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Propargyl Glycosides as Stable Glycosyl Donors: Anomeric Activation and Glycoside Syntheses

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Advances in glycobiology established the role played by oligosaccharides and glycoconjugates in various biological processes.[1] A major hindrance to the understanding and eventual modulation of these biosynthetic pathways is the access to pure well-defined oligosaccharides and glycoconjugates. Isolation of these oligosaccharides and glycoconjugates is difficult because they exist in very low concentrations and in micro-heterogeneous forms, and hence the chemical synthesis is the most sought after technique.[2]

The chemical synthesis of glycosides involves a glycosyl donor (**1**), a fully protected saccharide with a leaving group at the anomeric position, and an aglycone (R_1OH, Figure 1) frequently containing only one hydroxyl group.[3] Activators promote the easy formation of an oxocarbenium ion (**2**) which will then be attacked by the aglycone to form glycosides (**3**).[3] Glycosyl trichloroacetamidates,[4a] glycosyl halides,[4b] glycosyl sulfoxides,[4c] glycals,[4d] selenoglycosides,[4e] glycosyl phosphates[4f] and phosphites,[4g] *n*-pentenyl glycosides (NPGs),[4h] and thioglycosides[4i−k] are some of the well studied glycosyl donors.[4] Among these, NPGs and thioglycosides stand apart since they serve as stable anomeric protecting groups and become glycosyl donors upon activation with an appropriate promoter.

In this premise, we envisaged that transition metal mediated activation of propargyl glycosides would be advantageous as propargyl glycosides can be (i) synthesized from aldoses by modified Fisher glycosidation, (ii) stable to diverse chemical manipulations, (iii) directly used for saccharide coupling, and (iv) chemoselectively activated. Accordingly, as a part of the program toward the development of novel methods for glycoconjugate synthesis,[5] we explored the utility of propargyl glycosides for anomeric activation and glycoside synthesis. Here, we wish to disclose our results on anomeric activation and glycoside formation using propargyl glycosides.

Remarkable alkynophilicity exhibited by gold catalysts[6] encouraged us to explore the utility of propargyl glycosides as glycosyl donors along with other alkyne activators, such as $PtCl_2$, $Co_2(CO)_8$, and $RuCl_3$. Accordingly, to probe anomeric activation, propargyl 2,3,4,6-tetra-*O*-benzyl-α/*β*-glucoside (**4a**)[7] and H_2O was treated with 3 mol % of $AuCl_3$ in acetonitrile at room temperature for 12 h to observe complete hydrolysis of **4a** giving per-*O*-benzylated lactol (**5a**).[8] Encouraging results prompted us to swipe H_2O with an aglycone in order to facilitate transglycosylation, an interesting landscape for the synthesis of disaccharides (R_1 = sugar, Scheme 1).

Initial experiments for transglycosylation were performed with **4a** as a glycosyl donor and menthol (**6a**) as the glycosyl acceptor. Upon treatment of preformed acetonitrile solution of **4a** and **6a** with 3 mol % of $AuCl_3$ under inert atmosphere, menthyl glucoside (**5b**) formation was observed, though the reaction was not completed even after 24 h. However, the percentage of conversion of **4a** to product **5b** increased with incremental rise in the temperature, and complete conversion of **4a** was observed at 60 °C in 6 h to obtain

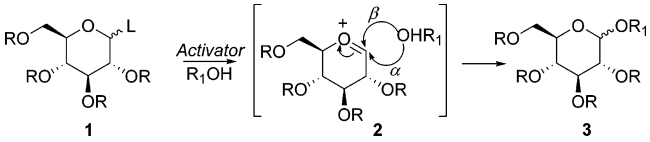
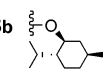


Figure 1. Glycosylation reaction.

Scheme 1. Propargyl Glycosides as Glycosyl Donors

R	Aglycone (R_1OH)	Time/ Temp/ Yield	R_1
Bn (**4a**)	H_2O	12 h/ RT/ 70%	**5a** H
Bn (**4a**)	 **6a**	6 h/ 60 °C/ 68%	**5b** 
Ac (**4b**)	**6a**	48 h/ 60 °C/ 0 %	No Reaction
Bz (**4c**)	**6a**	48 h/ 60 °C/ 0 %	No Reaction

a 1:1 α,*β*-mixture of menthyl glucosides (**5b**), which were separated by silica gel column chromatography in 68% overall yield (Scheme 1).[8] In addition, the α,*β* ratio of the transglycosylation product **5b** was found to be independent of the α,*β* ratio (at C-1) of donor **4a**. Further optimization of the glycosylation protocol by changing the temperature, solvents, and addition of 4 Å molecular sieves powder did not improve the yield. Glycosylation reaction between per-*O*-acetylated (**4b**) or per-*O*-benzoylated (**4c**) propargyl glucosides and menthol **6a** did not give transglycosylated products. It is significant to mention that the other alkyne activators, such as $PtCl_2$, $Co_2(CO)_8$, and $RuCl_3$, for the glycosylation reaction resulted in either the decomposition or isolation of the glycosyl donor (**4a**).

Furthermore, the scope of the reaction was gauged by means of several aglycones comprising 3-chloropropanol (**6b**), 4-penten-1-ol (**6c**), benzyl alcohol (**6d**), cholesterol (**6e**), and sugar aglycone (**6f**). It is pertinent to declare that propargyl glucoside acted as glycosyl donor in all the reactions, giving glycosides **5c**−**g** in good yields except with **6e** as the glycosyl acceptor (Table 1).[8] The low yield in the case of **5f** can be attributed to the poor solubility of cholesterol in acetonitrile. It is also important to mention that the current glycosylation strategy was extended to per-*O*-benzylated propargyl galactoside (**7**) and mannoside (**8**) to obtain glycosides (**9**, **10a**,**b**) in good yields. Mannosyl donor **8** reacted with **6a** and **6f** giving 1,2-*trans*-mannosides (**10a** and **10b**), which can be endorsed to the steric crowding due to the axially disposed benzyl ether at C-2 and anomeric effect.[8,9]

Though a detailed mechanism of the present protocol awaits further studies, a simple plausible pathway can be advanced (Figure 2). Coordination of alkynophilic $AuCl_3$ to the glycosyl donor **4a** (complex **A**) would be followed by formation of the cyclopropyl

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Table 1. Synthesis of Glycosides from Propargyl Glycosides[a]

entry	glycosyl donor	aglycone	product	*time* (yield)[b] *α:β ratio* [c]
1	**4a**	**6b**	**5c**	*6 h* (80%) *0.6:1.0*
2	**4a**	**6c**	**5d**	*10 h* (95%) *1.2:1.0*
3	**4a**	**6d**	**5e**	*4 h* (92%) *0.7:1.0*
4	**4a**	**6e**	**5f**	*15 h* (39%) *0.2:1.0*
5	**4a**	**6f**	**5g** R = OAc (R = Bn)	*5 h* (74%)[d] *0.7:1.0*
6	**7**	**6a**	**9**	*5 h* (73%) *0.5:1.0*
7	**8**	**6a**	**10a**	*5 h* (85 %)
8	**8**	**6f**	**10b**	*3 h* (60%)

[a] All reaction were performed with 3 mol % of $AuCl_3$, 1.0 equiv of glycosyl donor, 1.2 equiv of aglycone in acetonitrile at 60 °C. [b] Isolated and unoptimized yield. [c] The α:β ratio was obtained from ^1H and ^{13}C NMR analysis. [d] Purified by debenzylation ($Pd(OH)_2/C$, H_2, MeOH, 12 h) of the product followed by acetylation (Ac_2O, pyridine, 4 h).

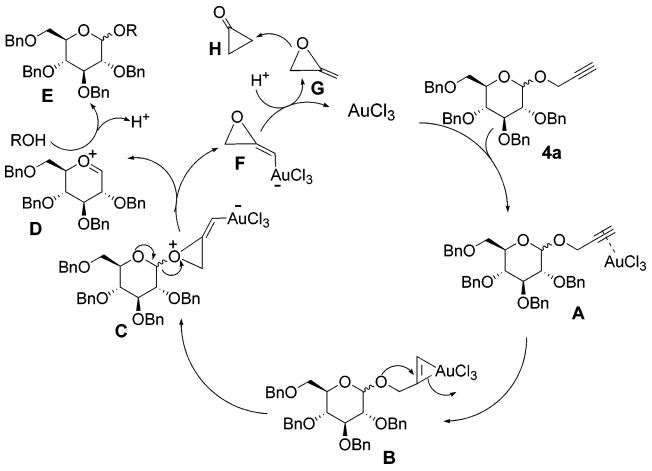

Figure 2. Tentative mechanism for glycoside formation.

gold carbene intermediate (**B**).[6i] As a result of increased electrophilicity, an intermediate of type **C** would be possible, which can lead to an oxocarbenium ion (**D**) with the expulsion of an alkenyl gold complex (**F**). Acid-mediated protodemetalation of the methyleneoxirane−$AuCl_3$ complex (**F**) generates $AuCl_3$ and extrudes methyleneoxirane (**G**), which can further rearrange to cyclopropanone (**H**).[10] Intermediate **D** can in turn be trapped by aglycones to yield observed glycosides (**E**).

In conclusion, propargyl glycosides were identified as novel and stable glycosyl donors. Various aglycones were reacted with propargyl glycosides, resulting in the formation of an α,β-mixture of glycosides and disaccharides in good yields.

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Supporting Information Available: Experimental procedures and characterization data for all glycosides. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) General procedure for $AuCl_3$-mediated transglycosylation: 3 mol % of $AuCl_3$ in acetonitrile was added to a solution of **4a** (1.0 equiv) and aglycone **6a** (1.2 equiv) and heated to 60 °C for 6 h, concentrated in vacuo, and purified by column chromatography.[8] Preparation of **4a**: A solution of propargyl alcohol (15 mL, 0.25 mol) and D-glucose (10 g, 0.06 mol) in dry dioxane−HCl (135 mL) was stirred at 70 °C for 18 h, neutralized with excess Et_3N, concentrated in vacuo, and then per-*O*-benzylated using NaH/BnBr/DMF.[8]

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