ORGANIC LETTERS

2005
Vol. 7, No. 15
3215−3218

Revisiting the Armed–Disarmed Concept Rationale: *S*-Benzoxazolyl Glycosides in Chemoselective Oligosaccharide Synthesis†

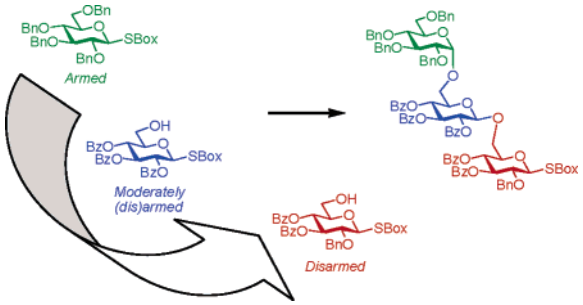
Medha N. Kamat and Alexei V. Demchenko*

Department of Chemistry and Biochemistry, University of Missouri—St. Louis, One University Boulevard, St. Louis, Missouri 63121

demchenkoa@umsl.edu

Received April 29, 2005

ABSTRACT



It has been discovered that 2-*O*-benzyl-3,4,6-tri-*O*-acyl SBox glycosides are significantly less reactive than even "disarmed" peracylated derivatives. This finding has been applied to the synthesis of various oligosaccharides, the monomeric units of which are connected via *cis*–*cis*, *trans*–*cis*, and *cis*–*trans* sequential glycosidic linkages. Two-stage activation of the *armed* (benzylated) donor over *moderately (dis)armed* (acylated) and, subsequently, over *disarmed* (2-*O*-benzyl-3,4-*O*-diacylated) acceptor has also proven to be feasible.

Carbohydrates are the most ubiquitous biomolecules on Earth, yet their chemistry and biology has been a "Cinderella" field. Our current knowledge about carbohydrates remains incomplete. However, thanks to the explosive growth of glycobiology in recent years, it is now recognized that these fascinating biomolecules are involved in many vital biological processes, such as fertilization, antiinflammation, immunoresponse, joint lubrication, antigenic determination, etc.[1] Carbohydrates are also responsible for many damaging processes in our cells, such as bacterial and viral infections, development and growth of tumors, metastasis, tissue rejection, etc.[2] Many of these processes are directly associated with various deadly diseases of the 21st Century: AIDS, cancer, meningitis, hepatitis, etc. Elucidation of the exact mechanisms of carbohydrate involvement in disease progression would be significantly facilitated if we could rely on the comprehensive knowledge of the structure, conformation, and properties of the carbohydrate molecules. Although scientists have learned to selectively cleave, isolate, purify, and characterize certain classes of naturally occurring glycostructures, their accessibility in pure form is still quite limited. It is critical to make complex carbohydrates more accessible to the general chemical, biochemical, and industrial audience to keep in pace with the exploding area of glycobiology. This can only be achieved by the development of reliable methods for glycoside synthesis and convergent oligosaccharide assembly that are applicable to both laboratory and industrial-scale preparation.

Many, if not all, known convergent strategies for oligosaccharide synthesis are based on the selective activation of one leaving group (LG) over another.[3] These approaches

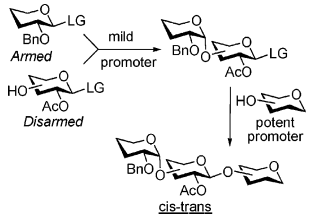
† Dedicated to Professor Nickolay Kochetkov on the occasion of his 90th birthday.

(1) Varki, A. *Glycobiology* **1993**, *3*, 97−130. Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683−720. *Essentials of Glycobiology*; Varki, A., Cummings, R., Esko, J., Freeze, H., Hart, G., Marth, J., Eds.; Cold Spring Harbor Laboratory Press: Cold Spring Harbor, NY, 1999. Nishimura, S. I. In *Glycoscience: Chemistry and Chemical Biology*; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer: Berlin , 2001; Vol. 3, pp 1993−2004.

(2) Witczak, Z. J. In *Carbohydrates in Drug Design*; Witczak, Z. J., Nieforth, K. A., Eds.; Marcel Dekker: New York, 1997; pp 1−37.

10.1021/ol050969y CCC: $30.25
Published on Web 06/22/2005

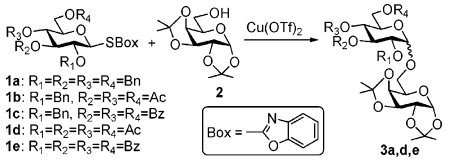
Scheme 1. Fraser-Reid's Armed−Disarmed Strategy Outline



significantly shorten oligosaccharide assembly by reducing the number of additional synthetic steps associated with the protecting group manipulations. One of the most efficient procedures, Fraser-Reid's armed−disarmed approach, is based on the chemoselectivity principle.[4,5] According to this principle, an *O*-benzylated (electronically activated, armed) glycosyl donor is chemoselectively activated over an *O*-acylated (electronically deactivated, disarmed) derivative bearing the same type of LG in the presence of a mild promoter (Scheme 1). 1,2-*cis*-Linked disaccharides are preferentially obtained when nonparticipating *O*-2-ether-arming substituents are employed as glycosyl donors. The obtained disaccharide can be then used for 1,2-*trans* glycosylation directly with the assistance of the neighboring *O*-2-acyl substituent. This can be achieved in the presence of a more potent promoter, capable of the activation of the disarmed LG, to afford a *cis*−*trans*-linked trisaccharide. In this context, the synthesis of *cis*−*cis*-linked derivatives is also possible (after reprotection OAc → OBn).

The central theme in our research is the invention of new techniques for the chemical synthesis of biologically important glycostructures and glycomimetics and investigation of the driving forces of the glycosylation process. We have already demonstrated that high stability of the SBox glycosides along with high stereoselectivity make these glycosyl donors suitable for both single-step stereoselective glycosylations and for the use as building blocks in sophisticated convergent oligosaccharide syntheses.[6−8] The heart of this communication is the investigation of the chemoselective activation of SBox glycosides and their application to oligosaccharide synthesis. Our studies were initiated in order to investigate the reactivity pattern of differently protected SBox glycosides. Having decided to explore the armed−disarmed properties of the SBox glycosides, we performed the activation of **1a** in the presence of various promoters. To distinguish between armed and disarmed glycosides, we needed to employ a mild promoter. In this respect, copper-

Table 1. Comparative Reactivity of the Differently Protected SBox Glycosides **1a**−**e** in the Presence of 1 Equiv of $Cu(OTf)_2$



entry	donor	product	yield (%)	α/β ratio
1	**1a**	**3a**	89	5.4/1
2	**1b**		no reaction	
3	**1c**		no reaction	
4	**1d**	**3d**	69	β only
5	**1e**	**3e**	70	β only

(II) trifluoromethanesulfonate seemed to be the most appropriate. Thus, activation of **1a** over glycosyl acceptor **2** proceeded smoothly, and as a result, the product **3a**[9] was isolated in a good yield of 89% (entry 1, Table 1). When essentially the same reaction conditions were applied to the glycosidation of 2-*O*-benzyl-tri-3,4,6-*O*-acyl-protected SBox glucosides **1b**[6] and **1c**, no product formation was detected. This result did not surprise us at first as we believed that the high stability of partially benzoylated derivatives was due to the remote disarming effect of the acyl substituents at C-3, -4, and -6. In fact, we have previously reported that $Cu(OTf)_2$ is unable to promote the glycosidation of **1b**.[6] Unexpectedly, we discovered that supposedly "disarmed" peracylated SBox glycosides **1d**[6] and **1e**,[7] which were anticipated to be even less reactive than either **1b** or **1c**, actually reacted readily in glycosylations. Although these glycosylations were marginally slower in comparison to that of the "armed" perbenzylated **1a**, they nevertheless smoothly proceeded, yet never went to completion. As a result, disaccharides **3d**[10] and **3e**[11] were isolated in 69 and 70% yield, respectively.

These interesting observations called for further studies, as Lemieux's halide stability theory,[12] Fraser-Reid's armed−disarmed concept rationale,[4,13] and Wong's programmable oligosaccharide synthesis concept[14] all predicted that 2-*O*-benzylated **1b** or **1c** would be more reactive than their peracylated counterparts **1d** and **1e**. Initially, we anticipated that the disarming effect of the protecting groups on the anomeric center could be rationalized by comparison of the chemical shift of H-1 in ^{1}H NMR spectra. Thus, H-1 would appear at the lower field if the electron-withdrawing groups were attached to the nearby atoms of the molecule. Indeed,

(3) Boons, G. J. *Tetrahedron* **1996**, *52*, 1095−1121. Kanie, O. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH: Weinheim, New York, 2000; Vol. 1, pp 407−426.
(4) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583−5584.
(5) Fraser-Reid, B.; Udodong, U. E.; Wu, Z. F.; Ottosson, H.; Merritt, J. R.; Rao, C. S.; Roberts, C.; Madsen, R. *Synlett* **1992**, 927−942 and references therein.
(6) Demchenko, A. V.; Malysheva, N. N.; De Meo, C. *Org. Lett.* **2003**, *5*, 455−458.
(7) Demchenko, A. V.; Kamat, M. N.; De Meo, C. *Synlett* **2003**, 1287−1290.
(8) De Meo, C.; Kamat, M. N.; Demchenko, A. V. *Eur. J. Org. Chem.* **2005**, 706−711.
(9) Fraser-Reid, B.; Konradsson, P.; Mootoo, D. R.; Udodong, U. *J. Chem. Soc., Chem. Commun.* **1988**, 823−825.
(10) Kochetkov, N. K.; Khorlin, A. Y.; Bochkov, A. F. *Tetrahedron* **1967**, *23*, 693−707.
(11) Demchenko, A. V.; Pornsuriyasak, P.; De Meo, C.; Malysheva, N. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 3069−3072.
(12) Lemieux, R. U. *Adv. Carbohydr. Chem. Biochem.* **1954**, *9*, 1−57. Lemieux, R. U. *Pure Appl. Chem.* **1971**, *25*, 527−548. Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056−4062.
(13) Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottosson, H. *J. Org. Chem.* **1990**, *55*, 6068−6070.
(14) Zhang, Z.; Ollmann, I. R.; Ye, X. S.; Wischnat, R.; Baasov, T.; Wong, C. H. *J. Am. Chem. Soc.* **1999**, *121*, 734−753.

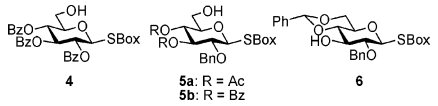
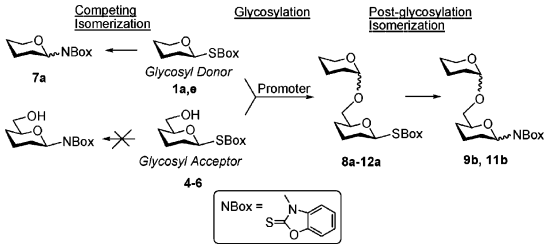


Figure 1.

the H-1 signal for **1b** is more shielded than that for **1e** (δ 5.54 vs 6.10 ppm). In addition, X-ray data suggested that **1b** should be more reactive than **1e** as the C1−S bond for the latter is somewhat shorter and, therefore, expected to be stronger (1.819 vs 1.803 Å).[15] Overall, the above data suggested that **1b** should be more reactive than **1e**. However, these predictions were not borne out by the preliminary activation experiments (Table 1).

Therefore, further experiments related to a direct comparison of these derivatives in chemoselective glycosylations were deemed necessary. We obtained a variety of partially protected SBox glycosides suitable for the use as glycosyl acceptors (**4**−**6**, Figure 1). Glycosylation of the glycosyl acceptors with armed **1a** or moderately disarmed glycosyl donor **1e** was proven to be feasible (Table 2). While

Table 2. Chemoselective Activation of SBox Glycosyl Donors over SBox Glycosyl Acceptors



no.	donor	acceptor	promoter	SBox disacch (yield, %, α/β ratio)	NBox disacch (yield, %)	isomerized donor (yield, %)
1	**1a**	**4**	$Cu(OTf)_2$	**8a** (64, 3/1)		**7a** (30)
2	**1a**	**5a**	$Cu(OTf)_2$	**9a** (51, 3/1)	**9b** (10)	**7a** (35)
3	**1e**	**5a**	$Cu(OTf)_2$/TfOH	none		
4	**1a**	**5b**	$Cu(OTf)_2$	**10a** (92, 3.5/1)		**7a** (5)
5	**1e**	**5b**	$Cu(OTf)_2$/TfOH	**11a** (65, β only)	**11b** (20)	
6	**1a**	**6**	$Cu(OTf)_2$	none		
7	**1e**	**6**	$Cu(OTf)_2$/TfOH	**12a** (80, β only)		

glycosidation of **1a** could be accomplished in the presence of 1 equiv of $Cu(OTf)_2$, efficient glycosidation of **1e** required more powerful activation conditions. $Cu(OTf)_2$ (2 equiv) in combination with TfOH (0.2 equiv) was found to be suitable for this purpose. In our opinion, these results serve as direct confirmation of the preliminary observation obtained in model glycosidations of the SBox glycosyl donors. It should be noted that some of these glycosylations were complicated

(15) Note: These results will be presented in the full version of the manuscript.

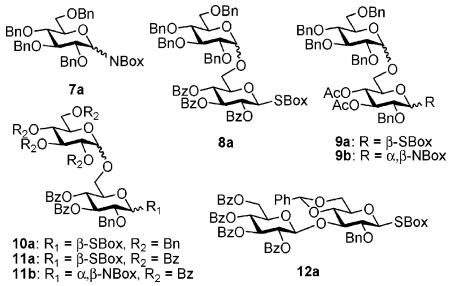
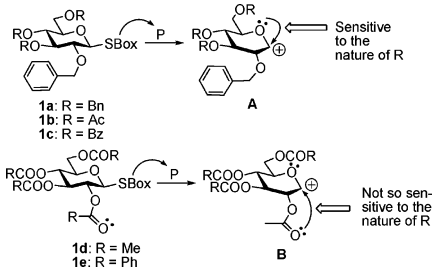


Figure 2.

by the competing anomeric SBox LG isomerization of the glycosyl donor **1a** into the stable NBox moiety (**7a**) (Figure 2), resulting in the compromised yields (see Entries 1 and 2, Table 2). In addition, around 10−20% disaccharides with NBox anomeric moiety (**9b**, **11b**) (Figure 2) were formed in some cases (see entries 2 and 5, Table 2). Prolonged reaction times for the seemingly incomplete processes did not result in increased yields. Instead, the increased formation of **9b** or **11b** was detected. Since investigation of the recovered acceptor has shown no traces of the NBox isomer, we believe that a post-glycosylation isomerization took place.

In this context, reaction between the very reactive glycosyl donor **1a** and the fairly unreactive **6** did not result in the expected disaccharide formation (see entry 6, Table 2). Instead, **1a** was rapidly hydrolyzed to the hemiacetal derivative, 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose, which could be an evidence for donor/acceptor "mismatch".[16]What are the driving forces responsible for this unusual reactivity pattern? Although direct evidence is not available yet, our hypothesis is as follows. In the case of **1a**, the LG at C-1 can be readily ejected because the O-5 lone pair is not electronically deactivated by the adjacent oxygen substituents

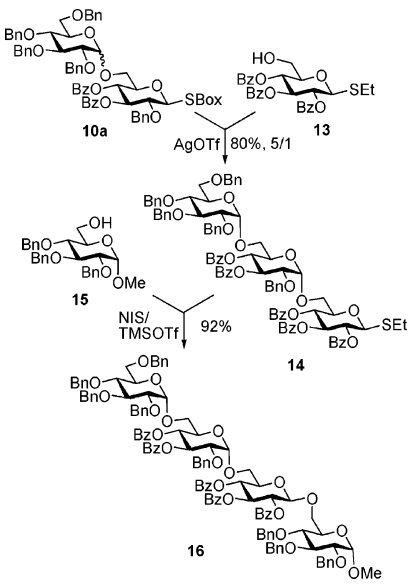
Scheme 2. O-2/O-5 Cooperative Effect in Glycosylation



(R = Bn, Scheme 2). The O-5 lone pair is therefore able to very effectively assist in the departure of the LG, and stabilize the resulting glycosyl cation (**A**, R = Bn). Although, in **1d** and **1e** the O-5 lone pair is much less able to assist in LG departure and subsequent stabilization of the C-1 glycosyl

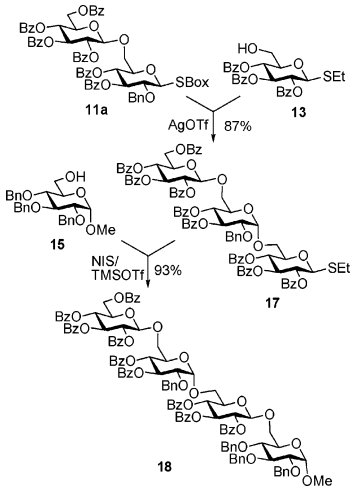
(16) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155−173. Spijker, N. M.; van Boeckel, C. A. A. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 180−183. Uriel, C.; Gomez, A. M.; Lopez, J. C.; Fraser-Reid, B. *Synlett* **2003**, 2203−2207.

Scheme 3. Convergent Synthesis of the *cis*−*cis*−*trans*-Linked Tetrasaccharide **16**



cation (because of the C-3, C-4, and C-6 electron-withdrawing *O*-acyl groups), the C-2 *O*-acyl group can nevertheless stabilize the cation **B** (Scheme 2).

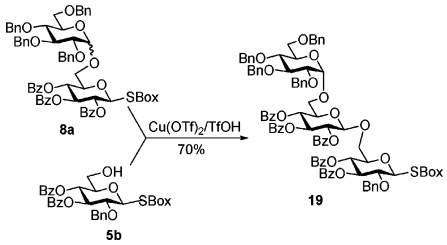
Scheme 4. Convergent Synthesis of the *trans*−*cis*−*trans*-Linked Tetrasaccharide **18**



Presumably, neither O-5 nor O-2 moieties can effectively stabilize the glycosyl cations derived from 3,4,6-tri-*O*-acyl-2-*O*-benzyl derivatives **1b** or **1c**, making the energy barrier for their formation prohibitively high.

To test the applicability of this interesting observation to useful oligosaccharide construction, we obtained two tetrasaccharide derivatives **16** and **18** via convergent activation pathways as shown in Schemes 3 and 4. For this purpose, SBox disaccharides **10a** and **11a** were selectively activated over *S*-ethyl glycoside acceptor **13**[17] in the presence of AgOTf to afford the trisaccharides **14** and **17**, respectively. The obtained **14** and **17** were then reacted with **15**[18] in the presence of NIS/TMSOTf to afford the tetrasaccharide derivatives **16** and **18**, respectively, in high overall yields.

Scheme 5. Synthesis of *cis*−*trans* and Potential *cis* Linkage



The ultimate demonstration of the advantages of these findings was the synthesis of the trisaccharide **19**, which was accomplished by sequential two-step activation pathway with the use of three SBox building blocks. For this purpose, disaccharide **8a**, obtained from **1a** and **4**, was then chemoselectively activated over **5b** to afford **19** (Scheme 5).

In conclusion, we have demonstrated that perbenzylated SBox glycosides are more reactive than their peracylated counterparts and, therefore, can be chemoselectively activated in accordance with the "armed−disarmed" strategy. Additional, and perhaps the most valuable, input was the discovery that 3,4,6-tri-*O*-acyl-2-*O*-benzyl SBox glycosides are significantly less reactive than even "disarmed" peracylated derivatives. This interesting observation has allowed us to obtain various oligosaccharides, the monomeric units of which are connected via *cis*−*cis*, *trans*−*cis*, and *cis*−*trans* sequential glycosidic linkages. Two-stage activation of the *armed* (benzylated) donor over a *moderately (dis)-armed* (acylated) acceptor and, subsequently, over a *disarmed* (3,4-di-*O*-acyl-2-*O*-benzyl) acceptor, all three with the same type of leaving group (SBox), was also proven to be feasible. It is quite possible that this phenomenon is independent of the nature of the leaving group and, therefore, is of general character. Further investigation of the driving forces of this reaction and its application to glycosyl donors of other series is underway in our laboratory.

Acknowledgment. We thank the University of Missouri−St. Louis for financial support and the NSF for grants to purchase the NMR spectrometer (CHE-9974801) and the mass spectrometer (CHE-9708640) used in this work. We also thank Dr. R. E. K. Winter and Mr. J. Kramer for HRMS determinations.

Supporting Information Available: Experimental procedures for the synthesis of **1a**,**c**, **4**−**6**, **8a**−**12a**, **14**, and **16**−**19** and their ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050969Y

(17) Veeneman, G. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 275−278.

(18) Kuester, J. M.; Dyong, I. *Justus Liebigs Ann. Chem.* **1975**, 2179−2189.