C2-Acyloxyglycosylation with Glycal Donors

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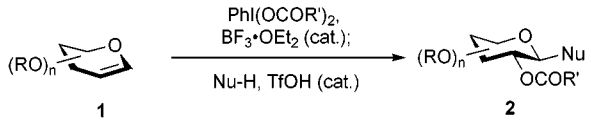
Glycals have proven to be extremely useful carbohydrate building blocks in the preparation of biologically important oligosaccharides and glycoconjugates.[1] This is a direct result of the versatile reactivity of the glycal enol ether functionality, which allows for the introduction of various functionalities at the C2-position as well as formation of the glycosidic bond at C1. In this context, a variety of substituents have been introduced at the C2-position of glycals, including hydroxyl,[2] nitrogen,[3] halides,[4] sulfur,[5] selenium,[5] and carbon functionalities.[6] Among these, the introduction of the hydroxyl group at C2 in combination with glycosidic bond formation has been highlighted in numerous elegant syntheses of complex carbohydrates.[7] In this regard, the strategy involves the epoxidation of glycal substrates to generate 1,2-anhydropyranosides that serve as effective glycosyl donors via epoxide ring opening. This strategy serves to install an unprotected hydroxyl substituent at the C2-position of the glycal donor, and thus is ideal for the preparation of C2-branched carbohydrate residues.

However, application of this glycal assembly strategy to the construction of non-C2-branched oligosaccharides usually necessitates an additional C2-*O*-protection step prior to subsequent anomeric bond formations.[7] We now report a new method for oxidative glycosylation that effects the stereoselective installation of a carboxylate functionality onto the C2-position of glycal donors with concomitant glycosidic bond formation. The novel method allows for the preparation of C2-acyloxy glycosides directly from glycal donors in a one-pot procedure employing readily available I^{III} reagents.

Scheme 1



Polycoordinate iodine reagents are well-known to engage in a variety of oxidative transformations with electron-rich π-systems;[8] however, reports on reactions with I^{III} reagents on glycal substrates have been comparatively limited.[9,10] Transformations involving glycal oxidation by I^{III} reagents have included selective C3-*O*-oxidation[11] as well as installation of several heteroatom substituents, such as halides,[12] and azides[13] at the C2-position of glycals; yet, the efficient installation of a protected oxygen substituent onto the C2-position of glycals has remained elusive.[14] In our efforts to explore new approaches to glycal assembly for the synthesis of complex carbohydrates, we have developed a simple C2-acyloxyglycosylation procedure (Scheme 1) in which I^{III} reagents, in combination with the appropriate Lewis acid catalyst, serve as ideal glycal oxidants. In this procedure, a solution of the glycal donor (**1**, 1.3 equiv) and a (diacyloxyiodo)benzene reagent (1.3 equiv) in dichloromethane at −45 °C is treated with $BF_3{\cdot}OEt_2$ (0.26 equiv). After allowing the reaction to warm to −25 °C, the glycosyl acceptor (Nu-H, 1 equiv) and TfOH (0.26 equiv) are introduced at −45 °C to provide the 1,2-*trans*-disubstituted C2-acyloxylglycoside **2**.

A possible pathway for this reaction involves activation of glycal **1** by $PhI(OCOR')_2$ to generate the glycosyl ester intermediate **3** (Scheme 2), incorporating a phenyl iodonium (I^{III}) functionality at C2. Transfer of a carboxylate functionality to the C2-position of **3** would then provide **4**,[15] an intermediate that can effectively glycosylate the appropriate acceptor in the presence

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(15) Glycal activation to generate **4** may proceed by β-approach of the I^{III} reagent to afford the C2-β-iodonium-C1-α-glycosyl ester stereoisomer of **3**. Migration of the C1-ester group to the C2-position via reductive elimination of iodobenzene and substitution of the second carboxylate group onto C1 would provide **4**. Conversely, another possibility might involve initial α-approach of the I^{III} reagent (see ref 14b), generating the C2-α-iodonium-C1-β-glycosyl ester stereoisomer of **3**. Transfer of the carboxylate group to C2 via S_Ni-type rearrangement of the α-C2-I^{III} functionality with retention of configuration would then afford **4**.

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Scheme 2

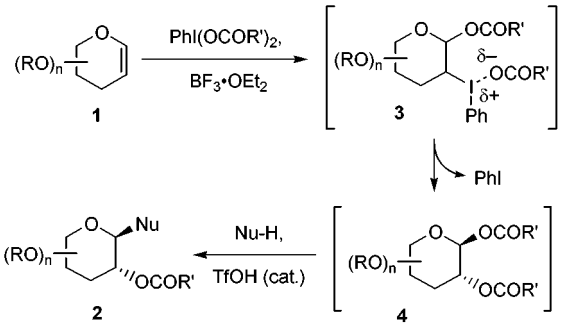
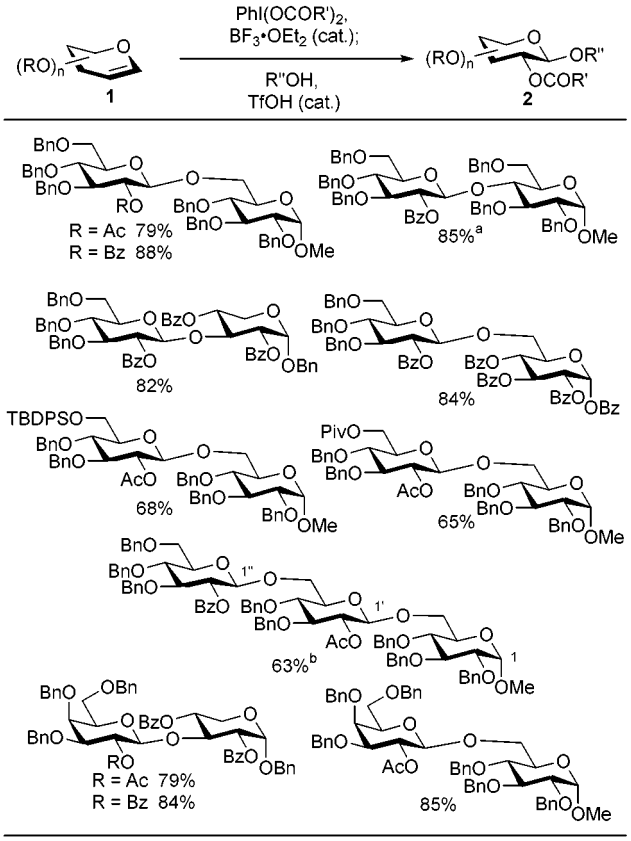


Chart 1



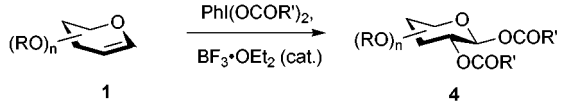
[a] The oxidative glycosylation was performed with 1.8 equiv of the glycal donor. [b] Yield refers to formation of the C1″-anomeric linkage employing 2.4 equiv of the glucal donor.

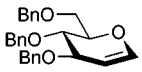
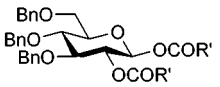
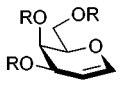
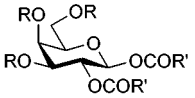
of catalytic TfOH[16] to afford the C2-acyloxyglycoside **2** with good anomeric selectivity as a consequence of C2-neighboring group participatory effects.

A series of couplings were performed with a variety of glycal donors employing several carbohydrate glycosyl acceptors (Chart 1) to prepare a series of C2-acyloxy glycosides. In these investigations, both commercially available (diacetoxyiodo)-benzene and readily available (dibenzoyloxyiodo)benzene[17] served as comparably efficient I^{III} oxidants, thereby installing either the

(16) Catalytic quantities of TMSOTf can also be employed to effect glycosylation. See: (a) Ogawa, T.; Beppu, K.; Nakabayashi, S. *Carbohydr. Res.* **1981**, *93*, C6−C9. (b) Kimura, Y.; Suzuki, M.; Matsumoto, T.; Abe, R.; Terashima, S. *Chem. Lett.* **1984**, 501−504. (c) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **1999**, *121*, 3541−3542.

Table 1



Entry	Donor	$PhI(OCOR')_2$	Glycoside (**4**)
1[a]		R' = Me	 R' = Me 87%
2[b]		R' = Ph	R' = Ph 95%
3	 R = Bn	R' = Me	 R = Bn, R' = Me 80%
4	R = Bn	R' = Ph	R = Bn, R' = Ph 83%
5	R = Ac	R' = Me	R = Ac, R' = Me 89%
6	R = Ac	R' = Ph	R = Ac, R' = Ph 95%

[a] Product isolated as a 5:1 mixture of diastereomers (β-glucopyranoside:α-mannopyranoside). [b] Product isolated as a 6:1 mixture of diastereomers (β-glucopyranoside:α-mannopyranoside).

acetate or benzoate functionality, respectively, at the C2-position of the glycal donor. Both glucal and galactal donors are amenable to this oxidative glycosylation reaction in which an α-C2-acyloxy substituent is installed with high stereoselectivity, yielding a variety of selectively protected β-glycoconjugates.

In the reaction pathway proposed in Scheme 2, the 1,2-bis-(acyloxy)glycoside **4** is presumably formed during the course of glycal oxidation and carboxylate transfer. Indeed, when the glycal donors are simply activated with the (diacyloxyiodo)benzene reagent (1.2 equiv, −45 to −25 °C) in the presence of a catalytic quantity of $BF_3{\cdot}OEt_2$ (0.2 equiv), the corresponding 1,2-*trans*-bis(acyloxy)glycosides can be isolated in high yields (Table 1).[18] As a result, this method also serves as a direct route to 1,2-bis-(acyloxy) glycosides from glycal substrates to generate selectively protected glycosyl esters.

In summary, a new method for oxidative glycosylation is described. By employing readily available (diacyloxyiodo)benzene reagents and catalytic quantities of an appropriate acid, one-pot glycosylations can be performed in which a carboxylate functionality is stereoselectively installed at the C2 position of glycal donors.

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Supporting Information Available: Experimental details and spectral/analytical data for the glycoside products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Although the bis(acyloxylation) of tri-*O*-benzyl-D-glucal led to the formation of small amounts of the corresponding α-manno isomer (entries 1 and 2), use of this donor (∼1.3 equiv) in the C2-acyloxyglycosylation reactions (Chart 1) still led to the exclusive formation of the β-glucopyranosides due to the lower reactivity of the minor quantities of the α-glycosyl ester donor. (See, for example, ref 16c.) It is worth noting that if the 1,2-bis(acyloxylation) procedure is performed on tri-*O*-benzyl-D-glucal at −60 °C with 1.2 equiv of $BF_3{\cdot}OEt_2$, the corresponding 1,2-diacetate (65%) and 1,2-dibenzoate (75%) are isolated with >20:1 (gluco:manno) diastereoselectivities.