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New chemical processes to streamline carbohydrate synthesis

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Abstract

Carbohydrates hold potential for the future of therapeutic development due to their important role in essential biological processes. However, it is still challenging to produce homogenous materials, especially for non-mammalian sugars that are considered rare. Recent developments in this field have focused on catalytic methods, including organometallic and organocatalytic approaches to regioselective functionalization. Many approaches to glycosylations also utilize catalysts, increasingly in combination with photoredox conditions, to achieve stereoselectivity. Additionally, there have been significant advancements in the automation of glycosylation to synthesize oligosaccharides in less time and with fewer manually conducted steps by the user.

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Automation, Catalysis, Glycosylation, Organocatalysis, Photoredox, Regioselectivity, Stereoselectivity.

Introduction

Carbohydrates play a significant role in many essential biological processes including cell recognition and the inflammatory and immune responses [1]. As a result, a better understanding of the role of carbohydrates has important implications for advancements in therapeutic development [2]. A major hurdle to the further development of carbohydrate-based therapeutics lies in the difficulty in obtaining homogeneous material for study. Unlike other classes of biopolymers, complex carbohydrates are often produced as complex mixtures, leaving synthesis as the only avenue for producing pure material. Despite decades of progress the synthesis of carbohydrates remains non-trivial. One of the primary challenges to carbohydrate synthesis lies in controlling the stereo- and regiochemical outcome of glycosylation reactions, especially in cases of "unusual" linkages found in non-mammalian glycans (Figure 1). The situation is even more complicated in the case of branched sugars, where special attention must be paid to orthogonal protecting groups at branching sites [3]. With such considerations in hand, much of recent research has focused on new, often catalytic, reactions to control the stereo- and regiochemical outcome of glycosylation reactions. The application of these methods to automated synthesis has also enjoyed increased attention over the past decade. This review will describe recent advances in all of these areas.

Preparation of monosaccharides

Monosaccharide manipulation

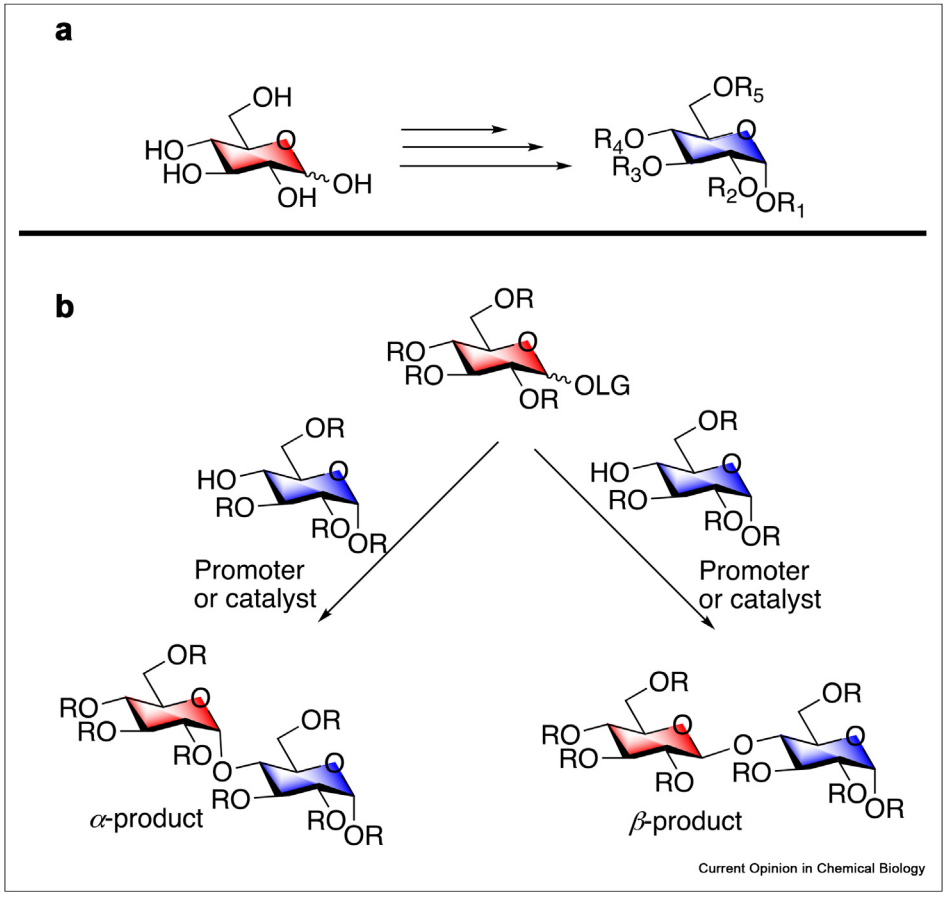
Many methods for the regioselective functionalization of mono- and polysaccharides have focused on activation of *cis* diols, typically with stoichiometric dialkyltin oxides. In more recent years there has been a move away from organotin catalysis owing to the perceived toxicity of these reagents. Notable among these methods has been the Taylor group's development of organoborinate-based regioselective activation of polyols [4**]. These reactions are proposed to involve a tetracoordinate complex formed between the catalyst and the diol. Subsequent work from this lab has demonstrated that this approach can be applied to a variety of transformations including sulfonylation, alkylation, C–H insertion, oxidation, and glycosylation [5–10].

Another area which has seen extensive investigations is the use of organocatalysis for the regioselective manipulation of monosaccharides. Unlike the above-mentioned methods, these latter approaches are capable of regioselectivity activating 1,2-*trans*-diols. In 2013, Nagorny and co-workers described the use of chiral BINOL-based phosphoric acid derivatives for the regioselective acetalization of carbohydrates [11*]. This work was later extended to regioselective glycosylation of non-carbohydrate acceptors, including 2-deoxystreptamine [12], and steroidal natural products [13]. More recently, this group demonstrated that the

Abbreviations

Ada	Adamantly
Boc	*tert*-butylcarboxy
BPhen	Bathophenanthroline
CZIPN	1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene, 2,4,5,6-Tetrakis(9*H*-carbazol-9-yl) isophthalonitrile
DCE	1,2-dichloroethane
DCM	Dichloromethane
DMSO	Dimethylsulfoxide;
dtbpy	2,6-di-*tert*-butylpyridine;
DTBMP	2,6-di-*tert*-butyl-3-methylpyridine;
imiz	Imidazole
IBO	Isobutylene oxide;
*i*Pr	Isopropyl
LED	Light emitting diode
MeCN	Acetonitrile;
MS	Molecular sieves
MTBE	Methyl-*tert*-butyl ether
PhI	Iodobenzene
PPTS	Pyridinium *p*-toluenesulfonate
TBSCl	*tert*-butyldimethylsilyl chloride;
*t*BuOH	*tert*-butyl alcohol
THF	Tetrahydrofuran
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

Figure 1



Challenges in carbohydrate synthesis being addressed through new technologies: (**a**). Controlling regiochemistry of protection and glycosylation reactions. (**b**). Controlling the stereochemical outcome of glycosylation reactions. LG is used to represent a generic leaving group.

chiral phosphoric acid catalysts could be immobilized on polystyrene supports and recycled for multiple site-selective acetalization reactions [14**]. Optimal results were obtained when the substrates were protected with a 4,6-*O*-benzylidene acetal, and interestingly different catalysts were required for selective reactions. While (*R*)-Ad-TRIP **1** was the best catalyst for C(2) protection, (*S*)-SPINOL catalyst **2** afforded products with high C (3) selectivity (Scheme 1A). Furthermore, the catalysts could be used in a one-pot protection-

glycosylation sequence for the regioselective introduction of sugars on the diols.

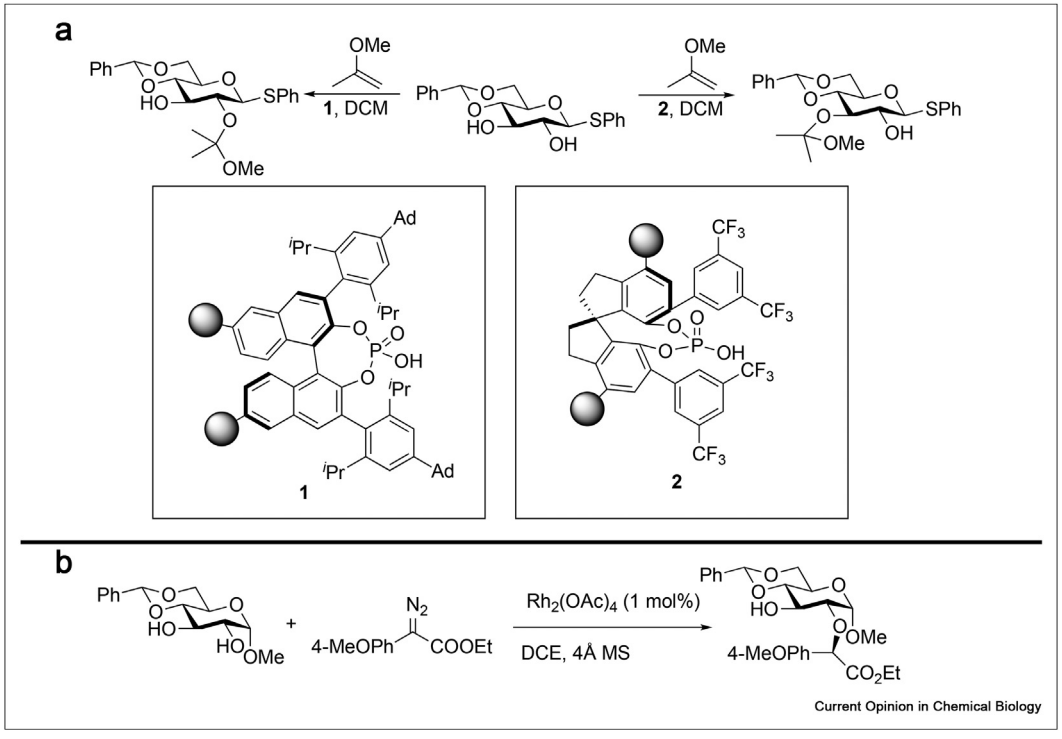
Tang et al. demonstrated a different approach for controlling regioselective acylation of 1,2-*trans*-diols using benzotetramisole catalysis [15]. Selectivity in these reactions is controlled through interactions between the cationic activated catalyst and lone pairs on adjacent ether oxygens. In (R)-benzotetramisole-catalyzed acylation of an α-O-methoxy-glucosides, these interactions lead to C(3) acylation. At C(2), the axial alkoxy substituent interferes with this cation-n interaction and disfavors acylation at this position. Interestingly when S-adamantyl glycosides are used as substrates for site-selective acylation with the same catalyst—the C(2)-position is favored over C(3). The authors attribute the origin of this latter selectivity to C−H-π interactions between the *S*-adamantyl group and the aromatic backbone of the catalyst [16].

The Tang group has also introduced a metal carbenoid-based method for the regioselective introduction of ethers onto 1,2-*trans*-diols [17**]. Using $Rh_2(OAc)_4$ the authors demonstrated that α-diazo esters could be activated for O−H insertion. Regiochemically, the reaction favored activation of alcohols adjacent to an axial ether (Scheme 1B). Furthermore, selectivity in the reaction could be further improved through the use of a chiral catalyst. When reactions took place at C(2), the resulting product could be manipulated into a donor possessing a Boons-type auxiliary that could be used for α-selective glycosylation reaction [18].

Access to rare sugars

Another area which has seen increased attention is the construction of so-called rare sugars. These compounds, which include 2-deoxy-hexoses and nonulsonic acids, are often found in bioactive natural products or the cell walls of pathogenic bacteria. As a result, providing facile access to these compounds could lead to new avenues for small molecule therapeutics, vaccine, and diagnostics development. Unfortunately, many of these compounds are not commercially available and multi-step synthesis remains the only avenue for their production [19−22]. Very recently, both the Taylor and Wendlandt groups have reported a solution to this issue using photoredox catalysis [23*], [24*]. The Taylor approach uses Ir $[dF(CF_3)(dtbppy)]_2PF_6$ to convert quinuclidine into a radical cation that abstracts a hydrogen from a C(3) of rhamnose pre-coordinated with 4-chlorobenzoate (Scheme 2 A). The resulting radical undergoes an acyl migration, resulting in a hemiacetal that collapses to an α-keto radical. Subsequent reduction and protonation of the radical then affords the product, which can be

Scheme 1



Regioselective protection of *trans*-1,2 diols using chiral phosphoric acid (**a**) and Rh (**b**) catalysis.

derivatized to a variety of deoxy sugars. Similarly, the Wendlandt approach uses the photocatalyst 4-CzIPN to activate quinuclidine into a radical cation, which demonstrates similar reactivity. Mn(II) promotes conversion of the radical into the corresponding ketone. Once again, the ketone can be derivatized into a number of deoxysugars. Very recently, Tang et al. demonstrated that epimerization of fully substituted sugars could be realized without photoredox catalysis using $MeB(OH)_2$ and catalytic $Rh(PPh_3)_3Cl_2$ [25].

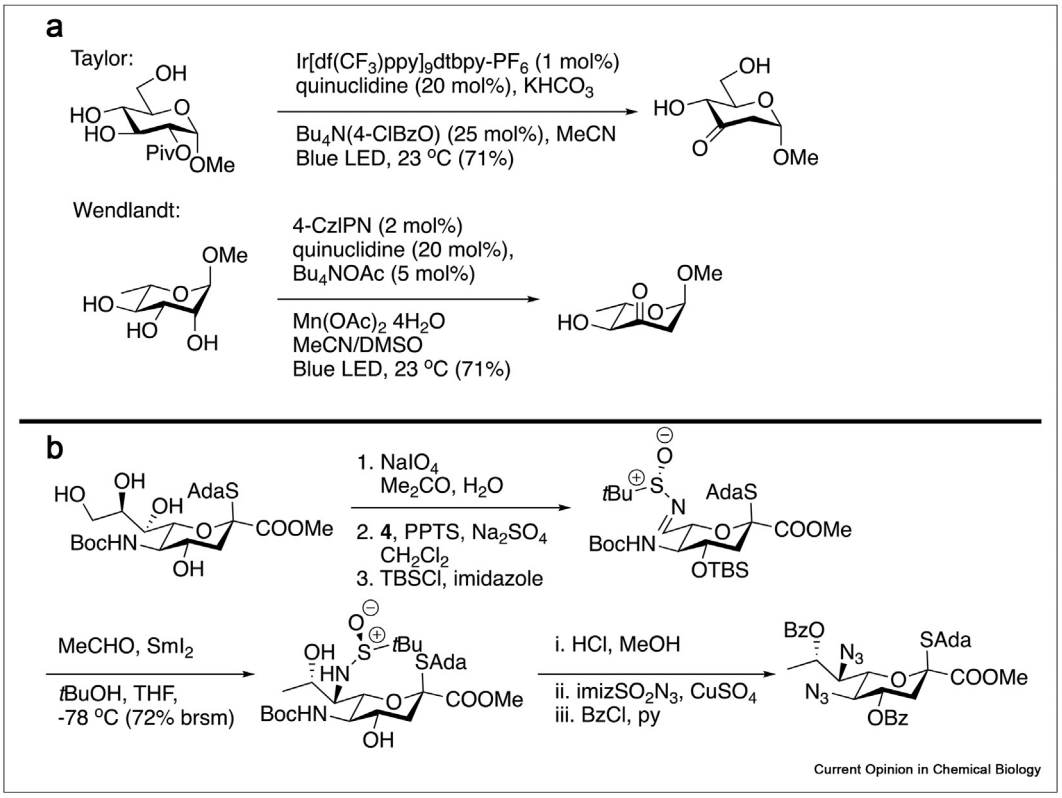
As an alternative to de novo synthesis, many rare sugars can also be obtained from natural products through chemical derivatization. In order to increase the efficiency of this process Thorson et al. introduced the concept of "sugar-pirating" in which a readily available natural product serves as a starting material for an array of rare sugars [26]. As proof of concept the authors demonstrated that the readily available natural product spectinomycin could be easily transformed into 12 different 4,6-dideoxy and 3,4,6-trideoxy sugars in 4–7 chemical transformations. Notably, the yields for this process were higher than those obtained using de novo synthesis.

There has also been increased interest in the synthesis of nonulosonic acids owing to their prevalence in a number of pathogens such as *Acenitobacter baumannii* and *Pseudomonas aeruginosa*. While there have been several elegant chemical and chemoenzymatic syntheses of these molecules, most of these approaches require over 15 chemical steps to successfully execute [19]. Very recently, however, Crich et al. demonstrated that it was possible to obtain these molecules in as little as eight chemical transformations using a divergent approach with sialic acid as a common starting material (Scheme 2B) [27]. Key to this approach was oxidative cleavage of the sialic acid side chain, followed by conversion of the resulting aldehyde to one of two diastereomeric *N*-sulfinylimmines. A subsequent aza–pinacol reaction, promoted by SmI_2, then afforded the resulting 7,9-dideoxy-7-aza sialic acids. Through this work, the authors were able to obtain access to five distinct rare nonulsonic acids.

Stereoselective manipulation

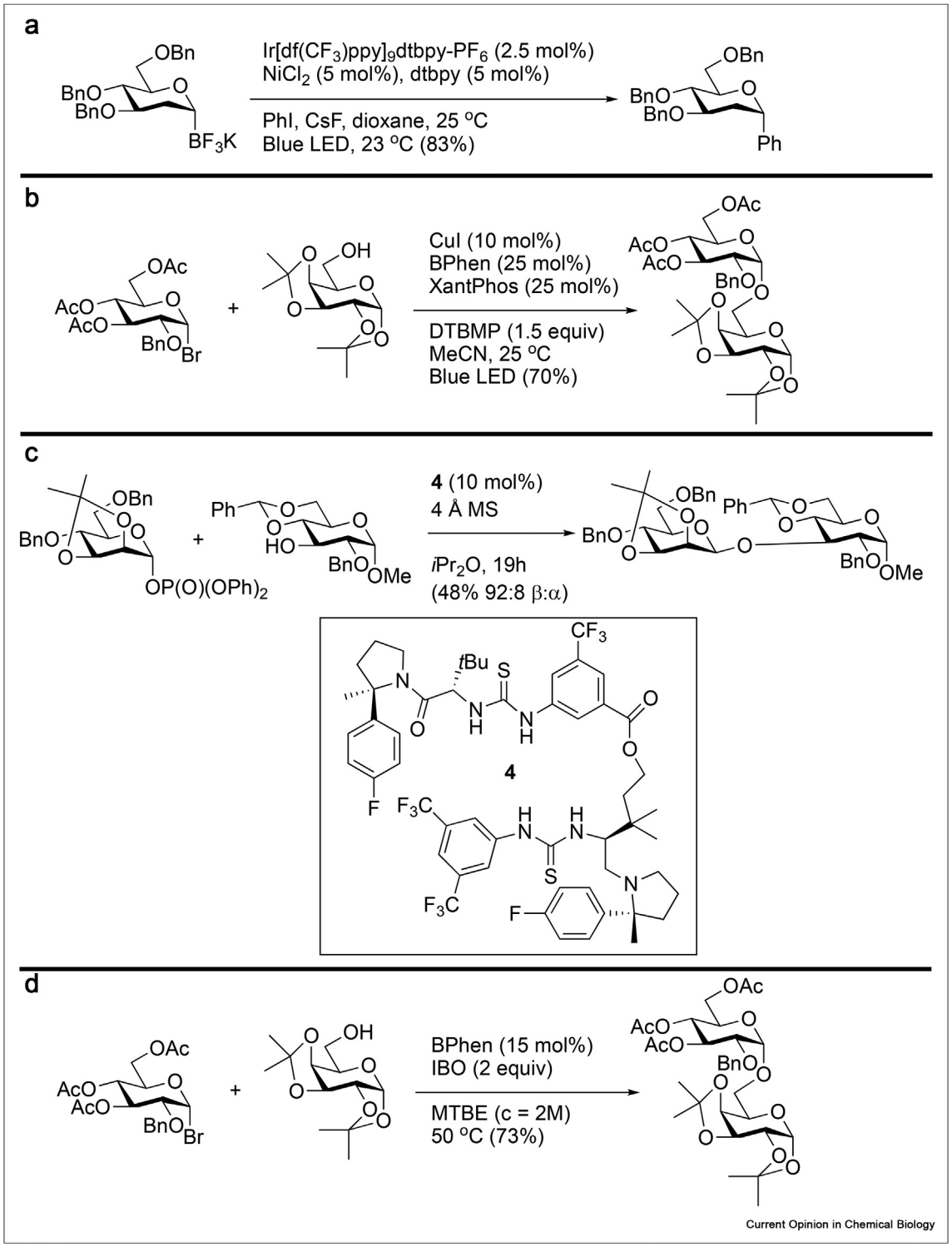
Perhaps one of the most important advances in our understanding of chemical glycosylation over the past decade has been the realization that many glycosylations proceed through an S_N2-like manifold [28**]. In the

Scheme 2



a. Taylor and Wendlandt's catalytic approaches to 2-deoxy-glycosides. **b.** Crich's synthesis of microbial nonulsonic acids.

Scheme 3



Glycosylations promoted by either photoredox catalysis (**a**, **b**) or organocatalysis (**c**, **d**).

case of reactions that proceed through the intermediacy of glycosyl sulfonates, this has been established concretely by the Crich [29**], Taylor [9**], and Bennett groups [30**], [31] through detailed mechanistic studies. In all of these cases, there is a unifying theme that S_N2-like glycosylations are possible, provided that the reaction is designed to proceed through a well-defined intermediate such as a sulfonate. Sulfonates do not provide a one-size-fits all solution to controlling selectivity in chemical glycosylation reactions, and exceptions to the rule have been observed, especially in cases where the donor possess an axial substituent at C(3) [32,33].

The above chemistries rely on stoichiometric promoters, which has led to a search for improved methods for catalytic glycoside activation. Catalytic transition metal promoted glycosylation reactions have been known for quite some time [34–36], however recent work has focused on developing catalytic systems capable of providing absolute control over the stereochemical outcome of glycosylation reactions. For example, Walczak et al. demonstrated that β-linked-2-deoxy glycosyl stannanes underwent stereoinvertive C–S coupling reactions in the presence of $CuCl_2$ and bipyridial ligands under photoredox condition [37*]. Subsequent work from this group and the Hirai lab demonstrated that α-linked 2-deoxy glycosyl boranes could also undergo stereoretentive *C*-glycosylation upon iridium-mediated photoredox activation in the presence of a Ni catalyst (Scheme 3A) [38,39]. Both reactions are presumed to proceed through a single-electron transfer process, and selectivity has been attributed to the propensity of many metals to coordinate to the α-face of glycans through a phenomenon the authors termed the "metallo-anomeric effect."[40**].

Nguyen also demonstrated that photoredox conditions could be used to activate glycosyl halides for α-selective C–O cross coupling reactions (Scheme 3B) [41]. Interestingly, these reactions have not relied on a traditional photocatalyst, but instead a combination of CuI, Bphen and XantPhos. Control experiments with radical traps demonstrated that the reaction does not proceed through an open sphere radical. This led the authors to conclude the reaction either proceeds through an α-linked glycosyl Cu(III) species or an oxocarbenium cation, although given the high selectivity observed in the reaction the latter appears unlikely.

The Jacobsen group demonstrated that bis-ureas could activate gluco-and galacto-configured α-linked glycosyl chlorides for β-selective glycosylation reactions [42]. Primary KIE studies demonstrated that the reaction was proceeding through an S_N2-like manifold following coordination of the catalyst to the halide [43**]. To broaden the scope of the reaction, this group explored the use of glycosyl phosphonate leaving groups. Using 2,3-isopropylidine protected glycans, the authors were able to obtain direct β-selective mannosylation and rhamnosylation reactions with impressive selectivity (Scheme 3C) [44*], [45] More recently, the authors have applied this approach to 1,2-*cis*-furanoside synthesis [46].

Nguyen et al. have demonstrated that electron-rich phenanthrolines can catalyze α-selective glycosylation reactions with glycosyl bromide donors (Scheme 3D) [47**] Kinetic studies indicate that the phenanthroline displaces the α-linked halide to afford a β-linked phenanthrolinium ion that undergoes S_N2-like displacement with sugar nucleophiles. The exact nature of the catalyst depends on the substrate in question, while 4,7-dipiperdine substituted phenanthrolines are optimal for 2-deoxy-2-fluorosugars [48], bathophenanthroline is a preferred catalyst for the construction of 1,2-*cis*-furanosides [49]. This reactivity tuning is similar to Jacobsen's reports of different catalysts for different substrates and the sulfonate matching described by the Bennett group (*Vida supra*). These results indicate that a single leaving group or catalyst may not provide a one-size-fits all solution to controlling selectivity in chemical glycosylation reactions, but rather a suite of promoters or catalysts, tailored to different donor reactivity, is necessary.

Automation of oligosaccharide synthesis

The technologies described above have the potential to greatly simplify oligosaccharide synthesis. Indeed, many of them have been used to address challenges that would have appeared insurmountable a decade ago. Furthermore, the use of one-pot synthesis, which has been extensively reviewed recently [50], permits the construction of many glycosidic bonds in a single reaction. All of these processes rely on manual operations, which can lead to issues with batch-to-batch reproducibility. Recent advances in automated synthesis are beginning to change this situation.

For many years the development of fully automated oligosaccharide synthesis lagged behind that of other biopolymers. A major advance to overcoming this hurdle was the introduction of the Glyconeer in 2012 by Seeberger et al. [51**]. Since its introduction and upgrade, this platform has been used for the construction of numerous oligosaccharides on much faster time scales than is possible using conventional solution-phase manipulations. Recent examples include the production of a 100-mer repeat of α-1,6-mannan in only 188 h [52]. In addition, this group has reported the use of an in-house system for the construction of more difficult to access 1,2-*cis*-glycans [53], including recent examples of an amylose 20-mer in 50 h and a hyperbranched glycogen 14-mer in 30 h [54*].

Despite these impressive advances, automated glycan assembly (AGA) is not yet comparable to DNA synthesizers in terms of speed and availability. To address the speed issue, Seeberger et al. introduced a modification to the Glyconeer that incorporated a microwave generator and a jacketed reaction system that allowed for rapid temperature adjustments from −40 to +100 °C [55**]. With the ability to rapidly cycle temperatures the authors were able to reduce reaction cycle times from 100 min to less than 1 h. The ability to achieve higher temperatures allowed for the use of a greater variety of temporary protecting groups, thereby permitting the construction of glycans containing different branches. Furthermore, recent advances in AGA permit the sulfation of glycans without microwaves, a process which had previously not been efficient [56].

To address concerns of cost and availability Demchenko et al. introduced a HPLC-based platform for solid-phase oligosaccharide synthesis [57]. Although the initial system did require substantial user input, in 2020, Demchenko demonstrated that incorporating an autosampler and two-way check valve fully automated the system [58**]. This group also introduced a new resin for automated oligosaccharide synthesis with high swelling abilities and increased sheer resistance [59]. Taken together, these advances have resulted in the creation of a synthesizer that is capable of producing many oligosaccharides of biological interest.

Both of these systems rely on pre-functionalized building blocks. Many of these molecules are not commercially available, especially in the case of unusual sugars, so prior to any automated glycan assembly it is necessary to carry out time-consuming solution-phase synthesis of the requisite protected monosaccharides. In 2020, the Bennett and Pohl labs introduced a continuous flow processing-based approach for protected monosaccharide production [60]. These flow-based reactions were significantly faster than they were in batch (minutes as opposed to hours). Subsequently, this team demonstrated that these processes could be telescoped to carry out several different reactions in a single run [61**]. Furthermore this process could be automated through the open-source Python-based Mechwolf program. While the focus of these reports was the production of rare deoxy-sugar monosaccharides, the flexibility of continuous flow processing should allow for automation of almost any manipulation that can be conducted in batch phase.

Conclusion

Recent developments in monosaccharide preparation, chemical glycosylation, and automation have greatly facilitated oligosaccharide synthesis. Indeed, many targets that were considered to present a formidable challenge a decade ago can now be routinely prepared. This is not to say that there are not still challenges in carbohydrate chemistry. Though many new and highly selective methods for glycosylation have been developed, many of these reactions have yet to be used to synthesize complex oligosaccharides. Additionally, while the construction of glycans from higher organisms is becoming a mature science, the same cannot be said of carbohydrates from bacteria and secondary metabolites. Many of these latter glycans are composed of so-called "unusual sugars" with configurations and functional groups not found in their mammalian counterparts. As such, methods developed for mammalian glycan synthesis cannot be directly applied to this latter group of compounds. Still recent advances have opened the door to exploring ways to gain access to these structures and put the synthetic carbohydrate community in a position to make new and exciting discoveries in the decade to come!

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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** of outstanding interest

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