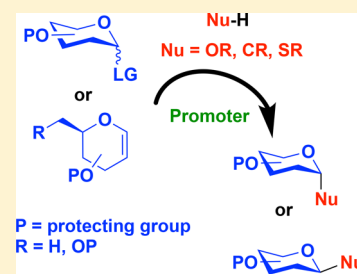# CHEMICAL REVIEWS

Review

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Methods for 2-Deoxyglycoside Synthesis

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ABSTRACT: Deoxy-sugars often play a critical role in modulating the potency of many bioactive natural products. Accordingly, there has been sustained interest in methods for their synthesis over the past several decades. The focus of much of this work has been on developing new glycosylation reactions that permit the mild and selective construction of deoxyglycosides. This Review covers classical approaches to deoxyglycoside synthesis, as well as more recently developed chemistry that aims to control the selectivity of the reaction through rational design of the promoter. Where relevant, the application of this chemistry to natural product synthesis will also be described.

CONTENTS

1. INTRODUCTION

It has been estimated that approximately one-fifth of all natural products are glycosylated, and the carbohydrates associated with these natural products are often essential for their biological activity.[1] In addition to common monosaccharides such as galactose and mannose, many of these secondary metabolites possess sugars lacking substitution at the position immediately adjacent to the anomeric center. These 2-deoxy-sugars frequently contain a number of additional modifications, including further deoxygenation (especially at the 6-position, but also frequently at the C-3 position), oxidized centers, the replacement of hydroxyl groups with amines, and the presence of tertiary centers. The number of units in the glycoside can vary from a single unit, such as in the angucycline jadomycin, to longer oligosaccharide chains, such as found in digitoxin and the
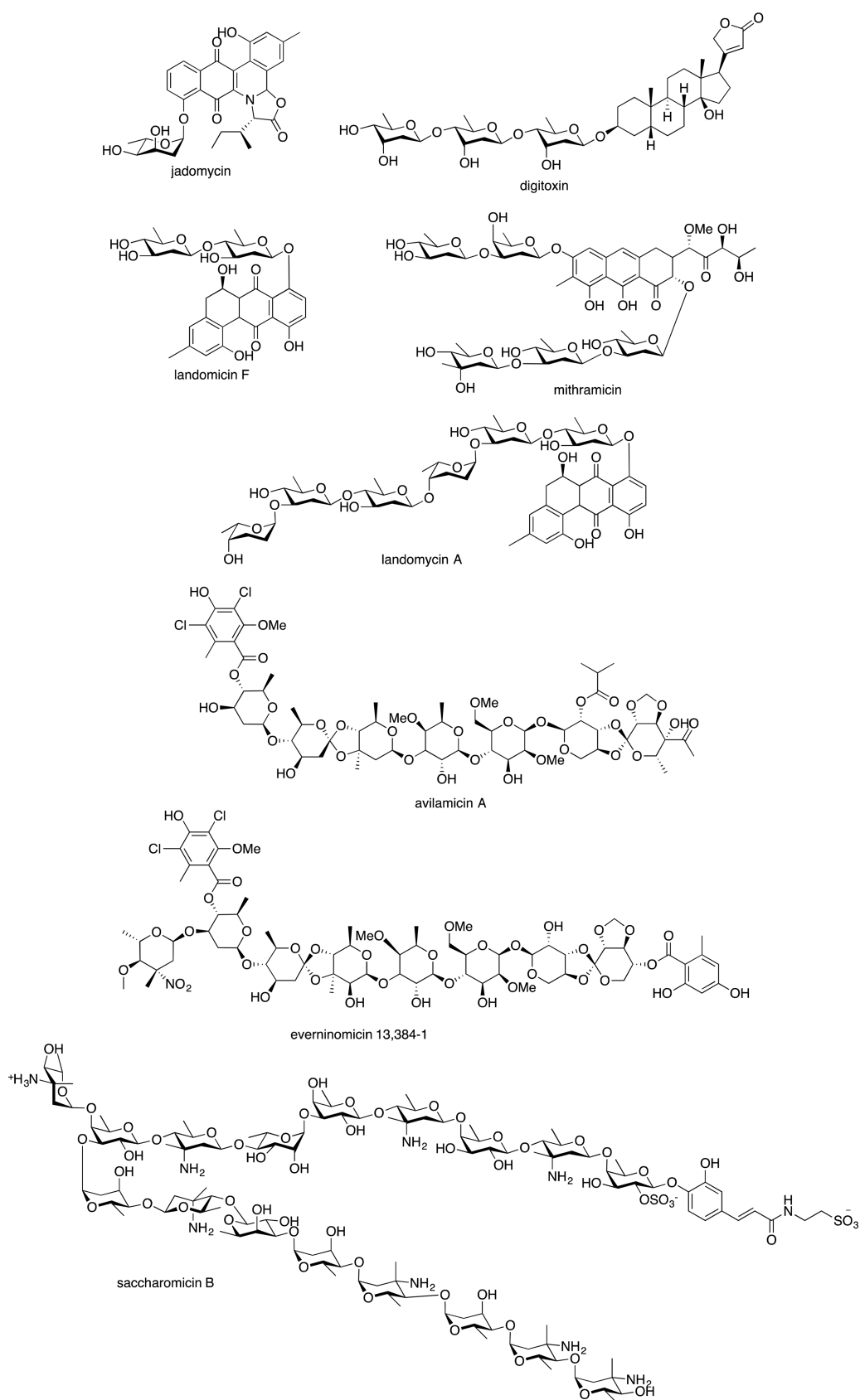
Figure 1. Representative deoxyglycoside-containing natural products.

landomycin (angucycline) and mithramycin (anthracycline) families of natural products. Although the deoxy-sugar oligosaccharide chains in most natural products are typically

short (2–6 residues), there are also examples of much larger deoxy-sugar oligosaccharides, such as those found in avilamycin

(a heptasaccharide), everninomicin (an octasaccharide), and saccharomicin B (a heptadecasaccharide, Figure 1).

Both the composition and length of these oligosaccharides can have a profound effect on the biological activity of the natural product. For example, a well-studied family of deoxy-sugar-containing natural products are the landomycins (Figure 1). First isolated by Rohr and co-workers, the landomycins are glycosylated at the C-8 position with a deoxy-sugar chain that can be anywhere from 2 to 6 residues in length.[2] These molecules possess potent anticancer activity, which is thought to arise through a mechanism shown to involve inhibition of the cell cycle between the first gap phase (G_1) to the DNA synthesis phase (S_0).[3] The activity of these molecules appears to be highly dependent on the length of the deoxy-sugar oligosaccharide chain attached to the aglycone, with longer chain structures displaying more potent levels of activity.[2]

Although the structures of deoxy-sugars are diverse, they all share one commonality. Specifically, the lack of oxygenation at C-2 precludes the use of well-established strategies for controlling the selectivity in the glycosylation reactions used for their assembly into larger oligosaccharides. As such, several research groups have undertaken studies directed at developing methods for controlling selectivity in glycosylation reactions using 2-deoxy-sugar donors. The approaches that have been developed can be broken down into five basic classes of reactivity: direct synthesis, indirect synthesis, addition to glycals, de novo synthesis, and anomeric alkylation-based approaches. These are summarized in Figure 2.
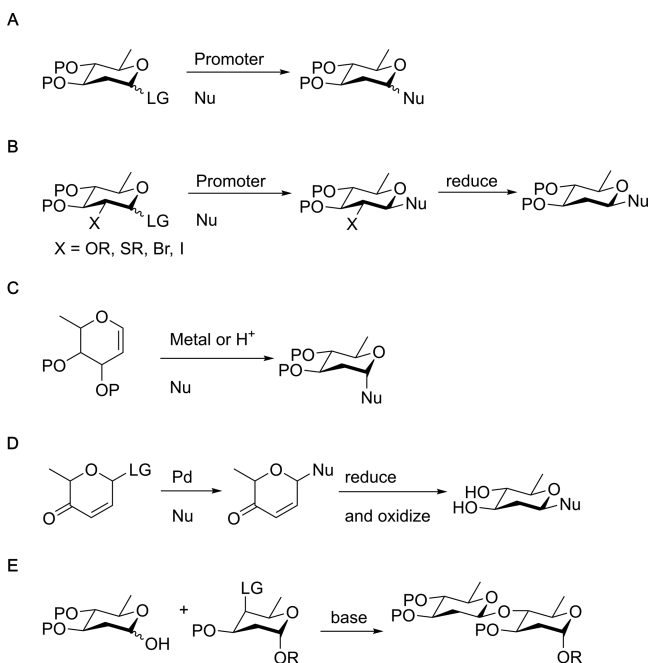
Figure 2. Examples of different approaches to deoxy-sugar synthesis. (A) Direct glycosylation; (B) indirect synthesis; (C) the use of glycals as electrophiles; (D) de novo synthesis; and (E) the anomeric alkylation approach.

Direct synthesis involves the reaction of an activated electrophilic deoxy-sugar donor with a nucleophile (referred to as the acceptor). While this is the most straightforward approach, controlling selectivity can be difficult, and a number of elegant approaches developed in recent years are addressing this issue. In contrast, indirect synthesis refers to procedures where a temporary group is introduced at C-2 of the molecule, typically an ester, thioether, or halide such as a bromide or iodide. These approaches have an advantage over many direct approaches in that they tend to undergo glycosylation reactions with very high selectivity. It is, however, necessary to remove the temporary group, necessitating additional steps in the overall synthetic scheme.

The two described approaches are very similar to standard glycosylation reactions in that they involve the reaction between a glycosyl donor with an activated leaving group and a nucleophilic acceptor. Other approaches have been developed to address the issue of selectivity in deoxy-sugar construction. For example, glycals can be activated with various electrophiles, Brønsted acids, or transition metals for reactions with nucleophiles. The selectivity in these reactions is somewhat dependent on both the stereochemical configuration of the C-3 substituent in the glycal donor and the glycosylation promoter. The vast majority of substrates and promoters tend to give α-linked products with a moderate to high degree of selectivity.

Both de novo and anomeric alkylation-based approaches have been developed more recently and tend to be mechanistically distinct from the above methods. In de novo approaches, either the donor or acceptor is not a carbohydrate but rather a carbohydrate precursor. The coupling partners are linked together through either acid−base chemistry or transition metal-mediated coupling, followed by transition metal-mediated conversion of the carbohydrate precursor to a deoxy-sugar. The advantages to these approaches are that they permit the construction of deoxy-sugars and linkages that may not be readily available using more conventional glycosylation methods. In contrast, in anomeric alkylation-based approaches, the "donor" is the nucleophile, while the "acceptor" is the electrophile. These reactions typically proceed through an S_N2-like manifold and afford products with near perfect selectivity.

This Review will examine all of these methods for the construction of deoxy-sugars. Given the extremely broad scope of this field, it will be limited to 2-deoxypyranoses. Most of the chemistries described in this Review will focus on the construction of O-glycosides; however, where relevant, S- and C-glycosides will also be discussed. There have been several excellent reviews on the construction of deoxy-sugars over the past 30 years,[4−8] with some of the most recent being the 2009 review by Hou and Lowary, the 2012 review by Borovika and Nagorny on the synthesis of β-linked 2-deoxy-sugars, and the 2017 review by Wan and co-workers. Most of these reports have focused on what at the time were recent advances in the field. Accordingly, in an effort to provide the reader with a historical context in which to evaluate more modern chemistries, this Review will begin with an introduction to important classical approaches and older but innovative methods, which perhaps deserve more attention. This will be followed by a discussion of more modern chemistries, including Brønsted acid and transition metal-catalyzed reactions as well as recent anomeric alkylation-based approaches. Where relevant, the application of these chemistries in natural product synthesis will be described under the appropriate sections. Finally, the focus of this Review will be on 2-deoxy-sugars commonly found in secondary metabolites. While sialic acids possess deoxygenation, the methods used to control selectivity in glycosylations with these molecules are very different than those employed for 2-deoxy-sugars and have been recently reviewed elsewhere.[9]

Scheme 1. Models for Selectivity in Additions to Oxocarbenium Cations of 2-Deoxy-sugars
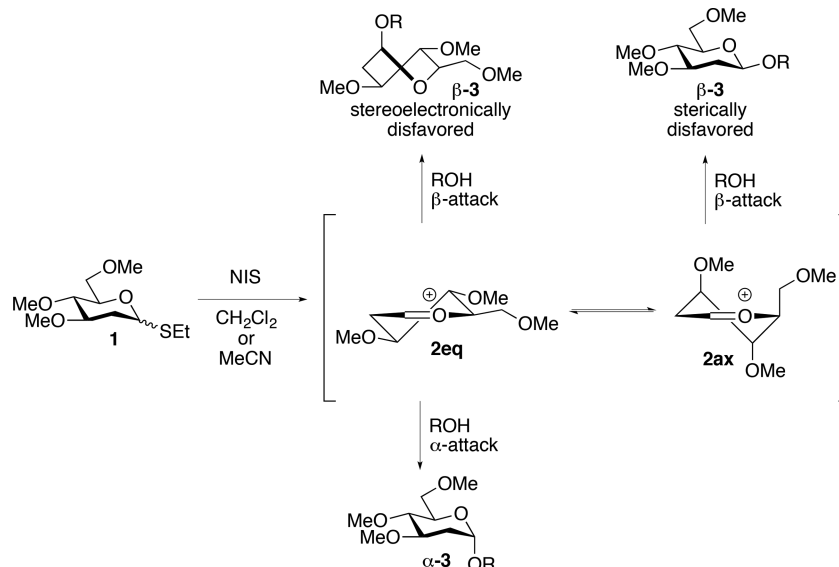
Scheme 2. Effect of Nucleophile Reactivity on Selectivity in *C*-Glycoside Synthesis
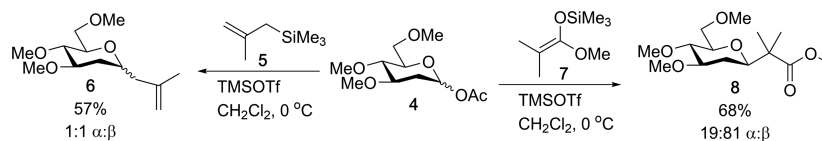
2. DIRECT SYNTHESIS

The direct synthesis of 2-deoxy-sugars most closely parallels more conventional oligosaccharide synthesis in that the glycosylation involves the reaction between an activated glycosyl donor and a nucleophilic acceptor, both of which only contain functionality in their ring systems that are found in the target compound. In the absence of anything else, these reactions would appear to be unselective, and this is often the case. There are, however, several examples in the literature where it is possible to obtain very high levels of selectivity through the proper selection of promoter, solvent, or protecting groups. Furthermore, selectivity can also sometimes be achieved through the selection of a proper combination of promoter and acceptor.

2.1. General Trends in the Reactivity of 2-Deoxy-sugars

Before going into a broader survey of direct methods for the construction of 2-deoxy-sugar linkages, it is necessary to understand something of the basic reactivity of these species. Woerpel and co-workers have done extensive studies on the stereochemical outcome of nucleophilic addition to 2-deoxy-sugar donors, as part of a larger program directed at examining stereoelectronic effects in the addition of nucleophiles to oxocarbenium ions.[10] Experiments looking at the reactions of thioglycosides with different alcohols under *N*-iodosuccinimide/triflic acid promotion showed that selectivity was highly dependent on the nucleophilicity of the acceptor,[11] with less nucleophilic acceptors reacting to provide products with higher levels of stereoselectivity (Scheme 1). The authors attribute this to how nucleophiles of varying reactivity interact with the putative oxocarbenium cation intermediate. Specifically, the oxocarbenium cation is thought to exist as a mixture of two different conformers, 2_{eq} and 2_{ax}. In this model, the latter conformer is lower in energy due to stereoelectronic stabilization by the C-3 and C-4 alkoxy-groups.[12] Although 2_{ax} is lower in

energy than the all-equatorial conformer, it is anticipated to be less reactive due to steric shielding from the C-5 substituent. Thus, conformer 2_{eq} reacts preferentially with weak nucleophiles to afford α-3 as the major product. With stronger nucleophiles whose reactivity approaches the diffusion limit (such as ethanol), reaction can occur through either the 2_{ax} conformer or the stereoelectronically disfavored face of 2_{eq} (which leads to a twist boat conformation) in addition to the preferred face of 2_{eq} to afford the product as a mixture of isomers.[13]

The above analysis is highly dependent on the nature of the promoter. In other studies with *C*-glycosides, Woerpel and co-workers found that, while reactions with glycosyl acetates promoted by $BF_3 \cdot OEt_2$ followed a similar trend, when the acetate was activated by TMSOTf more reactive nucleophiles provided products with high levels of β-selectivity. The authors attribute the observed selectivity as arising through the intermediacy of a α-glycosyl triflate, which reacts through an S_N2-like pathway.[14] In these situations, higher β-selectivity is observed with more reactive nucleophiles, as measured by Mayr's nucleophilicity parameters (N).[15,16] For example, the relatively weak allylsilane **5** ($N = 4.4$) reacts with the trimethoxy-protected 2-deoxyglucoside donor **4** upon activation with TMSOTf to afford **6** as a 1:1 mixture of isomers. On the other hand, the strong nucleophile silyl ketene acetal **7** ($N = 10.2$) reacts with this donor under otherwise identical conditions to afford **8** with ca. 4:1 β/α selectivity (Scheme 2). These observations indicate that, when a glycosyl triflate is a possible intermediate in the glycosylation process, there is a transition from an S_N1 to an S_N2 pathway that is highly dependent on the strength of the nucleophile.

Another consideration in glycosylation reactions is the impact of the reaction media. In fully substituted sugars, solvents can have a profound impact on the stereochemical outcome of the reaction, as evidenced by phenomena such as the nitrile effect[17−23] and the ether effect.[24−30] These phenomena are not

always observed with 2-deoxy-sugars, owing in part to their enhanced reactivity.[31] The effects of the solvent also depend on the intermediates in the reaction. For example, Woerpel has shown that glycosylations involving oxocarbenium cations display similar levels of selectivity if they are run in acetonitrile or CH_2Cl_2. Conversely, when there is more covalent character in the intermediate (such as a glycosyl triflate), it is possible to take advantage of solvent effects to afford high levels of selectivity. An interesting example of this is demonstrated in later studies by the Woerpel group, who showed that running reactions that proceed through the intermediacy of a glycosyl triflate in trichloro-ethylene displayed superior selectivity to those carried out in CH_2Cl_2. This was attributed to the fact that the former solvent suppresses dissociation of a glycosyl triflate to an oxocarbenium cation.[32] In general, solvent effects in deoxy-sugar syntheses are not well-understood, and care must be taken when attempting to apply a general model.

Finally, a brief discussion of the glycosyl cation is warranted here. In many instances, the selectivity is attributed to the formation of a glycosyl cation. There have been many reports of the direct observation of oxocarbenium cations by NMR spectroscopy.[33] The most common method for observing the cation is using a superacid solvent at low temperature.[34] Even in these instances, the most commonly reported species were tertiary cations or dioxocarbenium cations. In 2009, Yoshida and co-workers described the low-temperature observation of a pyranose-derived oxocarbenium cation in CH_2Cl_2 using electro-chemical oxidation (the cation pool method).[35] None of these systems, however, represented the glycosyl cation. Indirect evidence for the transient existence of the glycosyl cation came from the Yoshida lab using electrochemical activation of thioglycosides in flow systems, although the authors noted that this species could not be generated in batch reactors.[36] Later work by Crich and co-workers using ^{13}C kinetic isotope effect measurements and cation clock cyclizations provided additional indirect evidence for the formation of this species.[37,38] Finally, in 2016, Blériot and co-workers were able to directly observe the glycosyl cation of a 2-deoxy-sugar at −40 °C in superacid media.[39] Taken together, these studies provide strong evidence for the formation of glycosyl cations in at least some chemical glycosylation methods. The species are presumably extremely short-lived in conventional solvents, and it is extremely likely that the observed selectivities in glycosylation reactions can be the result of reactions of multiple species across the S_N1–S_N2 spectrum. These factors can all play subtle roles in direct glycosylation reactions with a number of different 2-deoxy-sugar donors.

2.2. Glycosyl Halides

Some of the earliest approaches to 2-deoxyglycosides synthesis relied on the use of glycosyl halides. With the exception of glycosyl fluorides, these compounds are extremely unstable and need to either be generated in situ or used immediately upon synthesis. As is the case with other classes of monosaccharides, the reactivity and selectivity of these compounds depend on the nature of the halide leaving group. Deoxy-sugar bromides and chlorides are typically activated under Koenigs–Knorr con-ditions, where selectivity in the glycosylation reaction depends on the nature of the silver salt used as the promoter. In addition, it has also been shown that 2-deoxyglycosyl bromides can be activated under halide ion conditions for highly α-selective reactions. In contrast, glycosyl iodides are highly reactive species, which can at times be used directly in S_N2-like reactions with

strong nucleophiles to afford β-linked products with high degrees of selectivity. Finally, glycosyl fluorides tend to be shelf-stable and display orthogonal reactivity to other classes of glycosyl halides. These donors are frequently activated for glycosylation by a variety of Lewis acids.

2.2.1. Glycosyl Bromides. Glycosyl bromides are among the oldest 2-deoxy-sugar donors. Reports on the synthesis of a 2-deoxyglucosyl bromide dates back to the work of Bergmann, Schotte, and Leschinsky, who described the conversion of the anomeric benzoate to the corresponding bromide using HBr/HOAc.[40] The first synthetic application of this donor was reported six years later in the construction of nucleoside analogues by Levene and Cortese.[41] Much of the work in the ensuing decades focused on the use of deoxyglycoside bromides for the preparation of nucleoside analogues,[42,43] or thioglyco-sides.[44] Two early reports describing the use (or attempted use) of 2-deoxyglycosyl halides in *O*-glycoside synthesis emerged in the early 1960s from Zorbach and co-workers during early synthetic studies on digitoxin.[45,46] Here the authors demon-strated that reacting 1-bromo-2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzol-yl ribopyranose **9** with digitoxigenin **10**, followed by removal of the *p*-nitrobenzoyl (PNB) protecting groups, afforded the desired digitoxin derivative **11** in 46% as a single β-anomer (Scheme 3).

Scheme 3. Zorbach's Synthesis of Digitoxin Analogues Using Deoxy-sugar Bromides (PNB = *p*-Nitrobenzoyl)
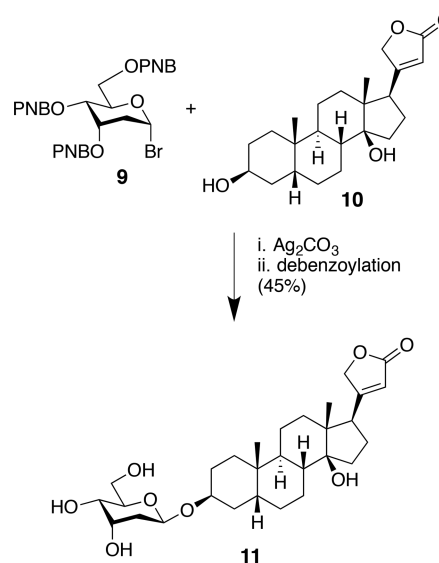
The use of 2-deoxyglycosyl bromides in *O*-glycosylation reactions became more prevalent in the 1980s. In 1980, Thiem and Meyer disclosed that methyl- and acetoxyglycosides could be readily converted to the corresponding glycosyl bromides and iodides using TMSBr and TMSI, respectively.[47] In a subsequent paper, the same investigators demonstrated that the protocol could be used for deoxy-sugar disaccharide synthesis through the construction of a fragment of chromomycin A_3.[48] In this case, the methylglycoside **12** was cleanly converted to the corresponding bromide **13** upon treatment with TMSBr in benzene followed by freeze-drying with benzene. Treating the bromide with a sugar acceptor **14** in the presence of *sym*-collidine and 4 Å molecular sieves in benzene afforded the resulting disaccharide **15** in 38% yield (Scheme 4).

Scheme 4. Thiem's Synthesis of the Chromomycin A₃ Disaccharide
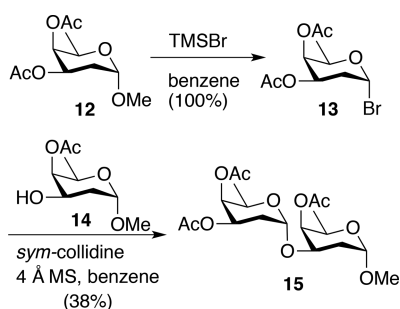
The utility of glycosyl bromides was further demonstrated by Takeuchi, Umezawa, and co-workers in their synthesis of 2-hydroxyaclacinomycin A (**18**).[49] In this approach, the requisite trideoxysaccharide was converted into the corresponding bromide **16** by treatment with Tf₂O in the presence of Et₄NBr. The product was not isolated but rather directly treated with 2,4-di-O-acetyl-2-hydroxyaklavinone **17** to afford the protected natural product in 30% yield as a single α-anomer (Scheme 5). Selectivity in the reaction was presumably the result of halide ion activation as described by Lemieux et al. for fully substituted sugars.[50]

Scheme 5. Takeuchi's Convergent Glycosylation for the Synthesis of a Protected 2-Hydroxyaclacinomycin A
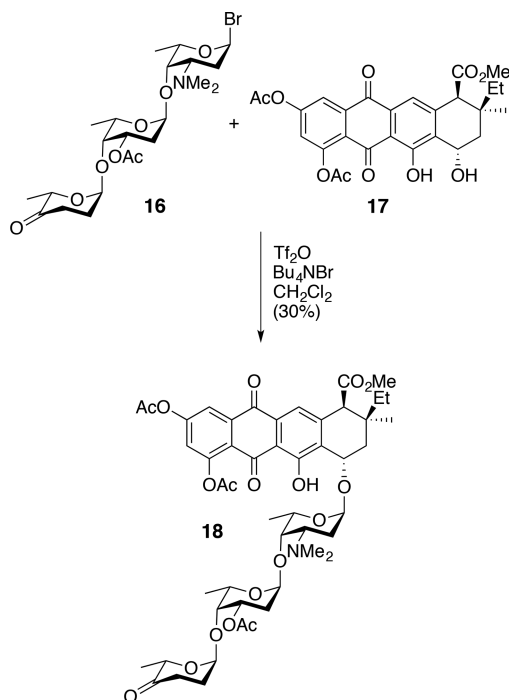
In many cases, classic Koenigs−Knorr activation of the bromide with a silver salt is superior in terms of both yield and ease of use. In a study on evatromonoside (a monoglycosylated digitoxin), Thiem and Köpper examined the effect of various silver salts on the glycosylation reaction between α-bromo-2,3-di-O-acetyl digitoxoside and digitoxigenin.[51] In these studies, either silver silicate or a 1:1 mixture of silver carbonate/silver perchlorate failed to deliver the desired target compound in yields above 24%. The authors found that the use of silver triflate

was clearly superior, however, delivering the target compound in 51% yield as a 2:3 mixture of α- and β-anomers. The same group later used this protocol in the construction of a disaccharide from mithramicin in 54% yield as a 2:1 mixture of α/β isomers.[52] The change in anomeric ratios in these latter studies illustrates the sensitivity of selectivity in the Koenigs−Knorr approach to the structure of the coupling partners.

Depending on the nature of the coupling partners, the Koenigs−Knorr couplings using AgOTf can be very selective. In studies directed at the synthesis of the cororubicin trisaccharide, Giuliano and co-workers found that treating an L-Oliose bromide donor **19** with various decilonitrose analogues (**20a−c**) as acceptors resulted in variable selectivities (Scheme 6).[53] While

Scheme 6. Giuliano's Study on the Effects of Acceptor Structure on Glycosylation Reactions with Oliose Bromide Donors

21a R = NHAc: 69% (2:3 α:β)
21b R = NHTFA: 70% (30:1 α:β)
21c R = NO₂: 20% (α only)
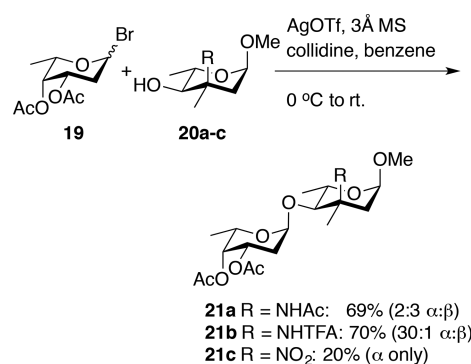
the N-acetyl-protected acceptor **20a** reacted with the donor to afford the target **21a** in good yield (69%), the selectivity of the reaction was modest (2:3, α:β). Changing the nitrogen protecting group on the acceptor from an acetate to a trifluoroacetate (**20b**) permitted coupling to the same donor in similar yield, but with vastly improved selectivity (70%, 30:1 α:β), while the use of a nitro group in this position afforded the product disaccharide **21c** as a single α-isomer in modest yield (20%). The Giuliano group would go on to demonstrate that a disaccharide acceptor was also a competent coupling partner in the reaction, permitting the construction of a protected cororubicin trisaccharide **23** in 68% yield (Scheme 7).[54]

Heterogeneous silver catalysts can offer advantages in these reactions in terms of both product purification and selectivity of the glycosylation reaction. For example, silver silicate was developed by Paulsen and co-workers for β-selective couplings.[55,56] While Thiem and co-workers found that this catalyst was not effective in their studies on the synthesis of digitoxin,[57] Binkley and co-workers found that it was useful for the construction of β-linked olivose sugars commonly found in the anthracycline antitumor antibiotics.[58,59] Interestingly, selectivity in these couplings appeared to be dependent on the acceptor. With a 4-tosyl-protected acceptor **25a**, the glycosylation with an olivose bromide donor **24** produced disaccharide **26a** in 84% yield with good selectivity (1:11 α:β). In contrast, the corresponding C-4 benzoate-protected acceptor **25b** reacted with the same donor to afford the disaccharide **26b** in 85% yield with attenuated selectivity (1:5.4 α:β), highlighting the sensitivity of these couplings to protecting group patterns on both the donor and the acceptor (Scheme 8).

The use of silver silicate for activation of deoxy-sugar bromides was relatively underexplored for several years, perhaps due in part

Scheme 7. AgOTf-Mediated Synthesis of the Cororubicin Trisaccharide
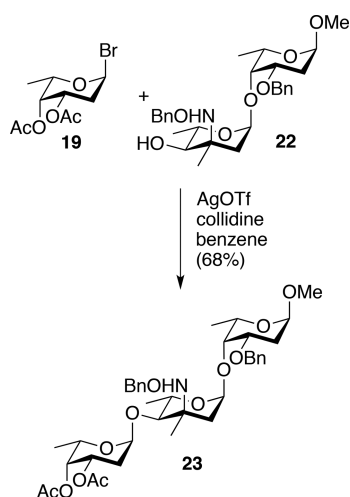
Scheme 8. Binkley's Study on the Effect of Acceptor Protecting Group on Selectivity in Glycosylations with Olivose Donors

26a R = Ts: 84% (1:11 α:β)
26b R = Bz: 75% (1: 5.4 α:β)
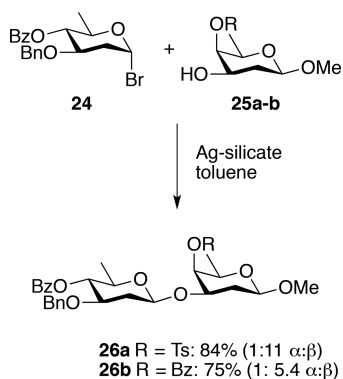
to the instability of deoxy-sugar bromides, as well as the sensitivity of the reaction to the coupling partners. For example, during their studies on the synthesis of concanamycin A, Paterson and McLeod found that a silyl-protected glycosyl bromide (**27**) reacted with a C19–C28 fragment of the natural product (**28**) in the presence of Ag silicate to afford the corresponding glycoconjugate **29** in moderate yields and low selectivity (21–39%, 1:1.3–2.5 α:β, Scheme 9).[60] More recently, in their studies on the synthesis of the apoptolidin disaccharide, Crimmins and Long found that coupling of oleandrose donor **30** with olivomycose acceptor **31** in the presence of silver silicate afforded the desired product disaccharide **32** in 68% yield as a 6:1 mixture of β- and α-anomers (Scheme 10).[61]

Most of the studies on the use of Ag-silicate for the activation of deoxy-sugar bromides were limited to particular cases; however, in 2014, Kaneko and Herzon explored the scope of this chemistry with a number of donor/acceptor pairs.[62] A series of deoxyglycosyl bromides was synthesized using trimethylsilyl bromide,[63,64] which allowed them to avoid trace acid and the aqueous workup required in other strategies that had made the synthesis of deoxy-sugar halides impractical. Through these studies, they found that the bromides reacted to form products in good to high yields (72–94%) and with moderate to high levels of β-selectivity (1:3.4 α:β to β-only). The exception was the use of C-3 benzoate-protected donor **33**, which reacted with

Scheme 9. Paterson's Studies on the Glycosylation of the C19–C28 Fragment of Concanamycin A Using Bromides
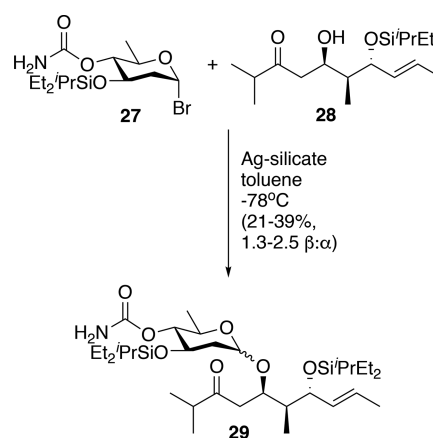
Scheme 10. Crimmins' Synthesis of the Apoptolidin Disaccharide
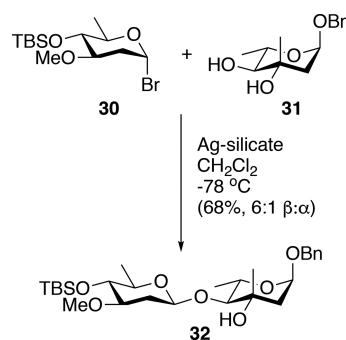
menthol in the presence of Ag-silicate to afford the coupling product **35** in 67% yield as a 1.5:1 (α:β) mixture of anomers (Scheme 11). The authors attribute this erosion of selectivity to possible long-range participation of the C-3 benzoate.

Scheme 11. Herzon's Explanation for β-Selectivity in Glycosylations with C-3 Benzoate-Protected Bromide Donors
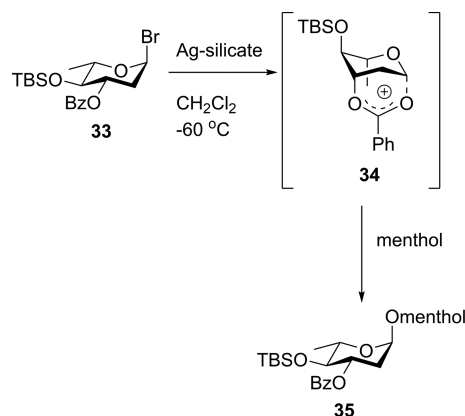
In addition to these examples, other heavy metal promoters have been used to activate deoxy-sugar bromides. This includes the use of silver zeolites[65] and mercuric salts (Helferich conditions).[66,67] These approaches have not been as widely used with deoxy-sugars as they have with their fully substituted counterparts.

2.2.2. Glycosyl Chlorides. Although less reactive than the corresponding bromides, deoxy-sugar chlorides are still moisture-sensitive species that must be handled with care.[68] Early reports from Zorbach and Payne on digitoxin mono-saccharides indicated that deoxy-sugar chlorides could be directly reacted with nucleophiles to afford glycoconjugates in moderate yield.[45,69] Most reports of the use of these donors involve Helferich conditions,[70−73] which necessarily require the use of toxic mercury salts. While the efficiency of the process varies with different substrates, it is possible to obtain synthetically useful yields under these conditions. For example, Ramiliarison and Monneret synthesized the disaccharide of musettamycine through the reaction of a 2-deoxy-3,4-di-*O*-acetylfucosyl chloride **36** with an azide-protected rhodosamine acceptor **37** in the presence of HgBr$_2$/HgO to afford **38** in 72% yield as a single *α*-linked isomer (Scheme 12).[74]

Scheme 12. Ramiliarison and Monneret's Synthesis of the Musettamycine Disaccharide under Helferich Conditions
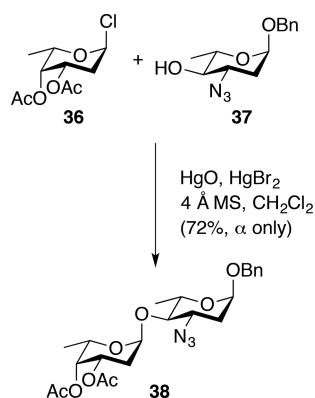
The intrinsic sensitivity of glycosyl halides to moisture is always a concern. One way around this is to generate the chloride in situ. In 2013, Verma and Wang repo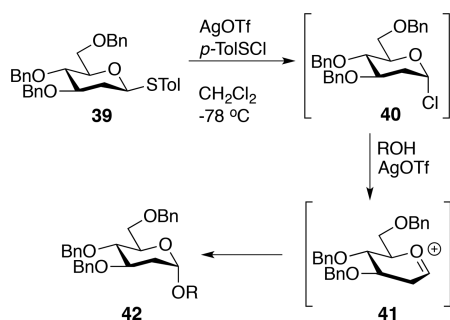rted that activating thioglycosides with a combination of AgOTf and *p*-TolSCl, followed by the addition of an acceptor, led to the formation of disaccharides with very good levels of *α*-selectivity (Scheme 13).[75] While the investigators had anticipated that the

**Scheme 13. Verma and Wang's Use of Thioglycosides as Latent Glycosyl Chlorides**

combination of AgOTf and *p*-TolSCl would convert the thioglycoside to the corresponding glycosyl triflate in situ,[76,77] ^{1}H NMR studies demonstrated that the reaction was actually proceeding through the formation of a glycosyl chloride. On the basis of further mechanistic studies, the authors concluded that in this reaction the role of the AgOTf was to remove chloride

byproducts from the reaction through a metathesis reaction to form insoluble AgCl.

2.2.3. Glycosyl Iodides. Although glycosyl iodides have been known for over 100 years,[78] they did not enjoy the same popularity as chlorides and bromides, presumably due to their sensitivity. As a consequence, it was not until the pioneering work of Gervay-Hague and co-workers in the late 1990s that these species began to gain wider appreciation as potent glycosyl donors.[79] In 2003, this same group reported that 2-deoxy-sugar acetates could be converted into the corresponding iodides using TMSI.[80] The iodides themselves were too reactive to isolate; however, they could be used in glycosylation reactions with potassium phenoxides (Scheme 14). In these reactions, the *α*-linked iodides were cleanly converted to the corresponding aryl glycosides, representing an early example of an S$_N$2-glycosylation with 2-deoxy-sugars.

Scheme 14. Lam and Gervay-Hague's Synthesis of Aryl 2-Deoxyglycosides by S$_N$2-Displacement on Glycosyl Iodides
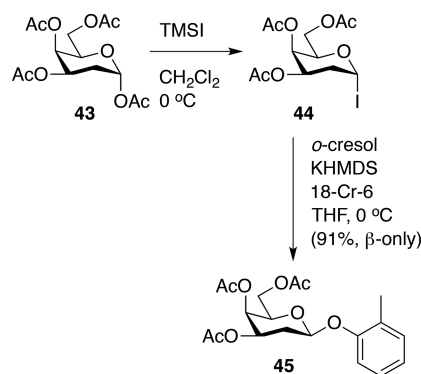
This approach has been adopted by several other groups. For example, in their studies on developing probes for *Bacillus* 1,3−1,4-*β*-glucanases, Planas and co-workers required the synthesis of a *p*-nitrophenyl (PNP) tetrasaccharide with a 2-deoxy-sugar at the reducing end.[81] To install the PNP on the tetrasaccharide, the authors converted the glycosyl acetate **46** into the corresponding iodide **47** in situ. This species was not purified but rather converted directly to the aryl glycoside **48** using the sodium salt of *p*-nitrophenol in the presence of 15-crown-5 in 30% yield over two steps (Scheme 15). While the yield is modest, it is notable that three glycosidic linkages were able to tolerate these strongly Lewis acidic conditions.

Increasing the stability of the glycosyl iodide can lead to enhanced yields. An example can be found in the syntheses by Yu and co-workers of landomycin A and D. To attach the sugar chain, the authors first glycosylated the landomycin aglycone with a 2,6-dideoxy-6-bromoglycosyl donor.[82,83] Conversion of the acetate **49** into the corresponding iodide **50**, followed by treatment of the potassium salt of the aglycone (**51**) in the presence of 18-crown-6, led to the formation of the glycoconjugate **52** in 63% yield (Scheme 16). It is noteworthy that the primary alkyl bromide tolerated the relatively basic conditions of the glycosylation reaction. This was important because the more armed 2,6-dideoxy-sugar reacted under the same conditions to afford only glycal product.

One limitation of the use of the glycosyl iodides in direct displacement reactions is that only weakly basic anionic nucleophiles (like phenoxides) cleanly undergo the reaction. For example, in their studies on the synthesis of *β*-Homo DNA

Scheme 15. Planas' Synthesis of a 4-Nitrophenyl (PNP) Glycoside via S$_N$2 Displacement of a Glycosyl Iodide

Scheme 16. Yu's Approach to Attaching the Core Sugar to the Landomycin Family of Natural Products

AgClO$_4$ and SnCl$_2$ for highly efficient glycosylations. To demonstrate the utility of this approach, the authors used the deoxy-sugar fluorides for the synthesis of the disaccharide from avermectin B$_{1a}$ (**53**) and attachment of this compound to the aglycone **54** (Scheme 17). Interestingly, the selectivity in the
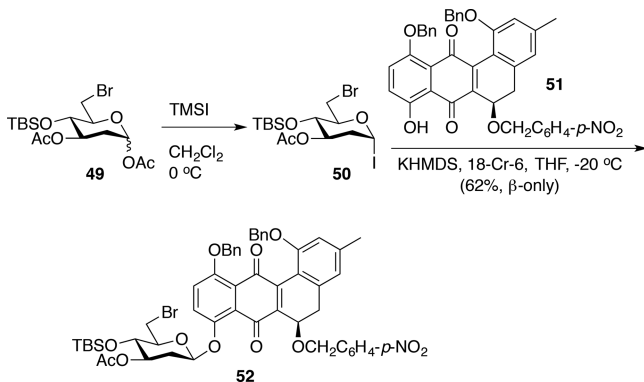
Scheme 17. Nicolaou's Use of Glycosyl Fluorides in the Synthesis of Avermectin B$_{1a}$
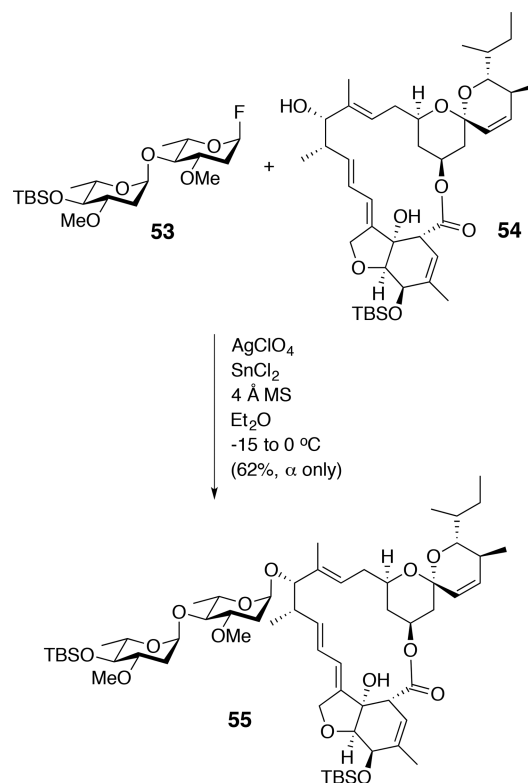
reaction appears to be highly dependent on the nature of the silver salt. In their 2016 synthesis of avermectin B$_{1a}$, Yamashita, Hirama, and co-workers found that the use of AgOTf using identical coupling partners provided higher yields in the reaction, at the expense of selectivity.[87]

This approach has also found use in oligosaccharide synthesis. For example, in a program directed at understanding the structure−activity relationship (SAR) of sialyl Lewis-X, DeFrees and co-workers reported that the coupling of a 2-deoxyfucosyl fluoride **57** with tetrasaccharide acceptor **56** using AgClO$_4$ and SnCl$_2$ in the presence of $N,N,N'N'$-tetramethylurea (TMU) afforded pentasaccharide **58** in excellent yield (85%) as a single isomer (Scheme 18).[88] In all of these cases, no explanation was provided for the origin of the observed α-selectivity.

The use of a silver salt is not necessary for the activation of the deoxy-sugar fluoride. In their 1989 synthesis of a concanamycin fragment, Tatsuta, Kinoshita, and co-workers used SnCl$_2$ alone to activate deoxy-sugar fluoride **59** for glycosylation with the C19−C28 fragment of the concanamycin backbone (**60**) in 30% yield and with moderate selectivity (Scheme 19).[89] These conditions, which were initially developed by Mukaiyama for the activation of fully substituted sugars, have been used in a number of natural product total syntheses.[90] For example, Nicolaou employed them for installing glycans in his everninomicin 13,384-1 synthesis. Treatment of a suitably functionalized disaccharide (**62**) with evernitrose fluoride **63** resulted in the formation of the ABC subunit of everninomicin (**64**) in 77% yield as a single α-

molecules, D'Alonzo and co-workers found that 2,3-dideoxy iodides reacted with metalated nucleobases in very low yield and selectivity.[84] This prompted Zhang et al. to examine the effect of various Lewis acids on deoxyglycosyl iodide activation. Through these studies, they identified AgNO$_3$ as a superior promoter for reactions between deoxy-sugar iodides and aliphatic nucleophiles.[85] Interestingly, other silver salts, including AgOTf, Ag$_2$O, Ag$_2$CO$_3$, and AgSiO$_3$, failed to promote reactions with the same level of selectivity. The origin of this counterion effect is unknown; however, the authors did demonstrate that the AgNO$_3$ system provides effective glycosylation reactions in moderate to good yield and β-selectivity with a range of acceptors.

2.2.4. Glycosyl Fluorides. Unlike other classes of glycosyl halides, glycosyl fluorides are stable donors. Common use of deoxyglycosyl fluorides began in the 1980s with the development of efficient methods for their preparation. In 1984, Nicolaou and co-workers reported that thioglycosides could be directly converted to glycosyl fluorides using a combination of N-bromosuccinimide (NBS) and either dimethylaminosulfur trifluoride (DAST) or HF-pyridine.[86] They further demonstrated that the fluoride could be activated using a combination of

Scheme 18. Synthesis of a Deoxyfucose Containing Sialyl Lewis-X Mimetic by De Frees and Co-workers
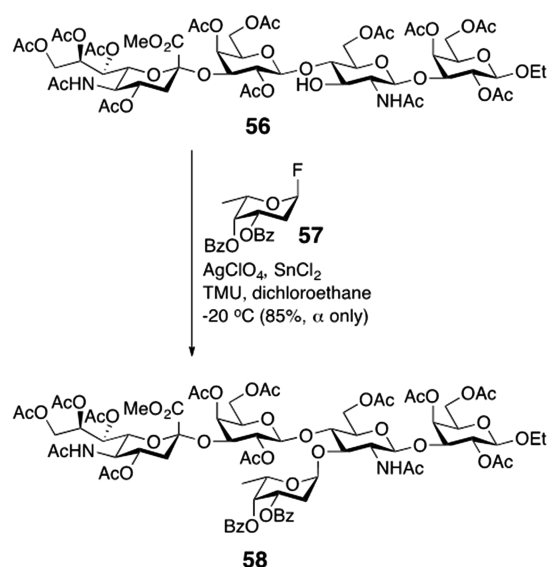
Scheme 19. Synthesis of the Glycosylated C19−28 Fragment of Concanamycin by Tatsuta, Kinoshita, and Co-workers

Scheme 20. Nicolaou's Use of an Evernitrose Fluoride in the Synthesis of the ABC Subunit of Everninomicin

Scheme 21. Nicolaou's Synthesis of the Vancomycin Disaccharide through BF₃·OEt₂-Mediated Activation of a Vancosamine Fluoride

anomer (Scheme 20).[91] A similar approach was taken by both the Nicolaou and Crimmins groups in their total syntheses of apoptolidin.[92,93]

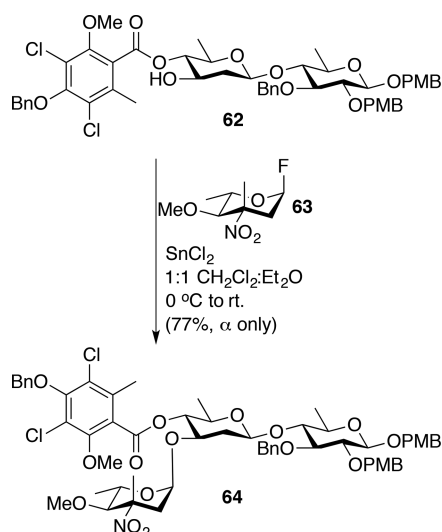Several other Lewis acids can be used for the activation of deoxy-sugar fluorides. In their synthesis of vancomycin, Nicolaou and co-workers demonstrated the utility of $BF_3 \cdot OEt_2$ and TMSOTf in coupling a vancosamine fluoride **65** to C2 of orthogonally protected glucose acceptor **66** to provide the vancomycin disaccharide **67** in 89% yield (based on 90% conversion) as a 10:1 (α:β) mixture of isomers (Scheme 21). The group further demonstrated the utility of this chemistry in coupling a monoglycosylated vancomycin derivative with a vancosamine fluoride to afford the fully protected natural product in 84% yield as a 8:1 (α:β) mixture of anomers.[94] Later, both this group and the Doi and Takahashi group would apply a similar strategy in the solid-phase synthesis of vancomycin.[95,96]

Several other Lewis acids have been shown to activate deoxy-sugar fluorides, many of which have been developed for specific cases. For example, Suzuki and co-workers have demonstrated that Cp_2HfCl_2−$AgClO_4$ is an excellent promoter for the reaction between fluoride donors and phenolic glycosides.[97,98] Further-

more, these investigators also showed that Cp_2HfCl_2−$AgClO_4$ is superior to $BF_3 \cdot OEt_2$ for promoting O- to C-rearrangements of aryl glycosides. Using this approach, the authors were able to synthesize the C-glycoside **70** found in vineomycinone B_2 (Scheme 22).

One area that has seen increasing interest in the past couple of decades is the development of more user-friendly and mild protocols for the activation of glycosyl fluorides. For example, in 1998 Schene and Waldmann reported that $LiClO_4/Et_2O$ mixtures activated glycosyl fluorides under essentially neutral conditions.[99] The yields in the reactions were generally good, although selectivity was dependent on the nature of the coupling partners. In another example, Toshima and co-workers demonstrated that the environmentally benign heterogeneous acid sulfated zirconia could also activate deoxy-sugar fluorides for glycosylation.[100,101] Throughout these studies, the authors noted that conducting the reaction in MeCN favored the formation of the α-anomer, while using Et_2O as a solvent led to β-enriched products. This runs counter to what is normally observed with these solvents. The authors attribute this unusual observation to

Scheme 22. Suzuki's Synthesis of the *C*-Glycoside Core of Vineomycinone B$_2$
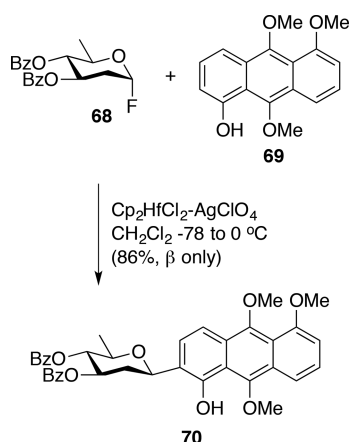
how the solvent interacts with both the Zr and the oxocarbenium intermediate. Specifically, the MeCN binds to the zirconia and is not involved in the reaction, while the ether coordinates to both the surface and the glycosyl cation, effectively blocking the α-face of the molecule from nucleophilic attack.

As with all classes of donors, the use of glycosyl fluorides can offer several advantages; however, it does not represent a universal solution to chemical glycosylation. An example of its utility comes from model studies on the cyclohexenone core of lomaiviticin A by Herzon and co-workers. While many classes of donors failed to provide useful reactions with the heavily congested aglycone **72**, the investigators found that the use of glycosyl fluoride **71** provided the desired target **73** in moderate yield as a single isomer (Scheme 23).[102] On the other hand,

Scheme 23. Glycosyl Fluorides in Herzon's Synthesis of the Lomaiviticin Cyclohexenone Core

Zeng, Wan, and co-workers found that fluorides were not the optimal leaving group for coupling a ristosamine donor to C-4 of a galactose acceptor.[103] As a consequence, many other classes of deoxyglycosyl donors have been developed, often mirroring donors used in conventional glycosylation reactions.

2.3. Thioglycosides and Their Derivatives

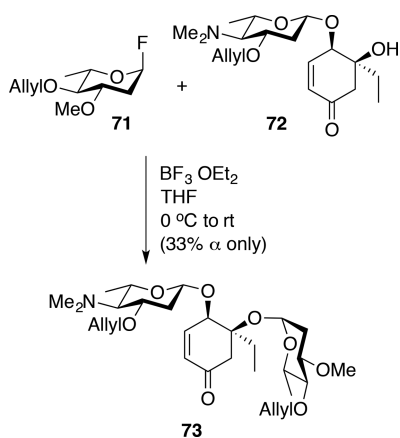**2.3.1. Thioglycosides.** Thioglycoside donors enjoy widespread popularity in carbohydrate synthesis owing to their stability and ease of activation under mild conditions. Furthermore, the ability to subject thioglycosides to preactivation allows for both iterative synthesis and the option of

transforming of these species into more reactive species in situ. A number of methods that closely mirror developments with fully substituted donors have been developed for 2-deoxy-sugars. More recently, modern concepts in oligosaccharide synthesis, such as the use of conformationally constrained donors, long-range participating groups, and glycosylation modulators, have been used with 2-deoxythioglycoside donors.

An early example of the direct glycosylation of a 2-deoxythioglycoside in complex molecule synthesis can be found in the seminal erythromycin synthesis by Woodward et al. (Scheme 24A).[104] In these studies the authors turned to the

Scheme 24. Woodward's (A) and Martin's (B) Use of Pyridyl Thioglycosides in the Synthesis of Erythromycins
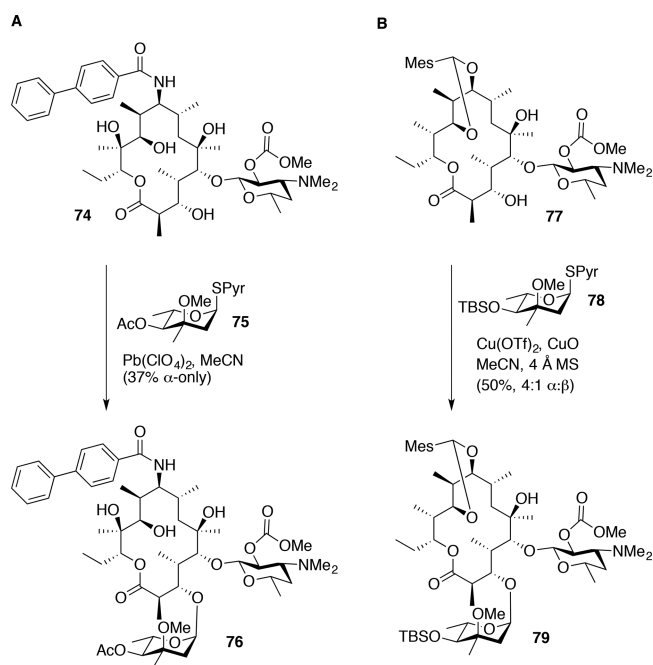
use of pyridyl glycosides[105] for the installation of the cladinose moiety on the final molecule. To this end, treating macrolide **74** with cladinoside thioglycoside **75** in the presence of Pb(ClO$_4$)$_2$ afforded the desired glycoconjugate **76** in 37% yield. Interestingly, in their synthesis of erythromycin B, Martin and co-workers reported that this protocol did not provide the desired product, albeit using a more armed donor (**78**) and slightly different acceptor (**77**). Instead, this group reported that a combination of Cu(OTf)$_2$/CuO was able to deliver the protected natural product **79** in 50% yield as a 4:1 (α:β) mixture of isomers (Scheme 24B).[106]

The low yield and toxicity of the reagents used in the Woodward synthesis led other groups to examine more attractive methods for the activation of pyridyl thioglycosides. In their 1986 avermectin B$_{1a}$ synthesis, Hanessian and co-workers reported that the avermectin disaccharide **80** could be coupled to the fully elaborated protected aglycone **54** in 72% yield using AgOTf as a promoter (Scheme 25).[107] These conditions were robust enough that both the Blizzard group at Merck[108] and the White group[109] adopted them in their synthesis of similar avermectins.

Although other approaches for the activation of 2-deoxypyridylthioglycosides have been developed,[110,111] the use of more conventional aglycones on the thioglycoside has been more widely adopted. An early example was the seminal report from the Nicolaou group in 1983 on the use of NBS to activate phenyl

Scheme 25. Hanessian's Use of Pyridyl Glycosides in the Synthesis of Avermectin B$_{1a}$

dicollidine perchlorate,[120] and ceric ammonium nitrate (CAN).[121] One promoter that has found increased usage in the current century is AgPF$_6$. In 2001, Hirama and co-workers reported that this mild promoter is capable of activating deoxythioglycosides for glycosylation reactions that provide products with moderate to good α-selectivity. Importantly, the promoter tolerates very sensitive substrates. For example, the authors demonstrated that treating advanced kedarcidin intermediate **85** with 6 equiv of mycarose thioglycoside **84** in the presence of AgPF$_6$ cleanly afforded the desired glycoconjugate **86** in 80% yield as a single isomer (Scheme 27).[122] These

thioglycosides.[112] While this work focused mostly on fully substituted sugars, it demonstrates that the conditions could be used for coupling deoxythioglycoside **81** with hindered sugar acceptor **82** to afford the desired disaccharide product **83** in 75% yield as a 3:1 (α:β) mixture of isomers (Scheme 26). These

Scheme 27. Use of AgPF$_6$ for Thioglycoside Activation As Applied to Hirama's Synthesis of the Kedarcidin Chromophore (PMBM = p-Methoxybenzyloxymethyl)

Scheme 26. NBS Activation of 2-Deoxythioglycosides in Oligosaccharide Synthesis

conditions were later adopted by the Roush group in their synthesis of the AB disaccharide unit of olivomycin A.[113] Similarly, the related *N*-iodosuccinimide (NIS) activation pro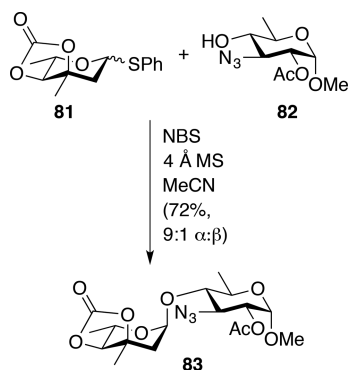tocols have also found use for the activation of deoxythioglycosides. Recent examples include the synthesis of deoxy-sugar disaccharides,[114] doxorubicin analogues,[115] and isoglobotrihexosylceramide analogues.[116]

Several other reagents for thioglycoside activation have been used as promoters in 2-deoxy-sugar synthesis, including HgCl$_2$/CdCO$_3$,[117] dimethyl(methylthio)sulfonium triflate (DMTST),[118] bis(trifluoroacetoxy)iodobenzene,[119] iodonium

conditions are mild enough that they have been adopted for the construction of sensitive natural products, such as the fully elaborated kedarcidin chromophore,[123] and libraries of duanorubicin analogues.[124−126]

Thioglycosides can also be activated using UV or visible light. In 2013, Toshima and co-workers reported that unprotected deoxythioglycosides can be activated in the presence of boronic acids using a combination of UV light and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) for very clean glycosylation reactions. The role of the boronic acid is to coordinate to diols, acting as a temporary protecting group to prevent self-condensation. Using this approach, the authors were able to glycosylate alcohols with a small excess of unprotected donor in good yield (Scheme 28).[127]

That same year, Bowers and co-workers showed that thioglycosides, including 2-deoxythioglycosides, could be activated for glycosylation by visible light if the reaction was conducted in the presence of an iridium photoredox catalyst

Scheme 28. Toshima's UV-Mediated Glycosylation of Unprotected Deoxythioglycosides in the Presence of 4-Methoxyphenylboronic Acid

Scheme 29. Bower's Visible-Light-Promoted Glycosylation

NBS, they underwent extremely selective reactions with simple glycosyl acceptors (Scheme 30A). Several years later, Ye and co-

Scheme 30. Use of Constrained Donors with Isopropylidene Acetals (A) or Cyclic Carbonates (B) in Selective Glycosylation Reactions

workers demonstrated that 2-deoxythioglycosides possessing a cyclic carbonate protecting group at C-3 and C-4, such as **95**, also underwent highly α-selective glycosylation reactions when the donor was preactivated with a combination of Tf$_2$O and benzenesulfinyl morpholine, followed by treatment with a nucleophile (Scheme 30B).[130] Importantly, under the preactivation protocol, both *cis-* and *trans-*cyclic carbonates reacted with very high selectivity, a result that was not possible with the isopropylidene acetal protocol. While the method is attractive, care must be taken when selecting constrained donors for deoxyglycoside synthesis. For example, Crich and Vinogradova demonstrated that using 4,6-benzylidene acetals of 2-deoxy-thioglycosides failed to provide selective reactions,[131] despite the successes this group has had using this protecting group for other classes of glycosyl donors.[132]

An alternative approach to protecting group control involves the use of protecting groups that can preorganize the reactants to favor the formation of one isomer over the other. In 2015, Mong and co-workers reported that the presence of a 2-picolyl (Pico) protecting group at C6 of 2-deoxythioglycoside donors permitted highly β-selective glycosylation reactions.[133] This protecting group had been developed by Demchenko and co-workers in order to control selectivity in glycosylation reactions by hydrogen bonding to the incoming nucleophile.[134−136] Mong and co-workers demonstrated that by activating the Pico-protected 2-deoxythioglycoside **98** with NIS at low temperatures (−50 °C) they were able to obtain extremely selective glycosylation reactions (α:β 1:19). The position of the protecting group did matter, as placement of the Pico group at other positions led to erosion of selectivity. Using this approach, the authors were able to synthesize the repeat unit of the landomycin E trisaccharide with good yield and selectivity (Scheme 31). Although powerful, a limitation of the approach is the need for deoxygenation at the C6 position of the donor, because most natural deoxy-sugars lack oxygen at both C2 and C6. This was achieved using a Barton−McCombie deoxygenation with Bu$_3$SnH.[137]

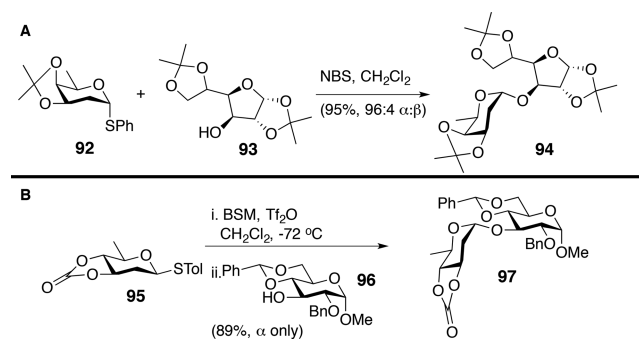In addition to hydrogen bonding, intramolecular aglycone delivery from the C-6 position has also been used for the construction of β-linked glycosides. In 2008, Sugimura and Watanabe reported the use of this tactic in their synthesis of the antibiotic cytosaminomycin C.[138] In their approach, 2-deoxythioglycoside **105** possessing a free hydroxyl at C-6 was reacted with 2-chloro-4-methoxypyrimidine to afford C-6

(Scheme 29).[128] Initial investigations into the reaction showed that it required a large excess of acceptor (10 equiv) and stoichiometric amounts of BrCCl$_3$ as a co-oxidant. Further optimization of the reaction revealed that, if it was conducted in the presence of hexafluoroisopropanol (HFIP), the stoichiometry of the acceptor and co-oxidant could be reduced to 2 equiv and 0.25 equiv, respectively. The HFIP apparently serves the role of a non-nucleophilic alcohol to help solvate and disrupt the charge-transfer complex formed upon irradiation of the Ir photocatalyst and prevent unproductive back-transfer of an electron.

While the above methods provide powerful approaches to deoxyglycoside synthesis, selectivity in these reactions is often determined on a case-by-case basis. This issue has led a number of investigators to develop strategies where selectivity in the reaction could be predicted in a more reliable manner. A common approach to doing this is through the use of specific protecting groups. In 1991, Tatsuta and co-workers demonstrated that conformationally constraining a 2-deoxythioglycoside donor would permit highly selective glycosylation reactions.[129] To this end, they examined the effect of protecting C-3 and C-4 alcohols in 2-deoxyfucose thioglycoside **92** as an isopropylidene acetal. When these sugars were activated with

Scheme 31. Mong's Use of the Pico Directing Group in the Synthesis of the Landomycin E Trisaccharide

Scheme 32. Sugimura and Watanabe's Use of Intermolecular Aglycone Delivery in Their Synthesis of Cytosaminomycin C

authors did demonstrate the application of this approach to the construction of a single 2-deoxy-sugar as proof-of-principle.

In addition to the use of protecting groups, other approaches to activation of deoxythioglycosides have been described. In one notable case, the Mong lab demonstrated that dimethylformamide (DMF) could be used as a modulator during thioglycoside activation to provide α-linked deoxy-sugars with good to excellent selectivity.[31] The reaction, which was based of their group's modification[142] of older protocols from the Koto lab,[143] involves activation of the deoxy-sugar thioglycoside **108** with NIS/TMSOTf in the presence of DMF to afford a glycosyl imidate (Scheme 33). This latter species exists in equilibrium between the more stable α-imidate **109** and more reactive β-imidate **110**. The latter imidate reacts with nucleophiles to afford products with good to excellent levels of α-selectivity (8:1 $\alp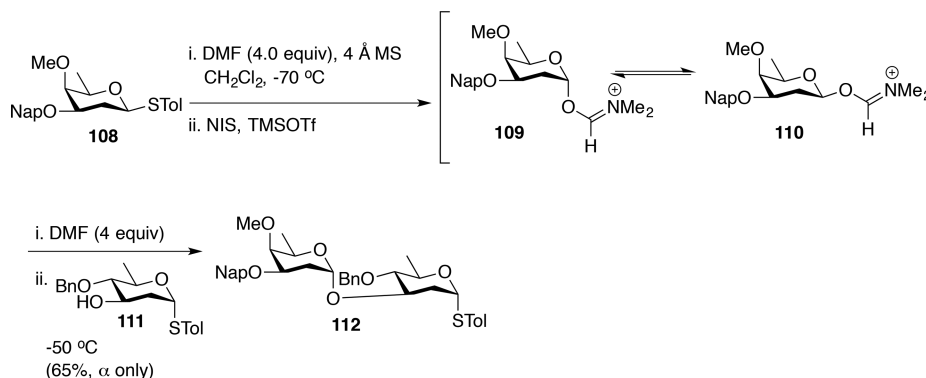ha/\beta$ to α only). Depending on the reactivity of the donor, anywhere between 4 and 12 equiv of DMF are required for the activation. Furthermore, additional DMF may need to be added after activation of the donor but before addition of the acceptor. Importantly, because the protocol relies on preactivation, it can be used in one-pot oligosaccharide syntheses to afford trisaccharides in good (45−59%) yield.

2.3.2. Thioglycoside Derivatives. In addition to standard thioglycosides, other donors possessing an S-linked leaving group have been developed for deoxy-sugar synthesis. An early example came from the Michalska lab, who reported that (2-deoxy-α-glucosyl)phosphorodithioates reacted with simple alcohols in the presence of sodium metal to afford β-linked products exclusively.[144] The donor is prepared through addition of *O,O*-dialkylphosphorodithioic acid to the corresponding glycal.[145] While the sodium metal procedure was only reported with simple alcohol acceptors, these species could also undergo reaction with sugar acceptors in moderate to excellent α-selectivity upon treatment with AgF.[146]

A particularly active variant of the thioglycosides is the glycosyl sulfoxides. In 1989, Kahne and co-workers reported that a glycosyl sulfoxide could be activated by Tf₂O at low temperatures to permit glycosylations with unreactive donors.[147] Two years later, this same group extended the use of this chemistry to deoxy-sugar donors during studies on the synthesis of the calicheamicin γ^1 trisaccharide.[148,149] Further studies by this group demonstrated that, by modulating the reactivity of the sulfoxide aglycone, it was possible to carry out one-pot synthesis of deoxy-sugar oligosaccharides. As proof-of-principle, the authors demonstrated that treating a mixture of two deoxy-sugar sulfoxides (**113** and **114**) and a deoxythioglycoside (**115**) with a catalytic amount of triflic acid in the presence of the

pyrimidine sugar **106** (Scheme 32). Activation of the thioglycoside with Me₂S(SMe)BF₄ led to the exclusive formation of the N-linked β-glycoside **107** in 74% yield. More recently, Montgomery and co-workers described a method for the construction of β-linked sugars using intramolecular aglycone delivery through a silane linker.[139] Building on earlier work from the Stork[140] and Bols[141] groups (who incorporated the linker at C2), the authors described the coupling of a C-6 hydroxyl with chlorodimethyl silane to afford a C-6 silanol. Coupling this compound to another alcohol with a catalytic amount of a N-heterocyclic carbene−copper complex resulted in the formation of a silyl acetal thioglycoside. Activation of the thioglycoside with NIS/TfOH resulted in the formation of the β-linked glycosides. Although the major focus of this work was on fully substituted sugars, the

Scheme 33. Mong's Use of DMF as a Modulator in the α-Selective Synthesis of 2-Deoxyglycosides

sulfenic acid scavenger methyl propiolate led to the formation of the ciclamycin trisaccharide **117** as the sole trisaccharide in 25% yield (Scheme 34).[150]

Scheme 34. Kahne's One-Pot Synthesis of the Ciclamycin Trisaccharide Using Glycosyl Sulfoxides
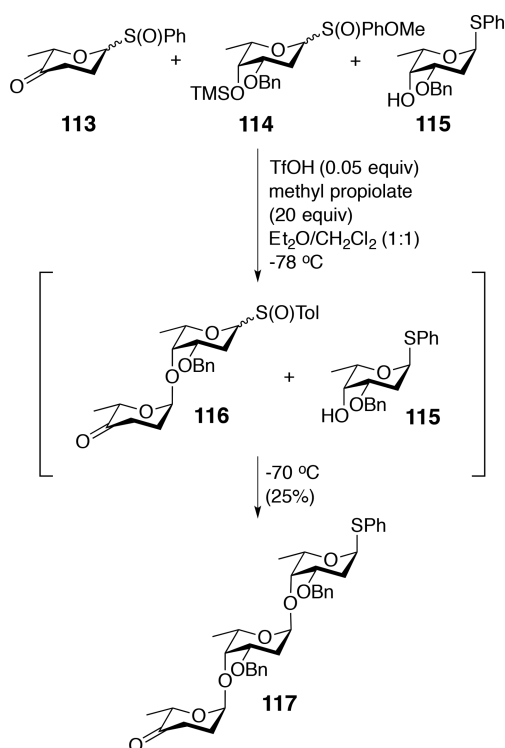
During their studies on ciclamycin, the Kahne group encountered issues with the glycosyl sulfoxide method. Specifically, they found that activation of the donor in the presence of thioglycoside acceptors could also lead to unwanted activation of the acceptor aglycone. This unwanted activation was traced back to the formation of phenylsulfenyl triflate, which is a potent activator of thioglycosides.[151,152] To suppress this background reaction, the authors examined the use of 4-allyl-1,2-dimethoxybenzene as a scavenger for the byproduct. The use of this reagent in combination with the more-hindered electron-deficient 2,6-dichlorophenyl sulfide as the acceptor aglycone led to a marked improvement in the yields of these glycosylation reactions.[153] Alternatively, milder acids could be used for the activation of the glycosyl sulfoxides. In 2000, Toshima and co-workers reported that deoxy-sugar sulfoxides could be activated for glycosylation using the heteropoly acid $H_3PW_{12}O_{40}$. These conditions are particularly mild, permitting glycosylation reactions at 0 °C in good yield and moderate α-selectivity.[154]

2.4. Activated Oxygen Leaving Groups

Many oxygen-based leaving groups (phosphates, trichloroacetimidates, etc.) tend to be both more reactive and less stable than the corresponding thioglycosides. This can present special challenges when using these groups to activate deoxy-sugars, which are significantly more reactive and less stable than their fully substituted counterparts. Despite this, these donors have found utility in a number of important applications. Furthermore, other types of donors (such as acetates) that are generally considered to be too stable for many applications in conventional

carbohydrate synthesis have been widely adopted in deoxy-sugar synthesis.

2.4.1. Glycosyl Acetates and Other Esters. The first reported use of 2-deoxy-sugar-1-O-esters as glycosyl donors came from Shafizadeh and Stacey, who demonstrated in 1957 that glycosyl acetates could be activated with $ZnCl_2$ and heat for reactions with phenols to form aryl glycosides.[155] Since that time, a number of Brønsted and Lewis acids have been used for the activation of glycosyl esters, including p-toluenesulfonic acid (p-TSA),[156] montmorillonite K-10,[157] tetraalkyl ammonium halides in the presence of other Lewis acids,[158] and $FeCl_3$.[159] Perhaps one of the most widely used promoters for this reaction is TMSOTf. First described by the Terashima group in their studies on 4-methoxydaunorubicin, it was shown that TMSOTf cleanly activates a p-nitrobenzoyl (4-NO_2Bz) ester of daunosamine (**118**) for glycosylation in excellent yield and selectivity (Scheme 35).[160]

Scheme 35. Terashima's Use of a 2-Deoxyglycosyl Acetate for the Synthesis of 4-Demethoxydaunorubicin
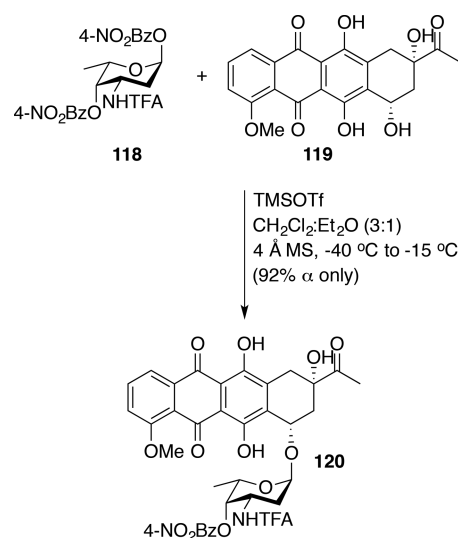
Early studies from this group using TMSOTf-mediated glycosylation of glycosyl esters indicated that simple esters, such as acetate, were compatible with this chemistry,[161] and they continue to be used up to the present day. One particularly striking recent example came from the synthesis of trioxacarin A analogues in Myers' lab (Scheme 36).[162] The synthetic plan called for late-stage attachment of the unusual sugar trioxacarcinose B to the natural product scaffold. Myers and co-workers found that this could be achieved by activating a large excess of acetate donor **121** (30 equiv) with 20 equiv of TMSOTf in the presence of acceptor **122** to afford the target structure **123** in 78% yield as a single α-isomer. Further experimentation revealed that the amount of donor required in the reaction could be reduced to 3.3 equiv without a loss in selectivity if the reaction was run at higher concentration and $TMSNTf_2$ was used as the promoter. The authors noted that attempts to carry out the reaction with other classes of donors (fluorides, thioglycosides, and pentenyl glycosides) failed to deliver product. The authors attribute the selectivity in the reaction to axial attack on the more stable oxocarbenium cation as described by Woerpel (vida supra); however, they could not rule out the possibility of in situ anomerization driving the product to the more thermodynamically stable product.

Scheme 36. Myers' Use of 2-Deoxyglycosyl Acetates in the Synthesis of Trioxacarin A Analogues

Scheme 38. Kim's α-Selective Glycosylation Using a 2-Deoxyglycosylbenzyl Phthalate Donor

for attack by the oxygen of the anomeric carbonyl to afford intermediate **130**. The activated leaving group is then ejected to afford the oxocarbenium cation **41**.

Murphy and co-workers reported that 1,6-anhydro-sugars derived from glucuronic acid derivatives, such as **131**, could be activated for glycosylation with silyl ether acceptors using SnCl$_4$ as a promoter.[167] The reactions are typically highly α-selective, especially in the 2-deoxy-sugar series (Scheme 39). A notable

Scheme 39. Murphy's Use of Constrained Glucuronic Acid Derivatives for α-Selective Glycosylation Reactions

As noted in section 2.2.4, aryl glycosides can readily undergo rearrangement to the corresponding C-glycosides in the presence of strong Lewis acids, such as BF$_3$·OEt$_2$.[163] In 1990, Suzuki and co-workers exploited this phenomenon to directly convert deoxyglycosyl acetates into the corresponding C-aryl glycosides.[164] The process involves carrying out the initial O-glycosylation at low temperature followed by warming to afford the corresponding C-glycoside (Scheme 37). From these studies,

Scheme 37. Glycosyl Acetates in O- to C-Rearrangements
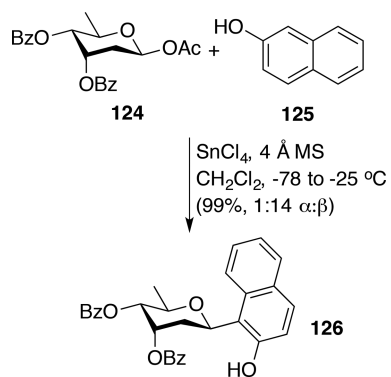
the authors determined that both SnCl$_4$ and Cp$_2$HfCl$_2$–AgOTf were efficient promoters for the reaction while BF$_3$·OEt$_2$ failed to provide completely rearranged products even at 0 °C.

Other ester-type leaving groups have been developed for glycoside synthesis, including deoxy-sugar synthesis. Kim and co-workers reported that 2-deoxyglycosylbenzyl phthalates and (2′-carboxy)benzyl glycosides could be activated with TMSOTf in the presence of acceptors to afford products in good yield with selectivity that varied with the acceptor (Scheme 38).[165,166] For example, benzyl ether-protected donors, such as **127**, tended to favor α-selective reactions, while moderate to excellent β-selectivity could be achieved by employing a 4,6-benzylidene acetal. The reaction represents an example of long-range activation where the promoter first activates the benzyl ester

exception is when 2-iodo-2-deoxy-sugars are used as donors in the reaction. Under the reaction conditions, the latter substituents react with O-acceptors to preferentially afford β-linked products. The authors attribute the selectivity to an S$_N$2-like displacement of the activated anomeric ester; however, they could not rule out in situ anomerization. In the case of the 2-iodo-sugars, they invoke anchimeric assistance to explain the selectivity. Such selectivity with these latter compounds is typical of what one would expect with 2-iodo-sugars, which have figured prominently in indirect synthesis (vide infra).

2.4.2. Trichloroacetimidates. Trichloroacetimidates were first developed by Schmidt to provide a facile method for the synthesis of glycosidic linkages under mild conditions.[168] While they have emerged as powerful donors for the synthesis of a variety of glycosidic linkages, their use in direct glycosylations for 2-deoxy-sugar construction is somewhat limited (however, see applications in indirect methods below). This is due to the fact that the highly reactive nature of 2-deoxy-sugars can render the

Scheme 40. Hirama's Synthesis of a Glycosylated Kedarcidin Intermediate Using Polymer-Bound DBU To Synthesize the Trichloroacetimidate Donor
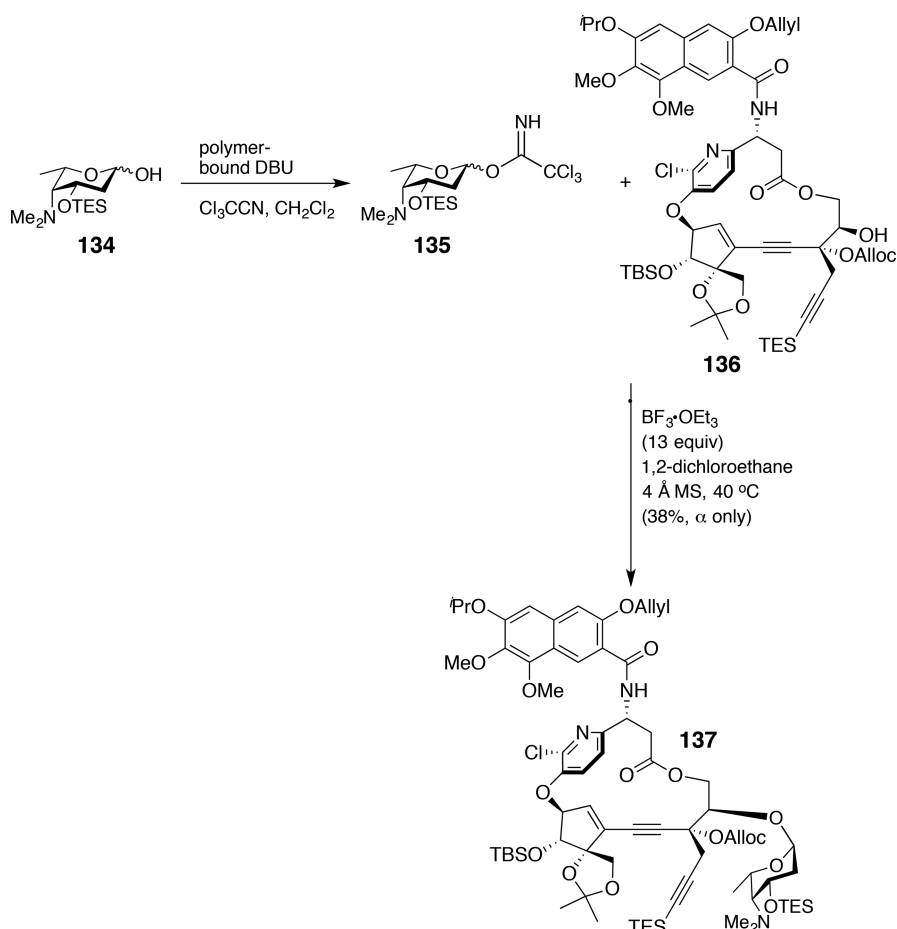
Scheme 41. Boons' Use of Chiral Auxiliaries (A) and Allyl Glycosides (B) for α-Selective Glycosylations
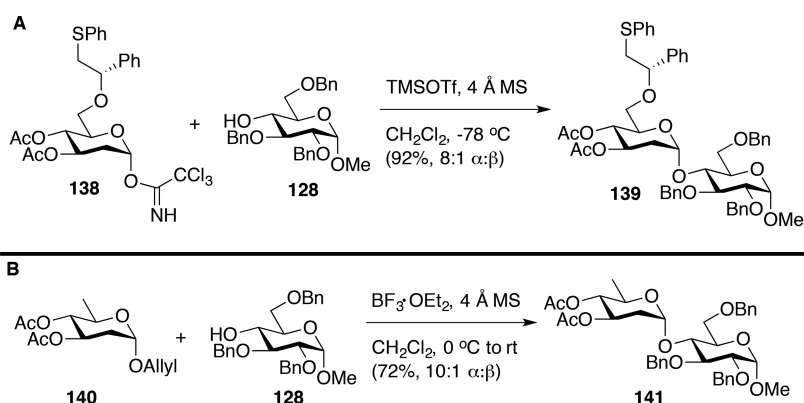
corresponding trichloroacetimidates unstable to water and mild acid. Despite this, they have proven to be useful donors for both natural products synthesis and the development of stereoselective glycosylation methods. In many cases, activation of 2-deoxyglycosyl trichloroacetimidates under standard Lewis acid conditions (TMSOTf, AgOTf, BF$_3$·OEt$_2$, etc.) provides generally unselective reactions.[169−173] There are exceptions to this rule, however. For example, as part of their studies on the kedarcidin chromophore, Hirama and co-workers needed a method for both synthesizing the unstable kedarosamine trichloroacetimidate and attaching it to an aglycone fragment that could be incorporated into the natural product (Scheme

40).[174] After a number of conventional approaches failed to deliver the desired trichloroacetimidate, the authors turned to using polymer-immobilized 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and trichloroacetonitrile to convert hemiacetal **134** into the corresponding trichloroacetimidate **135**. The product could be isolated by simple filtration and, following solvent evaporation, can be used in the subsequent reaction. The authors further found that activating the donor with excess BF$_3$·OEt$_2$ in the presence of kedarcidin intermediate **136** provided the desired product **137** in moderate yield (38%) as a single α-isomer. As with other reactions with highly selective glycosylations, the authors attribute selectivity to attack on the

more stable isomer of an oxocarbenium cation. It is unclear, however, why this appears to work for certain classes of deoxy-sugars and not others. Clearly, more work needs to be done to understand the stereochemical outcome of these reactions.

As with 2-deoxythioglycosides, protecting groups can also aid in controlling the selectivity of glycosylation reactions with 2-deoxy-sugar trichloroacetimidates. For example, in 2008, Boons and co-workers applied their chiral auxiliary-based approach[175] to the construction of α-linked 2-deoxy-sugars.[176] By installing the auxiliary at the C-6 position of the 2-deoxyglucose donor **138**, the authors were able to effect glycosylation reactions using TMSOTf to afford products in excellent yield with good to excellent α-selectivity (Scheme 41A). Interestingly, the chirality of the auxiliary did not affect the stereochemical outcome of the reaction. The authors also attempted to install the auxiliary at the C-4 position of an olivose derivative; however, treating a mixture of the allyl glycoside and the auxiliary precursor with BF₃·OEt₂ led to the formation of a disaccharide as a single isomer. Importantly, the result proved to be general, and activation of a variety of 2,6-dideoxy allyl glycosides with BF₃·OEt₂ led to the formation of α-linked products in good to excellent selectivity (Scheme 41B).

In another example of the use of protecting groups to control the selectivity in glycosylation reactions, Tanaka, Yoshizawa, and Takahashi reported that trichloroacetimidates possessing a 4-*O*-benzylsulfonate group at the C-4 position (such as **142**) underwent highly β-selective glycosylations when activated with a combination of I₂ and Et₃SiH (Scheme 42).[177] The

Scheme 42. Tanaka, Yoshizawa, and Takahashi's Use of the Benzylsulfonate Protecting Group for β-Selective Glycosylations
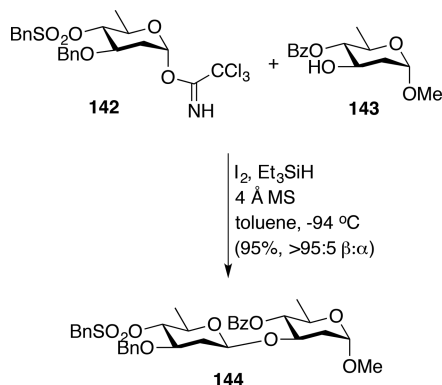
authors demonstrated that the selectivity in the reaction was highly dependent on the C-4 protecting group as the use of benzyl ethers in this position failed to provide selective reaction. Furthermore, the reaction was also sensitive to the configuration and electronics of the sugar. While olivose and digitoxose donors reacted to provide products with excellent levels of selectivity, oliose donors underwent reactions with slightly attenuated selectivity. The authors later illustrated the versatility of this chemistry by using it to synthesize a small library of landomycin hexasaccharide analogues.[178]

The reasons for the selectivity in the reaction are unclear but may be due to the electron-deficient nature of the donors or long-range participation from the sulfonate group. Another recent example of the use of a highly electron-deficient donor to achieve a β-selective glycosylation is Danishefsky and co-workers' studies toward the synthesis of pluraflavin A. This group's approach

required a late-stage installation of *epi*-vancosamine on the aglycone. This was achieved by activating the *epi*-vancosamine trichloroacetimidate **145** with BF₃·OEt₂ in the presence of the protected pluraflavin A aglycone **146** at −40 °C to afford the glycoside **147** in 48% yield as a single *β*-isomer (Scheme 43).[179]

Scheme 43. Installation of the *epi*-Vancosamine in Danishefsky's Synthesis of Pluraflavin A
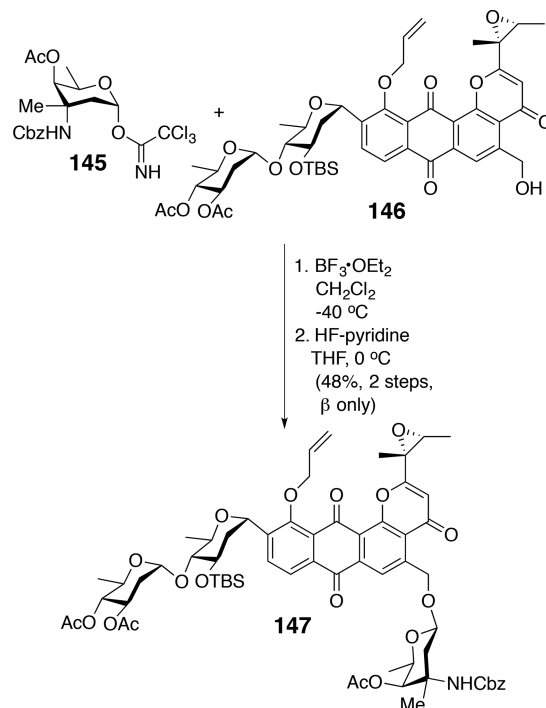
In addition to electronics, the nature of the activating agent can also play a role in the stereochemical outcome of glycosylation reactions. Tanaka, Takahashi, and co-workers reported that activating deoxy-sugar trichloroacetimidates possessing a sulfonate at the C-4 position (**142**) with a combination of IBr and Bu₄NBr led to highly α-selective reactions (Scheme 44).[180] Interestingly, just as with their β-selective chemistry, the use of a sulfonate protecting group on C-4 of the donor was critical for obtaining optimal selectivity. The authors did not speculate about the causes for the change in selectivity; however, they did

Scheme 44. Tanaka and Takahashi's α-Selective Glycosylation Controlled by a C-4 Sulfonate on the Donor
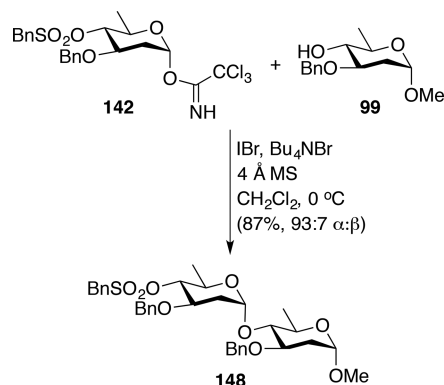
demonstrate its utility in the synthesis of the macrolide versipelostatin.

2.4.3. Phosphites. As noted above, 2-deoxyglycosyl trichloroacetimidates can be very sensitive to moisture and common purification media such as silica gel. In contrast, Thiem and co-workers demonstrated that 2-deoxy-sugar dialkyl phosphites were stable to column chromatography (although the corresponding 2,6-dideoxy species were not).[181] The enhanced stability of these species prompted Schmidt and co-workers to explore their utility as glycosyl donors in 1994.[182] Through these studies, the Schmidt group demonstrated that 2-deoxyglycosyl phosphite **149** could react with primary acceptor **90** in the presence of BF₃·OEt₂ to afford the disaccharide product **150** in 77% yield and good α-selectivity (Scheme 45). Secondary acceptors were also competent coupling partners in the reaction, provided that activation was carried out using SnCl₄.
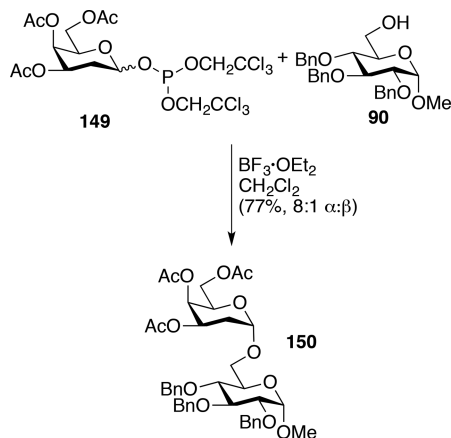
One year later, Hashimoto and co-workers demonstrated that 2-deoxyglycosyl diethyl phosphites could be activated with TMSOTf at −94 °C for β-selective glycosylation reactions.[183] In general, the selectivity of the reaction was substrate-dependent, and 2-deoxyglucosyl donors reacted with higher selectivity than the corresponding 2-deoxygalactose derivatives. This trend also held in the 2,6-dideoxy-sugar series, where donors with an equatorial benzyl ether at C-4 provided superior selectivity to those with an axial benzyl ether at the same position.

Guo and Sulikowski made extensive use of the Hashimoto protocol in their synthesis of the landomycin A hexasaccharide (Scheme 46).[184] During the course of these studies, they found that disaccharide phosphite **151** reacted with monosaccharide acceptor **152** to provide trisaccharide **153** in good yield and moderate selectivity. Attempts to convert the trisaccharide hemiacetal into the corresponding diethyl phosphite failed to provide the desired donor, owing to the instability of this leaving group. To address this issue, the authors examined the synthesis of the corresponding pinacol phosphite **154**. This latter donor was readily synthesized from **153** and underwent glycosylation with trisaccharide acceptor **155** to afford the desired landomycin A hexasaccharide **156** in 42% yield as a roughly 1:1 mixture of anomers.

Inspired by the observation that the nature of the alkyl groups on the phosphite impacts the reactivity of the donor, Sulikowski and co-workers next examined the possibility of using different phosphites in one-pot oligosaccharide synthesis.[185] By comparing the reactivity of a diethyl phosphite glycoside and pinacol phosphite glycoside using NMR, they were able to establish that the former would react with nucleophiles preferentially over the latter. To demonstrate the utility of these sugars in one-pot syntheses, they carried out the one-pot synthesis of a trisaccharide (Scheme 47). To this end, activation of the diethyl phosphite glycoside **157** by catalytic TMSOTf in the presence of the pinacol phosphite glycoside **158** led to the formation of a

Scheme 45. Schmidt's Use of Glycosyl Phosphates in 2-Deoxy-sugar Glycoside Synthesis

Scheme 46. Sulikowski's Use of Glycosyl Phosphates in the Synthesis of the Landomycin A Hexasaccharide
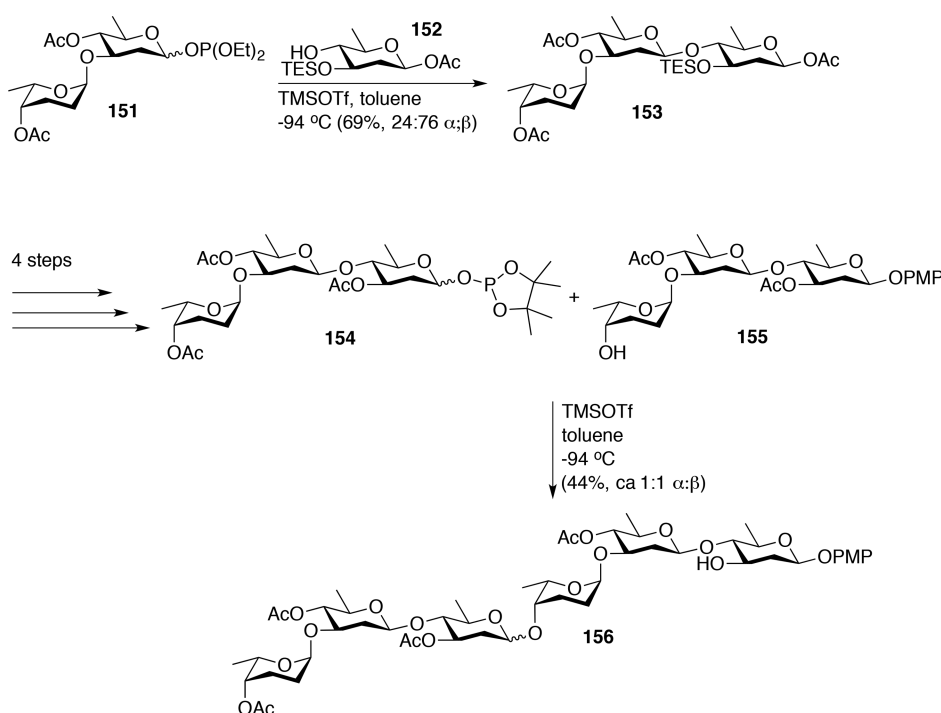
Scheme 47. Sulikowski's Use of Differential Glycosyl Phosphite Reactivity in the One-Pot Synthesis of a Trisaccharide
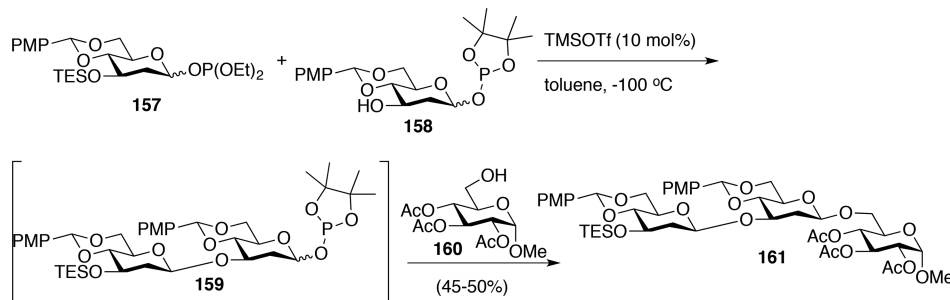
single disaccharide (**159**), which was not isolated but rather reacted further with acceptor **160** to afford the corresponding trisaccharide **161** in 50% overall yield in one pot. Several other methods are available for activating deoxysugar phosphites, such as LiClO$_4$/Et$_2$O[186] and montmorillonite K-10,[187,188] although these approaches have not been widely adopted.

2.4.5. Hemiacetals. Hemiacetals offer many advantages in carbohydrate synthesis in that they are shelf-stable donors that can be activated through a variety of methods. This can range from acid-promoted dehydration to reactions that convert the hemiacetal into a highly reactive species, which undergoes glycosylation in situ. One of the first reports of using a sugar hemiacetal as a glycosyl donor came from the Roush lab as part of their studies toward the synthesis of olivomycin.[189,190] During the course of these investigations, the authors found it necessary to develop methods for the synthesis of β-linked aryl deoxyglycosides. In an effort to effect this transformation, they opted to adapt the Mitsunobu glycosylation to deoxyglycoside synthesis.[191−193] To this end, they initially examined the reaction between deoxy-sugar hemiacetals and naphthol; however, they were only able to obtain products as a 2:1 β/α mixture of anomers.

Several years later, Yang and Yu reported that they were able to obtain moderate to high levels of selectivity in Mitsunobu glycosylations during their synthesis of the jadomycin family of natural products (Scheme 48).[194] Utilizing a strategy that would

Scheme 48. Yu's Use of the Mitsunobu Glycosylation in Their Synthesis of Jadomycin S

164a R = H, 62%, 5:1 α:β
164b R = Me, 60%, 10:1 α:β
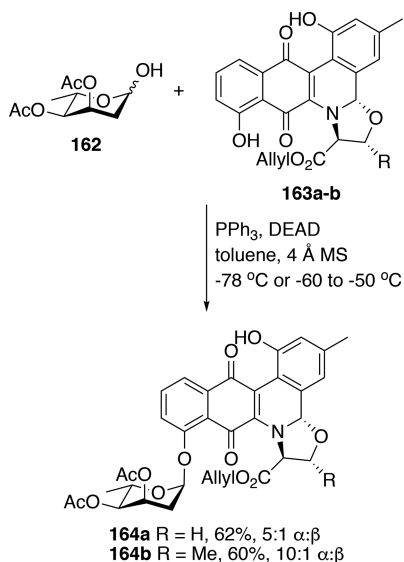
require late-stage installation of the digitoxose moieties found in jadomycins S and T, the authors examined the reaction between diacetyl digitoxose **162** and two jadomycin aglycones (**163a** and **163b**). Activation of the hemiacetal with a combination of PPh$_3$ and diethyl azodicarboxylate (DEAD) followed by treatment with the aglycone led to the formation of the desired products (**164a** and **164b**) in good yield and moderate to good α-selectivity (5:1 to 10:1 α/β). It is interesting to note that in these studies the glycosylation reaction appeared to be highly sensitive to distal functional groups in the aglycone. No explanation for this observation was provided.

An alternative approach to hemiacetal activation relies on the use of Lewis acid catalysis to effect dehydrative glycosylation. In 1997, Mukaiyama and co-workers reported that armed 3,4,6-tri-O-benzyl-2-deoxyglycopyranose could be activated for highly selective glycosylations using a catalytic amount of triphenyl-methyl tetrakis(pentafluorophenyl)borate in the presence of Drierite.[195] The reactions were highly α-selective, which the authors attribute to in situ anomerization. In a similar vein, Toshima and co-workers reported that the heteropoly acid H$_4$SiW$_{12}$O$_{40}$ also promoted dehydrative glycosylations with the same donor in good yield and high α-selectivity.[196] While no rationale was provided for the selectivity, it is conceivable that it is again the result of in situ anomerization.

One way to effect dehydrative glycosylation under milder conditions is the Gin glycosylation, which relies on the combination of diphenyl sulfoxide and Tf$_2$O to activate hemiacetals as triflates.[197] Surprisingly, while the method has been widely used in carbohydrate synthesis, it has been underutilized in glycosylations with deoxy-sugar donors. An exception is the report from the Burke lab directed at studying the effects of deoxygenated mycosamine derivatives on reducing the toxicity of amphotericin B.[198] To carry out these studies, it was necessary to glycosylate the amphotericin aglycone to a 2-deoxymycosamine derivative. This was achieved by using the Gin glycosylation between mycosamine hemiacetal **166** and aglycone **165** to afford the desired target **167** in excellent yield as a 2:1 mixture of α and β isomers (Scheme 49).

More recent studies on activating deoxy-sugar hemiacetal derivatives have focused on approaches designed to provide predictable selectivity in the glycosylation reactions. These will be discussed in section 4.7.

3. INDIRECT APPROACHES

Indirect approaches rely on the introduction of a prosthetic group to the glycosyl donor in order to control the selectivity of the glycosylation reaction. The earliest methods relied on the addition of a nucleophile acceptor and some other group (typically a halide) across the olefin of a glycal. Alternatively, a prosthetic group, such as a halide, thioether, or ester, may be

Scheme 49. Burke's Use of the Gin Glycosylation in the Synthesis of 2-Deoxy-sugar Analogues of Amphotericin B
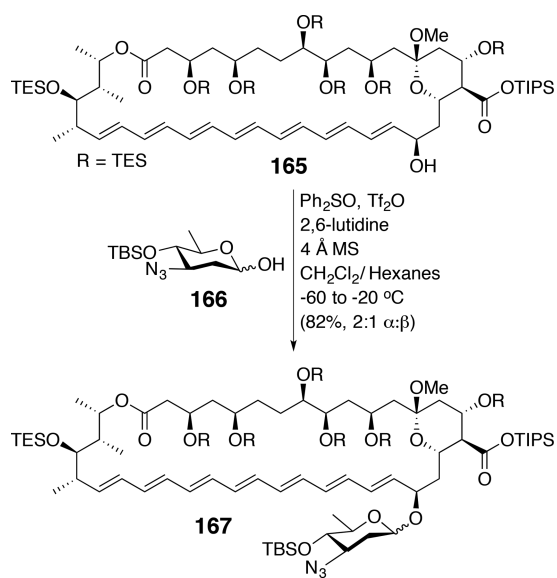
present in the donor prior to glycosylation reaction. In the latter case, the prosthetic group is typically introduced at the C2 position, but examples of introduction of these groups at other positions exist (notably C1). Both approaches add steps to the overall deoxyglycoside synthesis as the prosthetic groups must be removed following glycosylation. Despite this, indirect approaches are able to reproducibly provide extremely high levels of selectivity that are not possible with classical direct approaches. As a result, these strategies continue to be used in combination with more modern glycosylation chemistries. Accordingly, this section will serve to introduce the key concepts of indirect approaches, which will be elaborated on in discussions of modern approaches to deoxy-sugar synthesis later in this Review.

3.1. Additions to Glycals

Numerous methods have been developed for the addition of nucleophiles across the alkene of a glycal. Many classical approaches involve mild acid-promoted glycosylation using catalysts such as sulfonic acids,[199] triphenylphosphine hydrobromide,[200] or acidic resin AG50W-X2/LiBr.[201] In general, these reactions are α-selective provided there is not an axial ether or ester at the allylic C-3 position. Furthermore, the reactions afford the desired products in moderate to good yield, provided that there are no extremely acid-sensitive functional groups in the target. Importantly, these approaches serve as the basis of many of the modern catalytic processes that have been developed in the past decade (vide infra). Still, there are many cases where these classical acid-based approaches are less than ideal, and alternative methods for glycal activation have to be explored.

In 1965, Lemieux and Morgan reported that iodonium di-*sym*-collidine perchlorate could activate glycals for nucleophilic addition to afford glycosylation products possessing an iodide at C-2 of the donor glycan.[202] The newly formed glycosidic linkage is formed in approximately 4:1 α:β ratio, and the iodide can be removed using hydrogenolysis following the reaction. In an effort to improve upon this, Thiem and co-workers reported the use of NIS as an iodonium source. These latter reactions were high yielding and highly α-selective with a range of substrates. It was proposed that the selectivity arises through the conversion of the

alkene to an iodonium ion on the β-face of the molecule. Attack by the nucleophile at the anomeric center from the α-face of the molecule then generates the product. Because of the sheer bulk of the NIS, this approach permits the construction of α-linked glycosides on substrates that normally favor the formation of the β-anomer. For example, digitoxals such as **168** typically react to afford β-enriched products; however, using the NIS method, Thiem and Köpper were able to construct α-linked digitoxosides as single isomers in moderate yield. This allowed them to synthesize the trisaccharide core of the kijanimicin oligosaccharide (**170**, Scheme 50).[72]

Scheme 50. Activation of Glycals for the Construction of the Core Tetrasaccharide of Kijanimicin
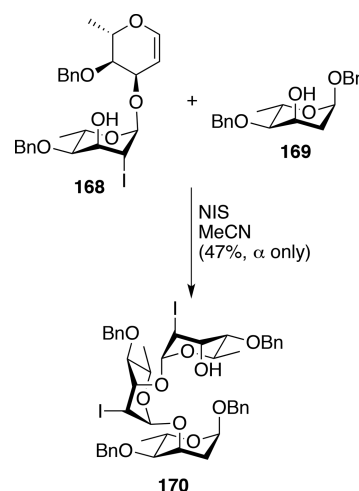
Electrophilic chalcogens have also been used to activate glycals for addition of an acceptor. The selectivity in these reactions depends on several factors; however, as a somewhat general rule, the larger selenium-based electrophiles favor α-addition of the acceptor. On the other hand, smaller oxygen- and sulfur-based electrophiles favor β-attack by the nucleophile. An early example came from the Sinaÿ lab, who demonstrated that glycals can be activated using phenylselenyl chloride followed by treatment with a nucleophile to afford predominantly α-linked products.[203] Deselenation using Ph$_3$SnH in refluxing toluene afforded the desired glycoside.

In 1987, Ito and Ogawa reported that glycals could be activated by sulfenate esters (ROSPh) in the presence of TMSOTf to afford 2-deoxy-2-phenylthioglycosides in good yield.[204] Desulfurization could be achieved by treating the products with Raney Ni in refluxing EtOH. Although this approach afforded 2-deoxyglycosides in good yield, it had drawbacks in that the reactions were not selective and it was necessary to prepare the sulfenate esters of the acceptor prior to glycosylation.

Franck and co-workers later developed an improved procedure that relied on the use of arylbis(arylthio)sulfonium salts to activate glycals for glycosylation reactions (Scheme 51).[205] After extensive studies, the authors found that TolS-(STol)$_2$SbCl$_6$ with 0.5 equiv of SbCl$_3$ was the optimal promoter for several reactions, providing products in good yield and moderate selectivity. In many cases, it was necessary to use the stannyl ether of the acceptor to improve the yields of the reaction.[206] Desulfurization of the products afforded the desired 2-deoxyglycosides.

Scheme 51. Activation of Glycals for Glycosylation Using TolS(STol)₂SbCl₆
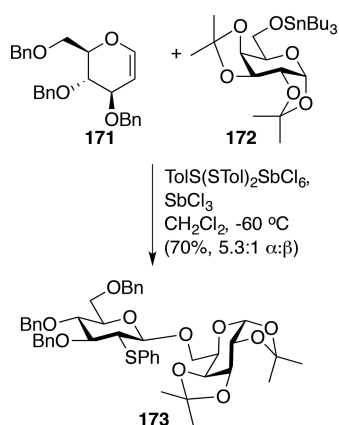
In 1989, Halcomb and Danishefsky reported that glycals could be epoxidized using dimethyldioxirane (DMDO) to cleanly generate 1,2-anhydro sugars. In the presence of ZnCl₂ and various acceptors, these compounds underwent β-specific glycosylation reactions.[207] The resulting products possessed a free hydroxyl group at the C-2 position of the glycosyl donor, which could be made to undergo further derivatization. Two years later, Gervay and Danishefsky reported that these alcohols could be converted to the corresponding pentafluorophenyl thiocarbonates, which could be subjected to Barton deoxygenation (Ph₃SnH and azobisisobutyronitrile (AIBN)) to afford β-linked 2-deoxy-sugars.[208] The procedure worked well with both aryl glycosides and disaccharides. Furthermore, glycals were tolerated as acceptors, indicating that the approach could be used for iterative synthesis.

3.2. Prosthetic Groups

An alternative approach to controlling selectivity in the glycosylation reactions relies on attaching a prosthetic group to the C-2 position of the glycosyl donors. Often, these prosthetic groups are introduced into the donor through the intermediacy of the corresponding glycal. In 1984, Pedersen and co-workers reported that 3,4-di-O-acetyl-2,6-dibromo-2,6-dideoxy-α-D-glu-copyranosyl bromides reacted with alcohol acceptors to give β-linked products upon activation with Ag-silicate.[209] Both the use of the Ag-silicate and the C-6 bromo group were necessary for selectivity. The use of other silver salts or other substituents at C-6 led to an erosion of selectivity. Furthermore, using the 2,6-dibromo-2,6-dideoxymannopyranosyl bromide afforded the α-glycosides in good yield. The resulting products could be dehalogenated using either tin hydride reduction or hydrogenolysis to afford dideoxy-sugar products. Although this approach did find some utility in synthesis,[210] the relative instability of the bromides led to the search for alternative glycosylation conditions.

In 1986, Nicolaou and co-workers found that treating 2-hydroxythioglycosides with DAST resulted in the formation of 2-phenythio-2-deoxyglycosyl fluorides such as **174**.[211] Treating these compounds with SnCl₄ and an acceptor led to the clean formation of disaccharides. Interestingly, there appears to be a very pronounced solvent effect in the reaction with Et₂O favoring the formation of β-isomers, and that with CH₂Cl₂ favoring α-isomer formation (Scheme 52A). Two years later, Preuss and Schmidt reported that the corresponding 2-phenylthio-2-deoxy trichloroacetimidates (such as **176**) could be prepared in a two-step synthesis from the corresponding glycal by treatment with PhSCl and NaHCO₃/H₂O (to generate the hemiacetal) followed by trichloroacetimidate formation.[212] Again, the reactions underwent β-selective glycosylation (Scheme 52B), which, upon desulfurization by hydrogenolysis, afforded 2-deoxyglycosides. It was found that the β-directing effect of the 2-arylthioether appears to be independent of the nature of the leaving group. For example, Shiro and co-workers reported that very high levels of β-selectivity (up to <1:99 α/β) can be achieved by activating 2-deoxy-2-[(p-methoxyphenyl)thio]-glycopyranosyl N,N,N′,N′-tetramethylphosphoramidate donor **178** with TMSOTf in the presence of acceptor **128** (Scheme 52C).[213] Desulfurization of the products with Raney Ni cleanly afforded the desired β-linked deoxyglycosides.

The selectivity in these reactions presumably arises through the formation of an episulfonium ion. This has led to the development of other methods for accessing this intermediate (such as **181** or **185** in Scheme 53). In 1993, van Boom and co-

Scheme 52. Use of C-2 Thioethers to Promote Selectivity with Glycosyl Fluorides (A), Trichloroacetimidates (B), and N,N,N′,N′-Tetramethylphosphoramidate Donors (C)
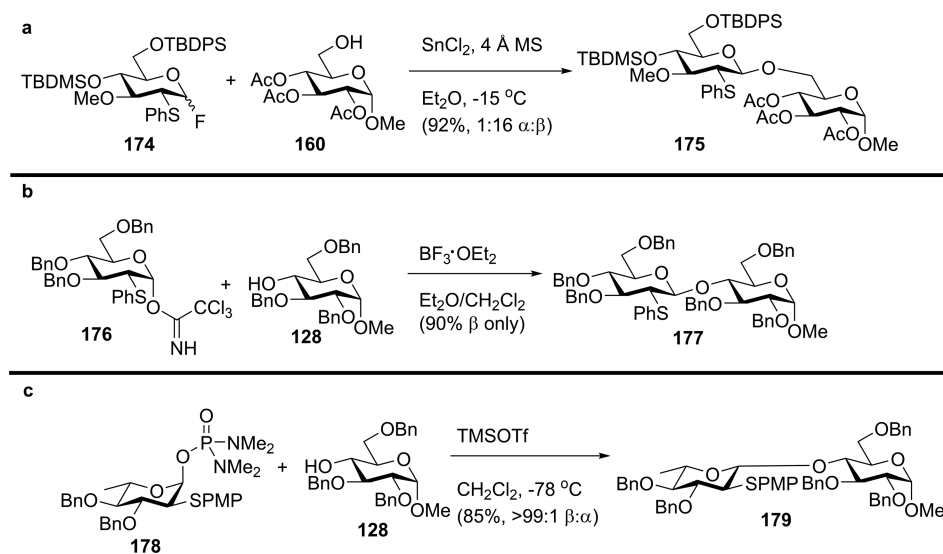
Scheme 53. Glycosylations Proceeding through the Intermediacy of an *epi*-Sulfonium Cation for the Construction of β-Linked Deoxy-sugars

Scheme 54. Roush's Use of 2-Iodoglycosides for β-Specific Glycosylation Reactions
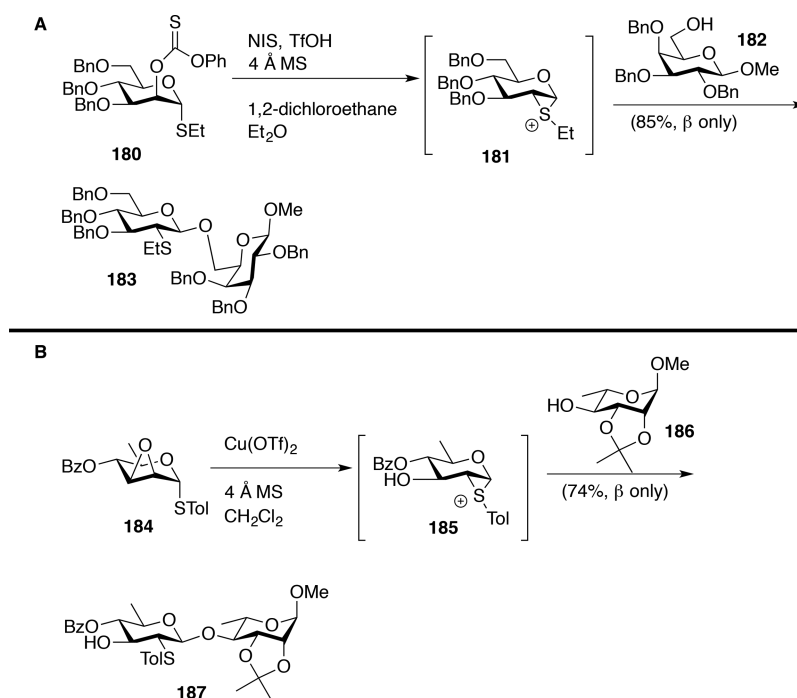
workers reported that activating thioglycosides possessing a C-2 *trans*-phenoxythiocarbonyl group with NIS/TfOH in the presence of acceptor led to the formation of glycosides with high levels of selectivity.[214] The stereochemical outcome of the reaction depended on the configuration of the starting material. Specifically, α-mannothioglycosides, such as **180**, led to the formation of β-linked products while β-glucothioglycosides afforded the corresponding α-linked products (Scheme 53A). A similar observation was made by Hou and Lowary in their studies on 2,3-anhydrothioglycosides (Scheme 53B).[215]

Several additional indirect approaches to stereospecific deoxy-sugar construction were reported during the late 1980s and early 1990s. These include C2 deoxygenation of glycosides formed under standard conditions,[216] the use of 2,6-anhydro-2-thiosugars,[217] and radical desulfurization[218] or decarboxylation.[219] Most of these approaches, however, were not widely adopted. In 1999, Roush and Bennett reported that 2-deoxy-2-iodoglucopyranosides underwent highly β-selective glycosylation reactions.[220] Their initial studies focused on the glycosyl acetates, such as **188**, which were readily available by treating the corresponding glycal with NIS in acetic acid. Activating these species with TMSOTf in the presence of a glycosyl donor resulted in the formation of β-linked products as a single diastereomer (Scheme 54). The highly reproducible selectivity observed with this reaction coupled with its ease of use has led to 2-iodo-2-deoxy donors being used for a number of glycosylation methods that have been developed in the current century.

The classical approaches described above are very powerful tools for the construction of deoxyglycosides, and many are still commonly used today. In more recent years, however, there has been a push to develop glycosylation reactions that can be conducted using a catalytic amount of promoter. Furthermore, many of the more recent methods are focused on developing reactions that can predictably and reliably provide highly stereo- or regioselective glycosylation reactions without the need for directing groups. The next section of this Review will provide a
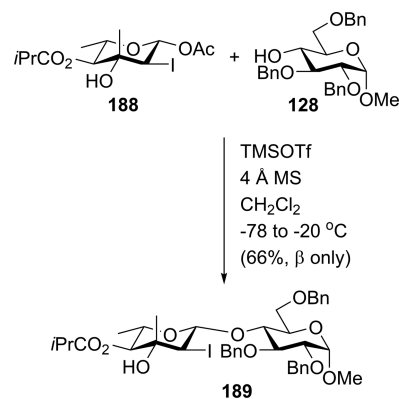
survey of the methods developed since 2000 that have attempted to achieve these goals.

4. ORGANOCATALYSIS APPLIED TO DEOXYGLYCOSIDE SYNTHESIS

The application of enantioselective organocatalysis as a powerful synthetic tool to catalyze challenging transformations in many branches of synthetic chemistry has accelerated the development of new methods to efficiently make diverse chiral molecules with excellent regio-, chemo-, and enantioselective control.[221−224] The operational simplicity, ready availability of catalysts, and low toxicity makes organocatalysis an attractive method to synthesize complex structures including oligosaccharides.[225] The past decade has seen an emergence of organocatalysis applied to carbohydrate synthesis including applications in stereoselective glycosylation reactions as well as regioselective protecting group manipulations. The methods are mild, high-yielding, and semiorthogonal to other glycosylation strategies available,

which allows for efficient access to oligosaccharide targets.[226−228] Organocatalytic glycosylations can be grouped into three main categories based on the type of catalyst used: thioureas, Brønsted acids, and organoboron promoters. However, as chemists continue to explore the available chemical space, other classes of organocatalysts are now emerging and will be discussed herein.

4.1. Thiourea-Catalyzed Glycosylations

Recent years have seen an emergence in the application of thioureas as small-molecule catalysts in a myriad of synthetic transformations.[229−233] Inspired by enzymatic active sites, thioureas have been designed to catalyze reactions through stabilization of the transition state by coordination of electron-deficient thiourea N−H protons to areas of (partial) negative charge. Thioureas can act as dual hydrogen-bond donors or as general weak acids, and, because the degree of proton donation from the thiourea depends on the substrate, a full mechanistic understanding of the reaction mechanisms has proven difficult experimentally thus far.[234] Thioureas as hydrogen-bond donors/ Brønsted acids are much weaker than traditional strong acid catalysts, imparting greater functional group tolerance, chemo-selectivity, and often better stereocontrol. It is not surprising then that these organocatalysts often have been hailed as improved alternatives to Brønsted or Lewis acidic catalysts.[234] In addition, thiourea-type catalysts can be synthesized easily from commonly available starting materials. They are readily diversifiable as the N-substituents can be changed to tune the electronic, steric, and chiral environment around the thiourea functionality.

Taking inspiration from the work of Kotke and Schreiner,[235,236] in which N,N′-bis[3,5-bis(trifluoromethyl)-phenyl]thiourea (Schreiner's thiourea) was shown to act as an efficient organocatalyst for the addition of alcohols to the enol ether in dihydropyran, Galan, McGarrigle, and co-workers[237] reported the α-stereoselective synthesis of 2-deoxyglycosides from glycals. The reaction proceeds with excellent yields and high selectivity for the α-anomer with only 1.2 equiv of the galactal donor. It was also shown to be tolerant of a range of common protecting groups (e.g., ethyl, allyl, benzyl, methox-ymethyl ether (MOM), and silyl ether) in both donor and acceptor; acetate groups are also tolerated but not in close proximity to the reacting alkene (at C-3 of the galactal) as they can deactivate the double bond. Mechanistic investigation of the reaction using deuterated galactal **190** demonstrated that the newly formed bonds are cis to each other, suggesting a syn addition of the alcohol to the α face of the galactal (Scheme 55). Galan, McGarrigle, and co-workers proposed a reaction mechanism by which formation of an alcohol−thiourea complex
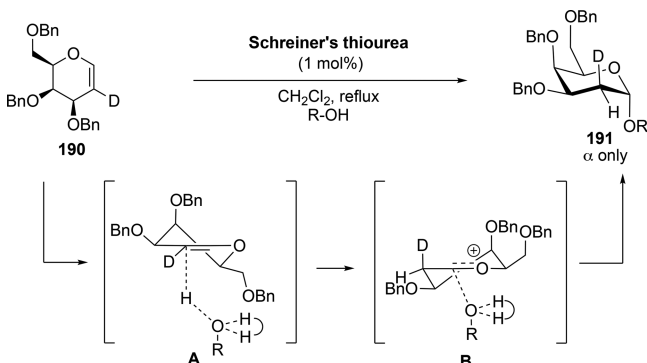
is able to deliver the proton selectively to the less-hindered face of the galactal (A), followed by rapid collapse of the transient ion pair (B) to give the product **191**. It is suggested that the α anomer is formed preferentially during the C−O bond-forming step due to favorable sterics, the electronic preference conferred by the anomeric effect, and a lower-energy chair-like transition state. This mechanistically interesting reaction proceeds smoothly with a wide range of primary and secondary OH acceptors with excellent yields and complete α-selectivity in all cases. Furthermore, the method is semiorthogonal to thioglycoside-type glycosylations, and to that end, the versatility of the approach was demonstrated in the one-pot synthesis of a trisaccharide that was prepared in 58% yield with complete stereocontrol. It is important to highlight that the purity of the reagents and starting materials is of paramount importance for these thiourea-catalyzed transformations as small amounts of impurities can poison the catalyst, particularly giving the low catalyst loadings (1 mol %) employed.[238] Recent experimental and computational investigations by Pápai and co-workers[239] challenge the common view that Schreiner's thiourea acts as a double-hydrogen-bond donor in its organocatalytic capacity for the thiourea-catalyzed tetrahydropyranylation of alcohols. Instead, this group suggests that the thiourea acts as a Brønsted acid, protonating 3,4-dihydro-2H-pyran (DHP) to form an oxocarbenium ion, which then reacts with the alcohol. This new proposed mechanism might also be relevant to the thiourea-catalyzed glycosylations discussed herein.

Initial work from Jacobsen and co-workers[232] demonstrated the principle of H-bond catalysis by anion binding to transformations involving oxocarbenium ions. Following this, an elegant demonstration of the use of a thiourea to facilitate a Koenigs−Knorr activation of glycosyl chlorides such as **192** was subsequently demonstrated by the Ye group.[240] It was found that the combination of a urea catalyst with additives such as K₂CO₃ leads to the desired disaccharides (**193**), after 24 h at 80 °C, in excellent yield and with good to excellent stereoselectivity for most glycosyl donors, including examples of 2-deoxy- and 6-deoxyglycosides (Scheme 56). In the absence of neighboring

Scheme 56. Urea-Catalyzed Koenigs−Knorr Glycosylation

193
71-99%
α:β 2:1 to α only
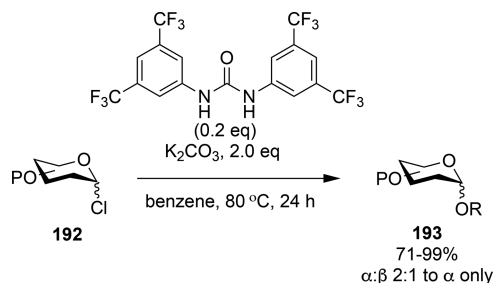
group participation, α-selectivity was obtained in most examples, with the exception of perbenzylated glucosyl donors, which required tri-(2,4,6-trimethoxyphenyl)phosphine (TTMPP) as the additive to give high α-selectivity. In this case, challenging disaccharides could be synthesized in yields of 70−95% and α/β ratios ranging from 8:1 to 20:1. Preliminary mechanistic experiments suggest a urea-mediated hydrogen-bond activation followed by glycosylation. Awaiting further mechanistic investigations, the authors proposed that the high levels of α-stereocontrol are likely due to a noncovalent electronic interaction between the sterically bulky TTMPP and the β-face

Scheme 55. Galan and McGarrigle's Thiourea-Catalyzed Glycosylation of Galactals to Furnish 2-Deoxyglycosides

of the anomeric carbon of the glycosyl donor, which directs the attack of the nucleophile to the α-face.

2-Amino-2-deoxyglycosides, often found in their N-acylated form, are common structural motifs present in oligosaccharides and glycoconjugates of biological significance.[241−244] The stereoselective glycosylation of 1,2-*cis*-aminoglycosides still remains a challenge because most amino protecting groups (e.g., amides and carbamates) tend to form 1,2-trans-type glycosides via neighboring group participation.[245] Inspired by the base-catalyzed 2-nitroglycal concatenation reaction,[246−248] whereby anchimerically inactive 2-nitroglycosides can be used as glycosyl donors to yield deoxyglycosides that contain a masked amine/amide functionality at C-2, the Galan team described in 2016 the first application of a bifunctional cinchona/thiourea organocatalyst **195** for the direct and α-stereoselective glycosylation of 2-nitrogalactals **194** to afford 2-amino-2-deoxygalactosides **196** in moderate to excellent yields and α-selectivity (Scheme 57).[249] The authors proposed that, while the

Scheme 57. Glycosylation of 2-Nitroglycals Using Thiourea/Cinchona Bifunctional Organocatalyst
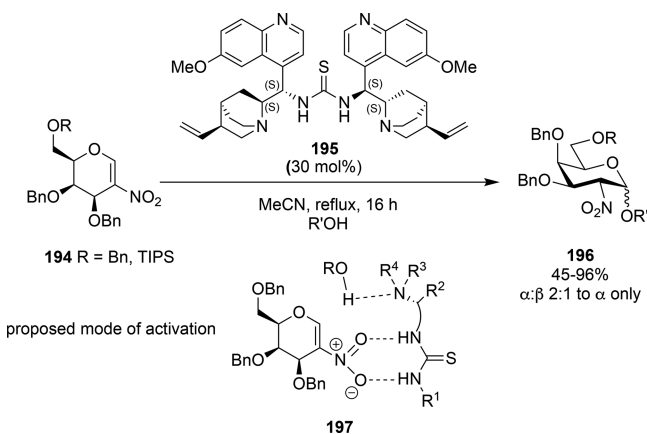
thiourea functionality coordinates to the nitro group (**197**) and thus increases the electrophilicity of the nitroalkene, the pendant amine activates and directs the addition of the nucleophile into the prochiral alkene.[250] In this way, the electrophilicity of the donor and the nucleophilicity of the alcohol are simultaneously enhanced while the stereochemical configuration of the organocatalyst helps to direct glycosylation to the α-face of the donor. The reaction conditions are mild, practical, and applicable to a range of glycoside acceptors. Moreover, the applicability of the method is exemplified in the synthesis of mucin-type Core 6 and 7 glycopeptides. A few weeks later, the group of Yoshida and Takao also reported the use of a thiourea/pyrrolidine bifunctional organocatalyst **199** for the highly α-selective organocatalytic glycosylation of 2-nitroglycals (galactals **194** and glucals **198** in Scheme 58) with phenol nucleophiles.[251] After initial mechanistic investigations, the authors proposed that the stereoselectivity of the reaction is kinetically controlled by the catalyst while the high α-selectivity observed is attributed to the chirality of the thiourea employed. These parallel reports demonstrate the scope of H-bond organocatalysis in oligosaccharide chemistry and further support that, in addition to solvent effects and the influence of the glycosyl donor and nucleophile acceptor, the chirality of the organocatalyst can be used to effect control on the stereoselectivity.

Another mild and efficient activation of 2-deoxy-2-nitrogalactals, such as **194**, using N-heterocyclic carbenes (NHC) **201**

Scheme 58. Glycosylation of 2-Nitroglycals Using Thiourea/Pyrrolidine Bifunctional Organocatalyst
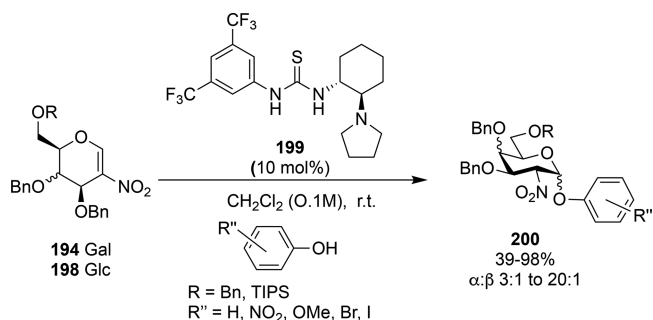
was reported in 2017 by Chen, Zhou, and co-workers (Scheme 59).[252] Glycosylation of alcohols and phenol was achieved with

Scheme 59. NHC-Catalyzed Stereoselective Glycosylation of 2-Nitrogalactals with Alcohols and Phenol
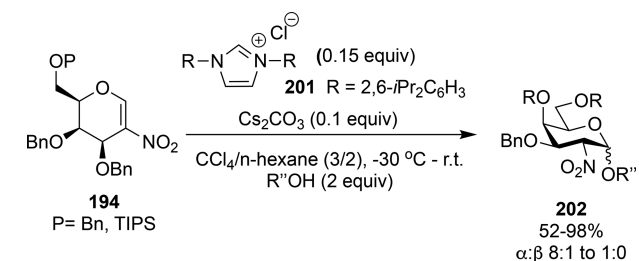
good to excellent yields and high to excellent α-selectivity. The glycosylation outcome was dependent on the type of protecting groups on the galactal, the nature of the OH nucleophile, and the reaction solvent. Interestingly, an increase in 1,2-cis glycosylation was observed in the presence of a nonpolar solvent (e.g., CCl_4, CH_2Cl_2, toluene, or *n*-hexane (α/β 13:1−20:1) with selectivity being optimal when a mixed solvent was used (e.g., CCl_4/n-hexane)).

The very elegant use of chiral macrocyclic bisthioureas such as **204** to catalyze stereospecific glycosylation reactions involving glycosyl chlorides has been recently described by the Jacobsen group (Scheme 60).[253] The reaction is showcased in the synthesis of *trans*-1,2-, *cis*-1,2-, and 2-deoxy-β-glycosides. Reactions generally take 48 h at room temperature or 40 °C to give the disaccharide products in good to excellent yield (62−88% yield) and with β-stereocontrol. The donor scope of the reaction is general, and 12 different glycosyl donors (e.g., glucose, galactose, mannose, and a number of deoxyglycosides such as 2-deoxyglucose, L-rhamnose, L-fucose, D-xylose, and 2-deoxyaminoglycosides) were amenable to the reaction conditions, including the preparation of challenging 1,2-*cis*-mannosides and 2-deoxy-β-glycosides. Remarkably, the stereocontrol of the reaction is shown to depend almost entirely on the configuration of the electrophilic glycosyl donor **192**. Experiments devoted to independently alter the chirality of both the catalyst and the alcohol acceptor produced only very minor changes in the β-selectivity of the reaction, which is indicative of an S_N2-type glycosylation. Moreover, small changes in linker length or type of amide in the organocatalyst were detrimental to yield and diastereoselectivity, demonstrating that the macrocyclic R,R-bisthiourea is finely attuned to allow the reaction to occur. The authors propose that the reaction follows a stereospecific invertive substitution pathway consistent with a cooperative

Scheme 60. Glycosylation of Glycosyl Chlorides Using a Macrocyclic Bisthiourea Organocatalyst
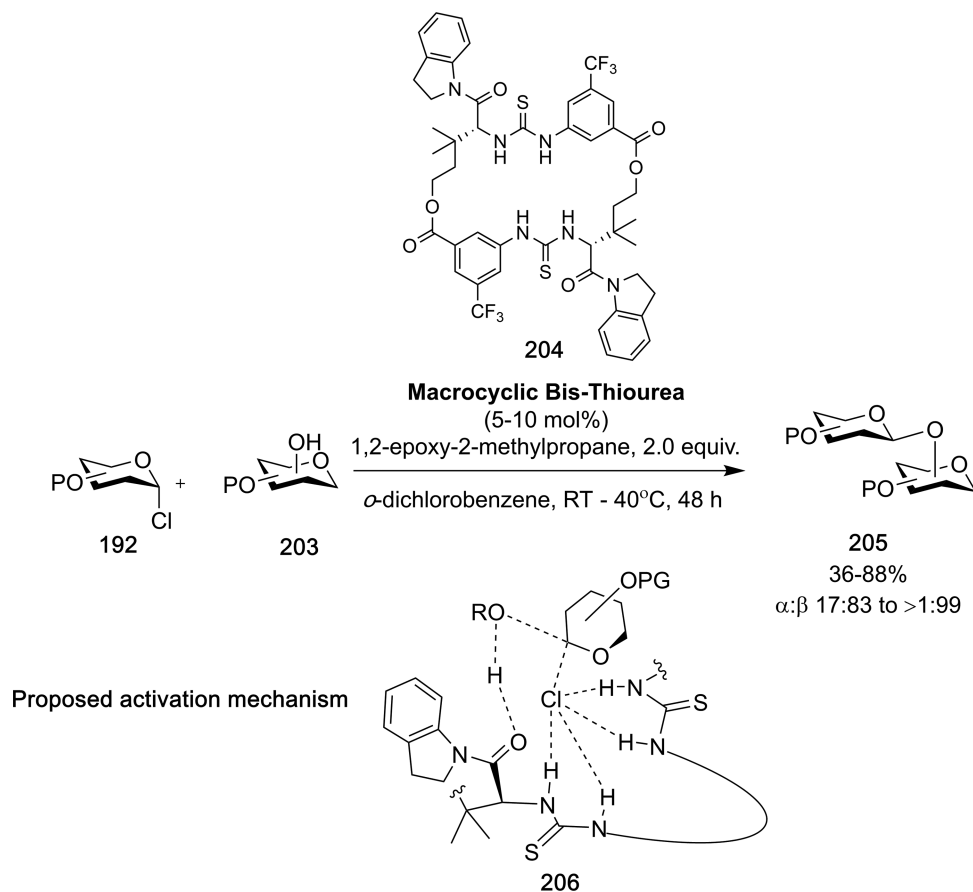
mechanism. The transition state structure **206** forms from simultaneous hydrogen-bond activation of the reacting partners (nucleophile and electrophile) encouraging an S_N2-type substitution to occur. This mode of activation is evocative of the mechanisms employed by glycan processing enzymes.

There is no doubt that thioureas have become, and will continue to be, invaluable tools as organocatalytic glycosylation activators. Thus far, these mild reagents have proven to be useful in stereoselective transformations involving a variety of glycosyl donors and acceptors. Moreover, their catalytic utility and scope can be further expanded as glycosylation promoters by combining these small-molecule organocatalysts with other reagents (e.g., cooperative catalysis with Brønsted acids) or strategies (e.g., photochemistry).

4.2. Brønsted and Lewis Acid Catalysis

Brønsted acids are effective catalysts in different areas of organic chemistry[254−256] including glycosylation chemistry.[227,257] These types of acid catalysts tend to be generally air- and moisture-stable over long periods of time and thus amenable to large-scale syntheses. These features, in combination with the commercial availability of both chiral and achiral acids, have made them very useful catalysts for glycosylation chemistry. To that respect, considerable efforts have been devoted to the discovery of Brønsted acid catalysts that can efficiently promote stereoselective glycosylation with regio- and chemoselective control of the coupling reaction. Anomeric activation with chiral Brønsted acids is dictated by a complex relationship between the glycosyl donor, acceptor nucleophile, and acid. Thus, it is not surprising that induction of high stereoselectivity in glycosylations with chiral acids has proven to be challenging.

Following reports on the activation of fully substituted trichloroacetimidate glycosyl donors using chiral 1,1′-bi-2-naphthol (BINOL)-derived phosphoric acids by the teams of Fairbanks[258] and Toshima,[259] Bennett and co-workers described the activation of α- or β-trichloroacetimidate perbenzylated 2-deoxyglycosyl donors **207** and **209** using chiral BINOL-derived phosphoric acids in coupling reactions with 1-octanol to prepare the corresponding 2-deoxyglycosides such as **208** and **210**. The stereoselectivity of the reaction was dependent on the matched/mismatched relationship between the chiral catalyst and anomeric configuration of the leaving group in the donor. For instance, high levels of β-selectivity were observed (1:16 α/β) when using sterically demanding chiral Brønsted acid catalyst (**S**)-**Cat1** and an α-trichloroacetimidate donor, while reaction involving the same glycosyl donor with (**R**)-**Cat1** required longer reaction times and gave lower selectivities. On the other hand, a significant enrichment of the α-anomer (6.6:1 α/β) was obtained in glycosylation with β-trichloroacetimidate donor with (**R**)-**Cat1** as the catalyst (Scheme 61).[260] The results further demonstrate the importance of matching the configuration of the anomeric leaving group with that of the chiral Brønsted acid.

Cooperative catalysis—whereby a Brønsted acid is used in combination with a hydrogen-bond donor (e.g., thiourea) to enhance the catalytic activity of the acid and thus achieve increased yields, reaction rates, and sometimes enantiocontrol—has been shown to be a very effective alternative to using acids alone in many synthetic transformations,[261−266] including examples in oligosaccharide synthesis.[267] In the context of glycosylation chemistry of deoxyglycosides, Galan and co-workers[268] reported in 2017 the efficient and stereoselective

Scheme 61. Matched/Mismatched Catalyst/Substrate Glycosylation To Yield 2-Deoxyglycosides

Ar = 4-adamantyl-2,6-diisopropylphenyl

Scheme 62. Glycosylation of Glycals Using Thiourea/Brønsted Acid Cooperative Catalysis
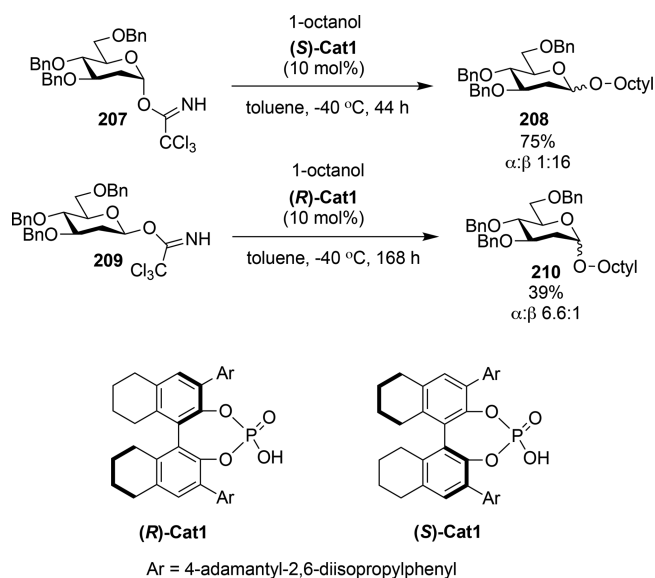
activation of glycals **211** using cooperative activation of a chiral Brønsted acid with Schreiner's thiourea. Although Schreiner's thiourea had been shown to catalyze the reaction of galactal donors to give 2-deoxygalactosides,[237] reactions times were long (24−48 h) and other less-reactive substrates (e.g., glucals) could not be activated under the mild reaction conditions.[235,236] To address this, the group employed synergistic acid/thiourea activation as a more efficient glycosylation system than using either a hydrogen-bond or acid catalyst as the sole promoter of the glycosylation reaction. To that end, a series of BINOL-derived phosphoric acids and an achiral phosphoric acid were screened in the absence and presence of Schreiner's thiourea. It was found that the stereoselectivity of the reaction was highly dependent on the chirality of the acid, with (R)-3,3′-bis[3,5-bis(trifluoromethyl)phenyl]-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (R)-**Cat2** being optimal for the formation of α-glycosides preferentially, while both yield and rate of reaction were greatly enhanced by the synergistic interaction between thiourea and acid (Scheme 62).

Ionic liquids (ILs) have recently emerged as a new class of recyclable solvents for a broad range of synthetic applications including those in oligosaccharide synthesis.[269−273] In the area of deoxyglycosides, Bravo and co-workers[274] have demonstrated that the combination of p-TSA/[bmim][BF$_4$] IL (bmim = 1-butyl-3-methylimidazolium) can effectively promote the synthesis of 2-deoxyglycosides from glycals with good yields albeit with moderate α-selectivity. This simple and mild catalytic system can also promote the hydration of glycals to afford 1-hydroxy-2-deoxyglycosides in very good yields. The key advantage of this methodology is the ability to recover and reuse the catalyst for up to 4 times without significant loss of activity. Although more work needs to be carried out to achieve both reactivity and stereocontrol in these reactions, the approach offers some promise in terms of developing green methodologies for acid-catalyzed reactions.

As already discussed at the start of this Review (section 2.2), most traditional glycosylation methods employed glycosyl bromides, glycosyl trichloroacetimidates, thioglycosides, or glycosyl fluorides as donors that can be activated with standard Lewis acids (e.g., SnCl$_4$, BF$_3$·Et$_2$O, AgOTf, ZnCl$_2$, or TMSOTf)
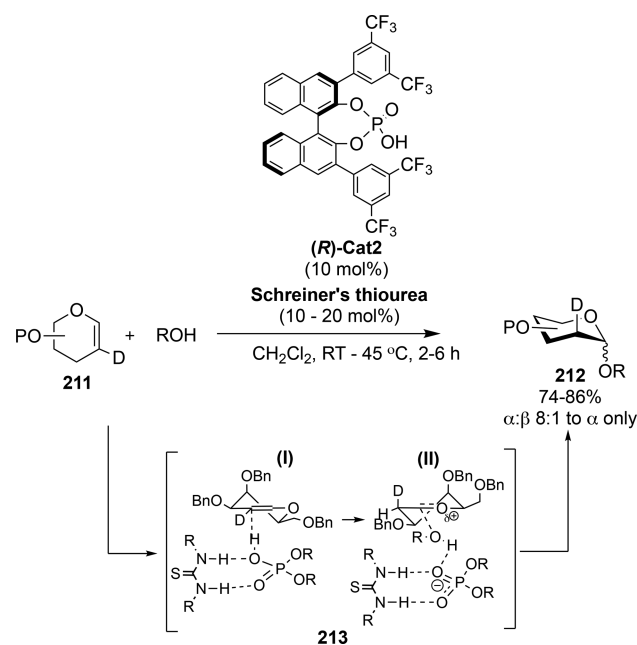
and, in most cases, the presence of a C-2 participating group is used to direct the nucleophilic attack.[227] An interesting 2002 study on the acid-catalyzed de novo synthesis of 2-deoxy-L-fucose and 2,6-dideoxy-L-galactose (L-oliose) α-glycosides of a diastereomer of digitoxin by the McDonald group[275] provided valuable insights into the generality and protecting-group dependence of acid-catalyzed glycosylations with glycals to generate 2-deoxyglycosides. The group had previously described an iterative process involving the tungsten-catalyzed alkynol cycloisomerization to generate glycal donors such as **218** (Scheme 63A).[276] The strategy was further showcased on the stereoselective synthesis of the D-digitoxose trisaccharide of digitoxin[277] The method involves the use of a differentially protected alkynyl triol **215** that, upon initial conjugation to give glycoside **216**, can be selectively deprotected to release monohydroxylated **217** that can then be subjected to the cycloisomerization reaction to afford L-oliose (lyxo)glycal **218**. The team found that acid-catalyzed glycosylations of oligosaccharides bearing L-fucose glycal at the reducing termini are generally α-stereoselective, as expected for acid-catalyzed glycosylations with L-fucal.[278−280] It was also found that glycosylation using camphorsulfonic acid or triphenylphosphine hydrogen bromide as promoters occurs without Ferrier elimination when both trialkylsilyl ether and acetate ester protecting groups at the allylic center (C-3 of the glycal) are used. This iterative strategy is amenable toward the synthesis of complex targets. More recently, in 2009, the McDonald group reported the application of this elegant Brønsted acid-promoted glycosylation and alkynol cycloisomerization iterative process to the synthesis of the 2-deoxytrisaccharide **220** corresponding to the fucose−saccharosamine−digitoxose structure of saccharomicin B (Scheme 63B).[281] Particularly noteworthy is the synthesis of the fucose−saccharosamine disaccharide, which the authors built by resolving a racemic N-PMP-protected β-lactam (PMP = p-methoxyphenyl) by stereoselective glycosylation at temperatures above 0 °C with peracetylated L-fucosyl trichloroacetimidate.

Inspired by earlier reports of thioglycoside activation using nitrosyl tetrafluoroborate (NOBF$_4$),[282] Misra and co-workers

Scheme 63. Iterative Tungsten-Catalyzed Alkynol Cycloisomerization (A) and Stereoselective Acid-Catalyzed Glycosyation Reactions (B)
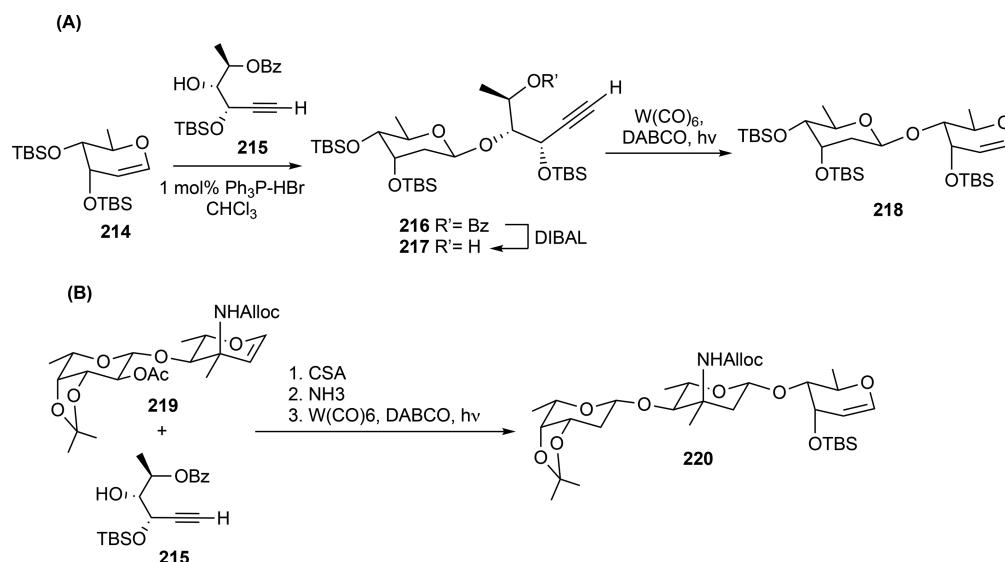
reported in 2012 the efficient activation of glycosyl trichloroacetimidate donors **221** catalyzed by NOBF$_4$.[283] A plethora of differentially protected glycosyl donors were screened with a series of alcohol nucleophiles to give the desired glycosides in excellent yield and stereoselectivity within 20−40 min (Scheme 64). The authors proposed that a nitrosyl cation activates the

Scheme 64. NOBF$_4$ As a Lewis Acid for the Glycosylation of Trichloroacetimidates
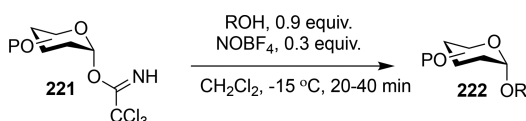
trichloroacetimidate to form a transient oxocarbenium ion intermediate, which then undergoes nucleophilic attack by the alcohol via an S$_N$1-type mechanism, although no experiments to confirm this were carried out. The use of NOBF$_4$ was later extended by the same group to the reaction between glycals (D-glucal, D-galactal, and L-rhamnal) and hindered alcohols, thiols, and sulfonamides to form either the corresponding 2,3-dideoxyglycosides or 2-deoxyglycosides in 70−80% yields with moderate to excellent α-selectivity. It was found that, under the reaction conditions, peracetylated glucal and rhamnal donors gave exclusively Ferrier-glycosylation products while reactions with galactal donors favored 2-deoxyglycoside formation.[284]

4.3. Organoboron-Catalyzed Glycosylations

The use of boron compounds as transmetallating agents in catalytic processes is a well-documented process; however, organoboron catalysis is comparatively underexplored, and the development of organoboron catalysts for synthesis has become an attractive area of research.[285,286] Trivalent boron species are Lewis acidic and can reversibly form bonds with oxygen. In addition, the molecular recognition of carbohydrates by organoboron derivatives through binding to cis-1,2-diol groups in a tetracoordinate manner is well-documented.[286] These features makes organoboron catalysts a valuable tool for organocatalytic glycosylations.[287,288]

Taylor and co-workers reported in 2011 a very elegant example of the application of organoboron catalysis in Koenigs−Knorr glycosylations.[289] A diphenylborinic acid-derived catalyst **225** was used in the presence of stoichiometric silver(I) oxide to activate partially protected (at C-1 and C-6) glycosyl acceptors **224**. Taking advantage of the presence of a 1,2-cis-diol moiety in the glycoside acceptor, completely regioselective glycosylations could be achieved (Scheme 65). Mechanistic studies performed

Scheme 65. Regioselective Glycosylation Using Diphenylborinic-Derived Ethanolamine Adduct
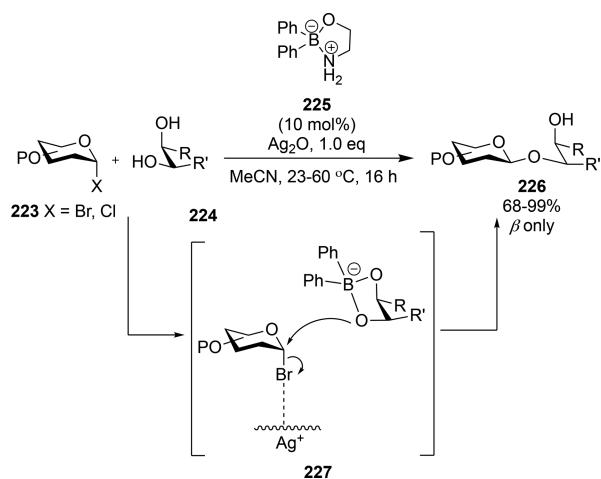
by the authors suggest that the diphenyl borinate esters activate 1,2-cis-diols toward electrophilic attack at the equatorial oxygen in a manner that is similar to organotin reagents.[290,291] The reaction proceeds in good yields and complete β-stereocontrol. The reaction scope was demonstrated using a range of differentially protected glycosyl donors bearing common protecting groups (e.g., acyl, benzyl, and pivaloyl) in reactions with a number of partially unprotected glycoside acceptors (e.g., manno-, galacto-, and arabino-) including examples of deoxyglycosides (fuco- and rhamnosides). It was also found that the diastereoselectvity of the reaction is not controlled by the catalyst but is determined by the configuration of the glycosyl

Scheme 66. Choice of Lewis Base and/or Organoboron Catalyst Is Important To Facilitate Challenging Glycosylations
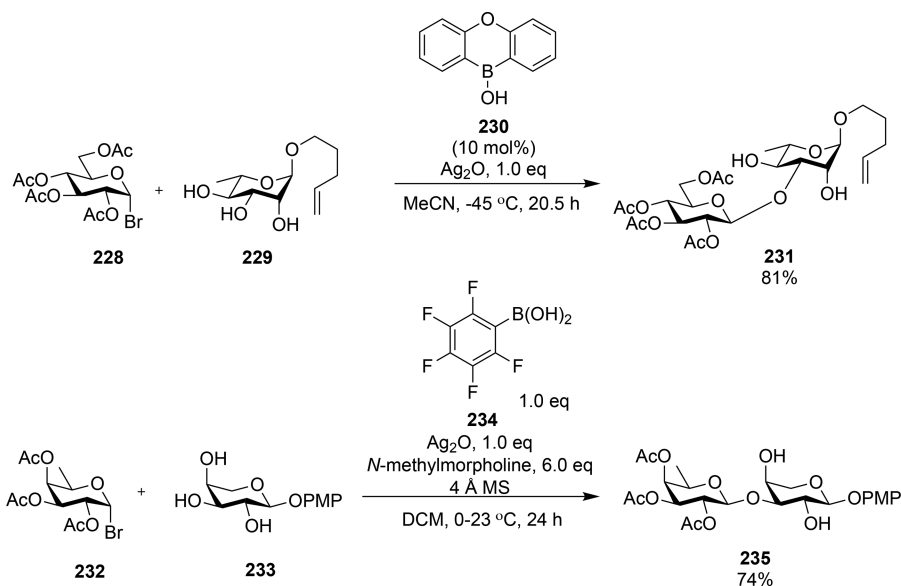
Scheme 67. In Situ Formation of Glycosyl Mesylate Donors and Subsequent Glycosylation Using a Diarylorganoboron Catalyst
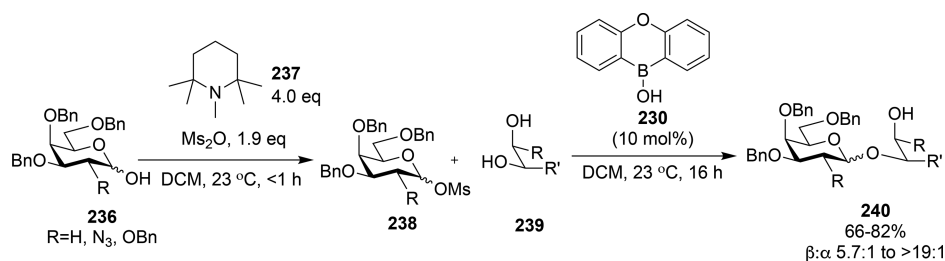
halide, which reacts through an S_N2-like inversion. Another advantage of this reagent is that, unlike most glycosylation protocols, this method does not require the strict use of anhydrous conditions. This methodology was later successfully applied to the regioselective glycosylation of the cardiac glycoside natural product digitoxin.[292] More recently, in 2014, the Taylor group extended their use of the organoboron catalyst to the preparation of 2-deoxy- and 2,6-dideoxyglycosides using 2-deoxyglucosyl, 2-deoxygalactosyl, and L-rhamnosyl donors in reactions with either 1,2- or 1,3-*cis*-diol-containing saccharide acceptors.[293] Regioselectivity could be maintained at high levels by employing electron-withdrawing acyl protecting groups on 2-deoxyglycosyl donors, while the anomeric α-chloride leaving group ensured β-selectivity was favored as expected for an S_N2-like reaction pathway. The scope of Taylor's catalyst **225** was further demonstrated by O'Doherty and co-workers[294] in a dual nucleophilic boron/electrophilic palladium-catalyzed regioselective glycosylation, which allows the group to minimize the number of protecting groups required to synthesize all of the targets. Further details on O'Doherty's Pd(0)-catalyzed glycosylation for the de novo synthesis of oligosaccharides will be discussed in section 5.1.

Following their initial reports, the Taylor group described the development of two different organoboron precatalysts that were more effective in glycosylations involving bromoglycosides in cases where the first-generation diphenylborinic acid-derived catalyst[289] gave poor yields and/or regioselectivity.[295] For example, oxaboraanthracene-derived borinic acid **230** was found to be a more-reactive catalyst to effect the low-temperature

glycosylation reaction between a peracetylated α-bromoglucosyl donor **228** and rhamnoside acceptor **229**, and in this manner, the total synthesis of a saponin-derived pentasaccharide natural product could be accomplished with improved yields and regioselectivity. The team also showed that the choice of boronic acid and Lewis base combination is important, particularly where there is a case of matched/mismatched glycosyl donor configuration that adversely affects the regioselectivity of the glycosylation. The strategy was demonstrated in the successful synthesis of β-(1→3)-D-fuc-L-ara disaccharide **235** in 74% yield using a combination of pentafluorophenylboronic acid **234** and N-methylmorpholine (Scheme 66).

More recently, the scope of the oxaboraanthracene-derived borinic acid **230** catalyst was further demonstrated on glycosylations with glycosyl mesylate donors.[296] Glycosyl mesylates such as **238**, which can be prepared in situ by reaction of a glycosyl hemiacetal **236** and methanesulfonic anhydride, can act as substrates in an organoboron-catalyzed glycosylation. 1,2- or 1,3-*cis*-diols were used as glycosyl acceptors **239**, and disaccharides **240** were obtained over 16 h in high yields and with good to excellent β-selectivity and regioselectivity toward the free equatorial OH, including an example showcasing the synthesis of perbenzylated 2-deoxyglucoside with moderate β-selectivity (Scheme 67). Interestingly, reactions carried out in the absence of the organoboron catalyst afforded the products with modest to high α-selectivity, demonstrating the stereochemical influence exerted by the organocatalyst. Extensive mechanistic and kinetic studies provide evidence for an associative mechanism in which an intermediate boronic ester formed

Scheme 68. Electron-Deficient Pyridinium Salt-Catalyzed 2-Deoxyglycosylation and Proposed Intermolecular (A) and Intramolecular (B) Mechanisms
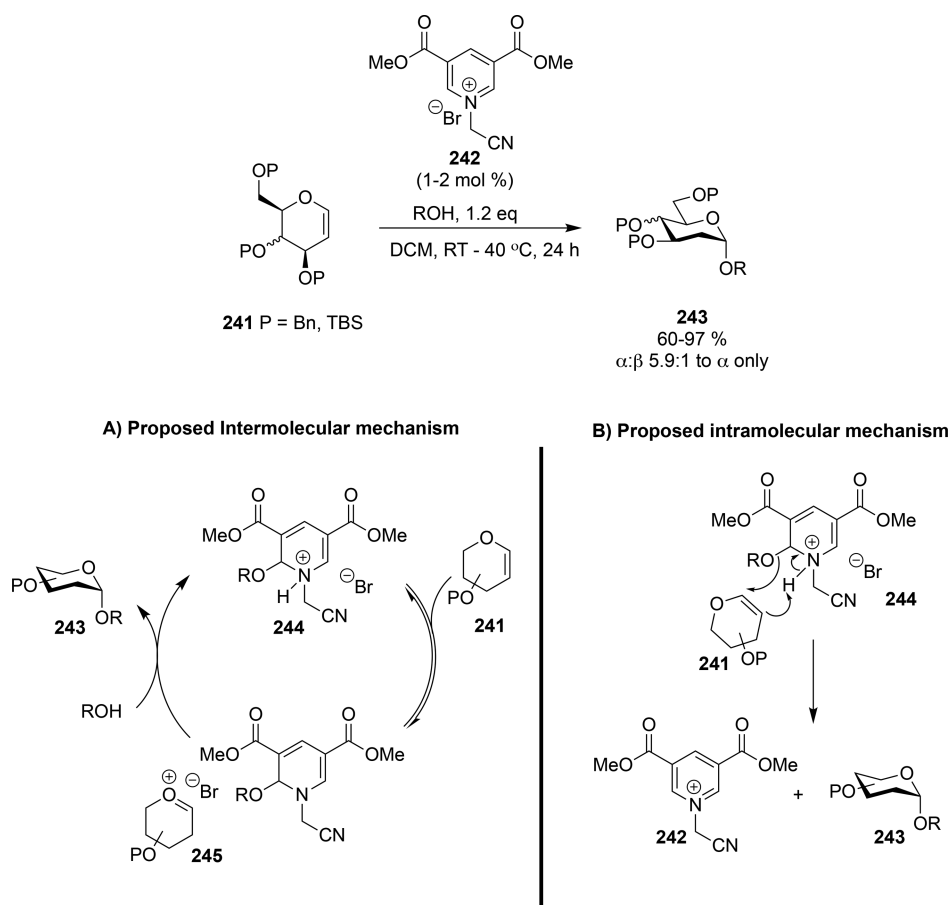
through reaction of the diarylborinic acid and the glycosyl acceptor undergoes glycosylation with the α anomer of the glycosyl mesylate, favoring β-linked products. These results indicate that reagent-controlled glycosylations that start by OH differentiation steps are promising strategies for the rapid construction of glycans.

4.4. Pyridinium-Catalyzed Glycosylations

As chemists continue to explore the organocatalytic chemical toolbox for application in glycosylation chemistry, a number of other approaches have also emerged. In 2015, Berkessel and co-workers reported the use of electron-deficient pyridinium salts as catalysts to access 2-deoxyglycosides from glycals.[297] After some investigation, it was found that 1–2 mol % of an electron-deficient diester pyridinium salt was the optimal catalyst for glycosylation with glucals and galactals such as 241 of a series of primary and secondary OH nucleophiles within 14 h in excellent yields and with complete α-stereocontrol (Scheme 68). The reaction was tolerant of most common protecting groups in both donor and acceptor. Mechanistic investigations led to the proposal of two plausible mechanisms: an intermolecular process (A), whereby an acid catalyst 244 is generated in situ by addition of the alcohol nucleophile to the 2-position of the pyridinium salt, forming a protonated hemiaminal, acid-catalyzed glycal activation via oxocarbenium ion 245, followed by nucleophilic attack by a second OH molecule, yielding the glycoside product. The alternative is an intramolecular mechanism (B) in which proton transfer from the pyridinium cation followed by

alcoholate transfer from the aminal in a concerted manner could also occur (Scheme 68).

4.5. Glycosyl Halides As Transient Intermediates in Catalyzed Glycosylations

Glycosyl bromides, which form the basis of the Koenigs–Knorr glycosylation method, are among the most reactive glycosyl donors available, as already discussed in section 2. However, their application in the synthesis of dexoyglycosides is limited[61,298−300] due to difficulties associated with their preparation and handling because these electron-rich donors readily ionize, leading to hydrolysis, elimination, and other decomposition products.

To exploit the benefits that glycosyl halides provide in terms of achieving optimal reactivity and stereocontrol without the many drawbacks, Bennett and co-workers developed a new mode of activation using 3,3-dichloro-1,2-diphenylcyclopropene to generate a cyclopropenium cation that can activate the anomeric hydroxyl of 2-deoxy- and 2,6-dideoxy-sugar donors via dehydrative glycosylations.[301] The reaction proceeded through the formation of a transient glycosyl chloride that, in the presence of excess iodide, becomes a competent donor presumably through the in situ formation of a reactive glycosyl iodide. The method is mild and has good functional group tolerance, and reactions proceeded in good yields. However, the selectivity was only moderate, and the system was only suitable for armed deoxy-sugar donors. Subsequently, Bennett and co-workers[302] reported an improved second-generation promoter **CP-1** whereby the chlorides in the cyclopropenium catalyst were

replaced by bromides. Under these conditions, a more-reactive glycosyl halide that is able to carry out a faster exchange with the iodide is generated (Scheme 70A). The new catalyst yields 2-deoxy-α-glycosides such as **248** with very high selectivities from the corresponding hemiacetal donors (**246** and **247**). The optimal conditions required the addition of base in combination with an excess of tetrabutylammonium iodide (TBAI) and ethereal solvents. Using this catalytic system, both "armed" and "disarmed" 2-deoxy- and 2,6-dideoxy-sugars reacted smoothly with a range of acceptors, affording glycoside products with moderate to excellent yields and α-selectivities ranging from 6:1 to α-only (Scheme 69A). Following this work, Bennett and co-

Scheme 69. α-Selective Dehydrative Glycosylation Protocols for the Synthesis of β-Deoxyglycosidic Linkages
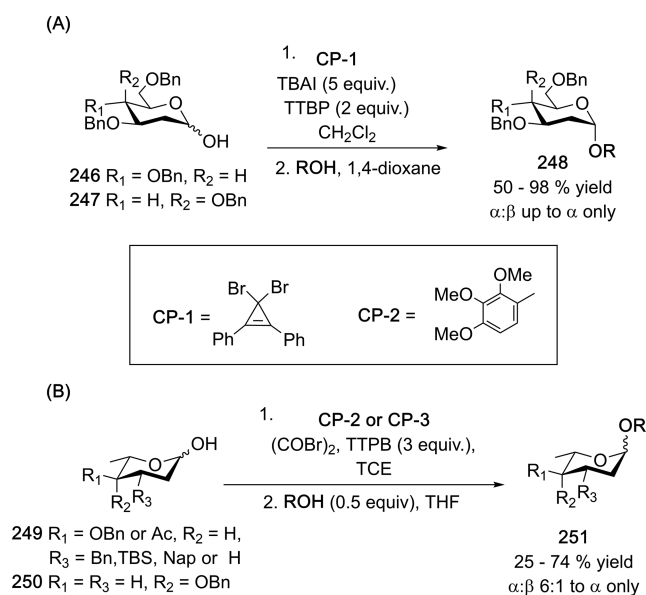
workers[303] found that mild activation of 2,6-dideoxy-sugar hemiacetals, such as **249** and **250**, at room temperature to yield glycosylation products with high α-selectivity was possible by employing either 2,3-bis(2,3,4-trimethoxyphenyl)-cyclopropenone (**CP-2**) or 2,3-bis(2,3,4-trimethoxyphenyl)-cyclopropene-1-thione (**CP-3**) in combination with oxalyl bromide (Scheme 69B). The reaction conditions are amenable to labile functional groups, including highly acid-sensitive 2,3,6-trideoxyglycosidic linkages. Interestingly, the authors found that, while promoter system **CP-2**/oxalyl bromide was optimal for primary OH, the combination of oxalyl bromide and **CP-3** was an effective promoter for most secondary alcohol nucleophiles. Preliminary NMR studies undertaken for this reagent-controlled α-selective dehydrative glycosylation protocol indicated the presence of a transient glycosyl bromide as the key reaction intermediate, although a glycosyl bromide synthesized through more traditional methods (TMSBr) displayed marked differences in yield and selectivity.

4.6. 2-Deoxy-2-iodoglycosides As 2-Deoxyglycoside Precursors

2-Deoxy-2-haloglycosides are a class of deoxyglycosides containing a halo group at C-2 that can be used as a temporary directing group to bias the stereoselectivity of the glycosylation reaction. Examples of synthetic applications for 2-deoxy-2-iodopyranosyl acetates,[220,304−307] 2-deoxy-2-bromo-/iodoglucopyranosyl trichloroacetimidates,[308] and 2-deoxy-2-bromoglucopyranosyl fluorides[309] have been reported, although 2-deoxy-2-iodoglycosides are more commonly featured.

For example, Blanchard and Roush[309] described the application of 2-deoxy-2-iodo-β-glucopyranosyl fluoride **253**, which contains a C6-bromo substituent. The halo-containing glycosyl donor could be activated under mild conditions. This was particularly important in glycosylation with β-hydroxy ketone acceptors such as **252** that are susceptible to acidic conditions. The conditions afforded β-glycosides in high yields and stereocontrol (Scheme 70).

Scheme 70. Glycosylation of C6-Bromo 2-Deoxy-2-iodo-β-glucopyranosyl Fluorides
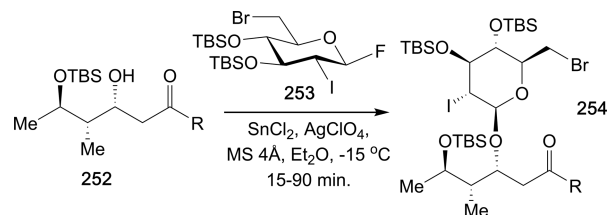
Following initial reports, Castillon and co-workers[310] also devoted efforts to the stereoselective synthesis of 2-deoxy-2-iodohexopyranosyl and 2-deoxy-2-iodoheptopyranosyl glycosides from furanoses as a route to access 2-deoxy-oligosaccharides. Starting from protected furanoses, a three-reaction sequence that included examples of all four isomeric configurations was developed (Scheme 71). The sequence involves Wittig−Horner olefination of the furanose substrate **255** by reaction with diphenylphenylsulfanylmethyl phosphine oxide to give the corresponding alkenylsulfanyl derivatives **256**, followed by electrophilic iodine-induced 6-endo cyclization that yields the phenyl 2-deoxy-2-iodo-1-thiohexoglycosides **257**, with practically complete regio- and stereoselectivity, in which the iodine at C-2 was in a cis relationship with the alkoxy at C-3. Finally NIS/TfOH-catalyzed thioglycosylation affords the desired deoxyglycosides **258** with good yields and stereoselectivities, with the major isomer being the glycoside in which the glycosidic bond is trans to the iodine at C-2. More recently, Castillon and co-workers were able to tune the stereoelectronic properties of the alkenyl sulfide intermediate by olefination of a protected furanose hemiacetal (D-ribose and D-arabinofuranose) with (sulfanylmethyl)diphenylphosphine oxide. In this manner, the diastereoselectivity of the cyclization step was improved and thus the methodology could be expanded to the preparation of challenging 2-deoxy-2-iodo-β-D-alloglycosides as precursors of 2-deoxy-β-D-ribohexopyranosides.[311]

The stereoselective synthesis of amino acid glycoside conjugates from their 2-deoxy-2-iodo counterparts also has been described. Hotha and co-workers[312] described a simple and efficient method to access 2-deoxy-2-iodo glycoconjugates such as **262**. Reaction of a peracetylated glycal **259** with the corresponding acid in the presence of cetronium bromide and KI afforded the 2-deoxy-2-iodo anomeric ester **261** with complete diastereocontrol (Scheme 72). Lewis acid-catalyzed intramolecular glycosylation reaction of the anomeric serinyl esters followed by dehalogenation afforded the β-serinyl glycosides **263** in a glycosylation process reminiscent of intramolecular aglycon delivery type glycosylations.

One of the first examples of polymer-supported deoxyglycoside synthesis includes seminal work by Hunt and Roush[313] demonstrating the synthesis of 6-deoxydi- and -trisaccharides in

Scheme 71. Castillon's Synthesis of 2-Deoxy-2-iodoglycosides
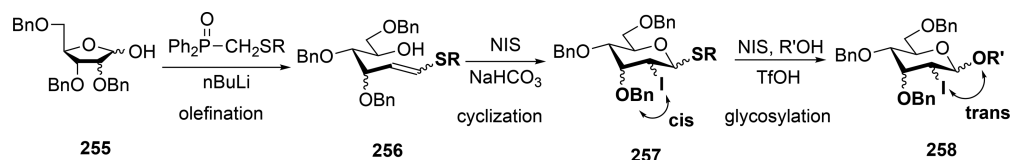
Scheme 72. Hypervalent Iodine-Mediated Synthesis of Amino Acid 2-Deoxyglycoside Conjugates
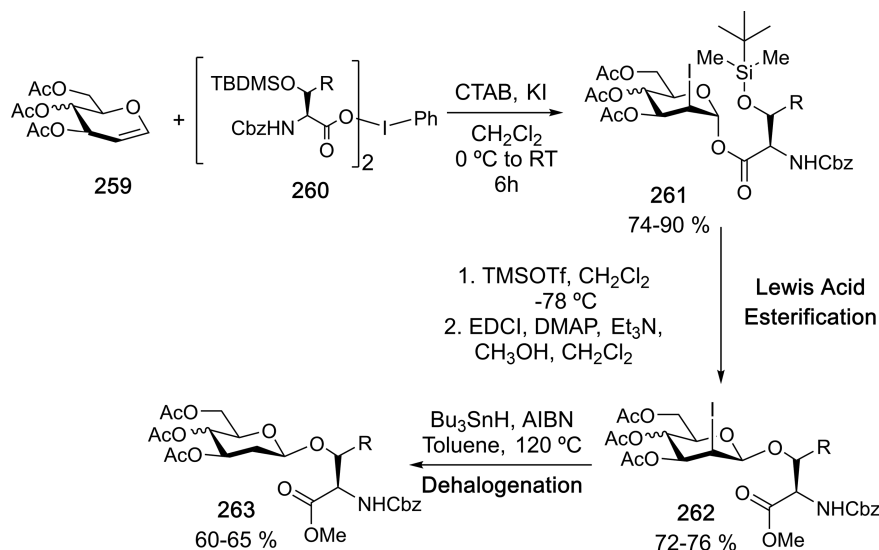
Scheme 73. Polymer-Assisted Activation of Glycals and Subsequent Glycosidation
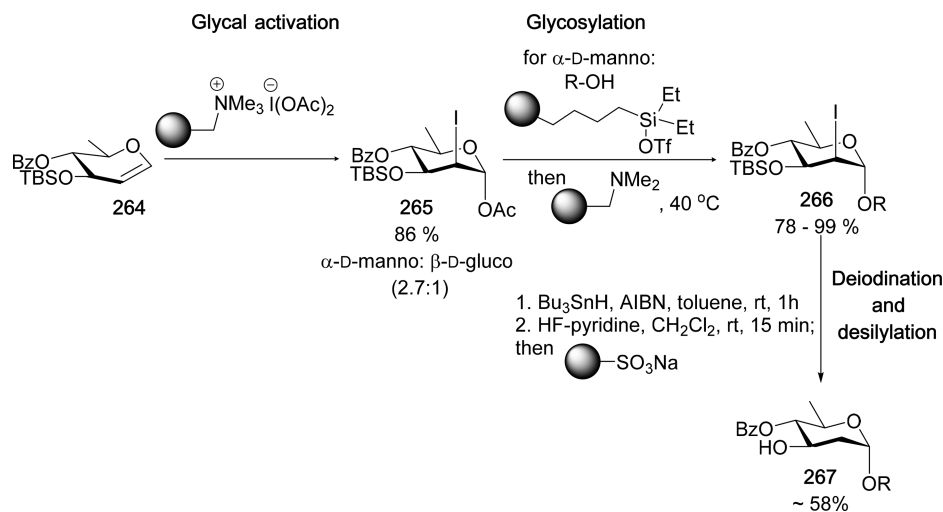
high yields using a sulfonyl chloride resin as an insoluble solid support. Subsequently, the Kirschning group demonstrated that higher selectivities for glycosylation reactions involving glycals could be achieved when the linker between the solid support and the glycal was at C-4. The same team also showed that solid polymeric supports are better suited for the synthesis of glycosylated products such as glycoconjugate steroids than for soluble MPEG-ethers.[314] In 2001, Kirschning and co-workers reported a glycosylation protocol using polymer-bound reagents instead of having the glycal attached to the polymer.[315] The team wanted to address some of the drawbacks of solid-phase synthesis: the requirement for functional linkers that are stable under various reaction conditions and the final cleavage of the often expensive and labile glycoside product without affecting the

diverse functionalities present. Their strategy includes polymer-assisted glycal activation, glycosidation, and O-desilylation to give the target deoxyglycosides in good to excellent yield (44–97%) and without the need for laborious workup and chromatography purification steps. In this manner, 2-iodoglyco-syl acetates such as 265 prepared from glycal starting materials using a polymer-bound bis(acetoxy)iodate(I) complex could be activated at the anomeric center by employing polymer-bound silyl triflate, which, in the presence of structurally diverse OH acceptors, gives the corresponding glycosides 266 in very good yields. Further protecting-group manipulations are also possible, and, for instance, desilylation could be achieved using HF-pyridine complex followed by treatment with Amberlite A-200 (Na⁺ form) to remove the excess desilylating reagent (Scheme

73). It was noted that the addition of a TfOH scavenger resin (Amberlyst A-21) was required to avoid product decomposition upon solvent evaporation. Furthermore, it was also shown that the method could be embedded in multistep sequences toward glycosylated testosterone and rhodinosyl—olivosyl—olivoside.[315]

While the utility of 2-deoxy-2-iodoglycosides as suitable precursors for deoxyglycosides has been demonstrated, the removal of the 2-iodo group after glycoside formation can sometimes be troublesome because most widely used deiodination methods employ toxic organotin reagents to effect the radical reduction. In 2014, inspired by advances from Lee and Stephenson on the reductive deiodination of organohalides that could be performed under visible-light irradiation in the presence of an iridium catalyst,[316,317] Wan and co-workers[318] described an efficient protocol to access 2-deoxy-α-glycosides such as **269** by glycosylation with 2-iodoglycosyl acetate to give **268** and subsequent visible-light-mediated tin-free reductive deiodination (Scheme 74). As previously demonstrated by Sebesta and

Scheme 74. Visible-Light-Mediated Tin-Free Reductive Deiodination of 2-Iodo-2-deoxyglycosides
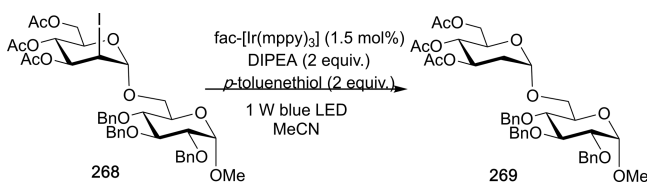
Roush,[319] TMSOTf-activation of a trans-diaxial 2-iodoglycosyl acetate afforded the corresponding 2-deoxy-2-iodo-α-glycosides. Deiodination is then carried out in the presence of *fac*-tris[2-(*p*-tolyl)pyridinato-C2,N′]iridium(III) (fac-[Ir(mppy)$_3$]), *N,N*-diisopropylethylamine (DIPEA), and *p*-toluenethiol under irradiation with a 1 W blue LED light. Using this protocol, >30 mono-, di-, tri-, tetra-, and pentadeoxysaccharides, including a 2-deoxy-tetrasaccharide, were prepared with excellent stereoselectivity and efficiency (60−80% overall yield).

In 2015, Toshima and co-workers developed a mild approach to prepare both 2-deoxy-2-iodoglycosides and 2-deoxyglycosides from glycals. The method did not require the use of strong Brønsted acids that may interfere with acid-sensitive substrates. Inspired by earlier work by Ishihara and co-workers,[320] Toshima and co-workers were able to access 2-deoxy-2-iodoglycosides (**270** and **271**) after 12 h in excellent yield and good α/β stereoselectivity using *N*-iodosuccinimide (NIS) in combination with triphenylphosphine at low temperatures (Scheme 75A).[321] A number of alcohols were screened in reactions with tri-*O*-benzylglucal **171**, including several substrates bearing acid-sensitive groups such as acetals and silyl ethers. In these cases, using triphenylphosphine as an additive in place of the more traditional triflic acid gave superior yields. The reaction is thought to proceed via activation of the glycal by a reactive iodophosphonium ion to give a glycosyl iodonium cation with concomitant regeneration of catalytically active triphenylphosphine. The activated glycoside donor undergoes the nucleophilic addition by the alcohol to furnish the product. Interestingly, the use of triphenylphosphite in place of triphenylphosphine in the presence of catalytic amounts of NIS (0.1 equiv) at room temperature permits the synthesis of 2-deoxyglycosides in excellent yields and good stereocontrol (Scheme 75B). Initial mechanistic investigations with deuterated alcohol (ROD) led to a proposed glycosylation mechanism that begins with the

Scheme 75. NIS/Phosphorus Compound-Catalyzed Synthesis of (A) 2-Deoxy-2-iodoglycosides and (B) 2-Deoxyglycosides and Proposed Mechanism of Glycosylation Using NIS and P(OPh)$_3$
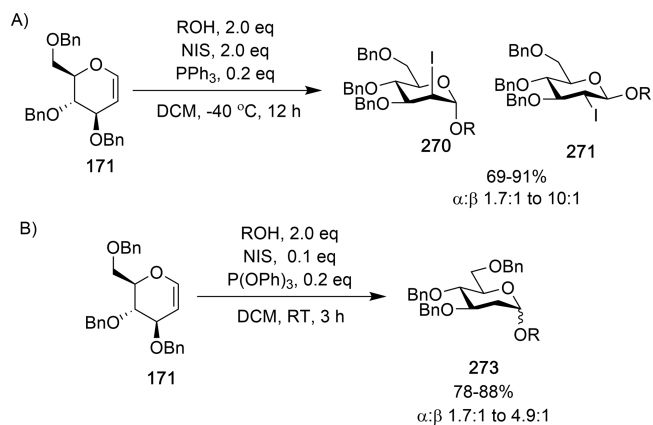
Proposed mechanism
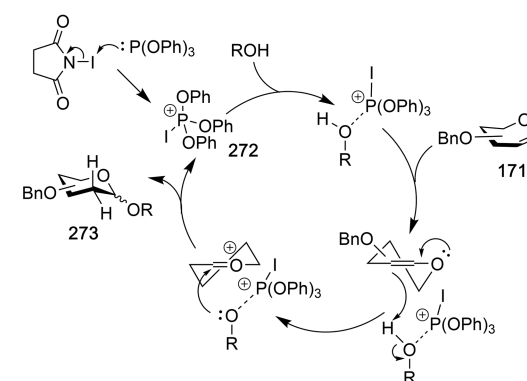
formation of a iodophosphonium ion **272** generated from the reaction between NIS and P(OPh)$_3$, which can accept electron density from the alcohol owing to the electron-withdrawing effect of the phenoxy groups. The reacting glycal is able to abstract the alcoholic proton to form an oxocarbenium ion, which is then trapped by the activated aglycon, furnishing the 2-deoxyglycoside product and regenerating the iodophosphonium cation **274** in an organocatalytic manner.

4.7. Anomeric Alkylation

Anomeric *O*-alkylation was initially developed by the Schmidt group[322] as an alternative to traditional glycosylation methods for the stereoselective synthesis of β-linked oligosaccharides and glycoconjugates. It has been proposed that the axial anomeric alkoxide is in rapid equilibrium with its equatorial isomer via an acyclic intermediate. Moreover, it is believed that the axial alkoxide is less reactive than the equatorial configuration because of the "*kinetic anomeric effect*".[322] Thus, selective *O*-alkylation of the more-reactive equatorial anomeric alkoxide by an electrophile should lead to the formation of β-glycosides preferentially. The key advantage of this approach is that a neighboring participating group at C2 is not required to achieve selectivity, which is ideal for the synthesis of 2-deoxy-β-glycosides.

The Bennett group[323] described a strategy to access β-linked 2-deoxy-sugars based on anomeric *O*-sulfonation followed by nucleophilic displacement. The method entails activation of 2-deoxy hemiacetals **246** with *N*-sulfonyl imidazoles, to generate a reactive electrophilic species in situ, presumably a glycosyl

sulfonate, that can react with different nucleophiles in a S$_N$2 or S$_N$2-type fashion. The reaction afforded β-glycosidic products such as **274** exclusively when the reactivity of the donor is matched with the leaving-group ability of the sulfonate (Scheme 76). The best results were obtained when the reaction was

Scheme 76. *N*-Sulfonylimidazole-Catalyzed Synthesis of 2-Deoxy-β-glycosides
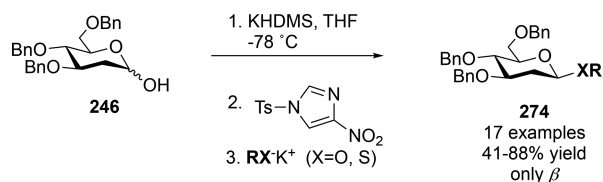
performed in tetrahydrofuran (THF) at −78 °C using tosyl 4-nitroimidazole as the glycosylation promoter in the presence of a slight excess of activated donor. These conditions afforded the desired product in very good yields and complete β-selectivity. Various nucleophiles, including thiol and aryloxy nucleophiles, were screened to evaluate the scope of the reaction, and, in all cases, the β-anomer was obtained with moderate to good yields. In the latter case, diglyme was needed as a coordinating solvent to improve reaction performance. Although the methodology is not effective with all classes of glycosyl donors (e.g., mannose, rhamnose, etc.), the authors were optimistic that, given the range of reactivities of different sulfonates, it should be possible to match each class of glycosyl donor to a proper leaving group for β-specific glycosylation reactions.

Further investigations from Bennett and co-workers[324] allowed them to extend the methodology to the synthesis of β-linked 2-deoxydisaccharides such as **275** and **276** from hemiacetal donors (**246** and **249**) with complete stereocontrol. The reaction conditions were optimized, and a more potent sulfonylating agent such as *p*-toluensulfonic anhydride was used in combination with the non-nucleophilic base tri-*tert*-butylpyrimidine (TTBP) in the reaction (Scheme 77). The method is

Scheme 77. *N*-Tosyl-4-nitroimidazole-Catalyzed Synthesis of 2-Deoxy-β-glycosides
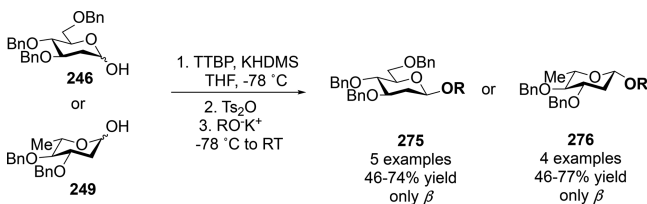
applicable to a wide range of acceptors and is not sensitive to the absolute configuration of the glycosyl donor. Moreover, the reaction conditions are also amenable to activation of the more-reactive 2,6-dideoxy-L-arabinose. All reactions provided the glycosylated products as a single anomer in moderate to good yields, with the exception of examples where the acceptor bore acetonides as protecting groups. These reactions proceeded in lower yield. Low-temperature heteronuclear single quantum coherence (HSQC) NMR experiments of the reaction mixture helped Bennett and co-workers identify signals consistent with the presence of an α-glycosyl sulfonate species, which presumably reacts through an S$_N$2-like pathway to generate the β-linked product stereospecifically.

Most anomeric *O*-alkylation protocols that are employed to achieve stereoselective glycosylation are limited to primary or aromatic electrophiles. This is exemplified by the report by Morris and Shair in 2009[325] on the stereoselective synthesis of 2-deoxy-β-glycosides from orthogonally protected deoxyglycoside hemiacetals such as **246** using anomeric *O*-alkylation/arylation. Reaction of the lactol with NaH in dioxane to generate the anomeric alkoxide followed by addition of electrophiles leads to the formation of the desired glycoside products **278** in high yield and β-selectivity (Scheme 78). To shed light on the reaction

Scheme 78. Synthesis of 2-Deoxy-β-glycosides Using Anomeric *O*-Alkylation/Arylation
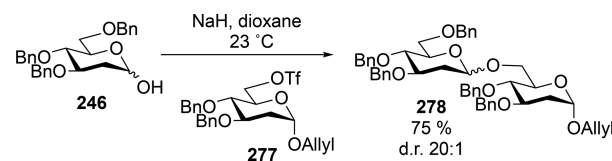
mechanism, the team also performed glycosylation competition experiments in the presence of a cyclohexyl alkoxide. The latter did not inhibit the glycosylation reaction or react under the reaction conditions, suggesting that the nucleophilicity of β-configured anomeric alkoxides is also enhanced relative to other similar cyclohexyl alkoxides, presumably due to the proximity of the alkoxide and the lone-pair electrons of the ring oxygen. On the basis of their results, the authors suggest that the high diastereoselectivity observed supports the theory that the β-effect, and not the substituent at C2, is what controls the stereo-outcome in anomeric *O*-alkylations/arylations and that this powerful stereoelectronic effect may be useful in designing other stereoselective reactions.

A more recent report by Zhu et al.[326] describes the direct synthesis of 2-deoxy-β-glycosides involving anomeric *O*-alkylation with triflates as secondary electrophiles. To avoid side-products, the method requires a free OH group at the C-3 position of the deoxy-sugar-derived lactol. Because the vast majority of 2-deoxy-β-glycosides found in nature have 1 → 3 or 1 → 4 linkages, this elegant *O*-alkylation protocol serves as an ideal synthetic tool for this class of glycosides. The best results were obtained when reacting the corresponding lactol in 1,4-dioxane with sodium hydride followed by addition of triflate and a sodium chelating agent (15-crown-5). Using this methodology, three different 2,6-deoxy-sugar derived lactols, such as **279**, bearing a free C3-hydroxyl group were reacted with a variety of sugar-derived secondary and primary triflates **280** as nucleophiles to afford the desired β-oligosaccharides **281** with good to excellent yields and complete β-selectivity (Scheme 79). The procedure was also successfully applied to the preparation of synthetically challenging 2,3,6-trideoxy and 2,4,6-trideoxy-4-azido-β-glyco-

Scheme 79. Anomeric Alkylation Involving Triflates As Leaving Groups
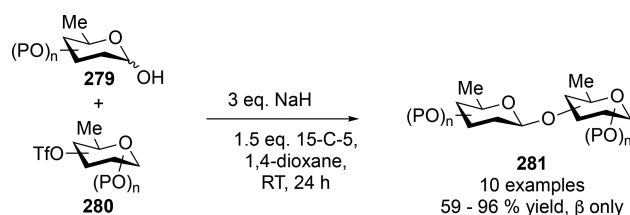
sides. A 2-deoxy-D-glucose-derived lactol was also screened against secondary triflates using this method. Although the products were formed as β-anomers, the reactions proceeded in low yields. This result is not unexpected as these substrates are relatively less reactive than their 2,6-dideoxy counterparts. The versatility of the approach was demonstrated in the efficient synthesis of a 2,6-dideoxytrisaccharide and a tetrasaccharide containing all β-linkages.

More recently, the same team expanded the utility of this methodology to the synthesis of α-digitoxosides and α-boivinosides via chelation-controlled anomeric O-alkylation.[327] Unlike the previous studies, the lactol donors have C-3 axial OH substituents instead of an equatorial configuration. Zhu and co-workers speculated that 2-deoxy-sugar-derived equatorial anomeric alkoxides containing a C-3 axial alkoxide should undergo anomerization in favor of the corresponding axial anomeric alkoxides due to the potential chelation effect. Such chelation should then lock the axial conformation of the anomeric alkoxides, leading to the selective formation of the corresponding α-glycosides upon alkylation with a suitable electrophile. Indeed, reaction between 2,6-dideoxy-sugar bearing the C3 axial hydroxyl group 4-O-p-methoxybenzyl-D-digitoxose and a variety of primary and secondary sugar triflates gave the desired digitoxosides in high yields and complete stereo-selectivity in most cases, with the exception of diacetonide-protected D-galactose in which the α-selectivity decreased to an α/β ratio of 7:1. Benzyl-protected α-boivinose also afforded the corresponding α-disaccharides (such as **283**) with complete stereoselectivity, although, in this case, with moderate yields (Scheme 80).

Scheme 80. Synthesis of α-D-Boivinoside 283
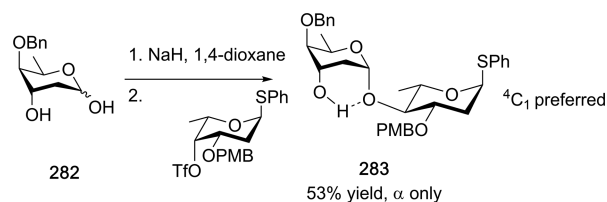
4.8. Glycosylations of Unprotected and Unactivated Carbohydrates

Most glycosylation reactions are carried out using partially protected carbohydrate building blocks as a means to control the regioselectivity and reactivity of the reaction. Typically, a leaving group is installed at the anomeric position of the glycosyl donor, which can be activated to effect glycosylation in the presence of the chosen nucleophile. Fisher-type glycosylation is one of the few examples where a direct glycosylation of unprotected and unactivated glycosides is described; however, those processes rely on the use of a strong acid catalyst, high temperatures, and an excess of OH nucleophile, which is often the reaction solvent.

In this context, Lewis acids have also been deployed in glycosylation reactions of unprotected carbohydrates, including examples where the reactions are performed in ionic liquids.[328,329] In 2013 Schmalisch and Mahrwald reported the organocatalytic glycosylation of unprotected sugars such as **284** using triphenylphosphine (PPh$_3$) and tetrabromomethane (CBr$_4$) under neutral conditions.[330] A series of unprotected monosaccharides (hexoses and D-ribose) were glycosylated with simple alcohols at room temperature. Glycoside products were obtained after 16 h in low to excellent yields and with poor to

good α/β stereoselectivity (Scheme 81A). It is proposed that, under the reaction conditions, thermodynamic control of the glycosylation is observed. As a consequence, the formation of pyranosides is favored.

Scheme 81. Glycosylation of Unprotected Sugars Using PPh$_3$/CBr$_4$ under Neutral Conditions
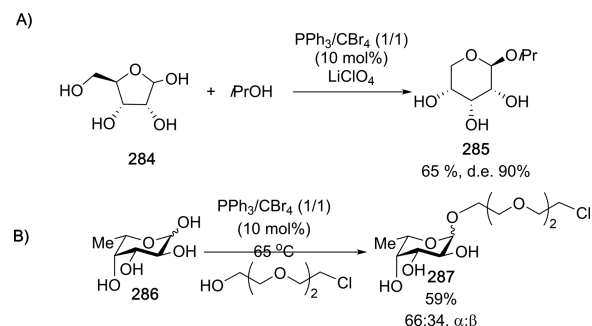

L-Fucose (6-deoxy-L-galactose) is also an important epitope that is known to bind several pathogenic lectins.[331,332] Thus, the stereoselective synthesis of fucoside probes is of particular relevance. Vincent, Vidal, and co-workers further capitalized from Mahrwald's conditions, and, in 2014, the group reported the PPh$_3$/CBr$_4$-promoted glycosylation with fully unprotected L-fucose **286** of chloro- and alkyne-functionalized triethylene glycols (Scheme 81B).[333] Although the results are modest (59% yield and anomeric selectivity of 66:34 α/β) and the reaction is not applicable to orthogonally protected glycosyl acceptors, this approach offers a fast and straightforward access to PEG-conjugated building blocks ready for multivalent array conjugation. This is a practical alternative to the time-consuming and costly preparation of a fully protected fucoside glycosylation donor.

4.9. Conformationally Retricted Donors in the Synthesis of Deoxyglycosides

As already discussed in sections 3.2 and 4.6, 2-deoxy-2-haloglycopyranosyl donors have been used as highly diastereoselective glycosidating agents for the synthesis of 2-deoxy-β-glucosides (and also 2-deoxy-α-glucosides). To try to shed light on the origin of the high β-selectivity for deoxyglucosides and to evaluate the possible involvement of "conformationally inverted" oxonium ion intermediates in glycosidation reactions with 2-deoxy-2-iodoglucopyranosyl donors, Roush and co-workers[334] performed a study employing 4,6-O-benzylidine acetal-protected glycosyl imidates such as **288**, which differ in their anomeric configuration. The team found that, regardless of anomeric configuration, reaction solvent, or temperature, a high β-stereoselectivity was still obtained. A twist boat conformation and the presence of an iodonium ion (**289**) may be invoked to rationalize the β-selectivity observed and may also apply to the unconstrained 2-deoxy-2-iodoglucopyranosyl donors (Scheme 82).

While the synthesis of 2-deoxy-β-glucosides from 2-deoxy-2-iodoglycosyl donors is well-documented as previously discussed, obtaining 2-deoxy-β-galactosides is significantly more challenging. In 2003, the Roush group[335] described the use of conformationally constrained 2-bromo- and 2-iodogalactopyranosyl acetates such as **291** and trichloroacetimidate glycosyl donors for the synthesis of 2-deoxygalactopyranosides such as **293** (Scheme 83). The team found that the best selectivities for the β-glycosidic linkage were achieved when using conforma-

Scheme 82. Stereoselective Synthesis of Conformationally Constrained 2-Deoxy-β-glucosides
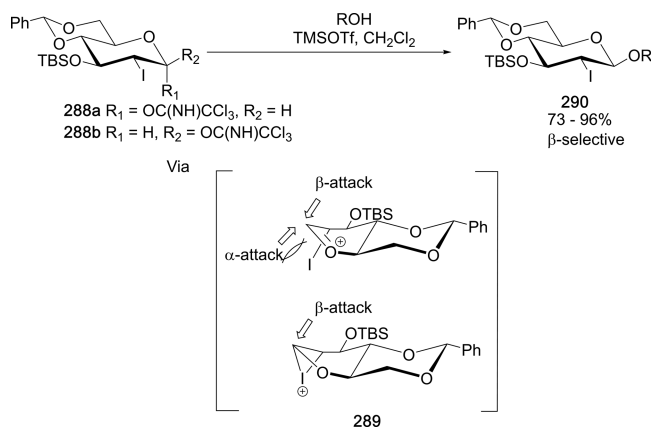
tionally constrained 6-deoxy-3,4-carbonate-protected galactosyl donors. Interestingly, it was noted that a decrease in diastereoselectivity was observed when 3,4-carbonate protected donors bear oxygenated substituents at C6 or when the donor lacks the cyclic 3,4-protecting group. These results further support the authors' proposal that the conformational constraint induced by the 3,4-carbonate group biases the conformational preference of the intermediate pyranosyl oxocarbenium ion (via **294**) to give the β-stereoselectivity observed. Also in agreement are earlier studies from the Danishefsky team, which demonstrated that the β-selectivity of glycosidation reactions of 2,3-epoxy-sugars in the galactose series were considerably enhanced when the 3,4-hydroxyl groups were protected as a 3,4-carbonate group.[336]

Controlling the stereoselectivity of glycosylation reactions involving glucals as glycosyl donors is particularly challenging due to the lack of the C-4 OH as the axial substituent, which leads to the attack of the nucleophile from both faces of the ring[5] and often produces 2,3-unsaturated Ferrier-type products.[5,337] Another example of Brønsted acid-catalyzed glycosylations to access deoxyglycosides has been demonstrated in the activation of conformationally constrained glycal donors. Galan, McGarrigle, and co-workers described a practical and efficient direct glycosylation protocol for the preparation of α-linked deoxyglucosides with high selectivity and yields using commercial tosic acid (TsOH·H₂O) (1 mol %) as the Brønsted acid catalyst.[338] Acid-catalyzed direct nucleophilic substitution on a glycal is thought to proceed via oxocarbenium ion intermediates, which generally adopt two half-chair conformations ($^4H_3$ vs $^3H_4$). Nucleophilic addition on these transient cationic species leads to different diastereomeric products. The team hypothesized that, because conformational equilibrium between the different species is influenced by steric effects as well as the electronic

nature of the substituents,[10,339] protecting group-induced conformational constraints on the charged glucal-derived oxocarbenium ion could be used to influence the stereoselectivity of the glycosylation. As demonstrated by their investigations, the stereocontrol during the reaction is controlled by the presence of a trans-fused cyclic 3,4-O-disiloxane protecting group in the glycal donor (**295** and **296**). The intermediate oxocarbenium cation **298** that is formed during the reaction is locked in a conformation in which the C6-OSiR₃ group adopts a *gauche–gauche* conformation with respect to the endocyclic oxygen and C-4. This conformation orientates the C6–O bond approximately parallel to the pseudoaxial substituents, favoring an axial attack from the nucleophile (Scheme 84). Reactions with glucal substrates **295** gave products with higher stereocontrol than rhamnals **296**, which was attributed to the conformational preference of the C6 side-chain,[340] which is lacking in the rhamnal moieties. This report further highlights the importance of considering the effect that protecting groups have on the conformation of putative reaction intermediates and how these can be used to achieve stereocontrol.

5. TRANSITION METAL CATALYSIS APPLIED TO 2-DEOXYGLYCOSIDE SYNTHESIS

Recent years have seen a steady increase in the application of transition metal catalysis to oligosaccharide synthesis[341−343] because the careful choice of ligand/transition metal combination can offer significant improvements over traditional methods in terms of atom economy, high yields, and control of anomeric selectivity. The metal complex in combination with the careful selection of the ligands attached to the metal center contributes to stereodifferentiation during the coupling reaction.

5.1. Palladium-Catalyzed Glycosylations

Most palladium-catalyzed direct activation of 1,2-unsaturated glycals tend to yield the corresponding 2,3-unsaturated Ferrier products (such as **303**) with good to excellent selectivities. Those protocols are believed to proceed via π-allyl intermediates.[342,344]

O'Doherty and co-workers[345,346] disclosed a Pd(0)-catalyzed glycosylation for the de novo synthesis of all-D- or all-L-1,4- and -1,6-α-mannotrisaccharides such as **304** (Scheme 85). Subsequently, in 2012, the group expanded their methodology to the preparation of various highly branched all-D-, all-L-, and mixed D-/L-oligosaccharides using asymmetric and diasteroselective catalysis for stereocontrol.[347] A bidirectional strategy that combines the use of Pd(0)-catalyzed glycosylation/postglycosylation transformations allowed the team to access the four possible D-/L-diastereomeric α-1,4-linked rhamnotrisaccharides and dideoxy congeners in 10 steps starting from achiral acylfuran **299**. In a similar fashion, highly branched heptasaccharides, such **305** or **306**, were stereoselectively constructed in 12 steps from **299**. The methodology is mild, amenable to acid

Scheme 83. Synthesis of 2-Deoxy-β-galactosides from 2-Deoxy-2-halogalactopyranosyl Donors
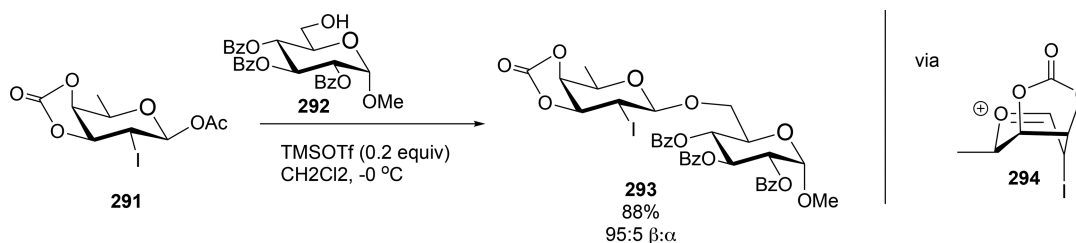
Scheme 84. Stereoselective Glycosylations with Trans-Fused Cyclic 3,4-O-Disiloxane Protected Glucals
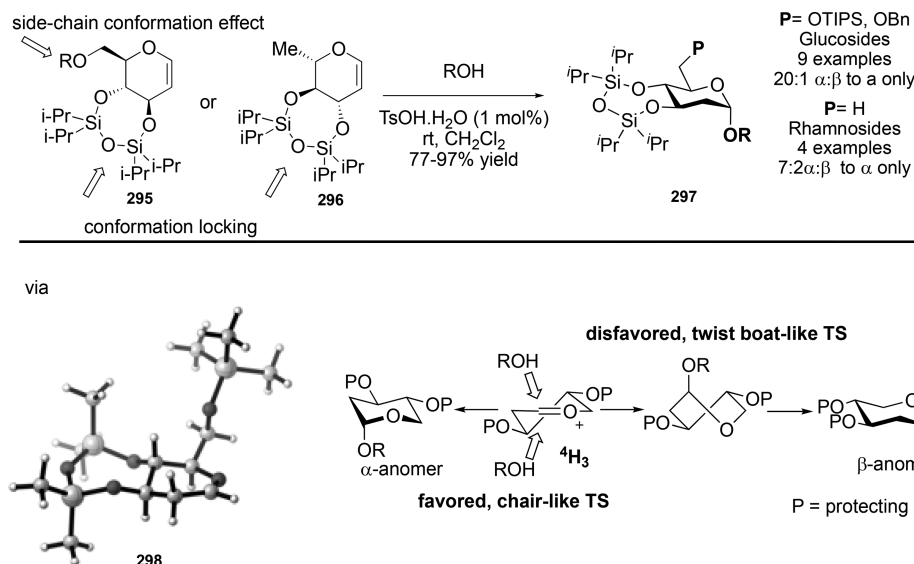
Scheme 85. Pd(0)-Catalyzed Glycosylation for the De Novo Synthesis of α-Mannoheptasaccharide
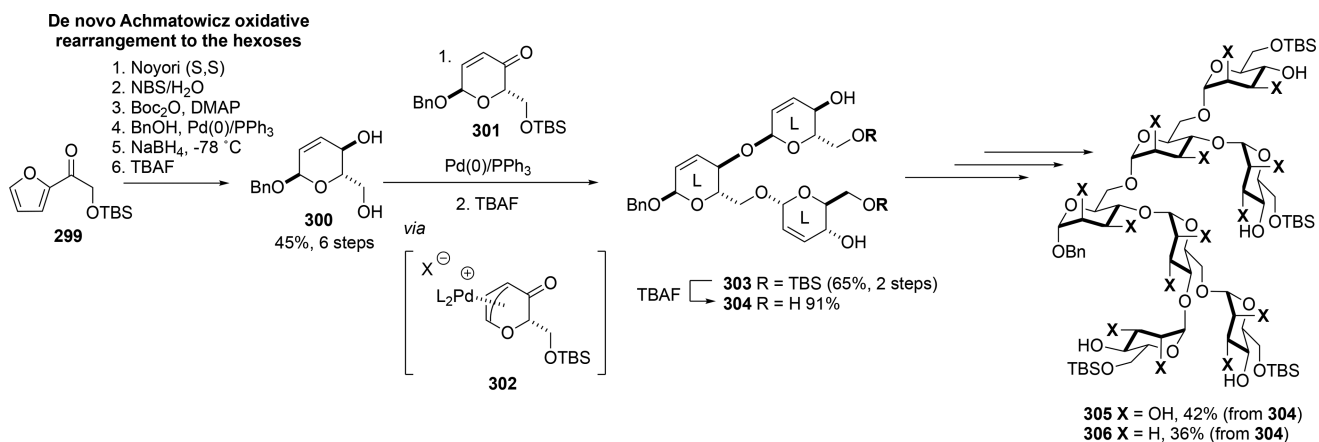
Scheme 86. Pd-Catalyzed O-Glycosylation
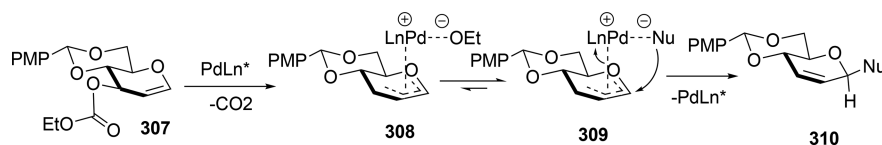
sensitive deoxy-sugars and capable of being diversified into any of the D- and/or L-sugar diastereomers with complete stereocontrol.

An interesting approach that relies on the Pd-catalyzed decarboxylative allylation of glucal-derived carbonates to prepare a number of 2,3-unsaturated O-deoxyglycosides in good yields and with excellent selectivity was developed by Liu et al. in 2014.[348] The process involves a tandem decarboxylation/proton abstraction followed by nucleophilic addition with a number of phenolic, aliphatic, and glycoside alcohols. The reaction appears to be sensitive to the type and loading of the base, reaction temperature, and electronic nature of the substrates. Moreover, the authors propose that selectivity is determined by the nontraditional Pd-π-allyl intermediate **309** on the glycal system, which helps deliver the nucleophile from the top face of the molecule (Scheme 86).

More recently, Galan and co-workers[349] reported the first example of a non-π-allyl-mediated Pd-catalyzed direct and stereoselective glycosylation of glycal enol ethers. Interestingly, glycoside products resulting from addition of the proton and alkoxide nucleophile across the carbon−carbon double bond are formed when monodentate N-phenyl-2-(di-tert-butylphosphino)pyrrole (**L**) **312** is employed as the ligand. The mechanistically interesting reaction is mild and widely applicable to a range of glycal donors and nucleophile acceptors including some bearing alkene functionalities. On the basis of mechanistic investigations, it is proposed that, in the presence of **312**, palladium-catalyzed coupling of glycals with alcohol nucleophiles involves the initial insertion of Pd into the RO−H bond. This stands in contrast to the traditional pathway of palladium-mediated alkene activation, to produce an alkoxypalladium species (A) in Scheme 87, with concomitant H+ release

Scheme 87. Palladium-Catalyzed Synthesis of 2-Deoxyglycosides from Glycals

311
P = protecting group
R = H, OP

313
21 examples
66–96%
α-selective
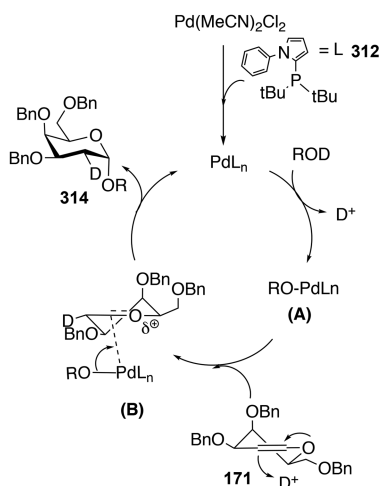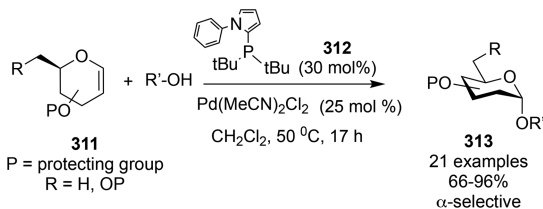
from the OH nucleophile. Protonation of the glycal can then take place from the less-hindered face, which leads to the formation of a transient oxocarbenium ion (B) that quickly reacts with the activated oxygen nucleophile in (A) in a stereoselective manner to give the corresponding α-glycoside. The reaction proceeds with good to excellent yields (66–96%) and high selectivity for the α-anomer and is tolerant of most common protecting groups. The generality and versatility of the approach is demonstrated with the stereoselective synthesis of a series of disaccharides, glycosyl amino acids, and other glycoconjugates (Scheme 87).

As already discussed above, palladium(II) catalysis has been used for the direct activation of 1,2-unsaturated glycals to yield the corresponding 2,3-unsaturated products with good to excellent selectivities and yields. In most examples, activated or "armed" glycals are required to facilitate the reaction due to the poor reactivity of both the glycal donors and alcohol acceptors for a η3-metal mediated reaction.[348,350] Elegant reports from Lee and co-workers[351] describe the use of zinc(II) alkoxides, in addition to Pd(OAc)$_2$ and ancillary ligands, to activate both the acceptor for the nucleophilic addition and the leaving group for the ionization. Reactions with both acetate or *t*-butyl carbonate as protecting groups at C(3) were found to work equally well. Notably, the anomeric stereochemistry is effectively controlled by the reagent, independent of the steric and electronic nature of the substrates. For instance, when bulky ligand di(*tert*-butyl)-phosphine (DTBBP) is used, the β-anomer is formed almost exclusively. On the other hand, using trimethyl phosphite afforded the α-anomer with good selectivity (7:1 α/β). More recently, the Nguyen group also reported a palladium-catalyzed Ferrier-type glycosylation using glycal donors with a trichloroacetimidate leaving group at C-3. Similarly, prior activation of the glycoside acceptor is required via zinc alkoxide formation for the reaction to proceed.[352]

Sau and Galan[353] also demonstrated that Pd(MeCN)$_2$Cl$_2$ can be used to enable the α-stereoselective catalytic synthesis of 2,3-unsaturated O-glycosides from deactivated or "disarmed" glycals such as **315** without the requirement for additives to preactivate either donor or nucleophile. Mechanistic studies suggest that, unlike traditional (η3-allyl)palladium-mediated processes, the reaction proceeds via an alkoxypalladium intermediate (A) that increases the proton acidity and oxygen nucleophilicity of the alcohol under the reaction conditions (e.g., deactivated glycal and absence of anciliary ligands) (Scheme 88). Proton-catalyzed

Scheme 88. Palladium-Catalyzed Synthesis of 2,3-Unsaturated Deoxyglycosides from Glycals

315

316
15 examples
54–96%
α-selective

P'=Deactivating protecting groups
P"=H, OP'

Readily available donor
No need for anciliary ligands
No need for additives
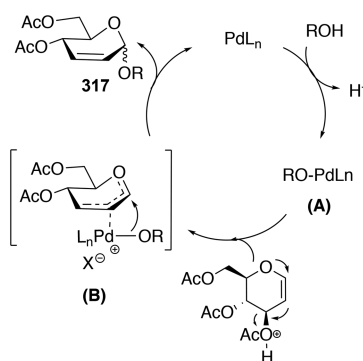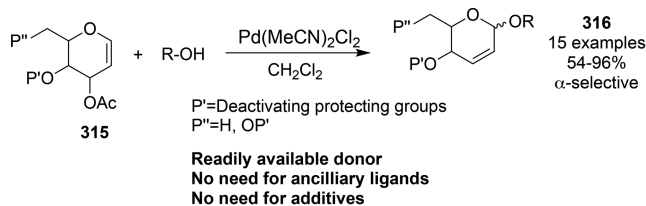
allylic rearrangement takes place, leading to the formation of a transient oxocarbenium ion that can undergo reversible coordination with complex (A) preferentially from the α-face to form short-lived intermediate (B) (Scheme 88). Concomitant deoxypalladation and nucleophilic addition of the activated oxygen in a stereoselective manner can thus take place to yield the desired 2,3-unsaturated glycosides. The reaction is mild and proceeds with good to excellent yields (54–96%) and high selectivity for the α-anomer. The method utilizes commercial starting materials and is widely applicable to a range of nucleophile acceptors. The team exemplified the utility of their approach in the stereoselective synthesis of a series of disaccharides, glycosyl amino acids, and other glycoconjugates, including saturated chiral scaffolds of medicinal relevance.

Overall, these results clearly demonstrate that the electronics and protecting group scheme of the glycal substrate and the choice of Pd/ligand combination are key to control the anomeric selectivity and the glycosylation pathway.

5.2. Gold-Catalyzed Glycosylation Reactions

The alkynophilic nature of gold catalysts has led to the development of new glycosylation methodologies whereby gold complexes are used to perform glycosylation reactions by activation of glycosyl donors bearing an anomeric alkyne moiety. A recent example of gold(I)-promoted α-2-deoxyglycoside formation comes from Zhu's group.[354] The team uses bench-stable 2-deoxy-S-but-3-ynyl thioglycosides **318** as glycoside donors in glycosylation reactions with a variety of glycoside acceptors to obtain glycosides with α-selectivity in good to

excellent yields and with moderate stereocontrol (Scheme 89). The proposed mechanism involves the formation of sulfonium

Scheme 89. Au(I)-Catalyzed Synthesis of 2-Deoxyglycosides Using S-But-3-ynyl Thioglycosides and Proposed Catalytic Cycle
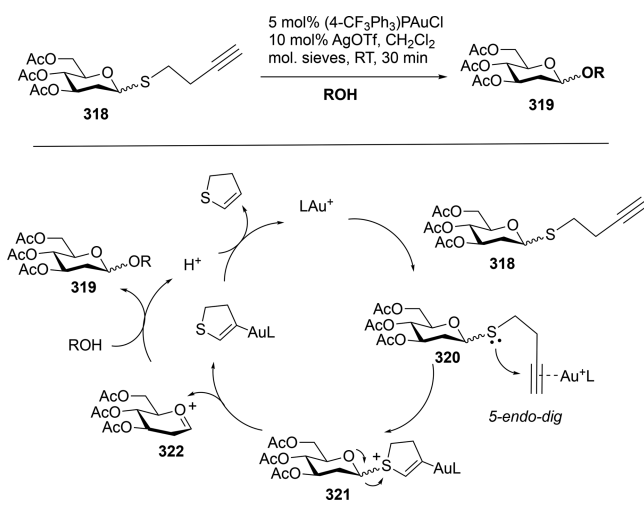
ion **321**, which is generated by the attack of the sulfur atom onto the activated alkyne as in **320**. Subsequent cleavage of the glycosidic bond leads to the formation of the corresponding oxocarbenium ion **322**, which undergoes glycosylation with an alcohol acceptor to afford product **319**. The release of a proton during the procedure allows the regeneration of the catalyst. The authors highlight that the reaction yields are closely tied to the phosphine ligand selected. Moreover, the presence of AgOTf as an additive is needed to facilitate the protodeauration and regeneration of the cationic gold(I) catalyst.

The combination of gold(III) chloride with phenylacetylene has also been devised by the Vankar group as a new relay catalytic system to promote the Ferrier rearrangement of acetyl-protected glycals and 2-acetoxymethylglycals as well as the O-glycosylation of 1-O-acetyl sugars with different nucleophiles.[355] Reaction times are short and the desired products were obtained in good to excellent yields and with high anomeric selectivity in the case of glycals, while moderate to good selectivities were observed for the 1-O-acetyl glycosyl donors **324** (Scheme 90). Subsequently, the same group expanded the scope of the Au(III)-based relay catalytic system to glycosylations using glycosyl trichloroacetimidates **221**, which was shown to be more efficient than AuCl₃ alone.[356] Reactions proceeded efficiently at room temperature and with good yields and diastereoselectivity for 2-acetyl-protected disarmed donors. Anomeric mixtures were obtained for armed glycosides, and the use of acid-sensitive nucleophiles afforded moderate yields. The Vankar team proposed that coordination of AuCl₃ with phenylacetylene makes the phenyl-acetylene somewhat electron-deficient so that it becomes susceptible to nucleophilic attack by the lone pair of the trichloroacetimidate nitrogen, thus effecting its departure. This makes the gold salt/alkyne combination a more powerful catalyst than AuCl₃ alone. Protonation by the alcohol nucleophile to form the amide as a byproduct regenerates the catalytic system for the next cycle. However, the team does not rule out that direct activation of the trichloroacetimidate moiety on the glycosyl donors with AuCl₃ as the Lewis acid also may be taking place.

Scheme 90. Au(III)/Phenylacetylene-Catalyzed Glycosylation of Glycals, Glycosyl Acetates, and Trichloroacetimidates
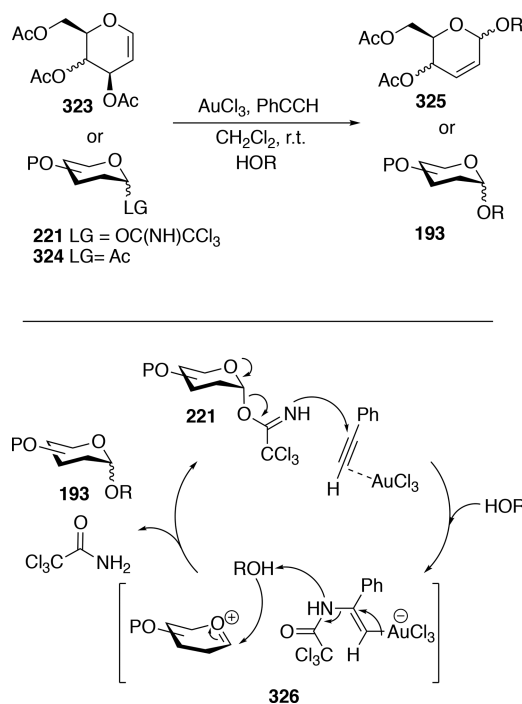
Most of the reports on the development of Au(III)- and Au(I)-catalyzed O-glycosylation protocols proceed via the Au-activation of an anomeric alkyne in the glycosyl donor to furnish the corresponding oxonium ion, which then reacts with the incoming OH nucleophile.[342] Galan and co-workers[357] recently described an unprecedented Au(I) direct activation of glycals to yield α-deoxyglycosides in excellent yields and high stereocontrol. The glycoside products such as **327** resulted from the syn addition of a proton and oxygen from the OH nucleophile across the carbon−carbon double bond when [((pCF₃Ph)₃P)-AuCl] and AgOTf were used as the glycosylation promoter (Scheme 91). On the basis of preliminary mechanistic studies, it was proposed that the reaction proceeds via Au(I)-catalyzed hydrofunctionalization of the enol ether to yield the desired glycoside with high stereocontrol. Reversible coordination of the Au(I) cation to the C═C double bond leads to π-complex (A), which can lead to the formation of transient oxacarbenium ion (B) that is quickly trapped by the OH nucleophile with concomitant protonolysis of the Au−C bond to yield the glycoside products **314** and regenerate the Au(I) catalyst (Scheme 91). The reaction is mild and applicable to a range of glycal donors and nucleophile acceptors including primary and secondary type OHs and most common protecting groups. The utility of this transformation was exemplified in the stereo-selective synthesis of a series of oligosaccharides, glycosyl amino acids, and other glycoconjugates.

5.3. Rhenium-Catalyzed Glycosylations

Rhenium(V) complexes have also been successfully applied as catalysts for the stereoselective synthesis of 2-deoxyglycosides. The Toste group reported the direct synthesis of 2-deoxy-α-glycosides from glycals bearing equatorial C-3 substituents as in D-glucal, D-rhamnal, and D-galactal.[358] More recently, Zhu and co-workers[359] demonstrated that the presence of axial substituents at C-3 in 6-deoxy-D-allal derivatives such as **329**

Scheme 91. Au(I)-Catalyzed Synthesis of 2-Deoxyglycosides from Glycals

The strategy allowed the group to obtain the cardiac glycosides digitoxin (**334**) and C1′-epi-digitoxin (**335**) as a β-enriched mixture of anomers (1:5) with a 61% yield for the glycosylation step (Scheme 92).

5.4. Ruthenium-Catalyzed Glycosylations

In the context of ruthenium-catalyzed glycosylations, Boutureira and co-workers capitalized on the 6-endo cyclization of 3-deoxysulfanyl alkenes[310] to access glycosides under microwave conditions, and, in 2014, a ruthenium-catalyzed cross-metathesis reaction of a sugar-derived hydroxyalkene was reported.[360] The first step of their improved protocol involved the five-to-six carbon homologation of 2-deoxy-D-ribofuranose hemiacetal **336** via Wittig olefination. The corresponding terminal alkene **337** was then subjected to a microwave-assisted cross-metathesis reaction with electron-rich phenyl vinyl sulfide (with second-generation Grubbs catalyst giving optimal results) to give the corresponding 3-deoxysulfanyl alkenes **338** that can undergo NIS- or NBS-mediated 6-endo cyclization to access the 2-iodothioglycoside products. In this manner, challenging 2,3-dideoxy-D-ribosides could be prepared in good yields (Scheme 93).

6. DEOXY-C-GLYCOSYL COMPOUNDS

leads preferentially to β-glycosides upon glycosylation using Re(V), owing to the presence of 1,3-diaxial interactions. Moderate to good yields and β-selectivities were achieved using nonpolar solvents, with benzene being the optimal one, in reactions involving a range of 6-deoxy-D-allal derivatives with a number of primary and secondary alcohols as well as thiophenol.

C-glycosyl compounds are carbohydrates in which the anomeric oxygen has been replaced by a carbon atom, and they represent a very important class of molecules with interesting biological and pharmaceutical activities. The lack of the anomeric carbon imparts an increased stability on the glycosides, making them resistant to enzymatic and chemical cleavage. Moreover, these

Scheme 92. Direct Synthesis of Digitoxin

Scheme 93. Ruthenium-Catalyzed Synthesis of 2,3-Dideoxy-D-ribosides
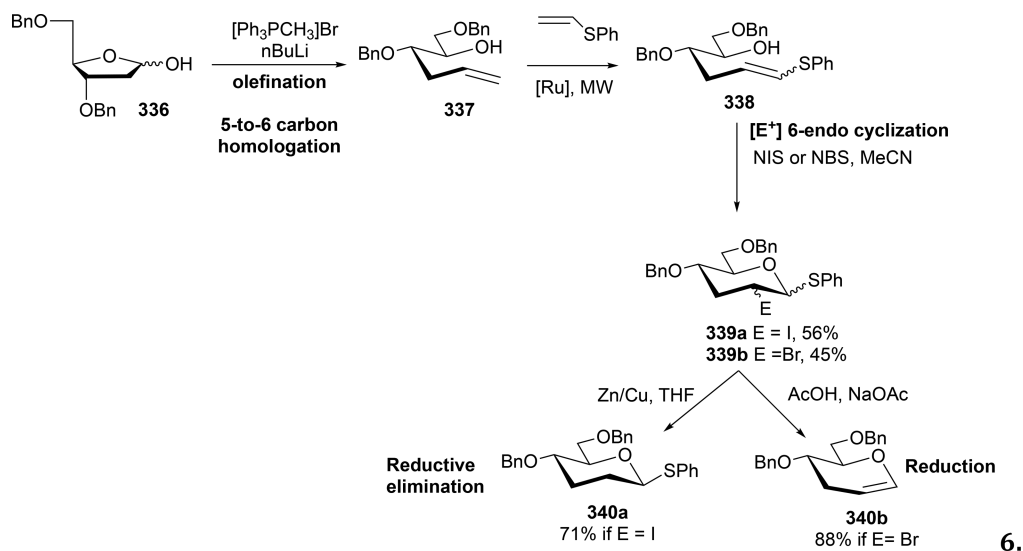
Scheme 94. Synthesis of 2-Deoxy-C-glycosyl Compounds via Stille Cross-couplings
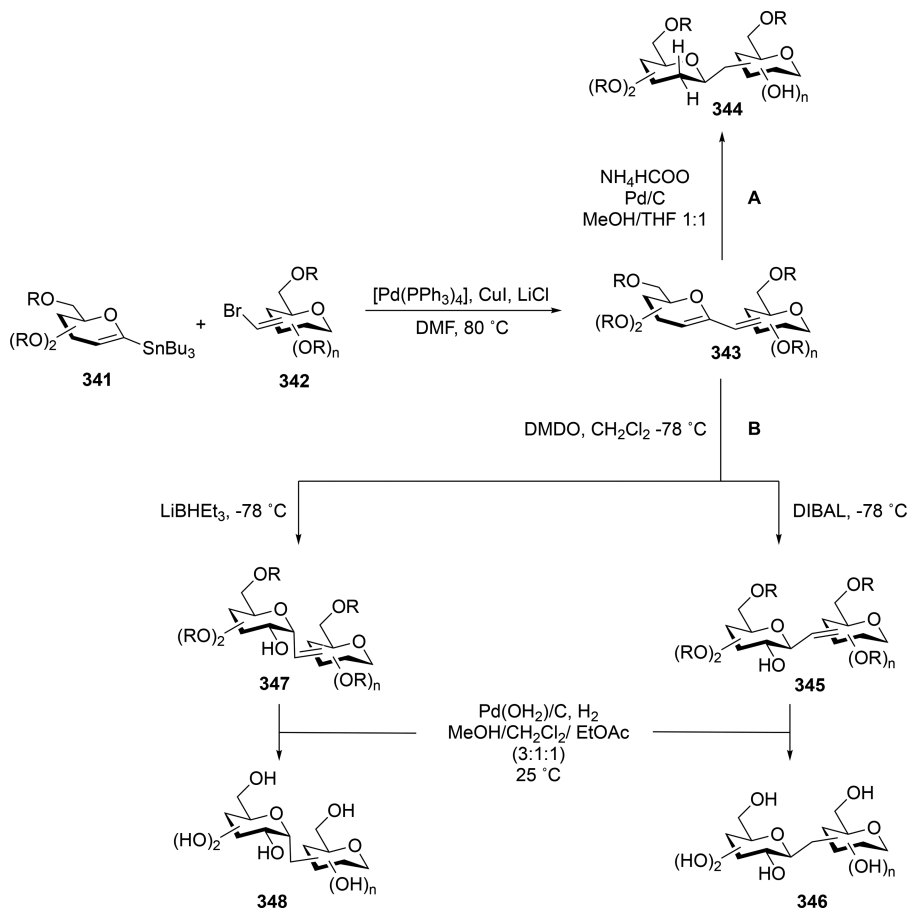
glycosyl derivatives are very useful analogues to study the role that common O-linked sugars play in biological processes. Therefore, there is a lot of interest in the development of efficient methodologies to access these sugar derivatives in a stereoselective manner. Different strategies involving processes such as electrophilic substitutions, O—C migration from O-glycosyl to C-glycosyl compounds, transition metal- or Lewis acid-mediated glycosylation, and de novo synthesis have been reported.[361,362]

The synthesis of 2-deoxy-C-glycosyl compounds is, however, more challenging because of the lack of a participating group at C-2, and most reported methodologies rely on the removal of a temporary group at C-2 after the glycosidic bond has been formed. Herein, we highlight the most recent achievements in the construction of these glycosides using direct approaches that do not require a directing hydroxyl group at C-2.

Scheme 95. Synthesis of β-C-Glycosyl Compounds by Intramolecular Palladium-Catalyzed Decarboxylative Coupling

349 → 350 (88%, β only) → 351 Aspergillide A
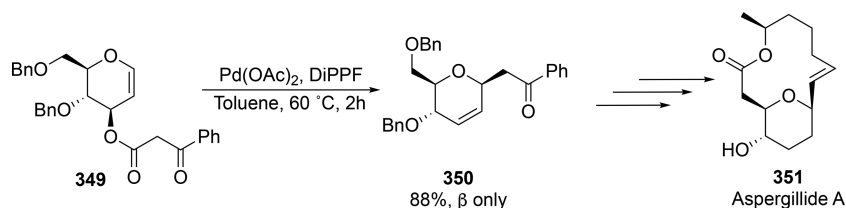
6.1. Transition Metal Catalysis

A versatile new approach for the synthesis of 2-deoxy-C-glycosyl compounds through a Stille cross-coupling reaction between 1-stannylglycals such as **341** and exocyclic bromo-olefin sugar derivatives **342** has been reported by the Werz team.[363] The strategy leads to carbohydrate analogues containing a diene that can be further derivatized to the corresponding C-glycosyl compounds. Complete reduction of the pseudodisaccharides obtained by Stille coupling with ammonium formate and Pd/C afforded 2-deoxy-C-disaccharides **344** with high diastereoselectivity (Scheme 94A). On the other hand, refunctionalization of the diene-containing sugars by oxidation of the endocyclic enol ether with DMDO followed by stereoselective reduction of the acetalic epoxide led to the regeneration of the native hydroxyl group. In the latter step, the stereochemical configuration of the pseudoanomeric carbon can be tuned by the choice of hydride agent. For example, coordinating hydride such as diisobutylaluminum hydride (DIBAL) afforded the β-anomer **345**, while the use of a strong hydride such as LiBHEt$_3$ provided the α-product **347** (Scheme 94B). Final reduction of the exocyclic double bond with Pearlman's catalyst afforded the desired (1→2)-, (1→3)-, or (1→4)-C-glycosyl compounds (**346** and **348**) with high selectivities after concomitant global deprotection of the C-linked targets.

Another interesting and practical approach for the selective construction of β-C-glycosyl compounds by intramolecular palladium-catalyzed decarboxylative coupling has been reported by Liu and co-workers.[364] The mild direct method encompasses a tandem process involving a rearrangement followed by decarboxylation of the unsaturated glycoside. The team found the best results when using Pd(OAc)$_2$ and 1,1′-bis-(diisopropylphosphino)ferrocene (DiPPF) as the ligand in toluene at 60 °C. Under these conditions, a wide variety of substituted β-ketones such as **349** were screened to yield the desired products in high yields and excellent regio- and diastereoselectivity in most cases with the exception of β-ketones bearing a secondary substitution, which afforded mixtures due to the prochirality of the α-carbon. Moreover, the method was exemplified in the formal synthesis of aspergillide A **351**, a 14-member macrolactone (Scheme 95).

As a complementary general approach to the synthesis of C-linked deoxyglycosides, Liu and co-workers[365] have also reported an iron-catalyzed decarboxylative Ferrier rearrangement of glycals to achieve 2,3-unsaturated β-keto-C-glycosyl compounds with moderate to good yields and stereocontrol. The method uses catalytic FeCl$_3$ at room temperature to produce a range of C-glycosyl-β-ketones with glycals such as glucal, galactal, and arabinal and various β-keto acids. The glycosylated products showed an α-preference, which was more potent in reactions with D-galactal and when hindered substituents were employed.

C-Glycosyl alkynes are attractive carbohydrate synthetic tools that can undergo further transformations to achieve more complex carbohydrate analogues. To that respect, Mukherjee and co-workers[366] have recently developed a new methodology to access C-alkynyl sugars by copper-mediated glycosylation of glycals with unactivated alkynes using copper triflate (10 mol %) and ascorbic acid at room temperature. The reaction was shown to work with a range of glycals (e.g., glucal, galactal, and rhamnal) such as **352**, providing the corresponding C-glycosyl compounds **353** with high α-selectivity (Scheme 96). The proposed

Scheme 96. Cu(I)-Catalyzed Synthesis of C-Glycosyl Alkynes and Proposed Mechanism

352 → 353 Up to 70% yield α:β up to >99 α

354 → 355 → 356
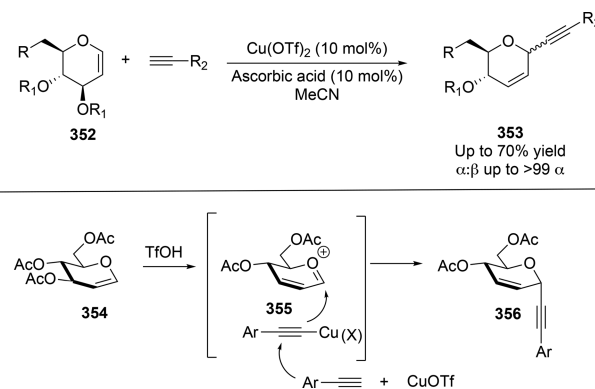
mechanism involves in situ reduction of Cu(II) to Cu(I) by ascorbic acid. It is suggested that the in situ generation of TfOH during the reduction is what drives the formation of the oxocarbenium ion **355** while the Cu(I) species facilitates the formation of the copper acetylide nucleophile, which attacks the oxocarbenium intermediate in a stereoselective manner.

Ye and co-workers[367] also reported a new strategy for the synthesis of C-glycosyl aromatic compounds based on a "ring-opening−ring-closure" methodology. This elegant approach allowed the group to obtain aryl-C-Δ^3-glycosides and 2-deoxy-α- or -β-C-glycosyl compounds from the ring-opened alcohols **357** by the microwave-assisted nickel-catalyzed reaction between glycals such as **171** and aryl boronic acids or potassium aryltrifluoroborates. The ring-opened products are subsequently converted into the various aryl-C-glycosyl compounds by treatment with Lewis acid-, protic acid-, PhSeCl-, or NBS-mediated ring-closure reactions (Scheme 97). The protocol tolerates functionalities with different electronic properties including halides and bulky substituents as well as various glycals (e.g., galactals, glucals, and xylal) without any loss of efficiency. For the ring-closing step, a series of Lewis and protic acids were screened and it was found that Sc(OTf)$_3$ gave preferentially the β-aryl-C-Δ^3-glycoside **359** while the protic acid PPh$_3$·HBr provided the C-Δ^3-glycoside **360** with high α-selectivity. Moreover, 2-deoxy-C-glycosyl aromatic compounds were accessed by two different sequences: the β-anomer was synthesized by selenyl-mediated cyclization followed by C-2 deselenation with Bu$_3$SnH/AIBN, while NIS- or NBS-mediated

Scheme 97. Synthesis of *C*-Glycosyl Aromatic Compounds via "Ring-Opening−Ring-Closure" Methodology of Functionalized Alcohols
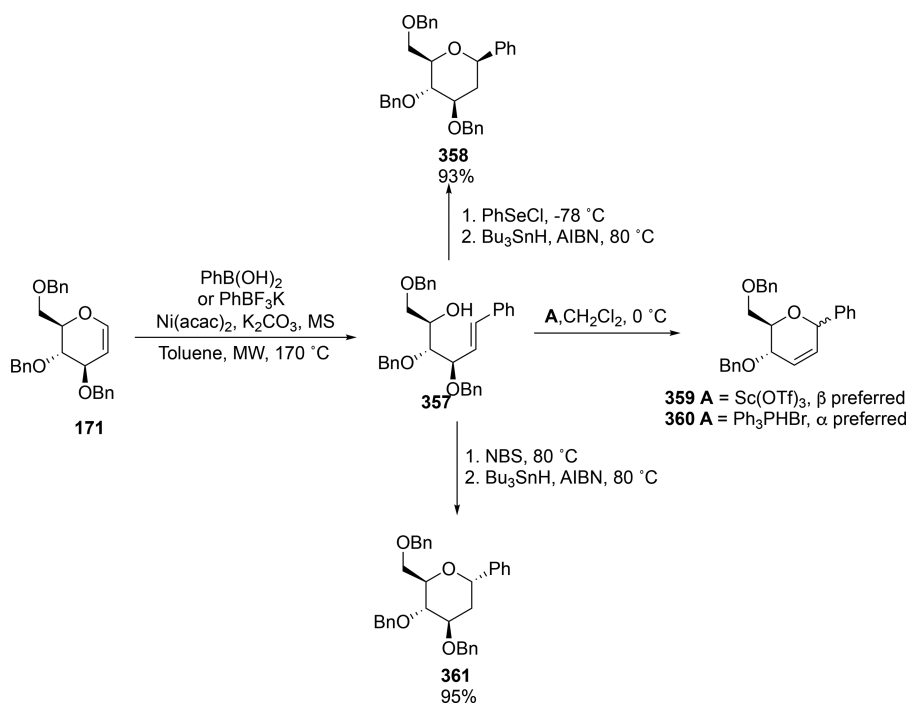
ring closure afforded the *α*-product after reductive dehalogenation.

In a subsequent report from the Ye team,[368] 2,3-anhydro-1-thioglycosides such as **362** were converted into 2-thio-2-deoxy-*C*-glycosyl compounds in a regio- and stereoselective fashion via a Lewis acid-catalyzed tandem *O*-glycosylation and Fries-like O to C rearrangement using phenols, naphthols, or trimethylsilylated or stannyl nucleophiles (Scheme 98). The best results were

Scheme 98. Lewis Acid-Catalyzed Synthesis of 2-Thio-2-deoxy-*C*-glycosyl Compounds
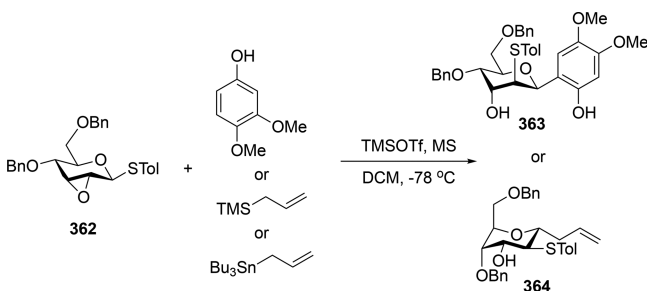
obtained when TMSOTf was used as the Lewis acid. Moreover, it was found that the nature of the nucleophile had a great effect on the stereochemical outcome of the reaction. For instance, when phenols or naphthols were used, the final product exhibited an equatorial anomeric configuration in all cases, but not always opposite to the thio group, depending on the nature of the substituent. On the other hand, reactions with TMS or Bu₃Sn nucleophiles always led to *C*-glycosyl compounds in which C-1 and C-2 substituents were opposite to each other. Further desulfurization reaction with AIBN and *n*-Bu₃SnH provided the desired 2-deoxy-*C*-glycosyl compounds in very good yields.

Another application of Lewis acid catalysis for the synthesis of *C*-glycosyl compounds was reported by the group of Font-

Bardia.[369] The team described the synthesis of *syn-α-C*-glycosyl compounds by addition of titanium enolates that bear a thiazolidine-2-thione moiety that acts as a chiral auxiliary to direct the nucleophilic addition onto a series of protected glycals. In all cases, *C*-glycosyl compounds were obtained in high yields and as single diastereomers, with a preference for the *α*-products. The authors rationalized that the *α*-bias comes from both the usual preference in *C*-glycosylation toward axial-type glycosides and the control applied by the chiral auxiliary on the oxygenated center.

Most procedures reported for the synthesis of *C*-glycosides involved the reaction between a glycoside equipped with an anomeric leaving group (which will become the electrophile) and the corresponding nucleophile. Walczak and co-workers[370] have recently described a novel approach for the stereoselective synthesis of *C*-glycosides that exploits the highly stereospecific reaction of anomeric nucleophiles. The strategy involves the catalytic activation of anomeric stannanes such as **365** (of mono- and oligosaccharides) with Pd₂(dba)₃ (2.5 mol %) and a bulky ligand (JackiePhos, 10 mol %) to give the corresponding *C*-glycosides and glycoconjugates in a highly stereoretentive cross-coupling reaction with aryl halides in good to excellent yields (Scheme 99). Further work by Liu, Walczak, and co-workers[371] on the scope, mechanism, and application of this *C*-glycosylation revealed that the reaction exhibits a broad substrate scope including the synthesis of 2- and 6-deoxyglycosides and has excellent functional group compatibility and consistently high stereospecificity in the cross-coupling reactions for both anomers. Experimental and computational studies showed that the reaction proceeds via a *β*-elimination pathway and that the choice of ligand has an effect on the rate of reaction. For instance, biphenyl-type ligands had a detrimental effect on rate due to the shielding of Pd(II) by the sterically demanding JackiePhos, whereas smaller ligands, which allow for the formation of a Pd−F complex, predominantly result in a glycal product. Similar steric effects account for the diminished rates of cross-couplings of 1,2-

Scheme 99. Synthesis of *C*-Glycosides by Glycosyl Cross-coupling of Anomeric Stannates and Simplified Proposed Mechanism
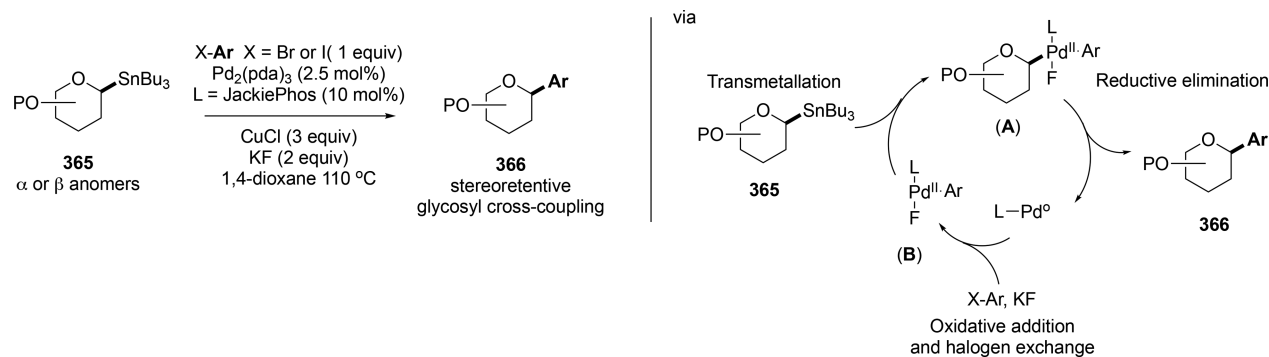
Scheme 100. Synthesis of 2-Nitro-2-deoxyglycosides by Stetter Reaction
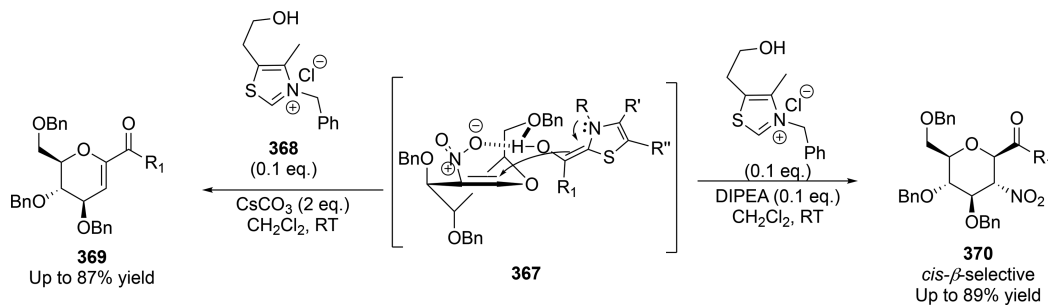
Scheme 101. Total Synthesis of Vineomycinone B$_2$ Methyl Ester

vineomycinone B$_2$ methyl ester
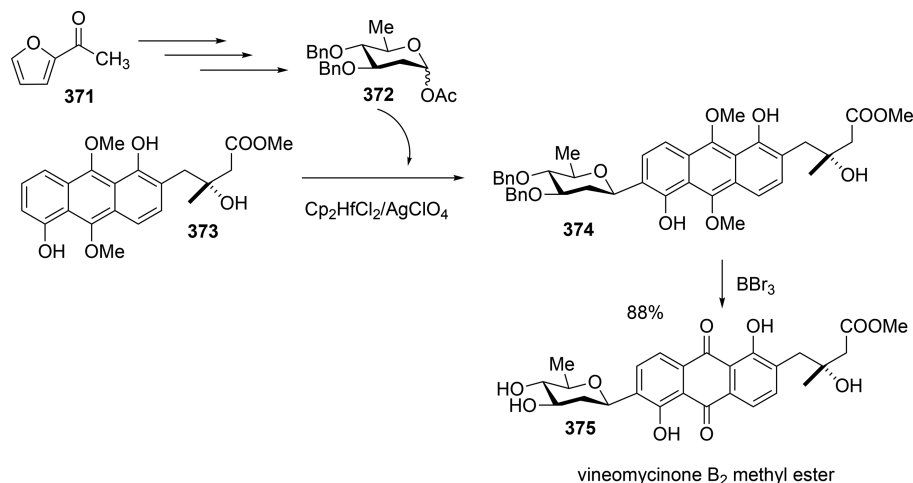
cis-C1-stannanes with aryl halides. Density functional theory (DFT) calculations also revealed that the transmetalation occurs via a cyclic transition state with retention of configuration at the anomeric position.

Glycosides bearing an *exo*-carbon–carbon double bond near the ring oxygen are named exoglycals and are an interesting class of substrate for the formation of *C*-glycosyl compounds.[372] This was exemplified in 2014 by Bravo and co-workers,[373] who synthesized 2-deoxy-*β*-benzyl-*C*-glycosyl compounds from the chemo- and stereoselective hydrogenation of exoglycals. Wittig reaction of an *α*/*β* mixture of 2-deoxygalactosyl phosphonium salt with different aromatic aldehydes afforded the corresponding exoglycals in moderate yields and *E*/*Z* ratios. The authors were targeting glycosides functionalized with *O*-benzyl ethers as a means to boost the antiproliferative and apoptotic activity of these sugar analogues in biological assays. Thus, selective

catalytic hydrogenation of the exoglycal double bond was performed using Pd/C-ethylenediamine to give the protected *β*-*C*-glycoside products with high yields.

2-Nitro-2-deoxyglycosides, which can be used as mimics or precursors for 2-NHAc-containing glycosides, as noted earlier in section 4.2, have become a class of deoxyglycosides of interest.[374] Thus, the *C*-linked type represents an important class of pharmaceutical targets. In this area, Liu and co-workers[375] have recently reported the synthesis of 2-nitro-*β*-*C*-glycosyl compounds or the nitro-eliminated *C*-glycosyl compounds using an *N*-heterocyclic carbene catalyst that undergoes acylation to the anomeric carbon of 2-nitroglycals. By fine-tuning the reaction conditions, the authors were able to achieve complete *β*-selectivity in some cases and nitro-elimination in others (Scheme 100). For instance, when DIPEA is used, formation of 2-nitro-*β*-*C*-glycosyl compounds is favored while a stronger base such as

Scheme 102. De Novo Synthesis of *C*-Glycosides by Prins-Cyclization and Oxidation of Silyl-Protected Alchohols
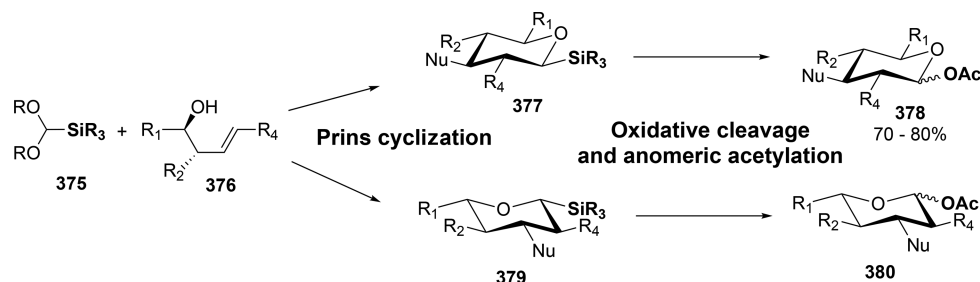
Scheme 103. Synthesis of *S*-Linked 2-Deoxyglycosides via Glycosyl Lithium Intermediates
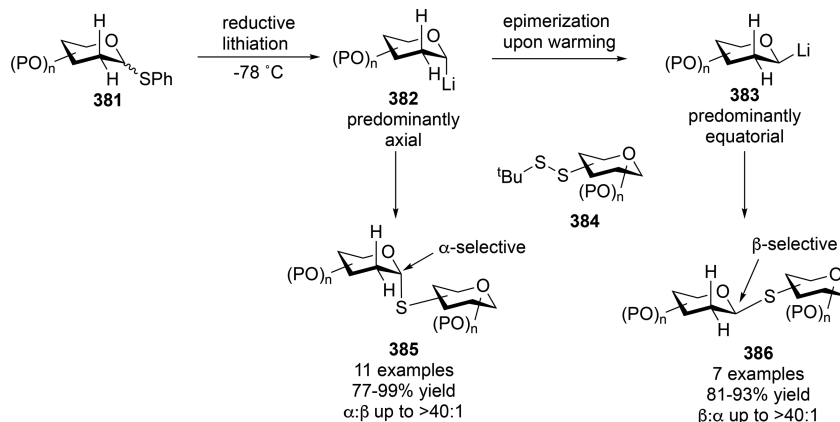
Cs_2CO_3 facilitates the nitro-elimination to afford the 1,2-unsaturated acyl derivatives. The β-stereoselectivity observed in the Stetter-type products is explained by the fact that 2-nitroglucals prefer a $^5H_4$ half-chair conformation. This conformation avoids a 1,2-interaction between the nitro group at the 2-position and the benzyloxy at C-3, which favors the addition of the nucleophile from the β-face.

6.2. De Novo Syntheses of *C*-Deoxyglycosides

Expanding on their Pd(0)-catalyzed de novo synthesis of oligosaccharides,[347] the O'Doherty group[376] also developed a convergent de novo strategy starting from achiral acylfuran **371** and anthrafuran **373** for the synthesis of vineomycinone B2 methyl ester **375**, a secondary metabolite of the anthracycline antibiotic vineomycine B2 (Scheme 101). The two key fragments **372** and **373** were coupled by a Suzuki's glycosylation to give the aryl β-*C*-glycoside. Final one-pot global deprotection and oxidation using an excess of BBr_3 afforded the targeted vineomycinone B2 methyl ester **375** in 14 steps and 4% overall yield.

Galan, Willis, and co-workers have also reported an elegant de novo approach for the rapid construction of orthogonally protected L- and D-deoxy-sugars and analogues.[377] The method capitalizes on the use of a novel and robust silicon acetal **375** that undergoes Prins cyclization with a series of homoallylic alcohols **376** under acid catalysis to give the corresponding tetrahydropyrans in good yields and excellent diastereoselectivity (**377** and **379**). A modified Tamao−Fleming oxidation/acetylation protocol gave the target 2,4-dideoxy-sugars with an acetyl group at the anomeric position (**378** and **380**) (Scheme 102). Extending the utility of the new methodology to the synthesis of 2,6-dideoxy-sugars, the team found that the choice of protecting group was key to avoid formation of tetrahydrofuranals. *N,N*-Diisopropylcarbamoyl was used as a protecting group

to access protected L-oliose, a component of the anticancer agent aclacinomycin A, enantioselectively. This practical protocol is amenable to large-scale syntheses and can potentially give access to other 2,6-dideoxyhexoses.

7. DEOXY-*S*-GLYCOSIDES

Thioglycosides, in which the anomeric glycosidic oxygen is replaced by a sulfur atom, have emerged as powerful tools for glycobiology research as these compounds are more resistant toward enzymatic hydrolysis and chemical degradation while retaining the biological activity of the parent *O*-glycoside. Similarly to *C*-glycosyl compounds, these compounds represent a very interesting class of potential therapeutic agents as glycoside mimetics. The synthesis of 2-deoxythioglycosides is, however, an underdeveloped area of research with only a limited number of efficient methods for their stereoselective synthesis reported to date.[378]

Zhu and co-workers[379] have developed a very elegant approach for the stereoselective synthesis of *S*-linked 2-deoxyglycosides that includes both the α-linked and the more-challenging β-linked counterparts. The method relies on the sulfenylation of 2-deoxyglycosyl lithium species **382** and **383**, which are stereochemically defined, with disulfide glycoside acceptors such as **384** to yield the desired products (**385** and **386**) with excellent stereocontrol (Scheme 103). The anomeric selectivity in this process is defined by the stereochemistry of the glycosyl lithium intermediates, which are synthesized by reductive lithiation of 2-deoxythioglycosides followed by temperature-controlled anomerization. The group found that, at lower temperatures, the axial anomer is formed while epimerization to the equatorial (β) anomer is favored at higher temperatures. Both anomers are then susceptible to nucleophilic attack on a sugar-derived disulfide to give the corresponding *S*-linked 2-deoxyglycosides. Using this methodology, a wide range

of 2-deoxythioglycosides were synthesized with selectivities of up to >40:1 and good to excellent yields. To further evaluate the utility of this new strategy, a S-linked 2-deoxytrisaccharide containing α- and β-linked 2,6-dideoxy-sugar moieties was also synthesized with excellent yields and comparable selectivities to previous examples.

8. CONCLUSIONS AND OUTLOOK

Efficient routes to access 2-deoxyglycosides and their conjugates with high yields and stereocontrol are in great demand due to the biological significance of this important class of carbohydrates. Furthermore, the ability of these deoxy-sugars to modulate the bioactivity of natural products holds great promise as a tool for future drug discovery. Better access to these glycosides will benefit glycobiology research and will facilitate a greater understanding of structural aspects of carbohydrate interactions, thereby realizing the potential to develop new drugs and therapeutics.

Several very elegant approaches for the direct regio- and stereoselective synthesis of *O*-, *C*-, and *S*-deoxyglycosides have been reported thus far. These advancements in the field have improved the synthesis of these complex molecules greatly; however, efforts are still needed to develop general and effective methodologies that can give us direct and quick access to all required oligosaccharide motifs and on scale. It is important to recognize the challenges involved in developing such methods. The heterogeneity of glycoside structures combined with the capricious nature of the glycosylation process, which is dependent on the reaction conditions and also dictated by the nature/chirality of the catalytic system, makes this a very challenging task. The effect of these factors must be studied and understood if progress is to be made in this area.

This is especially true in deoxy-sugar glycoside synthesis, where there are a staggering number of monosaccharides. Most recent methodological studies have focused on relatively easy-to-access donors, such as 2-deoxyglucose and olivose. In many cases, glycosylation reactions with less-accessible donors are only reported as stand-alone reactions in the context of total synthesis, and comprehensive studies of the utility of a particular glycosylation reaction with these more-unusual sugars simply do not exist. As a consequence, despite over 40 years of progress, the field has still not yet reached a point where it is possible to predict what the stereochemical outcome of a particular glycosylation reaction will be. Even minor structural variations in a donor can have a severe impact on the outcome of even the most-reliable methods. For example, while glycals normally react in an α-selective fashion, the presence of the axial ether in protected digitoxose glycals often leads to the formation of β-linked products. It is therefore incumbent on those who are developing new glycosylation reactions to take a more comprehensive view of donor/acceptor pairs that are found in real systems.

As has been highlighted in this Review, by gaining a better molecular understanding of the glycosylation process, novel and improved catalytic systems and strategies have been developed over the last few decades. It has become evident that, by taking inspiration from seminal work in the field in combination with the application of novel catalytic methods to glycosylation chemistry as a milder alternative to more traditional reagents, new opportunities in the field have opened. New promoters have been developed that are able to effect the coupling reaction in an efficient manner, including examples where not only the stereoselectivity but also the regioselectivity of the reaction can

be controlled by the catalyst. The potential for small-molecule biomimetic strategies is tantalizing as the successful imitation of the sublime chemical control seen in enzyme-catalyzed glycosylations would be a great advancement to the field.

Looking forward, as research in the field develops, novel strategies and catalysts to suit the unique and formidable requirements of the glycosylation reaction with high control of chemo-, regio-, and stereoselectivity will be developed. While a universal glycosylation catalyst might not be possible, we are confident that one can be developed for all required glycosylations.

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Notes

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