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Minireview

The use of cyclic bifunctional protecting groups in oligosaccharide synthesis—an overview

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Dedicated to the memory of Professor Nikolay K. Kochetkov

Abstract—A historical overview is presented on stereo-directing effects of cis- and trans-fused diol protective groups used on both donor and acceptor glycosides. Attention is focused on the use of cyclic carbonates and carbamates, diacetals and acetals and finally the special case of 1,2-*O*-orthoesters and 1,2-*O*-cyanoalkylidene functionalised residues.

Keywords: Cyclic protection; Benzylidene; Diacetal protection; Cyclic carbonate; Cyclic carbamate; Stereoselective glycosylation; Orthoester; Cyanoalkylidene

Contents

1. Introduction

The development of synthetic procedures for the stereoselective introduction of glycosidic linkages is a main objective in carbohydrate chemistry.[1] Many factors can influence the outcome of a glycosylation event. These include the leaving group on the donor, the activating system, the reaction conditions and, importantly, also the nature of the protective groups on both donor and acceptor glycosides. Originally devised to ensure regioselectivity, protective groups on the reaction partners also exhibit a major influence on the efficiency

Abbreviations: Ac, acetyl; All, allyl; BDA, butane-2,3-diacetal; Bn, benzyl; BSP, benzene sulfinylpiperidine; Bz, benzoyl; Cbz, benzyloxycarbonyl; CDA, cyclohexane-1,2-diacetal; DCE, dichloroethane; DCM, dichloromethane; DTBMP, di-*tert*-butyldimethylpyridine; IDCP, iodonium di-*sym*-collidineperchlorate; HCB, 2-(hydroxycarbonyl)benzyl; MPBT, *S*-(4-methoxyphenyl) benzenethiosulfinate; NGP, neighboring group participation; NIS, *N*-iodosuccinimide; Pent., pentenyl; Ph, phenyl; PhSOTf, phenylsulfenyltriflate; Tf, trifluoromethanesulfonyl; TBDMS (or TBS), *tert*-butyldimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; TMS, trimethylsilyl; Tr, trityl; TTBP, tri-*tert*-butylpyrimidine.

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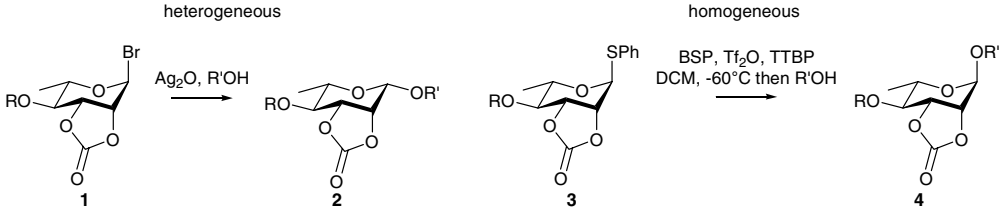
and stereoselectivity of glycosylation events.[2] This is illustrated by the stereoselective introduction of 1,2-trans glycosides by neighbouring group participation (NGP) of 2-*O*-acyl protective groups on the donor glycosides.[3] In recent years, interest in exploiting the influence of specific diol protective groups on the stereochemical outcome of glycosylations has re-emerged. Here, a historical overview on stereoselective glycosylation involving diol-protected donor glycosides is presented, and recent results are highlighted.

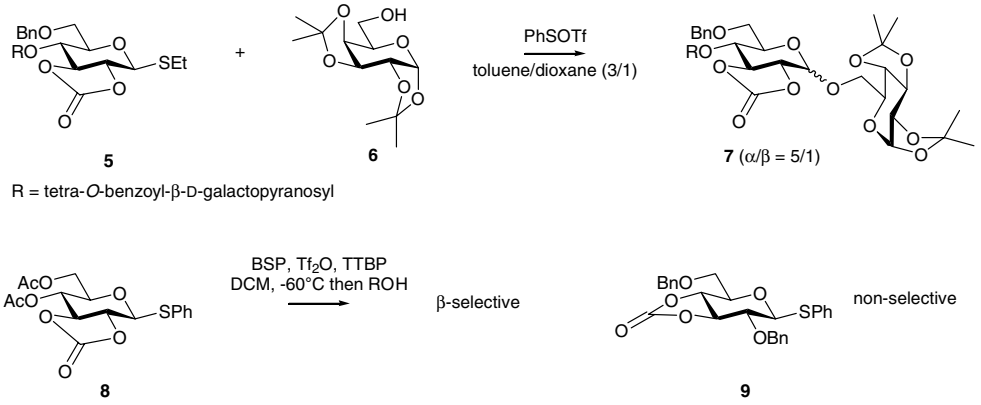
2. Cyclic carbonates and carbamates

Already in 1961, Gorin and Perlin applied 2,3-*O*-carbonate protection in the synthesis of β-mannosides from α-mannosyl bromides with the aid of heterogeneous catalysis.[4] In a similar approach, Kochetkov and co-workers demonstrated that 2,3-*O*-carbonyl protected α-L-rhamnosyl bromides can selectively β-glycosylate various acceptors (for instance **1** → **2**, Scheme 1) using silver oxide as the heterogeneous catalyst.[5] The stereochemical outcome in the coupling of 2,3-*O*-carbonyl rhamnosyl bromides can be explained as follows. Complexation of the anomeric bromide in **1** with the insoluble silver salt, as proposed by van Boeckel et al., leads to the formation of an activated complex in which the α-face is shielded. Ensuing S_N2-type attack of the nucleophile from the β-side then results in the selective formation of β-linked disaccharides **2**.[6] In contrast, Crich and Li found that the 1-benzenesulfinyl piperidine (BSP)/trifluoromethanesulfonic anhydride (Tf_2O) mediated glycosylation of similarly protected phenyl 1-thio-α-D-mannopyranosides[7] and phenyl 1-thio-α-L-rhamnopyranosides[8] gave in a stereoselective manner the axially coupled disaccharides (for instance **3** → **4**, Scheme 1). The α-selectivity observed with 1-thiorhamnosides **3** is explained by taking into account that the 2,3-*O*-carbonyl group locks the pyranose ring in a $^{O}H_5$ half chair conformation, which is thought to facilitate the formation of the α-selective oxocarbenium ion upon pre-activation.[9] Treatment with a range of acceptors then affords the corresponding α-linked disaccharides **4**. In another study, Crich et al. compared the glycosylation properties of donor rhamnosides having either a 2,3-*O*-carbonate or a 3,4-*O*-carbonate protective group. The outcome of these studies was that 3,4-*O*-carbonate protected donor rhamnosides are always selective in β-glycosylation reactions, both under heterogeneous (rhamnosyl bromide, silver carbonate) and homogeneous (thioglycoside, BSP/Tf_2O) conditions. The authors concluded that for the 3,4-*O*-carbonate series the electron withdrawing nature of the carbonate, combined with its inability to partake in neighbouring group participation, guides the observed β-selectivity.[10]

Several reports have appeared describing the stereodirecting effect of the 2,3-*O*-carbonate protective group in the glycosylations of various 1-thioglucopyranosides (Scheme 2). Zhu and Boons showed that the phenylsulfenyltriflate (PhSOTf) mediated coupling of ethyl



Scheme 1.

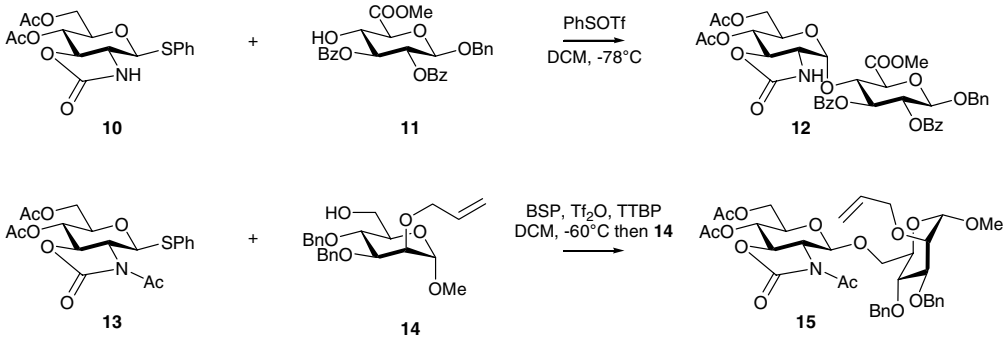


Scheme 2.

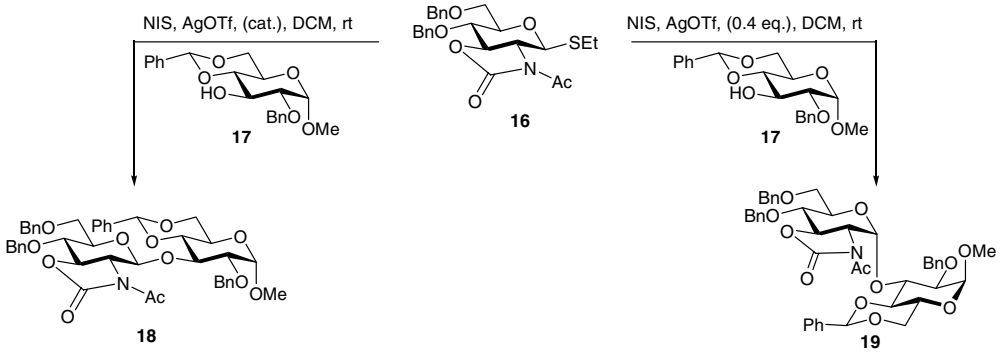
2,3-*O*-carbonyl-1-thio-β-D-glucopyranoside **5** with diacetonegalactose **6** in a mixture of toluene and dioxane preferentially afforded α-disaccharide **7** (Scheme 2).[11] In a comparative study, Crich and Jayalath found that 2,3-*O*-carbonate protected donor **8** preferentially gives β-disaccharides when subjected to their two-step glycosylation protocol, using dichloromethane as a solvent.[12] They concluded that the difference in stereochemical outcome of the two glycosylations is most likely due to the different solvent systems, that is, dichloromethane versus the much more polar mixture of toluene and dioxane. It was also observed that the β-selectivity was lost when switching from 2,3-*O*-carbonate **8** to 3,4-*O*-carbonate **9**.

Kerns and co-workers published several papers in which they described the use of 2-*N*-3-*O*-carbamate protected glucosamine donors in glycosylation procedures. In their initial studies, oxazoline **10** (Scheme 3) was used without further N-protection in glycosylations using PhSOTf as the activating agent in dichloromethane at −78 °C.[13] Under these conditions, excellent to complete α-selectivity was observed (for instance **10** + **11** → **12** in 75% yield, Scheme 3). In a later contribution, the disadvantages of the N-unprotected oxazolidinone (side reactions arising form N-sulfenylation and N-glycosylation) were recognised and the N-acetylated counterpart **13** was used in glycosylations, now using the BSP/Tf_2O protocol.[14] From the results the authors deduced a trend in which reactive and sterically undemanding acceptors react in a β-selective fashion (for instance **13** + **14** → **15**), presumably through the intermediate α-triflate that is present in the reaction mixture upon pre-activation of the donor. Sterically more demanding and/or electron-poor acceptors predominantly give the α-glycoside and the authors argue that these are formed by nucleophilic attack of the acceptor on the more reactive β-triflate intermediate.

In a related report, Oscarson and co-workers evaluated the glycosylation properties of carbamate donor **16** (Scheme 4), which differs from donor **13** in that the electron-withdrawing acetates on positions C-4 and C-6 are replaced by benzyl protective groups.[15] In accordance with their expectations, the authors observed selective formation of β-disaccharide **18** after treatment of a mixture of donor **16** and acceptor **17** with the *N*-iodosuccinimide (NIS)/silver triflate (AgOTf) combination in dry dichloromethane at ambient temperature. However, when using larger amounts of silver triflate, the stereoselectivity appeared to be completely reversed, and α-linked disaccharide **19** was obtained as the sole product, which the authors suspect is due to in situ anomerisation. In this respect, it is of interest to note that the application of oxazolidinone protection on N-acetylated glucosamine acceptors has shown increased reactivity of the OH-4 position.[16]



Scheme 3.



Scheme 4.

3. Diacetal protecting groups

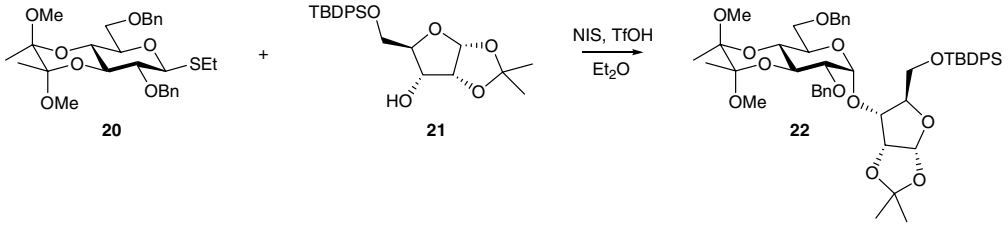
The pioneering work of the Ley laboratory with respect to the application of 1,2-diacetals such as the dispiroketal (dispoke),[17] the cyclohexane-1,2-diacetal (CDA)[18] and the butane-2,3-diacetal (BDA)[19] in carbohydrate synthesis has found widespread application.[20] In general, 1,2-diacetals are employed to mask di-equatorial diol systems.

En route to the synthesis of a clustered disaccharide polyphosphate analogue of adenophostin A, it was shown that the NIS/triflic acid (TfOH) promoted[21] coupling of **20** and **21** led to the formation of α-anomer **22** (Scheme 5).[22] In a related study, Crich et al. found that α-selectivity is predominant when 3,4-BDA-protected mannopyranosyl sulfoxides and 1-thiomannosides that have no participating protective groups are used in glycosylation events.[7]

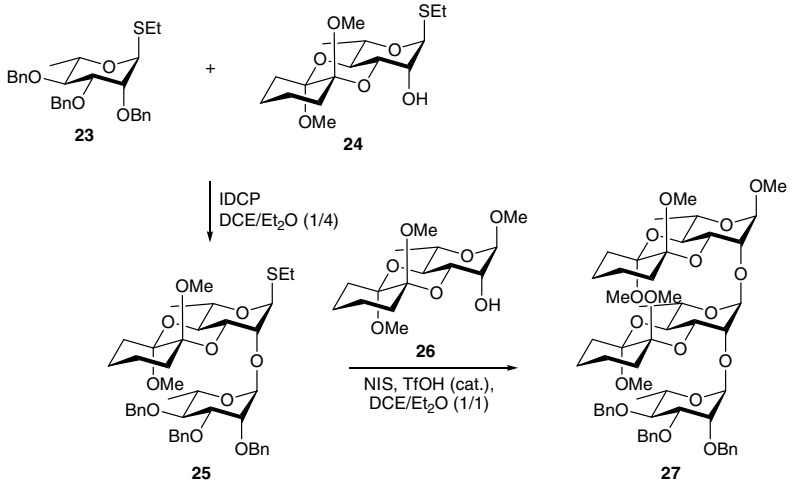
The perception that 1,2-diacetals induce torsional strain owing to their rigidity has prompted the development of reactivity tuning in chemoselective glycosylation reactions.[23–25] Ley and Priepke applied this concept in a one-pot synthesis of a trisaccharide unit found in the common Group B *Streptococci* polysaccharide antigen (Scheme 6). In a chemoselective fashion, armed donor 1-thiorhamnoside **23** was condensed with torsionally disarmed acceptor 1-thiorhamnoside **24** featuring the 3,4-CDA protecting group using IDCP as catalyst, to give[26] in a selective manner the α-disaccharide **25**. In the second glycosylation event, **25** was condensed with acceptor **26** to give the target trisaccharide **27**.[27]

Ley and co-workers further elaborated on their chemoselective glycosylation strategy by combining 1-phenylseleno donors with ethyl 1-thioglycosides, which have an intrinsic lower reactivity. Armed selenodonor **28** was selectively activated in the presence of the torsionally disarmed acceptor selenoglycoside **29**, affording **30** in good yield. Ensuing chemoselective condensation of disaccharide **30** with 1-thioglycoside **31** gave trisaccharide **32** in one-pot. Conversion of the anomeric ethylthio functionality into an α-bromide and subsequent treatment with acceptor **33** afforded, after prolonged reaction time, tetrasaccharide **34** in an elegant manner.[28]

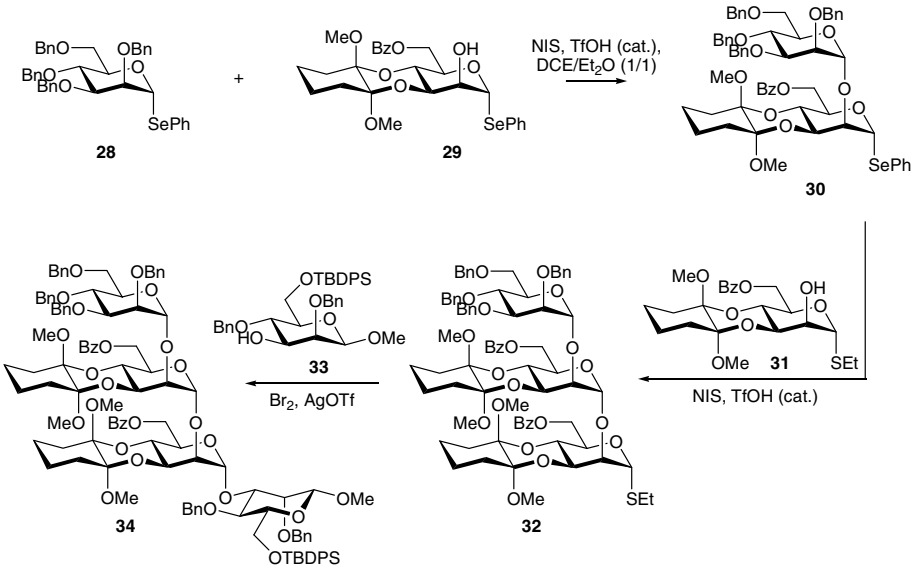
A next development from the Ley group entailed the combination of the above described chemoselective glycosylation approach with the concept of orthogonal glycosylation. This approach was shown to enable one-pot syntheses of linear as well as branched pentameric oligosaccharides employing up to three different anomeric leaving groups, such as fluoride, phenylselenide and ethylthio groups (Scheme 7).[29,30]



Scheme 5.



Scheme 6.



Scheme 7.

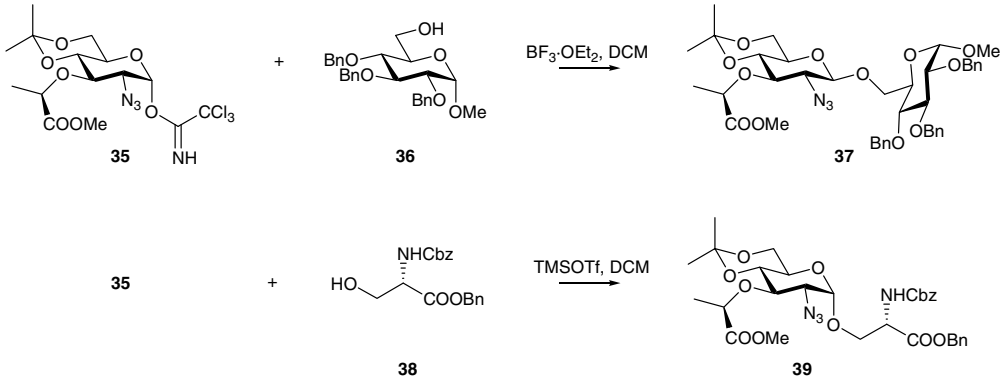
4. Acetal protecting groups

The isopropylidene acetal, formally a ketal, and its derivatives such as the cyclohexylidene and cyclopentylidene acetal, can be effectively used in the regioselective protection of 1,2-cis diol systems. Rhamno- and mannopyranosides equipped with a 2,3-cyclic acetal essentially exhibit the same behaviour as their cyclic carbonate counterparts: heterogeneous catalysis of anomeric bromides affords β-selectivity,[31–34] while homogeneous reactions preferentially guide the glycosylation towards the axially linked product.[35,36,8]

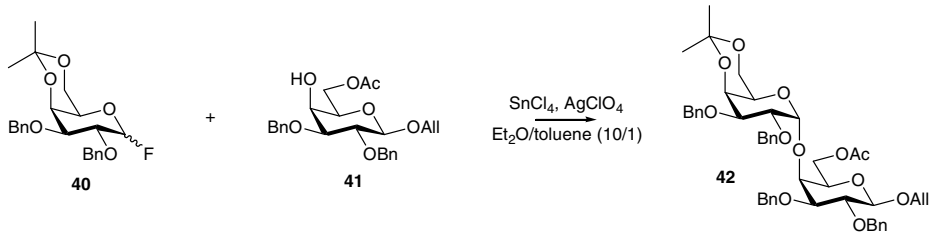
Apart from the protection of vicinal diols, cyclic acetals are also applied to mask the 4,6-diol function of pyranoses. An interesting report by Kinzy and Schmidt described that 4,6-*O*-isopropylidene protected 2-azido-2-deoxy glucopyranosyl trichloroacetimidates can be α- or β-selectively glycosylated by reactive glycosyl acceptors depending on the potency of the promoter (Scheme 8).[37] Glycosylation of trichloroacetimidate **35** with primary alcohol **36** using $BF_3{\cdot}OEt_2$ afforded β-anomer **37** selectively. On the other hand, condensation of **35** with protected amino acid **38** by TMSOTf-catalysed reaction afforded α-product **39** exclusively. An explanation for these observations may be that complexation of $BF_3{\cdot}OEt_2$ with the anomeric leaving group leads to an activated complex which does not collapse to an oxocarbenium ion-like species, thereby enabling S_N2-type nucleophilic substitution.[38] Activation of the α-trichloroacetimidate with the more potent TMSOTf affords the α-selective cation.

Nakahara and Ogawa applied a 4,6-*O*-isopropylidene acetal in the α-selective coupling of galactosyl fluorides with several OH-4 unprotected galactosyl acceptors. For instance, fluoride donor **40** was condensed with galactose acceptor **41** to give the α-linked disaccharide **42** (Scheme 9).[39]

Later, the Ogawa group studied the effect of 4,6-*O*-cyclic protection in the intramolecular aglycon delivery based β-glycosylation of 2-*O*-*p*-methoxybenzyl



Scheme 8.



Scheme 9.

mannopyranosides.[40,41] In terms of yield and selectivity, it was established that the 4,6-*O*-cyclohexylidene protecting group gave the best results as compared with the 4,6-*O*-isopropylidene and 4,6-*O*-benzylidene.[42]

The Crich laboratory, following initial research on sulfoxides by the Kahne group,[43] developed a highly β-selective mannosylation protocol using 4,6-*O*-benzylidene[†] protected mannopyranosyl sulfoxides **42**.[44] The reaction involves a two step one-pot activation-coupling sequence in which first the sulfoxide is treated with Tf_2O at −60 °C in dichloromethane in the presence of the acid scavenger 4-methyl-2,6-di-*tert*-butylpyridine (DTBMP), followed by the addition of an acceptor.

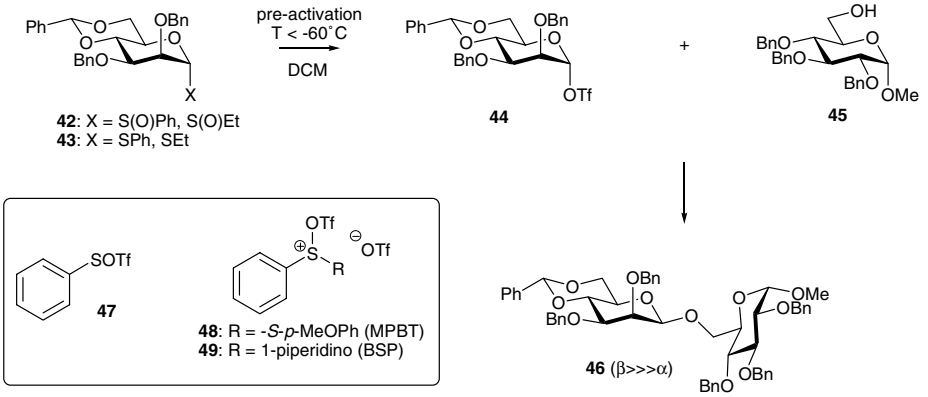
Mechanistic scrutiny of the reaction path by low temperature NMR analysis strongly suggests the presence of α-anomeric triflate **44** (Scheme 10), which is thought to undergo S_N2-type displacement upon addition of for instance acceptor **45**, leading to the formation of β-mannoside **46**.[45] On the basis of α-deuterium kinetic isotope effects in 4,6-*O*-benzylidene for selected β-mannosylation, Crich and Chandrasekera concluded that displacement of the anomeric triflate by the carbohydrate acceptor proceeds with the development of substantial oxocarbenium ion character.[46]

The importance of the 4,6-*O*-benzylidene group for β-selective mannosylation was confirmed by Crich and Sun, who demonstrated that 4,6-*O*-benzylidene protected thiomannosides **43** could be preferentially glycosidated equatorially employing in situ generated PhSOTf **47** as an activator using the pre-activation-coupling sequence (Scheme 10).[47,48] The PhSOTf–thiomannoside protocol was further improved from an experimental point of view by employing crystalline and stable *S*-(4-methoxyphenyl) benzenethiosulfinate **48** (MPBT) in combination with Tf_2O as an activator system instead of PhSOTf.[49] Shortly afterwards, the highly potent 1-benzenesulfinyl piperidine **49** (BSP)/Tf_2O activation system was introduced for the selective synthesis of the β-mannoside (Scheme 10).[50]

Studies of Bols and co-workers indicate that the influence of the 4,6-*O*-benzylidene group on selective β-mannosylation can be explained by locking of the C-6–O-6 bond in the more disarming *tg* conformer, thereby destabilising the transient contact ion pair that is in equilibrium with the covalent anomeric triflate.[51] The β-directing effect of the 4,6-*O*-benzylidene group on mannosylation reactions proved to be independent of the glycosylation procedure and activator system.[49–54] Schmidt's group established that 4,6-*O*-benzylidene protected α-mannopyranosyl trichloroacetimidates can be glycosidated under inverse conditions at low temperature to give β-mannosides with similar efficiency, as observed in the sulfoxide method.[52] Kim et al. applied 4,6-*O*-benzylidene protection in their β-selective mannosylation protocol using 2-(hydroxycarbonyl)benzyl (HCB) mannosides.[53] This approach, like the work of Crich, entails low temperature Tf_2O mediated preactivation of the donor in the presence of DTBMP followed by acceptor addition. Seeberger and co-workers[54] showed that β-mannosylation can be attained by the use of 4,6-*O*-benzylidene mannopyranoses in the dehydrative coupling strategy, as developed by the group of Gin.[55] Toshima and co-workers[56] have reported that the triflate deficient montmorillonite K-10 clay assisted glycosylation of 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosyl diethyl phosphite with various acceptors gave access to β-mannosides in high yields and selectivities. Comparable results were independently obtained by Hashimoto's group using TMSOTf as an activator for these donors.[57]

We contributed to this area of research by the investigation of the glycosylation properties of a series of 2-azido-4,6-*O*-benzylidene-2-deoxy-1-thiomannosyl azide.[58] As an example, we found that phenyl 1-thiomannosyl-azide **50** could be converted, after activation with diphenylsulfoxide (Ph_2SO)/Tf_2O and treatment with acceptor **51**, into β-disaccharide **52** in a highly stereoselective manner. This β-selectivity appeared to be a general trend, as is also demonstrated by the transformation of 1-thiodisaccharide **53** into trisaccharide **54** using the same activation procedure. It should be noted that the electron-withdrawing effect of the azide functionality somewhat impairs the reactivity of this set of donors, as compared to the 2-*O*-benzyl-thiomannosides, necessitating tuning of the reaction conditions in some specific example. The β-selective outcome in the synthesis of trisaccharide **54** is somewhat

[†] Fraser-Reid and co-workers for the first time suggested restricted flexibility (torsional strain) in 4,6-*O*-benzylidene protected glucopyranosides: see Ref. 23.

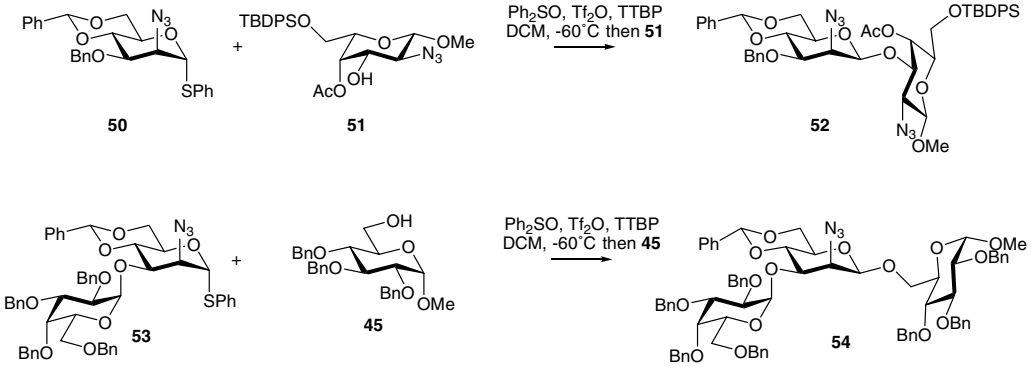


Scheme 10.

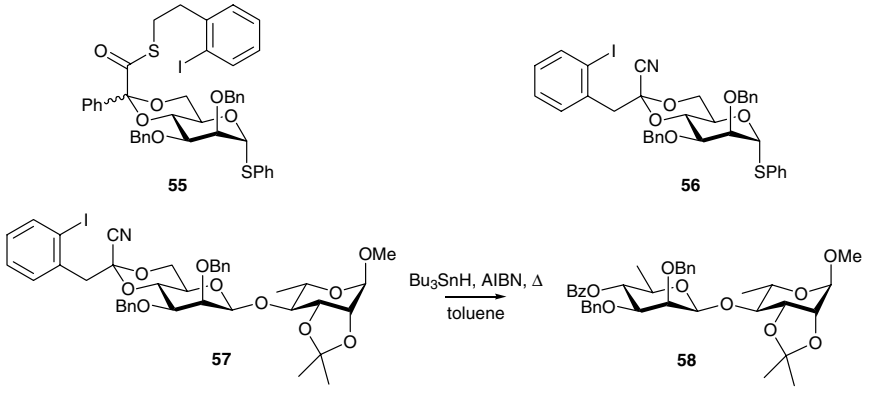
surprising, given the fact that glycosylation of arylthio-2-*O*-benzyl-4,6-*O*-benzylidene mannosides having a bulky group at C-3 position normally gives mixtures of α- and β-glycosides.

The Crich group realised that there must be an interplay between the steric bulk of the C-2, C-3 functionalities on the thiomannoside core. They noted the relatively small size of the azide group, as compared to the benzyloxy, and demonstrated that the corresponding 2-*O*-propargyl mannosides give good β-selectivity, both with silyl protection and glycoside substitution at the 3′ position.[59] We in turn applied the β-aminomannosylation to the first synthesis of the repeating trisaccharide unit of the bactereolytic complex lysoamidase, which contains a 2-acetamido-2-deoxy-β-mannuronic acid derivative (Scheme 11).[60]

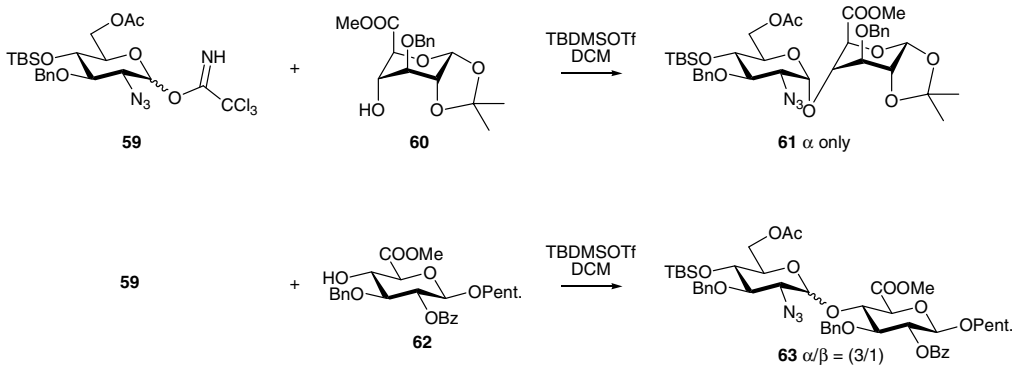
The Crich group extended their β-mannosylation approach also to the introduction of β-D-rhamnosidic linkages.[61] First, thiomannoside **55** (Scheme 12) carrying a 4,6-*O*-benzylidene that is functionalised with a thiol ester at the benzylic position was coupled β-selectively. Ensuing radical fragmentation of the ketal afforded the



Scheme 11.



Scheme 12.



Scheme 13.

β-D-rhamnoside (**58**).[62] Recently the [1-cyano-2-(2-iodophenyl)]ethylidene group (**56**) was developed as a second generation acetal-protective group, which could be introduced more efficiently. Besides the use of this cyclic acetal protection in the synthesis of β-rhamnosides, it was recently shown that this approach could also be applied to the stereoselective synthesis of β-*manno*-heptopyranosides.[63]

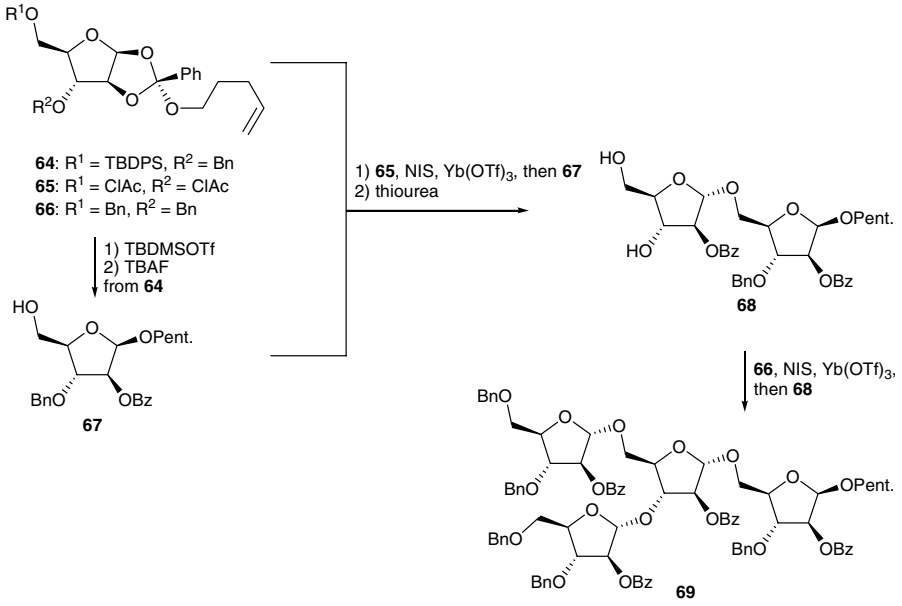
The protective group pattern in the acceptor glycoside also has a profound influence on the outcome of a glycosylation reaction. An interesting example, in which cyclic protection is used on the acceptor glycoside to induce stereoselectivity in a glycosylation reaction is described by Seeberger and co-workers.[64] Locking the conformation of glucuronic acid acceptor **60** in the $^1C_4$ conformation and glycosylation with glycosyl donor **59** gave only the desired 1,2-cis-linked disaccharide **61** (Scheme 13). Glycosylation of **59** with unlocked acceptor **62**, having an equatorially oriented OH-4, gave a mixture of α- and β-anomers (**63**).

4.1. 1,2-*O*-Orthoester and 1,2-*O*-cyanoalkylidene derivatives

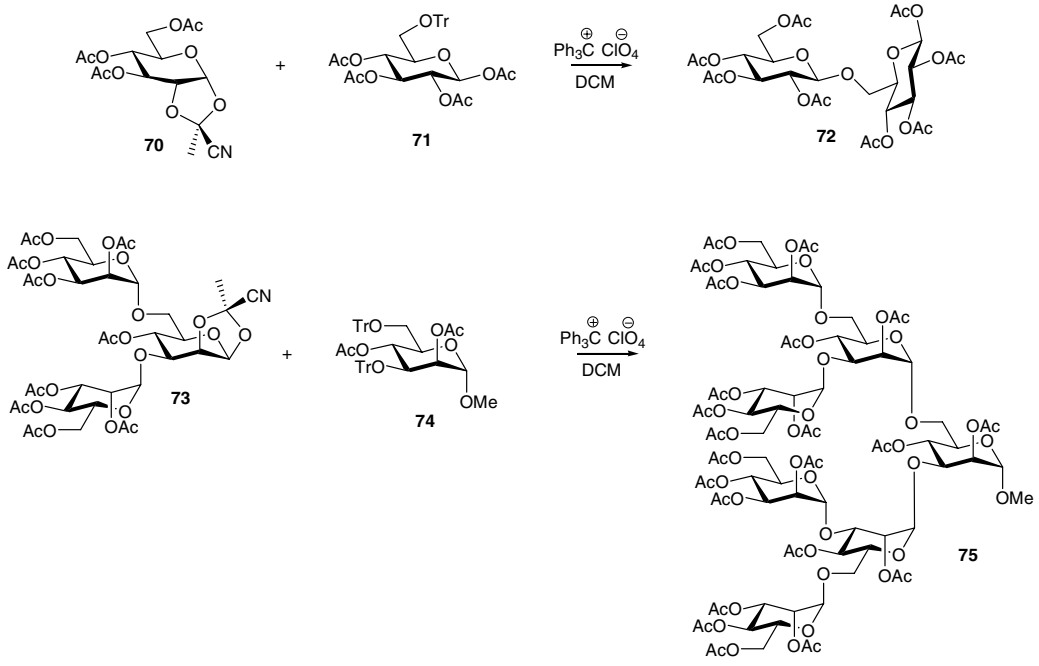
Besides 1,2-diol protective groups in acceptor glycosides such as the isopropylidene group in **60** that are stable during glycosylation, attention has been devoted to the development of functionalities that (1) mask the 1,2-diol of donor glycosides and (2) can be activated to allow a glycosylation reaction with a suitable acceptor. Prompted by the observation that the introduction of 1,2-trans glycosides proceeds *via* an acyloxonium ion that is formed *via* participation of 2-*O*-acyl protective groups on donor glycosides, a search was started for a more direct formation of this intermediate. Both 1,2-orthoester[65] and 1,2-thio-orthoester[66] derivatives of monosaccharides were investigated, but their glycosylation properties did not show improvements compared to 'normally' activated[††] glycosyl donors. In line with these results, oxazoline donors derived from 2-acetamido-2-deoxyglycosides are considered to be unreactive and harsh conditions are required for glycosylations. Recently new activator systems for oxazoline donors, such as $Yb(OTf)_3$ and $CuCl_2$, have been reported.[67]

Fraser-Reid and co-workers developed furanose- and pyranose-derived *n*-pentenyl orthoesters that nicely complement their *n*-pentenyl counterparts in oligosaccharide synthesis.[68] Their studies led to an orthogonal strategy for oligosaccharide synthesis in which partially unprotected *n*-pentenyl-orthoesters could be regioselectively coupled with polyol acceptors.[69] The viability of their approach is illustrated by the synthesis of a lipomannan component of the cell-wall complex of *Mycobacterium tuberculosis*. Furthermore, a multi-branched dodecafuranoarabinan of *Mycobacterium* species has been assembled from single *n*-pentenyl furanosyl-1,2-orthoester **64**. Part of the synthesis is depicted in Scheme 14.[70] Armed furanosyl-1,2-orthoester **64** was rearranged and subsequently desilylated to the more disarmed *n*-pentenyl acceptor **67**. Chemoselective NIS/$Yb(OTf)_3$ mediated coupling of orthoester **65** and acceptor **67** led to the expected disaccharide. Removal of the chloroacetate esters in this disaccharide gave diol **68**, which underwent double glycosylation using dibenzylated orthoester **66** to give tetrasaccharide **69**. This tetrasaccharide was further explored as a donor in the assembly of dodecafuranoarabinan.[70] Bochkov and Kochetkov[71] developed a glycosylation approach based on the use of 1,2-*O*-cyanoethylidene protected glycosides as donors. As exemplified in Scheme 15, gentiobiose octaacetate **72** was obtained by the reaction of 3,4,6-tetra-*O*-acetyl-1,2-*O*-cyanoethylidene-α-D-glucopyranose **70** and 1,2,3,4-tetra-*O*-acetyl-6-*O*-trityl-β-D-glucose **71** using tritylum perchlorate ($TrClO_4$) as catalyst. It was shown that the glycosylation properties of 1,2-*O*-cyanoethylidene derivatives of di-, tri- and tetrasaccharides do not differ from those of monosaccharides. Moreover, acceptors having a secondary trityl ether proved to be more reactive than their primary counterparts. Mechanistic studies have shown that the stereochemical outcome of the glycosylation reaction can be influenced

[††] Donors that have no cyclic protection between C1 and C2, like 1-thioglycosides, trichloroacetimidates and C1-phosphates.



Scheme 14.



Scheme 15.

by the concentration of the catalyst and the nature as well as protective group pattern in the acceptor. The advantages of the trityl-cyanoethylidene condensation have been demonstrated in the assembly of several complex polysaccharides of bacterial origin, cyclodextrin analogues and dendritic carbohydrate structures.[72] As depicted in Scheme 15, the 3,6-di-*O*-trityl ether of mannopyranoside **74** was efficiently bis-glycosylated with cyanoethylidene donor **73** to afford the corresponding protected mannoheptanoside **75**.[73]

5. Conclusions and outlook

The presented examples demonstrate the potential of cyclic protection in oligosaccharide synthesis. Varying

the type and position of the diol protection may not only steer the stereochemical outcome of a glycosylation reaction, but also gives access to chemoselective and/or orthogonal glycosylation strategies.

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