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Site-Selective, Copper-Mediated *O*-Arylation of Carbohydrate Derivatives

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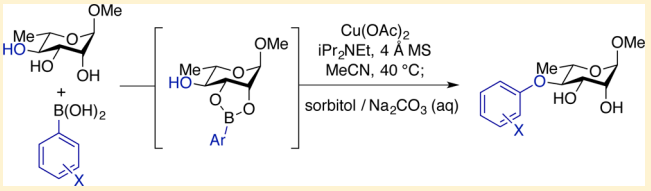
Supporting Information

ABSTRACT: Site-selective functionalization of hydroxy groups in sugar derivatives is a major challenge in carbohydrate synthesis. Methods for achieving this goal will provide efficient access to new sugar-derived chemical building blocks and will facilitate the preparation or late-stage modification of complex oligosaccharides for applications in glycobiology research and drug discovery. Here, we describe site-selective, copper-promoted couplings of boronic acids with carbohydrate derivatives. These reactions generate sugar-derived aryl ethers, a structural class that is challenging to generate by other means and has not previously been accessed in a site-selective fashion. Experimental evidence and computational modeling suggest that the formation of a sugar-derived boronic ester intermediate is crucial to the selectivity of these processes, accelerating the arylation of an adjacent hydroxy group. The results demonstrate how the interactions of sugars with boron compounds can be combined with transition metal catalysis to achieve new chemical reactivity.



INTRODUCTION

Transition-metal-catalyzed methods for coupling of aryl groups with amines, alcohols, and thiols have provided new ways to approach the synthesis of pharmaceutical agents, natural products, and heteroatom-containing polymers.[1−3] The prospect of adapting such methods to achieve site-selective arylations of multiply functionalized substrates has attracted interest,[4] as it could enable access to unprecedented derivatives of complex biomolecules. Recently reported protocols for transition-metal-mediated, selective *S*-arylation of cysteine motifs,[5−9] *Se*-arylation of selenocysteine derivatives,[10] and *N*-arylations of lysine groups[11] or backbone amide NH groups[12] in complex peptide derivatives illustrate the power of this approach. Analogous methods for site-selective *O*-arylation have not been reported, despite the prevalence of biomolecules bearing multiple hydroxy (OH) groups, of which carbohydrates are an especially important and widespread class. Here, we disclose a method for site-selective *O*-arylation of carbohydrate derivatives based on the copper-mediated Chan−Lam coupling of boronic acids. This protocol facilitates the direct preparation of carbohydrate-derived aryl ethers that would be challenging to prepare by other means. Crucial to this approach is the in situ formation of a sugar-derived boronic ester, which serves as a transient protective group while also accelerating arylation of an appropriately oriented OH group.

Efficient methods for the preparation of sugar-derived aryl ethers could facilitate the discovery of medicinal agents,[13] chiral catalysts,[14] new protective groups for carbohydrate chemistry, and metabolically stable tags for glycobiology research. Certain substitution patterns can be accessed through nucleophilic substitution reactions of phenols with sugar-derived electrophiles such as glycosyl donors,[15] anhydrosugars,[16] and sulfonate esters. Whereas several methods for *N*- or *S*-arylation of functionalized monosaccharides have been developed,[17−25] direct arylation of OH groups in sugars remains a challenge (Scheme 1a). Aryl ethers can be installed with inversion of configuration by nucleophilic substitution of OH groups in protected carbohydrate derivatives, through in situ activation as alkoxyphosphonium[26] or alkoxyimidazolium salts.[27] Nucleophilic aromatic substitution (S_NAr) reactions have been used to generate electron-deficient aryl or heteroaryl ethers from protected carbohydrates.[28] Recently, Olofsson and co-workers found that electrophilic diaryiodonium salts could be used to effect *O*-arylation of carbohydrate-derived substrates.[29] The ability to generate aryl ethers lacking the strong activating substituents needed for S_NAr reactivity (e.g., fluoro or nitro groups) represented a significant advance. Other arylation methods that have been applied to OH groups in protected sugar derivatives include couplings with arylbismuth reagents[30] and photoredox substitutions of aryl halides.[31] Site-selective variants of the reactions listed above have not yet been reported.

In the course of research aimed at employing organoboron compounds in carbohydrate chemistry,[32] our attention was drawn to the possibility of using copper-mediated Chan−Lam couplings[33−35] to achieve selective *O*-arylation of sugars (Scheme 1b). These oxidative couplings employ readily available boronic acids as arylating reagents, occur under relatively mild conditions, and are tolerant of diverse organic functional groups.[36] However, couplings of boronic acids with aliphatic alcohols—especially secondary alcohols and other

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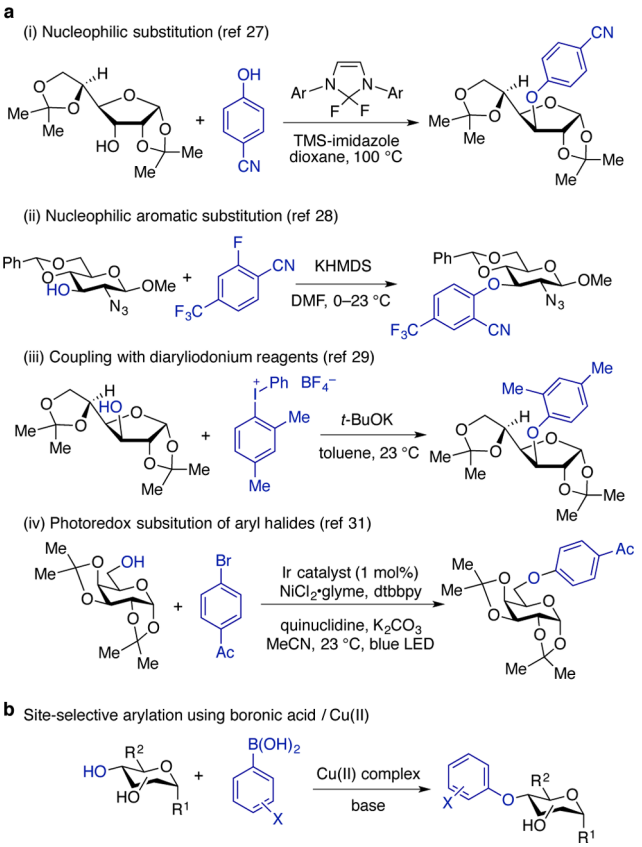
Scheme 1. Approaches to Arylation of OH Groups in Carbohydrate Derivatives: (a) Reported Methods for *O*-Arylation of Protected Carbohydrate Derivatives; (b) Proposed Method Based on Chan–Lam Couplings of Boronic Acids with Unprotected Glycosides

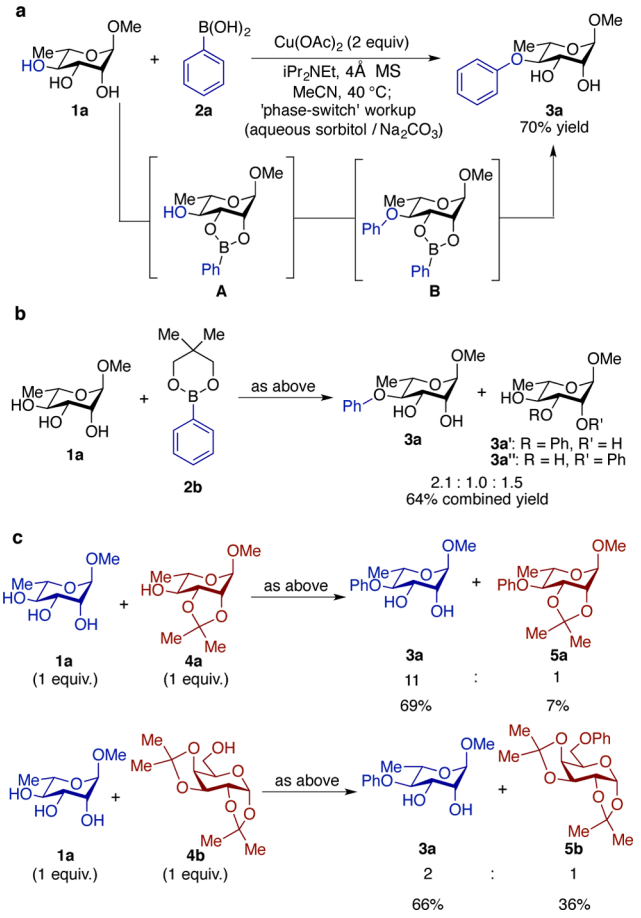


sterically hindered groups—are generally challenging, requiring distinct conditions from those used for arylations of phenols and amines.[37,38] In the case of carbohydrate derivatives, site-selectivity poses a significant additional challenge. It is likely because of these issues that Chan–Lam conditions have not been explored previously for selective *O*-arylation of carbohydrates, despite the progress that has been made in other copper-mediated and -catalyzed transformations of sugar derivatives.[39−43]

RESULTS AND DISCUSSION

Reaction Development and Control Experiments. Methyl α-L-rhamnopyranoside **1a** was chosen as a sugar-derived substrate for investigation of selective *O*-arylation under Chan–Lam coupling conditions. This pyranoside-derived triol was treated with phenylboronic acid (**2a**) in the presence of copper(II) acetate, diisopropylethylamine (iPr_2NEt), and 4 Å molecular sieves (MS) in acetonitrile at 40 °C (Scheme 2a). The reaction was carried out under an inert, argon atmosphere, and thus two equivalents of $Cu(OAc)_2$ were employed.[44] (Attempts to carry out the reaction using catalytic amounts of copper complex under an oxygen atmosphere resulted in low yields of *O*-arylated carbohydrate product, with formation of the boronic acid-derived diaryl ether being the predominant side reaction. Furthermore, diminished yield and site-selectivity were observed when the reaction was conducted under the optimal conditions, but with an ambient atmosphere rather

Scheme 2. Copper-Mediated *O*-Arylation of Methyl α-L-Rhamnopyranoside with Phenylboronic Acid[a]



[a](a) Site-selective coupling with phenylboronic acid. Proposed intermediates **A** and **B** are shown below the reaction equation. (b) Coupling with phenylboronic acid neopentyl glycol ester yields a mixture of *O*-arylated regioisomers. (c) Competition experiments gauging the relative reactivity of **1a** and protected carbohydrate derivatives **4a** and **4b**.

than under argon. See the Supporting Information, Table S1.) A "phase-switching" workup with aqueous, basic sorbitol solution was conducted to separate the sugar-derived product from phenylboronic acid[45] and also served to remove the copper(II) salts prior to further purification. The 4-*O*-monoarylated product **3a** was obtained in 72% yield and greater than 20:1 regioselectivity. Analysis of the unpurified reaction mixture revealed that the primary side products were three isomeric bis-aryl ethers, which were generated in a combined 27% yield (see the Supporting Information). The efficiency of this reaction was noteworthy, given that only a handful of examples of Chan–Lam arylation of secondary OH groups have been reported to date.[37] The regiochemical outcome was also intriguing: equatorial OH groups flanked by other equatorial substituents are sterically encumbered and show relatively low reactivity with electrophiles.[46,47] In keeping with this trend, direct, selective *O*-functionalizations of unprotected α-rhamnopyranosides at the 4-position have not been reported to date. However, the selectivity shown in Scheme 2 would be consistent with transient protection of the rhamnopyranoside as the boronic ester at the *cis*-diol group, followed by *O*-arylation of the free 4-OH group.[48] Consistent

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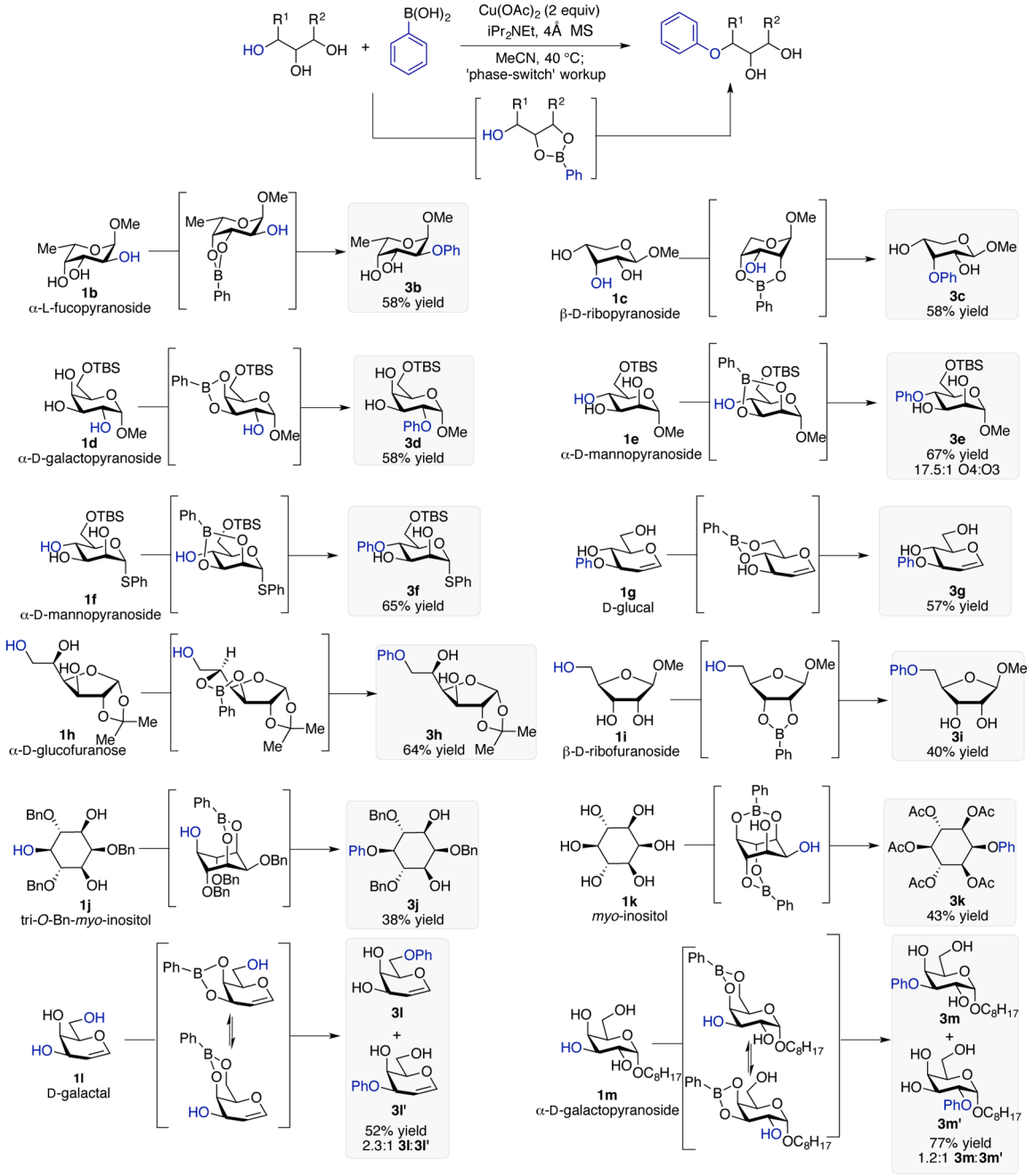
Scheme 3. Copper-Mediated Site-Selective *O*-Arylation[a]



[a]Yields after purification by chromatography on silica gel are listed. The isomer ratios were determined by ^{1}H NMR spectroscopic analysis of unpurified reaction mixtures. Unless otherwise noted, the selectivity for the isomer depicted was greater than 20:1. For product **3k**, treatment with excess acetic anhydride in pyridine at 23 °C was conducted prior to the phase-switching workup with aqueous Na_2CO_3/sorbitol solution.

with this hypothesis, treatment of **1a** under the reaction conditions in the absence of the copper(II) salt led to formation of the 2,3-*O*-phenylboronate ester (**A**, Scheme 2). Moreover, the 4-*O*-aryl ether-derived boronic ester **B** was observed by ^{1}H NMR spectroscopy after passing the unpurified reaction mixture through a short plug of silica gel in place of the phase-switching workup. Cleavage of the product-derived phenylboronic ester thus takes place by transesterification with sorbitol, as demonstrated previously.[48]

Additional evidence for the importance of the formation of a substrate-derived boronic ester is depicted in Scheme 2b: when the phenylboronic ester of neopentyl glycol (**2b**)[49] was employed in place of $PhB(OH)_2$, a mixture of isomeric aryl ethers was obtained. Suppressing the condensation of the pyranoside with the organoboron reagent thus results in loss of site-selectivity.

Competition experiments suggested that formation of a boronic ester under the coupling conditions not only serves to transiently protect a diol group in the pyranoside substrate but also accelerates the arylation of the remaining free OH group (Scheme 2c). When a mixture of **1a** and 2,3-*O*-isopropylidene-protected derivative **4a** was subjected to the conditions for Chan–Lam coupling, a roughly 11:1 selectivity for the phenyl ether derived from the free rhamnopyranoside was observed.

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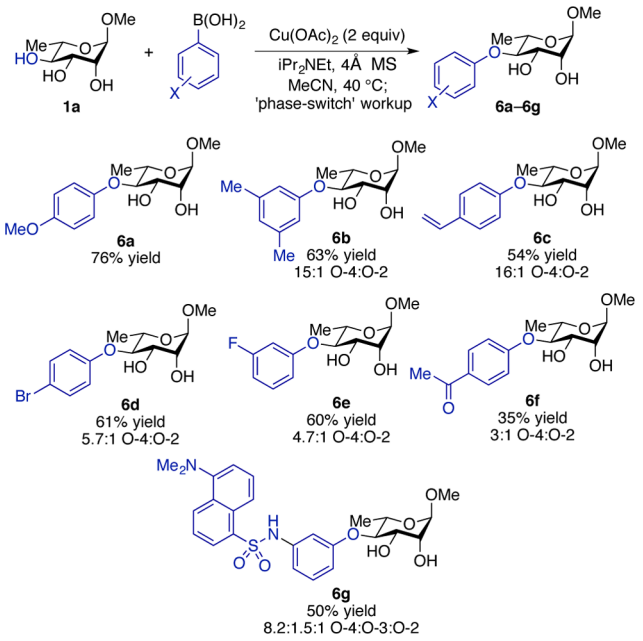
Since isopropylidene ketal **4a** is structurally similar to the proposed boronic ester intermediate **A**, this result suggests that the presence of the 2,3-*O*-boronate group increases the rate of arylation of the 4-OH group. A second competition experiment was conducted using **1a** and protected galactose derivative **4b**, having a free primary OH group. The 2:1 selectivity for arylation of **1a** indicates that the rate acceleration provided by formation of a substrate-derived boronic ester is enough to overcome the differences in steric demand that would favor the reaction of **4b** under these conditions. Mechanistic hypotheses related to these observations are provided below.

Substrate Scope. Copper-mediated coupling with arylboronic acids provides access to diverse mono-*O*-arylated pyranoside and furanoside derivatives **3b**−**3m** (Scheme 3). For each of the cases shown, the regiochemical outcome was consistent with formation of the most stable substrate-derived boronic ester (structure depicted in square brackets),[48,50] followed by arylation of the remaining free OH group. Analysis of unpurified reaction mixtures was conducted to assess the site-selectivity and to identify the major side products of the reactions (see the Supporting Information). The yields were generally on par with reported methods for preparation of phenyl ethers from protected carbohydrate derivatives, and in the majority of the cases shown (e.g., products **3b**−**3g**), the OH group that underwent arylation is one that cannot be functionalized directly by existing methods. For the ribopyranoside **1c**, the boronic ester group of the product was resistant to transesterification under the conditions of the phase-switching workup, and so an oxidative cleavage with basic hydrogen peroxide solution was employed. The copper-mediated protocol was also applied to protected *myo*-inositol derivative **1j** and free *myo*-inositol **1k**, yielding *O*-arylation products consistent with boronic ester intermediates through complexation of 1,3-diaxial OH groups.[51] In the latter case, cleavage of the product-derived boronic ester was accomplished by acetolysis rather than by phase-switching workup, to facilitate isolation of the monoarylated product. Although the yield was modest, this 2-*O*-arylation of *myo*-inositol is a noteworthy result: direct monofunctionalization of **1k** is challenging, with multistep sequences involving orthoester or acetal-type intermediates generally being employed.[52]

In cases where an equilibrium between isomeric substrate-derived boronic esters was possible, mixtures of products were obtained. Substrates **1l** and **1m**, possessing both 4,6-diol and *cis*-vicinal diol motifs known to form stable boronic esters, illustrate this point. In each case, the major product can be rationalized as arising from one of the two isomeric boronic esters. For galactopyranoside **1m**, it is striking that neither of the products arises from arylation of the primary OH group: instead, the reaction of a secondary OH vicinal to the boronic ester appears to be preferred. A mixture of *O*-arylated regioisomers was also obtained when the protocol was applied to the acyclic triol glycerol (see the Supporting Information).

Substituted arylboronic esters were coupled with rhamnopyranoside substrate **1a** (Scheme 4). The copper-mediated *O*-arylation enabled installation of the *para*-methoxyphenyl ether protective group (product **6a**),[26] as well as functionalized aryl groups (styrene **6c**, haloarenes **6d** and **6e**, methyl ketone **6f**, dansylamino derivative **6g**). A dependence of the level of site-selectivity on the electronic properties of the arylboronic acid was observed, with electron-deficient arylboronic acids resulting in increased proportions of 2-*O*-arylated side product. Prestirring the substituted arylboronic acids with **1a** prior to

Scheme 4. Copper-Mediated Site-Selective Installation of Substituted Aryl Ethers[a]



[a]Yields after purification by chromatography on silica gel are listed. The isomer ratios were determined by ^{1}H NMR spectroscopic analysis of unpurified reaction mixtures.

addition of $Cu(OAc)_2$ had a subtle but reproducible effect on the level of site-selectivity (Table S3). A rationale for the reduced site-selectivity with electron-deficient arylboronic acids is not readily apparent, although it has been noted that electron-rich congeners undergo more rapid transmetalation to copper(II).[53] Existing methods for *O*-arylation of carbohydrates tend to give higher yields for electron-deficient versus electron-rich aryl coupling partners,[28,29] and so the present method is complementary from this perspective. Other limitations of the copper-mediated methodology described here include heteroaromatic partners such 4-pyridinyl- and *N*-Boc-2-pyrroleboronic acid, as well as *ortho*-substituted arylboronic acids (<5% yields; results not shown). Preliminary attempts at applying this protocol to more complex substrates resulted in mixtures of products: the coupling of phenylboronic acid with octyl *β*-D-lactoside, having seven free OH groups, generated a complex mixture of mono- and bis-*O*-arylated disaccharides, and an estradiol-derived arylboronic acid[54,55] resulted in a roughly 2:1:1 mixture of isomeric ethers upon coupling with **1a** (see the Supporting Information). Further refinements of the protocol to enable couplings of such highly functionalized partners are an objective of our ongoing research.

Mechanistic Hypotheses. Stahl and co-workers have used kinetics and in situ spectroscopy to probe the mechanism of copper-catalyzed coupling of arylboronic acids with methanol.[44,53] The results point toward a reaction pathway involving formation of an arylcopper(II) species by transmetalation with the arylboron reagent, followed by disproportionation of two Cu(II) species to give an arylcopper(III) complex. Reductive elimination results in formation of the C−O bond and liberates a copper(I) complex. In the absence of oxygen, the reaction requires two equivalents of the copper(II) complex, whereas in the presence of oxygen oxidation of the Cu(I) to Cu(II) closes the catalytic cycle. Studies of the reactivity of three-coordinate

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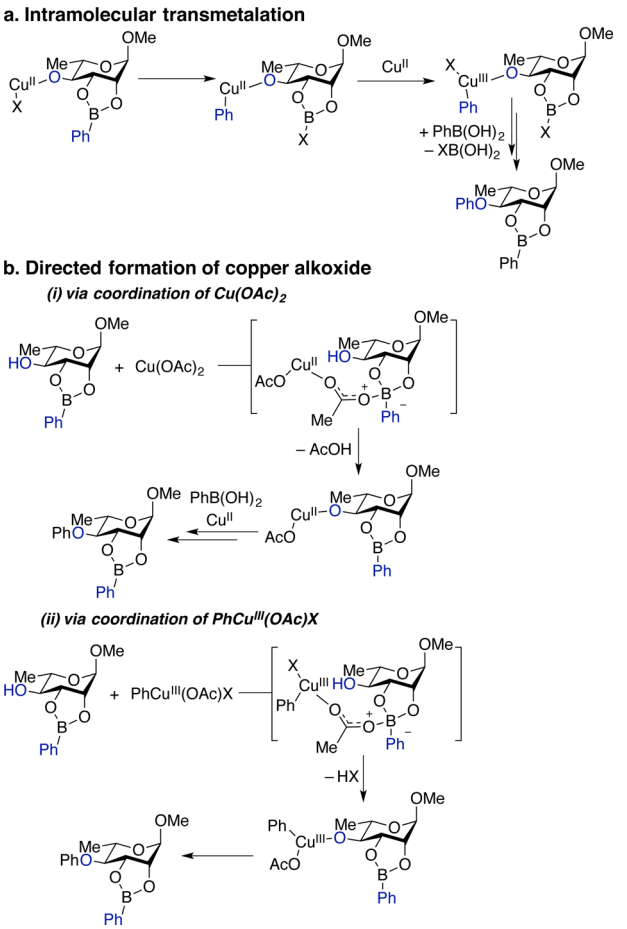
copper(II) aryl complexes are consistent with this general picture.[56] For the copper-catalyzed arylations of methanol studied by the Stahl group, the transmetalation step was proposed to be turnover-limiting. It is based on this general mechanistic framework that we have attempted to understand the accelerating effect of boronic ester substitution that is evident from the experiments shown in Scheme 2 and which underlies the selective arylations shown in Scheme 3.

Possible pathways by which formation of a substrate-derived boronic ester can facilitate the arylation of a neighboring OH group are depicted in Scheme 5. Although the rate-determining step has not been identified for the present system, it should be noted that the depicted steps need not be rate-determining for selectivity to be observed in a competition experiment of the type shown in Scheme 2. Path **a** involves an intramolecular transmetalation step, in which an aryl group migrates from the boronic ester to the copper(II) alkoxide. In pathways of type **b**, the Lewis acidic boronic ester group serves to direct[57] the formation of the copper alkoxide, either prior to transmetalation (**i**) or at a later stage (e.g., mechanism **ii**). Of the latter two possibilities, mechanism **i** would be most consistent with Stahl's studies of the aerobic methoxylation reaction.[44,53] The directing effect of a histidine moiety has been invoked to account for site-selective Chan–Lam-type *N*-arylations of backbone amide moieties in peptides.[12] Ultimately, each of these pathways would lead to a copper(III) alkoxide intermediate capable of C–O bond-forming reductive elimination to form the aryl ether product.

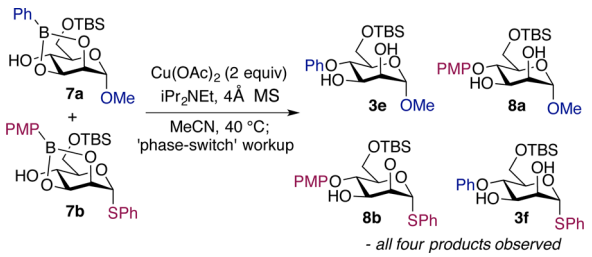
A distinguishing feature between these proposals is the nature of the transfer of the aryl group: intramolecular for path **a** versus intermolecular for paths **b**. A crossover experiment was conducted to probe this issue (Scheme 6). However, because the two carbohydrate-derived arylboronic esters **7a** and **7b** underwent rapid transesterification in the absence of $Cu(OAc)_2$, the fact that all four possible 3-*O*-aryl ether products (**3e**, **3f**, **8a**, and **8b**) were obtained could not be used to rule out a purely intramolecular mechanism (see the Supporting Information). Further crossover experiments involving substrate-derived boronic esters gave similar inconclusive results due to competing transesterification.

Given the ambiguity associated with the crossover experiments, computational modeling was used to assess the feasibility of the two proposed reaction pathways. Density functional theory (DFT) calculations were carried out using the dispersion-corrected B97-D3 functional[58] and the Def2-TZVP basis set,[59] using the polarized continuum model (PCM) for acetonitrile. Geometry optimizations and transition state searches were initially conducted for complexes lacking coordinated acetonitrile molecules. These geometries were used as starting points for additional calculations incorporating one or two acetonitrile ligands. A transition state for intramolecular transmetalation from a boronate-functionalized, monosolvated copper alkoxide was identified (Figure 1a), having a C–B bond distance of 2.16 Å and a C–Cu distance of 2.06 Å. Computational support for the boronic ester-directed pathway was also obtained: Figure 1b depicts the calculated transition state for ligand exchange to generate a phenylcopper(III) alkoxide (path **b**, mechanism **ii**). In both transition state structures, a Lewis acid–base interaction between the boron ester group and an acetate ligand is evident, reminiscent of coordination modes suggested by the Stahl group's spectroscopic studies of Chan–Lam couplings.[53] Although further mechanistic work is warranted, a carboxylate-mediated interaction between copper and boron centers appears to be a plausible basis for the accelerating effect of a boronic ester group on the arylation of a nearby OH group. Consistent with this idea, when $CuBr_2$ was employed in place of $Cu(OAc)_2$ for the coupling of **1h** and **2a**, *O*-arylation was not observed (see the Supporting Information).

Scheme 5. Mechanistic Proposals Consistent with the Accelerating Effect of an Adjacent Boronic Ester Group on Copper-Mediated *O*-Arylation



Scheme 6. Crossover Experiment Using Boronic Esters 7a and 7b



CONCLUSIONS

In summary, we have shown that carbohydrate-derived aryl ethers can be generated in a site-selective fashion by copper-mediated couplings of boronic acids with pyranosides or furanosides. This reactivity enables the selective preparation of

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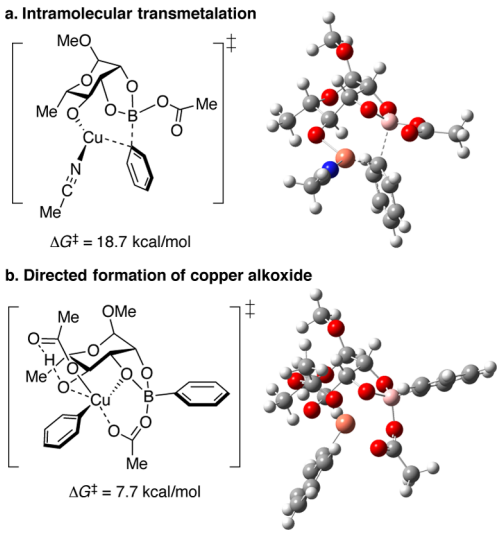

Figure 1. Calculated transition state structures. (a) Boronic ester-assisted transmetalation. (b) Boronic ester-directed copper(III) alkoxide formation. Calculations were carried out using density functional theory with the B97-D3 functional and Def2-TZVP basis set.

functionalized carbohydrate derivatives that would be difficult to generate by existing methods. Sugars show considerable potential as scaffolds or linkers in medicinal chemistry,[60−62] and the ability to conduct new types of selective *O*-functionalizations may create opportunities in this regard. The efficiency and site-selectivity of the reactions described here are striking in light of the challenges associated with copper-mediated *O*-arylation of aliphatic alcohols. Both of these features appear to hinge on the involvement of a boronic ester intermediate generated by condensation of the boronic acid and carbohydrate reagents. The formation of the boronic ester not only transiently protects a diol moiety in the sugar substrate but also accelerates the arylation of an adjacent hydroxyl group. The acceleration of *O*-arylation provided by a neighboring boronic ester substituent has been probed through competition experiments, and possible origins of such an effect have been suggested based on computational modeling of proposed transition states. These observations have revealed a new facet of the reactivity of boronic acids with sugar derivatives and may facilitate applications of sugar-derived aryl ethers in organic synthesis, medicinal chemistry, and glycobiology.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b09420.

Experimental and computational details, characterization data for new compounds, copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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