Selective Glycosylations

DOI: 10.1002/anie.200502694

Development of an Arming Participating Group for Stereoselective Glycosylation and Chemoselective Oligosaccharide Synthesis**

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Dedicated to Professor Andras Liptak on the occasion of his 70th birthday

Carbohydrates are involved in many harmful processes such as bacterial and viral infections, development and growth of tumors, metastasis, tissue rejection, etc. Many of these processes are directly associated with deadly diseases of the 21st century including AIDS, cancer, meningitis, hepatitis, septicemia, etc.[1] Elucidation of the exact mechanisms of the carbohydrate involvement in disease pathogenesis would be significantly facilitated if we could rely on the comprehensive knowledge of the structure, conformation, and properties of the carbohydrate molecules. It is critical to make complex carbohydrates more accessible to general chemical, biochemical, and industrial audiences to keep pace with the exploding area of glycobiology.[2] One way to increase the access to carbohydrates is to develop reliable methods for stereoselective glycoside synthesis and convergent oligosaccharide assembly that would be applicable to both laboratory and industrial preparation.

Many, if not all, known convergent strategies for oligosaccharide synthesis are based on the selective activation of one leaving group (LG) over another, which allows a decrease in the number of synthetic steps.[3,4] One of the most efficient procedures, the Fraser–Reid "armed–disarmed" approach, is based on the chemoselectivity principle.[5,6] Accordingly, in the presence of a mild promoter, a benzylated (armed) glycosyl donor is chemoselectively activated in preference to an acylated (disarmed) derivative bearing the same type of leaving group (Scheme 1). At this stage, a 1,2-*cis*-linked disaccharide is obtained preferentially as a result of the necessity to use the ether-type substituent (arming nonparticipating group). The obtained disaccharide can then be used

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[**] The authors thank the University of Missouri–St. Louis and the ACS PRF 42397-G1 for financial support of this research; the NSF for grants to purchase an NMR spectrometer (CHE-9974801) and the mass spectrometer (CHE-9708640) used in this work, Dr. R. S. Luo for assistance with 500 MHz 2D NMR experiments, and Dr. R. E. K. Winter and Mr. J. Kramer for HRMS determinations.

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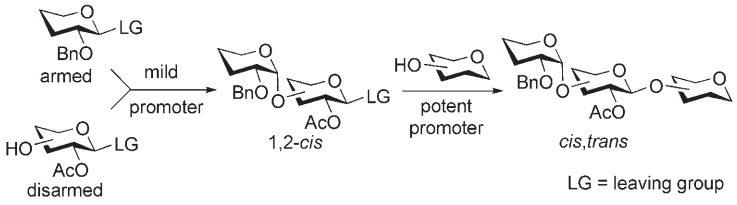
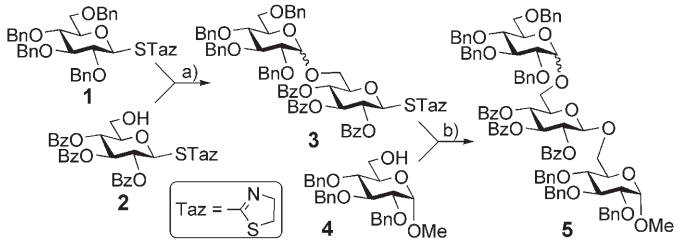


Scheme 1. The "armed–disarmed" strategy. Bn = benzyl

directly for 1,2-*trans* glycosylation (in the presence of a more potent promoter that can activate the disarmed leaving group) to afford a *cis*,*trans*-linked trisaccharide.

This concept was initially designed for *O*-pentenyl glycosides and was further explored for the chemoselective glycosidations of other glycosyl donors, including thioglycosides,[7] selenoglycosides,[8] fluorides,[9] phosphoroamidates,[10] substituted thioformimidates,[11] and S-benzoxazolyl glycosides.[12] Glycal reactivity was also found to be influenced by disarming acyl substituents.[13] Fraser-Reid et al.[14] and Ley and co-workers[15] found that torsional effects of cyclic acetal and dispiroketal protecting groups also promote anomeric deactivation. Moreover, Zhu and Boons demonstrated that thioglycosides that are protected as cyclic 2,3-carbonates are even less reactive than traditional disarmed acylated derivatives.[16] The chemoselective activation principles were summarized and expanded on by Ley and co-workers,[17] Wong and co-workers,[18–20] and other groups.[21,22] As a result, programmable multistep reactivity-based techniques, including highly efficient one-pot approaches, have become available.

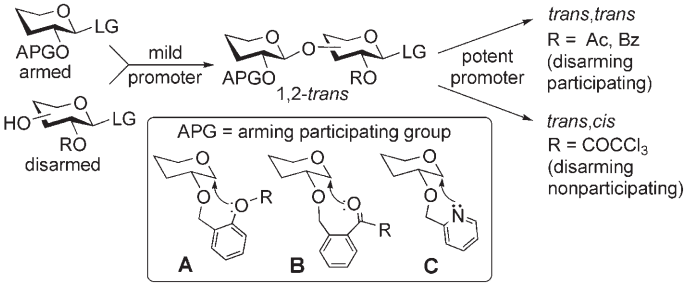
S-thiazolinyl (STaz) glycosides, recently developed in our laboratory, were found to be compatible with the armed–disarmed procedure. Thus, chemoselective activation of **1**[23] over **2**[24] in the presence of either AgOTf or $Cu(OTf)_2$ afforded the disaccharide **3** as an anomeric mixture in 79–88% yield (Scheme 2). The latter was then converted into the *cis*,*trans*-linked trisaccharide **5** by treatment with the acceptor **4**.



Scheme 2. Chemoselective activation of the STaz glycosides. a) 1. AgOTf, 1,2-DCE, 1 h, room temperature, 79%, $\alpha/\beta = 2:1$; or 2. $Cu(OTf)_2$, 1,2-DCE, 3.5 h, room temperature, 88%, $\alpha/\beta = 1.5:1$; b) AgOTf, 1,2-DCE, 2.5 h, room temperature, 83%. Bz = benzoyl, Tf = trifluoromethanesulfonyl, DCE = dichloroethane.

The armed–disarmed strategy thus offers an efficient tool for the synthesis of oligosaccharides with a *cis*,*trans* glycosylation pattern. Although the synthesis of *cis*,*cis*-linked derivatives is also possible,[5,6] this method is not applicable to the synthesis of *trans*,*cis*- or *trans*,*trans*-linked oligosaccharide fragments. The use of other techniques, such as orthogonal[25] or semiorthogonal synthesis[26] offer further advantages; however, these strategies require a set of at least two orthogonal leaving groups, which may not always be accessible. To address this challenge, we initiated studies of the "inverse armed–disarmed strategy", which would enable the stereoselective introduction of a 1,2-*trans* linkage prior to another 1,2-*trans* or 1,2-*cis* linkage.

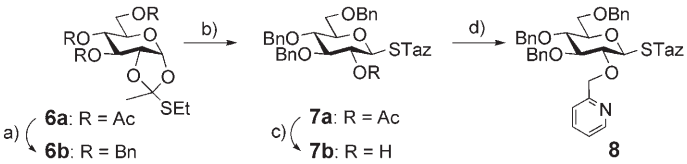
Such an inverse approach would require the use of a neighboring substituent that is capable of both activation and participation (arming participating group (APG)). For this purpose we investigated a number of substituents **A**–**C** as APGs (Scheme 3). Our studies were based on STaz glycosides



Scheme 3. Outline of an inverse armed–disarmed strategy.

owing to their superb glycosyl-donor properties.[23] The preliminary results obtained with a 2-*O*-(*o*,*o*-dimethoxybenzyl) glycosyl donor (type **A**) showed a fairly high diastereoselectivity (up to α/β 1:5), which was a significant improvement over the 2:1 α/β ratio found with perbenzylated STaz glycosyl donor **1** under the same reaction conditions. Nevertheless, it remained uncertain if the high β stereoselectivity is attributable to the anticipated participation of a seven-membered transition state (Scheme 3 or rather to the increased steric hindrance of the bottom face of the ring. The same uncertainty was anticipated for glycosyl donors of type **B**. To exclude the possibility of the increased steric hindrance, our further studies focused on the investigation of the 2-pyridylmethylpicolyl group, which is capable of a six-membered ring participation through the nitrogen atom (**C**, Scheme 3).

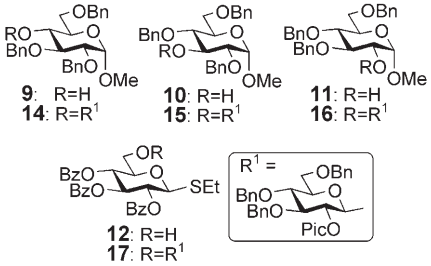
The glycosyl donor **8** bearing a picolyl substituent at C2 was synthesized from thioorthoester **6a**[27] (Scheme 4). Conveniently, the picolyl moiety was introduced with commercial picolyl bromide in the presence of NaH in DMF. In this



Scheme 4. Synthesis of the glycosyl donor **8**. a) 1) MeONa, MeOH, 2) BnBr, NaH, DMF, 85%; b) HSTaz/TMSOTf, CH_2Cl_2, 85%; c) MeONa, MeOH, 92%; d) PicBr, NaH, DMF, 90%. DMF = *N*,*N*-dimethylformamide, Pic = picolyl, TMS = trimethylsilyl.

context, although an approach for the control of the anomeric stereoselectivity with a neighboring substituent that is capable of six-membered participation is relatively unexplored, a number of moieties for stereoselective glycosylation have recently been reported.[28,29]

Having synthesized the glycosyl donor **8**, we turned our attention to glycosidation studies. For this purpose, a range of differently protected glycosyl acceptors **2**, **4**, and **9**–**12** was selected. Based on our preliminary results



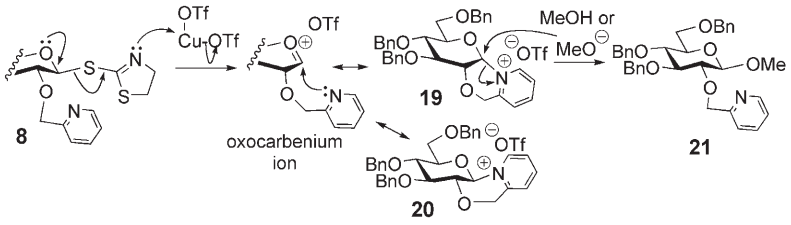
(Scheme 2), we employed $Cu(OTf)_2$ either alone, or in combination with catalytic TfOH as a promoter. All of the glycosylations summarized in Table 1 proceeded with complete 1,2-*trans* stereoselectivity.

Table 1: Synthesis of 1,2-*trans*-linked disaccharides **13**–**18**.

Entry	Acceptor	Promoter	Product	Yield [%]
1	**4**	$Cu(OTf)_2$	**13**	80
2	**9**	$Cu(OTf)_2$	**14**	84
3	**10**	$Cu(OTf)_2$/TfOH	**15**	82
4	**11**	$Cu(OTf)_2$/TfOH	**16**	80
5	**12**	$Cu(OTf)_2$	**17**	77
6	**2**	$Cu(OTf)_2$/TfOH	**18**	74

Notably, the glycosidation of **8** at room temperature required significantly more time than that of **1** (48 vs. 1–3 h, respectively). Therefore, to shorten the reaction time (12–16 h), all of the glycosylations shown in Table 1 were performed in 1,2-DCE at 50 °C. As the chemoselective activation of **8** in reference to the benzoylated acceptor **2** was also possible under these reaction conditions, the observed phenomenon could not be simply explained by the very low reactivity of **8**. In this context, perbenzoylated STaz glycosides typically require 1–20 h for glycosidation at room temperature.[23] The working hypothesis for subsequent studies was that upon departure of the promoter-assisted leaving group, the formed oxocarbenium ion is converted into a stable intermediate, such as **19**, which results from the anticipated 2-*O*-picolyl participation through a six-membered ring (Scheme 5).

To establish whether the process actually follows the anticipated pathway, the AgOTf-promoted glycosidation of **8** with methanol was monitored by ^{1}H NMR spectroscopy (synthesis of **21**, Scheme 5). It was determined that **8** is entirely consumed in approximately 1 h, regardless of whether the reaction is performed at room temperature or at 50 °C. At this stage, the ^{1}H NMR spectrum shows the



Scheme 5. Proposed reaction mechanism for the glycosidation of **8**.

presence of peaks that correspond to two compounds, presumably **19** (major) and **20** (minor) with a ratio that varied with the reaction conditions (5:1 (50 °C) to 20:1 (room temperature)). During this transition, the signal for the anomeric H atom of **8** (1-H, Figure 1 a) shifted downfield from $\delta \approx 5.30$ to ≈ 6.15 ppm for the anticipated intermediate **19** (1-β-H) and $\delta \approx 5.75$ ppm for the anticipated intermediate **20** (1-α-H, Figure 1 b), which could be an indication of the N-glycosidic linkage.

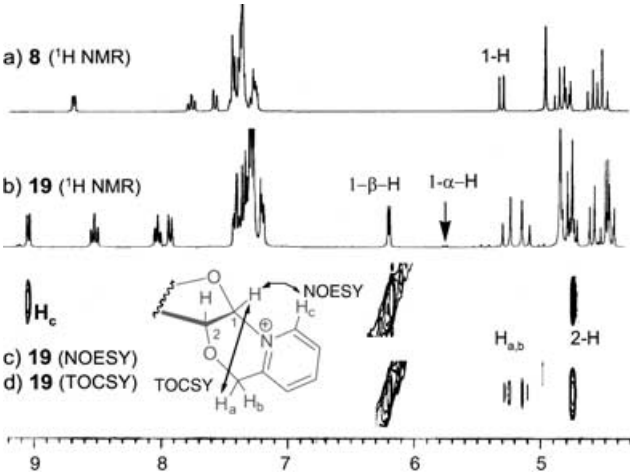


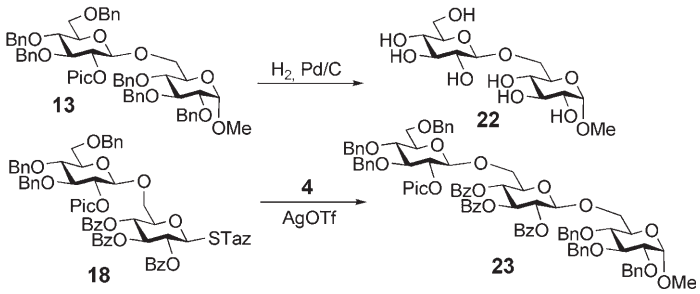
Figure 1. NMR analysis of the reaction of **8**, indicating the formation of the major intermediate **19**. a) 1H NMR spectum of **8**; b) 1H NMR spectrum of the major intermediate **19** and the minor intermediate **20**; c) NOESY spectrum of **19**; d) TOCSY spectrum of **19**.

Glycosylation experiments performed through glycosyl donor preactivation with subsequent addition of the glycosyl acceptor, provided a very similar outcome. The bicyclic intermediate **19** was isolated from the reaction of **8** with $Cu(OTf)_2$ (2 h at room temperature) and purified by column chromatography (silica gel).[30,31] The intermediate **19** was found to be reactive with potent nucleophiles such as NaOMe, even in the absence of a promoter, to afford **21** (Scheme 5). However, in all cases the β intermediate **20** remained completely inert and could typically be isolated from the reaction mixture.[32]

The 2D NMR determinations were also found to be very informative for the structural elucidation of **19**. Thus, correlations in the NOESY experiment between 1-H ($\delta =$ 6.15 ppm) and the aromatic H atom located adjacent to the picolyl nitrogen atom (H_c, $\delta = 9.00$ ppm) indicated that these

H atoms were situated in close proximity (Figure 1c). The TOCSY data revealed that 1-H and the benzylic H atoms of the picolyl group (H_a and H_b, $\delta = 5.15$ ppm) were part of the same spin system (Figure 1d). Furthermore, long-range coupling between C1 ($\delta = 84.89$ ppm) and H_c was confirmed by the HMBC data, which indicated that C1 and H_c were three bonds apart.

Subsequently, to broaden the scope of the developed approach, we demonstrated that the 2-*O*-picolyl moiety could be removed under conventional catalytic hydrogenation conditions (Pd/C). Thus, hydrogenolysis of the *O*-picolyl moiety in **13** with concomitant removal of the benzyl protecting groups afforded **22** in 92% yield (Scheme 6). The



Scheme 6. Picolyl moiety removal and the synthesis of a *trans,trans*-linked trisaccharide **23**.

disaccharide **18**, obtained by the chemoselective activation of **8** in preference to **2** (Table 1), was glycosidated with **4** in the presence of AgOTf to afford *trans,trans*-linked trisaccharide **23** in 91% yield (Scheme 6). Further investigation of this approach and its application to convergent target synthesis is underway in our laboratory. We anticipated that the use of a disarming nonparticipating group for the second activation step would be required to achieve the 'inverse' *trans*, *cis*-linked oligosaccharide pattern. This type of a neighboring moiety includes, but perhaps is not limited to, halodenoacyls (trichloroacetyl, Scheme 3) or other functionalities recently reported by Crich et al.[33]

In conclusion, a new method for stereocontrolled glycosylation was developed. We demonstrated that complete 1,2-*trans* selectivity can be achieved with the use of a 2-*O*-picolyl moiety, a novel neighboring group that is capable of efficient participation through a six-membered intermediate. The 2-*O*-picolyl moiety has been shown to retain the glycosyl donor in the armed state as opposed to conventional acyl participating moieties. The application of a novel arming participating moiety to complementary chemoselective oligosaccharide synthesis also has been developed. This new armed–disarmed glycosylation strategy allows chemoselective introduction of a 1,2-*trans* glycosidic linkage prior to other linkages, in contrast to the Fraser-Reid approach. We expect that the developed technique, along with the classic armed–disarmed approach will allow convergent chemoselective synthesis of virtually any oligosaccharide sequence.

Received: August 1, 2005
Published online: October 13, 2005

Keywords: carbohydrates · glycosides · glycosylation · oligosaccharides · thioimidates

[1] Z. J. Witczak in *Carbohydrates in Drug Design* (Eds.: Z. J. Witczak, K. A. Nieforth), Marcel Dekker, New York, **1997**, p. 1.
[2] S. I. Nishimura in *Glycoscience: Chemistry and Chemical Biology, Vol. 3* (Eds.: B. Fraser-Reid, K. Tatsuta, J. Thiem), Springer, Berlin, **2001**, p. 1993.
[3] G.-J. Boons, *Tetrahedron* **1996**, *52*, 1095.
[4] A. V. Demchenko, *Lett. Org. Chem.* **2005**, *2*, 580.
[5] D. R. Mootoo, P. Konradsson, U. Udodong, B. Fraser-Reid, *J. Am. Chem. Soc.* **1988**, *110*, 5583.
[6] B. Fraser-Reid, U. E. Udodong, Z. F. Wu, H. Ottosson, J. R. Merritt, C. S. Rao, C. Roberts, R. Madsen, *Synlett* **1992**, 927.
[7] G. H. Veeneman, J. H. van Boom, *Tetrahedron Lett.* **1990**, *31*, 275.
[8] D. K. Baeschlin, A. R. Chaperon, V. Charbonneau, L. G. Green, S. V. Ley, U. Lucking, E. Walther, *Angew. Chem.* **1998**, *110*, 3609; *Angew. Chem. Int. Ed.* **1998**, *37*, 3423.
[9] M. I. Barrena, R. Echarri, S. Castillon, *Synlett* **1996**, 675.
[10] S. I. Hashimoto, H. Sakamoto, T. Honda, H. Abe, S. I. Nakamura, S. Ikegami, *Tetrahedron Lett.* **1997**, *38*, 8969.
[11] H. Chiba, S. Funasaka, K. Kiyota, T. Mukaiyama, *Chem. Lett.* **2002**, 746.
[12] M. N. Kamat, A. V. Demchenko, *Org. Lett.* **2005**, *7*, 3215.
[13] R. W. Friesen, S. J. Danishefsky, *J. Am. Chem. Soc.* **1989**, *111*, 6656.
[14] B. Fraser-Reid, Z. Wu, C. W. Andrews, E. Skowronski, *J. Am. Chem. Soc.* **1991**, *113*, 1434.
[15] G.-J. Boons, P. Grice, R. Leslie, S. V. Ley, L. L. Yeung, *Tetrahedron Lett.* **1993**, *34*, 8523.
[16] T. Zhu, G.-J. Boons, *Org. Lett.* **2001**, *3*, 4201.
[17] N. L. Douglas, S. V. Ley, U. Lucking, S. L. Warriner, *J. Chem. Soc. Perkin Trans. 1* **1998**, 51.
[18] Z. Zhang, I. R. Ollmann, X. S. Ye, R. Wischnat, T. Baasov, C. H. Wong, *J. Am. Chem. Soc.* **1999**, *121*, 734.
[19] X. S. Ye, C. H. Wong, *J. Org. Chem.* **2000**, *65*, 2410.
[20] F. Burkhart, A. Zhang, S. Wacowich-Sgarbi, C. H. Wong, *Angew. Chem.* **2001**, *113*, 1314; *Angew. Chem. Int. Ed.* **2001**, *40*, 1274.
[21] M. Fridman, D. Solomon, S. Yogev, T. Baasov, *Org. Lett.* **2002**, *4*, 281.
[22] Y. Wang, X. Huang, L. H. Zhang, X. S. Ye, *Org. Lett.* **2004**, *6*, 4415.
[23] A. V. Demchenko, P. Pornsuriyasak, C. De Meo, N. N. Malysheva, *Angew. Chem.* **2004**, *116*, 3131; *Angew. Chem. Int. Ed.* **2004**, *43*, 3069.
[24] P. Pornsuriyasak, U. B. Gangadharmath, N. P. Rath, A. V. Demchenko, *Org. Lett.* **2004**, *6*, 4515.
[25] O. Kanie, Y. Ito, T. Ogawa, *J. Am. Chem. Soc.* **1994**, *116*, 12073.
[26] A. V. Demchenko, C. De Meo, *Tetrahedron Lett.* **2002**, *43*, 8819.
[27] N. K. Kochetkov, L. V. Backinowsky, Y. E. Tsvetkov, *Tetrahedron Lett.* **1977**, 3681.
[28] J. H. Kim, H. Yang, J. Park, G. J. Boons, *J. Am. Chem. Soc.* **2005**, *127*, 12090.
[29] J. H. Kim, H. Yang, G. J. Boons, *Angew. Chem.* **2005**, *117*, 969; *Angew. Chem. Int. Ed.* **2005**, *44*, 947.
[30] Notably, the ^{1}H and ^{13}C NMR data of **19** and **20** are in good aggreement with those reported for α- and β-N-pyridinium salts: R. U. Lemieux, A. R. Morgan, *Can. J. Chem.* **1965**, *43*, 2205.
[31] K. Bock, C. Pedersen, *J. Chem. Soc. Perkin Trans. 2* **1974**, 293.
[32] One of the possible explanations for the higher stability of **20** could be the influence of the reverse anomeric effect: I. Tvaroska, T. Bleha, *Adv. Carbohydr. Chem. Biochem.* **1989**, *47*, 45.
[33] D. Crich, T. K. Hutton, A. Bangerjee, P. Jayalath, J. Picione, *Tetrahedron: Asymmetry* **2005**, *16*, 105.

