CJC Chinese Journal of Chemistry
中国化学 - An International Journal

Check for updates

Accepted Article

Title: Dehydrative Glycosylation Enabled by a Comproportionation Reaction of 2-Aryl-1,3-Dithiane 1-Oxide

Authors: Lei Cai, Jing Zeng, Ting Li, Ying Xiao, Xiang Ma, Xiong Xiao, Qin Zhang, Lingkui Meng, and Qian Wan*

This work may now be cited as: *Chin. J. Chem.* **2019**, *37,* 10.1002/cjoc.201900419.

The final Version of Record (VoR) of it with formal page numbers will soon be published online in Early View: http://dx.doi.org/10.1002/cjoc.201900419.

WILEY-VCH SIOC CCS

ISSN 1001-604X • CN 31-1547/O6
mc.manuscriptcentral.com/cjoc
www.cjc.wiley-vch.de

Dehydrative Glycosylation Enabled by a Comproportionation Reaction of 2-Aryl-1,3-Dithiane 1-Oxide†

Lei Cai,[a] Jing Zeng,[a] Ting Li,[a] Ying Xiao,[a] Xiang Ma,[a] Xiong Xiao,[a] Qin Zhang,[a] Lingkui Meng,[a] and Qian Wan*[a,b]

[a] Hubei Key Laboratory of Natural Medicinal Chemistry and Resource Evaluation, School of Pharmacy, Huazhong University of Science and Technology, 13 Hangkong Road, Wuhan, Hubei, 430030, P. R. of China
[b] Institute of Brain Research Huazhong University of Science and Technology, 13 Hangkong Road, Wuhan, Hubei, 430030, P. R. of China

Cite this paper: *Chin. J. Chem.* **2019**, *37*, XXX—XXX. **DOI: 10.1002/cjoc.201900XXX**

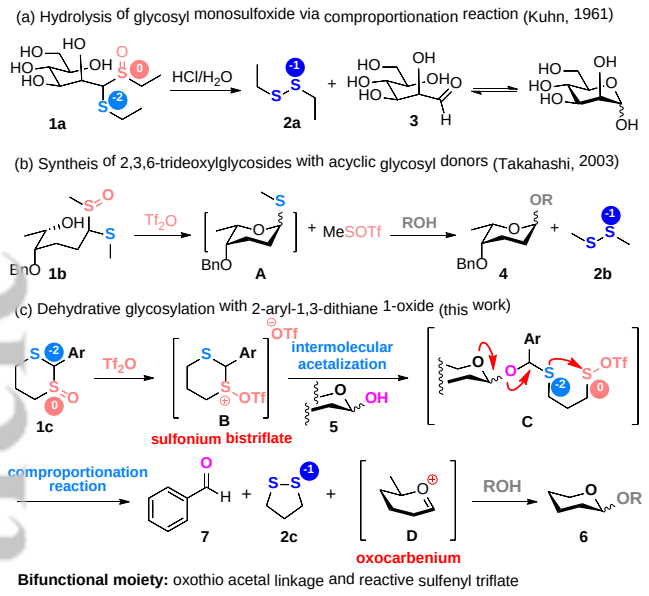
Summary of main observation and conclusion A new dehydrative glycosylation reaction has been established by capitalizing on the comproportionation reaction of 2-aryl-1,3-dithiane 1-oxides promoted by triflic anhydride (Tf_2O). By wedding the high potency of thiophilic promoter system with the step efficiency of dehydrative glycosylation, this reagent underwent facile intermolecular oxothio acetalization with C1-hemiacetal donor to install a temporary leaving group, rendering a transient electrophilic center at the remote site to the anomeric position. The sulfenyl triflate tethered at the terminus concomitantly activated the sulfide intramolecularly to afford the oxocarbenium ion, thereby facilitating the title glycosylation. Aside from accommodating broad range functional groups and inactive hemiacetal substrates, present activation protocol also proved expedient for 1,3-diol protection. Most importantly, this method further provided a fresh perspective for the application of sulfur chemistry to carbohydrate chemistry.

Background and Originality Content

The complex molecular framework of oligosaccharides and glycoconjugates presents an enduring challenge for the pursuit of increasingly efficient glycosylation methods in carbohydrate chemistry.[1] By virtue of elegant glycosylation strategies developed in the past century, Ye's recent landmark synthesis of arabinogalactan, a 92-mer polysaccharide, has endorsed the tremendous achievements in the odyssey of complex carbohydrate synthesis.[2] In this exemplary synthesis, sulfenyl triflates (RSOTf) generated *in situ* from a combination of sulfenyl chloride and silver triflate was applied sturdily as thioglycoside activation reagent.[3] Noteworthily, the highly reactive sulfenyl triflate species were also yielded upon the activation of glycosyl sulfoxide with triflic anhydride (Tf_2O) in Kahne glycosylation,[4] which could compete with triflic anhydride to activate sulfoxide donor.[5] The nondiscriminatory sulfide activations by RSOTf were also cited, which hampered the efficiency of glycosylation particularly for thioglycoside acceptors.[6] The intricate attribute of glycosyl sulfoxide activation mode have stymied its broad applications albeit the otherwise high potency. In continuation with our research interests to seek new reaction mode of sulfoxide chemistry in forging glycosidic bonds,[7] we surmised that this potent thiophilic glycosylation promoter system could be harnessed for one-pot sequential sulfoxide and sulfide activation as novel glycosidic bonds construction strategy given meticulous control. This conjecture was galvanized by a report of Kuhn *et al.* in 1961 which featured facile cleavage of *S*-oxide of mannosyl thioacetal **1a** to the D-mannose and diethyldisulfide **2a** (Scheme 1a).[8] A more recent example was documented by Takahashi *et. al* in an elegant synthesis of 2,3,6-trideoxy glycosides **4**, derived from an intramolecular cyclization of **1b** and subsequent intermolecular glycosylation with *in situ* generated thioglycosides **A** and electrophilic methyl sulfenyl triflate (MeSOTf) (Scheme 1b).[9] Along with formation of 2,3,6-trideoxy glycosides **4**, dimethyldisulfide **2b** was assumed to be a co-product.

Scheme 1 Comproportionation reactions of dithioacetal monosulfoxide

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/cjoc.201900419

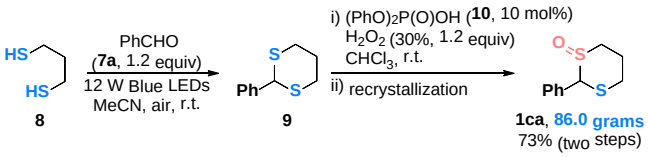


While conventional glycosylation reactions require exhaustive manipulation and activation of anomeric functional leaving groups,[10] the dehydrative variant which was first reported in 1893,[11] authorizes the direct activation of C1-hemiacetals. The obviation to install C1-leaving groups and isolation of glycosyl donor intermediates, streamline the tedious multi-glycosylation sequences.[12] Seemingly stands at marked advantage, the dehydrative glycosylation is plagued with substrate-dependent reactivity and selectivity issues which stem from higher stability of C1-hemiacetals thus requiring harsh activation conditions; furthermore, preferential self-condensation often precedes to form 1,1-linked disaccharides. Nonetheless, Gin,[13] Kobayashi,[14] Kim,[15] Panza,[16] Bennett,[17] Walczak,[18] Kancharla[19] and Taylor[20] *et al*. have respectively implemented intelligent refinements for accomplishing a suite of representative dehydrative glycosylation protocols. Drawing inspiration from these antecedent successes, our pursuit of novel dehydrative glycosylation commenced with the design of molecules (**1c**) containing dithioacetal monosulfoxide moiety as activation reagents. An abbreviated working mechanism is postulated herein (Scheme 1c): Selective activation of sulfoxide in **1c** by triflic anhydride (Tf_2O) could form sulfonium bistriflate (**B**) to induce intermolecular acetalization with glycosyl donor. This temporary anomeric leaving group with terminally tethered sulfenyl triflate moiety (**C**, Scheme 1c) would incite intramolecular sulfide activation, thus primes the glycosyl donor for glycosylation. In the process, the activation reagent **1c** would comproportionate to inert aldehyde **7** and disulfide **2c**.

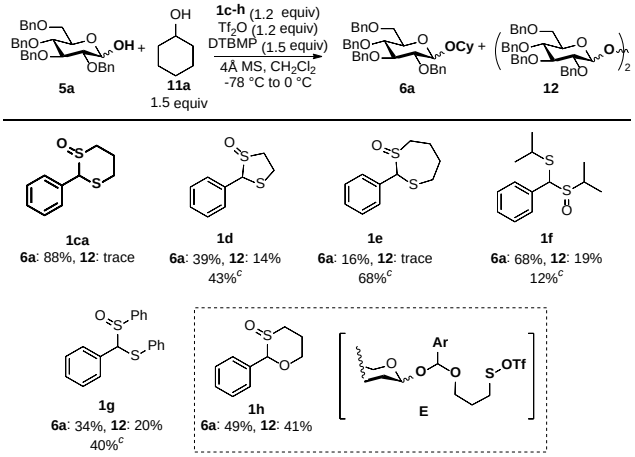
Results and Discussion

As proof of concept, various dithioacetal monosulfoxide dehydrative reagents (**1c**-**h**) were prepared employing an efficient two-step procedure. A typical synthetic way exemplified by the eighty-grams scale synthesis of 2-phenyl-1,3-dithiane 1-oxide **1ca** was outlined in Scheme 2.[21,22] Enlisting armed glucosyl **5a** as glycosyl donor and cyclohexanol **11a** as acceptor (Scheme 3), these reagents were examined adopting a pre-activation procedure;[3g-j,23] wherein Tf_2O, **1c**-**h**, **5a** and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) were pre-mixed prior to the addition of acceptor **11a**. While non-pre-activation procedure generally provided much lower yield of **6a** with the recovery of hemiacetal **5a**. Among the examined reagents, **1ca** proved to be the optimal which provided **6a** in 88% yield. The dithioacetal monosulfoxides with smaller (**1d**) or larger rings (**1e**) were inefficient, acyclic **1f** produced the desired product with 68% yield. It should be noted that small amount of self-condensed product **12** was obtained in the cases of **1d** and **1f**. By replacement of isopropyl group of **1f** with phenyl ring, reagent **1g** generated much lower yield of **6a** however increased yields of **12** and recovered **5a**. 1,3-oxathine 3-oxide **1h** was then assessed. Unfortunately, large amount of **12** was isolated, possibly due to intermediate **E** with an anomeric acetal functional group was unstable[24] in the pre-activation stage, it was activated under the acid conditions to form the oxocarbenium which reacted with the unreacted **5a** quickly. These results implied that intermediate **C** played a crucial role in the dehydrative reactions. This intermediate should possess certain stability in low temperature in the pre-activation stage but enough activity when warmed up. Finally, after carefully examination of the reaction conditions (see ESI), the optimal conditions for active C1-hydroxy glycosyl donors were then concluded as follows: after addition of Tf_2O (1.2 equiv) to the mixture of hemiacetal **5a**, sulfoxide **1ca** (1.2 equiv), DTBMP (1.5 equiv) and 4Å MS in CH_2Cl_2 at -78 °C, the reaction mixture was stirred for 10 min before addition of acceptor **11a** (1.5 equiv). The reaction temperature was maintained for 20 min before warming up to 0 °C and allowed to stir for 1 h.

Scheme 2 Preparation of 2-phenyl-1,3-dithiane 1-oxide **1ca**

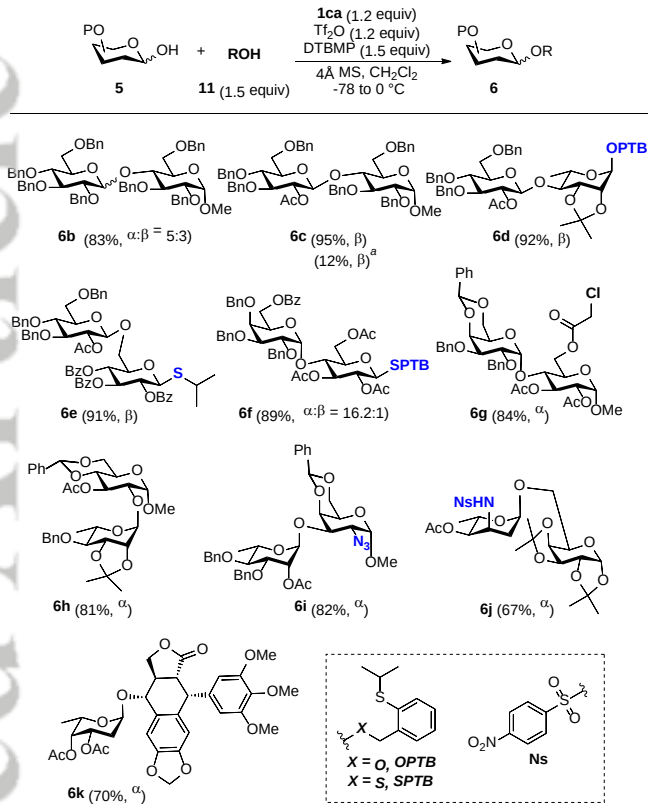


Scheme 3 Optimization of reaction conditions for active hemiacetal donors[a,b]



[a] General procedure: Tf_2O was added to the mixture of hemiacetal **5a**, sulfoxide **1c**-**h**, DTBMP and 4Å MS in CH_2Cl_2 at -78 °C, after 10 min, acceptor **11a** was added and stirred for additional 20 min, then warmed up to 0 °C and stirred for 1 h. [b] Isolated yield. **6a** were obtained as anomeric mixtures. [c] Recovered yield of **5a**.

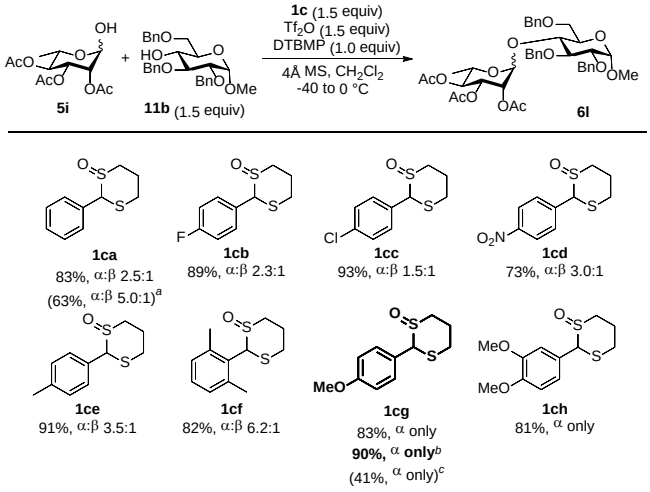
Scheme 4 Substrate scope of active donors



[c] Yield with Gin's condition: 1. Tf_2O (1.4 equiv), **5b** (1.0 equiv), Ph_2SO (2.8 equiv), $PhCH_3/CH_2Cl_2$ (3:1, v:v), -78 °C (10 min), then -40 °C (1 h); 2. 2-Chloropyridine (5.0 equiv), **11b** (1.6 equiv), $PhCH_3$, -40 °C (30 min), then 0 °C (25 min) and rt (4 h).

To illustrate the scope of current dehydrative glycosylation method, a variety of hemiacetal donors and acceptors were examined with sulfoxide **1ca** as activation reagent and hemiacetal donors as the limiting substrates (Scheme 4). Various acceptors acted as competent nucleophiles under this protocol. It is worth-mentioning that: 1) superarmed hemiacetal donors with C-2 neighbouring participation groups reacted smoothly to afford disaccharides **6c**-**e** and **6i** in good to excellent yields with absolute 1,2-*trans* stereo-control. Interestingly, when subjecting **5b** to Gin's dehydrative conditions,[13a] extremely low yields of **6c** was observed (12%). This result highlighted that the present method would be an important supplementary to Gin's conditions in terms of acetate protected substrates which are more commonly used in oligosaccharide assembly compared to benzoate ones. 2) galactopyranosyl donor with remote participation group[25] or benzylidene group, and rhamnopyranoside with 2,3-acetonide group coupled with $Glu^{O\text{-}4}$ or $Glu^{O\text{-}2}$ acceptors in good yields with excellent α-selectivity (**6f**-**h**). 3) the lower reactivity of multi-deoxy sugars with electron-withdrawing groups was successfully endured to furnish the desired disaccharide **6j** and **6k** in reasonable yields. 4) various functional groups including chloride (**6g**), azide (**6i**), *p*-nitrobenzenesulfonyl amide (**6j**), lactone (**6k**) as well as acid-sensitive ketal (**6e**, **6h** and **6j**) and acetal (**6g**) groups were well tolerated under present reaction conditions. 5) most prominently, the orthogonality established with thioglycoside (**6e**), OPTB glycoside (**6d**)[7a] and SPTB glycoside (**6f**)[7b] should augur well for downstream glycosidic bond construction.

Scheme 5 Optimization of reaction conditions for peracylated hemiacetal donors



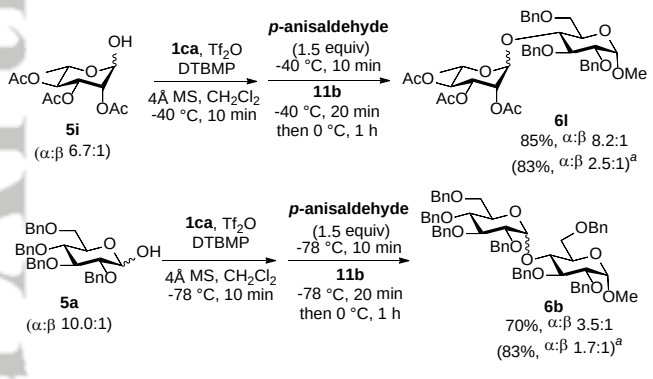
[a] **1ca** (1.2 equiv), Tf_2O (1.2 equiv), DTBMP (1.5 equiv), -78 to 0 °C. [b] DTBMP (1.5 equiv), **11b** (2.0 equiv). [c] Yield with Gin's conditions: 1. Tf_2O (1.4 equiv), **5i** (1.0 equiv), Ph_2SO (2.8 equiv), $PhCH_3/CH_2Cl_2$ (3:1, v:v), -78 °C (10 min), then -40 °C (1 h); 2. 2-Chloropyridine (5.0 equiv), **11b** (1.6 equiv), $PhCH_3$, -40 °C (30 min), then 0 °C (25 min) and rt (4 h).

In spite of the satisfactory results obtained for the armed hemiacetal donors and even the peracylated multi-deoxy sugars, extension of these conditions to peracetylated rhamnose **5i** provided **6l** only in 63% yield with moderate selectivity (Scheme 5). This selectivity was deemed exceptional given existence of neighboring group participation effect generally instills high level of 1,2-*trans* selectivity. To suppress the speculated formation of orthoester by-product due to the presence of C-2 acetate group under non-acidic conditions, the amount of **1ca** and triflic anhydride were increased to 1.5 equiv and only 1.0 equiv of base was used to uphold the acidity of the reaction system. Alongside with higher pre-activation temperature at -40 °C, the product yield could be promoted up to 83% but at the expense of attenuated selectivity (α:β ratio of 2.5:1). We then considered to permutate electronic properties of the aryl 1,3-dithiane 1-oxides core by introducing varied substituents on the phenyl ring (**1cb**-**1ch**). While all candidates mediated the delivery of cross coupled product **6l** in good to excellent yields; the selectivity engendered by the 1,3-

dithiane 1-oxides with electron rich phenyl groups outperformed, especially **1cg** and **1ch** which gave forth exclusive α-selectivity. Applying **1cg** as activation reagent, further increment of the amount of DTBMP and **11b** produced **6l** in 90% yield. Notably, only 41% yield of **6l** was obtained when employing Gin's conditions.

We conjectured that the dramatically increasing of α-selectivity by **1cg** might be resulted from the participation of *in situ* released *p*-anisaldehyde. To verify this hypothesis, a control experiment was carried out with **1ca** as dehydrative reagent. Upon pre-activation of **5i** and **1ca** with Tf_2O, 1.5 equiv of *p*-anisaldehyde was then added into the reaction mixture. With this modification, the α to β ratio of **6l** was exactly augmented from 2.5:1 to 8.2:1. This tendency was also observed when glycosydation of **5a** with *p*-anisaldehyde as additive. Given the electron enrichment of *p*-anisaldehyde, this aldehyde possibly acted as an exogenous nucleophile to modulate the selectivity.[26]

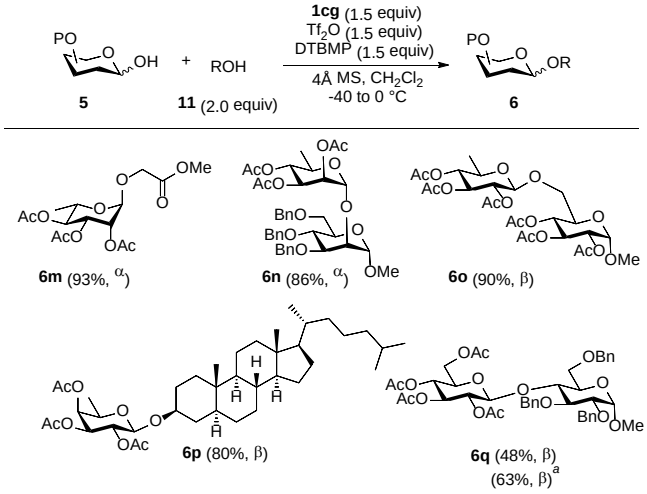
Scheme 6 The role of *p*-anisaldehyde



[a] Without *p*-anisaldehyde.

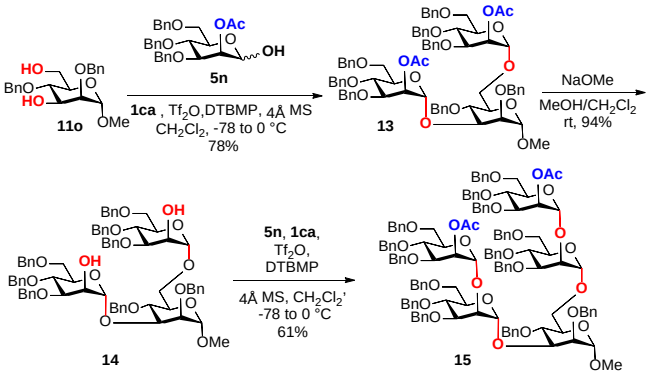
With this improvised reaction condition in hand, several inactive peracylated donors were examined as outlined in Scheme 7. In addition to L-rhamnose, peracetylated D-rhamnose, D-quinovose and D-fucose were amenable for activation to furnish the corresponding disaccharides in good yields with absolute 1,2-*trans* stereo-control (**6m**-**p**). The same conditions applied to peracetylated glucose formed **6q** in exclusive β-selectivity, and the modest reaction yield could be augmented with higher pre-activation temperature of -20 °C.

Scheme 7 Substrate scope for inactive donors



[a] DTBMP (1.0 equiv), **11b** (1.5 equiv), -20 to 0 °C.

Scheme 8 Synthesis of pentamannan **15**



As a final endeavor to vouch for the utilitarian potential of current protocol, a synthesis towards a protected form of pentamannan core **15** of HIV-1 envelop protein gp120 was initiated.[27] As shown in Scheme 8, our synthesis commenced from the cross coupling of **11o** with two molecules of hemiacetal **5n** activated by the combination of **1ca** and Tf_2O. Having secured trisaccharide **13** in 78% yield, removal of the acetate groups before another title coupling with two **5n** units auspiciously afforded the pentamannan **15** in 45% overall yield in three steps.

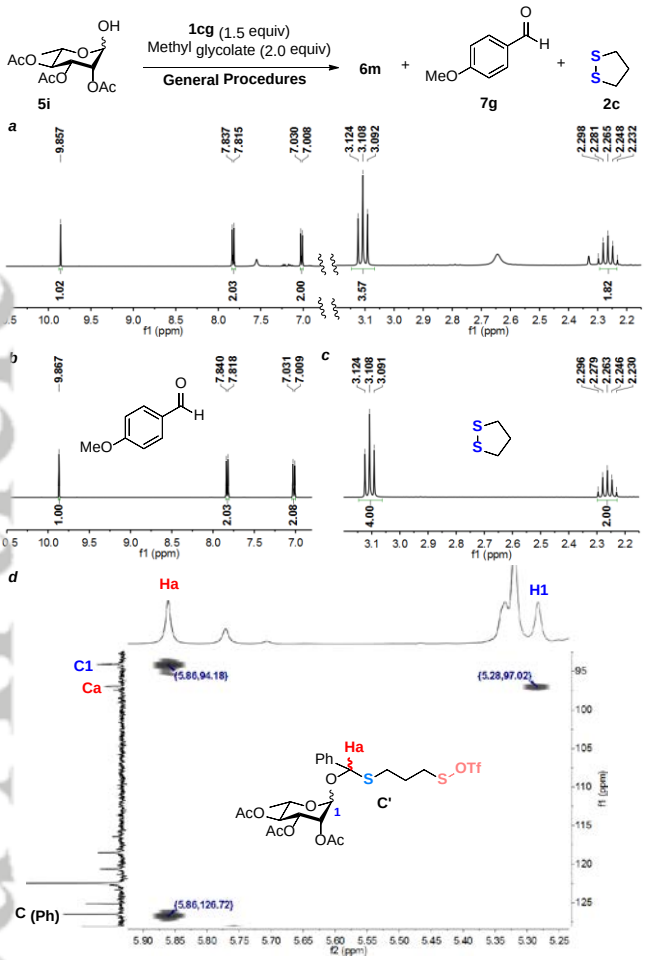
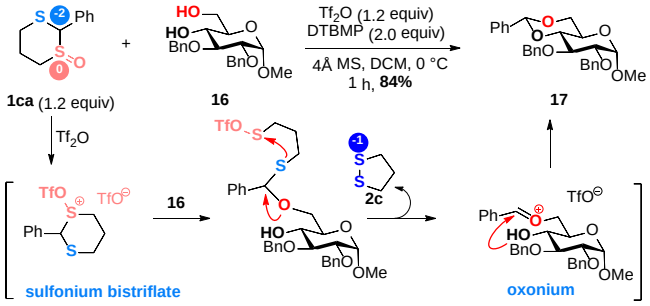


Figure 1 Identification of intermediate **C'** and leaving groups by ^{1}H NMR. [a] ^{1}H NMR of reaction mixture of **5i**, **1cg**, DTBMP and Tf_2O at rt. [b] ^{1}H NMR of **7g**. [c] ^{1}H NMR of **2c**. [d] HMBC spectrum of reaction mixture of **5i**, **1ca**, DTBMP and Tf_2O at -40 °C (for details, see: ESI).

Mechanism wise, the reaction was postulated to proceed through a sequential activation of sulfoxide and sulphide; and in process, the activation reagent dithiane oxides **1c** comproportionates to corresponding aryl aldehydes **7** and 1,2-dithiolane **2c**. Whilst the aldehydes were indeed isolated almost quantitatively in above reactions, isolation of 1,2-dithiolane was futile owing to its low polarity, high volatility and instability.[28] To validate the occurrence of this small molecule, the reaction was monitored in-situ by ^{1}H NMR employing coupling reaction of **5i** with methyl glycolate to produce **6m** (Figure 1). Expectedly, the formation of 4-methoxy-benzaldehyde (**7g**) and 1,2-dithiolane (**2c**) in quantitative were clearly evident in ^{1}H NMR spectrum.[29] This evidence strongly supposed the proposed mechanism. Additionally, low temperature NMR studies were carried out to capture the proposed intermediate **C'** when **5i** and **1ca** was activated with Tf_2O at -40 °C. In the ^{1}H NMR spectrum, typical singlet located at 5.861 ppm was observed which could be attributed to the thioacetal proton (Ha) of intermediate **C'**. Correlations of this signal to the aromatic carbon and anomeric carbon (C1) in the HMBC spectrum were also observed. This observation suggested that intermediate **C'** really exist, consequently, endorsed the proposed mechanism again.

Scheme 9 Protection of diol with **1ca**



When **1ca** was introduced as protection reagent for 1,3-diols (Scheme 9), the dihydroxy group of **16** was favourably protected as benzylidene acetal **17** in the presence of Tf_2O and DTBMP. This reaction was reckoned to mirror the dehydrative glycosylation pathway. Activation of **1ca** with Tf_2O generated a thionium ion possessing sulfenyl triflate functionality. Attachment of one hydroxyl group of **16** to thionium ion furnished the oxothioacetal species; subsequent intramolecular activation of sulfide with sulfenyl triflate produced oxonium which induced the cyclization to form the benzylidene acetal **17**. This reaction evinced the reaction mechanism of dehydrative glycosylation mediated by the 1,3-dithiane 1-oxide, but also availed as new alternative for diol protection under mild conditions.[30]

Conclusions

In conclusion, a new strategy for dehydrative glycosylation was delineated employing an unprecedented activation reagent, 2-aryl-1,3-dithiane 1-oxide and Tf_2O system. The activation of sulfoxide moiety of the reagent with Tf_2O initiated the installation a temporary anomeric leaving group bearing both active sulfenyl triflate and sulfide moieties at the C1 position. Intramolecular activation of the thus-formed oxothio acetal group by sulfenyl triflate facilitated the generation of glycosyl oxocarbenium ion susceptible for glycosidic bond formation. The activation reagent concomitantly transformed to neutral small molecules: an aldehyde and a 1,2-dithilane, which eased the isolation and purification steps. Wide range of substrates including inactive hemiacetals undertook the chemistry well. Compatibility of variegated functional groups highlighted the wide applicability of this protocol. Moreover, the method was pertinent for protection of diols to acetals warranted by the mild reaction conditions.

Experimental

Large scale preparation of 2-phenyl-1,3-dithiane 1-oxide 1ca: Benzaldehyde (**7a**, 67.6 mL, 0.665 mol, 1.2 equiv) and 1,3-dimercaptopropane (**8**, 55.7 mL, 0.554 mol, 1.0 equiv) were

dissolved in MeCN (185 mL, C = 0.3 mol/L) and irradiated with 12 W Blue LEDs under air at room temperature for 24 h. After consumption of 1,3-dimercaptopropane, the mixture was concentrated in vacuo to give dithiane **9** as crude products. To a stirred solution of the above crude product (1.0 equiv) and diphenyl phosphate (**10**, 13.9 g, 0.055 mol, 10 mol%) in $CHCl_3$ (185 mL, C = 0.3 mol/L) was added 30% H_2O_2 (66.8 mL, 0.665 mol, 1.2 equiv) at 0 °C. The mixture was stirred at room temperature for 5 h and extracted with EtOAc. The organic phase was washed with saturated $Na_2S_2O_3$, $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by recrystallization with petroleum ether/CH_2Cl_2 to give **1ca** (86.0 g, 73%) as white solid.

General procedure for the dehydrative glycosylation: Tf_2O (1.2-1.5 equiv) was added to the mixture of hemiacetal donor **5** (1.0 equiv), sulfoxide **1ca** (1.2-1.5 equiv), DTBMP (1.0-1.5 equiv) and 4Å MS (100 wt%) in CH_2Cl_2 (C = 0.1 mol/L) at -78 °C or -40 °C. After the mixture was stirred for 10 minutes, acceptors (1.5-2.0 equiv) in CH_2Cl_2 (0.2 mL) was added dropwise. The resulting mixture was stirred at this temperature for additional 20 minutes, then warmed up to 0 °C and stirred for 1 h.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

Acknowledgement

This research is partially supported by the National Natural Science Foundation of China (21877043, 21761132014, 21772050, 21672077). Wuhan Creative Talent Development Fund, the Fundamental Research Funds for the Central Universities (2019kfyRCPY034, 2019JYCXJJ047) and Huazhong University of Science and Technology are greatly appreciated. We thank Analytical and Testing Center of HUST for NMR tests.

References

[1] For recent reviews on glycosylation strategies: (a) Bennett, C. S.; Galan, M. C. Methods for 2-Deoxyglycoside Synthesis. *Chem. Rev.* **2018**, *118*, 7931-7985; (b) Kulkarni, S. S.; Wang, C.-C.; Sabbavarapu, N. M.; Podilapu, A. R.; Liao, P.-H.; Hung, S.-C. "One-Pot" Protection, Glycosylation, and Protection-Glycosylation Strategies of Carbohydrates. *Chem. Rev.* **2018**, *118*, 8025-8104; (c) Nielsen, M. M.; Pedersen, C. M. Catalytic Glycosylations in Oligosaccharide Synthesis. *Chem. Rev.* **2018**, *118*, 8285-8358; (d) Peng, P.; Schmidt, R. R. Acid-Base Catalysis in Glycosidations: A Nature Derived Alternative to the Generally Employed Methodology. *Acc. Chem. Res.* **2017**, *50*, 1171-1183; (e) Yu, B. Gold(I)-Catalyzed Glycosylation with Glycosyl *o*-Alkynylbenzoates as Donors. *Acc. Chem. Res.* **2018**, *51*, 507-516; (f) Leng, W.-L.; Yao, H.; He, J.-X.; Liu, X.-W. Venturing beyond Donor-Controlled Glycosylation: New Perspectives toward Anomeric Selectivity. *Acc. Chem. Res.* **2018**, *51*, 628-639; (g) Yang, B.; Yang, W.; Ramadan, S.; Huang, X. Pre-Activation-Based Stereoselective Glycosylations. *Eur. J. Org. Chem.* **2018**, 1075-1096; (h) Das, R.; Mukhopadhyay, B. Chemical O-Glycosylations: An Overview. *ChemistryOpen* **2016**, *5*, 401-433; (i) Lawandi, J.; Rocheleau, S.; Moitessier, N. Regioselective acylation, alkylation, silylation and glycosylation of Monosaccharides. *Tetrahedron* **2016**, *72*, 6283-6319; (j) Nigudkar, S. S.; Demchenko, A. V. Stereocontrolled 1,2-*cis* glycosylation as the driving force of progress in synthetic carbohydrate chemistry. *Chem. Sci.* **2015**, *6*, 2687-2704.

[2] Wu, Y.; Xiong, D.-C.; Chen, S.-C.; Wang, Y.-S.; Ye, X.-S. Total synthesis of mycobacterial arabinogalactan containing 92 monosac-charide units. *Nat. Commun.* **2017**, *8*, 14851.

[3] For examples of the activation of thioglycosides with alkyl/phenyl sulfenyl triflates, see: (a) Dasgupta, F.; Garegg, P. J. Alkyl sulfenyl triflate as activator in the thioglycoside-mediated formation of pglycosidic linkages during oligosaccharide synthesis. *Carbohydr. Res.* **1988**, *177*, C13-C17; (b) Dasgupta, F.; Garegg, P. J. Use of the methylsulfenyl cation as an activator for glycosylation reactions with alkyl (aryl) 1-thioglycopyranosides: synthesis of methyl *O*-(2-acetamido-2-deoxy-*β*-D-glucopyranosyl)-(1→6)-*O*-*α*-D-glucopyranosyl-(1→2)-*α*-D-glucopyranoside, a derivative of the core trisaccharide of *E.coli* K12. *Carbohydr. Res.* **1990**, *202*, 225-238; (c) Birberg, W.; Lönn, H. α-Selectivity and Glycal Formation are Temperature Dependent in Glycosylation with Sialic Acid. Synthesis of a Neu5Acα(2-6)Gal Thioglycoside Building Block. *Tetrahedron Lett.* **1991**, *32*, 7453-7456; (d) Lönn, H.; Stenvall, K. Exceptionally High Yield in Glycosylation with Sialic Acid. Synthesis of a GM_3 Glycoside. *Tetrahedron Lett.* **1992**, *33*, 115-116; (e) Martichonok, V.; Whitesides, G. M. A Practical Method for the Synthesis of Sialyl α-Glycosides. *J. Am. Chem. Soc.* **1996**, *118*, 8187-8191; (f) Martichonok, V.; Whitesides, G. M. Studies on α-sialylation using sialyl donors with an auxiliary 3-thiophenyl group. *Carbohydr. Res.* **1997**, *302*, 123-129; (g) Crich, D.; Sun, S. Direct Formation of *β*-Mannopyranosides and Other Hindered Glycosides from Thioglycosides. *J. Am. Chem. Soc.* **1998**, *120*, 435-436; (h) Crich, D.; Sun, S. Direct Chemical Synthesis of β-Mannopyranosides and Other Glycosides via Giycosyl Triflates. *Tetrahedron* **1998**, *54*, 8321-8348; (i) Crich, D.; Cai, W. Chemistry of 4,6-*O*-Benzylidene-D-glycopyranosyl Triflates: Contrasting Behavior between the Gluco and Manno Series. *J. Org. Chem.* **1999**, *64*, 4926-4930; (j) Huang, X.; Huang, L.; Wang, H.; Ye, X.-S. Iterative One-Pot Synthesis of Oligosaccharides. *Angew. Chem. Int. Ed.* **2004**, *43*, 5221-5224; (k) Jeon, I.; Iyer, K.; Danishefsky, S. J. A Practical Total Synthesis of Globo-H for Use in Anticancer Vaccines. *J. Org. Chem.* **2009**, *74*, 8452-8455; (l) Cai, F.; Yang, F. Sulfenyl Triflates as Glycosylation Promoters: Applications in Synthesis and Mechanistic Studies. *J. Carbohydr. Chem.* **2014**, *33*, 1-19; (m) Lian, G.; Zhang, X.; Yu, B. Thioglycosides in Carbohydrate Research. *Carbohydr. Res.* **2015**, *403*, 13-22.

[4] Kahne, D.; Walker, S.; Cheng, Y.; Engen, D. V. Glycosylation of Unreactive Substrates. *J. Am. Chem. Soc.* **1989**, *111*, 6881-6882; for review, see: Aversa, M. C.; Barattucci, A.; Bonaccorsi, P. Glycosulfoxides in carbohydrate chemistry. *Tetrahedron* **2008**, *64*, 7659-7683.

[5] Crich, D.; Sun, S. Are Glycosyl Triflates Intermediates in the Sulfoxide Glycosylation Method? A Chemical and ^{1}H, ^{13}C, and ^{19}F NMR Spectroscopic Investigation. *J. Am. Chem. Soc.* **1997**, *119*, 11217-11223.

[6] (a) Gildersleeve, J.; Smith, A.; Sakurai, K.; Raghavan, S.; Kahne, D. Scavenging Byproducts in the Sulfoxide Glycosylation Reaction: Application to the Synthesis of Ciclamycin 0. *J. Am. Chem. Soc.* **1999**,

121, 6176-6182; (b) Xuereb, H.; Maletic, M.; Gildersleeve, J.; Pelczer, I.; Kahne, D. Design of an Oligosaccharide Scaffold That Binds in the Minor Groove of DNA. *J. Am. Chem. Soc.* **2000**, *122*, 1883-1890. A similar side reaction occurred with 1-Benzenesulfinyl Piperidine (BSP)/Tf_2O system, see: (c) Codée, J. D. C.; Litjens, R. E. J. N.; Heeten, R. den; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. Ph_2SO/Tf_2O: a Powerful Promotor System in Chemoselective Glycosylations Using Thioglycosides. *Org. Lett.* **2003**, *5*, 1519-1522.

[7] (a) Shu, P.; Xiao, X.; Zhao, Y.; Xu, Y.; Yao, W.; Tao, J.; Wang, H.; Yao, G.; Lu, Z.; Zeng, J.; Wan, Q. Interrupted Pummerer Reaction in Latent-Active Glycosylation: Glycosyl Donors with a Recyclable and Regenerative Leaving Group. *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. Remote Activation of Disarmed Thioglycosides in Latent-Active Glycosylation via Interrupted Pummerer Reaction. *J. Am. Chem. Soc.* **2016**, *138*, 13402-13407; (c) Shu, P.; Yao, W.; Xiao, X.; Sun, J.; Zhao, X.; Zhao, Y.; Xu, Y.; Tao, J.; Yao, G.; Zeng, J.; Wan, Q. Glycosylation *via* remote activation of anomeric leaving groups: development of 2-(2-propylsulfinyl)benzyl glycosides as novel glycosyl donors. *Org. Chem. Front.* **2016**, *3*, 177-183; (d) Chen, W.; Zeng, J.; Wang, H.; Xiao, X.; Meng, L.; Wan, Q. Tracking the leaving group in the remote activation of *O*-2-[(propan-2-yl)sulfinyl]benzyl (OPSB) glycoside. *Carbohydr. Res.* **2017**, *452*, 1-5; (e) Chen, W.; Zeng, J.; Liao, Z.; Teng, S.; Xiao, X.; Meng, L.; Wan, Q. Mechanism investigations of the activation process of *S*-2-[(propan-2-yl)sulfinyl]benzyl (SPSB) glycosides. *J. Carbohydr. Chem.* **2018**, *37*, 498-506; (f) Zeng, J.; Liu, Y.; Chen, W.; Zhao, X.; Meng, L.; Wan, Q. Glycosyl Sulfoxides in Glycosylation Reactions. *Top. Curr. Chem.* **2018**, *376*, 27; (g) Zeng, J.; Wang, R.; Yao, W.; Zhang, S.; Sun, G.; Liao, Z.; Meng, L.; Wan, Q. Diversified synthesis and α-selective glycosylation of 3-amino-2,3,6-trideoxy sugars. *Org. Chem. Front.* **2018**, *5*, 3391-3395; (h) Zhao, Y.; Zeng, J.; Liu, Y.; Xiao, X.; Sun, G.; Sun, J.; Shu, P.; Fu, D.; Meng, L.; Wan, Q. Collective syntheses of phenylethanoid glycosides by interrupted Pummerer reaction mediated glycosylations. *J. Carbohydr. Chem.* **2018**, *37*, 471-497; (i) Fang, J.; Zeng, J.; Sun, J.; Zhang, S.; Xiao, X.; Lu, Z.; Meng, L.; Wan, Q. Total Syntheses of Resin Glycosides Murucoidins IV and V. *Org. Lett.* **2019**, *21*, 6213-6216.

[8] (a) Kuhn, R.; Baschang-Bister, W.; Dafeldecker, W. Über *S*-Oxyde der Zuckermercaptale und Eine Neue Glykosidsynthese. *Justus Liebigs Ann. Chem.* **1961**, *641*, 160-176; (b) Kuhn, R.; Neugebauer, F. A. *S*-Oxyde und *S*-Dioxyde cyclischer Mercaptole. *Chem. Ber.* **1961**, *94*, 2629-2644.

[9] (a) Amaya, T.; Takahashi, D.; Tanaksa, H.; Takahashi, T. Synthesis of 2,3,6-Trideoxysugar-Containing Disaccharides by Cyclization and Glycosidation through the Sequential Activation of Sulfoxide and Methylsulfanyl Groups in a One-Pot Procedure. *Angew. Chem. Int. Ed.* **2003**, *42*, 1833-1836; (b) Tanaka, H.; Takahashi, D.; Takahashi, T. Stereoselective Synthesis of Oligo-α(2,8)-3-deoxy-D-*manno*-2-octulosonic Acid Derivatives. *Angew. Chem. Int. Ed.* **2006**, *45*, 770-773. A similar cyclization see: (c) Yoshida, S.; Yorimitsu, H.; Oshima, K. Rhodium-Catalyzed Addition of Arylboronic Acids to 2-Methylene-1,3-dithiane Monoxide. *Synlett* **2007**, *10*, 1622-1624.

[10] (a) Zhu, X. M.; Schmidt, R. R. New Principles for Glycoside-Bond Formation. *Angew. Chem. Int. Ed.* **2009**, *48*, 1900-1934; (b) Toshima, K.; Tatsuta, K. Recent Progress in *O*-Glycosylation Methods and Its Application to Natural Products Synthesis. *Chem. Rev.* **1993**, *93*, 1503-1531; (c) Boons, G.-J. Strategies in Oligosaccharide Synthesis. *Tetrahedron* **1996**, *52*, 1095-1121.

[11] Fischer, E. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 2400-2412.

[12] For reviews, see: (a) Gin, D. Dehydrative Glycosylation with 1-Hydroxy Donors. *J. Carbohydr. Chem.* **2002**, *21*, 645-665; (b) O'Neill, S.; Rodriguez, J.; Walczak, M. A. Direct Dehydrative Glycosylation of C1-Alcohols. *Chem. Asian J.* **2018**, *13*, 2978-2990; (c) Ryan, D. A.; Gin, D. Y. Glycoside Synthesis from 1-Oxygen Substituted Glycosyl Donors. In *Handbook of chemical glycosylation*; Demchenko, A. V. Ed.; Wiley-Ver & Co. KGaA, Weinheim, **2008**, pp. 95-143.

[13] (a) Garcia, B. A.; Poole, J. L.; Gin, D. Y. Direct Glycosylations with 1-Hydroxy Glycosyl Donors using Trifluoromethanesulfonic Anhydride and Diphenyl Sulfoxide. *J. Am. Chem. Soc.* **1997**, *119*, 7597-7598; (b) Garcia, B. A.; Gin, D. Y. Dehydrative Glycosylation with Activated Diphenyl Sulfonium Reagents. Scope, Mode of *C*(1)-Hemiacetal Activation, and Detection of Reactive Glycosyl Intermediates. *J. Am. Chem. Soc.* **2000**, *122*, 4269-4279; (c) Nguyen, H. M.; Poole, J. L.; Gin, D. Y. Chemoselective Iterative Dehydrative Glycosylation. *Angew. Chem. Int. Ed.* **2001**, *40*, 414-417; (d) Nguyen, H. M.; Chen, Y.; Duron, S. G.; Gin, D. Y. Sulfide-Mediated Dehydrative Glycosylation. *J. Am. Chem. Soc.* **2001**, *123*, 8766-8772; (e) Boebel, T. A.; Gin, D. Y. Sulfoxide Covalent Catalysis: Application to Glycosidic Bond Formation. *Angew. Chem. Int. Ed.* **2003**, *42*, 5874-5877; (f) Boebel, T. A.; Gin, D. Y. Probing the Mechanism of Sulfoxide-Catalyzed Hemiacetal Activation in Dehydrative Glycosylation. *J. Org. Chem.* **2005**, *70*, 5818-5826.

[14] Nishida, Y.; Shingu, Y.; Dohi, H.; Kobayashi, K. One-Pot α-Glycosylation Method Using Appel Agents in *N,N*-Dimethylformamide. *Org. Lett.* **2003**, *5*, 2377-2380.

[15] (a) Kim, K. S.; Lee, Y. J.; Kim, H. Y.; Kang, S. S.; Kwon, S. Y. Glycosylation with glycosyl benzyl phthalates as a new type of glycosyl donor. *Org. Biomol. Chem.* **2004**, *2*, 2408-2410; (b) Kim, K. S.; Fulse, D. B.; Baek, J. Y.; Lee, B.-Y.; Jeon, H. B. Stereoselective Direct Glycosylation with Anomeric Hydroxy Sugars by Activation with Phthalic Anhydride and Trifluoromethanesulfonic Anhydride Involving Glycosyl Phthalate Intermediates. *J. Am. Chem. Soc.* **2008**, *130*, 8537-8547; (c) Baek, J. Y.; Lee, B.-Y.; Pal, R.; Lee, W.-Y.; Kim, K. S. Direct glycosylation with anomeric hydroxy sugars by activation with 3-fluorophthalic anhydride and trifluoromethanesulfonic anhydride. *Tetrahedron Lett.* **2010**, *51*, 6250-6254.

[16] Mossotti, M.; Panza, L. Dehydrative Glycosylation with the Hendrickson Reagent. *J. Org. Chem.* **2011**, *76*, 9122-9126.

[17] (a) Nogueira, J. M.; Nguyen, S. H.; Bennett, C. S. Cyclopropenium Cation Promoted Dehydrative Glycosylations Using 2-Deoxy- and 2,6-Dideoxy-Sugar Donors. *Org. Lett.* **2011**, *13*, 2814-2817; (b) Issa, J. P.; Lloyd, D.; Steliotes, E.; Bennett, C. S. Reagent Controlled *β*-Specific Dehydrative Glycosylation Reactions with 2-Deoxy-Sugars. *Org. Lett.* **2013**, *15*, 4170-4173; (c) Nogueira, J. M.; Bylsma, M.; Bright, D. K.; Bennett, C. S. Reagent-Controlled α-Selective Dehydrative Glycosylation of 2,6-Dideoxy- and 2,3,6-Trideoxy Sugars. *Angew. Chem. Int. Ed.* **2016**, *55*, 10088-10092; (d) Mizia, J. C.; Bennett, C. S. Reagent Controlled Direct Dehydrative Glycosylation with 2-Deoxy Sugars: Construction of the Saquayamycin Z Pentasaccharide. *Org. Lett.* **2019**, *21*, 5922-5927; (e) Zhou, M.-H.; Wilbur, D. J.; Kwan, E. E.; Bennett, C. S. Matching Glycosyl Donor Reactivity to Sulfonate Leaving Group Ability Permits S_N2 Glycosylations. *J. Am. Chem. Soc.* doi.org/10.1021/jacs.9b07022.

[18] Dyapa, R.; Dockery, L. T.; Walczak, M. A. Dehydrative glycosylation

with cyclic phosphonium anhydrides. *Org. Biomol. Chem.* **2017**, *15*, 51-55.

[19] Ghosh, T.; Mukherji, A.; Srivastava, H. K.; Kancharla, P. K. Secondary amine salt catalyzed controlled activation of 2-deoxy sugar lactols towards alphaselective dehydrative glycosylation. *Org. Biomol. Chem.* **2018**, *16*, 2870-2875.

[20] Manhas, S.; Taylor, M. S. Dehydrative glycosidations of 2-deoxysugar derivatives catalyzed by an arylboronic ester. *Carbohydr. Res.* **2018**, *470*, 42-49.

[21] Xing, Z.; Yang, M.; Sun, H.; Wang, Z.; Chen, P.; Liu, L.; Wang, X.; Xie, X.; She, X. Visible-light promoted dithioacetalization of aldehydes with thiols under aerobic and photocatalyst-free conditions. *Green Chem.* **2018**, *20*, 5117-5122.

[22] Zhang, J.; Li, M.; Wang, X.; Zhang, Y.; Jia, J. Oxidation of Thioether and Mercaptal to Sulfoxide Catalyzed by Hydrogen Phosphates. *Chin. J. Org. Chem.* **2015**, *35*, 2405-2411.

[23] For review, see: (a) Yang, L.; Qin, Q.; Ye, X.-S. Preactivation: An Alternative Strategy in Stereoselective Glycosylation and Oligosaccharide Synthesis. *Asian J. Org. Chem.* **2013**, *2*, 30-49; for earlier examples, see: ref 4g-4j and (b) Crich, D.; Sun, S. Formation of *β*-Mannopyranosides of Primary Alcohols Using the Sulfoxide Method. *J. Org. Chem.* **1996**, *61*, 4506-4507; (c) Codée, J. D. C.; van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; van Boeckel, C. A. A.; van Boom, J. H.; van der Marel, G. A. Chemoselective glycosylations using sulfonium triflate activator systems. *Tetrahedron* **2004**, *60*, 1057-1064.

[24] (a) Jegge, S.; Lehmann, J. Comparative Stability of 1-Alkoxyalkyl *α*-D-Glucosides in The Presence of Acid or *α*-D-Glucosidase from Yeast. *Carbohydr. Res.* **1985**, *142*, 47-59; (b) Hughes, K. D.; Nguyen, T.-L. N.; Dyckman, D.; Dulay, D.; Boyko, W. J.; Giuliano, R. M. Synthesis of vinyl glycosides and carbohydrate vinyl ethers from mixed acetals: a hetero-Diels-Alder approach to deoxygenated disaccharides. *Tetrahedron: Asymmetry* **2005**, *16*, 273-282; (c) Yang, H.; Wang, P. Mechanistic Study of Glycosylation Using a Prop-1-enyl Donor. *J. Org. Chem.* **2013**, *78*, 1858-1863; (d) Zhang, X.; Zhou, Y.; Zuo, J.; Yu, B. Total synthesis of periploside A, a unique pregnane hexasaccharide with potent immunosuppressive effects. *Nat. Commun.* **2015**, *6*, 5879.

[25] (a) Cheng, Y.-P.; Chen, H.-T.; Lin, C.-C. A convenient and highly stereoselective approach for α-galactosylation performed by galactopyranosyl dibenzyl phosphite with remote participating groups. *Tetrahedron Lett.* **2002**, *43*, 7721-7723; (b) Komarova, B. S.; Tsvetkov, Y. E.; Nifantiev, N. E. Stereocontrol of 1,2-*cis*-Glycosylation by Remote *O*-Acyl Protecting Groups. In *Modern Synthetic Methods in Carbohydrate Chemistry*; Werz, D. B.; Vidal, S. Eds.; Wiley-Ver & Co. KGaA, Weinheim, **2014**, pp. 125-159; (c) Komarova, B. S.; Orekhova, M. V.; Tsvetkov, Y. E.; Beau, R.; Aimanianda, V.; Latgé, J.-P.; Nifantiev, N. E. Synthesis of a Pentasaccharide and Neoglycoconjugates Related to Fungal α-(1→3)-Glucan and Their Use in the Generation of Antibodies to Trace *Aspergillus fumigatus* Cell Wall. *Chem. Eur. J.* **2015**, *21*, 1029-1035; (d) Komarova, B. S.; Tsvetkov, Y. E.; Nifantiev, N. E. Design of α-Selective Glycopyranosyl Donors Relying on Remote Anchimeric Assistance. *Chem. Rec.* **2016**, *16*, 488-506; (e) Zhang, Y.; Zhou, S.; Wang, X.; Zhang, H.; Guo, Z.; Gao, J. A new method for α-specific glucosylation and its application to the one-pot synthesis of a branched α-glucan. *Org. Chem. Front.* **2019**, *6*, 762-772.

[26] Mulani, S. K.; Hung, W.-C.; Ingle, A. B.; Shiau, K.-S.; Mong, K.-K. T. Modulating glycosylation with exogenous nucleophiles: an overview. *Org. Biomol. Chem.* **2014**, *12*, 1184-1197.

[27] (a) Bewley, C. A.; Kiyonaka, S.; Hamachi, I. Site-specific Discrimination by Cyanovirin-N for *α*-Linked Trisaccharides Comprising the Three Arms of Man_8 and Man_9. *J. Mol. Biol.* **2002**, *322*, 881-889; (b) Barrientos, L. G.; Gronenborn, A. M. The Highly Specific Carbohydrate-Binding Protein Cyanovirin-N: Structure, Anti-HIV/Ebola Activity and Possibilities for Therapy. *Mini-Rev. Med. Chem.* **2005**, *5*, 21-31; (c) Du, Y.; Zhang, M.; Kong, F. Efficient and practical syntheses of three pentasaccharides core structures corresponding to *N*-glycans. *Tetrahedron* **2001**, *57*, 1757-1763; (d) Jiang, L.; Chan, T. H. Efficient synthesis of the nonamannoside residue of high mannose glycoproteins[1]. *Can. J. Chem.* **2005**, *83*, 693-701; (e) Lam, S. N.; Gervay-Hague, J. Efficient Synthesis of Man_2, Man_3, and Man_5 Oligosaccharides, Using Mannosyl Iodide Donors. *J. Org. Chem.* **2005**, *70*, 8772-8779; (f) Teumelsan, N.; Huang, X. Synthesis of Branched Man5 Oligosaccharides and an Unusual Stereochemical Observation. *J. Org. Chem.* **2007**, *72*, 8976-8979; (g) Neralkar, M.; Mishra, B.; Hotha, S. Nucleofuge Generating Glycosidations by the Remote Activation of Hydroxybenzotriazolyl Glycosides. *J. Org. Chem.* **2017**, *82*, 11494-11504.

[28] Green, M.; Lown, E. M.; Strausz, O. P. Reactions of *S* Atoms with Dimethyl Sulfide and Thietane. *J. Am. Chem. Soc.* **1984**, *106*, 6938-6946.

[29] Ghosh, S. S.; Martin, J. C.; Fried, J. A Total Synthesis of the Methyl Ester of the 9,11-Dithia Analogue of 13,14-Dehydro-PGH_2. *J. Org. Chem.* **1987**, *52*, 862-876.

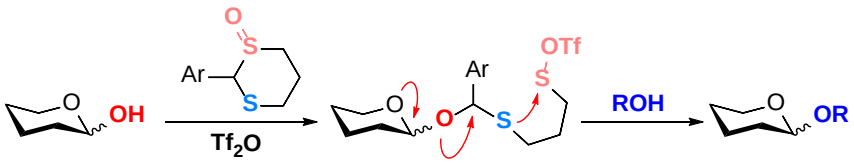
[30] (a) Tatina, M.; Yousuf, S. K.; Mukherjee, D. 2,4,6-Trichloro-1,3,5-triazine (TCT) mediated one-pot sequential functionalisation of glycosides for the generation of orthogonally protected monosaccharide building blocks. *Org. Biomol. Chem.* **2012**, *10*, 5357-5360; (b) Tran, A.-T.; Jones, R. A.; Pastor, J.; Boisson, J.; Smith, N.; Galan, M. C. Copper(II) Triflate: AVersatile Catalyst for the One-Pot Preparation of Orthogonally Protected Glycosides. *Adv. Synth. Catal.* **2011**, *353*, 2593-2598; (c) Geng, Y.; Faidallah, H. M.; Albar, H. A.; Mhkalid, I. A.; Schmidt, R. R. Organocatalysis for the Acid-Free *O*-Arylidenation of Carbohydrates. *Eur. J. Org. Chem.* **2013**, 7035-7040; (d) Kotke, M.; Schreiner, P. R. Acid-free, organocatalytic acetalization. *Tetrahedron* **2006**, *62*, 434-439.

Manuscript received: XXXX, 2019
Manuscript revised: XXXX, 2019
Manuscript accepted: XXXX, 2019
Accepted manuscript online: XXXX, 2019
Version of record online: XXXX, 2019

Entry for the Table of Contents

Page No.

Dehydrative Glycosylation Enabled by a Comproportionation Reaction of 2-Aryl-1,3-Dithiane 1-Oxide



2-Aryl-1,3-dithiane 1-oxides were employed as a new class of dehydrative reagents for 1-OH glycosyl donors. The sequential activation of sulfoxide and sulfide groups enabled the effcient dehydrative glycosylation of various substrates.

Lei Cai, Jing Zeng, Ting Li, Ying Xiao, Xiang Ma, Jiong Xiao, Qin Zhang, Lingkui Meng, and Qian Wan*

