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Organophotocatalytic Access to *C*-Glycosides: Multicomponent Coupling Reactions Using Glycosyl Bromides

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Photochemical multi-component coupling reactions initiated by the activation of glycosyl bromides in the presence of 1,4-bis(diphenylamino)benzene (BDB) as an organic photocatalyst were developed. *C*-glycosides accompanied by olefin (di)functionalization were obtained. This method allows us to access various *C*-glycosides with alkene, carbonyl, alcohol, ether, and amide functionalities.

C-glycosides, which include an important class of molecules such as pharmaceuticals and biologically stable analogues of glycoconjugate are carbon analogues of glycosides.[1] Recently, synthetic methods for *C*-glycosides via glycosyl radicals have been extensively investigated because photocatalysts enable activation of glycosyl radical precursors under mild reaction conditions, and a variety of transformations have been reported by the combination of photocatalysts and metal catalysts.[2]

Glycosyl bromides **I**, which are obtained by two-step synthesis from monosaccharides, are storable precursors of glycosyl radicals and glycosyl cation equivalents (Fig. 1).[3] The pioneering work of photochemical generation of glycosyl radicals **II** from glycosyl bromides **I** and their application to the synthesis of *C*-glycosides **IV** have been reported by Giese and co-workers (Fig. 1a).[4] Photocatalysts such as the ruthenium complex $[Ru(bpy)_3]X_2$[5] have already been investigated to generate glycosyl radicals **II**; however, further functionalization via the thus-generated radical intermediates **III** has never been reported.

Since the last decade, organophotocatalysts such as triarylamines with high reduction potentials have been developed to achieve various transformations including olefin difunctionalizations.[6] Therefore, we envisioned that radical polar crossover reactions (RPCRs)[7] can be used to synthesize multicomponent coupling products **VI** via cation intermediate **V** (Fig. 1b). Here, we report the development of a practical method for synthesizing *C*-glycosides by multicomponent coupling reactions of glycosyl bromides as precursors of glycosyl radicals and 1,4-bis(diphenylamino)benzene (BDB) as an organophotocatalyst.[6l]

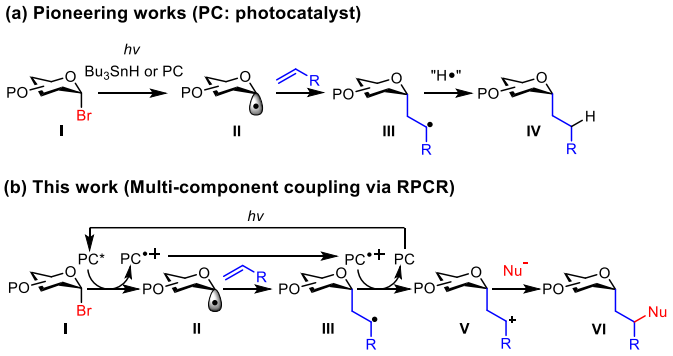

Figure 1 Synthesis of *C*-glycoside via photochemical generation of glycosyl radicals and subsequent reactions with alkenes.

We initiated our synthetic study by coupling glycosyl bromide **1** and alkene **2** in the presence of a catalytic amount of BDB with high reduction potentials (E_{red} = -2.91 V vs. Fc/Fc^+)[6l] (Table 1). As predicted by the reduction potential of BDB, α-mannosyl bromide **1a** with benzoyl protecting groups (E_{red} = -2.30 V vs. Fc/Fc^+) was consumed within 12 h, and the coupling product **3aa** was obtained in 86% yield together with by-products **4a** and **5aaa** (entry 1). Although **5aaa** was interesting as a three-component coupling product, the formation of **4a** and **5aaa** was suppressed with a shorter reaction time, and **3aa** was obtained in 99% yield (entry 2). An excess amount of K_2CO_3 was crucial to perform the reaction with high conversion and yield (entries 3 and 4); however, the role of K_2CO_3 other than as a base is not clear, as mentioned later. Although 1,4-bis(diphenylamino)naphthalene (BDN) with a lower reduction potential (E_{red} = -2.35 V vs. Fc/Fc^+)[6f] was not as effective as BDB, **1a** was consumed >99% within 3 h (entry 5). These results

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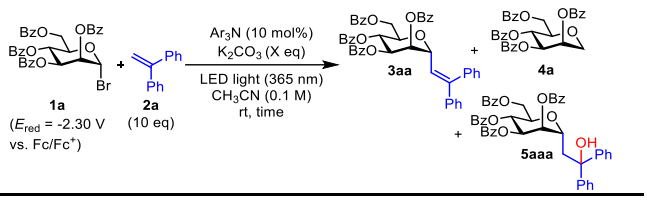
encouraged us to optimize other multicomponent coupling reactions under photochemical conditions using BDB as a catalyst.

Table 1 Reaction optimization of the coupling of mannosyl bromide **1a** and 1,1'-diphenylethylene (**2a**)[a]



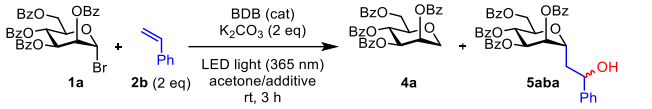
entry	Ar_3N (E_{red} vs. Fc/Fc$^+$)	K_2CO_3	time	**1a** conv.	**3aa** yield	**4a** yield	**5aaa** yield
1	BDB (-2.91 V)	2.0 eq	12 h	99%	86%	1%	9%
2[b]	BDB	2.0 eq	3 h	>99%	99%	0%	0%
3[b]	BDB	1.2 eq	3 h	48%	46%	0%	0%
4[b]	BDB	0 eq	3 h	33%	33%	0%	0%
5	BDN (-2.35 V)	2.0 eq	3 h	>99%	79%	2%	3%

[a]Conversions and yields were determined by ^{1}H NMR. [b]5 eq. of **2a** was added.

Although 1,1'-diphenylethene (**2a**) is a good coupling partner, it may generate a diphenylmethyl cation that is too stable to react with nucleophiles. To selectively obtain three-component coupling products, we performed the reaction between mannosyl bromide **1a** and styrene (**2b**), which may produce the benzylic cation intermediate, and obtained the corresponding hydrated product **5aba** exclusively (Table 2, entry 1). By reducing the amount of BDB catalyst from 10 mol% to 2 mol%, the yield of **5aba** was increased to 80%; however, the ratio of isomers was not changed (entry 2). Even 1 mol% of the BDB catalyst was sufficient to convert mannosyl bromide **1a** within 3 h, a certain amount of reduction product **4a** was formed, and the yield of **5aba** was moderate (entry 3). It is still unclear why the reaction in dry acetone afforded the hydrated product **5aba**; however, a trace amount of water was sufficient to produce **4a** because the reaction in the presence of water (5 equiv) did not change the results (entry 4).

During the investigation of the scope of the three-component coupling reactions, we obtained four-component coupling products via the Ritter reaction (Table 3, entry 1).[8] This is the major reason acetone was used as the solvent in the reaction optimization shown in Table 2. It is interesting that a lower amount of BDB catalyst increased the desired product **6aba** significantly (entries 2 and 3). Even 0.1 mol% of BDB catalysed the reaction; however, conversion dropped to 36% and the yield of **6aba** became moderate (entry 4). The reaction requires aryl amines as catalysts, and 2 eq. of K_2CO_3 is necessary to obtain Ritter-type product **6aba** in high yields (entries 5-7).

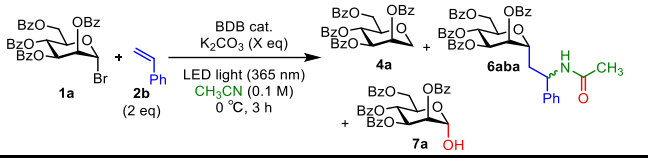
Table 2 Reaction optimization of the coupling of mannosyl bromide **1a**, styrene (**2b**), and water[a]



entry	BDB (mol%)	additive	**1a** conv.	**4a** yield	**5aba** yield (ratio)
1	10	-	99%	0%	61% (61:39)
2	2	-	99%	trace	80% (63:37)
3	1	-	97%	15%	57% (63:37)
4	2	H_2O (5 eq)	99%	trace	81% (63:37)

[a]Determined by ^{1}H NMR.

Table 3 Reaction optimization of the coupling of mannosyl bromide **1a**, styrene (**2b**), acetonitrile, and water[a]



entry	BDB (mol%)	K_2CO_3	**1a** conv.	**4a** yield	**6aba** yield (ratio)	**7a** yield
1	10	2.0 eq	96%	2%	49% (78:22)	1%
2	2	2.0 eq	>99%	0%	77% (73:27)	0%
3	1	2.0 eq	99%	0%	96% (71:29)	0%
4	0.1	2.0 eq	36%	0%	27% (70:30)	0%
5	-	2.0 eq	0%	0%	0%	0%
6	1	0 eq	34%	7%	trace	2%
7	1	1.2 eq	>99%	0%	74% (72:28)	0%

[a]Determined by ^{1}H NMR.

We investigated the scope and limitations of the proposed method (Fig. 2). Not only 1,1-diphenylethylene **2a** but also 4-methoxystyrene (**2c**) and 1-Phenyl-1-trimethylsiloxyethylene (**2h**) afforded two-component coupling products **3aa**, **3ac,** and **3ah**. These results indicate that cation intermediates are involved in the reaction mechanism. Galactosyl bromide **1b** also afforded two-component coupling **3ba** in 71% yield by elongating the reaction time; however, the reaction of glucosyl bromide **1c** with **2a** was sluggish.

The three-component coupling products **5aba** and **5ada** were obtained from the reaction with styrene (**2b**) and α-methyl styrene (**2d**) in higher yields. In the presence of alcohols as nucleophiles, a methoxy or an ethoxy group can be introduced to the reaction with 1,1-diphenylethylene (**2a**); **5aab** and **5aac** were obtained in moderate yields (67% and 58%) together with **3aa**, which was a two-component coupling product. In the three-component coupling reaction α-glucosyl bromide **1c** gave better result than that of α-galactosyl bromide **1b**. Therefore, the lower conversion of **1c** in the reaction with **2a** cannot be explained by the poor reactivity of **1c** under photochemical activation.

The four-component coupling products **6** were obtained in good to excellent yields. Although α-glucosyl bromide **1c** gave product 6cba in lower yield, the stereoselectivity was slightly better than that of **6aba** derived from α-mannosyl bromide **1c**, styrene (**2a**), acetonitrile, and water. Propionitrile (EtCN) was also incorporated into product **6abb** via the Ritter-type process. Styrene derivatives **2e**-**g** gave four-component coupling products **6aea**, **6afa**, and **6aga** exclusively. These results illustrate the considerable influence of the electron-donating group in 4-methoxystyrene (**2c**), which afforded two-component coupling product **3ac**. Both three- and four-component coupling reactions suffered from poor stereoselectivities; however, most of the isomers can be separable by conventional silica-gel chromatography. Although we examined the Ritter-type reaction using methylenecyclohexane, its yield was very low. Therefore, reactions with aliphatic alkenes are a challenge at this stage.

To elucidate the reaction mechanism, transient absorption spectra of BDB were measured in the presence of glycosyl bromide **1a-c** at various concentrations (see the ESI for details). By increasing the concentration of glucosyl bromide **1c** a decrease in absorbance was observed (Fig. 3). Glucosyl bromide **1c** functions as a quencher of the photoexcited species BDB*, and single electron transfer must generate $BDB^{+\bullet}$ together with the glycosyl radical intermediate. Although quenching rate constants of glycosyl bromides **1a**-**c** were obtained (mannosyl bromide **1a**: 3.23 × 10 s^{-1} mol^{-1} L, galactosyl bromide **1b**: 2.38 × 10 s^{-1} mol^{-1} L, glucosyl bromide **1c**: 2.44 × 10 s^{-1} mol^{-1} L), these values were almost of the same magnitude. Thus, the lower yield of the two-component coupling product **3ca** and the lower conversion of glycosyl bromide **1c** remain uncertain. To confirm the generation of the anomeric glycosyl radical as an intermediate, the reaction between mannosyl bromide **1a** and styrene (**2a**) was performed in the presence of 2 equiv. of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) (Fig. 4). The reaction product of TEMPO **8a** was obtained in 81% yield, and no Ritter-type reaction product **6aba** was detected. Although the formation of a glycosyl cation as a reactive intermediate cannot be excluded, hydroxy sugars must be obtained as a by-product if the reaction proceeds via glycosyl cations, which may be formed by single-electron oxidation of glycosyl radicals.

Based on these results, we propose the following reaction mechanism involving the radical-polar crossover process (Fig. 5). The single electron transfer (SET) between mannosyl bromide **1a** and photoexcited BDB* generates a glycosyl radical species with α anomeric configuration. The subsequent reaction of the glycosyl radical and 1,1'-diphenylethylene **2a** affords radical intermediate **10**, which may be oxidized by the BDB radical cation to form cation intermediate **11**. The β-elimination or the desilylation from the cation intermediate **11** may afford alkenylation products **3aa**, **3ac** and **3bc** or alkylation product **3ah**. The nucleophilic addition toward the cation intermediate yields hydrated, methylated, and Ritter-type products **5** and **6**. Although the hydration toward the alkenylation product **3aa** also produces **5aaa**, this may not be the major route because the corresponding alkenylation products have never been observed in the reactions with styrene (**2a**). BDB should be regenerated by the reduction of the corresponding radical cation $BDB^{\bullet+}$ because the catalytic amount of BDB is sufficient to promote the reaction in the presence of K_2CO_3. There is a possibility that K_2CO_3 works not only as a base but also as a mediator that facilitates SET between BDB and radical intermediate **10**.[9] Further study will reveal the functions of K_2CO_3.[10]

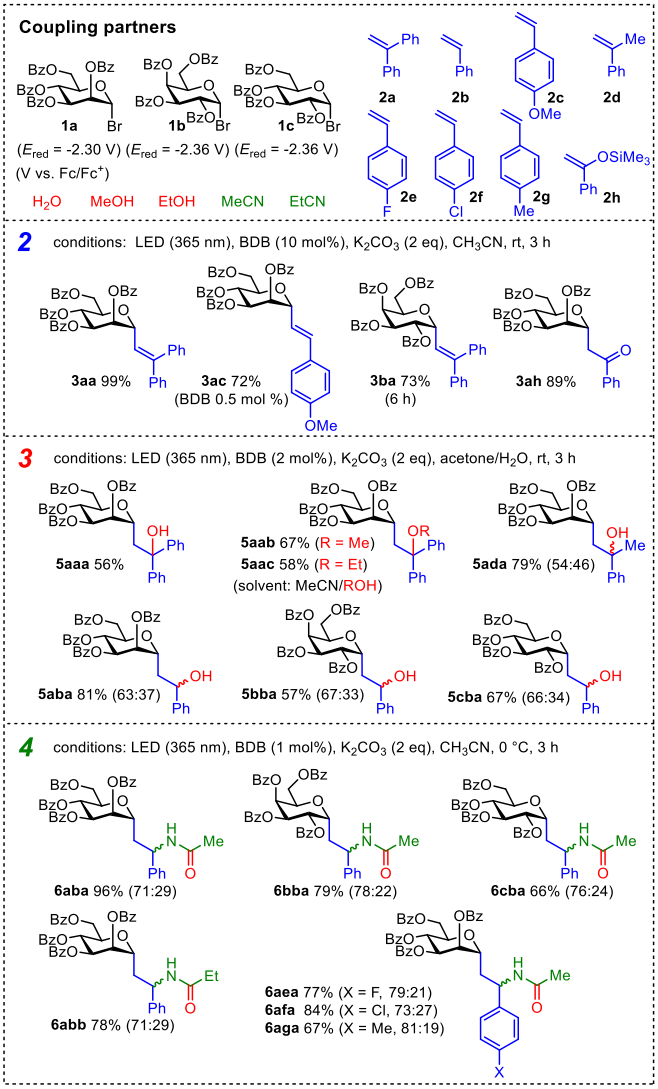


Figure 2 Scope and limitations of the proposed method.

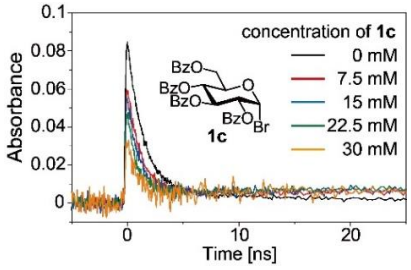


Figure 3 Transient absorption spectra of BDB in acetone at 900 nm (excitation wavelength: 355 nm) with various concentrations of glycosyl bromide **1c**.

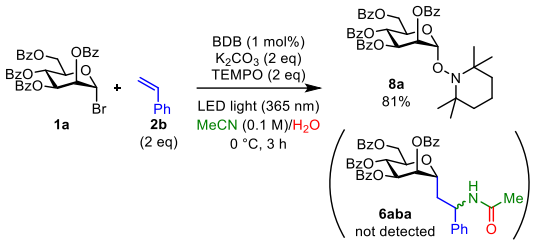


Figure 4 Control experiment in the presence of TEMPO.

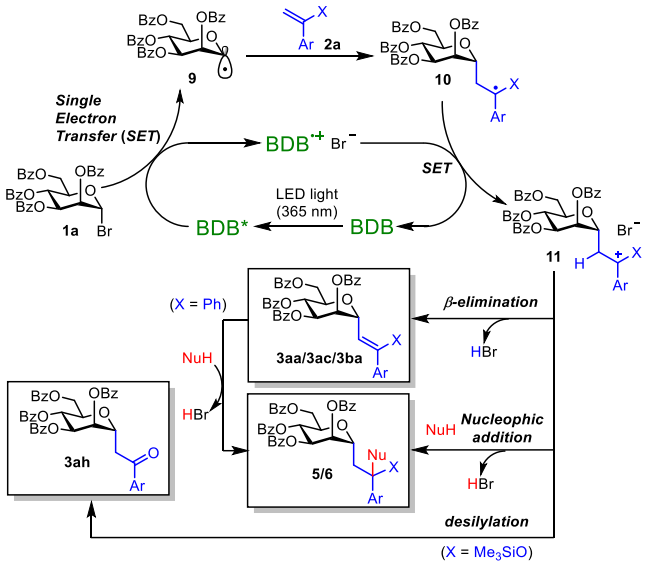


Figure 5 Proposed reaction mechanism via the radical-polar crossover.

In conclusion, we have developed a practical multi-component coupling reaction to synthesize *C*-glycosides under photochemical conditions. The reactions proceed at ambient temperatures with a short reaction time and low catalyst loading, especially for four-component coupling via the Ritter-type reaction. Glycosyl bromides are abundant, and triarylamines are common organic molecules. Therefore, this MCCR may provide an alternative synthetic route to the target *C*-glycosides. Further scope of the method and its synthetic application are underway in our laboratory. The authors acknowledge JST CREST (No. JPMJCR18R4) for financial support. T.N., T.T., M.A., and T.K. organized the study. N.S., Z.Y., D. I. and H.T. synthesized and characterized the compounds. M.A. and T.N. measured the transient absorption spectra. N.S. and T.N. principally wrote the manuscript, and T.G. and N.S. checked the ESI. All authors have proofread and approved the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data Availability Statement

The data supporting this article were included in the ESI.

Notes and references

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10 Although Na_2CO_3 also gave the product **6aba**, the yield was moderate (45% yield). The reagent grade of K_2CO_3 should be higher than 99.5%.

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Data Availability Statement

Professor Lutz Ackermann
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Institut für Organische und Biomolekulare Chemie

Dear Professor Ackermann

We are sending the manuscript of our paper entitled **Organo Photocatalytic Access to *C*-Glycosides: Multicomponent Coupling Reactions Using Glycosyl Bromides**, which we would like to submit to *Chemical Communications* as a communication. The data supporting this article have been included as part of the Supplementary Information.

Your consideration of this paper is greatly appreciated.

Sincerely yours,

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