ChemPubSoc Europe

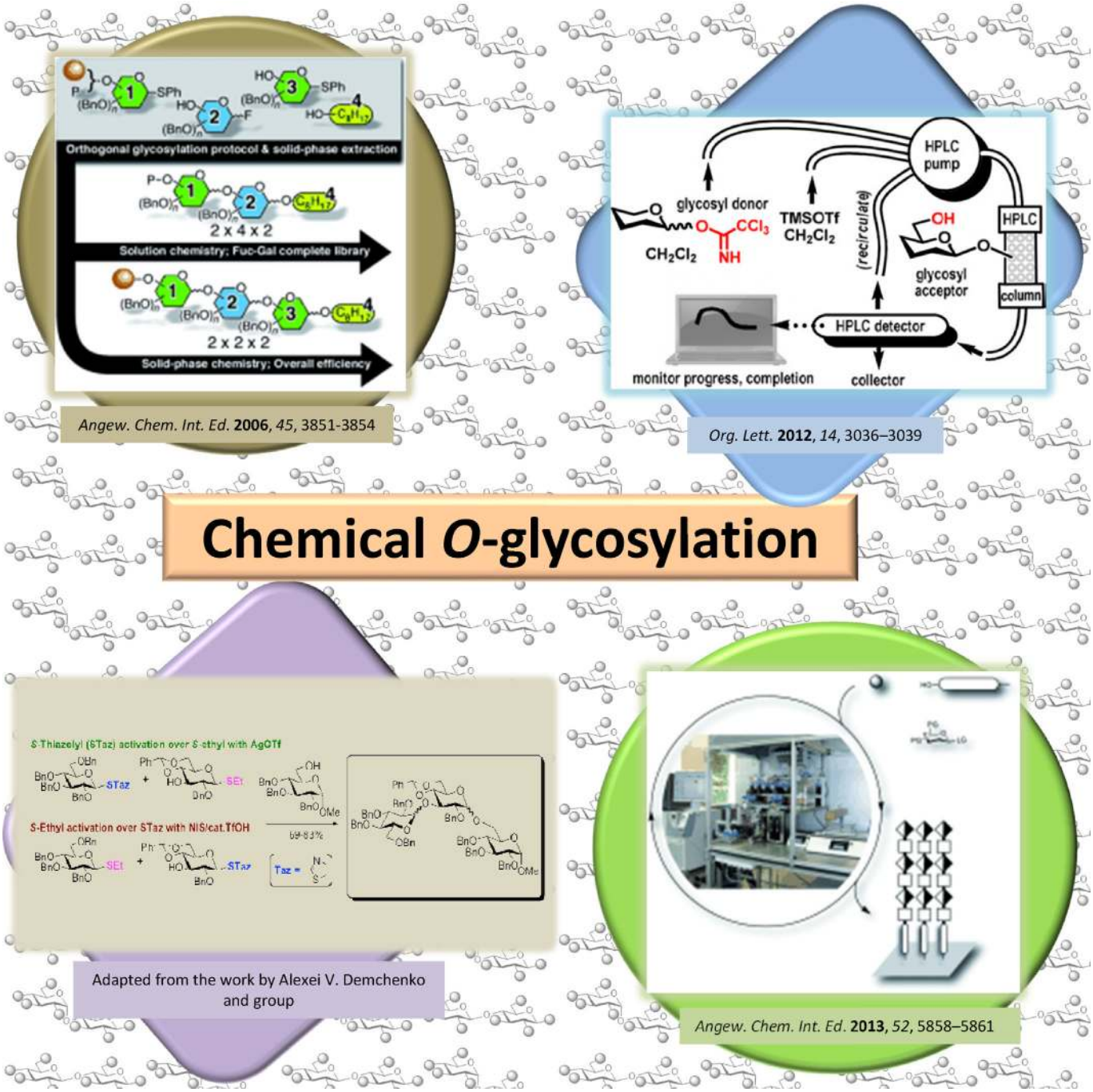
DOI: 10.1002/open.201600043

Open Access ChemistryOPEN Reviews

Chemical O-Glycosylations: An Overview

Rituparna Das* and Balaram Mukhopadhyay*[a]

Dedicated to Prof. Dr. Richard R. Schmidt, University of Konstanz, Germany



The development of glycobiology relies on the sources of particular oligosaccharides in their purest forms. As the isolation of the oligosaccharide structures from natural sources is not a reliable option for providing samples with homogeneity, chemical means become pertinent. The growing demand for diverse oligosaccharide structures has prompted the advancement of chemical strategies to stitch sugar molecules with precise stereo- and regioselectivity through the formation of glycosidic bonds. This Review will focus on the key developments towards chemical O-glycosylations in the current century. Synthesis of novel glycosyl donors and acceptors and their unique activation for successful glycosylation are discussed. This Review concludes with a summary of recent developments and comments on future prospects.

1. Introduction

Carbohydrates, or sugars, have been deemed an important weapon in solving many of nature's mysteries. They are the most diverse and the most abundant biomolecules on earth. Apart from their energy-storage functions, they were only assumed to serve as the structural and protective elements in the plant, bacterial, and animal cell walls.[1] It was only in the later part of the 20th century that the involvement of carbohydrates in various other biological processes[2] became apparent. The renaissance witnessed over the past few years in the field of glycobiology shows that glycoconjugates have enormous significance in various biochemical processes, such as molecular recognition, cell–cell interaction, immunological recognition, transmission of biological information, and so forth.[3] Proper scientific knowledge of the mechanism of these biological processes, in turn, leads to the study of various new applications in biomedical research. These applications invariably lead to the advancement of modern day science, thereby increasing its fundamental interest to scientists.[4] Thus, the demand for homogenous carbohydrate samples and their derivatives for biological research have increased extensively over the past decade.

In nature, carbohydrates exist as polysaccharides, glycoconjugates, or glycosides. But, the isolation of pure carbohydrate samples in sufficient amounts is difficult and cumbersome. In such cases, chemical syntheses of the relevant glyco-structures become pertinent.[5] For the chemical synthesis of complex carbohydrate molecules, the main challenge is to build glycosidic linkages connecting the monomeric units with proper stereo- and regiochemical orientation. Over the last few decades, many new and sophisticated procedures have been established for the successful synthesis of complex oligosaccharides. Thus, development of new methodologies for chemical glycosylation has emerged as an active area of research. More and more intriguing glycosidic bond syntheses are being standardized. However, achieving complete stereocontrol over glycosylation remains an eluding area of carbohydrate chemistry.[6] Hence, optimizing the reaction conditions has long been the basic theme in carbohydrate synthesis.

Various types of novel glycosyl donors for glycosylation reactions have been synthesized and implemented.[7,8] Different activation strategies have been developed for the successful assembly of oligosaccharides from protected building blocks.[9] Solid-phase oligosaccharide synthesis has also made significant progress and is of high interest, as the process avoids the necessity to purify the intermediates.[10] Automated oligosaccharide synthesis has also been developed, which has given a new edge in the field of synthetic oligosaccharide chemistry.[11]

Fundamental concepts of glycosylation have been covered in a wide range of Review articles.[7] In this Review, we aim to indicate all of the different types of donors and their activation protocols, as well as the different types of O-glycosylation processes developed after the onset of the 21st century. We will primarily stick to all newly developed methodologies of O-glycoside formation reported in the 21st century.

2. General Aspects

2.1. Historical Background

Glycosylation, with all of its complexity, has long been a topic of research. The end of the 19th century witnessed the chemical formation of the first aryl and alkyl glycosidic bond formulated by Michael[12] (*p*-methoxy phenyl β-D-glucopyranoside) and Fischer[13] (methyl α-D-glucopyranoside), respectively. Following their lead, Knoenigs and Knorr formulated a more controlled and modified glycosylation protocol.[14] New methodologies are still being developed with more advanced variations in the mechanistic pathways. Later Zémplén and Gerecs,[15] and subsequently Helferich and Wedermeyer,[16] illustrated the principle of the metal(II) salt-induced removal of leaving groups.[17] With the general standardization of glycosyl protocols, efforts were made to control the stereochemical outcome of glycosylations. The requirement for the efficient syntheses of the two anomeric stereoisomers, 1,2-*cis* and 1,2-*trans* glycoside led to more advanced and detailed studies to introduce variation in the mechanistic pathways. The works of Lemieux et al.[18] as well as Ness and Fletcher[19] instigated the importance of the nature of the protecting groups, especially at the C-2 position for its correlation with the stereoselective outcome of the glycosylations. This observation was further documented by Hashimoto et al and Fraser-Reid et al.,[20] whereby the concept of the 'armed–disarmed' approach was initiated, claiming ether linkage at the C-2 position to be arming, leading to the 1,2-*cis*

[a] *Dr. R. Das, Dr. B. Mukhopadhyay*
Department of Chemical Sciences
Indian Institute of Science Education and Research (IISER) Kolkata
Mohanpur, Nadia 741246 (India)
E-mail: sugarnet73@hotmail.com
ritu_iiser@yahoo.com

glycoside, whereas an acyl linkage at the same position yielded the 1,2-*trans* glycoside by virtue of the disarming property and neighboring group participation. Roy et al. introduced the 'active' and 'latent' thioglycoside donors that further expanded the concept of selective anomeric reactivity.[21] The latent-active glycosylation strategy was further utilized by Boons and Isles to form trisaccharide libraries, using vinyl and allyl donors with selective reactivity.[22] Furthermore, Ogawa and co-workers investigated the possibility of using orthogonal glycosyl donors and implemented the 'orthogonal glycosylation strategy' in the synthesis of various oligosaccharides.[23]

The search to find the ideal conditions for an effective glycoside formation revealed various modifications in the already established protocols. Varied promoter systems were implemented, newer activating groups established, and more versatile protecting groups were introduced. With further advanced control on the glycosidic linkages and reaction conditions, one-pot glycosylation also came into vogue.[24] More advances in computational chemistry and subsequent kinetic studies aided in solving the mystery behind the mechanism of glycosylation to a considerable degree. But, despite all of these efforts in the refinement of reaction conditions, the recognition of a single general procedure to describe chemical glycosylation in its entirety is yet to be accomplished.[6]

Rituparna Das was born in 1987 in India. She studied Chemistry at St. Xavier's College (Kolkata, India), where she obtained her B.Sc. in 2009. She then entered the Integrated Ph.D. at IISER Kolkata (India) and obtained her Ph.D. in 2015 under the supervision of Dr. Balaram Mukhopadhyay, working in the field of synthetic oligosaccharide chemistry. Currently, she is a Postdoctoral Fellow in the research group of Dr. Mukhopadhyay, working with glyco-dendrimers focusing on multivalent carbohydrate–protein interactions.

Balaram Mukhopadhyay obtained his Ph.D. in 2001 from the IACS, Jadavpur (India) under the supervision of Prof. Nirmolendu Roy, working in the field of synthetic carbohydrate chemistry. He then continued his Postdoctoral studies at the University of East Anglia (Norwich, UK; 2001–2005) with Prof. Robert A. Field. He started his independent career at CDRI, Lucknow (India) as Scientist-C in 2005. In 2008, he moved to IISER Kolkata (India) as Assistant Professor and became Associate Professor in 2012. His research interests include the synthesis of oligosaccharides, glyco-nanoparticles, and supramolecular chemistry of carbohydrates.

2.2. Anomeric Effect

It was between 1955 and 1958 that Edward and Lemieux first defined the '*anomeric effect*', based on the stereochemistry of the C-1 carbon of the pyranose ring, that is, the *anomeric* carbon.[25,26] It is also referred to as the Edward–Lemieux effect. It was originally defined as the tendency of an electronegative substituent attached to the anomeric carbon to reside in the axial position. However, further studies have revealed various physical interpretations behind it.

A popular and widely accepted theory is based on molecular orbital interaction, employing the hyperconjugation of the nonbonding electron pair on the ring oxygen atom with the vacant σ* orbital of the C–X bond, thereby stabilizing the axial configuration[27] (Figure 1 A). However, extensive computational

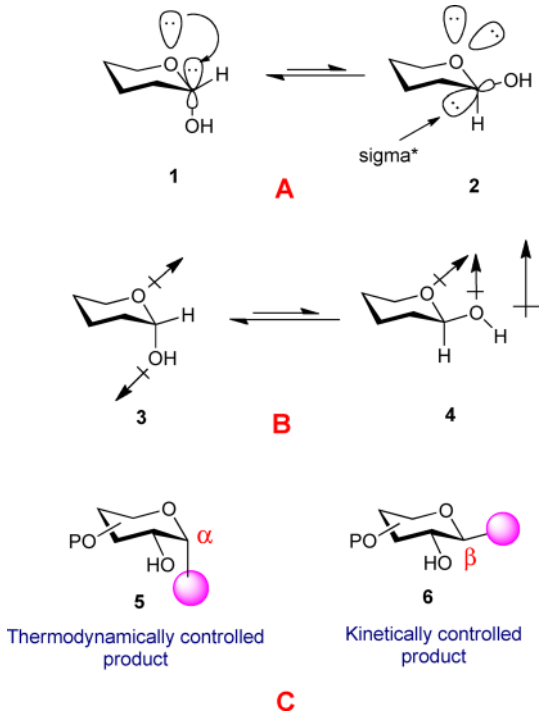


Figure 1. A) Explanation based on molecular orbital theory; B) explanation based on the dipole moment theory; C) the thermodynamically and kinetically controlled product.

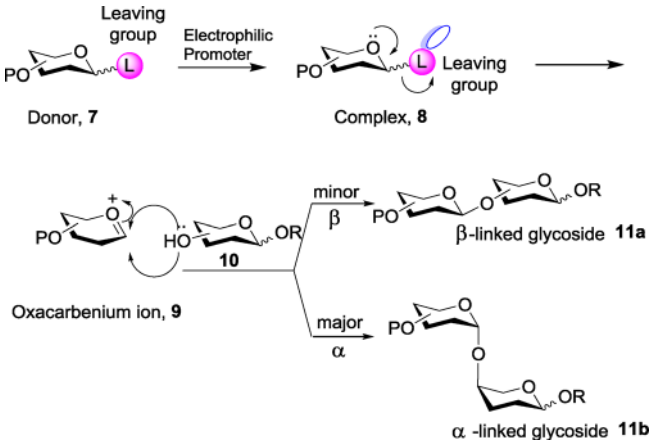
studies revealed that the energy due to hyperconjugation is not the bulk contributor in establishing the energy difference between the axial and equatorial configuration.[28] Further, dipole moment theory[26] says that, in the equatorial isomer, the dipoles of the heteroatoms are partially aligned, thereby repelling each other. But, in the axial configuration, the opposite orientation of the dipoles stabilizes the system by implicating a lower energy barrier (Figure 1 B). Studies have, thus, led to the hypothesis that the dipole–dipole interaction and electrostatic interaction form the bulk of the reasoning behind the conformational preferences of the carbohydrates; whereas, the hyperconjugation is only a minor factor. In view of the explanations, the axial stereoisomer represents the thermodynamical-

ly controlled product, whereas the equatorial isomer represents the kinetically controlled product (except for sugars with axial 2-OH groups like D-mannose and L-rhamnose, where the axial product is both kinetically and thermodynamically controlled) (Figure 1 c).

2.3. Mechanistic Pathways

For proper, methodical chemical synthesis of glycosides, the most important phenomenon involved is called glycosylation. Chemical glycosylation is the coupling of the two monomeric sugar units, with each other or with other aglycons, through the formation of a new linkage, known as the glycosidic bond. The linkage may be of different types depending on the linking heteroatom. Herein, we primarily deal with O-glycosides. However, other heteroatomic glycosides such as C, S, and N glycosides are also widely known in literature. Complete categorization of chemical glycosylation as an S_N1 or S_N2 reactions was tedious, as each theory brought forth many evidences in their support.[29]

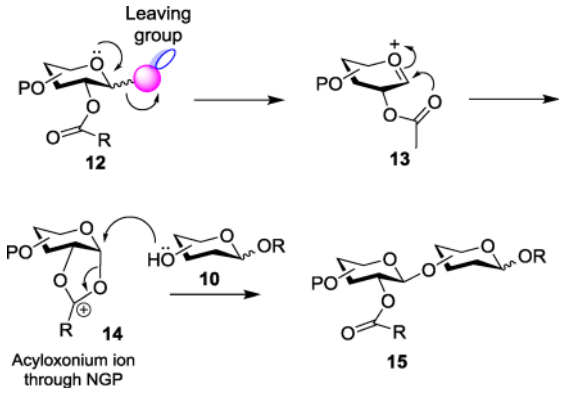
For a more generalized mechanistic pathway (Scheme 1), the donor **7** is first pre-activated with a leaving group attached



Scheme 1. Mechanistic pathway depicting glycosylation.

to its anomeric hydroxyl group. The addition of an electrophilic promoter activates the leaving group of the donor to form complex **8**. The next step initiates the formation of oxacarbenium ion **9** in its flattened half-chair conformation. After this, nucleophilic attack by acceptor **10** occurs, thereby leading to the required glycoside formation **11**. However, the attack of the acceptor can occur via two pathways, owing to the structural property of the oxacarbenium intermediate. The attack of the glycosyl acceptor from the bottom of the sugar ring leads to the formation of alpha (α) or 1,2-*cis* glycoside **11 b**; attack of the glycosyl acceptor from the top of the sugar ring yields beta (β) or 1,2-*trans* glycoside **11 a**. Furthermore, manipulation of the stability of the intermediate oxacarbenium ion remains responsible for the anomerization of the compound.[30]

Presence of a participating acyl group in the C-2 position governs the stereochemistry of the glycosidic bond formed. The oxacarbenium ion formed owing to the departure of the leaving group further (Scheme 2) interacts with the acyl group in the C-2 position to form the acyloxonium ion complex **14** by virtue of neighboring group participation.[31] This enables the acceptor **10** to attack the anomeric carbon from only one side, that is, the 1,2-*trans* side to form the 1,2-*trans* glycoside **15**.



Scheme 2. Mechanism for the formation of 1,2-*trans* glycoside.

For the formation of 1,2-*cis* glycoside **5**, the presence of a non-participating group is required in the C-2 position of the donor molecule. Thus, increasing the stability of the oxacarbenium ion and its various electronic and steric factors may lead to the formation of the more thermodynamically controlled product, caused by the action of the anomeric effect described above (Figure 1 **C**).

Thus, starting from Michael's vision of glycosylation, where the glycosyl acceptor was converted into its corresponding salt,[12] to Fischer's use of hemiacetals as the donor,[13] we have come a long way via Fraser-Reid's idea of 'armed–disarmed' glycosylation.[20b] However, the details of the newer and the more developed concepts in decoding the mystery behind the mechanism of chemical glycosylations are beyond the scope of this Review.[32]

3. Glycosylations

3.1. Glycosyl Halides

3.1.1. Glycosyl Bromides and Chlorides

In 1901, Koenigs and Knorr[14] and Fischer and Armstrong[33] independently introduced the concept of glycosyl halides as donors, where glycosyl chlorides and bromides were reacted with alcohols in the presence of $AgCO_3$ or Ag_2O. Since then, there have been extensive studies on the preparation of glycosyl halides,[34] including the treatment of free sugar units with AcBr[35] (AcBr–AcOH),[36] treatment of *per*-acetylated sugars with HBr–AcOH[37] ($BiBr_3$–Me_3SiBr),[38] and subsequent conversion of the sugar hemiacetals under modified Mitsunobu conditions with PPh_3/*N*-halosuccinimide[39] or PBr_3.[40] However, the harsh conditions in the established protocols often cause difficulties in extensive oligosaccharide synthesis, where acid-labile protecting groups in substrates are a general phenomenon.

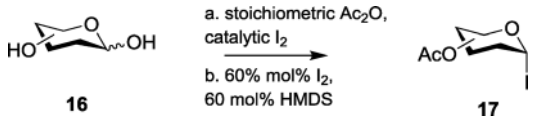
Hence, in the search for more environmentally friendly and greener methodologies, photocatalytic synthesis came into vogue.[41] Likewise, while Mizuno and co-workers established the photo-irradiative phase-vanishing method for α-glycosyl bromide synthesis[42] by applying UV light (irradiation at 352 nm), Xue and co-workers introduced the more versatile visible-light-mediated halide synthesis.[43] However, in the latter case, an additional photocatalyst, tris(2,2′-bipyridyl)ruthenium(II) chloride [$Ru(bpy)_3Cl_2$], was essential. Various protocols for the activation of glycosyl bromides are in use for the synthesis of 1,2-*cis* glycosides with the help of Ag salts (AgOTf, Ag_2CO_3, $AgClO_4$, etc.) or Hg salts [$Hg(CN)_2$, $HgBr_2$, $HgCl_2$, etc.].[44] The versatile use of Ag_2O for glycosyl bromide activation was shown by Beejmohun et al. in the synthesis of monolignol glucosides.[45]

Owing to the restrictions offered by glycosyl halides in terms of their moisture stability and handling, glycosylations with glycosyl halides as donors require optimized low temperatures and inert conditions. Requirement of such conditions was usually managed with various limitations. However, the present century saw the emergence of room-temperature ionic liquids (RTILs), which came as a ready solution for all of the constraints. Malhotra and co-workers[46] implemented a series of RTILs and molten halide salts for the glycosylation of acetabromo-α-D-galactose with *p*-nitrophenol. By virtue of their unique ionic combination and their probable role in the glycosylation pathway, ILs holds the promise of being an extensively used solvent and activator in the future. It has been shown that the activation of glycosyl bromides neat in ILs in the presence of $AgCO_3$ gave β-products in moderate yields.

In terms of reactivity, glycosyl bromides have lower reactivity than glycosyl iodides.[47] However, glycosyl bromides exhibit less stability than glycosyl chlorides. In 2006, Oscarson and co-workers reported the total synthesis of a tetrasaccharide O139 through the activation of glycosyl bromide over its corresponding thioethyl glycoside acceptor by using AgOTf as the promoter.[48] This selective activation process, in turn, marks the initial steps towards more convenient one-pot oligosaccharide synthesis. This method also promotes the selective activation of glycosyl chlorides with the help of AgOTf in the presence of thioglycosides.[49] Recently, Nitz and co-workers reported the activation of unprotected glycosyl chloride donors by using *p*-toluene sulfonylhydrazide and it has been proven to be more reactive than its protected counterpart.[50]

3.1.2. Glycosyl Iodides

The limited shelf-life of glycosyl iodides has always rendered them disadvantageous as donors for glycosylation. This restriction requires the in situ formation of glycosyl iodides and their subsequent involvement in glycosylation. In this context, many research groups have demonstrated reliable methods for generating glycosyl iodides from *per*-O-acetylated sugars through treatment of trimethylsilyl iodide (TMSI)[51] or HI equivalents.[52] The instability of TMSI was addressed by Koreeda and co-workers who utilized the possibility of the synthesis of anhydrous HI by the reaction of solid iodine with a thiol component in an organic solvent.[52a] In line with this, Field and co-workers also generated TMSI in situ by reacting hexamethyldisilane (HMDS) with iodine.[53] The same group further modified their established procedures in 2004, by presenting the synthesis of *per*-O-acetylated glycosyl iodides **16** from unprotected free sugars **15** in significant yields (Scheme 3).[54] This protocol, equipped

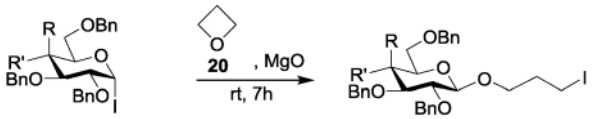


Scheme 3. Preparation of glycosyl iodide from unprotected free sugars.

with a no-solvent system and inexpensive reagents, proved a versatile method, enabling the effective formation of glycosyl iodides.

Field and co-workers later studied the stability, reactivity, and characterization of glycosyl iodides as donors.[55] Over extensive studies, it has been observed that, although glycosyl iodides are usually less effective for glycosylations, many research groups have illustrated its unique advantages over other glycosyl halides in terms of efficiency and stereospecificity.[56] Thus, by using these glycosyl iodide donors, various glycosides have been synthesized. Here, the work of Gervay-Hague and group deserve special mention. They have illustrated how glucosyl, galactosyl, and mannosyl iodides can react with oxa (**20**) and thio cycloalkanes to yield O-glycosides, **21** and **22**, respectively, with high β-selectivity (Scheme 4).[57] They also demonstrated the selectivity with decreasing temperature, where the β-isomer was dominant at lower temperatures (Table 1).[58] The most noteworthy point in this study was the realization that reactions did not require pre-activation of the donor, which is exclusive for glycosyl iodides.

Glycosyl iodides can also be selectively activated in the presence of other donor systems. In this respect, Gervay-Hague and co-workers demonstrated iterative oligosaccharide synthe-

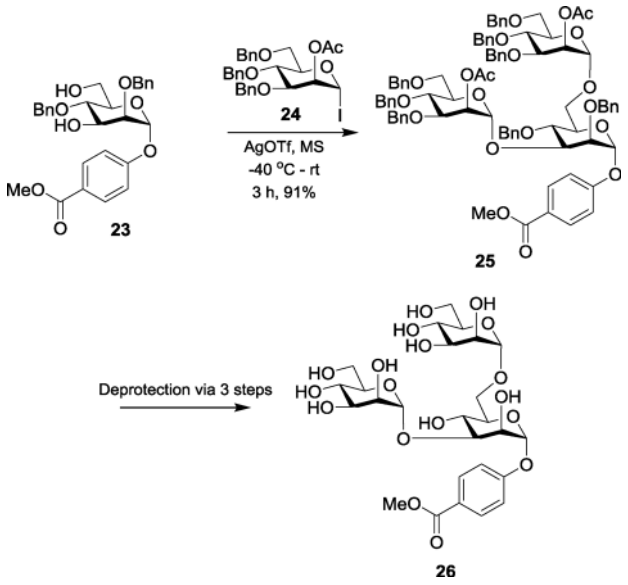


Scheme 4. Synthesis of oxacycloalkane with glycosyl iodides.

Table 1. Dependence of β-selectivity with decreasing temperature.

No.	Donor	Temp [°C]	Time	Yield [%]	α/β ratio
1	18	40	2 h	82	1:2
2	18	0	5 h	76	1:5
3	18	−60	3 days	76	1:29
4	19	40	5 min	83	1:4
5	19	0	30 min	74	1:9
6	19	−60	12 h	73	1:50

sis by selective activation of glycosyl iodides[59] over *per*-O-acetylated glycosyl donors with TBAI/DIPEA. Selective activation of glycosyl iodides over thioglycosides was also implemented, where glycosides were formed though the activation of glycosyl iodides in the presence of triphenylphosphine oxide (Ph_3PO).[60] In another interesting example, Lam and Gervay-Hague[61] illustrated the double glycosylation of an orthogonally protected acceptor **23** with mannosyl iodide **24** by using AgOTf to yield the desired glycoside **25** (Scheme 5).

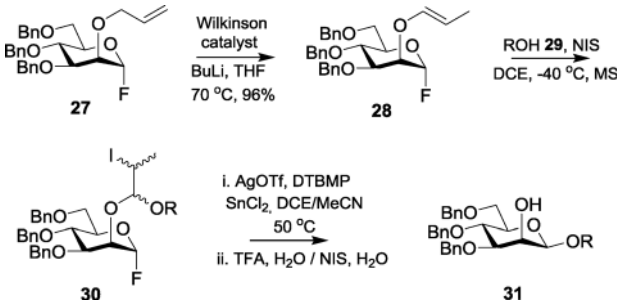


Scheme 5. Synthesis of trimannoside (**26**) through double glycosylation.

Citing more studies in terms of glycoside synthesis,[62] Castillon et al. converted *per*-O-acetylated *iso*-globotrihexose to a glycosyl iodide and coupled it with stannylceramide in the presence of TBAI.[63] In 2014, Gervay-Hague and co-workers activated glycosyl iodides with I_2 to their corresponding reactive glycosyl donors and proceeded towards glycosylation to yield various glycoconjugates.[64] Though there has been much study of glycosylations with typically benzyl-protected glycosyl iodides,[65] Stachulski and co-workers presented a detailed study of glycosylation reaction of 'disarmed' glycosyl iodides with various types of alcohols promoted by the NIS–I_2–TMSOTf system.[66] Various types of 'non-heavy-metal' salts were also demonstrated as effective catalysts in the formation of α-glycosides. Thus, it is evident that the promoter systems required for glycosyl iodides are widely varied. Glycosylations with glycosyl iodides have been reviewed extensively by Murakami et al.[67]

3.1.3. Glycosyl Fluorides

Mukaiyama et al.[68] asserted the activation of glycosyl fluorides by $SnCl_2$–$AgClO_4$ and their role as glycosyl donors. Their versatility resides in their readily accessible nature and their higher thermal and chemical stability compared to other glycosyl halide counterparts. After the onset of the 21st century, the synthesis of glycosyl fluorides has been broadly developed and used for glycoside formation.[69] The IPy_2BF_4-catalyzed synthesis of glycosyl fluorides from thioglycosides was reported in 2007,[70] which provided the best output being activated by TfOH, which mechanistically formed a co-ordination complex with the pyridine moiety to liberate the iodonium species. More successful illustrations of glycosyl fluoride synthesis from thio-, seleno-, telluro-, and *n*-pentenyl glycosides have been reported.[71] Kanie and co-workers used *N*,*N*-diethylaminosulfur trifluoride (DAST) in the absence of N-bromosuccinimide (NBS).[72] Dimethyl(methylthio)sulfoniumtrifluoromethanesulfonate (DMTS) was used as a substitute for NBS to give excellent yields. Glycosyl fluorides have also been widely used for intramolecular aglycon delivery (IAD) in the synthesis of β-mannosides (Scheme 6).[73]



Scheme 6. β-Mannoside synthesis from glycosyl fluorides through IAD.

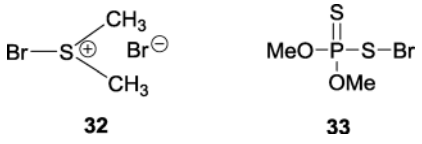
For the next generation of oligosaccharide synthesis, selective activation of donors based on their activating groups is a major area of research. There has been much research aimed toward selective activation of glycosyl fluorides.[74] Mukaiyama et al. selectively activated glycosyl fluorides over thioglycosides by using catalytic amounts of TfOH, $HClO_4$, or $C_4F_9SO_3H$.[75] Interestingly, in a report by Yang and Yu in 2014,[76] there is an illustration of the use of glycosyl fluoride as an acceptor in the presence of a thioglycoside donor for the synthesis of disaccharide in its fluoride form, which could subsequently be activated in the presence of a thioglycosides acceptor to form the trisaccharide. Glycosyl fluorides can also be activated in the presence of glycols with the help of $Sn(OTf)_2$.[77] Thus, these selective activation protocols are stepping stones for the formulation of more versatile iterative and automated oligosaccharide syntheses. Utilizing the different activation protocols, these donors have helped in the broader aspect of natural product syntheses.[8]

3.2. Thioglycosides

Thioglycosides are the most versatile glycosyl donor in oligosaccharide synthesis. Although the anomeric thio functionality is highly stable towards varied protecting-group manipulations, it can be activated under extremely mild conditions and, hence, can be used in varied types of glycosylation conditions. The soft sulfur atom provides easy and selective reactivity with soft electrophiles. Various modifications have been made to

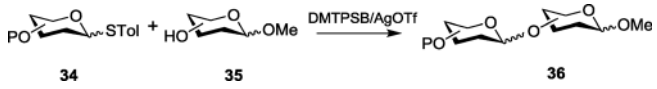
the nature of thioglycosides over the years and many novel and mild promoter systems have been developed. The present century has seen modification in the use of harsh thiophilic promoters like Hg^{2+}, Cu^{2+}, and Ag^{+} salts to halonium ions, which have more thiophilic character. They revealed the promise of being activated under highly moderate conditions. Starting with the use of NBS[78] to activate armed thioglycosides, much progress has been made in utilizing bromonium and iodonium salts for the activation process with promoters like $NOBF_4$,[79] NBS/TfOH,[80] Br_2/AgOTf,[81] NIS/HOTf or AgOTf,[82] IDCP (iodoniumdicollidine perchlorate),[83] IDCT (iodonium *sym*-collidiniumtriflate),[84] I_2,[85] PhIO/Tf_2O,[86] and Ipy_2BF_4.[70]

In an attempt to develop more versatile promoter systems, Ye and co-workers implemented the 'soft' nature of the bromonium species to report a bromodimethylsulfonium bromide (BDMS)/AgOTf[87] system for the activation of thioglycosides. The low cost and easy accessibility of the BDMS (**32**) catalyst made it an effective glycosylating promoter (Figure 2). In a similar attempt, the same group went on to establish an O,O-dimethylthiophosphonosulfenyl bromide (DMTPSB)–AgOTf[88] (**33**) system for the pre-activation of thioglycosides and subsequent glycosylations (Scheme 7).



32 33

Figure 2. 32: bromodimethylsulfonium bromide (BDMS); **33**: O,O-dimethylthiophosphonosulfenyl bromide (DMTPSB).

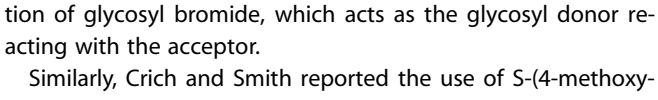


34 35 36

Scheme 7. Synthesis of a disaccharide with DMTBSB/AgOTf as the promoter.

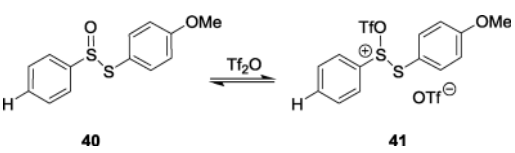
The presence of bromine was also shown to activate β-ethyl thioglycoside **37** to provide disaccharide **39** as the exclusive α-linked diastereomer (Scheme 8).[89] Interestingly, the mechanistic rationale behind such activation lies in the in situ generation of glycosyl bromide, which acts as the glycosyl donor reacting with the acceptor.

Similarly, Crich and Smith reported the use of S-(4-methoxyphenyl) benzenethiosulfinate (MPBT, **40**) and trifluoromethanesulfonic anhydride (Tf_2O)[90], which react with each other to form an electrophile **41**, aiding the in situ conversion of thioglycosides to their corresponding triflates. These glycosyl triflates were further implemented for the generation of the challenging β-mannoside linkages (Scheme 9). 1-Benzenesulfinyl piperidine (BSP) and Tf_2O[91] also served the same purpose, and it was further used for double glycosylation, using carbohydrate diol as the acceptor **43** (Scheme 10). Later, van der Marel and co-workers proved the versatility of the system successfully applied the system.[92]



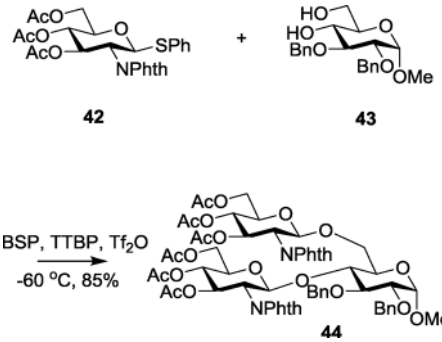
37 38 39

Scheme 8. Glycosylation with Br_2 as the promoter.



40 41

Scheme 9. Activation of MPBT.

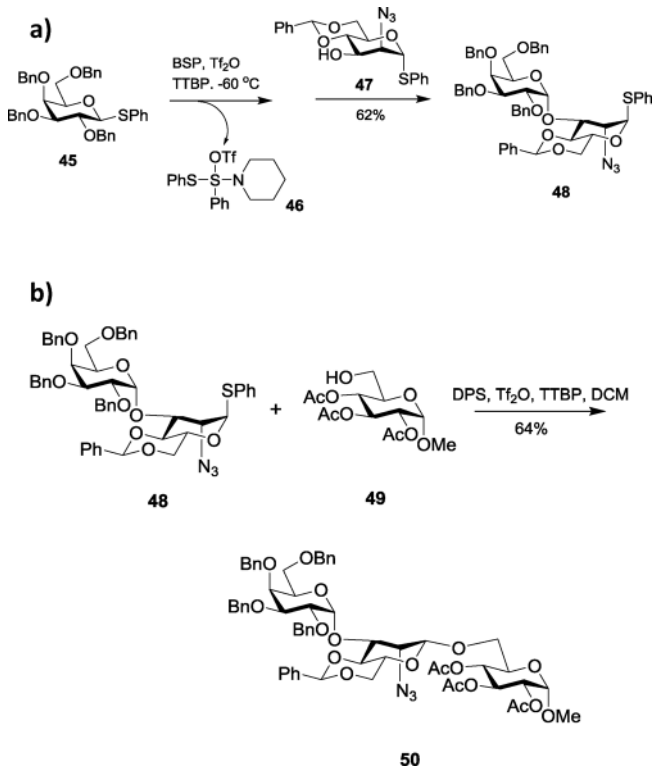


42 43 44

Scheme 10. Example depicting double glycosylation.

Van der Marel et al.[93] also introduced the diphenyl sulfoxide (DPS)–triflic anhydride combination for thioglycoside activation in β-mannoside synthesis. They first activated a relatively armed thioglycoside **45** with the BSP/Tf_2O activator system and coupled it with a thio acceptor **47** to yield disaccharide **48** in its thio form (Scheme 11 a). (*N*-piperidino)phenyl(*S*-thiophenyl)sulfide triflate (**46**) is formed as a by-product. After quenching the by-product with triethylphosphite, thio-disaccharide **48** was activated with a more versatile DPS/Tf_2O activator system for its coupling with another monosaccharide **49** for successful glycosylation (Scheme 11 b). This example extensively illustrates the difference in reactivity between the two activator systems. Similar pre-activation of thioglycosides have also been achieved by benzenesulfinylmorpholine (BSM)–Tf_2O[94] as well as Me_2S_2–Tf_2O,[95] and was further utilized for glycosylation through both primary and secondary hydroxyl groups.

Thioglycosides, owing to their unique reactivity pattern, are promising candidates for one-pot oligosaccharide synthesis. To establish this system, Wong and co-workers implemented the novel reagent *N*-(phenylthio)caprolactum for thioglycoside activation at room temperature.[96] *N*-(Phenylthio)caprolactam was first reacted with Tf_2O, which further proceeded for thio-

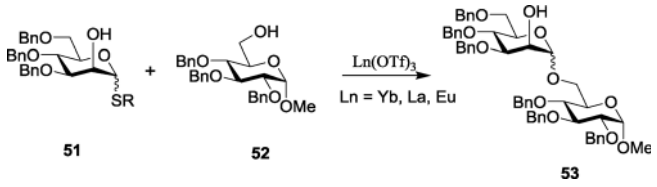


Scheme 11. a) Pre-activation of the donor. b) Subsequent glycosylation with DPS and TTBP as the promoter in the presence of Tf_2O.

glycoside activation. In a similar example, instead of Tf_2O, TMSOTf was used for the pre-activation of *N*-(*p*-methylphenylthio)-ε-caprolactam by Ghosh and co-workers.[97] They also reported the use of trichloroisocyanuric acid (TCCA),[98] a readily available, inexpensive, and shelf-stable reagent, in combination with a catalytic amount of TMSOTf for the efficient activation of the thioglycosides.

In 2000, Takeuchi et al.[99] introduced the activation of disarmed thioglycosides through the combination of trityltetrakis(pentafluorophenyl)borate [$TrB(C_6F_5)_4$], iodine, and DDQ. On a similar hypothesis, they also put forward another activator system, PhthNSEt in the presence of $TrB(C_6F_5)_4$.[100] The same complex was used in presence of both NIS and NBS for successful glycosylations.[101]

Various lanthanide(III) salts were also introduced for the activation of the thioglycoside donors. Employing the concept of lanthanide-ion co-ordination, Chung and Park reported a comparative study by using various lanthanide(III) salts to envisage the noncovalent approach of the IAD strategy in the process of the formation of β-mannosides.[102] The Lewis acidity and high co-ordination numbers of the lanthanide salts were considered to be highly favorable for the desired co-ordination. Yb^{III} and Eu^{III} were especially effective (Scheme 12) in the presence of NIS–TfOH as the activator system (Table 2).



Scheme 12. Glycoside formation with the help of lanthanide(III) salts.

Thus, NIS–NBS-based activator systems that were introduced long ago saw a number of important modifications after the onset of the 21st century. Mukaiyama and co-workers used TrOTf[103] in conjunction with NIS for the convergent synthesis of oligosaccharides. Simultaneously, Li and co-workers used Me_3SiOTf with both NIS and NBS for the activation of phenyl and ethyl thioglycosides to introduce spacer arms.[104] Moreover, the catalyst system involved for effective glycosylations demands highly moisture tolerant properties. In that respect, Mukherjee and Mukhopadhyay reported the use of $La(OTf)_3$ as the Lewis acid activator with NIS for the activation of disarmed thioglycoside donors,[105] which, by virtue of its solid nature and moisture-tolerant capability, became more effective than other traditional reagents like TfOH or TMSOTf.[106] Similarly, supported acid catalysts became interesting alternatives to traditional Lewis acid promoters. $HClO_4$–silica was used for the activation of 'disarmed' thioglycosides in conjunction with NIS in 2005 by Field and co-workers,[107] which promised to be a better protic acid source under milder and safer reaction conditions. Later, Mukhopadhyay and co-workers introduced a better and environmentally friendly H_2SO_4–silica system for the same purpose.[108] The good availability of H_2SO_4–silica and its effective desiccant properties were reasons for its wide use for various bacterial and plant oligosaccharide syntheses in moderate to high yields (Figure 3).[109] Specific acid-washed

Table 2. The activation of glycosyl sulfoxide using different La^{III} salts.

No.	Ln[OTf]$_3$ (equiv)	Activator	Solvent	Temp [°C]	Time	Yield [%]	α/β
1	Yb (1)	Tf_2O	CH_2Cl_2	−78→RT	10 h	63	1:2
2	Yb (1)	Tf_2O	CH_3CN	−40→RT	12 h	63	1:2.8
3	Yb (1)	NIS	CH_2Cl_2	RT	20 min	47	1:1.5
4	Yb (1)	NIS–TfOH (cat.)	CH_2Cl_2	−78	8.5 h	59	1:2.9
5	Eu (1)	Tf_2O	CH_2Cl_2	−78→RT	10 h	76	1:1.5
6	Eu (1)	Tf_2O	CH_3CN	−40→RT	10 h	82	1:4.3
7	Eu (1)	NIS	CH_2Cl_2	RT	20 min	48	1:2
8	Eu (1)	NIS–TfOH (cat.)	CH_2Cl_2	−78	6 h	64	1:3
9	La (1)	Tf_2O	CH_2Cl_2	−78→RT	12 h	51	1.7:1

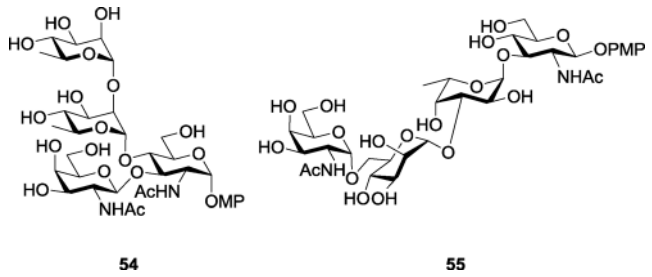


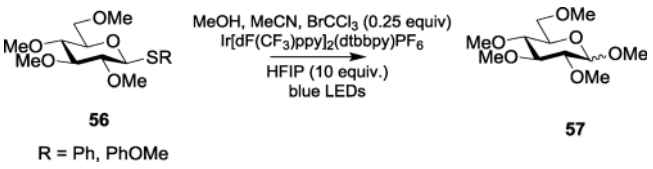
Figure 3. Oligosaccharides synthesized with H_2SO_4–silica as the promoter.

molecular sieves (AW-300 MS) along with NIS have also been shown to function as glycosylation promoters by Yao and Lee.[110] Owing to its ease of handling and storage, and its capacity to scavenge water, AW-300 MS proved beneficial as a Lewis acid in the NIS-mediated glycosylation of thioglycosides.

For expeditious oligosaccharide synthesis, various modifications in the protecting groups and the catalyst in the presence of NIS/NBS-based promoters have been widely investigated. Périon et al. have used both $Sn(OTf)_2$ and $Cu(OTf)_2$ to perform critical glycosylation with the fucosyl donor by varying the protecting group in its C-4 position.[111] In another example, a stoichiometric amount of NBS was used with $Bi(OTf)_3$ for the activation of alkyl and phenyl thioglycoside donors by Valerio et al.[112]

Introducing a novel promoter-free glycosylation technique, Pohl and co-workers efficiently used sub-stoichiometric amounts of triphenyl bismuth ditriflate [$Ph_3Bi(OTf)_2$] to activate various thiopropyl glycosides.[113] The highly robust nature and solubility of bismuth(V) salts made it a highly advantageous glycosylation catalyst, employing just catalytic amounts of the promoter. This glycosylation protocol opened more doors to investigate elegant glycosylations without the involvement of any co-promoter. In sync, Vibhute et al. recently showed that only 3 mol% of $AuCl_3$ catalyst was sufficient to trigger thioglycoside activation.[114]

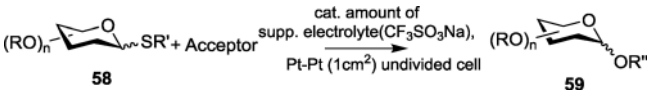
Light-induced activation of thioglycoside donors has also been investigated.[115] In 2013, Bowers and co-workers demonstrated the efficient use of visible light for mediating O-glycosylation through the activation of thioglycosides.[116] $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ was used as the catalyst to oxidize an electron-rich aryl thioglycoside, yielding an oxocarbenium-ion intermediate. Then, effective glycosides were obtained in the presence of bromotrichloromethane and a non-nucleophilic and protic solvent, hexafluoroisopropanol (HFIP) (Scheme 13). The proposed mechanism involved the unique visible-light-activated single-electron oxidation of sulfur. In a similar mechanism, photosensitizer $[Ru(bpy)_3]^{2+}$ was used along with DTBMP for the activation of thioglucosides.[117] Recently, glycosylations avoiding the use of photosensitizers were also reported, where UV irradiation was used to cleave the C–S bond[118] and $Cu(OTf)_2$ was oxidized to generate the species capable of undergoing glycosylation. In a similar proposal, O-glycosylation of unprotected deoxythioglycosides was also performed with alcohols in the presence of DDQ under



Scheme 13. Light-induced activation of thioglycoside donor.

long-wavelength UV irradiation through the single electron transfer (SET) mechanism.[119] During the process, a boronic acid was used as a temporary protecting group for the glycosyl donors to prevent self-coupling or formation of 1,6-anhydro glycoside.

Bennett et al. reported the use of air- and water-stable iodonium salt phenyl(trifluoroethyl)-iodoniumtriflimide to activate a wide array of both armed and disarmed thioglycosides for glycosylation at room temperature.[120] A special advantage of this process is that low-temperature reactions or additives used to remove water from the reaction, such as molecular sieves, are not necessary. Electrochemical O-glycosylation of primary alcohols with thioglycoside donors have been reported by Nokamia and co-workers[121] in the presence of a small amount of sodium trifluoromethansulfonate as the supporting electrolyte (Scheme 14).



Scheme 14. Electrochemical O-glycosylation.

3.3. Glycosyl Imidates

Glycosyl imidates represent another versatile leaving group in addition to the thioglycosides, whose extensive use in the domain of oligosaccharide glycosylations is noteworthy.

3.3.1. O-Imidates

Since its inception by Schmidt et al. in 1980,[122] glycosyl trichloroacetimidates and trifluoroacetimidates have become widely used glycosylating reagents. Glycosyl trichloroacetimidates can be readily prepared through the base-promoted addition of an anomeric hydroxyl group to trichloroacetonitrile, using either inorganic (NaH, K_2CO_3, Cs_2CO_3, etc.) or organic (DBU) bases. Imidate-based glycosylations require strong Lewis acids like TMSOTf,[123] $BF_3{\cdot}Et_2O$,[124] TBDMSOTf,[125] Tf_2O,[126] $ZnBr_2$,[127] or AgOTf[128] and moisture-stable activating reagents such as I_2/Et_3SiH.[129]

In special cases, such as fructofuranosides, where the synthesis of the trichloroacetimidate donor proved to be challenging, *N*-phenyltrifluoroacetimidate was established as an efficient substitute.[130] The leaving group showed effective α-selectivity when performing glycosylations with various flavonoids.[131] Their versatility has also been effectively established in the syn-

thesis of kaempferol derivations by virtue of its subsequent activation with $BF_3{\cdot}Et_2O$.[132] Versatility of $BF_3{\cdot}Et_2O$ over TMSOTf for the activation of trichloroacetimidate or (*N*-phenyl)trifluoroacetimidate donors, leading to the selective formation of 1,2-*trans* glycosides in high yields, has been widely studied.[133] However, with more recent studies in 2012, Cloninger and co-workers have established that In^{III} salts serve as even better and more effective promoters than $BF_3{\cdot}Et_2O$ for performing glycosylations with glycosylacetimidate donors.[134] To establish the novelty of the salts, $InCl_3$, $InBr_3$, and $In(OTf)_3$ were reacted with various protecting-group-manipulated glycosyltrichloroacetimidate donors,[134] and all of them led to the formation of the glycosylated products in high yields.

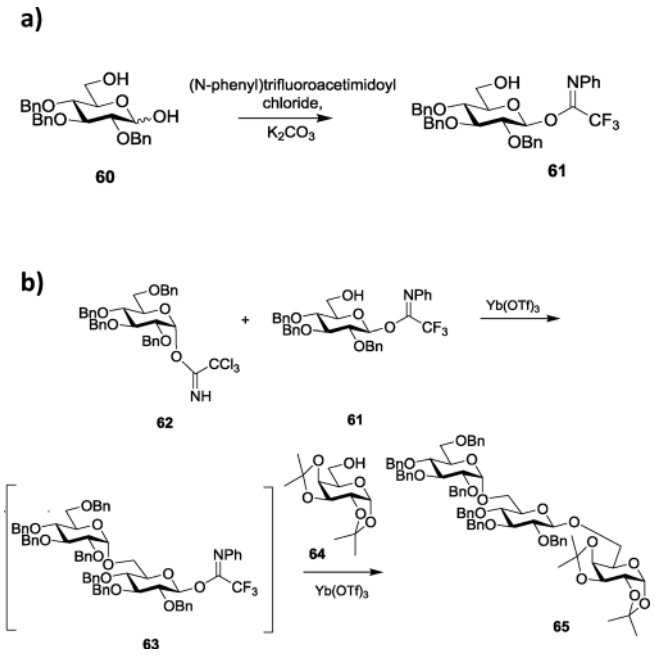
Use of iodine for the activation of armed and disarmed acetimidates was reported by Iadonisi and co-workers.[129] Addition of a catalytic amount of triethylsilane to trigger the in situ generation of HI was the key step for such an activation strategy. The same group previously[135] established the use of catalytic amounts of $Sm(OTf)_3$ to activate armed glycosyl trichloroacetimides. In analogous conditions, salts of other lanthanides like $Sc(OTf)_3$, $Tb(OTf)_3$, and $Yb(OTf)_3$ were also used to activate trichloroacetimidate donors and promote glycosylations at room temperature.[136] A catalytic amount of $Yb(OTf)_3$ was also efficient for performing one-pot glycosylation of glycosyltrichloro- and (*N*-phenyl)trifluoroacetimidates.[137]

The similar activation properties of trichloro- and trifluoroacetimidates led to studies comparing their reactivities, which proved trichloroacetimidates to have more reactivity than glycosyl trifluoroactimidates.[138] For instance, the readily accessible glucopyranose **60** was reacted with (*N*-phenyl)trifluoroacetimidoyl chloride in the presence of a slight excess of K_2CO_3 in acetone to yield the trifluoroacetimidate derivative **61**, which was then reacted with a trichloroacetimidate glycoside **62** in the presence of a catalytic amount of $Yb(OTf)_3$, where the more reactive compound, **62**, was readily consumed to yield disaccharide **63**. In the same pot, acceptor **64** was added with extra catalyst at room temperature to give the required trisaccharide **65** (Scheme 15 a, b). To reduce the toxicity involved in the use of lanthanide salts, they also reported the alternate use of $Bi(OTf)_3$ for the activation of perbenzylatedtrichloro (*N*-phenyl)trifluoroacetimidate glycosyl donors.[139]

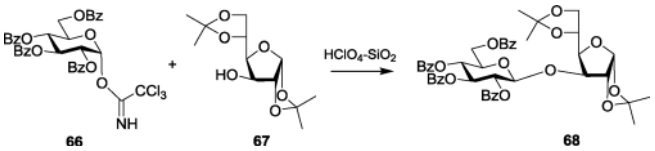
Considering the high effectiveness of the catalyst in thioglycosides activation, Linhardt and co-workers introduced easily accessible and environmentally benign $HClO_4$–silica (optimized to 100:3 molar ratio) to perform the glycosylation with trichloroacetimidates (Scheme 16).[140] This activation also allowed glycosylations with glycosides having various protecting-group manipulations, giving excellent yields. In sync, Gildersleeve and co-workers also used $HClO_4$–silica for enhanced α-selectivity.[141] The moisture stability and easy handling of the catalyst made it highly useful in performing glycosylations with glycosyl trichloroacetimidates.

Similarly, acid-washed molecular sieves (4 Å AW-300 MS) have also been used to activate trichloroacetimidates along with the thioglycoside donors.[142] Its moisture-absorbent property was the key factor behind its successful use in glycosylations. The use of Amberlyst 15 H^+ acidic resin has also been reported.[143] β-Mannosylation was also performed by Fukase and co-workers with suitably protected *N*-phenyl trifluoroacetimidatemannosyl pyranoside by utilizing $TMSB(C_6F_5)_4$, which served as a dual Lewis acid/cation trap catalyst.[144] Reactions with sensitive glycosyl trichloroacetimidates were achieved by Kunz et al.[145] by using an Au catalyst, which provided high α-diastereoselectivity. Subsequently, Vankar and co-workers studied the application of gold catalysts in glycosylations and modified it to use $AuCl_3$ and the $AuCl_3$–phenylacetylene combination, which acted as good activators, both[146] for armed and disarmed trichloroacetimidates. Notably, in this case, high β-stereoselectivity was obtained. Recently, further investigation into gold catalysts by Peng and Schmidt has demonstrated the successful synthesis of glycosides with trichloroacetimidate donors[147] via an intramolecular dual catalysis pathway, where $AuCl_3$ acted as an initiator for the formation of catalyst–acceptor adducts. Interestingly, they obtained high β-stereoselective products even with the use of armed glycoside donors.

A commercially available cationic Pd^{II} reagent, $Pd(CH_3CN)_4(BF_4)_2$, was used by Nguyen and co-workers[148] as the Lewis acid, because of its vacant d orbitals. The easily accessible Pd salt has, thus, been used for stereoselective glycosylations with trichloroacetimidate donors to give exclusive α-products. The use of a larger mol% of the Pd^{II} source gave



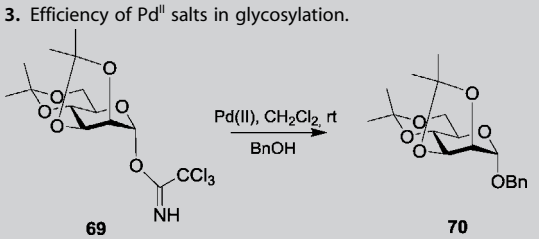
Scheme 15. a) Synthesis of (*N*-phenyl)trifluoroacetimide glycosyl donor. b) Glycosylations using O-imidates.



Scheme 16. Glycosylation of trichloroacetimidate donor with $HClO_4$–SiO_2 as the promoter.

a higher yield, whereas the use of additives like DTBP with the same amount of Pd^{II} source did not show much difference in the yield (Table 3). To facilitate the synthesis of β-glycoside products, Baati and co-workers used $TMSNTf_2$ as an efficient promoter in the glycosylation reaction when using *per*-methacrylated Schmidt reagents.[149]

Table 3. Efficiency of Pd^{II} salts in glycosylation.



69 70

Entry	Pd [II] source	Pd^{II} [mol%]	Additive	Time [h]	Yield [%]	α/β
1	$Pd(CH_3CN)_4(BF_4)_2$	3	none	5	70	α only
2	$Pd(CH_3CN)_4(BF_4)_2$	5	none	3	85	α only
3	$Pd(CH_3CN)_4(BF_4)_2$	5	DTBP	4	83	α only

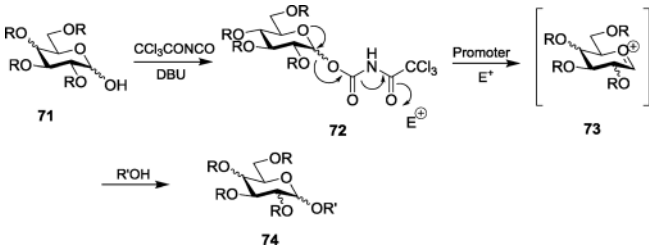
Photoinduced reactions have attracted much interest in the last few years. Organic photoacids have been implemented for the activation of trichloroacetimidates under photoirradiation.[150] An organic photoacid excited upon photoirradiation subsequently activates glycosyl imidates and facilitates coupling with corresponding alcohols as acceptors.

In addition to trichloro- and *N*-phenyl trifluoroacetimidate, trichloroacetyl carbamate glycosyl donors have also been reported to be effective glycosyl donors. Glycosyl trichloroacetyl carbamate synthesized upon reaction of the hemiacetal **71** with trichloroacetyl isocyanate at 0 °C was utilized as the donor for performing glycosylation with various acceptors, using a catalytic amount of TMSOTf as the promoter (Scheme 17).[151] Many other electrophilic promoters have been used for the activation of such donors. Interestingly, $Zn(OTf)_2$ was unable to activate the imidate donor, whereas the glycosylation with TfOH and $Sc(OTf)_3$ was seen to proceed moderately. The same reaction was slow with other Lewis acids such as $Mg(ClO_4)_2$ and $Cu(OTf)_2$, even at room temperature. However, the reaction provided high yields of glycosylated products with $TMSClO_4$.[152] Selective activations in different promoter systems invariably hold promise for the use of such imidate donors in iterative one-pot glycoside synthesis.

O-Glycosyl trichloro cyano acetimidates have also been popular as powerful glycosyl donors.[153] To increase the donor properties of the glycosylimidate, one chlorine group of the trichloroacetinitrile was replaced with a more electronegative cyano group, that is, trichloromalonitrile was used as the activating agent.

3.3.2. S-Imidates

Thioimidates have been developed as versatile building blocks for selective glycoside formation. Special mention is credited

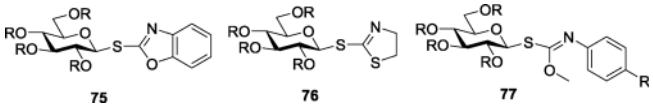


71 72 73 74

Scheme 17. Synthesis of trichloroacetylcarbamate and its use in glycosylation.

to Demchenko and co-workers, who significantly contributed towards the development and establishment of various thioimidate donors.[154]

Demchenko and co-workers introduced S-benzoxazolyl (SBox) as a novel thioimidate donor.[155] SBox proved to be a stable and efficient glycosyl donor for performing several types of glycosylations under mild conditions. Both 1,2-*cis* and 1,2-*trans* glycoside formations have been reported with SBox-protected thioglycosides, **75** (Figure 4). The synthesis of SBox

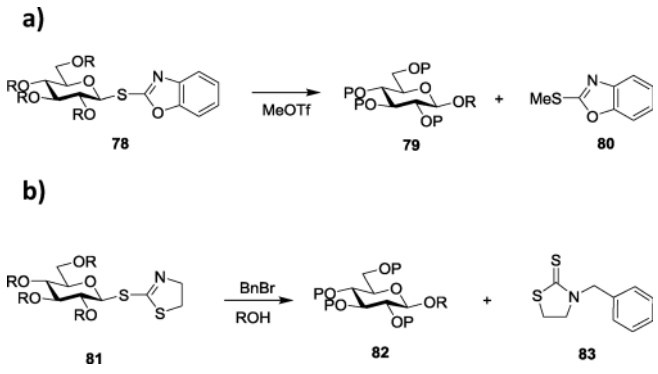


75 76 77

Figure 4. SBox (**75**), STaz (**76**), and SNea (**77**) glycosides.

glycosides and the probable mechanism for its activation was reported by the same group.[156] Standard thiophilic promoters like NIS/TfOH, AgOTf,[157] $Cu(OTf)_2$,[158] MeOTf,[159] and so forth have been used to activate this class of donors.[160] SBox glycosides also showed selective activation over thioglycosides and pentenyl glycosides.[157] Several glycosides with different protecting groups were also tested for activation,[158a] which revealed that *per*-benzylated glycosides showed the optimum activation. Demchenko and co-workers gave a detailed analysis about the effects and logistics behind variable activation patterns observed by armed and disarmed SBox glycosides. Armed glycosides could be chemoselectively activated over its disarmed counterpart[161] to give *trans*-glycosides. Oligosaccharides formed by using armed SBox donors showed high α-stereoselectivity.

However, SBox glycosides showed certain instability towards some extreme reaction conditions when being activated by triflic acid (TfOH). To bypass this limitation, Demchenko and co-workers later introduced S-thiazolinyl (STaz) glycosides, **76** (Figure 4), as building blocks for chemoselective and orthogonal oligosaccharide synthesis.[162] SBox and STaz thioimidates were also implemented in solid-phase glycosylation strategies (Scheme 18a,b),[163] where the thioimidates were utilized as donors for glycosylations with resin-bound acceptors after being activated by promoters like AgOTf, TMSOTf, NIS/TMSOTf, MeOTf, and so forth.[164] STaz glycosides proved to be highly stable towards extensive protecting-group manipulations.[165] These glycosides also showed activation in line with Fraser-



Scheme 18. a) Activation of SBox glycosides. b) Activation of STaz glycosides.

Reid's armed–disarmed activation strategy. Armed STaz glycosides could be chemoselectively activated over their disarmed counterparts.[31b] Demchenko and co-workers also explored other analogs of silver salts to activate the STaz glycosides, and they successfully reported the application and versatility of silver tetrafluoroborate, $AgBF_4$,[166] as an excellent promoter for the activation of such donors. The more popular thiophilic promoter AgOTf was also found to be effective towards the activation of STaz donors.

S-glycosyl O-methyl phenylcarbamothioates (SNea carbamothioates) (**77**) (Figure 4) were introduced as the next-generation glycosyl thioimidate donor.[167] The SNea leaving group was illustrated to represent a bridging compound between acyclic thiocyanates (SCN) and cyclic SBox glycosides. These donors showed similar properties to SBox glycosides and extensive studies were performed to compare the activation properties of the two. Activation of SNea donors with promoters like $Cu(OTf)_2$, AgOTf, or MeOTf afforded the α-glycosides in significant yields.[168] Other thioimidate S-benzothiazolyl (SBaz) glycosides, **84** (Figure 5), have also been commonly used for

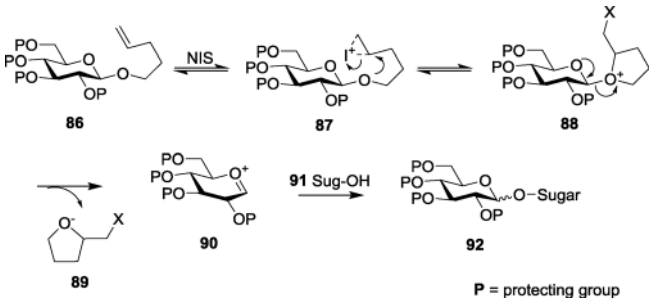
Figure 5. SBaz (**84**) and SBiz (**85**) glycosides.

glycosylation. This derivative was first introduced for glycosylation by Mukaiyama et al.[169] In 2011, Hasty and Demchenko introduced another variant of thioglycoside donor, S-benzimidazolyl (SBiz) glycosides, **85** (Figure 5), suitable for extensive oligosaccharide synthesis.[170]

Glycosyl dithiocarbamates (DTCs) have been used for glycosylations to give β-selective products upon being activated by Cu^{I} or Cu^{II} triflates.[171] They have been specifically used for glycosides with no protecting group in the C-2 position.

3.4. Alkenyl Glycosides

Although thioglycosides are established as highly versatile donors that facilitate glycosylation reactions, the use of thioglycosides sometimes becomes highly unwanted because of the obnoxious smell of the thiols. Alkenyl glycosides fit perfectly in this void. Pent-*n*-enyl glycosides (NPGs) **86** pose as the most apt alternative in terms of their versatility and environmentally friendly nature. Similar to thioglycoside activation, activation of *n*-pentenyl glycosides is achieved either by bromonium (NBS) or iodonium (NIS) ions. The subsequent cyclization leads to the transition state, that is, the tetrahydrofuranyl oxonium ion (**88**) (Scheme 19). The increased leaving-group prop-



Scheme 19. *n*-Propargyl glycoside (NPG) activation.

erty of the tetrahydrofuran moiety **89** leads to the formation of the corresponding oxocarbenium ion, **90**, which, upon addition of the attacking nucleophile (the acceptor **91**), culminates in the proper glycosylated product **92**.

The concept of activation of the pentenyl glycosides by Lewis acids was utilized by Hung and co-workers in 2006[172] for the introduction of 2-allyloxyphenyl glycoside as an efficient donor system. This glycosyl donor could easily be activated by NIS/TfOH to give the product in moderate-to-high yields. The same group also introduced allylphenyl glycosides as a donor, which could be effectively activated by iodonium chloride (ICl)/AgOTf[173] to produce the required glycosides. In 2009, *gem*-2,2-dimethyl and 2,3-dimethyl 4-pentenyl glycosides (Figure 6) were activated by cheaper and more versatile NBS promoter and claimed to undergo coupling 11- and 3-times faster, respectively, than the master *n*-pentenyl glycosides.[174] The steric hindrance offered by the *geminal* methyl groups was assessed to trigger the ring-closing step, causing more effective coupling.

The present century has also seen a rise in the use of *n*-pentenyl orthoesters **95** as a highly versatile donor system. Orthoesters can readily undergo electrophilic attack to form the

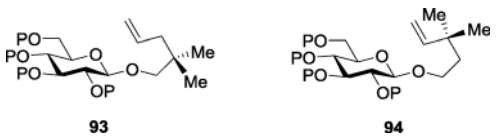
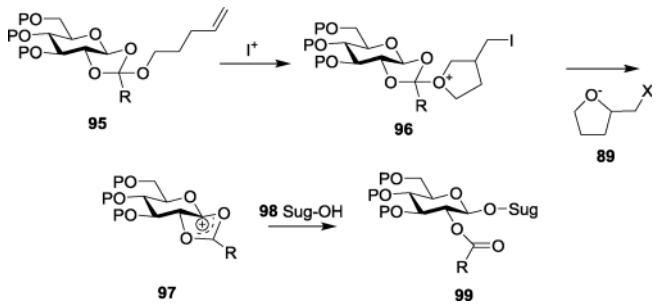


Figure 6. *gem*-Dimethyl analogs of *n*-pentenyl glycosides.



Scheme 20. Mechanism of activation of *n*-pentenyl orthoesters (NPOEs).

furanylium intermediate **96** (Scheme 20). The enhanced leaving-group property of the halomethyl furan moiety **89** aids in the easy conversion of intermediate **96** to **97**. Furthermore, the attack of acceptor **98** effectively forms the required glycoside **99**. Interestingly, the released moiety **89**, which is highly non-nucleophilic, fails to compete with the sugar nucleophile **98**, which attacks the intermediate, dioxolenium ion **97**, and forms the required glycoside **99**.

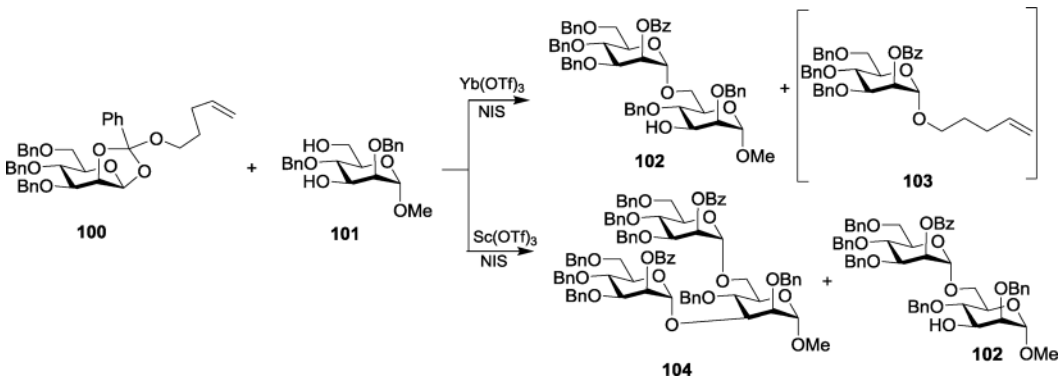
There have been various reports establishing the activation of *n*-pentenyl orthoesters (NPOEs) by lanthanide triflates to form the glycosylated product. In an exemplary illustration, Fraser-Reid and co-workers showed that NPOE **100**, upon being activated by NIS followed by $Yb(OTf)_3$ (Scheme 21), produced highly regioselective glycosylated product **102** after reacting with the acceptor **101**.[175] The *n*-pentenyl intermediate, **103**, formed as a by-product, however, remains inactivated. This *n*-pentenyl glycoside **103** can be activated by $Sc(OTf)_3$, which goes on to form the doubly glycosylated product **104** along with the normal glycoside**102**. Thus, NPOE glycosides prove to be better donors than *n*-pentenyl glycosides, as they overcome reactivity restrictions faced in case of the latter.[176]

The implementation of NPOEs for glycosylation was also evident in performing selective glycosylations with more than one free hydroxyl groups in the synthons. This facilitated the possibility of performing iterative glycosylations in the synthesis of larger oligosaccharide building blocks.[177] In a comparative study, it was illustrated that *n*-pentenyl glycosides gave a mixture of products, whereas NPOE yielded strictly the equatorial product in a clean reaction[178] with a higher conversion ratio. Mathew et al. also demonstrated that NPOEs provided better yields upon being irradiated under microwave conditions.[179] A detailed comparison between the activation of NPOEs under thermal and microwave conditions shows a distinct increase in the yield under the latter conditions. Microwave irradiation features the reaction mixture reaching the target temperature rapidly and maintaining the temperature throughout the entire reaction time, which becomes instrumental in obtaining better yields.

Fraser-Reid and co-workers also introduced mannopyranoside-derived methyl orthoesters[180] as possible donors for glycosylation. They underwent easy activation with the help of $BF_3{\cdot}Et_2O$ and demonstrated proceedings analogous to that of NPOEs. It was also observed that the iodonium-ion activation and the stoichiometry of the Lewis acid had significant roles in the regioselectivity of the product formed.

3.5. Alkynyl Glycosides

Propargyl glycoside remains the most prominent alkynyl glycoside used in oligosaccharide synthesis to date. The versatility of the propargyl glycosides led to their introduction as a probable glycosyl donor suitable for oligosaccharide synthesis. The alkynophilicity of gold catalysts has been utilized by using Au^{III} halides as the catalyst to activate propargyl glycosides. Optimization of reaction conditions showed that, through $AuCl_3$ activation, complete conversion of the starting material occurred at 60 °C after approximately 6 h. However, upon coupling with various aliphatic, alicyclic, steroidal, and sugar alcohols, the stereoselectivity of the product was a 1:1 α/β mixture.[181] Other alkyne-activating promoters like $PtCl_2$, $Co_2(CO)_8$, and $RuCl_3$, however, failed to give the product and resulted in decomposition of the donor. Building upon the concept of activation of propargyl glycosides with gold catalysts, the possibility of using the 'armed–disarmed principle' to build higher analogs of oligosaccharides was also explored. They coupled the armed *per*-benzylated propargyl mannopyranoside **103** with disarmed *per*-benzoylated mannopyranoside **104** to get the desired disaccharide **105** (Scheme 22 a), where the armed propargyl monosaccharide **103** acted as the donor, as anticipated.[182] However, when the disarmed disaccharide formed, **105** was further utilized for sequential glycosylations by con-



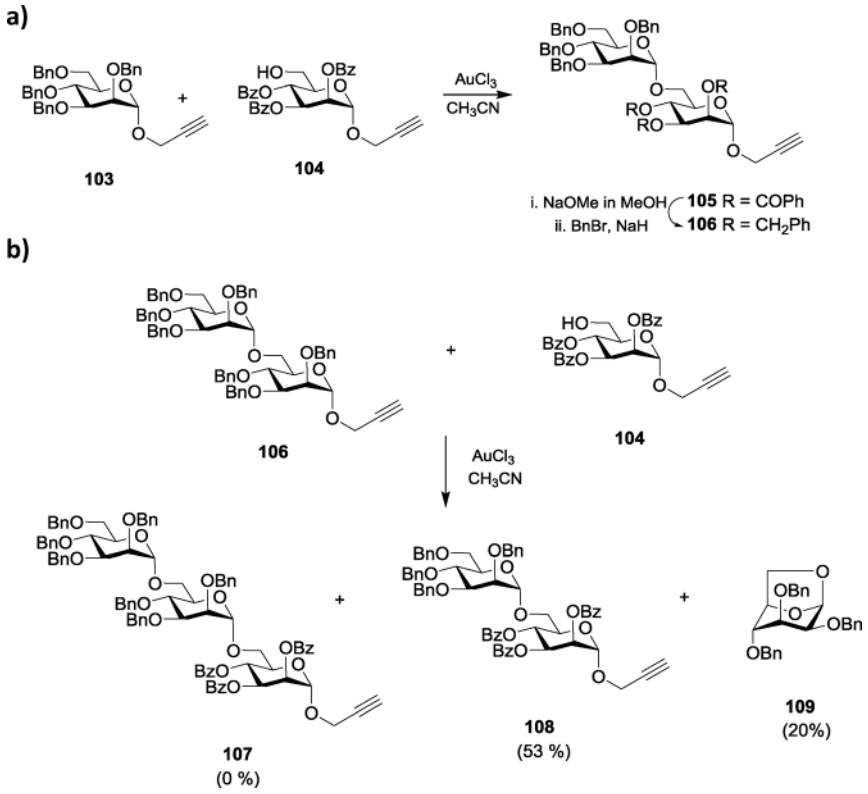
Scheme 21. Different activation patterns of *n*-pentenyl orthoesters.

verting it to its armed counterpart **106**; it was observed that instead of the desired trisaccharide, **107**, disaccharide **108** was formed along with the anhydro sugar, **109** (Scheme 22 b). The reason behind such unnatural phenomenon was also explained by a mechanistic rationale (Scheme 23), stating the concept of 'double-activation' of the armed glycosyl donor, **106**, as the probable cause. Upon reacting with further disarmed aglycon, higher oligosaccharides were synthesized effectively. Hotha and co-workers also reported glycosylation with propargyl glycosides at ambient temperature.[183]

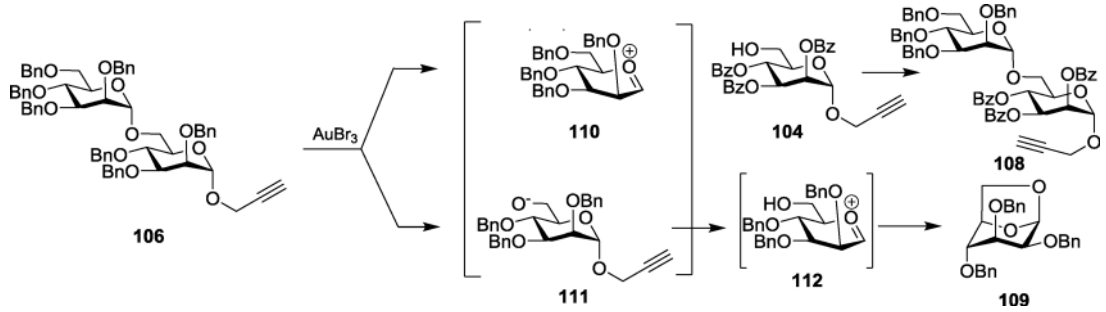
Interestingly, gold catalyst $AuBr_3$ alone led to a very slow reaction where propargyl furanosides were used as the donor, and the disaccharides were also formed in a low yield. Addition of AgOTf along with $AuBr_3$, in turn, improved the reaction[184] considerably, making it more spontaneous and high yielding. Benzylated propargyl furanoside**113**, acting as the armed donor, was also coupled with benzoylated propargyl pyranoside**114** (Scheme 24) to give product **115** in line with the 'armed–disarmed' concept.

Apart from propargyl glycosides, reports of the implementation of S-but-3-ynyl glycoside donors and derivatives have also been revealed.[185] These donors were used for gold-catalyzed glycosylations for the synthesis of 2-deoxy glycosides. Another set of alkynyl derivatives, *o*-(methyltosylaminoethynyl)benzyl glycosides, was also developed as donors[186] suitable for expeditious oligosaccharide synthesis and for the introduction of various aglycons.

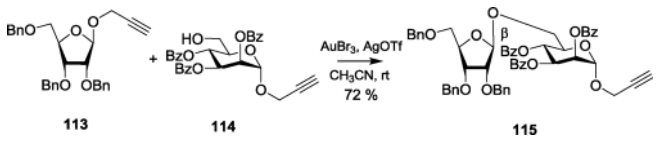
Similar to the concept of alkenyl orthoesters, alkynyl orthoesters were developed as a versatile leaving group aiding in glycosylations. Propargyl orthoesters were glycosylated with



Scheme 22. a) Selective glycosylation with propargyl glycosides. b) Unnatural inter-glycosidic bond cleavage.



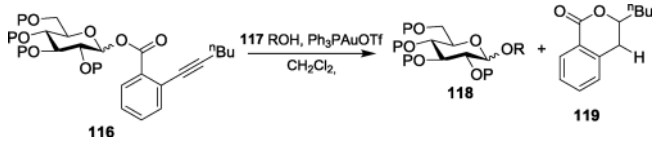
Scheme 23. Mechanistic rationale.



Scheme 24. Glycosylation with propargyl furanosides.

various aglycons[187] through gold (III) activation to give the highly stereoselective 1,2-*trans* glycosylated product in moderate-to-high yields.[188] However, Hotha and co-workers revealed that the propargyl orthoesters, when coupled with carbohydrate-derived secondary alcohols as the acceptor gave comparatively lower yields,[189] when compared with coupling with primary carbohydrate alcohols. The same group also reported the selective activation of the propargyloxy group of the propargyl orthoesters in the presence of the competing propargyl glycosides by $AuBr_3$ activation.[190]

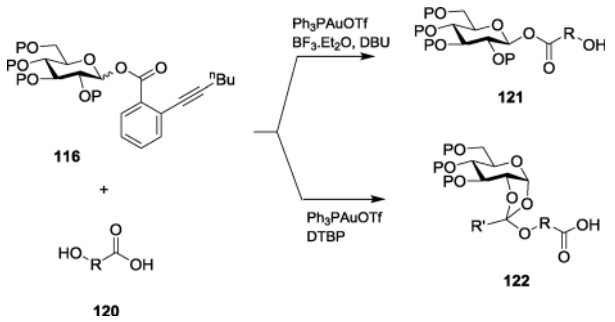
With a similar intention to develop new and modified glycosylation strategies, Li et al. failed to activate 4-pentynyl or 5-hexynyl glycosides by gold(III) catalysis. To overcome the limitation, they introduced *ortho*-alkynyl benzoate glycosides,[191] a more active alkynyl group that can be activated by gold catalysts and illustrated the detailed mechanistic insight towards the glycosylation procedure.[192] This protocol for activation has been implemented for the synthesis of various saponins[193] and higher oligosaccharides.[194] O-Hexynyl benzoate glycosides **116** were glycosylated with various aglycons on being activated by $Ph_3PAuOTf$ at room temperature to get high β-selective products (Scheme 25). The same alkynyl benzoate glycoside



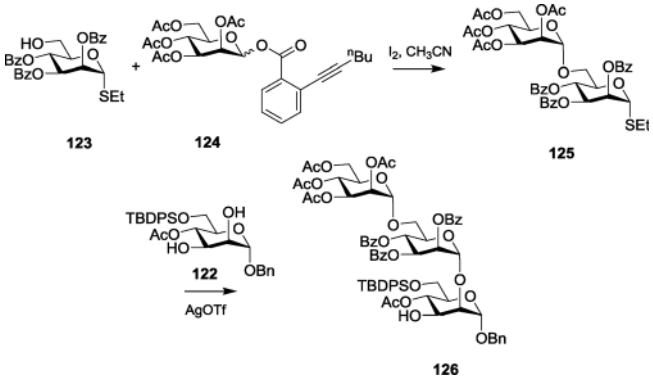
Scheme 25. β-Glycoside formation using *o*-hexynyl benzoate glycosides.

was also used for its coupling with acid alcohols.[195] A chemoselective protocol has also been employed, where it was observed that $Ph_3PAuOTf$ activation in the presence of $BF_3{\cdot}Et_2O$ and DBU gave exclusive coupling with the acid alcohols, whereas the same coupling through $Ph_3PAuOTf$ in the presence of DTBP led to the exclusive formation of alcohol orthoester in high yields (Scheme 26). Further studies revealed that the loading of gold catalysts could be lowered to 0.01 equivalents or 0.5 mol% with the external assistance of an additional strong protic acid[196] (10 mol% or 0.1 equiv HOTf).

There have been reports where glycosyl *ortho*-alkynyl benzoates were efficiently activated by using cheap and easily available molecular iodine.[197] The mild iodine was also capable of selectively activating these donors over thioglycosides, which helped in performing various sequential glycosylations (Scheme 27). Activation of alkynoate glycosides using $Hg(OTf)_2$ as the promoter[198] has also been reported.



Scheme 26. Chemoselective strategy to obtain different products from the same starting material.



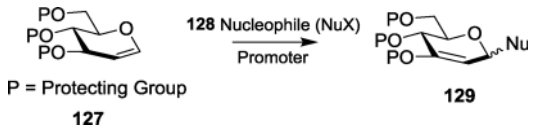
Scheme 27. Synthesis of a trisaccharide with alkynoate glycosides.

A linear η_2-alkyne π complex of $[Ph_3PAu]^+$, namely Au^I π-bis-(*tert*-butyldimethylsilyl)acetylene triphenylphosphine,[199] was explored to activate *ortho*-cyclopropylethynylbenzoate glycosides and subsequent glycosylations with both acceptors and non-sugar aglycons. The same gold-catalyzed activation of *ortho*-alkynyl benzoate glycosides has been achieved by Seeberger and co-workers in a continuous flow reactor.[200] The procedure gave high yields of the glycoside products in much less time.

Yu and co-workers introduced *ortho*-alkynylphenyl thioglycosides,[201] a similar glycosyl donor that could be activated by gold catalysts. Glycosylations with catalysts like [Btz–Au–PPh_3]OTf and $Ph_3PAuOTf$ were seen to give the required product in excellent yields. Recently, Balamurugan and co-workers introduced yet another easily accessible alkynyl leaving group, dipropargyl cyano acetate.[202] *per*-Acetylated glycosyl analogs with this leaving group were optimized for glycosylation with various sugar acceptors and non-sugar aglycons by varying both the solvent and catalyst systems.

3.6. Glycals

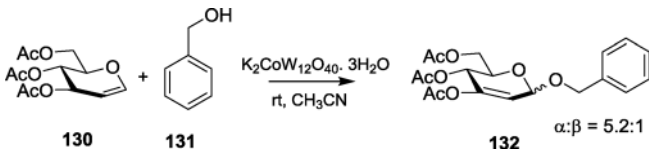
Glycals are highly important components in carbohydrate chemistry that can be effectively used for the formation of 2,3-unsaturated glycosides. The transformation of glycals **127** into unsaturated-O-glycosides **129** takes place in the presence of various catalysts like Lewis acids, metal salts, or other activat-



Scheme 28. Ferrier reaction.

ing agents (Scheme 28). This methodology was first introduced by Ferrier[203] and is more commonly identified as the Ferrier reaction.[204] Catalysts represent the most important aspect of the Ferrier reaction, and various studies and investigations are being done to modify and improve the nature of the catalysts. The 21st century witnessed substantial modifications in the use of metal salts and metal triflates as catalysts for the coupling of the glycals.

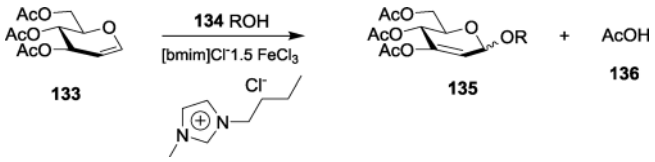
Starting with alkali metals, potassium dodecatungstocobaltate, $K_5CoW_{12}O_{40}\cdot 3H_2O$ (POM), was explored to understand the role of potassium as the catalyst. Various glycosylations with different acetylated glycals **130** and POM as the catalyst in varied solvents afforded α-glycosides **132** as the major product in good-to-excellent yields (Scheme 29). Substantial optimization revealed acetonitrile as the best choice of solvent. Rafiee et al. also showed the probable mechanistic pathway that elegantly described the reason behind the effective use of perfect outer-sphere one-electron oxidants for such glycosylations.[205] The catalyst showed high yields, even after being recovered four times, thus proving the high efficiency of the alkali metal as the catalyst.



Scheme 29. Use of potassium as the catalyst in the Ferrier(I) rearrangement.

Proceeding to the more versatile transition metals, iron(III) chloride was established as an efficient catalyst for Ferrier rearrangement by Bettadaiah and Srinivas,[206] where it was used for the glycosylation of tri-O-acetyl-D-glucal with butan-1-ol, yielding the α-isomer as the major product. Among the reaction conditions tested, refluxing acetonitrile was found to be best. In such optimized conditions, the loading of the catalysts could be lowered to 0.001 mol equivalents.[207] $FeCl_3$ has also been used in ionic-liquid medium. The versatility of ionic liquid resides in the phenomenon of their adjustable solubility. [bmim]Cl–$x$$FeCl_3$-based ionic liquid was prepared by mixing anhydrous $FeCl_3$ with 1-butyl-3-methylimidazolium chloride, [bmim]Cl. This ionic medium was further utilized as the catalyst for the reaction of glucals with various alcohols (Scheme 30).

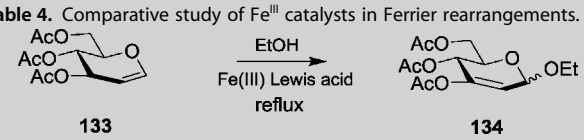
A comparative assessment has also been shown for the Ferrier reaction by using CAN (ceric ammonium nitrate) and $Fe_2(SO_4)_3\cdot xH_2O$, respectively.[208] The latter was shown to yield exclusive 2,3-unsaturated-α-glucosides with both *per*-acetyl and *per*-benzyl glucals. From the schematic study with various



Scheme 30. Ionic-liquid-induced Ferrier glycosylation.

iron(III) salts by Wang and Chen in 2012, it is evident that ferric triflate is the most versatile iron-based Lewis acid for performing the glycosylation of peracetyl glycals with alcohols in terms of selectivity and yield (Table 4). The use of only 10 mol% of the catalyst in dichloromethane as the solvent gave a maximum of 87% yield with the α-isomer as the major product.[209]

Table 4. Comparative study of Fe^{III} catalysts in Ferrier rearrangements.

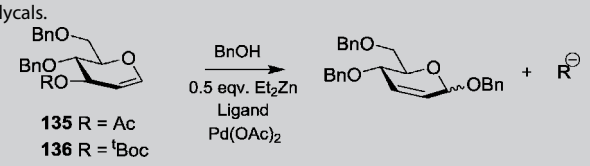


No.	Catalyst	Time [min]	Yield [%]	α/β
1	$FeCl_3$	120	31	5:1
2	$Fe_2(SO_4)_3$	120	negligible	nil
3	$Fe(NO_3)_3$	120	41	9:1
4	$Fe(OTf)_3$	30	88	10:1

The inexpensive $ZnCl_2$ was also shown to catalyze Ferrier glycosylation when using S_N1 active nucleophiles. The catalyst provided good-to-excellent yields upon reaction of 3,4,6-tri-O-acetyl-D-glucal **133** with allylic, benzylic, and tertiary alcohols in dichloromethane medium.[206] Liu and co-workers illustrated that $ZnCl_2$ impregnated with activated alumina can be optimally utilized for the preparation of 2,3-unsaturated glycosides. They have shown the use of this catalyst system both in the presence and absence of solvent system.[210] The same catalyst system was also used in the subsequent year for Ferrier aza-glycosylation.[211] More recently, $Zn(OTf)_3$ has been estimated to be a cheaper, milder, and more efficient catalyst for the stereoselective synthesis of α-glycosides with a variety of O and S nucleophiles adorned with a wide range of functionalities.[212] In 2014, Srinivas and co-workers reported the use of the otherwise unreactive $ZnBr_2$ in the α-glycosylation reaction of 3,4,6-tri-O-acetyl glucal **133** with a variety of primary, secondary, tertiary, allyl, and benzyl alcohols under microwave conditions.[188]

In another noteworthy set of experimental results, Et_2Zn was used to activate the alcoholic acceptor. However, the synthesis of 2,3-unsaturated glycosides was achieved by reacting the substituted glucal with the Zn-salt-activated alcohol in the presence of a Pd catalyst.[213] Special consideration was given to the fact that, in such reactions, the anomeric stereoselectivity was governed by the reagent and solvent system rather than the protecting group. Addition of di(*tert*-butyl)-2-biphenylphosphine, DTBBP yielded the β-product, whereas the employment of $P(OMe)_3$ produced the α-isomer as the major

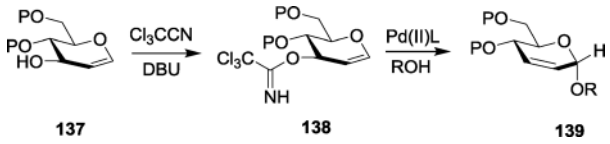
Table 5. Difference in stereoselectivity in Pd-catalyzed glycosylation of glycals.



135 R = Ac
136 R = ^{t}Boc

No.	Compound	Ligand	Yield [%]	α/β
1	135	15% DTBBP	92	< 1:25
2	135	30% $P(OMe)_3$	90	7:1
3	136	15% DTBBP	92	< 1:25
4	136	30% $P(OMe)_3$	90	5:1

product (Table 5). Nguyen and co-workers also implemented the use of Pd^{II}/L system for the direct construction of the α-glycoside from the glycals through the formation of glycal trichloroacetimidates (Scheme 31).[214] Following extensive work



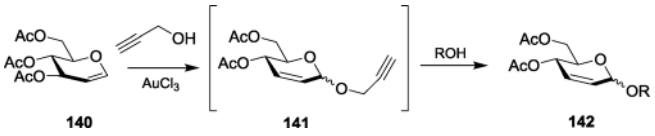
137 **138** **139**

Scheme 31. Pd^{II} catalyzed conversion of glycal to the glycoside.

with several ligand systems, $Pd(PhCN)_2Cl_2$ was reported to give the maximum stereoselectivity in the presence of DTTBP providing the α-isomer in 84% yield. Furthermore, many derivatives of 2,3-unsaturated glycosides have been prepared by using the same concept of implementing a Pd^{II}/L catalyst to activate the glycal π system.[215] Recently, Liu and co-workers employed decarboxylative strategy by using $Pd_2(dba)_3$ as the catalyst and D*t*BPF [1,1′-bis(di-*tert*-butylphosphino)ferrocene] as the ligand in the presence of the base, Cs_2CO_3, for the formation of 1,2-unsaturated O-glycosides.[216] Higher base loading (2.0 equiv) led to the effective formation of the β-glycoside. Excellent α-selectivity was obtained by coupling carbohydrate acceptors with glycals when being activated by Re^V-oxo complex, $ReOCl_3(SMe_2)(Ph_3PO)$.[217]

Similarly, with other variety of donors, the high alkynophilicity and oxophilicity of Au catalysts were utilized to perform Ferrier glycosylation. Later, depending on the same phenomenon, Balamurugan and Koppolu used $AuCl_3$ as the catalyst under mild reaction conditions to synthesize 2,3-unsaturated glycoside with high α-stereoselectivity.[218] When glycal **140** was reacted with propargyl alcohol in the presence of $AuCl_3$ in acetonitrile medium, intermediate **141** was formed in situ, which was subsequently subjected to glycosylation with acceptors to give the product in moderate-to-good yield with the α-isomer predominating (Scheme 32). Thus, wide studies of glycosylations with gold catalysts have established their versatility in the successful formation of products with a wide range of nucleophiles.

Studies have also been done with other transition-metal salts. Copper(II) triflate has been reported to give 2,3-unsaturated product under milder conditions.[219] Kashyap and coworkers introduced $RuCl_3{\cdot}3H_2O$ as an efficient Lewis acid catalyst for such reactions.[220] Niobium(V) chloride was also implemented as an efficient catalyst for the synthesis of unsaturated glycosides from *per*-O-acetylated glucal[221] by virtue of its high stability, moisture tolerance, and economic viability. In a corresponding report, the phenomenon of water solubility of scandium(III) triflate was utilized to perform Ferrier glycosylations in aqueous medium. In non-aqueous medium, only 5% w/w of $Sc(OTf)_3$ proved to be adequate to complete the reaction within a maximum time period of 3.5 h with a wide variety of aryl and alkyl alcohols.[222] A variety of yttrium salts were also explored, of which $Y(OTf)_3$ was found to be the most efficient, 10 mol% of which was optimum to bring the reaction to completion.[223] Among other transition-metal salts, $TiCl_3(OTf)$,[224] organozinc reagents,[225] and zirconium(IV) chloride[226] have also been used as highly efficient catalysts for type I Ferrier rearrangement.



140 **141** **142**

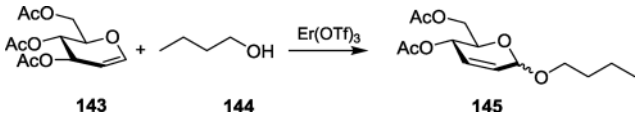
Scheme 32. $AuCl_3$-catalyzed propargylation and subsequent glycosylation.

Proceeding to the use of lanthanides as catalysts for Ferrier rearrangements, Yadav et al. illustrated $Dy(OTf)_3$-catalyzed glycosylation of glycals with alcohols, phenols, and hydroxy-α-amino acids in 1-butyl-3-methylimidazolium hexafluorophosphate, ([bmim]PF_6) ionic liquid.[227] High yields of unsaturated glycopyranosides with the α-isomer predominating were obtained in mild, solvent-free conditions by glycosylation of glycals mediated by inexpensive, versatile, and environmentally friendly lanthanum(III) nitrate catalyst.[228] However, this catalyst failed to provide a significant yield with solvents like CH_2Cl_2, THF, diethyl ether, and so forth, but on using nitromethane as the solvent, the yield improved significantly (Table 6).[229] The good stability of the catalyst and milder reaction conditions made $Er(OTf)_3$ one of the most efficient catalysts for triggering Ferrier glycosylation (Scheme 33). In almost all the cases, the α-anomer was found to be predominant. A recent addition in Ferrier glycosylation is the electrochemical generation of zirconium catalyst, which provided a novel protocol for the effective glycosylation of acetylated glycals.[230]

Basic metals, such as aluminum, have also been used as catalysts. The use of aluminum triflate as a potential catalyst in Ferrier reaction has also been widely studied. In 2002, it was revealed that tri-O-benzyl-D-glucal catalyzed by $Al(OTf)_3$ gave both 2-deoxy glycosides and Ferrier-rearranged pseudoglycal products at 60 and 0 °C, respectively.[231] The versatility of the aluminum salt was verified when a wide range of acceptors were used ranging from alkyl alcohols to phenolic alcohols. $Al(OTf)_3$ was also used to show the temperature dependence in Ferrier rearrangement. Williams and co-workers noticed that different temperatures yielded different products upon reacting glycals with alcohols in the presence of an Al catalyst.[231]

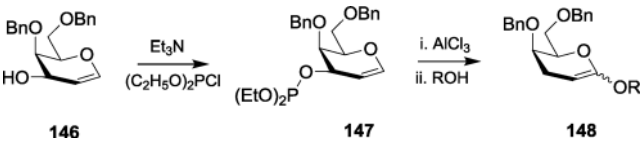
Table 6. Comparative study of glycosylations with glucals in various solvents.

No.	Solvent	Time [h]	Yield [%]
1	CH_2Cl_2	48	25
2	Et_2O	48	15
3	THF	48	10
4	CH_3CN	48	35
5	CH_2Cl_2(dry)	12	46
6	Et_2O	12	25
7	CH_3CN (dry)	12	58
8	CH_3NO_2 (dry)	2	90
9	CH_3NO_2 (dry)	6	90



Scheme 33. The use of erbium triflate as a catalyst.

At 60 °C, 2-deoxy-1-O-glycosides were obtained, whereas on lowering the temperature to 0 °C, Ferrier product 2,3-unsaturated-O-glycosides were obtained. Both products were obtained in high α-selectivity. Sequential glycosylation has also been illustrated on being catalyzed by $AlCl_3$.[232] In this reaction, derivatives of 3-hydroxy galactal **146** were reacted with diethyl phosphorochloridite and Et_3N, which provided the corresponding 3-O-diethoxyphosphanyl-D-galactal, **147**. It subsequently underwent Ferrier rearrangement with various nucleophiles in the presence of $AlCl_3$ to give the required 2,3-unsaturated glycosides **148** (Scheme 34). Indium is another basic metal that



Scheme 34. Glycosylation induced by diethyl phosphorochloridite.

has been frequently reported to catalyze the Ferrier reaction with glycals. In an interesting finding, Boga and Balasubramanian reported a Ferrier glycosylation where glycals were reacted with varied nucleophilic acceptors catalyzed by 20 mol% of highly anhydrous $InCl_3$.[233a] They, however, continued the reaction for a longer time to observe the conversion of O-glycoside to the corresponding C-glycoside.[233] It was found to provide a better yield compared to the other metal-based catalysts. Unactivated glycals with no protecting group in the C-3 position have also been successfully activated to undergo Ferrier rearrangement by $InCl_3$.[234] In a similar protocol, basic $BiCl_3$[235] has also been used. Bismuth(III) triflate was implemented as a probable catalyst for Ferrier rearrangement both in the presence and absence of silica.[236] Various types of alkyl and aromatic alcohols have been illustrated to undergo the glycosylation to stereoselectively produce the α-isomer as the major product in a considerably high yield.

Addition of glycols to the glycals through Ferrier glycosylation using tellurium salts[237] was also reported for the expeditious synthesis of various macromolecules. Thus, metal-catalyzed Ferrier reaction has been extensively studied in the present century. However, more protocols to promote the formation of β-selective products are still in demand.

Advancing from metal-based Ferrier glycosylations, immediate interest is directed towards the importance of the development of metal-free strategies. In 2008, De et al. showed the effectiveness of metal-free synthesis of 2,3-unsatrated glycosides from corresponding glycals.[238] They showed that the glucal reacted with various nucleophilic alcohols in a greater amount (20 equiv) to give the corresponding 2,3-unsaturated product without the addition of any metal or Lewis acid catalyst, provided HFIP is used. The solvent-free rearrangement reaction was further facilitated by the use of Montmorillonite K-10 as the catalyst.[239] Application of microwave heating was also reported to be advantageous over standard heating conditions, leading to less effective reaction time. In both cases, exclusive α-products were obtained with a cleaner and milder method. Montmorillonite K-10 clay-supported $Bi(OTf)_3$[240] has also been illustrated to achieve the synthesis of various types of sialic acid through Ferrier transformation. Other versatile catalyst systems, for example $HClO_4$–silica,[241] CF_3SO_3H–silica,[242] $NaHSO_4$–silica,[243] and H_2SO_4—silica,[244] have been used for the synthesis of a wide range of pseudoglycosides. In the context of organic acid catalysts, when acetic acid failed to yield any desired unsaturated glycoside, Liu and co-workers decided to test the effectiveness of camphorsulfonic acid (CSA)[245] as a probable catalyst for triggering the formation of pseudoglycosides. Both (*R*) and (*S*)-CSA, in their optically pure forms, were reported to give the desired product, the (*S*)-isomer being the more efficient one.

Various other catalyst systems have been developed over the decade, promoting the formation of 2,3-unsaturated O- and C-glycosides from glycals. Notable ones are cyanuric chloride-catalyzed Ferrier reaction,[246] bromodimethylsulfonium (BDMS)-mediated rearrangement,[247] and 3,5-dinitrobenzoic acid (DNBA)-mediated synthesis of O and S-glycoside.[248] The incorporation of potassium alkynyltrifluoroborate group to the glucal has also been implemented by $BF_3{\cdot}Et_2O$-mediated[249] Ferrier glycosidation.

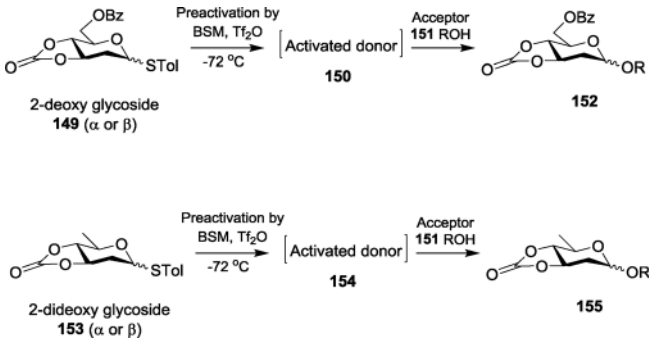
The vinyl oxirane chemistry was implemented by Crotti and co-workers who mastered the synthesis of the oxirane or epoxide from the corresponding glycal and further used it for subsequent catalyzed or uncatalyzed[250] glycosylation with a wide range of nucleophiles under different reaction conditions.[251] This glycosylation protocol led to yield the β-isomer as the major product, whereas the use of benzene as the solvent gave the β-product exclusively.[252] However, the synthesis of α-derivatives has also been reported by using the same protocol.[253] The addition of organolithium reagents[254] onto the oxiranes by using the same procedure also gave efficient reactions to give the desired product.

3.7. Deoxy Sugars

3.7.1. 2-Deoxy Sugars

2-Deoxy sugars with the OH group in the C-2 position replaced by a hydrogen atom are widely distributed in various natural products. The wide biological importances of the 2-deoxy sugars have made them a highly novel synthon in chemical glycosylations. However, the formation of glycosidic linkages with these 2-deoxy glycosides pose quite a challenging task, owing to the absence of any directing group in the C-2 position. Moreover, the absence of any electron-withdrawing group in the strategic C-2 position makes the moieties highly acid labile, leading to hydrolysis of the compound. Various analyses have been performed over the years to control the stereoselectivity of the glycosides formed at the anomeric position of the 2-deoxy sugars. Many of the earlier developed protocols have been extensively discussed in various Reviews.[255]

Employing direct methodology for the stereoselective synthesis of natural 2-deoxy glycosides, Lear et al.[256] established the use of the mild activating system, $AgPF_6$/DTBMP (2,6-di-tert-butyl-4-methylpyridine). Amongst the various Ag catalysts, this promoter system was found to give the maximum α-stereoselectivity under optimized conditions. Recently, in the entire domain of glycosylation, pre-activation of the donors is much in demand. In the case of glycals, this has also been established to give better products. As an illustration, Ye and co-workers first activated 2-deoxy thioglycosides **149** by using BSM–Tf_2O.[257] Subsequently, addition of acceptor **151** to the same reaction mixture gave the 1,2-*cis*-glycosylated product **152** with high stereoselectivity (Scheme 35). 2,6-Dideoxy thio-



Scheme 35. Glycosylations based on pre-activation protocol with 2-deoxy and 2-dideoxy glycosides.

sugars **153** were also observed to give similar results. In a side reaction, when the mixture of donor and acceptor was directly exposed to the promoter system, the yield diminished drastically, indicating the importance of pre-activation of the donor.

For the synthesis of higher analogs of 2-deoxy oligosaccharides, Issa and Benett established the use of potassium hexamethyldisilazane (KHMDS)/*p*-toluenesulfonic anhydride[258] as an effective promoter system, leading to the exclusive synthesis of β-linked 2-deoxy-sugar disaccharides from hemiacetal donors. The reaction was presumed to go through a S_N2 pathway via an in situ glycosyl sulfonate intermediate to accomplish a highly β-stereoselective glycosylation.

Glycosylation of glycals mediated by metal catalysts is, in itself, a wide area of research. Zhu and co-workers investigated the role of 2-deoxy S-but-3-ynyl thioglycosides as an effective glycoside donor[185] for performing O-glycosylation through the homogeneous cationic gold(I)-catalyzed selective activation of the alkyne group attached with the more nucleophilic thio functionality. The reaction conditions were optimized by the use of 5 mol% $(4\text{-}CF_3\text{—}Ph)_3PAuCl$ along with 10 mol% AgOTf, which gave almost quantitative yield. Coming to organoboron-catalyzed glycosylations, *per*-acetylated 2-deoxy as well as 2,6-dideoxy chlorides were reported to show high regio- and β-stereoselectivity on activation with diphenylborinate **156** (Figure 7) in moderate-to-good yields. However, the require-

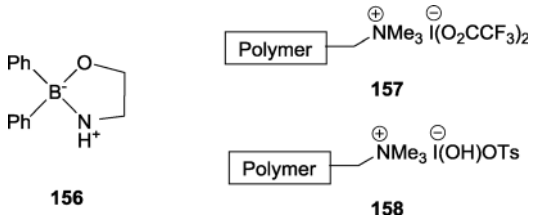


Figure 7. 156: Borinic acid pre-catalyst; **157**, **158**: Polymer-supported haloate complexes.

ment of a more nucleophilic acceptor was essential and, hence, sugar diols were employed, limiting the scope of such glycosylations[259] with the halide counterparts. Polymer-assisted activation of 2-deoxy thioglycosides has also been investigated by Kirschning and co-workers.[260] Polymer-supported haloate(I) complexes **157** and **158** were used to activate the thioglycosides for the subsequent formation of higher oligosaccharides.

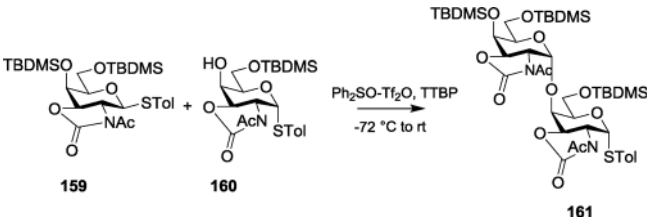
Remote participation of certain protecting groups to facilitate the glycosidic bond formation with 2-deoxy thioglycosides has also been studied.[261] Mong and co-workers have shown the effects of picoloyl (Pico) group, illustrating their role for the glycosylation[262] with deoxy glycoside donors. Thioglycosides with the picolyl protecting group at the C-6 position, on being activated with NIS/TMSOTf, was seen to give significant β-stereoselectivity. Introduction of S-(phenylthiomethyl)benzyl moiety at the C-6 position of 2-deoxy or 2,6-dideoxy glycosyl donors was also responsible for the synthesis the α-isomer.[263]

3.7.2. 2-Amino-2-deoxy Sugars

By virtue of their structures and reactivities, 2-amino-2-deoxy sugars are widely distributed in various living organisms as glycoconjugates.[2,264] Previous Reviews[265] have widely explained the strategy behind the introduction of the participation and non-participating group in the C-2 position to direct the glycosylation to the required stereochemistry. 2-Amino-2-deoxy sugars have been widely used in oligosaccharide syntheses.[266] Repeating sequence of α-GalNAc was found to be effectively

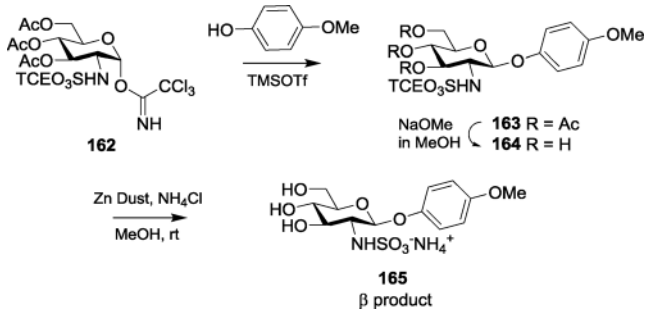
synthesized by the introduction of oxazolidinone group.[267] The *N*-acetyloxazolidinone-protected thioglycosides both as the glycosyl donor **159** and acceptor **160** was effective (Scheme 36) when activated with Ph_2SO–Tf_2O promoter system to give exclusive α-stereoselective product **161** in good yields. The synthesis of various important core glycoside parts of GPI anchors, heparin, heparin sulfate, and heparosan had also been successfully accomplished by Hung and co-workers.[268] In 2008, anhydrous $FeCl_3$-catalyzed direct formation of α-*N*-acetyl-glycosaminides was also successfully achieved by Wei et al.[269] and it was effectively implemented in the large-scale preparation of fluorogenic T_N-antigen probes.

Recently, glycosides with a phthalimido group in the C-2 position were found to be activated by the hypervalent iodine compound, phenyliodine bis(trifluoroacetate) (PIFA) in the presence of triflic acid.[270] Proper optimization of the reaction conditions of this metal-free glycosylation afforded the coupled product in significant yields. Direct glycosylation with GlcNAc has also been reported by Jensen and co-workers[271] through the activation of thioglycosides **166** or pentenyl glycosides **167** by using various metal triflates (Table 7). However, when glycosylated with carbohydrate acceptors, the yields obtained were poorer than simple acceptors like 1-octanol or (−)-menthol. 2-Deoxy-2-*N*-sulfate glycosides **162** were also successfully utilized (Scheme 37) to give the desired β-glycosylated products **163** in excellent yields[272] on being protected with 2,2,2-trichloroethyl (TCE) group, after which it could be easily deprotected by reacting Zn in the presence of ammonium chloride in methanol. A $Yb(OTf)_3$-mediated synthesis of *N*-



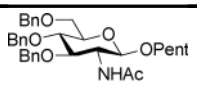
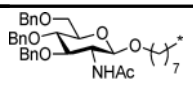
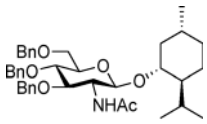
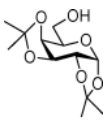
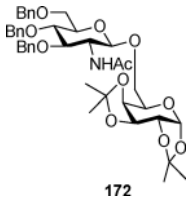
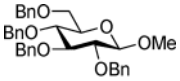
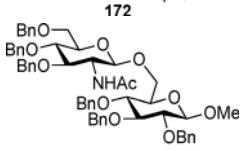
Scheme 36. The use of *N*-acetyloxazolidinone protected thioglycosides as both donor and acceptor.

acetyl glucosamine derivatives[273] has also been established by Crasto and Jones, which gave β-glycosylated product in high yields. Direct synthesis of 1,2-amino glycosides with *p*-methoxybenzylidene group in the C-2 position was achieved by Mensah and Nguyen by using nickel catalysts.[274] Optimization



Scheme 37. Use of 2-deoxy −2-*N*-sulfate glycosides in glycosidations.

Table 7. A comparative study of metal-catalyzed glycosylations with 2-amino-2-deoxy donors with different acceptors.

No	Donor	Acceptor	Product	Activation	Temp	Time	Yield [%]
1	 **166**	1-octanol (1 equiv)	 **168**	$Sc(OTf)_3$, NIS	RT	16 h	88
2	**167** (2 equiv)	1-octanol (1 equiv)	168	$Cu(OTf)_3$, NIS	RT	16 h	84
3	**167** (2 equiv)	1-octanol (1 equiv)	168	$Zn(OTf)_3$, NIS	RT	16 h	88
4	**167** (2 equiv)	(−)-menthol (1 equiv)	 **170**	$Cu(OTf)_3$, NIS	RT	25 h	76
5	**167** (3 equiv)	 **171**	 **172**	$Cu(OTf)_3$, NIS	RT	5 days	37
6	**167** (3 equiv)	 **173**	 **174**	$Cu(OTf)_3$, NIS	RT	2 days	50

of the reaction showed that $Ni(4\text{-}FPhCN)_4(OTf)_2$ gave the best stereoselectivity with maximum effectiveness within a short reaction time.

Thus, for amino sugars, the stereochemistry of the products largely depended on the directing properties of the protecting group in the C-2 position. Modifications in the nature of the protecting group are still an active area of research.

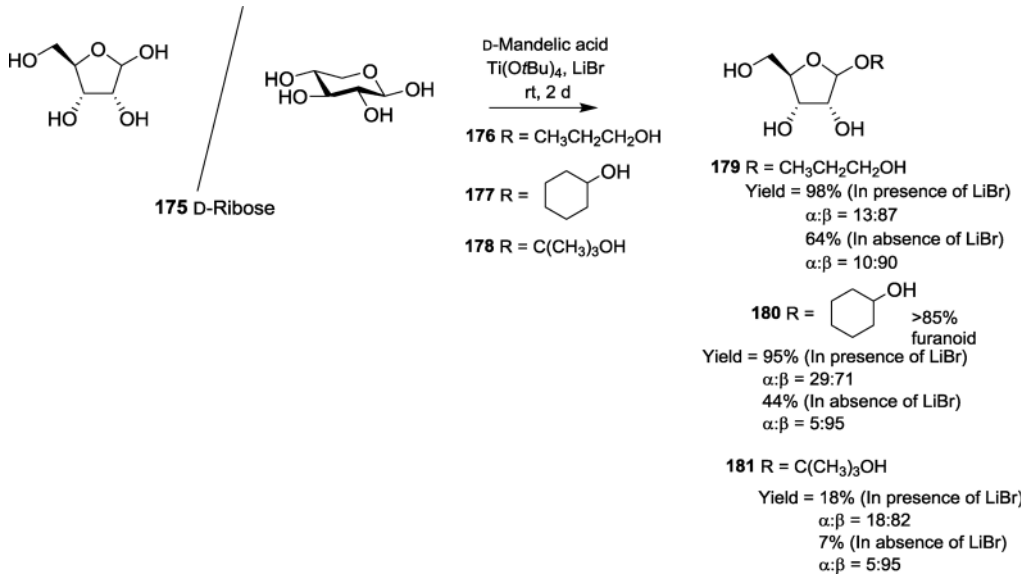
3.8. Other Types of Glycosylation

3.8.1. Protecting-Group-Free Glycosylation

Until now, most of the glycosylating protocols described dealt with O-protected glycosyl donors, aiding in the synthesis of varied glyconjugates and higher oligosaccharides. However, there has been much discontent about glycosylations performed with unprotected glycosyl donors with activated anomeric center. This is largely because accomplishing glycosylations without protecting the hydroxyl groups brings forth a number of advantages, the prime issue being the reduction in the protecting-group manipulation steps of the complex oligosaccharide synthesis. It also opens the scope for iterative glycosylations, which lead to the continued coupling of the sugar fragments. Moreover, these hydroxyl glycosides also promises to overcome the issue of reduced reactivity with the acyl-protected glycosides. The free hydroxyl groups also leave the opportunity for its ready use in various antibodies and therapeutics.

Despite all of the advantages, performing glycosylations with unprotected glycosyl donors present some major hurdles. Similar to 2-deoxy glycosides, the absence of any directing group in the C-2 position makes it highly difficult to control the stereochemistry of the formed glycosidic bond in the anomeric center. Moreover, the easy accessibility of more than one reactive hydroxyl groups requires the application of highly selective reagents capable of performing the coupling in the desired position. Hence, studies to optimize the reagents and the conditions to attain the best possible output are underway. Describing all glycosylation protocols developed in this field would require a complete detailed Review in its own right. The strategies of the past century have already been extensively reviewed.[275] However, we aim here to describe the ones that show the most significant promise and can contribute to the challenges in performing regular glycosylations.

In an attempt to find a suitable robust donor capable of being activated in its unprotected state, Roy and Mukhopadhyay performed Fischer-type glycosylation to establish the use of H_2SO_4–silica to couple unprotected free sugars with different alcohols.[276] Interestingly, Pfaffe and Mahrwald showed that, when variously functionalized alcohols were reacted with free D-ribose **175** catalyzed by 10 mol% of titanium-(IV) *tert*-butoxide and 50 mol% D-mandelic acid at room temperature, only coupled ribose furanosides (Scheme 38) were obtained.[277] Addition of lithium bromide significantly enhanced the yield in acetonitrile medium. The same group in the following year introduced the concept of organo-catalyzed glycosylation of unprotected and unactivated glycosides.[278] Here, traces of PPh_3 and CBr_4 were used as the catalyst with $LiClO_4$ as the essential additive. Surprisingly, this catalyst was successful in facilitating the formation of exclusive β-products. Recently, Bhattacharrya and co-workers also described the activation of both unprotected and unactivated glycosides by using 10 mol% of bismuth nitrate pentahydrate.[279] The yields of the desired products were significantly increased when unprotected sugars were subjected to Fischer glycosylation by sulfamic acid.[280] Sharma et al. reported the coupling of free unprotected and unactivated sugar molecules with alcohols on being mediated by NH_4Cl at 90 °C.[281] The yields of the products obtained were claimed to be higher and the process less time consuming compared to the standard glycosylation protocols using unpro-



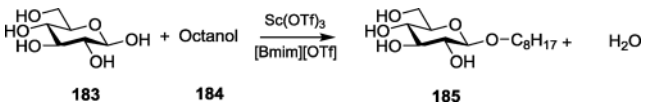
Scheme 38. Reaction of D-ribose with different alcohols.

tected glycosyl donors in the presence of common catalysts like Amberlite IR-120 (H^+) resin, $InCl_3$, $In(OTf)_3$, $Sc(OTf)_3$, and HCl.

The use of ionic liquids for performing glycosylations with unprotected glycosyl donors has also been explored. RTILs such as 1-ethyl-3-methylimidazolium benzoate ([emIm][ba]) in the presence of Amberlite IR-120 (H^+) resin or *p*-toluenesulfonic acid (TsOH) were used[282] as promoters. These ionic liquids were reported to be successful in activating various unprotected sugar units for the desired oligosaccharide synthesis. Glycoconjugates derived from the glycosylations with this ionic liquid were also studied for their affinity towards lectins.[283] Auǵe and Sizun reported the use of ionic liquids in Lewis-acid-catalyzed glycosylations in 2009. They first explored the catalytic efficiency of various metal salts like $InCl_3$, $In(OTf)_3$, $Sc(OTf)_3$, and $Yb(OTf)_3$ at different temperatures. The studies revealed that even a catalytic amount of $Sc(OTf)_3$ provided the optimum yield at 80 °C on continuing the reaction for a longer period. Considering this and predicting the mechanism following the oxocarbenium ion intermediate, Auǵe and Sizun attributed the increase in yield and regioselectivity by the use of ionic liquids.[284] A variety of ionic liquids, varying in their ionic part, were tested, among which 1-butyl-3-methylimidazolium trifluoromethanesulfonate [bmim][OTf] gave encouraging results. Optimization of the reaction was, thus, accomplished with different unprotected sugars **182** and alcohol **183** catalyzed by $Sc(OTf)_3$ in the presence of 1 mol% of [bmim][OTf] as the solvent (Scheme 39). The results of the reactions with octanol as the acceptor alcohol (Table 8) showed that the reagent is capable of generating the desired product in subtle α-selectivity. $Sc(OTf)_3$ as the catalyst has also been utilized for glycosylation of carbohydrates with different amino acids have also been accomplished in [bmim][OTf].[285]

Unprotected alkynyl glycosides were also explored for activation by Mamidyala and Finn,[286] who tried to optimize the reaction conditions by using different solvent systems and employing variable temperatures catalyzed by Au^{III} salts. Detailed studies revealed the versatility of refluxing acetonitrile as the solvent to achieve the best possible yield. The same protocol was also verified by applying it for the synthesis of a trisaccharide. However, the stereoselectivity obtained in the reaction did not show much promise.

A photoinduced protocol was also employed by Toshima and co-workers in 2013, who described a novel glycosylation protocol through photoinduced activation of unactivated deoxy thioglycosyl donors.[119] Here, DDQ served as the SET reagent, whereas boronic acid was used as a temporary 1,3-diol protection, leaving the primary hydroxyl group available for reaction to prevent the corresponding self-coupling and the formation of anhydrosugars.

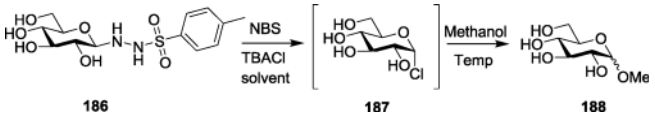


Scheme 39. Reaction of unprotected sugars with alcohol.

Table 8. Different yields obtained on the reaction of free sugars with octanol.

Sugar	Temp [°C]	Time [h]	Yield [%]	α/β
D-glucose	80	24	74	75:25
D-galactose	80	24	70	61:39
D-mannose	80	24	88	100:0
L-fucose	80	24	51	67:33
N-acetyl-glucosamine	110	24	60	79:21

Nitz and co-workers introduced different anomeric protecting groups that show promise to be activated in protecting-group-free conditions.[287] *N*′-Glycosyltoluenesulfonohydrazides (GSHs) (**186**) have also been used in the formation of various glycosyl O-phosphates[288] upon being activated by NBS in DMF. Glycosylation of these GSHs with non-volatile alcohols were demonstrated to give moderate yields, but with poor stereoselectivity.[50] However, the possibility of the formation of unprotected glycosyl chloride **187** from GSH was explored in situ (Scheme 40), which can further undergo coupling with



Scheme 40. Glycosylation of unprotected *N*′-glycosyltoluenesulfonohydrazides through the formation of glycosyl chlorides.

alcohols at a faster rate, giving better yields. But, in both cases, poor stereoselectivity (β-anomer predominating) limits the scope of such anomeric leaving groups.

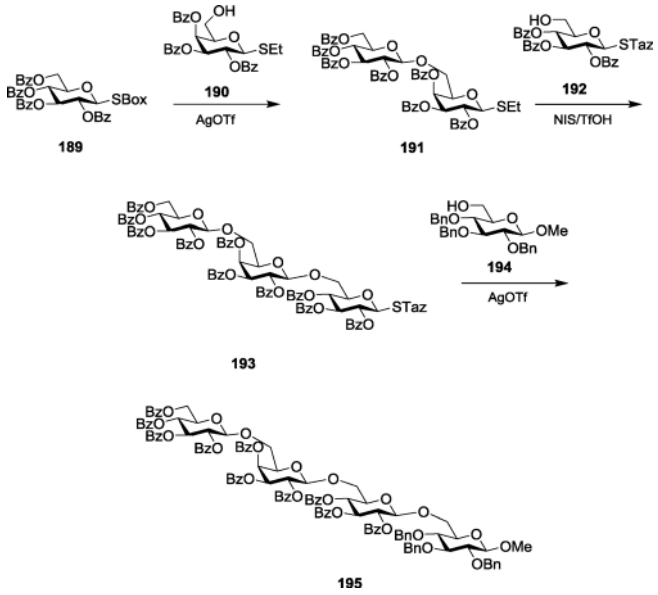
Further efforts are still being made in improving the stereoselectivity of glycosylation involving unprotected glycosyl donors. Atom economy and faster protocols show much promise towards expeditious oligosaccharide synthesis.

3.8.2. One-Pot Glycosylation

Among the various progress achieved in oligosaccharide synthesis in the current century, the one-pot glycosylation strategy has emerged as an important strategy. One-pot glycosylations claim to be the shortest possible route for oligosaccharide synthesis. The strategies focus on an easy solution for issues related to purification and isolation of the intermediate products. However, one-pot iterative glycosylations demand the use of strategically synthesized sugars. Such glycosylation strategies may be accomplished by employing either 'armed–disarmed' concept[24] or chemoselective activation of the glycosyl donor. Thus, it becomes highly evident that one-pot iterative glycosylations are primarily based on the reactivity difference of synthons at a particular reaction condition.

The present century has seen significant development in the domain of one-pot glycosylations.[289] In this Review, we report some of the most distinct illustrations that prove the versatility

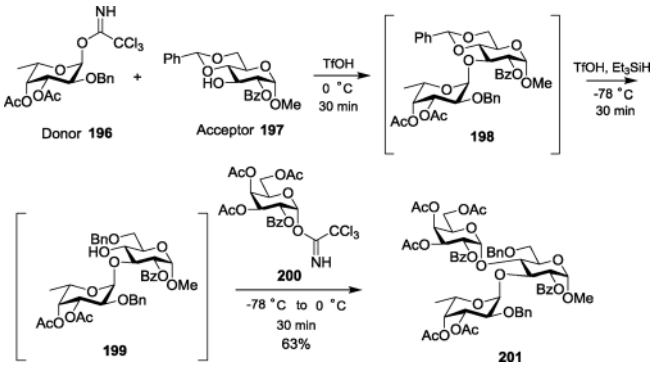
and novelty of such a glycosylation protocol and make it clear that one-pot glycosylations are here to stay. In 2005, Demchenko and co-workers utilized the reactivity difference of various thioimidates in convergent oligosaccharide synthesis.[290] They illustrated the successful one-pot synthesis of a tetrasaccharide, utilizing the reactivity difference of SBox, STaz, and SEt derivatives. Starting with an SBox **189** and a thioethyl glycoside **190**, the first glycosylation was performed at room temperature in the presence of AgOTf as the catalyst, which selectively activated the SBox derivative to give the desired SEt disaccharide **191** exclusively. It was followed by the addition of another STaz acceptor **192** in the same reaction pot, and now the SEt group was activated by using the NIS/TfOH promoter system to afford the desired STaz trisaccharides **193** exclusively. Finally, the methyl glycoside acceptor **194** was added along with AgOTf to afford the required tetrasaccharide **195** (Scheme 41)



Scheme 41. One-pot glycosylation exploit reactivity differences of different thioglycosides donors.

through the activation of STaz. The final yield of the product obtained was quite significant, which highlighted the versatility of the iterative sequence. The advantage of one-pot protocols over stepwise methodologies with leaving groups having different reactivities has also been illustrated by Cao and co-workers[291] in a recent report of synthesis of a branched pentamannoside.

Fine tuning of the donors has also facilitated synthesis of various convergent oligosaccharides. Polat and Wong demonstrated the successful one-pot synthesis of the biologically relevant heparin-like oligosaccharides[292] by strategically synthesizing monosaccharide synthons. One-pot glycosylations can also be performed by implementing the pre-activation protocol. In 2008, Boons and co-workers combined the reductive opening of the benzylidene acetals with sequential glycosylations in the course of synthesizing a trisaccharide.[293] The most essential attribute of the whole process remains the selection of the proper reagent system. Likewise, after the first set of glycosylations with the trichloroacetimidate donor **196** and benzylidene protected acceptor **197** in the presence of TfOH, more TfOH and Et_3SiH were added, following the reduction of the reaction temperature to −78 °C. The reagents were capable of selectively deprotecting the benzylidene group, which extended the scope to further coupling with another trichloroacetimidate donor **200** in the same reaction pot (Scheme 42). Desired trisaccharide **201** was subsequently formed in 63% yield.

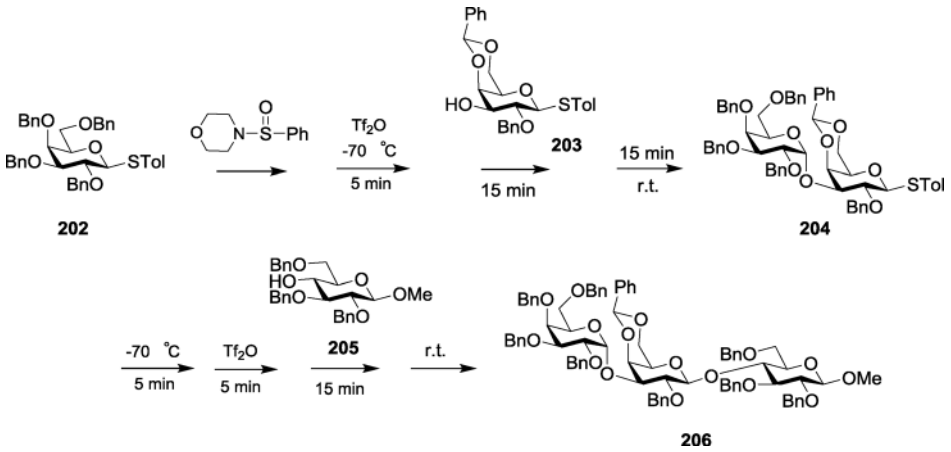


Scheme 42. Synthesis of a trisaccharide through one-pot glycosylation.

In a different sequence, using chemically different functionality in the anomeric center, Iadonisi and co-workers modified the stepwise assembly of the biologically relevant antitumor PI-88 pentasaccharide to a more robust and convenient one-pot reaction strategy.[138] The product was obtained by the use of mild Lewis acid catalysts like $Yb(OTf)_3$ and $Bi(OTf)_3$. Similarly, tumor-associated carbohydrate antigen Globo-H hexasaccharide was synthesized through the pre-activation protocol[294] in near-stoichiometric yield. Various other expeditious oligosaccharide syntheses have been successfully achieved by using chemoselective one-pot strategies.[295] Ye and co-workers introduced a new promoter system, benzenesulfinyl morpholine (BSM), to increase the efficiency of one-pot glycosylations through pre-activation method.[296] For the synthesis of the trisaccharide **205**, BSM was added for the complete activation of the thioglycoside **202** in the presence of Tf_2O at −70 °C. Further addition of **203** after bringing the reaction temperature back to ambient led to the exclusive formation of disaccharide **204**. Subsequent reduction of the reaction temperature to −70 °C and activation of the thioglycosides with BSM/Tf_2O promoter system followed by addition of acceptor **205** provided trisaccharide **206** (Scheme 43) within 1 h in moderate yield.

In different activation methods, polymer-assisted one-pot synthesis of trisialic acid has been effectively achieved by Tanaka et al.[297] Ionic liquids have also facilitated one-pot syntheses. Galan et al. introduced the use of [bmim][OTf] as promoter in the presence of NIS for the region- and chemoselective glycosylation of glycosides with different reactivities.[298]

Despite the progress of one-pot synthesis methods in the last two decades, there are still many limitations in its universal application. Studies and extensive investigations are being



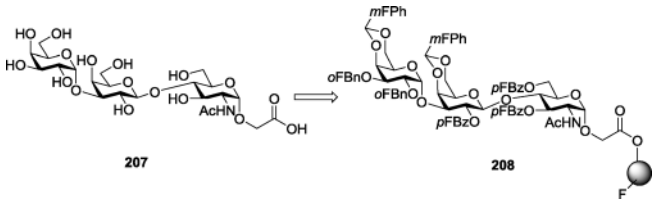
Scheme 43. Chemoselective one-pot glycosylation of a trisaccharide.

made to implement such processes in the expeditious synthesis of more natural oligosaccharides. However, this strategy shows immense promise, having the potential to emerge as a powerful synthetic tool in the domain of carbohydrate synthesis.

3.8.3. Solid-Phase Synthesis

Solid-phase oligosaccharide synthesis (SPOS) is an emerging field in carbohydrate chemistry that has attracted overwhelming interest in the present century. This modern method of carbohydrate synthesis claims to overcome various shortcomings of solution-phase synthesis. Moreover, the need to perform purification at each step of a solution-phase synthesis limits the applicability of the process, to a large extent, whereas SPOS involves a protocol that removes the excess reagents and other solution-phase impurities by simple washing of the resin, thereby reducing the number of chromatographic steps involved. However, solid-support-based carbohydrate synthesis requires judicious planning and systematic implementation. The polymer support and the linker for its attachment to the sugar need to be planned very carefully so that it can withstand the conditions for the essential protecting-group manipulations. However, at the same time, it should be labile so that it can be cleaved as and when required. Solid-phase iterative strategies may be accomplished either by attaching the reducing or the non-reducing end of the sugar to the solid polymeric support, leaving the growing end subjected to glycosylations. Attainment of stereospecific glycosylations in high yields through rationally designed strategies has made SPOS a widely used protocol. Taking cue from the first solid-phase oligosaccharide synthesis by Fréchet and Schuerch[299a] in 1971 using Merrifield resin, rigorous attempts to develop smarter strategies have been observed in the later part of the last century.[299b,300] Various Reviews[301] have revealed versatile and comprehensive overviews on SPOS. A study by Kanie et al. gives a broad comparative picture, as the group synthesized a wide range of fucosyl–galactosyl oligosaccharides in both the solution and solid phase.[302]

Monitoring the progress of reactions in SPOS is extremely essential. The crudest way is to take aliquots of the reacting resins and subject them to thin-layer chromatography after cleaving them from the resins. Moreover, knowledge of the exact time required for the total completion of the reaction is crucial, as it has been observed that both a shorterned reaction time and exposure to excess time have been detrimental, increasing the amount of impurities in the product library. Thus, analysis of the on-support conversions and yields becomes inevitable for the development of SPOS. ^{1}H and ^{13}C NMR spectroscopy has been explored in combination with other methods; but, it requires some time consuming and expensive protocols. Hence, in early 2001, Kihlberg and co-workers implemented the use of gel-phase ^{19}F NMR spectroscopy[303] by using fluorine-labeled protecting groups in combination with fluorinated linkers. No countering signals were observed, owing to the absence of any fluorine group in the resins. Hence, monitoring solid-phase oligosaccharide reactions by ^{19}F NMR promised to provide much impact in the times to follow. By using the same protection protocols of fluorinated analogs, the same group utilized ^{19}F NMR spectroscopy to monitor the solid-phase synthesis of α-Gal trisaccharide epitopes **207**[304] after loading them with ArgoGel resin (Scheme 44). ^{13}C NMR spectroscopy has also been found to monitor SPOS successfully, where the gated decoupling technique was implemented.[305] Other methods for monitoring SPOS include single-bead FTIR microspectroscopy, but it leads to significant overlap of spectra from the presence of multiple components including starting material, the involved resin, along with the formed product. To overcome this shortcoming,



Scheme 44. Solid-phase synthesis of α-Gal trisaccharide epitope.

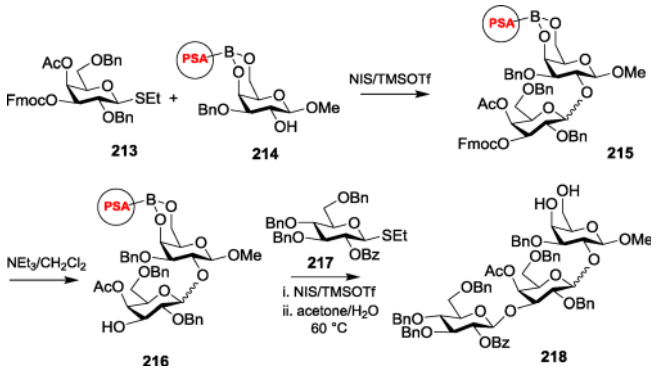
Yan and Yan introduced partial least squares (PLS), a chemometrics method for qualitative and quantitative analyses of samples.[306] In this method, the removal or introduction of the organic functionalities in the ongoing reactions was displayed as positive or negative signals, respectively, thereby establishing itself as an effective and powerful analytical tool for SPOS.

In another method, Manabe and Ito utilized a colorimetric method to establish real-time monitoring of the on-resin oligosaccharide synthesis by employing disperse red ($C_{16}H_{18}N_4O_3$) and (*p*-nitrobenzyl)pyridine (PNBP) color tests.[307] Owing to the complementary nature of the two tests, the progress of glycosylation reactions were successfully established by using these methods. The removal of the chloroacetyl group in the monosaccharide **209** was established by the positive red color in the disperse red test and negative result in the PNBP test. Subsequently, the disappearance of the hydroxyl groups in the glycosylation reaction was indicated by the negative disperse red and strongly positive PNBP tests (Table 9).

In SPOS, studies have shown that the presence of longer spacer connecting the synthons with the resin helps the coupling more than glycosides with a shorter spacer.[308] Longer spacers help in bringing the sugar part more into the solution phase and provide more accelerated reactive platform.

Resin-bound thioglycoside donors have successfully undergone glycosylation reactions with various acceptors under standard reaction conditions.[309] Direct transfer of resin-bound (JandaJel)[310] thio glycosyl donors to complex aglycons was accomplished by Bennett and co-workers.[311] Optimization of reaction conditions implied benzenesulfinyl piperidine/triflic anhydride (BSP/Tf_2O) as the best candidate of promoter in such a transformation. Glycosyl thioimidates have been successfully utilized for solid-supported glycosylation strategies. In 2007, Demchenko and co-workers performed glycosylations and, in one case, the solid-bound acceptor was coupled with the imidate (SBox or STaz) donor and, in another case, the glycosyl thioimidate was bound to the resin followed by its glycosylation with the acceptor.[164] Normal activation protocols using TMSOTf or AgOTf were employed for the glycosylations.

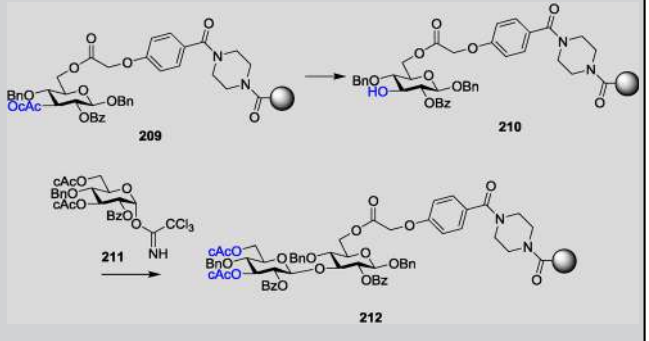
To establish a versatile SPOS strategy, Boons and co-workers introduced polystyrene boronic acid (PSA)[312] as the resin support that proved to be apt in its role. The ease of its preparation, the use of minimum amount of solvents for its loading, the cleavage, and its reusable nature made this resin widely used in oligosaccharide synthesis. When using PSA as the resin in oligosaccharide synthesis, protecting groups were selected, taking into consideration that the boronic ester linkage hydrolyzed in protic solvents. Hence, Fmoc protection was selected, as it is inert to protic solvents and could be cleaved by the treatment of triethylamine. Fmoc-protected thioglycosides donor **213** was coupled with PSA-immobilized acceptor **214** with the help of NIS/TMSOTf to obtain the resin-bound disaccharide **215**. The Fmoc group was then selectively cleaved to obtain the disaccharide acceptor **216**, with the solid support intact. This PSA-bound disaccharide was further coupled with thioglycoside donor **217** to obtain the final trisaccharide. Eventually, the resin could be cleanly cleaved by the application of an acetone–water mixture, obtaining trisaccharide **218** (Scheme 45), which can be further characterized by using spectroscopy. Capping reagents like benzoyl isocyanate have also been implemented, which aid in performing glycosylations by blocking the unconsumed acceptors and helping with cleaner SPOS.[313] It helped in the purification of the formed glycosides, as it conveniently prevented the formation of unwanted sugar analogs with the unreacted counterparts.



Scheme 45. Glycosylations on polymer support.

Based on the convenient principles of solid-phase polymer-supported oligosaccharide synthesis, there have been examples of the synthesis of higher analogs of carbohydrates.[314] Crich and Smith successfully applied a method for the synthesis of the unnatural β-mannoside linkage.[315] Schmidt and co-workers also performed SPOS to synthesize a branched hexasaccharide, lacto-*N*-neohexaose derivative (found in human milk) by immobilization of linker-loaded polystyrene resin.[316] Glycosyl trichloroacetimidates were used as the efficient donors, whereas Fmoc and Lev protecting groups were exploited.

Table 9. Colorimetric assessment of solid-phase glycosylations.



Compound	PNBP test	Disperse red test	Remarks
209	positive	negative	positive PNBP test confirms presence of chloroacetyl group
210	negative	positive	positive disperse red test confirms presence of OH group
212	positive	negative	confirms of the presence of chloroacetyl group

Thus, from where it was left in the previous century, SPOS has seen much progress in recent years. More vivid study on SPOS methods reveals widespread use of various glycoside donors like sulfoxides, thioglycosides, trichloroacetimidates, pentenyl glycoside, and so forth for effective glycosylation methodologies. However, solid-phase synthesis still suffers certain limitations. These challenges open broader scopes of study to ascertain higher levels of stereochemistry, optimum, and suitable protecting-group manipulations as well as the efficient use of the reagents in the synthesis of the solid-supported glycosides. It is noteworthy that the present century promises to open new dimensions of solid-phase oligosaccharide synthesis with its innovative and successful implementation in the introduction of a new domain involving automated oligosaccharide synthesis.

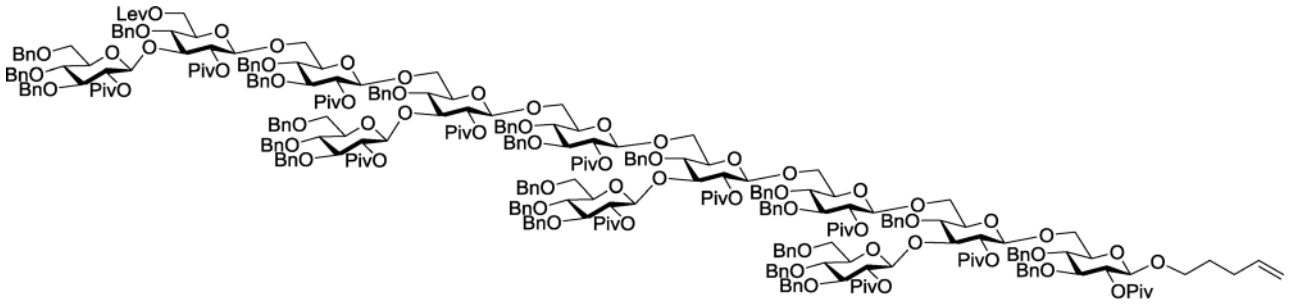
3.8.4. Automated Oligosaccharide Synthesis

Building on solid-phase oligosaccharide synthesis, Seeberger et al. introduced the concept of automated oligosaccharide synthesis.[317] Automated oligosaccharide synthesis is based on the same principle of SPOS, where the choice of the solid support and the linker plays a major role in the determination of the synthetic strategy. Moreover, protecting-group manipulations should also be planned accordingly, with the inertness of the solid support and the linker with the glycosides. Considering the various aspects, Seeberger first utilized peptide synthesizer to develop an automated method for glycoside synthesis. Automated synthetic procedures enable the number various manual routine functions to be reduced by employing iterative synthesis comprising of selective deprotection, glycosylation, removal of the resin, and deprotection in a programmed reactor.[317] The reactor was designed to perform conversions at variable temperatures subject to external programming, thus simplifying the synthesis of complex oligosaccharides. The widely used temporary protecting group suitable for such programmed reaction strategies, owing to their capability of selective cleavage, include Fmoc, Lev, and Nap, whereas the permanent protecting groups include benzyl, benzoyl, benzylidine, or azide.

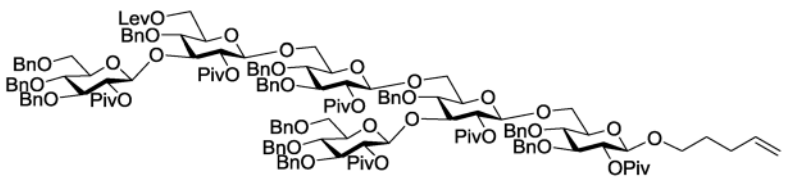
With systematic synthetic strategy, Seeberger and co-workers accomplished the first automated synthesis of two phytoalexin elicitors, a hexasaccharide **220** and a dodecasaccharide **219** (Figure 8).[318] The widespread applicability of the glycosphingolipids, such as Globo-H and Gb-3, as probable antigens in a variety of cancers made them highly attractive biological targets. Automation of oligosaccharide synthesis has accomplished their synthesis in a linear fashion with glycosyl phosphates as the building blocks,[319] facilitating the formation of the α-galactosidic linkages immobilized on a solid support. LC–MS was successfully used to monitor reaction steps. Synthesis of the difficult β-mannosidic bond was also achieved by using an automated protocol. Codée et al. demonstrated the β-mannosylation by using carboxybenzyl glycosides[320] on a solid support through automated synthetic cycles. Purification of the synthesized oligosaccharides through an automated strategy was also optimized by using the capping and tagging method of Seeberger and co-workers.[321] The use of any scavenger resin or proper filtration through a fluorinated silica gel has proved to be the best choice for such a process.

Although many reactions have been accomplished with the peptide reactor turned carbohydrate reactor, Seeberger and co-workers developed the first fully automated solid-phase oligosaccharide synthesizer in 2012.[322] The reactor not only allowed the iterative steps involved in the multistep synthesis, but is also equipped with various essential gadgets that facilitate the controlled syringe–pump driver reagent delivery and computerized temperature control ranging from -50 to 90 °C.

The choice of linker has always been the most significant aspect in planning the strategy for performing automated



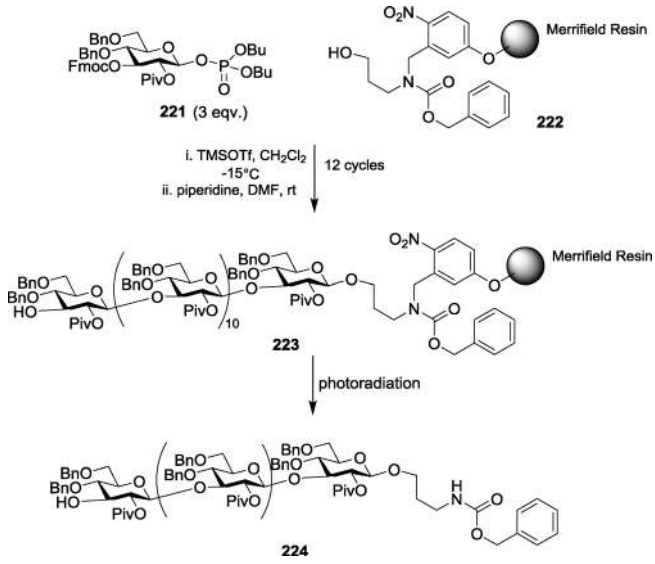
219



220

Figure 8. First oligosaccharides synthesized by using the automated protocol.

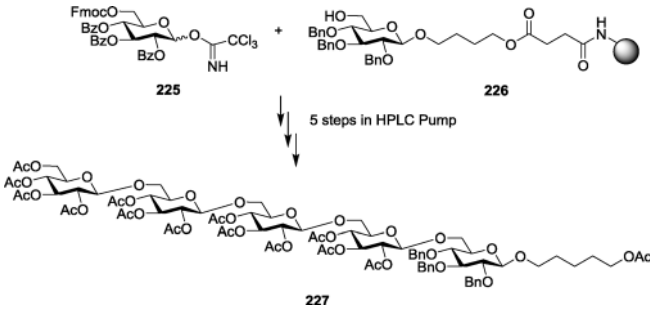
solid-support-based oligosaccharide synthesis. The limitations of their instability in different acidic and basic conditions prompted to develop photo-labile linkers as a suitable choice in such automated synthesis. A photolabile nitrobenzyl-ether-based linker has been used to synthesize two chondroitin hexasaccharide fragments of glycosaminoglycans in a continuous flow reactor, implementing a carefully planned protecting group manipulations and glycosylation strategy.[323] Seeberger's group carried out the synthesis of β-(1,3)-glucan dodecasaccharides by using both thio and phosphate glycosides as donors in the presence of photo-labile linker immobilized on Merrifield's resin.[324] Solid support **222** was used for the immobilization, which utilized three equivalents of glycosyl phosphate **221** in three repeats over 12 glycosylation cycles. TMSOTf was used as the Lewis acid promoter that could be conveniently added to the building blocks, **221** and the attacking acceptor glycoside through strategically designed syringe pumps in the automated flow reactor (Scheme 46). In between



Scheme 46. Oligosaccahride synthesis in automated flow reactor.

each glycosylation steps, the temporary Fmoc protecting group had to be selectively removed. After the successful completion of the glycosylation sequences, the cleavage of the solid support was also performed in the same reactor by photoradiation. The use of fully automated synthesizers has also been used for the synthesis of sialyl oligosaccharides,[325] β-mannuronic acid alginates,[326] oligoarabinofuranosides and galactans,[327] and hyaluronan oligosaccharides[328] that offer broad scopes in conveniently evaluating their biological properties. Higher oligosaccahrides, such as a 30-mer polysaccharide of mannose, were also synthesized by using an automated flow reactor where the purification was done by the catch-release method.[329] The yields obtained through this protocol were significant, with an average of 96% in each step and the entire synthesis of the polysaccharide accomplished in less than a week.

Nullifying the requirement of a sophisticated automated oligosaccharide synthesizer, methods of automated oligosaccharide synthesis in solution phase were also developed. Jaipuri and Pohl effectively synthesized linear and branched mannoside fragments based on solution-phase automated iterative synthesis.[330] The same group recently used the same protocol to synthesize β-1,4-mannuronate and β-1,4-mannan by using glycosyl trichloroacetimidates as the subsequent donors.[331] Recently, Demchenko and co-workers introduced the concept of HPLC-based carbohydrate synthesis.[332] They included a normal HPLC setup in order to facilitate all standard reaction steps essential in automated synthesis of a pentasaccharide **227** using repeated glycosylations with **225** and **226** as the synthons (Scheme 47). However, optimization of the various re-



Scheme 47. HPLC-assisted synthesis of a pentasacchaide.

action conditions for the setup is under way. A suitable carbohydrate building block was rigorously optimized for performing glycosylations in an automated electrochemical assembly to synthesize a tetrasaccharide fragment from *N,N,N*-trimethyl-D-glucosaminyl (TMG)–chitotriomycin.[333] Thioglycosides have also been implemented in such an electrochemical assembly to synthesize poly-β-D-(1-6)-*N*-acetylglucosamine (PNAG),[334] using six thioglycosides in a sequential one-pot setup. Recently Seeberger's group performed a gold-catalyzed solution-phase oligosaccharide synthesis in a continuous flow reactor.[200] Glycosyl *ortho*-hexynylbenzoates were used as the donor for coupling with various sugar and non-sugar derivatives catalyzed by PPh_3AuOTf, furnishing the required glycosides/glycoconjugates in significant yields.

Automated glycoside synthesis in flow reactors is the latest addition in the chemistry of carbohydrate glycosylations based on the available instrumental facilities. This protocol claims to show much applicability in the following years by virtue of its ability to furnish complex higher analogs of polysaccharides in shorter time and in significant yields. However, the procedure still awaits further optimizations by solving the limitations it offers. The applicability of the process would facilitate interdisciplinary aid to the biologists in understanding the role of carbohydrates in the biological systems and in the development of carbohydrate-derived antigens, thereby facilitating the advancement of the domain of therapeutics.

4. Conclusions and Outlook

Significant development in the area of chemical O-glycosylation strategies is evident from the literature. These novel approaches offer a solid platform to deal with various complex oligosaccharides relevant for biological applications. The methods developed in the current century have helped us to get a better insight into the reactivity of glycosyl donors and acceptors. Novel promoter systems have enabled us to form glycosidic linkages with better stereoselectivity. Introduction of one-pot iterative synthesis has minimized the labor required for complex oligosaccharide synthesis. With the development of solid-phase synthesis and sophisticated automated glycosylation techniques, the future looks truly promising. However, the challenge of oligosaccharide synthesis is not yet over. Other than few ventures with protecting-group-free syntheses, chemical O-glycosylations still suffer from the requirement of cumbersome protecting-group manipulations that seriously defy the urge for atom economy. Moreover, the number of truly green reaction strategies is low in this domain. A sincere effort is needed to develop green and atom economic glycosylation strategies that can take us to a comparable domain of nature's enzymatic means of oligosaccharide preparation. We sincerely hope that the present survey of chemical O-glycosylation strategies will help researchers to have a better understanding of the current scenario and pave the way for future developments in this important area.

Acknowledgements

R.D. is thankful to IISER Kolkata for a Postdoctoral fellowship. The work is partially funded by the Science and Engineering Research Board (SERB), New Delhi through Grant No. SB/S1/OC-48/2013 to B.M.

Keywords: catalysis · glycosylation reactions · promoters · protecting groups · stereoselectivity

[1] a) L. Stryer, *Biochemistry,* W. H. Freeman, New York, **1988**; b) D. E. Metzler, *Biochemistry-The Chemical Reactions of Living Cells*, Academic, New York, **1977**; c) D. Voet, J. G. Voet in *Biochemie* (Eds.: A. Maelicke, W. Muller-Esterl), Wiley-VCH, Weinheim, **1994**; d) J. Montreuil, *Adv. Carbohydr. Chem. Biochem.* **1980**, *37*, 157 – 223.

[2] a) A. Varki, *Glycobiology* **1993**, *3*, 97 – 130; b) A. Varki, R. Cummings, J. Esko, H. Freeze, G. Hart, J. Marth, *Essentials of Glycobiology*, Cold Springer Harbor Laboratory Press, New York, **1999**; c) G. E. Bertozzi, L. L. Keissling, *Science* **2001**, *291*, 2357 – 2364; d) P. Sears, C. H. Wong, *Science* **2001**, *291*, 2344 – 2350.

[3] a) G. E. Ritchie, B. E. Mofatt, R. B. Sim, B. P. Morgan, R. A. Dwek, P. M. Rudd, *Chem. Rev.* **2002**, *102*, 305 – 319; b) B. G. Davis, *Chem. Rev.* **2002**, *102*, 579 – 601; c) K. OhtSubo, J. D. Marth, *Cell* **2006**, *126*, 855 – 867; d) J. R. Bishop, M. Schukz, J. D. Esko, *Nature* **2007**, *446*, 1030 – 1037; e) R. J. Linhardt, *J. Med. Chem.* **2003**, *46*, 2551 – 2564.

[4] a) L. L. Kiessling, R. A. Splain, *Annu. Rev. Biochem.* **2010**, *79*, 619 – 653; b) T. Boltje, T. Buskas, G. J. Boons, *Nat. Chem.* **2009**, *1*, 611 – 622.

[5] R. A. Dwek, *Chem. Rev.* **1996**, *96*, 683 – 720.

[6] Although we have now learned to synthesize oligosaccharides, it should be emphasized that each oligosaccharide synthesis remains an independent problem, whose resolution requires considerable systematic research and a good deal of know-how. There are no universal reaction condition for oligosaccharide synthesis''–Hans Paulsen.

[7] a) K. Toshima, K. Tatsuta, *Chem. Rev.* **1993**, *93*, 1503 – 1531; b) L. Bohé, D. Crich, *C. R. Chim. C. R. Chimie* **2011**, *14*, 3 – 16; c) X. Zhu, R. R. Schmidt, *Angew. Chem. Int. Ed.* **2009**, *48*, 1900 – 1934; *Angew. Chem.* **2009**, *121*, 1932 – 1967; d) A. V. Demchenko, *Synlett* **2003**, *9*, 1225 – 1240; e) K. J. Jensen, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2219 – 2233; f) S. K. Mulani, W. C. Hung, A. B. Ingle, K. S. Shiau, K.-K. Tony Mong, *Org. Biomol. Chem.* **2014**, *12*, 1184 – 1197; g) B. G. Davis, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2137 – 2160.

[8] K. C. Nicolaou, H. J. Mitchell, *Angew. Chem. Int. Ed.* **2001**, *40*, 1576 – 1624; *Angew. Chem.* **2001**, *113*, 1624 – 1672.

[9] D. B. Werz, R. Ranzinger, S. Herget, A. Adibekian, C. W. von der Lieth, P. H. Seeberger, *ACS Chem. Biol.* **2007**, *2*, 685 – 691.

[10] a) P. H. Seeberger, W. C. Haase, *Chem. Rev.* **2000**, *100*, 4349 – 4393; b) P. H. Seeberger, *J. Carbohydr. Chem.* **2002**, *21*, 613 – 643.

[11] a) C. H. Hsu, S. C. Hung, C. Y. Wu, C. H. Wong, *Angew. Chem. Int. Ed.* **2011**, *50*, 11872 – 11923; *Angew. Chem.* **2011**, *123*, 12076 – 12129; b) P. H. Seeberger, *Chem. Commun.* **2003**, 1115 – 1121; c) P. H. Seeberger, D. B. Werz, *Nature* **2007**, *446*, 1046 – 1051.

[12] A. Michael, *Am. Chem. J.* **1879**, *1*, 305 – 312.

[13] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 2400 – 2412.

[14] W. Koenigs, E. Knorr, *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 957 – 981.

[15] G. Zémplén, A. Gerecs, *Ber. Dtsch. Chem. Ges.* **1930**, *63*, 2720 – 2729.

[16] B. Helferich, K. F. Wedermeyer, *Justus Liebigs Ann. Chem.* **1949**, *563*, 139 – 145.

[17] S. Bernstein, R. B. Conrow, *J. Org. Chem.* **1971**, *36*, 863 – 870.

[18] R. U. Lemieux, K. B. Hendriks, R. V. Stick, K. James, *J. Am. Chem. Soc.* **1975**, *97*, 4056 – 4062.

[19] R. K. Ness, H. G. Fletcher, *J. Am. Chem. Soc.* **1956**, *78*, 4710 – 4714.

[20] a) S. Hashimoto, H. Sakamoto, T. Honda, H. Abe, S. Nakamura, S. Ikegami, *Tetrahedron Lett.* **1997**, *38*, 8969 – 8972; b) B. Fraser-Reid, U. E. Udodong, Z. F. Wu, Z. H. Ottosson, J. R. Merritt, C. S. Rao, C. Roberts, R. Madsen, *Synlett* **1992**, 927 – 942.

[21] R. Roy, F. O. Andersson, M. Letellier, *Tetrahedron Lett.* **1992**, *33*, 6053 – 6056.

[22] G. J. Boons, S. Isles, *J. Org. Chem.* **1996**, *61*, 4262 – 4271.

[23] a) O. Kanie, Y. Ito, T. Ogawa, *Tetrahedron Lett.* **1996**, *37*, 4551 – 4554; b) Y. Ito, T. Ogawa, *J. Am. Chem. Soc.* **1997**, *119*, 5562 – 5566.

[24] a) N. L. Douglas, S. V. Ley, U. Lucking, S. L. Warrier, *J. Chem. Soc. Perkin Trans. 1* **1998**, 51 – 65; b) Z. Zhang, I. R. Ollmann, X. S. Ye, R. Wischnat, T. Baasov, C.-H. Wong, *J. Am. Chem. Soc.* **1999**, *121*, 734 – 753.

[25] R. U. Lemieux, *Pure Appl. Chem.* **1971**, *25*, 527 – 548.

[26] J. T. Edward, *Chem. Ind.* **1955**, 1102 – 1104.

[27] a) C. Romers, C. Altona, H. R. Buys, E. Havinga, *Top. Stereochem.* **1969**, *4*, 39 – 97; b) Z. Ardalan, E. A. C. Lucken, *Helv. Chim. Acta* **1973**, *56*, 1715 – 1719.

[28] Y. Mo, *Nat. Chem.* **2010**, *2*, 666 – 671.

[29] T. Nukada, A. Berces, D. M. Whitfield, *Carbohydr. Res.* **2002**, *337*, 765 – 774.

[30] a) T. J. Boltje, J. H. Kim, J. Park, G.-J. Boons, *Org. Lett.* **2011**, *13*, 284 – 287; b) M. T. C. Walvoort, J. Dinkelaar, L. J. van der Bos, G. Lodder, H. S. Overkleeft, J. D. C. Codeé, G. A. van der Marel, *Carbohydr. Res.* **2010**, *345*, 1252 – 1263; c) R. Kumar, D. M. Whitfield, *J. Org. Chem.* **2012**, *77*, 3724 – 3739.

[31] a) J.-H. Kim, H. Yang, J. Park, G. J. Boons, *J. Am. Chem. Soc.* **2005**, *127*, 12090 – 12097; b) J. T. Smoot, P. Pornsuriyasak, A. V. Demchenko, *Angew. Chem. Int. Ed.* **2005**, *44*, 7123 – 7126; *Angew. Chem.* **2005**, *117*, 7285 – 7288.

[32] a) H. H. Jensen, C. M. Pederson, M. Bols, *Chem. Eur. J.* **2007**, *13*, 7576 – 7582; b) D. Crich, O. Vinogradova, *J. Org. Chem.* **2006**, *71*, 8473 – 8480; c) D. Crich, *J. Org. Chem.* **2011**, *76*, 9193 – 9209; d) D. Crich, *Acc. Chem. Res.* **2010**, *43*, 1144 – 1153; e) S. C. Ranade, A. V. Demchenko, *J. Carbohydr. Chem.* **2013**, *32*, 1 – 43; f) L. K. Mydock, A. V. Demchenko, *Org. Biomol. Chem.* **2010**, *8*, 497 – 510.

[33] E. Fischer, E. F. Armstrong, *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 2885 – 2900.

[34] M. Nitz, D. R. Bundle in *Glycoscience: Chemistry and Chemical Biology*, Vol. 1 (Eds.: B. Fraser-Reid, K. Tatsuta, J. Thiem), Springer, Berlin, Heidelberg, New York, **2001**, pp. 1497 – 1542.

[35] E. Fischer, H. Fischer, *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 2521 – 2536.

[36] S. Koto, N. Morishima, S. Shichi, H. Haigoh, M. Hirooka, M. Okamoto, T. Higuchi, K. Shimizu, Y. Hashimoto, T. Iriawa, H. Kawasaki, Y. Takahashi, M. Yamazaki, Y. Mori, K. Kudo, T. Ikegaki, S. Suzuki, S. Zen, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3257 – 3274.
[37] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 1898 – 1904.
[38] J. L. Montero, J. Y. Winum, A. Leydet, M. Kamal, A. A. Pavia, J. P. Roque, *Carbohydr. Res.* **1997**, *297*, 175 – 180.
[39] S. Hanessian, M. M. Ponpipom, P. Lavalle, *Carbohydr. Res.* **1972**, *24*, 45.
[40] R. R. Schmidt, E. Rücker, *Tetrahedron Lett.* **1980**, *21*, 1421 – 1424.
[41] T. P. Yoon, M. A. Ischay, J. Du, *Nat. Chem.* **2010**, *2*, 527 – 532.
[42] M. Tojino, Y. Hirose, M. Mizuno, *Tetrahedron Lett.* **2013**, *54*, 7124 – 7126.
[43] X. Yuan, S. Cheng, Y. Shi, W. Xue, *Synthesis* **2014**, *46*, 331 – 335.
[44] a) L. Kröger, J. Thiem, *J. Carbohydr. Chem.* **2003**, *22*, 9 – 23; b) Y. Watanabe, M. Shiozaki, *Carbohydr. Res.* **2001**, *335*, 283 – 289.
[45] V. Beejmohun, E. Grand, F. Mesnard, M. A. Fliniaux, J. Kovensky, *Tetrahedron Lett.* **2004**, *45*, 8745 – 8747.
[46] V. Kumar, I. J. Talisman, S. V. Malhotra, *Eur. J. Org. Chem.* **2010**, 3377 – 3381.
[47] M. Adinolfi, A. Iadonisi, A. Pezzella, A. Ravida, *Synlett* **2005**, 1848 – 1852.
[48] a) D. Turek, A. Sundgren, M. Lahmann, S. Oscarson, *Org. Biomol. Chem.* **2006**, *4*, 1236 – 1241; b) S. Hou, P. Kovac, *Carbohydr. Res.* **2011**, *346*, 1394 – 1397; c) B. Ruttens, R. Saksena, P. Kovac, *Eur. J. Org. Chem.* **2007**, 4366 – 4375.
[49] a) K. H. Jung, M. Müller, R. R. Schmidt, *Chem. Rev.* **2000**, *100*, 4423 – 4442; b) K. Iino, S. Iwamoto, Y. Kasahara, I. Matsuo, *Tetrahedron Lett.* **2012**, *53*, 4452 – 4456.
[50] R. J. Williams, C. E. Paul, M. Nitz, *Carbohydr. Res.* **2014**, *386*, 73 – 77.
[51] J. Gervay, T. N. Nguyen, M. J. Hadd, *Carbohydr. Res.* **1997**, *300*, 119 – 125.
[52] a) S. M. Chervin, P. Abada, M. Koreeda, *Org. Lett.* **2000**, *2*, 369 – 372; b) M. Adinolfi, A. Iadonisi, A. Ravida, M. Schiattarella, *Tetrahedron Lett.* **2003**, *44*, 7863 – 7866.
[53] R. M. van Well, K. P. R. Kartha, R. A. Field, *J. Carbohydr. Chem.* **2005**, *24*, 463 – 474.
[54] B. Mukhopadhyay, K. P. R. Kartha, D. A. Russell, R. A. Field, *J. Org. Chem.* **2004**, *69*, 7758 – 7760.
[55] J. Bickley, J. A. Cottrel, J. R. Ferguson, R. A. Field, J. R. Harding, D. L. Hughes, K. P. R. Kartha, J. L. Law, F. Scheinmann, A. V. Stachulski, *Chem. Commun.* **2003**, 1266 – 1267.
[56] N. Miquel, S. Vignando, G. Russo, L. Lay, *Synlett* **2004**, 341 – 343.
[57] D. R. Dabideen, J. Gervay-Hague, *Org. Lett.* **2004**, *6*, 973 – 975.
[58] M. H. El-Badry, J. Gervay-Hague, *Tetrahedron Lett.* **2005**, *46*, 6727 – 6728.
[59] S. N. Lam, J. Gervay-Hague, *Org. Lett.* **2002**, *4*, 2039 – 2042.
[60] a) Y. Kobashi, T. Mukaiyama, *Chem. Lett.* **2004**, *33*, 874 – 875; b) E. Gemma, M. Lahmann, S. Oscarson, *Carbohydr. Res.* **2005**, *340*, 2558 – 2562.
[61] S. N. Lam, J. Gervay-Hague, *J. Org. Chem.* **2005**, *70*, 8772 – 8779.
[62] a) L. Baldoni, C. Marino, *Carbohydr. Res.* **2013**, *374*, 75 – 81; b) L. Baldoni, C. Marino, *J. Org. Chem.* **2009**, *74*, 1994 – 2003; c) X. Gu, L. Chen, X. Wang, X. Liu, Q. You, W. Xi, L. Gao, G. Chen, Y.-L. Chen, B. Xiong, J. Shen, *J. Org. Chem.* **2014**, *79*, 1100 – 1110; d) M. Adinolfi, A. Iadonisi, A. Pezzella, A. Ravidà, *Synlett* **2005**, *12*, 1848 – 1852.
[63] a) J. A. Morales-Serna, Y. Diaz, I. Mattheu, S. Castillon, *Eur. J. Org. Chem.* **2009**, 3849 – 3852; b) H.-W. Hsieh, M. W. Schombs, J. Gervay-Hague, *J. Org. Chem.* **2014**, *79*, 1736 – 1748.
[64] H.-W. Hsieh, R. A. Davis, J. A. Hoch, J. Gervay-Hague, *Chem. Eur. J.* **2014**, *20*, 6444 – 6454.
[65] L. Ying, J. Gervay-Hague, *Carbohydr. Res.* **2003**, *338*, 835 – 841.
[66] J. A. Perrie, J. R. Harding, C. King, D. Sinnott, A. V. Stachulski, *Org. Lett.* **2003**, *5*, 4545 – 4548.
[67] T. Murakami, Y. Sato, M. Shibakami, *Carbohydr. Res.* **2008**, *343*, 1297 – 1308.
[68] T. Mukaiyama, Y. Murai, S. Shoda, *Chem. Lett.* **1981**, 431 – 432.
[69] a) H. Yokoyama, *Carbohydr. Res.* **2000**, *327*, 5 – 14; b) K. Toshima, *Carbohydr. Res.* **2000**, *327*, 15 – 26.
[70] K. T. Huang, N. Winssinger, *Eur. J. Org. Chem.* **2007**, 1887 – 1890.
[71] a) J. C. López, P. Bernal-Albert, C. Uriel, S. Valverde, A. M. Gómez, *J. Org. Chem.* **2007**, *72*, 10268 – 10271; b) S. Tsegay, R. J. Williams, S. J. Williams, *Carbohydr. Res.* **2012**, *357*, 16 – 22; c) M. Kunigami, S. Hara, *Carbohydr. Res.* **2015**, *417*, 78 – 80; d) B. Fraser-Reid, J. C. Lopez, P. Bernal-Albert, A. M. Gomez, C. Uriel, J. Ventura, *Can. J. Chem.* **2013**, *91*, 51 – 65.
[72] a) I. Ohtsuka, T. Ako, R. Kato, S. Daikoku, S. Koroghi, T. Kanemitsu, O. Kanie, *Carbohydr. Res.* **2006**, *341*, 1476 – 1487; b) K. Suzuki, Y. Ito, O. Kanie, *Carbohydr. Res.* **2012**, *359*, 81 – 91.
[73] a) O. Francesconi, C. Nativi, G. Gabrielli, M. Gentili, M. Palchetti, B. Bonora, S. Roelens, *Chem. Eur. J.* **2013**, *19*, 11742 – 11752; b) H. Hojo, H. Tanaka, M. Hagiwara, Y. Asahina, A. Ueki, H. Katayama, Y. Nakahara, A. Yoneshige, J. Matsuda, Y. Ito, Y. Nakahara, *J. Org. Chem.* **2012**, *77*, 9437 – 9446.
[74] a) K. C. Nicolaou, T. J. Caulfield, H. Kataoka, *Carbohydr. Res.* **1990**, *202*, 177 – 191; b) T. Kondo, T. Tomoo, H. Abe, M. Isobe, T. Goto, *Chem. Lett.* **1996**, 337 – 338.
[75] a) T. Mukaiyama, H. Jona, K. Takeuchi, *Chem. Lett.* **2000**, 696 – 697; b) H. Jona, H. Mandai, W. Chavasiri, K. Takeuchi, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 291 – 309; c) H. Jona, K. Takeuchi, T. Muaiyama, *Chem. Lett.* **2000**, 1278 – 1279.
[76] a) Y. Yang, B. Yu, *Tetrahedron* **2014**, *70*, 1023 – 1046.
[77] H. M. Kim, I. J. Kim, S. J. Danishefsky, *J. Am. Chem. Soc.* **2001**, *123*, 35 – 48.
[78] K. C. Nicolaou, S. P. Seitz, D. P. Papahatjis, *J. Am. Chem. Soc.* **1983**, *105*, 2430 – 2434.
[79] V. Pozsgay, H. J. Jennings, *J. Org. Chem.* **1987**, *52*, 4635 – 4637.
[80] M. Sasaki, K. Tachibana, H. Nakanishi, *Tetrahedron Lett.* **1991**, *32*, 6873 – 6876.
[81] J. O. Kihlberg, D. A. Leigh, D. R. Bundle, *J. Org. Chem.* **1990**, *55*, 2860 – 2863.
[82] a) G. H. Veeneman, S. H. van Leeuwen, J. H. van Boom, *Tetrahedron Lett.* **1990**, *31*, 1331 – 1334; b) P. Konradsson, D. R. Mootoo, R. E. McDevitt, B. Fraser-Reid, *J. Chem. Soc. Chem. Commun.* **1990**, 270 – 272; c) P. Konradsson, U. E. Udodong, B. Fraser-Reid, *Tetrahedron Lett.* **1990**, *31*, 4313 – 4316.
[83] G. H. Veeneman, J. H. van Boom, *Tetrahedron Lett.* **1990**, *31*, 275 – 278.
[84] G. H. Veeneman, S. H. van Leeuwen, H. Zuurmond, J. H. van Boom, *J. Carbohydr. Chem.* **1990**, *9*, 783 – 796.
[85] a) K. P. R. Kartha, P. Cura, M. Aloui, S. K. Readman, T. J. Rutherford, R. A. Field, *Tetrahedron: Asymmetry* **2000**, *11*, 581 – 593; b) P. Cura, M. Aloui, K. P. R. Kartha, R. A. Field, *Synlett* **2000**, 1279 – 1280.
[86] K. Fukase, A. Hasuoka, I. Kinoshita, S. Kusumoto, *Tetrahedron Lett.* **1992**, *33*, 7165 – 7168.
[87] D.-C. Xiong, L. H. Zhang, X. S. Ye, *Adv. Synth. Catal.* **2008**, *350*, 1696 – 1700.
[88] P. Peng, X. S. Ye, *Org. Biomol. Chem.* **2011**, *9*, 616 – 622.
[89] S. Kaeothip, P. Jagodige, J. P. Yasomanee, A. V. Demchenko, *J. Org. Chem.* **2012**, *77*, 291 – 299.
[90] D. Crich, M. Smith, *Org. Lett.* **2000**, *2*, 4067 – 4069.
[91] D. Crich, M. Smith, *J. Am. Chem. Soc.* **2001**, *123*, 9015 – 9020.
[92] J. D. C. Codée, R. E. J. N. Litjens, R. Heeten, H. S. Overkleeft, J. H. van Boom, G. A. van der Marel, *Org. Lett.* **2003**, *5*, 1519 – 1522.
[93] J. D. C. Codée, L. J. van den Bos, R. E. J. N. Litjens, H. S. Overkleeft, C. A. van Boeckel, J. H. van Boom, G. A. van der Marel, *Tetrahedron* **2004**, *60*, 1057 – 1064.
[94] C. Wang, H. Wang, H. Huang, L. H. Zhang, X. S. Ye, *Synlett* **2006**, 2846 – 2850.
[95] J. Tatai, P. Fügedi, *Org. Lett.* **2007**, *9*, 4647 – 4650.
[96] S. G. Durón, T. Polat, C. H. Wong, *Org. Lett.* **2004**, *6*, 839 – 841.
[97] S. K. Maity, N. Basu, R. Ghosh, *Carbohydr. Res.* **2012**, *354*, 40 – 48.
[98] N. Basu, S. K. Maity, R. Ghosh, *RSC Adv.* **2012**, *2*, 12661 – 12664.
[99] K. Takeuchi, T. Tamura, H. Jona, T. Mukaiyama, *Chem. Lett.* **2000**, *29*, 692 – 693.
[100] H. Jona, K. Takeuchi, T. Saitoh, T. Mukaiyama, *Chem. Lett.* **2000**, *29*, 1178 – 1179.
[101] T. Takeuchi, T. Tamura, T. Mukaiyama, *Chem. Lett.* **2000**, *29*, 124 – 125.
[102] S.-K. Chung, K. H. Park, *Tetrahedron Lett.* **2001**, *42*, 4005 – 4007.
[103] T. Hashihayata, K. Ikegai, K. Takeuchi, H. Jona, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1829.
[104] Z. H. Qin, H. Li, M. S. Cai, Z. J. Li, *Carbohydr. Res.* **2002**, *337*, 31 – 36.
[105] S. Mukherjee, B. Mukhopadhyay, *Synlett* **2010**, *19*, 2853 – 2856.
[106] a) D. Budhadev, B. Mukhopadhyay, *Carbohydr. Res.* **2014**, *384*, 51 – 55; b) D. Budhadev, B. Mukhopadhyay, *Carbohydr. Res.* **2014**, *394*, 26 – 31.

[107] B. Mukhopadhyay, B. Collet, R. A. Field, *Tetrahedron Lett.* **2005**, *46*, 5923 – 5925.
[108] a) B. Roy, K. Pramanik, B. Mukhopadhyay, *Glycoconjugate J.* **2008**, *25*, 157 – 166; b) S. Dasgupta, K. Pramanik, B. Mukhopadhyay, *Tetrahedron* **2007**, *63*, 12310 – 12316; c) S. Mandal, B. Mukhopadhyay, *Tetrahedron* **2007**, *63*, 11363 – 11370; d) S. Dasgupta, B. Mukhopadhyay, *Eur. J. Org. Chem.* **2008**, 5770 – 5777; e) P. R. Verma, B. Mukhopadhyay, *Carbohydr. Res.* **2010**, *345*, 432 – 436; f) B. Roy, R. A. Field, B. Mukhopadhyay, *Carbohydr. Res.* **2009**, *344*, 2311 – 2316; g) P. Verma, B. Mukhopadhyay, *Carbohydr. Res.* **2009**, *344*, 2554 – 2558.
[109] a) R. Das, B. Mukhopadhyay, *Carbohydr. Res.* **2013**, *376*, 1 – 6; b) P. R. Verma, B. Mukhopadhyay, *RSC Adv.* **2013**, *3*, 201 – 207; c) K. B. Pal, B. Mukhopadhyay, *Carbohydr. Res.* **2013**, *379*, 26 – 29.
[110] C. H. Yao, J. C. Lee, *Tetrahedron* **2014**, *70*, 6757 – 6762.
[111] R. Périon, L. Lemée, V. Ferriéres, R. Duval, D. Plusquellec, *Carbohydr. Res.* **2003**, *338*, 2779 – 2792.
[112] S. Valerio, A. Iadonisi, M. Adinolfi, A. Ravidà, *J. Org. Chem.* **2007**, *72*, 6097 – 6106.
[113] M. Goswami, A. Ellern, N. L. B. Pohl, *Angew. Chem. Int. Ed.* **2013**, *52*, 8441 – 8445; *Angew. Chem.* **2013**, *125*, 8599 – 8603.
[114] A. M. Vibhute, A. Dhaka, V. Athiyarath, K. M. Sureshan, *Chem. Sci.* **2016**, *7*, 4259.
[115] R.-Z. Mao, D.-C. Xiong, F. Guo, Q. Li, J. Duan, X.-S. Ye, *Org. Chem. Front.* **2016**, *3*, 737.
[116] W. J. Wever, M. A. Cinelli, A. A. Bowers, *Org. Lett.* **2013**, *15*, 30 – 33.
[117] M. L. Spell, K. Deveaux, C. G. Bresnahan, B. L. Bernard, W. Sheffield, R. Kumar, J. R. Ragains, *Angew. Chem. Int. Ed.* **2016**, *55*, 6515 – 6519; *Angew. Chem.* **2016**, *128*, 6625 – 6629.
[118] R.-Z. Mao, F. Guo, D. C. Xiong, Q. Li, J. Duan, X. S. Ye, *Org. Lett.* **2015**, *17*, 5606 – 5609.
[119] M. Nakanishi, D. Takahashi, K. Toshima, *Org. Biomol. Chem.* **2013**, *11*, 5079 – 5082.
[120] A.-H. A. Chu, A. Minciunescu, V. Montanari, K. Kumar, C. S. Bennett, *Org. Lett.* **2014**, *16*, 1780 – 1782.
[121] N. Tanaka, F. Ohnishi, D. Uchihata, S. Toriib, J. Nokamia, *Tetrahedron Lett.* **2007**, *48*, 7383 – 7387.
[122] R. R. Schmidt, J. Michel, *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 731 – 732; *Angew. Chem.* **1980**, *92*, 763 – 764.
[123] R. Schaubach, J. Hemberger, W. Kinzy, *Liebigs Ann. Chem.* **1991**, 607 – 614.
[124] P. Zimmermann, B. Bommer, T. Bär, R. R. Schmidt, *J. Carbohydr. Chem.* **1988**, *7*, 435.
[125] B. Wegmann, R. R. Schmidt, *J. Carbohydr. Chem.* **1987**, *6*, 357 – 375.
[126] A. Dobarro-Rodriguez, M. Trumtel, H. P. Wessel, *J. Carbohydr. Chem.* **1992**, *11*, 255 – 263.
[127] F. J. Urban, B. S. Moore, R. Breitenbach, *Tetrahedron Lett.* **1990**, *31*, 4421 – 4424.
[128] S. P. Douglas, D. M. Whitfield, J. J. Krepinsky, *J. Carbohydr. Chem.* **1993**, *12*, 131 – 136.
[129] M. Adinolfi, G. Barone, A. Iadonisi, M. Schiattarella, *Synlett* **2002**, 0269 – 0270.
[130] G. Lian, Q. Gao, F. Lin, *Carbohydr. Res.* **2008**, *343*, 2992 – 2996.
[131] M. Li, X. Han, B. Yu, *J. Org. Chem.* **2003**, *68*, 6842 – 6845.
[132] W. Yang, J. Sun, Z. Yang, W. Han, W. D. Zhang, B. Yu, *Tetrahedron Lett.* **2012**, *53*, 2773 – 2776.
[133] Y. Li, H. Mo, G. Lian, B. Yu, *Carbohydr. Res.* **2012**, *363*, 14 – 22.
[134] A. L. Mattson, A. K. Michel, M. J. Cloninger, *Carbohydr. Res.* **2012**, *347*, 142 – 146.
[135] M. Adinolfi, G. Barone, L. Guariniello, A. Iadonisi, *Tetrahedron Lett.* **2000**, *41*, 9005 – 9008.
[136] M. Adinolfi, G. Barone, A. Iadonisi, L. Mangoni, M. Schiattarella, *Tetrahedron Lett.* **2001**, *42*, 5967 – 5969.
[137] a) M. Adinolfi, A. Iadonisi, A. Ravidà, *Synlett* **2006**, *4*, 583 – 586; b) M. Adinolfi, G. Barone, A. Iadonisi, M. Schiattarella, *Tetrahedron Lett.* **2002**, *43*, 5573 – 5577.
[138] S. Valerio, A. Pastore, M. Adinolfi, A. Iadonisi, *J. Org. Chem.* **2008**, *73*, 4496 – 4503.
[139] M. Adinolfi, A. Iadonisi, A. Ravidà, S. Valerio, *Tetrahedron Lett.* **2006**, *47*, 2595 – 2599.
[140] Y. Du, G. Wei, S. Cheng, Y. Huaa, R. J. Linhardt, *Tetrahedron Lett.* **2006**, *47*, 307 – 310.
[141] O. R. Ludek, W. Gu, C. J. Gildersleeve, *Carbohydr. Res.* **2010**, *345*, 2074 – 2078.
[142] M. Adinolfi, G. Barone, A. Iadonisi, M. Schiattarella, *Org. Lett.* **2003**, *5*, 987 – 989.
[143] Q. Tian, S. Zhang, Q. Yu, M. B. He, J. S. Yang, *Tetrahedron* **2007**, *63*, 2142 – 2147.
[144] S. Tanaka, M. Takashina, H. Tokimoto, Y. Fujimoto, K. Tanaka, K. Fukase, *Synlett* **2005**, 2325 – 2328.
[145] S. Goetze, R. Fitzner, H. Kunz, *Synlett* **2009**, 3346 – 3348.
[146] R. Roy, A. K. Palanivel, A. Mallick, Y. D. Vankar, *Eur. J. Org. Chem.* **2015**, 4000 – 4005.
[147] P. Peng, R. R. Schmidt, *J. Am. Chem. Soc.* **2015**, *137*, 12653 – 12659.
[148] J. Yang, C. Cooper-Vanosdell, E. A. Mensah, H. M. Nguyen, *J. Org. Chem.* **2008**, *73*, 794 – 800.
[149] C. Zandanel, L. Dehuyser, A. Wagner, R. Baati, *Tetrahedron* **2010**, *66*, 3365 – 3369.
[150] R. Iwata, K. Uda, D. Takahashi, K. Toshima, *Chem. Commun.* **2014**, *50*, 10695.
[151] K. Jayakanthan, Y. D. Vankar, *Carbohydr. Res.* **2005**, *340*, 2688 – 2692.
[152] T. Shirahata, J.-I. Matsuo, S. Teruya, N. Hirata, T. Kurimoto, N. Akimoto, T. Sunazuka, E. Kaji, S. Omura, *Carbohydr. Res.* **2010**, *345*, 740 – 749.
[153] a) *Carbohydrates in Chemistry and Biology, Vol. 1* (Eds.: R. R. Schmidt, K.-H. Jung, B. Ernst, G. W. Hart, P. Sinaÿ), Wiley-VCH, Weinheim, **2000**, pp. 5 – 59; b) U. Schmelzer, Z. Zhang, R. R. Schmidt, *J. Carbohydr. Chem.* **2007**, *26*, 223 – 238.
[154] S. C. Ranade, S. C. Hasty, A. V. Demchenko, *J. Carbohydr. Chem.* **2013**, *32*, 360 – 379.
[155] M. N. Kamat, C. D. Meo, A. V. Demchenko, *J. Org. Chem.* **2007**, *72*, 6947 – 6955.
[156] M. N. Kamat, N. P. Rath, A. V. Demchenko, *J. Org. Chem.* **2007**, *72*, 6938 – 6946.
[157] A. V. Demchenko, N. N. Malysheva, C. D. Meo, *Org. Lett.* **2003**, *5*, 455 – 458.
[158] a) M. N. Kamat, A. V. Demchenko, *Org. Lett.* **2005**, *7*, 3215 – 3218; b) D. Crich, M. Li, *Org. Lett.* **2007**, *9*, 4115 – 4118.
[159] S. Kaeothip, P. Pornsuriyasak, N. P. Rath, A. V. Demchenko, *Org. Lett.* **2009**, *11*, 799 – 802.
[160] A. V. Demchenko, M. N. Kamat, C. De Meo, *Synlett* **2003**, *9*, 1287 – 1290.
[161] A. F. G. Bongat, M. N. Kamat, A. V. Demchenko, *J. Org. Chem.* **2007**, *72*, 1480 – 1483.
[162] a) S. J. Hasty, M. A. Kleine, A. V. Demchenko, *Angew. Chem. Int. Ed.* **2011**, *50*, 4197 – 4201; *Angew. Chem.* **2011**, *123*, 4283 – 4287; b) A. V. Demchenko, P. Pornsuriyasak, C. De Meo, N. N. Malysheva, *Angew. Chem. Int. Ed.* **2004**, *43*, 3069 – 3072; *Angew. Chem.* **2004**, *116*, 3131 – 3134.
[163] S. Kaeothip, A. V. Demchenko, *J. Org. Chem.* **2011**, *76*, 7388 – 7398.
[164] M. C. Parlato, M. N. Kamat, H. Wang, K. J. Stine, A. V. Demchenko, *J. Org. Chem.* **2008**, *73*, 1716 – 1725.
[165] P. Pornsuriyasak, A. V. Demchenko, *Chem. Eur. J.* **2006**, *12*, 6630 – 6646.
[166] S. Kaeothip, P. Pornsuriyasak, A. V. Demchenko, *Tetrahedron Lett.* **2008**, *49*, 1542 – 1545.
[167] S. C. Ranade, S. Kaeothip, A. V. Demchenko, *Org. Lett.* **2010**, *12*, 5628 – 5631.
[168] S. N. Ranade, A. V. Demchenko, *Carbohydr. Res.* **2015**, *403*, 115 – 122.
[169] T. Mukaiyama, T. Nakatsuka, S.-i. Shoda, *Chem. Lett.* **1979**, *8*, 487.
[170] S. J. Hasty, A. V. Demchenko, *Chem. Heterocycl. Compd.* **2012**, *48*, 220 – 240.
[171] P. Padungros, L. Alberch, A. Wei, *J. Org. Chem.* **2014**, *79*, 2611 – 2624.
[172] J.-C. Lee, G.-R. Pan, S. S. Kulkarni, S.-Y. Luo, C.-C. Liao, S.-C. Hung, *Tetrahedron Lett.* **2006**, *47*, 1621 – 1624.
[173] S.-Y. Luo, A. Tripathi, M. Manuel, L. Zulueta, S.-C. Hung, *Carbohydr. Res.* **2012**, *352*, 197 – 201.
[174] M. Fortin, J. Kaplan, K. Pham, S. Kirk, R. B. Andrade, *Org. Lett.* **2009**, *11*, 3594 – 3597.
[175] a) K. N. Jayaprakash, B. Fraser-Reid, *Carbohydr. Res.* **2007**, *342*, 490 – 498; b) K. N. Jayaprakash, K. V. Radhakrishnan, B. Fraser-Reid, *Tetrahedron Lett.* **2002**, *43*, 6953 – 6955.
[176] a) B. Fraser-Reid, S. Grimme, M. Piacenza, M. Mach, U. Schlueter, *Chem. Eur. J.* **2003**, *9*, 4687 – 4692; b) K. N. Jayaprakash, B. Fraser-Reid, *Org. Lett.* **2004**, *6*, 4211 – 4214; c) K. N. Jayaprakash, B. Fraser-Reid, *Synlett* **2004**, 301 – 305.

[177] J. C. López, A. Agocs, C. Uriel, A. M. Gómeza, B. Fraser-Reid, *Chem. Commun.* **2005**, 5088 – 5090.
[178] G. Anilkumar, L. G. Nair, B. Fraser-Reid, *Org. Lett.* **2000**, *2*, 2587 – 2589.
[179] F. Mathew, K. N. Jayaprakash, B. Fraser-Reid, J. Mathew, J. Scicinski, *Tetrahedron Lett.* **2003**, *44*, 9051 – 9054.
[180] C. Uriel, J. Ventura, A. M. Gómez, J. C. López, B. Fraser-Reid, *Eur. J. Org. Chem.* **2012**, 3122 – 3131.
[181] S. Hotha, S. Kashyap, *J. Am. Chem. Soc.* **2006**, *128*, 9620 – 9621.
[182] A. K. Kayastha, S. Hotha, *Tetrahedron Lett.* **2010**, *51*, 5269 – 5272.
[183] A. K. Kayastha, S. Hotha, *Chem. Commun.* **2012**, *48*, 7161 – 7163.
[184] S. R. Vidadala, G. Gayatri, N. Sastry, S. Hotha, *Chem. Commun.* **2011**, *47*, 9906 – 9908.
[185] S. Adhikari, K. N. Baryal, D. Zhu, L. Xiaohua, J. Zhu, *ACS Catal.* **2013**, *3*, 57 – 60.
[186] X. Chen, D. Shen, Q. Wang, Y. Yang, B. Yu, *Chem. Commun.* **2015**, *51*, 13957 – 13960.
[187] a) S. A. Thadke, B. Mishra, S. Hotha, *J. Org. Chem.* **2014**, *79*, 7358 – 7371; b) S. A. Thadke, B. Mishra, S. Hotha, *Org. Lett.* **2013**, *15*, 2466 – 2469.
[188] D. J. Bound, B. K. Bettadaiah, P. Srinivas, *Synth. Commun.* **2014**, *44*, 2565 – 2576.
[189] G. Sureshkumar, S. Hotha, *Tetrahedron Lett.* **2007**, *48*, 6564 – 6568.
[190] G. Sureshkumar, S. Hotha, *Chem. Commun.* **2008**, 4282 – 4284.
[191] Y. Li, Y. Yang, B. Yu, *Tetrahedron Lett.* **2008**, *49*, 3604 – 3608.
[192] Y. Tang, J. Li, Y. Zhu, Y. Li, B. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 18396 – 18405.
[193] a) J. Liao, J. Sun, Y. Niu, B. Yu, *Tetrahedron Lett.* **2011**, *52*, 3075 – 3078; b) Y. Li, J. Sun, B. Yu, *Org. Lett.* **2011**, *13*, 5508 – 5511; c) Y. Li, X. Yang, Y. Liu, C. Zhu, Y. Yang, B. Yu, *Chem. Eur. J.* **2010**, *16*, 1871 – 1882; d) Y. Ma, Z. Li, H. Shi, J. Zhang, J. Yu, *J. Org. Chem.* **2011**, *76*, 9748 – 9756; e) Y. Li, W. Yang, Y. Ma, J. Sun, L. Shan, W. D. Zhang, B. Yu, *Synlett* **2011**, 915 – 918.
[194] a) P. Sun, P. Wang, Y. Zhang, X. Zhang, C. Wang, S. Liu, J. Lu, M. Li, *J. Org. Chem.* **2015**, *80*, 4164 – 4175; b) Y. Zhu, B. Yu, *Chem. Eur. J.* **2015**, *21*, 8771 – 8780.
[195] Y. Yang, Y. Li, B. Yu, *Tetrahedron Lett.* **2010**, *51*, 1504 – 1507.
[196] Y. Zhu, B. Yu, *Angew. Chem. Int. Ed.* **2011**, *50*, 8329 – 8332; *Angew. Chem.* **2011**, *123*, 8479 – 8482.
[197] S. Dutta, S. Sarkar, S. J. Gupta, A. K. Sen, *Tetrahedron Lett.* **2013**, *54*, 865 – 870.
[198] H. Imagawa, A. Kinoshita, T. Fukuyama, H. Yamamoto, M. Nishizawa, *Tetrahedron Lett.* **2006**, *47*, 4729 – 4731.
[199] D. Zhu, X. Cao, B. Yu, *Org. Chem. Front.* **2015**, *2*, 360 – 365.
[200] S. Matthies, D. T. McQuade, P. H. Seeberger, *Org. Lett.* **2015**, *17*, 3670 – 673.
[201] F. Yang, Q. Wang, B. Yu, *Tetrahedron Lett.* **2012**, *53*, 5231 – 5234.
[202] S. R. Koppolu, R. Niddana, R. Balamurugan, *Org. Biomol. Chem.* **2015**, *13*, 5094 – 5097.
[203] R. J. Ferrier, W. G. Overend, A. E. Ryan, *J. Chem. Soc. C* **1962**, 3667 – 3670.
[204] R. J. Ferrier, O. A. Zubkov in *Organic Reactions*; L. E. Overman (Ed.); John Wiley & Sons, Inc.: New York, **2003***; 62,* 569 – 736.
[205] E. Rafiee, S. Tangestaninejad, M. H. Habibi, V. Mirkhani, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3611 – 3614.
[206] B. K. Bettadaiah, P. Srinivas, *Tetrahedron Lett.* **2003**, *44*, 7257 – 7259.
[207] C. Masson, J. Soto, M. Bessodes, *Synlett* **2000**, 1281 – 1282.
[208] G. Zhang, Q. Liu, L. Shi, J. Wang, *Tetrahedron* **2008**, *64*, 339 – 344.
[209] P. Chen, S. Wang, *Tetrahedron* **2012**, *68*, 5356 – 5362.
[210] B. K. Gorityala, R. Lorpitthaya, Y. Bai, X. W. Liu, *Tetrahedron* **2009**, *65*, 5844 – 5848.
[211] F. Ding, R. William, B. K. Gorityala, J. Ma, S. Wang, X. W. Liu, *Tetrahedron Lett.* **2010**, *51*, 3146 – 3148.
[212] G. Narasimha, B. Srinivas, P. R. Krishna, S. Kashyap, *Synlett* **2014**, 523 – 526.
[213] H. Kim, H. Men, C. Lee, *J. Am. Chem. Soc.* **2004**, *126*, 1336 – 1337.
[214] B. P. Schuff, G. J. Mercer, H. M. Nguyen, *Org. Lett.* **2007**, *9*, 3173 – 3176.
[215] a) L. Ji, S.-H. Xiang, W.-L. Leng, K. L. M. Hoang, X.-W. Liu, *Org. Lett.* **2015**, *17*, 1357 – 1360; b) Y. S. Reddy, R. Lahiri, Y. D. Vankar, *Eur. J. Org. Chem.* **2012**, 4751 – 4761.
[216] a) S. Xiang, J. He, Y. J. Tan, X.-W. Liu, *J. Org. Chem.* **2014**, *79*, 11473 – 11482; b) S. Xiang, J. He, J. Ma, X.-W. Liu, *Chem. Commun.* **2014**, *50*, 4222 – 4224.
[217] B. D. Sherry, R. N. Loy, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 4510 – 4511.
[218] R. Balamurugan, S. R. Koppolu, *Tetrahedron* **2009**, *65*, 8139 – 8142.
[219] B. Srinivas, T. R. Reddy, P. Radha Krishna, S. Kashyap, *Synlett* **2014**, 1325 – 1330.
[220] a) B. Srinivas, G. Narasimha, P. R. Krishna, S. Kashyap, *Synthesis* **2014**, 1191 – 1196; b) P. Chen, L. Lin, *Tetrahedron* **2013**, *69*, 10045 – 10051; c) S. K. Battina, T. R. Reddy, P. R. Krishna, S. Kashyap, *Tetrahedron Lett.* **2015**, *56*, 1798 – 1800; d) B. Srinivas, T. R. Reddy, S. Kashyap, *Carbohydr. Res.* **2015**, *406*, 86 – 92.
[221] S. Hotha, A. Tripathi, *Tetrahedron Lett.* **2005**, *46*, 4555 – 4558.
[222] J. S. Yadav, B. V. S. Reddy, C. V. S. R. Murthy, G. M. Kumar, *Synlett* **2000**, 1450 – 1451.
[223] P. Chen, S. Li, *Tetrahedron Lett.* **2014**, *55*, 5813 – 5816.
[224] P. Chen, S. Li, *Tetrahedron* **2013**, *69*, 4524 – 4531.
[225] S. Xue, L. He, K.-Z. Han, X.-Q. Zheng, Q.-X. Guo, *Carbohydr. Res.* **2005**, *340*, 303 – 307.
[226] G. Smitha, C. S. Reddy, *Synthesis* **2004**, 834 – 836.
[227] J. S. Yadav, B. V. Subba Reddy, J. S. S. Reddy, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2390 – 2394.
[228] N. Suryakiran, S. M. Reddy, M. Srinivasulu, Y. Venkateswarlu, *Synth. Commun.* **2008**, *38*, 170 – 176.
[229] A. Procopio, R. Dalpozzo, A. D. Nino, L. Maiuolo, M. Nardi, M. Oliverioa, B. Russoa, *Carbohydr. Res.* **2007**, *342*, 2125 – 2131.
[230] a) D. Stevanović, A. Pejović, I. Damljanović, M. Vukićević, G. A. Bogdanović, R. D. Vukićević, *Tetrahedron Lett.* **2012**, *53*, 6257 – 6260; b) D. Stevanovic, A. Pejovic, I. Damljanovic, A. Minic, G. A. Bogdanovic, M. Vukicevic, N. S. Radulovic, R. D. Vukicevic, *Carbohydr. Res.* **2015**, *407*, 111 – 121.
[231] D. B. G. Williams, S. B. Simelanea, H. H. Kinfea, *Org. Biomol. Chem.* **2012**, *10*, 5636.
[232] Y.-B. Chen, S. I. Wang, Z.-P. Lin, C.-H. Lin, M. T. Hsieh, H.-C. Lin, *Tetrahedron* **2015**, *71*, 350 – 358.
[233] a) S. B. Boga, K. K. Balasubramanian, *Arkivoc* **2004** (*viii*) 87 – 102; b) J. S. Yadav, B. V. S. Reddy, J. V. Raman, N. Niranjan, S. K. Kumar, A. C. Kunwar, *Tetrahedron Lett.* **2002**, *43*, 2095 – 2098; c) S. K. Das, K. A. Reddy, C. Abbineni, J. Roy, K. V. L. N. Rao, R. H. Sachwani, J. Iqbal, *Tetrahedron Lett.* **2003**, *44*, 4507 – 4509; d) S. K. Das, K. A. Reddy, J. Roy, *Synlett* **2003**, *11*, 1607 – 1610; e) D. Mukherjee, S. K. Yousuf, S. C. Taneja, *Tetrahedron Lett.* **2008**, *49*, 4944 – 4948.
[234] P. Nagaraj, N. G. Ramesh, *Tetrahedron Lett.* **2009**, *50*, 3970 – 3973.
[235] N. R. Swamy, Y. Venkateswarlu, *Synthesis* **2002**, *5*, 598 – 600.
[236] J. L. Babu, J. A. Khare, Y. D. Vankar, *Molecules* **2005**, *10*, 884 – 892.
[237] a) J. C. R. Freitas, J. R. de Freitas, P. H. Menezes, *J. Braz. Chem. Soc.* **2010**, *21*, 2169 – 2172; b) J. C. R. Freitas, T. R. Couto, A. A. S. Paulino, J. R. de Freitas Filho, I. Malvestiti, R. A. Oliveira, P. H. Menezes, *Tetrahedron* **2012**, *68*, 10611 – 10620.
[238] K. De, L. Legros, B. Crousse, D. Bonnet-Delpon, *Tetrahedron* **2008**, *64*, 10497 – 10500.
[239] a) R. N. de Oliveira, J. R. de Freitas Filho, R. M. Srivastava, *Tetrahedron Lett.* **2002**, *43*, 2141 – 2143; b) B. Shanmugasundaram, A. K. Bose, K. K. Balasubramanian, *Tetrahedron Lett.* **2002**, *43*, 6795 – 6798.
[240] M. Oba, Y. Ueno, S. Kitani, T. Hayakawa, T. Takahashi, T. Suzuki, M. Sato, K. Ikeda, *Heterocycles* **2014**, *89*, 69 – 81.
[241] a) A. Agarwal, S. Rani, Y. D. Vankar, *J. Org. Chem.* **2004**, *69*, 6137 – 6140; b) A. K. Misra, P. Tiwari, G. Agnihotri, *Synthesis* **2005**, *2*, 260 – 266; c) P. Tiwari, G. Agnihotri, A. K. Misra, *Carbohydr. Res.* **2005**, *340*, 749 – 752.
[242] P. Chen, S. Wang, *Tetrahedron* **2013**, *69*, 583 – 588.
[243] H. H. Kinfe, F. M. Mebrahtu, K. Sithole, *Carbohydr. Res.* **2011**, *346*, 2528 – 2532.
[244] J. Zhang, B. Zhanga, J. Zhou, H. Chena, J. Li, G. Yang, Z. Wang, J. Tang, *J. Carbohydr. Chem.* **2013**, *32*, 380 – 391.
[245] B. K. Gorityala, S. Cai, J. Ma, X.-W. Liu, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3093 – 3095.
[246] X. Yang, N. Li, *Scientific World Journal* **2014**, *2014*, 307895, 1 – 6.
[247] A. T. Khan, R. S. Basha, M. Lal, *Arkivoc* **2013** (*ii*) 201 – 212.
[248] N. Bodipati, S. R. Palla, V. Komera, R. K. Peddinti, *Tetrahedron Lett.* **2014**, *55*, 6878 – 6881.
[249] A. S. Vieira, P. F. Fiorante, T. L. S. Hough, F. P. Ferreira, D. S. Lüdtke, H. A. Stefani, *Org. Lett.* **2008**, *10*, 5215 – 5218.

[250] V. Di Bussolo, M. Caselli, M. R. Romano, M. Pineschi, P. Crotti, *J. Org. Chem.* **2004**, *69*, 7383 – 7386.
[251] a) V. Di Bussolo, M. Caselli, M. R. Romano, M. Pineschi, P. Crotti, *J. Org. Chem.* **2004**, *69*, 8702 – 8708; b) V. Di Bussolo, I. Frau, L. Favero, G. Uccello-Barretta, F. Balzano, P. Crotti, *Tetrahedron* **2015**, *71*, 6276 – 6284.
[252] V. Di Bussolo, M. Caselli, M. Pineschi, P. Crotti, *Org. Lett.* **2002**, *4*, 3695 – 3698.
[253] V. Di Bussolo, M. R. Romano, M. Pineschi, P. Crotti, *Org. Lett.* **2005**, *7*, 1299 – 1302.
[254] V. Di Bussolo, M. Caselli, M. Pineschi, P. Crotti, *Org. Lett.* **2003**, *5*, 2173 – 2176.
[255] a) C. H. Marzabadi, R. W. Franck, *Tetrahedron* **2000**, *56*, 8385 – 8417; b) R. M. De Lederkremer, C. Marino, *Adv. Carbohydr. Chem. Biochem.* **2007**, *61*, 143 – 216; c) D. Hou, T. L. Lowary, *Carbohydr. Res.* **2009**, *344*, 1911 – 1940; d) A. Borovika, P. Nagorny, *J. Carbohydr. Chem.* **2012**, *31*, 255 – 283.
[256] M. J. Lear, F. Yoshimura, M. Hirama, *Angew. Chem. Int. Ed.* **2001**, *40*, 946 – 949; *Angew. Chem.* **2001**, *113*, 972 – 975.
[257] Y. S. Lu, Q. Li, L. H. Zhang, X. S. Ye, *Org. Lett.* **2008**, *10*, 3445 – 3448.
[258] J. P. Issa, C. S. Bennett, *J. Am. Chem. Soc.* **2014**, *136*, 5740 – 5744.
[259] M. Kaneko, S. B. Herzon, *Org. Lett.* **2014**, *16*, 2776 – 2779.
[260] J. Jaunzems, G. Sourkouni-Argirusi, M. Jesberger, A. Kirschning, *Tetrahedron Lett.* **2003**, *44*, 637 – 639.
[261] S. Tomono, S. Kusumi, D. Takahashi, K. Toshima, *Tetrahedron Lett.* **2011**, *52*, 2399 – 2403.
[262] J.-H. Ruei, P. Venukumar, A. B. Ingle, K. K. Tony Mong, *Chem. Commun.* **2015**, *51*, 5394 – 5397.
[263] J. Park, T. J. Boltje, G. J. Boons, *Org. Lett.* **2008**, *10*, 4367 – 4370.
[264] a) M. Petitou, C. A. A. van Boeckel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3118; *Angew. Chem.* **2004**, *116*, 3180; b) S. J. Danishefsky, J. R. Allen, *Angew. Chem. Int. Ed.* **2000**, *39*, 836; *Angew. Chem.* **2000**, *112*, 882.
[265] a) J. Banoub, P. Boullanger, D. Lafont, *Chem. Rev.* **1992**, *92*, 1167 – 1195; b) J. Debenham, R. Rodebaugh, B. Fraser-Reid, *Liebigs Ann. Recl.* **1997**, 791 – 802.
[266] a) S. Mandal, R. Das, B. Mukhopadhyay, *Tetrahedron: Asymmetry* **2011**, *22*, 1108 – 1113; b) A. Mitra, B. Mukhopadhyay, *Synthesis* **2015**, 3061 – 3066; c) V. Sarkar, B. Mukhopadhyay, *Carbohydr. Res.* **2015**, *406*, 65 – 70; d) A. K. Misra, Y. Ding, J. B. Lowe, O. Hindsgaul, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1505 – 1509; e) S.-S. Chang, C.-C. Lin, Y.-K. Li, K.-K. Tony Mong, *Carbohydr. Res.* **2009**, *344*, 432 – 438.
[267] L. Yang, X. Y. Ye, *Carbohydr. Res.* **2010**, *345*, 1713 – 1721.
[268] M. M. L. Zulueta, S.-Y. Lin, Y.-T. Lin, C.-J. Huang, C.-C. Wang, C.-C. Ku, Z. Shi, C.-L. Chyan, D. Irene, L.-H. Lim, T.-I. Tsai, Y. P. Hu, S. D. Arco, C.-H. Wong, S.-C. Hung, *J. Am. Chem. Soc.* **2012**, *134*, 8988 – 8995.
[269] G. Wei, X. Lv, Y. Du, *Carbohydr. Res.* **2008**, *343*, 3096 – 3099.
[270] T. Kajimoto, K. Morimoto, R. Ogawa, T. Dohi, Y. Kita, *Eur. J. Org. Chem.* **2015**, 2138 – 2142.
[271] J. Krag, M. S. Christiansen, J. G. Petersen, H. H. Jensen, *Carbohydr. Res.* **2010**, *345*, 872 – 879.
[272] J. Chen, B. Yu, *Tetrahedron Lett.* **2008**, *49*, 1682 – 1685.
[273] C. F. Crasto, G. B. Jones, *Tetrahedron Lett.* **2004**, *45*, 4891 – 4894.
[274] a) E. A. Mensah, H. M. Nguyen, *J. Am. Chem. Soc.* **2009**, *131*, 8778; b) E. A. Mensah, F. Yu, H. M. Nguyen, *J. Am. Chem. Soc.* **2010**, *132*, 14288 – 14302.
[275] S. Hanessian, *Chem. Rev.* **2000**, *100*, 4443 – 4463.
[276] B. Roy, B. Mukhopadhyay, *Tetrahedron Lett.* **2007**, *48*, 3783 – 3787.
[277] M. Pfaffe, R. Mahrwald, *Org. Lett.* **2012**, *14*, 792 – 795.
[278] S. Schmalisch, R. Mahrwald, *Org. Lett.* **2013**, *15*, 5854 – 5857.
[279] I. K. Polanki, S. H. Kurma, A. K. Bhattacharya, *J. Carbohydr. Chem.* **2015**, *34*, 196 – 205.
[280] G. Guchhait, A. K. Misra, *Catal. Commun.* **2011**, *14*, 52 – 57.
[281] D. K. Sharma, M. R. Lambu, T. Sidiq, A. Khajuria, A. K. Tripathi, S. K. Yousuf, D. Mukherjee, *RSC Adv.* **2013**, *3*, 11450 – 11455.
[282] T.-J. Park, M. Weiwer, X. Yuan, S. N. Baytas, E. M. Munoz, S. Murugesana, R. J. Linhardt, *Carbohydr. Res.* **2007**, *342*, 614 – 620.
[283] F. J. Mũnoz, S. Andŕe, H.-J. Gabius, J. V. Sinisterra, M. J. Herńaiz, R. J. Linhardt, *Green Chem.* **2009**, *11*, 373 – 379.
[284] J. Auǵe, G. Sizun, *Green Chem.* **2009**, *11*, 1179 – 1183.
[285] O. Monasson, G. Sizun-Thomé, N. Lubin-Germain, J. Uziel, J. Augé, *Carbohydr. Res.* **2012**, *352*, 202 – 205.
[286] S. K. Mamidyala, M. G. Finn, *J. Org. Chem.* **2009**, *74*, 8417 – 8420.
[287] a) A. V. Gudmundsdottir, M. Nitz, *Org. Lett.* **2008**, *10*, 3461 – 3463; b) S. Dasgupta, M. Nitz, *J. Org. Chem.* **2011**, *76*, 1918 – 1921.
[288] L. J. G. Edgar, S. Dasgupta, M. Nitz, *Org. Lett.* **2012**, *14*, 4226 – 4229.
[289] a) Y. Wang, X.-S. Ye, L.-H. Zhang, *Org. Biomol. Chem.* **2007**, *5*, 2189 – 2200; b) M. L. L. Zulueta, D. Janreddy, S.-C. Hung, *Isr. J. Chem.* **2015**, *55*, 347 – 359; c) J. D. C. Codée, R. Litjens, L. J. van den Bos, H. S. Overkleeft, G. A. van der Marel, *Chem. Soc. Rev.* **2005**, *34*, 769 – 782; d) K. M. Koeller, C. H. Wong, *Chem. Rev.* **2000**, *100*, 4465 – 4493; e) T.-Y. Huang, M. M. L. Zulueta, S.-C. Hung, *Org. Biomol. Chem.* **2014**, *12*, 376 – 382.
[290] P. Pornsuriyasak, A. V. Demchenko, *Tetrahedron: Asymmetry* **2005**, *16*, 433 – 439.
[291] Y. Zhang, C. Chen, L. Jin, H. Tan, F. Wang, H. Cao, *Carbohydr. Res.* **2015**, *401*, 109 – 114.
[292] T. Polat, C.-H. Wong, *J. Am. Chem. Soc.* **2007**, *129*, 12795 – 12800.
[293] Y. Vohra, M. Vasan, A. Venot, G. J. Boons, *Org. Lett.* **2008**, *10*, 3247 – 3250.
[294] Z. Wang, L. Zhou, K. El-Boubbou, X.-S. Ye, X. Huang, *J. Org. Chem.* **2007**, *72*, 6409 – 6420.
[295] a) J. Dinkelaar, H. Gold, H. S. Overkleeft, J. D. C. Codée, G. A. van der Marel, *J. Org. Chem.* **2009**, *74*, 4208 – 4216; b) I. Ohtsuka, N. Hada, T. Atsumi, N. Kakiuchi, *Tetrahedron* **2013**, *69*, 1470 – 1475; c) S. Sarkar, S. Dutta, G. Das, A. K. Sen, *Tetrahedron* **2011**, *67*, 4118 – 4122; d) S. Bhattacharyya, B. G. Magnusson, U. Wellmar, U. J. Nilsson, *J. Chem. Soc. Perkin Trans. 1* **2001**, 886 – 890; e) A. Pastore, M. Adinolfi, A. Iadonisi, A. Valerio, *Eur. J. Org. Chem.* **2010**, 711 – 718; f) S. Manabe, K. Ishii, Y. Ito, *J. Am. Chem. Soc.* **2006**, *128*, 10666 – 10667; g) L.-M. Deng, X. Liu, X.-Y. Liang, J.-S. Yang, *J. Org. Chem.* **2012**, *77*, 3025 – 3037.
[296] C. Wang, H. Wang, X. Huang, L.-H. Zhang, X.-S. Ye, *Synlett* **2006**, 2846 – 2850.
[297] H. Tanaka, Y. Tateno, Y. Nishiura, T. Takahashi, *Org. Lett.* **2008**, *10*, 5597 – 5600.
[298] M. C. Galan, A. T. Tran, S. Whitaker, *Chem. Commun.* **2010**, *46*, 2106 – 2108.
[299] a) J. M. J. Fréchet, C. Schuerch, *J. Am. Chem. Soc.* **1971**, *93*, 492 – 496; b) L. Yan, C. M. Taylor, R. Goodnow, Jr., D. Kahne, *J. Am. Chem. Soc.* **1994**, *116*, 6953 – 6954.
[300] a) L. O. Kononov, Y. Ito, T. Ogawa, *Tetrahedron Lett.* **1997**, *38*, 1599 – 1602; b) T. Doi, M. Sugiki, H. Yamada, T. Takahasi, *Tetrahedron Lett.* **1999**, *40*, 2141 – 2144; c) T. Nukada, A. Berces, D. M. Whitfield, *J. Org. Chem.* **1999**, *64*, 9030 – 9045.
[301] a) J. M. Fréchet in *Polymer-supported Reactions in Organic Synthesis* (Eds.: P. Hodge, D. Sherrington), Wiley, Chichester, **1980**, 407 – 434; b) Y. Ito, S. Manabe, *Curr. Opin. Chem. Biol.* **1998**, *2*, 701 – 708; c) P. H. Seeberger, W.-C. Haase, *Chem. Rev.* **2000**, *100*, 4349 – 4393; d) C. S. Bennett, *Org. Biomol. Chem.* **2014**, *12*, 1686 – 1698.
[302] O. Kanie, I. Ohtsuka, T. Ako, S. Daikoku, Y. Kanie, R. Kato, *Angew. Chem. Int. Ed.* **2006**, *45*, 3851 – 3854; *Angew. Chem.* **2006**, *118*, 3935 – 3938.
[303] M. Mogemark, M. Elofsson, J. Kihlberg, *Org. Lett.* **2001**, *3*, 1463 – 1466.
[304] M. Mogemark, M. Elofsson, J. Kihlberg, *J. Org. Chem.* **2003**, *68*, 7281 – 7288.
[305] T. Kanemitsu, C. H. Wong, O. Kanie, *J. Am. Chem. Soc.* **2002**, *124*, 3591 – 3599.
[306] B. Yan, H. Yan, *J. Comb. Chem.* **2001**, *3*, 78 – 84.
[307] S. Manabe, Y. Ito, *J. Am. Chem. Soc.* **2002**, *124*, 12638 – 12639.
[308] N. V. Ganesh, K. Fujikawa, Y. H. Tan, S. S. Nigudkar, K. J. Stine, A. V. Demchenko, *J. Org. Chem.* **2013**, *78*, 6849 – 6857.
[309] J. Ferguson, C. M. Marzabadi, *Tetrahedron Lett.* **2003**, *44*, 3573 – 3577.
[310] T. Ako, S. Daikoku, I. Ohtsuka, R. Kato, O. Kanie, *Chem. Asian J.* **2006**, *1*, 798 – 813.
[311] S. H. Nguyen, A. H. Trotta, J. Cao, T. J. Straub, C. S. Bennett, *Org. Biomol. Chem.* **2012**, *10*, 2373 – 2376.
[312] a) G. Belogi, T. Zhu, G.-J. Boons, *Tetrahedron Lett.* **2000**, *41*, 6965 – 6968; b) G. Belogi, T. Zhu, G.-J. Boons, *Tetrahedron Lett.* **2000**, *41*, 6969 – 6972.
[313] a) X. Wu, R. R. Schmidt, *J. Org. Chem.* **2004**, *69*, 1853 – 1857; b) J. Wu, Z. Guo, *J. Org. Chem.* **2006**, *71*, 7067 – 7070.
[314] N. Guedes, P. Czechura, B. Echeverria, A. Ruiz, O. Michelena, M. Martin-Lomas, N.-C. Reichardt, *J. Org. Chem.* **2013**, *78*, 6911 – 6934.
[315] D. Crich, M. Smith, *J. Am. Chem. Soc.* **2002**, *124*, 8867 – 8869.
[316] F. Roussel, M. Mohamed Takhi, R. R. Schmidt, *J. Org. Chem.* **2001**, *66*, 8540 – 8548.

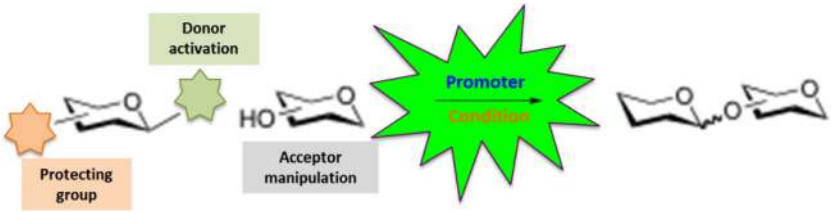
[317] a) P. H. Seeberger, D. B. Werz, *Nat. Rev. Drug Discovery Nat. Rev.* **2005**, *4*, 751 – 763; b) P. H. Seeberger, *Acc. Chem. Res.* **2015**, *48*, 1450 – 1463.
[318] O. J. Plante, E. R. Palmacci, P. H. Seeberger, *Science* **2001**, *291*, 1523 – 1527.
[319] D. B. Werz, B. Castagner, P. H. Seeberger, *J. Am. Chem. Soc.* **2007**, *129*, 2770 – 2771.
[320] J. D. C. Codée, L. Kröck, B. Castagner, P. H. Seeberger, *Chem. Eur. J.* **2008**, *14*, 3987 – 3994.
[321] E. R. Palmacci, M. C. Hewitt, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2001**, *40*, 4433 – 4437; *Angew. Chem.* **2001**, *113*, 4565 – 4569.
[322] L. Kröck, D. Esposito, B. Castagner, C.-C. Wang, P. Bindschädler, P. H. Seeberger, *Chem. Sci.* **2012**, *3*, 1617 – 1622.
[323] E. Eller, M. Collot, J. Yin, H. S. Hahm, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2013**, *52*, 5858 – 5861; *Angew. Chem.* **2013**, *125*, 5970 – 5973.
[324] M. W. Weishaupt, S. Matthies, P. H. Seeberger, *Chem. Eur. J.* **2013**, *19*, 12497 – 12503.
[325] D. Esposito, M. Hurevich, B. Castagner, C.-C. Wang, P. H. Seeberger, *Beilstein J. Org. Chem.* **2012**, *8*, 1601 – 1609.
[326] M. T. C. Walvoort, H. van den Elst, O. J. Plante, L. Kröck, P. H. Seeberger, H. S. Overkleeft, G. A. van der Marel, J. D. C. Codée, *Angew. Chem. Int. Ed.* **2012**, *51*, 4393 – 4396; *Angew. Chem.* **2012**, *124*, 4469 – 4472.
[327] a) J. Kandasamy, M. Hurevich, P. H. Seeberger, *Chem. Commun.* **2013**, *49*, 4453 – 4455; b) M. P. Bartetzko, F. Schuhmacher, H. S. Hahm, P. H. Seeberger, F. Pfrengle, *Org. Lett.* **2015**, *17*, 4344 – 4347; c) D. Schmidt, F. Schuhmacher, A. Geissner, P. H. Seeberger, F. Pfrengle, *Chem. Eur. J.* **2015**, *21*, 5709 – 5713.
[328] M. T. C. Walvoort, A. G. Volbeda, N. R. M. Reintjens, H. van den Elst, O. J. Plante, H. S. Overkleeft, G. A. van der Marel, J. D. C. Codée, *Org. Lett.* **2012**, *14*, 3776 – 3779.
[329] O. Calin, S. Eller, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2013**, *52*, 5862 – 5865; *Angew. Chem.* **2013**, *125*, 5974 – 5977.
[330] F. A. Jaipuri, N. L. B. Pohl, *Org. Biomol. Chem.* **2008**, *6*, 2686 – 2691.
[331] S.-L. Tang, N. L. B. Pohl, *Org. Lett.* **2015**, *17*, 2642 – 2645.
[332] N. V. Ganesh, K. Fujikawa, Y. H. Tan, K. J. Stine, A. V. Demchenko, *Org. Lett.* **2012**, *14*, 3036 – 3039.
[333] T. Nokami, Y. Isoda, N. Sasaki, A. Takaiso, S. Hayase, T. Itoh, R. Hayashi, A. Shimizu, J.-I. Yoshida, *Org. Lett.* **2015**, *17*, 1525 – 1528.
[334] T. Nokami, R. Hayashi, Y. Saigusa, A. Shimizu, C.-Y. Liu, K.-K. T. Mong, J.-I. Yoshida, *Org. Lett.* **2013**, *15*, 4520 – 4523.

Received: May 2, 2016
Published online on ■■ ■■, 2016

R. Das,* B. Mukhopadhyay*

■■ – ■■

Chemical O-Glycosylations: An Overview



Chasing diversity: Chemical O-glycosylation remains a challenge for the preparation of diverse glycosidic linkages that are present in nature. The 21st century has seen a significant development in the area of chemical O-glycosylation. This Review illustrates these developments in a comprehensive manner and concludes with the scope for further development.

