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COMMUNICATION

Access to *C*-aryl/alkenylglycosides by directed Pd-catalyzed C-H functionalisation of the anomeric position in glycal-type substrates

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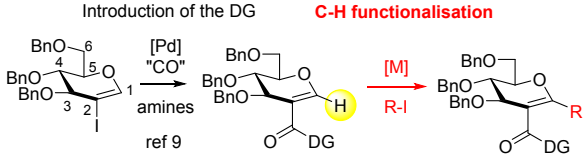
Directed palladium-catalyzed C-H functionalisation of *C2*-amido glycals onto the anomeric position is described as novel access to *C*-aryl/alkenylglycosides. Aminoquinoline-type directing group was used to successfully introduce diverse (hetero)aryl and alkenyl groups at the position 1 of the sugar (20 examples). Application to the synthesis of a Dapagliflozin analogue is presented.

Carbohydrates and glycoconjugates have proved to possess crucial roles in biological processes. Development of general synthetic methods to build these structures are thus highly desirable in terms of therapeutic applications.[1] In particular, methodologies allowing the replacement of natural links by stable mimic carbon-carbon (C-C) bonds (*C*-glycosides) is widely explored.[2] Especially, *C*-arylglycosides proved to be excellent drug candidates as witnessed gliflozin family, whose five members have been already commercialized for type 2 diabete treatment.[3] Despite their great interest, current synthetic routes to *C*-arylglycosides involve most often several steps *via* prefunctionalised intermediates and frequently use, in addition, strong bases.[4] Recently, C-H bond functionalisation became very attractive[5] but faced regioselectivity issues due to the similarity of C-H bonds in organic molecules. The common strategy in metal-catalyzed C-H functionalisation (MCF) consists thus in using a directing group (DG), placed at a chosen position.[5b] Currently, C-H functionalisation of sugar substrates is very limited due to the complexity and the sensitivity of these scaffolds.[6] In term of reactivity, Csp^2-H bonds being more explored in C-H functionalisation, glycals appears to be ideal partners to reach *C*-arylglycosides *via* the C-H functionalisation of the anomeric position. In the literature, undirected MCF on glycals run almost exclusively on C2 position and are very limited in terms of functionality (only perfluoroalkylated, alkenes or borylated reagents).[7] To switch the reactivity to the targeted C1 position, we thought to introduce a DG on the close C2 position. Our choice turned to the commonly used amide-type DG. This strategy was validated on simple dihydropyran (DHP) on one example of C1-H phenylation using nickel (Ni) catalyst in harsh conditions leading to 54% yield.[8] Very recently, we developed a palladium (Pd)-catalyzed aminocarbonylation reaction using 2-iodoglycals leading to *C2*-amidoglycals.[9] Herein, we develop a new access to *C*-aryl/alkenylglycosides by directed C-H functionalisation of anomeric position on *C2*-amidoglycals (Scheme 1). Regarding the popularity of bidentate 8-amidoquinoline DG in MCF examples, our previously aminocarbonylation conditions were tested on per-benzylated 2-iodo-D-glucal using 8-aminoquinoline as amine partner and desired compound **1a** was successfully obtained in 85% yield. C-H functionalisation reactivity was thus investigated on **1a**, starting from standard C-H activation conditions using Pd complex in presence of silver salts in toluene at 130°C with 4-iodoanisole as aryl partner. After screening of the different parameters (Table 1, see SI for complete study), it appears that adding a weak base (K_2CO_3) in excess, sub-stoichiometric amount of citric acid in the presence of $Pd(cod)Cl_2$ was suitable and yielded the desired compound **2a** in 72% NMR yield and 58% isolated yield (Table 1, entry 8). The bidentate character of the DG is crucial to the reaction process since replacement of the 8-amidoquinolyl part by a monodentate benzylamide moiety does not yield to the expected C-H functionalised product.



Scheme 1: Proposed strategy to C-H functionalise anomeric position

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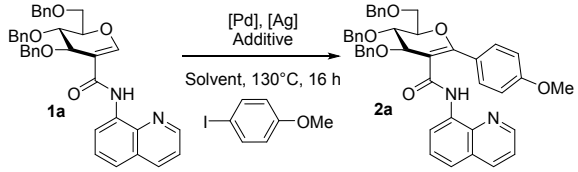
Table 1: Optimisation of the C-H functionalisation of **1a**[a]



	"Pd"	AgOAc equiv.	Additive (equiv.)	Solvent (mL)	Yield[b]: 2a/1a
1	$Pd(OAc)_2$	3.5	-	Toluene (1 mL)	19% /42%
2	$Pd(OAc)_2$	3.5	K_2CO_3 (2.6)	Toluene (1 mL)	34% /0%
3	$Pd(OAc)_2$	3.5	K_2CO_3 (2.6)	Dioxane (1 mL)	14% /44%
4	$Pd(OAc)_2$	3.5	K_2CO_3 (2.6), Citric acid (0.85)	Toluene (1 mL)	36% /64%
5	Pd(cod)Cl$_2$	3.5	K_2CO_3 (2.6), Citric acid (0.85)	Toluene (1 mL)	60% /40%
6	Pd(cod)Cl$_2$	1.5	K_2CO_3 (2.6), Citric acid (0.85)	Toluene (1 mL)	46% /32%
7	Pd(cod)Cl$_2$	1.5	K_2CO_3 (3.6), Citric acid (0.85)	Toluene (1 mL)	52% /37%
8[c]	Pd(cod)Cl$_2$	1.5	K_2CO_3 (3.6), Citric acid (0.85)	Toluene (2 mL)	72% /26%

[a]Conditions: **1a** (0.085 mmol), [Pd] (20 mol%), AgOAc (x equiv.), additive (x equiv.), 4-iodoanisole (6 equiv.), solvent (x mL), 130 °C, 16 h under air. [b]Yields were determined by ^{1}H-NMR using acetophenone as internal reference. [c]Catalytic system ([Pd], [Ag], and Additive) was added in two halves (t0 and t+3h), Isolated **2a** : 58%

Only traces of a compound where the aryl was added in anomeric α position, but presenting a shift of the double bond in position 2-3, was observed (see SI). This reactivity was already described on simple glycals *via* a Pd-catalyzed process in the presence of aryl bromides, aryl boronic acids or benzoic acids.[10] The first step of the mechanism leading to this undesired product could follow a *syn*-carbopalladation on the bottom side of the glycal double bond. Then, a *syn*-β-elimination of H-[Pd] involving hydrogen 3 finally re-generates the double bond in position 2-3. This β-elimination process can only occur with a hydrogen atom, which is *syn* to the [Pd]. By this mechanism, the double bond can thus be recovered only on position 2-3 and not in position 1-2. In our case, we can rule out this type of mechanism (carbopalladation/ β-elimination) since we keep the double bond on the desired position 1-2. We can assume that the strong binding of the amidoquinolyl part to the [Pd] promotes another reactivity probably following a Pd(II)/Pd(IV) C-H functionalisation mechanism in accordance with the literature.[5b] Moreover, only reactive iodide partners are suitable, since 4-bromoanisole failed to yield **2a**. The compatibility of our developed method with different aryl and alkenyl iodides was then evaluated (Table 2). Both iodoaryl partners possessing electron-withdrawing and electron-donating groups are tolerated in *para* or *meta* position leading to modest to good yields (Table 2, **2a**-**2i**). Pharmacologically active moiety such as 3,4,5-trimethoxyphenyl[11] was introduced in a good 67% yield (Table 2, **2j**). Sensitive functionalities such as methyl ester, cyano or chloride groups are compatible (Table 2, **2d**, **2e** and **2h** respectively). This last example is particularly interesting since it allows the possibility to post-functionalise the obtained structure *via* cross-coupling reactions. Heteroaryl and activated alkenyl iodides could be also successfully coupled (Table 2, **2k**-**2l**). Interestingly, protected iodo phenylalanine partner led to the corresponding product in a satisfying 61% yield given access to a *C*-glycosyl amino acid analogue (Table 2, **2m**). When *p*-diiodobenzene was used, **2n** resulting from the double C-H functionalisation, was obtained in good yield (76%). Other glycal structures were tested (Table 3) such as D-galactal (**3a**,**b**) and D-lactal (**5**), which led to the corresponding products with comparable yields as their glucal analogues. Interestingly, a disaccharide-type *C*-glycosyl amino acid was successfully obtained (**5**). Sensitive isopropylidene protecting group tolerates both the aminocarbonylation conditions and the C-H functionalisation process with the same range of yields (**4a,b**). Nevertheless, the presence of ester-type protecting groups on glycal inhibits completely the reactivity. Only starting material was recovered in these cases. Ester groups are known in sugar chemistry to have a disarming effect on the glycosylation process.[12]

Table 2: Aryl/alkenyl iodides scope of the C-H functionalisation

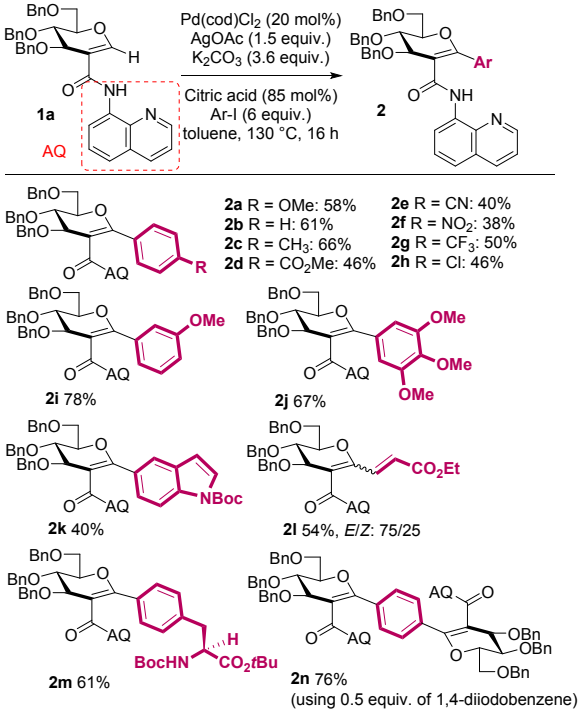
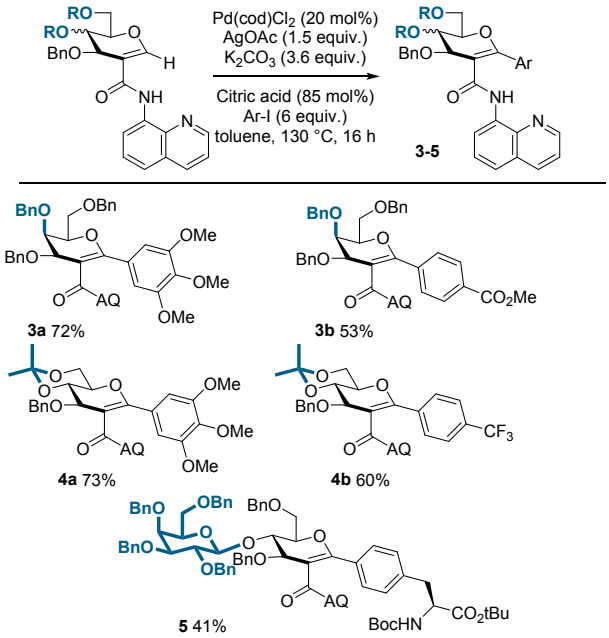
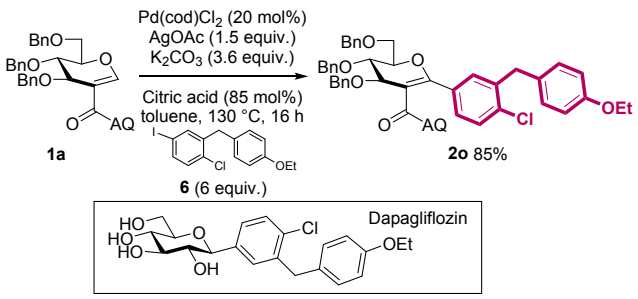


Table 3: Glycals scope for the C-H functionalisation



This effect could explain the absence of reactivity in our methodology and give us clue about the mechanism. Indeed, in concerted metalation-protonation mechanism proposed in some C-H functionalisation literature, the acidity of the proton is crucial to observe reactivity.[13]Following this postulate, a disarming effect should increase the acidity of the anomeric proton and thus promote the reactivity. This type of mechanism is thus unlikely. On the contrary, it was proved that C-H bond energy is an important parameter to explain some reactivities. Indeed, in transition-metal catalyzed processes, activation of a strong C-H bond leads to a favorable strong metal-carbon bond.[13] C-H bond energy could be, in our case, the crucial point. Further investigations will be performed to explore this hypothesis. Our methodology was scaled up by submitting 800 mg of **1** with phenyl iodide as coupling partner. Satisfyingly, the corresponding *C*-arylglycoside **2b** is obtained in a similar yield than in the 50 mg scale (57% versus 61%). Finally, we applied our method to the synthesis of an analogue of the Dapagliflozin drug, commercialized (FORXIGA®) to treat type 2 diabetes (Scheme 2). Compound **1** was thus reacted in the optimised conditions in presence of diaryl iodide **6** leading successfully to the desired Dapagliflozin analogue **2o** in an excellent 85% yield.



Scheme 2: Application of the developed methodology to the synthesis of a Dapagliflozin analogue

Conclusions

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A Pd-catalyzed directed C-H functionalisation of the anomeric position on *C2*-amidoglycals was presented as a novel route to *C*-aryl/alkenylglycosides. Diverse aryl/alkenyl iodides and glycals could be successfully engaged leading to good to excellent yields. Application of the methodology to the synthesis of glycosylated (mono- and disaccharide) amino acids and to the synthesis of an analogue of Dapagliflozin is depicted. Mechanistic investigation is undergoing to understand the role of each reagent.

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Conflicts of interest

There are no conflicts to declare.

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