A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202004476

Link to VoR: https://doi.org/10.1002/anie.202004476

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10.1002/anie.202004476

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Stereoselective Synthesis of 1,1′-Disaccharides by Organoboron Catalysis

Sanae Izumi, [a] Yusuke Kobayashi, [a] and Yoshiji Takemoto*[a]

Abstract: The highly stereoselective synthesis of 1,1′-disaccharides was achieved using 1,2-dihydroxyglycosyl acceptors and glycosyl donors in the presence of a tricyclic borinic acid catalyst. In this reaction, the complexation of the diols and the catalyst is crucial for the activation of glycosyl donors, as well as for the 1,2-*cis*-configuration of the products. The anomeric stereochemistry of the glycosyl donor depends on the employed glycosyl donor. Applications of the produced 1,1′-disaccharides are also described.

Nonsymmetrical 1,1′-disaccharides are structural motifs in various biologically active compounds, including bacterial envelope components and natural products such as succinoyl trehalose lipids, tunicamycin V, and avilamycin A (Figure 1).[1-5] Due to their unique structure and biological activity, the derivatization of 1,1′-disaccharides has received substantial attention. In particular, the regioselective protection of hydroxy groups in commercially available 1,1′-α,α-trehalose has commonly been employed as a synthetic strategy for the generation of 1,1′-disaccharides, although the protection and deprotection procedures usually result in longwinded synthetic routes.[6]

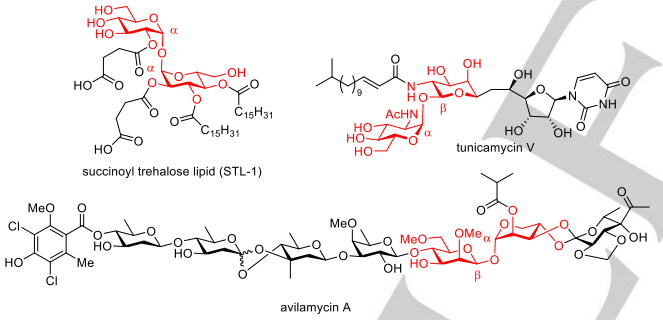

Figure 1. Selected natural products that contain 1,1′-disaccharides.

Compared to the well-established 1,n-*O*-glycosylation (n ≠ 1′), the stereoselective synthesis of non-reducing 1,1′-glycosides via glycosidic bond formation between two anomeric centers is much more challenging,[7] as the stereochemistry of both anomers must be controlled simultaneously in order to synthesize the desired isomer from among the four possible stereoisomers.[2-5] Furthermore, in contrast to that of glycosyl donors, the role of glycosyl acceptors in determining the stereochemistry of glycosylation has been less thoroughly investigated. Thus, despite the fact that 1,1′-glycosidic bond formation provides the possibility of controlling the α/β-selectivity of each anomeric position, only a limited number of catalytic couplings of glycosyl donors and acceptors bearing appropriately protected hydroxy groups has been reported to date.

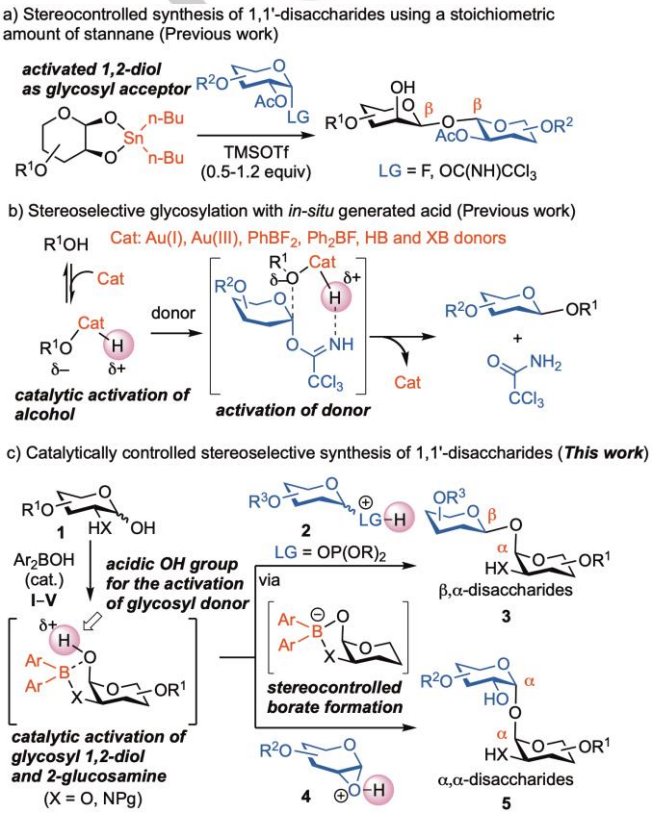

Figure 2. Summary of this work.

So far, several efficient methods to control the stereochemistry of the anomeric centers of 1,1′-disaccharides have been developed using cyclic stannanes,[5c,d] mixed acetals,[7d,e] and picolyl-protected trimethylsilyl ethers[8] as glycosyl acceptors (Figure 2a). However, there is still room for further exploration of the catalytic and divergent synthesis of various 1,1′-disaccharides from the same glycosyl acceptor. In 1994, Yamamoto has proposed the novel concept of Lewis-acid-assisted Brønsted acid (LBA) catalysis based on chiral diol·$SnCl_4$ complexes.[9] Recent studies have also reported stereoselective 1,n-*O*-glycosylations in which glycosyl trichloroacetimidates and glycals are activated by *in-situ*-generated complexes that are comprised of a Lewis or Brønsted acid and a glycosyl acceptor (Figure 2b).[10] Moreover, Taylor has

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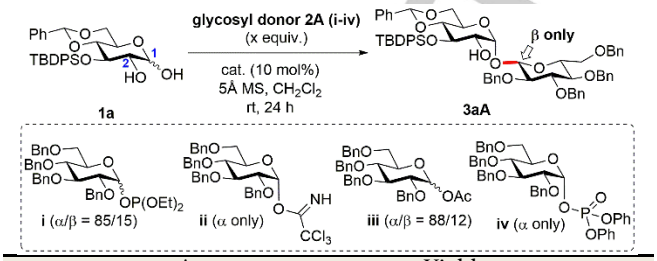
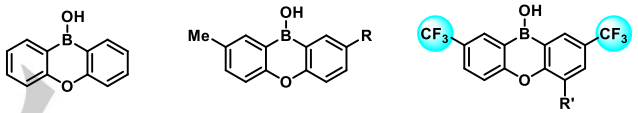
developed a series of mono-functionalizations of various 1,2- and 1,3-diols including acylation, sulfonylation, alkylation, and arylation reactions using arylboronic acids or diarylborinic acids in the presence of bases.[11] Diarylborinic acids in particular showed excellent catalytic performance for the site-selective glycosylation of polyhydroxy glycosyl acceptors; in these reactions, one of the alcohols of the glycosyl acceptor is deprotonated by the base to generate the borate complex.[11d] Based on these reports, we envisaged that complexation of a diarylborinic acid with a 1,2-dihydroxyglycosyl acceptor could give a mono-borinate ester. As the boron center would then coordinate with the remaining hydroxy group, the acidity of this OH group could be expected to increase according to LBA theory.[9] In this communication, we report that in the absence of a base, borinic acid[11] forms a mono-borinate ester complex with 1,2-dihydroxy (or 1-hydroxy-2-amino) glycosyl acceptors **1**. The 1,1′-glycosylation of appropriate glycosyl donors, such as glycosyl phosphites **2**[12] and anhydrosugars **4**,[13] by **1** proceeds smoothly to give the corresponding 1,1′-*β,α*- and 1,1′-*α,α*-disaccharides **3** and **5**, respectively, in a *cis*-fashion relative to the C1 and C2 positions of the glycosyl acceptors (Figure 2c).

We initially investigated the reaction conditions for the synthesis of 1,1′-β,α-disaccharide using various organoboron catalysts,[14-16] glycosyl 1,2-diol **1a**, and glycosyl donors **2A** (**i-iv**), which are known to be activated by Brønsted acids (Table 1). Although glycosyl phosphite **2A** (**i**, pKa of $(EtO)_2POH$ = 9.2) was not activated by phenylboronic acid (entry 1), diphenylborinic acid slightly promoted the reaction to give the desired β,α-adduct **3aA** in 14% yield (entry 2), while the use of the tricyclic borinic acid catalyst **I** increased the yield to 29% (entry 3). The regio- and stereochemistry of **3aA** were unambiguously determined as 1,1′-β,α based on the 1D and 2D NMR spectra of **3aA**.[17] The use of dimethylated tricyclic catalyst **II**, which we employed in our previous work,[15] decreased the yield of **3aA** (19%; entry 4). We then designed tricyclic borinic acid catalyst **III**, which bears an electron-withdrawing group on one aromatic ring; the use of catalyst **III** improved the yield of **3aA** to 80% (entry 5). To our delight, bis-trifluoromethylated catalyst **IV** furnished **3aA** in almost quantitative yield (entry 6). Notably, the β,α-isomer was obtained as the major isomer (β,β/β,α = 13.1/1), while the introduction of an additional CF_3 group on one of the aromatic rings of catalyst **V** decreased the selectivity (entry 7). Furthermore, when a catalytic amount of the typical Brønsted acid activator triflic acid[12] was employed, the major product was the glycoside of the 2-OH group of **1a** (33%), while **3aA** was obtained in only 15% yield with no selectivity at the anomeric position (entry 8). These results suggest that the complexation of diol **1a** and the borinic acid catalyst play an important role in promoting the desired reaction with high anomeric stereoselectivity. The selectivity could be improved by changing the solvent to Et_2O or MeCN, but this resulted in decreased chemical yields despite using 1.5 equiv of the glycosyl donor (entries 10 and 11). The choice of glycosyl donor was found to be crucial, as glycosyl trichloroacetimidate[18] (**ii**, pKa of Cl_3CONH_2 = 11.2) similarly provided the adduct in good yield with slightly decreased selectivity (entry 12), whereas glycosyl acetate (**iii**, pKa of CH_3COOH = 4.7) and glycosyl phosphate (**iv**, pKa of $(HO)_2P(O)OH$ = 2.2)[19] resulted no reaction (entries 13 and 14). Therefore, the substrate scope was investigated using various glycosyl phosphites and catalyst **IV** in dichloromethane at room temperature.

Table 1. Optimization of the reaction conditions for β,α-disaccharides.[a]



Entry	2A (x equiv)	Cat.	Yield [%]	β,α/β,β
1	**i** (1.2)	$PhB(OH)_2$	0	–
2	**i** (1.2)	Ph_2BOH	14[b]	β,α only
3	**i** (1.2)	**I**	29	β,α only
4	**i** (1.2)	**II**	19	β,α only
5	**i** (1.2)	**III**	80	β,α only
6	**i** (1.2)	**IV**	**99**	**13.1/1**
7	**i** (1.2)	**V**	99	7.3/1
8[c]	**i** (1.2)	Triflic acid	15[d]	1.1/1
9	**i** (1.5)	**IV**	100	9.0/1
10[e]	**i** (1.5)	**IV**	79	25.3/1
11[f]	**i** (1.5)	**IV**	63	β,α only
12	**ii** (1.5)	**IV**	86[g]	13.3/1
13	**iii** (1.5)	**IV**	0	–
14	**iv** (1.5)	**IV**	0	–



[a] Isolated yield. [b] The anomeric stereoisomer (α,β: 9%) was also isolated. [c] The reaction was performed at −78 °C using 30 mol% triflic acid. [d] In addition to the other anomeric stereoisomer (α,β: 25%), the regioisomer (glycoside of the 2-OH group) was also isolated (33%). For details, see the Supporting Information. [e] Et_2O was used as the solvent instead of CH_2Cl_2. [f] MeCN was used as the solvent instead of CH_2Cl_2. [g] The anomeric stereoisomer (α,β: 4%) was also isolated (for details, see the Supporting Information).

To investigate the substrate scope with respect to glycosyl acceptors, glycosyl phosphite **2A-i** was used as the glycosyl donor (Scheme 1). Glucose with three unprotected -OH groups at the 1, 2, and 6 positions provided the corresponding adduct **3cA** in 92% yield with perfect β,α-selectivity, while the OH group at the C6 position did not react. In contrast, glucose with four unprotected -OH groups at the 1, 2, 4, and 6 positions gave the 1,6-diglycosylated adduct **3dAA** in 61% yield when treated with 2.4 equiv of **2A-i**. These results corroborate the importance of the complexation of the catalyst with 1,2- and 1,3-diols. Similarly, 3,4,6-tri-*O*-protected galactose afforded exclusively the β,α-disaccharide **3eA** in 86% yield. Using protected mannose and L-lyxose, β,β-disaccharides **3fA** and **3gA** were obtained as the major isomers in excellent yield with high selectivity. *N*-protected

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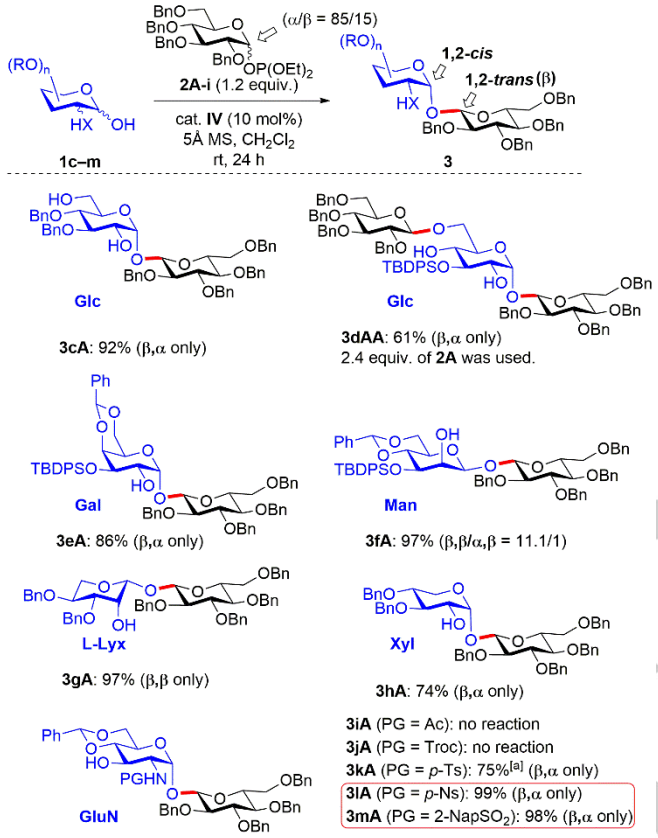
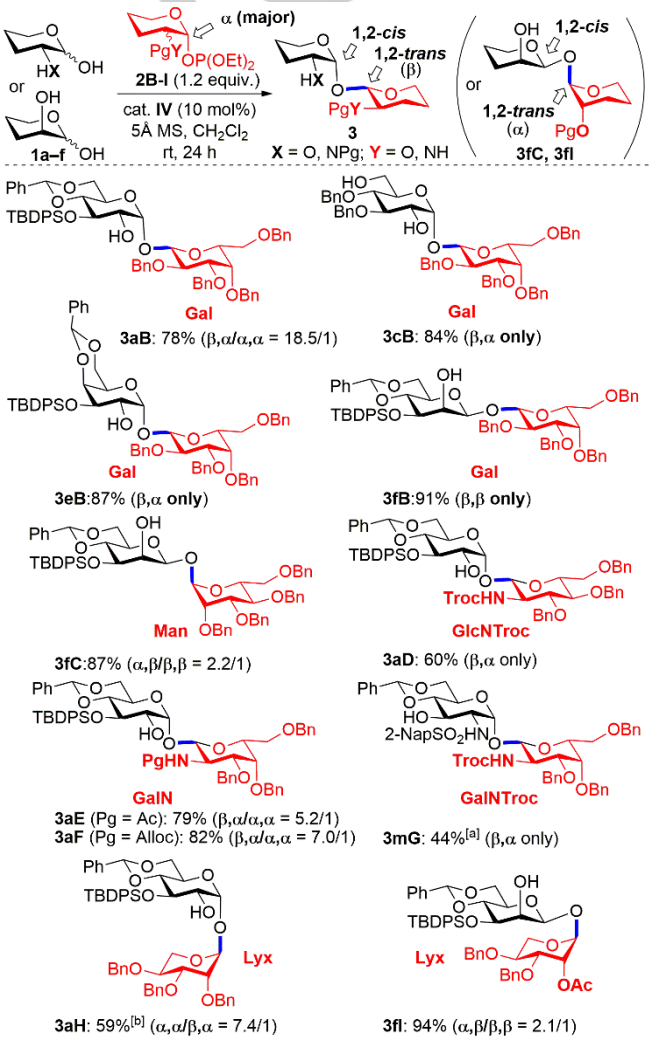
glucosamine was also applicable to the 1,1′-β,α-disaccharide synthesis, whereby the nature of the protecting group is important. For example, the *N*-Ac and *N*-Troc derivatives did not engage in the reaction, whereas the *N*-*p*-Ns- and *N*-2-NapSO$_2$-protected glucosamines afforded the corresponding adducts (**3lA** and **3mA**) in almost quantitative yield. These results imply that the acidity of the N-H group is crucial for the success of the reaction, possibly due to its role in the formation of the complex[20] with the borinic acid catalyst.



[a] The 3-OH group of GluN was glycosylated in 11% yield; for details, see the Supporting Information.

Scheme 1. Scope with respect to glycosyl acceptors

To broaden the substrate scope of this borinic-acid-catalyzed reaction, we then investigated the use of various glycosyl phosphites (Scheme 2). To our delight, the reactions of glucosyl 1,2-diol, galactosyl 1,2-diol, and mannosyl 1,2-diol with galactosyl phosphite afforded the 1,1′-β,α-, 1,1′-β,α-, and 1,1′-β,β-disaccharides **3cB**, **3eB**, and **3fB** as single isomers in 84%, 87%, and 91% yield, respectively. Glycosyl phosphites derived from glucosamine and galactosamine (GlcN and GalN)[17] also reacted with 1,2-diol **1a** to give the corresponding β,α-disaccharides (**3aD**-**3aF**) as the major isomers in good to high yield. We then applied this methodology to the synthesis of the core 1,1′-trehalosamine structure of tunicamycin V using glucosamine as the glycosyl acceptor and galactosamine as the glycosyl donor. This combination was expected to be one of the most challenging, as both the acceptor and donor have lower reactivity compared to substrates without 2-amino groups.[2,21] After investigating a variety of combinations of *N*-protecting groups on the acceptors and donors,[17] the reaction of *N*-NapSO$_2$-protected glucosamine with *N*-Troc-protected galactosamine in the presence of 10 mol% of borinic acid catalyst was found to furnish the desired product (**3mG**) in 44% yield with perfect anomeric selectivity. We finally focused on the reaction with lyxose-derived phosphite, as 1,1′-lyxoside is the core scaffold of natural products such as avilamycin A.[4] The reaction with glucosyl 1,2-diol furnished adduct **3aH** in 59% yield with good α,α-selectivity. The reaction with mannosyl 1,2-diol proceeded efficiently to afford adduct **3fl** in 94% yield, albeit with moderate selectivity.



[a] The 3-OH group of GluN was glycosylated in 26% yield; for details, see the Supporting Information. [b] The anomeric stereoisomer α,β–**3aH** was also isolated (7%).

Scheme 2. Scope with respect to glycosyl donors

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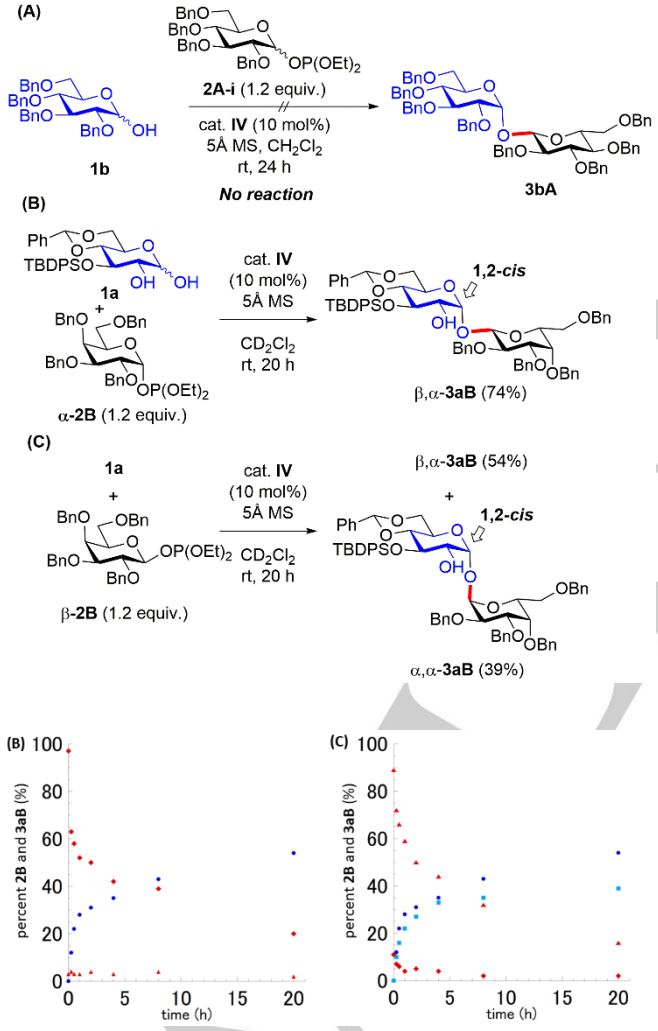
We hypothesized that the decreased 1,2-*trans*-(α)-selectivity of **3fI** (and **3fC**) at the anomeric position of the glycosyl donor originated from the glycosyl phosphites employed, as the prepared glycosyl phosphites have been found to be mostly α-isomers,[17] and therefore, a significant ratio of 1,2-*cis*-(β)-isomer would be competitively obtained via an S_N2-type mechanism.[22] Thus, we subsequently performed mechanistic studies of this reaction (Scheme 3). First, the Lewis acidity of catalyst **IV** was confirmed to be insufficient for the activation of glycosyl phosphite **2A-i** (Scheme 3A). When glycosyl acceptor **1b** was treated with **2A-i** under the optimized conditions, glycosylation did not occur, and the substrates were recovered. These results strongly support our hypothesis that the glycosyl donor is activated by the 'acidic OH group' coordinated by the mono-borinate ester of the glycosyl 1,2-diol.



Scheme 3. (A) A control experiment using **1b**. (B) Time course studies of the reaction of diol **1a** using ^1H and ^{31}P NMR spectroscopy in CD_2Cl_2 with α-phosphite (α-**2B**) or (C) β-phosphite (β-**2B**). ●:β,α-**3aB**, ■: α,α-**3aB**, ◆: α-**2B**, ▲: β-**2B**.

To clarify the origin of the high anomeric selectivity derived from the glycosyl phosphites, we carried out time course studies of the reaction of diol **1a** with an α-phosphite (α-**2B**) or β-phosphite (β-**2B**) using ^1H and ^{31}P NMR spectroscopy in CD_2Cl_2.[22] When α-**2B** was employed, the product exhibited almost perfect β-selectivity (Scheme 3B). On the other hand, an α/β product was obtained using β-**2B**, whereby the β-isomer was still preferentially produced (Scheme 3C). Isomerization between α-**2B** and β-**2B** was not observed during the time course study, not even when 0.5 equiv. of $(EtO)_2POH$ was added prior to the start of the reaction (Figure S1). These results indicate that the glycosylation of the alcohol using glycosyl phosphite proceeds mainly via an S_N2 pathway, in parallel to a minor S_N1 pathway, and that the ratio of the S_N1 pathway increases when the β-phosphite is used. A similar 1,2-trans-selective glycosidic bond formation has been reported in the diarylborinic acid-catalyzed glycosylation due to the bulkiness of the nucleophiles.[11e]

We then turned our attention to the divergent synthesis of 1,1′-disaccharides based on the reaction mechanism that involves the activation of the glycosyl donor via the 'activated OH group' of glycosyl 1,2-diol **1** by the borinic acid catalyst. We anticipated that the anhydro sugar **4** could also be activated by the 'acidic OH group' to obtain 1,1′-α,α-disaccharide (Figure 3).[14] After various reaction parameters, including the catalyst, solvent, and temperature, were screened,[17] the desired α,α-trehalose **5a** was obtained as the major isomer by treating diol **1a** with **4** at 0 °C in acetonitrile in the presence of 20 mol% of catalyst **I**. The Lewis acidity of catalyst **IV** seems to be sufficient to activate donor **4**, albeit that it promoted polymerization; thus, catalyst **I** was chosen as the optimal catalyst for the reaction. Under the optimized conditions, galactosyl 1,2-diol furnished the 1,1′-α,α-disaccharides **5b** and **5c** as the major isomers in good to high yield.

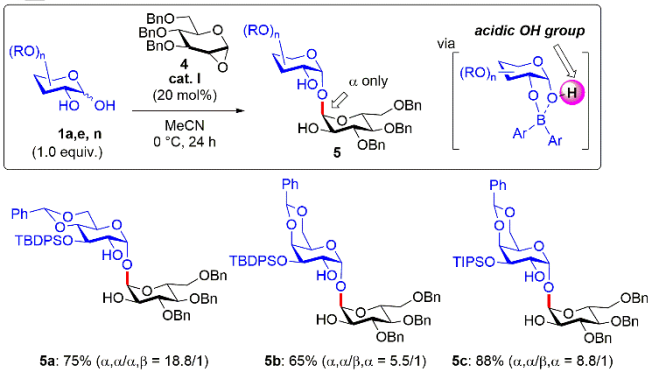


Figure 3. Synthesis of 1,1′-α,α-disaccharides.

One of the major advantages of this method is that the free 2-OH groups of the product can be directly functionalized, whereas fully protected glycosides sometimes suffer from selective deprotection and functionalization. To demonstrate the utility of the products, we carried out the total synthesis of STL-1 using α,α-trehalose **5a** (Scheme 4). The two free 2-OH groups were acylated with mono-benzylsuccinic acid **6** to give the diester **7** in 86% yield. Regioselective reductive ring-opening of the

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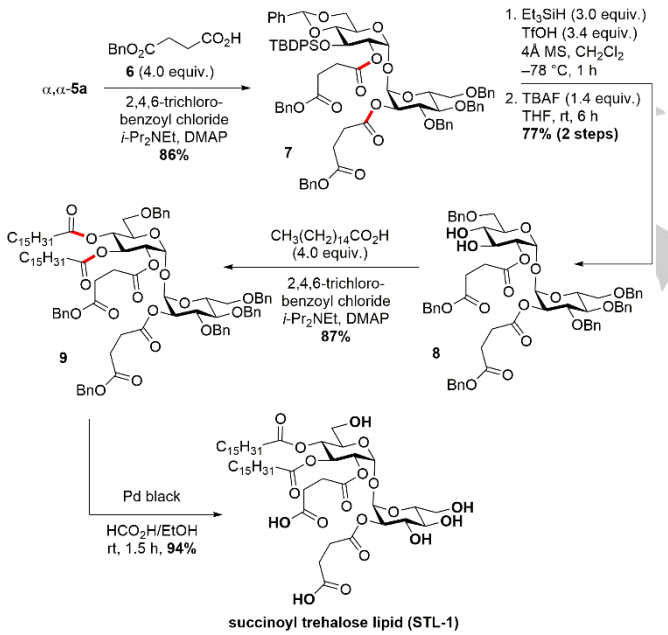
benzylidene acetal of **7**[23] and subsequent deprotection of the TBDPS group afforded 3,4-dihydroxy trehalose **8** in high yield. The 3,4-dihydroxy groups were then acylated with a fatty acid using Yamaguchi's esterification conditions[24] to furnish the tetraester **9** in 87% yield. Finally, the two benzyl esters and four benzyl ethers were reductively removed using palladium black and formic acid to obtain STL-1 in 94% yield. Thus, we successfully achieved the first total synthesis of a nonsymmetrical α,α-trehalose derivative using the catalytic formation of 1,1′-glycosidic bonds.

In conclusion, we have developed a divergent and stereoselective synthesis to obtain 1,1′-disaccharides from glycosyl 1,2-diols and glycosyl donors in the presence of a borinic acid catalyst. The stereochemistry of the glycosyl 1,2-diol is almost completely controlled in *cis*-fashion due to the complexation with the borinic acid, while the stereochemistry of the other anomer (α or β) is controlled by the glycosyl donor used. Furthermore, the complexation of 1,2- and 1,3-diols with borinic acid may generate an 'acidic OH group' that can activate glycosyl donors such as glycosyl phosphites. This activation mode is fundamentally different from the previously reported mechanism using an organoboron catalysts as a Lewis acid. These findings can be expected to lead to further developments in organoboron catalysis and glycosylation chemistry; related studies are currently underway in our laboratory and the results will be reported in due course.



Scheme 4. Application of the adduct α,α-**5a** in the synthesis of STL-1.

Acknowledgements

This work was partly supported by JSPS KAKENHI grant 16H06384. S.I. is grateful for a JSPS Fellowship for Young Scientists (17J08174).

Keywords: trehalose • carbohydrates • glycosylation • organocatalysis • total synthesis

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10.1002/anie.202004476

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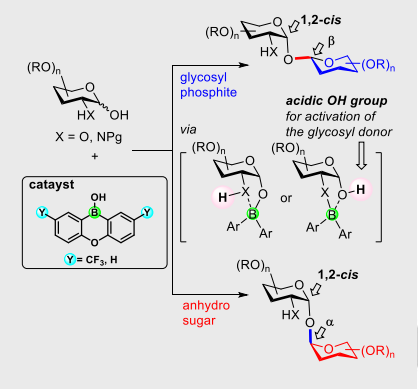
The highly stereoselective synthesis of 1,1′-disaccharides was achieved using glycosyl 1,2-diols and glycosyl donors in the presence of a tricyclic borinic acid catalyst. While the complexation between the diol and the catalyst is crucial for the activation of the glycosyl donors and the *cis* configuration of the product, the anomeric stereochemistry of the glycosyl donor depends on the glycosyl donor. In addition, applications of the products are described.



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