

## ARTICLE

# Direct, Stereoselective Thioglycosylation Enabled by an Organophotoredox Radical Strategy

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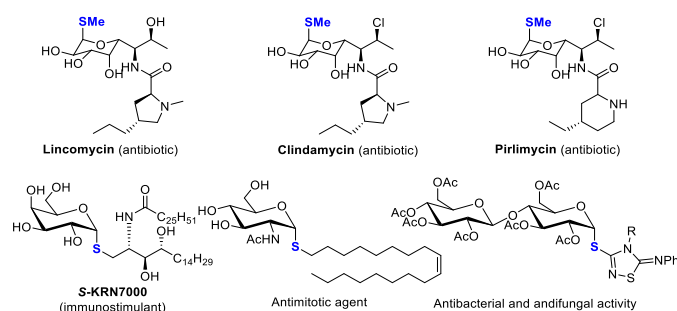
While strategies involved  $2e^-$  transfer pathway have dictated glycosylation development, direct glycosylation of readily accessible glycosyl donors as radical precursors is particularly appealing because of high radical anomeric selectivity and atom- and step-economy. However, the development of the radical process has been challenging owing 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  $\alpha$ -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,<sup>1</sup> 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.<sup>2</sup> 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).<sup>2–5</sup> Moreover, they are widely used as glycosyl donors in glycosylation reactions.<sup>6</sup> 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.<sup>7–13</sup> 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  $\alpha/\beta$  anomers in most cases (Scheme 2a).<sup>8</sup> To overcome these limitations, the methods by reversing the polarity at the anomeric carbon have been developed (Scheme 2b).<sup>9</sup> These elegant methods enable the stereoselective control formation of both  $\alpha$  and  $\beta$  anomers but with limited scope of saccharides.<sup>9a</sup> Indirect methods using preformed anomeric thiols offer versatile approaches to thioglycosides (Scheme 2c).<sup>10–13</sup>

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  $\alpha$ -1,2-*cis*-thioglycosides,<sup>8b</sup> featured in a number of nature products and bioactive molecules (Scheme 1).



**Scheme 1.** Selected examples of thioglycosides with  $\alpha$ -1,2-*cis*-configuration.

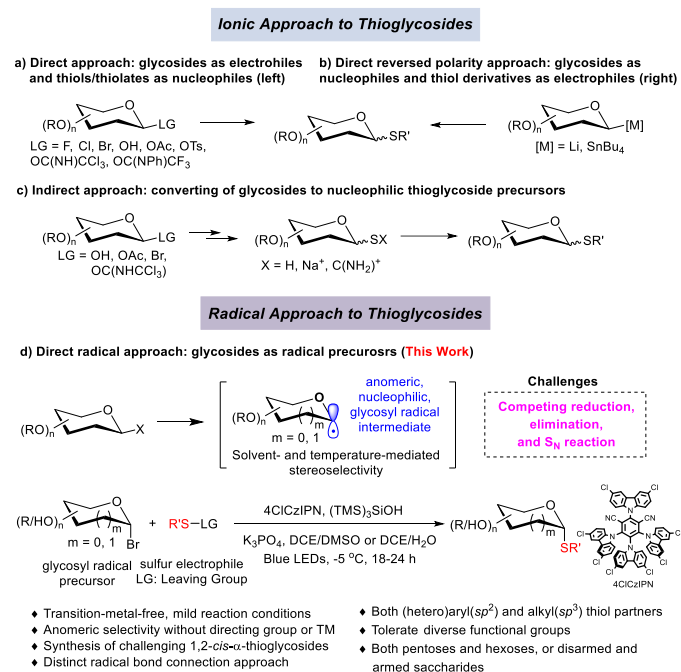
Radical cross coupling offers a distinct paradigm for stereoselective construction of glycosidic bonds.<sup>14</sup> Anomeric radicals have been elegantly explored for the highly stereoselective C-glycosidic bond formation with a transition metal (TM).<sup>15–17</sup> However, the stereoselective C-S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

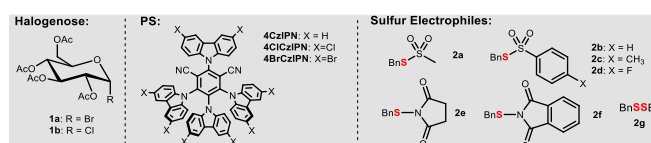
## Results and discussion

In our own efforts, recently we have developed visible-light-mediated glycosyl radical reactions for synthesis of *C*-glycosylsides.<sup>15</sup> In addition, we reported an organophotocatalytic thiolation of acyl radical method with thiosulfonates.<sup>20</sup> These chemistries guided us to explore the new thioglycosylation reaction. The reaction of  $\alpha$ -glucopyranosyl bromide **1a** with thiosulfonate **2a** and 4CzIPN<sup>21</sup> as photocatalyst (PS) was probed (Table 1 and Tables S1-6). First, we examined several commonly used reductants including *i*Pr<sub>2</sub>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.<sup>18</sup> 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.<sup>22</sup> Therefore, various silanes were screened and (TMS)<sub>3</sub>SiOH was the best, giving **3a** in 37% yield (Table S1, entries 3-5 and 8-9). Survey of PSs revealed 4CzIPN<sup>21b,c</sup> 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<sub>3</sub>PO<sub>4</sub> 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 ( $E_{\text{red}} = -1.65$  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<sub>2</sub>O = 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)<sub>3</sub>SiOH, and PS were essential for this transformation (entries 16-17).

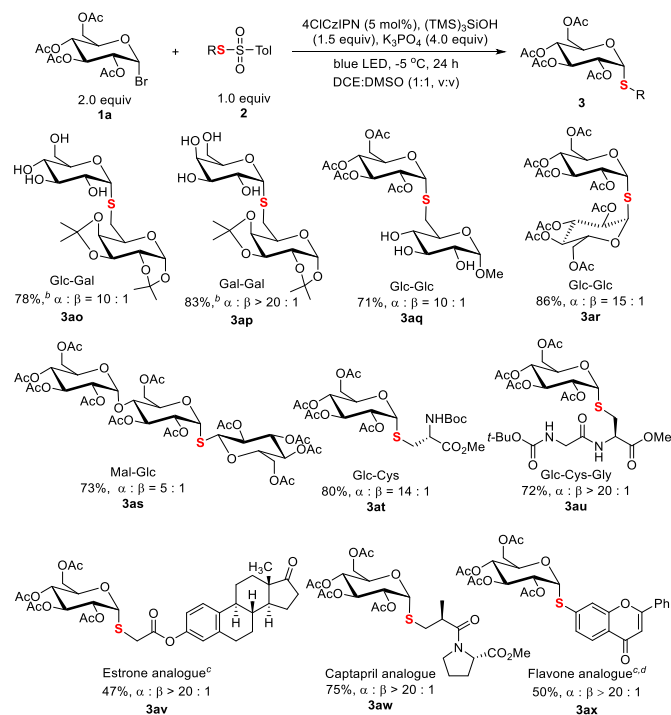
**Table 1.** Reaction Optimization.

Entry	Variation from the "Standard Conditions" [a]	Yield ( <b>3a</b> , %)[b]	$\alpha : \beta$ [c]
1	none	76 (72) <sup>[d]</sup>	>20:1
2	4CzIPN (5 mol%), <b>2c</b> , Na <sub>2</sub> CO <sub>3</sub> (4.0 equiv), DMSO, rt	37	<10:1
3	4BrCzIPN (5 mol%), <b>2c</b> , Na <sub>2</sub> CO <sub>3</sub> (4.0 equiv), DMSO, rt	33	<10:1
4	4CzIPN (5 mol%), <b>2c</b> , Na <sub>2</sub> CO <sub>3</sub> (4.0 equiv), DMSO, rt	65	<10:1
5	Cs <sub>2</sub> CO <sub>3</sub> instead of K <sub>3</sub> PO <sub>4</sub> , DCE:DMSO (1:1, v/v), rt	trace	-
6	DCE:DMSO (1:1, v/v), rt	80	<10:1
7	<b>2b</b> instead of <b>2a</b> , DCE:DMSO (1:1, v/v), rt	72	<10:1
8	<b>2d</b> instead of <b>2a</b> , DCE:DMSO (1:1, v/v), rt	66	<10:1
9	<b>2d</b> instead of <b>2a</b> , DCE:DMSO (1:1, v/v), rt	68	<10:1
10	<b>2e</b> instead of <b>2a</b> , DCE:DMSO (1:1, v/v), rt	trace	-
11	<b>2f</b> instead of <b>2a</b> , DCE:DMSO (1:1, v/v), rt	66	<10:1
12	<b>2g</b> instead of <b>2a</b> , DCE:DMSO (1:1, v/v), rt	trace	-
13	<b>1b</b> instead of <b>1a</b>	trace	-
14	DCE instead of DCE:H <sub>2</sub> O (2:1, v/v), rt	60	17:1
15	DCE instead of DCE:H <sub>2</sub> O (2:1, v/v), -5 °C	67	>20:1
16	without 4CzIPN, (TMS) <sub>3</sub> SiOH or K <sub>3</sub> PO <sub>4</sub>	trace	-
17	under dark condition	trace	-





challenging  $\alpha$ -1,2-*cis*-selenoglycosides (Scheme 4 and Table S7).<sup>24</sup> As showcase, under the reaction conditions (DCE:H<sub>2</sub>O (2:1, v/v), coupling of 4 different glycosyl bromides with methyl phenylselenenyl sulfonate delivered the corresponding  $\alpha$ -selenoglycosides **3ak-3an** with uniformly high stereoselectivity ( $\alpha$ : $\beta$  > 20:1).

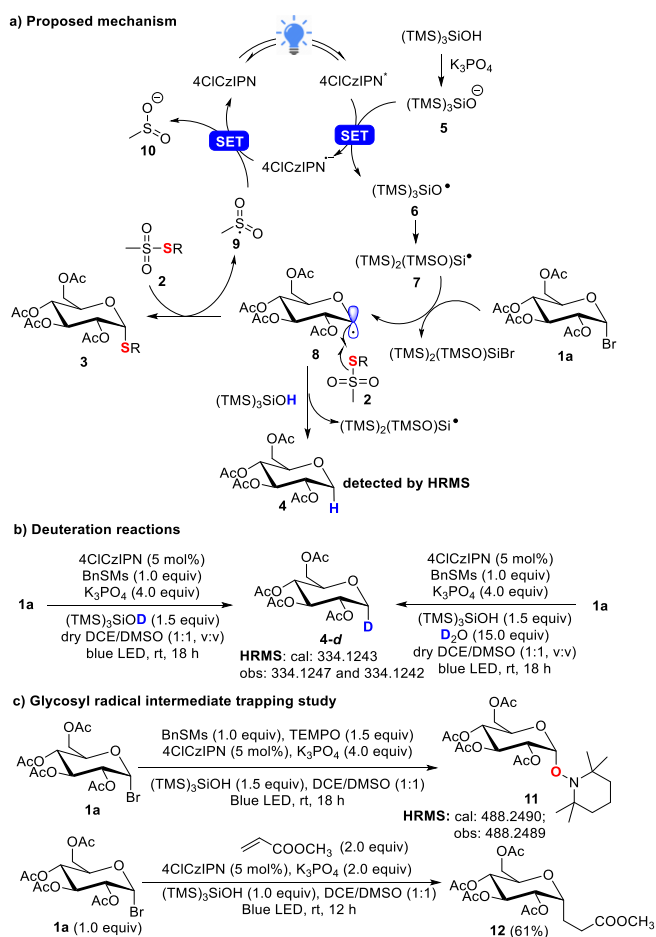


**Scheme 5.** Thiodiversification of Pharmaceutically Relevant Structures. [a] Reaction conditions: unless specified, see footnote a and SI; isolated yield; ratio of  $\alpha$  and  $\beta$  anomers determined by crude <sup>1</sup>H NMR. [b] The product after hydrolysis. [c] Methylthiosulfonate used. [d] DCE:H<sub>2</sub>O (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  $\alpha$ -S-linked 1,1'-disaccharides with C1 thiol electrophiles, a synthetic challenge in glycosylation,<sup>25</sup> as demonstrated in 1-thiodisaccharides (**3ar**) and thiotrisaccharide (**3as**). Furthermore,  $\alpha$ -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)<sub>3</sub>SiOH 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)<sup>26,27</sup> and steric hindrance, making the H difficult to be abstracted by **8**. This strong bond also echoes the use of stronger 4ClCzIPN ( $E^*/E^{*-} = 1.58$  V vs SCE)<sup>21</sup> to oxidize the silyloxy (TMS)<sub>3</sub>SiO<sup>-</sup> [(TMS)<sub>3</sub>SiO<sup>-</sup>/ (TMS)<sub>3</sub>SiO<sup>•</sup> = 1.54 V vs SCE]. A spontaneous Brook rearrangement of silyloxy radical **6** forms silicon-centred radical **7**,<sup>28,21b</sup> which acts as an effective debrominator. The anomeric effect makes the radical **8** axially positioned and directs  $\alpha$ -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)<sub>3</sub>SiOH, 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<sup>16d</sup> 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

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  $\alpha$ -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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