Pre-activation protocol leading to highly stereoselectivity-controllable glycosylations of oxazolidinone protected glucosamines†

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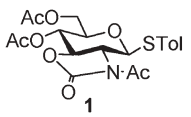
Under pre-activation glycosylation conditions, the 4,6-di-*O*-acetyl-*N*-acetyloxazolidinone protected donor afforded either excellent β- or α-stereoselectivity simply by means of the addition of hindered base TTBP or the absence of base, leading to the controllable stereochemistry of coupling reactions.

2-Amino-2-deoxy sugars are essential residues incorporated in a spread of oligosaccharides and glycoconjugates with biologically important roles.[1] However, the stereoselective formation of the glycosidic bond is still a challenge to synthetic chemists. The β-linked glycosides are usually constructed by means of a participating neighboring group at the 2-amino position,[2] while the formation of α-linked glycosides remains a difficult task.[3] The present methods for α-stereoselective glycosylation of amino sugars mainly involve in strategies of various protective groups for the amino group such as the introduction of an azido moiety at the 2-position as a non-participating group,[4] but the anomeric stereoselectivities during coupling reactions vary greatly,[5] good stereoselectivity often requires considering reactivity or conformational constraints of the acceptors.[6]

The development of new protocols for stereoselective glycosylations is a major focus in synthetic carbohydrate chemistry due to its essentiality for oligosaccharide assembly. In recent years, "pre-activation" as a new glycosylation approach has received increasing interest.[7] Especially, this protocol was developed as an effective strategy for iterative one-pot synthesis of oligosaccharides in this laboratory.[8] The "pre-activation" protocol means that a glycosyl donor is completely activated and consumed (by TLC detection) prior to the addition of a glycosyl acceptor. We reasoned that a pre-activation protocol might influence the stereochemistry outcomes of glycosylations. Since the 1,2-*cis* stereoselective glycosylation for 2-amino-2-deoxy sugars is a principal challenge, we want to tackle this problem by applying the pre-activation strategy. Although great advances in this field have been achieved recently by the use of 2,3-*trans*-oxazolidinone as a non-participating group for glucosamine donors including 2,3-oxazolidinone protected 2-amino-2-deoxy-D-glucose thioglycosides,[9a,b] its *N*-acetyl[9c,10] and *N*-benzyl[11] analogues, some drawbacks such as the undesired glycosylation and sulfenylation of the nitrogen atom,[9a,b] reduction of α-selectivity,[9c] low yields,[11] and limited scope of acceptors[10,11] still exist. To overcome the above-mentioned shortages and verify the influence on glycosylations by the activation manner, we focused on our studies on stereoselective glycosylations using a oxazolidinone-containing glucosamine donor by a pre-activation protocol.



1

To examine the distinction between the pre-activation protocol and the reported procedure,[9c] the known 2,3-oxazolidinone protected thioglycoside **1**[9c] was chosen as the glycosyl donor. Combination of benzenesulfinyl morpholine (BSM) and triflic anhydride (Tf_2O)[12] was used as the promoter system in the presence of hindered base 2,4,6-tri-*tert*-butylpyrimidine (TTBP)[13,14] in the pre-activation operations. Donor **1** was pre-activated at −73 °C in anhydrous dichloromethane using BSM–TTBP–Tf_2O, and after disappearance of donor **1** by TLC detection after several minutes, the acceptor was added to the reaction mixture to furnish the glycosidic bond formation. The coupling reaction of **1** and **2a** was carried out. Very fortunately, donor **1** exhibited complete β-selectivity with high yield as shown in Table 1 (entry 1). Next, our investigation was expanded to other glycosyl acceptors **2b–2k**, and the results are listed in Table 1. The yields are high and all the glycosylations proceeded with excellent β-selectivity (only β-anomer) except for the acceptor **2j** (entry 10, Table 1). The β-anomers were identified by their ^{1}H NMR coupling constants for the anomeric protons ($J_{1,2}$ = 6.5–7.5 Hz). Compared with the reported work using the same donor,[9c] it was found that the pre-activation protocol dramatically increased the β-selectivity and almost complete β-selective glycosylations for the glucosamine donor was obtained. According to the literature work,[9c] a 2-*N*-acyl group appended to the 2,3-oxazolidinone ring did not provide anchimeric assistance during glycosidation, so the β-selectivity is not caused by neighboring group participation. Neglecting this factor, we reasoned that the glycosylation could be a S_N2-like process *via* the α-glycosyl triflate[9c,15] intermediate based on the pre-activation protocol.

Since the use of hindered base is not necessary in our previous pre-activation protocol,[8,12] our attention turned to BSM–Tf_2O promoted pre-activation in the absence of TTBP. The glycosylation reaction between **1** and **2a** was performed again at −73 °C in CH_2Cl_2 pre-activated by the BSM–Tf_2O system without base. Surprisingly, the stereochemistry outcome was completely reversed to give α-linked coupling product **4a** in 90% isolated yield (entry 1, Table 2). Encouraged by this result, a series of glycosylations with the same donor **1** and acceptors **2b–2k** using the same protocol

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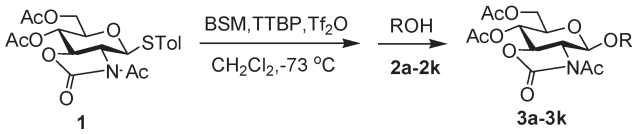
† Electronic supplementary information (ESI) available: NMR spectra and characterization data for all new compounds, details on the glycosylation couplings. See DOI: 10.1039/b712591g

Table 1 The glycosylation of donor **1** with various acceptors by pre-activation in the presence of TTBP



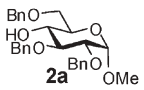
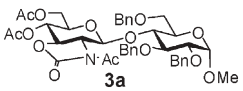
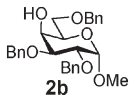
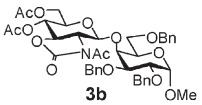
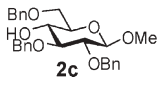
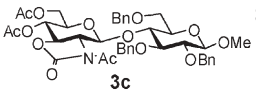
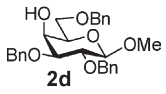
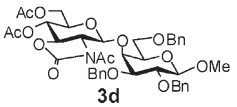
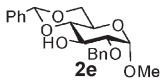
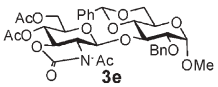
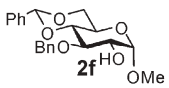
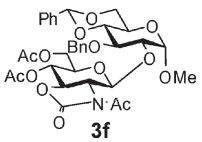
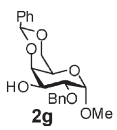
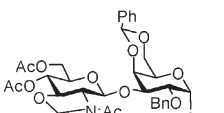
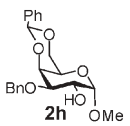
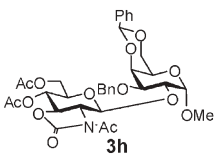
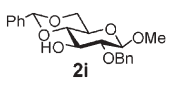
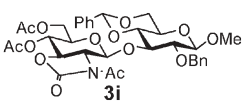
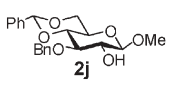
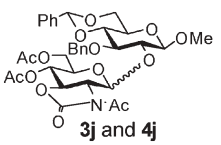
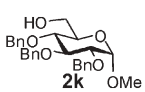
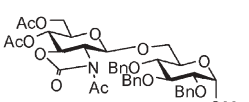
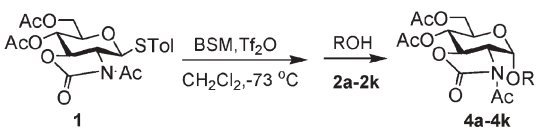
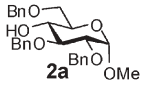
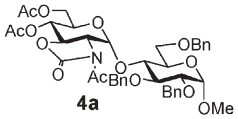
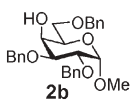
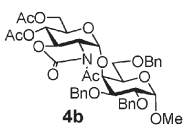
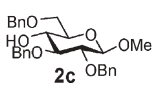
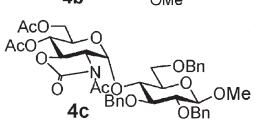
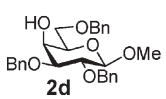
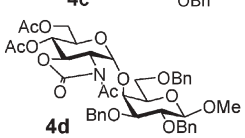
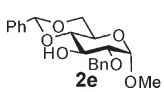
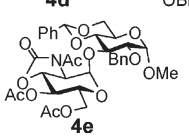
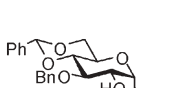
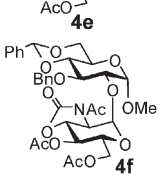
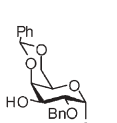
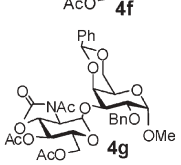
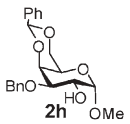
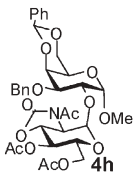
Entry	Acceptor (ROH)	Product	Isolated yield (%)	Anomeric ratio (α : β)
1	 **2a**	 **3a**	83	β only
2	 **2b**	 **3b**	83	β only
3	 **2c**	 **3c**	83	β only
4	 **2d**	 **3d**	84	β only
5	 **2e**	 **3e**	85	β only
6	 **2f**	 **3f**	89	β only
7	 **2g**	 **3g**	82	β only
8	 **2h**	 **3h**	87	β only
9	 **2i**	 **3i**	98	β only
10	 **2j**	 **3j and 4j**	87	1 : 5
11	 **2k**	 **3k**	87	β only

Table 2 The glycosylation of donor **1** with various acceptors by pre-activation in the absence of TTBP



Entry	Acceptor (ROH)	Product	Isolated yield (%)	Anomeric Ratio (α : β)
1	 **2a**	 **4a**	90	α only
2	 **2b**	 **4b**	81	α only
3	 **2c**	 **4c**	85	α only
4	 **2d**	 **4d**	82	α only
5	 **2e**	 **4e**	82	α only
6	 **2f**	 **4f**	86	α only
7	 **2g**	 **4g**	80	α only
8	 **2h**	 **4h**	83	α only
9	**2i**	**3i and 4i**	87	1.5 : 1
10	**2j**	**4j**	84	α only
11	**2k**	**3k and 4k**	81	3 : 1

were also undertaken and the results are displayed in Table 2. Excitingly, the yields are high and all the glycosylations proceeded with excellent α-selectivity (only α-anomer) except for the acceptors **2i** and **2k** (entries 9 and 11, Table 2). The α-anomers were identified by their ^{1}H NMR coupling constants for anomeric protons ($J_{1,2}$ = 2.5–3.0 Hz). That is, the absence of TTBP during the pre-activation glycosylations led to a totally reversed stereochemistry outcome (*cf.* Table 1 and Table 2). The reversal of the stereoselectivity in the absence of TTBP perhaps resulted from *in situ* anomerisation of the β-glycoside under acidic conditions.[10,16] Another possible reason would be that the glycosylation is a S_N2-like process *via* the β-glycosyl triflate intermediate.[15a] In terms of these results, it appears that the glycosylation stereochemistry of donor **1** can be controllable and predictable based on the pre-activation strategy, either α- or β-linked coupling products towards multifarious glycosyl acceptors can be obtained simply by the addition of hindered base or without base.

In summary, a new efficient strategy for both α- and β-stereoselective glycosylations of glucosamine donors based on pre-activation protocol was developed. By comparison with the routine glycosylation operations, the pre-activation manner can greatly influence the stereochemistry outcomes of glycosylations. The 4,6-di-*O*-acetyl-*N*-acetyloxazolidinone protected donor **1** displays excellent α-selectivity for the couplings of a series of glycosyl acceptors conducted by the BSM–Tf_2O pre-activation protocol, more importantly, the presence of hindered base TTBP leads to totally reversed stereochemistry outcomes with excellent β-selectivity towards glycosylations. Thus, by virtue of the BSM–Tf_2O pre-activation strategy, either α- or β-linked glucosamine-containing glycosides can be efficiently prepared by the use of 2,3-oxazolidinone protected thioglycoside **1**, by the addition of hindered base or the absence of base. It seems that the controllable and stereoselective glycosylations are realized by this protocol. It is expected that the disclosed pre-activation methodology may be widely applied to the assembly of either α- or β-linked 2-amino-2-deoxy-D-glycopyranose-containing complex oligosaccharides with important biological functions. Further extension of this protocol to other sugars and the mechanistic understandings of stereoselectivity are currently under investigation.

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