) δ 9.31 (br s, 1H), 8.11 (dd, J = 8.6, 1.2 Hz, 1H), 7.32–7.24 (m, 1H), 7.22–7.12 (m, 2H), 7.08–6.99 (m, 2H), 6.96 (d, J = 8.6 Hz, 1H), 6.73–6.64 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 160.6 (d, J = 245.8 Hz), 143.6, 135.8, 134.6 (d, J = 3.0 Hz), 133.0, 127.0 (d, J = 8.3 Hz), 126.7, 117.5, 116.6 (d, J = 22.5 Hz), 115.7. HRMS calc. for $\text{C}_{12}\text{H}_{10}\text{FN}_2\text{O}_2^+$ ($M + \text{H}$) $^+$: 233.0721; found: 233.0725.

3ae. ^1H NMR (400 MHz, CDCl_3) δ 9.32 (br s, 1H), 8.11 (dd, J = 8.6, 1.5 Hz, 1H), 7.32–7.28 (m, 3H), 7.15–7.12 (m, 2H), 7.09 (dd, J = 8.6, 1.0 Hz, 1H), 6.74–6.70 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 142.6, 137.4, 135.8, 133.5, 130.8, 129.9, 126.8, 125.5, 118.0, 115.9. HRMS calc. for $\text{C}_{12}\text{H}_{10}\text{ClN}_2\text{O}_2^+$ ($M + \text{H}$) $^+$: 249.0425; found: 249.0428.

3af. ^1H NMR (400 MHz, CDCl_3) δ 9.39 (br s, 1H), 8.20 (dd, J = 8.6, 1.4 Hz, 1H), 7.57–7.47 (m, 2H), 7.43–7.35 (m, 1H), 7.24–7.11 (m, 3H), 6.83–6.79 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 142.4, 138.0, 135.8, 133.6, 132.8, 126.8, 125.7, 118.4, 118.1, 116.0. HRMS calc. for $\text{C}_{12}\text{H}_{10}\text{BrN}_2\text{O}_2^+$ ($M + \text{H}$) $^+$: 292.9920; found: 292.9922.

3ag. ^1H NMR (400 MHz, CDCl_3) δ 9.38 (br s, 1H), 8.20 (dd, J = 8.6, 1.2 Hz, 1H), 7.77–7.67 (m, 2H), 7.43–7.35 (m, 1H), 7.22 (dd, J = 8.6, 0.8 Hz, 1H), 7.05–7.03 (m, 2H), 6.84–6.80 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 142.2, 138.8, 138.7, 135.8, 133.8, 126.8, 125.8, 118.2, 116.1, 89.0. HRMS calc. for $\text{C}_{12}\text{H}_{10}\text{IN}_2\text{O}_2^+$ ($M + \text{H}$) $^+$: 340.9781; found: 340.9785.

3ah. ^1H NMR (400 MHz, CDCl_3) δ 9.56 (br s, 1H), 8.23 (dd, J = 8.6, 1.5 Hz, 1H), 7.67–7.62 (m, 4H), 7.50–7.46 (m, 2H), 7.44–7.38 (m, 2H), 7.36–7.32 (m, 3H), 6.83–6.79 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 142.9, 140.2, 138.4, 138.0, 135.8, 133.4, 128.9, 128.4, 127.5, 126.9, 126.8, 124.4, 117.7, 116.3. HRMS calc. for $\text{C}_{18}\text{H}_{15}\text{N}_2\text{O}_2^+$ ($M + \text{H}$) $^+$: 291.1128; found: 291.1131.

3ai. ^1H NMR (400 MHz, CDCl_3) δ 9.43 (br s, 1H), 8.20 (dd, J = 8.6, 1.3 Hz, 1H), 7.40–7.34 (m, 1H), 7.31–7.26 (m, 2H), 7.19 (d, J = 8.6 Hz, 1H), 7.17–7.11 (m, 2H), 6.82–6.74 (m, 1H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 169.5, 148.2, 143.1, 136.3, 135.8, 133.2, 126.7, 125.6, 122.9, 117.7, 116.0, 21.1. HRMS calc. for $\text{C}_{14}\text{H}_{13}\text{N}_2\text{O}_4^+$ ($M + \text{H}$) $^+$: 273.0870; found: 273.0874.

3aj. ^1H NMR (400 MHz, CDCl_3) δ 9.43 (br s, 1H), 8.20 (dd, J = 8.6, 1.3 Hz, 1H), 7.50–7.40 (m, 4H), 7.39–7.30 (m, 2H), 7.22–7.19 (m, 2H), 7.10–7.01 (m, 3H), 6.77–6.67 (m, 1H), 5.11 (s, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 157.1, 144.4, 136.8, 135.8, 132.5, 131.5, 128.7, 128.2, 127.5, 127.0, 126.6, 116.9, 116.0, 115.8, 70.4. HRMS calc. for $\text{C}_{19}\text{H}_{17}\text{N}_2\text{O}_3^+$ ($M + \text{H}$) $^+$: 321.1234; found: 321.1236.

3ak. ^1H NMR (400 MHz, CDCl_3) δ 9.92 (s, 1H), 9.48 (br s, 1H), 8.20 (dd, $J = 8.5, 1.0$ Hz, 1H), 7.89–7.86 (m, 2H), 7.57–7.46 (m, 2H), 7.40–7.33 (m, 2H), 6.98–6.94 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 190.6, 145.3, 139.7, 135.6, 135.6, 132.2, 131.7, 126.8, 120.8, 120.1, 117.6. HRMS calc. for $\text{C}_{13}\text{H}_{11}\text{N}_2\text{O}_3^+$ ($M + \text{H}$) $^+$: 243.0764; found: 243.0767.

3al. ^1H NMR (400 MHz, CDCl_3) δ 9.48 (br s, 1H), 8.21 (d, $J = 8.4$ Hz, 1H), 8.05 (d, $J = 8.5$ Hz, 2H), 7.46–7.44 (m, 2H), 7.31–7.29 (m, 2H), 6.96–6.84 (m, 1H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.4, 143.6, 140.6, 135.7, 134.8, 131.4, 126.8, 125.9, 121.2, 119.3, 117.0, 52.1. HRMS calc. for $\text{C}_{14}\text{H}_{13}\text{N}_2\text{O}_4^+$ ($M + \text{H}$) $^+$: 273.0870; found: 273.0874.

3am. ^1H NMR (400 MHz, CDCl_3) δ 9.37 (br s, 1H), 8.10 (dd, $J = 8.6, 1.3$ Hz, 1H), 7.30–7.23 (m, 1H), 7.23–7.17 (m, 1H), 7.17–7.10 (m, 1H), 7.00–6.94 (m, 3H), 6.68–6.64 (m, 1H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 143.2, 139.8, 138.6, 135.7, 133.1, 129.5, 126.7, 126.5, 125.1, 121.4, 117.4, 116.2, 21.4. HRMS calc. for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_2^+$ ($M + \text{H}$) $^+$: 229.0972; found: 229.0976.

3an. ^1H NMR (400 MHz, CDCl_3) δ 9.45 (br s, 1H), 8.18 (dd, $J = 8.6, 1.4$ Hz, 1H), 7.40–7.33 (m, 1H), 7.33–7.26 (m, 2H), 6.86 (dd, $J = 7.9, 1.7$ Hz, 1H), 6.81 (t, $J = 2.2$ Hz, 1H), 6.79–6.74 (m, 2H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 160.8, 142.8, 140.0, 135.7, 133.3, 130.4, 126.6, 117.6, 116.4, 116.38, 111.1, 109.9, 55.41. HRMS calc. for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_3^+$ ($M + \text{H}$) $^+$: 245.0921; found: 245.0923.

3ao. ^1H NMR (400 MHz, CDCl_3) δ 9.43 (br s, 1H), 8.20 (dd, $J = 8.5, 1.0$ Hz, 1H), 7.45–7.39 (m, 1H), 7.39–7.28 (m, 2H), 7.08–7.03 (m, 1H), 7.03–6.97 (m, 1H), 6.94–6.87 (m, 1H), 6.86–6.82 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 163.5 (d, $J = 247.0$ Hz), 141.9, 140.7 (d, $J = 10.0$ Hz), 135.8, 133.9, 130.9 (d, $J = 9.5$ Hz), 126.7, 119.2 (d, $J = 3.0$ Hz), 118.4, 116.3, 112.1 (d, $J = 21.1$ Hz), 110.7 (d, $J = 23.5$ Hz). HRMS calc. for $\text{C}_{12}\text{H}_{10}\text{FN}_2\text{O}_2^+$ ($M + \text{H}$) $^+$: 233.0721; found: 233.0723.

3ap. ^1H NMR (400 MHz, CDCl_3) δ 9.40 (br s, 1H), 8.19 (dd, $J = 8.6, 1.5$ Hz, 1H), 7.43–7.39 (m, 2H), 7.36–7.30 (m, 1H), 7.29–7.25 (m, 2H), 7.23–7.17 (m, 1H), 6.85–6.81 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 142.0, 140.4, 135.8, 133.8, 131.0, 128.3, 126.8, 126.7, 123.2, 122.4, 118.4, 116.2. HRMS calc. for $\text{C}_{12}\text{H}_{10}\text{BrN}_2\text{O}_2^+$ ($M + \text{H}$) $^+$: 292.9920; found: 292.9918.

3aq. ^1H NMR (400 MHz, CDCl_3) δ 9.39 (br s, 1H), 8.14 (dd, $J = 8.5, 1.3$ Hz, 1H), 7.47–7.43 (m, 2H), 7.39–7.32 (m, 3H), 7.17 (m, 1H), 6.83–6.75 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 141.8, 139.7, 135.9, 134.1, 132.3 (q, $J = 32.7$ Hz), 130.4, 126.8, 126.79, 123.7 (q, $J = 272.5$ Hz), 121.8 (q, $J = 3.8$ Hz), 120.3 (q, $J = 3.8$ Hz), 118.7, 116.0. HRMS calc. for $\text{C}_{13}\text{H}_{10}\text{F}_3\text{N}_2\text{O}_2^+$ ($M + \text{H}$) $^+$: 283.0689; found: 283.0692.

3ar. ^1H NMR (400 MHz, CDCl_3) δ 9.48 (br s, 1H), 8.19 (d, $J = 8.6$ Hz, 1H), 7.41–7.35 (m, 2H), 7.29 (s, 1H), 7.27–7.17 (m, 3H), 6.78 (t, $J = 7.7$ Hz, 1H), 4.72 (s, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 142.8, 142.79, 139.0, 135.7, 133.3, 129.8, 126.6, 123.9, 123.2, 122.5, 117.6, 116.1, 64.8. HRMS calc. for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_3^+$ ($M + \text{H}$) $^+$: 245.0921; found: 245.0921.

3as. ^1H NMR (400 MHz, CDCl_3) δ 9.47 (br s, 1H), 8.22 (dd, $J = 8.5, 1.3$ Hz, 1H), 7.51 (dd, $J = 8.0, 1.3$ Hz, 1H), 7.48–7.37 (m, 2H), 7.30 (td, $J = 7.8, 1.2$ Hz, 1H), 7.21–7.11 (m, 2H), 6.90–6.80 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 141.5, 136.2, 135.6, 134.3,

130.6, 128.7, 127.6, 126.7, 126.1, 124.4, 118.5, 116.3. HRMS calc. for $\text{C}_{12}\text{H}_{10}\text{ClN}_2\text{O}_2^+$ ($M + \text{H}$) $^+$: 249.0425; found: 249.0426.

3at. ^1H NMR (400 MHz, CDCl_3) δ 9.46 (br s, 1H), 8.22 (dd, $J = 8.6, 1.5$ Hz, 1H), 7.69 (dd, $J = 8.0, 1.3$ Hz, 1H), 7.47–7.37 (m, 2H), 7.34 (td, $J = 7.9, 1.3$ Hz, 1H), 7.16 (dd, $J = 8.6, 0.9$ Hz, 1H), 7.09 (td, $J = 7.9, 1.5$ Hz, 1H), 6.87–6.83 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 141.6, 137.6, 135.6, 134.2, 133.8, 128.3, 126.8, 126.5, 124.6, 119.2, 118.5, 116.3. HRMS calc. for $\text{C}_{12}\text{H}_{10}\text{BrN}_2\text{O}_2^+$ ($M + \text{H}$) $^+$: 292.9920; found: 292.9923.

3ba + 3ba' (0.5:1) **3ba.** ^1H NMR (400 MHz, CDCl_3) δ 9.53 (br s, 1H), 8.10 (d, $J = 8.7$ Hz, 1H), 7.43 (t, $J = 7.8$ Hz, 2H), 7.29–7.24 (m, 3H), 6.99 (s, 1H), 6.58 (d, $J = 8.7$ Hz, 1H), 2.26 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 147.5, 143.3, 138.9, 131.4, 129.9, 126.8, 125.7, 124.7, 119.3, 115.6, 22.1. **3ba'.** ^1H NMR (400 MHz, CDCl_3) δ 9.36 (br s, 1H), 8.00 (s, 1H), 7.40 (t, $J = 7.8$ Hz, 2H), 7.25 (d, $J = 7.3$ Hz, 2H), 7.21–7.16 (m, 3H), 2.30 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 141.0, 139.3, 137.2, 133.2, 129.8, 127.5, 126.0, 125.3, 124.0, 116.4, 20.3. HRMS calc. for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_2^+$ ($M + \text{H}$) $^+$: 229.0972; found: 229.0975.

3ca+3ca' (1:0.9) **3ca.** ^1H NMR (400 MHz, CDCl_3) δ 9.39 (br s, 1H), 8.17 (s, 1H), 7.45–7.38 (m, 3H), 7.29–7.27 (m, 2H), 7.22–7.19 (m, 2H), 1.31 (s, 9H). **3ca'.** ^1H NMR (400 MHz, CDCl_3) δ 9.55 (br s, 1H), 8.13 (d, $J = 9.0$ Hz, 1H), 7.45–7.38 (m, 3H), 7.29–7.27 (m, 2H), 7.22–7.19 (m, 1H), 6.82 (d, $J = 7.8$ Hz, 1H), 1.23 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) mixture δ 160.1, 142.7, 141.1, 141.0, 139.2, 139.1, 133.8, 133.0, 131.3, 129.8 (2C), 126.5, 125.4 (2C), 124.1, 123.9, 122.5, 116.3, 116.0, 112.5, 35.6, 34.2, 31.1, 30.7. HRMS calc. for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_2^+$ ($M + \text{H}$) $^+$: 271.1441; found: 271.1447.

3da+3da' (0.6:1) **3da.** ^1H NMR (400 MHz, CDCl_3) [66] δ 9.55 (br s, 1H), 8.32 (d, $J = 8.9$ Hz, 1H), 7.49–7.45 (m, 3H), 7.35–7.22 (m, 3H), 6.97 (d, $J = 8.9$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 143.2, 137.8, 137.0 (d, $J = 33.1$ Hz), 134.4, 130.2, 127.9, 126.7, 124.7, 123.0 (d, $J = 273.6$ Hz), 113.6 (d, $J = 4.2$ Hz), 113.5 (d, $J = 3.3$ Hz). **3da'.** ^1H NMR (400 MHz, CDCl_3) [66] δ 9.73 (br s, 1H), 8.51 (s, 1H), 7.53 (d, $J = 9.1$ Hz, 1H), 7.49–7.45 (m, 3H), 7.35–7.22 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 145.4, 137.6, 131.9, 130.1, 127.0, 125.3, 124.9 (d, $J = 4.1$ Hz), 121.6, 119.6, 119.3, 116.7. HRMS calc. for $\text{C}_{13}\text{H}_{10}\text{F}_3\text{N}_2\text{O}_2^+$ ($M + \text{H}$) $^+$: 283.0689; found: 283.0693.

3ea + 3ea' (0.5:1) **3ea.** ^1H NMR (400 MHz, CDCl_3) [66] δ 9.35 (br s, 1H), 7.92 (dd, $J = 8.9, 2.8$ Hz, 1H), 7.47–7.40 (m, 2H), 7.31–7.14 (m, 5H). ^{13}C NMR (100 MHz, CDCl_3) δ 155.0, 152.6, 140.2, 138.8, 125.9, 124.6, 124.3, 117.8 (d, $J = 7.2$ Hz), 112.0 (d, $J = 26.5$ Hz). **3ea'.** ^1H NMR (400 MHz, CDCl_3) [66] δ 9.64 (br s, 1H), 8.26 (dd, $J = 9.5, 6.0$ Hz, 1H), 7.47–7.40 (m, 2H), 7.31–7.14 (m, 3H), 6.80 (dd, $J = 11.4, 2.6$ Hz, 1H), 6.48 (dt, $J = 9.6, 2.6$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.3 (d, $J = 256.3$ Hz), 145.8 (d, $J = 13.3$ Hz), 138.1, 130.1, 130.0, 129.9, 126.6, 125.0, 106.1 (d, $J = 24.8$ Hz), 101.5 (d, $J = 27.9$ Hz). HRMS: calc. for $\text{C}_{12}\text{H}_{10}\text{FN}_2\text{O}_2^+$ ($M + \text{H}$) $^+$: 233.0721; found: 233.0726.

3fa+3fa' (0.7:1) **3fa.** ^1H NMR (400 MHz, CDCl_3) [66] δ 9.45 (br s, 1H), 8.20 (d, $J = 2.5$ Hz, 1H), 7.48–7.41 (m, 2H), 7.32–7.24 (m, 4H), 7.15–7.14 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 142.0, 138.3, 136.0, 133.1, 130.0, 126.3, 125.9, 124.7, 122.2, 117.6. **3fa'.** ^1H NMR (400 MHz, CDCl_3) [66] δ 9.54 (br s, 1H), 8.16 (d, $J = 9.1$ Hz, 1H), 7.48–7.41 (m, 2H), 7.32–7.24 (m, 3H), 7.17 (s, 1H),

6.72 (dd, $J = 9.1, 2.2$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 144.0, 142.6, 138.0, 131.6, 130.1, 128.2, 126.6, 125.0, 118.0, 115.3. HRMS calc. for $\text{C}_{12}\text{H}_{10}\text{ClN}_2\text{O}_2^+$ ($\text{M} + \text{H}$) $^+$: 249.0425; found: 249.0428.

3ga+3ga' (1:0.7) **3ga**. ^1H NMR (400 MHz, CDCl_3) [66] δ 9.45 (br s, 1H), 8.34 (d, $J = 2.4$ Hz, 1H), 7.47–7.39 (m, 3H), 7.30–7.24 (m, 3H), 7.09 (d, $J = 9.2$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 142.4, 138.6, 138.3, 133.5, 130.0, 128.9, 126.3, 124.7, 117.9, 108.6. **3ga'**. ^1H NMR (400 MHz, CDCl_3) [66] δ 9.50 (br s, 1H), 8.06 (d, $J = 9.1$ Hz, 1H), 7.47–7.39 (m, 2H), 7.31 (d, $J = 2.0$ Hz, 1H), 7.30–7.24 (m, 3H), 6.86 (dd, $J = 9.1, 2.0$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 143.9, 137.9, 132.0, 131.4, 130.1, 128.1, 126.6, 124.9, 120.9, 118.4. HRMS calc. for $\text{C}_{12}\text{H}_{10}\text{BrN}_2\text{O}_2^+$ ($\text{M} + \text{H}$) $^+$: 292.9920; found: 292.9922.

3ha'. ^1H NMR (400 MHz, CDCl_3) [67] δ 9.34 (br s, 1H), 7.64 (d, $J = 3.0$ Hz, 1H), 7.39 (t, $J = 7.9$ Hz, 2H), 7.25–7.23 (m, 3H), 7.19 (t, $J = 7.4$ Hz, 1H), 7.07 (dd, $J = 9.4, 3.0$ Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 151.4, 139.5, 138.1, 133.1, 129.8, 126.4, 125.2, 123.7, 118.2, 107.1, 56.0. HRMS calc. for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_3^+$ ($\text{M} + \text{H}$) $^+$: 245.0921; found: 245.0925.

3ia'. ^1H NMR (400 MHz, CDCl_3) [68] δ 9.47 (br s, 1H), 8.24 (d, $J = 8.9$ Hz, 1H), 7.94 (d, $J = 1.5$ Hz, 1H), 7.44 (t, $J = 7.8$ Hz, 2H), 7.35 (dd, $J = 8.9, 1.6$ Hz, 1H), 7.30–7.26 (m, 3H), 4.34 (q, $J = 7.1$ Hz, 2H), 1.35 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.1, 142.7, 138.4, 136.8, 135.2, 130.0, 127.0, 126.1, 124.2, 118.1, 117.5, 61.9, 14.3. HRMS calc. for $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}_4^+$ ($\text{M} + \text{H}$) $^+$: 287.1026; found: 287.1030.

3ja'. ^1H NMR (400 MHz, CDCl_3) δ 8.29 (br s, 1H), 7.97 (d, $J = 8.3$ Hz, 1H), 7.42 (d, $J = 7.4$ Hz, 1H), 7.25–7.22 (m, 2H), 7.06 (t, $J = 7.9$ Hz, 1H), 6.97 (t, $J = 7.4$ Hz, 1H), 6.76 (d, $J = 7.9$ Hz, 2H), 2.09 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 143.0, 142.6, 137.7, 137.4, 134.6, 129.3, 124.0, 122.2, 122.1, 118.8, 20.15. HRMS calc. for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_2^+$ ($\text{M} + \text{H}$) $^+$: 229.0972; found: 229.0978.

3ka'. ^1H NMR (400 MHz, CDCl_3) [69] δ 8.16 (br s, 1H), 8.04 (dd, $J = 8.4, 1.5$ Hz, 1H), 7.65 (dd, $J = 7.9, 1.5$ Hz, 1H), 7.31–7.27 (m, 2H), 7.09–7.04 (m, 2H), 6.88 (d, $J = 7.6$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 142.2, 141.5, 136.5, 129.2, 128.9, 125.1, 123.3, 121.6, 119.3. HRMS calc. for $\text{C}_{12}\text{H}_{10}\text{ClN}_2\text{O}_2^+$ ($\text{M} + \text{H}$) $^+$: 249.0425; found: 249.0429.

3la'. ^1H NMR (400 MHz, CDCl_3) [69] δ 8.04 (dd, $J = 8.3, 1.5$ Hz, 1H), 7.93 (br s, 1H), 7.82 (dd, $J = 7.9, 1.5$ Hz, 1H), 7.29–7.25 (m, 2H), 7.05–6.98 (m, 2H), 6.84 (d, $J = 7.7$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 142.6, 141.6, 139.7, 137.4, 129.3, 125.7, 123.2, 122.5, 119.2, 119.0. HRMS calc. for $\text{C}_{12}\text{H}_{10}\text{BrN}_2\text{O}_2^+$ ($\text{M} + \text{H}$) $^+$: 292.9920; found: 292.9926.

6. ^1H NMR (400 MHz, CDCl_3) δ 7.24–7.20 (m, 2H), 7.14 (dd, $J = 7.8, 1.3$ Hz, 1H), 7.02 (dt, $J = 7.6, 1.3$ Hz, 1H), 6.86–6.81 (m, 2H), 6.79–6.75 (m, 3H), 5.20 (br s, 1H), 3.74 (br s, 2H).

7. ^1H NMR (400 MHz, CDCl_3) δ 8.14 (d, $J = 8.3$ Hz, 1H), 7.77 (d, $J = 7.7$ Hz, 2H), 7.73 (d, $J = 8.4$ Hz, 1H), 7.60 (t, $J = 7.8$ Hz, 2H), 7.55–7.47 (m, 2H), 7.42 (t, $J = 7.6$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 146.6, 137.1, 132.3, 129.9, 128.7, 128.3, 124.4, 122.9, 120.3, 110.4.

3. Results and discussion

Then we initiated our studies with the optimization of the

reaction conditions of the coupling between benzofurazan 1-oxide (**1a**) and phenylboronic acid (**2a**). Initial studies using different copper catalysts revealed that CuBr and CuCl are active at 90 °C (Table 1, entries 1–4). Nevertheless the desired amination product **3aa** was isolated in ~20% yield (Table 1, entry 3). Introduction of different inorganic bases had only marginal effects (Table 1, entries 5–8). Addition of phen as a ligand significantly improved the coupling efficiency and the product was isolated in 60% yield (Table 1, entry 9). Further optimization using different carbonates revealed that Na_2CO_3 is optimal (Table 1, entries 9–14). The catalyst loading could be reduced to 10 mol% without loss of reactivity, and 60 °C is sufficient for this reaction (Table 1, entry 16). Further lowering the catalyst loading, equivalent of **2a** or reaction temperature all resulted in low efficiency (Table 1, entries 15–17), and control experiments revealed that no reaction occurred when the catalyst was omitted.

Having identified the optimal reaction conditions, we next examined the scope and limitation of this coupling system. The scope of the arylboronic acid was first explored in the coupling with **1a** (Table 2). It was found that phenylboronic acids bearing an electron-donating, -withdrawing, and halogen group at the *para* position were fully compatible, and the aminated product was isolated in consistently good to excellent yield (**3ab–3al**). Thus, sensitive functional groups such as iodo and formyl are well tolerated. Comparably high or somewhat lower reactivity was also realized for various *meta*-substituted phenylboronic acids (**3am–3aq**), including one with a hydroxyme-

Table 1
Optimization studies.

Entry	Cat. (x/mol%)	Ligand (y/mol%)	Base	T/°C	Isolated yield (%)
1	CuI (20)	—	—	90	<5
2	CuBr (20)	—	—	90	18
3	CuCl (20)	—	—	90	20
4	Cu(OTf) ₂ (20)	—	—	90	<5
5	CuCl (20)	—	NaOAc	90	23
6	CuCl (20)	—	Cs_2CO_3	90	35
7	CuCl (20)	—	K_2CO_3	90	28
8	CuCl (20)	—	K_3PO_4	90	8
9	CuCl (20)	phen (30)	Cs_2CO_3	90	60
10	CuCl (10)	phen (10)	Cs_2CO_3	25	63
11	CuCl (10)	phen (10)	K_2CO_3	90	83
12	CuCl (10)	phen (10)	K_3PO_4	90	85
13	CuCl (10)	phen (10)	Li_2CO_3	90	69
14	CuCl (10)	phen (10)	Na_2CO_3	90	88
15	CuCl (5)	phen (5)	Na_2CO_3	90	71
16	CuCl (10)	phen (10)	Na_2CO_3	60	92
17*	CuCl (10)	phen (10)	Na_2CO_3	60	81
18	CuCl (10)	phen (10)	Na_2CO_3	25	26

Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), copper catalyst (10–20 mol%), ligand, base (0.4 mmol) in 1,4-dioxane (2 mL) at 25–90 °C for 12 h. *2 equiv. of **2a** was used.

Table 2
Scope of phenylboronic acids.

Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), CuCl (10 mol %), phen (10 mol %), Na₂CO₃ (0.4 mmol) in 1,4-dioxane (2 mL) at 60 °C for 12 h. *Yield obtained when 4 mmol of **1a** was used.

thyl group (**3ar**). Introduction of an *ortho*-halide group to the phenyl ring decreased the coupling efficiency likely due to steric effects. Nevertheless, the aminated product was still isolated in moderate to good yield (**3as**, **3at**).

The scope of the benzofurazan 1-oxides was next examined (Table 3). In contrast to the high selectivity and hence single product observed for symmetrically substituted benzofurazan 1-oxides, two isomeric products were generally obtained for 5- or 6-substituted unsymmetrical benzofurazan 1-oxides (Table 3, entries 1–9). Thus, 5- or 6-alkyl, CF₃, and halo substituted substrates all coupled smoothly with **2a** to give two regioisomeric products in good total yield with a ratio ranging from 0.5:1 to 1:0.65. Of note, the isomeric ratios remain essentially the same when starting from a substrate bearing a specific group either at the 4- or the 5-position. Exceptions with respect to the selectivity were observed for 5-OMe (**1h**) and 6-ester (**1i**) substituted substrates, where only a single product was isolated in low to good yield. This is likely due to electronic effect of such substituents. For these reactions, it follows that

amination tends to occur at the more electron-rich nitrogen. A single product was also observed for 7-methyl and -halogen substituted benzofurazan 1-oxides (Table 3, entries 12–14). Surprisingly, amination occurred at the more hindered nitrogen in moderate to good yield, where steric effect of these substituents is likely accountable.

To demonstrate the synthetic usefulness of the coupled product, representative derivatization reactions have been performed (Scheme 2). Reductive cyclization-aromatization of **3aa** using PPh₃ afforded phenazine (**4**) in 75% yield [70]. Palladium-catalyzed intramolecular oxidative C–H/C–H cross-dehydrogenative coupling of **3aa** afforded a carbazole (**5**) in 80% yield [71]. Hydrogenation of the nitro group of **3aa** gave an aniline **6**. Subsequent diazotization and intramolecular trapping of the diazonium intermediate afforded a benzotriazole **7** in excellent yield.

It has been reported that benzofurazan 1-oxide can undergo reversible ring opening to deliver a dinitroso intermediate (Scheme 3) [60,61]. This process leads to isomerization of the benzofurazan 1-oxide and should occur in the NMR timescale because significant line broadening was observed in the ¹H and ¹³C NMR spectra (CDCl₃) of 5- and 6-substituted benzofurazan 1-oxides. Thus, the molecular fluxionality of benzofurazan 1-oxides correlates well with the observed two regioisomeric products. Accordingly, only a single product was isolated in the case of 7-substituted benzofurazan 1-oxides whose NMR spectra showed no fluxionality.

Two possible reaction pathways have been proposed for the coupling of PhB(OH)₂ and **1-R**, a 7-substituted benzofurazan 1-oxide (Scheme 4). In path a, the dinitroso tautomer of the benzofurazan 1-oxide undergoes coordination at the less hindered N=O site. Migratory insertion of the phenyl group into this N=O bond from backside of the other nitroso group generates a Cu(I) aminoxide that further nucleophilically attacks the pendant nitroso to give intermediate **A**. Subsequent elimination of the amino group is proposed to deliver a copper amide species **B**, protonolysis of which eventually furnishes an aminated product together with regeneration of the Cu(I) catalyst. This pathway, however, delivers a product that is not consistent with the observed structure. Alternatively (path b), although two tautomers **1-R** and **1-R'** can be present, the former should be predominant both thermodynamically and kinetically. Kinetically, the steric repulsion of the R group aligns the *ortho* nitroso group of the dinitroso intermediate in a suitable orientation so that it nucleophilically attacks the *meta* nitroso group. Subsequent coordination (**C**) and elimination of a nitro group gives a nitrene intermediate (**D**). In fact, this copper nitrene species could also be generated from oxidative addition of the bridging N–O bond (**E**). Migratory insertion and protonolysis eventually furnished the observed product. This path way also agrees with the observed preference of amination at the more electron-rich nitrogen atom because this more electron-rich nitroso preferentially attacks the other one, and this attacking nitroso nitrogen eventually ends up as an N ligand for copper coordination and subsequent N–O cleavage. Thus, the path b is preferred.

Table 3

Scope of the benzofurazan 1-oxide.

$ \begin{array}{c} \text{R} \\ \\ \text{C}_6\text{H}_3\text{N}_2\text{O} \\ \text{1} \end{array} + \text{Ph-B(OH)}_2 \text{ (2a)} \xrightarrow[\text{1,4-dioxane, 60 }^\circ\text{C, N}_2, 12 \text{ h}]{\text{CuCl (10 mol\%), Phen (10 mol\%), Na}_2\text{CO}_3 \text{ (2 equiv.)}} \begin{array}{c} \text{R} \\ \\ \text{C}_6\text{H}_3\text{N}_2\text{O} \\ \text{3} \end{array} + \begin{array}{c} \text{R} \\ \\ \text{C}_6\text{H}_3\text{N}_2\text{O} \\ \text{3'} \end{array} $									
Entry	Substrate	Product	Isolated yield	3:3'	Entry	Substrate	Product	Isolated yield	3:3'
1		 + 	81%	0.5:1	8		 + 	87%	1:0.65
2		 + 	85%	1:0.5	9		 + 	81%	1:0.7
3		 + 	85%	1:0.9	10			23%	
4		 + 	73%	0.6:1	11			70%	
5		 + 	86%	0.5:1	12			60%	
6		 + 	92%	1:0.5	13			52%	
7		 + 	85%	0.7:1	14			50%	

Reaction conditions: **1** (0.2 mmol), **2a** (0.6 mmol), CuCl (10 mol%), phen (10 mol%), Na₂CO₃ (0.4 mmol) in 1,4-dioxane (2 mL) at 60 °C for 12 h.

4. Conclusions

In summary, we have realized a copper(I)-catalyzed C–N coupling between phenylboronic acid and benzofurazan

Scheme 2. Derivatization of a coupled product.

1-oxide. The reaction occurred under mild and redox-neutral conditions to yield an *ortho* aminonitrobenzene. The benzofurazan 1-oxide likely reacts in the heterocyclic form, although a dinitroso benzene intermediate may exist and rapidly equilibrates with benzofurazan 1-oxide tautomers. The amino and the nitro functional groups can be further utilized in subsequent functionalization reactions. Further studies on employment of other cyclic aminating reagents are underway.

Scheme 3. Possible nitroso intermediates.

Scheme 4. Possible pathways.

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Graphical Abstract

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Copper-catalyzed amination of phenylboronic acids with benzofurazan 1-oxides

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CuCl/Phen can catalyze the C–N coupling between arylboronic acid and benzofurazan 1-oxide. This reaction occurred under mild and redox-neutral conditions with benzofurazan 1-oxide as an aminating reagent via ring scission, leading to a bifunctionalized aminonitrobenzene.

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铜催化苯硼酸与苯并呋咱-1-氧化物的胺化反应

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摘要: C–N键普遍存在于药物和有机功能分子中, 传统构建C–N键的方法包括Goldberg反应、Buchwald-Hartwig偶联、Chan-Lam偶联和C–H键活化胺化。虽然这些方法都可以高效构建C–N键, 但它们需要使用官能化的芳基底物、官能化的胺化试剂或在氧化条件下进行。理想的胺化反应应在氧化还原中性条件下进行, 更为理想的则是在引入氨基的同时引入另外一个官能团。实现这个目标最直接的策略就是使用氮杂环, 通过N–E(E=N或O)键的断裂, N原子和E原子可同时被引入。最近我们课题组利用氮杂内酐和氮杂苯并降冰片烯的C–H键活化反应成功实现了这种双官能团化。

尽管该法很有吸引力, 但是要通过氮杂环的断裂实现双官能团化, 需要发生非张力环的开环, 这在热力学上是非常不利的。苯并呋咱-1-氧化物可以开环得到邻二硝基苯中间体。基于对胺化反应的兴趣, 我们推测苯并呋咱-1-氧化物可以作为一个胺化试剂实现苯硼酸的胺化。尽管亚硝基苯对芳基硼酸进行简单的胺化已经被报道, 但需要化学计量的铜盐, 或是引入还原剂。因此本文报道铜催化的苯硼酸的胺化反应, 该反应以苯并呋咱-1-氧化物为胺化试剂, 在温和及氧化还原中性条

件下成功实现了双官能团化。

本文共完成了31个不同官能团取代的硝基苯胺骨架结构的合成, 反应均以中等到良好的收率得到目标产物, 最高收率可达99%。为了增加反应的实用性, 我们还进行了放大实验, 实验表明, 当苯并咪唑-1-氧化物的量由0.2 mmol放大至4 mmol时, 反应仍能以较高的收率得到目标产物。此外, 目标产物通过进一步的衍生化反应还可方便地转化为其他杂环类化合物。例如, 在 PPh_3 作用下, 通过还原环化作用可生成吩嗪。在钯催化下可发生分子内碳氢键氧化反应得到咪唑类化合物。通过还原及重氮化反应还可方便地转化为苯并三唑。

总之, 我们以苯并咪唑-1-氧化物为胺化试剂, 在铜催化下成功实现了苯硼酸的胺化反应, 合成了一系列双官能团化产物。该催化体系反应条件温和, 底物适用范围广, 对各种官能团具有很好的兼容性。

关键词: C–N偶联; 芳基硼酸; 苯并咪唑-1-氧化物; 氧化还原中性; 双官能团化

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