Glycosylation

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Dimethylformamide: An Unusual Glycosylation Modulator**

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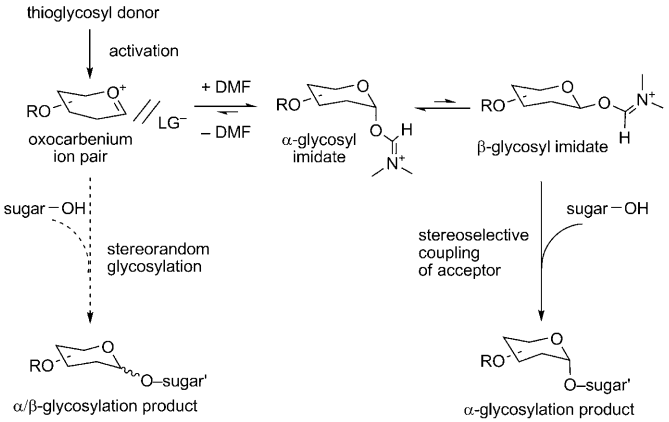
Dedicated to Professor Chi-Huey Wong

The key steps in oligosaccharide synthesis are protecting-group manipulation and stereoselective glycosylation.[1] Various strategies have emerged to expedite glycosylation, and some of these strategies have been elaborated for automated solid-phase synthesis[2] and one-pot cascade glycosylation.[3] Most glycosylation strategies rely on traditional methods for stereochemical control over glycosidic-bond formation. Although such tactics work well for the formation of 1,2-*trans* β-glycosidic bonds,[4] there is no straightforward solution for the formation of a 1,2-*cis* α-glycosidic bond.[1a,5] Existing methods often require extensive optimization of the reaction conditions, including the selection of an ethereal solvent,[6] a transition-metal-complex promoting system,[7] a remote participating group,[8] a silylidene protecting group,[9] and a chiral or achiral accessory group at the C2 position,[10–13] or the installation of a fluoride substituent at the C2 position.[14] However, most of these methods require additional steps for the installation of a specific functionality and are therefore less convenient for routine synthesis. Herein, we report a simple and general α-glycosylation method in which *N*,*N*-dimethylformamide (DMF) is used as a modulating molecule to direct the stereochemical course of glycosylation. Further elaboration of this approach led to a practical α-selective procedure based on preactivation that is useful for the glycosylaton of both O-glycoside and thioglycoside acceptors.

In a previous study of the chlorination of glycosyl hemiacetals, we observed that residual DMF in the glycosylation mixture promoted the formation of 1,2-*cis* α-glycosidic bonds.[15] A search of the literature revealed that DMF has been utilized as a glycosylation solvent[16] and as a component in the Vilsmeier–Haack reaction for glycosylations.[17] Koto et al. reported the use of DMF as an additive to effect α-glycosylation; however, this protocol suffered from undesired glycosyl formate formation.[17d] Lemieux and Driguez employed DMF (20–30 vol%) as one component of a mixed solvent system in particular glycosylations; however, such reactions required 4 days to reach completion, and the role of DMF was not stated.[18] We hypothesized that the activation of a thioglycoside generates an oxocarbenium ion pair, which upon trapping by nucleophilic DMF gives rise to an equilibrium mixture of α-/β-glycosyl imidates. Assuming that the β imidate is more reactive than its α counterpart; subsequent coupling of the β imidate with an acceptor produces the desired α anomer as the major product (Scheme 1). Since DMF has a modulating function in the reaction, we coined the term DMF-modulated glycosylation strategy for this approach.



Scheme 1. Proposed mechanism of the DMF-modulated glycosylation.

Initially, we examined two DMF-modulated procedures (Scheme 2a,b). In procedure A, adapted from a standard glycosylation protocol, a mixture of a thioglycosyl donor, a glycosyl acceptor, and DMF is treated with *N*-iodosuccinimide (NIS) and trimethylsilyl triflate (TMSOTf) (Scheme 2a).[19] In procedure B, the thioglycosyl donor is first preactivated with NIS and TMSOTf in the presence of DMF. Following activation, the glycosyl acceptor is added and reacts with the glycosyl imidate to furnish the desired glycosylation product (Scheme 2b).

At the outset, we followed procedure A to couple the commercially available galactosyl acceptor **3** with the perbenzyl thiogalactoside **1**.[20] After some experimentation, we found that one molar equivalent of TMSOTf (with respect to the glycosyl donor) was required for effective activation of the donor, probably owing to the mild Lewis basicity of DMF. DMF exhibited an α-directing effect in glycosylation reactions: a result which is in line with our previous findings.[15] We observed a quantity–selectivity dependence between the stoichiometric amount of DMF added and the degree of glycosylation selectivity. Explicitly, when the amount of DMF was increased from 0 to 1.5 equivalents, the α/β-anomer ratio of the glycosylation product **4** increased from 1:1 to 3:1

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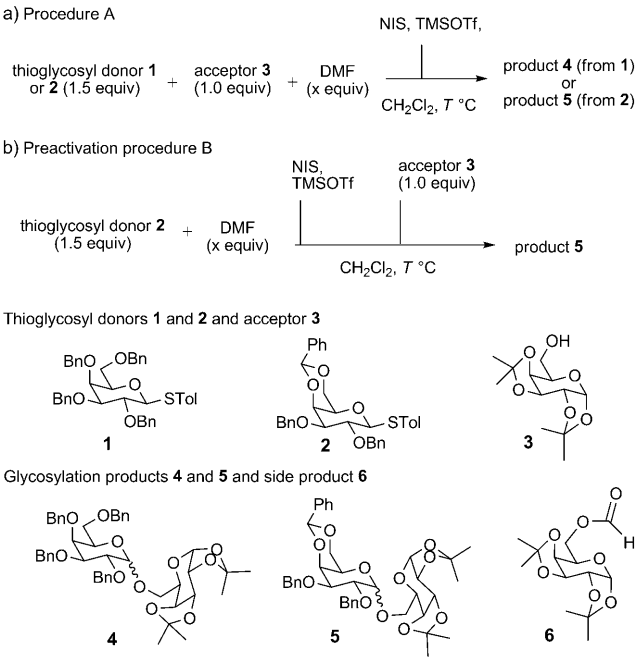


Scheme 2. a) First DMF-modulated glycosylation procedure (procedure A). b) Second DMF-modulated glycosylation procedure (procedure B). Bn = benzyl, Tol = *p*-tolyl.

(Table 1, entries 1–4). However, such moderate selectivity remains inadequate for synthetic utility; a further increase in the amount of DMF added (> 1.5 equiv) did not improve the selectivity owing to the formation of a formyl-transfer product **6**.[17d] We reasoned that the arming benzyl groups of donor **1** may promote the departure of DMF from the glycosyl imidate; consequently, the α-directing effect of DMF was attenuated.[21] Therefore, a conformationally restrained benzylidene thiogalactoside **2** was used in place of **1**.[20] However, the replacement of the donor alone did not bring about significant improvement: glycosylation product **5** was obtained with a 6:1 α/β-anomer ratio (Table 1, entry 5). Nevertheless, when the preactivation procedure B was adopted in conjunction with an increase in the amount of DMF added (from 1.5 to 6.0 equivalents), the α/β-anomer ratio of **5** was increased to 19:1 (Table 1, entries 6–8). To investigate whether an ethereal solvent could reproduce the α-directing effect, as implicated in previous studies,[6a] we repeated the glycosylation of **3** with **2** in pure THF, CH_2Cl_2/Et_2O (1:3), and toluene/dioxane (1:2) by procedure A, as procedure B does not work in the absence of DMF.[22] No significant selectivity was observed in these glycosylation reactions, irrespective of the type of ethereal solvent used (Table 1, entries 9–12). In the past, dimethylacetamide (DMA) has been used as an additive to promote α selectivity in glycosylation reactions.[17d] We were curious whether DMA could replace DMF in our procedure and repeated the glycosylation of **3** with **2** according to procedure B with the addition of DMA; however, the observed selectivity was not attractive (Table 1, entry 13).

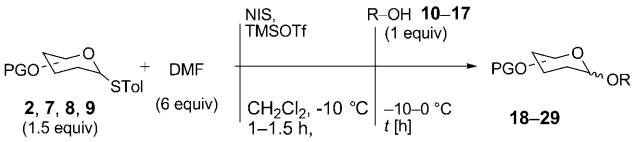
After confirming the effectiveness of the preactivation glycosylation procedure B, we next investigated its scope of application. Thus, aglycone acceptors **10**–**13** and O-glycoside acceptors **14**–**17** were coupled with thioglycosyl donors **2**, **7**, **8**, and **9** (Scheme 3, Table 2).[23] For comparison, these glycosylation reactions were performed with and without the addition of DMF. Generally, reaction rates were lower in the presence of DMF than in its absence; nonetheless, the time required for the completion of DMF-modulated glycosylation remained acceptable (2–6 h). Regarding stereochemical control, DMF exerted a powerful α-directing effect on all glycosylations. In some cases, the selectivity was reversed dramatically by the addition of DMF (Table 2, entries 2, 4, 5,

Table 1: Investigation of DMF-modulated glycosylation procedures A and B with galactosyl acceptor **3**.

Entry	Donor (equiv)	DMF [equiv]	*T* [°C]	*T* [h]	Product, yield [%], α/β[a]
1	**1** (1.2)[b]	0	−25	0.5	**4**, 90, 1:1
2	**1** (1.2)[b]	0.8	−10	1.0	**4**, 70, 3:2
3	**1** (1.2)[b]	0.8	0	1.0	**4**, 77, 3:2
4	**1** (1.2)[b]	1.5	0	1.0	**4**, 80, 3:1
5	**2** (1.5)[b]	1.5	−10	2.0	**5**, 82, 6:1
6	**2** (1.5)[c]	1.5	−10	2.0	**5**, 80, 8:1
7	**2** (1.5)[c]	3.0	−10	2.0	**5**, 87, 15:1
8	**2** (1.5)[c]	6.0	−10	2.0	**5**, 87, 19:1
9	**2** (1.5)[b]	0[d]	−10	0.3	**5**, 90, 1:1
10	**2** (1.5)[b]	0[e]	−10	0.2	**5**, 85, 1.5:1
11	**2** (1.5)[b]	0[f]	−10	0.5	**5**, 83, 1:1.5
12	**2** (1.5)[b]	0[f]	0	4.0	**5**, 40, 1:1.5
13	**2** (1.5)[c]	–[g]	−10	3.0	**5**, 80, 4:1

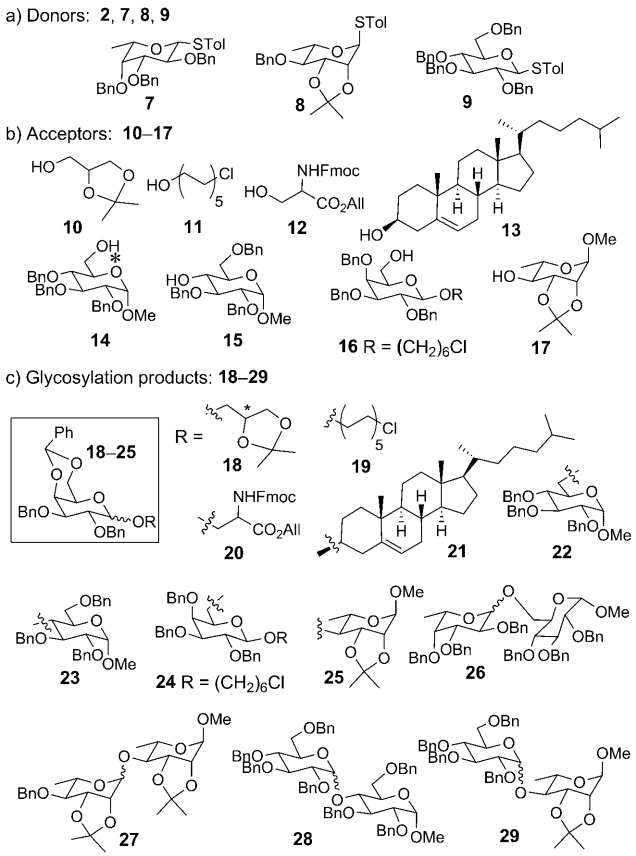
[a] The α/β ratio was determined by HPLC (conditions given in the Supporting Information). [b] Procedure A was used. [c] Procedure B was applied. [d] A 1:3 CH_2Cl_2/Et_2O mixture was used as the solvent. [e] THF was used as the solvent. [f] A 1:2 toluene/dioxane mixture was used as the solvent. [g] DMA (6 equiv) was added.[17d]

Table 2: Glycosylation of acceptors **10**–**17** by glycosylation procedure B.



Entry	D[a]	A[a]	*T* [°C]	*t* [h]	Product	Yield [%], α/β[b] with DMF	without DMF[c]
1	**2**	**10**	−10	2	**18**	83, 12:1	80, 1:1
2	**2**	**11**	−10	2	**19**	76, 8:1	85, 2:5
3	**2**	**12**	−10	6	**20**	45, 19:1	50, 15:1
4	**2**	**13**	0	2	**21**	79, 8:1	73, 2:5
5	**2**	**14**	−10	5.5	**22**	75, 12:1	80, 2:3
6	**2**	**15**	0	6	**23**	80, 49:1	50, 2:1
7	**2**	**16**	−10	2	**24**	82, 12:1	80, 3:2
8	**2**	**17**	0	4	**25**	60, 25:1	63, 5:1
9	**7**	**14**	−10	4.5	**26**	75, 5:1	77, 1:1
10	**8**	**17**	−10	4	**27**	70, 49:1	80, 5:1
11	**9**	**15**	0	6	**28**[d]	76, 49:1	60, 2:3
12	**9**	**17**	0	5	**29**[d]	75, 9:1	70, 2:5

[a] D is the donor; A is the acceptor. [b] The α/β-anomer ratio was determined by HPLC (settings are given in the Supporting Information). [c] A routine glycosylation (without the addition of DMF) was carried out. [d] The glycosylation was performed with ultrasonification.[24] PG = protecting group.

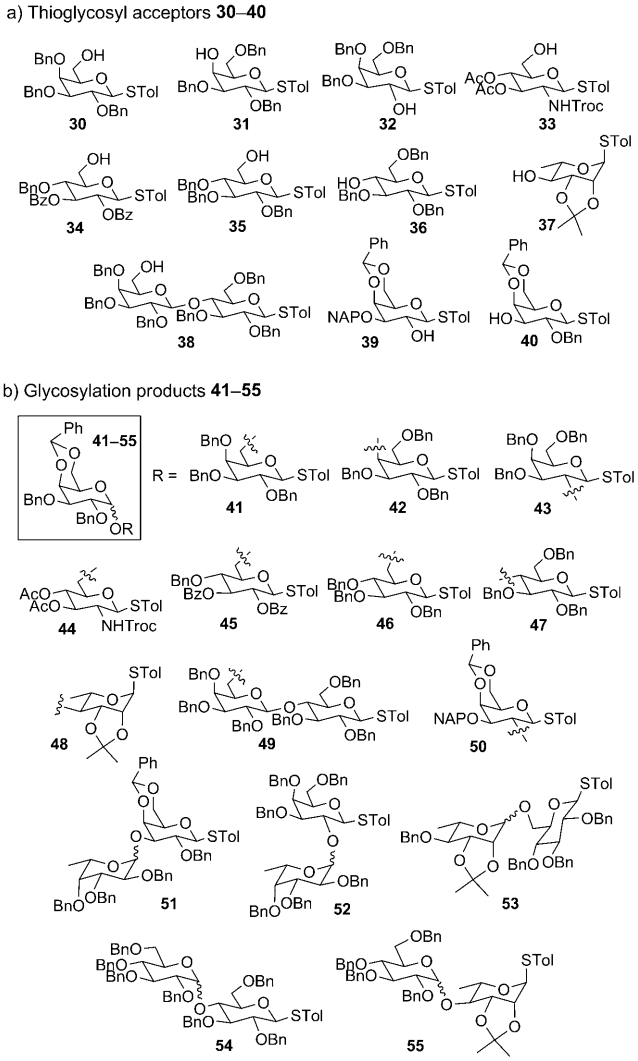


Scheme 3. Structures of a) thioglycosyl donors **7**–**9**; b) acceptors **10**–**17**; c) glycosylation products **18**–**29**. All = allyl, Fmoc = 9-fluorenylmethoxycarbonyl.

11, and 12). More importantly, this effect was not restricted to galactosyl donors, but also occurred with L-thiofucoside **7**, L-thiorhamnoside **8**, and D-thioglucoside **9** (Table 2, entries 9–12). However, the stereoelectronic features of a particular donor does affect the reaction efficiency. Therefore, some optimization of the reaction conditions is required. For example, the glycosylations of **15** and **17** with thioglucoside donor **9** were conducted with ultrasound irradiation to shorten the reaction time (Table 2, entries 11 and 12).[24]

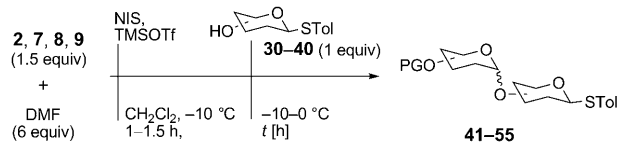
A unique feature of the DMF-modulated glycosylation is the entrapment of oxocarbenium ions as glycosyl imidates. This feature provides an opportunity for the development of a new glycosylation procedure with preactivation. In a typical oligosaccharide synthesis, the introduction of different anomeric functional groups in the glycosyl donor and acceptor is required so that the activation of the former does not affect the later. Although the reactivities of the glycosyl donor and acceptor can also be tuned to create reactivity disparity that enables their coupling by reactivity-based glycosylation, this strategy requires extensive protecting-group manipulation for building-block preparation.[3,21a,25] The merit of a glycosylation involving preactivation is that it enables the coupling of glycosyl substrates with the same anomeric functionality and thus renders the use of different anomeric functionalities or the tuning of chemical reactivity unnecessary. Such an approach not only shortens the synthetic route in oligosaccharide synthesis, but it also paves the way to an iterative one-pot glycosylation method.[3] To the best of our knowledge, there is no previously reported preactivation procedure that causes an α-directing effect.[26] To demonstrate the applicability of the DMF-modulated procedure, thioglycoside acceptors **30**–**40** were glycosylated with thioglycoside donors **2**, **7**, **8**, and **9** according to procedure B (Scheme 4).[27] Table 3 summarizes the yields and α/β-anomer ratios of the corresponding glycosylation products **41**–**55**.

A known side reaction in glycosylations of thioglycosides is the transfer of the thioacetal functionality from the acceptor to the donor.[28] Gratifyingly, such a transfer reaction did not occur in the DMF-modulated procedure, perhaps as a result of masking of the reactive oxocarbenium ion by a DMF molecule. The glycosylations in this study proceeded smoothly, and the corresponding α anomers were furnished in 45–85 % yield with high to excellent α selectivity. However, the reaction yields were on average lower than those observed for the glycosylation of O-glycosides. We attributed the lower



Scheme 4. Structures of a) thioglycosyl acceptors **30**–**40**; b) glycosylation products **41**–**55**. Bz = benzoyl, NAP = 2-naphthylmethyl, Troc = trichloroethoxycarbonyl.

Table 3: Glycosylation of thioglycosyl acceptors **30–40** by glycosylation procedure B.



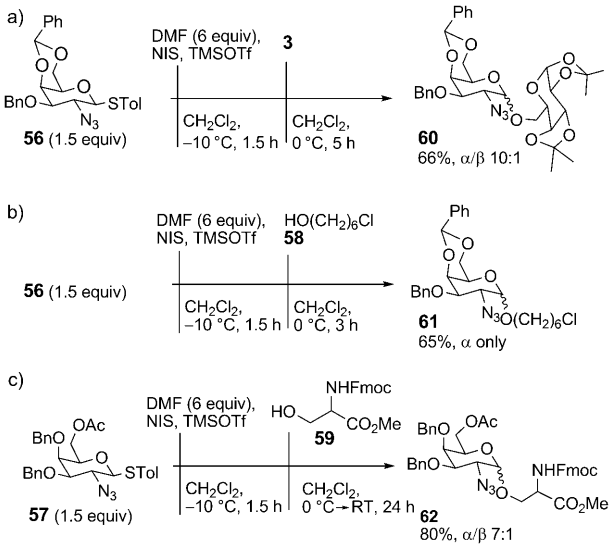
Entry	Donor	Acceptor	T [°C]	t [h]	α anomer (yield [%]),[a] α/β[b]
1	**2**	**30**	−10	3	**41** (60), 36:1
2	**2**	**31**	0	6	**42** (55), 6:1
3	**2**	**32**	0	3	**43** (55), 11:1
4	**2**	**33**	−10	3	**44** (45), 11:1
5	**2**	**34**	−10	3	**45** (85), 49:1
6	**2**	**35**	−10	2	**46** (65), 12:1
7	**2**	**36**	0	4	**47** (70), 49:1[29]
8	**2**	**37**	0	2	**48** (50), 13:1
9	**2**	**38**	−10	3	**49** (75), 19:1
10	**2**	**39**	0	4	**50** (85), 49:1
11	**7**	**40**	−10	3	**51** (56), 49:1
12	**7**	**32**	−10	6	**52** (61), 49:1
13	**8**	**35**	−10	3	**53** (55), 6:1
14	**9**	**36**	0	5	**54** (50), 49:1[c]
15	**9**	**37**	0	3	**55** (55), 8:1[c]

[a] The yield of the isolated α anomer is given. [b] The α/β ratio of the glycosylation product was determined by HPLC analysis (HPLC conditions are given in the Supporting Information). [c] The glycosylation was performed with ultrasonification.[24]

yields to the activation of the thioglycoside product by residual NIS and/or side reactions stemming from the imidate intermediates. To revalidate the α-directing effect of DMF, the glycosylation of **36** with **2** was repeated with a smaller amount of DMF (1.5 equiv); under these conditions, the α/β-anomer ratio of glycosylation product **47** decreased sharply to 4:1 (results not shown).[29]

Encouraged by the aforementioned results, we extended the applicability of the DMF-modulated glycosylation to 2-amino-2-deoxyglycosyl donors. Thus, 2-azido-2-deoxythiogalactosides **56** and **57** were coupled with acceptors **3**, **58**, and **59** by glycosylation procedure B (Scheme 5).[30] The α-directing effect of DMF was observed in all reactions examined, but the reaction time was generally longer than that required for non-amino glycosyl donors. The glycosylation of serine acceptor **59** with **57** was repeated in the absence of DMF, under which conditions **62** was produced with a 1:1 α/β-anomer ratio (results not shown). This comparison distinguishes the intrinsic selectivity of the serine acceptor from the α-directing effect of DMF. However, glycosylation with 2-azido-2-deoxythioglucosides has not met with success so far; further optimization of the reaction conditions is required.

Since the formation of a glycosyl imidate is the key step in DMF-modulated glycosylation, the detection of the glycosyl imidate is crucial for validation of the proposed mechanism (see Scheme 1). In this regard, we prepared a simpler 4,6-*O*-benzylidene-2,3-di-*O*-methylthiogalactoside **63**, which was activated with NIS and TMSOTf in $CDCl_3$ and then used for the glycosylation of acceptor **58** by procedure B (Figure 1 a).[31] ^{1}H, ^{13}C, and HSQC NMR spectroscopy of the reaction mixture was carried out at 0, 90, and 180 min time points. Figure 1 b–d shows selected regions of the corresponding ^{1}H NMR spectra. Comparison of the spectra of the preactivated reaction mixture at 0 min and the TMSOTf-activated mixture at 90 min (Figure 1 b,c) showed the appearance of a new set of clearly identifiable ^{1}H NMR signals, including those for an anomeric proton at $\delta = 6.39$ ppm ($^3J =$ 3 Hz, **64**-H^a), a benzylidene proton at $\delta = 5.60$ ppm (**64**-H^b), an imidoyl proton at $\delta = 8.90$ ppm (**64**-H^c), and *N*,*N*-dimethyl protons at $\delta = 3.40$ and 3.32 ppm (**64**-H^d). These signals are presumably generated from the α-glycosyl imidate **64**.[16a,b,31,32] The relative downfield positions of **64**-H^{a,c,d} indicate the close proximity of these hydrogen atoms to an electron-deficient center. Following the addition of acceptor **58**, the signals stemming from imidate **64** vanished, and another two sets of signals emerged. One set includes the signals for an anomeric proton at $\delta = 5.13$ ppm ($^3J = 3$ Hz, **65**-H^a) and a benzylidene proton at $\delta = 5.59$ ppm (**65**-H^b); these signals correspond to the expected α-glycoside **65**. Another set (indicated by asterisks in Figure 1 d) originated from an α-*N*-galactosyl succinimide: a common side product in NIS-promoted glycosylation reactions.[25]



Scheme 5. Glycosylation of acceptors **3**, **58**, and **59** with 2-azido-2-deoxythiogalactosides **56** and **57** by glycosylation procedure B.

As the real-time NMR spectroscopic study provided evidence for the presence of the α-glycosyl imidate, it is reasonable to propose the formation of α-/β-glycosyl imidates in DMF-modulated glycosylations. The β-glycosyl imidate, owing to its more reactive nature, reacts preferentially with the acceptor to give the α-glycosylation product. Until now, we have not been able to detect the presence of the β imidate; therefore, it is too early to exclude the possibility of the other mechanism outlined in Scheme 1.[33,34] Further experimental investigations toward the elucidation of the reaction mechanism are in progress.

In summary, we have described a new DMF-modulated glycosylation strategy which enables excellent α selectivity in glycosylation reactions through the simple addition of DMF. Further elaboration led to the development of a useful α-selective glcyosylation procedure involving preactivation. Considering the availability of DMF, we anticipate that the

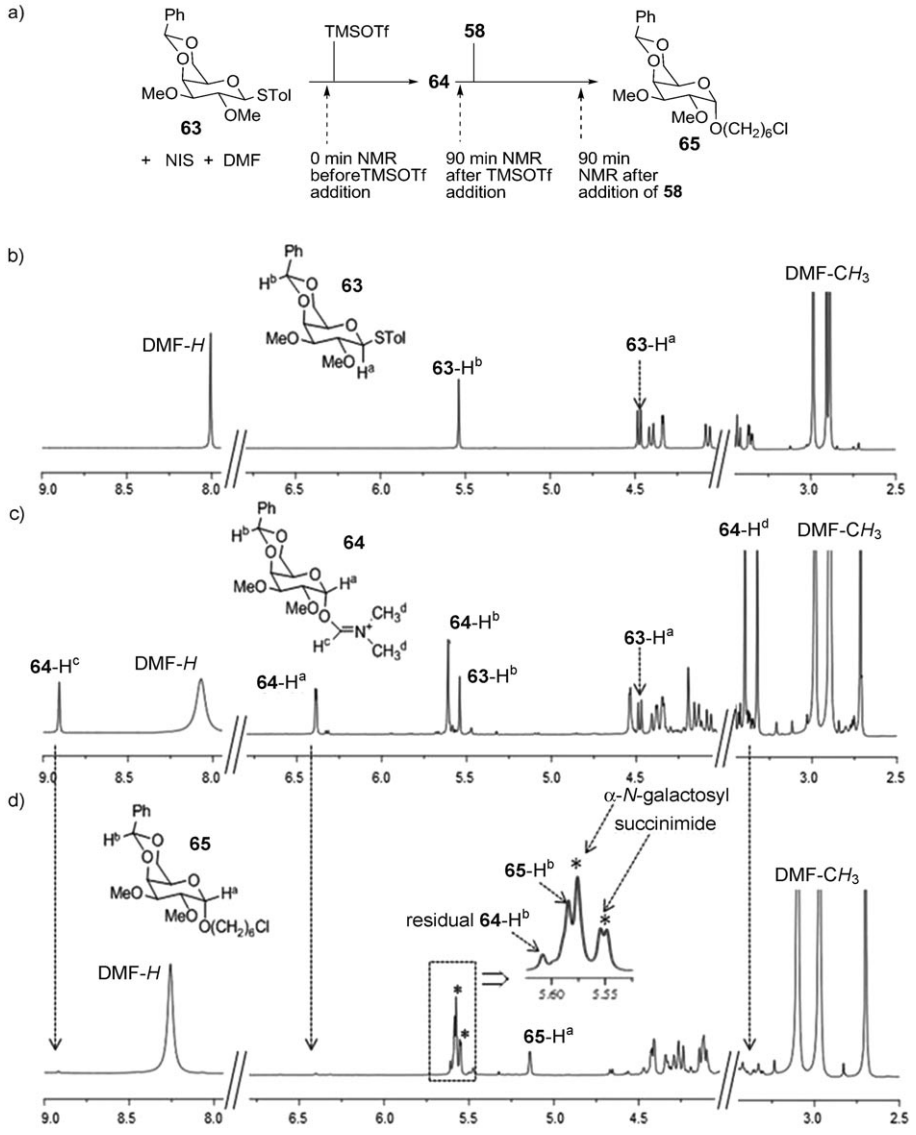


Figure 1. a) Glycosylation of **63** with **58** by procedure B. b) ^{1}H NMR spectrum recorded just prior to the addition of TMSOTf (0 min). c) ^{1}H NMR spectrum recorded 90 min after the addition of TMSOTf (90 min). d) ^{1}H NMR spectrum recorded 90 min after the addition of **58**.

synthetic concept described herein will find broad application in oligosaccharide synthesis.

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[23] The preparation of and/or references to aglycone acceptors **10**–**13**, O-glycoside acceptors **14**–**17**, and thioglycosyl donors **7**–**9** are given in the Supporting Information.
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[30] The preparation of and/or references to 2-azido-2-deoxythiogalactosides **56** and **57** and the protected serine acceptor **59** are given in the Supporting Information.
[31] For the preparation of thiogalactoside **63**, see the Supporting Information.
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