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Superarming of Glycosyl Donors by Combined Neighboring and Conformational Effects

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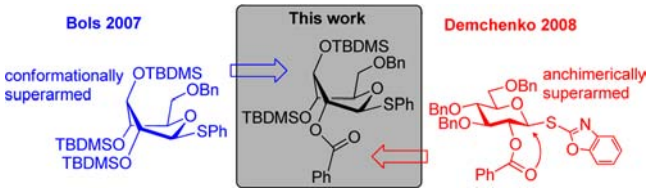
ABSTRACT



A novel glycosyl donor that combines the concepts of both conformational and electronic superarming has been synthesized. The reactivity and selectivity of the donor have been tested in competition experiments.

Traditionally oligosaccharide synthesis relies on protective group manipulations and the use of orthogonal glycosylation methods, such as different types of glycosyl donors. Due to the increased interest in biologically relevant oligosaccharides the development of new methodologies have been impressive during the past couple of decades and paved the way for more efficient synthesis.[1,2] These developments include, but are not limited to, one-pot protection[3] and glycosylation strategies,[4,5] polymer-supported[6] and automated synthesis,[7,8] ionic liquid supported,[9,10] fluorous tag assisted,[11,12] surface-tethered (STICS),[13] and HPLC-assisted syntheses.[14]

The control of the glycosyl donor's reactivity belongs to the tools available for improving oligosaccharide synthesis. The armed−disarmed concept was introduced by the group of Fraser-Reid[15] and utilizes selective activation of one donor over another with the same anomeric leaving group. The reactivity of the donor relies on the protective groups used; more electron-withdrawing groups reduce (disarm) the donor reactivity and *vice versa*. Glycosyl donor **A1** is armed (benzylated) whereas **A2** is disarmed (more electron-withdrawing protective groups) and acts as the glycosyl acceptor (Scheme 1A).[15,16]

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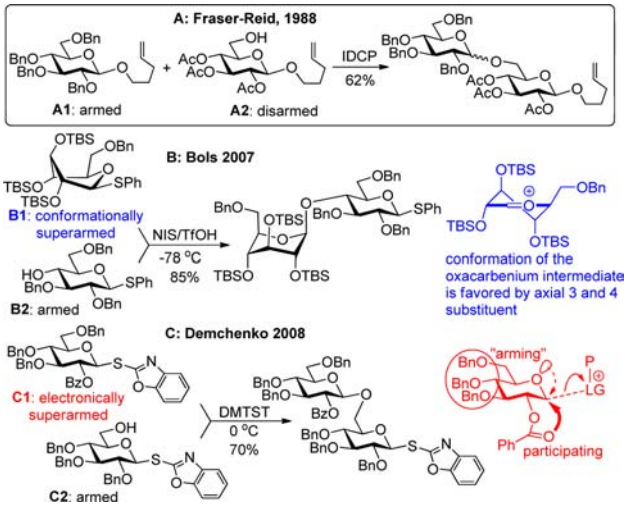
With the insight into manipulation of reactivity by protective groups, new methodologies for oligosaccharides have been developed; one example is "one-pot" oligosaccharide strategies, introduced by the groups of Fraser-Reid, Ley, and Wong.[17−23] For instance, a very detailed work by Wong and collaborators[22,23] showed that the reactivity of an armed or a disarmed donor varied considerably depending on the stereochemistry and whether deoxy groups were present.[24]

The stereochemical effect of hydroxyl groups on the development of a positive charge in heterocycles has been further demonstrated using piperidines as the model compounds. By comparing the pK_a values for the conjugate acid it was found that equatorial substituents are significantly more deactivating (EWD) than their axial counterparts.[25−28] The same effects were found for glycosyl donors and used by Bols and co-workers to conformationally arm glycosyl donors by changing the equatorial rich $^4C_1$ conformation to an axial rich conformation.[29−33] The conformational changes were induced by creating steric congestion at the equatorial C-2, C-3, and C-4 positions of D-glucosides,[34] resulting in a skew-boat conformation (donor **B1**, Scheme 1B). The new type of donors showed a 20-fold increase in reactivity as compared to its per-*O*-benzylated counterpart.[32] The superarmed glycosyl donor **B1** could be effectively coupled with "armed" acceptor **B2** promoted by NIS/TfOH at −78 °C to afford the corresponding disaccharide in 85% yield (Scheme 1B).[30]

Derived from the discovery of the O2/O5 cooperative effect in glycosylation[35] Demchenko and co-workers

Scheme 1. Chemoselective Strategies for Oligosaccharide Synthesis: (A) Armed−disarmed; (B) Conformational Superarming; (C) Electronic Superarming



reported that a glycosyl donor containing a 2-*O*-benzoyl group, instead of a 2-*O*-benzyl, increased the reactivity compared with a fully benzylated analogue and hence be considered "superarmed". The arming was found to be due to anchimeric assistance,[41] which overrules the EWD properties of the benzoyl group.[36,37] Thus, glycosylation with 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl protected *S*-benzoxazolyl (SBox) glucoside **C1** with per-benzylated "armed" glycosyl acceptor **C2** in the presence of dimethyl(methylthio)sulfonium triflate (DMTST) provided a disaccharide in 70% yield (Scheme 1C). This concept for superarming was found to be universally applicable to common leaving groups including *O*-pentenyl, *S*-ethyl, *S*-phenyl, *S*-tolyl, and *S*-thiazolinyl.[38]

With two different approaches to superarm glycosyl donors, we wondered which superarmed donor is more reactive. To investigate this, a direct competition experiment was performed wherein the conformationally superarmed *S*-phenyl glycosyl donor **1a** was set to compete with electronically superarmed glycosyl donor **1b** for cyclohexanol (Scheme 2). The most reliable comparison was achieved in the NIS/TfOH-promoted competition experiment starting at −78 °C and slowly warming up to 0 °C, essentially the same reaction conditions as reported by Bols and co-workers.[30] Formation of disaccharide **2a** derived from the conformationally superarmed glycosyl donor **1a** was predominant (**2a** isolated in 91% yield), whereas **1b** was recovered in 94% yield. This result clearly indicated that donor **1a** has superior reactivity in comparison to donor **1b** under these reaction conditions.

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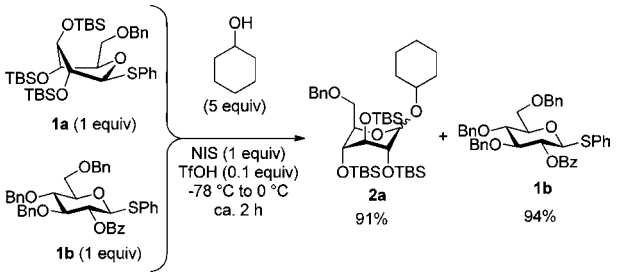
Scheme 2. Competition Experiment between Conformationally Superarmed Donor **1a** and Electronically Superarmed Donor **1b**



This result lead to the question of whether further enhancement in reactivity could be achieved by using a combination of both conformational and electronic effects. To address this question and with the goal of incorporating all key structural features from both approaches into a single hybrid donor, **1c**, equipped with both the 2-*O*-benzoyl substituent and remote *O*-TBS substituents at 3,4-positions in combination with 6-*O*-benzyl (glycosyl donor **1c**; see the Supporting Information (SI) for its synthesis), was obtained. The conformation of donor **1c** was investigated by ^{1}H NMR, where the coupling constants suggested a skew-boat conformation similar to the one found for conformationally armed donors.[30]

The conformation was further proved by obtaining the first reported crystal structure of the superarmed donor **1a**, which has similar (to **1c**) ^{3}J coupling constants in its ^{1}H NMR (Figure 1). The crystal structure confirms the suggested skew-boat conformation and confirms that **1c** is in a similar conformation.[39,40]

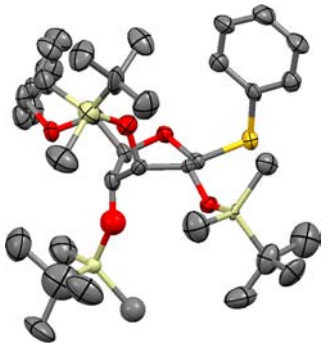
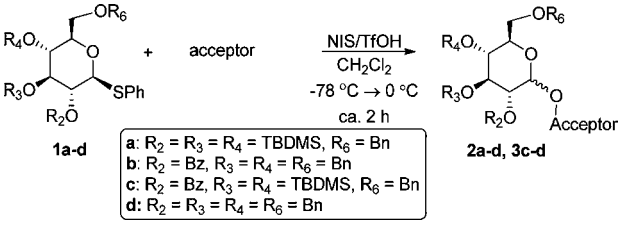


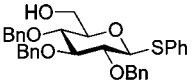
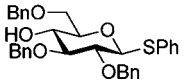
Figure 1. Crystal structure of **1a**.

Having established that **1c** indeed has changed the conformation to an axial-rich skew-boat, the properties of the hybrid donor **1c** could be investigated in more detail. For this purpose, glycosyl donors **1a**–**c** were compared under standard reaction conditions (NIS/TfOH, −78 to 0 °C). Since **1c** has incorporated a 2-*O*-benzoyl substituent, the stereoselectivity was expected to be excellent due to neighboring group participation. The stereoselectivity obtained with donor **1a** having a nonparticipating TBS-group at *O*-2 is normally excellent with poor acceptors, such as other carbohydrates, but can be reduced when using simple alcohols as acceptors.[30] The results of this study are summarized in Table 1. All glycosylations were giving good-to-excellent yields and for entries 2 and 3 complete β-selectivity was observed, whereas donor **1a** (entry 1) was less selective. Glycosylations of benzylated "armed" glycosyl acceptors equipped with the *S*-phenyl anomeric group with donor **1c** gave moderate-to-good yields and complete stereoselectivity (entries 5 and 6), with an acceptor site. The lower yield observed with the primary acceptor (entry 5) is mainly due to migration of the TBS protective group from donor **1c** to the acceptor. The new donor can therefore be considered superarmed, as it is more reactive than a conventionally armed donor.

With the glycosylation properties of donor **1c** established, its reactivity was studied by competition experiments with donors **1a** and **1b** using essentially the same reaction conditions as those described in Scheme 2. From the first experiment between the hybrid donor **1c** and the electronically superarmed donor **1b**, it was obvious that compound **1c** was significantly more reactive; *i.e.*, complete conversion of **1c** to glycoside **2c** and almost full recovery of unreacted **1b** was observed (Scheme 3). Competition between donor **1c** and the conformationally superarmed donor **1a** revealed that donor **1a** was much more reactive. The high conversion of donor **1a** to glycoside **2a** was observed, whereas most of donor **1c** was recovered.

Table 1. Comparative Study of Glycosyl Donors **1a**–**c**[a]



entry	donor	acceptor	product, yield (α/β ratio)
1	**1a**	[c]Hexanol	**2a**, 82% (1:2.8)
2	**1b**	[c]Hexanol	**2b**, 91% (β only)
3	**1c**	[c]Hexanol	**2c**, 97% (β only)
4	**1d**	[c]Hexanol	**2d**, 84% (1:2)
5	**1c**		**3c**, 53% (β only)
6	**1c**		**4c**, 70% (β only)

[a] [c]Hexanol = cyclohexanol.

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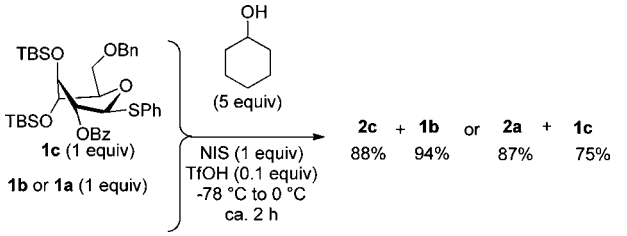
Scheme 3. Competition Experiment between the Hybrid Donor **1c** and Previously Developed Donors **1a** and **1b**



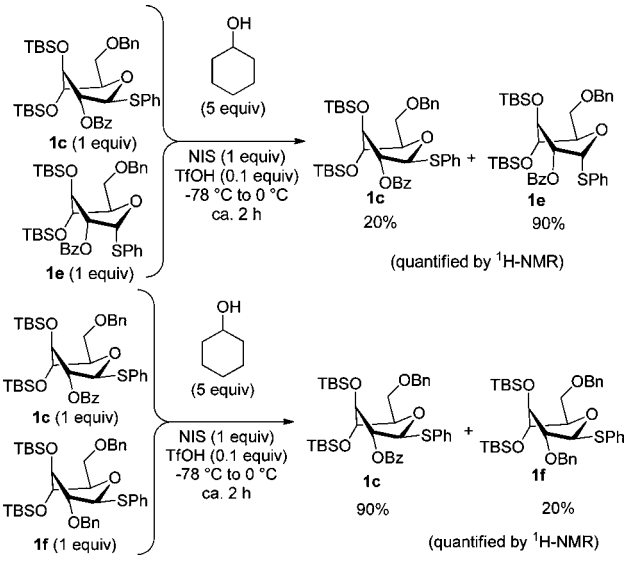
Puzzled by the lower reactivity of the hybrid donor **1c** the question arose whether the *trans-vicinal* 2-*O*-benzoyl group in **1c** is able to increase the reactivity by the anchimeric effect or if it is overall disarming due to its electron-withdrawing nature. To investigate this, the α-counterpart **1e** of *β*-donor **1c** was synthesized (see the SI for its synthesis). Due to the 1,2-*cis* orientation in donor **1e**, the 2-*O*-benzoyl group is unable to provide the anchimeric assistance. Therefore, if this effect prevails α-linked donor **1e** would be less reactive than its *β*-linked counterpart **1c**.

A competition experiment between donors **1c** and **1e** carried out under the standard conditions clearly showed that *β*-linked donor **1c** (80% conversion) was more reactive than its α-linked conterpart 1e (10% conversion). The higher reactivity of **1c** compared to **1e** suggests that the 2-*O*-benzoyl group is providing an arming effect by means of the anchimeric assistance.[41] On the other hand, the reactivity difference between **1c** and **1e** could also be partly due to the anomeric effect lowering the ground state energy of the α-anomer.[42,43] In the absence of the anchimeric assistance, axial thioglycosides have been found to be more reactive than their equatorial counterparts. This has been explained with the importance of an antiperiplanar arrangement between the leaving group and one of the ring-oxygen lone pairs.[44,43]

To gain a better understanding of the effects caused by the 2-*O*-protective group, 2-*O*-benzyl superarmed donor **1f** was synthesized.[30] A competition experiment between donors **1c** and **1f** was performed (Scheme 4), and in this case donor **1f** (80% conversion) was found to be more reactive than donor **1c** (10% conversion). This result suggests that the 2-*O*-benzoyl in **1c** is having an overall disarming effect in comparison to that of the 2-*O*-benzyl group in donor **1f**.

Since donor **1c** is more reactive than **1e**, but less reactive than **1f**, the arming anchimeric assistance of the 2-*O*-benzoyl group is overruled by the electron-withdrawing properties. The higher reactivity of **1c** compared to **1b** is

Scheme 4. Competition Experiment between Donor **1c** and Donor **1e** as well as Donor **1f**



arguably due to the altered axial-rich conformation, which results in a smaller electron-withdrawing effect from substituents on the sugar ring. The altered, and not so flexible, conformation could, however, also diminish the effect of the anchimeric assistance since the 2-*O*-benzoyl is not perfectly *antiperiplanar* to the anomeric leaving group in the skew-boat conformation.

In conclusion, we have successfully synthesized a new type of donor **1c** that combines conformational arming and anchimeric assistance effects. Glycosylations with this donor are high yielding and stereoselective. From this work it is clear that conformational arming is the more powerful tool when it comes to increasing the reactivity of the glycosyl donor. Anchimeric assistance does not increase the reactivity further in this particular case, but does lead to stereocontrol. Thus the combined donor obtained is highly reactive (superarmed), useful in one-pot glycosylations, and stereoselective. Alternative promoter systems for thioglycosides were investigated, but without providing additional insight; the NIS/TfOH promotor system remains the most successful in terms of yields and simplicity.

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Supporting Information Available. Experimental details for preparation of new compounds, NMR spectra, and X-ray crystal data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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