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Advances in glycoside and oligosaccharide synthesis

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The structural complexity of glycans poses a serious challenge in the chemical synthesis of glycosides, oligosaccharides and glycoconjugates. Glycan complexity, determined by composition, connectivity, and configuration far exceeds what nature achieves with nucleic acids and proteins. Consequently, glycoside synthesis ranks among the most complex tasks in organic synthesis, despite involving only a simple type of bond-forming reaction. Here, we introduce the fundamental principles of glycoside bond formation and summarize recent advances in glycoside bond formation and oligosaccharide synthesis.

1. Introduction

Glycans are the most abundant biomolecules in nature and constitute the majority of earth's biomass. The chemical bonds that connect glycans and link them to other biomolecules are called glycosidic bonds. Over the past century, the biological importance of glycans and glycoconjugates is becoming increasingly clear, as the field of glycobiology continues to develop.[1–3] The complexity of glycans, has rendered insights into the structure and function of these biomolecules more difficult to gain than for proteins and nucleic acids. Consequently, glycans have been referred to as the 'dark matter of the biological universe'.[3] The lack of template-encoded expression, homogeneous biological samples and access to defined standards have made it difficult to establish structure–function relationship on the molecular level (Fig. 1).[4–11]

Pure, well-defined glycans are essential tools to advance the glycosciences as they enable molecular investigations into the interactions between glycans and proteins, such as antibodies[11,12] and carbohydrate-active enzymes (CAZy);[13,14] facilitate the creation of well-defined microarrays;[10,15,16] allow for the examination of glycan secondary structure;[17–20] and contribute to the development of vaccines[21–23] and chemical biology tools.[24,25] Synthetic glycans can play many other roles in environmental, material and health research.

Proteins and nucleic acids can be obtained in homogeneous form using biological methods, such as recombinant expression

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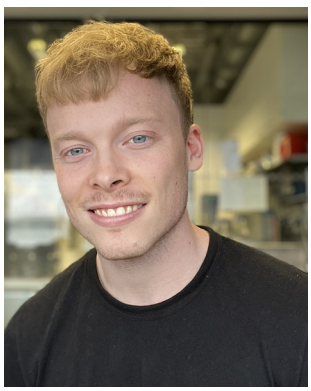

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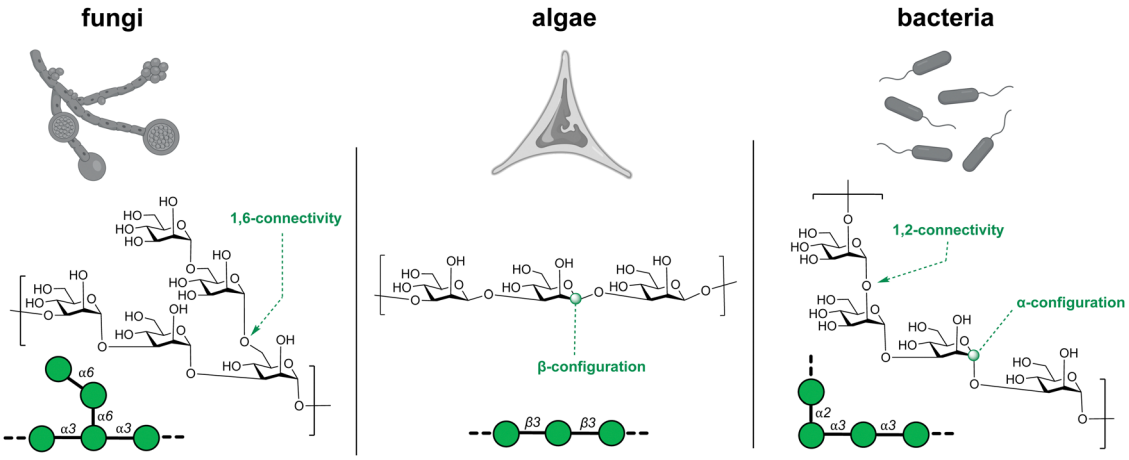


Fig. 1 The glycan structural diversity barrier. Glycans with identical monosaccharide compositions but different connectivity and configurations perform diverse functions in nature.

or the polymerase chain reaction (PCR). On the other hand, glycans produced in biological systems are inherently heterogeneous and chemical synthesis is the primary method for obtaining homogeneous glycans. Enzyme-based approaches exist and can be used in combination with chemical methods to produce well-defined glycans.[26–34] Enzymatic syntheses are limited by access to well-defined enzymes, such that most enzymatic syntheses target mammalian glycans.[35–44] Given the importance of chemical synthesis to procure oligosaccharides, this review will focus on the chemical methods for glycosidic bond formation.

The molecular complexity of glycans has been a challenge to generations of chemists. Glycan complexity can be described by: (i) composition, (ii) connectivity and (iii) configuration (Fig. 1).

(i) The composition of monosaccharides is frequently that of stereoisomers, *e.g.*, glucose and mannose. They differ in the orientation of a single hydroxyl group (epimer), which complicates structural analysis and potential sequencing efforts. An important consequence of this structural similarity is that many monosaccharides are indistinguishable by classical mass spectrometry.[45–51]

(ii) Connectivity describes how monosaccharides are connected to each other. Each monosaccharide contains multiple hydroxyl groups, each of which can serve as a point of attachment to others glycosides, including branches, as well as other non-glycosidic groups such as sulfates or acetates. In the context of chemical synthesis, this means that chemists often use protecting groups to assemble complex glycosides and oligosaccharides. Protecting group manipulations frequently represent the majority of the chemical steps.

(iii) Configuration describes the information embedded in the glycosidic linkage that is essential for the function of a given glycan. For instance, cellulose and amylose are both polymers connected polymers by 1–4 glucose linkages, yet they serve completely different functions in nature. Cellulose is β-linked (1,2-*trans*) and provides strength to plant cell walls,[52] while amylose is α-linked (1,2-*cis*) and functions as an energy storage molecule in plants.[53] As chemists connect glycans, they must control the configuration of this stereogenic centre (Fig. 2).

Collectively, composition, connectivity and configuration combinatorially multiply the molecular diversity of glycans by orders of magnitude beyond what nature achieves with nucleic

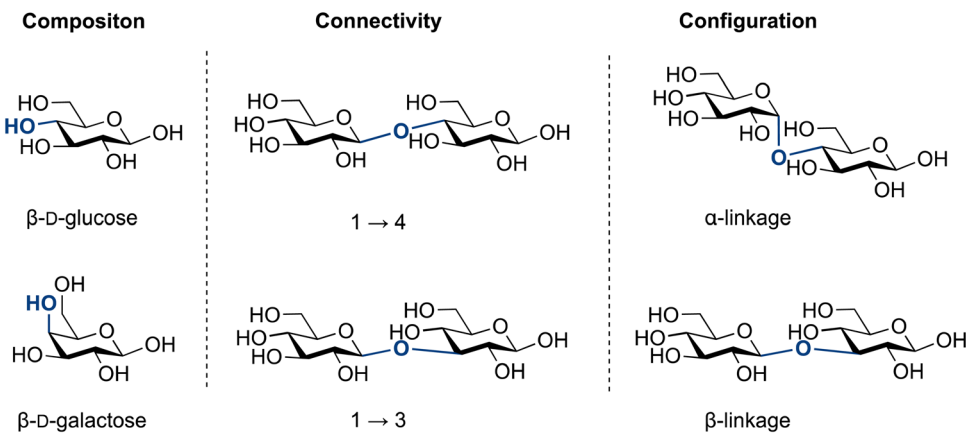


Fig. 2 Levels of complexity in glycans: composition, connectivity and configuration.

acids and proteins. This complexity renders the synthesis of glycosides as one the major challenges in organic chemistry.[54–60]

Below, the following topics will be discussed: (i) general mechanistic aspects of the glycosylation reaction, (ii) variables in the glycosylation reaction, (iii) robust methods for the synthesis of glycosides, and (iv) recent examples highlighting advances in the synthesis of complex glycosides and oligosaccharides.

2. Glycan composition

Glycans possess diverse chemical architectures, exhibiting molecular complexity and diversity beyond other biomolecules.[61] Particularly, microbial, plant and algal glycans, utilize many different monosaccharides as building blocks.[62–64] Bacteria employ hundreds of monosaccharides including heptose, 3-deoxy-D-manno-2-octulosonic acid (Kdo), legionaminic acid, bacillosamine and fucoseamine (Fig. 3). Currently, these monosaccharide building blocks are not commercially available such as D-glucose or D-mannose. Therefore, chemical and enzymatic processes are being developed to provide better access to these monosaccharides.[65–73]

The synthesis of 'rare' sugars can be accomplished *via* chemical and enzymatic approaches. Chemical methods encompass epimerization,[74] deoxygenation,[75] and chain elongation,[76] which have been employed in the chemical synthesis of a variety of glycans. These include *N*-acetylgalactosamine,[77,78] 6-deoxy-L-gulose,[79] di-*N*-acetyl D-bacillosamine,[80–82] *N*-acetyl L-pneumosamine,[83] Kdo,[72,76,84] 2-keto-3-deoxy-D-*glycero*-D-galactononulosonic acid (Kdn),[85–87] legionaminic acid[88,89] and L-fucosamine (Fig. 3).[80,90]

Epimerisation of biomass-derived carbohydrates can produce rare sugar isomers using either chemical or enzymatic methods.[91,92] Photochemical conditions to site-selectively epimerize a variety of minimally protected and non-protected carbohydrates (Scheme 1) employed catalytic quantities of 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4-CzIPN), quinuclidine, adamantane thiol and tetrabutylammonium *p*-chlorobenzoate in acetonitrile and DMSO at room temperature under blue light irradiation. The kinetic products of epimerization are formed through two sequential steps: (i) hydrogen-atom abstraction and (ii) hydrogen-atom donation. Thereby, several valuable monosaccharide building blocks were prepared on gram scale as demonstrated for the conversion of glucose to methy α-D-allopyranoside (Scheme 1).

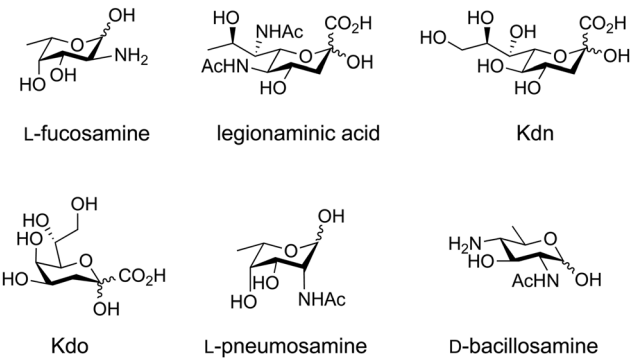


Fig. 3 Examples of rare monosaccharides. Abbreviations: 2-keto-3-deoxy-D-*glycero*-D-galacto-nononic acid (Kdn) and 3-deoxy-D-manno-2-octulosonic acid (Kdo).

Improved synthetic routes to rare monosaccharides provided sufficient material to establish their inherent chemical properties as glycosylating agents and nucleophiles.[71,88] These insights were applied in the synthesis of complex glycosides that incorporate these rare monosaccharides to study their structure and function.[66,93–96]

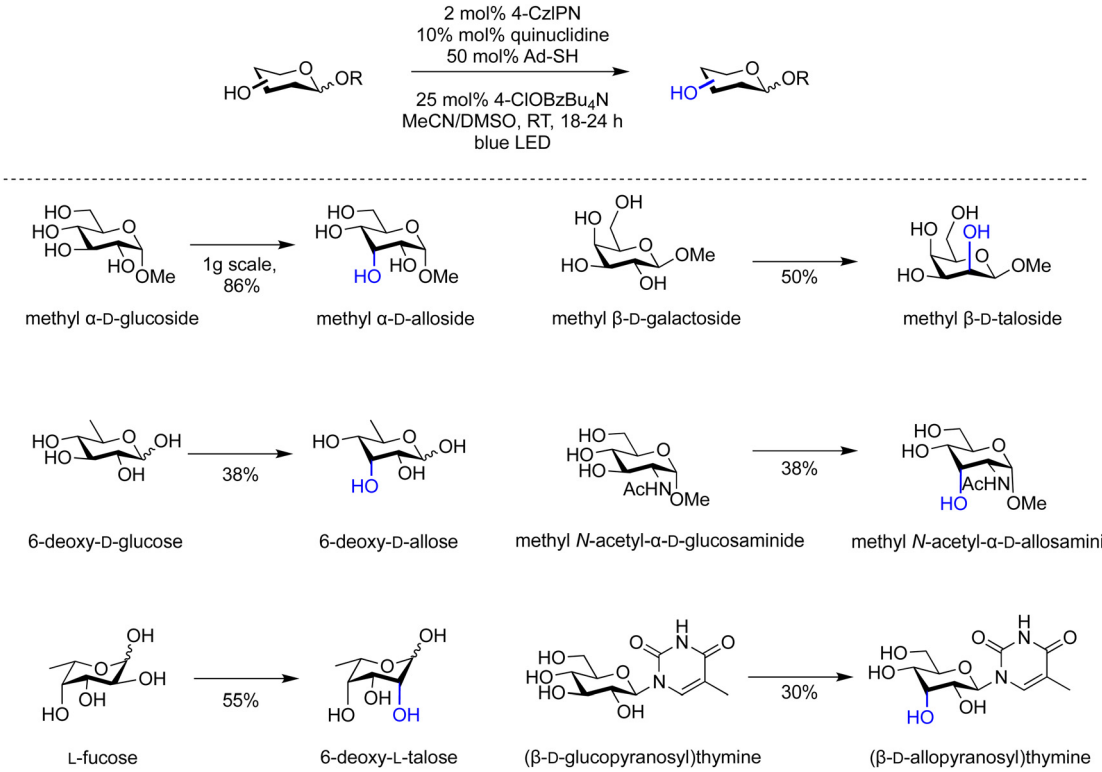
3. Glycan connectivity

A challenge in glycan synthesis is the necessity to selectively modify one specific hydroxyl group at a time in the presence of many others. Therefore, chemical glycan synthesis demands meticulous planning to achieve the desired protecting group pattern on both mono- and oligosaccharides. These protecting groups serve to 'mask' the inherent reactivity of a hydroxyl group. These chemical modifications enable the precise assembly of molecules in a controlled manner.[58,97] Ideally, hydroxyl-protecting groups are selectively added and removed from a glycan to manipulate the exposed hydroxyl group. Particularly valuable are protecting groups and methods that permit the selective modification of carbohydrate polyols such as benzylidene acetals that can be regioselectively opened under reductive conditions.[98–102] Some one-pot protocols allow for the preparation of advanced synthetic intermediates.[103–105] Dibutyltin oxide and diarylborinic acid catalysts enable regioselective acylation or alkylation in the presence of multiple hydroxyl groups.[106–114] In a typical synthetic scheme, the selectively exposed hydroxyl group serves as a nucleophile for the regioselective addition of another saccharide unit.[59] Glycosides with amine groups are found in animals, plants and microbes[115–119] and a host of nitrogen protecting groups have been developed (Fig. 4).[120] Selecting the best nitrogen protecting group for a particular target involves often trial and error experimentation (see Section 6.4, Scheme 3).[115,117,121–124]

Similarly, the choice of hydroxyl protecting groups impacts the synthesis and the order of manipulation is essential for a successful synthesis.[125–130] Permanent protecting groups,[131,132] such as benzyl ethers (Fig. 4) stay in place throughout the synthesis and are removed after assembling the target structure. Temporary protecting groups,[97,132,133] such as chloroacetyl esters,[134,135] are selectively removed during the synthesis reveal the desired hydroxyl group for selective functionalization (Fig. 4).

4. Glycoside configuration

A glycosidic linkage is formed through the activation of a glycosylating agent (donor) to create a reactive electrophilic species that couples with the nucleophile (glycosyl acceptor) (Fig. 5). This coupling reaction results in the formation of α- or β-stereoisomers. The stereospecific formation of glycosidic bonds is a major synthetic challenge in glycan synthesis. A variety of methods are available to generate stereospecific glycosidic linkages whereby the yield and the stereochemical



Scheme 1 Site-selective epimerisation of glycans.[91]

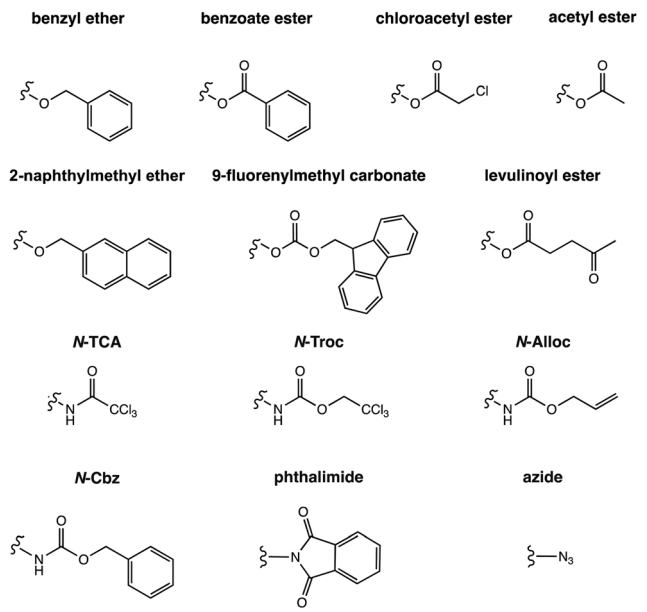


Fig. 4 Examples of common protecting groups masking hydroxyl and nitrogen atoms.

outcome of these reactions depend on steric and electronic effects of both glycosylating agent and nucleophile.[136–138]

1,2-*trans* stereochemistry at the anomeric centre can be ensured by the use of participating protecting groups, such as an ester, on the 2-hydroxyl group. Neighbouring protecting group participation,[139–142] in the glycosylation reaction means that ester protecting groups form a cyclic oxonium ion intermediate, that shields one face of the glycosylating agent intermediate from reacting with the nucleophile that approaches from the opposite face and results in the formation of the 1,2-*trans* glycosidic linkage (Section 6.5, Fig. 9a).

The construction of 1,2-*cis* glycosides is more difficult[126,143–148] as a general method has yet to be established. Often mixtures of anomers are formed and separated by column chromatography. Recent developments in this area are discussed in Section 6.

5. Glycosylation reaction mechanism

An improved understanding of the glycosylation reaction mechanism informs the design and execution of more efficient protocols for the selective synthesis of glycosides. Much effort has been directed towards understanding this complex chemical event.[149–152]

Different reaction pathways, on a spectrum from S_N2 to S_N1,[153,154] are possible for glycoside formation, resulting in distinct diastereomeric products (α/β) (Fig. 5). The first step involves activating a glycosylating agent, which leads to the formation of an array of electrophilic intermediates, including contact ion-pairs that contain the activator-derived counterion (X) (Fig. 5).

In the absence of a participating group on C2, the reaction mechanism is more complex. Covalent reactive intermediates and the reactive oxocarbenium ion species are responsible for product formation. Low-temperature NMR techniques have

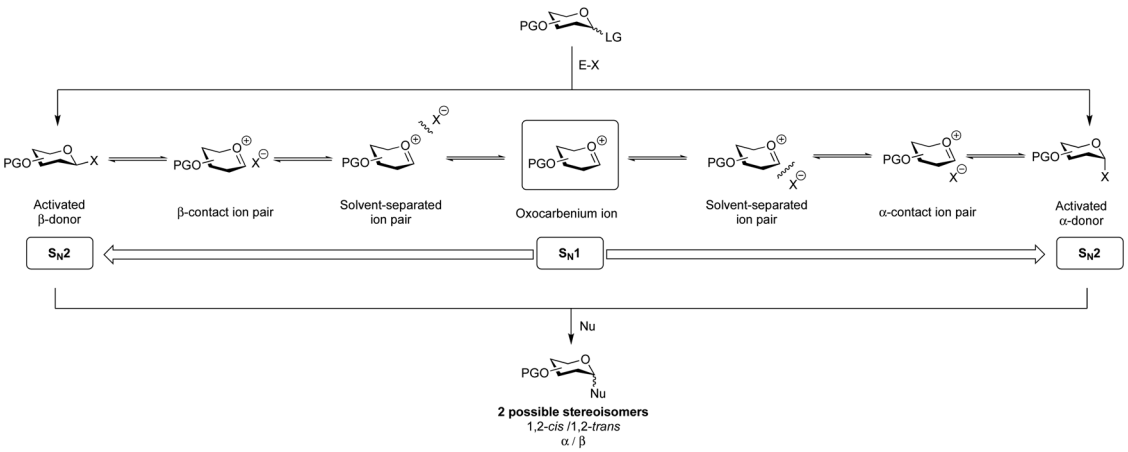


Fig. 5 Possible reaction mechanisms of glycosylation reactions. Glycosylation reactions can take place on a spectrum ranging from S_N1 to S_N2 mechanisms. PG, protecting group; E-X, promoter system; and Nu, nucleophile.

detected covalent intermediates on the S_N2 end of the reaction mechanism spectrum, including reactive species such as glycosyl triflates and imidates.[151,155] Subsequent substitution of these reactive species with nucleophiles defines the S_N2 side of the reaction mechanism spectrum.

In contrast, the S_N1 side of the spectrum is less well understood and is a focus of current research. The substitution pattern on the glycosylating agent impacts the stability and reactivity of the various reactive intermediates. Efforts to establish structure–reactivity–stereoselectivity relationships of these S_N1 species have been reported.[154]

6. Variables in glycoside bond formation

The stability and reactivity of glycosylating agents, and the factors that control their diastereoselective substitution with nucleophiles, are affected by a multitude of variables (Fig. 6). Predicting the outcome of a particular glycosylation reaction in a complex oligosaccharide is difficult. The order of assembly, protecting group patterns, temperatures and solvents all contribute the success of glycoside formation.[138,149,156] This inherent complexity often requires experimental trial and error to identify a viable synthetic route.

For less complex substrates the following levels of difficulty are broadly accepted. The formation of α-manno-type structures is favoured by the anomeric effect, and neighbouring group participation can be enlisted (Fig. 7).[157–159] β-Glucosides are readily accessible when neighbouring group participation is possible. However, the formation of α-glucosides structures depends strongly on thermodynamic control or S_N2-type reactions without neighbouring group participation. The synthesis of β-mannosides does not benefit from either the thermodynamic anomeric effect or neighbouring group participation but relies strictly dependent on an S_N2-type reaction, which starts with the readily accessible α-mannosylating agents. β-Mannosides pose one of the greatest challenges in glycoside to preparation.[160]

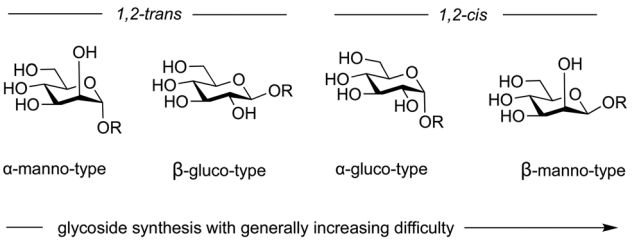


Fig. 7 Scale of difficulty in glycoside synthesis.

6.1. Influence of the promoter on activation of glycosylating agent

The choice of promoter significantly influences the outcome of glycosylation reactions. Often, iterative testing is required to

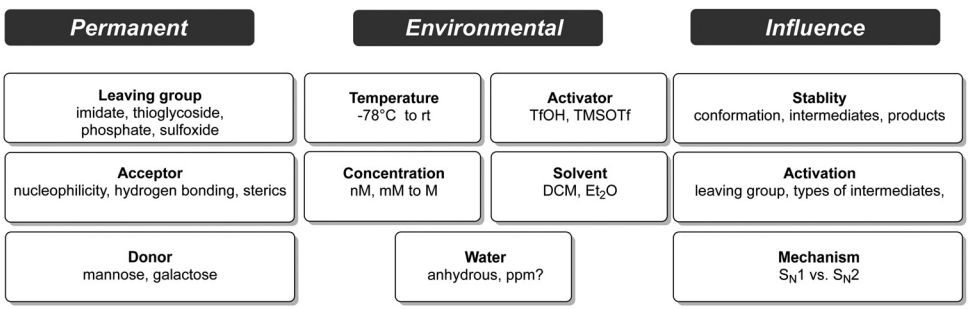


Fig. 6 Variables in glycoside synthesis.

identify the most suitable promoter system for a specific glycosylation as different types of anomeric leaving groups are explored. The possibility to interconvert different types of glycosylating agents is important.

Thioglycosides are very stable, can be converted into most commonly used glycosylating agents and are stable to many protecting group manipulations (Fig. 8).[161]

6.2. Solvent

The choice of solvent has a major impact on glycosylation reactions, as it affects the abundance of the various covalent and ion pair species present during the reaction. Solvents with poor electron-donating properties, such as dichloromethane and toluene, are commonly employed in glycoside synthesis because they promote S_N2-type reactions. Solvents capable of donating electron lone pairs, such as ethers (*e.g.* diethyl ether, dioxane) and acetonitrile, lead to distinct changes in the reaction course due to their varying roles in stabilizing cationic reaction intermediates (Table 1).

Ethereal solvents have a tendency to drive glycosylations in an α-selective fashion, while nitrile solvents give higher ratios of β-products.[167–170] These results are rationalized as follows: ethereal solvents, such as diethyl ether or dioxane lead to higher levels of equatorial intermediates,[144,167,169–176] resulting in an S_N2 type mechanism giving rise to higher levels of α-product. Solvents with higher dielectric constants often lead to lower diastereocontrol in glycoside synthesis. These higher polarity solvents are thought to better stabilize ion pairs and individual ions to a greater extent, thus promoting dissociative mechanisms and the resulting lower stereoselectivity (Fig. 5).

Solvent additives can alter the course and outcome of glycosylations. DMF as solvent or co-solvent facilitates the formation of 1,2-*cis* glycosides,[155] similar to the selectivity of halide ion catalysed glycosylation reactions.[177,178] Glycosylations in the presence of DMF produce the axial glycosyl imidate, as observed by NMR. The reaction may proceed *via* a minor but more reactive equatorial imidate, leading to high selectivity (Scheme 2).[155]

Glycosylations in acetonitrile produce the axial nitrilium cation *in situ*, that in turn results in higher stereoselectivity in the synthesis of equatorially substituted α-sialosides or β-glucosides.[162] Thereby, 1,2-*trans* glucosides are formed even with glycosylating agents bearing a non-participating protecting group.

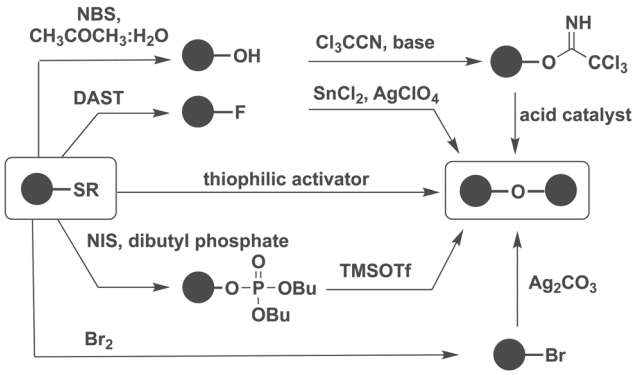


Fig. 8 Conversion of thioglycosides into other types of glycosylating agents.

Table 1 Stereodirecting solvent effects

Solvent	Influence
MeCN	β-Directing[162–164]
Ether	α-Directing[165,166]
Dioxane	α-Directing[166]
DMF	α-Directing[155]

6.3. Temperature

Many glycosylating agents are very temperature sensitive and reaction temperatures at or above room temperature are uncommon. However, exceptions do exist *e.g.*, synthesis of *Shigella flexneri* oligosaccharides, (Section 7.4, Scheme 12), where temperatures of 75 °C were required for effective glycosylations.

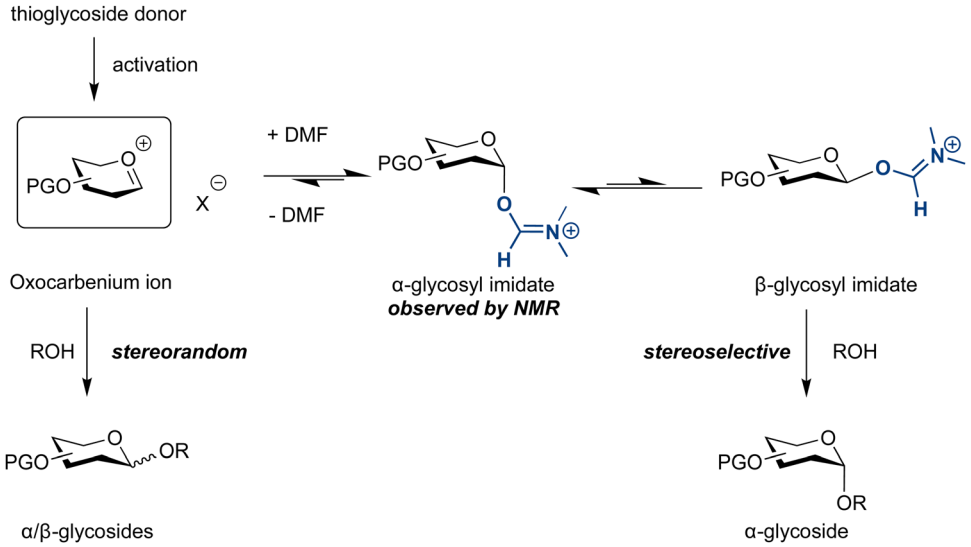
In addition, low reaction temperatures facilitate stereoelectronic control *via* S_N2-type reactions. Systematic studies of glycosylations reactions in flow reactors have identified temperature as the strongest influence on α/β selectivity.[149] However, solubility and reactivity are significantly affected by the reaction temperature selection. Classically, solution-phase glycosylations are initiated at low temperature, to lower the chance of unwanted side-reactions and allowed to warm slowly to ambient temperatures, in hopes of coupling with minimal side-product formation.

A more systematic temperature selection for glycosylations aims at quantifying the differing thermal stability of thioglycosides to guide temperature selection. To date, this approach does not account for differing acceptor nucleophilicity[150] but this shortcoming is being addressed right now. This approach is now being united with the relative reactivity values (RRV) to create a path forward towards models for chemists to more effectively synthesize glycosides.[179–183]

Quantifying the reactivity of different thioglycosides will help to rationalise chemoselective one-pot protocols varying the of thioglycoside aglycon with different electron withdrawing groups.[184–188] Thioglycoside aglycon modifications enable reactivity tuning of building block reactivity without the need to alter protecting group patterns.[184] An orthogonal approach is discussed in Section 6.5.[189,190] The utility of quantifying donor temperature stability was demonstrated in the context of an automated assembly of a β-1–4 glucan tetrasaccharide, where the crude HPLC trace improved while the amount of building block used was reduced.[150]

6.4. Influence of protecting groups on the nucleophile

The reactivity of the nucleophile can vary widely due to a combination of steric, stereoelectronic and inductive effects.[137,138,190–197] The nature of the glycosyl acceptor can influence the outcome of a glycosylation reaction, both in terms of isolated yield and stereoselectivity.[198] When all groups are equatorial, as is the case of a glucose acceptor, in the $^1C_4$-conformation, the following reactivity order is observed: 6-OH > 3-OH > 2-OH > 4-OH. These considerations can be used to estimate and tune the reactivity of a given carbohydrate alcohol: (i) axial alcohols are less reactive than equatorial alcohols. This observation has been applied in regioselective saccharide syntheses with partially *O*-protected



Scheme 2 Proposed mechanism of the DMF-modulated glycosylation.[155]

glycosyl acceptors (Scheme 14).[16,115,199] (ii) Glycosyl acceptors with a neighbouring alcohol in an equatorial position, are more reactive than acceptors where one of the adjoining alcohol is axial, *e.g.* the 3-OH of mannose *vs.* glucose acceptor (iii) ester protecting (electron withdrawing group) groups beside the acceptor decrease the reactivity of the acceptor in comparison to electron donating groups, *e.g.* benzyl ethers (iv) the nucleophilicity of the acceptor affects glycosylation stereoselectivity, with reactive nucleophiles being β-selective and weaker nucleophiles having higher α-selectivity.[136,200–202] Robust structure–reactivity relationships for nucleophiles are currently being established,[198,203] in order to prevent poor stereoselectivities and yields as a result of a lack of insight into acceptor reactivity.[204–217]

The C4 hydroxyl of glucosamine is well-studied and generally considered to be a poor nucleophile.[218–220] Different nitrogen protecting groups and the bulk of neighbouring hydroxyl protecting groups have been shown to affect the 4-OH acceptor nucleophilicity. It is hypothesised that intermolecular hydrogen-bonding networks involving the *N*-acetyl group play a key role. The *N*-acetyl-2*N*,3*O*-oxazolidinone-protected system renders the alcohol more reactive as it apparently reduces the steric hindrance around the C4 hydroxyl group.[123,221] This linkage posed a challenge in the automated glycan assembly (AGA) of chitin and chitosan oligosaccharides (Scheme 3).[222] Glycosyl phosphates were found to be more effective than thioglycosides with final yields of 34% *vs.* 8%, respectively. The choice of nitrogen protecting group influences the synthesis, with incorporation of any *N*-benzyloxycarbonyl (Cbz) bearing glycosides anywhere in the growing oligosaccharide chain decreasing the overall yield when compared to oligosaccharides containing exclusively *N*-trichloroacetyl protecting groups (Scheme 3).

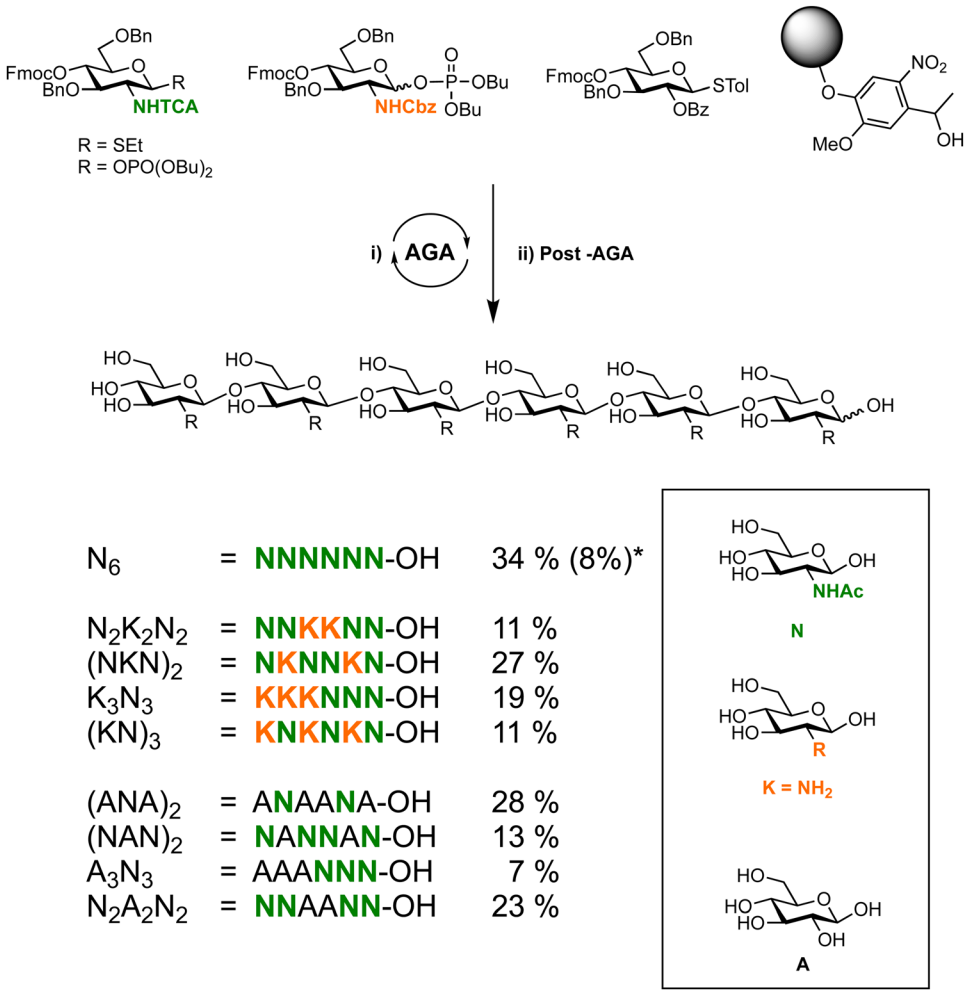
The role of the protecting group pattern on acceptor nucleophilicity can be observed in the synthesis of the trisaccharide repeating unit of *Pseudomonas aeruginosa* O11 antigen (Scheme 4).[126] Coupling disaccharide acceptors revealed that results depended upon the protecting group on the C3 hydroxyl group of the fucosamine nucleophile. Acetate, allyl and 2-naphthylmethyl ether protecting groups were compared with the 2-naphthylmethyl ether protecting group performing best. Lowering the temperature from 0 °C (25% yield) and to −60 °C to −10 °C drastically improved the yield to 84% (Scheme 4).

The optimization of glycosylation reactions typically focuses on the glycosylating agent and external factors such as solvent and reaction temperature. However, there is growing recognition that fine-tuning the reactivity of the nucleophile can improve both yield and stereoselectivity in glycosylations. Unlike glycosylating agents, where relative reactivity values have been assigned in a number of cases,[224] glycosyl acceptors remain less thoroughly understood. Establishing a robust numerical method to compare the reactivity of various acceptors will enable synthetic chemists to make informed decisions and develop of more efficient and selective processes for synthesizing complex glycans.[225]

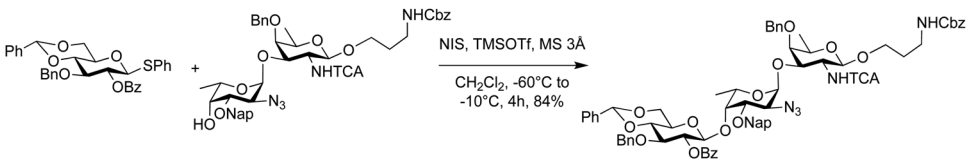
6.5. Influence of protecting groups on the glycosylating agent

Protecting groups influence the reactivity of the glycosylating agent and the stereochemical outcome of glycosylations.[57] Inductively donating protecting groups, such as benzyl ethers, stabilize electron-deficient transition states of S_N2-type reactions and S_N1-type reaction intermediates. These protecting groups accelerate glycosylation reactions, as they enhance the overall reactivity of the glycosyl donor. Electron-withdrawing protecting groups, such as benzoyl esters, have the opposite effect as they reduce the reactivity of the glycosyl donor and make glycosylation reactions slower and less efficient.[226] By judiciously selecting the appropriate protecting groups, chemists can finely control the reactivity and selectivity of glycosylation reactions, thus influencing the formation of specific glycosidic linkages with the desired stereochemistry.

Electronic effects of protecting groups on the reactivity of glycosylating agents have been labelled as 'arming' and 'disarming', as glycosylating agents bearing benzyl groups on pentenyl



Scheme 3 Automated glycan assembly of a library of chitin oligosaccharides.[222] *Yield obtained when synthesis was complete using BB1a.



Scheme 4 Synthesis of the trisaccharide repeating unit of *Pseudomonas aeruginosa* O11 antigen.[223]

glycosides can be selectively activated in the presence of 'disarmed' ones.[226] Subsequent efforts to quantify this effect enabled one-pot syntheses of oligosaccharides.[227–231] The systematic quantification of donor reactivity established an extensive series of relative reactivity values (RRVs) for thioglycosides as the foundation for the 'programmable' one-pot synthesis of complex oligosaccharides. The sequential addition and activation of mono-hydroxylated donors in a reaction flask resulted in a growing oligomeric chain.[179,181,182,232]

Controlling stereoselectivity in glycosylations remains a major challenge in the synthesis of complex oligosaccharides, especially for 1,2-*cis* linkages. While no general solution for the construction of 1,2-*cis* linkages exists, remote participation by distal acyl groups has shown promise in improving stereoselectivity (Fig. 9b).[144,233–235] However, the role and strength of this effect, primarily due to the transient nature of the dioxolenium ion intermediate, is still under discussion.[234,236–238] An in-depth study of distal acyl groups using cryogenic infrared spectroscopy, DFT computations, and a series of systematic glycosylations, has revealed that certain ester groups can play a decisive role in shaping the stereochemical outcome of glycosylations.[234,237,238] For example, remote participation of 3-OH ester groups on mannosides is stronger than 3-OH ester groups on galactosides, while remote participation of 3-OH ester groups in glucosyl and galactosyl donors provide less assistance in guiding the stereochemical course of glycosylations. Reports on the role of 6-OH ester groups are

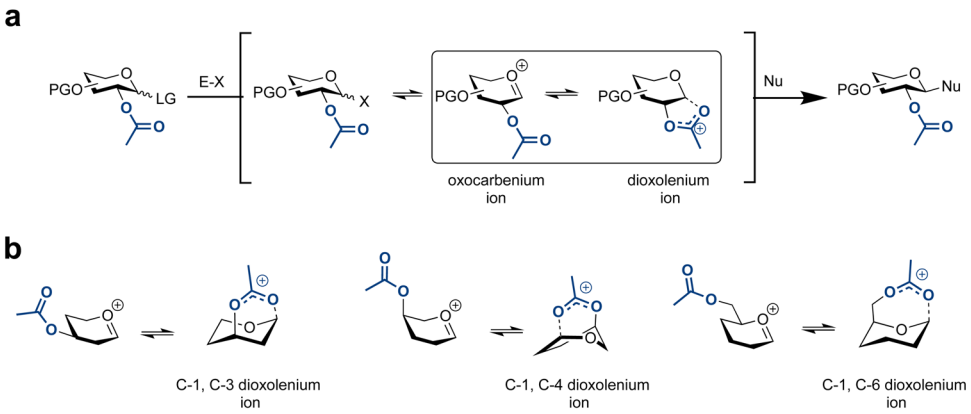


Fig. 9 (a) Neighbouring protecting group participation. (b) Long-range participation. E-X promoter system, Nu nucleophile.

mixed.[144,237,238] The remote participation of 4-OH ester groups in galactose can lead to covalent bonds between the carbonyl oxygen and the anomeric carbon, to promote α-selective galactosylations.[234,238] Although the strength of remote participation requires further clarification for different types of glycosides, it offers a viable option for improving stereocontrol in glycoside synthesis.

Cyclic protecting groups such as 4,6-*O*-benzylidene can significantly impact the stereochemical outcome of glycosylations as shown most prominently for the synthesis of challenging β-mannosidic linkages.[239,240] Initially, this methodology relied on a pre-activation promoter system involving sulfoxides and thioglycosides, resulting in superior β-selectivity compared to glycosylating agents lacking this protecting group. The 4,6-*O*-benzylidene protecting group effect also applies to other glycosylating agents such as trichloroacetimidates and phosphates.[241,242] Anomeric tethers influence the stereochemical outcome of glycosylations as first applied to the β-selective synthesis of fructofuranosides and the first stereospecific synthesis of sucrose.[243] The selectivity was attributed to the tetraisopropyldisiloxane tethering group blocking the α-face, ensuring that the acceptor approaches only from the β-face. The stereoselective synthesis of β-xylulofuranoses used a siloxane tether[244] on a thioglycoside to yield the desired β-linked xylofuranose. Similarly, a macrocyclic anomeric tether for α-sialylation, relied on the tethering group blocking the β-face for the nucleophile to approach from the α-face.[245] The cyclic di-*tert*-butylsilylene (DTBS) protecting group can improve selectivity[246] in particular for α-selective galactosylation. This reaction remains α-selective even in the presence of a C-2 participating benzoate ester protecting group (Scheme 5).[247,248]

Protecting group control of glycosylating agents was enlisted in the synthesis of the capsular polysaccharide repeating unit of *Campylobacter jejuni* 81–176 to determine the absolute configuration of its *O*-methyl phosphoramidate motif.[249] This synthesis required addressing several challenges, including the stereoselective installation of the α-galactoside, the preparation of the 6-deoxyheptose building block with correct stereochemistry, and the introduction of the *O*-methyl phosphoramidate motif. A key in the construction was the use of a glycosyl trichloroacetimidate, that was prepared from the corresponding thioglycoside (Scheme 5). This glycosyl imidate was coupled with the C3 hydroxyl group of galactose using trimethylsilyltrifluoromethanesulfonate (TMSOTf) as the catalyst, yielding the desired β-linked disaccharide in 85% yield. The galactose portion of this disaccharide bore a di-*tert*-butylsilyl acetal on O-4 and O-6, enabling α-selective galactosylation, even in the presence of a neighbouring participating group (Scheme 5).[247,248] This strategy was used to stereoselectively couple a disaccharide with the 6-deoxy-altro-heptoside acceptor by activating the thioglycoside with *N*-iodosuccimide and triflic acid in 88% yield.

7. Commonly used glycosylating agents

The pursuit of developing broadly applicable, stereocontrolled glycosylation reactions remains an ongoing challenge in chemical synthesis due to the numerous variables involved in the process, including anomeric leaving groups, protecting groups, promoters, acceptor nucleophilicity and solvents. Much effort has focused on the anomeric leaving group, leading to the development of a range of glycosylating agents.[250–256] Here, six major approaches for glycoside synthesis are discussed:

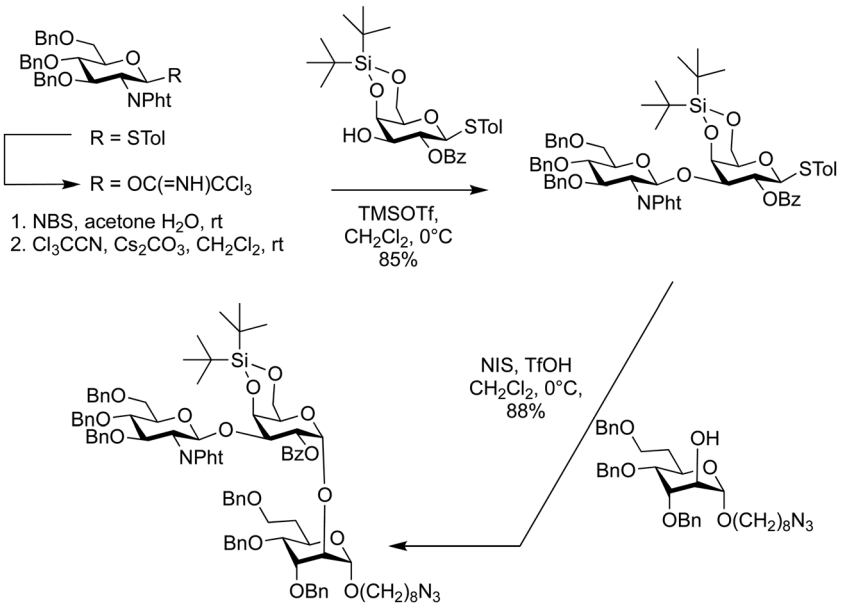
(1) the Fischer–Helferich method; (2) anomeric halides; (3) thioglycosides; (4) glycosyl imidates and (5) glycosyl phosphates; and (6) organic and transition-metal catalysis.

Each of these methods possesses its own advantages and limitations. The synthesis of oligosaccharides often requires a pragmatic approach that combines multiple methods to achieve the desired outcomes effectively. Despite the challenges, continuous research and innovation are paving the way for advancements in glycoside synthesis, thereby expanding the possibilities in chemical synthesis.

7.1. The Fischer–Helferich method

In the classical Fischer–Helferich method, *O*-glycosides are formed *via* an acid-catalyzed reaction between hemiacetals and alcohols (Fig. 10).[257] This reaction is reversible and not applicable to the synthesis of oligosaccharides.[54]

Diastereocontrol at the anomeric position is based on thermodynamic energy differences between the corresponding



Scheme 5 Combination of conformational restriction and glycosyl imidates for the synthesis of *Campylobacter jejuni* capsular polysaccharide repeating unit.[249]

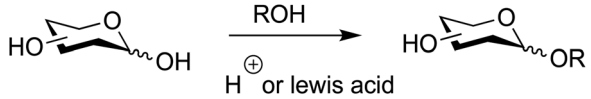


Fig. 10 Fischer–Helferich mediated synthesis of glycosides.

α- and β-anomers. The axial position for the anomeric OR group is disfavoured by 1,3-diaxial interactions and favoured by the anomeric effect (stereoelectronic interactions between the ring oxygen and the anomeric carbon–oxygen bond).[176] These two opposing effects often have similar magnitudes, to yield mixtures of products that, due to a slight dominance of the anomeric effect, contain more of the α-anomer. The α : β ratios vary with individual sugars and the reaction conditions.

The method produces a mixture of α- and β-furanosides and pyranosides, through a competing equilibrium that likely proceeds *via* open-chain intermediates, α,β anomerizations, and oxocarbenium ions. Furanosides are first formed and the equilibrium subsequently shifts towards pyranosides (Fig. 11).[258,259] Chromatography is often required to isolate pure anomers from such reaction mixtures.[55]

Combining this simple acid-catalysed glycoside synthesis with additional acetal formation in the presence of a ketone such as acetone can allow access advanced synthetic intermediates

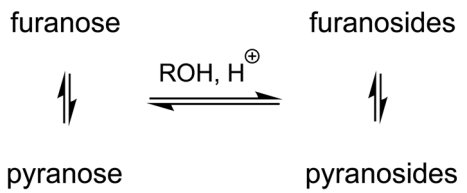
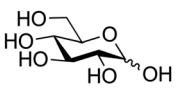
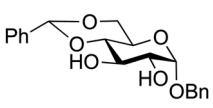
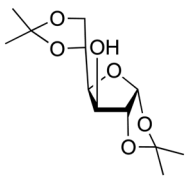
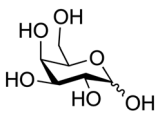
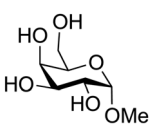
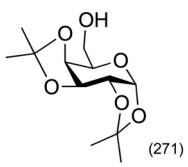
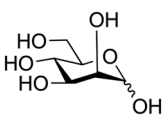
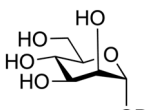
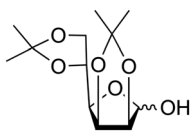
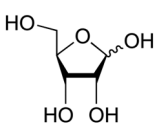
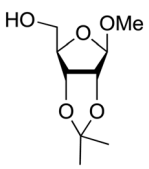
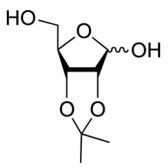


Fig. 11 Equilibrium present in Fischer glycosylation.

in one pot (Table 2). Therefore, many such compounds are now commercially available. Diacetone sorbose is obtained from acetone and L-sorbose under acidic conditions as an intermediate in the synthesis of vitamin C.[260] Today, the Fischer–Helferich method is used in the synthesis of simple glycosides, chiral

Table 2 Examples of the Fischer–Helferich method[a 268–274]

Starting material	Product	
 D-glucose	 (269)	
 D-galactose	 (270)	 (271)
 D-mannose	 (272)	 (273)
 D-ribose	 274)	 (275)

[a] References are in brackets.

synthons for total synthesis or in the preparation of chemical biology probes.[260–267]

A Fischer glycosylation was used in the synthesis of UDP-galactofuranose (Scheme 6), whereby, D-galactose was converted to an anomeric mixture of methyl furanosides and methyl α-D-galactopyranoside under ferric chloride-catalyzed conditions.[275] Thereafter, several protecting group manipulations and a glycosylation with dibenzyl phosphate yielded the desired phosphorylated furanoside. This 1-phosphorylated monosaccharide was then coupled with an activated 5′-*N*-methyl phosphorylimidazolide nucleoside to yield UDP-Galf (Scheme 6).

7.2. Glycosyl halides

Anomeric halides are a classical means to synthesise glycosides dating back to 1901 (Fig. 12) (Table 3).[276] The Koenigs–Knorr method and its subsequently developed variants[277–281] utilize glycosyl halides (bromide, chloride, iodide and fluoride) activated by heavy metal salts such as silver or tin to facilitate coupling with a glycosyl acceptor.[276–278,282–284]

The exchange of the anomeric hydroxyl group for bromine, chlorine, iodine or fluorine is typically carried out with halogenating agents with all other hydroxy groups *O*-protected.[285–292] Glycosyl bromides, chlorides and iodides mainly lead to the product with the halogen atom in an axial position, whereas fluoride glycosyl donors can occur in α/β mixtures with the ratio depending on the solvent.[292]

The stability and reactivity of glycosyl halides is greatly dependent on the halogen, the sugar and the protecting groups.[304] The

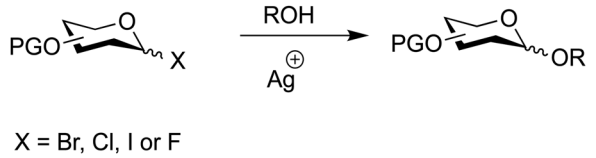


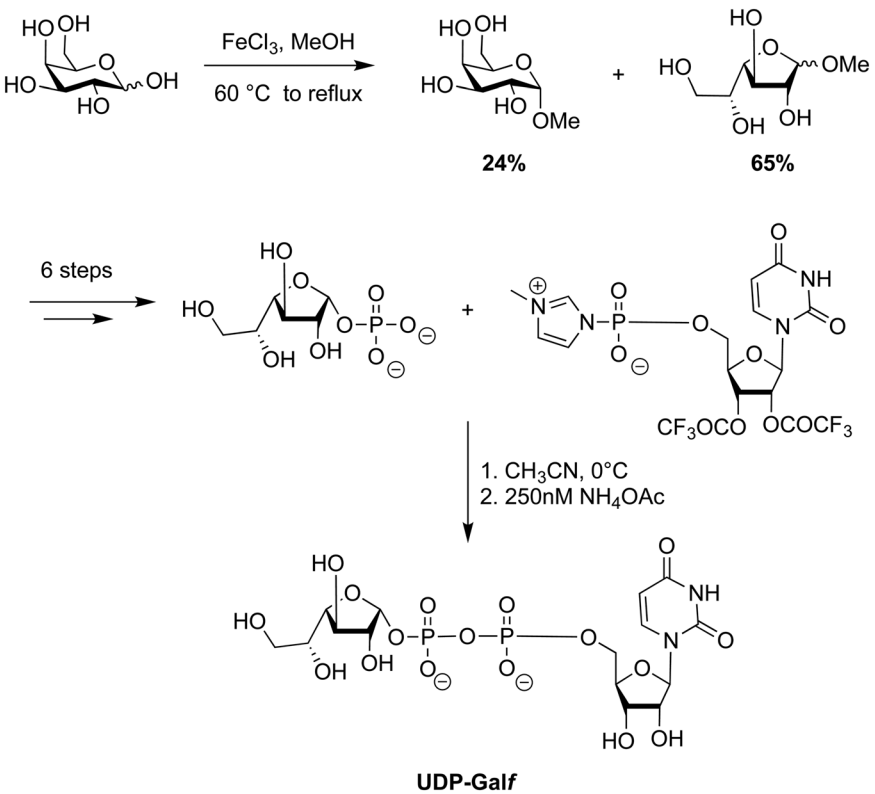
Fig. 12 Anomeric halide mediated synthesis of glycosides.

thermal stability of these glycosyl donors increases from iodide, to bromide, to chloride, to fluoride. The protective groups electron-donating or electron-withdrawing character also affects the stability of glycosyl halides.[304]

For instance, 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide can be prepared and stored at 0 °C, whereas 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide is thermally unstable at as low as −78 °C. Glycosyl iodides are usually very unstable and are prepared *in situ*.[146,177,305]

In general, many glycosyl halides are: (1) prepared *in situ*; (2) used with minimal further purification and (3) are highly sensitive to hydrolysis. These stability issues can sometimes necessitate the use of non-homogeneous/impure compounds, with the exception of glycosyl fluorides, that are more stable to heat, less sensitive to hydrolysis and can often be purified by chromatography.[306–309] Initially, glycosyl fluorides were thought to be too stable for glycosylation reactions due to the large bond-dissociation energy of the C–F bond (552 kJ mol^{-1}) but this has been found not to be the case.[296]

The reactivity trend of the glycosyl halides is the inverse to their stability (I > Br > Cl > F) with protecting groups exerting



Scheme 6 Utility of the Fischer–Helferich method in the synthesis of UDP-galactofuranose.[265]

Table 3 Common promoters for glycosyl halides

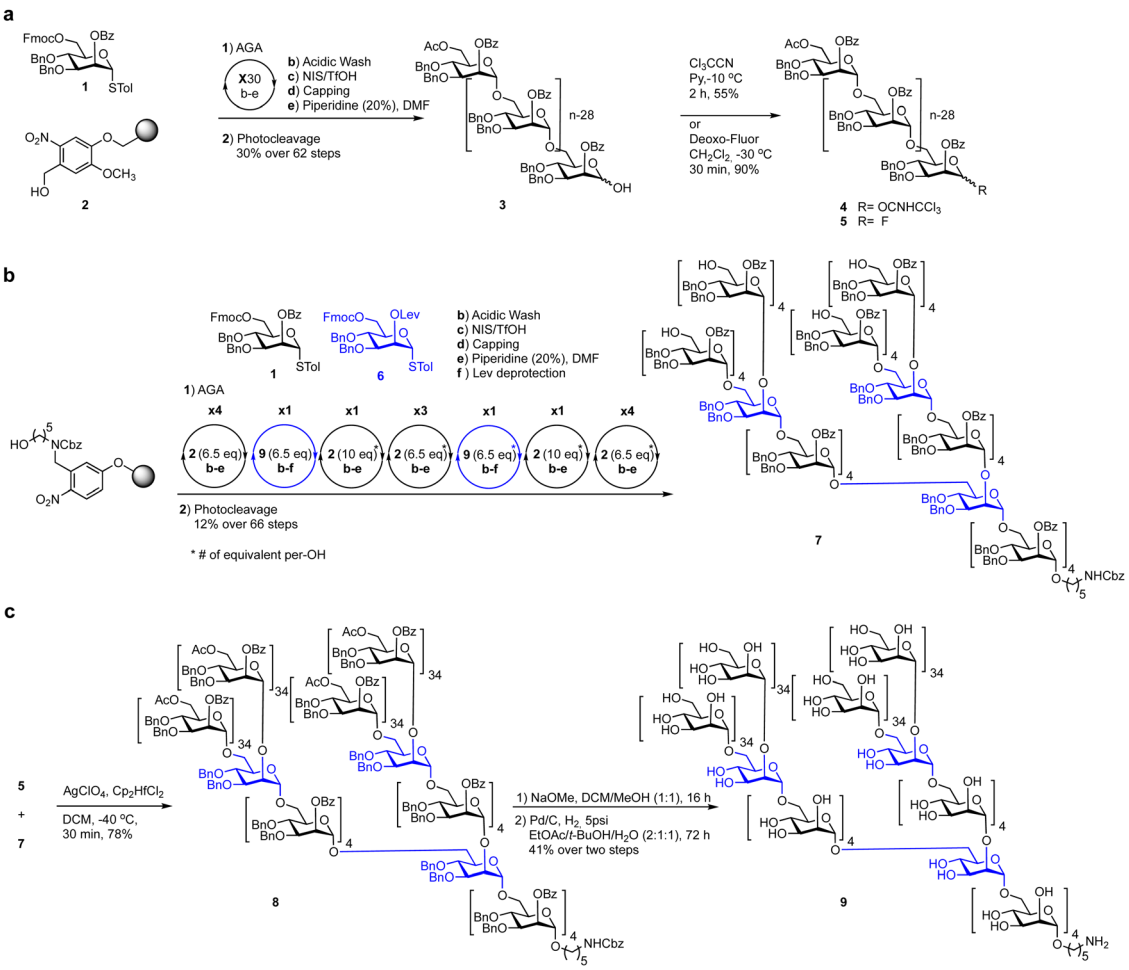
Leaving group	Promoter	Lead author(s)
Bromide and chloride	Ag_2CO_3	Koenigs and Knorr[293]
Bromide and chloride	$Hg(CN)_2$	Helferich[294]
Bromide and chloride	AgOTf	Lemieux[295]
Fluoride	$SnCl_2/AgClO_4$	Mukaiyama,[296]
Fluoride	$BF_3{\cdot}Et_2O$	Nicolaou[297] and Kunz[298]
Fluoride	Cp_2ZrCl_2 (or Cp_2HfCl_2)/$AgClO_4$ (or AgOTf)	Suzuki[299,300]
Iodide	No promoter	Helferich[301]
Iodide	TBAI	Gervay-Hague[302,303]

remote electronic effects. The relative influence of the protecting group is not only dependent on its distance from the anomeric carbon atom but in general, electron-withdrawing *O*-protective groups can lower the reactivity of a glycosylating agent if too unstable.

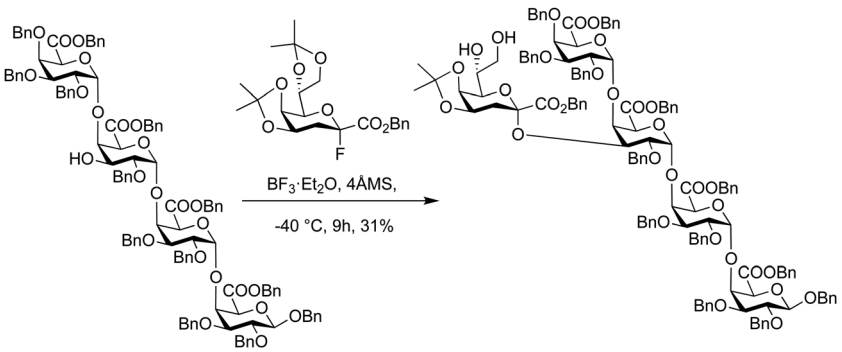
Anomeric halides have been employed in the synthesis of a wide range of complex glycans and glycoconjugates[307,310–317] as well as AGA of mannan polysaccharides (Scheme 7), rhamnogalacturonan-II (Scheme 8) and *Mycobacterium tuberculosis* cell wall α-glucans (Fig. 13).[146,306,318,319]

Glycosyl fluorides were key to the assembly of a 151-mer mannan polysaccharide, *via* block coupling of four linear 30-mer α-(1–6) polymannosides with a branched 31-mer polymannoside tetraol acceptor (Schemes 7a and b).[306,320,321] While a glycosyl trichloroacetimidate failed to give the desired product in the block coupling strategy glycosyl fluorides furnished the desired 151-mer *via* a 31 + 30 + 30 + 30 + 30 block coupling to (Scheme 7c). Silver perchlorate performed better than silver triflate–hafnocene dichloride as it resulted in complete glycosylation in 30 minutes with only minimal levels of by-products formed.[299] Purification by HPLC gave the desired 151-mer that was subsequently deprotected to yield the 151-mer.

Glycosyl fluorides have been used in the synthesis of portions of rhamnogalacturonan-II that contain 3-deoxy-D-manno-



Scheme 7 Glycosyl fluorides enable the late-stage assembly of 151-mer mannan polysaccharide.[306]



Scheme 8 Synthesis of rhamnogalacturonan-II structures using glycosyl fluorides.

oct-2-ulosonic acid (Kdo) branches.[307] Different Kdo-glycosyl fluoride were iteratively tested with the glycosyl acceptor at different temperatures, promoters and glycosyl donor protecting group patterns. Addition of one equivalent of $BF_3{\cdot}Et_2O$ every three hours at −40 °C proved be best to suppress donor elimination and minimize acetal protecting group cleavage. Thereby, the target pentasaccharide was obtained in 31% yield with complete α-stereoselectivity without the 7,8-*O*-isopropylidene acetal protecting group. Following hydrolysis of the 4,5-*O*-isopropylidene acetal with acetic acid and hydrogenolysis of the benzyl ethers the desired RG-II fragment was obtained (Scheme 8).

For the synthesis of α-glucans from the cell wall of *Mycobacterium tuberculosis* a combination of glycosyl imidates, anomeric halides and additives was employed to stereoselectively construct *cis*-glucosidic linkages with both primary and secondary alcohols (Fig. 13). The higher reactivity of the primary compared to the secondary alcohol meant the use of trimethylsilyl iodide and triphenylphosphine oxide was ideal for the stereoselective *cis*-glucosylation with primary alcohols. For secondary alcohols, a combination of trimethylsilyltriflate (TMSOTf) and DMF was selected. Using these two glycosylation conditions in combination with selective protecting group manipulations allowed for the assembly of a nonasaccharide α-glucan following global deprotection.[146]

In summary, the reactivity of the glycosyl halides can be varied over a wide range of conditions and can be modulated the choice of the halogen, the protecting group pattern, the promoter, the solvent and the temperature.[322] In addition, the reactivity of the nucleophile can be adjusted.[138] The diastereoselectivity during the glycoside formation is attained by participation of neighbouring groups for 1,2-*trans* glycosides and for 1,2-*cis* glycosides by the *in situ* anomerization method.[177] The anomeric halide method has some inherent disadvantages that are difficult to overcome, including the low thermal stability of the glycosylating agent and its sensitivity to hydrolysis (with the exception of glycosyl fluorides) as well as the the use of excess often toxic heavy metal salts that make them unsuitable for large scale synthesis.

7.3. Thioglycosides

Thioglycosides are versatile glycosylation agents that were first explored in the early 1970s,[323] but their full potential was realized in the 1980s when several new promoters emerged.[175,324,325] Today, thioglycosides are popular glycosylating agents, especially for the synthesis of oligosaccharides (Fig. 14).[223,326–331]

Thioglycosides can be used directly in the synthesis of *O*-glycosides by coupling with a nucleophile in the presence of a thiophilic promoter and they can be converted into most other glycosylating agents (Fig. 8). Thereby, thioglycosides provide chemists with the flexibility required for the construction of oligosaccharides and glycoconjugates that often requires trial and error.

Most thioglycosides are simple alkyl and aryl glycosides and can be synthesized on a large scale. The products are often crystalline and can be purified without chromatography. Many

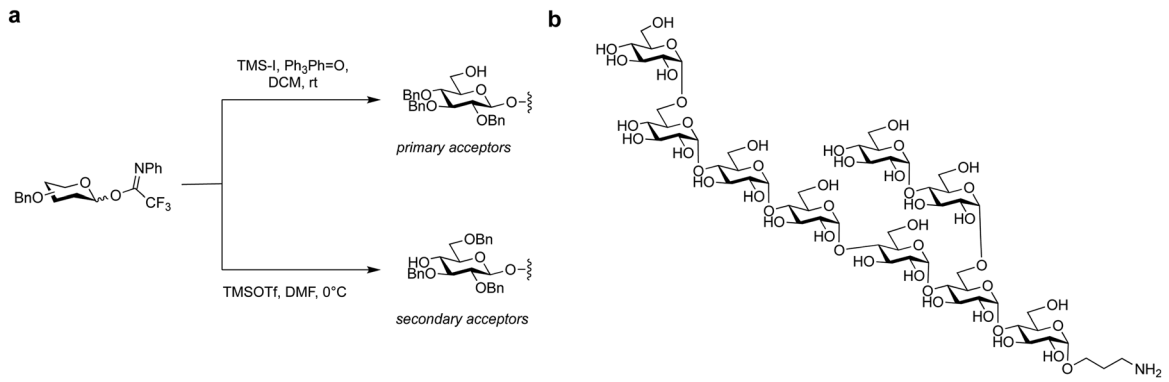


Fig. 13 Reagent controlled stereoselective synthesis of α-glucans. (a) Reagent-controlled methodology and (b) target α-glucan nonasaccharide.[146]

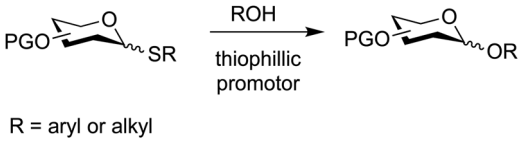


Fig. 14 Glycosylation based on thioglycosides.

paths to prepare thioglycosides have been described, but frequently peracetylated saccharides are reacted with a thiol in the presence of a Lewis acid such as $BF_3{\cdot}Et_2O$. Alternatively, thioglycosides can be synthesized from glycosyl halides or phosphates.[150,161]

Common protecting groups such as esters (benzoates, levulinates), ethers (benzyl, allyl, silyl), acetals (isopropylidene, benzylidene) and orthoesters can be introduced, manipulated and removed on thioglycosides rendering them distinct among other types of glycosylating agents. The removal of benzyl groups using hydrogenolysis is difficult, as the sulfur atom can poison the catalyst but the chemoselective removal of 2-naphthylmethyl ether protecting groups in the presence of benzyl ethers on thioglycosides has been demonstrated.[332] A new oxidative photocatalytic method for benzyl ether removal can overcome this challenge.[333] Oxidation reactions, *e.g.* to obtain glycan uronic acids, using thioglycoside building blocks requires vigilance as oxidation of the sulfur group to a sulfoxide is possible but often DMSO, TEMPO-BAIB and PDC-mediated oxidations can be performed successfully.[334] Aryl thioglycosides are less prone to this oxidation when compared to alkyl thioglycosides.

The first report glycosylations involving thioglycosides used mercuric acetate that was soon replaced by other promoters.[175] Using methyl triflate as activator meant thioglycosides having a neighbouring participating substituent at *O*-2 gave the expected 1,2-*trans* glycosides, whereas those with a non-participating *O*-2 substituent gave anomeric mixtures. Subsequently, several other, high-yielding thiophilic promoters have been developed (Table 4).

Thioglycosides can be effective in the construction of 1,2-*trans* and 1,2-*cis* linkages, including a recent AGA of starch and glycogen α-glucan oligosaccharides (Scheme 9).[144] Key to the assembly of these complex structures was the synergistic use of remote participation, solvent effects and optimal building blocks. The ideal building blocks for the repeated synthesis of α-(1 → 4) and α-(1 → 6) glycosides were identified by a series of systematic glycosylations. Two building blocks from a set of twenty-one were found to be ideal for the stereoselective synthesis of these glycans (Fig. 14). AGA of the α-(1 → 4) glucan backbone worked best when a 3,6-di-*O*-benzoylated thioglycoside with a 4-*O*-fluorenylmethyloxycarbonyl (Fmoc) protecting group was used. The building block for α-(1 → 6) linkages, contained a 3-*O*-benzoate ester, a 4-*O*-Fmoc and a 6-*O*-levulinoyl ester. Using AGA these two thioglycoside building blocks were combined with the help of *N*-iodosuccimide and triflic acid for the construction of a collection of linear and branched α-glucans, including a 20-mer amylopectin polysaccharide, one of the largest synthetic 1,2-*cis*-linked glycan to date.

Table 4 Common activators of thioglycosides

Activator	Lead author(s)
MeOTf	Lönn[175]
DMTST	Fügedi and Garegg[335]
NIS-TfOH	Van Boom[336]
BSP, Tf_2O	Crich[337]
PhSeOTf	Ogawa[338]
I_2	Field[339]
I_2, AgOTf	Fraser-Reid[340]

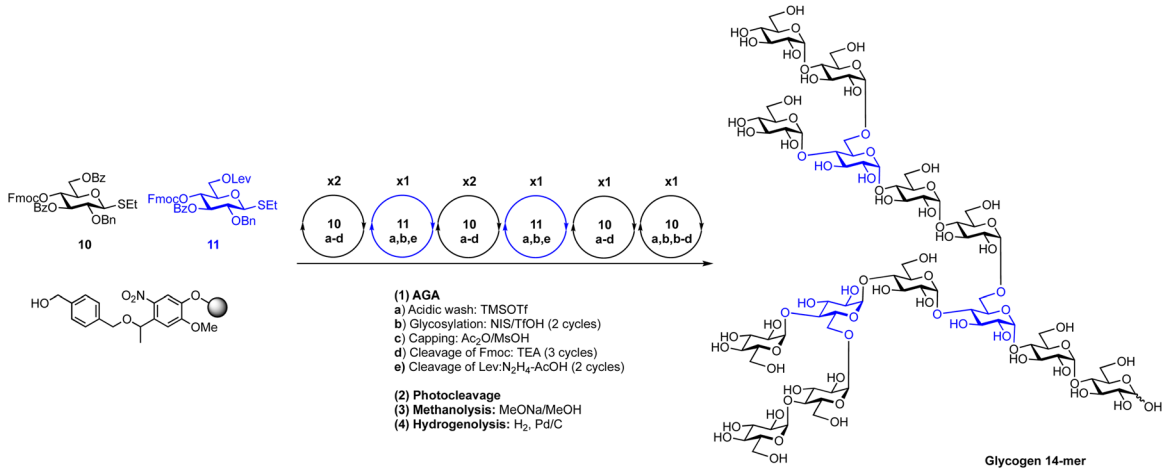
Thioglycosides can be used in block syntheses of oligosaccharides,[341–344] such as the convergent synthesis of a library of glucuronoxylomannans from *Cryptococcus neoformans* (Scheme 10).[345] The β-xylose and β-glucuronic acid branches were installed at the disaccharide stage using neighbouring protecting group participation before multi-step protecting group manipulations were required to install the 6-*O*-acetylation pattern of the α-mannan backbone. Tetra- and hexasaccharide thioglycoside building blocks were assembled from glycosyl imidates. These thioglycoside building blocks were assembled using dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST) as a promoter, with diethyl ether as a solvent to enhance α-selectivity. Hexasaccharide thioglycoside building blocks allowed for the assembly of glycans up to an 18-mer with yields ranging from 78–86%.

Many shelf-stable thioglycosides with diverse protecting group patterns can be prepared and are commercially available as reagents for oligosaccharide synthesis.[346] A wide range of promoter systems for thioglycoside activation, offer significant flexibility for glycosylations. The ability to readily convert thioglycosides into other glycosylating agents makes them one of the most reliable and robust methods for synthesizing complex glycans.

7.4. Glycosyl imidates

O-Glycosyl imidates are useful glycosylating agents under acidic conditions (Fig. 15).[54,347–352] *N*-Methylacetimidate donors, initially developed, did not gain broad application due to their low reactivity.[353,354] Subsequently, electron deficient trichloroacetimidates proved more robust and reliable in the synthesis of glycosides.[348] Today, reactions with nucleophiles are performed with catalytic amounts of Brønsted or Lewis acids such as TMSOTf and $BF_3{\cdot}OEt_2$. Typically, TMSOTf is the catalyst of first choice and is used in 0.1 equivalents based on the glycosylating agent. The glycosyl imidate is prepared by reacting the free reducing end of pyranose or furanose with an electron deficient nitrile, *e.g.* trichloroacetonitrile, under basic conditions to furnish the desired glycosyl imidate. This glycosyl imidate can then be used in a subsequent glycosylation under acid catalysis.

Controlling the anomeric configuration of the glycosylating agent is possible by careful choice of base, for instance K_2CO_3 can be used to prepare the β-anomer, while DBU, can be used to prepare the α-anomer (Scheme 11).[355] This selectivity is a result of the greater nucleophilicity of the β-oxide, that is attributed to kinetic effects, while the use of DBU leads to the thermodynamically

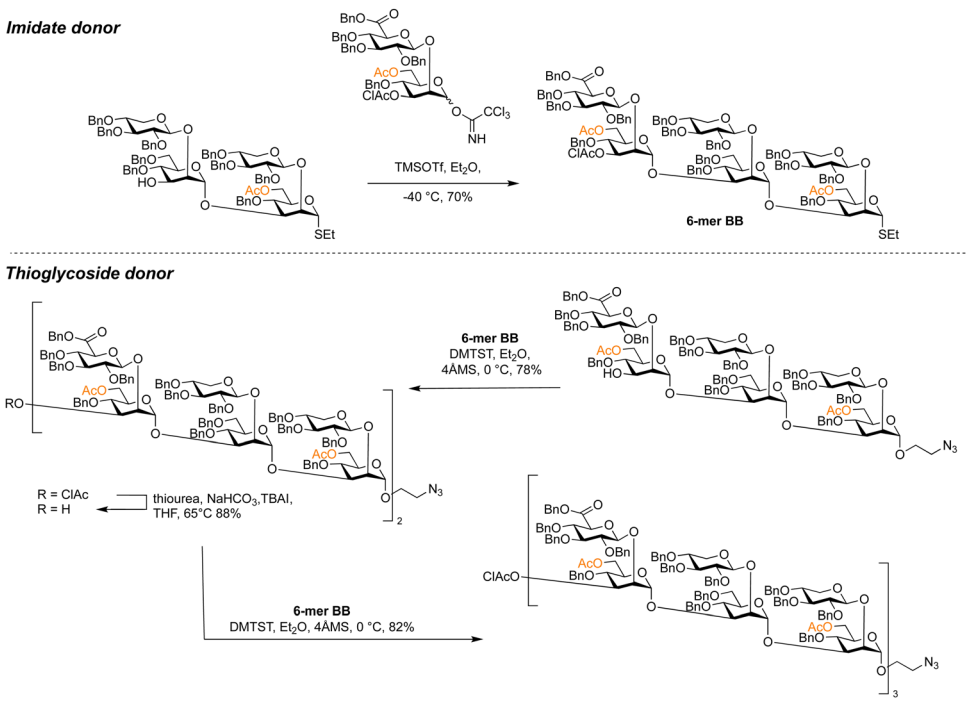


Scheme 9 Combination of building block optimization, solvent effects and remote participation for the automated assembly of 1,2-*cis* starch and glycogen oligosaccharides.[144]

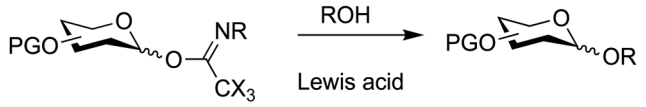
more stable α-product.[356] Glycosyl trichloroacetimidates bearing multiple electron donating groups are sensitive to hydrolysis. Chromatographic purification can require pre-neutralisation of silica gel with a base, *e.g.* 1% solution of triethylamine, and pure building blocks should be stored frozen. An alternative to glycosyl trichloroacetimidates is the use of the less reactive glycosyl *N*-(phenyl)trifluoroacetimidate that is more stable than the corresponding trichloroacetimidates but also less reactive.[357–360]

In contrast to most other glycosylation methods that require stoichiometric amounts of promoters *O*-glycosyl imidates are acid catalyzed and have been used to synthesise a variety of complex glycosides.

Activation of glycosyl imidates using boron trifluoride etherate starting at −40 °C and raising slowly to room temperature in dichloromethane is a popular set of conditions shown to be suitable to synthesise a range of glycosides.[307] When neighbouring groups such as 2-*O*-benzoyl esters are present, the expected 1,2-*trans* products are obtained. With the non-participating protecting groups, *e.g.* a benzyl ether, the inversion of configuration at the anomeric centre is preferred. The amount of 1,2-*cis*-glycosides can be further enhanced by using diethyl ether as the solvent and trimethylsilyl triflate or *tert*-butyldimethylsilyl trifluoromethanesulfonate as the catalyst.[361]



Scheme 10 Glycosyl imidates and thioglycosides used in the assembly of a library of fungal glucuronoxylomannans.[345]



R = H, X = Cl or R = Ph, X = F

Fig. 15 Glycoside synthesis based on glycosyl imidates.

Glycosyl trichloroacetimidates can rearrange to the corresponding stable *N*-trichloroacetylglycosyl amine *via* acid catalysis. This reaction can be minimized by lower temperatures,[362] altering the solvent[363–365] and changing the quantity and nature of the promoter.[366,367] Using "inverse glycosylation conditions" can also improve the outcome of the synthesis. *N*-Phenyl based glycosyl imidate donors are less prone to the rearrangement reaction.[368,369]

Glycosyl imidates method have been used for block couplings of complex oligosaccharides[128,345,350,370] such as the assembly of di-, tri- and tetrasaccharides for the synthesis of lipopolysaccharide *O*-antigens of *Shigella flexneri* vaccines (Scheme 12).[371–373] The coupling of a trisaccharide trichloroacetimidate donor and a glucosamine acceptor had to be optimized. Initial experiments at low and room temperature failed to give satisfactory yields of the hexasaccharide, possibly due to poor acceptor solubility. However, when the coupling was carried out at 75 °C in 1,2-dichloroethane with a catalytic amount of triflic acid, 76% of the coupled product were obtained.[371,374] Following selective removal of the temporary *O*-acetyl group, the 3-OH glucosamine acceptor was coupled under similar conditions but notably a different temperature regime of −35 °C to 10 °C, to furnish target decasaccharide in 82% yield. (Scheme 12).

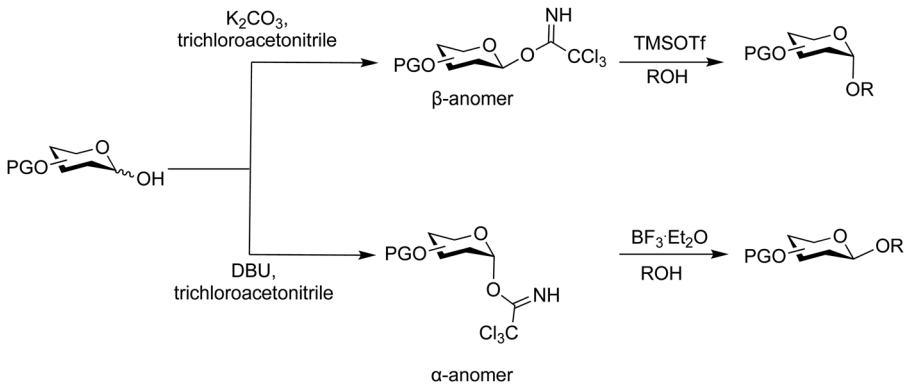
Imidates were used in the synthesis of glycosylated peptides that bear a phosphonate group (Scheme 13).[375] This phosphonate group mimics naturally occurring mannose-6-phosphate that causes glycoproteins to be trafficked to the lysosome.[376–379] The trichloroacetimidate donor was prepared using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford exclusively the α-anomer and reacted with a L-serine benzyl ester at −78 °C using TMSOTf as a catalyst. After the successful coupling, the amino acid was polymerized and conjugated to antibodies creating chimaeras that can cause proteins to be degraded catalytically.[375]

7.5. Glycosyl phosphates and phosphites

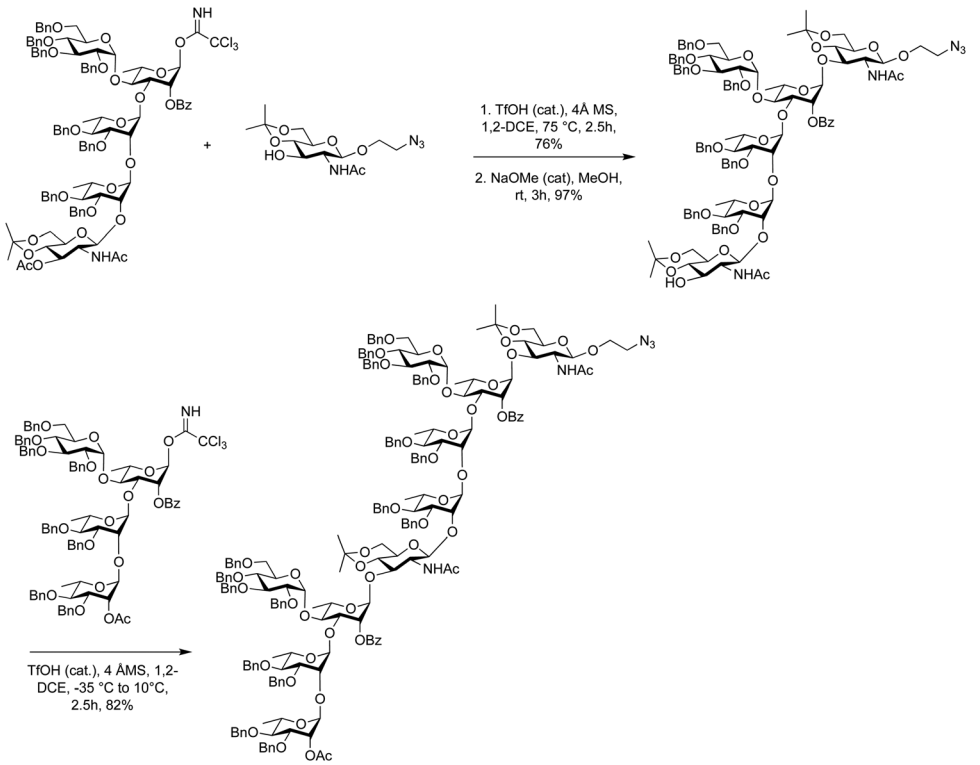
Glycosyl phosphates are key intermediates in the biosynthesis of glycans, and have found application in chemical synthesis as anomeric leaving groups.[380,381] Early reports included diphenylphosphate and glycosyl phosphites for effective chemical glycosylations.[199,382–388] Subsequently several variants have been synthesized by varying the substituents on the phosphorus atom (Fig. 16).[385]

Diphenyl, dialkyl and propane-1,3-diyl glycosyl phosphates can be introduced at the anomeric carbon and utilized as leaving groups for the glycosylation reactions.[199,382–384,386,388,389] Mostly, either the starting material is a free reducing sugar (1-OH free) or the glycosyl phosphate is prepared by converting one type of glycosylating agent, such as a thioglycosides, into a glycosyl phosphate. The stability of glycosyl phosphates depends on the chemical substituents that decorate the phosphorus atom but dibutyl phosphate donors can be purified by flash chromatography and stored at sub-zero temperatures for months. Under acidic conditions, β-phosphates anomerize to the thermodynamically more stable α-phosphates, making it theoretically possible that during the glycoside forming reaction, anomerization of the glycosyl phosphate can occur.

Dibutyl phosphates are a frequently used anomeric leaving group on glycosylating agents.[389] The ratio of the resulting α- and β-glycosyl phosphates is solvent dependent, toluene and dichloromethane gave β-phosphates and the use of THF produced almost exclusively α-phosphates. Generally, in glycosylations where neighbouring protecting groups are present, the expected 1,2-*trans* glycoside is formed.[390] In the synthesis of 1,2-*cis* glycosides, anomeric phosphates have shown good utility, *e.g.* in the formation of challenging α-sialosides.[16,199] A dibutyl phosphate donor was used in the synthesis of *O*-acetylated sialosides to probe virus receptor binding preferences (Scheme 14).[16] Dibutyl glycosyl phosphates have been used to construct a wide range of glycans by AGA.[116,235,390] such as a collection of β-(1 → 3) glucans (Scheme 15). Constructing these branched structures required two building blocks, one for the β-1,3 backbone and one for the β-1,6 branching points. The backbone building block was a di-4,6-*O*-benzylated building block with a 3-*O*-Fmoc temporary protecting group and a 2-*O*-



Scheme 11 Reagent-controlled synthesis of different glycosyl imidate anomers.



Scheme 12 Using glycosyl imidates in the assembly of *Shigella flexneri* Serotype 2a oligosaccharides.

benzoate ester ensured the formation of the desired 1,2-*trans* selectivity. The branching building block contained a 6-*O*-levulinoyl ester protecting group for orthogonal removal and the subsequent installation of branches. These two building blocks were combined together *via* TMSOTf promoted glycosylations to construct a collection of β-1,3 glucans. These synthetic glucans were printed on a microarray and scanned with human sera to explore aspects of fungal immunology.

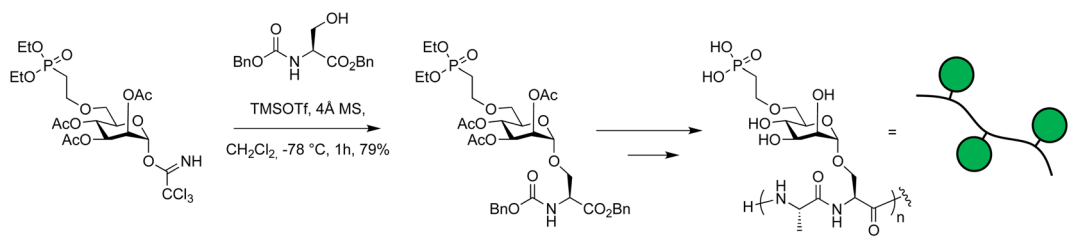
Phosphorus-based glycosylating agents have gained prominence as a viable option for glycoside synthesis. By altering the substituents on the phosphorus atom, it becomes possible to fine-tune the glycosyl donor properties. An advantage of this method, is its operational simplicity, requiring the use of stoichiometric amounts of Lewis acid promoters *e.g.*, TMSOTf. The glycosylations are high yielding and highly stereoselective. Dibutyl phosphate donors, in particular, have proven valuable in AGA of a wide range of glycans.[391,392]

7.6. Organic and transition-metal catalysis

New approaches to construct glycosides *via* organocatalytic and transition metal-mediated methodologies have been developed. Among the catalytic methods, the glycosyl imidate approach, discussed in Section 7.4, has seen by far the most widespread use.

7.6.1. Organocatalytic glycoside synthesis. Enantioselective organocatalysis can be used to effect a diverse range of transformations in synthetic chemistry.[393–405] Both stereo- and regioselective, mild and high-yielding organocatalysis methods for glycoside syntheses have been reported[406–408] using organoboron,[110,111,408–415] thiourea,[74,407,416–418] and Brønsted acid scaffolds.[419–421] While initial reports focused on method development, organocatalysts have found use in the context of complex glycoside synthesis.[406,413,415,421,422]

Both thiourea and organoboron-based catalysts have been used for selective glycosylations of unprotected or partially protected glycosyl acceptors.[74,408] Selective glycosylations of



Scheme 13 Glycosyl imidate building blocks used in the synthesis of glycopeptides.[375]

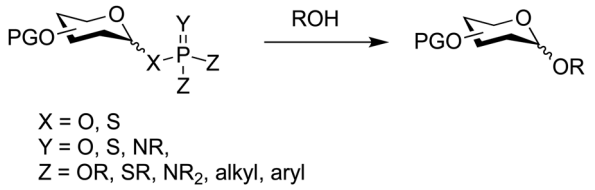
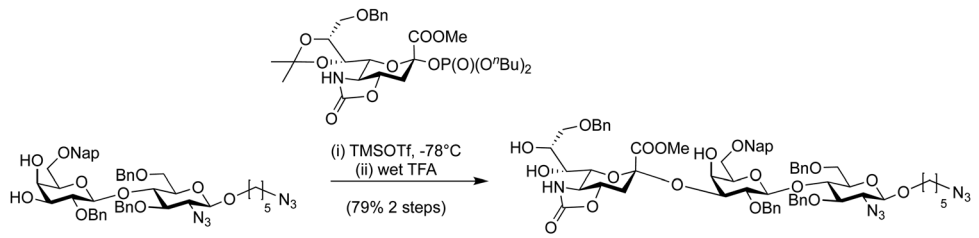


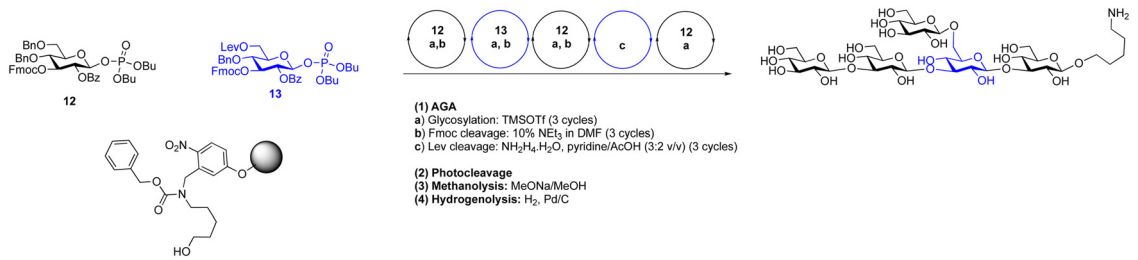
Fig. 16 Anomeric phosphates as glycosylating agents.

molecules containing multiple hydroxyl groups with similar reactivity is possible by discriminating nucleophiles based on complex stereochemical environments.[409,423,424] Regioselective glycosylations of carbohydrate polyols have been reported using dibutyltin oxide[424–427] and diarylborinic acid catalysts.[106–113] Both organoboron and tin-based reagents offer the same regioselectivity and can be used in building block synthesis to enable regioselective acylation and alkylation of polyols (discussed in Section 3).

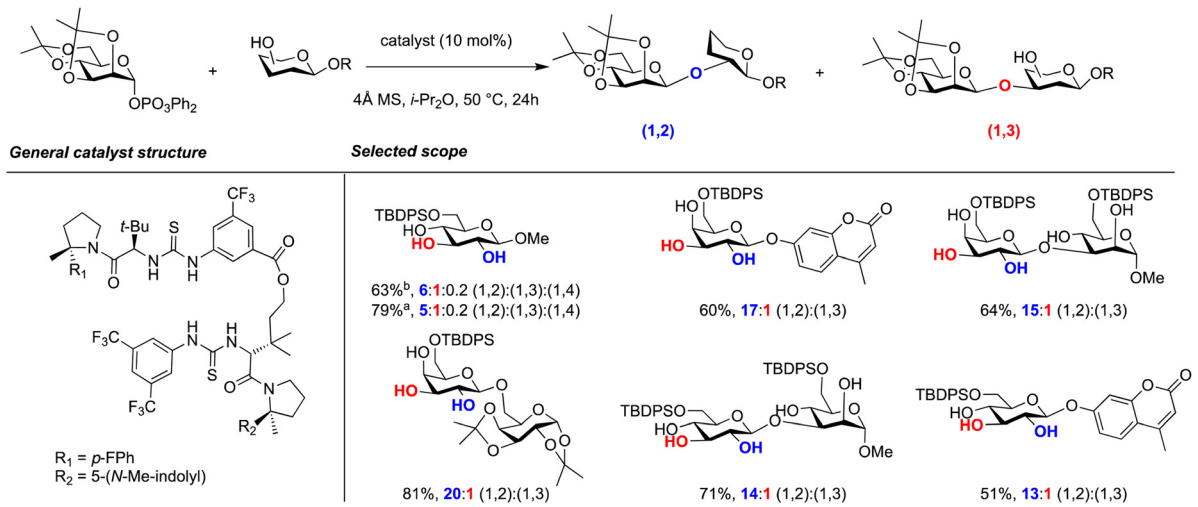
A recent example of regioselective organocatalysis in glycoside synthesis was reported using a bis-thiourea catalyst to synthesise 1,2-*cis* glycosides with partially and unprotected glycosyl acceptors (Scheme 16).[74] Stereo- and regio-selective galactosylations and mannosylations were reported using an assortment of polyfunctional nucleophiles. The anomeric configuration of glycosyl acceptors was found to impact the regioselectivity with α-acceptors affording lower regioselectivity. Eight catalysts were screened with different aryl groups and more electron-rich arenes resulted in higher selectivity for (1,2)-galactosylations.



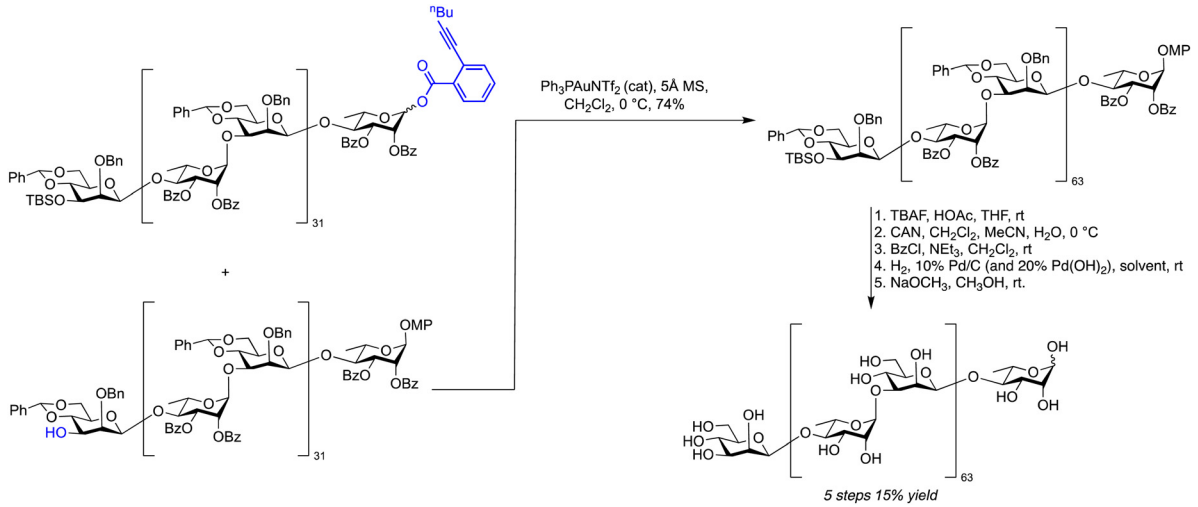
Scheme 14 Regioselective glycosylation with sialic acid dibutyl phosphate.[16]



Scheme 15 AGA of a β-glucan pentasaccharide using glycosyl phosphates.[390]



Scheme 16 Regioselective organocatalysis using a bis-thiourea catalyst for site-selective mannosylation.[74] High stereoselectivities (>20 : 1 β : α) were observed in every case. [a] Reaction performed at 40 °C. [b] Reaction performed at 23 °C.



Scheme 17 Iterative gold-mediated catalysis for the assembly of a 128-mer O-antigen of *Bacteroides vulgatus*.

Computational studies suggested that catalyst selectivity arose in part from stabilizing C–H/π interactions between the catalyst and the acceptor, a phenomenon well established for carbohydrate–protein interactions.

7.6.2. Transition metal mediated glycoside synthesis. Transition-metal-mediated catalysis can be used to perform a wide range of transformations[428–439] including glycoside formation using palladium, nickel and gold.[440–449] Transition metals can catalytically activate glycosylating agents such as trichloroacetimidates[448,449] and glycals,[420,443,450,451] and have been used in the syntheses of complex glycosides.[440,450,452]

Gold-mediated glycosylations are distinct from other transition-metal-mediated glycoside syntheses as novel leaving groups have been introduced.[453–456] Glycosyl *ortho*-alkynyl benzoates and propargyl 1,2-orthoesters share a similar mechanism that exploits the alkynophilic nature of gold.[452,457] Glycosyl *ortho*-alkynyl benzoates were used to synthesise a 128-mer of the O-antigen from *Bacteroides vulgatus* (Scheme 17).[458] The challenging 1,2-*cis*-mannopyranoside linkages were completed early in the synthesis and neighbouring group participation was enlisted to stereoselectivity assembly the 1,2-*trans*-rhamnopyranoside linkages. This transition-metal-mediated approach allowed for the decagram-scale synthesis of a tetrasaccharide building block that was then used in iterative 2^{n+1}-mer cycles, to assemble an 8-mer, 16-mer and a 32-mer on gram-scale. Two 64-mers were combined under gold(I)-mediated catalysis to yield 74% of protected 128-mer.

Transition metal and organo-catalysis methods have been used to synthesize a variety of *N*-, *C*- and *S*-linked glycosides. Overall, they provide complementary for efficiently synthesizing of complex glycosides.

8. Global deprotection of synthetic glycosides

After completing a synthesis, permanent protecting groups are removed to furnish glycosides found in nature. This "global deprotection" at the final stage is often the least optimised part of the synthesis.[458–462] High-quality reagents are essential to maximise the yields of target glycans, especially in the case of hydrogenolysis reactions, where the quality of palladium on carbon catalysts varies widely among commercial suppliers.[463] Additional consideration should be given to the glycan structure, the role of solvent(s) (and solvent combinations),[464,465] temperature(s) and pressure(s), that can play a decisive role in determining the success of the hydrogenolysis reaction.[462,463] Hydrogenation of trichloroacetamide or hydrogenolysis of benzyl ethers can be difficult to remove or convert. Saturation of aromatic protecting groups such as benzyl and 2-naphthylmethyl ethers, has been reported on some glycosides and may be an overlooked side-reaction (Fig. 17).[459,462,466–468]

Difficulties in removing ester protecting groups can arise during global deprotection as pivalate and benzoate esters can be difficult to remove from oligosaccharides at times.[125,469] Adjusting temperature, base, solvent and protecting group patterns can be used to optimise a synthesis.

The challenge of global deprotection is exemplified by the synthesis of a 128-mer polysaccharide resembling the repeating unit of *Bacteroides vulgatus via* gold-promoted glycosylations (Scheme 17). The global deprotection involved five steps: (1) cleavage of one TBS ether with tetrabutylammonium (TBAF); (2) removal of the anomeric *p*-methoxyphenyl (MP) with ammonium

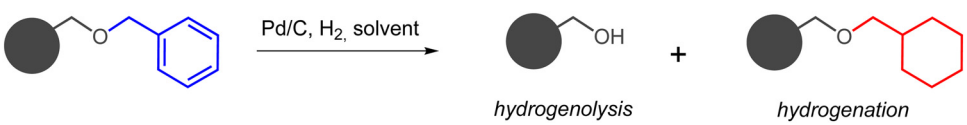


Fig. 17 Hydrogenation of aromatic protecting groups in global deprotection reactions.

cerium(IV) nitrate (CAN); (3) benzoylation of the resulting hemiacetal; (4) hydrogenolysis of the 64 benzyl ethers and 64 benzylidene acetals and (5) methanolysis of the 128 benzoyl groups with sodium methoxide solution. A capping step (3) was important for hydrogenolysis to avoid glycan degradation. Hydrogenolysis of glycans larger than 16-mers were challenging due to solubility issues that are not uncommon when transforming a fully protected, hydrophobic structure into a hydrophilic. The solubility of a range of amphiphilic intermediates that form over the course of a hydrogenolysis reaction, as benzyl ethers are cleaved has to be considered. In this case, a combination of 10% Pd/C and 10% $Pd(OH)_2$ was used to deprotect the 128-mer, before chromatography using a Sephadex column yielded 15% of the 128-mer over five steps.

The global deprotection of oligosaccharides is not yet routine. Enhancing the efficiency of this chemical step(s) holds the potential to significantly advance oligosaccharide synthesis.

9. Summary and outlook

There is no universal glycosylation method to synthesize all possible glycosides. However, methodological advancements are enabling the synthesis of increasingly complex glycans and automated glycan synthesis. Glycoside synthesis remains more complex than the synthesis of both nucleic acids and oligopeptides. The chemical synthesis of well-defined glycosides and oligosaccharides remains essential to explore the many roles glycans play in nature.

Conflicts of interest

There are no conflicts to declare.

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