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Synthetic Methods

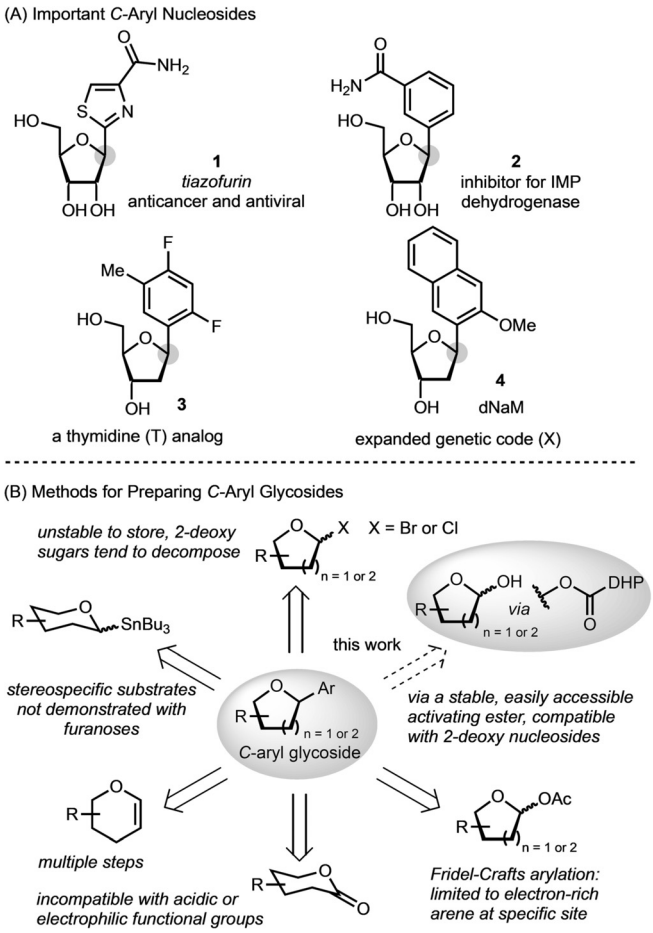
Diastereoselective Synthesis of Aryl *C*-Glycosides from Glycosyl Esters via C–O Bond Homolysis

*Yongliang Wei, Benjamin Ben-zvi, and Tianning Diao**

Abstract: *C-aryl glycosyl compounds offer better in vivo stability relative to O- and N-glycoside analogues. C-aryl glycosides are extensively investigated as drug candidates and applied to chemical biology studies. Previously, C-aryl glycosides were derived from lactones, glycals, glycosyl stannanes, and halides, via methods displaying various limitations with respect to the scope, functional-group compatibility, and practicality. Challenges remain in the synthesis of C-aryl nucleosides and 2-deoxysugars from easily accessible carbohydrate precursors. Herein, we report a cross-coupling method to prepare C-aryl and heteroaryl glycosides, including nucleosides and 2-deoxysugars, from glycosyl esters and bromoarenes. Activation of the carbohydrate substrates leverages dihydropyridine (DHP) as an activating group followed by decarboxylation to generate a glycosyl radical via C–O bond homolysis. This strategy represents a new means to activate alcohols as a cross-coupling partner. The convenient preparation of glycosyl esters and their stability exemplifies the potential of this method in medicinal chemistry.*

C-aryl glycosyl compounds are prevalent drug candidates, since the *C*-glycosidic linkage confers in vivo stability through resistance to hydrolysis and enzymatic degradation.[1] *C*-aryl nucleosides, such as tiazofurin **1**,[2] are prototypical antiviral compounds as they can be recognized by cellular or viral polymerases,[3] while modifications to their structure lead to disruption and/or termination of replication.[4] *C*-aryl nucleosides, including **1**[5] and benzamide *C*-ribose **2**,[6] show antiproliferative activity (Scheme 1 A). Moreover, synthetic *C*-aryl nucleoside analogues, including **3**, are essential to studying the origins of mutagenicity and understanding the mechanism of replication and evolution.[7] Expanded genetic codes, including dNaM (X) **4**, provide a platform for creating therapeutic proteins.[8] Since nucleosides have high solubility, cell permeability, and in vivo stability, replacing nucleobases with organic fluorophores creates fluorescent tags that can be readily assembled on a DNA synthesizer and applied to bioimaging.[9]

Efficient and sustainable synthesis of *C*-aryl glycosides would facilitate drug discovery and chemical biology studies (Scheme 1 B).[10] Current methods exhibit various limitations. The Friedel–Crafts type glycosylation of electron-rich arenes offers a simple synthetic solution, but lacks the general regiochemical control on the arene.[11] The nucleophilic addition of aryllithium reagents to lactones precludes many electrophilic and acidic functional groups.[12] Arylation of glycals via the Heck reaction entails multiple steps from the native sugars.[13] Stereospecific cross-coupling of glycosyl stannanes provides excellent stereocontrol, but requires pre-generation of the tin reagents with defined stereochemistry and has not been applied to furanosides.[14] Cross-coupling of glycosyl halides with organometalloarenes,[15] aromatic nucleophiles,[16] or aromatic electrophiles[17] achieved success with a range of carbohydrates, but 2-deoxy sugar substrates, especially 2-deoxyriboses, are susceptible to decomposition, due to the rapid elimination of glycosyl chlorides and bromides to form glycals.[18] Thus, many glycosyl halides often require in situ generation.[19] The Diels–Alder reaction



Scheme 1. A) Selected *C*-aryl nucleosides with medicinal and chemical biology significance and B) synthetic strategies.

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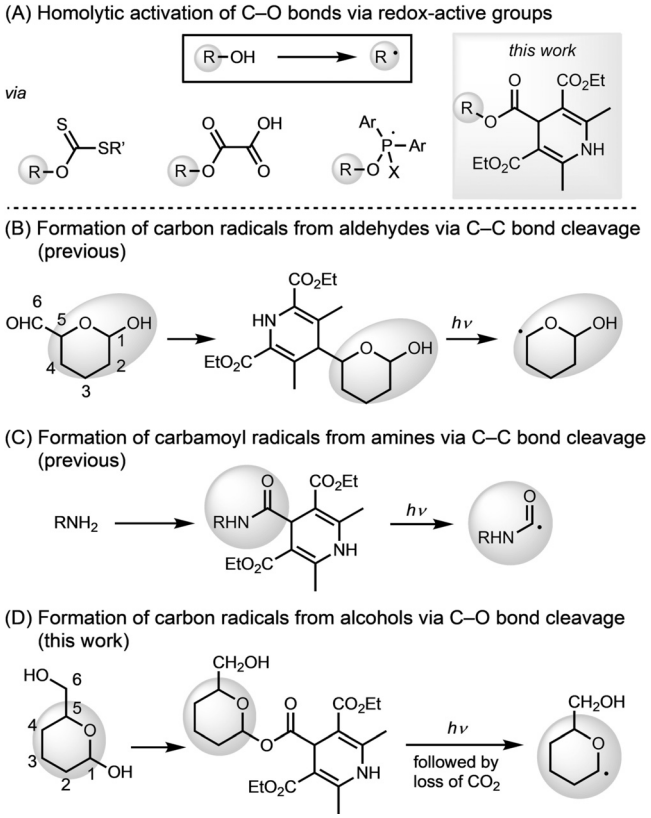
is useful for preparing pyranoses, but cannot be applied to furanosides.[20] A photoredox decarboxylation reaction leverages an unnatural tetrahydrofuran derivative with a carboxylic acid group at the C1 position, and therefore lacks a general scope of sugar substrates.[21] Other photoredox coupling reactions based on redox auxiliaries serve as an excellent approach to non-classical C4 or C5-substituted sugars, but do not offer substitution at the anomeric position.[22]

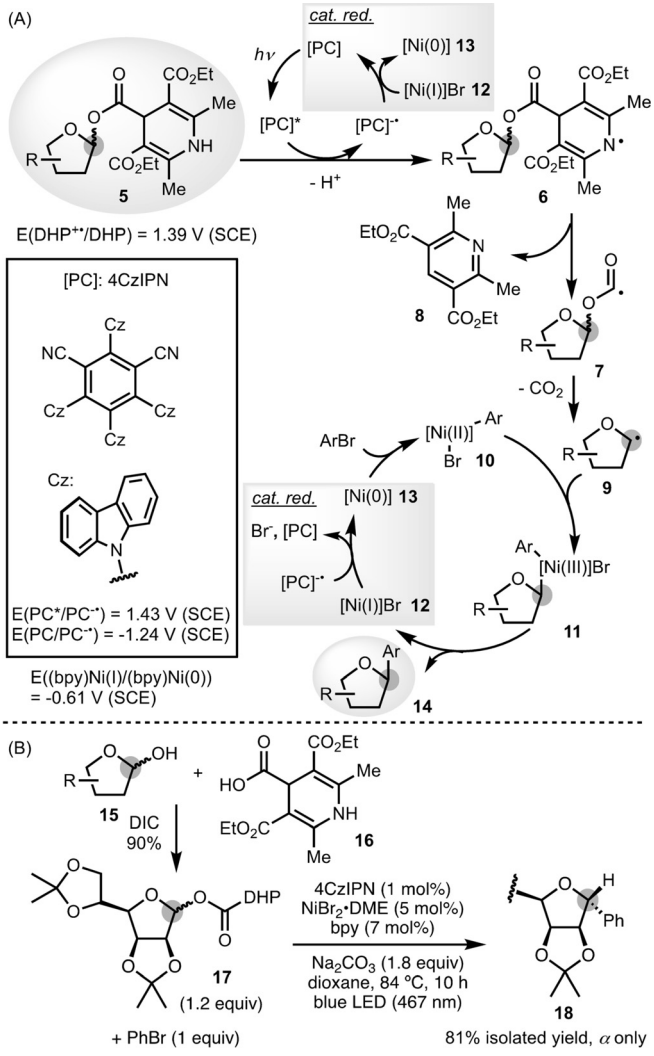
Glycosyl esters represent the ideal precursor to *C*-glycosides. Herein, we describe a method to synthesize *C*-aryl and heteroaryl glycosides, including β-nucleosides and 2-deoxysugars, via the cross-coupling of a redox-active glycosyl ester with aryl and heteroaryl bromides. Upon photoredox activation and electron transfer, the anomeric C–O bond undergoes homolysis and generates a glycosyl radical intermediate. Convenient access to the glycosyl ester and its stability exemplifies the potential of this method in medicinal chemistry.

Redox auxiliaries can transform hydroxyl groups into viable leaving groups via C–O bond homolysis to form radical intermediates (Scheme 2A). Typical auxiliaries include xanthates,[23] phosphites,[24] and oxalates[25] activated through electron transfer or light irradiation (Scheme 2A). These methods, however, have not been applied to glycosylation, possibly due to the instability of the corresponding glycosyl esters.[26] Dihydropyridine (DHP) has emerged as a versatile activating group to produce carbon radicals and carbamoyl radicals, from aldehydes and amines, respectively, via C–C bond homolysis (Schemes 2B and C).[27] The former has been applied to synthesize unconventional glycosides via C–C bond cleavage at the C4 or C5 position (Scheme 2B).[20] We hypothesize that DHP-mediated radical formation could be combined with subsequent decarboxylation of an alkoxycarbonyl radical to activate the anomeric C–O bond (Scheme 2D). This mechanism represents a new strategy for homolytic activation of hydroxyl groups and formation of radicals.

We envision that ester **5** is readily available from the condensation of carbohydrates to DHP carboxylic acid (Scheme 3A). Oxidation of **5** by an excited photosensitizer (PC*), followed by deprotonation, can afford radical **6**.[25c] Subsequent fragmentation is driven by the formation of Hantzsch pyridine **8** and generates an alkoxycarbonyl radical **7**. Upon ejection of CO_2, **7** can be transformed to glycosyl radical **9**,[28] which enters the catalytic cycle mediated by nickel and cross-couples with aryl bromides. Coordination of **9** to Ni^{II} **10** affords Ni^{III} **11**, followed by reductive elimination to give *C*-aryl glycoside **14**. The resulting Ni^{I} **12** is readily reduced to Ni^{0} by $[PC]^{-\bullet}$.[29] The initial formation of Ni^{0} **13**



Scheme 2. Comparison of radical-formation strategies based on photoredox activation of DHP.



Scheme 3. A) Proposed mechanism for *C*-aryl glycosylation based on dihydropyridine (DHP) derived esters and B) optimized conditions.

from a Ni^{II} precatalyst may be accomplished by reduction with $[PC]^{-\bullet}$, as well.

Catalyst development focused on bis-acetonide protected D-mannofuranose as a model substrate (Scheme 3B). A DHP auxiliary **16** is readily available by the condensation of aminocrotonate with glyoxylic acid.[30] Coupling DHP acid **16** with the bis-acetonide protected D-mannofuranose **15** afforded *O*-mannofuranosyl ester **17** in 90% yield. We applied a modified variant of the photoredox-nickel dual catalytic condition for carbamoyl radical generation to couple **17** with PhBr, using 4CzIPN as the photosensitizer,[25c,31] $NiBr_2$·DME (DME = 1,2-dimethoxyethane) as the catalyst,[32] and bipyridine (bpy) as the ligand. The desired *C*-phenyl-1-deoxy D-mannofuranose **18** was obtained in 81% isolated yield under blue light (467 nm) irradiation at 84 °C, a temperature required to facilitate DHP fragmentation and the subsequent decarboxylation. A lower temperature led to the formation of an ester byproduct, derived from the coupling of **7** to PhBr. Slight excess of **17** ensures a high yield of **18**; Using equal molarity of **17** and PhBr gave **18** in 74% yield. The α and β anomers of **17** were separately subjected to the conditions, and both transformed to **18** in comparable yields and high α-selectivity. The stereochemistry was assigned based on NOESY, COSY, and HSQC experiments and compared with literature reports.

We applied the optimized conditions to couple *O*-mannofuranosyl ester **17** with a range of aryl bromides (Table 1). Due to fluctuations caused by light irradiation, we recorded the actual temperature of the oil bath for each reaction. In general, electron-deficient aryl bromides gave excellent yields of the corresponding *C*-glycosyl arenes (**19**–**23, 27**–**29**). Performing the synthesis of **17** on a 1.94-gram-scale afforded **21** in 82% isolated yield. Electron-rich electrophiles, including *para*-methyl and *para*-methoxy phenyl bromides also gave good to excellent yields (**24**, **25**). *Para*-dimethylaminophenyl bromide, however, is unsuccessful in generating **26**. Coupling of **17** with heterocycles, including thiophene with electron-withdrawing substituents, pyrimidine, and pyridines, proceeded to afford the corresponding *C*-heteroaryl glycosides (**32**–**37**) in modest yields. All reactions favor formation of the α-anomer, since the concave β-face is sterically protected by C2, C3, and C4 substituents. The limitation with some electron-rich arenes (**26**) and heterocycles, such as furan and pyrrole (**28** and **29**), could be attributed to the incompatibility of these easily oxidizable substrates with the excited photocatalyst.

We explored the scope of furanoses with various protecting groups.[33] D-Ribofuranoses containing common protecting groups, such as benzyl, silyl, and benzoyl, underwent smooth *C*-arylation, forming **38**–**40** with excellent selectivity for the β-anomer. Immediate application features the synthesis of nucleoside analogues **41**–**44**, precursors to pharmaceuticals **1**, **2** and unnatural nucleosides **3**, **4**. The low yield of **42** may be attributed to the decomposition of thiazole at the elevated temperature.

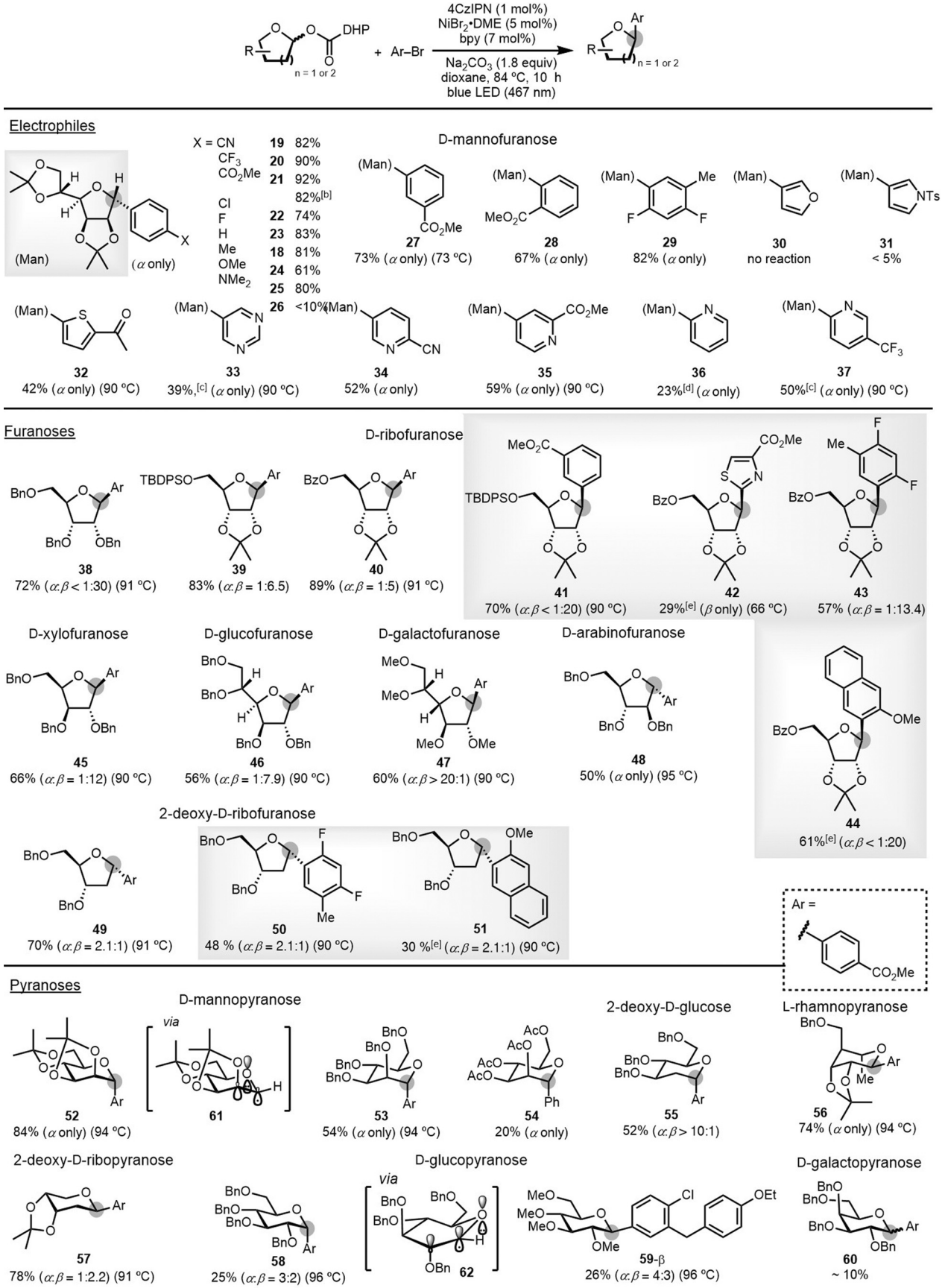
D-Xylofuranose and D-glucofuranose underwent β-arylation to afford **45**, **46**. The stereoselectivity was altered to favor the α-anomer for D-galactofuranose **47** and D-arabinofuranose **48**, reflecting a dominating effect of the C2 substituent on the stereochemical outcome. Arylation of the benzyl protected 2-deoxy-D-ribose generated a mixture of α and β anomers of **49**–**51** in a ratio of 2.1:1, presumably due to the lack of steric strains to distinguish the β face from the α face. β-2-deoxyriboses **50**, **51** are unnatural nucleoside analogues crucial to chemical biology studies. Although the yields for β-**50** and β-**51** are low, the overall efficiency could still compete with previous multiple-step syntheses based on the Heck reaction and addition of lithium reagents to lactones.[7a] An alternative approach to **50**, **51** involves the preparation of their β-*C*-aryl ribose analogues through this cross-coupling reaction, followed by reduction of the 2-hydroxyl group.[34]

A variety of pyranoses, including D-mannopyranose, 2-deoxy-D-glucopyranose, L-rhamnopyranose, and 2-deoxy-D-ribopyranose, proceeded to form *C*-aryl glycosides **52**–**58** under the standard conditions. Acetyl protected D-mannopyranose gave a low yield of **52**, due to facile β-elimination to afford glycals as the by-product. The observed α-selectivity can be attributed to the kinetic anomeric effect.[35,36] The mannopyranosyl radical intermediate adapts a chair-like conformation **61**,[37] stabilized by the hyperconjugation of the nonbonding orbital of the ring oxygen, the radical orbital (SOMO), and the σ^* orbital of the adjacent C2–O bond. The attack of the nickel intermediate to the mannopyranosyl radical favors the axial direction because the transition state can be stabilized by the donation of the nonbonding electron pairs on the ring oxygen to the antibonding orbital (σ^{*+}) of the newly formed C1-Ni σ-bond. In addition, the approach of nickel from the α-face avoids the steric hindrance in the β-face created by the C2-substituent. Benzyl and methyl-protected glucopyranoses display poor reactivity to afford glucopyranosides **58**, **59** in low yields and as a mixture of α and β-anomers. Product **57** is a precursor to dapagliflozin, a treatment for type II diabetes.[38] The glucopyranosyl radical intermediate prefers to accommodate a boat conformer **62**.[30] The poor selectivity can be attributed to the contradictory preferences by the steric and the stereoelectronic effect. The steric hindrance at C2 favors the β-attack, whereas the transition state for the α-attack can be stabilized by the kinetic anomeric effect. For a similar reason, D-galactopyranose **60** also displayed unsatisfactory yield and selectivity.

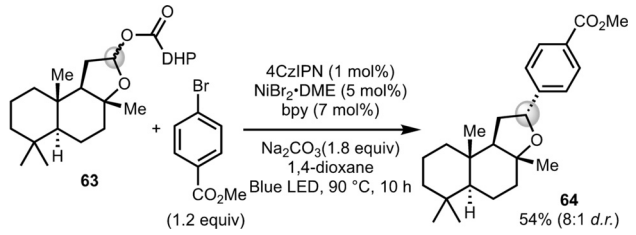
The generality of this deoxygenative coupling method implies applications in complex molecule synthesis via late-state functionalization. We applied the method to derivatizing natural product (+)-sclareolide (Scheme 4). DHP ester **63** underwent cross-coupling with *para*-bromobenzoate to afford **64** in 54% yield and 8:1 *d.r.*

In summary, we prepared *C*-aryl and heteroaryl glycosides through the cross-coupling of a redox-active glycosyl ester. Upon light-induced electron-transfer of DHP, the glycosyl ester can fragmentize and eject CO_2 to generate a glycosyl radical, which cross-couples with aryl and heteroaryl bromides in the presence of nickel catalysts. The innovation centers at the combination of DHP with decarboxylation as a new means to induce C–O bond homolysis and form radicals. This method overcomes several limitations in existing glycosylation reactions for preparing furanoses and pyranoses. The reaction is particularly useful in synthesizing unnatural β-nucleosides, due to the accessibility, stability and

Table 1: Scope of C-aryl glycosylation with DHP-derived glycosyl esters.[a]



[a] Isolated yields. Reaction conditions: ArBr, 0.20 mmol; glycosyl ester, 0.24 mmol (1.2 equiv). [b] Reaction performed with 1.94 grams of **17**. [c] 2,2′-Bipyridine-4,4′-dicarboxylic acid as the ligand. [d] $NiBr_2$·DME (10 mol%), bpy (14 mol%). [e] 4,4′-Dimethoxy-2,2′-bipyridine as the ligand.



Scheme 4. Derivatization of (+)-sclareolide from deoxygenative cross-coupling.

availability of the glycosyl DHP ester precursor. Limitations remain in the coupling of some easily oxidizable electron-rich arenes and heteroarenes and the conversion of D-glucopyranoses.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: *C*-glycosylation · cross-coupling · glycosyl radicals · nucleoside analogues · photoredox

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