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Advancements in O-Glycosylation Techniques with Diverse Donor Molecules

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Abstract

Since the early stages of carbohydrate chemistry, numerous researchers have employed alkynyl glycosyl donors as key reagents in glycosylation reactions. These donors have played a crucial role in facilitating the synthesis of glycosidic bonds, an essential aspect of carbohydrate-based compounds. Over time, various modifications and improvements have been introduced by different research groups to enhance the efficiency, selectivity, and sustainability of glycosylation processes. A major focus has been on designing glycosyl donors that align with the principles of green chemistry, reducing the reliance on hazardous reagents and improving reaction efficiency. The continuous evolution of alkynyl glycosyl donors has led to innovative approaches that minimize waste, enhance atom economy, and utilize environmentally benign catalysts and solvents. Researchers have explored diverse structural modifications to optimize these donors, improving their reactivity and stability under different reaction conditions. Additionally, advancements in protecting group strategies and activation methodologies have contributed to making these glycosylation reactions more practical and widely applicable in carbohydrate synthesis. Over the past decade, significant progress has been made in this field, with numerous studies reporting novel alkynyl glycosyl donors capable of achieving high yields and excellent stereoselectivity. This review provides an in-depth analysis of the recent developments in alkynyl glycosyl donor chemistry, focusing on their structural diversity, reaction mechanisms, and applications in sustainable glycosylation strategies. By highlighting these advancements, this work aims to provide valuable insights into the future directions and potential applications of these glycosyl donors in carbohydrate synthesis.

Keywords: Glycosyl donor, glycosylation, glycosyl acceptor, glycosides, nucleophilic species

INTRODUCTION

Glycosylation is the process by which a carbohydrate or glycosyl donor is joined to a hydroxyl or other functional group of another molecule or glycosyl acceptor (Figure 1) [1]. The primary bonds found in a significant class of biomolecules, such as oligosaccharides and glycol conjugates, are glycosidic linkages [2]. Carbohydrates are among the most basic and common biomolecules in the universe. Carbohydrates are widely distributed and serve as essential structural elements in a wide range of biopolymers, including chitin in arthropod exoskeletons, cellulose in plant cell walls, DNA, and RNA [3]. Conversely, carbohydrates serve as both the primary energy source and the primary pathway for energy storage in living organisms, including starch, glycogen, and other forms of storage. Carbohydrates are essential for energy and structure but also have a significant impact on biological regulation [4]. The glycosidic bond is the

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main bond in a crucial class of biomolecules called oligosaccharides and glycol conjugates, which are composed of one sugar unit coupled with another sugar unit or any other molecule (glycan) [5]. Since one sugar unit is attached to another sugar unit or any other molecule via a carbon-oxygen (C-O) bond, glycosidic bonds, which are abundant in natural biopolymers, play a crucial and important role in regulating various biological processes [6]. Consequently, there has been persistent interest in developing a practical and efficient synthetic method for creating these bonds.

DIFFERENT TYPES OF DONORS

Alkynyl-Based Donors

In 2011, using a gold (I) catalyst, Yu et al. created ortho-alkynyl benzoate donors for N-glycosylation (C-N bond formation) of pyrimidines and purines [7].

Nucleobases compete adversely for glycosidation with other nucleophilic species, such as promoters and leaving groups, which are present in glycosylation systems because they are not highly soluble or nucleophilic. Although glycosylortho-alkynyl benzoates are just as stable as sugar acetates, they can be catalyzed for glycosidation under mild conditions with a gold(I) complex (e.g., the shelf-stable, commercially available [$Ph_3PAuNTf_2$]; Tf = trifluoromethanesulfonyl) [8]. Furthermore, no competing nucleophilic species were introduced by the promoter or departing entity (an isocoumarin) [9].

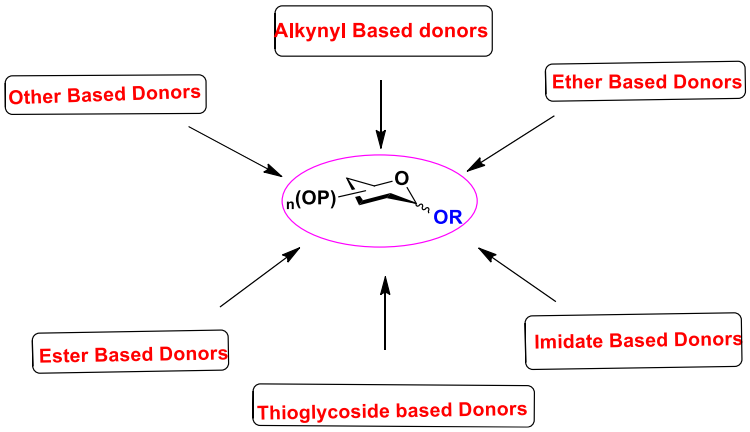

Figure 1. Glycosylation with different donors.

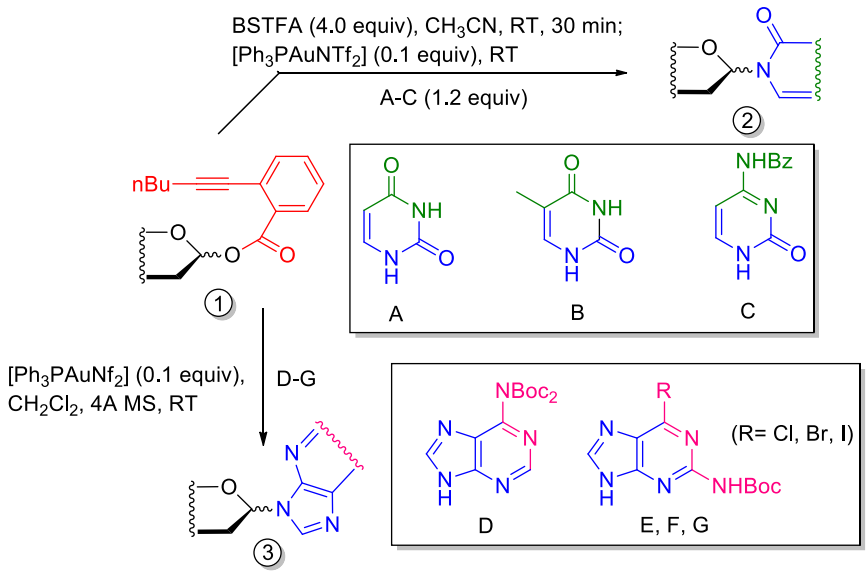

Figure 2. N-glycosylation (C-N bond formation) of pyrimidines and Boc-protected purine with glycosyl ortho-hexnylbenzoate.

To solve this purine glycosylation problem, the authors planned to employ this innovative glycosylation approach. Fortunately, moderate glycosylation conditions with ortho-alkynyl benzoates as donors would be ideal for a variety of protective groups on purines, including those that would not withstand typical N-glycosylation conditions (Figure 2). Boc-protected purine derivatives can be used as coupling partners for the first time because of the mild glycosylation conditions that enable highly effective and regioselective N-glycosylation of purines. It is anticipated that further improvements in coupling efficiency can be achieved by carefully adjusting the reaction parameters for each coupling partner and applying this effective technique to the synthesis of nucleosides. In 2012, Yu et al. prepared a novel class of thioglycoside donors that could undergo glycosylation in the presence of a gold catalyst (Figure 3). The Sonogashira coupling reaction of ortho-bromophenyl thioglycosides with alkynes simplifies the synthesis of the ortho-alkynyl phenylthioglycoside donors.

Ortho-alkynylphenylthioglycosides are potential novel donors, given that they might maintain the stability of thioglycosides despite undergoing glycosidation under moderate gold (I)-catalyzed conditions. Their research focused on the initial findings of the synthesis and donor characteristics of ortho-alkynylphenylthioglycosides. It is readily produced and can be used as a glycosyl donor for glycosidation with Ph3PAuOTf or [Btz-Au-PPh3]OTf. In 2012, using a catalytic quantity of gold salts, Hotha et al. demonstrated glycosidation with stable alkyl glycosyl donors (Figure 4) [10]. At room temperature, they created novel donors called 1-ethynylcyclohexanyl glycosides, and mechanistic analysis revealed that the departing group was extruded only. To identify a leaving group that would permit trans-glycosylation at room temperature, they conducted a methodical examination of several alkynes carrying attachments at the anomeric position.

In 2013, the same group demonstrated that the armed-disarmed technique can be used to glycosylate any glycosyl donor as well as other similar types of alkynyl donors. They achieved a moderate to good yield of trisaccharides under ambient reaction conditions by employing this technique [11]. In 2013, Yu et al. created a novel glycosylation process using a gold (I) complex as a catalyst and glycosyl ortho-alkynylbenzoates as donors [12]. Compared to traditional glycosylation processes, this innovative approach avoids strongly acidic, nucleophilic, or electrophilic species, which explains its wide range of applications in the synthesis of glycans and glycoconjugates. In particular, this method effectively exposes glycosylated substrates to acidic environments [13]. In crossover experiments, the presence of an exogenous isochromen-4-yl gold(I) complex verified that the anomerization process uses the exocleavage mechanism, which (surprisingly) involves the removal of Au+L from the vinyl gold(I) complex and the addition of the isochromen-4-yl gold(I) complex onto a sugar oxocarbenium (or dioxolenium) (Figure 5).

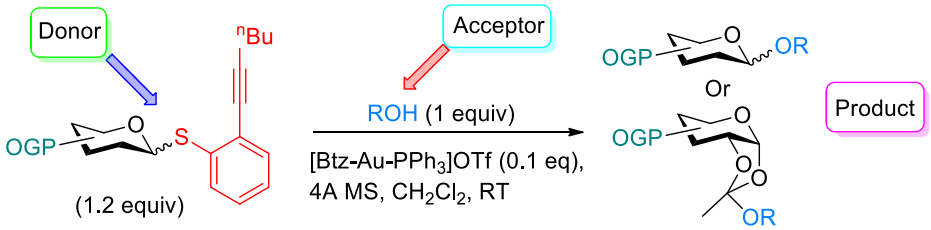

Figure 3. Glycosidic coupling of ortho-hexynylphenylthioglycosides donor with acceptor alcohols under the catalysis of [Btz-Au-PPh3]OTf.

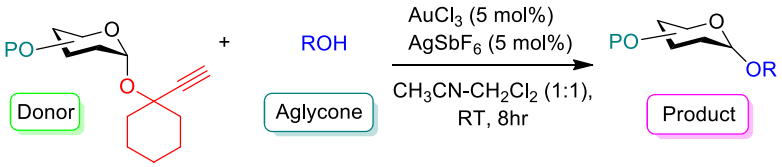

Figure 4. Glycosylation reaction using 1-ethynylcyclohexanylglycosyl donors and alcohol acceptors.

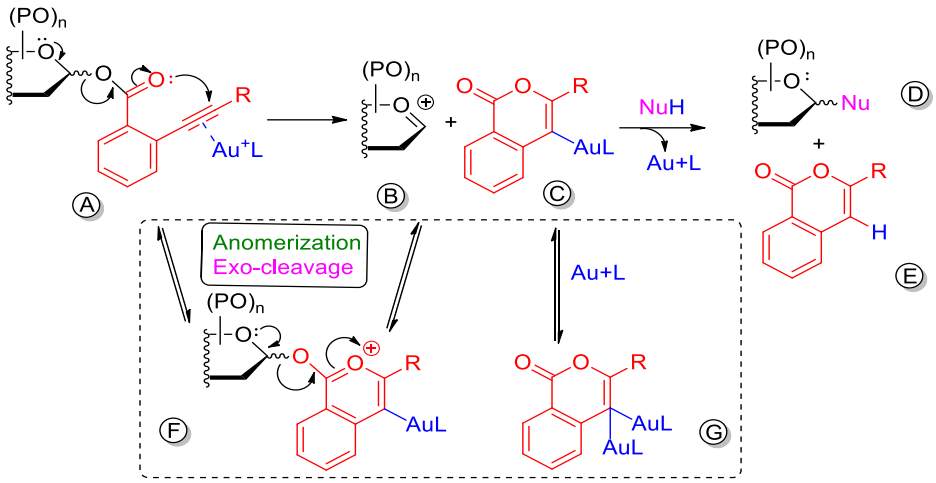

Figure 5. Gold(I) catalyzed-glycosylation reaction with glycosylorthoalkynylbenzoates as donors, the exo-cleavage pathway and the alternative endo-cleavage pathway for anomerization.

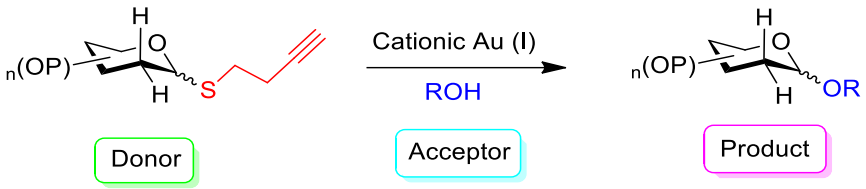

Figure 6. Synthesis of 2-deoxy glycosides catalyzed by Au(I) with S-But-3-ynyl thioglycosides.

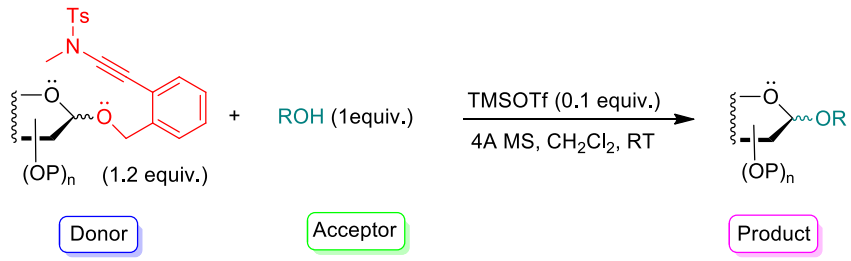

Figure 7. TMSOTf catalyzes the glycosylation process using ortho-(methyltosylaminoethynyl)benzyl glycosides as donors.

Thioglycosides are stable and survive a variety of transformations, including protecting group manipulations [14]. Bench-stable gold(I)-catalyzed glycosylation for the stereo-selective production of 2-deoxy α-glycosides under benign and cost-effective circumstances. Zhu et al. described donors of 2-deoxy S-But-3-ynyl thioglycoside in 2013(Figure 6) [15].

In 2015, Yu et al. reported a new kind of glycosyl donor and its use in the "latent active" synthesis of glycans (Figure 7) [16]. Under mild conditions, a catalytic amount of TMSOTf can activate its unique donor ortho-(methyltosylaminoethynyl) benzyl glycosides, which are easily generated from equivalent ortho-iodobenzyl glycosides by Sonogashira coupling with amide. They showed that their "latent active" method worked well for glycan assembly in a short time.

Balamurugan et al. synthesized a new and easily accessible leaving group from ethyl cyanoacetate in 2015 [17]. Using a gold (III) catalyst, a number of nucleophiles, including alcohols, thiols, allyltrimethylsilane, trimethylsilylazide, and triethylsilane, interacted to produce matching glycosides in good yields and with mediocre to outstanding α-selectivity. This departure group was made for two reasons: first, it makes it easy to propargylate ethyl cyanoacetates; and second, it increases the likelihood of a stereochemical glycosylation reaction by coordinating with the oxocarbenium ion intermediate to

the cyano group in the leaving group. However, at the time of leaving group preparation, monopropargylation was not performed on ethyl cyanoacetate because it consistently produced a predominantly dipropargylated product.

According to their hypothesis, the gold(III) catalyst activates the alkyne moiety of Aby coordinating with the triple bond of the leaving group. γ-Methylene lactone B and oxocarbenium ion intermediate C are formed because of the intramolecular attack of the carboxyl oxygen on the alkyne in a 5-exo-dig fashion. The nucleophile then attacks the anomeric carbon of the oxocarbenium intermediate C to form anomeric glycosides D. These observations (Figure 8) reveal that gold-catalyzed cycloisomerization takes place because of the presence of the ring oxygen of the sugar unit and forms the oxocarbenium ion required for glycosylation. In et year 2015Alkynyl 1,2-orthoesters were used as glycosyl donors to synthesize a variety of thioglycosides and 1-thiotrehaloses in the presence of a gold catalyst [18]. The reaction was fast, mild, catalytic, with good yield and diastereoselectivity (Figure 9).

Pyrimidine nucleosides were produced by the same group using Au(III)salt as a catalyst and identical propargyl 1,2-orthoesters. They attempted different combinations of CH_3CN and CH_2Cl_2 because they discovered in their earlier research that propargylorthoesters were better activated in CH_2Cl_2. They discovered that the 1:2 mixture of CH_3CN:CH_2Cl_2 is the most suitable (85% of 3 in Figure 10); where R1= -COPh and R2=-H) for the nucleosidation. However, the process is not suitable for purine nucleoside synthesis [19].

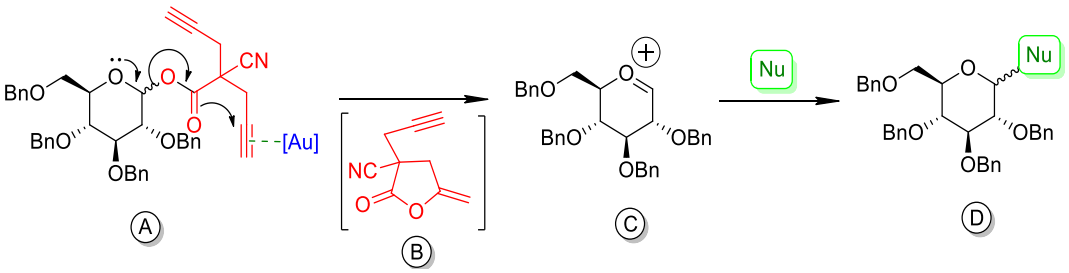

Figure 8. Plausible mechanism of gold-catalyzed glycosylation of easily accessible leaving group derived by Balamurugan et.al. [17].

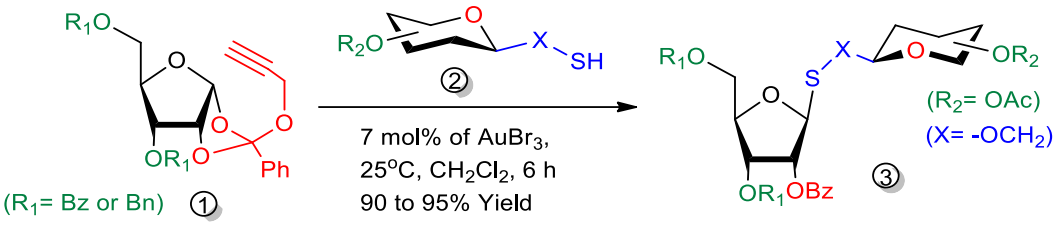

Figure 9. Synthesis of thioglycosides and 1-thiotrehaloses using alkynyl 1,2-orthoesters as glycosyl donors in the presence of a gold catalyst.

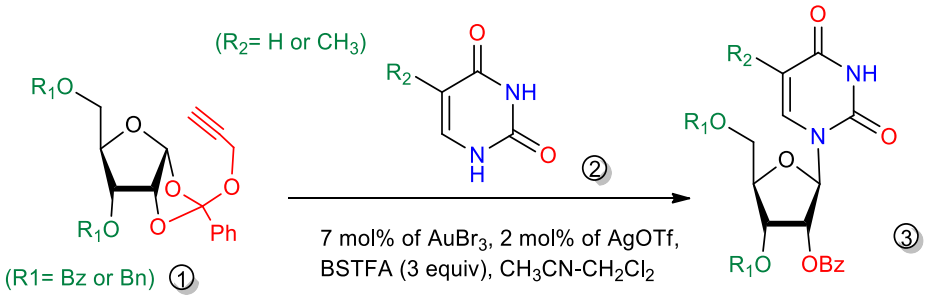

Figure 10. Gold-catalyzed glycosylation for pyrimidine nucleosides using propargyl 1,2-orthoesters.

Ether-Based Donors

A stable protection strategy in glycol chemistry has generally been employed using O-allylation [20]. Only appropriate activators can remove it; nonetheless, because of its greater stability, its promise as a glycosyl donor has not been fully utilized [21]. Interested in creating novel glycosylation and defense techniques [22, 23], Taneja et al. examined the potential of O-allyl glycosides as a versatile glycosyl donor in 2011 [24]. Based on their earlier work on the synthesis of tetrahydropyranylether as an alcohol/thiol protecting group by simple O-allyl replacement under mild reaction conditions, an alternative technique that can be used in 2,3-unsaturated α-glycosylation via O-allyl replacement was developed [25]. This method is simple to apply, stereo-selective for the α-glycosylation of a broad range of substrates, and effective as a replacement for 4-pentenyl substitution.

This method has many benefits, such as (i) the endocyclic double bond is nonreactive under the specified reaction conditions; (ii) it is suitable even in the presence of other sensitive functionalities such as acetonide, ester, nitro, and keto; and (iv) it is simple and stereo-selective 2,3-unsaturated α-glycosylation can be completed in a single step at room temperature by substituting the O-allyl group. One of several organic solvents was used to treat p-nitrobenzyl alcohol in the presence of halo-succinimide, either with or without a small quantity of the added cocatalyst. The best results for replacing the O-allyl group were obtained when $Zn(OTf)_2$ was used as a cocatalyst in Dichloromethane (DCM) with N-Bromosuccinimide (NBS), producing the intended product (8 h). (Figure 11). Other Lewis acids, such as $Yb(OTf)_2$, $Cu(OTf)_2$, $In(OTf)_3$, and BF_3, require longer reaction times and produce relatively poor yields. The groups employing Et_2O, $InCl_3$, $SnCl_4$, $TiCl_4$, and NBS outperformed N-Iodosuccinimide (NIS) and N-Chlorosuccinimide (NCS). This reagent system is gentle enough to be employed with natural goods that have additional sensitive multifunctional groups. Furthermore, because glycosylated products contain a double bond, they can readily undergo structural transformation into other advantageous bioactive molecules. Using 2-allylphenyl glycoside (AP), Hung et al. developed the concept of a new kind of stable donor. In 2012, they reported the synthesis of AP mannosidase and its activation for O-mannosylation in the presence of ICl/AgOTf [26]. AP glycosides can be easily obtained from low-cost commercial suppliers. 2-allyphenyl 2,3,4,6-tetra-O-benzyl-a-D-mannopyranoside was produced by the team (4). The related α-glycoside 3 was initially produced as a single isomer (3J1,2 = 1.8 Hz) in 93% yield by treating the per-O-acetylated mannoside with the inexpensive chemical 2-allyl phenol (2) in the presence of $BF_3.Et_2O$ [27]. Molecule 3 then yields a deacetylated product in the presence of Zemplén (NaOMe, MeOH), which is further per-O-benzylated using a combination of NaH/BnBr reagents to obtain the desired glycosyl donor 4 (Figure 12). The primary benefit of this new donor is its high stability in the presence of oxygen and moisture, which allows convenient storage for a few months with minimal care. It is also possible to illustrate glycosylation of different alcohols using this donor. The group synthesized the disaccharide moiety of bleomycins.

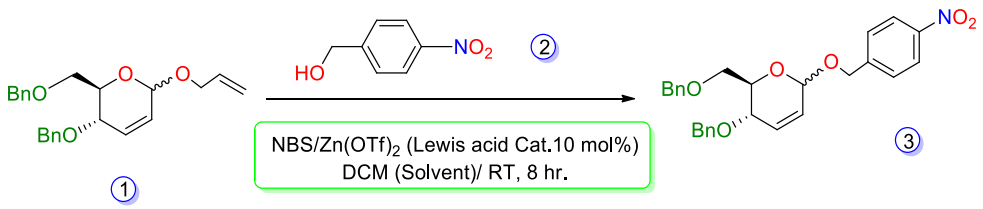

Figure 11. Glycosylation of allyl glycoside with p-nitrobenzyl alcohol (1.5 equiv).

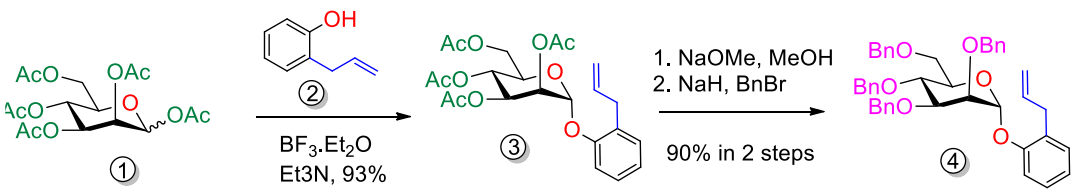

Figure 12. Preparation of the 2-allylphenyl manopyranoside (4) from inexpensive commercial sources.

Premathilake and Demchenko (2012) studied the O-allylphenyl (AP) anomeric moiety as a new leaving group concurrently with their research (Figure 13). Both direct and indirect methods can be used for chemical glycosylation [28]. These AP glycosides were chosen because they can be easily extracted from the corresponding peracetate using inexpensive 2-allylphenol in the presence of BF_3•Et_2O. The yield of acetylated AP β-d-glucopyranoside was 92%. They further hypothesized that the same promoters used for O-pentenyl activation might also activate the AP-leaving group [29]. TMSOTf or BF_3•Et_2O can likewise activate the AP-leaving group via a direct anomeric activation pathway, in contrast to O-pentenyl or thioglycosides. This was intended to be the primary feature of AP-mediated glycosylation. The AP group can be activated with TMSOTf but not with MeOTf, whereas thioglycosides show the opposite reactivity pattern, meaning that they do not react with TMSOTf and glycosylate with MeOTf without any issues [30]. Thus, in conjunction with thioglycosides, this mechanism may provide an appropriate platform for creating an entirely orthogonal strategy.

Cyclopropyl glycosides, which can be obtained from vinyl glycosides and other sources, may go through glycosidation when Lewis acid activation occurs, according to a 2012 study by Giuliano et al. [31]. The use of cyclopropyl glycosides as glycosyl donors has not been considered before this work. The synthesis of unsubstituted and substituted cyclopropyl glycosides and their use as glycosyl donors for Fmoc-protected serine, threonine, and monosaccharides are reported in this work. The synthesis of vinyl glycosides 1 and 2 was followed by cyclopropanation in a practical procedure for the production of unsubstituted (5a) and 1-methyl-substituted cyclopropyl glycosides (5b). They underwent Schmidt glycosidation and Kulinkovich reaction to generate 1-phenylsubstituted cyclopropyl glycosides (5c) (Figure 14) [32–34]. They also treated vinyl glycoside 1 with rhodium acetate and ethyl diazoacetate to create carboethoxy-substituted cyclopropyl glycoside [35, 36].

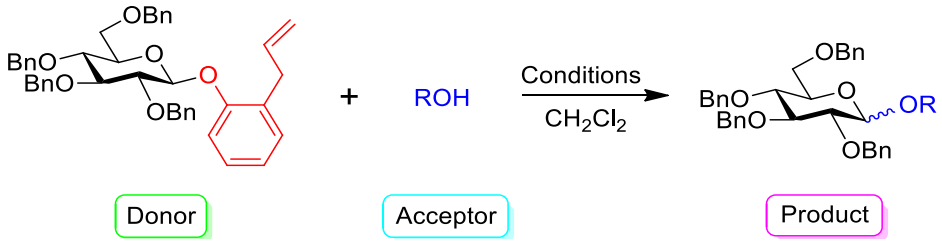

Figure 13. Glycosylation of O-allylphenylglycosyl donors.

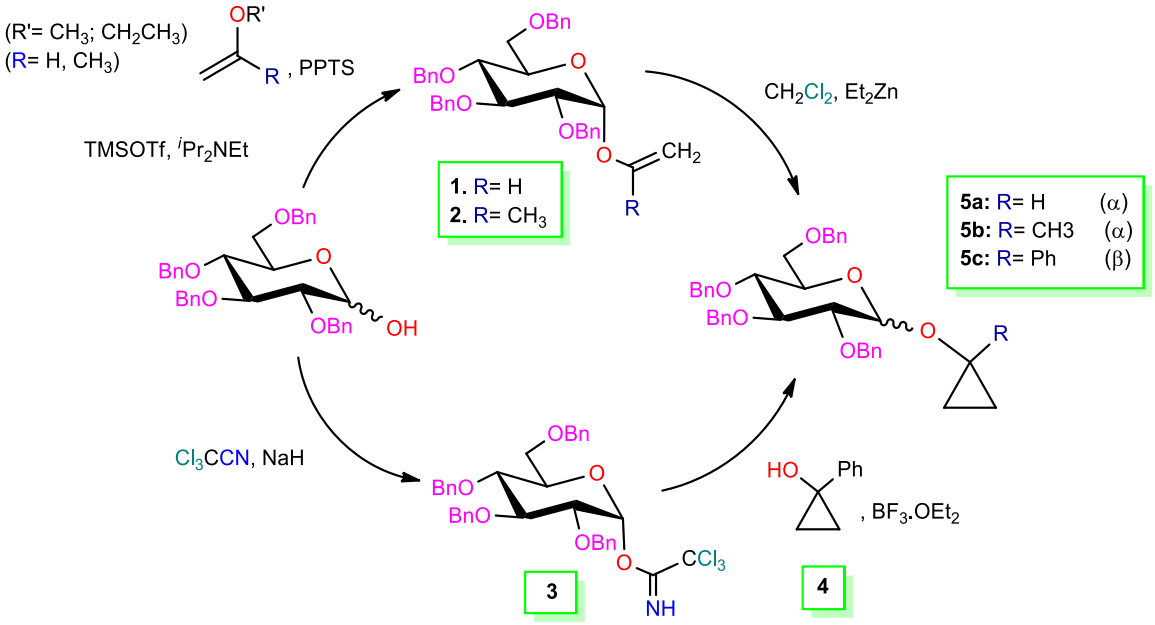

Figure 14. Methods available for the synthesis of cyclopropyl glycosides.

They showed the reaction mechanism for glycosidation with cyclopropyl glycoside donors in a simple schematic (Figure 15). To activate compound ① by starting the ring-opening of cyclopropanated carbohydrates and creating compound ② by adding an electrophile to a cyclopropyl carbon, the donor was first treated with reagents, such as mercury (II) trifluoroacetate, N-iodosuccinimide, and TMSOTf [37, 38]. Next, the ring oxygen participates in the reaction to produce the oxocarbenium ion intermediate and allows the acceptor to attack the anomeric carbon atom of the sugar unit of the donor to give the desired product ③. The primary drawback of this reaction, however, is that glycosidation does not occur when tetramethylurea, an amine base, or molecular sieves are present. Additionally, coupling did not occur when triflic acid was employed to activate the cyclopropyl sugar. Again, the glycosylation of cyclopropyl sugars was unsuccessful when other catalysts such as bismuth and aluminum triflates were used. Cyclopropyl glycosides are good donors for oligosaccharide synthesis under mild reaction conditions. Thioglycoside is the most widely used glycosyl donor because of its preactivation protocol [39]. Although it is a powerful donor, it still has some disadvantages, for example, the regeneration of the donor via aglycon transfer or the destruction of the acceptor by thiophilic species [40]. To overcome these problems, it is necessary to find an alternative glycosyl donor for preactivation-based oligosaccharide synthesis. In 2015, Ye et al. used pyridyl glycosides, which might be suitable building blocks for the pre-activation-based glycosylation protocol; thus, they chose the more stable 2-pyridyl glycosides as glycosyl donors to test the reactions [41]. The optimized conditions for the glycosylation reaction: donor (1.0 equiv), acceptor (0.8 equiv), Tf_2O (1.1 equiv), -72°C, DCM, 4Å molecular sieves (Figure 16).

Because of the adjacent group involvement in the glycosylation reactions of 2-acyl protected donors with acceptors, the anticipated 1,2-trans-linked disaccharides were produced. Et_2O might be the solvent of choice to improve the α-anomeric selectivity when donors with non-participating groups at the 2-position are employed. This process is effective for the synthesis of disaccharides.

In the same year, Wan et al. identified 2-(2-propylsulfinyl)benzyl (PSB) glycoside as a new active glycosyl donor that may be formed by selectively oxidizing the corresponding latent 2-(2-propylthiol)benzyl (PTB) glycoside under mild reaction conditions [42]. Additionally, they proposed, inspired by Kim and Yu's techniques, that adding Tf2O to the PSB glycosides would result in annulation by creating a ring with five or six members, activating the leaving group. Nevertheless, neither a cyclized product nor its hydrolyzed counterpart appeared to form during the reaction. Based on these findings, they hypothesized that a paused Pummerer reaction, not a Pummerer reaction per se, initiated the unique glycosylation process. Following a thorough examination of the production and suitability of the PSB glycosyl donor for chemical glycosylation, researchers examined the stability of PTB glycosides under reaction conditions that are frequently employed to activate thioglycosides (Figure 17).

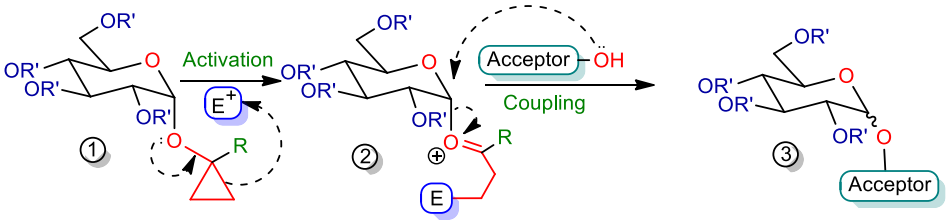

Figure 15. Schematic representation of glycosidation reaction via cyclopropyl glycosides.

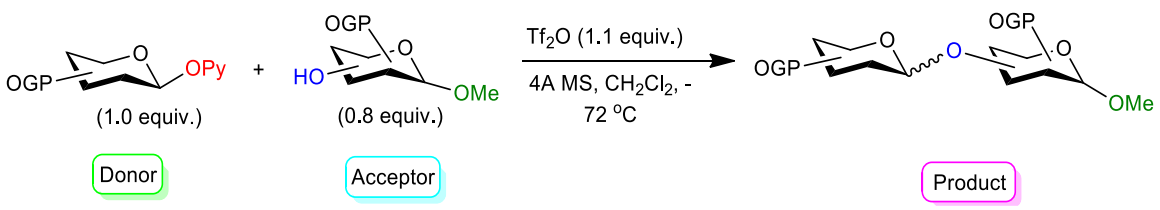

Figure 16. Glycosylation reaction using 2-pyridyl glycoside donor.

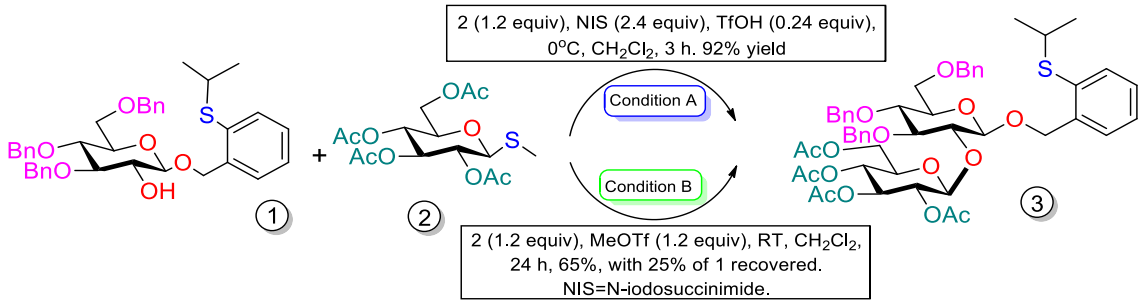

Figure 17. Phenylthiobenzyl (PTB) glycoside stability under various reaction circumstances.

They accomplished this by using 2-hydroxy PTB glycoside 1 as an acceptor and disarming methyl peracetylated 1-thio-β-D-glycopyranoside 2 as a low-reactivity donor, which typically requires powerful promoters for activation. Notably, a high yield of PTB disaccharide 3 could be obtained by accelerating the glycosylation processes using both NIS/TfOH and MeOTf. These studies showed that PTB glycosides are relatively stable under the conditions required for thioglycoside activation. The 2-(2-propylthiol)-benzyl (PTB) anomeric moiety acts as a new leaving group that facilitates rapid oligosaccharide assembly through latent active and convergent synthesis. Through effective oxidation, the equivalent stable PTB glycoside can be transformed into the PSB glycoside donor. Thus, the main advantage of this novel donor is that the active leaving group (PSB-OH) could be easily recycled from the reaction mixture and restored as the precursor (PTB-OH).

Imidate-Based Donors

Since Schmidt et al. first developed imidate-based glycosyl donors in 1980, they have been extensively employed in glycosylation processes. Imidate donors fall into two categories: i) O-imidates and ii) S-imidates. Glycosyl thioimidates are glycosyl donors with the leaving group SCR1 = NR2 [43]. For glycosylation processes, thioimidate donors exist in a variety of forms, including S-benzoxazolyl (SBox) and S-thiazolinyl (STaz) [44]. One-pot [45–47], solid-phase [48–50], chemoselective (armed-disarmed) [51–53], and orthogonal techniques are some of the current strategies for oligosaccharide synthesis. SBox and STaz glycosides can employ these strategies for glycosylation processes [54–57]. S-benzimidazolyl (SBiz) glycosides are another type of glycosyl thioimidate donor that has been studied in the past as a leaving group for the phosphorylation of unprotected glycosyl donors [58, 59]. This SBiz glycoside can be activated for chemical glycosylation under a number of circumstances, such as metal-assisted and alkylation routes. A new method for chemical glycosylation was developed in 2011 by Demchenko et al. [60]. Using active-latent and armed-disarmed-like principles, these SBiz glycosides can be used for rapid oligosaccharide synthesis.

They found that the N-anisoyl moiety in O-benzoylated compound A could be efficiently removed either in the presence of guanidine in MeOH or tetra-n-butylammonium fluoride (TBAF) in THF. The main advantage of this method is that under the reaction conditions, no competitive O-benzoyl group removal was detected, and the desired SBiz donor B was obtained quantitatively (Figure 18). In nature, oligosaccharide units, including α-linked N-acetylglucosamine (GlcNAc), have significant biological functions. However, the stereo-selective 1,2-cis-glycosidic bond formation (α-glycosylation) of N-acetylglucosamine is generally difficult because the 2-acetamido group in the GlcNAc unit participates in adjacent groups, which primarily yields undesirable 1,2-trans-isomers (β-anomers) [61]. A 2,3-cyclic carbamate-type protecting group for the N-acetylglucosaminylation of a galactose derivative and glycosyldonors with a 2-azido group for N-acetylglucosaminylation has demonstrated perfect α-selectivity [62–64]. However, the primary drawbacks of these tactics are the several procedures needed to preserve and deprotect the amino and hydroxy groups. In 2012, Shoda et al. developed a two-step chemo-enzymatic method to address these issues using a novel dimethoxytriazine-type glycosyl donor and α-N-acetylglucosaminidase (a-GlcNAcase) to generate α-N-acetylglucosaminylgalactose derivatives [65].

From their studies, it was found that a novel compound, 4,6-dimethoxy-1,3,5-triazin-2-yl α-N-acetylglucosaminide (DMT-α-GlcNAc), worked as an efficient glycosyl donor substrate for α-N-acetylglucosaminidase from *Bacteroides thetaiotaomicron* (α-GlcNAcase B1). An important advantage of this new glycosyl donor is that it can be prepared in water directly from GlcNAc, without using any protecting groups (Figure 19). The chemical glycosylation reaction is the greatest synthetic obstacle for chemists to obtain complex carbohydrates from simple building blocks. To overcome this difficulty, various researchers worldwide are trying to synthesize new types of leaving group containing donors or glycosylation methods. In 2013, Demchenko et al. reported a novel leaving group, O-benzoxazolyl (OBox) [66]. This is a bridging structure between the O-imidates and the SBox glycosides (Figure 20).

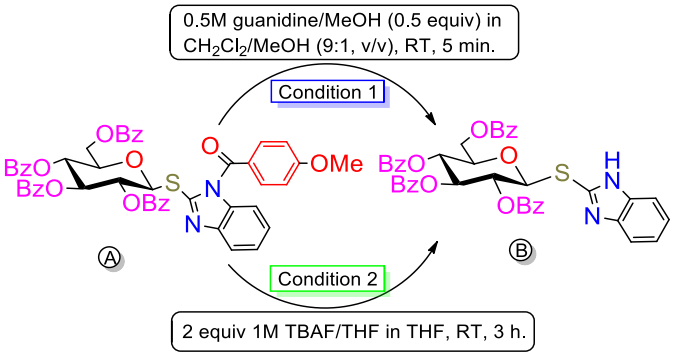

Figure 18. Conditions of the reaction for the elimination of the N-anisoyl group when the O-benzoyl group is present.

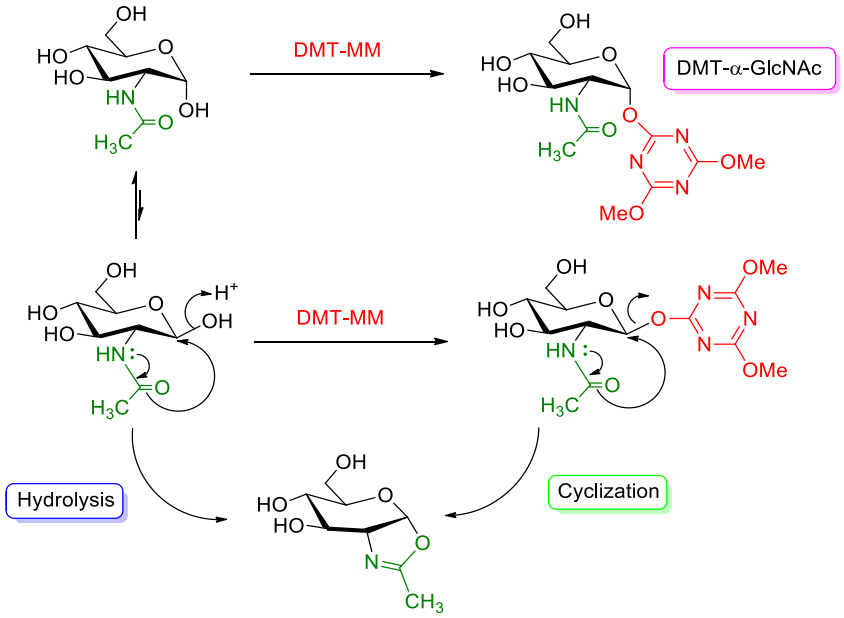

Figure 19. Reaction mechanism for the selective formation of DMT-alpha-GlcNAc.

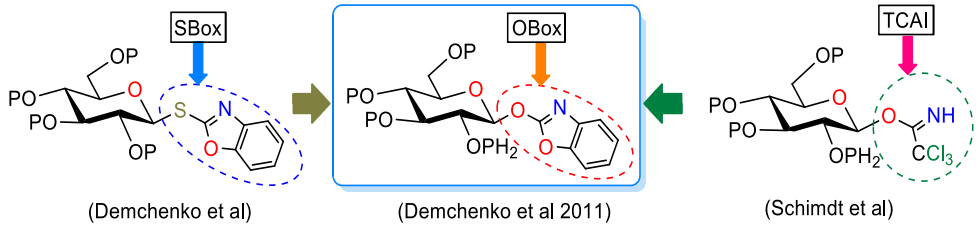

Figure 20. Designing a new O-benzoxazolyl leaving group as a bridging structure between O-imidates and SBox glycosides.

The main advantage of this leaving group is that the novel OBox leaving group can be made by several modes using commercially available and inexpensive precursors, which can be activated under a catalytic amount of a Lewis acid, as little as 3 mol%, to provide excellent yields in glycosylation reactions. This group performed a comparative test to judge the relative reactivity and stability of the OBox leaving group with similarly structured S-benzoxazolyl (SBox) glycosides (thioimidates) and glycosyltrichloroacetimidates (TCAI, O-imidates) and found that OBoximidates were more reactive than either SBox or TCAI donors. Although significant progress has been made in this field of chemical glycosylation, it remains challenging due to the requirement to achieve complete stereocontrol and minimize side reactions. To address this problem, Demchenko et al. (2014) presented a new type of O-imidate (OFox) leaving group containing a glycosyl donor, which can work upon regenerative glycosylation under nucleophilic catalysis (Figure 21) [67].

This new 3,3-difluoro-3H-indol-2-yl (OFox) leaving group is different from all other types of developed leaving groups because the aglycone structure needed to introduce OFox and that of the departed leaving group are the same, cyclic amide 3,3-difluoroxindole (HOFox) [68, 69]. The main advantage of this leaving group is that both the introduction and activation of this leaving group can be conducted in the catalytic "donor-regenerative" fashion. A stable precursor will first react with HOFoxaglycone to form a highly reactive OFoximidate donor. The latter will react with the acceptor while regenerating HOFoxaglycone, and it will be accessible for the next catalytic cycle to regenerate the OFox donor. By this regenerative approach, the side reactions are also reduced, which are commonly found in conventional glycosylations. Ranade and Demchenko (2014) had done a reactivity study upon glycosylalkoxythioimidates as building blocks for glycosylation (Figure 22) [70].

They performed structural modifications of the leaving group of S-glycosyl O-methyl phenylcarbamothioates (SNea) by changing the substituents that express different electronic effects.

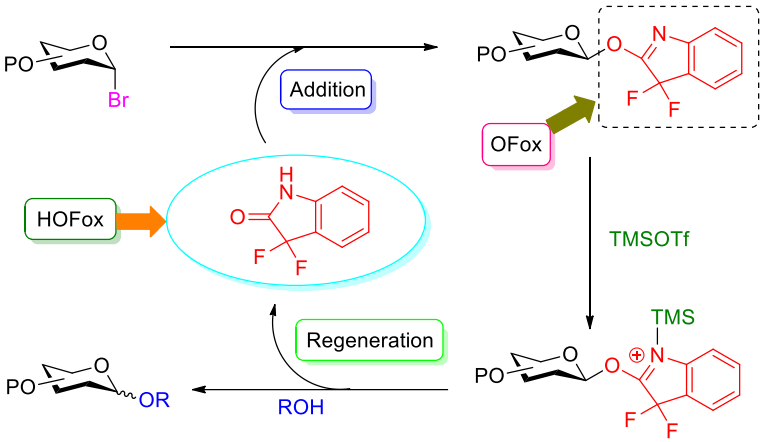

Figure 21. New concept of regenerative glycosylation using OFox donor.

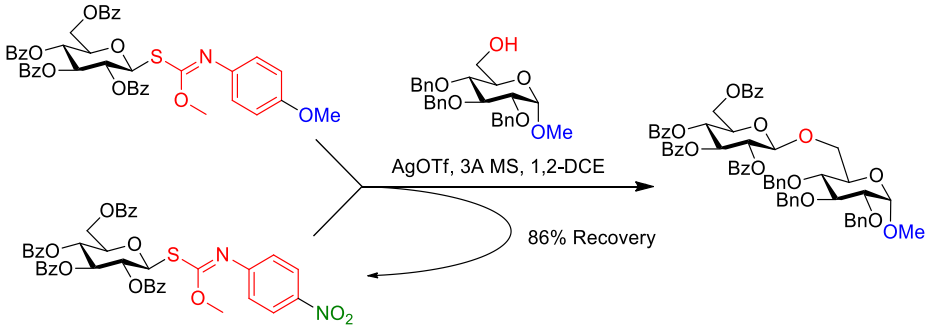

Figure 22. Competitive glycosylation between glycosyl donors with varying SNea-leaving group reactivities.

This led to a better understanding of the reactivity of these glycosyl donors, which can be modified by changing the structure of their leaving groups. Mechanistic studies also found that activation of both p-methoxy-SNea and p-nitro-SNea-leaving groups occurred via direct activation of the anomeric sulfur rather than the remote nitrogen atom, confirming that the p-methoxy-SNea donor is significantly more reactive in the presence of AgOTf than its p-nitro-SNea counterpart. Therefore, the advantage of this process lies in the expeditious oligosaccharide synthesis via selective activation of SNea-leaving groups owing to their reactivity difference. In this modern age, researchers are interested in chemical reactions that can be obtained using environmentally benign substances, that is, following the pathways of sustainable chemistry. Shoda et al. (2015) developed a new 4,6-Dimethoxy-1,3,5-triazin-2-yl (DMT) glycoside to produce stereo-selective 1,2-cis-glycosides using a catalytic amount of metal catalyst (Figure 23) [71].

DMT glycosyl donors were directly prepared in one step from free saccharides (without the protection of the hydroxy groups),2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), and N-methylmorpholine (NMM) for 24 h at room temperature in water. They also verified that the reaction worked well not only for monosaccharides, but also for di- and oligosaccharides. Another advantage of this method is that the metal catalyst can be glycosylated under neutral conditions, even an acid-labile oligosaccharide, without cleavage of the inner glycosidic bond. The use of metal catalysts is a disadvantage of this process because metal-free reactions are required for sustainable chemistry. At the end of the reaction, the metal catalyst was removed using a metal scavenger, and the detailed reaction mechanism is not clear. However, the preferential formation of 1,2-cis-glycoside suggests that the reaction proceeds via a stereospecific S_N2-type mechanism. They also assumed that either the nitrogen atom in the triazine ring or the glycosidic oxygen is protonated by the metal, or the anomeric center is activated. DMT-β-glycosides are completely converted to α-glycosides [72, 73].

Ester-Based Donors

Currently, conventional glycosyl donors are receiving more attention than palladium-catalyzed O-glycosylation using glycals as donors [74–78]. This is primarily due to the low reactivity and difficulty of producing palladium/π-allyl intermediates from the electron-rich glycal framework [79–81]. Using a palladium-catalyzed reaction with 3-O-picoloyl glucal, Liu et al. (2015) developed a concise and efficient method to form a range of stereo-selective and efficient O-glycosidic connections [82]. This picoloyl group functions as both a departing and coordinating group in the glycosyl donor. This newly developed unique method is especially useful for regulating the stereochemistry of the anomeric core by either an inner-sphere or an outer-sphere pathway (Figure 24).

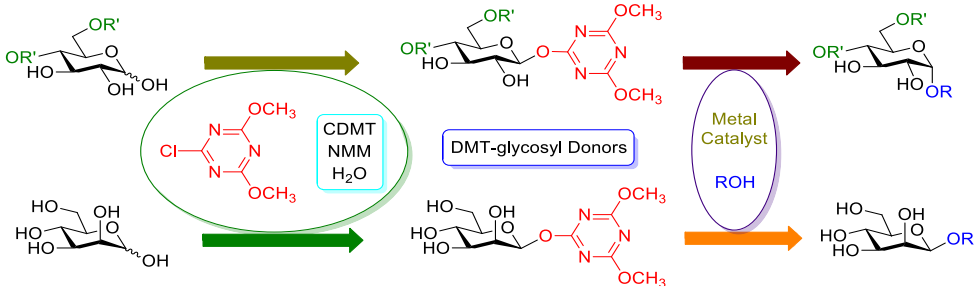

Figure 23. Metal-catalyzed synthesis of alkyl glycosides using DMT-glycosides synthesized from free saccharides.

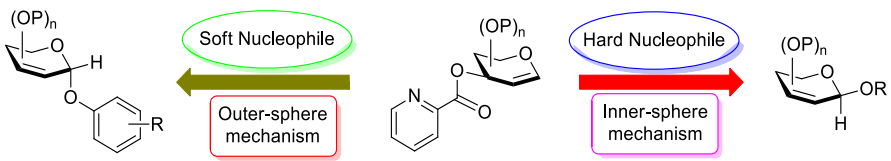

Figure 24. Palladium-catalyzed O-glycosylation stereoselectivity via an inner-sphere outer-sphere pathway.

Softer nucleophiles, such as phenol, produce α products by an outer-sphere process, whereas harder nucleophiles, such as alcohol and sodium phenoxide, use an inner-sphere pathway to produce β products. The nucleophilicity of the acceptors efficiently regulated the stereoselectivity of the products, and various acceptors produced the required products in good yields. It has been noted that this method can produce phenolic O-glycosides of both α-type and β-type.

Other Types of Donors

Numerous responses have been made globally by diverse research teams in an effort to address the obstacles facing the field of carbohydrate research. In recent years, several new categories of departing groups and contributors have emerged. Several of these fall outside of the conventional groups, which are departing groups or glycosyl donors. We have categorized these as other categories of donors in this review. In the past ten years, Fang, Mo, and Boons introduced the first example of this kind of unusual donor in 2012 [83]. They described 1,2-oxathiane ethers as novel glycosyl donors that are stable in acidic, basic, and reductive environments. Consequently, a variety of protecting group manipulations and the installation of selectively removable protective groups, such as levulinoyl (Lev) ester, 2-methyl naphthyl ethers (Nap), fluorenylmethyloxy (Fmoc)-, and allyloxy (Alloc)-carbonates, were made possible, and glycoside products were produced in high yields with superior anomeric control (Figure 25).

Because of their ring structure, this prevents the sulfur atom from taking part in the acid-catalyzed breakdown of the benzylic ether connection; these 1,2-oxathiane ethers remained stable in an acidic environment. 1,2-oxathiane ethers into bicyclic anomeric sulfonium ions by oxidizing them to sulfoxides and then arylating them using 1,3,5-trimethoxybenzene. This new form of building block can be used to prepare physiologically significant branched α-glucans through a latent active glycosylation approach. Glycosyl phosphate triesters and their analogs have proven to be effective glycosyl donors for oligosaccharide synthesis [84–88]. One of their important features is that their reactivity can be tuned by modifying the anomeric phosphate group. Their reactivity can be tuned [89–95]. However, only a few types of glycosyl phosphate derivatives have been reported to date, which are 'orthogonal' to each other, as this is a very challenging task [96–99]. In 2013, Wade et al. used glycosylboranophosphatetriesters as glycosyl donors and tritylcations (Tr^+) as activators [100]. They studied two types of reactions: (1) activation of the boranophosphatetriester with $TrNTf_2$ to react with an alcohol and (2) O-trityl ethers functioned as both glycosyl acceptors and Tr^+ sources (Figure 26).

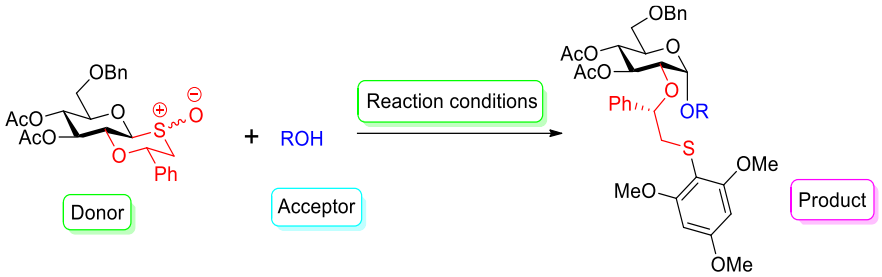

Figure 25. Stereo-selective glycosylation between 1,4-Oxathiane-protected donor and acceptor.

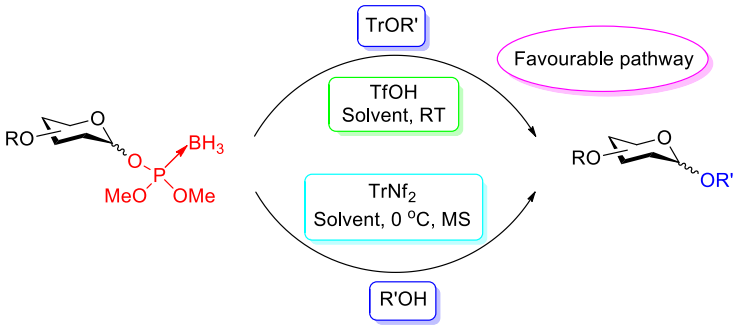

Figure 26. Glycosylations using glycosylboranophophotriesters as glycosyl donors.

The second scenario showed superior results, with the intended O-glycosylation products being produced quickly and separated in moderate to good yields. One benefit of using glycosylboranophosphate testers is their stability and ease of activation to match glycosylphosphite and phosphate testers in the presence of a Lewis acid [101]. Additionally, it has been found that glycosylboranophosphate derivatives undergo exceptional reactions. Such properties of glycosylboranophosphotriesters might be useful as orthogonal glycosyl donors to other types of glycosyl phosphates. In organic synthesis, 2,3-unsaturated glycosides are of great interest because the olefin moiety can be readily functionalized [102–111]. Commercially available glycals can be used to access 2,3-unsaturated α-O-glycosides via a Lewis acid-catalyzed Ferrier rearrangement [112–116]. In Ferrier-type reactions, α-isomers are generally obtained as the major products [117–119]. Therefore, it is necessary to develop other procedures and strategies with remarkable yield and selectivity (particularly β-selectivity). Inspired by taking inspiration from the work of Tunge, Trost, and Stoltzon metal-catalyzed decarboxylative allylation and its synthetic utility in organic chemistry, Liu et al. (2013) reported a palladium-catalyzed decarboxylative allylation from glycal carbonates for the synthesis of various β-O-glycosides, including oligosaccharides (Figure 27) [120–131].

Palladium-catalyzed decarboxylative allylation has been used to synthesize various glycosides, including phenolic O-glycosides, thiophenolic S-glycosides, aliphatic O-glycosides, and disaccharides, in good yields. This makes this method extremely helpful. Liu et al. (2014) presented a follow-up study on stereocontrolled intermolecular O-glycosylation with Pd-catalyzed decarboxylation, drawing on their earlier research [132]. They presented the initial findings of this intermolecular glycosylation of glucal-derived allylic carbonates catalyzed by palladium (Figure 28).

An effective glycosyl donor is a low-reactivity, electron-rich glycal system with a Pd-π-allyl intermediate. They discovered that base loading had a significant influence on the selectivity of the reaction during reaction optimization. Based on experimental findings, they also proposed that the temperature of the reaction and the electronic nature of the substituents on the phenol regulated the stereoselectivity of this reaction. Electron-rich phenol substrates typically offer strong selectivity at higher temperatures, whereas electron-deficient phenol substrates can only offer good selectivity at lower temperatures, such as 60°C. This newly developed method has the advantage of producing glycosides that are resistant to intramolecular glycosylation. When this reaction was attempted using different nucleophiles, the required phenolic O-glycosides, aliphatic O-glycosides, and disaccharides were produced in moderate to good yields with outstanding selectivity.

Thioglycoside-Based Donors

Among the many cutting-edge techniques, the conceptually fascinating intramolecular aglycon delivery is a special way to establish 1,2-cis glycosyl bonds [133–143]. Shen et al. speculated the possibility of using glycosyl aryl boronic acids for group-based aglycon administration based on their research on these molecules (Figure 29) [144].

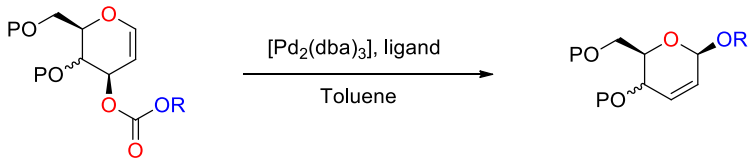

Figure 27. Palladium-catalyzed O-glycosylation using glycal carbonates as donor.

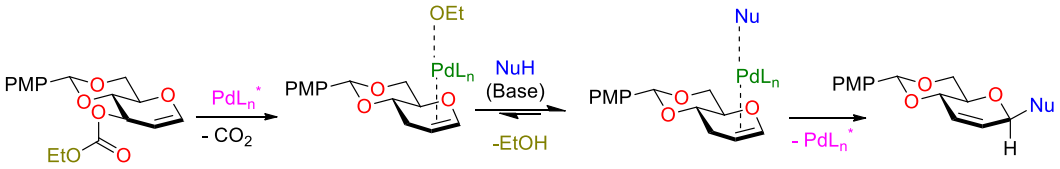

Figure 28. Stereocontrolled O-glycosylation with palladium-catalyzed decarboxylative allylation.

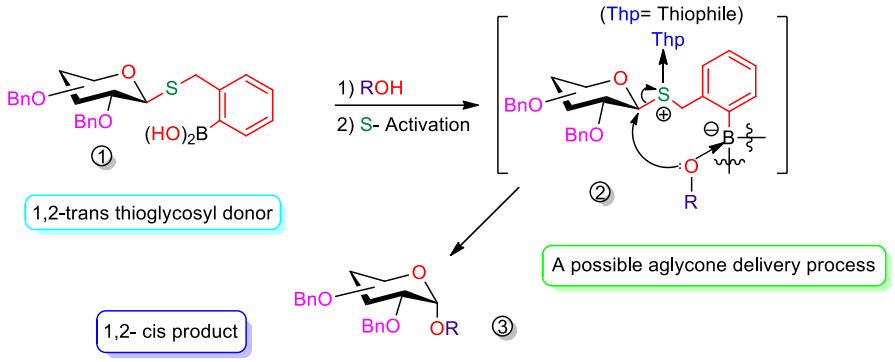

Figure 29. The design of a boronic acid-directed glycosylation reaction.

In order to create stereoselectively pure 1,2-cis-O-glycosides (3) in moderate yields, 1,2-trans-1-dihydroxyboryl benzyl S-glycoside (1) was easily obtainable as a glycosyl donor that may be activated by NBS.[77]By manipulating widely available glycosyl bromides through S-glycosylation, lithiation, and protection, 1-dihydroxyboryl phenyl and benzyl beta-S-glucosides and 1-dihydroxyboryl benzyl beta-S-galactosides were effectively produced in good yields. The boronic acid moiety was found to be essential for appropriate anomeric ratios and product synthesis during the glycosylation process. However, there is still room to increase the yield of glycosylation and broaden the range of substrates available for stereo-selective glycosylation [145].

CONCLUSION

In this insightful review, we meticulously detailed the remarkable strides achieved in the field of O-glycosylation synthesis techniques and have summarized the latest trends in the advancement of stereo-selective glycosylation in the last decade using different types of donors. This review serves as a beacon of clarity and focuses on elucidating the intricate reaction mechanisms that underpin the fascinating realm of O-glycosylation. It is our earnest aspiration that this succinct, yet potent exploration will serve as a catalyst for scientific minds to venture forward and engineer innovative methodologies that push the boundaries of O-glycosylation synthesis, ultimately shaping the landscape of organic chemistry through novel and creative approaches.

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