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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.0c03165 • Publication Date (Web): 24 Mar 2020

Fluoride Migration Catalysis Enables Simple, Stereoselective, and Iterative Glycosylation

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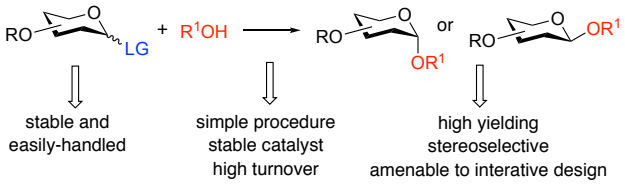
Abstract: Challenges in the assembly of glycosidic bonds in oligosaccharides and glycoconjugates pose a bottleneck in enabling the remarkable promise of advances in the glycosciences. Here, we report a strategy that applies unique features of highly electrophilic boron catalysts, such as tris(pentafluorophenyl)borane, in addressing a number of the current limitations of methods in glycoside synthesis. This approach utilizes glycosyl fluoride donors and silyl ether acceptors while tolerating the Lewis basic environment found in carbohydrates. The method can be carried out at room temperature using air- and moisture stable forms of the catalyst, with loadings as low as 0.5 mol %. These characteristics enable a wide array of glycosylation patterns to be accessed, including all C1-C2 stereochemical relationships in the glucose, mannose and rhamnose series. This method allows one-pot, iterative glycosylations to generate oligosaccharides directly from monosaccharide building blocks. These advances enable the rapid and experimentally straightforward preparation of complex oligosaccharide units from simple building blocks.

Introduction:

Advances in the glycosciences present enormous promise in the understanding of disease and the development of strategies for improving human health.[1-3] The structural diversity and resulting biological properties of oligosaccharides and glycoconjugates are amplified by the stereochemical variations present within monosaccharide building blocks, the positioning (or absence) of oxygen and nitrogen functionality, and the multitude of possible points of connection between monosaccharide units. These features, paired with the multivalency of binding interactions, provide oligosaccharide chains with exquisite properties that govern many molecular recognition events in biology.

The diversity of structural variations in carbohydrates present inherent complexities in their preparation that have been addressed by enzymatic and synthetic approaches. Enzymatic methods are generally unmatched in preparative efficiency once developed and optimized,[4-6] but organic synthesis methods have the advantages of being more accessible to non-specialists and are readily adapted to diverse structural motifs. State-of-the-art chemical synthesis methods in carbohydrate chemistry, however, often require specialized equipment and/or expert control of experimental variables including rigorous exclusion of moisture and air, precise temperature control, and the handling of sensitive and unstable reagents.[7] Despite the promise and potential generality of synthetic approaches, the development of rapid, robust, and operationally simple synthetic methods that are accessible to the broader biomedical research community remains as a critical need in glycoscience (Scheme 1).[8]



Scheme 1. Desirable Features of Catalytic Glycosylation Methods.

Many classes of glycosyl donors have been utilized with a broad range of promoters. The most commonly utilized anomeric leaving groups in carbohydrate chemistry include trichloroacetimidates, thioglycosides and glycosyl bromides.[9] Glycosyl leaving groups fall along a reactivity-stability continuum, with the most stable leaving groups, such as n-pentenyl glycosides,[10] requiring strongly electrophilic promoters, whereas the most active leaving groups, such as trichloroacetimidates,[11] are more reactive but challenging to carry through protecting group manipulations. Thioglycosides and glycosyl fluorides are highly attractive from a stability standpoint, but developing efficient catalytic protocols become progressively more challenging in comparison to their more reactive counterparts.[12-14] While many catalytic processes have been described with these various donor classes,[15] turnover numbers are often poor, and many of the most widely-used glycosylation methods require super-stoichiometric loadings of promotors.

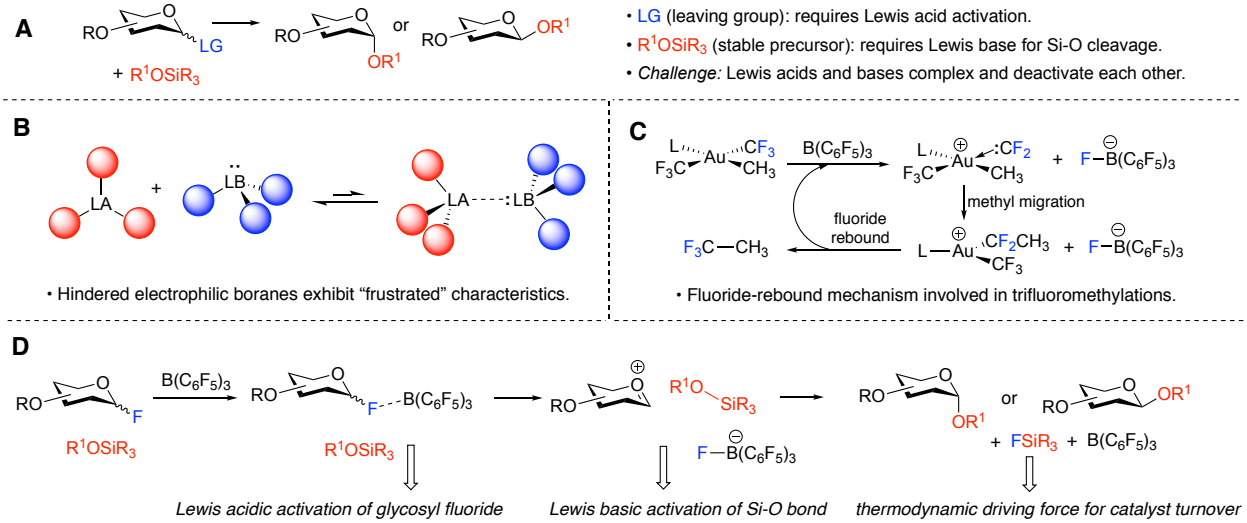
While stepwise approaches to oligosaccharide assembly are most commonly employed, innovative strategies for iterative assembly have been described.[10, 16-21] In order to enable the desired glycosylation sequence to be designed, these methods often require technically challenging

procedures with extensive variation of protecting groups, anomeric leaving groups, and/or activating reagents to impart stereoselectivity and regiocontrol. Automated methods provide the most promising non-enzymatic approaches towards the programmed synthesis of oligosaccharides,[22-25] but experimentally simple, iterative synthesis through conventional, non-automated methods without specialized equipment and procedures remains as a major gap in the field. In this study, we report a new boron catalyzed glycosylation method pairing glycosyl fluoride donors with silyl ether acceptors in an approach that addresses many of the current limitations of glycoside synthetic methods.

Results and Discussion:

The goals of our work include the development of a rapid and simple approach that proceeds at room temperature, avoids the rigorous exclusion of moisture and air, provides flexible control of stereochemistry, and offers opportunities for iterative assembly of oligosaccharides using common building blocks (Scheme 1). Our approach employs the use of anomeric fluoride building blocks as the glycosyl donor and silyl ethers as the glycosyl acceptor. Glycosyl fluorides have long been recognized as a useful building block for glycosylations, and they are typically activated by stoichiometric promoters that sequester the fluoride leaving group.[14, 26] Their ease of access, shelf life, and stability towards chromatographic purification position them as one of the most desirable classes of glycosyl donors, but more efficient and experimentally simple activation methods are needed in order to broaden their appeal. A potentially attractive but rarely employed glycosylation protocol involves the coupling of glycosyl fluorides with silyl ethers, which allows glycoside bond formation along with a stable silicon fluoride byproduct.[27-31] A challenge in developing more practical versions of this process is the need for a stable and catalytically active Lewis acid to activate the glycosyl fluoride donor and a nucleophilic Lewis base to render cleavage of the stable silicon-oxygen bond of the glycosyl acceptor (Scheme 2A). While the self-quenching characteristic of most Lewis acid-Lewis base pairs renders this approach untenable for efficient catalysis, we were attracted by the unique reactivity[32] and Frustrated Lewis Pair (FLP) characteristics[33-35] exhibited by $B(C_6F_5)_3$ (Scheme 2B). Specifically, the equilibrium concentration of free Lewis acids and Lewis bases that coexist with structures of this type seemed ideally suited for glycosyl fluoride couplings with silyl ethers while avoiding deactivation of the Lewis acid by the Lewis-basic oxygen-rich nature of the carbohydrate building blocks. In support of this rationale, a unique fluoride-rebound mechanism was recently elucidated in $B(C_6F_5)_3$ catalyzed

trifluoromethylations (Scheme 2C),[36-37] wherein the electrophilic triarylborane abstracts and then redelivers a fluoride ion in an efficient catalytic sequence. These observations in $B(C_6F_5)_3$ catalysis form the basis of a key hypothesis that electrophilic triarylborane catalysts might abstract the fluoride ion from a glycosyl donor, and then efficiently redeliver it as the Lewis base to activate the silyl ether component (Scheme 2D). Furthermore, we anticipated that silyl structure variation in the acceptor reagent might be used as an approach to reverse stereoselectivity using inter- and intramolecular versions and also to sequence the reactivity of multiple hydroxyls in iterative one-pot couplings.

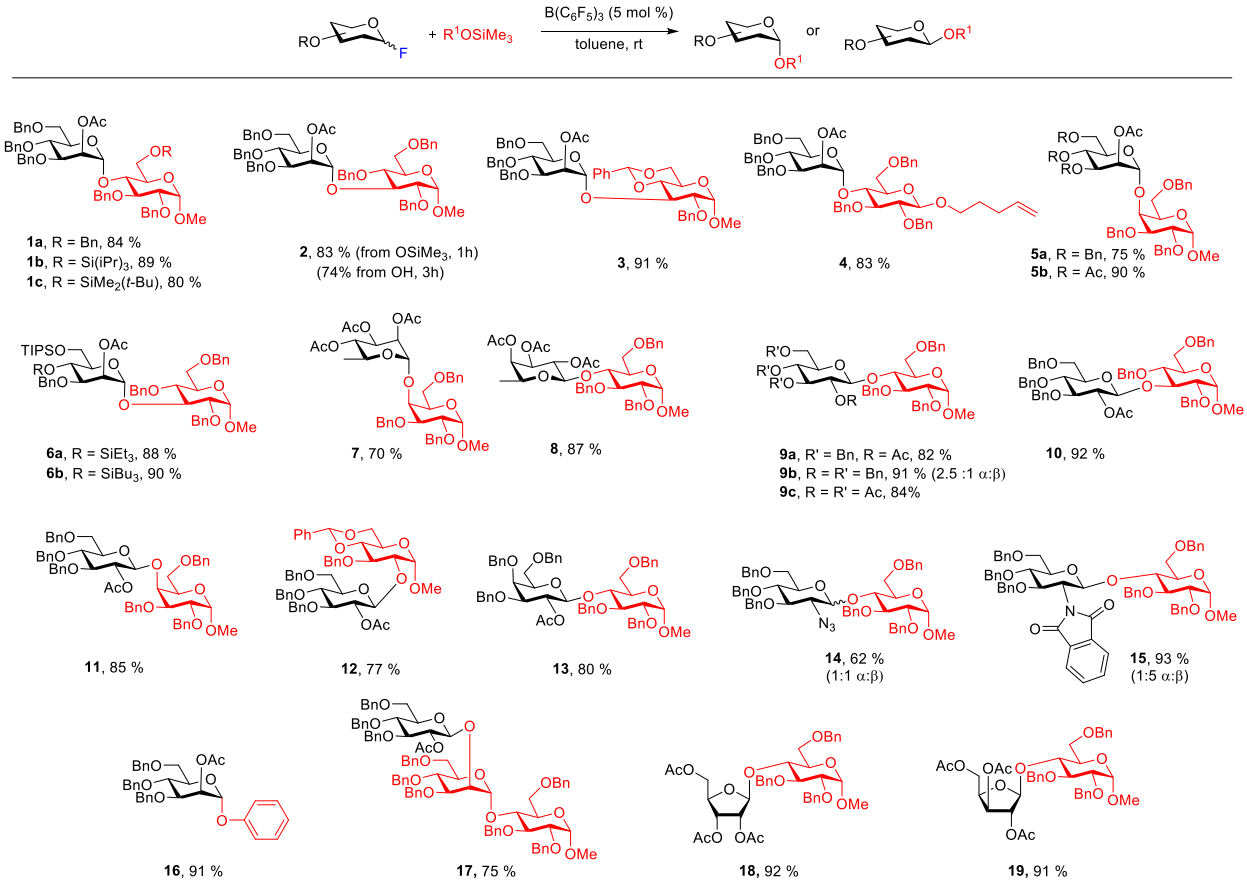


Scheme 2. Key design considerations of $B(C_6F_5)_3$ catalyzed glycosylations. (**A**) Challenges in direct utilization of silyl ethers in glycosylations. (**B**) Key characteristic of Frustrated Lewis Pairs (FLPs). (**C**) Fluoride rebound mechanism in trifluoromethylations using $B(C_6F_5)_3$. (**D**) Central hypothesis for the design of $B(C_6F_5)_3$-catalyzed coupling of glycosyl fluorides and silyl ethers.

The feasibility of this approach was examined in glycosidic couplings to install *trans* C1-C2 linkages using C2, C3, C4 and C6 acceptors across a range of monosaccharide combinations with various protecting groups (Scheme 3). Utilizing 5 mol % $B(C_6F_5)_3$ at room temperature in toluene or dichloromethane, high-yielding, rapid, and highly stereoselective glycosylations were observed. Acetate protection at the C2 position was typically employed since this protecting group is well established to direct the formation of C1-C2-*trans* glycosides through neighboring group participation. Orthoester formation between the C2 and C1 oxygenation was not observed, and an independently synthesized orthoester was illustrated to rearrange to the C2 acetate-protected

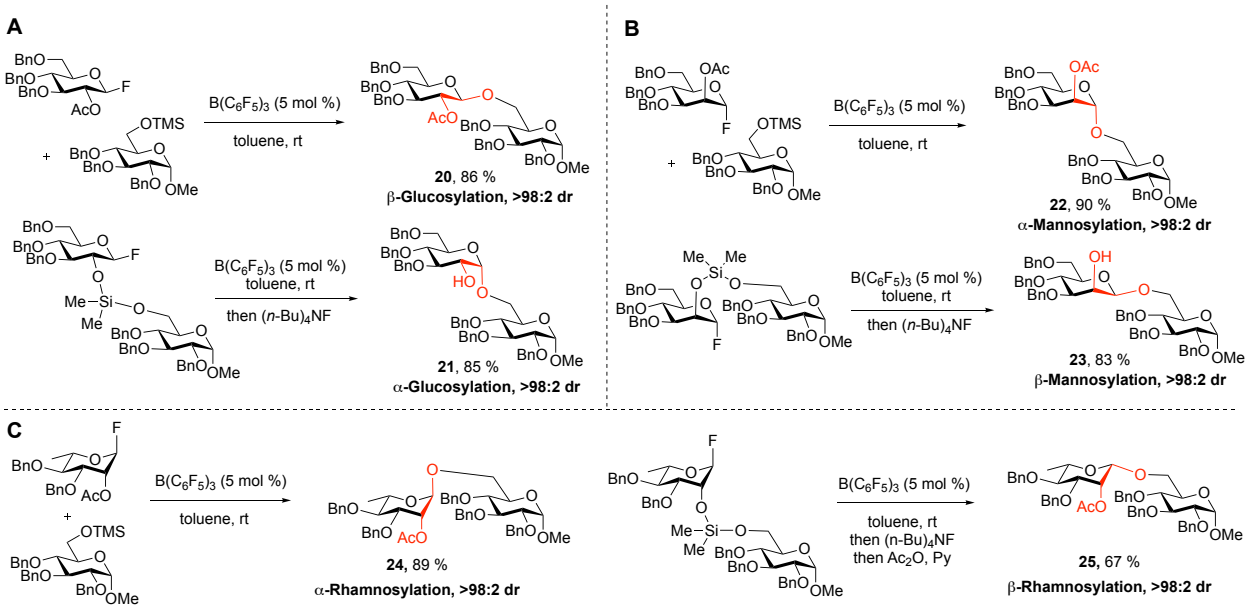
glycoside upon treatment with $B(C_6F_5)_3$ (see Scheme S3 in the supporting information). Glycosylations of armed glycosyl donors[10] that possess benzyl ether protecting groups at C3 to C6 were exceedingly efficient, often proceeding to completion in 5-10 min using equimolar quantities of the monosaccharide donor and acceptor, providing access to α-mannoside (**1**-**6**) products. Whereas the catalyst was typically weighed and handled under inert atmosphere conditions, no reduction in yield was observed when the catalyst was weighed in air. As the examples illustrate, mannose fluoride donors underwent efficient couplings with a range of sugars, including the C3- and C4-hydroxyls of glucose and the axial C4-hydroxyl of galactose. Notably, cyclic acetal protecting groups (**3**) and more hindered silyl ethers (**1b**, **1c**, and **6**) were cleanly tolerated in the method, allowing for selective deprotection and further synthetic elaboration. *n*-Pentenyl glycosides (**4**) were also tolerated, which thus allows subsequent couplings with orthogonal activation conditions. Glucosyl fluoride donors were also employed with C2-acetate direction, providing access to β-glucoside products (**9**-**12**). This stereochemical series was effective with hindered C2, C3, and C4 hydroxyls of the acceptors. Galactosyl fluoride donor also smoothly underwent glycosylation under the reaction conditions to provide a β-galactoside containing product **13**. Couplings with a fucose donor were also efficient, enabling the synthesis of product **8** with exclusive β-selectivity. Commonly employed 2-azidosugars underwent efficient coupling (**14**) with poor stereocontrol, as expected in the absence of a C2-directing group. The corresponding 2-phthalimido sugars were highly efficient with an improved 5:1 diastereoselectivity favoring the β-anomer (**15**). Therefore, while functional group compatibility with these nitrogen-containing groups is excellent, improvements in stereocontrol will require further variations of protecting groups and experimental variables. The glycosylation of disarmed glycosyl donors, which are deactivated by inductively withdrawing peracetylation, are also effective with this method as the above examples illustrate (**5b**, **7**, **8** and **9c**), although reaction times at room temperature typically extend to several hours. A silyl ether of phenol reacted efficiently, producing the *O*-aryl glycoside product in high yield as a single diastereomer (**16**). Disaccharide products such as **1a** were deacetylated and then further utilized as the acceptor to allow efficient formation of a trisaccharide product (**17**). Furanose donors were well tolerated in the chemistry, with ribose and xylose based donors rapidly and cleanly proceeding to the corresponding glycosylated products as a single β-anomer (**18** and **19**).

Additionally, free hydroxyls can be used as the acceptor (i.e. example **2**) although reactions require more than 3 hours and proceed in reduced yield compared with the corresponding trimethylsilyl ether acceptor. The reaction of glycosyl fluorides with free alcohols was not pursued further as these reactions have been shown to produce free HF which can etch glassware and itself act as a catalyst for glycosylation, resulting in diminished selectivity.[38] Furthermore, prior studies on the silylation of alcohols with $B(C_6F_5)_3$ illustrated that alcohols bind to and lower the reactivity of the catalyst, with less hindered alcohols exhibiting the most pronounced inhibitory effects.[39] The use of silyl ethers provides superior rates compared with alcohol acceptors because the inhibitory effect of free hydroxyls is avoided in this protocol.



Scheme 3. $B(C_6F_5)_3$-catalyzed couplings of glycosyl fluorides and silyl ethers. Reactions were conducted with 1.0 equiv of glycosyl fluoride and 1.1 equiv of silyl ether using 5 mol % $B(C_6F_5)_3$ in toluene at room temperature. Isolated yields are reported. A single diastereomer of each product was observed unless otherwise noted.

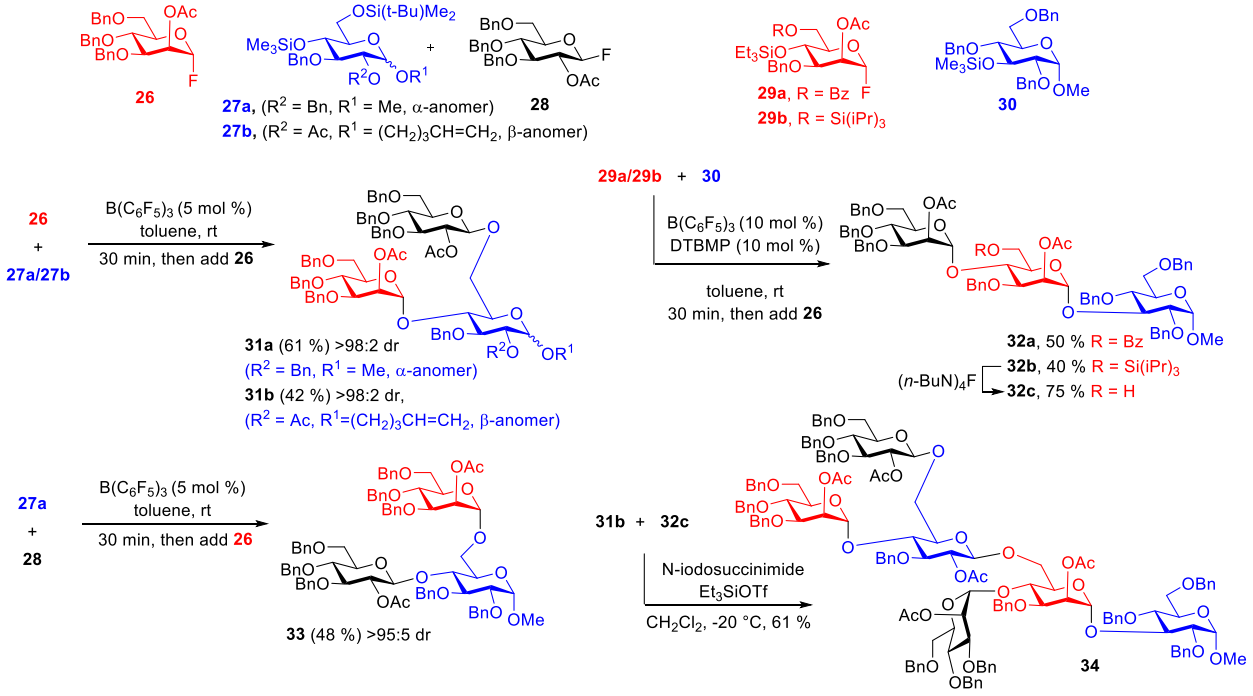
The method developed herein allows intermolecular couplings to provide highly selective access to the C1-C2-t*rans* glycosides using glucose and mannose donors. Since this approach utilizes substrate control as the feature that enables a highly stereoselective outcome, we envisioned pairing inter- and intramolecular versions of the method to enable access to all possible C1-C2 stereochemical outcomes. Silicon linkages have been used, typically with thioglycosides or anomeric sulfoxides, in an intramolecular aglycone delivery (IAD) strategy to access C1-C2-*cis* glycosides.[40-43] A prior report from our lab utilized glycosyl fluorides in intramolecular silicon-directed glycosylations using a superstoichiometric $TiF_4/AgBF_4$ promotor system,[44] but catalytic and operationally simple methods have not been described. To illustrate the stereochemical complementarity of inter- and intramolecular approaches, the C1-C2 *trans* glycosides **20** and **22** were first prepared utilizing C2-acetate direction. Alternatively, by assembling a silicon connection between C2 of the donor and the desired reactive hydroxyl on the acceptor (in this case C6), the IAD strategy using glycosyl fluorides with $B(C_6F_5)_3$ catalysis provided an effective way to access the C1-C2-*cis* α-glucoside **21** and β-mannoside **23** stereochemical relationships (Scheme 4A and 4B). This versatile strategy of coupling glycosyl fluorides of glucose or mannose with silyl ethers in either an inter- or intramolecular sense allows all four C1-C2 stereochemical relationships to be accessed in high yield with exceptional stereocontrol, without requiring modification of the protecting group pattern on the C3, C4, and C6 hydroxyls of the glycosyl donor. While powerful methods have been developed for accessing challenging β-mannosides using cyclic acetal protecting groups as a key design element,[45] a notable feature of the entry to glycosides **20** to **23** described herein is the access to all four stereochemical outcomes using a common protecting group pattern and a single catalyst and experimental protocol. To further highlight the utility of this methodology, we extended this approach to the synthesis of analogous α and β-L-rhamnosides (Scheme 4C, **24** and **25)**. β-L-Rhamnosides are one of the most challenging glycosidic linkages to construct and there are only limited literature examples in this area.[46-49] Recent work has focused on creative strategies for catalyst control to enable access to multiple stereochemical outcomes in glycosylations[50-51] and on the development of invertive[52] or retentive[53-54] strategies based on anomeric stereochemistry. The $B(C_6F_5)_3$-catalyzed approach for both inter- and intramolecular glycosylations described herein provides an alternative versatile and effective approach for the divergent assembly of diastereomeric glycosides from common building blocks.



Scheme 4. Evaluation of Inter- and Intramolecular glycosylation strategies for divergent stereoselectivity. (**A**) Stereoselective synthesis of β- and α-glucosides. (**B**) Stereoselective synthesis of α- and β- mannosides. (**C**) Stereoselective synthesis of α- and β-L-rhamnosides.

Finally, we sought to develop iterative, one-pot glycosylations using multiple monosaccharide building blocks. Such an approach through chemical catalysis requires several demanding features, namely fast couplings without an excess of any of the monosaccharide building blocks, paired with a strategy for differentiating the glycosyl donor leaving groups and the acceptor hydroxyls. We envisioned that the glycosyl fluorides could be differentiated through order of addition while the hydroxyls could be differentiated by varying the steric hindrance of the silicon protecting group. To explore this objective, we first examined three-component couplings of monosaccharides **26**-**28** (Scheme 5). Initial coupling of **26** and **27a** or **27b** proceeded through completely regioselective glycosylation of the trimethylsilyl-protected C4 hydroxyl of **27a/b**. Injecting **28** after 30 min led to the regio- and stereoselective production of **31a** or **31b** through glycosylation of the *tert*-butyldimethysilyl-protected C6 hydroxyl. Simply changing the order of addition (initial addition of **27a** and **28** followed by addition of **26** led to the regio- and stereoselective production of **33**. Similarly, monosaccharides **26**, **29a**, and **30** were utilized to allow production of trisaccharide **32a** by adding **29a** and **30** first, followed by addition of **26** after 30 min. Similarly, coupling of **26**, **29b**, and **30** by following the same protocol allowed production of **32b** in slightly diminished yield. The addition of catalytic amounts of 2,6-di-*tert*-butyl-4-methyl-

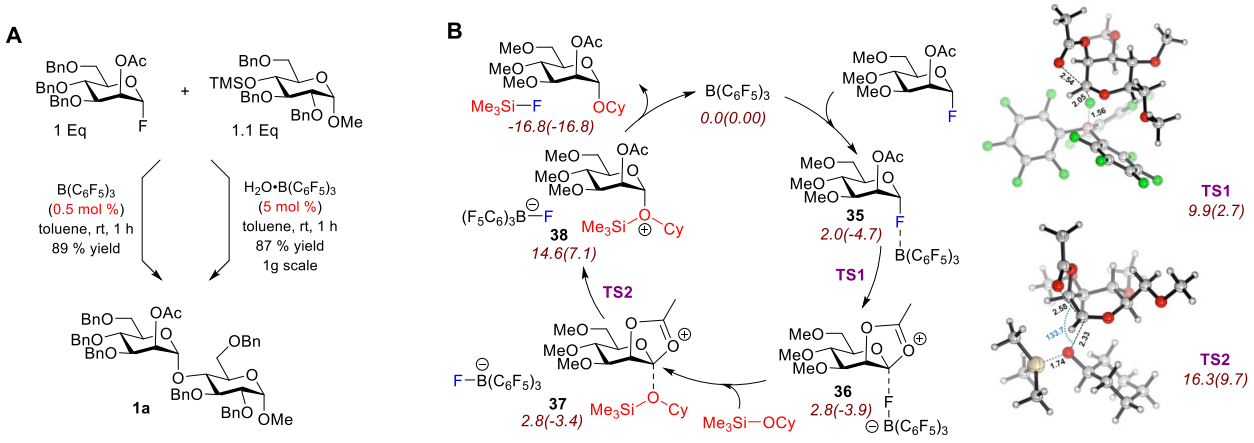
pyridine was found to improve the yield of this reaction by approximately 5%, although this trend was not generalizable across other glycosylation examples (see supporting information).



Scheme 5. Iterative Assembly of Oligosaccharides. $B(C_6F_5)_3$-catalyzed reactions were conducted using 5 mol % $B(C_6F_5)_3$ in toluene at room temperature. Isolated yields are reported and a single diastereomer of products was obtained.

These examples (Scheme 5) illustrate that the relative reactivity of hydroxyls is exclusively controlled by silicon protecting group rather than by the innate reactivity of the acceptor employed. Utilizing two or more silicon units on the acceptor (i.e. **27a/b**) enables installation of branched patterns, whereas utilizing one or more silicon units and a glycosyl fluoride on the same monosaccharide (i.e. **29a/b**) enables installation of linear patterns. Notably, *n*-pentenyl glycosides are tolerated (**31b**) and can be used in subsequent couplings using activation by *N*-iodosuccinimide/Et_3SiOTf. This approach allows hexasaccharide **34** to be produced as a single regio- and stereoisomer from monosaccharide precursors **26-30** in three linear steps (four total steps: three glycosylations and a single deprotection). The convergency of this approach demonstrates the practical advantages of the multicomponent nature of $B(C_6F_5)_3$-catalyzed glycosylations.

Finally, we sought to address the procedure practicality and better understand mechanism. The parent catalyst $B(C_6F_5)_3$ is hygroscopic and is typically stored and handled under inert atmosphere conditions. With an eye towards improving experimental ease and efficiency, we sought to explore the extent to which catalyst loadings can be lowered, and also to examine more stable catalyst variations (Scheme 6A). While the above studies employed 5 mol % catalyst, in a representative case (**1a**), catalyst loadings could be lowered to 0.5 mol %, which is markedly below the loading levels reported in other catalytic glycosylation methods. A recent extensive review of catalytic glycosylation methods[15] illustrates that most catalytic methods operate at the 10-50 mol % loading of catalyst, and examples operating effectively at the 1-2 mol % level are rare. The unique electrophilic properties of $B(C_6F_5)_3$, the frustrated character of its association with Lewis bases, and the absence of free hydroxyls in this silyl ether-based method combine to provide the exceptional catalytic efficiencies of this protocol. A number of catalyst structure modifications were examined, but most promising was the direct utilization of the simple hydrate $H_2O{\bullet}B(C_6F_5)_3$.[32, 55] This species is stable to air and moisture, and is an easily-handled, crystalline, highly-soluble catalyst that enables a simple benchtop setup for the catalytic glycosylations. The activity of this catalyst is lower than observed for the commercial form of $B(C_6F_5)_3$, but it still possesses sufficient reactivity for fast, room temperature reactions at the 5 mol % level in a 1 hour reaction time. Using the hydrate $H_2O{\bullet}B(C_6F_5)_3$, a preparative experiment conducted on a 1.0 g scale afforded the mannose-α-(1-4)-glucose linkage in **1a** in high yield (Scheme 4A). To further benchmark the operational ease of this method, the preparation of **1a** was conducted with $H_2O{\bullet}B(C_6F_5)_3$ as catalyst, using unpurified ACS grade dichloromethane in an open flask at room temperature. Under these conditions, glycoside **1a** was obtained in 77 % isolated yield.



Scheme 6. Optimization of catalyst structure, turnover capabilities and mechanism.

(**A**) Optimization of catalyst turnover and pre-catalyst stability and ease of handling. (**B**) Computational study of reaction mechanism using ωB97X-D3/(SMD, dichloromethane)/def2-TZVP//B97-D/B1 level of theory/method. Solvent phase Gibbs free energy (enthalpy in parentheses) values referenced against the starting value for the substrates and catalyst are in kcal/mol. Optimized bond distances and angles are in Å and degrees respectively.

Other common Lewis acids such BF_3•Et_2O and TMSOTf are also competent in promoting the glycosylations, but $B(C_6F_5)_3$ and its hydrate were the simplest, fastest, and most effective across the range of applications described in this study. Reaction progression plots comparing the reactivity of $B(C_6F_5)_3$, BF_3•Et_2O and TMSOTf are provided in the supporting information. Notably, the effectiveness of $B(C_6F_5)_3$ in 10 mol % loadings was described in glycosylations of free alcohols using trichloroacetimidate donors,[56-57] but its use with glycosyl fluoride donors or silyl ether acceptors has not been previously described. The very high catalytic activity of $B(C_6F_5)_3$, paired with its crystallinity, ease of handling, water tolerance, and tunable structure make this the optimum catalyst choice for these studies. While the hydrate H_2O•$B(C_6F_5)_3$ may offer advantages for long-term air and moisture stability, commercially available anhydrous $B(C_6F_5)_3$ is the catalyst of choice for most applications. Gradual exposure of $B(C_6F_5)_3$ to moisture up to the level of complete formation of the monohydrate reduces catalyst activity, but high yields and good turnovers with satisfactory reaction rates can still be obtained even after complete formation of the hydrate. Whereas $B(C_6F_5)_3$ was routinely stored and weighed under nitrogen, no significant change in rates or yields were noted when the anhydrous catalyst was handled and weighed in air.

While the mechanistic hypothesis for this work is outlined above, computational experiments[58] have been carried out to better understand the features of this catalytic system (Scheme 4B).[59-60] Using a mannose-α-fluoride donor, $B(C_6F_5)_3$ rapidly abstracts fluoride via transition state **TS1** from intermediate **35** to provide the charged glycosyl donor **36** with stabilization from the neighboring C2-acetate and ion pairing with the F-$B(C_6F_5)_3$ anion. The lowest energy pathway for glycosylation involves formation of adduct **37** followed by rate-determining addition of the silyl ether to the charged intermediate to form **38** via transition state **TS2**, and then the F-$B(C_6F_5)_3$ anion rapidly delivers fluoride to produce the α-mannoside product

and the Me_3Si-F byproduct while releasing the active $B(C_6F_5)_3$ catalyst. These mechanistic features elucidate the operative pathway of this procedure and are consistent with silyl group structure controlling the site-selectivity in iterative couplings.

Conclusions:

In summary, a boron-catalyzed glycosylation method involving the coupling of glycosyl fluorides and silyl ethers addresses a number of key challenges in the synthesis of glycosidic bonds. The preparative ease of the method allows simple reaction setup using a commercially-available catalyst, without requiring specialized equipment or expertise. Reactions are often completed in minutes at room temperature across a range of glycosyl donor and acceptor classes. Through the combination of inter- and intramolecular strategies, all possible C1-C2 stereochemical relationships may be accessed by this method. Computational studies illustrate a fluoride migration catalysis mechanism where the $B(C_6F_5)_3$ catalyst abstracts fluoride from the glycosyl donor and then delivers fluoride to silicon as the glycoside product and active catalyst are released. The relative reactivity of hydroxyls on the acceptor substrate are governed by silane structure rather than by the innate reactivity present in the substrates. This feature enables the regioselective, iterative assembly of oligosaccharides in a simple, one-pot operation utilizing monosaccharide precursors. The above features position this method as a powerful approach for addressing a number of synthetic challenges in glycoscience.

Acknowledgments:

Prof. Pavel Nagorny, Prof. Nathaniel Szymczak, Prof. David Sherman (University of Michigan) are thanked for helpful discussions and Dr. Andrew Robertson is thanked for assistance with HPLC purifications. The authors thank the National Institutes of Health Common Fund Program in Glycoscience (U01GM125274) for support for this work, and JLM acknowledges support from the National Institutes of Health through the Michigan CBI Training program (T32GM008597). The University of Michigan has submitted a provisional patent application based on this work.

Supporting information:

Methods and Materials, supplementary graphics, characterization data, and references.

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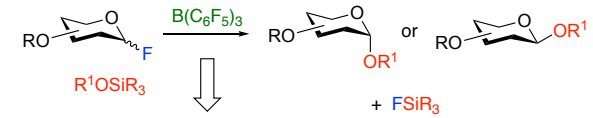
TOC Graphic



- *simple rt procedure*
- *water tolerant*
- *stereoselective*
- *one-pot iterative couplings*
- *catalyst loadings down to 0.5 mol %*
- *computational insights*
- *silicon structure dictates regioselectivity*