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Installation of Electron Donating Protective Groups, a Strategy for Glycosylating Unreactive Thioglycosyl Acceptors using the Pre-activation Based Glycosylation Method¹

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Abstract

The pre-activation based chemoselective glycosylation is a powerful strategy for oligosaccharide synthesis with its successful application in assemblies of many complex oligosaccharides. However, difficulties were encountered in reactions where glycosyl donors bearing multiple electron withdrawing groups failed to glycosylate hindered unreactive acceptors. In order to overcome this problem, it was discovered that the introduction of electron donating protective groups onto the glycosyl donors can considerably enhance their glycosylating power, leading to productive glycosylations even with unreactive acceptors. This observation is quite general, which can be extended to a wide range of glycosylation reactions, including one-pot syntheses of chondroitin and heparin trisaccharides. The structures of the reactive intermediates formed upon pre-activation were determined through low temperature NMR studies. It was found that for a donor with multiple electron withdrawing groups, the glycosyl triflate was formed following pre-activation, while the dioxalenium ion was the major intermediate with a donor bearing electron donating protective groups. As donors were all cleanly pre-activated prior to the addition of the acceptors, the observed reactivity difference between these donors was not due to selective activation encountered in the traditional armed-disarmed strategy. Rather, it was rationalized by the inherent internal energy difference between the reactive intermediates and associated oxacarbenium ion like transition states during nucleophilic attack by the acceptor.

Introduction

With the increasing recognition of the important biological functions of carbohydrates, carbohydrate synthesis is a very active research area with many innovative methodologies developed during the past two decades.^{2–5} In most glycosylation reactions, a promoter is added to a mixture of the glycosyl donor and the acceptor. The glycosyl donor is activated by the promoter, which undergoes *in situ* nucleophilic addition or displacement reaction with the acceptor leading to the glycoside product. As an alternative, a glycosyl donor can be activated in the absence of an acceptor (pre-activation).^{6–18} Upon complete donor activation, the acceptor is then added to the reaction mixture initiating glycoside formation. Using the pre-activation strategy, unique stereochemical outcomes^{6,9,16,17} and chemoselectivities^{10–13, 15} can be obtained. Boons and coworkers developed a novel α selective glycosylation strategy,⁹ where pre-activation of a trichloroacetimidate donor allowed for the 2-*O* protective group to participate and stabilize the oxacarbenium ion from the β face. Thus, S_N2 like displacement

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by the acceptor gave α glycosides highly selectively. The Crich group discovered that pre-activation of a benzylidene protected thiomannoside or mannosyl sulfoxide generated an α -mannosyl triflate,¹⁷ which upon triflate displacement by an acceptor led to the β -mannoside stereoselectively overcoming this long-standing challenge. Gin and coworkers reported that the pre-activated hemiacetal donor could chemoselectively glycosylate a hemiacetal acceptor.¹⁵ The glycoside product could then be directly activated using the identical condition and glycosylation can be carried out iteratively.

Recently, we^{7,8,11,19–22} and others^{12,13,23} applied the pre-activation scheme to the chemoselective glycosylation of a thioglycoside acceptor by a thioglycosyl donor. In this approach, the glycosyl donor is pre-activated by a stoichiometric promoter. Upon complete donor activation, a thioglycosyl acceptor is added to the reaction mixture. Nucleophilic attack on the activated donor by the acceptor yields a disaccharide product containing a thioether aglycon, which can be directly activated for the next round of glycosylation without any aglycon adjustment as typically required by other selective activation strategies. With the pre-activation scheme, because donor activation and addition of the acceptor are performed in two distinct steps, the anomeric reactivity of the thioglycosyl donor is independent of that of the thioglycosyl acceptor. This confers much freedom in protective group selection, greatly simplifying the overall synthetic design. This is in contrast with the traditional reactivity based armed-disarmed chemoselective glycosylation method,^{24–26} where the glycosyl donor must possess much higher anomeric reactivity (typically at least ten times higher) than the glycosyl acceptor,²⁴ as the donor is activated in the presence of the acceptor.

A wide range of thioglycosyl donor and acceptor pairs have been examined using the pre-activation protocol.^{7,8,11,12,19–23} In many cases, the chemoselective glycosylation reactions proceeded smoothly with good yields. It is particularly noteworthy that a disarmed donor (e.g. **1**) can glycosylate an armed acceptor (e.g. **2**).^{11,20} This reversal of anomeric reactivity is not possible using the reactivity based armed-disarmed method.^{24,25} The pre-activation based strategy has been successfully applied to total synthesis of a wide range of complex linear and branched oligosaccharides, including Lewis^x,²¹ dimeric Lewis^x,²¹ Globo-H,²⁰ hyaluronic acid oligosaccharides,⁸ chito-oligosaccharides^{13,22} and complex type sialylated core fucosylated N-glycan dodecasaccharide.⁷ However, difficulties were encountered in reactions of very unreactive secondary carbohydrate acceptors such as **3** and **4** with electron poor donors **1** and **5**.¹¹ In this article, we will explore a strategy to overcome this problem. We will also study the intermediates generated upon pre-activation to provide insights to design even better glycosylation strategies.

Results and discussion

The reaction of donor **5** with acceptor **3** was performed by first pre-activating donor **5** with the promoter system *p*-TolSCI/AgOTf¹¹ followed by addition of acceptor **3** and a sterically hindered base tri-*t*-butyl pyrimidine (TTBP)²⁷ (Table 1, entry 1). Although no desired disaccharide was formed, complete disappearance of the donor was observed by TLC and NMR (vide infra). Analysis of the reaction mixture showed that donor **5** was converted to the expected breakdown products (the hemiacetal or the glycal) of the oxacarbenium ion corresponding to **5**, with most of the acceptor **3** recovered. This demonstrated that despite the presence of multiple electron withdrawing benzoyl groups, the electron poor donor **5** was activated by the powerful promoter *p*-TolSCI/AgOTf. Similar phenomena were observed in the reaction of **4** with **5** (Table 1, entry 2) or donor **1**.¹¹ Interestingly, reaction of perbenzylated glucose donor

8 with acceptors **3** and **4** gave the corresponding disaccharides **9** and **10** smoothly in good yields following the identical reaction protocol (Table 1, entries 3,4).¹¹ The contrasting outcome in these glycosylations using the same acceptor can be due to two possible factors: 1) with donor **8**, α -glycoside product is pre-dominantly formed while donor **5** would favor the β -product due to neighboring group participation; and 2) electronic properties of the two glycosyl donors are quite different with donor **8** bearing multiple electron donating protective groups and donor **5** containing electron withdrawing protective groups only. These two factors correspond to an inherent α/β facial selectivity at the TS for **5** and **8** (Figure 1a) or an inherently lower transition state (TS) energy in reaction coordinates of **8** versus **5** (Figure 1b).

To better differentiate the factors governing the glycosylation, donor **11**²⁰ was prepared, which bears multiple electron donating groups and a participating protective group at O-2. After pre-activation by *p*-TolSCl/AgOTf, donor **11** successfully glycosylated acceptor **4** producing disaccharide **12 β** in 48% yield (Table 1, entry 5), suggesting that facial selectivity is not the dominating factor for determining the donor's ability to react with **4**. The identity of the sugar is not crucial as the electron rich glucoside donor **13**⁸ also smoothly glycosylated acceptors **3** and **4** to give disaccharides **14** and **15** (Table 1, entries 6,7). Thus, the observed dichotomy in reaction outcome must be resulting from different electronic properties of the glycosyl donors. To glycosylate unreactive acceptors, donors containing more electron donating groups are preferred as they inherently possess higher glycosylating activity following the reaction scheme of Figure 1b.

This observation turns out to be quite general and can be extended to a wide range of reactions, which are synthetically useful. Per-acetylated thioglucoside **16** failed to react with glucosamine **17**. Replacement of its 3,4,6-tri-*O*-acetyl groups with electron donating silyl and ether protective groups (donor **13**) renders it an effective donor to glycosylate **17** producing disaccharide **19** (Table 1, entry 9).⁸ Glucuronic acid residues exist in many naturally occurring oligosaccharides. However, due to the presence of the electron withdrawing carboxylic acid,

glucuronic acid thioglycoside derivatives have been rarely used as glycosyl donors.^{28–31} Instead, thioglucosides are typically employed, which require oxidation state adjustment after the glycosylation.^{28,32} It will be desirable to be able to use protected glucuronic acid derivatives directly as glycosyl donors. However, the electron poor glucuronic acid donor **20** did not undergo glycosylation with acceptor **21** at all. This problem was solved by using its electron rich counterpart **23**, which gave hyaluronic acid precursor disaccharide **24** in 73% yield (Table 1, entry 11). The electron rich thiogalactoside donor **11** also glycosylated the sterically hindered acceptor **25** in good yield (Table 1, entry 12).

There are high interests in acquiring glycosaminoglycans, such as chondroitin and heparin due to their important biological functions.^{33–38} Heparin synthesis requires glycosylation of the 4-OH of a glucosamine acceptor, which is known to be notoriously unreactive.³⁹ A similar challenge is also present for chondroitin preparation as the 3-hydroxyl group of most galactosamine acceptors is sterically hindered. We envision that the high glycosylating power of donor **13** bestowed by the electron donating protective groups can overcome the low reactivities of glucosamine and galactosamine acceptors. Moreover, we want to examine whether these syntheses can be performed in a one-pot fashion.

Pre-activation of donor **13** by *p*-TolSCI/AgOTf at –60 °C was followed by the addition of acceptor **25** (Scheme 1a). Upon complete consumption of the acceptor, a second acceptor **27**⁴⁰ and another equivalent of the promoter *p*-TolSCI/AgOTf were added to the same reaction flask. Chondroitin precursor trisaccharide **28** was successfully produced from this three-component one-pot synthesis in 67% overall yield within just five hours. A heparin precursor trisaccharide **30** was prepared in a similar manner through sequential reactions of **13**, **29**⁴¹ and **27** in one-pot in 49% yield (Scheme 1b).

Why do the more electron rich donors have higher glycosylating power? To answer this question, the reactive intermediates formed following pre-activation were examined. In general, it is a difficult task to thoroughly characterize the reactive intermediates due to their limited lifetime especially when donor activation is carried out in the presence of an acceptor. With the pre-activation scheme, because the activation and glycosylation are two distinct steps, it will be possible to observe the intermediates at low temperature following pre-activation.

Recently, low temperature NMR has been shown to be a powerful tool to monitor the glycosylation process.^{9,14,42–47} Crich and colleagues have carried out ground breaking work in studying the reactive intermediates of a glycosylation reaction.⁴⁷ They demonstrated that in the absence of neighboring group participation, glycosyl triflates, which have characteristic ¹H-, ¹³C-, and ¹⁹F- NMR profiles, were the dominant intermediates when several thiophenyl mannosylpyranosides and thiophenyl glucosylpyranosides were pre-activated by PhSOTf at low temperatures. The identification of glycosyl triflate was used to rationalize the high β-selectivity in glycosylation of benzylidene protected mannothiopyranosides. Lowary and coworkers showed that in activation of a furanosyl sulfoxide, although multiple intermediates existed at –60 °C, glycosyl triflate was the dominant one when the reaction was warmed up to –40 °C. This observation enabled them to modify the operations and enhance the yield and stereoselectivity of their synthesis.¹⁴

In our glycosylation reaction, upon addition of *p*-TolSCI to a mixture of *p*-tolylthioglycoside donor and AgOTf, *p*-TolSOTf is formed, which electrophilically attacks the anomeric sulfur atom of the donor to generate disulfonium ion **31** (step 1, Scheme 2). The disulfonium ion **31** can further evolve to several possible intermediates prior to the addition of the nucleophilic acceptor (step 2): 1) oxacarbenium ion pair **32**; 2) glycosyl triflate **33** by addition of the triflate anion to the anomeric center; 3) disulfonium ion **34** formed by equilibrating with the *p*-tolyl disulfide side product; and 4) dioxalenium ion **35** in the cases where the donor contains an O-2

acyl participating protective group. Nucleophilic attack of the reactive intermediate(s) by the acceptor will then generate the glycoside product (step 3). Although drawn as free ion pairs, **32**, **34** and **35** can also possibly exist as either solvent separated ion pairs or contact ion pairs.

Because the intermediates upon activation of glycosyl donors without 2-*O* participating neighboring groups have been quite extensively studied,^{14,17,47–49} we focused on donors containing O-2 acyl groups in this study. The pre-activation of per-*O*-benzoylated galactose donor **5** was monitored first by NMR. No significant differences in product yields or NMR spectra were observed when the reactions were performed in CD₂Cl₂, CDCl₃, CD₂Cl₂: Et₂O-D₁₀ (1:1) or CDCl₃: Et₂O-D₁₀ (1:1). Therefore, all subsequent studies were performed in anhydrous CDCl₃. Addition of *p*-TolSCl to a mixture of donor **5** and AgOTf at –60 °C led to rapid dissipation of the characteristic yellow color of *p*-TolSCl within seconds. Inspection of the ¹H-NMR spectrum revealed that the donor was transformed within a few minutes to one major new carbohydrate species characterized by its anomeric proton signal, a doublet at δ 6.57 ppm with *J*_{1,2} = 3.2 Hz (Figure 2). No signals around δ 9.5 ppm due to the anomeric proton of the possible oxacarbenium ion **36** were observed.⁵⁰

The methyl group of the *p*-tolyl moiety after pre-activation appeared as a singlet in its ¹H-NMR spectrum, which was the case for all *p*-tolyl thioglycosides examined. If the glycosyl disulfonium ion **37** were formed, the two *p*-TolS groups would have become non-equivalent leading to two separate methyl peaks in ¹H-NMR. This was supported by the fact that the ¹H-NMR of dimethyl(methylthio)sulfonium triflate (DMTST) exhibits two singlets at 3.27 ppm and 2.92 ppm with the integration ratio of 2:1.⁵¹ Furthermore, in glycosylation of **2** by **8**, addition of exogenous *p*-tolyl disulfide to the reaction did not cause significant changes in either reaction yield or stereoselectivity (data not shown). Thus, the glycosyl disulfonium ion does not play a significant role in the thioglycoside glycosylation but rather a transient function on route to other species.

The ¹³C-NMR spectrum of the activated intermediate from donor **5** at –60 °C corroborated the clean formation of a new carbohydrate species with its anomeric carbon signal resonating at δ 104.4 ppm and four carbonyl carbon signals at δ 166.4, 165.9, 165.8, 165.5 ppm (Figure 2). The chemical shift of the anomeric carbon also excluded the possibility of oxacarbenium ion **36** as the positively charged anomeric carbon in the oxacarbenium ion was expected to appear above 210 ppm⁴⁷ through analogy with other sp² hybridized alkoxy carbenium ions.^{50,52,53} By electrochemical oxidation, Crich, Yoshida and coworkers generated a series of glycosyl triflates for glucosides, galactosides and mannosides without participating neighboring groups on O-2. The anomeric protons of these glycosyl triflates appeared around 6.2 ppm and anomeric carbons around 106 ppm.⁴² Our NMR data is consistent with the intermediate structure following pre-activation of **5** being the α-glycosyl triflate **38**. Prior to the activation, the ¹⁹F-NMR spectrum showed a single peak at δ-4.2 ppm due to the triflate anion from AgOTf. The corresponding ¹⁹F-NMR after activation revealed two signals, δ-1.2 and δ-4.2 ppm assigned to glycosyl triflate **38** and excess AgOTf, respectively. The glycosyl triflate **38** was found to be quite stable because no significant changes were observed by NMR when the temperature was raised to –20 °C. The triflate **38** was a competent glycosyl donor with reactive acceptors as the addition of the primary galactoside acceptor **39** to the NMR tube led to the desired disaccharide **40** cleanly. Yet, adding the unreactive acceptor **3** to **38** did not produce any disaccharide **6**. This is consistent with a model that some nucleophilic push is required in order to activate anomeric triflates.

When the more electron rich donor **11** was pre-activated by *p*-TolSCl/AgOTf, one major intermediate was formed along with several minor ones. The ¹H-NMR of activated donor **11** was considerably broader than that of activated donor **5**, presumably due to residual silver cation complexation with aromatic residues⁵⁴ possibly the benzyl protecting groups of **11**

(Figure 3). A gCOSY correlation experiment showed that the anomeric proton of the major intermediate has undergone significant downfield shift from 4.98 ppm in donor **11** to 7.34 ppm, while H-2 shifted slightly to 5.77 ppm (Figure S1). To better probe this intermediate by ^{13}C -NMR, a ^{13}C -labeled benzoyl group was introduced onto O-2 of the galactoside (donor **11a**), which showed a chemical shift of 165.5 ppm by ^{13}C -NMR. An HMBC spectrum of the ^{13}C labeled donor **11a** displayed correlations between the ^{13}C 165.5 ppm peak and protons at 8.02 ppm (H_o , $\text{H}_{o'}$ protons of the Bz phenyl ring) and 5.66 ppm (H-2) with no correlations with the anomeric proton at 4.98 ppm (Figure S2a). Upon activation, a strong new resonance at δ 180.8 ppm appeared in the ^{13}C -NMR with the concomitant decrease of the resonance at δ 165.5 ppm (Figure 3c). For this new carbon signal, in addition to its HMBC correlations with ^1H -NMR signals at 8.02 ppm (H_o , $\text{H}_{o'}$) and 5.77 ppm (H-2), a new correlation with the H-1 proton signal at 7.34 ppm was observed (Figure S2b). These correlations strongly suggest the bridging dioxalenium ion **41** formed through participation by the neighboring O-2 benzoyl group. The chemical shift of 180.8 ppm for the bridging carbon in **41** was similar to the value of 180.3 ppm observed for the dioxalenium ion **42** formed from xyloside **43**.⁵⁵ The HSQC spectrum of **41** indicated that the anomeric carbon was also downfield shifted to 114.2 ppm (Figure S3). The positive charge of the dioxalenium ion **41** could be distributed over O-5, C-1, O-1 and C-7, explaining the significant downfield shift of H-1, C-1 and C-7. By quantum mechanical calculation the LUMO of dioxalenium ions has been shown to be a vacant *p*-like orbital centered on C-7 in agreement with these observations.⁵⁶ Compared with the glycosyl triflate **38**, the dioxalenium ion **41** was less stable with decomposition setting in when the temperature was raised to above -30°C .

Interestingly, pre-activation of the tetra-*O*-acetyl glucose **16** converted it into two reactive intermediates in roughly 1:1 ratio at -60°C (Figure 4a,b). Based on the resonances at δ 6.21 ppm ($J_{1,2} = 2.4$ Hz) and δ 104.1 ppm of the anomeric proton and carbon atoms, the first intermediate was assigned to be the α -glycosyl triflate **44**. The second intermediate has ^{13}C -NMR resonances at δ 191.7, 113.3 ppm for C-7 and C-1, and ^1H -NMR resonances at δ 7.35 and 2.82 ppm for H-1 and H-8 of the dioxalenium ion **45**. The glycosyl triflate **44** and dioxalenium ion **45** were shown to interconvert by warming the mixture to -20°C , which led to the disappearance of **45** (Figure 4c,d) with it reappearing upon re-cooling to -60°C . Addition of the primary galactoside acceptor **39** to the pre-activated donor **16** at -60°C generated disaccharide **46** in 85% yield with both the glycosyl triflate **44** and the dioxalenium ion **45** consumed at comparable rates.

Why do donors **5**, **11** and **16** form different intermediates following pre-activation? This can be explained by the fact that there are more electron withdrawing protecting groups (Bz is more deactivating than Ac) on the glycan ring of donors **5**, which greatly disfavor the formation of positively charged dioxalenium ions. On the other hand, the presence of multiple electron donating benzyl groups on **41** stabilizes the positive charge sufficiently, rendering it unnecessary for the covalent attachment of the poor nucleophile triflate anion. The tetraacetyl glucoside **16** presents the intermediate case between donors **5** and **11**, leading to a mixture of glycosyl triflate and dioxalenium ion upon pre-activation. Crich and coworkers reported the

dioxalenium ion **42** as the major intermediate when they activated the per-benzoylated thioxyloside **43**.⁵⁵ As xylose is a pentose, it contains one fewer highly electron withdrawing group on the sugar ring,^{57,58} which is likely the reason why the dioxalenium ion **42** was formed as the major intermediate.

It is known that donor **11** is more reactive than donor **5** towards a thiophilic promoter.²⁴ Wong and coworkers quantified relative reactivity values of a wide range of thiotolyl donors by having two different donors competing with a limiting amount of promoter in the presence of excess acceptor. Donor **11** was found to react with a promoter about 800 times faster than donor **5**.²⁴ which mostly reflected the internal free energy difference between the reactants and the activated intermediate (steps 1 and 2 for the glycosylation process). In contrast, pre-activation of a mixture of donors **11** and **5** completely converted both donors into reactive intermediates, thus removing the rate difference in reaction with the promoter. Upon addition of 1 eq of galactoside **39** to a pre-activated mixture of 1 eq of donor **5** and 1 eq of donor **11** at $-60\text{ }^{\circ}\text{C}$, disaccharide **40** and **47** were isolated in a 1 : 2.9 ratio with a combined yield of 90% based on the amount of the acceptor added, suggesting the activated intermediates from donor **11** were 2.9 times more reactive than that from donor **5** (Scheme 3). When the reactivity of the acceptor decreased, the reaction became more selective as donor **5** failed to glycosylate acceptor **4** while donor **11** gave disaccharide **12** in 56% yield. Since the glycosyl triflate **38** is more stable than the dioxalenium ion **41**, the different glycosylation outcome using donors **5** and **11** is not due to decomposition of the activated intermediate. The higher reactivity of dioxalenium ion **41** can be resulting from the lower free energy difference between **41** and the corresponding oxacarbenium ion like TS during nucleophilic attack of the acceptor (step 3) due to the higher electron density of the glycan ring and better stabilization of the TS. At the mean time, anomeric triflates may require some additional activation, which is dependent on the electron donating potential of the protecting groups of the donor. Possible mild activators include residual Ag^+ ions or the protonated base. In the absence of such promoters the reaction temperature needs to be raised to activate the anomeric triflates towards unreactive acceptors.

A TS connecting the dioxalenium ion derived from the reaction of methanol with 2-*O*-acetyl-3,4,6-tri-*O*-methyl-D-glucopyranosyl oxacarbenium ion has been found by quantum mechanical calculations.⁵⁹ This TS is only 12.9 kJ mol^{-1} above the complex between methanol and the dioxalenium ion and is initiated by C-2—O-2 bond rotation. The ease of C-2—O-2 bond rotation is expected to depend on the protecting groups of the donor. This TS is also stabilized by intramolecular H-bonding from the hydroxylic proton to electronegative oxygens of the donor. Such H-bonding is reasonably expected to be sensitive to the steric accessibility of the hydroxyl and the electronegativity of the donor's H-bonding acceptor oxygen. It was further postulated that in the absence of intramolecular H-bonding, species like the counterions such as triflate or others such as added bases, molecular sieves etc. could act as the proton acceptor.

Although we primarily focused on the pre-activation strategy using thioglycosides, there have been reports that electron rich glycosyl donors possessing higher glycosylation power in other glycosylation protocols and other glycosyl building blocks.^{60–63} Matta and coworkers discovered that while fucosylation of the hindered disaccharide **48** failed with donor **49**, mixing the more electron rich counterpart (donor **50**) with **48** under the *in situ* anomerization protocol led to trisaccharide **51** in high yield.⁶³ Similarly, substituting the electron withdrawing benzoyl groups on a per-*O*-benzoylated propargyl glycoside donor (donor **52**) with benzyl groups (donor **53**) transformed the failed glycosylation with donor **52** to one with 68% yield.⁶² Therefore, we propose that when a glycosylation reaction fails to yield the desired glycoside product, the installation of electron donating protective groups onto glycosyl donors can be explored in order to enhance the glycosylation yield. However, cautions need to be taken as

the more electron rich donors turn to be less stable after activation, thus the usage of lower reaction temperature is preferred for this type of reactions.

Conclusions

We have investigated the intermediate structures following pre-activation of several representative thioglycosyl donors bearing 2-*O* acyl groups by low temperature NMR. It was found that glycosyl triflates were the major intermediates formed for donors bearing multiple electron withdrawing groups, while with the electron rich donors the dioxalenium ions were produced. We demonstrated that the introduction of electron donating groups onto glycosyl donors can overcome the low reactivities of glycosyl acceptors using the pre-activation protocol. This can be applied to one-pot synthesis leading to chondroitin and heparin trisaccharide precursors in high yields. It should be emphasized that the high reactivity bestowed by electron donating groups in our study is observed in the glycosylating step, rather than in the selective donor activation step encountered in the armed-disarmed strategy. The installation of electron donating protective groups onto glycosyl donors may be a general strategy to enhance the glycosylation yield, especially for difficult glycosylation reactions with unreactive acceptors.

Experimental Section

General procedure for single step pre-activation based glycosylation

A solution of donor (0.060 mmol), AgOTf (0.18 mmol) and freshly activated molecular sieve MS 4 Å (200 mg) in diethyl ether/CH₂Cl₂ (V : V = 2 : 2 mL), CH₂Cl₂ (3 mL) or CDCl₃ (3 mL) was stirred at room temperature for 30 minutes, and cooled to -60 °C. After 5 minutes, orange colored *p*-TolSCl (9.5 μL, 0.060 mmol) was added through a microsyringe. Since the reaction temperature was lower than the freezing point of *p*-TolSCl, *p*-TolSCl was added directly into the reaction mixture to prevent it from freezing on the flask wall. The characteristic yellow color of *p*-TolSCl in the reaction solution dissipated rapidly within a few seconds indicating depletion of *p*-TolSCl. After the donor was completely consumed according to TLC analysis (less than 5 minutes at -60 °C), a solution of acceptor (0.054 mmol) and TTBP (1 eq) in CH₂Cl₂ (0.2 mL) was slowly added dropwise via a syringe. The reaction mixture was warmed to -20 °C under stirring in 2 hours. Then the mixture was diluted with CH₂Cl₂ (20 mL) and filtered over Celite. The Celite was further washed with CH₂Cl₂ until no organic compounds were observed in the filtrate by TLC. All CH₂Cl₂ solutions were combined and washed twice with saturated aqueous solution of NaHCO₃ (20 mL) and twice with water (10 mL). The organic layer was collected and dried over Na₂SO₄. After removal of the solvent, the desired disaccharide was purified from the reaction mixture via silica gel flash chromatography.

General procedure for monitoring pre-activation by NMR

Reactions were carried out in NMR tubes with anhydrous CDCl_3 at -60°C . The donor (1.0 eq) and AgOTf (3.0 eq) were added to an NMR tube and dried *in vacuo* for 3 hours. CDCl_3 (0.75 mL) was added slowly at -60°C . Then the donor was pre-activated by the addition of *p*-TolSCl (1.0 eq) at -60°C and the ^1H -, ^{13}C -, ^{19}F - and 2D NMR were acquired. Chemical shifts are downfield from tetramethylsilane for ^1H - and ^{13}C -NMR and from 1% trifluoroacetic acid in CDCl_3 for ^{19}F -NMR.

***p*-Tolyl 2-O-benzoyl-3,4,6-tri-O-benzyl-1-thio- β -D-galactopyranoside (11)—**

Compound **11** was synthesized following the literature procedure. $^{16}[\alpha]_{\text{D}}^{20} + 34.5^\circ$ (*c* 1.0, CHCl_3); ^1H -NMR (600 MHz, CDCl_3): δ 8.03–6.90 (m, 24 H, *COPh*, *SPhMe*, 3 CH_2Ph), 5.66 (t, 1 H, $J_{2,1} = J_{2,3} = 9.6$ Hz, H-2), 4.98 (d, 1 H, $J = 12.0$ Hz, *CHHPh*), 4.70 (d, 1 H, $J_{1,2} = 9.6$ Hz, H-1), 4.64–4.44 (m, 4 H, *CHHPh*, 2 CH_2Ph), 4.03 (d, 1 H, $J_{4,5} = 3.0$ Hz, H-4), 3.70–3.65 (m, 4 H, H-3, H-5, H-6_a, H-6_b), 2.27 (s, 3 H, *SPhMe*); ^{13}C -NMR (150 MHz, CDCl_3): δ 165.5 (1 C, 1 *COPh*), 138.7, 138.1, 137.9, 137.8, 133.2, 132.9, 130.4, 130.1, 130.0, 129.7, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.7 (CH_2Ph , *COPh*, *SPhMe*, some signals overlapped), 87.5 (1 C, $J_{\text{C-1,H-1}} = 166.3$ Hz, C-1), 81.4, 77.9, 74.6, 73.9, 72.9, 72.0, 70.7, 69.0, (C-2~6, 3 CH_2Ph), 21.4 (1 C, *SPhMe*). ESI-MS $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{41}\text{H}_{40}\text{NaO}_6\text{S}$: 683.2, found: 683.2.

***p*-Tolyl 2-O-benzoyl-3,4,6-tri-O-benzyl- α,β -D-galactopyranosyl-(1 $\rightarrow$ 4)-2,3-di-O-benzoyl-6-O-benzyl-1-thio- β -D-galactopyranoside (12 α and 12 β)—**

Donor **11** (25 mg, 37.8 μmol , 1.0 eq) and AgOTf (29.9 mg, 113.5 μmol , 3.0 eq) were placed in an NMR tube and dried *in vacuo* for 3 hours. CDCl_3 (0.75 mL) was added slowly at -60°C . Then the donor was pre-activated by the addition of *p*-TolSCl (6.0 μL , 37.8 μmol , 1.0 eq) at -60°C . After ^1H -, ^{13}C -, ^{19}F - and 2D NMR were acquired at -60°C , a solution of the acceptor **4** (20.0 mg, 34.2 μmol , 0.9 eq) and TTBP (9.0 mg, 37.8 μmol , 1.0 eq) in CDCl_3 (0.25 mL) was added to the NMR tube. The reaction mixture was gradually warmed up to rt in 3 hours. The reaction mixture was quenched by Et_3N , filtered through Celite. The filtrate was concentrated and purified by flash column chromatography (toluene: hexanes: ethyl acetate = 10 : 10 : 1) to give **12 α** (6.0 mg, 5.0 μmol , 8%) and **12 β** (37.0 mg, 33 μmol , 48%). For α -isomer **12 α** :

$[\alpha]_{\text{D}}^{20} + 44.6^\circ$ (*c* 1.0, CHCl_3); ^1H -NMR (600 MHz, CDCl_3): δ 8.23–7.00 (m, 34 H, 2 *COPh*, *SPhMe*, 4 CH_2Ph), 5.77 (t, 1 H, $J_{2,1} = J_{2,3} = 9.6$ Hz, H-2), 5.70 (dd, 1 H, $J_{2',1'} = 3.2$ Hz, $J_{2',3'} = 8.4$ Hz, H-2'), 5.24 (dd, 1 H, $J_{3,2} = 9.6$ Hz, $J_{3,4} = 2.4$ Hz, H-3), 5.20 (d, 1 H, $J_{1',2'} = 3.2$ Hz, H-1'), 4.84 (d, 1 H, $J = 11.2$ Hz, *CHHPh*), 4.83 (d, 1 H, $J_{1,2} = 9.6$ Hz, H-1), 4.70–4.44 (m, 4 H, *CHHPh*, CH_2Ph), 4.30–3.77 (m, 8 H, H-4, H-5, H-6_a, H-6_b, 2 CH_2Ph), 3.60–3.33 (m, 2 H, H-3', H-6'_a), 3.33 (dd, 1 H, $J_{6'b,5'} = J_{6'b,6'a} = 8.8$ Hz, H-6'_b), 2.80 (dd, 1 H, $J_{5',6'b} = 5.2$ Hz, $J_{5',6'a} = 8.8$ Hz, H-5'), 2.17 (s, 3 H, *SPhMe*); HRMS $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{68}\text{H}_{64}\text{NaO}_{13}\text{S}$: 1143.3965; found: 1143.3972. For β -isomer **12 β** : $[\alpha]_{\text{D}}^{20} + 57.5^\circ$ (*c* 1.0, CHCl_3); ^1H -NMR (600 MHz, CDCl_3): δ 8.10–6.90 (m, 34 H, 2 *COPh*, *SPhMe*, 4 CH_2Ph), 5.64 (dd, 1 H, $J_{2',1'} = 7.8$ Hz, $J_{2',3'} = 9.6$ Hz, H-2'), 5.48 (t, 1 H, $J_{2,1} = J_{2,3} = 9.6$ Hz, H-2), 5.38 (dd, 1 H, $J_{3,2} = 9.6$ Hz, $J_{3,4} = 2.4$ Hz, H-3), 4.98 (d, 1 H, $J = 11.8$ Hz, *CHHPh*), 4.79 (d, 1 H, $J_{1,2} = 9.6$ Hz, H-1), 4.71 (d, 1 H, $J_{1',2'} = 7.8$ Hz, H-1'), 4.60 (d, 1 H, $J = 12.6$ Hz, *CHHPh*), 4.57 (d, 1 H, $J = 12.0$ Hz, *CHHPh*), 4.55 (d, 1 H, $J = 12.0$ Hz, *CHHPh*), 4.50 (d, 1 H, $J = 11.8$ Hz, *CHHPh*), 4.45–4.41 (m, 2 H, H-4, *CHHPh*), 4.26 (s, 1 H, CH_2Ph), 3.92–3.73 (m, 3 H, H-4', H-5, H-6_a, H-6_b), 3.55 (dd, 1 H, $J_{6'a,5'} = J_{6'a,6'b} = 8.4$ Hz, H-6'_a), 3.43 (dd, 1 H, $J_{3',2'} = 9.6$ Hz, $J_{3',4'} = 2.4$ Hz, H-3'), 3.32 (dd, 1 H, $J_{6'b,5'} = 5.4$ Hz, $J_{6'b,6'a} = 8.4$ Hz, H-6'_b), 3.26 (dd, 1 H, $J_{5',6'b} = 5.4$ Hz, $J_{5',6'a} = 8.4$ Hz, H-5'), 2.21 (s, 3 H, *SPhMe*); ^{13}C -NMR (150 MHz, CDCl_3): δ 166.0, 165.8, 164.7 (3 C, 3 *COPh*), 138.8, 138.7, 137.9, 137.9, 133.6, 133.1, 132.8, 132.7, 130.8, 130.3, 130.0, 129.9, 129.7, 129.3, 129.2, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, (CH_2Ph , *COPh*, *SPhMe*, some signals overlapped), 101.0 (1 C, $J_{\text{C-1,H-1}}$

= 165.3 Hz, C-1), 87.0 (1 C, $J_{C-1',H-1'}$ = 162.4 Hz, C-1'), 80.5, 78.4, 75.7, 74.8, 73.8, 73.7, 72.8, 72.2, 72.1, 71.9, 70.0, 68.7, 68.3, (C-2~6, 4 CH₂Ph, some signals overlapped), 21.3 (1 C, SPhMe). HRMS [M+H]⁺ calcd. for C₆₈H₆₅O₁₃S: 1121.4146; found: 1121.4130.

***p*-Tolyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-*tert*-butyldimethylsilyl-6-*O*-*p*-methoxybenzyl-β-*D*-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-1-thio-β-*D*-glucopyranoside (14)**—Compound **14** (60 mg, 74%) was prepared according to the general procedure for glycosylation using donor **13** (50 mg, 69.9 μmol, 1.0 eq) and acceptor **3** (37.7 mg, 63.0 μmol) and purified by flash column chromatography (hexanes : ethyl acetate = 4:1).

[α]_D²⁰ +61.3° (c 1.0, CHCl₃); ¹H-NMR (600 MHz, CDCl₃): δ 8.10-6.70 (m, 33 H, 4 C₆H₅, SPhMe, CH₂Ph, CH₂PhOMe), 5.52 (t, 1 H, $J_{2,1}$ = $J_{2,3}$ = 9.6 Hz, H-2), 5.38 (dd, 1 H, $J_{3,2}$ = 9.6 Hz, $J_{3,4}$ = 3.0 Hz, H-3), 5.35 (dd, 1 H, $J_{2',1'}$ = $J_{2',3'}$ = 8.4 Hz, H-2'), 4.81 (d, 1 H, $J_{1,2}$ = 9.6 Hz, H-1), 4.74 (d, 1 H, $J_{1',2'}$ = 7.8 Hz, H-1'), 4.72 (dd, 1 H, $J_{6a,5}$ = 3.0 Hz, $J_{6a,6b}$ = 12.6 Hz, H-6a), 4.69 (d, 1 H, J = 11.4 Hz, CHHPh), 4.62 (dd, 1 H, $J_{6b,5}$ = 8.4 Hz, $J_{6a,6b}$ = 12.6 Hz, H-6b), 4.60 (d, 1 H, J = 11.4 Hz, CHHPh), 4.52 (d, 1 H, $J_{4,3}$ = 3.0 Hz, H-4), 4.47 (d, 1 H, J = 11.4 Hz, CHHPhOMe), 4.35 (d, 1 H, J = 11.4 Hz, CHHPhOMe), 4.08 (dd, 1 H, $J_{5,6a}$ = 3.0 Hz, $J_{5,6b}$ = 8.4 Hz, H-5), 3.72-3.62 (m, 4 H, H-4', CH₂PhOMe), 3.61 (dd, 1 H, $J_{6'a,5'}$ = 1.8 Hz, $J_{6'a,6'b}$ = 10.2 Hz, H-6'a), 3.53 (dd, 1 H, $J_{3',2'}$ = $J_{3,4}$ = 8.4 Hz, H-3'), 3.50 (dd, 1 H, $J_{6'b,5'}$ = 6.0 Hz, $J_{6'a,6'b}$ = 10.2 Hz, H-6'b), 3.33 (ddd, 1 H, $J_{5',4'}$ = 7.8 Hz, $J_{5',6'a}$ = 1.8 Hz, $J_{5',6'b}$ = 6.0 Hz, H-5'), 2.19 (s, 3 H, SPhMe), 0.76 (s, 9 H, *tert*-butyl), -0.05 (s, 3 H, Me), -0.10 (s, 3 H, Me); ¹³C-NMR (150 MHz, CDCl₃): δ 166.5, 166.0, 165.6, 164.8 (4 C, C₆H₅), 159.3, 138.1, 137.8, 133.6, 133.3, 133.2, 133.1, 132.4, 130.4, 130.2, 130.1, 130.0, 129.9, 129.8, 129.7, 129.6, 129.1, 128.7, 128.6, 128.5, 128.4, 128.3, 127.7, 127.5, 114.0, (CH₂Ph-C, CH₂PhOMe, SPhMe, some signals overlapped), 100.9 (1 C, $J_{C-1',H-1'}$ = 165.4 Hz, C-1'), 87.5 (1 C, $J_{C-1,H-1}$ = 163.6 Hz, C-1), 76.6, 76.5, 75.2, 74.8, 74.3, 73.3, 73.2, 71.2, 69.2, 68.5, 65.4 (12 C, C-2~6, CH₂Ph, CH₂PhOMe, some signals overlapped), 55.4 (1 C, H₂PhOMe), 26.1, 21.4, 18.2 (5 C, SPhMe, C(Me)₃, C(Me)₃, some signals overlapped), -3.64, -4.63 (2 C, SiMe). ESI-MS: [M + Na]⁺ calcd. for C₆₈H₇₂O₁₅NaSSi: 1211.4; found 1211.4. HRMS [M+Na]⁺ calcd. for C₆₈H₇₂O₁₅NaSSi: 1211.4259; found: 1211.4252.

***p*-Tolyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-*tert*-butyldimethylsilyl-6-*O*-*p*-methoxybenzyl-β-*D*-glucopyranosyl-(1→4)-2,3-di-*O*-benzoyl-6-*O*-benzyl-1-thio-β-*D*-galactopyranoside (15)**—Compound **15** (32 mg, 26.5 μmol, 70%) was prepared according to the general procedure for glycosylation using donor **13** (31 mg, 43.4 μmol, 1.0 eq) and acceptor **4** (20.0 mg, 34.2 μmol, 0.9 eq) and purified by flash column chromatography (hexanes: ethyl acetate = 4:1). [α]_D²⁰ +69.3° (c 1.0, CHCl₃); ¹H-NMR (600 MHz, CDCl₃): δ 8.00-6.80 (m, 33 H, 3 C₆H₅, SPhMe, 2 CH₂Ph, CH₂PhOMe), 5.47 (dd, 1 H, $J_{2,1}$ = $J_{2,3}$ = 9.6 Hz, H-2), 5.37 (dd, 1 H, $J_{3,2}$ = 9.6 Hz, $J_{3,4}$ = 3.0 Hz, H-3), 5.28 (dd, 1 H, $J_{2',1'}$ = 7.8 Hz, $J_{2',3'}$ = 8.4 Hz, H-2'), 4.80 (d, 1 H, $J_{1,2}$ = 9.6 Hz, H-1), 4.79 (d, 1 H, $J_{1',2'}$ = 7.8 Hz, H-1'), 4.66 (d, 1 H, J = 10.8 Hz, CHHPh), 4.56 (d, 1 H, J = 10.8 Hz, CHHPh), 4.52 (d, 1 H, J = 11.4 Hz, CHHPh), 4.47-4.45 (m, 2 H, CHHPh, H-4), 4.41 (d, 1 H, J = 12.0 Hz, CHHPh), 4.29 (d, 1 H, J = 12.0 Hz, CHHPh), 3.90-3.83 (m, 3 H, H-5, H-6_a, H-6_b), 3.75-3.71 (m, 4 H, H-4', CH₂PhOMe), 3.54-3.21 (m, 4 H, H-3', H-6'_a, H-6'_b, H-5'), 2.21 (s, 3 H, SPhMe), 0.77 (s, 9 H, *tert*-butyl), -0.07 (s, 3 H, Me), -0.12 (s, 3 H, Me); ¹³C-NMR (150 MHz, CDCl₃): δ 165.9, 165.7, 164.8 (3 C, C₆H₅), 159.4, 138.8, 138.1, 137.8, 133.3, 133.1, 132.8, 130.4, 130.2, 130.1, 129.9, 129.8, 129.3, 129.2, 128.6, 128.5, 128.4, 128.3, 127.8, 127.7, 127.6, 127.5, 114.0, (CH₂Ph-C, CH₂PhOMe, SPhMe, some signals overlapped), 103.8 (1 C, $J_{C-1',H-1'}$ = 166.0 Hz, C-1'), 87.2 (1 C, $J_{C-1,H-1}$ = 159.0 Hz, C-1), 83.4, 78.7, 76.6, 75.6, 74.7, 74.3, 73.7, 73.2, 72.8, 71.0, 70.9, 69.1, 68.7, 68.2, 66.7 (13 C, C-2~6, 2 CH₂Ph, CH₂PhOMe, some signals overlapped), 55.5 (1 C, CH₂PhOMe), 26.1, 26.1, 21.3, 18.5 (5 C, SPhMe, C(Me)₃, C(Me)₃, some signals overlapped), -3.66, -4.67 (2 C, SiMe); HRMS: [M + Na]⁺ calcd. for C₆₈H₇₄O₁₄NaSSi: 1197.4466; found 1197.4451.

***p*-Tolyl (benzyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-tert-butyldimethylsilyl- β -D-glucopyranosyluronate)-(1 $\rightarrow$ 3)-4,6-*O*-benzylidene-2-(2,2,2-trichloroacetyl-amino)-2-deoxy-1-thio- β -D-glucopyranoside (24)**—Compound **24** was synthesized from donor **23** and acceptor **21** in 73% yield following the general procedure of single step glycosylation and purified by flash column chromatography (hexanes : ethyl acetate = 3:1). $[\alpha]_D^{20} + 11.2$ ($c = 1$, CH_2Cl_2); $^1\text{H-NMR}$ (600 MHz, CDCl_3): δ 7.87-7.85 (m, 2H, aromatic), 7.52-7.49 (m, 1H, aromatic), 7.36-7.25 (m, 9H, aromatic), 7.16-7.08 (m, 6H, aromatic), 6.93-6.89 (m, 1H, aromatic), 5.30 (s, 1H, CHPh), 5.27 (d, 1H, $J_{1,2} = 10.2$ Hz, H-1), 5.17-5.10 (m, 3H, CH_2Ph , H-2'), 4.99 (d, 1H, $J_{1',2'} = 7.2$ Hz, H-1'), 4.64-4.56 (m, 2H, CH_2Ph), 4.52 (t, 1H, $J = 9.6$ Hz, H-4'), 4.29-4.26 (m, 1H, H-6a), 4.15-4.12 (m, 1H, H-4'), 3.80 (d, 1H, $J_{4',5'} = 6.0$ Hz, H-5'), 3.67-3.63 (m, 2H, H-4, H-6b), 3.52-3.47 (m, 2H, H-2, H-5), 3.27-3.25 (m, 1H, H-3'), 2.34 (s, 3H, SPhCH_3); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3): δ 168.3, 165.1, 161.5, 139.0, 137.6, 137.0, 135.0, 133.9, 133.2, 130.0, 129.8, 129.4, 129.1, 128.7, 128.6, 128.3 ($\times 2$), 128.1, 127.5, 127.4, 127.0, 126.2, 101.5, 98.8, 84.2, 81.0, 79.9, 77.3, 76.2, 74.0, 71.2, 70.5, 67.2, 57.2, 25.7, 21.2, 17.8, -4.5, -5.3; ESI-MS $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{55}\text{H}_{60}\text{Cl}_3\text{NNaO}_{12}\text{SSi}$ 1114.3, found 1114.6; HRMS $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{55}\text{H}_{60}\text{Cl}_3\text{NNaO}_{12}\text{SSi}$ 1114.2569, found 1114.2573; gHMQC (without ^1H decoupling): $^1J_{\text{C1,H1}} = 161.9$ Hz, $^1J_{\text{C1',H1'}} = 164.6$ Hz.

***p*-Tolyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl- β -D-galactopyranosyl-(1 $\rightarrow$ 3)-4,6-*O*-benzylidene-2-deoxy-2-*N*-phthalimido-1-thio- β -D-galactopyranoside (26)**—

Compound **26** was synthesized from donor **11** and acceptor **25** in 65% yield (51% β + 14% α) following the general procedure of single step glycosylation. $[\alpha]_D^{20} + 33.6$ ($c = 1$, CH_2Cl_2); **26 β** $^1\text{H-NMR}$ (600 MHz, CDCl_3): δ 7.70-7.68 (m, 2H), 7.56-7.55 (m, 1H), 7.50-7.42 (m, 4H, aromatic), 7.36-7.16 (m, 19H, aromatic), 7.12-7.10 (m, 1H, aromatic), 7.04-6.95 (m, 6H, aromatic), 5.53-5.50 (m, 1H), 5.52 (d, 1H, $J_{1,2} = 7.8$ Hz, H-1), 5.28 (s, 1H, CHPh), 4.93 (d, 1H, $J = 12$ Hz), 4.80-4.78 (m, 1H), 4.66 (d, 1H, $J_{1',2'} = 8.4$ Hz, H-1'), 4.62-4.56 (m, 2H), 4.50 (d, 1H, $J = 12$ Hz), 4.43-4.42 (m, 1H), 4.33-4.23 (m, 4H), 3.90-3.88 (m, 2H), 3.54 (s, 1H), 3.46-3.42 (m, 3H), 3.05-3.03 (m, 1H), 2.26 (s, 3H, SPhCH_3); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3): δ 168.9, 166.9, 165.3, 138.8, 138.1, 138.0, 137.6, 134.1, 133.9, 133.6, 133.0, 131.9, 131.7, 129.9, 129.8, 129.6, 128.8, 128.7, 128.5 ($\times 2$), 128.4, 128.1 ($\times 3$), 127.9, 127.8, 127.7 ($\times 2$), 127.6, 126.8, 123.7, 122.9, 101.3, 100.4, 82.9, 80.3, 75.1, 74.4, 73.6 ($\times 2$), 73.2, 72.1, 71.7, 71.4, 70.4, 69.5, 68.2, 50.7, 21.4; ESI-MS $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{62}\text{H}_{57}\text{NNaO}_{12}\text{S}$ 1063.3, found 1063.2; HRMS $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{62}\text{H}_{61}\text{N}_2\text{O}_{12}\text{S}$ 1057.3945, found 1057.3933; gHMQC (without ^1H decoupling): $^1J_{\text{C1,H1}} = 161.1$ Hz, $^1J_{\text{C1',H1'}} = 159.3$ Hz.

Methyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-tert-butyldimethylsilyl-6-*O*-*p*-methoxybenzyl- β -D-glucopyranosyl-(1 $\rightarrow$ 3)-4,6-*O*-benzylidene-2-deoxy-2-*N*-phthalimido- β -D-galactopyranosyl-(1 $\rightarrow$ 4)-2,3-di-*O*-benzyl-6-*O*-*p*-methoxybenzyl- β -D-glucopyranoside (28)—Compound **28** was synthesized by a three-component one-pot synthesis procedure. After the donor **13** (50 mg, 69.93 μmol) and activated molecular sieve MS-4 Å (500 mg) were stirred for 30 minutes at room temperature in CH_2Cl_2 (5 mL), the solution was cooled to -60°C , followed by addition of AgOTf (54 mg, 209 μmol) in Et_2O (1.5 mL). The mixture was stirred for 5 minutes at -60°C and then *p*-TolSCI (11.1 μL , 69.9 μmol) was added to the solution. (See the general procedure for single step pre-activation based glycosylation for precautions) The mixture was vigorously stirred for 10 minutes, followed by addition of a solution of building block **25** (28.2 mg, 56.0 μmol) and TTBP (17.4 mg, 69.9 μmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 2 hours from -60 to -20°C and then the mixture was cooled down to -60°C , followed by sequential addition of AgOTf (18 mg, 69.9 μmol) in Et_2O (1 mL), acceptor **27** (20.8 mg, 42.0 μmol) and TTBP (17.4 mg, 69.9 μmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 5 minutes at -60°C and then *p*-TolSCI (8.9 μL , 56.0 μmol) was added into the solution and the reaction mixture

was stirred for 2 h from -60 to -20 °C. The reaction was quenched with Et_3N (50 μL), concentrated under vacuum to dryness. The resulting residue was diluted with CH_2Cl_2 (20 mL), followed by filtration. The organic phase was washed with saturated aqueous NaHCO_3 , H_2O and then dried over Na_2SO_4 , filtered and concentrated. Silica gel column chromatography (3:1:1 hexanes - ethyl acetate - CH_2Cl_2) afforded **28** as a white solid (41.2 mg, 67 %). Mp 82 - 84 °C; $[\alpha]_D^{20} +30.4$ ($c = 1$, CH_2Cl_2); $^1\text{H-NMR}$ (600 MHz, CDCl_3): δ 7.50-7.34 (m, 7H, aromatic), 7.31-7.16 (m, 16H, aromatic), 7.12-7.00 (m, 8H, aromatic), 6.92-6.90 (m, 2H, aromatic), 6.83-6.79 (m, 4H, aromatic), 5.40 (s, 1H, CHPh), 5.30 (d, 1H, $J = 8.4$ Hz), 5.12 (t, 1H, $J = 7.8$ Hz), 5.02 (d, 1H, $J = 11.4$ Hz), 4.85 (d, 1H, $J = 12$ Hz), 4.76 (d, 1H, $J = 11.4$ Hz), 4.70 (d, 1H, $J = 7.2$ Hz), 4.66-4.64 (m, 1H), 4.60-4.57 (m, 2H), 4.46-4.32 (m, 5H), 4.10 (d, 1H, $J = 7.8$ Hz), 4.09-4.07 (m, 1H), 3.99-3.97 (m, 1H), 3.78-3.76 (m, 7H), 3.65-3.64 (m, 1H), 3.59-3.55 (m, 2H), 3.53-3.46 (m, 3H), 3.43-3.37 (m, 4H), 3.32-3.28 (m, 3H), 3.14-3.10 (m, 2H), 2.96 (s, 1H), 0.78 (s, 9H, $(\text{CH}_3)_3\text{CSi}$), -0.11 (s, 3H, CH_3Si), -0.15 (s, 3H, CH_3Si); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3): δ 169.4, 167.3, 164.4, 159.5, 159.1, 139.6, 138.7, 138.3, 137.8, 133.8, 133.6, 132.7, 131.4, 131.2, 130.7, 130.2, 129.6 ($\times 2$), 129.1, 128.7, 128.4 ($\times 2$), 128.3, 128.2 ($\times 2$), 128.1, 127.7, 127.5, 127.3 ($\times 2$), 127.1, 126.7, 123.4, 122.6, 114.0, 113.7, 104.5, 101.8, 100.7, 98.5, 83.6, 83.3, 82.3, 76.5, 76.3, 76.0, 75.1, 74.9, 74.8, 74.7, 74.3, 74.1, 73.3, 72.4, 71.3, 70.0, 69.0, 68.2, 67.0, 57.1, 55.5 ($\times 2$), 52.5, 26.1, 18.1, -3.7 , -4.5 ; HRMS: $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{84}\text{H}_{93}\text{NNaO}_{20}\text{Si}$ 1486.5958; found 1486.5946; gHMQC (without ^1H decoupling): $^1J_{\text{C1,H1}} = 159.3$ Hz, 162.2 Hz, 162.2 Hz.

Methyl 2-O-benzoyl-3-O-benzyl-4-O-tert-butylidimethylsilyl-6-O-p-methoxybenzyl- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-2-azido-3,6-di-O-benzyl-2-deoxy- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-2,3-di-O-benzyl-6-O-p-methoxybenzyl- β -D-glucopyranoside (30)—Compound **30** was synthesized by a three-component one-pot procedure. After the donor **13** (50 mg, 69.93 μmol) and activated molecular sieve MS-4 Å (500 mg) were stirred for 30 minutes at room temperature in CH_2Cl_2 (5 mL), the solution was cooled to -60 °C, followed by addition of AgOTf (54 mg, 209 μmol) in Et_2O (1.5 mL). The mixture was stirred for 5 minutes at -60 °C and then p -TolSCl (11.1 μL , 69.9 μmol) was added into the solution. (See the general procedure for single step pre-activation based glycosylation for precautions) The mixture was vigorously stirred for 10 minutes, followed by addition of a solution of acceptor **29** (32.7 mg, 66.4 μmol) and TTBP (17.4 mg, 69.9 μmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 2 hours from -60 to -20 °C and then the mixture was cooled down to -60 °C, followed by sequential addition of AgOTf (18 mg, 69.9 μmol) in Et_2O (1 mL), acceptor **27** (27.7 mg, 55.9 μmol) and TTBP (17.4 mg, 69.9 μmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 5 minutes at -60 °C and then p -TolSCl (10.5 μL , 66.4 μmol) was added to the solution and the reaction mixture was stirred for 2 h from -60 to -20 °C. The reaction was quenched with Et_3N (50 μL), concentrated under vacuum to dryness. The resulting residue was diluted with CH_2Cl_2 (20 mL), followed by filtration. The organic phase was washed with saturated aqueous NaHCO_3 , H_2O and then dried over Na_2SO_4 , filtered and concentrated. Silica gel column chromatography (5:1:1 hexanes - ethyl acetate - CH_2Cl_2) afforded **30** as a gel (39.7 mg, 49 %). $[\alpha]_D^{20} +34.3$ ($c = 1$, CH_2Cl_2); $^1\text{H-NMR}$ (600 MHz, CDCl_3): δ 7.77-7.75 (m, 2H, aromatic), 7.44-7.20 (m, 21H, aromatic), 7.12-7.06 (m, 9H, aromatic), 6.98-6.97 (m, 2H, aromatic), 6.84-6.82 (m, 2H, aromatic), 6.77-6.76 (m, 2H, aromatic), 5.66 (d, 1H, $J = 4.2$ Hz), 5.19 (t, 1H, $J = 8.4$ Hz), 5.13 (d, 1H, $J = 11.4$ Hz), 5.00 (d, 1H, $J = 10.2$ Hz), 4.89 (d, 1H, $J = 11.4$ Hz), 4.75-4.59 (m, 6H), 4.47-4.42 (m, 3H), 4.24 (d, 1H, $J = 7.8$ Hz), 4.11 (d, 1H, $J = 12$ Hz), 4.02-3.95 (m, 3H), 3.87-3.84 (m, 1H), 3.79-3.61 (m, 9H), 3.60-3.58 (m, 1H), 3.51-3.50 (m, 4H), 3.41-3.25 (m, 8H), 3.12-3.06 (m, 2H), 3.43-3.37 (m, 4H), 3.32-3.28 (m, 3H), 3.14-3.10 (m, 2H), 2.96 (s, 1H), 0.87 (s, 9H, $(\text{CH}_3)_3\text{CSi}$), -0.02 (s, 3H, CH_3Si), -0.04 (s, 3H, CH_3Si). $^{13}\text{C-NMR}$ (150 MHz, CDCl_3): δ 164.7, 158.9, 158.8, 138.7, 138.3 ($\times 2$), 137.8, 137.7, 133.2, 130.6, 130.2, 129.5 ($\times 2$), 129.0, 128.9 ($\times 2$), 128.7, 128.4 ($\times 2$), 128.3 ($\times 3$), 128.2, 128.0 ($\times 2$), 127.7, 127.6, 127.5 ($\times 2$), 127.4, 127.3, 113.6, 113.4, 104.5,

99.7, 97.3, 84.9, 83.1, 82.6, 77.5, 76.8, 75.6, 75.1 ($\times 2$), 75.0, 74.5 ($\times 2$), 74.0, 73.7, 73.0, 72.4, 72.3, 71.3, 70.8, 69.0, 68.3, 66.8, 62.4, 57.0, 55.2 ($\times 2$), 25.9 ($\times 2$), 17.9, -3.8, -4.7; HRMS: $[M+Na]^+$ calcd for $C_{83}H_{97}N_3NaO_{18}Si$ 1474.6434; obsd 1474.6414; gHMQC (without 1H decoupling): $^1J_{C1',H1'}$ = 172.6 Hz, other two $^1J_{C1,H1}$ = 160.2 Hz, 162.8 Hz.

2,3,4,6-Tetra-O-benzoyl- α -D-galactopyranosyl triflate (38)—Compound **38** was obtained according to the general procedure. 1H -NMR (400 MHz, $CDCl_3$, $-60^\circ C$): δ 8.12-7.20 (m, 28 H, 4 *COPh*, (*SPhMe*)₂), 6.57 (d, 1 H, $J_{1,2}$ = 3.2 Hz, H-1), 6.17 (d, 1 H, $J_{1,2}$ = 2.0 Hz, H-4), 6.11-5.80 (m, 2 H, H-2, H-3), 4.94 (dd, 1 H, $J_{5,6a}$ = 8.0 Hz, $J_{5,6b}$ = 5.2 Hz, H-5), 4.66 (dd, 1 H, $J_{6a,5}$ = 8.0 Hz, $J_{6a,6b}$ = 11.6 Hz, H-6a), 4.43 (dd, 1 H, $J_{6b,5}$ = 5.2 Hz, $J_{6b,6a}$ = 11.6 Hz, H-6b), 2.44 (s, 6 H, (*SPhMe*)₂); ^{13}C -NMR (100 MHz, $CDCl_3$, $-60^\circ C$): δ 166.4, 165.8, 165.8, 165.5 (4 C, *COPh*), 134.7, 134.3, 134.2, 131.9, 130.4, 130.3, 130.2, 130.0, 129.3, 129.2, 129.0, 128.9, 128.8, 128.3, 128.2, 127.7 (*COPh*-C, (*SPhMe*)₂, some signals overlapped), 104.4 (1 C, C-1), 71.6, 67.7, 67.4, 66.7, 62.4 (5C, C-2~6), 22.4 (2 C, (*SPhMe*)₂).

2,3,4,6-Tetra-O-benzoyl- β -D-galactopyranosyl-(1 $\rightarrow$ 6)-1,2:3,4-diisopropylidene- α -D-galactopyranoside (40)—Donor **5** (31 mg, 44.1 μ mol, 1.0 eq) and AgOTf (33.9 mg, 132.3 μ mol, 3.0 eq) were added to an NMR tube and dried *in vacuo* for 3 hours. $CDCl_3$ (0.75 mL) was added slowly at $-60^\circ C$. Then the donor was pre-activated by the addition of *p*-TolSCl (7.1 μ L, 44.1 μ mol, 1.0 eq) at $-60^\circ C$ and 1H -, ^{13}C -, ^{19}F - and 2D NMR were acquired at $-60^\circ C$. This was followed by the addition of acceptor **39** (10.3 mg, 39.7 μ mol, 0.9 eq) and TTBP (11.0 mg, 44.1 μ mol, 1.0 eq) as acid scavenger in $CDCl_3$ (0.25 mL). The reaction mixture was quenched by Et_3N , and purified by flash column chromatograph (hexanes : ethyl acetate = 4:1) to give **40** (29.9 mg, 35.7 μ mol, 90%) as a colorless syrup. $[\alpha]_D^{20} +37.4^\circ$ (c 1.0, $CHCl_3$); 1H -NMR (600 MHz, $CDCl_3$): δ 8.07-7.20 (m, 20 H, 4 *COPh*), 5.83 (d, 1 H, $J_{4',3'}$ = 3.6 Hz, H-4'), 5.80 (dd, 1 H, $J_{2',1'}$ = 7.8 Hz, $J_{2',3'}$ = 10.8 Hz, H-2'), 5.60 (dd, 1 H, $J_{3',2'}$ = 10.8 Hz, $J_{3',4'}$ = 3.6 Hz, H-3'), 5.40 (d, 1 H, $J_{1,2}$ = 3.2 Hz, H-1), 5.01 (d, 1 H, $J_{1',2'}$ = 7.8 Hz, H-1'), 4.67 (dd, 1 H, $J_{6a',5'}$ = 5.4 Hz, $J_{6a',6b'}$ = 11.4 Hz, H-6'a), 4.42-3.38 (m, 2 H, H-5', H-6'b), 4.33 (t, 1 H, $J_{3,2} = J_{3,4} = 6.6$ Hz, H-3), 4.20 (dd, 1 H, $J_{2,1}$ = 3.2 Hz, $J_{2,3} = 6.6$ Hz, H-2), 4.06 (dd, 1 H, $J_{6a,5} = 7.2$ Hz, $J_{6a,6b} = 10.8$ Hz, H-6a), 3.95-3.70 (m, 2 H, H-5, H-6b), 1.38 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3); ^{13}C -NMR (150 MHz, $CDCl_3$): δ 166.3, 165.8, 165.7, 165.5 (4 C, 4 *COPh*), 133.8, 133.5, 133.3, 130.3, 130.2, 130.0, 129.6, 129.2, 129.0, 128.8, 128.7, 128.5, (*COPh*-C, some signals overlapped), 109.4 (1 C, $C(CH_3)_2$), 108.7 (1 C, $C(CH_3)_2$), 101.9 (1 C, $J_{C-1',H-1'}$ = 165.4 Hz, C-1'), 96.4 (1 C, $J_{C-1,H-1}$ = 176.1 Hz, C-1), 72.0, 71.5, 71.2, 70.7, 70.5, 69.9, 68.6, 68.4, 67.7, 62.3 (C-2~6, some signals overlapped), 26.1, 25.9, 25.1, 24.4 (4 C, 2 $C(CH_3)_2$); ESI-MS: $[M + Na]^+$ calcd for $C_{46}H_{46}NaO_{15}$ 861.3; found 861.2; HRMS: $[M + NH_4]^+$ calcd for $C_{46}H_{50}NO_{15}$ 856.3180; found 856.3162.

3,4,6-Tri-O-benzyl-D-galactopyranosyl benzoxonium ion (41)—Compound **41** was obtained according to the general experimental procedure. 1H -NMR (400 MHz, $CDCl_3$, $-60^\circ C$): δ 8.10-7.24 (m, 29 H, H-1, 3 CH_2Ph , *CPh*, (*SPhMe*)₂), 5.77 (bs, 1 H, H-2), 4.89-4.67 (m, 3 H, 2 *CHHPh*, *CHHPh*), 4.62-4.58 (m, 2 H, *CHHPh*, H-5), 4.42-4.34 (m, 2 H, *CHHPh*, H-3), 4.30-4.20 (m, 2 H, *CHHPh*, H-4), 3.79-3.76 (1 H, H-6a), 3.64-3.58 (1 H, H-6b), 2.44 (s, 6 H, (*SPhMe*)₂); ^{13}C -NMR (100 MHz, $CDCl_3$, $-60^\circ C$): δ 180.8 (1 C, C-7), 140.9, 137.7, 137.5, 133.9, 131.8, 131.0, 130.3, 130.0, 129.4, 128.8, 128.7, 128.5, 128.3, 128.1, 127.5, 125.0, 121.8, 118.6, 118.0 (*CPh*-C, CH_2Ph , (*SPhMe*)₂, some signals overlapped), 114.2 (1 C, C-1), 83.9 (1 C, C-2), 75.6, 74.8, 73.6, 71.6, 69.0 (7 C, C-3~6, CH_2Ph), 22.4 (1 C, (*SPhMe*)₂).

2,3,4,6-Tetra-O-acetyl- α -D-glucopyranosyl triflate (44) and 3,4,6-tri-O-acetyl-D-glucopyranosyl acetoxonium ion (45)—The mixture of intermediates **44** and **45** was obtained following the general experimental procedure. For the mixture of **44** and **45** in 1 : 1 ratio: 1H -NMR (400 MHz, $CDCl_3$, $-60^\circ C$): δ 7.41-7.24 (m, 9 H, H-1, 2 (*SPhMe*)₂), 6.21 (d,

1 H, $J_{1,2} = 2.4$ Hz, H-1 from **44**), 5.73 (1 H, H-3 from **45**), 5.57 (3 H, H-2 from **45**, H-3 from **44**, H-4 from **45**), 5.31 (2 H, H-2 from **44**, H-4 from **44**), 4.82 (1 H, H-5 from **45**), 4.44 (1 H, H-5 from **44**), 4.14 (4 H, 2 H-6 from **44**, 2 H-6 from **45**), 2.82 (3 H, CCH_3 from **45**), 2.44 (s, 12 H, 2 (SPhMe)₂), 2.19, 2.15, 2.14, 2.09, 2.07, 2.03 (21 H, 7 COCH₃); ¹³C-NMR (100 MHz, CDCl₃, -60 °C): δ 191.7 (1 C, C-7 from **45**), 171.4, 171.3, 170.8, 170.8, 170.7, 170.5, 169.6 (7 C, 4 COCH₃ from **44** and 3 COCH₃ from **45**), 132.2, 128.8, 121.9, 118.7 ((SPhMe)₂, some signals overlapped), 113.3 (1 C, C-1 from **45**), 104.1 (1 C, C-1 from **44**), 80.3, 72.5, 70.9, 68.9, 66.7, 66.6, 65.8, 64.2, 62.5, 61.5 (12 C, C-2~6, some signals overlapped), 22.5, 21.4, 21.4, 21.3, 21.2, 21.0, 17.6 (9 C, 7 COCH₃, CCH₃, (SPhMe)₂, some signals overlapped). For **44**: ¹H-NMR (400 MHz, CDCl₃, -20 °C): δ 7.34-7.09 (m, 8 H, H-1, (SPhMe)₂), 6.21 (d, 1 H, $J_{1,2} = 2.4$ Hz, H-1), 5.57 (s, 1 H, H-3), 5.33-5.30 (m, 2 H, H-2, H-4), 4.46-4.41 (m, 1 H, H-5), 4.18-4.10 (m, 4 H, 2 H-6), 2.44 (s, 6 H, (SPhMe)₂), 2.18, 2.15, 2.14, 2.07, 2.03 (s, 12 H, 4 COCH₃); ¹³C-NMR (100 MHz, CDCl₃, -20 °C): δ 171.3, 170.5, 170.5, 170.5 (4 C, 4 COCH₃), 130.4, 129.4, 128.7, 118.7 ((SPhMe)₂, some signals overlapped), 104.1 (1 C, C-1), 71.0, 66.8, 66.7, 65.9, 61.4 (5 C, C-2~6), 21.6, 21.3, 21.2, 21.1, 21.0 (5 C, 5 COCH₃, (SPhMe)₂).

2,3,4,6-Tetra-O-acetyl- β -D-glucopyranosyl-(1 $\rightarrow$ 6)-1,2:3,4-diisopropylidene- α -D-galactopyranoside (46**)**—Donor **16** (20.0 mg, 44.0 μ mol, 1.0 eq) and AgOTf (33.9 mg, 132.0 μ mol, 3.0 eq) were added to an NMR tube and dried under *in vacuo* for 3 hours. CDCl₃ (0.75 mL) was added slowly at -60 °C. Then the donor was pre-activated by addition of the *p*-TolSCI (7.0 μ L, 44.0 μ mol, 1.0 eq) at -60 °C and the ¹H-, ¹³C-, ¹⁹F- and 2D NMR spectra were acquired. This was followed by addition of the acceptor **39** (10.3 mg, 39.7 μ mol, 0.9 eq) and TTBP (10.9 mg, 44.0 μ mol, 1.0 eq) as acid scavenger in CDCl₃ (0.25 mL). After reaching -20 °C, the reaction mixture was quenched by Et₃N and purified by flash column chromatograph (hexanes : ethyl acetate = 3:1) to give **46** (20.0 mg, 33.7 μ mol, 85.0%) as a white foam. $[\alpha]_D^{20} - 50.80^\circ$ (c 1.0, CHCl₃); ¹H-NMR (600 MHz, CDCl₃): δ 5.47 (d, 1 H, $J_{1,2} = 4.8$ Hz, H-1), 5.35 (d, 1 H, $J_{4,3} = 3.0$ Hz, H-4), 5.18 (dd, 1 H, $J_{2',1'} = 8.4$ Hz, $J_{2',3'} = 10.2$ Hz, H-2'), 4.98 (dd, 1 H, $J_{3',2'} = 10.8$ Hz, $J_{3',4'} = 3.0$ Hz, H-3'), 4.57-4.54 (m, 2 H, H-1', H-4'), 4.26 (dd, 1 H, $J_{2,1} = 4.8$ Hz, $J_{2,3} = 2.4$ Hz, H-2), 4.15-4.07 (m, 3 H, H-5', H-6'a, H-6'b), 4.01 (dd, 1 H, $J_{6a,5} = 3.0$ Hz, $J_{6a,6b} = 10.8$ Hz, H-6a), 3.91-3.84 (m, 2 H, H-3, H-5), 3.65 (dd, 1 H, $J_{6b,5} = 3.0$ Hz, $J_{6b,6a} = 10.8$ Hz, H-6b), 2.11 (s, 3 H, COCH₃), 2.04 (s, 3 H, COCH₃), 2.02 (s, 3 H, COCH₃), 1.95 (s, 3 H, COCH₃), 1.45 (s, 3 H, C(CH₃)₂), 1.42 (s, 3 H, C(CH₃)₂), 1.29 (s, 3 H, C(CH₃)₂), 1.29 (s, 3 H, C(CH₃)₂); ¹³C-NMR (150 MHz, CDCl₃): δ 170.7, 170.5, 170.4, 170.0 (4 C, 4 COCH₃), 109.6, 108.9 (2 C, 2 C(CH₃)₂), 102.2 (1 C, $J_{C-1',H-1'} = 167.4$ Hz, C-1'), 96.4 (1 C, $J_{C-1,H-1} = 177.6$ Hz, C-1), 71.5, 71.0, 70.8, 70.7, 70.6, 69.8, 68.8, 68.1, 67.2, 61.4 (C-2~6, some signals overlapped), 26.2, 26.1, 25.3, 24.5 (4 C, 2 C(CH₃)₂), 21.0, 20.9, 20.9, 20.8 (4 C, 4 COCH₃). ESI-MS: $[M + Na]^+$ calcd for C₂₆H₃₈NaO₁₅: 613.2; found 613.3; HRMS: $[M + Na]^+$ calcd for C₂₆H₃₈NaO₁₅: 613.2108; found 613.2114.

2-O-Benzoyl-3,4,6-tri-O-benzyl- β -D-galactopyranosyl-(1 $\rightarrow$ 6)-1,2:3,4-

diisopropylidene- α -D-galactopyranoside (47**)**— $[\alpha]_D^{20} - 19.7$ (c 1.0, CHCl₃); ¹H-NMR (600 MHz, CDCl₃): δ 8.05-7.11 (m 20 H, C(=O)Ph, 3 CH₂Ph), 5.64 (dd, 1 H, $J_{2',1'} = 7.8$ Hz, $J_{2',3'} = 10.2$ Hz, H-2'), 5.37 (d, 1 H, $J_{1,2} = 4.8$ Hz, H-1), 4.98 (d, 1 H, $J = 12.0$ Hz, CHHPh), 4.66-4.60 (3 H, H-1', CHHPh, CHHPh), 4.50-4.42 (3 H, 2 CHHPh, CHHPh), 4.40 (dd, 1 H, $J_{6a',5'} = 1.8$ Hz, $J_{6a',6b'} = 8.4$ Hz, H-6a'), 4.16 (dd, 1 H, $J_{2,1} = 4.8$ Hz, $J_{2,3} = 4.8$ Hz, H-2), 4.10 (dd, 1 H, $J_{6b',5'} = 1.8$ Hz, $J_{6b',6a'} = 8.4$ Hz, H-6b'), 4.01 (d, 1 H, $J_{3',4'} = 2.4$ Hz, H-4'), 3.96 (dd, 1 H, $J_{6a,5} = 4.8$ Hz, $J_{6a,6b} = 10.8$ Hz, H-6a), 3.80-3.50 (m, 6 H, H-3, H-3', H-4, H-5, H-5', H-6b), 1.37 (s, 3 H, C(CH₃)₂), 1.21 (s, 3 H, C(CH₃)₂), 1.15 (s, 3 H, C(CH₃)₂), 1.09 (s, 3 H, C(CH₃)₂); ¹³C-NMR (150 MHz, CDCl₃): δ 1165.6 (C, C(=O)Ph), 138.7, 138.1, 137.9, 133.0, 130.5, 130.3, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9 (CH₂Ph-C, C(=O)Ph-C, some signals overlapped), 109.2, 108.5 (2 C, 2 C(CH₃)₂), 102.0 (1 C, $J_{C-1',H-1'} = 164.3$ Hz, C-1'), 96.3 (1

C, $J_{C-1,H-1} = 175.3$ Hz, C-1), 80.9, 74.7, 73.8, 72.6, 72.0, 71.9, 71.0, 70.7, 70.6, 68.7, 68.0, 67.9, 67.6 (C-2~6, some signals overlapped), 26.1, 25.8, 25.1, 24.3 (4 C, 2 C(CH₃)₂); ESI-MS: [M + Na]⁺ calcd for C₄₆H₅₂NaO₁₆: 819.3; found 819.4; HRMS: [M + NH₄]⁺ calcd for C₄₆H₅₆NO₁₆: 814.3803; found 814.3806.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Schematic demonstrations of a) inherent α/β facial selectivity at the TS for **5** and **8** glycosylations with an acceptor; and b) TS energy difference in reaction coordinates of donor **8** versus **5**.

Figure 2. ¹H-NMR and ¹³C-NMR spectra of the intermediate formed after pre-activation of donor **5** in CDCl₃ at -60 °C.

Figure 3.

a) ^1H -NMR and b) ^{13}C -NMR spectra of the intermediates formed after pre-activation of donor **11** and c) ^{13}C -NMR after pre-activation of donor **11a** in CDCl_3 at -60°C .

Figure 4. a) ¹H-NMR and b) ¹³C-NMR spectra of the intermediates formed after pre-activation of donor **16** in CDCl₃ at -60 °C; c) ¹H-NMR and d) ¹³C-NMR spectra after warming to -20 °C.

Scheme 1.

Scheme 2.

Scheme 3.

Competitive glycosylation of acceptor **39** by a mixture of donors **5** and **11**.

Table 1

Glycosylation results of various donor/acceptor pairs

<div> <div>Donor (1 eq) + AgOTf</div> <div> 1) <i>p</i>-TolSCl, -60 °C → 2) acceptor (0.9 eq), TTBP, -60 -- -20 °C </div> <div>Product</div> </div>				
Entry #	Donor	Acceptor	Product	Yield
1	5	3	6	< 10%
2	5	4	7	< 10%
3	8	3	9	67%
4	8	4	10	65%
5	11	4	12	56% (48% β + 8% α)
6	13	3	14	74%
7	13	4	15	70%
8	16	17	18	< 10%
9	13	17	19	75%
10	20	21	22	< 10%
11	23	21	24	73%
12	11	25	26	65% (51% β + 14% α)