Communication

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.7b06785 • Publication Date (Web): 14 Aug 2017

Cu(II)-Catalyzed *ortho*-Selective Aminomethylation of Phenols

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Supporting Information Placeholder

ABSTRACT: A Cu(II)-catalyzed *ortho*-selective functionalization of free phenols with trifluoroborates to afford C_{sp2}–C_{sp3} coupling products under mild conditions has been developed. A variety of functional groups on the phenol and the potassium aminomethyltrifluoroborate substrates were found compatible, furnishing the corresponding products in moderate to excellent yields. A single-electron transfer radical coupling mechanism involving a six-membered transition state is proposed to rationalize the high levels of *ortho*-selectivity in the reaction. This protocol provides straightforward access to *ortho*-aminomethyl-substituted phenols, unnatural amino acids and other bioactive small molecules.

Phenol motifs are prevalent in natural products, dyes, medicines and materials,[1] and they represent an ideal and sustainable class of starting materials for diverse modes of bond construction in the chemical sciences.[2] Thus, site-selective functionalization of phenols is highly desirable. However, the chemo- and regioselective conversion of free phenol C–H bonds to C–C bonds constitutes a challenge for synthetic chemistry for several reasons. First, the free phenol hydroxyl group is acidic and nucleophilic, which typically results in O–H substitution in preference to C–H substitution. Second, both the *ortho*- and *para*- positions on the aromatic ring are nucleophilic, often leading to intractable product mixtures with various electrophiles. Third, as a classic electron-rich arene, phenols are sensitive towards oxidative decomposition.[3]

In the past decade, many indirect methods have been developed to effect *ortho*-C–H functionalization of phenols *via* installation of directing groups on the hydroxyl substituent, such as silanes/silanols,[4] esters, carbamates, ethers,[5] and traceless phosphites[6] (Fig. 1a). The use of the free hydroxyl group as a directing substituent to functionalize phenols, while underdeveloped, is a straightforward, atom-economic, and step-saving strategy to prepare highly substituted phenols. To this end, Miura and Rawal have previously reported seminal examples of hydroxyl-anchored C–H arylations with Pd-catalysts; Lewis, Bergman and Ellman have disclosed the pioneering alkylation of phenols with Ru- and Rh-catalysts.[7] Recently, radical single-electron transfer strategies have witnessed tremendous progress in oxidization and coupling reactions with free phenol substrates. With iron-based catalysts, asymmetric cross-coupling of phenols, phenol *ortho*-dehydrogenative-couplings with *α*-amino acids or *β*-ketoesters, and oxidative cross-coupling of phenols with arenes and alkenes have been achieved.[8] With copper-based catalysts, biomimetic *ortho*-selective oxidation and coupling reactions under O_2 atmosphere, oxidation of phenols to quinones, and the selective coupling of phenols with *ortho*-quinones have been realized.[9] Carbenoid insertion to unprotected phenol C–H bonds has also been successfully achieved; diazoesters were chemoselectively inserted into the *ortho*- or *para*-position of free phenols.[10] Other selective functionalization reactions of phenols, such as C–H activation to prepare dibenzofurans,[11] and catalytic asymmetric dearomatization of free phenols,[12] have also been developed.

Despite these successes, the catalytic, regioselective C_{sp2}–C_{sp3} cross-coupling with free phenols as reaction partners remains a challenge.[13] Herein, we report a Cu(II)-catalyzed aerobic *ortho*-aminomethylation of free phenols with potassium aminomethyltrifluoroborates. This transformation shows exclusively *ortho*-C–H selectivity and affords C_{sp2}–C_{sp3} coupling products in high yields, while leaving the hydroxyl groups unperturbed. We have also demonstrated the utility of this method in the synthesis of unnatural amino acids and medicinally-relevant small molecules.

Organoboron reagents are an established class of progenitors for carbon-centered radicals under photoredox catalysts[14] and oxidative conditions.[15] Inspired by the inner-sphere electron transfer strategy,[16] we envisioned that under thermal conditions,[17] a Cu(II) catalyst could coordinate with phenol (**1**) and aminomethyltrifluoroborate (**2a**), which would trigger radical coupling via a six-membered transition state (Fig. 1), thereby incorporating the aminomethyl group exclusively at the *ortho*-position of the phenol.

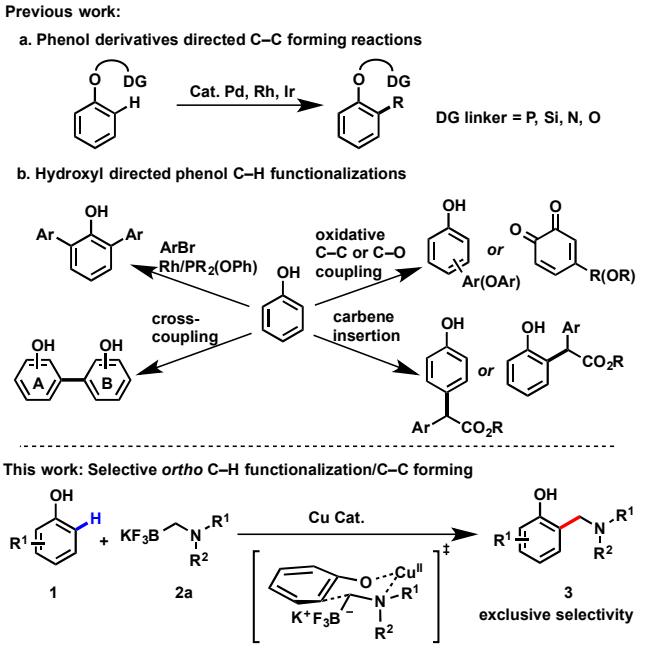
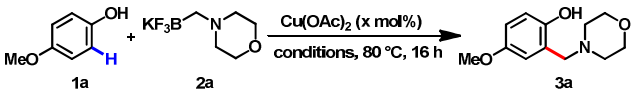


Figure 1. Selective Functionalization of Phenolic Compound.

We began our study by examining the reaction of 4-methoxyphenol (**1a**) and potassium *N*-morpholinylmethyltrifluoroborate (**2a**) in the presence of Na_2CO_3 and a catalytic amount of $Cu(OAc)_2$ under O_2 in THF at 80 °C. Encouragingly, under these conditions the isolated yield of the desired *ortho*-aminomethylated product **3a** was 31% (Table 1, entry 1). We next carefully examined the reaction parameters. Toluene was determined to be the optimal solvent and $NaOAc{\cdot}3H_2O$ proved to be the most efficient base, which together offered 98% conversion and 86% isolated yield (entry 5). We hypothesized that the water molecules from the base function as co-solvent or activator for the trifluoroborate. Indeed, the addition of 2.5% water to an otherwise anhydrous reaction mixture provided similar conversion (entry 6).[18] Molecular O_2 was found to be the best terminal oxidant, and only 16% isolated yield was obtained under N_2 atmosphere. Ambient air was also found to be an efficient oxidant, which enabled us to use open-flask technique (entry 8). Further reducing the catalyst loading to 10 mol% did not influence conversion (81% isolated yield, entry 9). Other copper salts, such as $CuCl_2$, $CuBr_2$, $Cu(OTf)_2$, $CuPF_6{\cdot}(MeCN)_4$, and $CuBF_4{\cdot}(MeCN)_4$, gave moderate conversions (See SI). Elevated temperature was found to shorten reaction time, while decreased temperature led low conversion and partial recovery of starting material (entries 14 and 15). It should be noted that in all cases only the *ortho*-C–C coupled product was detected; no other products were observed.

Table 1. Optimization of Reaction Conditions [a]



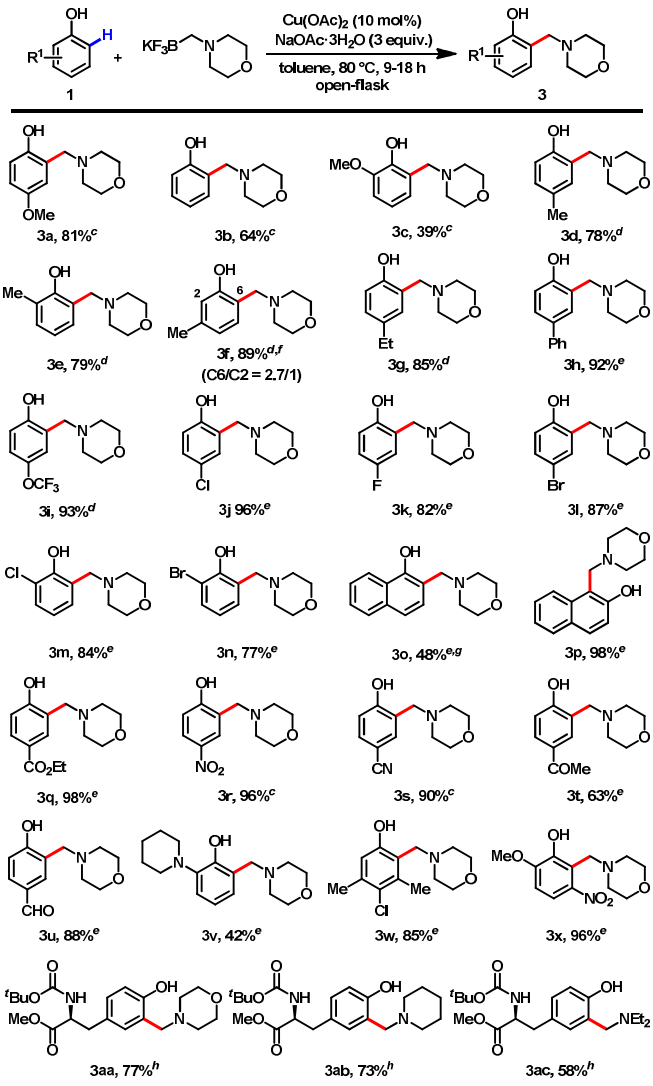
1a 2a 3a

Entry	Cu Salts	x (mol%)	Base	Solvent	Oxidant	Yield (%)[b]
1	$Cu(OAc)_2$	33	Na_2CO_3	THF	O_2	35 (31)
2	$Cu(OAc)_2$	33	Na_2CO_3	DCE	O_2	43
3	$Cu(OAc)_2$	33	Na_2CO_3	PhMe	O_2	58
4	$Cu(OAc)_2$	33	NaOAc	PhMe	O_2	80
5	$Cu(OAc)_2$	33	$NaOAc{\cdot}3H_2O$	PhMe	O_2	98 (86)
6	$Cu(OAc)_2$	33	NaOAc	PhMe:H_2O=40:1	O_2	95
7	$Cu(OAc)_2$	33	$NaOAc{\cdot}3H_2O$	PhMe	N_2	22 (16)
8	$Cu(OAc)_2$	33	$NaOAc{\cdot}3H_2O$	PhMe	air	97
9	$Cu(OAc)_2$	10	$NaOAc{\cdot}3H_2O$	PhMe	air	92 (81)
10	$CuCl_2$	10	$NaOAc{\cdot}3H_2O$	PhMe	air	63
11	$CuBr_2$	10	$NaOAc{\cdot}3H_2O$	PhMe	air	61
12	$Cu(OTf)_2$	10	$NaOAc{\cdot}3H_2O$	PhMe	air	78
13	$Cu(BF_4)(MeCN)_4$	10	$NaOAc{\cdot}3H_2O$	PhMe	air	74
14	$Cu(OAc)_2$	10	$NaOAc{\cdot}3H_2O$	PhMe	air	94[c]
15	$Cu(OAc)_2$	10	$NaOAc{\cdot}3H_2O$	PhMe	air	46[d]

[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.9 mmol), $Cu(OAc)_2$, base (1.8 mmol), solvent (4.0 mL), 1 atm pressure, sealed tube for O_2 and N_2, open flask for air, 16 h. [b] Yield was determined by ^1H NMR analysis of the crude reaction mixture using CH_2Br_2 as an internal standard. The number in parenthesis represents isolated yield. [c] 110 °C, 9 h. [d] 60 °C.

With the optimal conditions determined, we next explored the scope of phenols for this *ortho*-selective C–C bond-forming reaction. A series of differentially substituted phenols (**1**) was reacted with potassium *N*-morpholinylmethyltrifluoroborate (**2a**), providing the desired products (**3**) in good to excellent yields in 6–18 h (Table 2). We noticed that electron-donating groups on the aryl ring slightly inhibited the transformation (Table 2, **3a–3g**, **3v**), while electron-withdrawing groups dramatically promoted the reaction (**3h–3n**, **3q–3u**). In several cases, the reaction was highly efficient, providing quantitative yields of the corresponding products (**3p**, **3q**, **3r**, **3x**). Various types of functional groups were tolerated under this conditions. Methyl, ethyl, methoxy, trifluoromethoxy, phenyl, and amino substituents afforded good yields (Table 2, **3a–3i**, **3v**). Halides, such as fluoro, chloro and bromo, were compatible and provided high yields of the coupling products (Table 2, **3j–3n**). Ester, nitro, cyanide, ketone, and aldehyde substituents also afforded high yields (Table 2, **3q–3u**). The high functional group tolerance offers the opportunity for further synthetic elaboration, enhancing the overall practical utility. Naphthols were also competent substrates and could be aminomethylated in moderate to good yields (**3o** and **3p**). Multi-substituted phenol substrates were also compatible, affording excellent yields irrespective of the steric and electronic environment (85% for **3w** and 96% for **3x**). Amino acids are important chemicals in organic chemistry and in the life sciences. Indeed, recent research in antibody–drug conjugate (ADC) discovery[19] and unnatural amino acids synthesis have focused on the direct modification of natural amino acids.[20] To this end, tyrosine derivative, Boc-Tyr-OMe, was tested as a substrate, and it was found to couple smoothly with trifluoroborates, providing the aminoalkylated products in good yields (**3aa–3ac**). Throughout the series of phenolic starting materials were examined, we observed that only *ortho*-positions were alkylated under these conditions. We did not detect any *meta*- or *para*-C–H bonds activated products (for details, see SI).

Table 2. Substrate Scope of Phenols [a,b,c,d,e]

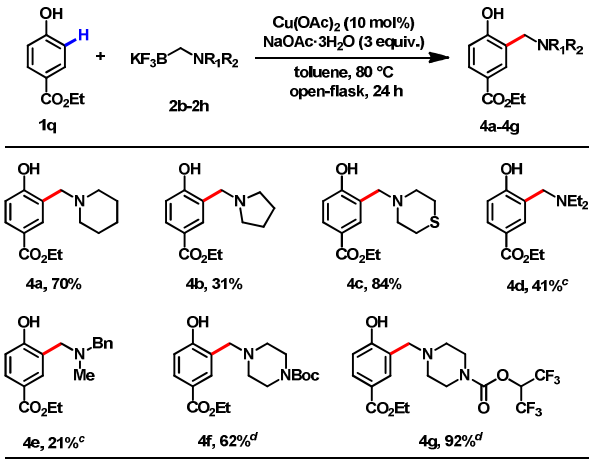


[a] Reaction conditions: **1** (1.0 mmol), **2** (1.5 mmol), $Cu(OAc)_2$ (0.1

mmol), $NaOAc{\cdot}3H_2O$ (3.0 mmol), toluene (6.0 mL), 80 °C, open flask. [b] Isolated yield. [c] 9 h. [d] 13 h. [e] 18 h. [f] C-2 and C-6 isomers are inseparable on silica gel. [g] 60 °C. [h] 30 mol% $Cu(OAc)_2$, 29 h.

The scope of potassium *N*,*N*-dialkylaminomethyltrifluoroborates (Table 3, **2a**–**2h**) was next examined using ethylparaben (**1q**) as the phenol substrate. For cyclic-amine-containing trifluoroborates (*e.g.*, piperidine and thiomorpholine), the reaction proceeded smoothly and afforded the desired products in good yields (**4a**–**4c**). For acyclic-amine-containing trifluoroborates (*e.g.*, diethylamine and methylbenzylamine), the coupling reaction formed the desired products, albeit in low yields (**4d** and **4e**). Interestingly, piperazine-substituted trifluoroborates provided the coupling products in good to excellent yields when using the more reactive oxidant $^tBuOO^tBu$ (62% for **4f**, 92% for **4g**) (see SI).

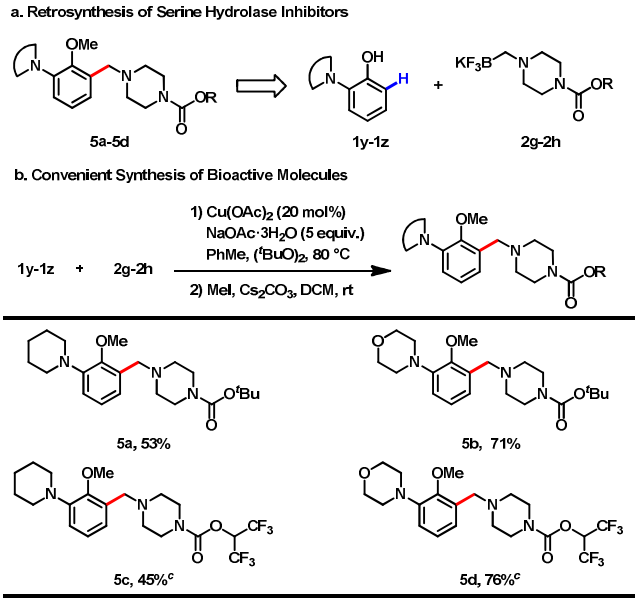
Table 3. Scope of Trifluoroborates [a, b]



[a] Reaction conditions: **1q** (1.0 mmol), **2** (1.5 mmol), $Cu(OAc)_2$ (0.1 mmol), $NaOAc{\cdot}3H_2O$ (3.0 mmol), toluene (4 mL), 80 °C, open-flask, 24 h. [b] Isolated yield. [c] 33 h. [d] $(^tBuO)_2$ was oxidant.

Having established the functional group compatibility, selectivity, and favorable operational characteristics of the reaction, we next sought to use this transformation to prepare medicinally relevant compounds. *ortho*-Aminomethyl phenolic subunits are common in enzyme modulators. For example, serine hydrolases inhibitors for MAGL and ABHD6 (Table 4, **5a**–**5d**)[21] and covalent inhibitors of Kars G12C.[22] The reported syntheses of these molecules required four or more linear steps. With this protocol, compounds **5a**–**5d** were promptly synthesized in two high-yielding steps from inexpensive and readily available starting materials.

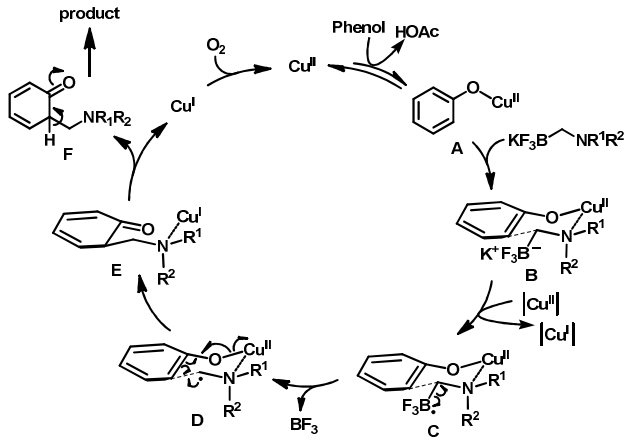
Table 4. Convenient Synthesis of Bioactive Molecules [a, b]



[a] Reaction conditions:1) **1y** or **1z** (0.3 mmol), **2g** or **2h** (0.6 mmol), $Cu(OAc)_2$ (0.1 mmol, 20 mol%), $NaOAc{\cdot}3H_2O$ (1.5 mmol), toluene (2.0 mL), $(^tBuO)_2$ (0.6 mmol), 80 °C, sealed tube, 36 h. 2) MeI (0.6 mmol), Cs_2CO_3 (0.5 mmol), DCM (3 mL), rt. [b] Isolated yields for 2 steps. [c] 24 h.

Though the mechanistic details of this copper-catalyzed *ortho*-selective phenol aminomethylation remain unclear at present, three points are worth noting: 1) Cu(II) oxidized trifluoroborate to generate alkyl radicals;[15a-c] 2) O_2 serves as the terminal oxidant for regeneration of catalytically active Cu(II);[23] and 3) the observation of C–C bond formation exclusively at the *ortho* position is suggestive of a six-membered cyclic transition state through simultaneous coordination of the phenol and the trifluoroborate to Cu(II); this inner-sphere model assures that the radical reaction proceeds. We propose the following radical mechanism for this C–C forming reaction (Scheme 1). Ligand exchange of phenol onto $Cu(OAc)_2$ provides copper phenolate **A**. The trifluoroborate coordinates with **A** and forms a six-membered inner-sphere intermediate **B**. The oxidation of trifluoroborate by Cu(II) affords boron radical species **C** and carbon radical **D**. Radical attack upon the phenol with concomitant single-electron reduction of Cu(II) then affords Cu(I)-coordinated ketone **E**. The final product is formed after tautomerization. Cu(I) was oxidized to Cu(II) by O_2 to close the catalytic cycle.[24]

Scheme 1. Mechanism Proposal



In conclusion, we have developed a practical Cu(II)-catalyzed *ortho*-selective aminomethylation of free phenols that provides access to C_{sp2}–C_{sp3} coupling products under mild conditions. This transformation was found to be high selective for functionalizing the position *ortho* to the hydroxyl group. A variety of functional groups were tolerated, and good to excellent yields were afforded. We also demonstrated a convenient synthesis of biologically active molecules with this method. Highly selective functionalization of free phenols has rarely been reported. Thus, we anticipate that this method will be highly useful, particularly in light of its simplicity and broad scope.

Supporting Information

Experimental procedures and spectral data for new compounds are available free of charge *via* the internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We gratefully acknowledge support from the National Key R&D Program of China (2016YFA0202900), the Strategic Priority Research Program of the Chinese Academy of Sciences (XDB20000000), and the "Thousand Recruitment Program for Young Professionals".

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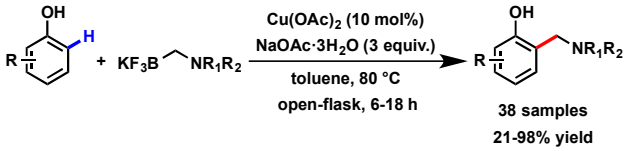
(24) The reviewer suggested an alternative mechanism that involved Chan-Lam type etherification followed by rearrangement *via* a tight-ion pair. Though many efforts and experiments have been done to probe this suggested mechanism, we could not draw a conclusion at this moment. However, the possibility of this pathway remains. For precedent reports about hydroxyl directed C–C coupling and selectivity for phenol derivatives, see: 6d and 7.


OH
H
R
+ KF3B NR1R2
Cu(OAc)2 (10 mol%)
NaOAc·3H2O (3 equiv.)
toluene, 80 °C
open-flask, 6-18 h
OH
R
NR1R2
38 samples
21-98% yield