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Authors: Weidong Shang, Sheng-Nan Su, Rong Shi, Ze-Dong Mou, Guo-Qiang Yu, Xia Zhang, and Dawen Niu

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COMMUNICATION

Generation of Glycosyl Radicals from Glycosyl Sulfoxides and Its Use in the Synthesis of *C*-linked Glycoconjugates

Weidong Shang,[a] Sheng-Nan Su,[a] Rong Shi,[a] Ze-Dong Mou,[a] Guo-Qiang Yu,[b] Xia Zhang*[a] and Dawen Niu*[a]

Dedicated to Professor Thomas R. Hoye on the occasion of his 70th birthday.

[a] W. Shang, S.-N. Su, R. Shi, Z.-D. Mou, Prof. X. Zhang, Prof. D. Niu
Department of Emergency, State Key Laboratory of Biotherapy, West China Hospital, and School of Chemical Engineering, Sichuan University
No. 17 Renmin Nan Road, Chengdu, 610041, China.
E-mail: zhang-xia@scu.edu.cn; niudawen@scu.edu.cn
Homepage: www.theniugroup.com
[b] G.-Q. Yu
Discovery Chemistry Unit, HitGen Inc.
Building 6, No. Huigu 1st East Road, Tianfu International Bio-Town, Shuangliu District, Chengdu, China 610200

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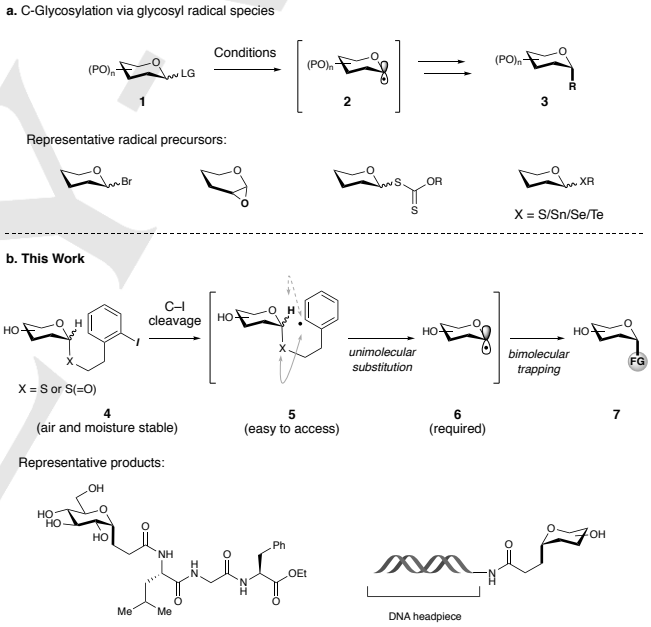
Abstract: We here report glycosyl sulfoxides appended with an aryl iodide moiety as readily available, air and moisture stable precursors to glycosyl radicals. These glycosyl sulfoxides could be converted to glycosyl radicals by way of a rapid and efficient intramolecular radical substitution event. The use of this type of precursors enabled the synthesis of various complex *C*-linked glycoconjugates under mild conditions. This reaction could be performed in aqueous media and is amenable to the synthesis of glycopeptidomimetics and carbohydrate-DNA conjugates.

Introduction

Glycosyl radicals[1-8] (**2**, Scheme 1a) are among the most well studied and versatile species in carbohydrate chemistry. These species show unique utility in the preparation of *C*-linked glycoconjugates[9] (**1** to **3** via **2**), compounds that are extensively studied as isosteres of their *O*-linked analogues[10] but more inert toward enzymatic degradation. Glycosyl radicals exhibit interesting stereoselectivity profiles when engaged in C–C bond forming reactions, usually providing *C*-glycosides with good to excellent axial selectivity.[1] From the perspective of chemoselectivity, radical-based reactions generally demonstrate excellent functional group compatibility.[11] Taken together, these features should render glycosyl radicals particularly attractive intermediates in the preparation of structurally complex *C*-linked glycoconjugates. However, it remains a challenge to apply glycosyl radical chemistry in aqueous media for the preparation of valuable, water-soluble glycoconjugates.

Our group has been interested in the development of efficient methods to prepare carbohydrate derivatives.[12] In a project aimed at making libraries of complex *C*-glycosides, a mild method to produce glycosyl radicals in aqueous media from bench-stable and readily available precursors is needed. Toward this end, we propose the sequence shown in Scheme 1b, in which glycosyl sulfides or sulfoxides **4** are intended as precursors to glycosyl radicals. Glycosyl sulfides or sulfoxides have long been employed in carbohydrate synthesis,[13] but mostly as precursors of glycosyl cations. We reason that the aryl iodide moiety in **4** could be readily converted to aryl radical **5** under mild conditions. Once the aryl



Scheme 1. (a) Glycosyl radicals as valuable intermediates in *C*-glycoside synthesis. (b) Our strategy to generate glycosyl radicals.

radical is generated, it would then attack the sulfur atom at the anomeric position via a radical substitution process[14] and result in the requisite glycosyl radical **6**. Subsequent bimolecular trapping of **6**, if viable and efficient, would afford various *C*-glycoconjugates. In this case, the task of generating glycosyl radicals is simplified to one that produces aryl radicals. The unimolecular radical substitution reaction on higher heteroatoms (e.g., S or P) is an established process.[14-16] However, the synthetic potential of radicals generated by this process remains relatively unexplored. In our design, we were curious, 1) if the aryl radical in **5** would attack the sulfur atom (solid double-headed arrow) faster than abstracting the hydrogen atom from the weak C–H bonds within the substrate (dashed double-headed arrow), such as the one at the anomeric position[17] 2) if complex *C*-linked glycoconjugates could be made by uniting the unimolecular radical substitution with a bimolecular radical trapping reaction. In

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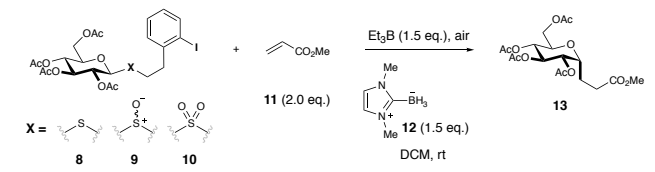
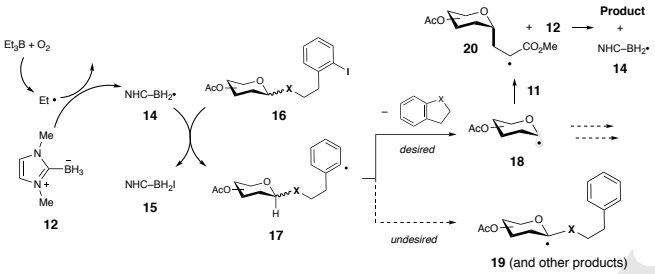
this work, we report the realization of the transformation. The general stability of **4** render them convenient substrates in synthesis, and meanwhile endow the process with remarkable functional group tolerance. This reaction is compatible with aqueous conditions, and amenable to the synthesis of various complex *C*-glycoconjugates, including glycopeptidomimetics and carbohydrate–DNA conjugates.

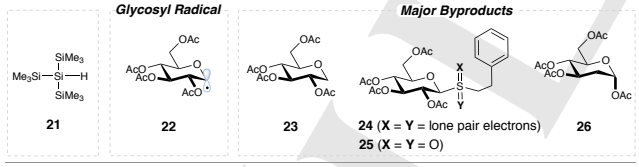
Results and Discussion

Table 1. Condition Optimization.[a]





Entry	Deviation from Standard Conditions	Yield[b]	by-product
1	None, with **9** used as precursor (Standard Conditions)	94%	**23** (< 5%)
2	Use **8** instead of **9**	59%	**24** (16%)
3	Use **10** instead of **9**	n.d.	**25** (60%)
4	**21** (1.5 eq.), Et_3B (1.5 equiv.), air, DCM	39%	**23** (23%)
5	$Ir(ppy)_3$ (0.05 eq.), 455 nm LED, **21** (1.0 eq.) DIPEA (3.0 eq.), CH_3CN, rt	61%	**23** (17%)
6	**12** (1.5 eq.), AIBN (0.2 eq.), CH_3CN, 80 °C	44%	**26** (5%)
7	THF instead of DCM	67%	**23** (23%)
8	Toluene instead of DCM	61%	**23** (22%)
9	CH_3CN instead of DCM	82%	**26** (2%)
10	Acetone instead of DCM	61%	
11	DMSO instead of DCM	85%	**26** (4%)
12	MeOH instead of DCM	66%	**23** (16%) / **26** (4%)
13	1,4-dioxane instead of DCM	70%	**23** (26%) / **26** (6%)

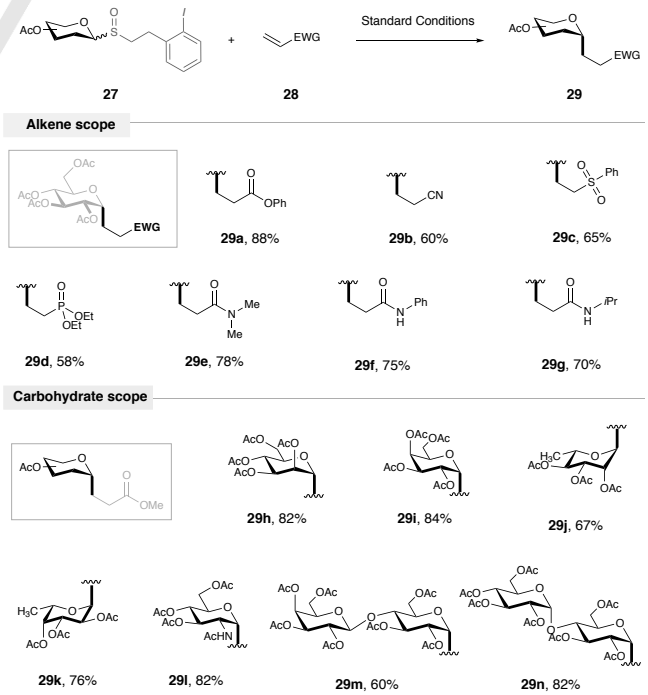


[a] Reactions in this Table were performed at 0.05 mmol scale. Yields were determined by ^1H NMR with 1,3,5-trimethoxybenzene used as internal standard. DCM, dichloromethane; LED, light-emitting diode; DIPEA, *N,N*-diisopropylethylamine; AIBN, azobisisobutyronitrile; THF, tetrahydrofuran; DMSO, dimethyl sulfoxide.

We commenced our study by using **8**-**10** as the model substrates (Table 1). Compounds **8**-**10** could be readily prepared from peracetylated glucose in 1-2 steps (see SI). Through optimization, we established that in the presence of Et_3B/O_2, a borane-carbene[18] complex **12** (1.5 equiv), sulfoxide **9** (1.0 equiv) as radical precursor, and CH_2Cl_2 as solvent, product **13** could be formed cleanly with almost exclusive α-selectivity[1] (Table 1, entry 1). Notably, a diastereomeric (R_S:S_S = ca. 1:2) mixture of sulfoxide **9** were used directly in this reaction. A plausible pathway was proposed for this transformation. Ethyl radical[19] generated from Et_3B and O_2 abstracts a hydrogen atom from **12** to afford boryl radical[20] **14**. This boryl radical attacks the iodine atom[21] in **16** to furnish aryl radical **17**, which then triggers the intramolecular radical substitution step to produce the desired glycosyl radical **18**. Further reaction of **18** with radical acceptors yields the final *C*-glycoside products via α-carbonyl radical **20**.

Control experiments in Table 1 indicate some key factors that affect the performance of this transformation. First, we found both sulfoxide **9** (entry 1) and the corresponding sulfide **8** (entry 2) could be employed as radical precursor. However, when the latter was used, product **13** was furnished in lower yield, along with a significant amount of the deiodinated byproduct **24**. These results suggest that: 1) aryl radicals could attack both the trivalent sulfur in the sulfoxide or the divalent sulfur in the sulfide group; and 2) the attack at sulfide is likely a slower process (see below).[22] The use of sulfone **10** failed to deliver any of the desired product, and only the deiodinated product **25** was formed (entry 3).[23] The use of carbene-borane complex **12** was critical. When silane **21** was employed instead, significant amount of byproduct **23** was formed (entry 4). We attribute the formation of **23** to the more rapid hydrogen donation to glycosyl radical **22** by **21** than by **12**.[24] We have examined the possibility of generating the aryl radicals under photocatalytic conditions[25] (entry 5). Although the desired product was indeed obtained in decent yield, concomitant formation of **23** was a problem. We have attempted heating AIBN as a way of generating the initiating radical (entry 6). In this case, the formation of 2-deoxy sugar derivative **26** was observed as a byproduct, presumably via the known 1,2-acyloxyl migration process[26] of **22**. We lastly investigated the impact of solvent properties on this reaction (entries 7-13). Interestingly, this reaction proceeds well in both polar and nonpolar solvents. Protic solvents such as MeOH could be employed, which bodes well for the use of water as (co)solvent in our future investigations (see below). However, the use of solvents such as THF and toluene that contain weak C–H bonds led to increased amount of **23** as byproduct.

Table 2. Initial substrate scope survey.



[a] Reactions were performed with carbohydrate donor (0.15 mmol, 1.0 equiv.), alkenes (2.0 equiv.), **12** (1.5 equiv.), and Et_3B (1.5 equiv.); Isolated yields are reported. EWG, electron withdrawing group.

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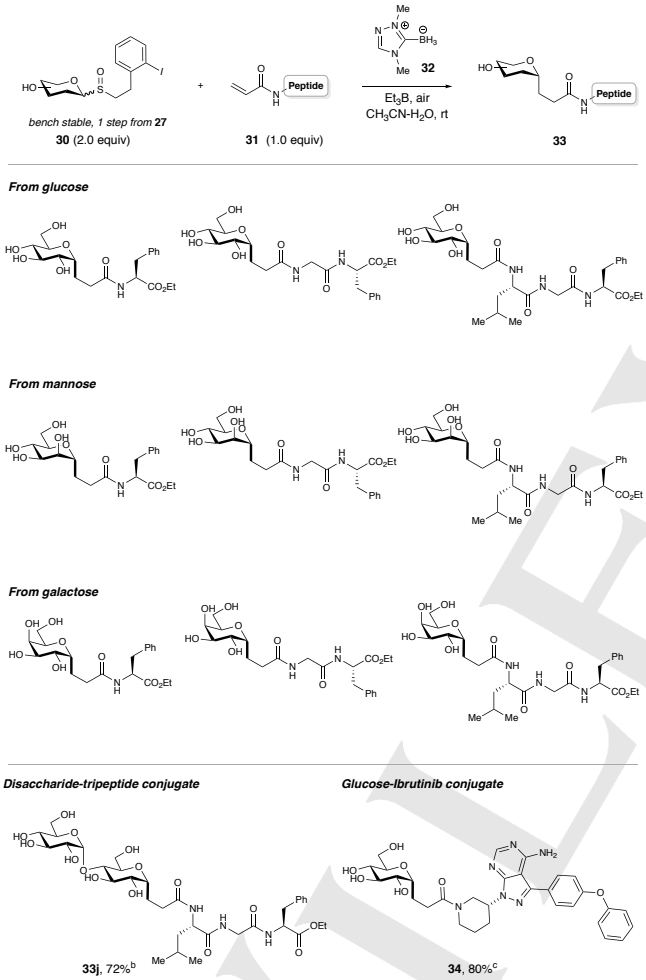
With the optimal reactions conditions established, we briefly examined the scope of both reaction partners (**27**+**28** to **29**, Table 2). With **9** employed as the precursor, we found a number of electron-deficient alkenes could participate in this reaction. Those bearing substituents such as phenoxylcarbonyl (**29a**), cyano (**29b**), sulfonyl (**29c**), phosphoryl (**29d**), and carbamoyl (**29e-g**) groups were tolerated, with the corresponding products formed in good yields and with excellent α-selectivity. The scope of radical precursors was examined as well (Table 2, bottom). Glycosyl sulfoxides derived from various monosaccharides, including mannose (**29h**), galactose (**29i**), rhamnose (**29j**), fucose (**29k**), and glu-NAc (**29l**) could participate in this reaction smoothly. Those prepared from disaccharides such as lactose (**29m**) and maltose (**29n**) are also competent substrates.

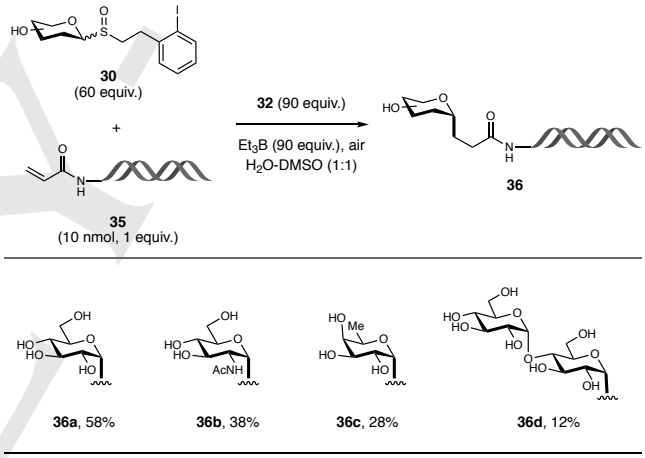
Table 3. Synthesis of glycopeptidomimetics and carbohydrate-drug conjugates.



[a] Reactions were performed with carbohydrate donor (2.0 equiv.), alkenes (0.15 mmol, 1.0 equiv.), **32** (3.0 equiv.), and Et_3B (3.0 equiv.). [b] 1.3 equiv. of carbohydrate donor was used. [c] NMR yield.

Having established proof-of-concept with the above results, we became interested if our reactions could be applied to prepare biologically important glycopeptidomimetics[27] by linking carbohydrate moieties with polypeptides via C–C bonds (Table 3). Toward this goal, the ability to perform our reactions in the presence of water is of practical value, since, besides the environmental considerations, many of these glycoconjugates are only sparingly soluble in pure organic solvents. However, methods capable of generating and utilizing glycosyl radicals in aqueous media remain largely unexplored. Thanks to the stability of sulfoxide unit to hydrolytic conditions, we could readily access the unprotected glycosyl sulfoxides **30** (Table 3) from **27** by ester hydrolysis. We found sulfoxides **30** are bench stable and water soluble. With the water-soluble borane complex **32** used as radical mediator, these unprotected precursors react smoothly with various amino acid/peptide derivatives in H_2O-CH_3CN (Table 3). Sulfoxides prepared from glucose (**33a-c**), mannose (**33d-f**), and galactose (**33g-i**) could all serve as effective substrates, and the corresponding carbohydrate-peptide conjugates were formed with good efficiency. To highlight the generality of this method, we showed that a disaccharide unit couple efficiently with a tripeptide derivative under our conditions, to furnish **33j** in good yield. The utility of this method was further demonstrated in the modification of commercial drugs. For example, our radical precursor coupled smoothly with the anti-cancer agent Ibrutinib to afford conjugate **34**. The above results established that glycosyl radicals undergo efficient addition to C=C bond in aqueous media. Moreover, the carbohydrate moieties installed are fully unprotected, an important feature of our reaction since the deprotection step on such complex products—if required—could be rather inefficient and challenging.

Table 4. Synthesis of carbohydrate-DNA conjugates.



[a] Yields were determined by HPLC-MS. See SI for details.

To further test the limit of this transformation, we applied it in the synthesis of carbohydrate–DNA conjugates. These conjugates found widespread use in antisense biotechnology and in the studies of sugar or DNA functioning.[28] Our interest in these conjugates, however, stems from the need to construct novel DNA-encoded libraries (DEL).[29] Given the stringent requirements for DEL synthesis such as high dilution and functional group tolerance,[30] transformations suitable for constructing DELs remain rare.[31,32] We found our reaction could be adapted to prepare carbohydrate-DNA conjugates. In our study, compound **35**, a 14-base DNA headpiece [HP-NH_2(5'-/5Phos/GAGTCA/iSp9/iUniAmM/iSp9/-TGACTCCC-3'), see Figure S1 in SI for exact structure] equipped with an acrylamide unit was employed as acceptor and as the limiting reagent. As shown in Table 4, when the reactions were performed in water/DMSO (1:1), **35** could couple with an excess amount of **30** (60 equiv.) to generate conjugate **36**. Various sugar moieties such as glucosyl (**36a**), 2-deoxy-2-amino glucosyl (**36b**), fucosyl (**36c**), and maltosyl (**36d**) group can be introduced.

We next employed density functional theory [UB3LYP/6-31g(d)] to evaluate the energetics of this process, with substrates **37a-c** chosen as the truncated models of our real system (Scheme 2). We have located transition structures **40a-c** for the

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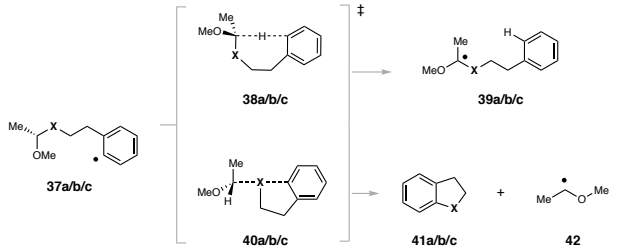
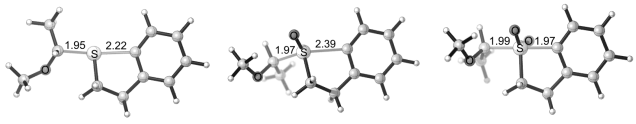
a



	X	$\Delta G^{\ddagger}_{sub}$ (G_{40}-G_{37})	$\Delta G^{\ddagger}_{HAT}$ (G_{38}-G_{37})	ΔG_{sub} [(G_{41}+G_{42})-G_{37}]
37a		7.3	12.7	–28.7
37b[b]		5.7	13.1	–25.6
37c		32.4	15.2	–24.8

b



[a] Energies are in kcal•mol^{-1}. Distances are in Å. [b] The sulfur center in **37b** is *S*-configured. Computation for the *R*-configured diastereomer gives qualitatively same results (see SI for details). sub, substitution.

Scheme 2. Mechanistic studies.

radical substitution event. For these substrates, the generation of alkyl radical **42** (along with **41a-c**) is thermodynamically favorable by similar degrees, but with different activation energies. The radical substitution step for both sulfide **37a** ($\Delta G^{\ddagger}$ = 7.3 kcal•mol^{-1}) and sulfoxide **37b** ($\Delta G^{\ddagger}$ = 5.7 kcal•mol^{-1}) is predicted to be very facile, with the latter slightly more rapid. However, the substitution on sulfone **37c** is significantly more challenging ($\Delta G^{\ddagger}$ = 32.4 kcal•mol^{-1}). Recall the results shown in Table 1, the use of sulfide led to the formation of a small amount of deiodinated product **24**, and the use of sulfone gave only **25**. It is reasonable to assume that the slower the intramolecular substitution event is, the more likelihood the hydrogen transfer to **37a-c** would occur. In this regard, the computed results agree well with our experimental observations.

Closer scrutiny of the transition structures **40a-c** (Scheme 2b) revealed some additional information. The sulfur atoms in these transition structures adopt (twisted) trigonal bipyramidal geometries, with the incoming aryl group and the departing alkyl group occupying the two apical positions. As in a classical SN2 reaction, the formation of new bond and breaking of old bond in these radical processes are concerted, causing inversion of the configuration of the sulfur atom.[22] In our case, experimental results are consistent with this prediction as well (See Figure S2 in SI).

We have also identified transition structures **38a-c** for the 1,6-hydrogen atom transfer (HAT) event leading to **39a-c**. These potentially competing processes are indeed viable. Fortuitously, for sulfoxide **37b**, the activation energy of this HAT process is over 7 kcal/mol higher than that of the desired substitution event. These results suggest our reaction may serve as a general method to prepare α-oxo radicals.

Conclusion

In conclusion, we have developed a class of readily accessible and bench-stable precursors to glycosyl radicals, and employed them in the synthesis of various *C*-glycosides. Capitalizing on a facile radical substitution reaction on sulfur atom, our method permits the generation of the valuable glycosyl radicals from the corresponding sulfoxides. This transformation proceeds under mild conditions, tolerates a broad array of functional groups, occurs smoothly in aqueous media, and is amenable to the preparation of complex glycopeptidomimetics and carbohydrate-DNA conjugates. Computational studies provide further insights into the mechanism of this process. We anticipate this method will be adopted for the preparation of advanced glycoconjugates that are needed in various fields.

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Keywords: radical reactions • C-glycosides • glycoconjugates

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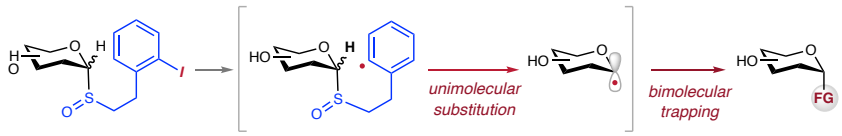

- ***bench stable precursors***
- ***mild conditions***
- ***complex glycoconjugates***

Glycosyl sulfoxides appended with an aryl iodide moiety were shown to be readily available, air and moisture stable precursors to glycosyl radicals. The use of these radical precursors enabled the synthesis of various complex *C*-linked glycoconjugates under mild conditions.