1-Benzenesulfinyl Piperidine/Trifluoromethanesulfonic Anhydride: A Potent Combination of Shelf-Stable Reagents for the Low-Temperature Conversion of Thioglycosides to Glycosyl Triflates and for the Formation of Diverse Glycosidic Linkages

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Abstract: The combination of 1-benzenesulfinyl piperidine (BSP) and trifluoromethanesulfonic anhydride (Tf_2O) forms a new, powerful, metal-free thiophile that can readily activate both armed and disarmed thioglycosides, via glycosyl triflates, in a matter of minutes at −60 °C in dichloromethane, in the presence of 2,4,6-tri-*tert*-butylpyrimidine (TTBP). The glycosyl triflates are rapidly and cleanly converted to glycosides, upon treatment with alcohols, in good yield and selectivity.

Introduction

Since their first reported use in the synthesis of a disaccharide,[1] thioglycosides have been among the most enduring and widely used of glycosyl donors. Their lasting popularity stems from a combination of relative ease of synthesis, stability, compatibility with numerous protection and deprotection steps, and orthogonality of activation with several other glycosyl donors. In short, they are readily prepared, easily handled, and very versatile.[2,3] Testaments to the current applicability of thioglycosides in synthesis include Oscarson's recent synthesis of sucrose,[4] while their central nature in the field and projected longevity is nowhere better displayed than in Ley and Wong's independent choice of this class of donors for their donor reactivity scales and programmed automated one-pot oligosaccharide syntheses.[5,6] The very stability that renders thioglycosides attractive, however, reduces their activity in glycosylation reactions. This has resulted in the continued development of a range of activating agents and conditions beginning with the original mercury and silver salt based methods, with their obvious environmental and toxicological drawbacks, and now encompassing a broad spectrum of nonmetallic thiophiles of varying stability and activity. Systems currently in broad common use include dimethyl(methylthio)sulfonium triflate (DMTST),[7] methylsulfenyl triflate (MeSOTf),[8] benzeneselenyl triflate (PhSeOTf),[9] iodonium dicollidine perchlorate (IDCP),[10] and *N*-iodosuccinimide-triflic acid (NIS/TfOH).[10,11] Kahne's sulfoxide glycosylation method[12] and related methods using glycosyl sulfimides[13] are distinct from the mainstream insofar as they require prior oxidation of the thioglycoside but, in doing so, permit the formation of highly reactive glycosylating species at low temperature. The need for ever more active yet milder activating species is continually driving the field forward with the current focus centered on iodine itself[14] and on interhalogen compounds.[15] One striking feature of the above methods, with the exception of the sulfoxide method,[16,17] is the lack of detailed mechanistic information and, in particular, of the precise nature of the actual glycosylating species.

Our contribution to the field stems from the discovery that benzenesulfenyl triflate is an extremely powerful thiophile that converts thioglycosides to glycosyl triflates in a matter of minutes at −78 °C and, thereby, enables the formation of extremely hindered glycosidic linkages that were previously the hallmark of the sulfoxide method.[18,19] Our work with benzenesulfenyl triflate differs from its previous application to the activation of glycosyl xanthates[20] and from the relatively widespread use of methylsulfenyl triflate (MeSOTf)[8,21,22] in the mode of operation, requiring premixing of the thioglycoside and

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(5) Douglas, N. L.; Ley, S. V.; Lucking, U.; Warriner, S. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 51−65.
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(10) Veenenman, G. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 275−278.
(11) Konradsson, P.; Udodong, U. E.; Fraser-Reid, B. *Tetrahedron Lett.* **1990**, *31*, 4313−4316.
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(14) Kartha, K. P. R.; Aloui, M.; Field, R. A. *Tetrahedron Lett.* **1996**, *37*, 5175−5178.
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(18) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435−436.
(19) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321−8348.
(20) Martichonok, V.; Whitesides, G. M. *J. Org. Chem.* **1996**, *61*, 1702−1706.
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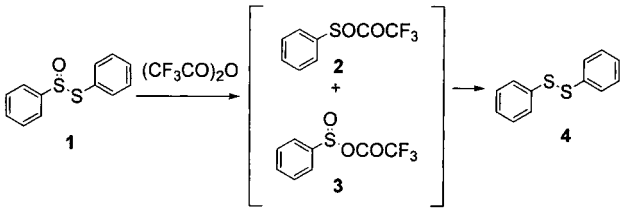
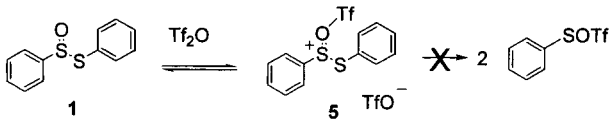
Scheme 1



Scheme 2



the sulfenyl triflate.[18,19] This enables formation of the extremely reactive glycosyl triflate and in doing so provides valuable mechanistic insight of the type that is necessarily lacking from methods involving activation of the donor in the presence of the activator.

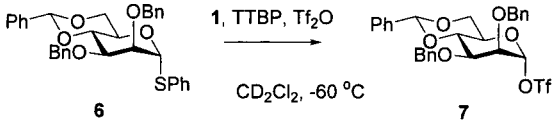
The main drawback with benzenesulfenyl triflate is its instability and the need to prepare it in situ from benzenesulfenyl chloride and silver triflate,[20,23] neither of which are ideal, with the former being both obnoxious and itself unstable and the latter light and water sensitive. For this reason a primary goal of our laboratory for several years has been the development of an alternative and more practical synthesis of benzenesulfenyl triflate or of an equivalent thereof capable of converting thioglycosides to glycosyl triflates at low temperature. Our first success was the combination of *S*-aryl arenethiosulfinates and trifluoromethanesulfonic anhydride which, while demonstrably not producing benzenesulfenyl triflate, did bring about glycosylation with armed[24,25] thioglycosides rapidly and in high yield at −60 °C.[26] We now report our continued work in this direction that has resulted in the development of an *S*-aryl sulfinamide as a shelf-stable reagent capable, when used in only minimal excess and in conjunction with trifluoromethanesulfonic anhydride, of converting thioglycosides, armed and disarmed,[24,25] to glycosyl triflates and so to glycosidic bonds cleanly and in high yield.

Results and Discussion

Our initial investigation of the thiosulfinates was based on earlier work from the Oae group in which it was established that thiosulfinate **1** reacts with trifluoroacetic anhydride at −20 °C to give a complex mixture of products, thought to contain the sulfenyl carboxylate **2** and sulfinyl carboxylate **3**, and resulting ultimately in the formation of diphenyl disulfide (**4**) (Scheme 1).[27]

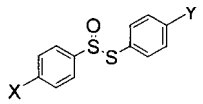
We reasoned that the more reactive Tf_2O would react rapidly with **1** at lower temperatures to provide an initial salt (**5**), which would further react with the formation of two molecules of benzenesulfenyl triflate (Scheme 2). Low-temperature ^1H and ^{19}F NMR spectra, however, revealed that this was not the case. Indeed conversion of the thiosulfinate **1** at −60 °C was low and there was no evidence for the formation of benzenesulfenyl triflate in the ^{19}F NMR spectrum which contained only two resonances (δ 4.26 and −3.07) corresponding to unreacted triflic anhydride and the triflate anion.[26] At higher temperatures decomposition set in.[26]

Scheme 3



A further low-temperature NMR experiment, however, revealed that the combination of **1** and Tf_2O and DTBMP or TTBP converted a thiomannoside **6** to the mannosyl triflate **7** (Scheme 3). We reasoned that the reaction of **1** and triflic anhydride is an equilibrium that favors the starting materials over the salt **5**. We further reasoned (i) that salt **5** does not proceed to give benzenesulfenyl triflate (Scheme 2) and (ii) that salt **5** was a potent thiophile in its own respect, capable of converting thioglycosides to glycosyl triflates which, in turn, pulls the initial equilibrium in the forward direction.

Based on this reasoning we investigated two further thiosulfinates **8** and **9** with a view to displacing the equilibrium in the forward direction and, so, of providing a more potent reagent.



8, MPBT: X = H, Y = OMe
9: X = Y = OMe

Ultimately, **8** was selected for development and was successfully employed, in conjunction with triflic anhydride, in a number of glycosylation reactions.[26] Although it represented a significant step in the right direction, the MPBT/Tf_2O combination suffered several shortcomings. First, unlike benzenesulfenyl triflate itself, it did not activate disarmed thioglycosides. Second, to achieve high conversion of the thioglycoside several equivalents of the reagent and triflic anhydride were required. Finally, isolation of the coupled product was sometimes tedious owing to the formation of several undetermined byproducts. We reasoned that a more potent reagent would result if the key equilibrium could be tipped further in favor of the thiophilic salt or, indeed, by encouraging fragmentation of the initial salt to benzenesulfenyl triflate. On this basis we have now prepared and investigated two sulfinate esters (**10**, **11**) and a sulfinamide (**12**) and find the latter to be an ideal reagent for the activation of both armed and disarmed thioglycosides.

The two sulfinate esters (**10**, **11**) were prepared in the hope that the adducts would undergo fragmentation to benzenesulfenyl triflate, and acetone and triflic acid, or formaldehyde and TMSOTf, respectively. In reality neither represented any improvement over MPBT, with low-temperature NMR experiments showing incomplete conversion of the sulfinate in the presence of Tf_2O alone and the need for several equivalents of Tf_2O to bring about complete activation of the standard thioglycoside (Table 1). Clearly, a more nucleophilic sulfinate was required and we therefore turned to the sulfinamides and, in particular, **12**. This substance was very readily prepared and isolated on a multigram scale. It is white, crystalline, readily dried, and appears to be completely shelf-stable under ambient laboratory conditions. Moreover, as demonstrated by the standard low-temperature NMR experiments, it reacts fully with triflic anhydride and converts the standard thioglycoside to the

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(26) Crich, D.; Smith, M. *Org. Lett.* **2000**, 4067−4069.
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Table 1. The Quantity of Tf_2O Required to Fully Activate the Thioglycoside **6** to Its Corresponding Triflate **7**

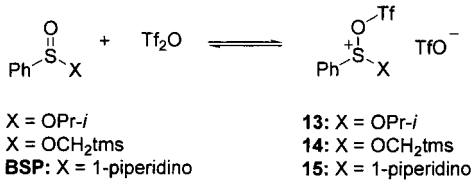
entry	coupling reagent	Tf_2O (mol equiv)
1	**1**	2
2	**8**	1.5
3	**9**	1.5
4	**10**	3
5	**11**	2
6	**12**	1

glycosyl triflate[16,19] in a matter of minutes at −60 °C more or less stoichiometrically (Table 1).

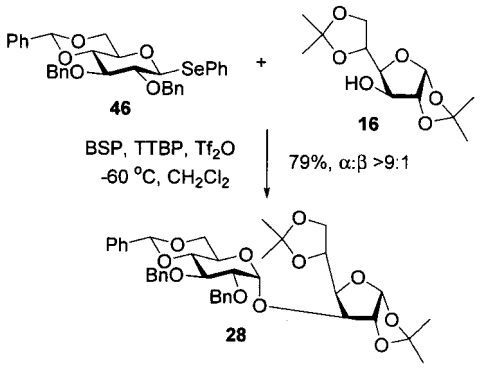
On the basis of the NMR experiments, a protocol was developed and optimized for glycosidic bond formation. This simply involved cooling a 1:1 mixture of the thioglycoside and BSP (**12**) to −60 °C in dichloromethane in the presence of the hindered base 2,4,6-tri-*tert*-butylpyrimidine (TTBP),[28] treatment with 1.1 equiv of triflic anhydride, and, after 5 min, addition of the acceptor alcohol, warming to room temperature, and work up. A series of disaccharides, selected to illustrate the wide range of coupling types possible, were prepared in this manner with the results presented in Table 2. Highlights include β-selective mannosylations (Entries 1−3),[18,19] α-selective glucosylations (Entries 6 and 7),[29] β-selective galactosylation with nonparticipating groups through the use of propionitrile as solvent[12] and the nitrile effect (Entry 10),[30] as well as such relatively standard linkages such as β-glucosides, β-galactosides, β-aminoglucosides, and β-xylosides (Entries 4, 5, 8, 9, 11, and 12) achieved through neighboring group participation, as well as similarly directed α-rhamnosides (Entries 13). With respect to neighboring group participation it is noteworthy that the perbenzoylated glucosyl and xylosyl donors **23** and **38**, as well as the peracetylated rhamnosyl donor **40**, gave high yields of ortho esters (Table 3) when the coupling was conducted under the standard conditions in the presence of TTBP as base. The saccharides from these donors (Table 2, entries 4, 5, 12, and 13) were obtained directly in high yield by the simple expedient of omitting the base.[31] In contrast the perbenzoylated galactosyl donor **30** provided the glycosides directly even in the presence of TTBP (Table 2, entries 8 and 9). TTBP is a very mild base (pK_a 1.02 in 50% aqueous ethanol)[32] and it is possible that its triflate salt is sufficiently acidic to rearrange the kinetic galactosyl ortho esters. This explanation of course assumes that galactosyl ortho esters are somewhat more reactive than comparable glucosyl ortho esters just as standard galactosyl donors are more reactive than their glucosyl counterparts.[33]

In general we have worked with phenyl thioglycosides as donors but the example of Table 2, entry 3 shows that this was a purely arbitrary choice with ethyl thioglycosides working equally well. With a view to further broadening the scope of our reaction we have also determined that a selenoglycoside **46**, such as popularized by Pinto and co-workers,[34,35] is activated by the standard BSP/TTBP/Tf_2O reagent combination (Scheme 5). As expected on the basis of our earlier work with 2,3-di-*O*-benyl-4,6-*O*-benzylidene protected glucosyl donors,[29] this reaction was extremely α-selective. Although we have not explored such possibilities at the present time, the probable differential reactivity of thioglycosides and selenoglycosides to the BSP/Tf_2O reagent combination should open up the way to one-pot oligosaccharide syntheses.

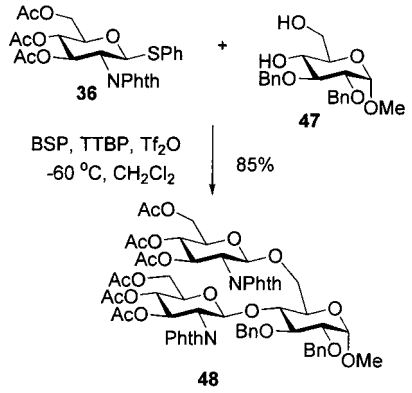
Scheme 4



Scheme 5



Scheme 6



As a final demonstration of the power of the new reagent combination, we turned to the double glycosylation of carbohydrate diols. A first example (Scheme 6) included the coupling of a 4,6-glucopyranosyl diol **47** to the phthalimide protected glucosamine donor **36** and resulted in the isolation of the trisaccharide **48** in 85% yield.

A second example included the coupling of a mannopyranosyl diol **50** to a highly α-selective mannosyl donor **49**[36] resulting in the formation of the mannotriose **51** (Scheme 7). This particular example constitutes a synthesis of a protected version of the trisaccharide substrate of the mannose binding protein concanavalin A.[37]

As is evident from the examples of Table 2 and Schemes 5−7 the BSP/Tf_2O combination is considerably more powerful than the original MPBT/Tf_2O combination. It activates the full range of armed and disarmed glycosyl donors and does so under a standard set of conditions, except when ortho ester formation

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(29) Crich, D.; Cai, W. *J. Org. Chem.* **1999**, *64*, 4926−4930.
(30) Schmidt, R. R.; Behrendt, M.; Toepfer, A. *Synlett* **1990**, 694−696.
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(33) Miljkovic, M.; Yeagley, D.; Deslongchamps, P.; Dory, Y. L. *J. Org. Chem.* **1997**, *62*, 7597−7604.
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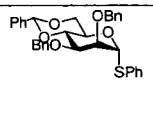
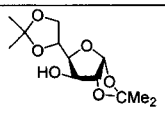
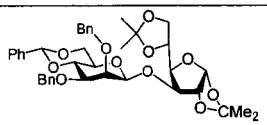
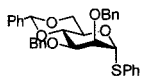
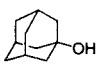
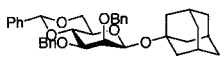
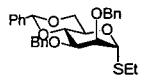
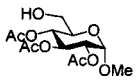
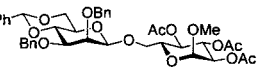
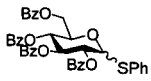
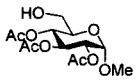
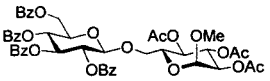
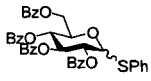
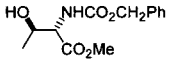
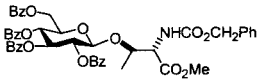
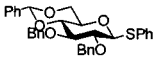
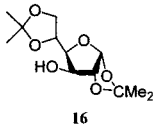
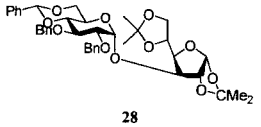
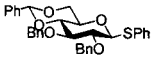
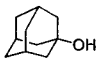
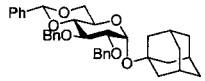
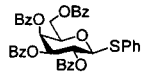
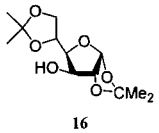
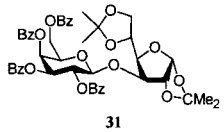
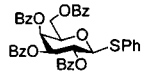
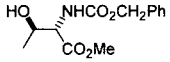
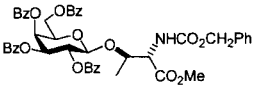
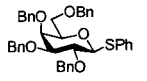
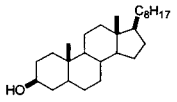
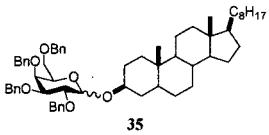
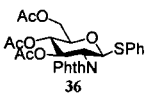
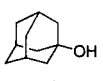
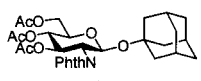
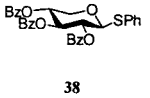
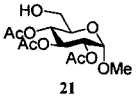
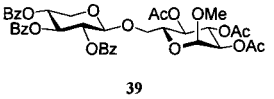
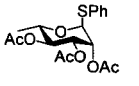
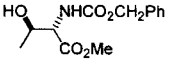
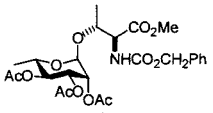
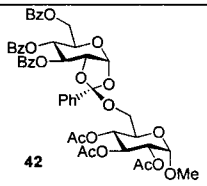
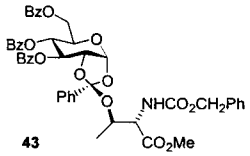
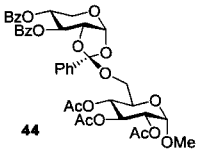
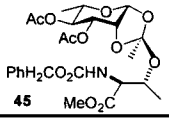
(35) Metha, S.; Pinto, B. M. In *Modern Methods in Carbohydrate Synthesis*; Kahn, S. H., O'Neill, R. A., Eds.; Harwood Academic: Amsterdam, The Netherlands, 1996; pp 107−129.
(36) Crich, D.; Cai, W.; Dai, Z. *J. Org. Chem.* **2000**, *65*, 1291−1297.
(37) Naismith, J. H.; Field, R. A. *J. Biol. Chem.* **1996**, *271*, 972−976.

Table 2. Coupling Reactions of Thioglycosides Using 1-Benzenesulfinyl Piperidine (BSP)/Tf_2O as Activator[a]

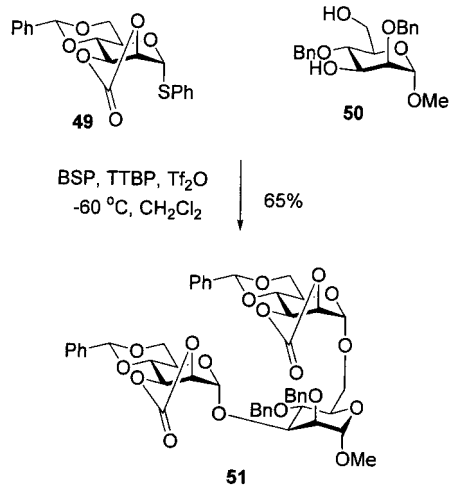
	Donor	Acceptor	Base	Product	Isolated Yield (%)	Anomeric Ratio (α:β)
1	 **6**	 **16**	TTBP	 **17**	77	1:>9[b]
2	 **6**	 **18**	TTBP	 **19**	88	1:>9[b]
3	 **20**	 **21**	TTBP	 **22**	73	1:>9[b]
4	 **23**	 **21**	—	 **24**	85	1:>9[b]
5	 **23**	 **25**	—	 **26**	77	1:>9[b]
6	 **27**	 **16**	TTBP	 **28**	74	>9:1[b]
7	 **27**	 **18**	TTBP	 **29**	72	>9:1[b]
8	 **30**	 **16**	TTBP	 **31**	72	1:>9[b]
9	 **30**	 **25**	TTBP	 **32**	72	1:>9[b]
10	 **33**	 **34**	TTBP TTBP	 **35**	78 73	1:1 1:4[c]
11	 **36**	 **18**	TTBP	 **37**	74	1:>9[b]
12	 **38**	 **21**	—	 **39**	80	1:>9[b]
13	 **40**	 **25**	—	 **41**	78	>9:1[b]

[a] All reactions, unless stated, were conducted in dichloromethane at −60 °C. [b] Anomeric ratios of 1:>9 and >9:1 are conservative minima; in all such cases the minor isomer was not detected in the NMR spectra of the reaction mixtures. [c] Reaction performed in propionitrile at −60 °C in the presence of TTBP.

Table 3. Formation of Ortho Esters in the Presence of TTBP

Donor	Acceptor	Product	Isolated Yield (%)
23	**21**	 **42**	80
23	**25**	 **43**	71
38	**21**	 **44**	70
40	**25**	 **45**	77

Scheme 7



is a problem and the base has to be omitted. In this matter it differs from most other methods of thioglycoside activation, indeed from most glycosylations methods, which, with few exceptions,[38] require alternative conditions for arming and disarming protecting groups. Such generalized reaction conditions should obviously facilitate use of the method by nonspecialists and can only be of benefit in the eventual development of fully automated oligosaccharide synthesizers.[39] It is also pertinent to draw attention to the much facilitated purification with BSP glycosylations than with the original MPBT ones. In effect, fewer byproducts are generated and, because less reagent is required, separation of these is considerably easier. In this chemistry we have employed 2,4,6-tri-*tert*-butylpyrimidine (TTBP) as the hindered, nonnucleophilic base in preference to the more common 2,6-di-*tert*-butylated pyridines. This is because TTBP is a white crystalline solid that is not hygroscopic and not readily sublimed on drying under vacuum.[28] As such it possesses numerous advantages over the analogous hindered pyridines. In addition it is considerably easier and more economical to prepare on a large scale.[28,40] Nevertheless, its more crystalline nature renders it somewhat insoluble in dichloromethane at −78 °C, which explains the choice of −60 °C as the reaction temperature for the new methodology. We see no reason the 2,6-di-*tert*-butylated pyridines should not be employed in this chemistry if the experimentalist prefers or if lower temperatures are required.

Finally, it is appropriate to compare and contrast the BSP/Tf_2O method with Gin's excellent dehydrative glycosylation.[41,42] The two methods obviously have close parallels insofar as both take readily accessible, stable glycosyl donors and couple them to acceptors by means of a combination of triflic anhydride and a nucleophilic sulfur IV reagent. Simple protected thioglycosides and pyranoses are both readily synthesized in two steps from the sugars themselves and there appears to be no substantial difference between the two methods at the level of donor preparation. The two methods diverge in the nature of the actual glycosylating species with the present chemistry involving intermediate glycosyl triflates, which have been conclusively excluded in the case of the dehydrative method. It appears that the two methods should be largely interchangeable with the BSP/Tf_2O definitely having the edge for the preparation of difficult linkages such as the β-mannosides (Table 2, entries 1−3).

Experimental Section

Preparation of 1-Benzenesulfinyl Piperidine 12. A solution of PhSOCl (58.0 g, 0.365 mol) in diethyl ether (200 mL) was slowly added to a cooled solution (5 °C) of piperidine (72 mL, 0.73 mol) in diethyl ether (200 mL). The reaction mixture was stirred at room temperature for 1 h, filtered, and then concentrated under reduced pressure. The solid residue was triturated with hexanes to give the title product as a white crystalline solid (53.4 g, 70%): mp 84−85 °C (lit.[43] mp 83−84 °C); ^{1}H NMR δ 1.41−1.53 (6 H, m), 2.83−2.87 and 2.89−3.04 (each 2 H, m), 7.37−7.42 (3 H, m), 7.56−7.59 (2 H, m); ^{13}C NMR δ 23.8, 26.1, 46.9, 126.1, 128.7, 130.6 and 143.3; MS (EI) *m*/*z* 210 (MH^+).

General Experimental Protocol for the Preparation of Glycosides. To a stirred solution containing the thioglycoside (0.185 mmol), 1-benzenesulfinyl piperidine (BSP **12**; 0.185 mmol), TTBP (0.370 mmol), and activated 3 Å powdered sieves in dichloromethane (5 mL), at −60 °C under an argon atmosphere, was added Tf_2O (0.203 mmol). After 5 min, a solution of the glycosyl acceptor (0.277 mmol) in dichloromethane (2 mL) was added. The reaction mixture was stirred for 2 min at −60 °C and then warmed to room temperature, filtered, washed with saturated aqueous $NaHCO_3$, followed by brine, dried ($MgSO_4$), and concentrated under reduced pressure. The glycosides were isolated by chromatography on silica gel.

Preparation of Methyl 2,4-Di-*O*-benzyl-3-*O*-(2,3-*O*-carbonyl-4,6-*O*-benzylidene-α-D-mannopyranosyl)-6-*O*-(2,3-*O*-carbonyl-4,6-*O*-benzylidene-α-D-mannopyranosyl)-α-D-mannoside (51). To a stirred solution containing the thioglycoside **49**[36] (0.140 g, 0.36 mmol), BSP **12** (0.080 g, 0.38 mmol), TTBP (0.164 g, 0.66 mmol), and activated 3 Å powdered sieves in dichloromethane (5 mL), at −60 °C under an argon atmosphere, was added Tf_2O (0.064 mL, 0.39 mmol). After 5 min, a solution of the glycosyl acceptor **50**[44] (0.062 g, 0.165 mmol) in dichloromethane (2 mL) was added. The reaction mixture was warmed to room temperature, filtered, washed with saturated aqueous $NaHCO_3$, followed by brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel [ethyl acetate:hexanes (1:1)] to give the title product as a clear viscous

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(42) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269−4279.
(43) Maricich, T. J.; Angeletakis, C. N. *J. Org. Chem.* **1984**, *49*, 1931−1934.
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oil (0.10 g, 65%). $[\alpha]^{20}_{D}$ +11.7 (*c* 0.8); ^{1}H NMR (C_6D_6) δ 3.13 (3 H, s), 3.37 and 3.44 (each 1 H, t, J = 10.5 Hz), 3.52 (1 H, dd, J = 8 and 10 Hz), 3.58−3.62 (2 H, m), 3.65−3.68 (2 H, m), 3.73−3.78 (2 H, m), 3.87 (1 H, dt, J = 5 and 10 Hz), 4.06 (1 H, d, J = 7 Hz), 4.10 (1 H, dd, J = 5 and 10 Hz), 4.17 (1 H, q, J 10 Hz), 4.20 (1 H, dd, J = 5 and 10 Hz), 4.25−4.28 (2 H, m), 4.33 (1 H, d, J = 11.5 Hz), 4.39 and 4.43 (each 1 H, t, J = 7.5 Hz), 4.50 (1 H, d, J = 11.5 Hz), 4.63 (1 H, d, J = 11 Hz), 4.66 (1 H, d, J = 1.5 Hz), 4.70 (1 H, d, J = 11 Hz), 5.11 and 5.15 (each 1 H, s), 5.43 and 5.49 (each 1 H, s), 7.24−7.63 (20 H, m); ^{13}C NMR δ 55.6, 60.0, 60.3, 66.9, 68.9, 69.0, 72.3, 73., 75.1, 75.4, 75.5, 75.8, 76.8, 77.6, 78.2, 78.6, 78.9, 79.1, 97.0, 98.2, 98.3, 102.3, 102.4, 126.5, 126.6, 128.4, 128.8, 128.9, 129.1, 129.2, 129.8, 136.8, 136.9, 137.7, 137.8; HRMS calcd for $C_{49}H_{50}O_{18}Na$ (MNa^+): 949.2895. Found: 949.2950.

Acknowledgment. We thank the NIH (GM 57335) for support of this work.

Supporting Information Available: Full experimental details, characterization data, and ^{1}H NMR spectra for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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