## Direct Oxidative Glycosylations with Glycal Donors

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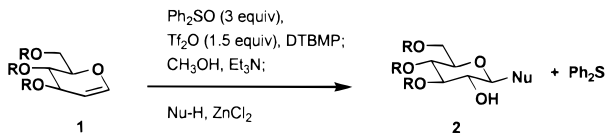
The development of new methods for glycosidic bond formation is a major focus in carbohydrate synthesis due to the many roles of complex oligosaccharides and glycoconjugates in biology.[1] Many methods have been developed for the anomeric activation of carbohydrates for coupling reactions;[2] however, the use of glycal substrates in oligosaccharide synthesis is particularly attractive in that glycosidic bond formation as well as C(2)-functionalization of the carbohydrate donor is achieved in the process.[3] Traditionally, procedures for glycosylation with concomitant C(2)-hydroxylation of glycal donors have involved (1) epoxidation of the glycal, followed by (2) acid-mediated oxirane ring-opening of the 1,2-anhydrosugar in the presence of a nucleophilic glycosyl acceptor. This strategy has been elegantly refined over the years by Danishefsky and co-workers, employing dimethyl dioxirane as the glycal oxidant.[3a,4] We now report a method for oxidative glycosylation with glycal donors, employing the reagent combination of triflic anhydride ($Tf_2O$) and diphenyl sulfoxide.[5,6] The method involves a new process for glycal activation and allows for the diastereoselective construction of C(2)-hydroxy-glucopyranosides from protected glucal substrates in a one-pot procedure.

This oxidative glycosidic coupling is illustrated in Scheme 1, employing a tri-*O*-protected-D-glucal **1** as a typical glycosyl donor.

**Scheme 1**




In this procedure, triflic anhydride (1.5 equiv) is added to a solution of glucal **1** (1 equiv), diphenyl sulfoxide (3 equiv), and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, 3−4 equiv)[7] in dichloromethane at −78 °C. Following an initial activation period of 1 h at −40 °C, anhydrous methyl alcohol (1 equiv) and triethylamine (3 equiv) are introduced. The reaction is allowed to proceed at 23 °C for 1 h, at which time the glycosyl acceptor (Nu-H, 2−3 equiv) and a Lewis acid ($ZnCl_2$, 1−2 equiv) are added to afford the C(2)-hydroxy-$\beta$-D-glucopyranoside product **2**.

The above-mentioned protocol outlines novel methodology for enol ether oxidation within the context of glycosidic bond formation.[8] In these reactions, an excess of the sulfoxide reagent (2:1 ratio, $Ph_2SO/Tf_2O$) is required for the coupling to proceed efficiently;[9] moreover, diphenyl sulfide is formed in significant amounts (70−80% yield) as a reaction byproduct. On the basis of these preliminary observations, it is likely that the oxidative coupling initially proceeds through oxygen transfer from diphenyl sulfoxide to the glycal donor to generate a transient 1,2-anhydropyranoside intermediate in situ.[10] This hypothesis is also in accord with the requirement of a Lewis acid to effect glycosidic bond formation in the final stage of the reaction.[3a]

To illustrate the scope of this glycosylation method, a number of glycosyl acceptors were employed in couplings with 3,4,6-tri-*O*-benzyl-D-glucal (**3**, Table 1). In these experiments, primary[11] and secondary alcohols (entries 1−3) as well as amino-glycosyl acceptors (e.g., benzylamine, entry 4) are glycosylated in good yields. In addition, one-pot glycosylation of hindered hydroxyl nucleophiles such as *tert*-butyl alcohol and methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**5**)[12] can be accomplished (entries 5 and 6) to afford the corresponding C(2)-hydroxy-glucopyranoside adducts. It is worth noting that the glycosylation of the sterically shielded carbohydrate hydroxyl in **5** (entry 6) could not be accomplished with $ZnCl_2$ as the Lewis acid in the final stage of the coupling. Instead, a stronger Lewis acid, $Sc(OTf)_3$ (0.3 equiv),[13] was required, leading to the selective formation of the

(1) (a) *Synthetic Oligosaccharides. Indispensable Probes for the Life Sciences*; Kovac, P., Ed.; ACS Symposium Series 560; American Chemical Society: Washington, DC, 1994. (b) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683.

(2) (a) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212. (b) Fugedi, P.; Garegg, P. J.; Lohn, H.; Norberg, T. *Glycoconjugate J.* **1987**, *4*, 97. (c) Sinay, P. *Pure Appl. Chem.* **1991**, *63*, 519. (d) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503. (e) Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095. (f) *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997, Chapters 12−22.

(3) Review (2-hydroxy-, 2-halo-, and 2-aza-glycosides): (a) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380. 2-Aza-glycosides: (b) Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1979**, *57*, 1244. (c) Leblanc, Y.; Fitzsimmons, B. J.; Springer, J. P.; Rokach, J. *J. Am. Chem. Soc.* **1989**, *111*, 2995. (d) Czernecki, S.; Ayadi, E. *Can. J. Chem.* **1995**, *73*, 343. (e) Rubinstenn, G.; Esnault, J.; Mallet, J.-M.; Sinay, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1327. (f) Du Bois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 3179. 2-Halo-glycosides: (g) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2190. (h) Tatsuta, K.; Fujimoto, K.; Kinoshita, M.; Umezawa, S. *Carbohydr. Res.* **1977**, *54*, 85. (i) Thiem, J.; Karl, H.; Schwentner, J. *Synthesis* **1978**, 696. (j) Burkart, M. D.; Zhang, Z.; Hung, S.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **1997**, *119*, 11743. 2-Thio- and 2-seleno-glycosides: (k) Jaurand, G.; Beau, J.-M.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1981**, 572. (l) Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 2723. (m) Preuss, R.; Schmidt, R. R. *Synthesis* **1988**, 694. (n) Perez, M.; Beau, J.-M. *Tetrahedron Lett.* **1989**, *30*, 75. (o) Grewal, G.; Kaila, N.; Franck, R. W. *J. Org. Chem.* **1992**, *57*, 2084. (p) Roush, W. R.; Sebesta, D. P.; James, R. A. *Tetrahedron* **1997**, *53*, 8837. 2-*C*-glycosides: (q) Linker, T.; Sommermann, T.; Kahlenberg, F. *J. Am. Chem. Soc.* **1997**, *119*, 9377.

(4) The reagent combination of *m*-chloroperoxybenzoic acid and potassium fluoride has also been shown to be effective in glycal epoxidation: Bellucci, G.; Catelani, G.; Chiappe, C.; D'Andrea, F. *Tetrahedron Lett.* **1994**, *35*, 8433.

(5) Garcia, B. A.; Poole, J. L.; Gin, D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597.

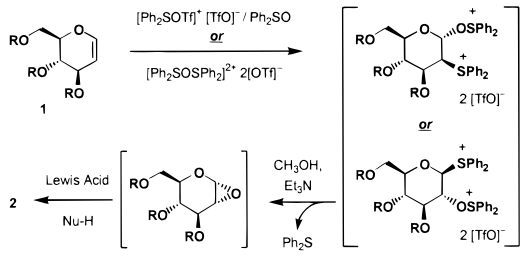
(6) Di*methyl*sulfide bis(triflate) has been employed for the functionalization of alkenes to form mixtures of vinylic and allylic sulfides: (a) Nenajdenko, V. G.; Vertelezkij, P. V.; Gridnev, I. D.; Shevchenko, N. E.; Balenkova, E. S. *Tetrahedron* **1997**, *53*, 8173. For other uses of di*methyl*sulfide bis(triflate), see: (b) Hendrickson, J. B.; Schwartzman, S. M. *Tetrahedron Lett.* **1975**, 273. (c) Coburn, M. D.; Hayden, H. H. *Synthesis* **1986**, 490. (d) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202. For the use of triflic anhydride in the activation of glycosyl sulfoxide donors, see: (e) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881. (f) Yan, L.; Kahne, D. *J. Am. Chem. Soc.* **1996**, *118*, 9239.

(7) The acid scavenger is introduced to neutralize trace amounts of triflic acid that can lead to decomposition of the glucal starting material.

(8) Investigations into the use of this oxidation protocol on acyclic enol ethers are currently underway.

(9) Glycosylations performed with a 1:1 ratio of $Ph_2SO/Tf_2O$ (1 equiv each) led to incomplete consumption of the glucal starting material, giving low yields (<20%) of C(2)-hydroxy-glycopyranoside products.

(10) A likely reaction pathway for the oxidative coupling involves enol ether activation with the triflated sulfoxide, followed by oxygen transfer to the pyranose ring from the excess sulfoxide reagent.




(11) For the synthesis of **4**, see: Jiang, L.; Chan, T.-H. *Tetrahedron Lett.* **1998**, *39*, 355.

(12) DeNinno, M. P.; Etienne, J. B.; Duplantier, K. C. *Tetrahedron Lett.* **1995**, *36*, 669.

(13) (a) Crotti, P.; Di Bussolo, V.; Favero, L.; Pineschi, M.; Pasero, M. *J. Org. Chem.* **1996**, *61*, 9548. (b) Crotti, P.; Di Bussolo, V.; Favero, L.; Minutolo, F.; Pineschi, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1347.

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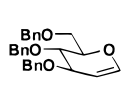
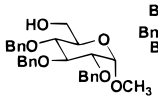
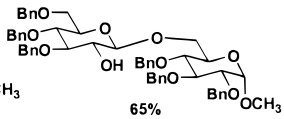
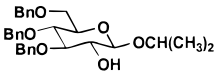
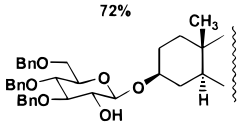
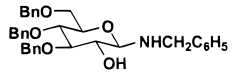
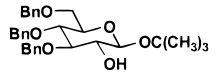
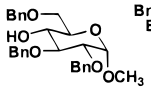
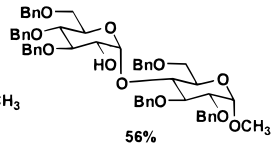
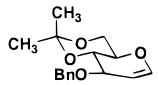
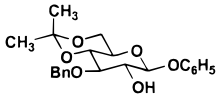
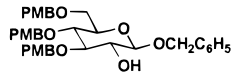
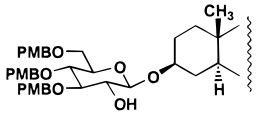
**Table 1.** Direct Oxidative Glycosylations

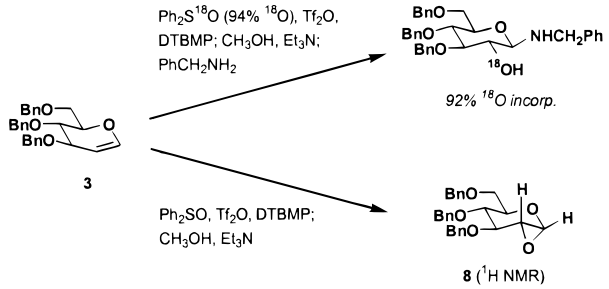
| Entry | Donor | Acceptor[a] | Product |
|---|---|---|---|
| (1) |  **3** |  **4** |  65% |
| (2) | | $(CH_3)_2CHOH$ |  72% |
| (3) | | Dihydro-cholesterol |  78% |
| (4)[b] | | $C_6H_5CH_2NH_2$ |  71% |
| (5) | | $(CH_3)_3COH$ |  68% |
| (6)[c] | |  **5** |  56% |
| (7) |  **6** |  |  61% |
| (8) |  **7** | $C_6H_5CH_2OH$ |  63% |
| (9) | | Dihydro-cholesterol |  61% |

[a] 2 to 3 equiv of glycosyl acceptor. [b] Lewis acid was not required for coupling to proceed. [c] The Lewis acid $Sc(OTf)_3$ (30 mol %) was required for the coupling to proceed.

corresponding α-linked disaccharide.[14,15] The latter entries in the table demonstrate that this glycosylation protocol is not exclusively compatible with glucal **3**. For example, 3-*O*-benzyl-4,6-di-*O*-isopropylidene-D-glucal (**6**)[16] was coupled with phenol to yield phenyl 3-*O*-benzyl-4,6-di-*O*-isopropylidene-*β*-D-glucopyranoside (entry 7) with complete stereoselectivity. Furthermore, both benzyl alcohol and dihydrocholesterol were glycosylated with tri-*O*-*p*-methoxybenzyl-D-glucal (**7**)[17] to afford the corresponding 2-hydroxy-*β*-D-glucopyranosides (entries 8 and 9).

(14) Epoxidation of **3** by established methods (see ref 4) followed by treatment with **5** and 0.3 equiv of $Sc(OTf)_3$ led to the generation of the α-linked 1,4-disaccharide as the principle disaccharide product, albeit in diminished yields.

**Scheme 2**




To probe the mechanism of this transformation, an $^{18}O$-labeling study was conducted to determine whether C(2)-hydroxylation of the glycal donor occurs via oxygen transfer from the sulfoxide reagent.[10] This indeed was verified (Scheme 2) when the $^{18}O$-labeled analogue of diphenyl sulfoxide was synthesized ($Ph_2S^{18}O$, 94% $^{18}O$ incorp.)[18] and employed in a coupling reaction with glucal **3** and a non-hydroxy-glycosyl acceptor (e.g., benzylamine). In this case, near quantitative transfer of $^{18}O$ from the sulfoxide reagent to the product glycopyranoside (92% $^{18}O$ incorp.)[19] was observed. Additional investigations focused on the detection of the proposed 1,2-anhydropyranoside intermediate which presumably is formed during the course of the reaction. This hypothesis was also confirmed (Scheme 2) as the 1,2-anhydropyranoside **8** was observed as the principle carbohydrate intermediate by $^1H$ NMR analysis upon activation of tri-*O*-benzyl-D-glucal (**3**) using the above-mentioned protocol.[20] Efforts are currently underway to further investigate the mechanistic details of the process, as well as to elucidate the origin of the oxidation/glycosylation stereoselectivity.

In summary, a new method employing the reagent combination of triflic anhydride and diphenyl sulfoxide for glycosylation with glucal donors is described. Key features of the coupling reaction include (1) a novel method for glycal oxidation/activation via oxygen transfer from the sulfoxide reagent to the C(2)-position of the product glycoside and (2) the one-pot diastereoselective synthesis of C(2)-hydroxy-glucopyranosides from glucal substrates.

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**Supporting Information Available:** Experimental details and spectral/analytical data for the glycosylation products (13 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(15) Anomeric selectivity in the opening of 1,2-anhydropyranosides has been found to be dependent on the nature of the Lewis acid (see: Evans, D. A.; Trotter, B. W.; Côté, B. *Tetrahedron Lett.* **1998**, *39*, 1709). For example, when $Sc(OTf)_3$ (0.3 equiv) was employed instead of $ZnCl_2$ in our oxidative glycosylation of isopropyl alcohol with tri-*O*-benzyl-D-glucal, a 3.5:1 α:*β* anomeric ratio ($^1H$ NMR) of the isopropyl glycoside was obtained. In addition, treatment of isopropyl-3,4,6-tri-*O*-benzyl-*β*-D-glucopyranoside with $Sc(OTf)_3$ (0.3 equiv) in the presence of $Ph_2SO$, $Ph_2S$, and DTBMP (1 equiv each) did not lead to anomeric epimerization after 24 h at 23 °C.

(16) Kjølberg, O.; Neumann, K. *Acta Chem. Scand.* **1993**, *47*, 843.

(17) Prepared from the treatment of D-glucal with sodium hydride and *p*-methoxybenzyl chloride.

(18) Prepared by the oxidation of $Ph_2S$ with *N*-chlorosuccinimide, followed by the addition of 98% $^{18}OH_2$.

(19) Determined by $FAB^+$ mass spectrometry.

(20) Following the initial activation of **3** as described in our oxidative coupling procedure ($Ph_2SO$, $Tf_2O$, DTBMP, $CH_3OH$, $Et_3N$), $^1H$ NMR data (see Supporting Information) of the reaction mixture were acquired and then compared to that of a sample of the 1,2-anhydropyranoside **8** that was prepared independently (see ref 4).