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Avoiding pyran ring opening during palladium acetate catalyzed *C*-glycosidation of peracetylated glycals

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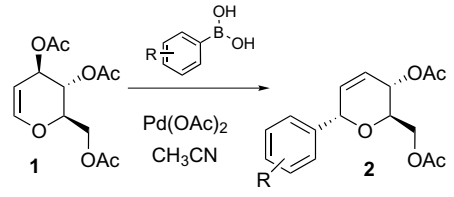
Abstract—Palladium acetate catalyzed *C*-glycosidation of peracetylated glycals with arylboronic acids in acetonitrile (CH_3CN) yields the desired 1-substituted 2,3-unsaturated glycal as well as a byproduct corresponding to the ring-opened pyran, present in varying proportions depending on the reaction conditions used. The byproduct is not formed when toluene/EtOH is used as reaction solvent.

C-Glycosides, natural products composed of a glycon (usually furanosyl or pyranosyl) and an aglycon (aryl or heterocyclic) linked via a C–C bond, have garnered great interest in the past few years due to their pharmacological potential.[1,2] Specifically, the C–C glycosylic linkage in *C*-glycosides is resistant to hydrolytic or enzymatic cleavage, suggesting their utility as inhibitors of carbohydrate-processing enzymes.[3] Among *C*-glycosides, *C*-arylglycopyranosides with a double bond in the 2,3-position are useful synthetic intermediates, since this unsaturation can be exploited for functionalization. Many of the synthetic routes to such unsaturated compounds are based on palladium-mediated coupling reactions of 1,2-unsaturated carbohydrates.[4] To date, three methods exist for in situ formation of the aryl palladium complex: treatment of an aryl iodide with palladium in the presence of a base,[5] treatment of an organomercury compound with a palladium salt,[6] and reaction of an aromatic compound with palladium acetate in acetic acid.[7] However, these reactions suffer from low yields, lack of regioselectivity, and instability of most of the reagents to air and moisture; hence alternate strategies are needed. Nucleophiles such as arylindiums[8] or organolithiums[9] have recently been used to obtain 2,3-unsaturated α-*C*-glycosides, although stereoselectivity is only obtained via the organolithium route, which is long and involves an epoxide intermediate.

The use of palladium acetate as a catalyst for formation of C–C bond formation is well established, namely in Heck-type reactions of aryl boronic acids with alkenes to give arylated alkenes.[10] Maddaford and co-workers[11] investigated the use of boronic acids as nucleophiles, which can undergo transmetalation with palladium salts to yield the corresponding aryl palladium complex. Boronic acids proved advantageous owing to their air and moisture stability, broad commercial availability, and low toxicity. The authors treated 3,4,6-tri-*O*-acetyl-D-glucal **1** in CH_3CN in the presence of 2 equiv of an arylboronic acid and stoichiometric palladium acetate to obtain the corresponding 2,3 dihydroarylglycopyrans in good yields (Scheme 1).[12]



Scheme 1. *C*-Glycosidation of 3,4,6-tri-*O*-acetyl-D-glucal.

Keywords: *C*-Glycosidation; Arylboronic acids; Catalysis; Pyran ring opening; Transacetylation; Palladium acetate; Solvent effects.
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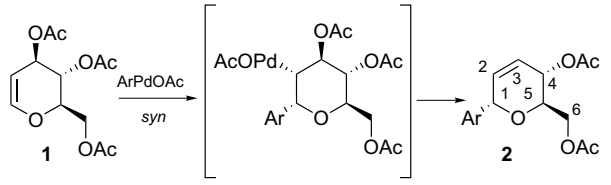


Scheme 2. Mechanism of the palladium acetate catalyzed *C*-glycosidation of **1** with arylboronic acids.

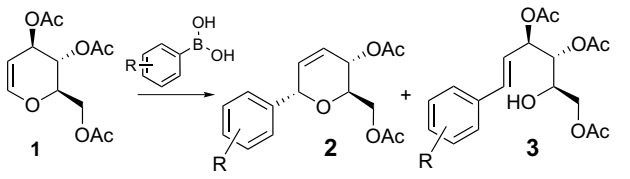
The key steps of the reaction mechanism are the *syn* insertion of the ArPdOAc and the antiperiplanar elimination of the OAc and PdOAc to generate the π bond (Scheme 2). The reaction is regio- and stereoselective. The regioselectivity stems from the fact that the σ-bond is formed by the electron deficient palladium(II) and the electron rich β-carbon of the enol ether. The stereochemistry of the reaction is determined by the relative accessibility of the two respective faces of the cyclic enol ether double bond to the organopalladium reagent for π-complex formation. In the case of **1**, only the α *C*-glycosil is obtained.

When we treated tri-*O*-acetyl-D-glucal in CH_3CN with 2 equiv of the corresponding phenyl boronic acid derivative, in the presence of 0.1 M of palladium acetate, during 24 h, the expected product, **2**, was obtained. However, aryl derivatives substituted with an electron-donor group yielded two products: the expected product, **2**, and a byproduct, **3**, in different yields (Table 1).[12]

Similar results were obtained with analogs having the *S* configuration at C-4, such as tri-*O*-acetyl-D-galactal. For instance, the ratios of **2**:**3** obtained for R = 4-PhO and R = 3-F-4-BnO were 2.0 and 1.1, respectively.

The MS spectrum of the product **3** was similar to that of **2**, but with an (MH^+) that contained an extra AcOH molecule. After purification of the crude by column chromatography, product **3** was identified by NMR as the ring-opened adduct. Upfield displacement of the H-2 chemical shift as compared to that of **2** (5.45 vs 6.20 ppm) revealed that the double bond is in resonance with the aryl group, leading to an increase in electronic density in this position. Observation of a ^1H NMR signal at 1.7 ppm corresponding to the hydroxyl, as well as the presence of three signals corresponding to the acetyls, seen in both the ^1H NMR and in ^{13}C NMR spectra of **3**, confirmed the structure.

Table 1. Yields for palladium acetate catalyzed *C*-glycosidation of tri-*O*-acetyl-D-glucal **1** with arylboronic acids, as determined by column chromatography (1) and HPLC (2)



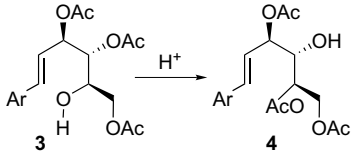
R	**2** Yield (%)	**3** Yield (%)	Ratio **2**:**3**
H[1]	80	nd[a]	—
2-Me[2]	77	nd[a]	—
4-^{i}PrO[2]	27	53	0.5
4-MeO[1]	34	59	0.6
3-CF_3O[2]	22	23	1.0
4-PhO[2]	51	37	1.4
3-F-4-BnO[2]	48	32	1.5
4-F[2]	51	26	2.0
3-Cl[2]	49	25	2.0

[a] nd = not detected.

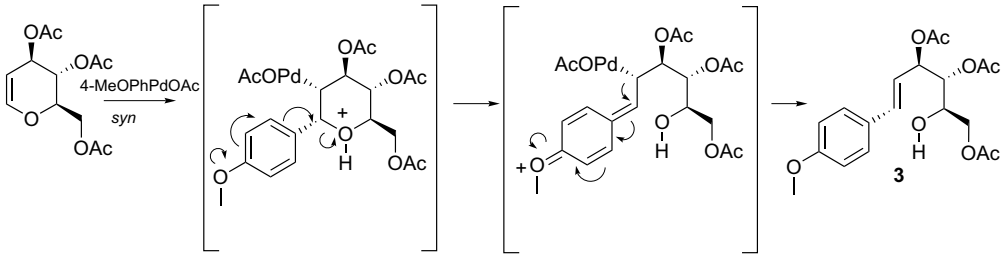
The byproduct **4** was also isolated in different amounts, and is a result of the acid-catalyzed transacetylation of **3** by the acidic reaction medium or the silica-gel used for work-up (Scheme 3).

Based on the results, we concluded that pyran rings with electron-donor substituents undergo ring opening during the reaction. Electron-donor groups are responsible for ring opening in acidic medium, due to mesomer effect, as shown in Scheme 4.

C-Glycosylation was also carried out with heterocyclic boronic acids instead of aryl boronic acids, in CH_3CN or THF at different temperatures. No reaction was observed for 2-thiophen boronic acid in THF at any temperature. On the other hand, using CH_3CN instead of THF gave the open product in 38% yield at temperatures between 35 and 80 °C, while higher temperatures led to decomposition of the product. The desired



Scheme 3. Transacetylation of the product **3** to give **4**.



Scheme 4. Proposed mechanism for the formation of the byproduct **3**.

product was not detected for any of these conditions. Similar results were obtained when 3-furan was used. In this case the ring-opened adduct was obtained in 61% yield in CH_3CN at 35 °C. These results are not surprising as the heterocycles used are π-excessive, behaving in a similar way to the boronic acids that contain an electron-donating group.

As the byproduct **3** is a result of the acidity of the reaction medium, we thought that addition of base to the reaction should prevent its formation. Thus, reaction of tri-*O*-acetyl-D-glucal with 4-methoxyphenylboronic acid in the presence of different organic and inorganic bases was studied. Addition of an organic base such as Et_3N slightly increases the yield of the desired product **2**, whereas inorganic bases prevented the reaction from proceeding (Table 2).

Finally, solvent effects on the reaction were studied (Table 3). In toluene/EtOH, the reaction gave product **2** exclusively. However, other solvents afforded mixtures of **2** and **3**. Thus, toluene/EtOH was found to be the solvent of choice for this reaction.

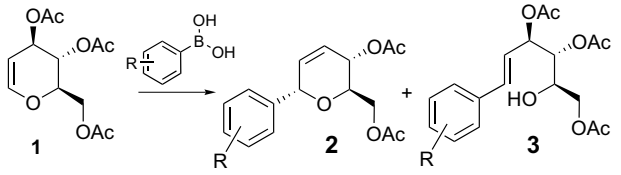
When the reaction was carried out using 3,4-di-*O*-acetyl-6-deoxy-L-glucal (**5**) in toluene/EtOH, the corresponding 2,3 dihydroarylglycopyrans **6** was obtained exclusively. In fact, no trace of the ring-opened adduct **7** could be detected (Table 4). Large proportions of starting material remained for all cases. Low yields were interpreted as a consequence of the reduction of the catalyst, $PdOAc_2$, to Pd^0.

Table 2. Yields for *C*-glycosidation of tri-*O*-acetyl-D-glucal (**1**) with 4-methoxyphenylboronic acid and palladium(II) acetate (0.1 equiv) in the presence of different bases, as determined by HPLC

Base	Equiv	**2** Yield (%)	**3** Yield (%)
—	—	34	59
Et_3N	1	39	40
	2	43	36
K_3PO_4	1	nd[a]	nd[a]
	2	nd[a]	nd[a]
Na_2CO_3	1	nd[a]	nd[a]
	2	nd[a]	nd[a]

[a] nd = not detected.

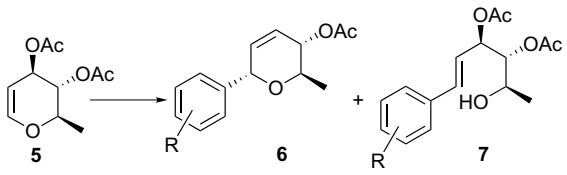
Table 3. Solvent effects for the reaction of tri-*O*-acetyl-D-glucal **1** with 3-chlorophenyl boronic acid (R = 3-chloro) and palladium(II) acetate (0.1 equiv)



Solvent	**2** Yield (%)	**3** Yield (%)
CH_3CN	49	25
CH_3CN/BuOH	nd[a]	nd[a]
THF	27	24
Toluene/EtOH (6:4)	60	nd[a]

[a] nd = not detected.

Table 4. Yields for the palladium(II) acetate catalyzed reaction of 3,4-di-*O*-acetyl-6-deoxy-L-glucal **5** with arylboronic acids containing electron-donating groups



R	**6** Yield (%)[a]
4-^{i}PrO	33
4-MeO	55
4-PhO	70
4-FBn	57
3-F-4-BnO	46

[a] The remainder is starting material.

In summary, we have reported the formation of a byproduct in the palladium(II) acetate catalyzed *C*-glycosylation of peracetylated glycols with arylboronic acids in CH_3CN. The byproduct was identified as the ring-opened adduct of the pyran, and a mechanism for its formation has been suggested. When toluene/EtOH is used as reaction solvent, the reaction proceeds in good yield, regio- and stereoselectivity, and no byproduct is formed. The reaction is currently being optimized, and yields are expected to increase upon performing the reaction in the presence of O_2.

Acknowledgments

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12. General procedure: To a solution of the 1,2-unsaturated glycal (0.35 mmol) and arylboronic acid (0.7 mmol) in CH_3CN (2.5 mL) was added $Pd(OAc)_2$ (0.035 mmol), and the mixture was stirred at room temperature for 24 h. The majority of the resulting Pd salt was then removed by centrifugation. The supernatant was then concentrated, taken up in CH_2Cl_2 and filtered through a BondElut silica gel column. The filtrate was then concentrated to dryness.