AuCl$_3$-Catalyzed Hemiacetal Activation for the Stereoselective Synthesis of 2-Deoxy Trehalose Derivatives

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ABSTRACT: A new practical, catalytic, and highly stereoselective method for directly accessing 1,1-$\alpha\alpha'$-linked 2-deoxy trehalose analogues via AuCl$_3$-catalyzed dehydrative glycosylation using hemiacetal glycosyl donors and acceptors is described. The method relies on the chemoselective Brønsted acid-type activation of tribenzylated 2-deoxy hemiacetals in the presence of other less reactive hemiacetals.

Accessing structurally defined carbohydrates is essential to probe the complex biological roles that carbohydrates play. Thus, the development of novel, efficient, and practical strategies for the stereoselective formation of glycosidic linkages, to add to the existing toolkit of carbohydrate chemistry, is still needed to push the boundaries of glycobiology research.

Trehalose is a symmetrical disaccharide composed of two 1,1-$\alpha\alpha'$-linked glucose subunits. Trehalose monomycolate (TMM) and dimycolate (TDM), bearing one and two 6-mycolyl substituents, respectively, are produced in all mycobacterial species and have been shown to be crucial mycolyl substituents, respectively, are produced in all mycobacterial species and have been shown to be crucial components of the outer layer of the cell wall of Mycobacterium tuberculosis (Mtb). These glycolipids play essential roles in Mtb cell wall biosynthesis and in the viability and virulence of the pathogen.

Targeting trehalose uptake and subsequent metabolism has garnered attention in recent years as an attractive route for the development of novel therapeutics and diagnostic agents. Previous elegant studies reported the synthesis of a series of symmetrical and unsymmetrical trehalose mimetics, including amino, azido, fluoro, iodo, 2-deoxy, and phosphate functionalities, as well as a fluorescent-functionalized analogue that was shown to label Mtb cell wall biosynthesis and in the viability and virulence of the pathogen.

A range of trehalose analogues has been reported. For instance, symmetrical 2-deoxy trehalose derivatives via dehydrative dimerization of the benzylated 2-iodo hemiacetal have been described. Other examples of 2-deoxy trehalose analogues have been reported. Moreover, the synthesis of ketoside-type analogues of trehalose via Lewis acid-catalyzed activation of exoglycosylates and ketoside hemiacetals has also been reported.

Our group is interested in the development of expedient and efficient catalytic methods for the synthesis of 2-deoxy glycosides, which are prominent components of a number of natural products. A number of glycosylation protocols exist for the stereoselective formation of 2-deoxy linkages, but few examples of 2-deoxy trehalose analogues have been reported. For instance, symmetrical 2-deoxy trehalose derivatives via deenzymylation deiodination of a 2,2'-diiodo derivative prepared by dehydrative dimerization of the benzylated 2-iodo hemiacetal have been described. McCarrigle et al. reported the

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organocatalytic synthesis of symmetrical and unsymmetrical 2-deoxy trehalose derivatives via activation of galactal 1; unfortunately, the products were formed as a mixture of anomers. Herein, we report the development of a new, practical, and stereoselective method for accessing 1,1-\(\alpha,\alpha'\)-linked 2-deoxy trehalose derivatives via AuCl\(_3\)-catalyzed dehydrative glycosylation using hemiacetal glycosyl donors and acceptors.

During our previous work on the synthesis of 2-deoxy glycosides via the Au(I)/Ag(I)-catalyzed activation of glycals, we found that activation of 1 using Lewis acidic AuCl\(_3\) formed an inseparable mixture of products, including 2,3-unsaturated Ferrier products (Scheme 1, top).

As part of our ongoing work on the development of catalytic glycosylation methods, AuCl\(_3\) was further investigated as a catalyst for the activation of 2-deoxy hemiacetals 2a\(^{33}\) and 3a\(^{34}\) as an alternative starting material to the 1,2-unsaturated glycals.

Gold catalysis has been widely applied to carbohydrate synthesis.\(^{35}\) For instance, AuCl\(_3\) has been reported for the catalytic activation of acetylated glycals to give 2,3-unsaturated Ferrier products,\(^{36}\) thioglycosides,\(^{37}\) trichloroacetimidates,\(^{38}\) and alkynyl donors.\(^{39,40}\) AuBr\(_3\) has also been reported for the activation of methyl glycosides.\(^{41}\) Moreover, a number of methods for the activation of glycosyl hemiacetals using Lewis and Brønsted acids have been reported for the activation of glycosyl hemiacetals,\(^{4,5}\) including gold chloride in combination with allyl trimethylsilane to generate C-glycosides.\(^{42}\) However, to the best of our knowledge, the application of AuCl\(_3\) for the direct activation of hemiacetals to access O-glycosides has not been reported to date.

In our initial studies, we found 1 mol % AuCl\(_3\) in EtOAc at 50 °C could catalyze the glycosylation of tribenzylated 2-deoxy galactosyl hemiacetal 2a with 4a to give the corresponding 2-deoxy galactoside 5a in 70% yield with an \(\alpha:\beta\) ratio of 12:1 (Table 1, entry 1). Following these encouraging results, hemiacetals 2a-c and 3a were reacted with a range of primary nucleophiles using between 1 and 3 mol % AuCl\(_3\) in either EtOAc or toluene to form the corresponding 2-deoxy glycosides in 59–84% yields. In all cases, the \(\alpha\)-anomer was favored (\(\alpha:\beta = 3.3:1\) to >15:1) (Table 1, entries 1–9). See the Supporting Information for full details and solvent and temperature optimization screening.\(^{43}\) Lower yields (10–
were reacted with 2a, 3a, and 2d using 2.5 mol % \( \text{AuCl}_3 \) in toluene at 50 °C, and the desired unsymmetrical products 15a–g, 16, and 17a–c were isolated in 32–76% yields and exclusively as \( \alpha\beta \)-linked products (Table 2). 46 Hemiacetal 2d protected with an acetate group at O-6 was also synthesized and successfully glycosylated with acceptor 13a to form disaccharide 16 in 54% yield (entry 4). 47

### Table 2. Synthesis of Unsymmetrical 2-Deoxy Trehalose Derivatives

| Entry | Donor | ROH | T | Product | % Yield |
|-------|-------|-----|---|---------|---------|
| 1     | 2a    | 3b  | 6 | 15a     | 75%     |
| 2     | 2a    | 3b  | 3 | 15b     | 35%     |
| 3     | 2d    | 13a | 1 | 16      | 54%     |
| 4     | 3a    | 13a | 3 | 17a     | 72%     |
| 5     | 2a    | 13a | 2.5 | 15c | 58% |
| 6     | 3a    | 13b | 6 | 17b     | 36%     |
| 7     | 2a    | 13b | 4 | 15e     | 54%     |
| 8     | 3a    | 13c | 4.5 | 17c | 32% |
| 9     | 2a    | 2c  | 4 | 15f     | 68%     |

46As determined by H NMR. 47With 15h (4%). 48With 15h (13%). 49With 17d (4%). 50With 17d (43%).

One of the advantages of this chemoselective strategy is the ability to perform orthogonal late-stage functionalizations. To exemplify this, the divergent synthesis of 6-azido derivatives 21 and 25 from common disaccharide 17c was carried out (Scheme 3). Selective deprotection of the benzyl or benzoyl protecting groups could be performed using palladium-mediated hydrogenolysis in 95% yield or LiOH-mediated ester hydrolysis (98% yield), respectively. In each case, a tosyl derivative 21 was accessed with the azido group installed on C, and the desired unsymmetrical products 17a–c were isolated in 82–86% yields. Following ester hydrolysis, 6-azido disaccharide 20 was obtained in 85% yield (Scheme 3).

### Scheme 2. Dimerization Reactions of Deoxy Hemiacetals 2a−c, 3a, 3b, and 8

![Scheme 2. Dimerization Reactions of Deoxy Hemiacetals 2a−c, 3a, 3b, and 8](image)

25% of the desired 2-deoxy glycoside products were observed with less reactive secondary alcohols 4h and 4i (Table 1, entries 10–12). This was proposed to be a result of competitive dimerization of the donor, even when an excess of the alcohol was used. When 4-thiocresol (4j) and propargyl alcohol (4k) were used as acceptors, no reaction occurred, which can be attributed to coordination of the gold catalyst to the acceptor (Table 1, entries 13 and 14, respectively). In the case of benzylidene-protected 4l (Table 1, entry 15), removal of the benzylidene group was observed as evidenced by NMR, which suggests the presence of a catalytic acid and/or moisture in the reaction. Finally, no reaction was observed with less reactive secondary alcohols (Table 1, entry 16) 44 (4%) of the desired 2-deoxy glycoside products were observed (Scheme 2). Reaction of 6-deoxy hemiacetals (e.g., 2a and 3a) as a method for providing access to unsymmetrical trehalose derivatives. To this end, differently protected hemiacetal acceptors 13a–c, 14, and 2c fucose hemiacetal 944 under the same conditions led to the formation of 12 in 60% yield (only the \( \alpha\alpha \)-linked). When less reactive donors 2b, 2c, and 3b were employed, no reaction was observed, suggesting the substrates are unreactive toward glycosylation and dimerization under the mild conditions. 45

The difference in reactivity of the functionalized hemiacetals under our reaction conditions paved the way for the investigation of the selective activation of more reactive 2-deoxy hemiacetals (e.g., 2a and 3a) as a method for providing access to unsymmetrical trehalose derivatives. To this end, differently protected hemiacetal acceptors 13a–c, 14, and 2c.
hydrogenated in the presence of palladium to form 24, and the 6-tosyl group was then converted into an azido group to give 25, whereby the glucose unit bears the 6-azido group. Mechanically, it was initially postulated that AuCl₃ could act as a Lewis acid, coordinating to the hydroxyl group of the 2-deoxy hemiacetal to promote the formation of a transient oxocarbenium ion that can react with the less reactive hemiacetal acceptor. However, we found addition of organic or inorganic bases (DIPEA or K₂CO₃) stopped the reaction (Scheme S1), indicating a Brønsted acid-type mechanism might be plausible. It was also found that dimerization of 2-deoxy hemiacetal donor 2a also occurred upon treatment with HCl, albeit in lower yields (Table S6). However, formation of unsymmetrical trehalose derivative 1Se using benzoylated hemiacetal 2a and acceptor 13c was not observed using HCl (Scheme S2). A number of different activation conditions were also tested for this reaction, but lower yields and/or less clean reaction profiles were observed compared to those with the use of AuCl₃ (Table S7). ¹H NMR spectroscopy studies in d₆-toluene with equimolar mixtures of AuCl₃ and hemiacetal acceptor 13c did not indicate any interaction or reaction between the gold catalyst and the nucleophile (Figure S1). Although it cannot be entirely ruled out as a reactive intermediate, 2-deoxy glycosyl chlorides were not observed at any point by NMR spectroscopy. Moreover, a 4:1 αα’/ββ’-anomeric mixture of 15b was subjected to the reaction conditions using 2.5 mol % AuCl₃ to investigate whether the αα’ selectivity was the result of in situ anomeration. An increase in the proportion of the αβ’ diastereomer as well as the formation of small amounts of hydroxylated hemiacetal 13a was observed (Table S5). These results indicate the αα’ selectivity of the reaction is not due to anomeration and highlights the importance of not leaving the reactions for longer than necessary.

In summary, we have developed a new practical and catalytic method for the synthesis of 2-deoxy trehalose derivatives via Au(III) chemoselective activation of tribenzylated 2-deoxy hemiacetals in the presence of other less reactive hemiacetals. Due to the catalytic nature of the activation system, the glycosylation reactions could be performed under non-anhydrous conditions. Despite starting with a mixture of anomers for both the donor and the acceptor, only the αα’-linked products were generated. The protecting group pattern of the acceptors could be varied, and this allows for the orthogonal modification of functionality at a later stage. The versatility of this approach was highlighted via the synthesis of 6- and 6’-azido-functionalized 2-deoxy trehalose analogues, which are useful tools for studying the biosynthetic pathway of Mtb.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c02530.

Experimental procedures, full characterization data and copies of NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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(45) It is important to note that when EtOAc was used as the
solvent with 2b or 3b, ethyl 2-deoxyglycosides S11 and S12 in
addition to unreacted starting material were observed (see the
Supporting Information for details). To minimize any side products,
for less reactive substrates toluene was used in subsequent screenings.
(46) In all cases, 2 equiv of the hemiacetal acceptor (less reactive
partner) was used to avoid the unwanted dimerization of the
hemiacetal donors. Moreover, excess acceptor could be recovered
from the reaction mixtures.
(47) Formation of 1-O-Bn derivatives 15h and 17d was observed as
a side product in some cases (entries 1, 2, 5, and 8) and could be
isolated from the reaction mixtures.
(48) A similar observation was made by Hotha and co-workers (see
ref 39).