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In situ formation of β-glycosyl imidinium triflate from participating thioglycosyl donors: elaboration to disarmed–armed iterative glycosylation†

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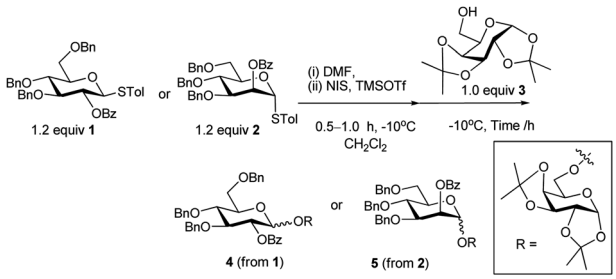
β-Glycosyl imidinium triflate is generated from participating thioglycoside donors for disarmed–armed iterative glycosylations and one-pot oligosaccharide synthesis.

Oligosaccharide synthesis is a challenging and tedious endeavour.[1] To streamline the process, sequential glycosylation strategies for oligosaccharide synthesis have emerged.[2,3] Recently, we developed a DMF-modulated glycosylation method for non-participating glycosyl donors, and this method was elaborated to iterative 1,2-cis α-glycosylations.[4] Because oligosaccharides contain β- and α-glycosidic bonds, it is reasonable and necessary to extend the modulation concept to the construction of β-glycosidic linkages.[5]

In glycosylation, activation of participating glycosyl donors produces the glycosyl oxacarbenium ion,[6] which under the influence of neighbouring group participation (NGP) would be converted to the glycosyl dioxalenium ion.[7–9] As the participating group blocks the α-stereotopic face of the dioxalenium ion, subsequent reaction with DMF produces β-glycosyl imidinium triflate. Given that the dioxalenium ion and β-imidinium triflate are in equilibrium, both may react with an acceptor to yield a mixture of α/β anomers. In previous studies, the amount of DMF used in modulated glycosylation was related to the degree of α-selectivity.[4] Extrapolating from this relationship, we hypothesized that the amount of DMF might be modified so as to subdue the α-directing effect and yet retain the pre-activation property of DMF.

Reducing the idea to practice, participating 2-*O*-benzoyl thioglucoside **1**[10] and thiomannoside **2** were employed as model donors for development of a new DMF-modulated glycosylation procedure. At the start, thioglucoside **1** (1.2 equiv.) was activated with *N*-iodosuccinimide (1.2 equiv., NIS) and trimethylsilyltrifluoromethane sulfonate (1.2 equiv., TMSOTf) in the absence or the presence of 0.6 to 7.2 equiv. of DMF.[11] Upon completion of the activation, galactose acceptor **3** (1.0 equiv.) was added (Scheme 1 and Table 1). In the presence of 7.2 equiv. of DMF, the glycosylation afforded the expected disaccharide **4** in 72% yield but with a 1 : 5 α/β-anomeric ratio (entry 1). Reducing the amount of DMF to 2.4 equiv. suppressed the α-anomer formation (entry 2), but complete elimination occurred with 1.2 equiv. of DMF (entry 3). Further reduction or absence of DMF was unproductive resulting in a complex reaction mixture (entries 4 and 5). The modulated glycosylation did not work when acetonitrile was used as solvent (entry 6). Some optimization of reaction temperature is required for the present glycosylation (see Table S1 in ESI†). Besides the thioglucoside **1**, the modulated glycosylation procedure was effective for glycosylation with thiomannoside **2** (entries 7 and 8).

Because the DMF-modulated glycosylation includes a pre-activation step, this opens the door to iterative glycosylations. Such a feature is particularly beneficial for thioglycosyl donors



Scheme 1 Development of a DMF-modulated glycosylation procedure with participating thioglycoside donors **1** and **2**.

Table 1 DMF-modulated glycosylation with participating thioglycoside donors **1** and **2**

				Product[a]		
Entry	Donor	DMF (equiv.)	Time (h)	No.	Yield%	α/β
1	**1**	7.2	6.0	**4**	72	1 : 5
2	**1**	2.4	3.0	**4**	70	1/22
3	**1**	1.2	4.0	**4**	75	β only
4	**1**	0.6	4.0	**4**	Trace[b]	ND[c]
5	**1**	0.0	4.0	**4**	Trace[b]	ND
6	**1**	1.2[d]	3	**4**	Trace[b]	ND
7	**2**	0.6	3	**5**	—	ND[c]
8	**2**	1.2	4	**5**	71	α only

[a] α/β-Anomeric ratios were determined by HPLC. [b] CH_3CN was used as solvent. [c] The reactions gave a complex reaction mixture. [d] ND stands for not determined.

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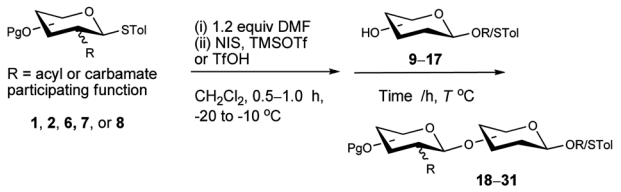
† Electronic supplementary information (ESI) available: Preparation of building blocks **2**, **6–17**, **32–34**, and **38** and NMR, MS data of glycosylation products. See DOI: 10.1039/c2cc35032g



Scheme 2 Disarmed–armed glycosylation approach directed by DMF modulation.

having a C2 acyl protecting function because they are often regarded as disarmed (less reactive) donors in conventional glycosylations though *S*-benzoxazolyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-D-glycosides have been found to be super-reactive under specific activation conditions.[12] In general, a disarmed donor would not be used for glycosylation of an armed (more reactive) glycosyl acceptor using the conventional procedure,[13] though several iterative glycosylations have been established to overcome the restriction.[14] We envisioned that by the application of the DMF modulation concept, a convenient disarmed–armed iterative glycosylation should be at our disposal.

As a proof-of-concept study, thioglycosides **1**, **2**, **6**, **7**, and **8** were employed as disarmed donors for glycosylations of armed (more reactive) thioglycoside acceptors **9–17** using the DMF modulation procedure (Scheme 2 and Fig. 1). The reactivity of the thioglycosides was unambiguously defined by relative reactivity values (RRV).[15–17]

At first, the glycosylation of *O*-glucoside **9** with thioglucoside **1** produced the desired β-anomer **18** in 65% yield, (Table 2, entry 1). Next we evaluated the glycosylations of armed thioglycosides **10** (RRV = 4470), **11a** (RRV = 4600), **16** (RRV = 50 000), and **17** (RRV = 11 000) with disarmed thioglucoside **1** (RRV = 1855) (entries 2, 3, 5, and 6). The glycosylations produced the expected disaccharides **19**, **20**, **21**, and **22**. Note that such glycosylations would not have been successful using the conventional protocol, as witnessed in glycosylation of thioglucoside **11a** with **1** (entry 4). In addition to **1**, the modulation procedure was applied to thioglucoside **6**, which contained different protecting functions (entries 7 and 8).

After preparation of β-glucosides, the modulated glycosylation method is utilized for synthesis of α-mannosides. For example, armed thiomannosides **12** (RRV = 12 500), **13a** (RRV = 6160), **13b** (RRV = 4644), and **14** (RRV = 8400) were coupled with disarmed thiomannoside **2** (RRV = 1912) affording expected disaccharides **25–28** exclusively in 60% to 73% yields (entries 9–12). For the glycosylation of **13b**, silylation of the C3 hydroxyl group occurred in the presence of TMSOTf; thus triflic acid (TfOH) was used as an acid promoter (entry 11).

To assess the scope of application of our method, 2-amino-2-deoxy thioglucoside **7** (RRV = 57)[15] and 2-*O*-benzoyl thiogalactoside **8** (RRV = 5200)[18] were investigated for coupling with thioglycosides **11a**, **15**, and **16**. Gratifyingly, the glycosylations furnished the desired disaccharides **29–31** (entries 13–15). However, the glycosylation with per-*O*-acetyl thiogalactoside did not bear fruit due to the acyl transfer reaction.[19] Except for disaccharide **30**, the yields of the present glycosylations fall between 55% and 73%. We reasoned that some un-reactive glycosyl intermediates might be formed during the pre-activation, which decreased the yield of reaction.[20]

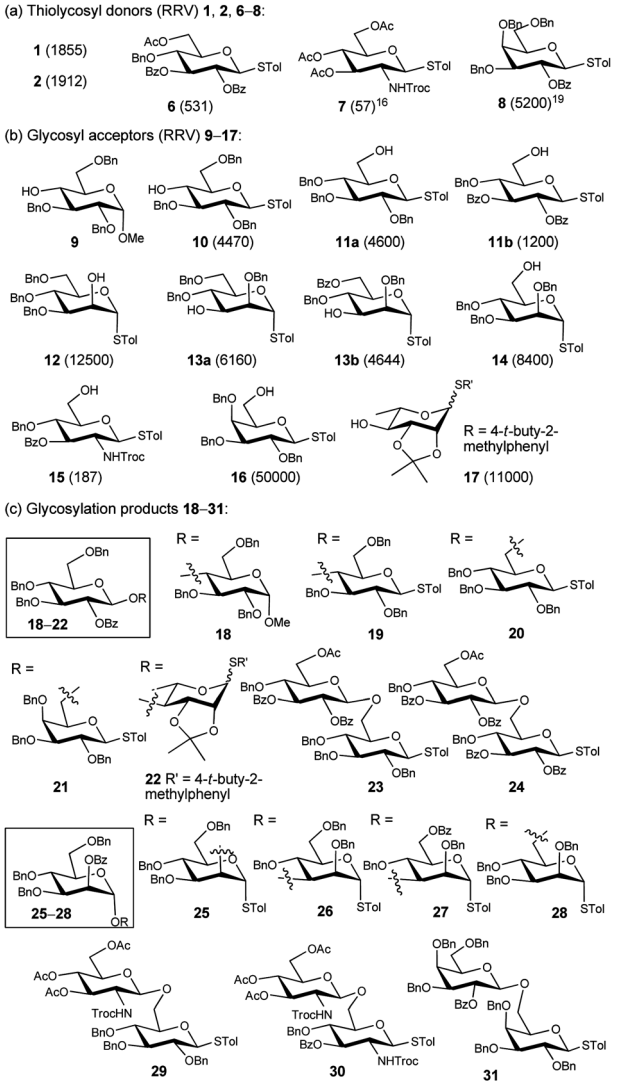


Fig. 1 (a) Thioglycoside donors **1**, **2**, **6**, **7**, and **8**. (b) Glycoside acceptors **9–17**. (c) Glycosylation products **18–31**.

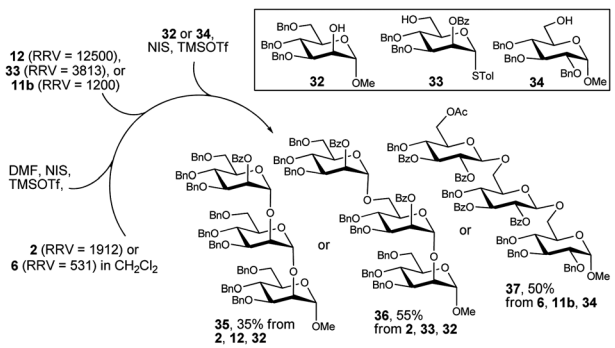
To demonstrate the utility of our method in oligosaccharide synthesis, trisaccharides including α-(1,2)-manan trisaccharide **35**, α-manan **36**, and β-(1,6)-glucan **37** were prepared from building blocks (**2**, **12**, **32**), (**2**, **33**, **32**), and (**6**, **11b**, **34**) respectively, by iterative one-pot disarmed–armed glycosylation (Scheme 3).

After the one-pot synthesis of the trisaccharides **35–37**, we investigated the reaction mechanism of the modulated glycosylation (Scheme 4). Selected 2-*O*-benzoyl thioglucoside **38** was activated in the presence of DMF in $CDCl_3$ at −20 °C (Scheme 4a). Upon completion of the activation, a fraction of the mixture was taken for NMR analysis, while the rest was treated with acceptor **39**. Referring to the NMR spectra of the pre-activation mixture, signals corresponding to glucosyl imidinium triflates **40**α, **40**β, and *N*-β-glucosyl succinimide **41** in a ratio of 1 : 7 : 1 were detected (Scheme 4b and Fig. S2 in ESI†). The configuration of **40**β is supported by the chemical shift of the anomeric proton at 5.79 ppm and a corresponding $^3J_{H1/H1}$ coupling constant of 7.8 Hz.[21] Additional evidence comes from the chemical shift of the anomeric carbon at 102 ppm and a

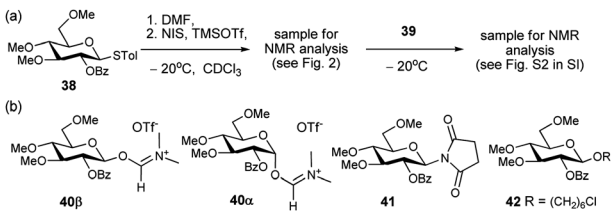
Table 2 Disarmed–armed glycosylations under DMF modulation

Entry	Donor, RRV	Acceptor, RRV	T^a (°C)	Time[b] (h)	Product No.	Yield (%)
1	**1**, 1855	**9**, —	−10	13.5	**18**	65
2	**1**, 1855	**10**, 4470	−10	11.0	**19**	67
3	**1**, 1855	**11a**, 4600	−10	4.5	**20**	70
4	**1**, 1855	**11a**, 4600	−10	18	ND[c]	—
5	**1**, 1855	**16**, 50 000	−10	2.5	**21**	70
6	**1**, 1855	**17**, 11 000	−10	2	**22**	55
7	**6**, 531	**11a**, 4600	−10	3	**23**	66
8	**6**, 531	**11b**, 1200	10	3	**24**	63
9	**2**, 1912	**12**, 12 500	0	5	**25**	61
10	**2**, 1912	**13a**, 6160	0	16	**26**	60
11	**2**, 1912	**13b**, 4644	0	4	**27**	73[d]
12	**2**, 1912	**14**, 8400	0	4	**28**	62
13	**7**, 57	**11a**, 4600	−10	5.5	**29**	64
14	**7**, 57	**15**, 187	−10	3.0	**30**	40[e]
15	**8**, 5200	**16**, 50 000	−30	3.0	**31**	57

[a] Temperature used for glycosylations. [b] Time required for glycosylation coupling. [c] The glycosylation was conducted by the conventional procedure without DMF modulation and 'ND' means not being detected. [d] TfOH was used as an acid promoter. [e] Modest 40% yield was due to the poor solubility of **30**, which affected the recovery of the product in purification.



Scheme 3 One-pot synthesis of trisaccharides **35**, **36**, and **37**.



Scheme 4 (a) NMR studies for modulated glycosylation of **39** with **38**. (b) Reaction intermediates **40**α, **40**β, **41** and product **42**.

$^1J_{C1/H1}$ coupling constant of 174 Hz (Table S2 in ESI†). Note that the $^1J_{C1/H1}$ values of the anomeric centers for **40**α and **40**β are *ca.* 10 Hz higher than that of $^4C_1$ *O*-glycoside. To the best of our knowledge, this set of NMR data represents the first of its kind. Further confirmation of the imidinium structure is provided by COSY, HSQC, and HMBC experiments (see NMR spectra and Fig. S3 in ESI†).

The aforementioned NMR data enable us to propose a mechanism for the glycosylation method (Fig. S4 in ESI†). Thioglycoside is activated to form the glycosyl oxacarbenium ion by NIS–TMSOTf, which under NGP is converted to the dioxalenium ion.[7–9] As the majority of dioxalenium ions react with DMF to form β-glycosyl imidinium triflate, remaining dioxalenium ions escape the NMR detection.[22] However, their presence would be inferred from the reaction with an acceptor. Upon addition of an acceptor **39**, the signals of the β-glucoside **42** appeared while the signals of **40** and **41** vanished (see Fig. S5 in ESI†). An explanation is that the β-imidinium triflate **40** and β-succinimide **41** are in equilibrium with the dioxalenium ion; when added the acceptor **39** is selectively coupled with the more-reactive dioxalenium ion affording the β-glycoside **42**. Such a mechanism appears to be in line with the Curtin–Hammet principle.[23]

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