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MINI REVIEW

# Glycosylation reactions – present status future directions

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Received 8 June 1995. Dedicated to Professor J.J. Krepinsky on the occasion of his 60th birthday

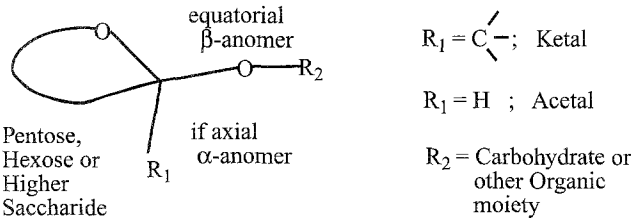
A short review of the present status of glycosylation reactions is presented. The reactivity of both proven and newer glycosylation methods are briefly discussed. Emphasis is placed on the control of stereochemistry and regiochemistry. As well, the identification and avoidance of side reactions is covered. Polymer-supported synthesis of oligosaccharides is noted as a promising direction for eliminating some of the problems associated with purification. It is suggested that a better understanding of the mechanism of glycosylation reactions is necessary for future improvements to stereoselectivity and regioselectivity. A key advance would be methods for enhancing the reactivity of weakly nucleophilic hydroxyls.

*Keywords*: glycosylation reactions, glycosyl donor, reactivity, stereoselectivity, regioselectivity, side reactions

*Abbreviations*: $BF_3$ $OEt_2$, boron trifluoride diethyl ether complex; TMSOTf, trimethylsilyl trifluoromethanesulfonate; NIS NBS, *N*-iodosuccinimide and *N*-bromosuccinimide; TfOH, trifluoromethanesulfonic acid or triflic acid; AgOTf $CuOTf_2$, silver triflate and copper(II)triflate; $Tf_2O$, triflic anhydride; IDCP, iodonium dicollidine perchlorate; TEP, triethyl phosphite; $HfCp_2Cl_2$, hafnium dicyclopentadienyl dichloride; Ac, acetyl; Bz, benzoyl; Bn, benzyl; Ph, phenyl; Me, methyl; Et, ethyl; $Bu_4NOTf$, tetrabutylammonium triflate; $Ph_2IOTf$, diphenyliodinium triflate; PhSeNPhth, *N*-(phenylseleno)phthalimide; Pent, 4-pentenyl. TCI, trichloroactemidyl; TBDPS, *t*-butyl diphenylsilyl; DTBP, 2,6-di-*t*-butylpyridine; Tr, trityl or triphenylmethyl.

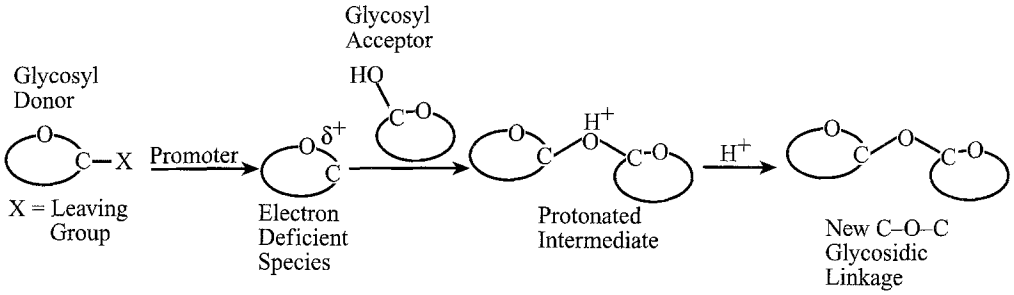
## Introduction

The possibilities of major biomedical applications based on glycobiology have dramatically increased the demand for glycoconjugates [1]. To meet this demand synthetic methodologies that are both inexpensive and efficient are necessary. Glycoconjugates are carbohydrates which are joined by acetal or ketal linkages (see Scheme 1) to another carbohydrate or organic moiety. The construction of such linkages via glycosylation reactions is the major challenge facing carbohydrate chemists. Stereocontrol (the ability to select from one of the $\alpha$ or $\beta$ anomers possible) remains the single most difficult hurdle to overcome. Regiochemical control (the ability to select one particular site of reaction) is also necessary for polyhydroxylated carbohydrates. Commercial applications of oligosaccharides depend on a solution to the control of stereochemistry and other problems which will be addressed in this account.




**Scheme 1.** Schematic representation of a glycosidic linkage.

This mini-review will not attempt to chronicle all the recent progress in carbohydrate chemistry which has been described in reviews [2], books [3] and specialized reports on heparin derived antithrombotics [4], aminoglycosides [5], glycopeptides [6], polysaccharides [7] and neoglycoconjugates [8]. Instead this report will focus on




**Scheme 2.** Schematic representation of a glycosylation reaction showing activation of the glycosyl donor by a promoter and subsequent reaction with an acceptor.

reactivity, stereoselectivity, regioselectivity and side reactions in glycosylation reactions.

Most glycosylation methods involve activation of one sugar residue, the glycosyl donor, to an electron deficient reactive intermediate followed by the nucleophilic attack of an oxygen atom of a second organic residue, the glycosyl acceptor. Subsequent deactivation, usually proton transfer, forms a new glycosidic linkage, as shown schematically in Scheme 2. A variety of leaving groups have been designed which generally lead in the presence of the appropriate promoters to electron deficient species. Electron deficient species are often called oxocarbenium ions in the literature but in the non-polar solvents used for glycosylation reactions it is unlikely that true discrete charged species actually exist. These reactive species are probably better described by polarized bonds $\delta^+$–$\delta^-$ where the partial negative charge accumulates on the counterion or solvent. Reactive donors have been developed for most of the sugars commonly found in nature. Furthermore, in most cases the desired stereochemistry of the linkage can be controlled by the stereoelectronic properties of the donor in conjunction with the appropriate choice of promoter and solvent [9]. However, with unreactive hydroxyls (weak nucleophiles) not only the yield but the stereochemistry depends on the acceptor [10]. Typically, acceptors are prepared with all hydroxyls but one derivatized with protecting groups. These protecting groups impart additional stereoelectronic factors to the free hydroxyl besides the intrinsic reactivity factors. At present no general explanation of these reactivity phenomena has been developed. Glycosylation reactions are also often accompanied by side reactions. Most commonly these involve decomposition of the activated glycosyl donor. Recent progress has been to develop methodologies which not only avoid these problems but allow them to be recognized in the planning stages of a synthesis [11].

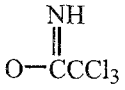
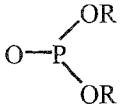
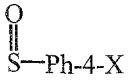
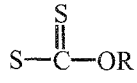
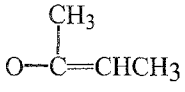
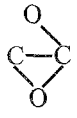
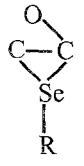
## Reactivity

For most glycosylation reactions the use of often unstable glycosyl halides and heavy metal salt promoters, the Koenigs Knorr reaction and its variants, has largely been replaced by newer methods. Today most glycosyl donors have non-halogen leaving group attached to the anomeric centre and are typically activated with Lewis acids as promoters, see Scheme 2. An older method which has been renewed is the activation by addition to the double bond of a glycal [12]. Many leaving groups have been introduced and an even greater number of activation conditions for existing leaving groups have been developed. A representative selection of glycosyl donors and activation methods is given in Table 1.

Widely used donors are glycosyl trichloroacetimidates [2h, 13], thioethers [14] and fluorides [15]. Glycosyl fluorides are not considered with the usual halides since they are more stable and are activated by different promoters [16]. Fluorides are usually activated by $HfCp_2Cl_2$ with or without AgOTf [17] or by $SnCl_2$/$AgClO_4$ [18]. Trichloroacetimidates are usually activated with catalytic quantities of $BF_3OEt$ or TMSOTf [19]. Improved yields are sometimes found by 'inverse addition' i.e. adding a solution of the donor to a catalyst plus acceptor solution [20]. This procedure is envisaged to proceed through a more reactive catalyst:acceptor complex (see below). Sometimes the Lewis acids react with the substrates or their protecting groups in which cases milder metal salts like $CoBr_2$, $CuOTf_2$ and AgOTf acting as Lewis acids can be a valuable alternative [21].

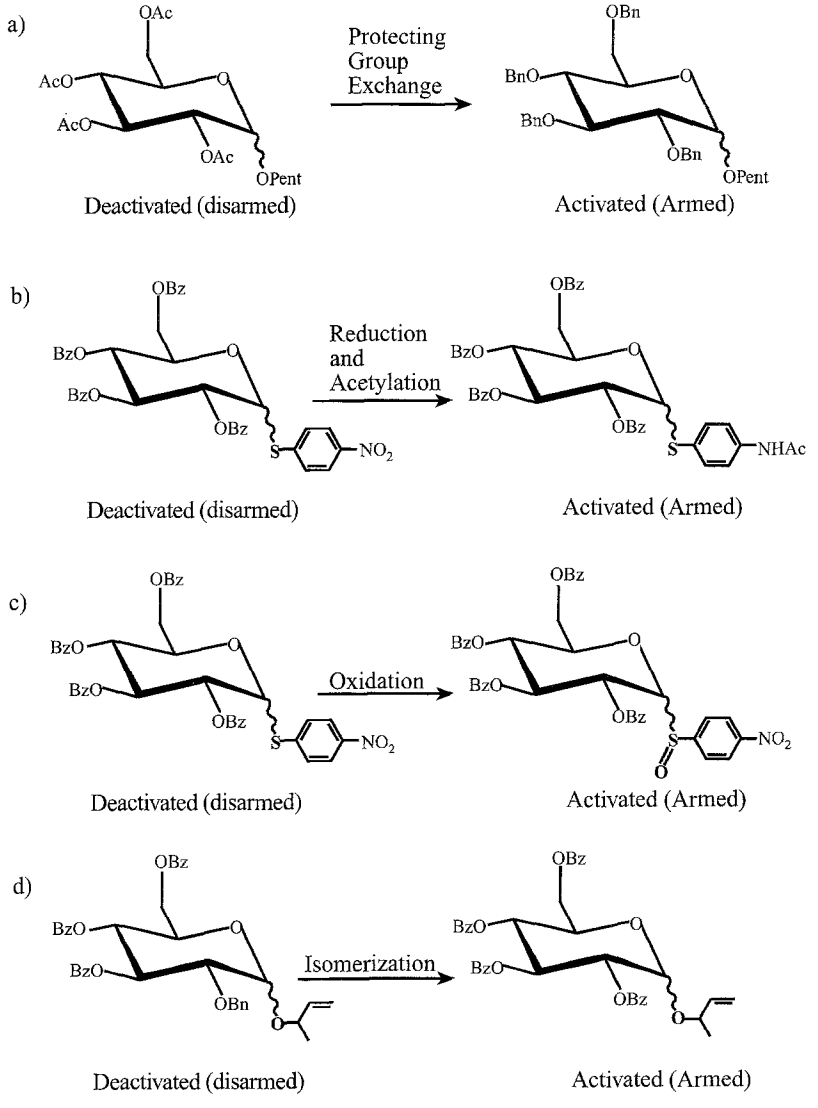
Alkyl or aryl thioglycosides are usually activated with NIS/catTfOH [22] or DMTST [23]. These reagents function by reacting with the sulfur atoms (thiophilic) to form cationic sulfonium ions ($R\text{-}S^+\text{-}Y$). The non-nucleophilic anions (e.g. $TfO^-$) presumably stabilize the formation of oxocarbenium ion species. With more reactive donors activation with NIS or NBS alone is sufficient. A variety of thiophilic reagent combinations have been developed such as NBS/$Bu_4NOTf$ or $Ph_2IOTf$ [24], Bis(trifluoroacetoxy)iodobenzene [25], PhSeNPhth/TMSOTf [26], $Tf_2O$ [27] and $Bu_2SnCl_2/2AgClO_4$ [28]. Oxidation of a glycosyl thioether to a glycosyl sulfoxide (Sug-SOR) leads to a very reactive donor which can be activated with $Tf_2O$. Similarly phosphites activated by Lewis acids have been shown to be very reactive glycosyl donors especially for the 2-ketose sugar *N*-acetylneuraminic acid [29]. Some other leaving groups and/or

**Table 1.** Selected recent developments for the activation of glycosyl donors.

| *Structure* | *Leaving group* | *Promoters* | *Type* | *Ref.* |
|---|---|---|---|---|
| F | Fluorides | $SnCl_2/AgClO_4$ | Common | 31 |
| | | $HfCp_2Cl_2(AgOTf)$ | Common | 17 |
|  | Trichloroacetimidates | $BF_3{\cdot}OEt_2$ TMSOTf | Common | 32 |
| | | AgOTf | Minimizes side reactions | 21 |
|  | Phosphites | $BF_3{\cdot}OEt_2$ TMSOTf | Common | 33 |
| S—R | Alkyl(aryl)thioglycosides | NIS/TfOH DMTST MeI | Common<br>Very mild conditions | 34 |
| S—Ph-4-X | *p*Xphenylthioglycosides | NIS/TfOH DMTST | Armed/disarmed | 35 |
|  | Sulfoxides | $Tf_2O$ | Very reactive | 36 |
|  | *p*Xphenylsulfenylglycosides | TMSOTf/TEP | Armed/disarmed | 37 |
| Se—R | Selenoglycosides | $AgOTf/K_2CO_3$ | Armed/disarmed | 38 |
|  | Xanthates | MeSBr/AgOTf | | 39 |
|  | O-Vinylglycosides | TMSOTf | Armed/disarmed | 40 |
| $O—(CH_2)_3CH=CH_2$ | O-Pentenylglycosides | NBS IDCP NIS-TfOH | Armed/disarmed | 41 |
|  | Glycalepoxides | $ZnCl_2$ | | 42 |
|  | Glycalselenylepoxides | PhSeCl | | 43 |

activation methods are listed in Table 1 which either provide alternative reactivities and protecting group compatibilities or are new relatively untested concepts.

Newer developments have led to extensions of the armed-disarmed concept introduced a few years ago. The original concept used electron withdrawing protecting groups on a glycosyl donor for deactivation (disarmed) and electron donating groups for reactive (armed) donors [2g]. By exchanging electron withdrawing acyl groups for electron donating allylic or benzylic ethers a disarmed donor could be activated. In the newer versions a less reactive glycosyl donor is activated either by oxidation of the leaving group or exchange of substituents on the leaving group [30], see Scheme 3 for examples. The most widely used feature of the disarmed/armed strategy is to build up an oligosaccharide with a disarmed group at the anomeric centre of the reducing end and then near the end of the synthesis activate the group so that the whole oligosaccharide can be used as a donor. In this way the oligosaccharide can be coupled to a variety of acceptors, significantly increasing synthetic efficiency. Such reactivity differences have also been manipulated to allow for one pot multiple glycosylation reactions [44]. In this way three or more sugars can be joined together in a single step [45] (for more recent examples see [46]). Further modifications of this approach have led to the development of orthogonal glycosylation strategies where by judicious choice of promoter donors can function as acceptors and the new oligosaccharide can then be activated as a donor by changing the promoter. For example, a glycosyl fluoride with a free hydroxyl can be glycosylated by a glycosyl thioether in the presence of



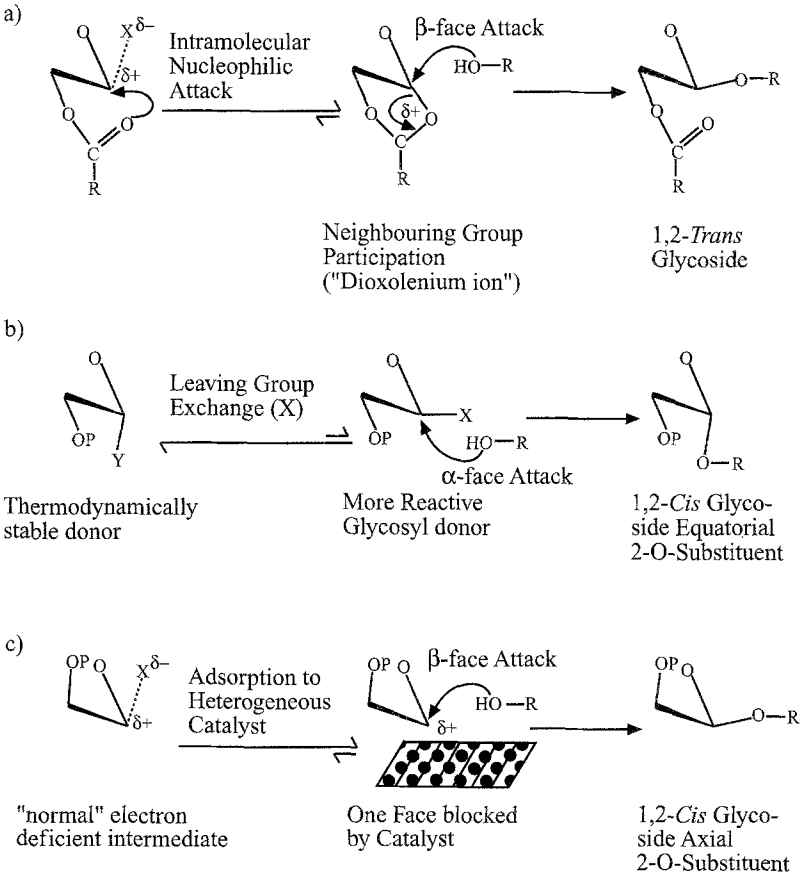

**Scheme 3.** Four methods of activating (arming) deactivated (disarmed) glycosyl donors: a) by protecting group exchange; b) by leaving group substituent manipulations; c) by oxidation of the leaving group; d) by isomerization of double bonds in the leaving group.

NIS/AgOTf and then the new disaccharide can be coupled to another acceptor using $Cp_2HfCl_2/AgClO_4$ as promoter [47].

## Stereospecificity

The control of stereochemistry is absolutely essential for glycosylation reactions in cases when only one of the two diastereoisomers ($\alpha$ or $\beta$) is desired. At present three methods of controlling stereochemistry are well developed [2e]. 1,2 *trans*-glycosides, i.e. the substituent adjacent to the glycosidic linkage is *trans* to the glycosidic bond, are formed by neighbouring group participation. This usually involves a 2-*O*-acyl protecting group reacting as an intramolecular nucleophile to give a cyclic electron deficient species (dioxolenium ion) as the kinetically controlled intermediate. Since the neighbouring group blocks one face of the molecule the nucleophilic acceptor can only react from the other face to give the *trans*-glycoside, see Scheme 4a. There are two distinct cases for *cis*-glycosides. If the glycosidic bond is axial (adjacent substituent equatorial) then because of the anomeric effect this is the most thermodynamically stable isomer, i.e. $\alpha$-glucosides. Under equilibrating conditions or by taking advantage of the greater lability of the equatorial leaving group under $S_N2$ conditions, the $\alpha$-glycoside can be formed preferentially (see Scheme 4b) [48]. Variants of this approach have recently been described [49, 50]. For *cis*-glycosides where the glycosidic bond is in the thermodynamically unfavourable equatorial orientation, e.g. $\beta$-D-mannosides and $\beta$-L-rhamnosides, then heterogeneous promoters are used. These probably function by forming associations between the insoluble promoter and the reactive intermediate which are most likely to form on the least hindered axial face and therefore the nucleophile will preferentially attack from the equatorial face, see Scheme 4c [51]. Complete stereoselectivity is rarely achieved for these *cis*-linkages.

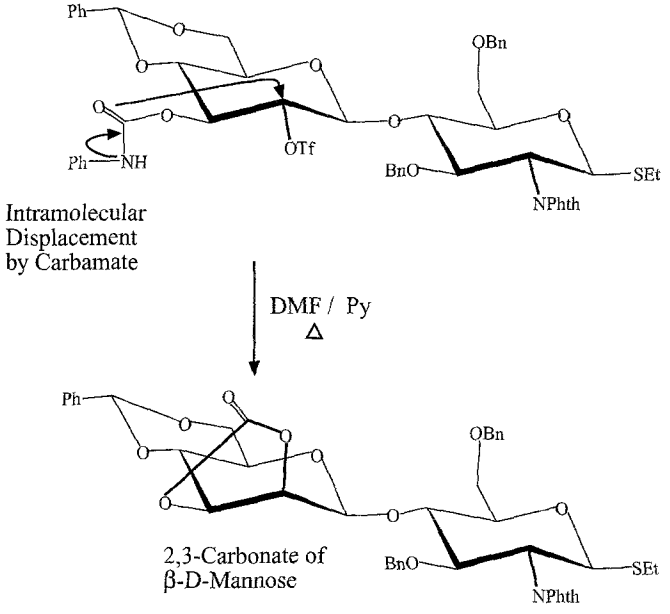
The presence of a neighbouring participating group does not guarantee absolute stereospecificity and several examples of the failure of neighbouring group participation have been reported [52]. This has been rationalized by the hypothesis that the bicyclic dioxolenium ion is less reactive than the monocyclic oxocarbenium ion. Therefore, in the case of very weak nucleophiles like secondary hydroxyls of carbohydrates the reaction proceeds without neighbouring group participation and hence loses stereoselectivity. In accordance with this



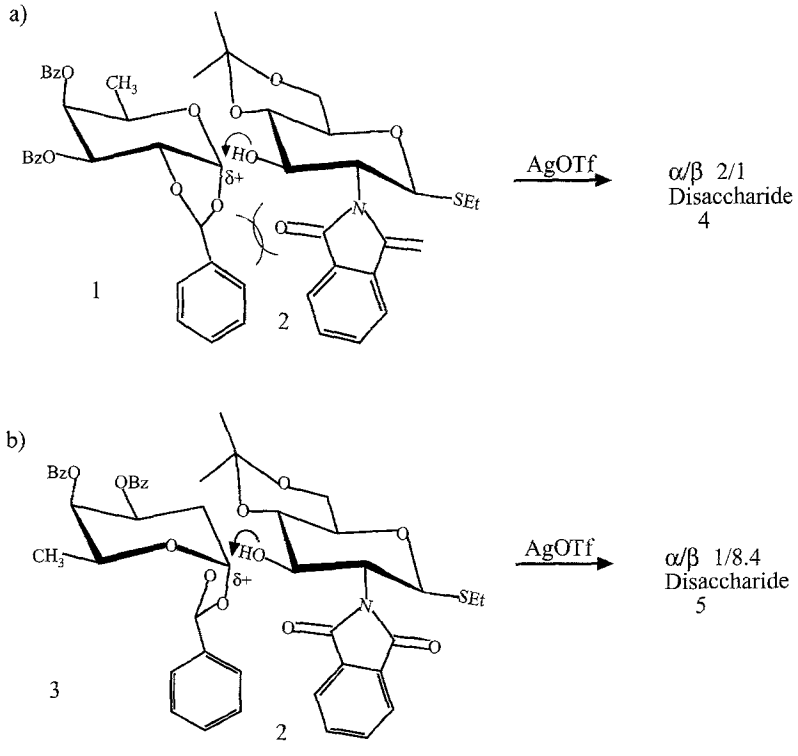

**Scheme 4.** Three established methods of controlling the stereochemistry of glycosylation reactions: a) neighbouring group participation; b) manipulation of the anomeric effect; c) adsorption to heterogeneous catalyst.

concept is the observation that high pressure dramatically improves stereoselectivity presumably by favouring the more compact bicyclic dioxolenium ion [53]. The solvent in glycosylation reactions directly affects the relative stabilities of the reactive intermediates and in some cases is postulated to directly participate in the reaction. In general non-polar solvents favour the formation of *cis*-glycosides [52b] and polar solvents favour β-glycosides but exceptions are numerous [2e]. Viewing models of the transition states leading to each isomer (α or β) has led to the recognition of mismatched interactions which can be recognized by a principle of double stereodifferentiation. This principle suggests that in mismatched cases there is an unfavourable steric interaction between the dioxolenium ion and one of the protecting groups of the acceptor in the transition state leading to glycosylation (cf. 1 + 2 in Scheme 5) [10]. This can be inferred by comparing the outcome of the glycosylation with the enantiomer of the glycosyl donor, e.g. D-fucose donor 1 versus a L-fucose donor 3 [54].

A proven approach to the synthesis of *cis*-glycosides involves preparation of the corresponding *trans*-glycoside and then inversion of the conSchemeuration at the adjacent 2 position by either $S_N2$ displacement or an oxidation/reduction sequence. This classic approach is still the method of choice for large scale preparation of the disaccharide Man(β1,4)GlcNAc [55]. A recent method has been developed which uses 2-oxosugars (hexopyranos-2-ulosyl bromides) as donors which obviates the need for oxidation of the oligosaccharide. Stereospecific reduction then leads to the *cis*-glycosides [56]. In yet another approach an $S_N2$ inversion reaction is performed intramolecularly from C-3, cf. 6 to 7 as shown



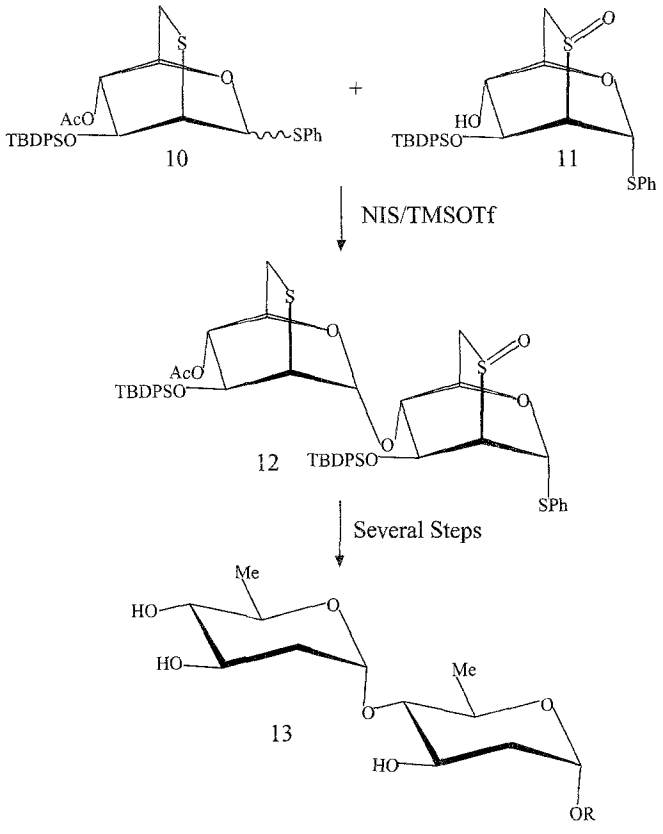

**Scheme 6.** Formation of a *cis*-β-mannose glycosidic linkage by intramolecular displacement from O-3 of β-glucose (reproduced with permission).



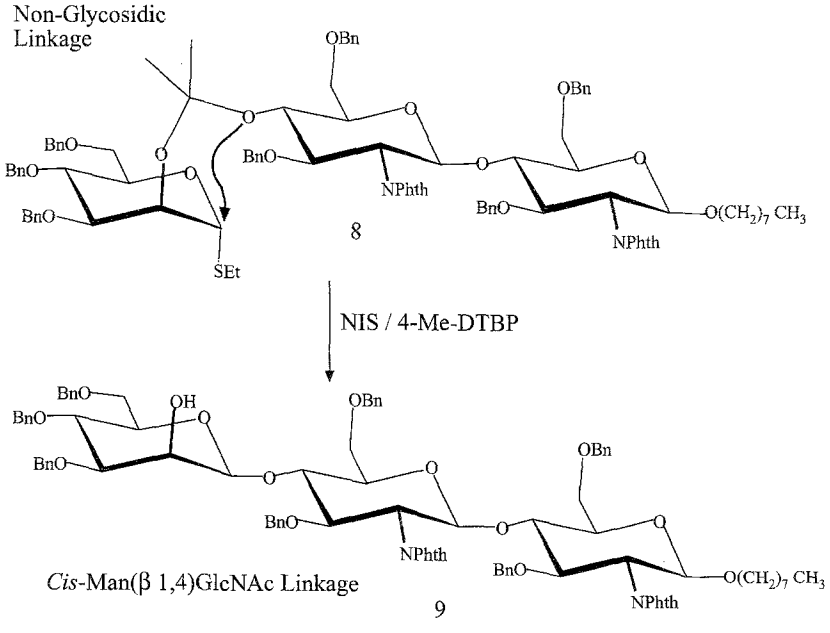

**Scheme 5.** Example of double stereo differentiation with: a) mismatched; and b) matched transition state (reproduced with permission).

schematically in Scheme 6 [57]. Several groups have devised intramolecular glycosylation reactions where the two sugars are first joined by a non-glycosidic linkage and then intramolecular glycosylation is performed, cf. 8 to 9. The desired stereoisomer is formed due to the constraints imposed by the initial tethering [58]. One example of the formation of the Man($\beta$1,4)GlcNAc linkage is shown in Scheme 7 [59]. All of these methods suffer from the disadvantage that all the protecting groups used must be compatible with the reaction conditions, e.g. tethering, oxidation, reduction, etc. These constraints severely limit the choice of protecting groups which significantly limits the generality of these approaches. A general method for the synthesis of *cis*-linkages compatible with a wide variety of protecting groups is still an elusive goal for carbohydrate chemists.

2-Deoxy glycosides present particular problems for stereospecificity since there is no substituent at position 2 to direct the glycosylation reaction. Conventional solutions to this problem have utilized glycals as donors [60]. More recently an elegant general solution to this problem has been developed which utilizes rigid 2,6-anhydro thio donors to control the stereochemistry. Scheme 8 shows one example in which the rigid armed donor 10 stereospecifically reacts with the disarmed acceptor 11 to form disaccharide 12. The disarmed sulfoxide protecting group can be activated by reduction and the disaccharide turned into an armed donor. The thio groups are readily removed reductively to yield 2,6-dideoxy oligosaccharides, cf. 13 [61].




**Scheme 8.** Stereospecific formation of 2,6-dideoxy-glycoside by use of conformationally rigid 2,6 anhydrothio donors (reproduced with permission).



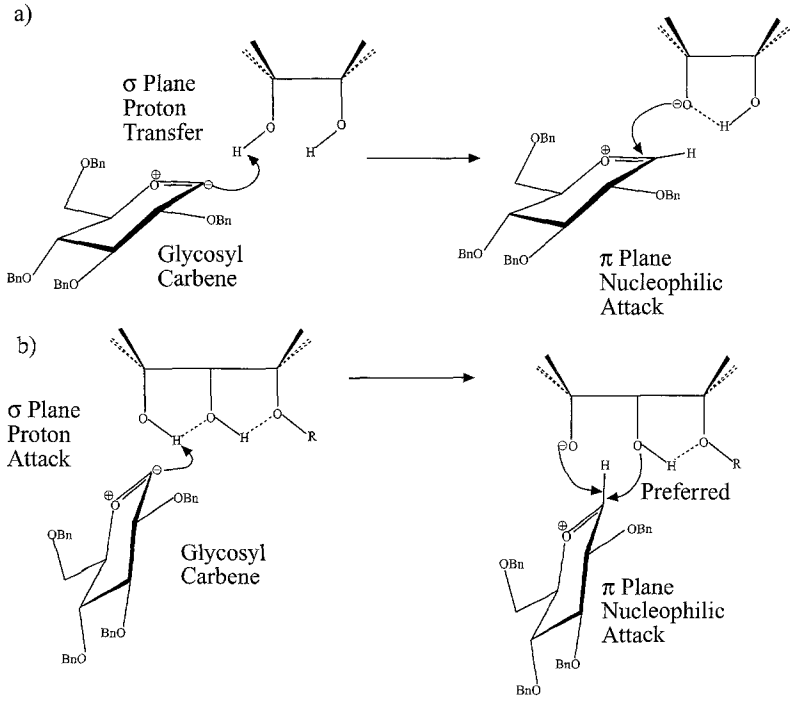

**Scheme 7.** Intramolecular formation of *cis*-$\beta$-mannose glycosidic linkage by initial tethering via a ketal linkage (reproduced with permission).

## Regiospecificity

Inherent to the control of regiochemistry in the synthesis of carbohydrates is the relative reactivity of the hydroxyl groups. While it is clear that both steric and electronic effects are important, to date no general reactivity theory exists. Sometimes empirical observations can be made. For example, in 3,4 diols of galactose (OH-3 equatorial, OH-4 axial) the equatorial OH-3 is usually more reactive and can often be selectively glycosylated [62]. Perhaps due to differential adsorption in the presence of heterogeneous catalysts this preference can be reversed to favour the axial OH-4 [63]. Using such minimal protection strategies not only reduces synthetic steps but often increases the yields of reactions as exemplified for reactions of sialic acid donors with galactose acceptors with OH-3, OH-3,4 or OH-2,3,4 positions unprotected. The triols are more reactive than the diols which are in turn more reactive than the mono-alcohols. This observation has been successfully used by several groups to prepare oligosaccharides [64].

A similar reactivity difference between the equatorial hydroxyls OH-3 and OH-4 of 6-O-protected-2-N-protected-glucosamine derivatives has been successfully exploited where OH-3 preferentially reacts [65]. However, with differently N-protected acceptors [66] or different promoters less selectivity was found [65]. Another example is the preferential glycosylation at the equatorial OH-3 of a $\beta$-mannose 2,3 diol [67]. It is anticipated that such a reactivity difference will be increasingly studied and exploited.

An extensive study of the regioselectivity in the glycosylation of diols and triols by diazirine-derived glycosylidene carbenes has shown that selectivity is determined both by the protonation of the carbene and the interception of the ensuing oxocarbenium ion by an oxy anion or an OH group [68]. Both processes are stereoelectronically controlled, protonation occurring in the $\sigma$-plane of the carbene and nucleophilic attack in the $\pi$-plane of the oxocarbenium cation. The regioselectivity of the deprotonation by the carbene is determined by the relative kinetic acidity of the individual OH groups which has been shown to depend mainly on intramolecular H-bonds. The regioselectivity of the C-O bond formation depends on the relative positions of the oxocarbenium ion to the hydroxyl nucleophiles. As shown in Scheme 9a the protonating hydroxyl can be the closest oxygen and then deprotonation determines the regioselectivity of C-O bond formation. However if the protonating hydroxyl is H-bonded to an adjacent hydroxyl then the adjacent hydroxyl can compete for C-O bond formation, see Scheme 9b. As drawn in Scheme 9a, preferential formation of equatorial glycosidic linkages is predicted and for 12b axial glycosidic linkages. These studies strongly implicate the importance of intramolecular H-bonding for reactivity [69] of hydroxyls in addition

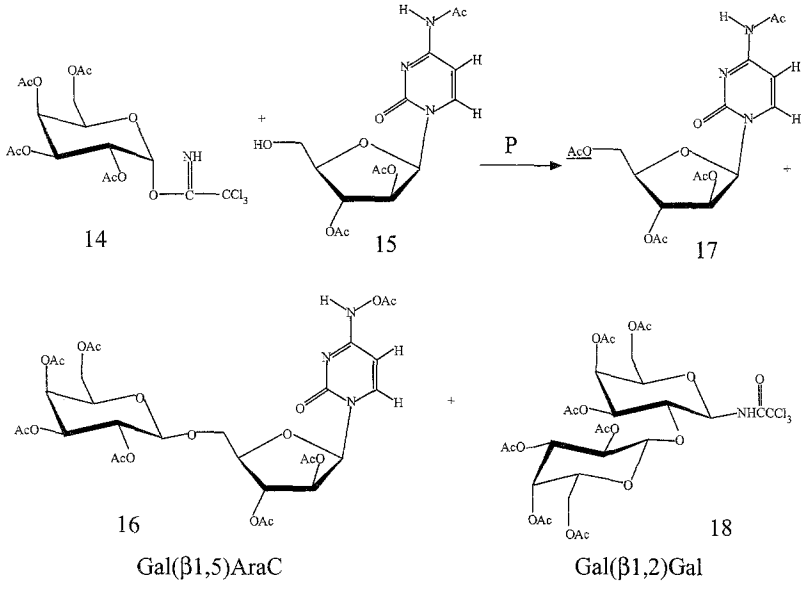



**Scheme 9.** Stereoelectronic control of glycosylation of glycosyl carbenes: a) $\sigma$-protonation followed by $\pi$-oxo-anion nucleophilic attack; b) $\sigma$-protonation followed by indiscriminate $\pi$-oxo nucleophilic attack (reproduced with permission).

to steric effects imposed by the sugars and their protecting groups.

H-bond donation by a hydroxyl proton leads to polarization of the $O^{\delta-}$-$H^{\delta+}$ bond such that the oxygen should be a better nucleophile and hence more reactive in glycosylation reactions. This general principle agrees with the previous results. For example, equatorial OH groups usually act as H-bond donors to axial hydroxyls and thus the equatorial hydroxyl should be the more reactive as seen for OH-3 of mannose and OH-3 of galactose above. Some hydroxyls are unreactive in glycosylation reactions. Frequently these hydroxyls are sterically hindered and this probably accounts for their unreactivity. Recent studies concerning the glycosylation of the 5′-OH of protected nucleosides 15 displayed a surprising unreactivity [11]. Typically many products were produced from which the desired oligosaccharide could be isolated in low yield. Under stoichiometric glycosylation conditions with strong Lewis acids and trichloroacetimidates as donors, cf. 14, the glycosides 16 could be isolated in moderate yields primarily contaminated with the products of acyl transfer to the nucleosides 17 and the disaccharide PerAcHex(β1,2)HexNHCOCCl$_3$ 18, see Scheme 10. Conformational analysis of the acceptors, cf. 15, strongly suggested that the 5′-OH in dry dichloromethane solution is in an intramolecular H-bonded conformation [70]. The combination of silver triflate in chloroform was found to minimize acyl transfer and maximize glycosylation. This combination alters the conformation of the acceptor by solvent competing for intramolecular H-bonds and by promoter complexation to the acceptor [71]. It was suggested that proton transfer from the intermediate (cf. Scheme 2) is inhibited by intramolecular strong H-bonding and this allows the reactive intermediate to equilibrate with other reaction pathways leading to decomposition of the donor and acyl transfer to the acceptor.

Attempts to overcome this low reactivity of sugar hydroxyls by conversion of the hydroxyls to more reactive ethers have been made. In face most glycosylations using trialkylsilyl triflates as promoters are thought to proceed via trialkylsilyl ethers of the reactive hydroxyl [52d]. The Brederek conditions for glycosylation involve activating the hydroxyl group as its trityl ether and using trityl perchlorate as promoter [72]. A more recent version of this procedure is the cyanoethylidene procedure which directly generates the dioxolenium ion by loss of cyanide anion from a cyanoethylidene donor, 19, as shown in Scheme 11 [7]. In yet another variant, *t*-butyl ethers of phenols [73] have been used for glycosylation reactions [74]. In this case only halides reacted as leaving groups whereas trichloroacetimidates did not react. Conditions which polarize the hydroxyl (or equivalent) bond should result in higher reactivity as seen in the above examples and as suggested by the success of the 'inverse reaction' conditions (vide supra). The question of hydroxyl




P = $BF_3$·$OEt_2$/$CH_2Cl_2$ 16/17 1.25/1.0

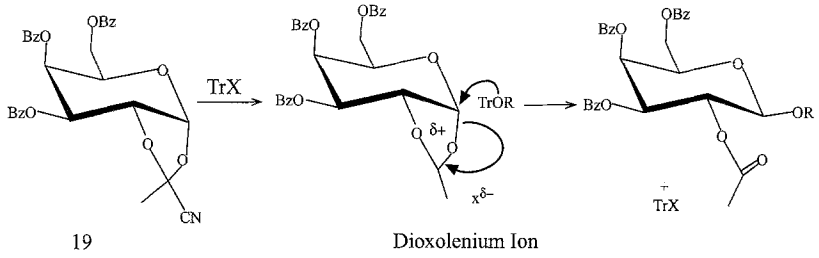
P = AgOTf/$CHCl_3$ 16/17 20.0/1.0

**Scheme 10.** Unusual unreactivity of the OH-5′ of a nucleoside acceptor which is accompanied by products resulting from acyl transfer 17 and 18.

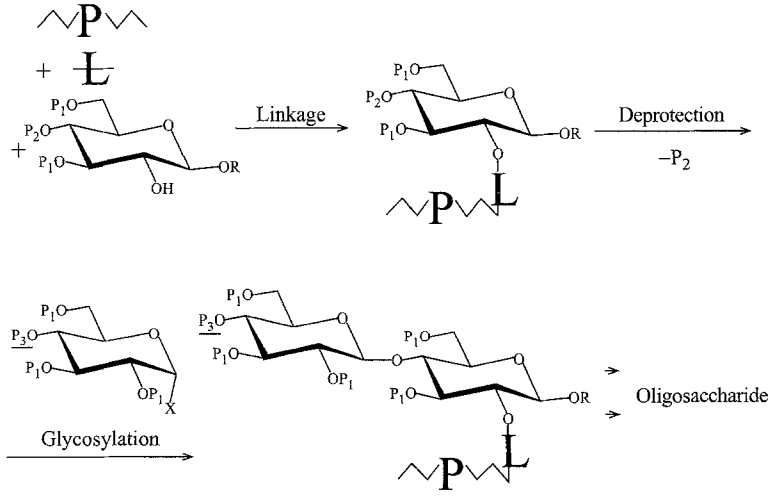
activation requires further study and it is anticipated that improvements in hydroxyl reactivity will lead to improved stereoselectivity and minimization of side reactions because the reactive glycosyl donor intermediates will be productively quenched.

## Side reactions

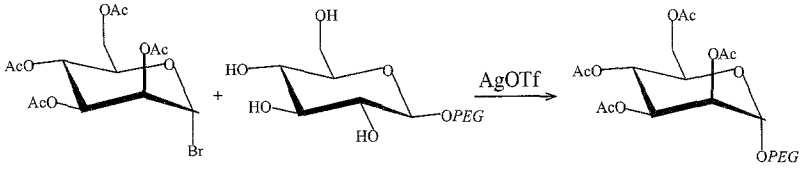
Perhaps the greatest hindrance to the development of inexpensive methods for oligosaccharide synthesis is the need for purification of the reaction products by chromatography. Typically unreacted starting materials and decomposed glycosyl donor are present in the reaction mixtures. If the reaction is driven to completion by the addition of excess donor then this purification problem is even more exacerbated. Such purification problems are to a large extent eliminated by attaching the growing oligosaccharide to a support from which all impurities can be eliminated by simple washing procedures. Polymer supported synthesis of oligosaccharides on polystyrene resins was attempted in the past but suffered from low yields and lack of stereochemical control (reviewed in [75]). Recently a procedure which has the glycosyl donor attached to the polymer has been presented [76]. A particularly promising approach is shown in Scheme 12. Initially the first monosaccharide is attached to the polymer polyethyleneglycol monomethyl ether [$HOCH_2CH_2(OCH_2CH_2)_nOCH_3$, $n = 80$–$160$; *PEG*, average MW 5 000], through a linker [77]. This *PEG*-bound saccharide is then activated by functional group manipulations such that the hydroxyl to be glycosylated is unmasked under conditions to which all the other protecting groups and the linker are absolutely stable. This hydroxyl is then exhaustively glycosylated either with excess donor or repeated additions of donor to give a disaccharide. The process can then be repeated until the desired oligosaccharide is synthesized [78]. All purifications are dependent on the solubility properties of the *PEG* polymer. *PEG* is insoluble in ethers and so soluble non-polar impurities are removed by precipitation with ethers. Furthermore *PEG* can be recrystallized from absolute ethanol to remove polar impurities. Several other groups have modified more traditional solid supports for oligosaccharide [79] and glycopeptide synthesis [80]. An important development involves the use of enzymes on solid supported substrates, thus also solving the problems of regio- and stereoselectivity [81]. A thorough discussion of this important topic is beyond the scope of this mini-review.




**Scheme 11.** Activation of acceptor hydroxyls by trityl ether formation – the cyanoethylidene approach (reproduced with permission).




**Scheme 12.** Schematic representation of polymer supported oligosaccharide synthesis which largely avoids tedious purifications. $P_1$ is a permanent protecting group whereas $P_2$ and $P_3$ are temporary protecting groups. -L- is the linker and -P- the polymer *PEG*.




**Scheme 13.** An example of metathesis of oligosaccharides during a glycosylation reaction.

All these approaches require that none of the reactions have side reactions that damage the support bound growing oligosaccharide chain. Such reactions include migrations or other reactions of the protecting groups on the support bound oligosaccharide. This requires careful choices of protecting groups and reagents. Another side reaction to be avoided is the acyl transfer reaction mentioned above, see Scheme 13. Since acyl groups are usually used for stereochemical control via neighbouring group participation this problem requires careful attention. At present it is still necessary to treat each linkage in each oligosaccharide as a uniquely different target.

Yet another troublesome side reaction has been discovered using polymer supported methods. This is metathesis of oligosaccharides [82]. In this case the original glycoside 21 is destroyed in the glycosylation reaction to be replaced by the donor 20 yielding new glycoside 22. Circumstantial evidence exists that this type of side reaction occurs in solution reactions and contributes to the plethora of side products. Avoiding metathesis requires a much better understanding of the glycosylation reaction.

## Conclusions

Recent developments have largely solved the problems of low reactivity of glycosyl donors. Also by building steric hindrance into the glycosyl donor some novel methods for achieving stereochemical control have been realized. As well the continued development of polymer-supported methods of oligosaccharide synthesis promises to alleviate the problems of purifications. However, the low reactivity of some hydroxyls in glycosylation reactions contributes significantly to the loss of stereochemical control and the creation of side products. Solving these problems remains a major challenge for carbohydrate chemists.

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