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Silver(I) tetrafluoroborate as a potent promoter for chemical glycosylation

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Abstract

We have identified silver tetrafluoroborate ($AgBF_4$) as an excellent promoter for the activation of various glycosyl donors including glycosyl halides, trichloroacetimidates, and thioimidates. Easy handling and no requirement for azeotropic dehydration prior to application makes $AgBF_4$ especially beneficial in comparison to the commonly used AgOTf. Selective activation of glycosyl halides or thioimidates over thioglycosides or *n*-pentenyl glycosides, including simple sequential one-pot syntheses, has also been demonstrated. Versatility of glycosyl thioimidates was further explored by converting these intermediates into a variety of other classes of glycosyl donors.

With increasing demand for the synthesis of biologically important and therapeutically active oligosaccharides and glycoconjugates, efforts to expand the arsenal of glycosylation methods and techniques have emerged. In spite of significant recent advances in the areas of stereoselective glycosylation[1,2] and expeditious oligosaccharide synthesis,[3,4] the construction of complex oligosaccharides with high efficiency and complete stereoselectivity remains a difficult task.

As a part of a program to develop new methods and strategies for glycochemistry, we became interested in glycosyl thioimidates, a class of glycosyl donors with the generic leaving group $SCR^1 = NR^2$.[5,6] We have already reported the synthesis of *S*-benzoxazolyl (SBox)[7,8] and *S*-thiazolinyl (STaz)[9,10] glycosides and evaluated their properties in stereoselective glycosylations and expeditious oligosaccharide syntheses. Metal salt-based promoters were shown to provide efficient activation of the thioimidoyl moiety for glycosylation.[8,11] Among a variety of metal salts investigated, arguably, silver trifluoromethanesulfonate (AgOTf) was one of the best choices for the activation of the SBox and STaz moieties for a variety of synthetic applications.

Beyond the scope of our own research program, AgOTf has been commonly employed as an activator for many other classes of glycosyl donors including glycosyl bromides,[12–14] chlorides,[15] trichloroacetimidates,[16] and seleno glycosides.[17] In spite of wide applicability and high versatility of AgOTf, there are some significant drawbacks that limit the usage of this promoter in synthesis. In a majority of applications, AgOTf requires fresh activation by repetitive co-evaporation with toluene followed by extended drying under vacuum directly prior to use. In addition, we noticed that the quality of commercial reagent may significantly vary depending on the supplier and the batch. It should be noted that the use of AgOTf as an acidic additive in NIS-promoted glycosidation of thioglycosides does not require preactivation of AgOTf.

Bearing in mind these drawbacks, we wondered if any other silver salts could be used to achieve an efficient glycosidation of a variety of glycosyl donors and would produce reproducible results without the requirement of the preactivation or azeotropic dehydration. Herein we present a report that demonstrates the use of silver tetrafluoroborate ($AgBF_4$) as a potent promoter for the activation of various types of glycosyl donors. It should be noted that

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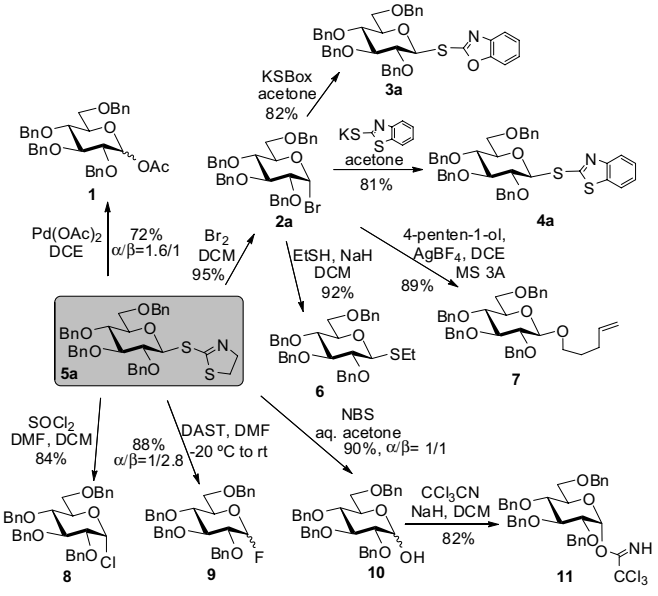
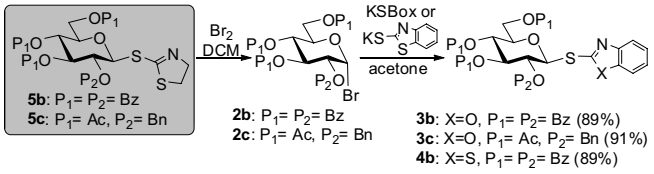
$AgBF_4$ has already been used in glycosylations, yet these applications, including alcoholysis of glycosyl bromides,[18,19] synthesis of C-glycosides from chlorides,[20] glycosidation of 2-deoxy thioglycosides,[21] and α-stereoselective glycosidation of 1,2-anhydro sugars,[22] were scarce and far apart. In this context, the combination of Cp_2ZrCl_2–$AgBF_4$ in benzene has proven to be a powerful promoter combination for the activation of tetra-*O*-benzyl-D-mannosyl fluoride.[23]

To generate a broad array of glycosyl donors we investigated whether thiazolinyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **5a**[10] could serve as a common precursor. These studies were successful and we discovered that the STaz glycoside **5a** can be directly converted into the following glycosyl donors: acetate **1**, bromide **2a**, chloride **8**, fluoride **9**, and hemiacetal **10** in excellent yields (84–95%, Scheme 1). Moreover, glycosyl bromide **2a** was then used as a precursor for the next synthetic steps to obtain benzoxazolyl, benzothiozolyl, and ethyl thioglycosides (**3a**, **4a**, and **6**), as well as *n*-pentenyl glycoside **7**—all with exclusive β stereoselectivity. The hemiacetal derivative **10** was converted into the corresponding glycosyl trichloroacetimidate **11** as shown in Scheme 1. Synthesis of a range of differently protected glycosyl thioimidates has been similarly accessed and is depicted in Scheme 2. Yields given are over-all yields for two synthetic steps.

Having synthesized a library of glycosyl donors, we performed a number of test glycosylation reactions using $AgBF_4$ as a promoter (Table 1). Since we wanted to determine whether the glycosylations could be performed without preactivation of $AgBF_4$, all reactions were performed with commercial reagent as received, without further conditioning. Glycosidation of glycosyl acetate **1** with glycosyl acceptor **13** in the presence of $AgBF_4$ did not proceed

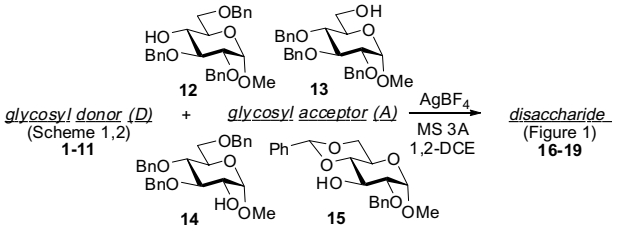


Scheme 1. Conversion of a common STaz building block (**5a**) into a range of glycosyl donors.



Scheme 2. Conversion of the STaz glycosides **5b**,**c** into thioimidates **3b**,**c** and **4**.

Table 1
$AgBF_4$ promoted glycosylations of glycosyl acceptors **12**–**15**



Entry	D	A	Time	Product	Yield (%)	α/β Ratio
1	**1**	**13**	24 h	**17a**	—[a]	—
2[b]	**1**	**13**	16 h	**17a**	91	1.4/1
3[c]	**1**	**13**	5 h	**17a**	95	2.0/1
4	**2a**	**13**	5 min	**17a**	92	2.4/1
5	**2b**	**13**	5 min	**17b**	96	β Only
6	**2b**	**14**	24 h	**18b**	82	β Only
7	**3a**	**13**	10 min	**17a**	89	1.2/1
8	**3b**	**13**	10 min	**17b**	91	β Only
9	**3b**	**14**	15 min	**18b**	84	β Only
10	**3c**	**13**	15 min	**17c**	91	1.6/1
11	**4a**	**15**	5 min	**19a**	87	7.4/1
12	**4b**	**13**	20 min	**17b**	90	β Only
13	**5a**	**13**	5 min	**17a**	95	1.3/1
14	**5a**	**14**	5 min	**18a**	92	1.4/1
15	**5b**	**13**	10 min	**17b**	90	β Only
16	**5c**	**13**	20 min	**17c**	75	1.2/1
17	**6**	**13**	24 h	**17a**	—[a]	—
18[d]	**6**	**13**	24 h	**17a**	91	1.2/1
19[e]	**6**	**13**	10 min	**17a**	92	1.2/1
20	**7**	**13**	24 h	**17a**	—[a]	—
21[d]	**7**	**13**	24 h	**17a**	89	1.0/1
22[e]	**7**	**13**	20 min	**17a**	76	1.2/1
23	**8**	**13**	5 min	**17a**	97	1.6/1
24	**8**	**12**	10 min	**16a**	91	1/3.4
25	**9**	**13**	20 h	**17a**	81	2.0/1
26	**9**	**15**	1.5 h	**19a**	81	2.3/1
27	**10**	**13**	24 h	**17a**	—[a]	—
28	**11**	**13**	5 min	**17a**	80	1/1.5
29	**11**	**12**	2 days	**16a**	65	1/5.4

[a] No product formation was detected; all glycosylations were promoted with $AgBF_4$ except the following.
[b] −3.0 equiv of BF_3–Et_2O were used.
[c] −3.0 equiv of BF_3–Et_2O and 0.5 equiv of $AgBF_4$ were used.
[d] −2.0 equiv of NIS was used.
[e] −2.0 equiv of NIS and 0.5 equiv of $AgBF_4$ were used.

(entry 1). A similar coupling in the presence of BF_3–Et_2O, a conventional promoter for the activation of glycosyl acetates,[24] gave disaccharide **17a** (Fig. 1) in 91% yield, although it required 16 h for the reaction to complete. We determined that the reaction time of this reaction could

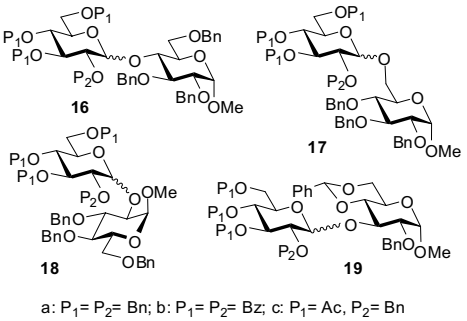


Fig. 1. Structures of disaccharides **16**–**19**.

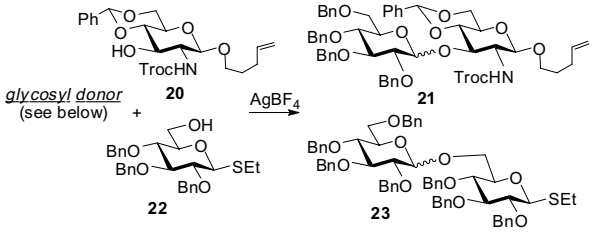
be significantly reduced (16 h vs 5 h, entries 2 and 3) by adding 20–50 mol % of $AgBF_4$. In these couplings, even higher yield of **17a** (95%) and an improved stereoselectivity were detected.

Glycosidation of glycosyl bromides **2a** and **2b** could be efficiently accomplished with $AgBF_4$, although the coupling of per-benzoylated bromide **2b**, prepared as shown in Scheme 2, with the sterically hindered acceptor **14** required prolonged reaction time (entries 4–6). These results were comparable with the glycosylations using traditional bromide activators—silver carbonate[25,26] or mercury salts.[27,28]

Glycosidation of glycosyl thioimidates **3**–**5** was smoothly driven to completion in a matter of minutes (entries 7–16). All glycosylations proceeded with very high conversion yields, comparable or even exceeding those achieved in glycosylations promoted with preactivated AgOTf. For example, $AgBF_4$-promoted couplings depicted in entries 14 and 16 (Table 1) proceeded in 92% (90% with AgOTf) and 75% (70% with AgOTf) yield, respectively.[9] While the anchimerically assisted couplings with benzoylated glycosyl donors were β-stereoselective, only fair α-stereoselectivity was achieved with 2-O-benzylated glycosyl donors. All couplings were performed in the neutral solvent since the stereoselectivity optimization was not a primary intention of these studies.

Promoters for thioglycoside and *n*-pentenyl glycoside activation include thiophilic reagents, among which NIS/TfOH or NIS/TMSOTf are arguably the most common.[29,30] Therefore, not surprisingly, the activation of stable glycosyl donors, ethyl thioglycoside **6** or *n*-pentenyl glycoside **7**, did not take place in the presence of $AgBF_4$. It should be noted that NIS alone can also activate both *S*-ethyl and pentenyl glycosides, however, these transformations require prolonged reaction time (entries 18 and 21). Having decided to investigate whether these glycosyl donors can be activated by NIS/$AgBF_4$ system, we discovered that these coupling reactions proceeded very rapidly and provided the corresponding disaccharide in minutes (entries 19 and 22). We then demonstrated that $AgBF_4$ could be employed as a suitable promoter for glycosidation of chloride **8**, fluoride **9**, or trichloroacetimidate **11**, whereas the hemiacetal derivative **10** remained inert under these reaction conditions (entries 23–29).

Table 2
Selective activation of various glycosyl donors over *n*-pentenyl acceptor **20** and SEt acceptor **22**

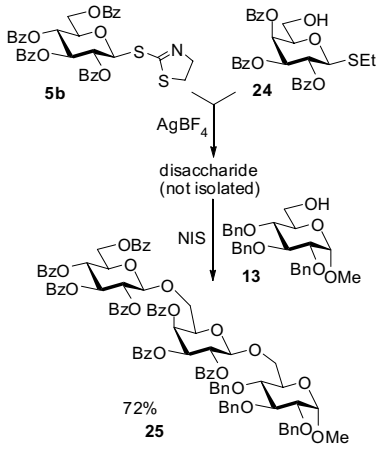


Entry	D	A	Time	Product	Yield (%)	α/β Ratio
1	**3a**	**20**	10 min	**21**	86	1.1/1
2	**4a**	**20**	20 min	**21**	85	3.3/1
3	**5a**	**20**	10 min	**21**	83	1/1.2
4	**9**	**20**	16 h	**21**	65[a]	1.6/1
5	**2a**	**22**	15 min	**23**	84	1.6/1
6	**3a**	**22**	20 min	**23**	87	2.0/1
7	**5a**	**22**	15 min	**23**	89	2.4/1
8	**8**	**22**	15 min	**23**	84	2.2/1
9	**9**	**22**	24 h	**23**	83[a]	2.4/1

[a] The yield is based on the recovered acceptor.

Based on the results summarized in Table 1, we anticipated that it might be possible to activate glycosyl halides, *S*-benzothiazolyl, SBox, or STaz glycosides over the SEt or *n*-pentenyl moieties in the presence of $AgBF_4$. We have already reported that selective activation of SBox and STaz glycosides over SEt glycosyl acceptor can be achieved in the presence of AgOTf.[7,31] Also in this case, $AgBF_4$ was found to be capable of providing smooth couplings with consistently high yields (Table 2). We observed that glycosidation of glycosyl fluoride **9** was sluggish and the moderate to good yields presented in Table 2 were based on the unreacted acceptor recovery (entries 4 and 9).

Based on the results of the selective activations, we assumed that it could be possible to perform the activation sequence in a highly efficient one-pot fashion. Presumably, any building block that can be activated with $AgBF_4$ can be used as the glycosyl donor for the first activation step. We chose to investigate SBox and STaz glycosides as well as glycosyl bromides as glycosyl donors. Glycosyl acceptor should withstand $AgBF_4$ activation, but in turn could be readily activated by addition of NIS. Either *S*-ethyl or *O*-pentenyl leaving groups could be used for this purpose. An example shown in Scheme 3 makes use of the STaz leaving group in **5b** for the first coupling step. At this stage the *S*-ethyl moiety of the glycosyl acceptor **24** remains inert. Upon the formation of the intermediate disaccharide, its SEt moiety can then be activated for the reaction with the newly added acceptor **13** by adding 2.0 equiv of NIS. As demonstrated above, NIS along with $AgBF_4$ (used in excess and is remaining from the previous step) serves as an efficient promoter for this type of glycosylation. As a result of this two-step activation, trisaccharide **25** was isolated in 72% yield. Other leaving group combinations mentioned above were also found to be capable of the one-pot



Scheme 3. One-pot glycosylation: synthesis of trisaccharide **25**.

activations and provided the corresponding trisaccharides in 55–70% overall yields.

In summary, we have identified silver tetrafluoroborate as an excellent promoter for the activation of various glycosyl donors, prepared from the common precursor bearing temporary STaz anomeric moiety. Easy handling and no requirement for azeotropic dehydration prior to the application makes $AgBF_4$ especially beneficial in comparison to the commonly used AgOTf. We also demonstrated that selective activation of glycosyl halides or thioimidates over thioglycosides or *n*-pentenyl glycosides could lead to simple one-pot syntheses via sequential selective activation of one leaving group over another. Therefore, we believe that $AgBF_4$ should be considered as a powerful and convenient alternative for silver(I) activated glycosylations.

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Supplementary data

Experimental procedures and characterization data for new compounds. Supplementary data associated with this article can be found, in the online version, at doi: 10.1016/j.tetlet.2007.12.105.

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