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Diastereoselective Pd-Catalyzed Anomeric C(sp³)-H Activation: Synthesis of α -(hetero)aryl C-Glycosides

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ABSTRACT: Anomeric C-H bond activation is an unsolved long-standing synthetic challenge. **Herein we report a diastereoselective** Pd-catalyzed anomeric C(sp³)-H activation methodology that allows the synthesis of elusive C-(hetero)arylglycosides with an exclusive α -selectivity.

1. INTRODUCTION

C-(hetero)aryl glycosides belong to a privileged class of carbohydrates in which the biologically labile C-O anomeric acetal bond is substituted by a C-C bond.¹ This strong glycosidic bond confers to such compounds a significantly enhanced *in vivo* resistance towards basic, acidic, and enzymatic hydrolysis.² A plethora of C-aryl glycosides are found in nature and serve as key **substrates** in **various** biological mechanisms or are used as antitumor,³ antibiotic,⁴ and type II antidiabetic agents (Figure 1).⁵ As an example, pseudouridine is the first modified C-nucleoside⁶ discovered in RNAs of living organisms. Different classes of RNAs are subject to pseudouridylation such as tRNAs, ribosomal RNAs and small nuclear RNAs (snRNAs). In a similar way, C-mannosyl tryptophan (C-Man-Trp) (Figure 1) is another structurally unique C-glycosylated aminoacid involved in post-translational modification of proteins (PTM).⁷ This C-glycoside, isolated in human urine, is employed as a biomarker of renal function. As a proof of the C-glycosides utility, Benner and coworkers⁸ reported recently novel DNA and RNA-like systems (Hachimoji DNA) built from eight nucleotides including dZ and dS C-nucleobases (Figure 1), which met the requirements needed to support Darwinian evolution. From the medicinal chemistry point of view, among the C-glycoside-derived drugs, dapagliflozin has been widely used for the treatment of type-2 diabetes.⁹ Moreover, a particular variety of anthraquinone C1-aryl glycoside,¹⁰ featuring an amino group at the C3 position of the sugar nucleus such as kidamycin, marmycin, lactoquinomycin or analogues **1** and **2** have been proposed to **act** *via* a similar mechanism than doxorubicin as DNA binders. Furthermore, it was **demonstrated** that these **compounds** may **operate** through other

original pathways including direct genome targeting.^{3a} Owing to the pharmacological properties **importance** of

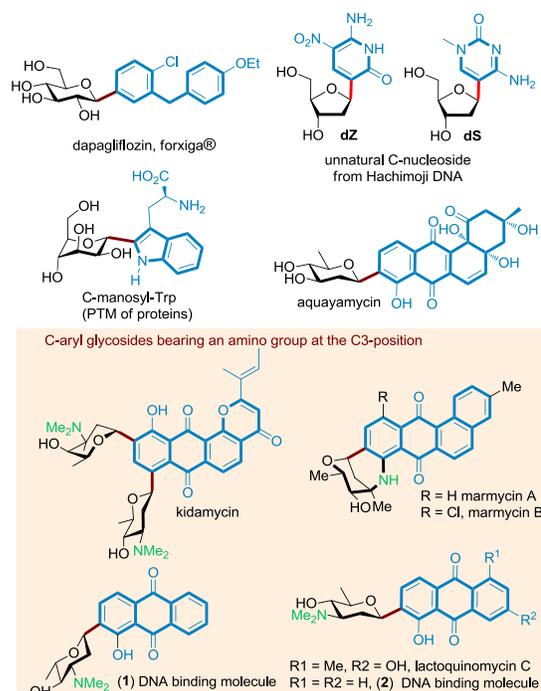


Figure 1. Examples of natural and unnatural bioactive C-glycosides

numerous C-glycosides, their synthesis is a thriving area of research. In addition to organic synthetic methods,¹¹ the development of organometallic **couplings** with two prefunctionalized substrates such as Stille,¹² Suzuki-Miyaura,¹³ Corriu-Kumada,¹⁴ Hiyama, Denmark¹⁵ and Negishi¹⁶ cross-couplings have emerged over the past few decades (Scheme 1-a). The majority of these methods are

focused on reactions between an organometallic partner and glycosyl precursors in which the anomeric position is pre-activated. However, these existing methods involve the use of pre-functionalized organometallic partners of high reactivity, requiring delicate operating conditions and sophisticated methods for their preparation. Then, the development of new synthetic methods to access C-glycosides is still one of the highly challenging topics in glycochemistry.

The persistent need from drug discovery programs for elaborate complex C-aryl glycosides has led to pioneering developments in the C-H functionalization¹⁷ which avoided the pre-activation of the aryl partners in the glycosylation reaction. In this context, several groups have reported efficient methods by using activation of C(sp²)-H bond of aromatic substrates with sugar partners (Scheme 1-b). These approaches, which are often in conjunction with a directing group strategy,¹⁸ have enabled the selective β -C(sp²)-H functionalization of arenes. The seminal work revealed by Ye¹⁹ highlighted the use of silylated 1-iodoglycals as the coupling partners in a Pd-catalyzed Csp²-H activation of benzamides by using *N*-quinolyl (N-Q) motif as a directing group. Ackermann *et al.*²⁰ reported recently the same approach of coupling involving a *N*-triazolyldimethylmethyl (*N*-TAM) directing group. Chen and co-workers²¹ described an additional notable example using this strategy for the synthesis of sutured C-aryl glycosides *via* palladium-catalysed *ortho*-directed C(sp²)-H activation of arenes and heteroarenes with glycosyl chloride donors. Glycals were also used as valuable partners in Ir-catalyzed stereoselective hydroarylation reaction with arenes bearing a pyridine motif as an *ortho*-directed C(sp²)-H group.²² More recently, Cheng²³ and Liang²⁴ reported independently, an elegant and modular approach

for the synthesis of α -C-aryl glycosides *via* Catellani-type C-H glycosylation reaction (Scheme 1-c). In an inversed strategy, Ferry *et al.*²⁵ demonstrated that the installation of the aminoquinoline at the C2 position of glycals is effective in a C(sp²)-H arylation of the anomeric position to access to unsaturated C-aryl glucosides (Scheme 1-d).

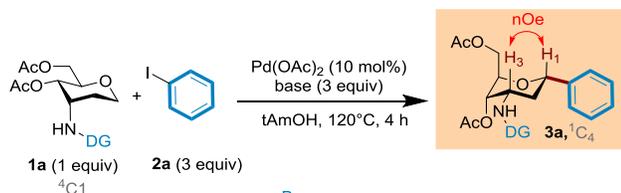
Albeit with considerable progress, all these strategies involve the C(sp²)-H activation of aromatic bonds or glycals but such methods are not amenable to the less active C(sp³)-H bond functionalization. In this context, stereoselective manipulations at the anomeric C(sp³)-H bond constitute one of the most challenging and unexplored problems for the preparation of C-aryl glycosides. In this context, we reported recently in a preliminary study, an intramolecular arylation of 2-bromophenyl glycosylcarboxamide through C(sp³)-H quaternization (Scheme 1-e).²⁶ However, this method suffers from the lack of diastereoselectivity. Accordingly, we believe that developing an intermolecular C(sp³)-H glycosylation method of sugars to readily access saturated C-aryl glycosides would find widespread utility (Scheme 1-f).

2. RESULTS AND DISCUSSION

2.1. Design plan. As part of our ongoing interest in C-H functionalization of sugar motifs²⁷ combined with the abundance of 3-amino-C-aryl glycosides as natural and bioactive molecules (Scheme 1), we sought to design a new, C(sp³)-H activation technology that allows the synthesis of complex 3-amino-C-aryl glycosides as well as provides single-step access to C-glycosyl analogs of pharmaceutically important molecules *via* late-stage functionalization (Scheme 1-f).

Scheme 1. Initial Plan and Related Formerly Published work: **a.** Traditional Cross-Coupling Involving Organometallics Species. **b.** C(sp²)-H Functionalization of Arenes With Halogenated Sugars and Glycals. **c.** Catellani-type C(sp²)-H Glycosylation of Sugar Chlorides **d.** C(sp²)-H Functionalization of Glycals with Aryl Iodides. **e.** Intramolecular anomeric C(sp³)-H Activation of glycosylcarboxamide. **f.** Intermolecular anomeric C(sp³)-H Activation of Saccharides.

tion solvent *t*AmOH can be replaced by toluene without affecting the yield (86% vs 84% yield). In addition, the use of phenyl bromide instead phenyl iodide produces **3a** in 50% yield demonstrating the generality of this procedure toward the aryl halide partner. Finally, control experiment showed that the Pd(OAc)₂ was necessary to achieve this transformation since **3a** was not observed when the coupling was conducted in the absence of the catalyst.

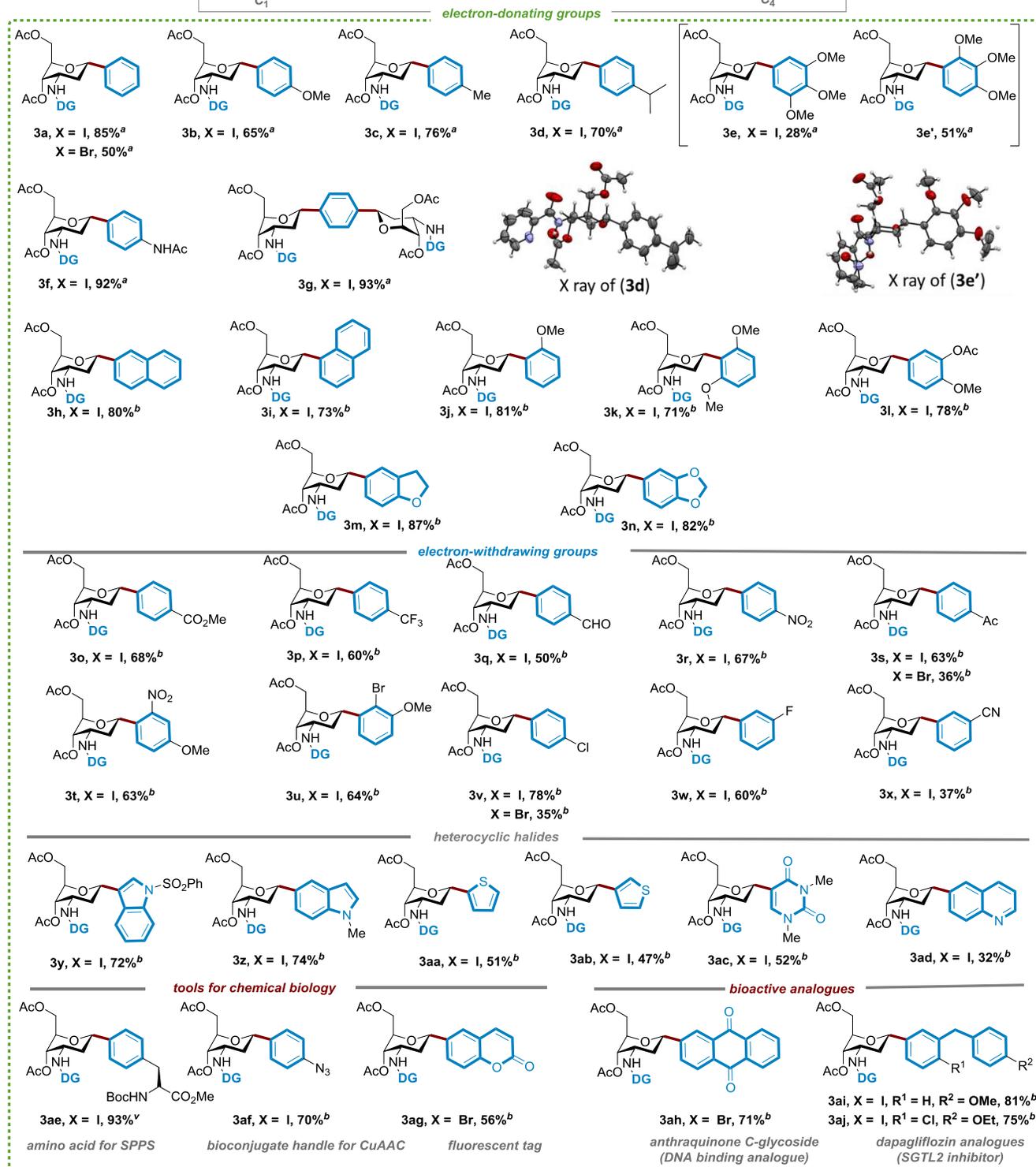
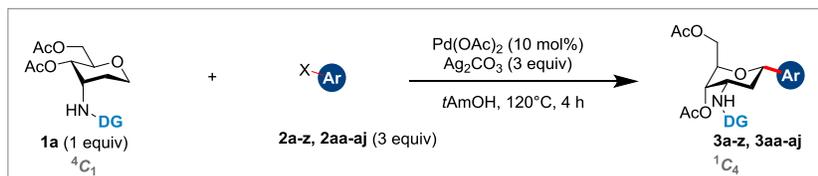


Bases		
Ag ₂ CO ₃		86%
Ag ₂ CO ₃ (2 equiv)		72%
KHCO ₃		traces
Ag ₂ O		40%
Solvents		
MePh versus <i>t</i> AmOH		84%
MeCN versus <i>t</i> AmOH		41%
Control experiments		
No catalyst		no conversion
PhBr versus PhI		50%

Table 1. Exploration of the Reaction Conditions for the Anomeric C(*sp*³)-H Arylation. nOe Correlations for the Structure Determination (¹C₄ Conformation and the α-Configuration) of **3a**.

2.3. Synthetic scope. Prompted by these exciting results, we subsequently investigated the substrate scope for the C(*sp*³)-H glycosylation of **1a** with a range of sterically and electronically diverse aryl bromides and iodides **2**. As showed in Scheme 2, *ortho*, *meta*- and *para*-substituted aryl iodides and bromides (**2a-z**, **2aa-aj**) were all suitable coupling partners, providing C-arylglycosides **3a-z** and **3aa-3aj** in moderate to good yields with a perfect control of the α-selectivity. Various reactive functions on the aromatic nucleus such as -OAc, -CO₂Me, -CHO, -Ac, -NO₂, -Br, -Cl, -F, -CN, -CF₃, -NHAc and -NH₂Boc are tolerated demonstrating the high efficiency of this methodology. Importantly, the sterically hindered *ortho*, *ortho'* substituted aromatic ring does not affect the glycosylation process as compounds **3k** was obtained in 71% yield. Surprisingly, the reaction of 3,4,5-trimethoxy iodobenzene **2e** gave a separable mixture of two C-glycoside regioisomers **3e** and **3e'** in 28% and 51% yield, respectively. The exact structure for both regioisomers were clearly determined by 1D and 2D NMR analysis,

Scheme 2. Diastereoselective C(*sp*³)-H Arylation of Sugar **1a**.^a



^a Reactions were performed in an oven dried re-sealable tube using sugar **1a** (0.1 mmol), ArX **2** (3 equiv), Pd(OAc)₂ (0.01 mmol), Ag₂CO₃ (3 equiv) in *t*AmOH (1.0 mL) at 120 °C. ^b Yield of isolated product.

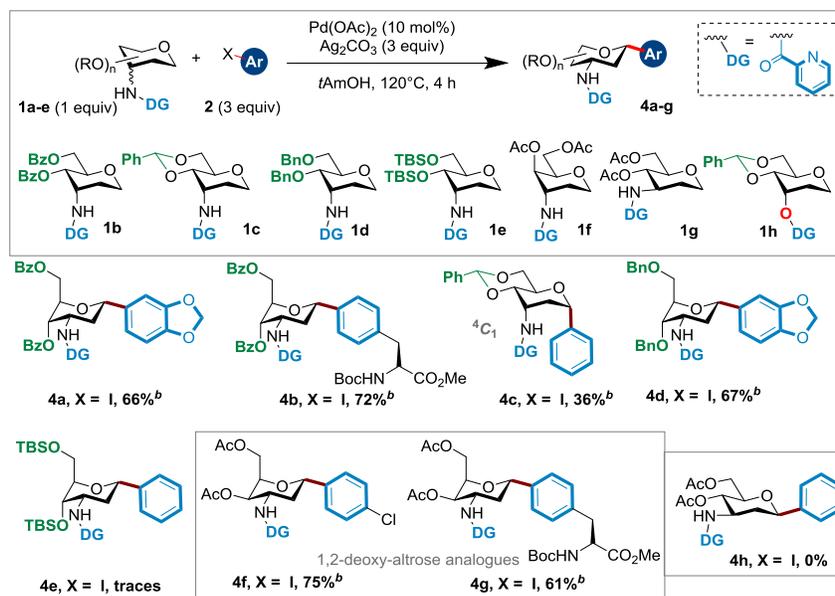
and **3e'** was unambiguously confirmed by crystal structure analysis. This phenomenon was never described before to our knowledge. Of note, performing the C-glycosidic bond forming reaction with 1,4-diiodobenzene **2g** (ratio **1a**:**2g** = 2:1) provides the bis-C-glycoside **3g** in an excellent 93% yield. Interestingly, this anomeric C(sp³)-H activation reaction is not limited to only aryl halides but tolerates also heteroaryl substrates. Thus, couplings with heteroaryl iodides derived from C3- or C5-indole (**2y** and **2z**), C2- or C-3 thiophene (**2aa** and **2ab**), quinoline (**2ad**) or the nucleobase thymine (**2ac**) have been successfully used, furnishing **3y-z** and **3aa-ad** in moderate to good yields.

2.4. Synthetic utility. Next, we moved on to investigate the synthetic utility of this methodology by the synthesis of some C-glycoside tools which may be useful for chemical biology. Thus, C-aryl glycosyl amino acid building block **3ae** which may be used in glycopeptide assembly or the C-aryl glycosyl phenylazide **3af** for CuAAC as well as the fluorescent C-glycoside coumarin tag **3ag** were prepared by this strategy in good to excellent yields (56%-93%). In addition, facile preparation of anthraquinone C-glycoside **3ah** which is an analog of the DNA binding drug (**1**) (Fig. 1), was also achieved in 71% yield offering a strategy for late-stage modification of drug molecules. Finally, the utility of this methodology was highlighted by the synthesis of two potentially bioactive C-glycosides **3ai** and **3aj** which are α -analogs of the dapagliflozin drug used to treat type 2 diabetes (Figure 1).

2.5. Scope of glycosides. To further test whether this strategy could be broadly used with different glycosides, we embarked on C(sp³)-H arylation of other protected forms of glycosides (**1b-h**). As depicted in Scheme 3, this glycosylation methodology tolerates other protecting groups such as benzoate (-OBz, **4a-b**), 4,6-benzylidene (**4c**) and benzyl group (**4d**). However, the TBS-O-protected glycoside **1e** showed poor reactivity under our reaction conditions, leading only to the formation of traces of C-glycoside **4c** detected by LCMS analysis. This result may be explained by a switch of the conformation of **1e** from ⁴C₁ to ¹C₄ that would be imposed by the bulky TBS groups.³⁰ This switch would induce an equatorial orientation of the directing group that is not compatible with the formation of the palladacycle.

Besides, glycoside **1a** derived from glucose, 1,2-deoxy altrose analog **1f** bearing an axial C4-OAc group is also an effective substrate for this methodology, giving the desired C-aryl glycosides **4f** and **4g** in good yields and with exclusive α -diastereoselectivity. Interestingly, the substrate **1g** bearing the directing group in an equatorial position is not an effective glycoside partner (even performing the reaction at higher temperature 160 °C and longer reaction time), implying that the formation of anomeric palladacycle intermediate is not facile for this substrate (*vide infra*). Finally, reaction of the substrate **1h** bearing a C3-picolinic ester directing group with phenyl iodide failed under our optimized conditions, demonstrating the crucial role played by the amide function in the C-H metalation process.

Scheme 3. Diastereoselective C(sp³)-H Arylation of Glycosides **1b-h**.^a



^a Reactions were performed in oven dried re-sealable tube using sugar **1a** (0.1 mmol), ArX **2** (3 equiv), Pd(OAc)₂ (0.01 mmol), Ag₂CO₃ (3 equiv) in tAmOH (1.0 mL) at 120 °C. ^b Yield of isolated product.

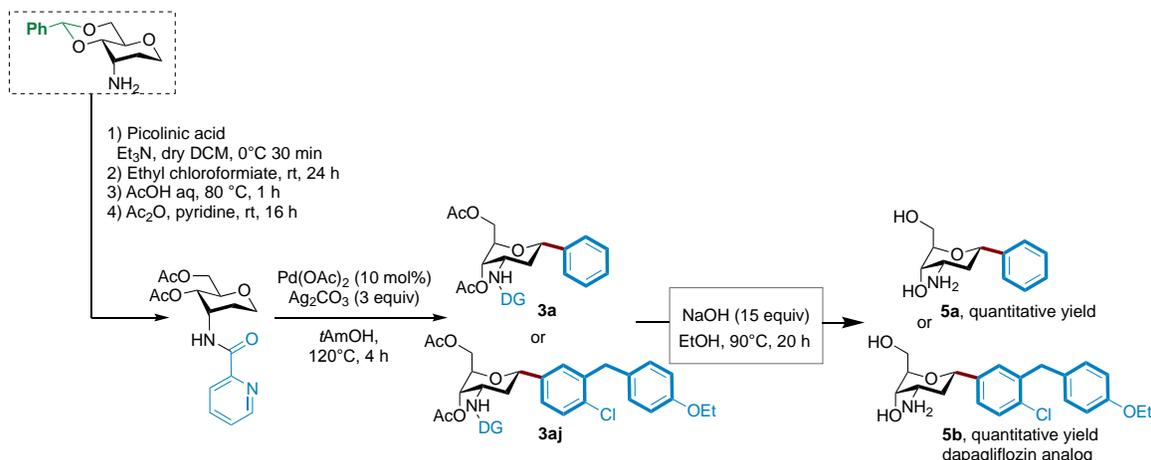
One of the most important challenge in the directed C-H activation strategy is to be able to remove the directing group at the end of the reaction without altering the final substrate. As shown in Scheme 4, the pyridyl amide direct-

ing group was cleanly removed from C-glycoside **3a** under basic conditions. By using sodium hydroxide in ethanol, both directing group and -OAc protecting groups were cleaved concomitantly to give the C-phenylglycoside **5a** in a quantitative yield. Treatment of compound **3aj** under the

same conditions enabled, for the first time, an easy access to the C3-amino α -dapagliflozin analog **5b** as a potential

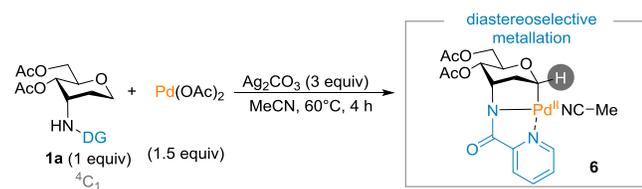
SGLT2 inhibitor (Scheme 4).

Scheme 4. Cleavage of the Directing Group



2.6. Mechanistic considerations. To probe the mechanism of the C(sp^3)-H glycosylation and the origin of the exclusive α selectivity, experimental investigations and density functional theory (DFT) calculations were performed. As shown in Scheme 5, glycoside **1a** was treated with a stoichiometric amount of Pd(OAc)₂ in the presence of Ag₂CO₃ as a base in MeCN. Under these conditions, the anomeric σ -organopalladium complex **6** was isolated, in which the C-Pd bond was formed in the α -configuration, clearly demonstrating that the C(sp^3)-H activation step is stereoselective and takes place preferentially at the axial anomeric C-H bond. The 1,3 diaxial geometry of palladacycle **6** was confirmed by two-dimensional

Scheme 5. Synthesis of the Anomeric Palladacycle **6**.



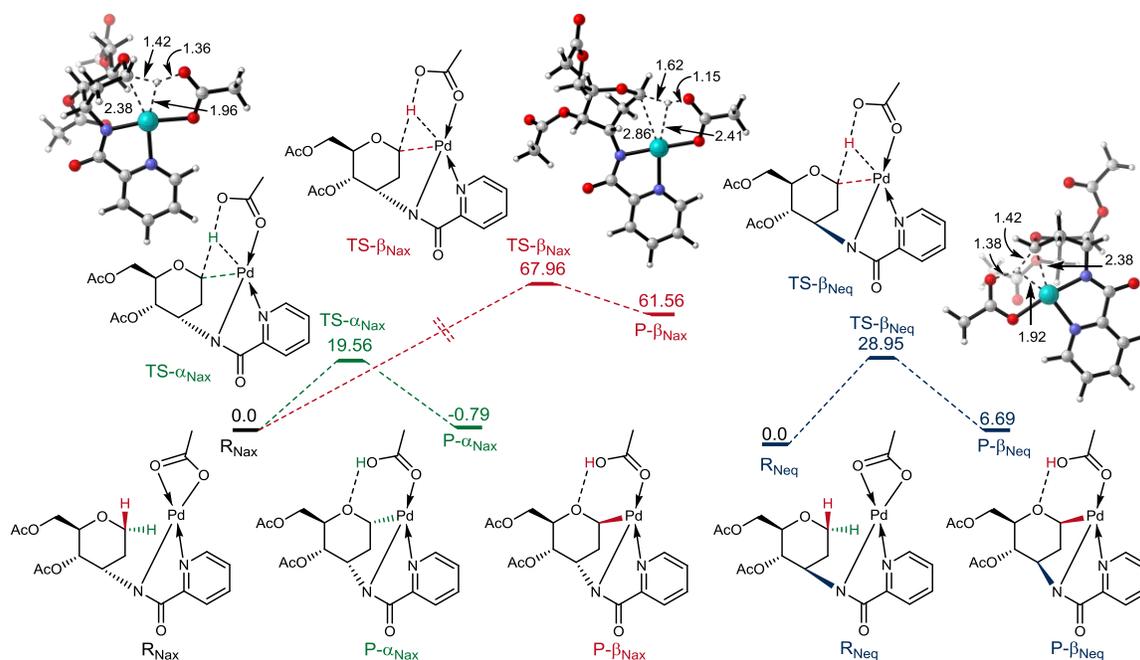
NMR spectroscopy (see the Supporting Information) indicating that the switch from ⁴C₁ conformation to ¹C₄ does not occur at this step but probably would take place at the oxidative addition/reductive elimination steps.

This stereoselective Pd-catalyzed anomeric C(sp^3)-H activation described in this work is highly dependent on the nature of substrate used and the position of the directing group.

To shed more light on the observations reported above, a computational study of the key CMD step was carried out at the M06//6-311++G(d,p)/SDD level of theory (Fig. 3 and SI). It was found that when the directing group is set in the axial position (Figure 3, green profile, left), the CMD pathway that gives rise to the α -configuration is slightly exergonic (-0.79 kcal/mol) and presents a low barrier considering the reaction conditions (19.56 kcal/mol, 120 °C). Contrastingly, the CMD-TS that would result in the β -configuration of the Pd-complex (Figure 3, red profile, middle), presents a barrier of almost 70 kcal/mol while being highly reversible. This is due to the spatial arrangement required, with a hindered face that must adopt a very distorted pyranose core, resulting in a high demand of energy.

We next set to understand the reasons why the β -configuration could not be obtained when the picolinic amide directing group is in the equatorial position (Figure 3, blue profile, right). At first glance, the CMD-TS core exhibits essentially the same 5-membered cycle as **6** (Scheme 5). However, in this scenario, the required energy is higher (28.95 kcal/mol) and the reaction is reversible due mainly to the 1,3-steric hindrance.

Figure 3. Free energy profile (relative $\Delta G_{393.15}$ in kcal/mol) of the CMD pathways. Selected distances (in Å) are shown in the transition structures



In summary, we have developed a new glycosylation reaction through a Pd-catalyzed anomeric $C(sp^3)$ -H activation. The rational design of glycoside substrates by employing the picolinic amide as the directing group shows outstanding reactivity and allowed us to access complex (hetero)aryl glycosides with a precise control of the α -anomeric configuration. The established approach is generally applicable to a wide range of commercially available aryl bromides and iodides as well as other classes of synthetically useful substrates. This methodology also offers a tool for late-stage modification of drug molecules as evidenced by its effective application to the direct $C(sp^3)$ -H arylation of medicinal agents. Furthermore, experimental and computational mechanistic studies have provided evidence that $C(sp^3)$ -aryl bond formation is derived by the spatial positioning of the directing group.

ASSOCIATED CONTENT

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Full optimization table, NMR spectra of all synthesized compounds and HPLC chromatograms.

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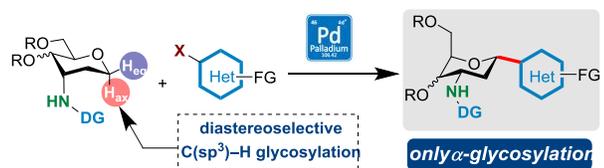
ABBREVIATIONS

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