REVIEW

O-Glycosylations under neutral or basic conditions

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1 Introduction

In 1879, the American chemist Arthur Michael published a report "On the Synthesis of Helicin and Phenolglucoside",[1] which appears to be the first published chemical glycosylation. Michael had dissolved 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl chloride and sodium phenolate in ethanol and obtained the *O*-deacetylated phenyl glucoside. Since then, the glycosylation of phenols under *basic* conditions has been highly successful for numerous phenolic substrates and many modifications of the original procedure have been reported. In 1893, Fischer reported on the glycosylation of simple, aliphatic alcohols in the presence of HCl.[2] This procedure, which came to be known as the 'Fischer glycosylation', has remained one of the mainstays of carbohydrate chemistry. When Koenigs and Knorr in 1901 reported the activation of glycosyl halides by heavy metal halophiles,[3] it became feasible to glycosylate more complex aliphatic alcohols. Since then, countless variations of the original Koenigs–Knorr conditions have allowed the synthesis of numerous glycosides and very complex oligosaccharides.[4] In recent decades, new families of glycosyl donors have become significant alternatives to glycosyl bromides and chlorides, most notably thioglycosides, trichloroacetimidates, glycosyl fluorides, and *n*-pentenyl glycosides. The development of new and ever more complex Lewis acids as 'promoters' in Koenigs–Knorr and 'post-Koenigs–Knorr' glycosylations, has covered much of the periodic table.[5]

In the following, the term 'glycosylation chemistry' will be used for the chemistry of establishing glycosidic bonds; the term 'glycosyl donor' will be used for the carbohydrate derivative employed to glycosylate the 'glycosyl acceptor', *e.g.* an alcohol. This review will focus on hydroxy glycosyl acceptors but the glycosyl acceptor could, *e.g.*, also be a thiol, an amine, or a carbanion. Although the glycosyl donor in most cases acts as the *electrophile*, in a few procedures it acts as the *nucleophile*, making the glycosyl acceptor an alkylating agent.

This review covers *O*-glycosylations which do not require a Lewis acid promotor for activation of the anomeric leaving group. For the sake of introducing the area of glycosylation chemistry and to present mechanistic studies relevant for understanding glycosylations under neutral conditions, some aspects of Lewis acid promoted reactions will be discussed first. Scheme 1 provides an overview of the principal steps in converting a lactol (or glycosyl donor) to aliphatic or aryl glycosides. Fischer glycosylation takes the unprotected monosaccharide directly to the glycoside, however, only for simple aliphatic alcohols (**A1**). Protected lactols can be converted directly into glycosides in so-called 'dehydrative' glycosylations (**A2**). Glycosyl donors with a better leaving group (X^n) can either be made directly from the lactol (**B**) or through steps **C** and **D**. The latter approach is mainly relevant for preparation of Schmidt's trichloroacetimidates. *O*-Acylated glycosyl halides are generally prepared from the per-*O*-acylated derivatives. Reaction of glycosyl halides with phenolates gives aryl glycosides, often with inversion of the anomeric configuration – in the following this will be referred to as the *Michael* procedure (**E**). Activation of glycosyl halides with heavy metal salts in the *Koenigs–Knorr* procedure, or of other glycosyl donors, *e.g.* trichloroacetimidates, with Lewis acids, are often reliable for the synthesis of aliphatic glycosides (**F**). Simple glycosides can also be prepared by *O*-alkylation of the anomeric hydroxy (**C**, **G**). Similarly, aryl glycosides with electron-withdrawing substituents on the aglycon can be prepared by nucleophilic aromatic substitution (**C**, **H**). In a few reports, aryl glycosides have been used as glycosyl donors for the preparation of aliphatic glycosides, either in the presence of Lewis acids or under neutral conditions (**I**).

Paulsen wrote in his highly influential 1982 review on the state-of-the-art of chemical oligosaccharide synthesis:

"Although we have now learned to synthesize oligosaccharides, it should be emphasized that each oligosaccharide synthesis remains an independent problem, whose resolution requires considerable systematic research and a good deal of know-how. There are no universal reaction conditions for oligosaccharide synthesis."[4a]

Despite very significant advances, Paulsen's statement has largely remained true.

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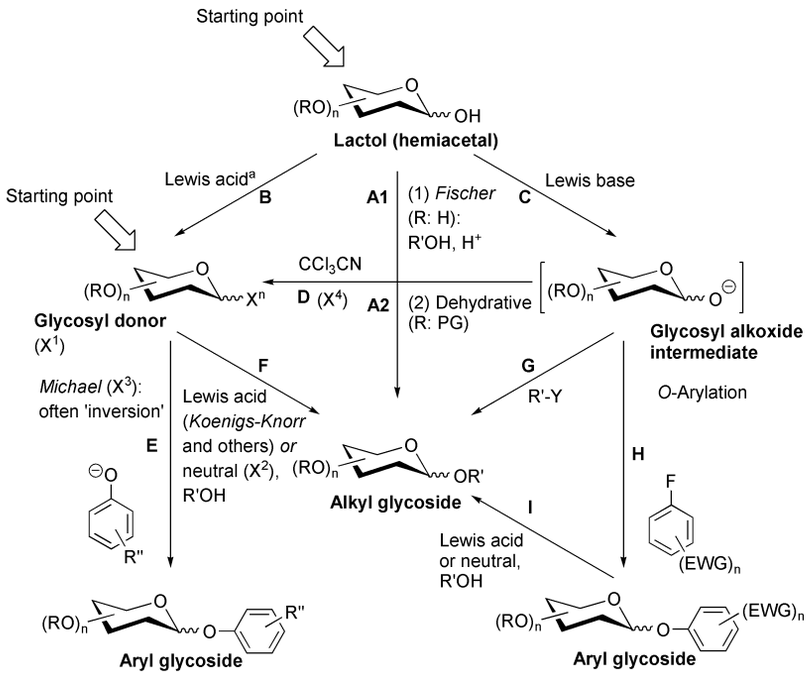


Scheme 1 Outline of steps for conversion of lactols or glycosyl donors to *O*-glycosides. R′OH: glycosyl acceptor; EWG: electron-withdrawing group; Y: leaving group; PG: protecting group; (a) may require several steps; X^1: F, Cl, Br, I, O–C(NH)CCl_3 and more; X^2: Br, Cl; X^3: F, Cl, Br, I; X^4: trichloroacetimidate; 'name' glycosylations are in italics. The scheme was inspired by Schmidt *et al.*, ref. 4*c*.

The problems and limitations in glycosylation of *aliphatic* alcohols can be summarized as follows:

(1) Anomeric selectivity, *i.e.*, the selective formation of either α- or β-glycosides, is often difficult to control, although reasonably good anomeric selectivities have been achieved for some 1,2-*cis* and 1,2-*trans* linkages.

(2) Regioselectivity requires protection of other hydroxys.

(3) Configurational, substituent, steric, and electronic effects frequently influence the outcome and yield of glycosylation reactions, sometimes in unpredictable ways.

(4) No *universal* methods have been established, which in a structure-independent way would give high yields without much optimization. Ideally, glycosylation chemistry should move from the special case of a total synthesis in which individual steps are highly optimized for a particular target, to a situation where highly optimized universal conditions are applicable to a wide range of substrates.

(5) No *universal* methods for solid-phase oligosaccharide synthesis have been developed.

The reactivity at the anomeric center of a glycopyranosyl *donor* depends very strongly on not only its leaving group and added promoters but also on the protecting groups on the glycosyl donor. The protecting group pattern on the glycosyl *acceptor* can also influence the coupling yield and the stereoselectivity. The hydroxy of methanol is significantly more reactive than the primary 6-OH, which again generally is more reactive than secondary hydroxys of saccharides. In some cases, the hydroxy group to be glycosylated can be activated by 'protection' as the *tert*-butyl,[6] trityl or TMS ethers.

Paulsen[4a] has summarized the following observations on glycosyl halides as donors: (1) *O*-benzyl protected glycosyl halides are more reactive than the corresponding acetylated or benzoylated derivatives, with the positions of the benzyl ethers being less important than their numbers; (2) bromides are more reactive than chlorides; (c) reactive halides can react with hydroxy groups of moderate reactivity to give α-glycosides with high selectivity. If the hydroxy group is very reactive, the reactivity of the halide or promoter must be reduced, in order to maintain α-selectivity.

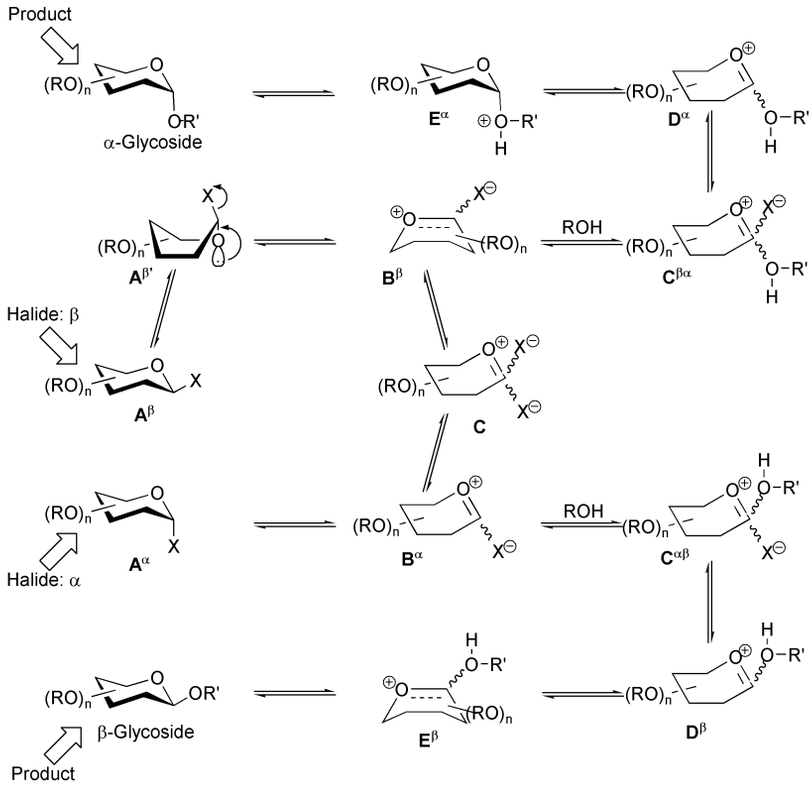
Common side-reactions during glycosylations include: (a) hydrolysis of the glycosyl donor; (b) 1,2-elimination to give a glycal; (c) for glycosyl donors with a 2-*O*-acyl moiety, transfer of a 2-*O*-acyl protecting group to the glycosyl acceptor has frequently been observed as a competing side-reaction.

The focus of this review is *O*-glycosylations that do *not require a Lewis acid* promotor dependent activation of the anomeric leaving group, hence reactions which proceed under neutral or basic conditions. Glycosylations in the absence of Lewis acids offer the prospect of better control of the stereochemical outcome of the glycosylation and avoidance of some of the many Lewis acid induced side-reactions. Glycosylation of phenols under basic conditions, *i.e.* when the phenolate anion is formed, has proved tremendously successful for the synthesis of many aryl glycosides. It bears testimony of the potential of this approach that in some cases glycosylation with inversion of the anomeric center has been achieved. An overview of the general classes of these procedures will be presented. Glycosylation of aliphatic (alkyl) alcohols under neutral conditions has been successful for some applications but has been far less predominant than basic glycosylations of phenolates. The recent 'rediscovery' of glycosyl iodides, the use of $LiClO_4$ solutions in glycosylations, and the development in the author's laboratories of glycosyl donors designed for glycosylations in the absence of Lewis acids has again raised the prospects of aliphatic glycosylations under neutral or basic conditions. The scope and limitation of these recent developments and their context will be presented.

2 Mechanistic aspects of glycosylation reactions

Most reviews on glycosylation chemistry have focused on the glycosylation of *aliphatic* alcohols, in particular of saccharides, with little mention of the glycosylation of phenols.[4,7] Glycosylation of a phenol is rather different from that of an aliphatic alcohol, the major difference being that stable, yet reactive phenolate anions can easily be generated under basic conditions. Also, the generally lower basicity of phenols compared to alkoxides is likely to induce fewer side-reactions, such as base-catalyzed 1,2-elimination in the glycosyl donor.

A stereospecific glycosylation should, in principle, be achievable *if* the stereochemistry of the glycosyl donor can be controlled and *if* glycoside bond formation occurs by an S_N2 rather than S_N1 type mechanism. As we shall see in the following, this



Scheme 2 Lemieux's glycosylation mechanism (halide assisted *in situ* anomerization).

ideal has been approached for the glycosylation of phenols when phenolate anions are used, whereas use of alkoxide anions of glycosyl acceptors rarely appear to be a feasible route in glycosylations.

Lemieux's mechanism for halide ion-catalyzed glycosylations is shown in Scheme 2.[8,9] Here, only some key features of this mechanism are presented – for a full discussion, the reader is referred to the original publications by Lemieux[8] and to general reviews on this topic.[4,7,9]

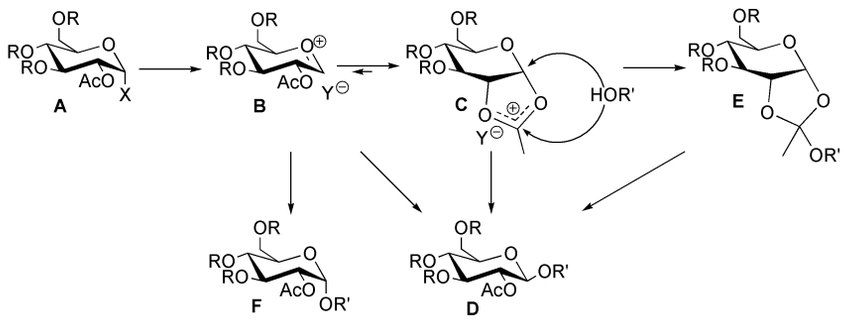
In the continuum between *limiting* (pure) S_N1 (*i.e.*, where the solvent solely assists in the departure of the leaving group from the frontside without backside participation by solvent molecules) and S_N2 mechanisms, glycosylation reactions generally fall in the border area between *limiting* S_N1 and S_N2 mechanisms.[10] Most glycosylations do not proceed through a free oxocarbenium ion (*i.e.*, solvent separated or fully dissociated from the counter ion) but rather through tight ion pairs.[11] They are thought to proceed through a transition state (Scheme 2, $\mathbf{C}^{\alpha\beta}$ and $\mathbf{C}^{\beta\alpha}$) in which the oxocarbenium ion is stabilized by both the leaving group and the incoming nucleophile. The interconversion of an α- to a β-configured tight ion pair does not occur by simple rearrangement but through this type of transition state (**C**).

For glycosyl bromides the α-anomer is the thermodynamically favored species but the interconversion between the α- and the β-configured glycosyl bromide is considerably faster than the rate of glycosylation, especially in the presence of added bromide, and when glycosylating alcohols with the reactivity of 'normal' glycosyl acceptors, *i.e.*, alcohols considerably less reactive than methanol. Thus, the reaction can mainly proceed through the less abundant but significantly more reactive β-bromide (higher ground-state energy) to give the α-glycoside. This reaction path is also favored by the chair-like intermediate (Scheme 2, $\mathbf{E}^{\alpha}$) generated from the β-halide, which is of lower energy than the corresponding boat-like intermediate ($\mathbf{E}^{\beta}$) generated from the α-halide. This halide ion-catalyzed glycosylation is often referred to as Lemieux's *in situ* anomerization procedure for achieving high α-selectivity. This has been referred to as a dynamic kinetic resolution, however, the term is misapplied here, as the process does not involve a resolution (of enantiomers). The general features of this mechanism are also applicable to Lewis acid promoted glycosylations if an activation step is added. Lemieux's mechanism will serve as our vantage point for discussions of the mechanisms of other glycosylations.

Lemieux and co-workers established the following reactivity order for the solvent used in the *in situ* anomerization procedure (decreasing reactivity): benzene, CH_2Cl_2 > CH_3CN > dioxane, CH_3NO_2 > DMF, DMSO. The α/β ratio of glycosylations decreased in the order: benzene, CH_2Cl_2, CH_3NO_2 > dioxane, CH_3CN. It may be speculated that the polar solvents could lead to solvent separated ion pairs, thus decreasing the anomeric selectivity. Green and Ley[9] emphasize that as with the bromide, any sufficiently competent leaving group will not be configurationally stable and the same mechanism for glycoside formation applies. However, the α-selectivity of these reactions is not usually as consistent as for the '*in situ* anomerization protocol' of anomeric bromides.

The generally accepted mechanism for glycosylation with 2-*O*-acyl glycosyl donors with anchimeric assistance is depicted in Scheme 3. Glycosyl donor (**A**) can be converted to the tight ion pair (**B**), most often by Lewis acid activation. The incipient oxocarbenium ion rapidly collapses to a 1,2-dioxocarbenium ion (**C**), which can be attacked either at C-1 to form the β-glycoside (**D**), or at the former carbonyl carbon to give the ortho ester (**E**). Under Lewis acidic conditions **E** rearranges to **D**; in at least some cases this appears to be the predominant route for formation of **D**. However, under some conditions, especially with relatively unreactive alcohols, varying amounts of the α-glycoside (**F**) is also formed, most likely by reaction of the reactive but low-abundance oxocarbenium ion **B**. †

† It should be emphasized that by definition, for a reaction to be *stereospecific*, a given isomer has to lead to one product, while another stereoisomer has to lead to the opposite product. Thus glycosylation reactions are stereospecific only if an α-configured glycosyl donor gives the β-glycoside, while the corresponding β-donor leads to the α-glycoside. Unfortunately, occasionally the literature on glycosylation chemistry is less than precise on this point. See ref. 12*c*.



Scheme 3 1,2-*trans*-Selectivity by anchimeric assistance.

Whitfield and co-workers have recently performed extensive Density Functional Theory calculations on 2-*O*-acyl glycosyl cations, especially on the conformationally less flexible 2,6-di-*O*-acetyl-3,4-*O*-isopropylidene-D-galactopyranosyl cation.[10,12] They demonstrated that these cations can exist mainly in two families of conformers, characterized as $^{2}S_{0}$ and $B_{2,5}$, respectively, and that these families have their own α/β selectivities. They suggest that the observed α/β ratios can be explained by reaction of the monocyclic oxocarbenium ion without going through the bicyclic dioxolenium ion (perhaps by equilibration with the monocyclic cation).

What potential benefits does it offer to *avoid* the use of Lewis acid promoters, either catalysts or reagents, in glycosylation reactions? First, Lewis acid promoted glycosylations generally proceed in a S_N1 type mechanism through a tight ion pair intermediate of an oxocarbenium ion and the leaving group or counter ion. The control of stereochemistry in glycosylation reactions, potentially offered by S_N2 type mechanisms, would most likely require the *absence* of Lewis acid promoters and *in situ* anomerization mechanisms, especially if universal glycosylation conditions were to be envisioned. Secondly, Lewis acids can be the cause of a number of side-reactions. Thirdly, addition of Lewis acids complicates the reaction mixture and makes the following purification step more tedious. Fourth, we anticipate that implementation of (semi-) automated protocols for oligosaccharide synthesis should be more facile without the requirement for repetitive treatment with Lewis acid reagents.

In view of the synthetic potential of glycosylations under neutral or basic conditions, this review summarizes the established methods and evaluates recent developments. First, an overview of the different procedures for glycosylation of phenols will be given. This then provides a backdrop for the presentation of methods for glycosylation of alcohols, especially recent, promising developments in this area.

3 Glycosylation of phenols under basic conditions

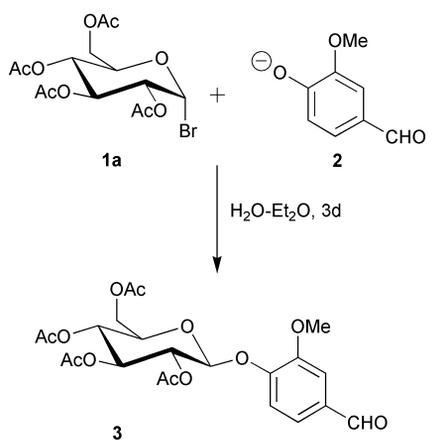
Following Michael's work, the glycosylation of phenols in the presence of base often proved successful. Numerous modifications have been developed and often with particular advantages. In this review, the term *Michael* and *Michael-type* glycosylation will be used for procedures derived from Michael's original work. In this section, first the original Michael glycosylation and its modifications will be presented, followed by other Michael-type glycosylations. Finally, synthesis of aryl glycosides by nucleophilic aromatic substitution and by the use of glycosylidene carbenes will be presented.

3.1 The Michael glycosylation

In the original Michael procedure, the *O*-deacetylated phenyl glucoside was obtained by reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl chloride with potassium phenolate in absolute ethanol.[1,13] The product obtained was later shown to have the β-configuration.

3.1.1 Biphasic reactions

While the original Michael procedure yields *O*-deacetylated aryl glycosides, Fischer and Raske in 1909 reported the use of a two-phase system, a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, **1a**, in diethyl ether and an aq. solution of the sodium salt of 4-hydroxy-3-methoxybenzaldehyde, **2** (vanillin), to obtain fully protected glucovanillin, **3** (Scheme 4).[14,15]



Scheme 4 Biphasic reactions.

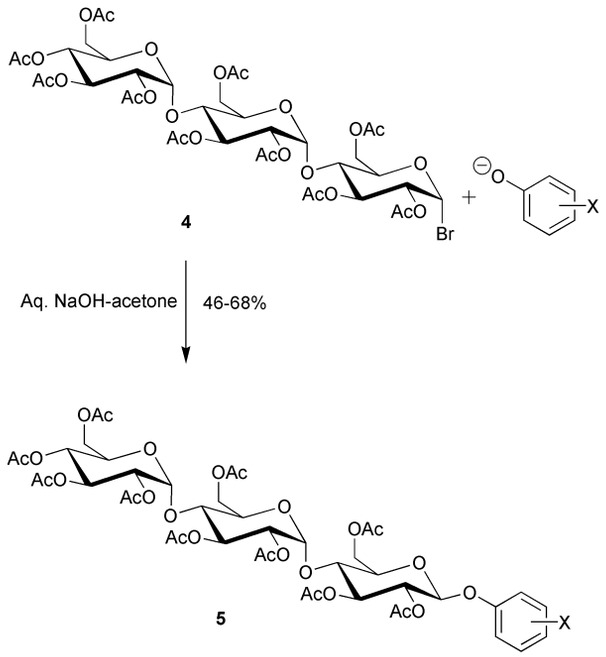
3.1.2 Aqueous organic basic media

In 1915 Mauthner introduced homogeneous reaction conditions, aq. NaOH with acetone as the organic cosolvent, which gave the protected glycosides.[16] This modification of the Michael procedure continues to find many applications.

Glaser and co-workers demonstrated the usefulness of this procedure by preparing 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosides of 2-, 3-, 4-nitrophenol, 2,4- and 2,5-dinitrophenol;[17] only for 2,4,6-trinitrophenol did the glycosylation under these conditions fail.[17b,18] In a study of the glycosylation of the three possible bromophenols and the three possible chlorophenols with deca-*O*-acetylmaltotriosyl bromide, **4**, Takeo *et al.* obtained the 1,2-*trans*-glycosides, **5**, in 46–68% yield.[18d] In this case, 3.7 equiv. of the phenol relative to the donor was used (Scheme 5). In contrast to many Lewis acid catalyzed glycosylations the yield did *not* decrease in the order *para* > *meta* > *ortho* for the substituted phenols.[19]

Although 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide[20] has been the most widely used glycosyl donor in these syntheses, other pyranoses[21] as well as furanoses,[18c] 2-acetamido-2-deoxypyranoses,[22] and di-[19a] and trisaccharides[22] have also been employed for the synthesis of aryl glycosides by this procedure. These reactions generally proceed with *inversion* at the anomeric center by substitution of the leaving group with the incoming phenol.

A limitation of this procedure (aq. acetone with strong bases) is the often poor yields obtained for 2,4-dinitrophenyl glycosides.[18b,e] Higher yields have been obtained by carrying out the

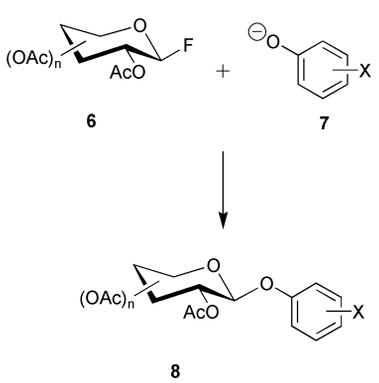


Scheme 5 Aqueous organic basic media.

reaction with the milder base K_2CO_3 in dry acetone.[18b,e] In some cases, the reactions have also been performed with KOH in MeOH–acetone,[21,23] or the preformed potassium phenolate,[3] also in MeOH.

3.1.3 Glycosyl fluorides

Glycosyl bromides have been the most widely used glycosyl donors in Michael type procedures but glycosyl fluorides have also proven useful. Voznyi and co-workers reacted acetyl or benzoyl protected 1,2-*trans*-glycosyl fluorides, **6**, with sodium phenolates, **7**, in either 96% ethanol or ethanol–CH_2Cl_2 obtaining the aryl 1,2-*trans*-glycosides, **8** (Scheme 6).[24] This

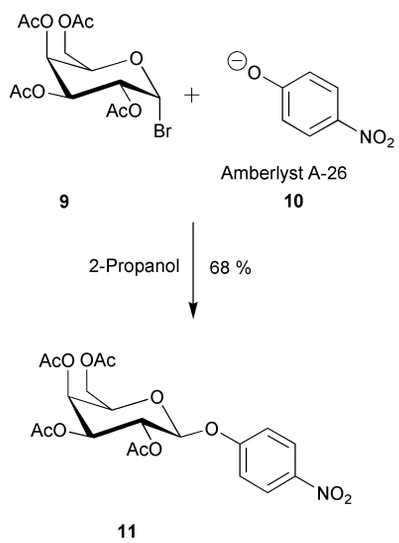


Scheme 6 1,2-*trans*-Glycosyl fluorides.

approach gave good yields when the phenol carried electron-donating substituents, such as 2-methoxyphenol, 4-methylphenol, and 1-naphthol; 5 equiv. of the glycosyl donor were used in these reactions. Both pyranosides (D-Glc, D-Gal, D-Xyl, L-Rha, and L-Ara pyranosides)[24a] and furanosides (D-Glc, D-Gal, L-Ara, and D-Rib furanosides)[24b] were synthesized. The formation of glycals is often a major side-reaction in base-catalyzed glycosylations but *no* glycals were detected in the glycosylation with these glycosyl fluorides. The authors attributed this to the 1,2-*cis*-configuration of the 1-F and 2-H which is unfavorable for β-elimination. However, formation of 1,6-anhydroglucopyranose was observed, and this approach therefore appears more valuable for 6-deoxysaccharides.[24a] It is remarkable that the 1,2-*trans*-configured glycosyl donors gave aryl 1,2-*trans*-glycosides with detection of traces of the 1,2-*cis*-anomers only in some cases. The explanation offered by the authors involves the intermediate formation of a 1,2-epoxide, thus causing double inversion at the anomeric center.[24b]

3.2 Ammonium counterions in Michael glycosylations

The above-mentioned variants of the Michael procedure all rely on group 1 and group 2 metals (Li, Na, K, and Ba), sometimes in the presence of a crown ether, for anionic activation of the phenol. In a deviation from this general approach, Iversen and Johansson reacted 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide, **9**, and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with 2-, 3-, or 4-nitrophenoxide, **10**, bound to quaternary ammonium type anion exchange resin (Scheme 7).[25] In the

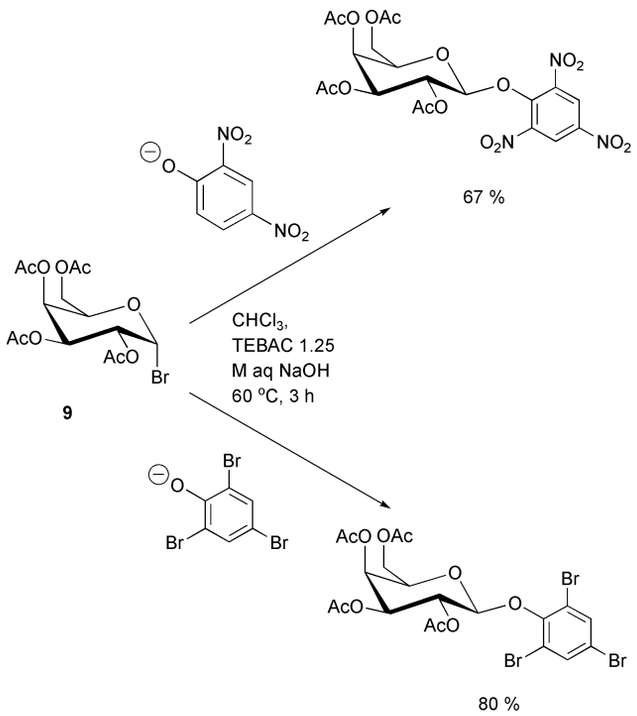


Scheme 7 Resin-bound phenoxides.

protic solvent propan-2-ol with 2.1 equiv. of the phenoxide resin, the reaction gave 1,2-*trans*-glycosides, **11**, in yields ranging from 40 to 98%. Substituting the protic solvent for an aprotic solvent (*i.e.* DMF) increased the amount of the glycal byproduct formed.[26]

More recently, quaternary ions that serve as phase transfer catalysts have found attention as counterions. In what may be conceived of as a two-stage variant of a phase-transfer catalyzed (PTC) reaction, Hansson and Rosengren prepared tetrabutylammonium 2-benzyloxy-4-formylphenolate by extracting an aq. solution of the phenol in the presence of tetrabutylammonium hydrogen sulfate (TBAHS) and excess sodium hydroxide with CH_2Cl_2. They then reacted the phenoxide with methyl 2,3,4-tri-*O*-acetyl-α-D-glucuronopyranosyl bromide.[27] The main product formed was a glycal, while the β-1,2-*trans*-glycoside was obtained in a yield of only 28%. A one-stage procedure for the phase-transfer catalyzed glycosylation of various phenols (phenol, 2-cresol, 3-chlorophenol, 4-methoxyphenol, 4-nitrophenol, 1-naphthol, and morphine) was developed by Inch and co-workers. They reacted 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide with phenols (2–3 equiv.) in a biphasic solvent system of CH_2Cl_2 and 2.5 M aq. sodium or potassium hydroxide containing triethyl(benzyl)-ammonium chloride (TEBAC) at ambient temperature.[28] For monosubstituted phenols the yields were generally good and the nature of the substituent (*i.e.*, whether it was electron-donating or -withdrawing) did *not* influence the yield in an obvious way. The efficiency of the phase-transfer catalysts was 'Adogen' > TEBAC > TBAHS > cetyl(trimethyl)ammonium bromide (CTAB). However, attempts to react *acetyl* protected glucosyl bromide **1a** with phenols under otherwise identical conditions, resulted in unacceptably low yields.[28] However, Kleine *et al.* prepared 44 aryl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosides from the corresponding α-bromide **9** and 2

equiv. of the nitro-, halogeno-, alkyl-, cyano-, alkenyl-, formyl-, or alkoxy substituted phenols by PTC in yields from 29 to 87% (Scheme 8).[29] Yields were higher in the *galacto* than in the *gluco*



Scheme 8 Glycosylation under PTC conditions.

series, presumably due to less β-elimination in the *galacto* series. It is worthy of notice that the galactosides of 4-nitro-, 3-nitro-, and 2,4-dinitrophenol were obtained in a yield of 70, 73, and 67%, respectively, while the galactosides of phenols carrying electron-*donating* substituents, with a few exceptions generally were obtained in *lower* yields, which might constitute a general tendency (in Michael glycosylations), although the authors did not explicitly draw this conclusion. Compared to a study by the same authors on aryl D-glucopyranosides, the yields in the D-galacto series were higher.[30]

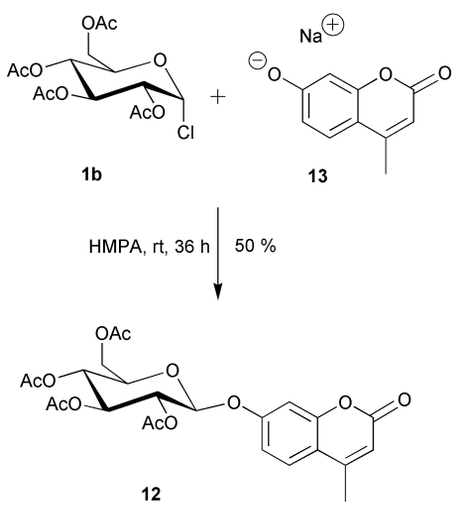
In the glycosylation of some phenols with 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide in the presence of CTAB in CH_2Cl_2 and 1.25 M aq. NaOH, Loganathan and Trivedi observed the formation of two side-products. Not only was 1,5-anhydro-2,3,4,6-tetra-*O*-benzoyl-D-arabinohex-1-enitol formed but also 1,2,3,4,6-penta-*O*-benzoyl-β-D-glucopyranoside.[31] However, Halazy *et al*. also employed these mildly basic conditions, using tetrabutylammonium bromide (TBAB) as the phase transfer catalyst, to obtain the 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosides of some sensitive phenols.[32,33] With benzyl(triethyl)ammonium bromide and 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl bromide, Lubineau *et al*. obtained the β-D-galactosides of highly substituted pesticide phenols, including 2-(*tert*-butyl)-4,6-dinitrophenol (Dinoterbe), in 40–97% yield.[34]

Roy and co-workers reacted a sialic acid derivative with 4-hydroxybenzaldehyde under PTC conditions using TBAHS.[35] The aryl sialoside was obtained in good yields with stereoselective inversion at the anomeric center. The 2,3-dehydro derivative formed by elimination of hydrogen chloride was a major byproduct. Attempts to use this approach for the synthesis of the peracetylated β-D-glucopyranoside and β-D-lactoside of 4-hydroxybenzaldehyde were only met with limited success; the corresponding glycals were formed as the major products.[35a] However, the peracetylated β-D-lactoside of 4-nitrophenol was obtained in a good yield by this procedure.[36]

3.3 Aprotic solvents: modification of the Michael glycosylation

The above variations of the Michael procedure use protic solvents either as the sole solvent, as cosolvent, or as one phase of a two-phase solvent system. An often useful variation of the Michael procedure uses anhydrous aprotic solvents (primarily DMF, HMPA, DMSO, and dimethoxyethane) as medium for the reaction of glycosyl halides with phenoxides.[37] In 1957, Vis and Fletcher reported the synthesis of phenyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside in a yield of 59% by reaction of the glycosyl bromide with sodium phenolate in dimethoxyethane for 1 h at 50 °C.[38]

The synthesis of glycosides of 2-aminopyranoses often presents special problems. However, 2-acylamino-2-deoxy-D-gluco- and D-galactopyranosides of 4-nitrophenol[37a–c,e] and umbelliferyl derivatives[37c] have been prepared in aprotic solvents in the presence of a base.[37] As an example may serve the glycosylation by Delmotte *et al.* of the sodium salt of 4-methylumbelliferone in DMF with 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxyglucopyranosyl chloride and with the corresponding chitobiose and -triose derivatives in yields of 65, 76, and 40%, respectively.[37c] Yields of 4-methylumbelliferyl glycosides were remarkably high in the reaction at ambient temperature with 2–3 equiv. of umbelliferone relative to the glycosyl donor. Glycosyl donors carrying an acetyl protecting group at C-2 were used for these syntheses of 1,2-*trans*[37g] and 1,2-*cis*[37f]-glycosides; the latter can otherwise only be accessed with difficulty. Courtin-Duchateau and Veyriéres reported the highly stereoselective synthesis of 4-methylumbelliferyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside, **12**, in 50% yield by the reaction of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl chloride, **1b**, with the sodium salt of 4-methylumbelliferone, **13**, (2 equiv.) in dry HMPA at ambient temperature (Scheme 9).[37f] The elimination product



Scheme 9 Glycosylations in aprotic solvents.

was formed as the major byproduct. The corresponding α-D-galactopyranoside was formed stereoselectively (trace amounts of the β-D-galacto derivative were observed) in a yield of 47%, but when 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide was reacted with the sodium salt of 4-methylumbelliferone an α/β ratio of 1 : 3 was found (43%). Starting from 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl chloride only the α-D-mannoside was obtained in a yield of 30%.[37f] The authors suggested that this lack of stereoselective inversion might be due to a stronger tendency in the D-manno series to form 1,2-dioxocarbenium ions with formation of 1,2-*trans* α-D-mannosides as a consequence. In summary, dry aprotic solvents are good alternatives to the Michael procedure in aq. solvent mixtures.

3.4 1,2-Epoxides

Danishefsky and co-workers reported the glycosylation of phenols with 1α,2α-epoxides under basic conditions in the

presence of a crown ether.[39] The 1α,2α-epoxides were prepared from the corresponding benzyl protected glycals; phenoxides were obtained from phenol, K_2CO_3 and 18-crown-6 in refluxing acetone. A pyranose,[39a,c] as well as a furanose derivative, were reacted with various phenols (most often 5 equiv. of the phenol were used) to give 1,2-*trans*-glycosides with an unprotected 2-OH in yields ranging from moderate to very high.

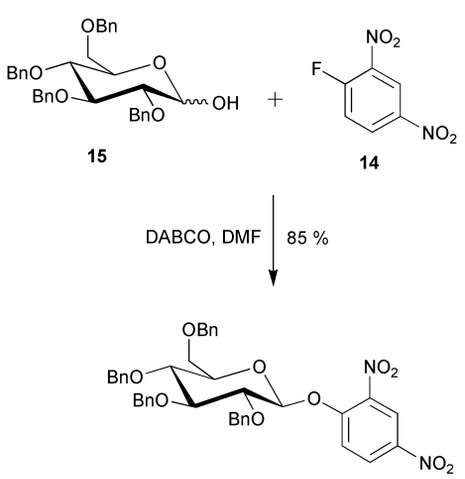
3.5 Various procedures

In 1916 Fischer and von Mechel reported the formation of the 1,2-*cis*-glucoside phenyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside by the reaction of phenol with glucosyl bromide **1a** at 100 °C with quinoline as solvent and base.[40] Only few reports on the application of this procedure have appeared since then.[41] However, this modification of the Michael procedure bears some similarity to a variant of the Koenigs–Knorr procedure in which Ag_2O is used as the halophile with quinoline as base and sole solvent.[40] In a single report, the glycosylation of 4-nitrophenol with 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride in CH_2Cl_2 promoted solely by molecular sieves 4 Å has been reported.[18c]

3.6 Nucleophilic aromatic substitution

In all of the procedures presented above, the phenol acted as the nucleophile attacking the electrophilic anomeric carbon of the glycosyl donor. The reverse situation, in which a glycosyl donor with a free 1-OH is the nucleophile attacking an electrophilic carbon in the glycosyl acceptor, is less common but has found several practical applications in the glycosylation of aliphatic alcohols.[42] In the glycosylation of phenols this situation implies a nucleophilic displacement at an aromatic nucleus and the potential glycosyl acceptors are most often aryl fluorides with electron-withdrawing groups, primarily nitro moieties.

Koeners *et al.* showed that the reaction of 1-fluoro-2,4-dinitrobenzene, **14**, (0.85–1.2 equiv.) with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose, **15**, 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose, or 2,3,4,6-tetra-*O*-acetyl-D-galactopyranose in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) in DMF at 20 °C gave the 2,4-dinitro-β-D-glycopyranosides in excellent yields of 85, 80, and 82%, respectively (Scheme 10).[43,44] Acidic



Scheme 10 Nucleophilic aromatic substitution.

deacetylation with methanol–$CHCl_3$ in the presence of HCl yielded the corresponding 2,4-dinitrophenyl-β-D-glycopyranosides.

Both Mukaiyama[45] and Schmidt[46] have also synthesized aryl glycosides by nucleophilic aromatic substitution for use as glycosyl donors. Mukaiyama's donors were reacted with activated, trimethylsilylated nucleoside bases as glycosyl acceptors. Schmidt's hetaryl glycosides required the presence of a Lewis acid (TMSOTf or $BF_3{\cdot}OEt_2$) for efficient glycosylation of alcohols. These aryl glycosyl donors are thus beyond the scope of this review. Nucleophilic aromatic substitution has also been used for the synthesis of DISAL glycosyl donor (section 4.5).

3.7 Glycosylidene carbenes

Briner and Vasella realized that the oxocarbenium ion pair **16** might be formed from the corresponding glycosyl ylide **17** by deprotonation of an alcohol.[47,48] Ylide **17** is a resonance form of glycosylidene carbene **18** which can be formed by decomposition of diazirines. Reaction of alcohols with glycosylidene carbenes could thus give *O*-glycosides by a (formal) insertion of the carbene into the O–H bond. The per-*O*-benzylated 1-azi-1-deoxy D-gluco-, **19**, D-galacto-, and D-mannopyranosides were prepared in five steps from the corresponding 2,3,4,6-tetra-*O*-benzylpyranoses, and reacted with several phenols. The representative reaction of equimolar amounts of the D-glycosylidene derived diazirine, **19**, with 4-methoxyphenol in CH_2Cl_2 at ambient temperature gave the *O*-glycosides (69%, α/β ratio 1 : 3) and the *C*-glycosides (16%, α/β ratio 1 : 1). (Scheme 11).

The reaction was catalyzed by initial protonation of the diazirine by the phenol. Thus, no external promoter was needed. Interesting features of this procedure include the regioselective glycosylation of methyl orsellinate at the 4-OH and glycosylation of sterically highly hindered 2,6-di(*tert*-butyl)-4-methylphenol in 81% yield (α/β ratio 1 : 4). In all glycosylations 1,2-*trans*-glycosides were the main products. Monosaccharides have also been glycosylated.[49] However, *O*-pivaloyl protected diazirines yielded orthoesters. Disadvantages of this innovative approach includes the lengthy synthesis of the glycosyl donor and the preference for glycosylation of acidic alcohols.

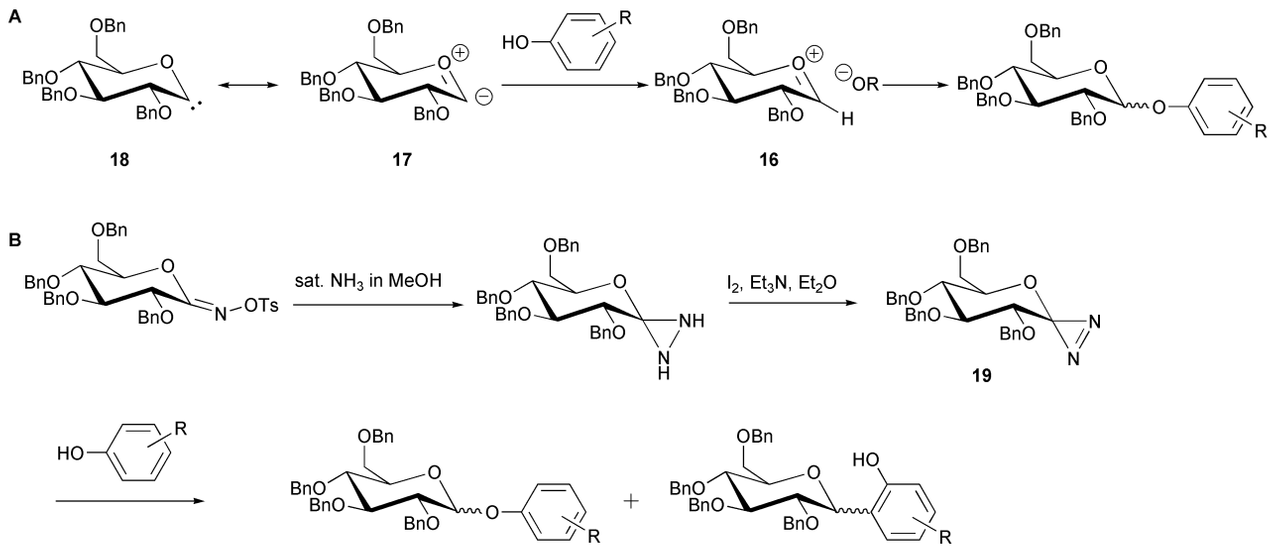
4 Glycosylation of aliphatic alcohols under neutral or basic conditions

4.1 Glycosyl bromides and chlorides

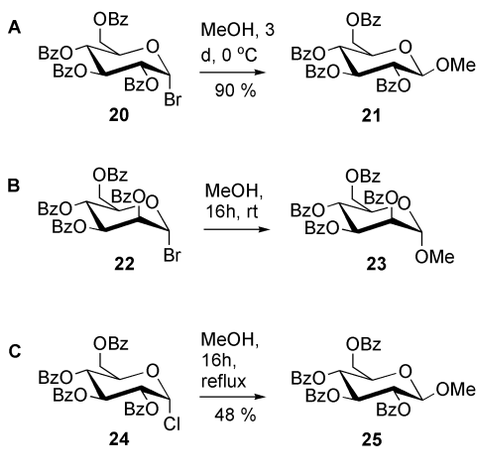
Fletcher, Hudson, and co-workers demonstrated around 1950, that *benzoyl* protected glycosyl bromides react with methanol under solvolytic conditions to give methyl glycosides (Scheme 12).[50] Whereas the α-glucosyl bromide **20** gave the β-configured product **21** with apparent inversion, the α-mannosyl bromide **22** gave the α-configured glycoside **23** with apparent retention. The corresponding α-glucosyl *chloride* **24** proved to be less reactive, as expected, in giving the β-configured glycoside **25**. However, per*benzylated* glycopyranosyl bromides are very sensitive to hydrolysis.

Fréchet and Schuerch reported in 1972 a systematic study of the alcoholysis of various 6-*O*-acyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl bromides.[51] They demonstrated that the 6-*O*-acyl substituent had a decisive influence on the glucoside α/β ratio. 6-*O*-(4-Methoxybenzoyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl bromide, **26a**, gave after methanolysis the methyl glucoside **27** with an α/β ratio of 7 : 93, while 6-*O*-(4-nitrobenzoyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl bromide, **26b**, gave an α/β ratio of 8 : 92 (Scheme 13). Addition of Bu_4NBr increased the rate of reaction; the half-life of methanolysis of 6-*O*-(4-methoxybenzoyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl bromide, **26a**, was reduced from 2.14 h to 0.23 h (156 equiv. of MeOH). In some cases, the stereoselectivity was improved by lowering the temperature. Corresponding glucosyl chlorides in all cases were found to solvolyze 20–30 times slower. However, 6-*O*-(4-nitrobenzoyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl chloride **28** reacted with MeOH to give predominantly the β-configured methyl glucoside.

Fréchet and Schuerch explained the apparent inversion observed in the solvolysis of some per-*O*-alkylglycosyl chlorides by formation of a tight ion pair followed by backside approach of the nucleophile. Analogous glycosyl bromides



Scheme 11 Glycosylidene carbenes.



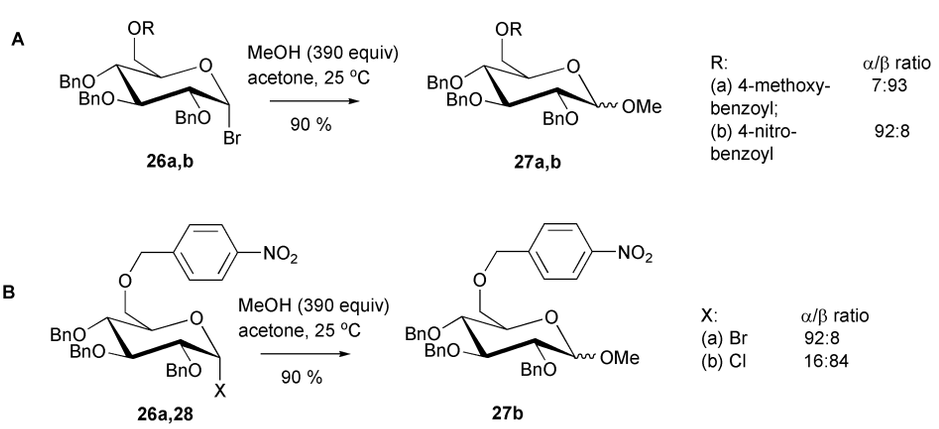
Scheme 12 Solvolysis of glycosyl bromides and chlorides.

generate loose or solvent-separated ion pairs giving an oxocarbenium ion in a half-chair conformation. They attributed the effect from the *O*-6 acyl moiety in the glycosyl bromides to formation of a loose ion pair with a half-chair conformation; the Lewis acid character of the C-1 attracts the carbonyl group of the *O*-6 acyl moiety so that there is substantial overlap with the p-orbitals of the *O*-6 carbonyl. The *para*-substituent on the *O*-6 benzoyl group influences the electron-density on the carbonyl. However, this rationalization of the stereochemical outcome has apparently not found many followers.

Fréchet and Schuerch modified these methanolysis conditions for the first successful implementation of solid-phase oligosaccharide synthesis.[52] However, they observed that not only were the reaction rates too low to be practical, they could also *not* control the stereochemistry of glycoside formation (di- and trisaccharides) by the *O*-6 acyl moiety. They concluded that new glycosylation methods, possibly involving metal ions, would be required for future attempts at solid-phase oligosaccharide synthesis.

Lemieux and co-workers developed the so-called *in situ* anomerization procedure, sometimes referred to as the halide-ion catalyzed glycosylation.[8,53] The mechanism outlined in Scheme 2 describes this method. Reactive glycosyl halides can be activated in glycosylation reactions by addition of a halide source, typically a tetraalkylammonium salt. For example, Paulsen and Kolar employed the *in situ* anomerization procedure for the coupling of a fucosyl bromide with a disaccharide in the presence of tetraethylammonium bromide to establish an α-linkage in 80%. The preferred solvent was CH_2Cl_2. Although Lemieux's procedure has been applied successfully many times, it is limited by the requirement for very reactive pyranosyl halides and by the relatively long reaction times.

Fields and co-workers used galactopyranosyl bromide **9** in the *O*-glycosylation of the tetrafunctional amino acid, L-hydroxylysine (L-Hyl).[54] The N^{ε}-Boc protected Cu complex (N^{a}-amino and carboxylate) of L-Hyl was first treated with NaH and then with **9** to give the β-galactoside. The reaction may have proceeded through the alkoxide.



Scheme 13 Solvolysis of glucosyl bromides: (A) influence of *O*-6 substituent and (B) influence of anomeric leaving group.

4.2 Glycosyl iodides

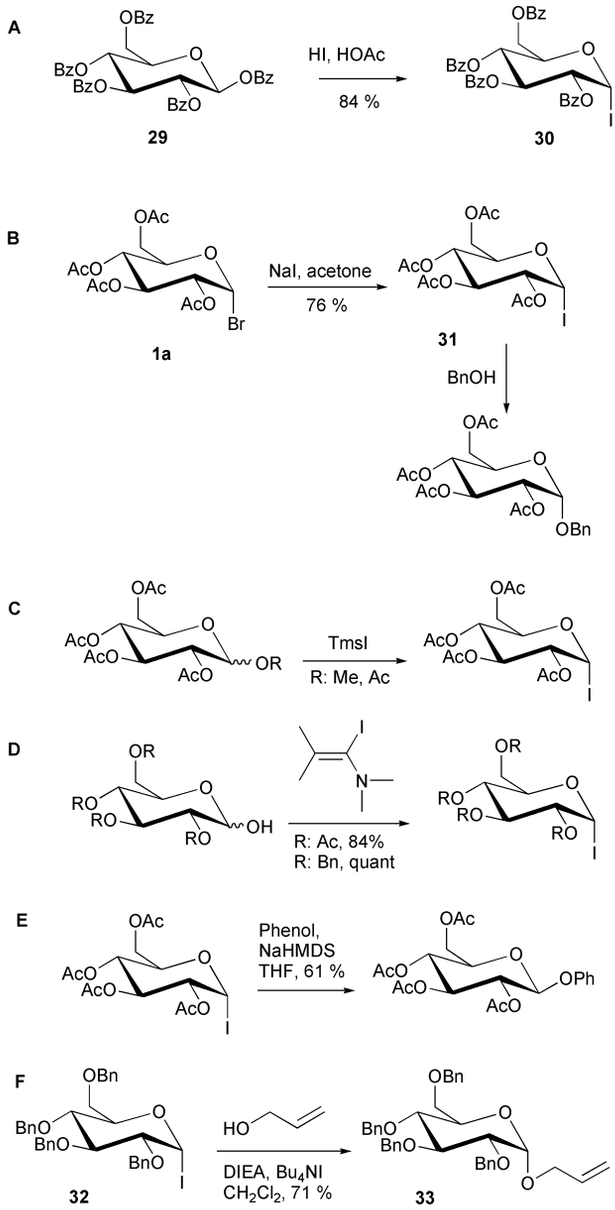
Glycosyl iodides were first reported in 1910 by Fischer[55] but they have not been used extensively since then, probably due to a belief that they were too unstable.[56] However, glycosyl iodides gained prominence when Lemieux and co-workers in the 1970's developed the *in situ* anomerization concept, especially for the synthesis of 1,2-*cis*-α-D-glycosides. This approach uses mainly glycosyl bromides that are activated by halide exchange with iodide.

However, glycosyl iodides have not only been reported as reaction intermediates. While *benzyl* protected iodides in general can only be prepared *in situ*, *acyl* protected glycosyl iodides are considerably more stable and can often be isolated.[56] This follows the general rule that electron-withdrawing *O*-acyl protecting groups render glycosides more stable ('disarmed')[57] and hence less reactive than *O*-benzyl protecting groups do ('armed' glycosyl donors). A number of procedures have been developed for the synthesis of glycosyl iodides.

Treatment of 1,2,3,4,6-penta-*O*-benzoyl-β-D-glucopyranose, **29**, with hydrogen iodide (HI) gave the corresponding α-glucosyl iodide, **30**, in 84% (Scheme 14A).[50b] The Finkelstein halide exchange reaction has also been used to prepare glycosyl iodides. Helferich and Gootz reported that treatment of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, **1a**, with NaI in acetone gave the α-glucosyl iodide, **31**, in 76% (Scheme 14B).[58] Thiem and Meyer have demonstrated that trimethylsilyl iodide (TMSI) can be a very useful reagent for converting 1-*O*-acetates and methyl glycosides into the corresponding glycosyl iodides (Scheme 14C).[59] Gervay and co-workers have shown that treatment of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose with TMSI results in initial formation of the β-glucosyl iodide, while the β-acetate gives the α-iodide.[60] Ernst and Winkler have reported the conversion of lactols (hemiacetals) to glycosyl iodides by the action of an iodoenamine, 1-iodo-2-methyl-*N*,*N*-dimethylpropenylamine (Scheme 14D).[61] The TMSI procedure appears to be the most convenient, as the byproduct of the reaction, TMS-OAc can be removed *in vacuo*; *O*-benzyl protected glycosyl iodides were prepared immediately prior to use by evaporation of the solvent.

These *O*-benzyl protected glycosyl iodides generally were not isolated, whereas their *O*-acyl protected analogs were stable enough to allow isolation. Fletcher and Hudson recommend storage of 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl iodide over NaOH at −5 °C. Corresponding *O-benzyl* protected glycosyl iodides were considerably more reactive and hence less stable. Reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl iodide, **31**, with phenol in the presence of NaHMDS in THF gave the phenyl β-glucopyranoside in 61% (Scheme 14E).[56] However, treatment of the glucosyl iodide with 1,2:3,4-di-*O*-propylidene galactose under the same conditions gave only the glycal elimination product. This difference in behavior can be rationalized by the lower basicity and higher stability of the phenoxide compared to the alkoxide, resulting in a Michael-type glycosylation of the phenolate with apparent inversion. Helferich and Gootz reported that reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl iodide with benzyl alcohol in refluxing benzene gave the α-glucoside, albeit in low yield.

Reaction of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl iodide, **32**, with allyl alcohol in the presence of *N*,*N*-diisopropylethylamine (DIEA) and Bu_4NI in CH_2Cl_2 gave the α-glucoside, **33**, in 71% yield (Scheme 14F).[62] Hadd and Gervay also established the reactivity order for *O*-benzyl protected glycosyl iodides Fuc*p* > Gal*p* > Glc*p*. Under similar conditions, except for refluxing benzene instead of CH_2Cl_2, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose was efficiently glycosylated giving the α-configured product, also by Fuc and Man donors. The latter did not require nucleophilic assistance by an added iodide source. Comparing preformed (immediately prior to use) glycosyl iodides with glycosyl bromides under halide ion catalysis,



Scheme 14 Synthesis of glycosyl iodides and their reactions.

Gervay and co-workers conclude that iodides give higher rates of glycosylation and more efficiently glycosylate sterically demanding acceptors. An allyl β-glucoside was synthesized with high stereoselectivity (α/β 1 : 9.8) when the reaction was carried out in CH_3CN; the β-directing effect of CH_3CN in the glycosylation of aliphatic alcohols is well established.

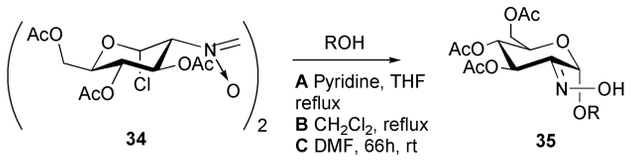
Gervay-Hague and co-workers very recently reported the synthesis of an α-1,6-linked hexasaccharide from mono- and disaccharide glycosyl iodide building blocks.[63] Glycosylations were promoted by tetrabutylammonium iodide in the presence of DIEA and 4 Å molecular sieves in benzene at reflux. The major side-reaction was formation of 2-benzyloxyglycal resulting from elimination of HI from the glycosyl donor.

However, Gervay and co-workers in a 1997 paper concluded "neither neutral alcoholic additions nor basic alkoxide additions to benzyl protected glucosyl and galactosyl iodides are likely to lead to efficient syntheses of β-*O*-alkyl glycosides. However, β-*O*-aryl and β-*O*-acyl glycosides are formed in a high-yielding and highly stereoselective process."[64] It is often a useful method for synthesis of 1,2-*cis*-(α)-*O*-alkyl glycosides.

4.3 Lemieux's synthesis of 2-oximino-α-D-hexopyranosides

Lemieux and co-workers employed an unusual class of glycosyl donors prepared[65] by addition of nitrosyl chloride to 3,4,6-

tri-*O*-acetyl-D-glucal or -galactal giving 3,4,6-tri-*O*-acetyl-2-deoxy-2-nitroso-α-D-glucopyranosyl chloride, **34**, or the galacto derivative, respectively, as the dimers (Scheme 15).[66]



Scheme 15 Synthesis of 2-oximino-α-D-hexopyranosides; A–C are different procedures.

Mainly simple aliphatic alcohols (*e.g.*, methanol and propan-2-ol) but also methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranoside were glycosylated in good yields in the absence of Lewis acids; phenols were also glycosylated. Remarkably, only the α-linked glycosides were observed. Highly reactive conjugated nitroso-olefins were believed to be intermediates. However, this procedure has since then only found few applications. First, the 2-oximino moiety in the products, **35**, requires further manipulations, which limits the convenience of the procedure. Secondly, formation of both α- and β-glycosides in these glycosylations have been reported.[67] Finally, these glycosyl donors are not easily prepared.

4.4 $LiClO_4$ promoted glycosylations

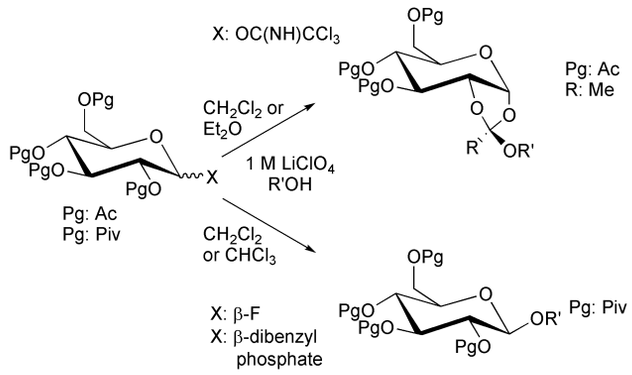
In general, the addition of an external salt affects the rates of S_N1 and S_N2 reactions in the same way as an increase in solvent polarity; *e.g.*, an increase in ionic strength of the solution usually increases the rate of an S_N1 reaction. Furthermore, there is a 'special salt effect' of $LiClO_4$. It would thus appear promising to attempt glycosylations in anhydrous salt solutions.

The highly polar concentrated salt solutions of anhydrous $LiClO_4$ in Et_2O (LPDE) exist as complex ionic clusters composed of $LiClO_4$ and Et_2O, rather than as simple aggregates of ions.[68] The number of solvent molecules coordinated to a lithium ion is concentration dependent, as the lithium ion binds two molecules of diethyl ether up to 4.25 M, at which concentration all diethyl ether is complexed and the solution becomes a room temperature molten salt. At higher concentrations the molten salt becomes progressively richer in lithium ions bound to one molecule of diethyl ether. LPDE is a solvent system that can provide dramatic rate increases of reactions that yield ions, *e.g.*, for reactions proceeding by a S_N1 mechanism. Thus, a 7×10^9-fold increase for trityl cation formation in the ionization of triphenyl chloride was observed in going from a Et_2O solution to LPDE (5.0 M). Several explanations for the ability of LPDE to increase the reaction rate have been offered, including for some reactions the combined effects of the lithium ion acting as a mild Lewis acid (the acidity being abated by competitive complexation to ethers) in conjunction with an increase in solvent polarity of the medium.[69]

Although in a particular reaction $LiClO_4$ may owe its effect to its Lewis acid character, in LPDE it is a very mild Lewis acid and other effects may also be at work. Thus, the few examples of $LiClO_4$ promoted glycosylations will be presented in this review.

Waldmann and co-workers have studied the activation of glycosyl fluorides, bromides, trichloroacetimidates, phosphates, and phosphites by $LiClO_4$ in Et_2O and other solvents (Scheme 16). Initial studies demonstrated that 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl fluoride became an efficient glycosyl donor in the presence of 1 M $LiClO_4$ in Et_2O.[70] A 1–6 linked disaccharide was prepared in 62% yield (α/β 1 : 1).

They also demonstrated that glycosylation of primary and secondary alcohols, including monosaccharides, with *O*-benzylated glucosyl phosphites in the presence of $LiClO_4$, $Mg(ClO_4)_2$, or $Ba(ClO_4)_2$ in either CH_2Cl_2 or CH_3CN solutions



Scheme 16 Glycosylations in $LiClO_4$ solutions.

gave the desired glycosides.[71] Best results were obtained with $Ba(ClO_4)_2$ and the diethyl phosphite proved the most reactive. Similarly, 2-deoxy and 2,6-dideoxy glycosides were prepared in the presence of 0.1 M $LiClO_4$ in Et_2O.[72]

Among *O*-acylated glycosyl donors, the pivaloyl protected β-fluoride and the β-glucopyranosyl dibenzyl phosphates in the presence of 1 M $LiClO_4$ in CH_2Cl_2 or $CHCl_3$ gave the desired glycosides, including 1-6 linked disaccharides.[73] However, the corresponding α- and β-trichloroacetimidates gave orthoesters, in either Et_2O or CH_2Cl_2 solutions. Acetyl protected glycosyl phosphates, acetyl or pivaloyl protected glycosyl bromides, and pivaloyl protected glycosyl trichloroacetimidates did not give the desired *O*-glycosides. However, the formation of orthoesters, *i.e.* their stability, under these conditions underscores the mildness of these glycosylation conditions.

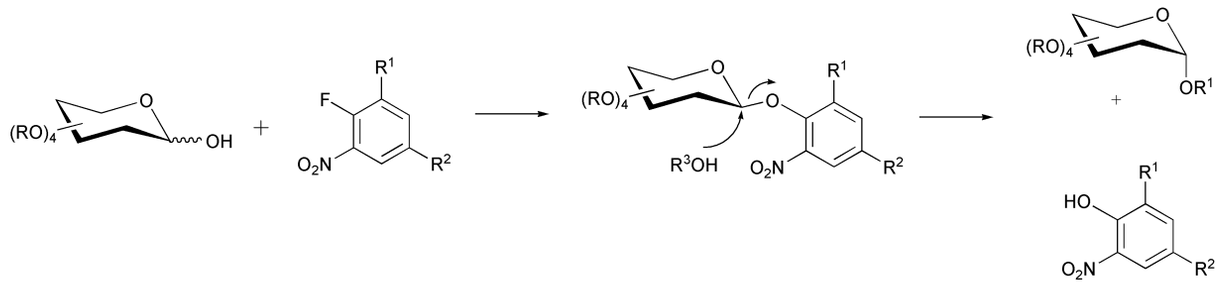
For the synthesis of more complex oligosaccharides carrying fucose moieties, it proved beneficial to use only two equiv. of $LiClO_4$ (0.07 M).[74] A β-fucosyl fluoride and 1,2-epoxides were employed. Lubineau *et al.* have reported LiOTf (0.05 equiv.) as an alternative to $LiClO_4$ as a promoter in glycosylation reactions and ascribed its effect to general acid catalysis.[75] $LiClO_4$ has also been employed in glycosylations with DISAL donors, especially for solid-phase applications (*vide supra*).

In summary, $LiClO_4$ solutions can provide efficient activation of benzyl protected, *i.e.* 'armed', glycosyl donors (especially fluorides and phosphites) under very mild conditions. Efficient glycosylations were achieved in not only Et_2O solutions but also in CH_2Cl_2, generally in 1 M concentration, but much lower amounts (CH_2Cl_2 solution) have also been successfully applied. The mechanism of activation may, at least in part, be that of a very mild Lewis acid.

4.5 DISAL glycosyl donors

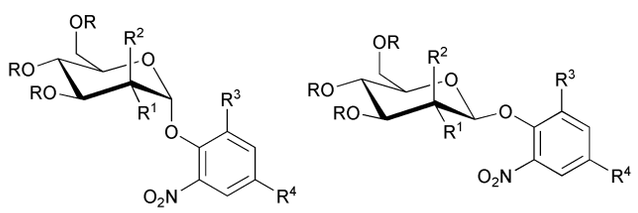
Until recently, glycosylations under neutral or basic conditions mainly employed glycosyl halides, with the exception of $LiClO_4$ promoted reactions. Petersen and Jensen[76] reasoned that glycosides of phenols carrying sufficiently electron-withdrawing substituents could possibly serve as glycosyl donors under neutral or mildly basic conditions. Glycosides of 2,4-dinitrophenol, while labile to nucleophiles such as ammonia in methanol,[17b,77] appeared not to be reactive enough in glycosylation reactions. In order to obtain more reactive glycosyl donors, glycosides of methyl 2-hydroxy-3,5-dinitrobenzoate[78] (DISAL, a *di*nitro*sal*icylic acid derivative) and methyl 4-hydroxy-3,5-dinitrobenzoate were prepared (Scheme 17).

The electron-withdrawing groups on the phenyl ring made these glycosides well suited for preparation by nucleophilic aromatic substitution. A double base system was developed for the *O*-arylation of hemiacetals with aryl fluorides, in which only a catalytic amount of the *soluble* base (4-(*N*,*N*-dimethylamino)pyridine, DMAP, or 1,4-dimethylpiperazine, DMP) was used as a 'shuttle' and an *insoluble* base (Li_2CO_3) acted as a drain for liberated HF from the reaction mixture.



Scheme 17 Conceptual outline for synthesis and application of DISAL glycosyl donors; $R^1 = CO_2Me$ and $R^2 = NO_2$, or $R^1 = NO_2$ and $R^2 = CO_2Me$.

The use of DMAP as base gave an α/β ratio similar to the starting 1-OH derivative, *i.e.* predominantly α. In contrast hereto, formation of, *e.g.*, aryl β-glycoside **36β** was favored using DMP as soluble base.[79] These two protocols were also applied to the synthesis of *benzoyl* protected glycoside **37α**,**β**. Also, the benzyl protected *para* donor **38** was synthesized in a DMAP catalyzed reaction in 65% yield. Finally, the *ortho* donor **39α** derived from 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose,[80] was synthesized *via* the DMAP protocol in 75% yield as the pure α-anomer (Fig. 1).

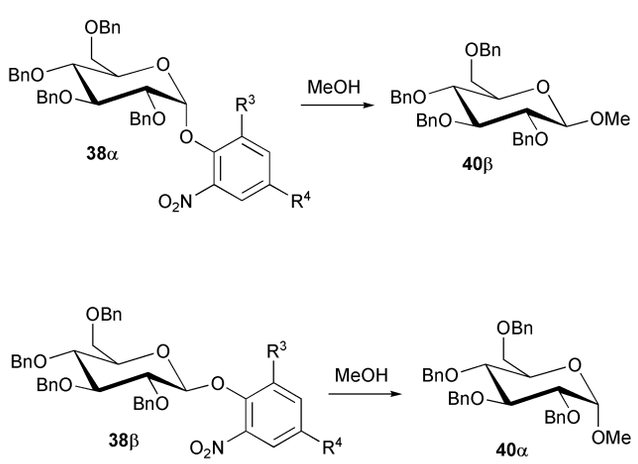


36α,β: R=Bn, R^1=OBn, R^2=H, R^3=CO_2Me, R^4=NO_2
37α,β: R=Bz, R^1=OBz, R^2=H, R^3=CO_2Me, R^4=NO_2
38α,β: R=Bn, R^1=OBn, R^2=H, R^3=NO_2, R^4=CO_2Me
39α : R=Bn, R^1=H, R^2=OBn, R^3=CO_2Me, R^4=NO_2

Fig. 1 DISAL glucosyl and mannosyl donors.

The selective synthesis of **36α** and **36β** was also carried out. The lactol as the pure α-anomer[81] gave with DMAP catalysis aryl glycoside **36α** (α/β 8.4 : 1) in 89% yield. To form **36β** selectively, the aryl fluoride was added slowly to a stirred solution of the lactol (α/β 4 : 1) and DMP to give 78% of donor **36β** (α/β 1 : 14.1). Importantly, DISAL donors do *not* anomerize under the conditions used for their synthesis, *i.e.*, in non-polar solvents.

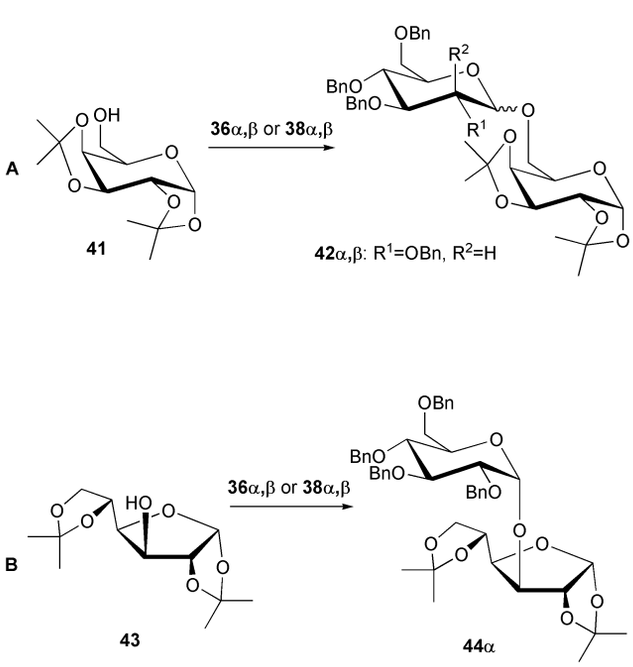
Interestingly, glycosylation of methanol with DISAL donors proceeded with *inversion*, as reaction of pure **38α** and **38β** with methanol gave methyl glucosides **40β** and **40α**, respectively; the former in 93% yield (Scheme 18). It is thus a *stereospecific* glycosylation. To develop conditions for the glycosylation of saccharides, a wide range of solvents were tested in the glycosylation of cyclohexanol. Best solvents were *N*,*N*-dimethylacetamide (DMA), 1-methylpyrrolidin-2-one (NMP), or mixtures of the latter with acetonitrile or nitromethane. The standard glycosylations conditions were NMP solutions at 40 °C, in the absence of Lewis acids.



Scheme 18 Stereospecific glycosylation of methanol with DISAL donors.

Thus, it seems that in a solvent with a sufficiently high polarity, such as NMP, glycosylations occurred smoothly. The fact that glycosylations also occurred in the presence of base indicated that the glycosylations were *not* auto-catalytically promoted by the released phenol, methyl 2-hydroxy-3,5-dinitrobenzoate. In a control experiment, 2,4-dinitrophenyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside gave *no* reaction or even breakdown,[82] thus confirming the initial hypothesis that additional electron-withdrawing groups on the leaving group were required.

Using the standard procedure (NMP at 40 °C), DISAL donors were used for the synthesis of oligosaccharides. Reaction of diisopropylidene protected galactose **41** carrying a *primary* hydroxy with glycosyl donor **36** (1.5 equiv.) gave the resultant disaccharide **42α**,**β** in 90% yield (α/β 2.4 : 1). From the diisopropylidene protected glucose derivative **43**, with a free secondary hydroxy, disaccharide **44** was obtained as the α-glycoside. Here it proved advantageous to raise the reaction temperature to 60 °C. The yield for the glycosylation of secondary alcohol **43** was improved to 74% by addition of a second 1.5 equiv. of the DISAL donor **36** (Scheme 19A). Lower yields were



Scheme 19 Synthesis of disaccharides with DISAL glycosyl donors.

obtained when adding DIEA to the glycosylation reaction due to increased formation of 2,3,4,6-tetra-*O*-benzyl-2-hydroxy-D-glucal, which was the major byproduct in all cases.

The *para*-glycosyl donor **38** also proved effective in the glycosylation of monosaccharide **41** to give the disaccharide **42** in 82% yield. Glycosylation of the secondary hydroxy in **43** proceeded in 46% yield of the pure α-anomer **44α** (Scheme 19B).

Thus, a new type of glycosyl donor was synthesized in high yields and with good control of the α/β ratio. Benzyl protected (*i.e.*, 'armed') aryl glycosides were efficient glycosyl donors for *O*-glycosylation under neutral or mild basic conditions. Glycosylation of methanol under solvolytic conditions was stereospecific with inversion of anomeric configuration, whereas with sterically more demanding alcohols, α-selectivity was observed, most likely by anomerization of the DISAL donor. DISAL donors were shown to undergo anomerization in the polar solvents used to promote glycosylation reactions. These donors are the first members in a new class of glycosyl donors, which are stable upon storage, yet do not require activation by a Lewis acid for efficient glycosylations. Whereas *benzyl* protected aryl glycosides were efficient glycosyl donors under neutral conditions, the analogous *benzoyl* protected donors did not give the expected glycosides under these strictly neutral conditions, in part due to trapping of intermediates as the orthoesters.

4.5.1 $LiClO_4$ promoted glycosylations with DISAL donors

$LiClO_4$ proved an efficient additive for activation of DISAL donors in non-polar solvents.[83] Even though only sparingly soluble in CH_2Cl_2, $LiClO_4$ (2.5 equiv.) gave a near quantitative yield of benzyl protected cyclohexyl glucoside **45** as an α/β mixture (Fig. 2). However, full conversion and slightly higher

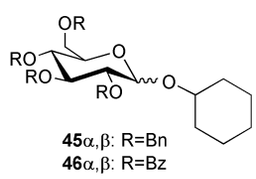
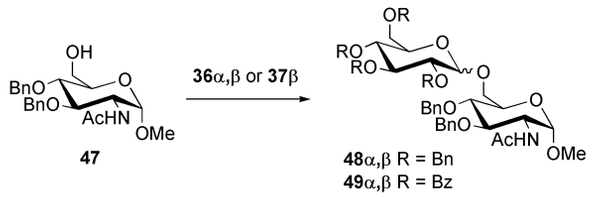


Fig. 2 Cyclohexyl glucosides.

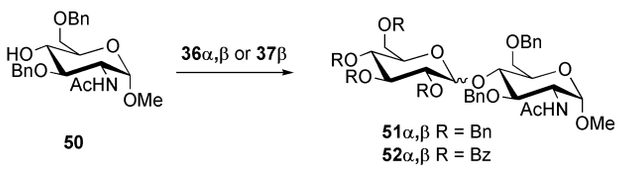
α-selectivity was observed in Et_2O solution. Addition of an auxiliary nucleophile, Bu_4NI, to the glycosylation in CH_2Cl_2 in the presence of $LiClO_4$, which likely gave the glycosyl iodide *in situ*, provided both a good yield of the glycoside and high α-selectivity. NMR evidence for formation of the α-glucosyl iodide,[84] in the absence of a glycosyl acceptor was obtained. With Bu_4NI alone, good yield and α-selectivity was achieved but under slightly more forcing conditions.

Addition of very strong Lewis acids, $BF_3{\cdot}Et_2O$ or TMSOTf, activated the *acylated* DISAL donor **37**, which had proven ineffectual for the glycosylation of cyclohexanol under neutral conditions. More relevant for the present review was that $LiClO_4$ (2.5 equiv.) in CH_3NO_2 at 40 °C proved efficient in activating **37β** giving cyclohexyl glucoside **46β** in 81% yield; no **46α** was detected. As expected the β-donor proved more reactive than the α-donor.

It is noteworthy that for the glycosylation of **47**, promotion by $LiClO_4$ gave a significantly higher yield (93%) of **48α,β** than promotion by the stronger Lewis acid $BF_3{\cdot}Et_2O$ (77%). Acceptor **47** was also glycosylated successfully with donor **37β** and the pure β-product **49** was obtained in an excellent 91% yield (Scheme 20). The 1–4 linkage to GlcNAc acceptors are among the most difficult to establish. It is testimony to the potential of DISAL donors that the secondary alcohol acceptor **50** was glycosylated efficiently in the presence of $LiClO_4$ in CH_3NO_2. Thus, using benzyl donor **36α,β**, disaccharide **51α,β** was isolated in 82% yield (α/β 1.9 : 1). For the benzoyl donor, disaccharide **52** was obtained as the pure β-anomer in a moderate yield (Scheme 21).



Scheme 20 Synthesis of a 1–6 linked disaccharide in the presence of $LiClO_4$.



Scheme 21 Synthesis of a 1–4 linked disaccharide in the presence of $LiClO_4$.

4.5.2 Solid-phase synthesis

This approach was extended to solid-phase glycosylation of D-glucosamine derivatives[85] anchored by the 2-amino group through a Backbone Amide Linker (BAL) to a solid support. Initial efforts on solid-phase glycosylation with DISAL donors started from the previously reported *neutral* conditions in solution, however, with only limited success.

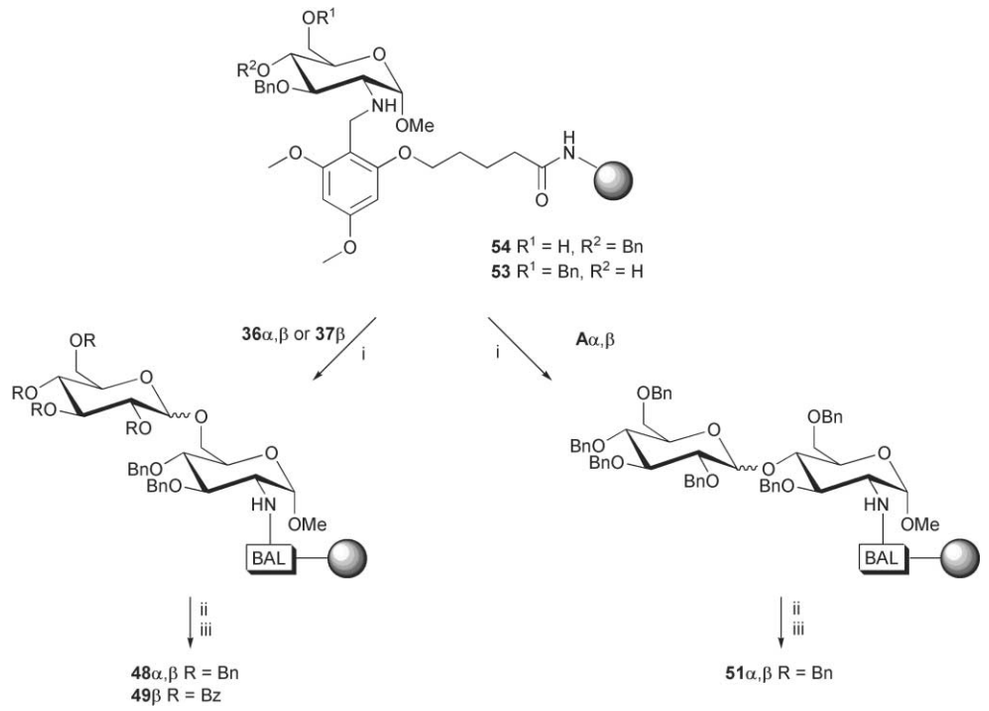
Instead, $LiClO_4$ activation of glycosyl donors was also used in solid-phase glycosylations. Donor **36** again proved efficient and gave an almost quantitative conversion to disaccharide **48** (Scheme 22), however, with a lower recovery than for the similar, $BF_3{\cdot}Et_2O$ promoted reaction. The very hindered resin-bound acceptor **53** was also glycosylated under these conditions to give 52% of disaccharide **51**. Donor **37β** with activation by $LiClO_4$ (38 equiv.) also glycosylated both resin-bound acceptors **54** and **53** to give disaccharides **49** in 88% (α/β 10 : 1). The halide additive Bu_4NI promoted (**36**) a high solid-phase conversion and with high α-selectivity (α/β 13 : 1). However, the yield of the synthesis was low.

4.5.3 Intramolecular glycosylation

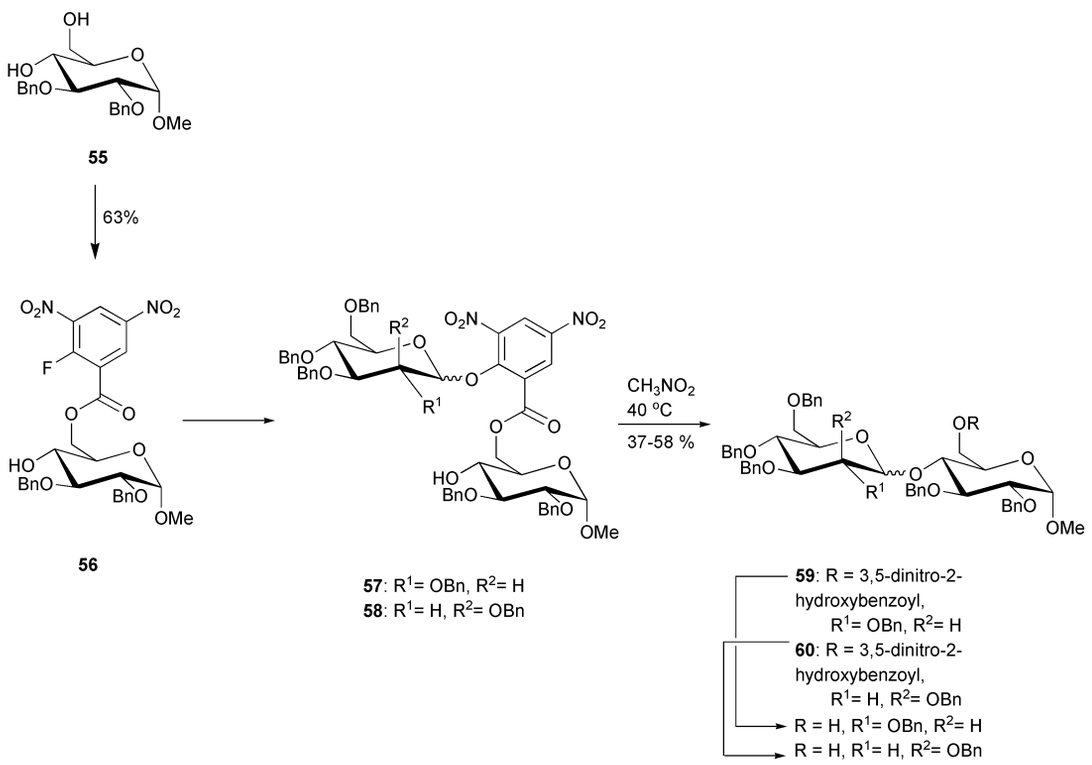
The DISAL donor concept was developed further to allow intramolecular glycosylations.[86] In this design, glycosyl donor and acceptor were linked through the DISAL leaving group positioned to allow intramolecular glycosyl transfer to 4-OH by a 1,9-glycosyl shift. The idea was to favor S_N2 type displacements at the anomeric center to allow control of the stereochemical outcome of glycosylations (Scheme 23).

The partially protected glycosyl acceptor methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside **55** was esterified with 2-fluoro-3,5-dinitrobenzoic acid to give the *O*-6 benzoic ester **56** in 63% yield. The high regioselectivity of the *O*-acylation obliterated the need for transient protection of *O*-4. The 'donors' 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose or 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose were attached to the linker moiety by nucleophilic aromatic substitution to form the aryl glycosides **57** and **58**, respectively. In the 'double base' system both DMAP and 1,4-dimethylpiperazine (DMP) were used as organic bases in substoichiometric amounts. With DMP promotion the β-glycosides were formed predominantly in all cases, whereas the faster DMAP promoted reaction led to formation of the α-glycosides. It was observed that upon dissolution in CH_3NO_2 and other polar solvents the tethered glycosides slowly underwent *in situ* anomerization (5–15% α from pure β) during glycosylation under neutral or basic conditions.

The tethered glycosides **57** and **58** did indeed undergo intramolecular transglycosylation to form the corresponding 1,4-linked disaccharides **59** and **60**, respectively. Under neutral conditions in CH_3NO_2 at 60 °C the intramolecular glycosylation reaction favored formation of β-glucosides and α-



Scheme 22 Solid-phase oligosaccharide synthesis with DISAL donors; i, $LiClO_4$; ii Ac_2O; iii TFA–H_2O 19 : 1.



Scheme 23 Intramolecular glycosylation with DISAL donors.

mannosides, in moderate yields. Finally, removal of the DISAL linker was performed by Zemplén deacylation liberating the 6-OH of disaccharides.

Thus, a new method for intramolecular glycosylation of 4-OH of D-glucose by a 1,9-glycosyl shift under neutral, hence extremely mild, conditions had been developed. However, yields were somewhat reduced by competing hydrolysis and inversion at the anomeric center was not observed, most likely due to anomerization prior to glycosylation.

5 Conclusions

In the following, the different glycosylation methods, with their particular advantages and limitations, will be summarized. Emphasis will be put on practical aspects.

Glycosylation of phenols under basic conditions, which generates a reactive yet stable phenolate, has been successful for many substrates. Glycosylation of phenols is different from similar reactions with aliphatic alcohols, as phenoxides are more stable and less reactive than alkoxides. Alkoxides may also cause more base-induced side-reactions than phenoxides. A number of distinct procedures have been developed, including aq.-organic homogeneous or two-phase systems, phase-transfer catalyzed reactions, and reactions in dry aprotic solvents. Advantages of these protocols over Lewis acid promoted glycosylations include a tendency towards inversion at the

anomeric center during the reaction and that glycosylations are generally compatible with the presence of water. Yields do *not* often decrease in the order *p* > *m* > *o* for the substituted phenols. Glycosyl bromides, chlorides, and fluorides have been used as glycosyl donors. Procedures used include (1) aq. NaOH with acetone as the organic cosolvent (which yields the protected glycosides); (2) K_2CO_3 in dry acetone for the preparation of 2,4-dinitrophenyl glycosides; (3) ammonium counter ions, *e.g.*, in phase-transfer catalysis (PTC) reactions; (4) aprotic solvents, primarily DMF, HMPA, DMSO, and dimethoxyethane, as medium for the reaction of glycosyl halides with sodium or potassium phenolates. It may be a tendency that the galactosides of phenols carrying electron-*withdrawing* substituents generally in PTC reactions were obtained in *higher* yields than the corresponding analogues with electron-*donating* substituents. β-Elimination to form glycals was the predominant side-reaction.

Aryl glycosides with several strongly electron-withdrawing groups, *e.g.*, 2,4-dinitrophenyl glycosides, can often conveniently be prepared by nucleophilic aromatic substitution. In the synthesis of DISAL glycosides, good control of the α/β ratio was achieved through choice of the substoichiometric base used.

Benzoylated glycosyl bromides can be methanolysized, whereas the analogous chlorides as expected are less reactive. Benzylated (partially) glycosyl bromides readily undergo methanolysis; while the chlorides again are less reactive, they can give methyl glycosides by inversion. Partially benzylated glycosyl bromides were used in the first successful attempt at solid-phase oligosaccharide synthesis. Lemieux's halide-ion assisted *in situ* anomerization protocol for use with glycosyl bromides generates an equilibrating mixture of the α- and β-glycosyl iodides which gives the glycoside often with good α-selectivity; the halide additive is often tetraalkylammonium iodide. While both *O*-acyl and *O*-benzyl protected glycosyl iodides can be prepared *prior* to the glycosylation step, only the former can be isolated. Acylated glycosyl iodides seem to be of low-to-modest reactivity; however, benzyl protected glycosyl iodides prepared immediately prior to use appear to give a higher rate of glycosylation and more efficiently glycosylate sterically demanding acceptor. High α-selectivity can be achieved, however, general synthesis of β-linked alkyl glycosides appears *not* possible from glycosyl iodides.

Solutions of $LiClO_4$ can provide efficient activation of benzyl protected, *i.e.* 'armed', glycosyl donors (especially fluorides and phosphites) under very mild conditions. Efficient glycosylations were achieved not only in Et_2O solutions but also in CH_2Cl_2; generally 1 M concentrations were used but in CH_2Cl_2 solutions much lower concentrations have also been successfully applied. The mechanism of activation may, at least in part, be that of a very mild Lewis acid.

The very recently developed DISAL donors have shown promise as: (a) benzyl protected DISAL donors can be isolated and stored for extended periods of time, where the corresponding iodides are very labile; (b) stereospecific glycosylation of methanol has been achieved; (c) three different sets of conditions for activation of DISAL donors, including neutral (just add NMP) and mild conditions ($LiClO_4$ or $LiClO_4$–Bu_4NI) have been established; (d) acyl protected DISAL donors can be activated in the presence of $LiClO_4$, whereas the corresponding glycosyl iodides have only found very limited use; (e) DISAL donors proved efficient in solid-phase oligosaccharide synthesis; (f) an intramolecular modification of the DISAL concept was developed for establishing 1,4-linkages, as 1,6-tethered glycosides underwent intramolecular transglycosylation to give 1,4-linked disaccharides by a 1,9-glycosyl shifts.

A current limitation of DISAL glycosyl donors is their apparent tendency to anomerize in the polar solvents required for glycosylation. Unless the incoming nucleophile is very reactive, such as methanol, glycosylations are not stereospecific but tend to be the more α-selective the less reactive the alcohol is. It should be emphasized that the anomerization occurs without addition of an auxiliary halide and that the actual glycosyl donors are stable compounds, thus the protocol is significantly different from Lemieux's protocol. However, the DISAL leaving group can most likely be 'fine-tuned' further. Further studies are required to ascertain whether DISAL donors will be of general use.

In summary, glycosylations in the absence of Lewis acids, *i.e.* under neutral or basic conditions, has been immensely successful for the synthesis of many aryl glycosides. It has been less predominant for the synthesis of aliphatic glycosides but the promising recent results presented here, could make this a viable approach.

6 Acknowledgements

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