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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.9b04619 • Publication Date (Web): 17 Jul 2019

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Glycosylation Enabled by Successive Rhodium(II) and Brønsted Acid Catalysis

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Supporting Information Placeholder

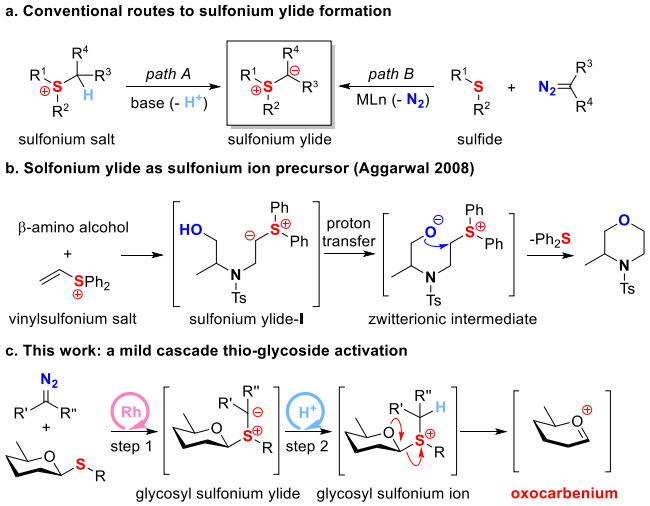
ABSTRACT: Herein, we reported on a highly efficient glycosylation reaction comprises two chronological meticulously-designed catalytic cycles: 1) rhodium-catalyzed formation of sulfonium ylide; 2) Brønsted acid-catalyzed formation of sulfonium ion. This protocol highlighted an effective and robust tactic to prepare glycosyl sulfonium ion from glycosyl sulfonium ylide precursor amenable for glycosylation.

Sulfonium ylides are conventionally prepared *via* (i) deprotonation of sulfonium salts under strong basic conditions or (ii) reactions of sulfides and carbenes or metal carbenoids (Scheme 1a, path A and B).[1,2] Alternatively, conjugate addition of nucleophiles to vinylsulfonium salts provide sulfonium ylide intermediates which upon protonation form sulfonium ions that also serve as valuable intermediates in multifarious synthetic pathways.[3] This appealing reaction mode was seminally explored by Gosselck,[4a] and further advanced by Aggarwal,[4b] and Xiao[4c] *et al*. In 2008, Aggarwal demonstrated an elegant synthesis of morpholines initiated by conjugate addition of β-amino alcohols to vinylsulfonium salts (Scheme 1b).[5a] An ensuing proton transfer from a tethered hydroxy group to the *in situ* generated sulfonium ylide-**I** produces a zwitterionic intermediate. The resulting nucleophilic alkoxide then facilitates a ring closure by displacement of the sulfonium leaving group.[5] Intriguingly, the formation of sulfonium intermediates *via* the protonation of sulfonium ylides can be viewed as a reverse process of deprotonation of sulfonium salts.[6]

Thioglycosides in carbohydrate chemistry offer distinct advantages[7] and the formation of glyco-sulfonium ions underlies the success of glycosylation.[8] As opposed to the well-established methods to generate glyco-sulfonium ions, the methodical studies of the chemistry of glyco-sulfonium ylides receives less attention.[9a-c] Galvanized on the Kametani[9a], Porter[9b-c] and Aggarwal's works[5a], we devised a novel glycosylation reaction[10] constitutes of successive Rh(II)-catalyzed sulfonium ylide formation[11] and Brønsted acid-catalyzed sulfonium formation[12] which facilely affords oxocarbenium ion susceptible for nucleophilic attack of acceptors (Scheme 1c).

Enlisting armed **1a-d** as donors and **2a-b** as the acceptors (Table 1), initial developmental trials for the titled reaction were performed at 0 °C to suppress the undesirable Stevens rearrangement.[9a] At the outset of this investigation, thio-donor **1a** alone was treated with rhodium(II) octanoate dimer ($Rh_2(oct)_4$) and methyl 4-chlorophenyldiazoacetate **3a**. The reaction was quenched after an hour upon complete consumption of **1a** to isolate hemiacetal **6a** (86%) and sulfide **9** (83%). The extension of reaction duration to 24 hours rendered *O*-glycoside **6b** as the major product while the Stevens rearrangement product *C*-glycoside **6c** was not observed.[9a] The formation of *O*-glycoside **6b** was speculated to be the rearrangement product of zwitterion **5'**; which in turn pointed to the intermediacy of glycosyl ylide **5** formed during the activation.[13a,b]

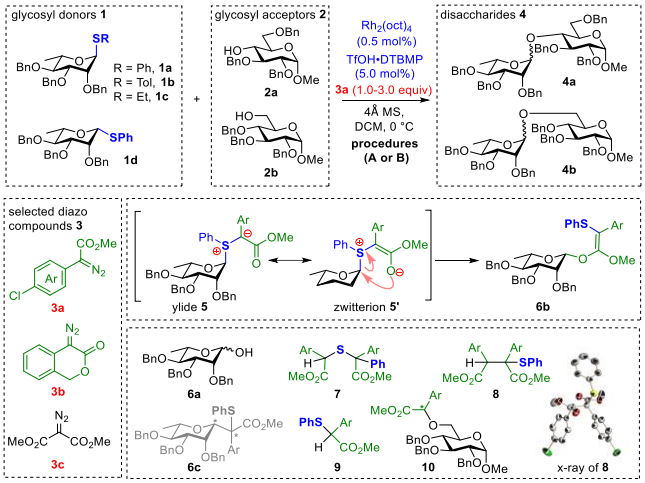
Scheme 1. Transformations within Sulfide, Sulfonium Ylide and Sulfonium Ion



At the same time, we reckoned the generation of oxo-carbenium species from glycosyl sulfonium ylide **5** could be difficult as the positively charged glycosyl sulfur atom was stabilized by the neighboring carbanion, rendering it a poor leaving group. Accordingly, catalytic amount of Brønsted acid was added to facilitate the formation of active sulfonium ion. We first pursued the reaction in a "one-shot" activation mode for coupling between **1a** and **2a** in the presence of diazo compound **3a** (3.0 equiv) (Table 1, procedure A). Gratifyingly, the disaccharide **4a** was isolated in 89% yield, together with two by-products **7** and **8** instead of **9** (entry 1). These by-products could be derived from the Stevens rearrangement of ylide which was generated from a competitive reaction between the *in situ* released sulfide **9** and rhodium carbenoid. To verify this hypothesis, a stepwise reaction (procedure B) was investigated; wherein the amount of the **3a** was reduced to 1.2 equiv. and the Brønsted acid was added until the yellow color of **3a** disappeared (entry 2). This

modification resulted in formation of **4a** and co-product **9** in 86% and 89% yield respectively while that of 7

Table 1. Reaction Development



Entry	procedures	1/2 (ratio)	4 [a,b]	byproduct[a]
1	A	1a/2a (1:1)	4a (89%)	7 (52%)
				8 (36%)
2	B	1a/2a (1:1)	4a (86%)	9 (89%)
3	A	1a/2a (1:1)	4a (23%)[c]	-[d]
4	A	1a/2a (1.2/1)	4a (95%)	-[d]
5	A	1b/2a (1.2/1)	4a (89%)	-[d]
6	A	1c/2a (1.2/1)	4a (82%)	-[d]
7	A	1d/2a (1.2/1)	4a (90%)	-[d]
8	A	1a/2b (1.2/1)	4b (12%)	10 (81%)
9	B	1a/2b (1.2/1)	4b (96%)	-[d]

Procedure A: to the mixture of **1**, **2** and **3** (3.0 equiv) in CH_2Cl_2 at 0 °C, $Rh_2(oct)_4$ (0.5 mol%) in CH_2Cl_2 and TfOH·DTBMP (5.0 mol%) in CH_2Cl_2 were added, the resulting mixture was stirred at 0 °C until the reaction was completed. **Procedure B:** the reaction mixture of **1**, **3** (1.2-1.5 equiv) and $Rh_2(oct)_4$ (0.5 mol%) in CH_2Cl_2 was stirred at 0 °C until the yellow color was disappeared, then **2** and TfOH·DTBMP (5.0 mol%) were added to the mixture. [a] Isolated yields based on **2a-b**. [b] Isolated as a mixture of α/β anomers. [c] Without TfOH·DTBMP. [d] by-products were not collected.

and **8** was completely inhibited. In view of the ease of operation, further optimizations were carried out based on procedure A. In the absence of TfOH·DTBMP, the yield of disaccharide **4a** was hampered to 23% even with longer reaction time (entry 3). Slight excess of **1a** (1.2 equiv.) promoted the yield up to 95% (entry 4). Screening of donors **1a-d** revealed that -SPh was the optimal anomeric leaving group and the coupling efficiency was unaffected by the anomeric configuration of the donor (entries 5-7). However, when primary alcohol **2b** was used as the acceptor with procedure A, significant amount of carbene O-H insertion by-product **10** was obtained (81%, entry 8).[14] In this case, reaction with procedure B furnished the desired product **4b** in excellent yield (96%, entry 9). This implied that "one-shot" activation mode was not suitable for the reaction with highly reactive alcohols as acceptors and the stepwise activation mode was recommended correspondingly.

On the basis of experimental results and prior reports,[11b] a plausible pathway for the successive rhodium(II)- and Brønsted acid-catalyzed glycosylation was illustrated in Scheme 2. In the first catalytic circle, $Rh_2(oct)_4$ promotes the decomposition of **3a** and forms a rhodium carbenoid (**A**), which is subsequently attacked by the sulfide **1** to provide the glycosyl ylide (**B**) and regenerates active Rh(II) species (Scheme 2, cycle 1). In the second catalytic

Scheme 2. Mechanistic Proposal

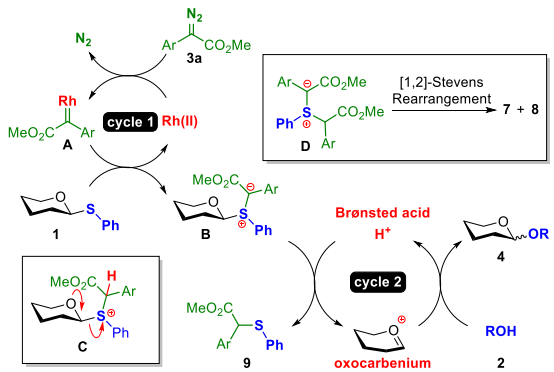
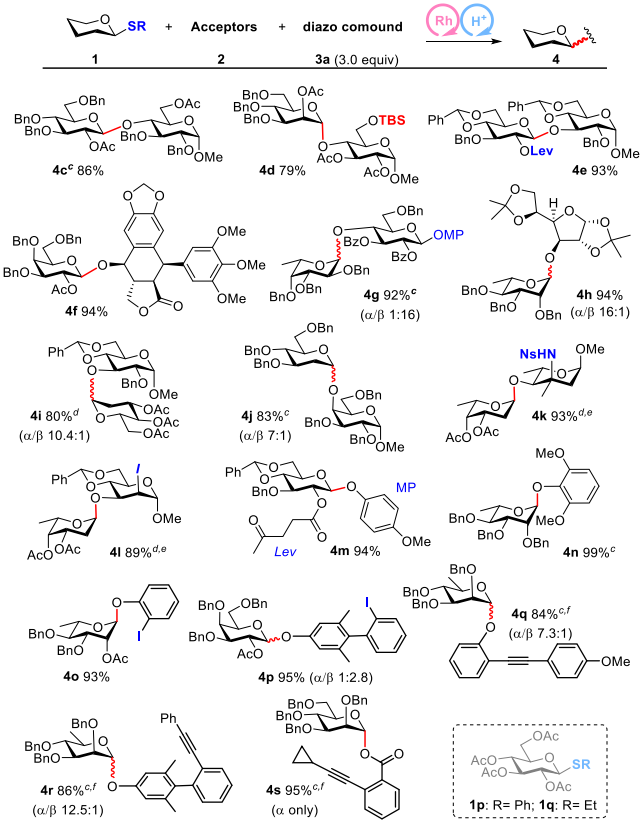


Table 2. Reaction Scope for Armed/Superarmed Thioglycosides.[a,b]



[a] Yield of isolated product. [b] Unless otherwise specified, the reactions were carried out according to Procedure A: to the solution of **1** (1.2 equiv, R = Tol), **2** and **3** (3.0 equiv) in CH_2Cl_2 at 0 °C, were added the solutions of $Rh_2(oct)_4$ (0.5 mol%) and TfOH·DTBMP (5.0 mol%) in CH_2Cl_2. [c] **1** (R = Ph). [d] $Rh_2(oct)_4$ (1.0 mol%). [e] **1** (1.5 equiv). [f] Procedure B (stepwise activation): **3a** (1.5 equiv), the acceptor and TfOH·DTBMP were added after the formation of glycosyl ylide.

cycle, protonation of the carbanion of glycosyl ylide (**B**) with catalytic amount of Brønsted acid furnishes the active sulfonium ion

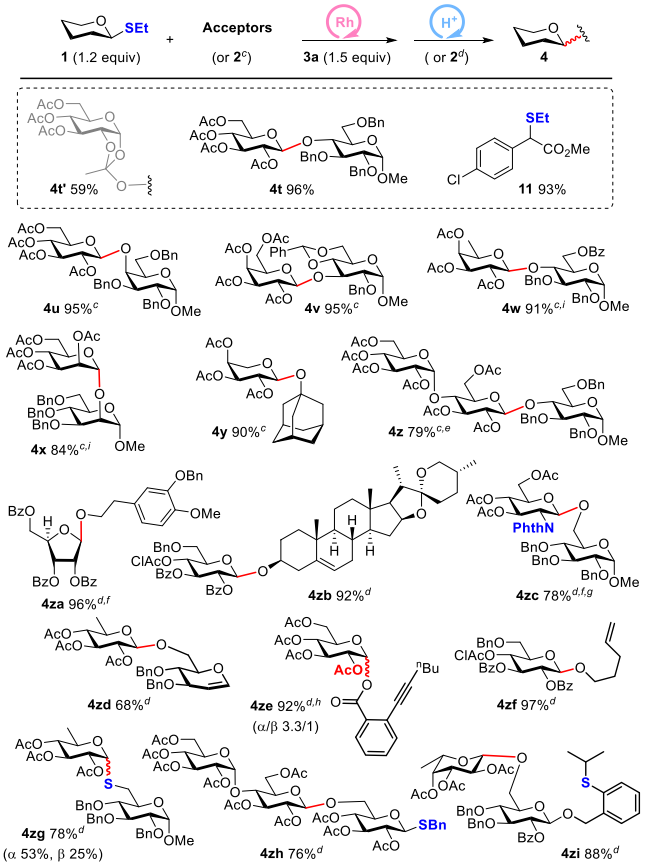
(C), the precursor of oxocarbenium ion.[15] Interception of the oxocarbenium ion or analogous intermediate by acceptor **2** produces the glycoside **4** and restores H^+. The H^+ released from acceptor **2** completes the second catalytic cycle (Scheme 2, cycle 2). Noteworthily, the protonation of ylide in second catalytic cycle not only provides active sulfonium species but also avoids the accumulation of H^+ which is crucial for accommodating acid labile substrates (vide infra). Both catalytic cycles are maneuvered under very mild conditions; which augurs well for the preparation of acid sensitive substrates or chemical manipulation of stagnant glycosylations.[16]

With two sets of optimal conditions in hand, we then set out to study the universality and versatility of current novel glycosylation reaction by coupling a manifold of armed/superarmed thioglycosides with acceptors bearing different protecting groups (details see Table S1). Wide variety of glycosidic bonds could be formed in good to excellent yields (**4c-s**, Table 2). Most coupling reactions proceeded with "one-shot" procedure (Table 1, procedure A). Of note, carbonyl groups, acetonide, benzylidene, silyl group, 4-methoxyphenyl group, *p*-nitrobenzenesulfonyl (Ns) amide group and iodide demonstrated exquisite compatibility with the glycosylation conditions. Current chemistry was also well undertaken by acid sensitive substrates to afford 6-deoxyl sugars (**4g-h**, **4l**, **4n-o**, **4q-r**), 2-deoxyl sugars (**4i-l**), 2,6-dideoxyl-L-fucose (**4l**, **4k**) and electron rich substrates (**4f**, **4m-n**, **4q-r**); attesting to the geniality and generality of the protocols.

Exceptionally, this new activation method was applicable for the synthesis of phenolic glycosides (**4m-r**).[17] Phenolic *O*-glycosylation are conventionally associated with long-standing challenges with the first being the poor nucleophilicity of phenols bearing electron-withdrawing group especially under acidic conditions. As for phenols with electron-donating substituents, Fries-type rearrangement of *O*-aryl glycosides to *C*-glycosides often precedes the desired *O*-glycosylation.[18] Lastly, the steric encumbrance posed by substituents on the phenol rings often jeopardize the glycosylation efficiency.[19] In our study, electron-rich phenols (4-methoxyphenol **2l**, 2,6-dimethoxyphenol **2m**, *o*-((*p*-methoxyphenyl)ethynyl)phenol (MPEP) **2p** and 3,5-dimethyl-4-(2'-phenylethynylphenyl)phenol (EPP) **2q**), electron-poor phenol (2-iodophenol **2o**), sterically hindered phenol (**2m**) and *ortho*-(cyclopropylethynyl)benzoic (CPEBz) acid **2r** were auspiciously glycosylated with various donors following "step-wise" or "one-shot" activation procedure in excellent yields (Table 2). More importantly, the synthetically significant MPEP glycoside[20] **4p**, EPP glycoside[21] **4q** and CPEBz glycoside[16e] **4s** were obtained in excellent yields in a single step from simple thioglycosides. While Sun's[20] studies evinced the synthetic infeasibility to obtain the active MPEP glycosyl donors directly from the super electron rich phenol **2p** due to its inherent high reactivity; current method presented an alternative straightforward approach towards MPEP, EPP and CPEBz glycosides.

Having determined the breadth of reaction scope with respect to armed/superamred thioglycosides, the compatibility of disarmed thioglycosides was evaluated next. The disarmed **1p** was hardly activated under conditions established afore. Upon replacement of the phenyl moiety of **1p** to an ethyl group, **1q** was successfully activated but only orthoester **4t'** was isolated in 59% yield with the customary TfOH·DTBMP (5.0 mol%). Given that disarmed sugars are non-acid sensitive and resistant to strong acidic conditions, 20 mol% of TfOH instead of TfOH·DTBMP was introduced into the reaction mixture. To our delights, this

Table 3. Reaction scope for 2-Acyl Thiolglycosides.[a,b]



[a] Yield of isolated product. [b] $Rh_2(oct)_4$ (0.5 mol%). [c] Reaction mixture of donor **1**, acceptor **2**, diazo compound **3** and Rh(II), in CH_2Cl_2 was stirred at 0 °C, then TfOH (20 mol%) was added while the yellow color of **3a** disappeared. [d] Reaction mixture of donor **1**, diazo compound **3a** and Rh(II) in CH_2Cl_2 was stirred at 0 °C, then acceptor **2** and TfOH (20 mol%) was added while the yellow color disappeared. [e] $Rh_2(oct)_4$ (1.0 mol%). [f] **1** (2.0 equiv), **3a** (4.0 equiv), Rh(II) (10.0 mol%). [g] *S*-Methyl donor **1x** was used. [h] *ortho*-Hexynylbenzoic acid **2t** (1.3 equiv) and **3a** (1.3 equiv) was used. [i] $Rh_2(oct)_4$ (4.0 mol%).

favored the desired reaction course and provided **4t** and co-product **11** in 96% and 93% isolated yields respectively. Hereupon, diversified secondary alcohols or sterically hindered acceptors were efficiently glycosylated with disarmed thioglycosides (details see table S2) in generally good yields (**4t-z**). In these reactions, the interference of the less reactive hydroxyl groups with the formation of the sulfonium ylides was virtually absent which allowed either pre-mixing of acceptors with donors at the beginning or addition of acceptors just before the acidic treatment. For acceptors bearing primary hydroxy group (**2b**, **2u**, **2x**, **2y**, **2za** and **2zb**), mercaptan (**2z**), sulfide (**2za**, **2zb**), glycan (**2y**), olefin (**2v**, **2x**), alkyne and acid functionalities (**2w**), the addition of acceptors after complete formation of sulfonium ylides became mandatory. Adopting the "stepwise" procedure, compounds **4za-zi** were prepared in good to excellent yields. Prominently, disarmed *ortho*-alkynylbenzoate (ABz) donor **4ze**, pentenyl donor **4zf** trisaccharide thiodonor **4zh**[22] and latent OPTB glycoside[23] **4zi** were directly prepared from thioglycoside. Since 2008, gold-catalyzed glycosylation with Yu's alkynyl donors became integral in the synthesis of many complex natural products.[24] Usually, the ABz donors are prepared as a mixture of α/β anomers in two steps, followed by removal of temporary anomeric protecting groups and subsequent coupling with *ortho*-alkynylbenzoic acid. Nonetheless, Yu and co-workers have demonstrated the

α-ABz donors could provide much better β-selectivities in mannosylations.[25] In this work, we accomplished the assembly of ABz glycoside **4ze** (α/β 3.3:1) and **4s** (a single α-isomer, table 1) directly from the corresponding thioglycosides **1q** and **1m** in good yields with an α-favored selectivity.

In summary, for the first time a generally applicable thioglycosides activation was realized *via* an unprecedented sequential rhodium- and Brønsted acid-catalyzed glycosylation. The rhodium-catalyzed glycosyl ylide formation and successive protonation paved a brand-new route to activate conventional thioglycosides. Under this novel strategy, the ylide served as the precursor or the reservoir of sulfonium ion. The low catalyst loading and mild reaction conditions were attractive features of this method. The applicability of protocol was substantiated by well tolerance of various acid sensitive and sterically-demanding substrates. A number of useful glycosyl donors were also facilely prepared from simple thioglycosides. We foresee current protocol to be soon adopted in the synthetic toolbox of chemists alike in the studies of carbohydrate chemistry and natural products synthesis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, NMR spectroscopic and analytical data for all compounds (PDF)
Crystallographic data for 8 (CIF)

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

Financial support from National Natural Science Foundation of China (201877043, 21702068, 21672077, 21761132014), Wuhan Creative Talent Development Fund, Fundamental Research Funds for the Central Universities (2017KFYXJJ150) are greatly appreciated. We would like to give our truthful thanks to Prof. Biao Yu (Shanghai Institute of Organic Chemistry) for providing 2'-iodo-2,6-dimethyl-[1,1'-biphenyl]-4-ol. We thank Mr. Xiaodi Yang (Shanghai University of Traditional Chinese Medicine) for X-ray testing and analysis. We also thank Analytical and Testing Center of HUST for NMR tests. This paper is dedicated to Prof. Claudine Augé (Universtié Paris-Sud).

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(13) (a)The ylide was unstable to chromatography, for NMR studies of the crude reaction mixtures, see the Supporting Information. (b) the reaction with 4-diazoisochroman-3-one **3b** also succeeded to activate **1a**, while dimethyl diazomalonate **3c** failed to activate **1a** under similar conditions.

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