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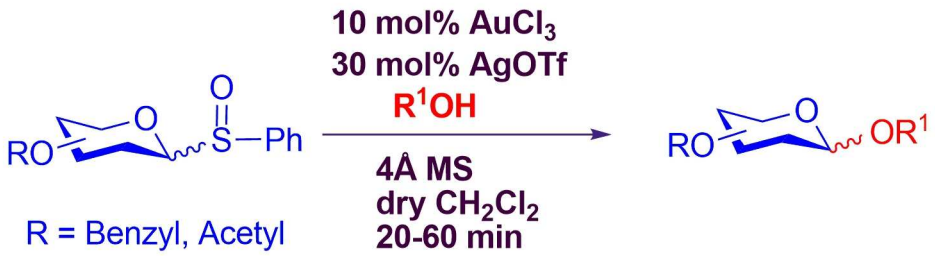


$AuCl_3$-AgOTf promoted *O*-glycosylation using anomeric sulfoxides as glycosyl donors at room temperature

*Ashokkumar Palanivel, Ande Chennaiah, Sateesh Dubbu, Asadulla Mallick and Yashwant D. Vankar**

Department of Chemistry, Indian Institute of Technology Kanpur 208 016, India

Fax: 0091-512-259 0007; E mail: vankar@iitk.ac.in

ABSTRACT

Activation of sulfoxide as glycosyl donors using $AuCl_3$/AgOTf reagent system has been described. Under optimal reaction conditions, both armed and disarmed glycosyl sulfoxide donors were found to react with a range of primary, secondary, and tertiary alcohol acceptors, and sugar derived glycosyl acceptors to afford the corresponding glycosides in moderate to good yields with predictable selectivity. The reactions are quick (20-60 min), facile at room temperature and the reactions conditions tolerate acid sensitive groups

KEYWORDS: gold(III) chloride, silver triflate, anomeric sulfoxides, *O*-glycosylation.

INTRODUCTION

Oligosaccharides and glycoconjugates (glycolipids and glycoproteins) constitute an important class of biomolecules that play crucial roles in many biological processes [1–3]. Synthesis of such molecules is an important area of modern research to procure them in pure forms and in good quantities. One of the most crucial steps that is needed in the synthesis of oligcosaccharides is glycosylation reaction [4–8] where a glycosidic bond is formed by reacting a glycosyl donor and a glycsoyl acceptor in the presence of a promoter or a catalyst. Different types of glycosyl donors and activators have been developed over the years and the search is still on, as not one set of conditions are good enough from the point of view of yield, α/β anomeric selectivity, stability of glycosyl donors etc. Nevertheless, a few glycosyl donors such as glycosyl trichloroacetimidates [8], thioglycosides and modifications thereof [9–10], n-pentenyl glycosides [11], glycosyl halides [12] including glycosyl fluorides [13], are routinely used by a number of

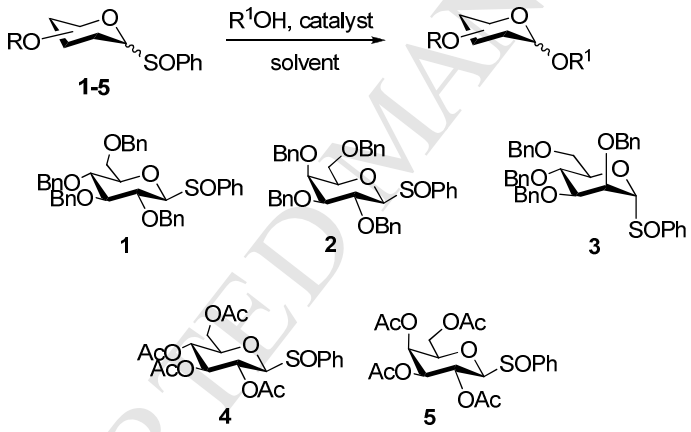
chemists. Depending on the type of glycosyl donor, different catalysts (or promoters) such as $BF_3.Et_2O$, TMSOTf, N-iodosuccinimide (NIS)-TfOH, $AgClO_4$ etc. are used to activate the leaving group at the anomeric carbon. Glycosyl sulfides are commonly used when there is a need to utilize a relatively stable glycosyl donor in an oligosaccharide synthesis. However, these thioglycosides need molar equivalent of an activator such as NIS along with a catalytic amount of TfOH to permit glycosylations effectively. In this regard, recently, an interesting report by Sureshan *et al.* [14] appeared but this also needs close to stoichiometric amount of activator ($AuCl_3$) to effect glycsoylation using thioglycosides. Prior to this report, we recently published the use of $AuCl_3$-Phenyl acetylene as a new relay catalyst system to activate glycosyl acetates for *O*-glycosylations [15]. This catalyst system was also found to activate both armed and disarmed glycosyl trichloroacetimidates [16], as well as 1-*O*-acetylfuranoses and pyranose 1,2-orthoesters [17]. During the period this work was being carried out, we had also explored the possible activation of a thioglycoside to effect glycosylation and found that the use of $AuCl_3$ alone, or along with phenylacetylene in catalytic amounts led to glycosylated products in only 5-10% yield. In continuation of our studies towards introducing new methods of glycosylations, we wondered if, instead of thioglycosides, anomeric sulfoxides could be activated with $AuCl_3$. Further, glycosyl sulfoxides can easily be prepared from the corresponding thioglycosides by oxidation, for example, with m-CPBA and thus thioglycosides can be used and be converted into sulfoxides when needed. Glycosyl sulfoxides have been used as glycosyl donors ever since the report by Kahne and co-workers [18] appeared where they activated the anomeric sulfoxides with triflic anhydride in the presence of stoichiometric 2,6-di-tert-butyl-4-methyl pyridine (DTBMP) as a triflic acid scavenger [19]. Later, some other reagents such as TMSOTf [20], triflic acid [21], $Cp_2ZrCl_2/AgClO_4$ [22], $H_3PW_{12}O_{40}$ (a heteropoly acid) [23], nafion-H [24], and iodine [25] have also been reported to activate glycosyl sulfoxides to lead to *O*-glycosylation. However, some of the drawbacks associated with these glycosylation methods are [18] (i) the use of stoichiometric amount of promoters, (ii) requirement of very low temperature [18] and (iii) longer reaction times in some cases [22].

In this communication, we report that a combination of 10 mol% of $AuCl_3$ and 30 mol% of AgOTf effectively activates both armed and disarmed glycosyl sulfoxides to lead to *O*-

glycosylations at room temperature. We believe that with this newly discovered reagent system, problems associated with the traditional activation of sulfoxides can be overcome.

RESULTS AND DISCUSSION

To demonstrate the utility of our methodology, we chose compounds **1**–**5** [26] (Scheme 1) as standard glycosyl donors. Initially, we examined the glycosylation using anomeric sulfoxide **1** with *l*-menthol in the presence of 10 mol% of $AuCl_3$ in dry dichloromethane as solvent which led to only 10% conversion in 12 h (Table 1, entry 1). Increasing the catalyst loading to 30 mol% led to a maximum of 30% conversion even after leaving the reaction to continue for a longer time (Table 1, entry 2). Further, we checked the reactivity of Au(III) bromide [17, 27] under the same set of reaction conditions but disappointingly its reactivity was no

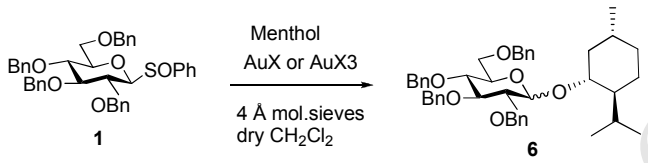


Scheme 1. Armed and disarmed glycosyl sulfoxide donors employed for glycosylation

better than that with $AuCl_3$ (Table 1, entry 3). Further, gold(I) salts like AuCl and $AuCl(PPh_3)$ [28] were found unreactive under the same reaction conditions (Table 1, entries 4 and 5). Later, after examining various combinations, we found that the use of 10 mol% of $AuCl_3$ along with 30 mol% of AgOTf as a co-catalyst promoted the reaction to completion in 30 min with 75% isolated yield of the glycoside **6** (Table 1, entry 6) possibly due to silver effect in gold catalysis [17, 29]. By using increased amount of $AuCl_3$ even upto 30 mol% either alone or along with AgOTf did not make any significant difference on yield or the selectivity. To check if AgOTf

alone can catalyse the glycosylation, we reacted glycosyl sulfoxide **1** with *l*-menthol in the presence of upto one equivalent of AgOTf, however, the reaction did not take place (Table 1, entry 8). It became evident that 10 mol% of $AuCl_3$ is essential along with AgOTf for the glycosylation to proceed.

Table 1. Optimization of reaction conditions for gold catalyzed glycosylation.[a]



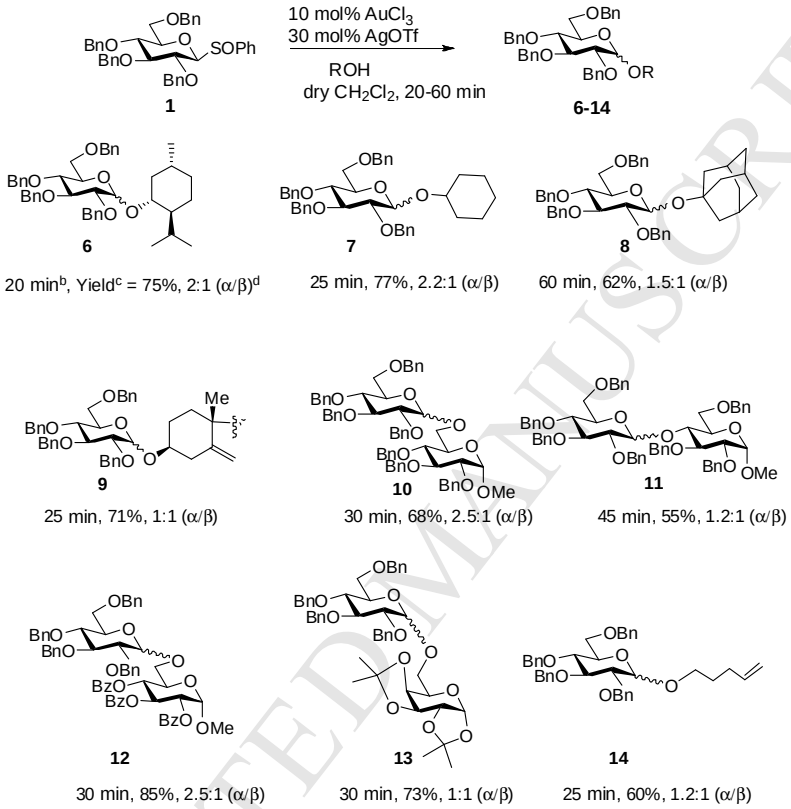
Entry	Catalyst	Time	Yield[b]	α/β ratio[c]
1	10 mol % $AuCl_3$	12 h	10% conversion	-
2	30 mol % $AuCl_3$	12 h	30% conversion	2:1
3	10 mol % $AuBr_3$	12 h	10%	2:1
4	10 mol % $AuCl(PPh_3)$	12 h	no reaction	-
5	10 mol % AuCl	12 h	no reaction	-
6	**10 mol % $AuCl_3$, 30 mol% AgOTf**	**20 m**	**75%**	**2:1**
7	10 mol % $AuBr_3$, 30 mol% AgOTf	12 h	10%	2:1
8	AgOTf[d]	12 h	no reaction	-
9	30 mol % $Yb(OTf)_3$	12 h	no reaction	-
10	30 mol % $Sc(OTf)_3$	12 h	no reaction	-
11	30 mol % $InCl_3$	12 h	no reaction	-
12	30 mol % $BF_3.OEt_2$	12 h	no reaction	-

[a] Room temperature was 35-39 ^{o}C. Reactions were performed in dry dichloromethane as solvent in the presence of 4 Å molecular sieves at room temperature. [b] Isolated yield. [c] The a/b ratio was determined from ^{1}H spectral analysis. [d] One equivalent of AgOTf was used

Reactions of glycosyl sulfoxide **1** with *l*-menthol in the presence of upto 30 mol% of some other Lewis acid catalysts such as $BF_3.OEt_2$, $Yb(OTf)_3$, $InCl_3$, and $Sc(OTf)_3$ were also screened (Table 1, entries 9-12). However, none of these catalysts was able to effect the

expected glycosylation. Thus, with the above described optimized conditions of a combination of 10 mol% $AuCl_3$ and 30 mol% of AgOTf we performed the remaining study, results of which are being reported here.

Table 2. Gold catalyzed glycosylation for the synthesis of glycosides **6-14**[a]

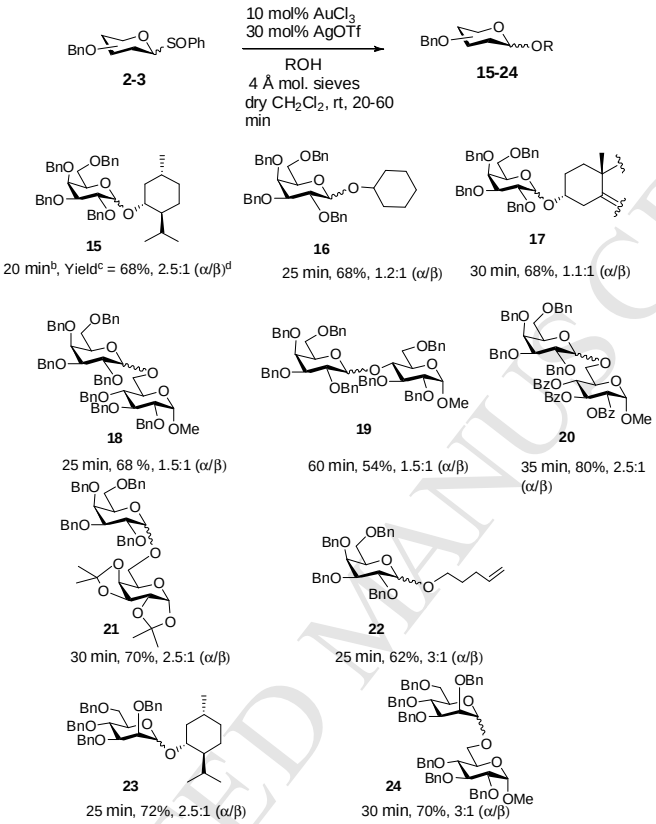


[a] Room temperature was 35-39 °C. Reactions were performed in dry dichloromethane as solvent in the presence of 4 Å molecular sieves at room temperature. [b] Time [c] Isolated yield. [d] The α/β ratio was determined from ^{1}H spectral analysis.

Accordingly, we next explored the scope of the reaction with variety of glycosyl acceptors with armed glycosyl sulfoxides (**1-3**). As shown in Table 2, the sulfoxide **1** underwent smooth reactions with primary, secondary, and tertiary alcohols as glycosyl acceptors to afford the desired glycosides, including some disaccharides, **6−14** in moderate good to yields. In these glycosylation reactions, it was found that acid sensitive groups present in glycosyl acceptors remained unaffected during the glycosylation reaction. Thus, glycosylation with diacetone D-

galactose, produced the corresponding glycoside **13** in 73% yield in 25 min. Similarly, with a benzoyl protected glycosyl acceptor, the disaccharide **12** was obtained in 85% yield in 30 min.

Table 3. Gold catalyzed glycosylation for the synthesis of glycosides **15**-**24**[a]



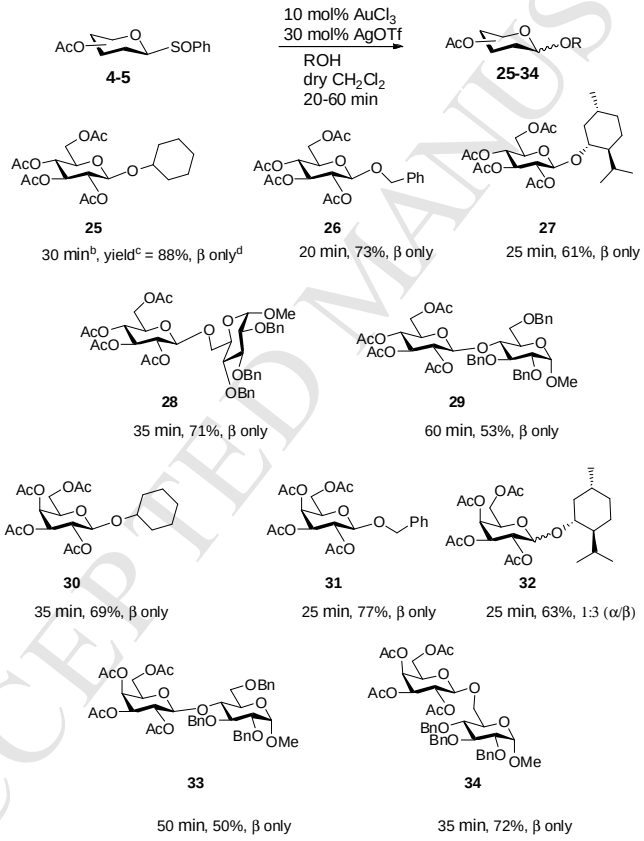
[a] Room temperature was 35-39 °C. Reactions were performed in dry dichloromethane as solvent in the presence of 4 Å molecular sieves at room temperature. [b] Time [c] Isolated yield. [d] The α/β ratio was determined from ^{1}H spectral analysis.

In a similar way, glycosyl sulfoxides **2** and **3** derived from D-galactose and D-mannose respectively were subjected to glycosylations with a range of nucleophiles to produce the corresponding glycosides **15-24** as a mixture of α– and β–anomers in good yields as depicted in Table 3. As expected, the α glycoside was the major product during glycosylation of mannosyl sulfoxide **3** as exemplified by the formation of glycosides **23** and **24** in 2.5:1 and 3:1 α/β ratio.

To explore further the synthetic utility of this convenient glycosylation method, the glycosylation of disarmed glycosyl donors **4** and **5** with a variety of glycosyl acceptors were

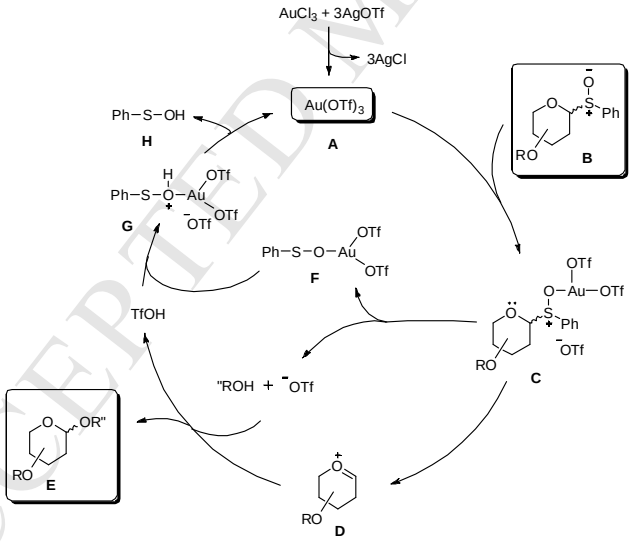
examined. These results are summarized in Table 4. All the glycosylations of **4** and **5** were performed using 10 mol% $AuCl_3$ and 30 mol% AgOTf in the presence of 100 wt% MS 4 Å in dry dichloromethane at room temperature which proceeded to give the corresponding glycosides **25-34** in good to high yields with high β–selectivity in all the cases due to anchimeric assistance from –OAc group at C2. Surprisingly, however, in case of galactose derived glycosyl donor **5** reacting with l-menthol we found that a small amount of α-glycoside **32** was found to form. It may be likely that the chair conformation of menthol may exert a steric hindrance when in β-position thus allowing the formation of the α-glycoside to some extent.

Table 4. Gold catalyzed glycosylations for the synthesis of glycosides **25-34**.[a]



[a] Room temperature was 35-39 °C. Reactions were performed in dry dichloromethane as solvent in the presence of 4 Å molecular sieves at room temperature. [b] Time [c] Isolated yield. [d] The α/β ratio was determined from ^1H spectral analysis.

A tentative mechanism is shown in scheme 2 proving that combination of one equivalent of $AuCl_3$ and three equivalents of AgOTf is required in a catalytic process. We propose that $AuCl_3$ reacts with AgOTf to form $Au(OTf)_3$, **A**, which further reacts with glycosyl sulfoxide **B** to form intermediate **C**. Next, the lone pair of the ring oxygen assists in the formation intermediates oxonium ion **D** and sulfoxide–gold complex **F**. The nucleophile then attacks at the anomeric centre to form the required glycoside **E**. Meanwhile, the sulfoxide–gold complex **F** gets protonated by triflic acid and breaks down in to benzenesulfenic acid and regenerates $Au(OTf)_3$ to enter into the next catalytic cycle. In order to prove the formation of benzenenesulfenic acid **H,** a crude reaction mixture was subjected to mass analysis and was confirmed its formation from ESI-HRMS data (m/z 125.0067). However, we did not observe any addition product of benzenenesulfenic acid on olefinic substrates/products. It is possible that since the olefinic substrates are either weekly nulceophilic being mono-substituted terminal olefin (1-pentenyl alcohol derived) or somewhat sterically hindered (cholesterol derived), the addition is not observed.



Scheme 2: Proposed mechanism

It is worth mentioning here that our previous attempts to activate the disarmed glycosyl acetates[9] with $AuCl_3$ were unsuccessful but pleasantly, our new catalyst system comprising of 10 mol% of

$AuCl_3$ and 30 mol% of AgOTf works well with both D-gluco and D-galacto derived disarmed glycosyl sulfoxides to produce the corresponding glycosides efficiently and all the glycosylations were completed in 20-60 min of duration (Table 4).

CONCLUSION

In conclusion, we have described for the first time that a combination of 10 mol% of $AuCl_3$-30 mol% of AgOTf is an effective, mild and selective promoter system for the activation of glycosyl sulfoxides. This reagent system works well with both armed and disarmed glycosyl sulfoxides and it overcomes the problems associated with the previous methods like use of stoichiometric amount of promoter, longer reaction time and temperature. Thus, the present method gives a platform for the synthesis of a variety of oligosaccharides and glycoconjugates.

EXPERIMENTAL SECTION

General Methods: All the experiments were performed in a oven dried apparatus and under inert atmosphere. All the solvents were dried using the standard procedures and stored in 4Å molecular sieves. ^1H (500 and 400 MHz) and ^{13}C (125 and 100 MHz) NMR spectra were recorded using JEOL ECX-500 and 386 JEOL JNM-LA 400 spectrometers in solutions of $CDCl_3$ using tetramethylsilane as the internal standard. High resolution mass spectra were recorded by Q-TOF using electrospray ionization (ESI) method. Column chromatography was carried out over silicagel (100–200 mesh), and TLC was carried out using silica gel plates made with grade G silica gel from S. D. Fine-chem Ltd., Mumbaion microscopic slides. Drying and purification of solvents as well as required reagents were done by standard procedures as described in the book of "Purification of Laboratory chemicals, third edition" by D. D. Perrin and W. L. F. Armarego. The salts $AuCl_3$ and AgOTf were purchased from Sigma-Aldrich.

General Procedure for glycosylation of glycosyl sulfoxides catalyzed by $AuCl_3$ and AgOTf:

To a solution of glycosyl sulfoxide 1-5 (100 mg) and 4 Å molecular sieves (100 mg) in anhydrous dichloromethane (5 mL), were added a glycosyl acceptor (1.2 equiv), $AuCl_3$ (10 mol

%) and AgOTf (30 mol %) at room temperature. The resulting solution was stirred at room temperature until the starting material was completely consumed (TLC monitoring). The organic layer was evaporated to dryness under reduced pressure to get crude glycoside which was further purified by silica-gel column chromatography using hexane and ethyl acetate as the eluting system to get pure glycosides, yield **6** (78 mg, 75%), **7** (74 mg, 77%), **8** (65 mg, 62%), **9** (100, 71%), **10** (104 mg, 68%), **11** (83 mg, 55%), **12** (135 mg, 85%), **13** (88 mg, 73%), **14** (54 mg, 60%), **15** (70 mg, 68%), **16** (65, 68%), **17** (95 mg, 68%), **18** (104 mg, 68%), **19** (82 mg, 54%), **20** (127 mg, 80%), **21** (84 mg, 70%), **22** (56 mg, 62%), **23** (74 mg, 72%), **24** (106 mg, 70%), **25** (94 mg, 88%), **26** (71 mg, 73%), **27** (65 mg, 61%), **28** (126 mg, 71%), **29** (92 mg, 53%), **30** (73 mg, 69%), **31** (75 mg, 77%), **32** (67 mg, 63%), **33** (88 mg, 50%), **34** (127 mg, 72%). The α/β ratio of the glycosides was determined by the integration values of the anomeric protons and those of the OMe- protons in their ^{1}H NMR spectra.

Supporting Information

^{1}H and ^{13}C for all synthesized compounds.

AUTHOR INFORMATION

Corresponding Author

*E-mail: vankar@iitk.ac.in

Notes

The authors declare no competing financial interest.

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Highlights

Our work in this manuscript describes the utility of a catalyst system ($AuCl_3$-AgOTf) for an important reaction that is O-glycosylation at room temperature. This has been discovered after screening different combinations of catalysts. Both armed as well as disarmed glycosyl sulfoxides are readily activated with this catalyst system to lead to the corresponding O-glycosides at room temperature within 25-60 min. Thus, we are sure that this method will find usefulness in organic synthesis, in general, and in carbohydrate chemistry in particular.