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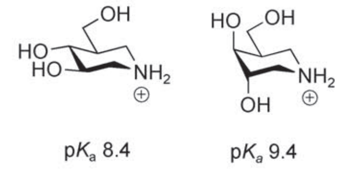
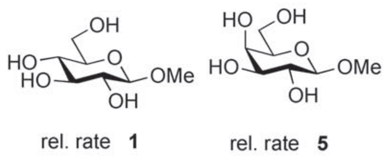


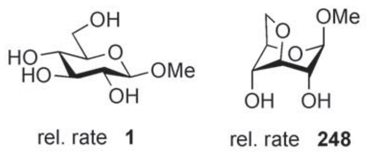
***Basicity increase with axial OH***

(*Chem. Eur. J.* **2002**, *8*, 1218-1226)



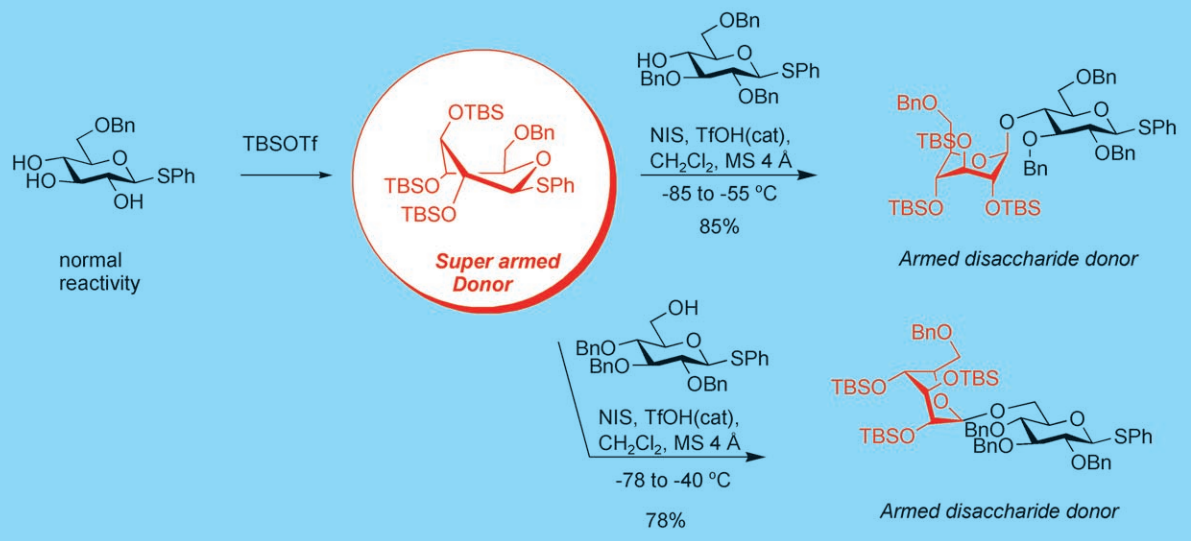
***Reactivity increase with axial OH***

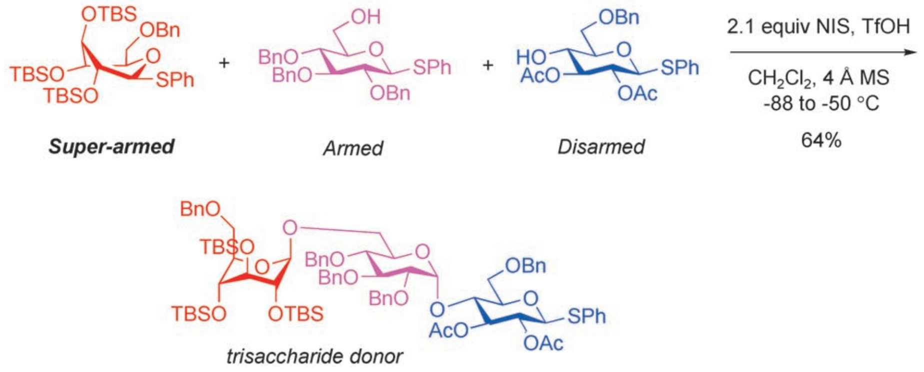
(*Angew. Chem. Int. Ed.* **2001**, *40*, 3447-3449)

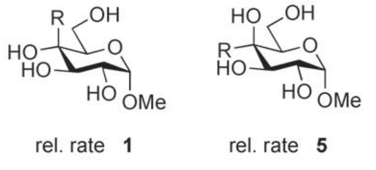


***Conformational change increases reactivity***

(*J. Am. Chem. Soc.* **2004**, *126*, 12374-12385)



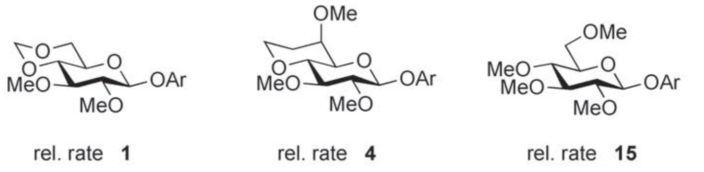




(R = H or Me)

***Sterics are of minor relevance***

(*Org. Lett.* **2003**, *5*, 3201-3203)



***Disarming effect of the position of the 6-oxygen atom***

(*J. Am. Chem. Soc.* **2004**, *126*, 9205-9213)

# Going to Extremes: “Super” Armed Glycosyl Donors in Glycosylation Chemistry

Henrik H. Jensen,*[b] Christian Marcus Pedersen,[b] and Mikael Bols*[a]

**Abstract:** This concept article gives an overview of stereoelectronic effects in monosaccharide systems and how these can be used to dramatically enhance the reactivity of glycosyl donors in oligosaccharide synthesis.

**Keywords:** carbohydrates • conformation analysis • glycosylation • protecting groups

## Introduction

Carbohydrate chemistry is a very important branch of organic chemistry as seen from many perspectives be it renewable resources, biology or medicine. The comparatively complex chemistry of carbohydrates has led to relatively slow progress in this area and in our understanding of these molecules. Despite much research over the past years the carbohydrate chemist is still frequently frustrated by the very different behaviour of carbohydrates compared with simpler organic molecules.

A central research theme in carbohydrate chemistry is and has long been glycoside synthesis, that is, oligosaccharide-forming reactions, due to the biological significance of these molecules and the considerable chemical challenges associated with making them. While traditional glycosylation chemistry was based on the Koenigs–Knorr reaction[1] ever since R. R. Schmidt asked his rhetoric question “Are there alternatives to the Koenigs–Knorr method?” the number of chemical methods for oligosaccharide synthesis have been ever growing.[2]

Given the many biological events currently being uncovered in which carbohydrates play an integral part,[3,4] the ability to efficiently synthesise oligosaccharides is probably more important than ever. Complex oligosaccharides such as the core pentasaccharide,[5] tumour-associated antigens,[6] and blood group determinants[6] have been prepared by automated solid-phase oligosaccharide synthesis.[7] However, the solution-phase method is nevertheless better suited to synthesis of difficult molecules than the solid-phase approach. One solution-phase technique is the iterative one-pot glycosylation protocol in which an oligosaccharide is build from the non-reducing end by sequentially adding promoter and an acceptor to a glycosyl donor.[8] Another rather similar approach is the Optimer method[9,10] by Wong and co-workers that builds on earlier findings by Paulsen,[11] Fraser-Reid,[12] Ley[13] and co-workers (Scheme 1).

This article will describe a new concept in glycoside synthesis, which we call “super”-armed glycosyl donors, because they have a reactivity beyond that found in conventional armed donors;[9,12] certain sugars can have their reactivity boosted by a conformational change. The increased reactivity originates from placing some of their electron withdrawing substituents, normally being equatorial, into an axial or pseudoaxial orientation, which renders them less destabilising of the electron deficient transition state.

A key remark was made by Paulsen in a 1982 paper[11] regarding the reactivity of glycosyl halides that would be the foundation for a powerful approach to one-pot oligosaccharide synthesis. He noticed that halide donors with ester protecting groups were considerably more stable than the analogous benzylated donor. This was later used by B. Fraser-Reid and co-workers in the synthesis of a trisaccharide (Scheme 1).[12] They mixed another type of donor, a pentenyl glycoside, with a sugar that could both act as donor and an acceptor (Scheme 1). Because the first donor was considerably more reactive due to the presence of benzyl protecting groups, this could be chemoselectively activated over the acetylated sugar that would exclusively act as an acceptor.

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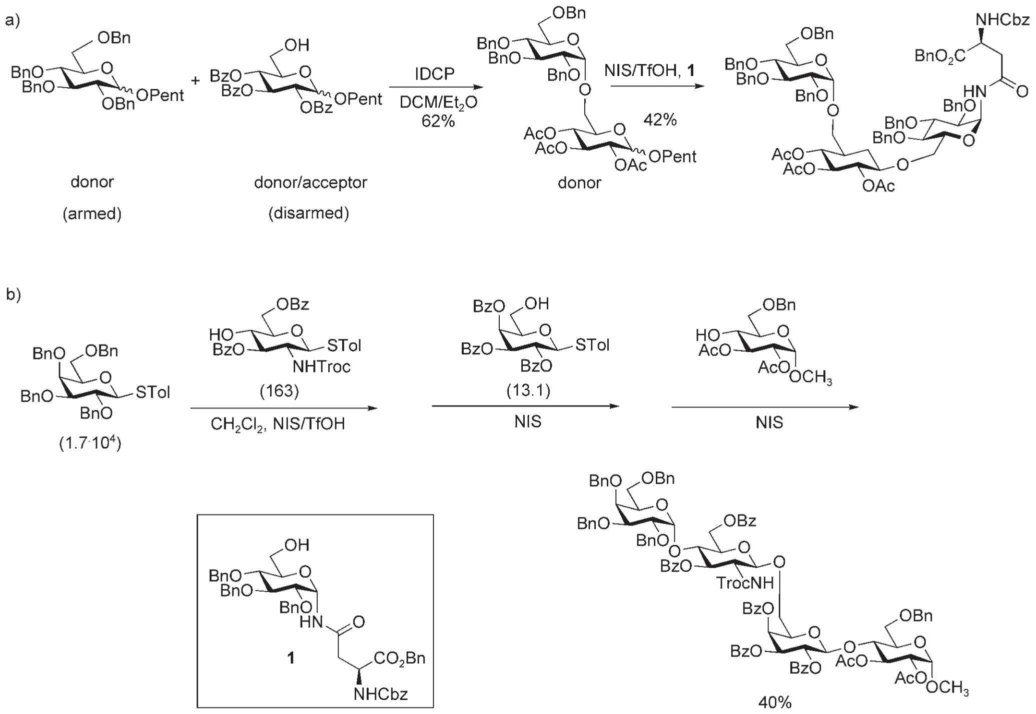


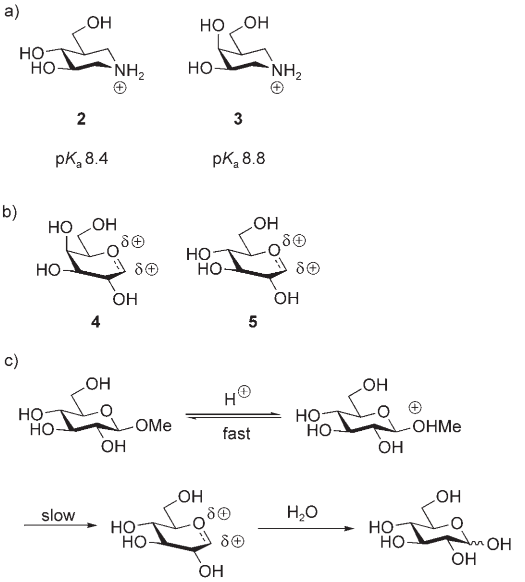
Scheme 1. a) Fraser-Reid's one-pot trisaccharide synthesis using the armed-disarmed concept, Pent = $CH_2CH_2CH_2CH{=}CH_2$, Bn = $CH_2Ph$, Bz = COPh. b) Wong's one-pot strategy, donors added having descending reactivity, relative reactivity shown in brackets.

Addition of another acceptor and another equivalent of promoter yielded a trisaccharide with no need for an intermediary purification and deprotection step (Scheme 1a). It is widely accepted that benzylated donors are more reactive than the analogous acylated donors since the former form of protection leaves the sugar hydroxyls less electron-withdrawing than the latter form of protection. Since the transition state for glycoside transfer is of oxacarbenium-type and hence electron deficient, the benzylated donors become more reactive than their acylated counterparts in accordance with the observation by Paulsen.[11] As coined by Fraser-Reid, the term *armed* glycosyl donors are now widely used to refer to the more reactive donors bearing benzyl protection, whereas *disarmed* donors are the less reactive acylated donors.[12]

Ley later pointed out that donor reactivity should be viewed as a continuum and not two extremes and associated values for reactivity which each type of donor depending on their protecting groups.[13] This was later further extended by Wong and co-workers[9] who published a comprehensive chart of compounds with a broad range of reactivity values that spanned more than five orders of magnitude.[10] With these values, determined from competition experiments, it was now possible to design a synthesis, starting from the non-reducing end, by ranking donor reactivity and starting with the most reactive donors as shown in Scheme 1b. The true benefit of this approach over traditional oligosaccharide synthesis is the possibility of carrying out multiple coupling steps in a one-pot procedure, which avoids isolation of intermediates and manipulation of protecting groups of these in separated steps.

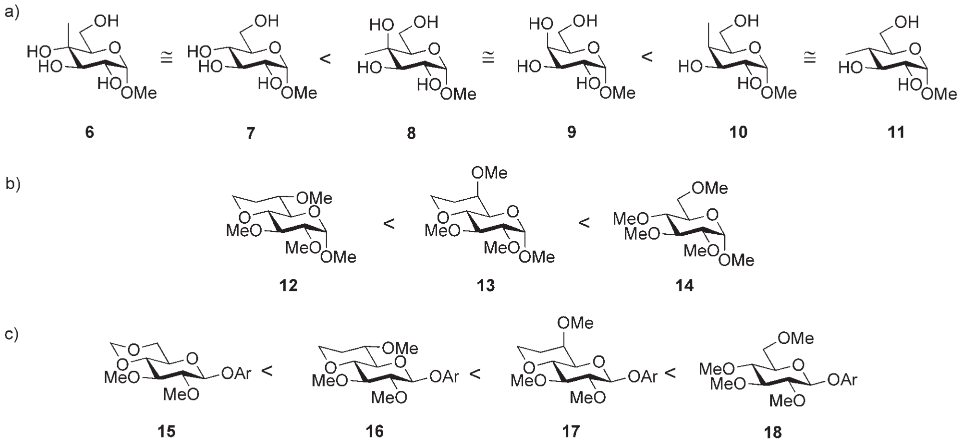
## Stereoelectronic Effects

Our interest in reactivity tuning comes from our recent exploration of stereoelectronic effects in carbohydrate and carbohydrate-like molecules.[14] Some time ago we noticed an unexpected difference in the p$K_a$ value of two similar hydroxylated piperidines that we were studying as glycosidase inhibitors.[15,16] The all-*cis galacto*-isofagomine (**2**) was found to be 0.4 p$K_a$ units more basic than its corresponding *trans-trans* gluco-configured analogue, **1** (Scheme 2a). A more careful study of a wide range piperidines with different electron-withdrawing groups revealed p$K_a$ variations to be highly systematic.[16] This allowed us to assign specific values, $\sigma_s$, to each type of substituent that by means of a simple formula[16] with high accuracy could predict the p$K_a$ value of a given protonated piperidine. Most striking, and with key importance to the concept of "super"-armed glycosyl donors (see below), was the fact that axially oriented electron-withdrawing group were found to be less electron-withdrawing than their equatorially placed counterparts. Charge-dipole interactions were found to be able to account for this phenomenon.[14] Equatorially oriented hydroxyl groups are hence more electron withdrawing than axially placed hydroxyl much in the same way that F is more electron withdrawing than OH.[17]



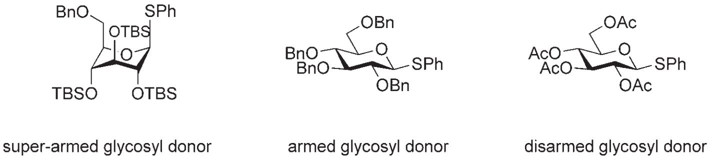
Scheme 2. a) Protonated galacto-configured piperidine **3** is more basic than gluco-configured piperidine **2**. b) Galactosyl cation **4** forms faster glucosyl cation **5** in acid catalysed glycoside hydrolysis. c) Mechanism for acid-catalysed glycoside hydrolysis of methyl β-D-glucopyranoside. Stability of glucosyl cation is reflected in the observed rate of hydrolysis and parallels the stability of the similar hydroxylated piperidine **2**.

After our discovery we soon realised that this effect could have bearing on other similar systems.[18] We used the substituent values to create a Hammett-type plot, to establish a one-to-one connection between the factors that determine the $pK_a$ of a hydroxylated piperidine and the rate of hydrolysis of a corresponding glycoside. This was to our knowledge the first linear free energy relationship established where substituent constants ($\sigma_s$) depend on stereochemistry.[19] This strongly suggests that the effects that govern piperidine basicity, which are expected to be electronic in nature, are the same that to a large degree influence glycoside reactivity. The common denominator in this case is the cationic structure of the protonated piperidine and the stability of the oxacarbenium ion-like transition state in glycoside hydrolysis a reflected in the hydrolysis rate constant $k_{obs}$ (Scheme 2c).



Scheme 4. a) Methyl glycopyranosides arranged in order of increasing reactivity towards acid-catalysed hydrolysis. Results show that the orientation of the electron withdrawing hydroxyl is much more important for hydrolytic reactivity than steric bulk. b) Hydrolysis of methyl glycosides, and c) hydrolysis of aryl glycosides having restricted conformation around the C5–C6 bond. The results show that the charge-dipole interaction (from the C6–O6 bond) play a greater role than torsional effects. Ar = 2,4-dinitrophenyl.

We managed to confirm our expectation that the glycoside reactivity was largely dependant on the orientation of the hydroxyl groups rather than the orientation of the sterically most bulky group (Scheme 3) as alluded to by Edward,[20] by hydrolysing probe molecules **6–11** (Scheme 4a):[21] Galactosides **8** and **9** were five times more reactive than glucosides **6** and **7**.

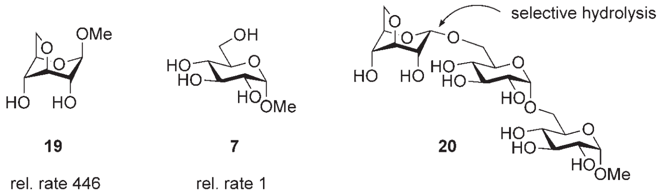


Scheme 3. Bulky silyl groups as protecting groups change pyranoside conformation to a more "axial-rich" conformer and results in increased donor reactivity.

We furthermore hydrolysed α-methyl- and β-dinitrophenyl glucopyranoside probes **12–18** confirming the major influence played by dipole directionality (Scheme 4b,c).[22] Although torsional effects from having a *trans*-decalin-like ring-fused system were indeed shown to play a role, electronic effects were found to be much more powerful in controlling glycoside reactivity. The presence of axially oriented hydroxyl groups would hence cause an enhancement of glycoside reactivity towards hydrolysis (Scheme 4).

Dehydrated sugars like 3,6-anhydrosugar **19** underwent a ring-flip from a $^4C_1$ to a $^1C_4$ and would have its hydroxyl substituents normally placed equatorially in an axial orientation. This would, following the results mentioned above, be expected to be much more reactive than the corresponding glycoside in a relaxed $^4C_1$ conformation and this was in actual fact found experimentally. A reactivity difference of more than 400-fold was observed (Scheme 5).[23]

We furthermore studied the reaction of a trisaccharide **20** (containing three glycosidic linkages) in acidic $D_2O$ and found as expected the 3,6-anhydroglycosidic linkage to be



Scheme 5. Forcing a glucoside into an all-axial conformation by by forming a 3,6-anhydride dramatically increases reactivity towards hydrolysis.

the most labile due to the presence of more axially oriented hydroxyl groups (Scheme 5).[23]

## Glycoside Synthesis

We were at this stage confident that we understood the reactivity of the glycosidic linkage towards hydrolysis and the basicity of hydroxylated piperidines in (Brønsted) aqueous acid. The influence played by axially versus equatorially oriented electron-withdrawing substituents in inert solvents such as $CH_2Cl_2$ was, however, a different matter. Results by Wong and co-workers[9] (NIS/TfOH activation) and Oscarson et al.[25] (DMTST activation) on armed and disarmed thioglycosides all supported the effect still being present making galactosyl donors considerably more reactive than glucosyl donors. This needed not necessarily to be the case since the transition state and the reaction mechanism itself for the two reactions might have been markedly different in terms of charge build-ups and concertedness.

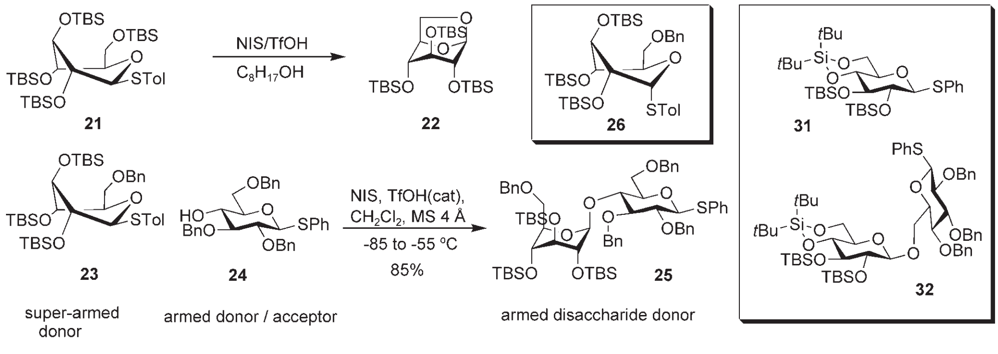
We extended the results by Wong by studying the perbenzylated glucosyl and galactosyl trichloroacetimidate donors in $CH2Cl_2$ in competition experiments and found the same trend.[25] We next asked ourselves whether it would be possible by flipping the conformation as was done in the above-mentioned anhydro case (Scheme 3) to enhance the reactivity of an already armed glycosyl donor and if these new types of donors would be anomerically selective. For our study we chose the donor function to be a thioglycoside because of their ease of preparation and stability towards a wide range of reactions.[26] It was known that bulky silyl groups such as the TBDMS group could force a conformational change upon a relaxed $^4C_1$ glucopyranoside since they cannot be accommodated in the equatorial position.[27]

We prepared the known compound phenyl tetra-*O*-TBDMS-1-thioglucopyranoside (**21**) which indeed was found not to be in a relaxed $^4C_1$ conformation. The conformation rather than being a $^1C_4$ can from $^1H,^1H$ coupling constants can possibly better be described as a twist boat. Activation of the thioglucoside with NIS/TfOH in the presence of an acceptor (1-octanol) only resulted 1,6-anhydro formation giving **22** (Scheme 6). The silyl group on O-6 was hence too labile and needed replacement with a more stabile protecting group such as benzyl to prevent it from acting as an internal acceptor. This 2,3,4-tri-*O*-TBDMS thioglucoside donor, **23** was then prepared and found, based on $^1H,^1H$ coupling constants, to have similar conformational preferences to the analogous tetrasilyl protected donor. Selective activation of this (**23**) with NIS/TfOH in the presence of armed glucosyl donors having an acceptor function (**24**) indeed demonstrated a significant enhanced reactivity of the trisilylated thioglycoside **23** as expected from the results obtained from our hydrolysis studies (see above).[14,28] The corresponding armed disaccharide **25** was obtained in excellent yield and stereoselectivity (Scheme 6). The NIS/TfOH activation systems proved far superior to NIS, NIS/TESOTf, or IDCP and the former resulted in good to excellent β-selectivity. The found selectivity is in good agreement with recently published findings by Yamada and co-workers who used triisopropylsilyl (TIPS) protection of O-2, O-3, and O-4 and MeOTf for thioglycoside activation.[29]

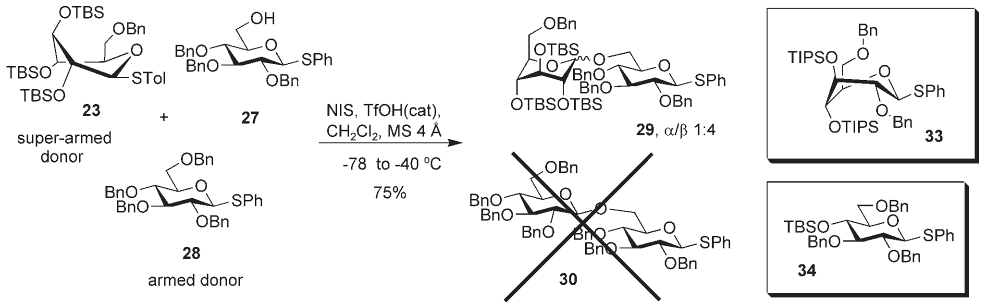
The anomeric configuration of the super-armed glucosyl donor was irrelevant: Glycosylation stereoselectivity was largely unchanged in changing from the α to the β donor and the yield only slightly lower with the α-anomer **26**.[28]

The reactivity difference between benzylated donors (**28**) and the conformationally twisted silylated donors (**23**) is even more clearly seen in a competition experiment between **23** and **28** competing for acceptor **27** (Scheme 7). Only disaccharide **29**, the coupling product of the super-armed donor, is formed while the product **30** from the armed donor is not.

The high reactivity of these silylated donors is intrinsically linked to their conformation. Thus 4,6-*O*-di-*tert*-butylsilylene glucopyranoside donor **31**,[30] which is locked in a $^4C_1$ conformation and cannot undergo a full ring inversion while at the same time being highly silylated, is very unreactive (Scheme 6). Only 7% yield of the cross-coupling product **32**



Scheme 6. Glycolsylation with super-armed glucosyl donors.



Scheme 7. Competition experiment between an armed and a super-armed donor.

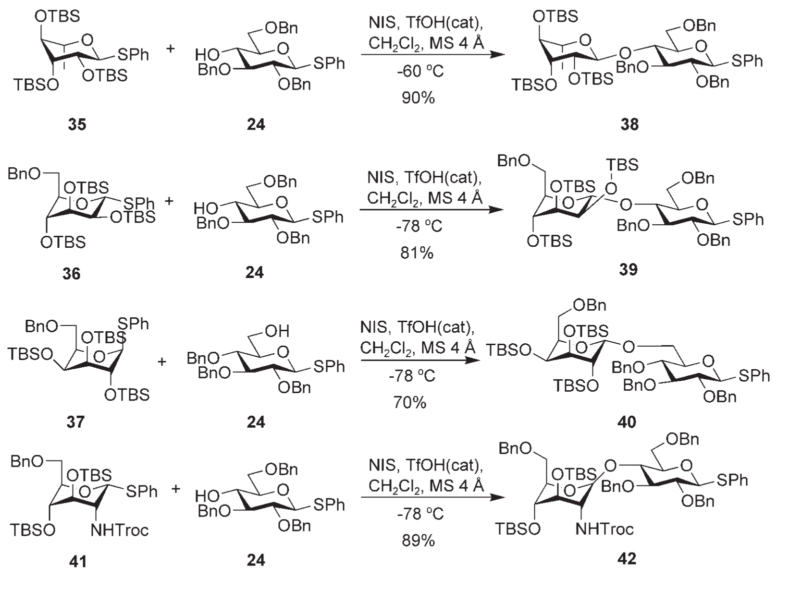
could be isolated when reacted with the armed glucosyl donor/acceptor **27**, while self-coupling of **27** (to **30** and oligomers) was pronounced.[28] Rather **31** is disarmed with a reactivity comparable to that of a 4,6-*O*-acetal protected donor, which has a decreased reactivity for both torsional and electronic reasons.[22]

On the other hand the 3,4-TIPS-protected glucosyl donor **33** (Scheme 7) is very reactive; it selectively cross-couples to **27** in 77% yield (not shown). However a mono-TBS protected donor such as **34** does not have extraordinarily high reactivity. Therefore the TBDMS group does not have an intrinsically arming effect, and the reactivity boost is clearly associated with conformational change.

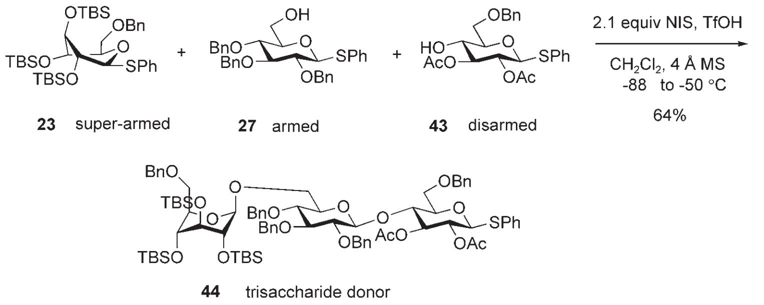
A glucosyl donor has three equatorial OR groups that can become axial upon persilylation giving the largest possible reactivity increase. Thiomannosides, thiogalactosides and thiorhamnosides have two equatorial and one axial group before conformational flipping, which potentially can lead to two axial and one equatorial OR groups; therefore silylation should result in an increase in reactivity for these molecules as well. The donors **35–37** (Scheme 8) were prepared and all were found to display complex NMR spectra indicating several conformational preferences in slow equilibrium.[28] α-L-Rhamnosyl donor **35** was found to give excellent results in terms of selectivity (α) and yield; coupling with armed acceptor **24** gave disaccharide donor **38** in excellent yield. α-D-Mannosyl donor **36** showed equally good selectivity (α) results but slightly lower yields; in this case the coupling to **24** gave 81% of α-glycoside **39**. β-D-Galactosyl donor **37** was also found to be able to couple to an armed glucosyl donor/acceptor (**27**) with complete α-selectivity but the yield is more moderate (70%). Importantly the selectivity of the silylated galactosyl donor **37** is completely opposite to that of the analogous glucosyl donor **28**. This change can possibly be attributed to sterical effects associated with the orientation of the 3-OTBDMS group. Similar, full α-selectivity has recently been observed for a 4,6-*O*-silylene protected galactosyl donor.[30]

The silylated glucosamine derivative **41**, which has TBS groups on 3-OH and 4-OH and Troc on the nitrogen is an excellent donor. It coupled to **24** in 89% yield giving only the β-linked disaccharide **42** (Scheme 8).

As is clear from the above the conformationally armed donors streches the spectrum of glycosyl donor reactivity, and it is now possible to carry one-pot glycosylations that were previously not possible. An example is shown in Scheme 9, where super-armed donor **23** is reacted with armed donor/acceptor **27** and disarmed donor/acceptor **43**. The result was a 48% yield of trisaccharide **44**, which itself is a glycosyl donor. This is reaction is carried as a true one-pot reaction, with the reactants being present simultaneously,[31] and not just added sequentially. The limitations of this reaction are therefore the lack of discrimination between the acceptor alcohols; the primary alcohol **27** is not much more reactive than secondary alcohol **43**.



Scheme 8. Glycosylation of armed acceptors with super-armed rhamnosyl, mannosyl and galactosyl donors.



Scheme 9. One-pot, one-reaction glycosylation between a disarmed (**43**), armed (**27**) and super-armed donor (**23**) giving 64 % of trisaccharide donor **44**.

## Conclusion

The study of azasugars has provided new important fundamental insight: By measuring p$K_a$ values of hydroxylated piperidines we found a difference in electron-withdrawing power of axial and equatorial OH groups, that is, the equatorial hydroxyl group is roughly three times more electron-withdrawing. This observation can not only explain the conformational behaviour of certain piperidines upon change of pH, but also be used to explain why glycosides with equatorial OH groups are less reactive than those with those with axial OH groups. As a consequence of the above, different carbohydrate conformers must have different reactivity, and it is therefore possible to construct glycosyl donors that are conformationally armed by making derivatives that favour axial rich conformers. Using bulky silyl groups as a tool to achieve these conformations we have given a number of examples of such super-armed glycosyl donors.

Two applications of these novel glycosyl donors can be foreseen. Since they stretch the armed-disarmed concept they can be used to make one-pot glycosylation procedures more efficient. Secondly they are a means to go beyond common glycosyl donor reactivity and can therefore be useful in difficult glycosylations.

## Acknowledgement

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[17] The formula p$K_a$ $10.7-\Sigma\sigma_s$, where $\sigma_s$ are substituent constants for a given substituent (e.g. OH, F, $CH_2OH$, $CO_2Me$) in a given position on a piperidine ring (i.e., $\alpha$, $\beta$ or $\gamma$) and depending on stereochemistry (axial or equatorial). Substituent constants were hence found to be larger for F than O as expected. Values for equatorially placed electron withdrawing groups were furthermore found to be larger than for the same axially placed substituent in the same position. For details, see ref. [15].

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