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Controlling the Stereoselectivity of Glycosylation via Solvent Effects

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Invited Review

Dedicated to Prof. David R. Bundle on the occasion of his retirement (Special Issue for
Prof. Bundle)

Draft

Abstract:

This review covers a special topic in carbohydrate chemistry – solvent effects on the stereoselectivity of glycosylation reactions. Obtaining highly stereoselective glycosidic linkages is one of the most challenging tasks in organic synthesis, as it is affected by various controlling factors. One of the least understood factors is the effect of solvents. We have described the known solvent effects while providing both general rules and specific examples. We hope this review will not only help fellow researchers understand the known aspects of solvent effects and use that in their experiments, moreover we expect more studies on this topic will be started and continued to expand our understanding of the mechanistic aspects of solvent effects in glycosylation reactions.

Key words: Glycosylation, Stereoselectivity, Synthesis, Solvent effect, Carbohydrate chemistry

Background

Naturally occurring carbohydrates exist in forms of monosaccharides, oligosaccharides (consisting a few covalently linked monosaccharide units), polysaccharides which are also commonly referred as glycans, composed of only one type or more of monosaccharides linked by glycosidic bonds, and their conjugates (glycoconjugates). Besides their common functions in metabolism and as structural building blocks and energy source, they are inevitable components of all cell surfaces, regulating various cellular recognition and communication processes,¹ such as cell adhesion, inflammation, immune response as well as cell growth.² Their involvement in various biochemical and pathological states makes them important targets to investigate their properties, structures and functions. However their low concentration availability in biological sources sets limitation in the studies investigating their properties, structures and functions³ which in turn leads to the necessities of methodological development on stereoselective O-glycosylation, as majority of the glycans are linked to aglycons (proteins and lipids in nature) via O- or N-linked glycosidic bonds.

In general, glycosylation reaction takes place by the displacement of a leaving group at the anomeric center of glycosyl donor by a nucleophile. Various efforts in the field of synthetic experiments and theoretical methods have been made to understand the mechanism and the stereoselectivity of the reaction.⁴ In most cases reactions are catalyzed or promoted by an activator which helps the departure of a leaving group to form an oxocarbenium cation intermediate. Most glycosylation reactions proceed through tight ion-pair rather than a free oxocarbenium ion.^{5,6} Although it is hard to delineate between S_N1 and S_N2 reaction,⁷ it was presumed that reaction conditions favor an S_N1 pathway.⁸ The mechanism for a reaction in which

donor has a non-participating group at C-2 can be better described by considering the following four steps (Figure 1)⁷: Step 1 involves formation of the donor-promoter complex, and Step 2 leads to departure of the leaving group, resulting in a highly resonance-stabilized oxocarbenium cation, and is the rate determine step (RDS). Since the anomeric carbon of the oxocarbenium cation is sp^2 hybridized, the structure changes to a flattened half chair that allows access from both planes (Figure 1, Path a and Path b) for the nucleophilic attack by an acceptor in Step 3, leading to the formation of two corresponding stereoisomers, *i.e.* α -(1,2-*cis*) or β -(1,2-*trans*) for D-glucosyl series. In the final step, proton transfer terminates the glycosylation reaction. As a general rule, the rate of glycosylation reaction mostly depends on the stability of the oxocarbenium ion, whereas the stereoselectivity depends on the step that involves preferential nucleophilic attack of an acceptor at the anomeric center. Although α -anomer is thermodynamically favored over kinetically controlled β -anomer due to *anomeric effect*,⁹ β -isomer is also substantially formed during the reaction. Therefore, in order to obtain stereoisomerically pure carbohydrate molecules, controlling the α/β selectivity in the glycosylation reaction is key.

Considerable progress has been made to develop strategies that offer high yield and good stereoselectivity to the glycosylation reaction, but challenges still remain. Many factors can impact the yield and stereoselectivity of glycosylation reactions, including but not limited to structures and properties of donor and acceptor, activator or promoter, reaction solvent, and temperature. Although formation of each specific glycosidic bond requires a particular condition that is most suitable, some general trends have been noticed over decades of investigation.

In general, donor and acceptor need to have matching reactivity; too reactive donor with a less active acceptor may lead to hydrolysis or other side reactions of donor, while pairing a

more active acceptor with a less reactive donor can lose control of the stereoselectivity. Often stereoselectivity can be better controlled when the acceptor is less active, as the more reactive nucleophiles tend to proceed faster, producing poor outcomes in α/β selectivity.¹⁰ Therefore electron-withdrawing protecting groups are often installed in the acceptor molecule to reduce the electron density of the hydroxyl group, thereby lowering its nucleophilicity.¹¹⁻¹⁴ Bert coined the concept of “armed” and “disarmed” glycosyl donors on the basis of the substituent present at C-2.¹⁵ For example, donors with an ether group on C-2 are armed (more reactive), and those with esters or amides at the same position are disarmed (less reactive) because the activated donor-activator complex leads to a full and a partial positive charges resulting in increase in the kinetic energy barrier.^{4,16,17} Protecting groups on the donor also have substantial impact on the stereoselectivity. For instance, an acyl group at the C-2 can work as a participating group to attack the oxocarbenium ion to form an acyloxonium ion, locking the face *cis* to the acyl group, directing the stereochemistry of the product as 1,2-*trans* mainly (Figure 2). Long-range participation effects of protecting groups at other positions, typically at C-3 and C-6, have also been reported (such as H-bond-mediated aglycone delivery) and reviewed elsewhere.¹⁸⁻²⁰ In the case of galactoside synthesis, an ester group at C-4 can perform remote neighboring group participation during glycosylation, leading to α -stereoselectivity predominantly.²¹ Reactivity of a donor also depends on the types of leaving groups and the corresponding activators. Restricting the conformation of the donor via introduction of cyclic protecting groups sometimes also affect the stereoselectivity of the reaction; this is of particular importance for the synthesis of furanosides.²²

In practice, the structures of donor and acceptor are carefully designed while considering the above factors together with strategies to install orthogonal protecting groups. When the

glycosylation reaction outcome is not satisfactory, e.g. low yield and/or low stereoselectivity, other reaction conditions need to be optimized before the structure of donor or acceptor is altered, since these changes require extensive effort in design and synthesis of the building block molecules again. Therefore, conditions such as temperature, activator, or solvent system are often adjusted accordingly to optimize the yield and/or stereoselectivity. Generally speaking, since α -isomer is thermodynamically favored via the anomeric effect, reactions at high temperatures tend to lead to α -glycoside as a major product; whereas kinetically favored β -glycoside forms predominantly at lower temperatures. Nature of glycosyl donor affects the choice of promoter for better yield as well as good stereoselectivity. For example, glycosyl halides give best results under the halide-ion catalyzed condition to form 1,2-*cis* glycosides.²³ Thioglycosides are remarkably stable and are inert under several glycosylation condition,²⁴ and often they can be activated by *N*-iodosuccinimide/triflic acid, iodonium dicollidine perchlorate,²⁵ methyl sulphenyl triflate (MeSOTf), benzeneselenenyl triflate (PhSeOTf),^{26,27} *N*-(phenylthio)- ϵ -caprolactam/triflic anhydride,²⁸ and S-(4-methoxyphenyl)benzenethiosulfinate/triflic anhydride (MPBT/Tf₂O).²⁹ Similarly, various promoters have been explored to activate haloglycosides (F, Cl, Br, and I)³⁰ and trichloroacetimidate donors.³¹

Solvent effects in glycosylation

Glycosylation reactions involve formation of charged intermediate species, the stability which is affected by the nature of solvent employed.^{12,28-35} These reactions are generally carried out in moderately polar solvents as they can render some sort of stability to the intermediate species. Most commonly used solvents are dichloromethane (DCM), diethyl ether (Et₂O), acetonitrile (CH₃CN or MeCN), 1,2-dichloroethane, toluene, and nitromethane. Beside these

pure solvents, their mixtures are also employed highly for glycosylation reactions. The nature of a solvent not only affects the yield of a reaction, but most importantly it also dictates stereoselectivity of the reaction outcome. It has been found that reactions preparing glucopyranosides carried out in the medium of 1,4-dioxane, THF or diethylether preferentially give 1, 2-*cis* products (α -linkage). In contrast to it, reaction in MeCN predominantly gives β -linkage.^{30,32-35} This stereoselection resulted from solvent effects, works if there is no participating group at C-2. In the presence of participating group, reaction's fate is almost completely driven by the neighbouring group participation effect, outweighing the solvent effect and leading predominantly to 1,2-*trans* linkage.³⁶

Two general hypotheses have been proposed for the explanation of solvent participation – one is *solvent coordinated hypothesis* and the other one is *conformer and counterion distribution hypothesis*.^{3,37} According to the *solvent coordinated hypothesis*, the solvent molecule gets coordinated with the anomeric carbon of the oxocarbenium cation preferentially on one side of the ring, as a result of which the incoming nucleophile has only one possible face to attack from (Figure 3a). Acetonitrile preferentially gets attached to the α -face of the oxocarbenium ion giving α -glycopyranosyl acetonitrilium ion and blocks the incoming nucleophile from choosing α -face to attack the intermediate. This leaves only the β -face to attack giving 1,2-*trans* (β -glucoside). Isolation of the nitrilium intermediate by Pougny and Sinay,^{38,39} which was later confirmed by Ratcliffe and Fraser-Reid,⁴⁰ was the first evidence for the formation of a covalent anomeric nitrilium with α -configuration. This was also independently demonstrated by other researchers.^{41,42} Taking into account of the conformational dynamics of the oxocarbenium ion with the counterion, Satoh and Hunenberger performed the first theoretical investigation using quantum mechanical calculation of the oxocarbenium-solvent interactions in the vacuum and in

solvent, as well as the classical molecular dynamics simulations.³ Their study put forward an alternative hypothesis called the *conformer and counterion distribution hypothesis* (Figure 3b) which does not support the most common *solvent coordination hypothesis*. In their study 2,3,4,6-tetra-*O*-methyl-D-glucopyranosyl-triflate was used as a model glycosyl donor and solvents employed were acetonitrile, diethyl ether (Et₂O), toluene, and 1,4-dioxane. Depending upon the nature of the solvent used, the oxocarbenium cation adopts different conformations. In acetonitrile, B_{2,5} boat conformation is suggested for the oxocarbenium cation. The counter ion resides close to this cation, leading to the formation of the β-glucoside. But in the case of toluene and 1,4 dioxane, the most favourable conformation for the intermediate is suggested to be ⁴H₃ half-chair with the counterion residing very closely on the β-side, thereby facilitating the formation of α-glucoside.³ Their study suggests that the solvent of the reaction induces preferential conformation changes in the oxocarbenium cation and the locations of the counterions which govern the stereoselectivity of the reaction.

In addition to controlling the stereoselectivity of glycosylation reactions, solvents were noticed to affect reaction rate. Generally speaking glycosylations in DCM proceed faster than the same reactions carried out in Et₂O or CH₃CN, and this solvent reactivity effect has allowed successful synthesis of a trisaccharide via one-pot sequential reactions.⁴³

In this review, effect of solvents will be discussed in the context of four different glycosidic linkages as shown in Figure 4.

1,2-*Trans*-β-*O*-glycosidic linkage.

1,2-*Trans*-β-glycosidic linkage (e.g. β-glucoside, β-galactoside) is easy and convenient to synthesize in comparison to 1,2-*cis*-linkage. This is usually achieved by introducing

participating groups such as *O*-acetyl (Ac), *O*-benzoyl (Bz), *O*-pivaloyl (Piv), and *N*-phthalimido (Phth) at C-2 of the donor.⁴⁴ The participating group at C-2 of glycosyl donor intramolecularly assists the departure of activated leaving group at anomeric carbon, thereby forming a more stable dioxolenium intermediate ion (Figure 2). Since the α -face of the intermediate ion is dynamically shielded by a ring, acceptor is directed to the β -face which leads to the formation of 1,2-*trans*- β -linkage predominantly.^{30,44} In the absence of participating group at C-2, the reaction leads to a mixture of α and β anomers, and in this case effect of solvent should be remarkable.⁴⁵ Although the formation of dioxolenium ion drives the reaction to give predominantly β -selectivity, formation of *cis*-isomers (α) has also been observed occasionally. This could be due to the reaction going through pathways involving either a reactive glycosyl cation or resonance stabilized oxocarbenium ion (Figure 2).³⁰

Thioglycosides are commonly used glycosyl donors, and they can be activated by various thiophilic reagents.³⁶ Solvent effects were investigated in glycosylation reactions of thioglycoside activated by NBS with the combination of various strong Lewis acid such as Ph₂IOTf, Bu₄NOTf, and Bu₄NClO₄.⁴⁶ The yields of the reactions were generally good. The reaction between glycosyl donor having non-participating group at C-2 and the acceptor gave high β -selectivity as a result of formation of α -nitrilium intermediate in acetonitrile solvent (Figure 3a).⁴⁷⁻⁴⁹ Similar mechanism was proposed for the reaction that employed *in situ* prepared mixture of iodosobenzene and triflic anhydride (PhIO-Tf₂O) for the activation of various thioglycosides. Reactions gave β -glycosides preferentially as a result of acetonitrile participation, whereas no such effect was observed in reactions carried out in dichloroethane or ether.⁵⁰

Glycosyl trichloroacetimidates are another class of commonly employed glycosyl donors in glycosylation reactions. In a study that involved the glycosylation of trichloroacetimidate donors with acceptors in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) promoter, Schmidt and coworkers observed a dominating β -directing properties of nitrile solvents.⁵¹ High reactivity of trichloroacetimidates gave high yields in the glycosylation reactions with various acceptors carried out in MeCN and EtCN and excellent β -selectivity. In the same study, other nitrile solvents (i Pr-CN, CH₂=CH-CN, and CCl₃CN) also exhibit good β -selectivities. Presumably, after activation of trichloroacetimidates, solvent coordination hypothesis applies here as well for nitrile solvents (Figure 3a).

Glycosylation of benzyl-protected glycopyranosyl *N,N,N,N*-tetramethylphosphoramidate donors **1** and **2** with different acceptors (Figure 5) in the presence of TMSOTf or BF₃•Et₂O was found to be efficient.⁵² Reactions gave high β -selectivity in propionitrile, which was decreased significantly when solvent was changed to CH₂Cl₂. The reaction proceeded with the formation of tight ion-pair of oxocarbenium ion and phosphoramidate-TMSOTf complex, which was then attacked by the acceptor from the opposite side. When BF₃•Et₂O was used instead of TMSOTf, β -isomer was predominant in CH₂Cl₂, suggesting the possibility of rapid β to α -anomerization before the glycosylation started. This generated more stable phosphoramidate-BF₃•Et₂O ion pair, which was then attacked by nucleophilic acceptor to give β -glycoside predominantly.⁵²

1,2-*Trans*- α -O-glycosidic linkage.

Synthesis of 1,2-*trans*- α -linkage (e.g. α -mannoside) is favored by anomeric effect, often with addition of neighbouring group participation when C-2 hydroxyl group is acyl group protected (formation of acyloxonium ion is similar to that for 1,2-*trans*- β -linkage in Figure 2).⁵³

In the presence of participating group at C-2, the effect of solvent on stereoselection is suppressed. For example, reaction of a mannosyl donor tetra-*O*-benzyl-D-mannosyl fluoride with cyclohexylmethanol in the presence of $\text{Cp}_2\text{ZrCl}_2\text{-AgBF}_4$ gave α -selectivity in all the solvents used (Et_2O , CH_2Cl_2 and MeCN).⁵⁴ α -Selectivity was surprisingly favored in CH_2Cl_2 and benzene with excellent yields. Presence of Et_2O was not found to affect the α -selectivity significantly. β -Directing nature of MeCN did not work at all, instead α -isomer was still obtained as a major product.

Benzyl group (OBn) is usually considered as a non-participating group, but in a study Mong and coworkers revealed a participating effect of OBn group in nitrile solvent, and applied the concept in the synthesis of 1,2-*trans*- α -linkage during the synthesis of $\alpha(1\rightarrow5)$ -arabinan oligomers (Figure 6).⁵⁵ The reaction between thioarabinosides **3** (armed, more reactive) and **5** in pure CH_2Cl_2 was found to give low α -selectivity (Figure 6a). When the solvent was changed to $\text{CH}_2\text{Cl}_2/\text{MeCN}/\text{EtCN}$ (1:2:1), good α -selectivity was observed. The α/β ratio increased to 10:1 when the reaction was performed at low concentrations.⁵⁶ High α -selectivity was observed with acceptors **6**, **7**, **8** and donor **4** as well in solvent system of $\text{CH}_2\text{Cl}_2/\text{MeCN}/\text{EtCN}$ (1:2:1). The formation of 1,2-*trans*- α -linkage was explained on the basis of nitrile solvent assistance on the formation of 1,2-oxazolinium ion (Figure 6b). The formation of the 1,2-*cis*-oxazolinium ion with the participation of C-2 benzyl group in nitrile solvent led to the formation of 1,2-*trans*- α -linkage when the incoming acceptor attack from the β -face.

1,2-*Cis*- α -O-glycosidic linkage.

Although 1,2-*cis*- α -glycosidic linkage is stereoelectronically favored over corresponding β -linkage due to anomeric effect,^{57,58} its highly stereoselective synthesis is difficult. Beside

having an advantage of anomeric effect, there are still different factors that affect the selectivity outcome of a reaction. Role of solvents is one of them that highly determines the fate of a reaction. Following the general rule, nitrile solvents direct the reaction towards β -selectivity whereas ethereal solvents favour α -configuration.³ For example, glycosylation of a thioglycoside **13** with an acceptor **14**, in the presence of iodonium di-collidine perchlorate (IDCP),²⁵ gave excellent α -selectivities when mixtures of toluene and dioxane (1:2) were employed (Figure 7).⁵⁹ α -Selectivity was remarkably increased going from DCM to a mixture of DCM and ether; the α -selectivity was further increased when the ratio of DCM/Et₂O was changed to 1:4. The α -selectivity of ether might be a result of its participation with oxocarcabenium intermediate during the reaction (Figure 3a).³² Also its less polar nature promote the anomeric effect as well.⁵⁸ This selectivity improved with toluene/dioxane mixture probably resulted from better participating ability of dioxane over ether. Van Boom and coworkers performed the same reaction in the presence of promoter N-iodosuccinimide (NIS)/TMSOTf⁶⁰ with different toluene-dioxane ratios. Good α -selectivity was observed in toluene/dioxane (1:3) system. The participating effect of ethereal solvents was also observed in a glycosylation reaction that involved 2,3,4,6-tetra-*O*-benzyl-1-*O*-tosyl- α -D-glucopyranose donor **15** and methyl 2,3,4-tri-*O*-benzyl- α -D-glucopyranoside acceptor **16** (Figure 7).⁶¹ Stereoselectivity was not good but the ratio of α : β isomers was still dependent on the solvent used - ethereal solvents THF and diethyl ether generally gave higher α -selectivity over non-ethereal solvents. Presumably, the incipient oxonium ion characteristics of the β -anomer of *p*-toluenesulfonate in ether would stabilize β -ion over the α -ion, thus favoring α -selectivity in the product.⁶¹

Ishiwata and Ito reported a high throughput screening of *O*-glycosylation reaction conditions. Taking a donor **17** and an acceptor **18** (Figure 8), they performed a series of reactions

with different solvents at room temperature and at 50 °C.⁶² Variable selectivity was observed among the halogenated hydrocarbon solvents, out of which, chloroform (CHCl_3) was found to be the best choice regarding its α -selectivity ($\alpha:\beta=10.9:1$). Similarly, among the aromatic solvents, those having electron withdrawing groups were found to render substantially higher α -selectivity. Cyclopentylmethyl ether ($\text{c-C}_5\text{H}_9\text{OMe}$, CPME) was the most effective among the ethereal solvents and provided the highest α -selectivity. No reaction took place in dipolar solvents such as dimethylformamide (DMF) and dimethyl sulfoxide (DMSO). Reactions were also performed in mixed solvent systems, among which 1:1 mixture of $\text{CHCl}_3:\text{c-C}_5\text{H}_9\text{OMe}$ was found to be the best solvent system, giving quantitative yield with $\alpha:\beta=11.4:1$. Further, they studied the synergistic effect of solvents in 1,2-*cis*-glycosylation,⁶³ and implemented it in the synthesis of a tetrasaccharide consisting of all 1,2-*cis*- α glycosidic linkage. For the study of solvent effect, 2,3-*O*-Bn-d7 protected donor **19** was reacted with acceptor **20** (Figure 8).

Comparison of the anomeric ratio (α/β) of the products formed revealed that the mixture of halogenated and ethereal solvent could lead to α -selectivity substantially. Benzene and toluene exhibited poor α -selectivity. Anomeric ratio (α/β) of the products was enhanced when employing mixture of halogenated and ethereal solvents. These α/β ratios were significantly higher than those using individual solvents suggesting some types of synergistic effect⁶³ in the co-existence of the ether with the other solvents. The result also revealed the sensitiveness of selectivity towards the ratio of the components in the mixture. α -Selectivity of the reaction was found to decrease when the solvent ($\text{CHCl}_3:\text{Et}_2\text{O}$) ratio was deviated from 1:1. The authors proposed that the presence of ether in the mixed solvent more likely formed ether-coordinated intermediates $\text{E}(\alpha)$ and $\text{E}(\beta)$, and more plausibly the reaction proceeded through the more abundant $\text{E}(\beta)$ resulting in α -anomer product (Figure 8).⁶³

The use of polar solvents DMF and DMSO is uncommon, and has been often found to be detrimental in glycosylation reactions including the ones performed by Ishiwata and Ito.⁶² But Mong *et. al* made a successful use of DMF as a co-solvent with DCM which rendered enhanced selectivity to the reaction (Figure 9).⁶⁴ In their study, the reaction mixture of donor **21**, acceptor **22**, and DMF (1.5-6 equiv) was activated by commonly employed NIS/TMSOTf. The α -selectivity of the reaction was greatly affected by the amount of DMF employed. As is evident from the data, the α/β was increased from 6:1 to 19:1 from 6:1 when the amount of DMF increased from 1.5 to 6 equivalent. This effect of DMF was more evident when they performed pre-activation based glycosylation, when donor was first activated by NIS/TMSOTf in the presence of DMF and then acceptor was added. All the glycosylation reactions were found to proceed with high α -selectivity. The authors proposed that the α -selectivity of the reaction, in the presence of DMF as a co-solvent, resulted from the formation of an equilibrating mixture of α/β -glycosyl-*O*-imidates once the oxocarbenium ion was trapped by DMF. Eventually, the more reactive β -imide was consumed, favoring the formation of the α -glycoside.

Huang and co-workers reported the use of an appropriate solvent (Et₂O or DCM) could switch the stereochemical outcome of the reaction (Figure 10).⁶⁵ α -Glycoside was favoured by Et₂O, whereas β -isomer was predominant when solvent was changed to DCM. For example, reaction between donor **23** (pre-activated by *p*-TolSOTf, formed *in situ* from the reaction of AgOTf and *p*-TolSCl) and acceptor **24**, when carried out in Et₂O, gave good α -selectivity (6:1), whereas the same reaction in DCM gave good yield with β -selectivity. Further, when the volume of the Et₂O was increased to 10 fold, the α -selectivity of the reaction increased presumably due to the higher accessibility of the solvent participation under the dilute condition.⁶⁵ The authors proposed that in non-polar and non-nucleophilic solvent DCM, reaction favored an S_N2 type

displacement to give β -selectivity (Figure 10, pathway b). In contrast, Et_2O could first attack the intermediate from β -face, which subsequently get displaced by the nucleophilic acceptor in S_N2 fashion leading to the formation of α -isomer (Figure 10, pathway a).

The effects of solvents on the stereoselective outcome in the synthesis of oligosaccharides on polymer support were studied using glycosyl donors **25** or **26** and acceptors **27**, **28** or **29** (Figure 11).³⁵ Soluble poly ethylene glycol (PEG) methyl ether and insoluble Merrifield resin were employed in the study. In the presence of promotor DMTST (dimethylthiomethylsulfonium triflate), α -selectivity for the solvents DCM ($\alpha:\beta=79:21$), toluene ($\alpha:\beta=79:21$), $\text{C}_6\text{H}_5\text{CF}_3$ ($\alpha:\beta=84:16$) and CH_2Cl_2 -ether ($\alpha:\beta=80:20$) were found to be significant, whereas in the presence of MeCN at room temperature, β -selectivity was enhanced over α giving 1,2-*trans*- β -isomer as a major isomer. Marginal stereoselectivity was observed for PhSeNPhth/TMSOTf system. In this case, β -directing property of acetonitrile was not effective to dictate β -selectivity, probably because of the participation of PhSeSMe on to the intermediate.⁶⁶ For donor **26** and acceptor **27** in the presence of $\text{AgClO}_4/\text{SnCl}_2$, acetonitrile containing solvent favored β -isomer whereas ether containing favored formation of α -isomer.

1,2-*Cis*- β -O-glycosidic linkage.

1,2-*Cis*- β -O-glycosides (e.g. β -mannosides) are important components of various biologically active molecules.⁶⁷⁻⁶⁹ This linkage is the most difficult linkage to form via direct glycosylation, because of anomeric effect that favors an axial orientation at anomeric center and the stereoelectronic factor that results in steric repulsion due 1,2-*cis* geometry. Also the presence of participating group on C-2 tends to drive the reaction towards α -selectivity.^{37,70} Instead, 1,2-*cis*- β -O-glycosides are often obtained through sequential oxidation-reduction at the C-2 position

from a 1,2-*cis*- β -glycoside.⁷¹ DCM is the most commonly employed solvent in the synthesis of β -mannosides (1,2-*cis*- β -linkage).⁷²⁻⁷⁴ Besides, MeCN, Et₂O, and toluene are also frequently employed. In a pre-activation glycosylation method (donor **30**, acceptor **16**), DCM was found to favor β -selective product over α -isomer whereas Et₂O rendered α -selectivity (Figure 12).⁶⁵ As mentioned above (Figure 10), intermediate glycosyl triflate can undergo efficient *S_N2* displacement by acceptor in non-polar solvent such as DCM to form β -isomer, whereas in ether due to the double inversion-mechanism α -isomer is predominantly formed (Figure 10).^{65,75} In another study, a strong electron withdrawing and non-participating group was introduced at O-2 forming a 3,4,6-tri-*O*-benzyl-2-*O*-mesyl- α -D-mannopyranosyl chloride donor **31** (Figure 12).^{76,77} Electron withdrawing group facilitate *S_N2* type displacement by creating an opposite dipole.^{76,77} The authors employed a polar solvent acetonitrile and silver trifluoroethanesulfonate for the glycosylation reaction with acceptor **16**, which yielded mannopyranoside in high yield with 95% β -selectivity via a double inversion mechanism.

The β -selectivity of the reaction was enhanced while changing the solvent from diethyl ether to DCM in the reactions between donors 32-36 and acceptor 37 (Figure 13a). This could possibly result from the shift of the equilibrium toward covalent triflate from an ion-pair (Figure 13b).^{78,79}

Zhu and Yu developed a gold (I)-catalyzed glycosylation of ortho-alkynylbenzoate donors (Figure 14).⁸⁰ To optimize the reaction condition, they employed a relatively uncommon solvent PhCl along with DCM and Et₂O for the reaction of **38** and acceptor **22**. The reaction was proposed to proceed with the activation of triple bond of *O*-hexynyl benzoate by Au(I) catalyst, thereby facilitating the nucleophilic attack by the carbonyl oxygen (Figure 14b). This resulted in

dissociation of glycosidic bond giving a reaction intermediate oxocarbenium ion, which simultaneously underwent reaction with an acceptor to give the glycoside (Figure 14).^{81,82} Although all of these solvents favored β -selectivity, Et₂O and DCM were found to be less effective solvents compared to PhCl which gave high β -selectivity when gold (I) catalyst loading (as a ether solution) was decreased to 0.1 equivalent (0.028 M in Et₂O). This could be attributed to the decrease in the volume of Et₂O which could participate in the reaction by associating with the oxocarbenium ion.⁸⁰ This ratio further increased highly when reaction was carried out using the same catalyst loading but at higher concentration (0.28 M of gold (I) in Et₂O).

Conclusions and outlook

We have outlined the known solvent effects on the stereoselectivity of glycosylation reactions. Although several general trends have been observed by researchers over the years, it is not possible to rely solely on the solvent effects to design or optimize the glycosylation reactions, because our knowledge of how solvent plays in glycosylation is still expanding, and solvent is only one of the many factors that control the stereoselectivity of glycosylation. Better understanding of the mechanistic aspects of various types of glycosylation reactions will help us to find more guidelines while designing the reagents and reaction conditions. We hope this review article can help the fellow researchers form a general idea of solvent selection, while we hope more detailed and broader solvent effects can be explored in the context of other factors controlling the stereoselectivity of glycosylation in the future studies.

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Figure captions:

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Figure 13. (a) Donors and acceptor used in direct glycosylation reactions to obtain β -mannosides (continued). (b) Proposed reaction mechanism for the β -selectivity.

Figure 14. Gold (I) catalyzed glycosylation. (a) Donors and acceptor used in gold (I) catalyzed glycosylation reactions to obtain β -mannosides. (b) Proposed reaction mechanism for the gold (I)-catalyzed glycosylation.

Draft

Controlling the Stereoselectivity of Glycosylation via Solvent Effects

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Invited Review

Dedicated to Prof. David R. Bundle on the occasion of his retirement (Special Issue for Prof. Bundle)

Figures

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