Reversing reactivity: stereoselective desulfurative β-*O*-glycosylation of anomeric thiosugars with carboxylic acids under copper or cobalt catalysis

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ABSTRACT: We have discovered a new mode of reactivity of 1-thiosugars in the presence of Cu(II) or Co(II) for a stereoselective *O*-glycosylation reaction. The process involves the use of a catalytic amount of $Cu(acac)_2$ or $Co(acac)_2$ and Ag_2CO_3 as an oxidant in α,α,α-trifluorotoluene (TFT). Moreover, this protocol turned out to have a broad scope, allowing to prepare a wide range of complex substituted *O*-glycoside esters in good to excellent yields with an exclusive β-selectivity. The late-stage modification of pharmaceuticals by this method was also demonstrated.

INTRODUCTION

Sugars are a very important family of biomolecules that play a pivotal role in living organisms. Their inherent structural complexity enables them to interact with myriad of biological receptors.[1] To understand the role of saccharides in biological systems, chemists need to prepare well-defined chemical glycosides. β-Acyl *O*-glycosides (AGs) is one of the common motif found in natural products or bioactive compounds such as phyllanthoside,[2] neurosporaxanthin,[3] cephasinenoside,[4] macrophylloside D[5], celecoxib acyl-β-D-glucuronide metabolite[6] (Figure 1) and the immunoadjuvant QS-21A[7]. Numerous members of the ellagitannin family also have a 1-acylglycoside unit, such as sanguiin H-4 and sanguiin H-5.[8] The use of AGs as surfactants also appeared to be an interesting strategy to increase the lignocellulosic biomass value.[9] Recently mannosamine lipid esters (Ac_4ManNAz lipid ester, Figure 1) were used as chemical tools for metabolic cell labeling strategy.[10] Moreover, β-1-acyl glucuronides are the major metabolites of most carboxylic acid containing drugs.[11] Several β-1-acyl glucosides were also identified as metabolites of bile acids and important bio-markers for patients with hepatic diseases.[12] More importantly, glycoacylation has been pointed out as an attractive pathway to target cancer cells exploiting the Warburg effect.[13] This antitumor strategy that gained much more attention in the last decades, is based on the use of several glucose-based conjugates to more specifically deliver the attached drug to cancer cells. There have been many examples of glucose-conjugated drugs in preclinical or clinical evaluation (paclitaxel,[14] adriamycin,[15] DNA alkylating agent including chlorambucil,[16] platinum[17] and cyclophosphamide[18]).

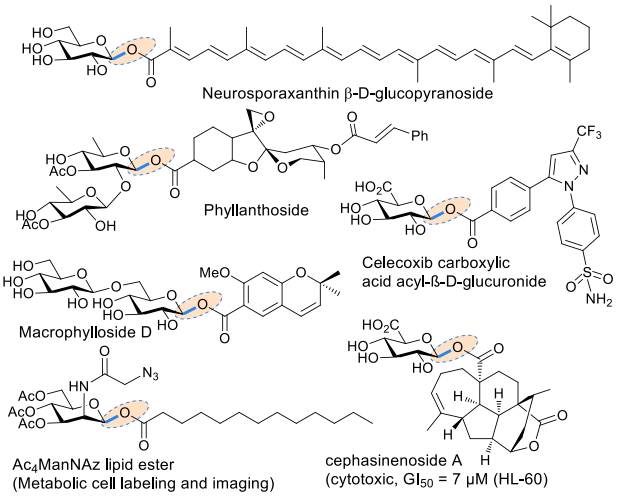


Figure 1. Examples of natural products and bioactive compounds bearing a 1-acyl sugar moiety.

Despite the high added-value of these substrates, a general catalytic-stereoselective acylation method of sugars has not been yet developed. Thus, it has become critical to stereoselectively prepare β-1-acyl glycosides. In vertebrates, acyl *O*-glucuronide are synthesized by the conjugation of carboxylic acids with uridine diphosphate glucuronic acid (UDPGA) mediated by various glucuronosyl transferases (UDPGTs) (Figure 2).[19] From a synthetic point-of-view, usually, these derivatives were prepared by treating benzoic acid derivatives with sugar lactols through an S_N2 Mitsunobu reaction[20] (Figure 2, path A). However a mixture of anomers were obtained in several cases. Some specific acyl glucuronides can be

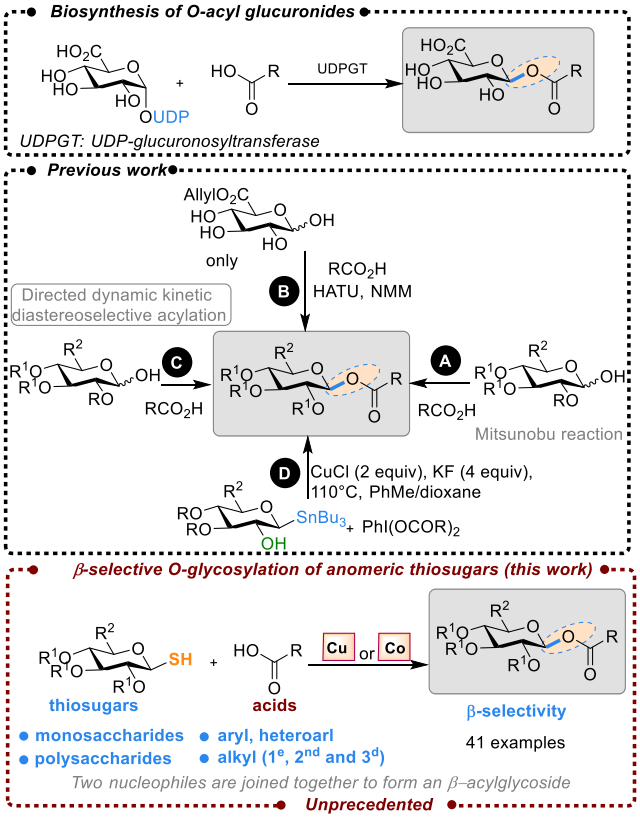
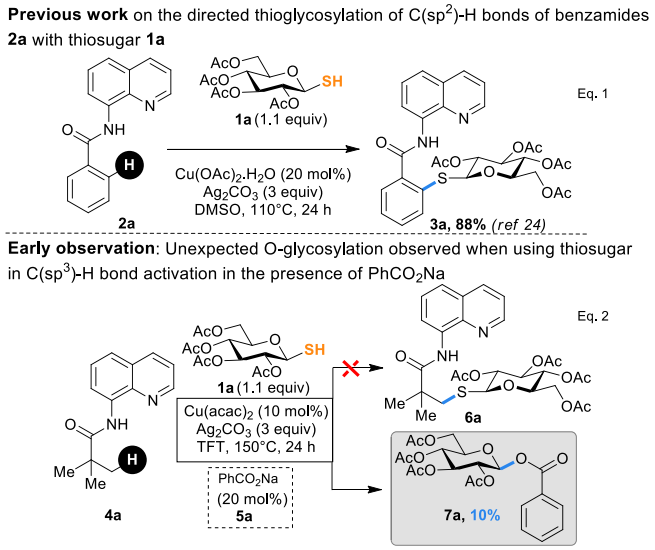


Figure 2. Strategies for *O*-glycosylation to access to acyl-O-glycosides.

prepared through β-acylation of allyl glucuronate with carboxylic acids catalyzed by HATU[21] and then mild deprotection after treatment with $Pd(PPh_3)_4$ in the presence of morpholine (Figure 2, Path B). However, the use of glycosyl lactols in all these strategies remains problematic because of the difficulty to prepare well-defined α– or β–anomers. Another way to prepare stereoselectively acyl-O-glycosides is the use of chiral catalyst in a directed dynamic kinetic stereoselective acylation of anomeric hydroxyl groups[22] (Figure 2, path C). Recently, Walczak group reported an elegant method to acylate glycosyl stannane donors[23] (Path D). This copper-mediated *O*-glycosylation reaction involved the coupling of anomeric stannane nucleophiles with carboxylic acids resulting in exclusive anomeric selectivities. These reactions required a C2-hydroxyl coordinating group on the sugar moiety. Despite these recent advances and the high added-value of these substrates, the development of a general catalytic-stereoselective acylation method of sugars has not been yet developed and remains highly desirable. In this work we showed for the first time, that thiosugars and acids can be joined together through a desulfurative β-glycosylation process to afford stereoselectively a variety of acyl- β-glycosides.

During the course of investigating the amenability of various thiosugars toward C–H activation processes[24] (Scheme 1, eq.1), we subjected *tetra-O*-acetylated-1-thio-β-D-glucopyranose **1a** and aliphatic amide **4a** to the Cu-catalyzed functionalization of unactivated Csp^3–H bonds under previously reported conditions.[25] Rather than obtaining the expected Csp^3–S bond formation (compound **6a**), an *O*-glycosylation process was serendipitously discovered leading to compound **7a** in 10% yield as a pure β-isomer (Scheme 1).

Scheme 1: Unexpected *O*-glycosylation observed when using β-thioglucose **1a** with benzoic acid **5a**.

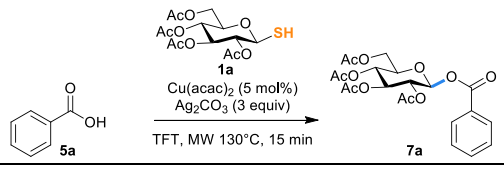


We hypothesized that formation of **7a** resulted from reaction of sodium benzoate, which was used in a catalytic amount (20 mol %), with the β-thioglucose **1a**. We therefore decided to explore the viability of this unusual outcome as a general method for the β-stereoselective *O*-glycosylation of thiosugars. Herein, we report the optimization of this reaction which appears as a new method for the β-stereoselective *O*-glycosylation of thiosugars.

RESULTS AND DISCUSSION

When conducting the reaction of **1a** with 1 equivalent of benzoic acid **5a** in the absence of the amide **4a**, *O*-glycosylation was still observed and the β-*O*-acyl glucoside **7a** was isolated in 29% yield (table 1, entry 2). The exact structure of **7a**, including its 1,2-diaxial geometry, was determined by 1D and 2D NMR spectroscopy and unambiguously confirmed by crystal structure analysis (Table 2). Then, an optimization study was carried out using β-thioglucose **1a** and benzoic acid **5a** as substrates (details can be found in Table S1 in the Supporting Information). To understand the observed *O*-glycosylation reaction and to verify that the outcome was derived from a catalytic process, several control studies were performed (Table 1). These studies led us to identify the best reaction conditions as the use of 5 mol % $Cu(acac)_2$ and 3 equivalents of Ag_2CO_3 in trifluorotoluene (TFT, 0.1 M) at 130 °C under microwave irradiation for 15 minutes. Under these conditions, the desired phenyl acylglycoside **7a**, was isolated in 79% yield (Table 1, entry 1). Running the reaction in oil bath at 130 °C for 1h instead of microwave irradiation led to the desired product in only 45% yield (entry 3). Moreover, performing the reaction in oil bath at 150°C for 1h furnished **7a** in 74% yield (entry 4). Interestingly, we observed during the optimization that the copper catalyst $Cu(acac)_2$ can be replaced by $Co(acac)_2$ without affecting the yield (77% yield, entry 8). We also confirmed that Ag_2CO_3 is required to accomplish *O*-glycosylation; without Ag_2CO_3 or performing the reaction with other bases (K_2CO_3 or Cs_2CO_3) instead of silver carbonate, no reaction occurred (entries 6 and 11). Interestingly, control experiment showed also that this reaction could be performed without catalyst, but **7a** was isolated in a lower yield (52%, entry 7). In addition, reaction with Cu(I) was less efficient and gave product **7a** in a yield similar to the reaction

Table 1 Reaction conditions optimization for the *O*-glycosylation of *tetra*-*O*-acetylated-1-thio-β-D-glucopyranose **1a** with phenylbenzoïc acid **5a**.[a]



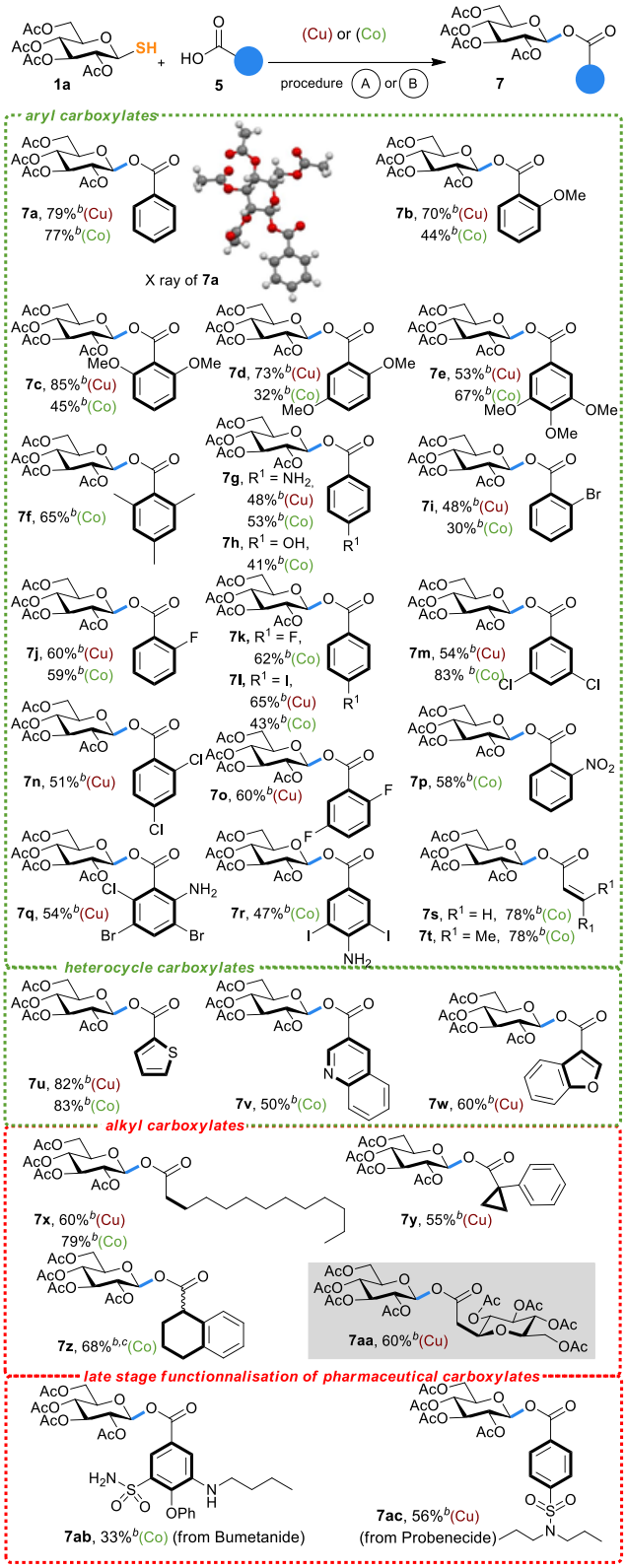
Entry	Deviation from the standard conditions	Yield (%)[b]
1	none	79
2	12 h at 150 °C (oil bath)	29
3	1 h at 130 °C (oil bath)	45
4	1 h at 150 °C (oil bath)	74
5	No metal, no silver base	0
6	No silver base	0
7	No catalyst	52
8	$Co(acac)_2$ instead of $Cu(acac)_2$	77[c]
9	CuI instead of $Cu(acac)_2$	46
10	$AlCl_3$ Lewis acid instead of $Cu(acac)_2$	59
11	K_2CO_3 or Cs_2CO_3 instead of Ag_2CO_3	0
12	Toluene instead of TFT	67

TFT = trifluorotoluene [a] Conditions: **1a** (1.5 equiv), **5a** (1 equiv), metal source (5 mol%), base (3 equiv), TFT [0.1 M] were heated in a sealed tube under argon atmosphere. [b] Yield of isolated **7a**. [c] 1h reaction time under thermal heating (at 150 °C).

without catalyst (46%, entry 9). We also checked whether the copper salt could act as a Lewis acid by performing the reaction in the presence of a Lewis acid $AlCl_3$ (entry 10), however under these conditions, only 59% yield of the desired product were obtained, suggesting that this pathway plays only a minor role.

Prompted by these exciting results, we subsequently investigated the substrate scope for the catalytic *O*-glycosylation of *tetra*-*O*-acetylated-1-thio-*β*-D-glucopyranose **1a** with various commercial carboxylic acids **5a-z, 5aa-ac** using either $Cu(acac)_2$ or $Co(acac)_2$. In most examples, yields arising from Cu- and Co-catalysis are provided, otherwise, in other cases, only one catalyst was used. Overall, the method works well and tolerates a large variety of acid partners (Table 2), and comparable yields were obtained with both copper and cobalt catalysts (Table 2). Benzoïc acids having electron-donating groups (**5b-h)** led to the formation of corresponding glycosyl esters **7b-h** in good yields, up to 85%. Delightfully, this protocol was efficient starting from benzoïc acids bearing free hydroxyl and amino groups on the aromatic ring (compounds **7g, 7h**, **7q** and **7r**). Likewise, 1-thio-β-D-glucose **1a** was readily coupled with carboxylic acids derivatives bearing electron-withdrawing group (*e.g.*, $–NO_2$, –F, –Cl, –Br, –I) to give the *O*-glycosylated products **7i-r**, which may be useful for further regioselective cross-coupling reaction concerning the halogenated substrates (Table 2). Vinyl carboxylic acids **5s,t** are also well tolerated in this coupling leading to the acrylic *O*-acyl glycosides **7s,t** in 78% yield. Importantly, heterocyclic acids such as thiophene, quinoleine and benzofuran reacted well with **1a**, leading to products **7u-w** in 83%, 50% and 60% yields, respectively. Finally, the synthetic potential of this protocol was well illustrated by its application on substrates containing alkyl groups. Thus, the tridecanoic acid **5x**, cyclopropyl carboxylic acid **5y** as well as tetrahydronaphthalene-1-

Table 2. Scope of commercial carboxylic acids **5a-z** in the *O*-glycosylation of β-thioglucose **1a**



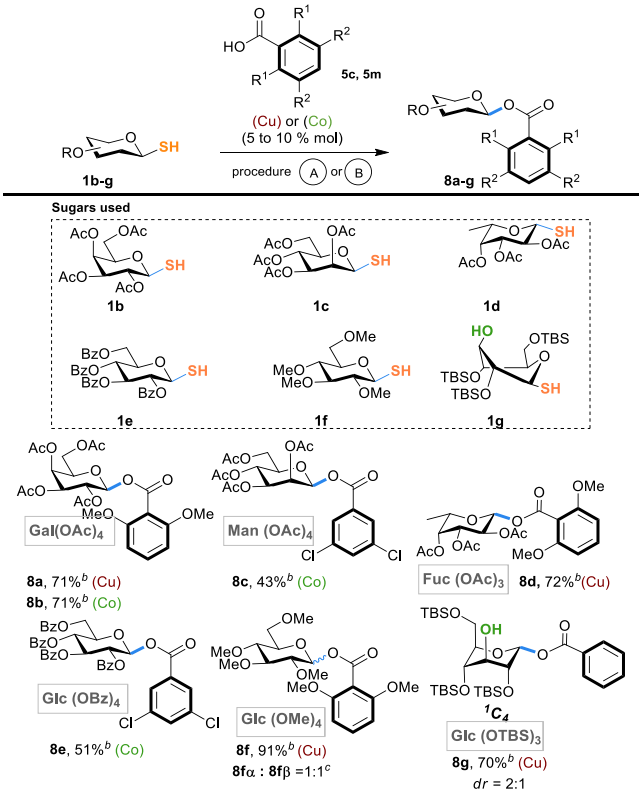
[a] Reactions conditions: procedure (A) with Cu : carboxylic acids **5** (1 equiv), *O*-acetylated 1-thio-β-D-glucose **1a** (1.5 equiv), $Cu(acac)_2$ (5 mol %), Ag_2CO_3 (3 equiv), TFT [0.1 M] in a sealed tube under argon at 130 °C under microwave irradiation for 15 min. Procedure (B) with Co: carboxylic acids **5** (1 equiv), *O*-acetylated 1-thio-β-D-glucose **1a** (1.5 equiv), $Co(acac)_2$ (10 mol %), Ag_2CO_3 (3 equiv), TFT [0.1 M] in a sealed tube under argon at 150 °C for 1 hour under thermal conditions. [b] yield for the isolated product. [c] diastereomeric mixture 1:1 calculated by ^1H NMR.

carboxylic **5z** were good partners leading to glycosyl esters **7x-z** in good to excellent yields (55-79%). Interestingly, the disaccharide ester **7aa** was obtained through this approach in 60% yield when the sugar carboxylic acid **5aa** was used.

After having demonstrated an excellent reactivity with simple substrates, we then examined if the *O*-glycosylation reaction could be extended to drug-like small molecules through a late stage modification process. In this context, Bumetanide (Bumex®), a marked-loop diuretic used to treat heart failure, and probenecide (benemide®), an uricosuric agent that inhibits the renal excretion, were successfully converted in one step into the corresponding β-acylglucosyl analogues **7ab** and **7ac** in synthetically useful yields (33 % and 56% yields, respectively). These new acyl glycosides may be considered as useful tool metabolites for studying their potential role in drug toxicity.

To further demonstrate the generality of this reaction, we applied the optimized conditions to carboxylic acid, **5c** and **5m** and structurally diverse mono-thiosugars **1b-g** (Table 3). This *O*-glycosylation appeared to be not limited to 1-thio-β-D-glucose: thiosugars derived from β-D-galactopyranose (**1b**), β-D-mannopyranose (**1c**) and β-D-fucose (**1d**) were also coupled with **5c** or **5m** to provide the corresponding β-*O*-glycosylated esters **8a-d** in good yields from either Cu- or Co-catalysts. In addition, this methodology tolerates other protecting groups such OBz in the disarmed donor (**1e**) and OMe ether (**1f**).

Table 3. Scope of 1 thio-β-glycosyls **1b-g** [a]



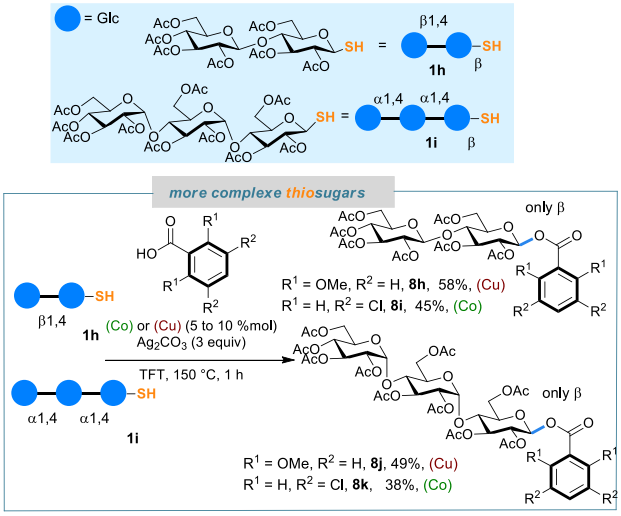
[a] Conditions: procedure (A) with Cu: carboxylic acids **5c** or **5k** (1 equiv), thiosugars **1b-g** (1.5 equiv), $Cu(acac)_2$ (5 mol %), Ag_2CO_3 (3 equiv), TFT [0.1 M] in a sealed tube under argon at 130 °C under microwave irradiation for 15 min. Procedure (B) with Co: carboxylic acids **5** (1 equiv), *O*-acetylated 1-thio-β-D-glucose **1a** (1.5 equiv), $Co(acac)_2$ (10 mol %), Ag_2CO_3 (3 equiv), TFT [0.1 M] in a sealed tube under argon at 150 °C for 1 hour. [b] yields of isolated product. [c] diastereomeric mixture 1:1 calculated by ^1H NMR.

Importantly, in the case of thioGlc(OMe)$_4$ (**1f**), a 1:1 mixture of both α/β anomers was obtained indicating that the anomeric stereochemistry is controlled by the neighboring participant group at the C2 position.

Glycosyl donors protected with tert-butyldimethylsilyl (TBS) group were well known to have superior reactivity and selectivity than other sugar donors.[26] This enhanced reactivity/selectivity was correlated to the stereoelectronic effects associated with the conformation change induced by the silyl groups. Inspired by this above literature, we were wondering whether the selectivity in our glycosylation reaction will be impacted by this conformation change. To this end, we prepared the conformationally super armed OTBS-protected thiosugar (**1g**) and we carried out the Cu-catalyzed glycosylation reaction in the presence of phenylbenzoic acid. Interestingly, under our standard conditions the desired $^1C_4$ glycoside **8g** was obtained in good 70% yield and 2:1 β-anomeric selectivity although no participating group was installed at C-2 position. This result evidenced the effect of conformation change on the glycosylation selectivity.

Having demonstrated the efficacy of our method with various thiosugars, we next turned our attention to the validation of the method with respect to more complex and biologically relevant saccharides (Scheme 2). We were pleased to find that di- and trisaccharide derivatives cellobiose **1h** and maltotriose **1i**, readily undergo *O*-glycosylation in this transformation. The desired *O*-acyl glycosides **8h,i** were isolated in 58% and 45% yields, respectively. Moreover, the *O*-acyl trisaccharide **8j,k** which are commonly used in bacterial imaging[27] were isolated in synthetically useful yields.

Scheme 2. Scope of complex 1 thio-β-glycosyls **1h,i**[a]



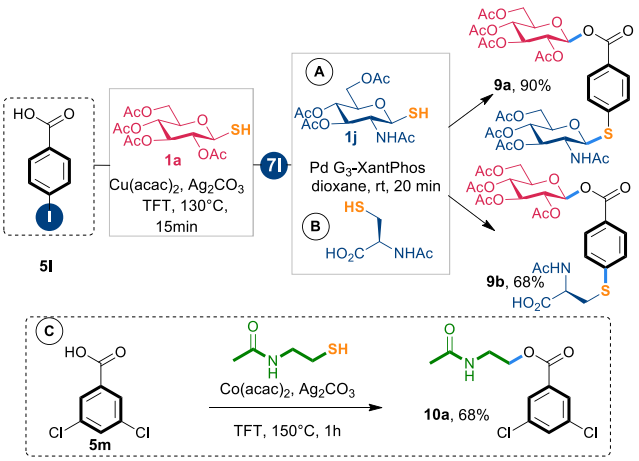
[a] Conditions: procedure (A) with Cu: carboxylic acids **5c** or **5m** (1 equiv), thiosugars **1h,i** (1.5 equiv), $Cu(acac)_2$ (5 mol %), Ag_2CO_3 (3 equiv), TFT [0.1 M] in a sealed tube under argon at 130 °C under microwave irradiation for 15 min. Procedure (B) with Co: carboxylic acids **5** (1 equiv), *O*-acetylated 1-thio-β-D-glucose **1a** (1.5 equiv), $Co(acac)_2$ (10 mol %), Ag_2CO_3 (3 equiv), TFT [0.1 M] in a sealed tube under argon at 150 °C for 1 hour. [b] yields of isolated product.

To broaden the synthetic applications of this method, we carried out studies on whether the iodinated substrate **7l** could be used as a suitable platform for introducing molecular diversity *via* cross coupling reactions. Thus, the glycosyl ester **9a** bearing both C–O and C–S β-glycosidic bonds was easily prepared

through this *O*-glycosylation approach (Scheme 3A) followed by the functionalization of the C–I bond by the coupling with the thioGluNAc **1j** under our previously reported Pd-catalyzed methodology.[28] We have also shown that this process was effective replacing thiosugar by a commercial NHAc-Cys, delivering the glycoamino acid **9b** in 68% yield (Scheme 3B).

With these encouraging results in hand, we next turned our attention to examine the reactivity of other thiols such as alkylthiols instead of thiosugars. Pleasantly, reaction of the commercially available *N*-acetylcysteamine with benzoic acid **5m** provided the ester product **10a** in a 68 % yield (Scheme 3C). The study of reactivity of a large variety of alkylthiols in this reaction is currently under progress in our group.

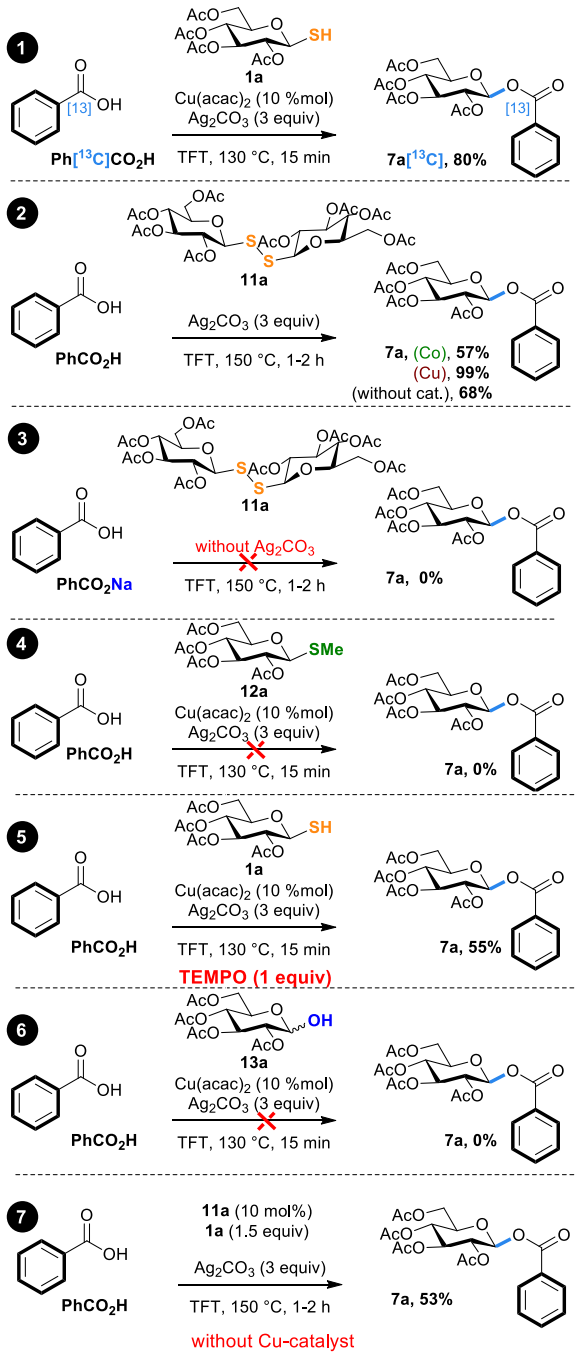
Scheme 3. Application of the methodology to molecular diversity



[a] Conditions: path A: *O*-acetylated 1-thio-β-D-glucose **1a** (1.5 equiv), iodophenylbenzoic acid **5n** (1 equiv), $Cu(acac)_2$ (10 mol %), Ag_2CO_3 (3 equiv), TFT [0.1 M] in a sealed tube under argon at 150 °C for 15 min under MW irradiation. path B: **7j** (1 equiv), **1j** or NHAcCys (1.2 equiv), PdG3 XantPhos (5 mol %), Et_3N (3 equiv), Dioxane [0.1 M] at rt for 20 min. path C: a commercially available *N*-acetylcysteamine (1.5 equiv), benzoic acid **5m** (1 equiv), $Co(acac)_2$ (10 mol %), Ag_2CO_3 (3 equiv), TFT [0.1 M] in a sealed tube under argon at 150 °C for 1 hour.

To gain further insight into the origin of this unconventional thiol- to-acid two nucleophiles coupling, we performed the C(13) isotope incorporation experiment conditions by using a ^{13}C–α labeled benzoic acid (Scheme 4, eq 1). The incorporation of ^{13}C in the phenylglycosyl ester **7a** proves unambiguously that the ester-group comes from the acid function and not from a decarboxylative/carboxylation sequence with CO_2 arising from the thermal decomposition of silver carbonate.[29] Because the formation of the disulfide **11a** (Scheme 4, eq.2) was observed during all the reactions (isolated and characterized), we were wondering if **11a** must be regarded as a by-product which may hamper the glycosylation process, or in contrary may be involved in the reaction pathway. In this context, we performed a series of control experiments with the disulfide **11a** (Scheme 4, eq.2). Thus, heating **11a** with benzoic acid **2a** at 150 °C for 1 h in the presence of silver carbonate furnished the desired β-*O*-glycoside **7a** in a 57 % yield when the Co-catalyst was used, and 99 % yield with $Cu(acac)_2$ as a catalyst (Scheme 4, eq. 2). Interestingly, omitting to add the catalyst led also to the same product **7a** in 68 % yield. This result clearly indicates that disulfide **11a** may be involved in the catalytic cycle. In addition, performing the reaction of **11a** with sodium benzoate in TFT at 150 °C did not furnish **7a** and only the starting material was recovered unchanged (Scheme 4, eq.3). This result indicates that a pathway including a simple nucleophilic substitution is discarded. In another way, the

Scheme 4. Mechanistic investigations.



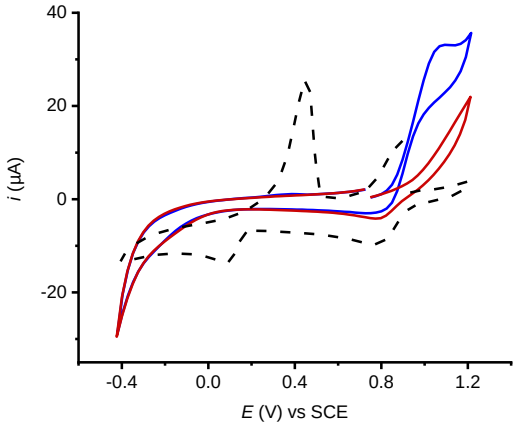
[a] Conditions: *O*-acetylated 1-thio-β-D-glucose **1a** or its dimer **11a** or S-methylated **12a** or **13a** (1.5 equiv), benzoic acid **2a** or sodium benzoate (1 equiv), $Cu(acac)_2$ (5 mol %) or $Co(acac)_2$ (10 mol %), Ag_2CO_3 (3 equiv), solvent [0.1 M] in a sealed tube under argon.

glycosylation reaction was completely inhibited when the thiol function of the sugar was protected (S-methyl glucose **12a)** (Scheme 4, eq. 4). It was also found that addition of the radical

inhibitor TEMPO, had no significant effect on the reaction, suggesting that a radical species may not be involved in the catalytic cycle (Scheme 4, eq. 5). Finally, the importance of the sulfhydryl (−SH) group was further demonstrated by the result with glycosyl lactol **13a** as a sugar donor (Scheme 4, eq. 6). Under the standard conditions, no desired product was observed by using **13a**.

The lack of any precedent for oxidative addition of thiols to Cu-catalyst makes a traditional oxidative addition-reductive elimination pathway for this new reaction unlikely. To get a closer insight into the reaction mechanism, cyclic voltammetry (CV) was performed (see SI). $Cu(OTf)_2$ was selected as Cu(II) sources and as expected no characteristic oxidation peak could be detected towards oxidation potentials as shown with the dashed line CV (Figure 3). Just after addition of 2 equiv. of thiosugar **1a**, the zero current potential of the solution was shifted by 180 mV towards negative potentials and an oxidation peak at + 1V *vs* SCE clearly evidenced the formation of Cu(I) as thiol is not electroactive in this range of potentials (see SI, Figure S1). A similar behavior was observed starting with $Cu(acac)_2$ but the CV of the metal salt alone is less informative (see SI, Figure S1). The formation of Cu(I) under these conditions is in agreement with previous reports in the literature.[30] After addition of 1 equiv of AgOAc, this oxidation peak completely disappears and a black solid precipitated, which was identified to be Ag_2S.[31] No further changes could be detected in the presence of a larger excess of **1a** and AgOAc even in the presence of sodium benzoate (see SI, Figure S2). One can be noted that the disulfide is not electroactive in the range of potentials scanned for this study nor in the presence of a stoichiometric amount of Cu(II) (see SI, Figure S3).

Figure 3. Cyclic voltammetry (CV) experiments

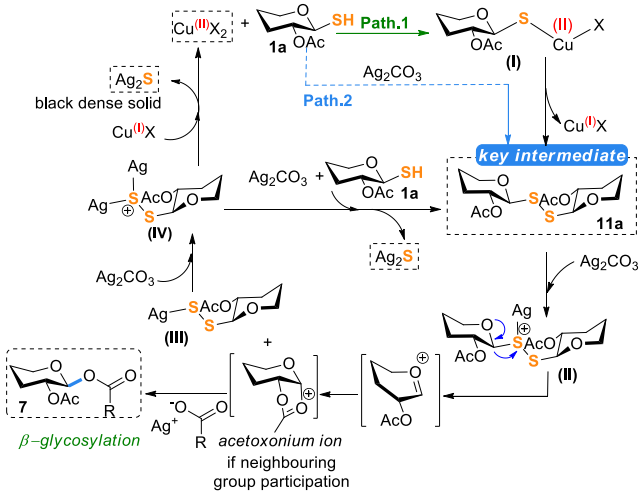


CV performed in $MeNO_2$ towards oxidation potentials containing *n*-Bu_4NBF_4 (0.1 M) at a steady GC electrode (d = 3 mm), at the scan rate of 0.5 $V.s^{-1}$, at 20 °C. Black dashed line: $Cu(OTf)_2$ (2 mM), blue line $Cu(OTf)_2$ (2 mM) with 2 equiv of thiol **1a**, red line: $Cu(OTf)_2$ (2 mM) with 2 equiv. of thiol **1a** and 1 equiv of AgOAc.

Based on all these experiments, we propose the following mechanistic path (Figure 4). The first step involves the oxidation of thiosugar **1a** by the Cu(II) catalyst to give the corresponding disulfide **11a** (Path.1) which has a great affinity for silver. We propose that the strong complexation with silver in complex (**II**) weakened the carbon–sulfur anomeric bond and generated a good leaving group allowing the formation of the acetoxonium ion. The latter is trapped by the carboxylate to give the desired product **7**. Along this process, we propose that a second silver cation was involved to form the sulfonium (**IV**) which can be reduced by Cu(I) to regenerate Cu(II) and one thiol with formation of silver sulfide (Ag_2S) which precipitated out from the solution (see supporting information). The intermediate (**IV**) might regenerate **11a** by reaction with thiosugar **1a** without the need of Cu-catalyst. This step led also to the formation of the silver sulfide (Ag_2S).

Regarding the result obtained in the absence of the catalyst (Table 1, entry 7), we proposed a concomitant pathway (Path.2, Figure 3) mediated by Ag_2CO_3. The disulfide **11a** might be formed in the presence of silver carbonate as an oxidant. Following a strong coordination of a second silver cation (Ag^+), the complex (**II**) led to the formation of an acetoxonium ion intermediate (if having a neighboring participating group at position 2). In the presence of carboxylate nucleophiles, the β-glycoside ester (**7**) could be formed producing the complex (**III**). This later evolves to (**IV**) through a second coordination with silver ion, and finally might react with **1a** to regenerate the disulfide key intermediate **11a** and the formation of the Ag_2S. This hypothesis is in agreement with the result highlighted in Scheme 4, Eq.3; when the reaction of **2a** was performed with the disulfide **11a** in the presence of only Ag_2CO_3 (yield of **7a** = 68%), thus suggesting that this path may be involved in the mechanism. However, when performed with a catalytic amount (10 mol%) of the disulfide **11a** and 1.5 equiv. of **1a** in the presence of **2a** and Ag_2CO_3, without adding the Cu-catalyst (Scheme 4, eq. 7), the reaction proceeded with only 53% yield of **7a** (see supporting information). The improvement observed in the presence of copper salt led us to propose an alternative path for the evolution of **IV**. The latter can react with Cu(I) to release Ag_2S regenerating the Cu(II) catalyst.

Figure 4. Proposed mechanism



CONCLUSIONS

In conclusion, we reported an unconventional thiol- to-acid two nucleophiles coupling method for the diastereoselective synthesis of β-O-glycosylated esters through a $Cu^{(II)}$- or $Co^{(II)}$-catalyzed activation of glycosyl thiols. This approach tolerates a wide range of functional groups, offers a unique strategy to access β-*O*-glycosylated esters, and streamlines synthesis of pharmaceutically important compounds. Furthermore, efforts to expand the scope of this transformation are undergoing.

ASSOCIATED CONTENT

Supporting Information

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

Full optimization table, NMR spectra of all synthesized compounds and HPLC chromatograms.

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Author Contributions

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ABBREVIATIONS

REFERENCES

(1) (a) Varki, A. *Glycobiology*, **2017**, 27, 3–49 (b) Gabius, H.-J. (**2009**) The Sugar Code: Fundamentals of Glycosciences, Wiley-Blackwell, Weinheim, Germany. (c) Varki, A.; Cummings, R.; Esko, J.; Freeze, H.; Hart, G.; Marth, J. (**1999**) Essentials of Glycobiology, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.

(2) (a) Smith, A. B. III; Rivero, R. A. Total synthesis of (+)-phyllanthoside, *J. Am. Chem. Soc.*, **1987**, 109, 1272-1274. (b) Pettit, G.; Cragg, G. M.; Gust, D.; Brown, P. The isolation and structure of phyllanthostatins 2 and 3, *Canadian Journal of Chemistry*, **1982**, 60, 544–546 .

(3) Marwan, A. G.; Nagel, C.W. Identification of the Hydroxycinnamtic Acid Derivatives in Cranberries *J. Food Sci.,* **1986**, *51*, 1069.

(4) Zhao, C.-X.; Li, B. Q.; Shao, Z. X.; Li, D-H.; Jing, Y. Q.; Li, Z. L. Hu, H. M. Cephasinenoside A, a new cephalotane diterpenoid glucoside from *Cephalotaxus sinensis. Tetrahedron Lett*. **2019**, https://doi.org/10.1016/j.tetlet.2019.151154

(5) (a) Xu, M.; Zhang, M.; Zhang, Y.-J.; Yang, C.-R. New Acylated Secoiridoid Glucosides from Gentiana straminea (Gentianaceae) *Helvetica Chimica Acta* **2009**, *92*, 321 - 327 (b) Rho, T.; Jung, M.; Lee, M.-W.; Chin, Y.-W.; Yoon, K.-D. Efficient methods for isolating five phytochemicals from Gentiana macrophylla using high-performance countercurrent chromatography. *J Sep Sci.* **2016**, *39*, 4723–4731.

(6) Ma, Y.; Gao, S.; Hu, M. Quantitation of celecoxib and four of its metabolites in rat blood by UPLC-MS/MS clarifies their blood distribution patterns and provides more accurate pharmacokinetics profiles *J Chromatogr B,* **2015,** *1001*, 202–211.

(7) Kim, Y.-J.; Wang, P. ; Navarro-Villalobos, M. ; Rohde, B. D. ; Mark, J.; Gin, D. Y. Synthetic Studies of Complex Immunostimulants from Quillaja saponaria: Synthesis of the Potent Clinical Immunoadju-vant QS-21Aapi, *J. Am. Chem. Soc.* **2006**, 11906 –11915.

(8) Su, X.; Surry, D. S.; Spandl, R. J.; Spring, D. R. Total Synthesis of Sanguiin H-5, *Org. Lett.*, **2008**, *10*, 2593–2596

(9) Smith III, A. B. ; Rivero, R. A. ; Hale, K. J.; Vaccaro, H. A. Phyllanthoside-phyllanthostatin synthetic studies. 8. Total synthesis of (+)-phyllanthoside. Development of the Mitsunobu glycosyl ester protocol *J. Am. Chem. Soc*., **1991**, *113*, 2092–2112

(10) Shen, L.; Cai, K.; Yu, J.; Cheng, J. Novel Liposomal Azido Mannosamine Lipids on Metabolic Cell Labeling and Imaging via Cu-Free Click Chemistry, *Bioconjugate Chem.* **2019**, doi.org/10.1021/acs.bioconjchem.9b00509

(11) Stachulski, A. V.; Harding, J. R.; Lindon, J. C.; Maggs, J. L.; Park, B. K.; Wilson, I. D. Acyl Glucuronides: Biological Activity, Chemical Reactivity, and Chemical Synthesis *J. Med. Chem.* **2006**, *49*, 6931–6945

(12) Wietholtz, H.; Marschall, H. U.; Reuschenbach, R.; Matern, H.; Matern, S. Urinary excretion of bile acid glucosides and glucuronides in extrahepatic cholestasis *Hepatology* **1991**, *13*, 656–662.

(13) Calvaresi, E. C.; Hergenrother, P. J. Glucose conjugation for the specific targeting and treatment of cancer *Chem Sci.* **2013**, *4*, 2319–2333

(14) (a) Liu, D.-Z.; Sinchaikul, S.; Reddy, P.V.G.; Chang, M.-Y.; Chen, S.-T. Synthesis of 2′-paclitaxel methyl 2-glucopyranosyl succinate for specific targeted delivery to cancer cells *Bioorg Med Chem Lett*, **2007**, *17*, 617–620 (b) Lin, Y.-S.; Tungpradit, R.; Sinchaikul, S.; An, F.-M.; Liu, D.-Z.; Phutrakul, S.; Chen, S.-T. Targeting the delivery of glycan-based paclitaxel prodrugs to cancer cells via glucose transporters *J. Med. Chem.*, **2008**, 51, 7428–7441 (c) Ma, J.; Liu, H.; Xi, Z.; Hou, J., Li, Y.; Niu, J.; Liu, T.; Bi, S.; Wang, X.; Wang, C.; Wang, J.; Xie, S.; Wang, P.G. Protected and De-protected Platinum(IV) Glycoconjugates With GLUT1 and OCT2-Mediated Selective Cancer Targeting: Demonstrated Enhanced Transporter-Mediated Cytotoxic Properties in vitro and in vivo. *Front. Chem.*, **2018**, *6*, 1–15

(15) Cao, J.; Cui, S.; Li, S.; Du, C.; Tian, J.; Wan, S.; Qian, Z.; Gu, Y.; Chen, W. R.; Wang, G. Targeted cancer therapy with a 2-deoxyglucose–based adriamycin complex *Cancer Res*., **2013**, *73*, 1362–1373

(16) (a) Iglesias-Guerra, F. ; Candela, J.I. ; Bautista, J. ; Alcudia, F.; Vega-Pérez, J.-M. Alkylating agents from sugars. Alkyl hexopyranoside derivatives as carrier systems for chlorambucil *Carbohydr Res*, **1999**, *316*, 71–84 (b)Halmos, T.; Santarromana, M.; Antonakis, K.; Scherman, D. Synthesis of glucose-chlorambucil derivatives and their recognition by the human GLUT1 glucose transporter *Eur. J. Pharmacol.*, **1996**, *318*, 477–484

(17) (a) Patra, M.; Awuah, S.G.; Lippard, S.J. Chemical approach to positional isomers of glucose-platinum conjugates reveals specific cancer targeting through glucose-transporter-mediated uptake in vitro and in vivo *J. Am. Chem. Soc.*, **2016**, *138*, 12541–1255; (b) Gao, X.; Liu, S.; Shi, Y.; Huang, Z.; Yi, M.; Mi, Q.; Yang, J.; Gao, Q. Mechanistic and biological characteristics of different sugar conjugated 2-methyl malonatoplatinum(II) complexes as new tumor targeting agents *Eur. J. Med. Chem.*, **2017**, *125*, 372–384 (c) Patra, M.; Johnstone, T.C.; Suntharalingam, K.; Lippard, S.J. A potent glucose-platinum conjugate exploits glucose transporters and preferentially accumulates in cancer cells *Angew. Chem. Int. Ed.* **2016**, *55*, 2550–2554

(18) Iglesias-Guerra, F.; Romero, I.; Alcudia, F.; Vega-Pérez, J.M. Alkylating agents from sugars. Cyclophosphamides derived from 2-amino-2-deoxy-D-allose *Carbohydr. Res*., **1998**, *308*, 57–62.

(19) Sakaguchi, K.; Green, M.; Stock, N.; Reger, T. S.; Zunic, J.; King, C. Glucuronidation of carboxylic acid containing com-pounds

by UDP-glucuronosyltransferase isoforms. *Arch. Biochem. Biophys*. **2004**, *424*, 219–225

(20) Smith III, A. B.; Hale, K. J.; Rivero, R. A. An efficient synthesis of glycosyl esters exploiting the mitsunobu reaction *Tetrahedron Letters*, **1986**, *27*, 5813–5816

(21) Perrie, J. A.; Harding, J. R.; Holt, D. W.; Johnston, A.; Meath, P.; Stachulski, A. V. Effective Synthesis of 1-α-AcylGlucuronides by Selective Acylation *Org. Lett.* **2005**, *7*, 2591–2594

(22) Wang, H.-Y.; Simmons, C. J.; Zhang, Y.; Smits, A. M.; Balzer, P. G.; Wang, S.; Tang, W. Chiral Catalyst-Directed Dynamic Kinetic Diastereoselective Acylation of Anomeric Hydroxyl Groups and a Controlled Reduction of the Glycosyl Ester Products *Org. Lett.* **2017**, *19*, 508−511

(23) Yang, T.; Zhu, F.; Walczak, M.A. Stereoselective oxidative glycosylation of anomeric nucleophiles with alcohols and carboxylic acids *Nat. Commun.*, **2018**, *9*, 1–9

(24) Chabrier, A.; Bruneau, A.; Benmahdjoub, S.; Benmerad, B.; Belaid, S.; Brion, J.-D.; Alami, M.; Messaoudi, S. Stereoretentive copper catalyzed directed thioglycosylation of C(sp2)-H bonds of benzamides, *Chem. Eur. J*, **2016**, *22*, 15006–15010

(25) Barsu, N.; Kumar Bolli, S.; Sundararaju, B. Cobalt catalyzed carbonylation of unactivated C(sp3)–H bonds *Chem. Sci.* **2017**, *8*, 2431–2435

(26) (a) Pedersen, C. M.; Nordstrøm, L. U.; Bols, M. "Super Armed" Glycosyl Donors: Conformational Arming of Thioglycosides by Silylation, *J. Am. Chem. Soc*. **2007**, *129*, 9222-9235. (b) Heuckendorff, M. Premathilake, H. D. Pornsuriyasak, P.; Madsen, A.; Pedersen, C. M.; Bols, M.; Demchenko, A. V. Superarming of Glycosyl Donors by Combined Neighboring and Conformational Effects. *Org. Lett.* **2013**, *15*, 4904–4907

(27) Axer, A.; Hermann, S.; Kehr, G.; Clases, D.; Karst, U.; Fischer-Riepe, L.; Roth, J.; Fobker, M.; Schafers, M.; Gilmour, R.; Faust, A.¨ Harnessing the Maltodextrin Transport Mechanism for Targeted Bacterial Imaging: Structural Requirements for Improved in vivo Stability in Tracer Design. *ChemMedChem* **2018**, *13*, 241–250

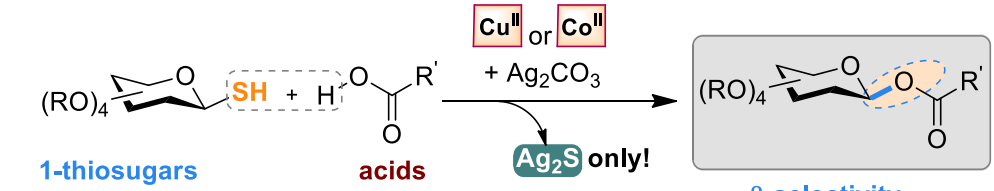
(28) (a) Bruneau, A.; Roche, M.; Hamze, A.; Brion, J.-D.; Alami, M.; Messaoudi, S. "Stereoretentive Palladium-Catalyzed Arylation, Alkenylation and Alkynylation of 1-Thiosugars and Thiols Using Aminobiphenyl Palladacycle Precatalyst at Room Temperature", *Chem. Eur. J*, **2015**, *21*, 8375 – 8379. (b) Montoir, D.; Amoura, M.; Ababsa, Z.E.-A.; Vishwanath, T. M.; Yen-Pon, E.; Robert, V.; Beltramo, M. ; Piller, V. ; Alami, M. ; Aucagne, A.; Messaoudi, S. Synthesis of Aryl-Thioglycopeptides Through Chemoselective Pd-Mediated Conjugation, *Chem.Sci.* **2018**, *9*, 8753–8759

(29) Nobuyoshi, K.; Yamada, S.; Kimura, T. Thermal Decomposition of Silver Carbonate: Phenomenology and Physicogeometrical Kinetics, *J. Phys. Chem. C*. **2013**, *117*, 326–336.

(30) Selected exempels (a) Robert C. Smith, Villel D. Reed & William E. Hill, Oxidation Of Thiols By Copper(II). *Phosphorus Sulfur*, **1994**, *90*, 147–154. (b) Kreitman,G. Y.; Danilewicz, J. C.; Jeffery, D. W.; Elias, R. J. Copper(II)-Mediated Hydrogen Sulfide and Thiol Oxidation to Disulfides and Organic Polysulfanes and Their Reductive Cleavage in Wine: Mechanistic Elucidation and Potential Applications, *J. Agric. Food Chem.* **2017**, *65*, 2564–2571. (c) Ngamchuea, K.; Batchelor-McAuley, C.; Compton, R. G. The Copper(II)-Catalyzed Oxidation of Glutathione *Chem. Eur. J*, **2016,** *24*, 15937–15944

(31) Bell, R.A.; Kramer, J.R. Structural chemistry and geochemistry of silver-sulfur compounds: Critical review, *Environ. Toxicol. Chem.*, **1999**, *18*, 9–22

β-selective O-glycosylation of anomeric thiosugars



1-thiosugars
- **monosaccharides**
- **polysaccharides**

acids
- **aryl, heteroarl**
- **alkyl (1^{e}, 2nd and 3^{d})**

β-selectivity

41 examples