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Reactivity of Alcohol Substrates and Boron-Containing Complexes in C−H Alkylation Enabled by Photoredox, Hydrogen Atom Transfer, and Boronic Acid Catalysis

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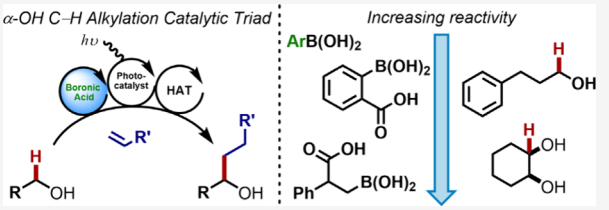
ABSTRACT: Using boronic acid, photoredox, and HAT catalysis, the relative alkylation reactivity of representative alkyl alcohols was evaluated through competition experiments, revealing higher initial reactivity for diols. Electron-poor arylboronic acid catalysts provide increased reaction efficiency for all substrates, which is attributed to a more dynamic and facile equilibrium between boron-containing species. Furthermore, β-carboxyboronic acids resulted in an additional increase in reaction efficiency, and the results from both catalyst classes were compared using kinetic profiles and a select scope of monoalcohols.



While C−H functionalization is a distinctly transformative, atom-economical synthetic tool, one of its greatest challenges is targeting particular C−H bonds in the presence of others with similar bond strengths and stereoelectronic environments.[1−3] As alcohols are a common, useful functional group, several methods for site selective α-hydroxy C−H functionalization have been achieved.[4−16] Nonetheless, functionalizing these stronger C−H bonds (e.g., α-OH C−H ∼ 92−96 kcal/mol) in the presence of weaker ones (e.g., benzylic C−H ∼ 90 kcal/mol) remains limited.[4,17] To activate the α-OH C−H for selective functionalization, polarity effects[18] and interactions of the alcohols have been exploited to increase the α-C−H bond's hydricity and to decrease its bond strength.[17,19−21] Additionally, the emergence of photoredox catalysis has enabled orthogonal reactivity compared to traditional C−H functionalization methods,[22−26] providing mild reaction conditions for specifically targeting these α-OH C−H bonds for activation and derivatization.[4−16] Photoredox-promoted C−H functionalization often proceeds via hydrogen atom transfer (HAT) from a photoexcited catalyst or mediator to form a carbon-centered radical intermediate that is intercepted by various coupling partners depending on the reaction conditions.[25] Thus, controlling the HAT step leads to site selective C−H functionalization.

Recent reports of site selective α-OH HAT have demonstrated that boron-containing complexes of alcoholic substrates are powerful intermediates under photocatalytic conditions.[27−32] These boron-substrate intermediates are proposed to increase the hydridic nature of the α-OH C−H bond and lower this bond's BDE, leading to site selective HAT at these α-positions.[19,28,33,34] For example, Taylor and co-workers reported a C−H alkylation of *cis*-diols with a photocatalyst, diphenylborinic acid, quinuclidine (**Q**), and electron-poor alkenes (Scheme 1a).[27,28] In this system, a quinuclidine radical cation is proposed to perform HAT on the boron-ate complex to enter the C−H alkylation cycle. Taylor and co-workers expanded upon this work to identify two other boron-containing catalyst scaffolds for alternate reactivity with both reactions putatively requiring boron-ate complexes to initiate the HAT process: 1) redox-isomerization of diols with arylboronic acids and **Q**[29] and 2) alcohol oxidation of diols using arylboracarboxylate and **Q** under aerobic conditions (Scheme 1b).[30] Under similar reaction conditions using catalytic arylboronic acids, Gómez-Suárez and co-workers investigated the **Q**-promoted α-OH C−H alkylation of amino-alcohols (Scheme 1c).[31] We have been inspired by these works and aim to (i) determine the reactivity of different alcohol substrate classes; (ii) understand the structure−function relationship of the boron-containing complexes on reactivity; and (iii) elucidate the equilibrium between boron species, alcohol substrates, and **Q** (Scheme 1d).

We were curious to define the relative reactivity between alkyl alcohol substrates in this C−H alkylation to inform a long-term objective of site selective functionalization of more complex targets. Therefore, competition reactions were performed with representative alcohols and $PhB(OH)_2$ as a

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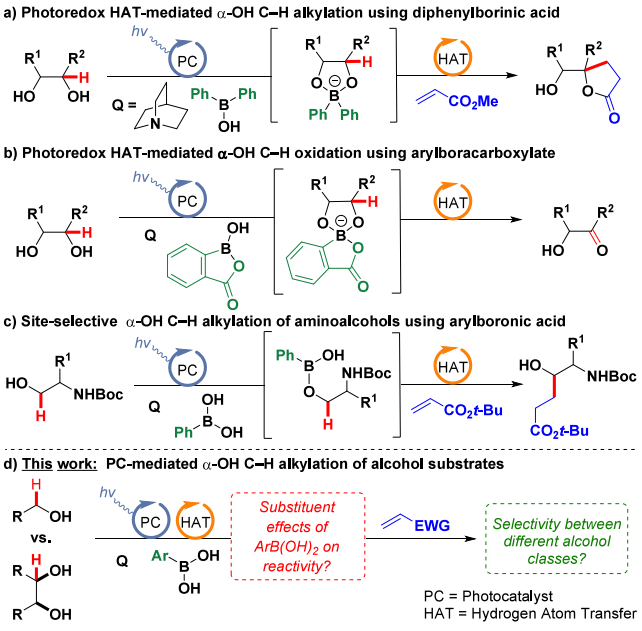
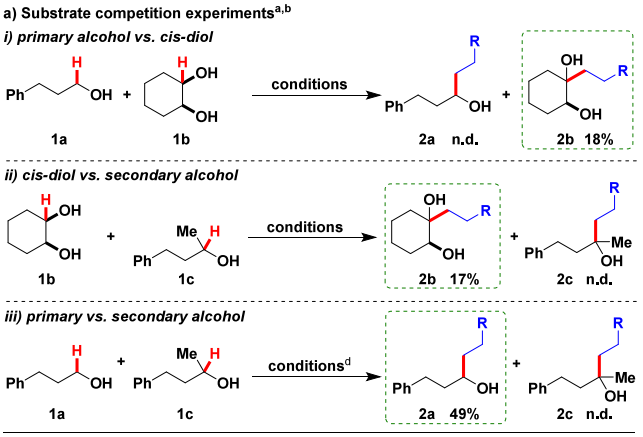
Scheme 1. Photoredox HAT-Mediated α-OH C−H Functionalization



catalyst (Figure 1a). When 3-phenyl-1-propanol (**1a**) competes with *cis*-1,2-cyclohexane diol (**1b**), only alkylated diol (**2b**) is observed, albeit in low yield (Figure 1a.i). Interestingly, reactivity is suppressed for both substrates in competition, suggesting a Curtin−Hammett pre-equilibrium between catalyst and substrate. For example, noncompeting **1a** results in alkylation around 80% NMR yield, and **1b** provides ∼ 40% NMR yield over 18 h (Figure 1b). Kinetic profiles of these substrates and catalysts are discussed later in the text. Of note, alkylation proceeds significantly more efficiently for **1a** in the presence versus absence of boronic acid. While similar yields are obtained for **1b** with and without boronic acid, the diastereoselectivity is greatly improved when boronic acid is present, suggesting the boron-substrate complex is the active species in the cycle. Additionally, comparing alternative catalysts[4,27,28] revealed superior conversion to product for **1a** and enhanced diastereoselectivity for **1b** with $PhB(OH)_2$. Further discussion of these conditions can be found in the Supporting Information.



b) Reaction efficiency for Non-Competing Substrates with Various Catalysts[a-c]

Catalyst	1a	1b	1c
None	10%	42% (dr 2:1)	16%
$PhB(OH)_2$	82%[d,e]	39% (dr >20:1)[d]	13%[e]
$Ph_2B\text{-}OCH_2CH_2NH_2$	13%[e]	39% (dr 5:1)	–
$NH_4H_2PO_4$	14%[e]	27% (dr 3:1)	–

[a]Conditions: *t*-butyl acrylate (0.1 mmol), alcohol 1 (0.1 mmol), alcohol 2 (0.1 mmol), $[Ir\{dFCF_3ppy\}_2(bpy)]PF_6$ (1 mol%), quinuclidine, **Q** (40 mol%), Catalyst (20 mol%), MeCN (0.6 mL), blue LED, rt, 18 h. [b]NMR yield with benzyl benzoate as internal standard. [c]non-competing alcohols: 0.2 mmol. [d]isolated yields reported in supporting information. [e]40 mol%. n.d. = not detected

Figure 1. a) Substrate competition reactions to probe relative reactivity. b) Reaction efficiency for noncompeting substrates.

Furthermore, preference for diol functionalization in competition suggests that increased complexation with boronic acid, which is favored by the diol (vide infra), leads to increased alkylation. Similar results are observed when **1b** competes with the secondary alcohol **1c**, supporting this hypothesis (Figure 1a.ii). When **1a** competes with **1c**, only **2a** is observed, resulting from the functionalization of primary alcohol **1a** (Figure 1a.iii). The inherent reactivity of **1c** alone is significantly lower than **1a** (Figure 1b), which translates to the competition experiment. Even though diol **1b** reacts preferentially in competition with monoalcohols, lower overall yields are observed for **2b** than **2a**, suggesting product inhibition or catalyst decomposition with diol substrates. Indeed, when substrate **1b** and product **2b** (1:1) are mixed with 4-$CF_3PhB(OH)_2$ (0.4 equiv), the boronic acid preferentially complexes with **2b** over **1b** in 4.5:1 ratio determined by ^1H NMR (Figure S7), supporting the hypothesis of catalyst inhibition by the product.

To investigate the higher initial reactivity of **1b** in competition, ^1H NMR experiments were conducted on mixtures containing both substrates and $PhB(OH)_2$ (Figure S8). Mimicking standard reaction conditions, a mixture of **1a** (1 equiv), **1b** (1 equiv), and $PhB(OH)_2$ (0.4 equiv) resulted in about equal amounts of diol boronic ester **3b** and diol (1:1.2 **1b**:**3b**). Boronic ester **3a** derived from **1a** was not detected. With 1 equiv boronic acid, **3b** increases in concentration ∼7-fold, and **3a** is detectable in a small amount (28:1 **3b**:**3a**). Further increasing the amount of boronic acid to 2 equiv increases the concentration of both esters. In this case, **1b** is fully converted to **3b**. Thus, the higher affinity of boronic acids to diols compared to monoalcohols is contributing to the higher reactivity of diols in this C−H alkylation in the ground state.

Since the boron-substrate complexes are proposed to be key intermediates in this C−H alkylation process,[28,31] and specifically in the HAT step, we evaluated the influence of substituted arylboronic acids on reaction efficiency over time with the model substrates **1a** (dotted lines) and **1b** (solid lines, Figure 2). Interestingly, the initial alkylation rate of **1b** is ∼ 2x faster compared to **1a** with $PhB(OH)_2$. Although, turnover plateaus around 6 h for **1b** yet remains rather linear with respect to time for **1a** (Figures S2−S3). Additionally, initial rate differences were observed with electron-poor arylboronic acids reacting faster in this C−H alkylation, which is consistent with previous reports.[27−31] For example, 4-$CF_3PhB(OH)_2$ leads to alkylation of **1a** and **1b** that is ∼4.0× and ∼2.2× faster, respectively, than with 4-$OMePhB(OH)_2$. Additional arylboronic acids examined with **1b** are provided in the Supporting Information (Figure S5).

As we have already observed significant influence of equilibrating boron-containing species on reactivity, we sought

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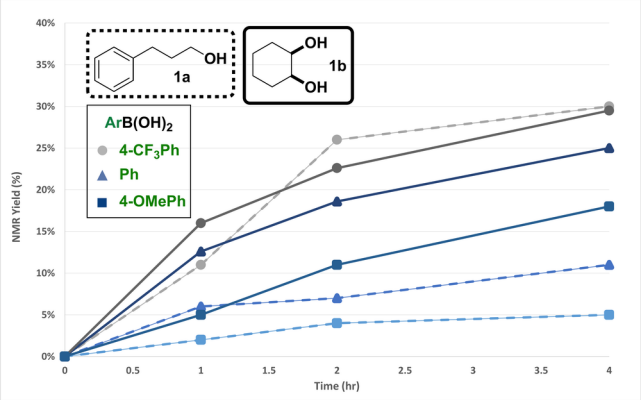

Figure 2. Initial time course analysis of **1a** and **1b** under standard reaction conditions using 4-CF_3PhB$(OH)_2$ (circles), PhB$(OH)_2$ (triangles), and 4-OMePhB$(OH)_2$ (squares). NMR yields of **2a** (dotted lines) and **2b** (solid lines) shown as an average of at least three trials.

to gain insight into the electronic influence of boronic acid on these equilibria. Furthermore, we were curious if boron-ate complex **4**, which is proposed as a key intermediate for HAT,[28] is observable spectroscopically. A series of stoichiometric NMR experiments were performed with either 4-CF_3PhB$(OH)_2$ or 4-OMePhB$(OH)_2$ and **1b** (Figure 3 and Figures S8−17). In a 1:1 mixture of **1b** and boronic acid, both boronic acids favor formation of the corresponding boronic esters (**3**), demonstrated by the major peaks at 31.4 and 31.7 ppm for 4-CF_3PhB$(OR)_2$ or 4-OMePhB$(OR)_2$, respectively, in contrast

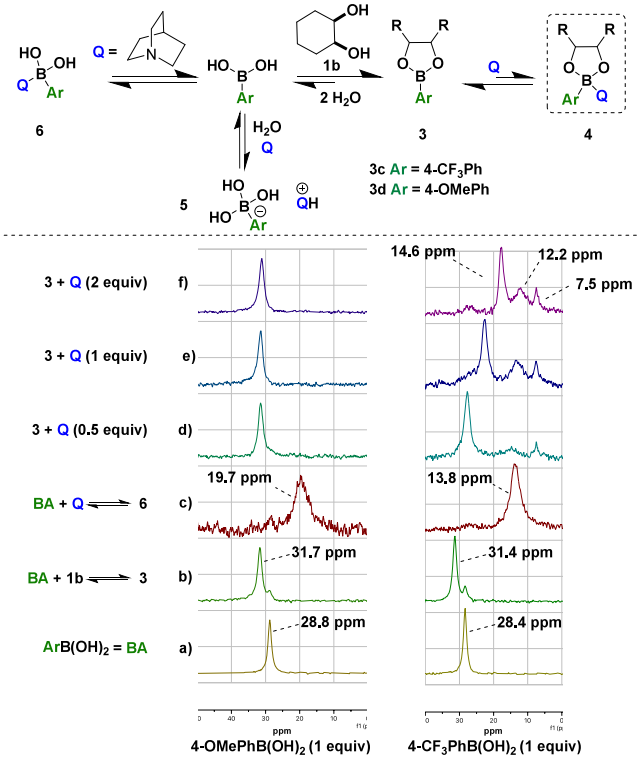

Figure 3. Equilibrium studies by ^{11}B NMR spectroscopy in MeCN-d_6 with diol **1b**, increasing amounts of quinuclidine, **Q**, and boronic acid, BA: 4-OMePhB$(OH)_2$ (left) or 4-CF_3PhB$(OH)_2$ (right). See Supporting Information for corresponding ^{1}H and ^{11}B NMR spectra for **1a** and **1b**.

to the corresponding boronic acid peaks at 28.4 and 28.8 ppm, respectively (Figure 3a-b). Upon addition of increasing amounts of **Q**, new species are observed with 4-CF_3PhB$(OR)_2$ but not with 4-OMePhB$(OR)_2$ (Figure 3d-f). By ^{1}H NMR, hydrolysis of **3c** can be observed as **Q** is added in both cases (Figures S9, S13). With 4-CF_3PhB$(OH)_2$, a small peak at 7.5 ppm is consistent with hydroxylated anionic boron-ate complex **5**, Ar−B$(OH)_3$.[35−37] Distinguishing between dative B−N complexes **6** and **4** is more challenging as both could be under dynamic equilibrium and represented by the signal at 12.2 ppm.[35−37] When 4-CF_3PhB$(OH)_2$ is titrated with **Q**, a similar downfield shift of this broad signal is observed from 13.8 to 12.2 ppm (Figure 3c-f). Thus, the peak at 12.2 ppm seems more consistent with boronic acid-**Q** adduct, **6**. In the ^{1}H NMR spectra, the α-OH protons in **3c** and **1b** also begin to coalesce, supporting a dynamic equilibrium between diol **1b** and ester **3** (Figure S13). A single species, **3d**, is observed in the 4-OMePhB$(OR)_2$ case, which suggests that boronic acid turnover is less facile with electron-rich groups. Consistent with the decreased Lewis acidity character of boron with electron-donating groups, **Q** is less likely to bind for an appreciable amount of time, decreasing the rate of diol hydrolysis and perhaps the formation of putative complex **4** required for HAT. Overall, we propose that a more dynamic system and facile exchange between boron-containing species, including putative boron-ate complex **4**, is more favorable in terms of overall reaction rate, which is achieved by using electron-poor boronic acids.

With the hypothesis that a pendant Lewis basic group on the boronic acid catalyst would better promote formation of proposed boron-substrate complex **4** and increase turnover of the boron-product adduct, we evaluated several carboxyboronic acids over time with substrate **1a** (Figure 4; full time course in Figure S6). First, 2-carboxyphenylboronic acid (2-CPBA), which was an effective catalyst for Taylor's site selective oxidation of diols,[30] resulted in a ∼6-fold increase in

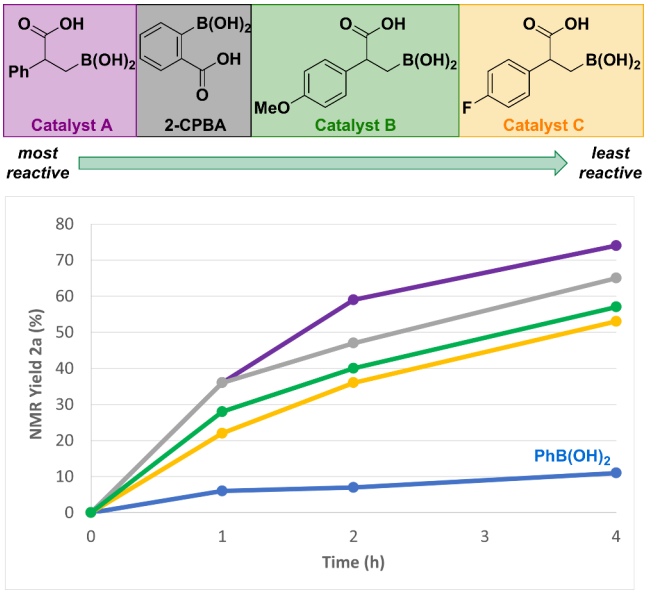

Figure 4. Initial time course analysis of **1a** with 2-carboxyboronic acid precatalysts (20 mol %) compared to phenylboronic acid (40 mol %). NMR yields of **2a** shown as an average of at least three trials under standard reaction conditions.

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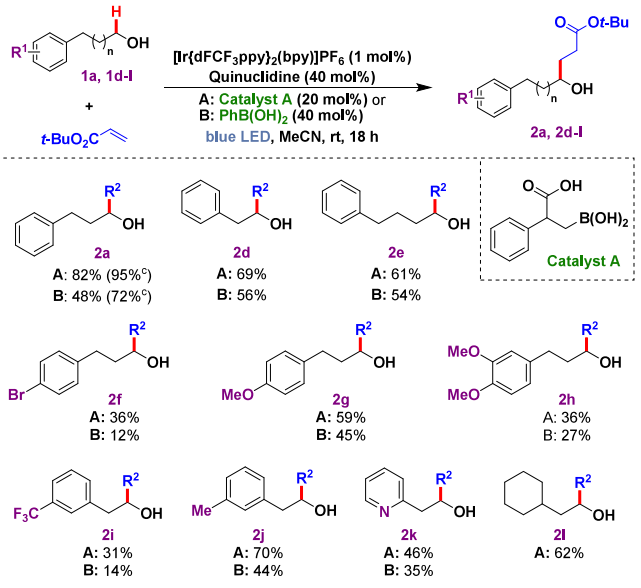
rate versus $PhB(OH)_2$. Second, three β-carboxyboronic acids, which were synthesized using Cu-catalyzed boracarboxylation of styrenes developed by the Popp research group,[38] were tested. Catalyst A provided ~7× faster alkylation in comparison to $PhB(OH)_2$, followed by the substituted Catalysts B and C. Therefore, we selected Catalyst A with which to explore reaction scope.

As previous reports have emphasized derivatization of diol-containing substrates and amino-alcohols,[28−32] we focused on exploring the C−H alkylation methodology for monoalcohols with 3-phenyl-1-propanol (**1a**) as a model substrate (Table S2). The versatility of this reaction was tested using optimized conditions and comparing Catalyst A and $PhB(OH)_2$ with a variety of monoalcohol substrates (Table 1). In all cases,

Table 1. Mono-alcohol Reaction Scope[a,b]



[a]Reaction conditions: *t*-butylacrylate (0.2 mmol, 1 equiv), **1** (0.4 mmol, 2 equiv), [Ir] (1 mol%), Quinuclidine (40 mol%), **A:** Catalyst A (20 mol%) or **B:** $PhB(OH)_2$ (40 mol%), MeCN (1.2 mL), blue LED, rt, 18 h. [b]Isolated yields. [c]NMR yield with benzyl benzoate as internal standard.

Catalyst A provides higher yields at a lower catalyst loading, consistent with the kinetic profiles of the two catalysts. Moreover, α-OH functionalization is the only pathway observed, which is significant as benzylic alkylation could be an easily accessible background reaction. Shorter (n = 0) and longer (n = 2) chain lengths between the alcohol and arene are well-tolerated (**2d**, **2e**, respectively). Electron-donating aryl substituents (**2g**, **2h**, **2j**) provide substantially higher yields than electron-withdrawing substituents (**2f**, **2i**). Of note, no side products were observed for reaction with **2f**; thus, the aryl electronics are inhibiting reactivity. This reaction is compatible with a pyridine (**2k**) in moderate yield. Lastly, an alkyl alcohol (**2l**) successfully alkylated, showing the arene is not necessary for reactivity. In the cases of low yielding reactions (e.g., **2f**, **2h**, **2i**, **2k**), the remaining mass balance is unreacted alcohol starting material.

In conclusion, we have optimized a photoredox-promoted α-OH C−H alkylation methodology for monoalcohols and identified a more reactive catalyst scaffold for this transformation. Furthermore, we established the relative reactivity of representative alcohol substrates classes and the electronic influence of arylboronic acids in this transformation. The alkylation rate for all substrates is increased when electron-poor boronic acids are used compared to electron-rich boronic acids. We propose that this observed rate difference is due to a more facile equilibrium between boron-containing species with electron-poor boronic acids. Future work aims to further investigate and develop β-carboxyboronic acids as catalysts and to gain additional mechanistic insight into the selectivity-determining steps of this reaction.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c02670.

Experimental procedures, compound characterization data, NMR spectra (PDF)

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Author Contributions

S.C.C., C.D.G., and M.J.H. wrote the manuscript. M.D.H. synthesized β-carboxyboronic acids. All authors contributed to collecting experimental data. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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