

Radical C-Glycosylation Using Photoexcitable Unprotected Glycosyl Borate

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Abstract: We have developed radical C-glycosylation using photoexcitable unprotected glycosyl borate. The direct excitation of glycosyl borate under visible light irradiation enabled the generation of anomeric radical without any photoredox catalysts. The in situ generated anomeric radical was applicable to the radical addition such as Giese-type addition and Minisci-type reaction to introduce alkyl and heteroaryl groups at the anomeric position. In addition, the radical–radical coupling between the glycosyl borate and acyl imidazolid provided unprotected acyl C-glycosides.

Introduction

Glycosides are universal structures commonly found in various bioactive compounds such as pharmaceuticals. Among them, C-glycosides, which attach to organic moiety called aglycone through carbon–carbon bond at the anomeric carbon, is one of the most attractive glycosides (Figure 1a).^[1] The C-glycosides have high tolerance to hydrolysis by enzymes, and different conformation and biological activities compared to O-glycosides that are abundant in nature.^[2] Therefore, C-glycosides are important synthetic targets for drug development targeting enzymes and proteins that recognize glycosides and sugar chains.^[1b, 2b] Based on this background, various types of glycosyl donors have been developed to establish the methods for access to C-glycosides.^[3] Out of all of them, glycosyl metal compounds such as glycosyl lithium^[4], stannane^[5] and boron^[6] have been used as useful glycosyl donor because of the unique reactivity derived from each metal elements that is applicable for carbon–carbon bond formation at the anomeric position (Figure 1b).

The development of protecting-group-free C-glycosylation using unprotected glycosyl metal compounds is highly required because it would shorten the protection and deprotection process of sugar hydroxyl groups.^[7] However, the C-glycosylation using unprotected glycosyl metals is still limited due to the difficulty in synthesizing and controlling its reactivity. Specifically, Walczak and coworkers developed the use of unprotected glycosyl stannane in palladium-catalyzed cross-coupling reaction.^[5c]

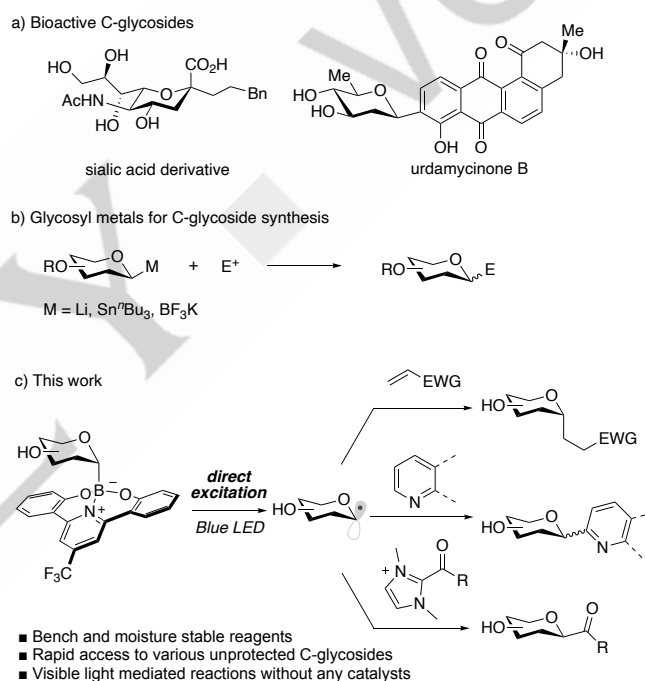


Figure 1. Summary of this work

Earlier, we developed photoexcitable borate that can work as strong reductants ($E_{1/2} = \text{ca. } -2.0 \text{ V vs SCE in MeCN}$).^[8] The borate can be directly excited under visible light irradiation to form a strong single electron donor, and generate an alkyl radical. The borate was prepared by alkyl boronic acid or potassium trifluoroborate with 2,2'-(pyridine-2,6-diyl)diphenol (PDP) as a tridentate ligand, representing highly functional tolerance.^[9] This study has achieved the synthesis and use of unprotected PDP-based glycosyl borate for C-glycosylation (Figure 1c). The direct excitation of glycosyl borate under visible light irradiation enabled the generation of anomeric radical without any photoredox catalysts. The in situ generated anomeric radical was applicable to the radical addition such as Giese-type addition and Minisci-type reaction to introduce C(sp³) and C(sp²) groups at the anomeric position. In addition, the radical–radical coupling

between the glycosyl borate and acyl imidazolide proceeded to obtain unprotected acyl C-glycosides that have never directly synthesized from unprotected glycosyl donor.

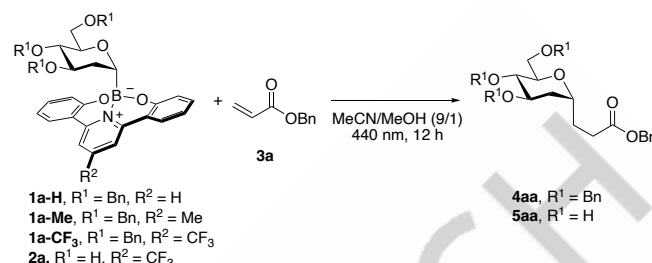
Results and Discussion

Initially, we investigated the reaction conditions for Giese-type reaction using benzyl-protected glycosyl borate **1a** (Table 1). The glycosyl borate **1a** was synthesized from glycosyl potassium trifluoroborate and PDP.^[10] We found the suitable reaction conditions that afforded C-glycoside **4aa** in 10% NMR yield using **1a-H**, benzyl acrylate (**3a**) in 9:1 mixture (100 mM) of acetonitrile and methanol under visible light irradiation (440 nm) (entry 1). The NMR analysis confirmed complete α -selectivity. Next, the structural modification of the 2,2'-(pyridine-2,6-diyl)diphenol skeleton was conducted. The introduction of methyl group exhibited comparable reactivity (entry 2). On the other hand, trifluoromethyl group-installed borate **1a-CF₃** showed higher yield (entry 3). After screenings of concentration of the reaction, the low concentration conditions (2.8 mM) significantly increased the product yield (entry 4).

Next, we examined the reaction using unprotected glycosyl borate **2a** bearing trifluoromethyl group and benzyl acrylate **3a** (Table 1, entry 5). Under the blue LED irradiation, the reaction afforded the desired alkyl C-glycoside **5aa** in 73% isolated yield (97% NMR yield) and complete α -selectivity. The glycosyl borate **2a** could be stored under dark at room temperature for more than 6 months. Koh, Niu and Hirai reported Giese-type C-glycosylation

to afford alkyl C-glycosides.^[7a, 7b, 7e, 11] However, the use of unprotected glycosyl boron is underdeveloped.

Table 1. Optimization of the reaction conditions for Giese-type reaction using several glycosyl borates.^[a]



entry	glycosyl borate	concentration (mM)	yields (%)
1	1a-H	100	10
2	1a-Me	100	10
3	1a-CF₃	100	27
4	1a-CF₃	2.8	94 (90) ^[b]
5	2a	2.8	97 (73) ^[b]

[a] Reaction was carried out with glycosyl borate (0.08 mmol), benzyl acrylate **3a** (0.05 mmol) in 9:1 mixture of acetonitrile and methanol under 440 nm (Kessil lamp) irradiation for 12 h. [b] Isolated yield.

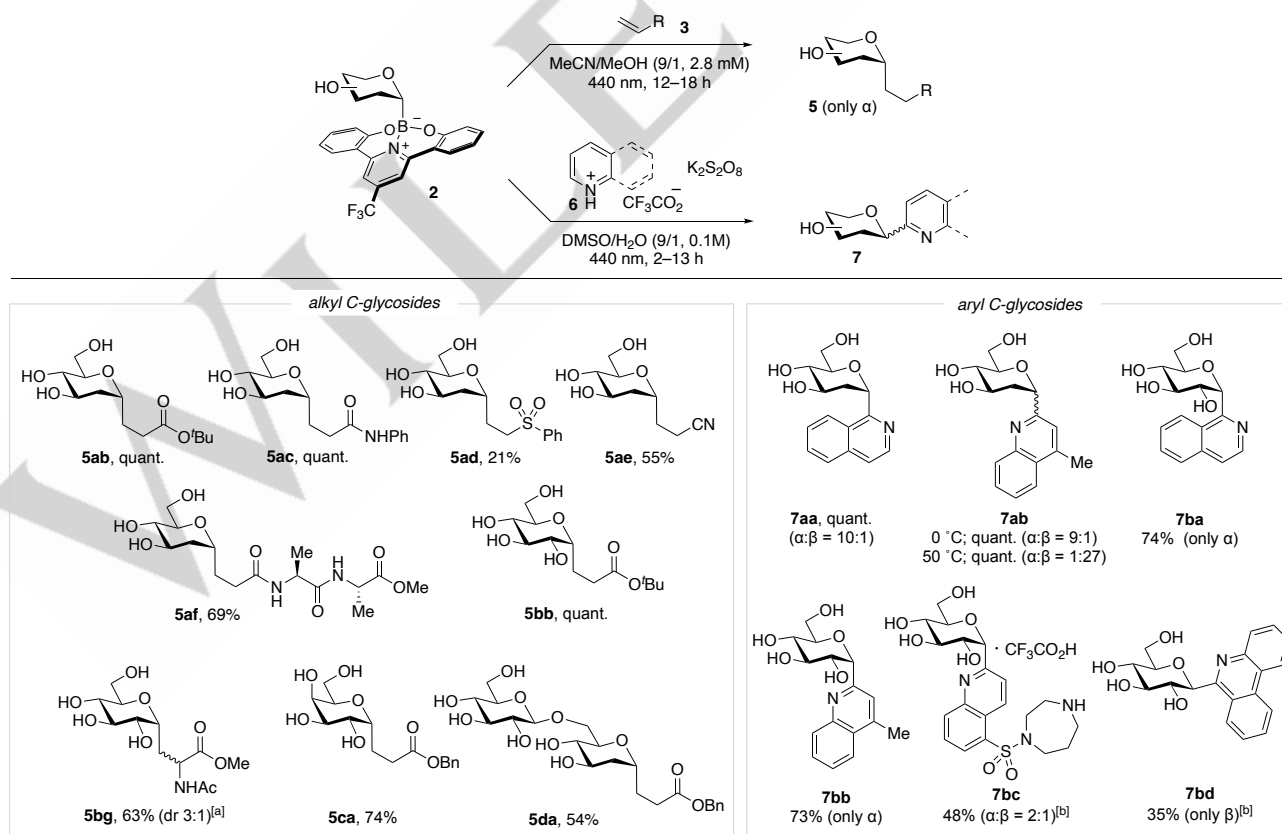


Figure 2. Substrate Scope. [a] **5bg** was purified after acetyl protection of hydroxy groups. [b] This reaction was conducted at 50 °C.

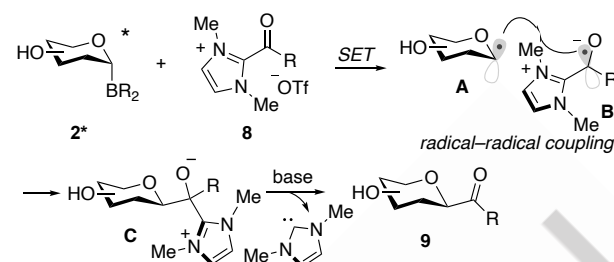
With the optimized reaction conditions in hand, the scope of Giese-type C-glycosylation using unprotected glycosyl borates was evaluated (Figure 2, left). Electron-deficient alkenes such as *tert*-butyl acrylate (**3b**), acrylamide (**3c**), phenyl vinyl sulfone (**3d**) and acrylonitrile (**3e**) underwent the reaction to afford desired alkyl C-glycosides in good yields and complete α -selectivity (**5ab–5ae**). When electron-deficient alkene containing in peptide was used as a substrate, the corresponding product was obtained in 69% yield (**5af**). Our protocol was applicable to glycosyl borate **2b** derived from glucose bearing hydroxyl group at C2 position. The addition to **3b** proceeded in excellent yield (**5bb**). The reaction using glycosyl borate **2b** and dehydroalanine afforded **5bg** in 63% yield and 3:1 diastereoselectivity. Galactose that has opposite conformation of hydroxyl group at C4 position could be applicable to our method (**5ca**). Furthermore, glycosyl borate **2d** derived from disaccharide was applicable to this reaction to obtain **5da** in 54% yield.

The Minisci-type reaction using unprotected photoexcitable glycosyl borate to produce aryl C-glycoside was examined (Figure 2, right).^[7d, 12] The reaction between glycosyl borate **2a** and isoquinoline with potassium persulfate in 9:1 mixture (100 mM) of dimethyl sulfoxide and water under visible light irradiation (440 nm) gave the desired product **7aa** in quantitative yield and high α selectivity ($\alpha:\beta = 10:1$). 4-Methylquinoline (**6b**) was a suitable substrate. The stereoselectivity depended on the reaction temperature (0 °C, $\alpha:\beta = 9:1$; 50 °C, $\alpha:\beta = 1:27$). The glycosyl borate **2b** bearing hydroxyl group at C2 position was also applicable to this reaction and gave the corresponding aryl C-glycoside **7ba** in 74 % yield and complete α selectivity. Moreover, glycosyl borate **2b** and **6b** participated to the reaction to obtain **7bb** in complete α selectivity. The α selectivity was confirmed by X-ray crystal structure analysis.^[13] Fasudil (**6c**) was also applicable to this reaction and gave the corresponding aryl C-glycoside **7bc** in 48 % yield and α selectivity ($\alpha:\beta = 2:1$). The radical acceptor such as phenanthridine (**6d**) resulted in moderate yield and complete β selectivity (**7bd**).

We commenced our investigation on the synthesis of unprotected acyl C-glycosides^[14] using the photoexcitable glycosyl borate. The protecting-group-free acyl C-glycosylation using unprotected glycosyl donor has never been reported due to the problem of the undesired acylation of free hydroxyl groups.^[14a, 14c] Moreover, the deprotection of protecting groups of acyl C-glycosides using base is difficult due to E2 elimination of the hydroxyl group at C2 position.^[14b] We found the radical–radical coupling between the glycosyl borate and acyl azolium^[15] to produce the unprotected acyl C-glycoside (Figure 3). The reaction pathway involves a single electron transfer (SET) process between the excited glycosyl borate **2*** and the acyl imidazolidine **8** to undergo the selective radical–radical coupling between anomeric radical **A** and ketyl radical **B** based on persistent radical effect (PRE) (Figure 3a). Specifically, the reaction between the PDP-based glycosyl borate **2a** and acyl imidazolium **8a** in dichloroethane under visible light irradiation (440 nm) produced the corresponding acyl C-glycoside **9aa** in 41% yield and complete β selectivity (Figure 3b). The β selectivity was confirmed by X-ray crystal structure analysis.^[16] After light irradiation, adding excess amount of DBU is necessary to complete the elimination

of N-heterocyclic carbene for better yield. Aliphatic acyl azolium **8b** was also applicable for this reaction to afford **9ab** in 59%.

a) Strategy for acyl C-glycoside synthesis



b) Substrate scope of acyl C-glycosides

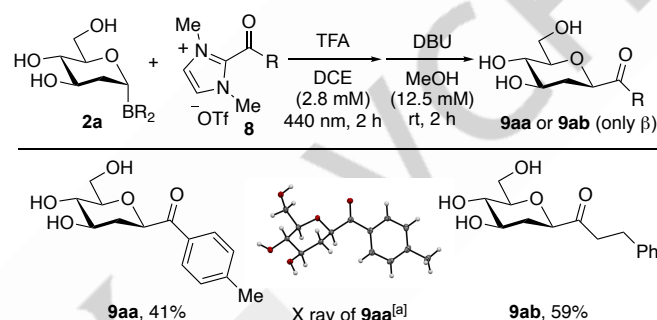
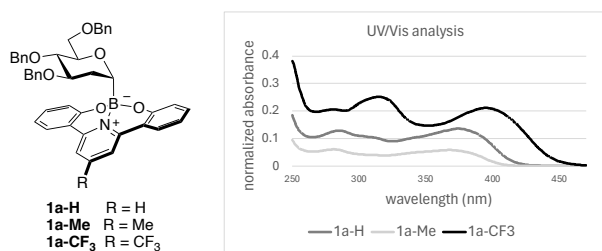


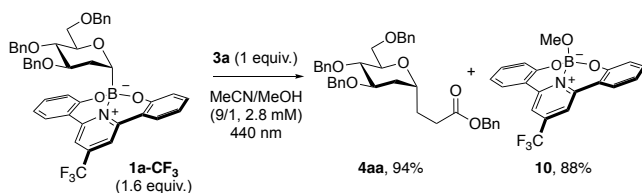
Figure 3. Unprotected acyl C-glycoside synthesis. [a] The CCDC number of **9aa** is 2353967.

To understand the role of the PDP-type borate, mechanistic studies were performed (Figure 4). Initially, we measured absorption spectrum of three benzyl-protected glycosyl borates **1a-H**, **1a-Me** and **1a-CF₃** that were used for optimization of Giese-type reaction (Figure 4a). As a result, trifluoromethyl group-installed borate **1a-CF₃** has longer wavelength absorption compared to **1a-H** and **1a-Me**. In addition, cyclic voltammetry analysis indicated that these borates have similar redox potential.^[17] These results suggested that efficient light absorbance of 440 nm LED light is essential for this reaction. Next, we focused on the effect of byproduct derived from glycosyl borate. After Giese-type reaction using **1a-CF₃** and benzyl acrylate **3a**, methoxy-substituted borate **10** was obtained in 88% yield (Figure 4b). Interestingly, the cyclic voltammetry analysis^[18] revealed that the excited state of borate **2** and **10** could act as photocatalyst to oxidize glycosyl borate **2** to promote reaction. Based on these results, the possible pathway of Giese-type reaction is shown in Figure 4c. This reaction was initiated by the generation of anomeric radical **A** via homolytic cleavage of carbon–boron bond of excited borate **2***. Anomeric radical **A** also generated by the single electron oxidation of **2** by excited **2*** or excited **10***. Anomeric radical **A** reacted with acrylate **3** to form the carbon radical **D** that is easily reduced by excited borate **2***, borate **2** radical anion or borate **10** radical anion to obtain C-glycoside **5**.

a) Physical properties of glycosyl borates



b) Byproduct derived from glycosyl borate



c) Proposed pathway of Giese-type reaction

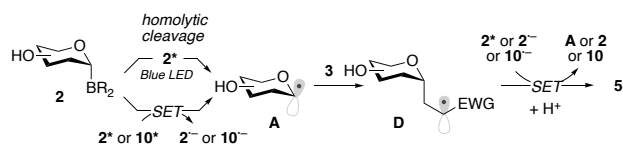


Figure 4. Mechanistic studies

Conclusion

In summary, we demonstrated the direct access to unprotected C-glycosides via anomeric radical species using the photoexcitable unprotected glycosyl borate. This C-glycosylation proceeded without an external photoredox catalyst and only visible light irradiation. This catalyst-free reaction design is the remarkable advantage of our glycosyl borate compared to other glycosyl radical precursor such as glycosyl trifluoroborate.^[6] Various unprotected C-glycosides such as alkyl C-glycosides, aryl C-glycosides and acyl C-glycosides could be obtained.

Experimental Section

General procedure for the Giese-type reaction: A screw-top 20 mL vial was charged with a stirring bar and PDP-borate **2** (0.08 mmol) under ambient atmosphere. The vial was brought to a glovebox, and dry MeCN (15.3 mL), dry MeOH (1.7 mL) and alkene **3** (0.05 mmol) in dry MeCN/dry MeOH (9:1, 1 mL) were added. After the vial was removed from the glovebox and sealed with Teflon tape, the vial was placed in EvoluChem photoreactor (PhotoRedOx Duo) equipped with two 45W blue LEDs and stirred for 12 h. After volatiles were removed under reduced pressure, flash column chromatography on silica gel gave desired product **5**.

Supporting Information

The authors have cited additional references within the Supporting Information.^[19–22]

Acknowledgements

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

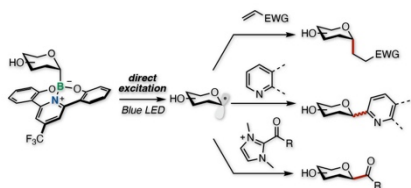
The data that support the findings of this study are available in the supplementary material of this article.

Keywords: C-glycosylation • radical • glycosyl borate • visible light

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Entry for the Table of Contents



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