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Glycosylation Using Unprotected Alkynyl Donors

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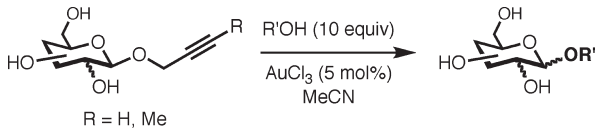

Gold(III) activation of unprotected propargyl glycosyl donors has been shown to be effective for the synthesis of saccharides. Terminal propargyl glycosides of glucose, galactose, and mannose required heating at reflux in acetonitrile with 5% $AuCl_3$ for reaction with various primary alcohol acceptors, the latter used in 10-fold molar excess relative to donor. Donors containing the 2-butynyl group were more reactive, giving good yields of glycoside products at lower temperatures. Secondary alcohols could also be used but with diminished efficiency. The propargylic family of donors is especially convenient because they can be easily prepared on large scale by Fischer glycosylation and stored indefinitely before chemoselective activation by the catalyst.

Carbohydrates are important components of glycolipids and glycoproteins, playing key roles in cell−cell communication, cell adhesion, development, differentiation, and immune response and in disease processes such as inflammation, tumor metastasis, and pathogen infection.[1−5] Thus the synthesis of carbohydrates and their analogues may provide novel therapeutic agents and diagnostic tools.[6−9]Although revolutionary advances have been made in carbohydrate synthesis in recent years, oligosaccharide synthesis remains far more difficult than the modular assembly of oligopeptides and oligonucleotides as a result of the extraordinary complexity of glycan structures.

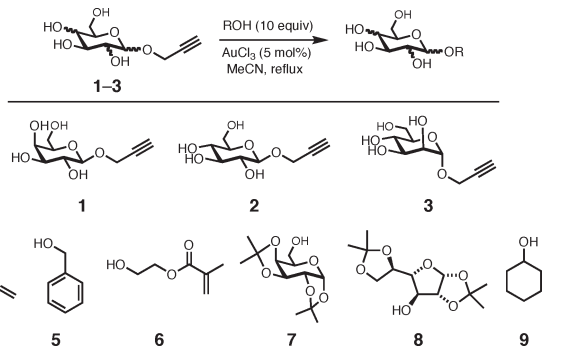

FIGURE 1. Synthesis of glycosides by the activation of propargyl donors **1**−**3** with $AuCl_3$.

TABLE 1. Effect of Various Reaction Parameters for Au(III)-Catalyzed Glycosylation Reactions[a]

entry	donor	acceptor[b]	solvent	temp (°C)	time (h)	yield (%)[c]	α:β
1	**1**	**4**	MeCN	rt	24	0	
2	**1**	**4**	MeCN	60	12	0	
3	**1**	**4**	MeCN	82	4	60	1.5:1
4	**1**	**4**	$MeNO_2$	82	4	25	2.3:1
5	**1**	**4**	DMF	82	24	0	
6	**1**	**4**	THF	82	1.5[d]	32	3.0:1
7	**1**	**4**	neat	82	2[d]	35	3.0:1
8	**1**	**4** (2 equiv)	MeCN	82	4	15	2.3:1

[a]In all cases $AuCl_3$ was used at 5 mol % with respect to donor. [b]Unless otherwise specified, 10 equiv was used with respect to donor. [c]Isolated yields of chromatographically purified products. [d]Heating for longer periods gave the same or lower yields.

Among recent developments have been the discovery of novel glycosyl donors,[10] adding to the repertoire of more established reagents such as trichloroacetamidates,[11] halides,[12] sulfoxides,[13] glycols,[14] phosphates,[15] phosphites,[16] *n*-pentenyl glycosides,[17] and thioglycosides.[18−20] A significant difficulty with many popular reagents is the need for protection and

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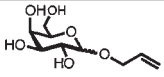
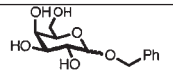
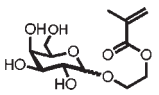
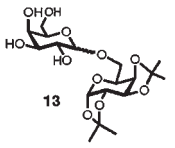
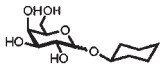
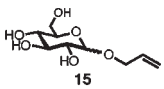
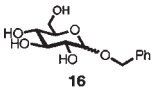
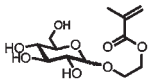
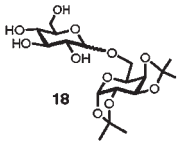
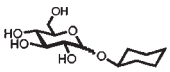
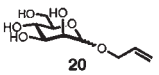
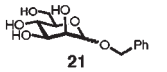
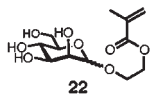
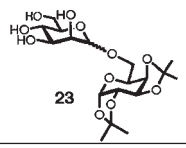
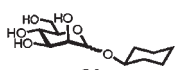
TABLE 2. Au(III)-Catalyzed Glycosylation with Various Propargyl Glycan Donors and Acceptors; All Reactions Performed As Shown in Figure 1

Entry	Reactants	Product	Time, yield [a]	α : β	Ref. [b]	Entry	Reactants	Product	Time, yield [a]	α : β	Ref. [b]
1	**1** + **4**	 **10**	4 h, 60%	2.3:1.0	32	2	**1** + **5**	 **11**	3 h, 62%	1.5:1.0	33
3	**1** + **6**	 **12**	3 h, 54%	1.4:1.0	34	4	**1** + **7**	 **13**	4 h, 51%	1.0:2.6	35
5	**1** + **8**	no glycosylation				6	**1** + **9**	 **14**	4 h, 33%	1.5:1.0	36
7	**2** + **4**	 **15**	4 h, 42%	2.3:1.0	32,33	8	**2** + **5**	 **16**	2 h, 38%	1.8:1.0	32,33, 37-39
9	**2** + **6**	 **17**	6 h, 33%	1.0:1.0	34,40	10	**2** + **7**	 **18**	6 h, 45%	1.0:1.0	41,42
11	**2** + **8**	no glycosylation				12	**2** + **9**	 **19**	4 h, 27%	4.0:1.0	42
13	**3** + **4**	 **20**	6 h, 47%	3.0:1.0	43	14	**3** + **5**	 **21**	5.5 h, 45%	2.5:1.0	43
15	**3** + **6**	 **22**	16 h, none [c]	—		16	**3** + **7**	 **23**	20 h, 47%	1.6:1.0	44
17	**3** + **8**	no glycosylation				18	**3** + **9**	 **24**	14 h, 28%	8.0:1.0	45

deprotection steps in order to achieve stereo-, chemo-, and regioselectivity. The use of glycosylation reactions with unprotected building blocks has certainly been explored,[21] but is less well developed. Among the most successful of these strategies is the use of 3-methoxy-2-pyridyloxy glycosyl donors based on a remote activation concept.[21]

In order to be useful as an unprotected glycosyl donor, the molecule should be stable, easily synthesized, and chemoselectively activated for assembly of the desired glycoconjugate. Toward this end, we became enamored of reports that alkyne-containing glycosyl donors could be selectively activated by alkynophilic metals such as Au(III),[22−26] Hg(II),[27] and Au(I).[28] Of these, the Au(III) method of Hotha and co-workers using propargyl glycosides of benzyl-protected glycan donors is particularly attractive.[24,26] This method seemed to be well suited to the use of unprotected glycosyl donors, since Au(III) is not strongly oxophilic and functions well in protic solvents.

We therefore explored the reactions of unprotected galactosyl, glucosyl, and mannosyl donors **1**−**3**,[29−31] using $AuCl_3$ to activate the propargyl unit (Figure 1). A survey of reaction conditions using allyl alcohol (**4**) as the glycosyl acceptor revealed the following trends: (1) Acetonitrile provided significantly better yields than reactions performed in

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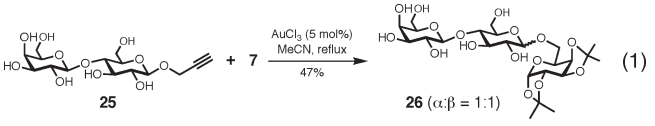
nitromethane, DMF, THF, or without solvent (Table 1, entries 3−7), suggesting that coordination of ligands to the metal may be an important factor. (2) Heating to reflux was required to achieve complete reactions within a few hours, which proved to be much better than reactions at 60 °C for propargyl donors such as **1** (Table 1, entries 1−3). (3) A large excess (10 equiv) of the aglycon acceptor was required for acceptable yields (Table 1, entry 8 vs 3). This common limitation[21] arises from the fact that unprotected donors can also act as acceptors if not swamped by the desired reaction partner.

The optimized glycosylation reaction conditions were used to test the reaction with donors 2-propynyl-*O*-β-D-glucopyranoside (**2**)[29] and 2-propynyl-*O*-α-D-mannopyranoside (**3**),[31] and acceptors **4**−**9**, shown in Figure 1, to afford glycosides **11**−**25** (Table 2). While the primary alcohol galactose diacetonide **7** afforded the expected disaccharides (entries 4, 10, and 16), diacetone-D-glucose (**8**), a secondary alcohol, did not. Instead, cleavage of the 5,6-isopropylidene group occurred to give the corresponding 1,2-*O*-isopropylidene-α-D-glucofuranose[32] as the major product, with little or no disaccharide formation detected. This presumably reflects steric hindrance of the capture of the activated donor. Adducts of a smaller secondary alcohol, cyclohexanol (**9**), were obtained from each of the three donors in modest yield (entries 6, 12, and 18). All of the reactions described here were quite clean when analyzed by thin-layer chromatography, with complete conversion of donor to the desired product and oligomeric material, the latter appearing at the bottom of the TLC plate and often adhering to the flask, making purification convenient. We presume that such oligomerization is responsible for the moderate yields obtained, and efforts are underway to optimize these procedures to boost yields and stereoselectivities.

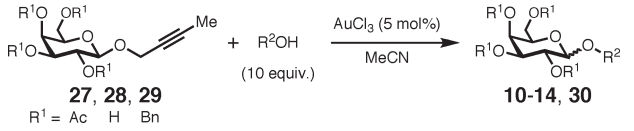
The formation of a 1,6-linked trisaccharide was accomplished without difficulty, as shown in eq 1. Propargylated lactosyl donor **25** and diacetone-D-galactose (**7**) provided an equimolar mixture of the α- and β-adducts **26** (1:1) in 47% yield under standard conditions, suggesting that complex oligosaccharides may be accessible with limited protection/deprotection steps.



(1)

The likely mechanism of Au(III) glycosylation catalysis begins with the formation of a π-complex between the alkyne and the metal.[24] Since σ-acetylide intermediates are presumably not involved, we reasoned that an internal alkyne, rather than a terminal propargyl group, might be beneficial. Accordingly, the protected and unprotected 2-butynyl galactosyl donors **27**−**29** were prepared. As expected,[24] the acetylated donor **27** was not activated by catalytic Au(III) (Table 3, entries 1−3). Donor **28** proved to be more reactive than its propargyl analogue, giving substantial yields of **11** at room temperature and 60 °C (entries 4 and 5), whereas heating to reflux was required for donor **1**. Perbenzylated **29** provided excellent yields at lower temperatures as well, of course allowing the use of lower concentrations of glycosyl acceptor because of its protected nature (entries 11−13). Lastly, unprotected **28** was found to couple to other glycosyl acceptors in straightforward fashion in refluxing acetonitrile (entries 7−10). When conducted at lower temperatures, substantial glycosylation was observed, but product purification was more difficult.

TABLE 3. Glycosylation Reactions Using 2-Butynyl Donors



entry	reactants	temp (°C)	time (h)	product	yield (%)	α:β
1	**27** + **5**	RT			no rxn	
2	**27** + **5**	60			no rxn	
3	**27** + **5**	82			no rxn	
4	**28** + **5**	24	24	**11**	35	1:1
5	**28** + **5**	60	12	**11**	52	1.5:1
6	**28** + **5**	82	3	**11**	61	1:1.4
7	**28** + **4**	82	7	**10**	61	1:1.2
8	**28** + **6**	82	6	**12**	64	1.3:1
9	**28** + **7**	82	3	**13**	47	1:1.6
10	**28** + **9**	82	7	**14**	36	3:1
11	**29** + **5**[a]	0		**30**	no rxn	
12	**29** + **5**[a]	24	12	**30**	85	1:1
13	**29** + **5**[a]	60	4	**30**	88	1:1

[a] 1.5−2 equiv of acceptor **5** was used.

Alkynophilic activation by Au(III) has been shown here to be practical for unprotected sugars, as long as the capturing nucleophile is used in excess and is not too sterically hindered. The propargylic ethers can be easily prepared by Fisher glycosylation and are stable toward hydrolysis. The greater reactivity provided by the 2-butynyl group does not provide definitive mechanistic information, as either of the steps of the Au-mediated activation process (π-complexation and oxocarbenium ion formation by cyclization of the anomeric oxygen on the Au-complexed alkyne) could be assisted by methylation at the terminal alkyne position. It does, however, provide encouragement for the further development of this process and for the use of Au-catalyzed activation for glycan synthesis under very mild conditions.

Experimental Section

General Procedure. To a solution of glycosyl donor (0.1 mmol) and aglycone (1.0 mmol; 0.2 mmol for donor **29**) in anhydrous CH_3CN (10 mL) was added a solution of 5 mol % of $AuCl_3$ in anhydrous acetonitrile (2 mL) under argon atmosphere at room temperature. The resulting mixture was heated to reflux, and the progress of the reaction was monitored by TLC. After completion, the reaction mixture was concentrated under vacuum to obtain a crude residue that was purified by conventional silica gel column chromatography using mixtures of MeOH and CH_2Cl_2 as mobile phase. All adducts are known compounds, and their identities were confirmed by comparison to published spectra.

Compound **28** was prepared by standard BF_3-mediated glycosylation of 2-butyn-1-ol, as described in Supporting Information, and was isolated as a hygroscopic white solid (1.25 g,

(32) Vic, G.; Crout, D. H. G. *Carbohydr. Res.* **1995**, *279*, 315–319.

90%). Mp 154 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.83 (t, 3H, J = 3.0, 6.0 Hz), 3.45−3.60 (m, 3H), 3.72−3.82 (m, 2H), 4.30 (2d, 1H, J = 3.0 Hz), 4.35−4.40 (m, 2H) 4.42 (d, 1H, J = 9.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.9 (CH_3), 59.3 (C-3), 67.1 (C-2), 69.1 (C-6′), 71.7 (C-5′), 72.3 (C-3′), 73.5 (C-4′), 80.2 (C-2′), 99.4 (C-1′). Anal. (after drying under vacuum) Calcd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.95; N, 0.00. Found: C, 51.82; H, 6.84; N, 0.00.

Acknowledgment. We are grateful to The Skaggs Institute for Chemical Biology and Pfizer, Inc. for financial support.

Supporting Information Available: Experimental details and representative HPLC and MALDI mass spectrometry data. This material is available free of charge via the Internet at http://pubs.acs.org.