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# Site-Selective and Stereoselective C−H Alkylations of Carbohydrates via Combined Diarylborinic Acid and Photoredox Catalysis

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Supporting Information

**ABSTRACT:** Diphenylborinic acid serves as a cocatalyst for site- and stereoselective C−H alkylation reactions of carbohydrates under photoredox conditions using quinuclidine as the hydrogen atom transfer mediator. Products arising from selective abstraction of the equatorial hydrogens of *cis*-1,2-diol moieties, followed by C−C bond formation with net retention of configuration, are obtained. Computational modeling supports a mechanism involving formation of a tetracoordinate borinic ester, which accelerates hydrogen atom transfer with the quinuclidine-derived radical cation through polarity-matching and/or ion-pairing effects.

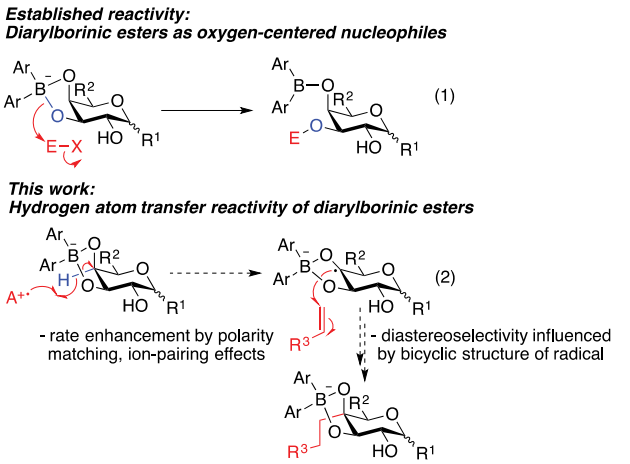


Photoredox-mediated hydrogen atom transfer (HAT) has emerged as a powerful mode of catalysis, enabling new methods for C−H bond functionalization.[1] The proposed mechanism for this class of reactions involves one-electron oxidation of a HAT mediator by the excited-state photocatalyst, generating a reactive intermediate that abstracts a hydrogen atom from the organic substrate. After reaction of the substrate-derived radical, reduction and proton transfer steps close the catalytic cycle. The ability to influence the rate and selectivity of hydrogen atom abstraction by variation of the HAT mediator is an advantage of this approach.[2] Opportunities exist to develop catalysts capable of interacting with the substrate to accelerate hydrogen atom abstraction at a particular site,[3] or to influence stereoselectivity in reactions of the resulting radical.[4] A pioneering example of such a catalytic process was reported by MacMillan and co-workers, who achieved selective functionalizations of C−H bonds $\alpha$ to hydroxyl groups using tetrabutylammonium dihydrogen phosphate as catalyst.[5] Hydrogen bond donation from the OH group to the $H_2PO_4^-$ anion was proposed to enhance the hydridic character of the $\alpha$-C−H bond, accelerating HAT to the electrophilic quinuclidine radical cation by polarity matching.[6] Other substrate activation modes for acceleration of HAT include zinc alkoxide formation from alcohols,[7] carboxylate formation from $\alpha$-amino acids,[8] and carbamate formation from primary amines.[9]

Here, we disclose a method for stereo- and site-selective C−H alkylation of carbohydrate derivatives, employing diphenylborinic acid as a cocatalyst under photoredox conditions with quinuclidine as the HAT mediator. In the presence of the organoboron catalyst, C−H abstraction occurs selectively at the equatorial hydrogens of *cis*-1,2-diol moieties, and the C−C bond-forming step takes place with net retention of configuration. Control experiments and computational studies suggest a mechanism involving formation of a tetracoordinate diarylborinic ester that is activated toward C−H abstraction by the quinuclidine radical cation. The bicyclic nature of the catalyst-bound radical intermediate influences the diastereoselectivity of the process.

Catalytic processes based on the nucleophilic reactivity of tetracoordinate diarylborinic esters have been developed by our group[10] and by other researchers (Scheme 1, eq 1).[11] We

**Scheme 1. Reactivity of Carbohydrate-Derived Diarylborinic Esters: *O*-Functionalization (1) and Envisioned HAT (2)**




hypothesized that borinic ester formation could also enable site-selective HAT, through a combination of increased hydridic character of the $\alpha$-C−H bonds[5,6] and electrostatic attraction to a radical cation (eq 2).[9,11] Selective oxidations of diols via organotin[12] and organoboron complexes[13] constitute support for the proposal that such species are activated toward C−H bond cleavage.

Quinuclidine-mediated C−H alkylation in the presence of a photoredox catalyst[5] was investigated to evaluate the effects of diarylborinic acid complexation on HAT-based reactivity of carbohydrates. Such C−H functionalizations of alcohols are accelerated by formation of hydrogen-bonded complexes or alkoxides,[5,7] suggesting that the interaction of an organoboron catalyst with a diol group might promote selective H-atom abstraction. Witte and Minnaard have adapted MacMillan's

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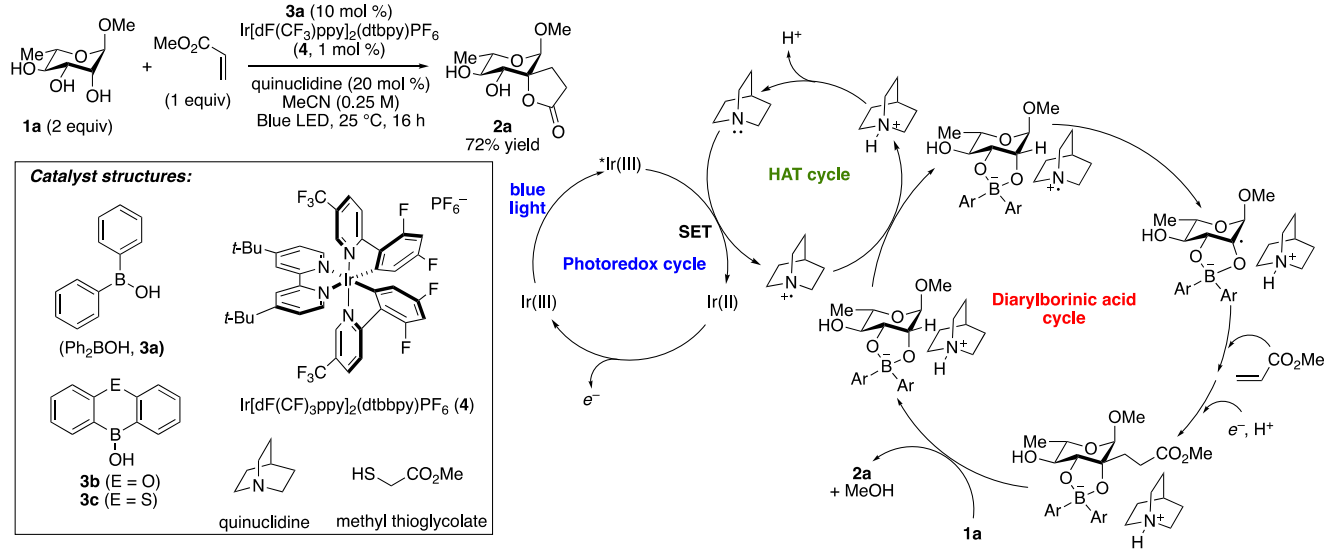
**Scheme 2. Selective C−H Alkylation of 1a and Proposed Cocatalytic Cycle**




$H_2PO_4^-$-catalyzed protocol to achieve C3-selective C−H alkylations of certain $\alpha$-pyranosides.[14] $\beta$-Glucopyranosides resulted in mixtures of stereoisomers, while manno- and galactopyranosides did not undergo selective alkylation under these conditions.

In the presence of diphenylborinic acid (**3a**, 10 mol %), quinuclidine (20 mol %) and Ir[dF($CF_3$)ppy]$_2$(dtbbpy)-$PF_6$[15,16] (**4**, 1 mol %), irradiation of rhamnopyranoside **1a** and methyl acrylate with a blue LED in acetonitrile at 25 °C generated *spiro*-fused butyrolactone[17] **2a** in 72% yield (Scheme 2). The structure of **2a** was established by nuclear magnetic resonance (NMR) analysis ($^1$H−$^1$H COSY, $^1$H−$^{13}$C HMBC and NOE difference spectra). The outcome is consistent with abstraction of the less hindered, equatorial $\alpha$-hydrogen from the *cis*-diol-derived borinic ester and approach of the acrylate from the convex face of the resulting radical. The fact that lactonization proceeded in situ, without the need for an acid treatment,[5] may reflect an accelerating effect of the borinic ester group on C−O bond formation.[18] A proposed catalytic cycle is depicted in Scheme 2.

Modifications of the reaction conditions were investigated (Table 1). In the absence of $Ph_2BOH$, **2a** was generated in 5% yield along its C-2 epimer (22%) and two dialkylated products (18% combined yield, entry 1). The effect of the diarylborinic acid on the stereochemical outcome of the reaction (>19:1 d.r. versus 1:4.1 for the uncatalyzed process) is apparent from this result. The hydrogen bond-acceptor catalyst $Bu_4N^+H_2PO_4^-$, under the conditions optimized by the MacMillan group,[5] gave <5% conversion of the pyranoside substrate (entry 2). Reactivity was restored under the conditions of Witte and Minnaard,[14] but a mixture of products was generated (5% yield of **2a** (1:4.4 d.r.), two dialkylated products in a combined 33% yield, entry 3). Boraanthracenes **3b** and **3c**,[19] which show lower affinity for diols relative to **3a** but form adducts of higher oxygen-centered nucleophilicity, gave diminished yields of **2a** (entries 4 and 5). Changing the loading of $Ph_2BOH$ resulted in appreciable decreases in yield (entries 6 and 7). Further experiments (see the SI) revealed that a roughly 10 mol % excess of quinuclidine relative to **3a** was optimal across a range of catalyst concentrations, perhaps reflecting a dual role for quinuclidine as Brønsted base (to promote borinic acid−diol complexation[10b]) and HAT mediator. Inhibition by $Ph_2BOH$ at higher loadings may result from a Lewis acid−base interaction with quinuclidine, preventing oxidation of the latter by the excited photocatalyst. No reaction was observed in the absence of photocatalyst (data not shown) or quinuclidine (entry 8). Employing $Bu_4N^+BzO^-$[2g] (O−H bond dissociation enthalpy (BDE) of BzOH: 111 kcal/mol[20]) or methyl thioglycolate[1a,b] (S−H BDE: 87 kcal/mol[21]) in place of quinuclidine (N−H BDE of quinuclidinium: 99 kcal/mol[22]) failed to give the C−H alkylation product. Of these HAT mediators, only quinuclidine would result in a radical cation capable of ion-pairing with the anionic diarylborinic ester as proposed in Scheme 2.

**Table 1. Effects of Catalyst Structure and Loading on C−H Alkylation of Pyranoside 1a**

| entry | change(s) to conditions of Scheme 2 | yield of **2a**[a] |
|---|---|---|
| 1 | **3a** omitted | 5%[b] |
| 2 | $Bu_4N^+H_2PO_4^-$ (25 mol %) used in place of **3a**[c] | <5%[d] |
| 3 | $Bu_4N^+H_2PO_4^-$ (25 mol %) used in place of **3a**[e] | 5%[b] |
| 4 | **3b** used in place of **3a** | 46% |
| 5 | **3c** used in place of **3a** | 55% |
| 6 | **3a** (5 mol %) | 54% |
| 7 | **3a** (20 mol %) | 20% |
| 8 | Quinuclidine omitted | <5%[d] |
| 9 | $Bu_4N^+BzO^-$ (20 mol %) in place of quinuclidine | <5%[d] |
| 10 | Methyl thioglycolate (20 mol %) in place of quinuclidine | <5%[d] |

[a]Yield determined by $^1$H NMR spectroscopy using a quantitative internal standard. [b]Obtained as a component of a mixture of C−H alkylation products. [c]10 mol % quinuclidine, MeCN (0.8 M), 23 °C; Amberlyst 15 resin, 50 °C (ref 6). [d]<5% conversion of the pyranoside. [e]10 mol % quinuclidine, DMSO (0.5 M), 23 °C; Amberlyst 15, 50 °C (ref 14).

The optimized protocol was applied to substrates having a *cis*-1,2-diol moiety (Scheme 3). Two equivalents of diol relative to methyl acrylate generally provided the highest yield, but in cases where dialkylation was less problematic (e.g., **2f**, **2g**, **2h**), a 1:1 or 1:2 diol:acrylate ratio was employed. Activation of the equatorial C−H bond of a *cis*-1,2-diol motif was observed consistently, leading to C2-alkylation of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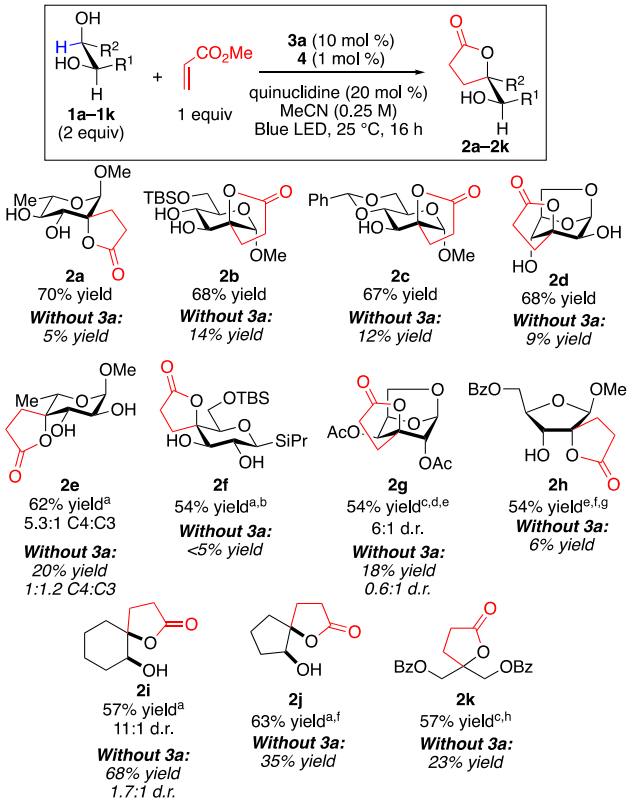
**Scheme 3. Site- and Stereoselective C–H Alkylations of Diol and Triol Derivatives**



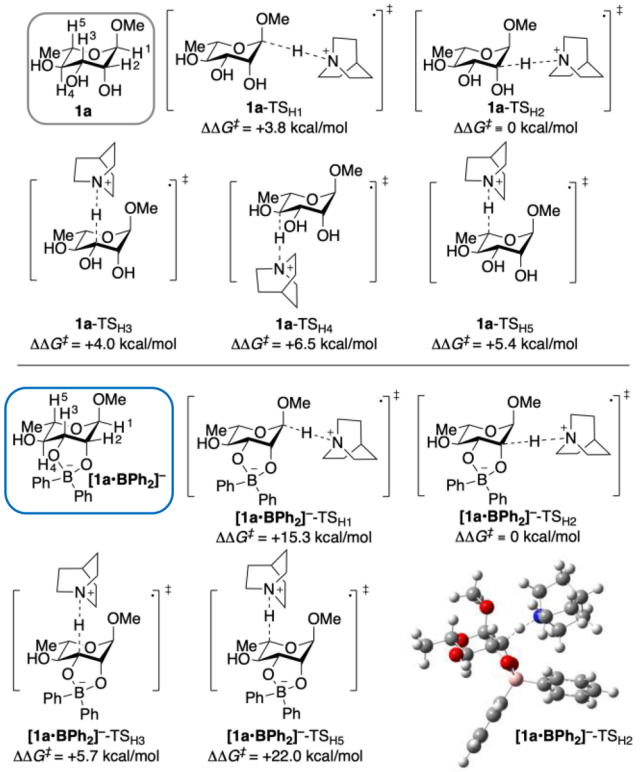

[a]5 mol % of **3a** was used. [b]1 equiv of pyranoside to methyl acrylate was employed. [c]The product was acylated (RCOCl, pyridine) prior to isolation. [d]18 h reaction time. [e]2 equiv of methyl acrylate to carbohydrate substrate was employed. [f]The reaction mixture was treated with Amberlyst 15 resin (50 °C, 3 h) prior to isolation. [g]19 h reaction time. [h]1 equiv of quinuclidine was employed.

mannopyranosides (**2a–2c**) and C4-alkylation of galactopyranosides (**2e**, **2f**). Transformations of 1,6-anhydrosugars constrained to the $^1C_4$ conformation enabled access to the C3-alkylated mannopyranoside (**2d**) and galactopyranoside (**2g**). The organoboron-catalyzed protocol was also applied to a ribofuranoside (**2h**), *cis*-cycloalkanediols (**2i**, **2j**) and glycerol (**2k**). The relative configurations were determined by analysis of the NOE difference spectra, and by single crystal X-ray diffraction analysis for **2f**. Results of control reactions conducted in the absence of catalyst **3a** are also reported. The use of $Ph_2BOH$ consistently provided an enhancement in the yield of the C–H alkylation reaction. Effects of the organoboron catalyst on site-selectivity and diastereoselectivity were also evident for several substrates, although relatively low rates of uncatalyzed C–H alkylation, compounded by sluggish lactonization and the formation of multiply alkylated side products, hampered such assessments in other instances. For *α*-fucopyranoside derivative **2e**, the C4:C3 site-selectivity was higher in the presence of **3a** than in its absence. Whereas the product of net retention of configuration of the C–H bond was favored in the presence of $Ph_2BOH$, the uncatalyzed process gave a low diasteroselectivity for **2i** (1.7:1 versus 12:1 d.r.) and favored the other diastereomer for **2g** (0.6:1 versus 6:1 d.r.). Limitations of the current protocol were encountered upon attempting C–H alkylations of *α*-*N*-acetylgalactosamine, *β*-arabinopyranoside and *α*-ribopyranoside derivatives, and when using acrylonitrile or phenyl vinyl sulfone in place of methyl acrylate (see the SI).

Computational modeling was employed to probe the effect of diarylborinic ester formation on the HAT reactivity of rhamnopyranoside **1a**. The BDEs were calculated to evaluate changes in bond strength, while transition states for HAT with the quinuclidine radical cation at various sites were modeled to obtain insight into the kinetic origins of selectivity (Table 2). The gas-phase DFT calculations (B97-D3/Def2-TZVP)[23,24] were carried out using Gaussian 16.[25]

The calculated BDEs showed *α*-C–H bond weakening at the 2- and 3-positions (by 4.5 and 4.2 kcal/mol, respectively)

**Table 2. Calculated BDEs and Relative Activation Energies ($\Delta\Delta G^{\ddagger}$) for HAT with the Quinuclidine Radical Cation[a]**




| rhamnopyranoside **1a** | | | |
|---|---|---|---|
| BDE (kcal/mol) | | $\Delta\Delta G^{\ddagger}$ for HAT (kcal/mol) | |
| position | BDE | transition state | $\Delta\Delta G^{\ddagger}$ |
| H-1 | 89.2 | **1a**-TS$_{H1}$ | +3.8 |
| H-2 | 89.6 | **1a**-TS$_{H2}$ | 0.0 |
| H-3 | 90.2 | **1a**-TS$_{H3}$ | +4.0 |
| H-4 | 87.4 | **1a**-TS$_{H4}$ | +6.5 |
| H-5 | 91.7 | **1a**-TS$_{H5}$ | +5.4 |
| diphenylborinate [**1a**·BPh$_2$]$^-$ | | | |
| BDE (kcal/mol) | | $\Delta\Delta G^{\ddagger}$ for HAT (kcal/mol) | |
| position | BDE | transition state | $\Delta\Delta G^{\ddagger}$ |
| H-1 | 91.2 | [**1a**·BPh$_2$]$^-$-TS$_{H1}$ | +15.3 |
| H-2 | 85.1 | [**1a**·BPh$_2$]$^-$-TS$_{H2}$ | 0.0 |
| H-3 | 86.0 | [**1a**·BPh$_2$]$^-$-TS$_{H3}$ | +5.7 |
| H-4 | 85.7 | [**1a**·BPh$_2$]$^-$-TS$_{H4}$ | – |
| H-5 | 91.8 | [**1a**·BPh$_2$]$^-$-TS$_{H5}$ | +22.0 |

[a]Structures of **1a** and [**1a**·BPh$_2$]$^-$, and transition state structures for H atom abstraction by the quinuclidine radical cation, are depicted.



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upon diarylborinate formation, and comparatively small changes (≤2 kcal/mol) at the other positions. Contrary to our initial expectations,[26] the lowest calculated C−H BDE for **1a** was at the 4-position, not the anomeric center: the results suggest that intramolecular hydrogen bonding causes stabilization of radicals $\alpha$ to OH groups. For borinic ester $[\mathbf{1a}{\cdot}BPh_2]^-$, the 2-position was calculated to have the weakest C−H bond, consistent with the observed site-selectivity, although the BDE at C4 was only marginally (0.6 kcal/mol) higher. The calculated energies of activation gave a more definitive result, revealing an appreciable kinetic preference for abstraction of H-2 from $[\mathbf{1a}{\cdot}BPh_2]^-$ by the quinuclidine radical cation ($\Delta\Delta G^{\ddagger}$ of −5.7 kcal/mol relative to abstraction of H-3). A transition state for abstraction of H-4 from $[\mathbf{1a}{\cdot}BPh_2]^-$ could not be identified, likely due to steric hindrance at this position. The 2-position was also calculated to be the kinetically favored site of HAT for the unbound substrate, but to a lesser extent (see the $\Delta\Delta G^{\ddagger}$ data for **1a**). For this pyranoside, it appears that diarylborinic ester formation accentuates an intrinsic level of site-selectivity while also increasing the rate of the C−H alkylation process. Although the calculations did not provide a direct estimate of the relative rates of catalyzed versus uncatalyzed HAT, the exergonic formation of a prereactive complex from $[\mathbf{1a}{\cdot}BPh_2]^-$ and the radical cation suggests a significant level of acceleration (see the SI). Further computational modeling to account for ion pairing and solvent effects, along with experimental studies of reaction rates, would be of interest.

In conclusion, diphenylborinic acid has a significant effect on quinuclidine-mediated C−H alkylations of *cis*-1,2-diol groups under photoredox conditions. The patterns of site-selectivity, along with computational modeling of the proposed intermediate, suggest acceleration of HAT between a tetracoordinate diarylborinic ester and the quinuclidine radical cation due to polarity matching and/or ion pairing effects. Association of the borinic acid with the resulting radical intermediate is likely responsible for the observed retention of configuration upon C−C bond formation. Considering that carbohydrate-derived radicals have been implicated in synthetic and enzyme-catalyzed transformations,[27] the ability to use a small-molecule catalyst to influence the rate and site-selectivity of H atom abstraction from a sugar-derived substrate (and to remain associated with the radical during subsequent transformations) is a significant advance. Opportunities exist to gain additional mechanistic insight into this activation mode, and to develop extensions that enable other useful transformations of carbohydrates and related molecules.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b01531.

Experimental and computational details, additional data regarding optimization and substrate scope, characterization data for new compounds, copies of $^1H$ and $^{13}C$ NMR, $^1H-^1H$ COSY, $^1H-^{13}C$ HSQC, $^1H-^{13}C$ HMBC and $^1H-^1H$ NOE difference spectra (PDF)

X-ray crystal structure data of **2f** (CIF)

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### Notes

The authors declare no competing financial interest.

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