A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201914557
Angew. Chem. 10.1002/ange.201914557

Link to VoR: http://dx.doi.org/10.1002/anie.201914557
http://dx.doi.org/10.1002/ange.201914557

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10.1002/anie.201914557

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Radical Dehydroxymethylative Fluorination of Carbohydrates and Divergent Transformations thereof

Xin Zhou[+], Han Ding[+], Pengwei Chen[+], Li Liu[+], Qikai Sun, Xianyang Wang, Peng Wang, Zhihua Lv, Ming Li*

Abstract: A mild and convenient protocol for synthesis of reversed glycosyl fluorides (RGFs) has been developed relying on silver-promoted radical dehydroxymethylative fluorination of carbohydrates. The salient feature of the reaction is that furanoid and pyranoid carbohydrates furnish structurally diverse RGFs bearing a wide variety of functional groups in good-to-excellent yields. Intramolecular hydrogen atom transfer experiments reveal that the reaction mechanistically involves an underexploited radical fluorination *via* β-fragmentation of sugar-derived primary alkoxyl radicals. Structural divergence of RGFs is achieved by catalytic activation of C-F bonds, offering a concise and efficient strategy for synthesis of reversed glycosides *via* late-stage diversification of RGFs. The potential of this method is showcased by the preparation and diversification of sotagliflozin, leading to the discovery of a promising candidate of SGLT2 inhibitors.

Introduction

Structurally unique reversed glycosides, a class of saccharides having skeletons of furanos-4-yl or pyranos-5-yl heteroatomic groups like *N*-, *O*-, *F*-, *S*-, or *P*-substituents, are frequently found in bioactive natural products, biological probes, and drug candidates. The representative examples of such substances are depicted in Figure 1 including the first fluorinated natural nucleoside nucleocidin displaying antibacterial, trypanocidal and antiviral activities,[1] pyranos-5-yl fluorides acting as useful probes of carbohydrate-processing enzymes to investigate the action mode of epimerases and dehydrases,[2] dragocin A with cytotoxicity,[3] and sotagliflozin[4] emerging as a potential dual inhibitor of sodium glucose co-transporter proteins 1 and 2 (SGLT1 and 2) for treatment of diabetes and so on.[5]

The uncommon structures and characteristic biological activities of reversed glycosides have inspired the development of numerous methods for their preparation. Current synthetic approaches can be grouped into three major classes (Scheme 1 A-C). The first involves functionalizations of polar intermediates

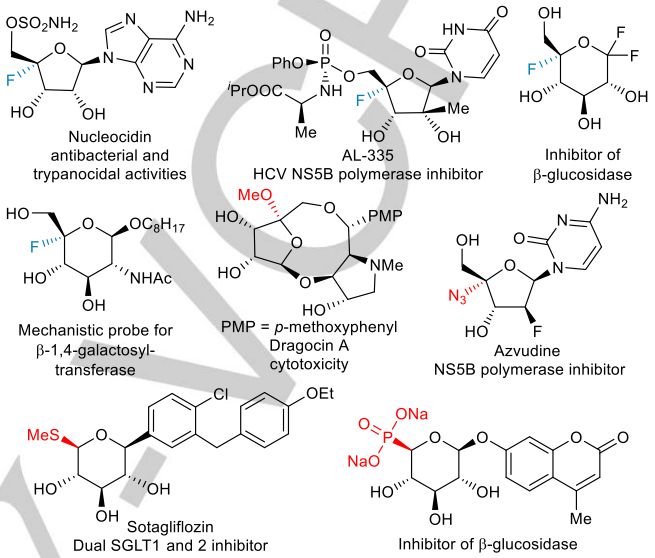

Figure 1. Representative Reversed Glycosides.

such as iodofluorination of furanosyl-4-*exo*-olefins,[6] nucleophilic ring opening of 5,6-epoxides of pyranosyl-5-*exo*-olefins,[2,7] and enolate capture by electrophiles.[8] The second class capitalizes on derivations of furanos-4-yl and pyranos-5-yl radicals[9] as exemplified by oxidative radical decarboxylation of uronic acids promoted by $Pb(OAc)_4$,[10] (diacetoxyiodo)benzene (DIB)/I_2,[11] and iridium-based photoredox catalysis,[12] radical dehydroxymethylation of furanoses mediated by DIB/I_2,[13] and 1,5-hydrogen atom transfer (HAT) of imine radical of 6-O-trichloroacetimides.[14] Ferrier's photobromination and ensuing displacement is the third widely used protocol for synthesis of reversed glycosides.[15] Despite being reliable, these methods suffer from tedious synthesis of sensitive alkenes from sugar alcohols, harsh conditions, and/or narrow substrate scope.[6-8, 10-13] Taken together, these features contribute to the perception that designing a mild, robust, and general protocol that enables ready access to reversed glycosides is deemed necessary.

As part of our interest in making novel functionalized molecules taking advantage of furanos-4-yl and pyranos-5-yl radicals,[16] we herein wish to explore dehydroxymethylative fluorination of carbohydrate-based alcohols via β-fragmentation of primary alkoxyl radicals, thus enabling concise synthesis of various reversed glycosyl fluorides (RGFs) and structural divergence thereof by catalytic activation of C-F bonds to contribute to the growing arsenal of diverse synthesis of functionalized sugars without opening the sugar rings (Scheme 1).[17] To reduce the idea to practice, several challenges have to be overcome. Of various scenarios of generating alkoxyl radicals which act as versatile intermediates applicable to a plethora of organic transformations,[18] direct generation from alcohols is an attractive approach since there is no necessity to convert

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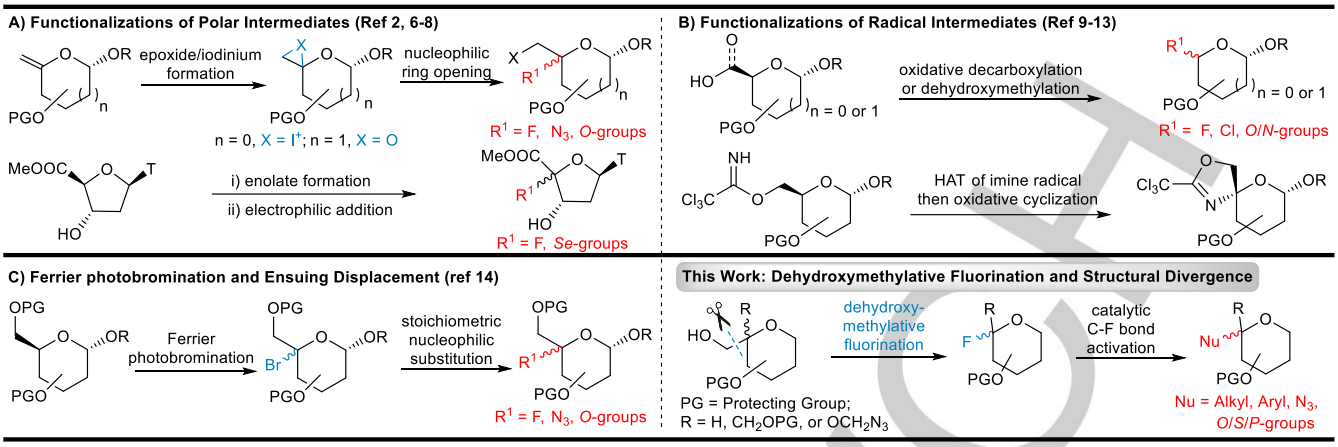
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:.((Please delete this text if not appropriate))



Scheme 1. Strategies for Synthesizing Reversed Glycosides.

hydroxyl group to *O*-functionalized compounds having a weak oxygen-heteroatom bond such as *N*-alkoxyphthalimides.[18] On the other side, it is challenging due to the high bond dissociation energy of O-H bond (105 kcal mol^{-1}).[19] Furthermore, compared with tertiary and strained cyclic alkoxyl radicals readily undergoing β-scission to construct various chemical bonds,[20] primary alkoxyl radicals has relatively small tendency to undergo β-fragmentation through homolytic cleavage of C-C bonds over commonly encountered intramolecular HAT.[21] It has been observed that pyranose-based primary alkoxyl radicals are susceptible to 1,n-HAT (n = 5, 6, even 8) instead of homolytic β-cleavage owing to the presence of multiple δ- or ε- hydrogen atoms and restricted conformations of inherently complex and highly functionalized carbohydrates.[22] These results indicate that it is demanding to achieve excellently selective β-scission of primary alkoxyl radicals for extending this strategy to carbohydrates.

Results and Discussion

Substrate Scope. It has been well recognized that Ag(II)-species are able to oxidize alcohols to the corresponding alkoxyl radicals[23] and their β-fragmentation is strongly accelerated by hydrogen-bond donating solvents.[24] As a consequence, we focused on silver-mediated dehydroxymethylative fluorination of carbohydrates in aqueous media. Mindful of the fact that radical deoxymethylation of pyranoid primary alcohols is underexploited,[25] we commenced our studies with glucopyranoside alcohol **1a** as the model substrate to optimize the reaction conditions (See the Supporting Information (SI), Table S1). After scrupulous evaluation of various reaction parameters including the type and amounts of silver salt, Selectfluor, and solvent, it was found that the reaction proceeded smoothly in the presence of Ag_2CO_3 (0.5 equiv) and Selectfluor (5-10 equiv) as the oxidant and fluorine source in acetone/H_2O (v/v 4:1) and provided fluorosugar **2a** in the best yield of 86% with a 5*R*/5*S* 1.7:1 ratio at room temperature in 3 h (Table 1). As far as we know, this transformation is a hitherto unknown fluorination reaction and presents a more straightforward approach to RGFs of interest compared with decarboxylative fluorination[12] since it avoids oxidation of alcohols to acids.

With the optimized conditions established, substrate scope of the reaction was examined (Table 1). Exposure of monosaccharide alcohols **1b−k** derived from glucose, glucosamine, galactose and ribose in pyranoid or furanoid form to dehydroxymethylative fluorination conditions smoothly furnished the desired RGFs **2b−k** in 58-94% yields. These transformations demonstrate that the reaction is distinguished by broad substrate scope and good accommodation of protecting groups and anomeric substituents including acetyl (Ac), benzoyl (Bz), azido, fluoro, alkoxyl, phthalimido (phthN) groups, and isopropylidene, attesting the mildness of the reaction conditions. Remarkably, **2a** could be prepared at gram-scale (1.15 g) in 90% yield and **2j** at subgram-scale (730 mg) in 62% yield, strongly demonstrating the feasibility of scale-up. The present methodology also allows for conversion of branched sugars into the corresponding RGFs having a tertiary C-F bond, a class of important structural motifs in biological and medicinal science.[1,2] Thus, branched lyxofuranoside, arabinofuranoside, and idopyranoside alcohols **1l−1q** worked well to produce fluorides **2l−2q**. Of note, ready access to **2o** demonstrates that uracil heterocycle is tolerated toward the present reaction, opening up an alternative approach to C-4' fluorinated nucleosides by a post-glycosylational functionalization strategy.[17]

Next, we focused on fluorination of more complex and challenging oligosaccharides. Successful access to RGFs **2r−2z** showed that trehalose, di- and trisaccharides **1r−1y**, even β-cyclodextrin (β-CD) **1z** connected by α,α-1,1'-, β-1,6-, β-1,3-, and/or α-1,4-linkages were competent substrates. Notably, fluorinated trehalose derivative **2r** was obtained in 79% yield with 5*R* configuration as the exclusive product. **2r** might be an intriguing structure since modified trehaloses have proven to be attractive synthetic targets due to their potential in investigating trehalose metabolism in *mycobacterium tuberculosis*.[26] β-CD-derived primary alkoxyl radicals have been observed to exclusively undergo 1,8-HAT with DIB/I_2 as the oxidant in structural modifications of β-CDs.[22a,d,e] However, in our hands, such reactive species were able to engender fluoride **2z** in 62%

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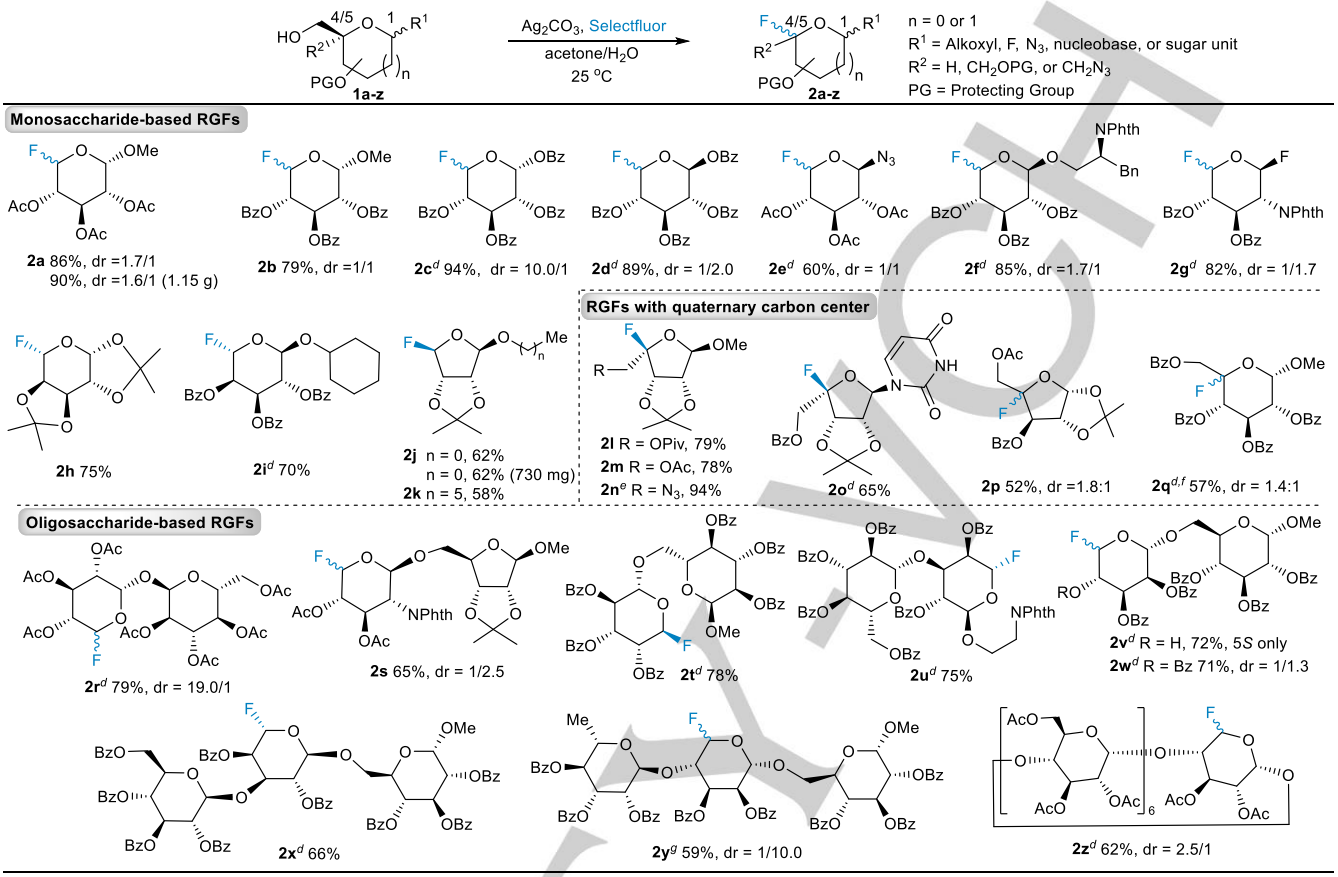
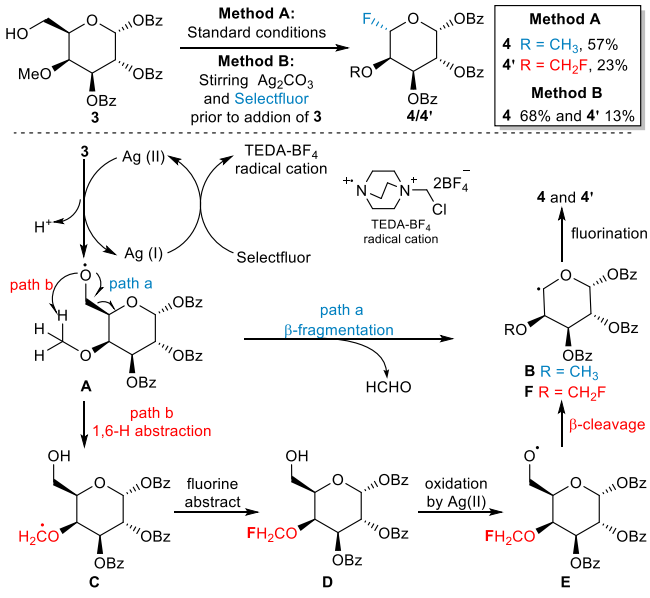
Table 1. Substrate Scope of Dehydroxymethylative Fluorination.[a,b,c]



[a]Unless otherwise noted, the reaction was conducted with alcohol (0.1 mmol), Ag_2CO_3 (0.5 equiv), and Selectfluor (5.0 equiv). [b]The products with the wedge C-F bond viewed in the plane of the paper is denoted as 4/5*R*-isomers and those with the dash C-F bond as 4/5*S*-isomers. [c]dr based on the ^{1}H NMR spectroscopic ratio of 4/5*R*- to 4/5*S*-isomer. [d]10.0 equiv of Selectfluor. [e]**1n** having 5*R* configuration as the reactant. [f]40 °C of the reaction temperature. [g]15.0 equiv of Selectfluor.

yield by exclusive β-scission of primary alkoxyl radicals. Fluorosugar **2z** is the first example of one-carbon less fluorinated β-CD derivative, offering opportunities for further structural elaborations. It should be noted that methyl 2, 3, 4-tri-*O*-benzyl-α-D-glucoside failed to give the desired product since the methylene moiety of benzyl ethers is vulnerable to intra- and/or intermolecular HAT mediated by alkoxyl radicals. The conformation of the obtained RGFs in solution could be inferred based on the coupling constants of vicinal protons on the sugar ring and X-ray crystallographic analysis of **2i** (see the SI).

Mechanistic Studies. To get insig into the reaction mechanism, galactopyranoside alcoholht **3** was subjected to dehydroxymethylative fluorination (**Scheme 2**). The reaction performed well to stereoselectively deliver the mono- and difluorosugars **4** and **4'** at a ratio of 2.5:1 in overall 80% isolated yield under the standard conditions (**Method A**). In addition, the reaction was executed stepwise, *i. e.* stirring Ag_2CO_3 and Selectfluor in acetone/H_2O prior to addition of alcohol **3**. Doing so, we observed that the original suspension with the same bright green color as Ag_2CO_3 turned to a homogenous and white solution after stirring for 30 min at room temperature, implying the formation of Ag(II) species.[27] Subsequent addition of **3** to the mixture produced **4** and **4'** in 68% and 13% yield, respectively, in 30 min (**Method B**, for the details, see SI). Combining these results and previous reports,[27] a plausible mechanism is suggested as shown in Scheme 2. Initially, Ag(II) species oxidizes primary hydroxyl group of **3** to give alkoxyl radical **A** with loss of proton alongside regeneration of Ag(I) species.[27] Alkoxyl radical **A** may react in two different ways, namely, direct β-fragmentation (path a) and intramolecular 1,6-hydrogen abstract (path b)[28] with the 4-OMe *via* a seven-membered cyclic transition state. These two routes lead to respective secondary and primary α-oxy C-radicals **B** and **C**. Subsequent fluorine abstraction from Selectfluor by active intermediate **B** forges fluorosugar **4**, whereas the radical **C** is converted into fluorinated alcohol **D**, which follows the same reaction sequence as that of the transformation of **3** to **4**, giving difluorosugar **4'** through the intermediates **E** and **F**. The formation of **4** as the major product indicates that β-scission of primary alkoxyl radical **A** is more energetically favorable than the competing intramolecular 1,6-HAT under the present reaction conditions. We assume that the driving force for this transformation is associated with the accelerated release of formaldehyde by solvation in aqueous acetone.[24] No other multifluorinated product except **4'** were observed, implying that alkoxyl radical **E**, unlike **A**, does not participate in 1,6-HAT at

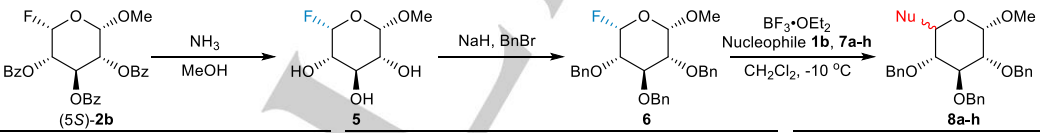


Scheme 2. Proposed Mechanism for Dehydroxymethylative Fluorination.

OCH_2F group due to the presence of electron-withdrawing fluorine atom.[29] The stereoselective formation of **4** and **4'** was attributed to $^4C_1$ conformation adopted by the intermediates **B** and **F**,[30] where the axially-oriented C-4 methoxyl group stabilizes vicinal C-radical through pseudo-homo-anomeric effect,[31] thus leading to attack of Selectfluor to the α face of such radicals. Combined these results with the literature,[9] the plausible intermediate radicals were proposed to explain the diastereoselectivity of RGF formation.

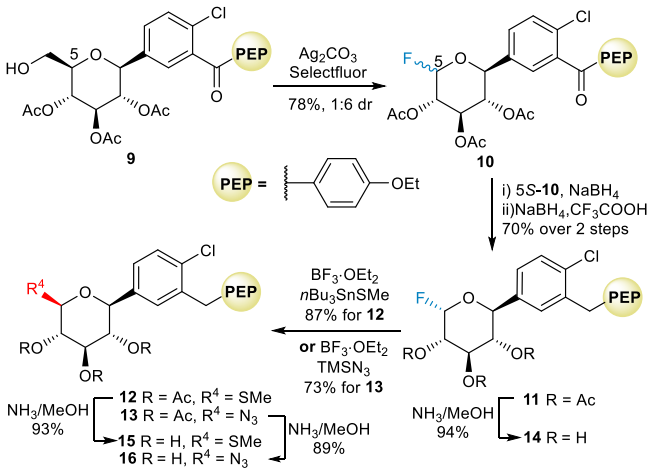
Structural Divergence of RGFs. Taking our cue from a variety of glycosyl fluorides and alkyl fluorides serving as glycosylating and alkylating agents to construct various C-C and C-heteroatomic bonds through C-F bond activation,[32] we assumed that RGFs would be powerful synthons for structurally diverse furanos-4-yl and pyranos-5-yl substituted compounds by activating C-F bond. We therefore screened several fluorophilic reagents such as $SnCl_4$, $SnCl_2/AgClO_4$, TMSOTf, and Tf_2O (See SI, Table S2), and found that 0.2 equiv of $BF_3{\cdot}Et_2O$ was the optimal catalyst of choice. Thus, armed RGF **6**, prepared from disarmed **2b**, reacted with allyltrimethylsilane to provide L-*ido* configured higher-carbon pyranoside **8a** as an α:β 1/2.8 anomeric mixture. These results imply that epimerization of the original glycosidic bond took place during the reaction. With silyl enol ether **7b** and **7c** as the nucleophiles, **8b** and **8c** were uneventfully obtained as mixtures of 5*R*-isomer with α-D-*gluco* configuration and 5*S*-isomer assuming β-L-*ido* configuration at the 1/2.2 and 1.8/1 ratios, respectively, without epimerization at the anomeric position. Significant efforts have been devoted to the synthesis of L-iduronic acids (L-*ido*As) and derivatives thereof since conformationally flexible L-*ido*A is a key monosaccharide component of glycosaminoglycans (GAGs) of biological relevance such as the well-known heparin, heparin sulfate, and dermatan.[33] The facile preparation of **8a-c** offers prospects for synthesis of novel *ido*A analogues due to the rich chemical reactivity of C-C double bond and carbonyl group, thus facilitating the synthesis of diverse GAGs. Friedel-Crafts reaction of **6** with furan **7** provided reversed aryl *C*-glycoside **8d** in 70% yield as a mixture of stereoisomer. Heteroatomic nucleophiles were also viable coupling partners, yielding novel reversed glycosides with the stereoselectivity depending on the nature of nucleophiles. Thiolysis of **6** with octanethiol **7e** provided 80% of **8e** with the C-5 axially substituted isomer as the major product while alcoholysis with sugar **1b** showed reverse stereoselectivity, furnishing **8f** in 86% yield favoring the isomer with the C-5

Table 2. Structural Divergence of RGFs through C-F Bond Activation.[a,b]



Entry	Nuclephile	Product
1	**7a**	**8a** 88%, α/β = 1:2.8
2	**7b**	**8b** 80%, dr 1:2.2
3	**7c**	**8c** 51%, dr 1.8:1
4	**7d**	**8d** 84%, dr 1:1.1
5	**7e**	**8e** 80%, dr 1:2.8
6	**1b**	**8f** 86%, dr 1:3.5
7	**7g**	**8g** 78%
8	**7h**	5*S*-**8h** 41% + 5*R*-**8h** 40%

[a]The ratio based on the isolated yield. [b]dr based on the ratio of 5*R*- to 5*S*-isomer.



Scheme 3. Synthesis and Diversification of Sotagliflozin.

equatorially oriented substituent. Notably, coupling with triphenyl phosphite **7g** produced **8g** with exclusive formation of equatorially oriented C-P bonds. $BF_3{\cdot}Et_2O$ also enabled C-F bond activation of **2b** bearing electron-withdrawing benzoates as substituents, thus the reaction with cylcohexanol **7h** furnished **8h** as a mixture of C-5 stereoisomers in almost identical yields (41% vs 40%) despite the potential presence of anchimerically assistant C-4 benzoate. Taken together, these studies indicate that RGFs are potential precursors for obtaining structurally unique furanos-4-yl and pyranos-5-yl substituted sugars, providing a straightforward protocol for divergent synthesis of functionalized sugars.

Synthesis and Diversification of Sotagliflozin. To further showcase the versatility of our methodology, we undertook synthesis of sotagliflozin which is a promising candidate for treatment of diabetes.[4] There is however a merely single *de novo* synthesis available.[34] Structurally, sotagliflozin could be recognized as a congener of the approved medicine dapagliflozin[35] with replaced hydroxymethyl by methylthio group. These properties suggest that preparation of sotagliflozin and analogues from dapagliflozin would be a stringent assessment of our developed method. Exposure of **9**, prepared from dapagliflozin acetate[35] in two steps, to dehydroxymethylative fluorination afforded a chromatographically separable mixture of **10** at the ratio of 5*R*/5*S* 1:6 in 78% yield. The combination of $NaBH_4$ and CF_3COOH enabled deoxygenation of ketone, giving **11** in 70% yield leaving C-F bond untouched. Under the promotion of $BF_3{\cdot}Et_2O$, fluoride **11** was treated with methylthiotri-*n*-butylstannane ($MeSSnBu_3$) and trimethylsilyl azide ($TMSN_3$) to give rise to sotagliflozin acetate **12** and azide analogue **13** in 87% and 73% yield, respectively. The neighboring group assistance of the acetate is responsible for the formation of 1,2-*trans* glycosidic linkage in **12** and **13**. Removing acetyl protecting groups in **11**−**13** with NH_3 in MeOH smoothly afforded sotagliflozin **15** and analogues **14** as well as **16** in excellent yields. Preliminary assessments showed that **16** equipped with the equatorially oriented azide exhibited 61% inhibition rate against SGLT2 at 10 nM while **16** having the axial fluorine possessed much less potency (See SI, Table S3). These results coupled with those of dapagliflozin and sotagliflozin demonstrate that the equatorial substituent at C-5 position of pyranosyl unit is crucial to SGLT2 inhibiting activities of sotagliflozin and other similar molecules. Owing to the versatility of glycosyl azides,[36] **16** might be an attractive platform for discovering novel SGLT2 inhibitors.

Conclusion

In summary, an expedient protocol for RGFs synthesis has been established through silver-promoted radical dehydroxymethylative fluorination of carbohydrate alcohols in aqueous acetone. This reaction is distinguished by versatility and excellent chemoselectivity profile, thus enabling access to diverse RGFs from a wide range of mono- and oligosaccharides under mild conditions. Mechanistic studies reveal that β-scission of primary alkoxyl radicals and ensuing fluorination of α-oxy C-radicals are involved. Divergent structural modifications of RGFs to afford valuable furanos-4-yl and pyranos-5-yl substituted carbohydrates have been achieved by reacting with *C*-, *O*-, *S*-, and *P*-nucleophiles through catalytic activation of C-F bonds. The application of present method in medicine discovery has been highlightened by discovery of a potential candidate of SGLT2 inhibitors based on synthesis of sotagliflozin and analogues. We anticipate that our strategy composed of radical dehydroxymethylative fluorination and ensuing C-F bond activation should be useful in synthesizing higher-carbon or exotic carbohydrates and other complex tetrahydrofuran and tetrahydropyran fragments in natural products.

Acknowledgements

We are grateful for financial support from the National Science Funding of China (21672194 and 21272220), the NSFC-Shandong Joint Fund (U1606403), the Shandong Provincial Natural Science Foundation (ZR2018MB015), and the National Science and Technology Major Project for Significant New Drugs Development (2018ZX09735004).

Conflict of interest

The authors declare no conflict of interest.

Keywords: alkoxyl radicals • dehydroxymethylative fluorination • β-scission • reversed glycosyl fluorides • C-F bond activation

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10.1002/anie.201914557

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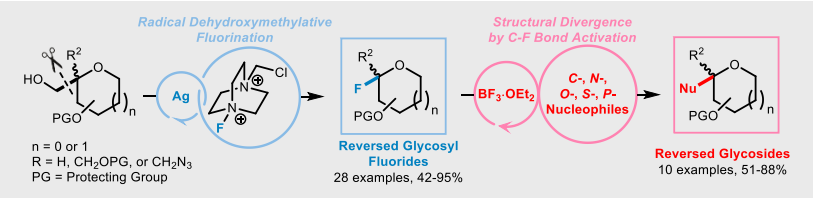

Sweet Fluorination: Radical dehydroxymethylative fluorination of carbohydrate alcohols has been achieved with versatility and excellent chemoselectivity profile, affording a wide arrange of reversed glycosyl fluorides (RGFs) in good to excellent yields. Structural divergence of RGFs with various nucleophiles by catalytic C-F bond activation provides unique sugar architectures difficult to obtain otherwise, demonstrating the potential of this method in the late-stage diversification of sugars.

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Page No. – Page No.

Radical Dehydroxymethylative Fluorination of Carbohydrates and Divergent Transformations thereof