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General Aspects of the Glycosidic Bond Formation*Alexei V. Demchenko*

1.1

Introduction

Since the first attempts at the turn of the twentieth century, enormous progress has been made in the area of the chemical synthesis of *O*-glycosides. However, it was only in the past two decades that the scientific world had witnessed a dramatic improvement in the methods used for chemical glycosylation. The development of new classes of glycosyl donors has not only allowed accessing novel types of glycosidic linkages but also led to the discovery of rapid and convergent strategies for expeditious oligosaccharide synthesis. This chapter summarizes major principles of the glycosidic bond formation and strategies to obtain certain classes of compounds, ranging from glycosides of uncommon sugars to complex oligosaccharide sequences.

1.2

Major Types of *O*-Glycosidic Linkages

There are two major types of *O*-glycosides, which are, depending on nomenclature, most commonly defined as α - and β -, or 1,2-*cis* and 1,2-*trans* glycosides. The 1,2-*cis* glycosyl residues, α -glycosides for D-glucose, D-galactose, L-fucose, D-xylose or β -glycosides for D-mannose, L-arabinose, as well as their 1,2-*trans* counterparts (β -glycosides for D-glucose, D-galactose, α -glycosides for D-mannose, etc.), are equally important components in a variety of natural compounds. Representative examples of common glycosides are shown in Figure 1.1. Some other types of glycosides, in particular 2-deoxyglycosides and sialosides, can be defined neither as 1,2-*cis* nor as 1,2-*trans* derivatives, yet are important targets because of their common occurrence as components of many classes of natural glycostructures.

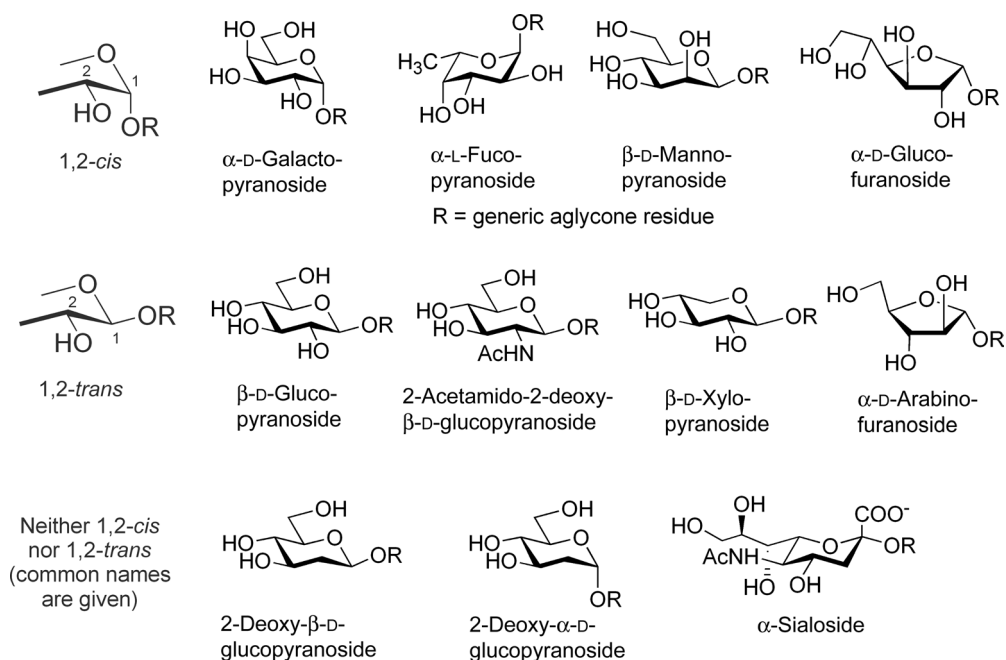


Figure 1.1 Common examples of O-glycosides.

1.3

Historical Development: Classes of Glycosyl Donors

The first reactions performed by Michael (synthesis of aryl glycosides from glycosyl halides) [1] and Fischer (synthesis of alkyl glycosides from hemiacetals) [2] at the end of the nineteenth century showed the complexity of the glycosylation process. The discovery of the first controlled, general glycosylation procedure involving the nucleophilic displacement of chlorine or bromine at the anomeric center is credited to Koenigs and Knorr [3]. The glycosylations were performed in the presence of Ag_2CO_3 , which primarily acted as an acid (HCl or HBr) scavenger. At that early stage, glycosylations of poorly nucleophilic acceptors such as sugar hydroxyls were sluggish and inefficient; hence, even the synthesis of disaccharides represented a notable challenge. The first attempts to solve this problem gave rise to the development of new catalytic systems that were thought to be actively involved in the glycosylation process [4]. Thus, Zemplen and Gerecs [5] and, subsequently, Helferich and Wedermeyer [6] assumed that the complexation of the anomeric bromides or chlorides with more reactive, heavy-metal-based catalysts would significantly improve their leaving-group ability. This approach that has become a valuable expansion of the classic Koenigs–Knorr method made it possible to replace Ag_2CO_3 or Ag_2O by more active mercury(II) salt catalysts. The early attempts

to improve the glycosylation process have revealed the necessity to find a delicate balance between the reactivity and stereoselectivity [7,8]. Indeed, it was noted that faster reactions often result in a decreased stereoselectivity. At around the same time, the first attempts to involve other classes of anomeric leaving groups (LGs) resulted in the investigation of peracetates as glycosyl donors [9].

Seminal work of Lemieux [10] and Fletcher and coworkers [11,12] has led to the appreciation that the reactivity of the glycosyl halides and the stereoselectivity of glycosylation are directly correlated to the nature of the protecting groups, especially at the neighboring C-2 position. From early days, it has been acknowledged that peracylated halides often allow stereoselective formation of 1,2-*trans* glycosides. Later, this phenomenon was rationalized by the so-called participatory effect of the neighboring acyl substituent at C-2. Although occasionally substantial amounts of 1,2-*cis* glycosides were obtained even with 2-acylated glycosyl donors, the purposeful 1,2-*cis* glycosylations were best achieved with a nonparticipating ether group at C-2, such as methyl or benzyl. Further search for suitable promoters for the activation of glycosyl halides led to the discovery of Ag-silicate that proved to be very efficient for direct β -mannosylation, as these reactions often proceed via a concerted S_N2 mechanism [13,14].

For many decades classic methods, in which anomeric bromides, chlorides, acetates or hemiacetals were used as glycosyl donors, had been the only procedure for the synthesis of a variety of synthetic targets ranging from simple glycosides to relatively complex oligosaccharides (Figure 1.2). Deeper understanding of the reaction mechanism, driving forces and principles of glycosylation have stimulated the development of other methods for glycosylation, with the main effort focusing on the development of new anomeric leaving groups [15,16]. During the 1970s to early 1980s, a few new classes of glycosyl donors were developed. The following compounds are only the most representative examples of the first wave of the leaving-group development: thioglycosides by Ferrier *et al.* [17], Nicolaou *et al.* [18], Garegg *et al.* [19] and others [20]; cyanoethylidene and orthoester derivatives by Kochetkov and coworkers [21,22]; O-imidates by Sinay and coworkers [23] and Schmidt and Michel [24]; thioimides including S-benzothiazolyl derivatives by Mukaiyama *et al.* [25]; thiopyridyl derivatives by Hanessian *et al.* [26] and Woodward *et al.* [27] and glycosyl fluorides by Mukaiyama *et al.* [28] (Figure 1.2). Many glycosyl donors introduced during that period gave rise to excellent complimentary glycosylation methodologies. Arguably, trichloroacetimidates [29,30], thioglycosides [31–33] and fluorides [34,35] have become the most common glycosyl donors nowadays.

A new wave of methods arose in the end of the 1980s, among which were glycosyl donors such as glycosyl acyl/carbonates [36–38], thiocyanates [39], diazirines [40], xanthates [41], glycals [42,43], phosphites [44,45], sulfoxides [46], sulfones [47], selenium glycosides [48], alkenyl glycosides [49–51] and heteroaryl glycosides [52] (Figure 1.2). These developments were followed by a variety of more recent methodologies and improvements, among which are glycosyl iodides [53], phosphates [54], Te-glycosides [55], sulfonylcarbamates [56], disulfides [57], 2-(hydroxycarbonyl) benzyl glycosides [58] and novel thio- [59,60] and O-imidates [61,62] (Figure 1.2). In

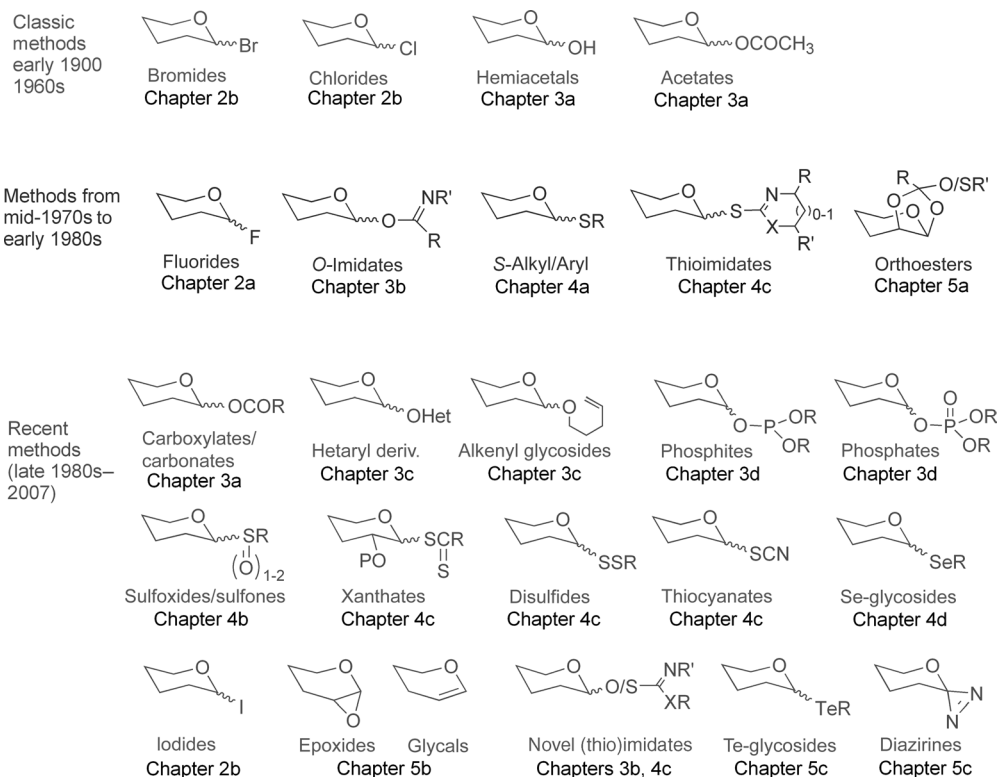


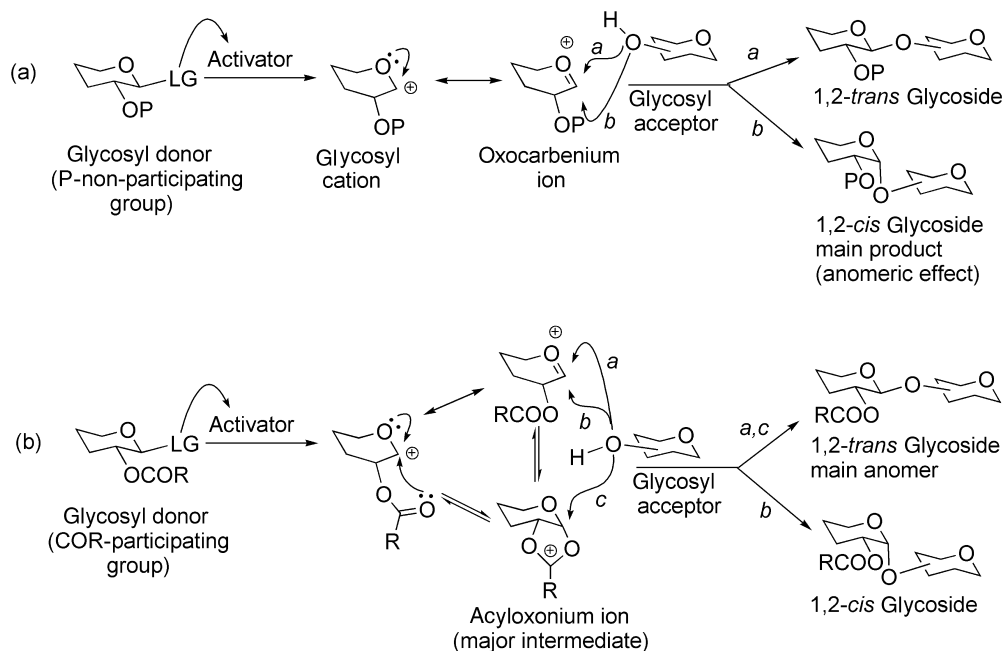
Figure 1.2 Survey of glycosyl donors.

addition, a variety of new recent methodologies bring the use of classic glycosyl donors such as hemiacetals to entirely different level of flexibility and usefulness [63]. These innovative concepts will be discussed in the subsequent chapters dealing with particular classes of glycosyl donors..

1.4

General Reaction Mechanism

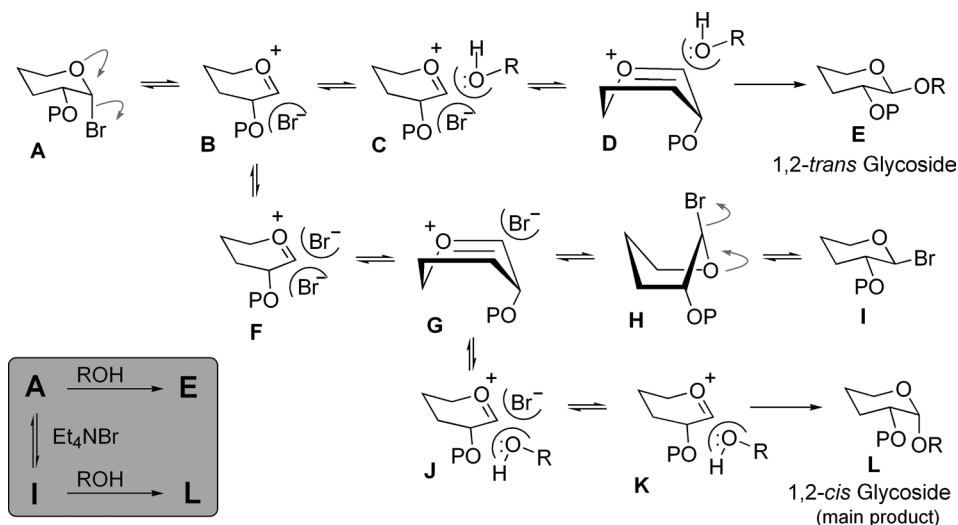
Detailed glycosylation mechanism has not been elucidated as yet; therefore, speculations and diagrams presented herein are a commonly accepted prototype of the glycosylation mechanism. Most commonly, the glycosylation reaction involves nucleophilic displacement at the anomeric center. As the reaction takes place at the secondary carbon atom with the use of weak nucleophiles (sugar acceptors), it often follows a unimolecular S_N1 mechanism. Glycosyl donors bearing a nonparticipating and a participating group will be discussed separately (Scheme 1.1a and b, respectively). In most cases, an activator (promoter or catalyst) assisted departure of the anomeric leaving group results in the formation of the glycosyl cation. The only



Scheme 1.1

possibility to intramolecularly stabilize glycosyl cation formed from the glycosyl donor bearing a non-participating group is by resonance from O-5 that results in oxocarbenium ion (Scheme 1.1a). The most commonly applied nonparticipating groups are benzyl (OBn) for neutral sugars and azide (N_3) for 2-amino-2-deoxy sugars; however, other moieties have also been occasionally used. The anomeric carbon of either resonance contributors is sp^2 hybridized; hence, the nucleophilic attack would be almost equally possible from either the top (*trans*, β - for the D-glucose series) or the bottom face (*cis*, α -) of the ring. Even though the α -product is thermodynamically favored because of the so-called anomeric effect (discussed in the subsequent section) [64], a substantial amount of the kinetic β -linked product is often obtained owing to the irreversible character of glycosylation of complex aglycones. Various factors such as temperature, protecting groups, conformation, solvent, promoter, steric hindrance or leaving groups may influence the glycosylation outcome (discussed below) [65,66].

1,2-*trans* Glycosidic linkage can be stereoselectively formed with the use of anchimeric assistance of a neighboring participating group, generally an acyl moiety such as *O*-acetyl (Ac), *O*-benzoyl (Bz), 2-phthalimido (NPhth) and so on [67–69]. These glycosylations proceed primarily via a bicyclic intermediate, the acyloxonium ion (Scheme 1.1b), formed as a result of the activator-assisted departure of the leaving group followed by the intramolecular stabilization of the glycosyl cation. In this case, the attack of a nucleophile (alcohol, glycosyl acceptor) is only possible from the top face of the ring (pathway c), therefore allowing stereoselective formation of a 1,2-*trans* glycoside. Occasionally, substantial amounts of 1,2-*cis*-linked products are also



Scheme 1.2

formed, most often when unreactive alcohols are used as the substrates and/or poorly nucleophilic participatory substituents are present at C-2. In these cases, glycosylation assumingly proceeds via oxocarbenium ion, via pathways a and b (Scheme 1.1b), resulting in the formation of 1,2-*trans* and 1,2-*cis* glycosides, respectively, or most commonly mixtures thereof.

Seminal work by Lemieux on the halide-ion-catalyzed glycosidation reaction involved extensive theoretical studies that gave rise to a more detailed understanding of the reaction mechanism [70]. Thus, it was postulated that a rapid equilibrium could be established between a relatively stable α -halide **A** and its far more reactive β -counterpart **I** by the addition of tetraalkylammonium bromide (Et_4NBr , Scheme 1.2). In this case, a glycosyl acceptor (ROH) would preferentially react with the more reactive glycosyl donor (**I**) in an $\text{S}_{\text{N}}2$ fashion, possibly via the tight ion-pair complex **K**, providing the α -glycoside **L**. It is likely that the energy barrier for a nucleophilic substitution $\text{I} \rightarrow \text{L}$ (formation of the α -glycoside) is marginally lower than that for the reaction $\text{A} \rightarrow \text{E}$ (formation of a β -glycoside). If the difference in the energy barrier were sufficient, it should be possible to direct the reaction toward the exclusive formation of α -anomers.

Therefore, to obtain complete stereoselectivity, 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 (R_4NBr), although very reactive substrates and prolonged reaction at times are required.

Other common approaches to control the stereoselectivity of glycosylation will be discussed in the subsequent sections. In addition to the apparent complexity of the glycosidation process, there are other competing processes that cannot be disregarded. These reactions often cause the compromised yields of the glycosylation products and further complicate the studies of the reaction mechanism.

Elimination, substitution (formation of unexpected substitution products or hydrolysis at the anomeric center), cyclization (inter- and intramolecular orthoesterification), migration and redox are only a few to mention [71].

1.5

Anomeric Effects

A basic rule of conformational analysis known from the introductory organic chemistry is that an *equatorial* substituent of cyclic six-membered hydrocarbons is energetically favored. Hence, it is more stable owing to 1,3-diaxial interactions that would have occurred if a large substituent were placed in the *axial* position (Figure 1.3). For sugars, this rule is only applicable to hemiacetals (1-hydroxy derivatives) that are stabilized in β -orientation via intramolecular hydrogen-bond formation with O-5. Other polar substituents such as halide, OR or SR attached to the anomeric center of pyranoses/pyranosides prefer the axial orientation, which would be exclusive if the equilibrium at the anomeric center could be achieved. This phenomenon, which was first observed by Edward [72] and defined as *anomeric effect* by Lemieux [73], is partially responsible for the stereochemical outcome of processes taking place at the anomeric center of sugars [64,74,75].

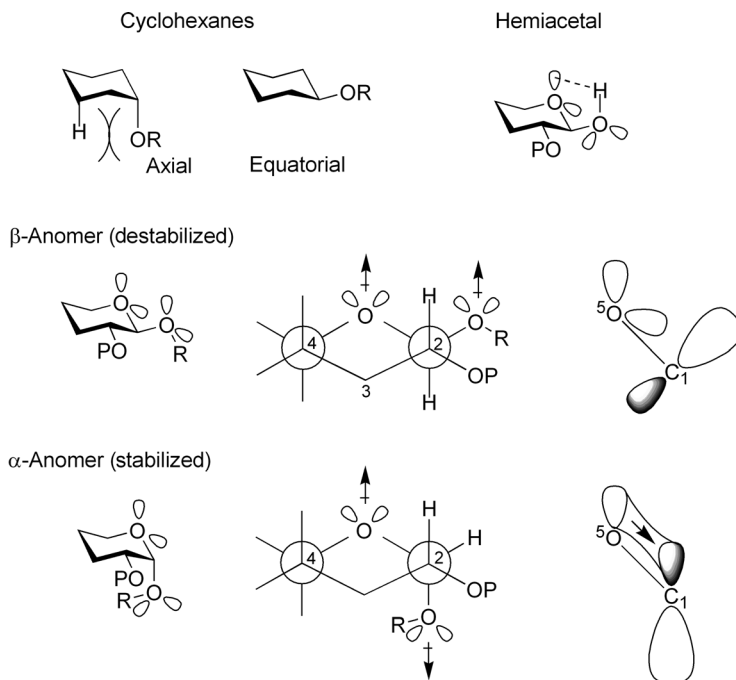


Figure 1.3 Anomeric effect.

What are the origins of the anomeric effect, sometimes referred to as *endo*-anomeric effect? In this context, the so-called *exo*-anomeric effect dealing with the stabilization of the β -anomer is of somewhat lesser influence on the overall process and will not be discussed herein [64]. One factor is that the substituent on the atom bonded to the ring at C-1 has lone-pair electrons, which would have repulsive interactions with those of the ring oxygen (O-5) if the anomeric substituent is in the equatorial position (β -position for D-sugars in 4C_1 conformation) but not if it is in the axial position (Figure 1.3). In addition, an electron-withdrawing axial substituent (α -anomer for D-sugars in 4C_1 conformation) is stabilized via hyperconjugation owing to the periplanar orientation of both nonbonding orbital of O-5 and antibonding orbital of C-1. This does not occur with the β -anomer, as the nonbonding orbital of O-5 and antibonding orbital of C-1 are in different planes and therefore are unable to interact.

1.6

Stereoselectivity of Glycosylation

As noted above, it is a general experience of carbohydrate synthesis that stereoselective preparation of 1,2-*cis* glycosides is more demanding than that of 1,2-*trans* glycosides. The formation of 1,2-*trans* glycosides is strongly favored by the neighboring-group participation (generation of intermediate acyloxonium ion). Typically, the use of a participating substituent at C-2 is sufficient to warrant stereoselective 1,2-*trans* glycosylation.

One of the factors affecting the stereochemical outcome of glycosidation of glycosyl donors bearing a nonparticipating substituent at C-2 is the anomeric effect, which favors α -glycoside formation (1,2-*cis* for the D-glucose series). However, because of the irreversible character of glycosylation, the role of the anomeric effect is diminished and other factors affecting the orientation of the new glycosidic bond (discussed below) often come to the fore. Although variation of reaction conditions or structural elements of the reactants may lead to excellent 1,2-*cis* stereoselectivity, no successful comprehensive method for 1,2-*cis* glycosylation has emerged as yet.

1.6.1

Structure of the Glycosyl Donor

1.6.1.1 Protecting Groups

The most powerful impact on the stereoselectivity is produced from the neighboring group at C-2. Neighboring-group participation is one of the most powerful tools to direct stereoselectivity toward the formation of a 1,2-*trans*-linked product. The neighboring substituent at C-2 is also responsible for the ‘armed–disarmed’ chemoselective glycosylation strategy [76]. The effects of the remote substituents are of lesser importance; however, there is strong evidence that a substituent at C-6 position may influence the stereochemical outcome of glycosylation dramatically. Although experimental proof has not emerged as yet, a possibility for the long-range 6-*O*-acyl or carbonate

group assistance resulting in the preferential formation of α -glucosides cannot be overruled [77–81]. It was also found that the steric bulkiness or strong electron-withdrawing properties of a substituent at C-6 are beneficial for 1,2-*cis* glucosylation, most likely because of shielding (sterically or electronically) the top face of the ring and, therefore, favoring the nucleophilic attack from the opposite side [14,82–88].

Although the effect of the C-6 substituent was found to be of minor importance for the derivatives of the D-galacto series [89], a remote effect is sufficiently strong when a participating moiety is present at C-4 [90,91]. Thus, the use of *p*-methoxybenzoyl (anisoyl) [91] and diethylthiocarbamoyl [81] groups was found to be exceptionally beneficial for the formation of α -galactosides. Similar effects (including C-3 participation) were also detected for the derivatives of the L-fuco [92,93], L-rhamno [94], D-manno and D-glucosyl [14,82,95] series [96]. It was noted that when the unprotected hydroxyl is present at C-4 of the sulfamidogalacto donor, the expected β -glycosyl formation occurs. However, when the hydroxyl group is blocked with benzyl or acyl, the process unexpectedly favors α -glycoside formation. This phenomenon was rationalized via the formation of the intramolecular hydrogen bonding (C4–O–H $\cdots$ O–C5), destabilizing oxocarbenium ion contribution to the reaction mechanism that favors α -glycosylation (pathway b, Scheme 1.1a). Torsional effects induced by the cyclic acetal protecting groups may also strongly affect the stereoselectivity at the anomeric center; however, these effects remain unpredictable at this stage [88,97–99].

1.6.1.2 Leaving Group

There are a large number of publications describing the comparison of various glycosylation methods applied for particular targets. However, only few principles could be reliably outlined. It has been unambiguously demonstrated that halides activated in the presence of a halide ion (from, e.g. Bu_4NBr) often provide the highest ratios of α -/ β -glycosides [100–104]. Since in most cases the glycosylation reactions proceed via unimolecular $\text{S}_{\text{N}}1$ mechanism, the orientation of the leaving group at the anomeric center is of lesser importance. However, the glycosylation reactions occasionally proceed via bimolecular $\text{S}_{\text{N}}2$ mechanism with the inversion of the anomeric configuration. In this context, glycosyl donors with 1,2-*cis* orientation form 1,2-*trans* glycosides: for example glycosyl halides with insoluble catalysts (also used for β -mannosylation) [105], α -imidates in the presence of boron trifluoride etherate ($\text{BF}_3\text{--Et}_2\text{O}$) at low temperature [106] and 1,2-anhydro sugars [107]. Conversely, 1,2-*trans*-oriented glycosyl donors stereospecifically afford 1,2-*cis* glycosides, for example highly reactive β -glucosyl halides [70], glycosyl thiocyanates [39,108] and anomeric triflates formed *in situ* were found superior for the synthesis of β -mannosides [109,110].

1.6.2

Structure of the Glycosyl Acceptor

1.6.2.1 Position of the Hydroxyl

Alcohol reactivity is typically inversely correlated with the 1,2-*cis* stereoselectivity – the most reactive hydroxyls give the lowest α -/ β -ratios – the stronger the nucleophile,

the faster the reaction, and hence the more difficult it is to control. Regarding the sugar or aliphatic glycosyl acceptors, the general rule normally states that glycosylation of more reactive primary hydroxyl provides poorer stereoselectivity in comparison to that when the secondary hydroxyls are involved [111]. The same principles are applicable for the synthesis of glycopeptides; thus, the glycosylation of the secondary hydroxyl of threonine typically gives higher α -stereoselectivity than when primary hydroxyl group of serine is glycosylated with 2-azido-2-deoxy-galactosyl bromide or trichloroacetimidates [112,113]. Occasionally, primary hydroxyls provide somewhat higher 1,2-*cis* stereoselectivity in comparison to that of the secondary hydroxyl groups. This can serve as an indirect evidence of the glycosylation reaction proceeding via the bimolecular mechanism, at least partially.

1.6.2.2 Protecting Groups

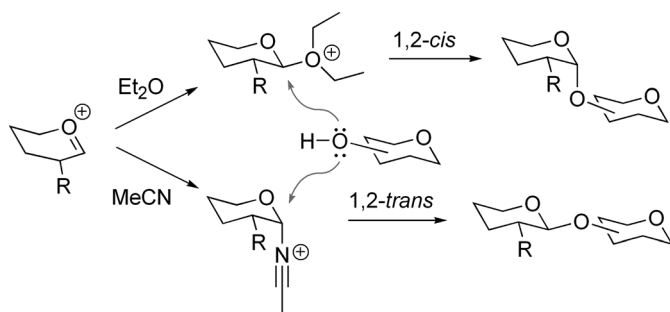
It is well established that ester-electron-withdrawing substituents reduce electron density of the neighboring hydroxyl group by lowering its nucleophilicity [88,105,114]. This may improve stereoselectivity, as the reaction can be carried out in a more controlled manner. As an example, glycosylation of axial 4-OH of galactose often gives excellent 1,2-*cis* stereoselectivity, especially in combination with electron-withdrawing substituents (e.g. *O*-benzoyl, OBz) [115]. However, poorly reactive hydroxyls can lose their marginal reactivity completely when surrounded by the deactivating species, resulting in lower glycosylation yields.

1.6.3

Reaction Conditions

1.6.3.1 Solvent Effect

Another important factor that influences the stereoselectivity at the anomeric center is the effect of the reaction solvent. In general, polar reaction solvents increase the rate of the β -glycoside formation via charge separation between O-5 and β -O-1. If the synthesis of α -glycosides is desired, CH_2Cl_2 , $\text{ClCH}_2\text{CH}_2\text{Cl}$ or toluene would be suitable candidates as reaction solvents. However, there are more powerful forces than simple solvation that have to be taken into consideration. The so-called participating solvents, such as acetonitrile and diethyl ether, were found to be the limiting cases for the preferential formation of β -D- and α -D-glucosides, respectively [78]. These observations were rationalized as follows: if the reactions are performed in acetonitrile, the nitrilium cation formed *in situ* exclusively adopts axial orientation, allowing stereoselective formation of equatorially substituted glycosides (Scheme 1.3). This approach allows obtaining 1,2-*trans* glucosides with good stereoselectivity even with glycosyl donors bearing a nonparticipating substituent. On the contrary, ether-type reaction solvents such as diethyl ether, tetrahydrofuran [116] or dioxane [117] can also participate in the glycosylation process. Differently, in these cases the equatorial intermediate is preferentially formed, leading toward the axial glycosidic bond formation [85,86,118–120]. Nitroethane was also employed as a suitable solvent for 1,2-*cis* glycosylation [121].



Scheme 1.3

1.6.3.2 Promoter (Catalyst), Additions

Milder activating conditions are generally beneficial for 1,2-*cis* glycosylation. Thus, halide-ion-catalyzed reactions give the best results for the glycosylation with glycosyl halides [70]; thioglycosides perform better when activated with a mild promoter, such as iodonium dicollidine perchlorate (IDCP) [122,123]; whereas trichloroacetimidates are best activated with the strong acidic catalysts, such as trimethylsilyl trifluoromethanesulfonate (TMS-triflate, TMSOTf) or trifluoromethanesulfonic acid (triflic acid, TfOH) [106]. Various additions to the promoter systems often influence the stereochemical outcome of the glycosylation. Among the most remarkable examples is the use of perchlorate ion additive that was found to be very influential in 1,2-*cis* glycosylations [118,124].

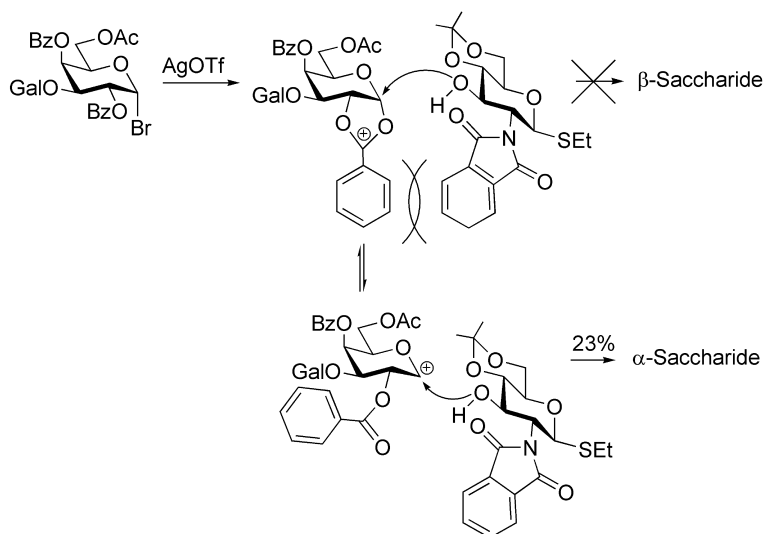
1.6.3.3 Temperature and Pressure

High pressure applied to the reactions with participating glycosyl donors further enhances 1,2-*trans* selectivity [125]; when the high-pressure conditions were applied for glycosylations with a nonparticipating glycosyl donor, remarkable increase in the reaction yield was noted with only marginal changes in stereoselectivity [126]. Kinetically controlled glycosylations at lower temperatures generally favor 1,2-*trans* glycoside formation [100,120,127–130], although converse observations have also been reported [131,132].

1.6.4

Other Factors

Unfavorable steric interactions that occur between glycosyl donor and acceptor in the transition state or other factors or conditions may unexpectedly govern the course and outcome of the glycosylation process. One of the most remarkable effects, the so-called ‘double stereodifferentiation’ takes place when stereochemical interactions between bulky substituents in glycosyl donor and glycosyl acceptor prevail the stereodirecting effect of a neighboring participating group. The pair of reagents where these interactions occur is called a ‘mismatched pair’. Thus, only α -linked product was unexpectedly formed with 2-phthalimido glycosyl acceptor (Scheme 1.4). [133]. A coupling of the same glycosyl donor with conformationally



Scheme 1.4

modified 1,6-anhydro acceptor afforded β -linked oligosaccharide with 75% yield. It was also demonstrated that if this effect takes place with a sugar of the D-series, its L-enantiomer forms a matched pair with the same glycosyl acceptor.

1.7

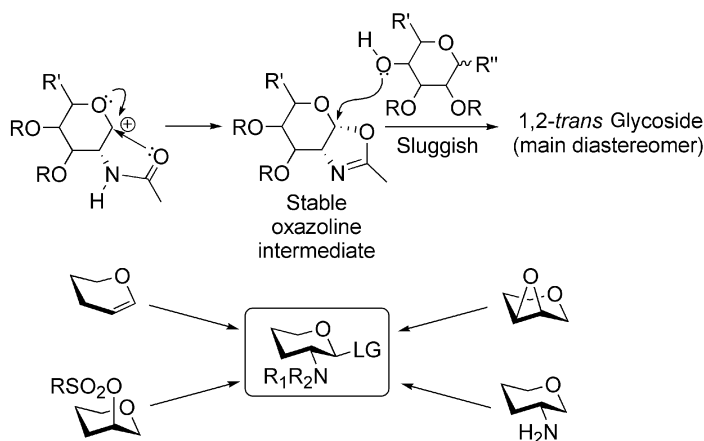
Special Cases of Glycosylation

This section outlines special cases of glycosylation, not necessarily uncommon, which do not follow general conventions discussed above. It is not unusual when general glycosylation methods do not work or cannot be applied to the synthesis of glycosides described herein. The synthesis of each of these classes of compounds requires careful selection of techniques, their modification or design of conceptually new approaches. Sometimes special indirect or total synthesis based technologies have been developed and applied specifically to the synthesis of these targets.

1.7.1

Aminosugars

Glycosides of 2-amino-2-deoxy sugars are present in the most important classes of glycoconjugates and naturally occurring oligosaccharides, in which they are connected to other residues via either 1,2-*cis* or, more frequently, 1,2-*trans* glycosidic linkage [134–136]. In particular, 2-acetamido-2-deoxyglycosides, most common of the D-glucose and D-galactose series, are widely distributed in living organisms as glycoconjugates (glycolipids, lipopolysaccharides, glycoproteins) [134], glycosaminoglycans (heparin,



Scheme 1.5

heparin sulfate, dermatan sulfate, chondroitin sulfate, hyaluronic acid) [137] and so on [138,139]. Special efforts for the synthesis of glycosyl donors of 2-amino-2-deoxy sugars have been focusing on the development of simple, efficient, regio- and stereo-selective procedures.

As a vast majority of naturally occurring 2-amino-2-deoxy sugars are *N*-acetylated, from the synthetic point of view, a 2-acetamido-2-deoxy substituted glycosyl donor would be desirable to minimize protecting-group manipulations. For this type of glycosyl donors, however, the oxocarbenium ion rearranges rapidly into an oxazoline intermediate (Scheme 1.5). Even under harsh Lewis acid catalysis, this highly stable oxazoline intermediate does not exert strong glycosyl-donor properties. Although the synthesis of 1,2-*trans* glycosides is possible with the use of this type of glycosyl donors, the synthesis of 1,2-*cis* glycosides is a burden. As a matter of fact, the participating nature of the *N*-acetyl moiety presents an obvious hindrance when the formation of the α -linkage is desired. A minimal requirement for the synthesis of 1,2-*cis* glycosides would be the use of a C-2 nonparticipating moiety.

Nowadays, a variety of synthetic approaches to the synthesis of 2-amino-2-deoxyglycosides have been developed, and progress in this area has been reviewed [140–142]. These syntheses are started either from a glycosamine directly or by the introduction of nitrogen functionality to glucose or glycal derivatives. To this end, various glycosamine donors with modified functionalities have been investigated; in particular, those bearing an N-2 substituent capable of either efficient participation via acyloxonium, but not (2-methyl) oxazoline, intermediate for 1,2-*trans* glycosylation or a nonparticipating moiety for 1,2-*cis* glycosylation.

1.7.2

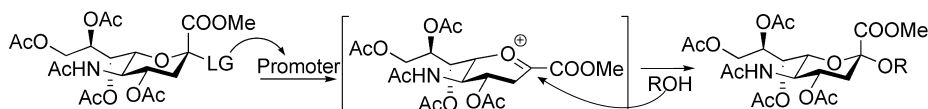
Sialosides

Sialic acids are nine-carbon monosaccharides involved in a wide range of biological phenomena. Their unique structure is characterized by the presence of a carboxylic

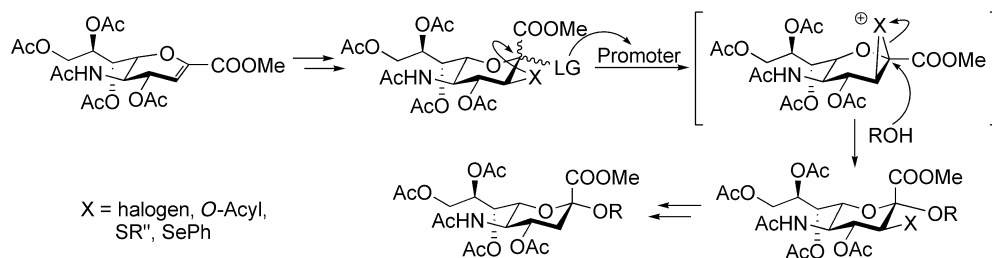
group (ionized at physiological pH), deoxygenated C-3, glycerol chain at C-6 and differently functionalized C-5. Among the 50 derivatives reported so far, *N*-acetylneuraminic acid (5-acetamido-3, 5-dideoxy-*D*-glycero-*D*-galacto-non-2-ulopyranosonic acid, Neu5Ac) is the most widespread. The natural equatorial glycosides and their unnatural axial counterparts are classified as α - and β -glycosides, respectively. In spite of extensive efforts and notable progress, the chemical synthesis of sialosides remains a significant challenge [143–146]. The presence of a destabilizing electron-withdrawing carboxylic group and the lack of a participating auxiliary often drive glycosylation reactions toward competitive elimination reactions, resulting in the formation of a 2,3-dehydro derivative and in poor stereoselectivity (β -anomer). To overcome these problems, a variety of leaving groups and activation conditions for direct sialylations have been developed. It was also demonstrated that the *N*-substituent at C-5 plays an influential role in both stereoselectivity of sialylation and the reactivity of sialyl donors [147].

Along with these studies, a variety of indirect methods for chemical sialylation have been developed. Several glycosyl donors derived from Neu5Ac have been prepared that possess an auxiliary at C-3. This auxiliary should control the anomeric selectivity of glycosylation by neighboring-group participation, leading to the formation of 2,3-*trans*-glycosides [143]. Thus, α -glycosides are favored in the case of equatorial auxiliaries (Scheme 1.6), whereas β -glycosides are preferentially formed when the participating auxiliary is axial. The auxiliaries also help in preventing 2,3-elimination that often constitutes a major side reaction in the direct *O*-sialylations. One of the most important requirements is that an auxiliary should be easily installed prior to, and removed after, glycosylation. Usually, the auxiliaries are introduced by a chemical modification of the readily accessible 2,3-dehydro derivative of Neu5Ac [148]. These transformations can be performed

Direct sialylations



Indirect sialylations



Scheme 1.6

either through a 2,3-oxirane derivative or by a direct addition reaction to the double bond.

1.7.3

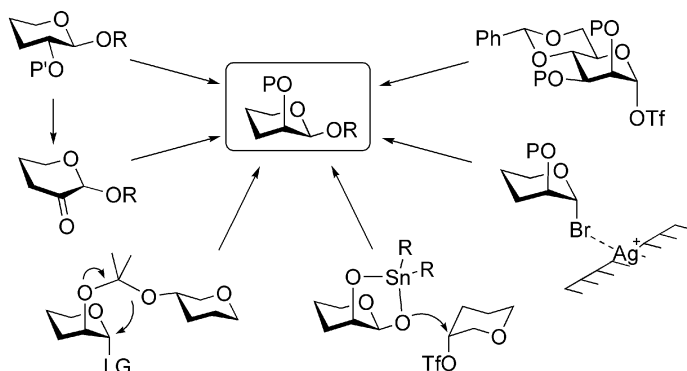
Synthesis of 2-Deoxyglycosides

2-Deoxyglycosides are important constituents of many classes of antibiotics. The development of reliable methods for stereoselective synthesis of both α - and β -2-deoxyglycosides has become an important area of research and development of new classes of drugs and glycomimetics [149,150]. It should be noted that because of the lack of anchimeric assistance of the substituent at C-2, the synthesis of both types of linkages represents a notable challenge. On one hand, the direct glycosylation of 2-deoxy glycosyl donors often results in the formation of anomeric mixtures. Similar to that of conventional glycosylation, the solvent and promoter effects play important stereodirecting roles in the synthesis. On the other hand, similar to that discussed for the sialosides, a participating auxiliary can be used to add to the stereoselectivity of glycosylation. Usually this moiety is introduced through 1,2-dehydro derivatives with concomitant or sequential introduction of the anomeric leaving group. The methods employing both axial and equatorial substituents are known to result in the formation of 1,2-*trans* glycosides, which upon 2-deoxygenation can be converted into the respective targets. Although this latter approach requires additional synthetic steps, it is often preferred because it provides higher level of stereocontrol.

1.7.4

Synthesis of β -Mannosides

β -Mannosyl residues are frequently found in glycoproteins. The chemical synthesis of 1,2-*cis*- β -mannosides cannot be achieved by relying on the anomeric effect that would favor axial α -mannosides at the equilibrium. In addition, it is further disfavored by the repulsive interactions that would have occurred between the axial C-2 substituent and the nucleophile approaching from the top face of the ring. For many years the only direct procedure applicable to β -mannosylation – Ag-silicate promoted glycosidation of α -halides – was assumed to follow bimolecular S_N2 mechanism [13,14]. The difficulty of the direct β -mannosylation was addressed by developing a variety of indirect approaches such as C-2 oxidation-reduction, C-2 inversion, anomeric alkylation and intramolecular aglycone delivery (Scheme 1.7) [151–155]. This was the standing in this field before Crich and coworkers discovered that 4,6-*O*-benzylidene protected sulfoxide [109] or thiomannoside [110] glycosyl donors provide excellent β -manno stereoselectivity. Mechanistic and spectroscopic studies showed that anomeric α -*O*-triflates generated *in situ* as reactive intermediates can be stereospecifically substituted. On a similar note, 2-(hydroxycarbonyl)benzyl glycosides have proven to be versatile glycosyl donors for the synthesis of β -mannosides via anomeric triflate intermediates [58].



Scheme 1.7

1.7.5

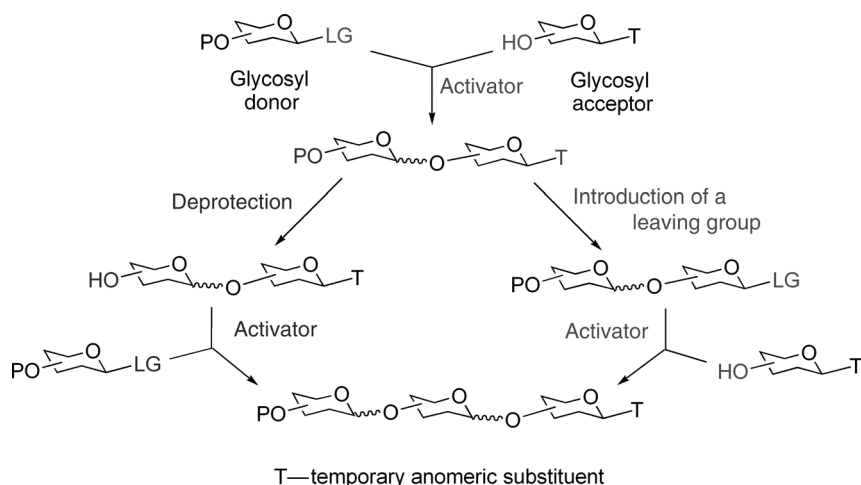
Synthesis of Furanosides

In comparison to their six-membered ring counterparts, furanosides are relatively rare. Nevertheless, their presence in a variety of glycostructures from bacteria, parasites and fungi makes this type of glycosidic linkage an important synthetic target [156,157]. The synthesis of 1,2-*trans* furanosides is relatively straightforward and, similar to that of pyranosides, can be reliably achieved with the use of glycosyl donors bearing a participating group at C-2. In contrast, the construction of 1,2-*cis*-glycofuranosidic linkage is difficult, even more so than with pyranosides, because the stereocontrol in glycofuranosylation cannot be added by the anomeric effect owing to the conformational flexibility of the five-membered ring. In fact, both stereoelectronic and steric effects favor the formation of 1,2-*trans* glycofuranosides. Despite some recent progress, stereoselective synthesis of 1,2-*cis* glycofuranosides has been one of the major challenges of synthetic chemistry. General glycosylation methods, involving glycosyl fluorides [158], trichloroacetimidates [159], and thioglycosides [156,160] along with less common and indirect techniques [161–164], were applied to 1,2-*cis* furanosylation. More recently, a notable improvement in stereoselectivity of 1,2-*cis* furanosylation was achieved by using glycosyl donors in which the ring has been locked into a single conformation. These examples include 2,3-anhydro [165–169], 3,5-*O*-(di-*tert*-butylsilylene) [170,171] and 3,5-*O*-tetraisopropylidisiloxanylidene [172] protected bicyclic glycosyl donors.

1.8

Glycosylation and Oligosaccharide Sequencing

Stereoselective glycosylation is only a part of the challenge that synthetic chemists confront during the synthesis of oligosaccharides. Regardless of the efficiency of a single glycosylation, a traditional stepwise approach requires subsequent conversion of the disaccharide derivative into the second-generation glycosyl acceptor or glycosyl



Scheme 1.8 Linear oligosaccharide synthesis.

donor (see Scheme 1.8). The modified disaccharides are then coupled with a glycosyl donor (or acceptor) to obtain a trisaccharide. This reaction sequence is then repeated again until oligosaccharide of the desired chain length is obtained.

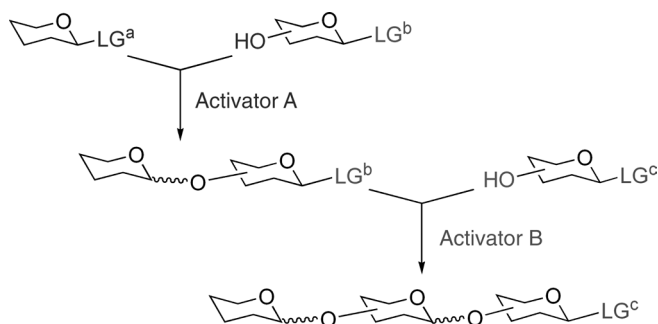
It has become apparent that the linear approach is too inefficient and lengthy, especially when applied to the synthesis of large oligosaccharides. As a result, the past two decades have witnessed a dramatic improvement in the methods and strategies used for oligosaccharide synthesis. The first attempt to address challenges associated with the linear stepwise approach was the development of a convergent approach [105,173,174]. According to this approach, oligosaccharide building blocks are obtained separately and then coupled together, which, in comparison to the linear approach, allows formation of larger saccharides faster. It is especially advantageous if the synthesis of two or more sequential repeat units is desired for the introduction of a ‘difficult’ linkage, such as 1,2-*cis*, at an earlier stage of the saccharide assembly to avoid complicated diastereomer separation at the later stage.

When the arsenal of the glycosylation techniques was limited to Fischer and Koenigs–Knorr approaches (or their variations), the oligosaccharide assembly was limited to the linear and block techniques. However, when stable glycosyl donors such as thioglycosides or *O*-alkenyl glycosides emerged, a question of selective or chemoselective activation arose. In brief, most recently developed strategies fit into three broad categories: leaving-group-based (selective or orthogonal activation), preactivation-based and protecting-group-based (armed–disarmed) strategies [175].

1.8.1

Leaving-Group-Based Strategies

The schematic outline of the stepwise selective activation is shown in Scheme 1.9; thus, a glycosyl donor, bearing a reactive LG^a, is coupled with a glycosyl acceptor,



Scheme 1.9 Stepwise selective activation.

bearing a relatively stable LG^b at the anomeric center. The major requirement for this reaction to take place is the use of a suitable activator that would selectively activate LG^a but not LG^b (Activator A). Early studies involved the activation of alkyl halides over *S*-alkyl/aryl glycosides [173,176–179]. Subsequently, other examples of suitable LG^a for selective activations have become available: trichloroacetimidates, phosphite, phosphate, thioimide, hemiacetal, sulfoxide, selenoglycoside, orthoester and so on [175]. Many of these couplings were performed with the use of either *S*-alkyl/aryl or *O*-alkenyl/hetaryl moieties as LG^b . In principle, the activation sequence can be continued providing that there is an LG^c that would withstand reaction conditions for the LG^b activation (Activator B). However, these elongated multistep sequences are not yet routinely available. Few available examples include the following three-step activation sequences: bromide as LG^a , Se-phenyl as LG^b , and *S*-ethyl as LG^c [180]; *S*-benzoxazolyl (SBox) as LG^a , *S*-ethyl as LG^b , and *O*-pentenyl as LG^c [181]; SBox as LG^a , *S*-thiazolinyl (STaz) as LG^b , *S*-ethyl as LG^c [182] and so on [183].

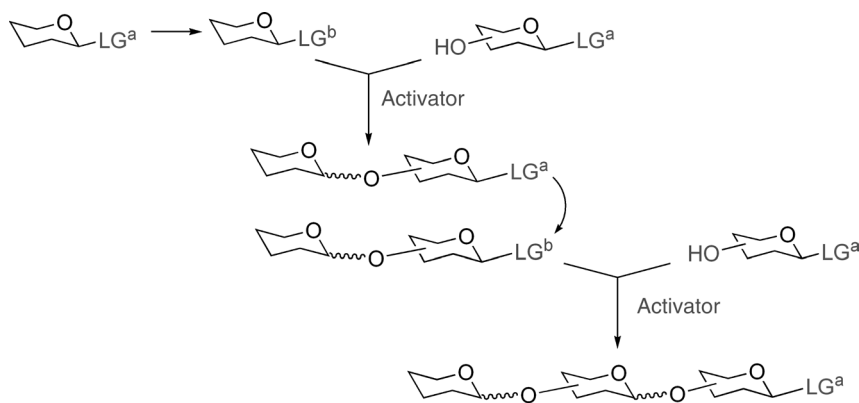
The combination of two chemically distinct glycosylation reactions, in which one of the leaving groups is activated while the other one remains intact and vice versa, has led to the discovery of the orthogonal glycosylation strategy [184]. This unique and virtually one of the most advanced techniques for oligosaccharide synthesis requires the use of orthogonal glycosyl donors [185]. Typically, phenyl thioglycosides are selectively activated over glycosyl fluorides and vice versa [184,186,187]. Recently, it has been discovered that a combination of *S*-ethyl and *S*-thiazolinyl glycosides also allows orthogonal activation [188].

A one-pot technique, combining two or more glycosylation steps based on activation of one donor over another, have also been developed [182,189–191]. This one-pot technique is virtually a variation of a simple stepwise selective activation strategy, which allows further improvement in the efficiency of the synthesis by avoiding the necessity for isolation (and purification) of the intermediates.

1.8.2

Two-Step Activation and Preactivation Strategies

According to the two-stage activation (or preactivation) approach, both glycosyl donor and glycosyl acceptor initially bear the same type of a leaving group (LG^a).



Scheme 1.10 Two-step activation concept.

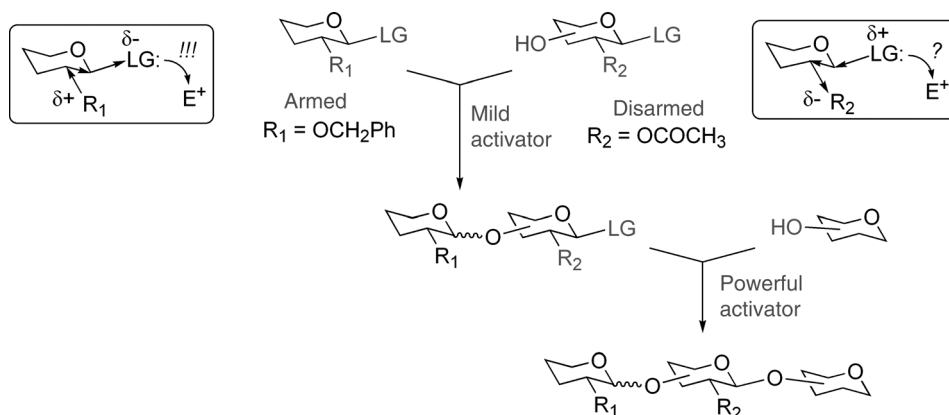
However, to couple these two reactants, the LG^a of the potential glycosyl donor unit is first converted into an LG^b , which is then selectively activated over LG^a of the glycosyl acceptor in the presence of a selective activator (Activator B, Scheme 1.10). This two-step activation sequence can be reiterated; for this purpose the leaving group of the obtained disaccharide LG^a is again converted into LG^b and so on. This concept was discovered for *S*-ethyl (LG^a) and bromo (LG^b) moieties [173] and further explored for other systems [176,192–194]. The same principle was applied by Danishefsky in the reiterative glycal assembly approach [43,195,196]. This technique involves the transformation of glycals into 1,2-anhydro sugars, which can be easily glycosidated with partially protected glycal-based glycosyl acceptors. Recently, the versatility of the two-step activation was demonstrated by a one-pot preactivation procedure [197,198], according to which *S*-tolyl glycosides are converted *in situ* into a reactive intermediate.

Similar principle is executed in the active–latent approach that has been applied to a number of systems [51,193,199,200]. It is important to note that the conversion between LG^a and LG^b in the active–latent approach does not involve substitution at the anomeric center; instead, a simple modification of the leaving group itself is executed. Recently, the application of this technique was enhanced by the discovery that 2-(benzyloxycarbonyl)benzyl glycosides are perfectly stable compounds, whereas the corresponding 2-(hydroxycarbonyl)benzyl moiety, obtained by the selective hydrogenolysis is an excellent leaving group that can be readily activated [58]. This and other conceptually similar recent discoveries [56,201] open new exciting perspectives for further development of the active–latent strategy.

1.8.3

Protecting-Group-Based Strategies

Another efficient strategy, the armed–disarmed approach, developed by Fraser-Reid is based on the chemoselectivity principle [193,202]. According to this



Scheme 1.11 Armed–disarmed strategy.

technique, a benzylated (electronically activated, armed) glycosyl donor is chemoselectively activated over the acylated (electronically deactivated, disarmed) derivative bearing the same type of LG in the presence of a mild promoter (Scheme 1.11). At the first step a 1,2-*cis*-linked disaccharide is preferentially obtained because of the use of the ether-type arming substituent, a nonparticipating group (O-benzyl). The obtained disaccharide can then be used for 1,2-*trans* glycosylation directly in the presence of a more potent promoter, capable of activating the disarmed LG.

Initially developed for O-pentenyl glycosides, this concept was further explored for the chemoselective glycosidations of ethyl thioglycosides, selenoglycosides, fluorides, phosphoroamidates, substituted thioformimidates, glycals, benzoxazolyl and thiazolynyl glycosides [175]. The chemoselective activation has become the basis of programmable multistep reactivity-based technique, including highly efficient one-pot approaches [203,204]. Further insights into the armed–disarmed approach came with the observation of the unusual reactivity pattern of the SBox glycosides. Thus, it was demonstrated that glycosyl donors with 2-O-benzyl-3,4,6-tri-O-acyl protecting-group pattern are even more deactivated than the corresponding ‘disarmed’ peracyl derivatives [205]. Although the exact nature of this so-called O-2/O-5 cooperative interesting effect is not yet understood, it has been postulated that the intermediate carbocation stabilization via the acyloxonium ion of the peracylated donor is favored over the oxocarbenium ion stabilization of the 2-O-benzyl-3,4,6-tri-O-acylated donors. Another interesting concept is the use of 2-O-picolyl substituent as an arming participating group. According to this so-called inverse armed–disarmed method, the 1,2-*trans* glycosidic linkage can be chemoselectively introduced at the first glycosylation step [206].

1.9

Conclusions and Outlook

The progress in the area of chemical glycosylation has significantly improved our ability to synthesize various glycosidic linkages with impressive yields and stereoselectivity. But, can we conclude that we have entirely solved the problem of chemical glycosylation? Unfortunately not, and hopefully this chapter introduced the reader to the challenge of chemical glycosylation, a variety of factors, conditions, and driving forces influencing all aspects of this complex chemical reaction as well as prepared for studying more specialized material dedicated to particular methods and strategies employed in modern carbohydrate chemistry. Recent progress made in the area of development of new coupling methods and highly efficient strategies for expeditious oligosaccharide synthesis will ultimately provide an efficient and trouble-free access to complex saccharides. This goal cannot be achieved without the comprehensive knowledge of the glycosylation mechanism and driving forces of glycosylation and competing side processes. It is likely that the consecutive scientific development in this field will be focusing on studying the fundamental mechanistic aspects of glycosylation rather than developing additional anomeric leaving groups.

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