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Carbohydrates

Stereoretentive Palladium-Catalyzed Arylation, Alkenylation, and Alkynylation of 1-Thiosugars and Thiols Using Aminobiphenyl Palladacycle Precatalyst at Room Temperature

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Abstract: A general and efficient protocol for the palladium-catalyzed functionalization of mono- and polyglycosyl thiols by using the palladacycle precatalyst G3-XantPhos was developed. The C–S bond-forming reaction was achieved rapidly at room temperature with various functionalized (hetero)aryl-, alkenyl-, and alkynyl halides. The functional group tolerance on the electrophilic partner is typically high and anomer selectivities of thioglycosides are high in all cases studied. New sulfur nucleophiles such as thiophenols, alkythiols, and thioaminoacids (cysteine) were also successfully coupled to lead to the most general and practical method yet reported for the functionalization of thiols.

The palladium-catalyzed Buchwald–Hartwig–Migita cross-coupling reaction has become a valuable tool in industrial and academic research for the synthesis of natural products and novel materials including a number of pharmaceuticals currently on the market.[1] Breakthroughs in this coupling have typically been driven by the implementation of a new class of ligands,[2] which are able to promote reactions with a diverse array of substrates including nitrogen-, sulfur-, and oxygen-containing nucleophiles. Unfortunately, this process is yet to approach generality and the goal of being able to couple any nucleophile with any aryl or heteroaryl halide is far from accomplished. One of the most important tasks in this area of organometallic chemistry is to discover mild and general methods for easy introduction of unprotected polyfunctionalized compounds into molecules with high selectivity. Among all polyfunctional compounds in organic chemistry, saccharides play diverse pivotal roles in biological systems, which make them attractive as subjects for chemical and biological research. Most of them found in nature or used in therapeutics, exist as glycoconjugates or heterosides in which the sugars are attached to aglycons through N–, S–, O–, or C–glycosidic bonds. When considering the importance of glycosides, particularly thioglycosides[3] in numerous fields of science, the development of new methods to functionalize them efficiently under simple and ecofriendly conditions is highly desirable. In this context, we are particularly interested in the direct palladium-catalyzed coupling of unprotected glycosyl thiols under mild and operationally simple conditions. Catalytic reactions of this nature would be of great interest for the construction of molecules that may be sensitive to the harsh conditions that can often be required for thioglycosidic[4] bond-forming reactions.[5] In 2013, our group reported the coupling of protected glycosyl thiols with aryl halides in the presence of $Pd(OAc)_2$/XantPhos as the catalytic system, NEt_3 as the base in dioxane at 100 °C (Scheme 1, path a).[6] While this method represents a notable advance, a relatively high temperature (> 75 °C) is usually required. To overcome this issue, we reported recently the first method for the arylation, alkenylation, and alkynylation of unprotected glycosyl thiols at room temperature under nickel catalysis (Scheme 1, path b).[7] This reaction was functional-group tolerant and proceeded stereoselectively in good to excellent yields. Nevertheless, we are mindful that high nickel loading (30 mol%) and excess of (heteroaryl)halide (2 equiv) are required for efficient coupling. Moreover, the toxicity of nickel salts[8] may be an inherent drawback to their use in large-scale industrial processes. Recently, Waser et al.[9] disclosed an elegant method for the alkynylation of glycosyl thiols also at room temperature. Although the procedure is efficient, it is, however, limited only to the alkynylation process and requires the preparation of ethynyl-1,2-benziodoxol-3(1*H*)one (EBX) substrates through multistep reaction sequences (Scheme 1, path c). Despite all these advances, a general and simple method for the functionalization of glycosyl thiols as well as other functionalized thiols at room temperature is still desired.

In light of the recent success using aminobiphenyl palladacycle precatalysts in C–N and C–O bond-forming reactions,[10] combined with our success using $Pd(OAc)_2$/XantPhos catalytic system in the coupling of glycosyl thiols with (hetero)aryl halides at 100 °C,[6] we decided to explore the ability of the G3-XantPhos precatalyst[11] (Scheme 2) to promote the construction of a C–S bond under mild conditions. Herein, we report for the first time, a fast, efficient and stereoretentive coupling

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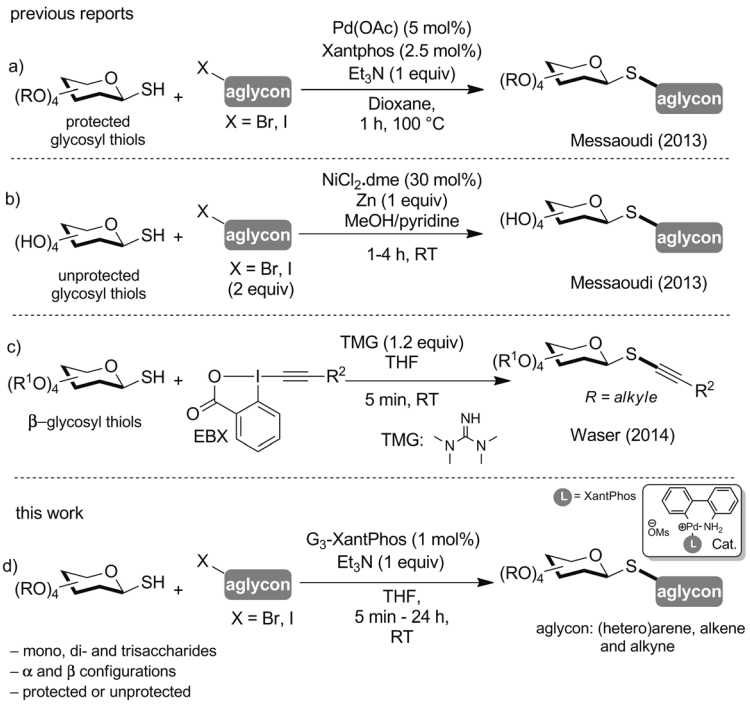


Scheme 1. Coupling of glycosyl thiols with aryl halides.

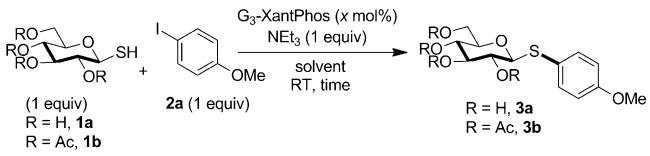
of various unprotected or protected glycosyl thiols (mono-, di-, or polythioglycosides) with aglycone halides at room temperature (Scheme 1, path d). Key to the success was the use of the Pd G-3 precatalyst at low catalyst loading (1 mol%), which is able to generate quickly under mild conditions the catalytically active 12-electron XantPhos-Pd^0 species (Scheme 2).

Our initial experiments focused on identifying optimal conditions for the coupling of unprotected 1-thio-β-D-glucopyranose **1a** with 4-iodoanisole **2a** at room temperature. Representative results from this study are summarized in Table 1. It was found that the reaction of **1a** (1 equiv) with **2a** (1 equiv) for 15 min in dioxane at room temperature, in the presence of G3-XantPhos[11] (5 mol%), furnished the expected β-arylthioglycoside **3a** in a quantitative yield (Table 1, entry 1). More interestingly, 1 mol% of precatalyst was sufficient to catalyze efficiently the reaction affording **3a** in a 98% yield (entry 2), while, incomplete conversion of the substrate was seen when the loading of precatalyst was decreased to 0.1 mol% (entry 3). A brief survey of solvents was therefore undertaken in which etheral solvents (1,4-dioxane and THF) were found to be the most effective (entries 2 and 6). The use of other solvents, such as methanol, acetonitrile, or water induced a lowering of the conversion rate (entries 4, 5 and 7). In summary, the best conditions were found to require 1 mol% of G3-precatalyst, 1 equivalent of Et_3N in dioxane or THF at room temperature for 1 h, furnishing **3a** in a 98% yield (entries 2 and 6). Surprisingly, when the coupling of acetylated β-thioglucose **1b** with **2a** was performed under our optimized conditions, the desired product **3b** was obtained quantitatively within only 5 min (entry 8) instead of 1 h required for the coupling of **1a** (entry 6). These results indicated that polyhydroxylated functions in **1a** may coordinate to the Pd^0 catalyst, thus decreasing its catalytic activity in the coupling of **1a**, and leading to a longer reaction time.

With a viable coupling procedure in hand, attention was turned to the generality of the process by studying the coupling of various aglycone halides with structurally diverse mono-, di-, and tri- glycosyl thiol derivatives. Remarkably, this glycosidic C–S coupling reaction appeared to be quite general with respect to the different partners and tolerate various functional groups (e.g., –Br, –OTs, –OH, –CN, $-CO_2Me$, $-CONR_2$, –C(Me)=NNHTs) (Schemes 3 and 4).

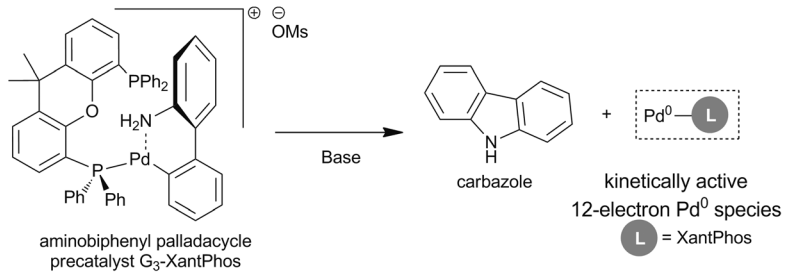
As depicted in Scheme 3, 1-thio-β-D-glucopyranose **1a** was readily coupled with aryl iodides containing *para* and *meta* electron-donating or -withdrawing

Table 1. Optimization of the coupling of **1a**,**b** with **2a**.

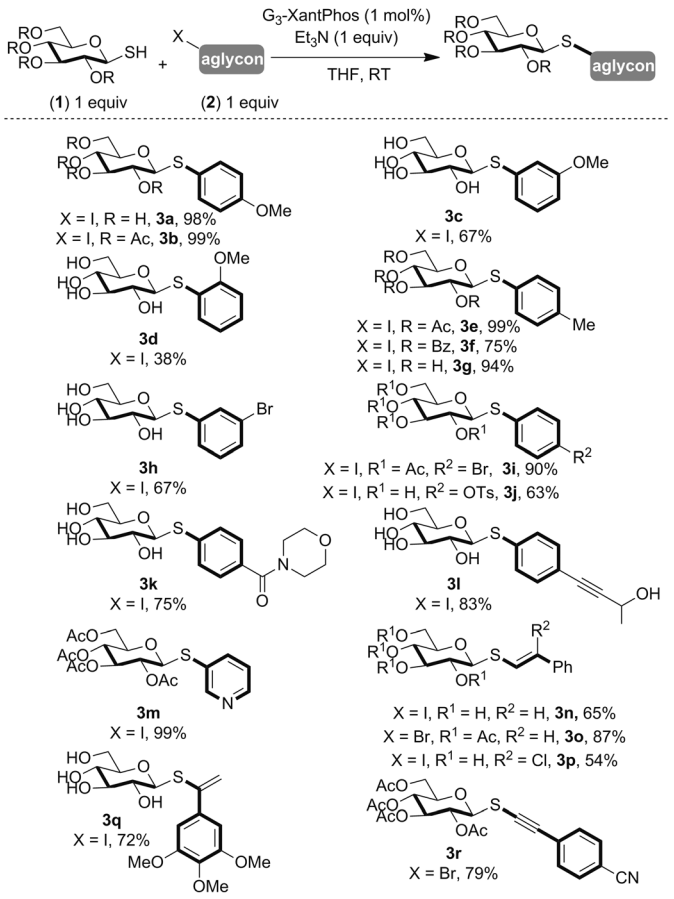


Entry	R	G$_3$-XantPhos (*x* mol%)	Solvent	*t* [min]	Conv. [%][b]	Yield [%][c]
1	H	5	dioxane	15	100	98
2	H	1	dioxane	60	100	98
3	H	0.1	dioxane	60	30	–
4	H	1	MeOH	60	10	–
5	H	1	CH_3CN	60	20	–
6	H	1	THF	60	100	98
7	H	1	H_2O	60	30	–
8	Ac	1	THF	5	100	99

[a] Reaction conditions: NEt_3 (1 mmol) was added to a mixture of **1** (1 mmol), **2a** (1 mmol), and G3-XantPhos (1 mol%) in solvent (0.25 M) and the mixture was stirred at 25 °C. [b] Conversion was determined by ^{1}H NMR spectroscopy on the crude reaction mixture and is based on the chemical shift of protons signals (ppm) at the aromatic moiety. [c] Yield of isolated products **3**.



Scheme 2. Highly active G3-XantPhos precatalyst and generation of kinetically active 12-electron Pd^0 species.



Scheme 3. G3-Xantphos precatalyst-catalyzed coupling of 1-thio-β-D-glucopyranose with aglycone halides. Reaction conditions: Et_3N (1 equiv) was added to a solution of **1** (1 mmol), **2** (1 mmol), and G3-XantPhos (1 mol%) in THF (0.25 M) and the mixture was stirred at RT.

substituents to give thioglycosylated products **3a**, **3c**, and **3g**–**l** in good to excellent yields with complete β-stereoretentive selectivity. Of note, the sterically demanding *ortho* substitution pattern influences the outcome of the coupling reaction of **1a**, furnishing the expected coupling product **3d** but with a modest 38% yield. Importantly, there is no significant impact of protecting groups on the reactivity of the thiosugar derivatives since acetate or benzoyl-protected carbohydrate **1b** and **1c** reacts similarly than unprotected derivative **1a**, furnishing the coupling product **3b**, **3e**, and **3f** in 99, 99, and 75% yields, respectively. Of note that compounds **3h,i** revealed an excellent chemical selectivity of the C–I bond over the C–Br bond which could enjoy further metal-catalyzed functionalization processes. In hope of further pushing the limit of this Pd-catalyzed S-arylation reaction, we examined the coupling of 1-thio-β-D-glucopyranose **1a**,**b** with alkenyl- and alkynyl halides as aglycone partners. Delightfully, when *E*-β-styryl bromides and α-styryl iodides were employed, the coupling with **1a**,**b** afforded stereoselectively the desired alkenylthioglycoside derivatives **3n**–**q** in excellent yields. Moreover, alkynylated thioglycoside product **3r** was obtained diastereoselectively in a 79% yield when 4-(bromoethynyl)benzonitrile was used as the aglycone coupling partner.

Application of this procedure to the multigram-scale was also investigated. In this context, the development of a practical and scalable method in organic synthesis is essential for plant-scale manufacturing. Here we showed that our procedure can be achieved safely by coupling **1b** with 4-iodotoluene in a multigram-scale reactor (50 mmol) by using 1 mol% of the precatalyst at room temperature within 10 min. Compound **3e**[12] was isolated in a nearly quantitative yield as a pure product after only filtration through Celite without any additional purification (see TLC in Figure 1and crude ^{1}H NMR spectra in the Supporting Information). This result clearly demonstrates that this procedure can be used in a scale-up industrial process.

Next, we turned our attention to the generality of the method with respect to mono-, di-, and triglycosyl thiols. As depicted in Scheme 4, coupling reactions proceeded cleanly in high yields without any side reaction, such as anomerization of the resulting arylthioglycosides. The reaction is general with respect to the sugar configuration as *N*-acetyl-1-thio-β-D-aminoglucopyranose, 1-thio-β-D-galactopyranose, and 1-thio-β-D-mannopyranose give the corresponding products **4a**–**g** in good to excellent yields. Of note is that there were little differences in reactivity between α- and β-anomers as a 94% yield of **3f** was obtained from the coupling of 4-iodotoluene with 1-thio-β-D-glucopyranose compared to 74% yield of **4i** obtained from the coupling of 1-thio-α-D-glucopyranose. Additionally, the coupling procedure is not only limited to unfunctionalized glycosyl thiols but also works successfully with challenging 6-bromo-1-thio-β-D-galactopyranose,[13] furnishing **4h** in a good 57% yield. Compound **4h** in which the C(sp^3)–Br bond survives, is an ideal entry for post-functionalization through azidation[14] and CuAAC bioconjugation[15] reactions. Finally, the efficiency of this C–S bond forming reaction was well-demonstrated by coupling more complex unprotected di- and trisaccharide derivatives. Thus, 1-thio-β-D-cellobiose as well as 1-thio-β-

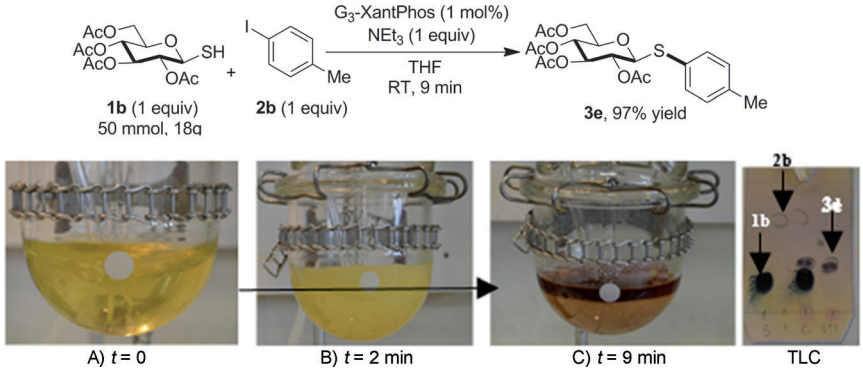
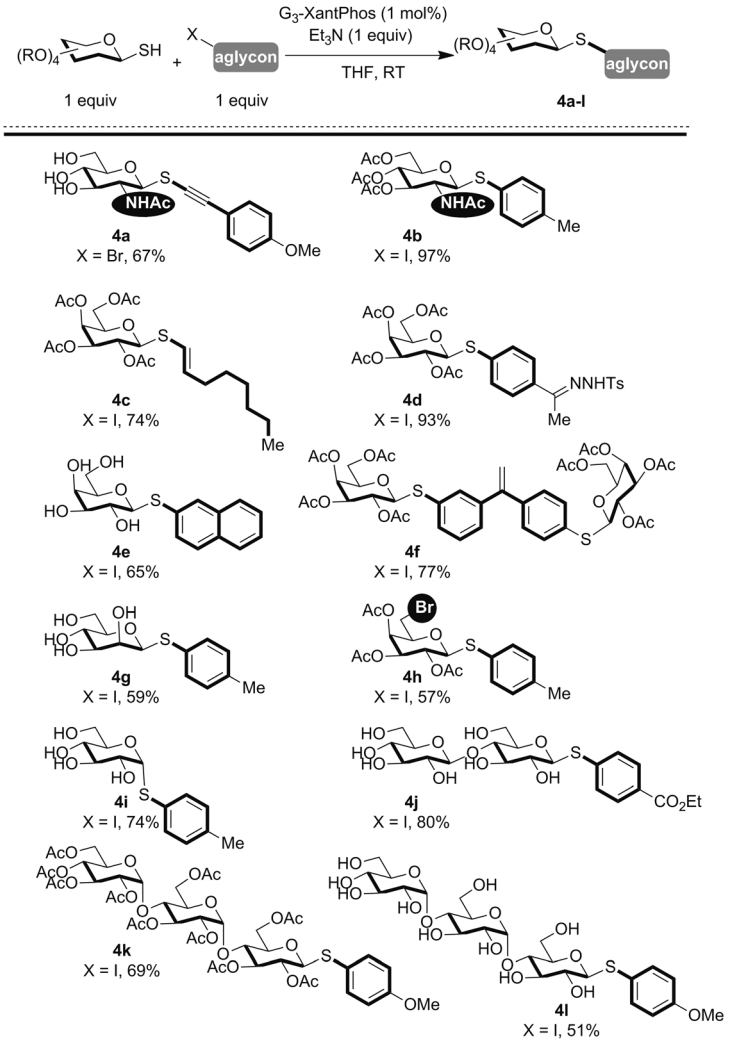
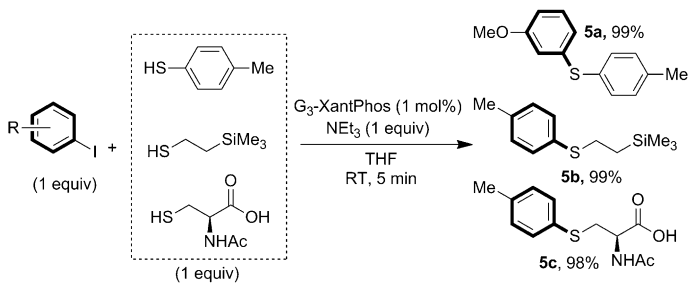


Figure 1. Multigram-scale coupling of 1-thio-β-D-glucopyranose **1b** with 4-iodotoluene **2b** at RT in a reactor.



Scheme 4. G3-Xantphos precatalyst-catalyzed coupling of mono-, di-, and polythiosaccharides with aglycone halides. Reaction conditions: Et_3N (1 equiv) was added to a solution of thiosaccharides (1 mmol), **2** (1 mmol), and G3-XantPhos (1 mol%) in THF (0.25 M) and the mixture was stirred at RT.



Scheme 5. Scope of the fast coupling of other aryl/alkylthiols with iodoarenes at RT.

D-maltotriose were readily arylated at room temperature to give the corresponding glycoconjugates **4j**–**l** in good yields (51–80%). Of note is that the stereochemistry of the 1-4′*O*-glycosidic bond in the β-diholoside **4j** or in β-triholosides **4k**,**l** remained intact.

After having demonstrated excellent reactivity of G3-XantPhos precatalyst with thiosaccharides, we then examined if the C–S bond-forming reaction could be extended to other aryl and alkylthiol derivatives. In fact, the coupling proceeds well with *p*-thiocresol within 5 min at room temperature, giving the coupled product **5a** in a 99% yield (Scheme 5). We were also pleased to find that nonaromatic thiols, in which the reductive elimination step have been shown to be significantly slower than thiophenols,[16] are good partners for this coupling procedure. Thus, 2-(trimethylsilyl)ethane-1-thiol could be coupled efficiently to produce **5b** in an excellent 99% yield. Encouraged by these results, we set out to examine the C–S bond-forming reaction using cysteine as a coupling partner. To our knowledge, this amino acid has never been used as a coupling partner in Buchwald-Hartwig S-arylation reaction. Thus, reacting *N*-acetyl cysteine with 4-iodotoluene under our optimized protocol furnished the desired coupling product **5c** in a 98% yield.

In conclusion, we have demonstrated that the palladacycle precatalyst G3-XantPhos displays a high catalytic activity for the coupling of an array of glycosyl thiols as well as aryl and alkyl thiol derivatives including cysteine. The room temperature at which this coupling is conducted provides access to a range of glycoconjugates that are otherwise not easily accessible. The reaction is highly diastereoselective, functional-group tolerant, step-economical, and proceeds stereoselectively in good to excellent yields. The value of this transformation has been highlighted by the synthesis of *p*-tolyl 1-thio-β-D-glucopyranoside acetate **3d** in a multigram scale. We expect this simple and general protocol to be of broad utility for the synthesis and development of new medicinal agents.

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Keywords: arylthioglycosides · bond-forming reactions · thiols · palladacycles · unprotected thiosugars

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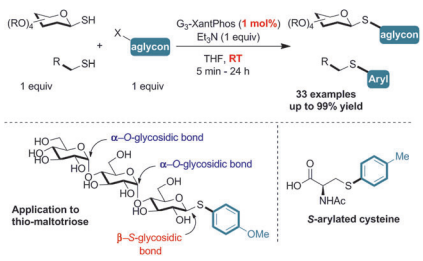
Stereoretentive Palladium-Catalyzed Arylation, Alkenylation, and Alkynylation of 1-Thiosugars and Thiols Using Aminobiphenyl Palladacycle Precatalyst at Room Temperature



Sweet and efficient: A general and efficient protocol for the palladium-catalyzed functionalization of mono- and polyglycosyl thiols by using the palladacycle precatalyst G3-XantPhos was developed. The C–S bond-forming reaction was achieved rapidly at room temperature with various functionalized (hetero)aryl-, alkenyl-, and alkynyl halides (see scheme).