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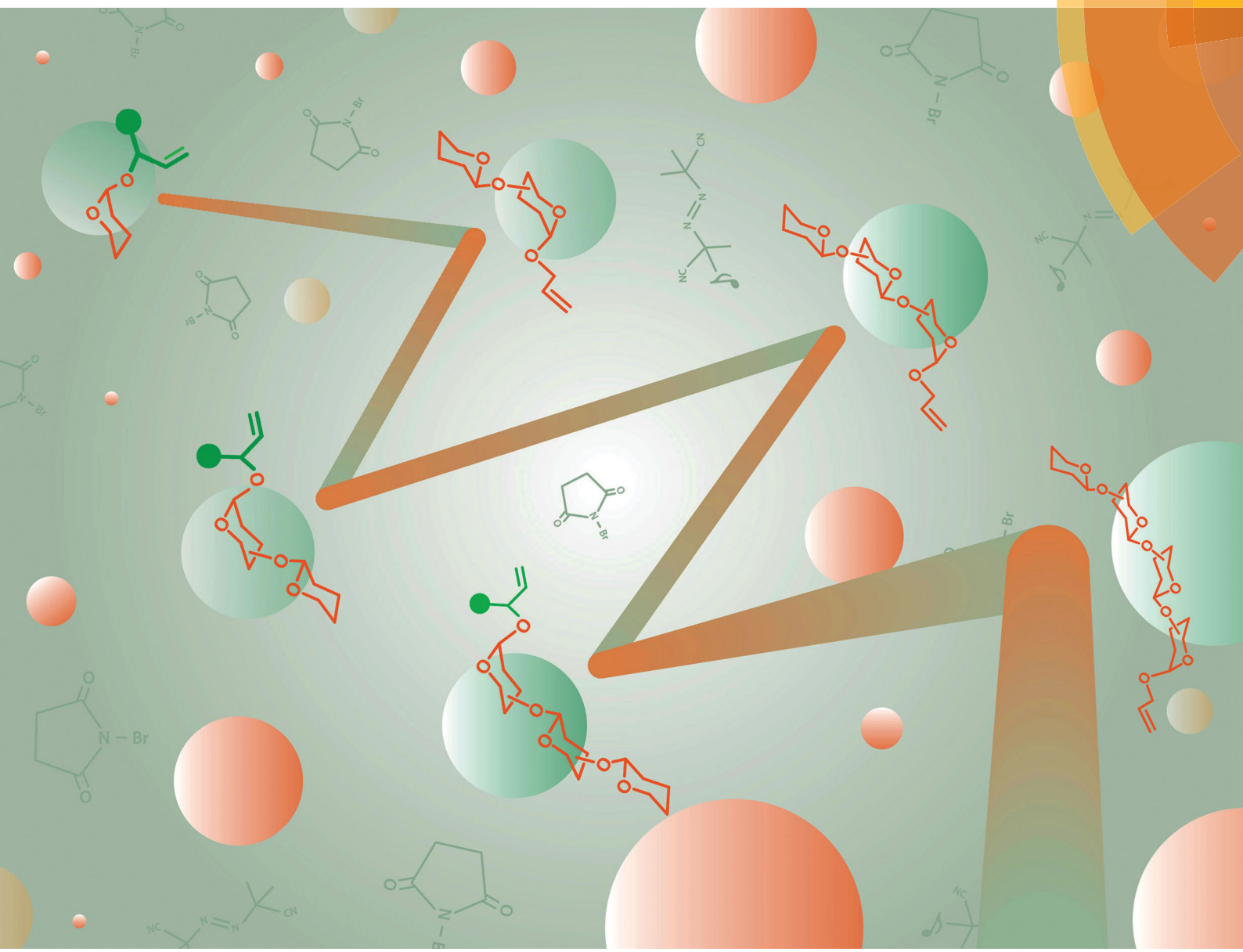

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Radical halogenation-mediated latent–active glycosylations of allyl glycosides†

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Radical halogenation-mediated glycosylation using allyl glycosides as donors and as acceptors emerges to be an efficient and hither-to unknown glycosylation method, adhering to the concept of the latent–active methodology. Several di- and trisaccharides that possess the allyl moiety at their reducing end are prepared through this new glycosylation methodology.

Chemical glycosylations bear a crucial importance in efforts to secure diverse, complex oligosaccharides and glycoconjugates of functional importance.[1] A plethora of glycosylation methods, including enzymatic routes, permit preparation of complex oligosaccharides under solution and solid phase conditions.[2,3] The allyl moiety is used commonly as a protecting group and is deprotected under mild conditions, prominently through a metal-mediated isomerization to vinyl ether, followed by an acid treatment.[4,5] The sugar vinyl ether is also used beneficially to conduct a glycosylation reaction with an acceptor alcohol.[6] Such a vinyl glycoside intermediate is established as a glycosyl donor under the 'latent–active' glycosylation methodology,[6b,7] wherein an allyl glycoside is activated as a reactive vinyl glycoside donor, whose reaction with an acceptor alcohol moiety leads to a glycoside product. The newly formed glycoside possesses the allyl moiety at the reducing end, which is useful to reiterate the reaction sequence, leading to the formation of a newer glycoside. An advantage is that it does not require installation of an alternate anomeric leaving group, such that the glycosyl donor and acceptor can be prepared from a common building block and the sequential glycosylation can be performed *via* a single glycosylation method.

We herein report a new, hither-to unknown glycosylation method that combines a free radical induced halogenation of an allyl glycoside, which in the presence of an acid promoter reacts with a glycosyl or aglycosyl acceptor, leading to the formation of a glycoside product. This new methodology is fine-tuned further such that an allyl glycoside forms a donor and an acceptor under the latent–active glycosylation methodology (Fig. 1). In this strategy, allyl glycoside donor **I** is subjected to (i) a free radical induced allylic halogenation, which forms an 'active' glycosyl donor moiety (**II**); and (ii) treatment of the glycosyl allylic halide intermediate **II** with an acid promoter, followed by reaction with a 'latent' allyl glycoside acceptor (**III**), which leads to the formation of glycoside **IV**. Reiteration of the above steps leads to higher glycoside product **VI**. The sequence of converting the allyl glycoside to a product oligosaccharide allyl glycoside is accomplished in one pot.

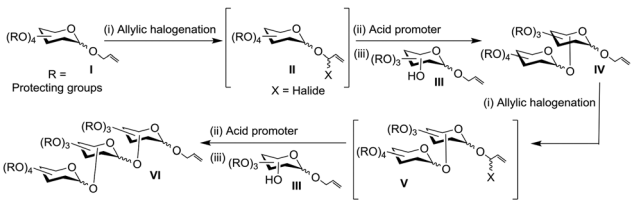

Fig. 1 Allylic halogenation mediated glycosylation using *O*-allyl glycosyl donors and acceptors.

The reaction of allyl tetra-*O*-acetyl-D-glucopyranoside (**1**) was carried out initially, in which **1** when reacted with *N*-bromosuccinimide (NBS) and azo-bis-isobutyronitrile (AIBN) in CCl_4 under refluxing conditions led to allyl bromide intermediate formation. Allylic bromination using NBS under irradiation is known earlier as a deprotection method, wherein the newly formed allyl bromide intermediate is hydrolysed to the corresponding sugar lactol.[8] Radical halogenations at the ring positions of carbohydrates are known.[9] The reaction of the allylic bromide intermediate with methanol in the presence of $AgClO_4$ or Ag_2CO_3 (1.2 molar equiv. relative to the donor) at 0 °C to room temperature led the reaction to only the methoxy substitution product **2** (Scheme 1). A similar substitution product was also obtained in the reaction of allyl tetra-*O*-acetyl-D-mannopyranoside with methanol. A change in solvent and optimizing reaction conditions were found to overcome the formation of a substitution

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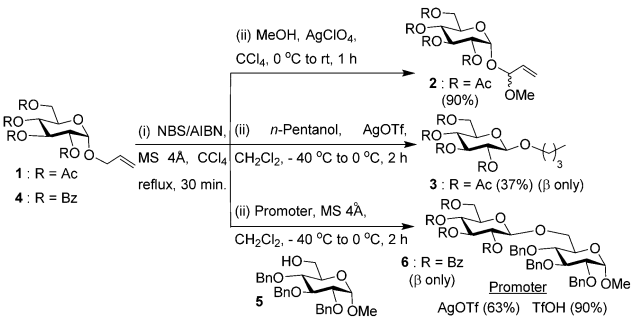
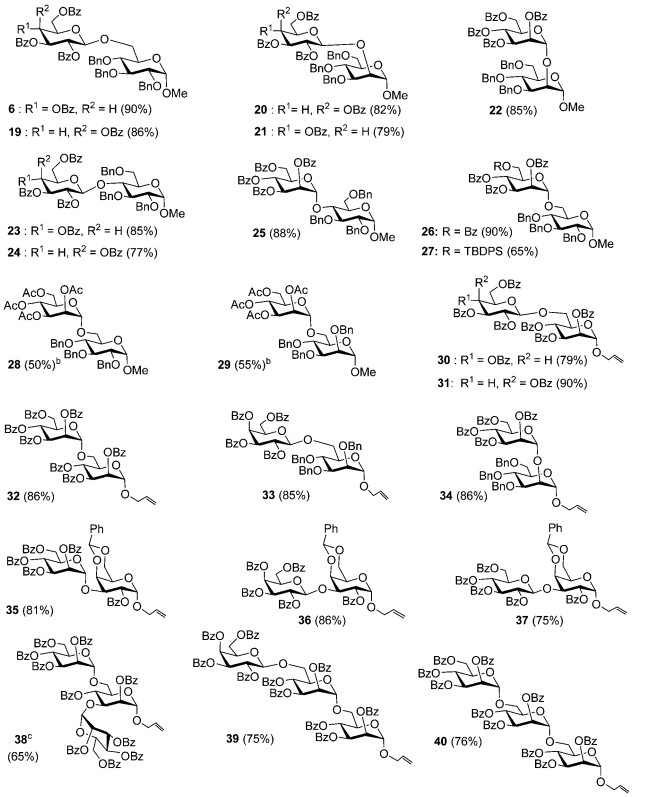


Scheme 1 Radical halogenation mediated reactions of allyl glycosides.

product and to promote the formation of an oxocarbenium ion required for a successful glycosylation. Radical bromination in CCl_4 followed by reaction with *n*-pentanol in the presence of AgOTf in CH_2Cl_2 at −40 °C afforded glycoside **3** as the β-anomer, in 37% yield, along with hemiacetal in 60% yield (Scheme 1). The unreacted aglycosyl acceptor also remained in the reaction. Similar results were observed with the acetate protected fucosyl donor and its reaction with *n*-pentanol (ESI†). The yield of the desired glycosylation product increased when the benzoyl protected allyl glycoside donor and AgOTf promoter were used. Thus, the reaction of *O*-benzoyl protected allyl glycoside **4** with acceptor **5** afforded disaccharide **6**, in 63% yield as the β-anomer (Scheme 1).

Modification of the promoter to a Brønsted acid in place of a halophilic reagent promoted the glycosylation even better. Glycosylation experiments were conducted using a catalytic amount of TfOH[10] as promoter in place of silver salts and, in this instance, the formation of glycoside **6** occurred, with an isolated yield of 90%, resulting from the reaction of allyl glycoside **4** with methyl glycoside acceptor **5**. We premise that protonation of the glycosidic oxygen by TfOH facilitates the generation of the oxocarbenium ion intermediate, along with the bromohydrin of acrolein as the by-product.[11] A series of reactions showed the following: (i) conducting the reaction at −78 °C or at room temperature led to either no reaction or the formation of a complex mixture, respectively; (ii) increasing the reaction duration to 24 h did not aid in the formation of the desired product in a quantitative yield; (iii) change of solvent for glycosylation to CH_3CN and CH_3NO_2 led to poor yields of the desired product and (iv) reaction between the glycosyl donor and acceptor did not occur in the absence of NBS/AIBN reagents in the first step and in the presence of TfOH alone. From these reactions, the following reaction conditions are optimized for the glycosylation reactions: (i) treatment of a mixture of the allyl glycoside donor (1 molar equiv.) and powdered molecular sieves (4 Å) (∼200 mg) with NBS (0.9 molar equiv.) in CCl_4 (20 mL for 100–150 mg of donor); (ii) degassing the reaction mixture under an Ar atmosphere for ∼5 min; (iii) addition of AIBN (cat.), again degassing for ∼5 min and refluxing the reaction mixture for ∼30 min; (iv) removal of solvents *in vacuo*, re-dissolving the reaction mixture in CH_2Cl_2 (5 mL) under an Ar atmosphere, and cooling to −40 °C and (v) adding TfOH (10 mol%), stirring for ∼10 min, then adding acceptor alcohol (0.7 molar equiv.) and work-up of the reaction after ∼2 h. The crude reaction mixture was purified (SiO_2, hexanes/EtOAc) to afford glycoside products, which were characterized by physical techniques (ESI†). The outcomes of the glycosylation thus performed using varied types of allyl glycoside donors and acceptors are given in Table 1. As listed in the table, a number of allylic glycoside donors and acceptors (Fig. 2) were tested in order to verify the efficacy of the new glycosylation method developed herein. The isolated yields are good to excellent in all cases and the anomeric configurations were essentially 1,2-*trans* at the newly formed glycosidic bond, which suggests that the glycosylation reaction occurs *via* the oxocarbenium ion intermediate, stabilized by a neighboring group participation. Further, the β-anomer of the allyl glycoside donor is also suitable as the glycosyl donor during glycosylation. Exclusion of moisture was necessary to avoid the lactol formation. Lower yields in the case of acetate and silyl protecting groups on the donors were observed, wherein these moieties were partially deprotected in the product glycosides, leading to decreasing the yields of fully protected products. In this instance, donors with benzoate protecting groups afforded glycoside products with considerably increased yields.[12] Benzyl and benzylidene protecting groups are well tolerated in the glycosyl acceptor component, although competitive to the allyl moiety in the donor component.

Table 1 List of glycosides formed by allylic halogenation and subsequent acid-catalyzed glycosylation between allyl glycoside donors and acceptors[a]



[a] Isolated yields based on the acceptor glycoside molar equivalent and anomeric linkage as determined using the NMR spectra. [b] *O*-Deacylated product was also observed. [c] Disaccharide with a 1,6-glycosidic linkage was also isolated in 20% yield.

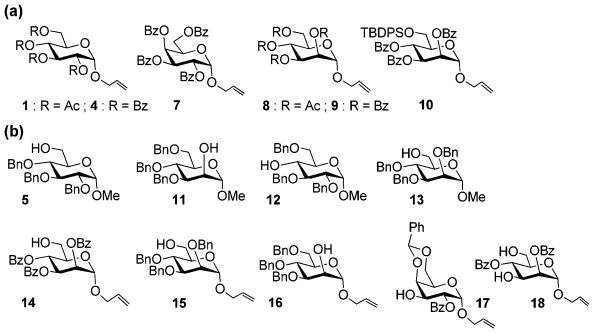


Fig. 2 List of (a) allyl glycoside donors and (b) methyl and allyl glycoside acceptors used to synthesize di- and trisaccharides as given in Table 1.

The importance of the reaction is that the presence of the allyl protecting moiety at the anomeric carbon of the glycosyl acceptor does not interfere in the reaction with the allyl glycoside donor and the desired glycoside products formed in good yields in all cases, adhering to the 'latent–active' glycosylation methodology. Further double glycosylation of an allyl glycoside having primary and secondary hydroxyl group acceptor sites (**18**) with an allyl glycoside donor (**9**) led to the desired product **38**, in a moderate yield. The glycosylation was conducted in a gram scale quantity in the case of the formation of **31** and the product was obtained in 80% yield.

Having established the successful glycosylation of allyl glycoside donors with glycosyl and aglycosyl acceptors through radical halogenation activation, leading to di- and trisaccharides, the feasibility of subjecting the newly formed allyl glycosides as glycosyl donors to further glycosylations was tested. Performing allylic activation through radical halogenation of glycosyl allyl halides **31** and **32** as active donors, followed by continuing the reactions with appropriate latent allyl glycoside acceptor **14**, in the presence of TfOH and molecular sieves in CH_2Cl_2, afforded trisaccharides **39** and **40** (Table 1), in good yields, as α-anomers. These reactions illustrate that the newly formed disaccharides are available for activation and further glycosylation reaction with allyl glycoside acceptors.

In conclusion, a new glycosylation methodology is developed, by utilizing an allyl glycoside as the common substrate, acting as a donor and an acceptor. Key reactions involved are the allyl glycoside activation through radical halogenation and the subsequent reaction with a glycosyl or aglycosyl acceptor in the presence of triflic acid. A range of allyl glycosides as donors and acceptors is utilized in a 'latent–active' manner, leading to the corresponding product glycosides, with the allylic moiety at the reducing end, in good to excellent yields. The presence of the allyl moiety at the reducing end of the newly formed glycoside facilitates further glycosylation. Thus product allyl glycosides are extended to the preparation of trisaccharides that possess the allyl moiety at the reducing end. In a plethora of chemical glycosylations,[1–3] the novelty and advantages of the method developed herein are as follows: (i) the reactions are performed using stable allyl glycosides as common precursors, suitable eminently in a 'latent–active' glycosylation method; and (ii) the reactions do not rely on precious metal catalysts for activation, in which case the reaction is aggravated further due to catalyst poisoning and reduction of the allyl moiety to the *n*-propyl moiety. Further, allyl glycosides are prepared directly from bench-top free sugars and the glycosylations conducted in one pot add advantage to the methodology developed herein.

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Conflicts of interest

There are no conflicts to declare.

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