Conformationally armed glycosyl donors: reactivity quantification, new donors and one pot reactions†‡

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The relative reactivity of conformationally armed thioglycosides is quantified.

Glycosylation reactions play a central role in the synthesis of complex oligosaccharides. One pot strategies based on the armed-disarmed concept has emerged as a powerful way of combining glycosylations in the efficient assembly of oligosaccharides.[1] Recently we introduced an extension of the armed-disarmed principle in the form of the conformationally armed (or so called superarmed) glycosyl donors.[2] The rationale behind conformational arming is that since axial OR groups have been found to be less electron withdrawing than equatorial ones, a reactivity increase is expected in glycoside when forced into a more axial rich conformation.[3] It has been shown that such conformational arming could be carried out through silylation with bulky silyl groups,[4] and that the resulting superarmed donors could be selectively coupled with an armed acceptor/donor in competition experiments.[5] The conformationally armed glycosyl donors appeared very reactive as seen from excellent yields in synthesis.

This study nevertheless raised the question: exactly how reactive are these superarmed donors compared to armed or disarmed donors? It therefore became necessary to follow the reactions by kinetics. In the present work, we report a fast and simple method to quantify the reactivities of thioglycosyl donors using methanol as acceptor and *N*-iodosuccinimide (NIS)/trifluoromethanesulfonic acid (TfOH) as promotor system, and use it to determine the reactivity of superarmed thioglycosides. Subsequently we have used the findings to carry out rapid assembly of larger sugar systems.

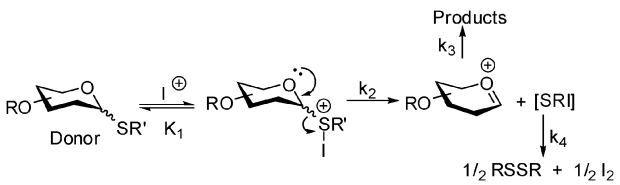
Over the years glycosyl donor reactivity has been determined by Fraser-Reid,[6] Wong,[7] and others[8] but most data has been relative rate values determined from competition experiments. In the present work we wished to have rate constants, which required a different method to be employed.

Thioglycosides activated with NIS/TfOH were used in this kinetic study as in our previous preparative experiments.[5] Assuming that the rate-determining step is the formation of the oxacarbenium ion (Scheme 1),[7] we could follow the formation of iodine in time, by UV, as an expression of the relative reaction rate.

The glycosylation reactions were carried out at room temperature under pseudo-first-order conditions, using excess of the acceptor and promotor. The kinetic data (k_{rel}) for a range of thioglycosides donors were obtained from v_{glyc} *vs.* [D] data (v_{glyc}: velocity of the reaction, D: donor) using nonlinear least-squares fitting and are shown in Table 1 and Fig. S1 (ESI).‡ Since it was noticed that under the reaction conditions NIS itself is releasing iodine, a minor background rate was subtracted for each donor concentration.

The results presented in Table 1 indeed demonstrate a significant enhanced reactivity of the silylated thioglycosides. A clear difference in the relative reactivity is observed between the main classes of thioglycosides: the disarmed (entry 1) is 40 fold slower than armed (entry 2), which is 20 fold slower than superarmed (entry 3, 5 and 9). The high reactivity of the silylated donors is attributed to a conformational flip from an equatorial rich $^4C_1$ conformation to a more axial rich conformation since the bulky silyl protection groups cannot be accommodated into the equatorial positions due to unfavorable steric repulsions (entry 3–7). Axial C–O bonds are perpendicular to the plane of the molecule, which leads to a more favorable charge–dipole interaction when a positive charge is formed in the glycosylation transition state.

When the preparative glycosylation reactions were performed with monosilylated donors (Table 1, entry 8, 12), having one *tert*-butyldimethylsilyl (TBS) or one *tert*-butyldiphenylsilyl (TBDPS) group, and a 6-OH armed acceptor/donor **4**, the yields were comparable with the per-benzylated armed thioglycoside donor (Table 1, entry 2) whereas the selectivity was poor, $\alpha : \beta$ 1 : 2.[5] The yields were improved by using the more bulky TBDPS group, a tendency that can also be observed in Table 1 through a higher relative reaction rate in the kinetic measurements (entry 8 and 12). The reactivity enhancement when having single silyl ether is presumably due to an easier transformation into the half chair intermediate in the transition state.



Scheme 1 Glycosylation using NIS/TfOH as activation system.

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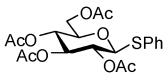
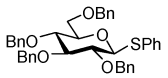
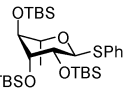
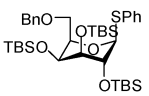
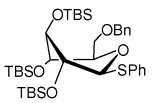
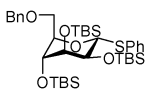
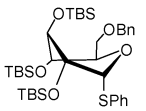
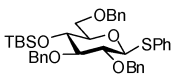
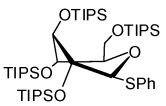
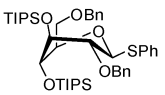
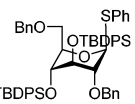
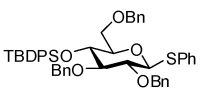
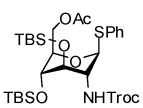
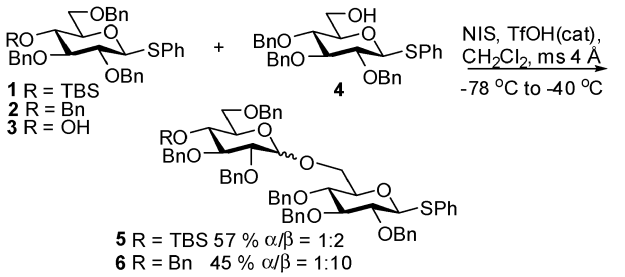
‡ Electronic supplementary information (ESI) available: Experimental procedures for determining the relative rate of hydrolysis and preparation of compounds. See DOI: 10.1039/b801305e

Table 1 Relative rate constants for the glycosylation reactions

Entry	Thioglycoside donor	$k_{rel}/\times 10^6$ s^{-1}
1		5.3 ± 0.6
2		207 ± 9
3		4315 ± 268
4		4075 ± 354
5		3970 ± 270
6		3428 ± 190
7		4020 ± 246
8		540 ± 20
9		4070 ± 417
10		2159 ± 388
11		990 ± 101
12		740 ± 93
13		1120 ± 81

Disilylated donors (entry 10, 11) were found to be very reactive both in preparative and kinetic studies. The triisopropylsilyl (TIPS) protected donor gave the best yields mainly due to their higher stability and greater reactivity, as seen from Table 1, entry 10. The conformation of the disilylated donors was determined from ^{1}H-NMR to be an axial-rich twisted boat conformation, which explains the elevated reactivity of these donors (Scheme 2).



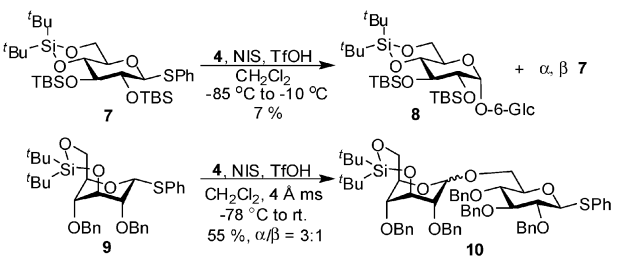
Scheme 2 Glycosylation with donors having one silyl group.

We have earlier demonstrated that it is possible to disarm a silicon rich donor by locking it into $^4C_1$ conformation, and it was now determined if one can arm a donor by tethering into an axial rich $^1C_4$ conformation. The 3,6 tethered donor **9** was prepared and tested in the competitive glycosylation of the armed 6-OH acceptor **4**. The cross-coupling product **10** was obtained in good yield showing that compound **9** is more reactive and the torsional disarming effect is limited (Scheme 3).

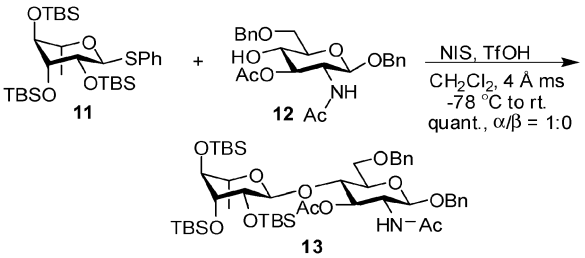
The previous work done in our group revealed a higher reactivity of the superarmed rhamnosyl donor which was also confirmed by our kinetic studies (Table 1, entry 3). This is probably due to the more electron donating methyl group that will stabilize the oxacarbenium ion intermediate. However the differences in reaction rates of different superarmed monosaccharides were not significant; a tendency of the rhamnosyl donor to be the most reactive (entry 3) and the mannosyl donor to be the less reactive (entry 6) can be predicted. The reaction rates of the superarmed thioglucoside and thiogalactoside donors were very similar (entry 5 and 4), as we expected from preparative experiments. From ^{1}H-NMR spectra it could be seen that all these compounds changed conformation and they exist in several conformers in slow equilibrium.[5]

To test the high reactivity of the superarmed donor, a glycosylation reaction with a "difficult" acceptor,[9] such as the glucosamine derivative **12**, and the rhamnosyl donor was performed and resulted in excellent yield and stereoselectivity (Scheme 4).

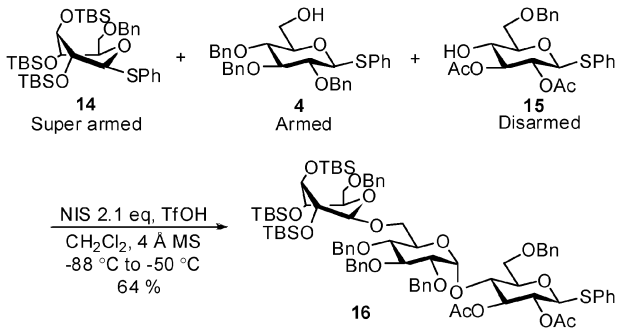
In practical competition experiments, the superarmed glycosyl donors showed high yields and very good selectivities when a 1/1 ratio between donor/acceptor was used in glycosylations. When comparative kinetic experiments were performed (Fig. S1, ESI),‡ the disarmed, armed and superarmed donors proved to have different times of activation; therefore it was possible by a fine-tuning of the reaction conditions to perform a well defined oligosaccharide synthesis.



Scheme 3 Glycosylation with torsional restricted donors.



Scheme 4 Glycosylation with glucosamine acceptor.

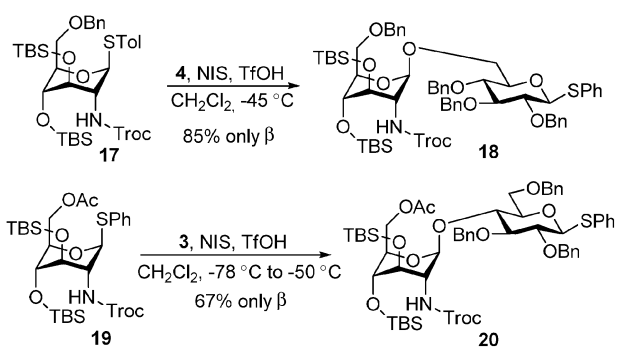


Scheme 5 One pot–one addition synthesis of trisaccharide **16**.

As expected, one pot–one addition synthesis of the trisaccharide **16** was performed and resulted in a good yield by a sequential temperature activation of the donors (Scheme 5).

In order to differentiate between the relative reactivities of donors and acceptors, an armed 6-OH acceptor **4** and a disarmed 4-OH acceptor **15** were chosen as components in the one pot glycosylation. The best yield was obtained when having 1.1 eq. of superarmed donor **14** together with 1.2 eq. of **15** and activation at low temperature. This procedure is a valuable method using the superarmed donors in oligosaccharide one-pot synthesis, since in the literature the trend is to use a stepwise addition of donor and acceptors.[10]

As a part of our kinetic studies we were interested in determining the relative rate of glucosaminyl donors, one example being shown in Table 1, entry 13. Amino sugars are known for their wide biological occurrence,[11] including those of the bacterial cell wall[12] and the constitution of the core pentasaccharide,[13] but also for their potential biomedical applications. There has been much research in developing new methods for the synthesis of glucosamine derivatives in the last decades. However, no general widely applicable



Scheme 6 Glycosylations with very reactive glucosaminyl donors.

method has emerged and they behave very differently in glycosylation reactions, their reactivity and selectivity being strongly depended on the N protective group.[14]

The superarmed glucosamine derivatives **17** and **19** couple very efficiently to glucose derivatives that are themselves thioglycosides (Scheme 6).

These experiments proved that it is also possible to increase the reactivity of a glucosamine donor through silylation with bulky silyl protecting groups. The stereoelectronical effects from the conformational change even overrules the unfavourable electron withdrawing effect of the 6-OAc group (Scheme 6).

In conclusion, we have developed a quantitative method to measure the rate of glycosylation reactions and demonstrated that the difference in reactivity between the superarmed and other donors is significant.

Notes and references

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