Directed C-H functionalization of *pseudo*-anomeric position of glycals substrates by metal-catalyzed processes

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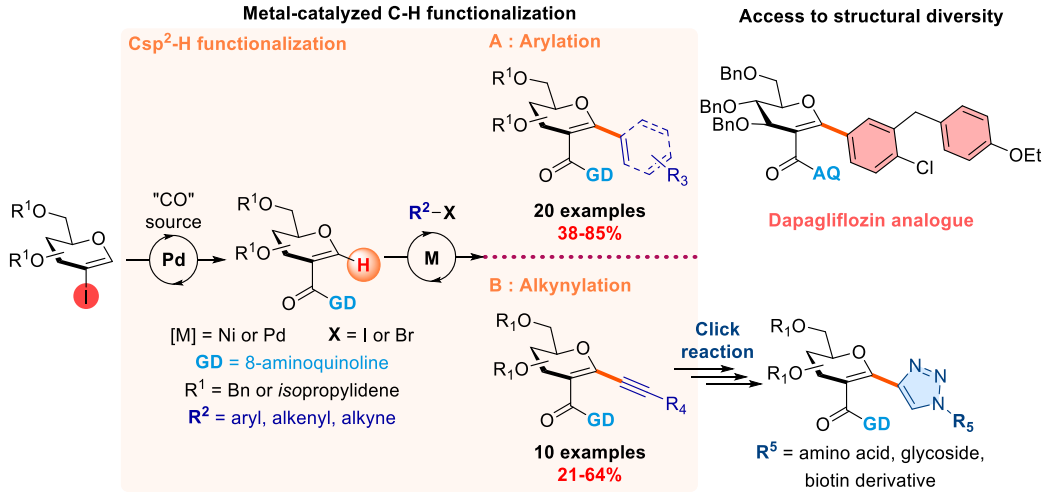
Current synthetic routes for *C*-arylglycosides involve multiple steps via prefunctionalized intermediates and frequently use strong bases. In recent years, C-H bond functionalization, which is an efficient transformation process, has become emerging in synthetic chemistry. To overcome the regioselectivity issues inherent in activating a specific C-H bond in complex substrates, the use of strategically placed directing groups (DG), has proven to be an effective strategy. However, examples of metal-catalyzed C-H functionalization (MCF) on sugars are still rare. MCF of Csp^2-H bonds remains more developed in the literature examples than that of Csp^3-H, thus making glycals (sugars possessing an intracyclic double bond) ideal partners to build C-C bonds at the anomeric position (position 1). Nevertheless, without DG, MCF on glycals occur almost exclusively at position 2 of the glycal. In order to direct the reactivity in position 1, it was considered in this PhD thesis project to place a DG at position 2 of the glycal. 8-Aminoquinoline (bidentate DG) is very popular in directed MCF examples and can be introduced in C2 via a pallado-catalyzed aminocarbonylation methodology previously developed in the laboratory. During this PhD thesis, a directed pallado-catalyzed C-H arylation in the *pseudo*-anomeric position was set up from these *C*2-amidoglycals (*Scheme 1*, **A**).[1] Through the use of different glycals and iodinated partners, various *C*-aryl/alkenylglycoside structures were synthesized. This allowed the synthesis of glycosylated amino acids and a Dapagliflozin analogue in excellent yields.



Scheme 1: Envisaged access to C-arylglycosides via directed FCM and molecules of interest

Inspired by this arylation, a nickel-catalyzed C-H alkynylation reaction was performed on the same *pseudo*-anomeric position of the glycal, using the same DG (*Scheme 1*, **B**).[2] This alkynylation gives access to *C*-alkynylglycosides by using various glycals and alkyne bromides. Subsequently, a Huisgen cycloaddition reaction in the presence of copper could be performed, allowing the synthesis of various glycoconjugates in good yields. In particular, a lysine and a biotin derivative were introduced by this route.

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[1] de Robichon, M.; Bordessa, A.; Malinowski, M.; Uziel, J.; Lubin-Germain, N.; Ferry, A. *Chem. Commun.*, **2019**, *55*, 11806-11808.

[2] de Robichon, M.; Branquet, D.; Uziel, J.; Lubin-Germain, N.; Ferry, A. *Adv. Synth. Catal.* **2021**, *363*, 5138– 5148.