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Synthesis of Biaryl Ethers by the Copper-Catalyzed Chan–Evans–Lam Etherification from Benzylic Amine Boronate Esters

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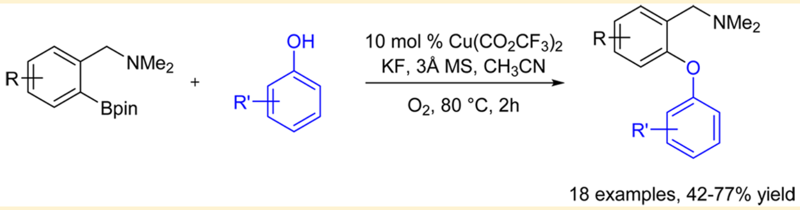
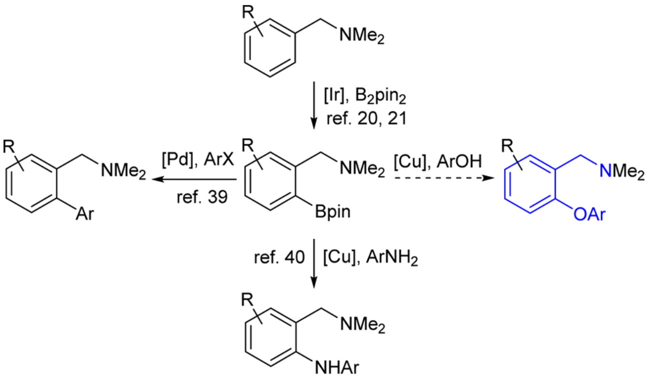
S Supporting Information



ABSTRACT: The copper-catalyzed etherification of ortho-borylated benzylic amines with phenols has been achieved to provide biaryl ethers that are prevalent in biologically active compounds. A variety of substitution patterns on the aryl boronate ester and the phenol are tolerated under the reaction conditions, providing moderate to high yields. A competition reaction between phenol and aniline revealed condition-dependent selectivity in which the phenol could be highly favored over the aniline.

Metal-catalyzed C–H borylation reactions have undergone exceptional growth since the initial discovery about 20 years ago.[1−3] Both arenes and alkanes are successfully borylated using a variety of reaction conditions and precatalysts.[4−8] Two complementary approaches to the C–H borylation of arenes have been developed: (1) sterically controlled C–H borylation that results in borylation *meta-* and *para-* to substituents in arenes;[4,5] (2) substrate-directed C–H borylation with numerous examples of *ortho*-directed borylation and recent select examples of *meta*-directed borylation.[9−11] Distinct approaches to *ortho*-directed C–H borylation reactions have been developed using a variety of directing groups (halides,[12] ethers,[12−14] carbonyls,[12−17] amines,[13,18−23] imines,[24−26] silanes,[27,28] and phosphines[29]) and strategies (covalent interactions with the metal catalyst,[27,28] H-bonding interactions,[22] and Lewis base coordination[12−20,23−26,29]). Although efficient approaches to access *ortho*-borylated arenes have been developed, reactions that explicitly utilize the resulting C–B bond with these products have been limited. Since much of the value of the C–H borylation methodology comes from the versatility of the C–B bond in synthesis,[30−38] it is important to determine if the presence of the directing group allows reactions of the C–B bond to take place efficiently. To this end, we have recently shown *ortho*-borylated benzylic amines can be used in Suzuki-Miyaura coupling reactions to form biphenyl benzylic amines[39] and Chan–Evans–Lam type amination with anilines to form diamines[40] (Scheme 1).

Scheme 1. Formation and Utility of *ortho*-Borylated Benzylic Amines



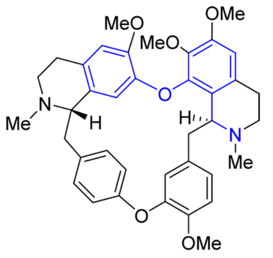


Figure 1. Structure of (+)-tetrandrine.

The Chan–Evans–Lam etherification of *ortho*-borylated benzylic amines was recognized as a valuable synthetic reaction based on the prevalence of biaryl ethers, with a benzylic amine in the *ortho* position, in biologically active compounds.[41−46] For example, tetrandrine, a bisbenzylisoquinoline alkaloid with extensive bioactivity is a cyclic diaryl ether with built-in benzylic amines (Figure 1).[47] Although this class of ethers has been accessed by the Ullman reaction or by nucleophilic aromatic substitution,[48] the Chan–Evans–Lam etherification[49−56] was

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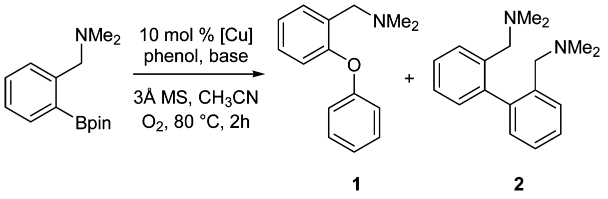
envisioned to have significant advantages over these methods including the ability to selectively incorporate the boronate ester into a readily available amine, and the orthogonal reactivity of the boronate ester to any other halides present in the arene. One challenge that was recognized in developing this reaction is the typical need to utilize the boronic acid rather than the boronate ester in Chan−Evans−Lam couplings.[57−59] Four examples of the direct coupling of amines or alcohols to organoboronate esters have been reported in the literature. Hartwig developed the amination of aryl boronate esters with alkylamines in 2007,[57] but boronic acids were required for anilines and alcohols. Kuninobu reported the direct coupling of anilines and phenols to sp^3-hybridized alkyl boronate esters in 2013,[59] requiring *tert*-butylperoxide as the oxidant. In 2016, Watson found that aryl and alkylamines could be coupled to aryl boronate esters,[58] but a stoichiometric amount of copper was required for the transformation. Finally, our recent work on the coupling of anilines to benzylic amine boronate esters[40] (see Scheme 1) revealed an alternative method to direct Chan−Evans−Lam coupling to arylboronate esters in which an adjacent Lewis base could facilitate the amination. Based on this work in amination reactions, we were optimiztic that the pendent benzylic amine would allow for direct coupling of the aryl boronate ester to phenols. We herein describe the copper-catalyzed Chan−Evans−Lam etherification of *ortho*-borylated benzylic amines with phenols.

Examination of the desired etherification reaction was initiated using the parent boronate ester with phenol. Copper salts and bases that have been shown to mediate the Chan−Evans−Lam coupling,[49−54] and in particular the amination of *ortho*-borylated benzylic amines,[40] were explored. Early reactions with copper(II) acetate and a series of bases resulted in good conversion of the starting material to **1** and **2**, but significant quantities of homocoupled product **2** was observed (Table 1, entries 1−4). In contrast to the amination reaction, the absence of added base provided an increased quantity of **2** with copper(II) acetate (entry 4). The copper salt had a significant impact on the distribution of **1**:**2** as well, favoring homocoupled product **2** when copper(II) acetylacetonate was employed (entry 5). Weakly coordinating copper counterions improved the selectivity toward **1** (entries 6, 7), providing high conversion and selectivity with copper(II) trifluoroacetate and copper(II) trifluoromethanesulfonate.



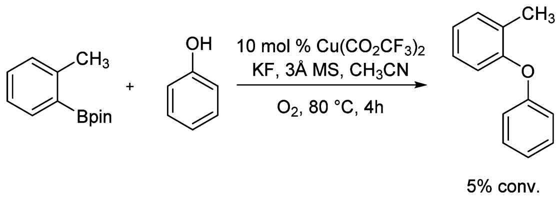
(1)

Table 1. Optimization of the Copper-Catalyzed Etherification of *ortho*-Borylated Benzylic Amines (Eq 1)

entry[a]	catalyst	base	conversion[b]	1:2[b]
1	$Cu(OAc)_2{\cdot}H_2O$	KF	100%	85:15
2	$Cu(OAc)_2{\cdot}H_2O$	LiF	95%	85:15
3	$Cu(OAc)_2{\cdot}H_2O$	Na_2CO_3	100%	70:30
4	$Cu(OAc)_2{\cdot}H_2O$	none	21%	60:40
5	$Cu(acac)_2$	KF	92%	36:64
6	$Cu(CO_2CF_3)_2{\cdot}H_2O$	KF	100%	>99:1
7	$Cu(SO_3CF_3)_2{\cdot}H_2O$	KF	100%	>99:1

[a] Yield based on boronate ester. Conditions: 3 equiv. phenol, 1.03 equiv. base, 0.2 M in CH_3CN, 1 atm O_2. [b] Determined by ^1H NMR spectroscopy of the unpurified reaction mixture.

The increased reactivity of benzylic amine boronate esters toward Chan−Evans−Lam coupling with phenols and anilines (previously reported) is consistent with the pendant amine activating the boronate ester toward coupling. To further examine this hypothesis, the optimized reaction conditions were applied to the coupling of phenol to 2-(pinacolboryl)-toluene (eq 2), which lacks the pendant benzylic amine. As expected, this simple boronate ester was nearly unreactive under the optimized conditions, resulting in 5% conversion to the corresponding ether, as determined by ^1H NMR spectroscopy.[60] This divergent reactivity supports the assertion that the amine coordinates to the catalyst to facilitate the coupling reaction, likely during the transmetalation of the copper salt with the carbon−boron bond.



(2)

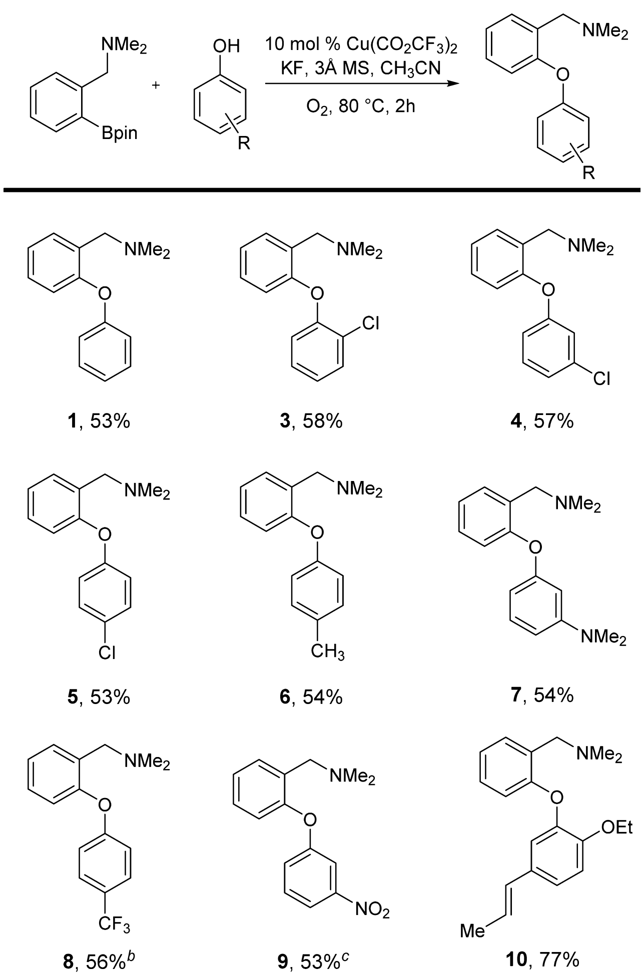
The optimized reaction conditions were examined with a variety of substituted phenols. Copper(II) trifluoroacetate was found to be more general than copper(II) trifluoromethanesulfonate, providing increased selectivity and yields with the phenols examined. Moderate to good yields were obtained in all cases (Scheme 2), including phenols with strongly electron-donating (**7** and **10**) and electron-withdrawing (**8** and **9**) substituents on the phenol. Electron-deficient phenols were found to be sluggish in the reaction, requiring 6 h to proceed to completion for **8** (4−CF_3). In the case of 3-nitrophenol, incomplete conversion was observed, even after 24 h, but the addition of sodium *tert*-butoxide in place of potassium fluoride provided **9** in 2 h. The presence of a chlorine substituent in the *ortho*-, *meta*-, and *para*-positions was tolerated (**3**−**5**), providing an additional synthetic handle for coupling reactions. The facile formation of **3**−**5** is notable in that they have been found to be active in serotonin/noradrenaline reuptake inhibition.[42] Remarkably, a styrene-derived phenol provided a 77% yield of **10** without any evidence of significant side reactions involving the olefin.

The effect of substituents on the aryl boronate ester was examined next with phenol, providing similar yields and selectivity for the desired ethers (Scheme 3). Electron-donating and electron-withdrawing substituents on the boronate ester were also readily tolerated (**13**−**15**).

Several examples of etherifications were conducted with both substituted benzylic amines and phenols to provide **17**−**19** in moderate yields (Figure 2). The rapid formation of **17**−**19** from readily available starting material demonstrates the utility of this C−H borylation/etherification sequence.

The ability to couple phenols and anilines[40] to aryl boronate esters under similar reaction conditions led us to probe the relative reactivity of these two coupling partners. A competition reaction was performed with three equivalents of both phenol and aniline with the parent boronate ester (Scheme 4). Two sets of reaction conditions were utilized for the competition, those utilized for anilines [$Cu(OAc)_2$ with no added base] and those

Scheme 2. Scope of Substituted Phenols in Etherification[a]



[a] Yield based on boronate ester. Conditions: 3 equiv. phenol, 1.03 equiv. base, 0.2 M in CH_3CN, 1 atm O_2. >99:1 selectivity of **1, 3–10**:**2** for all substrates. [b] Six hour reaction time. [c] NaO*t*-Bu used in place of KF.

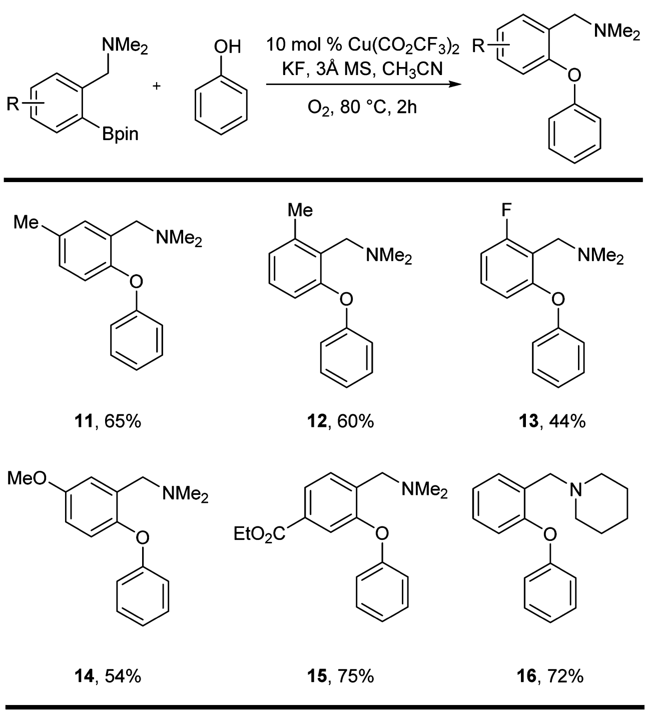
utilized for phenols [$Cu(O_2CCF_3)_2$ with KF]. Using $Cu(O_2CCF_3)_2$ with KF, the ratio of **1** to **20** was 37:63. Unexpectedly, however, using $Cu(OAc)_2$ with no added base provided ether **1** as the only observed product. While the source of this selectivity is not understood, it likely results from the increased acidity of phenol over aniline.

In summary, the Chan–Evans–Lam etherification of aryl boronate esters derived from benzylic amines has been achieved in moderate to high yields. The adjacent benzylic amine allows for direct coupling with the boronate ester without hydrolysis to the more reactive boronic acid. A variety of aryl boronate esters and phenols are tolerated under the reaction conditions. A competition experiment between phenol and aniline with a boronate ester revealed high selectivity for the phenol.

EXPERIMENTAL SECTION

General Methods. All procedures were performed in oven-dried glassware under purified nitrogen until O_2 gas was introduced. *N*,*N*-Dimethylbenzylamines and the corresponding boronate esters were synthesized following the published procedures.[20,21] All other materials, including solvents, were purchased and used as received. Concentration was performed by rotary evaporation. TLC analysis was performed on 60 Å silica layer fluorescence UV plates. Flash column chromatography was carried out on hand-packed columns of silica gel, 40–63 μm, 60 Å or aluminum oxide, basic, Brockman I, 50–200 μm, 60 Å. NMR spectra were collected at 500 or 400 MHz for ^1H NMR, 125 or 100 MHz for $^{13}C\{^1H\}$ NMR. ^1H NMR spectra are referenced to $CDCl_3$ at 7.26 ppm, or to an internal tetramethylsilane (TMS) standard at 0.00 ppm. The ^1H NMR spectral data are reported as follows: chemical shift ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, hex = hextet, sep = septet, oct = octet, m = multiplet), coupling constants (Hz), and integration. $^{13}C\{^1H\}$ NMR spectra are referenced to $CDCl_3$ at 77.0 ppm. Fourier transform infrared (FTIR) spectra were obtained from thin film in dichloromethane or chloroform-*d* and absorptions reported in cm^{-1}. High-resolution mass spectrometry was obtained by time-of-flight electrospray ionization.

Scheme 3. Scope of Substituted Aryl Boronate Esters[a]



[a] Yield based on boronate ester. Conditions: 3 equiv. phenol, 1.03 equiv. base, 0.2 M in CH_3CN, 1 atm O_2. >99:1 selectivity of **11–16**:**2** for all substrates.

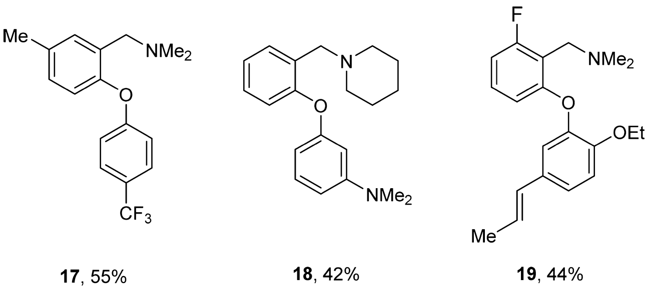
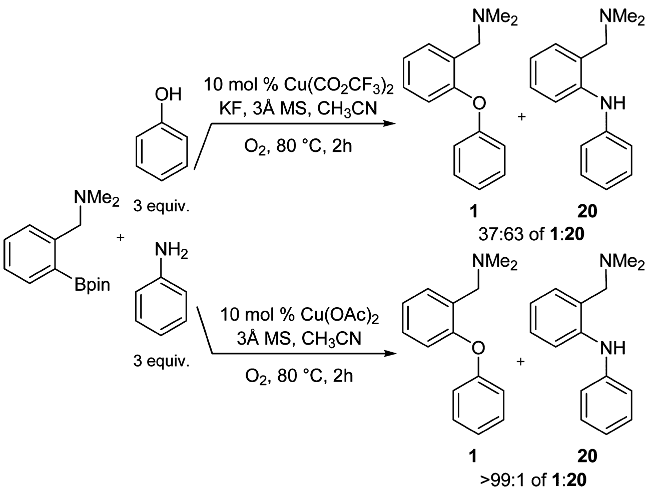


Figure 2. Examples of multi-substituted biaryl ethers under standard reaction conditions. **17** required a 4 h reaction time to proceed to completion.

Representative Procedure A. ***N*,*N*-Dimethyl-1-(2-phenoxyphenyl)methanamine, 1.** To a Schlenk flask containing 4 Å molecular sieves (0.300 g) was added 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*,*N*-dimethylbenzylamine (0.050 g, 0.191 mmol), potassium fluoride (0.0114 g, 0.197 mmol), phenol (0.0540 g, 0.574 mmol), copper(II) trifluoroacetate monohydrate (0.0055 g, 0.0191 mmol), and acetonitrile (2.0 mL). Oxygen gas was bubbled through the mixture for 5 min, followed by heating to 80 °C under positive oxygen

Scheme 4. Competition Experiment between Phenol and Aniline



pressure. After 2 h the mixture was allowed to cool to room temperature, then transferred using acetonitrile (10 mL), and concentrated in vacuo to give a dark brown oil. The crude product was purified by silica gel column chromatography (90:10 dichloromethane/ethyl acetate). The concentrated fractions were diluted with 95% ethanol and concentrated in vacuo (3 × 2 mL), to remove pinacol impurities azeotropically, providing **1** as a brown oil (0.0476 g, 0.1047 mmol, 53%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.47 (d, J = 7.4 Hz, 1H), 7.30 (t, J = 8.2 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 7.13 (t, J = 7.4 Hz, 1H), 7.05 (t, J = 7.4 Hz, 1H), 6.93−6.90 (m, 3H), 3.46 (s, 2H), 2.26 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 157.9, 154.7, 131.2, 130.4, 129.6, 128.3, 123.9, 122.5, 119.7, 117.7, 57.4, 45.5; IR (thin film, CH$_2$Cl$_2$) 3038, 2941, 2855, 2817, 2769, 1682, 1582.3, 1485, 1453, 1234, 751 cm^{-1}; HRMS (ESI): m/z calcd for (C$_{15}$H$_{17}$NO)$^+$ 227.1310, found 227.1317.

1-(2-(2-Chlorophenoxy)phenyl)-N,N-dimethylmethanamine, **3.** Following representative procedure A with substrate 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*,*N*-dimethylbenzylamine (0.050 g, 0.191 mmol) and 2-chlorophenol (0.0586 mL, 0.574 mmol), the crude mixture was purified by silica gel column chromatography (96.8:3:0.2) dichloromethane/ethyl acetate/triethylamine) to afford **3** as a yellow oil (0.0307g, 0.117 mmol, 58%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.50 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 7.9 Hz, 1H), 7.23−7.12 (m, 3H), 7.04 (t, J = 8.0 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 3.53 (s, 2H), 2.29 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 154.4, 153.0, 131.3, 130.7, 129.5, 128.2, 127.8, 124.8, 123.94, 123.90, 119.2, 118.2, 57.1, 45.4; IR (thin film, CH$_2$Cl$_2$) 3067, 2974, 2942, 2855, 2817, 2770, 1578, 1476, 1476, 1445, 1242, 751 cm^{-1}; HRMS (ESI): m/z calcd for (C$_{15}$H$_{16}$ClNO)$^+$ 261.0920, found 261.0918.

1-(2-(3-Chlorophenoxy)phenyl)-N,N-dimethylmethanamine, **4.** Following representative procedure A with substrate 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*,*N*-dimethylbenzylamine (0.050 g, 0.191 mmol) and 3-chlorophenol (0.0734 g, 0.574 mmol), the crude mixture was purified by silica gel column chromatography (94.8:5:0.2 dichloromethane/ethyl acetate/triethylamine) to afford **4** as a yellow oil (0.0285 g, 0.109 mmol, 57%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.49 (d, J = 7.4 Hz, 1H), 7.28−7.15 (m, 3H), 7.02 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.90 (s, 1H), 6.81 (d, J = 8.2 Hz, 1H), 3.42 (s, 2H), 2.25 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 158.9, 153.8, 135.0, 131.4, 130.7, 130.4, 128.5, 124.6, 122.6, 120.2, 117.6, 115.5, 57.4, 45.5; IR (thin film, CH$_2$Cl$_2$) 3066, 2974, 2942, 2856, 2818, 2770, 1580, 1471, 1233, 912, 767 cm^{-1}; HRMS (ESI): m/z calcd for (C$_{15}$H$_{16}$ClNO)$^+$ 261.0920, found 261.0925.

1-(2-(4-Chlorophenoxy)phenyl)-N,N-dimethylmethanamine, **5.** Following the representative procedure A with substrate 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*,*N*-dimethylbenzylamine (0.050 g, 0.191 mmol) and 4-chlorophenol (0.0734 g, 0.574 mmol), the crude mixture was purified by silica gel column chromatography (89.8:10:0.2 dichloromethane/ethyl acetate/triethylamine) to afford **5** as a yellow oil (0.0272 g, 0.104 mmol, 53%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.47 (d, J = 7.4 Hz, 1H), 7.27−7.20 (m, 3H), 7.15 (t, J = 7.3 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 7.9 Hz, 2H), 3.44 (s, 2H) 2.25 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 156.6, 154.3, 131.3, 130.4, 129.6, 128.4, 127.4, 124.3, 119.7, 118.7, 57.4, 45.5; IR (thin film, CH$_2$Cl$_2$) 2974, 2942, 2856, 2817, 2770, 1581, 1483, 1452, 1238 cm^{-1}; HRMS (ESI): m/z calcd for (C$_{15}$H$_{16}$ClNO)$^+$ 261.0920, found 261.0916.

N,N-Dimethyl-1-(2-(p-tolyloxy)phenyl)methanamine, **6.** Following representative procedure A with substrate 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*,*N*-dimethylbenzylamine (0.050 g, 0.191 mmol) and *para*-cresol (0.0603 mL, 0.574 mmol), the crude mixture was purified by silica gel column chromatography (87.99:12:0.01 dichloromethane/ethyl acetate/triethylamine) to afford **6** as a brown oil (0.0242 g, 0.100 mmol, 54%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.46 (d, J = 7.4 Hz, 1H), 7.20 (t, J = 7.9 Hz, 1H), 7.30−7.05 (m, 3H), 6.87−6.82 (m, 3H), 3.50 (s, 2H), 2.32 (s, 3H), 2.27 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 155.5, 155.3, 132.1, 131.2, 130.1, 129.9, 128.2, 123.5, 119.1, 117.9, 57.3, 45.4, 20.6; IR (thin film, CH$_2$Cl$_2$) 3030, 2973, 2941, 2856, 2817, 2769, 1506, 1486, 1452, 1236 cm^{-1}; HRMS (ESI): m/z calcd for (C$_{16}$H$_{19}$NO)$^+$ 241.1467, found 241.1471.

3-(2-((Dimethylamino)methyl)phenoxy)-N,N-dimethylaniline, **7.** Following representative procedure A with substrate 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*,*N*-dimethylbenzylamine (0.050 g, 0.191 mmol) and 3-dimethylamino phenol (0.079 g, 0.574 mmol), the crude mixture was purified by silica gel column chromatography (94.7:5:0.3 dichloromethane/ethyl acetate/triethylamine) to afford **7** as a brown oil (0.0269 g, 0.0996 mmol, 54%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.45 (d, J = 7.5 Hz, 1H), 7.20 (t, J = 7.3 Hz, 1H), 7.16−7.08 (m, 2H), 6.93 (d, J = 8.0 Hz, 1H) 6.45 (d, J = 8.3 Hz, 1H), 6.38 (s, 1H), 6.19 (d, J = 8.0 Hz, 1H), 3.50 (s, 2H), 2.92 (s, 6H), 2.28 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 158.9, 155.0, 152.1, 131.0, 130.0, 129.8, 128.2, 123.5, 119.5, 107.1, 105.6, 102.5, 57.3, 45.5, 40.5; IR (thin film, CH$_2$Cl$_2$) 2940, 2854, 2814, 2769, 1613, 1572, 1502, 1486, 1450, 1236 cm^{-1}; HRMS (ESI): m/z calcd for (C$_{17}$H$_{22}$N$_2$O)$^+$ 270.1732, found 270.1742.

N,N-Dimethyl-1-(2-(4-(trifluoromethyl)phenoxy)phenyl)-methanamine, **8.** Following representative procedure A with substrate 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*,*N*-dimethylbenzylamine (0.050 g, 0.191 mmol) and 4-trifluoromethyl phenol (0.0931 g, 0.574 mmol), the crude mixture was purified by silica gel column chromatography (94.5:5:0.5 dichloromethane/ethyl acetate/triethylamine) to afford **8** as a yellow oil (0.0312 g, 0.106 mmol, 56%): ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.54 (d, J = 8.6 Hz, 2H), 7.51 (d, J = 8.6 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.21 (t, J = 7.4 Hz, 1H), 6.98−6.94 (m, 3H) 3.40 (s, 2H), 2.24 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 160.9, 153.4, 131.5, 130.9, 128.7, 127.1 (q, J_F = 4.0 Hz), 125.1, 124.3 (q, J_F = 33.0 Hz), 124.2 (q, J_F = 270.0 Hz), 120.7, 116.8, 57.4, 45.4; IR (thin film, CH$_2$Cl$_2$) 2975, 2944, 2857, 2819, 2772, 1617, 1512, 1486, 1454, 1323, 1243, 1165 cm^{-1}; HRMS (ESI): m/z calcd for (C$_{16}$H$_{16}$F$_3$NO)$^+$ 295.1184, found 295.1192.

N,N-Dimethyl-1-(2-(3-nitrophenoxy)phenyl)methanamine, **9.** Following the representative procedure A with substrate 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*,*N*-dimethylbenzylamine (0.050 g, 0.191 mmol) and 3-nitrophenol (0.0799 g, 0.574 mmol), the crude mixture was purified by silica gel column chromatography (94.8:5:0.2 dichloromethane/ethyl acetate/triethylamine) to afford **9** as a brown oil (0.0276 g, 0.101 mmol, 53%).^{1}H NMR (400 MHz, CDCl$_3$) δ 7.90 (d, J = 8.0 Hz, 1H), 7.70 (s, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.46 (t, J = 8.2 Hz, 1H), 7.31−7.22 (m, 3H), 6.97 (d, J = 7.9 Hz, 1H) 3.41 (s, 2H), 2.23 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 159.0, 153.2, 149.2, 131.7, 131.0, 130.2, 128.9, 125.4, 123.1, 120.5, 117.1, 111.8, 57.6, 45.4; IR (thin film, CH$_2$Cl$_2$) 2942, 2857, 2818, 2770, 1532, 1351, 1238, 737 cm^{-1}; HRMS (ESI): m/z calcd for (C$_{15}$H$_{16}$N$_2$O$_3$)$^+$ 272.1161, found 272.1153.

(E)-1-(2-(2-Ethoxy-5-(prop-1-en-1-yl)phenoxy)phenyl)-N,N-dimethylmethanamine, **10.** Following representative procedure A with substrate 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*,*N*-dimethylbenzylamine (0.050 g, 0.191 mmol) and 2-ethoxy 5-(1-propenyl)-phenol (0.1024 g, 0.574 mmol), the crude mixture was purified by silica gel column chromatography (95:5 to 0:1 dichloromethane/ethyl

acetate) to afford **10** as a yellow oil (0.0444 g, 0.143 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 7.0 Hz, 1H), 7.13 (t, J = 7.4 Hz, 1H), 7.08−6.98 (m, 2H), 6.93 (s, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H), 6.27 (d, J = 15.7 Hz, 1H), 6.03 (m, 1H), 4.01 (q, J = 6.9 Hz, 2H), 3.62 (s, 2H), 2.32 (s, 6H), 1.82 (d, J = 6.5 Hz, 3H), 1.24 (t, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2, 149.4, 145.7, 131.5, 131.0, 130.0, 128.0, 124.3, 122.5, 122.0, 118.0, 116.4, 114.3, 64.6, 57.1, 45.4, 18.3, 14.7 (one overlapping peak); IR (thin film, CH_2Cl_2) 3021, 2977, 2937, 2912, 2817, 2770, 1509, 1263, 1222, 1043 cm^{-1}; HRMS (ESI): m/z calcd for $(C_{20}H_{25}NO_2)^+$ 311.1885, found 311.1875.

*N,N-Dimethyl-1-(5-methyl-2-phenoxyphenyl)methanamine, **11**.* Following representative procedure A with substrate 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*,*N*-dimethylbenzylamine (0.050 g, 0.182 mmol) and phenol (0.0513 g, 0.545 mmol), the crude mixture was purified by silica gel column chromatography (85:15 dichloromethane/ethyl acetate) to afford **11** as a brown oil (0.0266 g, 0.110 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.25 (m, 3H), 7.03−7.00 (m, 2H), 6.89 (d, J = 7.8 Hz, 2H), 6.82 (d, J = 8.2 Hz, 1H), 3.41 (s, 2H), 2.34 (s, 3H), 2.25 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 152.1, 133.7, 131.6, 130.3, 129.6, 128.9, 122.2, 120.0, 117.2, 57.3, 45.6, 20.8; IR (thin film, CH_2Cl_2) 3038, 2972, 2941, 2857, 2817, 2768, 1589, 1487, 1245, 1217, 853, 752, 691 cm^{-1}; HRMS (ESI): m/z calcd for $(C_{16}H_{19}NO)^+$ 241.1467, found 241.1463.

*N,N-Dimethyl-1-(2-methyl-6-phenoxyphenyl)methanamine, **12**.* Following representative procedure A with substrate 2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*,*N*-dimethylbenzylamine (0.050 g, 0.1717 mmol) and phenol (0.0485 g, 0.5151 mmol), the crude mixture was purified by silica gel column chromatography (89.9:10:0.1 dichloromethane/ethyl acetate/triethylamine) to afford **12** as a brown oil (0.0248 g, 0.1027 mmol, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, J = 8.4 Hz, 2H), 7.12 (t, J = 7.8 Hz, 1H), 7.04 (t, J = 7.4 Hz, 1H), 6.98 (d, J = 7.5 Hz, 1H), 6.92 (d, J = 7.8 Hz, 2H), 6.74 (d, J = 8.1 Hz, 1H), 3.43 (s, 2H), 2.45 (s, 3H), 2.25 (s, 6H); δ ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 155.2, 140.7, 129.6, 129.0, 128.0, 126.0, 122.4, 117.7, 117.0, 54.2, 45.6, 19.4; IR (thin film, CH_2Cl_2) 2941, 2855, 2815, 2767, 1578, 1490, 1465, 1241, 1214 cm^{-1}; HRMS (ESI): m/z calcd for $(C_{16}H_{19}NO)^+$ 241.1467, found 241.1461.

*1-(2-Fluoro-6-phenoxyphenyl)-N,N-dimethylmethanamine, **13**.* Following representative procedure A with substrate 2-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*,*N*-dimethylbenzylamine (0.050 g, 0.179 mmol) and phenol (0.0506 g, 0.537 mmol), the crude mixture was purified by silica gel column chromatography (89.9:10:0.1 dichloromethane/ethyl acetate/triethylamine) to afford product **13** as a brown oil (0.0196 g, 0.080 mmol, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, J = 7.6 Hz, 2H), 7.20−7.15 (m, 1H), 7.11 (t, J = 7.4 Hz, 1H) 6.98 (d, J = 7.8 Hz, 2H), 6.85 (t, J = 8.1 Hz, 1H), 6.66 (d, J = 8.2 Hz, 1H), 3.60 (s, 2H), 2.31 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6 (d, J_F = 246.0 Hz), 157.11, 157.0 (d, J_F = 7.0 Hz), 129.8, 128.9 (d, J_F = 10.0 Hz), 123.4, 118.6, 117.3 (d, J_F = 18.0 Hz), 114.2 (d, J_F = 3.0 Hz), 110.4 (d, J_F = 23.0 Hz), 50.3, 45.2; IR (thin film, CH_2Cl_2) 3041, 2974, 2942, 2859, 2819, 2770, 1587, 1491, 1464, 1235, 1213, 1035 cm^{-1}; HRMS (ESI): m/z calcd for $(C_{15}H_{16}FNO)^+$ 245.1216, found 245.1207.

*1-(5-Methoxy-2-phenoxyphenyl)-N,N-dimethylmethanamine, **14**.* Following representative procedure A with substrate 5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*,*N*-dimethylbenzylamine (0.050 g, 0.1717 mmol) and phenol (0.0485 g, 0.5151 mmol), the crude mixture was purified by silica gel column chromatography (89.9:10:0.1 dichloromethane/ethyl acetate/triethylamine) to afford **14** as a brown oil (0.0239 g, 0.0929 mmol, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, J = 7.6 Hz, 2H), 7.06 (br s, 1H), 7.00 (t, J = 6.9 Hz, 1H), 6.92−6.84 (m, 3H), 6.79 (m, 1H), 3.82 (s, 3H), 3.41 (s, 2H), 2.25 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 156.3, 147.5, 131.9, 129.6, 121.9, 121.8, 116.5, 115.3, 114.1, 57.5, 55.7, 45.47; IR (thin film, CH_2Cl_2) 2941, 2817, 2770, 1487, 1217, 1040, 852, 753 cm^{-1}; HRMS (ESI): m/z calcd for $(C_{16}H_{19}NO_2)^+$ 257.1416, found 257.1405.

*Ethyl 4-((Dimethylamino)methyl)-3-phenoxybenzoate, **15**.* Following representative procedure A with substrate 4-(dimethylaminomethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethylbenzoate (0.0840 g, 0.2535 mmol) and phenol (0.0716 g, 0.7608 mmol), the crude mixture was purified by silica gel column chromatography (89.8:10:0.2 dichloromethane/ethyl acetate/triethylamine) to afford **15** as a yellow oil (0.0376 g, 0.126 mmol, 75%). δ 7.82 (d, J = 7.8 Hz, 1H), 7.60−7.58 (m, 2H), 7.32 (t, J = 7.9 Hz, 2H), 7.08 (t, J = 7.3 Hz, 1H), 6.93 (d, J = 7.9 Hz, 2H), 4.33 (q, J = 7.1 Hz, 2H), 3.53 (s, 2H), 2.28 (s, 6H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 157.4, 154.6, 135.7, 130.8, 130.7, 129.8, 124.9, 123.0, 120.5, 117.7, 61.0, 57.2, 45.6, 14.3; IR (thin film, CH_2Cl_2) 2977, 2942, 2858, 2819, 2770, 1720, 1490, 1283, 1225, 762 cm^{-1}; HRMS (ESI): m/z calcd for $(C_{18}H_{21}NO_3)^+$ 299.1521, found 299.1512.

*1-(2-Phenoxybenzyl)piperidine, **16**.* Following representative procedure A with substrate 1-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperidine (0.050 g, 0.166 mmol) and phenol (0.0468 g, 0.498 mmol), the crude mixture was purified by silica gel column chromatography (90:10 dichloromethane/ethyl acetate) to afford **16** as a brown oil (0.0342 g, 0.128 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.3 Hz, 1H), 7.30 (t, J = 7.9 Hz, 2H), 7.20 (d, J = 7.5 Hz, 1H), 7.13 (t, J = 7.4 Hz, 1H), 7.05 (t, J = 7.3 Hz, 1H), 6.94−6.87 (m, 3H), 3.54 (br s, 2H), 2.43 (br s, 4H), 1.56 (br s, 4H), 1.40 (br s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 154.7, 131.2, 129.6, 128.1, 123.8, 122.4, 119.6, 118.3, 117.6, 56.7, 54.4, 25.9, 24.2; IR (thin film, CH_2Cl_2) 3064, 3037, 2933, 2852, 2795, 2756, 1581, 1486, 1235, 750 cm^{-1}; HRMS (ESI): m/z calcd for $(C_{18}H_{21}NO)^+$ 267.1623, found 267.1615.

*N,N-Dimethyl-1-(5-methyl-2-(4-(trifluoromethyl)phenoxy)phenyl)methanamine, **17**.* Following representative procedure A with substrate 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*,*N*-dimethylbenzylamine (0.100 g, 0.363 mmol) and 4-trifluoromethylphenol (0.1767 g, 1.090 mmol), the crude mixture was purified by silica gel column chromatography (90:10 dichloromethane/ethyl acetate) to afford product **17** as a yellow oil (0.0610 g, 0.197 mmol, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.6 Hz, 2H), 7.32 (s, 1H), 7.09 (d, J = 8.2 Hz, 1H), 6.94 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.2 Hz, 1H), 3.35 (s, 2H), 2.36 (s, 3H), 2.24 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2, 150.9, 134.9, 131.9, 130.6, 129.3, 127.0 (q, J_F = 4.0 Hz), 124.3 (q, J_F = 270.0 Hz), 124.0 (q, J_F = 32.5 Hz), 120.7, 116.4, 57.4, 45.5, 20.8; IR (thin film, CH_2Cl_2) 2975, 2944, 2859, 2819, 2771, 1616, 1514, 1493, 1327, 1250, 1163, 1121, 840 cm^{-1}; HRMS (ESI): m/z calcd for $(C_{17}H_{18}F_3NO)^+$ 309.1341, found 309.1339.

*N,N-Dimethyl-3-(2-(piperidin-1-ylmethyl)phenoxy)aniline, **18**.* Following representative procedure A with substrate 1-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperidine (0.050 g, 0.161 mmol) and 3-dimethylaminophenol (0.0683 g, 0.498 mmol), the crude mixture was purified by silica gel column chromatography (84.9:15:0.1 dichloromethane/ethyl acetate/triethylamine) to afford **18** as a brown oil (0.0215 g, 0.069 mmol, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 7.3 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.14−7.08 (m, 2H), 6.91 (d, J = 8.0 Hz, 1H), 6.43 (d, J = 8.3 Hz, 1H), 6.35 (s, 1H), 6.19 (d, J = 7.8 Hz, 1H), 3.56 (s, 2H), 2.92 (s, 6H), 2.43 (br s, 4H), 1.55 (br s, 4H), 1.38 (br s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 155.0, 152.0, 130.8, 129.8, 127.9, 125.8, 119.4, 107.0, 105.6, 102.4, 56.7, 54.4, 40.5, 26.0, 24.3 (one overlapping peak); IR (thin film, CH_2Cl_2) 2933, 2850, 2780, 2755, 1615, 1573, 1501, 1235, 1000, 756 cm^{-1}; HRMS (ESI): m/z calcd for $(C_{20}H_{26}N_2O)^+$ 310.2045, found 310.2035.

*(E)-1-(2-(2-Ethoxy-5-(prop-1-en-1-yl)phenoxy)-6-fluorophenyl)-N,N-dimethylmethanamine, **19**.* Following representative procedure A with substrate 2-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*,*N*-dimethylbenzylamine (0.050 g, 0.363 mmol) and 2-ethoxy 5-(1-propenyl)phenol (0.0958 g, 0.537 mmol), the crude mixture was purified by silica gel column chromatography (200 mL DCM then 75:25 dichloromethane/ethyl acetate) to afford **19** as a brown oil (0.0243 g, 0.0737 mmol, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10−7.05 (m, 3H), 6.89 (d, J = 8.2 Hz, 1H), 6.75 (t, J = 8.7, 1H), 6.44 (d, J = 8.3 Hz, 1H), 6.30 (d, J = 15.8 Hz, 1H), 6.10−6.02 (m, 1H), 3.97 (q, J = 7.0 Hz, 2H), 3.71 (s, 2H), 2.36 (s, 6H), 1.84 (d, J = 6.5 Hz, 3H), 1.20 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ163.8, 161.3, 158.3, 149.7, 131.5, 129.8, 128.4 (d, J_F = 11.1 Hz), 124.5, 122.8, 119.0, 114.1, 110.8 (d, J_F = 3.0 Hz), 109.0 (d, J_F = 23.2), 64.4, 50.1, 45.2, 18.4, 14.6; IR (thin film, CH_2Cl_2) 3021, 2978, 2938, 2820, 2772, 1616, 1506, 1464, 1268, 1130, 1036 cm^{-1}; HRMS (ESI): m/z calcd for $(C_{20}H_{24}FNO_2)^+$ 329.1791, found 329.1789.

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COMPETITION EXPERIMENTS

Representative Procedure of the Competition Reaction of Phenol and Aniline. To an oven-dried Schlenk flask containing 4 Å molecular sieves (0.300 g) was added 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*,*N*-dimethylbenzylamine (0.050 g, 0.191 mmol), a solution of phenol (0.0540 g, 0.574 mmol) and aniline (0.574 mmol) in acetonitrile (2 mL), and copper(II) acetate (0.0038 g, 0.0191 mmol). Oxygen gas was bubbled through the mixture for 5 min, followed by heating to 80 °C under positive oxygen pressure. After 2 h the mixture was allowed to cool to room temperature, then transferred using acetonitrile (10 mL) and concentrated in vacuo to give a dark brown oil. The unpurified reaction mixture was analyzed by ^{1}H NMR spectroscopy (500 MHz, $CDCl_3$, 10 s relaxation delay), comparing the characteristic benzyl hydrogen peaks of the characterized ether **1** and aniline **20**. Characteristic peaks for analysis: **1** δ 3.46 (s, 2H); **20** δ 3.50 (s, 2H).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01254.

Copies of all ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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