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Versatile Synthesis and Mechanism of Activation of *S*-Benzoxazolyl Glycosides

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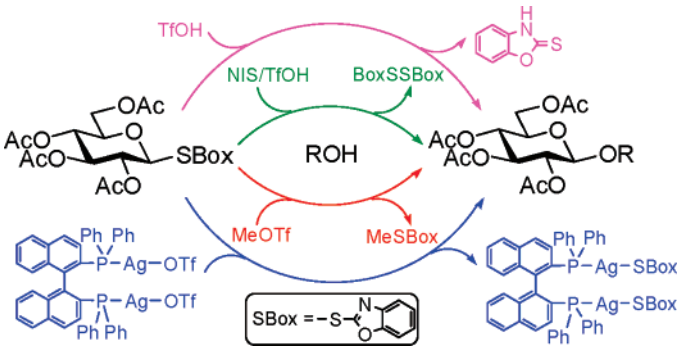

As a part of a program for developing new efficient procedures for stereoselective glycosylation, a range of *S*-benzoxazolyl (SBox) glycosides have been synthesized. The mechanistic aspects of the SBox moiety activation for glycosylation via a variety of conceptually different pathways in the presence of thiophilic, electrophilic, or metal-based promoters have been investigated.

Introduction

The field of carbohydrate chemistry has experienced explosive growth over the last two decades. This outbreak is mainly attributed to recent findings revealing the involvement of carbohydrates and their conjugates in a variety of biological processes including fundamental enzymatic and hormonal activities, interaction with invaders such as bacteria and viruses, and connection with the development, growth, and metastasis of tumors, among others.[1−5] The appreciation of the profound involvement of carbohydrates in a variety of processes in living organisms resulted in a strong demand for further investigation of these molecules. As a result of considerable difficulties associated with the isolation of pure natural glycostructures, the development of new and versatile methods for their chemical synthesis remains as a notable challenge for synthetic organic chemists.

Recent years have witnessed a broad spectrum of research dealing with the improvement of different aspects of carbohydrate chemistry. Among these, development of novel techniques for stereoselective glycosylation and convergent oligosaccharide synthesis occupy a special niche. In an effort to address these issues, a variety of structurally diverse glycosyl donors have been developed.[6,7] In spite of significant progress, no glycosyl donor that could solve all major challenges of the glycoside and oligosaccharide synthesis has yet emerged.

Our laboratory has been investigating a family of cyclic glycosyl thioimidates as complimentary glycosyl donors for di- and oligosaccharide synthesis. The roles and applications of this class of compounds have been recently reviewed.[8,9] Our preliminary investigations have determined that 1-*S*-thiazolinyl (STaz)[10,11] and 1-*S*-benzoxazolyl (SBox)[12,13] derivatives bear

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major positive traits of a modern glycosyl donor: accessibility, odorless preparation, stability toward many reaction conditions employed in carbohydrate chemistry, mild and selective activation for glycosylation, and excellent stereoselectivity. In addition, we have demonstrated the applicability of this class of compounds to convergent oligosaccharide synthesis via a variety of conceptually novel strategies.[14−17] Other useful application of glycosyl thioimidates in phosphorylation has also been developed.[18,19] Herein we present the synthesis of the SBox derivatives along with the first mechanistic investigation of their glycosidation.

Results and Discussion

Synthesis of the 1-SBox Derivatives. It should be noted that the synthesis of peracetylated SBox derivative **2** from acetobromoglucose **1** has been reported prior to our studies.[20,21] We expanded this methodology by optimizing the reaction conditions and applying the improved protocol to bromides of the D-gluco (**1**, **3**, and **9**), D-galacto (**5** and **11**), and D-manno (**7**) series. Commercial 2-mercaptobenzoxazole (HSBox), an odorless solid, or its potassium salt (KSBox), easily prepared from HSBox by treatment with K_2CO_3, were chosen as the aglycon source. As a result of the successful coupling reactions, a series of the SBox derivatives **2**, **4**, **6**, **8**, **10**, and **12** have been obtained in high yields of 87−96% (entries 1−6, Table 1). With the exception of the synthesis of the SBox mannoside **8** (α/β = 1/1), all anomeric substitutions proceeded stereoselectively affording 1,2-trans-linked SBox glycosides. Differently from the synthesis of the STaz derivatives, the synthesis of which from glycosyl halides was often accompanied by the formation of 1,2-dehydro derivatives and/or *N*-glycosides,[11] exclusively *S*-linked products **2**, **4**, **6**, **8**, **10**, and **12** have been obtained herein.

We reasoned that similarly to that of glycosyl donors of other classes, including previously investigated glycosyl thioimidates,[22−28] various synthetic precursors, such as anomeric acetates, 1,2-anhydrosugars, or *S*-ethyl glycosides, could serve as suitable precursors for the synthesis of the SBox glycosides. To explore these possibilities, we performed a number of additional experiments. The application of anomeric acetates as the starting material proved to be feasible, although it was significantly less efficient in comparison to the synthesis of the SBox glycosides from glycosyl bromides. Somewhat reduced yields, rarely exceeding 70−80%, and poor anomeric stereoselectivity were typically achieved in these reactions. For example, compound **2** was obtained from pentaacetate **13** in 79% yield as a mixture of anomers (α/β = 1/3.5, entry 7, Table 1). In contrast, the synthesis of STaz glycosides from anomeric acetates was entirely stereoselective and high yielding.[11]

1,2-Anhydro derivatives were also found to be suitable precursors for the introduction of the anomeric SBox moiety. For example, Lewis acid catalyzed transformation of the epoxide **14**[29] ($ZnCl_2$) gave the corresponding 2-hydroxyl SBox derivative **15** in 87% yield (entry 8, Table 1). Finally, the SBox glycosides could be efficiently obtained from the corresponding ethyl thioglycosides via a two-step conversion protocol. Thus, the treatment of thioglycosides **16** and **18** with bromine followed by the anomeric substitution with KSBox afforded the SBox glycosides **17** and **19** in 79% and 75% overall yields, respectively (entries 9 and 10, Table 1).

Glycosidation of the SBox Derivatives: Optimization of the Reaction Conditions. In principle, a stable anomeric leaving group should not depart on its own, or as a result of a simple solvolysis-assisted bond dissociation between C-1 and the anomeric heteroatom (sulfur, halogen, or oxygen). In this case, the leaving group ability is usually enhanced with the use of a suitable promoter. A promoter (P)-assisted leaving group (LG) departure (route **A** → **B** → **C**, Scheme 1) results in the formation of a neutral species (PLG). The resulting oxocarbenium intermediate **C** will then react with the glycosyl acceptor (R′OH) forming either 1,2-trans- or 1,2-cis-linked product **E** or **G**, respectively.

The structure of a thioimidoyl leaving group contains two nucleophilic (or basic) centers: harder nitrogen and softer sulfur. Although certain activation pathways have already been postulated for thioimidates,[12] evidence as to whether the glycosylations actually follow these pathways is limited. We anticipated that for thioimidates in general, soft thiophilic promoters, such as I^+, would preferentially proceed via the sulfur atom, whereas harder electrophiles, Me^+ or proton (H^+), would arguably target the nitrogen. The latter activation pathway resembles the remote activation concept introduced by Hanessian.[23,30] Taking into consideration that electron delocalization would decrease the electron density around the sulfur atom (**H**, Scheme 1), it is also possible that a generic thioimidate may be relatively unreactive toward I^+. It is thereby reasonable that thioimidates would react somewhat slower in comparison with *S*-alkyl glycosides under these reaction conditions. These considerations are supported by the fact that STaz derivatives were found to be completely stable in the presence of NIS/catalytic TfOH,[10] a source of I^+ commonly used in *S*-alkyl/aryl glycosides activation.[31] Conversely, the increased electron density on the nitrogen (**H**), as a consequence of charge delocalization, will favor the use of a harder electrophiles, Me^+ or H^+, as the

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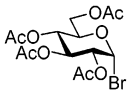
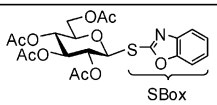
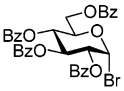
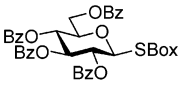
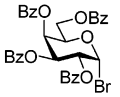
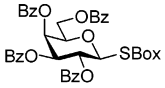
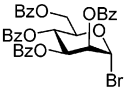
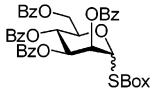
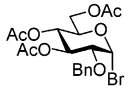
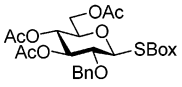
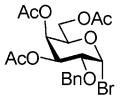
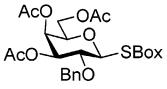
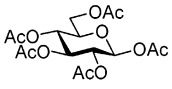
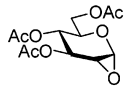
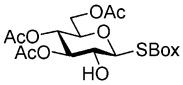
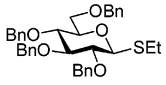
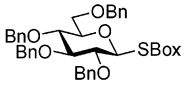
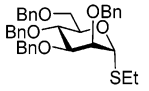
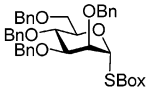
TABLE 1. Synthesis of 1-SBox Derivatives

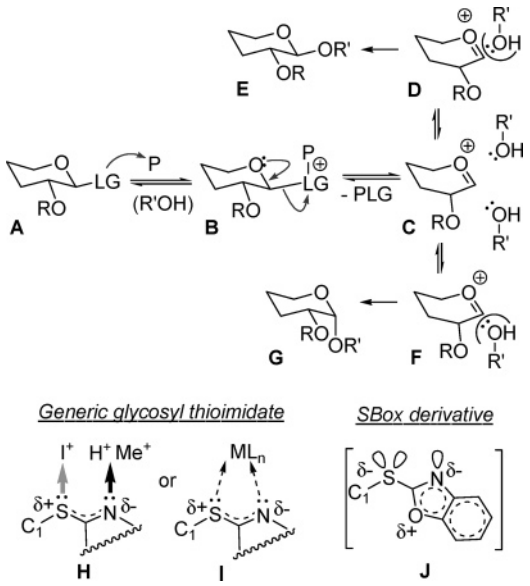
Entry	*Starting Material*	*Conditions*	*Product*	*Yield,%*	*α/β ratio*
1	 **1**	HSBox, K_2CO_3, acetone, 62 °C	 **2**	96	β only
2	 **3**	KSBox, 18-c-6, acetone, 55 °C	 **4**	87	β only
3	 **5**	KSBox, 18-c-6, acetone, 55 °C	 **6**	92	β only
4	 **7**	KSBox, 18-c-6, acetone, 55 °C	 **8**	92	1/1
5	 **9**	HSBox, K_2CO_3, acetone, 50 °C	 **10**	92	β only
6	 **11**	HSBox, K_2CO_3, acetone, 50 °C	 **12**	90	β only
7	 **13**	HSBox, BF_3-Et_2O, MS 3Å, CH_2Cl_2, rt	**2**	79	1/3.5
8	 **14**	HSBox, $ZnCl_2$, CH_2Cl_2, 0 °C	 **15**	87	β only
9	 **16**	a. Br_2, CH_2Cl_2, rt b. KSBox, 18-c-6, acetone, rt	 **17**	79	β only
10	 **18**	a. Br_2, CH_2Cl_2, rt b. KSBox, 18-c-6, acetone, rt	 **19**	75	α only

activators. In addition, thioimidates can also be activated with metal salts that may proceed via the interim complexation of sulfur or nitrogen or even bidentately (**I**, Scheme 1), depending on the nature of metal, ligands, conditions, etc.

Taking into consideration that the oxazole ring of the SBox moiety is aromatic (**J**, Scheme 1), it is possible that its activation for glycosylation will not follow the exact pathways that have been anticipated for a generic thioimidate. We expected the sulfur atom of the SBox moiety to be relatively reactive (similarly to that of *S*-alkyl glycosides and conversely to that of the STaz glycosides) since its involvement in the resonance would be minimal. In an effort to ascertain the verity of this expectation, we investigated all proposed pathways, i.e., activation with metal salts, protic and Lewis acids, as well as thiophilic and electrophilic reagents. The search for the best promoter(s) was performed with glycosyl donors **2**, **4**, **10**, and **17** and a range of glycosyl acceptors **20**, **22**, **25**, and **29**. Extended experimental data are available as a part of the Supporting Information.

It should be noted that the glycosidation of per-acetylated derivative **2** was rather impractical. Side reactions including hydrolysis of the glycosyl donor and acetylation of the acceptor lead to somewhat low efficiency and yields. For example the synthesis of the disaccharide **21** from acceptor **20** was achieved in a modest 40% yield (entry 1, Table 2). This result was improved with a very reactive glycosyl acceptor **22** in the presence of a relatively mild promoter, copper(II) triflate. Thus, the disaccharide **23** was obtained in an acceptable yield of 63% (entry 2). In contrast, glycosidation of the perbenzoylated derivative **4** with glycosyl acceptors **22** or **25** proceeded effortlessly and afforded the corresponding disaccharides **24** and **26** in good yields, especially in the presence of more powerful

SCHEME 1

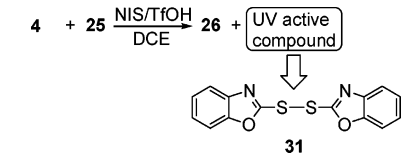


MeOTf as promoter (entries 3 and 4). Typically, reactions in the presence of NIS/TfOH or $Cu(OTf)_2$ required extended reaction time and gave somewhat lower yields of the products. Even after 24−48 h of reaction, substantial amount of the reactants could be recovered from these glycosylations. However, $Cu(OTf)_2$ could also be efficiently used for the activation of perbenzylated SBox glycoside **17**. This observation is in accordance with the reactivity trend described by Lemieux,[32] Fraser-Reid,[33] and others,[34−36] whereby benzylated glycosyl donors are significantly more reactive than their acylated counterparts.

Thus, in the presence of $Cu(OTf)_2$, the glycosylation of acceptors **25** with benzylated donor **17** gave the corresponding disaccharide **27** in 99% yield (entry 5). In addition, either silver and methyl triflate also provided excellent results for glycosidation of perbenzylated SBox glycoside **17**. For example, the synthesis of disaccharide **28** from acceptor **22** in the presence of MeOTf was accomplished in 98% yield (entry 6). It should be noted that while modest stereoselectivity was obtained with perbenzylated donor **17**, its 2-benzyltriacylated counterpart **10** provided complete stereoselectivity in the reaction with the glycosyl acceptor **29**. The disaccharide **30** was obtained in a respectable yield of 92% with the use of AgOTf as a promoter (entry 7). Interestingly, $Cu(OTf)_2$ was virtually ineffective in the case of the glycosyl donor **10** as no glycosidation took place.

Disappointingly, neither protic or Lewis acid promoted glycosylations could provide efficiency and yields that would be comparable to the best examples. We observed that the glycosyl donor undergoes rapid anomerization into the corresponding α-SBox derivative. While the latter was entirely stable under (Lewis) acid promoted reaction conditions, it could be readily glycosidated in the presence of a stronger promoter, such as AgOTf. It has been also determined that a combination of AgOTf and catalytic TfOH provides even more potent promoter system than either component alone. Further glycosylation experiments revealed versatility of the SBox glycosides for the synthesis of 1,2-cis and 1,2-trans glycosides.[37]

SCHEME 2



Glycosidation of the SBox Derivatives: Mechanistic Studies. As such, a variety of conceptually different activation pathways are suitable for efficient glycosidation of the SBox derivatives; yet, the exact involvement of the SBox leaving group in the activation process remains unknown. We reasoned, however, that an understanding of the driving forces behind the glycosidation of these derivatives would reveal the mechanism by which this leaving group departs during the displacement. To this end, we embarked on a thorough mechanistic investigation of the activation conditions described.

Activation with NIS/cat. TfOH. Coupling of the glycosyl donor **4** with glycosyl acceptor **25** in the presence of NIS, catalytic TfOH, and molecular sieves in 1,2-DCE was chosen as a standard reaction for the investigation of the reaction mechanism. Particular care was taken of isolating and characterizing UV-active species that formed along with the disaccharide **26**, with the anticipation that this UV active species was a derivative of the departed aglycon (SBox). Upon isolation, characterization, and comparison with the literature data,[38,39] we found that the UV active species was 2,2′-dibenzoxazolyldisulfide (BoxSSBox) **31** (Scheme 2). Formation of the disulfide **31** during the SBox glycosidation experiments can serve as a strong (though not explicit) indication that I^+-mediated activation proceeds via the sulfur atom. Thus, I^+-promoted SBox departure presumably results in the formation of ISBox, two molecules of which generate the disulfide **31** and molecular iodine. It should be noted that regardless of the species isolated herein, it is not possible to unambiguously prove the activation pathway (also true for the H^+-promoted activation studies described below). Although, to the best of our knowledge, no mechanistic studies have been published to date, a similar activation pathway was postulated and is generally accepted for the activation of *S*-alkyl/aryl glycosides.[40]

Activation by Protonation. We determined that glycosyl donor **4** can be glycosidated with glycosyl acceptor **25** in the presence of 0.11 molar equiv of TfOH in 1,2-DCE. Similarly to the previous experiment, it was anticipated that the UV-active species that could be detected along with the disaccharide **26** by TLC analysis of the reaction mixture derived from the

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(33) Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottosson, H. *J. Org. Chem.* **1990**, *55*, 6068−6070.
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(38) Arbuzova, S. N.; Brandsma, L.; Gusarova, N. K.; Van der Kerk, A. S. H. T. M.; Van Hooijdonk, M. J. M.; Trofimov, B. A. *Synthesis* **2000**, 65−66.
(39) Goyal, R. N.; Verma, M. S. *Ind. J. Chem., Sec. A* **1996**, *35A*, 281−287.
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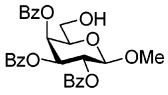
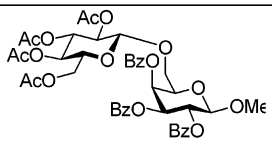
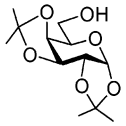
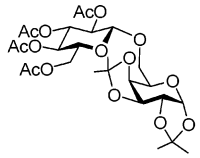
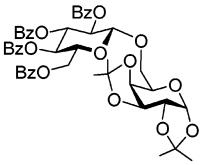
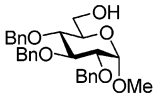
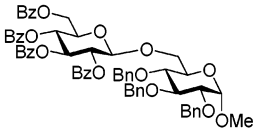
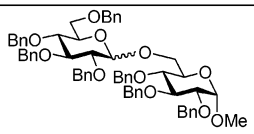
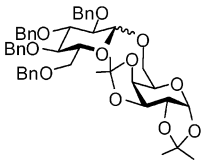
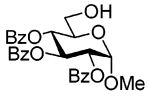
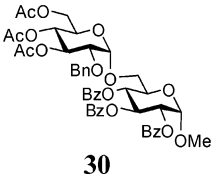
TABLE 2. Optimization of Glycosidation of the SBox Derivatives[a]

Entry	*Donor*	*Acceptor*	*Conditions* [b]	*Product*	*Yield, %*	*α/β ratio*
1	**2**	 **20**	AgOTf, DCE, MS 3Å, 1h	 **21**	40[c]	β only
2	**2**	 **22**	$Cu(OTf)_2$, DCE, MS 4Å, 20 min	 **23**	63	β only
3	**4**	**22**	$Cu(OTf)_2$, DCE, MS 4Å, 16 h	 **24**	70	β only
4	**4**	 **25**	MeOTf, DCE, MS 3Å, 1h	 **26**	95	β only
5	**17**	**25**	$Cu(OTf)_2$, DCE, MS 4Å, 1.5 h	 **27**	99	1.9/1
6	**17**	**22**	MeOTf, DCE, MS 3Å, 1.5 h	 **28**	98	1/1
7	**10**	 **29**	AgOTf, DCM, MS 3Å, 2 h	 **30**	92	α only[d]

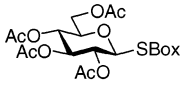
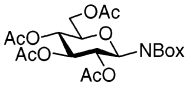
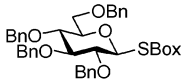
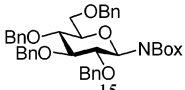
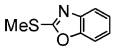
[a] Extended table can be found in the Supporting Information. [b] Abbreviations: MS, molecular sieves; DCE, 1,2-dichloroethane; DCM, dichloromethane. [c] Acetyl migration was the major side reaction observed. [d] No formation of the β-anomer has been detected by ^{1}H NMR (α/β > 95/5).

departed aglycon. Our goal was to verify whether 2-benzoxazolethione (**32a**, thioamide, thione, "NHBox") or 2-mercaptobenzoxazole (**32b**, thioimide, thiol, HSBox) had been formed (Scheme 3). The departed aglycon was isolated by column chromatography followed by crystallization and its structure was determined to be HNBox (**32a**). This conclusion was based on the NMR data and the X-ray crystal structure of the isolated UV active compound. Also, by comparing the NMR and X-ray crystallography data of the commercial and the isolated samples we noted that **32a** isolated from the reaction mixture was essentially the same compound as the commercial 2-mercaptobenzoxazole. Again, regardless of the species isolated herein, it is not possible to unambiguously prove the activation pathway due to the probability for the departed species to tautomerize (HSBox ⇌ NHBox).

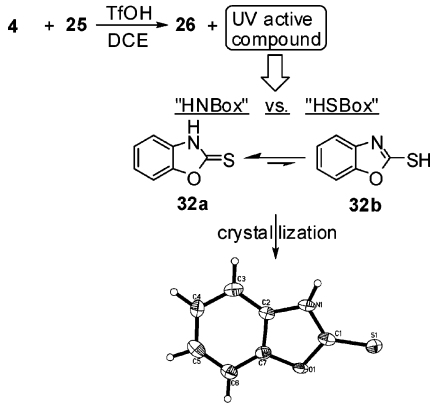
Activation by Alkylation (MeOTf). Since the migration of the methyl group would be less likely than that of a proton,[41] we anticipated the activation via methylation with MeOTf would provide more reliable information on the structure of the departed aglycon. To this end, studies were performed with glycosyl donor **2** under simplified glycosylation conditions in the presence of 2-propanol as a glycosyl acceptor and in the absence of molecular sieves (Scheme 4). Upon completion, the reaction mixture was evaporated under reduced pressure and

(41) Zinner, H.; Niendorf, K. *Chem. Ber.* **1956**, *89*, 1012−1016.

TABLE 3. Comparative UV Absorption of RSBox and RNBox Derivatives

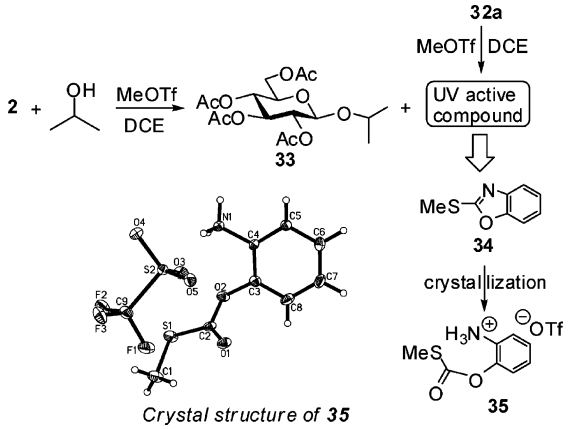
Entry	*Compound*	*Band 1, λ_{max} (nm)*	*Band 2, λ_{max} (nm)*	*Linkage*	*Reference*
1	 **2**	~280	~290	**SR**	[21]
2	 **36**	~300	--	**NR**	[21]
3	**2**	278	290	**SR**	This work
4	 **17**	280	290	**SR**	This work
5	 **37**[15]	300	--	**NR**	This work
6	 **32a**	300	--	**NR**	This work
7	 **34**	278	290	**SR**	This work

SCHEME 3



X-Ray crystal structure of ***32a***

SCHEME 4

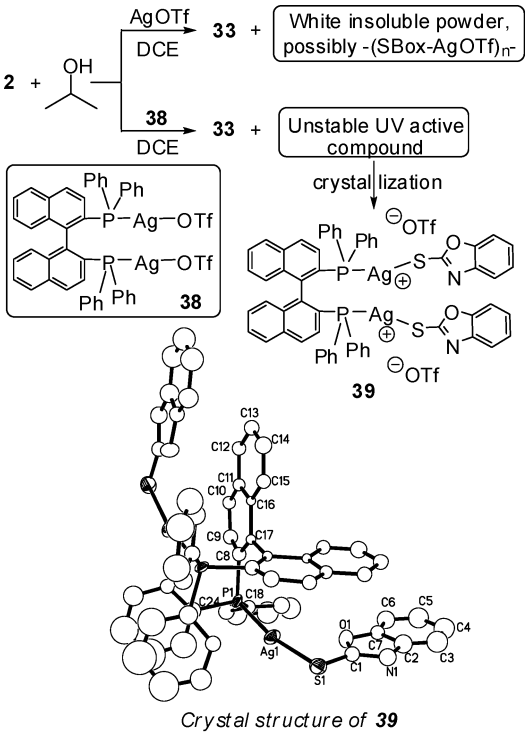


Crystal structure of ***35***

the UV-active compound was separated from isopropyl glycoside **33** and the remaining reactants by column chromatography. Characterization of the UV-active compound and comparison with the literature data[42−44] made us believe that the UV active species was S-methylated compound **34**. To ensure that the product had not undergone tautomerization during the course of the reaction, we also quenched the identical reaction mixture at an estimated 50% conversion. The experimental data suggested both products to be identical (**34**). To rule out the possibility of isomerization, we also performed NMR experiments using commercial 2-mercaptobenzoxazole (**32a**) and MeOTf. Even though we observed formation of the other tautomer in a very small quantity (<5%), the major product was identical to the compound isolated in the previous experiments (**34**). Interestingly, if the crude reaction mixture containing **34** was subjected to purification by crystallization, thiocarbonyl derivative **35** was obtained instead and its structure was confirmed by X-ray crystallography and NMR. Evidently, in spite of the hydrolysis, the *S*-methyl linkage remains intact.

In this context, it would be beneficial if we could operate with a reliable shortcut or an empirical rule that would allow one to determine whether the isolated compound is *N*- or *S*-methylated (or *N*- or *S*-linked in general). Based on the literature data for peracetylated SBox and NBox glycosides (**2** and **36**),[21] we found that UV spectroscopy could adequately serve our needs for the rapid and reliable structure determination. To this end, it should be possible to unambiguously distinguish the isomers by simple and reproducible comparison of the absorption bands. Thus, the thioimide (SH) derivative will have two narrow bands (λ) at around 280 and 290 nm (C═N), whereas the thioamide (NH) will have a single broad band at ~300 nm (C═S). A series of comparative UV experiments with both *S*- and *N*-linked derivatives are summarized in Table 3.

SCHEME 5



Crystal structure of ***39***

Unambiguously, the *S*-methyl linkage was determined in the compound **34**.

Activation by Complexation with Metal Ion (AgOTf). As mentioned earlier, we were also interested in investigating activation pathways via metal salts. To this end, our initial experiments with SBox glycosyl donor **2** and 2-propanol as glycosyl acceptor in the presence of AgOTf as promoter gave an insoluble white amorphous powder, possibly a metal insertion polymer of the type $-(\text{SBox-AgOTf})_n-$. Since its characterization appeared cumbersome, we bypassed this challenge by employing Yamamoto's AgOTf-BINAP (2/1) complex (**38**)[45] as a promoter. As a result of the reaction between glycosyl donor **2** and 2-propanol in the presence of promoter **38** a relatively unstable SBox-inclusion complex **39** was isolated by direct crystallization from the reaction mixture. The attachment point (sulfur), and the component molar ratio AgOTf-BINAP-SBox (2/1/2) was determined by X-ray crystallography (Scheme 5).

In brief, as a result of the mechanistic experiments presented herein, we conclude that either MeOTf or AgOTf-promoted activation of the SBox moiety proceed via the anomeric sulfur atom.

Conclusions

Based on the results presented, we conclude that the SBox glycosides can be successfully prepared from a variety of synthetic precursors and applied as glycosyl donors for stereoselective glycosylation. These derivatives fulfill major requirements for a versatile glycosyl donor: accessibility, odorless preparation, and activation under relatively mild reaction conditions. The activation pathways for glycosidation of the SBox moiety under a variety of reaction conditions were investigated in greater detail. As a result of these fundamental mechanistic studies, we acquired sufficient information to conclude that either MeOTf or AgOTf-promoted activation of the SBox glycosyl donors proceeds via the anomeric sulfur atom. It should be emphasized that future studies of protic or Lewis acid-catalyzed activations may open new exciting perspectives for the glycosidation of compounds of this class.

Experimental Part

Synthesis of 2-Benzoxazolethione, Potassium Salt ("KSBox"). Anhydrous K_2CO_3 (0.91 g, 6.6 mmol) was added to a stirred solution of 2-mercaptobenzoxazole (1.0 g, 6.6 mmol) in dry acetone (7 mL). The reaction mixture was refluxed for 3 h at 60 °C, acetone was then evaporated off, and the residue was dried in vacuo. UV data: λ 262, 296 nm.

Synthesis of the SBox Glycosides. Typical Procedures for the Preparation of the SBox Glycosides from Glycosyl Bromides. Method A. Preparation of the SBox Glycosyl Donors 2, 4, 6, and 8. 18-Crown-6 (0.6 mmol) and KSBox (3.45 mmol, prepared from HSBox and K_2CO_3) were added to a stirred solution of a glycosyl bromide (3.0 mmol) in dry acetone (4 mL) under an atmosphere of argon. The reaction mixture was stirred for 1 h at rt. Upon completion, the mixture was diluted with CH_2Cl_2 (30 mL) and washed with 1% aq NaOH (15 mL) and water (3 × 10 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate−hexane gradient elution) to afford the SBox glycoside.

Method B. Preparation of the SBox Glycosyl Donors 10 and 12. A solution of bromide **9**[46,47] or **11**[48,49] (2.0 mmol) in dry toluene was added dropwise to a stirred mixture of 2-mercaptobenzoxazole (2.4 mmol) and K_2CO_3 (2.4 mmol) in dry acetone at 40 °C. The reaction mixture was kept for 2 h at 50 °C and then for 16 h at rt. Upon completion, the mixture was diluted with toluene (30 mL) and washed with 1% aq NaOH (15 mL) and water (3 × 15 mL), and the organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate−hexane gradient elution) to afford the SBox glycoside.

Preparation of Disaccharides. Method A: Typical MeOTf-Promoted Glycosylation Procedure. A mixture of the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (3 Å, 200 mg) in 1,2-DCE or DCM (0.5 mL) was stirred for 2 h under argon. MeOTf (0.33 mmol) was added, and the reaction mixture was stirred for 2−24 h at room temperature; then Et_3N (0.5 mL) was added, the mixture was diluted with CH_2Cl_2 (30 mL), the solid was filtered off, and the residue was washed with CH_2Cl_2 (2 × 5 mL). The combined filtrate was washed with water (4 × 10 mL), and the organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate−hexane gradient elution) to yield the corresponding di- or oligosaccharide.

Method B: Typical AgOTf-Promoted Glycosylation Procedure. A mixture the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (3 Å, 200 mg) in 1,2-DCE or DCM (0.5 mL) was stirred under argon for 1.5 h.

(42) Beilenson, B.; Hamer, F. M. *J. Chem. Soc.* **1939**, 143−151.
(43) Llinares, J.; Galy, J.-P.; Faure, R.; Vincent et José Elguero, E.-J. *Can. J. Chem.* **1979**, *57*, 937−945.
(44) Harizi, A.; Romdhane, A.; Mighri, Z. *Tetrahedron Lett.* **2000**, *41*, 5833−5835.
(45) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5360−5361.
(46) Brennan, S.; Finan, P. A. *J. Chem. Soc., C* **1970**, 1742−1744.
(47) Excoffier, G.; Gagnaire, D. Y.; Vignon, M. R. *Carbohydr. Res.* **1976**, *46*, 215−226.
(48) Lemieux, R. U.; Kondo, T. *Carbohydr. Res.* **1974**, *35*, C4−C6.
(49) Kochetkov, N. K.; Klimov, E. M.; Malysheva, N. N.; Demchenko, A. V. *Carbohydr. Res.* **1991**, *212*, 77−91.

Freshly conditioned AgOTf (0.22 mmol) was added, the reaction mixture was stirred for 1−2 h at rt, then diluted with CH_2Cl_2 (30 mL), the solid was filtered off, and the residue was washed with CH_2Cl_2 (2 × 5 mL). The combined filtrate was washed with 20% aq $NaHCO_3$ (15 mL) and water (3 × 10 mL), and the organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate−hexane gradient elution) to afford a di- or an oligosaccharide derivative. Glycosylations in the presence of AgOTf (0.22 mmol)/TfOH (0.022 mmol) or AgOTf (0.22 mmol)/$AgCO_3$ (0.22 mmol) were performed in a similar fashion. In the latter case, molecular sieves 4 Å were employed.

Method C: Typical $Cu(OTf)_2$-promoted Glycosylation Procedure. A mixture the glycosyl donor (0.13 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in 1,2-DCE or DCM (0.5 mL) or toluene: dioxane (1:3, v/v, 1 mL) was stirred under argon for 1 h followed by addition of freshly conditioned $Cu(OTf)_2$ (141 mg, 0.39 mmol). The reaction mixture was stirred for 16−48 h at rt and then diluted with CH_2Cl_2 (30 mL), the solid was filtered off, and the residue was washed with CH_2Cl_2 (2 × 5 mL). The combined filtrate was washed with water (3 × 15 mL), and the organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate−toluene gradient elution) to yield the corresponding di- or oligosaccharide.

Method D: Typical NIS/TfOH (or NIS/TMSOTf)-Promoted Glycosylation Procedure. A mixture the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in 1,2-DCE (0.5 mL) was stirred under argon for 1.5 h. NIS (0.22 mmol) followed by TfOH or TMSOTf (0.022 mmol) was added, the reaction mixture was stirred for 30 min at rt and then diluted with CH_2Cl_2 (30 mL), the solid was filtered off, and the residue was washed with CH_2Cl_2 (2 × 5 mL). The combined filtrate was washed with 20% aq $Na_2S_2O_3$ (15 mL) and water (3 × 10 mL), and the organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate−hexane gradient elution) to afford a disaccharide derivative.

Method E: Typical TfOH-Promoted Glycosylation Procedure. A mixture of the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in 1,2-DCE (0.5 mL) was stirred under argon for 1.5 h. TfOH (0.11 mmol) was added, the reaction mixture was stirred for 30 min at rt and then diluted with CH_2Cl_2 (30 mL), the solid was filtered off, and the residue was washed with CH_2Cl_2 (2 × 5 mL). The combined filtrate was washed with 20% aq $NaHCO_3$ (15 mL) and water (3 × 10 mL), and the organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate−hexane gradient elution) to afford a disaccharide derivative.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-galactopyranoside (21) was obtained using method A or B from **2** and **20**[50] in 33 or 40% yield, respectively. Analytical data for **21** were essentially the same as reported previously.[51]

6-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (23) was obtained using method C from **2** and **22** in 63% yield. Analytical data for **23** were essentially the same as reported previously.[52]

6-*O*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (24) was obtained from **4** and **28** using method B in 91% or by method C in 70% yield. Analytical data for **24** were essentially the same as reported previously.[11]

Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**26**) was obtained using method A or B or E from **4** and **25**[53] in 95 or 94% yield, respectively. Analytical data for **26** were essentially the same as reported previously.[54]

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-α-D-glucopyranoside (**27**) was obtained using method C from **17** and **25** in toluene−dioxane (1/3, v/v, 1 mL) in 95% yield (α/β = 6/1) or in 1,2-DCE in 99% yield (α/β = 1.9/1). Analytical data for **27** were essentially the same as reported previously.[55]

6-*O*-(2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**28**) was obtained from **17** and **22** using method A in 98% yield (α/β = 1/1), method B in 78% yield (α/β = 1.1/1), and method C in 90% (α/β = 1.3/1). These glycosylations were performed in 1,2-DCE (0.5 mL). Compound **28** was also obtained from **17** and **22** by method C using toluene−dioxane (1 mL, 3/1, v/v) as solvent in 89% yield (α/β = 5.4/1). Analytical data for **28** were essentially the same as reported previously.[56]

Methyl 6-*O*-(3,4,6-tri-*O*-acetyl-2-*O*-benzyl-D-glucopyranosyl)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (**30**) was obtained using method B from **10** and **29**[57] in 92% yield (α only). Analytical data for **30**: R_f = 0.54 (ethyl acetate−hexane, 3/7, v/v); $[\alpha]^{22}_D$ 84.9 (c = 1.0, $CHCl_3$); ^{1}H NMR δ 1.92, 194, 2.00 (3 s, 9H, 3 × $COCH_3$), 3.47 (m, 1H, H-6b), 3.44 (s, 3H, OCH_3), 3.48 (dd, 1H, $J_{2',3'}$ = 9.9 Hz, H-2′), 3.76 (dd, 1H, $J_{6a,6b}$ = 10.6 Hz, H-6a), 3.95 (dd, 1H, H-6b′), 4.09−4.16 (m, 2H, $J_{5',6a'}$ = 4.3 Hz, $J_{6a',6b'}$ = 14.2 Hz, H-5′, 6a′), 4.29 (m, 1H, H-5), 4.52 (dd, 2H, J^2 = 12.2 Hz, CH_2Ph), 4.66 (d, 1H, $J_{1',2'}$ = 3.4 Hz, H-1′), 4.88 (dd, 1H, $J_{4',5'}$ = 9.4 Hz, H-4′), 5.13−5.19 (m, 2H, $J_{1,2}$ = 3.8 Hz, $J_{2,3}$ = 9.6 Hz, H-1, 2), 5.37 (dd, 1H, $J_{4,5}$ = 9.4 Hz, H-4), 5.40 (dd, 1H, $J_{3',4'}$ = 9.2 Hz, H-3′), 6.09 (dd, 1H, $J_{3,4}$ = 9.6 Hz, H-3), 7.09−7.92 (m, 20H, aromatic) ppm; ^{13}C-NMR δ 20.9, 21.0 (x 2), 29.9, 55.8, 62.2, 67.0, 67.6, 68.8, 68.9, 69.9, 70.6, 71.9, 72.4, 73.4, 96.8, 96.9, 128.0 (×3), 128.2, 128.5 (×2), 128.6 (×2), 128.7 (×3), 129.0, 129.3, 129.4, 129.9 (×2), 130.1 (×3), 130.2, 133.3, 133.6, 133.8, 138.0, 165.6, 166.0, 166.1, 170.1, 170.3, 170.9; HR-FAB MS $[M + Na]^+$ calcd for $C_{47}H_{48}NaO_{17}$ 907.2789, found 907.2798.

Mechanistic Investigations (performed in the absence of molecular sieves): 2,2′-dibenzoxazolyldisulfide (31): A mixture the glycosyl donor **4** (50 mg, 0.069 mmol) and glycosyl acceptor **31** (29 mg, 0.062 mmol) in 1,2-DCE (0.5 mL) was stirred under argon for 15 min. NIS (31 mg, 0.138 mmol) and TfOH (∼2 μL, 0.014 mmol) were added, and the reaction mixture was stirred for 30 min at rt. The reaction mixture was subjected to column chromatography on a silica gel column without any further treatment to yield the disaccharide **26** (42 mg, 65% yield) and the UV-active compound **31** (9.6 mg, 47% yield). Analytical data for **31**: R_f = 0.60 (acetone−hexanes−toluene, 1/2/4, v/v/v); ^{1}H NMR δ 7.34−7.37 (m, 2H, aromatic), 7.53 (m, 1H, aromatic), 7.71 (m, 1H, aromatic); ^{13}C NMR δ 110.9, 120.1, 125.3, 125.7, 142.1, 152.8, 160.1; HR-FAB MS $[M + H]^+$ calcd for $C_{14}H_9N_2O_2S_2$ 301.0105, found 301.0103. Analytical data for **26** were essentially the same as reported previously.[55]

2-Mercaptobenzoxazole (Benzoxazolinethione, **32a).** A mixture the glycosyl donor **4** (50 mg, 0.069 mmol) and glycosyl acceptor

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25 (29 mg, 0.062 mmol) in 1,2-DCE (0.5 mL) was stirred under argon for 15 min. TfOH (61 μL, 0.21 mmol) was added, and the reaction was monitored by TLC. Upon 75−100% consumption of **4**, the reaction mixture was concentrated under reduced pressure. The residue was coevaporated with CH_2Cl_2 (2 × 5.0 mL) and then purified by column chromatography on silica gel. The UV-active compound **32a** was obtained in 55% yield (5.6 mg). Analytical data for **32a** were the same as reported for the commercial compound. X-ray crystallography data were essentially the same as reported and have been included in Supporting Information. Analytical data for **26**, also obtained herein (33 mg, 82%), were essentially the same as reported previously.

2-Methyl-2-mercaptobenzoxazole (34). A mixture of the glycosyl donor **2** (50 mg, 0.1 mmol) and 2-propanol (7.2 μL, 0.09 mmol) in 1,2-DCE (0.5 mL) was stirred under argon for 15 min. MeOTf (36 μL, 0.3 mmol) was added, and the reaction progress was monitored by TLC. Upon 75−100% consumption of **2**, the reaction mixture was concentrated under reduced pressure. The residue was coevaporated with CH_2Cl_2 (2 × 5.0 mL) and then purified by column chromatography on silica gel to afford **34** (7.3 mg, 43%) and isopropyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside **33** (24.7 mg, 68%). Analytical data for **34**: R_f = 0.5 (ethyl acetate−toluene, 1/9, v/v); ^{1}H NMR δ 2.78 (s, 3H, SCH_3), 7.27 (m, 2H), 7.45 (dd, 1H), 7.62 (dd, 1H); ^{13}C NMR δ 14.7, 110.6, 118.5, 124.0, 124.5, 142.2, 152.2, 165.9; EI-GC/MS *m*/*z* 122 (79), 132 (92), 150 (21), 165 (100) amu. Analytical data for **33** were essentially the same as reported previously.[58]

Compound **34** (31 mg, 95% yield) was also prepared by reaction of 2-mercaptobenzoxazole **32a** (30 mg, 0.19 mmol) with MeOTf (69 μL, 0.59 mmol) in 1,2-DCE. For the related NMR experiment, compound **32a** (10 mg, 0.067 mmol) was dissolved in $CDCl_3$ (0.7 mL) under argon. The resulting mixture was transferred to the NMR tube, MeOTf (23 μL, 0.198 mmol) was added, and the tube was sealed and then vigorously shaken. The formation of **34** was monitored by ^{1}H NMR.

2-(Methylthiocarbonyloxy)benzenaminium Trifluoromethanesulfonate (35). 2-Mercaptobenzoxazole **32a** (30 mg, 0.19 mmol) was dissolved in 1,2-DCE (0.5 mL) and stirred under argon for 15 min. MeOTf (69 μL, 0.59 mmol) was added, and the reaction was monitored by TLC. Upon 100% consumption of **32a**, the reaction mixture was concentrated under reduced pressure. The residue was coevaporated with CH_2Cl_2 (2 × 5 mL) and then subjected to crystallization in chloroform. The formed crystals were separated and dried in vacuo to afford **35** in 60% yield (40 mg). Analytical data for **35**: R_f = 0.5 (ethyl acetate−toluene, 1/9, v/v); ^{1}H NMR δ 2.69 (s, 3H, SCH_3), 7.00 (broad s, 3H, NH_3) 7.41−7.85 (m, 4H, aromatic). X-ray crystallography data are given in the Supporting Information.

SBox-AgOTf-BINAP Inclusion Complex (39). The AgOTf−BINAP complex **38** (53 mg, 0.2 mmol), prepared in THF according to the reported procedure,[45] was added to the solution of donor **2** (50 mg, 0.1 mmol) and 2-propanol (7.2 μL, 0.09 mmol) in 1,2-DCE (0.5 mL). The reaction mixture was stirred for 1.5 h at rt. A mixture of ethyl acetate, ether, and hexanes (2 mL, 0.5/1.0/1.0 v/v/v) was added to initiate crystallization. The crystals were separated and dried in vacuo to afford complex **39** (6 mg, 5%). X-ray crystal structure data for complex **39** are given in the Supporting Information. Glycoside **33** was obtained in 65% yield (24 mg) by subjecting the mother liquor to column chromatography on silica gel.

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Supporting Information Available: Extended Table 2, experimental and characterization data for SBox glycosides, spectra for all new compounds, and X-ray data for compounds **4**, **10**, **32a**, **35**, and **39**. This material is available free of charge via the Internet at http://pubs.acs.org.

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