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# $B(C_6F_5)_3$-Catalyzed Stereoselective 1,2-*cis* Arabinofuranosylation with a Conformationally Constrained Donor

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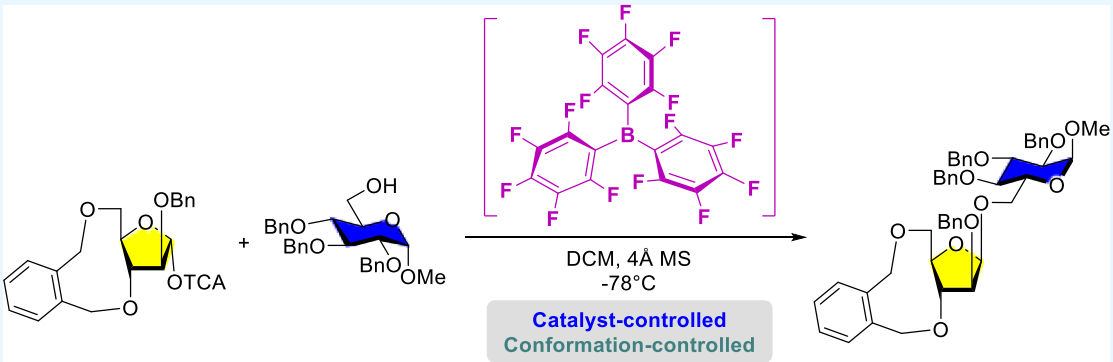


**ABSTRACT:** Compared with stereoselective glycosylation methods mainly addressed on the preparation of pyranose glycosides, the furanosylation has been more limited, especially for the 1,2-*cis* arabinofuranosylation. Herein, we report a novel stereoselective 1,2-*cis*-arabinofuranosylation strategy using a conformationally restricted 3,5-*O*-xylylene-protected arabinofuranosyl donor on activation with $B(C_6F_5)_3$ for desired targets in moderate to excellent yields and $\beta$-stereoselectivity. The effectiveness of the 1,2-*cis*-arabinofuranosylation strategy was demonstrated successfully with various acceptors, including carbohydrate alcohols.

## INTRODUCTION

Furanose-containing glycans are particularly important in *Mycobacterium tuberculosis* (TB), the organism that causes TB.[1] The cell wall complex of mycobacteria is a unique assembly of lipids and carbohydrates, which consist largely of two furanose-rich polysaccharides, an arabinogalactan (AG) and a lipoarabinomannan (LAM).[2] Common to both is an arabinan domain containing D-arabinofuranose (Ara*f*) residues which are of interest to develop probes for understanding their biological roles and play key roles in the infectivity and pathogenicity of bacteria.[3] There is a pressing need for the identification of new antibiotics, new drug targets, and vaccines of the bacterium. Thus, the synthetic cell wall glycans have been attracting particular attention for these purposes.[4]

Both AG and LAM have the hexasaccharide motif at their nonreducing terminal region, which has a branched structure with the two terminal $\beta$-Ara*f* residues (Figure 1).[5] The stereoselective formation of $\beta$-Ara*f* linkage has been a long-standing synthetic problem because of its unique pseudoaxial alignment at C-2 position and neighboring group participation from 2-*O*-acyl functionality to result in predominantly 1,2-*trans* glycosides. To achieve the stereoselective construction of $\beta$-linked Ara*f* glycoside, a variety of innovative glycosylation methodologies have been developed, including the use of

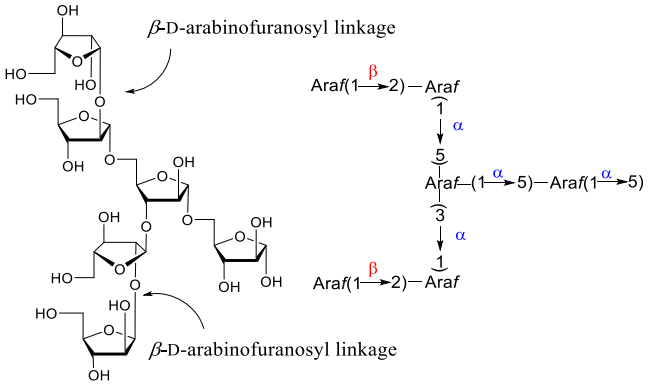


**Figure 1.** Structure of the $Araf_6$ motif in both AG and LAM.

intramolecular aglycone delivery,[6] hydrogen-bond-mediated aglycone delivery,[7] the glycosylation of 2,3-anhydro-*d*-lyxofur-

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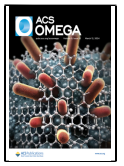

anosyl thioglycoside,[8] the use of conformationally locked donors,[9] and bis-thiourea hydrogen bond donors,[10] among others.[11] Of particular note, these studies have led to the successful synthesis of hexa- and larger saccharides.[12] Among these methods, approaches based on the use of donors with certain cyclic protections, such as 3,5-*O*-di-*t*-butylsilylene-, 3,5-*O*-tetra-*i*-propyldisiloxanylidene (TIPDS)-, and 2,3-*O*-xylylene-protected thioglycoside donors, have given substantial *β*-selectivity.[13]

Most recently, our group discovered that zinc-directed stereocontrolled 1,2-*cis*-glucosylation/mannosylation (Figure 2a).[14] The catalysts hypothesized that the zinc cation

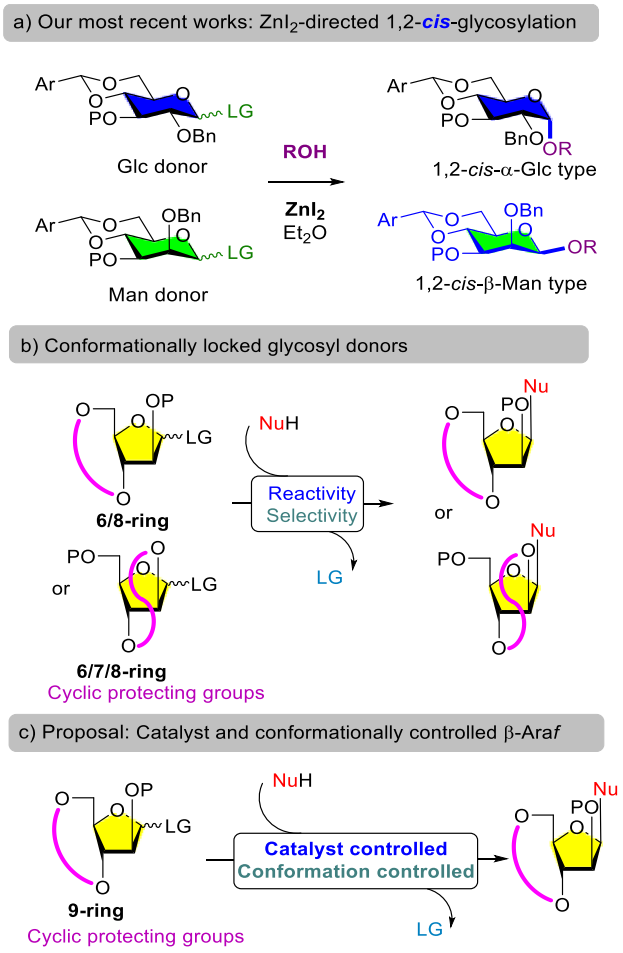


**Figure 2.** Strategies of stereocontrolled 1,2-*cis*-arabinofuranosylation.

coordinating the two-position of the donors and serving as a directing agent controls stereoselectivity for glycosylation enhanced by the fixed conformation of the pyranose ring. While inspired by the strategy using conformationally constrained furanosyl donors (Figure 2b),[13] we envisioned the extension of these strategies to furanose ring for 1,2-*cis* arabinofuranosylation reactions through the discovery of both appropriate catalysts and fixed conformation-controlled donors (Figure 2c).

## RESULTS AND DISCUSSION

To this end, we commenced our investigation by testing the feasibility of performing glycosylation reactions of three typical arabinofuranosyl donors (**1a**−**1c**) with glucosyl acceptor **2a** under previously developed Zinc(II) iodide-controlled 1,2-*cis*-glycosylation conditions (Scheme 1).[14] Results showed that tri-*O*-benzyl protected donor (**1a**) afforded the desired product **3aa** in good yield (80%), yet with poor stereoselectivity (*α*/*β* = 1:3), while the same reaction condition with known 3,5-*O*-TIPDS-protected donor (**1b**) gave the almost exclusively arabinofuranoside **3ab** with poor yield (35%), presumably due to low reactivity of the donor under $ZnI_2$ activation conditions. Interestingly, the moderate selectivity (*α*/*β* = 1:5) and acceptable yield (75%) of arabinofuranoside (**3ac**) was obtained using the donor (**1c**) equipped with the 3,5-*O*-xylylene-protected group, suggested that the donor (**1c**) is a potentially stereocontrolled donor properly favoring 1,2-*cis*-*β*-Ara*f* products among the tested donors. Therefore, we then reoptimized the reaction conditions by screening a series of promotors, solvents, substrate concentrations, and reaction temperatures, employing the 3,5-*O*-xylylene-protected trichloroacetimidate donor **1c** and the common glucosyl acceptor **2a**. As shown in Table 1, results of the glycosylation reactions performed in diethyl ether ($Et_2O$) solvent with a series of different promoters including Lewis acids or Brønsted acids (Tables 1, entries 1−4 and S1, entries 1−12) revealed that the $B(C_6F_5)_3$ promoter led to the glycosylation of **1a** with relatively high *β*-selectivity (Table 1, entry 4, *α*/*β* = 1:6) in excellent yield (92%). Encouraged by the previous reports[15] on the $B(C_6F_5)_3$ catalyst as the activation of Schmidt's trichloroacetimidates donors for stereocontrolled glycosylation, further solvent screening with $B(C_6F_5)_3$ employed as the promoter (Table 1, entries 4−8) revealed that glycosylation reactions performed to afford the glycoside products with even higher *β*-selectivity in toluene and DCM (Table 1, entries 5 and 6, *α*/*β* = 1:8) than the reactions performed in $Et_2O$, whereas glycosylation reactions in acetonitrile showed no selectivity (Table 1, entry 7, *α*/*β* = 1:1) and THF affected to show even *α*-selectivity (Table 1, entry 8, *α*/*β* = 2:1). The glycosylation reaction promoted with 20 mol % of $B(C_6F_5)_3$ at −40 °C (Table 1, entry 9) afforded the desired product with predominantly (*α*/*β* = 1:11), while, remarkably, at lower temperatures (−78 °C), glycosylation reactions afforded the glycoside product with the highest *β*-selectivity (Table 1, entries 10 and 11, *α*/*β* = 1:14). Importantly, pure *β*-glycoside could be easily separated from the reaction mixtures via thin-layer chromatography on silica gel with a 91% isolated yield (Table 1, entry 11). The stereochemistry of the anomeric center of arabinofuranosylated products was confirmed by *δ* C-1 and/or $^3J_{H1-H2}$ values: for *β*-isomer, *δ* C-1 = 97−103 ppm and/or $^3J_{H1-H2}$ = 4−5 Hz; for *α*-isomer, *δ* C-1 = 104−111 ppm and/or $^3J_{H1-H2}$ = 1−3 Hz.[16]

Having identified optimal reaction conditions (Table 1, entry 10), the scope of the $B(C_6F_5)_3$-catalyzed *β*-selective arabinofuranosylation reaction with the 3,5-*O*-xylylene-protected donor was explored (Scheme 2). Glycosylated with some simple alcohol acceptors, such as *n*-butanol (**2b**), *n*-hexanol (**2c**), cyclopentanol (**2d**), cyclohexanol (**2e**), *i*-propanol (**2f**), 3-pentanol (**2g**), and benzyl alcohol (**2j**) gave corresponding *β*-Ara*f* glycosides (**3b**−**3g** and **3j**) in excellent yields with high *β*-selectivity, whereas liner primarily alcohol with azido (**3h**) or benzyloxycarbonyl (Cbz) amino (**3i**) groups exhibited lower selectivity resulted in mixtures of isomers, probably due to the less nucleophilicity. Subsequently, protected amino acids (**2k** and **2L**) and 1-adamantanol (**2m**) as well as naturally occurring monoterpene alcohol (**2n**) and steroids (**2o** and **2p**), were examined as acceptors. In most cases, *β*-glucosylated products (**3k**−**3p**) were obtained in


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**Scheme 1. $ZnI_2$-Mediated 1,2-*cis*-Arabinofuranosylation**

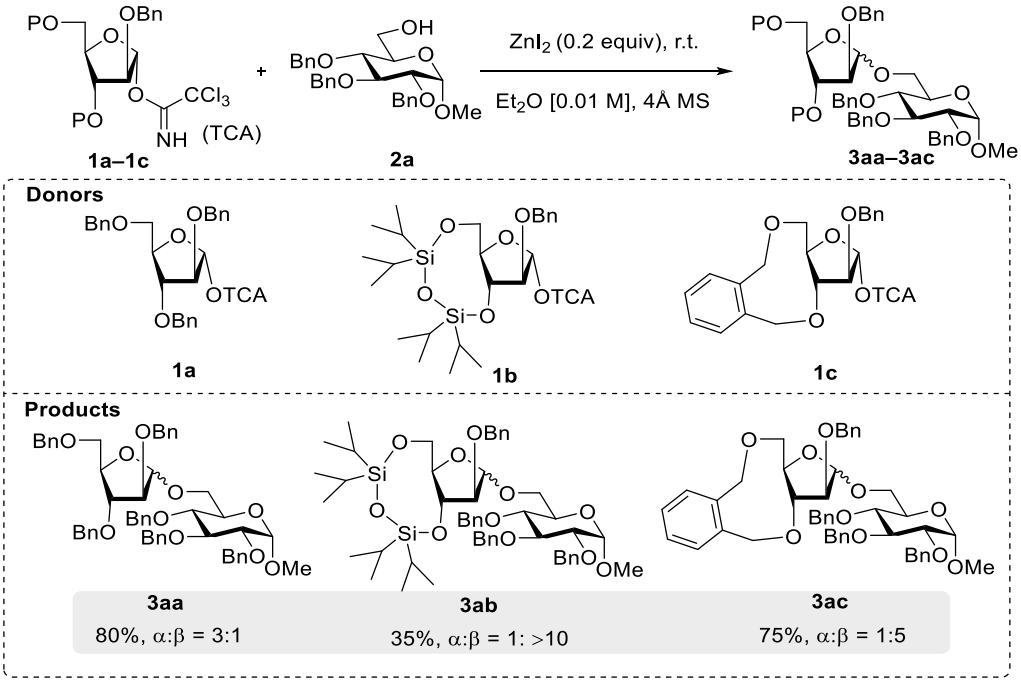
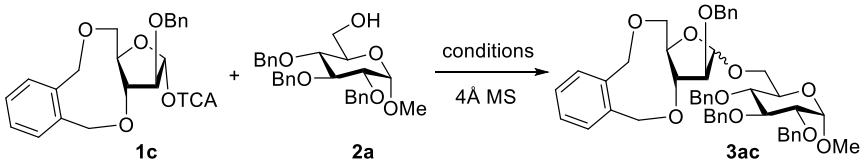



**Table 1. Optimization of the Arabinofuranosylation**




| entry[a] | promotor | solvent | temperature | yield (%)[b] | $\alpha/\beta$[c] |
|---|---|---|---|---|---|
| 1 | TMSOTf | $Et_2O$ | r.t. | 68 | 1:4 |
| 2 | $AuCl_3$ | $Et_2O$ | r.t. | 72 | 1:1 |
| 3 | $BF_3{\cdot}OEt_2$ | $Et_2O$ | r.t. | 91 | 3:1 |
| 4 | $B(C_6F_5)_3$ | $Et_2O$ | r.t. | 92 | 1:6 |
| 5 | $B(C_6F_5)_3$ | toluene | r.t. | 80 | 1:8 |
| 6 | $B(C_6F_5)_3$ | DCM | r.t. | 81 | 1:8 |
| 7 | $B(C_6F_5)_3$ | MeCN | r.t. | 54 | 1:1 |
| 8 | $B(C_6F_5)_3$ | THF | r.t. | 40 | 2:1 |
| 9 | $B(C_6F_5)_3$ | DCM | −40 °C | 90 | 1:11 |
| 10 | $B(C_6F_5)_3$ | DCM | −78 °C | 86 | 1:14 |
| 11[d] | $B(C_6F_5)_3$ | DCM | −78 °C | 91[e] | 1:14 |

[a]Reaction conditions: donor **1a** (1.5 equiv), acceptor **2a** (1.0 equiv), promotor (0.1 equiv), 4 Å MS (100 mg/mL). [b]Combined yield of the anomeric mixture of corresponding glycoside. [c]Determined by the integration ratio obtained from $^1$H NMR of crude mixture. [d]0.2 equiv of promotor was used. [e]Isolated yield of $\beta$-glycoside.

moderate to good yields predominantly. Glycosylation of a library of glycosyl acceptors including $Glc^{O-6}$ (**2a**), $Gal^{O-6}$ (**2q**), $Glcf^{O-3}$ (**2r**), $Glc^{O-4}$ (**2s**), $Glc^{O-3}$ (**2t**), $Glc^{O-2}$ (**2u** and **2v**), $Araf^{O-2}$ (**2w**), as well as $Gal^{O-4}$-$\beta$-(1 → 4)-Glc[16] (**2x**), with glucosyl donor **1c** afforded 1,2-*cis*-linked disaccharides (**3ac** and **3q**−**3w**) or trisaccharide (**3x**) in moderate to high yields with generally high 1,2-*cis*-stereoselectivity under the optimized conditions. However, the highly congested and weak nucleophiles (such as **2s** and **2x**) underwent glycosylation with a lower yield but good selectivity. Although disaccharide (**3w**) was assembled in moderate yield and 1,2-*cis*-stereoselectivity, it is important to synthesize a natural linkage of the mycobacterial cell wall. Notably, acid-labile groups such as Boc, TIPS, isopropylidene, and benzylidene acetal were well tolerant under both conditions despite in the absence of acid scavenger. To prove the utility of this methodology, a 1.0 mmol scale experiment with 3,5-*O*-xylylene-protected trichloroacetimidate donor **1c** and glucosyl acceptor **2a** was performed under the optimal conditions. 1,2-*cis*-arabinofurano-disaccharide (**3ac**) was obtained in a high yield of 85% and with the same level of stereoselectivity ($\alpha/\beta$ = 1:12). Then, the global deprotection of **3ac** in the presence of $Pd(OH)_2/C$ under a $H_2$ atmosphere to give methyl $\beta$-D-arabinofuranosyl-(1 → 6)-$\alpha$-D-glucopyranoside (**4**) in 89% yield at one-pot (Scheme 3).

Although the reaction mechanism is still uncertain, we have performed density functional theory (DFT) calculations to better understand the $\beta$-selectivity of this reaction and the catalytic system. On the basis of the DFT results and previous



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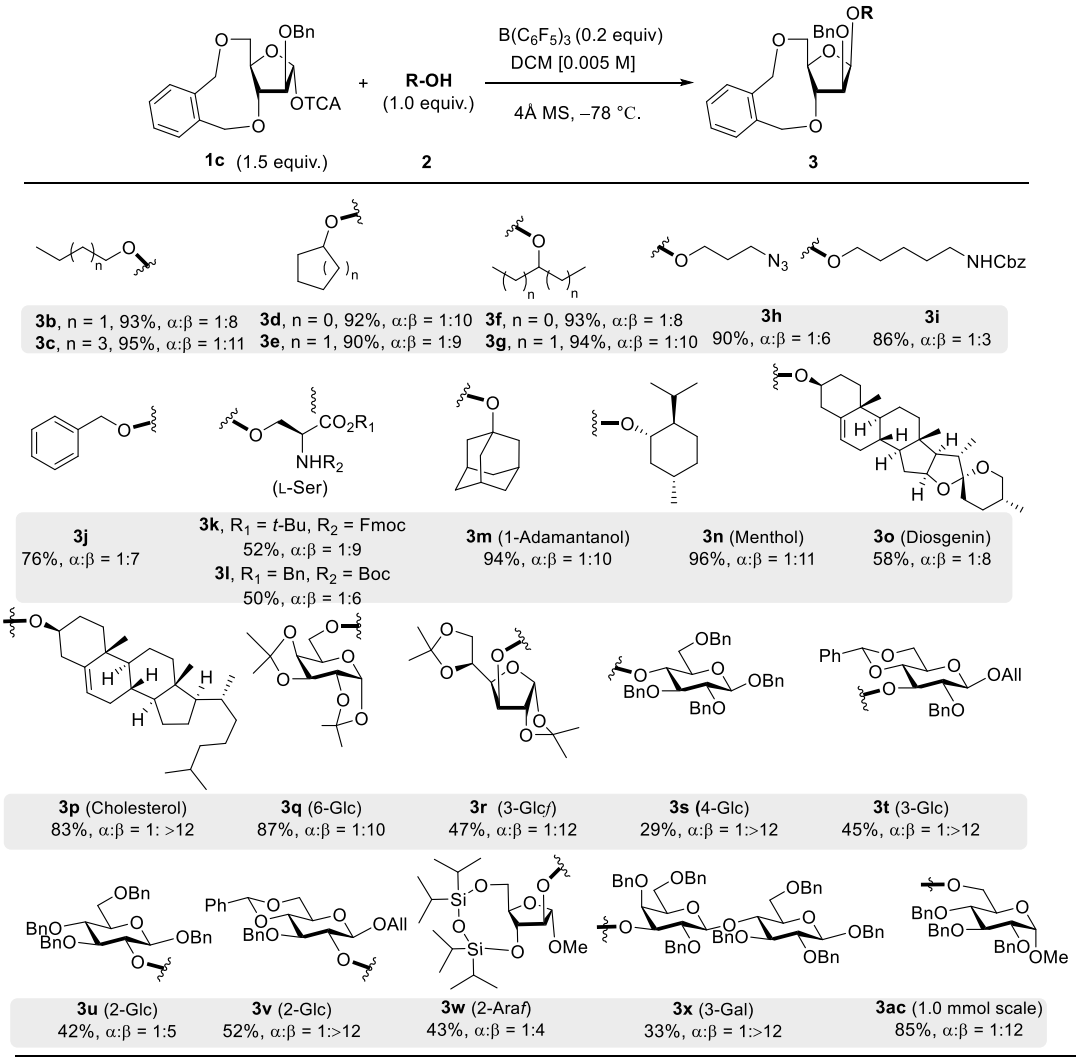
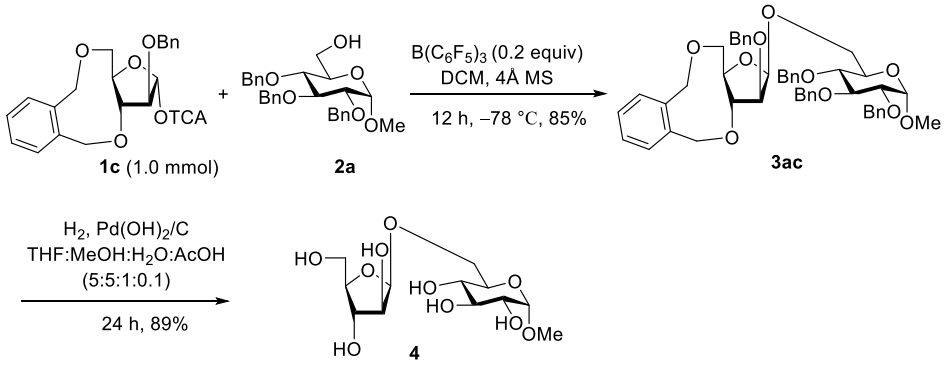
**Scheme 2. Substrate Scope of $B(C_6F_5)_3$-Directed 1,2-*cis*-Arabinofuranosylation**[a]




[a]Donor **1c** (1.5 equiv), acceptor **2** (1.0 equiv), promotor (0.2 equiv), 4 Å MS (100 mg/mL) were used unless otherwise specified. Combined yields of the anomeric mixture of corresponding glycosides were shown. Stereoselectivity was determined by the isolated weight.

**Scheme 3. 1.0 mmol Scale Synthesis and Global Deprotection**




literature reports,[15,17] the mechanistic hypothesis is proposed in Scheme 4. The mechanism of the transformation is likely to proceed through initial activation of the trichloroacetimidate leaving group. Both the unique electrophilic properties of $B(C_6F_5)_3$ and the character of its association ability with Lewis bases provide the catalytic efficiencies of the reaction. Given that $B(C_6F_5)_3$ is a kind of Lewis acid, it would prefer coordination to the more nucleophilic nitrogen atom on the leaving group other than the oxygen atom. We proposed that the catalyst $B(C_6F_5)_3$ rapidly activate the leaving group of the glycosyl donor by associating with the Lewis basic nitrogen atom which directs the $S_N2$ like nucleophilic attack of the acceptor hydroxyl at the $\alpha$-face of glycosyl donor via transition state **TS1** to afford the B-coordinated intermediate **int2** and



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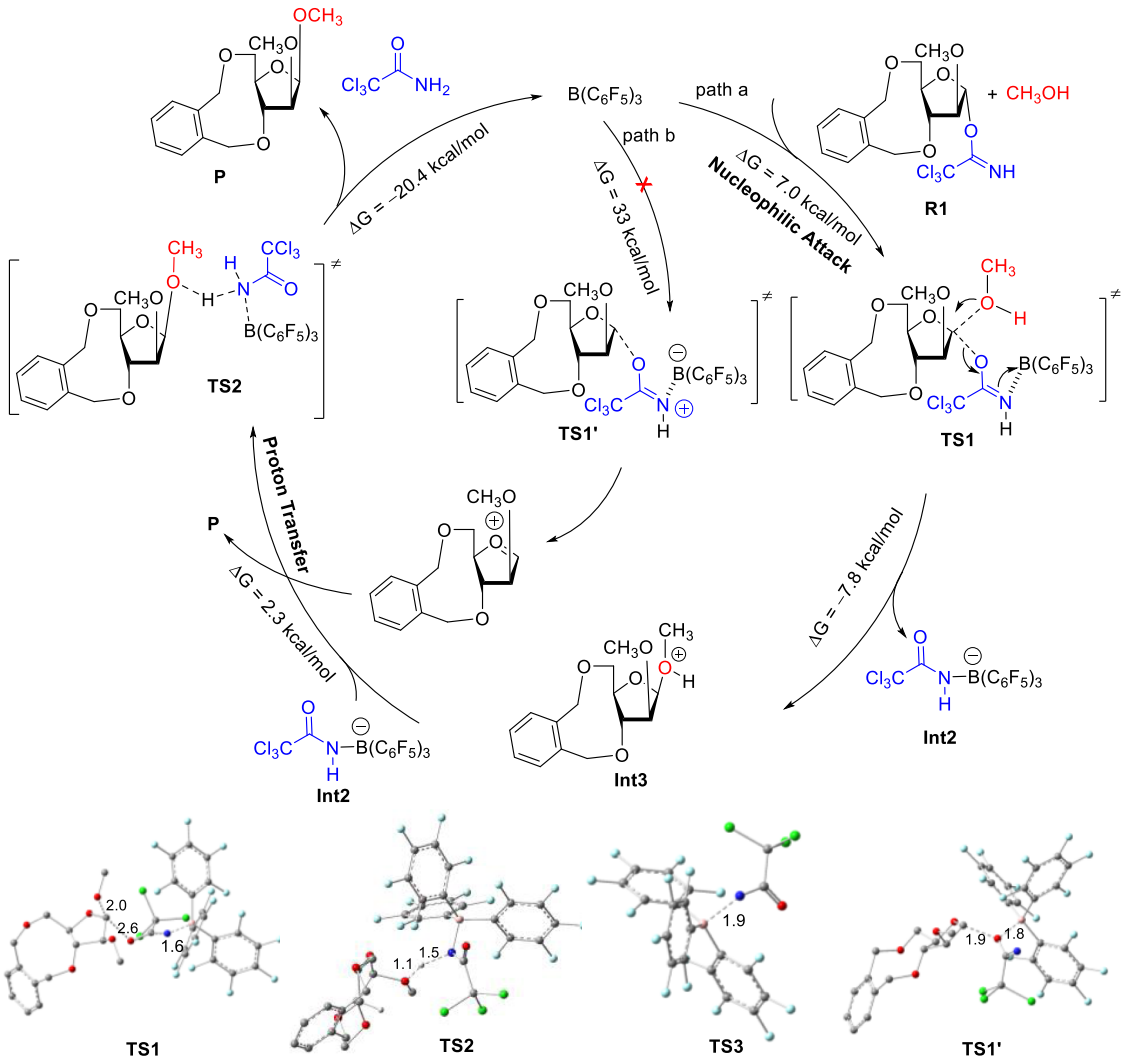
**Scheme 4. Proposed Catalytic Cycle of $B(C_6F_5)_3$-Catalyzed $\beta$-Selective Arabinofuranosylation**[a]




[a]The bond lengths of the key transition states are given in Å. The energy given are in kcal/mol. Color code, C: dark gray, O: red, H: light gray, N: dark blue, B: pink, and Cl: light green. Irrelevant hydrogen atoms are omitted for clarity.

the intermediate **int3** which immediately undergoes proton transfer via **TS2** (Scheme 4, path a). The process of the rate-determining step nucleophilic attack requires a low activation barrier of 7.0 kcal/mol, which is feasible under the reaction condition (−78 °C). Finally, the active $B(C_6F_5)_3$ catalyst was released to afford $\beta$-product concomitant with trichloroacetamide. The calculation result is consistent with the experimental observed $\beta$-selectivity.

Besides, we proposed a B-chelation induced $S_N1$ cleavage of glycosyl donor as show in Scheme 4 (path b). Calculations into the reaction indicated that the endocyclic cleavage mechanism is unfavorable under the reaction conditions with an activation barrier of 33.0 kcal/mol (**TS1′**) which is much higher in energy than the $S_N2$ like nucleophilic attack mechanism in Scheme 4 (path a) (7.0 kcal/mol). Thus, we proposed that the Lewis acid-catalyzed $S_N2$-like nucleophilic attack pathway predominates in this reaction. The acceptor such as methanol should react kinetically through this proposed mechanism. However, less nucleophilic acceptors such as **2h**, **2i**, and **2u** afforded less selective $\beta$-arabinofuranosylation, probably through undesired anomerization of $\alpha$-imidate or $\beta$-coordination of **Int2** counteranion before the formation of $\beta$-glycoside.

## CONCLUSIONS

In conclusion, a novel and versatile methodology toward $\beta$-selective arabinofuranosylation directed by $B(C_6F_5)_3$ has been developed with highly stereoselectivity. The effectiveness of the 1,2-*cis*-arabinofuranosylation strategy was demonstrated successfully with various acceptors, including carbohydrate alcohols. Further experimental examinations toward the elucidation of the reaction mechanism and exploration of applications of this $B(C_6F_5)_3$-mediated methodology for the synthesis of AG and LAM complex oligosaccharides containing $\beta$-Ara*f* linkage(s) are the focus of our continuing investigation.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c09761.

Experimental procedures and copies of NMR spectra of all new compounds (PDF)



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### Author Contributions

Q.X., S.F., J.A., and X.Z. contributed equally. F.D. and Q.X. conducted most of the experiments and wrote the initial manuscript draft with A.I., K.T., and Y.N., and W.D., J.A., S.F., and C.H. performed part of the experiments. X.Z. and Y.L. contributed to the DFT computations. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

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