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A One-Pot Assembly of Unsymmetrical Biaryl Thioglycosides
Through Chemoselective Palladium-Catalyzed Three-Component Tandem Reaction

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Supporting Information Placeholder

ABSTRACT: A range of unsymmetrical biaryls bearing thiosugars could be synthesized in a one-pot multicomponent approach using one catalytic palladium system that permitted the C–S and C–C bonds forming. The reaction showed a high selectivity and was applied to a broad variety of substrates giving access to novel glycosylated biaryl structures in good yields.

Functionalized unsymmetrical biaryls are of great prevalence in Nature and are found in many important medicinal compounds (Telmizartan, Boscalid). In addition, they are used in materials chemistry as semiconductors or as ligands for asymmetric catalysis. Biaryl platforms bearing donor and acceptor moieties have important optical properties and have been studied for photolability as two-photon sensitive photoremovable protecting groups for biologically-active molecules delivery. Interestingly, unsymmetrical biaryl functionalized with sugar groups are less reported in the literature. Several pharmacologically important biphenyl glycosides have been described (Figure 1). Lysilactone A is used in traditional Chinese folk medicine. Biphenylglycosides 2 and 3 have significant antioxidant activity. Mannoside 4 is a highly efficient FimH antagonist used for the treatment of urinary tract infections (UTIs). Moreover, several diphenylmethyl-β-C-glycosides such as dapagliflozin have been synthesized as potent inhibitors of SGLT2.

Usually, unsymmetrical biaryls are prepared from haloarenes or triflates, either by palladium or by nickel catalyzed cross couplings. They can also be obtained by coupling of two aryls with hypervalent silicon reagents, or by C–H bond activation. However, few examples of "one pot" sequential procedures have been reported in the literature. Among these are the Diels-Alder cycloaddition or the reaction of arylhalides with bis(pinacolato)diboron followed by coupling with

Figure 1. Example of Natural and Synthetic Biaryl Glycosides another arylhalide. Nevertheless, structures of biaryls bearing thiosugars and synthetic methods leading to their formation are non-existent. Thiosugars can be used as
sugar surrogates; therefore, their introduction into biaryls is highly relevant since biarylthioglycosides can be investigated as mimetics of biologically relevant O-glycosides. S-Glycosides are much more stable than O-glycosides to both chemical and enzymatic degradation and have been utilized as enzyme inhibitors in various biochemical studies.\(^9\) Owing to the significant importance of biphenylglycosides, there is a strong impetus to discover new chemical transformations for their efficient synthesis and functionalization.

As part of our continuing effort to provide the chemistry community with more efficient ways to produce high value thioglycosides,\(^9\) we became interested in extending our recently disclosed PdG3-catalyzed arylation of thioglycosides at room temperature with aryliodides\(^10\) into a tandem multicomponent reaction (MCR) involving iodo-bromoarenes, thioglycosides and arylboronic acids. The procedure consists on using one Pd-catalyst which, under the same catalytic cycle, will promote the catalysis of two individual steps; i) the first is the selective creation of the S–C bond 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 arylboronic acids. We could assume that in the presence of a nonselective catalyst, the reaction could statistically generate a complex mixture of up to three possible products (Table 1). In this regard, we wished to take advantages of the selectivity of oxidative addition of a C–I bond to Pd (0) species followed by the insertion of a thiol function at room temperature and to then perform a Suzuki-Miyaura coupling reaction at the remaining C–Br bond. We have focused our objective to find one catalytic system that will be highly selective toward the formation of the desired biarylglycoside product 4a. From a synthetic viewpoint, this procedure would offer the shortest and the most efficient route to biarylglycosides for the purpose of medicinal chemistry screening program. Herein, we report our success in the development of such protocol.

Initial selectivity tests were performed using PdG3 XantPhos (10 mol %) as a catalyst, which was reported previously by our group to be effective for the arylation of thiosugars.\(^10\) The selectivity was first examined in a model three-component reaction that utilized the tetraacetylated β-thiogalactose 1a (1 equiv), 1-bromo-3-iodobenzene 2a (1 equiv) and (4-methoxyphenyl)boronic acid 3a (1.5 equiv) (Table 1). Gratifyingly, by running the reaction in wet THF for 15 min at room temperature and 3 h at 100 °C using a combination of two bases NET\(_3\) and K\(_2\)CO\(_3\) (4 equiv), we were able to achieve a complete selectivity toward the C–I and C–Br bonds. Under these conditions, compound 4a was isolated in 48% yield without any side products (Table 1, entry 1). Then we attempted to omit NET\(_3\) and to our satisfaction, by adding K\(_2\)CO\(_3\) (4 equiv) and heating overnight at 80 °C, 4a was obtained in 55% yield (Table 1, entry 2). Since the latter conditions were superior, we settled on these, using K\(_2\)CO\(_3\) as a base. Stirring the mixture at 100 °C in the presence of two equivalents of arylboronic for 12 h, decreased the yield to 42% and led to by-product formation (Table 1, entry 3). Surprisingly, by shortening the reaction time from 12 h to 5 h, the biphenyl β-thioglycoside (\(J_{\beta} = 9.9\) Hz) 4a was isolated in 83% yield when 1.2 equiv of thiogalactose 1a were used (Table 1, entry 4). Fortunately, reducing the catalyst loading to 5 mol % gave 4a in a similar yield (82%, Table 1, entry 5). A second part of this optimization focused on investigating the feasibility of the reaction at the same temperature (100 °C). Simple mixing of the three components 1a (1.2 equiv), 2a (1 equiv) and 3a (2 equiv) at 100 °C furnished product 4a in a good 81% yield and with a perfect control of the anomeric configuration (\(J_{\beta} = 9.9\) Hz). One can be noted that in all cases, the monohalogenated thioglycoside intermediate has never been observed during the process.

Motivated by these exciting results, we subsequently investigated the substrate scope for this tandem catalytic process by systematically varying the boronic acids 3, iodo-bromoarenes 2a-e and the thioglycosidic substrates 1a-g (Scheme 1).

![Scheme 1](image)

**Table 1** Optimization of the Coupling Reaction of Tetracetylated β-thiogalactose 1a, 1-Bromo-3-iodobenzene 2a and (4-Methoxyphenyl)boronic acid 3a

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>t (°C)</th>
<th>time (h)</th>
<th>4a (%)</th>
<th>5a/6a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et(_3)N/K(_2)CO(_3)</td>
<td>rt then 100</td>
<td>3</td>
<td>48</td>
<td>0/0</td>
</tr>
<tr>
<td>2</td>
<td>K(_2)CO(_3)</td>
<td>rt then 80</td>
<td>5</td>
<td>55</td>
<td>0/0</td>
</tr>
<tr>
<td>3</td>
<td>K(_2)CO(_3)</td>
<td>rt then 100</td>
<td>5</td>
<td>42</td>
<td>0/0</td>
</tr>
<tr>
<td>4</td>
<td>K(_2)CO(_3)</td>
<td>rt then 100</td>
<td>5</td>
<td>83</td>
<td>0/0</td>
</tr>
<tr>
<td>5</td>
<td>K(_2)CO(_3)</td>
<td>100</td>
<td>5</td>
<td>82(^{+})</td>
<td>0/0</td>
</tr>
</tbody>
</table>

\(^{+}\)A scalable tube was charged with thiogalactose 1a (1 equiv), 1-bromo-3-iodobenzene 2a (1 equiv), 4-methoxyphenylboronic acid 3a (1 equiv), PdG3 XantPhos (10 mol %), base (4 equiv) in THF (0.22 M) at rt (15 min) then 5 h at 100 °C. \(^{b}\) Yield of isolated product. \(^{c}\) 5 mol % of PdG3 XantPhos. \(^{d}\) 1.2 equiv of 1a were used. \(^{e}\) The reaction was performed at the same temperature (100 °C).

 Gratifyingly, all the tandem S- and C-arylations proceeded cleanly and selectively in good yields. As illustrated in Scheme 1, a variety of electron-rich and electron-deficient, para and meta substituted arylboronic acids effectively underwent reaction with 1-bromo-3-iodobenzene 2a and tetra-O-acetylated 1-thio-β-D-glucopyranose 1a in yields up to 80% (products 4a-f, 4h, and 4i-k). In addition, the sterically demanding ortho substitution pattern engaged in the tandem coupling reaction of 1a, furnishing compounds 4g and 4l-m having an ortho substituent group. Interestingly, heteroaromatic boronic acids such as pyridyl-4-ylboronic acid and quinoline-6-ylboronic acid were good substrates in this reaction (compounds 4n,o). In addition this tandem process was successfully expanded to the coupling of styryl boronic acid providing thyroglycosylated stilbene 4p in an acceptable 56% yield (Scheme 1).

The reaction of unsubstituted para-iodo-bromobenzene 2b with thiogalactose 1a and boronic acids resulted also in selective formation of biphenyl para-β-thioglycoside 4q in a good yield, while the ortho-dihalogenated substrate 2c gave only a moderate yield of 4r (32% yield), probably due to steric hindrance. The same product was obtained in
68% yield over two steps when PdCl₂-dppf was used as the catalyst for the Suzuki-Miyaura coupling. Interestingly, the tri-halogenated substrate 2d was used successfully in this MCR coupling leading selectively to thioglycoside 4s in 51% yield without affecting the remaining C–Cl bond.

Finally, extending this method to dihalopyridine-based substrate where the catalyst could be deactivated via Pd-pyridine coordination, also proved to be successful. Thus, 3-bromo-5-iodopyridine 2e was a good partner with 1a and 3a under our optimized conditions, furnishing the desired product 4t in 54% yield.

Of note that in all the studied cases, compounds 4a-t were isolated as single anomers, clearly indicating that the tandem process is stereoretentive with report to the anomeric configuration of the sugar moiety.

Regarding the sugar partners, this coupling reaction tolerates a large variety of glycosylthiols 1a-g (Scheme 2): O-acetylated 1-thio-β-D-galactopyranose 1a, O-acetylated 1-thio-β-D-glucopyranose 1b, O-benzoylated 1-thio-β-D-glucopyranose 1c and O-acetylated N-Ac-1-thio-β-D-glucopyranose 1d all coupled with the dihalobenzenes 2a-b to give biphenythioglycosides 5a-e in respectable yields. Importantly, this procedure is not limited to only protected β-glycosyl thiols, but it also worked successfully with unprotected 1-thiogalactose 1e without any loss of reactivity. In this cases products 5f,g were obtained in 63% and 50% yields, respectively. Moreover, the reaction is not limited to monosaccharides, but can be applied to more complex dis- and trisaccharide derivatives. Thus, 1-thio-β-D-cellobiose 1f and 1-thio-β-D-maltotriose 1g were efficiently reacted with 1-bromo-3-iodobenzene 2a to give original biphenyl structures 5h,i featuring di- and trisaccharides. Importantly, the stereochemistry of the β-1,4'-O-glycosidic bond in the disaccharides 5h and the α-1,4' in β-trisaccharide 5i remained intact.

In summary, we have developed an efficient and versatile protocol for the one-pot multicomponent preparation of biphenythioglycosides. The method tolerates a wide range of functional groups and a variety of protected and unprotected glycosylthiols could be used. We expect this simple
and general method to be of broad utility for the synthesis and development of new medicinal agents.

**ASSOCIATED CONTENT**

**Supporting Information**
The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures, spectroscopic data and NMR spectra of new compounds.

**Scheme 2** Scope of One-Pot Thiosugars 1b-g Coupling With Boronic Acid 2a Iodo-bromoarenes 3a-d

Reaction conditions: Thiosugar 1a (0.6 mmol), bromo-iodo-benzene 2a-d (0.5 mmol), boronic acid 3 (2 equiv), PdG3 XantPhos (5 mol %), K2CO3 (4 equiv) in THF (wet) (0.22 M) at rt (15 min) then 5 h at 100 °C. * Yield of isolated product.

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