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Electrochemically Generated ArS(ArSSAr)$^+$B(C$_6$F$_5$)$_4^-$ as an Activator of Thioglycosides for Glycosylation

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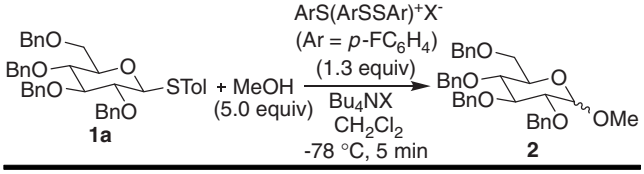
Electrochemically generated ArS(ArSSAr)$^+$ was found to be an effective activator for glycosylation of thioglycosides. Efficiency of the reaction strongly depends on the nature of the counter anion, and B(C$_6$F$_5$)$_4^-$ was the most effective among those examined. The method was applicable to various glyocosyl donors including thiogalactosides and thiomannosides and various acceptors including those having secondary hydroxy groups.

Thioglycosides[1] are widely utilized as glycosyl donors in the chemical synthesis of oligosaccharides,[2] because they are stable and easy to handle. Continuous efforts have been made to develop a new method for activating thioglycosides, which might open many possibilities of chemical glycosylation.[3]

We have already reported that arylbis(arylthio)sulfonium tetrafluoroborate [ArS(ArSSAr)$^+$BF$_4^-$][4] generated by electrochemical oxidation of diaryldisulfide (ArSSAr) reacts with thioacetals to generate alkoxycarbenium ions (indirect cation pool method).[5] We also found that electrochemically generated ArS(ArSSAr)$^+$B(C$_6$F$_5$)$_4^-$ was effective for generation of glycosyl cations or its equivalent from thioglycosides in the absence of glycosyl acceptors.[6] In the flow system, the resulting highly reactive glycosyl cations are transferred to another location to be used for the reaction with glycosyl acceptors. In this paper, we report another method for glycosylation using thioglycoside and ArS(ArSSAr)$^+$, which involves generation of glycosyl cations in the presence of glycosyl acceptors.

At first we examined the effect of the counter anion of ArS(ArSSAr)$^+$. Thus, glycosyl donor **1a** (0.1 mmol) was allowed to react with ArS(ArSSAr)$^+$X$^-$ (1.3 equiv) (Ar = *p*-FC$_6$H$_4$), which was generated by the anodic oxidation of ArSSAr using Bu$_4$NX as a supporting electrolyte.[7] Methanol (5 equiv) was used as a glycosyl acceptor (Table 1). The use of BF$_4^-$ as X$^-$ gave rise to the formation of methyl glycoside **2** in 60% yield (Entry 1). The glycosyl fluoride was also obtained in 33% yield,[8] indicating that the glycosyl cation or the cation equivalent was trapped by fluoride derived from BF$_4^-$. To avoid the nucleophilic attack of the fluoride, the use of ClO$_4^-$ as the counter anion was examined. However, ArS(ArSSAr)$^+$ClO$_4^-$ was not generated effectively by the anodic oxidation of ArSSAr using Bu$_4$NClO$_4$ as a supporting electrolyte (Entry 2).[9] On the other hand, the use of OTf$^-$ resulted in the formation of **2** in 72% yield (Entry 3). Interestingly, the β-selectivity was higher than that observed for BF$_4^-$, presumably because of the formation of a glycosyl triflate[10] as an intermediate. The use of B(C$_6$F$_5$)$_4^-$ caused further increase in the yield of **2** (88%), although the stereoselectivity decreased slightly (Entry 4). Thus, hereafter ArS(ArSSAr)$^+$B(C$_6$F$_5$)$_4^-$ was used as an activator for glycosylation reactions. It is interesting that the use of the additional amount of Bu$_4$NB(C$_6$F$_5$)$_4$ resulted in higher yield (compare Entry 4 and 5), although a solution of ArS(ArSSAr)$^+$B(C$_6$F$_5$)$_4^-$ contains Bu$_4$NB(C$_6$F$_5$)$_4$ (ca. 0.05 M after electrolysis). The reason is not clear at present.

Table 1. Effect of electrolytes



Entry	Counter anion	**2** Yield/% [α/β][a]
1	BF$_4^-$	60 [48/52]
2	ClO$_4^-$	N. R.
3	OTf$^-$	72 [14/86]
4	B(C$_6$F$_5$)$_4^-$	88 [38/62]
5	B(C$_6$F$_5$)$_4^-$	77 [32/68][b]

[a]Reactions were normally carried out with thioglycoside (0.1 mmol) and a glycosyl acceptor (0.5 mmol) in Bu$_4$NX/CH$_2$Cl$_2$ (X = BF$_4$, ClO$_4$, OTf: 0.3 M, X = B(C$_6$F$_5$)$_4$: 0.1 M, 1 mL), ArS(ArSSAr)$^+$X$^-$ in CH$_2$Cl$_2$ (ca. 0.046 M, 2.9 mL, 0.13 mmol). [b]The reaction was carried out without adding Bu$_4$NB(C$_6$F$_5$)$_4$.

Table 2. The effect of the subsituent on the Ar group[a]

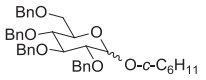
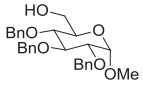
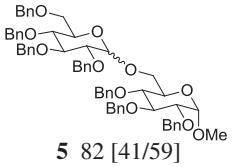
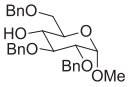
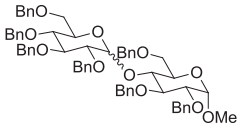
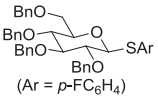
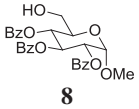
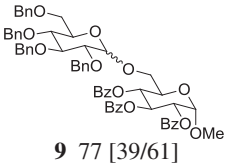
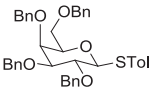
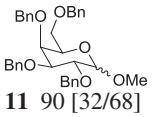
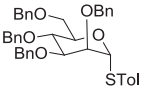
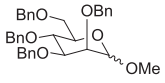
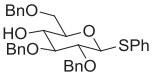
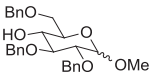
Entry	Ar	**2** Yield/% [α/β]
1	*p*-FC$_6$H$_4$	88 [38/62]
2	Ph	60 [44/56]
3	*p*-ClC$_6$H$_4$	66 [42/58]
4	Tol (*p*-MeC$_6$H$_4$)	55 [40/60]

[a]Reactions were carried out with 1.3 equiv of ArS(ArSSAr)$^+$B(C$_6$F$_5$)$_4^-$ and 5 equiv of MeOH at −78 °C.

Next, the effect of the substituent on the aryl group of ArS(ArSSAr)$^+$ was investigated (Table 2). As stated above the use of ArS(ArSSAr)$^+$ (Ar = *p*-FC$_6$H$_4$) gave **2** in 88% yield (Entry 1). The use of Ph and *p*-ClC$_6$H$_4$ as an aryl substituent resulted in the formation of **2** in 60% and 66% yield, respectively (Entries 2 and 3). The use of *p*-MeC$_6$H$_4$ (Tol) gave **2** in 55% yield (Entry 4). Thus, hereafter ArS(ArSSAr)$^+$B(C$_6$F$_5$)$_4^-$ (Ar = *p*-FC$_6$H$_4$) was used as an activator for glycosylation reactions.

The glycosylation was also carried out at higher reaction temperature and there were no significant effects of reaction temperature on glycosylation (See Supporting Informations for details[7]). Thus, glycosylation reactions of various glycosyl donors and acceptors were examined at −28 or 0 °C (Table 3). Secondary alcohols such as *c*-C$_6$H$_{11}$OH could be used for the glycosylation to afford the desired product **3** in 88% yield (Entry 1). Glycosides **4** and **6** were effective as acceptors to give

Table 3. ArS(ArSSAr)$^+$-mediated glycosylation of various glycosyl donors and acceptors[a]

Entry	Donor	Accepor	Product/Yield/% [α/β]
1[b]	**1a**	*c*-C_6H_{11}OH	 **3** 88 [31/69]
2[c]	**1a**	 **4**	 **5** 82 [41/59]
3[c]	**1a**	 **6**	 **7** 75 [40/60]
4	 (Ar = *p*-FC_6H_4) **1b**	MeOH	**2** 95 [45/55]
5[c]	**1b**	**4**	**5** 85 [28/72]
6[c]	**1b**	 **8**	 **9** 77 [39/61]
7	 **10**	MeOH	 **11** 90 [32/68]
8	 **12**	MeOH	 **13** 87 [52/48]
9	 **14**	MeOH	 **15** 83 [55/45]

[a]Reactions were carried out with 5.0 equiv of an acceptor and 1.3 equiv of ArS(ArSSAr)$^+$B$(C_6F_5)_4^-$ at 0 °C unless otherwise stated. [b]The reaction was carried out at −28 °C. [c]Reactions were carried out with 2.0 equiv of an acceptor at −28 °C.

the corresponding glycosylation products **5** and **7**, respectively in reasonable yields (Entries 2 and 3). Thioglycosides bearing *p*-fluorophenylsulfanyl group such as **1b** could be used as a donor to give the corresponding glycosylation products **2**, **5**, and **9** in good yields (Entries 4–6). Thiogalactoside **10** and thiomannoside **12** were also effective (Entries 7 and 8). Practical advantages of the present method include that a glycosyl donor containing a free hydroxy group **14** can be used for the reaction with methanol to give the corresponding methyl glycoside **15** in good yield (Entry 9).[11]

In conclusion, we have developed the ArS(ArSSAr)$^+$-B$(C_6F_5)_4^-$ mediated glycosylation, in which highly reactive glycosyl cations or its equivalents are generated from thioglycosides and are trapped in situ by glycosyl acceptors. It is hoped that the method will be widely utilized in synthesis of oligosaccharides.

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