OPEN ACCESS

University of BRISTOL

Jeanneret, R., Walz, C., van Meerbeek, M., Coppock, S., & Galan, M. C. (2022). AuCl3-Catalyzed Hemiacetal Activation for the Stereoselective Synthesis of 2-Deoxy Trehalose Derivatives. *Organic Letters*, *24*(34), 6304-6309. https://doi.org/10.1021/acs.orglett.2c02530

Publisher's PDF, also known as Version of record

License (if available):
CC BY

Link to published version (if available):
10.1021/acs.orglett.2c02530

Link to publication record in Explore Bristol Research
PDF-document

This is the final published version of the article (version of record). It first appeared online via ACS Publications at https://doi.org/10.1021/acs.orglett.2c02530.Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research
General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/

OL Organic Letters

pubs.acs.org/OrgLett

Letter

$AuCl_3$-Catalyzed Hemiacetal Activation for the Stereoselective Synthesis of 2-Deoxy Trehalose Derivatives

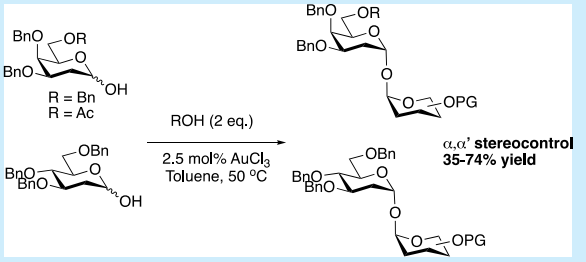
Robin Jeanneret, Carlo Walz,[†] Maarten van Meerbeek,[†] Sarah Coppock, and M. Carmen Galan*

Cite This: *Org. Lett.* 2022, 24, 6304–6309

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A new practical, catalytic, and highly stereoselective method for directly accessing 1,1-α,α'-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.



Downloaded via 2.25.6.89 on November 1, 2022 at 16:06:17 (UTC).
See https://pubs.acs.org/sharingguidelines for options on how to legitimately share published articles.

Accessing structurally defined carbohydrates is essential to probe the complex biological roles that carbohydrates play.[1,2] 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.[3−6]

Trehalose is a symmetrical disaccharide composed of two 1,1-α,α'-linked glucose subunits. Trehalose monomycolate (TMM) and dimycolate (TDM), bearing one and two 6-*O*-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.[2,7,8] 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.[9−14] 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 fluorescein-functionalized analogue that was shown to label *Mtb*.[10] Subsequently, a range of differently functionalized trehalose analogues with fluorescent dyes[12,15,16] and biorthogonal handles,[17] including azides,[18,19] alkynes,[11,20] and photoactivatable diazirines,[21] have been shown to be metabolically incorporated into the mycomembrane of live mycobacteria.

Different strategies exist by which unsymmetrical, functionalized trehalose derivatives can be accessed.[22,23] Enzymatic methods have been successfully applied to the synthesis of a range of trehalose analogues.[24,25] Alternatively, chemical synthesis involving either the desymmetrization of natural trehalose or chemical glycosylation of two separate building blocks is also possible. The former often requires long regioselective protection/deprotection and functional group interconversion sequences with the desymmetrisation step often being low-yielding.[26] On the contrary, chemical glycosylation can be used for the construction of the 1,1-α,α'-linkage, bringing together a glycosyl donor and a hemiacetal acceptor; however, unlike enzymatic syntheses, the chemical synthesis of unsymmetrical trehalose derivatives is often more problematic due to the potential for the formation of up to four diastereomers, unwanted dimerization of the reactive components, and the formation of side products, decreasing the efficiency of the overall synthesis. Alternative methods for the stereoselective synthesis of unsymmetrical α,α'-linked trehalose derivatives using intramolecular aglycone delivery have been described.[27,28] Moreover, the synthesis of ketoside-type analogues of trehalose via Lewis acid-catalyzed activation of exoglycals and ketoside hemiacetals has also been reported.[29]

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.[4] A number of glycosylation protocols exist for the stereoselective formation of 2-deoxy linkages,[4] but few examples of 2-deoxy trehalose analogues have been reported. For instance, symmetrical 2-deoxy trehalose derivatives via debenzylation deiodination of a 2,2′-diiodo derivative prepared by dehydrative dimerization of the benzylated 2-iodo hemiacetal have been described.[30] McGarrigle et al. reported the

Received: July 26, 2022
Published: August 22, 2022

ACS Publications

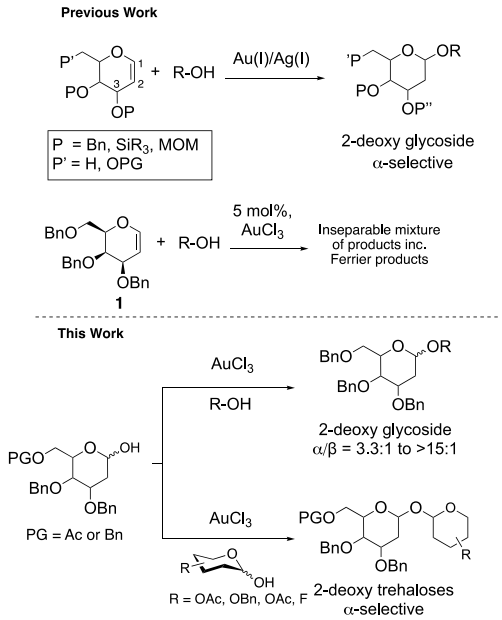
© 2022 The Authors. Published by American Chemical Society

https://doi.org/10.1021/acs.orglett.2c02530
Org. Lett. 2022, 24, 6304−6309

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.[31] Herein, we report the development of a new, practical, and stereoselective method for accessing 1,1-α,α'-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).[32] As part of our ongoing

Scheme 1. $AuCl_3$-Catalyzed Activation of 2-Deoxy Hemiacetals

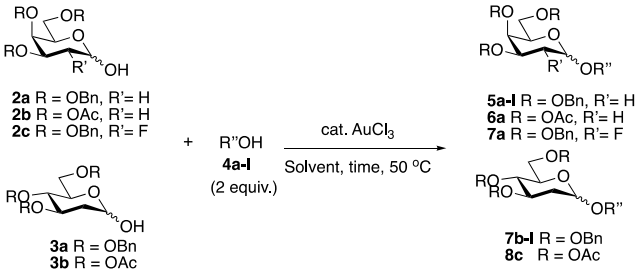


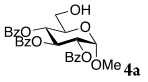
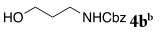
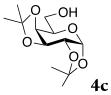
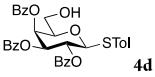
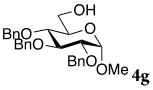
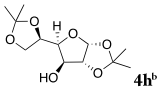
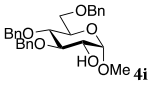
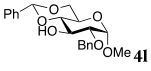
work on the development of catalytic glycosylation methods, $AuCl_3$ was further investigated as a catalyst for the activation of 2-deoxy hemiacetals **2a**[33] and **3a**[34] as an alternative starting material to the 1,2-unsaturated glycals.

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 α:β 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

Table 1. Glycosylation Reactions with Glycosyl Donors 2a–c, 3a, and 3b



Entry	Donor	R"OH	T (h)	Solvent	% Yield[a] (α:β)
1	2a	 4a	3	EtOAc	70 (12:1)
2	2a	 4b[b]	3	EtOAc	71 (6:1)
3	2a	 4c	0.5	EtOAc	84(11:1)
4	2a	 4d	2	Toluene	84 (11:1)
5	3a	4b	1.5	EtOAc	80 (5:1)
8	3a	4c	1.5	Toluene	74 (6:1)[c]
6	3a	 4e	2	EtOAc	70 (5.5:1)
7	3a	 4f	1	EtOAc	63 (4.5:1)
9	3a	 4g	2	Toluene	60(>15:1)
10	2a	 4h[b]	3	EtOAc	10 (3:1)
11	2a	 4i	4	Toluene	25 (7:1)
12	2a	4h	2	EtOAc	14 (4:1)
13	3a	 4j	24	EtOAc	NR
14	3a	 4k[b]	24	EtOAc	NR
15	3a	 4l	1.5	Toluene	0[d]
16	2b	4a	24	Toluene	NR
17	3b	4c	24	Toluene	NR
18	2c	4a	24	Toluene	NR

[a]As determined by H NMR. [b]With 1.5 equiv. [c]With 55% unreacted **4c** recovered. [d]Benzylidene acetal cleavage occurred. NR = no reaction.

EtOAc or toluene to form the corresponding 2-deoxy glycosides in 59–84% yields. In all cases, the α-anomer was favored (α:β = 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–

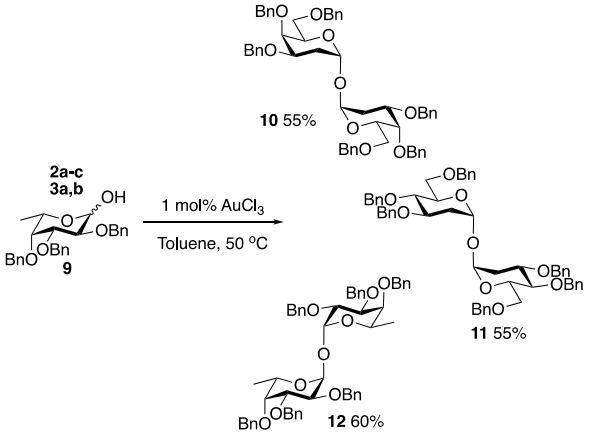
https://doi.org/10.1021/acs.orglett.2c02530
Org. Lett. 2022, 24, 6304–6309

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 triacetylated 2-deoxy hemiacetals **2b**[34] and **3b** and 2-fluorogalactoside **2c**[33] glycosyl donors under the optimized reaction conditions in toluene using primary acceptor **4a** or **4c** after 24 h (entries 16−18).

Generally, glycosylation reactions are conducted under strictly anhydrous conditions to minimize unwanted hydrolysis of the glycosyl donor. In our case, performing the $AuCl_3$-catalyzed reactions under an inert atmosphere or using anhydrous solvents did not have an effect on the reaction yield or time, demonstrating that the process is compatible with the use of "wet" solvents and can be performed under air.

Dimerization of the hemiacetal donors was detected when secondary alcohols were used as acceptors in the Au(III)-catalyzed reactions, which suggested the reaction condition could be amenable to the direct synthesis of 2,2′-deoxy trehalose mimetics. To that end, hemiacetal donors **2a** or **3a** were treated with 1 mol % $AuCl_3$ in toluene in the absence of any alternative OH nucleophile. Pleasingly, dimers **10** and **11** were isolated in 55% yields. In both cases, only the α,α'-linked products were observed (Scheme 2). Reaction of 6-deoxy

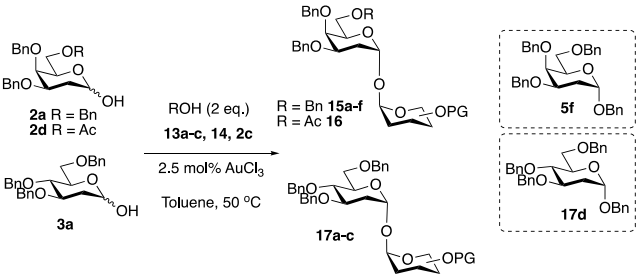
Scheme 2. Dimerization Reactions of Deoxy Hemiacetals 2a−c, 3a, 3b, and 8

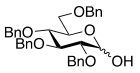
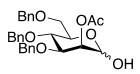
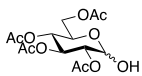
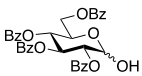


fucose hemiacetal **9**[44] under the same conditions led to the formation of **12** in 60% yield (only the α,α'-linked). When less reactive donors **2b**, **2c**, and **3b** were employed, no reaction was observed, suggesting the substrates are unreactive toward glycosylation and dimerization under 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** were reacted with **2a**, **3a**, and **2d** using 2.5 mol % $AuCl_3$ 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 α,α'-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



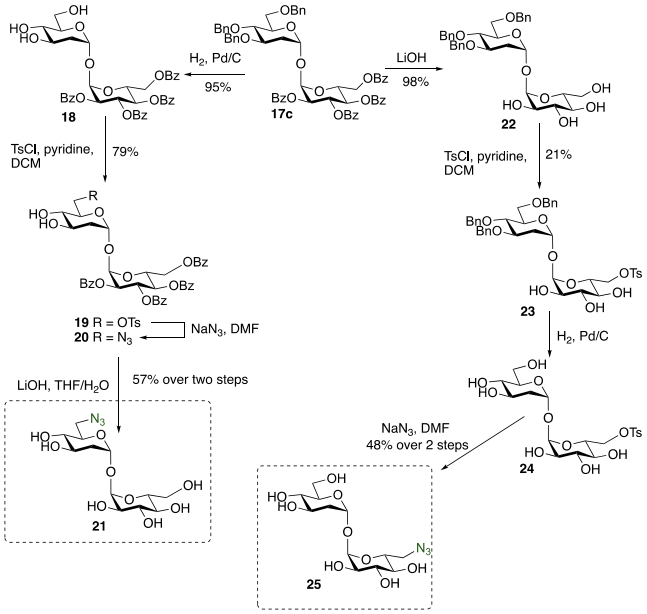
Entry	Donor	ROH	T (h)	Product	% Yield[a]
1	2a	**3b** (α/β = 10:1)	3.5	15a	75[b]
2	2a	 **13a** (α/β = 5:1)	3	15b	35[c]
4	2d	**13a** (α/β = 5:1)	6	16	54
3	3a	**13a** (α/β = 5:1)	3	17a	72[d]
5	2a	 **14** (α/β = 10:1)	2.5	15c	58
8	2a	 **13b** (α/β = 3.3:1)	2	15d	76
6	3a	**13b** (α/β = 3.3:1)	6	17b	36
7	2a	 **13c** (α/β = 5:1)	4	15e	54
8	3a	**13c** (α/β = 5:1)	4.5	17c	32[e]
9	2a	2c	4	15f	68

[a]As determined by H NMR. [b]With **15h** (4%). [c]With **15h** (13%). [d]With **17d** (4%). [e]With **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 group was selectively installed at the more reactive *O*-6 hydroxyl group. In the case of **19**, NaN_3 treatment gave 6-azido disaccharide **20**. Following ester hydrolysis, 6-azido trehalose derivative **21** was accessed with the azido group installed on the 2-deoxyglucose unit. Due to the instability of azido groups to common reductive methods, 6-tosyl disaccharide **23** was

https://doi.org/10.1021/acs.orglett.2c02530
Org. Lett. 2022, 24, 6304−6309

Scheme 3. Synthesis of 6-Azido and 6′-Azido 2-Deoxy Trehalose Derivatives 21 and 25



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.

Mechanistically, it was initially postulated that $AuCl_3$ 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 K_2CO_3) stopped the reaction (Scheme S1), indicating a Brønsted acid-type mechanism might be plausible.[48] 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 **15e** 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 $AuCl_3$ (Table S7). ^{1}H NMR spectroscopy studies in d_8-toluene with equimolar mixtures of $AuCl_3$ 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 $\alpha,\alpha'/\alpha,\beta'$-anomeric mixture of **15b**[31] was subjected to the reaction conditions using 2.5 mol % $AuCl_3$ to investigate whether the α,α' selectivity was the result of *in situ* anomerization. An increase in the proportion of the α,β' diastereomer as well as the formation of small amounts of hydrolyzed hemiacetal **13a** was observed (Table S5). These results indicate the α,α' selectivity of the reaction is not due to anomerization 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 α,α'-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)

■ AUTHOR INFORMATION

Corresponding Author

M. Carmen Galan − *School of Chemistry, University of Bristol, Bristol BS8 1TS, United Kingdom;* orcid.org/0000-0001-7307-2871; Email: m.c.galan@bristol.ac.uk

Authors

Robin Jeanneret − *School of Chemistry, University of Bristol, Bristol BS8 1TS, United Kingdom*

Carlo Walz − *School of Chemistry, University of Bristol, Bristol BS8 1TS, United Kingdom*

Maarten van Meerbeek − *School of Chemistry, University of Bristol, Bristol BS8 1TS, United Kingdom;* orcid.org/0000-0002-3383-5608

Sarah Coppock − *School of Chemistry, University of Bristol, Bristol BS8 1TS, United Kingdom*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.2c02530

Author Contributions

†C.W. and M.v.M. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

M.C.G. thanks the European Research Council (ERC-COG, 648239) and EPSRC GCRF EP/T020288/1 and EP/S026215/1.

■ REFERENCES

(1) Galan, M. C.; Benito-Alifonso, D.; Watt, G. M. Carbohydrate chemistry in drug discovery. *Org. Biomol. Chem.* **2011**, *9* (10), 3598−3610.

(2) Elshahawi, S. I.; Shaaban, K. A.; Kharel, M. K.; Thorson, J. S. A comprehensive review of glycosylated bacterial natural products. *Chem. Soc. Rev.* **2015**, *44* (21), 7591−697.

(3) Panza, M.; Pistorio, S. G.; Stine, K. J.; Demchenko, A. V. Automated Chemical Oligosaccharide Synthesis: Novel Approach to Traditional Challenges. *Chem. Rev.* **2018**, *118* (17), 8105−8150.

(4) Bennett, C. S.; Galan, M. C. Methods for 2-Deoxyglycoside Synthesis. *Chem. Rev.* **2018**, *118* (17), 7931−7985.

(5) Williams, R.; Galan, M. C. Recent Advances in Organocatalytic Glycosylations. *Eur. J. Org. Chem.* **2017**, *2017* (42), 6247−6264.
(6) Ling, J.; Bennett, C. S. Recent Developments in Stereoselective Chemical Glycosylation. *Asian J. Org. Chem.* **2019**, *8* (6), 802−813.
(7) Lowary, T. L. Twenty Years of Mycobacterial Glycans: Furanosides and Beyond. *Acc. Chem. Res.* **2016**, *49* (7), 1379−1388.
(8) Justen, A. M.; Hodges, H. L.; Kim, L. M.; Sadecki, P. W.; Porfirio, S.; Ultee, E.; Black, I.; Chung, G. S.; Briegel, A.; Azadi, P.; Kiessling, L. L. Polysaccharide length affects mycobacterial cell shape and antibiotic susceptibility. *Sci. Adv.* **2020**, *6* (38), No. eaba4015.
(9) Belisle, J. T.; Vissa, V. D.; Sievert, T.; Takayama, K.; Brennan, P. J.; Besra, G. S. Role of the major antigen of Mycobacterium tuberculosis in cell wall biogenesis. *Science* **1997**, *276* (5317), 1420−1422.
(10) Backus, K. M.; Boshoff, H. L.; Barry, C. S.; Boutureira, O.; Patel, M. K.; D'Hooge, F.; Lee, S. S.; Via, L. E.; Tahlan, K.; Barry, C. E.; Davis, B. G. Uptake of unnatural trehalose analogs as a reporter for Mycobacterium tuberculosis. *Nat. Chem. Biol.* **2011**, *7* (4), 228−235.
(11) Foley, H. N.; Stewart, J. A.; Kavunja, H. W.; Rundell, S. R.; Swarts, B. M. Bioorthogonal Chemical Reporters for Selective In Situ Probing of Mycomembrane Components in Mycobacteria. *Angew. Chem., Int. Ed.* **2016**, *55* (6), 2053−7.
(12) Hodges, H. L.; Brown, R. A.; Crooks, J. A.; Weibel, D. B.; Kiessling, L. L. Imaging mycobacterial growth and division with a fluorogenic probe. *Proc. Natl. Acad. Sci. U. S. A.* **2018**, *115* (20), 5271−5276.
(13) Cheng, Y.; Xie, J.; Lee, K. H.; Gaur, R. L.; Song, A.; Dai, T.; Ren, H.; Wu, J.; Sun, Z.; Banaei, N.; Akin, D.; Rao, J. Rapid and specific labeling of single live Mycobacterium tuberculosis with a dual-targeting fluorogenic probe. *Sci. Transl. Med.* **2018**, *10* (454), eaar4470.
(14) Kamariza, M.; Keyser, S. G. L.; Utz, A.; Knapp, B. D.; Ealand, C.; Ahn, G.; Cambier, C. J.; Chen, T.; Kana, B.; Huang, K. C.; Bertozzi, C. R. Toward Point-of-Care Detection of Mycobacterium tuberculosis: A Brighter Solvatochromic Probe Detects Mycobacteria within Minutes. *JACS Au* **2021**, *1* (9), 1368−1379.
(15) Kamariza, M.; Shieh, P.; Ealand, C. S.; Peters, J. S.; Chu, B.; Rodriguez-Rivera, F. P.; Babu Sait, M. R.; Treuren, W. V.; Martinson, N.; Kalscheuer, R.; Kana, B. D.; Bertozzi, C. R. Rapid detection of *Mycobacterium tuberculosis* in sputum with a solvatochromic trehalose probe. *Sci. Transl. Med.* **2018**, *10* (430), aam6310.
(16) Dai, T.; Xie, J.; Zhu, Q.; Kamariza, M.; Jiang, K.; Bertozzi, C. R.; Rao, J. A Fluorogenic Trehalose Probe for Tracking Phagocytosed Mycobacterium tuberculosis. *J. Am. Chem. Soc.* **2020**, *142* (36), 15259−15264.
(17) Fiolek, T. J.; Banahene, N.; Kavunja, H. W.; Holmes, N. J.; Rylski, A. K.; Pohane, A. A.; Siegrist, M. S.; Swarts, B. M. Engineering the Mycomembrane of Live Mycobacteria with an Expanded Set of Trehalose Monomycolate Analogues. *Chembiochem* **2019**, *20* (10), 1282−1291.
(18) Swarts, B. M.; Holsclaw, C. M.; Jewett, J. C.; Alber, M.; Fox, D. M.; Siegrist, M. S.; Leary, J. A.; Kalscheuer, R.; Bertozzi, C. R. Probing the mycobacterial trehalome with bioorthogonal chemistry. *J. Am. Chem. Soc.* **2012**, *134* (39), 16123−6.
(19) Parker, H. L.; Tomas, R. M. F.; Furze, C. M.; Guy, C. S.; Fullam, E. Asymmetric trehalose analogues to probe disaccharide processing pathways in mycobacteria. *Org. Biomol. Chem.* **2020**, *18* (18), 3607−3612.
(20) Kavunja, H. W.; Piligian, B. F.; Fiolek, T. J.; Foley, H. N.; Nathan, T. O.; Swarts, B. M. A chemical reporter strategy for detecting and identifying O-mycoloylated proteins in Corynebacterium. *Chem. Commun.* **2016**, *52* (95), 13795−13798.
(21) Kavunja, H. W.; Biegas, K. J.; Banahene, N.; Stewart, J. A.; Piligian, B. F.; Groenevelt, J. M.; Sein, C. E.; Morita, Y. S.; Niederweis, M.; Siegrist, M. S.; Swarts, B. M. Photoactivatable Glycolipid Probes for Identifying Mycolate-Protein Interactions in Live Mycobacteria. *J. Am. Chem. Soc.* **2020**, *142* (17), 7725−7731.
(22) O'Neill, M. K.; Piligian, B. F.; Olson, C. D.; Woodruff, P. J.; Swarts, B. M. Tailoring Trehalose for Biomedical and Biotechnological Applications. *Pure Appl. Chem.* **2017**, *89* (9), 1223−1249.
(23) Jana, S.; Kulkarni, S. S. Synthesis of trehalose glycolipids. *Org. Biomol. Chem.* **2020**, *18* (11), 2013−2037.
(24) Kalera, K.; Stothard, A. I.; Woodruff, P. J.; Swarts, B. M. The role of chemoenzymatic synthesis in advancing trehalose analogues as tools for combatting bacterial pathogens. *Chem. Commun.* **2020**, *56* (78), 11528−11547.
(25) Groenevelt, J. M.; Meints, L. M.; Stothard, A. I.; Poston, A. W.; Fiolek, T. J.; Finocchietti, D. H.; Mulholand, V. M.; Woodruff, P. J.; Swarts, B. M. Chemoenzymatic Synthesis of Trehalosamine, an Aminoglycoside Antibiotic and Precursor to Mycobacterial Imaging Probes. *J. Org. Chem.* **2018**, *83* (15), 8662−8667.
(26) Wu, C. H.; Wang, C. C. Strategies for desymmetrising trehalose to synthesise trehalose glycolipids. *Org. Biomol. Chem.* **2014**, *12* (30), 5558−62.
(27) Pratt, M. R.; Leigh, C. D.; Bertozzi, C. R. Formation of 1,1-alpha,alpha-glycosidic bonds by intramolecular aglycone delivery. A convergent synthesis of trehalose. *Org. Lett.* **2003**, *5* (18), 3185−8.
(28) Chaube, M. A.; Kulkarni, S. S. First Total Synthesis of Trehalose-Containing Branched Oligosaccharide OSE-1 of Mycobacterium gordonae (Strain 990). *Chem. - Eur. J.* **2015**, *21* (39), 13544−8.
(29) Namme, R.; Mitsugi, T.; Takahashi, H.; Ikegami, S. Development of Ketoside-Type Analogues of Trehalose by Using α-Stereoselective O-Glycosidation of Ketose. *Eur. J. Org. Chem.* **2007**, *2007* (22), 3758−3764.
(30) Rodriguez, M. A.; Boutureira, O.; Matheu, M. I.; Diaz, Y.; Castillon, S.; Seeberger, P. H. Synthesis of 2-iodoglycals, glycals, and 1,1'-disaccharides from 2-Deoxy-2-iodopyranoses under dehydrative glycosylation conditions. *J. Org. Chem.* **2007**, *72* (23), 8998−9001.
(31) Bradshaw, G. A.; Colgan, A. C.; Allen, N. P.; Pongener, I.; Boland, M. B.; Ortin, Y.; McGarrigle, E. M. Stereoselective organocatalyzed glycosylations - thiouracil, thioureas and monothiophthalimide act as Bronsted acid catalysts at low loadings. *Chem. Sci.* **2019**, *10* (2), 508−514.
(32) Palo-Nieto, C.; Sau, A.; Galan, M. C. Gold(I)-Catalyzed Direct Stereoselective Synthesis of Deoxyglycosides from Glycals. *J. Am. Chem. Soc.* **2017**, *139* (40), 14041−14044.
(33) Durantie, E.; Bucher, C.; Gilmour, R. Fluorine-directed beta-galactosylation: chemical glycosylation development by molecular editing. *Chem. - Eur. J.* **2012**, *18* (26), 8208−8215.
(34) Bucher, C.; Gilmour, R. Fluorine-directed glycosylation. *Angew. Chem., Int. Ed.* **2010**, *49* (46), 8724−8.
(35) Li, W.; Yu, B. Gold-catalyzed glycosylation in the synthesis of complex carbohydrate-containing natural products. *Chem. Soc. Rev.* **2018**, *47* (21), 7954−7984.
(36) Balamurugan, R.; Koppolu, S. R. Scope of AuCl3 in the activation of per-O-acetylglycals. *Tetrahedron* **2009**, *65* (39), 8139−8142.
(37) Vibhute, A. M.; Dhaka, A.; Athiyarath, V.; Sureshan, K. M. A versatile glycosylation strategy via Au(iii) catalyzed activation of thioglycoside donors. *Chem. Sci.* **2016**, *7* (7), 4259−4263.
(38) Peng, P.; Schmidt, R. R. An Alternative Reaction Course in O-Glycosidation with O-Glycosyl Trichloroacetimidates as Glycosyl Donors and Lewis Acidic Metal Salts as Catalyst: Acid-Base Catalysis with Gold Chloride-Glycosyl Acceptor Adducts. *J. Am. Chem. Soc.* **2015**, *137* (39), 12653−12659.
(39) Hotha, S.; Kashyap, S. Propargyl Glycosides as Stable Glycosyl Donors: Anomeric Activation and Glycoside Syntheses. *J. Am. Chem. Soc.* **2006**, *128* (30), 9620−9621.
(40) Shaw, M.; Thakur, R.; Kumar, A. Gold(III)-Catalyzed Glycosylation using Phenylpropiolate Glycosides: Phenylpropiolic Acid, An Easily Separable and Reusable Leaving Group. *J. Org. Chem.* **2019**, *84* (2), 589−605.
(41) Vidadala, S. R.; Hotha, S. Methyl glycosides are identified as glycosyl donors for the synthesis of glycosides, disaccharides and oligosaccharides. *Chem. Commun.* **2009**, No. 18, 2505−2507.

https://doi.org/10.1021/acs.orglett.2c02530
Org. Lett. 2022, 24, 6304−6309

(42) Padhi, B.; Reddy, D. S.; Mohapatra, D. K. Gold-catalyzed diastereoselective synthesis of 2,6-trans-disubstituted tetrahydropyran derivatives: application for the synthesis of the C1-C13 fragment of bistramide A and B. *RSC Adv.* **2015**, *5* (117), 96758−96768.
(43) It is important to note that 1.5 or 2 equiv of glycosyl acceptors **4a−l** was used, to minimise the dimerization of the hemiacetal donors (cf. Scheme 1).
(44) Wiebe, C.; Schlemmer, C.; Weck, S.; Opatz, T. Sweet (hetero)aromatics: glycosylated templates for the construction of saccharide mimetics. *Chem. Commun.* **2011**, *47* (32), 9212−4.
(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).

Recommended by ACS

Ni(II)-Catalyzed Regio- and Stereoselective O-Alkylation for the Construction of 1,2-*cis*-Glycosidic Linkages
Yingle Feng, Yonghai Chai, *et al.*
AUGUST 18, 2022
ORGANIC LETTERS
READ

Glycosyl *o*-[1-(*p*-MeO-Phenyl)vinyl]benzoates (PMPVB) as Easily Accessible, Stable, and Reactive Glycosyl Donors for O-, S-, and C-Glycosylations under Brønsted Acid Catalysis
Suvendu Halder, Pavan K. Kancharla, *et al.*
MAY 13, 2022
THE JOURNAL OF ORGANIC CHEMISTRY
READ

Glycosyl 3-Phenyl-4-pentenoates as Versatile Glycosyl Donors: Reactivity and Their Application in One-Pot Oligosaccharide Assemblies
, Pintu Kumar Mandal, *et al.*
MAY 06, 2022
THE JOURNAL OF ORGANIC CHEMISTRY
READ

Anomeric Thioglycosides Give Different Anomeric Product Distributions under NIS/TfOH Activation
Helle H. Trinderup, Henrik H. Jensen, *et al.*
MARCH 03, 2022
THE JOURNAL OF ORGANIC CHEMISTRY
READ

Get More Suggestions >

https://doi.org/10.1021/acs.orglett.2c02530
Org. Lett. 2022, 24, 6304−6309