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Modulating glycosylation with exogenous nucleophiles: an overview

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The major challenge in carbohydrate synthesis is stereochemical control of glycosidic bond formation. Different glycosylation methods have been developed that are based on the modulation effect of external nucleophiles. This review highlights the development, synthetic application, challenges and outlook of the modulated glycosylation methods.

1. Introduction

Natural glycosides, oligosaccharides, and glycoconjugates have been shown to play roles in diverse biological processes such as anti-oxidation, bactericidal property, modulation of immunological processes, cell-to-cell recognition, regulation of protein-folding, *etc*.[1–4] Understanding the mechanism of these biological events sparks new applications in the pharmaceutical industry and advancements in basic science, which are of fundamental interest to scientists.[5,6] Because the demand for homogeneous carbohydrate samples and their derivatives for biological research has grown continuously, developing practical synthetic methods is crucial for scientific exploration.[7–9]

The key to synthesis of oligosaccharides is the formation of a glycosidic bond between a glycosyl donor and an acceptor.[10–12] Despite impressive progress in the recent development of glycosylation methods, the synthesis of a newly identified oligosaccharide compound or glycoconjugate still requires a new set of reaction conditions and glycosyl building blocks, which render the synthesis time-consuming and inefficient.[8,13–16]

The major challenge in carbohydrate synthesis is the stereochemical control of glycosidic bond formation. This issue is further complicated by the diverse structure of oligosaccharides and a wide variety of monosaccharide units.[17]

From the mechanistic viewpoint, the challenge of glycosylation stems from the formation of the glycosyl oxacarbenium ion in the donor activation. Such cationic species may react with a counterion forming a covalent glycosyl adduct and/or it is accompanied by a counter-ion as a continuum series of equilibrating close-contact, loosely bound, solvent-separated ion pairs, *etc*. (Scheme 1).[10,11] These ion-pairs or covalent adducts react with an acceptor in different pathways ranging from S_N1-like to S_N2-like mechanisms depending on a combination

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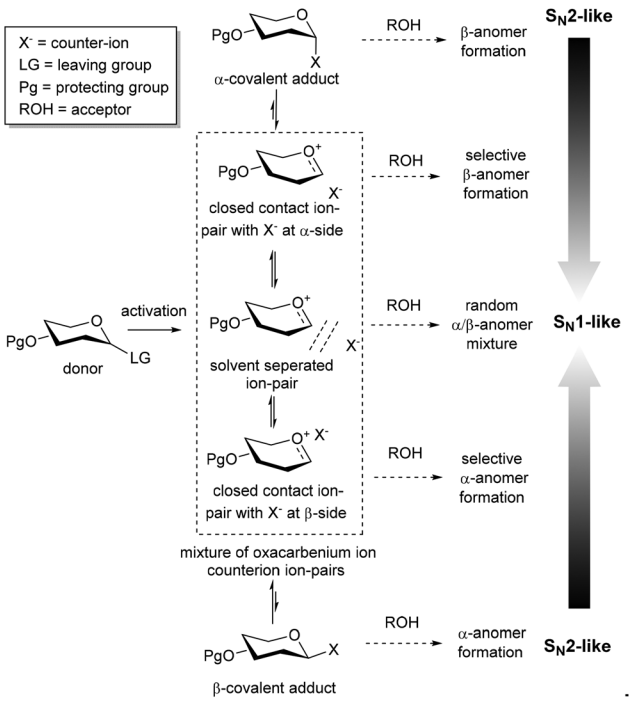

Scheme 1 Possible S_N1-like to S_N2-like glycosylation mechanisms for (oxacarbenium ion)-counterion ion-pairs and α/β-glycosyl covalent adducts in a glycosylation mixture.

of factors. For example, a change of stereochemistry of a mannosyl donor can alter the mechanism of glycosylation.[18] Accordingly, it is difficult to predict the outcome of a glycosylation reaction.

A common strategy for stereochemical control of glycosylation is the application of specific protecting functions. In general, these protecting functions can participate in the anomeric center of the oxacarbenium ion that blocks the pathway for the S_N1 reaction. A typical example is the neighbouring group participation (NGP) for 1,2-*trans* glycosidic bond formation, which is widely practised in carbohydrate synthesis.[19–21] The NGP concept was also extended to 1,2-*cis* α-glycosidic bond formation as witnessed by the use of a C-2 chiral auxiliary protecting function.[22,23] A similar chemistry concept is explored by Turnbull for the use of a specific oxathiane function at the anomeric center.[24,25] Recently, protecting groups with a hydrogen-bonding acceptor property such as picolinoyl and 2-quinolinecarbonyl functions have been shown to direct the stereochemistry of glycosylation.[26,27]

As most of the stereo-directing protecting groups contain a nucleophilic site for participation, this sheds light on using an exogenous nucleophile as a substitute of the protecting function for modulating glycosylation. We coin this approach 'modulated glycosylation'. The advantage of the modulated glycosylation is that there are no additional steps for protecting group manipulation, which simplifies the preparation of glycosyl building blocks. In addition, the modulation with a nucleophile may influence the stereochemistry of glycosylation. Some of the modulated glycosylation methods can also be elaborated to iterative glycosylation, thus accelerating the oligosaccharide synthesis.

The use of nucleophiles in modulation of glycosylation dates back to 1973.[28] Schuerch prepared β-glucosyl sulfonium adduct **2**, ammonium adduct **3** and phosphonium adduct **4** by reaction of α-glucosyl bromide **1** with dimethyl sulfide (Me_2S), triethylamine (Et_3N), and triphenyl phosphine (Ph_3P) nucleophile, respectively (Scheme 2a). The β-glucosyl onium adducts **2**, **3**, and **4** were reacted with a methanol acceptor to produce methyl α-glucoside **5**. Among the onium adducts, the β-sulfonium adduct **2** was the most reactive, but it produced a lower 6 : 1 α : β ratio of **5**.

It is well known that nucleophilic solvents such as alkyl ether and acetonitrile (CH_3CN) influence the stereochemistry of glycosylation.[29,30] For the nitrile solvent, the participatory effect of acetonitrile accounts for the 1,2-*trans* β-selectivity of glycosylation. As for example, the glycosylations with per-*O*-benzyl glucosyl (or galactosyl) trichloroacetimidate **7** in nitrile

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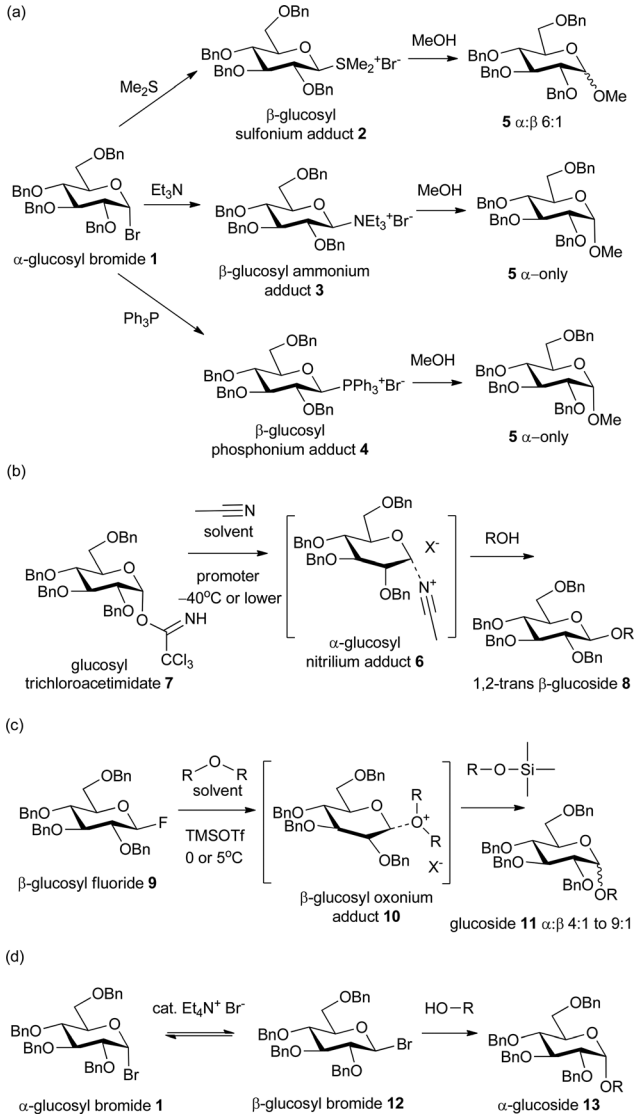


Scheme 2 (a) Use of Me_2S, Et_3N, and Ph_3P as nucleophiles in modulated glycosylation context by Schuerch; (b) use of β-directing nitrile solvent by Sinaÿ and Schmidt; (c) use of α-directing ether solvent by Noyori; and (d) use of bromide nucleophile as a catalyst for anomerization by Lemieux.

solvent at low reaction temperature (<−40 °C) furnished the β-glycosylation product **8** (Scheme 2b).[30b] Some evidence for the presence of α-glycosyl nitrilium adduct **6** were given by Sinaÿ and other researchers. Such an intermediate is presumably formed from coordination of a nitrile solvent molecule to the anomeric center of the oxacarbenium ion.[31,32] Recent studies also found that the nitrile solvent effect is concentration dependent, and a higher β-selectivity is obtained at conditions of low concentration.[33] A similar concentration dependence was reported by Yu in N-glycosylation with ribofuranosyl donors.[34]

Et_2O, dioxane, and tetrahydrofuran (THF) have been used to promote 1,2-*cis* α-glycosidic bond formation under different glycosylation settings. Noyori reported that the glycosylation of a silylated acceptor with glucosyl fluoride **9** in diethyl ether at 0 or 5 °C afforded the α-glycoside **11** in moderate to good α-selectivities (Scheme 2c).[29c] Later, Boons showed that the use of a dioxane–toluene cosolvent was better than ether solvent alone for α-selective glycosylation.[29d] Although the ether solvent effect has widely been explored on α-glycoside synthesis, the mechanism of the participation has seldom been studied. Recent computational studies proposed a conformer-counterion distribution hypothesis to account for the stereo-directing effect of the ether and nitrile solvent.[35]

Halide ion is a leaving group in Koenig–Knorr reactions, but it can be a stereo-directing agent. In the 1970s, Lemieux utilized bromide ion (Br^-) as a nucleophile catalyst in the so-called halide-ion catalysed glycosylation (Scheme 2d).[36] In this method, Br^- stemming from tetraethylammonium bromide (TEAB) catalysed the conversion of α-glucosyl bromide **1** to β-glucosyl bromide **12**. The β-bromide **12** was then coupled with an acceptor to yield 1,2-*cis* α-glucoside **13** (Scheme 2d). A drawback of the Lemieux glycosylation is the long reaction time of >2 days. Later investigators employed tetrabutylammonium iodide (TBAI) as the nucleophile additive with the intention to accelerate the glycosylation.[37]

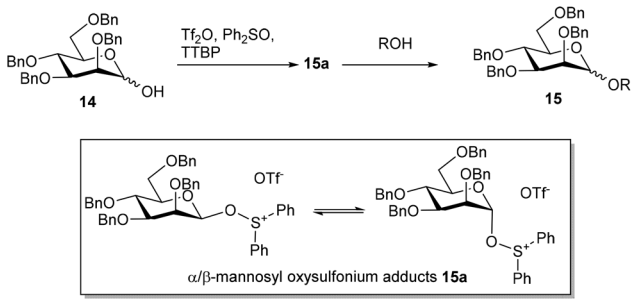
A message from the predecessors' studies is the capacity of the nucleophile in modifying the course of glycosylation. This inspiration motivates chemists to investigate the utility of exogenous nucleophiles as a modulator in glycosylation. From 1970 until the present, different exogenous nucleophiles have been examined as a modulator. Examples of these nucleophiles include dimethyl acetamide (DMA) by Koto,[38] hexamethylphosphoric triamide (HMPA) and phosphine oxides ($R_3P{=}O$) by Mukaiyama,[39] aryl sulfoxide ($Ar_2S{=}O$) by Crich,[40] thioethers (RSR′) by Boons[41] and Yoshida,[42] TABI by Gervay-Hague[37] and Bennett,[43] tetrabutylammonium triflate (Bu_4NOTf) by Yoshida and Nokami,[44] and dimethylformamide (DMF)[45] and *N*-formylmorpholine (NFM) by Mong.[46]

The aim of this perspective is to overview (i) the development of stereoselective glycosylation methods on the basis of nucleophile modulation, (ii) elaboration of these methods to iterative one-pot glycosylation, (iii) utility of modulated glycosylation methods in total synthesis of natural glycolipids, and (iv) outlook of the modulated glycosylation methods.

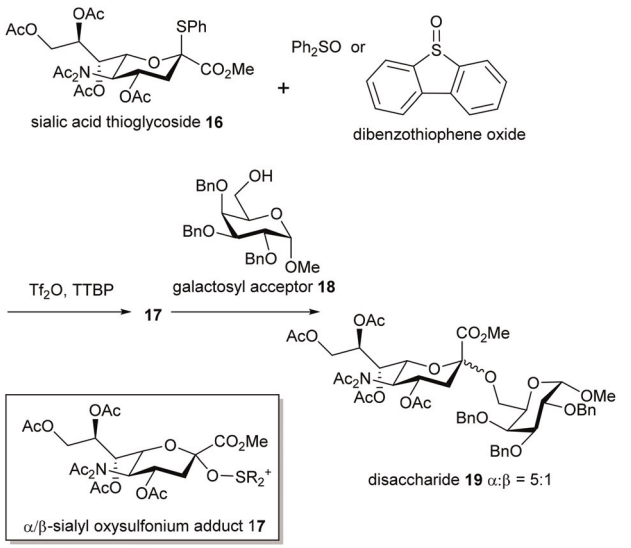
2. Development of modulated glycosylation methods on the basis of exogenous nucleophiles

2.1. Modulated glycosylation with sulfoxide nucleophile

The use of exogenous nucleophiles can always be traced back to research on the dehydrating glycosylation method. For example, in the development of a dehydrating glycosylation, Gin and co-workers applied diphenyl sulfoxide (Ph_2SO), triflic anhydride (Tf_2O), and 2,4,6-tri-(*t*-butyl)-pyrimidine (TTBP) as the promoters for mannosyl hemiacetal **14** (Scheme 3).[47] In the promotion process, the α/β-mannosyl oxy-sulfonium adducts **15a** were formed (as detected by NMR spectroscopy),



Scheme 3 Formation of α/β-mannosyl-oxysulfonium adducts **15a** from mannosyl hemiacetal donor **14** in dehydrative glycosylation.



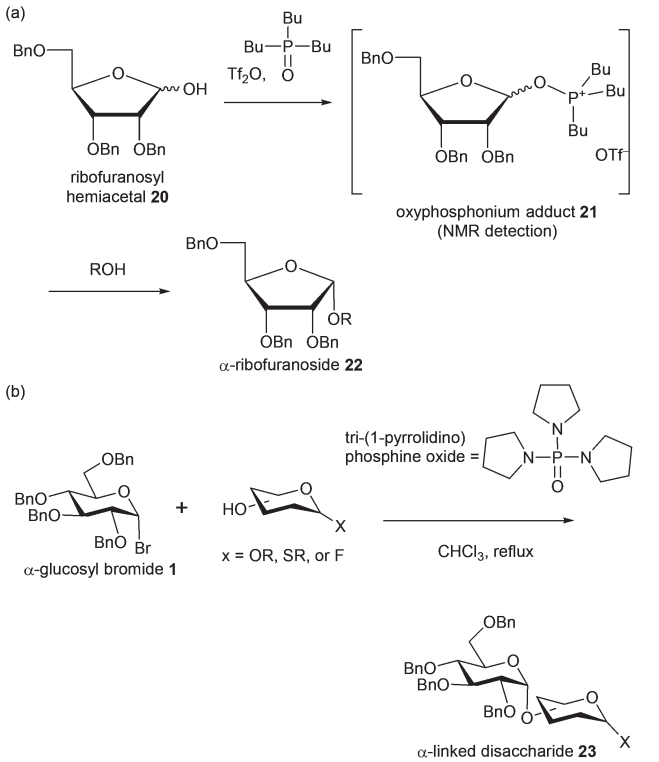
Scheme 4 Modulating glycosylation with dibenzothiophene oxide nucleophile for sialic acid thioglycoside donor **16**.

which were reacted with an acceptor to produce α/β-mannoside **15**.

Inspired by the detection of the oxysulfonium adduct, Crich *et al*. applied Ph_2SO or dibenzothiophene oxide as a nucleophile for glycosylation with a sialic acid thioglycoside donor **16** (Scheme 4).[40] In their method, the donor **16** was activated in the presence of Ph_2SO or dibenzothiophene oxide to form a sialyl oxy-sulfonium adduct **17**, which was coupled with a galactosyl acceptor **18** to produce the α-(2 → 6)-linked disaccharide **19** in a 5 : 1 α : β ratio. However, the α-directing property of such sulfoxide nucleophiles is confined to very few acceptors and improvement is needed for a wider application.

2.2. Modulated glycosylation with phosphine-oxide nucleophile

Similar to the sulfoxide nucleophile, the development of modulated glycosylation with phosphine-oxide nucleophile also connects with research on dehydrating glycosylation. In the activation of a ribofuranosyl hemiacetal donor **20** with tributyl phosphine oxide ($Bu_3P{=}O$) and Tf_2O promoters, Mukaiyama *et al*. observed the formation of α/β-ribofuranosyl



Scheme 5 (a) Production of glycosyl oxyphosphonium adduct **21** from ribofuranosyl hemiacetal **20** in dehydrative glycosylation. (b) Modulating glycosylation with tri-(1-pyrrolidino)-phosphine oxide.

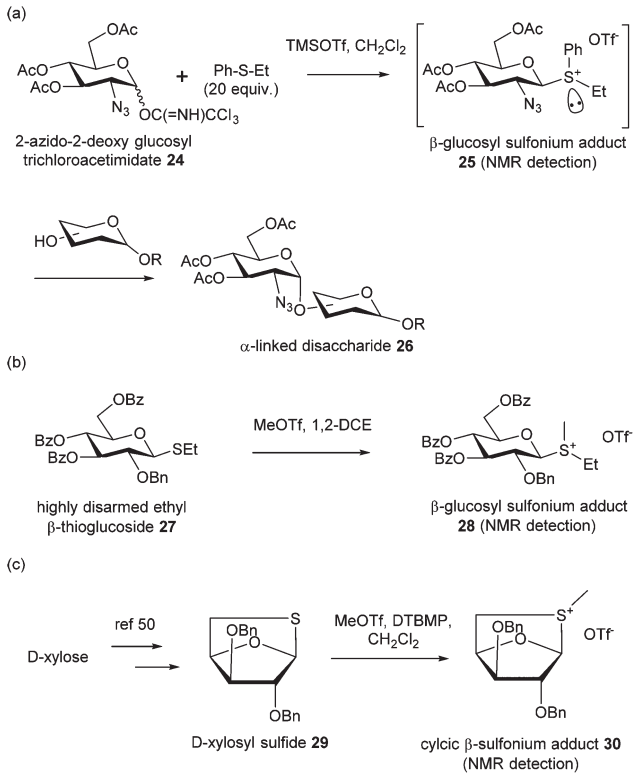
oxyphosphonium adduct **21** with ^{31}P NMR spectroscopy (Scheme 5a).[48] Subsequent coupling of **21** with an acceptor yielded the α-linked ribofuranoside **22**.

Further study by the same group applied tri-(1-pyrrolidino) phosphine oxide as the nucleophile additive. The α-glucosyl bromide **1** was treated with the phosphine oxide nucleophile to produce a glucosyl oxy-phosphonium adduct, which was then coupled with an acceptor to produce α-linked disaccharide **23** (Scheme 5b).[39] This method is also applicable for glycosyl fluoride and thioglycosyl acceptors.

2.3. Modulated glycosylation with thioether nucleophile

Although the use of thioether as a nucleophile modulator of glycosylation dates back to 70s,[28] further studies on this subject received little attention until 2007. Boons and coworkers investigated the application of ethylphenyl sulphide (PhSEt) and thiophene nucleophile as stereo-directing agents for 2-azido-2-deoxyglucosyl trichloroacetimidate donor **24** (Scheme 6a).[41] The glycosylation of an acceptor with **24** in the presence of 20 equiv. of PhSEt furnished the α-linked disaccharide glycoside **26** in good yield and excellent selectivity. Further NMR study provided evidence for the existence of the β-glucosyl sulfonium adduct **25**. However, this method is less effective for secondary glycosyl acceptors due to the formation of undesired *N*-glycosyl amide.

Besides the use of thioether nucleophile, β-glycosyl sulfonium adducts could be generated by alternative methods. For



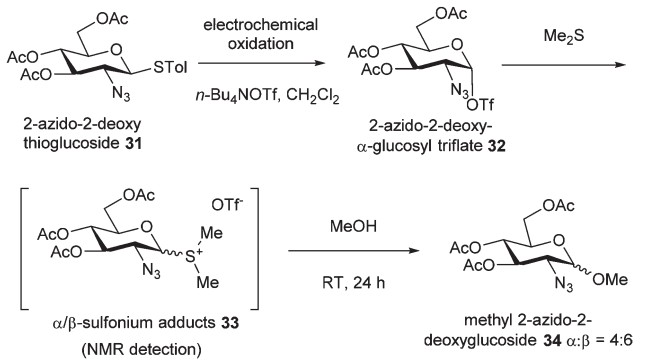
Scheme 6 (a) Use of thioether nucleophile as α-stereo-directing agent in glycosylation with 2-azido-2-deoxy-glucosyl trichloroacetimidate **24**. (b) Formation of β-sulfonium adduct from methylation of highly disarmed β-thioglucoside **27**. (c) Formation of bicyclic β-sulfonium adduct **30** from methylation of D-xylosyl sulfide **29**.

example, the methylation of highly disarmed β-thioglucoside **27** with methyl trifluoromethanesulfonate (MeOTf) afforded β-glucosyl sulfonium adduct **28** (Scheme 6b).[49] In addition, the methylation of a bicyclic D-xylosyl sulfide **29** with MeOTf gave a β-xylosyl sulfonium adduct **30** (Scheme 6c).[50] Both β-sulfonium adducts **28** and **30** could react with a sugar acceptor to afford the α-glycosylation product, albeit with moderate selectivities.

2.4. Modulated electrochemical glycosylation by thioether nucleophile

In the aforementioned modulated glycosylations, the major function of the thioether nucleophile is to stabilize the glycosyl oxacarbenium ion through the formation of a covalent adduct. This feature was capitalized in electrochemical glycosylation, whereby α-glycosyl triflate was generated from electrochemical oxidation of a thioglycoside donor and transformed by thioether nucleophile to produce a relatively storable glycosyl sulfonium adduct.

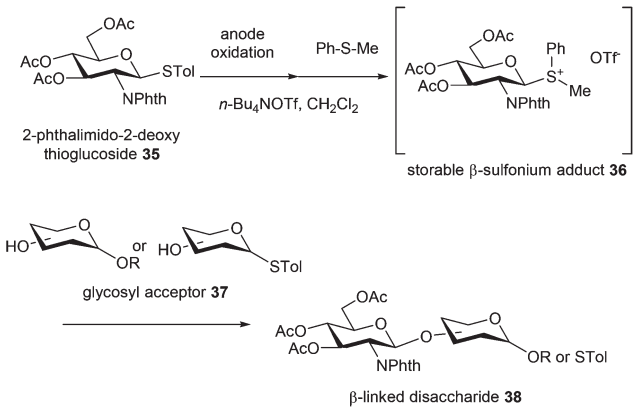
In practise, 2-azido-2-deoxythioglucoside **31** was activated in *n*-butylammonium triflate (*n*-Bu_4NOTf) electrolyte solution (CH_2Cl_2) by electrochemical oxidation to afford 2-azido-2-deoxy-α-glucosyl triflate **32** (Scheme 7). The intermediate **32** was then reacted with Me_2S nucleophile to furnish 2-azido-2-deoxy-α/β-glucosyl sulfonium adducts **33**, which was



Scheme 7 Modulating electrochemical glycosylation with dimethyl sulfide (Me_2S) nucleophile.

subsequently reacted with a methanol acceptor to produce the methyl 2-azido-2-deoxy-glucoside **34**.[42] It was noted that the detection of the α-sulfonium adduct in glycosylation has not been reported before this study. However, no α-selectivity of glycosylation was detected for the sulfonium adducts **33**, which is different from the glycosylation depicted in Scheme 6a. The investigators also revealed that the 2-azido-2-deoxy-α-glucosyl sulfonium adduct **33** was more reactive than the β-one. This finding is in contrast to other glycosyl adduct intermediates, for which, the β-anomer is often found to be more reactive than the α-anomer.

In a later study, the same research group applied the storable intermediate concept for glycosylation purpose.[51] 2-Phthalimido-2-deoxy-thioglucoside **35** was selected as a model donor (Scheme 8). As the donor **35** contains a participatory phthalimido (Phth) group at the C-2 position, thus ensuring the 1,2-*trans* glycosylation. The thioglycoside **35** was activated with electrochemical oxidation to produce a α-glycosyl triflate, which was coupled with methylphenyl sulfide (PhSMe) nucleophile to form a 2-Phth-2-deoxy-β-glucosyl-sulfonium adduct **36**. The reaction of the adduct **36** with either *O*-glycosyl or thioglycosyl acceptor **37** yielded the 1,2-*trans* β-linked disaccharide **38**.

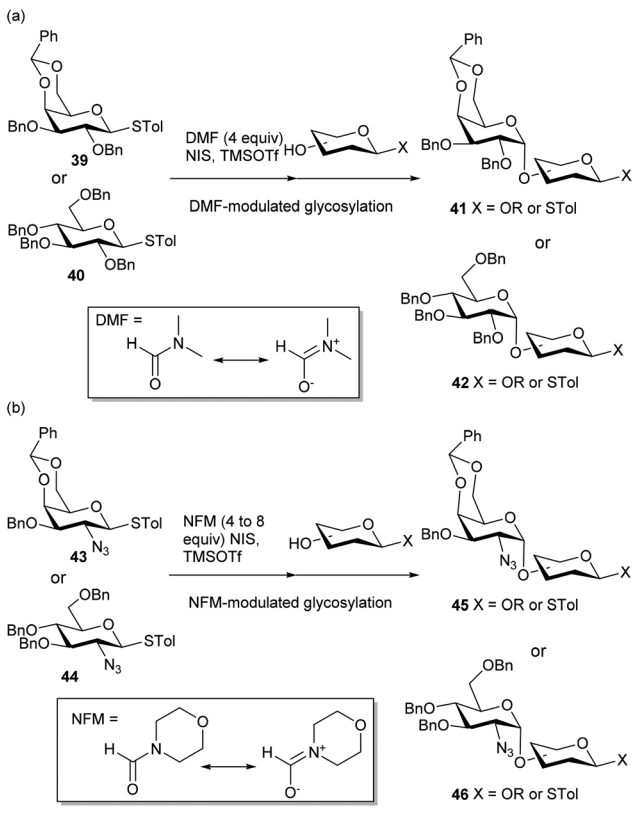


Scheme 8 Preparation of storable 2-phthalimido-2-deoxy-β-glucosyl sulfonium adduct **36** from 2-phthalimido-2-deoxy-thioglucoside **35**.

2.5. Modulated glycosylation with DMF nucleophile for non-participating thioglycosyl donors

DMF is a common solvent used for polar reactions, and it functions as an electrophilic or a nucleophilic agent in functional group transformation.[52] In 1983, Gross *et al*. prepared Vilsmeier–Haack (V–H) reagent from DMF and oxalyl chloride. Such V–H reagent was used for activation of a furanosyl-hemiacetal through a dehydration mechanism.[53] In a NMR study, α/β-furanosyl imidinium adducts were observed. Later, Kobayashi *et al*. also observed the formation of an α-glycosyl-imidinium adduct in glycosylation using DMF as a solvent.[54] Collectively, the above reports hint at the modulating capacity of DMF in glycosylation.

The application of DMF for modulating glycosylation commenced with a serendipitous finding. In a Koenig–Knorr glycosylation, Chang noted that the contamination of DMF increased the α-selectivity of the reaction.[55] Such findings initiated the exploration on the use of DMF nucleophile for modulated glycosylation.[45] A general DMF-modulated glycosylation procedure includes pre-activation of a glycosyl donor in the presence of DMF to form α/β-glycosyl imidinium adducts. The more reactive β-glycosyl imidinium adduct is subsequently coupled with an acceptor to yield the α-glycosylation product. For examples, thioglycoside donors **39** and **40** were coupled with a sugar acceptor to give the 1,2-*cis* α-glycosylation products **41** and **42**, respectively, in good to excellent selectivity (Scheme 9a).



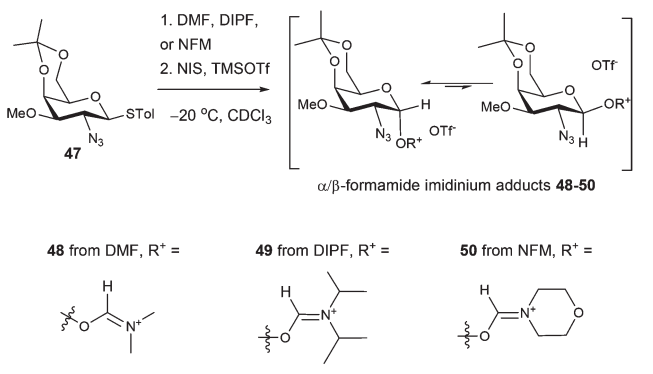
Scheme 9 (a) DMF-modulated glycosylation with thioglycosides **39** and **40**; (b) NFM-modulated glycosylation with 2-azido-2-deoxy-thioglycosides **43** and **44**.

2.6. Modulated glycosylation with NFM nucleophile for 2-azido-2-deoxythioglycosyl donors

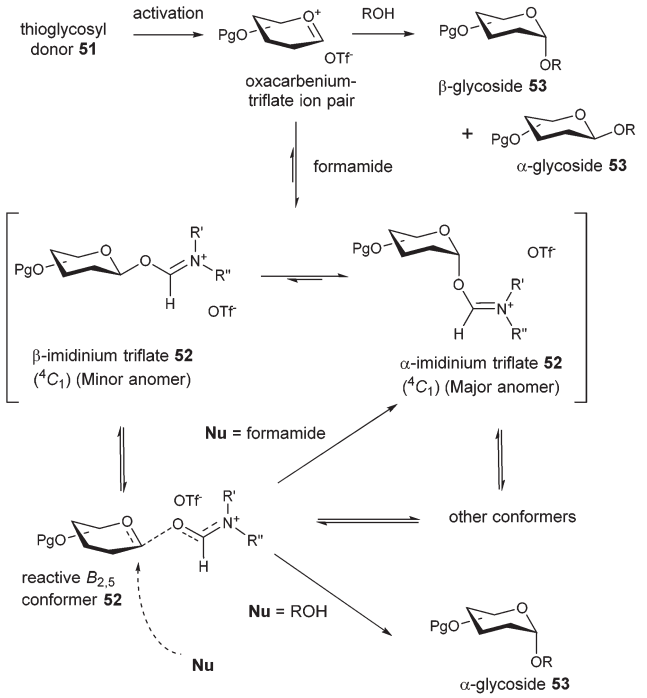
Although the DMF-modulated glycosylation works well for thioglucosyl and thiogalactosyl donors, this method is less effective for 2-azido-2-deoxyglycosyl donors due to the less reactive nature of the donors. To overcome the reactivity issue, the same research group examined the modulation capacity of a series of nucleophiles using the DMF-modulated glycosylation procedure. In this study, NMF was found to be a more reactive nucleophile than DMF in glycosylation, particularly for reaction with 2-azido-2-deoxy-thioglycosyl donors.[46] Up to 16 equiv. of NFM can be used to increase the α-selectivity of the glycosylation. The glycosylation of acceptors with 2-azido-2-deoxy-thiogalactoside **43** and 2-azido-2-deoxy-thioglucoside **44** under the NFM modulation produced the corresponding α-linked disaccharides **45** and **46** in good selectivity (Scheme 9b).[46] However, it should be pointed out that for glycosylation of the primary acceptor with 2-azido-2-deoxy-thioglucoside **44**, the α-selectivity of the reaction remains modest.

In the above glycosylation study, the β-glycosyl imidinium adduct was detected under formamide modulation conditions.[46] In a series of NMR experiments, 2-azido-2-deoxy-thiogalactoside **47** was activated in the presence of DMF, diisopropylformamide (DIPF), or NFM nucleophile (Scheme 10). From the NMR spectra of corresponding reaction mixtures, the α- and β-anomers of 2-azido-2-deoxygalactosyl imidinium adducts **48**, **49**, and **50** were identified and characterised fully by 1D and 2D NMR spectroscopy.

Based on the NMR studies, the mechanism of the formamide-modulated glycosylation is depicted in Scheme 11. In pre-activation, a thioglycosyl donor **51** is activated to produce an oxacarbenium ion triflate ion-pair, which is subsequently reacted with a formamide nucleophile to form a mixture of α- and β-glycosyl imidinium adducts **52**. Presumably, the β-glycosyl imidinium adduct **52** undergoes a series of conformational change to produce a reactive boat conformer, which by coupling with an acceptor furnishes the α-glycosylation product **53**. Such a mechanism is consistent with Curtin–Hammett kinetics.[56]



Scheme 10 NMR detection of α/β-glycosyl imidinium adducts **48–50**.

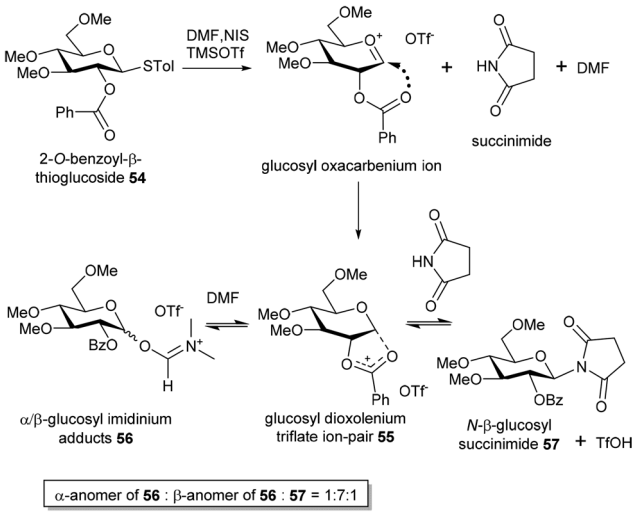


Scheme 11 Proposed mechanism of the formamide-modulated glycosylation.

2.7. Formamide modulated glycosylation with DMF nucleophiles for participating glycosyl donors

The key to the modulated reaction is to trap the cationic oxacarbenium ion with an exogenous nucleophile. As 2-*O*-acyl protected glycosyl donors are widely used for 1,2-*trans* glycosidic bond formation, and the activation of such donors produces a cationic dioxolenium ion intermediate. It is reasonable to investigate whether the DMF nucleophile can react with the dioxolenium ion. In an NMR experiment, 2-*O*-benzoyl-protected β-thioglucoside **54** was activated by NIS and TMSOTf to produce the glucosyl oxacarbenium ion, which under the influence of NGP was converted to the dioxolenium ion triflate ion-pair **55** (Scheme 12).[57] The reaction of **55** with DMF and succinimide (byproduct of NIS) produced α/β-glucosyl imidinium adducts **56** and *N*-β-glucosyl succinimide **57**, respectively. Both α/β-anomers of **56** and **57** were identified by NMR spectroscopy and they were present in a 1 : 7 : 1 ratio at −20 °C. Although the β-anomer of **56** was the major species in the mixture, subsequent reaction of the intermediates with an acceptor furnished a β-linked glycosylation product. The investigation indicates that the dioxolenium triflate ion-pair **55** remains the key player in the coupling reaction and the β-imidinium adduct **56** is just a bystander.

As the dioxolenium ions generated from participating glycosyl donors can be trapped by a DMF nucleophile, the DMF-modulated glycosylation method should be applicable to such class of donors. In general, the 2-*O*-acyl protected glycosyl donor is used for construction of a 1,2-*trans* glycosidic bond, but the presence of the acyl protecting function(s) decreases the reactivity of the glycosyl donor. Based on this property, the

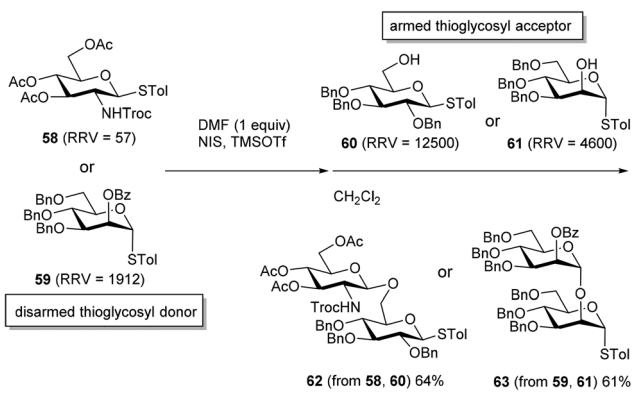


Scheme 12 Evaluation of DMF for entrapment of glucosyl dioxolenium ion derivative **55** by NMR spectroscopy.

armed–disarmed glycosylation concept was established.[58,59] This concept states that an armed (more reactive) glycosyl donor can be coupled with a disarmed (less reactive) glycosyl acceptor even though they contain the same anomeric function. However, if the glycosyl donor is less reactive than the acceptor, such disarmed–armed glycosylation would not be successful because the glycosyl donor and the acceptor would be activated to react with a hydroxyl acceptor. As the DMF-modulated glycosylation procedure includes a pre-activation step which paves way for disarmed–armed glycosylation.[57]

For example, the glycosylations of the more reactive (armed) thioglucoside acceptor **60** (relative reactivity value (RRV) = 12 500) and the thiomannoside acceptor **61** (RRV = 4600) with the less reactive (disarmed) *N*-Troc thioglucosaminyl donor **58** (RRV = 57) and the thiomannoside donor **59** (RRV = 1912) furnished the desired glycosylation products **62** and **63**, respectively (Scheme 13). The RRV is a numerical datum depicting the reactivity of a thioglycoside in glycosylation.[60]

Conceptually, the use of DMF for stabilization of the dioxolenium ions is similar to the pre-activated glycosylation



Scheme 13 Disarmed–armed glycosylation on the basis of the DMF modulation.

method developed by Huang and Ye. This method employs *in situ* generated toluenyl sulfenyl triflate (TolSOTf) as the promoter and the α-glycosyl triflate was supposed to be the intermediate for the subsequent coupling reaction.[61] However, a recent study found that when the 2-deoxy-thioglucosyl donor was undertaken the same procedure as used by Huang, the 2-deoxy-α-glucosyl chloride was detected by the NMR method.[62] Thus, further studies are needed to confirm the nature of the glycosyl intermediates in these reactions.

2.8. Modulated glycosylation with iodide nucleophile

All exogenous nucleophiles discussed so far are neutral and they give rise to cationic glycosyl adducts. These cationic species are accompanied by a counter-ion as ion-pairs. As the halide nucleophile is anionic, the β-glycosyl halide adduct in halide-modulated glycosylation is therefore neutral. Both bromide (developed by Lemieux) and iodide (developed by Gervay-Hague) nucleophiles are widely exploited in the preparation of 1,2-*cis* α-glycosides.[36,37] For the iodide nucleophile, a shorter reaction time is expected.

In the iodide-modulated glycosylation, per-*O*-benzyl protected glucosyl acetate **64** was treated with trimethyl iodosilane (TMSI) to produce the α-glucosyl iodide **65a** (Scheme 14a).[37] Without isolation, the α-iodide **65a** was reacted with excessive iodide nucleophile (from TBAI) to afford the β-glucosyl iodide **65b**. The subsequent reaction of **65b** with an acceptor in basic conditions gave the α-glucoside **66** in excellent selectivity, though this method is less effective for secondary sugar acceptors.

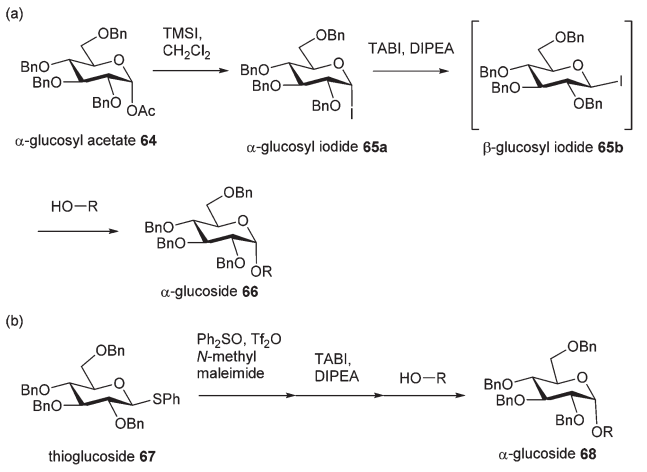
Recently, extended application of the iodide-modulated glycosylation to the chemically stable thioglucosyl donor was achieved by Bennett *et al*. In their method, the thioglucoside donor **67** was activated by triflic anhydride (Tf_2O) and Ph_2SO.[43] Subsequent addition of TBAI and diisopropylethylamine (DIPEA) presumably afforded the glucosyl iodide intermediate (Scheme 14b). The subsequent coupling reaction of the glucosyl iodide with an acceptor furnished the α-glycosylation product **68** in high selectivity. However, this method requires the addition of *N*-methyl maleimide to remove the thiolate by-product.

3. One-pot glycosylation protocols on the basis of the modulated glycosylation method

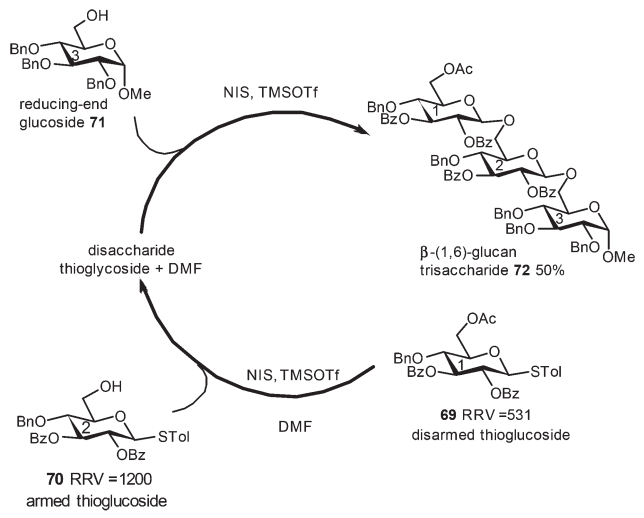
Having discussed different modulated glycosylation methods, we next look into several one-pot glycosylation strategies. One-pot glycosylation refers to the preparation of an oligosaccharide compound by sequential coupling of carbohydrate building blocks in one reaction vessel.[63,64] This approach eliminates the need for intermediate isolation and modification of the anomeric function in routine glycosylations. There are three common one-pot glycosylation strategies, namely orthogonal, reactivity-based, and iterative one-pot glycosylation. Particularly attractive is the iterative one-pot glycosylation, which in principle may use a single set of glycosyl building blocks and one type of promoter system. The following are recent examples of iterative one-pot glycosylation methods that are developed by exploring the modulation concept.

3.1. Iterative one-pot disarmed–armed glycosylation on the basis of DMF modulation

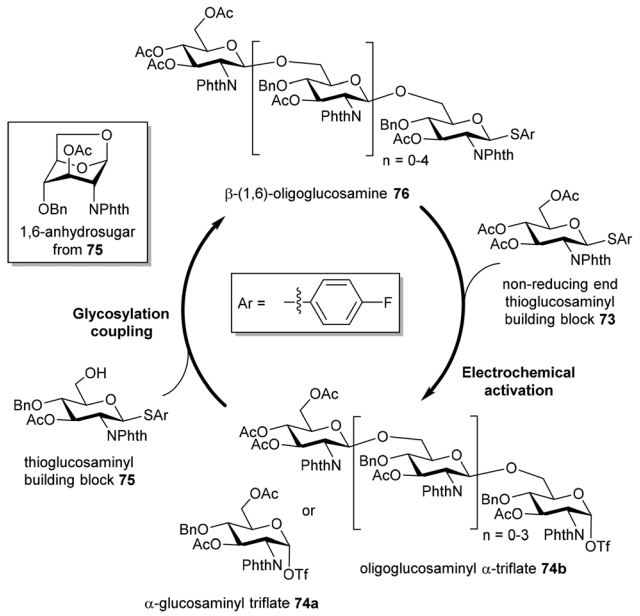
In the formamide modulated glycosylation, the oxacarbenium ion is trapped by formamide nucleophile to form an imidinium adduct. Such chemical property can be elaborated to one-pot disarmed–armed glycosylation. For example, in the synthesis of β-(1,6)-glucan trisaccharide **72**, the disarmed thioglucosyl donor **69** (RRV = 531) was activated and reacted with an armed thioglucosyl acceptor **70** (RRV = 1200) to give a disaccharide intermediate, which was then employed as a donor for glycosylation of the reducing-end glucoside **71** to furnish the target trisaccharide glycan **72** (Scheme 15).[57]



Scheme 14 Modulated glycosylation methods with iodide nucleophile for (a) glucosyl acetate donor **64** and (b) thioglucosyl donor **67**.



Scheme 15 Iterative one-pot disarmed–armed glycosylation based on the DMF modulation.



Scheme 16 Automated iterative one-pot synthesis of oligoglucosamines **76** from thioglucosaminyl building blocks **73** and **75**.

3.2. Automated one-pot electrochemical glycosylation

In electrochemical glycosylation, *n*-Bu_4NOTf is used as a supporting electrolyte. In addition to conduction of electricity, the triflate electrolyte can also be a modulator to react with the oxacarbenium ion to produce the α-glycosyl triflate. The glycosyl triflate can be coupled with an acceptor to yield the glycosylation product. When the acceptor contains an oxidative anomeric function, it is able to react iteratively in the next electrochemical glycosylation cycle. This iterative reaction cycle laid the foundation for the automated one-pot synthesis of oligoglucosamines (Scheme 16).[44]

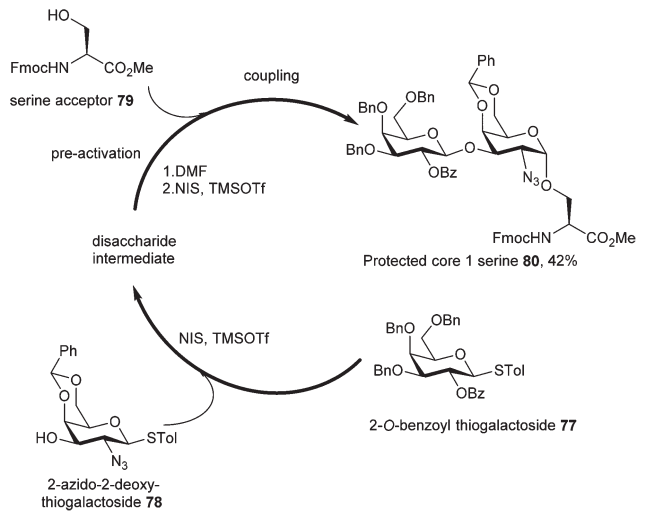
For automated synthesis of oligoglucosamines, *N*-Phth-protected thioglucosaminyl building block **73** underwent electrochemical oxidation in *n*-Bu_4NOTf solution to produce α-glucosaminyl triflate **74a**. The coupling of **74a** with thioglucosaminyl building block **75** furnished a disaccharide thioglycoside **76** (n = 0). Repeating the electrochemical glycosylation cycle with the same building block **75** enabled the growth of the β-(1,6)-oligoglucosamine **76** (n = 1 to 4) *via* α-oligoglucosaminyl triflate **74b** (n = 0 to 3). It should be noted that if the common *p*-toluenyl thioglucosaminyl acceptor was employed, the electrochemical glycosylation suffered from the formation of 1,6-anhydro-sugar (see inset in Scheme 16). After some experimentation, these authors found that the thioglucosaminyl building block **75** having a *p*-fluorophenyl group effectively suppress the formation of the anhydro-sugar byproduct.

3.3. Iterative one-pot α-glycosylation based on DMF modulation

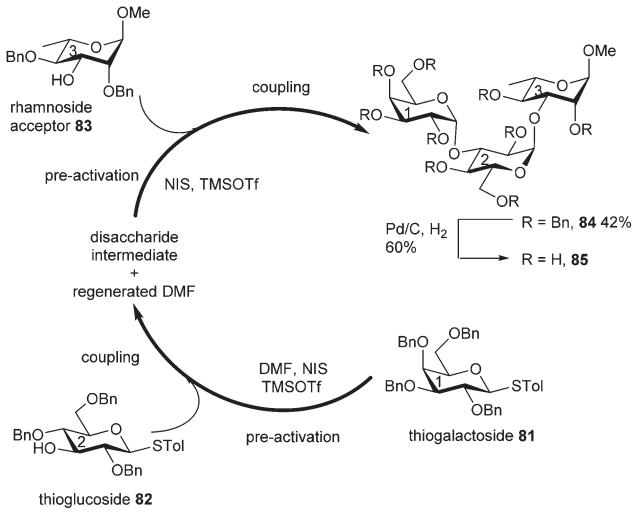
The aforementioned iterative one-pot glycosylation methods are useful for synthesis of oligosaccharides with 1,2-*trans* β-glycosidic bonds. From a mechanistic perspective, one-pot glycosylation invoking 1,2-*cis* α-glycosidic bond formation is challenging because the β-glycosidic bonds can be constructed under the NGP mechanism;[19–21] however, there is no general protocol for 1,2-*cis* α-glycosidic bond formation. Previous reports on one-pot α-glycosylation were mainly concerned with D-galactosyl and L-fucosyl donors.[65–67] Moreover, the α-glycosidic bonds constructed have usually been located at the non-reducing end of an oligosaccharide target. It was worth mentioning that the glycosaminyl donors protected with a *N*-benzyl-2,3-oxazolidinone function were explored for orthogonal one-pot α-glycosylation; but this method is limited to amino sugar building blocks.[68]

In theory, DMF-modulated glycosylation can be applied at different stages of a one-pot glycosylation. Therefore, this method should be useful for introduction of an α-glycosidic bond at different positions of an oligosaccharide structure. Furthermore, DMF is regenerated after the modulated glycosylation cycle, and the regenerated DMF can be used iteratively in the next modulated reaction cycle. These properties taken together constitute the foundation for development of iterative one-pot α-glycosylation.[69] The following are two representative examples for demonstrating the utility of these one-pot α-glycosylation methods.

3.3.1. Iterative one-pot (β,α)-glycosylation for synthesis of oligosaccharides with a (β,α)-anomeric configuration. In the synthesis of oligosaccharide with a (β,α)-anomeric configuration, a conventional procedure is applied in the first glycosylation step, which is followed by the DMF-modulated glycosylation protocol. The utility of such a one-pot (β,α)-glycosylation method was demonstrated in the synthesis of the protected core 1 serine **80**. The *O*-linked glycans contain a carbohydrate component conjugating to the hydroxyl of a serine or threonine acceptor through a 1,2-*cis* α-glycosidic bond.[70,71] In the one-pot synthesis of **80**, 2-*O*-benzoyl-thiogalactosyl donor **77** was reacted with 2-azido-2-deoxy-thiogalactosyl acceptor **78** to furnish a β-linked disaccharide thioglycoside (Scheme 17). Without isolation, the



Scheme 17 Iterative one-pot (β,α)-glycosylation for synthesis of core 1 serine conjugate **80** from building blocks **77**, **78**, and **79**.



Scheme 18 Iterative one-pot (α,α)-glycosylation for synthesis of trisaccharide repeating unit of the capsular polysaccharides in *Streptococcus pneumoniae* 6A **85** from building blocks **81**, **82**, and **83**.

disaccharide intermediate was coupled with serine acceptor **79** using the DMF modulated glycosylation procedure to produce the core 1 serine conjugate **80** in 42% yield.[69]

3.3.2. Iterative one-pot (α,α)-glycosylation for oligosaccharide synthesis with a (α,α)-anomeric configuration. For the synthesis of oligosaccharide with a (α,α)-anomeric configuration, two DMF-modulated glycosylation procedures are performed in sequence. The DMF regenerated from the first modulated glycosylation can be used again in the second modulated glycosylation. This iterative one-pot α-glycosylation protocol was applied for the synthesis of the trisaccharide repeating unit of capsular polysaccharide in the cell wall of *Streptococcus pneumoniae* 6A **85** (Scheme 18).[72,73]

A previous synthesis of the trisaccharide **85** required a stepwise-glycosylation approach.[74] With the iterative one-pot (α,α)-glycosylation method, the synthesis was simplified. Thus, a non-participating thiogalactoside donor **81** was coupled with a non-participating thioglucoside acceptor **82** under the DMF-modulated glycosylation conditions to produce an α-Gal-(1 → 3)-Glc disaccharide intermediate. In the presence of the regenerated DMF, the disaccharide intermediate was subjected to the second DMF-modulated glycosylation cycle to couple with rhamnoside acceptor **83** furnishing the protected trisaccharide **84**.[69] Global deprotection of **84** was simply achieved by a single-step hydrogenolysis to furnish the trisaccharide target **85**.

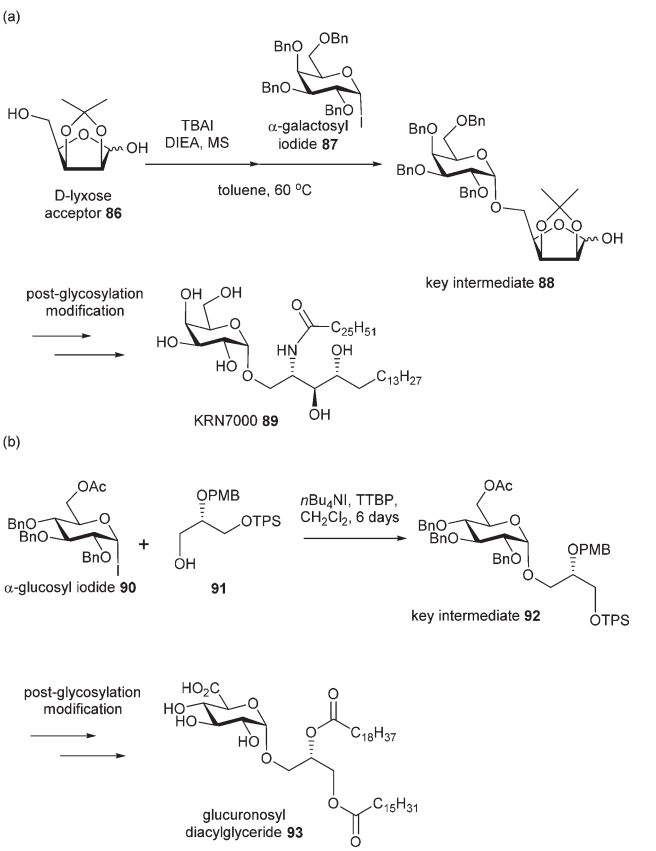
4. Modulated glycosylation for total synthesis of natural glycolipids

After reviewing the development of various modulated glycosylation methods and their elaboration to one-pot glycosylation protocols, we discussed the utility of these methods in total synthesis of natural glycoconjugates. Due to space limitations, only few recent examples are selected in present article, and we apologise for not covering other relevant studies.

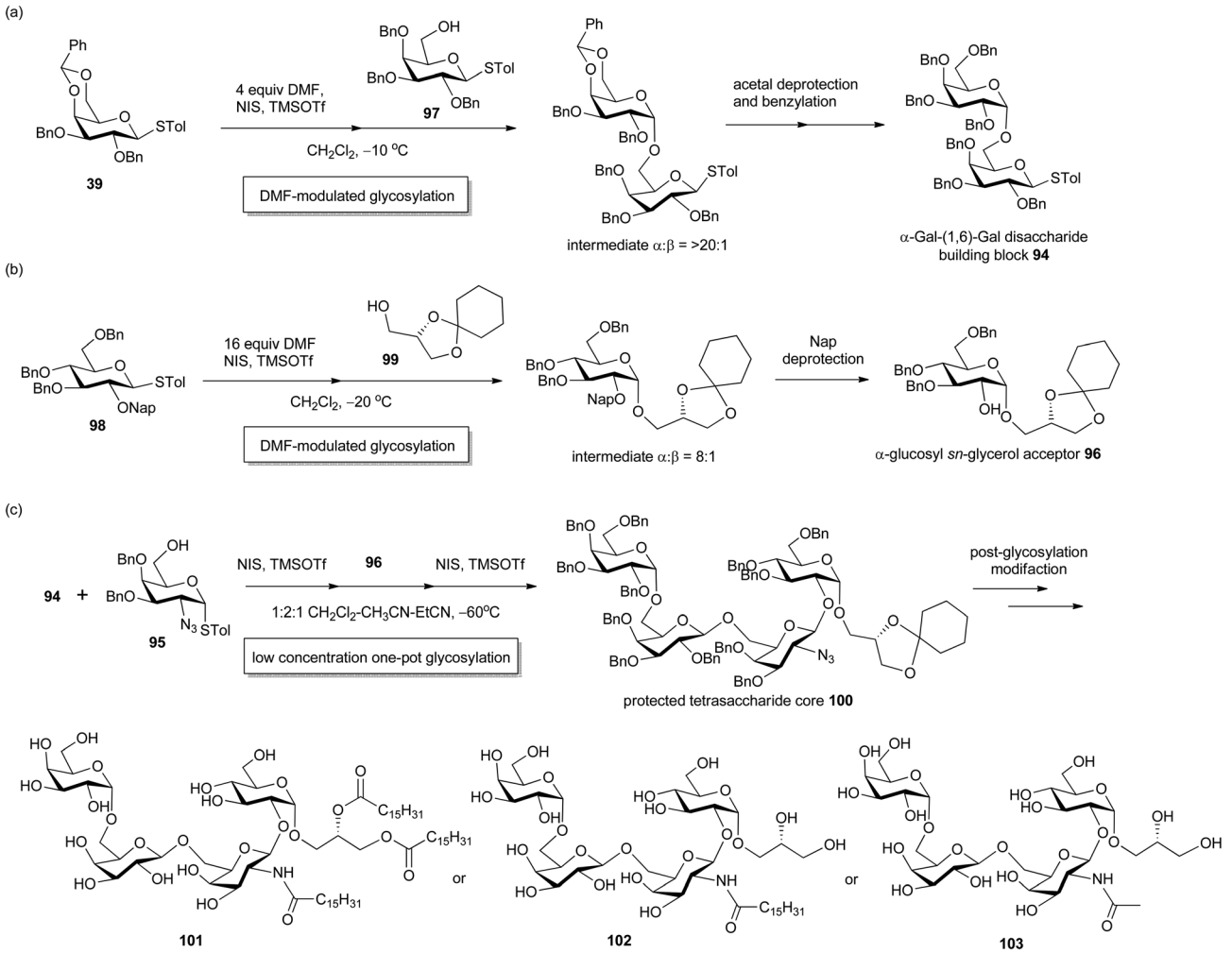
4.1. Total synthesis of monosaccharide glycolipids

The α-glycosylation method based on the modulation of iodide nucleophile is widely practised for total synthesis of simple monosaccharide glycolipids. In the synthesis of KRN 7000 **89**, Luo *et al*. prepared the key intermediate α-Gal-(1,5)-Lyx disaccharide **88** in good yield and excellent α-selectivity from the glycosylation of protected D-lyxose acceptor **86** with per-*O*-benzyl galactosyl iodide **87** in the presence of TBAI (Scheme 19a).[74] The lyxose component constituted the structure of the aglycone component of KRN7000. The subsequent post-glycosylation modification of the disaccharide **88** produced the desired KRN7000 **89**.

In the total synthesis of a glucuronosyl diacylglyceride isolate of particular Mycobacteria species, a key α-linked glucoside intermediate **92** was needed, which was prepared from coupling of a 6-*O*-acetyl-α-glucosyl iodide **90** with a protected *sn*-glycerol acceptor **91** using iodide nucleophile as the modulator (Scheme 19b).[75] The reaction required 6 days for completion and the glucoside intermediate **92** was obtained in high selectivity. Upon post-glycosylation modification, the glucoside **92** was converted to the target glucuronosyl diacylglyceride **93**.



Scheme 19 (a) Total synthesis of KRN7000 **89** by Luo *et al*. (b) Total synthesis of glucuronosyl diacylglyceride **93** by Williams *et al*.



Scheme 20 Total synthesis of tetrasaccharide glycoglycerolipid isolate **101** and its truncated analogues **102** and **103** of the glycolipid component in *Meiothermus taiwanesis* by Mong *et al*.

4.2. Total synthesis of tetrasaccharide glycoglycerolipid

In the total synthesis of a bacterial glycoglycerolipid isolate **101**,[76] the β-directing effect of the nitrile solvent and the α-directing effect of DMF nucleophile are required because the glycoglycerolipid isolate contains the 1,2-*trans* β- and 1,2-*cis* α-glycosidic bonds.[77,78] The glycoglycerolipid **101** was derived from a protected tetrasaccharide core **100**, which in turn was prepared from α-Gal-(1,6)-Gal disaccharide **94**, 2-azido-2-deoxy-thiogalactoside ($GalN_3$) **95** and 3-*O*-(α-glucosyl)-*sn*-glycerol **96** (Scheme 20).

The disaccharide building block **94** was constructed from the glycosylation of thiogalactosyl acceptor **97** with thiogalactosyl donor **39** by (i) standard DMF-modulated glycosylation and (ii) simple protecting group modification (Scheme 20a). For the synthesis of the 3-*O*-(α-glucosyl) *sn*-glycerol **96**, an optimized DMF-modulated glycosylation procedure was applied, for which, 16.0 equiv. of DMF and lower reaction temperature of −20 °C were employed to achieve the coupling of *sn*-glycerol acceptor **99** with thioglucosyl donor **98** to afford a fully protected 3-*O*-(α-glucosyl)-*sn*-glycerol intermediate (Scheme 20b). The removal of the Nap protection in the intermediate furnished the 3-*O*-(α-glucosyl)-*sn*-glycerol building block **96**. Preparation of the $GalN_3$ building block **95** followed a known literature procedure.[79] With the glycosyl building blocks **94**, **95**, and **96** in hand, the protected tetrasaccharide core **100** was assembled in good 60% yield by the application of the low concentration one-pot glycosylation method (Scheme 20c).[80,81] The subsequent post-glycosylation modification and global deprotection of **100** concluded the first synthesis of the glycoglycerolipid **101** and two structural truncated analogues **102** and **103** for studies on immunological properties.

5. Outlook and conclusion

The concept of the modulated glycosylation is to entrap the glycosyl oxacarbenium ion as a covalent glycosyl adduct by the nucleophile. The methods provide alternative entries to assess 1,2-*trans* β- and 1,2-*cis* α-glycosidic bonds in the absence of the participatory protecting function. This feature is beneficial to total synthesis of natural glycosides and glycoconjugates,

which may contain chemical functions that can be vulnerable to modification or hydrolysis during common protection group manipulation. An example in this review is the total synthesis of glycoglycerolipid isolate **101**.[76] The target glycoglycerolipid contains two ester functions that can be hydrolysed under basic conditions. Such conditions are required in global deprotection if the protected glycoglycerolipid, *i.e.* **100**, contained ester-type protecting functions. Nonetheless, using the nitrile solvent effect and low concentration conditions, the β-glycosidic bonds in **100** could be constructed without invoking any C2–acyl protecting function (Scheme 20c).

Despite the aforementioned advantages, there are some concerns and challenges for particular modulated glycosylation methods. Generally, the glycosyl adduct formed in modulated glycosylation is less reactive than the oxacarbenium ion. This decreases the rate of glycosylation; and on some occasions, the reaction does not go to completion. In the synthesis of the key glucoside **92** (Scheme 19b), the iodide-modulated glycosylation required 6 days for completion (Scheme 19b).[75] Indeed, the iodide-modulated glycosylation is seldom applied for glycosylation of secondary acceptors.[37c]

A similar reactivity issue is also observed in the DMF-modulated glycosylation, in particular for glycosylation of a hindered acceptor with a 2-azido-2-deoxy-glycosyl donor.[45] Although this reactivity problem was solved by the use of the more reactive NFM nucleophile, the selectivity of NMF-modulated glycosylation is modest for primary hydroxyl acceptors.[46]

Besides the issue of coupling efficiency, the α-selectivity of some modulated glycosylation methods is inconsistent in different settings as exemplified by the thioether-modulated glycosylations.[41,42,49] The inconsistency implies that the selectivities of the modulated glycosylation methods are kinetic controlled, thus depends on multiple factors such as procedure, solvent system, temperature, *etc*. Modification of even one of these factors would change the reaction mechanism leading to erosion of reaction selectivity. Before gaining a wider application in carbohydrate synthesis, the inconsistency issue must be solved.

Taken together, the aforementioned modulated glycosylation studies clearly indicate that the glycosyl adducts arising from different nucleophiles exhibit a range of chemical properties. These properties should be closely correlated to the selectivity of glycosylation. Up to now, kinetic studies and/or computational calculations on free energy levels of these glycosyl adducts are scarcely available. This information would be crucial for delineating the exact mechanism and paving the way for improvement of stereoselectivity.

The ultimate goals of the modulated glycosylation methods are to (i) use an external agent instead of a specialized protecting function to control the stereochemistry of the glycosylation and (ii) to shorten the procedure for carbohydrate synthesis. Presently, several expedite glycosylation strategies based on the nucleophile modulation have been developed and applied in the synthesis of natural glycoconjugates. Collectively, these achievements are encouraging, but the consistency and coupling efficiency of particular modulated glycosylation methods need further improvement. We hope that additional mechanistic studies and kinetic investigations may shed light to researchers overcoming the present challenges.

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