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Room-Temperature Pd-Catalyzed Synthesis of 1-(Hetero)aryl Selenoglycosides

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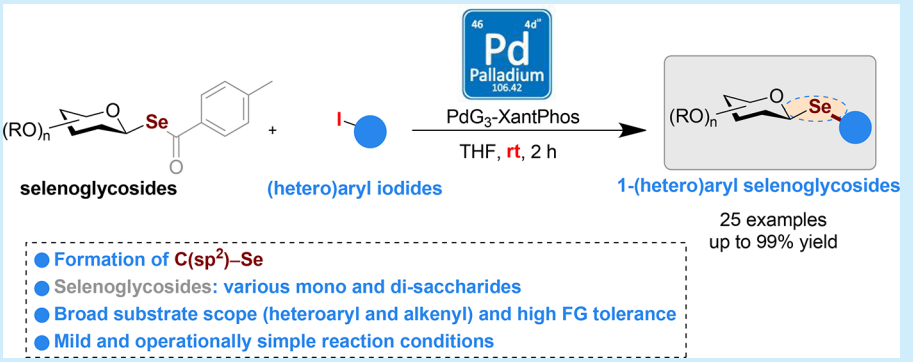

ABSTRACT: A general protocol for functionalization of an anomeric selonate anion at room temperature has been reported. By using the PdG3 XantPhos catalyst, the cross-coupling between the *in situ*-generated glycosyl selenolate and a broad range of (hetero)aryl and alkenyl iodides furnished a series of functionalized selenoglycosides in excellent yields with perfect control of the anomeric configuration.

1-Selenoglycosides constitute a privileged class of glycosides and are considered as one of the promising families of glycomimetics with some significantly enhanced *in vivo* stabilities. Although they have been less explored in carbohydrate chemistry, over the past several years they have attracted an increasing amount of attention due to their versatile biologically significant applications,[1] including ligand-based therapeutics to carbohydrate-binding proteins,[2] X-ray crystallographic studies of carbohydrate−protein complexes,[3] and ^{77}Se NMR spectroscopy handles for carbohydrate−protein interactions [compound **1** (Figure 1)].[4] Since the discovery of the first selenoglycoside (**2**) (Figure 1) in rat and human urine as a hepatic Se metabolite,[5] the design and synthesis of bioactive seleglycosides have attracted more attention within the chemistry community. Selected biologically active 1-selenoglycosides are represented in Figure 1, including Se-KRN7000 (**3**)[6] as an analogue of the potent immunostimulant α-GalCer (KRN7000), the anti-invasive and antimetastatic organoselenium glycoconjugate (**4**)[7] that targets multiple kinases in preclinical models, the di-β-D-galactopyranosyl diselenide (**5**)[8] with antitumoral activity and as a ligand for lectin, and the selenoglycoside AcSG (**6**)[9] as the activator of phosphatases 1 and 2A, two proteins involved in cancers. From the point of view of organic synthesis, selenoglycosides have been investigated as unique glycosyl donors in glycosylation reactions.[10]

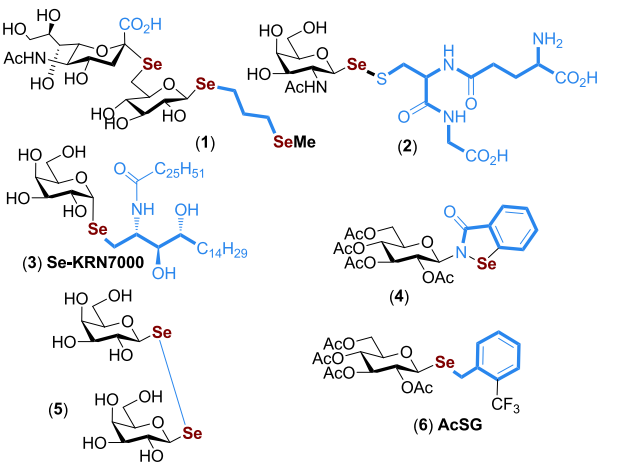

Figure 1. Examples of biologically active selenoglycosides.

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The usual approach employed for the synthesis of selenoglycosides relies on the use of selenium sources in the nucleophilic substitution of 1-halosugars[11] (Figure 2A) or a

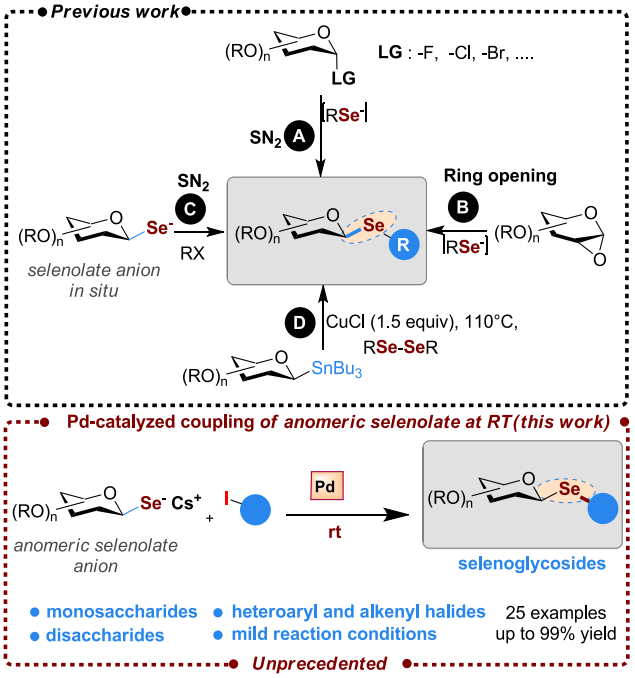


Figure 2. Strategies for the synthesis of selenoglycosides.

nucleophilic opening of the Danishefsky 1,2-anhydro sugars (Figure 2B).[12] Azidophenylselenation of glycals[13] was also an efficient method for preparing selenoglycosides bearing an azido group at position C2. However, selenium nucleophiles such as arylselenols are not commercially available and must be prepared most often from potassium selenocyanate (KSeCN) and aryliodonium salts followed by the reduction of the Se−CN bond in the presence of a reducing agent such as $NaBH_4$.[11e] Another major drawback of this approach is the use of toxic, unstable, and malodorous arylselenols and diselenides.

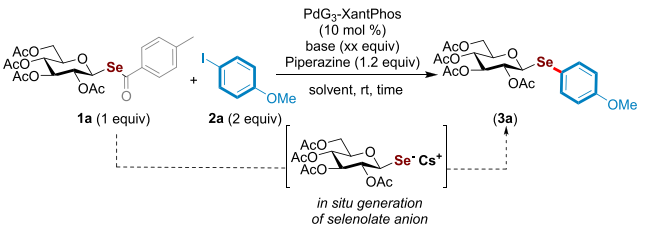
Ando, Ishihira, and co-workers[14] developed an elegant method for preparing various alkyl Se glycosides by *in situ* generation of an anomeric selenolate anion from *β*-*p*-methylbenzoylselenoglycoside, which reacts with alkyl halides (Cl, Br, and I) to yield selenoglycosides with retention of the anomeric stereochemistry (Figure 2C). However, this method is limited to alkyl halides. Only one example for the synthesis of aryl selenoglycoside by this approach has been reported using the highly activated 4-nitro fluorobenzene substrate in a nucleophilic aromatic substitution reaction (SN_{Ar}).

Recently, Walczak and co-workers[1a] described an original approach (path D) for the preparation of selenoglycosides based on the coupling of glycosyl stannane with symmetrical diselenide in the presence of 1.5 equiv of CuCl. This method is clearly attractive. However, it necessitates a high reaction temperature (110 °C) and requires the use of the toxic alkyltin species in a multistep approach to prepare the starting 1-stanylated sugars.

To fully harness the potential of this class of carbohydrates, there is a strong impetus to develop mild and general reactions for the synthesis of complex selenoglycosides. As part of our interest in exploring the reactivity of sugars under transition metal catalysis,[15] combined with the lack of a general method for Se glycosides, we became interested in developing an efficient and simple Pd-catalyzed cross-coupling protocol for the preparation of (hetero)aryl selenoglycosides that may occur under mild reaction conditions. Catalytic methods generally avoid the use of harsh reaction conditions and maintain compatibility with most organic functions. However, the use of selenium nucleophilic partners in Pd(0) cross-couplings is highly challenging as they are well-known to be a poison of the catalyst through the formation of off-cycle complexes.[16] Herein, we report a direct and programmable synthesis of selenoglycosides via PdG3 XantPhos-catalyzed coupling of an *in situ*-generated anomeric selenolate anion with various (hetero)aryl and alkenyl iodides at room temperature.

In the first part of this study, the coupling of tetra-O-acetylated *β*-*p*-methylbenzoylselenoglycoside **1a** (1 equiv) with *p*-iodoanisole **2a** (2 equiv) was used as a model study, and various reaction conditions were examined. Representative results are summarized in Table 1, and the full optimization is

Table 1. Optimization of the Coupling Reaction of 1a with 2a[a]



entry	base	solvent	time (h)	3a (%)[b]
1	Cs_2CO_3	THF	12	95
2	Cs_2CO_3	THF	12	81[c]
3	CsF	THF	2	83
4	NaOAc	THF	2	65
5	Cs_2CO_3	dioxane	2	95
6	Cs_2CO_3	DCE	2	83
7	Cs_2CO_3	DMF	2	89
8	Cs_2CO_3	THF	1	80
9	Cs_2CO_3	THF	2	95

[a]A sealable tube was charged with *β*-*p*-methylbenzoylselenoglycoside **1a** (1 equiv, 0.1 mmol), iodoanisole **2a** (2 equiv), the PdG3 XantPhos precatalyst (10 mol %), piperazine (1.2 equiv), and a base (3 equiv) in a dry and degassed solvent (0.1 M). [b]Yield of the isolated product. [c]With 5 mol % PdG3 XantPhos.

reported in the Supporting Information. The coupling of **1a** with **2a** was first investigated under our previously reported protocol for the coupling of thiosugars[17] using the PdG3 XantPhos precatalyst (10 mol %). Cs_2CO_3 (3 equiv) and piperazine (1.2 equiv) were added, and the reaction was performed in THF at room temperature (Table 1, entry 1). By the action of piperazine and Cs_2CO_3, the *β*-selenolate anomer anion was readily generated *in situ* (according to the methods of Ando and Ishihira[14]) and fully converted under our conditions to *β*-selenoglycoside **3a** in 95% yield as a single *β*-anomer ($J_{1,2}$ = 9 Hz). Decreasing the catalyst loading from 10 to 5 mol % led to **3a** in a slightly lower yield (81%, entry 2). With these encouraging results, we continued the optimization of the reaction conditions with respect to other parameters (base, solvent, reaction time, and amount of reagents). We confirmed that Cs_2CO_3 is the base of choice because the use of CsF or NaOAc produced the desired selenoglycoside **3a** in

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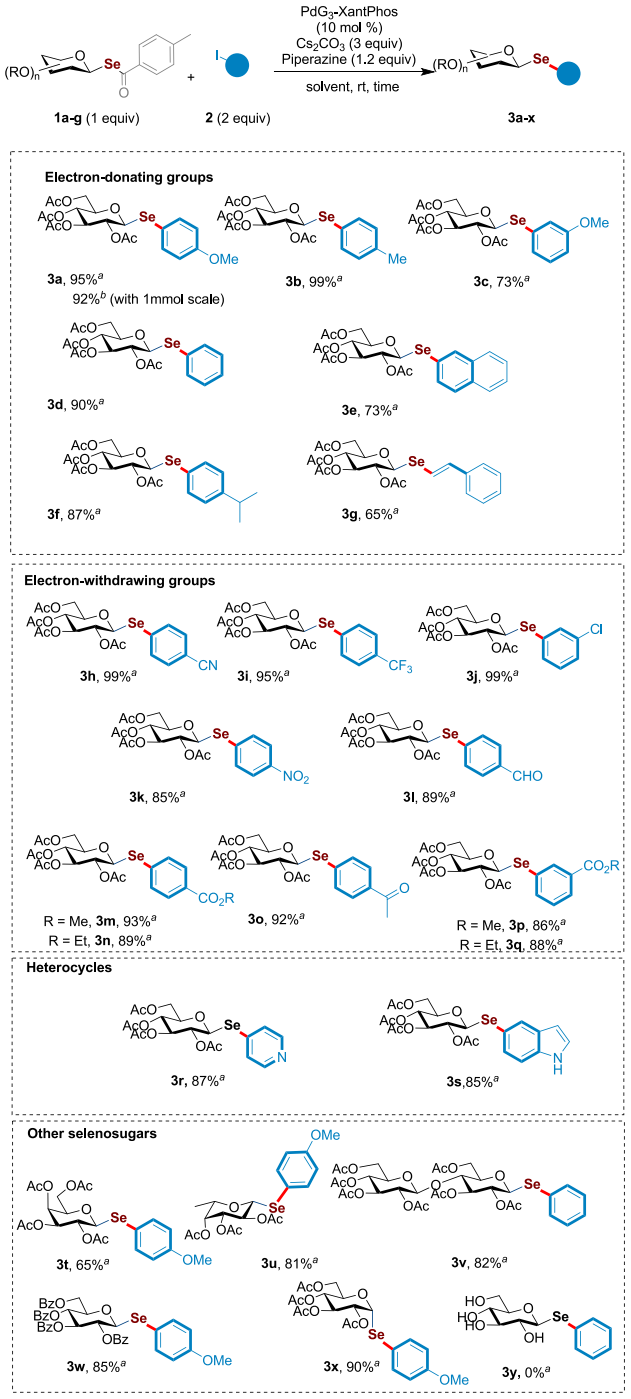
83% or 65% yield, respectively. Moreover, performing the cross-coupling in other polar solvents such as dioxane, DCE and DMF produced the desired product **3a** in yields ranging from 83% to 95% (entries 5−7, respectively). Finally, performing the reaction for 1 h furnished **3a** in only 80% yield (entry 8), while a 95% yield was obtained when the reaction time was adjusted to 2 h (entry 9). A control experiment showed that the PdG3 XantPhos precatalyst was essential for this coupling because no reaction occurred when $Pd(OAc)_2$ (10 mol %) and XantPhos (10 mol %) were used (see the Supporting Information).

With these results in hand, we investigated the scope of this coupling by varying the nature of the aryl iodide partner **2** and the *p*-methylbenzoylselenyl glycosides **1a−g** (Scheme 1). Pleasantly, this coupling proceeded cleanly in excellent yields. Various electron-rich and electron-deficient aryl iodides having *para* and *meta* substituents effectively underwent reaction with *β*-*p*-methylbenzoylselenoglycoside **1a** in yields of ≤99% (products **3a−q**). Interestingly, this coupling tolerates various reactive functional groups such as isopropyl (**3f**), nitrile (**3h**), halogens (**3j**), nitro (**3k**), aldehyde (**3l**), ketone (**3o**), and ester (**3m**, **3n**, **3p**, and **3q**). Moreover, the coupling is not limited to aryl halides; it also works with halogenated alkenes such as (*E*)-*β*-styryl iodide (compound **3g**). In addition, the reaction of **1a** with heteroaryl halides such as 4-iodopyridine and 5-iodoindole has been performed successfully, furnishing **3r** and **3s** in 87% and 85% yields, respectively. *ortho*-substituted aryl iodides such as *o*-methoxyl iodobenzene, *o*-cyano iodobenzene, and *o*-CF_3 iodobenzene were not effective coupling partners probably due to the hindrance effect, implying that the oxidative addition of aryl iodides to a palladacycle is not facile. Finally, this method tolerates other selenosugars such selenogalactose, selenofucose, and seleno-cellobiose or OBz-protected selenoglucose that were successfully coupled with **2a** or **2d** to give *β*-Se-glycosides **3t−v** in good yields. Besides *p*-methylbenzoylselenyl *β*-glycosides, *α*-glycoside is an effective substrate for this methodology giving the desired Se glycosides **3x** in excellent yield with exclusive *α* selectivity. It is worth noting that attempts to react the unprotected selenoglycoside failed: **3y** was never detected, and only the degradation of starting materials was observed.

In the next part of this study, we focused our attention on demonstrating whether our cross-coupling could be employed with functionalized aryl iodides bearing a secondary amino group (Figure 3). We may assume that these bis-electrophilic−nucleophilic partners could be involved in two concomitant reactions: at first by a nucleophilic action, a secondary amine such as piperazine traps the *p*-methylbenzoyl group of selenoglycoside **1a** and generates the anomeric selenolate anion. Then, this later will react with the electrophilic part (C−I bond) via the Pd-catalzyed Se−C(sp^2) bond-forming reaction. In this way, all of the atoms of the reactants will be incorporated into the final desired products, resulting in high atom economy and an environmental process that avoids the generation of waste.

As shown in Scheme 2, the proof of concept of this green process was demonstrated by coupling of bis-electrophilic−nucleophilic partners **5a−c** with *p*-methylbenzoylselenoglycoside **1a** in the presence of PdG3 XantPhos (10 mol %) and Cs_2CO_3 (3 equiv) in THF at room temperature. Under these conditions, the syntheses of phenylpiperazine-functionalized selenoglycosides **6a** and **6c** were achieved with 90% and 82% yields, respectively. This finding is of great interest because

Scheme 1. Scope of Coupling of *β*-*p*-Methylbenzoylselenoglycoside 1a with Halo(hetero)arenes and Alkenyl Halides 2[b]



[a]Yield of the isolated product. [b]A sealable tube was charged with *β*-*p*-methylbenzoylselenoglycoside **1a** (1 equiv, 0.1 mmol), **2** (2 equiv), the PdG3 XantPhos precatalyst (10 mol %), piperazine (1.2 equiv), and Cs_2CO_3 (3 equiv) in dry and degassed THF (0.1 M) under Ar for 2 h.

piperazine is known as one of the most promising rings displaying various biological activities for the treatmentof Parkinson's disease, Alzheimer's disease, and depression.[18] In addition, this methodology led to the synthesis of *N*-benzyl selenoglycoside **6b** in a good 95% yield (Scheme 2).

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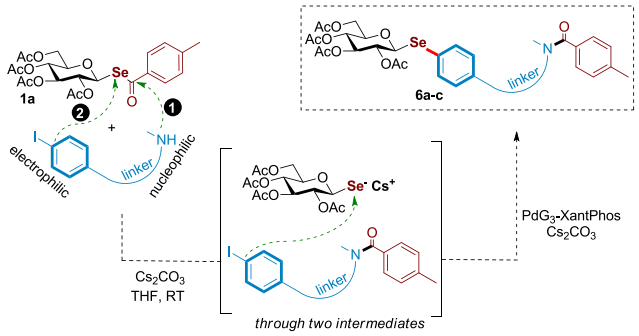
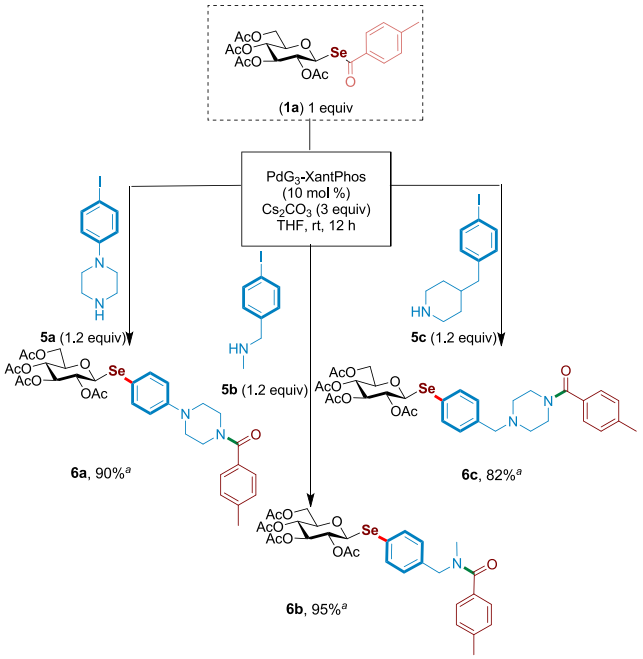


Figure 3. Strategy for the trapping of the *p*-methylbenzoyl group of **1a** by using a double action (electrophilic and nucleophilic) of the partner.

Scheme 2. Scope of Coupling of 1a with Functionalized Aryl Iodides Bearing a Secondary Amino Group (5a−c)[b]



[a]Yield of isolated products **6a−c**. [b]A sealable tube was charged with *β*-*p*-methylbenzoylselenoglycoside **1a** (1 equiv, 0.1 mmol), **5a−c** (1.2 equiv), the PdG3 XantPhos precatalyst (10 mol %), and Cs_2CO_3 (3 equiv) in dry and degassed THF (0.1 M) under Ar for 12 h.

In summary, we have shown that anomeric selenolate anions are competent nucleophilic partners in the Pd-catalyzed cross-coupling reactions. To the best of our knowledge, the C(sp^2)−Se bond of (hetero)aryl selenoglycosides was formed, for the first time, directly by a Pd-catalyzed cross-coupling of a selenosugar with aryl halides at room temperature. Because the reaction conditions are mild, this protocol tolerates a wide range of functional groups and proceeds in good to excellent yields. In addition, a variety of selenosugars could be used. This method opens new opportunities for using glycosyl selenolate in synthetic methodology and medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02352.

Experimental procedures, spectroscopic data, and NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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