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Review

Synthesis and Glycosidation of Anomeric Halides: Evolution from Early Studies to Modern Methods of the 21st Century

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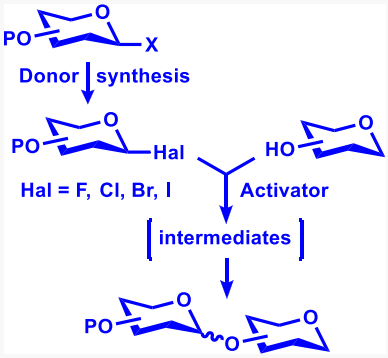
ABSTRACT: Advances in synthetic carbohydrate chemistry have dramatically improved access to common glycans. However, many novel methods still fail to adequately address challenges associated with chemical glycosylation and glycan synthesis. Since a challenge of glycosylation has remained, scientists have been frequently returning to the traditional glycosyl donors. This review is dedicated to glycosyl halides that have played crucial roles in shaping the field of glycosciences and continue to pave the way toward our understanding of chemical glycosylation.



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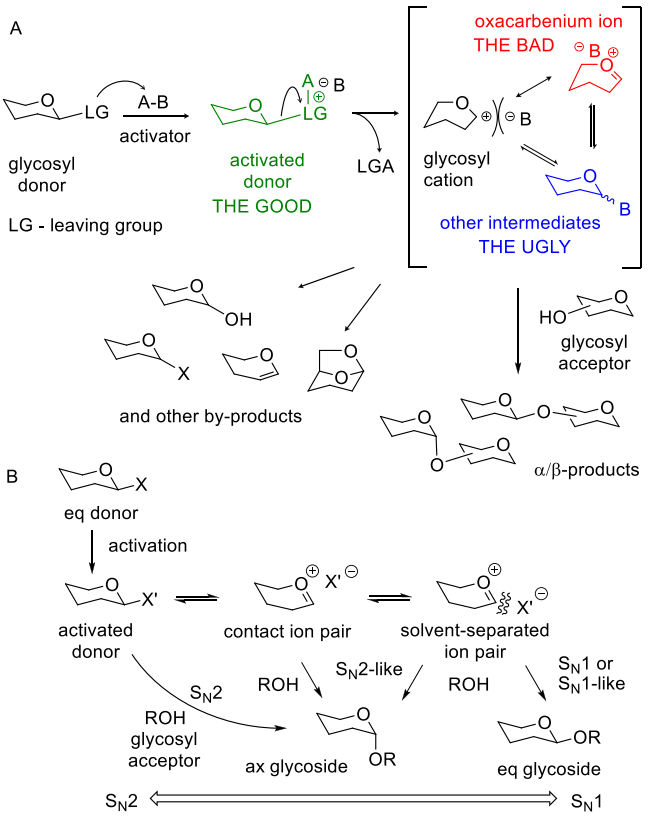
1. INTRODUCTION: GLYCOSYLATION AS A CENTRAL REACTION OF TRADITIONAL AND MODERN GLYCOSCIENCES

From the building blocks of nature to disease-battling pharmaceuticals, carbohydrates have had a broad impact on many scientific and industrial fields. Numerous applications of these essential biomolecules line up at the frontier of pharmaceutical, diagnostic, and functional food development. Consequently, carbohydrates have been extensively studied by biological and medical communities. Earth-abundant and renewable sources of chirally pure materials, monosaccharides remain popular building blocks for synthetic chemists. Oligomers, glycans, or oligosaccharides, wherein multiple monosaccharides are connected to each other via glycosidic linkages, have also been popular targets for chemists. However, complex carbohydrates remain challenging targets due to the requirement for elaborate protecting group manipulations and functionalization at all stages of the synthesis. Many glycosylation methods have been developed, but performing glycosylation reactions with complete chemo-, regio-, and stereoselectivity represents a notable challenge.

Nature flawlessly executes the glycosylation reaction enzymatically,[1,2] but chemical glycosylation remains cumbersome.[3] The first chemical glycosylation reactions were performed by Michael,[4] Fischer,[5,6] and Koenigs/Knorr[7] at the turn of the 20th century. With the exception of the Fischer glycosylation that relies on unprotected sugars as glycosyl donors,[5] all other early methods relied on glycosyl halides, chlorides or bromides.[4,6,7] Already those initial studies led to the development of glycosylation methodologies that paved the way to obtaining simple alkyl/aryl glycosides for decades. However, glycosylations of sugar acceptors were less efficient, and the synthesis of complex oligosaccharide targets was deemed practically impossible. Terminology used herein refers to "glycosylation of the acceptor with the donor" or "glycosidation of the donor with the acceptor." One of the main directions to improve synthetic capabilities has been the investigation of leaving groups beyond the original chlorides/bromides and hemiacetals. These studies lead to the discovery of other glycosyl halides, fluorides,[8] and iodides.[9] However, many other classes of alternative glycosyl donors including glycosyl esters,[10−13] thioglycosides,[14−17] 1,2-orthoesters,[18,19] *O*-imidates,[20−23] thioimidates,[24−29] alkenyl glycosides,[30−32] sulfones,[33] thiocyanates,[34] diazirines,[35] glycals,[36−40] sulfoxides,[41] xanthates,[42] selenium glycosides,[43] phosphites,[44,45] tellurium glycosides,[46] sulfonylcarbamates,[47] heteroaryl glycosides,[48] phosphates,[49] disulfides,[50] 2-(hydroxycarbonyl)benzyl glycosides,[51] and compounds equipped with alkynyl-based leaving groups[52−61] have been developed.

Regardless of the glycosylation reaction conditions and mechanism, unimolecular S_N1-like or bimolecular S_N2-like, the following steps are typically identified (Scheme 1A).[62] The first step involves the formation of the activated donor as a result of the interaction of the leaving group (LG) and the promoter (A-B); this step can be reversible or irreversible depending on

Scheme 1. Outline of General Glycosylation Mechanisms



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the leaving group and the method of activation.[63] There are a few reports indicating that the glycosyl acceptor attack may be directed to the activated donor. This pure S_N2 displacement pathway would be quite desirable (THE GOOD) in terms of potential stereocontrol because it would allow for the stereospecific inversion of the leaving group: equatorial LG will produce axial glycoside whereas axial LG will lead to equatorial glycoside. However, examples of such reactions remain rare.[64−71] Examples wherein double S_N2-like inversion would lead to the retention of the original LG configuration are also known. In a majority of cases, the second step involves the dissociation of the glycosyl donor, a typically irreversible expulsion of the activated leaving group (LGA), which is the rate-determining step (RDS) of the glycosylation reaction.

This process leads to the formation of the respective glycosyl carbocation and/or its stabilized form, oxacarbenium ion, along with the associated counteranion (B^-). The oxacarbenium intermediate is often blamed for scrambling the stereoselectivity of the reaction (THE BAD). This is due to the existence of the oxacarbenium ion in a flattened half-chair conformation because of the sp^2-hybridization of the anomeric carbon. It should be noted that other conformations of oxacarbenium intermediates are possible depending on the nature of substrates, protecting groups, and various steric and/or electronic factors. The next step involves a nucleophilic attack on the oxacarbenium ion, which is possible from either the bottom face or the top face of the ring. As a result, uncontrolled glycosylations often lead to the formation of a mixture of α/β-diastereomers. Other intermediates, the existence of which is often ignored (THE UGLY), or their impact on the reaction is underestimated, may also form at this stage with or without covalently attached B. However, there are some extended studies related to such intermediates, examples of which include tosylates, triflates, intermediates of dehydrative glycosylations among others, which can lead to unexpected side products and/or be responsible for scrambling the stereoselectivity of glycosylations. On the other hand, is the involvement of these intermediates is understood, this could lead to excellent stereocontrol how it has been proven by Schuerch,[72,73] Crich,[74−77] Gin,[78−82] Woerpel,[83−87] Bennett,[69,88,89] and others.[90] The last step, the existence of which is also often overlooked, involves the proton transfer. This is the termination step, after which the formation of the glycosidic bond becomes irreversible.[91]

The simplified mechanistic outline of glycosylation presented in Scheme 1A implies that the RDS is unimolecular and is independent of the glycosyl acceptor. However, the donor−acceptor mismatch concept by Paulsen[92] and Fraser-Reid and Lopez,[93−97] the double stereodifferentiation phenomenon,[98] and other studies[99−102] present a strong counterargument. In fact, a number of kinetic studies that have emerged in the past decade indicate that a majority of glycosylations follow a mixed mono- and bimolecular displacement mechanism,[71,103−106] and the reaction order differs between various sugar series, and can even depend on the leaving group and/or covalently attached counterion type and orientation.[107−111] As stated by Crich et al, the exact mechanism of a leaving group departure in a typical glycosylation reaction generally falls at a certain position on a continuum of mechanisms spanning from ideal S_N1 extreme to ideal S_N2 extreme (Scheme 1B).[71,105−112]

The goal of controlling glycosylation has been pursued in many other ways with much effort dedicated to the optimization of the reaction conditions, suppressing side reactions,[113,114] studying stereoelectronics and conformation of the starting material and key reaction intermediates.[62,80−84,86,87,91,115−129] Fraser-Reid's seminal work on the armed-disarmed approach showed that the building block reactivity can be modulated through the choice of protecting groups.[130,131] The scope of the original armed-disarmed concept has been expanded and a number of efforts to quantify or even predict the reactivity of building blocks have been reported by Fraser-Reid,[132] Ley[133,134] and Wong.[135,136] Wong's study also revealed a number of building blocks that extend beyond the traditional armed-disarmed boundary. This discovery opened a new avenue for studying building block reactivity,[137] and Boons[138] and, subsequently, Demchenko[139] reported superdisarmed building blocks.

Two concepts for superarming glycosyl donors have also emerged. Bols showed that superarming can be achieved by changing the equatorial-rich $^4C_1$ conformation.[124−127] Demchenko then reported building blocks wherein the electronic superarming was achieved via the O2/O5 cooperative effect.[140−142] While the stereoelectronic and conformational effects on reactivity have been studied extensively, the impact on stereoselectivity (beyond building blocks equipped with 2-*O*-participating group) remain elusive. Although some model studies helped to establish general trends,[83−86,115,116,128,129,143] practical applications of the stereoelectronic and conformational factors to stereocontrolling glycosylation reactions are still lacking.

Despite all these recent improvements, the challenge of glycosylation has remained, and scientists have turned their attention to reinvestigating the original glycosyl donors, hemiacetals, and halides. More recent work with hemiacetals[69,81,144] and glycosyl halides[70,145−147] brought these glycosylation reactions to an entirely different level of flexibility and versatility. These simple donors are typically easily accessible from a variety of precursors, can be readily activated, and offer superior atom economy. This review, dedicated to glycosyl halides, guides the reader from the first known glycosylation reactions to recent advances in the field that helped to navigate glycosciences forward. The first glycosylations performed by Michael involved glycosyl chlorides. However, in subsequent years, glycosyl chlorides were largely outshadowed by glycosyl bromides. Because of the ease of the synthesis and their higher reactivity profile, glycosyl bromides have traditionally been considered advantageous over their chloride counterparts. As a result, most of the efforts were focused on reactions of glycosyl bromides that have become prevalent glycosyl donors in the first 100 years of synthetic carbohydrate chemistry. Therefore, we will open our review with a summary of the early studies (Section 2) and then move directly to the discussion of glycosyl bromides (Section 3). Many methods developed for the activation of glycosyl bromides are also effective for the activation of glycosyl chlorides. Hence, Section 4, dedicated to glycosyl chlorides, will mainly focus on the reagent-specific or condition-specific activations of glycosyl chlorides rather than repeating the same data presented for glycosyl bromides. We will then turn our attention to glycosyl iodides (Section 5), which were outshadowed by both glycosyl bromides and glycosyl chlorides, and only recently found some notable synthetic utility. Finally, we will discuss glycosyl fluorides (Section 6), which became very prominent glycosyl donors in recent decades.

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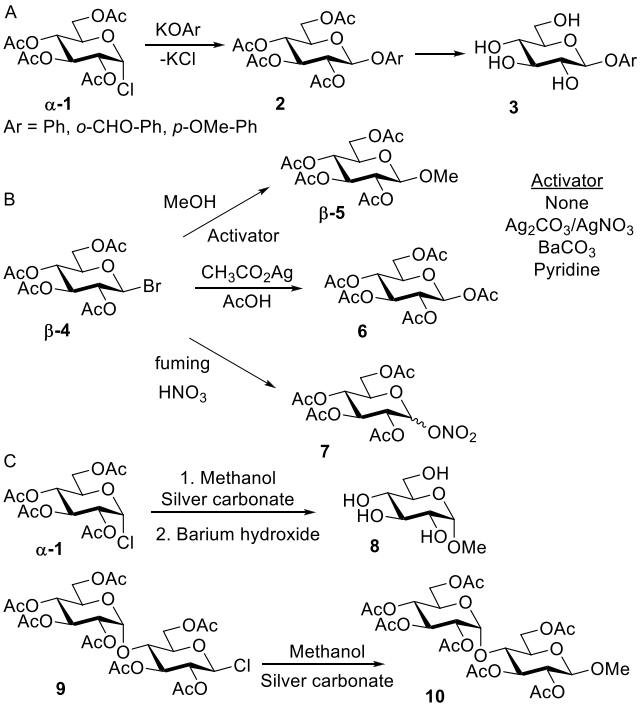
2. KEY ACCOMPLISHMENTS OF (AND LESSONS FROM) EARLY GLYCOSIDATIONS OF GLYCOSYL HALIDES AT THE TURN OF THE 20TH CENTURY

The first glycosylation was reported by Arthur Michael in 1879, about a decade before the famous addition reaction that carries his name, the Michael addition, was discovered. This reaction is depicted in Scheme 2A, wherein glycosidation of

Scheme 2. First Glycosylation Reactions Reported by Michael (A), Koenigs and Knorr (B), and Fischer (C)



chloride α-**1** with alkoxide produced glycoside **2**, which was deprotected under these basic reaction conditions to produce glycoside **3**. In Michael's own words, the synthesis was "*...starting from the interesting compound discovered by A. Colley...known under the name of acetochlorhydrose. This compound..., I have allowed to act on potassium phenate and potassium salicylite, and have obtained compounds which possess all the characteristic properties of the glucosides. After numerous experiments, I found the following conditions to yield the most satisfactory results: 27.5 gr. of acetochlorhydrose were mixed with about twice its volume of absolute alcohol, and the solution added to a cold alcoholic solution of 10 gr. of potassium phenate. After a few minutes, a crystalline precipitate began to separate from the solution, and at the same time a strong odor of acetic ether was noticed. The reaction proceeded very rapidly, and after four or five hours no further separation of the crystalline substance was observed. . . The most interesting property of this substance is its behavior towards dilute acids and emulsin. A dilute solution of sulfuric or chlorhydric acid decomposes it on gently warming very readily in glucose and phenol...*"[4]

In 1901, Koenigs and Knorr introduced silver salt-promoted activation of glycosyl bromides for the synthesis of glycosides.[7] This approach is considered as a major milestone in glycochemistry because the outcome of this reaction was much easier to control or predict than that of the Fischer glycosylation with unprotected donors. It was also shown that alcohols rather than charged nucleophiles used in the Michael approach can be glycosylated directly. The first reactions involved glycosidation of acetylated glucosyl bromide β-**4** with simple alcohols (methanol or ethanol) in the presence of silver carbonate (Ag_2CO_3) or silver nitrate ($AgNO_3$) as shown in Scheme 2B. It should be noted that current understanding of the reaction and its mechanisms implies that the formation of pure β-anomer of acetobromoglucose is very unlikely. It is possible that during those times, the anomeric configuration of glycosyl halides was simply unknown. To preserve integrity of the discussion, we will be using configurations that were originally proposed by the authors. Contrary to the Michael glycosylation approach[4] wherein neutral KCl was generated, in the Koenigs–Knorr reaction the formation of HBr was inevitable. The exact role of the silver salt was not known at that moment, but it was assumed that it acted as the acid scavenger. The synthesis of methyl glucoside β-**5** was also achieved by the treatment of glycosyl bromide β-**4** in the presence of either barium carbonate ($BaCO_3$) or pyridine. It was also demonstrated that methyl glycoside can be generated in the presence of an excess of methanol without activators or additives. On the other hand, the treatment of glycosyl bromide **4** with silver acetate (CH_3COOAg) in acetic acid afforded pentaacetate **6**, and a similar treatment with fuming nitric acid afforded tetra-acetylated glycosyl nitrate **7**. An interesting observation was made that methyl glycoside **5** and pentaacetate **6** had the same anomeric configuration as that of the starting material, β-glycosyl bromide **4**. This methodology was also extended to per-acetylated galactosyl bromides. Again, it is quite possible that the authors were dealing with α-bromides that were mistakenly presented as their β-counterparts.

Independently from Koenigs and Knorr, Fischer and co-workers also synthesized methyl glucoside from α-acetochloroglucose **1** in the presence of methanol and silver carbonate, and the product was deprotected with barium hydroxide.[6] Differently from the results reported by Koenigs and Knorr (*vide supra*), glycosidation of α-chloride **1** resulted in the formation of methyl α-glucoside **8** (Scheme 2C). Additionally, Fischer and co-workers synthesized tetra-acetylated methyl galactoside from galactosyl chloride. Apart from monosaccharides, the authors were able to synthesize hepta-acetylated maltosyl chloride **9** that was glycosidated with methanol in the presence of silver carbonate. In this case β-linked methyl maltoside **10** was obtained.[6] Similarly to studies by Koenigs and Knorr, Fischer also considered silver acetate AgOAc, but noticed a significant level of the acetate transfer.[6]

Following these early efforts dedicated to glycosylation of simple alcohols, Fischer and co-workers synthesized a variety of relatively complex β-glycosides including hepta-acetyl menthol maltoside.[148,149] The authors also tried to synthesize a 1→1-linked tetrasaccharide assuming that hepta-acetyl lactosyl bromide will self-condense with the hemiacetal produced *in situ* in the presence of Ag_2CO_3.[148] Since the role of silver salt was considered to be as acid scavenger, Fischer thought of replacing it with an organic base, such as quinoline. This study showed unprecedented formation of significant amounts of α-phenyl glucoside when per-acetylated glycosyl bromide was heated with phenol in the presence of quinoline.[150] The continuation of this work led to the implementation of silver oxide as an alternate acid scavenger.[151] In addition to acetylated bromides, glycosidation of per-benzoylated glucosyl bromide β-**11** with MeOH was

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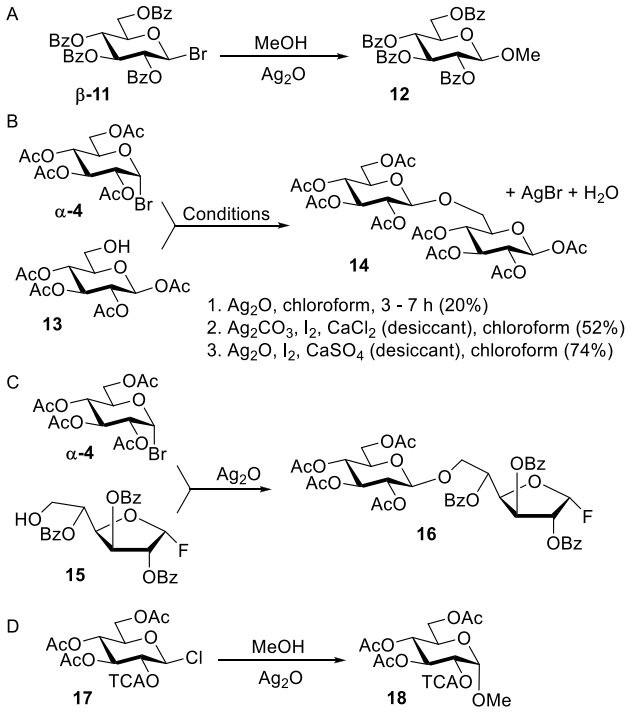
proven possible in the presence of Ag_2O to afford methyl glycoside **12** (Scheme 3A).

Scheme 3. First Attempts to Enhance Utility of the Koenigs−Knorr Reaction



Helferich and co-workers were the first to synthesize a disaccharide by coupling two monosaccharide building blocks. As shown in Scheme 3B, this was achieved by treating glucosyl bromide α-**4** with 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose acceptor **13** under classical Koenigs−Knorr glycosylation conditions to afford per-acetylated β-gentiobiose **14** (conditions 1).[152] However, only a modest yield of 20% was achieved, which was attributed to the presence of water in the reaction mixture. It was suggested that water molecules interfere with the reaction by continuously consuming glycosyl bromide α-**4** and producing hydrolyzed byproducts. Helferich and co-workers then attempted to remove water by adding finely powdered calcium chloride as a desiccant. However, this led to a significant drop in the rate of glycosylation.[153] It was then discovered that the reaction can be accelerated when molecular iodine was added to a silver carbonate-promoted glycosylation reaction in the presence of a desiccant (conditions 2). In this case, β-gentiobiose **14** was obtained in a significantly improved yield of 52%. Reynolds and Evans also developed reaction conditions that helped to achieve complete exclusion of water, both present in the reactants from the beginning and also that generated during the reaction.[154] These reaction conditions involved preliminary stirring of glycosyl acceptor **13** and silver oxide with Drierite ($CaSO_4$) in chloroform for 1 h. Iodine was then added followed by a slow addition of a solution of glycosyl bromide α-**4** in chloroform. As a result of these improvements, a very high yield of 74% for the synthesis of gentiobiose **14** was achieved (conditions 3, Scheme 3B).

Helferich and co-workers were also the first to achieve a selective activation of one leaving group over another. Some 60−70 years later, this selective activation strategy became a very useful tool for streamlining glycan assembly because the products can be used as glycosyl donors directly, without any modification (*vide infra*).[155] In this application, selective activation of glycosyl bromide donor α-**4** over glycosyl fluoride acceptor **15** was achieved in the presence of silver oxide to produce disaccharide **16** (Scheme 3C).[152] The deprotection of acyl groups furnished gentiobiosyl fluoride which was then treated with calcium carbonate to produce a fully unprotected disaccharide.

Formation of the α-phenyl glucoside in the quinoline-promoted reaction at a high temperature by Fischer (*vide supra*),[150] demonstrated that 1,2-*cis* glycosides can also be obtained.[156] Following this lead, Brigl and co-workers described the stereoselective synthesis of α-glycosides from β-chloride **17** protected with the 2-*O*-trichloroacetyl group shown in Scheme 3D.[157] The authors assumed that the Walden inversion occurs during the glycosylation of methanol in the presence of silver carbonate to afford α-glycoside **18**. The α/β-ratio of glycosides was found to depend on the reaction time and temperature. Similar to Brigl's investigation, Schlubach and Schroter[158] and also Hickinbottom[159] investigated the synthesis of α-glycosides from β-acetochloroglucose. Over the course of this study, the authors anticipated that the synthesis of α-glycosides from β-glycosyl chlorides can be achieved only when the experimental conditions are maintained in the way that the rate of glycosylation is greater than that of the β-chloride anomerization to its α-counterpart. The authors also anticipated that the anomerization can be suppressed by using a suitable solvent. It was further reinforced that higher α-selectivity of glycosylations is achieved at lower glycosyl acceptor concentrations. To further advance the classical Koenigs−Knorr glycosylation approach, Zemplen and co-workers switched from silver salts and showed that an efficient activation of cellobiosyl bromide can be achieved with mercuric acetate.[160,161] Over the course of this investigation, anomeric mixtures have been obtained, and a dedicated study revealed that the ratio of α/β-glycosides mainly depends on the amount and types of alcohol used.[160,162,163]

During those times, many reactions were hampered by the formation of side products. One of the most exciting observations was Fischer's discovery of the existence of an additional isomeric glycoside that was observed to exist besides α- and β-glycosides.[164] The authors coined the term of the γ-form (or third form) and suggested that it might have a different ring structure than pyranose as a result of the ring-opening, acyl migration, and subsequent ring closure during the glycosylation reaction. Also reported by Dale,[165] and puzzled many others,[166−170] it was not until studies by Freudenberg[171,172] and, independently, Haworth et al.[173,174] who suggested the γ-form to be 1,2-orthoester **19** shown in Scheme 4. To understand mechanistic details for the formation of glycosides and orthoesters, Isbell investigated various factors affecting Koenigs and Knorr reactions and byproduct formation, such as the orientation of the substituent at C-2, solvents, temperature, and the presence of water. Apart from these, the authors conducted an expansive study of physical and chemical properties of products to understand chemical composition, structure, and conformation of products.[175−179]

On the basis of these studies, Isbell and co-workers concluded that 1,2-*trans* glycosylation occurs when there is a participating ester group present at the C-2 position. Taking into consideration the neighboring group participation, Isbell proposed two distinct pathways for glycosidation of 1,2-*cis* and

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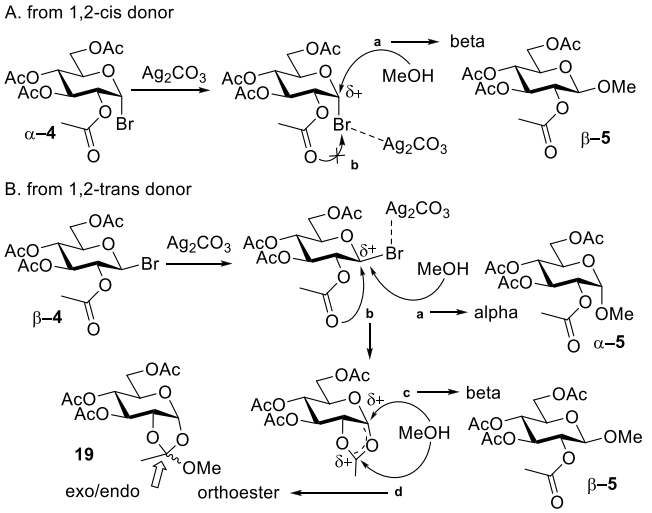
Scheme 4. Glycosidation of 1,2-*cis* and 1,2-*trans* Glycosyl Halides and the Formation of 1,2-Orthoesters



1,2-*trans* glycosyl halides, α-**4** and β-**4**, respectively.[176] The activation process wherein the anomeric bromide complexes with the silver salt is the same for both glycosyl donor configurations (Scheme 4). This decreases the electron density at the anomeric center, making it more susceptible to nucleophilic attack. In the case of the 1,2-*cis* glycosyl halide α-**4**, only the expected inversion product β-**5** can be obtained (Scheme 4A, pathway a). In this case, the 1,2-orthoester does not form (pathway b) because the approach of the 2-*O*-acetyl group is blocked by the halide. Conversely, the 1,2-*trans* bromide β-**4** yielded two anomeric glycosides α/β-**5** and the orthoesters *exo/endo*-**19** (Scheme 4B). Following the activation, the 1,2-*cis* product α-**5** was obtained via direct nucleophilic displacement from the bottom face of the ring (pathway a). Additionally, the intramolecular attack from the adjacent carbonyl oxygen leads to the formation of a reactive acyloxonium intermediate (pathway b). Depending on the site of nucleophilic attack, the latter can produce a 1,2-*trans* glycoside β-**5** (pathway c) and a 1,2-orthoester *exo/endo*-**19** (pathway d). In this case, the neighboring group participation may or may not offer anchimeric assistance and hence accelerate the leaving group departure. It should be noted that although sometimes (inaccurately) used interchangeably, "neighboring group participation" and "anchimeric assistance" are not the same: while the former refers to the effect on stereoselectivity, the latter refers to the acceleration of the reaction rate. It was originally believed that that the formation of orthoesters and participation is only possible when the leaving halogen (bromide) is present in the 1,2-*trans* position to the participating group on the neighboring carbon atom. However, later it was clearly demonstrated are orthoesters can also form from 1,2-*cis* glycosyl halides.[180−190] Subsequent studies of orthoesters were extended to sugar alcohols[191] and led to observation of diastereomeric *exo/endo*-orthoesters the existence of which was later proven by nuclear magnetic resonance (NMR).[192]

Over the years, Koenigs−Knorr glycosylation reactions found broad application in glycosylation of simple alcohols. Glycosylations of sugar acceptors were less efficient and the synthesis of complex oligosaccharide targets was deemed practically impossible. One of the main directions to improve synthetic capabilities has been the investigation of different activation conditions. It should be particularly emphasized that it is seminal studies of glycosyl halide donors discussed in this section that have enabled our understanding of many basic aspects and mechanisms behind glycosylation reactions. This, in turn, helped to resolve challenges in synthesizing many targets ranging from simple glycosides to complex glycans and glycoconjugates.

3. GLYCOSYL BROMIDES

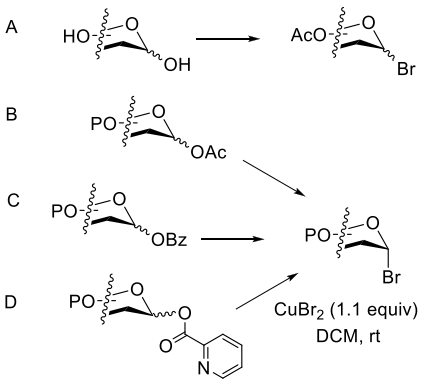
Since first silver salt-promoted activations of glucosyl bromides, innumerable reagents for the activation of glycosyl bromides have emerged. Not only glycosidation but also the synthesis of glycosyl bromides underwent significant improvements over the years with the introduction of mild reagents and developing efficient reaction conditions.

3.1. Synthesis of Glycosyl Bromides

Synthesis of glycosyl bromides is very crucial since many compounds of this class are not crystalline and their stability differs drastically based on their structure and protecting group pattern. Numerous methods have been developed for the synthesis of glycosyl bromides that are categorized below by the type of the starting material (anomeric protecting/leaving group) used for the introduction of the anomeric bromide moiety.

3.1.1. Preparation from Unprotected Sugars with Concomitant Per-acetylation. As aforementioned, synthesis of glycosyl chlorides was known since studies by Colley and then Michael. These syntheses were accomplished from the corresponding free sugars that were treated with acetyl chloride. Following this general concept, Koenigs and Knorr synthesized acetobromoglucose by treating glucose with neat acetyl bromide. The authors were able to isolate β-bromide in a good yield after crystallization (Scheme 5A).[7] For many

Scheme 5. Synthesis of Glycosyl Bromides from Unprotected Sugars and Glycosyl Esters



years, this method remained popular for the synthesis of acetylated glycosyl bromides.[7,148,193] Decades later, Koto and co-workers showed that the synthesis of glycosyl bromides can be achieved by treating the corresponding free sugars with acetyl bromide that was diluted with acetic acid.[194,195] The authors demonstrated that acetic acid helps to prevent sudden evolution of toxic HBr gas compared to previously known methods for the formation of glycosyl bromide donor. Kartha and Jennings reported a one-pot synthesis of per-acetylated glycosyl bromide wherein free sugars were first treated with acetic anhydride followed by the addition of HBr in AcOH.[196] Another method for the synthesis of glycosyl bromides

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involves the treatment of free sugars with acetic anhydride in the presence of catalytic $HClO_4$ in acetic acid followed by bromination with AcBr-MeOH with or without sonication.[197,198] A reversal in the order of the reagent addition wherein sugar and acetic anhydride were added to a mixture of acetyl bromide and methanol in acetic acid also produced glycosyl bromides in excellent yields.[167] Lin et al. treated unprotected sugars with $LiClO_4$-Ac_2O followed by the reaction with HBr-AcOH.[199] Recently, Bennett, Pohl, and co-workers developed a continuous flow platform for the synthesis of orthogonally protected monosaccharide building blocks.[200] One relevant example includes acetylation and bromination of unprotected sugars performed in a single step. This transformation was rapidly achieved by employing acetyl bromide as acetylating and brominating reagent in a continuous flow manner. Saturated aq. $NaHCO_3$ was then used for in-line quench of excess HBr.

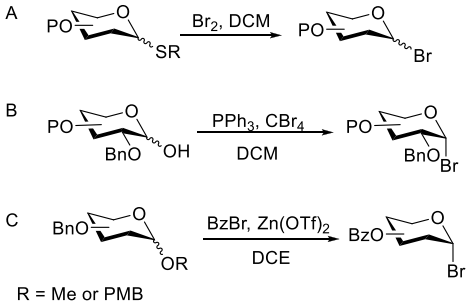
3.1.2. Preparation from Glycosyl Esters of Differentially Protected Sugars. The synthesis of acetylated glycosyl bromides can also be performed starting from presynthesized per-acetates (Scheme 5B). As described by Fischer, the treatment of glucose pentaacetate with HBr neat or in glacial acetic acid produced per-acetylated β-glucosyl bromide.[149] In early days, a few other methods such as red phosphorus/bromine or PBr_3 were commonly used for the synthesis of bromides.[201] Zemplen and co-worker employed titanium tetrabromide for the synthesis of glycosyl bromide wherein a solution of titanium tetrabromide in chloroform was added to a solution of tetra-acetylated rhamnose in chloroform to produce acetobromo-α-L-rhamnose in an excellent yield and in crystalline form.[202] This protocol works well for the synthesis of 2-azido-2-deoxy bromides.[203]

More recent methods were predominantly focused on the development of milder reaction conditions for the formation of anomeric bromides. One such procedure for bromination involves a dilute solution of HBr in dichloromethane (DCM).[204−206] A convenient method to generate HBr *in situ* is by reaction of MeOH and AcBr; this protocol is particularly advantageous for the synthesis of highly reactive bromides and/or those equipped with acid-sensitive protecting groups.[64] Hunsen and co-workers utilized this protocol also for the synthesis of glycosyl bromides from the corresponding free sugars in the presence of Ac_2O.[197] Thiem and co-workers discovered that anomeric acetates can be efficiently converted to corresponding anomeric bromides upon treatment with trimethylsilyl bromide (TMSBr) in chloroform or benzene.[207] The side product, trimethylsilyl acetate can be removed *in vacuo* owing to its low boiling point. Around the same time, a similar observation was independently made by Gillard and co-worker who converted different anomeric acetates to the corresponding bromides.[208] The use of TMSBr is attractive since it eliminated the aqueous work up, which is a common operation used in many other methods. Apart from this, many common protecting groups are compatible with TMSBr. Later, Montero and co-workers reported a milder approach for halogenation by employing bismuth(III)-based reagents complexed with halosilanes.[209] The treatment of per-acetylated sugars with $BiBr_3$-Me_3SiBr produced corresponding glycosyl bromides in excellent yields. Mizuno and co-workers reported light-induced (352 nm, 15 W) conversion of per-acetylated sugars to the corresponding glycosyl bromides in the presence of bromine.[210]

Preparation of glycosyl bromides from per-benzoylated sugars has also been reported (Scheme 5C). Fischer and Helferich treated per-benzoylated glucose with a saturated a solution of HBr in glacial acetic acid.[151] This method was further modified by Hudson and co-workers.[211,212] Another efficient method for the synthesis of benzoylated glycosyl bromides involves the treatment of per-benzoylated sugars with AcBr-MeOH using ultrasound irradiation.[198] All the previous methods for the synthesis of glycosyl bromides from the corresponding 1-*O*-acyl derivatives rely on highly reactive, toxic, sensitive, and corrosive acids. To address these issues, Tang and co-workers described a milder reaction conditions for an efficient synthesis of glycosyl bromides.[213] In this approach, 1-*O*-picoloyl (Pico) derivatives were treated with copper(II) bromide in DCM at ambient temperature (Scheme 5D). This reaction produced the corresponding α-glycosyl bromides in good to excellent yields, and the method was found to be compatible with several protecting groups including acid-sensitive groups.

3.1.3. Preparation from Thioglycosides or Other Substrates. One of the most convenient methods for the formation of glycosyl bromides involves treatment of thioglycosides with bromine to produce the corresponding glycosyl bromides (Scheme 6A). This reaction typically

Scheme 6. Synthesis of Glycosyl Bromides from Thioglycosides (A), Hemiacetals (B), and *O*-Glycosides (C)



completes in minutes, does not require any work up, and the glycosyl bromides can be used immediately after solvent evaporation.[214−217] Because of mild reaction conditions, a broad range of protecting groups including acyl, alkyl, silyl, acetal, and ketal are tolerated. A few other methods have been developed. Kobayashi and co-workers reported the conversion of 2-*O*-benzylated hemiacetals to corresponding glycosyl bromides by the treatment with PPh_3-CBr_4, commonly known as Appel conditions (Scheme 6B).[218] A one-pot conversion of benzyl-protected methyl or *p*-methoxyphenyl glycosides to per-benzoylated glycosyl bromides by treating with zinc triflate and benzoyl bromide, is another useful approach to the synthesis of per-benzoylated glycosyl bromides (Scheme 6C).[219]

3.2. Glycosidation of Glycosyl Bromides

Since the first silver salt-promoted activation of glucosyl bromides (*vide supra*), innumerable reagents for the activation of glycosyl bromides have emerged. To streamline the discussion, we chose to divide the activating reagents into different categories based on their halophilic nature (Table 1). The discussion begins from silver salts that were very instrumental for understanding the metal salt involvement in splitting the anomeric C−Br bond and investigating the effects

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Table 1. Activation of Glycosyl Bromide Donors

promoter	additive
	silver and copper salts
Ag_2CO_3[6,7]	I_2,[153,220] Lewis acid[221]
$AgNO_3$[7,151]	crown ether[222,223]
AgOAc[6,7]	
Ag_2O[151]	I_2,[154] borinic acid,[224] HOFox/Lewis acid,[217,225] TMSOTf,[146,221,226] TfOH[221]
$AgClO_4$[227−229]	
$AgBF_4$[227,230]	
$AgPF_6$[230]	
AgOTf[230]	TMU[231]
other organic Ag salts[221,232−234]	TfOH[221]
Ag silicate-alumina[235]	
Ag zeolite[236]	
Ag silica-alumina[237]	
silver imidazole	$ZnCl_2$[238]
Ag_2SO_4	TfOH,[221,226]
CuI + BPhen + Xantphos[147]	DTBMP[147]
	mercury, zinc, and cadmium salts
$Hg(OCOCH_3)_2$[160,161]	
$Hg(CN)_2$[239]	$HgBr_2$[239]
HgO[239]	$HgBr_2$[240]
$HgBr_2$[241,242]	
$Hg(PhCOO)_2$[243]	
$Hg(NpCOO)_2$[243]	
HgI_2[244]	
ZnO[239]	
$ZnCl_2$[245,246]	TrCl;[245] TMSCl[247]
$ZnBr_2$[245,246]	TrBr;[245] TMSBr[246,247]
$Zn(OTf)_2$	TMSBr[248]
CdO[239]	
$CdCO_3$[249−251]	
CdS[249]	
	indium, tin, and bismuth salts
$InCl_3$[252,253]	
$InBr_3$[253]	
InI_3[254]	
$In(OTf)_3$[254]	
$In(NTf_2)_3$[254]	
$SnCl_4$[255]	
$Sn(OTf)_2$	base[256]
$PbCO_3$[251]	
	non-nucleophilic bases
pyridine[7,148,182,257]	
quinoline[150,156]	
collidine[180]	
phenanthroline derivatives[257]	
2,2′-bipyridine[257]	
	halogens or halide ions
NR_4Br[258,259]	
I_2[260,261]	DDQ[260]
IBr[262,263]	DABCO[262]
ICl[263]	
NIS[261,263]	I_2;[263] protic acids[261]
	other methods
NR_3[264−266]	
PR_3[265,266]	
SR_2[265,266]	
solvolysis[7,230,267,268]	NR_4Br;[267,268] silver salts[230]

of the counteranion of silver salts. We will then focus the discussion on how those studies enabled scientists to better understand the glycosylation reaction, helped develop improved methods, and how the improved methods enhanced our synthetic capabilities.

3.2.1. Activation with Silver Salts or Other Group 11 Metal Salts (Copper). As mentioned previously, glycosylation reactions in the presence of insoluble silver salts such as Ag_2O and Ag_2CO_3 proceed slowly and may result in inefficient glycosylations despite using large excess of reagents and, sometimes, excess reactants. This ultimately affects the yield of glycosides that typically fall within 30 to 70%. To improve the glycoside synthesis, several soluble silver salts were introduced as promoters for the activation of glycosyl bromides. These salts include silver acetate,[6,7] which led to the predominant 1-*O*-acetylation, silver nitrate first studied by Koenigs and Knorr,[7] and in a greater detail investigated by Knöchel et al.[222,223] Several other soluble silver salts were explored including perchlorate,[227,229] tetrafluoroborate,[227,230] hexafluorophosphate,[230] and trifluoromethanesulfonate (triflate).[230] While being efficient activators, these silver salts required multiple equivalents of the acid scavenger to be added in these reactions. Wulff and co-workers studied glycosylation of steroidal alcohols in the presence of several silver salts of hydroxyacids and dicarboxylic acids.[232−234,269,270] In a majority of cases, glycosides were observed as major products, but in some cases significant amounts of 1-*O*-acyl and 1,2-orthoester derivatives were also present. A direct correlation was paved between the formation of products and the distance between the hydroxy and carboxy groups in the organo-silver salts. As depicted in Figure 1, interactions between OH or OAg and the

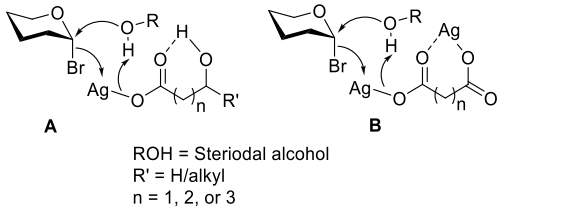

Figure 1. Mechanistic interpretation of action of hydroxyl carboxylate and dicarboxylate silver salts.

carbonyl group in 2-, 3-, and 4-hydroxycarboxylate salts (A), and 1,2-, 1,3-, 1,4-dicarboxylate salts (B) may have a role in suppressing the nucleophilic attack of the carboxylate ion. Stronger interactions help to lower the formation of 1-*O*-acyl derivatives. For hydroxy acids, silver 3-hydroxypentanoate and salicylate provided the highest yields, whereas disilver maleate outperformed all other diacids investigated.

Apart from the above-mentioned silver salts, numerous other silver-based promoters were reported for the activation of glycosyl bromides such as silver imidazole-$ZnCl_2$,[238] silver silicate,[235] silver silicate-alumina,[235] silver zeolite,[236] silver silica-alumina.[237] As discovered by Paulsen and co-workers, silver silicates are very advantageous for the synthesis of β-linked glycosides.[235] This study was recently extended by Herzon and co-worker to the stereoselective synthesis of 2-deoxy and 2,6-dideoxy β-glycosides, from corresponding anomeric bromides upon activation with silver silicate.[271] The authors employed in situ formation of glycosyl bromides α-**22** and α-**23** from the corresponding anomeric acetates in the presence of TMSBr in dichloromethane as shown in

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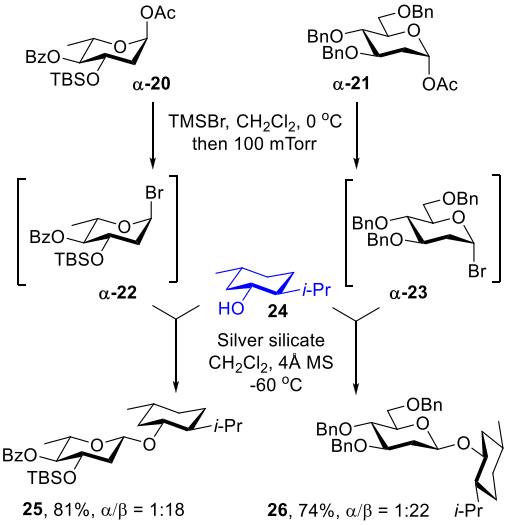
Scheme 7. The synthesized glycosyl bromides α-**22** and α-**23** were then reacted with (−)-menthol acceptor **24** in the

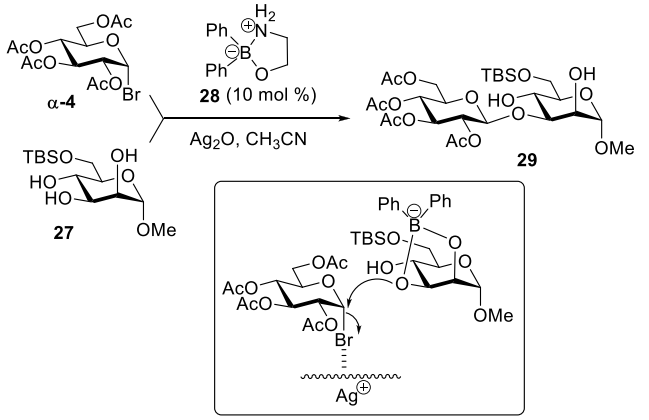
Scheme 7. Silver Silicate-Promoted Glycosidation of 2-Deoxy- and 2,6-Dideoxyglycosyl Bromides



presence of silver silicate to produce the respective β-linked glycosides in good yields and with high stereoselectivity: **25** (81%, α/β = 1:18) and **26** (74%, α/β = 1:22). The authors pointed out that the nature of protecting groups of the glycosyl bromide donors may play an important role in enhancing or reducing the stereoselectivity. It was also observed that acid sensitive and azide protecting groups remained unaffected during these reaction conditions.

Borinic acid-catalyzed regioselective glycosidation of glycosyl bromide (and chloride) was developed by Taylor and co-workers[224] in accordance with their approach, complexation of partially protected *cis*-diol glycosyl acceptor **27** with borinic acid **28** to afford a borinate complex takes place first (Scheme 8).[272] The nucleophilicity of sugar hydroxyl groups is predicted by Fukui index calculation,[273−275] which states that the boron-bound oxygen to be more nucleophilic than the free hydroxyl group. The borinate complex subsequently attacks glycosyl bromide α-**4** to furnish disaccharide **28**. The outcome of the glycosylation in terms of yields and stereoselectivity mainly depends on the stereochemistry of the glycosyl halide and

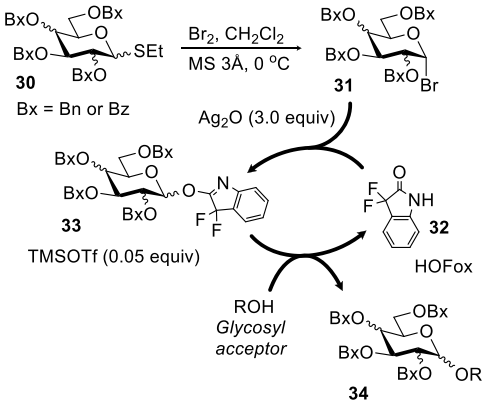
Scheme 8. Borinic Acid-Catalyzed Glycosidation of Glycosyl Bromide



reactivity of the acceptor. Exclusive 1,2-*trans* selectivity was observed in borinic acid-catalyzed glycosylation wherein α-glycosyl halides were used.

Demchenko and co-workers have developed a regenerative strategy to activate glycosyl bromides.[217,225] As shown in Scheme 9, ethylthio glycoside **30** was first treated with a

Scheme 9. Regenerative Glycosylation



Sugar	HOFox	TMSOTf	Temp	Time	Yield
Glc	--	0.10	0 °C→rt	12 h	35%
Glc	0.25	0.10	0 °C→rt	12 h	85%
Gal	--	0.05	0 °C	1.5 h	19%
Gal	0.25	0.05	0 °C	1.5 h	90%
Man	--	0.08	0 °C	2.5 h	42%
Man	0.25	0.08	0 °C	2.5 h	98%

stoichiometric amount of bromine to afford glycosyl bromide **31**. The latter was dried *in vacuo* and used without purification for the regenerative glycosylation cycle wherein both the synthesis of the reactive OFox imidate intermediate **33** and its glycosidation were performed in a catalytic, regenerative fashion. First, HOFox aglycone **32** used in catalytic amounts was reacted with glycosyl bromide **31** in the presence of silver oxide to afford OFox imidate **33**.[276] Second, glycosyl acceptor and a Lewis acid (TMSOTf) were added afford the corresponding glycosides **34**. The leaving group from the OFox intermediate departs as HOFox aglycone **32** that can be used to generate the next batch of OFox imidate **33**. It was also shown that the rate of glycosylation reaction can be increased by increasing the amount of HOFox used. As illustrated in Scheme 8, only 0.25 equiv of HOFox additive was very effective at enhancing glycosidations of glycosyl bromides of the gluco, galacto, and manno series. More recently, a streamlined procedure that allows for bypassing the intermediacy of glycosyl bromides was reported.[277]

Very recently, Singh and Demchenko discovered an acid-catalyzed silver salt-promoted glycosyl halide activation. It was observed that the addition of a catalytic amount of TMSOTf to a silver oxide-promoted glycosylation dramatically accelerates the reaction and rapidly affords glycosides in very high

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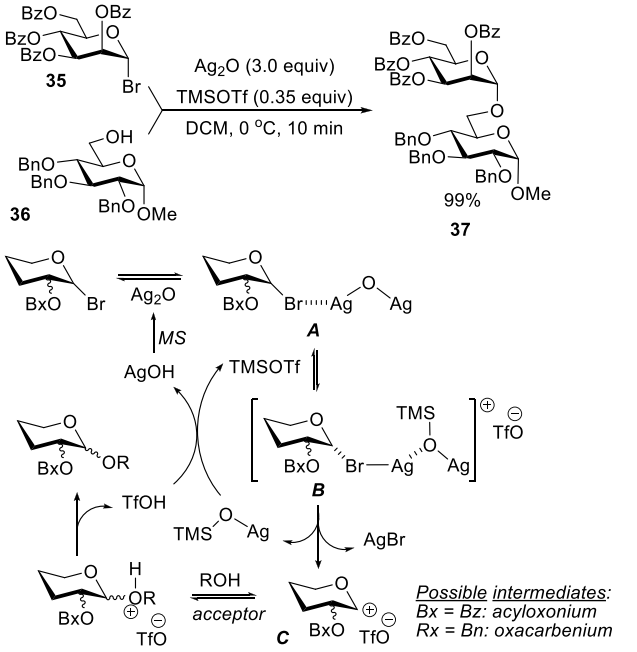
yields.[146] As depicted in Scheme 10, TMSOTf-catalyzed glycosidation of mannosyl bromide **35** with glycosyl acceptor

Scheme 10. TMSOTf-Catalyzed Koenigs–Knorr Glycosylation



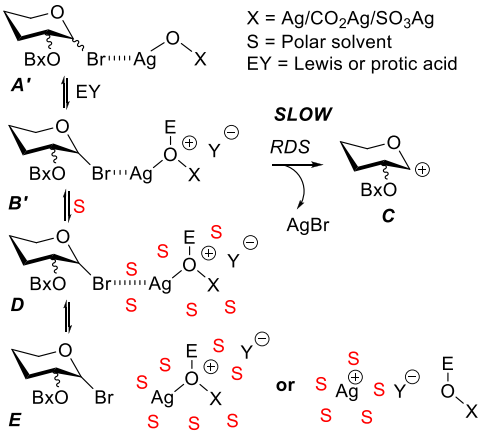
36 afforded disaccharide **37** in 99% yield in 10 min. This new reaction was applied to the synthesis of a variety of glycosides of different series. A tentative mechanism was proposed, wherein it was assumed that silver oxide coordinates with anomeric bromide (Intermediate A) and the oxide oxygen gets silylated with TMSOTf (intermediate B). This helps to shift the equilibrium of the reaction, reinforces the Ag–Br bond formation, and results in the release of AgBr that precipitates from the reaction mixture making the reaction irreversible (Scheme 10).

Depending on the C-2 protection group, either an oxacarbenium or acyloxonimun ion is formed as a reactive intermediate (intermediate C), which then reacts with the glycosyl acceptor. After deprotonation and TMS exchange, TMSOTf along with silver hydroxide are formed. TMSOTf gets cycled back into the reaction, and AgOH is decomposed to silver oxide by losing a water molecule to the desiccant (molecular sieves). The authors eliminated a possibility of the *in situ* formation of AgOTf by showing that these conditions are ineffective for the activation of glycosyl STaz[29] and SBox[27,28] glycosyl donors that are readily activated with AgOTf. While no further mechanistic evidence has been presented, it is certainly possible that the intermediate B may undergo an S_N2-like displacement instead of leading to the oxacarbenium ion. Modest stereoselectivity observed in reactions with glycosyl donors equipped with a nonparticipating group at C-2 is indicative of the intermediacy of the oxacarbenium ion.

From the proposed mechanistic pathway, it became clear that as little as 0.50 equiv of silver oxide (stoichiometric silver) should be sufficient for the complete consumption of glycosyl bromide donor. Further investigation of roles of different silver salts, Lewis/Bronsted acid additives, and solvents revealed further particulars of this cooperatively catalyzed reaction.[221]

Thus, it was noted that reactions in polar solvents proceed much slower and are prone to side processes. Silver(I) oxide and acid-catalyzed glycosylation in nonpolar solvents proceed as explained in Scheme 10, and the identical reaction pathway was envisaged for both Lewis acid and protic acid cocatalysis. In polar solvents, however, it was assumed that upon addition of Lewis or Bronsted acids, strongly ionized species get solvated in polar solvents as shown for intermediate D in Scheme 11. The solvation reduces the effective interaction with

Scheme 11. Cooperatively Catalyzed Koenigs–Knorr Glycosylation in Polar and Nonpolar Solvents



the anomeric bromide E thus resulting in longer reaction times or incomplete consumption of glycosyl bromide or formation of side products. Ultimately, this investigation led to a successful activation of glycosyl bromides in the presence of 0.50 equiv of silver oxide and 0.35 equiv of TfOH in toluene. One of the most interesting aspects of the reaction was that the progress and completion of the reaction could be monitored by eye due to stark visual changes, when the glycosidation proceeds from dark brown-black appearance due the presence of Ag_2O of the reaction mixture to complete decolorization when 0.50 equiv of Ag_2O has been entirely consumed.

An unusual reactivity trend has been unveiled in these cooperatively catalyzed glycosylation conditions where benzoylated α-bromides **35** and **11** turned out to be much more reactive compared to their benzylated counterparts **39** and **38** (Figure 2). The higher reactivity of benzoylated α-bromides compared to their benzylated counterparts strikingly contradicts the armed-disarmed theory proposed by Fraser-Reid.[278]

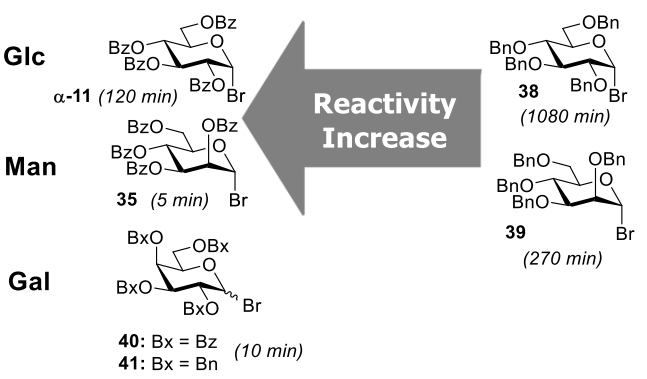


Figure 2. Contradicting reactivity trends in the cooperatively catalyzed Koenigs–Knorr glycosylations.

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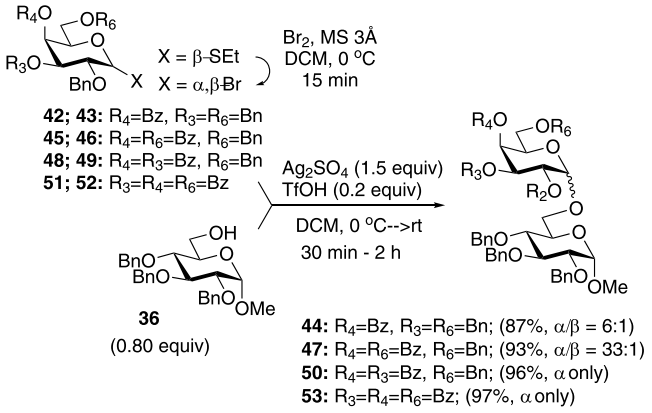
This was found to be consistent irrespective of silver salts, acids, and sugar series employed with a less pronounced effect in highly reactive galactosyl bromide donors **40** and **41**.

The glycosidation of glycosyl bromide donors bearing a nonparticipating (benzyl) group at C-2 under cooperative catalysis produce glycosides in good yield albeit no stereoselectivity. To address this issue, Demchenko and co-workers performed a preliminary investigation of 1,2-*cis* selective galactosylation reaction by optimizing the reaction conditions in combination with switching the location of common protecting groups OBn and OBz across different position of galactosyl bromides.[226] For this purpose, galactosyl bromide **43**, obtained from bromination thioglycoside **42**, was used as glycosyl donor and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside acceptor **36** in the presence of Ag_2SO_4 and TfOH (Scheme 12). Disaccharide **44** was obtained in 87% yield with

Scheme 12. Acyl Group-Directed α-Stereoselective Galactosylation in Cooperatively Catalyzed Glycosylations

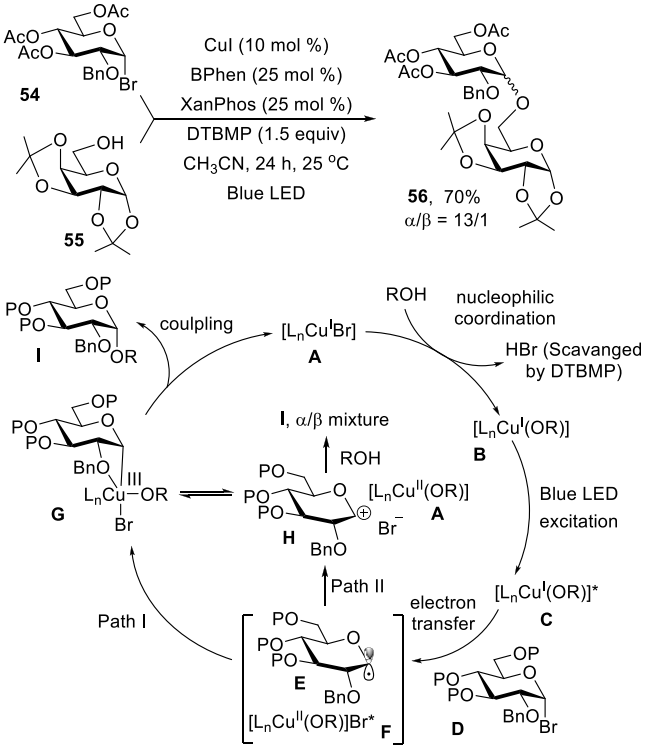


predominant α-selectivity (α/β = 6.0:1). From this study, the authors concluded that the 4-*O*-acyl group is strictly necessary, as previously discovered by Boons,[279] but it may be insufficient to drive α-selective galactosylation under cooperative catalysis of Ag_2SO_4 (1.5 equiv) and TfOH (0.20 equiv) in dichloromethane.

Subsequently, the authors achieved an excellent 1,2-*cis* α-galactosylation from galactosyl bromide **46** having 4- and 6-OBz groups. The bromide donor **46** was obtained by bromination of thiogalactoside **45**. Glycosidation of donor **46** with glycosyl acceptor **36** produced disaccharide **47** in 93% yield (α/β = 33.0:1) as shown in Scheme 12. Following this general line of thought, thiogalactoside **48** having 3- and 4-OBz groups and **51** having 3-, 4-, and 6-OBz groups were synthesized, which were later brominated to produce galactosyl bromides **49** and **52**, respectively. Glycosidation of both galactosyl bromides **49** and **52** with glycosyl acceptor **36** produced the respective disaccharides **50** and **53** in excellent yields and with exclusive α-selectivity. Construction of different types of 1,2-*cis* galactosidic linkages was then extended to a variety of differently protected glycosyl acceptors.

Very recently, Nguyen and co-workers developed a method for copper-catalyzed activation of glycosyl bromides in the presence of visible light.[147] Reaction optimization revealed that copper iodide (CuI), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (XantPhos), 4,7-diphenyl-1,10-phenanthroline (BPhen), and di-*tert*-butylmethylpyridine (DTBMP) are strictly necessary to induce an efficient coupling between glycosyl bromide **54** and glycosyl acceptor **55** in acetonitrile affording disaccharide **56** in 72% yield (Scheme 13). The

Scheme 13. Visible Light-Mediated Cu(I)-Catalyzed 1,2-*cis* α-Selective Glycosylation



comparison of chemical shift value (^{31}P NMR, δ = −11.99 ppm) obtained from in situ generated complex was identical with the isolated complex [Cu(BPhen)(Xantphos)]BF_4 (^{31}P NMR, δ = −11.87 ppm) and the glycosylation outcome from the isolated catalyst, [Cu(BPhen)(Xantphos)]BF_4 was similar to the aforementioned conditions, indicating [Cu(BPhen)-(Xantphos)]$^+$ as an active catalyst for this transformation. The optimized reaction conditions facilitated the construction of glycosidic linkages using coupling partners of different sugar series.

In addition to the outcome of glycosylations, data from absorption and emission spectroscopies and electrochemistry experiments suggested the following mechanistic pathway for the visible light-mediated copper-catalyzed activation of glycosyl bromide. The initial step includes the reaction of Cu(I) catalyst A with alcohol to produce Cu(I)-oxygen complex B (Scheme 13).[280,281] Upon photoirradiation (blue light) the latter is converted to excited Cu(I)-complex C that enables electron transfer to glycosyl bromide D to afford glycosyl radical E and Cu(II) complex F. This can potentially lead to either Cu(III) complex G[282−285] via Path I or oxacarbenium ion intermediate H via Path II.[286] Control experiments were performed by replacing oxygen at C-2 with fluorine/hydrogen atom. Fluorine is known to interact with the copper center;[287] indeed, 2-fluoro-2-deoxy-derivative favored α-1,2-*cis* selectivity. Conversely, the 2-deoxy derivative led to the formation of an α/β mixture, which could be due to the formation of a 2-deoxy cation. These observations strongly suggest that α-1,2-*cis* selectivity does not arise from the oxacarbenium ion intermediate H generated either via Path II

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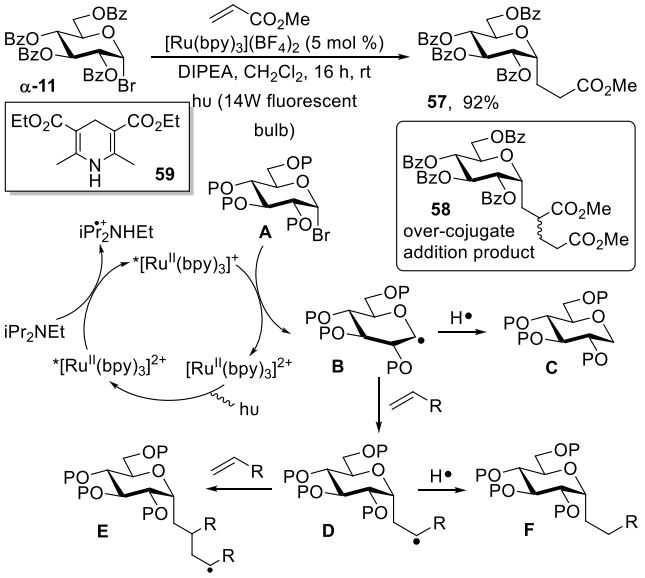
or from the collapse of Cu(III) complex G. This concludes the Path I is more likely to be operative wherein reductive elimination of Cu(III) complex G affords glycoside I and regenerates Cu (I) catalysts to endure the catalytic glycosylation cycle.

Herein, we are describing a representative example to construct C-glycosidic linkages by activating glycosyl bromides with a combined effect of visible light and $[Ru(bpy)_3]^{2+}$.[288] Thus, as described by Gagné and co-workers, these reactions produce a glycosyl radical from glycosyl bromide, which gets intermolecularly trapped with electron-deficient alkene to afford C-glycosides in a stereoselective manner. For example, per-benzoylated glycosyl bromide α-**11** produced the corresponding glycosyl radical upon visible light-mediated activation in the presence of $[Ru(bpy)_3](BF_4)_2$ (5 mol %) and a stoichiometric amount of *N*,*N*-diisopropylethylamine (DIPEA) in DCM. Once formed, the glycosyl radical gets immediately consumed by methyl acrylate to produce the corresponding α-C-glycoside **57** (Scheme 14). The authors observed the

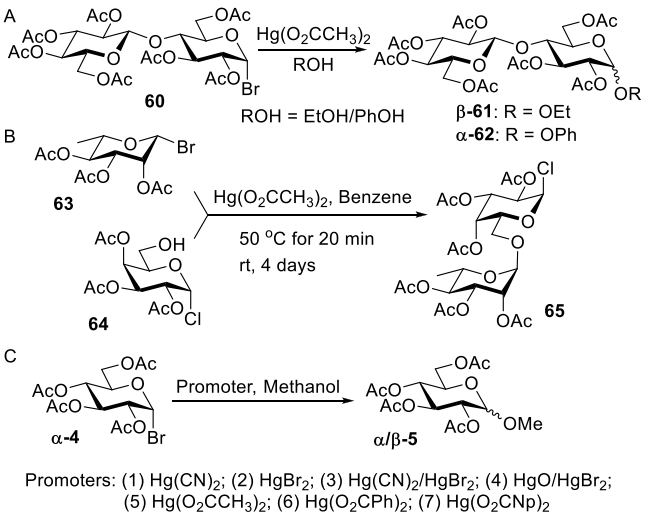
Scheme 14. Visible Light-Mediated Intermolecular Addition of Glycosyl Bromide to Methyl Acrylate



formation of an overconjugate addition product **58**. This side reaction could be suppressed by the addition of Hantzsch ester **59**, which also was found to accelerate the reaction. This observation allowed to obtain α-*C*-glycoside **57** in a very impressive 92% yield and led to an improved understanding of the mechanistic pathway. As shown in Scheme 14, as electron transfer occurs from the photogenerated species $[Ru(bpy)_3]^{+}$ to anomeric bromide A producing glycosyl radical B. The latter can get reduced to produce C or can be trapped by an electron-deficient alkene to produce C-glycoside radical D. Subsequent step depends on relative rates for the formation of overconjugate product E versus that of the formation of expected C-glycoside F. As it was mentioned, Hantzsch ester **59** accelerates the reduction of D into F.

3.2.2. Activation with Mercury and Other Group 12 Metal Salts (Zinc or Cadmium). As aforementioned, Zemplen and co-workers showed an efficient activation of cellobiosyl bromide **60** in the presence of aluminum metal and mercuric acetate $Hg(OAc)_2$. However, it was later realized that aluminum did not play an active role in splitting the C−Br bond.[160,161] The anomeric distribution of glucosides was difficult to predict, and a subsequent dedicated study revealed that the ratio of α/β-linked glycosides mainly depends on the amount and types of alcohol used.[160,162,163] For example, as shown in Scheme 15A, the treatment of glycosyl bromide **60**

Scheme 15. Mercury Salt-Promoted Glycosidations of Glycosyl Bromides



with ethanol or phenol in the presence of $Hg(OAc)_2$ produces the respective β-glycoside **61** and α-glycoside **62**. The α-anomer formation was favored when the reaction was performed with an excess of alcohol. Zemplen and co-workers applied this methodology to the synthesis of several disaccharides wherein selective activation of the leaving group was employed. For example, selective glycosidation of acetobromorhamnose **63** with partially protected galactosyl chloride acceptor **64** was performed in the presence of $Hg(OAc)_2$ to produce disaccharide chloride **65** (Scheme 15B).[289] Several other disaccharide chlorides were synthesized employing this selective activation of glycosyl bromides over chlorides in the presence of $Hg(OAc)_2$.[290] The selective activation approach helps to streamline oligosaccharide assembly because the products are already equipped with a leaving group, chloride in this case, and hence can be used as glycosyl donors in subsequent glycosylations directly.

Helferich and co-workers showed that a very fast activation of glycosyl bromide α-**4** can take place in the presence of mercuric cyanide. This powerful improvement of the basic methodology earned a name of the Helferich modification of the classical Koenigs−Knorr method.[239] By varying the amount of alcohol and mercuric cyanide, a rapid formation (30−100 min) of methyl β-glycoside **5** from glycosyl bromide α-**4** and methanol has been achieved in good yields (up to 83%, Scheme 15C). It was also found that the addition of mercuric bromide to a mercuric cyanide-promoted glycosylation, further increases the rate of the reaction, whereas mercuric bromide used by itself did not produce any glycoside product. However, later it was shown that mercuric bromide can activate glycosyl bromide donors in the presence of MS 4 Å in refluxing methylene chloride. These reactions produced α-glycosides.[241,242] Several other mercuric salts were tested (Scheme 15C), and some aryl mercuric salts such as phenyl mercury acetate, and naphthyl mercury acetate turned out to be effective promoters due to their better solubility in organic

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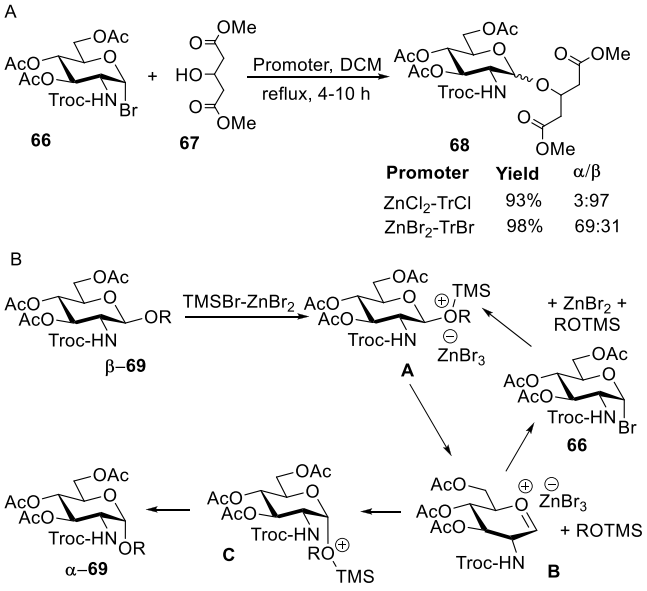
solvents.[243] Green and co-workers have shown that mercuric oxide in combination with a small amount of mercuric bromide is also capable of an effective activation of glycosyl bromides.[240] Meldal and Bock showed that mercuric iodide alone is capable of activating glycosyl bromides.[244] Mercuric salt-catalyzed glycosylation method was employed for the synthesis of different types of biologically relevant glycosides and oligosaccharides.[181,242,291,292]

In other attempts to replace silver salts in glycosylations, Helferich and co-workers investigated zinc salts as activators of glycosyl bromides.[239] For example, when glycosidation of bromide α-**4** with methanol was conducted in the presence of zinc oxide methyl β-glycoside, **5** was obtained in 37% yield. Different primary alcohols were tested, and the corresponding glycosides were obtained in good yields (41−76%). Increasing the amount of zinc oxide was detrimental for the glycosylation reaction and led to decreased yields of glycosides. However, changing the reaction solvent from nonpolar to polar showed a positive effect. A slower activation was observed when zinc acetate was used instead under otherwise identical reaction conditions. Kusama and co-workers showed that glycosyl bromide **66** can be activated with equimolar amounts of zinc chloride and trityl chloride. Glycosylation of acceptor **67** produced glucoside **68** in a high yield with excellent β-stereoselectivity (Scheme 16A).[245]

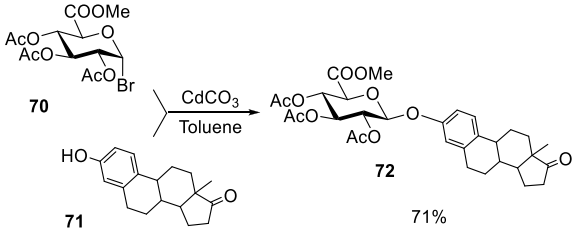
Scheme 16. Glycosylation and Anomerization in Zinc Salt-Promoted Glycosylations



A similar activation was also observed with $ZnBr_2$ and trityl bromide (TrBr), but a notable loss of stereoselectivity was observed (Scheme 16A). In this case, α-glucoside **68** was obtained as the major product.[247] Several other alcohols were glycosylated, and a similar stereoselectivity trend was observed. It is well-known that Lewis acids such as $TiCl_4$, $AlCl_3$, $ZnCl_2$, $SnCl_2$, and BF_3-Et_2O promote anomerization of glycosides.[293−299] Analysis of the reaction mixture revealed that in this case the formation of β-glucoside takes place first, which is then followed by anomerization as the reaction progresses. A dedicated study confirmed that HBr generated during glycosylation induces the anomerization of the kinetic β-glucoside product to the thermodynamic α-glucoside. A plausible mechanistic pathway for anomerization in the presence of $ZnBr_2$ and TMSBr was proposed (Scheme 16B).[247,248] Reaction of β-glycoside β-**69** in the presence of TMSBr-$ZnBr_2$ produced salt A, which collapsed to oxacarbenium ion B and trimethylsilyl ether. Nucleophilic displacement by bromide ion ($ZnBr_3^=$) can produce glycosyl bromide **66**. Conversely, a more thermodynamically stable product C can be formed by the nucleophilic attack of trimethylsilyl ether to form α-**69**. It was later discovered that adding 1.0−2.0 equiv of a glycosyl acceptor can drastically decrease the formation of glycosyl bromide and afford predominantly α-linked products. This methodology was applied to the synthesis of 1→6-linked glycolipid derivatives.[300,301] Surprisingly, only β-disaccharides were obtained irrespective of the promoter system (TrCl-Zn salts or zinc salts alone). When β-linked disaccharides were exposed to the anomerization conditions (TMSBr-$ZnBr_2$), only the starting material was recovered. The stability of β-linked disaccharide lipid derivatives was attributed to the inductive effect of the oxygen functional group at the reducing end. Shibakami and co-workers presented a similar activation protocol for per-benzoylated glucosyl bromide wherein NBS and catalytic ZnI_2 or $ZnBr_2$ were employed.[246] In the case of ZnI_2, the reaction was found to proceed via intermediacy of the respective glycosyl iodide formed *in situ*.

Helferich and co-workers reported a cadmium salt-promoted activation of glycosyl bromide donors.[239] The authors demonstrated that reaction of per-acetylated glucosyl bromides with MeOH in the presence of cadmium oxide afforded the corresponding methyl β-glucoside in a moderate yield. Bernstein and Conrow investigated the Cd salt-promoted glycosylation in a greater detail by employing glycosyl halides of different sugar series.[249] For example, glycosidation of glycosyl uronide donor **70** with estrone acceptor **71** in the presence of $CdCO_3$ produced glucuronide **72** in 71% yield (Scheme 17). Cadmium sulfide was also investigated for the

Scheme 17. Cadmium Salt-Promoted Glycosylation



activation of donor **70**; however, the yield of product **72** was only 20%. Several other steroidal phenolic glucuronides, glycosides, and acetyl glucosaminides were successfully synthesized using similar glycosylation conditions.[250,302,303] In addition to β-glycosides, small amounts of the corresponding α-glucosides and/or *C*-glycosides were also isolated, and the ratio of products was found to depend on the coupling partners and the reaction conditions employed. It was suggested that the generated cadmium bromide was the actual activator, but cadmium bromide by itself was ineffective, similar to Helfrich's observations made with mercuric cyanide activation.[239] Later, it was also confirmed that the product composition depends on the surface area of cadmium carbonate.[251]

3.2.3. Activation with Group 13−15 Post-transition Metal Salts (Indium, Tin, Lead, or Bismuth). Chowdhury

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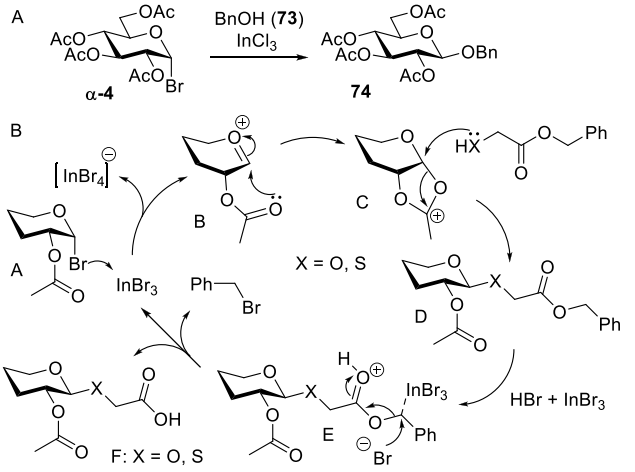
and co-workers developed indium chloride-promoted activation of glycosyl bromides (Scheme 18A).[252] A catalytic amount

Scheme 18. Indium Salt-Promoted Glycosidations of Glycosyl Bromides

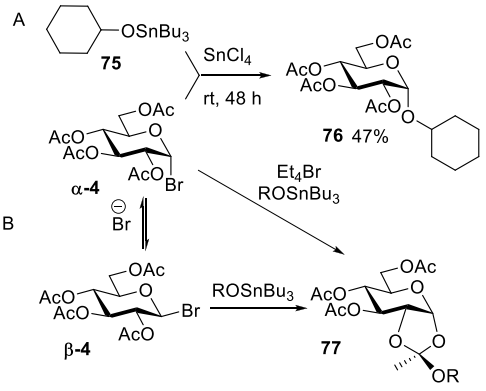


of indium chloride without any additive was sufficient to promote the glycosylation. For example, when tetra-acetylated glucosyl bromide α-**4** was treated with benzyl alcohol (**73**, 1.0 equiv) in the presence of $InCl_3$ (0.4 equiv), glucoside **74** was obtained in 68% yield. Several other glycosides and disaccharides were successfully synthesized in good yields (62−90%). Indium chloride-catalyzed *C*-glycosylations of pyrrole and indoles were also described.[304] In addition, various *O*- and *S*-glycosyl esters were synthesized by activation of glycosyl bromides with catalytic $InCl_3$.[253]

It was also found that glycosylation and removal of benzyl esters can be achieved in one pot in the presence of indium bromide ($InBr_3$). A tentative mechanism involving coordination of the anomeric bromide A with indium tribromide to afford the reactive intermediate, oxacarbenium ion B, which gets stabilized as the acyloxonium ion C has been proposed (Scheme 18B). Following the nucleophilic attack and proton exchange, $InBr_3$ and HBr were generated. The latter is capable of protonating benzyl ester D to produce intermediate E, which undergoes the nucleophilic attack by the bromide ion to produce *O*- or *S*-glycosyl acids F and benzyl bromide as a side product. To broaden the scope of indium salt-catalyzed glycosylations, Xue and co-workers investigated several other indium salts. The authors found that as low as 0.05−0.15 equiv of $In(NTf_2)_3$ without any external additive can catalyze glycosidations of glycosyl bromides with simple alcohols.[254] To achieve efficient glycosylation of sugar alcohols, 2.0 equiv of glycosyl acceptors was needed.

Matsui and Ogawa showed that glycosidation of glycosyl bromides with trialkylstannyl alkoxide acceptors can be achieved in the presence of and tin(IV) chloride.[255] Different alkoxide acceptors produced either α- or β-glycosides albeit with fair stereoselectivity. For example, when tetra-acetylated glucosyl bromide α-**4** was reacted with tributylstannylated cyclohexyloxide **75** in the presence of $SnCl_4$. The corresponding α-glucoside **76** was obtained in 47% yield, as shown in Scheme 19A. When similar reaction conditions were applied to glycosylation of the tributylstannyl benzyloxide acceptor, the corresponding β-glucoside was obtained in 52% yield. By employing the halide ion-catalyzed anomerization procedure in

Scheme 19. Tin Salt-Mediated Glycosidation of Glycosyl Bromides



the presence of Et_4NBr,[305] several trilalkylstannyl alkoxide acceptors were converted to 1,2-orthoesters **77** (Scheme 19B).[183]

Malleron and Lubineau developed β-stereoselective glycosidations of glycosyl bromides by employing tin triflate as an activator.[256] One equivalent of a base as an acid scavenger was necessary to produce glycosides in good yields. The authors observed a competitive transesterification side reaction when primary alcohols were used as glycosyl acceptors. This led to compromised yields, for example, methyl glycoside was obtained in 33% yield. Secondary alcohols, however, did not seem to encounter this side reaction and produced glycosides in better yields. Several β-glycosides, β-disaccharides, β-aminosugars,[306] and *N*-linked-β-disaccharides[307] were successfully synthesized. In another study, the authors successfully applied tin triflate-promoted activation of glycosyl chloride donors (*vide infra*).[306] Dick has reported activation of glycosyl bromides in the presence of lead(II) carbonate, wherein a moderate yield (37%) for the synthesis of tetra-acetylated α,β-phenyl glucosides was obtained when per-acetylated glucosyl bromide was treated with PhOH in the presence of $PbCO_3$.[251]

Recently, Demchenko and co-workers have shown an efficient activation of glycosyl halides in the presence of $Bi(OTf)_3$.[308] Compared to most common metal salt activators of glycosyl halides wherein stoichiometric amount of activators is needed, a rapid activation of glycosyl bromides was achieved in the presence of 0.35 equiv of $Bi(OTf)_3$. Due to the detrimental effect of strongly acidic TfOH produced as a byproduct, the authors have increased the amount of molecular sieves and identified nitromethane-DCM as the preferred reaction solvent. As a result, glycosidation of benzoylated and benzylated galactosyl bromides **40** and **41** with glycosyl acceptor **36** in the presence of $Bi(OTf)_2$ (0.35 equiv) afforded respective galactosides **78** and **79** in good yields (Scheme 20). An effective glycosylation of a variety of glycosyl acceptors was achieved for sugars of the gluco, manno, rhamno, and glucosamino series equipped with different protecting groups.[308]

3.2.4. Activation with Non-nucleophilic Organic Bases. Koenigs and Knorr were the first to report non-metal-based activation of glycosyl bromides, wherein glycosyl bromide was treated with methanol in the presence of pyridine that afforded methyl β-glycoside.[7] The exact mechanistic action of pyridine was not discussed or known, rather it was assumed that pyridine acts as hydrogen bromide scavenger. A few years later, Fischer and co-workers showed the formation

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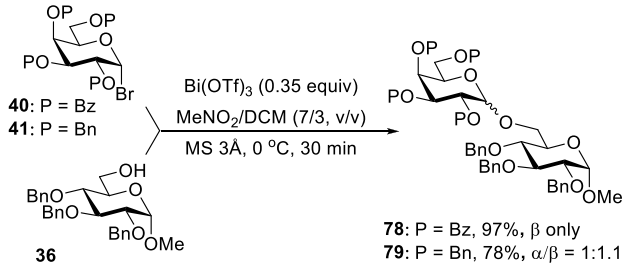
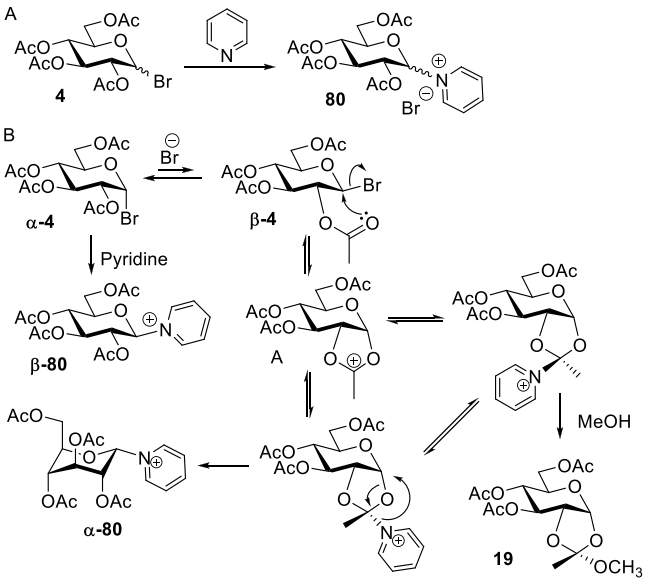
Scheme 20. Bismuth(III) Salt-Promoted Activation of Glycosyl Halides



of anomeric mixtures of pyridinium salts α/β-**80** when tetra-*O*-acetylated glucosyl bromide α/β-**4** was treated with pyridine in the absence of an alcohol (Scheme 21A).[148] This undoubtedly excluded the possibility of pyridine purpose solely as the hydrogen halide scavenger.

Scheme 21. Reaction of Glycosyl Bromide 4 in the Presence of Pyridine

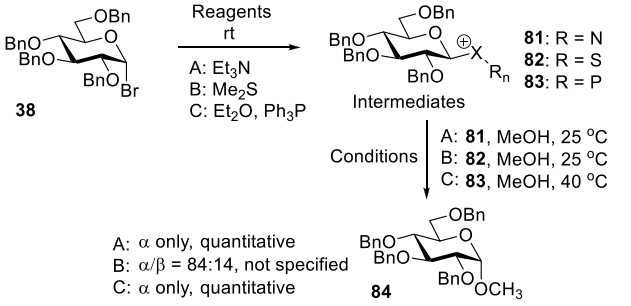


Fischer also investigated glycosylations in the presence of quinoline.[150] Lemieux and Morgan also observed the formation of anomeric pyridinium salts.[182] To gain mechanistic insights for this reaction, the authors performed an extensive concentration-dependence study depicted in Scheme 21B. It was found that the anomeric distribution of α- and β-pyridinium salts **80** depends on the concentration of glycosyl bromide α-**4** in pyridine. At a low concentration, the formation of β-**80** predominates, but at higher concentrations both α- and β-**80** are produced and the ratio of anomers was found to depend on the concentration of glycosyl bromide α-**4**. When the equimolar amount of tetra-*n*-butyl ammonium bromide was added to the reaction, only α-pyridinium salt **80** was obtained, whereas reactions in the presence of tetra-*n*-butylammonium perchlorate produced the anomeric mixture.

These results were indicative of the intermediacy of β-bromide β-**4** and acyloxonium intermediate A. In the presence of methanol this reaction led to a significant amount of orthoester **19**. NMR spectroscopy studies suggested that α-pyridinium salt α-**80** adopts the $^1C_4$ conformation, as shown in Scheme 21B.[309] Further experiments were conducted to support the routes for the formation of α-**80** and its β-linked counterpart,[183,310] which ultimately led to appreciation that charged intermediates can serve as glycosyl donors. A variety of other approaches to obtain charged intermediates followed by their glycosidation have been explored. Micheel and Micheel examined the formation of positively charged anomeric salts from triethylamine. However, the authors never used these salts as a glycosyl donors.[264,311] Hess and Heumann treated a glycosyl chloride with trimethylamine in the presence of ethyl alcohol and observed the formation of ethyl α-glycosides in addition to the anticipated anomeric salts.[312]

Expanding upon these findings, Schuerch and co-workers performed a dedicated study of the formation and glycosidation of positively charged intermediates that led to the development of a highly stereocontrolled α-glycosylation.[265,266] It was shown that positively charged intermediates **81**−**83** depicted in Scheme 22 can be synthesized by treating

Scheme 22. Synthesis of α-Glycoside via Positively Charged Glycosyl Donors



glycosyl bromide **38** with triethylamine, dimethyl sulfide, or triphenylphosphine, respectively. These intermediates can be isolated and purified. The positively charged anomeric substituents would have a strong propensity to adopt the equatorial position due to the reverse anomeric effect.[309] As a result, these positively charged equatorially placed leaving groups would undergo the nucleophilic attack from the α-face to give axial glycoside products.

Thus, glycosidation of ammonium **81** and phosphonium **83** salts produced α-glycosides **84** exclusively, whereas glycosidation of sulfonium **82** salt showed somewhat relaxed stereoselectivity (Scheme 22).[265] An attempt to synthesize an α-1→3-linked disaccharide has failed, and this outcome was attributed to low reactivity of the sugar alcohol. Upon subsequent optimization of the reaction conditions wherein reaction solvents and temperatures were refined, a successful synthesis of an α-1→6-linked disaccharide has been achieved.[313]

Very recently, Nguyen and co-workers presented an improved approach to achieve stereoselective activation of glycosyl bromides bearing a nonparticipating group at C-2.[257] It was discovered that the activation of glycosyl bromide **54** with phenanthroline catalyst **85** in the presence of isobutylene oxide (as hydrogen bromide scavenger) preferentially afforded 1,2-*cis* glycosides. For example, glycosylation of glycosyl acceptor **55** produced disaccharide **56** in 73% with excellent α-stereoselectivity, as shown in Scheme 23A. The mechanistic pathway involves double S_N2-like displacement wherein the first step involves the formation of β-phenanthrolium intermediate A depicted in Scheme 23B. The stability of intermediate A was attributed to noncovalent interaction of

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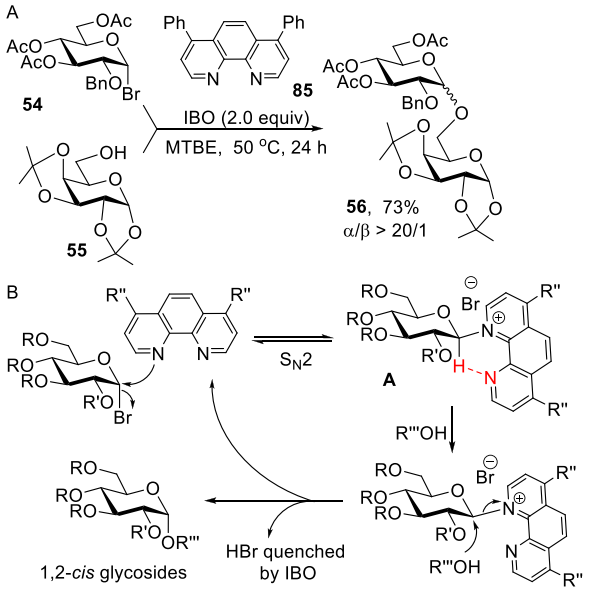
Scheme 23. 1,2-*cis* Glycosylation via β-Phenanthrolium Intermediates

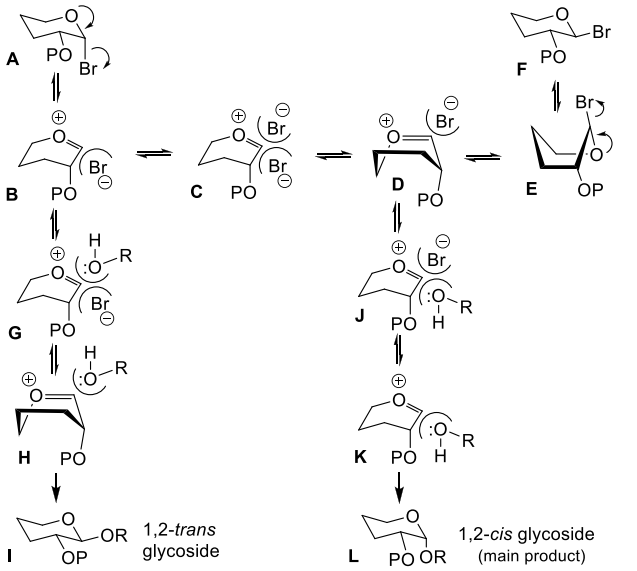


anomeric α-hydrogen with nitrogen of phenanthroline. Subsequently, intermediate A reacts with a glycosyl acceptor to form an α-linked product. This stereoselective glycosylation methodology was utilized to synthesize many glycosidic linkages as well as a series of α-glycans (*vide infra*).

3.2.5. Activation with Halogens, Halide Ions, or Halonium Ions. Lemieux and co-workers performed an extensive study of a halide ion-catalyzed glycosylation with glycosyl halides. This approach has led to effective 1,2-*cis* stereoselective syntheses of glycosides and oligosaccharides.[258] The early attempts to address the issues of stereoselectivity were primarily directed on the development of new catalytic systems, as well as optimization of the reaction conditions (solvent, temperature, pressure).[314] Many valuable developments for the synthesis of 1,2-*cis* glycosides have been published by Schuerch and co-workers,[72,230,265,315−318] However, a major breakthrough in the understanding of the principles of the α-glycosidic bond formation emerged with the discovery and thorough elaboration of the *in situ* anomerization concept, so-called "halide ion catalyzed glycosidation reactions" by Lemieux and co-workers (Scheme 24).[258] Thus, it was observed that a rapid equilibrium could be established between a relatively stable α-halide **A** and its far more reactive β-counterpart **F** by the addition of tetraalkyl ammonium bromide (Et_4NBr). Therefore, a glycosyl acceptor (ROH) would attack the more reactive intermediate in an overall S_N2 fashion (via **D**), providing α-glycoside **L**. More detailed analysis of the glycosylation process showed that the energy barrier for a nucleophilic substitution **F** to **L** (formation of α-glycosides from the highly reactive β-bromide **F**) is somewhat lower than that for the reaction from **A** to **I** (formation of β-glycosides from the less reactive α-bromide **A**).

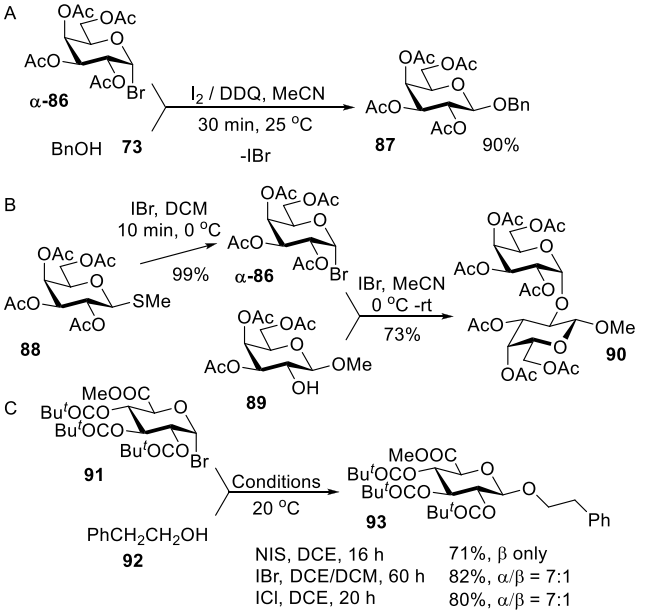
Indeed, α-glycoside **L** is formed faster than its β-linked counterpart **I**, which in combination with higher thermodynamic stability of the α-anomer makes this glycosylation process very favorable overall. If the difference in the energy barrier had been sufficient, it would be possible to direct the reaction toward the formation of α-anomers with complete stereoselectivity. Therefore, in order to achieve high stereo-

Scheme 24. Formation of 1,2-*cis* Glycosides via *In Situ* Anomerization



selectivity, the entire glycosylation process has to be performed in a highly controlled manner. In this particular case the control is achieved by the use of extremely mild catalyst (Et_4NBr), although very reactive substrates and prolonged reaction times are thus required. A series of per-benzylated glycosyl halides of the gluco, galacto, and fuco series were tested. These reactions produced good yields of glycosides with excellent α-stereoselectivity. This method found practical application in synthesizing blood group determinants and other biologically relevant oligosaccharides having α-glycosidic linkages (*vide infra*).[259,319] In another effort to find a substitute to heavy metal promoters, Field and co-workers studied the activation of per-acetylated glycosyl bromides by utilizing I_2 alone or with DDQ as an additive. As shown in Scheme 25A, when galactosyl bromide α-**86** was reacted with benzyl alcohol

Scheme 25. Iodine or Iodine Monobromide/Chloride-Promoted Glycosylations



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73 in the presence of I_2 and DDQ at rt, an excellent yield of galactoside **87** was achieved within 30 min.[260] It was proposed that iodine acts as a halophilic reagent which, following the interaction with the anomeric bromide, fragments to give iodine monobromide and oxacarbenium or acyloxonium ion. Subsequently, the authors realized that iodine monobromide (IBr) could also be used as an efficient activator for glycosyl bromides. Indeed, IBr alone or with DABCO additive could activate glycosyl bromides to produce different disaccharides in 35−73% yields. The lower yields in this series were generally attributed to side reactions rather than promoter problems. All glycosyl bromide donors were synthesized by treating the corresponding thioglycosides with IBr.

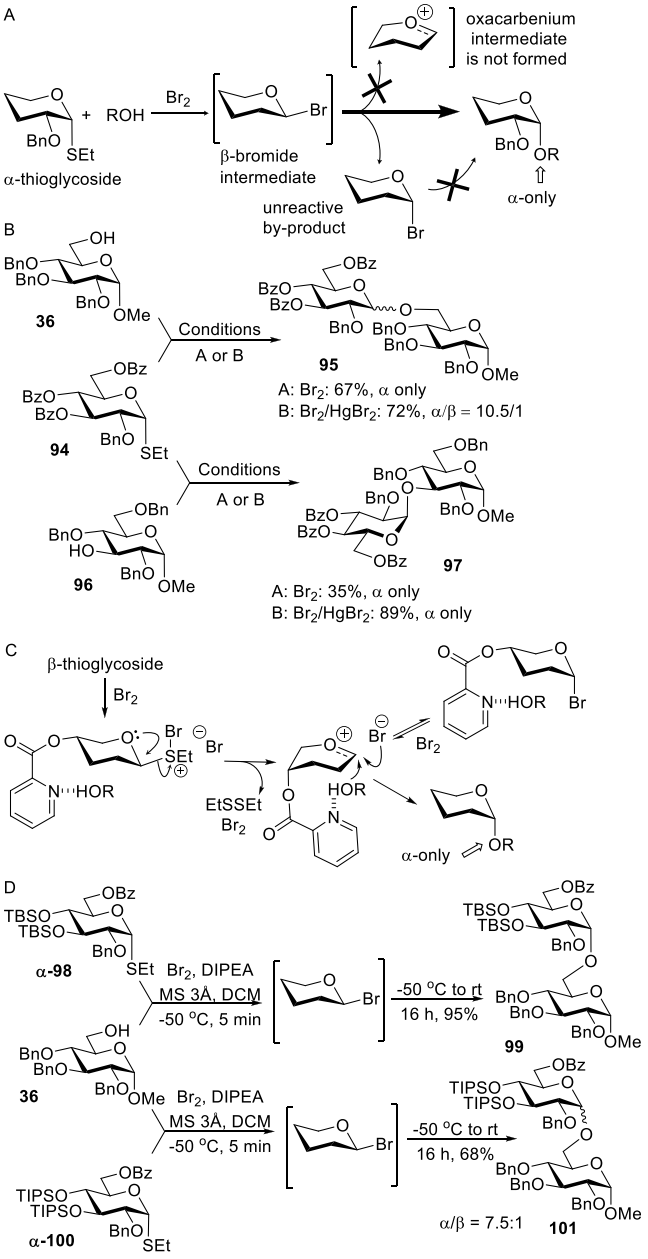
One such example is the synthesis of galactosyl bromide α-**86** from the corresponding methylthio galactoside **88** in the presence of IBr depicted in Scheme 25B. The bromide donor α-**86** was later glycosidated with secondary galactosyl acceptor **89** in the presence of IBr that produced disaccharide **90** in 73% yield.[262] Glycosyl chloride donors were also activated under identical reaction conditions. Besides glycosyl halide activation, thioglycoside activation was also shown to occur in the presence of IBr. Iodine-promoted glycosidation of glycosyl halide was further extended to amino acid acceptors.[320] Anhydrous potassium carbonate was used as a scavenger for a hydrogen iodide byproduct.

Stachulski employed *N*-iodosuccinimide as a source of the iodonium ion for the activation of glycosyl bromides.[263] An efficient activation of pivaloyl protected bromide **91** was achieved in the presence of NIS, IBr or ICl at 20 °C. For example, glycosylation of acceptor **92** produced glucuronide **93** in good yields of 71−82% as depicted in Scheme 25C. Excellent to good yields of other glucuronides were achieved with several primary and secondary alcohols. However, the stereoselectivity was found to differ drastically depending on the type of promoter used. Thus, NIS produced the product in high β-stereoselectivity, whereas IBr- or ICl-promoted reactions were α-stereoselective.

Demchenko developed reaction conditions wherein bromine was used both as the reagent to convert thioglycosides into bromides and to activate the latter for glycosylation.[321] To achieve highly stereocontrolled 1,2-*cis* glycosylation, it was deemed necessary to form reactive β-glycosyl bromides. It was assumed that α-thioglycoside upon bromination can produce the reactive β-bromide as shown in Scheme 26A. This reaction was monitored by NMR, showing that β-bromide is indeed the reactive intermediate, which can undergo a rapid anomerization into the α-linked counterpart. Once formed, the α-bromide was found to be totally unreactive under the established reaction conditions. The glycosylations of primary acceptors were smooth and stereoselective. For example, glycosidation of thioglycoside **94** with 6-OH glycosyl acceptor **36** in the presence of Br_2 produced disaccharide **95** in 67% yield with complete 1,2-*cis* stereoselectivity (Scheme 26B).

However, slower glycosylations of secondary acceptors were less efficient due to the competing $\beta \rightarrow \alpha$ halide anomerization, although all reactions were still α-stereoselective. For example, glycosidation of thioglycoside **94** with 3-OH glycosyl acceptor **96** in the presence of Br_2 produced disaccharide **97** in 35% yield with complete 1,2-*cis* stereoselectivity. It was also shown that the α-bromide can be reactivated in the presence of mercury(II) additive. This pathway was found to be very beneficial for the glycosylation of secondary alcohols. For example, glycosidation of thioglycoside **94** with 3-OH glycosyl

Scheme 26. Bromine-Promoted α-Selective Glycosylations



acceptor **96** in the presence of Br_2 and $HgBr_2$ produced disaccharide **97** in a significantly improved yield of 89% yield with complete 1,2-*cis* stereoselectivity. However, when applied to glycosylation of highly reactive primary acceptors, these reaction conditions can compromise α-selectivity. Thus, glycosidation of thioglycoside **94** with 6-OH glycosyl acceptor **36** in the presence of Br_2 and $HgBr_2$ produced disaccharide **95** in a slightly improved yield of 72% yield albeit reduced stereoselectivity (α/β = 10.5/1, Scheme 26B).

Bromine has also been used as a promoter in glycosylations by means of an H-bond-mediated Aglycone Delivery (HAD).[322] Glucosyl donors bearing the 4-*O*-picoloyl group exhibited excellent stereoselectivity with a number of different glycosyl and aliphatic acceptors.[323] Furthermore, bromine was also shown to activate a wide variety of leaving groups including thioglycosides, imidates, and thioimidates. A low temperature NMR monitoring of the reaction showed direct

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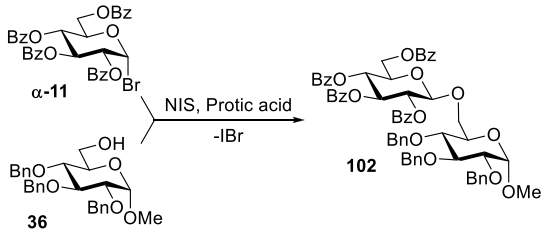
and rapid formation of the α-bromide. Differently from the benzoylated bromides (*vide supra*), a highly benzylated α-bromide was reactive under these reaction conditions. Upon departure of the bromide leaving group, the 4-*O*-picoloyl mediated HAD ensures that the nucleophile is delivered exclusively from the bottom face of the resulting oxacarbenium intermediate (Scheme 26C). Mercuric bromide could also be added to this reaction to improve the yield and shorten the reaction time.

Further efforts were made to apply the bromine-promoted glycosylation reaction to conformationally superarmed glycosyl donors.[124,125] Dedicated NMR experiments and computational studies revealed that introduction TBS and TIPS groups at C-3 and C-4 positions of β- or α-thioglycosides **98** and **100** distort the ring conformation.[143] Reactive β-glycosyl bromide formation was seen only with α-**98**, whereas β-**98** afforded an anomeric mixture of bromides. Glycosidation of α-**98** with primary glycosyl acceptor **36** in the presence of Br_2 and DIPEA as an additive provided 1,2-*cis* disaccharide **99** in an excellent yield of 95% (α only) as shown in Scheme 26D. The reactivity trend of the corresponding TIPS protected glycosyl donor **100** was similar; however, the yield and stereoselectivity both decreased. For example, when glycosyl donor α-**100** was glycosidated with acceptor **36** disaccharide **101** was produced in 68% yield with reduced stereoselectivity (α/β = 7.5:1). This reduced yield was attributed to competing silyl group cleavage occurring under these reaction conditions.

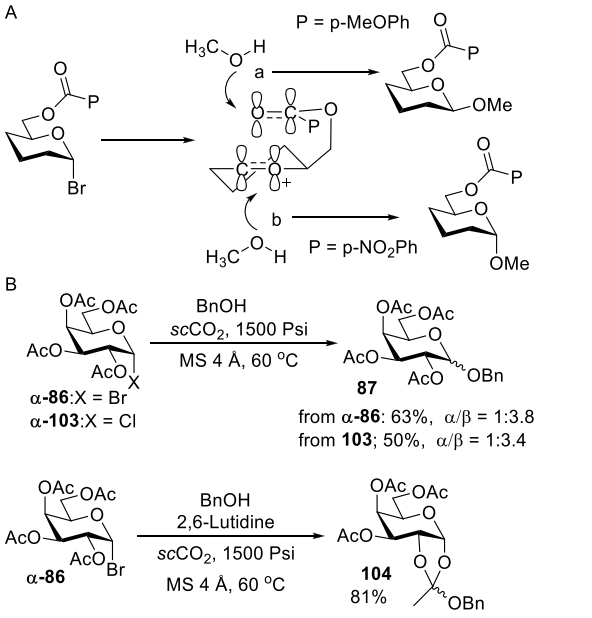
Madsen and co-workers used protic acid in combination with *N*-iodosuccinimide to achieve a facile release of the iodonium ion.[261] An efficient glycosidation of per-benzoylated glucosyl bromide α-**11** with reactive glycosyl acceptor **36** was achieved in the presence of NIS/TfOH to afford disaccharide **102** in yields up to 88% (Scheme 27). However, changing the sugar series and protecting groups of glycosyl donors led to reduced yields (60−80%) even in reactions with reactive glycosyl acceptors.

Scheme 27. NIS-TfOH-Promoted Glycosidation of Glycosyl Bromides



3.2.6. Solvolysis. Methanolysis of glycosyl bromides was studied both in the presence and the absence of various additives such as tetrabutylammonium bromide[267] or silver salts.[230] To understand the mechanistic details of solvolysis reactions, several experiments were conducted and it was determined that the concentration of alcohol plays a significant role on reaction rates and stereoselectivity.[230] At lower concentrations of methanol, less reactive α-glycosyl bromides are in anomeric equilibrium with the more reactive β-counterpart, which subsequently gives methyl α-glycoside as the major product.[230,267] At high concentrations of methanol, α-glycosyl bromides directly react with MeOH to preferentially produce methyl β-glycoside. A study by Frechet and Schuerch revealed variations in the rate of methanolysis or anomerization caused by steric and/or electronic effects of substituents at C-6 of glycosyl donors.[268] The study concluded that the anomeric distribution of methyl glycosides from methanolysis (solvolysis) of glycosyl bromides strongly depends on various factors such as structure of glycosyl halides, concentration of methanol, and reaction conditions. Several glycosyl bromides having different acyl groups at C-6 have been investigated revealing useful trends.[268] By changing the electronics of the functional groups at C-6, methyl glycosides were formed from 90% of α-anomer to over 90% of its β-counterpart. It was proposed that it is the interaction of the oxacarbenium ion with the carbonyl group of the substituent at C-6 that plays a significant role in deciding the stereochemistry of the product. For the instance, electron rich *p*-methoxybenzoyl group increases the electron density on the carbonyl group, stabilizes the positive charge on C-1, and facilitates the top face attack of the glycosyl acceptor (pathway a, Scheme 28A). The hydrogen

Scheme 28. Examples of Alcoholysis Reactions



bonding with acceptor could also be possible due to electron-rich carbonyl oxygen at C-6, which would also favor the formation of the β-linked product. Conversely, the *p*-nitrobenzoyl group with the electron deficient carbonyl group is unable to stabilize the positive charge on C-1. As a result, the attack of the glycosyl acceptor will take place from the less shielded bottom face resulting in the corresponding α-glycoside. The anomeric distribution of methyl glycosides produced from glycosyl bromides equipped with differentially *p*-substituted 6-*O*-benzoates was shown to follow the σ Hammett substituent constant value. Frechet and Schuerch extended the alcoholysis (methanolysis) of glycosyl bromide to solid phase synthesis wherein glycosyl bromides were coupled with polystyrene resin-immobilized glycosyl acceptors.[324,325]

Recently, Csuk and co-workers synthesized several β-glycosides by treating acetylated glycopyranosyl bromides with excess of *n*-alkyl alcohol without any additives.[326] Glycosides were produced on gram scale in good to moderate yields in 4−7 days at room temperature. Matheu and co-workers discovered a green approach to construct glycosidic linkages.[327] For that, glycosylation was conducted employing

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glycosyl halide donors in super critical CO_2 without any volatile organic solvent and metal catalysts. The authors demonstrated an efficient activation of tetra-acetylated galactosyl bromide α-**86** with benzyl alcohol **73** in the presence of $scCO_2$ at 1500 Psi and 60 °C to afford galactoside **87** in 63% yield (α/β = 1:3.8, Scheme 28B). To broaden the scope, differently protected galactosyl bromide donors in combination with various glycosyl acceptors were tested to afford the corresponding galactosides in moderate to good yields. Interestingly, pivaloyl-protected galactosyl bromide donor produced far better results in terms of yields and stereoselectivity in comparison to those achieved with its acetyl-, benzoyl-, or benzyl-protected counterparts. Reactions performed in the presence of 2,6-lutidine led to the formation of orthoester **104** in a good yield (81%, Scheme 28B). Glycosyl chlorides were investigated alongside providing comparable results; however, the activation of glycosyl chloride turned out to be slower and required high temperatures (90 °C).

3.3. Glycosyl Bromides in Glycan and Glycoconjugate Synthesis

3.3.1. Linear Synthesis. After understanding the mechanistic details for the formation of side products, strategies were developed for the synthesis of higher oligosaccharides. As depicted in Figure 3A, linear oligosaccharide synthesis consists of the glycosylation of a monosaccharide donor with a monosaccharide acceptor in the presence of a promoter to give the desired disaccharide. Most commonly, the latter is then converted into the second-generation glycosyl acceptor via liberation a specific hydroxyl group. The acceptor is then allowed to react with a glycosyl donor, resulting in the formation of trisaccharide, and this deprotection−glycosylation sequence can be then reiterated to yield a glycan of the desired length.

Alternatively, the intermediate oligosaccharides can be converted into a glycosyl donor via the introduction of a suitable leaving group. Many glycans have been synthesized using linear approaches; the only approach that was known in early days of oligosaccharide synthesis. Successful stepwise linear syntheses of gentiotriose **105** and gentiotetraose **106** were successfully demonstrated employing the Koenigs−Knorr glycosylation method in the presence of silver salt, iodine, and Drierite (Figure 3B).[220,228] Following the same strategy, Takiura et al. synthesized gentio-oligosaccharides **105**−**108**.[328] The halide ion-catalyzed glycosylation method was applied to the synthesis of blood group determinants **109**−**111** containing challenging α-glycosidic linkages (Figure 3C).[259,319]

3.3.2. Convergent Building Block Assembly. Pioneering studies by Zen,[329] Paulsen,[330] and Ogawa[331] paved the way to what is currently known as a convergent building-block strategy for oligosaccharide synthesis. According to this strategy, two di- (or oligo) saccharides, a glycosyl donor and a glycosyl acceptor, are constructed individually and then coupled together (converged) to afford a larger oligosaccharide. One benefit of such block synthesis is the decreased number of steps required for the overall assembly. One relevant example is a 2+3+2 assembly of a biantennary heptasaccharide **117** as depicted in Scheme 29.[332] According to the developed strategy, lactosamine bromide donor **112** was glycosidated with trimannosyl acceptor **113** in the presence of AgOTf and 2,6-lutidine to produce pentasaccharide **114** in

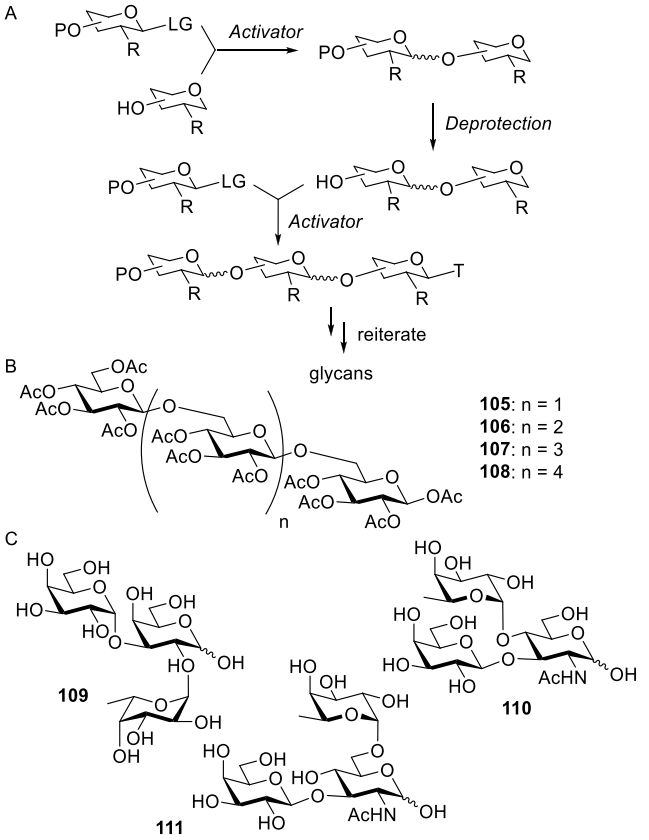
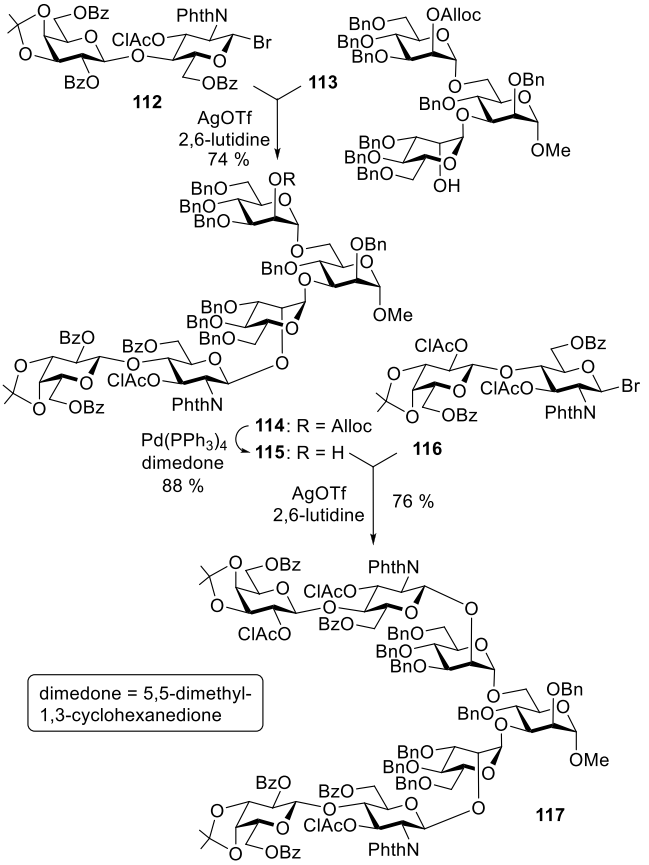


Figure 3. Linear oligosaccharides syntheses using Koenigs−Knorr (A) and halide-catalyzed (B) approaches

Scheme 29. Convergent Synthesis of Heptasaccharide 117



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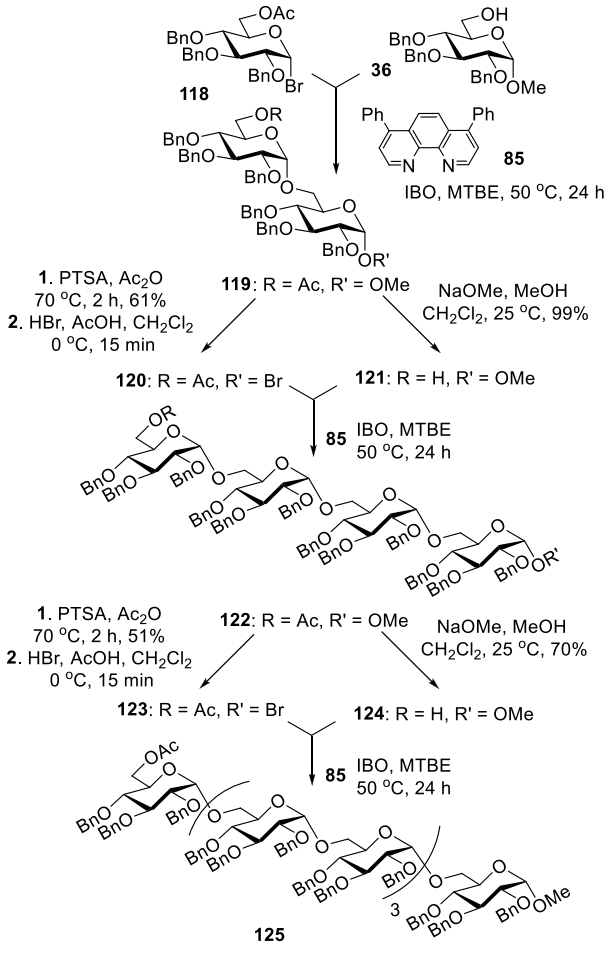
71% yield. The latter was subjected to the allyloxycarbonyl (Alloc) group removal with $Pd(PPh_3)_4$ to provide glycosyl acceptor **115** in 88% yield, which was then glycosylated with glycosyl donor **116** in the presence of AgOTf and 2,6-lutidine to produce the heptasaccharide **117** in 76% yield.

A conceptually related convergent approach has been proven particularly advantageous if the synthesis of two or more repeating units is required. In this case, an intermediate di- (or oligo) saccharide is divided into two portions: one portion is converted into a glycosyl donor and another into a glycosyl acceptor. Subsequently, the two reactants are coupled to afford a dimer. This manipulation can be then repeated for the synthesis of larger structures. A relevant recent example of such an approach was described by Nguyen and co-workers. The authors employed their phenanthroline-catalyzed glycosylation (*vide supra*) to assemble 1,2-*cis*-linked oligosaccharides as shown in Scheme 30.

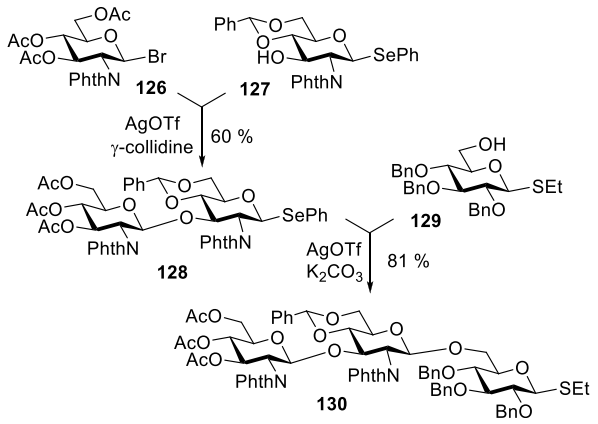
Scheme 30. Phenanthroline-Catalyzed Synthesis of 1,2-*cis* Glycans



Glycosyl bromide **118** was glycosidated with glycosyl acceptor **29** in the presence of 5% of phenanthroline **85** to obtain disaccharide **119** in 89% yield (α/β > 20:1). The latter was converted to glycosyl bromide donor **120** via sequential acetolysis-bromination. Intermediate **119** was also converted to glycosyl acceptor **121** by removing acetyl in the presence of sodium methoxide in methanol. Further, glycosyl bromide donor **120** was glycosidated with glycosyl acceptor **121** in the presence of phenanthroline **85** to obtain tetrasaccharide **122** in 86% yield (α/β > 20:1). The latter was the converted into tetrasaccharide bromide donor **123** and tetrasaccharide acceptor **124**, and the resulting counterparts were coupled in the presence of phenanthroline **85** to produce octasaccharide **125** in a good yield and excellent stereocontrol (77%, α/β > 20:1).

3.3.3. Selective Activation. When the arsenal of the glycosylation techniques was limited to Fischer and Koenigs–Knorr approaches (or their variations), selective activation of one leaving group over another was rare. A few relevant examples wherein more reactive glycosyl bromides were activated over less reactive glycosyl halides (chlorides, fluorides) that could act as glycosyl acceptors were discussed in previous subsections. However, when stable glycosyl donors such as thio- or selenoglycosides have emerged, the ability to activate one leaving group over another dramatically enhanced. Pioneering research of Zen,[329] Nicolaou,[333,334] Lonn,[335,336] Garegg,[216,337] and others[338,339] involved the activation of alkyl halides over *S*-alkyl/aryl glycosides. In addition to a few relevant examples discussed previously, an example of such a synthesis is presented in Scheme 31.[340] First, glycosyl bromide

Scheme 31. Selective Activation Utilizing Three Leaving Groups



donor **126** was activated over the phenylselenide acceptor **127** in the presence of AgOTf/γ-collidine to give the desired disaccharide **128** in 60% yield. The latter was then directly activated over the SEt acceptor **129** in the presence of AgOTf/K_2CO_3 to produce the desired trisaccharide **130** in 81% yield. Apparently, since the latter is equipped with the anomeric SEt leaving group, it can be directly activated for subsequent glycosylations under appropriate reaction conditions. A similar activation sequence was reported by the Ley group.[341]

3.3.4. Two-Step Activation and Regenerative Glycosylation Concept. Two-step activation of thioglycosides with bromine via glycosyl bromides has several potential applications for oligosaccharide synthesis. It can range from simple glycosylation to sophisticated iterative approaches. As shown in Scheme 32, the initial step involves the treatment of thioglycoside precursor **131** with bromine. The resulting glycosyl bromide is then directly reacted with glycosyl acceptor **132** in the presence of silver triflate to afford trisaccharide **133**.[231] Since the acceptor is not carrying a leaving group, it can be present in the reaction mixture from the beginning. The two-stage activation approach can also be applied to situations when both glycosyl donor and glycosyl acceptor initially bear the same type of a leaving group (thioglycoside).[329] In this

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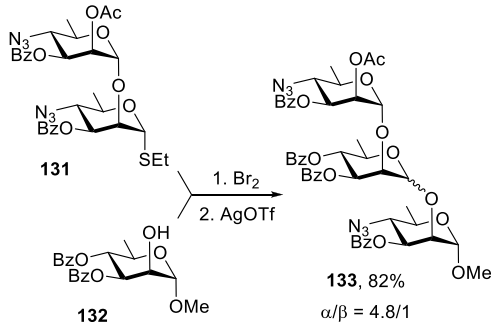
Scheme 32. In Situ Activation of Thioglycosides via Bromides



case, thioglycoside precursor of the donor is first converted to glycosyl bromide. The acceptor equipped with the SR leaving group is then added, and the glycosyl bromide is selectively activated in the presence of a suitable activator. Since the resulting product is a thioglycoside, this two-step activation sequence can be reiterated.

Demchenko and co-workers have developed a regenerative strategy to activate glycosyl bromides (*vide supra*).[217,225] In accordance with this approach, a thioglycosides precursor is first treated with bromine to afford the corresponding glycosyl bromide. The latter is then activated with HOFox/TMSOTf for the regenerative glycosylation cycle wherein both the synthesis of the reactive OFox imidate intermediate and its glycosidation is performed in a catalytic, regenerative fashion. Further, the regenerative glycosylation was applied to oligosaccharide synthesis. For this purpose, per-benzoylated galactosyl bromide **40**, generated from the corresponding thiogalactoside **134**, was glycosidated with thiogalactoside acceptor **135** in the presence of Ag_2O, HOFox, and TMSOTf, as depicted in Scheme 33. As a result, disaccharide **136** was obtained in 84% yield. Subsequently, thioglycoside **136** was converted to bromide donor **137** and coupled with acceptor **135** under the regenerative reaction conditions to produce trisaccharide **138** in 87% yield. Finally, the latter was converted into bromide **139**, which was then coupled with acceptor **135** to afford tetrasaccharide **140** in 76% yield.

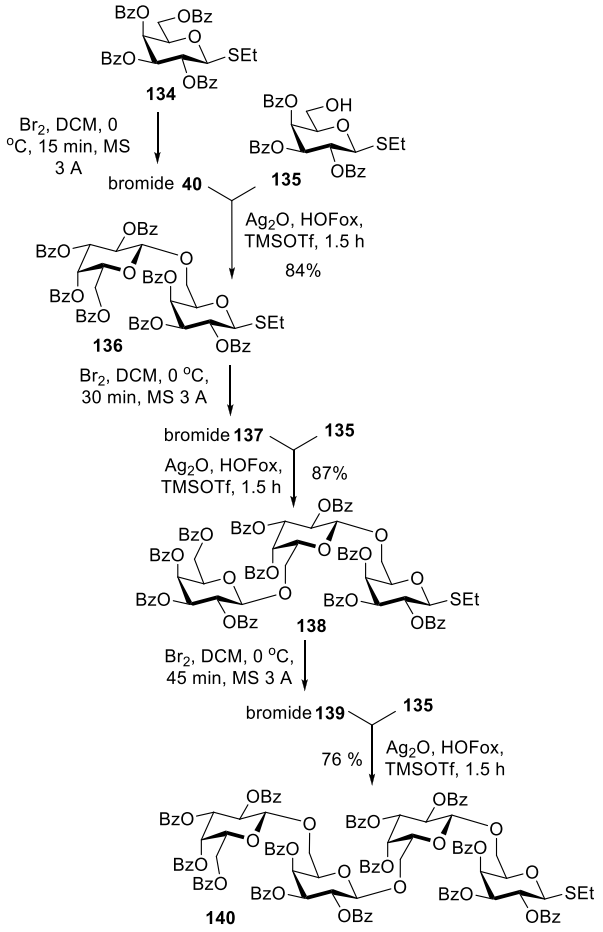
4. GLYCOSYL CHLORIDES

First glycosylations performed by Michael (*vide supra*) involved glycosyl chlorides.[4] However, in subsequent years, glycosyl chlorides were largely outshadowed by glycosyl bromides that have traditionally been considered advantageous over their chloride counterparts. After the thorough discussion of glycosyl bromides (Section 3), we note that many methods developed for the activation of glycosyl bromides are also effective for the activation of glycosyl chlorides. Hence, this section will mainly focus on the reagent-specific or condition-specific synthesis, activation, and application of glycosyl chlorides rather than repeating the same data presented for glycosyl bromides.

4.1. Synthesis of Glycosyl Chlorides

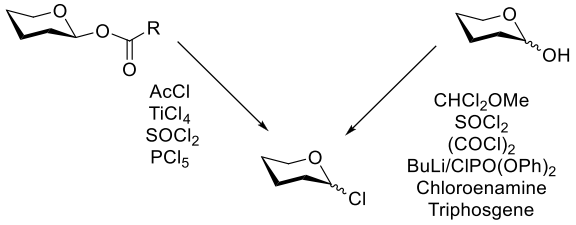
For the first time, glycosyl chlorides were synthesized from free glucose by treatment with acetyl chloride by Colley in 1870.[342] Expanding on this early work, others have also used AcCl for the synthesis of glycosyl chlorides of other sugar series.[343,344] Subsequently, more efficient methods, surveyed in this Section, have been developed for the synthesis of glycosyl chlorides from a variety of precursors.

Scheme 33. Oligosaccharide Synthesis via Regenerative Glycosylation



4.1.1. Preparation from Hemiacetals or Glycosyl Esters. Most commonly, glycosyl chlorides are prepared from two anomeric groups, either an ester such as acetate or a hemiacetal (Scheme 34). Selected reagents suitable for converting anomeric esters into glycosyl chlorides include $TiCl_4$,[345] $SOCl_2$,[346] and PCl_5.[347] Representative reagents used in the synthesis of chlorides from hemiacetals include $CHCl_2OMe$,[348,349] $SOCl_2$,[350] oxalyl chloride,[351−353] *n*-BuLi and $ClPO(OPh)_2$,[354] chloroenamine,[355] and triphosgene.[356] Evidently, many if not all of these reactions use harsh conditions and/or toxic reagents. Finding new methods to avoid some of these harsh conditions, toxic, or heavy metal reagents has been a vibrant area of study in recent years.

Scheme 34. Synthesis of Glycosyl Chlorides from Ethers or Hemiacetals



In 2017, Iadonisi developed a solvent-free method for the synthesis of a variety of glycosyl chlorides (Scheme 35A).[357]

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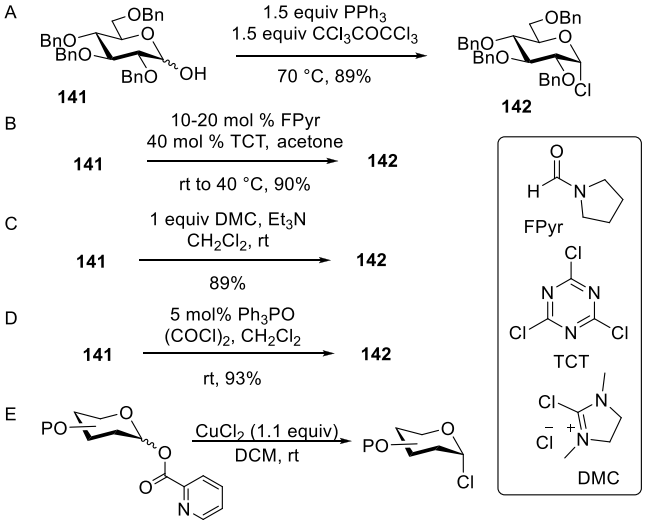
Scheme 35. New Methods for the Synthesis of Glycosyl Chlorides



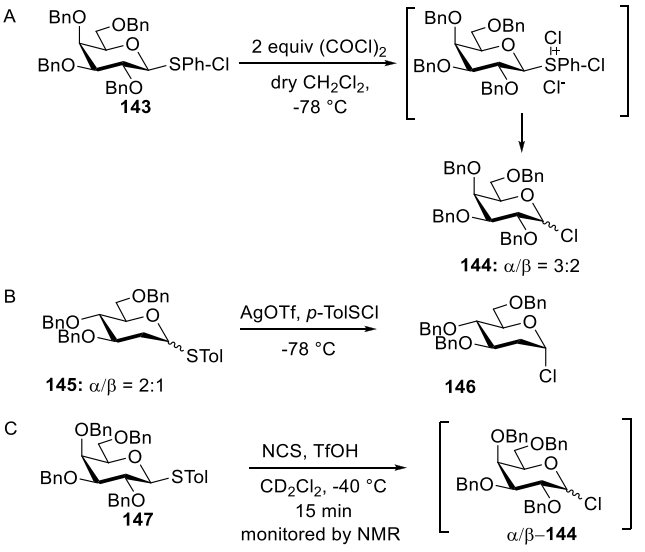
Using triphenyl phosphine and hexachloroacetone at 70 °C, glycosyl chloride **142** was obtained from the hemiacetal precursor **141** in 45 min. These conditions were applied to various sugar series including mannose, galactose, and fucose giving high yields (80%+) in most cases. This method was less effective when applied to nitrogen-containing sugar series. For example, the glycosyl chloride from glucosamine was obtained in only 44% yield.

Huy and Filbrich[358] have recently developed a method for the synthesis of glycosyl chlorides from the corresponding hemiacetal derivatives using as little as 34 mol % of trichlorotriazine (TCT) as a source of the stoichiometric chlorine. Thus, reaction of hemiacetal **141** with TCT in the presence of 10−20 mol % of *N*-formylpyrrolidine (FPyr) at 40 °C produced glycosyl chloride **142** in 90% yield (Scheme 35B). These conditions were shown to work both with sugar substrates such as glucose and fructose and with aliphatic alcohols. In 2018, Judeh et al.[359] introduced a chlorinating reagent 2-chloro-1,3-dimethylimidazolinum chloride (DMC) that was applied to the synthesis of glycosyl chlorides. Using stoichiometric DMC in the presence of triethylamine, hemiacetal **141** was converted into the corresponding glycosyl halide **142** in 15−30 min in 89% yield (Scheme 35C). This reaction worked well for a variety of sugars (glucose, mannose, galactose) giving 80−95% yield in most cases. The developed conditions were found to be compatible with many commonly used protecting groups such as acetates, silyl ethers, and acetals. McGarrigle et al.[360] found that catalytic Appel conditions using 5 mol % Ph_3PO and 1.5 equiv $(COCl)_2$ were also capable of chlorinating hemiacetals (Scheme 35D). Using these conditions, chloride **142** was synthesized from hemiacetal **141** in 93% yield. While this protocol worked well for glucose, most other sugars such as mannose, galactose, and 2-deoxy glucose gave lower yields between 67 and 79%. Glucosamine and galactosamine derivatives performed the worst under these reaction conditions, giving mixtures of products.

Recently, Tang and co-workers developed a milder reaction conditions for the synthesis of glycosyl chloride donors.[213] In accordance with their approach, 1-*O*-picoloyl (Pico) derivatives were treated with copper(II) chloride in DCM at ambient temperature (Scheme 35E). An interesting insight of this method is that 1-*O*-picoloyl (Pico) derivatives exclusively produced the corresponding α-glycosyl chlorides, and the method was found to be compatible with many commonly used protecting groups.

4.1.2. Preparation from Thioglycosides. Thioglycosides have many advantages such as being stable, allowing for protecting group manipulations, and can be stored for long periods of time. Hence, most modern building block syntheses today involve thioglycosides. Conversion from thioglycosides to glycosyl chlorides typically involved a two-step protocol with the first step being hydrolysis of the anomeric thioglycoside to the hemiacetal. This represented a notable disadvantage, and the effort has been made to develop methods for the direct conversion of thioglycosides to glycosyl chlorides. The first method was reported by Sugiyama and Diakur,[361] wherein 4-chlorophenylthio glycoside **143** was treated with oxalyl chloride in dichloromethane. The reaction was found to proceed through the intermediacy of a glycosyl halosulfonium salt shown in Scheme 36A. The latter is

Scheme 36. Direct Synthesis of Glycosyl Chlorides from Thioglycosides



unstable and falls apart to form the corresponding glycosyl chloride **144**. The resulting glycosyl chlorides were isolated in high yields (90%+) or crude chlorides could be used for subsequent glycosylations directly. While this protocol allowed for the one-step conversion, it still used harsh reaction conditions and the scope of this reaction was limited to 4-chlorophenylthio glycosides.

Verma and Wang[362] employed stoichiometric *p*-TolSCl in the presence of catalytic AgOTf to successfully convert *p*-tolylthio (STol) 2-deoxyglycoside **145** into the corresponding chloride **146** (Scheme 36B). Following this conversion, the corresponding chloride could be used for glycosylation without further purification. Subsequently, the authors discovered that the formation of anomeric chlorides can be accompanied by anomeric triflates, and the product distribution was dependent on the relative reactivity value (RRV)[135] of the tolylthio glycoside precursor. For example, when armed tolylthio galactoside **147** (RRV = 17 000) was treated with *N*-chlorosuccinimide NCS (1.0 equiv) and TfOH (0.3 equiv) in CD_2Cl_2 at −40 °C, exclusive formation of anomeric chloride

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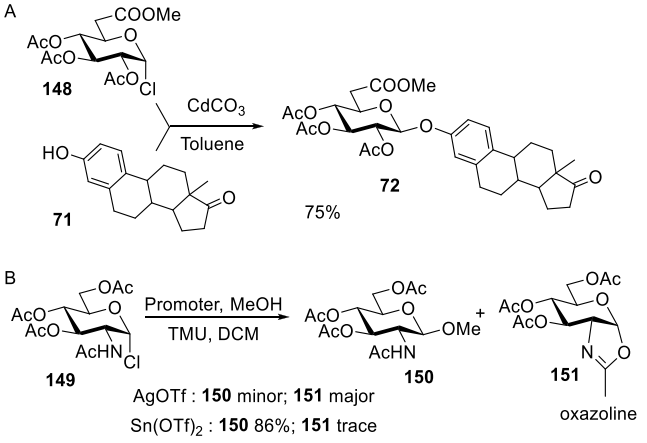
144 was observed by means of the NMR spectroscopy monitoring (Scheme 36C).[363] Regardless of the reaction intermediates, tolylthio glycosides could be glycosidated in the presence of a suitable glycosyl acceptor, NCS, and triflic acid. Reactions proceeding via the intermediacy of glycosyl chlorides were highly α-stereoselective.

4.2. Glycosidation of Glycosyl Chlorides

Michael in 1879 was the first to perform a glycosylation reaction with glycosyl chlorides (*vide supra*).[4] Per-acetylated glucosyl chloride was reacted with potassium phenoxide giving phenyl glucoside as the product. Then in 1901, the activation of glycosyl chlorides was performed by Koenigs and Knorr.[7] These reactions used insoluble silver(I) salts such as silver oxide or silver carbonate which were thought to act as an acid scavenger. Little was done to improve the activation of chlorides until 1949 when Helferich[364] introduced mercury salts as active promoters. While these methods can be used to synthesize oligosaccharides,[365,366] mercury salts are very toxic and the environmental considerations of the 21st century called for further quest of better activation conditions. Nevertheless, both the Koenigs-Knorr method and the Helferich modification have found broad utility in the synthesis of simple glycosides to date.

Some early work included the activation of glycosyl chlorides with cadmium(II) salts.[249] For example, glycosidation of glycosyl uronide donor **148** with estrone acceptor **71** in the presence of $CdCO_3$ produced glucuronide **72** in 71% yield (Scheme 37A). Cadmium sulfide was also investigated as the

Scheme 37. Cadmium or Tin Salt-Promoted Glycosidations of Glycosyl Chlorides

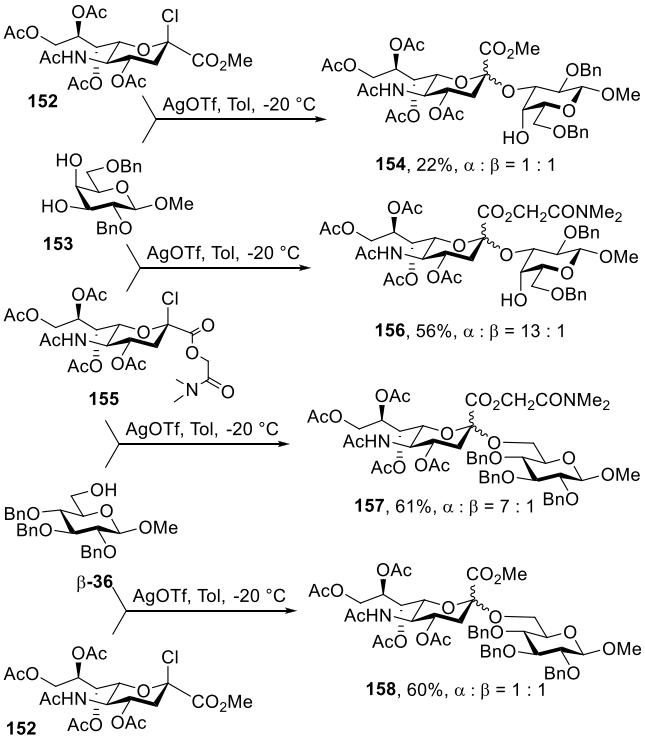


activator for the glycosidation of the anomeric chloride; however, the yield of the glucuronide was below the preparative value. Several other steroidal phenolic glucuronides, glycosides, and acetyl glucosaminides were successfully synthesized.[250,302,303] In addition to β-glycosides, a small amount of the corresponding α-glucosides and/or *C*-glycosides were also isolated, and the ratio of reagents was found to depend on coupling partners and reaction conditions employed. An interesting aspect of these reactions was the development of color as the reaction progresses. It was suggested that the generated cadmium chloride was the actual catalyst of activation. However, cadmium chloride by itself was ineffective, similar to Helferich's explanation for mercuric cyanide activation.[239] As discussed in Section 3.2.2, the product composition also in this case depends on the surface area of cadmium carbonate.[251]

In another study, the authors successfully applied the stannous triflate-promoted glycosylation for the activation of glycosyl chloride donors.[306] When glycosyl chloride **149** bearing a 2-acetamido (NHAc) group was employed as glycosyl donor in the presence of AgOTf, oxazoline **151** was observed as a major product (Scheme 37B). Changing AgOTf with $Sn(OTf)_2$ under otherwise identical reaction conditions suppressed the formation of oxazoline **151** while producing glycoside **150** as the major product. The control experiments showed that oxazoline does not serve as a reaction intermediate under these reaction conditions.

4.2.1. Activation with Silver Salts. Being partially soluble, silver(I) triflate is typically an effective promoter for the activation of glycosyl chlorides. However, these conditions were somewhat ineffective in cases of relatively unreactive glycosyl donors such as sialic acid chlorides.[367,368] Thus, glycosidation of chloride **152** with glycosyl acceptor **153** in the presence of AgOTf produced glycoside **154** in a poor yield of 22% without any preferred stereoselectivity (Scheme 38).

Scheme 38. Silver Triflate-Promoted Activation of Sialic Acid Chlorides



While investigating a participating moiety at C-1, Gin and coworkers introduced sialyl chloride donor **155** bearing an *N*,*N*-dimethylglycolamido ester functionality.[369] A commendable result was obtained with galactosyl acceptor **153** for the formation of disaccharide **156** in 56% yield and with high α-stereoselectivity α/β = 13/1. Glycosylation of the primary glycosyl acceptor β-**36** was nearly as effective with both sialyl donors **152** and **155** in terms of the yields of the respective products **158** and **157** that were isolated in 60−61% yields. However, the activation of the standard sialyl chloride donor **152** was nonstereoselective, and disaccharide **158** was isolated as a racemic mixture.

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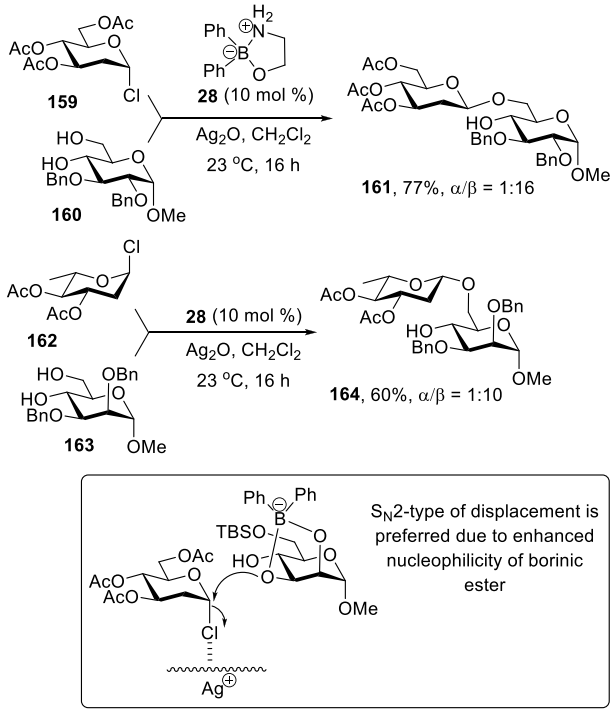
As described in Section 3.2.1, Taylor and co-workers developed borinic acid-catalyzed regioselective activation of glycosyl bromides.[224,272] A similar approach was later applied by the authors to the β-selective synthesis of 2-deoxy and 2,6-dideoxyglycosides.[370] Anomeric chlorides as glycosyl donors and partially protected cis-1,2- and 1,3-diols as glycosyl acceptors were found to be very effective. As shown in Scheme 39, per-acetylated 2-deoxyglycosyl chloride **159**,

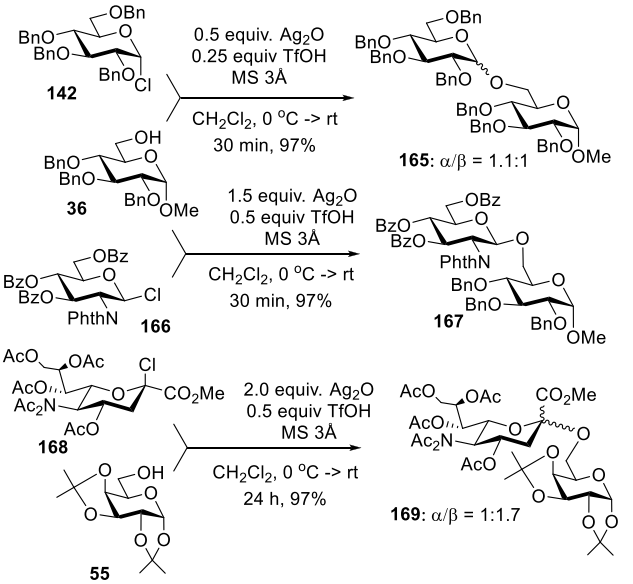
Scheme 39. Organoboron-Catalyzed Glycosidation of 2-Deoxy and 2,6-Dideoxy Glycosyl Chlorides



synthesized by treating with BCl_3, was reacted with glycosyl acceptor **160** in the presence of aminoethyl diphenylborinate **28** and silver oxide to produce 2-deoxy disaccharide **161** in 77% yield with high β-selectivity (α/β = 1:16). The authors also synthesized challenging β-2,6-dideoxy glycosides commonly found in bioactive natural products. For example, reaction of 2-deoxy-L-rhamnopyranosyl chloride **162** with glycosyl acceptor **163** under similar reaction conditions produced disaccharide **164** in a good yield of 60% with high β-selectivity (α/β = 1:10). Changing the protecting group from OAc to OBn turned out to be detrimental for both β-selectivity and yields. Similarly to that discussed in Section 3.2.1, the enhanced nucleophilicity of the hydroxyl group, as predicted by Fukui index calculation, in the borinate complex resulted in an S_N2-like attack on the glycosyl chloride donor.

Following the initial success with catalytic glycosidation of glycosyl chlorides, the Demchenko group investigated acid-catalyzed silver(I) oxide-mediated glycosylations that were initially developed for glycosyl bromides (*vide supra*).[221] Using Ag_2O combined with TfOH allows one to drastically increase the glycosylation reaction rate while reducing the amount of silver needed to 0.50 equiv. This reaction worked well with benzylated glucosyl chloride **142** and disaccharide **165** was obtained in 97% yield in the presence of just 0.50 equiv of Ag_2O and 0.25 equiv of TfOH in 30 min (Scheme 40).[371] Glycosylations of secondary glycosyl acceptors provided

Scheme 40. Glycosyl Chloride Activation Using Ag_2O and TfOH Promoter System



similar results. Benzylated mannosyl and galactosyl chlorides required a higher amount of TfOH (0.50 equiv). These reaction conditions provided high yields (98%+) and fast reaction times.

Nitrogen-containing sugar derivatives such as glucosamine and sialic acid could also be readily activated under these reaction conditions, but required higher amounts of activators. Thus, primary glycosyl acceptor **36** was coupled with phthalimide-protected glycosyl chloride donor **166** in the presence of 1.5 equiv of Ag_2O and 0.5 equiv of TfOH afforded disaccharide **167** in 97% yield. However, upon switching to less reactive secondary acceptors the yields dropped to 68–76%. Sialic acid chloride **168** was glycosidated with the primary glycosyl acceptor **55** allowing disaccharide **169** in an excellent yield of 97% yield, albeit with poor stereoselectivity.

4.2.2. Organocatalytic Activation. These classical methods were state-of-the-art until recently, when new methods for the activation of glycosyl chlorides have emerged. The first new method was introduced by the Ye group in 2016.[145] Using a variety of benzylated glycosyl chlorides, 20 mol % of Schreiner's catalyst **170** and 2.0 equiv K_2CO_3 in benzene at 80 °C the respective disaccharides were produced in high yields (80%+). At first, these reactions were rather slow (24 h), and the stereoselectivity was poor. Thus, glycosylation between glycosyl chloride donor **142** and primary acceptor **36** gave disaccharide **165** in 95% yield as an anomeric mixture (α/β = 1:1, Scheme 41A). When the same reaction was carried out in the presence of 1.5 equiv of tris(2,4,6-trimethoxyphenyl)-phosphine (TTMPP) as an additive, the anomeric stereoselectivity could be improved to a commendable α/β = 12.6:1. The improvement of stereoselectivity with TTMPP was seen throughout a series of glycosyl acceptors. On the basis of the NMR data, the authors theorized that TTMPP noncovalently interacted with the anomeric carbon from the β-face. This interaction directed the acceptor attack from the opposite face giving rise to α-linked glycosides.

In 2019, McGarrigle[360] applied the Appel conditions (*vide supra*) to the synthesis of glycosyl chlorides followed by their glycosidation in one pot. The treatment of hemiacetal **141** with

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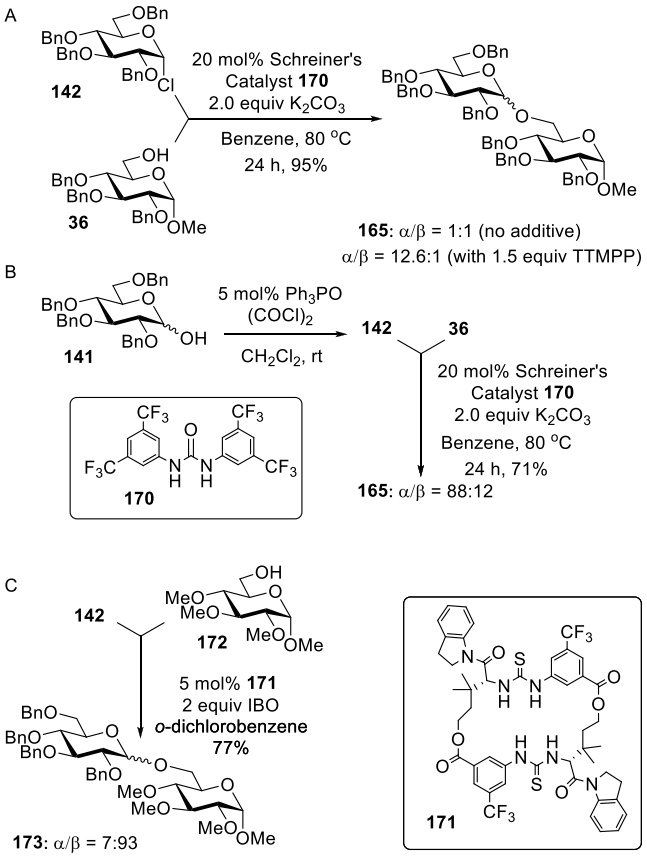
Scheme 41. Glycosyl Chloride Activation Using Thioureas

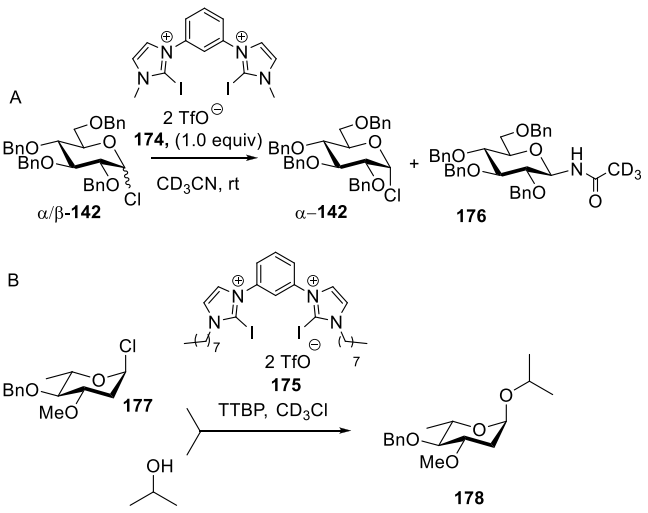


Ph_3PO and oxalyl chloride in dichloromethane produced glycosyl chloride **142**. Then glycosyl acceptor **36** was added *in situ* along with 20 mol % of Schreiner's catalyst **170**, 2.2 equiv of K_2CO_3, and 20 mol % of TTMPP (Ye's conditions, Scheme 41B). This one-pot approach led to a decrease in yield of disaccharide **165** that was obtained in 71% yield (vs 95% reported by Ye) with an anomeric ratio of α/β = 88:12.

The Jacobsen group developed thiourea catalyst **171**,[70] which cooperatively activates both the glycosyl chloride donor and the glycosyl acceptor. The glycosyl chloride donor hydrogen bonds with the thiourea portion of catalyst **171**, which enhances its leaving group ability. At the same time, the incoming nucleophile is also activated by the catalyst via Lewis basic interactions with the carbonyl oxygen of the amide of the catalyst. The combination of these two activations by the catalyst leads to an S_N2-like displacement. These reactions were conducted in the presence of 5 mol % of **171**, 2 equiv of isobutylene oxide (IBO), which acts as an electrophilic trap for the released HCl, in *o*-dichlorobenzene. Reacting donor **142** with acceptor **172** using the conditions above gave disaccharide **173** in 77% yield (α/β = 7:93, Scheme 41C). Other sugars showed similar yields and stereoselectivity. To prove that these glycosylations undergo an S_N2-like displacement, the authors also studied the glycosyl chloride configuration at the anomeric center. It was determined that an α-chloride leaving group gave primarily the β-linked product whereas a β-chloride gave predominantly the α-linked product. This trend was seen throughout a series of glycosyl chlorides, showing that these reactions follow an S_N2-like displacement of the leaving group, without the formation of an oxacarbenium ion intermediate.

Codee and co-workers developed a halogen bond-mediated activation method for glycosyl chlorides. For that purpose iodoimidazolium compounds **174** and **175** was employed as halogen-bond donors.[372] NMR experiments were performed to establish the activation of 2,3,4,6-tetra-*O*-benzyl α,β-glucosyl chloride **142** that was treated with bis(iodoimidazolium) compound **174** (1.0 equiv) in CD_3CN in an NMR tube (Scheme 42A). Based on NMR signals and LC-MS data it was

Scheme 42. Halogen Bond-Mediated Activation of Glycosyl Chloride



suggested that more reactive β-glycosyl chloride was completely consumed and furnished anomeric acetamide **176** by a Ritter type process[373] while the α-anomer did not react. Later, it was realized that the stable α-anomer requires longer duration (several weeks) for activation under these reaction conditions. Several control experiments were performed to confirm that halogen-bond activation was essential for activating the anomeric C−Cl bond. In a separate NMR experiment, it was shown that glucosyl bromide is more reactive than corresponding chloride however, its use is restricted by lower stability and spontaneous decomposition. To explore the ability of the dicationic halogen-bond donors to promote the synthesis of *O*-glycosidic linkages, several attempts were made. When the reactive L-oleandrosyl chloride **177** was treated with isopropyl alcohol in the presence of a lipophilic halogen bond activator **175** and 2,4,6-tri*tert*-butyl pyrimidine as an acid scavenger a satisfactory conversion to corresponding glycoside **178** was achieved as shown in Scheme 42B. This method was largely limited to highly reactive glycosyl chlorides.

4.2.3. Catalytic Activation with Iron, Bismuth, or Palladium Salts. In 2018, Geringer and Demchenko introduced the first catalytic glycosidation of glycosyl chlorides.[374] Thus, benzylated glucosyl chlorides could be readily glycosidated in the presence of only 20 mol % of iron(III) chloride ($FeCl_3$) and molecular sieves (4 Å) in dichloromethane. These glycosylations led to the corresponding disaccharides in moderate to good yields (47−80%). For example, glycosidation of chloride **142** with primary acceptor **36** afforded disaccharide **165** in 67% yield (α/β = 1.1:1, Scheme 43). Somewhat modest yields in these glycosylations were partially attributed to the formation of an undesirable side product, 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose.

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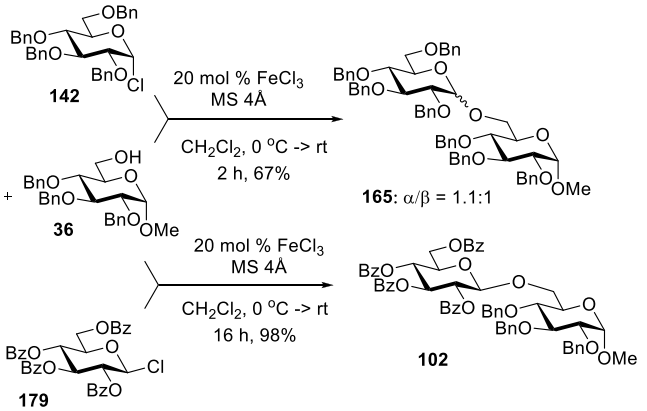
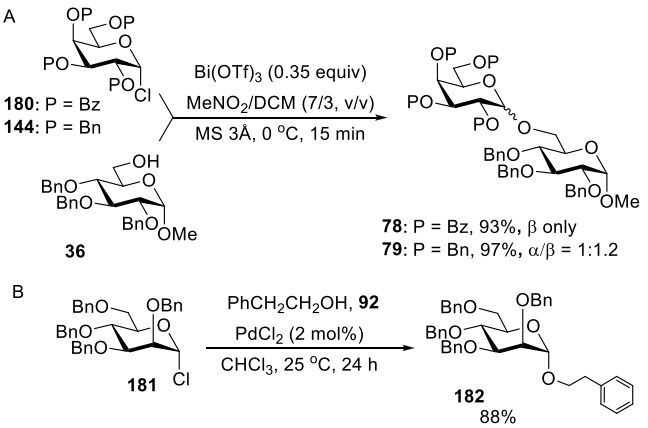
Scheme 43. Glycosyl Chloride Activation Using Catalytic $FeCl_3$



Notably, switching to benzoylated glucosyl chlorides or either mannosyl or galactosyl chlorides, resulted in an increase in yields to 52−98% depending on the acceptor. For example, the reaction of benzoylated chloride **179** with acceptor **36** afforded disaccharide **102** in 98% yield as shown in Scheme 43. In these cases, no 1,6-anhydro derivative formation was noticed. The proposed reaction mechanism follows a traditional Lewis acid-mediated reaction according to which $FeCl_3$ associates with the corresponding glycosyl chloride, causing the activated glycosyl donor to form. The chloride then leaves resulting in the formation of the oxacarbenium ion, which was the cause of the poor stereoselectivity observed in most glycosylations with benzylated glycosyl bromides due to the ability of the acceptor to attack from either side of the flattened chair. Besides being catalytic, the ability to glycosylate the disarmed, benzoylated sugars was advantageous over previously described methods.

In 2021, Demchenko and co-workers have developed very mild reaction conditions for the activation glycosyl chlorides in the presence of bismuth(III) triflate.[308] This reaction worked similarly to that of glycosylation with glycosyl bromides. Tetra-benzoylated and tetra-benzylated galactosyl chlorides **180** and **144** were glycosidated with glycosyl acceptor **36** in the presence of $Bi(OTf)_2$ (0.35 equiv) to produce galactosides **78** and **79**, respectively (Scheme 44A). An interesting observation was made when activation of glycosyl chlorides and bromides were compared. The activation of galactosyl chloride **180** was faster (15 min) when compared with the activation of a similarly protected galactosyl bromide **40** (30 min). Benzylated galactosyl chloride **144** produced galactoside **79** in a better yield (97%, α/β = 1/1.2) when compared to results from benzylated galactosyl bromide **34** (78%, α/β = 1/1.1).

Scheme 44. Bismuth(III)- and Palladium(II)-Catalyzed Activations of Glycosyl Chlorides

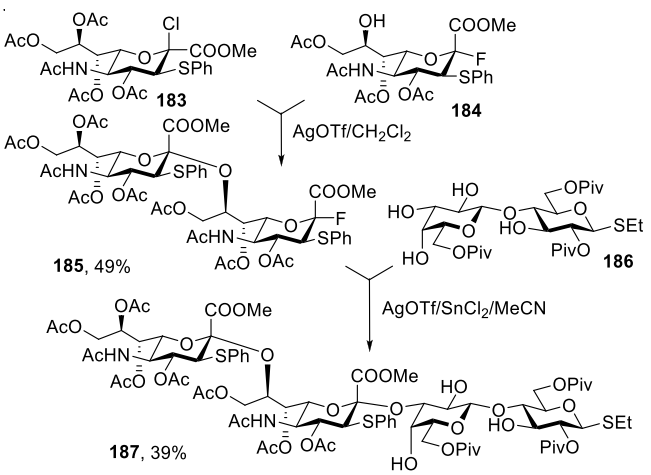


Very recently, Chen and co-workers developed a new protocol to activate glycosyl chloride donors to synthesize *O*-glycosides using palladium(II) reagents.[375] On the basis of their previous work of palladium-catalyzed *C*-aryl glycoside synthesis, the authors established that palladium acetate can serve as a Lewis acid that will interact with the chloride leaving group thereby activating the anomeric C−Cl bond.[376] To broaden the scope of this approach to the synthesis of *O*-glycosides, 2,3,4,6-tetrabenzyl mannosyl bromide **181** was treated with 2-phenylethanol **92** in the presence of 2 mol % of $Pd(OAc)_2$ in chloroform at room temperature (Scheme 44B). The glycosylation produced glycoside **182** in 88% yield with exclusive α-stereoselectivity. By tuning the reaction temperature (25 to 110 °C) and amount of $Pd(OAc)_2$ (2 to 5 mol %), various glycosyl acceptors were glycosylated producing the respective products in good to excellent yields with exclusive α-stereoselectivity. Glycosyl donors of different sugar series including gluco, galacto, rhamno, ribofurano, and mannofurano were also investigated. Glycoside products were obtained in good yields; however, the stereoselectivity was difficult to predict.

4.3. Glycosyl Chlorides in Glycan and Glycoconjugate Synthesis

2-Chloro and 2-fluoro sialic acid derivatives **183** and **184**, both bearing a participating 3-*S*-phenyl auxiliary, have been employed for the preparation of tetrasaccharide **187** using a selective activation strategy.[367,377] Glycosyl fluorides are stable toward the reaction conditions required for the activation of glycosyl chlorides. Thus, coupling of sialyl chloride donor **183** with 8-OH sialyl fluoride acceptor **184** in the presence of AgOTf gave (2→8)-linked dimer **185** in 49% yield with complete α-stereoselectivity (Scheme 45). The resulting dimer **185** was used in the subsequent glycosylation of thiolactosyl acceptor **186** in the presence of the $AgOTf/SnCl_2$ promoter system. The resulting tetrasaccharide **187** was obtained in 39% yield and its anomeric thioglycoside moiety can be activated for subsequent glycosylations directly.

Scheme 45. Selective Activation of Sialyl Chloride 142 over Sialyl Fluoride 167



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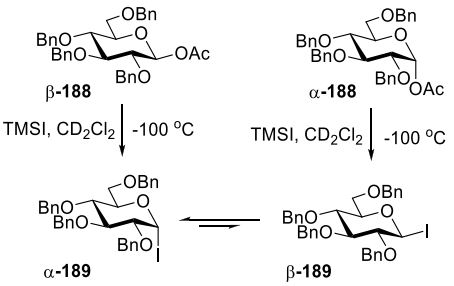
5. GLYCOSYL IODIDES

5.1. Synthesis of Glycosyl Iodides

The first synthesis of glycosyl iodides was reported by Fischer, who synthesized 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl iodide by reaction of per-*O*-acetylated glucose with HI.[148] Fischer also noted that the glycosyl iodide quickly reacted with methanol in the presence of silver carbonate to afford the methyl glycoside. The field did not have much growth until 1974 when Kronzer and Schuerch[315] discovered that the glycosidation of benzylated glucosyl bromides could be promoted by the addition of sodium iodide. These glycosylation reactions were performed under metal-free conditions and presumed to occur through the intermediacy of glycosyl iodides.

Shortly thereafter, Thiem and Meyer[207] reported that glycosyl iodides could be synthesized from a variety of precursors such as anhydrosugars, methyl glycosides, and per-acetylated hexoses using TMSI. This discovery allowed for the synthesis of many glycosyl iodide donors that for the first time became readily available. However, only acetylated glycosyl iodides were sufficiently stable to be fully characterized. Benzylated iodides were deemed too unstable and had to be synthesized and used in subsequent glycosylations *in situ*.[51] This was the case until Gervay et al. devised a technique to fully characterize benzylated glycosyl iodides by monitoring their formation in the presence of TMSI in CD_2Cl_2 at −100 °C in an NMR spectrometer.[378] The authors found that the anomeric peaks appeared as a doublet at either 6.68 ppm for α-glycosyl iodide **189** or at 5.61 ppm for β-glycosyl iodide. The ratios of these products depended on the configuration of the anomeric acetate in the substrate, α- or β-acetate **188**. Regardless of the initial configuration, the iodide displaced the acetates in an S_N2-like manner. Following the displacement, anomerization of the β-iodide rapidly occurs to the thermodynamically stable α-iodide (Scheme 46). Following these first major mechanistic studies, glycosyl iodides found a much broader application in synthetic chemistry.

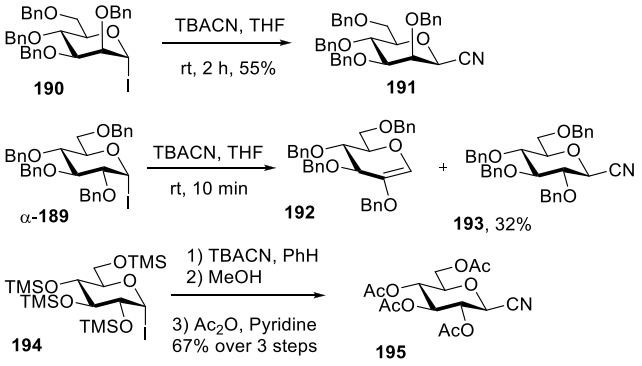
Scheme 46. Anomerization of Glycosyl Iodides



5.2. Glycosidation of Glycosyl Iodides

Among the first applications of glycosyl iodides as donors was the synthesis of *C*-glycosides that were shown to form in an S_N2-like manner with direct displacement of the glycosyl iodide with the nucleophile. Using tetrabutylammonium cyanide (TBACN) in tetrahydrofuran (THF) and α-mannosyl iodide **190**, β-cyanoglycoside **191** was obtained in 55% yield (Scheme 47).[379] While this reaction worked well with the mannose iodide, glucosyl iodide α-**189** produced β-cyanoglycoside **193** in a modest yield of 32% along with the major side product oxyglycal **192** resulting from the competing E2

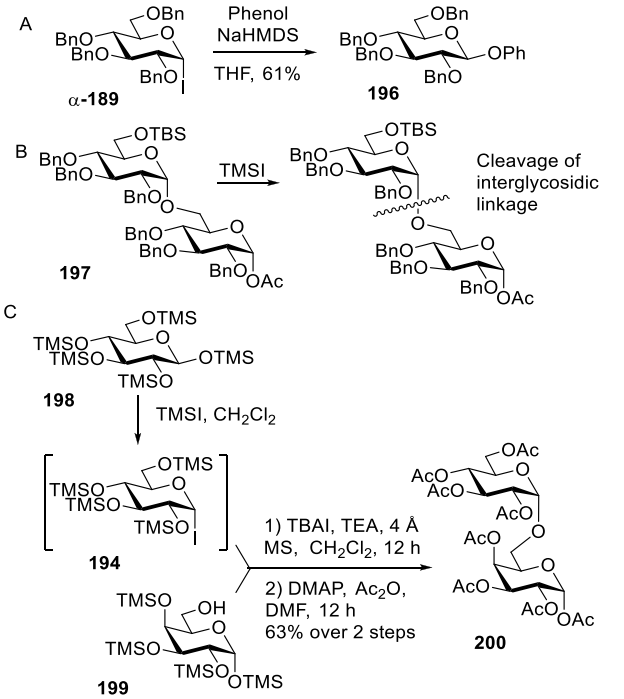
Scheme 47. Synthesis of *C*-Glycosides Using Glycosyl Iodides



elimination reaction. Switching to glucosyl iodide **194** equipped with TMS ethers allowed for a much more successful synthesis of the corresponding β-cyanoglucoside. This was accomplishe using TBACN in toluene, followed by the cleavage of the TMS groups that was affected by addition of MeOH, and subsequent acetylation using Ac_2O in pyridine to give **195** in an overall yield of 67%. Similar *C*-glycoside formation was accomplished by using Grignard reagents in the synthesis of the glycolipid BbGL2, as reported by Kulkarni and Gervay-Hague.[380]

The synthesis of *O*-glycosides has also been approached from glycosyl iodides. When small nucleophiles were used such as phenol with NaHMDS in THF, glycosyl iodide α-**189** gave phenol glycoside **196** in 61% yield (Scheme 48A). Other small nucleophiles such as sodium acetate or sodium tert-butoxide worked well giving complete β-stereoselectivity following direct displacement of the α-iodide.[9,381] Synthesis of the disaccharide has also proven to be straightforward, however, converting the disaccharide into the second-generation

Scheme 48. Synthesis of *O*-Glycosides Using Glycosyl Iodides



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glycosyl donor was troublesome. During displacement of the *O*-acetyl anomeric group from anomeric acetate **197** to the iodide donor, cleavage of the interglycosidic bond has occurred (Scheme 48B). This problem was solved by Lam and Gervay-Hague[382] by a simple addition of an acetate (or other electron-withdrawing) group at the C-6 position of the glycosyl donor. This modification allowed for the synthesis of oligosaccharide derivatives using both solid phase and solution phase strategies using TBAI as a promoter system. Other promoter systems used for the synthesis of oligosaccharides include AgOTf,[382] tetrabutylammonium bromide/Na_2CO_3,[383] $AgNO_3$,[384] ZnI,[385] and TBAI/DIPEA.[386]

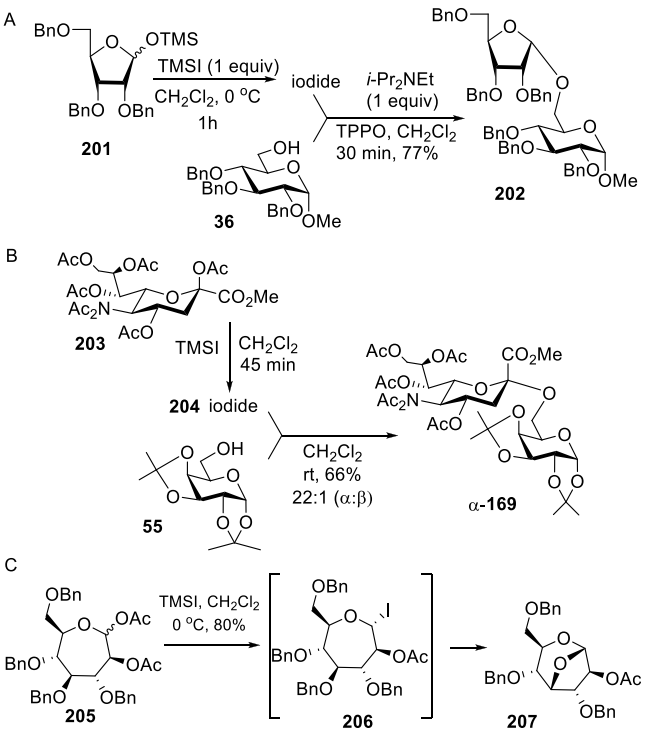
Another method to help combat the interglycosidic bond cleavage employs fully trimethylsilyl protected substrates. Introduced by Gervay-Hague and co-workers,[387] this approach allowed to achieve high yields in glycosidations of per-*O*-silylated galactosyl iodides. This approach was successfully applied to α-stereoselective synthesis of glycolipids, however some decline in yields was seen due to the formation of silylated acceptors as side products. The reaction was not perfected until later when Gervay-Hague[388] found that the formation of silylated side products can be suppressed by reducing the amount of TBAI to 1.5 equiv as opposed to 3.0 equiv used previously. Since this discovery, many research groups have used per-*O*-silylated sugars to synthesize a variety of natural products.[389−391] Glycosyl iodides have been used in a variety of ways that were comprehensively discussed in previous reviews by Kulkarni,[392] Lowary,[393] and Gervay-Hague.[394]

More recently, Zhang and co-workers[395] expanded the scope of per-silylated glycosyl donors such as **198** and improved the outcome of the reaction by supplementing TBAI-promoted glycosylations with triethylamine (Scheme 48C). Under these conditions, glycosyl donor **198** was reacted with glycosyl acceptor **199** to form disaccharide **200** in 63% yield over two steps after subsequent acetylation. These reactions worked well with a variety of sugar series such as glucosyl, galactosyl, and fucosyl donors.

Glycosyl iodides were also used in α-stereoselective ribofuranosylation of alcohols.[396] Ribofuranosyl iodide could be generated using TMSI from precursor **201** (Scheme 49A). Following the addition of *i*-Pr_2NEt and triphenylphosphine oxide, which acts as an additive to improve α-stereoselectivity, and glycosyl acceptor **36**, ribofuranosylation would occur. As a result, disaccharide **202** was obtained in 77% yield with complete α-stereoselectivity. These conditions worked well for a variety of glycosyl acceptors ranging from primary aliphatic alcohols to hindered sugar alcohols with yields of 75% or higher. Ribosylation was also studied by Houston and Koreeda[397] using *i*PrOH as the glycosyl acceptor in the presence of I_2 as a promoter in THF. This reaction gave the corresponding β-ribosides in high yields. The authors also found that ribosylations performed in the presence of acetone led to the formation of a 1,2-*O*-isopropylidene derivative instead.

The most recent advancement in the application of glycosyl iodides was reported by Park and Gervay-Hague.[398] The authors achieved the first, promoter-free sialylations with sialyl iodides, which was applied to the synthesis of steryl β-sialosides. These glycosylations only worked with C-5 modified sialic acid donors, whereas traditional *N*-acetamido sialic acids underwent 2,3-elimination upon the attempt to obtain a sialyl iodide donor. However, when 5-*N*-acetylacetamido precursor

Scheme 49. Glycosidation of Iodides of Different Series



203 was investigated, the corresponding α-iodide donor **204** was smoothly produced (Scheme 49B). Sialylation could then be performed in a one-pot manner at rt; for example, reaction of the primary glycosyl acceptor **55** gave disaccharide **169** in 66% yield with excellent α-stereoselectivity (α:β = 22:1). Cholesterol-based acceptors provided respectable yields ranging from 52% to 85% giving sialosides with complete β-stereoselectivity.

Applications of glycosyl iodides in synthesis span beyond their use as glycosyl donors. For instance, glycosyl iodides were used as precursors in the formation of 1,4-anhydroseptanoses.[399] As depicted in Scheme 49C, septanose **205** was reacted with TMSI to form septanosyl iodide **206** that readily rearranged to form 1,4-anhydroseptanose **207** in 30 min in 80% yield. This rapid cyclization was occurring in septanoses derived from glucose, mannose, xylose, and galactose.

Bennett and co-workers reported a dehydrative glycosidation of 2-deoxy and 2,6-dideoxy-sugars in the presence of 3,3-dichloro-1,2-diphenylcyclopropene **209**, tetrabutylammonium iodide (TBAI), and *N*,*N*-diisopropylethylamine (DIPEA).[400] The authors assumed that the treatment of benzyl protected 2-deoxy hemiacetal **210** under these reaction conditions will lead to the *in situ* formation of the corresponding glycosyl iodide **211**. The latter will then be trapped with cholesterol **212** to produce glycoside **213** in 72% yield with preferential α-selectivity (α/β = 4:1, Scheme 50A). Increasing the amount of TBAI to 5.0 equiv increased the yield of **213** to 82%, however, there was no apparent change in stereoselectivity. Similarly, an α-selective formation 2,6-dideoxyglycosides was achieved.

The authors proposed a stepwise mechanistic conversion. 3,3-Dichloro-1,2-diphenylcyclopropene **209** is postulated to exist in equilibrium with intermediate B (Scheme 50B). The latter assists conversion of hemiacetal **210** to the corresponding anomeric chloride **146** through a reactive intermediate C. As evident from NMR experiments, anomeric chloride **146**

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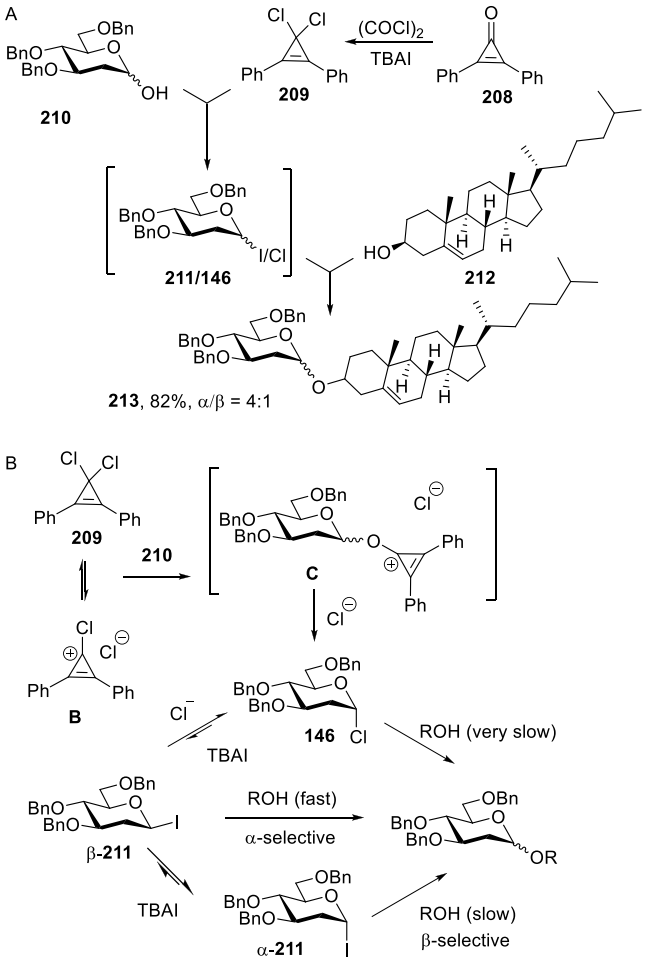
Scheme 50. Dehydrative Glycosidation of Hemiacetals

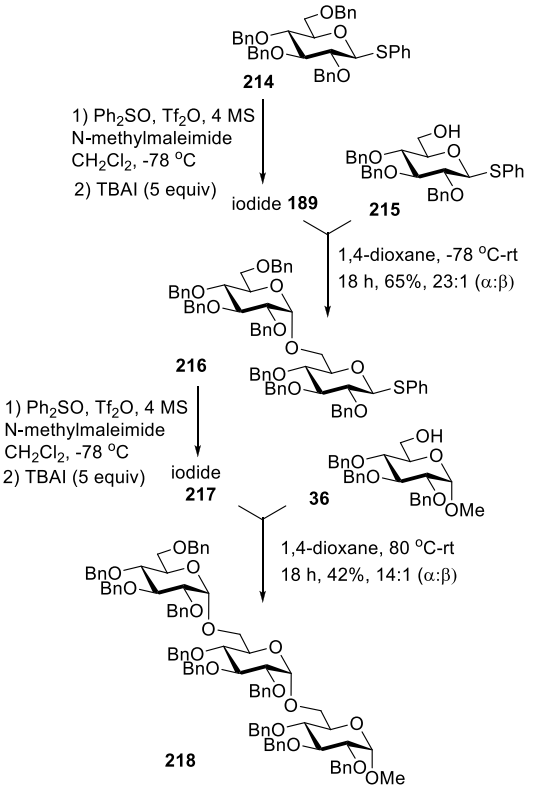


exists in equilibrium with another species that is postulated to be either α-**211** or β-**211**. Excess iodide (TBAI) in reaction mixture promotes equilibrium between stable α-**211** and its reactive counterpart β-**211**. The fact that preferential α-selective was observed for the products suggests that glycosyl acceptor might be approaching β-iodide intermediate **211** in an S_N2-like fashion.

5.3. Glycosyl Iodides in Glycan and Glycoconjugate Synthesis

Bennett used a glycosyl iodide generated *in situ* for the synthesis of α-glycosides without directing groups.[88] Starting from stable thioglycoside **214**, the corresponding anomeric triflate was generated in the presence of Ph_2SO, Tf_2O, and 4 Å molecular sieves in dichloromethane at −78 °C (Scheme 51). Following generation of the glycosyl triflate *in situ*, 5 equiv of TBAI was added to produce glycosyl iodide **189**. 1,4-Dioxane was then added to improve α-stereoselectivity along with glycosyl acceptor **215**. As a result, disaccharide **216** was synthesized in 65% yield in excellent α-stereoselectivity ($\alpha \rightarrow \beta$ = 23/1). This reaction sequence was reiterated with *in situ* generated iodide **217** and glycosyl acceptor **36** allowing for the synthesis of trisaccharide **218**. However, a modest yield of 42% was observed since a sterically bulky glycosyl donor was used at this stage.

Scheme 51. Iterative Synthesis of Trisaccharide 196 Using Glycosyl Iodides



6. GLYCOSYL FLUORIDES

The early expansion of synthetic carbohydrate chemistry was made possible due to the improved understanding of the mechanistic aspects of glycosylation with glycosyl halides (mainly chlorides and bromides) as donors. The synthesis of glycosyl fluorides has been known for a long time, but their glycosidation under Koenigs-Knorr conditions is impossible due to their higher stability. This demanded further investigation, and Mukaiyama and co-workers were the first to show the activation of glycosyl fluorides in the presence of Lewis acids such as tin(II) chloride ($SnCl_2$). The activation protocol was subsequently improved by using silver salts as additives. These early attempts led to the formation of 1,2-*cis* glycosides, which are difficult to synthesize. Following these early discoveries, glycosyl fluorides have become increasingly popular glycosyl donors in synthetic glycochemistry due to a unique combination of high stability and relatively mild Lewis acidic conditions required for their glycosidation.

6.1. Synthesis of Glycosyl Fluorides

Numerous methods for the synthesis of glycosyl fluorides from a variety of precursors have been developed. In the following, all known methods have been categorized by the type of the starting material used for the introduction of the anomeric fluoride moiety.

6.1.1. Preparation from Anomeric Acetates. The very first synthesis of glycosyl fluorides comprised the treatment of per-acetylated sugars with anhydrous hydrofluoric acid. The acid was generated by heating dry potassium hydrogen fluoride allowing for various glycosyl fluorides to be synthesized in 30 min (Scheme 52A).[401] Over the years, milder protocols that are compatible with acid-sensitive functional and protecting groups have been developed. One popular protocol involves

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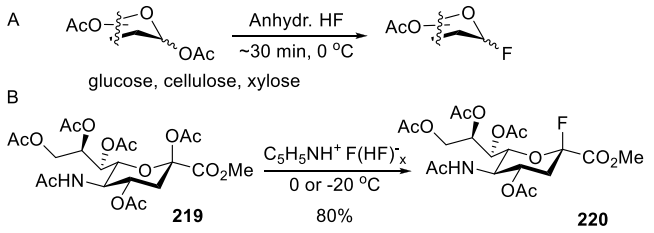
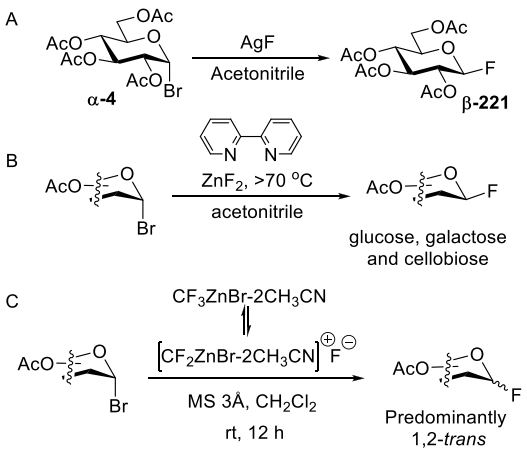
Scheme 52. Synthesis of Glycosyl Fluorides from Acetates



Py-HF complex as a source of HF. Thus, Sharma and Eby employed the fluorination procedure developed by Olah et al.[402] to convert sialic acid **219** to the corresponding β-fluoride **220** (Scheme 52B).[403] Noyori and co-workers extended this approach to different sugar series for the synthesis of anomeric fluorides.[404,405] It was shown that the treatment of a solution of benzyl or acetyl protected glycosyl acetates in toluene with 50 or 70% hydrogen fluoride-pyridine mixture readily produced the corresponding fluorides in good to excellent yields. This method turned out to be advantageous for the synthesis of thermodynamically favored α-fluorides. Differentially protected hemiacetals are also suitable substrates (*vide infra*), but their conversion to fluorides under these conditions was not as efficient as that from the anomeric acetates.[406]

6.1.2. Preparation from Glycosyl Chlorides and Bromides. Helferich and Gootz performed a halogen exchange reaction to synthesize glucosyl fluorides from the corresponding glucosyl bromides.[407] For example, when 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl bromide α-**4** was treated with silver fluoride (AgF) in acetonitrile the corresponding fluoride β-**221** was afforded in 54% yield after recrystallization (Scheme 53A). Klemer and Micheel extended this approach to

Scheme 53. Synthesis of Glycosyl Fluorides from Other Halides



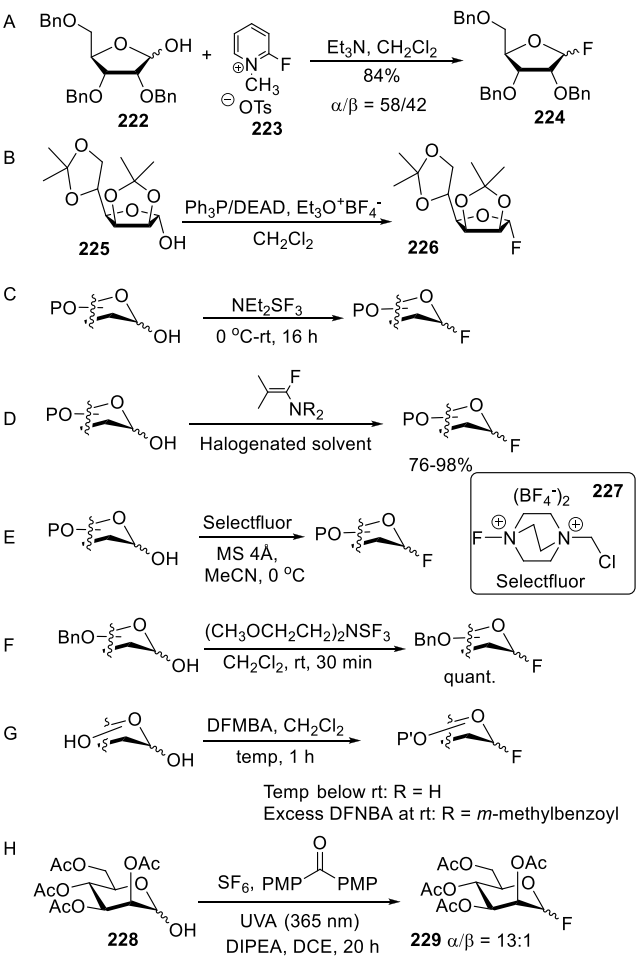
the synthesis of anomeric fluorides of other sugar series from the corresponding glycosyl bromides and chlorides.[408,409] Hall and co-workers employed a similar approach to obtain glycosyl fluorides to study their conformational properties.[410] Igarashi and co-workers reported the synthesis of glycosyl fluorides from the corresponding chlorides in the presence of $AgBF_4$ in ether or toluene.[411]

Walinsky and co-workers also investigated a halogen exchange procedure for the synthesis of glycosyl fluorides.[412] For that, they chose zinc fluoride and the conversion of glycosyl bromides to the corresponding fluorides was successfully conducted in the presence of ZnF_2 alone or in combination with 2,2′-bipyridine (Scheme 53B). Because of the poor solubility of zinc fluoride, these reactions worked best at higher temperatures in acetonitrile. Reactions in the presence of 2,2′-bipyridine were slower, but these conditions led to increased yields of glucosyl fluoride products.

Trifluoromethylzinc bromide (CF_3ZnBr-$2CH_3CN$) was known as a reagent for difluoromethylation reactions.[413−415] Naumann et al. suggested that it can also act as a potential nucleophilic fluorinating reagent.[416] Miethchen and co-workers successfully fluorinated α-bromides of per-acetylated glucose, galactose, mannose, lyxose, and rhamnose in DCM with CF_3ZnBr-$2CH_3CN$ in DCM (Scheme 53C).[417] Predominantly, 1,2-*trans* fluorides were obtained in these reactions. This protocol also worked with hemiacetals (*vide infra*), and the yield could be enhanced with TiF_4 additive. Miethchen and co-workers also achieved bromine−fluorine exchange in the presence of two-phase system Et_3N-3HF/CCl_4.[418,419] This protocol also worked with hemiacetals as starting materials.

6.1.3. Preparation from Hemiacetals. Mukaiyama and co-workers reported the synthesis of glycosyl fluorides from the corresponding hemiacetals.[420] Synthesis of 2,3,5-tri-*O*-benzyl-α/β-D-ribofuranosyl fluoride **224** was achieved by treating the corresponding hemiacetal **222** with 2-fluoro-L-methylpyridinium tosylate **223** in the presence of triethylamine as shown in Scheme 54A. The anomeric fluorides were

Scheme 54. Synthesis of Glycosyl Fluorides from Hemiacetals



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separated by column chromatography, and the α-anomer was shown to equilibrate to β-anomer in the presence of boron trifluoride etherate. Kunz and Sager applied a modified Mitsunobu reaction[421,422] to the synthesis of glycosyl fluorides equipped with acid-sensitive protecting groups.[423] For example, isopropylidene protected mannofuranose **225** was treated with triphenylphosphine (Ph_3P), diethyl azodicarboxylate (DEAD), and triethyloxonium tetrafluoroborate to afford fluoride **226** in 54% yield (Scheme 54B).

Rosenbrook and co-workers successfully applied diethylaminosulfur trifluoride (DAST), a well-known reagent for the direct conversion of alcohols to fluorides[424] to sugar hemiacetals. Thus, when hemiacetals were treated with neat DAST at 0 °C followed by warming to rt, the corresponding anomeric fluorides were produced in good yields (60−91%, Scheme 54C).[425] Concomitantly, Posner and Haines reported DAST-mediated fluorination reactions that were surprisingly fast (20 min) when conducted in THF as the reaction solvent.[426]

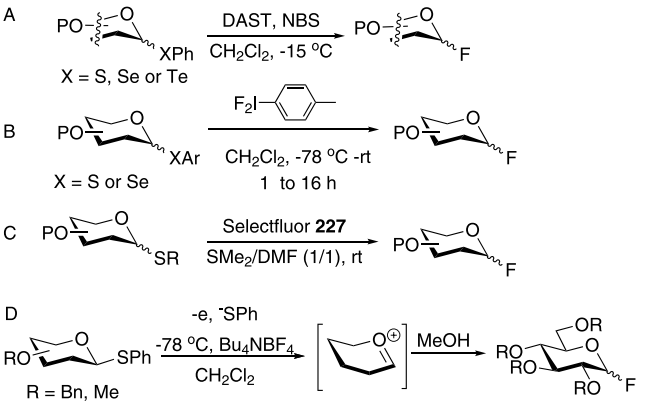
Ernst and Winkler extended the fluorinating property of α-haloenamines, known reagents for the synthesis of acyl[427] and alkyl halides,[428,429] to the synthesis of glycosyl fluorides.[355] Thus, when hemiacetals of pyranose of furanose sugars were treated with 1-fluoro-*N*,*N*,2-trimethylprop-1-en-1-amine or a similar reagent, glycosyl fluorides where produced in 76−98% yield (Scheme 54D). The mild nature of α-haloenamines along with the neutral reaction conditions were found to be compatible with various protecting groups including acetyl, benzoyl, isopropylidene, benzyl, and silyl. 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) **227**,[430] commonly known as Selectfluor, was found to be an efficient reagent for converting hemiacetals to the corresponding fluorides (Scheme 54E).[431] This electrophilic fluorinating reagent was also found to be effective for converting glycals into 2-deoxyglycosyl fluorides. In the presence of SMe_2 additive, Selectfluor also reacted with thioglycosides to produce glycosyl fluorides (*vide infra*).

Thermal instability of DAST hampered its application in large-scale syntheses or reactions at high temperatures.[432] Lal and co-workers developed the bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor) reagent, as a thermally stable analogue of DAST.[433] Deoxo-Fluor is also a more efficient fluorination reagent compared to DAST as evidenced by a quantitative conversion of hemiacetal derivatives to the corresponding anomeric fluorides (Scheme 54F). Hara and co-workers reported the synthesis of glycosyl fluorides by treating hemiacetal derivatives with *N*,*N*-diethyl-α,α-difluoro-(*m*-methylbenzyl)amine (DFMBA) as shown in Scheme 54G.[434,435] It was noticed that hydroxyl groups at nonanomeric positions were not affected at low temperatures. However, the reactions performed in the presence of excess DFMBA would lead to *m*-methylbenzoylation along with the anomeric fluorination.

Nagorny and co-workers developed photochemical reaction conditions for the synthesis of glycosyl fluorides from the corresponding hemiacetals.[436] For that, the authors employed sulfur(VI) hexafluoride, which is an inexpensive and mild fluorinating reagent, along with a photocatalyst. As shown in Scheme 54H, fluorination of 2,3,4,6-tetra-*O*-acetyl-D-mannose **228** with SF_6 (gas, 1 atm) in the presence of photocatalyst 4,4′- dimethoxybenzophenone (30 mol %) using a UV-A LED source (λ_{max} = 365 nm) produced the corresponding mannosyl fluoride **229** in 70% yield (α/β = 13:1). Different sugar series with a variety of protecting groups were investigated, and glycosyl fluorides were obtained in yields of 43−97%. Further, the authors successfully showed gram scale formation of glycosyl fluorides in continuous flow systems and using electrochemical synthesis.[437]

6.1.4. Preparation from Thio- and Selenoglycosides. Nicolaou and co-workers reported the direct conversion of phenylthio glycosides to glycosyl fluorides.[333] Phenylthio glycosides were first treated with DAST followed by *N*-bromosuccinimide (NBS) to afford the corresponding glycosyl fluorides (Scheme 55A). This method is very effective, and

Scheme 55. Synthesis of Glycosyl Fluorides from Chalcone Glycosides



several common protecting groups and *O*-glycosidic linkages were tolerated effortlessly. This method has created a basis for developing a two-stage activation and orthogonal strategies for glycan assembly (*vide infra*). Because of the similarity between thioglycosides and other chalcogen glycosides, Horne and Mackei converted phenylseleno and phenyltelluro glycosides to the corresponding glycosyl fluorides in the presence of DAST and NBS/NIS.[438] The stereochemistry of obtained glycosyl fluorides was found to depend on various factors such as substituents at C-2, the nature of solvents, and the stereochemistry of starting materials.

Synthesis of several glucosyl fluorides was also achieved by treating arylthio glycosides with iodoarene difluoride reagents. Originally developed for noncarbohydrate substrates,[439] Motherwell and co-workers then extended their studies to the synthesis of glycosyl fluorides from thioglycosides[440] and selenoglycosides (Scheme 55B).[441] As aforementioned, Wong's approach to synthesizing fluorides with Selectfluor could be applied to hemiacetals, glycals, and thioglycosides as substrates.[431] The latter required the use of dimethyl sulfide along with Selectfluor (Scheme 55C). Yoshida and co-workers attempted to isolate glycosyl cation intermediate by the "cation pool" method.[442] Although this attempt was unsuccessful, the formation of glycosyl fluorides was achieved with the right combination of electrolytes.[443] A low-temperature electrolysis reaction was conducted in the presence of Bu_4NBF_4 in CH_2Cl_2. Subsequent addition of methanol did not produce methyl glycosides, but rather afforded corresponding glycosyl fluorides in good yields (Scheme 55D). Subsequently, the authors figured out the one-pot glycosylation method by replacing Bu_4NBF_4 with other suitable electrolytes.

6.1.5. Preparation from Other Substrates. Danishefsky and Gordon reported the synthesis of 3,4,6-tri-*O*-benzyl-β-D-

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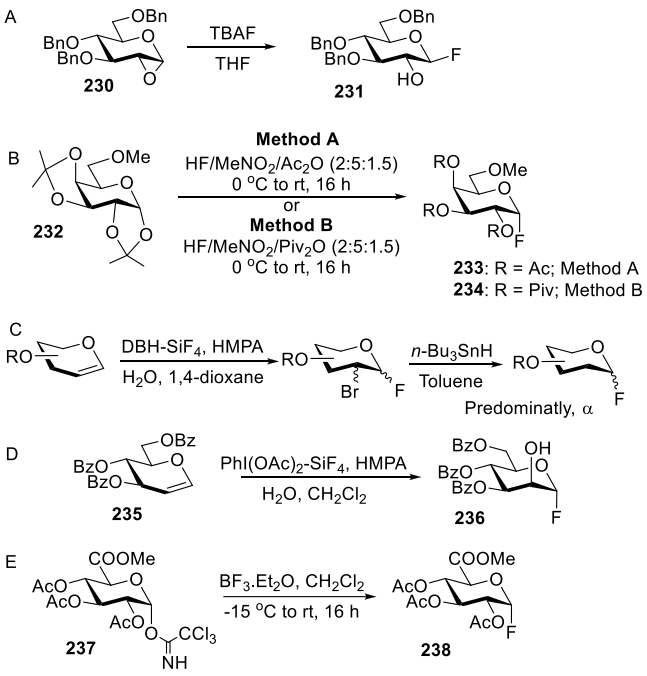
glucopyranosyl fluoride **231** by treating 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose **230** with tetrabutylammonium fluoride (TBAF, Scheme 56A).[444] Though the yield was

Scheme 56. Synthesis of Glycosyl Fluorides from Other Starting Materials



moderate (53%), the method is uniquely suited to produce the β-anomer only. Miethchen and co-workers prepared a fluorinating reagent by mixing anhydrous HF with acylating reagents to perform glycosyl fluoride synthesis and protection in one pot.[445] Thus, a homogeneous mixture of HF/$MeNO_2$/Ac_2O (2/5/1.5, Method A) or HF/$MeNO_2$/Piv_2O (2/5/1.5, Method B) was found to transform 1,2:3,4-di-*O*-isopropylidene-6-*O*-methyl-α-D-galactopyranose **232** and other similar derivatives to the corresponding tri-*O*-acylated fluorides such as **233** and **234** as depicted in Scheme 56B. Protecting groups that are compatible with these conditions are alkyl, acyl, alkyl sulfone, etc.

As aforementioned, Selectfluor is another efficient method for converting glycals to the corresponding 2-deoxy-2-fluoro derivatives.[431] Shimizu and co-workers developed a protocol for bromofluorination of olefins with silicon tetrafluoride and 1,3-dibromo-5,5-dimethylhydantoin (DBH),[446] which was later applied to the synthesis of 2-deoxyglycosyl fluorides.[447] This was accomplished via sequential bromofluorination of glycals followed by debromination as shown in Scheme 56C. First, bromofluorination of glycals derived from glucose, galactose, rhamnose, and fucose was conducted with SiF_4, DBH, hexamethylphosphoric triamide (HMPA) in water/1,4-dioxane to produce the corresponding 2-bromoglycosyl fluoride derivatives. The latter were then subjected to debromination with tributyltin hydride (n-Bu_3SnH) to afford the corresponding 2-deoxyglycosyl fluorides. The same authors also described hydroxyfluorination of glycals in the presence of $PhI(OAc)_2$, SiF_4, and HMPA. As shown in Scheme 56D, under these reaction conditions, α-mannosyl fluoride **236** was obtained from glucal precursor **235** in 73% yield.

Von Itzstein and co-workers observed the formation of glycosyl fluorides from *O*-imidates.[448] As shown in Scheme 56E, the treatment of glycosyl imidate **237** with BF_3-Et_2O (1.0 equiv) resulted in the formation of α-fluoride **238** in 24%. This reaction was accompanied by the formation of a hemiacetal derivative because of competing hydrolysis. Jones and co-workers reported the synthesis of 1-fluorocellobiosyl fluoride by treating the corresponding diazirine derivative with xenon difluoride (XeF_2).[449]

6.2. Glycosidation of Glycosyl Fluorides

Many different reagents and cooperative systems for the activation of glycosyl fluorides have been developed. To streamline the discussion, we chose to divide the activating reagents into different categories based on their fluorophilic nature (Table 2). The discussion begins from tin salts that were very instrumental for understanding the metal salt involvement in splitting the anomeric C−F bond and investigating the effects of different additives and the counteranions. We will then focus the discussion on how those studies enabled scientists to develop improved methods, and how the improved methods enhanced our synthetic capabilities. Recent studies dedicated to conformational analysis of glycosyl cations generated from glycosyl fluorides significantly enhanced our understanding of processes behind typical glycosylation reactions.[450]

6.2.1. Activation with Group 14-Based Reagents (Tin and Silicon). Mukaiyama and co-workers discovered that glycosyl fluorides can be activated by a cooperative effect of tin(II) chloride ($SnCl_2$, stannous chloride) and silver perchlorate ($AgClO_4$) to afford glycosides in excellent yields.[8] The glycosylation under these reaction conditions often proceeds in a stereoselective manner affording 1,2-*cis* α-glycosides predominantly. As shown in Scheme 57A, glycosidation of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl fluoride **239** with various aliphatic and sugar acceptors provided the respective products in good yields of 76−96% and respectable stereoselectivity. A similar approach was extended to the synthesis of 1,2-*cis* glycofuranosides.[420] However, these reactions were predominantly 1,2-*trans* stereoselective. Interestingly, replacing silver perchlorate with trityl perchlorate ($TrClO_4$) additive allowed to obtain the respective products with predominant 1,2-*cis* stereoselectivity (Scheme 57B).

Subsequently, Mukaiyama and co-workers extended their study to $SnCl_2$ in combination with $AgB(C_6F_5)_4$ as a stable and useful reagent for generating the active catalyst.[451] This study also revealed that MS 5 Å additive (3 g/mmol) is necessary to achieve efficient activations. The cooperative catalytic activation was achieved by the combined use of $SnCl_2$ and $AgB(C_6F_5)_4$, 20 mol % each, in toluene. It was suggested that $SnB(C_6F_5)_4Cl$ is an active catalyst for the activation of glycosyl fluoride **240** (Scheme 57C). An important aspect of this cooperative catalyst is that it does not work well in polar solvents, which was attributed to deactivation of Lewis acid by coordination to stannous cation. This cooperative system led to a successful installation of different linked disaccharides. For example, Yamada and co-workers activated the 3,6-*O*-bridged glucosyl fluoride donor **241** under these reaction conditions to obtain β-linked products, for example **242**, with complete stereoselectivity (Scheme 57D).[454] The key to this exclusive β-stereoselectivity was due to the following two factors. First, the ability of the bridging positions C-3 and C-6 to force the sugar substituents to lock into the axial positions. Second, isomer-

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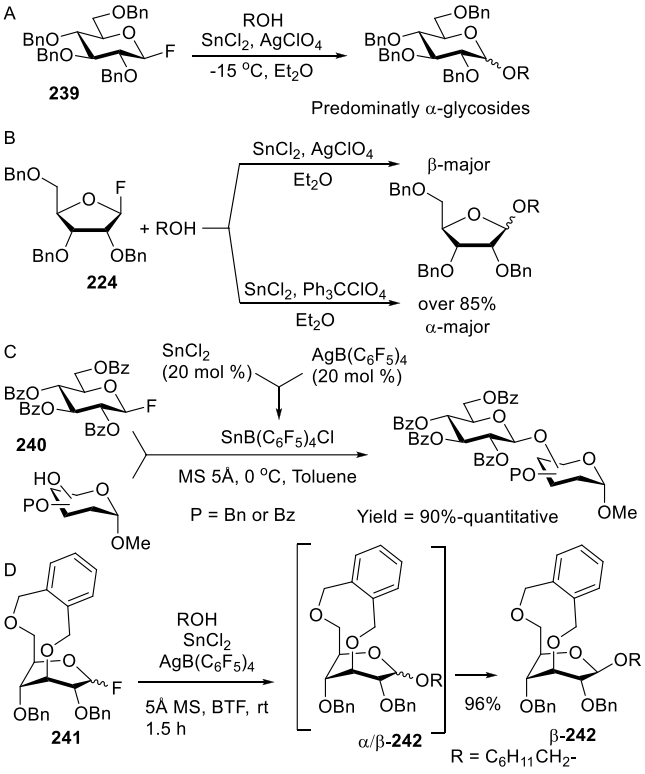
Table 2. Activation of Glycosyl Fluoride Donors

promoter	additive
tin- and silicon-based reagents	
$SnCl_2$[8,420]	$AgClO_4$,[8,451] $TrClO_4$,[420] AgOTf,[451,452] $AgB(C_6F_5)_4$[451,453,454]
$SnCl_4$[455]	$AgB(C_6F_5)_4$[453]
SnF_4[456]	
R_3SnCl or R_2SnCl_2[457]	$AgClO_4$[457]
$Sn(OTf)_2$[458]	BF_3-Et_2O, $TiCl_4$, $La(OTf)_3$, $Yb(OTf)_3$ or $La(ClO_4)_3$-nH_2O[459]
SiF_4[404]	
$CF_3SO_3SiMe_3$[404,456,460]	
$SiCl_4$ or Ph_3SiCl[453]	$AgB(C_6F_5)_4$[453]
boron-, aluminum-, and gallium-based reagents	
BF_3-Et_2O[423,455,461]	
$TrB(C_6F_5)_4$[462,463]	
$HB(C_6F_5)_4$[464,465]	
$B(C_6F_5)_3$[466]	
$AlMe_3$[455]	
Me_2GaCl, Me_2GaOTf or $MeGa(OTf)_2$[467]	
main group metal salts	
$MgBr_2$-Et_2O[455]	
$LiClO_4$[468,469]	CsF[468,469]
$CaBr_2$ or $Ca(NO_3)_2$[470]	NMe_3[470]
$Ca(OTf)_2$[470]	NMe_3[470,471]
$Ca(OH)_2$[471]	
transition metal salts	
TiF_4[456,460]	$AgClO_4$,[472] $AgBF_4$[473]
Cp_2TiCl_2[474]	$AgClO_4$,[474] $AgB(C_6F_5)_4$[453]
$TiCl_2$[453]	$AgB(C_6F_5)_4$[453]
Cp_2ZrCl_2[474]	$AgClO_4$,[474,475] AgOTf, $AgBF_4$, $AgPF_6$ or $AgSbF_6$,[475] $AgB(C_6F_5)_4$[453]
SO_4/ZrO_2[476]	
Cp_2HfCl_2[474]	$AgClO_4$,[474,477,478] $AgB(C_6F_5)_4$[453]
$Hf(OTf)_4$[479]	
$Cu(OTf)_2$[480]	
lanthanide metal salts	
$Yb(OTf)_3$[481]	K_2CO_3,[481,482] $CaCO_3$, K_2CO_3/ $ZnCl_2$ or $K_2CO_3/Ba(ClO_4)_2$[481]
$YbCl_3$[481]	$CaCO_3$[481]
Yb-Amberlyst-15[483]	
$Yb[N(O_2SC_4F_9)_2]_3$[484]	
$La(ClO_4)_3$-$7H_2O$[481,482]	K_2CO_3[481,482]
$La(ClO_4)_3$-nH_2O, $Pr(ClO_4)_3$-nH_2O, or $Eu(ClO_4)_3$-nH_2O[482]	K_2CO_3[482]
$Ce(ClO_4)_3$-nH_2O[482,485]	K_2CO_3[482,485]
anhydrides, protic acids, and other reagents	
Tf_2O[460]	
TfOH[465,486−488]	
$HClO_4$, $HOSO_2C_4F_9$, $HNTf_2$ or $HSbF_6$[464,465]	
$RN^{+}B(C_6F_5)_4$, $RN^{+}OTf$, $RN^{+}SbF_6$, $RN^{+}BF_4$ or $RN^{+}ClO_4$[489]	
solvolysis[490]	

ization propensity to produce thermodynamically stable anomer. Upon glycosylation, α/β-glycosides, such as **242**, are produced along with $HB(C_6F_5)_4$, and the latter can catalyze the anomerization cycle of the α- to β-glycosides and, along with SnClF, induce the regeneration of $SnB(C_6F_5)_4Cl$. Mechanistic investigation confirmed that $SnB(C_6F_5)_4Cl$ is the active catalyst for glycosylation.

Scheme 57. Glycosidation of Glycosyl Fluoride in the Presence of Tin(II)-Based Reagents



Beyond initial studies by Mukaiyama and co-workers wherein the activation was achieved with $SnCl_2$,[420] several other tin salts are investigated such as SnF_2, $SnBr_2$, $Sn(OAc)_2$. However, none of the salts provided satisfactory results without a copromoter.[8,420] Similar observations were made by Nicolaou for $SnCl_4$[455] and by Shibasaki for $Sn(OSO_2CF_3)_2$.[458] Thiem and co-workers reported the activation of glycosyl fluorides with tin(IV) fluoride (stannic fluoride, SnF_4) without any additive.[456] Glycosidation of acylated glycosyl fluoride β-**221** having 2-participating group with glycosyl acceptor **55** or its 6-*O*-TMS-protected counterpart **243** in the presence of SnF_4 produced 1,2-*trans* glycoside **244** (Scheme 58A).

However, the yields of glycosides were below the preparative value (42−48%). Conversely, glycosidation of the benzylated glycosyl fluoride β-**239** was more efficient and produced glycoside **245** in up to 93% yield, and the distribution of the products was found to be solvent-dependent, α-linked in ether or β-linked disaccharides in acetonitrile. It was then discovered that $SnCl_4$ is able to efficiently activate glycosyl fluorides in the presence of $AgB(C_6F_5)_4$.[453] Surprisingly, $SnCl_2$ in combination with $AgB(C_6F_5)_4$ (20 mol % each), only produced the expected disaccharide **248** in trace amounts when glycosyl donor **246** was glycosidated with acceptor **247**. In comparison, $SnCl_4$ in combination with $AgB(C_6F_5)_4$ (20 mol % each) produced disaccharide **248** in an excellent yield (Scheme 58B). Therefore, $SnCl_4$ was employed for further optimization of the amount of $AgB(C_6F_5)_4$ that helped to establish 20 mol % of $SnCl_4$ and 40 mol % of $AgB(C_6F_5)_4$ as the most effective catalytic system for activating glycosyl donor **246** in toluene at −20 °C. Finally, the optimized reaction conditions were extended to several disarmed glycosyl donors as well as

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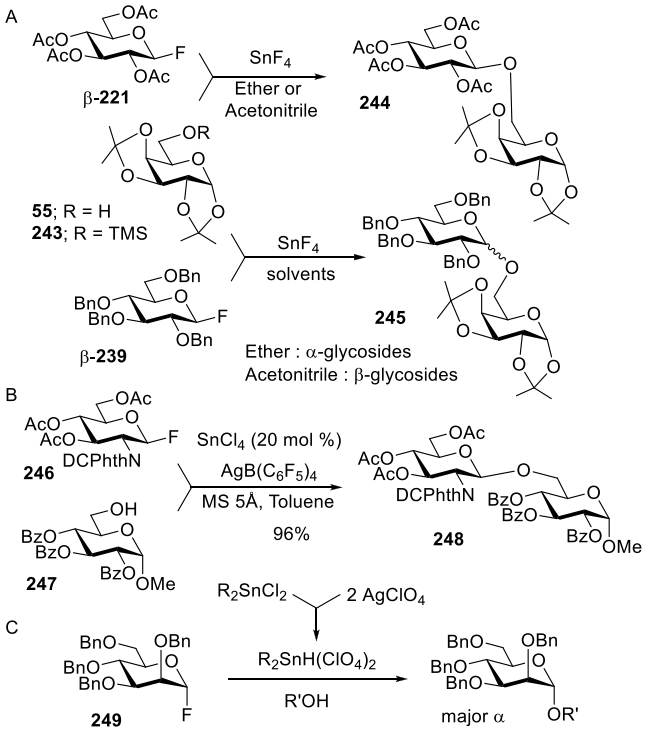
Scheme 58. Glycosidation of Glycosyl Fluoride in the Presence of Other Tin-Based Reagents



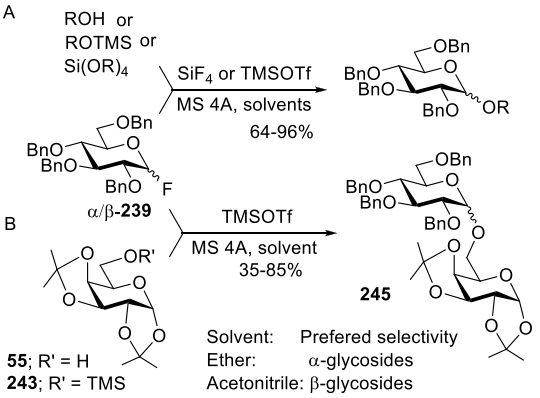
acceptors to synthesize the desired glycosides in excellent yields.

A metallocene-Ag salt-catalyzed approach was extended to organotin(IV) compounds to generate new activators for glycosyl fluoride donors.[457] Two types of organotin compounds, R_2SnCl_2 and R_3SnCl (R = aryl or alkyl), were used in the presence of $AgClO_4$. Whereas glycosidation of fluoride donor **249** in the presence of R_2SnCl_2 and $AgClO_4$ was almost instantaneous, reactions in the presence of R_3SnCl and $AgClO_4$ proceed slower. $R_2Sn(ClO_4)_2$ was proposed as the active catalyst for these reactions (Scheme 58C), and the stereoselectivity was found to depend on the nature of the alkyl/aryl ligands of tin.

Noyori co-workers presented the synthesis of glycosides by coupling glycosyl fluorides and trimethylsilyl ether-protected glycosyl acceptors in the presence of tetrafluorosilane (SiF_4) or trimethylsilyl triflate (TMSOTf).[404] Glycosidation of α- and β-glycosyl fluoride **239** was successfully achieved and the selectivity of glycoside products was found to depend on the type of solvents employed (Scheme 59A). Expectedly, acetonitrile predominantly produced 1,2-*trans* glycosides whereas ether favored 1,2-*cis* glycosides irrespective of anomeric conformation of glycosyl fluorides.

Further, it was confirmed that glycosides do not undergo anomerization over the course of the reaction. The efficiency of glycosylation reaction with glycosyl fluorides depends on the affinity of silicon atom to fluorine. Similarly, Thiem and co-workers also reported the activation of per-benzylated glycosyl fluorides in the presence of TMSOTf.[456] For example, glycosidation of donor **239** with glycosyl acceptors **55** or **243** produced disaccharide **245**. The yield of **245** could fall below preparative standards and the stereoselectivity of glycosides was also solvent dependent, as shown in Scheme 59B. An efficient activation was observed when glycosylation

Scheme 59. Glycosidation of Glycosyl Fluoride in the Presence of Silicon-Based Reagents



was conducted in the presence of $SiCl_4$ in combination with $AgB(C_6F_5)_4$ (20 mol % each). However, only moderate efficiency was achieved when the same glycosylation was conducted in the presence of Ph_3SiCl.[453]

6.2.2. Activation with Group 13-Based Reagents (Boron, Aluminum, and Gallium). Nicolaou and co-workers described the synthesis of *O*-, *S*-, and *N*-glycosides employing glycosyl fluoride donors in the presence of BF_3-Et_2O (0.3 equiv).[455] This activator was found to be effective in most cases, however, there were specific cases where other metal promoters were found to be more effective (*vide infra*). Following essentially the same principle, Kunz and Waldman synthesized a variety of pyranosides and furanosides. Among these, coupling β-2-fluoro-neuraminic acid donor **250** with diacetone galactose acceptor **55** in the presence of BF_3-Et_2O afforded disaccharide **251** in 44% yield (α/β = 1:5, Scheme 60A).[423,461] Recently, BF_3-Et_2O-mediated glycosylation was revisited by Fukase and co-workers wherein it was discovered that an efficient activation of glycosyl fluorides can be achieved in the presence of only 1 mol % of BF_3-Et_2O in a nitrogen-filled glovebox.[491] An interesting feature of this reaction is that it does not require any dehydrating reagent compared to most glycosylation reactions. Armed per-benzylated glycosyl fluoride **239** and disarmed per-benzoylated glycosyl fluoride **240** both were successfully glycosidated with glycosyl acceptor **36** in the presence of 1 mol % of BF_3-Et_2O in nitrogen-filled glovebox and to produce disaccharides **165** in 91% yield (α/β = 1:5/1) and **102** in 85% yield (β only), respectively (Scheme 60B). When the reaction was conducted in a polytetrafluoroethylene vessel, the yield has drastically declined suggesting the involvement of a glass vessel in glycosylation reaction. Earlier, a similar observation of glass vessel's involvement was made by Pedersen and co-workers wherein the formation of SiF_4 was suggested to occur from HF and glass vessel.[492] On the basis of the observations, the authors proposed a tentative mechanism according to which the anomeric activation is initiated by BF_3-Et_2O that produces HF. The latter then reacts with glass and produces SiF_4, which acts as the activator of the anomeric fluoride.

Mukaiyama and Takeuchi reported a stereocontrolled catalytic activation of glycosyl fluorides in the presence trityl tetrakis(pentafluorophenyl)borate.[462] Optimization of the reaction conditions such as catalyst loading, solvents, and temperature led to the establishment of a reaction conditions, which favored 1,2-*trans* β-glycosides. Differently linked disaccharides were synthesized in presence of 10−20 mol %

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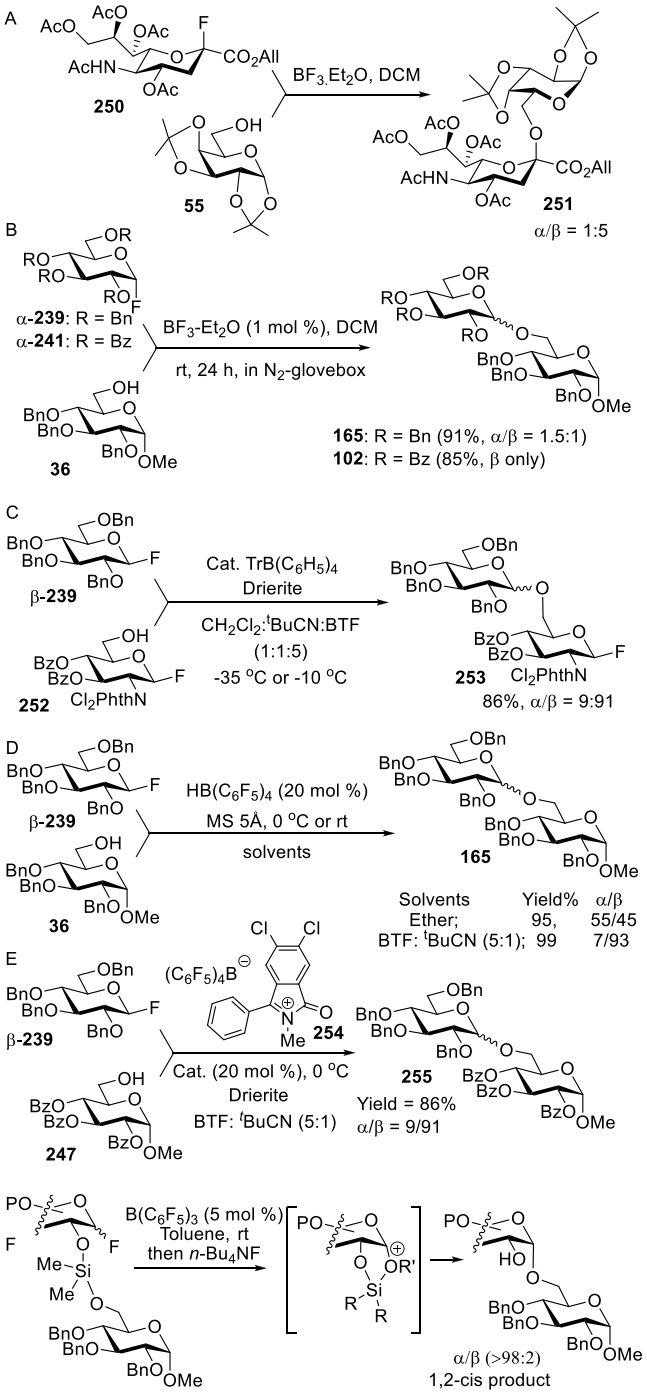
Scheme 60. Glycosidation of Glycosyl Fluoride in the Presence of Boron-Based Reagents



of trityl tetrakis(pentafluorophenyl) borate and Drierite in pivalonitrile-benzotrifluride (1:5) at −10 to 0 °C. Similarly, β-stereoselective glycosylation was observed with tetrabenzylated galactosyl fluoride and various glycosyl acceptors.[486] Further, $TrB(C_6F_5)_4$-catalyzed glycosylation was successfully applied to an armed-disarmed glycosylation concept, wherein armed glycosyl fluoride donor β-**239** was coupled with disarmed glycosyl fluoride acceptor **252** to afford the corresponding disaccharide **253** in a good yield (Scheme 60C).[486] Several other disarmed fluoride acceptors were successfully glycosylated with armed glycosyl donor β-**239**.

Tetrakis(pentafluorophenyl)boric acid-catalyzed activation was also investigated. As shown in Scheme 60D, reaction of glycosyl fluoride donor β-**239** with acceptor **36** produced disaccharide **165** with practically no stereoselectivity.[464] Solvent investigation studies showed that $HB(C_6F_5)_4$-catalyzed glycosylation in a mixture of solvent, i.e. benzotrifluoride/*tert*-butyl nitrile (5:1), produced disaccharides with excellent β-selectivity. The above observations suggested that the counteranion together with solvents play a crucial role in directing the stereoselectivity of the reaction. β-Stereoselective glycosidation of glycosyl fluoride β-**239** was extended with a variety of glycosyl acceptors. In all cases disaccharides were obtained in high yields and with excellent β-selectivity (up to α/β = 2/98). $HB(C_6F_5)_4$-catalyzed α-stereoselective glycosylation was also achieved when a glycosyl fluoride having diethylthiocarbamoyl group at C-6 was used as the glycosyl donor and diethyl ether was used as the reaction solvent.[493]

Mukaiyama and co-workers investigated the activation of glycosyl fluorides in the presence of catalytic carbocationic species paired with counterion such as tetrakis (pentafluorophenyl) borate or other anions.[489] Glycosidation of glycosyl fluoride β-**239** with glycosyl acceptor **247** in ^{t}BuCN in the presence of a cationic catalyst **254** produced disaccharide **255** in 86% yield with excellent β-selectivity (Scheme 60E). Boron-based catalytic activation of glycosyl fluorides was extended by Montgomery and co-workers for silyl ethers as glycosyl acceptors.[466] The Frustrated Lewis Pair (FLP) characteristics of $B(C_6F_5)_3$[494,495] and $B(C_6F_5)_3$-catalyzed trifluoromethylation *via* fluoride-rebound mechanism[496,497] inspired the idea for the coupling glycosyl fluoride with silyl ethers in the presence of $B(C_6F_5)_3$.

Efficient coupling of numerous glycosyl fluorides equipped with a 2-*O*-acyl group with silyl ether acceptors in the presence of 5 mol % of $B(C_6F_5)_3$ rapidly provided the corresponding 1,2-*trans*-linked glycosides in good to excellent yields at rt. Exploitation of silicon-tethered intramolecular aglycone delivery (IAD) method was employed to construct 1,2-*cis* linkages. As shown in Scheme 60F, the glycosidation of the tethered donor−acceptor pair led to glycosides with excellent stereoselectivity. It was assumed that the reaction proceeds via the key five-membered intermediate that collapsed to produce 1,2-*cis*-linked products with concomitant removal of the silicon tether.

Nicolaou and co-workers described the synthesis of *O*-, *S*-, and *N*-glycosides employing glycosyl fluoride donors in the presence of $AlMe_3$.[455] Kobayashi and co-workers utilized different methylgallium chlorides and triflates that were found to activate glycosyl fluorides.[467] Simple aliphatic alcohols produced glycosides in excellent yields (77% to quantitative) with moderate stereoselectivity; however, switching to hindered or sugar alcohols led to decrease in yields.

6.2.3. Activation with Main Group Metal Salts (Magnesium, Lithium, and Calcium). Nicolaou and co-workers investigated the synthesis of *O*-, *S*-, and *N*-glycosides employing glycosyl fluoride donors in the presence of $MgBr_2$-Et_2O.[455] Waldmann and Bohm discovered neutral reaction conditions for the activation of glycosyl fluorides.[468] As shown in Scheme 61A, fluoride donor **256** was reacted with glycosyl acceptor **257** in a 1 M solution of $LiClO_4$ in the presence of CsF as the proton scavenger to afford disaccharide **258** in 98% yield with exclusive α-stereoselectivity. Different types of glycosyl acceptors produced both glycosides with predominant α-stereoselectivity. This methodology was later applied to

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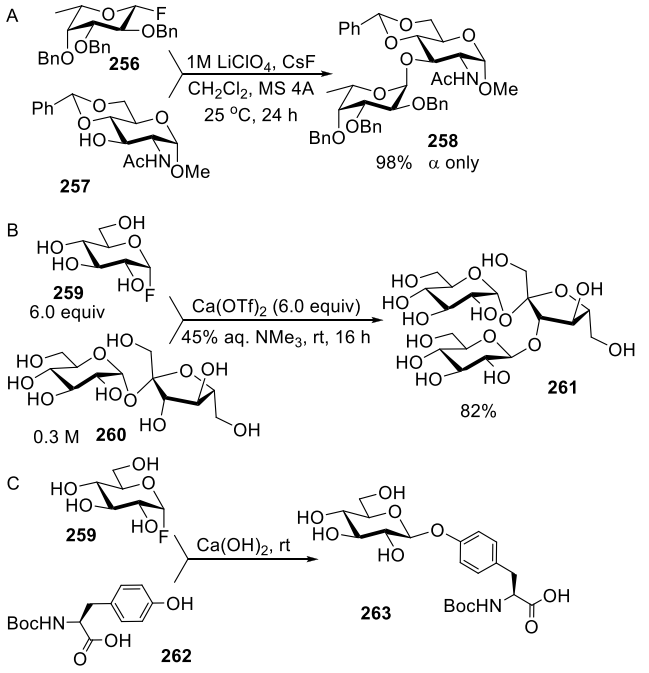
Scheme 61. Glycosyl Fluoride Activation with Main Group Metal Salts



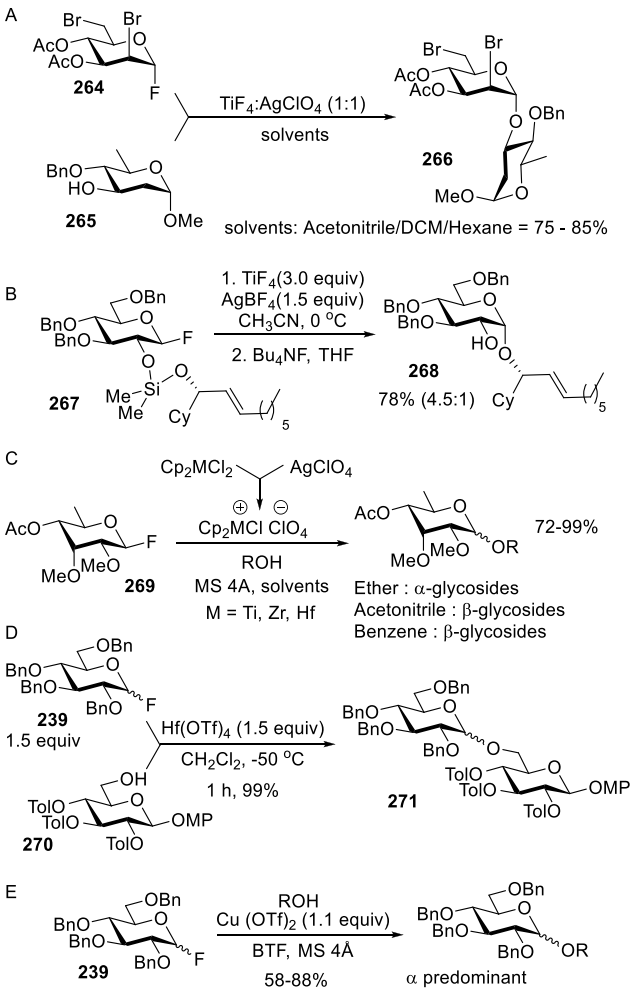
glycosidation of benzylated glucosyl fluorides.[498] The glucosides were obtained in moderate yields, but increasing the concentration of $LiClO_4$ promoted the formation of the respective 1,6-anhydro derivative. Further, acylated glucosyl fluorides were tested; while pivaloyl-protected fluoride produced 1,2-*trans*-linked products, acetylated fluoride was unreactive.[469]

Glycosylations with unprotected sugars in aqueous solutions are challenging.[499−501] Encouraged by the seminal work of Jencks[502−504] and Bennett,[490,505] Miller and co-workers described the activation of glycosyl fluorides in the aqueous phase to produce glycosides.[470] After investigation of a number of metal salts and careful optimization of the reaction conditions, glycosidation of glycosyl fluoride **259** (6.0 equiv) with sucrose **260** (1.0 equiv, 0.3 M) was accomplished in the presence of $Ca(OTf)_2$ (6.0 equiv) in aqueous trimethylamine to produce trisaccharide **261** in a good yield of 82% (Scheme 61B). The unique feature of this method is its β-stereoselectivity and regioselectivity for the 3′-position of sucrose. Extended glycosylation and NMR studies, similar to those described by Davies[506−508] and by O'Leary,[509−512] revealed that the unprecedented regioselectivity and reactivity of sucrose and its derivatives could be related to the hydrogen-bonding network. This network could have a significant impact on nucleophilicity of different hydroxyls of sugars and, hence, influence their interaction with Ca^{2+} during glycosylation.

In another report, Miller and co-workers extended the aqueous phase glycosidation of glycosyl fluorides to phenolic derivatives of biological relevance.[471] Glycosylation of amino acids in aqueous phase remains an immense task,[513−518] and calcium(II)-mediated aqueous phase glycosylation in the presence of $Ca(OH)_2$ worked very well. As depicted in Scheme 61C, glycosylation between glycosyl fluoride **259** (3.0 equiv) and *N*-Boc-protected tyrosine derivative **262** (1.0 equiv) 1.0 M in H_2O in the presence of $Ca(OH)_2$ (3.0 equiv) produced glycoside **263** with complete β-stereoselectivity. The concentration dependence of the reaction rate offered strong evidence of the S_N2-like mechanism.[109,503,505,519] Subsequently, the standardized glycosylation conditions were applied to various phenolic derivatives wherein electron-rich (less acidic) phenolic derivatives turned out to perform better compared to the electron-deficient ones.

6.2.4. Activation with Transition Metal Salts (Titanium, Zirconium, Hafnium, and Copper). Thiem and co-workers showed the activation of glycosyl fluorides with titanium fluoride (TiF_4).[456] Per-acetylated, per-benzylated, and 2-deoxyglycosyl fluorides were investigated. These studies evolved into investigation of the cooperative catalyst comprising titanium and silver salts.[472] To enhance the stereoselectivity, the authors investigated brominated glycosyl fluoride donors depicted in Scheme 62A. Glycosidation of

Scheme 62. Glycosyl Fluoride Activation with Transition Metals Salts



mannosyl fluoride in the presence of TiF_4 and $AgClO_4$ produced α-disaccharides irrespective of the solvents employed. When mannosyl fluoride **264** was reacted with glycosyl acceptor **265** in acetonitrile, diethyl ether, or hexane α-disaccharide **266** was obtained in a good yield and exclusive stereoselectivity. Montgomery and co-workers reported facile construction of 1,2-*cis* glycosidic linkages by means of silicon-directed intramolecular aglycone delivery (IAD) method (*vide supra*) in the presence of TiF_4 and $AgBF_4$.[473] As depicted in Scheme 62B, silyl-tethered precursor **267** was subjected to

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intramolecular glycosylation to give the corresponding glycoside **268** in 78% yield. Functional groups such as ketones, hydroxy groups, silyl ethers, and esters were shown to remain unaffected during these transformations.

Suzuki and co-workers discovered a new cooperative promoter system Cp_2MCl_2-$AgClO_4$ (M = Zr, Hf, Ti) for glycosyl fluoride donors, which enabled very promising glycosylations (Scheme 62C).[474] A controlled experiment showed that Cp_2MCl_2 alone is practically inert in glycosylations, and it was suggested that Cp_2MCl_2 and $AgClO_4$ are required in molar equivalent to drive the reaction to completion. A rough order of reactivity of Zr ≥ Hf ≫ Ti was estimated by glycosylation between glycosyl fluoride **269** and cyclohexyl methanol. Later, the authors explored the activation of anomeric fluoride of amino sugars with Cp_2MCl_2-$AgClO_4$ promoter systems.[477] In this application, Cp_2HfCl_2-$AgClO_4$ was superior to its Zr counterpart. Subsequently, the cooperative catalyst Cp_2MCl_2-$AgClO_4$ (M = Zr, Hf) was utilized for the total synthesis of mycinamicin IV by the stereoselective glycosidation of D-mycinosyl and D-desosaminyl fluorides with mycinamicin VII.[520]

Further investigations revealed that Cp_2MCl_2-$AgClO_4$ (M = Hf, Zr) in a ratio of 1:2 is more efficient for the activation of glycosyl fluorides.[478,521] The authors suggested that the activation of glycosyl fluorides depends on the fluorophilicity of early transition metals and their ability to form the reactive promoter shown in Scheme 62C. The driving force for the glycosylation reaction is believed to be due to the formation of a strong M-F bond. To enhance the efficiency of glycosylation of hindered alcohols, several silver salts ($AgBF_4$, AgOTf, $AgPF_6$, and $AgSbF_6$,) in combination with Cp_2ZrCl_2 were examined, and $AgBF_4$ was found to be superior in this application, both in terms of reactivity and stereoselectivity.[475]

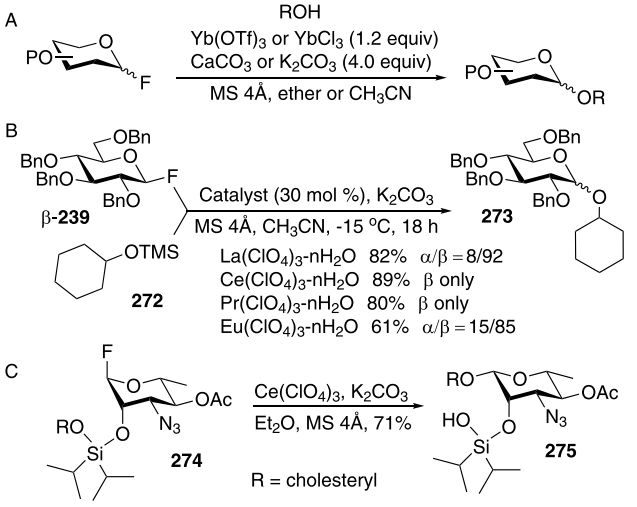
Matsumura and co-workers reported the stereocontrolled mannosylation in the presence of sulfated zirconia (SO_4/ZrO_2) and MS 5 Å.[476] The advantage of solid acid-promoted glycosylation is that the acid can be recovered by filtration and then reused. Also, 2-deoxy-α-D-glucopyranosyl fluoride was investigated in the presence of sulfated zirconia.[522]

Ito and Manabe investigated hafnium(IV) reagents such as $Hf(OTf)_4$, a well-known Lewis acid used for many synthetic transformations,[523−526] for the activation of glycosyl fluorides.[479] Optimization of the reaction conditions led to an effective glycosylation reaction between glycosyl donor **239** and acceptor **270** in CH_2Cl_2 to afford disaccharide **271** in 99% yield (α/β = 20:80, Scheme 62D). Participating solvents were found to influence the stereochemistry of glycosylated products,[404,527,528] a mixture of dioxane/toluene provided mainly α-glycosides, and β-selectivity was observed in acetonitrile. Glycosyl fluorides of other sugar series with different protection patterns were glycosylated with primary and secondary glycosyl acceptors under the identical reaction conditions and the corresponding glycosides were obtained in good to excellent yields (58−94%). The method was then applied for solid-phase oligosaccharide synthesis (*vide infra*).

Yamada and Hayashi reported activation of glycosyl fluorides in the presence of $Cu(OTf)_2$.[480] As depicted in Scheme 62E, glycosyl fluoride **239** was reacted with various alcohols in the presence of the stoichiometric amount of $Cu(OTf)_2$ in benzotrifluoride at temperatures above 60 °C to afford the corresponding glycosides in good yields with predominant α-stereoselectivity.

6.2.5. Activation with Lanthanide Metal Salts (Lanthanum, Cerium, Ytterbium, etc.). Relying on a high dissociation energy of the Ln−F bond,[529,530] Shibasaki and co-workers employed rare earth metal salts for the activation of glycosyl fluorides.[481] Ytterbium(III) triflate or chloride were found to be very effective for the activation of different glycosyl fluorides (Scheme 63A). The authors suggested that the

Scheme 63. Glycosyl Fluoride Activation with Lanthanide Metals Salts



reaction proceeds through the formation of the oxacarbenium ion intermediate since the stereoselectivity of glycosides was reaction solvent dependent. Predominant 1,2-*trans* stereoselective glycosylation was observed in the presence of $Yb(OTf)_3$ and K_2CO_3 in acetonitrile, whereas 1,2-*cis* stereoselectivity was achieved in a similar reaction conducted in the presence of $Yb(OTf)_3$ and $CaCO_3$ in ether. The authors also showed that the addition of Lewis acid such as $ZnCl_2$ or $Ba(ClO_4)_2$ to ytterbium(III)-promoted glycosylation enhances the rate and improves the yield of glycosides.[481] Wang and co-workers immobilized lanthanide ions on ion exchange resins and utilized these catalysts in several chemical modifications.[483] Glycosylation reaction between glycosyl fluorides and methanol was shown to be promoted by Yb-Amberlyst-15. Interestingly, complete inversion at the anomeric center was observed in these reactions. Inazu and co-workers showed the activation of glycosyl fluorides in the presence of catalytic amounts of ytterbium(III) tris[bis(perfluorobutylsulfonyl) amide] ($Yb[N(O_2SC_4F_9)_2]_3$, 5 mol %).[484]

Other rare earth metals were found to promote the glycosidation of glycosyl fluorides.[481,482] Detailed investigation led to the development of a catalytic activation of glycosyl fluorides with trimethylsilyl ether acceptors.[482] Thus, coupling of glycosyl fluoride β-**239** with trimethylsilyl hexyl ether **272** in the presence of rare earth metal perchlorate hydrates in acetonitrile produced product **273** in good yields and with high β-stereoselectivity (Scheme 63B). Catalytic activation of glycosyl fluorides with rare earth metal perchlorates was attributed to the increased fluorophilicity of metal cations.[531−534] Further, ^{19}F NMR experiments confirmed the formation of trimethylsilyl fluoride, which suggested the formation of oxacarbenium ion resulted from the interaction of naked metal cation (perchlorate) with anomeric fluoride which was then attacked by trimethylsilyl ether to produce

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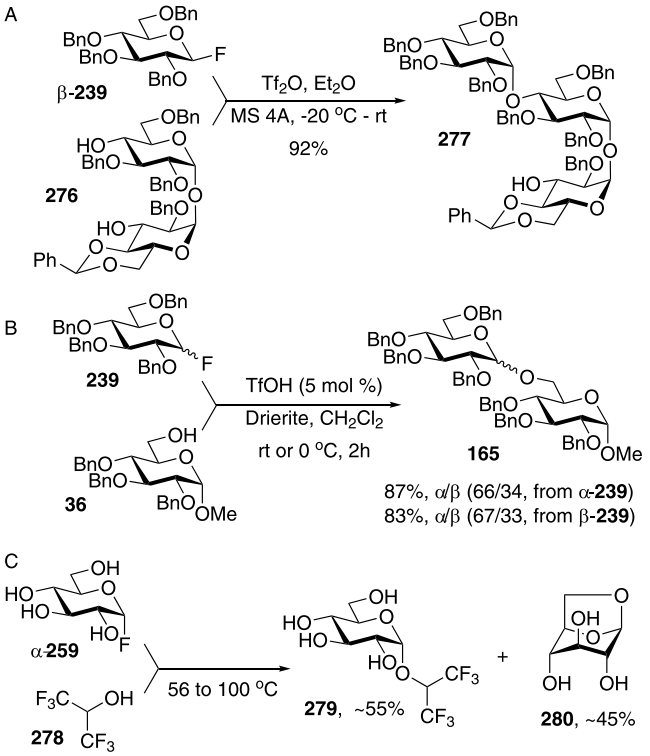
glycosides, trimethyl fluoride and regenerates metal perchlorates to run the catalytic cycle. It was also suggested that glycosylation occurred with a certain range of ionic radii, it was supported by the failed glycosylation by metal perchlorate hydrates of gadolinium, holmium, ytterbium, and yttrium. Differently protected glycosyl fluorides were couples with several alcohols in the presence of $La(ClO_4)_3$-nH_2O to obtain the respective glycosides in good to excellent yields.[535] Packard and Rychnovsky investigated the activation of anomeric fluorides in the presence of $Ce(ClO_4)_3$,[485] wherein β-stereoselective glycosidation of anomeric fluoride derivative of D-mycosamine **274** was conducted via the IAD.[536,537] This reaction afforded cholesteryl β-glycoside **275** in 71% yield as shown in Scheme 63C.

6.2.6. Activation with Anhydrides, Protic Acids, and Other Reagents. Wessel introduced triflic anhydride as a new activator for glycosyl fluorides.[460] The author proposed that the activation of glycosyl fluorides occurred due to a higher affinity of $CF_3SO_2^{\delta+}$ to fluorine than oxygen. As depicted in Scheme 64A, glycosidation of fluoride β-**239** with glycosyl

Scheme 64. Other Methods for the Activation of Glycosyl Fluorides



acceptor **276** afforded α-glycoside **277** in 92% yield. Further, this promoter was applied for the synthesis of differently linked disaccharides.[538] Interestingly, it was discovered that low and moderately reactive alcohols successfully delivered products, whereas reactive alcohols provided fair yields due to the competing sulfonation of the hydroxyl group. Mukaiyama and co-workers discovered the activation of glycosyl fluorides with cat. trifluoromethanesulfonic acid (TfOH).[465,486,487] Glycosidation of glycosyl fluoride α- or β-**239** with glycosyl acceptor **36** in dichloromethane in the presence of a catalytic amount of TfOH (5 mol %) produced disaccharide **165** within 2 h in a good yield (Scheme 64B).

TfOH-catalyzed activation was extended to reactions of differently protected glycosyl fluoride donors with various glycosyl acceptors. Without a nonparticipating group at C-2, the stereochemical outcome was difficult to predict. To address the problem associated with stereoselectivity, a thorough investigation for optimal reaction conditions was conducted. It was established that TfOH-catalyzed glycosylations produce good to excellent 1,2-*cis* selectivity in ethereal solvents in the presence of MS 5 Å or Drierite.[488] Further investigation revealed that efficient activation of glycosyl fluoride donors can also be achieved in the presence of other protic acids such as $HClO_4$, $HOSO_2C_4F_9$, $HNTf_2$, $HSbF_6$, and $HB(C_6F_5)_4$.[464] Some of the strong acids were generated *in situ* in a similar way to the procedures described by Kevill[539] or Kato.[540] The diastereomeric ratio of glycoside products was found to be a subject of reaction conditions such as the nature of solvents, counteranions, and protecting groups.[493] As previously discussed, Mukaiyama and co-workers performed the activation of glycosyl fluorides in the presence of catalytic carbocationic species paired with counterion such as tetrakis-(pentafluorophenyl)borate.[489] Accordingly, trifluoromethanesulfonate and perchlorate were found to be effective in activating glycosyl fluoride donors.

Chan and Bennett described the solvolysis of glycosyl fluorides in weak nucleophilic solvents such as hexafluoro-2-propanol **278** (HFIP).[490] The formation of the retained solvolysis product, 1,1,1,3,3,3-hexafluoropropan-2-yl α-D-glucopyranoside **279**, and the inverted product, 1,6-anhydro-β-D-glucopyranose **280** from glucosyl fluoride α-**259** in HFIP or HFIP-*d* was observed (Scheme 64C). To understand the product distribution and pathway of the formation, the solvolysis of fluoride α-**259** in HFIP was conducted at different temperatures and the activation parameters were calculated from Eyring plot. The obtained results suggested that solvolysis occurs via a highly ordered transition state, which resulted from solvation of the fluoride ion by the HFIP solvent.[541] The expansive experimental and computed KIE measurements suggest solvolysis of fluorides α-**259** in HFIP solvent involves cleavage of the C−F bond as the rate-determining step, wherein proton transfer occurs from solvating HFIP molecule to the leaving group fluoride to afford the solvent-separated ion pair. Concurrently, the formation of solvolysis product **279** proceeds via the collapse of the solvent-separated ion pair in the S_Ni reaction, whereas the formation of inverted product **280** proceeds via the intramolecular capture of the solvent-equilibrated glycosyl cation generated from the dissociation of the solvent-separated ion pair. The authors also showed that an S_N2-like nucleophilic displacement of anomeric fluoride of unprotected fluoride donor α-**259** with an aqueous solution of sodium azide produces corresponding β-glycosyl azide,[505,541] wherein the anomeric center displayed that the reaction proceeds through a loose (exploded) transition state.[505]

6.3. Glycosyl Fluorides in Glycan and Glycoconjugate Synthesis

6.3.1. Convergent Building Block Assembly. Early examples of impressive convergent syntheses employing fluorides as glycosyl donors involve synthesis of α-cyclodextrin Ogawa and Takahashi wherein glycosylations were promoted with $SnCl_2$+AgOTf.[542] Nicolaou and co-workers employed the cooperative catalytic systems $SnCl_2$-Ag salts and also Cp_2MCl_2-Ag salts for the total synthesis of the tumor-associated Le^x glycosphingolipids and sialyl dimeric Le^x.[543,544] A representa-

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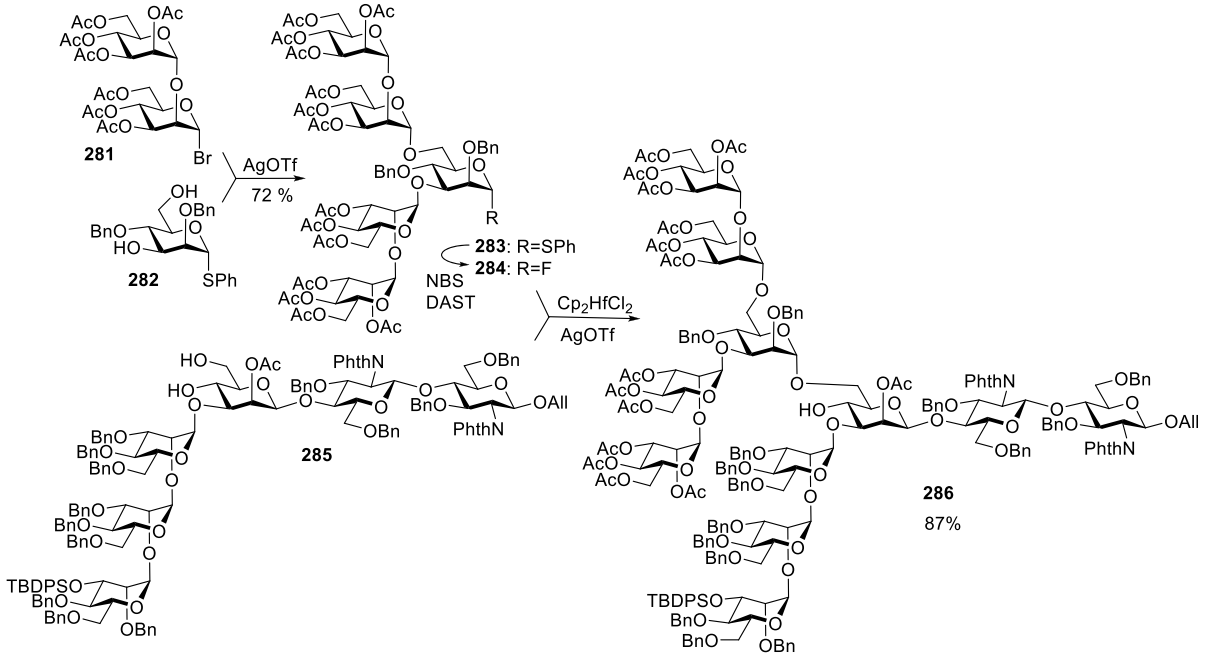
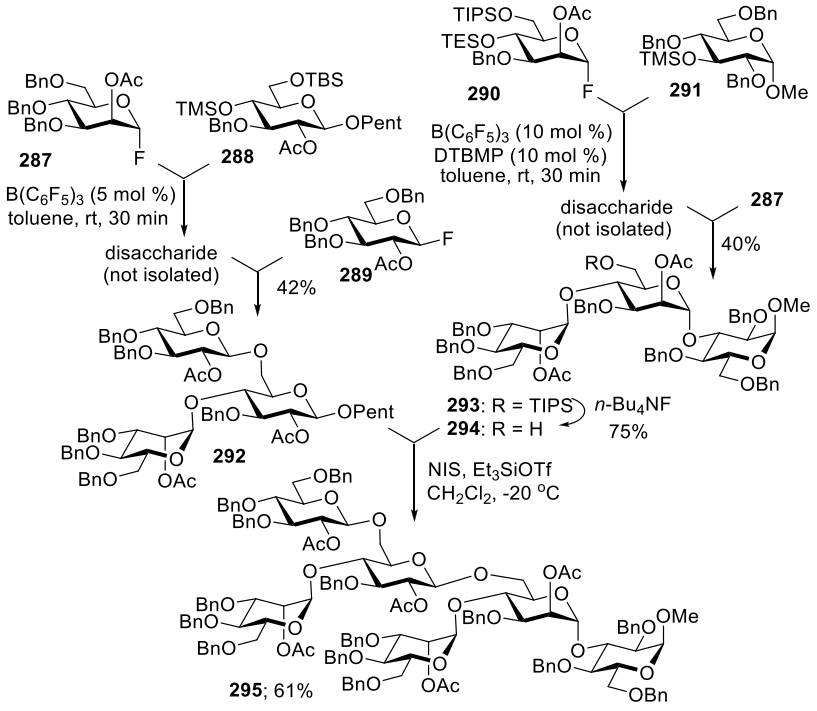
Scheme 65. Convergent Assembly of High Mannose Type *N*-Glycan



Scheme 66. Borane-Catalyzed Convergent Oligosaccharides Synthesis



tive example of such an approach is the synthesis of the high mannose-type *N*-glycan **286** illustrated in Scheme 65.[545] Glycosyl acceptor diol **282** was bis-glycosylated with the bromide donor **281** in the presence of AgOTf to afford the pentasaccharide **283** in 72% yield. The latter was then converted into a glycosyl fluoride donor **284** by reaction with DAST in the presence of NBS. The presynthesized hexasaccharide acceptor **285** was then regioselectively glycosylated with fluoride donor **284** in the presence of a Cp_2HfCl_2/AgOTf promoter system to afford oligosaccharide **286** in an excellent yield of 87%.

A recent convergent assembly reported by Montgomery and co-workers comprises elements of one-pot synthesis.[466] A three-component coupling was performed between monosaccharides **287**−**291** as shown in Scheme 66. The coupling of fluoride **287** with glycosyl acceptor **288** proceeded regioselectively at the C-4 position protected with TMS ether. Glycosyl fluoride donor **289** was then added to the reaction mixtures to produce the corresponding trisaccharide **292** in a good yield. In this reaction, TBS-protected C-6 position was glycosylated. Applying a similar approach for controlling the relative reactivity of silylated hydroxyl groups (TMS vs

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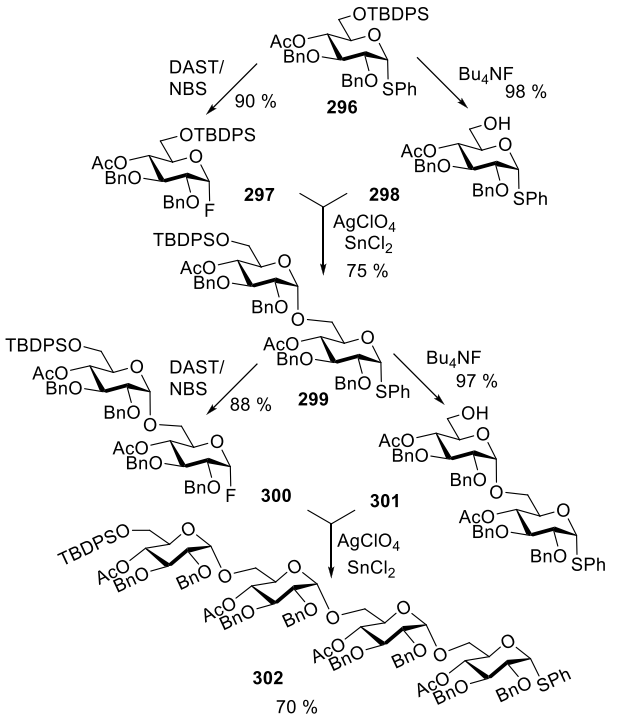
triethylsilyl vs triisopropylsilyl) trisaccharide **293** was synthesized. For this purpose, mannosyl fluoride donor **290** was coupled with glucosyl acceptor **291** to produce the corresponding disaccharide that was then reacted with mannosyl donor **287**. Trisaccharide **293** was converted to glycosyl acceptor **294** by TIPS group removal with *n*-tetrabutylammonium fluoride (*n*-Bu_4NF). Finally, *n*-pentenyl leaving group of trisaccharide donor **292** was activated for reaction with acceptor **294** in the presence of NIS/Et_3SiOTf to afford hexasaccharide **295** in 61% yield.

6.3.2. Two-Step Activation. According to the two-stage activation approach, both glycosyl donor and glycosyl acceptor initially bear the same type of leaving group. However, to couple these two reactants, the LG of the potential glycosyl donor unit is first converted into a different (more reactive) LG, which is then selectively activated. This two-step activation sequence can be reiterated. This concept was discovered by Zen for *S*-ethyl and bromo groups[329] and further expanded by Nicolaou for *S*-phenyl and fluoro groups.[333,546] For a relevant example, see the synthesis of **302** depicted in Scheme 67.[333] First thioglycoside **296** was converted into

Scheme 67. Two-Step Activation with Fluorides and Thioglycosides

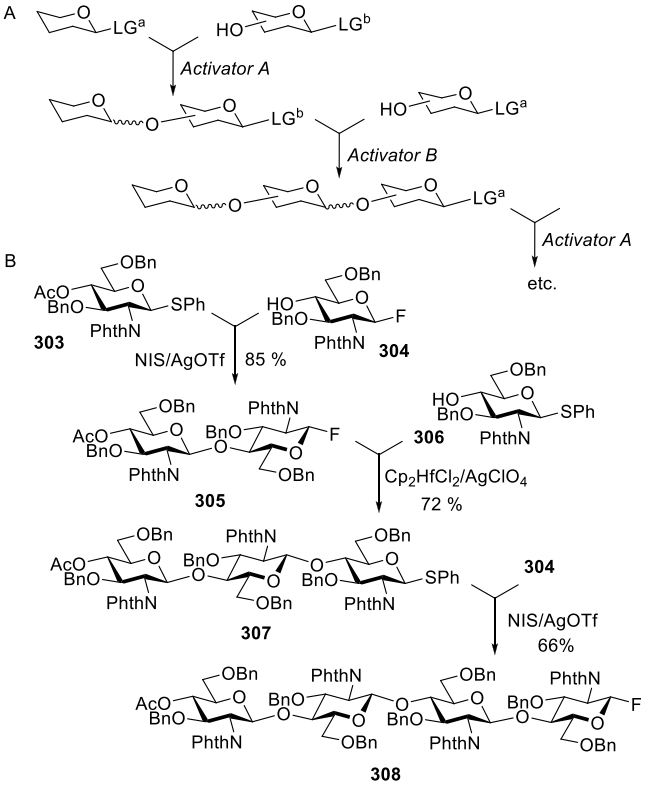


glycosyl fluoride **297** by the treatment with NBS/DAST. The latter was then coupled with a thioglycoside acceptor **298**, which was generated from **296** by the treatment with TBAF, in the presence of $SnCl_2/AgClO_4$ to provide disaccharide **299** in 75% yield. This sequence is then repeated to furnish the desired fluoride donor **300** and thioglycoside acceptor **301**, followed by glycosylation in a 2+2 fashion to provide tetrasaccharide **302**. This approach combines advantages offered by the two-step activation and convergent strategies.

6.3.3. Selective and Orthogonal Activation. Another general concept to expedite oligosaccharide synthesis is to achieve selective activation of different leaving groups. In a typical application, a glycosyl fluoride donor is activated over a thioglycoside acceptor in the presence of a suitable promoter. The thio-leaving group of the resulting disaccharide is then activated directly to afford a trisaccharide. Examples of these applications include TfOH as the promoter for the first step, and NIS added for the second step.[488] Another example involves $HB(C_6F_5)_4$ and NIS as activators for the activation of fluoride and thioglycoside, respectively.[465] Demchenko and co-workers synthesized a hexasaccharide in only five steps via sequential selective activation of five leaving groups, including fluorides.[547] As a part of their strategy, *S*-benzoxazolyl (SBox) trisaccharide donor was coupled with fluoride acceptor in the presence of MeOTf, and the resulting tetrasaccharide was then activated in the presence of $AgClO_4/Cp_2ZrCl_2$ to afford a pentasaccharide in 84% yield.

The combination of two chemically distinct glycosylation reactions, in which one of the leaving groups is activated while the other one remains intact, and *vice versa*, has led to the discovery of the orthogonal strategy for oligosaccharide synthesis.[548] It requires the use of two orthogonal classes of glycosyl donors.[549,550] As with the selective activation strategy, at the first step the glycosyl donor bearing LG^a is activated over the glycosyl acceptor bearing LG^b. Uniquely to the orthogonal strategy, the LG^b is then activated over LG^a of the new glycosyl acceptor (Scheme 68A). This activation sequence can then be

Scheme 68. Orthogonal Activation Was Discovered with Fluorides and Thioglycosides



reiterated to give straightforward access to larger oligosaccharides. Specifically, this unique strategy was discovered with glycosyl fluorides, and the classic variation of the orthogonal activation route also involves building blocks bearing the *S*-phenyl leaving group. Thus, Ogawa and co-workers illustrated that phenylthio glycoside **303** can be selectively activated over glycosyl fluoride **304** in the presence of NIS/AgOTf to afford

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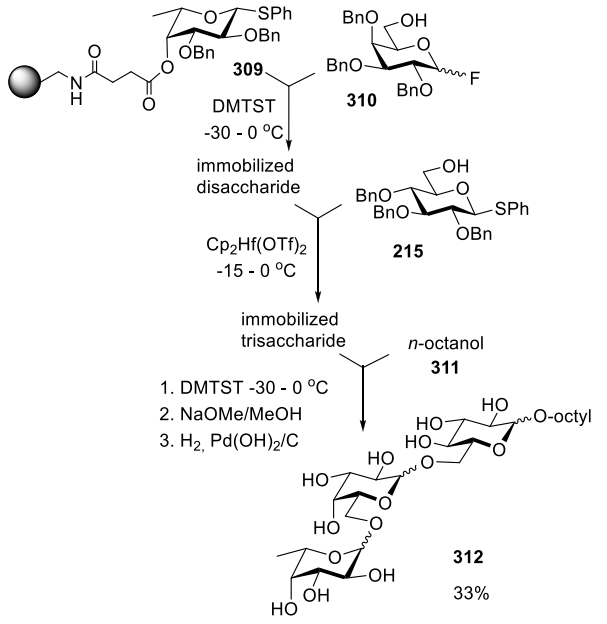
disaccharide **305** (Scheme 68B).[548] The fluoro leaving group of disaccharide donor **305** can then be activated over the SPh moiety of glycosyl acceptor **306** in the presence Cp_2HfCl_2 and $AgClO_4$ to afford trisaccharide **307** in 72% yield. Phenylthio glycosyl donor **307** was then activated over fluoride acceptor **304** to provide tetrasaccharide **308** in 66% yield. These reactions have been performed both in solution[548,551] and on the polymer support (*vide infra*).[551,552]

6.3.4. Polymer- and Tag-Supported Synthesis. Among major breakthroughs that have emerged in the area of synthetic chemistry is the development of organic synthesis on the solid phase.[553−556] As a consequence, the past two decades have witnessed dramatic improvements in the area of solid phase-supported oligosaccharide synthesis,[557−561] particularly in the context of automation.[3,562−566] Polymer-supported synthesis allows for rapid synthesis of oligosaccharide sequences without the necessity of purifying and characterizing the intermediates. Another advantage of oligosaccharide synthesis on solid-phase support is the ease of excess reagent removal (by filtration). Among multiple methods and approaches that have been developed to date, two main strategies for solid-phase saccharide synthesis that differ in the type of the attachment can be identified. In the most common glycosyl acceptor bound approach excess of the glycosyl donor and promoter are present in the solution phase. In the rarer glycosyl donor-bound approach, glycosyl acceptor and promoters are present in the solution phase. Application of the orthogonal strategy is a rare example of a donor-bound approach in polymer supported synthesis.[551] As reported Kanie et al.,[552,567] polymer-bound donor **309** was activated selectively over the solution-phase glycosyl fluoride acceptor **310** in the presence of dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST) shown in Scheme 69. The immobilized disaccharide fluoride was then activated over *S*-phenyl acceptor **215** in the presence of $Cp_2Hf(OTf)_2$. Finally, the immobilized *S*-phenyl trisaccharide was glycosidated with octanol **311** in the presence of DMTST. The resulting oligosaccharide **312** was cleaved off the polymer support.[567] The $Hf(OTf)_4$-promoted

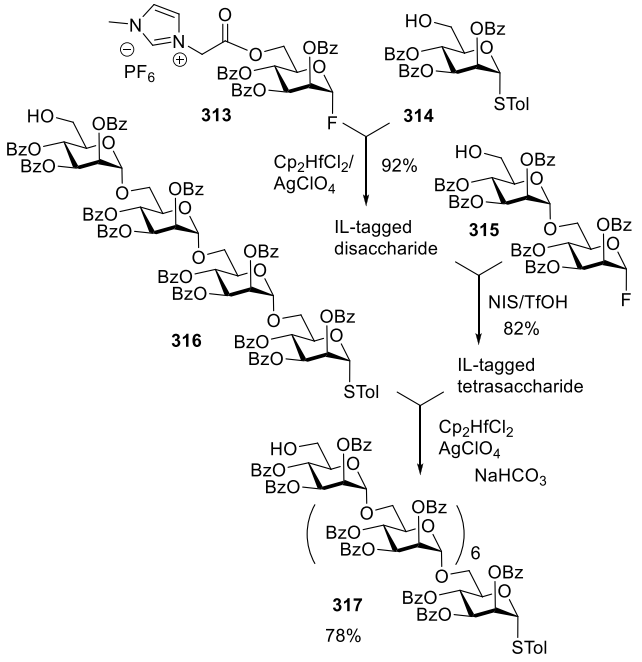
Scheme 69. Orthogonal Synthesis on Solid Phase



activation of solution phase mannosyl fluoride donor was applied to glycosylation of an acceptor immobilized on TentaGel.[568]

Another promising technique for supported oligosaccharide synthesis makes use of an ionic-liquid tag.[569,570] Ionic liquid-supported assembly also expedites oligosaccharide synthesis by eliminating the need for chromatographic purification of the intermediates. After the desired reaction of the tagged compound has been completed, the reaction mixture is concentrated. The excess of organic reagents is removed by extraction with low polarity solvents in which the tagged compounds are insoluble. This approach is illustrated by a synthesis that incorporates elements of an orthogonal strategy making use of alternating activations of STol and F leaving groups and the convergent approach.[571,572] A (1-methylimdazoliumhexafluorophospho) acetyl ionic liquid (IL) tag was introduced via the corresponding 6-chloroacetylated starting material by reaction with *N*-methylimidazole and potassium hexafluorophosphate. As depicted in Scheme 70, the tagged

Scheme 70. Ionic Liquid-Tagged Synthesis of Mannans



mannosyl fluoride donor **313** was glycosidated with thioglycoside acceptor **314** to afford the IL-tagged disaccharide. Meanwhile, disaccharide **315** was produced using tagged thioglycoside as the donor and a fluoride acceptor. Each disaccharide was split into portions, and the tag was removed from one portion. Coupling of the two disaccharides in the presence of NIS/TfOH produced a tagged tetrasaccharide. The latter was then coupled with tetrasaccharide **316**, which was prepared in a similar fashion. The resulting glycan was then cleaved off from the IL support to afford mannan **317**.

6.3.5. Oligosaccharide Synthesis with Hydrolases. In the natural environment, these enzymes hydrolyze glycosidic bonds and therefore are responsible for degradation of oligosaccharides. However, the reverse hydrolytic activity of hydrolases can also be exploited for the glycosidic bond-formation process.[573,574] Glycosyl hydrolases are much more readily available than glycosyltransferases. They also are typically less regioselective, and the transformation yields are

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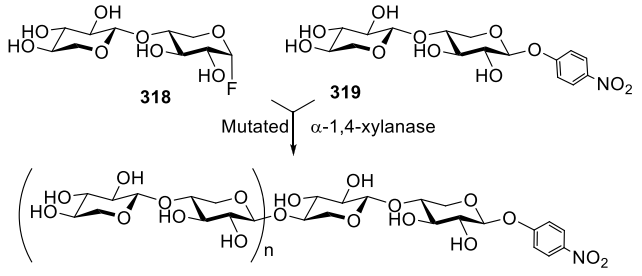
lower. There are two main catalytic mechanisms for hydrolases: one leading to inversion of the anomeric configuration and the other leading to retention.[575,576] The easiest way to employ this approach is to perform the glycosylation under thermodynamically controlled conditions, where the reverse hydrolysis is achieved at equilibrium, but the yields can be low. A significantly improved outcome can be achieved under kinetically controlled glycosylation conditions. In this case, activated glycosyl fluoride donors can be employed. Kinetically controlled glycosylations employing glycosidases (often called "transglycosylation" reactions) have been employed for the synthesis of a variety of oligosaccharides.[574] As shown in Scheme 71, the application of glycosynthase, a synthetic enzyme derived from a retaining glycosidase, allowed irreversible glycosidation of glycosyl fluoride donor **318** with disaccharide acceptor **319**.[577] Application of the glycosynthase derived from the β-1,4-xylanase of *Cellulomonas fimi* resulted in a very efficient synthesis of a series of xylans. The (1→4)-linked xylooligosaccharides **320**, ranging from tetra- to dodecasaccharides, have been obtained regio- and stereoselectively in over 60% combined yield.

Scheme 71. Synthesis of Xylans 320 Using an Engineered Xylanase



7. CONCLUSIONS AND OUTLOOK

To keep pace with the expanding areas of glycosciences, it is critical to make glycans more accessible to the general chemical, biomedical, and industrial audiences. The advancement of glycosylation methods and strategies and their broader adoption is crucial to meeting this need. While new developments are required both in the generalization of the strategies and in the optimization of methods for glycoside synthesis all existing methods of carbohydrate chemistry require further tuning of reactivity levels and reaction conditions. The goal of optimizing glycosylation has been pursued in many ways. This significantly enhanced our understanding and ability to refine the reaction conditions, suppress side reactions, understand stereoelectronics and conformation of the starting material and key reaction intermediates, and predict the outcomes of many glycosylations. Despite all these recent improvements, the challenge of glycosylation has remained, and many scientists have turned their attention to reinvestigating glycosyl halides. These simple donors are typically easily accessible from a variety of precursors, fairly stable, can be readily activated, and offer superior atom economy. Recent work has demonstrated that many glycosyl halides can be activated with less toxic promoters. These studies with glycosyl chlorides and bromides brought these glycosylation reactions to an entirely different level of flexibility and versatility. Conversely, glycosyl fluorides, once prominent glycosyl donors, have been used more and more rarely in the past decade. The authors of this review believe that the full potential of glycosyl fluorides is yet to be revealed, and the glycosynthetic audience will witness further improvements of this promising method already in the next decade.

With further improvement of our synthetic capabilities, new effective approaches to stereoselective chemical glycosylation that will be broadly applicable to a wide range of substrates and synthetic targets will emerge. We anticipate that exploring glycosyl halide donors in combination with other methods and approaches will contribute significantly to the general methodological field by enhancing our ability to monitor all steps of the glycosylation and study the key reaction intermediates. This, in turn, will open exciting opportunities for studying and understanding general aspects of glycosylation, reveal and solve problem spots, and develop reliable strategies for troubleshooting and sidetracking, all of which will improve our ability to obtain glycosides with high stereocontrol. As a result, the methodological advances made in the synthetic field will boost innovations in the related fields of glycosciences. It is our belief that a dedicated study of the methods and mechanisms of the glycosylation process will strategically advance the field such that both one-step glycosylation and multistep syntheses of glycans will be considered standard.

Many current methods for chemical glycosylation remain highly sophisticated, operationally complex, and require significant user know-how. By contrast, automation of glycosylation reactions showcases a highly accessible method of synthesis because it offers an idea of operational simplicity and reproducibility. At this stage it is still unclear whether a dedicated glycosylation reaction needs to be developed or existing methods used in solution can simply be repurposed to fulfill the requirements of automated synthesis. Upon achieving a reliable and simple platform for completely automated glycosylation, anybody should be able to perform automated synthesis of glycans. Machine-assisted synthesis will help to eliminate variability, and to accurately reproduce experiments multiple times by different users.[3,200,562−564,566,578−596] Synthesis of glycans using user-friendly automated platforms will accelerate discovery of new carbohydrate-based or carbohydrate-containing diagnostics,[597−612] pharmaceuticals,[597,613−624] and vaccines.[625−635] This will lead to innovations in many scientific disciplines and can significantly impact technology, society, the economy, and public health.

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Notes

The authors declare no competing financial interest.

Biographies

Yashapal Singh graduated from Deen Dayal Upadhyaya Gorakhpur University, UP in India with a Master of Science (M.Sc.) degree in Chemistry (2008). In 2010, he joined Professor Narayanaswamy Jayaraman's lab in the Department of Organic Chemistry at Indian Institute of Science Bangalore, India. In 2016, he received his Ph.D. degree for his work in the area of Macromolecular Chemistry including dendrimers and carbohydrates, directed particularly toward design and synthesis of organic materials for sensing applications. In February 2017, he joined the Demchenko lab at the University of Missouri−St. Louis (USA) as a postdoctoral research associate. His work entailed the identification of novel aglycones as organocatalysts for atom-efficient regenerative glycosylation reaction. Along with Professor Demchenko, he discovered the catalytic role of an acid in the Koenigs−Knorr glycosylation. He also worked on developing methods for the synthesis and activation of glycosyl nitrates and thioglycosides. Further, he was engaged in developing a robust large-scale method for the synthesis of human milk oligosaccharides, and HPLC-based automation for the synthesis of biologically relevant glycans. Currently, Dr. Singh is working as a postdoctoral research associate in Professor Philip S. Low's lab at Purdue University (USA) where his research is directed toward cancer immunotherapy.

Scott Geringer graduated from the Southern Illinois University−Edwardsville (SIUe) with a Bachelor of Science (B.S.) in Chemistry in 2013. He continued his education at SIUe and graduated with a Master of Science (M.Sc.) in Chemistry in 2015. He worked with Dr. Cristina De Meo. He completed his thesis studying the effects of the picoloyl protecting group on sialic acid glycosylation as well as studying the conformational equilibrium of the oxacarbenium ion intermediate. In August of 2015, Scott joined Dr. Alexei Demchenko's lab at University of Missouri−St. Louis (UMSL) as a Ph.D. student. He successfully graduated from UMSL in May of 2020 with a Doctor of Philosophy in Chemistry with an emphasis on Organic Chemistry. Here Scott worked on developing new catalytic reactions in carbohydrate chemistry. These methods include developing a method for catalytic glycosylation of glycosyl chlorides using iron(III) chloride, a new method for chemoselective picoloyl cleavage using catalytic iron(III) chloride, and activation of glycosyl chlorides using the cooperative silver(I) oxide-triflic acid catalyst system. Dr. Geringer currently works as a senior scientist at MilliporeSigma.

Alexei Demchenko graduated from the Mendeleev University of Chemical Technology of Russia with a Diploma (M.S.) in Chemical Engineering (1988) before joining the laboratory of the late Professor Kochetkov at the Zelinsky Institute of Organic Chemistry in Moscow. In 1993, he was awarded a Ph.D. in Organic Chemistry by the Russian Academy of Sciences for his work on the development of thiocyanate methodology for glycosylation. After two postdoctoral years under Kochetkov, he joined Professor Boons' group at the University of Birmingham (UK) as a BBSRC postdoctoral research fellow. In 1998, he moved to the Complex Carbohydrate Research Center, University of Georgia (USA) as a research associate. In 2001, he joined the faculty at the University of Missouri−St. Louis (UMSL) as an assistant professor where he was promoted to the rank of associate professor with tenure (2007) and professor (2011). In 2014, Dr. Demchenko was appointed Curators' Distinguished Professor of Chemistry and Biochemistry. In 2021, Demchenko joined the faculty at Saint Louis University as professor and department chair. His research interests are in the area of synthetic carbohydrate chemistry that include streamlined synthesis of carbohydrate building blocks, development of new glycosylation reactions, strategies for expeditious assembly of complex glycans and glycopharmaceuticals, and automated synthesis.

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