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Aspects of chemical transglycosylations in modern glycoside synthesis†

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Application of chemical methods forms as a powerful approach to achieve synthesis of custom-designed oligosaccharides. Chemical glycosylation methods continue to evolve till date even when the first such method dates back more than a century ago. The recent past has witnessed the emergence of the transglycosylations, wherein a preponderant *O*-glycoside acts as a glycosyl donor to afford yet another *O*-glycoside product bearing the newly introduced glycan/aglycan at the reducing end. Critical requirements of the aglycan portion of a glycoside donor are discussed, as also the mechanistic formulations based on a set of experimental observations. A critical review of the expanding facets of transglycosylations in the garb of modern glycosylation methods is presented herein.

Keywords: Carbohydrates, conformations, glycosylations, oligosaccharides, oxocarbenium ion.

1. Introduction

Chemical glycosylations constitute to be one of the major concurrent advancements in the general area in carbohydrate chemistry[1]. Multiple hydroxyl groups containing sugars present a plethora of challenges at the outset, yet a judicious underpinning of the reactivities of each hydroxyl groups also provides a facile route to implement chosen reactions on such sugar scaffolds. One of the earliest reactions of sugars is the so-called glycosylation, particularly involving the chemical methods. Fischer glycosylation in 1895[2] and Koenigs-Knorr glycosylation in 1901[3] continue to be hall-mark reactions benefitting their applications in glycoside synthesis. Improvements on these very early methods add further values and these reactions are practiced rather routinely through the improved chemical methods, examples of such improvements are the Helferich condition in 1930's[4] and Hanessian-Banoub method[5] of glycosylations, reported in 1977. A major change in the outlook of chemical glycosylations can be attributed to the early establishing of thioglycosides as a versatile glycosyl donor by Lönn, and Garegg and Fügedi in mid-1980's[6]. An imminent understanding is the control of chemical glycosylations under the oxocarbenium or the glycosyl cation manifold, upon removal of the anomeric substituent as the leaving moiety. The resulting oxocarbenium ion acts as the reactive intermediate to react with a glycosyl acceptor nucleophile and yield the glycoside product. Chemical glycosylations to date practically relied on the generation of the oxocarbenium ion as the intermediate. Although commendable efforts pertain to the recent reports of *endocylic* oxygen cleavage and anomerization as fruitful approaches to alter anomeric stereochemistry of glycosides[7]. Significant advancements in glycosylation started to emerge from late 1980's, advancing chemical methods to conduct glycosylations using a number of reagents and reaction conditions. These advancements helped not only to increase the arsenal of methods for glycosylations under varying substrate conditions, but also to uncover the finer details of the glycosylation reactions. Further, elegant developments relating to glycosylation reactions to be conducted under solid-phase methods have emerged, leading to secure oligomeric glycosides in a facile manner and in a short duration[8]. Excellent reviews on general glycosylation reactions can be referred to many articles that appear in the recent years[9–11].

Glycosylations in natural systems eminently adopt enzymes as a source to catalyze the reaction, bringing together

†Review.

reactivities between the glycosyl donor and acceptor to afford the glycoside. Glycosyl transferases and glycosyl hydrolases are two classes of enzymes that catalyze the glycosylation reactions. Within these enzymes, requirements of nucleotide factors in the case of glycosyl transferases, and favorable thermodynamic equilibrium in the case of glycosyl hydrolases are stringent. Excellent reviews are referred to read through the enzyme-mediated glycosylations[12–14].

A defining feature of chemical glycosylations is the ability to generate the oxocarbenium ion as the reactive partner to react with acceptor nucleophile. Stringent requirements further are the activator of the glycosyl donor, promoter of the reaction, temperature, solvent, presence of molecular sieves and above all, the nature of protecting groups in the reactive partners. Paulsen's statement[1] in 1982 that there is no single reagent or reaction condition that allow glycosylations on the varieties of glycosyl donors and acceptors to secure assortment of glycosides still stands largely true.

Within the preamble of the present article, chemical transglycosylations are considered as a viable and fruitful approach to conduct glycosylations, having the merits that are otherwise un-available through other types of chemical glycosylations. Herein, *a transglycosylation refers to the reactions wherein a glycosyl donor is an O-glycoside, which reacts with the hydroxyl moiety in a glycosyl/aglycosyl acceptor and affords the newly formed O-glycoside.*

2.1. Relevance of oxocarbenium ion

Chemical glycosylations are warranted immensely, in order to secure homogeneous oligosaccharides and their conjugates of biological importance. Chemical glycosylation methodologies are improved upon and newer methods are being identified continuously. A major focus in glycosylation reactions is the generation of the oxocarbenium ion or glycosyl cation intermediate from the glycosyl donor under the reaction conditions and the reactivity of this intermediate with incoming alcohols as nucleophiles, leading to the glycoside bond formation. Generation of this intermediate with the estimated lifetime of $>2.5\times10^{-12}$ s in aq. solution bears greater relevance and importance in glycosylation reaction in general[15].

Although the generation of the oxocarbenium ion forms the key step of a glycosylation, conformational preferences of this species possess a crucial role in the stereochemical outcome of the glycosylation, along with factors as that arising from reactivities of individual hydroxyl moieties, protecting groups, reagents, promoters, temperature and solvent polarity. Few salient aspects of these controls on glycosylation are discussed below briefly.

Concerning the oxocarbenium ion generation in the presence of triflate promoter, the work of Hosoya and co-workers demonstrates further that intermediate species in the form of α/β contact ion pairs (CIP) (**I**, **II** and **V**) or solvent separated ion pairs (SSIP) (**III** and **IV**) form and these species equilibrate with one another in the solution phase between anomeric triflates **1a** and **1b** (Fig. 1)[16,17].

Inducing conformational constraints in the oxocarbenium ion species through bicyclic formation: Inducing conformational constraints onto the oxocarbenium ion species through protecting groups, particularly benzylidene acetal, leads the species to be bicyclic in nature. This approach of conformational constraints was systematically studied by Crich and co-workers, in order to ascertain the conformational equilibrium associated with the oxocarbenium ion. Among gluco-

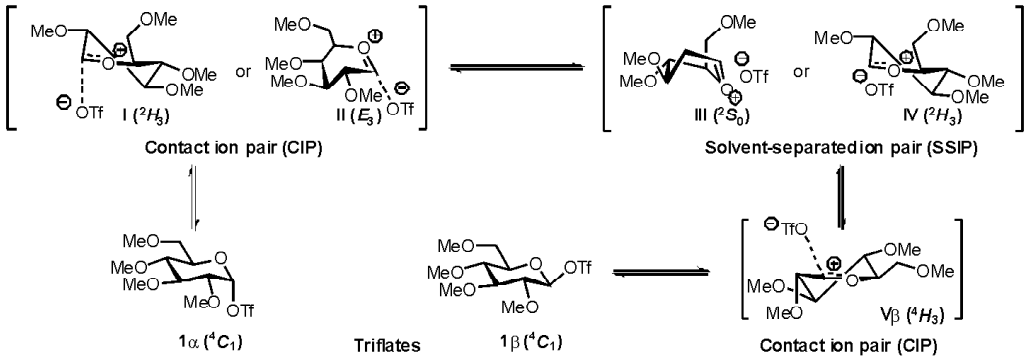


Fig. 1. Oxocarbenium ion equilibration in the CIP, SSIP and covalent forms in the presence of triflate promoter[16,17].

and mannopyranose derived oxocarbenium ions, having the benzylidene acetal, the axial-orientation of the hydroxyl moiety in mannopyranose-derived intermediate species shifted the covalent triflate-CIP-SSIP equilibria towards the covalent intermediate, resulting in a high β-selectivity of the glycosidic bond. As a corollary, glucopyranose-derived oxocarbenium ion species, having the equatorial hydroxyl moiety at *C*-2 carbon, shifted the equilibrium far away from the covalent triflate[18].

The stereoselectivity observed in the *O*- and *C*-glycosylation of gluco- and mannopyranosides having 4,6-*O*-benzylidene moiety was evaluated by invoking the bent bond model, advanced by Deslongchamps and co-workers[19]. The model predicts that $^4H_3$ (**Gluco-2**) (Fig. 2) conformation evolves on the oxocarbenium ion having the *gluco*-configuration, whereas that in *manno*-configured species is the $B_{2,5}$ conformation (**Manno-5**).

In these preferred conformations, the *C*2-O bond is placed antiperiplanar to the bent (τ) bond. In glucopyranose-derived oxocarbenium ion, the antiperiplanarity of the *C*2-O bond would block the equatorial (β-) face at *C*-1 anomeric carbon, thereby the axial (α-) attack at *C*-1 carbon by the nucleophile become feasible, in the course of the formation of the glycoside product with the chair conformation. Whereas mannosyl oxocarbenium ion species adopts $B_{2,5}$ conformation and projects the *C*2-O bond in the α-face, lying antiperiplanar to the τ bond. As a result, the nucleophilic attack occurs through the β-face, resulting in the glycoside with an initial $^1S_5$ conformation (**7**β).

Blériot and co-workers used superacid HF/SbF_5 on peracetate-protected 2-deoxy sugars **8** and **10**, in an attempt to monitor the oxocarbenium formation (Scheme 1), during the formation of the corresponding methyl glycosides **9** and **11**[20,21]. Under the conditions, the oxocarbenium ion was stable at room temperature, the corresponding ^{1}H and ^{13}C NMR spectrum showed that all the acetyl groups were protonated and the intermediate persisted either in the ^4E or in the $^4H_5$ conformations.

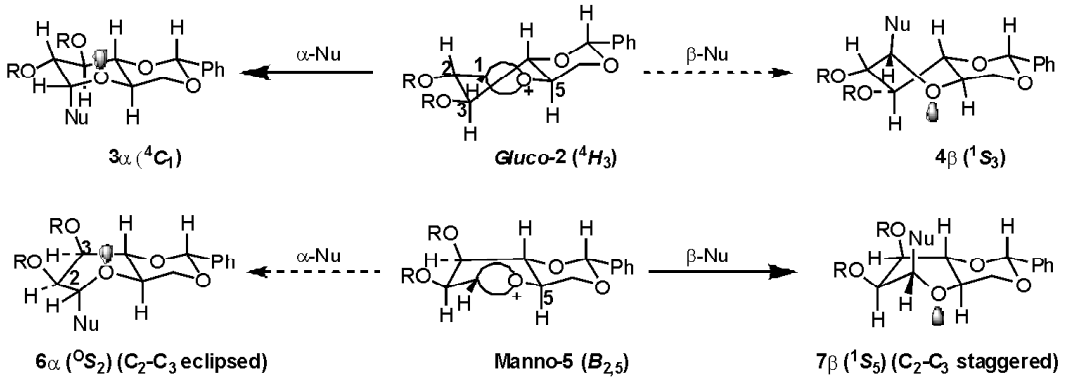
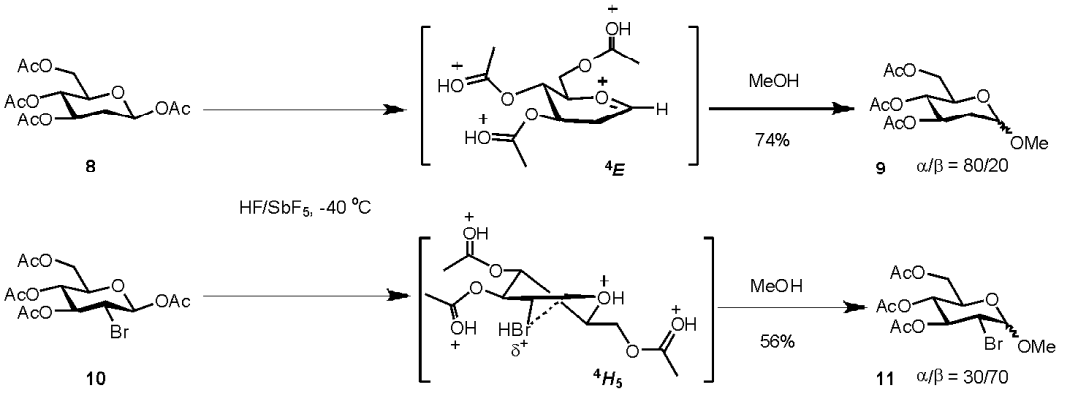


Fig. 2. Stereochemical outcome prediction by the bent-bond model hypothesis[19].



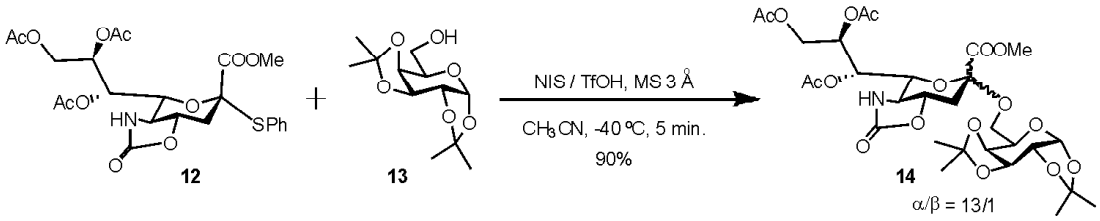
Scheme 1.Conformational preference adopted by the oxocarbenium ion species on the *O*-acetyl-protected 2-deoxy sugars[20,21].

2.2. Factors directing the conformational stability

The conformational preferences are further influenced by solvent in which the species forms. As the oxocarbenium ion possesses polar sp^2-centre, differences in the stereoselectivity can be anticipated by variations in the nature of the solvent in which the reaction is conducted. Solvent coordination or otherwise at the anomeric carbon of the ionic species would depend on the solvent system in which the species is generated. The role of the solvent was investigated by De Meo and co-workers on the stereoselectivities of products emerged during synthesis of sialosyl-(1-2)-galactoside**14**, from glycosyl donor **12** and acceptor **13** (Scheme 2)[22]. In a co-ordinating CH_3CN as the solvent, a stereoselectivity 13:1, in favor of the α-product, when the reaction was conducted at –40°C. CH_2Cl_2as solvent reduced the stereoselectivity to 9:1 in favor of the α-product, even when the reaction was conducted at –78°C and product formation was excellent (98%). A change to toluene as solvent resulted in prolonged reaction time to several hours with no improvement in the yield or stereoselectivity. These experiments highlight the importance of solvents mediating the reaction to achieve the product stereoselectivities.

The ability of the solvent to stabilize the oxocarbenium ion is further considered to determine the course of the glycosidic bond formation as that following from either an S_{N1} or an S_{N2} pathway. In a nutshell, the higher the polarity of the solvent mediating the reaction, more the inclination towards the S_{N1} region, whereas the lower the polarity of the solvent, product formation tends to follow the S_{N2} region[23].

Hünenberger and co-workers studied the preferred conformation of the oxocarbenium intermediate in glycosylation reactions conducted in acetonitrile and dioxane as solvents (Fig. 3). The preferential formation of α or β anomers **VII**-α



Scheme 2. Synthesis of sialosyl-(1-2)-galactosides[22].

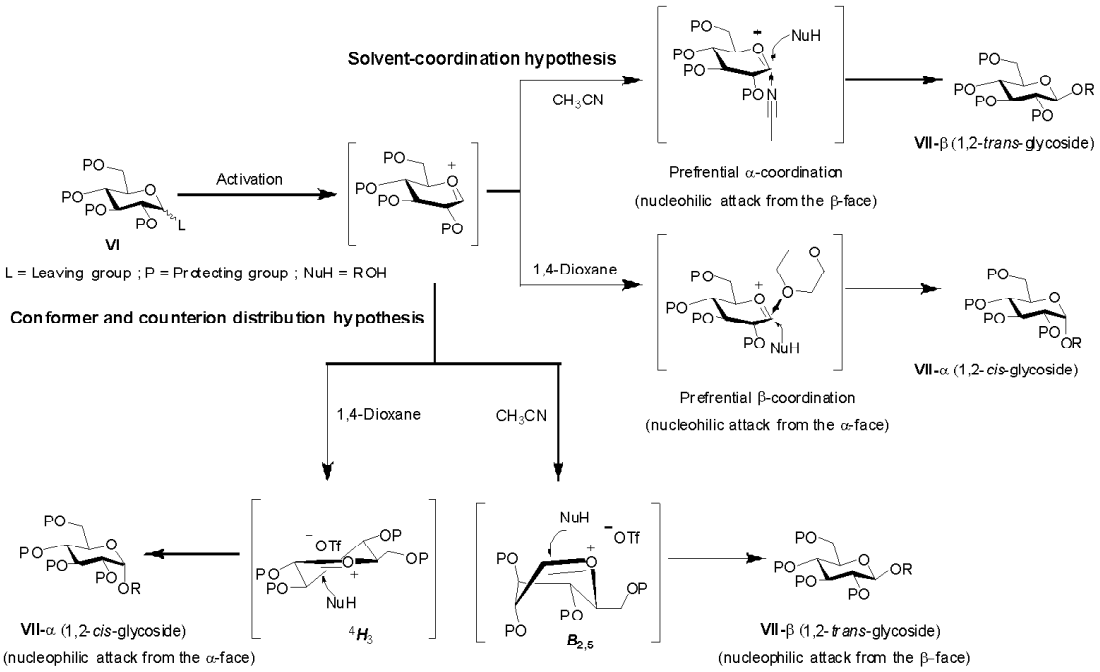


Fig. 3. Stereoselectivity achieved by solvent coordination hypothesis and conformer and counterion distribution hypothesis[24].

and **VII**-β from an anomeric mixture of glycosyl donor **VI** was studied. Interestingly, solvent-coordination as the hypothesis for α/β selectivity was thought not fully justifiable, rather the conformer and counterion distribution appear to provide an alternate rationale for the observed stereoselectivities[24]. The stereochemical outcome of the reaction is thought to follow two inter-related conformational property of the reactive species, namely, (i) the conformation adopted by the oxocarbenium ion, depending on the steric effect and (ii) preferred coordination of the counterion associated with the oxocarbenium ion.

The observations show that in the case of acetonitrile, the oxocarbenium ion prefers the $B_{2,5}$ conformation and the counter ion to coordinate the α-face, leading to the formation of the β-linked glycoside product. In contrary, the species exists predominantly in the $^4H_3$ conformation, with the counterion occupying the β-face in 1,4-dioxane solvent medium, giving rise to the α-glycoside formation.

As described earlier, a conformational change in the oxocarbenium ion is subjected to steric bulkiness of the protecting groups, in order to avoid 1,3-diaxial interactions (Fig. 4)[25]. Having bulkier TBS (**17**) or TBDPS (**18**) protecting groups will force the pyranose system to adopt an $^1C_4$ conformation. Similarly, smaller groups such as benzyl (**16**) or acetate (**15**) will result in the formation of $^4C_1$ conformation.

In a glycosylation involving ethyl thioglycosides having TIPS (triisopropylsilyl ether) protecting group and cyclohexanemethanol (**20**), the donor (**19**) as well as the product **21** formed in the reaction adopt a skew $^3S_1$ conformation, as interpreted from the ^{1}H NMR coupling constants (Scheme 3)[26]. The twist-boat conformation enforced upon by the presence of bulky TIPS protecting groups enabled β-selective product formation, even when the product glycoside resides in the $^1C_4$ conformation. The substituent at *C*-6 carbon do not hinder the β-face in the twist-boat conformation, added further with the steric hindrance of the substituent at *C*-2 carbon at the α-face, leading to the maximal formation of the β-glycoside formation as seen in the intermediate **VIII**.

Presence of 2,4-*O*-di-*tert*-butylsilylene (DTBS) as a protecting group in the glycosyl donor did not influence the reactivity, yet increased selectivity was observed in the glycosylation reaction. Kiso and co-workers reported that, despite having an ester group at *C*2 galactopyranoside donor **22** displayed an exclusive α selectivity with acceptor alcohol **23** (Scheme 4). The disaccharide **24** was isolated in 74% yield as the single product. DTBS group being bulkier can shield the β face and prevent the nucleophilic attack from that face of the oxocarbenium ion[27].

Differing stereoselectivities are observed when alkoxy substituent is electron withdrawing (EWG) or electron donating (EDG) in nature. The stereoselectivity obtained with oxocarbenium ion having electronegative substituent like alkoxy derivative is opposite to that of alkyl substituted cations. The reactions involving the alkyl substituent is consid-

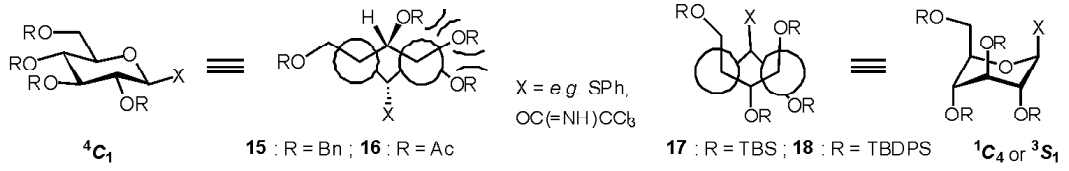
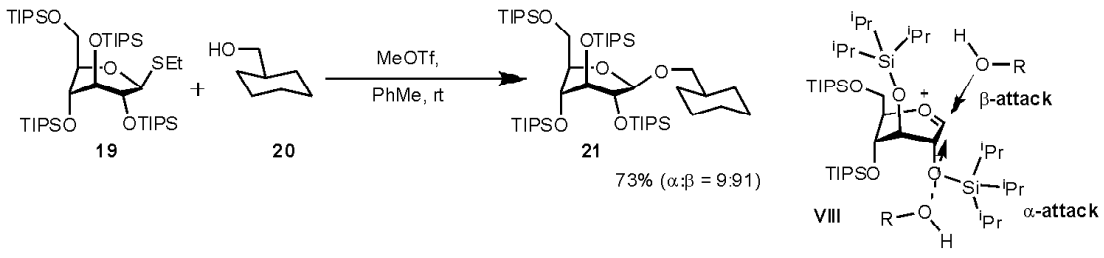
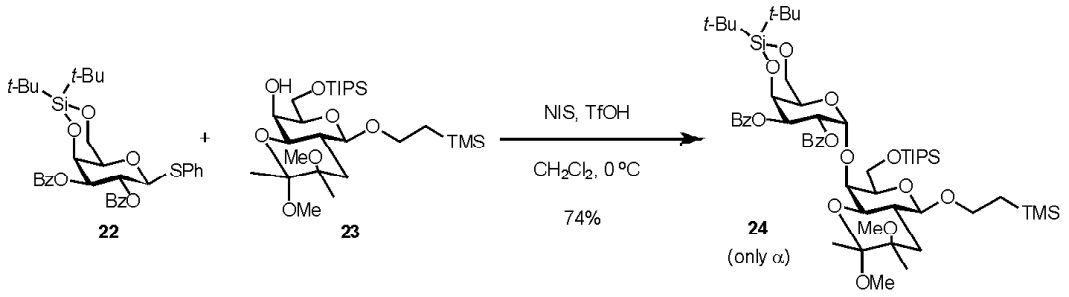


Fig. 4. Conformational changes induced by the protecting groups[25].



Scheme 3. Mechanism for the β-selective glycosylation from the $^3S_1$ glycosyl donor[26].



Scheme 4. DTBS directed α selective glycosylation of galactosyl donors[27].

ered to be governed by the steric factors which is not the case with heteroatom substituted system. This can further be attributed to the numerous conformational preferences existing for the carbocations compared with the neutral systems. A *C*-4 substituted oxocarbenium ion can exist in two different diastereomeric half chair conformations **X** and **XI** (Fig. 5). A heteroatom nucleophile results in the formation of axially substituted conformer **IX**, whereas an alkyl group prefers equatorial conformer **XII**.

In order to study the stereoselectivity difference obtained in a six-membered ring, Woerpel and co-workers conducted a systematic study on acetoxytetrahydropyrans[28,29]. The nucleophilic substitution on the acetoxytetrahydropyrans **25**, in presence of Lewis acid, is believed to proceed via oxocarbenium ion intermediate (Scheme 5). The reactions showed a completely different stereoselectivity for the alkyl and heteroatom substituents, supporting the possible formation of two half-chair conformations for the oxocarbenium ion. As the substituent at *C*-4 does not obstruct the path of incoming nucleophile, the reaction is completely dominated by the conformational preferences over the steric factors. So the alkyl groups gives 1,4-*cis* product **26** adopting the pseudo equatorial position, whereas alkyloxy and acyloxy prefers the pseudo axial position giving 1,4-*trans* selectivity (**27**). Electrostatic attraction between the electronegative substituent and partial positive charge on the carbocation stabilizes the pseudo-axial conformation.

3.1. Glycosylation methods with unsaturated alkyl leaving group

Substituent at the anomeric carbon is activated directly in the course of the oxocarbenium ion formation in a stable glycosyl donor, involving a promoter. In a sequential glycosylation, the reactivity of the anomeric substituent is crucial and the reactivity varies, depending on the stereoelectronic environment posed by the protecting groups on hydroxyl moieties in a glycosyl donor. A direction of rich development is the so-called latent-active glycosylation method, the protecting group at the anomeric carbon is transformed into a good leaving group and enable the oxocarbenium ion formation. The advantage of latent-active glycosylation over the other strategies is that the method does not require deprotection and activation by yet another

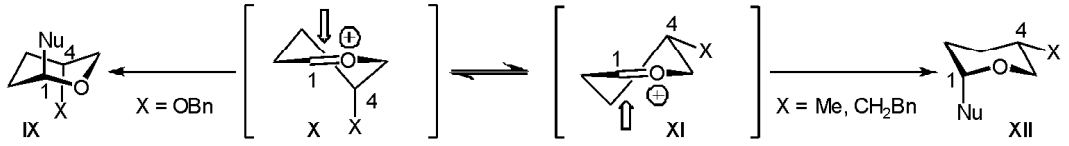
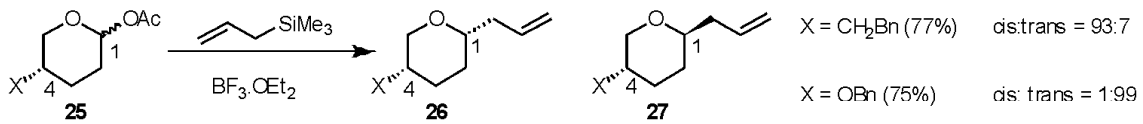


Fig. 5. Conformation preference of EDG and EWG at *C*4 position[28].



Scheme 5. Difference in the stereoselectivity observed with alkyl and alkyloxy substituent[28].

substituent at the anomeric carbon in a glycosyl donor. In a perspective, the method permits utilization of the glycosyl donor and the acceptor arising from a common precursor. Further, the method could facilitate the sequential glycosylation to be performed iteratively with the aid of a single glycosylation method[30]. The most studied anomeric moieties suitable to the requirement of the latent-active method of glycosylation are those presenting an unsaturation, as in, *n*-pent-4-enyl, allyl and propargyl moieties.

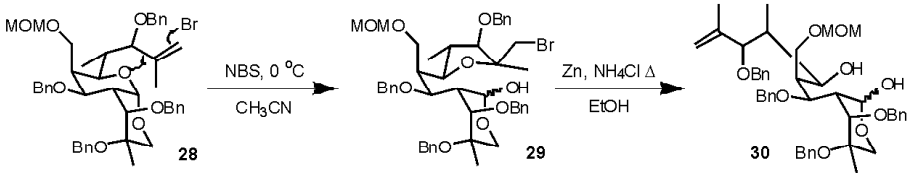
(a) Development of n-pent-4-enyl group as a leaving group in glycosylation chemistry: The value of *n*-pent-4-enyl moiety as a facile leaving group at the anomeric carbon in sequential glycosylations was developed early by Fraser-Reid and co-workers. The feasibility to utilize *n*-pent-4-enyl moiety either as a protecting group or as moiety for activation towards oxocarbenium ion formation formed the basis of this valuable glycosylation methodology[31]. Thus, the *n*-pent-4-enyl moiety serves the dual purpose as a leaving group as well as a protecting group[32]. Further, the moiety could be linked to a carrier protein for further glycoconjugations[33] pertaining to the vaccine development, as demonstrated in the sialyl Lewis^a conjugation to an immunogenic sLe^a vaccine by Livingston and co-workers[34].

The discovery of *n*-pent-4-enyl glycoside as a glycosyl donor was made by Fraser-Reid and co-workers in 1988[35]. The reaction of pyranoside **28** with NBS/CH_3CN/H_2O afforded the bromomethyl tetrahydrofuran **29**, instead of the anticipated bromohydrin product. It was noted that an acetal could be opened up by oxidation of the remote double bond in **30** (Scheme 6). The reaction was considered as a unique case of the *C*-5–*O*-5 participation in the process of opening up of putative cyclic bromonium ion, which was not very common occurrance. This observation was further explored and led to the development of *n*-pent-4-enyl moiety as an effective leaving group for the glycosidic donor in glycosylations[36].

An electrophilic activation of the pent-1-enyl glycoside **XIII** affords an onium ion **XIV**, which upon further remote participation by glycosidic oxygen leads cyclization to the tetrahydrofuran oxonium ion **XV**. Concomitant participation of the *endocyclic* oxygen leads to facile cleavage of the glycosidic bond and the formation of the reactive oxocarbenium ion **XVI** and substituted THF **XVII** (Fig. 6).This observation was elaborated elegantly and led to the development of *n*-pentenyl glycosides as effective glycosyl donors in glycosylations[36].

The feasibility for 1,2-disubstitution, for example, 1,2-dibromination and their removal to retrieve the unsaturation add further value to the *n*-pent-4-enyl moiety. Thus, a tuning of the anomeric moiety becomes feasible, so as to consider *n*-pent-4-enyl glycoside as either a glycosyl donor or acceptor in a latent-active fashion.

Studies on the reactivity of the *n*-pent-4-enyl glycoside further demonstrate the role of the substituent at the *C*-2 carbon in promoting the reaction at the anomeric carbon. Protecting group as a reaction parameter became a re-sounding principle since then. In simpler terms, an ether protecting group accelerated the reaction of glycosyl donor **XVIII**, in the course of the oxocarbenium ion formation **XIX** and **XX**, whereas the reverse occurred with an ester protecting group present at the *C*-2 carbon (**XXI**). The ester group being electro-negative destabilises the oxocarbenium ion. Thus, an arming-disarming possibility to generate the reactive



Scheme 6. Participation of ring oxygen in the opening up of pyranoside ring[35].

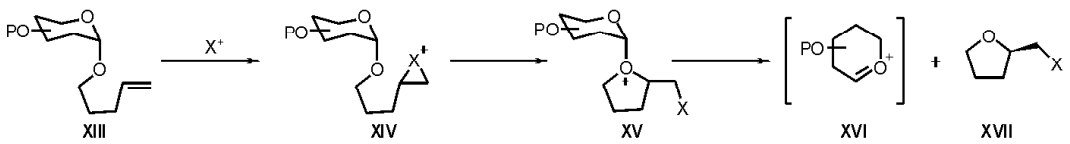


Fig. 6. Mechanism of *n*-pent-1-enyl glycoside mediated glycosylation[35].

oxocarbenium ion emerged, based on the electronic influence arising from the protecting group at *C*-2. The ether protecting group enhances the oxocarbenium ion than an ester protecting group at *C*-2 (Fig. 7).

In order to investigate this reaction in greater detail, a pair of armed (**XXIV**) and disarmed (**XXV**) glycosyl donors were subjected to activation under the appropriate conditions. It was observed that the armed glycosyl donors was activated preferentially and led to the formation of the glycoside product in which the ester protected glycosyl moiety was located at the reducing end. Thus, the product of the reaction is the cross-coupled product (**XXVI**), rather than the self-coupled product (**XXVII**) (Fig. 8).

When an armed **XXIX** and disarmed donor **XXVII** are made to compete for an electrophile, a transfer of electrophile would take place form the disarmed one to the armed donor as in **XXX** and **XXXI**, which would react immediately and results in the formation of oxocarbenium ion **XXXII** (Fig. 9). As this observation can be related to the Le-Chatelier's principle the same result can be extended to other glycosyl donors as well.

The reactivity of the disarmed *n*-pent-4-enyl donors is completely dependent on the electrophilic source used for activation[37]. The reaction of disarmed donor, where IDCP failed to give reaction, were effectively promoted by the NIS-triflate catalytic system.

Validity of the *n*-pent-4-enyl glycoside with varied protecting groups that aid reactivity differences was demonstrated with the synthesis of several oligosaccharide of biological relevance, an example is the high mannan oligosaccharide present in the viral coat protein of HIV1[38]. Few further advancements brought in this glycosylation method are:

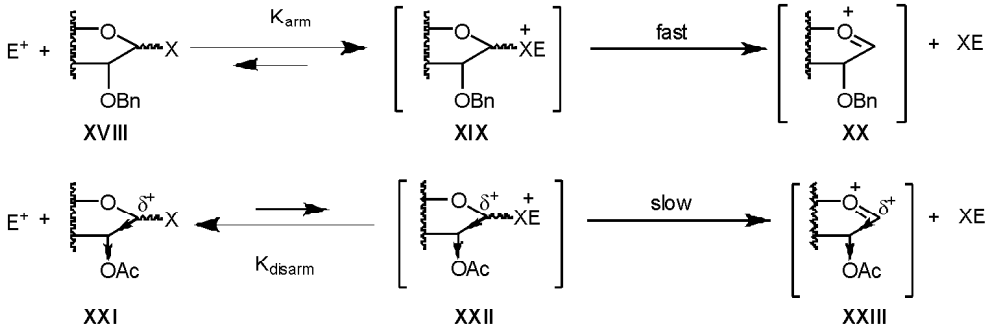


Fig. 7. Effect of ether vs ester type protecting groups at *C*-2 carbon of a glycosyl donor in the course of the generation of the oxocarbenium ion[36].

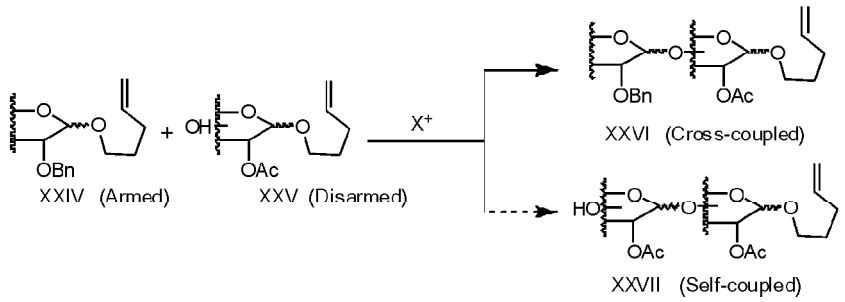


Fig. 8. A glycosylation reaction with reactivity differences between an ether and ester protecting group[36].

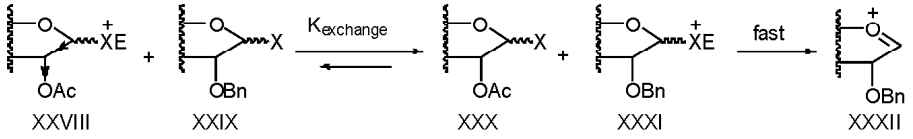


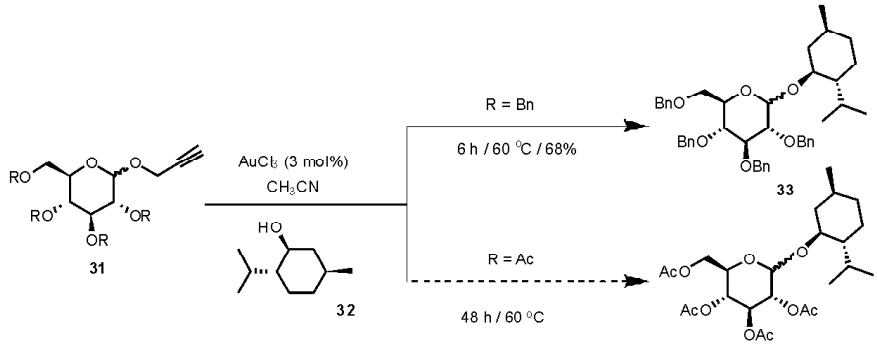
Fig. 9. Transfer of electrophile from a disarmed glycosyl donor to an armed donor[32].

(i) triflate promoters in glycosylation which aided higher reactivity of the glycosyl donor, irrespective of the protecting group[38]; (ii) altering the anomeric selectivity of the glycosylated product by change of solvent polarities; (iii) nature of electrophile activators, e.g. iodonium dicollidine perchlorate vs *N*-iodosuccinimide activator and (iv) utilizing *n*-pentenyl orthoester, in place of *n*-pentenyl glycoside as glycosyl donor, wherein the orthoester is more reactive relative to *n*-pentenyl glycoside donor, which permitted to achieve better chemoselectivities in the glycosylations[39].

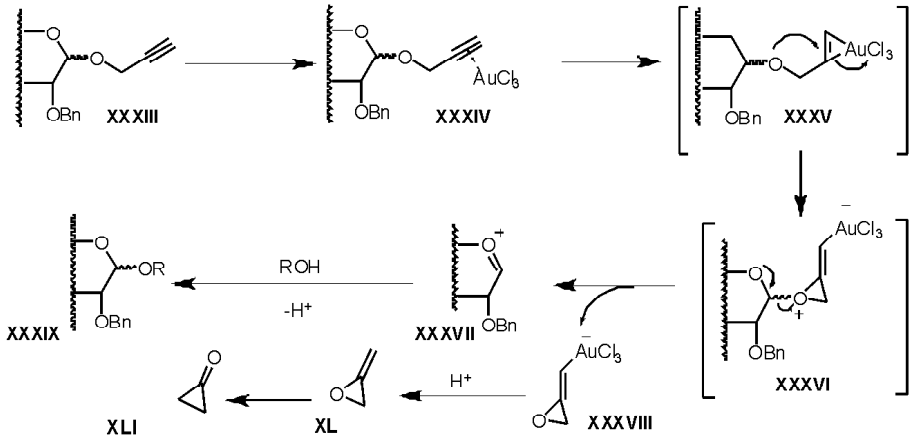
(b) Propargyl group as a leaving group in glycosylation chemistry: Propargyl glycosides are developed as another unsaturated aglycan of profound value as glycosyl donors, as advanced by Hotha and co-workers[40]. Propargyl glycosides could be secured through Fischer glycosylation, such glycosides are stable, orthogonal to many reactions and can be subjected to facile activation through alkynophilic gold salt activator. The α/β ratio of the glycosidic products formed was independent of the anomeric ratio of the glycosidic donor **31**. Further the per-*O*-acetylated and per-*O*-benzoylated glycosidic donors failed to afford the corresponding product compared to the glycosylation of *per*-*O*-benzylated glycosidic donor with an aglycan acceptor **32**, which afforded glycoside **33** in glucopyranoses (Scheme 7).

The coordination of Au(III) to the alkynyl moiety **XXXIV** results in the formation of 3-membered gold-carbene complex **XXXV**. Propensity to the formation of oxocarbenium ion enforces a rearrangement in **XXXVI** and the removal of oxirinium-gold complex **XXXVIII**. The oxocarbenium ion undergoes nucleophilic attack to yield the corresponding glycoside **XXXIX**. The oxirinium gold complex further undergoes rearrangement to form cyclopropenones **XL** and **XLI**. The highly strained aglycan portion of the glycosyl donor also requires a higher temperature to realize the glycosyl cation formation, unlike many other glycosylation methods, where lower temperatures are adopted for the glycosyl cation formation and subsequent glycosylation (Scheme 8).

The method afforded excellent yields of glycosides, par-



Scheme 7. Synthesis of glycosides from propargyl donors and effect of protecting groups[40].



Scheme 8. Activation of propargyl moiety in propargyl glycosides and the formation of the glycosyl cation[40].

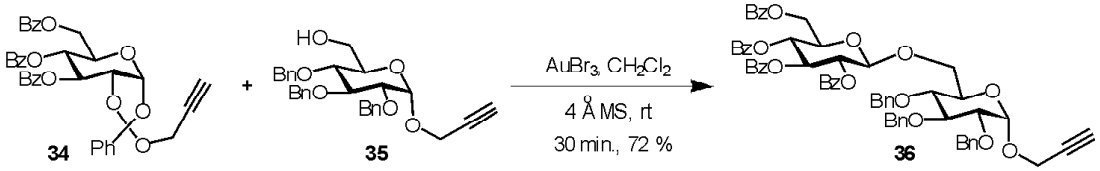
ticularly with non-sugar acceptors and the stereoselectivities were good to moderate. In this context, a further development is the evolution of propargyl orthoesters as glycosyl donors in place of propargyl glycosides, added with the feasibility that orthoesters are orthogonal to propargyl glycosides, even when the activation to form glycosyl cation requires Au(III) catalyst. Utilizing $AuBr_3$ as promoter, the propargyloxy functionality present in the orthoesters (**34**) could be activated selectively at room temperature and subsequent glycosylation afforded glycoside **36**, with the corresponding glycosyl acceptor **35**, having propargyl functionality at the reducing end (Scheme 9)[41].

The formation of anhydro-sugar **42**, arising from the disaccharide donor **37** pointed towards the glycosidic bond cleavage giving oxocarbenium ion and anionic sugar moiety **40** and thereby competing intramolecular reaction under the activation conditions (Scheme 10)[42].

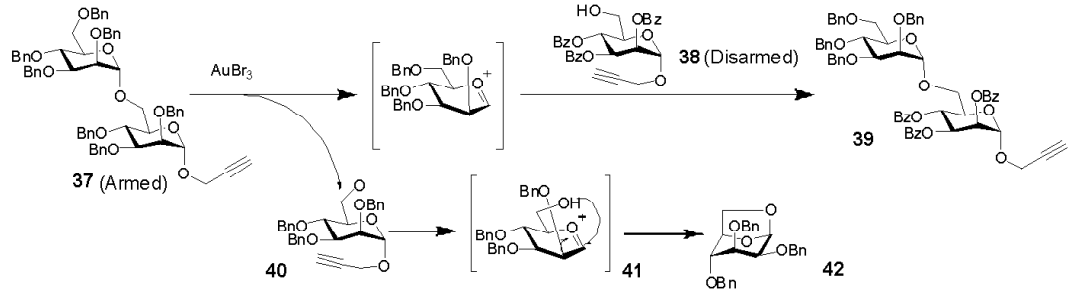
Successful glycosylations depend on judicious choice of protecting groups that participate in the reactions through electronic effects. Cross-coupled product **39** forms when glycosyl donor undergoes glycosidic bond cleavage under the reaction conditions (Scheme 11). Thus, reaction of disaccharide donor **43** with propargyl glycoside **38** afforded not only the required trisaccharide **44**, but also cross-coupled disaccharide **39** and monosaccharide glycoside **45**, resulting from the glycosidic bond cleavage in donor **43**.

The activation of glycosyl donor and reaction with acceptor could be conducted even when the hydroxyl moieties are kept free without a protection[43]. Scheme 12 shows such a reaction involving unprotected propargyl glycoside **46**, with acceptor **47**, which afford trisaccharide **48**. The reaction required reflux temperature and use of excess glycosyl donor, as much as 10 molar equivalents.

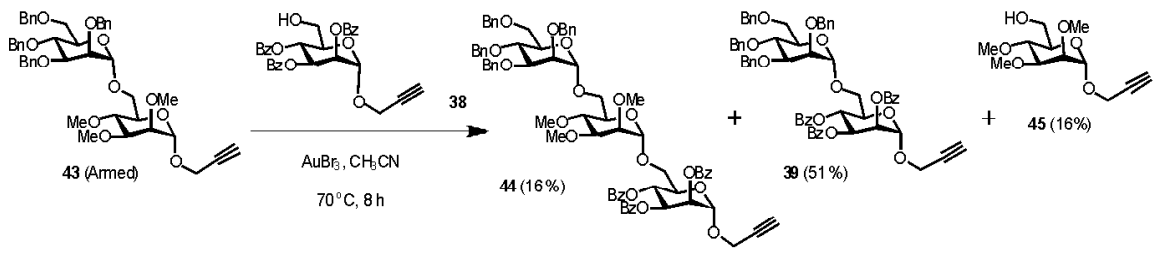
Greater advancements were made, leading to demon-



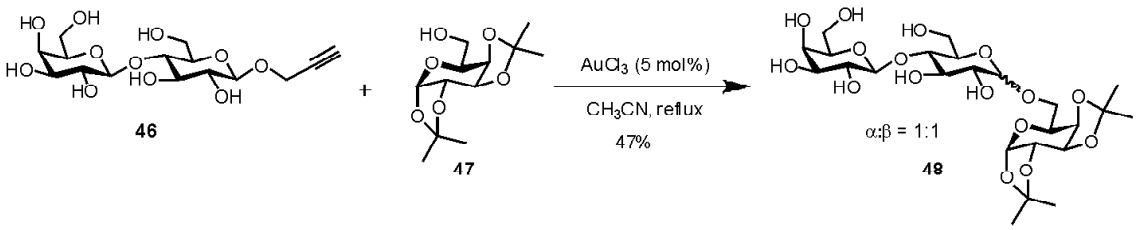
Scheme 9. Gold-catalyzed synthesis of disaccharide with propargyl orthoesters being orthogonal to propargyl group[41].



Scheme 10. Competing reactions leading to anhydro-sugar **42** from glycoside **37**[42].



Scheme 11. Armed-disarmed effect in a trisaccharide synthesis[42].

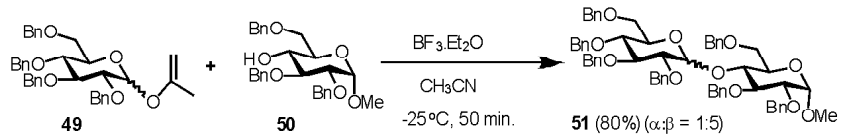


Scheme 12. Gold-catalyzed reaction with unprotected sugar[43].

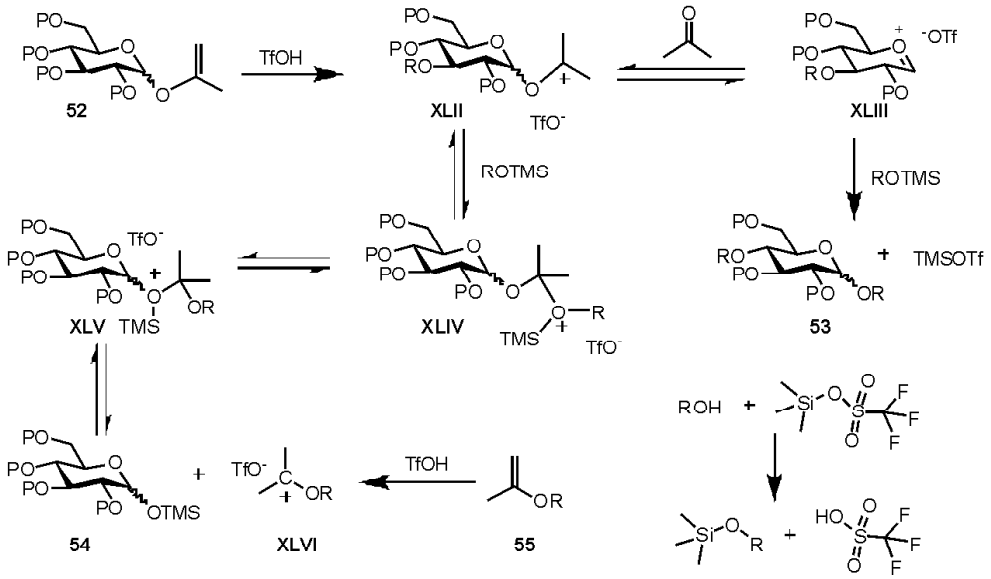
stration of the synthesis of 21-*mer* oligosaccharide recently, by reiterative glycosylations involving glycosyl donors and acceptors having propargyl moiety at the reducing end[44].

(c) Allyl vinylether as a leaving group: Thio-, propargyl and *n*-pentenyl glycosides are competent to certain reaction conditions, yet subject to oxocarbenium ion formation under suitable reaction conditions. As a result, these anomeric moieties are latent and are also active depending on the reaction activation conditions. The latent-active nature permits these anomeric moieties to be utilized in a beneficial manner, particularly for conducting consecutive glycosylations.

Sinay and co-workers in 1992 proposed isopropenyl moiety as a glycoside donor (Scheme 13)[45]. The isopropenyl glycosyl donor **49** effectively underwent a glycosylation reaction with the acceptor alcohol **50**, giving the required product **51**, in 80% yield. Glycosylation required promotors, such as, TMSOTf or $BF_3.OEt_2$, leading to the generation of the reactive glycosyl cation **XLIII** (Scheme 14), the reaction of which with glycosyl acceptors completed the formation of the glycosidic bond. Within promoters, TMSOTf induced a better β-selectivity than Lewis acids. A change of solvent to CH_2Cl_2 from CH_3CN resulted in lower yield of the resulting glycoside, formation of non-reducing trehalose-type 1,1′-dis-



Scheme 13. Preparation of disaccharide using isopropenyl glycoysl donor[45].



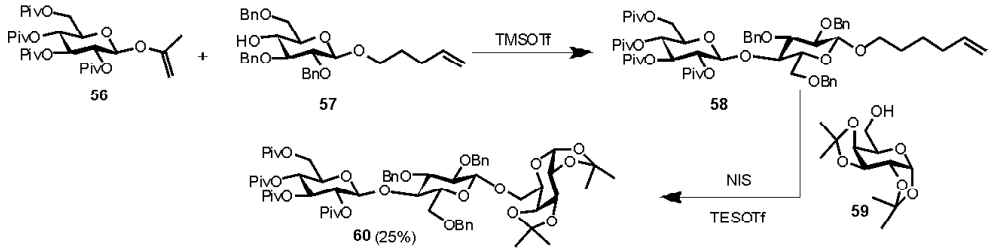
Scheme 14. Generation of TfOH from the TMSOTf interaction with acceptor alcohol and subsequent promotion of glycosylation[45].

accharide occurred when the reaction conducted using a glycosyl acceptor. Whereas, none of product formation occurred with diethyl ether as solvent of the reaction. It was suggested that promoter TMSOTf would silylate acceptor hydroxyl moiety, resulting in the generation of TfOH in the reaction medium. Upon treatment with TfOH, anomeric enol ether moiety of glycosyl donor **52** is protonated to **XLII** and would further lead to oxocarbenium **XLIII** formation, following a series of transformation (Scheme 14). The reaction with nucleophile results in the glycoside **53** formation. The reaction of ROTMS on the protonated species results in the formation of an ion pair **XLIV**. Further rearrangement to **XLV** leads to the formation of a silylated glycoside **54**, with the liberation of an ionic species **XLVI**. The choice of promoters and solvents becomes important determining factors of the glycosylation reactions in general.

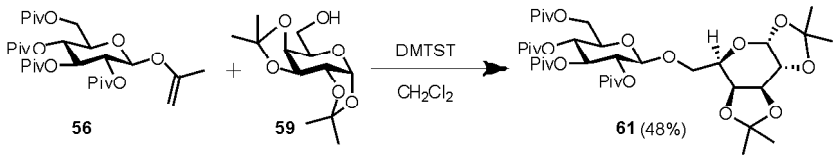
The value isopropenyl glycosyl donor was explored further by Chenault for *trans*-glycosylations[46,47]. With the appropriate combination of isopropenyl donor **56** and *n*-pent-4-enyl acceptor **57**, synthesis of a disaccharide **58** was performed and carried further towards subsequent step as a glycosyl donor, along with a varied glycosyl acceptor **59**, to afford a trisaccharide **60**, in a one-pot synthesis fashion (Scheme 15).

Formation of mixed acetals is a serious impediment on isopropenyl glycoside when promoters NIS/TfOH or IDCP are used, along with the required glycoside product. Use of TfOH alone did not promote the reaction, suggesting the lack of *in situ* generation of TfOH when TMSOTf is used as the promotor (Scheme 14). Further experiments showed that DMTST promoter could activate the pivaloyl protected glycosyl donor **56**, to afford the required glycoside **61** exclusively (Scheme 16).

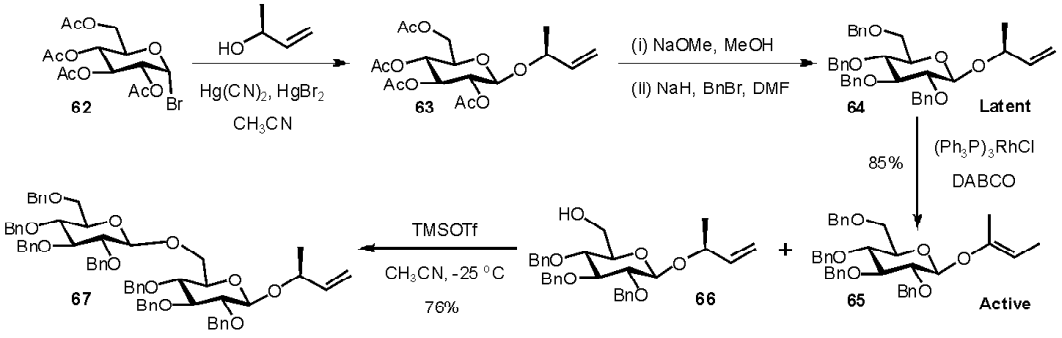
Boons and co-workers reported a novel latent-active glycosylation, using substituted allyl glycoside **63** as the donor, prepared from bromide **62**. Scheme 17 illustrates the sequence of reactions, leading to the effective use of substituted allyl glycoside as the donor. The acetyl group present in the glycosyl donor **63** was de-protected and introduced with benzyl ether, so as to enable as an armed glycosyl donor **64**, prior to glycosylation. The required reaction herein is the isomerization of allyl moiety in **64**, to the corresponding vinyl moiety **65**, mediated by a rhodium catalyst[48]. Thus, a latent 3-butene-2-enyl glycoside **64** was transformed to the active 2-buten-2-yl glycoside **65** and, in the presence of a Lewis acid, activation would occur towards the glycosyl cation formation. This activation through double bond isomerization enables the method to be befitting in a latent-active method of glycosylations. A vinyl glycoside undergoes reaction to afford a glycosyl cation, the reaction of which with an allyl glycoside acceptor **66** would complete the glycoside bond formation. The latent allyl moiety at the reducing end glycosyl moiety in **67** is, in turn, available for isomerization to an active vinyl glycoside for further glycosylations. A reiterative glycosylation in one-pot is a clear possibility with this glycosylation method[49]. An impediment is that the promo-



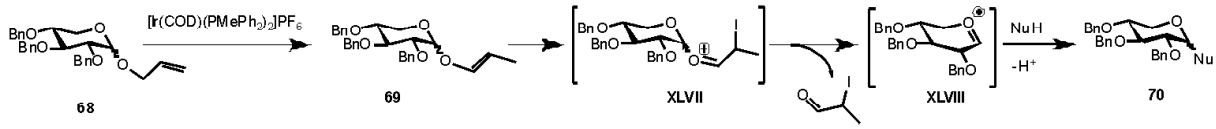
Scheme 15. Sythesis of trisaccharide in one-pot using isopropenyl and *n*-pent-4-enyl glycosyl acceptor[46].



Scheme 16. DMTST promoted glycosylation of isoproenyl glycosidic donor[47].



Scheme 17. Rh complex catalyzed isomerisation and subsequent glycosylation reaction of allylic glycosides[48].



Scheme 18. Mechanism for glycosylation using isomerized vinyl glycosyl donors[50].

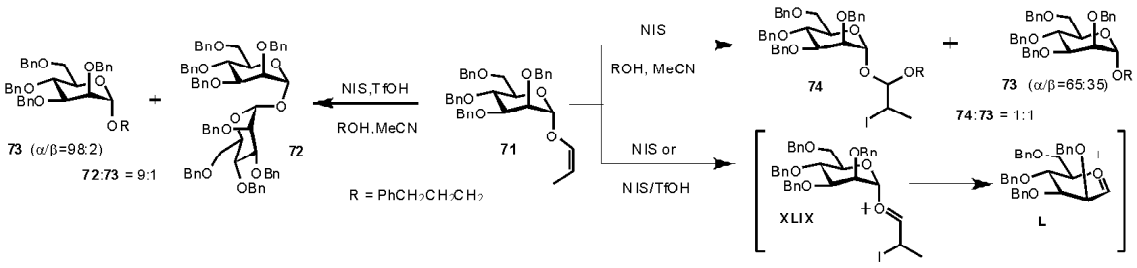
ters of the glycosyl cation formation, such as, TMSOTf or $BF_3.OEt_2$, encounter quenching in the presence of the metal catalyst and only a lactol formation results. A possibility to overcome this impediment is to expose the metal catalyst to oxygen, prior to the glycosylation and treated subsequently with $BF_3.OEt_2$, to afford the required disaccharide, for example, **67**. A combination of TMSOTf promoter in MeCN as solvent could lead to stereoselective β-anomer formation as the major product, whereas α-anomer selectivity would occur in the combination of Et_2O/CH_2Cl_2 solvents. Substitution at the vinylic carbon with the methyl substituent in isopropenyl glycoside donor favors the protonation of the anomeric oxygen, suitable for an efficient glycosylation without encountering competing reactions leading to trehalose type 1,1′-glycosidic bond formation and lactol formation.

Identification of alternate metal catalysts has also been developed. The work of Wang and co-workers[50] achieved isomerization of allyl glycoside **68** to the corresponding vinyl glycoside **69**, with the aid of hydrogen-preactivated $[Ir(COD)(PMePh_2)_2]$-PF_6 catalyst (1 mol%), in THF as solvent (Scheme 18). Upon isomerization, THF was removed and the glycosyl acceptor in acetonitrile was added, followed by the addition of NIS at room temperature, to afford the desired glycoside **70** in a few minutes, via the formation of intermediate **XLVII** and its subsequent rearrangement to the oxocarbenium ion **XLVIII**. An improvement in the yield was observed when the donor:electrophilic promoter:acceptor ratio of 1.5:1.5:1. Disarmed glycoside did not undergo the reaction efficiently under the reaction conditions.

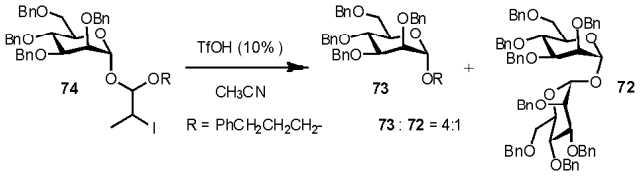
The reaction also encounters difficulties as a result of the addition of promoter electrophile across the anomeric enol ether double bond[51]. Presence of electrophile, namely, NIS, and TfOH during the glycosylation reaction, which forms IOTf species, results in both competing reactions of glycosyl cation formation and addition across double bond. However, an excess of TfOH is found to diminish addition product **74** formation, as also reactions conducted under dilute concentrations, whereas increased glycosyl donor concentration increased the electrophilic species addition across enol ether moiety. The reaction of mannosyl donor **71** with NIS alone, as well as, NIS/TfOH combination, in the presence of a nucleophile, afforded two different by-products, trehalose **72** and a mixed acetal **74**, along with the desired glycoside **73**, indicating the presence of two competing reactions (Scheme 19)[52].

In presence of the TfOH, intermediate **XLIX**, common in both the methods, promotes the reaction towards formation of the required glycoside, through reformation of the addition product **74** (Scheme 20).

Further studies of the reaction mechanism in the presence of TfOH (10%) in MeCN on the substituted product showed the formation of the required glycoside **73** and 1,1′-trehalose **72** type by-product, in a 4:1 ratio. It was hypoth-



Scheme 19. Reactions of vinyl mannopyranoside in the presence of varying promoter and activator[52].



Scheme 20. Conversion of mixed acetal side product to the required glycoside[52].

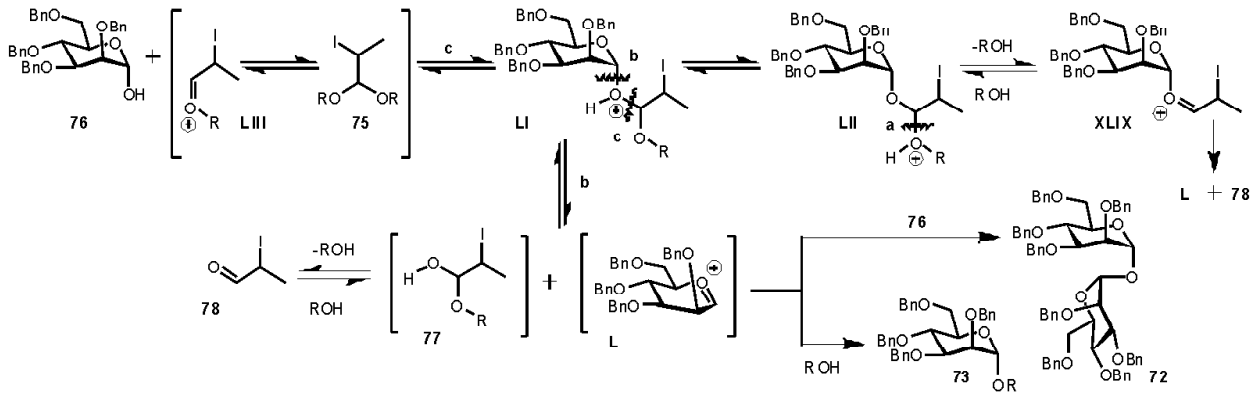
esized that an equilibrium would establish between the reaction intermediates and the role of TfOH would be to promote the reaction through activation of the double bond and conversion of the mixed acetal formed towards the desired product (Scheme 21).

The mixed acetal **74** would have varying possibilities for protonation (**LI** and **LII**) and *C-O* bond cleavage. Whereas, cleavage possibilities **a** and **b** would afford the glycosyl cation **L**, cleavage through possibility **c** would lead to a hemiacetal **76**, which formed the source of 1,1′-trehalose type product **72**, upon reaction with the oxocarbenium ion **L**. Pathway **b** gives oxocarbenium ion **L** and hemiacetal **77**. The hemiacetal would further undergo fragmentation to yield an aldehyde **78** and ROH. The mixed acetal **LII** is assumed to be in equilibrium with the intermediate **XLIX**, which leads to aldehyde **78** and oxocarbenium ion **L**. Whereas the intermediates formed in pathways **a** and **b** are similar, pathway **c** gives rise to a different type of oxocarbenium ion **LIII**, along with glycosyl hemiacetal **76**[52].

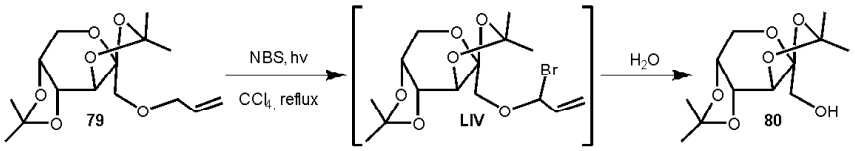
3.2. Radical activation of allylic glycosides

A further approach to activate the allylic glycosides is through the allylic halogenation-based activation. A novel allylic halogenation-based activation and glycosylation was reported recently by our group[53]. The allyl glycoside was directly activated by performing allylic bromination.

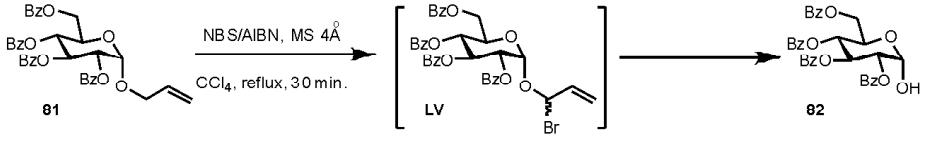
The method allylic activation through radical-mediated halogenation was reported earlier for the purpose of the allylic moiety deprotection (Scheme 22). Diaz and co-workers reported earlier the deprotection of anomeric allylic moiety in **79**, through activation of allylic carbon by a radical halogenation. Radical halogenation of the allylic bond resulting in the allyl bromide **LIV**, followed by hydrolysis afforded the hemiacetal **80**, quantitatively (Scheme 23)[54].



Scheme 21. Proposed reaction mechanism involving the addition product **74-H$^+$** as synthon[52].



Scheme 22. Deprotection of allylic glycoside through allylic halide formation[54].



Scheme 23. Hydrolysis of allyl moiety in allyl glycoside **81** to the corresponding hemiacetal **82** through allylic halogenation intermediate **LV**[54].

It is found further that the allylic halide **LVII**, which is prepared from the allyl glycoside **LVI**, is suitable to the formation of oxocarbenium ion **LXI**, under an appropriate condition. The reaction required a halophilic promoter and further involvement of the lone pairs of electrons of the *endocycic* oxygen (**LVIII-LX**) for the oxocarbenium ion generation and glycoside **LXII** formation (Fig. 10). This anticipation was taken forward and assessed as a potential route to glycosylations. Radical-mediated allylic halogenation was performed on allyl glycosides, using AIBN as the catalyst. The reaction would lead to allylic halide formation in a facile manner. The use of AIBN/CCl_4 in place of photolytic method finds a merit in complete conversion to allylic halide, although reaction required reflux condition.

Among the commonly used protecting groups in glycosylations, esters, isopropylidene and silyl ethers are compatible to allylic halogenation. Whereas, the most commonly used benzylic ethers are incompatible and only a complex mixture of un-tractable products result from multiple brominations on such benzyl ether protected allyl glycosides.

Upon completion of radical halogenation, attempts to isolate the allylic halide were not successful, rather the instability of such allylic halides led to the isolation of only the hydrolyzed product, namely, the hemiacetal. Due to instability of the newly generated allylic bromide, subsequent glycosylation reactions required to be conducted in one-pot, without the isolation of the allylic halide. Further activation of the allylic halide towards glycosyl cation formation was conducted in CH_2Cl_2. Thus, removal of solvent for radical halogenation and re-dissolving the resulting allylic halide for further reactions in another solvent was required.

A search of a suitable promotor for glycosylation reaction led to use of halophilic silver salts initially (Fig. 10). The high affinity of Ag(I) for the halides was anticipated to initiate the reaction, by which the participation of lone pairs of electrons of *endocyclic* oxygen would lead to the cleavage of the glycosidic bond and formation of the glycosyl cation, with the concomitant loss of an acrolein adduct. Three different halophilic reagents were screened initially. Glycosylation reaction of allyl-tetra-*O*-acetyl-D-glucopyranoside (**83**) with aglycan acceptor was studied with various promotor systems, such as, AgOTf, $AgClO_4$ and $AgCO_3$ in CH_2Cl_2 solution. The allyl bromide intermediate in CH_2Cl_2 was admixed with one of the above promoters, reaction mixture was cooled to –40°C, stirred for ~10 min, followed by which acceptor alcohol was added and the reaction was left stirring at room temperature for 2 h (Scheme 24)[53].

The use of $AgClO_4$ as promotor to the activated bromi-

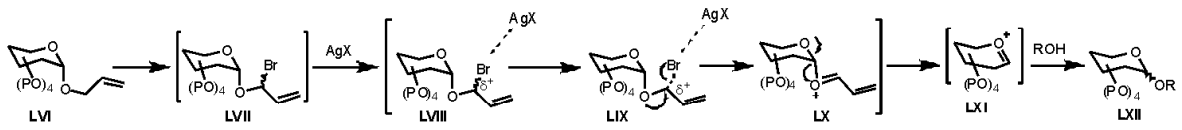
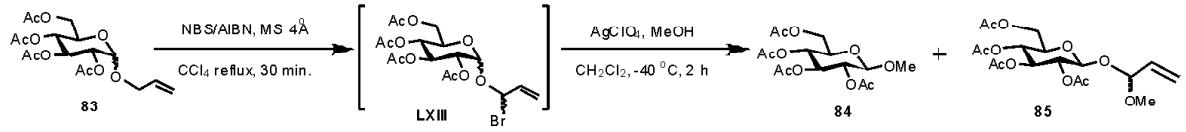


Fig. 10. Allylic activation for the glycosidic bond formation using allyl glycoside donor.



Scheme 24. Allylic halide activation and glycosylation with MeOH as acceptor[53].

nated species **LXIII**, prepared from the glycosyl donor **83**, afforded the desired glycoside **84**, along with another major, which was identified as the substitution product **85**. Substitution product appeared to form by an S_{N2} type reaction. The allylic bromide formed being an unstable molecule can undergo elimination, with the participation from the anomeric oxygen, resulting in the formation of a glycosyl intermediate **LXIV** and oxocarbenium ion **LXV**. If the nucleophilic attack occurs before the formation of oxocarbenium ion, substitution product **LXVI** dominates over the required glycoside **LXVII** (Fig. 11). The higher reactivity and higher temperature at which the reaction was performed might lead to this substitution product, in addition to the glycosylation product (Scheme 25).

The glycosyl donor **83α** showed different reaction pattern when made to undergo reaction with two different aglycan acceptors, MeOH and pentanol, in the presence of AgOTf promotor. Whereas pentanol led to the required glycoside **86**, MeOH yielded primarily the allylic substituted product **87**. The formation of substitution product also indicated the formation of allyl halide from the allylic halogenation reaction in the earlier step of synthesis. Analysis of the reaction mixture by mass spectrometry aided identification of the acrolein adduct, which formed due to anomeric bond cleavage in the course of evolution of the oxocabenium ion.

A change of the promoter from $AgClO_4$ to $AgCO_3$ or the combination of both the promoters completely ceased the desired product formation and the substitution product, namely, the mixed acetal formed as a single product (Table 1). These observations suggested that Ag(I) promoter would have a higher propensity for an S_{N2} reaction at the allylic carbon, rather than promoting the glycosyl cation formation. Allyl tetra-*O*-acetyl mannopyranoside and allyl tri-*O*-acetyl fucopyranoside also afforded substitution products in significant amounts. The exclusion of moisture was critical, in order to avoid the formation of hemiacetal **C**.

AgOTf as promoter improved the glycoside product **A** formation considerably and also suppressed the formation of substitution or mixed acetal product **B**. The improvement in glycoside product formation was also dependent on the nature of the acceptor alcohol. Whereas aglycosyl acceptors appeared to prefer substitution product formation, that of gly-

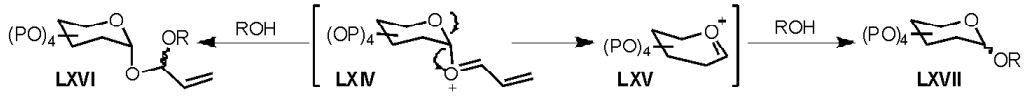
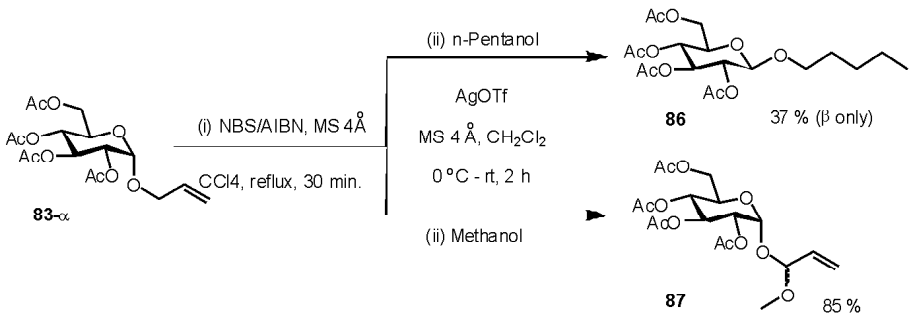
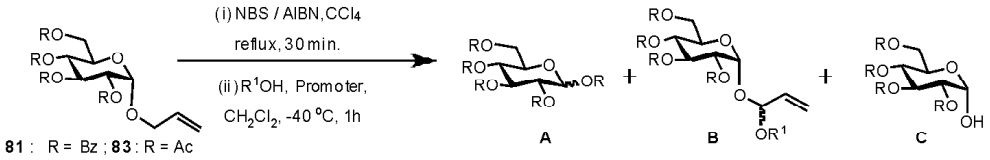


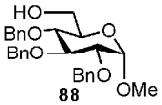
Fig. 11. Formation of glycosidic bond vs mixed acetal formation.



Scheme 25. Variations in the product formation depending on the glycosyl acceptor.

Table 1. Effect of promotor in glycosidic bond formation

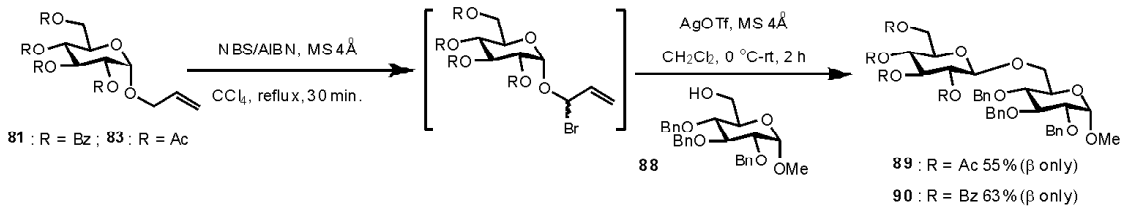


Entry	Donor	ROH	Promoter (molar equiv.)	Product
1	113	MeOH	$AgCO_3$ (1.2)	B
2	113	MeOH	$AgCO_3$ (1.5), $AgClO_4$ (1.2)	B
3	113	MeOH	$AgClO_4$ (1.2)	A + B + C (major)
4	113	MeOH	AgOTf (1.2)	A (major) + C
5	110		AgOTf (1.2)	A (55%)

cosyl acceptors afforded the glycoside as the major product, under AgOTf promoted reactions. These observations reiterated the importance of counter ion constituting the promoter, but also finer nucleophilicities associated with acceptor alcohols[53].

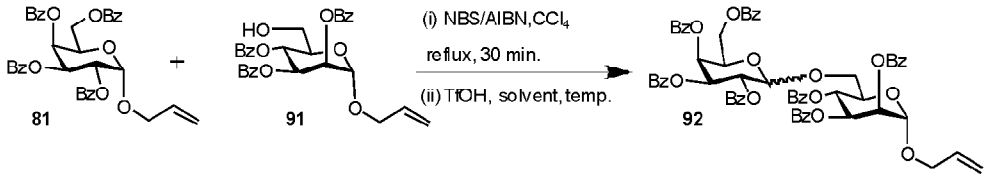
An influence of the protecting group to promote the reaction towards the glycoside product was observed in case of acetate **83** and benzoate **81** as protecting groups in the glycosyl donor (Scheme 26). The reaction with the primary glycosyl acceptor **88** led to the stereoselective formation of exclusive β-anomers **89** and **90**. The disarming nature of the ester groups in glycosylation reactions might be plausible in the present method too. Yet reactions with armed glycosyl acceptor provided a clue to the extent to glycosyl donor ability with two differing ester protecting groups. An improvement in the yield of the glycoside product occurred when glycosyl donor presented with benzoate protecting group, as opposed to acetates. Further, the stereoselectivity remained to be β-anomer selective, suggesting an anchimeric assistance which would enblock the axial face in a half-chair conformation of an oxocarbenium ion, leaving the equatorial face for the nucleophile approach. In effect, the α-anomer of the glycoside product could not be detected perceptibly in the reaction mixtures, as adjudged through NMR spectroscopy analysis of the reaction mixtures.

In an effort to improve upon towards a metal-free promoter mediating the reaction, the observations of AgOTf as a comparatively efficient promoter formed a basis. Reactions mediated by TfOH, in place of AgOTf, were thus conducted. Glycosyl donor allyl-tetra-*O*-benzoyl-D-galactopyranoside **81** and mannopyranosyl acceptor **91** were undertaken for the reaction. The first step of allylic halide formation with glycoside **81**, under radical halogenation condition, followed by utilizing the newly formed allylic halide as an active glycosyl donor reacting with latent mannopyranoside **91**, in the presence of TfOH as promoter, afforded disaccharide **92**, in 90% yield, which is very impressive, particularly for a disarmed donor. For optimising the reaction conditions, glycosylation was conducted with varying solvents in a range of temperature for 2 h (Table 2).



Scheme 26. Allylic halide mediated glycosylation with glycosyl donors differing in the nature of ester protecting groups.

Table 2. Solvent and temperature effects on TfOH promoted glycosylation



Entry	Solvent	Temp. (°C)	Yield (α/β)
1	CH_2Cl_2	–78	No reaction
2	CH_2Cl_2	–40 to 0	90% (β only)
3	CH_3CN	–30 to 0	α/β mixture
4	CH_3NO_2	–20 to 0	Complex mixture

Among the different solvents evaluated, reactions in CH_2Cl_2 afforded the glycoside excellent whereas that in CH_3NO_2 and MeCN were not effective, either leading to an anomeric or complex mixture of products. Further, it was observed that higher the temperature, the mixed acetal formation was more prominent. Reactions conducted between –78 and 0°C showed that the optimal temperature was ~40°C, whereas –78°C did not promote the reaction and reactions at 0°C led to a mixture of products. Thus, for the method developed herein with TfOH as the promoter, reaction temperature at ~ 40°C appeared to be most optimal and the reaction led to stereoselective β-anomer product only. The presumption is that protonation of anomeric oxygen in **LXIX** occurs on allylic halide **LXVIII**, with the aid of TfOH promoter, which then undergoes participation of the lone pairs of electrons of *endocyclic* oxygen towards the formation of oxocarbenium ion **LXX** (Fig. 12).

When comparing the mechanism of the TfOH vs Ag-metal catalysed reactions, direct protonation of the anomeric oxygen results in the formation of oxocarbenium ion. In the case of the Ag(I) salt, the metal coordination with the halide occurs intially, which is then subjected to either glycosidic bond cleavage and oxocarbenium ion formation or a direct $S_{N}2$ type substitution of halide with the incoming nucleophile. The effectiveness of these two competing reactions depend on the nature of nucleophile, solvent and temperature of the reaction. Absence of such a competing reaction in the case of TfOH as the promoter appears to favor the reaction towards the glycoside product formation.

It is also consistently observed that hemiacetal of the glycosyl donor formed in varying amounts, which is presumed to be due to presence of inadvertent moisture encountered during the reaction, by which water acted as nucleophile reacting with the glycosyl oxocarbenium ion species. Thus, exclusion of moisture is critical to conduct the glycosylation. A number of glycosylations were conducted to optimize reaction conditions with gluco-, galacto- and mannopyranosyl donors and different types of glycan acceptors. The reaction procedure is as follows: molecular sieves (4 Å), dried previously at ~400°C under vacuum is admixed with NBS (recrystallized and dried) (0.9 molar equiv.), an amount of CCl_4 is added, followed by the addition of the glycosyl donor in CCl_4, the reaction degassed with argon gas and a catalytic amount of AIBN added. The reaction mixture is refluxed for 30 min, upon completion of the reaction, as verified by TLC, CCl_4 is distilled *in vacuo*, the crude reaction mixture re-dissolved in CH_2Cl_2 and cooled to –41°C. A catalytic amount of TfOH is added, stirred for ~10 min, followed by the addition of acceptor alcohol. After 1 h reaction duration at –41°C, the reaction mixture stirred at room temperature for ~1 h, added with NEt_3,

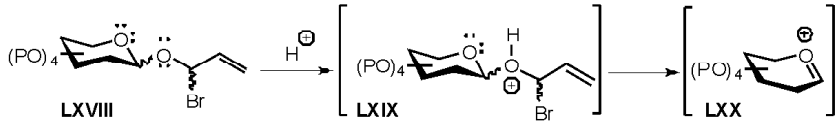


Fig. 12. Possible mechanism for TfOH activation of allylic halide **LXIX**.

filtered, worked-up and purified using a linear gradient of pet. ether/EtOAc or PhMe/EtOAc solvent mixtures to secure the glycoside products.

It was also observed that under the reaction conditions, acetate protecting groups underwent deprotection, which led to reduction in the yields during isolation and purification. Among the protecting groups, benzoate turn out to be a choice, although more protecting groups compatible to the reactions are yet to be fully realized. At present, protecting groups isopropylidene and silyl ethers are found to be compatible to the latent glycosyl donor undergoing allylic halogenation reaction to afford the active glycoside donor.

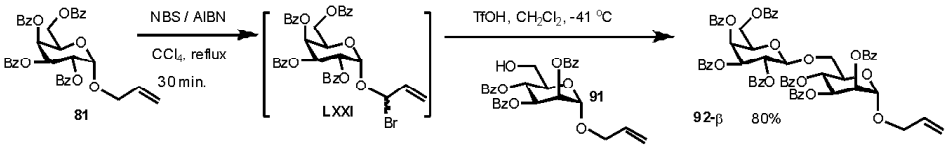
The reaction is amenable to a molar scale synthesis of glycosides, initiated from allyl glycosyl donor and acceptor (Scheme 27). The reaction between tetra-*O*-benzoyl allyl galactopyranoside (**81**) was performed with mannosyl donor **91** to afford disaccharide **92β**[53].

At larger scales of the reaction, the yields of the reactions remained similar to that of the reactions conducted in millimoles and the anomeric β-stereoselectivity also remained, though the reaction required longer duration.

The fact that activation is conducted prior to glycosylation in the absence of acceptor alcohol and is carried further towards the reaction without any purification merits the new glycosylation method[55]. Addition of the acceptor component **LXXIV** in a subsequent step after the initial activation to **LXXIII** leads to an advantage, wherein the allyl glycosides act both as glycosyl donor **LXXII**, as well as, acceptor **LXXIV**. The resulting glycoside **LXXV** having allyl moiety at the anomeric carbon can be subjected to an activation for further glycosylations until the desired glycoside **LXXVI** is obtained (Fig. 13), in a latent-active fashion of glycosylation methodology.

An allyl glycoside is not reactive until activated under the reaction conditions of glycosylation, thereby assumed it to be a latent glycoside. Upon allylic halogenation, this latent glycoside becomes active for glycosylation. This prior activation procedure affords further advantage of reduced protecting group manipulations encountered generally in glycosylation methods. The latent-active glycosylation method thus relies on prior activation of a common precursor to an active donor component to react with the same precursor acting as the acceptor component. The resulting product is competent for a subsequent activation and continuation of the glycosylation reactions, without protecting group manipulations. The following two examples illustrate the latent-active methodology adopted herein (Scheme 28). Disaccharides **92β** and **95** are prepared from glycosidic donors **81** and **94**, and acceptor **91**. The disaccharides are activated by allylic bromination and further treated with a latent allyl glycosidic acceptor to synthesize the linear trisaccharide **93** and **96**, respectively, in a latent-active manner[55].

There are instances where the reactivity differences arising from the mismatch-pair concept demands the opposite combination, i.e., a monosaccharide acting as the donor and a disaccharide acting as the acceptor.Introduction of a silyl ether, such as, TBDPS in the glycosyl donor **97** component remained intact in the course of the allylic bromination to intermediate **LXXVII**, as well as, under the glycosylation reaction conditions to afford a disaccharide **98** (Scheme 29).



Scheme 27. Glycosylation conducted in a gram scale.

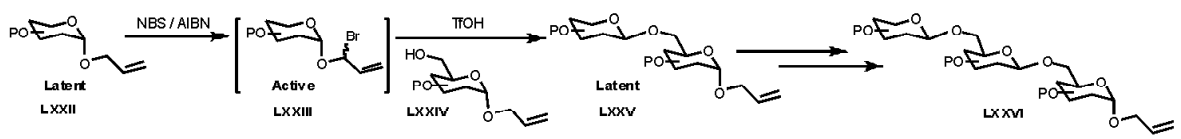
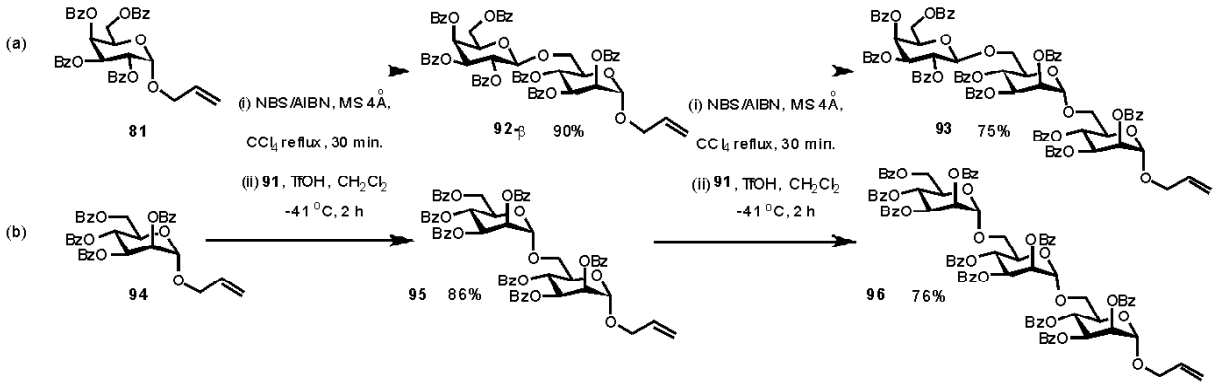
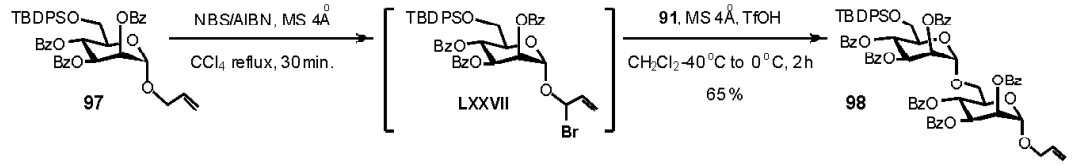


Fig. 13. Latent-active glycosylation strategy with allyl glycosides.



Scheme 28. Synthesis of trisaccharides **93** and **96**, through a consecutive glycosylation involving latent-active strategy.

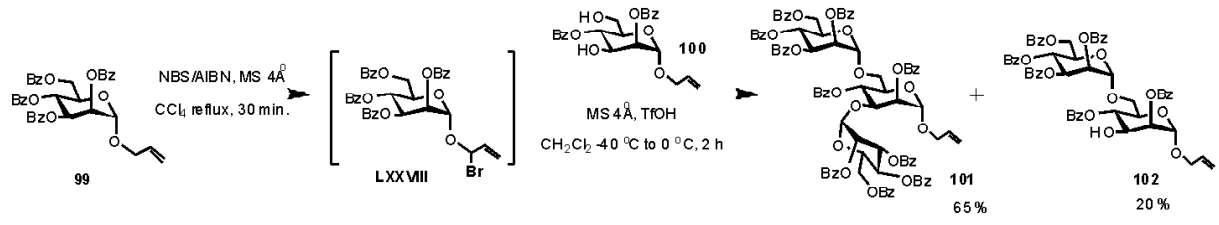


Scheme 29. Glycosylation reaction of a TBDPS-protected donor.

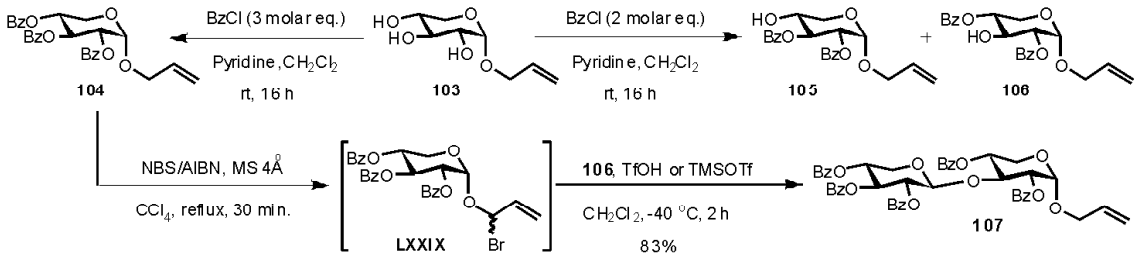
Upon silyl moiety deprotection, the disaccharide can be subjected as an acceptor for further glycosylation.

The allylic halide as an active glycosyl donor has also been evaluated in double glycosylation reactions. An active mannopyranosyl donor **99** reacting with mannopyranosyl acceptor **100**, having *C*-3 and *C*-6 hydroxyl moieties, led to a double glycosylation and the corresponding trisaccharide **101** was obtained in good yields, along with the disaccharide **102** as a minor product (Scheme 30)[53]. Such double glycosylation reactions yet remained to be optimized to include different types of glycosyl donors and acceptors. In instances where galactosyl donor was used in double glycosylation reactions, the anticipated trisaccharide did not form, rather only a hydrolysed monosaccharide resulted. This contradictory reactivity pattern might be due to the incompatibility or mismatch pair of the donor and acceptor.

Application of the newly developed latent-active glycosylation method utilising allyl glycosides, synthesis of β-(1→3)-linked xylan molecule was undertaken[55]. Importance of xylans as one of the most abundant natural polysaccharides has been well documented. Xylose adopts a pyranose form, with equatorial orientation of *C*-2–*C*-4 hydroxyl moieties. The reactivities of these secondary hydroxyl groups in xylose is dependent on the configuration of substituent at *C*-1. As a result, reactivity at a chosen hydroxyl moiety in xylose requires a judicious approach[56]. Preparation of *C*-3 and *C*-4 free hydroxyl containing xyloside derivatives is shown in Scheme 31. Glycosyl donor **104** and glycosyl acceptors **106** and **105** could be prepared by direct benzoylation of α-allyl xylopyranoside **103**.



Scheme 30. Synthesis of branched trisaccharide from double glycosylation.



Scheme 31. Preparation of xyloside precursors for glycosylation and synthesis of β-(1-3)-xylobiose disaccharide **107**.

Scheme 32. Attempt for the preparation of xylotriose.

Allylic halide activation of allyl 2,3,4-tri-*O*-benzoyl-α-D-xylopyranoside **104**, followed by reaction of the allylic halide with allyl xylopyranoside **106**, having free *C*-3 hydroxy moiety led to the disaccharide **107**, in good yields. The reaction afforded exclusively the product, with TfOH or TMSOTf as the promoter.

Further attempts to synthesize a trisaccharide starting from disaccharide **107** encountered difficulties, rather allylic halide activation of **107** and subsequent reaction with monosaccharide **106**, having free *C*-3 hydroxyl moiety led only to the recovery of the hydrolyzed lactol **108**, in place of anticipated trisaccharide (Scheme 32).

The possibility of glycosyl donor and acceptor being match and mis-match pair might be a limitation, with respect to nucleophilic reactivities of varied hydroxyl functionalities. Coupled with dis-arming effect of benzoate protecting groups in the glycosyl donor, a careful choice of reactive pairs and other parameters remain to be important factors in order to achieve successful glycosylations.

Conclusion

The foregoing compilation shows that transglycosylation is a powerful methodology in contemporary glycosylations. The participation of *endocyclic* oxygen to induce formation of the reactive oxocarbenium ion and the conformation of this intermediate species are critical in these glycosylations, as in the case of the varied other types of glycosyl donor activations. The presence of unsaturation in the aglycon moiety in a glycoside initiates the reaction through an electrophilic activation and subsequent formation of the reactive oxocarbenium ion enables the donor competent for a glycosylation. In addition to activation of the unsaturation, activation through the vinylic carbon is also a viable approach in the effort to generate the reactive oxocarbenium ion. Current developments demonstrate this possibility in the case of *O*-allyl glycosides. The facile latent-active transformation of a common glycoside precursor to be unreactive-to-a-reactive glycosyl donor is a novel outcome of the transglycosylation method. The recently evolved allylic halide activation method features conducting sequential glycosylation from a common allyl glycoside precursor. In glycosylations mediated by varied types of glycosyl donors, the transglycosylations merit from both conceptual and application points of view.

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