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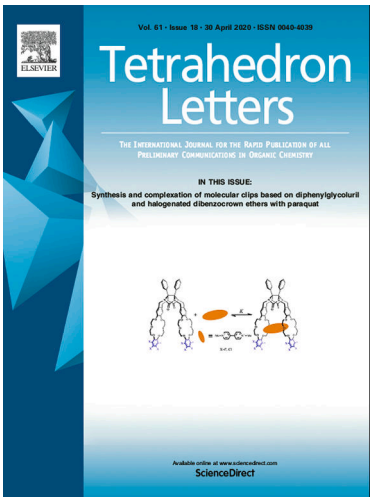

Lewis acid/base pair as a catalytic system for α-stereoselective synthesis of 2-deoxyglycosides through the addition of alcohols to glycals

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PII: S0040-4039(20)31148-5
DOI: https://doi.org/10.1016/j.tetlet.2020.152643
Reference: TETL 152643

To appear in: *Tetrahedron Letters*

Received Date: 7 September 2020
Revised Date: 2 November 2020
Accepted Date: 8 November 2020

Please cite this article as: Wang, C., Liang, H., Hang, Z., Wang, Z-y., Xie, Q., Xue, W., Lewis acid/base pair as a catalytic system for α-stereoselective synthesis of 2-deoxyglycosides through the addition of alcohols to glycals, *Tetrahedron Letters* (2020), doi: https://doi.org/10.1016/j.tetlet.2020.152643

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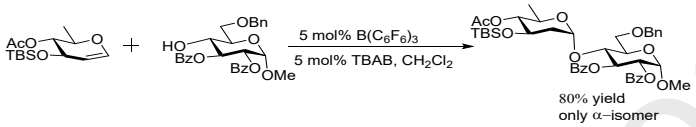

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
$B(C_6F_5)_3$
tetrabutylammonium bromide
glycals
2-deoxylglycosidation
α-stereoselective

ABSTRACT

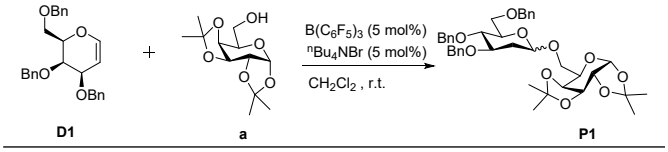
This report describes the α-stereoselective addition of alcohols to glycals promoted by a cooperative Lewis acid/base pair catalytic system composed of $B(C_6F_5)_3$ and tetrabutylammonium bromide (TBAB), which provides access to 2-deoxylglycosides in high yields. A mechanistic investigation supported by NMR analysis highlights the possible involvement of nucleophilic addition through boron-induced activation of alcohols under the assistance of TBAB. The protocol discussed here features the high stereoselectivity, mild reaction conditions, inexpensive and stable catalysts, and a broad substrate scopes.

2-deoxyglycosides represent an important class of saccharide motifs that have been incorporated into medicinal molecules, particularly because of their effects on various biological processes, including the cancer development, platelet aggregation, and immune responses. [1] These structures are found in numerous natural resources; however, stereoselective construction of 2-deoxyglycosidic linkages poses a synthetic challenge because of the absence of any directing group at the C2 position. [2] Glycals are useful building blocks for forming glycosidic bonds. The catalytic glycosylation of glycals with alcohols, which involves the direct addition of hydrogen and an alkoxyl group to an olefinic bond, is the most atom-efficient approach to synthesizing 2-deoxyglycosides. Noble-transition-metal-catalysts [3] and organocatalysts[4] have played a crucial roles in promoting the hydroalkoxylation of glycals by performing the electrophilic activation of double bonds or hydroxyl groups. For example, the Wan and Wang teams successively reported stereoselective synthesis of 2-deoxyglycosides from glycals by visible-light-induced catalysis. [5] More recently, Ye and co-workers reported the electro-2-deoxyglycosylation from glycals, [6] which provides access to a variety of medicinal glycoconjugates. These results sparked renewed interest in developing novel catalytic systems capable of stereoselectively synthesizing functionalized 2-deoxyglycosides and understanding their mechanisms. The rich chemistry of boron reagents has been applied for diverse couplings, [7] bioconjugation, [8] and drug discovery. [9] In particular, the strong nonmetallic Lewis acid, $B(C_6F_5)_3$, has been successfully employed for glycosylation catalysis using glycosyl trichloroimidate as a donor; conventional Lewis acid were ineffective in such reactions. [10] Moreover, the Galan group recently demonstrated that $B(C_6F_5)_3$ is an effective catalyst for addition reactions involving glycals and various alcohols. [11] However, the undesired products derived from Ferrier rearrangement can't be suppressed, and in many cases the 2, 3-unsatured glycosides were isolated as the predominant products. Interestingly, perfluorophenylboronic acid was also demonstrated proficient catalytic activity, enabling the direct stereoselective addition of nucleophilic alcohols to deactivated peracetylated D-galactal to afford 2-deoxygalactosides. [12] However, this 2-deoxygalactosidation procedure is only effective for a small range of glycals. In general, the sterically bulky organoboron compounds working in combination with Lewis bases allow for the construction of Lewis pair catalytic systems, which can activate small molecules for further utilization. [13] Considering the findings presented above, it is reasonable to propose that a cooperative Lewis acid/base pair could facilitate addition reactions between glycals and alcohols to form *O*-glycosidic bonds. This report describes a procedure for the catalytic glycosylation of glycals with various alcohols using a system comprising a Lewis acid, $B(C_6F_5)_3$, and a Lewis base, tetrabutylammonium bromide (TBAB).

First, the addition reaction involving readily-accessible 1, 2:3, 4-di-*O*-isopropylidene-D-galactopyranose (**a**) and perbenzylated galactal (**D1**) using $B(C_6F_5)_3$ as a catalyst was evaluated under various conditions. After analyzing the results (**Table 1**) in terms of the applied reaction parameters, it was determined that the reaction achieved a maximum 93% yield and proceeded with a significant preference for the α-glycoside products, when performed in CH_2Cl_2 for 12 h at room temperature using 5 mol% $B(C_6F_5)_3$ with 5 mol% TBAB (entry 1). The use of an equimolar amount of *n*-Bu_4NI or *n*-Bu_4PBr instead of TBAB led to a slightly reduced yield, while the anomeric center retained only α-stereoselectivity (entries 2 and 3, respectively). It was further observed that *n*-Bu_4PCl_4, *n*-Bu_4NCl, and *n*-Bu_4NNO_3 were

ess was either TBAB or $B(C_6F_5)_3$ loading was reduced to 2.5 mol%, **P1** was obtained in around 80% yield, predominantly in the form of its α-isomer (entries 7 and 8, respectively). However, in the absence of TBAB or $B(C_6F_5)_3$, no reaction occurred (entries 9 and 10, respectively). Replacing CH_2Cl_2 with other polar solvents, such as THF (entry 11) or CH_3CN (entry 12), also led to relatively much lower yields (entries 11 and 12). In the performed addition reactions, ^{1}H NMR spectroscopic analysis verified that mainly the α-*O*-glycosidic anomer was formed (α: β > 20:1).

Table 1 Optimization of 2-deoxyglycosylation catalyzed by $B(C_6F_5)_3$-Lewis base [a]



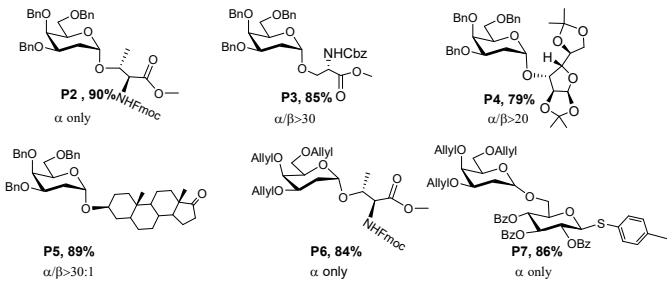
Entry	variation from the standard conditions	Yield (%)[b]
1	None	95
2	*n*-Bu_4NI instead of TBAB	87[c]
3	*n*-Bu_4PBr instead of TBAB	90[c]
4	*n*-Bu_4NCl instead of TBAB	0
5	*n*-Bu_4PCl instead of TBAB	0
6	*n*-Bu_4NNO_3 instead of TBAB	0
7	TBAB (2.5%)	80[c]
8	$B(C_6F_5)_3$(2.5%)	71[c]
9	Without $B(C_6F_5)_3$	0
10	Without TBAB	0
11	THF	63[c]
12	CH_3CN	57[c]

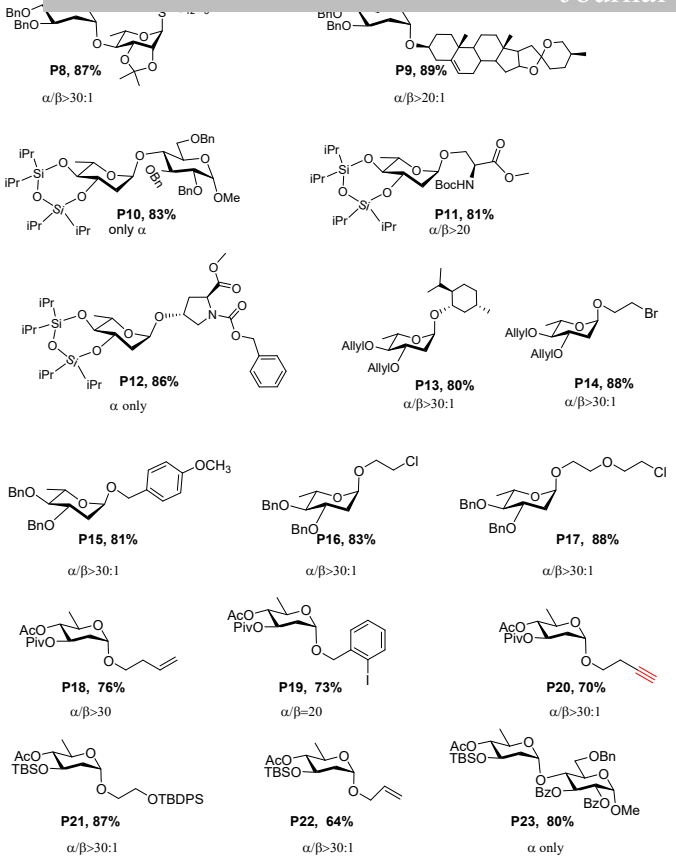
Reaction conditions: **D1** (0.1 mmol), **a** (0.12 mmol), $B(C_6F_5)_3$, Lewis base, and solvent under Ar for 12 h, unless otherwise noted. [b] Yields of isolated products. [c] α/β>20:1; determined by ^{1}H NMR analysis of the crude products. r.t. = room temperature

After determining the optimal reaction conditions, the next goal involved exploring the scope of this transformation. As shown in **Scheme 1**, **D1** reacted with some hindered alcohols to rapidly generate the corresponding 2-deoxglycosides (**P2-5**) in satisfactory yields and with α-selectivity. As expected, the reactions between **D1**'s allylated counterpart and an *N*-protected amino acid ester or a primary thiosugar alcohol proceeded very cleanly, generating only the α-isomers of the corresponding glycosides, **P6** and **P7**, in over 80% yields. Further experiments revealed that the protective features of glycals were closely associated with their reactivities; differentially protected glucal (**D3**) and L-rhamnals (**D4-6**) were prepared and then subjected to the addition reaction conditions to evaluate the formation of glycosidic bonds. When the glucal donor with 3, 4-di-*O*-Bn-6-*O*-TBS protection experienced the same reaction conditions in the presence of diosgenin or a thioglycoside acceptor with a free C4-OH, these reagents were smoothly 2-deoxyglycosylated to give **P8** and **P9**, respectively, in yields of approximately 90% with high α-stereocontrol. Such 2, 6-dideoxyglycosides are biologically important carbohydrates found in numerous natural products and clinical medicines. In general, the stereoselective reduced because of the absence of directing groups at C2 and C6. Therefore, the preparation of 2, 6-dideoxyglycosides was investigated using rhamnals as donors. A previous report showed that cyclic protecting groups influenced glycosylation reactivity. [13] Similarly, the crucial role of the 3, 4-*trans*-fused cyclic disiloxane protecting group in directing the stereochemistry of glycoside formation has been intensively studied by Galan and co-workers. [14] The cyclic protective strategy applied in the present study favored the formation of α-glycosides (**P10-12**), consistent with previous observations. Similarly, fully allylated and benzylated rhamnals were suitable donors to promote this transformation, and these reagents demonstrated superior α-stereoselectivity and satisfactory yields in the synthesis of 2, 6-dideoxy-rhamnosides (**P13-17**).

The methods described for the direct synthesis of 2-deoxyglycosides from glycals are limited by the potential competitive formation of Ferrier-type side products, because glycals bearing C3 acetates are prone to rearrangement under the action of acid catalysts. However, the cooperative activity of $B(C_6F_5)_3$ and TBAB enables the direct glycosylation reaction between diacylated 6-deoxyglucal (**D7**) and an array of alcohols to give corresponding products (**P18-20**) in good yields (70~76%) and with excellent α-selectivity. Additionally, orthogonally-protected 6-deoxyglucal (**D8**) exhibits high reactivity, generating satisfactory yields of α-glycosidic products (**P21-23**). Notably, the disaccharide products with anomeric thioether moieties (**P7** and **P8**) help carry out late-stage glycosylation, thus demonstrating the synthetic potential of this method for preparing 2-deoxyoligosaccharides. The functionalized *ortho*-iodobenzyl glycoside, [15] **P19**, has the potential to act as a latent glycosyl donor for assembling glycans.

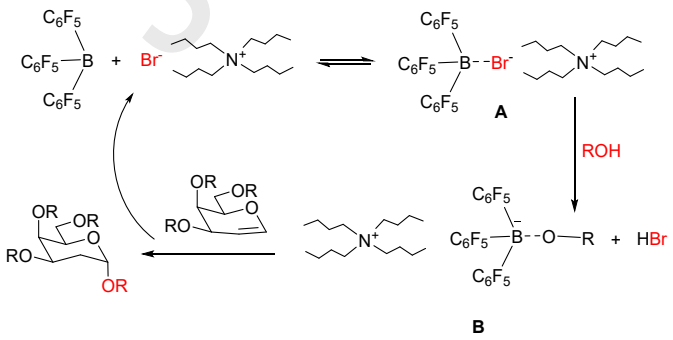
In all cases, experiments were conducted at room temperature for 12 h, at which point the 2-deoxyglycosylated products were isolated in high yields (64~93%), primarily as the α-anomers (α:β > 20:1). Moreover, the described catalysis accommodates a diverse set of functional groups including halogens, esters, amides, ethers, olefins, and alkynes, thus highlighting the strong chemoselectivity of the *O*-glycosidic bond forming reaction. The high functional group tolerance also presents an opportunity for further chemical modification and product tuning. [16] The key reagents, $B(C_6F_5)_3$ and TBAB, are commercially-available, air- and moisture-stable, and can be stored indefinitely in a freezer. They are also highly soluble in common organic solvents, including dichloromethane. Overall, the described catalytic system is advantageous for mediating the desired chemical transformations because the reagents are easy to handle, and the reaction procedures are simple.





Scheme 1 Scope with respect to alcohol nucleophiles and glycals. Reactions were carried out at room temperature in CH_2Cl_2 (2 mL) with glycal (0.1 mmol) and nucleophile alcohols (0.12 mmol) in the presence of $B(C_6F_5)_3$(5 mol%) and TBAB (5 mol%) for 12 h. Yields of isolated products are given. The α/β ratios were determined by ^1H NMR analysis of the crude products.

To gain insight into the catalytic mechanism, 2-iodobenzyl alcohol was selected as a model substrate and its interactions with $B(C_6F_5)_3$ and TBAB in $CDCl_3$ were monitored using ^1H NMR spectroscopy (see Supporting Information S69-73 for details). Addition of $B(C_6F_5)_3$ or TBAB to a solution of 2-iodobenzyl alcohol in $CDCl_3$ caused a clear downfield shift in the peak representing OH protons (from δ = 2.0 ppm for 2-iodobenzyl alcohol alone, to δ = 2.44 ppm), and this OH signal appeared at 3.28 ppm in the spectrum of a solution containing all three components. These results clearly showed that there were interactions among the reagents. Specifically, the enhanced oxygen-centered nucleophilicity (relative to a free alcohol) supported the smooth hydroalkoxylation of glycal. On the basis of these experimental observations, a plausible reaction mechanism is shown in **Scheme 2**.



Scheme 2 Proposed reaction mechanism

generate species (**A**). Subsequently, the hydroxyl group of the alcohol was deprotonated to afford the corresponding alkoxide anion (**B**) because of the strong coordination between the electron-rich oxygen and the electron-poor **A** complex. Such $B(C_6F_5)_3$-bound alkoxide anions are typically more nucleophilic toward the anomeric carbon than the corresponding alcohols. Finally, addition of a proton and the alkoxide to the olefinic bond in glycal formed the *O*-glycoside with preferential α-stereochemistry at the anomeric center due to the anomeric effect. Of course, the mechanism proposed by Galan and co-workers [11] may also function during the 2-deoxyglycosidation reaction.

In conclusion, this work demonstrated that $B(C_6F_5)_3$ and TBAB comprise an efficient catalytic system for promoting addition reactions between glycals and a diverse set of alcohols to produce a range of glycosides, with a strong preference for generating the α-configuration. Furthermore, the heterogeneous catalytic components are inexpensive, stable, and commercially available. The glycosidation reaction, featuring an intersting reaction mechanism, enjoys a broad substrate scope and simple operation. Overall, the described method demonstrated the potential for producing 2-deoxyglycosylation from various glycals. Application of this catalytic system to other olefin addition reactions is currently underway.

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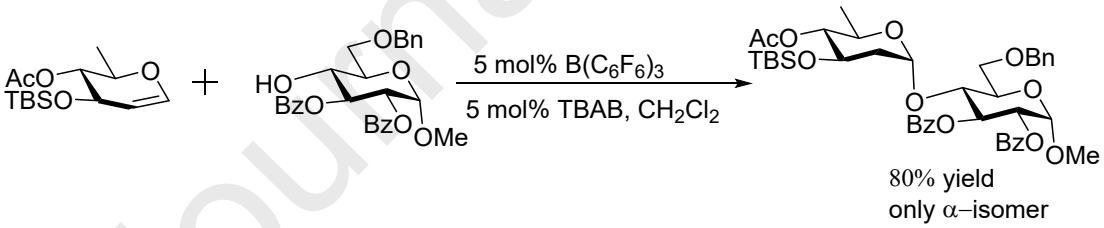

Highlights

- α-Stereoselective 2-deoxyglycosidation
- Inexpensive and stable catalysts
- A wide substrate scope, the simple operation, and an interesting mechanism