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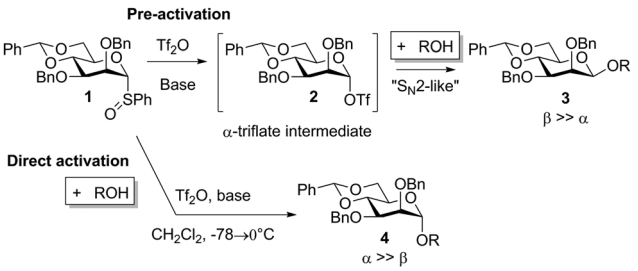
β-Mannosylation with 4,6-benzylidene protected mannosyl donors without preactivation†

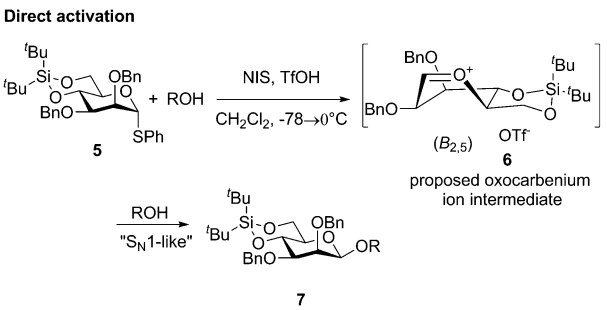
Mads Heuckendorff, Pernille Sørensen Bols, Collin Bartholomew Barry, Tobias Gylling Frihed, Christian Marcus Pedersen* and Mikael Bols*

Mannosylations with benzylidene protected mannosyl donors were found to be β-selective even when no preactivation was performed. It was also found that the kinetic β-product in some cases anomerizes fast to the thermodynamically favored α-anomer under typical reaction conditions.

Chemical glycosylation, a reaction for the synthesis of oligosaccharides and other biologically or medicinally crucial glycosides, is a very important reaction.[1] Many excellent glycosylation protocols that lead to high yield and stereocontrol have been developed, even when alcohol and the glycosylation agent are used in equimolar amounts.[2] Nevertheless, stereochemistry is always an issue in glycosylation reactions and this simple fact leaves the impression that they are largely S_N1-type reactions.[2d,3] It was therefore remarkable when the Crich laboratory discovered that β-mannosides, a stereochemical pattern that is notoriously difficult to obtain by direct glycosylation, could be obtained directly when a 4,6-benzylidene protective group was present in the mannosyl donor.[4,5] It was also remarkable that a special pre-activation procedure was critical for β-selectivity: when the sulfoxide donor **1** was pre-activated with triflic anhydride at −78 °C before the addition of the acceptor, β-selectivity (β-mannoside **3**) was obtained (Scheme 1), but if alcohol was present when triflic anhydride was added α-mannoside **4** was formed.[6] These observations, together with the low temperature observation of an α-triflate **2** upon pre-activation, led to the proposal that the β-manno selectivity is a result of an S_N2 substitution (Scheme 1),[7,8] albeit several papers have reported that preactivation is not necessary.[9] We were therefore surprised when we recently performed mannosylation reactions with a 4,6-silylene protected thiomannoside **5** and found that β-mannoside **7** was formed by simple direct activation of the thioglycoside with NIS/TfOH (cat.) in the presence of an acceptor (Scheme 2) – this worked even at



Scheme 1 The crucial effect of the order of addition order on stereoselectivity in mannosylation reactions observed (ref. 4 and 6).



Scheme 2 The use of the 4,6-di-*tert*-butylsilylene tethered donor for selective β-mannosylation using direct activation.

room temperature, regardless of the anomeric configuration of the thiomannoside. This indicates that the oxocarbenium ion **6** was the glycosylating species and was attacked from the β-face.[10]

Conclusions made with this 4,6-silylene protected thiomannoside may not hold for the commonly used 4,6-benzylidene protected mannosyl donors. Indeed the literature, including the results reported above, indicated that it did not; NIS-promoted glycosylations with 4,6-benzylidene protected phenyl thiomannosides, as an example, were less β-selective than when using the pre-activation procedure.[11] So we were interested in seeing if the apparent indiscriminate β-selectivity of the 4,6-silylene protected thiomannoside **5** was also found for the commonly used benzylidene protected mannosyl donors (such as **1**) and if this would also hold for other

Department of Chemistry, University of Copenhagen, Universitetsparken 5, 2100 Copenhagen Ø, Denmark. E-mail: cmp@chem.ku.dk, bols@chem.ku.dk

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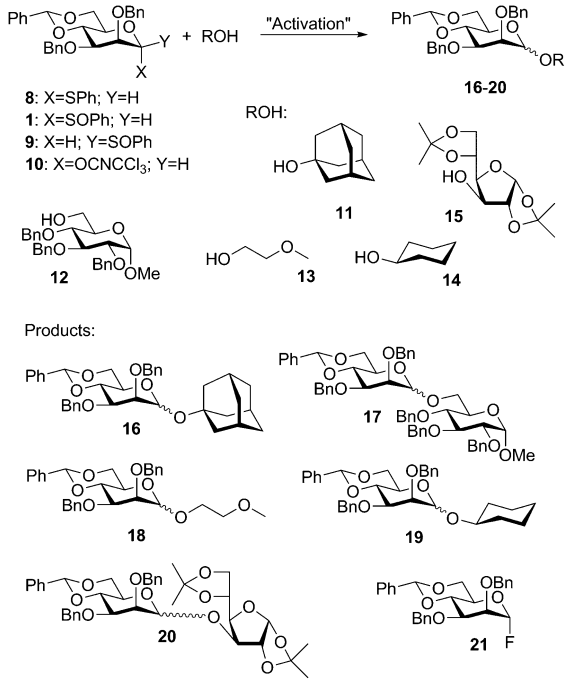

Scheme 3 Donors, acceptors and products.

common donor types such as trichloroacetimidates and sulfoxides. The results of this investigation are reported in the present paper. Benzylidene protected mannosyl donors give β mannosides as the kinetic products and significant α mannoside formation in some cases may be a result of subsequent anomerisation.

As seen above the benzylidene analogue of **5**, the α-thioglycoside **8**, was reacted with a series of relevant acceptors **11–15** (Scheme 3) promoted by NIS/TfOH. These reactions gave mostly high yield and high β-selectivity (Table 1, entries 1–5).[12]

This is essentially the same outcome as with the silylene-tethered donor **5**[10] and comparable to what one obtains with a pre-activation procedure.[13] It is noteworthy that β-selectivity is obtained at 0 °C or 25 °C (Table 1, entries 2 & 3) even though α-triflate is not stable at such high temperatures.[5c]

We now reinvestigated the original protocol for β mannosylation,[4,6] which uses α-anomeric sulfoxide **1** that is activated using Kahne's method,[14] and included the corresponding β-sulfoxide **9** in the study. When the anomeric set of donors **1** and **9** were preactivated and allowed to react with cyclohexanol **14** at −78 °C both donors gave the β-mannoside **17** with high selectivities (9 : 1 and β-only respectively – Table 1, entries 6 & 12). When alcohol **14** was present from the beginning, prior to activation, the β : α ratio remained high (9 : 1 for the α-sulfoxide **1** and 4 : 1 for the β-sulfoxide **9**, Table 1, entries 7 & 13). The acceptor alcohols **13** and **15** gave similar results (Table 1, entries 8–11 & 14). When pre-activation was omitted the yields were significantly lower, which we suspect is due to some triflation of the acceptor alcohol.[5c] This side reaction becomes a larger problem when the alcohol is a better nucleophile or when the glycosylation is hampered.[15] So while preactivation is a good idea as it provides better yields it is not a requirement for β-mannoside formation.

The experiments without pre-activation (Table 1, entries 7, 9, 11 and 13) appears to contradict earlier findings[4,6] where such conditions gave either α-mannosides or low selectivity. We speculated that the α-mannoside formation sometimes may be caused by an acid catalyzed anomerisation if insufficient amount of base was present. To test this hypothesis, two reactions were carried out with activation of **9**, in the presence of the acceptor **14** (2 equiv.), at −78 °C using sub-stoichiometric amounts of base (1 equiv.) relative to Tf_2O (1.7 equiv., Table 1, entries 15 & 16). One reaction was quenched at −70 °C, whereas the other was allowed to reach 0 °C and kept there for 5 min. before quenching it with Et_3N. The change in stereoselectivity was dramatic: The first experiment gave mainly β (7 : 2) and the latter mainly α (1 : 12). It is clear that, similar to what was observed with the silylene donor,[10] *in situ* anomerisation has occurred and obviously led to an erosion of β-selectivity.

We also investigated the popular trichloroacetimidate (TCA) donors. Schmidt has already reported that TCA donor **10** gave β-mannosides promoted by excess TMSOTf,[8a] but in light of the findings above we wished to see if triflate could be omitted. First we carried out 7 glycosylations with donor **10** and acceptors **11–13** (Table 2, entries 1–7) using TMSOTf catalysis (0.1 equiv.). These experiments confirmed the β-selectivity and yield were high, provided the reaction was run in a nonpolar solvent and quenched at low temperature (entries 1, 3–4) or an acid scavenger (1 equiv. 2,4,6-tri-*tert*-butylpyrimidine (TTBP))[16] was added (entries 2, 5 and 6). If no such precaution against anomerisation was taken the α-anomer was predominant (Table 2, entry 7).

To investigate the necessity of triflate in these reactions 13 glycosylations using $BF_3{\cdot}OEt_2$ activation were performed (Table 2, entries 8–20). At low temperature only a small amount of the glycosylation product was obtained, but with β-selectivity (Table 2, entries 8, 11 and 12), while a major sideproduct was mannosyl fluoride **21**. At room temperature it was possible to obtain good yield, but now the β-selectivity was lost due to anomerisation

Table 1 Results of glycosylation with sulfur containing mannosyl donors **1**, **8** & **9**

Entry	Dnr	Ac	Conditions	Yield/β : α
1	**8**	**11**	NIS, TfOH, −78 → 0 °C	98%/7 : 1[a]
2	**8**	**11**	NIS, TfOH, 0 °C	94%/6 : 1
3	**8**	**11**	NIS, TfOH, 25 °C	93%/6 : 1
4	**8**	**12**	NIS, TfOH, 25 °C	26%/5 : 1
5	**8**	**15**	NIS, TfOH, 25 °C	34%/2 : 1[b]
6	**1**	**14**	Tf_2O, TTBP, −78 °C[d]	82%/>9 : 1
7	**1**	**14**	Tf_2O, TTBP, −78 °C	47%/9 : 1[b]
8	**1**	**15**	Tf_2O, DTBMP, −78 °C[d]	ND/>20 : 1
9	**1**	**15**	Tf_2O, DTBMP, −78 °C	64%/>20 : 1
10	**1**	**13**	Tf_2O, DTBMP, −78 °C[d]	67%/5 : 1
11	**1**	**13**	Tf_2O, DTBMP, −78 °C	42%/5 : 1
12	**9**	**14**	Tf_2O, DTBMP, −78 °C[d]	ND/β-only
13	**9**	**14**	Tf_2O, DTBMP, −78 °C	33%/4 : 1[c]
14	**9**	**13**	Tf_2O, DTBMP, −78 °C	ND/3 : 1
15	**9**	**14**	Tf_2O, DTBMP, −78 °C	41%/7 : 2
16	**9**	**14**	Tf_2O, DTBMP, −78 → rt	34%/1 : 12

0.1 equiv. TfOH was used, ND: not determined, TTBP: 2,4,6-tri-*tert*-butylpyrimidine, NIS: *N*-iodosuccinimide and DTBMP = di-*tert*-butyl-4-methylpyridine. CH_2Cl_2 is used as solvent in all glycosylations. [a] Literature reference reaction >9/1 88%.[13a,b] [b] 34% **1**. [c] 30% **9**. [d] Preactivation.

Table 2 Results of glycosylation with trichloroacetimidate donor **10**

Entry	Dnr	Ac	Conditions	Yield/β : α
1	**10**	**11**	TMSOTf, CH_2Cl_2, −78 °C	Quan./>6 : 1
2	**10**	**11**	TMSOTf, TTBP, CH_2Cl_2, rt	ND/>6 : 1
3	**10**	**11**	TMSOTf, HFIP, −78 °C → rt	0%
4	**10**	**11**	TMSOTf, PhMe, −78 °C → rt	92%/>10 : 1
5	**10**	**12**	TMSOTf, TTBP, CH_2Cl_2, 25 °C	ND/8 : 1
6	**10**	**13**	TMSOTf, TTBP, CH_2Cl_2, 0 °C	ND/2.2 : 1
7	**10**	**13**	TMSOTf, CH_2Cl_2, −78 → rt	ND/1 : 2.5
8	**10**	**11**	$BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C	<5%/>6 : 1[a]
9	**10**	**11**	$BF_3{\cdot}OEt_2$, CH_2Cl_2, LiOTf[b]	10%/>10 : 1
10	**10**	**11**	LiOTf (0.1 equiv.), TTBP, BF_3	ND/>10 : 1
11	**10**	**15**	BF_3, CH_2Cl_2, −78 °C	**21**
12	**10**	**15**	BF_3, CH_2Cl_2, LiOTf, TTBP	ND/~5 : 1
13	**10**	**12**	BF_3, TTBP, CH_2Cl_2, 25 °C	**21**
14	**10**	**12**	TTBP, LiOTf, CH_2Cl_2, 25 °C	NR
15	**10**	**12**	TTBP, LiOTf, CH_2Cl_2, 25 °C, BF_3	ND/>8 : 1[a]
16	**10**	**12**	$AgClO_4$, TTBP, CH_2Cl_2, 25 °C	NR
17	**10**	**12**	$AgClO_4$, TTBP, CH_2Cl_2, 25 °C, BF_3	**21**
18	**10**	**12**	$LiClO_4$, TTBP, CH_2Cl_2, 25 °C	NR
19	**10**	**12**	$LiClO_4$, TTBP, CH_2Cl_2, 25 °C, BF_3	**21**
20	**10**	**13**	BF_3, CH_2Cl_2, 25 °C	77%/1 : 2[a]

Dnr: donor, Ac: acceptor, ND: not determined, NR: no reaction; HFIB: 1,1,1,3,3,3-hexafluoro-2-propanol and TTBP: 2,4,6-tri-*tert*-butylpyrimidine. [a] **21** sideproduct. [b] Quenched after 10% conversion.

(entry 20); adding TTBP did not work here (entry 13). Remarkably, adding LiOTf significantly enhanced the reaction rate. The β-anomer was the kinetic product (entry 9), and adding an acid scavenger allowed full conversion with high β-selectivity (Table 2, entries 10 and 15). LiOTf alone did not activate (entry 14) and silver or lithium perchlorate could not substitute the effect of triflate (entries 16–19).

The above studies show that preactivation is not necessary in order to get good yield and β-selectivity. Regardless of the configuration of the donor the β-mannoside appears to be the kinetic product; however acid catalysed anomerisation, especially at prolonged reaction times at ambient temperature, can erode the stereoselectivity as it gives α-mannoside. This can be prevented by the addition of an acid scavenger.

While triflate is not always necessary in order to get β-selectivity we find it has a clear catalytic effect that appears, at least in some cases, to be caused by the triflate ion itself (Table 2, entry 10). This suggests that formation of a tight ionpair with triflate[17] facilitates formation of the oxocarbenium ion and indeed, in accordance with the Crich mechanism,[18,19] is an intermediate in the reaction. Recent work with gold-catalyzed glycosylations also indicate that the role of triflate in these reactions is non-trivial.[20,21] Perhaps, β-selectivity is attributed to the intermediacy of an oxocarbenium ion ionpair in $B_{2,5}$ conformation[22] either solvent separated as we proposed for the 4,6-silylene donor,[10] or as a contact ion pair with triflate in the α-position as recent calculations support.[22c] This ion pair is glycosylated with β-selectivity either for steric reasons or simply due to the shielding effect of the triflate.

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