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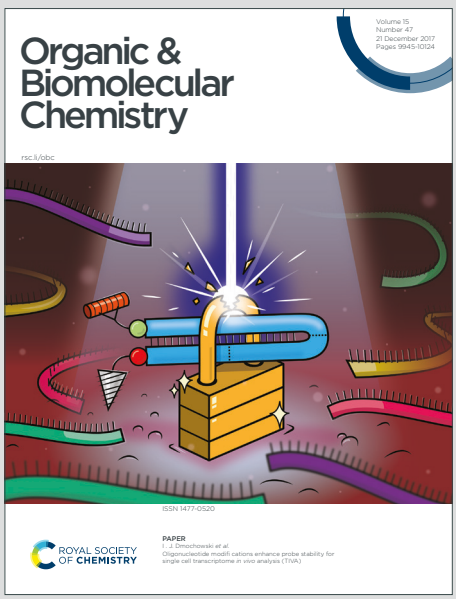

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Use of Remote Acyl Groups for Stereoselective 1,2-*Cis*-Glycosylation with Fluorinated Glucosazide Thiodonors

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Abstract. Fluorinated glycans are valuable probes for studying carbohydrate-protein interactions at the atomic level. Glucosamine is a ubiquitous component of glycans, and the stereoselective synthesis of α-linked fluorinated glucosamine is a challenge associated with the chemical synthesis of fluorinated glycans. We found that introducing a 6-*O*-acyl protecting group onto 3-fluoro and 4-fluoro glucosazide thiodonors endowed them with moderate α-selectivity in the glycosylation of carbohydrate acceptors, which was further improved by adjusting the acceptor reactivity via O-benzoylation. Excellent stereoselectivity was achieved for 3,6-di-*O*-acyl-4-fluoro analogues. The glycosylation of threonine-derived acceptors enabled the stereoselective synthesis of the protected fluorinated analogue of α-GlcNAc-*O*-Thr, a moiety abundant in cell-surface O-glycans of protozoan parasite *Trypanosoma cruzi*. DFT calculations supported the involvement of transient cationic species which resulted from the stabilization of the oxocarbenium ion through O-6 acyl group participation.

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Introduction.

2-Amino-2-deoxy-glucopyranoses (GlcN) linked as both 1,2-*cis*- and 1,2-*trans*-glycosides are structures found in various bioactive oligosaccharides.[1] While 1,2-*trans* (β-)glucosaminyl linkage can be reliably installed by taking advantage of neighbouring group participation by a C-2 amide or carbamate, there is no general method for the synthesis of 1,2-*cis* (α-)linked glucosamine. Several glycosylation strategies for the construction of 1,2-*cis*-linked 2-aminoglucopyranosides have been developed,[2-5] but glycosylation with 2-azido-2-deoxy-glucopyranosyl (also known as glucosazide) donors, first investigated by Paulsen,[6] is still widely used.[7-9] The presence of a non-participating C-2 azide does not guarantee α-selectivity, and a substantial amount of 1,2-*trans* glycosides can be formed.[8] Owing to the importance of fluorinated carbohydrates as inhibitors and probes for carbohydrate-protein interactions,[10-18] we have extended our initial interest in the synthesis of fluorinated aminopyranoses[19,20] to the systematic investigation of procedures for α-selective glucosaminylation with fluorinated GlcN donors. We have prepared O-benzylated deoxofluorinated glucosazide thiodonors **1** and **2** (Fig. 1) and examined their stereoselectivity in preactivation-based glycosylation with a Tf_2O/Ph_2SO promoter system against a set of model carbohydrate acceptors.[21] Both thiodonors favoured formation of the corresponding 2-azido-2-deoxy-β-glucosides with reactive acceptors, gradually loosing selectivity with decreasing acceptor reactivity. The stereoselective construction of 1,2-*cis*-linkages could not be accomplished under these conditions. The overall tendency of compounds **1** and **2** to form β-glycosides probably resulted from the destabilization of cationic intermediates by the combined electron-withdrawing effects of azide and fluorine substituents.[8,21]

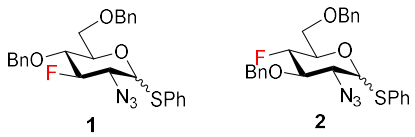

Figure 1. O-Benzylated 3-fluoro and 4-fluoro glucosazide thiodonors.

As thiodonors **1** and **2** were unsuitable for the stereoselective synthesis of 1,2-*cis* glycosidic linkages, we searched for an alternative. The α-stereodirecting effects of remote (non-vicinal) *O*-acyl protecting groups are increasingly recognized and applied synthetically, [22-27] although the involvement of putative bicyclic cationic intermediates shielding the *trans*-face of the donor has been questioned.[28,29] However, the

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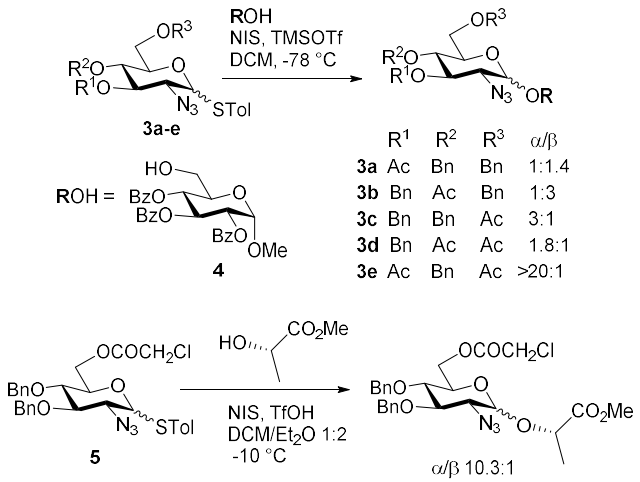
stereocontrol is reduced compared with participating functionalities at C-2, and empirical adjustment of the protecting groups and reaction conditions typically precedes successful α-glycosylation. For example, Li et al. showed that combining acetyl groups at the 3- and 6-positions in glucosazide thiodonor **3e** (Scheme 1) gave better α-selectivity in the glycosylation of primary acceptor **4** compared with 6-*O*-acetyl donor **3c**, while 3-*O*-acetyl donor **3a** was not selective, 4-*O*-acetyl donor **3b** was moderately β-selective and 4,6-di-*O*-acetyl donor **3d** was marginally α-selective.[30] Ventura reported that good α-stereoselectivity in the glycosylation of lactic acid ester with 6-*O*-chloroacetyl thiodonor **5** (Scheme 1) was achieved in CH_2Cl_2/Et_2O 1:2 at −10 °C, while the α-selectivity was eroded by omitting Et_2O, lower reaction temperatures, or using a 6-*O*-acetyl group.[31]

Scheme 1. Reported effects of remote acyl groups on stereoselectivity with glucosazide thiodonors.[30,31]



Inspired by these reports, we decided to evaluate the stereodirecting effects of remote *O*-acyl groups in deoxofluorinated glucosazide thiodonors. Accordingly, we prepared a series of *O*-acyl protected 3- and 4-deoxofluorinated phenyl 2-azido-2-deoxy-1-thioglucopyranosides and investigated the influence of protecting groups on glycosylation stereoselectivity. We also prepared and tested donors carrying large 6-*O*-*tert*-butyldimethylsilyl (TBS) and 6-*O*-*tert*-butyldiphenylsilyl (TBDPS) groups that were reported to increase α-selectivity by shielding the donor β-face.[32] The *N*-iodosuccinimide (NIS)/triflic acid (TfOH) activation system was selected because it is widely used,[33] making comparison with the results obtained for nonfluorinated glucosazide thiodonors possible.[30,31] Herein, we present the results of this investigation. The versatility of 1,6-anhydropyranose chemistry is demonstrated by the synthesis of orthogonally protected 3- and 4-deoxofluorinated phenyl 2-azido-2-deoxy-1-thioglucopyranosides. We also show that installing remote 6-*O*-acyl groups, combined with adjusting the acceptor reactivity, is a viable strategy for α-glycosylation with

fluorinated glucosazide thiodonors. The applicability of this glycosylation method is illustrated by the synthesis of a fluorinated α-GlcNAc-*O*-Thr moiety found in abundance in O-glycans of protozoan parasite *Trypanosoma cruzi*.

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Results and Discussion.

The *O*-acylated thiodonors were prepared as described in Scheme 2. Protecting group patterns were selected in which only the primary O-6 hydroxyl group or both the primary and secondary hydroxyl groups (O-3/O-4) were acylated. Selective acylation of a secondary hydroxyl group only was not attempted. The key transformation was cleavage of the internal acetal in 2-azido-3- or 4-fluoro-1,6-anhydropyranoses by reaction with phenyl trimethylsilyl sulfide (PhSTMS)/ZnI_2, followed by O-6 acylation or silylation. This approach allowed independent protection of the primary and secondary hydroxyls. 3-Fluoro analogues were prepared from known 2-azido-3-fluoro-1,6-anhydropyranoses **6** and **7**.[20] Reaction of compound **6** with PhSTMS[34] gave thioglycosides **α-8** and **β-8** as separable anomers that were converted to 6-*O*-benzyl derivative **1**[21] and 6-*O*-chloroacetyl derivatives **α-** and **β-9** in parallel. Separation of the anomers of thioglycoside **8** was necessary owing to an impurity that elutes between them during chromatography. For synthetic convenience, only the α-anomer (**α-8**) was converted to 6-*O*-benzoyl and 6-*O*-TBS derivatives **10** and **11**, respectively, using routine procedures. Microwave-assisted fluorination[35] of thioglycoside **α-8** yielded 3,6-difluoro analogue **12**. The β-anomer (**β-8**) was not reacted with diethylaminosulfur trifluoride (DAST) owing to the risk of SPh migration.[36] 4,6-*O*-Benzylidene derivative **13** was obtained from compound **7**[20] by trimethylsilylation, followed by reaction with PhSTMS, removal of the trimethylsilyl groups during workup and conventional 4,6-*O*-benzylidenation. O-Acetylation of compound **7**, followed by cleavage of the internal acetal to give thioglycoside **15** and subsequent acylation, furnished **16** and **17**. The synthesis of 4-fluoro thiodonors followed a similar sequence, commencing with known compounds **18** and **22**.[20,21] Therefore, 4-fluoro analogue **18**[21] was transformed into thioglycosides **2**,[21] **20**, and **21** via compound **19**,[21] while compound **22**[20] was converted into thioglycosides **25** and **26** via intermediates **23** and **24** (Scheme 2).

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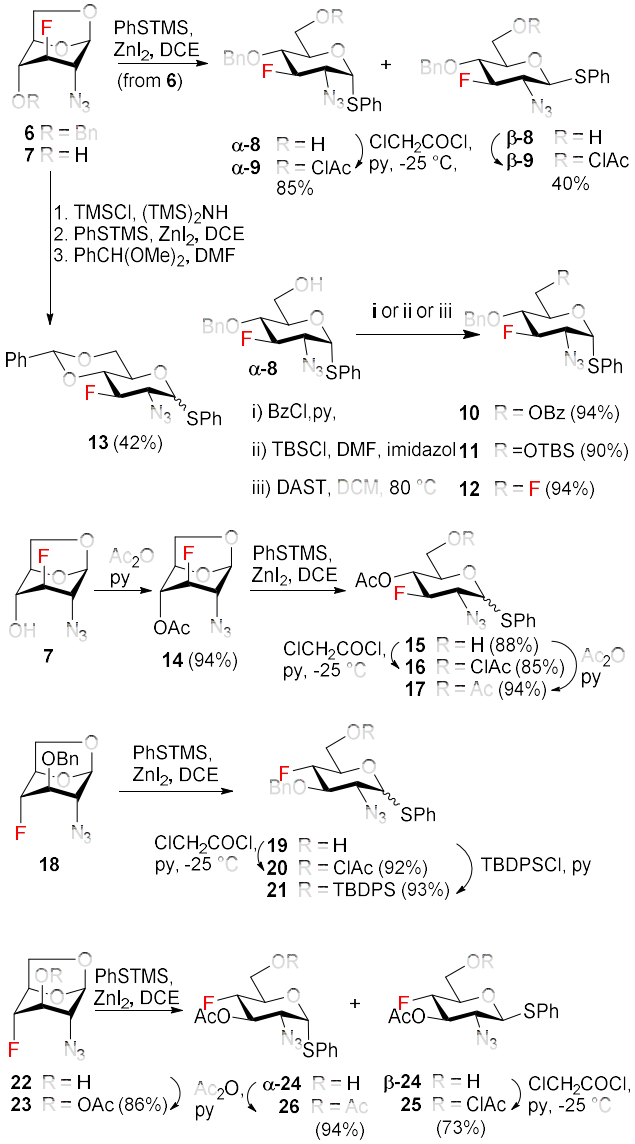
Scheme 2. Synthesis of deoxofluorinated thiodonors (ClAc = chloroacetyl).



Stereoselectivity in the glycosylation with 3-fluoro donors was evaluated against carbohydrate acceptors **A**,[37] **B**,[38] **C**,[38] **D**,[39] and **E**[40] (Table 1). A mixture of acceptor and thiodonor (1.2 equiv.) in dichloromethane was treated with NIS (2.2 equiv.) and TfOH (0.4–1.1 equiv.) to afford the corresponding glycosylation product. The anomeric configuration of the newly formed glycosidic bond was deduced from the magnitude of the vicinal $^{3}J_{H1,H2}$ coupling constants (3.5–3.9 Hz for 1,2-*cis* products and 7.5–8.5 Hz for 1,2-*trans* products). The anomeric ratio was determined by integration of the ^{19}F NMR signals of both anomers after aqueous workup, but prior to chromatography.

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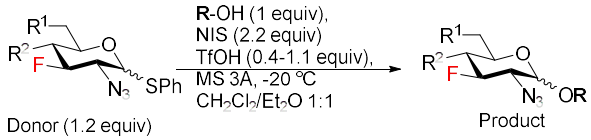
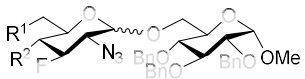
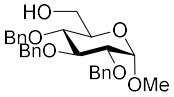
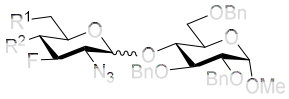
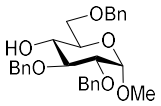
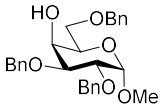
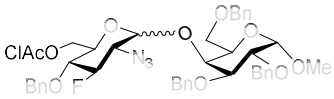
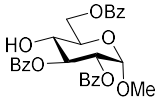
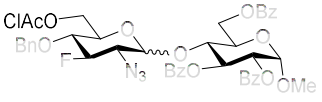
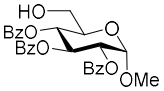
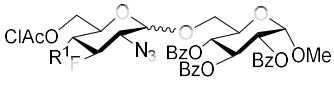
Table 1. Glycosylation of acceptors **R**-OH with 3-fluoro donors.



entry	Donor	R^1	R^2	Acceptor **R**-OH	Product	α/β	Yield
							
1	**α-1**	OBn	OBn		**A1**	1.2:1	85%
2	**β-9**	**OClAc**	OBn		**A9**	4.5:1	83%
3	**α-9**	**OClAc**	OBn		**A9**	5.2:1	78%
4	**10**	**OBz**	OBn	**A**	**A10**	5.2:1	82%
5	**11**	**OTBS**	OBn		**A11**	4.3:1	28%
6	**12**	**F**	OBn		**A12**	1.3:1	39%[a]
7	**13**	**PhCH<(O)O**			**A13**	1.8:1	[b]
							
8	**α-1**	OBn	OBn		**B1**	2.0:1	82%
9	**α-1**	OBn	OBn		**B1**	1:1.2[c]	86%
10	**α-9**	**OClAc**	OBn		**B9**	7.3:1	83%
11	**β-9**	**OClAc**	OBn	**B**	**B9**	9.6:1[d]	75%
12	**β-9**	**OClAc**	OBn		**B9**	9.7:1[e]	70%
13	**10**	**OBz**	OBn		**B10**	6.6:1	71%
14	**12**	**F**	OBn		**B12**	3.0:1	52%
15	**β-9**	**OClAc**	OBn	 **C**	 **C9**	8.7:1	68%
16	**β-9**	**OClAc**	OBn	 **D**	 **D9**	17.0:1[f]	59%
17	**16**	**OClAc**	**OAc**	 **E**	 **E16**	4.6:1	49%
18	**β-9**	**OClAc**	OBn		**E9**	7.6:1	67%

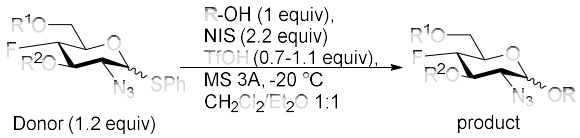
[a]Yield of β-anomer **A12-β** only, inseparable byproducts detected in α-anomer by ^{19}F NMR; [b]partial decomposition occurred during chromatography; [c]Et_2O omitted from the reaction mixture; [d]reaction conducted at 0 °C; [e]reaction conducted at 20 °C; [f]2 equiv of glycosyl donor used.

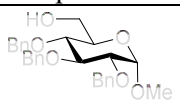
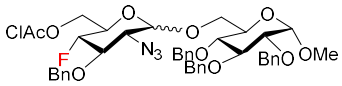
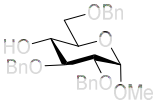
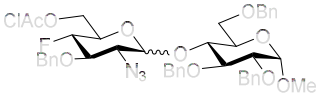
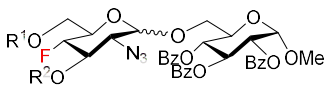
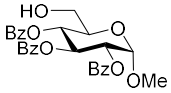
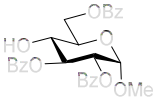
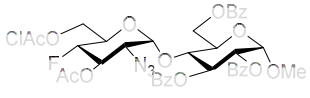
The results showed that the 1,2-*cis* stereoselectivity of the 3-fluoro glucosazide donors was improved by 6-*O*-acyl protection. For example, the glycosylation of primary acceptor **A** with O-benzylated donor **α-1** showed almost no selectivity (entry 1), while introducing chloroacetyl (entries 2 and 3) and benzoyl (entry 4) groups at O-6 improved the 1,2-*cis* stereoselectivity to 4.5–5.2:1. The nature of the tested acyl groups (chloroacetyl or benzoyl, entries 2–4, 10 and 13) and the anomeric configuration of the donor (entries 2 and 3) only marginally influenced the stereoselectivity. 6-*O*-TBS donor **11** gave selectivity comparable to 6-*O*-acyl donors, but a low yield (entry 5). Glycosylation with 4,6-*O*-benzylidene donor **13** resulted in low α-selectivity and decomposition during chromatographic purification (entry 7). Donors **11** and **13** were omitted from further experiments. Glycosylation with 3,6-difluoro donor **12** showed lower stereoselectivity compared with 6-*O*-acyl donors (entries 6 and 14), further indicating the α-directing effect of *O*-acyl groups at the 6-position. Decreased reactivity of the acceptor hydroxyl group due to its position and configuration in the hexopyranose framework (primary hydroxyl → secondary equatorial → secondary axial) improved the 1,2-*cis*/1,2-*trans* ratio (entries 1 vs. 8, 2 and 3 vs. 10 and 15, 4 vs. 13).[41] A significant improvement in α-stereoselectivity resulted from the glycosylation of secondary benzoyl protected ("disarmed") acceptor **D** (entry 16).[42] Using diethyl ether in the reaction mixture as co-solvent (entries 8 vs. 9), and increasing the temperature from −20 to 0 °C (entries 10 and 11) also improved the α-selectivity. Further increasing the temperature to 20 °C did not promote selectivity (entry 12). Reducing the reactivity of the primary acceptor through O-benzoylation, as in acceptor **E**, to compensate for the 4-*O*-acetyl β-directing effect in the glycosidation of 4,6-di-*O*-acyl donor **16** resulted in usable anomeric stereoselectivity (α/β = 4.6:1, entry 17). Related non-fluorinated 4,6-di-*O*-acetyl-3-*O*-benzyl D-glucosazide thiodonor **3d** (Scheme 1) has been reported as only slightly α-selective with the same acceptor (α/β = 1.8:1, Scheme 1),[30] probably due to glycosylation being conducted at a low temperature (−78 °C). As expected, 4-*O*-benzyl analogue **β-9**, which lacked the eroding influence of the 4-*O*-acetyl group, gave higher α-selectivity (α/β = 7.6:1, entry 18) compared with 4-*O*-acetyl thiodonor **16**.

Having established that an ester functionality at the 6-position improves the α-selectivity of 3-fluoro-D-glucosazide thiodonors, we further explored this concept with 4-fluoro-D-glucosazide thiodonors (Table 2). 6-*O*-Chloroacetyl-4-fluoro thiodonor **20** exhibited somewhat inferior α-selectivity compared with its 3-fluoro counterpart **9**. Thus, glycosylation of acceptor **A** with thiodonor **20** resulted in an anomeric (α/β) stereoselectivity of 2.9:1 (Table 2, entry 1) compared with values of 4.5:1 and 5.2:1 for thiodonors **β-9** and **α-**

9, respectively (Table 1, entries 2 and 3). The glycosylation of secondary acceptor **B** with thiodonor **20** gave a disappointing α/β selectivity of 3.3:1 (Table 2, entry 2), in contrast with the value of 7.3:1 obtained for thiodonor **α-9** (Table 1, entry 10). However, using disarmed *O*-benzoyl protected primary acceptor **E** improved the α/β stereoselectivity from 2.9:1 (Table 2, entry 1) to 5.6:1 (Table 2, entry 3). Thiodonor **21** with a bulky TBDPS group gave comparable results (Table 2, entry 4). In agreement with the literature,[30] the combined effects of 3-*O*-acetyl and 6-*O*-choroacetyl substituents in donor **25** resulted in a marked improvement in 1,2-*cis* selectivity (Table 2, entries 5 and 6). Unfortunately, product **E25** was isolated in only about 85% purity, owing to difficulties in chromatographic separation. Highly stereoselective glycosylation of the acceptor **D** with donor **25** did not reach completion, probably owing to the low reactivity of both reactants **D** and **25**, leading to a diminished yield (46%) and recovery of unreacted acceptor **D** from the reaction mixture (Table 2, entry 6).

Table 2. Glycosylation of acceptors **R**-OH with 4-fluoro glucosazide thiodonors.



entry	Donor	R^1	R^2	Acceptor **R**-OH	Product	α/β	Yield
1	**20**	**ClAc**	**Bn**	 **A**	 **A20**	2.9:1	63%
2	**20**	**ClAc**	**Bn**	 **B**	 **B20**	3.3:1	69%
							
3	**20**	**ClAc**	**Bn**	 **C**	**E20**	5.6:1	72%
4	**21**	**TBDPS**	**Bn**		**E21**	6.1:1	56%
5	**25**	**ClAc**	**Ac**		**E25**	>20:1	76%[a]
6	**25**	**ClAc**	**Ac**	 **D**	 **D25**	α only	46%[b]

[a]Isolated in approx. 85% purity (^{19}F NMR); [b]36% unreacted acceptor isolated.

Altogether, the results for the glycosylation of carbohydrate acceptors with 3-fluoro and 4-fluoro thiodonors indicated that, although O-6 acylation can reverse glycosylation diastereoselectivity in favour of

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the 1,2-*cis*-product, the α/β ratio of the resulting diastereoisomers mostly achieved moderate values. Significant improvement can be achieved by adjusting the acceptor reactivity by installing benzoate esters instead of benzyl ethers,[42] by increasing the reaction temperature to 0 °C, and by combining O-6 and O-3 acylation. The impact of acceptor reactivity on glycosylation stereoselectivity has recently been reviewed, and our results are consistent with the general trends.[41] Furthermore, the bulky O-6 TBS and TBDPS silyl protecting groups also exhibited an α-directing effect.[32]

As experiments in this study were being completed, Zhang et al. reported[43] glycosylation with 6-*O*-benzoyl or 6-*O*-TBS derivatives of *p*-tolyl 2-azido-3,4-di-*O*-benzyl-2-deoxy-1-thio-α-D-glucopyranosides **26** and **27** (Fig. 2) using preactivation protocol with the TolSCl/AgOTf promoter system.[44] Although moderate α-stereoselectivity comparable to our values was observed for some primary acceptors, excellent (α/β ≥ 15:1) or exclusive α-selectivity was achieved in the glycosylation of various secondary acceptors and disarmed *O*-benzoyl protected primary acceptors. The superior performance of **26** and **27** relative to the fluorinated thiodonors in this study can probably be attributed to not only the fluorine electron-withdrawing effect, but also differences in the reaction mechanism. Although anomeric α-triflate is the dominant covalent intermediate in preactivation-based glycosylation using the TolSCl/AgOTf promoter system, both anomers of glycosyl iodide,[33] anomeric α-triflate, and potentially other covalent species can form and react with the acceptor using the NIS/TfOH promoter system under pre-mix conditions.

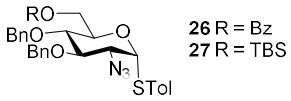

Figure 2. α-Stereoselective thiodonors used by Zhang et al.[43]

To further examine the synthetic utility of fluorinated thiodonors prepared in this study, we turned our attention to the synthesis of fluorinated analogues of α-glucosaminyl threonine (α-GlcNAc-*O*-Thr) found in *Trypanosoma cruzi.* The cell surface of this protozoan parasite responsible for Chagas disease is covered by a dense coat of glycoproteins implicated in parasite entry and persistence in the cells of its mammalian host.[45] Unlike mammalian mucin O-glycans, which commence with α-GalNAc-*O*-Thr/Ser, O-glycans in these mucin-like glycoproteins are attached to threonine residues via an α-linked *N*-acetyl-glucosamine moiety. We

investigated the glycosylation of protected threonine with O-acylated deoxofluorinated thiodonors, with the results shown in Table 3.

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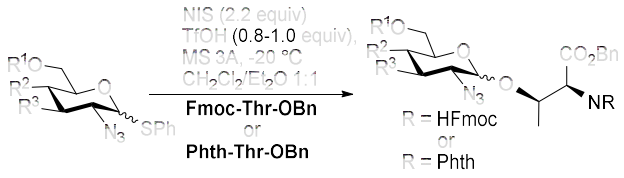
Table 3. Glycosylation of threonine.



entry	Donor	R^1	R^2	R^3	Acceptor **R**-OH	Product	α/β	Yield[a]
1	**16**	**ClAc**	**OAc**	**F**	**Fmoc-Thr-OBn**	**28**	2.1:1	28%
2	**16**	**ClAc**	**OAc**	**F**	**Phth-Thr-OBn**	**29**	5.1:1	71%
3	**17**	**Ac**	**OAc**	**F**	**Phth-Thr-OBn**	**30**	7.4:1[b]	68%
4	**25**	**ClAc**	**F**	**OAc**	**Fmoc-Thr-OBn**	**31**	6.6:1	[c]
5	**26**	**Ac**	**F**	**OAc**	**Phth-Thr-OBn**	**32**	18.0:1[b]	49%

[a]Isolated yield of α-anomer; [b]reaction conducted at 0 °C; [c] 53% isolated yield containing approx. 17% inseparable byproducts detected in ^{19}F NMR.

The phthalimide protecting group on the threonine acceptor was superior to the *N*-fluorenylmethoxycarbonyl group in terms of anomeric selectivity, product purity, and yield. This is consistent with the results obtained for non-fluorinated galactosazide donors in the synthesis of the Thomsen-nouveau antigen (α-GalNAc-*O*-Thr/Ser).[46] Coupling *N*-Fmoc threonine benzyl ester with 3-fluoro thiodonor **16** gave anomeric α/β ratio of 2.1:1 and a low yield (entry 1), whereas using *N*-phthaloyl threonine benzyl ester as acceptor improved the diastereoselectivity to 5.1:1 (α/β). A further increase in anomeric stereoselectivity was attained with 4,6-di-*O*-acetyl thiodonor **17** at 0 °C (entry 3). Glycosylation of *N*-Fmoc threonine benzyl ester with thiodonor **25** was accompanied by the formation of inseparable side products (entry 4). The coupling of *N*-phthaloyl threonine benzyl ester with 3,6-*O*-diacetyl-4-fluoro thiodonor **26** resulted in excellent

stereoselectivity (α/β = 18.0:1; entry 5). Conventional azide reduction and acetylation converted threonine glycosides **30** and **32** into protected α-GlcNAc-*O*-Thr **33** and **34** (Scheme 3).

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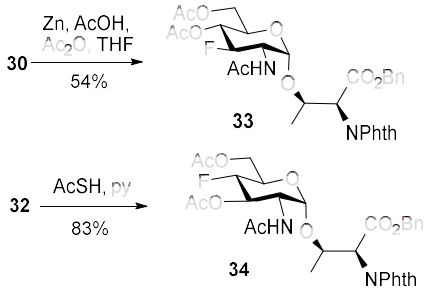
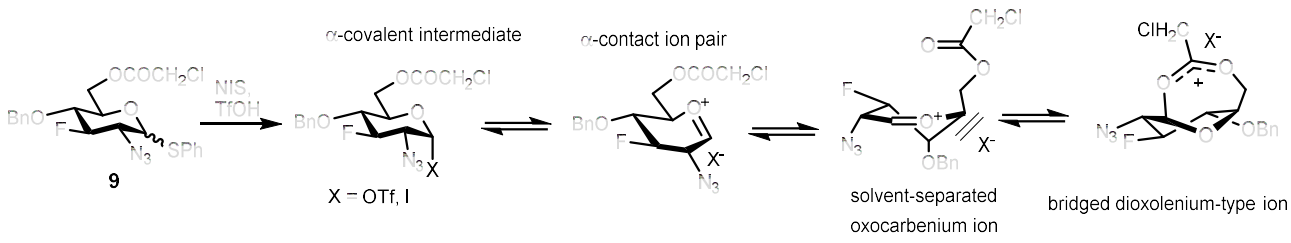
Scheme 3. Azide reduction.



Activation of thioglycoside donors with the NIS/TfOH promoter system leads to the formation of covalent intermediates, among which α-glycosyl triflate, and α- and β-glycosyl iodides appear to be dominant.[33] These function as substrates for S_N2-type stereospecific glycosylation and as a reservoir for the formation of transient highly unstable covalent species (presumably β-triflate), contact ion pairs, and solvent-separated oxocarbenium ions. To rationalize the stereodirecting effects of ester groups at C-6 and C-3, it has been suggested that the oxocarbenium ion can be stabilized by forming bicyclic bridged dioxolenium-type cations if suitable C-6 or C-3 positioned acyl groups are available, as shown in Scheme 4 for thiodonor **9**.[30] Stereospecific nucleophilic attack opposite to the acetoxonium-type bridge at C-1 then gives rise to anomeric α-stereoselectivity. The enhanced α-selectivity observed for less nucleophilic benzoyl ester protected acceptors supported this rationalization, because low-reactivity acceptors favour displacement of the more reactive bicyclic cations over S_N2-type displacement of anomeric α-triflates leading to β-glycosides. The increase in α-selectivity with increasing temperature from −20 to 0 °C might be related to the increased dissociation of covalent intermediates into ion pairs at higher temperatures.

Scheme 4. Examples of covalent and cationic intermediates formed upon NIS/TfOH activation of **9**.



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The proposed bicyclic cations are short-lived and, therefore, difficult to characterize spectroscopically. However, the bridging cations resulting from O-4 acetyl participation in D-*manno*- and D-*gluco*-configured 3,6-uronic acid lactones have been generated in the gas phase by collision-induced dissociation after electrospray ionization, and characterized by infrared ion spectroscopy.[26] Recently, bicyclic cations resulting from O-4 acetyl participation in D-*galacto* donors were characterized by cryogenic vibrational spectroscopy.[47] To the best of our knowledge, spectroscopic characterization of D-*gluco*-configured bicyclic dioxolenium-type cations has not yet been reported.

The hypothesis of oxocarbenium ion stabilization through formation of bicyclic bridged dioxolenium-type cations leading to increased 1,2-*cis*-selectivity was supported by computational optimization of 2-azido-3-fluoro-D-*gluco*-configured (3F) and 2-azido-4-fluoro-D-*gluco*-configured (4F) 6-*O*-acyl-substituted oxocarbenium ions using density functional theory (DFT; see SI for details). To simplify these calculations, OBn and $OCOCH_2Cl$ groups were substituted with OMe and OAc groups, respectively, in the model oxocarbenium ions (Fig. 3). Calculations were performed to identify possible conformers of the model solvent-separated oxocarbenium ions and compare their energies with the corresponding bridged dioxolenium-type ions.[48]

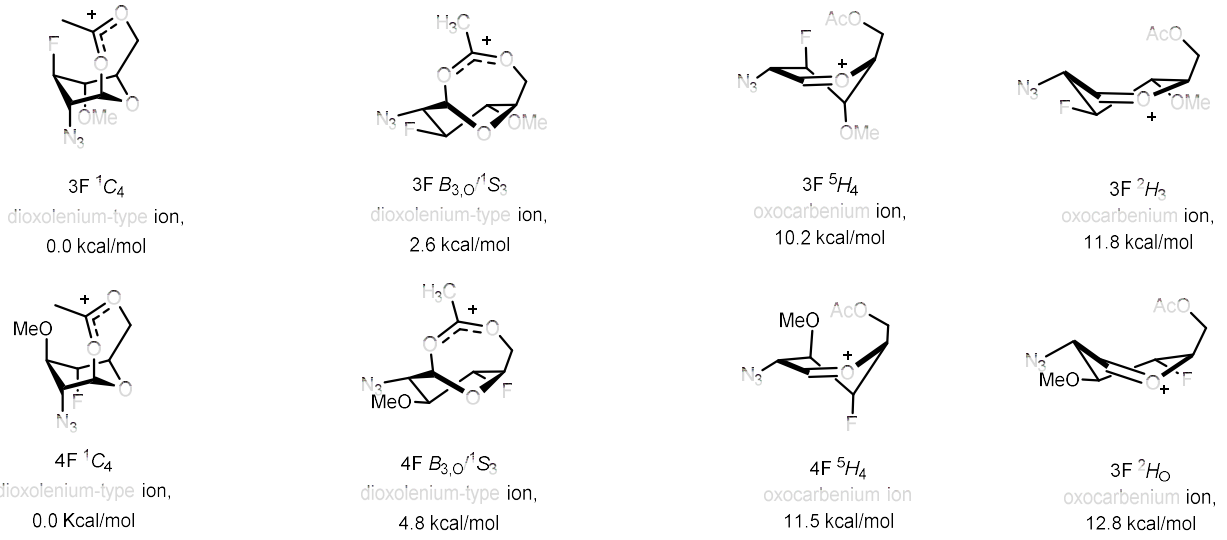

Figure 3. Conformations and relative energies of the most stable 3F and 4F geometry-optimized bridged dioxolenium-type and oxocarbenium ions calculated by DFT (see Experimental in SI); implicit Et_2O solvation was considered.

On the basis of the QM calculations, conformations $B_{3,O}/^1S_3$ and $^1C_4$ of bridged dioxolenium-type 3F and 4F ions were identified as significantly more stable than the corresponding oxocarbenium ions. Therefore, bridged dioxolenium-type ions formed by the participation of the 6-*O*-acyl group in 3F and 4F oxocarbenium

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ions are presumably important glycosylation reaction intermediates that give rise to enhanced α-selectivity. Energies of the optimized geometries of oxocarbenium ions were strongly affected by the C5–C6 conformations used as input geometry in calculations (stable conformers defined by dihedral angles O5–C5–C6–O6 and C4–C5–C6–O6 as *gg*, *gt*, and *tg*).[49] In our calculations, using the *gg* conformation as input geometry led to the most stable conformers close to $^{5}H_{4}$ and $^{2}H_{3}$ for 3F oxocarbenium ion, and $^{5}H_{4}$ and $^{2}H_{O}$ for 4F oxocarbenium ions (Fig. 3). In contrast, when the *gt* and *tg* conformers were used as input geometries, the optimization converged at energetically much higher conformers (see SI).

In conclusion, we have synthesized a series of acyl protected fluorinated glucosazide thiodonors that exhibit moderate to excellent 1,2-*cis* stereoselectivity using NIS/TfOH-promoted glycosylation. Consistent with recent investigations,[41–44,46] our results underscore the importance of acceptor protecting groups for manipulation of glycosylation stereoselectivity. We have also demonstrated the versatility of 1,6-anhydrohexopyranose chemistry for the synthesis of orthogonally protected fluorinated glucosazide thiodonors.

Conflicts of Interest

There are no conflicts of interest to declare.

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Introducing remote *O*-acyl protecting groups enabled 1,2-*cis* stereoselective glycosylation with fluorinated glucosazide glycosyl donors.