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Sterically Hindered 2,4,6-Tri-*tert*-butylpyridinium Salts as Single Hydrogen Bond Donors for Highly Stereoselective Glycosylation Reactions of Glycals

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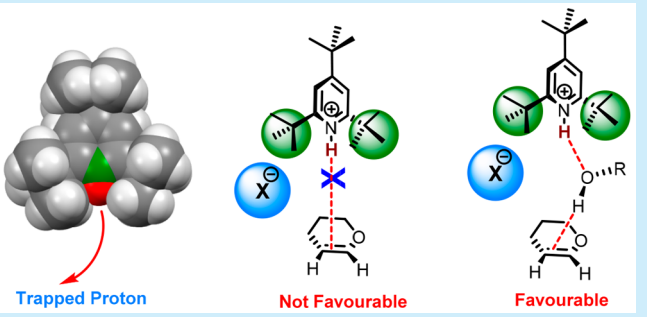
Supporting Information

ABSTRACT: We demonstrate here that the strained and bulky protonated 2,4,6-tri-*tert*-butylpyridine salts serve as efficient catalysts for highly stereoselective glycosylations of various glycals. Moreover, the mechanism of action involves an interesting single hydrogen bond mediated protonation of glycals and not via the generally conceived Brønsted acid pathway. The counteranions also play a role in the outcome of the reaction.



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2,4,6-Tri-*tert*-butylpyridine (TTBPy), a highly hindered pyridine derivative, was first synthesized by Mach and Dimroth in 1968 from stable oxonium salts.[1] TTBPy, along with its well-studied analogue, 2,6-di-*tert*-butylpyridine (DTBP),[2−5] are known for their inability to coordinate even to smaller Lewis acids like CH_3^+ or BF_3 except with a proton.[2,6] This typical non-nucleophilic basicity has been exploited in a variety of reactions, in particular, as an acid scavenger or as a buffering agent in studies of reactions of metal ions in aqueous solutions.[6] Effenberger and co-workers used TTBPy in characterizing the concentration of acylium ions in aromatic acylation reactions to exploit its ability to trap the released triflic acid.[7] The profound effect of TTBPy on k_H/k_D values in these reactions has also been studied. Shibata and co-workers used the TTBPy/Tf_2O system for the synthesis of indole triflones.[8] More recently, Berke and co-workers found that the bulky TTBPy in the presence of $B(C_6F_5)_3$ can heterolytically cleave H_2, showing frustrated Lewis pair (FLP) activity (Scheme 1, a). In addition, it was also found that TTBPy can form a stable frustrated Lewis pair with [(acridine)BCl_2]-[$AlCl_4$] that can also heterolytically cleave H_2.[9] Intriguingly, Ingleson and co-workers observed that the position of the hydride from H_2 has been found to be the C9 position of acridine and not the usually expected boron.

The best and the most common use of the 2,4,6-tri-*tert*-butylpyridine (TTBPy), along with other hindered bases, 2,4,6-tri-*tert*-butylpyrimidine (TTBP), 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), and 2,6-di-*tert*-butylpyridine (DTBP), has been in glycosylation reactions again as a trap to capture the released sulfonic acids at lower temperatures.[10]

Gin and co-workers introduced the use of excess of TTBPy in the sulfoxide-catalyzed activation of glycosyl hemiacetals (Scheme 1, b).[11,12] However, Crich later introduced TTBP as a potential alternative to TTBPy on the grounds that the former is a nonhygroscopic white crystalline powder unlike the hindered pyridine derivatives.[13] Though the mechanism is not clear, Ye and co-workers observed an intriguing stereoswitch[14] in glycosylation reactions of glucosamine derivatives in the presence and absence of 2,4,6-tri-*tert*-butylpyrimidine.

However, curiosity lingers on the reactivity of these hindered pyridine and pyrimidine compounds as bases. For example, it is known that the aqueous pK_a of DTBP is about ∼2 units lower than expected, though the gaseous state pK_a is in line with predicted values.[4,5] The weak basicity of 2,4,6-tri-*tert*-butylpyridine, similar to that of DTBP or TTBP, is attributed to the inability of TTBPyH to be solvated in aqueous solutions due to high steric shielding and hence behaves as a weak base (pK_a = 3.4). This effect is more pertinent in DMSO in which the pK_{DMSO} of DTBP is 0.81, suggesting an extremely weak hydrogen bonding of DTBPH with a large DMSO molecule (relative to H_2O). It is evident that the ability of the cationic Brønsted acid TTBPyH depends extensively on the hydrogen-bonding character of the solvent. However, we were curious to understand the behavior of TTBPyH in the more generally used solvents like DCE or DCM with low dielectric constants (ε = 10.36 and ε = 8.93, respectively) where it is used as a proton-trapping agent. On the other hand, very recently, it has been shown that Schrenier's thiourea, whose pK_{DMSO} is 8.5, catalyzes the tetrahydropyranylation of alcohols via a Brønsted acid mechanism.[15−24] This led us to question whether TTBPy, whose conjugate acid is a much stronger acid in DMSO, is safe as a non-nucleophilic base in glycosylation reactions, particularly in reactions involving glycals. This thought carries

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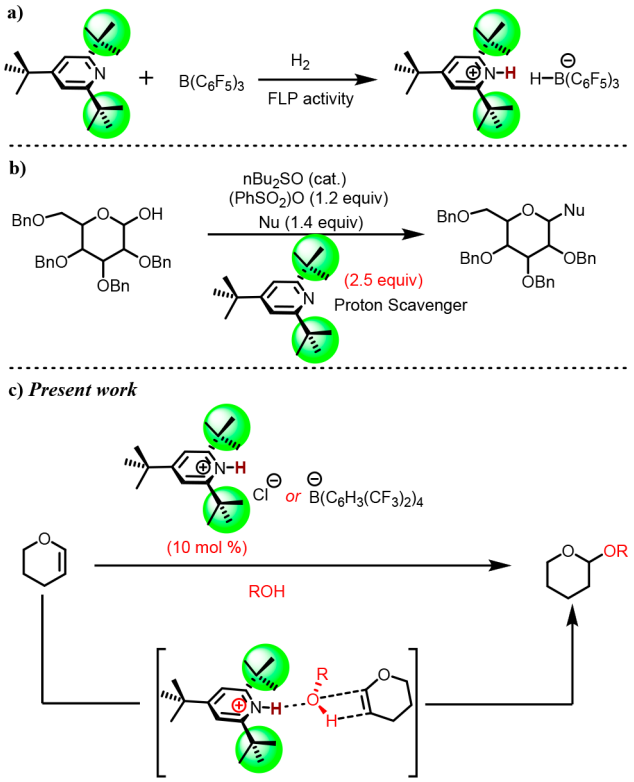
Scheme 1. Reactions Involving TTBPy



significance as, in general, more than 1 equiv of TTBPy salt is produced in glycosylation reactions owing to the excess usage of TTBPy as an acid quencher. However, we note in passing that a huge difference in reactivity could exist between neutral Brønsted acids versus cationic Brønsted acids, specifically in nonpolar solvents like DCM/DCE.[25] It is pertinent to ask if the trapped proton in the TTBPyH, once formed, can behave as a cationic Brønsted acid (Figure 1) to protonate the

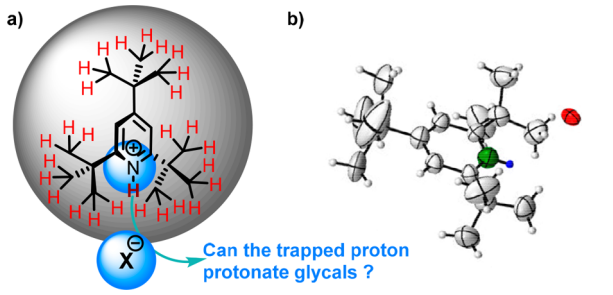


Figure 1. (a) Molecular structure and (b) ORTEP diagram of TTBPyHCl.

sterically demanding glycal substrates in solvents of poor solvation ability or if it forms a tight ion pair with the counterion, thus showing neutral character.

In the present study, we show that TTBPy salts not only catalyze the glycosylation of glycals but do it very effectively with 10 mol % of the catalyst and also in a highly stereoselective fashion leading to the synthesis of various deoxyhexoses. Further, our observations also throw some light on the mechanism, which reveals that TTBPyH catalyzes the reaction *not* via a Brønsted acid mechanism (BA) but via its hydrogen-bonding-assisted activation (HB activation) (Scheme 1, c).[26] In addition, the effect of the catalytic acitivity also seems to be controlled by the nature of the counterion.[27]

Our study commenced with the synthesis of two TTBPy salts with chloride and BArF as counteranions. The chloride salt of TTBPyH has been achieved by dissolving TTBPy in methanolic HCl and evaporating the solvent to dryness. The BArF salt of TTBPyH is synthesized via a simple anion-exchange reaction[28] with the chloride salt triggered by the precipitation of sodium chloride in dichloromethane. 2-Deoxy and 2,6-dideoxy sugars form a part of several antibiotics and anticancer agents.[29−32] Despite the recent surge in development of methods for the synthesis of 2-deoxyglycosides,[18,23,24,33] there is still a need to develop a general organocatalytic method for the stereoselective synthesis of various 2-deoxy- and 2,6-dideoxyglycosides. Initially, we have reacted glucal **1a** and primary sugar acceptor **2a** as substrates using 20 mol % of chloride salt of TTBPyH **3a** as the organocatalyst at 40 °C in DCE as solvent. Interestingly, this led to the glycosylated product **5a** after 24 h in 86% yield with 4:1 α/β selectivity (Table 1, entry 1). A 1.1 equiv portion of acceptor was sufficient enough to drive the excellent conversion of starting material to glycosylated product.

Surprisingly, the organocatalyst **3c** with the weakly coordinating BArF anion[34−36] in DCM at rt gave the corresponding Ferrier[37,38] glycosylated product **5ag** along with the expected product **5a** in the presence of primary sugar acceptor with 30% and 56% yields, respectively (Table 1, entry 5). The difference in reactivity with the change of anion suggests the unique role of cation−anion interactions[39] in the observed catalysis. In addition, catalyst **3c** is active even at temperatures as low as −40 °C, providing decent conversion of glucal to the corresponding products. Since our target molecules are not Ferrier products we have chosen the chloride salt of TTBPy **3a** for further optimization.

The reaction with pyridinium chloride **3b** to give the product in 58% yield was not clean (Table 1, entry 2). Studies to find the right solvent have been performed using the tri-OBn-galactal **1b** and diacetonide-protected 6-OH acceptor **2d** as coupling partners.

A quick study revealed that the chlorinated solvents like DCM and DCE are the best solvents for this cationic Brønsted acid catalyzed glycosylation (Table 1, entries 10 and 11). The coupling reaction when performed in DCE gave the best yields and also led to the exclusive formation of the α-glycosylated product **4b**. However, the reaction when performed in the presence of only TTBPy instead of it is salt in DCE at 40 °C for 24 h did not lead to any glycosylated product, thus indicating that this is not a base-catalyzed glycosylation reaction.

With the optimized conditions in hand, we sought to evaluate the ability of the new organocatalyst toward glycals with various protecting groups (Scheme 2). The armed benzyl and *p*-methylbenzyl (*p*-MeBn) protected glucal donors **1a** and **1g** when reacted with 1.1 equiv of acetonide protected primary sugar acceptor **2d** and 20 mol % of **3a** at 40 °C in DCE as a solvent gave the products **4a** and **4c** in 76% and 89% yield with 7:1 and 10:1 α/β selectivity, respectively. Remarkably, the sterically bulky TBDPS protected glucal **1c** provided the 2-deoxyglycosylated product **4e** with 6:1 (α:β) selectivity in 83% yield. Under similar reaction conditions, benzyl **1b**, *p*-methylbenzyl **1h**, and TBDPS-protected galactal **1d** reacted with primary sugar acceptor **2d** to give only α-products **4b**, **4d**, and **4f**, respectively, in high yields.

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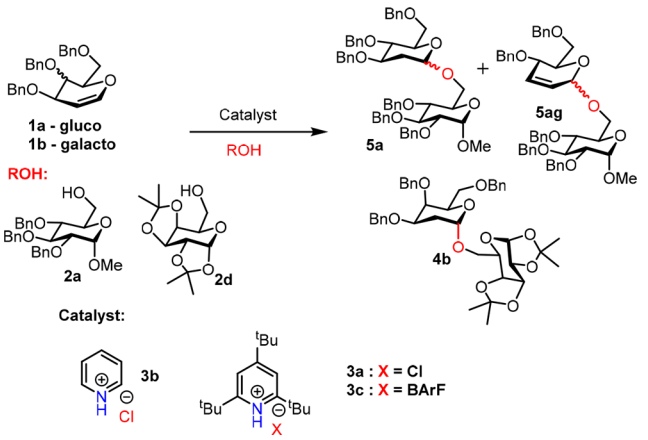
Table 1. Optimization Studies[a]



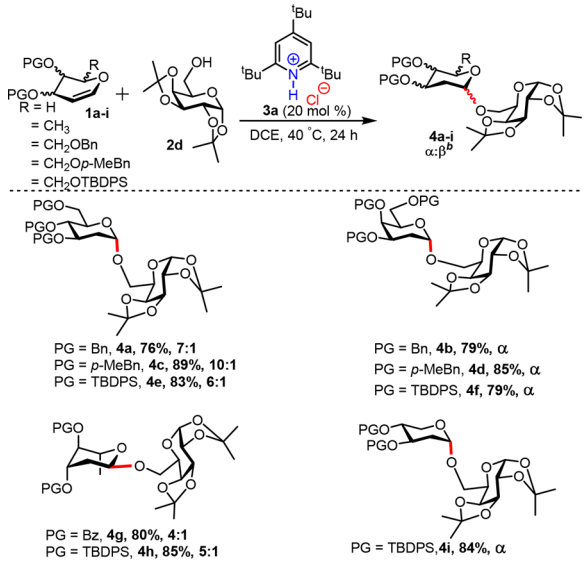
entry	cat.	solvent	compd	yield (%) (α/β)[g]	5ag yield (%) (α/β)[g]
1	**3a**	DCE	**5a**	86 (4:1)	
2	**3b**	DCE	**5a**	58 (2:1)	
3	TTBPy	DCE	**5a**		
4[b]	**3a**	Et_2O	**5a**	64 (2:1)	
5	**3c**	DCM	**5a**	56 (1:1)	30 (2:1)
6[c]	**3c**	DCM	**5a**	26 (1:1)	10 (2:1)
7[d]	**3c**	DCM	**5a**	34 (1:1)	21 (3:1)
8[e]	**3c**	Et_2O	**5a**	49 (1:1)	42 (2:1)
9[f]	**3c**	Et_2O	**5a**	46 (2:1)	40 (2:1)
10[e]	**3a**	DCM	**4b**	75 (α)	
11	**3a**	DCE	**4b**	79 (α)	
12	**3a**	PhMe	**4b**	44 (α)	
13	**3a**	ACN	**4b**	40 (α)	
14	**3a**	*m*-xyl	**4b**	41 (α)	
15	**3a**	PhH	**4b**	25 (α)	
16	**3a**	THF	**4b**	67 (α)	

[a]Reaction conditions: 0.12 mmol of **1a,b**, 0.13 mmol of **2a**, and 20 mol % of **3a–c** and TTBPy, 24 h [(DCE at 40 °C, for **3a,b** and TTBPy) and (DCM at rt for **3c**)], **1a** for entries 1–9 and **1b** for entries 10–16. [b]At rt for 7 days. [c]At −40 °C. [d]5 mol % of **3c** was used. [e]At rt. [f]Ether as a solvent at −30 °C. [g]Anomeric selectivities were determined from crude NMR analysis.

We then decided to test the efficiency of the method toward the synthesis of 2,6-dideoxy glycosides, utilizing the L-rhamnal (**1e** and **1i**) donors. The disarmed benzoyl-protected L-rhamnal **1i** gave the coupled product **4g** in 80% yield with 4:1 α/β selectivity, whereas the bulky TBDPS-protected L-rhamnal **1e** gave the product **4h** in 85% yield with 5:1 selectivity. We next focused on the scope of derivatives with different donors and acceptors to investigate the potential applicability of this method.

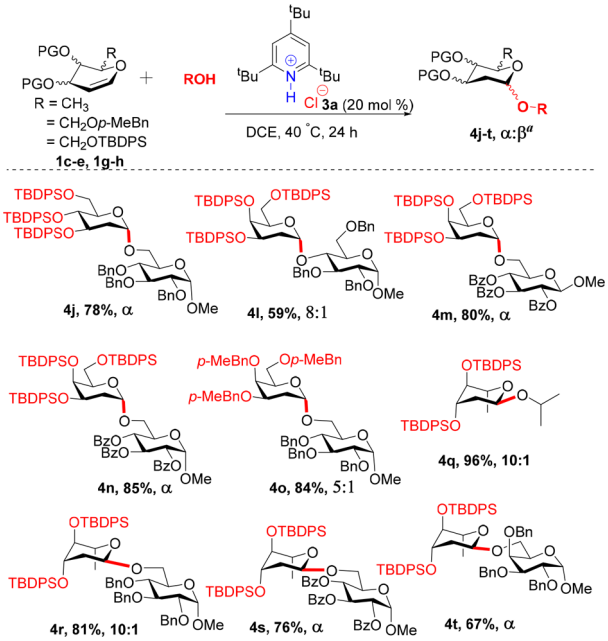
Since it has been observed that the bulky TBDPS protecting group in combination with the bulky TTBPy catalyst led to the highly selective glycosylation reactions, all of the further studies have been carried out with glycals bearing the same protecting group. TBDPS-protected glucal and galactal donors under the currently developed organocatalytic conditions led to exclusive formation of α-product with both reactive and electron-deficient acceptors (Scheme 3, **4j–n**) except in the case of product **4l**, where the selectivity has dropped to 8:1 in favor of α. The coupling reactions with *p*-MeBn protected galactal **1h** with glucose-derived 6-OH acceptor led to the product **4o** in 84% yield and 5:1 α/β selectivity. Synthesis of 2,6-dideoxyglycosides (Scheme 3, **4q–t**) has also been

Scheme 2. Glycosylation of Benzyl-, *p*-Methylbenzyl-, and TBDPS-Protected Glycals with Diacetonide-Protected Galactosyl 6-OH Acceptor*



*Reaction conditions: 1 equiv of **1a–i**, 1.1 equiv of **2d** ,and 20 mol % of **3a**, 24 h in DCE at 40 °C. [b]Anomeric selectivities were determined from crude NMR analysis.

Scheme 3. Glycosylation of TBDPS-Protected Glycals with Various Acceptors*



*Reaction conditions: 1 equiv of **1c–e,g,h**, 1.1 equiv of **2a–c,e**, and 20 mol % of **3a**, 24 h in DCE at 40 °C. [a]Anomeric selectivities were determined from crude NMR analysis.

achieved in a highly stereoselective fashion under the organocatalytic conditions. The method has also been extended for the synthesis of galactosyl amino acids (Scheme 4). The Fmoc-protected methyl ester of serine **2h** was coupled with galactals (**1b,d,h**) to provide the corresponding glycoamino acids **6a–c** as only α products, whereas the threonine derivative **2i** gave the corresponding product **6d** in

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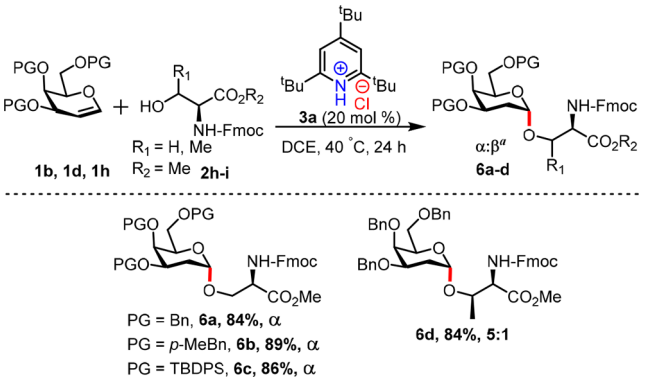
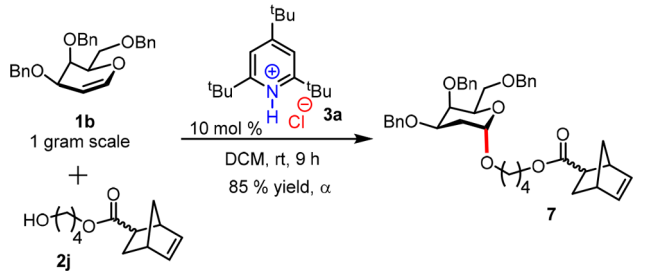
Scheme 4. Synthesis of Glycosyl Amino Acids*



*Reaction conditions: 1 equiv of **1b,d,h**, 1.1 equiv of **2h–i**, and 20 mol % of **3a**, 24 h in DCE at 40 °C. [a]Anomeric selectivities were determined from crude NMR analysis.

84% yield with a drop in stereoselectivity (5:1, α/β). The organocatalytic glycosylation method was then applied on a gram-scale synthesis. We were delighted to find that 1 g of benzyl-protected galactal **1b** with a norbornene-derived ROMP precursor **2j** in the presence of reduced catalytic loading (10 mol %) of **3a** in DCM at rt afforded the corresponding monosaccharide **7** in 85% yield with α selectivity (Scheme 5).

Scheme 5. Gram-Scale Demonstration of Glycosylation[a]



[a]Reaction conditions: 1 equiv of **1b**, 2 equiv of **2j**. Anomeric selectivity was determined from crude NMR analysis.

As discussed vide supra, the attempted coupling reaction in the presence of only TTBPy and not TTBPy salt led to no conversion of the starting material, suggesting that this is not a base-catalyzed reaction. In addition, the reaction of stoichiometric amounts of TTBPy·HCl in the absence of any acceptor in ultradry DCE failed to provide the expected glycosyl chlorides (Figure 2a). This result signifies that the initiation step is not the proton transfer from TTBPyH to the glycal. The transfer of the trapped proton that is sterically shielded in the bulky TTBPyH to the bulky sugar enol ethers is highly disfavored, thus ruling out the BA mechanism. In order to gain more insight into the mechanism, we focused on NMR experiments in $CDCl_3$. An ^1H NMR experiment performed by mixing the catalyst **3a** and 2-propanol in an equimolar ratio led to a significant shift in the chemical shift of the OH peak of 2-propanol (from δ −1.59 to −3.12, Figure 2b-3). Besides, a slight shift has also been observed in the α-hydroxy proton H_D (from δ 4.03 to 4.07, Figure 2b-3) and in the methyl doublet H_E (from δ 1.22 to 1.24, Figure 2b-3). The OH peak of 2-propanol shifted downfield, whereas the NH peak of the catalyst shifted upfield (from δ 14.25 to 14.19) (see the SI for a detailed analysis). The shift in the nonexchangeble protons,

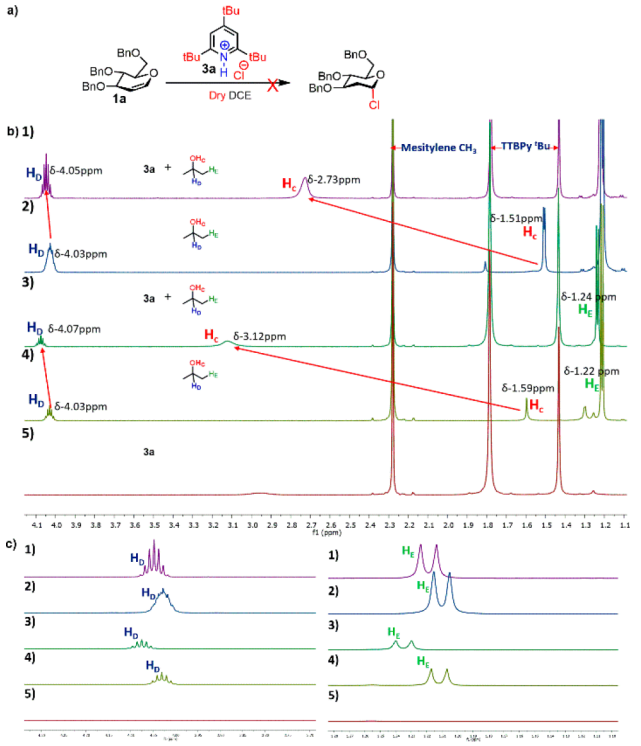


Figure 2. Investigation of the mechanism. (a) Control experiment. (b) ^1H NMR titration of **3a** with 2-propanol in 600 μL of $CDCl_3$: (1) 0.018 mmol of **3a** and 0.108 mmol of 2-propanol (1:6 ratio), (2) 0.108 mmol of 2-propanol, (3) 0.018 mmol of **3a** and 0.018 mmol of 2-propanol (1:1 ratio), (4) 0.018 mmol of 2-propanol, and (5) 0.018 mmol of **3a**. 0.018 mmol of mesitylene is used as an internal standard in all the experiments for the purpose of calibration (see the SI for more details). (c) Expanded for H_D and H_E regions.

albeit present, is slightly less (from δ 4.03 to 4.05, Figure 2b-1) when 2-propanol is taken as 6 equiv (0.108 mmol) with respect to the catalyst **3a** (0.018 mmol) in 600 μL of $CDCl_3$ (exactly replicating the concentrations of reaction conditions). These observations strongly suggest a hydrogen bond between TTBPyH and alcohol. We note in passing that a slight change in the chemical shift of the $CHCl_3$ peak has been observed in the titration of catalyst **3a** with 2-propanol. Therefore, the ^1H NMR of 2-propanol has been recorded at different concentrations[40] (see the SI), where it was found that the change in the chemical shift of $CHCl_3$ peak is significant with increasing concentration, revealing the weak hydrogen-bonding character of $D/HCCl_3$. Based on the above observations, we propose a hydrogen-bond-mediated mechanism (HB mechanism) for the observed catalysis as depicted in Figure 3. A strong hydrogen bond between the catalyst and the alcohol leading to an increased acidity of the alcoholic OH results in the protonation of glycals, thus forming the oxocarbenium ion. The thus-formed oxocarbenium ion is trapped by the alkoxide ion bound to TTBPyH, thereby regenerating the catalyst. More studies to gain insights into the mechanism of the reaction are in progress in our laboratory.

In conclusion, we have showcased the utility of the conjugate acids of the sterically bulky 2,4,6-tri-*tert*-butylpyridine as efficient catalysts for the stereoselective synthesis of 2-deoxy- and 2,6-dideoxyglycosides. The steric bulk of the organocatalyst in conjunction with the sterically bulky TBDPS protecting group of glycals seems to be working in tandem for

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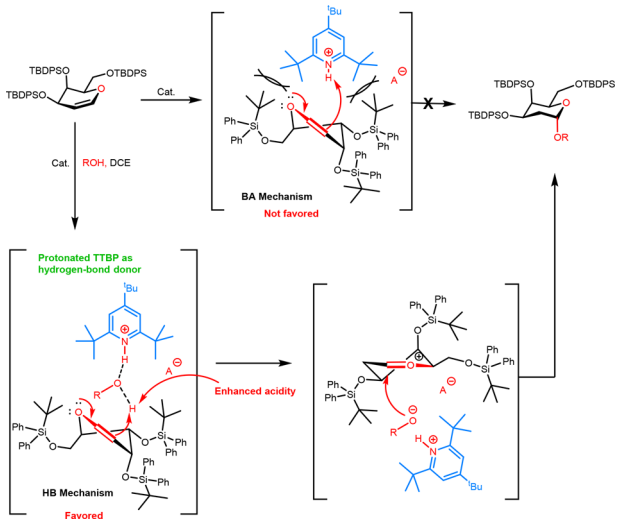

Figure 3. Potential pathways for the transformation.

the observed stereoselective α-glycosylations. Moreover, despite the low pK_a of the conjugate acids observed in polar solvents like water and DMSO, TTBPy hydrochloride seems to be not acidic enough to protonate glycals via a Brønsted acid mechanism in nonpolar solvents like DCM and DCE to generate glycosyl halides. In addition, the catalytic activity of the new organocatalyst occurs through an unprecedented ionic hydrogen bond activation of alcohols as evidenced by the NMR studies and the control experiments. Interestingly, the observed catalytic activity also seems to be influenced by the counterion. Further studies on the anionic activity could result in better understanding of the unique mode of activation. These results will not only be useful for chemists to judiciously use the bulky base TTBPy as an acid scavenger but also will help in the design of new cationic Brønsted acids. Further studies on the mechanism and utility of these salts in various other reactions are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00626.

Experimental procedures, spectroscopic data for all new compounds, and crystallographic data for **3a** and **3c** (PDF)

Accession Codes

CCDC 1897053−1897054 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Y. D. Vankar on the occasion of his retirement.

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