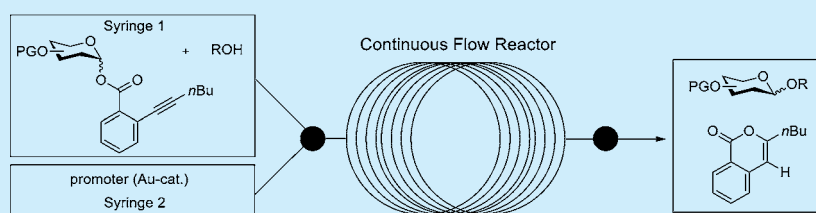


## Homogeneous Gold-Catalyzed Glycosylations in Continuous Flow

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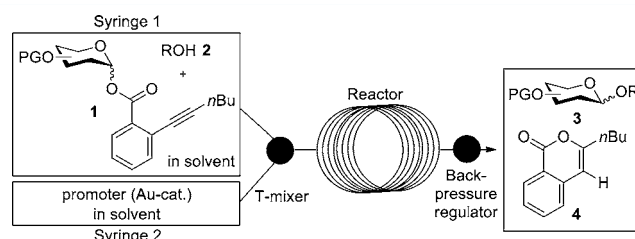
## Supporting Information



**ABSTRACT:** The use of versatile alkynyl-building blocks that are activated by gold(I)-catalysis is demonstrated to efficiently generate a variety of glycosides in continuous flow. The application of a continuous flow setting to gold(I)-catalyzed glycosylations enables very short reaction times and excellent control of the reaction conditions.

The efficient and selective formation of *O*-glycosidic bonds is key to the synthesis of complex oligosaccharides. So far, no general approach is available that would address all synthetic challenges associated with the construction of oligosaccharides.<sup>1–6</sup> Most common glycosylation protocols make use of stoichiometric amounts of promoter and require extensive cooling or harsh reaction conditions, hence rendering them incompatible to labile substrates or protecting groups. An ideal addition to the toolbox of glycosylation procedures would involve mild reaction conditions combined with the use of catalytic amounts of the activating agent. While transition metal catalysis for many reactions is far advanced,<sup>7–15</sup> glycochemists only recently adapted this method to *O*-glycosylation.<sup>16–18</sup> Initially, propargyl glycosides activated by gold(III)-catalysts were used; yet, they were proven to be unsuitable for complex oligosaccharide synthesis.<sup>19</sup> An improved method allowing for complex oligosaccharide synthesis replaced the propargylic leaving group with *ortho*-hexynylbenzoates via gold(I)-activation.<sup>20–22</sup> Initial results using a gold-catalysis protocol proved to be both mild and versatile.<sup>22</sup> The development of reliable glycosylating protocol using mild conditions would be beneficial for oligosaccharide synthesis on solid support<sup>23–31</sup> or by flow chemistry.<sup>32–42</sup>

Continuous chemical syntheses exhibit many advantages<sup>43–45</sup> including high material throughput and improved control over the reaction conditions. Here, we report on gold(I)-catalyzed glycosylation protocols developed for a continuous flow setting. The continuous glycosylation setup is composed of two syringes containing (a) the solution of the nucleophile (glycosyl acceptor) and glycosylating agent (donor) and (b) the catalyst in a suitable solvent and a syringe pump to deliver the solutions through a T-mixer followed by a check valve into the reactor loop (5 mL, PFA coil reactor, Figure 1). The reaction is allowed to proceed at the given temperature before the reaction mixture



**Figure 1.** Experimental setup for Au-catalyzed glycosylation in continuous flow.

passes a 5 bar backpressure regulator. Studies by Yu et al. report the use of 0.1 equiv of  $\text{PPh}_3\text{AuOTf}$  with respect to the glycosyl acceptor to efficiently promote the gold(I)-catalyzed glycosylation.<sup>22</sup>

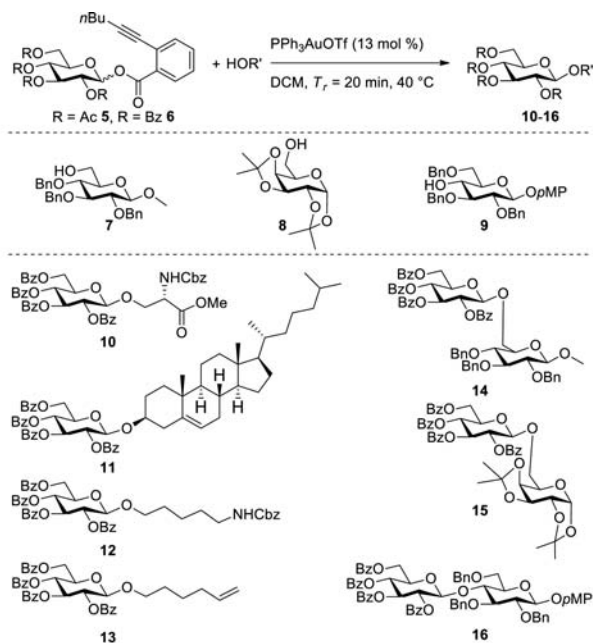
First, the in-flow protocol was optimized for the reaction of glycosylating agents bearing a C2-ester with selected nucleophiles. Activation of C2-*O*-acetate building block **5** by  $\text{PPh}_3\text{AuOTf}$  furnished the corresponding glycosides; yet, the formation of orthoester- and other byproducts was also observed.<sup>46</sup> In contrast, the desired glycosides **10–16** were obtained when glycosyl *ortho*-hexynylbenzoate **6** (1.3 equiv with respect to the glycosyl acceptor) was activated by  $\text{PPh}_3\text{AuOTf}$  (0.13 equiv) with a residence time of 20 min at slightly elevated temperatures (40 °C, Scheme 1). As expected, the exclusive formation of the *trans*-glycosides was observed.

The reaction of the nucleophiles *N*-Cbz-*L*-serine methyl ester, *N*-Cbz-5-aminopentanol, and cholesterol with glycosyl *ortho*-hexynylbenzoate **6** in the presence of 13 mol % catalyst gave access to the desired  $\beta$ -glycosides **10**, **11**, and **12** in good to

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Scheme 1. Glycosylations Using C2-Ester Building Blocks



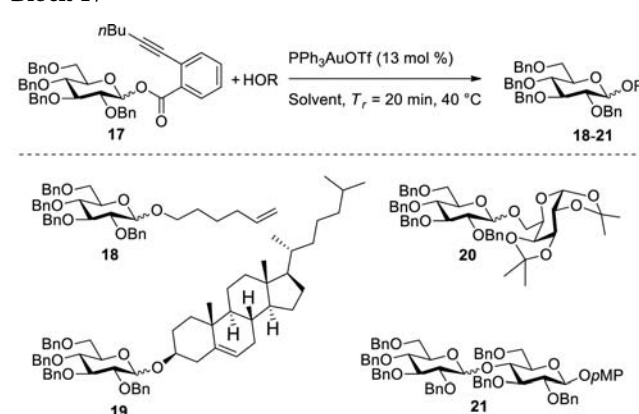
entry	acceptor	product	yield
1	<i>N</i> -Cbz-L-serine methyl ester	10	71%
2	cholesterol	11	87%
3	<i>N</i> -Cbz-5-aminopentanol	12	80%
4	5-hexen-1-ol	13	n.d. <sup>[a]</sup>
5	7	14	51%
6	8	15	50% <sup>[b]</sup>
7	9	16	<10% <sup>[b]</sup>

<sup>a</sup>Not reproducible. <sup>b</sup>Not isolated, yield estimated using the characteristic <sup>1</sup>H NMR signal of 4 as internal standard.

excellent yields (71%–87%, entries 1–3). Trials to attach glucoside 6 to a hexenol-linker, however, proved irreproducible (entry 4). Coupling methylglycoside 7 to donor 6 resulted in the formation of the desired disaccharide 14 in good yield (51%, entry 5). Entry 6 shows the construction of disaccharide 15 from galactose acceptor 8 in 50%, while the formation of unidentified byproducts was observed. Due to the comparatively low nucleophilicity of glucoside 9, attempts to form disaccharide 16 did not afford the desired product without optimization (entry 7).

Next, benzylated building blocks without C2-anchimeric assistance were examined for their potential in gold(I)-catalyzed in-flow glycosylations (Scheme 2). These highly armed glycosylating agents are more reactive than the disarmed representatives applied previously.<sup>47</sup> Higher reactivity in glycosylation reactions often leads to high conversion and yet also to the formation of anomeric mixtures. When tetra-*O*-benzyl-gluco-pyranoside 17 was used as the donor for the coupling with hex-5-en-1-ol, glycoside 18 was obtained in good yield (73%,  $\alpha/\beta = 1:2$ , entry 1, Scheme 2). The reaction of cholesterol with *ortho*-hexynylbenzoate 17 furnished glycoside 19 in high yields (84–88%) in both ether and DCM. As expected, the anomeric ratio was altered toward the preferential formation of the  $\alpha$ -anomer in the presence of ether as the solvent (1:1 to 4:1, entries 2 and 3). The union of perbenzylated building

Scheme 2. Glycosylations Using Perbenzylated Building Block 17



entry	acceptor	product	solvent	yield	$\alpha/\beta$ ratio <sup>[a]</sup>
1	5-hexen-1-ol	18	DCM	73%	1:2
2	cholesterol	19	DCM	84%	1:1
3	cholesterol	19	Et <sub>2</sub> O	88%	4:1
4	8	20	DCM	92%	1.25:1
5	8	20	Et <sub>2</sub> O	48%	5:1
6	9	21	DCM	36%	2:1

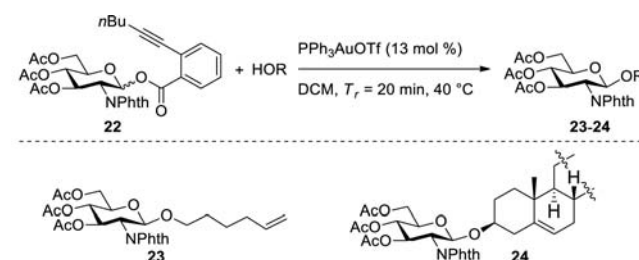
<sup>a</sup>The anomeric ratio was determined by <sup>1</sup>H NMR.

block 17 with galactose derivative 8 afforded glycoside 20 in high to good yield depending on the solvent used (92%,  $\alpha/\beta = 1.25:1$  in DCM, 48%  $\alpha/\beta = 5:1$  in Et<sub>2</sub>O, entries 4 and 5). Lower efficiency for the formation of diglycoside 21 was observed due to a lower conversion (entry 6). Longer reaction time (1 h) did not significantly increase the yield because the formation of byproducts was observed.

Starting from protected glucosamine building block 22, excellent yields of the corresponding hexenol- and cholesterol  $\beta$ -glucosides 23 and 24 were obtained (87% and 86%, Scheme 3). It is noteworthy that 22 in contrast to perbenzoylated glucose building block 6 reacted efficiently with 1-hexenol to form linker-derivative 23 (cf. Scheme 1).

When tri-*O*-acetyl-2-deoxy donors 25 and 26 were glycosylated to galactose acceptor 8, high yields of the respective

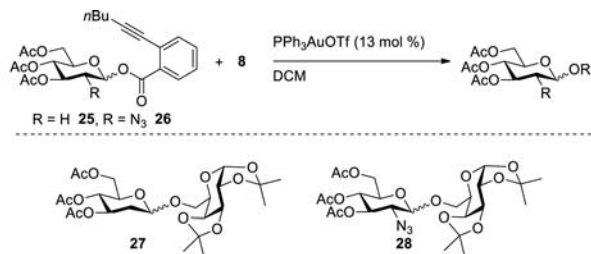
Scheme 3. Glycosylations Using Glucosamine Building Block 22



entry	acceptor	product	yield
1	5-hexen-1-ol	23	87%
2	cholesterol	24	86%

disaccharides **27** and **28** were obtained (75% and 98%, Scheme 4).

Scheme 4. Glycosylations Using Deoxy Glucosides **25** and **26**



entry	acceptor	product	yield	temp	T <sub>r</sub>	α/β ratio <sup>[a]</sup>
1	<b>10</b>	<b>27</b>	75%	0°C→rt	30 min	11:1
2	<b>10</b>	<b>28</b>	98%	40°C	20 min	4.5:1

<sup>a</sup>The anomeric ratio was determined by <sup>1</sup>H NMR.

Gold(I)-catalyzed glycosylations that are typically executed in a conventional round-bottom flask for several hours provide higher yields in some cases.<sup>22</sup> The elevated temperatures used in the in-flow setup to achieve short reaction times (20 to 30 min) can result in benzoate migration byproducts when using C2-participating group glycosylating agents thereby lowering the overall yield. This explains cases of discrepancy of the product yield between a conventional batch and an in-flow reaction setup.

In summary, the first gold(I)-catalyzed glycosylations in a continuous flow reactor were demonstrated. The reaction setup allows for access to a variety of glycosides in good to high yields. The glycosylations proceed in short reaction times of only 20 to 30 min. The anomeric ratio can be controlled by neighboring group participation or the selection of solvent in the same way as for a conventional batch setup. For one particular set of reaction conditions, in principle, the release of the isocoumarin leaving group enables in-line monitoring to provide real time information on the glycosylation reactions in flow.<sup>48</sup>

## ■ ASSOCIATED CONTENT

### Supporting Information

Schematic representation of the reactor setup, experimental procedures, and spectroscopic data of new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01584.

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### Author Contributions

The project was conceived by P.H.S., S.M., and D.T.M., and the experiments were conducted by S.M. The manuscript was written through contributions of S.M. and P.H.S. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

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