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S-Benzoxazolyl (SBox) Glycosides as Novel, Versatile Glycosyl Donors for Stereoselective 1,2-Cis Glycosylation

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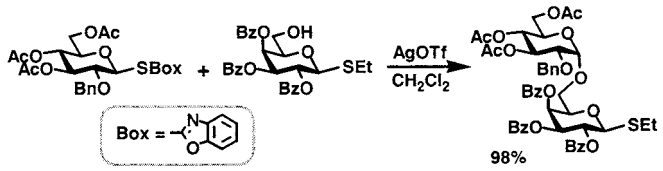
ABSTRACT



Novel glycosyl donors, *S*-benzoxazolyl (SBox) glycosides, have been synthesized, tested toward various protecting group manipulations, and applied to the highly stereoselective 1,2-cis glycosylation. These compounds fulfill the requirements for a modern glycosyl donor such as accessibility, high stability toward protecting group manipulations, and mild activation conditions. It was also demonstrated that SBox glycosides withstand other glycosyl donor activation conditions and therefore allow selective glycosylations of *O*-pentenyl and thioglycosides.

The majority of carbohydrates found in nature exist as polysaccharides, glycoconjugates, or glycosides in which monosaccharide units are joined together via O-glycosidic bonds. The necessity to form either a 1,2-cis or 1,2-trans glycosidic bond with complete stereoselectivity is the main reason chemical O-glycosylation is placed among the most challenging problems of modern synthetic chemistry. To address these challenges, many new glycosyl donors that can be synthesized under mild reaction conditions and are sufficiently stable to be purified, modified, and stored have been developed.[1,2] Highly efficient strategies for the oligosaccharide synthesis have become available.[3] Methods for solid-phase synthesis have been reported, and these procedures often shorten oligosaccharide synthesis.[4] However, these developments are often compromised when applied to the stereoselective synthesis of 1,2-cis glycosides, which are often present as components in a wide variety of natural compounds.[5−8]

It is well established that 1,2-trans glycosides can be prepared with the assistance of a neighboring participating group.[9] In principle, 1,2-cis glycosides (α-glycosides for D-glucose, D-galactose, and L-fucose, or β-glycosides for D-mannose, L-arabinose, etc.) can be synthesized with a glycosyl donor bearing a nonparticipating group at C-2 (*O*-benzyl, azido). However, the reaction often proceeds via an S_N1 mechanism and therefore with poor stereoselectivity. Despite considerable progress, no successful *general* method for 1,2-cis glycosylation has yet emerged.[10] Although the first 1,2-cis glycosylations were performed many decades ago,[10] even nowadays each particular case requires a careful selection of techniques, especially when applied to the synthesis of complex oligosaccharides.

As a part of the program to develop novel, versatile methods and strategies for the oligosaccharide synthesis, we have become interested in a class of glycosyl donors with a

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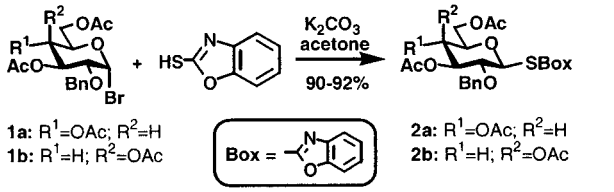
generic leaving group $SCR_1{=}NR_2$ (substituted thioimidoyl derivatives). It should be noted that a number of such moieties have been previously employed at the anomeric center in an attempt to achieve better stereocontrol of the glycosylation process.[10] For example, benzothiazolyl,[11] pyridin-2-yl,[12−14] pyrimidin-2-yl,[12,15] imidazolin-2-yl,[12] and 1′-phenyl-1*H*-tetrazolyl[16] 1-thio derivatives performed exceptionally well, in most cases providing high anomeric selectivity. Unfortunately, the lower stability of these derivatives in comparison to that of "stable" glycosyl donors, *O*-pentenyl[17] or thioglycosides,[18,19] toward protecting group manipulations is the major drawback of these glycosylation approaches, which limits their application for convergent oligosaccharide synthesis. We decided to explore this concept taking into consideration the following advantageous features of the substituted thioimidates. First, these compounds can be synthesized via a number of well-established reaction pathways starting from anomeric halides, acetates, or 1,2-anhydro sugars and are therefore easily accessible. Second, we assumed that their glycosyl donor reactivity can be adjusted by varying the electronic properties of R_1 and R_2 substituents. Third, the overall size of the anomeric substituent may influence the reactivity/stability of these thio derivatives dramatically,[20] which would allow the application of various (chemo)selective glycosylation approaches.[3]

Here we describe the synthesis of novel 1,2-*trans*-*S*-benzoxazolyl derivatives (SBox glycosides) and their application for stereoselective 1,2-cis glycosylation.[21] For this purpose 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl bromide (**1a**)[22,23] was reacted with 2-mercapto-benzoxazole in the presence of K_2CO_3 in acetone at 50 °C to afford benzoxazolyl 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-1-thio-*β*-D-glycopyranoside (**2a**) in 92% yield (Scheme 1). Similarly, the SBox glycoside of D-galactose **2b** was prepared from **1b**[24,25] in 90% yield. Interestingly, the newly synthesized compounds were shown to be able to withstand rather harsh reaction conditions required for protective group manipulations, i.e., acetylation, deacetylation, benzylation, and triphenylmethylation, as well as benzylidene acetal formation and cleavage.

Scheme 1. Synthesis of Novel SBox Derivatives **2a** and **2b**



In addition, alternative approaches for the synthesis of nonparticipating SBox glycosides have been explored. Thus, acetobromoglucose was reacted with 2-mercaptobenzoxazole in the presence of K_2CO_3 in acetone at 50 °C, followed by Zemplen deacetylation (MeONa/MeOH) and benzylation (BnBr/NaH), to allow benzoxazolyl 2,3,4,6-tetra-*O*-benzyl-1-thio-*β*-D-glycopyranoside in 52% yield over three steps. The SBox moiety could also be introduced via Lewis acid ($BF_3{\cdot}Et_2O$, TMSOTf)-catalyzed glycosidation of pentaacetyl *β*-D-glucose. Analogous thiazolyl 2,3,4,6-tetra-*O*-benzyl-1-thio-*β*-D-glucopyranoside has been accordingly prepared by reaction of acetobromoglucose with 2-mercaptothiazoline in the presence of NaH in MeCN, followed by deacetylation and benzylation. Application of these derivatives for glycosylation will be reported in due course. It should be noted that syntheses of per-acetylated thiazolylthio[26] and benzoxazolylthio[27,28] derivatives have been previously reported.

Having synthesized SBox glycosides **2a** and **2b**, we turned our attention to the evaluation of their glycosyl donor properties. Considering the multifunctional character of the leaving group, we anticipated that these donors could be activated via a number of conceptually different modes (Figure 1).

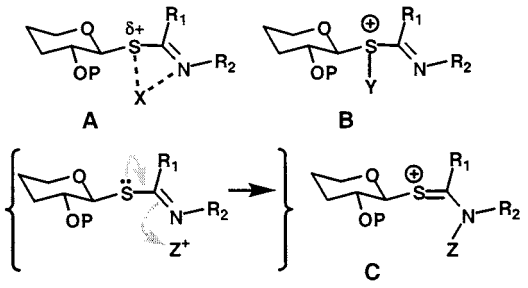


Figure 1. Plausible Reaction Intermediates for the Activation of SBox Glycosides.

Thus, heavy metal salt-based promoter systems would complex sulfur and nitrogen, improving the leaving group ability by producing a partial positive charge on sulfur (**A**).

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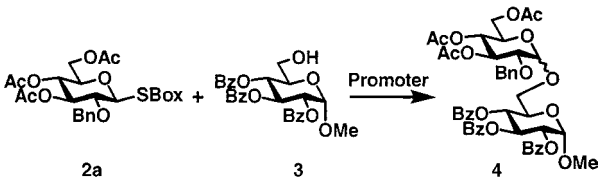
Table 1. Glycosylation Reaction between **2a** and **3**[a]



entry	promoter system	time	yield	α/β ratio[b]
1	NIS/TMSOTf/4 Å MS	3 h	82%	15/1
2	MeOTf/3 Å MS	16 h	89%	α only[c]
3	TMSOTf	24 h	d	
4	$AgCO_3$	48 h	e	
5	$AgCO_3$/AgOTf	16 h	75%	α only
6	$ZrCl_4/AgCO_3$	2 h	70%	10/1[f]
7	AgOTf/3 Å MS	1 h	92%[g]	α only
8[h]	$TrClO_4$	40 h	88%	15/1

[a] All glycosylations were performed in CH_2Cl_2 under argon at room temperature. [b] Anomeric ratios were obtained by comparison of the integral intensities of the corresponding signals in ^1H NMR spectra. [c] No 1,2-trans-linked product could be detected; anomeric selectivity > 20/1. [d] Sluggish reaction (incomplete in 24−48 h) and high or complete anomeric selectivity; however, low isolated yield (35−60%) was observed; similar results were obtained with $BF_3{\cdot}Et_2O$, $BF_3{\cdot}Me_2O$, and $Cu(OTf)_2$/TMSOTf. [e] No reaction within 48 h, similar results were obtained in the presence of $Cu(OTf)_2$, HgO/$HgBr_2$, CSA, IDCP, or NBS. [f] Reaction proceeded via 1-chloro derivative generated in situ. [g] AgOTf-Promoted glycosylations in the absence of added MS or in the presence of 4 Å MS provided glycosylation products with complete stereoselectivity but lower yields (82−84%). [h] Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-triphenylmethyl-α-D-glucopyranoside was used as a glycosyl acceptor.

Alternatively, thiophilic, alkylating, or electrophilic reagents would act via **B** or **C**.

With these considerations in mind, and in order to evaluate the glycosyl donor properties of SBox glycosides, **2a** was coupled with methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (**3**)[29] in the presence of a promoter and in the presence or absence of molecular sieves (MS) in dry CH_2Cl_2. These results are summarized in Table 1. Thus, the highest stereoselectivities and yields for the synthesis of **4** were obtained not only with the conventional promoters used for the activation of alkyl/aryl thioglycosides such as NIS/TMSOTf (entry 1, Table 1) or MeOTf (entry 2)[19] but also in the presence of AgOTf (2.0 mol equiv, entry 7), which is more typically used for the activation of glycosyl halides[30] or selenoglycosides.[31] In addition, the 6-O-triphenylmethylated derivative of the glycosyl acceptor **3** could be glycosylated in the presence of $TrClO_4$ (entry 8).

Surprisingly, **2a** has remained inert in the presence of other common thioglycoside activating agents such as iodonium-(di-γ-collidine)perchlorate (IDCP) or NBS. In this context, high stability toward IDCP, a promoter that is often used for the activation of "armed" thioglycosides,[32] can be correlated with the number of the remote deactivating

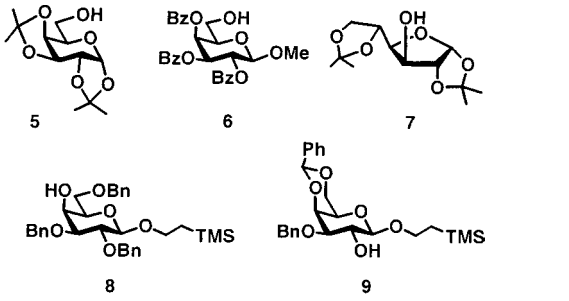


Figure 2. Glycosyl Acceptors Tested for the Glycosylations with **2a** and **2b**.

O-acetyl substituents. These observations make SBox derivatives suitable candidates for the development of various chemoselective and orthogonal strategies for convergent oligosaccharide synthesis.[3]

To reveal the scope and possible limitations of the novel approach for the synthesis of glycosidic linkages of different origin, a number of partially protected glycosyl acceptors were investigated (Figure 2). Thus, commercially available diacetone acetals of galactose **5** and glucose **7**, as well as other common building blocks **6**,[33] **8**,[34] and **9**,[35] were glycosylated with **2a** and **2b**. Results of these glycosylation experiments are summarized in Table 2. Most commonly,

Table 2. Glycosylation Reaction between **2a**,**b** and **5**−**9** in the Presence of AgOTf or MeOTf[a,b]

entry	donor	acceptor	promoter	yield	α/β ratio
1	**2a**	**5**	AgOTf	99%	11/1
2	**2a**	**6**	AgOTf[c]	85%	15/1
3	**2a**	**6**	AgOTf	97%	α only
4	**2a**	**7**	MeOTf	88%	8/1
5	**2a**	**8**	MeOTf	88%	α only
6	**2a**	**9**	MeOTf	78%	3/1
7	**2b**	**5**	AgOTf	90%	10/1
8	**2b**	**6**	AgOTf	80%	α only

[a] Typically, the glycosyl acceptor was reacted with a glycosyl donor (10 mol % excess) in the presence of MeOTf (3 equiv) or AgOTf (2.0 equiv) and activated MS (3 Å, unless otherwise noted) in CH_2Cl_2 at room temperature until completion (typically 1−2 h). All synthesized di- and trisaccharides have adequate ^1H and ^{13}C NMR and HRMS data. [b] All glycosylations were performed in the presence of each promoter; however, only the best results are listed. [c] Used 4 Å MS.

alcohol reactivity is inversely correlated with the 1,2-cis stereoselectivity.[10] Remarkably, somewhat better results in terms of both stereoselectivity and yields were achieved when highly nucleophilic primary hydroxyl-containing glycosyl acceptors were employed. For example, glycosylation of **5**

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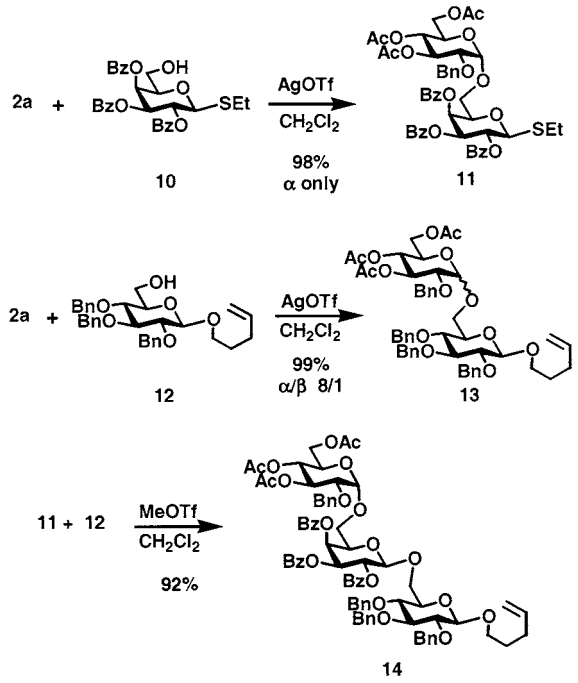
Scheme 2. Selective Activation of SBox Derivatives in the Presence of *S*-Ethyl and *O*-Pentenyl Glycosides



with **2a** in the presence of AgOTf afforded the corresponding disaccharide in 99% yield as an 11/1 α/*β*-mixture (entry 1, Table 2). Also, glycosylation of **6** afforded the disaccharide with complete stereoselectivity in 97% yield (entry 3). Interestingly, when the latter reaction was performed in the presence of 4 Å MS, lower anomeric selectivity (15/1) and yield (85%) were detected (entry 2). In this context, galactosyl donor **2b** performed similarly (entries 7 and 8).

To extend this novel method for the rapid synthesis of oligosaccharides with multiple 1,2-cis glycosidic residues without requiring any protecting group manipulations, we tested a number of conditions for selective activation of SBox glycosides in the presence of other common glycosyl donors. Thus, pilot glycosylation of ethyl thiogalactoside **10**[36] with **2a** in the presence of AgOTf and 3 or 4 Å MS provided disaccharide **11** with complete stereoselectivity in 98% yield (Scheme 2), whereas application of other suitable promoters, e.g., TMSOTf or $ZrCl_4/AgCO_3$, resulted in lower stereoselectivities and yields.

In addition, a range of reaction conditions (MeOTf, AgOTf, TMSOTf, etc.) allowed efficient synthesis of the disaccharide derivative **13** by selective activation of **2a** over *O*-pentenyl glycoside **12**.[37] For example, using standard reaction conditions in the presence of AgOTf afforded disaccharide **13** in 76% yield as an anomeric mixture (8/1 α/*β*). This result could be sufficiently improved by applying a larger excess (up to 2.0 equiv) of the glycosyl donor; in this case, **13** was isolated in 99% yield (Scheme 2). Furthermore, disaccharide **11** can be also reacted with **12** in accordance with the recently introduced "*semi*-orthogonal" glycosylation strategy[38] to afford **14** in the high yield of 92%. Clearly, trisaccharide **14** could be employed for subsequent glycosylation without protecting group manipulations.

It is to be expected that the observed high stability of SBox glycosides toward electrophilic activators would also allow selective activation of SPh glycosides with NBS[39] or armed *O*-pentenyl glycosides (IDCP).[40] Further exploration of these interesting features of SBox derivatives as well as their application for convergent oligosaccharide synthesis is on the way.

In summary, we developed a new class of glycosyl donors, benzoxazolyl (Box) thioglycosides, which were applied to the highly stereoselective 1,2-cis glycosylation. These compounds fulfill the necessary requirements of a modern glycosyl donor such as accessibility, high stability toward major protecting group manipulations, and mild activation conditions. It was also demonstrated that SBox glycosides withstand other glycosyl donor activation conditions and therefore allow selective glycosylations of *O*-pentenyl and thioglycosides. Considering the unique glycosyl donor properties of the SBox glycosides, we believe that they will occupy an important niche in the arsenal of modern synthetic methods.

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Supporting Information Available: Experimental procedures for the synthesis of **2a**, **2b**, **11**, **13**, and **14** and their ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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