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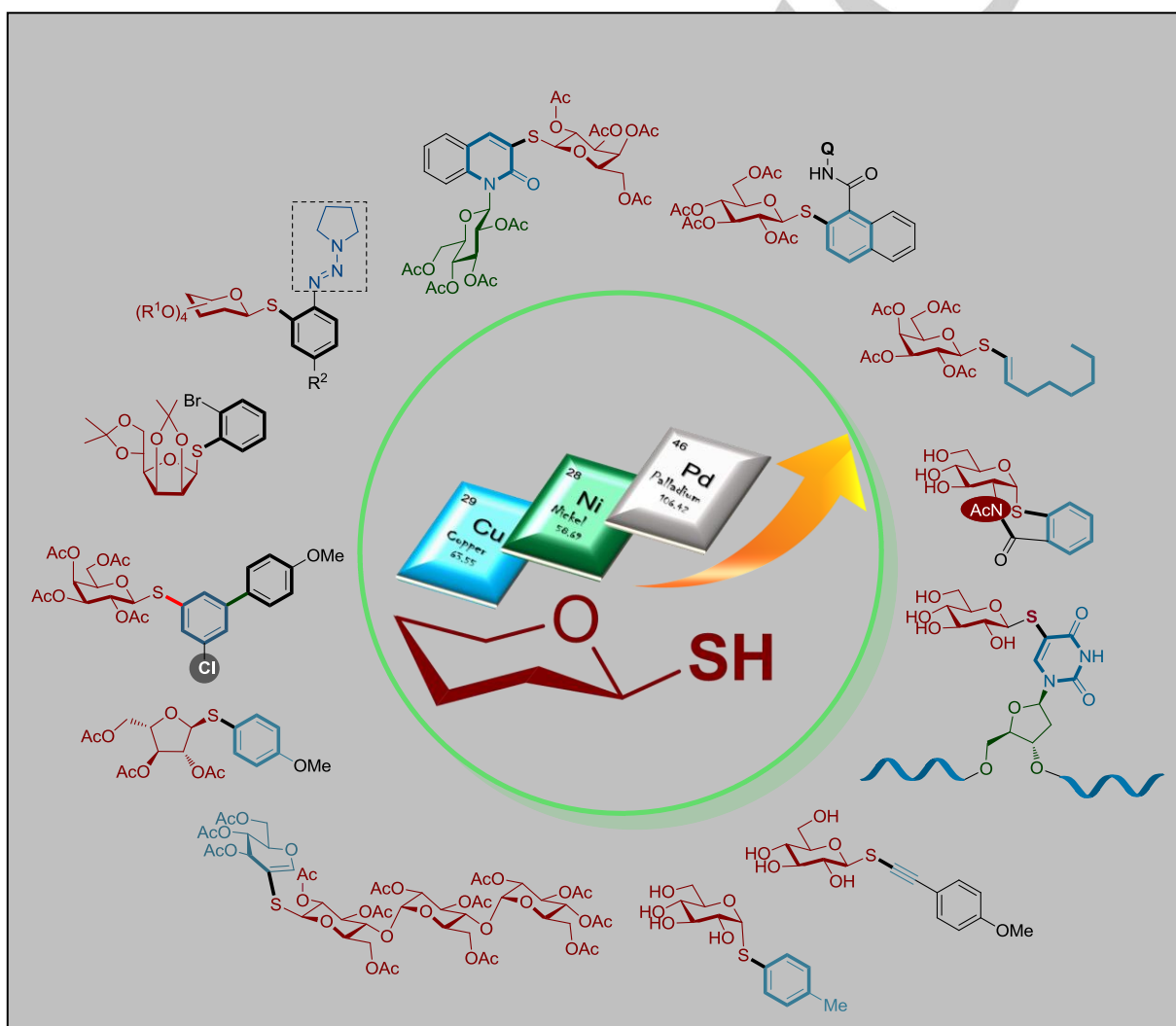
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Recent Advances in Transition Metal-Catalyzed Functionalization of 1-Thiosugars

Nada Ibrahim, Mouad Alami and Samir Messaoudi*

Dedicated to Professors Gérard Cahiez and Gérard Linstrumelle



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Abstract: Thioglycosides are valuable glycomimetic derivatives that have attracted much attention as mimetics of *O*-glycosides. Thioglycosides are among the most important glycomimetics reported to date due to their powerful activities. Owing to their importance, building up methods for their construction has drawn considerable attention. However, the classical methods of their synthesis presenting many shortcomings such as the use of harsh acidic media, and are generally limited in substrate scope. Therefore, metal-catalyzed coupling of thiosugars with halogenated electrophiles can be a superior and highly versatile approach to the synthesis of thioglycosides. The central objective of this Focus Review is to highlight metal-catalyzed reactions for the creation of aromatic and heteroaromatic thioglycosides.

1. Introduction

The relevance of sulfur-containing carbohydrates is gaining seminal attention in a wide area of biological studies. [1] Thioglycoside derivatives have been extensively explored as mimetics of biologically active *O*-glycosides. *S*-glycosides are more stable than their *O*-glycosides analogs to both chemical and enzymatic degradations and are employed as inhibitors of enzymes in various biochemical studies. [2] In addition, the thiosugar moiety has been found in various drugs, natural products and medicinal active agents [3]. Examples in Figure 1 highlight some biological activities of selected thioglycosides, including glycosidase inhibitors, [4] cytotoxic Hsp90 inhibitor, hSGLT1 inhibitor, antimicrobial agent as well as ligand of lectine A. however, 1-thioglycosides are routinely used as glycosyl donors in building a variety of glycosidic linkages. [5] Whilst emerging effort is being spent on construction of specific thiooligosaccharides and thiopeptides, little attention has been devoted to the synthesis of (hetero)arylthioglycosides. The latter are more usually prepared by treating per-*O*-acetylated glycosyl precursors with thiophenol derivatives in the presence of Lewis acid, [6] or by substituting the halogen atom of an acetohaloglycoside with a thiolate anion [7] (Scheme 1a). These procedures are limited by the use of an excess of harsh acidic reagents, and are generally restricted in substrate scope with respect to thiophenols. Moreover, reactions can be long, and undesired anomeric mixtures are sometimes observed. [8] An attractive option to access (hetero)arylthioglycosides would be the use of thioglycosides as nucleophiles under transition metal-catalysis (Scheme 1b).

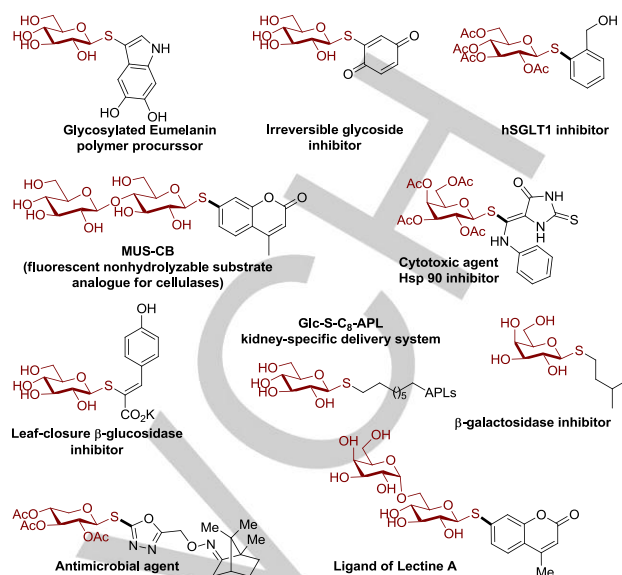


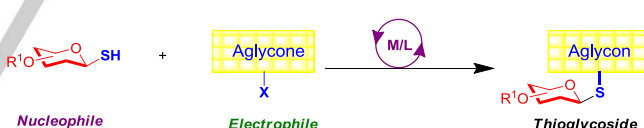
Figure 1. Examples of biologically active thioglycosides

This particular focus review aims to highlight the concepts and the current status in the expanding area of thiosugars functionalization under transition-metal-catalyzed C–S bond formation in comparison with traditional methods.

1a. Traditional methods



1b. Metal-catalyzed cross-coupling



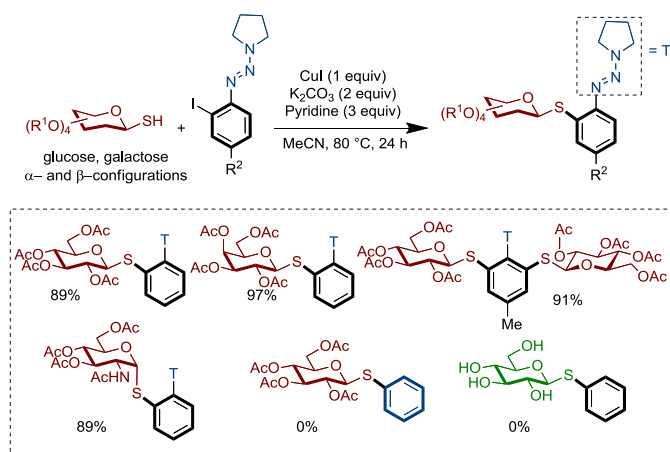
Scheme 1. Traditional methods and the emerging new concept to synthesize glycosides under metal catalysis.

2. Metal Catalysed Cross-Coupling of Thiosugars and arylhalides

2.1. Copper Catalyzed Coupling of Thiosugars and Arylhalides

Early work on copper catalyzed functionalization of thiosugars traces back to 2003 with Sticha and co-workers [9] The authors have reported the first copper mediated arylation of sugar thiols by *o*-haloaryl triazenes under mild conditions and showed for the first time the utilization of thiols sugars as nucleophile in copper catalysis.

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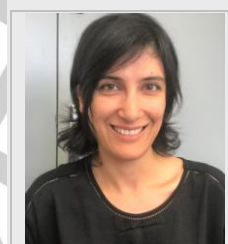
Scheme 2. Early work on copper catalyzed functionalization of thiosugars: Selected examples

This arylation proceeded well by stirring *o*-iodoaryl triazene, per-*O*-acetylated 1-thiosugar, CuI (1 equiv), K₂CO₃ (2 equiv), and pyridine (3 equiv) in MeCN at 80 °C for 24 hours (Scheme 2). The reaction appears to be suitable for both α - and β - anomeric configurations and was conducted with per-*O*-acetylated 1-thio- β -D-glucose, galactose, *N*-acetyl- α -D-glucosamine to give the corresponding products (Scheme 2). The reaction was also flexible with respect to the substituents on the iodoaryl triazenes moieties such as ester and acyl. Yields of these transformations were quite high ranging from 82 to 97 %. This methodology has been extended to the construction of bivalent S-glycoclusters. Thus *o,o*-dihaloaryl triazenes (1 equiv) with per-*O*-acetylated sugar mercaptans (2.2 equiv) were treated under similar reaction conditions providing 1,3-(glycopyranosylthio)benzenes in up to 95 % yields (Scheme 2). The developed method allowed the preparation of symmetrical and unsymmetrical 1,3-bis(glycopyranosylthio)benzene derivatives as well.

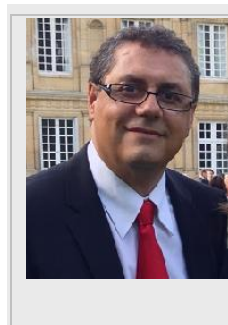
The initial motivation of this work was to prepare precursors for potential radioiodinated photoaffinity^[10] justifying the presence of triazene on the iodoaryls as partners of the coupling procedure. It was demonstrated that triazene moiety placed *ortho* to the halogen leaving group had beneficial effect, through chelation, on copper^[11] which probably allowed reactions to proceed under mild conditions in high yields. However, the presence of a triazene group *ortho* to the iodide was crucial for a successful course of reaction which seems for us a major limitation making the substrates scope very narrow. In fact, authors never succeeded to arylate thioglucose with unsubstituted iodobenzene with various stoichiometric (CuI, Cu₂O) and catalytic (Pd, CuI) with satisfactory yield, they observed in some cases anomerization leading to a mixtures of α - and β -anomers. Regarding the aforementioned, we believe that this protocol is far from being generalizable and extendable to thiol sugars arylation protocols.

In 2015, Xue *et al.*^[12] reported a new copper catalyzed method for synthesis of (hetero)aryl thioglycosides. This method relies on the use 2'-cyanoethyl thioglycosides nucleophiles, which generate *in situ* the glycosyl thioanion that reacts with electrophiles under copper catalysis to furnish a wide variety of (hetero)aryl thioglycosides. The procedure consists on reactions

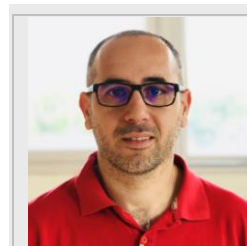
Nada Ibrahim graduated in 2010 as a Ph.D. in organic chemistry at the Institut Curie from the University of Paris-Sud under the supervision of Dr. M. Legraverend. Thereafter, she joined CaRLa-BASF laboratory in Heidelberg as postdoctoral fellow in the field of metal catalysis under the supervision of Prof. Dr. A. S. K. Hashmi. Then, she did research in carbohydrates and medicinal chemistry at BioCIS in the faculty of Pharmacy, University of Paris-Sud under the supervision of Drs M. Alami and S. Messaoudi and at The Institut Galien (IGPS) where she is currently working in the field of drug delivery under the supervision of Drs N. Tsapis and J. Nicolas.



Mouad Alami did his PhD at the University Pierre and Marie Curie in Paris (G. Cahiez). After a two post-doctoral position (Elf-Atochem company and University of Santa-Barbara - Prof. B. H. Lipshutz), he joined the CNRS at the Ecole Normale Supérieure, ENS-Paris (G. Linstrumelle). Since 1999, he accepted a position at the, Faculty of Pharmacy (University Paris-Sud) where he became CNRS Research Director. Dr Alami's field of specialization includes: (i) the development of novel selective synthetic methodologies involving organometallic chemistry, and (ii) the synthesis of structurally challenging and biologically relevant products with antitumoral activity. In this context, we have a special interest in the design and synthesis of vascular disrupting agents and dual molecules with applications in antibody drug conjugate strategy.

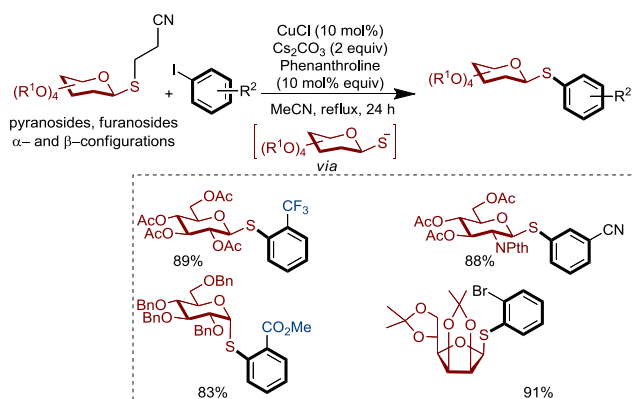


Samir Messaoudi completed his PhD in 2004 at Blaise Pascal University, Clermont Ferrand, France. After two years as postdoctoral fellow, he joined the group of "Therapeutic Chemistry" in 2007 as a junior CNRS-researcher at BioCIS UMR 8076, university of Paris Sud. In 2017, he was promoted as Director of Research DR-CNRS. His main research concern deals with glycochemistry (functionalization of carbohydrates under transition-metal catalysis), as well as with the preparation of molecules and molecular scaffolds of biological and therapeutic interest.



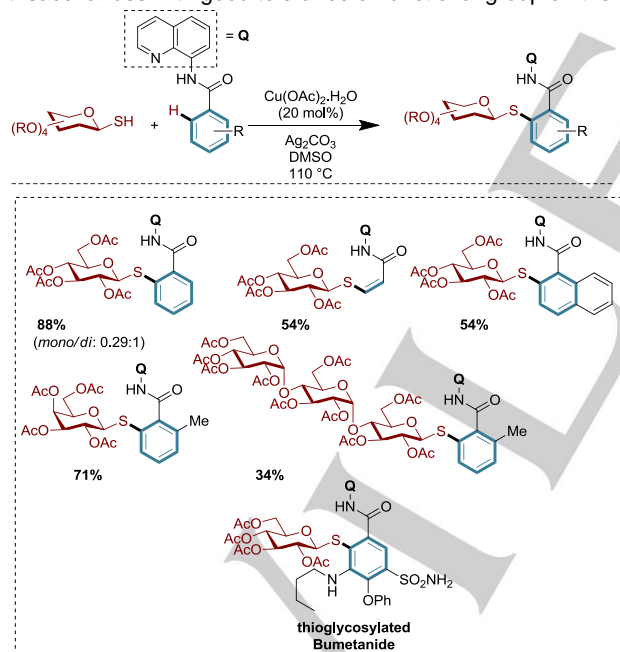
between protected thioglycosides with various (hetero)aryl iodide in presence of catalytic amount of CuCl (10 mol%), phenantroline as ligand (10 mol%) and 2 equivalents of Cs₂CO₃ as the base in refluxing acetonitrile for 24 h. The reaction scope has been investigated with aldose derivatives and highly functionalized organic iodides. The resulting products were obtained in good to excellent isolated yields (83–91%, Scheme 3).

This protocol seemed to be general with a wide range of functional groups such as esters, olefins, acetals, ethers, halides, amides, and ketals even free amino group was tolerated. The reaction conditions, albeit mild and efficient, would not be applicable, in our point of view, to fully unprotected (free OH) thioglycosides, accordingly the overall synthesis required two additional steps of protection and deprotection along with the protection of the anomeric position with 2'-cyanoethyl.



Scheme 3. Selected examples for the copper catalyzed functionalization of thiosugars using 2'-cyanoethyl thioglycosides

Recently, the group of Messaoudi has published an interesting approach in copper catalyzed C–H activation by using thiosugars as nucleophilic partners.^[13] The reaction consists on $\text{Csp}^2\text{-H}$ activation of benzamides and takes advantages from the *ortho*-directing effect of 4-aminoquinoline which should be installed on the substrates prior to reactions. 20 mol% of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ and 2 equivalents of Ag_2CO_3 were used in DMSO at 110°C to achieve the couplings. Under these conditions, various thio glycosides (Scheme 4) were isolated in up to 98% yields. Authors have succeeded to prepare a representative selection of (hetero)arylglycosides bearing mono- di- and trisaccharides with good tolerance of functional group on the aryl

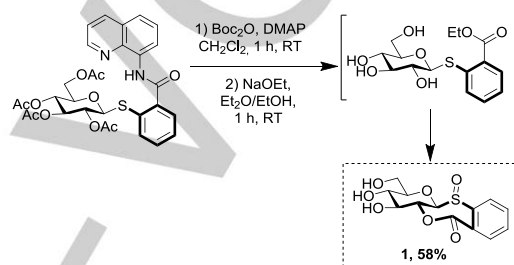


Scheme 4. Selected examples for the first Cu-catalyzed C–H functionalization of benzamide with thiosugars.

moieties. It is worth pointing out on the β -stereoretentive aspect of the procedure, all products were obtained without anomerization and with good yields (Scheme 4). Furthermore, vinylbenzamide substrate worked satisfactory to provide stereoselectively the *Z*-vinyl β -thioglycoside in 54% yield

(Scheme 4). It is of note that no thermal isomerization of the double bond was observed, demonstrating the *Z*-stereoselectivity of the C–H thioglycosylation reaction.

Although preinstallation and removal of the *ortho*-directing group is required for substrate scope, this strategy remains unique and mechanistically very considerable in the field of thioglycosylation catalyzed by copper, as it addressed challenging issues such as affording exclusively one single β anomer. The *ortho*-directing group was cleaved by using the Miura's protocol^[14] in which the *Boc*-protection of the secondary amide moiety was performed as the first step, followed by ethanolysis with EtONa in a mixture of $\text{EtOH}/\text{Et}_2\text{O}$ affording the benzoxathiepinones (**1**) in good yield (Scheme 5).



Scheme 5. Removal of directing group followed by further transformations.

Although the exact mechanism of the reaction is still not clear, based on literature reports^[15] the authors proposed a possible mechanism for the thioglycosylation of $\text{C}(\text{sp}^2)\text{-H}$ bonds of benzamides as depicted in Figure 2.

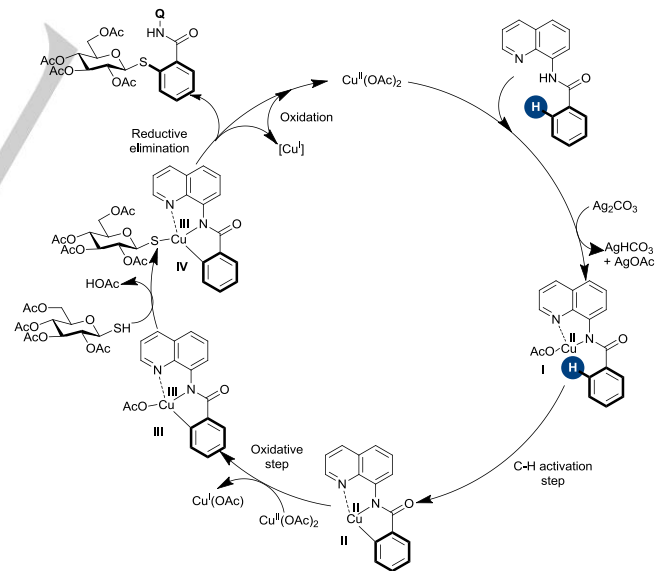


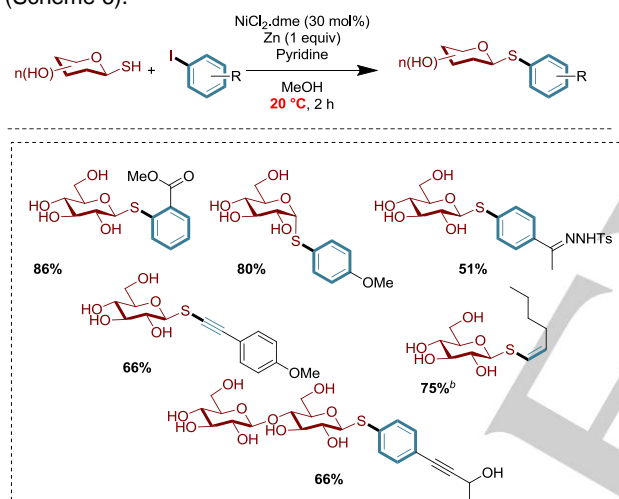
Figure 2. Proposed mechanism of the Cu-catalyzed C–H functionalization of benzamide with thiosugars.

Intermediate complex (**I**) which is formed by the coordination of benzamide to $\text{Cu}(\text{OAc})_2$ followed by ligand exchange, is envisioned to take place as an initial step. This later evolves through C–H activation mechanism to give the copper(II)

complex (**II**). Subsequent oxidation of **II** promoted by $\text{Cu}(\text{OAc})_2$ produces a copper(III) complex,^[16] which reacts with glycosyl thiol to afford copper(III) complex (**IV**).^[17] As the final step of the catalytic cycle, reductive elimination of **VI** produces thioglycosylated product.

2.2. Nickel catalyzed thioglycosylation

Recent notable progress in the use of naturally more abundant and extremely cheap nickel catalysts in the C–S bond forming reaction has found wide applications in organic synthesis. Although Ni-catalyzed arylation of thiophenols to form diaryl sulfides has been extensively studied, only few isolated examples on the use of aliphatic thiols have been reported to date. In this context, Messaoudi and co-workers disclosed in 2013 a general and robust coupling of unprotected thioglycosides with (hetero)aryl halides as well as alkenyl and alkynylhalides.^[18] The $\text{C}(\text{sp}^2)\text{--S}$ and $\text{C}(\text{sp})\text{--S}$ bonds can be realized stereoselectively under mild conditions in the presence of a catalytic amount of Ni(0) in methanol at room temperature (Scheme 6).

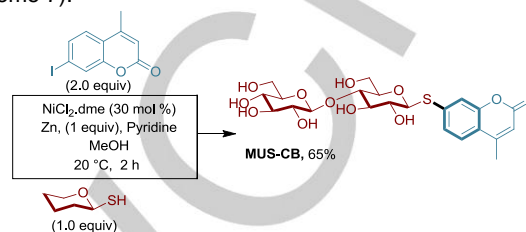


Scheme 6: Selected examples for the Ni-Catalyzed coupling of unprotected glycosyl thiols with aryl-, alkenyl- and alkynyl halides. Notably this reaction represents the first functionalization of free thiosugars catalyzed by Nickel. The conversion was rapid, within 1 to 2 hours all the final products were formed at room temperature with perfect stereo-control of the anomeric position. The coupling procedure is not limited only to β -thiosugars but also works successfully with thiols of α configuration. Moreover, there were no significant differences in reactivity between α - and β -anomers as similar yields were obtained with both anomers. In addition, the reaction was not limited to monosaccharide but could be extended to di- and tri-saccharide.

Not only (hetero)aryl iodides were good partners of the reaction but also alkenyl- and alkynylhalides were coupled successfully. the coupling reactions with sugars stereoselectively afforded the desired alkenylthioglycoside derivatives in good yields without any thermal isomerization, thereby demonstrating the mild nature of this selective coupling reaction. If this method met its success it's because of the selectivity of Ni towards thiol and as shown in some examples hydroxy, free-amino, or boronic-acid

groups on the aryl-halide didn't seem to hamper the nickel catalytic system.

A representative illustration of the strength of the catalyst was demonstrated by the preparation of 4-methyl-7-thioubelliferyl- β -D-cellobioside (MUS-CB) by coupling reaction between 7-iodocoumarin^[19] and fully deprotected β -D-disaccharide to give the product in a good 65% yield, with exclusive β -selectivity (Scheme 7).



Scheme 7. Synthesis of (MUS-CB)

Notably, the above reaction is not limited to a small scale (0.25 mmol) as it could be conveniently performed on a 1.2 g scale (5 mmol; 20-fold scale up) with only 5 mol % of Ni(0) in good yield, indicating that this protocol would be practically valuable.

2.3. Palladium-Catalyzed Buchwald-Hartwig-Migita Cross-Coupling of Thiosugars and Arylhalides

The ubiquitous presence of C–S bonds in materials and organic chemistry, built up with a relatively mild, selective, and highly efficient Pd-catalyzed methodologies, has made sulfination reactions of functionalized carbon backbones one of the most popular transformations over the past decade.^[20] The palladium-catalyzed Buchwald–Hartwig–Migita cross-coupling reaction has become an effective tool in industrial and academic research giving access to natural products and novel materials as well as a wide number of pharmaceuticals currently on the market.^[21] Advances in this coupling reactions have been driven by the discovery of a new class of ligands,^[22] which are able to promote reactions with a variety of substrates including nitrogen-, sulfur-, and oxygen-containing nucleophiles.

Historically, the draw-off Pd(II) intermediates into thiolate derived off-cycle resting states (Figure 3, resting states A, B and C)^[23] has plagued Pd-catalyzed sulfinations and in turn limited widespread adoption of this transformation.^[24] One approach to resolve this problem is to lower the activation barrier of reductive elimination (RE) in a way to keep the catalyst involved in the catalytic cycle and to keep the equilibrium away from the nonproductive resting states of the higher order (resting state B) and thiolate-bridged (resting state C) Pd(II) oxidative addition adducts (see below).

Ligand design and optimization through iterative modifications was an obvious and productive means to fine-tune the steric topography around the Pd center and alter the kinetics of reductive elimination (RE). In spite of the ability of bulky phosphines to promote facile RE, they typically require elevated

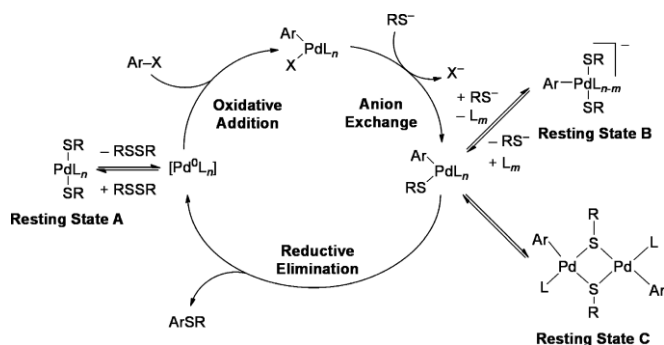
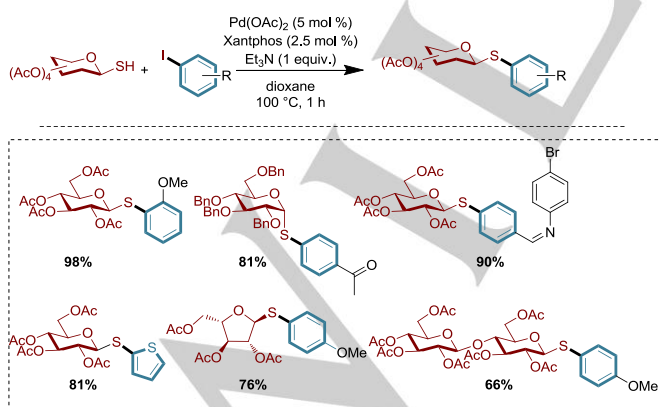


Figure 3. General catalytic cycle for aryl sulfinations highlighting thiol-poisoning pathways that lead to catalyst resting states. Adapted from Valente *et al.*^[23]

temperatures to perform efficient catalysis.^[25] Moreover, when the steric topography around Pd is essential for catalyst turnover, and the limiting sulfur-poisoning pathways lead to catalyst resting states, even the most transient dissociation of the ligand can be detrimental. Decreasing the basicity of the phosphine atom by substituents modification at the phosphorus atom can certainly help minimize ligand dissociation.^[26] To that end, the PEPPSI class of Pd–NHC complexes has been studied and systematically modified to enable one of the most generally mild sulfinating protocols to date.^[23]

In the context of functionalization of thiosugars, the first report on Pd-catalyzed reaction has been published by Messaoudi and coworkers^[27] using α - and β -thiosugars as nucleophiles. Screening of different palladium sources and ligands allowed authors to settle on the use of Pd(OAc)₂ (5 mol%), Xantphos (2.5 mol%), and Et₃N (0.25 mmol) as standard conditions for coupling to accommodate a very wide combination of bromo- or iodo- (hetero)aryles with β - and α - 1-thio mono- di and trisaccharides in dioxane at 100°C (Scheme 8). The conversion is very efficient and products formation has been achieved within only one hour. Authors investigated extensively the scope of the developed strategy and unprecedentedly succeed to synthesize



Scheme 8. Selected examples for the first Pd-catalyzed functionalization of thiosugars with (hetero)aryl iodides

up to 32 examples in excellent yields without any significant side reaction such as anomization. As depicted in Schemes 8, α -

and β -thiosugars are readily coupled with any aryl iodides having *para*-, *meta*-, and *ortho*-electron-donating or electron-withdrawing groups to give thioglycosylated products in good to excellent yields with complete stereoselectivity regardless the nature of the protecting group on the sugar moiety. The protocol was applied successfully for the synthesis of 4-methyl-7-thioubelliferyl- β -D-cellobioside (MUSCB) (Figure 4). The latter highlighted the value of this transformation in the thioglycosylation of biologically active molecules for the development of new medicinal agents. For instance, **2** and **3** which are analogs of *isocombretastatin A-4* (*isoCA-4*),^[28] and phenstatin,^[29] two promising cytotoxic and antitubulin agents, were selectively thioglycosylated with 1-thio- β -D-galactose under Pd-catalysis. The couplings furnished β -thioglycosides **5** and **6** with excellent efficiency (yields up to 97%). In addition this method allowed the rapid preparation of thioglycoside **4** analogue of 6BrCaQ (Figure 4), a potent hsp90 inhibitor.^[30] In the context of drug discovery, this strategy offers a potential for a rapid testing of biological actives thioglycosylated analogues issued from a single late-stage glycosylation reaction.

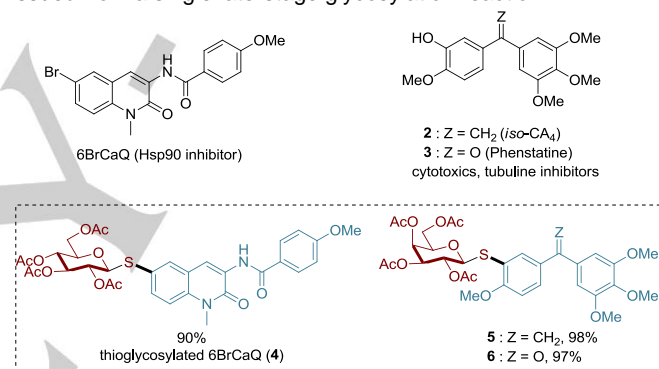
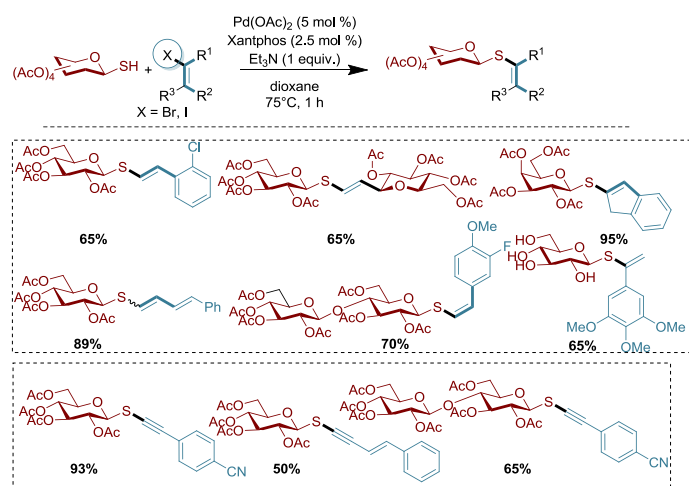


Figure 4. Late-stage thioglycoconjugation of biologically active compounds.

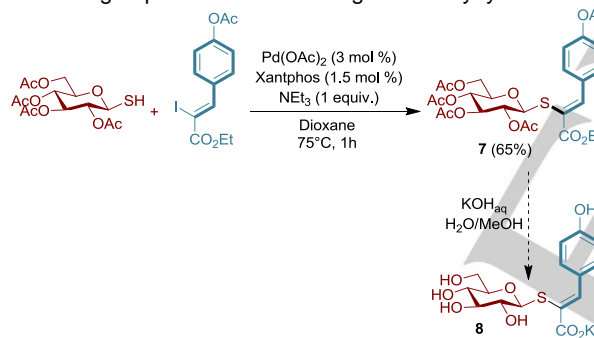
Given the success of the previous protocol, the authors smartly used these conditions in an alternative report^[31] to perform alkenylation, alkylation and alkylation of thiosugars. Alkenylthioglycosides are important biological derivatives^[32] and their obtention is limited by their low yields and non-general multisteps synthesis such as reaction of an electrophilic acetohaloglycoside precursor with a thioenol ether under basic conditions.^[33] Therefore, applying the initial protocol of Messaoudi *et al.* for (hetero)arylation of thiosugars to their synthesis was an appealing alternative, especially that it was possible to operate at lower temperature to 75°C which makes it a milder protocol (Scheme 9).

As summarized in scheme 9, (*E*) styryl bromides, both *E*- and *Z*-iodostyrene isomers as well as a mixture of diene *1E,3E/1E,3Z* (30:70). Noteworthy, *Z*-alkene reactants with long alkyl chains displayed excellent reactivity. These molecules are still of interest and may be used as scaffolds to build compounds such as Glc-S-C₈-APL (Figure 1). Besides β -styrylhalides, α -styrylhalides such as α -iodostyrene and cyclic alkenylhalides also worked well, affording the corresponding alkenylthioglycosides in a good yields. (Scheme 9).



Scheme 9. Selected examples for the Pd-catalyzed functionalization of thiosugars with alkenyl- and alkynylhalides

More interestingly, coupling of unprotected β -D-thioglucose with α -iodostyrene under this procedure furnished exclusively β -anomer in a good yield without any side product resulting from O-arylation under Pd-catalysis. In addition, alkynylated thioglycoside products were obtained diastereoselectively in good to excellent yields (Scheme 9) regardless the nature of the substituent group on the aromatic ring of the alkynylbromide.

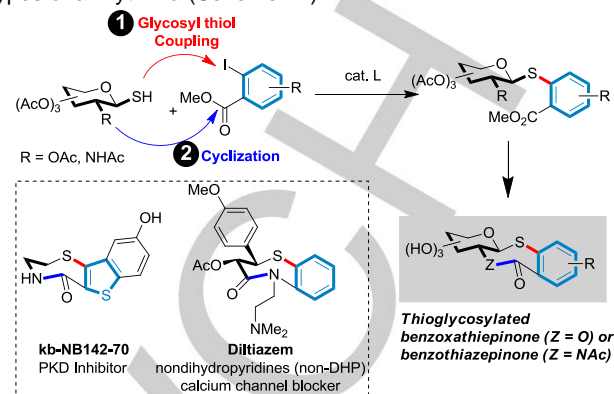


Scheme 10: Formal synthesis of leaf-movement inhibitor (**8**).

The synthetic potential of this protocol was well-illustrated by the formal synthesis of a leaf-closure β -glucosidase inhibitor. The key step was the coupling of 2-iodoacrylate with peracetylated β -D-thioglucopyranose under optimized conditions to give acetylated thioglycoside **7** in a good 65% yield with exclusive β -selectivity (Scheme 10). Compound **7** can be converted to the leaf-closure β -glucosidase inhibitor **8** by a known procedure.^[4a]

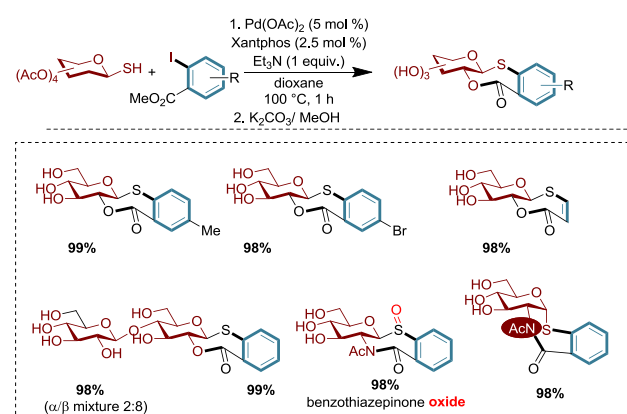
A recent application of this methodology was illustrated in the synthesis of fused thioglycosyl benzo[e][1,4]oxathiepin-5-ones and benzo[f][1,4]thiazepin-5(2*H*)-ones by a sequence of palladium-catalyzed arylation of glycosyl thiol followed by deprotection-lactonization reactions in a program aiming at diversity-oriented synthesis (DOS).^[34] This modular strategy is conceptually attractive in terms of diversifying the benzoxathiepinone and benzothiazepinone frameworks with the aim to identify novel scaffolds of biological interest such as kb-NB142-70^[35], a protein kinase D inhibitor, or Diltiazem^[36], a

marketed drug to treat hypertension, angina pectoris and some types of arrhythmia (Scheme 11).



Scheme 11. General strategy to fused thioglycosyl benzo[e][1,4]oxathiepin-5-ones and benzo[f][1,4]thiazepin-5(2*H*)-ones

The strategy relies on an efficient coupling of various glycosyl thiols and methyl 2-iodobenzoates in the presence of Pd(OAc)₂ (5 mol%) Xantphos (2.5 mol %), the couplings products were obtained in good to excellent yields (30% – 100%). This coupling was sequentially followed by deprotection-lactonization (or lactamization) to afford thioglycosylated benzo[e][1,4]oxathiepin-5-one and benzothiazepinone in very good yields up to 99 %. Fused thioglycosyl benzoxathiepinones bearing a wide variety of functional groups could be synthesized in good to excellent yields (Scheme 12). Electron-donating and electro-withdrawing functions on the aromatic ring, were well tolerated. The presence of C–Br (and C–Cl) bonds provided a handle for further diversifications under transition metal-catalysis. It is noteworthy that the lactonization reaction of vinylthioglycoside derivative having a *Z*-double bond, succeeded and led to the formation of the bicyclic compound with an original structure in a 98% yield.

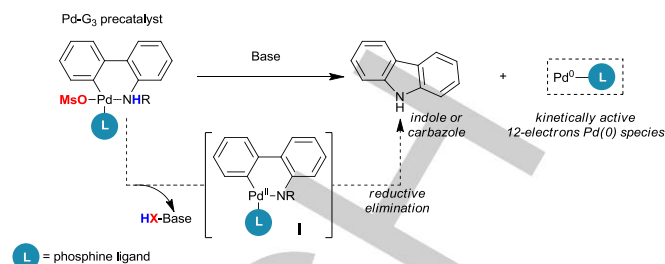


Scheme 12: Selected examples for the Pd-Catalyzed coupling of peracetylated glycosyl thiols with various methyl 2-iodobenzoates

In a further set of experiments, authors investigated the scope of the method with respect to substrates bearing an *N*-acetyl

function at C2' position of the sugar moiety (Scheme 12). It was found that the rate of the cyclisation step strongly depends on the nature of the nucleophile at the C2' position (*O*- vs *N*-nucleophile). Thus, the lactonization reaction took place within 10 min, whereas the lactamization of the *N*-acetyl-1-thio- β -D-aminoglycoside was found to be sluggish. The cyclization step occurred only when five equivalents of the base were used during seven days stirring at room temperature. Under these conditions, removal of the *O*-acetate groups of the sugar moiety followed by the lactamization step as well as the sulfur atom oxidation led to the benzothiazepinone oxide in a 99% yield (Scheme 12). Interestingly, when α -NHAc-thioglycoside was used instead of its β - anomer, only 1 equivalent of the base and 12 h reaction time were required for total conversion, leading to α -fused glycosylbenzothiazepinone (Scheme 12) in a quantitative yield without anomerization. This result clearly indicates that the lactamization reaction of the α -anomer is faster than β -substrate probably due to conformational issues.

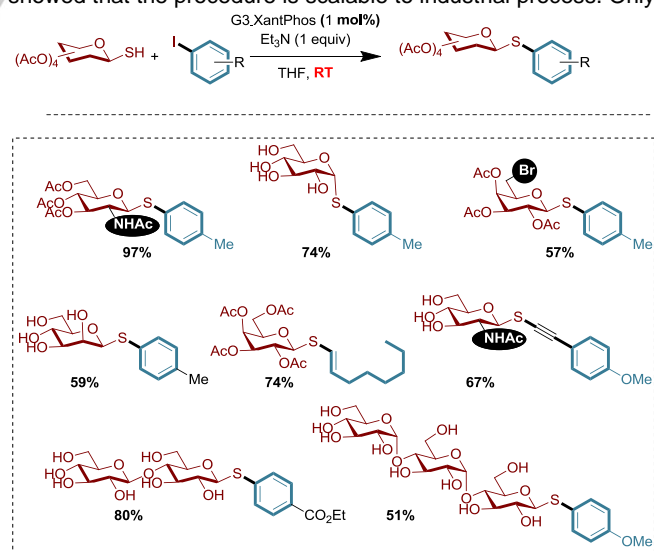
Despite all the described advances, a general and simple method for the functionalization of thiosugars at room temperature is still desired. One of the most important tasks in the area of organometallic chemistry is to discover mild and general methods for easy introduction of unprotected polyfunctionalized structures into molecules with high selectivity. When highlighting the importance of glycosides, particularly thioglycosides in numerous fields of sciences, the development of new methods to functionalize them efficiently under simple and eco-friendly conditions is highly desirable. In this context, the group of Messaoudi became particularly interested in the direct palladium-catalyzed coupling of unprotected glycosyl thiols under mild and operationally simple conditions. The catalytic reactions of this nature may be of great interest for the construction of molecules that are sensitive to the harsh conditions often required for thioglycosidic^[37] bond-formation.^[38] In light of the recent success of Buchwald group in using aminobiphenyl palladacycle precatalysts in C–N and C–O bond-forming reactions,^[39] Messaoudi and co-workers decided to explore the ability of the G3-XantPhos precatalyst^[40] to promote the construction of a C–S bond under mild conditions and they have reported for the first time, a fast, efficient and stereoretentive coupling of various unprotected and protected glycosyl thiols (mono-, di- or polythioglycosides) with aglycon halides at room temperature. The key success was the use of the Pd G-3 XantPhos precatalyst with low catalyst loading (1 mol%), which was able to generate very fast under mild conditions the catalytically active 12-electron XantPhos-Pd(0) species (Scheme 13). Activation of these precatalysts may occur through the action of a mild base to form the key intermediate palladium (II) complex I (Scheme 13). Next, the reductive elimination occurs to form the kinetically active 12-electrons LPd(0) species and produces the carbazole side-product in a catalytic quantity.



Scheme 13. Highly active G3-XantPhos precatalyst and generation of kinetically active 12-electrons Pd(0) species

This catalytic system was applied in the coupling of 4-iodoanisole with 1-thio- β -D-glucopyranose using PdG3-Xantphos^[41] 1 mol%, and one equivalent of triethylamine in THF or dioxane. The conversion was achieved within one hour at r.t. and when using protected sugars the time was reduced to only five minutes. Remarkably, this glycosidic C–S coupling reaction appeared to be quite general with respect to the different partners and tolerated various functional groups (Scheme 14) (e.g., –Br, –OTs, –OH, –CN, –CO₂Me, –CONR₂, –C(Me)=NNHTs).

The authors demonstrated that there was no significant impact of protecting groups on the reactivity of the thiosugar derivatives since acetate or benzoyl-protected carbohydrate reacted similar to the unprotected derivatives, furnishing the coupling products with up to 99 % yield. Coupling with alkenyl and alkynyl halides as aglycon partners afforded stereoselectively the desired alkenylthioglycoside derivatives in excellent yields. Moreover, alkynylated thioglycoside product were obtained in good yields with this method. In addition, the efficiency of this C–S bond forming reaction was well-demonstrated by coupling more complex unprotected di- and trisaccharide derivatives at room temperature such as 1-thio β -D-cellobiose and 1-thio β -D-maltotriose to give the corresponding glycoconjugates in good yields. Also multi-gram scale was investigated, and the results showed that the procedure is scalable to industrial process. Only



Scheme 14. Selected examples for the G3-Xantphos precatalyst catalyzed coupling of 1-thiosugars with aglycone halides

1 mol% of palladium precatalyst were enough to achieve the conversion at room temperature of 50 mmoles of each of thiosugar and iodoaryl into the desired thioglycoside in 97 % yield without any loss of the stereocontrol outcome at the anomeric position.

This striking result can be considered as one of the major advances in the field of thiosugar chemistry. As it could be performed with perfect stereoselectivity, either using α - or β -thio mon- di- and tri glycosides without protection of the sugars OH groups. Moreover, it could be performed under mild conditions with very low catalytic charge (1 mol%) at room temperature, which are suitable conditions for carbohydrates chemistry.

Application of this procedure to the multigram-scale was also performed by the authors. In this context, the development of a simple and scalable method in is essential for plant-scale manufacturing in organic synthesis. Here Messaoudi and co-workers showed that this procedure could be achieved safely by coupling 1-thio- β -D-glucopyranose **8** with 4-iodotoluene **9** in a multigram-scale reactor (50 mmol) by using 1 mol% of the precatalyst at room temperature within 10 min (Figure 5). Compound **10** was isolated in almost a quantitative yield as a pure product after only filtration through celite without any additional purification. This result demonstrates clearly that this procedure can be used in a scale-up industrial process.

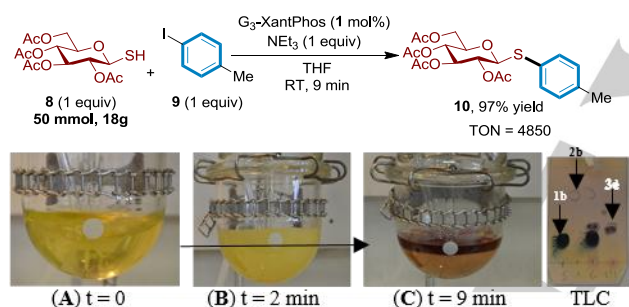
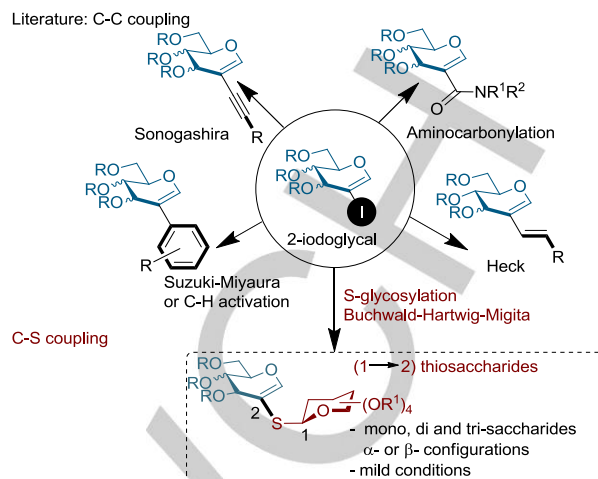


Figure 5. In reactor multigram-scale coupling of 1-thio- β -D-glucopyranose **8** with 4-iodotoluene **9** at RT.

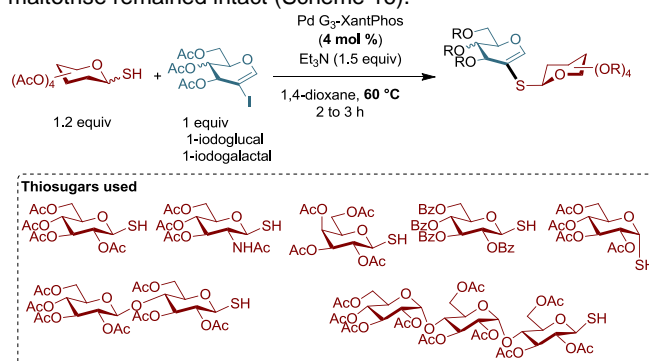
In later reports Messaoudi and co-authors showed largely the potential application of this protocol. The authors started by highlighting the synthesis of (1 \rightarrow 2)-S-Linked saccharides and S-linked glycoconjugates *via* a Pd-G3-XantPhos precatalyst catalysis^[42]. This efficient methods allowed successfully the synthesis of various (1 \rightarrow 2)-S-linked saccharides *via* a palladium precatalyst-catalyzed coupling of α - or β -mono-, di-, and polythiosugar derivatives with 2-iodoglycals.

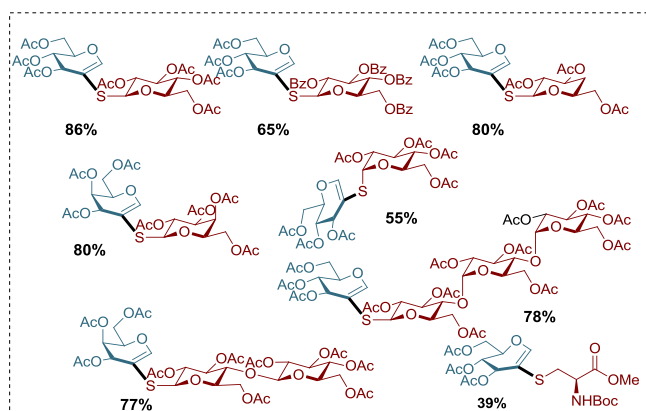
2-Haloglycals are widely used as important synthons in carbohydrate chemistry and have become a new entry to the synthesis of 2-functionalized carbohydrate derivatives (Scheme 13). Starting from 2-iodoglycals as coupling partners, some reactions such as Suzuki-Miyaura,^[43] Heck,^[44] Sonogashira,^[45] C-H activation^[46] and aminocarbonylation^[47] have been applied successfully to synthesize 2-C-branched glycosides. The first study concerning the coupling of 2-iodoglycals with sulfur heteroatom nucleophiles (such as α - and β -glycosyl thiols) was reported by the group of Messaoudi.



Scheme 15. Iodoglycals as coupling partners in some Pd-catalyzed cross-couplings.

This new methodology is of great utility and has been successfully applied to a variety of α - or β -mono-, di-, and polythiosugar derivatives to synthesize efficiently a series of (1 \rightarrow 2)-S-linked thiosaccharides and S-linked glycoconjugates which are difficult to synthesize by classical methods. While in the literature only a few examples of S-linked saccharides mainly α - α -(1 \rightarrow 1'),^[48] α - or β -(1 \rightarrow 2),^[49] α -(1 \rightarrow 4),^[50] or α -(1 \rightarrow 6),^[51] are known, their synthesis using the classical pathway is not well established and this new methodology offered a good alternative to make them. The authors showed that the coupling of diverse α - and β -mono-, di- and poly-thiosugar derivatives with iodoglycals proceeded in good yields and with a retention of the anomeric configuration. This reaction tolerated a large variety of thiosugars: O-acetylated 1-thio- β -D-glucopyranose, O-acetylated N-Ac-1-thio- β -D-glucopyranose, O-acetylated 1-thio- β -D-galactopyranose and O-benzoylated 1-thio- β -D-glucopyranose. Importantly, this procedure is not limited to only β -glycosyl thiols, but also worked successfully with 1-thiogluco which had an anomeric α -configuration. Moreover, the reaction can be applied to more complex di- and trisaccharide derivatives such as 1-thio- β -D-cellobiose 1-thio- β -D-maltotriose. The authors noted that the stereochemistry of the β -1,4' -O-glycosidic bond in the trisaccharide cellobiose and the α -1,4' in β -tetrasaccharide maltotriose remained intact (Scheme 16).





Scheme 16. Selected examples for the G3-Xantphos precatalyst catalyzed coupling of 1-thiosugars with aglycone halides

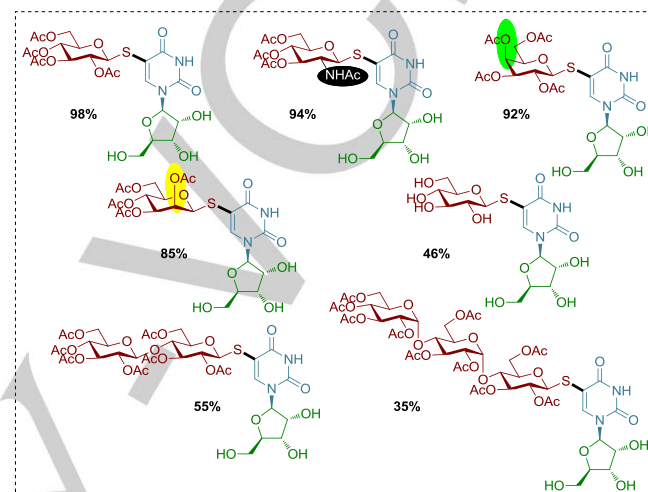
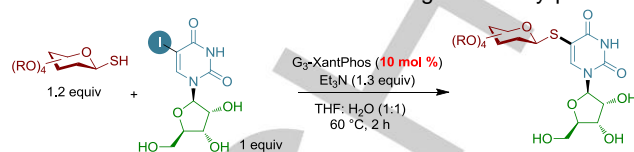
In their study, authors showed with some examples the possibility to couple amino acids with 2-iodoglycal to give thioglycoconjugates. This interesting result may pave the way for the synthesis of new glycoconjugates peptides for medical approach (Scheme 16).

Nowadays, synthetic oligonucleotides are investigated in a considerable number of applications in medical fields (e.g. control of gene expression),^[52] molecular diagnostic (e.g. DNA-based biosensors)^[53], biotechnology (e.g. catalysts)^[54] and nanotechnology (e.g. origami DNA for nanomaterials)^[55]. Tremendous work has been made to improve the intrinsic properties of oligonucleotides by either incorporating chemical modifications (e.g. phosphorothioate, 2'-methoxyethoxy, locked nucleic acids...) or by covalently linking reporter groups with relevant properties to them. The conjugation with a reporter group is of great interest because it can be used not only to improve the existing oligonucleotide properties but also to give it entirely new properties.^[56]

Messaoudi and co-workers demonstrated recently that their previously reported methodology on coupling of thiosugars is compatible with DNA bearing a 5-iodo 2'-deoxyuridine (5-IdU) moiety and is applicable to a wide variety of oligonucleotides (i.e. with different lengths and containing purines and pyrimidines nucleobases) and carbohydrate derivatives.^[57] The authors have demonstrated the prevalence of the methodology in the post modifications of oligonucleotides (ODNs), which may add significant contribution to the chemical biology.

First, the authors have adapted their protocol on the linkage of thiosugars with 5-iodouridine in the presence of 10 mol% of PdG3-XantPhos at 60 °C. They have demonstrated that structurally diverse β - mono-, di- and poly-thiosugar derivatives (Scheme 14) could be coupled with 5-iodo 2'-deoxyuridine (5-IdU) in good yields and without epimerisation at anomeric position ($J_{1,2} = 9$ Hz). *O*-acetylated 1-thio- β -D-glucopyranose, *N*-Ac-1-thio- β -D-glucopyranose, 1-thio- β -D-galactopyranose and 1-thio- β -D-mannopyranose were efficiently used in this protocol to give corresponding thioglycoconjugates. Once again, the reaction is not limited to monosaccharides, but can be applied to more complex di- and trisaccharide derivatives such as *O*-acetylated 1-thio- β -D-cellobiose and 1-thio- β -D-maltotriose (Scheme 17). It is noteworthy that fully deprotected sugars can

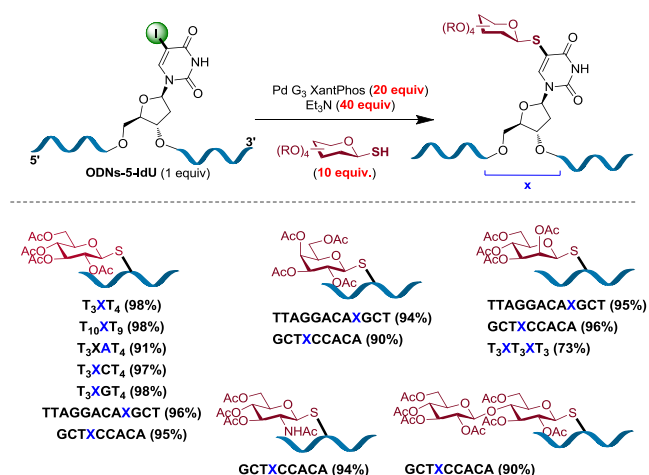
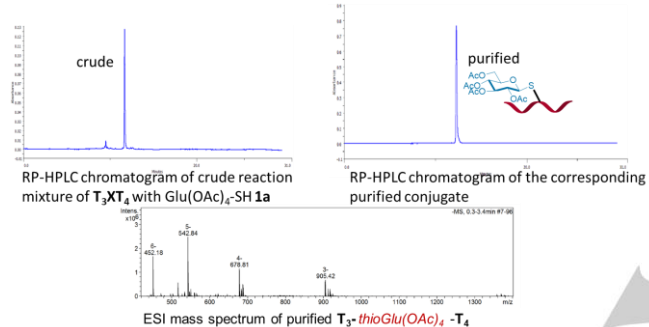
be also used: as an example, the reaction of 5-IdU with 1-thio- β -D-glucose afforded the desired product in satisfactory 46% yield. Importantly, the slow addition of thiosugar (for ~ 1 h) proved efficient and limited the formation of thiosugar dimer by-product.



Scheme 17. Selected examples on the Palladium-catalyzed thioglycoconjugation of 5-iodouridine.

The previous results with nucleoside 5-IdU encouraged the authors to explore the coupling of iodine containing oligonucleotides with several thiosugars (Scheme 18). These optimized conditions were applied successfully for the conjugation of oligonucleotides **T₃XAT₄**, **T₃XCT₄** and **T₃XGT₄** demonstrating that Pd catalyst does not affect the integrity of A, C and G nucleobases. The coupling reaction has been performed with hetero-oligonucleotides **TTAGGACAXGCT** and **GCTXCACA** along with the longer **T₁₀XT₉** oligonucleotide and appeared to be very efficient to furnish the corresponding conjugates (Scheme 15). Incorporation of two reporter moieties was achieved by using bis-modified oligonucleotide **T₃XT₃XT₃**. Monitoring of reactions was done by RP-HPLC. It is noteworthy that the use of unprotected thiosugars for the coupling reaction was discarded because of some purification issues.

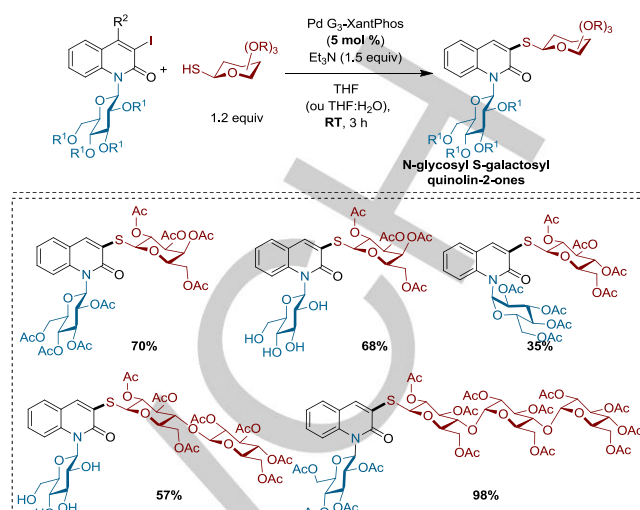
During this study, it was observed that the quantity of G3-XantPhos reagent is important as the addition of almost 20 equivalents was required to achieve a complete conversion of the starting material. Similarly, the quantity of Et₃N must be adjusted to 40 equivalents; Diminishing these quantities led to an incomplete conversion of the starting oligonucleotide. The effect of the temperature was also investigated and showed a slight impact on the coupling reaction. Nevertheless the temperature was kept at 60°C since at room temperature reactions showed some undesired products formation.

(B) Example of HPLC profile for the coupling reaction: T₃XT₄ with Glu(OAc)₄-SH 1a

Scheme 18. Pd-catalyzed thioglycoconjugation of 5-iodo-2'-deoxyuridine containing oligonucleotides. (B) Example of HPLC profile for the coupling reaction: RP-HPLC chromatogram of crude reaction mixture (on left) of T₃XT₄ with Glu(OAc)₄-SH 1a and corresponding purified conjugate (on right).

The mild reaction conditions allow direct access to a range of glycoconjugates that are otherwise not easily accessible. However some issues have to be revisited such as the high catalytic charge of palladium and the relative high temperature that might not be compatible with ODNs chains.

Another application was illustrated by the authors recently in the synthesis of interesting heteroaryl bis-glycosides based on *N*-glycosyl quinolin-2-ones^[58] in which a glycosyl unit is attached to a quinolin-2-one core; one of the most important heterocycle in medicinal chemistry. The synthesis of these *N*-β-glycosyl *S*-β-galactosyl quinolin-2-ones has been achieved sequentially, after building the 3-iodo *N*-glycosyl quinoline, followed by the Pd-catalyzed cross coupling with various thiosugars. The screening of condition gave the best results with 5 mol% of PdG3 in a mixture of THF:water at room temperature. A set of examples has been delivered including challenging trisaccharide 1-thio-β-D-maltotriose (Scheme 19).



Scheme 19. Selected examples on the Palladium-catalyzed synthesis of *N*-β-glycosyl *S*-β-galactosyl quinolin-2-ones

In addition to the described above, recently Messaoudi and coworkers used for the first time the PdG3 XantPhos in a tandem process for the synthesis of unsymmetrical biaryls thioglycosides^[59]

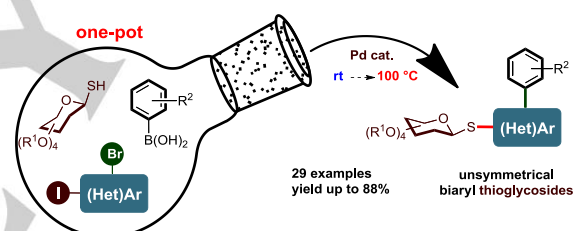
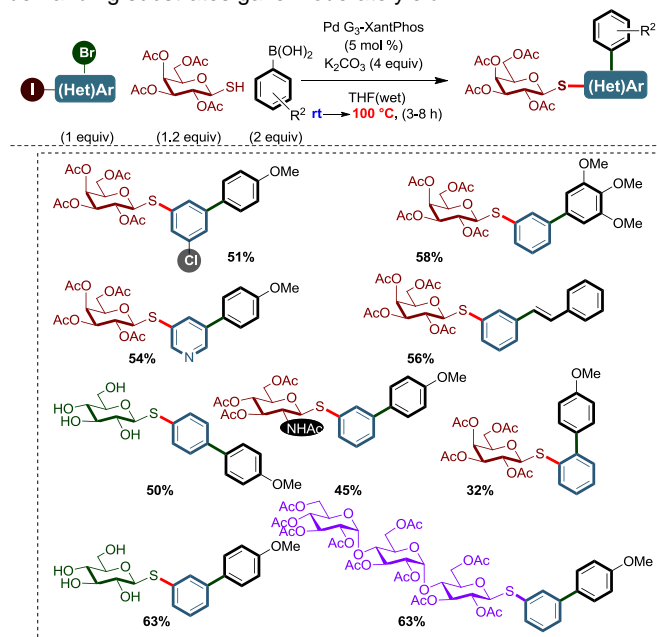


Figure 6. First use of the PdG3 XantPhos in a tandem process for the synthesis of unsymmetrical biaryls thioglycosides

The procedure consists of using a single Pd-catalyst which promoted under the same catalytic cycle, the catalysis of two individual steps: (i) the first is a selective coupling reaction between β-thiosugars and dihalogenated arenes (iodo-bromoarenes); (ii) the second is based on C–C bond formation between the monohalogenated thioglycoside intermediate and diverse aryl boronic acids (Figure 6). The selective procedure started with oxidative addition of a Pd(0) species to a C–I bond followed by insertion of a thiol function followed by a subsequent Suzuki–Miyaura coupling reaction at the remaining C–Br bond. In the presence of 5 mol% of palladium, 4 equivalents of K₂CO₃, the (MCR) was successful either at room temperature for the first C–S bond formation or at high temperature for both steps. Authors conducted their study on a large scope of substrates and examined high diversity of functional groups. First, with respect to the thiol sugars, the reaction worked with mon-, di- and trisaccharide either protected and unprotected ones (Scheme 20). The reaction showed a high tolerance to functional group on the hetero(aryl) boronic acids partners as well. Interestingly, iodo-bromoarenes and heteroarenes could be

used as well, whereas challenging coupling with sterically demanding substrates gave moderate yield.



Scheme 20. One-Pot Thiosugars Coupling With Boronic Acid Iodobromoarenes

This procedure showed for the first use PdG3-XantPhos in a multicomponent process under mild conditions and offered the simplest and shortest way to biaryl thio-glycosides that could be further explored for range of medicinal chemistry screening programs.

3. Conclusion

This Focus Review highlighted metal-catalyzed functionalization of 1-thiosugars for the synthesis of thioglycosides. Several metals such as copper, nickel and palladium have been employed for the construction of functionalized thioglycosides through cross-coupling reactions. All these previous reports mentioned above showed that allegedly functionalization of thiosugars by using the Pd-G3 XantPhos precatalyst is expected to be the first and one of the most robust methods ever witnessed in the thioglycoconjugation chemistry. The expectation of the outcomes were very high and authors showed success in highly challenging couplings patterns (e.g. heterocycles, alkenyles, alkynyles and oligonucleotides) using palladium precatalyst albeit commercially expensive but its synthesis in the laboratory is handful and easy.

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Keywords: 1-thiosugars • thioglycosides • Palladium catalysis • Copper • Nickel

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REVIEW

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