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SHORT COMMUNICATION

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Palladium-Catalyzed Stereoselective *C*-Glycosylation of Glycals with Sodium Arylsulfinates

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Keywords: Glycosylation / Glycals / Palladium / Sulfur / Regioselectivity

An efficient glycosylation method to synthesize 2-deoxy-*C*-aryl glycosides was developed. This *C*-glycosylation strategy is based on a palladium-catalyzed desulfitative Ferrier-type coupling reaction of glycals and sodium arylsulfinates. A series of *C*-aryl glycosides were obtained in moderate to good yields with exclusive regio- and stereoselectivities. The anomeric selectivity was found to depend on the configuration of the C3 substituent of the glycals.

Introduction

C-Aryl glycosides are a class of *C*-glycosides possessing a carbon–carbon bond between the carbohydrate and aromatic moieties; they are more stable than *O*-glycosides under acidic and enzymatic hydrolysis. Most natural *C*-aryl glycosides are endowed with unique biological properties. For example, kendomycin, polytoxin, and *C*-glycosyl flavonoids exhibit strong antibacteria, antitumor, and anti-inflammatory activities.[1] In addition, quite a few *C*-aryl glycosides are effective glycosidase inhibitors.[2] They are also valuable building blocks in the synthesis of natural products and potential medicines. Thus, the development of methods for stereoselective *C*-glycosylation has attracted great attention.[3] A general strategy is the construction of a carbon–carbon linkage between the glycosyl donors and aryl acceptors.[3c–3e] Among these methods, metal-mediated coupling reactions provide facile access to *C*-aryl glycosides.[4] D-Glycal substrates with arylboronic acids,[5] aryl halides,[6] arylzinc reagents,[7] and arylindium reagents[8] generally provide α-selective glycosides as the major products (Figure 1). In our previous studies, aryl carboxylic acids and aryl hydrazines were employed as coupling partners for the construction of different types of glycosidic bonds with the use of a palladium catalyst.[9] Notably, the structures of the *C*-glycoside products could be affected by the reaction conditions and different β-elimination pathways of the palladium complex.[6b] Though many efficient methods have been established over the past few decades, the development of other kinds of readily available glycosyl acceptors is still in great demand.

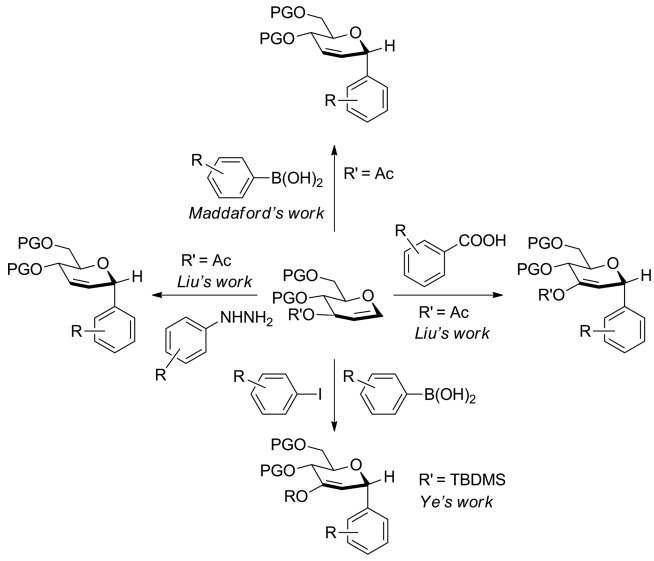

Figure 1. Selected palladium-catalyzed *C*-aryl glycosylation strategies; PG = protecting group, TBDMS = *tert*-butyldimethylsilyl.

Aryl sulfinic acids and their salts have many similarities to aryl carboxylic acids as aryl donors through desulfitative coupling.[10] Thus, we consider this kind of compound to be a suitable glycosyl partner in the generation of *C*-aryl glycosides. Herein, we describe our preliminary results for the synthesis of *C*-aryl glycosides by a palladium-catalyzed Ferrier-type coupling of glycals with various commercially available aryl sulfinic acid salts.

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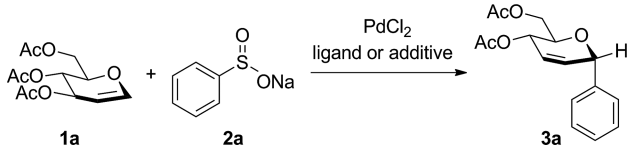
Results and Discussion

Our initial study focused on the glycosylation between commercially available 3,4,6-tri-*O*-acetyl-D-glucal (**1a**) and sodium benzenesulfinate (**2a**). The reaction was performed in the presence of a $PdCl_2$ catalyst and various phosphine ligands as previously reported.[9,10c] After preliminary screening, it was found that bis(2-diphenylphosphinophenyl) ether (DPEphos) was the most efficient ligand for this reaction: desired α-anomeric aryl product **3a** was obtained in 40% yield with MeCN as the solvent (Table 1, entry 1). Other ligands gave less than 20% yield (Table 1, entries 2–4). However, starting glucal **1a** was not completely consumed in these reactions. Upon adding AcOH as the additive, the yield increased to 53% (Table 1, entry 5). Inspired by the reported coupling conditions,[11] we turned to screening oxidants and additives. Our first attempts with $Cu(OAc)_2$ and $CuCl_2$ individually gave rather low yields (Table 1, entries 6 and 7). However, the combination of $CuCl_2$ and LiCl[12] resulted in a yield of 66% (Table 1, entry 8). Increasing the amount of $CuCl_2$ did not improve the conversion rate, whereas the yield decreased to 52% upon reducing the loading of $CuCl_2$ (Table 1, entry 9). Considering that carbohydrates might decompose under high temperatures, we conducted the reaction at a lower temperature of 75 °C. Fortunately, this reaction gave 70% yield of the desired product (Table 1, entry 10). A further decrease in the temperature resulted in incomplete consumption of the starting material. Solvent screening indicated that MeCN was optimal for this glycosylation (Table 1, entries 11–14).

Table 1. Optimization of the reaction conditions.[a]



1a **2a** **3a**

Entry	Ligand[b]	Additive	Solvent[c]	*T* [°C]	Yield [%][d]
1	DPEphos	–	MeCN	85	40
2	PPh_3	–	MeCN	85	20
3	dppe	–	MeCN	85	n.d.[e]
4	dppf	–	MeCN	85	18
5	DPEphos	AcOH[f]	MeCN	85	53
6	–	$Cu(OAc)_2$ + AcOH	MeCN	85	trace
7	–	$CuCl_2$ + AcOH	MeCN	85	10
8	–	$CuCl_2$ + LiCl[g]	MeCN	85	66
9	–	$CuCl_2$ + LiCl	MeCN	85	52[h]
10	–	$CuCl_2$ + LiCl	MeCN	75	70
11	–	$CuCl_2$ + LiCl	DCE	75	trace
12	–	$CuCl_2$ + LiCl	toluene	75	50
13	–	$CuCl_2$ + LiCl	DMSO	75	n.d.[e]
14	–	$CuCl_2$ + LiCl	THF	75	30

[a] The reaction was performed with **1a** (0.15 mmol), **2a** (0.6 mmol), $PdCl_2$ (0.015 mmol), ligand (0.03 mmol) or copper salt (0.15 mmol) in solvent (3 mL) in air (balloon) for 12 h in a Schlenk tube. [b] dppe = 1,2-bis(diphenylphosphino)ethane, dppf = 1,1′-bis(diphenylphosphino)ferrocene. [c] DCE = 1,2-dichloroethane. [d] Yield of isolated product. [e] Not detected. [f] 4 equiv. of AcOH was added. [g] 1 equiv. of LiCl was added. [h] 0.3 equiv. of $CuCl_2$ was added.

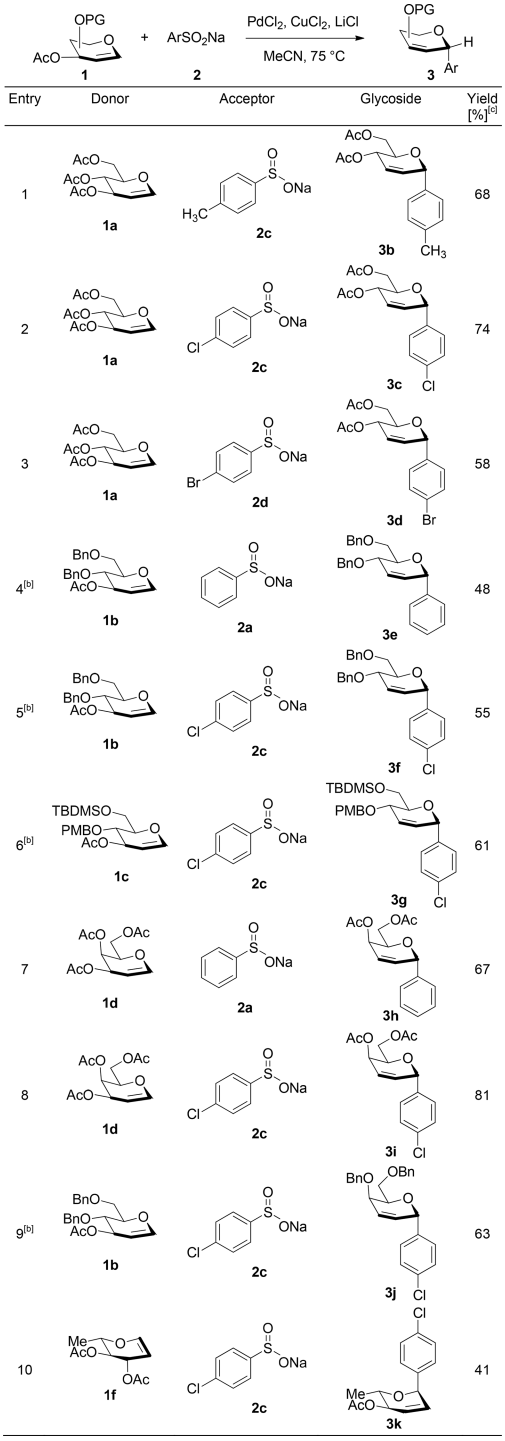
Thus, we concluded that the reaction between **1a** (1 equiv.) and **2a** (4 equiv.) required $PdCl_2$ (0.1 equiv.), $CuCl_2$ (1 equiv.), and LiCl (1 equiv.) in MeCN at 75 °C.

With the optimized conditions in hand, we then expanded the substrate scope to investigate the efficacy of this *C*-aryl glycosylation. Various sodium benzenesulfinates substituted with either electron-donating or electron-withdrawing groups in the *para* position were treated with 3,4,6-tri-*O*-acetyl-D-glucal to afford the corresponding products in reasonable yields with pure α-selectivity (Table 2, entries 1–3). Glucals with benzyl protecting groups in the 4,6-positions were also tested and gave poor yields at the outset. The glucal protected with an acid-sensitive *tert*-butyldimethylsilyl (TBDMS) group failed to produce the desired product. Interestingly, the problem was solved by the addition of NaOAc (5 equiv.). The reactions gave moderate yields of the products, even though slightly longer reaction times were used (Table 2, entries 4–6). The yields were slightly lower than that obtained with 3,4,6-tri-*O*-acetyl-D-glucal, and this can be ascribed to an increase in the size of the protecting group. The versatility of this reaction was further demonstrated by the observation that galactals with different protecting groups also provided good results (Table 2, entries 7–9). In particular, the yield of the reaction between 3,4,6-tri-*O*-triacetyl galactal and sodium *para*-chlorobenzenesulfinate was marginally higher than that between 3,4,6-tri-*O*-acetyl-D-glucal and sodium *para*-chlorobenzenesulfinate. This could be due to the configuration at C4 of **1a**, which is detrimental to attack of the α-face of the arylpalladium intermediate. Moreover, a glycal derived from rhamnose was also examined, and it furnished the corresponding *C*-aryl glycoside in 41% yield (Table 2, entry 10).

According to the above results and literature reports,[6b,11a,13] a plausible mechanism for the palladium-catalyzed glycosylation of 3,4,6-tri-*O*-acetyl-D-glucal with sodium benzenesulfinate is proposed in Scheme 1. Pd complex **B** is first generated through ligand exchange between Pd^{II} species **A** and sodium benzenesulfinate (**2a**). Subsequent elimination of SO_2 from complex **A** results in aryl Pd^{II} species **B**. Species **B** attacks glucal **1a** from the bottom side owing to steric hindrance induced by the C3 substituent to form π–Pd complex **D**, which is converted into intermediate **E** through *syn* addition. Subsequently, *anti* β-elimination of the Pd species and an acetyloxy group provides desired 2-deoxy-*C*-aryl glycoside **3a** and regenerates Pd^{II} species **A**.

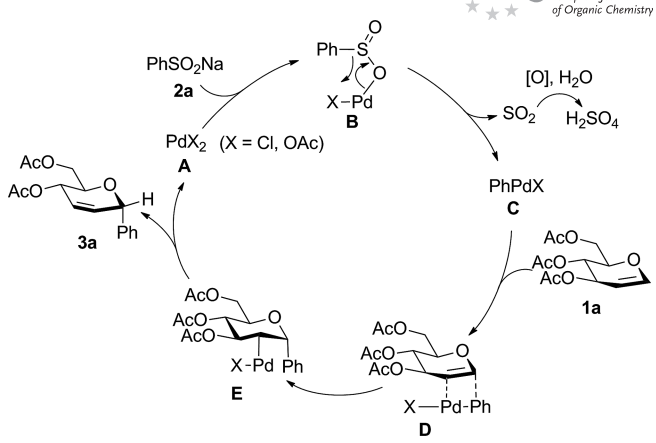
We speculated that the anomeric stereoselectivity of the *C*-aryl glycosides adopted a configuration opposite to that of the C3 substituent of the glycals. To validate this hypothesis, a comparative experiment was performed by individual reactions of **2c** with D-xylal **4a** and D-arabinal **4b**. As expected, the chlorophenyl group was linked to D-xylal in an (*S*) configuration, which is opposite to the (3*R*)-acetyloxy group of **4a**, whereas the (*R*) configuration of the anomeric carbon atom was obtained for D-arabinal **4b** from the (3*S*)-acetyloxy group (Scheme 2). This further suggested that the configuration of the C3 substituent contributed to the stereoselectivity of the *C*-glycosylation.[6a,13]

Table 2. *C*-Glycosylation of various glycals with sodium arylsulfinates.[a]

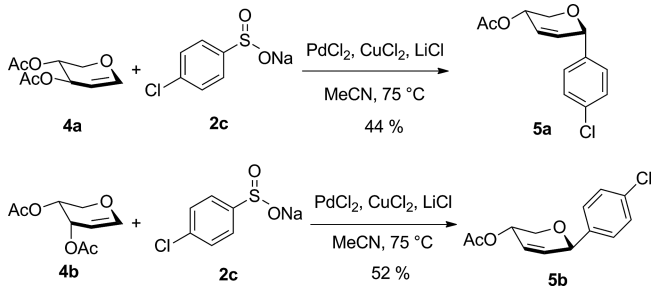


[a] Unless otherwise specified, the reaction was performed with **1a** (0.15 mmol), **2a** (0.6 mmol), $PdCl_2$ (0.015 mmol), $CuCl_2$ (0.15 mmol), and LiCl (0.15 mmol) in MeCN (3 mL) at 75 °C in air (balloon) in a Schlenk tube for 8 h. PMB = *p*-methoxybenzyl. [b] The reaction was conducted with an extra 5 equiv. NaOAc for 12 h. [c] Yield of isolated product.

During investigation of the substrate scope, an interesting finding was observed. Reaction of glucal **6** with **2c** did not furnish the Ferrier-type glycoside. Instead, product **7**

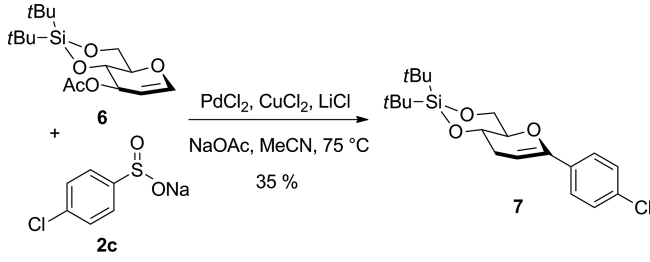


Scheme 1. Proposed mechanism for the *C*-glycosylation of glycals with sodium arylsulfinates.



Scheme 2. *C*-Glycosylation of **4a** and **4b** with sodium *p*-chlorobenzene sulfinate.

was isolated with elimination of the acetyloxy group (Scheme 3). This is probably attributed to the conformationally rigid protecting group. The bicyclic torsion strain resulted in more stable compound **7**, which could be generated by proton transfer from the routinely formed Ferrier-type glycosylated product.[9f]



Scheme 3. *C*-Glycosylation of glycal **6** with sodium *p*-benzenesulfinate.

Conclusions

In conclusion, a desulfitative *C*-glycosylation strategy between commercially available 3-*O*-acetyl glycals and sodium arylsulfinates was developed. The *C*-aryl glycosides were formed by palladium-catalyzed carbon-Ferrier-type coupling with high regioselectivity and stereoselectivity. Notably, the double bond in the products could be readily functionalized by epoxidation or hydroxylation,[8,14] which

makes them useful precursors to synthesize many natural *C*-aryl glycosides or other important pyran structures.

Experimental Section

General Experimental Procedure: Glycal (0.15 mmol), sodium arylsulfinate (0.6 mmol), $PdCl_2$ (0.015 mmol), $CuCl_2$ (0.15 mmol), and LiCl (0.15 mmol) were added to a 25 mL Schlenk tube. MeCN (3 mL) was then added by syringe. The tube was sealed with a rubber stopper and equipped with a balloon. The mixture was heated to 75 °C (external temperature) for 8–12 h. The mixture was cooled to room temperature and filtered. The filtered cake was rinsed with EtOAc. The filtrate was concentrated and purified by column chromatography on silica gel (EtOAc/hexanes) to give the desired product.

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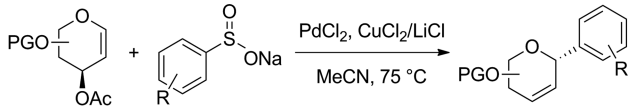

PG = protecting group

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