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Trends in Carbohydrate Research

Glycosyl Fluorides: An Overview of Recent Synthesis and Activation

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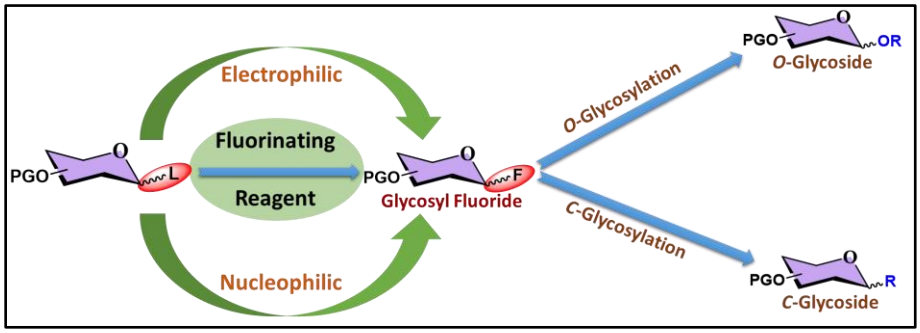
We dedicate this article to the fond memory of (Late) Professor Ashok K. Prasad, Department of Chemistry, University of Delhi.

Graphical Abstract



Abstract

Glycosylation, the chemical reaction of linking sugar molecules to create complex carbohydrates, plays a crucial role in diverse biological processes and medicinal applications. Over the past decade, significant advancements have been made in glycosylation methodologies, enabling the efficient synthesis of complex oligosaccharides with high stereoselectivity and yield. This review article compiles the studies of key advances in glycosylation techniques that have emerged between 2000 and 2023 on the synthesis and activation of glycosyl fluorides. These methodologies cover a variety of catalysts, solvents, and strategies for glycosyl fluoride activation, including the use of metal catalyst, Lewis's acid catalysts, specific solvent systems, and innovative fluorinating reagents. We provide a comprehensive overview of the strategies, mechanisms, and applications of these methodologies, highlighting their contributions to carbohydrate chemistry.

Keywords: Glycosyl fluorides; Fluorinating reagents; Glycosylation; Stereoselectivity; Oligosaccharides; Glycoconjugates

1. Introduction

Oligosaccharides and glycoconjugates play significant roles in biological processes and the development of drugs and therapeutics.[1] Most of the human proteins and natural products are glycosylated.[2] Glycosylation is a fundamental biochemical reaction that forms glycosidic bonds among carbohydrates and other biomolecules in living cells. Consequently, the synthesis of well-defined glycosides and glycosylated compounds is of paramount importance for unraveling the intricate roles of carbohydrates in biology.[3] In a chemical glycosylation reaction, one nucleophile (acceptor) reacts with one glycosyl donor in the presence of an activator.[4] There are several types of glycosyl donors like glycosyl acetates, glycosyl trichloroacetimidates, glycosyl halides, glycosyl phosphates, etc. Among all glycosyl halides mainly glycosyl fluoride has recently been one of the most demanding donors due to their unique reactivity and efficiency in glycosylation reactions,[5] leading to enhanced yields of desired glycosylated products also offer several advantages in terms of chemoselectivity,

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stereoselectivity, and orthogonality. A glycosyl fluoride donor is more effective as an enzyme inhibitor and glycosylation substrate in biochemistry.[6] Glycosyl fluoride has huge importance in enzymatic reaction.[7] Due to their unique reactivity and versatility, glycosyl fluorides, characterized by a fluorine atom at the anomeric position[8], have gained considerable attention in recent years. Developing glycosyl fluoride-based glycosylation has led to remarkable advances in glycoscience, enabling researchers to probe glycan roles in health and disease at the molecular level.[9] Glycosyl fluoride donors are known for their easy manageability and offer a highly efficient method in terms of utilizing atoms for glycosylation processes.[10] Additionally, the orthogonal reactivity of glycosyl fluoride donors will be discussed, showcasing their compatibility with other glycosylation methods and strategies.

2. Synthesis of Glycosyl Fluoride Donors

Glycosyl fluoride donors have many important roles in the field of carbohydrate and natural product chemistry. Glycosyl chlorides and bromides were used as glycosyl donors but after 1981 glycosyl fluorides were used for glycosylation reaction as it is stable, and stereoselective compared to others. By utilizing strategic transformations, glycosyl fluoride donors can be synthesized while preserving their protective groups. It is vital nowadays to synthesize glycosyl fluoride donors in a simple and effective manner.[5,11] This review discusses synthetic methods that have been developed in the last 23 years.

2.1 Fluorination through Nucleophilic Fluorinating Reagents:

Nucleophilic fluorinating agents have been used extensively in fluorination reactions for numerous years, finding wide application in diverse organic transformations, ranging from pharmaceutical synthesis to material science.[12,13,14] Notably, their usage has been particularly prominent in the field of carbohydrate synthesis, where these agents enable the strategic introduction of fluorine atoms, often imparting valuable structural and functional modifications to carbohydrate molecules with potential implications for biological activity and chemical reactivity (Figure 1).[1]

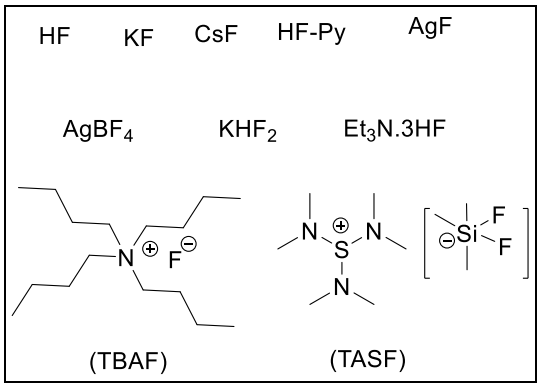
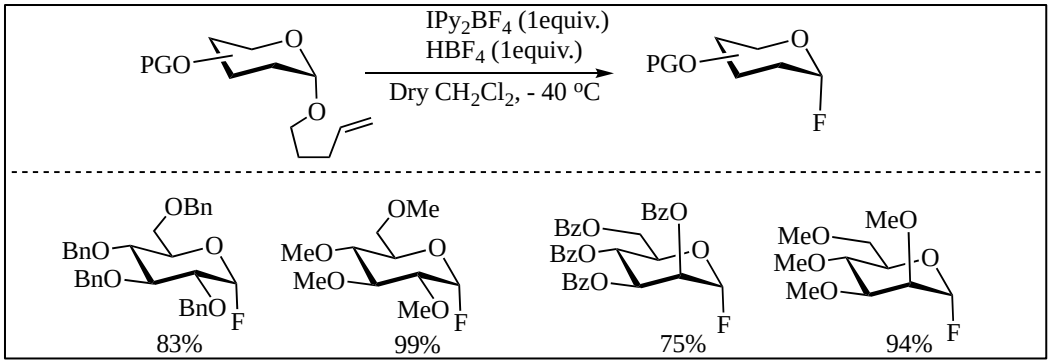


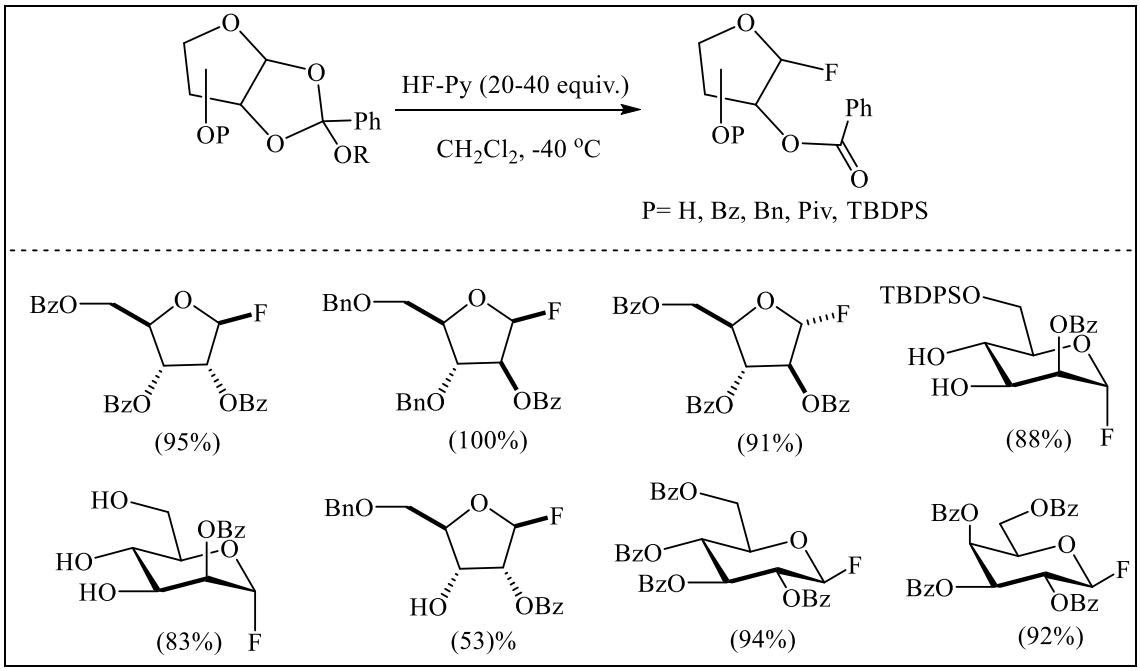
Figure 1. List of Nucleophilic Fluorinating Regents used in Carbohydrate Chemistry

Ana M. Gomez and co-workers introduced an innovative method in 2007 for the synthesis of glycosyl fluorides and used it for the synthesis of saccharides. The research unveils a new pair of semiorthogonal glycosyl donors by harnessing *n*-pentenyl glycosides versatility and transforming to glycosyl fluorides through Bis(pyridinium) iodonium(I) tetrafluoroborate (IPy_2BF_4) mediated reactions (Scheme 1). The use of IPy_2BF_4 as a reagent enables efficient and mild conversion of *n*-pentenyl glycosides into glycosyl fluorides, offering good to excellent yields of the desired products.[15] The study highlights the successful application of this approach to both armed and disarmed glycosyl donors. The research demonstrates that silyl protecting groups are compatible with the IPy_2BF_4-mediated reaction conditions, expanding the versatility of the method. The orthogonality of glycosyl fluorides and *n*-pentenyl glycosides, elucidating the selective activation of glycosyl fluorides using ytterbium triflate $Yb(OTf)_3$ and *n*-pentenyl glycosides using iodonium dicollidine perchlorate (IDCP). The method is showcased by its use in the one-pot synthesis of complex glycosides, demonstrating its potential for streamlined and efficient saccharide assembly.[15]



Scheme 1. Synthesis of Glycosyl Fluorides from *n*-Pentenyl Glycosides with IPy_2BF_4

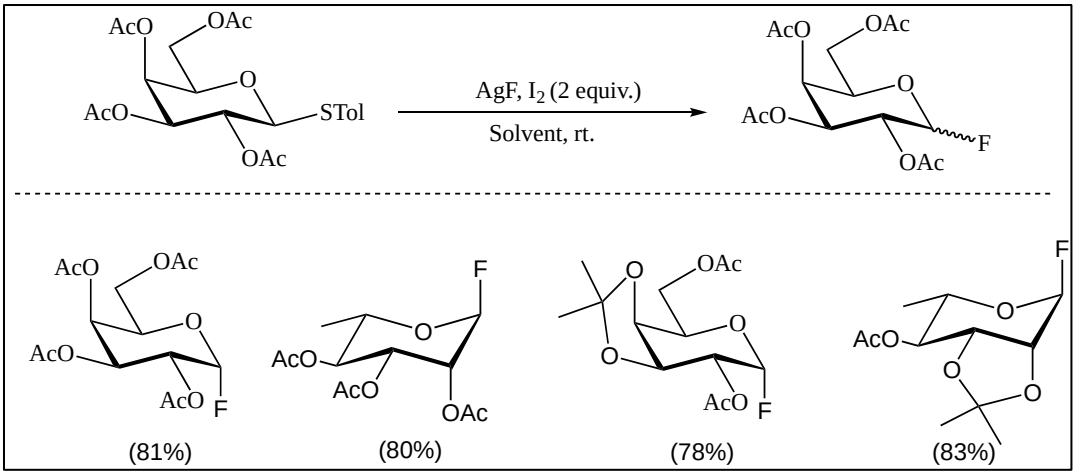
Bert Fraser-Reid and co-workers in 2009 prepared glycosyl fluoride efficiently from 1,2-orthoesters using hydrogen fluoride pyridine (HF-Py) as a fluoride source (Scheme 2).



Scheme 2. Synthesis of Glycosyl Fluoride from 1,2-Orthoesters

In this procedure, they converted pyranosyl and furanosyl 1,2-orthoesters to glycosyl fluorides. This method was useful for the synthesis of triol glycosyl fluoride and different glycosyl fluoride derivatives were prepared using this approach (Scheme 2).[16]

In 2012, Kartha and his research team successfully introduced a practical approach to synthesis of disarmed glycosyl fluorides using iodine monofluoride (IF) (Scheme 3). This is significant as disarmed glycosyl donors have unique reactivity patterns and can overcome the reactivity challenges to traditional glycosylation approaches. IF is highlighted as a cost-effective and easy-to-handle reagent, contributing to the overall convenience and practicality of the synthesis process. This study emphasizes the efficiency of the method by achieving good yields of the desired products. The research explores the influence of different solvents on the reaction outcome, revealing that the choice of solvent has a notable impact on the reaction yield and selectivity of the products.[17] Notably, this approach presented an additional advantage as IF could be generated in-situ from the combination of AgF and molecular iodine (Figure 2).



Scheme 3. Synthesis of Fluoride Glycosides from Thio-donor using AgF-I_2

The reaction proceeded within a 15-minute in acetonitrile yielding a product in a 52% with major β-anomer. Conversely, when the reaction was conducted in a medium of 1,4-dioxane, an impressive yield of nearly 81% was achieved, with the prominent emergence of the α-anomer as the major product.

Shoji Hara and his team introduced an innovative approach to synthesize glycosyl fluoride (2015) using a specific combination of reagents, IF_5, pyridine, and HF (Scheme 4). The research focuses on (phenylthio)glycosides as the starting materials for glycosyl fluoride synthesis. They highlighted IF_5 as a crucial fluorinating agent in the process as the reactivity of IF_5 and its role in promoting the conversion of (phenylthio)glycosides into glycosyl fluorides.

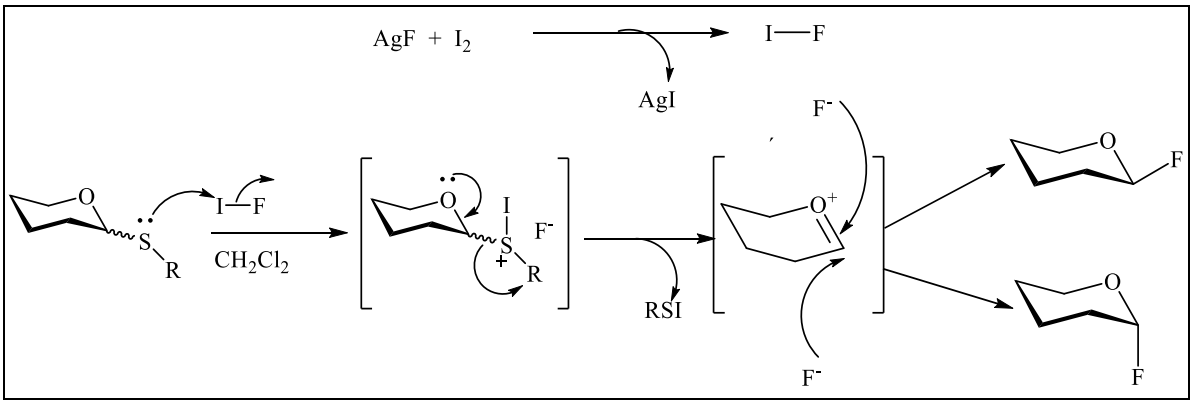
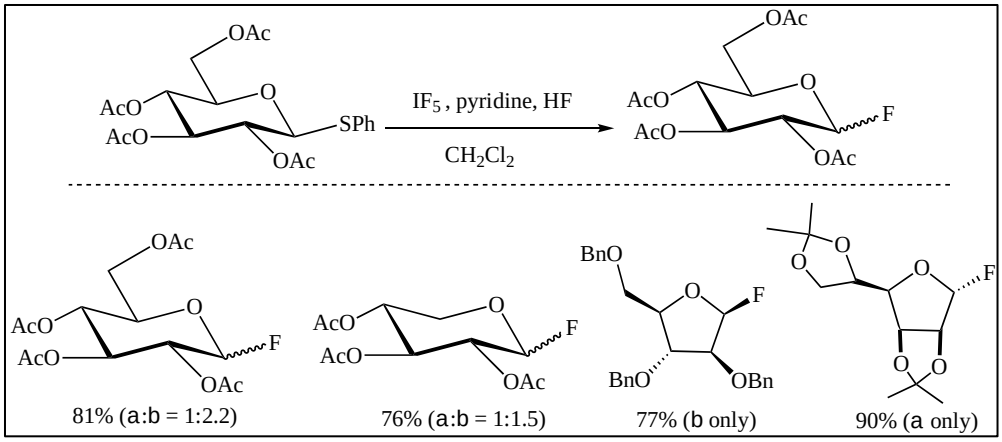


Figure 2. Mechanism of Fluro-glycosides formation from Thioglycosides using AgF-I_2

HF-pyridine acted as both an acid catalyst and as a source of nucleophilic fluoride ion. The presence of HF in the reaction mixture is explored as a promoter enhancing the efficiency of the transformation for glycosyl fluoride synthesis. This fluorination reagent exhibited robust moisture stability.[18] The research assesses the yield and selectivity of various glycosyl fluorides that have been synthesized through these methodologies.



Scheme 4. Synthesis of Glycoside Fluorides using IF_5-Pyridine-HF

2.2 Fluorination through Electrophilic Fluorinating Reagents:

Fluorination of carbohydrates enhances enzymatic and chemical stabilities, decreases hydrophilicity, and improves drug discovery potential. Electrophilic fluorinating agents also find applicability in effecting fluorination of saccharide molecules. A selection of electrophilic agents suitable for fluorination strategies is presented in Figure 3.

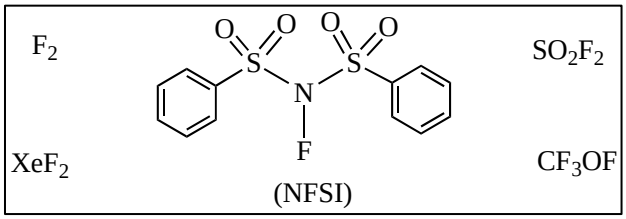
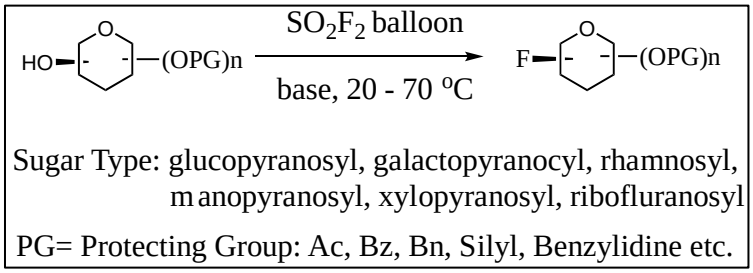


Figure 3. Electrophilic Fluorinating Agents

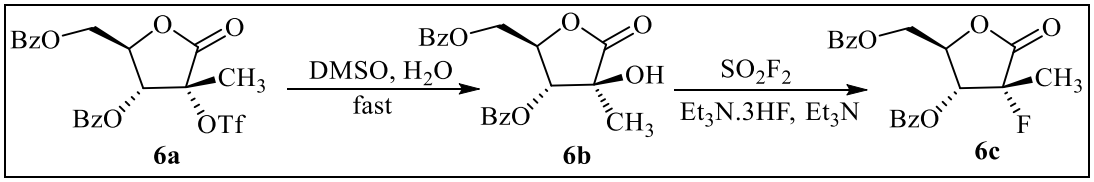
Ding and co-researchers reported a new synthetic approach for glycosyl fluoride formation, involving the usage of modified monofluorinated carbohydrates under mild conditions (Scheme 5). This strategy incorporates SO_2F_2 gas as a deoxyfluorination reagent in the presence of a base, obviating the requirement for additional fluoride additives. This method exhibited several merits including diminished toxicity, cost-effectiveness, ready accessibility, and heightened efficiency. It offers a practical and versatile approach to synthesizing fluorinated carbohydrates. Various sugar units with diverse protecting groups (acyl, benzyl, silyl) are suitable substrates for this method, demonstrating its broad applicability. The reaction was conducted within a temperature range of 20-70 ^oC. The method enables regioselective fluorination at different positions on sugar units, with different protecting groups tolerated. Conditions for optimal deoxyfluorination were determined based on protecting group effects. Under modest reaction conditions, significant transformations were obtained. The method allowed the synthesis of various glycosyl fluorides, which have applications in chemical and enzymatic oligosaccharide synthesis. Gram-scale preparation of glycosyl fluorides demonstrated the scalability and practicality of the approach for industrial applications.[19]



Scheme 5. Synthesis of Glycosyl Fluoride using SO_2F_2

In 2015 Shen and his collaborative researchers reported a new approach to synthesize a fluoro-substituted lactone through a neighbouring group participation mechanism. Lactones hold

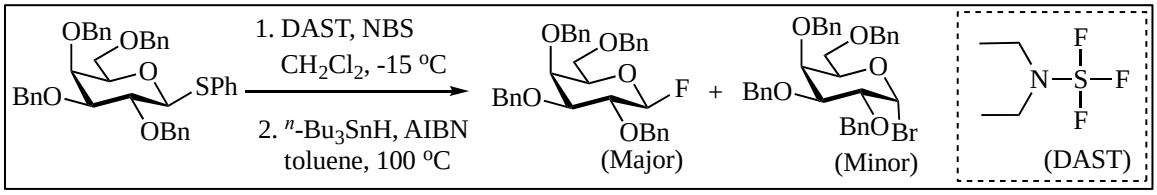
significant utility in drug synthesis and the formulation of nucleoside antiviral agents, including sofosbuvir, which is approved for treating chronic hepatitis C. The compound also plays a role in synthesizing other nucleoside HCV NS5B polymerase inhibitors. While lactone synthesis could be achieved using DAST, however its outcomes in terms of yield were limited, and it incurred higher costs compared to their formulated procedure. Sulfuryl fluoride (SO_2F_2) has been recognized as an effective agent for dehydroxylating fluorination of alcoholic compounds. The research study introduced a method that utilizes SO_2F_2 as a fluoride source during the synthesis of compound **6c** from its corresponding alcohols **6b** (Scheme 6).[20]



Scheme 6. Synthesis of Fluoro-lactone by using SO_2F_2

2.3 Fluorination through Sulfur-based Fluorinating Reagents:

Kanie and his team explores the direct conversion of thioglycosides to glycosyl fluorides using N,N-diethylaminosulfur trifluoride (DAST) without using for N-bromosuccinimide (NBS) (Scheme 7) in 2012. The conventional method utilizing NBS generates glycosyl bromides as by-products and reacts with olefinic substrate. DAST-promoted fluorination reactions are examined at varying temperatures and solvent systems. Substrates with phenylthio groups are transformed to glycosyl fluorides, and conditions are optimized for different types of monosaccharides. The reaction mechanism leads to stereochemical inversion for certain substrates, suggesting dependence on the stereo and electronic environment of the anomeric carbon. Both S_N1 and S_N2 mechanisms are proposed based on the substrate characteristics. The method proves effective in fluorinating allyl-protected thioglycosides, demonstrating its broader applicability compared to traditional NBS-based methods. For less-reactive substrates, the presence of dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST) accelerates the reaction, leading to improved product yields. The method's success offers a practical route to synthesize a diverse range of glycosyl fluorides. The synthesized compounds exhibit valuable utility in the domain of oligosaccharide chemistry. The approach eliminates the generation of unwanted by-products, simplifying purification processes. It enhances substrate compatibility, especially for substrates with alkene functionalities.[21]



Scheme 7. Glycosyl Fluoride Synthesis using DAST

In 2012 Williams and his team discovered a new approach for synthesizing glycosyl fluoride from seleno-, thio-, telluroglycosides using aminodifluorosulfinium tetrafluoroborates. They used Xtalfluor-E and -M as reagents without using N-bromosuccinimide (figure 4).[22] Another fluorinating reagent fluolead was also used in this process, but it was not explored enough due to highly moisture sensitivity. The study investigates the synthesis of glycosyl fluorides using aminodifluorosulfinium tetrafluoroborate reagents Xtalfluor-E and -M. These reagents are moisture-stable and can be used as alternatives to DAST for deoxofluorination reactions.

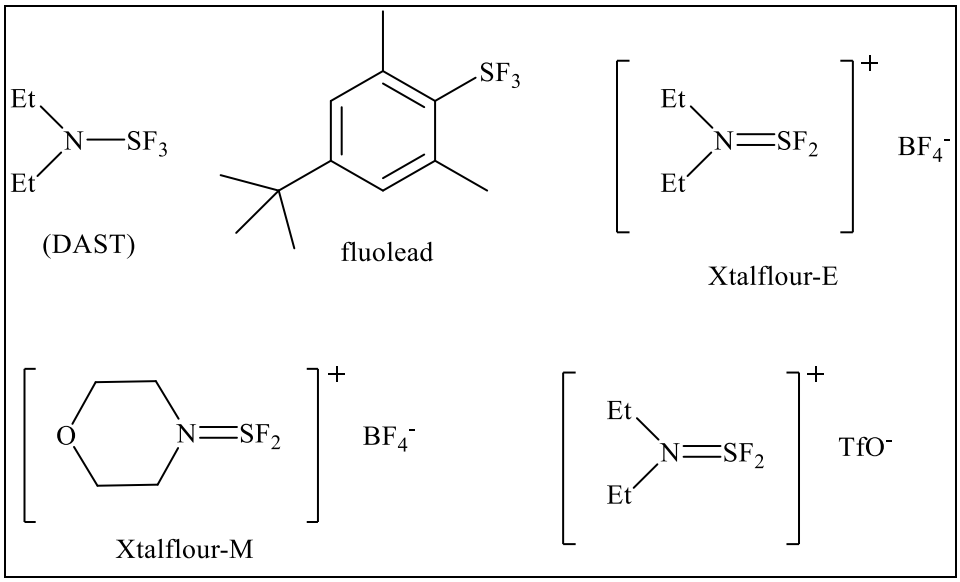
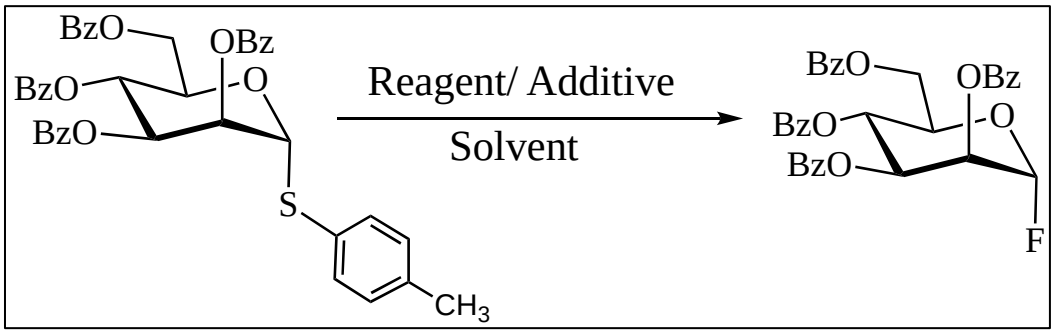


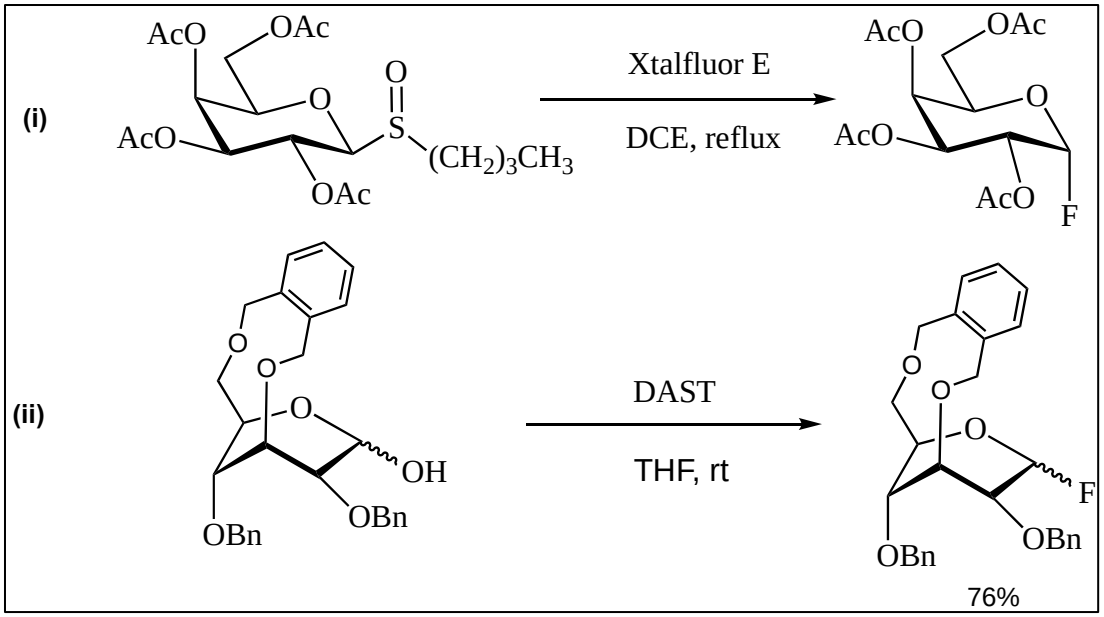
Figure 4. Different Sulfur-based Fluorinating Agents

The transformation is demonstrated with various thioglycosides, including acetylated, benzoylated, and alkyl derivatives. Additionally, glycosyl sulfoxides are efficiently converted to glycosyl fluorides, broadening the reaction scope (Scheme 8b). Mechanistic insights suggest that the fluoride ion in the product arises from the tetrafluoroborate counterion of the aminodifluorosulfinium reagents. The reactivity of these reagents is complex due to the nature of their counterions.



Reagents	Additive	Solvents/conditions	Yield (%)
DAST	NBS	CH_2Cl_2, 0°C to rt, 18h	62
XtalF-E	-	CH_2Cl_2, 0 °C to rt, 18h	No reaction
XtalF-E	NBS	CH_2Cl_2, 0 °C to rt, 18 h	80
XtalF-E	-	DCE, reflux, 15 min	90
XtalF-M	-	DCE, reflux, 15 min	84
Et_2N-SF_2OTf	Bu_4NBF_4	DCE, reflux, 15 min	83

Scheme 8a. Table of different conditions for Synthesis of Glycosyl Fluoride with DAST



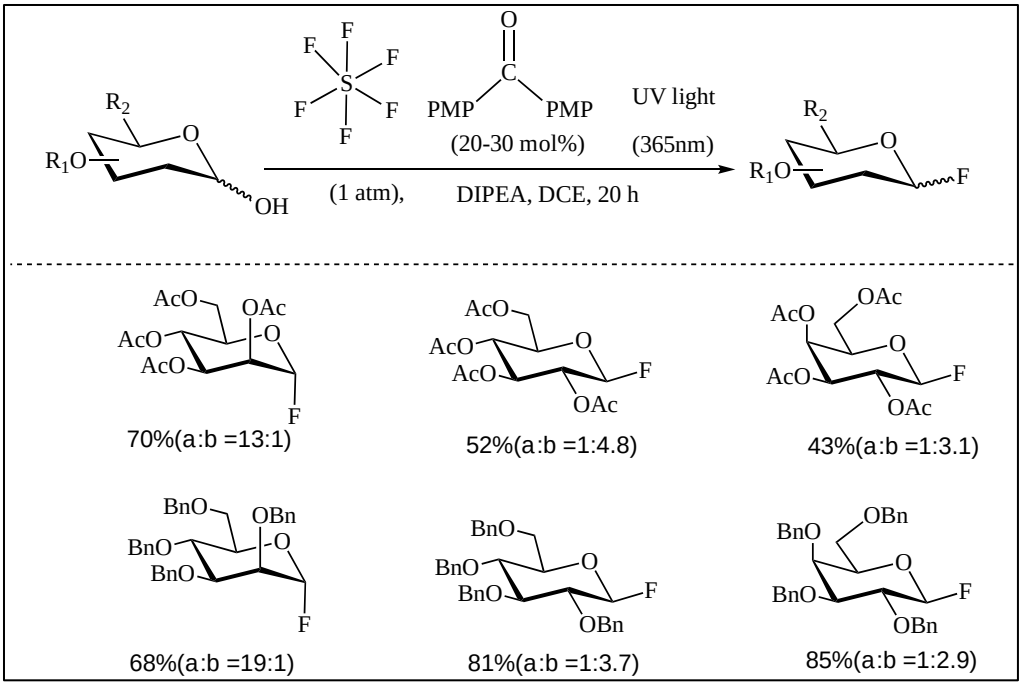
Scheme 8b. i) Synthesis of Glycosyl Fluoride from Glycosyl Sulfoxide; ii) Synthesis of 2,4-Di-*O*-benzyl-3,6-*O*-(o-xylylene)glucopyranosyl Fluoride

Xtalfluor-E and -M can smoothly convert thioglycosides to glycosyl fluorides in the presence of NBS, with optimal conditions achieved by refluxing in 1,2-dichloroethane. Even in the absence of NBS, the reaction can be conducted at reflux conditions with similar yield. The approach is also successful for glycosyl sulfoxides (Scheme 8b).[22] The source of fluorine in the product is traced back to the tetrafluoroborate counterion, revealing the intricate reactivity patterns of the aminodifluorosulfinium reagents in nucleophilic fluorination reactions. They performed the reaction with different conditions. They showed the reaction with DAST-NBS, XtaIF-E with NBS and without NBS, XtaIF-M, etc. (Table, Scheme 8a).

Yamada and co-workers reported the synthesis of 2,4-di-*O*-benzyl-3,6-*O*-(o-xylylene)glucopyranosyl fluoride, a key glycosyl donor from glycosyl hemiacetal. This is an axial-rich donor molecule provide complete β-selectivity in glycosylation reactions (Scheme 8b).[23]

2.4 Fluorination by the Photochemical Method

In recent years, organic reaction through photochemical approach has been recognized as a greener and more economical process for sustainable chemistry.[24,25] It is used as an alternative method to avoid toxic and costly metal reagents for various redox-active reactions. Synthesis and activation of glycosyl donor through photochemical method is a promising strategy for the synthesis of complex oligosaccharides.[26,27]



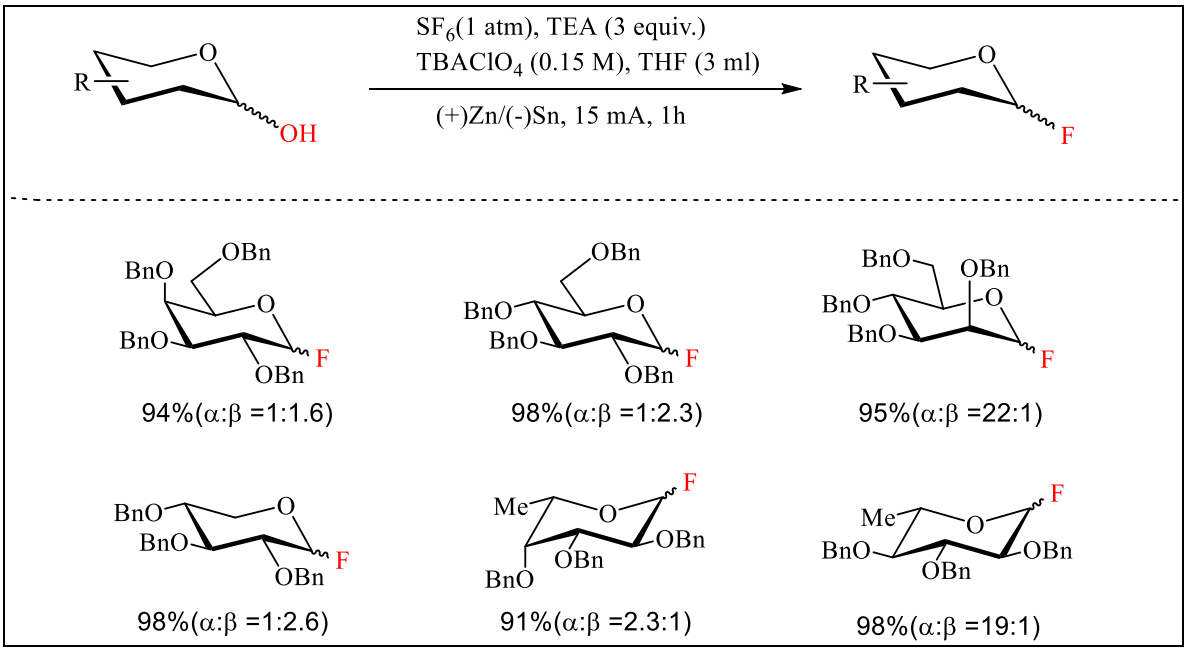
Scheme 9. Photochemical Synthesis of Glycosyl Fluorides

In 2021, Nagorny and his group reported a new method for the photocatalytic generation of glycosyl fluorides using sulfur(VI) hexafluoride (SF_6) as a safe and inexpensive fluorinating agent and 4,4′-dimethoxybenzophenone (DMBP) as an easily accessible organic photocatalyst, which enables the synthesis of various glycosyl fluorides, including substrates with acid and base labile functionalities, in yields ranging from 43% to 97%.[28] It offers a mild and efficient approach to glycosyl fluoride synthesis. This reaction methodology demonstrates versatility by enabling the formation of glycosyl fluorides from different protected carbohydrates and its adaptability to continuous flow reactions is exemplified, encompassing the successful execution of gram-scale fluorination. Although the mechanism is not fully elucidated, they proposed that the reaction may involve the transient formation of SF_4, which acts as a fluorinating agent. The mechanism is attributed to the photoexcitation of DMBP, generating ketyl radicals that reduce SF_6 to form SF_4 or related species (Scheme 9).

The use of SF_6 as a fluorinating agent is highlighted as significant, considering its chemical inertness and potential as a greenhouse gas. This method provides a safer and more environment friendly for glycosyl fluoride synthesis compared to other methods using hazardous reagents. The demonstrated mild and safe method has the potential to enhance the synthesis of glycosyl fluorides from stable glycosyl hemiacetal.

2.5 Electrochemical Synthesis of Glycosyl Fluorides

Organic Synthesis through electrochemical method is considered as a greener approach in recent times.[29,30] Nowadays organic electrosynthesis is an emerging field for the sustainable molecular assembly.[31] Nagorny and co-workers reported an electrochemical synthetic method for obtaining glycosyl fluorides, in high yields using sulfur hexafluoride (SF_6) as a fluorinating agent (Scheme 10). SF_6 is a stable and nontoxic gas commonly used as a dielectric insulator but is also a potent greenhouse gas. They conducted galvanostatic electrolysis of various glycosides in the presence of SF_6, utilizing tin and zinc electrodes. The optimal conditions were determined through a series of experiments, and the electrochemical fluorination process was found to be efficient, scalable, and compatible with various sugar derivatives and different protecting groups.[32]

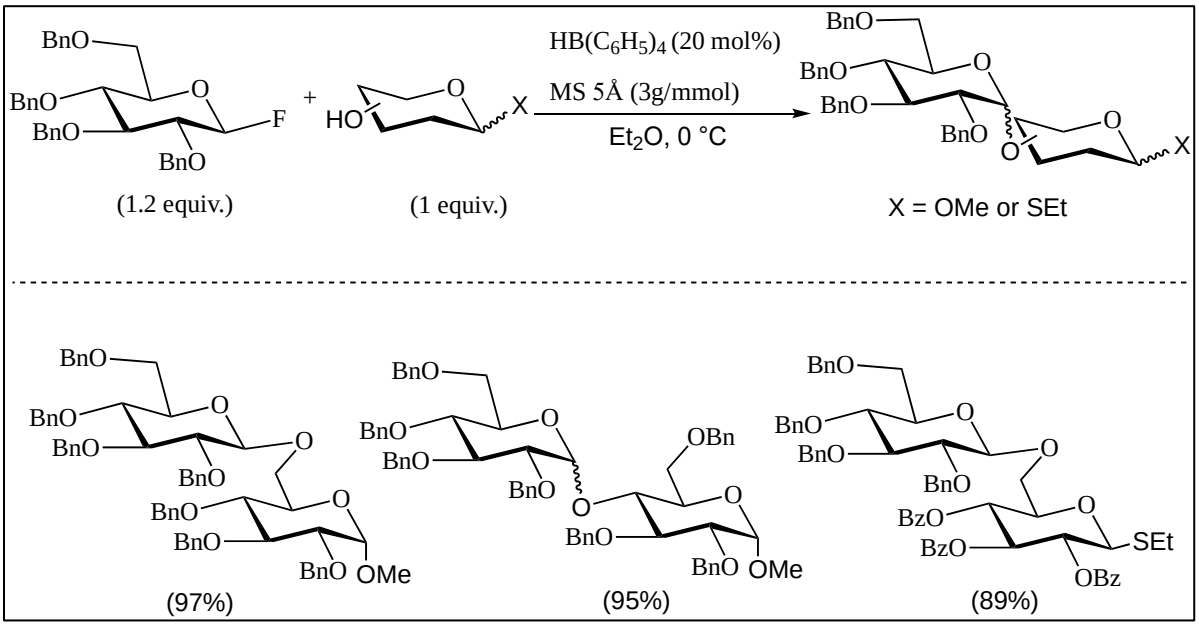


Scheme 10. Electrochemical Synthesis of Glycosyl Fluorides Using Sulfur(VI) Hexafluoride.

3. Activation of Glycosyl Fluoride

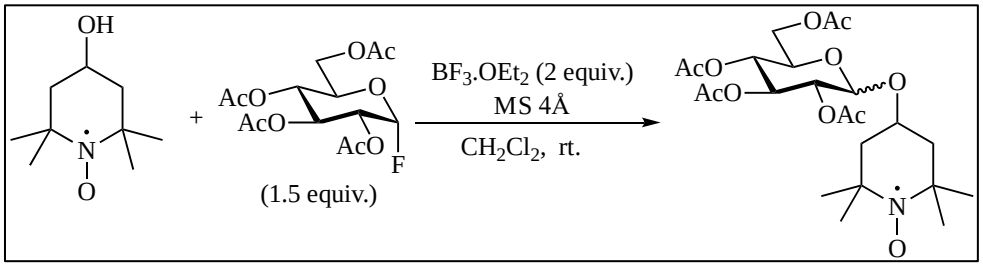
Activation of glycosyl fluoride is imperative for glycosylation, as this step facilitates the generation of highly reactive glycosyl cations or radicals, enhancing the efficiency and selectivity of the glycosylation process.[10] Over the past few years, glycosyl fluoride donors largely used to perform different kinds of glycosylation such as *O*-glycosylation and *C*-glycosylation.

Mukaiyama research group developed a new catalytic stereoselective glycosylation method in 2001 using glycosyl fluoride donor and with the help of different types of protic acids. In the reaction condition perchloric acid ($HClO_4$) in diethyl ether (Et_2O), α- glycosides were obtained as the major product.



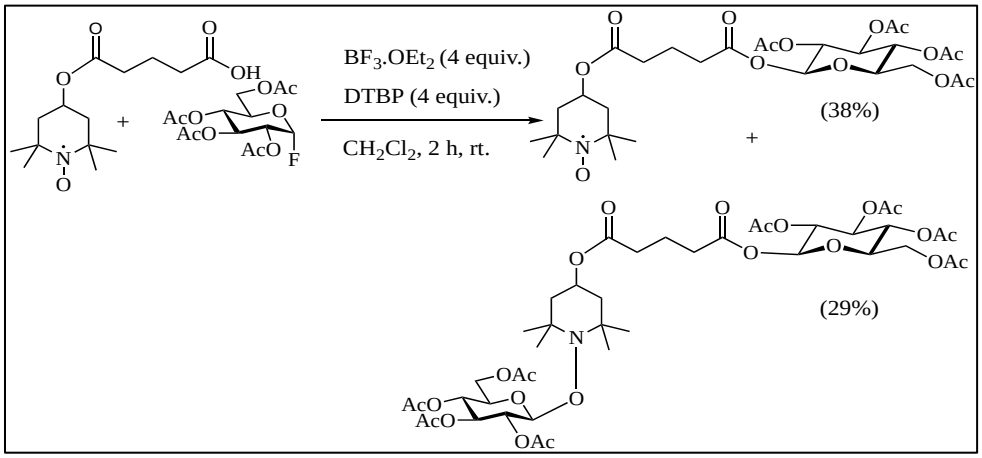
Scheme 11. Formation of Selective β-glycosides by Activation of Glucosyl Fluoride

On the other hand, when they used tetrakis(pentafluorophenyl)boric acid [$HB(C_6F_5)_4$] in a mixed solvent of trifluoromethyl benzene (BTF)-pivalonitrile (^{t}BuCN) in a ratio of 5:1 then β-glycosides were obtained as a major product (Scheme 11).[33] With this technique, they were able to control the stereoselectivity both by the influence of the solvents and by the kind of the catalyst's counter anion, such as ClO_4- or $B(C_6F_5)$-.



Scheme 12. Glycosylation Reaction with Nitoxyl Radical using $BF_3.OEt_2$

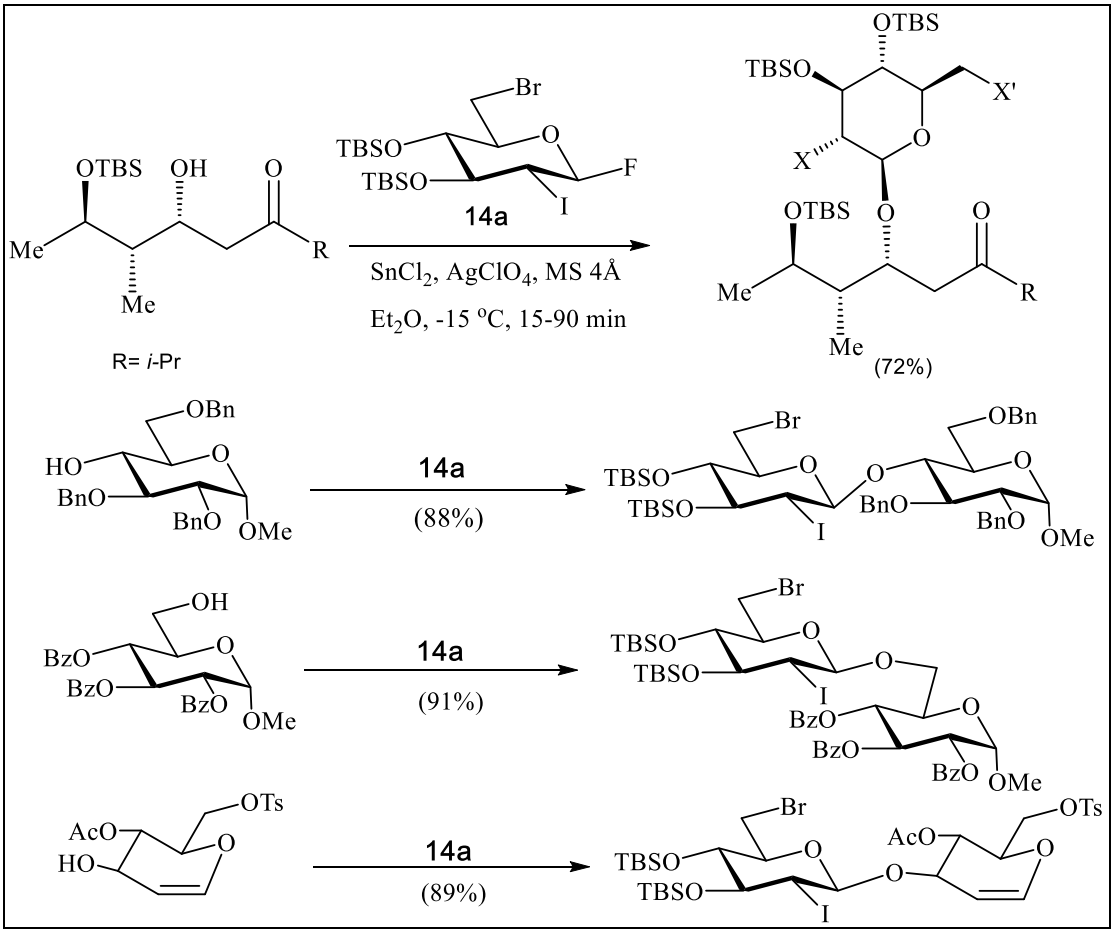
In 2001 Matsuba and their group developed a method for the glycosylation of nitroxyl radicals using glycosyl fluoride as a glycosyl donor, with the goal of producing hydroxylamine-*O*-glycosides for use as spin-probe reagents. The combination of $BF_3{\cdot}OEt_2$ and amine bases such as 2,6-di-tert-butylpyridine (DTBP) or 1,1,3,3-tetramethylguanidine (TMG) in CH_3CN proved effective in promoting glycosylation. Reactions using strongly basic amines, such as TMG and DBU, resulted in better yields and selectivity compared to hindered amines (Scheme 13). They explored the reactions methodology on various monosaccharides such as 2,3,4,6-tetra-*O*-acetyl-α- and β-D-glucopyranosyl fluorides (Glc α- and β-F) and 2,3,4,6-tetra-*O*-acetyl-α- D-galactopyranosyl fluoride (Gal α-F) as glycosyl donors.[34] They found 4-*O*-(2,3,4,6-tetra-*O*-acetylglucopyranosyl)-TEMPO to be the major product of the glycosylation reaction using Glc α-F as a donor and $BF_3.OEt_2$ as the promoter in CH_2Cl_2. Under the identical conditions, the glycosylation process did not proceed with 4-*O*-acetyl-protected nitroxyl radical (Scheme 14).



Scheme 13. Glycosylations with Fluoride Glycoside and Nitroxyl Radical

In the year 2003, Blanchard and his group focused on developing a highly efficient and stereoselective method for the synthesis of 2-deoxy-β-glycosides, which are important structural units found in various natural and biologically active compounds. They aimed to overcome the challenges associated with β-selective glycosidation reactions of β-hydroxy ketones (Scheme 14), which are often hindered by the intramolecular hydrogen bonding in the acceptor molecules and limited methods available for stereoselective construction of 2-deoxy-β-glycosidic linkages.[35] 2-Deoxy-2-iodo-β-glucopyranosyl fluoride **14a** was designed as a highly reactive and stereoselective glycosyl donor, incorporating a C(2)-iodo directing group and an anomeric fluoride leaving group. Application of glycosyl donor **14a** to glycosidation reactions of β-hydroxy ketones led to high yields and excellent anomeric stereoselectivity, overcoming limitations of existing methods. Use of promoters such as silver triflate or stannous chloride, along with controlled temperature, enabled efficient glycosidation with excellent stereoselectivity. The glycosylation method was successfully applied to various acceptors,

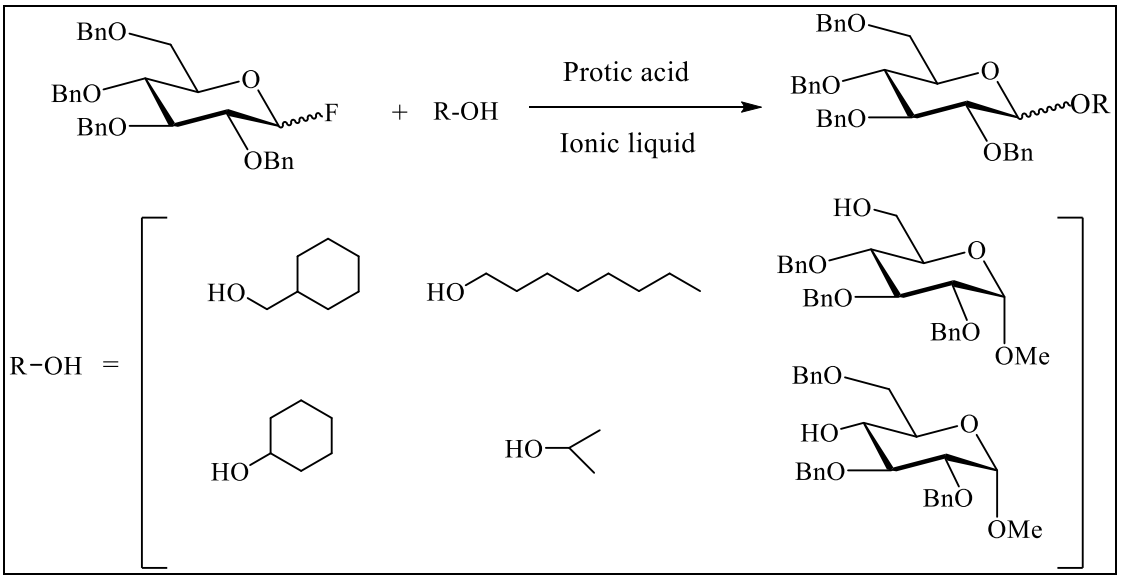
including primary and secondary alcohols, while maintaining high efficiency and selectivity.



Scheme 14. Glycosyl Fluoride Activation by Sn-Ag Promoters

Glycosylation reaction using a variety of acceptors, such as β-hydroxy ketones at -15 °C with high β-stereoselectivity and good yield (Scheme 14).

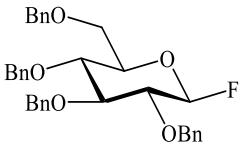
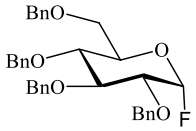
Matsumara and their group discovered a new glycosylation technique using glycosyl fluoride donors with ionic liquid catalyst in 2004. They used ionic liquid containing protic acid which could be activated under mild conditions to get the glycosides in high yield (Scheme 15). Different ionic liquids with protic acids were evaluated for their effectiveness in promoting glycosylation reactions. 1-*n*-Hexyl-3-methylimidazolium trifluoromethanesulfonate (C_6mim[OTf]), containing a trifluoromethanesulfonate anion and 1-(3-cyanopropyl)-3-methylimidazolium trifluoromethanesulfonimidide (CNC_3mim[NTf_2]) containing a cyano group were used as ionic liquids.



Scheme 15. Glycosyl Fluoride Activation by Acid/Ionic liquid

The β-stereoselectivity in glycosylation was induced by the coordination of the trifluoromethanesulfonate anion from the ionic liquid with the oxonium intermediate.[36] The glycosylation reactions were successful with various primary and secondary alcohols, and the stereoselectivity was modulated by the choice of ionic liquid.

Table, Scheme 15a. Activation of Glycosyl Flourides using different Ionic Liquid/Protic Acid Systems

Entry	Donor	Ionic liquid	Acid	Time/h	Yield/%	α/β
1		C mim[BF_4]	HBF_4	24	41	47/53
2		C mim[NTf_2]	$HNTf_2$	1	86	68/32
3		C mim[ClO_4]	$HClO_4$	1	83	30/70
4		C mim[OTf]	HOTf	1	89	24/76
5		C mim[OTf]	$HNTf_2$	1	88	25/75
6		C mim[NTf_2]	HOTf	1	82	52/48
7		C mim[OTf]	HOTf	4	85	26/74

Table, Scheme 15a essentially demonstrates the impact of different ionic liquid systems on the glycosidation reactions, emphasizing the influence of the ionic liquid itself, specifically the anion, on the stereoselectivity of the reactions. It was concluded that β-stereoselectivity was induced by the α-oriented coordination of the trifluoromethanesulfonate anion from the ionic liquid (C_6mim[OTf]) with the oxonium intermediate, and this was not significantly affected by the choice of protic acid

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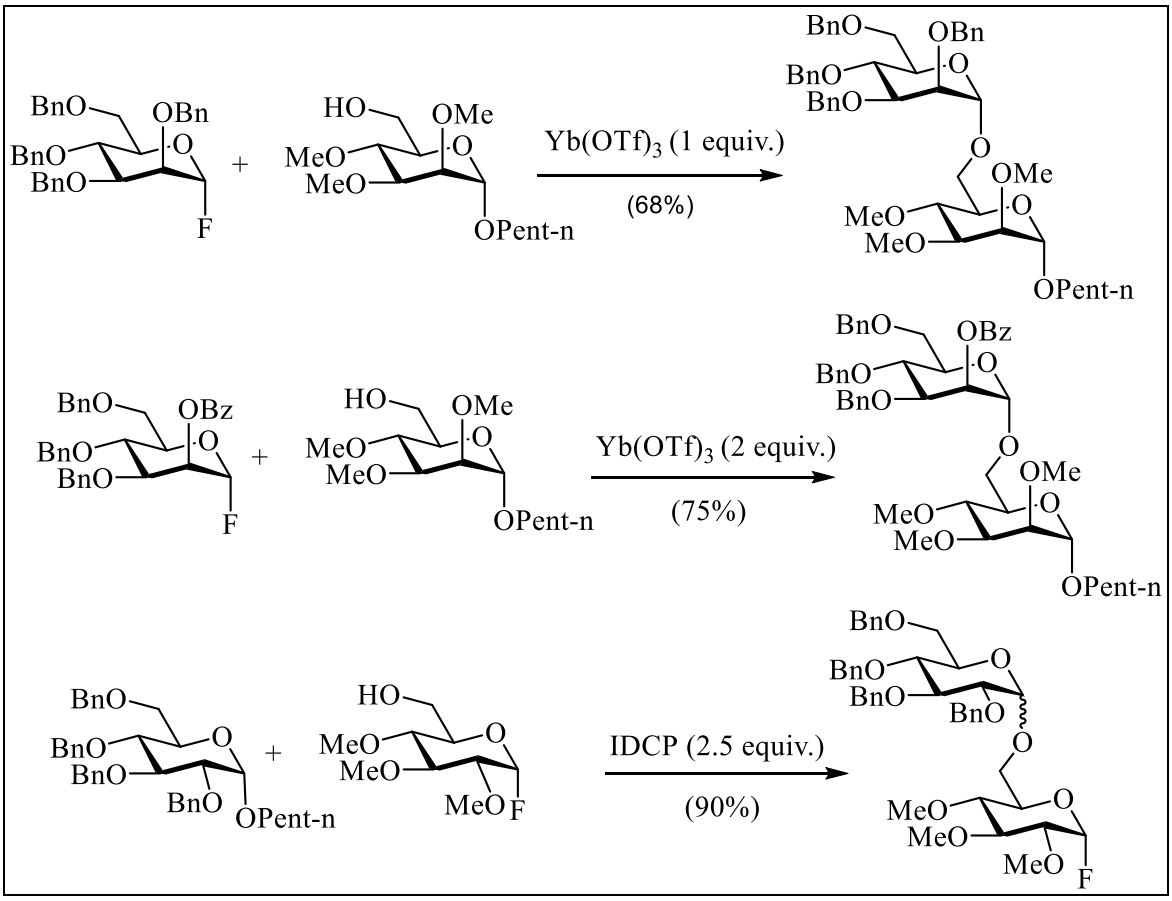
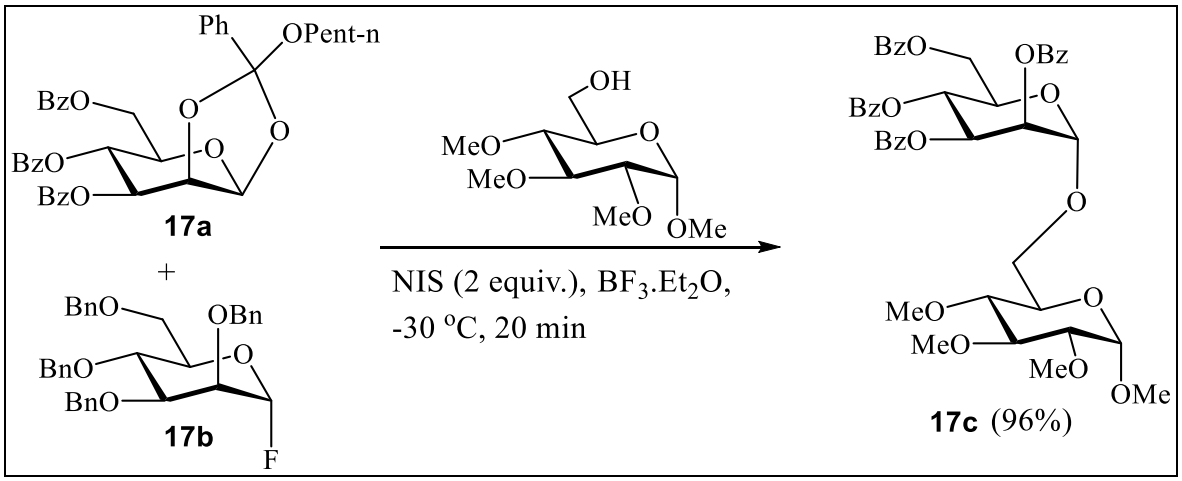


Scheme 16. Glycosylation between *n*-Pentenyl Glycosides and Glycosyl Fluorides.

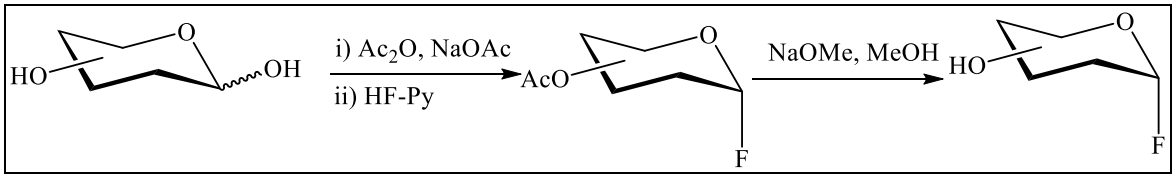
In 2007 Lopez, and the team develop an efficient method for preparing glycosyl fluorides using furanose- and pyranose-derived 1,2-orthoesters with HF-pyridine. The method was compatible with various protecting groups, including tert-butyldiphenyl silyl ethers, allowing glycosylation without the need for protection-deprotection steps. The approach was successfully applied to furanosyl and pyranosyl 1,2-orthoesters, including those with secondary and primary hydroxyl groups. Compared to diethylaminosulfur trifluoride (DAST)-mediated fluorinations, the HF-pyridine method did not require an additional step to free anomeric OH groups, making it more versatile. They activated the glycosyl fluoride selectively by ytterbium triflate Yb(OTf)[15] in dichloromethane solvent without reacting with *n*-pentenyl glycosides (NPGs) (Scheme 16).

Coupling reactions between glycosyl fluoride **17b** and *n*-Pentenyl orthoester (NPOE) **17a** were carried out with N-iodosuccinimide (NIS) and ytterbium triflate ($Yb(OTf)_3$) in dichloromethane (CH_2Cl_2) at -20 ºC. In this case, glycosyl fluoride **17b** is selectively activated, leading to the formation of disaccharide **17c**. The selectivity of glycosyl donor activation depends on the specific conditions and reagents used, therefore the reaction proceeds with high selectivity towards glycosyl fluoride **17b**, and NPOE **17a** remains relatively unreacted. This selective activation allows for the controlled formation of disaccharide **17c**. (Scheme 17).[15]



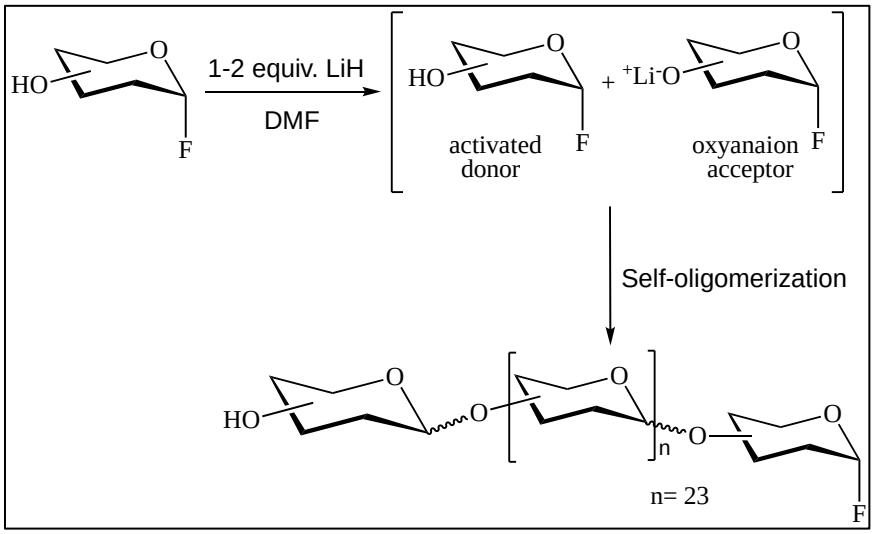
Scheme 17. Orthogonal Glycosyl Coupling between Glycosyl Fluoride and *n*-Pentenyl Glycoside

Joachim Thiem and his team developed a new synthetic method in 2010 for the formation of homo-oligosaccharides from unprotected glycosyl fluorides through a base-promoted glycosylation reaction.[37] They first synthesized unprotected glucopyranosyl fluorides (Scheme 18).



Scheme 18. Synthesis of Unprotected Glucopyranosyl Fluorides

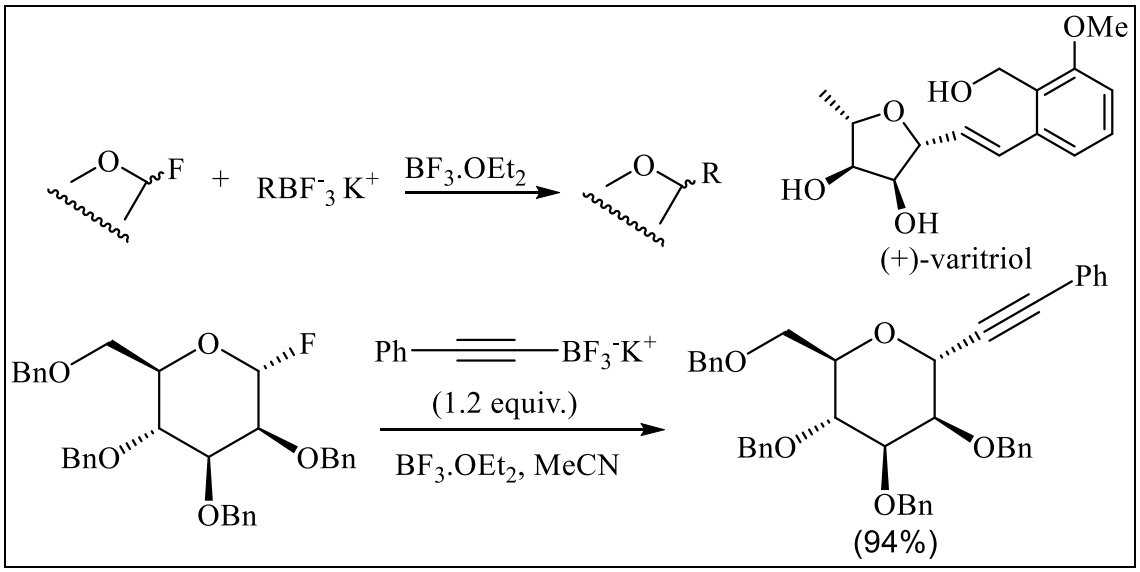
Following that, they carried out the base-promoted single-step self-oligomerization up to 25 saccharide units to activate the fluoride donor (Scheme 19).[37]



Scheme 19. Activation of Glycosyl Fluoride by Base-promoted Single-step Self-oligomerization

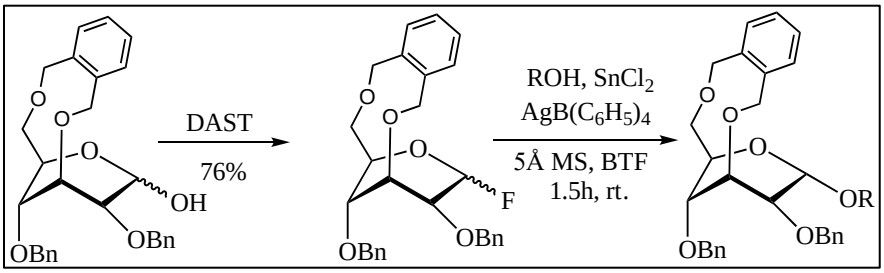
In 2011 Xue-Wei Liu and his team developed a mild and stereoselective method for the synthesis of alkynyl and alkenyl C-glycosides through the coupling of organotrifluoroborates and glycosyl fluorides using $BF_3{\cdot}Et_2O$ (Scheme 20). C-Glycosides are valuable due to their unique structures and stability against glycosidases and hydrolytic conditions. The method involves the coupling of potassium organotrifluoroborates with sugar oxocarbonium ions, utilizing $BF_3{\cdot}Et_2O$ as a Lewis acid. Various alkynyl and alkenyl trifluoroborates were successfully coupled with glycosyl fluorides to generate C-glycosides with good to excellent yields and high diastereoselectivity.[38] When glycosyl

fluoride was subjected to the reaction conditions of acetonitrile solvent at room temperature and in the presence of $BF_3{\cdot}Et_2O$, the reaction proceeded promptly to completion in just under 20 minutes, with a yield of the desired C-glycoside of about 94%. The method was used in total synthesis of (+)-varitriol, (a naturally occurring C-glycoside with potent cytotoxic activity).[38]



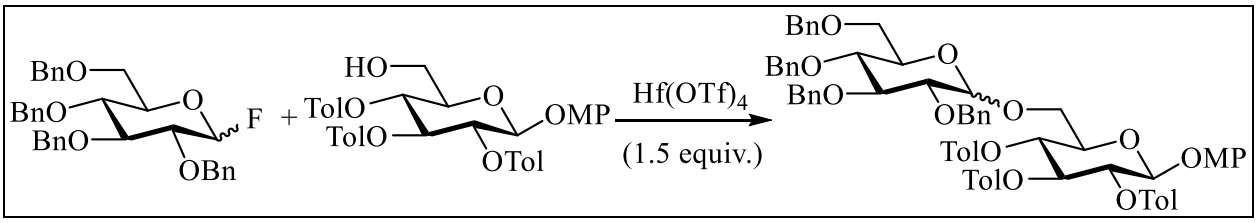
Scheme 20. Synthesis of C-Glycosides by Coupling Reaction with Fluro-glycosides

In 2012, Yamada and his research team introduced a novel glycosylation approach that enabled the synthesis of β-stereoselective products without relying on neighbouring group participation. In this methodology, a glycosyl fluoride bearing a 3,6-*O*-(o-xylylene)-bridged axial-rich configuration was used as the glycosyl donor. The catalytic system involved the use of $SnCl_2{-}AgB(C_6F_5)_4$, which facilitated the glycosylation reaction. Additionally, the actual active catalyst was identified as $SnB(C_6F_5)_4Cl$, generated in-situ. This catalyst exhibited broad applicability across various alcohol substrates.[39] The overall process encompassed the synthesis of the glycosyl fluoride and its subsequent activation through the generation of the catalyst in-situ (Scheme 21).



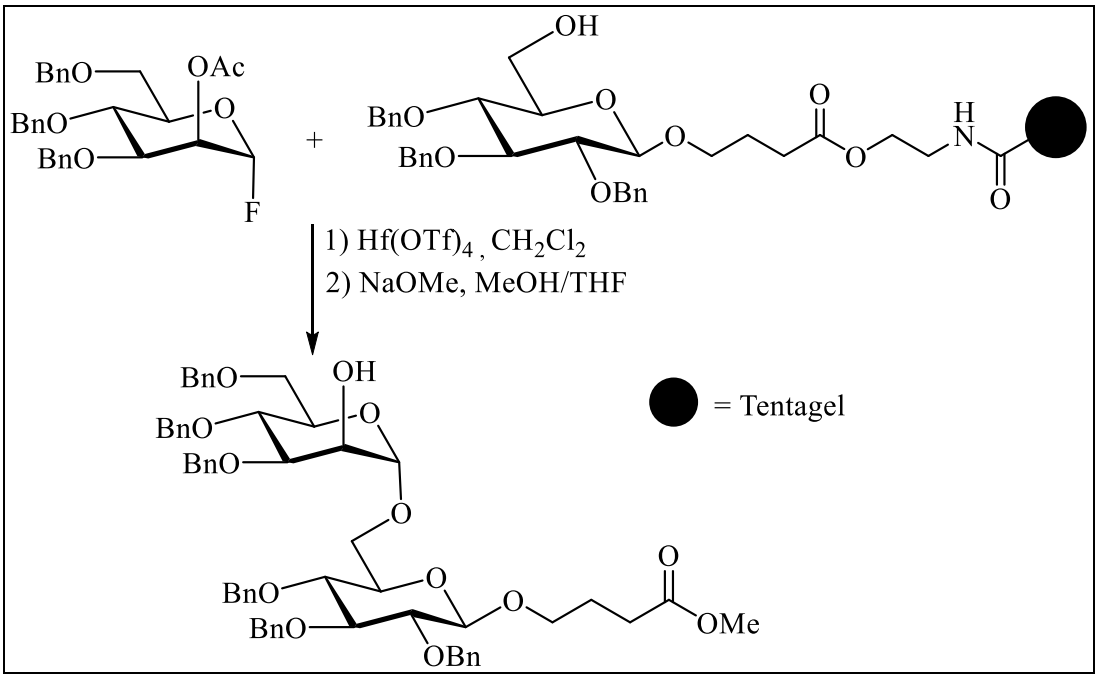
Scheme 21. In-situ Synthesis and Activation of Glycosyl Fluoride using Bimetallic Catalyst

In 2013 Manabe and his group developed a unique approach which describes the utilization of Hafnium(IV) tetratriflate ($Hf(OTf)_4$) as an effective activator of glycosyl fluoride. The developed protocol offers operational simplicity and broad applicability for both solid-phase and solution-phase glycosylation reactions. $Hf(OTf)_4$ demonstrates efficient activation of glycosyl fluoride even at low temperatures.[40]



Scheme 22. Activation of Glycosyl fluorides by $Hf(OTf)_4$

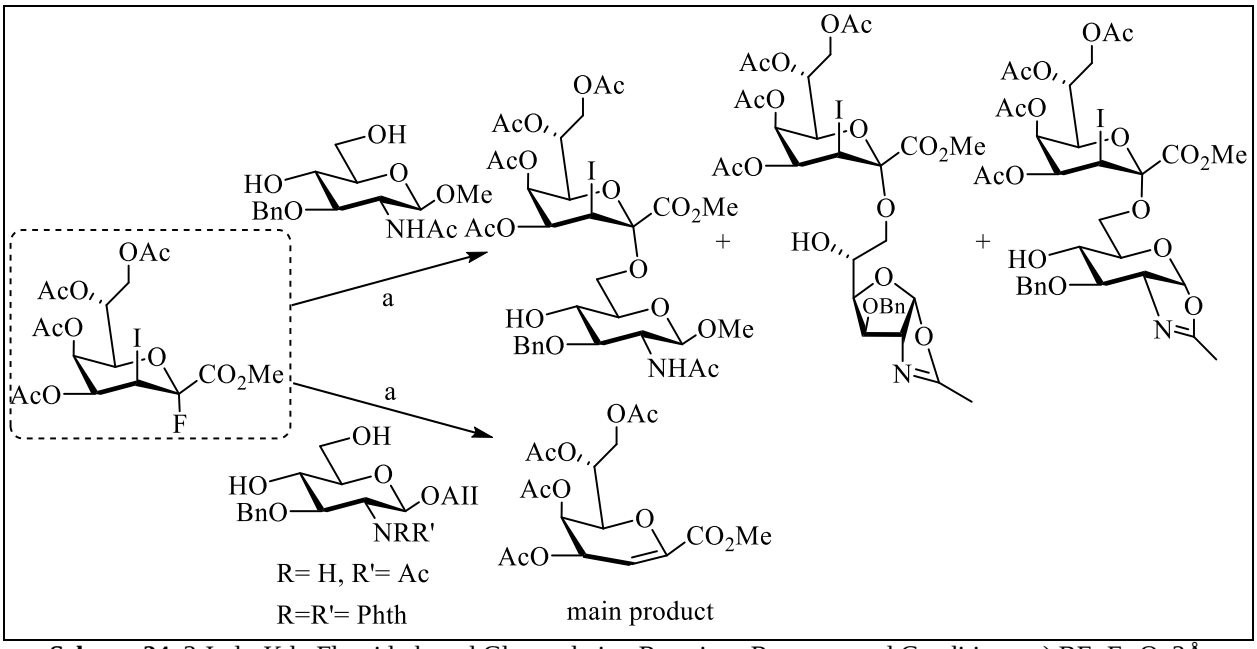
The methodology enables β-selective glycosylation reactions, producing disaccharides and more complex oligosaccharides with good to excellent yield even at a low temperature (Scheme 22).



Scheme 23. Solid Phase Glycosylation using Glycosyl Fluoride

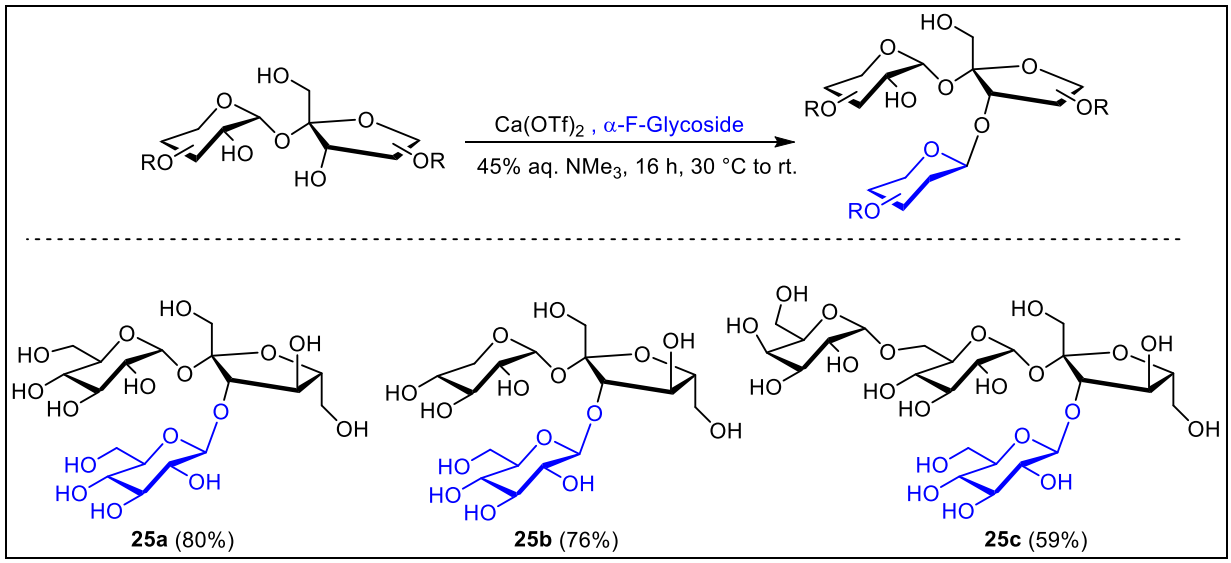
The developed approach was successfully used for the efficient synthesis of oligosaccharides on a solid phase using a polymer support. In this strategy, methyl poly(ethylene glycol) (MPEG) was used to create an acid-stable linker, which acted as a proficient acceptor. The high polarity of MPEG facilitated rapid purification.[40] After the removal of the chloroacetyl temporary protecting group under basic conditions, the resultant MPEG-glycoside was subjected to the subsequent glycosylation step, leading to the quantitative production of the desired compound (Scheme 23).

In the year 2015, Kosma and colleagues conducted research on 3-Iodo-Kdo fluoride-based glycosylation chemistry, with a focus on using N-Acetyl Glucosamine acceptors. The study involved the selection of N-acetyl-protected monosaccharide derivatives as glycosyl acceptor molecules. Subsequently, glycosylation reactions were carried out involving the primary alcohol moiety of N-Acyl, N-Acetyl, N-Cbz, and N-Troc protected glucosamine derivatives, utilizing various types of Kdo donors.[41] The outcomes of these investigations revealed good yields and significant anomeric selectivity (Scheme 24).



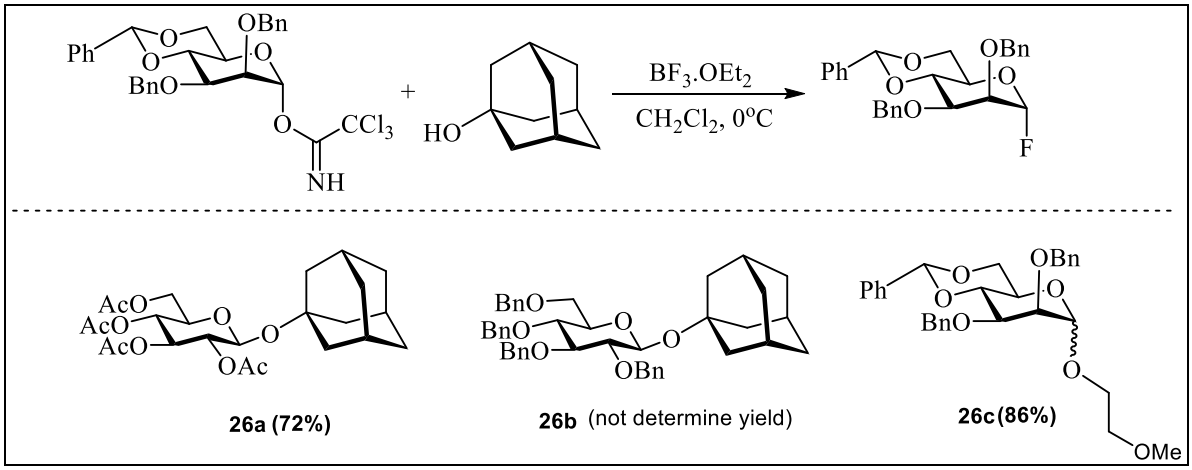
Scheme 24. 3-Iodo-Kdo Fluoride-based Glycosylation Reactions Reagents and Conditions: a) $BF_3.Et_2O$, 3Å Molecular Sieves, CH_2Cl_2, 0 °C

In 2016, Miller and his research group focuses on developing a glycosylation reaction that can be conducted entirely in an aqueous solvent mixture, which is a significant departure from traditional glycosylation methods that often require organic solvents. Therefore, Glycosyl fluorides are selected as glycosyl donors due to their stability in water and their potential reactivity at the C1-position. They used the strategy involving the use of calcium salts (Ca^{2+} ions) and a tertiary amine base (NMe_3) to promote glycosylation while inhibiting hydrolysis, achieving high site-selectivity for either 3'-position or 1'-position of the fructofuranoside unit in sucrose. Additionally, the glycosylation results in complete stereoinversion at the anomeric center of the glycosyl donor. The research involves an analysis of the solution conformations of sucrose and its deoxysucrose analogs using NMR techniques, which provide insights into the role of intramolecular hydrogen bonds in determining reactivity and regioselectivity. However, the regioselectivity can be altered by using different metal salts (e.g., $Ca(OTf)_2$ vs. $Ca(OH)_2$), leading to the formation of either the 3'- or 1'-glycosylated products. This optimized glycosylation method is successfully applied to various sucrose-like oligosaccharides, expanding the scope of substrates that can be glycosylated in an aqueous medium (Scheme 25).[42]



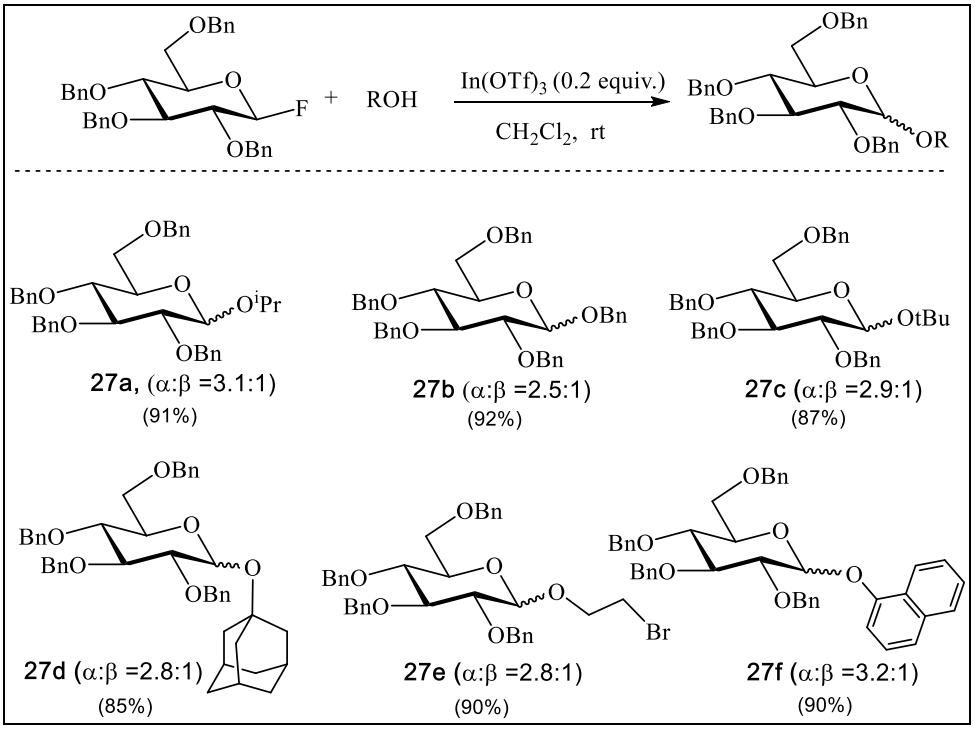
Scheme 25. 3′-Glycosylation with α-F-Glycoside using $Ca(OTf)_2$

In 2017, Pedersen and colleagues introduced a glycosylation methodology facilitated by $BF_3.OEt_2$, using trichloroacetimidate (TCA) donor (Scheme 26). Conformationally restricted donors, such as benzylidene-protected donors, typically yielded glycosyl fluorides, indicating the influence of donor structure on fluoride formation. They showed that glycosyl fluoride was an important intermediate with trichloroacetimidate donors in $BF_3.OEt_2$ activated glycosylation technique. The important thing was that the stability of the intermediate depends on the reactivity of the donor molecules. Low-temperature NMR experiments revealed that, α-TCA donor gave β-fluoride but β-TCA gave mixtures.[43]



Scheme 26. Formation of Fluoride Donor from TCA Donor and its Activation

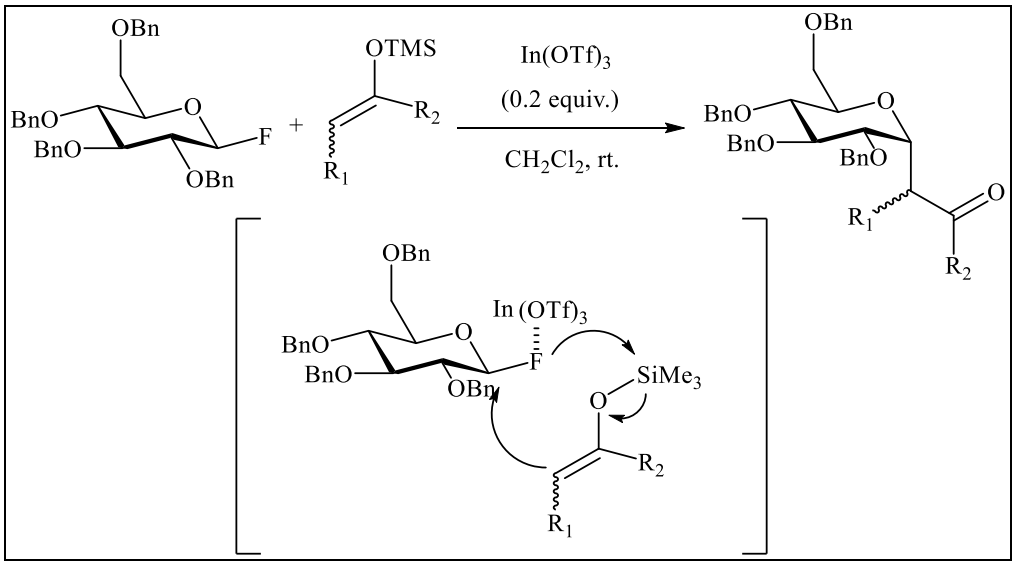
Glucose benzyl glycoside (**26b)** suggests that the formation of glycosyl fluoride in this reaction from the perbenzylated glucosyl trichloroacetimidate donor which was confirmed by mass spectra but isolated yield was not determined.[43]



Scheme 27. *O*-Glycosylation Catalyzed by $In(OTf)_3$

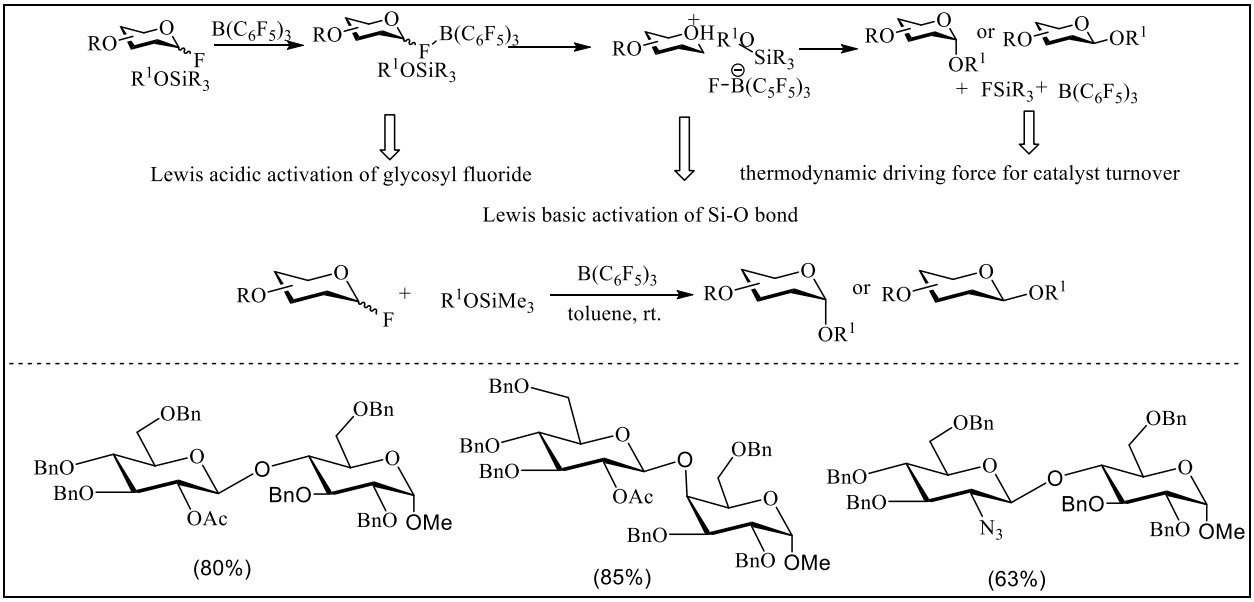
In 2018 Young-Ger Suh and his group developed a highly efficient glycosylation method catalyzed by indium(III) triflate which is mild reaction condition eliminating the need for preactivation steps or complex work-up procedures. The procedure is conducive to a wide array of alcohol acceptors and is compatible with various protecting groups. This methodology allows for both *O*-

(Scheme 27) and *C*-(Scheme 28) glycosylation. They addressed the challenges posed by the C-F bond of glycosyl fluoride and demonstrates that the catalyst operates through a combination of S_N^2 and S_N^1-type mechanisms.[44]



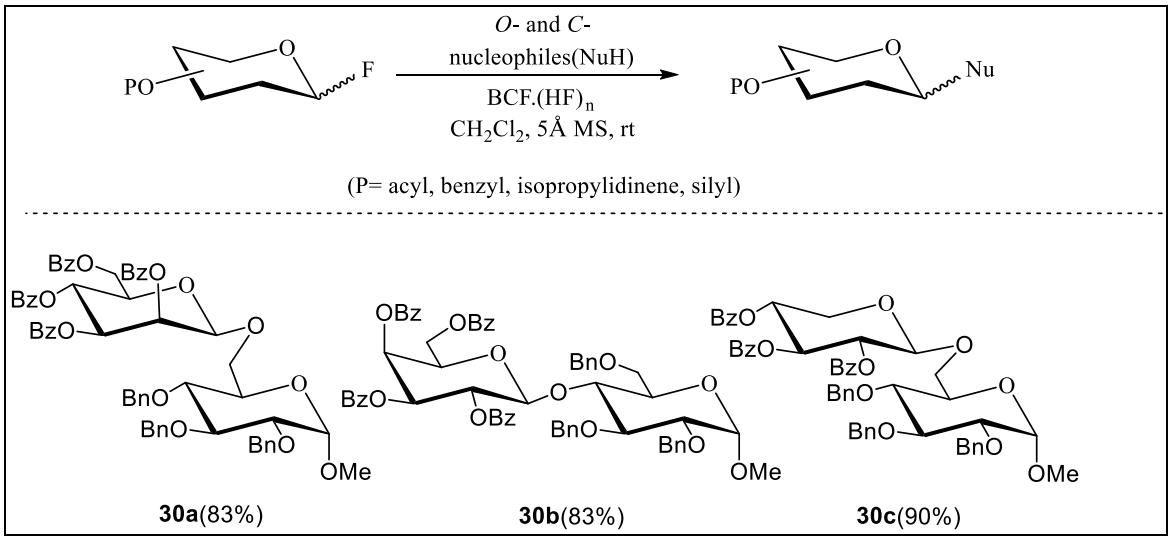
Scheme 28. Indium Triflate-induced Catalytic Glycosylation

A boron-catalyzed glycosylation method using glycosyl fluorides and silyl ethers as a glycosyl acceptors is developed by John Montgomery and his team (Scheme 29). Catalyst $B(C_6F_5)_3$ is used for fluoride abstraction from glycosyl donors and fluoride delivery to silyl ethers to make glycosyl nucleophiles. The reaction proceeds at room temperature, with low catalyst loadings. The approach allows for inter- and intramolecular glycosylations, accessing all possible C1- C2 stereochemical relationships. Iterative, one-pot glycosylations are achieved by controlling the reactivity of hydroxyls through silicon protecting groups. This methodology has several notable advantages, encompassing straightforward reaction setup and ready accessibility of the catalyst, both of which contribute to its exceptional practicality. Furthermore, there is no need for specialist skill or intricate instrumentation sets because the reaction progresses quickly and is finished in just a few minutes.[45]



Scheme 29. Glycosylation with Electrophilic Boron Catalyst

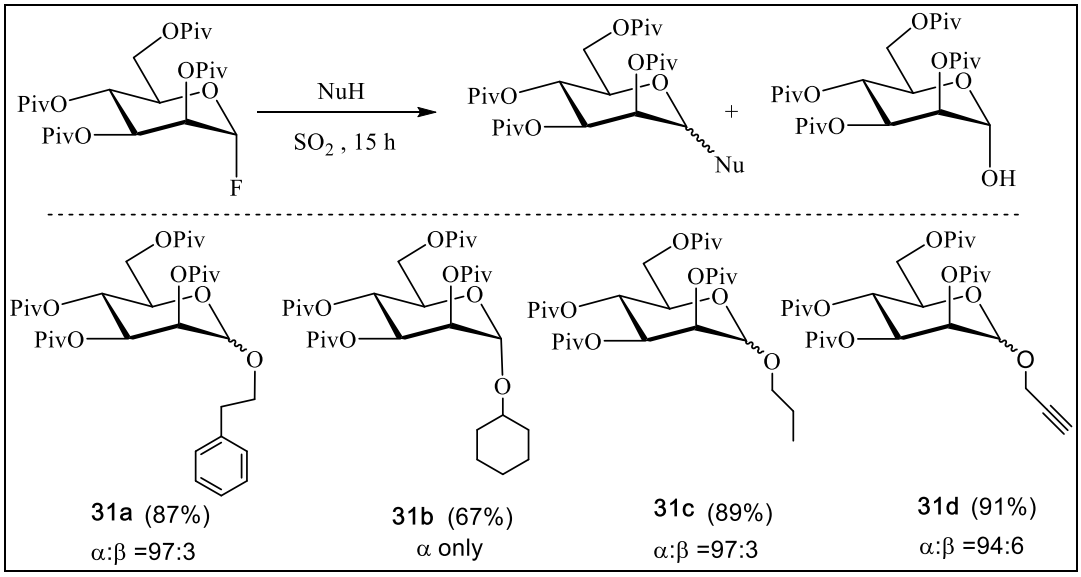
In 2021, Ming Li and colleagues established a glycosylation process by using glycosyl fluoride donors in conjunction with $(C_6F_5)_3B\cdot(HF)n$ as a catalyst (Scheme 30).[46]



Scheme 30. Activation of Glycosyl Fluoride by BCF(HF)n Catalyst

The catalyst, BCF(HF)n, is in-situ generated from the exchange of $BCF(H_2O)n$ with HF, providing the required acidity for glycosylation. The catalytic system enables one-pot synthesis of oligosaccharides based on selective activation of α- and β-glycosyl fluorides, streamlining multistep glycosylation processes. The work highlights the efficiency of Lewis acid assisted Brønsted acid activation for glycosylation. They applied this method over a wide range of glycosyl fluorides in good yields. The method's versatility is demonstrated by successful synthesis of C-glycosides, higher-carbon sugars, and even self-condensation reactions to yield cyclic and anhydro-sugar products.

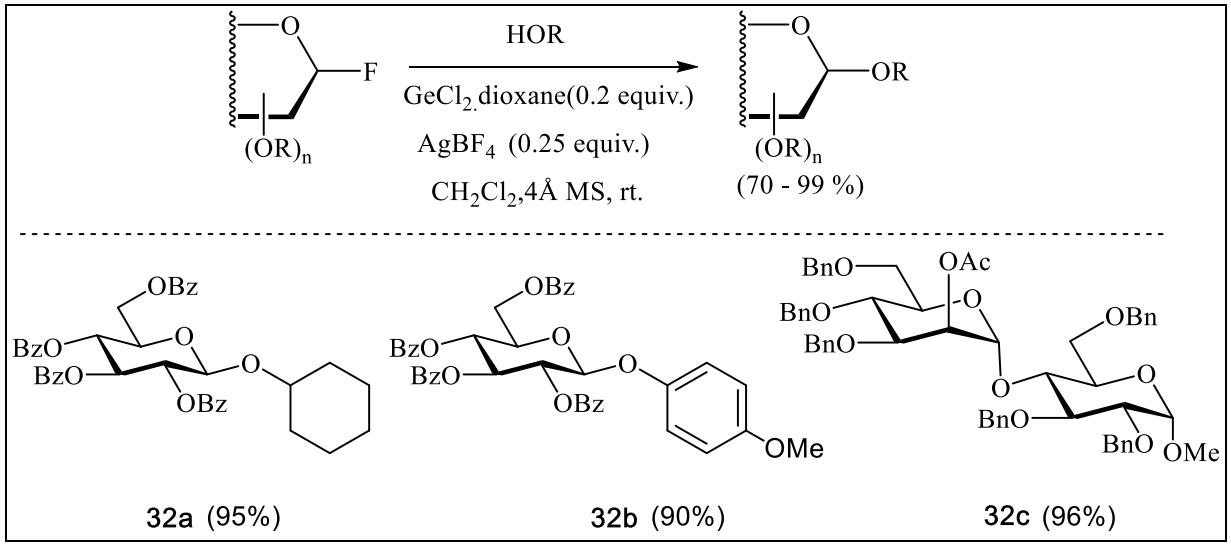
Turks and his group developed a method in which liquid SO_2 serves as a polar solvent with Lewis's acid properties, enabling glycosylation of glycosyl fluorides without external additives in 2021 (Scheme 31). The glycosylation method applies to disarmed and armed glucose and mannose-derived glycosyl fluorides. Glycosylation reactions in liquid SO_2 exhibit substrate-controlled α-selectivity, influenced by the neighbouring protecting groups and the anomeric effect. Stereoselectivity of glycosylation in liquid SO_2 is thermodynamically controlled and substrate-dependent, facilitated by solvent-separated ion pairs. Formation of fluorosulfite species during glycosylation in liquid SO_2 is confirmed using ^{19}F NMR spectroscopy.



Scheme 31. Glycosylation in Liquid SO_2 with Glycosyl Fluoride Donor

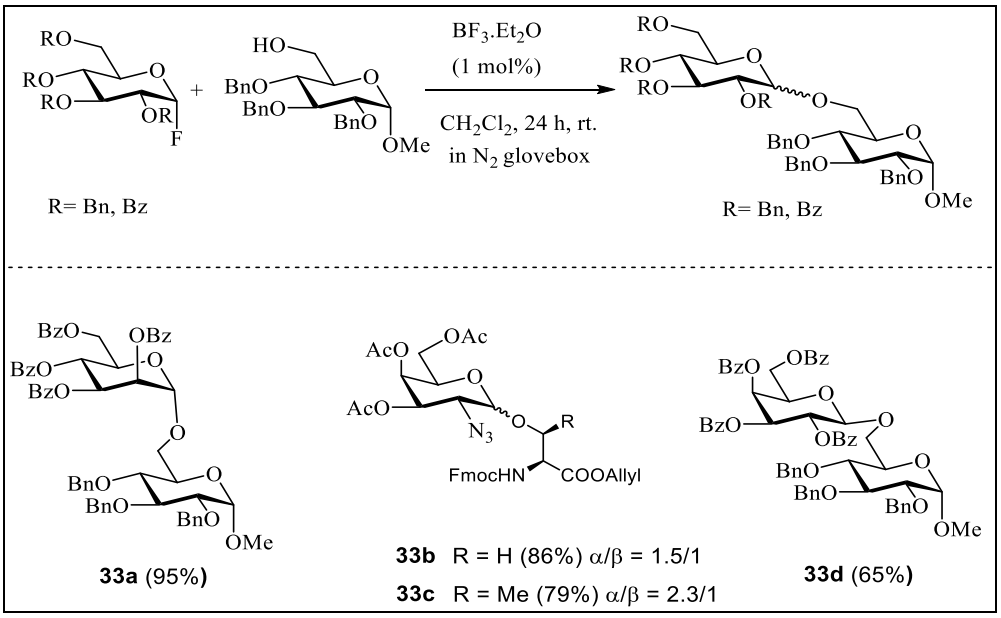
This approach offers an environment friendly, atom-efficient, and metal-free glycosylation strategy with application potential in carbohydrate chemistry.[47]

Biao Yu and his group activated glycosyl fluoride donors with a unique catalytic glycosylation pathway using a combination of $GeCl_2$.Dioxane and $AgBF_4$ as a catalyst (Scheme 32). This system facilitates reversible activation of the anomeric C−F bond. The activation involves reversible bonding between $[Ge(II)-Cl]^+$ cations and the anomeric C−F bond, leading to glycosyl cations and Cl−Ge(II)−F species. The process also includes reversible transfer of chloride ions between Ge(II) species and glycosyl cations. Ge(II) cations were found to be effective activators for glycosyl fluorides, including disarmed peracylated glycosyl fluoride donors. This catalytic system operates at room temperature and offers a broad range of substrate compatibility (Scheme 32).[48]



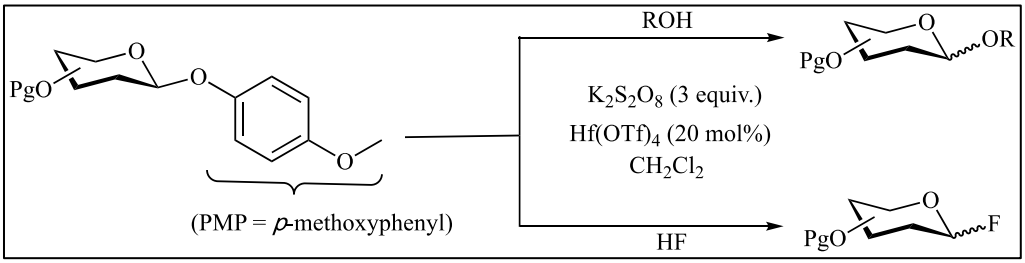
Scheme 32. Activation of Glycosyl-Fluorides Donor by $GeCl_2$.Dioxane-$AgBF_4$

Manabe and his team developed a catalytic glycosylation method using 1 mol% of $BF_3{\cdot}Et_2O$ in glovebox without any dehydrating agents (Scheme 33). The catalytic system efficiently activates both armed and disarmed glycosyl fluorides (difficult to use as a glycosyl donor). The $BF_3{\cdot}Et_2O$-catalyzed glycosylation allows for selective glycosylation by exploiting differences in substrate reactivity. This feature is demonstrated through α-galactosaminylations of serine and threonine selectively.[49]They got kinetically stable β-isomer as the major product. The catalytic glycosylation method offers a practical and efficient approach for synthesizing biologically relevant glycans, such as α-3-deoxy-D-manno-oct-2-ulosonic acid (Kdo) linkages and immunogenic α-galactosides.



Scheme 33. Catalytic Glycosylation with Fluro-glycosyl Donor using $BF_3.Et_2O$

Jaehoon Sim and co-workers reported a glycosylation method with p-methoxyphenyl (PMP) glycosides as stable and accessible glycosyl donors and it will provide glycosyl fluorides by reacting with HF (Scheme 34).



Scheme 34. Glycosylation with *p*-Methoxyphenyl (PMP) Glycosides Donor

The research demonstrates the significance of $K_2S_2O_8$ as an oxidant and $Hf(OTf)_4$ as a Lewis acid catalyst in activating the PMP group, transforming it into a reactive leaving group. Hydroquinone-based leaving groups, like the PMP group, are explored for oxidative activation due to their unique properties, showing potential for application in chemical glycosylation.[50] This new method presents several benefits, including the use of green and inexpensive persulfate salt as an oxidant, versatile compatibility with functional groups and protecting groups, and the ability to produce glycosyl fluorides.

Conclusions

Glycosyl fluoride donors have emerged as powerful tools in glycosylation reactions, offering unique advantages in terms of stereoselectivity, chemoselectivity, and compatibility with diverse substrates. This review has highlighted the recent advancements in fluoride donor-based glycosylation methods, from their synthesis using fluorinating reagents to their activation and application in diverse glycosylation reactions. The development of efficient glycosylation strategies has enabled the synthesis of complex glycoconjugates, furthering our understanding of carbohydrate biology at the molecular level. The versatility and atom-economical nature of glycosyl fluoride donors have paved the way for significant progress in glycoscience, facilitating glycoscience research in health, disease, and drug discovery.

Conflict of interest

The authors do not have any conflict of interest to declare.

Acknowledgements

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