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ARTICLE TYPE

Regio- and Diastereoselective Pd-catalyzed Synthesis of C2-Aryl Glycosides

Juba Ghouilem,[a] Rémy Franco,[a] Pascal Retailleau,[b] Mouad Alami,[a] Vincent Gandon[c,d]* and Samir Messaoudi[a]*

An efficient regio- and diastereoselective arylation method of readily available 2,3-glycals with various aryl iodides has been established. Using the $Pd(OAc)_2/AsPh_3$ precatalytic system, this protocol proved to be general to prepare a variety of substituted C2-aryl glycosides in good yields with complete diastereoselectivity.

C-aryl glycosides are key motifs in medicinal chemistry and drug discovery including antibiotics, antitumors, as well as antidiabetic agents (Figure 1).[1] These common motifs are also found in many natural bioactive compounds.[1] C-aryl glycosides are considered as glycomimetics of biologically relevant *O/N*-glycosides and usually show enhanced resilience to enzymatic and hydrolytic cleavage under biological conditions.[2] Thus, C-aryl glycosides have emerged as a privileged class of saccharides with diverse potential applications. In this context, a plethora of methods[3] related to the synthesis of C1-aryl glycosides has been reported, in which the aryl nucleus is linked to the sugar unit through the C-glycosidic bond. In contrast to this well-developed series, there are still only few reports on the preparation of C2-aryl glycosides (Scheme 1). C−C bond formation of $C(sp^3)$-hybridized glycosides suffers from a difficult installation of a reactive function at the C2 position of the sugar that could be further elaborated to furnish the targeted C2-aryl glycoside. Adding to this the difficulty to control the stereoselectivity, C2-arylation is actually a very challenging synthetic endeavor.

Davis and co-workers reported a Suzuki cross-coupling approach[4] of 2-iodoglycals to furnish $C2(sp^2)$-aryl glycosides in excellent yields (Scheme 1a). While this method highlights an important achievement in this underdeveloped area, the narrow scope of only *O*-benzylated glycals and poor functional group tolerance limits its utilization. Recently, Mukherjee group

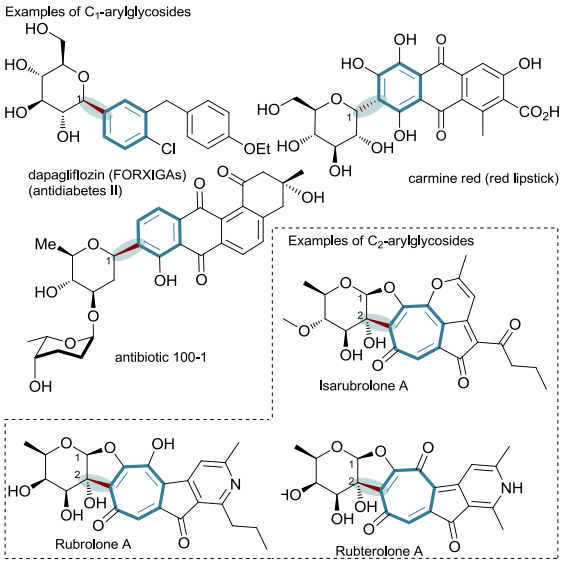

Figure 1. C-aryl glycosides-based bioactive molecules

reported an elegant method for the diarylation of glycals and pseudoglycals with aryl boronic acids under Pd-catalysis (Scheme 1b).[5] Selectivity was C1−C2(α,α) in the case of glycals but C2−C3(β,β) for pseudoglycals. However, this method is limited to acetylated glycals and only leads to symmetrical diarylated C-glycosides. Another way to prepare C2-aryl glycosides reported by Tenaglia *et al.*,[6] consists in the transformation of *o*-iodoaryl branched hex-2-enopyranosides through an intramolecular Heck reaction to *cis*-fused aryl pyranosides (Scheme 1c). Based on these few literature reports to access to C2-aryl glycosides, we became interested in developing a direct approach. In this context, we reported recently an efficient protocol for the synthesis of functionalized C2-aryl glycosides *via* a Pd(II)-catalyzed diastereoselective $C(sp^3)$–H activation approach using a proximity-driven metalation strategy (Figure 1d).[7] This method exhibits a 2,3-*trans*-arylation selectivity and tolerates a wide range of functional groups. Despite the substantial improvement of this approach, the stoichiometric installation and removal of the directing group is time consuming and generates wastes, which limits its efficiency and applicability. To avoid these additional steps, we decided to pursue our investigations in developing direct and diastereoselective methods for the synthesis of C2-aryl glycosides. In this context, we became interested in the reactivity of 2,3-pseudoglucals. Although these substrates are easily accessible in a single step from commercially available glycals,

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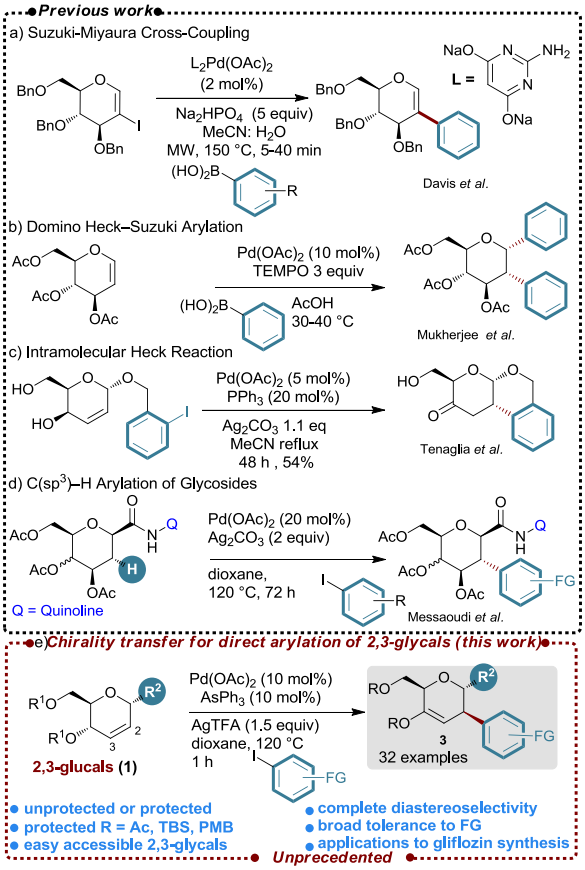
† Electronic Supplementary Information (ESI) available: General, experimental procedures for starting materials and ^1H and ^{13}C spectra for all new compounds. SeeDOI: 10.1039/b000000x/



Scheme 1. Strategies to access C2-aryl glycosides.

only few studies report their functionalization. We envisaged that the C2-diastereoselective introduction of an aryl moiety on these substrates could be accomplished through a Mizoroki-Heck reaction (Scheme 1e). We hypothesized at this stage that the aryl-palladium$^{(II)}$ complex will approach the double bond of pseudoglucal at the opposite face of the C_3–OR bond (Figure 2). This pathway will lead to complex (**B**), which possesses H4 as the only hydrogen that may be involved in a *syn*-β-elimination process. We anticipated that the stereochemistry at the C2 position of the coupling product would be dictated by the stereochemistry at the C4 position of the pseudoglucal through a chirality transfer mechanism. Thus, through this work, we show for the first time, that pseudoglucals can be successfully arylated

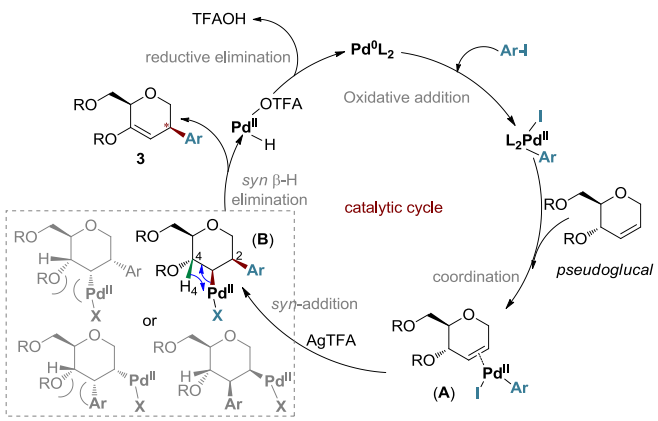
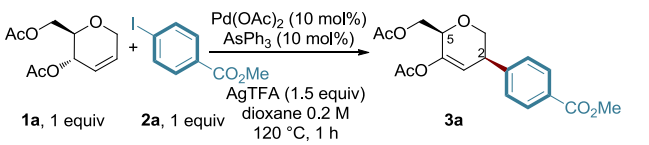


Figure 2. Proposed mechanism for the Mizoroki-Heck C2-arylation of pseudoglucals.

by a Mizoroki-Heck process to afford in a single step a variety of substituted C2-aryl glycosides in a diastereoselective fashion (Figure 1e). Interestingly, we evidenced during this study the crucial directing effect of the C_4–OR substituent to control the regio- and the stereoselectivity.

To initiate this study, we conducted the coupling of acetylated 2,3-pseudoglucal **1a** with 4-iodomethylbenzoate **2a** under various reaction conditions. Representative results are summarized in Table 1 (see the ESI for the full optimization). In preliminary experiments, the Heck reaction was first examined in the presence of $Pd(OAc)_2$ as a pre-catalyst (10 mol%), PPh_3 (20 mol%) as ligand and Ag_2CO_3 as a base in acetonitrile at 120 °C for 36 h. Under these conditions, we observed 63% conversion of the starting pseudoglucal and only 37% of isolated yield of the desired product, as a single diastereoisomer (entry 2). 1D and 2D NMR analyses clearly showed the 2,5-*cis* configuration and demonstrated the high diastereoselectivity of this reaction. After screening several parameters (Table 1 or ESI), we finally found that the C2-arylation occurred smoothly with 76% yield when using $Pd(OAc)_2$ as a pre-catalyst (10 mol%), $AsPh_3$ (10 mol%) as ligand and AgTFA as a base in dioxane at 120 °C for 1h. Interestingly, in all conditions examined during this optimization step, only one diastereoisomer **3a** was isolated. It should be noted that the $Pd(OAc)_2$ and $AsPh_3$ were necessary to achieve this transformation since **3a** was not observed when the coupling was conducted in their absence.

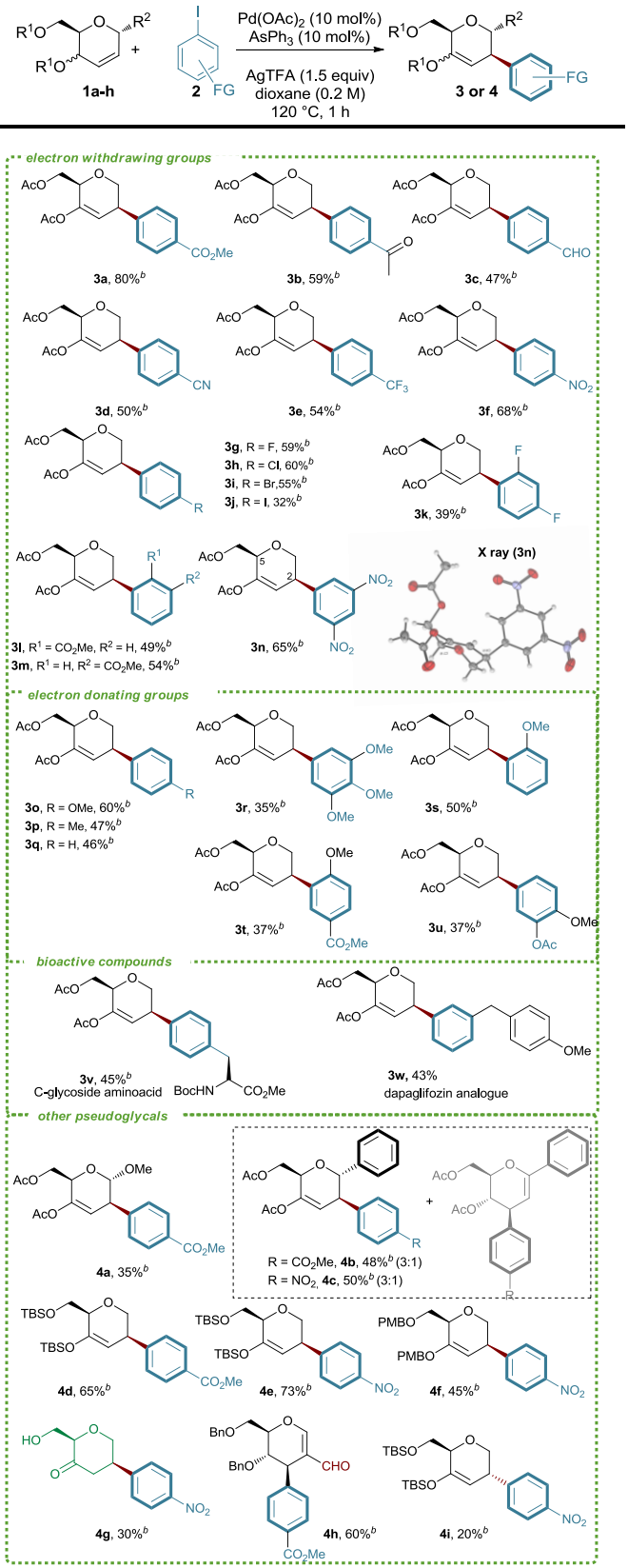
Table 1 Survey of the conditions for the C2-arylation of **1a** with **2a**[a]



Entry	Deviation from the standard conditions	Yield (%)[b]
1	none	76
2	PPh_3 (20 mol%), Ag_2CO_3 in MeCN for 36 h	37
3	2.5 equiv of AgTFA	80
4	5 mol% of Pd cat. and 7.5 mol% of $AsPh_3$	70
5	DMF instead of dioxane	33
6	CPME instead of dioxane	27
7	Toluene instead of dioxane	32

Reactions were conducted with substrate **1a** (0.4 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$ (0.04 mmol), additive, and solvent (2.0 mL). [b] Yield of isolated product **3a**.

Motivated by these results, we next explored the scope of the direct C2-arylation of various pseudoglycals **1a-h** with aryl iodides. At first, we were pleased to see that various aryl iodides bearing diverse functions (–CO_2Me,–CHO, –COMe, –Cl, –F, –Br, –I, –CF_3, –CN, –NO_2, –OAc and –OMe) reacted smoothly with **1a** to afford the desired C2-aryl glycosides **3a-w** in moderate to good yields and high diasteroselectivity (Scheme 2). The exact structure of **3n**, including its relative 2,5-*cis* geometry, was unambiguously confirmed by crystal structure analysis. Of note, the presence of an *ortho* substituent at the aromatic ring of the coupling partner did not affect the reaction process, as compounds **3k, 3l, 3s** and **3t** were obtained in satisfactory yields. Finally, the synthetic utility of this methodology was



Scheme 2. Scope of the coupling of **1a-h** with various aryl iodides **2**[a]

[a] Reactions were performed in a flame dried re-sealable Schlenk tube using pseudoglucals **1a-h** (0.4 mmol), ArI (0.4 mmol), $Pd(OAc)_2$ (0.04 mmol), $AsPh_3$ (0.04 mmol), AgTFA (0.6 mmol) in dioxane (2.0 mL) at 120 °C. [b] Yield of isolated product.

demonstrated by the synthesis of the C-glycosyl amino acid analogue **3v** through the coupling of *p*-iodo phenylalanine with **1a**. This finding holds major potential for the preparation of *C*-aryl glycosyl amino acid building blocks for their subsequent use in glycopeptide assembly. In addition, C-glycoside **3w**, an analogue of the dapagliflozin drug (FORXIGAs)[8] used to treat type 2 diabetes (Figure 1) was successfully synthesized in 43% yield by this methodology. Next, we moved on to investigate the reactivity of a series of pseudoglycals **1b-h**. As depicted in Table 2, this coupling reaction tolerates different substituents at the C1 position of pseudoglucals such as –OMe (product **4a)** or –Ph (compounds **4b-c)**. Noteworthy, in the case of C-glycosides **4b** and **4c**, a mixture of separated regioisomers was obtained in a 3:1 ratio. In addition, this methodology tolerates other protecting groups such –OTBS (compounds **4d-e**) and –PMB (compound **4f**). Interestingly, the reaction tolerates unprotected pseudoglucals such as the C-glycoside **4g**. One can note that when the benzylated pseudoglucal **1g** bearing a formyl group at the C2-position was used, inverted reactivity was observed in favor the C3-aryl glycoside **4h**, which was obtained in 60% yield as a single stereoisomer. Finally, to confirm that the diastereoselectivity of this coupling was driven by the configuration at the C4-position, we performed the reaction with pseudogalactal **1h** instead of **1a**. Interestingly, the expected product **4i**, in which the C2-configuration was inverted (2,5-*trans*), was obtained. However, the yield did not exceed 20%.

DFT computations were performed to rationalize the regio- and the diastereoselectivity observed, focusing on the insertion step (Figure 3). Pseudoglucal **1a** was used as substrate. Two possible pathways were envisioned for the *syn* arylpalladation of this compound (Figure 3): *i*) a cationic mechanism involving $[Ph–Pd(AsPh_3)]^+$; *ii*) a neutral mechanism involving $[Ph–Pd(TFA)(AsPh_3)]$. Coordination of palladium to the substrate leads to intermediates of type **Int-*cis*** or **Int-*trans***, in which the metal fragment is in a *cis*- or *trans*-relationship with the substituent at C5. **Int-C2-*cis*** has been taken as reference complex for the free energies (0.0 kcal/mol). From **Int-*cis*** and **Int-*trans*** intermediates, arylation at C2 and C3 has been computed.

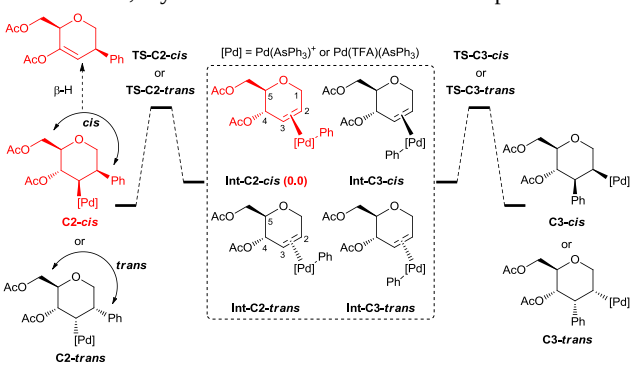


Figure 3. Free energy profile of the *syn*-insertion pathways.

Of note, only **C2-*cis*** can lead to the experimentally observed product after *syn* β-H elimination and reductive elimination. The free energies related to Figure 3 were calculated and are reported in Table 2 (see also Figures S2 and S3 in the ESI). Complexes of type **C2-*trans*** cannot give rise to a β–H elimination and should

therefore be considered as unproductive. They were included nonetheless for comparison. On the basis of the free energy of activations, it seems clear that the fastest reaction is the one corresponding to the formation of **C2-*cis***. In the cationic series, the barrier of 15.3 kcal/mol is markedly lower than those leading to the other isomers (22.6-24.3 kcal/mol). In the neutral series, the barrier of 15.0 kcal/mol is 1.2 kcal/mol lower than the one leading to **C3-*cis*** (16.2 kcal/mol). The formation of the *trans* isomers is significantly more demanding in free energy of activation (18.1 and 17.4 kcal/mol). In the two series, the formation of **C2-*cis*** is also more exergonic (-10.4 and -6.5 kcal/mol for the cationic and neutral pathways respectively). Although it is difficult to make a clear cut between the cationic and the neutral pathways, any of the two favors the arylation at C2 and place the aryl group in the *cis*-relationship with the CH_2OAc substituent at C5.

Table 2. Free energies (ΔG_{393}, kcal/mol) of the computed intermediates and transition states referenced to **Int-C2-*cis***

[Pd] = [Pd(AsPh$_3$)]$^+$					
TS$_{C2\text{-}cis}$	**C2-*cis***	**Int-C3-*cis***	**TS$_{C3\text{-}cis}$**	**C3-*cis***	**Int-C2-*trans***
15.3	-10.4	-1.8	24.0	-9.9	-2.6
TS$_{C2\text{-}trans}$	**C2-*trans***	**Int-C3-*trans***	**TS$_{C3\text{-}trans}$**	**C3-*trans***	
24.3	5.2	-1.5	22.6	-2.4	
[Pd] = [Pd(TFA)(AsPh$_3$)]					
TS$_{C2\text{-}cis}$	**C2-*cis***	**Int-C3-*cis***	**TS$_{C3\text{-}cis}$**	**C3-*cis***	**Int-C2-*trans***
15.0	-6.5	3.0	16.2	-1.8	0.3
TS$_{C2\text{-}trans}$	**C2-*trans***	**Int-C3-*trans***	**TS$_{C3\text{-}trans}$**	**C3-*trans***	
18.1	-3.5	4.7	17.4	-3.5	

The geometries corresponding to the **C2-*cis*** series are collected in Figure S1 of the ESI. With the cationic catalyst, a strong interaction between the acetate at C4 and palladium is clearly revealed. It leads to a η^1-coodination of Pd to the C=C bond of the substrate and engage the metal into a 6-membered ring system. This Pd-O interaction is still present in the transition state (Figure 4) and in the product (ESI). Interestingly, this type of control is reminiscent to DG-arylation, with the acetates thus being crucial to control the regio- and the stereoselectivity. Such an electronic directing effect is in principle also possible from **Int-C3-*trans***. However, in this case, it does not involve the carbonyl oxygen but the one directly connected to the glucal ring. It is therefore less efficient as the resulting metallacycle is a 4-membered ring instead of a 6-membered one. On the other hand, the rationalization of the regio- and diastereochemistry of the neutral pathway can be made on the basis of steric effects. The metal fragment prefers the most accessible side of the C=C bond, *i.e*. *anti* to the OAc group at C4. The Ph group is oriented towards C2, which is a CH_2, rather than C3, to limit the steric demand imposed by C4, which is trisubstituted.

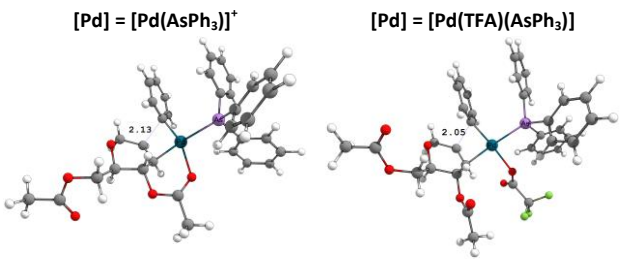


Figure 4. Geometries of **TS$_{C2\text{-}cis}$** (selected distances in Å).

In conclusion, we successfully developed an efficient and diastereoselective method for the synthesis of C2-aryl glycosides by coupling 2,3-pseudoglucals with aryl iodides under palladium catalysis. The protocol exhibits a broad substrate scope with respect to the coupling partners, thus providing an attractive access to a large molecular diversity of C2-substituted glycosides. Moreover, DFT calculations were performed to elucidate the unexpected 2,5-*cis dia*stereoselectivity of this reaction.

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