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Site-Selective C−O Bond Editing of Unprotected Saccharides

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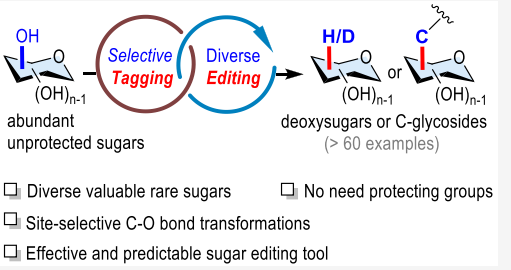
ABSTRACT: Glucose and its polyhydroxy saccharide analogs are complex molecules that serve as essential structural components in biomacromolecules, natural products, medicines, and agrochemicals. Within the expansive realm of saccharides, a significant area of research revolves around chemically transforming naturally abundant saccharide units to intricate or uncommon molecules such as oligosaccharides or rare sugars. However, partly due to the presence of multiple hydroxyl groups with similar reactivities and the structural complexities arising from stereochemistry, the transformation of unprotected sugars to the desired target molecules remains challenging. One such formidable challenge lies in the efficient and selective activation and modification of the C−O bonds in saccharides. In this study, we disclose a modular 2-fold "tagging−editing" strategy that allows for direct and selective editing of C−O bonds of saccharides, enabling rapid preparation of valuable molecules such as rare sugars and drug derivatives. The first step, referred to as "tagging", involves catalytic site-selective installation of a photoredox active carboxylic ester group to a specific hydroxyl unit of an unprotected sugar. The second step, namely, "editing", features a C−O bond cleavage to form a carbon radical intermediate that undergoes further transformations such as C−H and C−C bond formations. Our strategy constitutes the most effective and shortest route in direct transformation and modification of medicines and other molecules bearing unprotected sugars.



INTRODUCTION

Saccharides and their derivatives are complex molecules that play vital roles in various living processes and exhibit diverse biological activities.[1,2] The exploration of saccharide-containing molecules has led to several hundred medicines and pesticides with significant economic and social impacts[3−5] (Figure 1A). Most of these bioactive molecules contain mono- or complex oligo-saccharide fragments, as seen in mithramycin and validamycin, and are obtained from fermentation or biomass.[6,7] Another subset of these compounds, such as empagliflozin and remdesivir, contains simpler monosaccharides or their analogs and is prepared through chemical synthesis.[8,9] At present, effective strategies for synthesis or modification of the class of complex saccharide-based molecules are barely available.[10,11] Even for the relatively simple monosaccharide-based molecules, the presence of multiple hydroxyl groups (and C−H bonds) with similar reactivities makes the development of concise synthesis and modification methods challenging.[12,13] One main effort of research in saccharide synthesis chemistry involves manipulating the anomeric position of sugars particularly for glycosylation reactions[14] (Figure 1B). Examples of recent success include Jacobsen's catalytic stereoselective glycosylation coupling of (minimally protected) sugars to prepare disaccharides.[15,16] Another major effort is dedicated to converting saccharides, especially inexpensive biomass-derived monosaccharides, into their derivatives such as "rare sugars" with biological functions.[17,18] Indeed, approximately ten percent of glycosylated bacterial metabolites fall under the category of nontypical carbohydrates[17] that are not present on the human cell surface, making them excellent targets for drug discovery and carbohydrate-based vaccine development.[19−22] While the importance of rare sugars as essential pharmacophores has been demonstrated in these biological studies, synthetic challenges have limited the accessibility of these critical structures. Traditional synthetic strategies mainly rely on multiple-step synthesis (involving repetitive use of protection groups) from common monosaccharides or the implementation of the carefully designed de novo synthesis from simple feedstock chemicals.[18,23,24] In this context, the methodology for selectively editing common sugar skeletons directly to access diverse ranges of rare sugars is of the utmost importance and value. The impressive while still limited success mainly centers around manipulating the C−H bonds in saccharides[25,26] (Figure 1B). For example, Minnaard,[27] Waymouth,[28] and Muramatsu[29] developed metal-catalyzed oxidation of minimally protected monosaccharides to ketosugars. Minnaard[30] and Taylor[31] reported diastereoselective C−H alkylation of glucose derivatives via hydrogen atom

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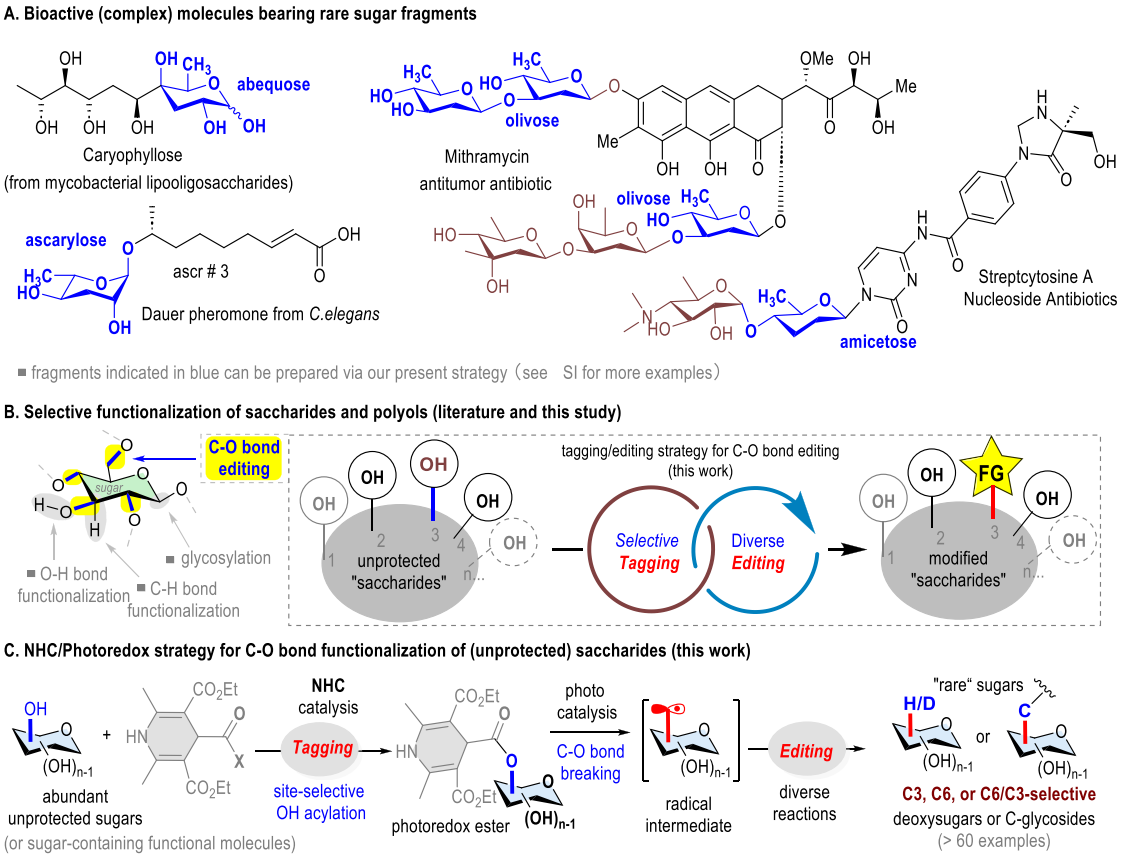

Figure 1. Selective C−O bond editing of unprotected saccharides.

abstraction by a quinuclidinium radical cation as a key step. Wendlandt[32,33] and Tang[34] developed new epimerization strategies capable of altering the stereochemistry of sugars to synthesize their rare analogs.

Another opportunity in transforming saccharides arises from breaking the C−O bonds of saccharides. This C−O bond cleavage is a common biological process for carbohydrates mediated by enzymes.[35] However, this is a challenging task in chemical synthesis, especially when unprotected saccharides are the substrates. Current success mainly comes from the implementation of the Barton−McCombie reaction involving a thiocarbonyl ester (for thioacylation of sugars) that can lead to reductive cleavage of the C−O bond of saccharides by treatment with a reducing agent such as AIBN/Bu_3SnH.[36] A representative report in this direction is from Miller and co-worker, who demonstrated selective deoxygenated derivatization of sugar-containing complex bioactive molecules using peptide-based organocatalysts.[37] Despite the progress, a modular approach for site-selective C−O bond editing of unprotected saccharides under mild conditions with broad substrate tolerance is yet to be developed.[38−40] Here we disclose a new modular 2-fold "tagging−editing" strategy for site-selective cleavage and editing of C−O bonds in unprotected saccharides and their polyol analogs (Figure 1B, right part). Built on our long-time interest in developing N-heterocyclic carbene organic catalysis for selective reactions, the first stage of our strategy (the "tagging" step) involves N-heterocyclic carbene (NHC)-catalyzed site-selective acylation of unprotected saccharides (Figure 1C). Our recent research on the site-selective acylation of unprotected saccharides, facilitated by NHC/boronic acid mediated systems, contributes significantly.[41] Indeed, the development of site-selective reactions (such as selective C−H bond functionalization and OH group acylation) mediated by small-molecule or peptide-based catalysts continues to be a very important topic in chemistry.[42,43] Our NHC-catalyzed site-selective acylation method allows for direct installation of a photoredox-active ester unit[44] to a specific hydroxyl group on unprotected saccharides. It should be noted that the carboxylic acid derivative of 1,4-dihydropyridine (DHP), as an easily accessible radical precursor in photochemical synthesis, has recently garnered increasing attention.[45−48] The Diao research group, in particular, has applied it to install on the anomeric position of sugars for the synthesis of C-glycosides.[49] Nevertheless, we are not aware of its success in any form of challenging selective acylation reaction. The second stage (the "editing" step) of our approach involves a photomediated process that eventually cleaves the C−O bond to form an alkyl radical intermediate. Further reactions (such as hydrogen atom abstractions and carbon−carbon bond formations) of the radical intermediates lead to uncommon sugars, such as deoxygenated sugars, that are otherwise difficult to prepare (Figure 1C). By using our approach, with a two-step operation, unprotected biomass-derived sugars can be converted to highly valuable rare sugars such as paratoses, abequose, ascarylose, and tyvelose.[24] Medicinally important molecules such as SGLT2 inhibitors canagliflozin, dapagliflozin, and empagliflozin[50] can be converted to their deoxygenated or C-alkylated derivatives, with dramatically reduced steps when compared with reported methods. We expect that our "tagging−editing" approach, with site-selective installations of a tunable functional group at the first stage and a subsequent chemical bond

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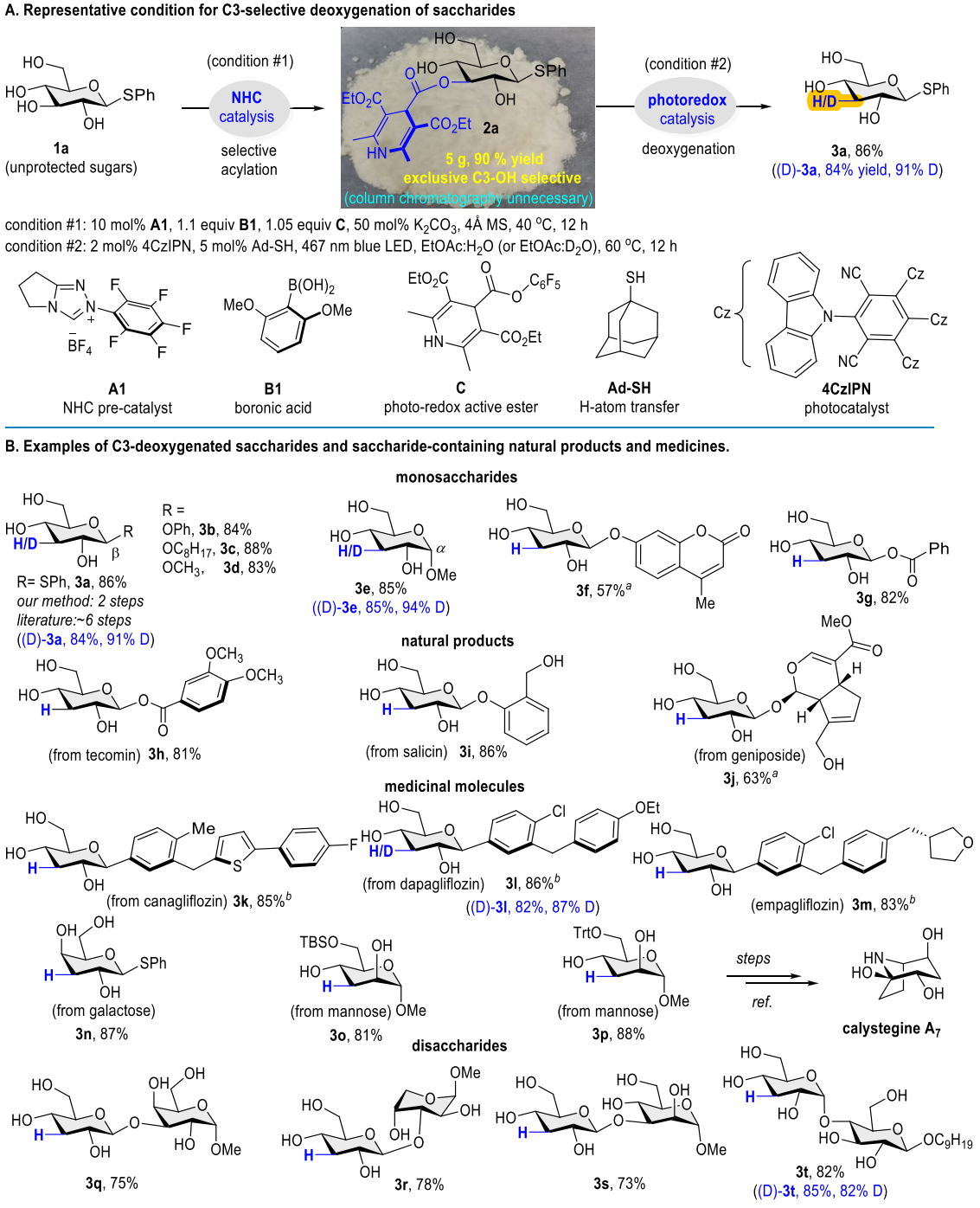

Figure 2. C3-selective deoxygenation of saccharides. All yields of deoxy sugars correspond to isolated yields based on the acylated sugar adduct **2**. [a]CH_3CN was used as the solvent instead of EtOAc. [b]Reaction at 80 °C. NHC, N-heterocyclic carbene; LED, light-emitting diode; Ad-SH, adamantanethiol; TBS, *tert*-butyldimethylsilyl; Trt, trityl.

manipulation step, offers a realistic and modular method for selective transformation of a large set of complex molecules bearing many similar chemical bonds.

RESULTS AND DISCUSSION

Reaction Development. A representative protocol for the C3-selective deoxygenation of saccharides and saccharide-containing molecules is illustrated in Figure 2A. Experimental details with condition optimizations can be found in Supplementary Table 1. By employing an NHC precatalyst (**A1**)/boronic acid (**B1**)-mediated condition,[41] with unprotected glucoside **1a** as a model substrate and a photoredox ester **C** as an acylation reagent, C3-OH-acylated sugar adduct **2a** could be prepared in gram scales and 90% yield with exclusive C3 selectivity. This "tagging" condition and its subtly tuned variants demonstrated consistent efficacy across various unprotected mono- and disaccharides as well as saccharide-containing molecules. The corresponding acylation products bearing photoredox-active esters were obtained with excellent yields and regioselectivities (around 90% yields and exclusive regioselectivity in many cases; see Supplementary Figure 3). Technically, these esters (e.g., **2a**) show remarkable stabilities

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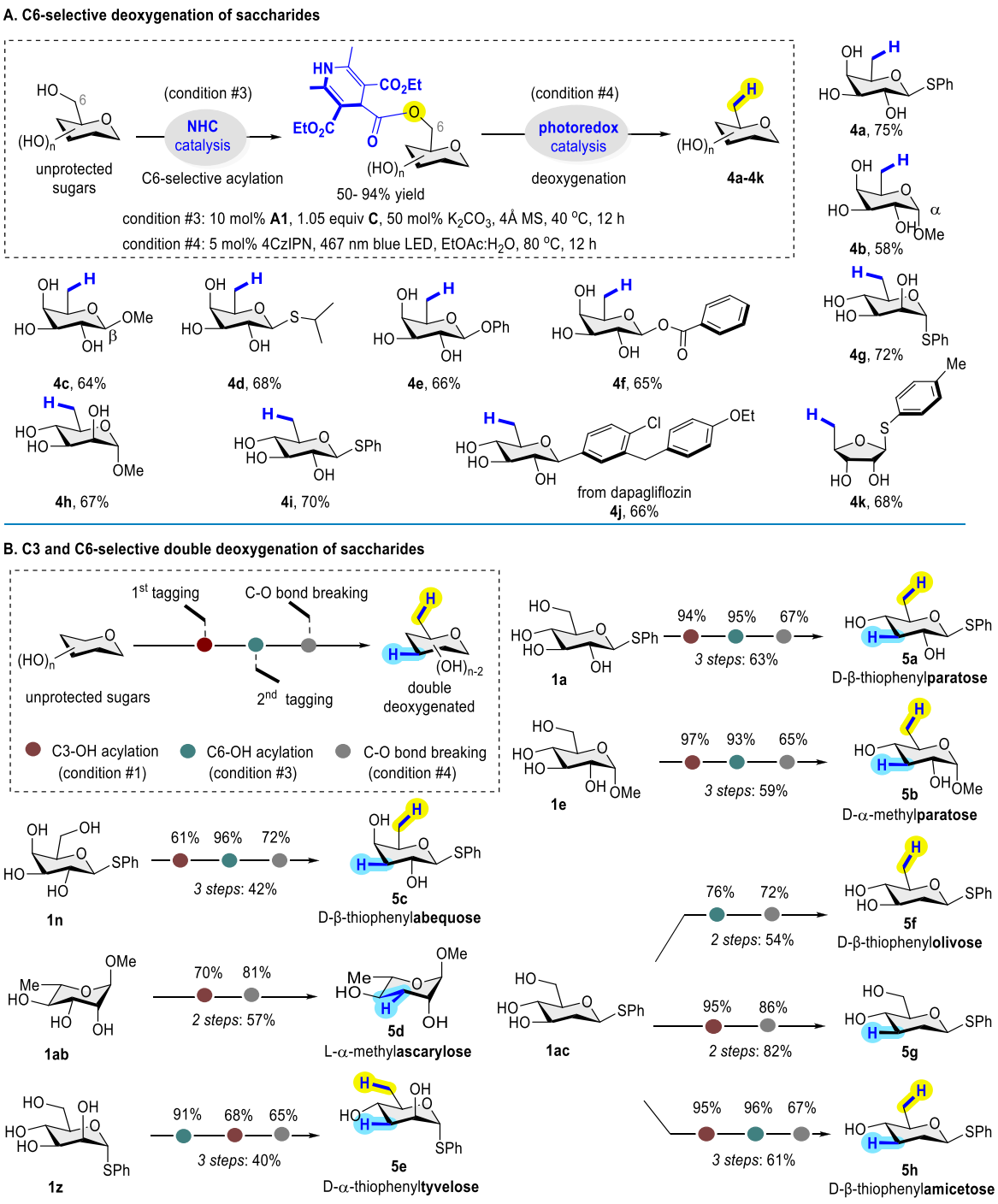

Figure 3. C6- and C6, C3-selective (double) deoxygenation of saccharides.

in air and silica gel and can be stored at room temperature over extended durations. Subsequently, the acylated sugars (e.g., **2a**) could undergo photomediated C−O bond cleavage under the influence of light and photocatalyst to give a carbon-centered alkyl radical intermediate that then engaged in hydrogen atom uptake (e.g., hydrogen atom transfer from adamantanethiol[51] (Ad-SH, Figure 2A) to give deoxygenated sugar derivative **3a** in 86% yield.

Reaction Scope. The substrate scope of C3-deoxygenation was then evaluated. Various functional groups attached to the saccharide anomeric carbon (via heteroatoms or carbon atoms) in both α and β configurations were well tolerated (**3a**−**3p**), allowing efficient deoxygenated transformation of various monosaccharides (**3a**−**3g**); saccharide-containing natural products (such as tecomin **3h**, salicin **3i**, and geniposide **3j**); and saccharide-derived bioactive molecules such as type-II diabetes medicines (**3k**−**3m**). It is noteworthy that, in comparison to the previous six-step linear synthesis method, we have significantly streamlined the synthetic pathway for deoxysugar **3a** here, achieving it in just two steps.[52] Moreover, the preparation of deoxygenated medicine derivatives such as C3-deoxygenated dapagliflozin required lengthy steps with low overall yields (nine steps with 29% overall yield) using previous methods.[53] In contrast, our approach involves only two steps, with 80% overall yield. It is worth highlighting that our photocatalytic deoxygenated

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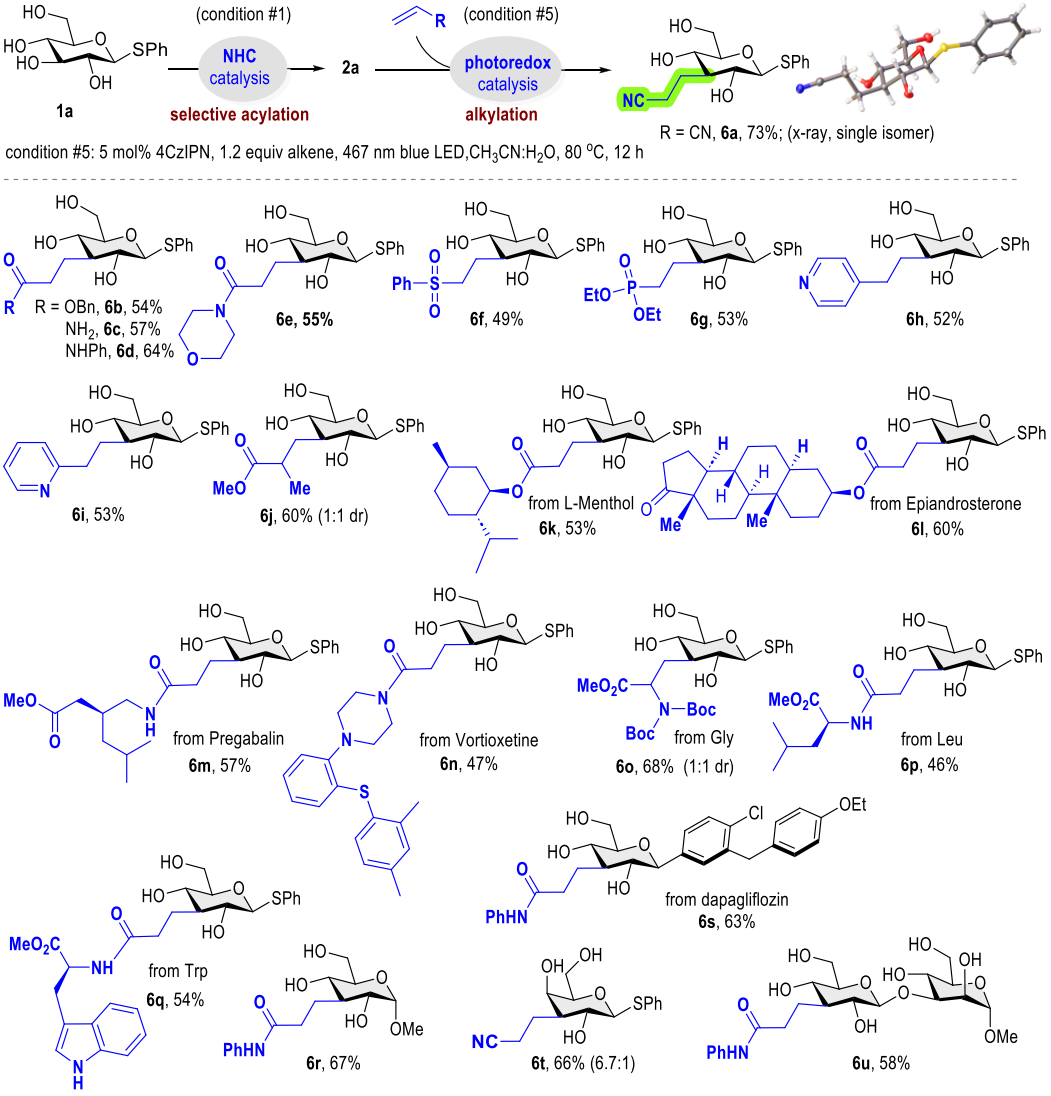

Figure 4. C3-selective C-alkylation of saccharides.

hydrogenation protocol operates under mild conditions and is compatible with a variety of functional groups that are typically not compatible with previous methods. In particular, ester groups play a crucial role in carbohydrate chemistry due to their extensive applications. However, this functional group often proves incompatible with traditional reduction methods that rely on metal hydride reagents. Apart from glucose, our method can also tolerate other saccharides with differing stereochemistry, such as galactose and mannose, allowing for the preparation of the corresponding deoxygenated saccharides (e.g., **3n**−**3p**). These deoxygenated saccharides obtained from commercially available and abundant sources are valuable building blocks to prepare various functional molecules. For example, deoxygenated sugar **3p** prepared from mannose can serve as a building block for the synthesis of calystegine A7, a natural product isolated from root of *Lycium chinense* acting as a competitive inhibitor against trehalase.[54] Remarkably, our strategy offers outstanding outcomes in the site-selective deoxygenation of disaccharides with relatively complex structures (e.g., **3q**−**3t**). These encouraging results underscore the potential application of our approach in the challenging domain of controlled site-selective editing of oligosaccharides and glycans. Encouragingly, when deuterium oxide (D_2O) was used to replace H_2O as the cosolvent during the photoredox deoxygenation step (see Supporting Information for details), the deuterium isotope can be effectively introduced onto the C3-carbon of the respective sugar substrates (e.g., **(D)-3a**, **(D)-3e**, **(D)-3l**, and **(D)-3t**). Deuterium-labeled sugars act as versatile probes for studying various biological processes such as metabolism and biosynthetic pathways.[35,55] These deuterium-labeled deoxygenated sugars also serve as building blocks to prepare other bioactive molecules containing deuterium isotopes.[56]

Our modular twofold "tagging−editing" strategy can also be employed for the targeted manipulation of the C−O bond at the C6 position of saccharides in a site-selective manner. Similarly, under condition #3 in Figure 3A, we first successfully tagged the C6-OH of a series of saccharides with photoredox-active ester **C**. Most of these tagging reactions proceed smoothly with excellent site selectivity and high yields (Supplementary Figure 5). To our mild surprise, the subsequent "editing" step involving these C6-OH-acylated saccharides, which targeted C−O cleavage, was well accommodated by our photocatalytic deoxygenation reaction. It is generally considered that primary alcohols exhibit reduced reactivity in C−O radical homolysis transformations.[57] Under

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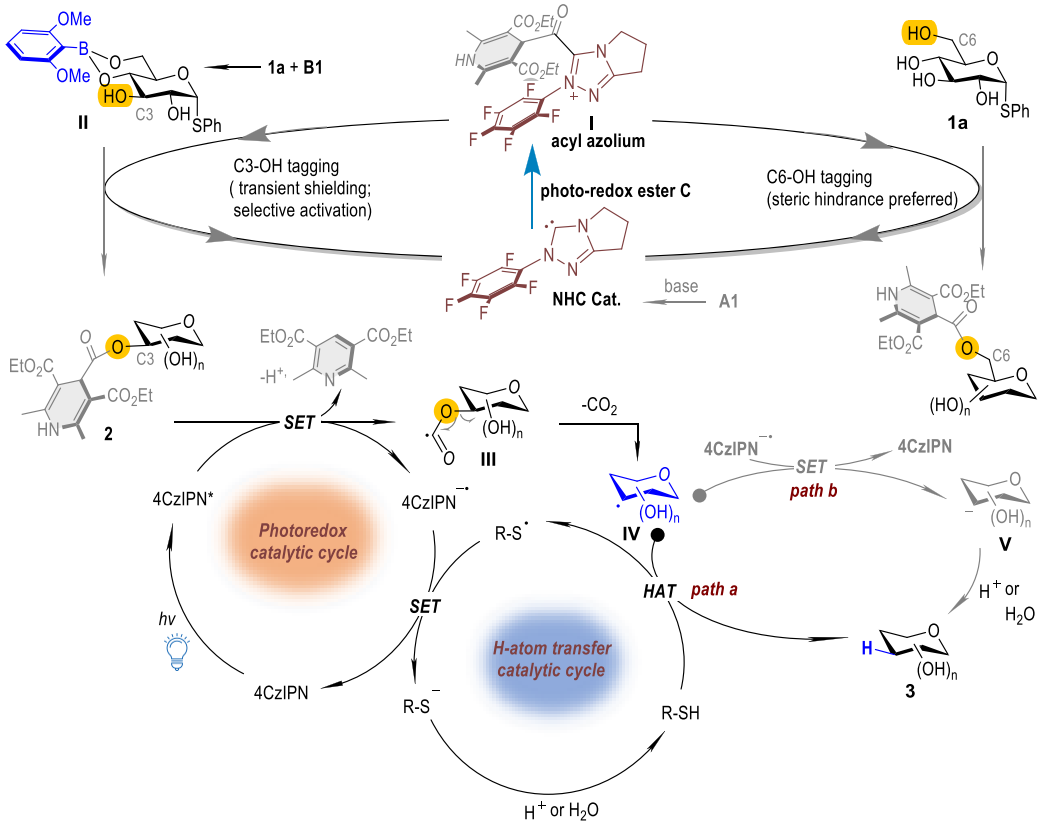

Figure 5. Postulated reaction pathways for site-selective deoxygenation of saccharides (see Supplementary Figure 6 for pathways of alkylation).

a slightly modified deoxygenated condition (condition 4 in Figure 3A), various representative saccharides and their derivatives were successfully transformed into their C6-deoxygenated forms. Unprotected furanoses also serve as suitable substrates and can be efficiently converted into C5-deoxysugars with good selectivity and yields, as exemplified by compound **4k**. We observed that a slightly elevated temperature promoted the reaction, and the use of a hydrogen atom transfer (HAT) cocatalyst was not required in these cases.

Having successfully accomplished the synthesis of C3 and C6-deoxygenated saccharides using our site-divergent "tagging−editing" strategy, we shifted our focus toward addressing the preparation of challenging di- or trideoxysugars (where multiple hydroxyl groups are substituted with hydrogen atoms). In comparison to monodeoxysugars, di- or trideoxysugars possess more intricate structures arising from variations in deoxygenation positions and stereochemistry. Current strategies to such sugar structures remain significantly backward and are often labor-intensive and time-consuming.[24,58] Building upon the results described above, we have extended and refined a procedural dehydrogenation strategy termed "tagging−tagging−editing" aimed at streamlining this complex process. Promisingly, a diverse array of monosaccharides, encompassing glucose, mannose, galactose, and rhamnose, exhibited seamless conversion into their respective dideoxy sugar derivatives **5a**−**5e**. Additionally, easily available 2-deoxysugar building block **1ac** was also a proper substrate, allowing efficient preparation of 2,6-dideoxy sugar olivose **5f**, 2,3-dideoxy sugar **5g**, and 2,3,6-trideoxysugar amicetose **5h**.

Building carbon−carbon bonds is a fundamental operation in drug investigation and the modification of bioactive molecules, allowing for significant increases in the molecular complexity and alterations in the physicochemical and biological activities of parent molecules. Within this context, we envisioned the sugar radical intermediate produced by photocatalyzed C−O bond cleavage can be trapped by proper alkenes, thereby yielding unnatural C-glycosides though C−C forming reaction (Figure 4). After careful exploration of reaction conditions (see Supporting Information for details), C3-OH-tagged sugar adduct **2a** was found to react with acrylonitrile under photochemical conditions to afford C3-deoxyalkylated glycoside **6a** in 73% yield with excellent stereoselectivities (only the equatorial isomer was observed; the configuration was confirmed by X-ray, CCDC number: 2287546). Using acylated glucose **2a** as a model saccharide substrate, a diverse range of alkenes were examined under optimal reaction conditions. Various functional groups including carboxylic ester, amide (primary, secondary, and tertiary), sulfone, cyano, phosphates, and pyridine were well tolerated, allowing efficient stereoselective C−C forming reactions with **2a** to give the corresponding C-glycosides (**6a**−**6j**). Moreover, alkenes containing intricate enantioenriched bioactive compounds such as L-menthol and epiandrosterone or pharmaceutical agents such as pregabalin and vortioxetine can also be seamlessly tethered to the saccharide substrates using our photocatalytic protocol (**6k**−**6n**). It is worth highlighting that under our optimal reaction conditions amino acids can be attached to the C3 position of sugars and provide the corresponding unnatural glycosyl amino acids in moderate to good yield (**6o**−**6q**). D-α-Methylglucose and drug molecule dapagliflozin were also examined as suitable substrates (**6r** and **6s**). When using D-β-thiophenylgalactose to react with acrylonitrile, C3-deoxyalkylated glycoside **6t** was formed in 66% yield with 6.7:1 equatorial/axial selectivity

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(isomer assignment was determined by NMR; see Supporting Information for details). To our delight, the disaccharide also tolerated the reaction conditions, yielding C3-deoxyalkylated glycoside **6u** in 58% yield.

Mechanistic Investigations. The principal reaction pathways and specific mechanistic details implicated in this study are depicted in Figure 5. The nucleophilic NHC catalyst generated in situ via deprotonation from NHC precatalyst **A1** undergoes attack on photoredox active ester **C**, affording the NHC-bound acyl azolium intermediate **I**. We posit that the pronounced electron-deficient nature of the carbonyl carbon center, in conjunction with substantial steric hindrance, confers a distinct advantage upon this intermediate for the purpose of selective acylation. According to our earlier studies,[41] boric acid as an additive has demonstrated the capacity to engage in reversible complexation and dissociation processes with unprotected saccharides (e.g., **1a** and boronic acid **B1** to form intermediate **II**). This facilitates the transient shielding of hydroxyl groups at nonreactive sites on the sugar substrate, along with a somewhat enigmatic augmentation of reactivity at the desired reaction sites. Intermediate **II** can undergo a selective acylation reaction with acyl azolium intermediate **I**, and the C3-OH-tagged product can be obtained after workup. In the absence of boronic acid, intermediate **I** preferentially acylates C6-OH on the saccharides, and this initial reactivity preference is largely dominated by steric hindrance. During the photocatalyzed deoxygenation transformation of the saccharides, the photocatalyst 4CzIPN is initially photoexcited to the excited state 4CzIPN* ($^*E_{red}$ = +1.35 V versus SCE). Acylated saccharides **2** (e.g., **2a**: E_{ox} = +1.32 V versus SCE) is oxidized by this highly reactive species, converting to the radical intermediate **III** after undergoing deprotonation and removal of aromatized pyridine byproducts. This carbon-centered radical undergoes rapid β-scission, generating deoxygenated sugar radical **IV** with the release of one molecule of CO_2. Importantly, the formation of CO_2 possessing a robust C═O double bond provides a ubiquitous thermodynamic driving force for alcohol C−O bond homolysis. The resulting sugar radical **IV** provides the deoxygenated product **3** by favorable HAT from adamantanethiol (S−H BDE = 87 kcal mol^{-1}) (path a). Finally, single-electron transfer occurs between the thiol radical and $4CzIPN^{\bullet-}$, followed by protonation to regenerate the thiol, together with the ground-state photocatalyst. Another parallel route involves the direct reduction of sugar radical **IV** by $4CzIPN^{\bullet-}$ into carbon anion intermediate **V**, followed by protonation to effectuate the transformation into the desired product (path b). This aligns with the reaction outcomes we have observed, wherein the addition of thiol cocatalysts is dispensable for certain deoxygenation reactions. The reaction mechanism for obtaining the deoxygenated alkylated product **6** can be found in Supplementary Figure 6. It is noteworthy that, although the chemical selectivity in the "tagging" step of this study depends on stoichiometric boric acid or substrate control, the advancement of catalytic systems with site-selective functionality, especially those achieving controlled site selectivity through a single catalyst, is essential for the challenging site editing of complex polyol molecules and the broadest application of our methodologies in the future.

CONCLUSIONS

In summary, we have developed a "tagging−editing" strategy that is modular and highly practical for the site-selective C−O bond editing of a wide range of unprotected saccharides and saccharide-containing molecules. Our approach enables the efficient creation of C3- and C6-selective deoxygenated saccharides, as well as double-deoxygenated saccharides with hydroxyl groups removed from both C3 and C6 carbons. Additionally, we can synthesize alkylated saccharides with new carbon−carbon bonds formed at the saccharide C3 position. Our method expedites the production of valuable rare sugar building blocks and simplifies the deoxygenated modification of glycosidic pharmaceuticals and glycosylated natural products, providing a direct and effective means of achieving these modifications. It is poised to play a pivotal role in various disciplines related to saccharides, including sugar-related drug screening and structure−activity relationship studies for medical and other biological applications. Furthermore, our approach should prove to be advantageous in the synthesis of a diverse array of structurally intricate natural products and active molecules containing uncommon sugar motifs. We anticipate that further development encouraged by this study will lead to valuable chemical synthesis or modification strategies for other complex molecules involving sophisticated site-selectivity challenges and will benefit multiple fields beyond chemistry.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c10963.

Full experimental details for the preparation of all new compounds and their spectroscopic and chromatographic data (PDF)

Accession Codes

CCDC 2287546 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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