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# An unusual glycosylation product from a partially protected fucosyl donor under silver triflate activation conditions†

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Partially protected glycosyl donors are extremely useful reagents for oligosaccharide synthesis allowing more facile deprotection and enhanced activity due to lower steric restraints. A partially protected fucosyl donor containing *tert*-butyldimethylsilyl (TBDMS) protecting groups was activated under bromine–silver triflate conditions in the presence of primary alcohols and found to give difucoside products exclusively, in good yield with excellent diastereoselectivity. The dimerisation reaction appears to require a conformational relaxation of steric crowding, induced upon activation of the glycosyl donor. The scope and limitations of this unusual glycosylation methodology are reported.

## Introduction

Access to pure synthetic carbohydrates with defined structure and stereochemistry is essential for developing an understanding of glycobiology.[1–5] Significant effort has been directed towards the development of efficient glycosylation methodologies that allow for the precise synthesis of defined oligosaccharides.[5–7] The vast majority of glycosylation methodologies employ protected glycosyl donors as reagents for achieving selective, high yielding, glycosylation reactions.[8,9] It is well known that the protecting groups can often participate in the glycosylation reaction either directly, to induce stereocontrol *via* a participating step[10–13] or indirectly, by enhancing the reactivity of the oxocarbenium ion through sterically-induced conformational changes.[14,15] In the case of anchiomeric assistance from neighbouring ester groups, this effect only becomes active following activation of the glycosyl donor.[10] The effects of protecting groups on the outcome of glycosylation reactions is an area of intense study in synthetic carbohydrate chemistry.

Partially protected glycosyl donors are extremely desirable for oligosaccharide synthesis, due to their atom economy and the potential of reducing the overall number of synthetic steps. Despite these advantages, only a very limited number of examples of partially protected glycosyl donors have been reported in the literature.[16–18] In order to avoid unwanted polymerisation reactions, the use of inverse glycosylation conditions is usually employed with these donors, maintaining a higher concentration of the acceptor relative to the donor during the glycosylation.

We have recently reported synthetic applications of both fully and partially *tert*-butyldimethylsilyl (TBDMS) protected fucosyl donors as reagents for the preparation of fucose containing oligosaccharides.[19] It was determined that the bulky silyl protecting groups could act as directing groups for achieving alpha-selectivity in the glycosylation reactions and moreover, that these protecting groups could be readily removed in the presence of unsaturated bonds. As part of this study we developed conditions for the preparation of a partially protected 2,4-disilyl fucosyl donor. The partially protected donor was found to be highly efficient for the alpha-fucosylation of both primary and sterically hindered secondary hydroxyl groups on activation with *N*-iodosuccinimide–trimethylsilyl trifluoromethanesulfonate (NIS–TMSOTf) (Fig. 1).

Unlike other partially protected glycosyl donors reported to date, the fucosyl donor **1** does not require the use of inverse glycosylation conditions in order to maintain a high concentration of the accepter and avoid unwanted polymerisation reactions. We rationalised that glycosylation of the secondary hydroxyl group at the C-3 position was prevented by the steric

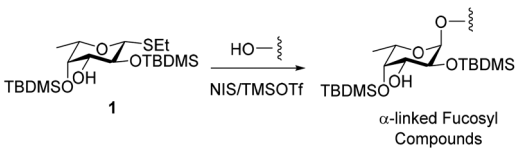


**Fig. 1** 2,4-Disilyl protected fucosyl donor.

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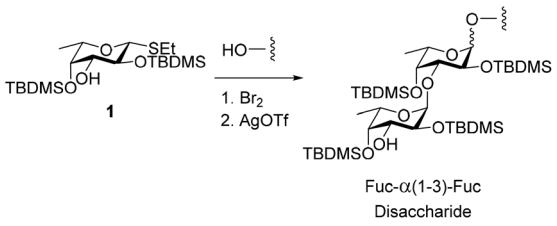
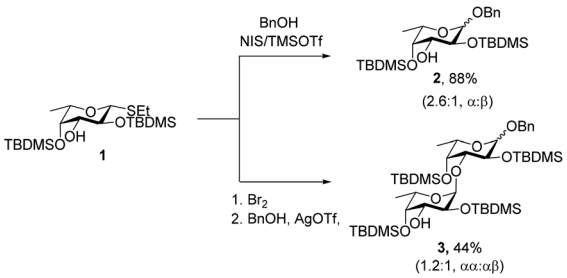



**Fig. 2** Dimerisation–glycosylation reaction observed upon conversion of **1** into the glycosyl bromide followed by activation with AgOTf.




**Scheme 1** Activation of fucosyl donor **1** in the presence of benzyl alcohol under both NIS–TMSOTf and $Br_2$–AgOTf conditions.

bulk of the neighbouring TBDMS protecting groups that imposed a steric shielding effect upon the remaining free 3-hydroxyl group.

As part of our ongoing studies into the synthetic applications of partially protected glycosyl donors for oligosaccharide synthesis, we have identified a very unusual, highly selective, dual-glycosylation reaction that occurs upon activation of the partially protected fucosyl donor **1** with bromine and silver triflate (Fig. 2). The reaction is unusual in that the 1,3-difucoside is formed as the major product. The result would not be so noteworthy were it not for the fact that the 3-OH position had previously been demonstrated to be completely unreactive towards glycosylation.[19] Also, the dimerisation product, which was the major product isolated, was not observed under NIS activation conditions. Finally, the apparent absence of higher polymers observed suggested the reaction was selective for dimer formation. We postulated that the product may be formed due to a change in the conformation of the pyranose ring that occurs upon activation of the glycosyl donor. The TBDMS protecting groups play a dual role in directing the stereoselectivity of the glycosylation and also preventing polymerisation of the dimerised product. To the best of our knowledge, a selective dimerisation reaction of this type has never previously been reported in the literature and this system, may offer new insights into the synthetic applications of partially protected glycosyl donors.

The resulting Fuc-α(1–3)-Fuc disaccharide is of general synthetic interest due to its structural homology with the fucose based polymer, *fucoidan*. This polymer has been shown to possess anti-sperm adhesion properties for use as contraceptives,[20] anti-HIV activity *in vitro*,[21] anti-tumourocidal properties,[22] and applications as lower molecular weight heparin mimics.[23] Herein we report the synthetic scope of this novel reaction and discuss some of the mechanistic considerations and the role of the protecting groups in the specific disaccharide formation.

## Results and discussion

Fucosylation reactions employing fucosyl bromide intermediates derived from thiofucosides have been studied in detail by a number of groups.[24] It has been established that activation of fucosyl donors in the presence of sterically demanding glycosyl acceptors preferentially form the alpha products *via* both $S_N1$ and $S_N2$ type reaction mechanisms.[25–27] These reactions are vital for accessing biologically important fucosides with stereocontrol of the glycosidic linkage. The potential role of partially protected donors in combinatorial approaches towards accessing complex glycoconjugate libraries has been highlighted by Seeberger and co-workers.[28] In the course of a systematic investigation into the synthetic potential of partially protected fucosyl thioglycoside donor **1**, we began to study activation of the donor under a variety of activation conditions using benzyl alcohol as an acceptor. We had previously demonstrated that the glycosyl donor could be activated using NIS–TMSOTf and DMDS–$Tf_2O$, but we were interested in investigating if alternative activation conditions could be employed. In the first instance, a two step glycosylation procedure (with *in situ* generation of a glycosyl bromide) between fucosyl donor **1** and benzyl alcohol as an acceptor was investigated (Scheme 1). Based on our previous studies of fucosyl donor **1**, the glycosylation reaction would be expected to furnish the benzyl fucoside monomer **2** as the major product. This was the major product that was isolated on activation of **1** with NIS–TMSOTf. To our surprise, only minor quantities of the expected monosaccharide product **2** was observed but the disaccharide **3** was isolated as the major product in 44% yield (based on donor **1**), as a separable mixture of two diastereoisomers (αα and αβ). Since the product formation requires two equivalents of the glycosyl donor, it can be considered that the benzyl alcohol acceptor was present in excess. No extended polymer products (trisaccharides, tetrasaccharides *etc.*) were observed and the only other major product isolated was the hydrolysed glycosyl donor.

The disaccharide product **3** represents a much more sophisticated glycosylation process than the NIS–TMSOTf activated system and poses a number of questions in relation to the stereochemistry of the product and the order of the glycosylation reactions. The yield for the disaccharide product, although modest at 44%, still represents an average yield of 66% per glycosylation step which is synthetically viable for a one-pot procedure. Other points of note for this reaction are the complete lack of the mono fucosyl product **2**, the total absence of any higher polymers (trisaccharides, tetrasaccharides *etc.*), the exclusive stereoselectivity of the α(1–3) fucose–fucose glycosidic linkage and the mainly alpha-selectivity observed for the glycosylation reaction with benzyl alcohol.

The variation in products observed between the two different activation conditions may be due to a greater degree of $S_N1$ character in the silver triflate activation which would promote conformational changes during the glycosylation. The activation of glycosyl halides have been studied in detail by Lemieux and co-workers.[24] Given the synthetic novelty of the product, the apparent selectivity and the synthetic interest in one-pot glycosylation systems, we decided to investigate this methodology further to determine the scope and limitations.

An optimisation study of the reaction conditions for the fucose dimerisation reaction was performed (Table 1). For mixed solvent systems, the ratio was always DCM–solvent (2 : 1 v : v). Low reaction temperatures and $Et_2O$ appeared to increase the αα stereoselectivity, however all conditions tested gave exclusive α selectivity for the fucose–fucose glycosidic linkage. Interestingly, the use of an alternative silver(I) source ($Ag_2CO_3$), prevented the reaction from occurring suggesting that both the silver source and the counter ion may play a role in the observed product formation. Why the presence of the carbonate counter ion prevented any formation of the desired product is not fully understood. Disappointingly the overall yield could not be improved beyond 44%, but it was interesting to note that the reaction appeared to function best within a tight set of reaction conditions.

Since the $Br_2$–AgOTf activation conditions involve initial formation of a glycosyl bromide[29] we first investigated if the unusual glycosylation reaction was due to $S_N2$ type displacement occurring on or during formation of the reactive anomeric bromide **4**. Attempts to isolate the fucosyl bromide failed due to the instability of this highly reactive glycosyl donor. In order to probe the stability of the fucosyl bromide donor **4** we carried out NMR analysis of the formation of the fucosyl bromide *in situ*. The formation and characterisation of glycosyl bromides using *in situ* NMR analysis has previously been described by Demchenko and co-workers.[30] Formation of the glycosyl bromide was carried out in $CDCl_3$ in a standard NMR tube equipped with a septum and immersed in liquid nitrogen (−196 °C). NMR analysis demonstrated that full conversion of the thioglycoside to the bromide **4** was complete within five minutes and that no disaccharide formation or anomerisation was observed even upon warming of the glycosyl bromide to room temperature (Fig. 3). The NMR experiments strongly suggest that both of the glycosylation reactions were occurring upon activation of the fucosyl bromide **4** with silver triflate.

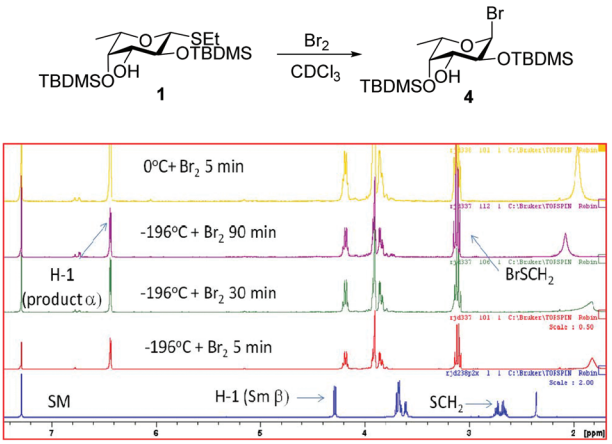
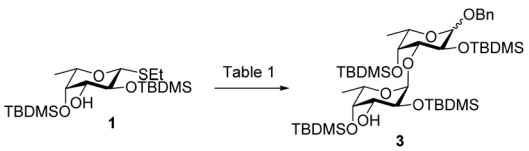



**Fig. 3** NMR analysis of fucosyl bromide **4** formation.

Once it had been confirmed that no glycosylation–dimerisation was occurring at the brominating step, we were interested in determining the order of the two glycosylation reactions. The predicted order of glycosylation for this process, based on reactivity of the acceptor alcohol, would involve initial glycosylation of the fucosyl donor **4** with the more reactive primary benzyl alcohol followed by a second fucosylation of the 3-OH of the resulting *O*-benzyl fucoside acceptor **2**. Previous studies on the disilyl protected donor **1** suggested that the 3-OH would be very sterically hindered and difficult to glycosylate. In order to investigate the order of the glycosylation events we first prepared acceptor **2** using the NIS–TMSOTf conditions. This is the glycosyl acceptor that would be formed if the benzyl alcohol glycosylation reaction was occurring first, and this product was subsequently fucosylated at the 3-OH position in a second glycosylation step. The partially protected fucosyl thioglycoside donor **1** was initiated under $Br_2$–AgOTf conditions in the presence of acceptor **2** but none of the disaccharide product **3** was formed after 25 min at −20 °C (Scheme 2). The fucosyl acceptor molecule **2** was recovered in almost quantitative yield.

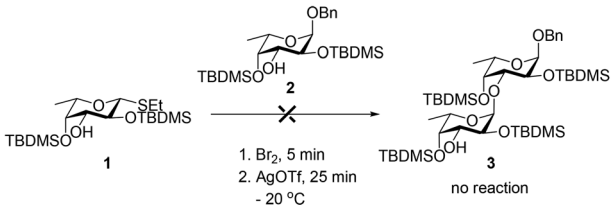
The result of this reaction strongly suggested that the glycosylation reaction was not occurring in the predicted stepwise manner *via* two sequential glycosylation reactions. The result was significant in that it explained why no further fucosylation of the disaccharide compound **3** was occurring (in the non-reducing direction) and why no higher-order oligosaccharides

**Table 1** Optimisation of reaction conditions for the formation of disaccharide **3**




| Entry | Activation conditions | °C[d] | Time[e] (min) | Yield (%) | Anomeric ratio αα : αβ |
|---|---|---|---|---|---|
| 1 | $Br_2$–AgOTf[a], DCM–THF | 0 | 25 | 25 | 2 : 1 |
| 2 | $Br_2$–AgOTf[a], DCM–THF | −20 | 25 | 44 | 1.2 : 1 |
| 3 | $Br_2$–AgOTf[a], DCM–THF | −40 | 25 | 38 | 1.4 : 1 |
| 4 | $Br_2$–AgOTf[a], DCM–THF | −60 | 25 | 22 | 3.9 : 1 |
| 5 | $Br_2$–AgOTf[a], DCM | −20 | 25 | 0 | N/A |
| 6 | $Br_2$–AgOTf[a], THF | −20 | 25 | 29 | 1 : 1.4 |
| 7 | $Br_2$–AgOTf[a], $Et_2O$ | −20 | 25 | 14 | 3.8 : 1 |
| 8 | $Br_2$–AgOTf[a], DCM–THF | −60 | 120 | 20 | 2.5 : 1 |
| 9 | $Br_2$–AgOTf[a], DCM–$Et_2O$ | −60 | 120 | 26 | 9.3 : 1 |
| 10 | $Br_2$–$Ag_2CO_3$[a], DCM–THF | −20 | 25 | 0 | N/A |
| 11 | $Br_2$–AgOTf[b], DCM–THF | −20 | 25 | 0 | N/A |
| 12 | $Br_2$–AgOTf[c], DCM–THF | −20 | 25 | 26 | 1.1 : 1 |

[a] 2 equivalents. [b] 0.5 equivalent. [c] Inverse glycosylation. [d] Refers to activation temperature of intermediate, after bromide formation. [e] Refers to reaction time following activation of glycosyl bromide.




**Scheme 2** Attempted glycosylation of benzylated fucoside **2**.

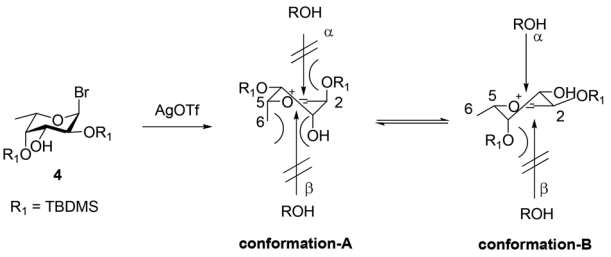



**Fig. 4** Oxocarbenium ion conformations of activated fucosyl donor.

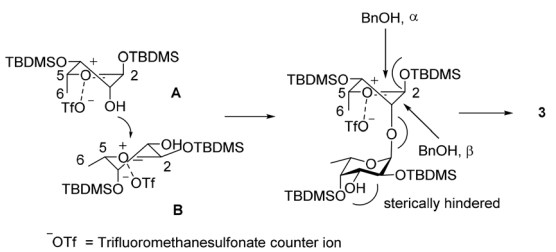


(trisaccharides, tetrasaccharides *etc*.) were observed. Once the terminal fucose was in place and the α(1–3) linkage had been established the terminal fucose moiety was locked in the $^1C_4$ conformation which prevented further glycosylation of the free 3-OH position due to the steric bulk of the neighbouring silyl protecting groups. The system in effect, self-terminated any further glycosylation reactions at the non-reducing end. This result however did not explain why extended polymerization was not occurring in the reducing direction and why more than two fucosyl residues did not assemble prior to being trapped by the benzyl alcohol. Finally, this result also suggested that the fucose–fucose α(1–3) glycosidic linkage was forming prior to the glycosylation with benzyl alcohol. This type of glycosylation pathway would be highly unusual in contemporary oligosaccharide synthesis. In an attempt to improve the overall yield of the desired disaccharide product and to gain further mechanistic insight into the process we investigated preactivation of the fucosyl bromide donor at 0, −20 and −40 °C, followed by delayed addition of the benzyl alcohol acceptor (addition following donor activation with AgOTf after 1, 10 and 15 min at each temperature). Despite several attempts at the preactivation strategy, only complex and inseparable mixtures of products were observed. Activation of the donor in the absence of any alcohol acceptor resulted in a complex mixture of products and hydrolysed donor.

Based on the experimental data acquired, we postulated that glycosylation of the 3-OH group of the 2,4-disilyl protected fucosyl donor would require an initial conformational change to occur that would induce a change the orientation of the bulky silyl protecting groups and would make the 3-OH position more accessible to glycosylation. NMR coupling constants are consistent with both the fucosyl bromide donor **4** and the fucosyl acceptor **2** occupying the $^1C_4$ conformation and therefore the 3-OH position is not available for glycosylation. It is widely accepted that the mechanism for glycosylation reactions proceeds *via* an oxocarbenium ion intermediate[10,31,32] and that formation of this electrophilic species requires a flattening of the carbohydrate ring that induces conformation changes to the side chains. The conformation of an oxocarbenium ion as proposed by Woods[33] and investigated by Woerpel[34] is described by a linear arrangement of C-5–O-5–C-1–C-2. When applied to the fucosyl donor **4** (Fig. 4), two possible conformations of oxocarbenium ion **A** ($^4H_3$) and **B** ($^3H_4$), can be drawn. Alabugin has described the importance of hyper conjugation in stabilising the oxocarbenium ion. The findings from this paper have been applied by Woerpel to justify the unusual reactivity of 6-deoxy sugars as well as the contribution of protecting groups to both arming and disarming effects. It is clear from these oxocarbenium ion conformations that the steric restraints conferred on the 3-OH group when the sugar is locked in the $^1C_4$ conformation become relaxed when the donor is activated and adopts an oxocarbenium ion conformation.

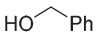
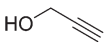
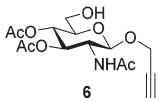
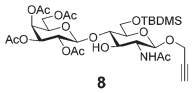
The potential implications of conformational changes on the 3-OH are presented in Fig. 4. It can be observed that in **A**, the 3-OH has dropped out of the plane of the ring, and is much less hindered. At the same time, the steric interactions of axial groups in the 2, 3, and 6 positions make nucleophilic attack at the oxocarbenium more difficult from both faces. Meanwhile for **B**, the oxocarbenium ion is much more accessible from the α-face, but the 3-OH is more hindered than in **A**.

In order to explain the unusual dimer formation, but the complete absence of polymerisation products, it can be postulated that the energy barrier between the interconversion of **A** and **B** is likely to be low enough to allow both to exist in solution.[35] If the accessible oxocarbenium in **B** were to be attacked from its least hindered face, by the less hindered 3-OH of **A**, then the intermediate resulting would be that shown in Scheme 3. It can be seen in the product that the terminal fucose has now reformed the sterically crowded $^1C_4$ conformation, thereby preventing further reaction at the unprotected 3-OH, meanwhile at the reducing terminus, the axial 2-OTBDMS group together with the axial 3-*O*-glycoside and axial 6-$CH_3$ create a steric pocket that severely restricts the accessibility of the remaining oxocarbenium, which could now be attacked at the reducing end, by a non-sterically hindered alcohol, over another oxocarbenium ion **A**. Such an attack would provide the experimentally observed α–β mixtures (Table 1). Why the initial fucose–fucose dimerisation reaction




**Scheme 3** Proposed pathway for formation of difucoside product **3**.

**Table 2** Investigation of the scope of the glycosylation reaction

| Entry | Acceptor | Activation conditions | Yield | Anomeric ratio αα : αβ |
|---|---|---|---|---|
| 1 |  | AgOTf, DCM–THF (2 : 1) | **3** 44% | 1.2 : 1 |
| 2 |  | AgOTf, DCM–THF (2 : 1) | **5** 53% | 5.6 : 1 |
| 3 |  **6** | AgOTf, DCM–THF (2 : 1) | **7** 8% | αα (only) |
| 4 |  **8** | AgOTf, DCM–THF (2 : 1) | **9** 0% | N/A |

would be kinetically favoured to trapping with benzyl alcohol is not fully understood and remains under investigation.

The proposed pathway outlined in Scheme 3 is most likely an over simplification of what is actually occurring in solution, however, it can explain some of the unusual requirements for the isolated dimer products. The approach of two oxocarbenium ions should be highly energetically disfavoured, however counter ions play a large and not entirely understood role in glycosylations,[36] possibly explaining why the reaction failed using a different source of Ag(I) (entry 10, Table 1). The proposed route (Scheme 3), would require a large concentration of oxocarbenium ions to be present in solution. Two equivalents of AgOTf were used to activate the fucosyl halide in accordance with literature procedure.[29] The excess Ag(I) would have the effect of largely increasing the rate of oxocarbenium formation *versus* a catalytic process. We also investigated the effect of lowering the AgOTf concentration to 0.5 equivalents (entry 11, Table 1). The reaction mixture showed a large amount of unidentified products by TLC, and no fucose–fucose dimer products were observed. Another unexpected result was the isolation of significant quantities of the fucosyl dimers, after adopting inverse glycosylation conditions (entry 12, Table 1). In this case benzyl alcohol should remain in excess compared to the fucosyl bromide acceptor. It was predicted that this method would prevent any disaccharide product formation, but from the observed results, the rate of dimer formation appears sufficiently high to furnish the fucosyl dimer product **3** in 26% yield. This result does indeed suggest that the fucose–fucose dimerisation reaction does occur faster than the benzyl trapping even though this result may be difficult to rationalize theoretically. Although we were unable to establish the exact mechanism of this process, the experimental results certainly pertain to a highly unusual glycosylation process. The reaction mechanism may also proceed *via* a concerted pathway where both glycosylation reactions occur simultaneously but this is difficult to determine experimentally.

In order to investigate the scope and generality of this reaction we screened a number of alcohols with varying reactivity to verify if the fucose dimerisation reaction was general. Using the conditions that gave the best yield of the disaccharide

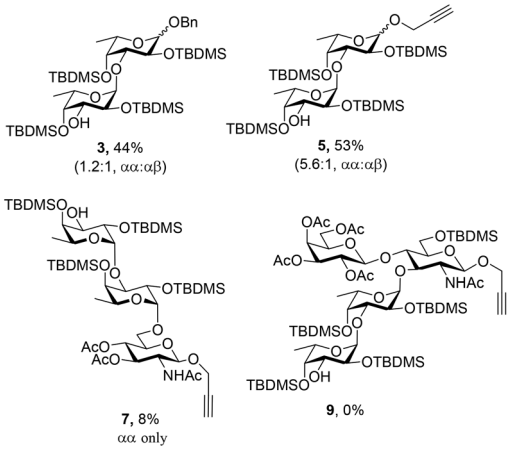



**Fig. 5** Difucosyl products obtained on initiation of fucosyl donor **1** in the presence of various alcohol acceptors.

product in the presence of benzyl alcohol (Table 1, entry 2), a number of other alcohols were screened. The results are outlined in Table 2 and Fig. 5.

From the data in Table 2 it was observed that the size of the acceptor alcohol was an important factor in determining the yield of the difucose products formed. The use of propargyl alcohol, which has a similar reactivity, but slightly less steric bulk than benzyl alcohol, furnished the desired *O*-propargyl difucoside **5** in 53% isolated yield. This represents an average of 73% yield per glycosylation and represented an improved yield over that obtained with benzyl alcohol. The reaction was also highly diastereoselective for the alpha-product in both glycosylation steps. The reaction provides, in one-pot, a propargyl functionalised disaccharide that can be employed in $[Cu]^{I}$ catalysed 1,3-dipolar cycloaddition 'click' reactions.[37,38] For entries 3 and 4, we investigated if the methodology was applicable to the primary hydroxyl group on a monosaccharide and to a highly sterically hindered secondary alcohol on a lactosamine disaccharide.[39] For the one pot trisaccharide synthesis the desired trisaccharide **7** was isolated in 8% yield which, although low, still represents an average of 29% per glycosylation step. This is significantly lower than the yields observed

for propargyl alcohol and for benzyl alcohol and suggest that the steric factors associated with the bulky carbohydrate may play a role in the reduced yield. In the case of the highly hindered secondary alcohol, none of the expected tetrasaccharide product was observed. Indeed, the starting disaccharide acceptor **8** was recovered almost quantitatively. It appears from these studies that the methodology, although general, is most applicable to non-bulky, primary alcohols.

## Conclusions

We have reported an unusual glycosylation reaction involving a partially protected fucosyl donor activated under bromine–silver triflate conditions. The activation conditions promote formation of difucosyl glycosides as the major products in moderate to good yields. The methodology is robust and stereoselective, allowing rapid access to disaccharide derivatives with high yields under carefully controlled conditions. An investigation into the order of glycosylation and the steric constraints imposed by the protecting groups suggest that the reaction proceeds by an unusual glycosylation pathway. Further mechanistic studies are ongoing to understand the glycosylation pathway in more detail. Studies involving other partially protected monosaccharides are also ongoing. The methodology may offer an additional advantage to the use of partially protected donors in glycosylation reactions.

## Acknowledgements

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