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ARTICLE

Direct, Stereoselective Thioglycosylation Enabled by an Organophotoredox Radical Strategy

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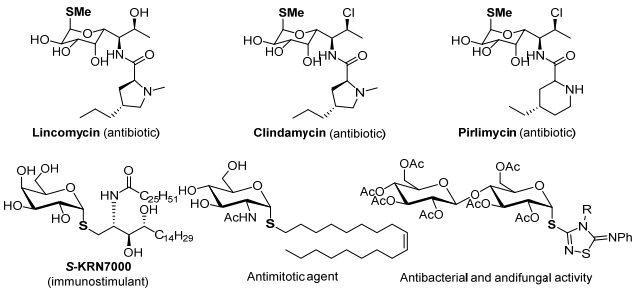
While strategies involved 2e⁻ transfer pathway have dictated glycosylation development, direct glycosylation of readily accessible glycosyl donors as radical precursors is particularly appealing because of high radical anomeric selectivity and atom- and step-economy. However, the development of the radical process has been challenging owning to notorious competing reduction, elimination and/or S_N side reactions of commonly used, labile glycosyl donors. Here we introduce an organophotocatalytic strategy that glycosyl bromides can be efficiently converted into corresponding anomeric radicals by a photoredox mediated HAT catalysis without a transition metal or a directing group and achieve highly anomeric selectivity. The power of this platform has been demonstrated by the mild reaction conditions enabling synthesis of challenging α-1,2-*cis*-thioglycosides, the tolerance of various functional groups and the broad substrate scope for both common pentoses and hexoses. Furthermore, this general approach is compatible to both sp^2 and sp^3 sulfur electrophiles and late-stage glycodiversification for total 48 substrates probed.

Introduction

Despite the fact that *O*-linked glycosides are a dominant form in biologically important glycoconjugates,[1] replacement of "*O*" by *C*-, *N*- and *S*-linked glycosides offers the merits of improved hydrolytic stability and/or bioactivity while maintaining similar conformational preferences.[2] In particular, thioglycosides have emerged as a privileged class of structures owing to their broad spectrum of biological activities (see representative examples in Scheme 1).[2-5] Moreover, they are widely used as glycosyl donors in glycosylation reactions.[6] The broad biological and synthetic utility has triggered significant interest in the development of efficient methods to construct the C-S bond with defined anomeric configuration, which plays key roles in biological activities.

Strategies involved ionic 2e⁻ transfer pathway have dictated the C-S bond formation development.[7-13] Direct replacement by a thiol with a glycosyl donor is an attractive approach in that both starting materials are readily accessible, but gives a mixture of α/β anomers in most cases (Scheme 2a).[8] To overcome these limitations, the methods by reversing the polarity at the anomeric carbon have been developed (Scheme 2b).[9] These elegant methods enable the stereoselective control formation of both α and β anomers but with limited scope of saccharides.[9a] Indirect methods using preformed anomeric thiols offer versatile approaches to thioglycosides (Scheme 2c).[10-13] Nonetheless, the anomeric stereoselectivity of these processes depends on the nature of the anomeric thiols. In particular, few methods are capable of selectively constructing the challenging α-1,2-*cis*-thioglycosides,[8b] featured in a number of nature products and bioactive molecules (Scheme 1).



Scheme 1. Selected examples of thioglycosides with α-1,2-*cis*-configuration.

Radical cross coupling offers a distinct paradigm for stereoselective construction of glycosidic bonds.[14] Anomeric radicals have been elegantly explored for the highly stereoselective *C*-glycosidic bond formation with a transition metal (TM).[15-17] However, the stereoselective C-S bond formation through glycosyl radical has remained elusive (Scheme 2d).[17] This attributes to: 1) reduction of glycosyl radicals by HAT (hydrogen atom transfer) donors;[18] 2) elimination reaction of labile glycosyl donors by a TM catalyst;[19] 3) competing S_N2 reaction with thiols, which could compromise the anomeric selectivity.[2b,7] Therefore, stable radical precursors such as glycosyl stannanes are designed to minimize these issues.[17] Given the fact that the glycosyl radical can favour formation of anomeric C1 conformation, we deliberately push

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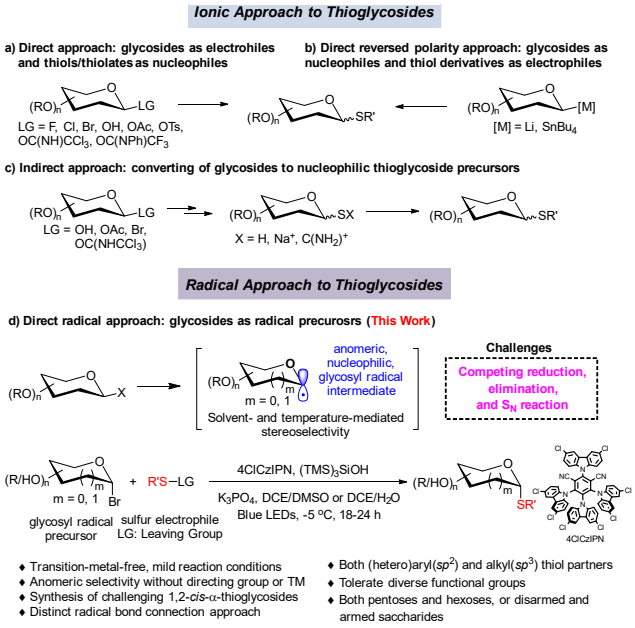
the limit by developing an organophotocatalytic approach without a directing group or a TM for stereoselective *S*-glycosylation. Herein, we wish to disclose the results of the investigation, which has led to a general organophotocatalyzed thiolation of glycosyl bromides with highly stereoselective control (Scheme 2d).

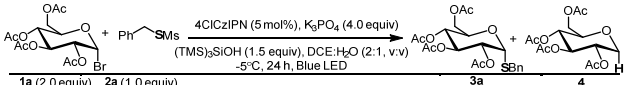


Scheme 2. Ionic and Radical Thioglycosylation.

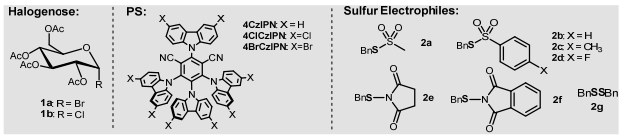
Results and discussion

In our own efforts, recently we have developed visible-light-mediated glycosyl radical reactions for synthesis of *C*-glycosylsides.[15] In addition, we reported an organophotocatalytic thiolation of acyl radial method with thiosulfonates.[20] These chemistries guided us to explore the new thioglycosylation reaction. The reaction of α-glucopyranosyl bromide **1a** with thiosulfonate **2a** and 4CzIPN[21] as photocatalyst (PS) was probed (Table 1 and Tables S1-6). First, we examined several commonly used reductants including *i*Pr$_2$NEt, Hantzsch ester, and ascorbic acid (Table S1, entries 2, 6 and 7) for the generation of the glycosyl radical. Disappointedly, only the reduced product **4** was obtained. It should be pointed out that this is a general problem in using glycosyl halides as radical progenitors in glycosylation.[18] Minimizing the issue requires a radical capable of effective dehalogenation whereas the hydrogenated product should be a weak H-donor. A silyl or a silyloxy radical can induce dehalogenation while the strong Si-H and Si-O-H makes them more difficult to be abstracted.[22] Therefore, various silanes were screened and (TMS)$_3$SiOH was the best, giving **3a** in 37% yield (Table S1, entries 3-5 and 8-9). Survey of PSs revealed 4ClCzIPN[21b,c] as the optimal promoter (65% yield, Table S2 and Table 1, entries 2-4). The process was also sensitive to bases (entries 4-6 and Table S4) and K_3PO_4 gave **3a** in high yield. Among the thiosulfonates probed (entries 6-12), methanethiosulfonate (**2a**) was the best, possibly attributing to the less hindrance and relatively redox stability (E_{red} = -1.65 V vs SCE, Figure S3). Glycosyl chloride (**1b**) did not undergo the dechlorination presumably due to strong C-Cl bond (entry 13). To further improve the stereoselectivity (entry 6), we conducted reaction optimization including solvent and reaction temperature (Table 1, entries 14-15 and Tables S3 and S6). It was found that the biphasic solvent (DCE:H_2O = 2:1) could not only retain the high anomeric selectivity but also increase the yield (76%, entry 1), and low temperature (- 5°C) is also required to maintain good yield and anomeric selectivity (entry 14, 15). The control experiments confirmed that base, light, (TMS)$_3$SiOH, and PS were essential for this transformation (entries 16-17).

Table 1. Reaction Optimization.



Entry	Variation from the "Standard Conditions" [a]	Yield (**3a**, %)[b]	α : β[c]
1	none	76 (72)[d]	>20:1
2	4CzIPN (5 mol%), **2c**, Na_2CO_3 (4.0 equiv), DMSO, rt	37	<10:1
3	4BrCzIPN (5 mol%), **2c**, Na_2CO_3 (4.0 equiv), DMSO, rt	33	<10:1
4	4ClCzIPN (5 mol%), **2c**, Na_2CO_3 (4.0 equiv), DMSO, rt	65	<10:1
5	Cs_2CO_3 instead of K_3PO_4, DCE:DMSO (1:1, v:v), rt	trace	-
6	DCE:DMSO (1:1, v:v), rt	80	<10:1
7	**2b** instead of **2a**, DCE:DMSO (1:1, v:v), rt	72	<10:1
8	**2d** instead of **2a**, DCE:DMSO (1:1, v:v), rt	66	<10:1
9	**2d** instead of **2a**, DCE:DMSO (1:1, v:v), rt	68	<10:1
10	**2e** instead of **2a**, DCE:DMSO (1:1, v:v), rt	trace	-
11	**2f** instead of **2a**, DCE:DMSO (1:1, v:v), rt	66	<10:1
12	**2g** instead of **2a**, DCE:DMSO (1:1, v:v), rt	trace	-
13	**1b** instead of **1a**	trace	-
14	DCE instead of DCE:H_2O (2:1, v:v), rt	60	17:1
15	DCE instead of DCE:H_2O (2:1, v:v), -5 °C	67	>20:1
16	without 4ClCzIPN, (TMS)$_3$SiOH or K_3PO_4	trace	-
17	under dark condition	trace	-



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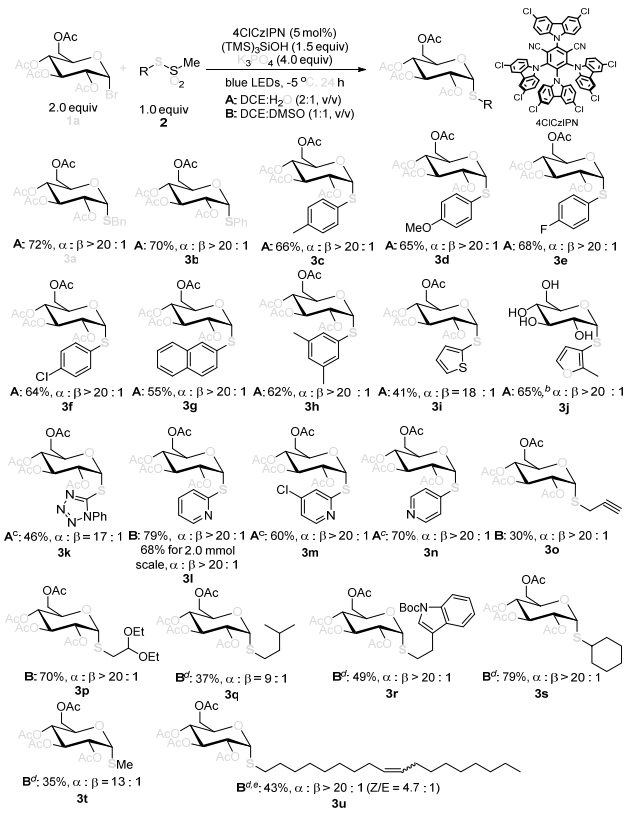
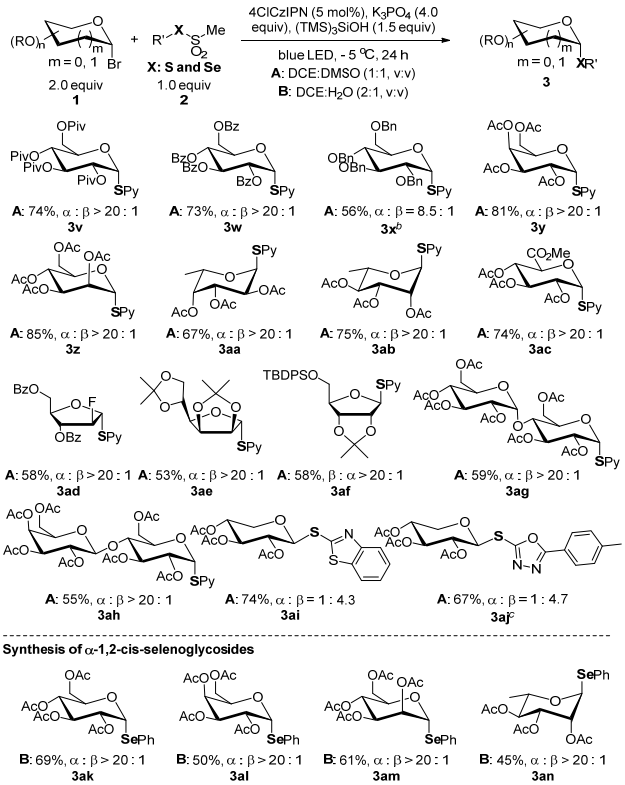
[a] Standard conditions: unless specified, a mixture of glycosyl bromide (0.2 mmol), sulfur electrophile (0.1 mmol), 4ClCzIPN (0.005 mmol), K_3PO_4 (0.4 mmol), and $(TMS)_3SiOH$ (0.15 mmol) in DCE/DMSO (1 mL, 1:1, v/v) or DCE/H_2O (1.5 mL, 2:1, v/v) was irradiated with 40 W Kessil blue LEDs in a N_2 atmosphere at -5 °C for 24 h. [b] Yield determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal reference. [c] Ratio determined by crude ^{1}H NMR. [d] Isolated yield.

The generality of the new *S*-glycosylation was examined. We first evaluated the performance using glucosyl bromide (**1a**) as radical donor for coupling with various thiosulfonates **2** (Scheme 3). The process serves as a general approach to both aryl and alkyl thioglycosides. Uniformly high axial selectivities are observed regardless of the nature of the sulfur electrophiles. With respect to aryls, electron-neutral (**3b**), -donating (**3c**-**3d**, **3h**), and -withdrawing (**3e**-**3f**) groups on the phenyl ring and fused aromatic (**3g**) can be tolerated. Moreover, heteroaromatic thiosulfonates such as the thiophenyl (**3i**) and furanyl (**3j**) enabled access to medicinally valued thioglycosides. The tetrazole derived disulfide instead of labile thiosulfonate could serve as alternative and delivered the desired **3k**. The reaction performed in DCE:H_2O failed for pyridinyl thiosulfonate. Decent results (**3l**, 79%, α:β > 20:1) were obtained with DCE:DMSO (condition B). The protocol can also be applied in gram scale synthesis. Notably, less reactive sp^3 alkyl glycosides **3o**-**3s** could be synthesized with the protocol.[17]



Scheme 3. Scope of Thiosulfonates. [a] Reaction conditions: unless specified, see footnote a and SI; isolated yield; the ratio of α and β anomers determined by crude ^{1}H NMR. [b] Yield after hydrolysis of acyl group. [c] Disulfide used. [d] Toluenethiosulfonate used. [e] *Z/E* ratio determined by ^{1}H NMR.

For even less electrophilic substrates, *p*-tolylthiosulfonates (**3q**-**3u**) displayed better performance than methylthiosulfonates. Particularly, the long alkyl chain with *Z*-double bond product (**3u**) , which exhibits intriguing antitumor activity (Scheme 1), isefficiently prepared with high diastereoselectivity. The limitation of the method is also realized. C_2-*N*-Ac-saccharides such as D-glucosamine failed to react due to the lability of these reactants (see Figure S5 in SI).



Scheme 4. Scope of Saccharides and Selenoglycosylation. [a] Reaction conditions: unless specified see footnote a and SI; isolated yield; the ratio of α and β anomers determined by crude ^{1}H NMR. [b] 3.0 equiv of glycosyl bromide used. [c] Disulfide used.

Alternation of sugars was probed next (Scheme 4). Both common hexoses (glucose **3v**-**3x**, galactose **3y**, mannose **3z**, fucose **3aa**, rhamnopyranose **3ab**, glucuronic acid **3ac**) and pentoses (**3ad**-**3af**) gave good yields and high stereoselectivity. Among the tested monosaccharides, except ribose (**3af**) adopting expected β selectivity owning to the steric effect, the others gave expected α-selectivity. Furthermore, disaccharides (**3ag** and **3ah**) could participate in the process smoothly. For xyloses (**3ai**-**3aj**), the obtained products adopted β orientation since the anomeric xylosyl radical is β selective.[23] Besides pyridyl (Py), other pharmaceutically relevant heteroaromatics such as benzothiazole and oxadiazole (**3ai**, **3aj**) could be efficiently incorporated. This offers a viable strategy for the synthesis of the xylose-derived bioactive analogs.[4c] Finally, the strategy can also be extended for the synthesis of synthetically

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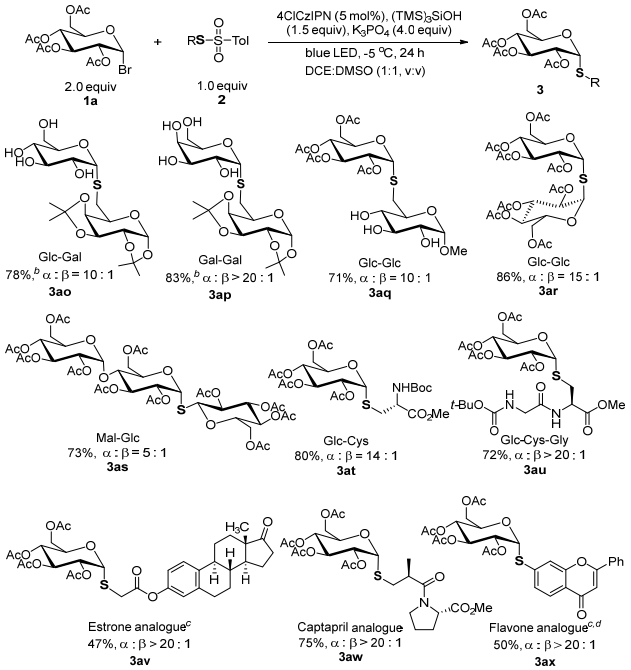
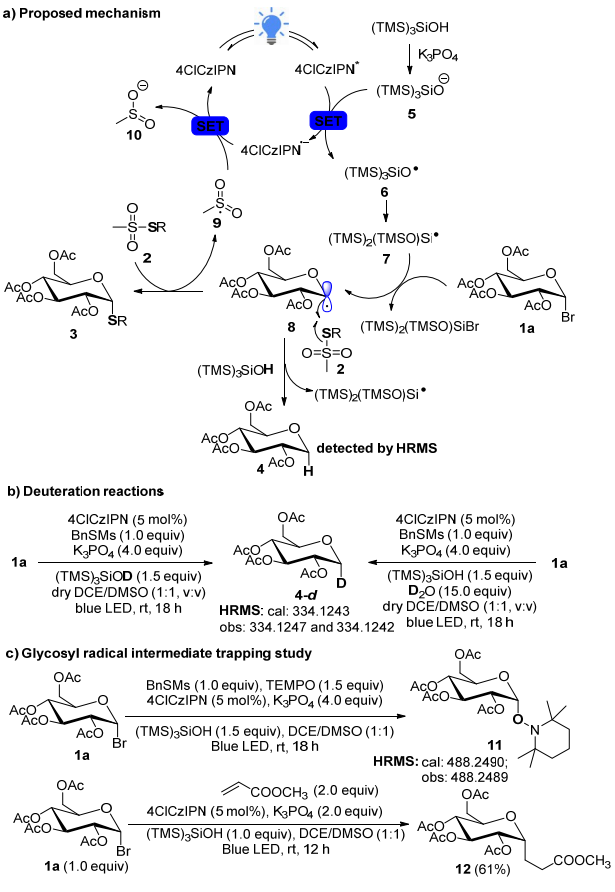
challenging α-1,2-*cis*-selenoglycosides (Scheme 4 and Table S7).[24] As showcase, under the reaction conditions (DCE:H_2O (2:1, v:v), coupling of 4 different glycosyl bromides with methyl phenylselenyl sulfonate delivered the corresponding α-seleno-glycosides **3ak**-**3an** with uniformly high stereoselectivity (α:β > 20:1).



Scheme 5. Thiodiversification of Pharmaceutically Relevant Structures. [a] Reaction conditions: unless specified, see footnote a and SI; isolated yield; ratio of α and β anomers determined by crude ^{1}H NMR. [b] The product after hydrolysis. [c] Methylthiosulfonate used. [d] DCE:H_2O (1.5 mL, 2:1, v/v) used as solvent.

The capacity of selective functionalization of biologically relevant structures and therapeutics is the testament to the synthetic power of a methodology. As demonstrated (Scheme 5), C1-6' connected thioglycosides **3ao**-**3aq** were efficiently synthesized. It is noted that native unprotected saccharide thiosulfonate could be used for the efficient cross coupling (**3aq**). Moreover, it is particularly noteworthy that the protocol is amenable for synthesis of α-*S*-linked 1,1'-disaccharides with C1 thiol electrophiles, a synthetic challenge in glycosylation,[25] as demonstrated in 1-thiodisaccharides (**3ar**) and thiotrisaccharide (**3as**). Furthermore, α-linked thioglycosyl amino acid **3at** and peptide **3au** could be efficiently constructed. The synthetic manifold was further exemplified by late-stage thioglycosylation of therapeutics. Installation of thioglycosyl moieties into estrone (**3av**), Captopril (**3aw**), and flavone (**3ax**) has been realized smoothly.

In the new thioglycosylation reaction, critically $(TMS)_3SiOH$ was identified as a HAT reagent, which could efficiently suppress the undesired reduction of the radical **8** (Scheme 6a). This may attribute to the strong O-H bond (calculated BDE = 98 kcal/mol, see SI, BDE of S-H: 83 kcal/mol)[26,27] and steric hindrance, making the H difficult to be abstracted by **8**. This strong bond also echoes the use of stronger 4ClCzIPN ($E^*/E^{\bullet-}$ = 1.58 V vs SCE)[21] to oxidize the silyloxide $(TMS)_3SiO^-$ [$(TMS)_3SiO^-/(TMS)_3SiO^\bullet$ = 1.54 V vs SCE)]. A spontaneous Brook rearrangement of silyloxy radical **6** forms silicon-centred radical **7**,[28,21b] which acts as an effective debrominator. The anomeric effect makes the radical **8** axially positioned and directs α-selective coupling with thiosulfonate **2**. In the reactions, we still observed a notable amount of the reduction product **4**. It is believed that it is produced from the reaction of **8** with $(TMS)_3SiOH$, which was confirmed by deuteration experiments with observed deuterated product **4-d** (Scheme 6b). This also rationalizes that 2 equiv of glycosyl bromide **1** is used to ensure high efficiency of the thioglycosylation process. Finally, a radical trapping study with TEMPO and methyl acrylate[16d] further confirms the radical engaged process (Scheme 6c)



Scheme 6. Proposed mechanism and mechanism studies.

Conclusions

In conclusion, we have developed a metal-free, glycosyl radical strategy for the stereoselective synthesis of thioglycosides by employing commonly used glycosyl bromides as radical

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precursors. The uncovered organophotoredox mediated HAT radical pathway can highly stereoselectively induce the formation of the anomeric C-S bond while minimizing the side reactions. The preparing power of the platform has been underscored by the mild reaction conditions enabling synthesis of challenging α-1,2-*cis*-thioglycosides, the tolerance of various functional groups and the broad substrate scope for both common pentoses and hexoses. Furthermore, this general approach is compatible to both sp^2 and sp^3 sulfur electrophiles and late-stage glycodiversification. It is expected that the strategy enabling the efficient generation of glycosyl radicals from labile glycosyl bromides can offer a reliable alternative for the synthesis of *C*- and other hetero-glycosides.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Direct, Stereoselective Thioglycosylation Enabled by an Organophotoredox Radical Strategy

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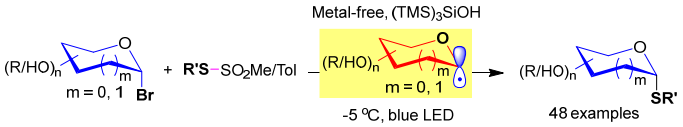

- Metal-free, mild reaction conditions
- Anomeric selectivity without directing group or TM
- Synthesis of challenging 1,2-*cis*-α-thioglycosides
- Both (hetero)aryl (sp^2) and alkyl (sp^3) sulfur electrophiles
- Both pentoses and hexoses

An organophotoredox mediated HAT catalysis is developed for achieving high anomerically selective thioglycosylation of glycosyl bromides.