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Intramolecular Pd-Catalyzed Anomeric C(sp^3)–H Activation of Glycosyl Carboxamides

Nicolas Probst,[†] Gwendal Grelier,[‡] NourEddine Ghermani,[§] Vincent Gandon,[‡,∥] Mouâd Alami,[†] and Samir Messaoudi*[,†]

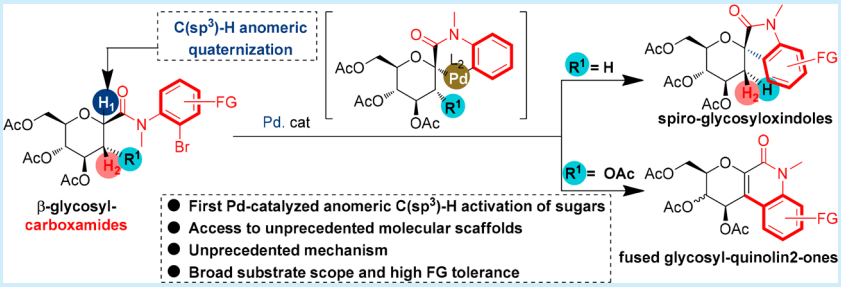
[†]BioCIS, Univ Paris-Sud, CNRS, University Paris-Saclay, Châtenay-Malabry, France

[‡]Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Univ Paris-Sud, Université Paris-Saclay, 1, av de la Terrasse, 91198 Gif-sur-Yvette, France

[§]Institut Galien, Univ-Sud, CNRS, University Paris-Saclay, Châtenay-Malabry 92296, France

[∥]Institut de Chimie Moléculaire et des Matériaux d'Orsay, CNRS UMR 8182, Univ Paris-Sud, Université Paris-Saclay, 91405 Orsay, France

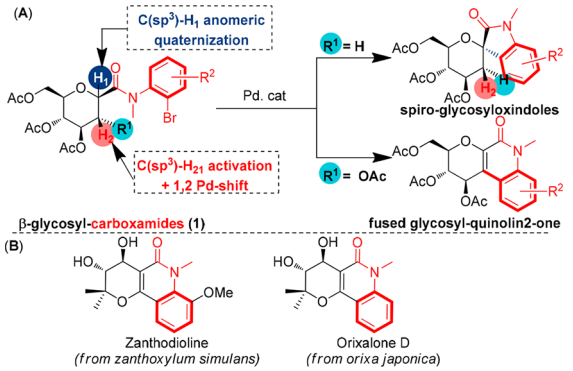
Supporting Information



ABSTRACT: An expedient method for the synthesis of fused glycosylquinolin-2-ones and glycosylspirooxindoles through an unprecedented intramolecular Pd-catalyzed anomeric C–H activation of the sugar moiety of 2-bromophenyl glycosylcarboxamides is reported. The scope of the reaction is broad and tolerates a wide range of functional groups.

The ability to synthesize complex molecules in a rapid and efficient manner still represents a major challenge in organic chemistry. In this context, C–H bond functionalization[1] offers a unique opportunity to access compounds of synthetic interest from readily available starting materials. Over the past decade, transition-metal-catalyzed functionalization of seemingly inert C(sp^3)–H bonds has emerged as an efficient method for C–C bond formation.[2] In particular, substantial progress has been achieved in the palladium-catalyzed activation of C(sp^3)–H bonds of challenging substrates (e.g., amino acids,[3] peptides,[4] cyclopropanes,[5] amines,[6] natural products,[7] etc.). However, the arylation of inert C(sp^3)–H bonds in carbohydrates has never been examined.[8] From a conceptual point of view, this methodology, if successful, would lead to greater scope in the C(sp^3)–H bond arylation, generating various motifs of synthetically useful fused glycosyl heterocycles. Moreover, the modification of carbohydrate scaffolds has attracted tremendous interest recently to investigate the complex nature of sugar-mediated molecular recognition processes in biological systems.[9] In this context, we initiated a research program focused on the C–H activation and functionalization[10] of sugars and envisioned that an intramolecular arylation of glycosylcarboxamides of type **1** (Scheme 1, A) could provide an efficient route for the preparation of spirooxindole glycosides. Herein, we disclose our efforts to develop the intramolecular direct arylation of glycosides employing an amide-based tether that proceeds under palladium catalysis, providing access to both spiro-glycosyloxindoles and fused glycosylquinolin-2-ones structurally close to the natural products zanthodiolone and orixalone D[11] (an inhibitor of the

Scheme 1. (A) Concept of the Intramolecular Csp^3–H Arylation of 2-Bromophenyl β-Glucosyl-1-carboxamides. (B) Natural Products Orixalone D and Zanthodiolone of Glycosylquinolin-2-ones



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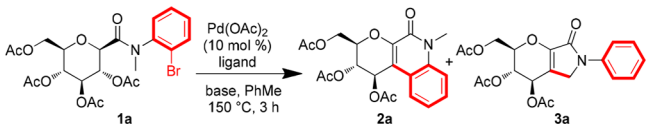
production of nitric oxide in murine macrophage-like cells,[11] Scheme 1, B). In addition, this study demonstrates the pivotal role played by the acetate group at C2 on the regioselectivity of the C(sp^3)−H bond cleavage. Additionally, we report experimental observations and DFT calculations on the key C(sp^3)−H activation mechanism.

We decided on initial experiments to explore the feasibility of the coupling of 2-bromophenyl β-glucosyl-1-carboxamide **1a** by investigating reaction product formation under fixed parameters: Pd catalyst ($Pd(OAc)_2$, 10 mol %), solvent (toluene), temperature (150 °C), and time (3 h). Some representative examples are listed in Table 1. Carrying out the reaction of **1a** in the presence of

Table 1. Optimization of the Coupling Reaction of 1a[a]



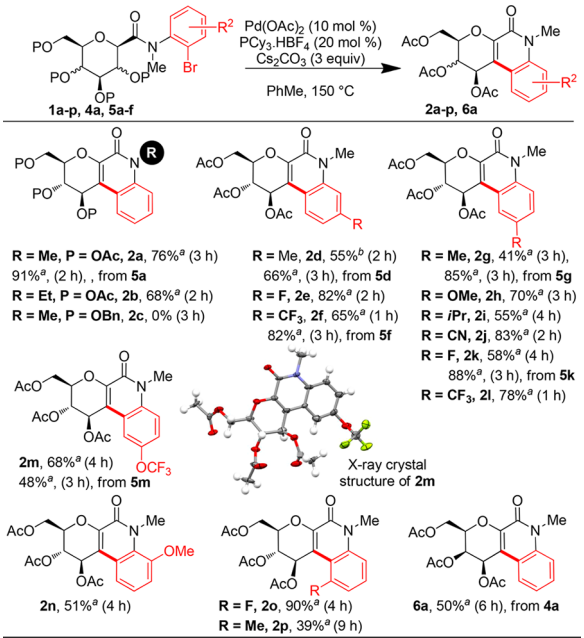
			HPLC yield[b] (%)	
entry	ligand	base	**2a**	**3a**
1	$PCy_3{\cdot}HBF_4$	K_3PO_4	22.5	8.3
2	$PCy_3{\cdot}HBF_4$	LiOAc	3.0	2.7
3	$PCy_3{\cdot}HBF_4$	AgOAc	0.0	0.0
4	$PCy_3{\cdot}HBF_4$	DIPEA	0.0	0.0
5	**$PCy_3{\cdot}HBF_4$**	**Cs_2CO_3**	**76.2 (76)**[c]	**8.0**
6	$PCy_3{\cdot}HBF_4$	Ag_2CO_3	0.0	0.0
7	$PCy_3{\cdot}HBF_4$	K_2CO_3	7.9	6.0
8	$PCy_3{\cdot}HBF_4$	LiHMDS	0.0	0.0
9	$PCy_3{\cdot}HBF_4$	NaO*t*Bu	0.0	0.0
10	PCy_3	Cs_2CO_3	52.9	8.5
11	$PCp_3{\cdot}HBF_4$	Cs_2CO_3	39.2	0.0
12	PPh_3	Cs_2CO_3	67.0	32.2
13	dppp	Cs_2CO_3	20.2	0.0
14	XantPhos	Cs_2CO_3	15.8	0.0
15	Davephos	Cs_2CO_3	12.8	11.5
16	PhDavephos	Cs_2CO_3	67.0	6.7
17	Sphos	Cs_2CO_3	14.0	4.2
18	Cphos	Cs_2CO_3	12.3	0.0
19	PCy_3·Pd G2	Cs_2CO_3	70.3	17.2
20	$PCy_3{\cdot}HBF_4$	Cs_2CO_3	53.9[d]	0.0

[a]A sealable tube was charged with anilideglycoside **1a** (0.06 mmol), $Pd(OAc)_2$ (10 mol %), ligand (20 mol %), base (3 equiv), 1,3,5-trimethoxybenzene (0.5 equiv, internal standard), and toluene (0.08 M). The tube was flushed with argon and sealed. The reaction mixture was heated at 150 °C during 3 h in an oil bath. [b]Yields calculated by HPLC with respect to 1,3,5-trimethoxybenzene as internal standard. [c]Yield of isolated product. [d]5 mol % of $Pd(OAc)_2$ and 10 mol % of $PCy_3{\cdot}HBF_4$ were used.

$PCy_3{\cdot}HBF_4$ (10 mol %) as ligand and K_3PO_4 (1.5 equiv) as base led to a partial conversion of the starting material and provided two new unexpected arylated compounds: compound **2a** as the major product (22.5% HPLC yield), and **3a**[12] as the minor one (8.3% HPLC yield). Compound **2a** could arise from Csp^3−H arylation at the C2-position followed by the loss of an *ipso*-acetate group. This product, although obtained in a small amount, showed the feasibility of the alluring conversion of 2-bromophenyl β-glucosyl-1-carboxamide **1a** into a fused glucosyl quinolin-2-one **2a**. With further optimization, such a transformation could provide an expedient access to unprecedented 1,2-fused glycosylquinolin-2-one systems, thus allowing the exploration of unknown chemical space which could lead to the identification of new bioactive compounds. Thus, we continued our investigations by fine-tuning the conditions of this novel transformation, and we found that the efficiency of the reaction was significantly affected by the choice of the base (entries 1−10). In fact, weak bases such as K_3PO_4, AgOAc, and LiOAc were ineffective as organic bases such as DIPEA (entries 1−4). On the other hand, the use of Cs_2CO_3 led to total conversion of **1a** and furnished **2a** in 76% isolated yield, combined with 8% of **3a** (entry 5). In terms of metal carbonates, Cs_2CO_3 was superior to K_2CO_3, while Ag_2CO_3 was ineffective. Strong bases such as NaO*t*Bu or KHMDS, which are usually used in the α-arylation of carbonyl compounds,[13] proved ineffective in our case. This last result may suggest that the formation of a putative Pd-enolate is not operative and the reaction proceeds via a C−H arylation pathway. In another set of experiments, we showed that the nature of the ligand also had a profound influence on the reaction yields (entries 10−18). Among all phosphines, PCy_3 used as its phosphonium salt proved to be the optimal ligand, furnishing **2a** in 76% yield (entry 5). The use of other bulky electron-rich phosphines was less effective in this model reaction, except PPh_3 and PhDavePhos, which afforded 67% HPLC yields in both cases (entries 12 and 16). Finally, a 70% yield of **2a** was obtained when the reaction of **1a** was carried out in the presence of PCy_3 Pd-G_2 precatalyst (5 mol %) instead of $Pd(OAc)_2/PCy_3{\cdot}HBF_4$ (entry 19). While one can note that the amount of the catalytic system was reduced to 5 mol % of $Pd(OAc)_2$ and 10 mol % of $PCy_3{\cdot}HBF_4$, the yield of **2a** dropped to 53.9% (entry 20).

Motivated by these results, we next explored the scope of the intramolecular coupling of various β-glycosylcarboxamides **1a−p**, **4a**, and **5a−f** (Scheme 2). Remarkably, this reaction appeared to be general with respect to different substituents on the aromatic nucleus of the glycosylcarboxamides (e.g., −F, $-CF_3$, −CN, −Me,

Scheme 2. C−H Activation of Anilide Glycosides 1a−p, 4a, or 5a−f*



*Reaction conditions: A sealable tube was charged with anilideglycoside **1a−p**, **4a**, or **5a−f** (0.06 mmol), $Pd(OAc)_2$ (10 mol %), $PCy_3{\cdot}HBF_4$ (20 mol %), Cs_2CO_3 (3 equiv) in toluene (0.08 M). The reaction mixture was heated at 150 °C during the time indicated in parentheses. [a]Yield of isolated product.

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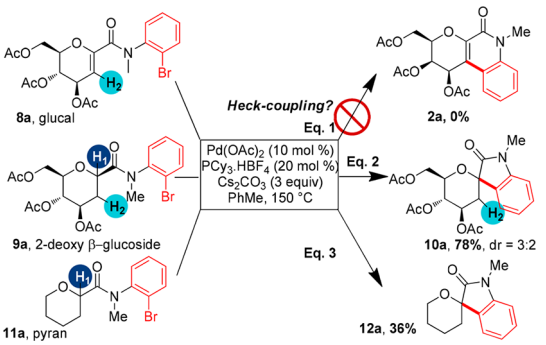
−OMe, −OCF_3). Substrates bearing a substituent *para* to the glycosylcarboxamide bond (substrates **1g−m**) were reacted under the optimized conditions to give the corresponding glycosides **2g−m** in moderate to good yields, regardless of their electron-withdrawing or -donating nature. The exact structure of **3m** was confirmed by the crystal structure analysis. In addition, the cyclization of bromoglycosylcarboxamides bearing a substituent *para* to the bromine atom (substrates **1d−f**) afforded the corresponding products **2d−f** in good yields. Importantly, the sterically demanding *ortho* substitution pattern either *ortho* to the carboxamide bond (substrate **1n**) or *ortho* to the bromine atom (substrate **1o,p**) was tolerant toward the C−H arylation reaction, leading to derivatives **2n−p** in 90%, 39%, and 51% yields, respectively. One can note that in all of the reactions shown in Scheme 2 a trace amount of the side products **3a−p** were detected by LCMC, but these compounds have never been isolated. Finally, alcohols of the sugar moiety had to be protected as acetates since no reaction occurred when hydroxyl groups were benzylated or left unprotected. This result suggests that the acetate groups play an important role in the reaction mechanism.

To shed more light on this reaction, we examined the influence of the acetate groups in this C−H activation process. As shown in Scheme 2, this reaction is not limited to only *β*-glucosides **1a−p** since *β*-galactoside **4a** and *β*-mannosides **5a−f** were also valuable substrates to give products **6a** and **2a**, **2d**, **2f**, **2g**, **2k**, and **2m** in yields ranging from 48% to 91%. These experimental data show that mannosides **5a−f**, which afforded products identical to those obtained from glucosides **1a**, **1d**, **1f**, **1g**, **1k**, and **1m**, are more reactive than their diastereoisomers, leading to better yields.

To probe whether the cyclization proceeds via a Heck-like mechanism or through C(sp^3)−H arylation followed by the loss of the acetate group, we performed the reaction using glucal **8a** (Scheme 3, eq 1). This substrate failed to cyclize under our

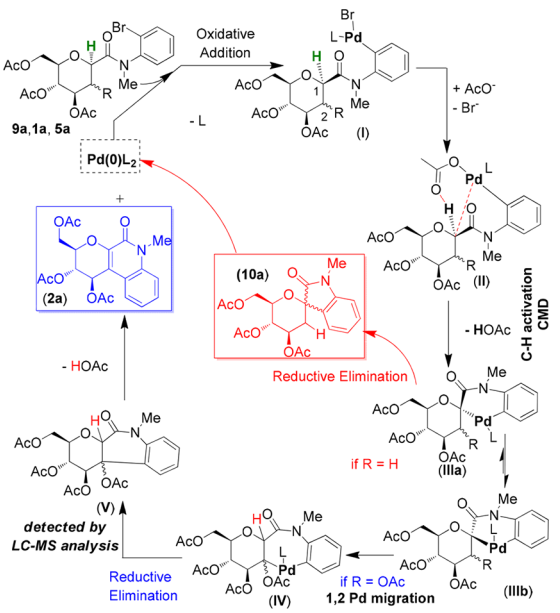
Scheme 3. C−H Activation of Other Glycosides (Glucal 8a, 2-Deoxyglucoside 9a), and Pyran 11a[a]



[a]Reaction conditions: A sealable tube was charged with an anilide (0.06 mmol), $Pd(OAc)_2$ (10 mol %), $PCy_3{\cdot}HBF_4$ (20 mol %), Cs_2CO_3 (3 equiv), and toluene (0.08 M).

conditions, indicating that the Heck-like mechanism is unlikely. We also explored the effect of the C2-acetate group. Surprisingly, when the 2-deoxy-*β*-glucosyl carboxamide **9a** was used as the coupling partner, the C(sp^3)−H activation occurred selectively at an anomeric position rather than at the C2 position, providing, for the first time, the spirooxindole **10a** in 78% yield (Scheme 4, eq 2). This result indicates clearly that the C2 acetate group plays a pivotal role in the regioselectivity of the C−H activation. However, in this case, we noticed the reaction proceeded with erosion of the diastereoselectivity (dr = 3:2). Moreover, reaction

Scheme 4. Mechanistic Proposal (L = PCy^3)



with pyran carboxamide **12a** occurred smoothly, furnishing, again, the spirooxindole **2a** in a moderate 36% yield[14] (eq 3).

In light of the above observations, we suggest the mechanism depicted in Scheme 4. It starts with the oxidative addition of Pd(0) into the C−Br bond of typical substrates such as **9a**, **1a**, or **5a** followed by ligand exchange to give **II**. The intramolecular C−H activation of the anomeric bond then occurs through a concerted metalation deprotonation (CMD) mechanism to produce the palladium *C*-enolate **IIIa**, which is in equilibrium with its diastereomeric form **IIIb** through a putative *O*-enolate. Depending on the nature of the R group at the C2 position, the **IIIa**/**IIIb** mixture may furnish the spirooxindole **10a** when R = H by reductive elimination or undergo a 1,2 Pd-migration[15] when R = OAc, followed by reductive elimination to produce **V**. This latter intermediate, which is not enough stable under basic conditions, evolves into **2a** through an anti-HOAc elimination. It is important to note that the intermediate **V** could be detected by LC−MS analysis with a retention time of 13.35 min corresponding the *m*/*z* of 464.1556 ($[M + H]^+$) and 386.1383 ($[M + Na]^+$) (see the SI) when the reaction of **2a** was performed by using only 0.5 equiv of the base. All of these results are in agreement with the mechanism suggested here. In fact, C−H activation can occur in various ways, including concerted or nonconcerted processes.[16] To check the validity of the proposed CMD mechanism, and also support the hypothesis of type **III** complexes as common intermediates for the two reaction products, DFT computations were carried out at the M06/SDD-6-311+G(2df,2p) level.[17,18] The only viable pathway that could be found was indeed a CMD. Using **9a** as substrate for the calculations (R = H), the free energy of activation was found to be +36.1 kcal/mol at C1.[19,20] The corresponding transition state is shown in Figure 1. By comparison, the CMD at C2 is more energetically demanding by 1.2 kcal/mol (37.2 kcal/mol). Using **1a** (R = OAc down) or **5a** (R = OAc up) as substrate, the CMD at C1 was also always favored (+41.9 vs +44.5 kcal/mol and +36.4 vs +43.5 kcal/mol, respectively). These values are corroborated by the higher reactivity of **5a** compared to **1a** observed experimentally. Thus, the spiro complexes **III** are expected to be common intermediates for both product types. Although not as yet elucidated, the reason for the ring expansion from **III** to **IV** should be due to the increased acidity of the proton

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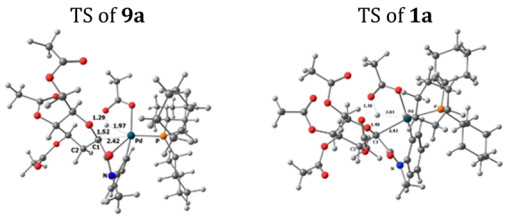

Figure 1. CMD transition states corresponding to **9a** and **1a** (selected distances in Å).

at C2 when R = OAc, which could allow a CMD after κ^1-coordination of a base (OAc^-, HCO_3^-, or CO_3^{2-}).[20]

In conclusion, we report an unprecedented method for the synthesis of fused glycosylquinolin-2-ones and glycosylspirooxindoles through an intramolecular Pd^0-catalyzed anomeric C(sp^3)−H activation of glycosylcarboxamides. The method tolerates a wide range of functional groups, and a variety of substituted glcosylquinolinones were prepared in good yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02170.

Experimental procedures, spectroscopic data, and NMR spectra of new compounds (PDF)

X-ray crystallographic data for compound **3m** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: samir.messaoudi@u-psud.fr.

ORCID

Vincent Gandon: 0000-0003-1108-9410

Samir Messaoudi: 0000-0002-4994-9001

Notes

The authors declare no competing financial interest.

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(20) Of note, the CMD barriers are much higher with a carbonate ligand instead of an acetate (~45 kcal/mol). For a discussion, see ref 18.

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