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ortho-(*para*-Methoxyphenylethynyl)phenyl (MPEP) Glycosides: Versatile and New Glycosylation Donors for the Highly Efficient Construction of Glycosidic Linkages

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ABSTRACT: A novel alkyne-activation based glycosylation protocol, *ortho*-(*para*-methoxyphenylethynyl)phenyl (MPEP) glycoside protocol, was established. The glycosyl MPEP donors were shelf-stable and could be prepared efficiently via Sonogashira reaction from the corresponding *ortho*-iodophenyl (IP) glycosides. The outstanding stability of IP glycosides as well as their efficient transformations to MPEP glycosides dramatically facilitates the syntheses of MPEP glycosyl donors and IP glycosyl acceptors. Furthermore, they make the MPEP glycosylation protocol applicable to the latent-active oligosaccharide and glycoconjugate synthetic strategy with IP glycosides as the latent form and MPEP glycosides as the active form, as illustrated by the highly efficient fabrication of *Streptococcus pneumoniae* type 3 trisaccharide. The phenolic glycoside nature of MPEP glycosides bestows the new glycosyl donors enhanced stability compared to their thioglycoside counterparts toward activation conditions applied for glycosyl trichloroacetimidate (TCAI) and *ortho*-alkynylbenzoate (ABz) donor. Thus, MPEPs can also be utilized in the selective one-pot glycosylation strategy, as exemplified by the syntheses of oligosaccharides via successive glycosylations with glycosyl TCAI, ABz, and EPMP as donors. Although sharing the identical promotion conditions with thioglycoside donors, the odor-free starting material (2-iodophenol), the stable departure structure of the leaving group (3-iodobenzofuran), as well as the decreased nucleophilicity of the *O*-MPEP glycoside helps to eliminate the major three shortcomings of the thioglycoside donors (unpleasant odor of starting material, detrimental interference of the cleaved leaving group, and aglycon intra- or inter-molecular migration) while maintaining the prominent features of thioglycoside methodology including the broad substrates scopes, the mild promotion conditions, the stability of glycosyl donors, and the versatile applications in existing glycoside synthesis strategies. Based on the experimental results, a mechanism of MPEP activation was proposed, which was supported by systematic mechanistic investigations, including trapping of active intermediates, design of a vital disarmed rhamnosyl donor, and isolation and characterization of the departure species of the leaving group.

INTRODUCTION

Oligosaccharide and glycoconjugates play critical roles in an array of biological processes;[1] meanwhile, as secondary metabolites, glycoconjugates are widely spread in nature, which have been deemed as indispensable sources for new drug development.[2] Due to the high microheterogeneities of oligosaccharide and glycoconjugate compounds in natural resources, the direct acquisition of them from natural resources homogeneously via separation is a formidable task. Therefore, chemical synthesis becomes an important tool for gaining access to these valuable compounds. Ever since the first glycosylation reaction reported by Fischer in 1893 with free glucose as the donor,[3] continuous efforts from generations of carbohydrate chemists have led to the discovery of a variety of glycosylation donors, among which glycosyl bromides,[4] thioglycosides,[5] and glycosyl trichloroacetimidates (TCAI)[6] are the most widely used ones and are playing cornerstone roles in the modern synthetic carbohydrate chemistry. Fueled by the continuously increasing demand of pure oligosaccharides and glycoconjugates with defined chemical structures, the discovery of new glycosylation protocols is still the most active direction in carbohydrate chemistry, resulting in the advents of quite a few conceptually new and efficient glycosylation methods, such as glycosyl thioimidate,[7] 2-(benzyloxycarbonyl)benzyl (BCB) glycoside,[8] dehydrative and oxidative,[9] glycosyl *ortho*-alkynylbenzoate (ABz),[10] and 2-(2-propylsulfinyl)benzyl (PSB)/S-2-(2-propylsulfinyl)benzyl (SPSP) glycosides methods.[11] Apart from the inherent chemical characters, the potential of a particular glycosylation protocol in glycosidic linkage construction is also influenced by the chosen synthetic strategies. Accordingly, sophisticated strategies including latent-active,[7,8,11,12] one-pot glycosylation,[13] and solid-phase synthesis strategies have been established.[14] Combination of modern glycosylation methods with appropriate strategies has greatly enhanced synthetic capability of chemists, with a vast number of complex oligosaccharides and glycoconjugates succumbed to the efficient total synthesis.[15]

As glycosyl donors, thioglycosides occupy an important niche in the modern carbohydrate synthesis field. A sur-

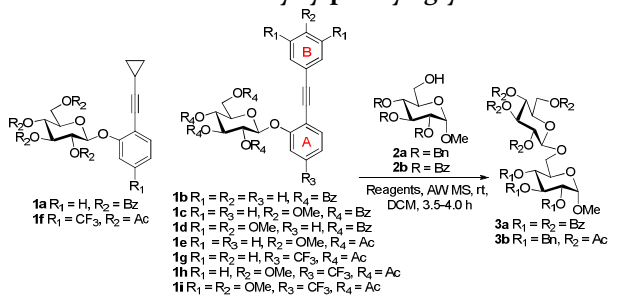
vey of 734 glycosidic linkage construction reactions published in 1995 revealed that about one quarter of them were fashioned by thioglycosides donors.[16] The high application frequency is determined by several advantages of thioglycosides over other types of glycosyl donors. These include easy activation under various conditions, high stabilities toward a wide range of reaction conditions, and easy accessibility. Meanwhile, thioglycosides have been fully proven to have impressive performance in latent-active[17] and one-pot synthesis strategies,[5a,13] lending additional credit to these traditional while important donors.[18] Despite these salient advantages, the shortcomings associated with them, including the unpleasant odor of volatile thiols used in thioglycoside preparation,[19] high electrophilic property of the departure species of the leaving groups,[20] and the propensity of aglycon transfer,[21] restrict the application scope, and sometimes can ruin the synthetic plan. Under such circumstances, a new type of glycosyl donors which can maintain the merits while overcoming the defects of thioglycosides is highly desirable. Based on alkyne-functionality activation with the combination of NIS/TMSOTf,[10,22] a new type of phenyl *O*-glycoside donor, *ortho*-(*para*-methoxyphenylethynyl)phenyl (MPEP) glycoside, was discovered.[23] The new glycosylation donors were so stable that they could be stored at room temperature for at least six months without noticeable decomposition. Moreover, the new glycosylation protocol not only enjoys broad substrate scopes both for glycosyl donors and for acceptor but also fit into latent-active and orthogonal one-pot synthesis strategies, whereby one bioactive trisaccharide as well as three complex oligosaccharides were synthesized efficiently.

RESULTS AND DISCUSSION

Although the previous work regarding the synthesis of benzofuran derivatives from *ortho*-alkynylphenyl ether starting materials implied the feasibility of using *ortho*-alkynylphenyl group as leaving group in design of a new type of glycosyl donors,[24] results from Yu group regarding the more reactive *ortho*-alkynylphenyl *S*-glycoside donors,[25] which preferably afforded orthoester side products when coupled with acceptors under the promotion of Au(I) catalyst, indicated that to utilize the less reactive *ortho*-alkynylphenyl *O*-glycoside as donor a systematic screening of substitution patterns on the *ortho*-alkynylphenyl group as well as promotion conditions was required. Thus, a series of *ortho*-alkynylphenyl glycosides **1a**-**i** with the core *ortho*-alkynylphenyl scaffold decorated with various substituents were synthesized via a two-step sequence of 2-iodophenol glycosylation and Sonogashira coupling with appropriate alkynes.[26] With all potential donors in hand, the optimal leaving group as well as corresponding activation conditions were screened extensively, and the representative results were listed in table 1. Expectedly, the *orhto*-alkynylphenyl glycosides **1a** and **1b** were proved to be inert to the generally applied reagents used for the activation of alkyne, including $Ph_3PAuNTf_2$, $Ph_3PAuOTf$, and TMSOTf at the presence of acceptor **2a**.[27] In order to improve the reactivity of the donors, a strategy to realize a favorable distribution of electron density in the alkyne functionality by introduction of electron-donating substituents on the B phenyl ring and electron-withdrawing substituents on the A ring of **1b** was adopted. Although donors carrying electron-withdrawing substituent CF_3 on the A phenyl ring such as **1f**-**i** still afforded disappointing results, donors with electron-donating substituents including **1c**-**e** provided more promising results. Glycoside **1c** carrying a *para*-located methoxy group on the B phenyl ring coupled with **2b**[28] under the effect of $Ph_3PAuOTf$, albeit with low glycosylation yield (trace amount of **3a**[29]) and high catalyst loading (0.8 eq, entries 1 and 2). The glycosylation yield was further improved to 26% by 0.4 equivalents of TMSOTf (entry 3). Surprisingly, $Ph_3PAuOTf$ and TMSOTf could not trigger the glycosylation between *ortho*-alkynylphenyl glycoside **1d** and **2a**/**2b**, although three methoxy groups were incorporated in the B phenyl ring of **1d** (entries 4-6). Nevertheless, stoichiometric amounts of either I_2 or TfOH effected the desired glycosylation of **1d** to afford **3a** (trace and 78% yield respectively, entries 7 and 8). The influence of sugar residue protecting groups on the donor activity was also evaluated with **1e**, in which all hydroxyl groups of the sugar residue were blocked with acetyl groups. The exchange of protecting groups resulted in a drop in reactivity as either Au(I) catalyst (0.4 eq) or TMSOTf (0.8 eq) could not lead to the formation of the desired glycosylation products (entries 9 and 10).

Reviewing all the results gleaned above revealed that only glycoside **1c** exhibited reasonable reactivity (entries 2 and 3). Detailed investigations regarding promotion conditions were then conducted. Although I_2 could not mediate an efficient coupling between **1c** and **2b**, the same reaction was promoted to reach completion under the effect of TMSOTf (1.2 eq) and a good yield of **3a** was isolated (71%, entries 11, 12). $Hg(OTf)_2$[30] was also screened, but inferior result was observed (entry 13). To our delight, when the combination of NIS/TMSOTf (1.5 eq NIS and 0.5 eq TMSOTf)[31] was invoked at -35 °C, the glycosylation reaction between **1c** and **2b** proceeded so efficiently that almost quantitative yield of **3a** was obtained within 3.5 hours (entry 14). Although donor **1d** could also be activated to couple with **2b**, an inferior yield of **3a** was obtained (entry 15). Thus, the leaving group as well as the optimal promotion conditions were fixed as *ortho*-(*para*-methoxyphenylethynyl)phenyl (MPEP) group and NIS/TMSOTf. Similarly, the peracetylated MPEP glucoside **1e** could also be activated with NIS/TMSOTf, and its coupling with **2a** proceeded smoothly to yield **3b** (76%, entry 16).[32] Moreover, to the best of our knowledge, these trials represent the first examples of alkyne activation by NIS/TMSOTf.

Table 1. Leaving group and activation conditions optimization of *ortho*-alkynylphenyl glycoside donors

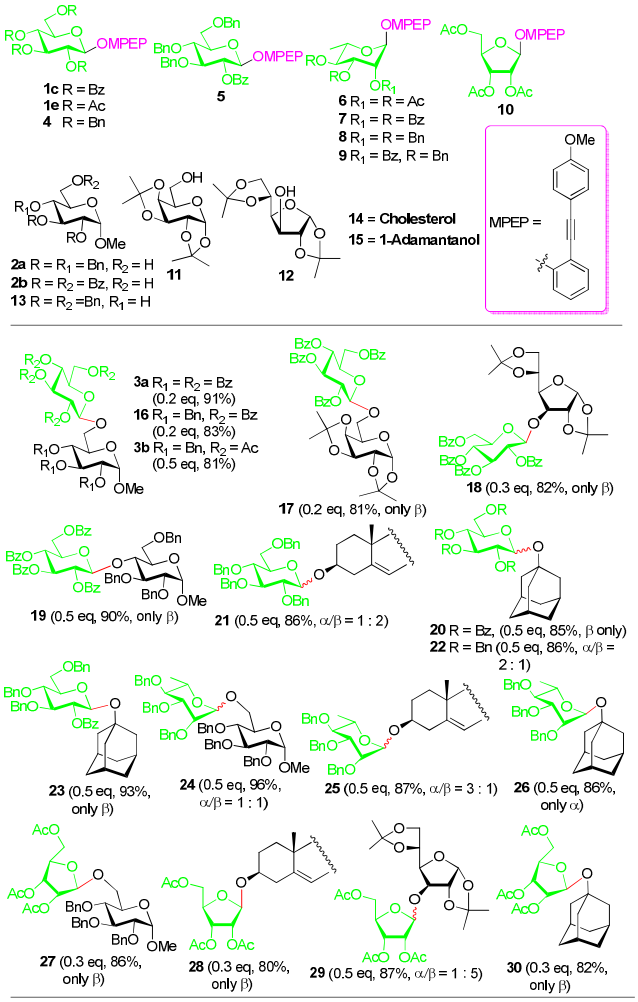


Entry	Donor	Acceptor	Reagents (equiv)	Product	Yield[a,b]
1	**1c**	**2b**	$Ph_3PAuOTf$ (0.3)	–	NR
2	**1c**	**2b**	$Ph_3PAuOTf$ (0.8)	**3a**	trace
3	**1c**	**2b**	TMSOTf (0.4)	**3a**	26%
4	**1d**	**2a**	$Ph_3PAuOTf$ (0.4)	--	NR
5	**1d**	**2b**	$Ph_3PAuOTf$ (0.4)	–	NR
6	**1d**	**2a**	TMSOTf (0.4)	–	NR
7	**1d**	**2b**	I_2 (2.0)	**3a**	trace
8	**1d**	**2b**	TfOH (1.5)	**3a**	78%
9	**1e**	**2b**	$Ph_3PAuOTf$ (0.4)	--	NR
10	**1e**	**2b**	TMSOTf (0.8)	–	NR
11	**1c**	**2b**	TMSOTf (1.2)	**3a**	71%
12	**1c**	**2b**	I_2 (2.0)	**3a**	10%
13	**1c**	**2b**	$Hg(OTf)_2$ (0.5)	**3a**	10%
14	**1c**	**2b**	NIS (1.5), TMSOTf (0.5)	**3a**	99%[c]
15	**1e**	**2a**	NIS (1.5), TMSOTf (0.3)	**3b**	76%[c]
16	**1d**	**2b**	NIS (1.5), TMSOTf (0.5)	**3a**	74%[c]

[a]NR meant no reaction was detected. [b]Isolated yield. [c]The reactions were conducted at -35 °C.

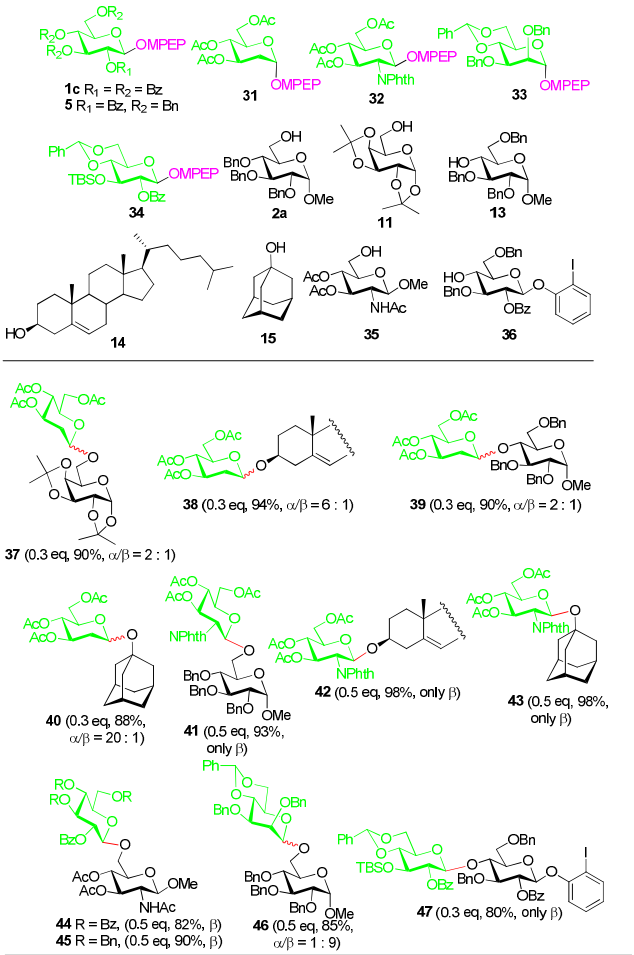
With the optimal leaving group and corresponding activation conditions settled, our attention was shifted to the substrate scope investigations for both donors and acceptors. Applications of MPEP donors in common glycosidic linkages construction was investigated first (Table 2). Thus, the condensation between **1c** and **2b** was reinvestigated with reduced amounts of TMSOTf (0.2 eq), and a slight drop in chemical yield of **3a** was observed (91% vs 99%). Upon raising the TMSOTf to 0.5 equivalents, the yield of the condensation between **1e** and **2a** was enhanced, and 81% yield of **3b** was recorded (*cf.*, table 1, entry 15). Similarly, **1c** could also react efficiently with **2a** to afford **16** in a good 83% yield,[33] and in this reaction, only 0.2 equivalents of TMSOTf were required. Thanks to the mild reaction conditions, primary and secondary acceptors carrying acid-sensitive isopropylidene groups were also proved to be suitable substrates for this new glycosylation protocol, and acceptors such as **11**[34] and **12**[35] afforded corresponding disaccharide products **17**[29b] and **18**[36] with good yields when coupled with **1c** (81%, 82% yields, respectively). Under the promotion of NIS/TMSOTf, glucosyl 4-OH acceptor **13**[37] could also couple fluently with **1c**, delivering **19** in 90% yield.[29b] Most noticeably, under standard reaction conditions, even the most hindered tertiary acceptor **15** could condensed efficiently with **1c**, affording **20** in a high 85% yield.[12d] Converting **1c** to its 'armed' and 'superarmed' counterparts led to MPEP glucoside donors **4** and **5**, both of which exhibited impressive glycosylation capability, as exemplified by their couplings with extremely hindered acceptors **14** and **15** to furnish **21**,[38] **22**,[38] and **23** (86%, 86%, and 93% yields). As typical representatives of L-series sugar donors, MPEP rhamnosides protected in disarmed (**6** and **7**), armed (**8**), and superarmed (**9**) patterns were then tested. As 6-deoxyglycosides, donors **6**-**9** were originally envisioned to give even better glycosylation results in comparison to their hexose counterparts. Nevertheless, results beyond our expectation were obtained: disarmed and superarmed donors **6**, **7**, and **9** were totally inert to the standard promotion conditions, while armed MPEP **8** was a vital donor to couple with **2a**, **14**, and **15**, delivering good to excellent yields of desired glycosylation products **24**,[39] **25**,[40] and **26** (96%, 87%, and 85%). As expected, the corresponding glycosylation reactions of perbenzylated donors **4** and **8**, in the absence of neighboring participating groups, led to the glycosylation products as mixtures of a pair of anomers. In terms of rhamnosyl MPEP **8**, benefited from the remote activation mechanism,[41] the S_N2 substitution was favored to a large extent, thus the β-rhamnosides were isolated in considerable amounts for the glycosylation of **8** with acceptors **2a** and **14** (for **24** and **25**). With the steric hindrance of the acceptors increased, the α-isomers prevailed, and for the condensation of **8** and **15**, only α glycosylation product was detected (for **26**). Furthermore, MPEP ribofuranoside **10** was also a capable donor to conjugate with acceptors **2a**, **12**, **14**, and **15** to furnish **27**, **28**, **29**, and **30** smoothly (86%, 80%, 87%, and 82%). Interestingly, despite installed with an acetyl group on the 2-OH, donor **10** still offered **29** as a mixture of α/β isomers when coupled with **12**, an extremely hindered acceptor.[42]

Table 2. Construction of common glycosidic linkages with MPEP glycosides as donors



To further expand the substrate scopes, the feasibility of MPEP glycosylation method in formations of special and challenging glycosidic linkages, including 2-deoxy glycosidic linkage, glycosamine-containing glycosidic linkage, β-mannopyranosyl linkage, as well as *ortho*-iodophenyl (IP) glycoside-containing glycosidic linkage, was examined (Table 3). Pleasantly, when the MPEP 2-deoxyglucoside donor **31** was put to the standard glycosylation conditions at the presence of **11**, **13**, **14**, and **15**, the corresponding glycosylation products **37**, **38**, **39**, and **40** were generated efficiently (90%, 94%, 90%, and 88% yields, respectively).[12d] Due to the absence of stereocontrolling element in donor **31**, glycosylation products **37**, **38**, and **39** were obtained as mixtures of α/β isomers, with the α-epimers predominating. Effected by serious steric hindrance and lowered reactivity, the coupling of **15** with **31** proceeded stereoselectively to furnish **40** almost solely (α/β = 20 : 1). Encouraged by these promising results, glycosylations with MPEP 2-aminoglucoside **32** were carried out subsequently. All acceptors tested including active primary acceptor **2a** or inert secondary and tertiary acceptors **14** and **15**, afforded excellent yields of the desired products (**41**: 93%,[43] **42**: 98%,[44] **43**: 98%).[44] Glycosylation of 2-acetamidoglycosyl acceptors with thioglycoside donors often gives unsatisfactory yield due to the undesired interference of departure species of the leaving groups.[20] In sharp contrast, with MPEP glucosides **1c** and **5** as donors, the glycosylations of acetamido-containing acceptor **35** [45] proceeded so efficiently that 82% yield of **44** as well as 90% yield of **45** were recorded, and no evidence supporting the existence of departure species interference was observed. In particular, the MPEP glycosylation protocol could also find application in the challenging β-mannopyranosyl glycosidic linkage construction,[46] as illustrated by the condensation between **33** and **2a** to give the desired β-mannopyranoside **46**[47] predominately (85%, α/β = 1 : 9) without further optimization. When IP glucoside **36** was selected as acceptor to condense with orthogonally protected MPEP donor **34**, the desired disaccharide **47** was isolated in a good 80% yield, and no premature activation of **36** was detected, implying that the present MPEP glycosylation protocol might find application in the highly efficient latent-active strategy.

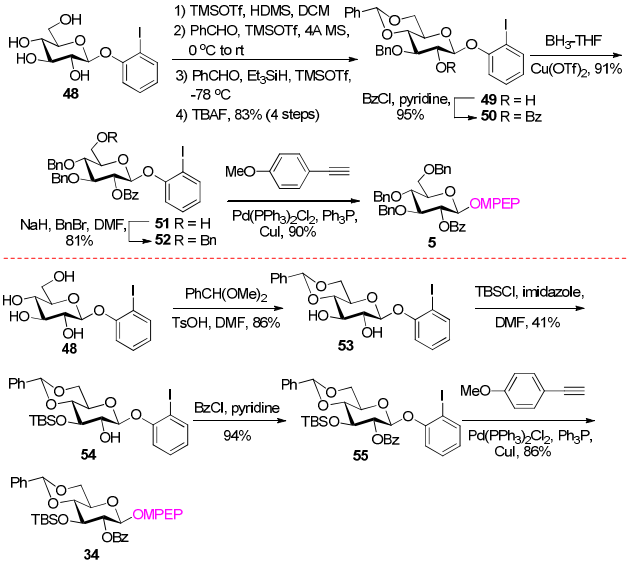
Table 3. Construction of special glycosidic linkages with MPEP glycosides as donors



Latent-active strategy has been proven to be a highly efficient strategy for the synthesis of complex oligosaccharides and glycoconjugates.[7,8,11,12,17] The appealing efficiency originates from the dual roles of the latent leaving group (both as precursor for active donor preparation and as protecting group for anomeric positions), which dramatically facilitate the synthesis of donors as well as acceptors decorated with appropriate protecting group sets

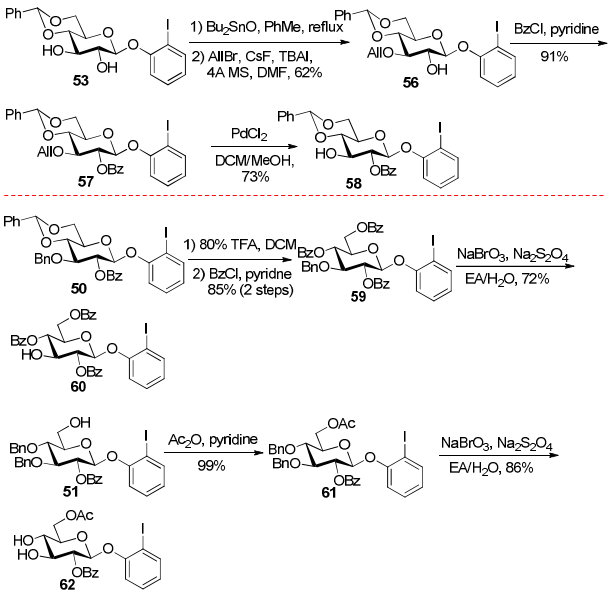
through omitting the handling of the bothering hemiacetal intermediate and/or the introduction of additional anomeric protecting groups. The prerequisites for a glycosylation protocol to be applicable in latent-active strategy are the stepwise procedure for fabrication of the leaving group (active form) and the inertness of leaving group precursor (latent form) to a vast variety of reaction conditions including glycosylation conditions. Regarding the MPEP glycosylation protocol, the MPEP glycoside (active form) was indeed synthesized from IP glycoside (latent form) via Sonogarshira reaction, and the IP glycoside has been proven to be intact under the TMSOTf/NIS condition (table 3). To ensure a broad application of the present protocol in the latent-active strategy, the stability of the IP groups at the anomeric position was further evaluated. Firstly, MPEP glucosides **5**, **34** were prepared with IP as a suitable protecting group for the anomeric positions (Scheme 1). Thus, tetraol intermediate **48**[26] was subjected to Hung's one-pot protection procedure, wherein silylation, benzylidene formation, benzylation, and desilylation were involved, to yield **49** (83%, 4 steps).[48] Benzoylation of the free OH in **49** delivered **50** (95%), which was then exposed to the conditions of regioselectively reductive opening of the benzylidene group to afford **51** (91%).[37] Benzylation was followed by Sonogashira reaction with *p*-methoxyphenylacetylene to convert **51** to MPEP glucoside **5**, the superarmed glucosyl donor,[49] via **52** (73%).[12d] The synthesis of orthogonally protected MPEP glucoside **34** also started with tetraol **48**. Benzylidenation of **48** under standard conditions furnished **53** (86%), which was then subjected to the regioselective silylation conditions to give **54** (41%). Benzoylation of **54** delivered **55**, the latent form of MPEP donor (94%), which was further transformed to the active form **34** via Sonogashira reaction (86%). In addition, rhamnosyl donors **8** and **9** from the same starting materials further supported that once the IP group was introduced to the anomeric position of a particular type of sugar, the MPEP donors differing in protecting patterns could be acquired conveniently.[26]

Scheme 1. *ortho*-Iodophenyl (IP) group as a stable protecting group for the anomeric positions in the synthesis of MPEP glycosides with diverse protecting groups



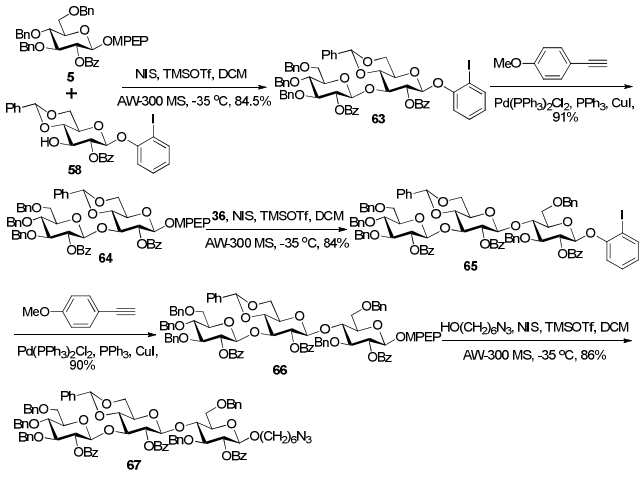
With IP as a protecting group for anomeric positions, the synthesis of acceptors could also be expedited, as exemplified by the synthesis of **58** (Scheme 2). With **53** as the starting material, **58** could be obtained through regioselective allylation (**56**, 62%),[50] benzoylation (**57**, 91%), and deallylation (73%). In particular, differing from benzylic-type latent donors,[11,12] the phenolic glycoside character of IP glycosides renders the IP groups withstand conditions for the cleavage of benzyl groups on the sugar residues, as demonstrated by the preparation of acceptors **60** and **62**. Acid mediated benzylidene removal and benzoylation of the resulting two OHs converted **50** to **59**, an ideal platform for the investigation of selective removal of benzyl group at the presence of anomeric IP. Pleasantly, under the oxidative debenzylation conditions ($NaBrO_3/Na_2S_2O_4$),[51] 72% yield of **60** was obtained. Identical conditions were then successfully applied to the more challenging dibenzylated compound **61**, which was synthesized from **51** (99%), and an even better yield of **62** was obtained (86%). In addition, the syntheses of acceptors **36** and **70** also reflected that with IP as anomeric protecting group, the synthetic efficiency of a particular type of sugar acceptor could be significantly enhanced by sharing the common starting materials.

Scheme 2. *ortho*-Iodophenyl group as a stable protecting group for the anomeric positions in the synthesis of glycosyl acceptors with diverse protecting groups



With the stability of IP glycosides toward a wide panel of reaction conditions, including glycosylation conditions, acidic and basic conditions, reductive and oxidative conditions, was fully confirmed, our attention was then turned to the application of the MPEP glycosylation method to the assembly of bioactive oligosaccharide via the latent-active strategy. Trisaccharide **67**, the key intermediate for synthesis of *Streptococcus pneumoniae* type 3 capsular trisaccharide fragment,[52] was selected as the target molecule (Scheme 3). Under the effect of TMSOTf/NIS, the coupling between donor **5** and acceptor **58** carrying a latent leaving group IP on its anomeric position proceeded without any event, yielding disaccharide **63** with 84% yield. With the assistance of neighboring group participation effect of the benzoyl group on 2-OH of the donor, the glycosylation proceeded stereoselectively, and only the desired β-isomer was obtained (for the anomeric proton of the donor residue in **63**: 4.84 ppm, J = 7.6 Hz). Activation of **63** was realized through Sonogashira reaction to give MPEP disaccharide donor **64** (91%), which was further coupled with **36** under standard glycosylation conditions to afford the trisaccharide latent donor **65** in a good 84% yield (for the three anomeric protons: 4.88 ppm, J = 8.0 Hz; 4.73 ppm, J = 8.0 Hz; 4.69 ppm, J = 7.6 Hz). Iterative activation of IP trisaccharide **65** by Sonogashira reaction delivered MPEP donor **66**, which was then put to condense with azido hexanol spacer to give the target molecule **67** in a highly efficient (86%) and stereoselective manner (for three anomeric protons: 4.70 ppm, J = 7.2 Hz, 4.63 ppm, J = 7.6 Hz, 4.28 ppm, J = 8.0 Hz). It should be pointed out that even using a trisaccharide MPEP donor in the final glycosylation step, an excellent glycosylation yield was still recorded. Thanks to the high potentials of MPEP protocol and latent-active strategy, the synthesis of **67** could be achieved in 5 linear steps with 50% overall yield from **5**, **58**, **36**, and azido hexanol building blocks. Thus, in combination with latent-active strategy, the synthetic efficiency of the MPEP glycosylation protocol could be further improved.

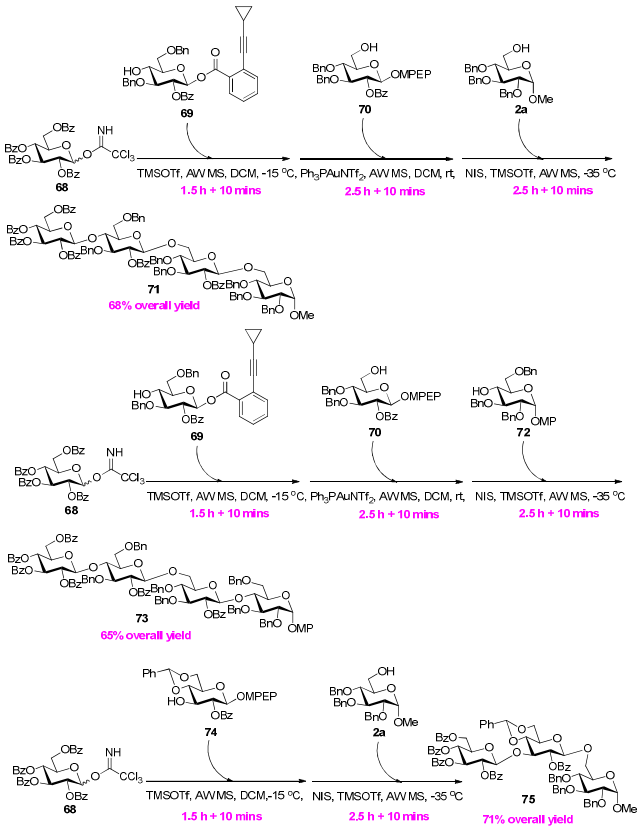
Scheme 3. Synthesis of trisaccharide 67 with MPEP glycosides as donors via the latent-active strategy



During the methodology establishment investigation, it was already confirmed that the MPEP donors were inert to catalytic amounts of TMSOTf and Au(I) complex, the generally applied conditions for the promotions of glycosyl TCAI[6] and ABz donors,[10] giving a hint for the possible use of MPEP protocol in selective one-pot strategy.[13] Thus, with oligosaccharides **71**, **73**, and **75** as the target molecules, we decided to explore the feasibility of applying MPEP donors to the selective one-pot oligosaccharide synthesis strategy. With the building blocks equipped with appropriate protecting sets in hand,[26] the synthesis of these oligosaccharides through one-pot strategy was investigated subsequently (Scheme 4). TCAI donor **68**[53] and ABz acceptor **69** was treated with TMSOTf (0.2 eq) at -15 °C. After the stirring was continued at the same temperature for 1.5 h, MPEP acceptor **70** and $Ph_3PAuNTf_2$ (0.2 eq) was added successively at the same temperature. The resulting reaction mixture was warmed up to room temperature and the stirring was continued for another 2.5 h. Thereafter, the reaction mixture was rechilled to -35 °C, to which acceptor **2a**, NIS, as well as TMSOTf were added successively. Stirring was continued for another 2.5 h at the same temperature to furnish **71** (68% overall yield). Encouraged by this result, we then turned to the synthetically more challenging tetrasaccharide **73** terminated by a 1,4-linked glucosyl residue. Apart from the synthetic challenge imposed by the chemical structure, the possible application of **73** in biological investigation after the temporary MP protecting group removal also justified the selection. Thus, following the similar procedures as those used for the one-pot synthesis of **71**, tetrasaccharide **73** was obtained in a 65% overall yield with **72** as the terminal acceptor. It deserved further comments that although a challenging 1,4-glycosidic linkage construction with MPEP trisaccharide donor was entailed in the last step, no evident overall yield drop was observed in the synthesis of **73**. Expectedly, the trisaccharide **75** could also be obtained by the same strategy with **68**, **74**, and **2a** as building blocks (71% overall yield). In all glycosylations with MPEP glycosides acting as acceptors, no MPEP group migration was observed. To ensure the correctness of all synthetic

oligosaccharides, either derivatization (for **71** and **73**) or re-syntheses via routine stepwise glycosylation procedure (for **71** and **75**) were carried out.[26] Compared with the conventional stepwise synthetic procedure, the MPEP donor involved one-pot procedure enjoys the advantages of efficiency (68%, 65%, and 71% overall yields), swiftness (7.0 h for each tetrasaccharide and 4.3 h for the trisaccharide), and convenience (avoiding the glycosylation-interval workups and intermediate purifications).

Scheme 4. Synthesis of oligosaccharides 71, 73 and 75 via selective 'one-pot' strategy



After the novel MPEP glycosylation protocol was successfully set up and the synthetic potential was showcased, a plausible mechanism of the NIS/TMSOTf mediated glycosylation was put forward as shown in figure 1. The combination of NIS and TMSOTf resulted in the formation of iodonium species, which attacks the adjacent terminus of alkyne C-C triple bond (relative to the sugar residue) regioselectively to generate iodovinyl cation species **B** (**B'**). The anomeric oxygen atom then attacks the originally remote alkyne carbon of **B** (**B'**) to generate oxocarbenium ion **D**. Meanwhile, as the departure form of the leaving group, 3-iodo-benzofuran **C** is ejected. The oxocarbenium **D** would accept the approach of alcoholic nucleophiles to deliver the glycosylation product **E** and H^+. H^+ can then be captured by silylated succinimide to produce succimide and regenerate TMSOTf, which can participate in the next catalysis cycle.

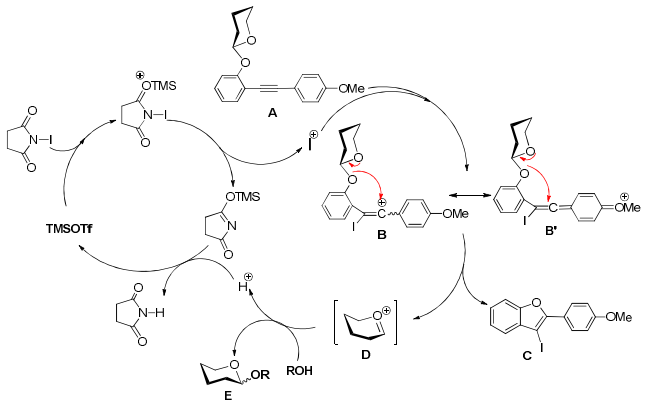
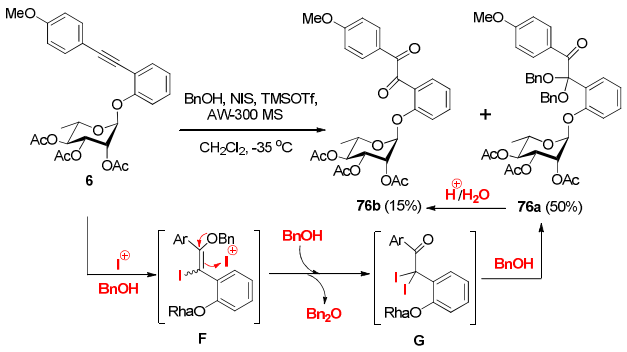


Figure 1. Proposed reaction mechanism of MPEP glycosylation protocol

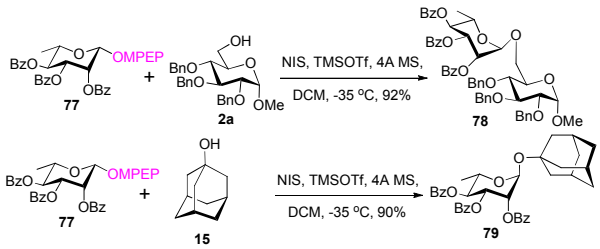
The proposed mechanism was supported by precedented literatures. Two pathways of alkyne iodination have been testified by spectroscopic and theoretical investigations: cyclic iodonium and iodovinyl cation pathways. Mild iodination reagents such as I_2 tended to afford products through symmetric cyclic iodonium pathway; while iodonium ions (I^+) tended to activate alkyne triple bond via an open iodovinyl cations.[54a,b] For alkyne structure factors, terminal alkynes inclined to be activated through cyclic iodonium pathway; while the internal alkynes were prone to be activated by iodovinyl cation intermediate.[54c,d] In the case of MPEP glycosylation protocol, as both iodonium ion and internal alkyne are involved, thus the iodovinyl cation pathway is presumably favored. The substitution pattern of the phenyl rings flanking the alkyne functionality in **A** induced the polarization of the C-C triple bond to a great extent (for **1c** the two alkynyl carbons resonated at 83.1 and 94.2 ppm, respectively), thus the regioselectivity of iodination was guaranteed (at the carbon close to the sugar residue with a chemical shift of 83.1 ppm). In fact, taking full advantage of the inertness of disarmed rhamnosyl MPEP donor **6**, the iodovinyl cation species could be trapped as **76a** and **76b** through the highly reactive intermediates **F** and **G** (Scheme 5). Thus, under the promotion of NIS/TMSOTf, the reactive iodovinyl cation species **B** (**B'**) is formed first, which is trapped by the nucleophile BnOH to form intermediate **F**. The enol ether character of the double bond in intermediate **F** would be more susceptible to iodonium attack, thus accepting a new round attack of iodonium to give gem-diiodo ketone **G** and to generate dibenzyl ether (Bn_2O), which was confirmed from the reaction mixture by GC-MS.[26] The gemdiiodo species is highly reactive, and can be trapped by BnOH to afford α-ketone ketal **76a**,[55] which was isolated and thoroughly characterized as the major product accompanied by di-ketone compound **76b**.[26] Compound **76a** could be gradually concerted to **76b** in a NMR tube in $CDCl_3$.

Scheme 5. Trapping of the iodovinyl cation species B/B' with donor 6 and BnOH



According to the mechanistic proposal, two factors would influence the glycosylation profoundly: the stability of cationic species **B** (**B'**) and the nucleophilicity of the anomeric oxygen. When the cationic species **B** (**B'**) is too stable such as those derived from donor **1d** with three electron-donating substituents on the terminal phenyl ring, the attack of anomeric oxygen to cationic species would be retarded, accordingly the reactivity the donor would be reduced. Indeed, our experimental results have demonstrated that donor **1d** had a reduced reactivity compared to its **1c** counterpart. Similarly, the reduced nucleophilicity of anomeric oxygens could also lead to reactivity decline in MPEP donors. The inert property of CF_3-containing donors **1f**-**1i** could be ascribed to the reduced nucleophilicity of the anomeric oxygen due to the electron-withdrawing property of CF_3. This is also the underlying reason responsible for the extremely low reactivity of disarmed and superarmed MPEP rhamnosyl donors **6**, **7** and **9**:[56] the antiperiplanar arranged (relative to the anomeric MPEP group) and electron-withdrawing 2-OBz groups decrease the nucleophilicity of the anomeric oxygens. Logically, it was deduced that the reactivity of MPEP rhamnosyl donors could be improved simply by changing the axial α configuration to the equatorial β configuration. To check this assumption, the disarmed, β-configured MPEP rhamnoside **77** was prepared and subjected to condensations with acceptors **2a** and **15** (Scheme 6). To our delight, the desired glycosides **78** and **79**[12d] were obtained stereoselectively (only α isomer) and efficiently (92% and 90%, respectively, Scheme 6), further supporting the correctness of the mechanistic proposal. Additional evidence to support the reaction mechanism was provided by the isolation and characterization 3-iodo-2-(4-methoxyphenyl)benzofuran **C**,[24] the cleaved form of the leaving group.

Scheme 6. Glycosylation of 2a and 15 with β-configured MPEP rhamnoside donor 77



CONCLUSIONS

In summary, *ortho*-(*para*-methoxyphenylethynyl)phenyl (MPEP) glycosides have been fully demonstrated to be novel and potential glycosyl donors, which could be applied in the constructions of a wide range of glycosidic linkages. The two-step preparation sequence of MPEP donors (2-iodophenol installation and Sonogashira reaction) as well as the outstanding stability of 2-iodophenyl (IP) glycosides against a wide variety of reaction conditions required for protecting group manipulations and glycosylations rendered the brand-new glycosylation protocol applicable in the latent-active synthetic strategy, wherein IP glycosides served as the latent donors while MPEP glycosides as the active donors. Transformation of the latent donors to their active forms utilized the Sonogashira reaction, whose high-yielding, scalable, and broad functional group compatibility properties safely guaranteed the efficiency of MPEP donor preparation. The combination of MPEP glycosyl donors with latent-active strategy led to the highly efficient synthesis of the key intermediate for *Streptococcus pneumoniae* type 3 capsular trisaccharide fragment (5 steps with 50% overall yield). Even in the active form, MPEP glycosides tolerated well the reaction conditions required for the activation of glycosyl TCAI donors and ABz donors, qualifying MPEP glycosides to be viable donors in the selective one-pot synthetic strategy. As a result, orchestrated application of MPEP glycoside donors, glycosyl TCAI and ABz donors to the selective one-pot synthesis strategy has been proved to be fruitful, and two complex tetrasaccharides as well as one trisaccharide were obtained in 68%, 65%, and 71% yields via successive glycosylation procedures omitting of glycosylation-interval workup, intermediates separation, and characterization. Although relying on identical activation conditions to thioglycosides, with odor-free *ortho*-iodophenol as starting material, stable 3-I benzofuran as the departure species of the leaving group, and phenyl *O*-glycosides with decreased nucleophilicity compared to their *S*-counterparts as donor, the MPEP protocol successfully overcame the three main defects plaguing thiglycoside donors, including unpleasant odor, detrimental interference of the cleaved leaving group, and undesired aglycon transfers. At the same time, the prominent features of thioglycoside donors, such as shelf-stability, dual roles of the leaving group, broad substrate scopes, mild activation conditions, and versatile application in different glycoside synthesis strategies, are largely maintained. Therefore, as a novel glycosylation protocol, the MPEP glycoside method may find broad applications in syntheses of complex oligosaccharides and glycoconjugates in the due future. Based on previous literatures and experimental results, a convincing reaction mechanism was also put forward, which was supported by the trapping of iodovinyl cation intermediates, design of the β-configured disarmed rhamnosyl MPEP donor, and isolation and characterization of the departure species of the leaving group.

ASSOCIATED CONTENT

Supporting Information

The supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental details, X-ray diffraction spectra, ^{1}H and ^{13}C spectra for all new compounds, and 2D NMR spectra (PDF)

Crystallographic data for **S2** (CIF)

Crystallographic data for **S9** (CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

1) a) Varki, A. *Glycobiology* **1993**, *3*, 97-130. b) Bertozzi, C. R.; Kiessling, L. L. *Science* **2001**, *291*, 2357-2364. c) Boltje, T. J.; Buskas, T.; Boons, G.-J. *Nat. Chem.* **2009**, *1*, 611-622.

2) a) Butler, M. S. *J. Nat. Prod.* **2004**, *67*, 2141-2153. b) Kuo, R.-Y.; Qian, K.-D.; Morris-Natschke, S. L.; Lee, K.-H. *Nat. Prod. Rep.* **2009**, *26*, 1321-1344. c) Kharel, M. K.; Pahari, P.; Shepherd, M. D.; Tibrewal, N.; Nybo, S. E.; Shaaban, K. A.; Rohr, J. *Nat. Prod. Rep.* **2012**, *29*, 264-325.

3) a) Fischer, E. *Chem. Ber.* **1893**, *26*, 2400-2412. (b) Fischer, E. *Chem. Ber.* **1895**, *28*, 1145-1167.

4) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503-1531.

5) a) Codee, J. D. C.; Litjens, R. E. J. N.; Van den Bos, L. J.; Overkleeft, H. S.; Van der Marel, G. A. *Chem. Soc. Rev.* **2005**, *34*, 769-782. b) Lian, G.; Zhang, X.; Yu, B. *Carbohydr. Res.* **2015**, *403*, 13-22.

6) a) Schmidt, R. R. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212-235. b) Zhu, X.; Schmidt, R. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 1900-1934.

7) a) Demchenko, A. V.; Pornsuriyasak, P.; Meo, C. D.; Malysheva, N. N. *Angew. Chem. Int. Ed.* **2004**, *43*, 3069-3072. b) Hasty, S. J.; Kleine, M. A.; Demchenko, A. V. *Angew. Chem. Int. Ed.* **2011**, *50*, 4197-4201.

8) Kim, K. S.; Kim, J. H.; Lee, Y. J.; Lee, Y. J.; Park, J. *J. Am. Chem. Soc.* **2001**, *123*, 8477-8481.

9) a) Garcia, B. A.; Poole, J. L.; Gin, D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597-7598. b) Bussolo, V. D.; Kim, Y.-J.; Gin, D. Y. *J. Am. Chem. Soc.* **1998**, *120*, 13515-13516.

10) a) Li, Y.; Yang, Y.; Yu, B. *Tetrahedron Lett.* **2008**, *49*, 3604-3608. b) Li, Y.; Yang, X.; Liu, Y.; Zhu, C.; Yang, Y.; Yu, B. *Chem. Eur. J.* **2010**, *16*, 1871-1882. c) Tang, Y.; Li, J.; Zhu, Y.; Li, Y.; Yu, B. *J. Am. Chem. Soc.* **2013**, *135*, 18396-18405.

11) a) Shu, P.; Xiao, X.; Zhao, Y.; Xu, Y.; Yao, W.; Tao, J. Wang, H.; Yao, G.; Lu, Z.; Zeng, J. Wan, Q. *Angew. Chem. Int. Ed.* **2015**, *54*, 14432-14436. b) Xiao, X.; Zhao, Y.; Shu, P.; Zhao, X.; Liu, Y.; Sun, J.; Zhang, Q.; Zeng, J.; Wan, Q. *J. Am. Chem. Soc.* **2016**, *138*, 13402-13407.

12) a) Fraser-Reid, B.; Udodong, U. E.; Wu, Z. F.; Ottoson, H.; Merritt, J. R.; Rao, C. S.; Roberts, C.; Madsen, R. *Synlett* **1992**, 927-942. b) Boons, G.-J.; Isles, S. *Tetrahedron Lett.* **1994**, *35*, 3593-3596. c) Wang, P.; Haldar, P.; Wang, Y.; Hu, H. *J. Org. Chem.* **2007**, *72*, 5870-5873. d) Chen, X.; Shen, D.; Wang, Q.; Yang, Y.; Yu, B. *Chem. Commun.* **2015**, *51*, 13957-13960.

13) For chemoselective one-pot glycosylation, see: a) Hsu, Y.; Lu, X.-A.; Zulueta, M. M. L.; Tsai, C.-M.; Lin, K.-I.; Hung, S.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **2012**, *134*, 4549-4552. For orthogonal one-pot glycosylation, see: b) Tanaka, H.; Adachi, M.; Tsukamoto, H.; Ikeda, T.; Yamada, H.; Takahashi, T. *Org. Lett.* **2002**, *4*, 4213-4216. c) Chuang, H.-Y.; Ren, C.-T.; Chao, C.-A.; Wu, C.-Y.; Shivatare, S. S.; Cheng, T.-J. R.; Wu, C.-Y.; Wong, C.-H. *J. Am. Chem. Soc.* **2013**, *135*, 11140-11150. For preactivative one-pot glycosylation, see: d) Huang, X.-F.; Huang, L.; Wang, H.; Ye, X.-S. *Angew. Chem. Int. Ed.* **2004**, *43*, 5221-5224. For a selected review, see: e) Koeller, K. M.; Wong, C.-H. *Chem. Rev.* **2000**, *100*, 4465-4493.

14) a) Seeberger, P. H.; Haase, W. C. *Chem. Rev.* **2000**, *100*, 4349. b) Wu, X.; Grathwohl, M.; Schmidt, R. R. *Angew. Chem. Int. Ed.* **2002**, *41*, 4489-4492.

15) For selected example, see: a) Wu, Y.; Xiong, D.-C.; Chen, S.-C.; Wang, Y.-S.; Ye, X.-S. *Nat. Commun.* **2017**, *8*, 14851. For reviews, see: b) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 1576-1624. c) Yang, Y.; Zhang, X.; Yu, B. *Nat. Prod. Rep.* **2015**, *32*, 1331-1355.

16) Barresi, F.; Hindsgaul, O. *J. Carbohydr. Chem.* **1995**, *14*, 1043-1087.

17) Roy, R.; Andersson, F. O.; Letellier, M. *Tetrahedron Lett.* **1992**, *33*, 6053-6056.

18) Ferrier, R. J.; Hay, R. W.; Vethaviyasa, N. *Carbohydr. Res.* **1973**, *27*, 55-61.

19) For the remedy of the unpleasant odor shortcomings, see: Crich, D.; Li, W. *J. Org. Chem.* **2007**, *72*, 7794-7797.

20) a) Nifantiev, N. E.; Sherman, A. A.; Yudina, O. N.; Cheshev, P. E.; Tsvetkov, Y. E.; Khatuntseva, E. A.; Kornilov, A. V.; Shashkov, A. S. *Pure Appl. Chem.* **2004**, *76*, 1705-1714. b) Yu, J.; Sun, J.; Niu, Y.; Li, R.; Liao, J.; Zhang, F.; Yu, B. *Chem. Sci.* **2013**, *4*, 3899-3905.

21) a) Yu, H.; Yu, B.; Wu, X.; Hui, Y.; Han, X. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1445-1453. b) Tanaka, H.; Adachi, M.; Takahashi, T. *Tetrahedron Lett.* **2004**, *45*, 1433-1436. c) Codee, J. D. C.; Stubba, B.; Schiattarella, M.; Overkleeft, H. S.; van Boeckel, C. A. A.; van Boom, J. H.; van der Marel, G. A. *J. Am. Chem. Soc.* **2005**, *127*, 3767-3773.

22) a) Hotha, S.; Kashyap, S. *J. Am. Chem. Soc.* **2006**, *128*, 9620-9621. b) Adhikari, S.; Baryal, K. N.; Zhu, D.; Li, X.; Zhu, J. *ACS Catal.* **2013**, *3*, 57-60.

23) For precedented phenyl glycoside donors, see: a) Laursen, J. B.; Petersen, L.; Jensen, K. J. *Org. Lett.* **2001**, *3*, 687-690. b) Petersen, L.; Laursen, J. B.; Larsen, K.; Motawia, M. S.; Jensen, K. J. *Org. Lett.* **2003**, *5*, 1309-1312. c) Luo, S.-Y.; Tripathi, A.; Zulueta, M. M. L.; Hung, S.-C. *Carbohydr. Res.* **2012**, *352*, 197-201. d) Premathilake, H. D.; Demchenko, A. V. *Beilstein J. Org. Chem.* **2012**, *8*, 597-605.

24) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292-10296.

25) Yang, F.; Wang, Q.; Yu, B. *Tetrahedron Lett.* **2012**, *53*, 5231-5234.

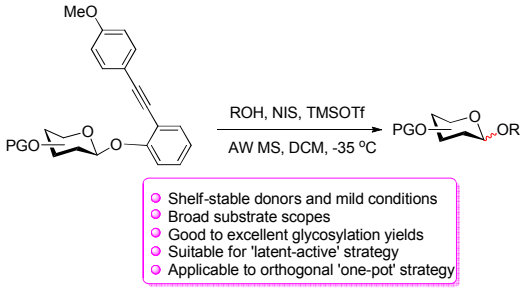
26) See supporting information.

27) Yin, Z.-J.; Wang, B.; Li, Y.-B.; Meng, X.-B.; Li, Z.-J. Org. Lett. 2010, 12, 536-539.

28) Stevenin, A.; Boyer, F.-D.; Beau, J.-M. *J. Org. Chem.* **2010**, *75*, 1783-1786.

29) a) Yamago, S.; Kokubo, K.; Hara, O.; Masuda, S.; Yoshida, J.-i. *J. Org. Chem.* **2002**, *67*, 8584-8592. b) Zhu, Y.; Yu, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 8329-8332.

30) Imagawa, H.; Kinoshita, A.; Fukuyama, T.; Yamamoto, H.; Nishizawa, M. *Tetrahedron Lett*. **2006**, *47*, 4729-4731.
31) a) Navarre, N.; van Oijen, A. H.; Boons, G. J. *Tetrahedron Lett*. **1997**, *38*, 2032-2026. b) Gu, G.; Du, Y.; Linhardt, R. J. *J. Org. Chem*. **2004**, *69*, 5497-5500.
32) Dieskau, A. P.; Plietker, B. *Org. Lett*. **2011**, *13*, 5544-5547.
33) Peng, P.; Ye, X.-S. *Org. Biomol. Chem*. **2011**, *9*, 616-622.
34) Kumar, G. D. K.; Baskaran, S. *J. Org. Chem*. **2005**, *70*, 4520-4523.
35) Ennins, S. C.; Cumpstey, I.; Fairbanks, A. J.; Butters, T. D.; Mackeen, M.; Wormald, M. R. *Tetrahedron* **2002**, *58*, 9403-9411.
36) Zeng, Y.; Zhang, W.; Ning, J.; Kong, F. *Carbohydr. Res*. **2002**, *337*, 2383-2391.
37) Shie, C.-R.; Tzeng, Z.-H.; Kulkarni, S. S.; Uang, B.-J.; Hsu, C.-Y.; Hung, S.-C. *Angew. Chem. Int. Ed*. **2005**, *44*, 1665-1668.
38) Koshiba, M.; Suzuki, N.; Arihara, R.; Tsuda, T.; Nambu, H.; Nakamura, S.; Hashimoto, S. *Chem. Asian J*. **2008**, *3*, 1664-1677.
39) Sun, L.; Wu, X.; Xiong, D.-C.; Ye, X.-S. *Angew. Chem. Int. Ed*. **2016**, *55*, 8041-8044.
40) Nishizawa, M.; Kan, Y.; Shimomoto, W.; Yamada, H. *Tetrahedron Lett*. **1990**, *31*, 2431-2434.
41) For remote activation review, see: Hanessian, S.; Lou, B. *Chem. Rev*. **2000**, *100*, 4443-4463.
42) Wan, J.-H.; Hu, Y.; Liu, H.; Tu, Y.-H.; He, Z.-Y.; Sun, J.-S. *J. Org. Chem*. **2017**, *82*, 5652-5662.
43) Nokami, T.; Nozaki, Y.; Saigusa, Y.; Shibuya, A.; Manabe, S.; Ito, Y.; Yoshida, J.-i. *Org. Lett*. **2011**, *13*, 1544-1547.
44) Kajimoto, T.; Morimoto, K.; Ogawa, R.; Dohi, T.; Kita, Y. *Eur. J. Org. Chem*. **2015**, 2138-2142.
45) Berkin, A.; Szarek, W. A.; Kisilevsky, R. *Carbohydr. Res*. **2002**, *337*, 37-44.
46) For a β-mannose glycosylation review, see: Crich D. *Acc. Chem. Res*. **2010**, *43*, 1144-1153. For selected examples, see: b) Crich, D.; Sun, S. *J. Org. Chem*. **1996**, *61*, 4506-4507. c) Crich, D.; Sun, S. *J. Am. Chem. Soc*. **1998**, *120*, 435-4.36.
47) a) Kim, K. S.; Fulse, O. B.; Beak, J. Y.; Lee, B. Y.; Jeon, H. B. *J. Am. Chem. Soc*. **2008**, *130*, 8537-8547. b) Nagai, H.; Sasaki, K.; Matsumura, S.; Toshima, K. *Carbohydr. Res*. **2005**, *340*, 337-353.
48) Wang, C.-C.; Lee, J.-C.; Luo, S.-Y.; Kulkarni, S. S.; Huang, Y.-W.; Lee, C.-C.; Chang, K.-L.; Hung, S.-C. *Nature* **2007**, *446*, 896-899.
49) Mydock, L. K.; Demchenko, A. V. *Org. Lett*. **2008**, *10*, 2107-2110.
50) Lu, S.-F.; O'yang, Q.-Q.; Guo, Z.-W.; Yu, B.; Hui, Y.-Z. *J. Org. Chem*. **1997**, *62*, 8400-8405.
51) Zhu, S. Li, Y.; Yu, B. *J. Org. Chem*. **2008**, *73*, 4978-4985.
52) De Jong, A.-R.; Hagen, B.; van der Ark, V.; Overkleeft, H. S.; Codee, J. D. C.; der Marel, G. A. V. *J. Org. Chem*. **2012**, *77*, 108-125.
53) a) Mbadugha, B. N. A.; Menger, F. M. *Org. Lett*. **2003**, *5*, 4041-4044. b) Pilgrim, W.; Murphy, P. V. *J. Org. Chem*. **2010**, *75*, 6747-6755.
54) a) Aurelio, L.; Volpe, R.; Halim, R.; Scammells, P. J.; Flynn, B. L. *Adv. Synth. Catal*. **2014**, *356*, 1974-1978. b) Volpe, R.; Aurelio, L.; Gilin, M. G.; Krenske, E. H.; Flynn, B. L. *Chem. Eur. J*. **2015**, *21*, 10191-10199. c) Barluenga, J.; Rodriguez, M. A.; Campos, P. J. *J. Org. Chem*. **1990**, *55*, 3104-3106. Okamoto, N.; Miwa, Y.; Minami, H.; Takeda, K.; Yanada, R. *J. Org. Chem*. **2011**, *76*, 9133-9138.
55) For the hydrolysis of α-keto-gemdibromo compounds, see: Qiu, G.; Li, Y.; Ma, L.; Zhou, H. *Org. Chem. Front*. **2017**, *4*, 1069-1073.
56) Hu, Y.; Tu, Y.-H.; Liu, D.-Y.; Liao, J.-X.; Sun, J.-S. *Org. Biomol. Chem*. **2016**, *14*, 4842-4847.


MeO
PGO
O
O
ROH, NIS, TMSOTf
AW MS, DCM, -35 °C
PGO
O
OR
Shelf-stable donors and mild conditions
Broad substrate scopes
Good to excellent glycosylation yields
Suitable for 'latent-active' strategy
Applicable to orthogonal 'one-pot' strategy