Conference paper

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One-pot oligosaccharide synthesis: latent-active method of glycosylations and radical halogenation activation of allyl glycosides

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Abstract: Chemical glycosylations occupy a central importance to synthesize tailor-made oligo- and polysaccharides of functional importance. Generation of the oxocarbenium ion or the glycosyl cation is the method of choice in order to form the glycosidic bond interconnecting a glycosyl moiety with a glycosyl/aglycosyl moiety. A number of elegant methods have been devised that allow the glycosyl cation formation in a fairly stream-lined manner to a large extent. The latent-active method provides a powerful approach in the protecting group controlled glycosylations. In this context, allyl glycosides have been developed to meet the requirement of latent-active reactivities under appropriate glycosylation conditions. Radical halogenation provides a newer route of activation of allyl glycosides to an activated allylic glycoside. Such an allylic halide activation subjects the glycoside reactive under acid catalysis, leading to the conversion to a glycosyl cation and subsequent glycosylation with a number of acceptors. The complete anomeric selectivity favoring the 1,2-trans-anomeric glycosides points to the possibility of a preferred conformation of the glycosyl cation. This article discusses about advancements in the selectivity of glycosylations, followed by delineating the allylic halogenation of allyl glycoside as a glycosylation method and demonstrates synthesis of a repertoire of di- and trisaccharides, including xylosides, with varied protecting groups.

Keywords: allyl glycosides; carbohydrates; glycosylation; ICS-29; oligosaccharides; oxocarbenium ion; radical halogenation.

Introduction

Chemical glycosylations provide an optimal route to prepare designed oligo- and polysaccharides, and glycoconjugates of functional importance. The seminal article by Paulsen provided a foundation to this flourishing area in the last few decades [1]. Chemical glycosylations are practiced for more than a century, the first such method which is utilized till date is the Konigs–Knorr glycosylation method [2, 3]. Fischer glycosidation is known even earlier [4], wherein an acid treatment of the hemiacetal provides the electrophilic reactive intermediate, namely, the oxocarbenium ion or the glycosyl cation, the reaction of which with an alcohol nucleophile completes the formation of the glycosidic bond. The glycosyl synthon leading to the formation of the oxocarbenium ion and the nucleophile which is required for reaction with the oxocarbnium ion are referred to as glycosyl donor and glycosyl acceptor, respectively. The notion that the glycosyl cation formation is an

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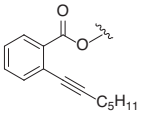
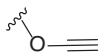
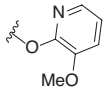
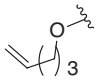
intermediate of the reaction has prompted developments of chemical glycosylations in many innovative ways and continues to attract the attention of practitioners even more (Table 1) [5, 6]. As opposed to enzymatic glycosylations, chemical glycosylations pose stringent requirements of protecting the hydroxyl moieties judiciously on both the glycosyl donor and acceptor components [7]. In addition, such protecting groups are being realized increasingly as moieties that influence the course of the glycosylation reactions. Stereoelectronic, steric and conformational features arising from the protecting groups determine the formation and stability of the glycosyl cation, thereby assuming greater importance in the glycosylation reactions. The emphasis is extended further to the role of the solvents in which the glycosylation is conducted, as a result of the solvent coordination abilities on to the evolving glycosyl cation intermediate. Hydrogen bonding abilities of auxiliary substituents in the protecting groups to stabilize the glycosyl cation are also being advanced [8, 9].

The ability of the leaving group on the glycosyl donor promoted by a catalyst, namely, the promoter, further adds to the finer details of the oxocarbenium ion stability, through either non-covalent or covalent bond formation. The reactive glycosyl cation formation and reactivity is thus governed by several factors that finally affect the outcome of the glycosylation reaction. The nucleophile entry either through the equatorial or the axial face of the reactive intermediate, leading to the formation of the β- or the α-glycoside product, respectively, relates directly to the stereoselectivity requirement on the target glycoside product. The illustrative reviews by Nielsen and Pedersen [10], Crich *et al.* [11], Bols and Jensen [12] and Oscarson *et al.* [13] impart a closer scrutiny of the factors in detail on the glycosyl cation formation and reactivity.

The anomeric halides, thio, trichloroacetimidates, glucal, phosphates/phosphites, esters/carbonates/thiocarbonates and aryloxy groups can be efficiently activated by the corresponding halo-, oxo-, aza- or thiophilic reagents. In addition, anomeric *O*-derived glycosyl donors, such as, pentenyl, propargyl glycoside can also be activated efficiently using electrophilic halogen reagents or metal ion. Organocatalytic methods also have been developed for stereoselective synthesis of glycosides [5, 6]. One of the pertinent challenges in glycosylations is the regioselective protection-deprotection of the chosen hydroxyl moieties. Further, some of the activations compiled in Table 1 are to be introduced just prior to the glycosylation reaction.

One pot glycosylations attract greater interest, the strategies for the efficient construction of oligosaccharides, wherein two or more glycosylation steps are conducted sequentially without the protecting group manipulation and isolation of the intermediates, yet requiring a pre-activation for the sequential reactivity of the donors. The one-pot glycosylations can be categorised in four major categories: (i) chemoselective; (ii) orthogonal; (iii) pre-activation and (iv) latent-active strategies, based on the factors for the sequential reactivities of the donors. Each of these strategies is described briefly in the following sections.

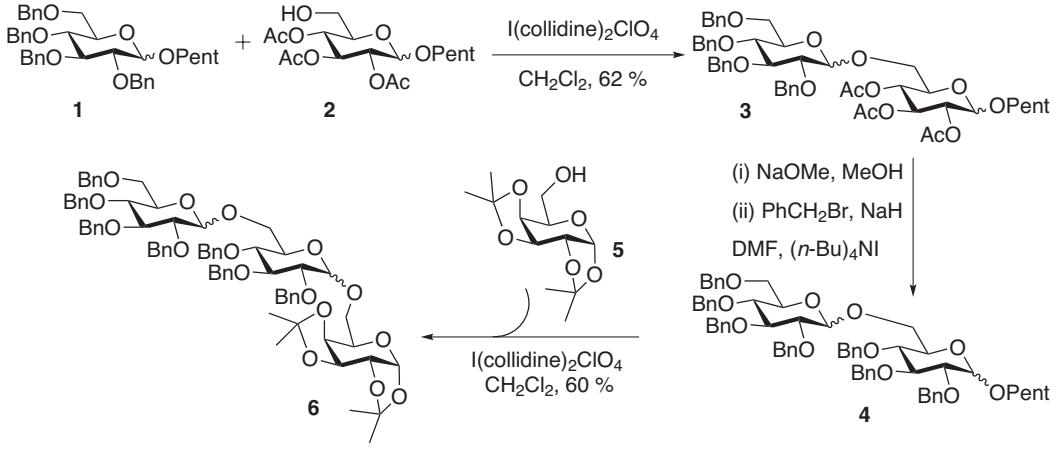
Table 1: The glycosylation reaction involving the formation of oxocarbenium ion intermediate and few commonly used leaving groups on the glycosyl donor component and their activations.

Leaving group	Examples of activating agents	Leaving group	Examples of activating agents
–F, –Cl, –Br, –I	Halophilic metal		Br^+, I^+, Hg^+, RS^+, Tf_2O
$-OCNHCCl_3$	Me_3SiOTf $BF_3 \cdot OEt$		$Ph_3PAuOTf$ $Ph_3PAuNTf_2$
–SR	Br^+, I^+		$AuCl_3$
Glucal	I^+		H^+, Cu^+
	$Me_3Si\text{-}OTf$		Br^+, I^+

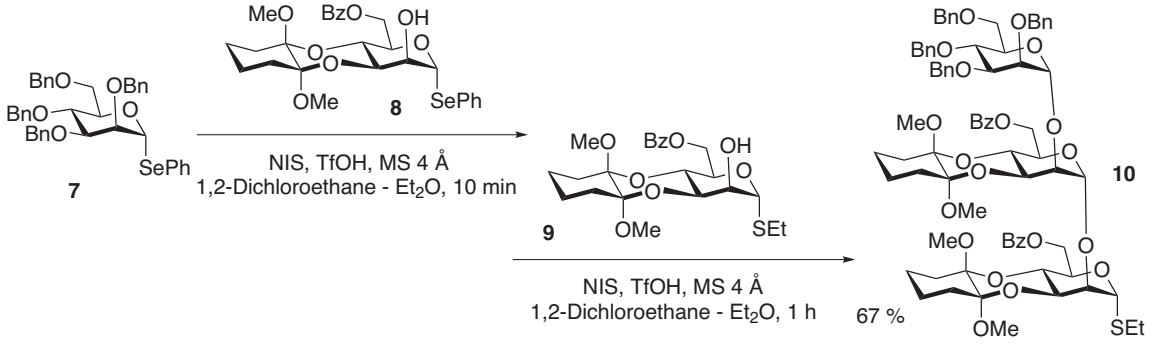
I. (i) Chemoselective strategy

The influence of the benzyl vs. benzoate protecting groups on the rate of hydrolysis of a glycosyl halide [14] was noticed early by Paulsen, wherein the benzoyl protected glycosyl halide donors underwent slower hydrolysis than that with benzyl protecting groups. A series of elegant work by Fraser-Reid and co-workers advanced the concept of armed-disarmed glycosyl donors, in which protection of hydroxyl moieties with ether protecting groups activated the glycosyl donor ability faster than the glycosyl donor activation in the presence of electron withdrawing group [15]. An early example is the demonstration of this concept as shown in Scheme 1. The *O*-benzyl protected armed donor **1** and the *O*-acetyl protected disarmed acceptor **2** reacted, leading to the formation of disaccharide **3**, which upon *O*-deacetylation and installation of benzyl protecting groups to the disaccharide **4** aided a subsequent activation. The reaction of the armed disaccharide **4** with the glycosyl acceptor **5** allowed formation of the trisaccharide **6**.

Ley and co-workers developed "semi-disarmed" concept [16] wherein torsional effect caused by the presence of a cyclic acetal protection on the glycosyl donor was utilized to develop a one pot glycosylation strategy. Utilizing the concept of semi-disarmed glycosyl donors, the first efforts on tuning the effects of parameters such as the protecting groups, the anomeric leaving group and the nature and stereochemistry of the monosaccharide skeleton were addressed. The sequential glycosylation for the preparation of a trisaccharide **10** from monomers **7–9** on the basis of reactivity of glycoside donor was thus accomplished. The more reactive donor **7** was activated initially, the reaction of which with acceptor **8** afforded the intermediate disaccharide. A repetition of the reaction condition permitted further glycosylation of the disaccharide intermediate with a second acceptor **9**, leading to the formation of the trisaccharide **10**, in 67 % yield (Scheme 2).



Scheme 1: Glycosylations leading to the formation of trisaccharide **6** using armed-disarmed glycosyl donors and acceptors [15].



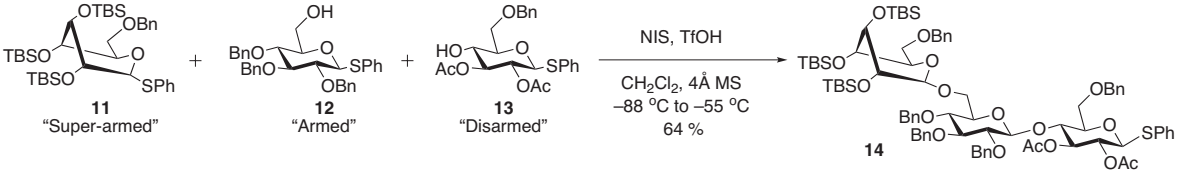
Scheme 2: Synthesis of trisaccharide **10** by a sequential glycosylation [16].

Progress of the concept of 'armed-disarmed' glycosyl donor was developed further towards glycosyl donors that are 'super-armed'. Bols and co-workers [17, 18], and Yamada and coworkers [19] introduced the term super-armed donors, based on installation of sterically bulkier silyl protecting groups on hydroxyl moieties and the evolving altered conformation of the donor permitting the facile formation of glycosyl cation in a twist-boat conformation. A combination of 'super-armed' (**11**) and 'armed-disarmed' glycosyl donors and acceptors (**12** and **13**) was put through to demonstrate the synthesis of a trisaccharide **14** in one-pot, as shown in Scheme 3.

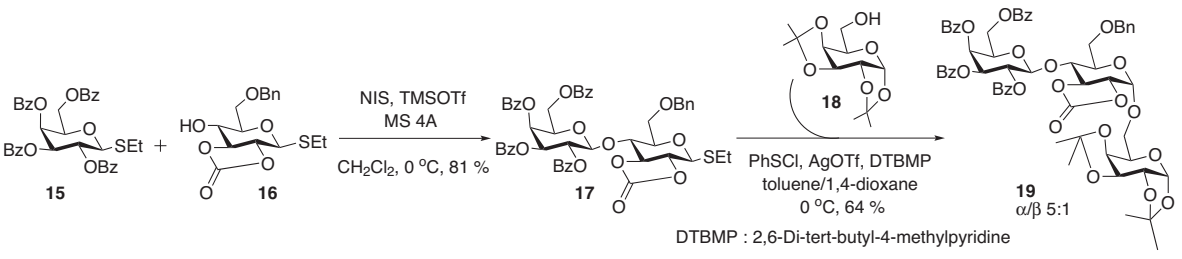
The arming-disarming effect of glycosyl donor is largely relied on the ether and ester protecting groups. Whereas glycosylation with ether protecting groups in the glycosyl donor largely lead to 1,2-cis glycosidic bond, that of with ester protecting groups, 1,2-trans-glycosidic bond forms. In order to overcome this stereoselectivity issue, Zhu and Boons developed *C*2–*C*3 cyclic carbonate **16** as a non-participating disarming group, in the synthesis of trisaccharide **19**, involving intermediate disaccharide donor **17** (Scheme 4) [20].

Wong and co-workers developed an approach to the protecting group control on the reactivity of glycosyl donor and acceptor, where an extensive set of experimental results helped to formulate a 'relative reactivity value (RRV)' to a number of glycosyl donors and acceptors [21, 22]. The RRV values enabled appropriate choice of donors and acceptors in multiple one-pot oligosaccharides, namely, a programmable one-pot oligosaccharide synthesis. The programming was also made through machine learning methods, wherein a computer programme called Optimer was developed to aid identification of the best possible combination of building blocks based on the RRV. For example, the deactivating ability of protecting groups at *C*-2 of a given galactosyl core was established to be in the order of $-N_3 > -O(ClAc) > -NPhth > -OBz > -OBn$. The effect of the benzoate group in a galactose modifies depending on the carbon site in the order of *C*-4 > *C*-3 > *C*-2 > *C*-6. Concerning the reactivity of a sugar moiety, the known trend is galactose > mannose > glucose. The RRV values of hundreds of building blocks were used effectively to synthesize several complex oligosaccharides in a one pot fashion by a sequential addition of the thioglycoside building blocks, starting from the most reactive donor at the non-reducing end. Further development of this machine-learning tool is the creation of a new software called Auto-CHO that aids synthesis of complex oligosaccharides.

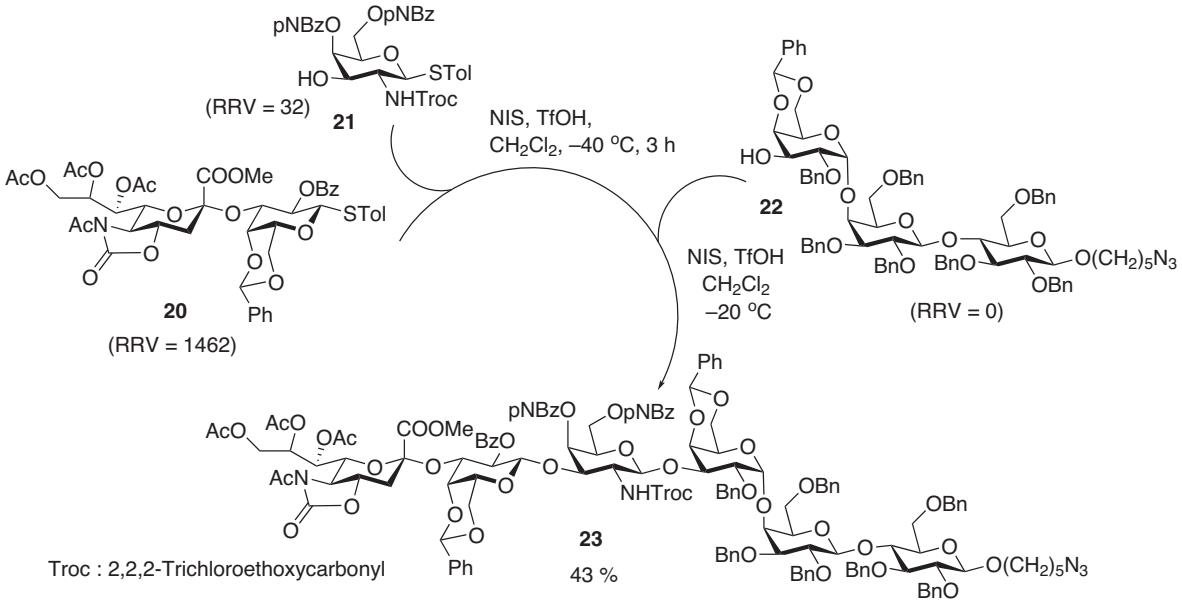
The programmable one-pot strategy was employed to synthesize complex oligosaccharides, such as, SSEA-4, heparine pentasaccharide, N-glycans with LacNAc repeats. The hexasaccharide SSEA-4 (**23**) (Scheme 5) was thus synthesized using three building blocks in the decreasing order of reactivity in a one-pot manner. The most reactive S-tolyl sialo-galactoside **20** was reacted with the monosaccharide **21**, in the presence of NIS and a catalytic amount of TfOH at −40 °C. The resulting trisaccharide was reacted subsequently



Scheme 3: Synthesis of a trisaccharide **14** using synthons that have altered glycosyl donor abilities.



Scheme 4: Synthesis of trisaccharide **19**, involving a carbonate protected synthon **16** [20].



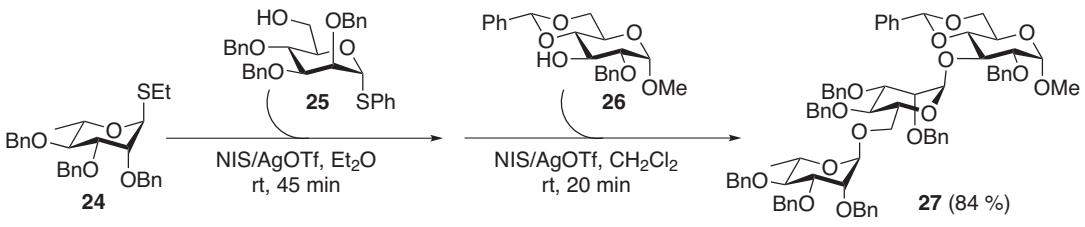
Scheme 5: Synthesis of a hexasaccharide **23**, through programmable one-pot oligosaccharide synthesis guided by the RRV [21, 22].

with another trisaccharide **22** of least RRV, at –20 °C, leading to the formation of the target hexasaccharide **23**, in 43 % yield. Similar methods have been applied for the synthesis of many oligosaccharides. Although computer programming helps in identifying the best possible combination of building blocks, there is an imminent need to have a pool of building blocks with defined reactivities, in both α- and β- anomeric linkages.

Utilizing the effect of solvent on the rate of glycosylation, one-pot synthesis of a trisaccharide was demonstrated by Lahman and Oscarson (Scheme 6) [23]. Ethylthio rhamnoside **24** could be activated selectively using NIS–AgOTf in Et_2O in the presence of phenylthio mannoside **25** to synthesize the rhamnose-mannose disaccharide. Change of a solvent in the subsequent glycosylation of the disaccharide intermediate with acceptor glucoside **26** in presence of same activator in CH_2Cl_2 afforded the trisaccharide **27**.

I. (ii) Orthogonal strategy

Figure 1 shows an approach wherein a leaving group '**X**' in one glycosyl donor **I** is activated preferentially in the presence of another leaving group '**Y**' in a competent glycosyl donor **II**, to afford disaccharide **III**. This disaccharide, having the leaving group '**Y**' at the reducing end reacts with another acceptor **IV** to form trisaccharide **V**. The fine-tuning of the reactivity of the anomeric leaving groups '**X**' and '**Y**' is aided either by changing the steric or the electronic environment and is independent of the nature protecting groups on the glycosyl donor. This strategy developed by Mukaiyama and co-workers [24] relied on anomeric fluoride



Scheme 6: One-pot synthesis of trisaccharide **27**, with differing solvents for the glycosylations [23].

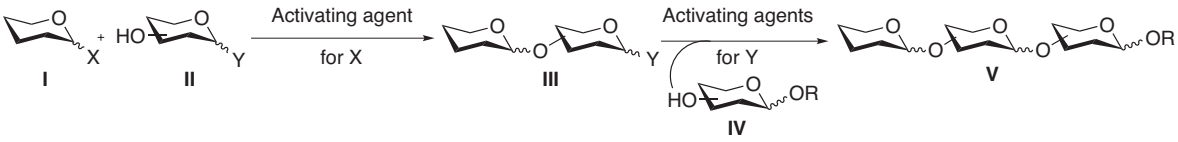
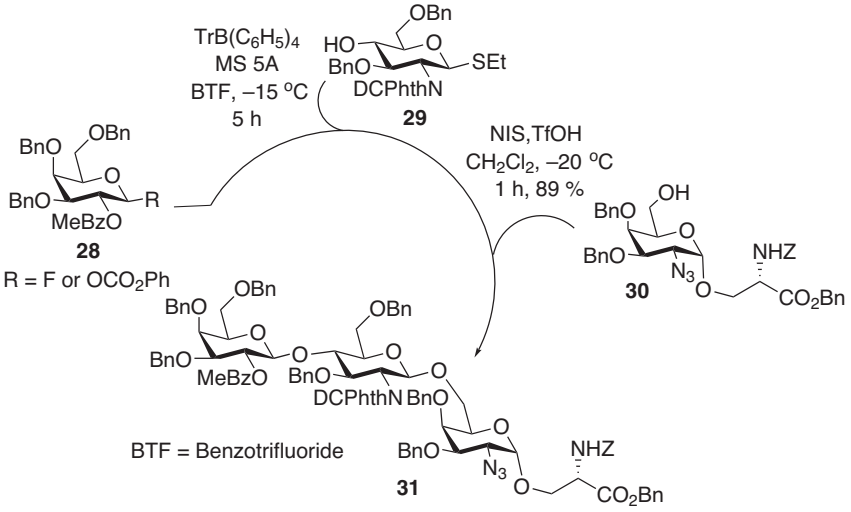


Fig. 1: The approach of orthogonality of the leaving groups 'X' and 'Y' to conduct the one-pot sequential glycosylations.

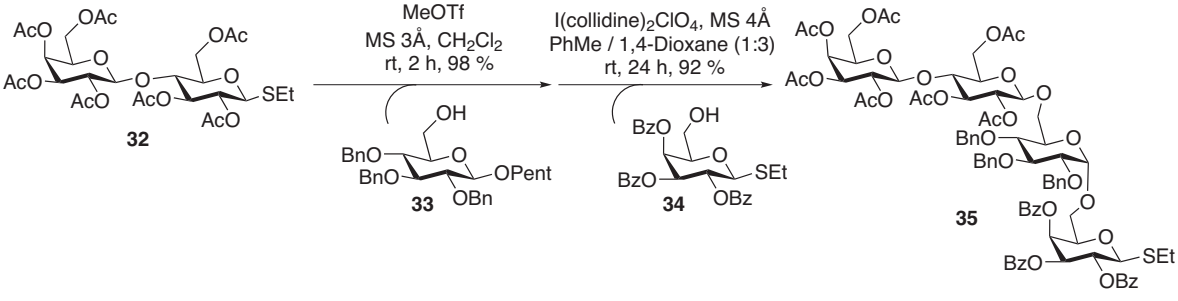
and carbonate leaving groups in donor **28** (Scheme 7). Glycosylation with the thioglycoside acceptor **29** was promoted by either TfOH or a tetravalent borane reagent to afford a disaccharide intermediate containing the thioglycoside at the reducing end. The reaction of this disaccharide intermediate with the glycosyl acceptor **30**, promoted by NIS in TfOH afforded the trisaccharide **31**, which is a mucin related F1a antigen, in a one pot manner. Several other oligosaccharides were also synthesized by this protocol.

Demchenko and De Meo developed a "semi-orthogonal" [25] method to synthesize a tetrasaccharide **35**, wherein thio- **32**, **34** and pentenyl **33** glycosides were activated sequentially in a one pot manner (Scheme 8). A set of new thioglycosides, such as, S-benzoxazolyl, S-thiazolyl (STaz) and S-benzimidazolyl (SBiz) that could be activated preferentially in the presence of alkyl thioglycosides and these new thioglycosides were implemented to obtain several oligosaccharides. Both STaz and SBiz were used in latent-active glycosylations (*vide infra*).

A combination of chemoselective and orthogonal strategies was used to synthesize an oligosaccharide. As a proof of concept, Ghosh and co-workers [26] reported synthesis of *O*-antigen of *E. coli* through mixed



Scheme 7: Orthogonal methodology to the synthesis of glucosyl amino acid **31** [24].

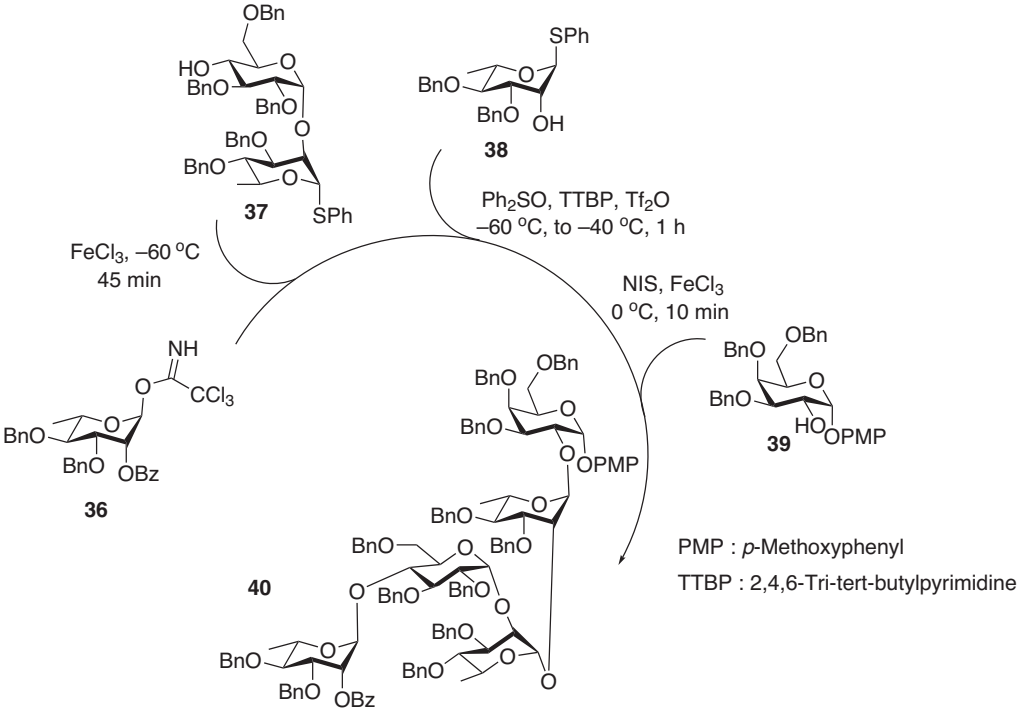


Scheme 8: Synthesis of tetrasaccharide **35** using a semi-orthogonal strategy of glycosylations [25].

one-pot sequential glycosylation. The imidate donor **36** was activated using $FeCl_3$, which was then reacted with the thioglycoside acceptor **37** (Scheme 9). The trisaccharide was activated subsequently with Ph_2O/2,4,6-tri-*tert*-butylpyrimidine (TTBP) – and reacted with thioglycoside acceptor **38**. Yet another glycosylation of acceptor **39** with the tetrasaccharide donor intermediate afforded **40**, in an impressive overall yield of 72 %.

I. (iii) Pre-activation strategy

This strategy relies on activation of a glycosyl donor and reaction with an acceptor which possesses the same anomeric leaving group. The resulting glycoside can be activated *in situ* for further glycosylation in an iterative manner. The method facilitates generating the glycosyl donor and acceptor from common building block. Danishefsky and co-workers demonstrated early on utilizing this approach in an iterative synthesis of oligosaccharides [27]. Figure 2 illustrates the glycal methodology to prepare oligosaccharide in an iterative manner. Activation of glycal **VI** with an electrophile and the reaction of activated donor **VII** with an acceptor **VIII** possessing a glycal functionality occurred to afford disaccharide glycal **IX**. The iterative glycosylation further afforded the trisaccharide **X** in an excellent yield.



Scheme 9: Synthesis of pentasacchride **40** through chemoselective and orthogonal strategies [26].

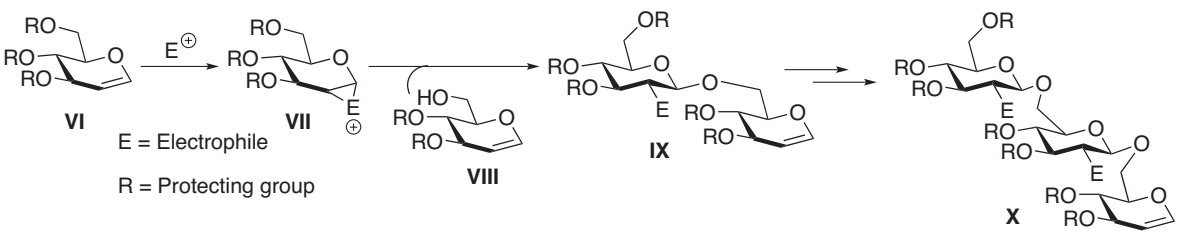


Fig. 2: The pre-activation strategy for the synthesis of a oligosaccharide [27].

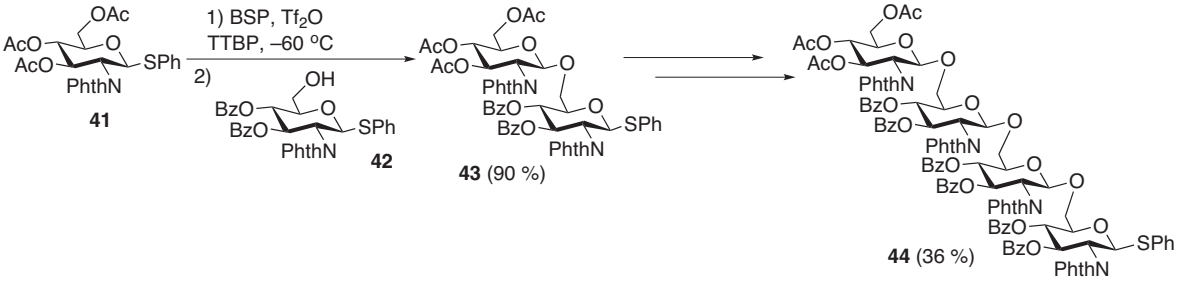
Later Gin and co-workers [28] developed chemoselective dehydrative glycosylation and Yamago and co-workers [29] reported selenoglycoside activation with bromine methodology. The glycal method was used for the automated solid phase synthesis of oligosaccharide.

van Boom and co-workers [30], and Yamago and co-workers [31] utilized thioglycoside donors in a pre-activation strategy using 1-benzene sulfinyl piperidine (BSP)/Tf_2O as the activating agent. Yamago and co-workers used the BSP–Tf_2O mediated activation of thioglycosides for the synthesis of a tetraglucosamines in an iterative manner. In this synthesis, glycosyl donor **41** was activated and reacted with acceptor **42** to afford disaccharide **43**. Iteration of glycosylation of the resulting glycoside products with the acceptor **42** afforded tetrasaccharide **44** (Scheme 10).

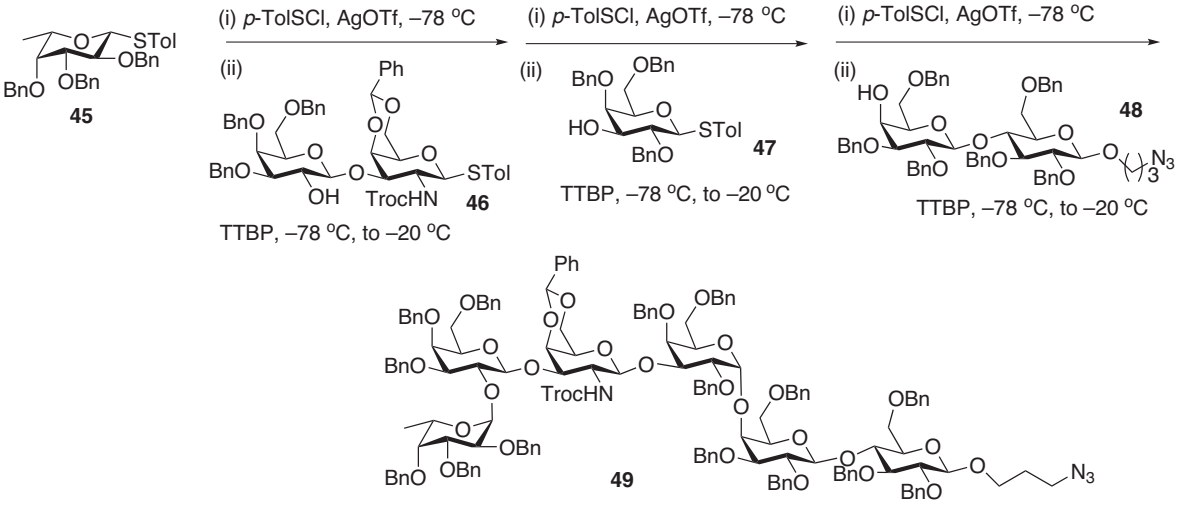
In a similar strategy, Huang and co-workers [32] utilized p-TolSOTf, formed *in situ* by the reaction of p-TolSCl and AgOTf, as the promoter for the synthesis of oligosaccharide Globo-H 45 (Scheme 11). In this synthesis, a one-pot synthesis consisting of 5 iterative glycosylations, involving donors and acceptors **45–48** was conducted to secure the Globo-H hexasaccharide **49**, in overall 47 % yield. A stoichiometric amount of the promoter was required to in this iterative glycosylation.

I. (iv) Latent-active glycosylations

Both the preactivation and latent-active methods allow the glycosyl acceptor and the donor to possess identical functionalities at the anomeric carbon. Yet a difference in the terminology emerges between these two strategies. In the case of the latent-active glycosylation strategy, the latent moiety is made active by a transfor-



Scheme 10: Synthesis of tetrasaccharide **44** by iterative glycosylation using thioglycoside donors and acceptors **41–43** [31].



Scheme 11: Iterative glycosylation using a pre-activation strategy to synthesize hexasaccharide **49** [32].

mation, thereby enabling the moiety to become an active glycosyl donor, which in the presence of a promoter undergoes reaction with an acceptor. On the other hand, the preactivation strategy refers to the *in situ* activation of the donor by a promoter to generate a reactive intermediate, which is then subjected to glycosylation with the acceptor.

An efficient and rapid assembly of oligosaccharides where donors and acceptors can be synthesized from a common building block has the most potential in an iterative one-pot glycosylations. The emphasis is also to minimize multiple protection-deprotection reactions on glycosyl donors and acceptors. In the latent-active glycosylation strategy, a leaving group (LG) is activated selectively over another LG, with the aid of a suitable promoter. The latent LG, in turn, is made active in a subsequent glycosylation on the resulting glycoside. Such an approach has the potential to avoid protection and deprotection reactions, benefitting a complex target oligosaccharide synthesis.

The latent-active concept was advanced by Roy and co-workers [33], by demonstration of thioglycoside donor **XI** and acceptor **XII** as glycosyl components (Fig. 3). The reactivity of the donor was tuned by changing the substitution pattern on arylthio-moiety from an electron withdrawing substituent to an electron donating substituent, thereby enabling donor reactivity of the thioglycoside when reacted with an electrophilic promoter to afford a disaccharide **XIII**.

Boons and co-workers [34] reported 1,2-oxathiane ethers that are stable under acidic, basic, and reductive conditions, yet can be converted to an active glycosyl donor upon oxidation to a sulfonium species. This method was employed successfully to synthesize a branched tetrasaccharide **54**, originating from *Pseudallescheria boydii* fungus (Scheme 12). The tetrasaccharide was assembled by a latent-active glycosylation strategy using oxathiane **51** as an acceptor in a glycosylation with a sulfoxide donor **50**. The disaccharide **52**, in turn, was subjected to oxidation to an active sulfoxide donor **53** for a subsequent glycosylation with appropriate oxathiane glycosyl acceptor.

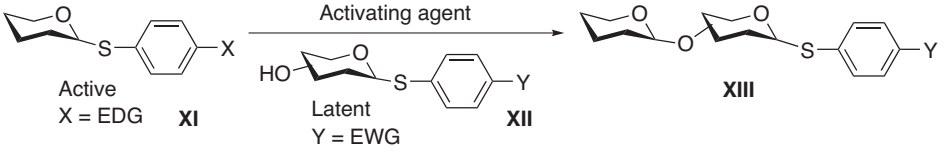
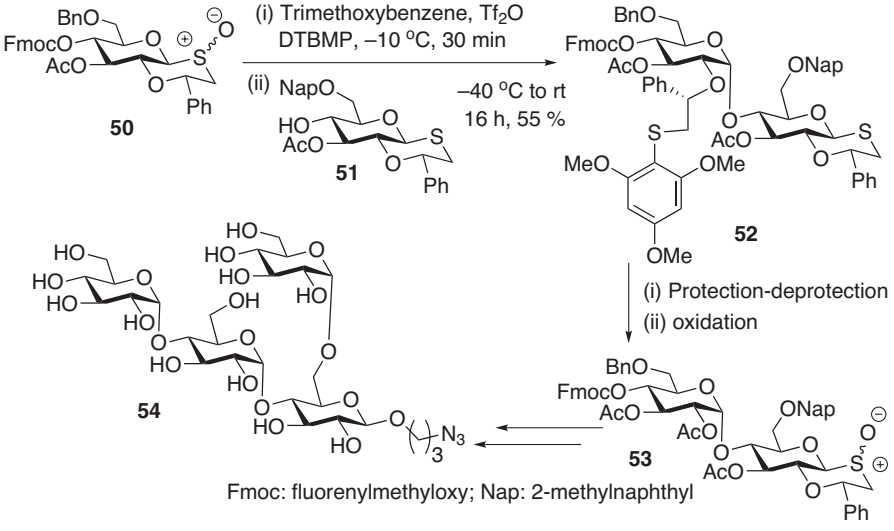


Fig. 3: A general scheme of latent-active approach to glycosylation using thioglycosides.

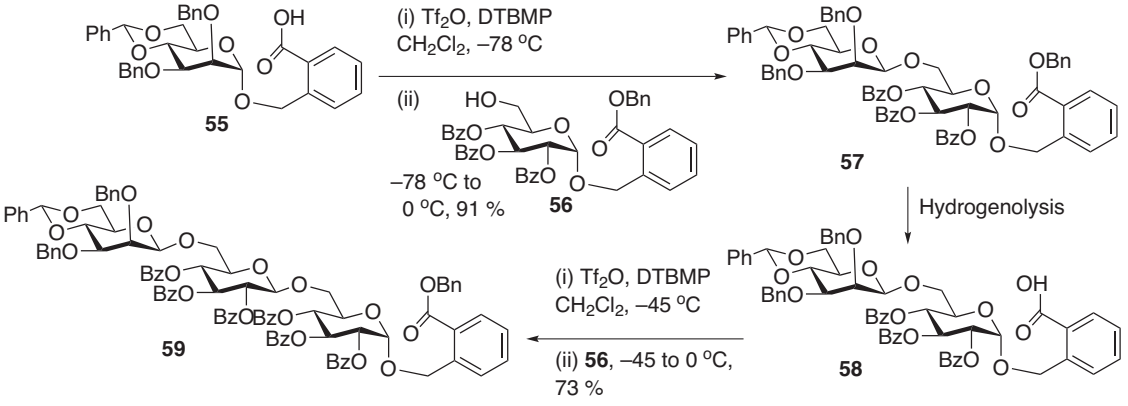


Scheme 12: Glycosylation using a bicyclic anomeric sulfonium ion in a latent-active active strategy to synthesize tetrasaccharide **54** [34].

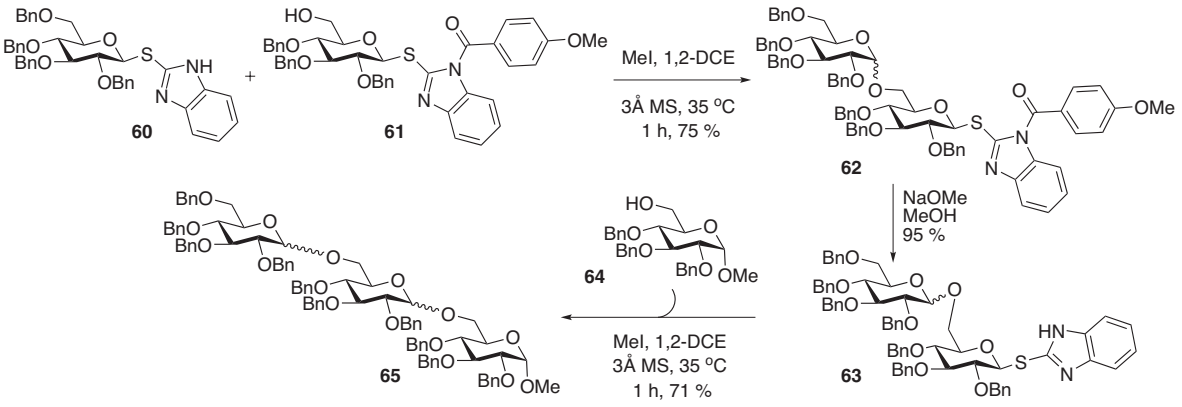
A new type of latent-active glycosylation reaction by utilizing 2-(benzyloxycarbonyl)benzyl (BCB) glycosides as a latent donor was developed by Kim and co-workers [35]. The BCB glycoside is converted to the corresponding 2-(hydroxycarbonyl)benzyl (HCB) glycoside by hydrogenolysis (Scheme 13). In presence of triflic anhydride and di-*tert*-butylmethylpyridine, glycosyl donor **55** undergoes glycosylation with acceptor **56**, possessing a BCB moiety at the anomeric position, to afford disaccharide **57**, with β-mannopyranosyl linkage. The latent BCB-disaccharide was, in turn, converted to an active HCB-disaccharide by hydrogenolysis to acid **58**. Repetitive glycosylation of the donor with the same acceptor **56** afforded the BCB-trisaccharide **59**.

S-Benzimidazolyl (SBiz) glycosides were utilized by Demchenko and co-workers [36] to develop a new latent-active glycosylation, wherein the SBiz donor **60** was selectively activated in the presence of the *N*-anisoylated SBiz acceptor **61**. The initial glycosylation reaction was conducted between the donor and the acceptor, in the presence of MeI to obtain the latent disaccharide **62** (Scheme 14). Deprotection of the *N*-anisoyl group was achieved on treatment with NaOMe in MeOH to get the active disaccharide **63** which was used to conduct glycosylation under same condition with the acceptor **64** to afford the trisaccharide **65**.

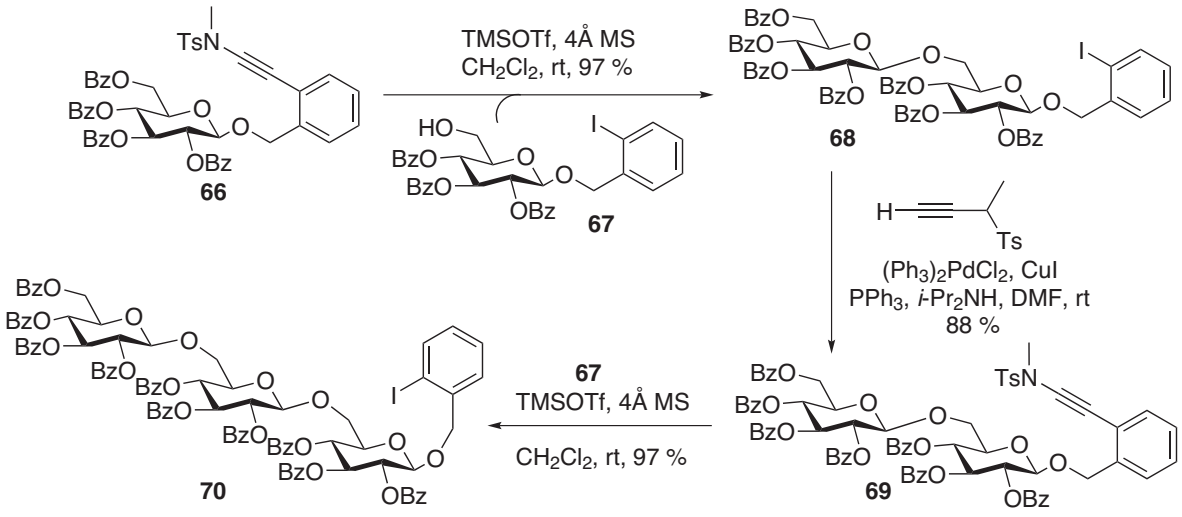
A new glycosyl donor ortho-(methyltosylaminoethynyl)benzyl glycoside was developed by Yu and co-workers [37], wherein the glycosides were prepared from the corresponding ortho-iodobenzyl glycosides *via* a Sonogashira coupling with a ynamide. The glycosides were used in the synthesis of oligosaccharides in a latent-active manner. In the 'latent-active' assembly of glycans, the 'active' ortho-(methyltosylaminoethynyl)-benzyl glycoside **66** was coupled with the 'latent' ortho-iodobenzyl glucoside derivative **67** in the presence of TMSOTf (0.1 eq.) to obtain disaccharide **68** (Scheme 15), which, in turn, was activated via the iterative Sonogashira coupling to derivative **69** and subjected to the glycosylation sequence to afford trisaccharide **70**.



Scheme 13: Synthesis of trisaccharide **59** through BCB/HCB donors in a latent-active glycosylation [35].



Scheme 14: Synthesis of a trisaccharide **65** initiated from S-benzimidazolyl (SBiz) glycosides **60** and **61**, through a latent-active glycosylation method [36].



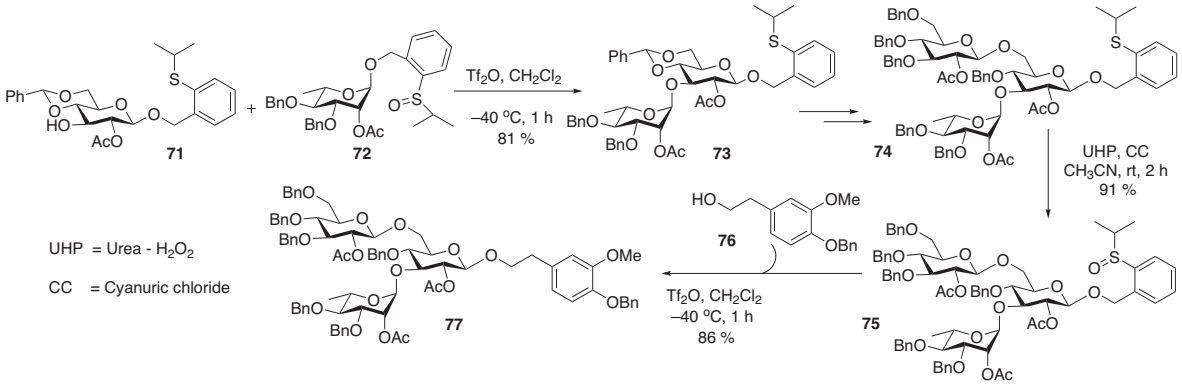
Scheme 15: Synthesis of trisaccharide **70** through activation ortho-(methyltosylaminoethynyl)benzyl glycoside **66**, in a latent-active glycosylation methodology [37].

Recently, 2-(2-propylthio)benzyl (PTB) glycosides were exploited as a donor in a new latent-active glycosylation method [38]. An example is shown in Scheme 16. The active glycosyl donor **72**, 2-(2-propylsulfinyl) benzyl (PSB) glycoside was synthesised by oxidation of the corresponding PTB glycoside. Treatment of the PSB donor with acceptor **71**, in the presence of triflic anhydride provided the desired disaccharide **73** in a good yield. This methodology was extended for the synthesis of natural hepatoprotective glycoside, leonoside F **77**, involving intermediates **74** and **75**, and acceptor aglycon **76**.

The problem associated with the disarmed donor in this method was resolved by introducing a new thioglycoside, namely, *S*-2-(2-propylsulfinyl)benzyl (SPSB) glycoside as a glycosyl donor that was efficiently activated in a tandem remote mode [39]. The SPSB glycoside was synthesized from the corresponding *S*-2-(2-propylthio)benzyl (SPTB) glycoside by oxidation.

II. (i) Allyl glycoside in latent-active glycosylations

As a protecting group, allyl moiety is orthogonal to other protecting groups and is deprotected under mild conditions through many methods, such as, the metal-mediated isomerization and acidolytic cleavage. The

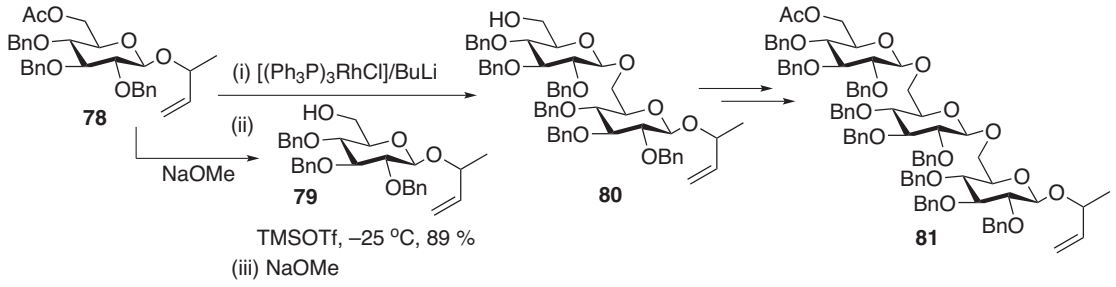


Scheme 16: 2-(2-Propylthiol)benzyl (PTB) glycosides as glycosyl donors to synthesize trisaccharide **77**, in latent-active glycosylation methodology [39].

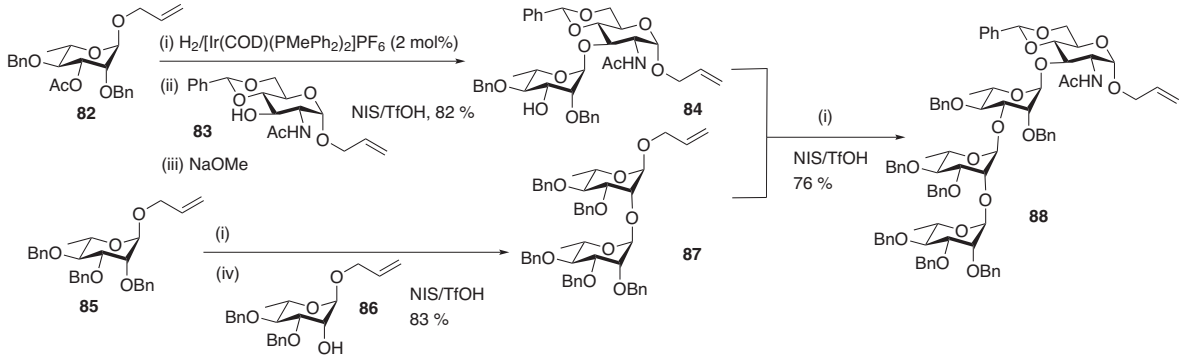
metal-mediated isomerization of allyl ether to vinyl ether is also used beneficially to conduct a glycosylation reaction with an acceptor alcohol. Further elegant development pertains to establishing such vinyl glycoside intermediate as a glycosyl donor within the preamble of latent-active glycosylation concept. In a latent-active glycosylation, an allyl glycoside is activated as a reactive vinyl glycoside donor, which upon reaction with an allyl glycoside having an acceptor alcohol moiety, leads to a glycoside product. The newly formed glycoside possesses the allyl moiety at the reducing end, which is activated as the isomerized vinyl ether donor for subsequent reaction with a latent allyl glycoside acceptor, leading to the formation of a newer glycoside.

Isomerisation of a latent substituted allyl glycoside to an active vinyl glycoside enabled the glycosylation reaction in the presence of a Lewis acid, as reported early by Boons and co-workers [40, 41]. This protocol was utilized to synthesize saccharide libraries. In the first step of glycosylation, the substituted allyl glycoside **78** is isomerised to the substituted vinyl ethers, using Wilkinson catalyst. The vinyl ether intermediate is used as an active glycosyl donor promoted by TMSOTf to an allyl glycoside acceptor **79**, leading to the formation of disaccharide **80**, in an excellent yield (89 %) (α/β 1/20). The allyl moiety in disaccharide is subjected to the metal-mediated activation to an active vinyl glycoside intermediate and the glycosylation is enabled repetitively to secure trisaccharide **81** (Scheme 17).

The use of allyl glycosides for glycosylations in a latent-active fashion was utilized for the synthesis of *Shigella flexneri* serotype Y *O*-antigen by Wang and co-workers [42]. Thus, the allyl glycosyl donor **82** was isomerized to its corresponding vinyl glycoside with iridium catalyst, followed by an activation with NIS/TfOH and glycosylation with the allyl glycosyl acceptor **83** led to the disaccharide **84** in 82 % (Scheme 18). Repeating the reactions, the disaccharide **87** was obtained from the glycosylation of the donor **85** and the acceptor **86** in 83 % yield. Glycosylation of disaccharides **87** as isomerized active glycosyl donor and **84** as latent glycosyl acceptor afforded the desired fully protected tetrasaccharide **88**, in 76 % yield.



Scheme 17: Synthesis of trisaccharide **81** using allyl glycoside as a latent glycosyl acceptor moiety and the corresponding isomerized vinyl glycoside as an active glycosyl donor [40, 41].



Scheme 18: Synthesis of tetrasaccharide **88** by the latent-active glycosylation methodology using appropriate ally1 glycosides [42].

II. (ii) Allylic halide activation of allyl glycosides

A newer allylic glycoside activation was developed recently in our research group [43]. The newly developed synthetic method combines radical-mediated activation of an allyl glycoside to an allyl halide, which upon reaction with a glycosyl and aglycosyl acceptor in the presence of an acid promoter leads to a glycoside product. Development of this new glycosylation methodology is fine-tuned further so as to implement the latent-active concept, in which a reactive allyl glycoside donor undergoes glycosylation with a latent allyl glycoside acceptor to form a glycosylated product. The glycosylated product, in turn, possesses the allyl moiety at its reducing end suitable for further activation. The synthetic scheme initiated with an allyl glycoside as synthon of the present work is shown in Fig. 4.

In this strategy, allyl glycoside **XIV** is subjected to (i) a free radical-mediated allylic halogenation to afford allylic halide **XV**; (ii) treatment of the allylic halide intermediate with an acid promoter and (iii) reaction with an acceptor allylic glycoside **XVI**, thereby leading to the formation of glycoside **XVII**. Reiteration of the above steps leads to higher glycoside product **XVIII**. The sequence of converting allyl glycoside **XIV** to product oligosaccharide allyl glycosides **XVII** and **XVIII** is accomplished in one pot.

The anomeric allyl protecting group of the donor was activated by brominating the allylic position using the prototypical reagent system *N*-bromosuccinimide (NBS)/azobisisobutyronitrile (AIBN) in CCl_4. The newly formed allylic halide moiety is highly unstable and upon exposure to moisture leads to the formation of hemiacetal. Among the protecting groups on the glycosyl donor, esters were found to be optimal, whereas benzyl ethers are incompatible due to competitive benzylic halogenation. Upon allylic halogenation of the ester protected allylic glycoside donors, the resulting allylic halide was reacted with acceptor glycosyl/aglycosyl alcohols, in presence of a promoter. Halophiles AgOTf, $AgClO_4$ and $AgCO_3$ were assessed as the promoter of the reaction, so as to derive the oxocarbenium ion and subsequent of the same with alcohols. Initial reactions conducted using MeOH as the acceptor is shown in Scheme 19.

It was observed that using $AgClO_4$ as the promotor, the reaction of allyl tetra-*O*-acetyl glucopyranoside **89** afforded the desired glycosylated product **90**, along with a varied product, characterization of which revealed it to be the substitution product **91** as the major product. Further, $AgCO_3$ as promotor also led to only the substitution product. Similar results were observed when the reactions were conducted with allyl tetra-*O*-acetyl mannopyranoside and allyl tri-*O*-acetyl fucopyranoside. The higher reactivity of MeOH coupled with ambient temperature might promote the reaction towards substitution of the halide, rather than the formation of the oxocarbenium ion.

An improvement in the glycosylation product **90** was observed when using AgOTf as the promotor. Approximately, 60 % yield of **90** was obtained, along with the substitution product **91** in 20 % yield. Thus, among the promoters verified, AgOTf was found to be optimal and further initial glycosylations were conducted with this promoter. Relating to the glycosylated product **90**, the β-anomer formed exclusively,

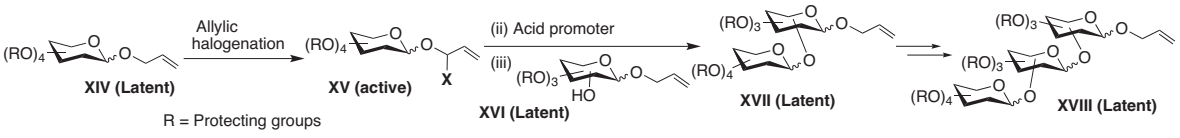
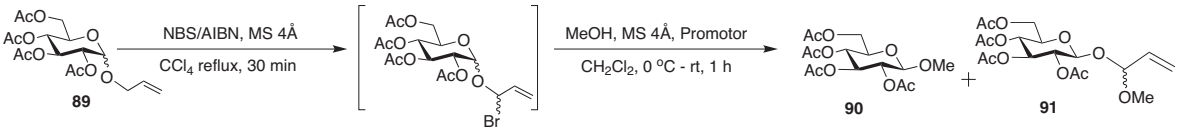


Fig. 4: A scheme of latent-active glycosylation involving an allyl glycoside, initiated by a radical-mediated allylic halogenations [43].



Scheme 19: Reaction of allyl tetra-*O*-acetyl glucopyranoside **89** with MeOH.

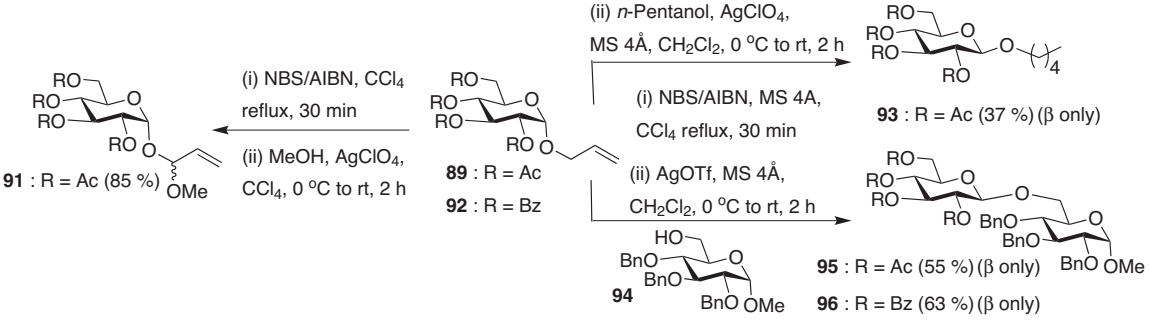
corresponding *C*1–*C*2 *trans*-configurations, adhering to the nominal expectation of a neighbouring group participation in the glycosidic bond formation.

A change of the protecting group from *O*-acetyl to *O*-benzoyl on the donor moiety increased the yield of the glycosylation product. Scheme 20 shows the glycosylation reactions using these two protecting groups in allyl glucopyranosides (**89** and **92**), promoters $AgClO_4$, AgOTf, acceptors MeOH, *n*-pentanol and glycosyl acceptor. Whereas *n*-pentanol afforded pentyl glycoside **93** when AgOTf was used as the promoter, MeOH afforded exclusively substitution product **91**. A difference in the reactivities of alcohols thus contributes to the glycosylation *vs* substitution products. The glycosyl acceptor **94** afforded disaccharides products **95** and **96**, in moderate yields.

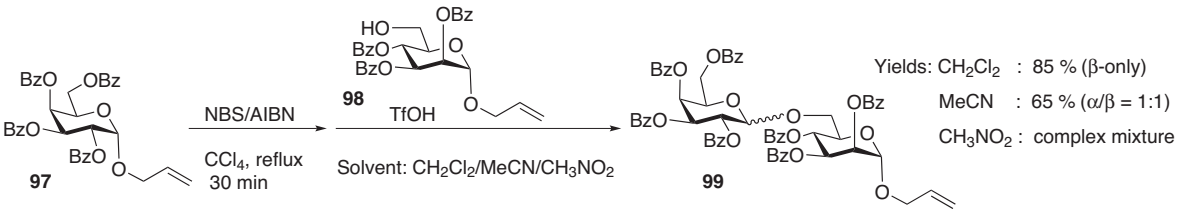
Continuing optimization, a metal-free promoter TfOH was used to mediate the glycosylation. In the event, a significant increase in the yield of the required glycosylation product obtained. The formation of the allylic substitution product was absent in this reaction, implying that the oxocarbenium ion formation is the preferred reaction of the glycosyl donor with TfOH promoter. Rigorous exclusion of moisture is necessary, without which hemiacetal formation competes the glycosylation reaction. It is also pertinent to note that a glycosylation reaction did not proceed in the absence of a promoter reacting with the glycosyl allylic halide intermediate, implying the role of the promoter in the reaction.

The new glycosylation reaction temperature was assessed between −40 °C and 0 °C, for reactions involving MeOH as the acceptor and glycosyl donor **89**, during 2 h of reaction duration. Initial attempts to conduct the reaction at −78 °C showed a lack of the reaction and the acceptor alcohol was recovered, along with the hemiacetal arising from the donor. On the other hand, when the reaction was conducted at 0 °C, the reaction course preferred a substitution reaction, wherein the halide was substituted with the incoming alcohol, along with the desired glycoside as a minor product, whereas, reaction at ambient temperature led to only a mixture of products. Reactions conducted at –30 °C afforded the glycoside as the exclusive product, thereby warranting further reactions to be conducted at this temperature.

Varying the solvent for glycosylation of glycosyl acceptor **98** with donor **97** was exercised and the reactions were conducted in CH_2Cl_2, CH_3CN and CH_3NO_2. Among these solvents, CH_2Cl_2 afforded the glycoside product **99** in better yields than remaining solvents (Scheme 21). Whereas CH_3NO_2 as solvent led to a complex mixture of the crude reaction mixture, CH_3CN mediated the glycosylation to afford the desired glycoside in



Scheme 20: Reactions of allyl glycoside **89** and **92** in the presence of $AgClO_4$ and AgOTf promoters in the glycosylation reaction.

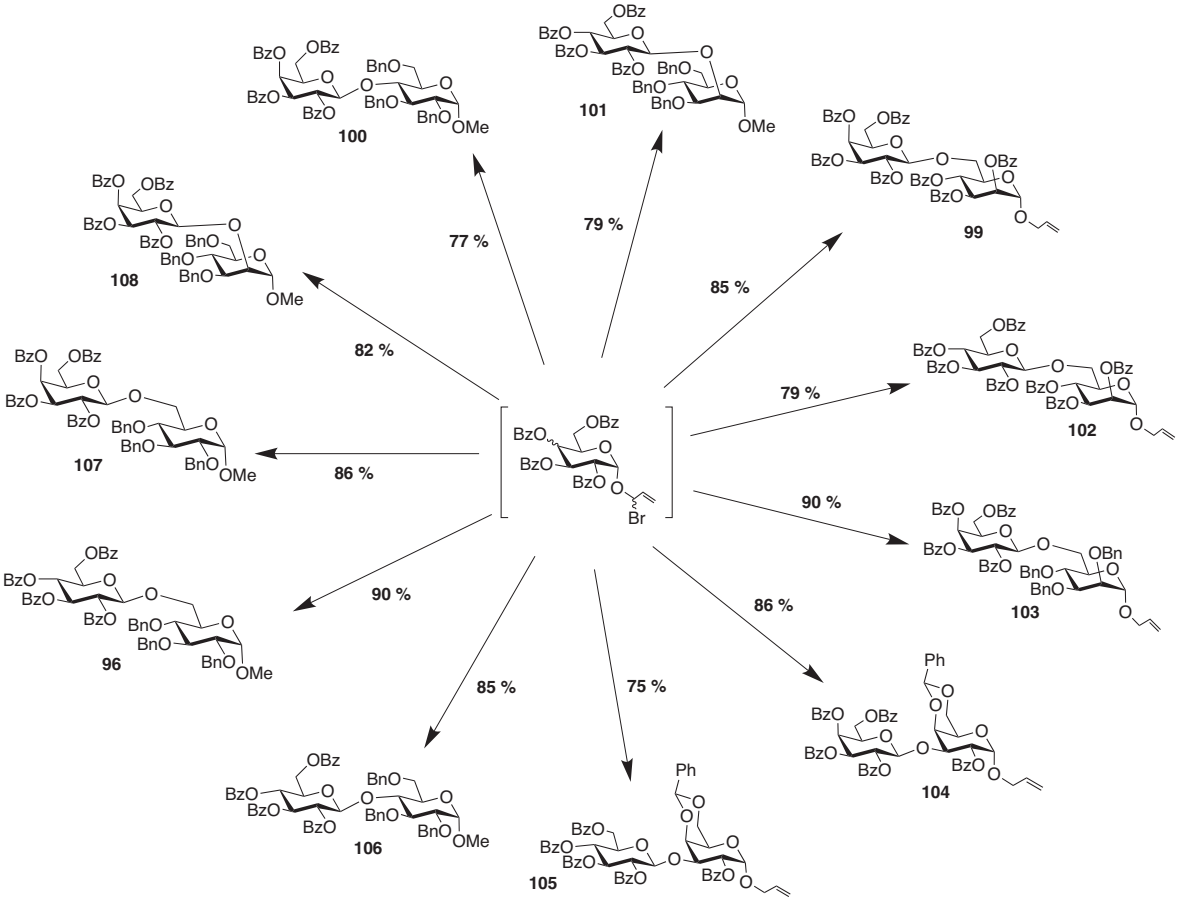


Scheme 21: Allylic halide mediated glycosylation, with varying solvents for the glycosylation step.

65 % yield, as 1:1 α/β anomers. The coordination ability of CH_3CN is observed by which there is considerable percentage of α-anomer was also obtained along with the β-anomer, implying the role of solvents on the oxocarbenium ion species.

With the optimised reaction conditions, glycosylation reactions were performed with various glycosyl donors and acceptors, originating from pyranosides of glucose, galactose, mannose and fucose. Further, the glycosylations were conducted so as to secure glycosides with *C*1–*C*2–*C*4 and *C*1–*C*6 glycosidic bond connectivities. Among the glycosyl donors, a general observation was that the galactopyranosyl-donor was more reactive, underwent complete activation and glycosylation occurred rather facile. Similarly, primary alcohol as acceptor underwent efficient glycosylation compared to secondary alcohols. Scheme 22 summarizes disaccharide formation from the gluco- and galactopyranosyl donors, reacting with appropriate glycosyl acceptor, using TfOH as the promoter in CH_2Cl_2 at −40 °C. As can be seen, the new glycosylation method is facile, providing the glycoside products in good to excellent yields, covering the glycosidic bond connectivities arising from all secondary and primary alcohols as the acceptor sites.

Whereas the ester protecting groups on the glycosyl donors are optimal, glycosyl acceptors might possess varying protecting groups, including benzyl ethers. As can be seen with examples **96**, **100**, **101**, **103** and **106–108** glycosyl acceptors with benzyl ether protecting groups do not encounter limitations under the glycosylation reaction conditions and glycosides form in excellent yields. Similarly, glycosylation with 4,6-benzylidene protected glycosyl acceptors affords the disaccharides in good yields, examples are formation of disaccharides **104** and **105**. Secondary hydroxyl functionalities as glycosyl acceptors did not differ greatly in reactivities, as adjudged through the corresponding disaccharide formation with comparable yields. Scaling up of glycosylation reactions to grams could be conducted, without a loss in the efficiency of the reaction,

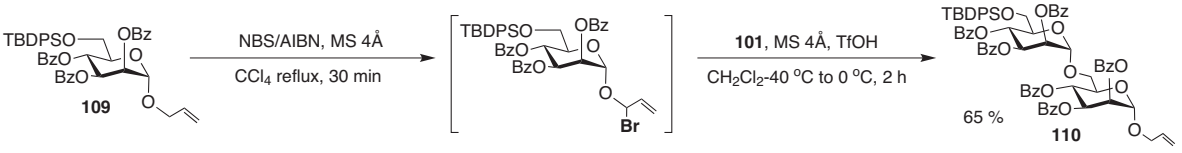


Scheme 22: Glycosylation products formed from reactions of glucose and galactose donors with appropriate glycosyl acceptors.

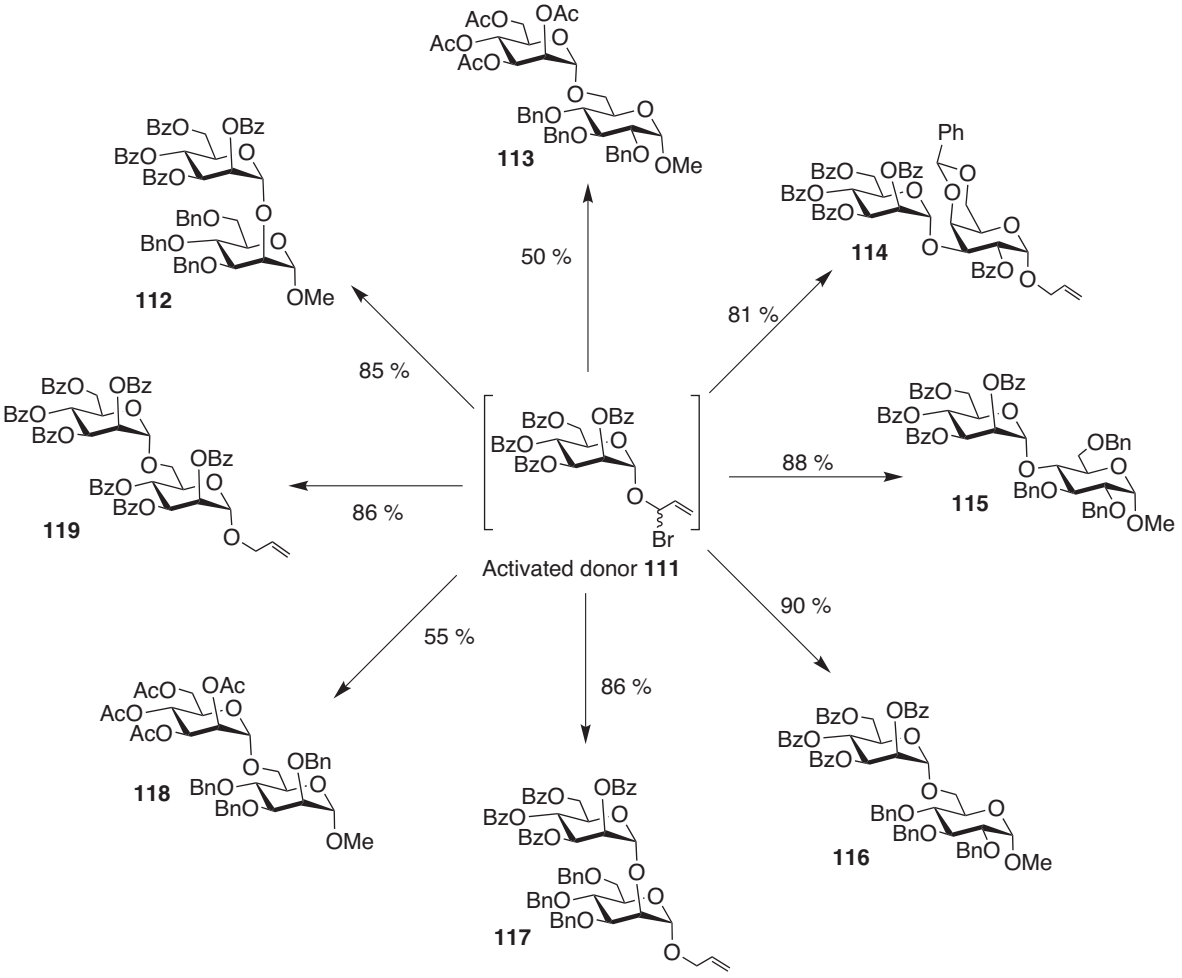
thereby indicating that this new allylic halide activation extends scope for glycosylations in larger quantities of donors and acceptors.

The lability of acetate protecting group under TfOH mediated glycosylation reaction was observed, wherein the acetate moiety underwent deprotection, thereby the newly generated alcohol functionality turn out to be an acceptor site. In the light of this lability, glycosylations involving glycosyl donors and acceptors with acetate protecting groups might not be preferred. Silyl protecting group on the donor component is compatible, as given in Scheme 23 for the preparation of mannose 1–6-linked disaccharide **110**, from donor **109**.

Glycosylations involving the activated mannopyranosyl donor **111** and varied glycosyl acceptors led to disaccharide formation in good yields, depending on the protecting groups on the donor, using reaction conditions of TfOH promoter in CH_2Cl_2 at −40 °C. Synthesis of several disaccharides using a common mannopyranosyl donor with appropriate acceptors is shown in Scheme 24. Thus, with acetate protecting groups,



Scheme 23: Silyl protecting group in glycosyl donor **109** and the glycosylation leading to the formation of disaccharide **110**.



Scheme 24: Glycosylation of allylic halide activated mannopyranosyl donor with varying glycosyl acceptors and the formation of corresponding disaccharides.

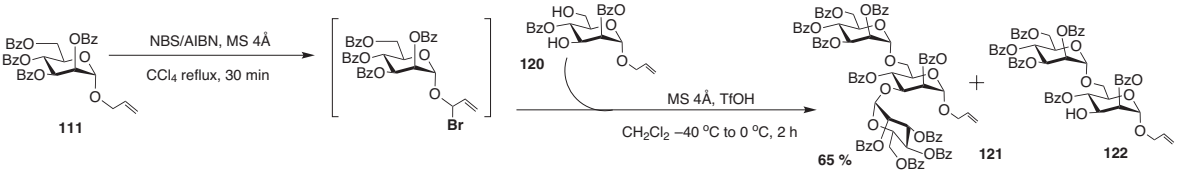
the disaccharide formation is only moderate, as a result of the lability of acetate groups under acidic reaction conditions. Benzyl, benzylidene and benzoate protecting groups on the acceptor moieties are compatible to the reaction and the disaccharides form as the exclusive product. With ester as the protecting groups in the donor component, the reactions are under the manifold of anchimeric or neighbouring group assistance and afford 1,2-*trans*-configured disaccharides.

Following synthesis of disaccharides, the new glycosylation method was subjected to double glycosylation possibilities. In these instances, glycosyl acceptors having two hydroxyl functionalities were planned. The reaction sequence leading to a trisaccharide **121** is shown in Scheme 25. The mannopyranosyl donor **111** was activated to an allylic halide with the aid of NBS/AIBN reagent system. Reaction of allylic halide intermediate with diol acceptor **120**, in the presence of catalytic TfOH, leads to the formation of the double glycosylated product, namely, the (1,3), (1,6)-linked trisaccharide **121**, in a moderate yield. The disaccharide **122** also formed as a minor product in the reaction.

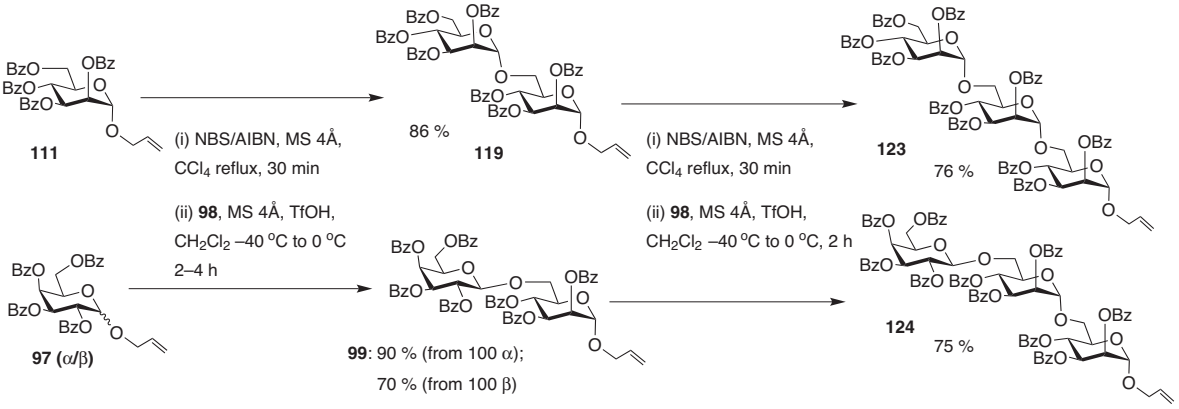
A step-wise glycosylation of the synthesis of a trisaccharide was also feasible, wherein mannosyl donor **111** reacts with acceptor **98** to afford disaccharide **119**, having the allyl moiety at the reducing end (Scheme 26). Iteration of the glycosylation reaction of halide activated **119** with the acceptor **98** subsequently affords the (1–6), (1–6)-linked trisaccharide **123**, in a moderate yield after two-stage glycosylation starting from donor **111**. Stereoselectivity of the reaction remains 1,2-*trans*-selective. Similarly, the two-stage glycosylation could also be accomplished on galactosyl donor **97**, which upon allylic halide activation and reaction with allyl mannopyranoside **98** in the first step to afford disaccharide **99**, followed by another iteration on **99** leads to formation of trisaccharide **124**, in a good yield.

The above reactions illustrate that allylic halide activation mediated glycosylation method is suitable to sequential reactions, expanding the principle of latent-active glycosylation methodology.

The β-allyl galactopyranoside anomer (**97β**) was reacted as a glycosyl donor, similar to that of the corresponding α-anomer. Whereas the halogenation occurred in the first step within 30 min., subsequent glycosylation with acceptor alcohol for 4 h afforded the disaccharide **99** in a good yield, with 1,2-*trans*-configuration at the newly formed glycosidic bond.



Scheme 25: Preparation of trisaccharide by double glycosylation of glycosyl donor **111,** with acceptor **122**.



Scheme 26: Preparation of trisaccharides **123** and **124** by the latent-active glycosylation method.

The newly developed allylic halide mediated glycosylation method was utilized towards synthesis of β-(1→3)-linked xylan. Xylans being one of the major constituents of the plant hemicelluloses [44] and are also known to play a major role in initiating the biosynthesis of GAG [45], there have been efforts to synthesize xylo-oligosaccharides. The reactivities of three secondary equatorial hydroxyl groups in xylose is dependent on the *C*-1 configuration [46]. For example, regioselectivity of protection among the 3 secondary hydroxyl groups are dependent on whether the anomer is α- of β-. Further, in homo- and heteroxylans, the xylose moieties can be linked to one another in either β-(1→3) or β-(1→4) linkage [47]. Figure 5 represents a few early works reported on the synthesis of homoxylans.

Utille and co-workers reported the synthesis of β-(1→3)-linked homoxylan tetrasaccharide, utilising the Koenigs-Knorr method, through glycosylation of the disaccharide acceptor with the halide activated disaccharide glycosyl donor [45]. A similar block condensation of a disaccharide donor and a disaccharide acceptor alcohol was also reported by Kong and Chen [44] to prepare homoxylan up to hexasaccharide by trichloroacetimidate activation method.

As described earlier, the latent-active glycosylation method involves (i) allylic halogenation and (ii) reaction with the acceptor alcohol in the presence of a promoter. Synthesis of the 1,3-linked xylose disaccharide is shown in Scheme 27. Activation of the monosaccharide donor **125**, using the prototypical NBS/AIBN/CCl_4 reagent system, affords the corresponding allylic halide intermediate. In comparison to other allyl hexopyranosides, an observation was that the allylic halogenation of xyloside **125** required longer duration. Subsequent treatment with TfOH or TMSOTf at 0 °C and the acceptor allyl xylopyranoside acceptor **126** afforded the xylobioside **127**, as the β-anomer exclusively.

Efforts to synthesize (1–3)-linked xylotrioside through glycosylation of acceptor **126** with the activated xylobioside donor **127** by repeating the above reaction sequence, however, did not afford the desired

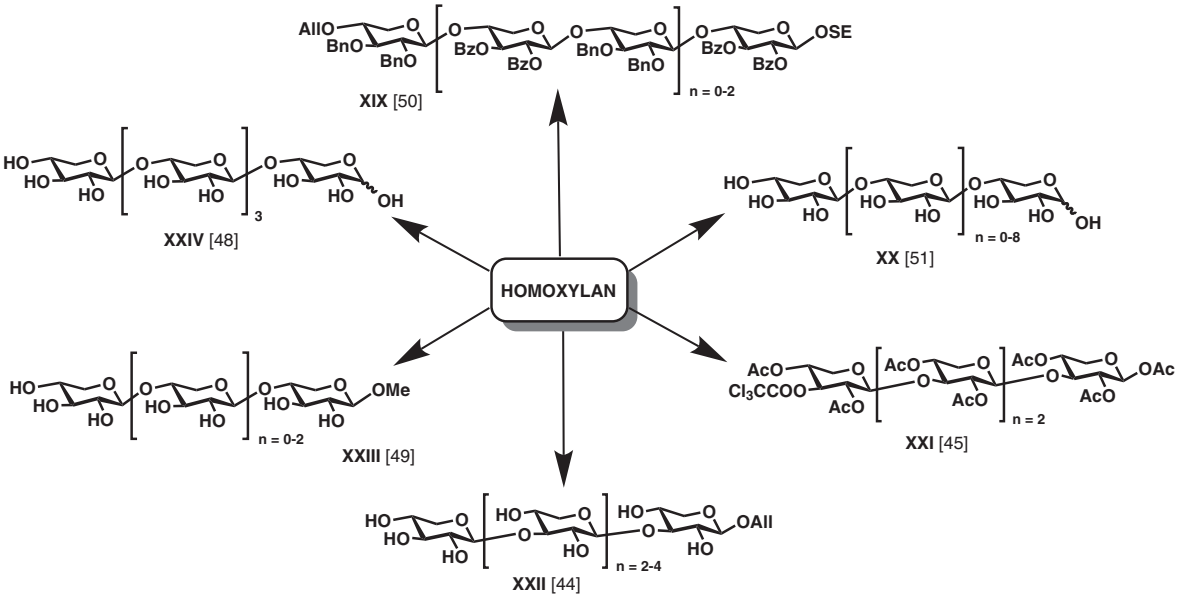
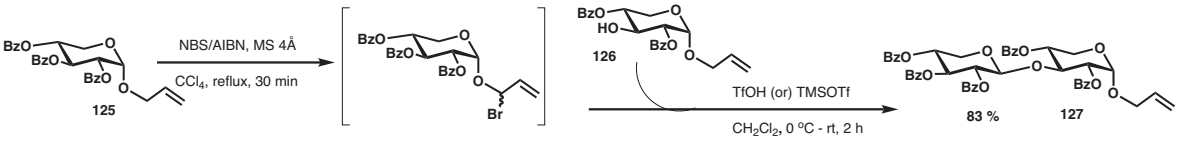


Fig. 5: Reports on the synthesis of xylo-oligosaccharides.



Scheme 27: Synthesis of (1–3)-linked xylobioside **127**.

trisaccharide. Rather, intermediate allylic halide afforded only the hydrolysed disaccharide hemiacetal, in spite of repeated attempts conducting the reaction under complete anhydrous conditions. The reactivity of the disaccharide donor **127** to monosaccharide acceptor **126** is inferred to be not efficacious. In order to verify this inefficacy of trisaccharide formation, a glycosylation of the disaccharide donor having the trichloroacetimidate with acceptor **126** was attempted. However, here too, trisaccharide formation was not observed.

Conclusion

Glycosylation chemistry continues to expand addressing a number of issues relating to chemo-, regio- and stereoselectivities. The notion that protecting groups are required to mask the reactivities of otherwise reactive functionalities has been re-engineered and strategies have emerged now to gain the role of the protecting groups in the above selectivity issues. The generation of the oxocarbenium ion with a predictable conformation has the most potential to afford a glycosidic bond with a defined stereoselectivity. Many glycosylation methods involve installation of the leaving group just prior to the glycosylation. Such activated glycosides installed with a leaving group could be unstable also. Strategies that require a chemoselectivity, orthogonality and pre-activation are important in order to develop glycosylation methods beyond the oxocarbenium generation manifold. Utilizing a protecting group to an activated leaving moiety at the anomeric carbon of glycosyl donor allows a latent protecting group to an active glycosyl donor. In this effort, the new development pertains to activating an allyl glycoside to an activated allylic halide donor. Allyl glycosides are acid-base stable and their conversion to a halo-allylic glycoside involves a prototypical radical halogenation reaction. A complete allylic halogenation results, thereby the transformation of the latent moiety to an active glycosyl moiety is ensured fully. The high reactivity of the active halo-allylic glycosyl donor ensures the formation of the oxocarbenium ion and the subsequent reaction with the glycosyl acceptor to afford the desired glycoside. Whereas benzylic moiety is incompatible to the radical halogenation of allylic glycosides, other protecting groups are compatible with the newly developed glycosylation methodology. The presence of the allyl moiety at the reducing end of the growing oligosaccharide enables continuing the glycosylation through activation of the latent allyl moiety, thus adding an advantage of allyl glycosides as donors and acceptors in a oligosaccharide synthesis. Whereas allylic halide formation as a new glycosyl donor moiety is uncovered, issues relating to the formation of 1,2-*cis*-glycosides, use of benign solvents for radical halogenation and more are to be investigated further.

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