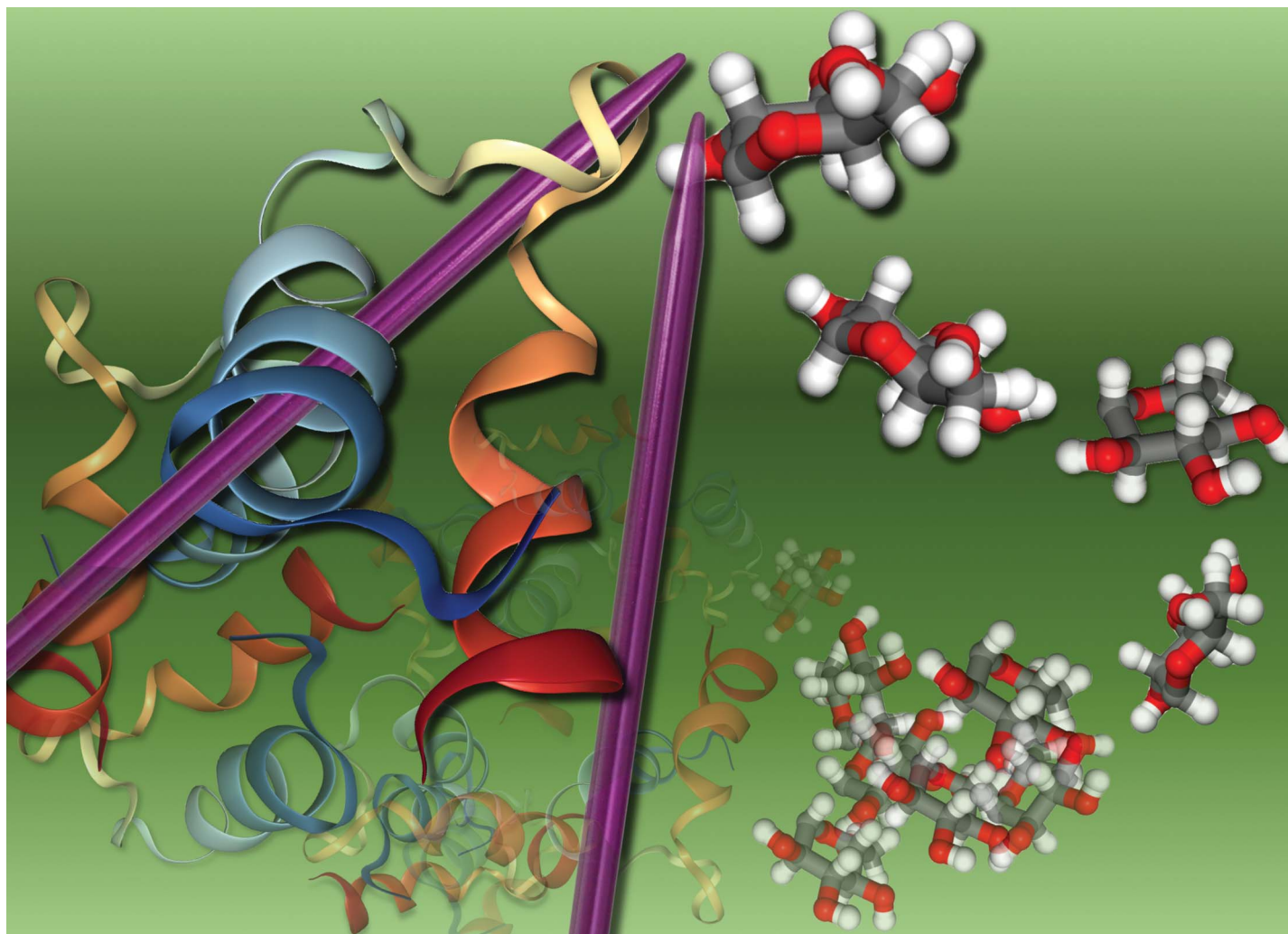




Showcasing research from Professors Hien Nguyen and Jenn Stockdill's laboratories, Department of Chemistry, Wayne State University, Detroit, MI, USA.

Facile triflic acid-catalyzed  $\alpha$ -1,2-*cis*-thio glycosylations: scope and application to the synthesis of S-linked oligosaccharides, glycolipids, sublancin glycopeptides, and T<sub>N</sub>/T<sub>F</sub> antigens

Catalytic triflic acid cleanly knits together glycan donors with thiol acceptors to form glycosyl linkages to peptides, sugars and lipids with excellent  $\alpha$ -selectivity. This back cover art was generated from images downloaded from the Protein Data Bank's NGL viewer. (Rose et. al., *Bioinformatics* **2018**, 34, 3755–3758.)

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# Facile triflic acid-catalyzed $\alpha$ -1,2-*cis*-thio glycosylations: scope and application to the synthesis of *S*-linked oligosaccharides, glycolipids, sublancin glycopeptides, and T<sub>N</sub>/T<sub>F</sub> antigens†

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Studies of *S*-linked glycoconjugates have attracted growing interest because of their enhanced chemical stability and enzymatic resistance over *O*-glycoside counterparts. We here report a facile approach to access  $\alpha$ -1,2-*cis*-*S*-linked glycosides using triflic acid as a catalyst to promote the glycosylation of a series of thiols with *D*-glucosamine, galactosamine, glucose, and galactose electrophiles. This method is broadly applicable for the stereoselective synthesis of *S*-linked glycopeptides, oligosaccharides and glycolipids in high yield and excellent  $\alpha$ -selectivity. Many of the synthetic limitations associated with the preparation of these *S*-linked products are overcome by this catalytic method.

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## Introduction

Protein glycosylation, one of the most ubiquitous post-translational modifications, typically involves the attachment of carbohydrate chains to proteins through the hydroxyl group of serine or threonine (*O*-glycans) or the amido group of asparagine (*N*-glycans).<sup>1–5</sup> The resulting glycoproteins exhibit a diverse array of biological functions such as cell adhesion, protein folding, signal transduction, and immune response.<sup>1–5</sup> However, naturally occurring glycoproteins exist as mixtures of glycoforms, and their isolation as homogeneous species is a complicated process.<sup>6</sup> As such, there is a great demand for methods to efficiently access structurally defined glycoproteins. Recently, replacement of the anomeric oxygen of *O*-linked glycosides with a sulfur atom to generate *S*-linked glycosides has attracted considerable attention because of the enhanced resistance of the latter to chemical and enzymatic hydrolysis.<sup>7,8</sup> In addition, *S*-linked glycosides exhibit similar conformational preferences and equal or even improved biological activities compared to their native *O*-glycoside counterparts.<sup>9–11</sup> In this context, *S*-linked glycan analogs could be utilized as structural mimetics and serve as powerful tools for the biological study of the natural *O*-linked substrates. The recent discovery of *S*-glycosylation, the addition of carbohydrate residues to the sulfur atom of cysteine on bacterial peptides,<sup>12–14</sup> suggests that

naturally existing *S*-linked glycoproteins may be more widespread than was previously thought and may lead to the development of new therapeutics.

Given the significant importance of thiol-containing carbohydrate molecules, methods that enable access to the challenging  $\alpha$ -1,2-*cis* thiol glycosidic linkages are of high synthetic value. Formation of  $\beta$ -1,2-*trans* glycosides can be readily accomplished by employing electrophiles with C(2)-participatory groups.<sup>15</sup> The stereoselective formation of  $\alpha$ -1,2-*cis* glycosides, however, has proven challenging, and a mixture of  $\alpha$ - and  $\beta$ -glycosides is often obtained.<sup>15</sup> A variety of strategies have been reported for the synthesis of mucin-related  $\alpha$ -thiol-containing GalNAc glycopeptide mimetics.<sup>16–24</sup> Representative methods include stereoselective preparation of  $\alpha$ -GalNAc thiols followed by (1) an S<sub>N</sub>2 displacement with  $\beta$ -bromoalanine-containing peptides,<sup>16,17</sup> (2) site-selective conjugation with aziridine-containing peptides,<sup>18,19</sup> or (3) conjugate addition to dehydroalanine-containing peptides.<sup>20</sup> S<sub>N</sub>2 reaction of  $\alpha$ -glycosyl thiols with 4-axial triflate glycosides<sup>21,22</sup> 6-iodinated glycosides,<sup>23–25</sup> enzymatic glycosylation,<sup>26–29</sup> and metal-catalyzed cross coupling,<sup>30,31</sup> have also been reported to generate  $\alpha$ -1,2 *cis* *S*-linked oligosaccharides and glycopeptides. Despite these important advances over the past decades, numerous challenges remain, including the need for highly specialized coupling partners and the multistep preparation of bromoalanine-, aziridine-, and dehydroalanine-containing amino acid residues or peptides.<sup>32</sup> In addition, most of the current methods are limited to specific classes of thiol nucleophiles. To date, there is only one reported method that is applicable for a variety of sulfur nucleophiles, and it uses glycosyl stannane to promote *S*-linked glycoside formation.<sup>31</sup>

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† Electronic supplementary information (ESI) available: Procedures, analytical data, and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra. See DOI: 10.1039/c9sc04079j

We recently found that triflic acid, released from nickel triflate, can effectively promote the glycosylations of serine/threonine amino acids and hydroxyl groups of carbohydrates with the C(2)-*N-ortho*-(trifluoromethyl)benzylidenamino *N*-phenyl trifluoroacetimidates.<sup>33–36</sup> This catalytic system features several advantages such as mild conditions, short reaction time, good yields and excellent levels of  $\alpha$ -selectivity. However, the question remains whether it will be suited for *S*-glycosylations as Lewis acid-promoted reactions are known to be incompatible with thiol nucleophiles.<sup>37–40</sup> Lewis acid-promoted *S*-glycosylations were underutilized with a few limited examples.<sup>37–40</sup> The reactions generally proceed to provide the coupling products with low yields and require stoichiometric amount of promoter. An inherent issue with the *S*-nucleophiles is their tendency to undergo oxidation to form disulfide and other side products.<sup>38</sup> They also react with the TMSOTf catalyst during the glycosylation process.<sup>40</sup> All those factors make it more challenging to handle *S*-nucleophiles than their *O*-counterparts.

Herein we report a distinct approach to *S*-linked glycosylations: a triflic acid catalyst is shown to enable the facile  $\alpha$ -1,2-*cis* synthesis of thiol-oligosaccharides, glycopeptide of antimicrobial sublancin, *S*-linked tumor-associated T<sub>N</sub>/T<sub>F</sub> antigens, and thiol-glycolipids. This strategy obviates the need for substrate prefunctionalization and can proceed by direct coupling of thiol-containing molecules or cysteine-containing peptides with *N*-phenyl trifluoroacetimidates.

## Results and discussions

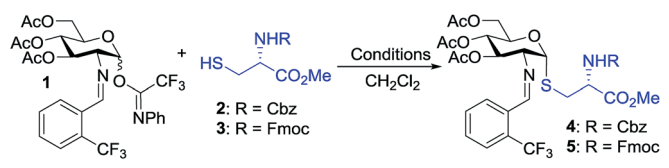
To test our hypothesis, we initiated our study by examining the glycosylation of *N*-Cbz cysteine methyl ester **2** with C(2)-*N-ortho*-(trifluoromethyl)benzylidene glucosamine *N*-phenyl trifluoroacetimidate **1** under previously established conditions (Table 1).<sup>36</sup> To our delight, the coupling of **2** with **1** was

successful using 15 mol% nickel triflate, Ni(OTf)<sub>2</sub>, (entry 1). As we expected based on the previously reported conditions,<sup>36</sup> the reaction with 5 mol% triflic acid, TfOH, proceeded to completion within 1 h at 35 °C (entry 2) to afford the desired thiol-linked glycoconjugate **4** in 68% yield with excellent selectivity ( $\alpha$  :  $\beta$  > 20 : 1). This result is consistent with our recently reported mechanism of the triflic acid-catalyzed  $\alpha$ -selective 1,2-*cis* glycosylation with *N*-phenyl trifluoroacetimidate electrophiles.<sup>36</sup> Specifically, triflic acid engages in the activation of electrophile **1** to generate a glycosyl triflate intermediate, which then undergoes equilibration from the stable  $\alpha$ -anomer to the more reactive  $\beta$ -anomer. Subsequent S<sub>N</sub>2-like displacement of the reactive  $\beta$ -anomer of glycosyl triflate by **2** results in the formation of **4** with exclusive  $\alpha$ -configuration.

We observed that while the reaction proceeded to completion faster with use of triflic acid, the glycol elimination product derived from donor **1** was also detected (see Fig. S1† for details). Lowering the reaction temperature (entry 3) and catalyst loading (entry 4) provided a similar outcome (Table 1). To address the problem of **1** from undergoing elimination, the cysteine residue **2** was utilized as the limiting reagent in the presence of 1.5 equiv. of donor **1**. This modification improved the yield to 76% (entry 5). Further increasing the donor **1** to two equivalents gave the desired coupling product **4** in an enhanced 81% yield while maintaining high levels of selectivity (entry 6). Most notably, the glycosylation reached completion within 1 h at 25 °C with use of 5 mol% TfOH to provide **4** with comparable yield and  $\alpha$ -selectivity (entry 7). The cysteine residue **3** with *N*-Fmoc protection, commonly utilized in the solid-phase peptide synthesis (SPPS), also displayed good efficiency (entry 8) to provide the desired glycoconjugate **5** (Table 1) in good yield and  $\alpha$ -selectivity.

With the optimized conditions in hand, we evaluated the scope of the triflic acid-catalyzed *S*-glycosylations (Fig. 1) using

Table 1 Optimization of the reaction conditions<sup>a</sup>

|  |                      |                           |                              |            |          |                                            |
|--------------------------------------------------------------------------------------|----------------------|---------------------------|------------------------------|------------|----------|--------------------------------------------|
| Entry                                                                                | <b>1</b><br>(equiv.) | <b>2 or 3</b><br>(equiv.) | Catalyst                     | Temp. (°C) | Time (h) | <b>4 or 5</b> yield ( $\alpha$ : $\beta$ ) |
| 1                                                                                    | 1                    | <b>2</b> (1.5)            | 15 mol% Ni(OTf) <sub>2</sub> | 35         | 16       | <b>4</b> : 66% (>20 : 1)                   |
| 2                                                                                    | 1                    | <b>2</b> (1.5)            | 5 mol% TfOH                  | 35         | 1        | <b>4</b> : 64% (>20 : 1)                   |
| 3                                                                                    | 1                    | <b>2</b> (1.5)            | 5 mol% TfOH                  | 25         | 2        | <b>4</b> : 68% (>20 : 1)                   |
| 4                                                                                    | 1                    | <b>2</b> (1.5)            | 1 mol% TfOH                  | 25         | 20       | <b>4</b> : 67% (>20 : 1)                   |
| 5                                                                                    | 1.5                  | <b>2</b> (1.0)            | 3 mol% TfOH                  | 25         | 3        | <b>4</b> : 76% (>20 : 1)                   |
| 6                                                                                    | 2                    | <b>2</b> (1.0)            | 3 mol% TfOH                  | 25         | 3        | <b>4</b> : 81% (>20 : 1)                   |
| 7                                                                                    | 2                    | <b>2</b> (1.0)            | 5 mol% TfOH                  | 25         | 1        | <b>4</b> : 80% (>20 : 1)                   |
| 8                                                                                    | 2                    | <b>3</b> (1.0)            | 5 mol% TfOH                  | 25         | 1        | <b>5</b> : 78% (>20 : 1)                   |

<sup>a</sup> The reaction was conducted with 0.1–0.2 mmol of donor **1**. Yields of the isolated product averaged two runs. The ( $\alpha$ / $\beta$ ) ratios were determined by <sup>1</sup>H NMR analysis.



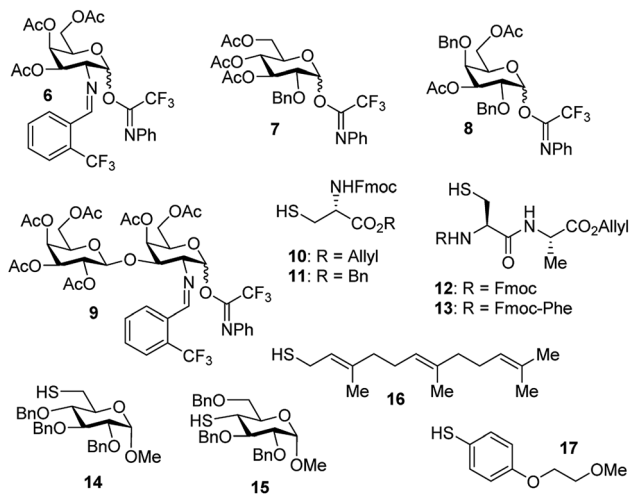


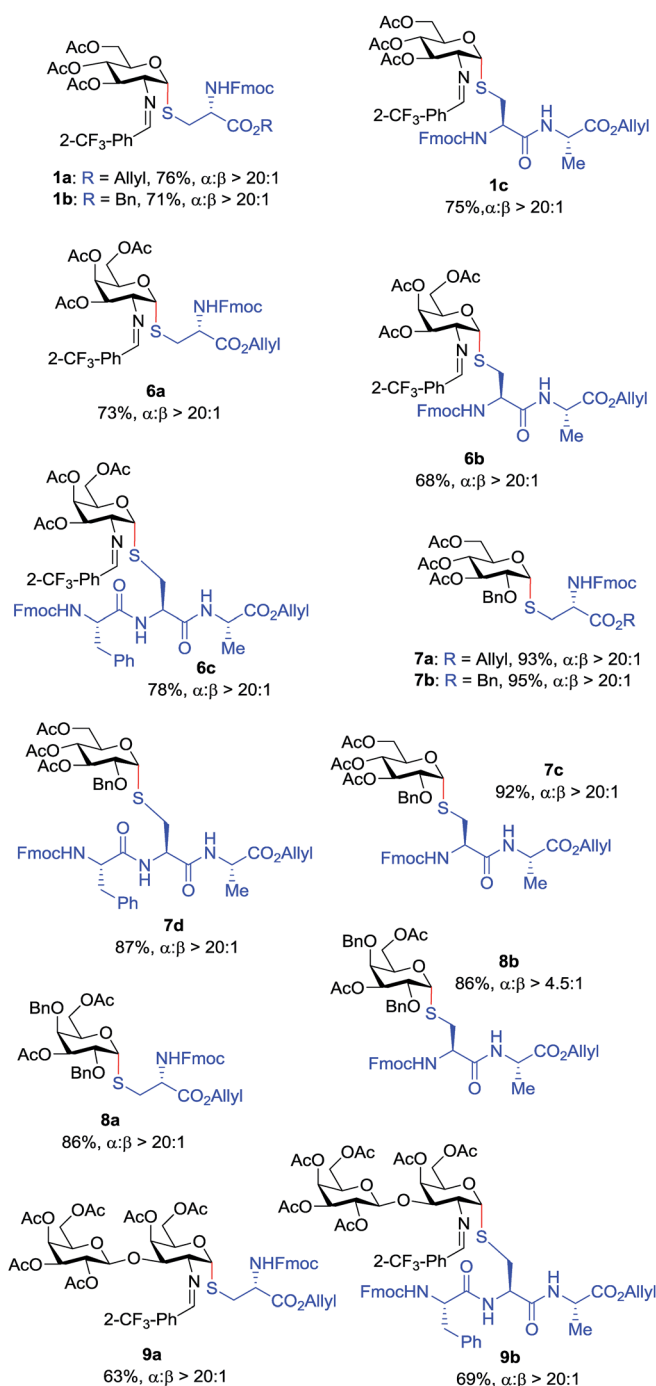
Fig. 1 Carbohydrate donors and thiol-containing acceptors.

glycosyl *N*-phenyl trifluoroacetimidate donors (**1**, **6**–**9**) and thiol-containing molecules (**10**–**17**). Based on our previous study,<sup>36</sup> we anticipated that *N*-phenyl trifluoroacetimidates **1**, **6** and **7** would exhibit high  $\alpha$ -selectivity because their C(2)-*N*-benzylidene and C(2)-benzyl ether can modulate the electronic properties of the anomeric carbon, facilitating isomerization of the glycosyl triflate intermediate. Indeed, both donors **1** and **6** were effectively glycosylated to cysteine amino acids **10** and **11** to provide **1a**, **1b**, and **6a**, respectively, in good yield and with excellent  $\alpha$ -selectivity (Table 2). There are several underlying factors that could influence the stereochemical outcome of the coupling event. To confirm that the  $\alpha$ -selectivity arise from the directing ability of the C(2)-*N*-benzylidene group, we also coupled C(2)-azido donors **18** and **19** with cysteine residue **10** under standard conditions (Scheme 1). The desired products **18a** and **19a** were obtained with poor levels of  $\alpha$ -selectivity ( $\alpha$  :  $\beta$  = 1.6 : 1 to 2 : 1).

These results in Scheme 1 support the importance of the C(2)-*N*-benzylidene group in the triflic acid-catalyzed stereoselective  $\alpha$ -1,2-*cis* *S*-linked glycosylation. Next, we expanded nucleophilic scope from single cysteine amino acid to more complex peptides. Both dipeptide **12** and tripeptide **13** (Fig. 1) performed well under the standard conditions with **1** and **6** to afford glycopeptides **1c**, **6b**, and **6c** (Table 2), presaging the potential utility of this transformation for access *S*-linked glycopeptides of tumor-associated mucin T<sub>N</sub> and T<sub>F</sub> antigens (*vide infra*).<sup>11,44</sup>

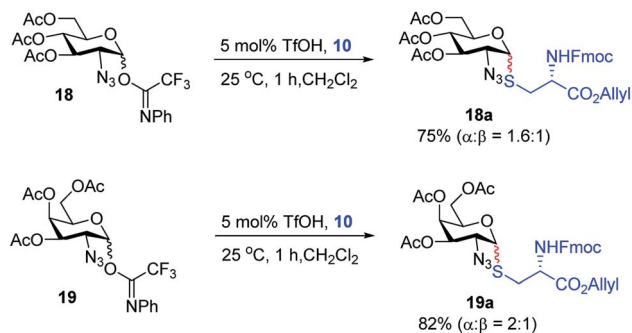
In addition to C(2)-*N*-benzylidene electrophiles **1** and **6**, the C(2)-*O*-benzyl protecting group is tolerated. Glucose donor **7** (Table 2) was an effective electrophilic partner, providing the coupling products **7a**–**7d** in excellent yields (87–95%) with exclusive  $\alpha$ -configuration. More importantly, donor **7** does not generate a glycal elimination product. Employing the axial 4-*O*-benzyl protected donor **8** in place of the equatorial 4-*O*-acetyl group (**7**) slightly diminished the  $\alpha$ -selectivity (**8a**:  $\alpha$  :  $\beta$  > 20 : 1, **8b**:  $\alpha$  :  $\beta$  = 4.5 : 1). Nevertheless, this result illustrates the ability of this catalytic system to overturn the inherent bias of *D*-galactose donors whose axial C(4)-*O*-benzyl protecting group

Table 2 Scope with respect to cysteine-containing peptides<sup>a</sup>

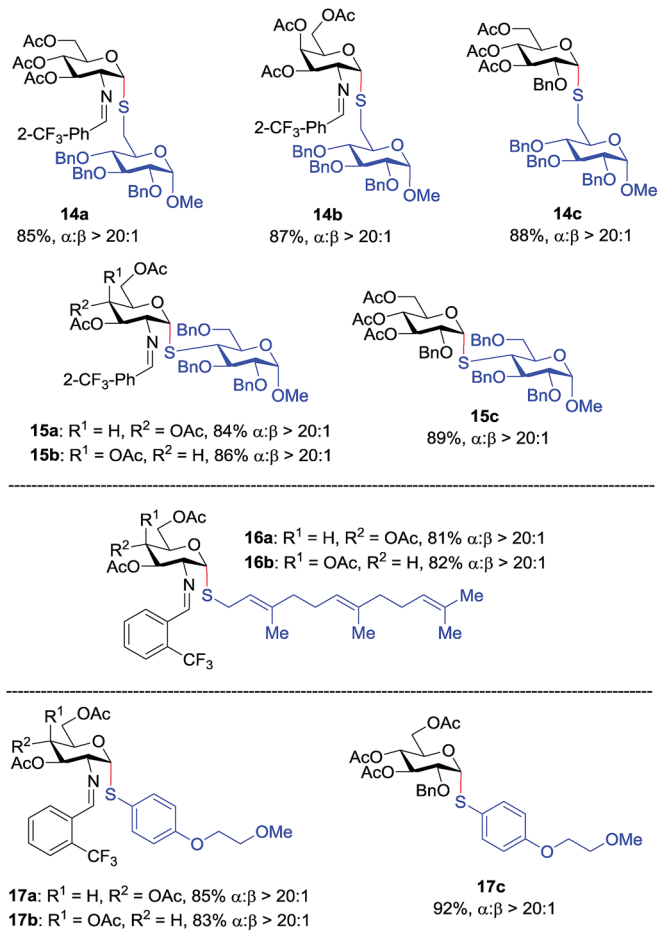


<sup>a</sup> All reactions were conducted with donor (2 equiv.), acceptor (1 equiv.) and 5 mol% TfOH in CH<sub>2</sub>Cl<sub>2</sub> at 25 °C for 1 h. Yields of isolated *S*-linked glycopeptides averaged two runs. The ( $\alpha$ / $\beta$ ) ratios were determined by <sup>1</sup>H NMR analysis.

has been reported to favor  $\beta$ -products.<sup>41</sup> The difference in  $\alpha$ -selectivity between the coupling products **8a** and **8b** could be explained by the relative rate for anomerization of the  $\alpha$ -to the  $\beta$ -glycosyl triflate intermediate generated from the reaction of glycosyl electrophile **8** with triflic acid. Since a dipeptide is

Scheme 1 Glycosylation with C(2)-azido donors **18** and **19**.

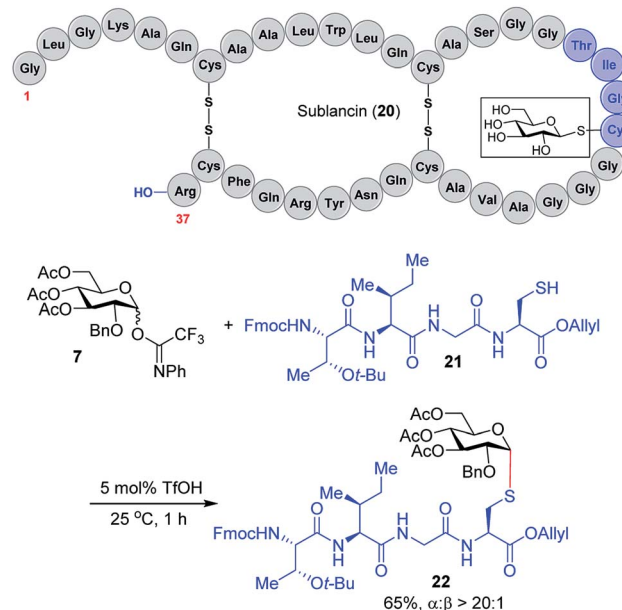
a more reactive nucleophile than a cysteine amino acid residue, less time is allowed for anomerization of the  $\alpha$ -triflate to the more reactive  $\beta$ -triflate, resulting in decreasing the  $\alpha$ -selectivity observed in the coupling product **8b**. Finally, disaccharide donor **9**, a carbohydrate motif of T<sub>F</sub> antigen,<sup>42</sup> was readily coupled to provide the corresponding 1,2-*cis* *S*-glycoconjugates **9a** and **9b** (63–69%,  $\alpha : \beta > 20 : 1$ ).

Table 3 Scope with respect to thiol-containing acceptors<sup>a</sup>

<sup>a</sup> See Table 2.

Inspired by the above discovery, we next examined the scope with respect to nucleophilic coupling partners **14–17**. As illustrated in Table 3, the glycosylations of primary (**14**) and secondary (**15**) thiol acceptors with donors **1**, **6**, and **7** proceeded smoothly to produce the desired *S*-linked disaccharides **14a–c** and **15a–c** in good yields (84–89%) with exclusive  $\alpha$ -selectivity. The *trans,trans*-farnesyl mercaptan **16** was also a suitable nucleophile (**16a, b**), revealing the potential utility of this method for preparation of *S*-linked glycolipids. Recently, Mes-saudi and co-workers reported the Pd-mediated cross coupling of aryl iodides with  $\beta$ -glycosyl thiols to generate *S*-linked glycosides with exclusive  $\beta$ -configuration.<sup>30</sup> For comparison, we examined the coupling efficiency of our method with aryl thiol **17**. To our delight, the reaction compared favorably with excellent  $\alpha$ -stereoselectivity and yield (**17a–c**).

We expect that the triflic acid-catalyzed  $\alpha$ -1,2-*cis* *S*-linked glycosylation method will be particularly useful when applied to the synthesis of bioactive glycopeptides. To establish the potential of a late-stage glycosylation approach, we prepared the tetrapeptide sequence surrounding the  $\beta$ -linked D-glucose unit in sublancin **20** (Scheme 2). This *S*-linked glycosyl unit is essential for antimicrobial activity.<sup>12</sup> SunS, the recently discovered *S*-glycosyl transferase enzyme, is responsible for the unusual glycosylation of cysteine residues with carbohydrates.<sup>12</sup> It has a relaxed substrate specificity and is able to glycosylate other hexose sugars, which has allowed its use in the preparation of sublancin analogs bearing other  $\beta$ -linked glycans.<sup>12,13</sup> However, to the best of our knowledge, the activity of  $\alpha$ -1,2-*cis* *S*-linked sublancin analogs has not been investigated,<sup>10</sup> presumably because of the difficulty of  $\alpha$ -1,2-*cis* *S*-glycosylations. Our current catalytic method would provide an ideal approach for the assembly of such analogs. Accordingly, we investigated the coupling of tetrapeptide **21** with glucose donor **7** in the presence of 5 mol% triflic acid. The



Scheme 2 Synthesis of the sublancin glycopeptide fragment.

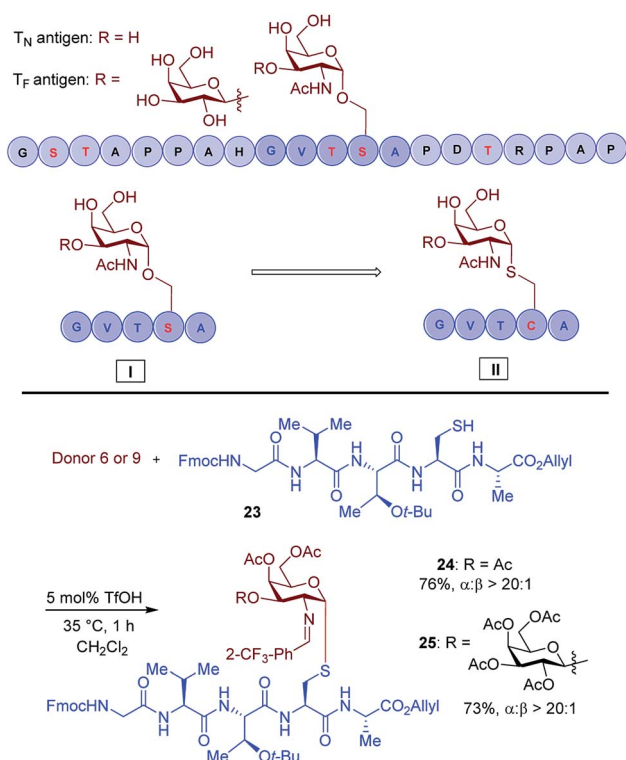
Another important application of this method is the preparation of *S*-linked glycopeptides as analogs of MUC1 type tumor-associated T<sub>N</sub>/T<sub>F</sub> antigens. MUC1 is a glycoprotein that consists of a tandem 20 amino acids repeating unit, with five possible *O*-glycosylation sites (serine or threonine) (Scheme 3).<sup>43</sup> In normal cells, the protein backbone is decorated with complex oligosaccharides, while the glycosylation is incomplete in cancer cells. As such, multiple epitopes such as T<sub>N</sub>/T<sub>F</sub> antigens are exposed to the immune system and can be targeted for the development of antitumor vaccines. A therapeutic vaccine employing multivalent T<sub>N</sub>-antigen clusters and CS4+ T-cell epitopes (MAG-Tn3) has entered to clinical trials.<sup>44</sup> It has been reported that anti-T<sub>N</sub> monoclonal antibodies (mAbs) have a binding preference for T<sub>N</sub>-Ser antigen, and the short MUC1 pentapeptide, GVTSA, is a suitable binding motif for mAbs.<sup>43</sup> Since the *S*-linked T<sub>N</sub> antigen has been proved to enhance the immunogenicity,<sup>11</sup> we sought to prepare *S*-linked T<sub>N</sub>/T<sub>F</sub> antigen mimetics by exchanging the GVTSA sequence (I) for the GVTCA sequence (II) (Scheme 3). Accordingly, we investigated the coupling of GVTCA pentapeptide **23** with both monosaccharide donor **6** and disaccharide donor **9** in the presence of 5 mol% TfOH. The coupling proceeded smoothly at 35 °C for 1 h to provide the corresponding 1,2-*cis* *S*-linked glycopeptides **24** (T<sub>N</sub>) and **25** (T<sub>F</sub>) in 76% and 73% yield, respectively, with exclusive  $\alpha$ -selectivity (Scheme 3).

In conclusion, we have illustrated the utility of the triflic acid-catalyzed  $\alpha$ -1,2-*cis* thiol glycosylation reaction using stable glycosyl *N*-phenyl trifluoroacetimidates and thiol-containing molecules. This catalytic system obviates the need for substrate prefunctionalization and furnishes a diverse collection of synthetically valuable *S*-linked glycopeptides, oligosaccharides, and glycolipids with excellent  $\alpha$ -selectivity under mild and operationally simple conditions. Notably, the facile nature of this reaction have also successfully applied to the synthesis of *S*-linked glycopeptides of antimicrobial sublancin and tumor-associated mucin T<sub>N</sub>/T<sub>F</sub> antigens. Our future investigations will focus on transforming the current method to automated synthesis for the synthesis of the  $\alpha$ -1,2-*cis* *S*-linked glycosides.

There are no conflicts to declare.

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**Scheme 3** Substrate synthesis of S-linked T<sub>N</sub> and T<sub>F</sub> glycopeptide fragments.

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