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1,2-*trans* and regioselective glycosylation of multihydroxy sugars *via* a simple yet synergistic combination of BF₃·Et₂O in THF†

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Carbohydrates play pivotal roles in numerous biological processes. The precise synthesis of structurally defined and pure carbohydrates is of paramount importance in pathological research and drug development. However, achieving stereo- and regioselective glycosylation during carbohydrate synthesis is often a tedious process that exhibits low atom economy. Herein, we present a surprisingly simple yet synergistic combination of BF₃·Et₂O in THF as a green solution to shorten the synthetic procedures, utilizing readily accessible imidate donor mixtures, regardless of their anomeric configuration. Glycosylation selectively occurs on the more nucleophilic hydroxyl group, giving 1,2-*trans* glycosides across a broad substrate scope in a highly stereo- and regioselective manner. This strategy is easy to apply and scale up, as demonstrated by an atom-economical synthetic route to achieve an oligosaccharide framework related to the *Enterococcus faecalis* antigen. Variable-temperature (VT) NMR studies revealed the formation of BF₃·ROH complexes, suggesting their roles as the true promoters and acceptors during glycosylation. Density functional theory (DFT) calculations suggested that 1,2-*trans* selectivity arises from the energy discrepancy between putative transition states involving [BF₃OR]⁻ and the oxocarbenium–solvent complex.

Green foundation

1. This work allows for 1,2-*trans* and regioselective glycosylation of multihydroxy sugars with minimal protection in an environmentally friendly manner. It can significantly shorten the synthetic procedures required for obtaining complex carbohydrates and reduces the reliance on protecting and directing groups.

2. The advantages of this strategy in terms of green chemistry include the use of readily available donors and acceptors, a metal-free system, short reaction time, good scalability, inexpensive reagents, and halogen-free solvents.

3. Future research endeavors can focus on refining reagent design to minimize the amount of promoters utilized and enable selective glycosylation reactions at room temperatures.

Introduction

Carbohydrates serve as the primary energy source and play a crucial role in numerous essential biological processes, including cell recognition and interaction.[1,2] Studies on carbohydrates provide valuable insights into their pathomechanism and facilitate drug development for combating diseases, such as cancers, viral infections, and diabetes.[3,4] Currently, access to structurally precise oligosaccharides, glycoconjugates, and glycans[5–10] heavily relies on chemical synthesis *via* crucial glycosylation reactions.[11–15] In order to achieve high stereo- and regioselectivity in glycosylation during complex carbohydrate synthesis, directing/protecting groups are frequently manipu-

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lated on both donors and acceptors,[13,16–21] such as in our recent studies on preparing challenging β/α-2-deoxyglycosides, β-rhamnosides, α-glucosides, and β/α-2′-deoxynucleosides.[22–26] However, these tactics usually suffer from a poor atom economy, long synthetic route, and low overall efficiency due to the tedious introduction, replacement, and cleavage of directing/protecting groups. To make carbohydrate synthesis greener, many reagent-controlled strategies for glycosylation have emerged over the past decade, primarily focusing on stereoselectivity,[27–41] with a limited number also offering simultaneous regioselectivity toward multihydroxy sugars bearing few protecting groups (Fig. 1a).[42–52] These include the effective utilization of borinic acid, boronic acid, noble metal chloride, and Ca(OTf)₂ with α-configured donors (Fig. 1b).[43–45,47–51,53] Recent studies have reported precisely designed catalysts bearing multiple functional sites as stereocontrol and regiocontrol factors, such as synthetic bis-thioureas for (1→2)-selective β-galactosylation with α-configured donors and aminoboronic acid for 1,2-cis-glycosylation (Fig. 1b).[42,52]

Despite these innovative achievements, the synthesis of complex carbohydrates still calls for a greener and more atom-economical strategy favoring sustainable development. While pursuing high yields and selectivity in glycosylation, several aspects are also noteworthy. For example, simple and cheap reagents are preferred for achieving a better atom economy and easier preparation of donors, acceptors, and promoters. Some strategies depend on donor anomeric configuration and only employ specific anomers as donors. However, obtaining such single α- or β-specific donors can be difficult during complex carbohydrate synthesis, particularly for donors bearing multiple functional groups or oligosaccharide donors.
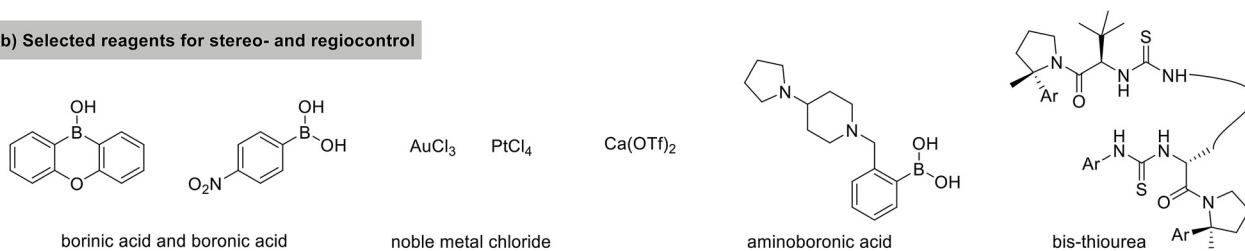
This would require careful separation and result in wastage of other undesired anomers.[40] Furthermore, the recent ban by the US Environmental Protection Agency (EPA) on most uses of CH₂Cl₂, a widely used solvent in glycosylation, poses additional challenges for finding more eco-friendly solvents. Scale-up, operation, functional group tolerance, and reaction time are also of great concern. Therefore, it is still a highly desirable but challenging goal to develop a green and efficient strategy for glycosylation to synthesize complex carbohydrates.

Herein, we present a solution to utilize a simple combination of BF₃·Et₂O in ether solvent (Fig. 1c) to enable the highly 1,2-trans and regioselective glycosylation of multihydroxy acceptors with readily accessible imidate donors, regardless of the donor anomeric configuration. BF₃·Et₂O, a cheap Lewis acid widely employed in organic synthesis, was recommended by Yu and co-workers as a better catalyst for phenol O-glycosylation to suppress the formation of side-products during neighbouring group participation.[54] However, BF₃·Et₂O itself is generally considered a poor factor for stereocontrol;[55,56] ether solvents, on the other hand, are typically expected to lead to the reverse 1,2-cis α-selectivity.[57–62] Neither has been known as a regiocontrol factor to date. However, their combination resulted in high 1,2-trans and regioselectivity (Fig. 1c). Furthermore, ether solvents, such as THF in our protocol, are more eco-friendly than regularly used halogen solvents (e.g., CH₂Cl₂ and DCE) in glycosylation, providing an alternative to comply with the ban on CH₂Cl₂ by the EPA. We consider this strategy greener and highly practical due to the simple and eco-friendly reagents/promoters/solvents utilized, readily accessible donors/acceptors, ease of handling, broad substrate scope, easy scale-up, mild conditions, reasonable reaction time, and low cost.
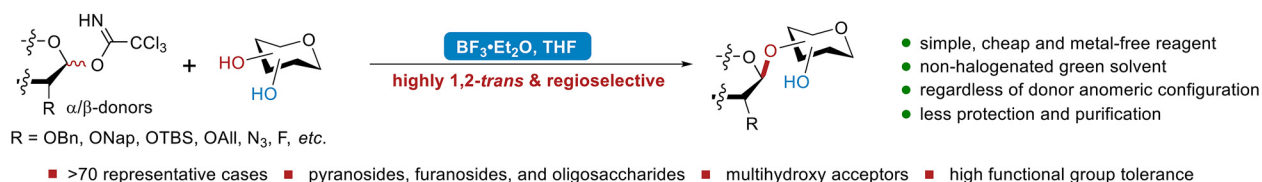

Fig. 1 Stereo- and regioselective glycosylation.

Results and discussion

Reaction discovery and validation

As control reactions during our pursuit of new reagents for stereoselective glycosylation using regular imidate donors, we were surprised to discover that a simple combination of $BF_3 \cdot Et_2O$ (stored or freshly distilled) in ether solvent (Table S1†), without any additives, resulted in high β-selectivity in glucosylation with the benzylated imidate donor **1** (a mixture of anomers, α/β = 7 : 1). Despite the general perception that β-glucosylation has already been addressed by the 2-*O*-acyl directing group-controlled strategy, we perceived this finding still holds high value in consideration of a practical reagent-controlled strategy. It promises more straightforward access to base-labile glycosides and 2-*O*-glycosylated glycosides.[63] In addition, it can circumvent the issues associated with the 2-*O*-acyl strategy,[64] including orthoester formation, selective installation/cleavage of the 2-*O*-acyl groups, and diminished reactivity due to the disarming effect of acyl groups. Further optimization showed that the standard conditions were 0.4 eq. of $BF_3 \cdot Et_2O$ in THF at −50 °C (Table 1, entry 1), which led to the desired disaccharide **4** with complete β-selectivity and a high 91% yield. Although THF is generally avoided in glycosylation due to concerns about sluggish reactions and potential side reactions, such as polymerization,[65] this reaction proceeded smoothly and could be easily scaled up (entry 2).

Schmidt and co-workers reported $BF_3 \cdot Et_2O$-directed β/α ratios of up to 6 : 1 by using pure α-imidate donors in CH_2Cl_2 *via* a presumed intramolecular S_N2 attack on the α-donors.[55,56] However, this could not rationalize the complete β-selectivity

we obtained from a mixture of α- and β-donors (α/β = 7 : 1) in THF. For further verification, we prepared glucosyl imidate **2** as a pure β-donor and then evaluated it under the standard conditions of 0.4 eq. of $BF_3 \cdot Et_2O$ in THF at −50 °C (Table 1, entry 3). Gratifyingly, we still obtained complete β-selectivity with a similar 92% yield, indicating the presence of other strong β-directing factors independent of the anomeric configuration of the imidate donors. To gain further insights into the β-directing effect of $BF_3 \cdot Et_2O$ and THF, we conducted four control reactions (entries 4–7) by replacing them with TMSOTf and CH_2Cl_2, respectively. The condensation of **1** and **3** with TMSOTf in CH_2Cl_2 (entry 4) was found to be almost non-stereoselective (β/α = 1.3 : 1) at −50 °C. Utilizing $BF_3 \cdot Et_2O$ in CH_2Cl_2 (entry 5) increased the β/α ratio to 5.1 : 1, which was in agreement with Schmidt's report.[56] Replacement of donor **1** (predominantly α-donor) with β-donor **2** in CH_2Cl_2 (entry 6) also led to β-selectivity (β/α = 3.5 : 1), reaffirming the presence of alternative β-directing pathways distinct from the direct S_N2 attack on α-donors.
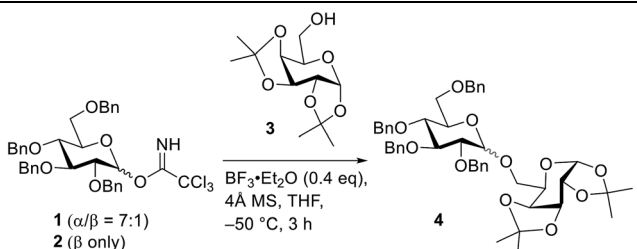
On the other hand, the β-selectivity (β/α = 2.5 : 1, entry 7) that we achieved with TMSOTf in THF was not expected. It is well-known that ether solvents, such as Et_2O and 1,4-dioxane, are experimentally α-directing in glucosylation.[57–62] However, by comparing the β/α ratios in THF and CH_2Cl_2 (2.5 : 1 in entry 7 *vs.* 1.3 : 1 in entry 4), we found that THF could actually be β-directing at −50 °C. Although the β-directing effects of $BF_3 \cdot Et_2O$ (entries 5 and 6) and THF (entry 7) did not seem significant individually, it seemed their combination could, in some way, provide a strong synergistic effect to give complete β-selectivity (entries 1–3) in glucosylation. In fact, the combination of $BF_3 \cdot Et_2O$ in Et_2O also offered a high β/α ratio of 20 : 1 at −50 °C (entry 8), compared to the poor β/α ratio of 1 : 1.2 with TMSOTf in Et_2O (entry 9). Additionally, we also achieved high β-selectivity (β/α > 20 : 1 or β only) with $BF_3 \cdot Et_2O$ in MTBE, 2-methyl-THF, and 2,5-dimethyl-THF (Table S1†), suggesting that this synergistic effect with $BF_3 \cdot Et_2O$ may be common among ether solvents.

A low temperature of −50 °C was found necessary to ensure the high 91% yield for the glycosylation in THF (entry 1), while increasing the reaction temperature to −25 °C maintained the β-specificity but reduced the yield to 70% (entry 10) due to the formation of glucosyl fluoride. In comparison, other ether solvents, such as Et_2O (entry 11), at −25 °C decreased the β/α ratio down to 3 : 1 (Table S1†). Nevertheless, the results in Table 1 indicate that the present high stereoselectivity could primarily be attributed to the synergistic effect of $BF_3 \cdot Et_2O$ and THF rather than to the donors being α- or β-configured. Low temperatures, such as −50 °C, could further increase the β-selectivity and yields.

Scope for stereoselectivity

To further understand the unexpected stereoselectivity induced by $BF_3 \cdot Et_2O$ and THF, we investigated 11 pyranosyl and furanosyl imidate donors (**5–15**) varying in sugar types and protecting groups (Fig. 2b). These donors were prepared from their corresponding hemiacetals using the routine proto-

Table 1 Reaction validation

Entry	Deviation	Yield[a] (β/α ratio)[b]
1	None (donor **1**)	91% (β only)
2	Gram scale	99% (β only)
3	Pure β-donor (**2**)	92% (β only)
4	TMSOTf (0.1 eq.), CH_2Cl_2	85% (1.3 : 1)
5	CH_2Cl_2	70% (5.1 : 1)
6	Pure β-donor (**2**), CH_2Cl_2	80% (3.5 : 1)
7	TMSOTf	86% (2.5 : 1)
8	Et_2O	71% (20 : 1)
9	TMSOTf, Et_2O	68% (1 : 1.2)
10	−25 °C	70% (β only)
11	Et_2O, −25 °C	66% (3 : 1)

[a] Products were isolated *via* chromatography. [b] Ratios were determined through ^1H NMR.
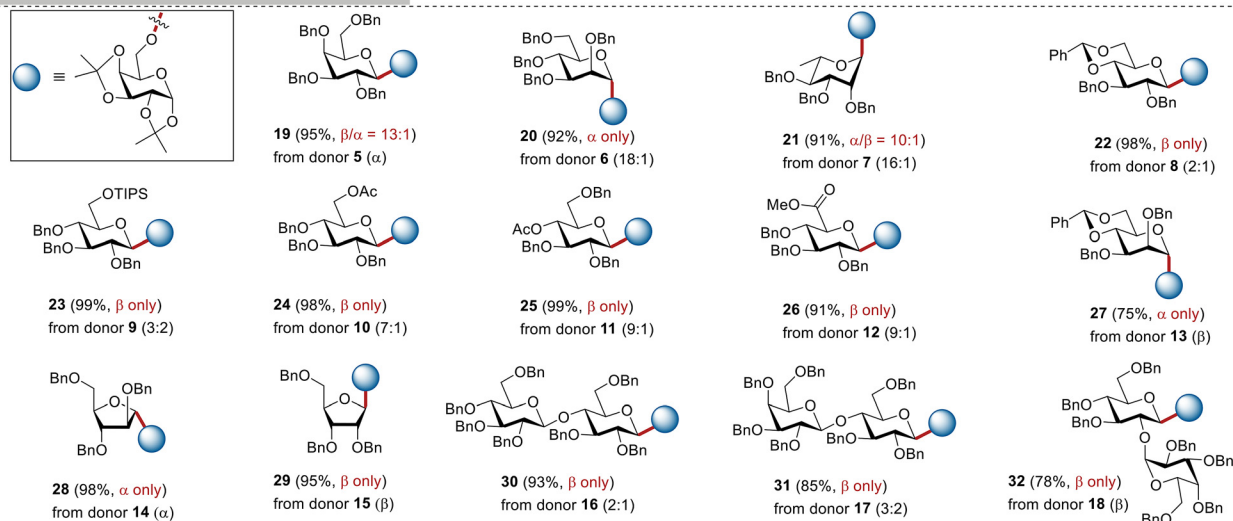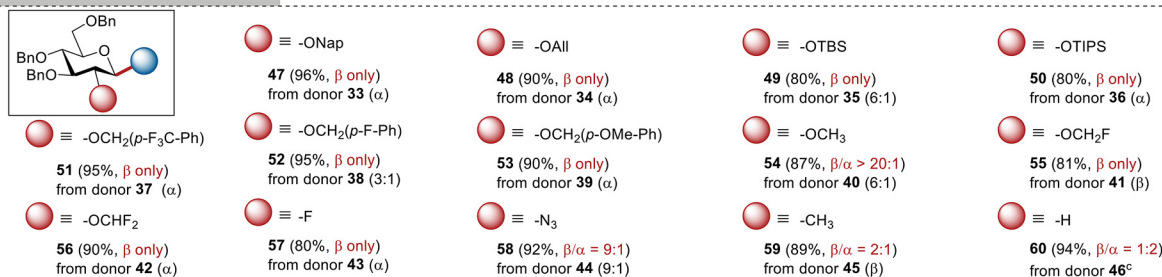
Fig. 2 Scope for stereoselectivity. [a] Products were isolated using chromatography. [b] Ratios were determined via ^{1}H NMR. [c] α/β ratio of donor 46 was not determined due to its lability. [d] Reactions were sluggish.

col (NCCCl$_3$ and DBU in CH$_2$Cl$_2$) without deliberately separating the anomers, leading to α-donors (*e.g.*, **5**), β-donors (*e.g.*, **13**), and α/β mixtures (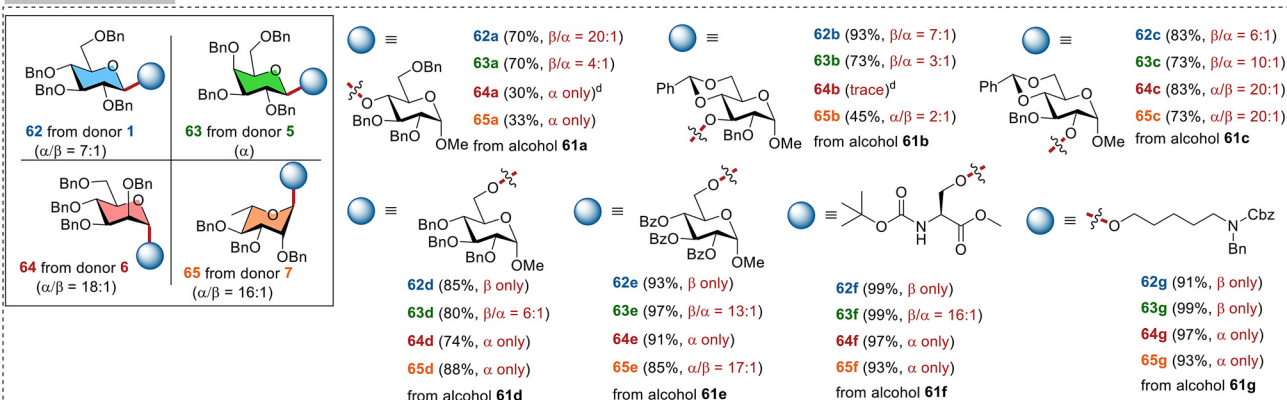*e.g.*, **9**). Regardless of their anomeric configuration, they were employed to glycosylate alcohol **3** under the standard conditions (0.4 eq. of BF$_3$·Et$_2$O, THF, −50 °C) to evaluate the stereoselectivity and donor scope (Fig. 2a). To our delight, the results in Fig. 2b clearly show that the glycosylation was 1,2-*trans* selective rather than axial- or equatorial-selective for both pyranoses and furanoses, giving the corresponding β-glucosides **22–26**, β-galactoside **19**, α-mannosides **20/27**, α-rhamnoside **21**, α-arabinofuranoside **28**, and β-ribofuranoside **29**. Most reactions exhibited complete stereoselectivity with yields exceeding 90%, indicating a broad substrate scope and robust compatibility with various functional groups. Taking glucosylation as an example, an α-directing 6-OAc group (donor **10**) or a bulky 6-OTIPS group (donor **9**) did not diminish the β-selectivity. Donor **8** with a benzylidene-restrained conformation also resulted in complete β-selectivity for the disaccharide **22** with a yield of 98%. Even the glucuronic donor **12** bearing the electron-withdrawing methyl ester group, which is usually considered to be a poor donor due to its tendency toward elimination and epimerization, was smoothly converted into the disaccharide **26** with a high 91% yield and complete β-selectivity. Arabinosyl imidate **14** and ribosyl imidate **15** as representative furanosyl donors also led to the desired α-arabinoside **28** and β-riboside **29** with complete stereoselectivity and high yields.

Compared to monosaccharide donors, achieving stereocontrol with oligosaccharide donors is more challenging yet crucial for implementing a convergent strategy for the efficient synthesis of complex carbohydrates.[22–24] Thus, we prepared cellobiosyl imidate **16**, lactosyl imidate **17**, and the 2-*O*-glycosylated disaccharide donor **18** for further evaluation (Fig. 2b). Gratifyingly, all these donors resulted in complete 1,2-*trans* selectivity to give the desired trisaccharides **30–32**. These results highlight the valuable potential of BF$_3$·Et$_2$O/THF glycosylation in the convergent synthesis of complex carbohydrates, particularly in cases involving the use of 2-*O*-glycosylated donors,[63] which cannot adopt the conventional 2-*O*-acyl directing strategy for stereocontrol.

All the donors in Fig. 2b share a benzyl group at O2. We were curious about whether this could be replaced with other groups while maintaining high 1,2-*trans* selectivity. Thus, 10 additional glucosyl imidate donors (**33–42**) bearing diverse groups at the O2 position were prepared and evaluated. As depicted in Fig. 2c, all the reactions were 1,2-*trans* β-specific, giving the corresponding disaccharides **47–56** in high yields. These results indicated the broad compatibility with various groups at O2. Notably, the stereoselectivity was barely affected by the electron density (*e.g.*, **54** *vs.* **56**) or steric hindrance (*e.g.*, **54** *vs.* **50**) of the substituents at O2, suggesting that direct repulsion was unlikely the primary factor for the stereocontrol. Additionally, we prepared four 2-deoxy donors (**43–46**) bearing different substituents at C2. The donor with a 2-fluoro group or a 2-azide group (**43** or **44**) still exhibited satisfactory β-selectivity in glycosylation, while the 2-methyl donor **45**

resulted in a poor β/α ratio of 2 : 1, and the 2-deoxy donor **46** even led to a reversed β/α ratio of 1 : 2. These findings underscore the necessity of a heteroatom at C2 for maintaining high stereoselectivity.

Meanwhile, we conducted studies on the acceptor scope for the BF$_3$·Et$_2$O/THF glycosylation (Fig. 2d). In addition to glucosyl imidate **1**, we also employed galactosyl, mannosyl, and rhamnosyl imidates **5–7** to glycosylate seven representative acceptors (**61a–61g**) varying in electron density, steric hindrance, and structural rigidity. These acceptors included five glucosides with 2-OH, 3-OH, 4-OH, and 6-OH, among which the 4,6-*O*-benzylidene-restrained 3-OH glucoside **61b** was one of the poorest acceptors in terms of stereocontrol.[22,24,66] As depicted in Fig. 2d, primary alcohols generally led to both high yields and 1,2-*trans* selectivity, giving β-configured glucosides/galactosides and α-configured mannosides/rhamnosides. This protocol was also found to be highly efficient for coupling the fatty alcohol **61g**, a prevalent linker for preparing carbohydrate vaccines.[67,68] On the other hand, secondary alcohols resulted in decreased stereoselectivity due to the increased hindrance and rigidity.[66,69,70] Their yields also decreased due to the formation of glycosyl fluorides that were inert under these conditions, particularly in the mannosylation and rhamnosylation of hindered alcohols **61a** and **61b**. The reactions were also found to be sluggish to further reduce the yields. Among these four donors, glucosyl donor **1** proved to be the most effective one in terms of both yield and stereoselectivity. Even with the poorest acceptor **61b**, donor **1** led to a satisfactory β/α ratio of 7 : 1 for **62b**, compared to 2 : 1 in our previous studies.[22]
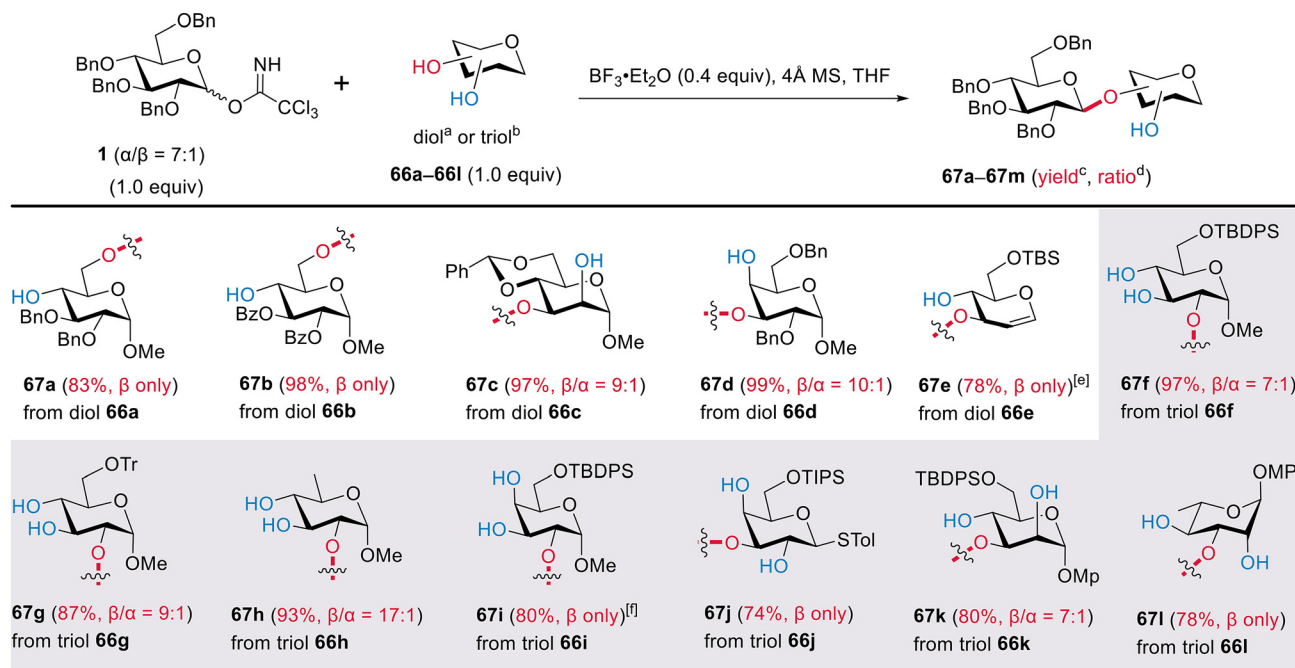
Scope for regioselectivity and synthetic application

The results in Fig. 2d suggest a valuable sensitivity to the nucleophilicity of the acceptors in glycosylation, inspiring us to pursue regioselective glycosylation under the conditions of BF$_3$·Et$_2$O in THF. Thus, 1.0 eq. of glucosyl donor **1** was utilized to glycosylate 1.0 eq. of multihydroxy acceptors (Fig. 3a). First, we evaluated benzylated glucoside **66a** and benzoylated glucoside **66b** as diol acceptors possessing a primary 6-OH and a secondary 4-OH but different electron densities. Their glycosylation with donor **1** proceeded smoothly, resulting in 6-*O*-glycosylated disaccharides **67a** (83%) and **67b** (98%) with complete β-selectivity, indicating the excellent regioselectivity of the primary 6-OH. For the secondary diols **66c** and **66d** bearing an equatorial 3-OH and an axial 2-OH or 4-OH, only the equatorial 3-OH was glycosylated to give **67c** and **67d** in over 95% yields. The glycosylated hydroxyl group was confirmed based on the downfield-shifted δ_H related to the unglycosylated one after acetylation. However, we also observed minor components in the ^{1}H NMR spectra of both **67c** and **67d**, which were assigned to the α-anomers rather than the regioisomers based on their $\delta_{C1'}$ values being less than 100 ppm. An acid-labile glucal **66e**, with its 2-OH and 3-OH both in the equatorial orientation, was also found to be effective, providing 3-*O*-glycosylated **67e** with complete β-selectivity.
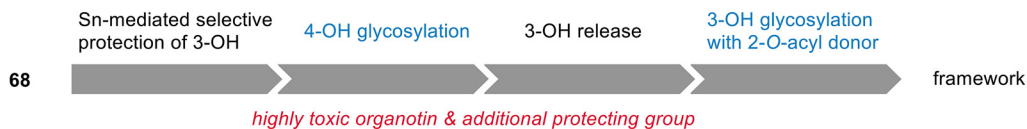
The high regio- and stereoselectivity toward diols encouraged us to extend the studies to more challenging secondary

(a) Regio- and stereoselective glycosylation of diols and triols

1 (α/β = 7:1)
(1.0 equiv)

66a–66l (1.0 equiv)

BF$_3$·Et$_2$O (0.4 equiv), 4Å MS, THF

diol^a or triol^b

67a–67m (yield^c, ratio^d)

67a (83%, β only)
from diol **66a**

67b (98%, β only)
from diol **66b**

67c (97%, β/α = 9:1)
from diol **66c**

67d (99%, β/α = 10:1)
from diol **66d**

67e (78%, β only)$^{[e]}$
from diol **66e**

67f (97%, β/α = 7:1)
from triol **66f**

67g (87%, β/α = 9:1)
from triol **66g**

67h (93%, β/α = 17:1)
from triol **66h**

67i (80%, β only)$^{[f]}$
from triol **66i**

67j (74%, β only)
from triol **66j**

67k (80%, β/α = 7:1)
from triol **66k**

67l (78%, β only)
from triol **66l**

(b) Synthesis of oligosaccharide framework 70 related to *Enterococcus faecalis* antigen

Conventional procedure

68 → Sn-mediated selective protection of 3-OH → 4-OH glycosylation → 3-OH release → 3-OH glycosylation with 2-O-acyl donor → framework

highly toxic organotin & additional protecting group

Our greener strategy

68 → BF$_3$·Et$_2$O, 4Å MS, THF, −50 °C, 76%, (β only, 940 mg) → **1** → TMSOTf, 4Å MS, Et$_2$O, −60 °C, 81% (α) → **69** → **70**
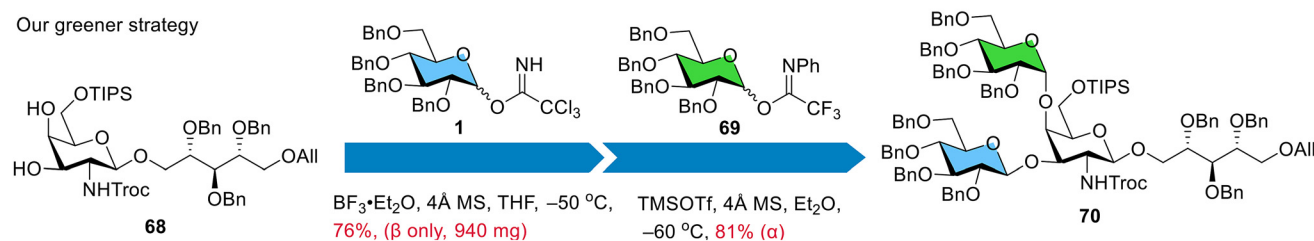
Fig. 3 Scope for regioselectivity and synthetic applications. ^{a} Reactions of diols were conducted at −50 °C. ^{b} Reactions of triols were conducted at −60 °C. ^{c} Products were isolated by chromatography. ^{d} Ratios were determined by ^{1}H NMR. ^{e} 0.1 eq. of BF$_3$·Et$_2$O was used for **67e** to obtain β only. ^{f} **67i** was contaminated with 3-O-(β-glucosyl)-galactoside in a 10% yield.

triol acceptors (Fig. 3a).[42,43,48,49,52,71] Using THF as the solvent ensures good solubility for these polar and hydrophilic triols. Thus, seven easily accessible glycoside 2,3,4-triols, *i.e.*, glucosides **66f/66g**, 6-deoxyglucoside **66h**, galactosides **66i/66j**, mannoside **66k**, and rhamnoside **66l**, were utilized with variations in the protecting group at C6/C1 and the anomeric configuration. Gratifyingly, upon treatment with 1.0 eq. of glucosyl donor **1**, these 2,3,4-triols were glycosylated at the relatively more nucleophilic hydroxyl group in a highly regioselective manner, *i.e.*, 2-OH on α-glucosides/α-galactosides or 3-OH on β-galactosides/α-mannosides/α-rhamnosides. The corresponding products **67f–67l** were successfully isolated with both satisfactory yields (74%–97%) and β-selectivity (β/α = 7 : 1 to β

only). Compared to the protected acceptor **61c** with 2-OH (Fig. 2d), glucoside triol **66f** and **66g** even provided improved yields and β-selectivity for 2-O-glycosylated **67f** (97%, β/α = 7 : 1) and **67g** (87%, β/α = 9 : 1). Removal of the substituent at C6 led to 6-deoxyglucoside **66h** and further increased the β/α ratio to 17 : 1 for 2-O-glycosylated **67h** in a high 93% yield.

It is noteworthy that the glycosylation of α-galactoside **66i** resulted in 2-O-glycosylated **67i** in an 80% yield with complete β-selectivity, while β-galactoside **66j** led to the regioisomeric 3-O-glycosylated **67j** in a 74% yield, also with complete β-selectivity. These results suggest a practical manipulation of the regioselectivity between O2 and O3 was possible by using α- or β-configured galactoside acceptors. On the other hand,

both the mannoside and rhamnoside triols **66k** and **66l** were converted into 3-*O*-glycosylated **67k** and **67l** with good yields and β-selectivity.

This 1,2-*trans* and regioselective glycosylation can enable concise access to an oligosaccharide antigen (Fig. 3b) related to *Enterococcus faecalis*,[72] a common nosocomial pathogen that causes severe urinary tract infections, surgical wound infections, pneumonia, bacteremia, *etc.*[73,74] A conventional synthesis from precursor **68** would require at least four chemical steps, including a selective protection of 3-OH with the toxic organotin reagent and a β-selective glucosylation reaction of 3-OH with 2-*O*-acyl donors. However, previous reports with such disarmed 2-*O*-acyl donors and similar acceptors raised our concern about the undesired orthoesters that would arise as the predominant products,[75,76] and so an alternative β-(1→3)-selective approach with an armed 2-OBn donor would be highly preferred. Thus, we subjected diol **68** to condensation with benzylated imidate **1** under BF$_3$·Et$_2$O (0.2 eq.) in THF at −50 °C. To our delight, the reaction was highly β- and O3-selective, giving the desired 3-*O*-glucosylated galactoside in a 76% yield (β only, scaled up to 940 mg). The remaining 4-OH was then glycosylated with donor **69** to provide the branched oligosaccharide **70** in an 81% yield. Compared to the conventional four-step route, this two-step route was straightforward, with a considerable decrease in *E* factor (see the SI† for the detailed calculations), and eliminated concerns about organotin toxicity, orthoester formation, and the need for the additional removal of acyl groups.

Mechanism studies

It was intriguing to explore the intricate mechanism underlying this stereo- and regioselective glycosylation driven by such a simple combination of BF$_3$·Et$_2$O in THF. In fact, our current findings appear to challenge or even contradict the previously proposed stereocontrol mechanisms associated with ether solvents or BF$_3$·Et$_2$O. For instance, ether solvents are generally expected to induce α-selectivity in glucosylation,[57–62] which is contrary to the β-selectivity we observed. The model of direct S$_N$2-type attack to α-donors[55] could not justify the formation of β-glucosides from β-donors, since no isomerization from β-donors to α-donors was observed during our variable-temperature (VT) NMR studies (Fig. S1†). Some reports suggest glycosyl fluorides are important intermediates or that there is an involvement of *in situ* HF or SiF$_4$.[77–80] However, we found glycosyl fluorides were stable with BF$_3$·Et$_2$O in THF, and our VT NMR studies did not detect any signals for HF or SiF$_4$. These disparities indicate that the BF$_3$·Et$_2$O/THF glycosylation proceeded *via* a different pathway from the regular BF$_3$·Et$_2$O-promoted glycosylation.

Nevertheless, we conducted multiple VT NMR studies to seek out any meaningful intermediates. To minimize interference from other stereocontrol pathways, such as direct S$_N$2 attack on glucosyl α-imidates, we preferred to use glucosyl β-imidates because the resulting β-selectivity should rely more on this unknown mechanism. In terms of stability and accessibility, we chose the β-anomer of the benzylidene-restrained

donor **8**, *i.e.*, **8β**. Although our VT NMR studies did not reveal intermediates that were directly responsible for the selectivity, they provided valuable information, particularly on the formation and transformation of fluoroboron species. We were aware that the promoter BF$_3$·Et$_2$O is unlikely to survive in THF solvent due to the replacement of the coordinated Et$_2$O with THF. Indeed, δ_H was upfield-shifted to 3.37 (CH$_2$) and 1.12 (CH$_3$) ppm (Fig. S3†) after the addition of BF$_3$·Et$_2$O to deuterated THF (THF-*d*8) at −70 °C, compared to the reported δ_H at around 4.2 and 1.5 ppm for BF$_3$·Et$_2$O in CDCl$_3$,[81,82] indicating an instant and complete release of Et$_2$O from BF$_3$·Et$_2$O. In the corresponding ^{19}F NMR spectrum, two sets of two singlets, corresponding to [10]B and [11]B, were observed at −151.6 and −156.5 ppm at −70 °C (Fig. 4b), assigned to BF$_3$·H$_2$O (Fig. S3 and S4†) and BF$_3$·THF (Fig. S5†), respectively.

Interestingly, these signals of BF$_3$·THF vanished upon the addition of MeOH (0.2 M) as an acceptor to the solution of BF$_3$·Et$_2$O (0.02 M) in THF-*d*8 at −70 °C (Fig. 4b). Instead, a new set of two singlets was observed at −157.0 ppm, assigned to BF$_3$·MeOH as a minor component (Fig. S6†). Increasing the amount of BF$_3$·Et$_2$O provided BF$_3$·THF in coexistence with BF$_3$·H$_2$O and BF$_3$·MeOH (Fig. S6†). Consequently, the coordination ability order with BF$_3$ appeared to be in the order: H$_2$O > MeOH > THF. Moreover, the signals of BF$_3$·MeOH were broadened and slightly downfield-shifted in the presence of the imidate donor **8β** (Fig. 4b), suggesting an interaction between BF$_3$·MeOH and the imidate. This leads to an assumption that the coordinated complexes of BF$_3$ with acceptors (*i.e.*, BF$_3$·ROH) might be the true promoters acting as Brønsted acids, releasing anions [BF$_3$OR]$^-$ as nucleophiles for glycosylation. This assumption aligns with an interesting finding in the VT NMR studies, wherein donor **8β** remained intact at −50 °C in the absence of acceptors (Fig. S1†), suggesting the involvement of acceptors in initiating the glycosylation. Furthermore, this assumption was experimentally supported by the similar glycosylation results obtained from the control reactions using either commercially available BF$_3$·MeOH or BF$_3$·Et$_2$O/MeOH (Fig. 4a).

We propose that BF$_3$·ROH complexes act as Brønsted acids to activate imidate donors and release anions [BF$_3$OR]$^-$ (Fig. 4c). Under this assumption, the resulting anions [BF$_3$OR]$^-$ are not only more reactive but also closer to the reaction center than regular alcohols, thereby rationalizing the high regioselectivity in Fig. 3a. Given the similar reaction results with α- or β-imidate donors, the selective outcomes were not associated with the departure of the imidate group. Thereupon the post-activation reaction system presumably consisted of a glycosyl cation, anion [BF$_3$OR]$^-$, inactive trichloroacetamide, and solvent before the stereoselective formation of glycosidic bonds. Therefore, we propose a putative mechanism involving nucleophilic attack of [BF$_3$OR]$^-$ on the oxocarbenium–solvent complex **Int-2** (Fig. 4c),[11] wherein THF can stabilize the oxocarbenium.

Next, we conducted density functional theory (DFT) calculations on the glucosylation and mannosylation of methanol as models (Fig. 4c and Fig. S7†). To simplify the calculations, we employed donors (*e.g.*, **72**) with a restrained conformation,
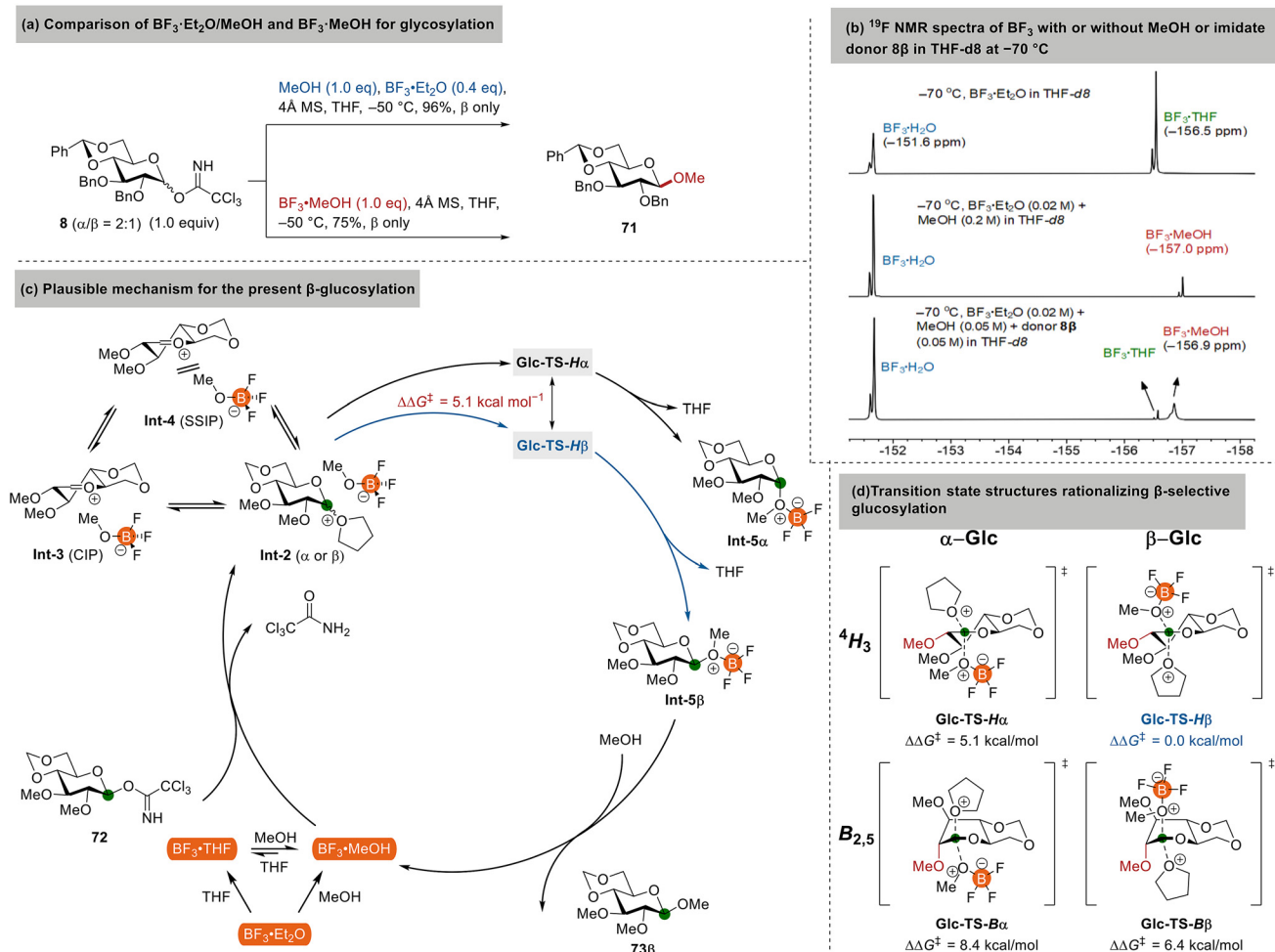
Fig. 4 Mechanistic studies of highly 1,2-*trans* and regioselective glycosylation. DFT calculations were performed at the M06-2X/6-311+G(d,p)/PCM (THF)//M06-2X/6-31G(d,p)/PCM(THF) level of theory. See ESI† for mannosylation results and additional details. CIP, contact ion pair; SSIP, solvent-separated ion pair; **Int**, intermediate; **Glc-TS-$H\alpha$**, transition state in $^4H_3$ conformation for α-attack on the glucosyl cation; **Glc-TS-$H\beta$**, transition state in $^4H_3$ conformation for β-attack on the glucosyl cation; **Glc-TS-$B\alpha$**, transition state in $B_{2,5}$ conformation for α-attack on the glucosyl cation; **Glc-TS-$B\beta$**, transition state in $B_{2,5}$ conformation for β-attack on the glucosyl cation.

replacing benzyl and benzylidene groups with methyl and methylene groups, respectively. Specifically, we focused on the energy differences of the reaction pathways with the $^4H_3$ and $B_{2,5}$ conformations based on previous reports and conformational analysis.[83–85] Calculations at the M06-2X/6-31G**/ PCM(THF) quantum chemical level for structure optimization and frequency, with single-point energy correction at the higher M06-2X/6-311+G**/PCM(THF) level, were performed. The computed results for the glycosylation process are depicted in Fig. 4d. Notably, the glucosyl cation favored the $^4H_3$ conformation while the mannosyl cation preferred the $B_{2,5}$ conformation (Fig. S7†), with both desirable transition states featuring the pseudoequatorial C-2 substituent. The free energy barrier for the β-attack on the glucosyl cation was significantly lower than that for α-attack by 5.1 kcal mol^{-1}. This causes the β-side attack preference and predominate outcome of **Int-5β**, resulting in the β-glucoside **73β** (Fig. 4c) after the release of BF₃. Conversely, α-attack on the mannosyl cation led

to a more stable transition state than in the case of the β-attack (Fig. S7†). As a result, mannosylation under the same condition primarily afforded the α-product.

Conclusions

In conclusion, we discovered a straightforward approach for 1,2-*trans* and regioselective glycosylation enabled by a simple yet synergistic combination of BF₃·Et₂O in THF. Ether solvents, including THF, are typically regarded as promoting 1,2-*cis* α-selectivity, while BF₃·Et₂O is considered to be a poor stereo-control factor. However, their combination permits the construction of multiple 1,2-*trans* glycosides with remarkable stereo-outcomes, irrespective of whether using α- or β-imidate donors. This ensures facile access to both pyranosides and furanosides. This protocol is applicable to oligosaccharide donors and demonstrates broad compatibility with variations

of the protecting groups, including those at O2. Furthermore, the glycosylation of diols or triols under these conditions exhibits exceptional regioselectivity by amplifying the reactivity differences among hydroxyl groups, favoring the one with a relatively higher nucleophilicity. We utilized this approach, avoiding laborious protection and deprotection on the central Gal$p$NAc, to synthesize an oligosaccharide antigen precursor related to *Enterococcus faecalis*. In addition, experimental studies on the mechanism revealed an unconventional process promoted by the BF$_3$–acceptor complex BF$_3$·ROH, leading to a putative pathway involving nucleophilic attack of the anion [BF$_3$OR]$^-$ on the THF-stabilized anomeric center. DFT calculations rationalized the stereoselectivity through comparing the energy barriers during the process.

We consider this a green and practical strategy for 1,2-*trans* glycosides construction. With its high stereo- and regioselectivity, this strategy utilizes a concise, cheap, and eco-friendly protocol to shorten the synthetic routes to obtain complex carbohydrates and reduces the reliance on the protecting groups, thereby enhancing the flexibility of carbohydrate synthesis. Atom-economical imidate donors, especially a mixture of anomers, can be utilized avoiding extra separation and waste of the undesired anomer. Furthermore, the need for noble metals and halogenated solvents is circumvented, making these transformations sustainable. This study demonstrates that a longstanding challenge in chemical synthesis can be addressed using a simple yet often overlooked system.

Author contributions

W. L. and Z. Z. designed the research and wrote the manuscript. Z. W., L. G., J. S., S. P., X. H., and P. Z. conducted the synthetic work. Y. W. and F. Y. conducted VT NMR studies. Z. Z. contributed computational calculations. W. X., X. W., B. Y., P. X., and X. Z. revised the manuscript and fully engaged in discussion.

Data availability

All data related to this study, including the characterization data for new chemical compounds, are included within the paper and its ESI† and are available from the authors upon reasonable request.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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