VIP Glycosylation

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Bismuth(V)-Mediated Thioglycoside Activation**

*Manibarsha Goswami, Arkady Ellern, and Nicola L. B. Pohl**

Chemical glycosylation[1,2] is a crucial step in any oligosaccharide[3] synthesis.[4,5] Among the different classes of commonly used glycosyl donors,[2] thioglycosides[6,7] offer distinct advantages. Thioglycoside donors are relatively simple to prepare, are stable under various reactions for protecting-group manipulations, and offer orthogonality in their activation in the presence of other glycosyl donors.[8] As a result, a wide variety of promoters have been developed for activation of these donors in the past 20 years:[2] from heavy metal-cation-based promoters (Hg^{II} sulfate),[9] to the current halonium-based reagents [e.g., *N*-iodosuccinimide/trifluoromethane sulfonic acid (NIS/TfOH),[10] *N*-bromosuccinimide (NBS),[11] ICl or IBr/AgOTf,[12] etc.], alkylating reagents [methyl triflate (MeOTf)],[13] and organosulfur-based promoters [e.g., dimethyl(thiomethyl)sulfonium triflate (DMTST),[14] methylsulfenyl triflate (MeSOTf),[15] dimethyl disulfide/triflic anhydride (Me_2S/Tf_2O),[16] benzenesulfinylpiperidine/triflic anhydride (BSP/TTBP),[17] *N*-(phenylthio)-ε-caprolactam-Tf_2O,[18] etc.]. A recent method applies single-electron transfer using ruthenium or iridium-containing catalysts that are active under visible light[19] to activate thioglycosides. Although these methods have been effective in carrying out a range of glycosylations, most of these still have a limited scope. Generally, these activations need excess amounts of promoters,[2,9–18] or require a co-promoter to form the reactive intermediates. Moreover, present methods often require extremely low temperatures ($< -20\,^{\circ}C$) as a result of generating reactive intermediates. Some of the popular halonium-based promoters are challenging to use in the presence of alkenes,[20] because they tend to give various addition by-products, thereby ultimately resulting in the cleavage of the alkenyl moiety. These issues with solubility, undesired by-products, stability, or reagent handling are particularly problematic in the context of the development of robust automated protocols[21,22] for oligosaccharide synthesis. To circumvent some of these issues with current promoter systems, we herein report a straightforward method for the activation of thiopropylglycosides for coupling to various acceptors in good to excellent yields by utilizing a bismuth(V) compound without additional additives/co-promoters.

In lieu of the available promoters based on heavy-metal cations, bismuth presents interesting possibilities. Bismuth is a post-transition metal and like its neighboring metals such as mercury and lead, it is considered thiophilic as well as soft Lewis acidic. However, unlike Hg and Pb compounds, bismuth[23] is not only inexpensive, but also nontoxic. Unfortunately, despite its popularity as a treatment for digestive problems,[24] the synthetic utility of bismuth compounds remains relatively unexplored. However, the chemistry of this element[25] has gained considerable interest[26,27] over the past decade.[28] Various bismuth(III) compounds have been developed that play crucial roles in different functional-group transformations. In carbohydrate chemistry, bismuth(III) triflate combined with NBS[29] was reported as a promoter for the activation of thio- and selenoglycosides. Moreover, $Bi(OTf)_3$ by itself can also be used for selective activation[30] of an *S*-benzoxazolyl (SBox) sialyl donor over a galactosyl acceptor equipped with a thioethyl anomeric moiety. However, in both cases, it was observed that $Bi(OTf)_3$ was not only used in excess amounts, but owing to its insolubility in the organic solvents often used for glycosylations, it has to be used in the presence of co-solvents like 1,4-dioxane and tetrahydrofuran that play a significant role[31] in the diastereoselectivity of the glycosylation products. Ideally, a method for thioglycoside activation using bismuth chemistry could be developed that avoided the use of additives, co-solvents, low temperatures, and even the requirement for excess amounts of promoter.

Though a variety of bismuth(III) reagents have been used in oxidation, phenyl addition, and glycosylation reactions, applications of bismuth(V)[32] compounds remain relatively unexplored. A recent report[33] demonstrates the use of Bi^{V} salts and ylides in carbon–carbon and carbon–heteroatom bond-forming reactions. We were curious as to the thiophilicity of Bi^{V} complexes as well as the possibility of the addition of solubilizing ligands on Bi^{III}, but soon we discovered the challenges of trying to synthesize and characterize new bismuth-containing compounds.

Given the current limitations in the definitive characterization[22] of new bismuth compounds in solution, we next sought a complex that was amenable to crystallization. We chose a pentavalent bismuth compound containing three phenyl and two triflate groups, namely triphenyl bismuth ditriflate (**2**). $Ph_3Bi(OTf)_2$ was synthesized in two steps (Scheme 1) starting from relatively inexpensive triphenyl bismuth, which was first oxidized to triphenyl bismuth diacetate (**1**) and then later converted to the desired

[*] Prof. N. L. B. Pohl
Department of Chemistry, Indiana University
Bloomington, IN 47405 (USA)
E-mail: npohl@indiana.edu
Homepage: http://www.indiana.edu/~pohllab/index.html

M. Goswami, Dr. A. Ellern, Prof. N. L. B. Pohl
Department of Chemistry, Iowa State University
Ames, IA 50010 (USA)

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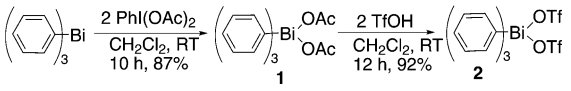
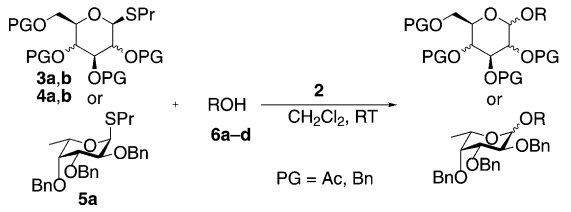


Scheme 1. Preparation of a bismuth(V) promoter.

compound **2** in an 80% overall yield. Compound **2** is a colorless solid that crystallizes[34] in a highly disordered orthorhombic space group with trigonal bipyramidal coordination geometry around the bismuth metal center; this geometry is similar[35] to reported Bi^V-containing compounds. More importantly, the compound surprisingly proved to have activity in an initial glycosylation reaction screen.

Further exploration of this Bi^V reagent revealed several advantages. Solubility has been a major drawback with most promoters, thereby complicating their employment in automation platforms (solution[21] or solid phase[22]) that carry out iterative oligosaccharide synthesis. Interestingly, compound **2** was found to be readily soluble in most organic solvents, particularly dichloromethane and toluene, which are desirable nonparticipating solvents in glycosylation. Furthermore, the promoter was also found to be stable in an oxygen atmosphere and under irradiation with light. No degradation or decomposition was seen when kept under anhydrous conditions for months. So, unlike many thioglycoside promoters, complex **2** does not need to be synthesized just prior to the activation reaction, but can be made in batches and stored. In addition, the promoter **2** does not require a co-promoter like NBS/NIS to first make a soft electrophilic halonium species to attach to the soft nucleophilic sulfur. Finally, the activation does not require extreme low temperatures (−20 to −78 °C) primarily to control side reactions or unwanted by-products.

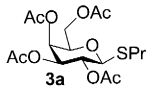
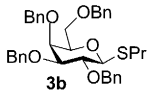
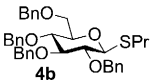
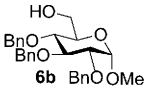
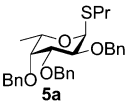
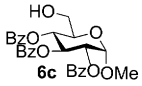
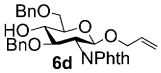
To test the scope of the developed methodology, a range of thiopropyl analogues of glucosyl (**3a**,**b**), galactosyl (**4a**,**b**), and fucosyl (**5a**) donors were prepared (Scheme 2). A



Scheme 2. Activation of thiopropylglycosides with **2**.

number of alkyl- and aryl-containing thiols were examined for the preparation of thioglycoside donors. Thiols in general are difficult to handle owing to their unpleasant odor. We therefore eschewed the more common volatile methane/ethanethiols and the highly pungent, more toxic aryl thiols and settled on *n*-propylthiol,[36] a compound that is safe enough to be approved as a food additive for its savory onion-like smell. Next, the solvent chosen for the activation was dichloromethane, since it is relatively inert, easy to handle, has negligible solvent effects,[31] and completely solubilizes the donor/acceptor/promoter. After examining various temperatures (0 °C–reflux), the glycosylations were found to be best (without degradation of starting material) when carried out at ambient temperature. These propanethiol-modified sugars were then subjected to these optimized reaction conditions with a range of glycosyl acceptors in presence of **2** (Scheme 2 and Table 1).

Table 1: Reaction of glycosyl donors and acceptors.[a]

Entry	Donor	Acceptor	*t* [h]	Yield [%][b]	α/β[c]
1	 **3a**	 **6a**	4.5	78	1:10
2	 **3b**	**6a**	1	86	2:1
3	 **4b**	**6a**	3	69	1.2:1
4	**3a**	 **6b**	6	86	1:9
5	**3b**	**6b**	0.5	91	1.5:1
6	**4b**	**6b**	3.5	87	1.2:1
7	 **5a**	**6b**	0.2	80	2.3:1
8	**3a**	 **6c**	8	71	1:12
9	**3b**	**6c**	1	81	1:1
10	**4b**	**6c**	4	64	2:1
11	**3b**	 **6d**	0.5	72	2:1
12	**5a**	**6d**	0.33	85	7:1

[a] Reaction conditions: donor (1 equiv), acceptor (0.9 equiv), **2** (1 equiv), CH_2Cl_2, RT, 0.5 M. [b] Yield of isolated products after silica gel chromatography, [c] calculated by NMR spectroscopy.

The study of thioglycoside activation with our model promoter **2** was started with a simple acceptor: allyl alcohol **6a**. The presence of double bonds is remarkable, as they are generally avoided in donor/acceptor compounds, since they tend to compete as a potential soft nucleophilic center with sulfur. Though some controlled activation[37] protocols can avoid these issues, alkenyl protecting groups always have the potential to be cleaved.[38] Fortunately, the "armed"[39] perbenzylated galactosyl donor **3b** and the disarmed peracetylated galactosyl donor **3a** gave the desired *O*-allyl galacto-

sides in high yields (Table 1, entries 1–2). The armed glucosyl donor **4b** could also be activated (Table 1, entry 3) to give the *O*-allyl glucoside in good yield. The alkenyl system remained intact throughout these reactions, and formation of an addition side product was not observed.

With our initial success with acceptor **6a**, the method was applied to various glycosyl acceptors containing a wide range of functional groups. The glucosyl acceptor **6b** was selected to test the method for the formation of 1→6-linked disaccharides as well as glycosylation with a primary hydroxy acceptor. Both the galactosyl donors **3a** and **3b** (Table 1, entries 4–5) gave the disaccharides in excellent yields. As predicted, the 1,2-*trans*-glycosides were favored for the disarmed thioglycosides, and a low stereoselectivity was observed in the case of armed thioglycosides. Similarly, the armed glucosyl donor **4b** (Table 1, entry 6) was also activated to give the 1→6 disaccharide in high yield with a slight preference for the α-anomer.

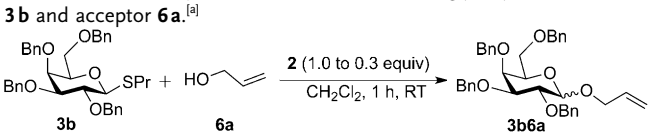
Next, from common sugars like D-glucose and D-galactose, we moved to less common sugars. An armed L-fucosyl donor **5a** was chosen for this purpose and was synthesized from its acetate analogue (see the Supporting Information). The activations were investigated with α-thiopropyl L-fucoside donors; these are more-stable anomers for L-fucose. Interestingly, the initial glycosylation with the glucosyl acceptor **6b** (Table 1, entry 7) was extremely fast, since the donor was consumed in 12 min to give the fucose 1→6-linked glycoside in good yield. The formation of the α-anomer of the disaccharide was favored, as generally seen with fucose analogues.[40]

To explore another acceptor containing a commonly used protecting group, acceptor **6c** was selected. Unlike the benzyl groups (OBn) on **6b**, the benzoate groups (OBz) on **6c** lead to a deactivated acceptor. This acceptor was particularly selected, because previously[41] it was observed that coupling similarly deactivated acceptors with reactive donors in the presence of NIS resulted in the formation of irreversible *N*-succinimide glycosides of the donors as major products. However, when using promoter **2**, the required disaccharides were obtained in high to good yields with both reactive donors (Table 1, entries 9–10) and a deactivated donor (entry 8). Interestingly, the rate of glycosylation did not differ much with alterations in the electronics of the acceptor (Table 1, entries 5 and 9, 6 and 8), but a change from disarmed to armed donors (entries 8, 9) had a significant impact on the reaction times.

To extend the method to amino sugars, a glucosamine acceptor **6d** containing a variety of functional groups, including benzyl and allyl as alcohol protecting groups and phthalimido (Phth) as amine protecting group, was chosen. This acceptor with a free 4-hydroxy group would also validate our promoter for making 1→4-linked disaccharides, which in general are difficult to construct owing to the low reactivity[42] of the C-4 hydroxy group. On reaction of acceptor **6d** with the perbenzylated galactosyl donor **3b** (Table 1, entry 11) using promoter **2**, the 1→4-linked galactose–glucosamine disaccharide was obtained in 72% yield without any interference with the other functional groups. Coupling of acceptor **6d** to fucosyl donor **5a** (Table 1, entry 12) met with similar success. The glycosylation was observed to be very fast, resulting in the formation of the 1→4-linked fucose–glucosamine disaccharide in very high yield, favoring the α-anomer. Comparing all the entries in Table 1, we can conclude that the glycosylation time depends on the nature of the donor (armed or disarmed) more so than on the incoming acceptor.

Another noteworthy limitation with available thioglycoside activators has been the amounts of promoter/co-promoter needed for thioglycoside activation. To our knowledge, none of the available methods to date require less than stoichiometric amounts of promoter. Considering this and the above successful glycosylations, experiments were then designed to probe the amounts needed for full consumption of the glycosyl donor (Table 2) and isolation of the desired

Table 2: Promoter equivalence studies with model glycosylation of donor **3b** and acceptor **6a**.[a]



Entry	Promoter equivalence	Yield [%][b]
1	1	86
2	0.7	82
3	0.5	76
4	0.3	68

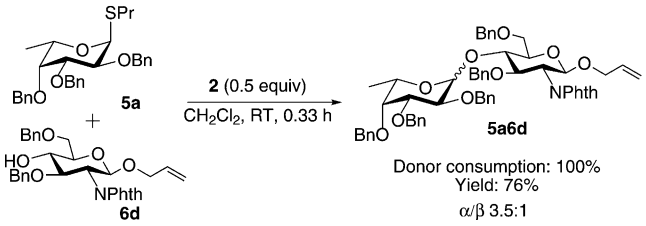
[a] Reaction conditions: donor, acceptor (1 equiv), RT, CH_2Cl_2, 1 h.
[b] Yield of isolated product after silica gel chromatography.

glycosides. Here, the coupling of benzylated galactoside donor **3b** to allyl acceptor **6a** in the presence of promoter **2** was considered as our model thioglycoside activation reaction. Moreover, to make accurate and consistent comparison of the differential loading, we quenched the reactions (Table 2) after one hour, since the total reaction time was already determined for the same reaction in Table 1, entry 2.

Fortunately, very high to good conversion rates were still seen as the amount of promoter was steadily decreased (Table 2). Only a modest decrease in yields (86% to 68%) was observed as the loading was decreased from 100% to 30%. Nevertheless, a high yield of 76% was obtained even when decreasing the amount of promoter to 50% of that previously used. This result is particularly remarkable, since none of the reported thioglycoside promoters have been able to effect such activations with less than stoichiometric amounts of promoter without other additives or co-promoters.

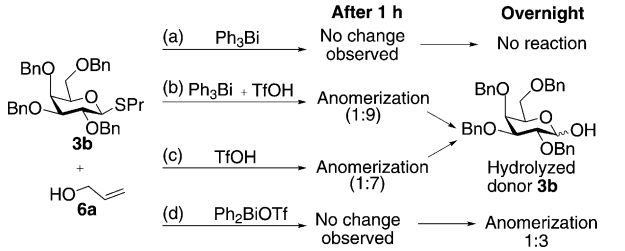
To further authenticate as well as to confirm our finding with another thioglycoside activation, we chose the glycosylation of fucosyl donor **5a** and glucosamine acceptor **6d** (Scheme 3) with only half the amount of promoter previously used. The activation was achieved in similar times (Table 1, entry 12). The donor was completely consumed and the yield was also comparable to the earlier trial. These trials show that less than a stoichiometric amount of promoter **2** (≤ 0.7 equiv) is sufficient for complete activation.

The two common oxidation states for Bi are Bi^{III} and Bi^{V}; the +3 state is to date better known. For a preliminary



Scheme 3. Glycosylation with donor **5a** and acceptor **6d**.

investigation into the activity of the Bi species, a set of control experiments (Scheme 4) was designed. For these studies, we went back to the model glycosylation of donor **3b** and acceptor **6a**, which was also selected for the loading experiments. To compare the reactivity with that observed in the previous study (Table 2), the reaction was also analyzed after one hour. At first, a trial glycosylation using only triphenyl bismuth (Scheme 4a) as a promoter was performed. However, no change in the reaction mixture or formation of product after 1 h, or even after reaction overnight, was observed. Next, a 1:2 mixture of Ph_3Bi and triflic acid was used as an activator (Scheme 4b), which resembles the composition of the promoter $Ph_3Bi(OTf)_2$. Product formation again was not observed, although a slow anomerization of the β-galactosyl donor was seen, likely owing to the presence of the strong acid, TfOH. When examining the reaction over time, the donor was hydrolyzed completely without any formation of desired product. This result led to the inference that Bi in the Bi^V state is necessary; it is not a mixture of Ph_3Bi and TfOH that performs the activation.



Scheme 4. Control studies with model glycosylation of donor **3b** and acceptor **6a**. Reaction conditions: donor, acceptor, promoter (1 equiv), a–c) CH_2Cl_2, RT, d) CH_3CN, RT.

Next, the activity of TfOH (Scheme 4c) as a promoter in thioglycoside activation was tested. The donor anomerized slightly faster, thereby indicating that previously the reactivity of TfOH was slowed perhaps in association with Ph_3Bi. The hydrolyzed donor was also found to be the major product after an overnight reaction. Finally, another Bi^{III} compound (Ph_2BiOTf)[43] was checked for its reactivity, since it resembles the promoter $Ph_3Bi(OTf)_2$. The mechanistic pathway of the activation is still unclear (NMR experiments were not definitive), yet the soft Lewis acidity of the Bi compound can be imagined to play a pivotal role. The glycosylation (Scheme 4d) was closely monitored, but no formation of our desired product was seen in 1 h. After an overnight observation, the β-galactosyl donor was noticed to be anomerizing to the α-anomer, yet still no product was detected. However, the donor was not seen to be hydrolyzed in this case. Considering the results above, we can assume that Bi^V is responsible for the activation of thioglycosides rather than Bi^{III}. Previously Bi^V was used[32] in oxidation and some addition reactions, particularly phenylation. David and Thieffry also tried to selectively oxidize carbohydrate alcohols with $Ph_3Bi(OAc)_2$, which incidentally is the first example[44] of Bi^V in carbohydrate chemistry. Nonetheless, formation of such addition products was not observed with the thioglycosyl donors or glycosyl acceptors under consideration.

In conclusion, the first demonstration of the catalytic utility of pentavalent bismuth compounds, specifically $Ph_3Bi(OTf)_2$, has been shown in the context of a thioglycoside activation reaction. This new promoter has shown distinct advantages over most current thioglycoside activators, namely high solubility, air/light stability, and a long shelf life. Most importantly, this promoter can activate thioglycosides with as little as 0.5 equivalent and at room temperatures. The scope of reactivity was studied with a wide variety of sugar donors carrying diverse protecting groups, and products were seen to form in good to excellent yields. The diastereoselectivity of the reactions seem to follow reported trends. Unexpectedly, the activation was found to be uniquely related to pentavalent and not trivalent bismuth, a fact that should spur additional work in developing the chemistry of this relatively nontoxic metal.

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