Direct, stereoselective thioglycosylation enabled by an organophotoredox radical strategy†

Peng Ji, Yueteng Zhang, Feng Gao, Fangchao Bi and Wei Wang‡

While strategies involving a $2e^-$ transfer pathway have dictated glycosylation development, the direct glycosylation of readily accessible glycosyl donors as radical precursors is particularly appealing because of high radical anomic 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 organophotoredox radical strategy through which glycosyl bromides can be efficiently converted into corresponding anomic radicals by photoredox mediated HAT catalysis without a transition metal or a directing group and achieve highly anomic selectivity. The power of this platform has been demonstrated by the mild reaction conditions enabling the 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 with both sp$^2$ and sp$^3$ sulfur electrophiles and late-stage glycodiversification for a total of 50 substrates probed.

Introduction

Despite the fact that O-linked glycosides are a dominant form in biologically important glycoconjugates, the 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. 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). Moreover, they are widely used as glycosyl donors in glycosylation reactions. The broad biological and synthetic utility has triggered significant interest in the development of efficient methods to construct a C–S bond with a defined anomeric configuration, which plays key roles in biological activities.

Strategies involving an ionic $2e^-$ transfer pathway have dictated the C–S bond formation development. 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). To overcome these limitations, the methods of reversing the polarity at the anomeric carbon have been developed (Scheme 2b). These elegant methods enable the stereoselective control formation of both $\alpha$ and $\beta$ anomers but with limited scope of saccharides. Indirect methods using preformed anomic thiols offer versatile approaches to thioglycosides (Scheme 2c). Nonetheless, the anomic 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, featured in a number of natural products and bioactive molecules (Scheme 1).

Radical cross coupling offers a distinct paradigm for stereoselective construction of glycosidic bonds. Anomeric radicals have been elegantly explored for highly stereoselective C-glycosidic bond formation with a transition metal (TM). However, stereoselective C–S bond formation through the glycosyl radical has remained elusive (Scheme 2d). This is attributed to: (1) reduction of glycosyl radicals by HAT (hydrogen atom transfer) donors; (2) elimination reaction of labile glycosyl donors with a TM catalyst; (3) competing $S_N$2 reaction with thiols, which could compromise the anomeric selectivity. Therefore, stable radical precursors such as...

![Scheme 1](image-url) Selected examples of thioglycosides with $\alpha$-1,2-cis-configuration.
glycosyl stannanes are designed to minimize these issues.\textsuperscript{17} Given the fact that the glycosyl radical can favour the formation of anomeric C1 conformation, we deliberately push 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).

**Results and discussion**

In our own efforts, recently we have developed visible-light-mediated glycosyl radical reactions for the synthesis of C-glycosides.\textsuperscript{15} In addition, we reported an organophotocatalytic thiolation of acyl radical method with thiosulfonates.\textsuperscript{20} These chemistries guided us to explore a new thioglycosylation reaction. The reaction of $\alpha$-glucopyranosyl bromide 1a with thiosulfonate 2a and 4CzIPN\textsuperscript{21} as a photocatalyst (PS) was probed (Table 1 and Tables S1–S6\textsuperscript{†}). First, we examined several commonly used reductants including iPr\textsubscript{2}NEt, Hantzsch ester, and ascorbic acid (Table S1,\textsuperscript{†} entries 2, 6 and 7) for the

### Table 1 Reaction optimization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Variation from the “standard conditions”\textsuperscript{ab}</th>
<th>Yield\textsuperscript{b} (3a, %)</th>
<th>$\alpha : \beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>76 (72)\textsuperscript{d}</td>
<td>$&gt;20 : 1$</td>
</tr>
<tr>
<td>2</td>
<td>4CICzIPN (5 mol%), 2c, Na\textsubscript{2}CO\textsubscript{3} (4.0 equiv.), DMSO, rt</td>
<td>37</td>
<td>$&lt;10 : 1$</td>
</tr>
<tr>
<td>3</td>
<td>4BrCzIPN (5 mol%), 2c, Na\textsubscript{2}CO\textsubscript{3} (4.0 equiv.), DMSO, rt</td>
<td>33</td>
<td>$&lt;10 : 1$</td>
</tr>
<tr>
<td>4</td>
<td>4ClCzIPN (5 mol%), 2c, Na\textsubscript{2}CO\textsubscript{3} (4.0 equiv.), DMSO, rt</td>
<td>65</td>
<td>$&lt;10 : 1$</td>
</tr>
<tr>
<td>5</td>
<td>Cs\textsubscript{2}CO\textsubscript{3} instead of K\textsubscript{3}PO\textsubscript{4}, DCE : DMSO (1 : 1, v/v), rt</td>
<td>Trace</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>DCE : DMSO (1 : 1, v/v), rt</td>
<td>80</td>
<td>$&lt;10 : 1$</td>
</tr>
<tr>
<td>7</td>
<td>2b instead of 2a, DCE : DMSO (1 : 1, v/v), rt</td>
<td>72</td>
<td>$&lt;10 : 1$</td>
</tr>
<tr>
<td>8</td>
<td>2d instead of 2a, DCE : DMSO (1 : 1, v/v), rt</td>
<td>66</td>
<td>$&lt;10 : 1$</td>
</tr>
<tr>
<td>9</td>
<td>2d instead of 2a, DCE : DMSO (1 : 1, v/v), rt</td>
<td>68</td>
<td>$&lt;10 : 1$</td>
</tr>
<tr>
<td>10</td>
<td>2e instead of 2a, DCE : DMSO (1 : 1, v/v), rt</td>
<td>Trace</td>
<td>—</td>
</tr>
<tr>
<td>11</td>
<td>2f instead of 2a, DCE : DMSO (1 : 1, v/v), rt</td>
<td>66</td>
<td>$&lt;10 : 1$</td>
</tr>
<tr>
<td>12</td>
<td>2g instead of 2a, DCE : DMSO (1 : 1, v/v), rt</td>
<td>Trace</td>
<td>—</td>
</tr>
<tr>
<td>13</td>
<td>1b instead of 1a</td>
<td>Trace</td>
<td>—</td>
</tr>
<tr>
<td>14</td>
<td>DCE instead of DCE : H\textsubscript{2}O (2 : 1, v/v), rt</td>
<td>60</td>
<td>17 : 1</td>
</tr>
<tr>
<td>15</td>
<td>DCE instead of DCE : H\textsubscript{2}O (2 : 1, v/v), $-5$ °C</td>
<td>67</td>
<td>$&gt;20 : 1$</td>
</tr>
<tr>
<td>16</td>
<td>Without 4CICzIPN, (TMS)\textsubscript{3}SO\textsubscript{2}H or K\textsubscript{3}PO\textsubscript{4}</td>
<td>Trace</td>
<td>—</td>
</tr>
<tr>
<td>17</td>
<td>Under dark conditions</td>
<td>Trace</td>
<td>—</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Standard conditions: unless specified, a mixture of glycosyl bromide (0.2 mmol), sulfur electrophile (0.1 mmol), 4CICzIPN (0.005 mmol), K\textsubscript{3}PO\textsubscript{4} (0.4 mmol), and (TMS)\textsubscript{3}SO\textsubscript{2}H (0.15 mmol) in DCE:DMSO (1 mL, 1 : 1, v/v) or DCE:H\textsubscript{2}O (1.5 mL, 2 : 1, v/v) was irradiated with 40 W Kessil blue LEDs in a N\textsubscript{2} atmosphere at $-5$ °C for 24 h. \textsuperscript{b} Yield determined by $^1$H NMR using 1,1,2,2-tetrachloroethane as an internal reference. \textsuperscript{c} Ratio determined by crude $^1$H NMR. \textsuperscript{d} Isolated yield.
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.\textsuperscript{14} 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 make them more difficult to abstract.\textsuperscript{15} Therefore, various silanes were screened and (TMS)\textsubscript{3}SiOH was the best, giving 3a in 37% yield (Table S1, entries 3–5 and 8–9). A survey of PSs revealed 4ClCzIPN\textsubscript{21b,c} as the optimal promoter starting from entry 11 (Table 1), giving 3a in high yield. Among the thiosulfonates probed (entries 6–12), methanethiosulfonate (2a) was the best, possibly attributed to the lower hindrance and relatively high redox stability ($E_{\text{red}} = -1.65$ V vs. SCE, Fig. S3\textsuperscript{†}). Glycosyl chloride (1b) did not undergo the dechlorination presumably due to its strong C–Cl bond (entry 13). To further improve the stereoselectivity (entry 6), we conducted reaction optimization including the solvent and reaction temperature (Table 1, entries 14–15 and Tables S3 and S6\textsuperscript{†}). It was found that the biphasic solvent (DCE : H\textsubscript{2}O = 2 : 1) could not only retain the high anomeric selectivity but also increase the yield (76%, entry 1), and a 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)\textsubscript{3}SiOH, and PS were essential for this transformation (entries 16–17).

The generality of the new S-glycosylation was examined. We first evaluated the performance using glucosyl bromide (1a) as a 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 thiophenyl (3i) and furanyl (3j) enabled access to medicinally valued thioglycosides. The tetrazole derived disulfide instead of labile thiosulfonate could serve as an alternative and delivered the desired 3k. The reaction performed in DCE : H\textsubscript{2}O failed for pyridinyl thiosulfonate. Decent results (3l, 79%, $\alpha : \beta > 20 : 1$) were obtained with DCE : DMSO (condition B). The protocol can also be applied in gram scale synthesis. Notably, less reactive sp\textsuperscript{3} alkyl glycosides 3o–3s could be synthesized with the protocol.\textsuperscript{17}

For even less electrophilic substrates, p-tolylthiosulfonates (3q–3u) displayed better performance than methylthiosulfonates. Particularly, a long alkyl chain with a Z-double bond product (3u), which exhibits intriguing antitumor activity

**Scheme 3** Scope of thiosulfonates. \textsuperscript{a}Reaction conditions: unless specified, see footnote a of Table 1 and the ESI; \textsuperscript{†}isolated yield; the ratio of $\alpha$ and $\beta$ anomers determined by crude $^1$H NMR. \textsuperscript{b}Yield after hydrolysis of the acyl group. \textsuperscript{c}Disulfide used. \textsuperscript{d}Toluenethiosulfonate used. \textsuperscript{e}Z/E ratio determined by $^1$H NMR.
(Scheme 1), is efficiently prepared with high diastereoselectivity. The limitation of the method is also realized. C$_2$–N-Ac-saccharides such as $\alpha$-glucosamine failed to react due to the lability of these reactants (see Fig. S5 in the ESI).

The alternation of sugars was probed next (Scheme 4). Both common hexoses (glucose 3v–3x, galactose 3y, mannose 3z, fucose 3aa, rhamnopyranose 3ah, and glucuronic acid 3ac) and pentoses (3ad–3af) gave good yields and high stereoselectivity. Among the tested monosaccharides, except ribose (3ai), the others gave expected $\alpha$-selectivity owing to the steric effect, the others gave expected $\beta$-selectivity. Furthermore, disaccharides (3ag and 3ah) could participate in the process smoothly. For xyloses (3ai–3aj), the obtained products adopted $\beta$ orientation since the anomeric xylosyl radical is $\beta$ selective. 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 xylose-derived bioactive analogs. Finally, the strategy can also be extended for the synthesis of synthetically challenging $\alpha$-2-cis-selenoglycosides (Scheme 4 and Table S7†). For example, under the reaction conditions (see footnote a of Table 1, DCE : H$_2$O, v/v, 2 : 1), four glycosyl bromides could couple with methyl phenylselenyl sulfonate to deliver the corresponding $\alpha$-seleno-glycosides 3ak–3am with uniformly high stereoselectivity ($\alpha$ : $\beta$ > 20 : 1).

The capacity of selective functionalization of biologically relevant structures is exemplified by late-stage thio-glycosylation of therapeutics. The incorporation of thioglycosyl moieties into estrone (3av), Captoporil (3aw), and flavone (3ax) has been realized smoothly.

In the new thio-glycosylation reaction, critically (TMS)$_3$SiOH was identified as a HAT reagent, which could efficiently suppress the undesired reduction of the radical 8 (Scheme 6a). This may be attributed to the strong O–H bond (calculated BDE = 98 kcal mol$^{-1}$, see the ESI†) of B–H: 83 kcal mol$^{-1}$) and steric hindrance, making the H difficult for 8 to abstract. This strong bond also echoes the use of stronger 4ClCzIPN (E$^\dagger$/E$^\ominus$ = 1.58 V vs. SCE) to oxidize the silyloxide [(TMS)$_3$SiO]/(TMS)$_3$SiO$^\dagger$ = 1.54 V vs. SCE). A spontaneous Brook rearrangement of silyloxy radical 6 forms a silicon-centred radical 7, which acts as an effective debrominator. The anomic effect makes the radical 8 axially positioned and directs $\alpha$-selective coupling with 1,6'-C1-6' connected thioglycosides 3ao–3aq were efficiently synthesized. It is noted that a native unprotected saccharide thiosulfonate could be used for efficient cross coupling (3aq).

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thiosulfonate. In the reactions, we still observed a notable amount of the reduction product. 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 thio-
glycosylation process. Finally, a radical trapping study with TEMPO and methyl acrylate further confirms the radical engaged process (Scheme 6c).

Conclusions

In conclusion, we have developed a metal-free, glycosyl radical strategy for the stereoselective synthesis of thioglycosides as radical precursors. The uncovered organophotoredox mediated HAT radical pathway can highly stereoselectively induce the formation of an anemic C-S bond while minimizing the side reactions. The power of the platform has been underscored by the mild reaction conditions enabling the 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 with both sp² and sp³ 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.

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Notes and references


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