Cu-Catalyzed Phenol O-Methylation with Methylboronic Acid

Mairead E. Bartlett  
*Smith College*

Yingchuan Zhu  
*Smith College*

Uma Bhagwat Gaffney  
*Smith College*

Joyce Lee  
*Smith College*

Miranda Wu  
*Smith College*

See next page for additional authors

Follow this and additional works at: https://scholarworks.smith.edu/chm_facpubs

Part of the Chemistry Commons

**Recommended Citation**
Bartlett, Mairead E.; Zhu, Yingchuan; Gaffney, Uma Bhagwat; Lee, Joyce; Wu, Miranda; Sharew, Betemariam; Chavez, Angela K.; and Gorin, David J., "Cu-Catalyzed Phenol O-Methylation with Methylboronic Acid" (2021). Chemistry: Faculty Publications, Smith College, Northampton, MA.  
https://scholarworks.smith.edu/chm_facpubs/62

This Article has been accepted for inclusion in Chemistry: Faculty Publications by an authorized administrator of Smith ScholarWorks. For more information, please contact scholarworks@smith.edu
Authors
Mairead E. Bartlett, Yingchuan Zhu, Uma Bhagwat Gaffney, Joyce Lee, Miranda Wu, Betemariam Sharew, Angela K. Chavez, and David J. Gorin

This article is available at Smith ScholarWorks: https://scholarworks.smith.edu/chm_facpubs/62
Cu-Catalyzed Phenol O-Methylation with Methylboronic Acid


A Cu-catalyzed oxidative cross-coupling of phenols with methylboronic acid to form aryl methyl ethers has been developed, expanding the scope of Chan-Evans-Lam alkylation. Electron-deficient phenol derivatives with a broad array of functional groups are methylated in high yields. Increased reaction temperature and catalyst loading enables the methylation of substrates incorporating pyridine and dihydroquinolone motifs. Electron-rich phenol derivatives are poor substrates for the methylation; the characterization of C–H homodimerization products formed from these substrates illuminates a competing mechanistic pathway.

Aryl methyl ether moieties are omnipresent in small molecule pharmaceuticals, agrochemicals, and natural products (Figure 1). Synthetically, such ethers are generally accessed by methylation of phenols with electrophilic reagents, such as diazomethane, dimethylsulfate, and methyl iodide.[1] Although effective, these reagents are toxic and/or unstable,[2] leading to the development of methods that use less hazardous electrophilic methyl sources, such as dimethyl carbonate (DMC).[3] Since DMC and related reagents are often intrinsically less reactive than the traditional, more hazardous reagents, relatively harsh reaction conditions, such as high temperature, are often required to facilitate methyl transfer to oxygen nucleophiles. Mechanistically distinct strategies for phenol methylation that use non-hazardous reagents and proceed under mild reaction conditions are therefore of interest.

Oxidative cross-coupling of oxygen nucleophiles with methylboronic acid represents an alternative to the use of electrophilic methylaing agents.[4] This strategy, a variant of the well-established Chan-Evans-Lam reaction between arylboronic acids and a wide variety of nucleophiles, avoids the intrinsic toxicity associated with electrophiles[5] since a formally nucleophilic methyl source is used. Furthermore, the operative mechanistic pathway for oxidative cross-coupling is quite distinct from traditional O-methylation reactions, potentially enabling complementary chemoselectivity and substrate scope.

Although O-arylation of phenols with arylboronic acids is well-established,[6] the corresponding O-alkylation is limitedly developed.[7] Cu-catalyzed phenol O-benzylation with Bn(BPin) proceeds with addition of a stoichiometric terminal oxidant (tBuO2),[8] while aerobic Cu-catalyzed O-cyclopropylation occurs with potassium cyclopropyltrifluoroborate (Scheme 1).[9] Reports of Chan-Evans-Lam O-methylation are rare; to the best of our knowledge, our aerobic Cu-catalyzed esterification of carboxylic acids with methylboronic acid (1) is the only published example (Scheme 1).[10] Cu-mediated N-methylation of anilines and sulfoximines with 1 has also been reported, further demonstrating the feasibility of this approach to oxidative methylation.[11]

Despite their rare application in Chan-Evans-Lam reactions, 1 and related compounds such as trimethylboroxine and methyltrifluoroborate salts are established reagents for C–H methylation and other methyl transfer reactions.[12] There is currently a broad surge of interest in new methods and alternative methyl sources for C–H methylation,[13] and this work on O-methylation is complementary. Herein, we report a Cu-mediated Chan-Lam O-methylation of phenols with 1 that proceeds with substoichiometric quantities of copper under open flask conditions, without need for any additional oxidant. This work significantly expands the scope of Chan-Evans-Lam alkylation[14] and offers an alternative strategy for the synthesis of aryl methyl ethers.
As a starting point, literature conditions for Chan-Evans-Lam methylation of other nucleophiles were investigated with 4-fluorophenol (2a). Neither conditions adapted from our carboxylic acid methylation\[10a\] nor Cruces' aniline methylation\[11a\] yielded any 4-fluoroanisole (3a) (See SI). To move forward, we began testing conditions reported for other alkylations, and gratifyingly found that Mudryk's conditions for sulfonamide N-cyclopropylation\[14c\] could be adapted for reaction of 2a with 1 to produce 3a in 21% yield (Table 1, entry 1).

A brief screen of copper sources revealed that 3a was obtained in higher yield with CuBr$_2$ than with Cu(OAc)$_2$ or Cu(acac)$_2$ (entries 1–3). While no reaction occurred with omission of Na$_2$CO$_3$, increasing yield was observed in switching the cation from Na$^+$ to K$^+$ and then to Cs$^+$ (entries 3–6). This correlation of increased yield with base solubility has previously been observed in Cu-catalyzed Ullman coupling; Reider ultimately reported that tetraethylammonium carbonate led to optimal yields in that system.\[15\] In analogy, commercially-available tetraethylammonium bicarbonate (TEAB) was identified as the optimal base for Chan-Evans-Lam phenol methylation, as it provided 3b in 76% yield (entry 7).

A further significant yield increase was observed upon increasing 1 from 1.5 equiv. to 2.5 equiv. relative to 2a. With this increase, product 3b formed in 86% yield even with a decrease in catalyst loading from 0.5 to 0.3 equivalents (entry 8). Reduced yield of product resulted when the reaction was run under a nitrogen atmosphere, which is consistent with molecular oxygen having a role in the catalytic cycle (entry 9).

Other N-donor ligands were screened; pyridine (pyr) and triethylamine were ineffective (entries 10–11), while 2,2-bipyridine (bipy) and 1,10-phenanthroline (phen) provided product in comparable yield (entries 8,12), which suggests the importance of a bidentate ligand.

The reaction scope was then explored. For substrates with electron-withdrawing substituents, high product yields were obtained with 0.3 equiv. CuBr$_2$ at 55 °C (Table 2, Conditions A, entries 1–3, 6, 9). Some substrates exhibited limited conversion to product under conditions A, and satisfactory yields could be obtained with higher catalyst loading and temperature (entry 4 and Conditions B, entries 5, 7–8, 10–11).

An array of functional groups was tolerated by the reaction. 4-substituted phenols with electron-withdrawing substituents such as an ester (2b), nitro group (2c), and ketone (2d) were smoothly methylated with 1 and catalytic CuBr$_2$ (entries 1–3). 4-phenyl-substituted 2e required higher catalyst loading to achieve full conversion of starting material, which ultimately provided 3e in 82% yield.

Ortho-substitution was also tolerated in the methylation, as in the transformations of 2-nitro- and 2-cyano-substituted 2f and 2g (entries 5–6). While a substrate with an aryl chloride substituent (2h) was methylated in 68% yield (entry 7), aryl bromides and iodides were not tolerated under the current conditions, resulting in an unidentified mixture of products.

Chemoselective phenol methylation was observed in the presence of an aliphatic alcohol, as only the anisole derivative

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Yield[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>X = 4-CO$_2$Me 2b</td>
<td>1.0 equiv CuBr$_2$/L</td>
<td>99%</td>
</tr>
<tr>
<td>2</td>
<td>4-NO$_2$ 2c</td>
<td>A</td>
<td>92%</td>
</tr>
<tr>
<td>3</td>
<td>4-Ac 2d</td>
<td>A</td>
<td>71% (64%)</td>
</tr>
<tr>
<td>4</td>
<td>4-Ph 2e</td>
<td>A &amp; L</td>
<td>82%</td>
</tr>
<tr>
<td>5</td>
<td>2-NO$_2$ 2f</td>
<td>B</td>
<td>83%</td>
</tr>
<tr>
<td>6</td>
<td>2-CN 2g</td>
<td>A</td>
<td>75% (95%)</td>
</tr>
<tr>
<td>7</td>
<td>4-Cl-3-Et 2h</td>
<td>B</td>
<td>68%</td>
</tr>
<tr>
<td>8</td>
<td>4-CH$_3$CH$_2$OH 2i</td>
<td>B</td>
<td>48%</td>
</tr>
</tbody>
</table>

[a] Yield determined by $^{19}$F NMR against an internal standard.

Table 2. Scope of Cu-mediated phenol O-methylation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Yield[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>X = 4-OH 3j</td>
<td>A</td>
<td>84%</td>
</tr>
<tr>
<td>10</td>
<td>2k</td>
<td>B &amp; L</td>
<td>54%</td>
</tr>
<tr>
<td>11</td>
<td>2l</td>
<td>B</td>
<td>61% (60%)</td>
</tr>
<tr>
<td>12</td>
<td>2m</td>
<td>C</td>
<td>56% (70%)</td>
</tr>
</tbody>
</table>

[a] Yield with L = bipy (yield with L = phen) [b] Reaction run using 1.0 equiv. CuBr$_2$/L. [c] Reaction time = 7 h.
was observed in the reaction of 2i, albeit in a modest 48% yield (entry 8).

Annulated heterocyclic substrates were also investigated. Umbelliferone (2j), an important chromophore, was smoothly methylated in 84% yield. Substrate (2k) with a dihydro-2-quinoline core was also successfully transformed, although in lower yield. No evidence for methylation at the potentially nucleophilic amide in 2k was observed. 4-pyridyl-phenol (2l) also was transformed into the corresponding aryl methyl ether in 61% yield, demonstrating the reaction's tolerance of a Lewis basic nitrogen in the substrate. Although the yields of product obtained from 2k and 2l are modest, successful methylation of these substrates suggests that this strategy may have potential use in medicinal chemistry or other applications that rely heavily on N-heterocycles.

To demonstrate the potential for derivatizing multiple sites within a molecule, we subjected bisphenol A (2m) to the methylation conditions. Upon increasing the stoichiometric ratio of 1 to account for the two reaction sites, the dimethylated product (3m) was obtained in 59% yield (entry 12).

Since bipy and phen were comparably effective ligands for the transformation in our optimization studies, a subset of substrates was tested with each ligand to determine whether one better promoted methylation (entries 3, 6, 11–12). Although improved yields were observed with phen compared with bipy in some cases, such as in the reactions of 2g and 2m (entries 6, 12), this was not a general pattern. For example, the yields of product obtained from 2l (entry 11) were essentially identical with each ligand, and the reaction with bipy provided a superior yield in the reaction of 2d (entry 3). Overall, we conclude that each ligand promotes the reaction with similar efficiency.

Investigation of electron-rich phenol derivatives revealed that the methylation reaction is quite sensitive to electronic factors. Simple alkyl-substituted phenols such as 2n and 2o did not cleanly product the desired anisole derivatives (Scheme 2).

3-tert-butyl-phenol (2n) yielded the desired product as the major product with an inseparable 10% impurity. Analysis of the $^1$H NMR data suggested that oxidative dimerization of the arene may be occurring, since one aromatic C–H signal is lost from the starting material. The isomeric 4-substituted substrate 2o was a poor substrate for methylation, yielding no anisole derivative, but was valuable in shedding further light on operative side reactions. Only the arene homodimer 4o could be isolated, in 34% yield. The analogous homodimer 4p was isolated in 17% yield upon reaction of 4-ethyl-phenol (2p). Both 4o and 4p were characterized by NMR and HRMS (see SI).

It is noteworthy that an ethyl substituent was tolerated in the methylation of 2h (Table 2, entry 7), when an additional electronically deactivating chloride substituent was also present (Table 2, entry 7).

Given these results, substrate-dependent divergent mechanistic pathways are apparently operative under the reaction conditions (Scheme 3). Electron-rich phenol derivatives are susceptible to oxidation to form phenoxy radical intermediates (6) and ultimately undergo radical-mediated C–H homodimerization (and likely also related processes). Oxidation of phenols with Cu(II) complexes is well-established, but the extent to which further organometallic intermediates participate in the transformation of phenoxy radical (6) to the homodimer product is uncertain.

In contrast, electron-deficient phenol derivatives undergo oxidative cross-coupling with methylboronic acid. Although the mechanism of Chan-Evans-Lam O-methylation has not been studied in detail, it may proceed similarly to the more deeply investigated O-arylation. In analogy with Stahl’s proposal, we suggest that reductive elimination from a Cu$^{II}$ intermediate, such as 5, yields the aryl methyl ether product. Formation of 5 requires transmetallation from methylboronic acid to [Cu]. Stahl et al. found the analogous transmetallation from aryloboronic acids to [Cu(II)] to be the turnover-limiting step in their study of Chan-Evans-Lam alcohol arylation and we speculate that a decreased rate of transmetallation in our system necessitates the use of higher reaction temperature, catalyst loading, and stoichiometric equivalents of methylboronic acid. Slow transmetallation relative to phenol oxidation may also account for the observed competition between phenol homocoupling and the desired cross-coupling product.

In conclusion, the Cu-mediated oxidative cross-coupling of methylboronic acid and phenols has been developed, providing access to an array of aryl methyl ethers. The O-methylation proceeds efficiently with catalytic quantities of CuBr$_2$ for several electron-deficient phenols, and increased catalyst-loading and temperature enables the methylation of more challenging substrates, such as those with dihydroquinoline and pyridine.

Scheme 2. Homodimerization of electron rich phenols.
cores. Investigation of electron-rich phenol derivatives, which are poor substrates for the methylation, revealed phenol C–H homodimerization as an operative pathway for formation of side-products. Work to understand the mechanism and further expand the scope of Chan-Evans-Lam methylation and alkyla-
tion more broadly are underway and will be reported in due course.

Acknowledgements

We gratefully acknowledge financial support from Smith College, including the AEMES Scholars program (M.W.), and the American Chemical Society-Connecticut Valley Section Summer Undergraduate Research Fellowship program (M.B.). Mass spectral data were obtained at the University of Massachusetts Mass Spectrometry Core Facility, RRID:SCR_019063. We thank Dr. Charles Amass and Prof. Cristina Suarez for assistance with instrumentation, as well as Dr. Alexis Courtney and Dr. Moira Flanagan for technical assistance and training.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Alkylation  ·  Catalysis  ·  Copper  ·  Cross-coupling reactions  ·  Methylation


Manuscript received: July 28, 2021
Revised manuscript received: October 7, 2021
Accepted manuscript online: October 13, 2021