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Glycosylation with 3,5-Dimethyl-4-(2'-phenylethynylphenyl)phenyl (EPP) Glycosides via a Dearomative Activation Mechanism

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Supporting Information Placeholder

ABSTRACT: A highly effective and versatile glycosylation method is developed, which uses 3,5-dimethyl-4-(2'-phenylethynylphenyl)phenyl (EPP) glycosides as donors and NIS/TMSOTf as promoter and proceeds via an unprecedented dearomative activation mechanism.

The last decade witnesses the development of various new glycosylation methods in efforts to tackle the challenges occurring in the effective synthesis of glycans and glycoconjugates of great structural diversity.[1,2] A category of these reactions capitalizes on selective activation of a C-C triple bond installed in the aglycone of the glycosylation donors by alkynophilic reagents (Figure 1).[3] Upon activation, the ester type donors (e.g., **A**[4a] and **B**[4b]) readily undergo cleavage of the anomeric C-O bond, leading to the glycosyl oxacarbenium related species (e.g., **I**) for glycosylation.[1d] In comparison, the ether type donors (e.g., **C**[5a]) require much stronger conditions for breaking of the glycosidic C-O bond, thus limiting the scope of the resultant glycosylation reactions. Nevertheless, the stability of the ether type donors would allow various protecting group manipulations, thus to facilitate the streamlined assembly of glycans and glycoconjugates (*cf.*, the versatility of thioglycosides in the synthesis of glycan).[1b,6] Although we have disclosed that the glycosyl *ortho*-alkynylbenzoates (**B**) are the optimal ester type donors under the gold(I) catalysis,[3a] our efforts toward development of an ether type donors basing on a similar activation mechanism met with no success. We found both glycosyl *ortho*-alkynylbenzyl and *ortho*-alkynylphenyl glycosides were inert toward gold(I) catalyst (e.g., $Ph_3PAuNTf_2$ and $Ph_3PAuOTf$) under mild glycosylation conditions. Further engineering of the aglycone led to *ortho*-(methyltosylaminoethynyl)benzyl glycosides (**D**)[5b] and *ortho*-(*p*-methoxyphenylethynyl)phenyl (MPEP) glycosides (**E**),[5c] respectively. The former can undergo glycosylation under the catalysis of TMSOTf more effectively than under $Ph_3PAuNTf_2$ or $Ph_3PAuOTf$, and the latter, remaining inert toward the gold(I) catalyst, can be activated under NIS/TMSOTf to proceed glycosylation.

During the course of these studies, we once tried 2'-(phenylethynyl)biphenyl glycoside **1** as a potential glycosylation donor (Scheme 1). Glycoside **1** stayed inert in the presence of $Ph_3PAuNTf_2$ or $Ph_3PAuOTf$. Interestingly, it was converted under the action of NIS/TMSOTf into phenanthrene glycoside **3** (37%) and lactol **4** (43%). The phenanthrene derivative **3** was produced apparently via an intramolecular Friedel-Crafts type of reaction (Route 2). The presence of the hydrolyzed product **4** implied generation of the glycosyl oxacarbenium species (**I**) and aglycone derivative **III** in the reaction, that involved exactly the occurrence of the expected glycosylation pathway (Route 1). To our surprise, the aglycone derivative was determined to be spiroindene **5** rather than the expected benzo[c]chromene **III**.[7] Thus, a dearomative pathway actually took place (Route 3).[8] Such an activation mode resulting in the cleavage of a *O*-glycoside is unprecedented.[9] Herein, we disclose a new glycosylation protocol which capitalizes on a relevant dearomative activation mechanism.

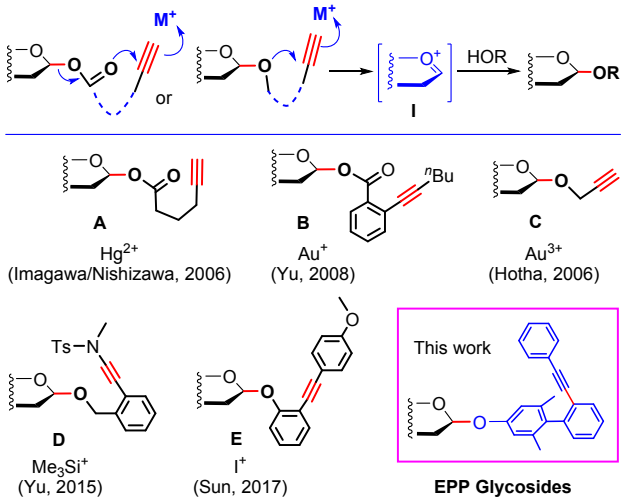
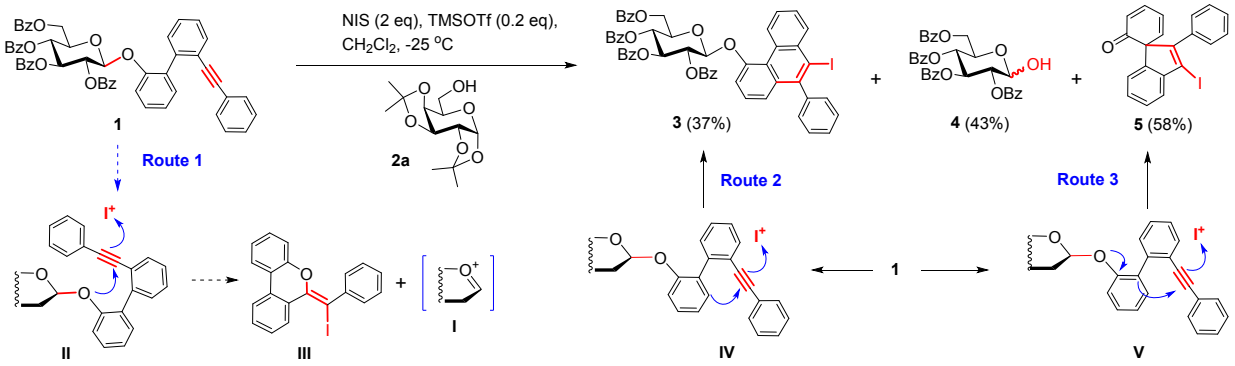


Figure 1. The glycosylation protocols based on activation of C-C triple bond and the representative glycosyl donors and promoters. Bu = butyl, Ts = *p*-toluenesulfonyl.

To facilitate the dearomative pathway and for the reason of easy preparation, we designed 3,5-dimethyl-4-(2'-phenylethynylphenyl) phenyl (EPP) glycosides (**9**) as potential glycosylation donors (Scheme 2). Compared to the original biphenyl-2-yl glycoside **1**, the new EPP glycosides are biphenyl-4-yl glycosides, which are easier to synthesize, in addition, two methyl substituents are introduced to avoid the competitive Friedel-Crafts type of reaction. Indeed, an effective procedure was developed for the synthesis of EPP glycosides, which generally

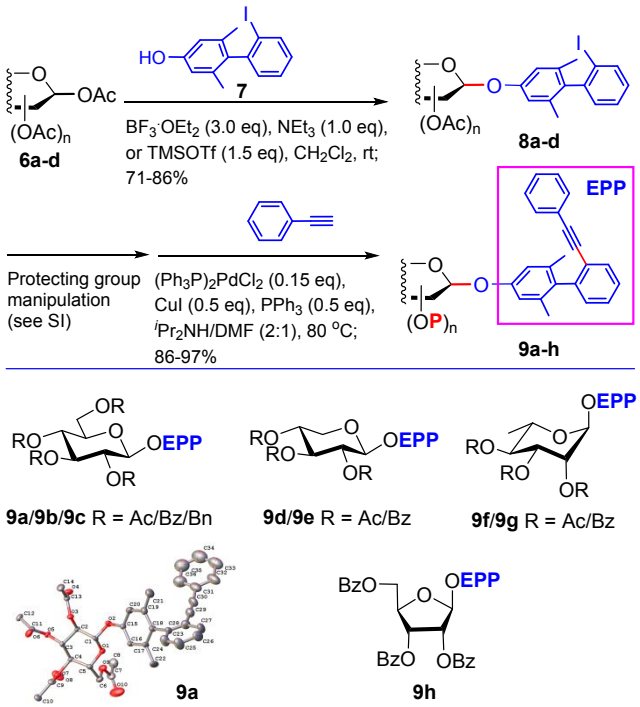
involved: (1) treatment of peracetyl monosaccharides (i.e., **6a-d**) and



Scheme 1. A proposed pathway for the glycosylation of 2'-(phenylethynyl)biphenyl glycoside **1** (Route 1) and the unexpected reactions (Routes 2 and 3). Bz = benzoyl, NIS = *N*-iodosuccinimide, TMSOTf = trimethylsilyl trifluoromethanesulfonate.

2'-iodo-2,6-dimethyl-[1,1'-biphenyl]-4-ol (**7**; CCDC1882371) with $BF_3{\cdot}OEt_2$ or TMSOTf to give the corresponding phenyl glycosides (**8a-d**) (71-86%); (2) protecting group transformation or functional group conversion on the sugar unit; and (3) installation of the phenylethynyl moiety on the aglycone via Sonagashira coupling (86-97%).[7] The resultant EPP glycosides (**9a-h**) are crystalline compounds and stay inert on shelf for at least three months. The structure of **9a** was confirmed by X-ray diffraction analysis (CCDC1881794).

Using perbenzoyl EPP glucopyranoside **9b** as donor and methyl 2,3,6-tri-*O*-benzyl-α-glucopyranoside (**2b**), a hindered sugar alcohol, as acceptor, we screened a series of promoters for the glycosylation in CH_2Cl_2 at RT, to provide the coupled (1→4)-disaccharide **10a**.[7] As expected, EPP glycoside **9b** stayed inert in the presence of $Ph_3PAuNTf_2$, $Ph_3PAuOTf$, $AuCl_3$, AgOTf, TMSOTf, and HOTf, nevertheless, it underwent glycosylation effectively under the action of NIS and TMSOTf.[7] Where the glycosylation took place, the spiroindene derivative **12** was readily isolable, and its structure was confirmed unambiguously by X-ray diffraction analysis (CCDC1881796)(Scheme 3).

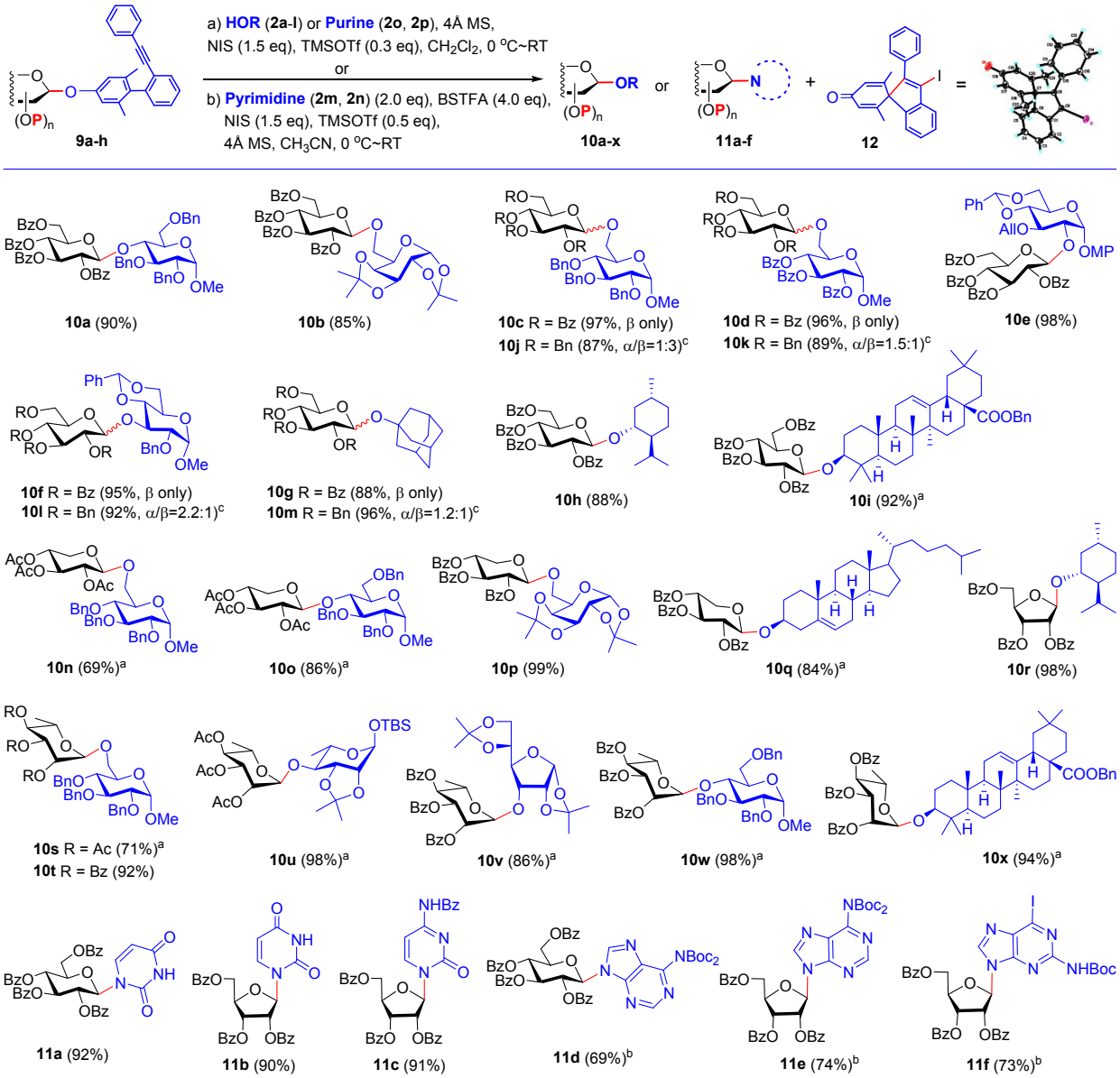


Scheme 2. A general procedure for the preparation of EPP glycosides and those studied in this report. Ac = acetyl, Bn = benzyl.

The model glycosylation reaction (**9b** + **2b** → **10a**), employing a disarmed donor and a hindered acceptor, could give the coupling product in 90% yield under the action of NIS (1.5 eq) and TMSOTf (0.3 eq) in CH_2Cl_2 at 0°C-RT. We were therefore confident that this new glycosylation protocol would possess a wide reaction scope. Indeed, under the present or slightly modified conditions, the glycosylation of EPP donors (**9a-9h**) with a wide array of alcoholic acceptors (**2a-j**)[7] all led to the desired *O*-glycosides (**10a-x**) in satisfactory yields (Scheme 3). Thus, employing perbenzoyl EPP glucopyranoside **9b** as donor, β-(1→6)-, (1→2)-, (1→3)-, besides the (1→4)-disaccharide, were synthesized in excellent yields (**10a-f**; 85-98%); the glycosylation of aglycones, i.e., 1-adamantanol, menthol, and benzyl oleanolate, provided the coupled glycosides (**10g-i**) in ~90% yields. With perbenzyl EPP glucopyranoside (**9c**) as donor, the glycosylation proceeded smoothly and led expectedly

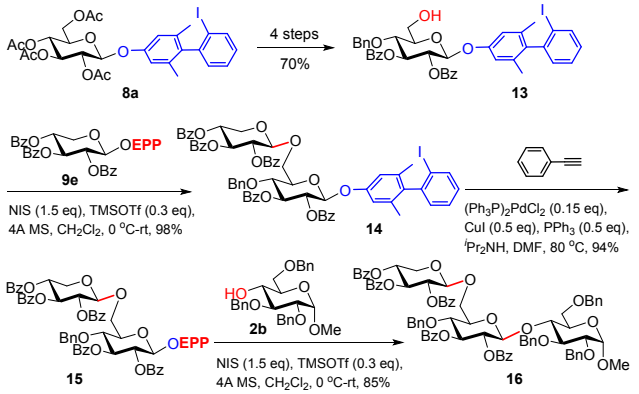
to an anomeric mixture of the glycosides (**10j-m**, 87-96%, α/β = 1:3 to 2.2:1). The peracetyl EPP glucopyranoside (**9a**), like the corresponding *ortho*-alkynylbenzoate,[10] was a poor donor due to formation of orthoester derived products. The peracetyl EPP xylopyranosyl- and rhamnopyranosyl donors (**9d** and **9f**) reacted with the primary sugar alcohol **2b** to give the desired glycosides (**10n** and **10s**) in ~70% yields along with by-products derived from the donors;[10] in comparison, their reactions with secondary alcohols and the reactions of their perbenzoyl counterparts (**9e** and **9g**) proceeded much cleanly, providing the corresponding coupled glycosides (**10o-q** and **10t-x**) in 84-98% yields. It is noteworthy that the corresponding MPEP α-rhamnopyranosides (**E**) did not undergo glycosylation under the activation of NIS/TMSOTf.[5c]

The donor properties of the EPP glycosides were further tested in the *N*-glycosylation of pyrimidine and purine derivatives, which are known to be poor nucleophiles.[11] To our good fortune, purines (**2o** and **2p**) were glycosylated with perbenzoyl EPP glucopyranoside (**9b**) and ribofuranoside (**9h**) to give the desired nucleosides (**11d-f**) in satisfactory yields (~70%). Upon activation and solvation with BSTFA in CH_3CN, pyrimidines (**2m** and **2n**) were glycosylated to provide the corresponding pyrimidine nucleosides (**11a-c**) in excellent yields (>90%).



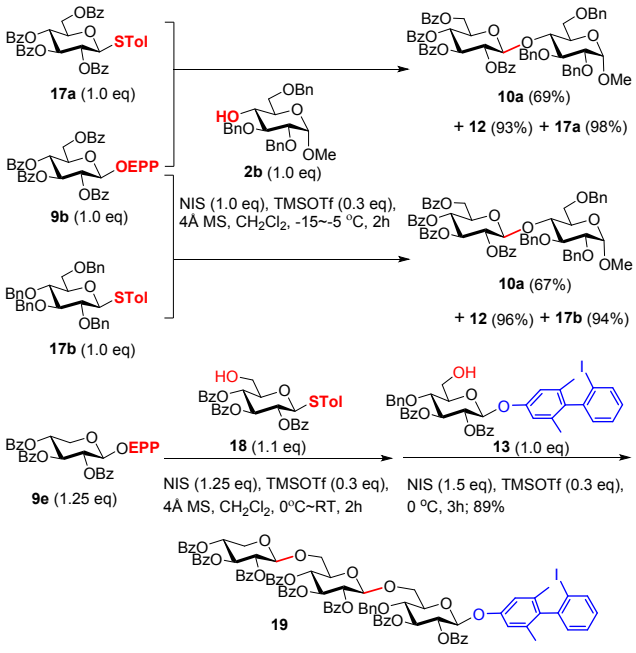
Scheme 3. Scope of the glycosylation reaction with EPP glycosides as donors under the action of NIS/TMSOTf. All = allyl, Boc = *tert*-butoxycarbonyl, BSTFA = *N*,*O*-bis(trimethylsilyl)trifluoroacetamide, Ph = phenyl, TBS = *tert*-butyldimethylsilyl. [a]The amount of TMSOTf was increased to 0.5 equiv. [b]The donor was used in excess (1.2 equiv) and the reaction performed at -20 °C-RT. [c]The α/β ratio was determined by ^{1}H NMR analysis of the product mixture.

Given the fact that the EPP donors are derived from the corresponding 2'-iodo-2,6-dimethylbiphenyl-4-yl glycosides (**8**), which are inactive in the glycosylation conditions of the formers, these donors could be applied to the expeditious synthesis of glycans based on the 'latent-active' strategy.[12] To prove the concept, 2,3-di-*O*-benzoyl-4-*O*-benzyl-glucopyranoside **13**, readily prepared from peracetyl 2'-iodo-2,6-dimethylbiphenyl-4-yl glycoside **8a** via routine protecting group transformations (4 steps, 70% yield),[7] was subjected to glycosylation with EPP xylosyl donor **9e**. Under the present glycosylation conditions, disaccharide **14** was obtained in an excellent 98% yield, which was then converted readily into disaccharide EPP donor **15** via Sonagashira coupling (94%). Subjection of the nascent donor **15** to the next glycosylation with sugar alcohol **2b** furnished trisaccharide **16** (85%).



Scheme 4. A latent-active strategy for the synthesis of trisaccharide **16**.

It is noted that the activation conditions (with NIS and TMSOTf as promoter) for the present EPP glycosides have been effectively applied for the glycosylation reactions with thioglycosides as donors.[6,13] Thus, we compared the donor reactivity of two pairs of the EPP glycosides and thioglycosides (Scheme 5). In a mixture of EPP and *p*-tolylthio perbenzoyl glucopyranoside (**9b** and **17a**, 1.0 eq each) and sugar alcohol **2b** (1.0 eq) in CH_2Cl_2 at -15 °C were added NIS (1.0 eq) and TMSOTf (0.3 eq). After 2 h, the EPP donor **9b** was completely consumed, leading to the coupled disaccharide **10a** and spiroindene derivative **12** in 69% and 93% isolated yield, respectively; while the thioglycoside **17a** was fully recovered (98%). Moreover, in a similar competition reaction of EPP donor **9b** and perbenzyl thioglycoside **17b**, which is ~2000 times more reactive than its perbenzoyl counterpart (**17a**),[14] EPP donor **9b** was still the one being fully activated, leading to coupled disaccharide **10a** (67%) and spiroindene **12** (96%), while the thioglycoside **17b** remained largely intact (94% recovery).[15] This dramatic disparity in reactivity would enable a one-pot synthesis of glycan with combined use of an EPP donor and a thioglycoside acceptor without a concern on the protecting group pattern.[1b,6] To prove the concept, EPP glycoside **9e** was condensed with thioglycoside **18** under the action of NIS/TMSOTf to give the corresponding thiodisaccharide, upon addition of acceptor **13** and another portion of NIS/TMSOTf, the desired trisaccharide **19** was obtained in a high 89% yield. Trisaccharide **19**, which bears a 2'-iodo-2,6-dimethylbiphenyl aglycone, could be further applied in the latent-active synthesis (Scheme 5).



Scheme 5. Comparison of the donor reactivity of the EPP glycosides and thioglycosides under the action of NIS/TMSOTf and a one-pot synthesis of trisaccharide **19**.

In conclusion, we have developed a new glycosylation protocol with EPP glycosides (**9**) as donors, which proceeds via an unprecedented dearomative activation mechanism. This protocol, which can proceed under mild conditions, has demonstrated a broad reaction scope, including in the effective *N*-glycosylation of nucleobases. The stability of the EPP glycosides and their precursors allows various protecting group manipulations and enables application in the streamlined synthesis of glycans and glycoconjugates, as demonstrated here by the synthesis of trisaccharide **16** with the latent-active strategy. In comparison to the thioglycosides, which represent one of the most useful types of glycosylation donors, the present EPP glycosides can be activated much easily for glycosylation under the action of NIS/TMSOTf. In fact, the combined use of EPP glycosides and thioglycosides has demonstrated to be a new combination for one-pot synthesis of glycans. More importantly, the aglycone transfer side reaction of thioglycosides[16] is completely avoided with the EPP donors, which release spiroindene derivative **12** as an innocuous side product. With these promising features, this new glycosylation method deserves further studies and shall find wide application.

ASSOCIATED CONTENT

Supporting Information

Supporting Information. Experimental procedures, analytical data (^1H and ^{13}C NMR, MS) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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(15) According to a reviewer comment, we performed a similar competition reaction between perbenzoyl EPP donor **9b** and its perbenzyl counterpart **9c**. Interestingly, **9c** was found to be only two times more reactive than **9b** (see Supporting Information for details), indicating a greatly diminished armed-disarmed effect imposed by the protecting groups of the donors in the present glycosylation reaction.

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