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Site- and Stereoselective C−H Alkylations of Carbohydrates Enabled by Cooperative Photoredox, Hydrogen Atom Transfer, and Organotin Catalysis

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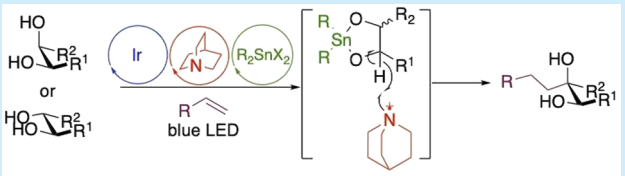
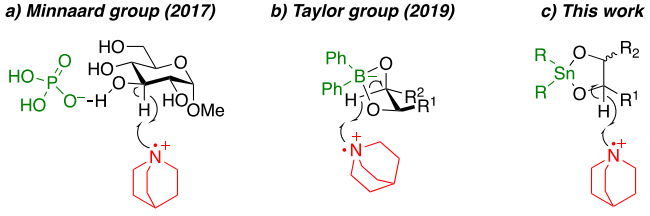
ABSTRACT: Diorganotin dihalides act as cocatalysts for site-selective and stereoselective couplings of diol-containing carbohydrates with electron-deficient alkenes in the presence of an Ir(III) photoredox catalyst and quinuclidine, a hydrogen atom transfer mediator. Quantum-chemical calculations support a proposed mechanism involving the formation of a cyclic stannylene acetal intermediate that shows enhanced reactivity toward hydrogen atom abstraction by the quinuclidinium radical cation. Addition of the carbon-centered radical to the alkene partner results in *C*-alkylation of the carbohydrate substrate.



Catalytic, site-selective hydrogen atom transfer (HAT) has emerged as a powerful approach for the modification of complex molecules.[1,2] Catalyst systems that combine a visible-light photocatalyst with a HAT mediator have been a key development, allowing for the generation of radicals under mild conditions and enabling tuning of the reactivity and selectivity profile of the hydrogen-atom-abstracting agent. The radicals generated upon electron transfer from the HAT mediator to the excited-state photocatalyst can vary in hydrogen atom affinity, polarity, and steric demand, enabling "matching" with different C−H bond types.[3−9] Nonetheless, complex substrates often possess several C−H bonds that react with hydrogen-atom-abstracting agents at similar rates. To address this challenge, activation of functional groups toward HAT has been investigated, leading to the discovery of approaches for site-selective radical formation at the α-positions of alcohols (see below), amines, and carboxylic acids.[10]

Selective α-C−H functionalizations of alcohols have been pursued intensively, motivated by the importance of the hydroxyl (OH) functional group in biomass-derived compounds and natural products (e.g., carbohydrates, polyketides) as well as pharmaceutical agents and synthetic intermediates. A key advance was reported by MacMillan and co-workers, who found that the hydrogen-bonding interaction between dihydrogen phosphate anion and the OH group results in increased hydridic character at the α-position, accelerating HAT to the quinuclidinium radical cation through a polarity matching effect.[4,11] Catalysis by hydrogen-bond acceptors has been employed by the groups of Minnaard[12] (Scheme 1a) and Wendlandt[13] to activate carbohydrates toward site-selective C−H alkylation and epimerization reactions, respectively.

Scheme 1. Approaches for Substrate Activation in Site-Selective C−H Alkylations of Glycosides



The formation of alkoxides and related intermediates has been another productive approach for activation of alcohols toward selective HAT at the α-position. MacMillan and co-workers showed that zinc(II) alkoxides undergo α-arylation with haloarene partners in the presence of a photoredox catalyst, HAT mediator, and nickel−phenanthroline complex.[14] Murakami's group later found that the formation of a sodium alkoxide at the anomeric position facilitates the photocatalytic C1 oxidation/C2 reduction isomerization of pyranoses.[15] Our group has shown that organoboron cocatalysts, upon complexation with the *cis*-1,2 diols of carbohydrates, selectively activate a hydrogen at the α-position toward abstraction by the quinuclidinium radical cation. Using diarylborinic acids (Ar_2BOH), site-selective and stereoselective C−H alkylations of carbohydrates[16] were achieved (Scheme

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1b), whereas an electron-deficient arylboronic acid was optimal for redox isomerization of furanoses to 2-keto-3-deoxysugars.[17] Kanai and co-workers have also made important contributions to this area, employing spirosilane and diarylborinic ester catalysts for selective α-alkylations of primary and secondary alcohols.[18]

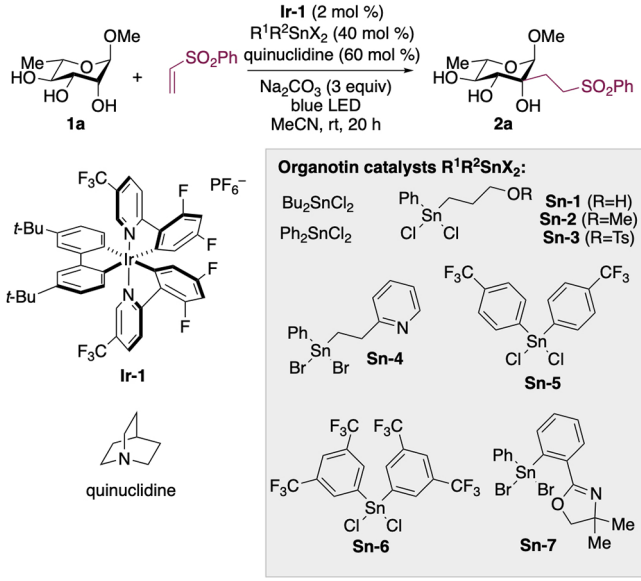
It has been recognized for decades that carbohydrates can be activated toward selective *O*-functionalization reactions by the formation (stoichiometric or catalytic) of organotin complexes.[19,20] We set out to determine whether the formation of cyclic organotin adducts could be used to activate diols toward HAT at the α-position (Scheme 1c). In contrast to the numerous examples of selective organotin-promoted functionalization of OH groups, there are few observations suggesting that organotin complexes display enhanced reactivity toward C−H bond cleavage; selective oxidation reactions of carbohydrates using organotin promoters[21] or catalysts[22] (perhaps involving a radical mechanism) constitute the closest precedent for this idea. Here we show that diorganotin dihalides are effective cocatalysts (along with an Ir(III) photoredox catalyst and quinuclidine as a HAT mediator) for site-selective C−H alkylation reactions of diol groups in carbohydrates. In comparison with our previous work using a diarylborinic acid, the organotin catalyst provides higher yields for certain substrate classes (*e.g.*, *trans*-1,2-diol-containing carbohydrate substrates, alkene reaction partners other than acrylates) and is less susceptible to decomposition under the conditions of C−H alkylation.

Optimization was conducted on the C−H alkylation of methyl-α-L-rhamnopyranoside (**1a**) with phenyl vinyl sulfone (Table 1). In the presence of diorganotin dihalide catalysts, along with the $Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ photocatalyst (**Ir-1**), quinuclidine, and sodium bicarbonate (likely serving to promote stannylene acetal formation), product **2a** was generated. The site selectivity and stereochemical outcome were consistent with the diphenylborinic acid-catalyzed coupling of this substrate using methyl acrylate and likely arise from abstraction of the more sterically accessible hydrogen atom from the 2,3-*O*-stannylene adduct followed by C−C bond formation with net retention of configuration. A screen of organotin catalysts revealed that Ph_2SnCl_2[23] outperformed Bu_2SnCl_2 as well as the dichloro(aryl)(alkyl)tin compounds **Sn-1**−**Sn-3**; for the latter, pendent Lewis basic groups capable of generating a pentavalent organotin adduct[24,25] did not provide improved activity. Decomposition of the Ph_2SnCl_2 and Bu_2SnCl_2 catalysts was ruled out by ^{119}Sn NMR spectroscopy. Speculating that the higher Lewis acidity of Ph_2SnCl_2 might be responsible for its superior catalytic activity relative to the alkyl-substituted derivatives, we investigated substituted diaryltin dichlorides **Sn-5** and **Sn-6**. However, these substituted congeners gave lower yields of the C−H alkylation product. Again, the incorporation of a Lewis basic oxazoline group (**Sn-7**) did not have a beneficial effect.[26]

Further optimization of the catalyst loadings revealed that with 1 mol % **Ir-1**, 10 mol % Ph_2SnCl_2, and 20 mol % quinuclidine, **2a** could be obtained in 64% yield with 10:1 site selectivity and 10:1 diastereomeric ratio (Scheme 2). A similar result (a 63% yield of **2a**) was achieved when the reaction was conducted on a 1.0 mmol scale. Control experiments (see the Supporting Information (SI)) showed that each component of the optimized reaction protocol was necessary to generate product **2a**. The optimized reaction conditions were employed in C−H alkylations of a range of diol substrates (Scheme 2). In addition to the vinyl sulfone, acrylonitrile, diethyl vinylphosphonate, and methyl acrylate were tolerated as reaction partners (products **3a**−**5a**). In each case, the yield obtained using Ph_2BOH in place of Ph_2SnCl_2 is also presented. The results for products **2a**−**4a** illustrate the improvement in yield obtained using the organotin catalyst for couplings of alkenes other than methyl acrylate; we speculate that the formation of the spiro-fused lactone in **5a** is important for achieving efficient catalytic turnover using the organoboron catalyst.

The method was found to tolerate variation of the aglycon substituent in the α-rhamnopyranoside substrate (products **2b**−**2d**); it is noteworthy that C-alkylations of disaccharides could be accomplished (products **2c** and **2d**), considering that these substrates present numerous types of C−H bonds in similar steric and electronic environments. Tolerance for a variety of protecting groups was also demonstrated: the substrate scope includes silyl ethers (at the 4-position of an α-rhamnopyranoside (**2e**) or the 6-position of an α-mannopyranoside (**2f**)), trimethylphenyl (trityl) ethers (6-*O*-tritylated α-mannopyranoside **2g**), and benzylidene acetals (mannopyranoside **2h**). In the case of 1,6-anhydromannopyranose, which adopts the $^1C_4$ conformation, alkylation at C3 was observed (product **2i**), consistent with the general pattern of selective abstraction of the equatorial hydrogen atom from a *cis*-1,2-diol

Table 1. Optimization of Organotin Catalysts for the C−H Alkylation of Methyl α-L-Rhamnopyranoside (1a)[a]



entry	organotin catalyst $R^1R^2SnX_2$	yield of **2a** (%)[b]
1	Bu_2SnCl_2	18
2	Ph_2SnCl_2	60
3	**Sn-1**	27
4	**Sn-2**	48
5	**Sn-3**	10
6	**Sn-4**	17
7	**Sn-5**	29
8	**Sn-6**	27
9	**Sn-7**	22

[a]Conditions: Phenyl vinyl sulfone (1.0 equiv), **1a** (2.0 equiv), $R_1R_2SnX_2$ (40 mol %), $Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ (**Ir-1**, 2 mol %), quinuclidine (60 mol %), Na_2CO_3, MeCN, blue LED, room temperature, 20 h. [b]Determined by ^1H NMR spectroscopic analysis (CD_3CN) with a quantitative internal standard.

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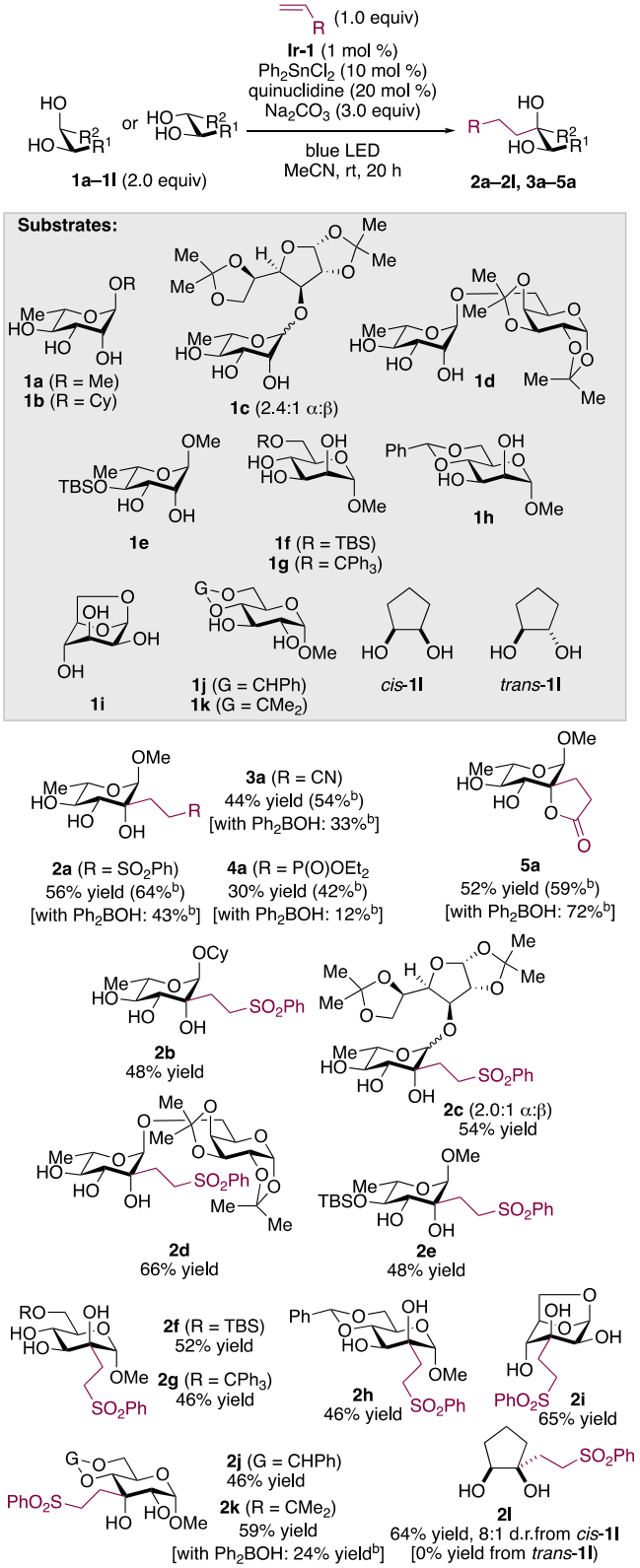
Scheme 2. Site- and Stereoselective C−H Alkylation Reactions of Diol-Containing Compounds[a]



[a]Yields of isolated products after purification by silica gel chromatography are shown, unless otherwise noted. [b]The yield was determined by ^{1}H NMR spectroscopic analysis (CD_3CN) with a quantitative internal standard.

moiety. Net retention of configuration at the position undergoing alkylation was observed for all of the *cis*-1,2-diols examined. This outcome was also obtained using our previously reported diarylborinic acid-catalyzed method and likely arises from the sterically favored approach of the alkene to the convex face of the stannylene acetal-derived radical intermediate.

A distinctive feature of stannylene acetals is their utility for selective functionalizations of *trans*-1,2-diols, motifs that are generally not subject to efficient activation with organoboron compounds.[19b−d] Consistent with this pattern, we found that *α*-glucopyranosides underwent selective alkylation at C3 in the presence of Ph_2SnCl_2 as the cocatalyst (products **2j** and **2k**). When Ph_2BOH was used in place of Ph_2SnCl_2, the yield of **2k** was considerably lower (24% vs 59%). The *allo* configuration of products **2j** and **2k** is in agreement with the stereochemical outcomes of alkylation and HAT reactions of related *α*-glucopyranoside C3 radicals reported by the groups of Minnaard[12] and Wendlandt.[13] In the present case, the formation of the *allo*-configured products suggests that the presumed stannylene acetal-derived radical is capable of conformational relaxation to permit the sterically preferred equatorial approach of the vinyl sulfone partner. Subjecting *cis*- and *trans*-1,2-cyclopentanediol to the optimized conditions revealed that only the former was reactive, delivering the *cis*-configured *C*-alkylation product **2l**. Presumably, the *trans*-fused 5−5 ring system that would result from stannylene acetal formation from the latter is less favorable than the corresponding 5−6-fused congener. Limitations of the organotin-catalyzed protocol include ester-protected pyranosides, thioglycosides, galactopyranosides, *β*-glucopyranosides, and substrates having free primary OH groups (see the SI for details). Further studies are needed to understand the effects of relative configuration and substitution on the rates and selectivities of these C−H alkylation reactions.

Quantum-chemical calculations were conducted to assess the effect of stannylene acetal formation on the thermodynamics and kinetics of HAT from rhamnopyranoside **1a**. The diphenylstannylene acetal **1a·SnPh$_2$** was modeled in the gas phase with density functional theory using the B97 functional with Grimme's D3BJ dispersion correction (B97-D3)[27] and the Def2-TZVP basis set.[28] In Table 2, the calculated gas-phase C−H bond dissociation enthalpies (BDEs) at C1−C5 of **1a·SnPh$_2$** are compared with those of free **1a** and diphenylborinic ester $[\mathbf{1a{\cdot}BPh_2}]^-$ (calculated at the same level of theory in our previously reported study).[16] The C−H BDE at the 2-position of **1a·SnPh$_2$** was found to decrease slightly (by 0.5 kcal/mol) relative to that of the free rhamnopyranoside. The magnitude of this bond weakening effect at C2 is less pronounced than that calculated for $[\mathbf{1a{\cdot}BPh_2}]^-$ (4.5 kcal/mol).

Free energies of activation for gas-phase HAT from the five secondary C−H bonds of **1a·SnPh$_2$** to the quinuclidinium radical cation were calculated at the same level of theory. The results are summarized in Table 2 along with those for **1a** and $[\mathbf{1a{\cdot}BPh_2}]^-$. Transition state searches for HAT from the 4-position of **1a·SnPh$_2$** and $[\mathbf{1a{\cdot}BPh_2}]^-$ were not successful, likely because of steric hindrance at this site. In each case, the 2-position was found to be the kinetically preferred site of abstraction; the free energy of this transition state was set to zero in each series for the purposes of comparison. The calculated transition state energies suggest that the formation of the stannylene acetal enhances an intrinsic selectivity for C2, thus enabling efficient C−H alkylation by reducing the extent

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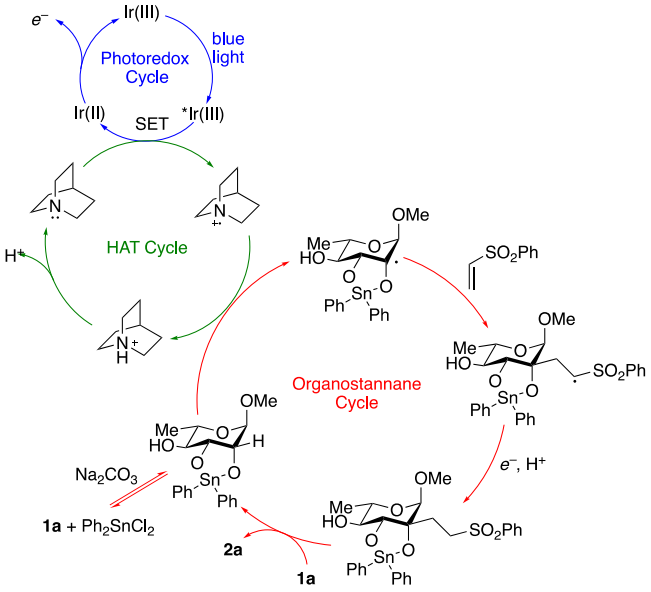
Table 2. Gas-Phase BDEs and Relative Transition State Energies for Hydrogen Atom Transfer to Quinuclidinium Radical Cation from C1−C5 of 1a, 1a·$SnPh_2$, and $[1a·BPh_2]^-$ (in kcal/mol)[a,b]

	1a	1a·$SnPh_2$	$[1a·BPh_2]^-$
BDE (kcal/mol)			
C1−H BDE	89.2	92.9	91.2
C2−H BDE	89.6	89.1	85.1
C3−H BDE	90.2	91.0	86.0
C4−H BDE	87.4	86.9	85.7
C5−H BDE	91.7	92.0	91.8
$\Delta\Delta G^{\ddagger}$ (kcal/mol)[c]			
C1	+3.8	+7.7	+15.3
C2	0.0	0.0	0.0
C3	+4.0	+6.2	+5.7
C4	+6.5	–	–
C5	+5.4	+8.2	+22.0

[a]The B97-D3 functional and Def2-TZVP basis set were employed. [b]Values for **1a** and $[1a·BPh_2]^-$ are from ref 16. [c]The energy of the lowest-energy transition state in each series was set to zero.

Scheme 3. Proposed Cocatalytic Cycle



of formation of isomeric or bisalkylated products; the enhancement of selectivity appears to be slightly higher for the stannylene acetal than for the borinic ester ($\Delta\Delta G^{\ddagger}$ = +6.2 vs +5.7 kcal/mol).

The relative free energies of activation also provide an indirect measure of the extent of rate acceleration of HAT achieved by stannylene acetal and borinic ester formation: by comparison of the free energy of activation at C2 with that of a position at which the reactivity of the C−H bond is unlikely to be significantly changed by catalyst complexation (C5 in the case of rhamnopyranoside **1a**), the degree of transition state stabilization resulting from diol complexation can be estimated. The difference in free energies of activation $\Delta\Delta G^{\ddagger}$(C5 vs C2) is +5.4 kcal/mol for **1a**, +8.2 kcal/mol for **1a·SnPh$_2$** and +22.0 kcal/mol for $[$**1a·BPh$_2$**$]^-$, suggesting that both stannylene acetal and borinic ester formation cause an acceleration of the HAT step, with the degree of rate enhancement being significantly higher for the latter.

A cocatalytic cycle is proposed in Scheme 3, taking into account previous mechanistic proposals for organotin-catalyzed reactions of diols[19] as well as transformations of C−H bonds mediated by photoredox catalyst/quinuclidine combinations.[4,16] Excitation of the Ir(III) photocatalyst results in single-electron oxidation of quinuclidine, generating an electrophilic radical cation. Ph_2SnCl_2, with assistance from Na_2CO_3, complexes to **1a**, forming a stannylene acetal and enhancing the reactivity of the C2−H bond toward HAT. The stereochemical outcome of the alkylation arises from approach of the alkene from the convex face of the bicyclic α-oxy radical. Reduction of the resulting radical by the reduced Ir(II) photocatalyst followed by protonation of the anion and ligand exchange at tin regenerates the Ir(III) photocatalyst and yields **2a**.

In conclusion, this study has established diorganotin dihalides as a new class of C−H bond-weakening catalysts for radical reactions of diol substrates. The extension of the chemistry of stannylene acetals from site-selective *O*-functionalization to C−H bond functionalization is a significant one and may create new opportunities to achieve useful homologations, rearrangements, or functional group interconversions of carbohydrates. In the context of C−H alkylation, catalysis by Ph_2SnCl_2 provides an expansion in the alkene scope in comparison with diarylborinic acid catalysis while also enabling activation of *trans*-1,2-diol motifs. The products are structurally novel carbohydrate analogues that would be challenging to generate by other means. Computational modeling suggests that the formation of the organotin adduct alters the thermodynamics and kinetics of radical formation, resulting in a decrease in C−H BDE at the α-position while accelerating HAT to the quinuclidinium radical cation. Further studies are needed to understand how the interplay between the structures of the organotin catalyst, carbohydrate substrate, and HAT mediator contributes to the selectivity and scope of this transformation. It will also be of interest to explore differences in the reactivity of the radicals generated from organotin versus organoboron complexes of carbohydrates and to determine whether the two types of catalysts show distinct tolerances to other reagents or conditions that may facilitate the development of new transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01718.

Optimizations, control experiments, computational data, experimental procedures, and characterization data for products (PDF)

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Notes

The authors declare no competing financial interest.

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