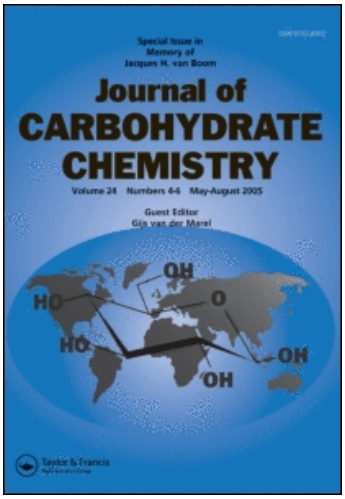

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DEHYDRATIVE GLYCOSYLATION WITH 1-HYDROXY DONORS

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DEHYDRATIVE GLYCOSYLATION WITH 1-HYDROXY DONORS*

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INTRODUCTION

The preparation of complex carbohydrates has emerged as a major focus in synthetic organic chemistry, and this is no doubt a result of the growing awareness of the many important roles of this class of molecules in biology.[1] Perhaps the most important reaction in the chemical synthesis of carbohydrates is the formation of the glycosidic bond, for this is the primary means for the controlled assembly of complex oligosaccharides and glycoconjugates from monosaccharide precursors. Thus a variety of methods have been developed to effect the glycosylation process. Much of the effort has focused on the general coupling strategy outlined in Scheme 1.[2] In this strategy, one begins with a carbohydrate coupling partner (**1**), which is subjected to initial derivatization whereby the anomeric substituent is transformed into a latent leaving group (LG). The resulting intermediate **2**, or glycosyl donor, is typically isolated, and in a second step the anomeric leaving group is activated with an appropriate glycosylation promoter or catalyst. This process usually takes place in the presence of a nucleophilic glycosyl acceptor (Nu-H), which undergoes an effective displacement of the leaving group to form the anomeric bond in the product glycoside (**3**). Within the last century, a variety of leaving groups have been developed for the generation of various glycosyl donors that can undergo efficient coupling in the second step. Some of these are listed in Scheme 1, and all have proven to be useful to some extent in complex carbohydrate synthesis.[2]

A far less developed strategy for glycosidic bond formation is a direct dehydrative coupling procedure in which one begins with a 1-hydroxy carbohydrate (**1**) as the

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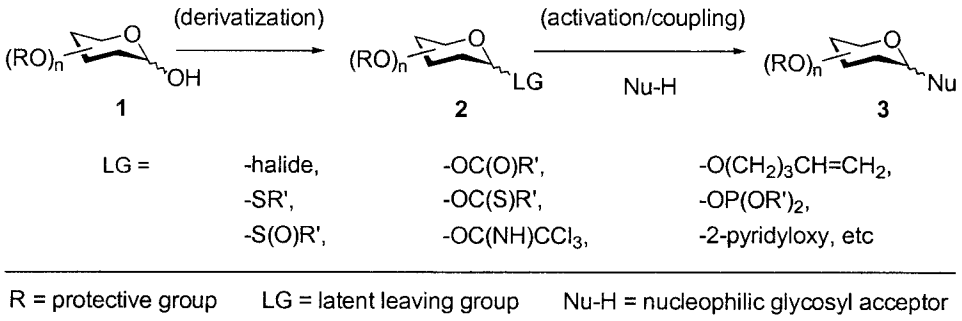
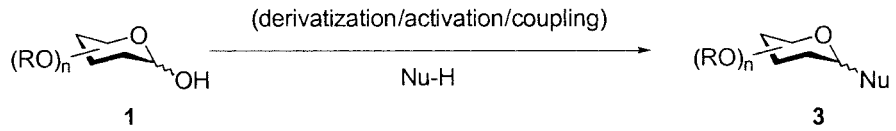


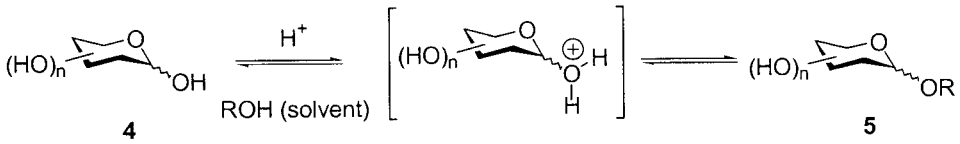
Scheme 1. Traditional glycosylation strategies.[2]

glycosyl donor (Scheme 2). This approach offers a complementary if not more efficient strategy for glycosylation in that a distinct anomeric derivatization step to generate an isolable glycosyl donor **2** is obviated. As such, all the operations of anomeric derivatization, activation, and bond formation are combined into a one-pot procedure. Despite its potential advantages, however, this strategy has not been extensively employed in complex oligosaccharide synthesis. The establishment of a viable synthetic method calls for the overcoming of such inherent difficulties associated with this approach as the reversibility of the process and the propensity for hemiacetal self-coupling, in addition to the common glycosylation obstacles such as coupling efficiency and high anomeric stereoselectivity. This chapter summarizes recent advances in the development of non-enzymatic direct dehydrative glycosylations with 1-hydroxy glycosyl donors.

The concept of direct dehydrative glycosylation is not a new one. One of the earliest glycosylation methods is the Fischer procedure,[3] currently adopted for preparation of simple glycosides (Scheme 3). In this process an unprotected monosaccharide (**4**) is trated with an excess of an alkyl alcohol in the presence of an acid catalyst, resulting in the net loss of water and substitution at the anomeric position by the alcohol acceptor. Usually a desiccant is not present in this hemiacetal-to-acetal exchange process; as a result, the equilibrium can favor the formation of the glycoside product **5** only through the use of a large excess of the alcohol acceptor (typically employed as the reaction solvent or cosolvent). In the original glycosylation procedure, HCl was used as the acid catalyst, with the coupling event usually proceeding at elevated temperatures. Over the years, a number of other Brønsted acid catalysts have been found to be effective in this process, including various inorganic and sulfonic acids[4,5] as well as acidic resins.[6] In addition, a host of Lewis acid catalysts have been employed,[7] giving rise to substrate-specific variants of the Fischer protocol. In fact, with selected Lewis acid promoters such as $FeCl_3$,[8] it is possible to favor the



Scheme 2. Direct dehydrative glycosylations.



Scheme 3. Fischer glycosylation.[3] R = methyl, ethyl, *n*-propyl, *i*-propyl, amyl, allyl, benzyl, etc.

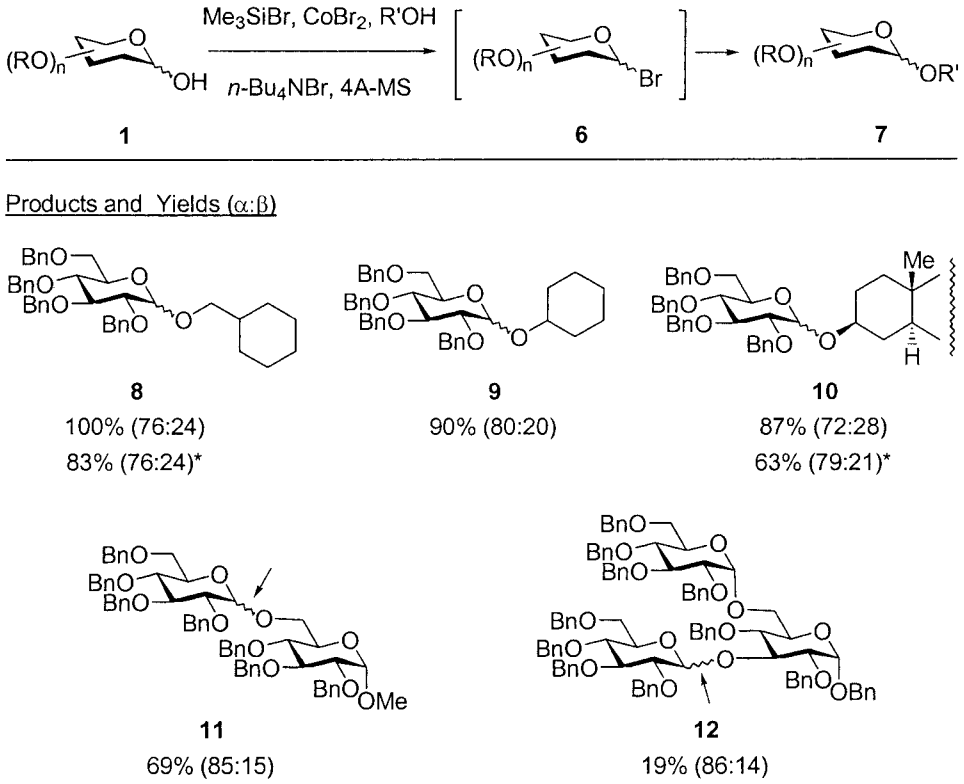
formation of the kinetic furanoside product over the thermodynamically more stable pyranoside adducts.[9] While it is not the goal of this section of the chapter to present a comprehensive summary of Fischer glycosylation methods, it is worth emphasizing that this protocol and its variants have, over the last century, remained one of the most popular methods for the preparation of simple alkyl glycosides. Indeed, this venerable method, with its simplicity and versatility, has frequently been chosen as the starting point for the preparation of of simple alkyl glycosides. Indeed, this venerable method, with its simplicity and versatility, has frequently been chosen as the starting point for the preparation of C1-protected monosaccharide building blocks for complex molecule syntheses.

Despite the widespread use of the Fischer method, it has yet to be shown to be effective in the controlled assembly of complex oligosaccharides. Because of the acidic medium under which the acetal exchange process occurs, only simple alcohols devoid of acid-labile functionality are employed as glycosyl acceptors. Moreover, the necessity of a large excess of acceptor to favor equilibrium formation of glycoside **5** precludes the use of complex or valuable molecules as nucleophilic acceptors. Typically the preparation of oligosaccharides by modified Fischer protocols has been limited to the preparation of carbohydrate oligomers of varying size and complexity.[10,11]

To establish a method for controlled glycosylation with 1-hydroxy carbohydrates, mild dehydrative coupling conditions are required that favor the cross-condensation of distinct hemiacetal donor and nucleophilic acceptor substrates. One approach toward this end is to employ a set of reagents that can rapidly and completely activate the C1-hydroxyl functionality in **1** to generate, in situ, a highly reactive intermediate that incorporates a transient leaving group at the anomeric position. The requirement for rapid activation of the anomeric hydroxyl is obviously necessary to minimize the extent of hemiacetal self-condensation, and the in situ formation of an extremely potent leaving group at C1 would allow for facile glycosidic bond construction with a nucleophilic acceptor without the need for isolation of an intermediate glycosyl donor.

COUPLING VIA GLYCOSYL HALIDES

Koto and coworkers have developed a dehydrative coupling procedure employing the in situ generation of a glycosyl bromide intermediate (**6**, Scheme 4).[12,13] In this procedure, a stoichiometric quantity of TMS-Br is introduced into a reaction mixture containing equimolar quantities of the 1-hydroxy glycosyl donor **1**, the alcohol acceptor (R′OH), $CoBr_2$, and tetrabutylammonium bromide. The glycosyl bromide **6**, generated in situ, then proceeds to glycosylate the alcohol acceptor. Glycosyl bromides are well-established donors in the Koenigs–Knorr procedure,[14] wherein these intermediates are



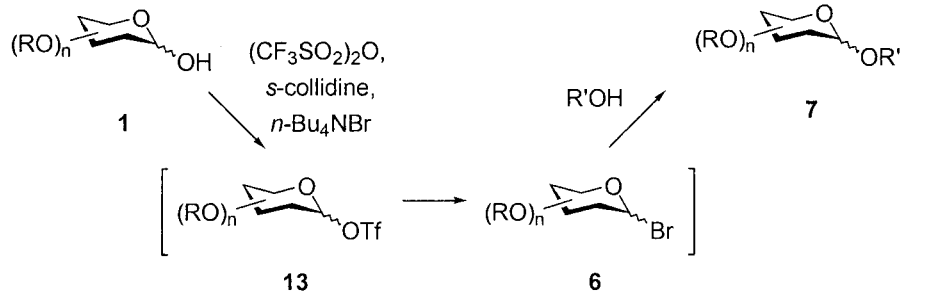
Scheme 4. Dehydrative glycosylations via glycosyl bromides.[12,13,15] *Using alternate method: $MeSO_3H$, $CoBr_2$, Et_4NClO_4.

typically isolated and activated with a halophilic promoter to effect glycosylation. However, the method of Koto and coworkers is distinct in that the intermediate **6** is both generated and consumed in situ under the reaction conditions, resulting in a net dehydration via a one-pot coupling process. The authors tentatively attribute the feasibility of this one-pot procedure to 1) the favorable effects of the 4 Å molecular sieves acting both as a HBr scavenger and as a desiccant, and 2) the functioning of $CoBr_2$ both as an effective desiccant and as a glycosyl bromide activator in the coupling stage with R′OH.

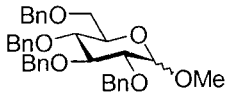
This procedure was used to glycosylate a number of alkyl alcohols with 2,3,4,6-tetra-*O*-benzyl-D-glucose, resulting in very good to moderate yields, depending on the complexity of the alcohol acceptor (e.g., **8**–**12**). In these couplings, only trace amounts of products arising from hemiacetal self-coupling were detected, and the presence of Bu_4NBr favored the formation of the α anomer of the product glycosides. It is worth noting that in an earlier related report, the reagent combination of [$MeSO_3H$, $CoBr_2$, Et_4NClO_4] was also employed by Koto to effect the desired dehydrative glycosylation.[15] Under these reaction conditions, it is presumed that HBr is generated, leading to the formation of **6**; however, this protocol generally led to diminished yields (e.g., **8** and **10**) compared with the above-mentioned TMS-Br·$CoBr_2$ procedure.

COUPLING VIA GLYCOSYL SULFONATES

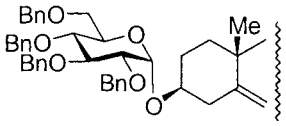
The in situ generation and coupling of glycosyl sulfonate esters of 1-hydroxy glycosyl donors has also been investigated in the context of direct dehydrative glycosylation. Early work by Leroux and Perlin highlighted the generation of glycosyl trifluoromethanesulfonates **13** as useful reactive intermediates for glycosylation in the presence of Bu_4NBr and the acid scavenger *s*-collidine (Scheme 5).[16] Their initial attempts at the glycosylation of the acceptor R′OH directly with triflate **13** in the absence of Bu_4NBr were unsuccessful (i.e., **1** → **13** → **7**), presumably as a consequence of the instability of the highly reactive triflate species. However, the introduction of Bu_4NBr served to rapidly convert **13** into the more stable glycosyl bromide **6**, which then proceeds to glycosylate the acceptor R′OH. With this protocol, isolation of the glycosyl bromide **6** is again unnecessary, allowing for an overall one-pot process. The



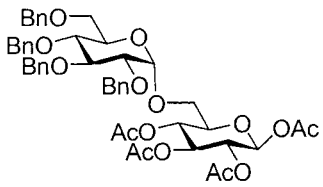
Products and Yields (α:β)



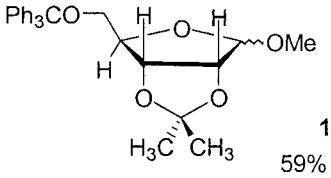
14
94% (3:2)
87% (3:2)*



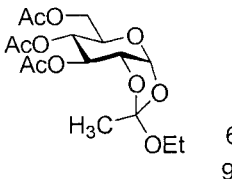
15
62% (α)



16
63% (α)



17
59% (3:2)

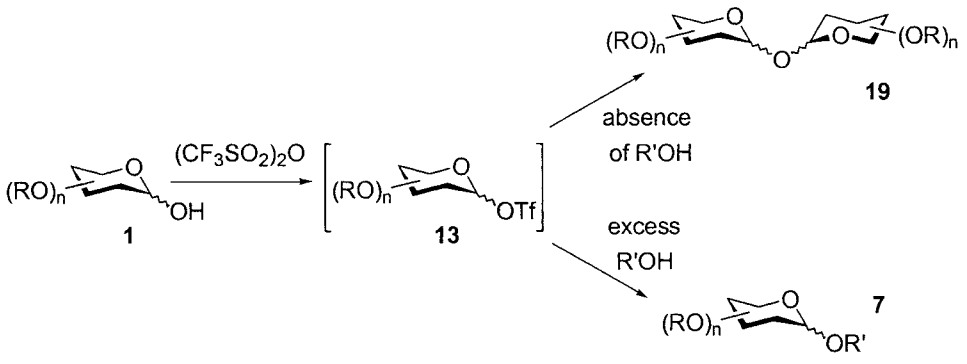


18
66%
98%*

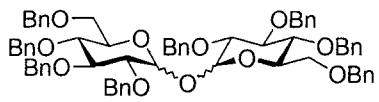
Scheme 5. Dehydrative glycosylations via glycosyl triflates.[16] *Using alternate method: $(Me_2SO_2)_2O$, *s*-collidine; R′OH.

authors also highlight this as a useful method for the generation of glycosyl bromides under nonacidic conditions.

With this procedure, a number of simple alcohols were glycosylated to generate carbohydrate products such as **14**–**17**. With glycosyl donors incorporating a C2-acyl functionality such as an acetate ester, the corresponding orthoester adduct (e.g., **18**) is generated, the obvious result of acceptor addition to the bicyclic oxygen-stabilized carbocation that arises through neighboring group participation. It should be noted that the use of methanesulfonic anhydride in place of triflic anhydride also led to similar glycoside adducts (e.g., **14** and **18**). When $(MeSO_2)_2O$ is used as the dehydrating reagent, however, the addition of Bu_4NBr is not necessary because the intermediate glycosyl methanesulfonate, which can directly glycosylate the acceptor at ambient temperature, has increased stability.

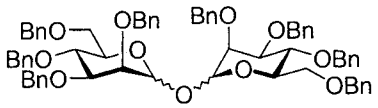


Products and Yields (α:β)



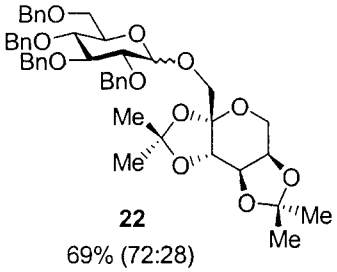
20

54% (αα), 25% (αβ)



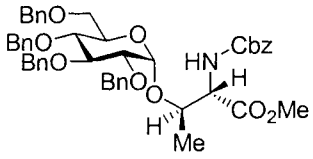
21

65% (αα)



22

69% (72:28)

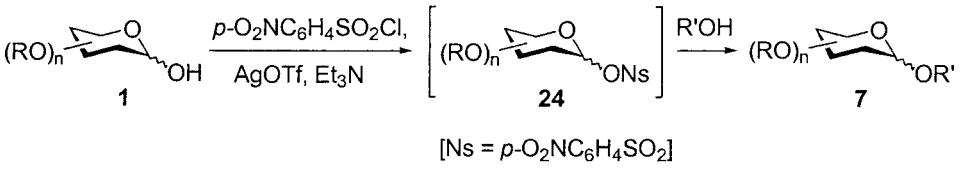


23

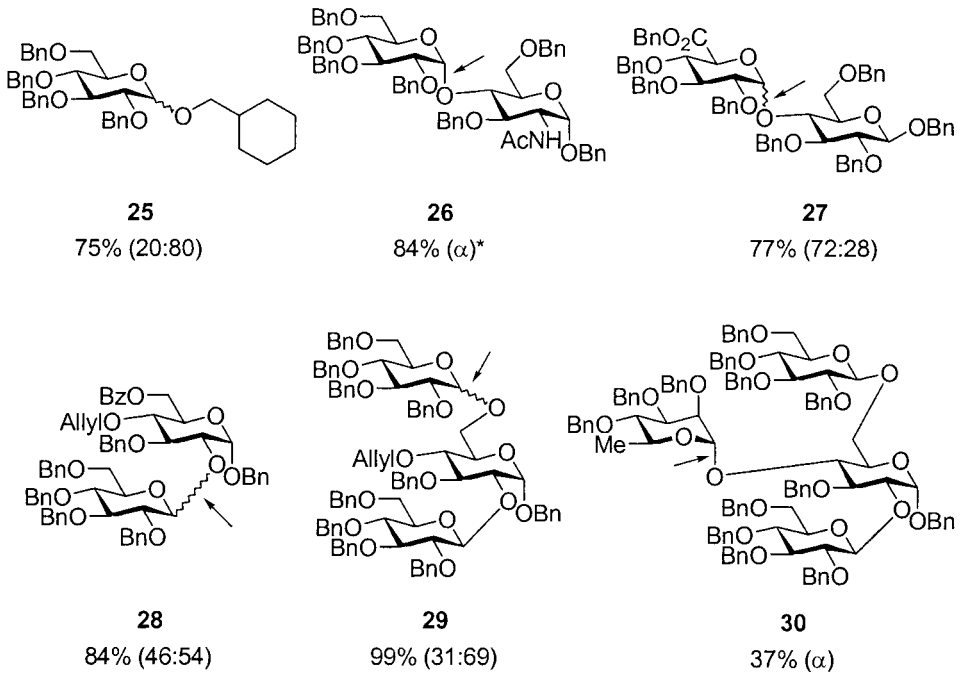
65% (α)

Scheme 6. Dehydrative glycosylations via glycosyl triflates.[17–19]

Although the use of triflic anhydride and *s*-collidine in the absence of bromide ion was ineffective for glycosylation, the use of triflic anhydride alone was found to be useful for the coupling of 1-hydroxy glycosyl donors. Pavia et al.[17] have shown that the treatment of 1-hydroxy donors with triflic anhydride in the absence of any acid scavenger led to the formation of (1,1′)-linked disaccharides **19**, the products of self-coupling of the 1-hydroxy donor (Scheme 6). The presumed mechanism[18] of this transformation involves 1) activation of the hemiacetal with trace amounts of triflic acid for conversion to the glycosyl triflate **13** (or the corresponding oxo-carbenium triflate), 2) the rapid coupling of the highly reactive intermediate **13** with unactivated **1**, and 3) the action of triflic anhydride as a desiccant to favor formation of the (1,1′)-disaccharide **19**. Although this is a relatively efficient method for the preparation of



Products and Yields (α:β)

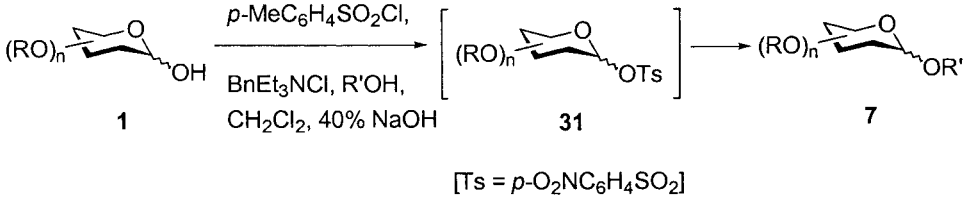


Scheme 7. Dehydrative glycosylations via glycosyl arylsulfonates.[20–23] *Coupling performed in the presence of 2.5 equiv $AcNMe_2$.

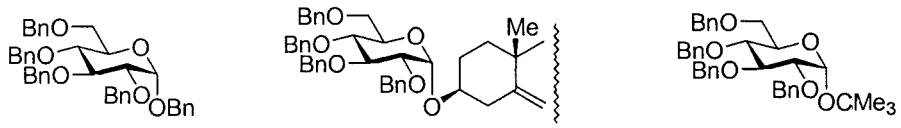
symmetrical trehalose analogs (e.g., **20** and **21**), it is often the case that the self-condensation product of the hemiacetal donor is an unwanted side product of dehydrative glycosylation. However, if this coupling procedure is performed in the presence of an excess (2–4 equiv) of an alcohol glycosyl acceptor R′OH, heterocouplings do take place (e.g., **22** and **23**). Pavia has used this protocol to prepare complex galactosyl-*O*-glycopeptides.[19]

Koto has shown that glycosyl arylsulfonates can also be used as intermediates in couplings with 1-hydroxy glycosyl donors. The direct glucosylation of several simple alcohol acceptors with 2,3,4,6-tetra-*O*-benzyl-D-glucose can be accomplished with the ternary mixture of *p*-nitrobenzenesulfonyl chloride, silver triflate, and triethylamine as the acid scavenger (Scheme 7).[20] Simple alcohols such as methyl alcohol, cyclohexylmethyl alcohol, and dihydrocholesterol are glycosylated efficiently via the glycosyl sulfonate **24**, and the formation of trehalose by-products is minimized as a result of rapid anomeric sulfonylation. In addition, couplings performed in the presence of *N,N*-dimethylacetamide generally lead to higher proportions of the α anomer (**26**).[21] This procedure can be used to prepare glucuronides (**27**),[22] as well as other complex oligosaccharides such as the branched-chain oligosaccharides of the sarsasaponins (e.g., **28**–**30**).[23]

Other dehydrative glycosylations employing glycosyl arylsulfonates include the formation of transient glycosyl tosylates from 1-hydroxy donors, reported by Szeja (Scheme 8).[24] For obvious reasons, all the preceding dehydrative coupling methods call for care to exclude moisture from the reaction. However, the method of Szeja is distinct in that it effects a dehydrative coupling with 2,3,4,6-tetra-*O*-benzyl-D-glucose in an aqueous cosolvent under phase transfer conditions, presumably via in situ formation of the intermediate tosylate **31**. Using a mixture of *p*-toluenesulfonyl chloride, an excess (4 equiv) of the alcohol acceptor, a solvent mixture of CH_2Cl_2 and 40% NaOH(aq), and $BnEt_3NCl$ as the phase transfer catalyst, simple alcohols such as benzyl



Products and Yields (α:β)



32 75% (90:10) **15** 68% (95:5) **33** 65% (95:5)

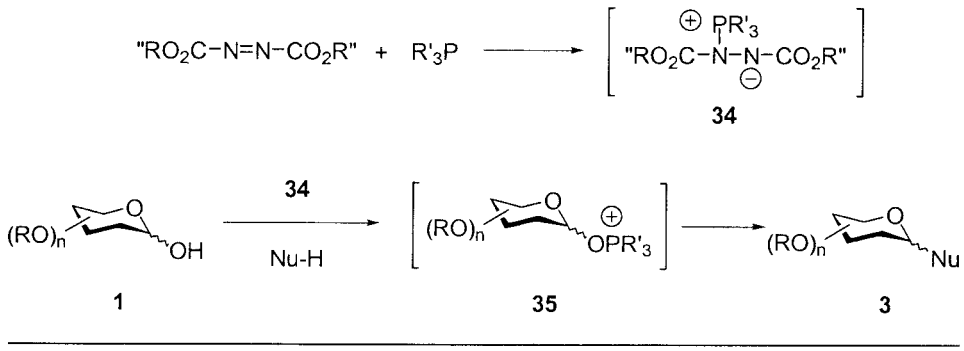
Scheme 8. Dehydrative glycosylations via glycosyl arylsulfonates.[24]

alcohol, cholesterol, and even tertiary alcohols such at *t*-butyl alcohol can be glucosylated with good α-selectivity (e.g., **15**, **32**, **33**).

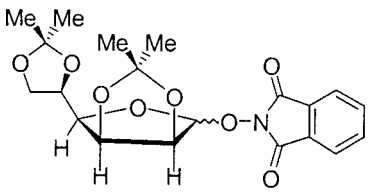
COUPLING VIA GLYCOSYL OXOPHOSPHONIUM INTERMEDIATES

The in situ generation of glycosyl oxophosphonium salts has been shown to be useful for one-pot couplings with 1-hydroxy glycosyl donors. The most common method employed for the generation of the carbohydrate oxophosphonium intermediates **35** occurs by way of the Mitsunobu protocol[25] or variants thereof (Scheme 9). The method typically employs the initial reaction of a dialkyl azodicarboxylate with a phosphine substrate in the presence of a weak acid to generate a quaternary phosphonium salt, **34**. With this reagent, it is known that a variety of alcohols can be activated to form the corresponding oxophosphonium species, which can then be displaced (S_N2) by a variety of weak-acid nucleophiles, including carboxylic acids, phenols, *N*-hydroxyimides, imides, and oximes. The process, being a one-pot dehydration, was therefore studied in the context of activation of the carbohydrate C1-hemiacetal function. Early reports by Jurczak et al.[26] focused on the preparation of *N*-glycosylphthalimides from various furanoses and pyranoses employing diethyl azodicarboxylate, triphenylphosphine, and phthalimide as glycosyl acceptor; however, yields were typically low (5–43%). The use of *N*-hydroxyphthalimide as the glycosyl acceptor, on the other hand, led to a dramatic increase in coupling efficiency (e.g., **36**)[27] with both pyranose and furanose donors. The utility of this particular glycosylation was demonstrated in the preparation of a key alkoxyamino glycosyl linker in Nicolaou's synthesis of the oligosaccharide portion of calicheamicin γ.[28] Simple alkyl alcohols are typically poor acceptor substrates for this type of coupling owing to the insufficient acidity of the acceptor component to aid in the formation of the phosphonium salt **34**. To overcome this difficulty, Szarek and coworkers[29] introduced a mercuric halide salt to facilitate the formation of **34**, thereby effecting dehydrative glycosylation of alcohol acceptors (e.g., **37**) with hemiacetal donors. Carboxylic acids are generally good nucleophiles in the Mitsunobu reaction and have also been demonstrated to function as efficient glycosyl acceptors with this protocol. Smith has refined and used this method for glycosyl ester formation[30] as one of the key convergent steps (i.e., **38**) in the synthesis of a (+)-phyllanthoside.[31] Likewise, phenolic nucleophiles have also been shown to be useful acceptors. Early reports involved efficient glycosylations to prepare simple phenyl glycosides[32–34] followed by the preparation of more complex ones such as **39**,[35] an intermediate in Ogawa's total of synthesis of hygromycin A.[36] Roush's preparation of the olivomycin fragment **40**,[37] highlighting the utility of the method in complex molecule synthesis and its tolerance to a wide variety of sensitive functionalities, is of particular interest.

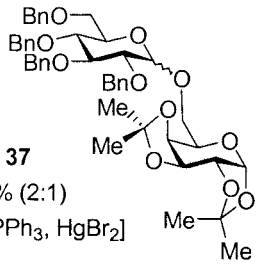
Mukaiyama and coworkers have developed an alternate method for the generation of glycosyl oxophosphonium intermediates. This method is based on Hendrickson's earlier work concerning the development of phosphonium anhydride dehydrating reagents, prepared by the reaction of triphenylphosphine oxide (2 equiv) and triflic anhydride (1 equiv).[38] With the reagent combination of tributyl phosphine oxide (2 equiv) and triflic anhydride (1 equiv), Mukaiyama reported that the resulting diphosphonium salt **41** (Scheme 10)[39] efficiently converted the hemiacetal functionality of



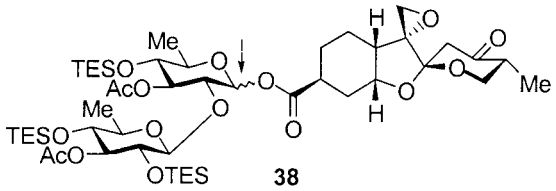
Products and Yields (α:β), (Reagents)



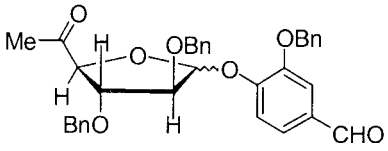
36
76% (1:6)
[DEAD, PPh_3]



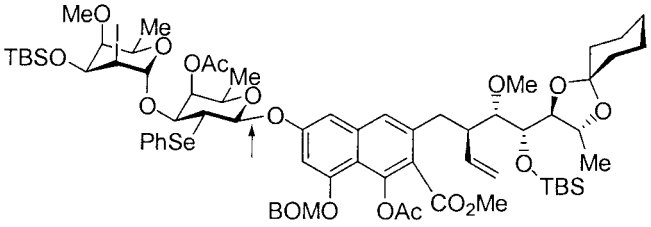
37
80% (2:1)
[DEAD, PPh_3, $HgBr_2$]



38
55% (1:2)
[DIAD, PPh_3]

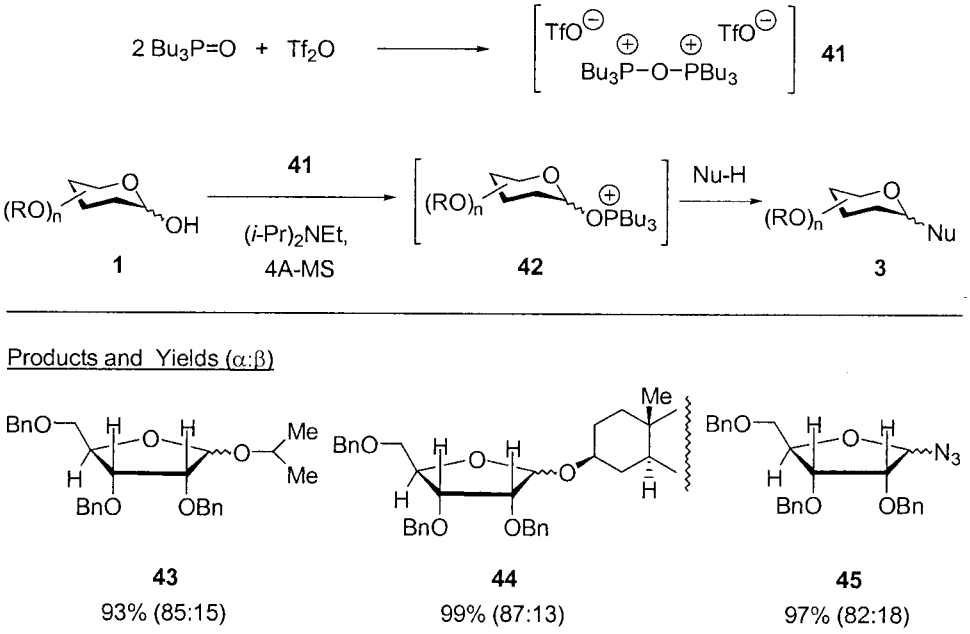


39
77% (4:5)
[DEAD, PPh_3]



40
57% (β)
[DEAD, PPh_3, 4A-MS]

Scheme 9. Dehydrative glycoslations via glycosyl oxophosphonium intermediates.[26–37] DEAD = diethyl azodicarboxylate; DIAD = diisopropyl azodicarboxylate.

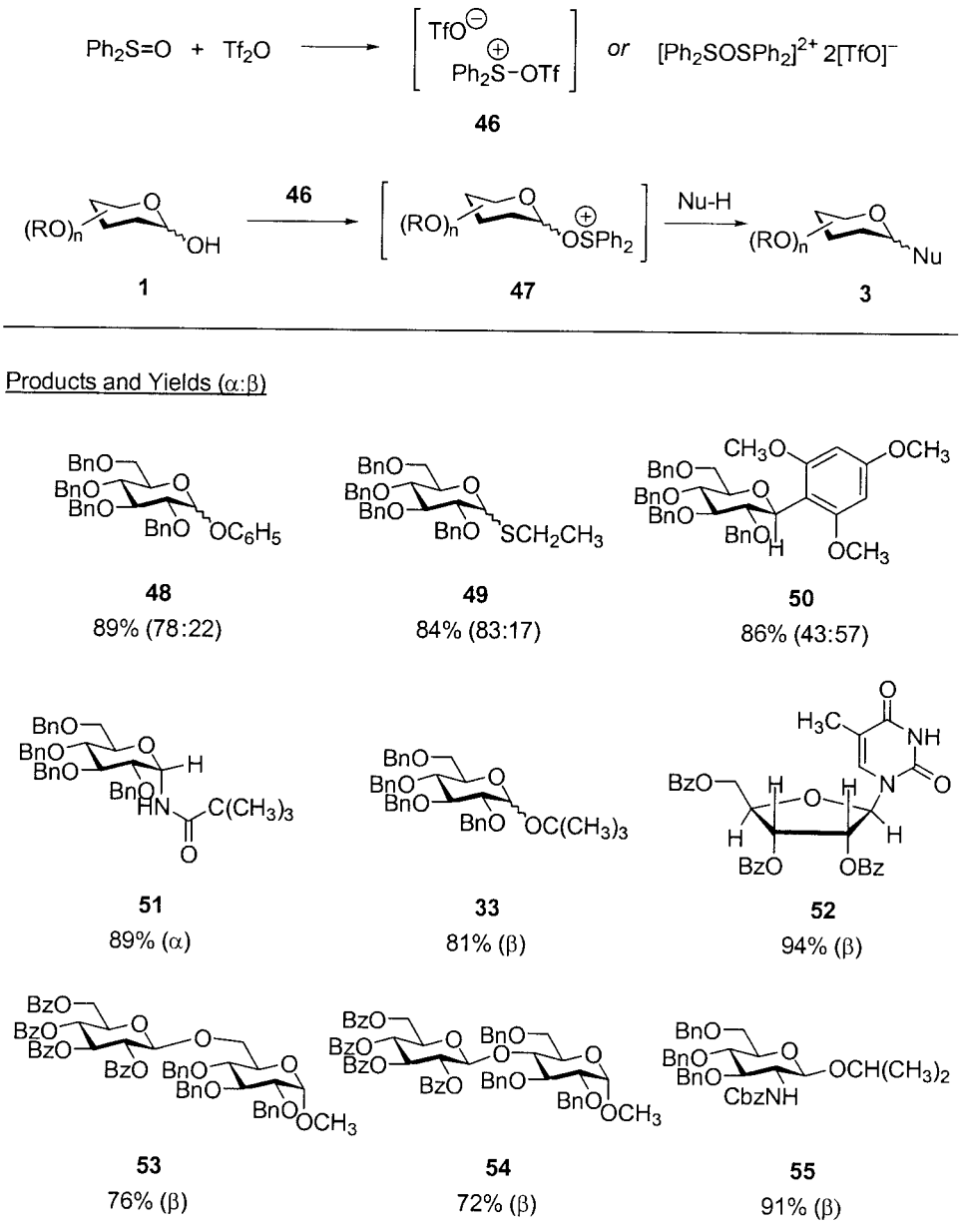


Scheme 10. Dehydrative glycosylations via glycosyl oxophosphonium intermediates.[39]

1-hydroxy carbohydrates to the anomeric oxophosphonium species **42**, an effective glycosylating agent. In the presence of *i*-Pr_2NEt as an acid scavenger, glycosylation of a number of simple alcohols, *O*-TMS-protected alcohol acceptors, and even azide acceptors, can be effected with 2,3,5-tri-*O*-benzyl-D-furanose to afford the product glycosides (e.g., **43**–**45**).

COUPLING VIA GLYCOSYL OXOSULFONIUM INTERMEDIATES

We have developed a new method for dehydrative glycosylation involving the in situ generation of glycosyl oxosulfonium species.[40] The use of reactive dimethylsulfonium reagents for hydroxyl activation has been investigated in depth, primarily in the context of hydroxyl oxidation to form a carbonyl functionality.[41] Similar activation of a carbohydrate hemiacetal should therefore lead to the formation of an anomeric oxosulfonium species such as **47** (Scheme 11), which would likely function as an efficient glycosyl donor. The key challenge is the development of a reaction protocol in which sulfoxide displacement (or dissociation) at the anomeric center of **47** is favored over other possible reaction manifolds such as oxidation or elimination. In our procedure (Scheme 11), initial activation of diphenyl sulfoxide with triflic anhydride presumably generates diphenyl sulfide bis(triflate) **46**. In situ activation of the hemiacetal hydroxyl function in **1** by **46** would afford the oxosulfonium triflate **47**, which then undergoes coupling with the appropriate acceptor to afford the glycosylated product **3**. By employing diphenyl sulfoxide, which does not incorporate protons adjacent to the sulfur center, ylide formation from **47** is precluded, and thus oxidation via intramolecular

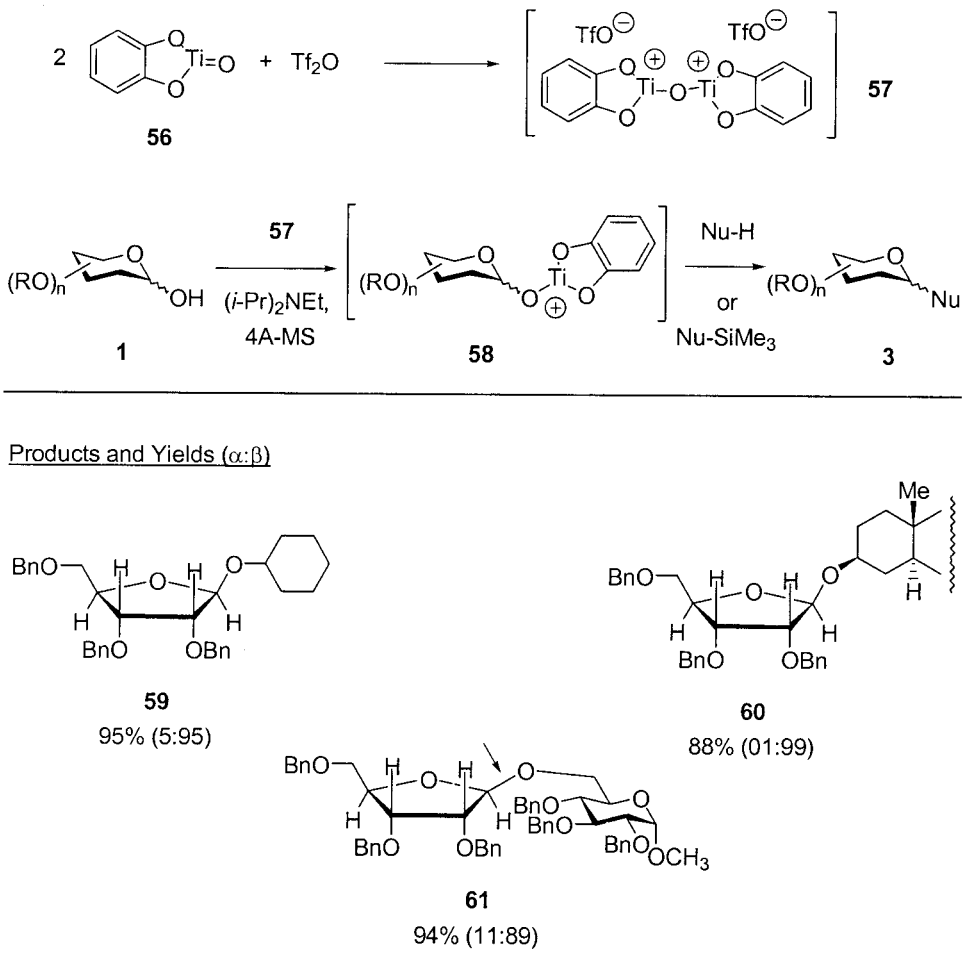


Scheme 11. Dehydrative glycosylations via glycosyl oxosulfonium intermediates.[40]

proton transfer (i.e., Moffatt-Swern oxidation) is avoided. Furthermore, triflic anhydride serves as an ideal reagent for sulfoxide activation in that 1) activation of dimethyl sulfoxide with triflic anhydride to induce nucleophilic attack at sulfur has been reported in a limited number of cases in the contexts of Swern-type oxidations,[42] sulfilimine synthesis,[43] alkene functionalization,[44] and quinone methide generation;[45] and 2) the

anionic by-product of activation, triflate, is a weak nucleophile and thus should not obstruct glycosidic bond formation with the desired acceptor.

The glycosylation method just described was used to couple a variety of acceptors with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose. For example, phenol, ethanethiol, and 1,3,5-trimethoxybenzene underwent efficient glycosylation to yield the corresponding *O*-aryl, *S*-alkyl, and *C*-aryl glycosides in good yield (**48**–**50**). Moreover, the N-glycosylation of amide functionalities, which has been reported to occur with only the most reactive of nonenzymatic glycosylation procedures,[46] was found to proceed smoothly with *N*-(trimethylsilyl)trimethylacetamide to afford **51**. In addition, the glycosylation of tertiary alcohols (e.g., **33**) was shown to be equally efficient when this new method was used. To determine whether C2-neighboring group effects would influence the glycosylation stereochemistry in this procedure, 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranose, a donor incorporating multiple electron-withdrawing protective groups,



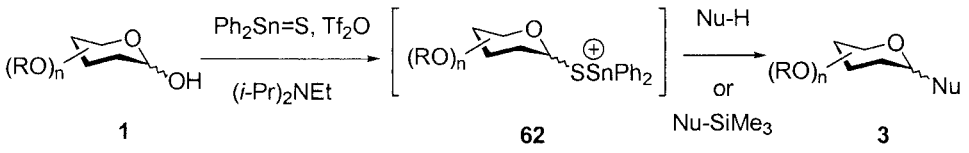
Scheme 12. Dehydrative glycosylations via glycosyl oxotitanium intermediates.[49]

was also employed as a coupling partner. This donor was coupled with carbohydrate acceptors to form the corresponding (1 → 6)- and (1 → 4)-linked disaccharides **53** and **54** with complete β-selectivity. Furanose donors are also compatible with this method, as evidenced by the formation of **52**, the product of dehydrative N-glycosylation of bis(*O*-TMS)-thymine. Finally, the free N-H functionality of a carbamate is compatible under these reaction conditions, allowing access to 2-amino-2-deoxy-glycosides (e.g., **55**) with this protocol.

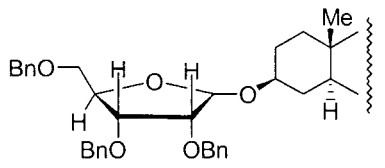
COUPLINGS VIA GLYCOSYL OXOTITANIUM AND THIO-TIN INTERMEDIATES

Glycosyl oxotitanium intermediates were found to be useful in the furanosylation of various glycosyl acceptors. As long ago as 1989, Mukaiyama and coworkers had shown that [1,2-benzenediolato(2-)-*O*,*O*′]-oxotitanium (**56**) is a useful Lewis acid catalyst for aldol[47] and Michael reactions of ketene silyl acetals.[48] Used in combination with triflic anhydride, this Lewis acid was also found to be an effective dehydrating agent (Scheme 12).[49] Treatment of **56** with triflic anhydride presumably leads to the formation of the bis(titanium) salt **57**, which activates a 1-hydroxy glycosyl donor to form the intermediate anomeric oxotitanium species **58**. This intermediate was shown to be an effective glycosyl donor to various alcohol and trimethylsilyl ether nucleophiles (e.g., **59**–**61**).

Mukaiyama et al. also found the use of diphenyltin sulfide and triflic anhydride to be suitable for furanoside formation with C1-hydroxy furanose donors (Scheme 13).[50] Following activation of the hemiacetal with this pair of reagents, a glycosyl acceptor is



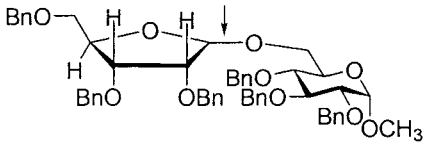
Products and Yields (α:β)



60

95% (1:99) [with Nu-SiMe$_3$]

91% (99:1) [with Nu-H, LiClO$_4$]

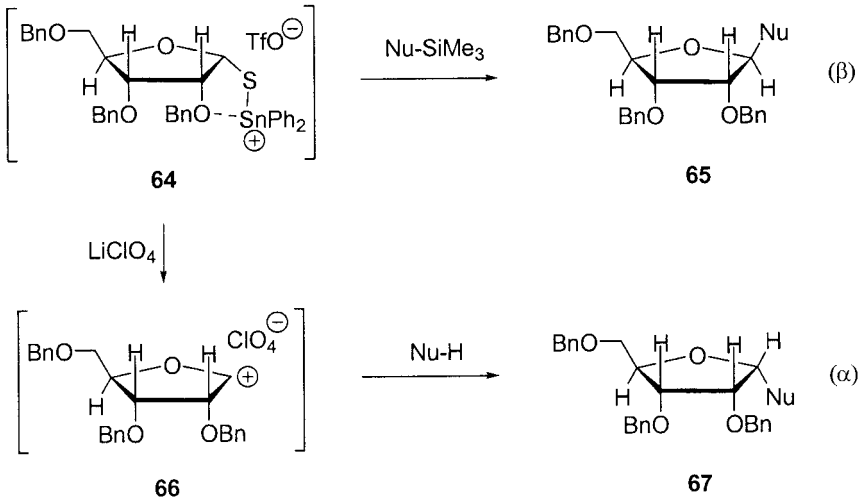


63

98% (10:90) [with Nu-SiMe$_3$]

98% (99:1) [with Nu-H, LiClO$_4$]

Scheme 13. Dehydrative glycosylations via glycosyl thio-tin intermediates.[50,51]

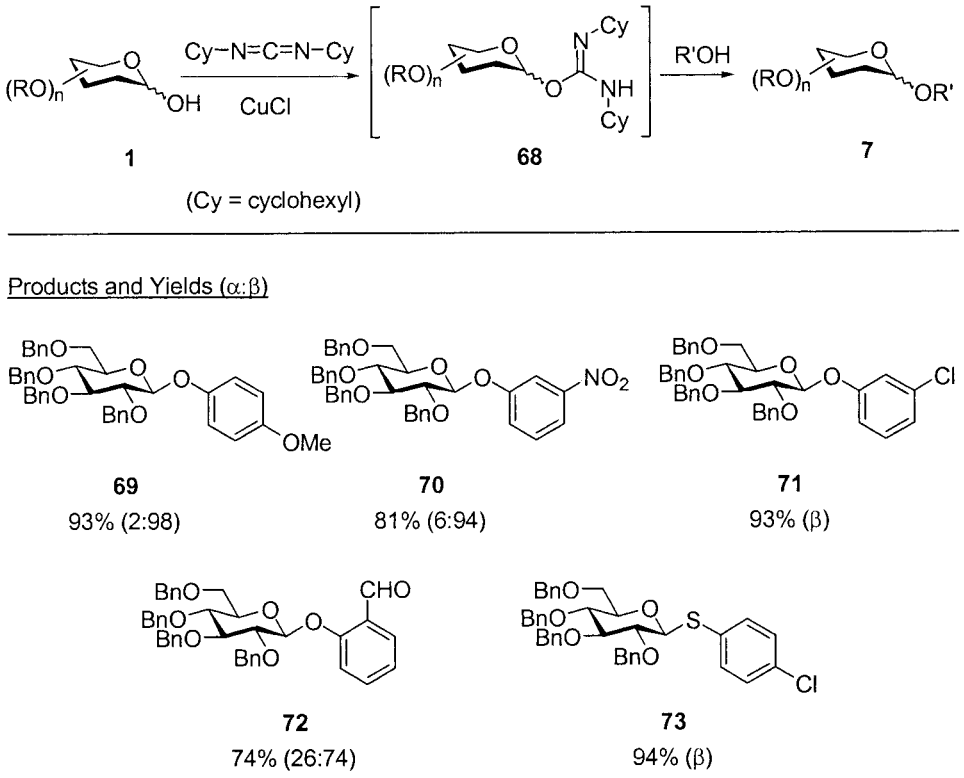


Scheme 14. Perchlorate ion and anomeric selectivity.[50]

introduced, in the form of an alcohol or a TMS-ether, to yield the product glycoside. Excellent anomeric selectivity can be achieved with 2,3,5-tri-*O*-benzyl-D-ribofuranose as the donor (e.g., **60**, **63**), with the selectivity depending on the presence or absence of $LiClO_4$ as an additive. The authors presumed that in the absence of $LiClO_4$, the reactive intermediate **64** (Scheme 14) is generated, whereby the α face is sterically shielded by virtue of coordination of tin(IV) with the C2-oxygen of the donor, leading to near exclusive information of the β adduct **65**. Conversely, the presence of $LiClO_4$ (15 equiv) may serve to convert **64** into the ion pair **66**, in which the perchlorate anion is situated on the β face, trans to the C2 substituent, favoring acceptor approach onto the α face. It is worth noting that the intermediacy of the corresponding C1-*O*-TMS derivative of the 1-hydroxy donor has also been suggested in these coupling reactions when TMS–ether acceptors are employed.[51]

COUPLINGS VIA GLYCOSYL ISOUREA INTERMEDIATES

Carbodiimide reagents have long been known to be effective dehydrating agents in coupling reactions.[52] Tsutsumi et al. have shown that simple carbodiimide reagents are also effective in the context of dehydrative couplings with 1-hydroxy glycosyl donors (Scheme 15).[53] Reactions of alcohols with carbodiimides have been known to occur in the presence of CuCl to form *O*-alkyl isoureas.[54] This transformation was applied to C1-glycosyl hemiacetals **1** with dicyclohexyl carbodiimide to generate the corresponding *O*-glycosyl isourea **68**, which proceeds to glycosylate appropriate acceptors via expulsion of dicyclohexyl urea from the anomeric center. This one-pot procedure was found to be effective at elevated temperatures (80–85°C) with a variety of phenolic nucleophiles (e.g., **69**–**72**) in addition to several thiophenolic nucleophiles (e.g., **73**). The high β-selectivity of the coupling reactions presumably arises from S_N2



Scheme 15. Dehydrative glycosylations via glycosyl isoureas.[53]

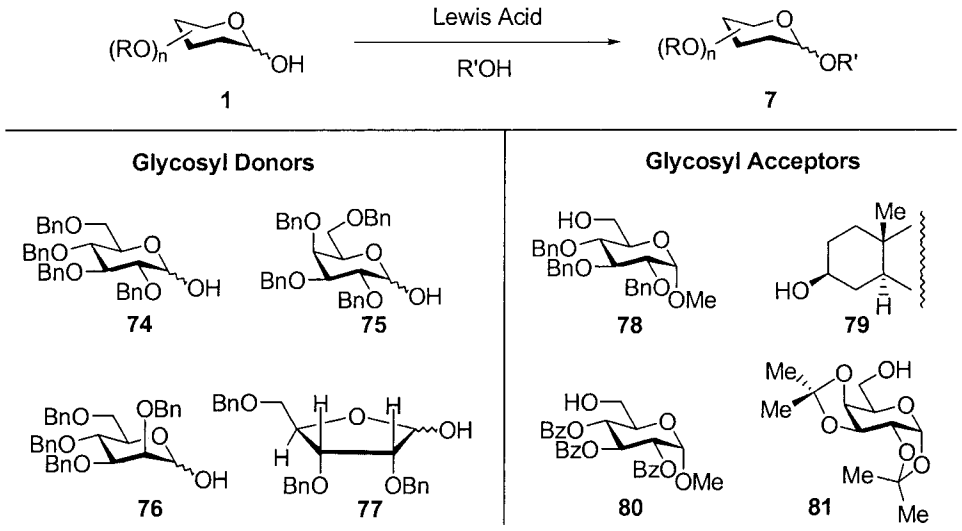
displacement of the corresponding α-glycosyl isourea intermediate, which is generated at elevated temperatures in the activation stage.

COUPLING VIA LEWIS ACID CATALYSIS

Acid catalysis in glycosylations with 1-hydroxy glycosyl donors has traditionally employed the Fischer glycosylation procedure or variants thereof in which simple glycosyl acceptors are employed in vast excess. Within the last several years, a series of dehydrative glycosylations using Lewis acid catalysts in the presence of a desiccant has been reported, employing equimolar or only slight excesses of various nucleophilic acceptors (Scheme 16, Table 1).

Inanaga and coworkers reported the use of the catalyst combination of $Yb(OTf)_3$ and methoxyacetic acid (0.1 equiv of each) employing only 1.2 equiv of the glycosyl acceptor (Table 1, entries 1–3).[55] Anomeric mixtures were obtained with pyranose donors, while the ribofuranose donor **77** afforded high β-selectivities. The authors found that simple thiols also are effective acceptors in this coupling method, and, in the presence of 4 Å molecular sieves, the glycoside yields were uniformly high.

The work of Susaki established that $Zn(OTf)_2$ can be employed in dehydrative glycosylation.[56] The combination of $Zn(OTf)_2$ and TMSCl was found to be useful for



Scheme 16. Dehydrative glycosylations via Lewis acid catalysis: Selected coupling partners.[55–60]

glycosidic bond formation with both glycosyl ester donors, as well as 1-hydroxy carbohydrate donors (entries 4–6). In these couplings, the ratio of donor to acceptor to TMSCl to $Zn(OTf)_2$ is 1:2:1.5:0:3, with either acetonitrile or CH_2Cl_2 as the reaction solvent. Benzylated gluco-, galacto-, and mannopyranose donors generally afforded good yields of alkyl glycosides with anomeric selectivities that vary with the nature of the coupling substrates. It is worth noting that couplings were significantly less efficient when an excess (1.5 equiv) of $Zn(OTf)_2$ was employed.

In a variety of the Lewis acid catalysts also surveyed by Mukaiyama and coworkers, benzylated furanose and pyranose substrates were found to be effective donors.[57,58] With the catalyst combination of the $Sn(OTf)_2$ (0.01 equiv) and TMS_2O (0.1 equiv) in the presence of anhydrous calcium sulfate, 2,3,5-tri-*O*-benzyl-D-furanose **77** can be used to directly glycosylate the alcohols **78** and **79** with high β-stereoselectivity (Table 1, entries 7, 8). The couplings are presumed to proceed via the TMS ether derivatives of the coupling partners, which are generated in situ, and the high β-selectivity is likely a result of product formation under thermodynamic control. In the presence of $LiClO_4$ (1.5 equiv) as an additive, however, a dramatic reversal of the anomeric selectivity is observed, likely owing to the formation of the oxocarbenium perchlorate **66** (Scheme 14) as the active glycosylating agent (entries 9, 10). Various other glycosyl acceptors in addition to those in Table 1 were shown to be compatible with the $Sn(OTf)_2/TMS_2O$ method, including C-nucleophiles such as 1,3,5-trimethoxybenzene and *O*-silyl ketene acetals. Although the $Sn(OTf)_2/TMS_2O$ Lewis acid system is highlighted in Table 1, Mukaiyama has also demonstrated that other Lewis acid catalyst systems can be used, such as those incorporating $Yb(OTf)_3$, $La(OTf)_3$, and $SnCl_2$, leading to comparable coupling efficiencies and stereoselectivities.

In addition to metallic Lewis acid catalysts, it has been demonstrated that trityl salts can be used for the efficient ribofuranosylation of alcohols.[59] With **77** as the donor and 3 mol% of $[Ph_3C]^+$ $[B(C_6F_5)_4]^-$ catalyst in thepresence of anhydrous $CaSO_4$, high yields of various furanosides were obtained with only 1.3 equiv of the

Table 1. Dehydrative Glycosylations via Lewis Acid Catalysis

Entry	Coupling Partners	Catalyst(s)	Reagents	Yield (%) (α:β)	Ref.
1	**77** + **78**	$Yb(OTf)_3$, $MeOCH_2CO_2H$	4A-MS, CH_2Cl_2 (reflux)	92 (0:100)	[55]
2	**77** + **79**	$Yb(OTf)_3$, $MeOCH_2CO_2H$	4A-MS, CH_2Cl_2 (reflux)	98 (04:96)	[55]
3	**74** + **81**	$Yb(OTf)_3$, $MeOCH_2CO_2H$	$Cl(CH_2)_2Cl$ (53°C)	85 (48:52)	[55]
4	**74** + **78**	$Zn(OTf)_2$	TMSCl (1.5 equiv), CH_3CN (23°C)	76 (55:45)	[56]
5	**75** + **79**	$Zn(OTf)_2$	TMSCl (1.5 equiv), CH_2Cl_2 (23°C)	61 (62:38)	[56]
6	**76** + **79**	$Zn(OTf)_2$	TMSCl (1.5 equiv), CH_2Cl_2 (23°C)	43 (88:12)	[56]
7	**77** + **78**	$Sn(OTf)_2$, $(TMS)_2O$	Drierite, $MeNO_2$ (23°C)	97 (05:95)	[57]
8	**77** + **79**	$Sn(OTf)_2$, $(TMS)_2O$	Drierite, $MeNO_2$ (23°C)	97 (05:95)	[57]
9	**77** + **78**	$Sn(OTf)_2$, $(TMS)_2O$	Drierite, $LiClO_4$ (1.5 equiv), $MeNO_2$ (23°C)	96 (94:06)	[57]
10	**75** + **80**	$Sn(OTf)_2$ TMSCl	Drierite, $LiClO_4$ (3.5 equiv), PhH (23°C)	86 (96:04)	[58]
11	**77** + **78**	$[Ph_3C]^+$ $[B(C_6F_5)_4]^-$	Drierite, $EtNO_2$ (0°C)	90 (09:91)	[59]
12	**77** + **80**	$[Ph_3C]^+$ $[B(C_6F_5)_4]^-$	Drierite, $EtNO_2$ (0°C)	92 (04:96)	[59]
13	**77** + **78**	$Ph_2Sn{=}S$, $AgClO_4$	PhH, 3A-MS (23°C)	89 (13:87)	[60]
14	**77** + **79**	$Ph_2Sn{=}S$, $AgClO_4$	PhH, 3A-MS (23°C)	90 (04:96)	[60]
15	**77** + **78**	Lawesson's reagent, $AgClO_4$	$PhCH_3$, 3A-MS (23°C)	79 (24:76)	[60]
16	**77** + **79**	Lawesson's reagent, $AgClO_4$	$PhCH_3$, 3A-MS (23°C)	90 (04:96)	[60]

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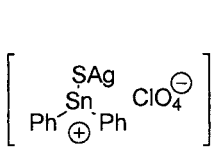
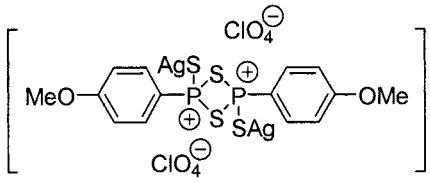
alcohol acceptors, affording high selectivity for the thermodynamic β isomer (entries 11, 12). In these studies, other counterions for the trityl cation were investigated in Mukaiyama's survey of catalysts, including BF_4^-, ClO_4^-, and $SbCl_6^-$, but $[Ph_3C]^+[B(C_6F_5)_4]^-$ was found to be the most efficient in terms of yield, anomeric selectivity, and ease of catalyst handling.

Two-component dehydrative catalysts have also been reported by Mukaiyama and coworkers for ribofuranosylation of alcohols. One such system is based on an earlier report by these investigators of the $Ph_2Sn{=}S/Tf_2O$ reagent combination for dehydrative coupling. When a catalytic amount of $Ph_2Sn{=}S$ in combination with $AgClO_4$ (0.2 equiv each)[60] were employed in the coupling of **77** with alkyl alcohols (1.2 equiv), good yields were obtained favoring the β anomer of the product furanosides (entries 13, 14). The presumed active catalytic agent in the reaction is the Sn(IV) species **82**. In like manner, the two-component catalyst system of Lawesson's reagent and $AgClO_4$ (0.2 equiv each) was found to be effective for coupling transformations (entires 15, 16), where the phosphonium species **83** is believed to be the active catalyst.



82



83

CONCLUSION

The importance of the development of new glycosylation methods cannot be disputed. Although many new variants of the traditional glycosylation processes have been developed over the years, comparatively fewer methods have been developed for direct dehydrative coupling with 1-hydroxy donors. The methods summarized in this chapter address many of the inherent obstacles associated with this strategy. For example, with the appropriate dehydrating agent in the glycosylation, the formation of the undesired by-products of hemiacetal self-condensation can be minimized, even when only a slight excess of the glycosyl acceptor component is employed in the coupling. Further development of these and other dehydrative coupling strategies will certainly establish this to be an efficient approach for the controlled assembly of complex carbohydrates.

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