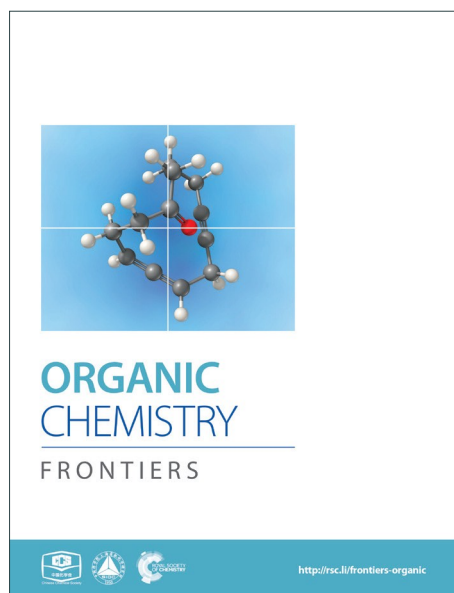
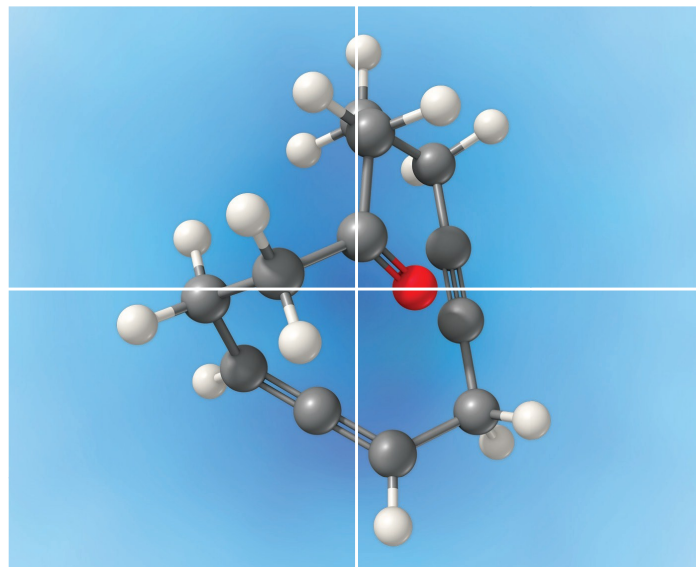


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Glycosylation *via* Remote Activation of Anomeric Leaving Groups: Development of 2-(2-Propylsulfinyl)benzyl Glycosides as Novel Glycosyl Donors

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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2-(2-Propylsulfinyl)benzyl glycoside was designed as new type of glycosyl donor which could be activated *via* remote mode. This glycosyl donor and its reduced form could act as active and latent donors respectively in a latent-active glycosylation strategy. Details of discovery of this novel glycosyl donors were reported in this article.

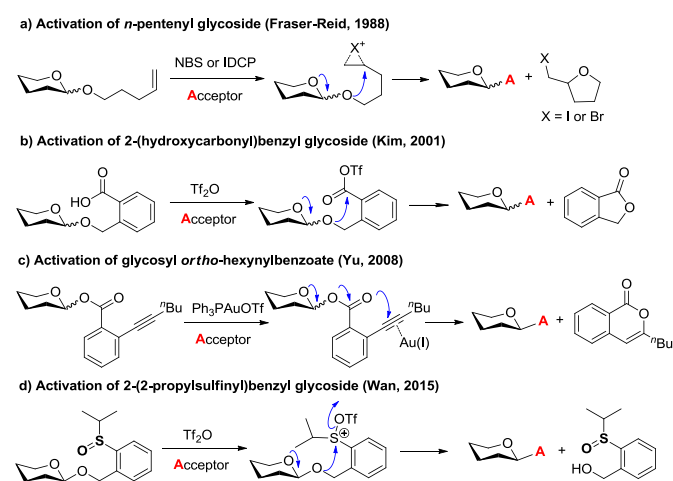
Introduction

Glycosidic bond formation plays the central role in carbohydrate chemistry.¹ Past decades have witnessed a dramatic improvement for the development of efficient chemical glycosylation strategies.² The common activation mode of these strategies involves stimulating functional groups which directly linked to the glycosyl donors' anomeric position. The major used glycosyl donors include glycosyl halides,^{3a} thioglycosides,^{3b-d} glycosyl imidates and thioimidates,^{3e-3h} glycosyl sulfoxides,³ⁱ glycosyl phosphates,^{3j} glycosyl phosphites,^{3k} 1-hydroxyl sugars,^{3l} glycosyl orthoesters,^{3m} 1,2-anhydro sugars³ⁿ et al. Other than these donors, glycosyl donors activated by remote activation mode⁴ were also discovered by Fraser-Reid (*n*-pentenyl glycoside),⁵ Kim (2-(hydroxycarbonyl)benzyl glycoside),⁶ Hotha (propargyl glycoside)⁷ and Yu (glycosyl *ortho*-alkynylbenzoate)⁸ et al (Scheme 1). Although less investigated, glycosylation *via* remote activation exhibited some advantages: 1) glycosylation conditions of these donors are normally orthogonal to that of most of other glycosyl donors; 2) latent-active strategy⁹ could be easily applied to these donors in oligosaccharide synthesis. Inspired by these pioneering work, we have reported a development of 2-(2-propylsulfinyl)benzyl (PSB) glycosides as novel glycosyl donors which were activated *via* a remote mode.¹⁰ With this new developed glycosyl donor, a natural hepatoprotective glycoside was synthesized based on a latent-active strategy. Herein, we further reported the details on our efforts in the establishment and understanding of this novel glycosylation process.

Sulfoxide compounds are widely utilized in organic

synthesis. It is well known that the sulfinyl group of sulfoxide could be activated by electrophiles to generate an active electrophilic species.¹¹ This intrinsic nature of sulfoxide promoted chemists to apply it in practical organic transformations. For example, sulfoxide has been widely used in Moffatt reaction,^{12a} Corey-Kim oxidation,^{12b-d} Swern oxidation^{12e-g} and Pummerer reaction. Since the first report of Pummerer reaction in 1909,¹³ a lot of related reactions have been developed for the construction of new carbon-carbon bonds and carbon-heteroatom bonds.¹⁴ The distinctive nature of sulfoxide also stimulates its application in carbohydrate chemistry. Kahne,³ⁱ Crich¹⁵ and Gin¹⁶ have made significant contributions in this area. In Kahne's and Crich's glycosylations, sulfoxide was employed as anomeric leaving group. Activation of this leaving group by Tf₂O formed a sulfonium intermediate, which instantly degraded to oxocarbenium and allowed the glycosylation proceeded smoothly.

In view of the advantages of glycosylation *via* remote activation and high activity of sulfoxide, we engaged to design a new type of glycosyl donors with sulfinyl group located at remote site of anomeric position. We envisaged that the activated mode would pass through Pummerer reaction

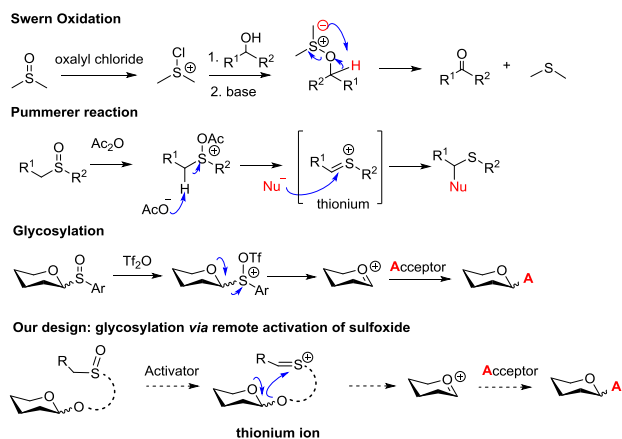


Scheme 1 Selected examples of glycosylation *via* remote activation mode.

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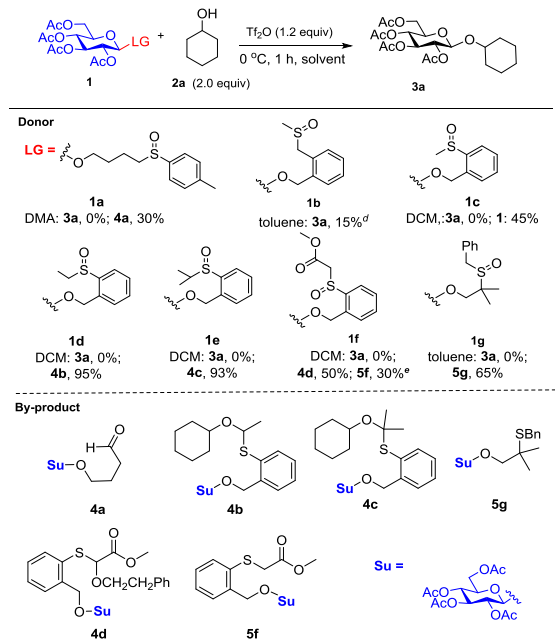
**Scheme 2** Reaction with sulfinyl functional group

pathway: the thionium possibly induced the intramolecular attack of anomeric oxygen atom *via* a 5- or 6-membered ring to form glycosyl oxocarbenium (Scheme 2).

Results and discussion

Donor design Initially, peracetylated glucosides with various leaving groups possessing sulfinyl group were chosen as glycosyl donors to conceive the idea (Table 1). Unfortunately, the commonly used activator for Pummerer reaction such as Ac_2O and trifluoroacetic anhydride (TFAA) under various conditions failed to activate the sulfinyl groups, and in most cases, only starting materials were recovered (see ESI). While Tf_2O was used as activator, we observed the fully consumption of most examined donors, however, no desired product was formed and the major by-products were listed in table 1. When **1a** was used as glycosyl donor, dimethylacetamide (DMA) as solvent, surprisingly, the reaction afforded an aldehyde **4a** in 30% yield. Reaction with donors **1d** and **1e** in dichloromethane (DCM), acetonitrile (CH_3CN) or toluene furnished **4b** and **4c** in high yields respectively. However, activation of structural similar donor **1c** was much difficult, under same reaction conditions, 45% of **1c** was still recovered. While **1f** with higher acidity of α -proton of sulfinyl group and better stability of generated thionium was used as donor, and toluene as solvent, the reaction gave unwanted compound **4d** as the major product. In DCM, a reduced product **5f** was observed as well. Donor **1g** failed to give any desired product either, if base such as triethyl amine or NaHCO_3 was introduced into the reaction system, moderate yield of sulfinyl group reduced product **5g** was isolated. An exception is donor **1b** which produced desired product **3a** in 15% yield, however, attempts to further improve the reaction efficiency failed.

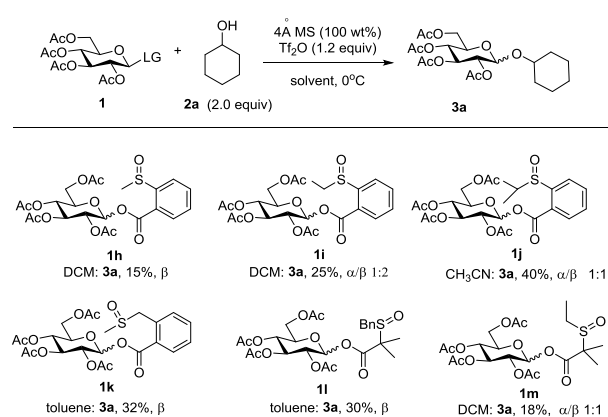
Despite frustrating results were obtained for donors **1a-1g** under various conditions, it is notable that sulfinyl group was successfully activated by Tf_2O . However, after activation, intermolecular Pummerer reaction (Path A2) and/or oxidation reaction (Path B) occurred as competition reactions to our anticipated intramolecular Pummerer reaction mediated glycosylation (Path A1) (Scheme 3). These results implied that possibly the nucleophilicity of anomeric oxygen atom was not strong enough. This speculation promoted us to further examine donors **1h-1m** with ester type anomeric leaving groups. Interestingly, reaction with all of these glycosyl donors

Table 1 Screen of ether type leaving groups ^{a,b,c}

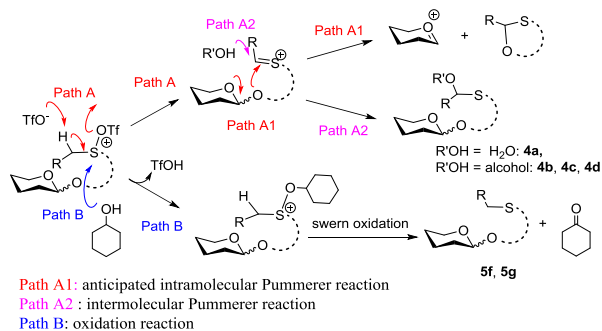
^a Isolated yield. ^b **1** (0.1 mmol, 1.0 equiv), **2** (0.2 mmol, 2.0 equiv), solvent (2.0 mL), 4 Å MS (100 wt%), Tf_2O (0.12 mmol, 1.2 equiv), reacted at 0 °C for 1 h. ^c Detailed optimization conditions, see ESI. ^d Most of **1b** degraded. ^e $\text{PhCH}_2\text{CH}_2\text{OH}$ was used as acceptor.

could produce the desired products albeit with low to moderate yields. But again, we could not improve the yields after screening a lot of reaction conditions (Table 2).

Since modification of the leaving groups could not lead to successful glycosylation, we then considered changing the disarmed protecting group of donors to armed protecting group which definitely increased the activity of anomeric oxygen atom (Table 3). First, perbenzylated donor **1n** was examined (entry 1). To our delight, the reaction proceeded smoothly under the activation of Tf_2O in DCM at 0 °C, which generated the desired product **3a** in 78% yield without any stereoselectivity. Changing solvents lead to moderate

Table 2 Screen of ester type leaving groups ^{a,b,c}

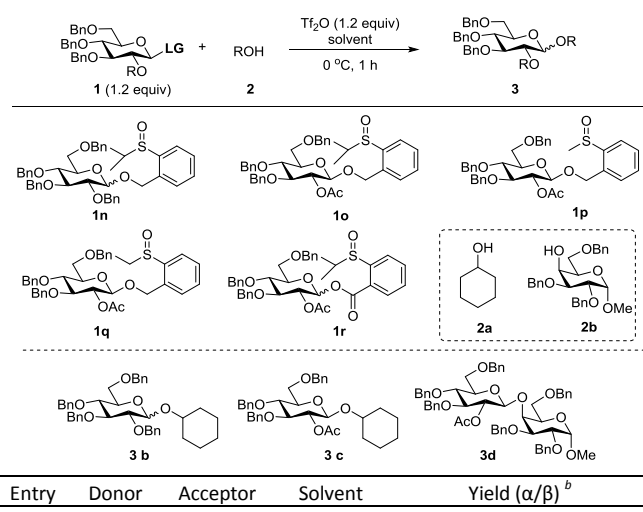
^a Isolated yield. ^b **1** (0.1 mmol, 1.0 equiv), **2** (0.2 mmol, 2.0 equiv), Tf_2O (0.12 mmol, 1.2 equiv), solvent (2.0 mL), 4 Å MS (100 wt%), reacted at 0 °C. ^c Detailed optimization conditions, see ESI.



Scheme 3 Possible competition reactions

selectivity and higher yields (entries 2 and 3). To validate the concept, super armed donor **1o** was then subjected to the reaction conditions, and the desired product **3c** was obtained in excellent yield with exclusive β -selectivity (entry 4). The reaction with 4-OH galactose acceptor **2b** still provided exclusive β -disaccharide **3d** in 95% yield (entry 5). Donors **1p** and **1q** also provided good results (entries 6 and 7), however, slight amount of acceptor **2b** was recovered. Interestingly, donor **1r** with ester leaving group was less efficient and only moderate yield of β -disaccharide was isolated (entry 8), possibly due to the instability of the donor.

With the discovery of 2-(2-propylsulfanyl)benzyl (PSB) glycosides as novel glycosyl donors and the optimized reaction conditions in hand, we have examined this new glycosylation strategy by employing various glycosyl acceptors, and these results have been previously reported.¹⁰

Table 3 Screen of armed glycosyl donor^a

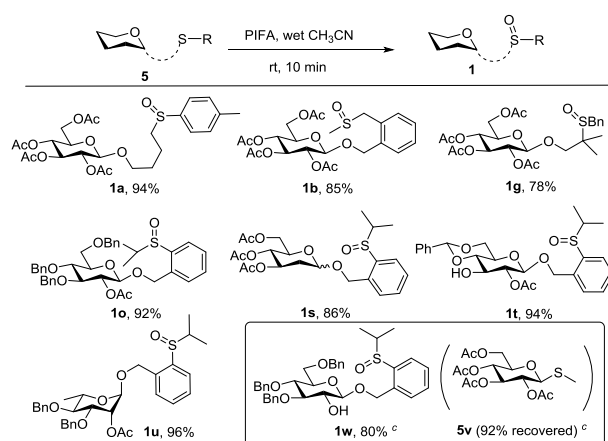
Entry	Donor	Acceptor	Solvent	Yield (α/β) ^b
1	1n	2a	DCM	3b , 78% (1:1)
2	1n	2a	Et ₂ O	3b , 82% (5:1)
3	1n	2a	CH ₃ CN	3b , 84% (1:5)
4	1o	2a	DCM	3c , 87%, β only
5	1o	2b	DCM	3d , 95%, β only
6	1p	2b	DCM	3d , 79%, β only ^c
7	1q	2b	DCM	3d , 82%, β only ^d
8	1r	2b	DCM	3d , 68%, β only ^e

^a **1** (0.12 mmol, 1.2 equiv), **2** (0.1 mmol, 1.0 equiv), Tf₂O (0.12 mmol, 1.2 equiv), solvent (2.0 mL), 4 Å MS (100 wt%). ^b Isolated yield. ^c 13% of **2b** recovered. ^d 11% of **2b** recovered. ^e 21% of **2b** recovered

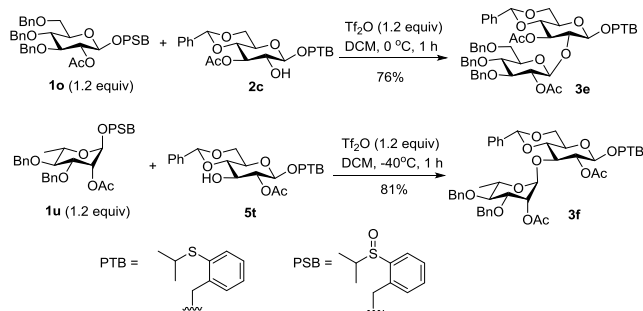
“Latent-active” We next considered the possibility of merging this remote activation glycosylation reaction with latent-active strategy in synthesis of oligosaccharides. Two basic requirements of a successful latent-active strategy are: 1) latent glycosyl donor should be easily converted to active glycosyl donor; 2) latent glycosyl donor must be stable enough under the glycosylation conditions with active glycosyl donor. In our case, we envisioned that the 2-(2-propylsulfanyl)benzyl (PSB) glycoside could act as an active donor, while its reduced form 2-(2-propylthiol)benzyl (PTB) glycoside which was readily obtained could play as a latent donor.

First, we investigated the oxidative conditions of transforming PTB donor **5o** to PSB donor **1o**. Although a lot of oxidants could oxidize thioether to sulfoxide, most of the conditions required careful control of the reaction conditions. Even though, the over-oxidation to sulfone was inevitable. After screening of several conditions,¹⁷ we found that the best condition was usage of PIFA (bis(trifluoroacetoxy)iodobenzene, 1.2 equiv) in wet CH₃CN (containing ca. 5% water). Under this condition, 92% yield of **1o** was obtained from the corresponding thioether (**5o**) without any over-oxidation product even extended the reaction time.¹⁸ This condition was also successfully applied to oxidize other thioethers to form sulfoxides as depicted in Table 4. Most interestingly, when **5w** (corresponding thioether of **1w**) mixed with 1.2 equiv of PIFA in anhydrous DCM, after aqueous work up of the reaction mixture, **5w** was selectively oxidized to **1w** in 80% yield with only trace amount of **1v** formed.

Having established the effective transformation from latent donor to active donor, we next investigated the tolerance of PTB donor in conditions activating PSB donor. First, PTB containing acceptor **2c** was reacted with PSB donor **1o** under our remote activation condition, the desired disaccharide **3e** was isolated in 76% yield without affecting the PTB group. The stability was also demonstrated by the high yield of **3f** from PTB donor **5t** and PSB donor **1u** (Scheme 4).

Table 4 Oxidation of thioether to sulfoxide^{a,b}

^a Isolated yield. ^b **5** (1.0 mmol, 1.0 equiv), PIFA (1.2 mmol, 1.2 equiv), wet CH₃CN (10 mL). ^c **5v** (1.2 equiv) mixed with **5w** (1.0 equiv) in anhydrous DCM, PIFA (1.2 equiv), 6 h, followed by aqueous work up. PIFA = bis(trifluoroacetoxy)iodobenzene.



Scheme 4 Latent-active strategy.

In addition, the ground applicability of latent-active strategy on our developed new glycosyl donors was finally proved by the successful total synthesis of leonoside F as previously reported,¹⁰ and will be further established by synthesis of complex naturally occurring polysaccharides.

Orthogonality The orthogonality of PTB and PSB glycosides to other glycosyl donors was further discovered. Normally, O-alkyl glycosides are rather stable towards activation conditions of most glycosyl donors. PTB glycosides could be prepared from glycosyl acetates, glycosyl imidates and glycosyl orthoesters.¹⁰ Undoubtedly, activation conditions of these donors will not affect PTB group. Since PTB glycosides contained a thioether group, we then examined its stability towards the conditions of activating thioglycosides by reaction of PTB containing acceptor **5w** with thioglycoside **5v** which is a less active disarmed glycosyl donor. Commonly used NIS in combination with TfOH for glycosylation with thioglycosides performed very well in this reaction, which furnished disaccharide **6** in 92% yield. MeOTf also did not affect the PTB functional group and activated **5v** to produce **6** in 65% yield, with 25% PTB glycoside **5w** recovered. These results clearly indicated that PTB glycoside is stable enough to tolerate various activation conditions for most commonly used glycosyl donors.

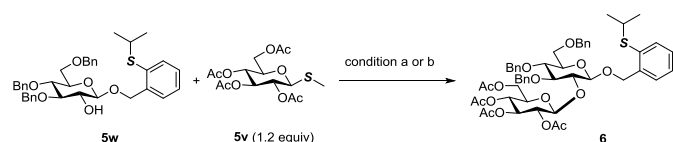
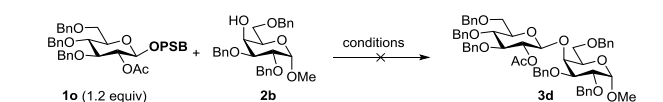
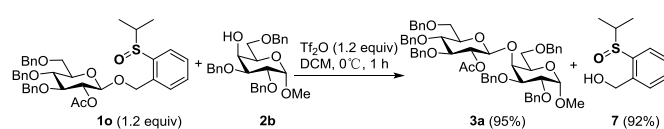
Scheme 5. Condition a: NIS (2.4 equiv), TfOH (0.24 equiv), DCM, 0 °C, 92%; b: MeOTf (1.2 equiv), DCM, 0 °C, rt, 24 h, 65%, with 25% of **5w** recovered. NIS = *N*-Iodosuccinimide.

Table 5 Stability of PSB donor.



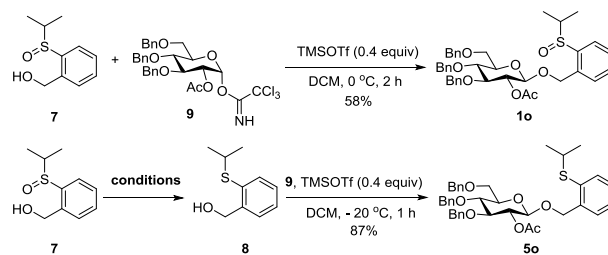
Entry	Conditions	Recovery Yield ^{a,b}
1	TfOH (1.2 equiv), 4Å MS, DCM, 0 °C	2b (98%), 1o (97%)
2	TfOH (1.2 equiv), NIS (1.2 equiv), 4Å MS, DCM, 0 °C	2b (96%), 1o (98%)
3	MeOTf, 4Å MS, DCM, 0 °C – rt	2b (98%), 1o (91%)

^a Isolated yield. ^b In all cases, **3d** was not observed.



Scheme 6 Recovery of leaving group.

Table 6 Recycle and regenerate of leaving group.



Entry	Conditions	Yield ^a
1	AcSH (2.2 equiv), I ₂ (0.01 equiv), CH ₃ CN, rt, 12 h	10% (75%)
2	NaBH ₄ (1.0 equiv), I ₂ (2.0 equiv), THF, rt, 0.5 h	74% (8%)
3	Mg (20.0 equiv), MeOH, rt, 4 h	71% (15%)
4	TSA (3.0 equiv), NBS (0.1 equiv), DCM, rt, 16 h	90%
5	TSA (3.0 equiv), I ₂ (0.1 equiv), DCM, rt, 6 h	95%

^a Isolated yield, yield in parentheses was recovered **7**. AcSH = thioacetic acid. TSA = thiosalicylic acid. NBS = *N*-Bromosuccinimide.

Stability of PSB donors was tested by reaction of **1o** with **2b** towards various strong acidic activators, including TfOH or TfOH in combination with NIS, even MeOTf. In each case, **1o** and **2b** were recovered perfectly, implying the extreme stability of PSB donors to acidic conditions (Table 5).

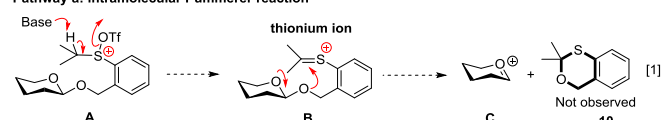
Leaving group recovery In the performance of these remote activation glycosylation reactions, a polar compound other than the glycoside products was always isolated in high yield. For example, reaction of **1o** with **2b** furnished compound **7** in 92% yield. This compound was characterized as exactly the leaving group of PSB donor (Scheme 6). The recovery of the leaving group promoted us to test its recyclability and regenerality.

First, compound **7** was directly coupled with glycosyl imidate **9** to generate PSB donor **1o**, albeit moderated yield was obtained due to the poor solubility of **7**, which suggested that leaving group could be recycled. We then tried to reduce compound **7** to its thioether form which was the leaving group of PTB donors. Several reported reducing conditions was screened for this reaction. Among them, AcSH/I₂ was inefficient and most of the starting material was recovered;¹⁹ NaBH₄/I₂²⁰ and Mg²¹ produced better results. The best reducing agents are thiosalicylic acid in combination with catalytic amount of NBS or I₂,²² which generated the reduced PTB-OH **8** in 90% and 95% respectively. Obviously, this regenerated PTB-OH coupled with **9** efficiently to provide the latent donor **5o** (Table 6).

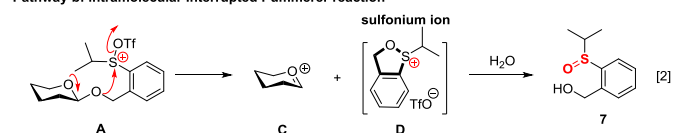
Mechanism The high recovery yield of compound **7** promoted us to reconsider the reaction mechanism. In our initial design, we envisaged that the reaction could pass through an intramolecular Pummerer reaction pathway. In this pathway, after activation of the sulfinyl group, the abstraction of α-

proton led to a thionium ion **B** that allowed the anomeric oxygen atom attacking the α -carbon position to form an oxocarbenium **C** and an oxathiane **10**. Therefore, in the reaction mixture, we should obtain compound **10** or its hydrolyzed product. However, in all of the reactions we carried out, neither of them was observed. Instead, compound **7** was always isolated in high yield. This phenomenon implied that the reaction should pass through a different way. Possibly, the thionium ion was not formed due to the weak basicity of triflate anion, instead, anomeric oxygen atom prior to directly attack the sulfur cation of **A** to form oxocarbenium **C** and a sulfonium ion **D**. The sulfonium ion further hydrolyzed to form **7** during aqueous work up. The latter pathway is actually an intramolecular interrupted Pummerer reaction.²³ In addition, since we have proved that the PSB glycosides are quite stable in strong acidic conditions, therefore, the possibility that formation of **7** by direct cleavage of the anomeric C-O bond by TfOH should be excluded.

Pathway a: intramolecular Pummerer reaction



Pathway b: intramolecular interrupted Pummerer reaction



Scheme 7 Proposed mechanism.

Conclusion

In conclusion, we further reported the details of the discovery of 2-(2-propylsulfanyl)benzyl (PSB) glycoside as novel glycosyl donors which could be efficiently activated via a remote mode. With this type of glycosyl donor, the latent-active strategy was successfully applied by utilizing 2-(2-propylsulfanyl)benzyl (PSB) glycoside as active glycosyl donor and 2-(2-propylthiol)benzyl (PTB) glycoside as latent glycosyl donor. The orthogonality and stability of donors were examined and implied their practical applicability in combination with other known glycosyl donors in oligosaccharide synthesis. Further extension of this strategy to disarmed glycosyl donors as well as new application to naturally occurring oligosaccharide synthesis is under way.

Acknowledgements

We thank the National Natural Science Foundation of China (21272082, 21402055, 21472054), the State Key Laboratory of Bio-organic and Natural Products Chemistry (SKLBNPC13425), Natural Science Funds of Hubei Province for Distinguished Young Scholars (2015CFA035), the Specialized Research Fund for the Doctoral Program of Higher Education (20120142120092), "Thousand Talents Program" Young Investigator Award, and Huazhong University of Science and Technology (2014ZZGH015) for support.

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