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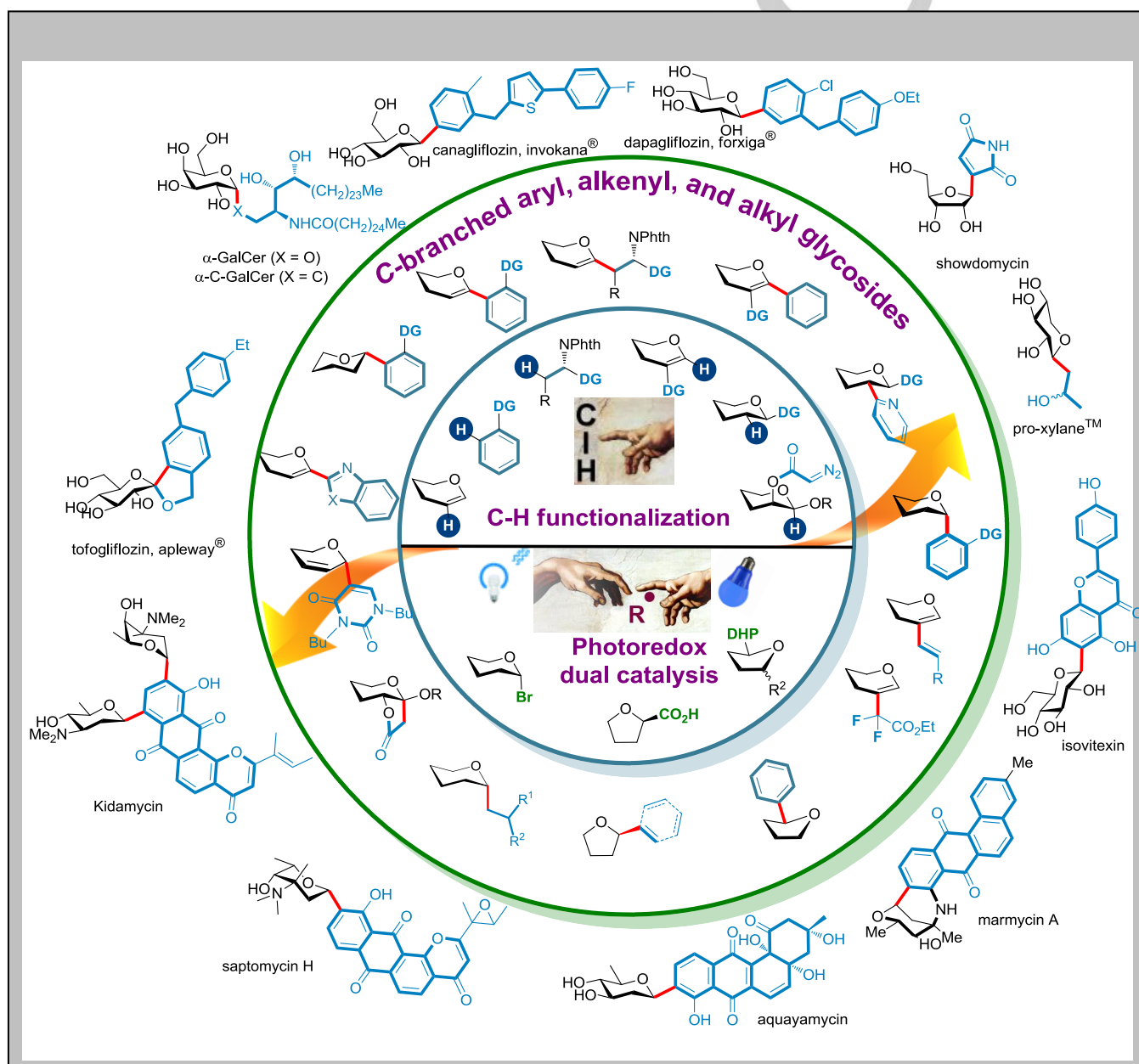
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Emerging organometallic methods for the synthesis of C-branched (hetero)aryl, alkenyl and alkyl glycosides: C–H functionalization and dual photoredox approaches

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Abstract: Transition-metal catalyzed C–H functionalization and photoredox-nickel dual catalysis have emerged as innovative and powerful avenues for the synthesis of C-branched glycosides. These two concepts have been recently established and provide efficient and mild methods for accessing a series of valuable complex C-branched glycosides of great interest. Herein, we highlight recent developments in the synthesis of C-branched aryl/alkenyl/alkyl glycosides through these two approaches.

1. Introduction

Vitexin was the first known C-glycoside extracted at the turn of the 20th century by Perkin (Figure 1),¹ from a New Zealand tree, *Vitex littoralis*. This discovery followed a request of an Auckland resident for an expertise on the commercial value of a yellow substance as a dye contained in this wood. Nevertheless, the full determination of its structure was established only in 1964 by Horowitz and Gentili,² although Perkin had already guessed³ that this stable compound consisted of a sugar residue linked in an abnormal way to apigenin. This stability results from the presence of an unnatural C–C bond between the carbohydrate and its aglycone, the very definition of a C-branched glycoside, making them less sensitive to acidic or enzymatic hydrolysis than the usual C–O and C–N glycosidic bonds. Since the discovery of vitexin, other C-glycosides have been extracted from the living world, as illustrated by the few examples reported in Figure 1. Isovitexin, an isomer of vitexin, differs from the vitexin by the position where the sugar is linked to the apigenin aglycone. Both were found to possess various biological effects including anti-cancer, anti-oxidant, anti-inflammatory, anti-nociceptive, anti-AD (AD, Alzheimer's disease), anti-hypertensive, anti-spasmodic, anti-hypoxia/ischemia injury, anti-depressant-like actions and antiviral activities.⁴ In the same vein, orientin and isoorientin, which incorporate an extra hydroxyl group, were also the subject of diverse pharmacological studies.⁵ Apart from these flavonoids, C-glycosides are also found in the angucycline family, antibiotics of microbial origin, whose aquayamycin is one of the members.⁶ The latter was found to inhibit tyrosine hydroxylase and is active against Gram-positive bacteria, Ehrlich ascites carcinoma, and Yoshida rat sarcoma cells but showed no particular effect on a wide range of human tumor cells.⁷ Pyrazomycin, also called pyrazofurin, found in *Streptomyces candidus*, is a pyrazole-linked C-furanoside, which is a potent inhibitor of orotidine 5'-monophosphate decarboxylase and which possesses broad-spectrum antiviral and antitumor activities.⁸ Showdomycin, whose gene cluster for its biosynthesis was recently discovered,⁹ is another example of a natural C-furanoside bearing a maleimide moiety. Gilvocarcin V, the main product of *Streptomyces griseoflavus* Gö 3592, showed strong anti-tumor activities in comparison with its analogs gilvocarcins E and M lacking the aglycone vinyl group.¹⁰ The antibiotic granaticin, first isolated in 1957¹¹ from the culture of *Streptomyces olivaceus*, is a rare example of fused C-aryl glycoside incorporating two C-C bonds between the sugar and its aglycon. Surprisingly, despite

its originality, it has only been the subject of one racemic and one enantioselective syntheses to date.¹² Papulacandin D is the simplest member of a series of naturally occurring anti-fungal agents, displaying a benzannulated spiroketal unit.¹³

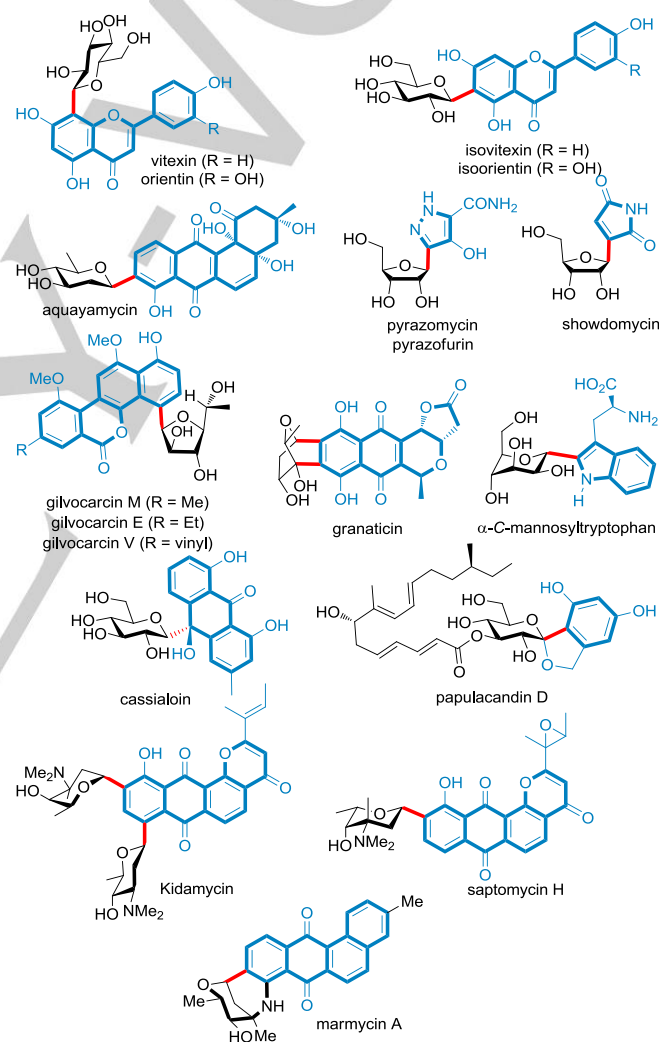


Figure 1. Selected examples of natural products including a C-glycoside unit.

α -C-Mannosyltryptophan, based on an indole motif, observed in Ribonuclease 2 from human urine, is the first example of a C-glycosyl amino acid found in proteins.¹⁴ Eventually, cassialoin, like showdomycin, is a rare example of a C-glycoside linked to a Csp³ carbon of the aglycone.¹⁵ It was isolated from the heartwood of *Cassia garrettiana* Craib and shows anti-cancer effects. Anthracycline-type C-glycosides¹⁶ such as marmycin, kidamycin and saptomycin exhibit very promising antiproliferative properties and have been proposed to

operate via similar mechanism than doxorubicin as DNA intercalants. In addition, it was reported recently that these C-glycosides may act through other original mechanisms including direct genome targeting.^{16a}

The existence of many natural C-glycosides possessing various biological properties has stimulated the interest of medicinal chemists, which led to the development of several commercial synthetic C-glycoside drugs (Figure 2) bearing mainly anti-diabetic properties. Among them, empagliflozin, dapagliflozin, canagliflozin, ipragliflozin, ertugliflozin and tofogliflozin have been approved for the treatment of type 2 diabetes mellitus recently.¹⁷ Empagliflozin, dapagliflozin and canagliflozin were also found to possess cardio-renal benefits in adults with type 2 diabetes mellitus who either have established cardiovascular disease or multiple cardiovascular risk factors.¹⁸ Tofogliflozin displays a benzannulated spiroketal unit found in natural papulacandin D.

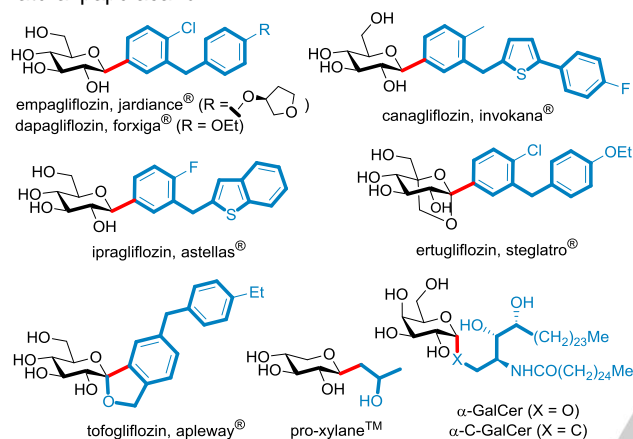
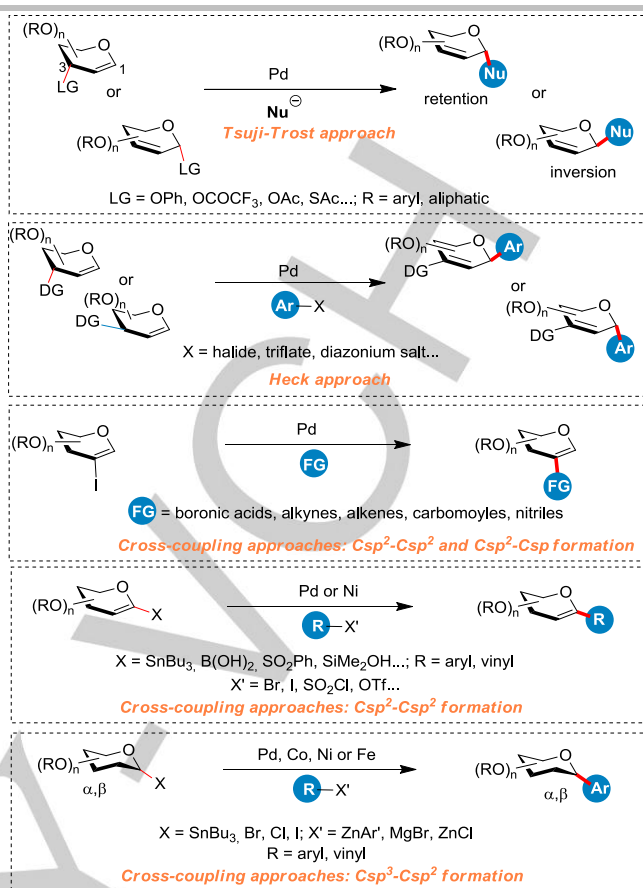


Figure 2. Selected examples of synthetic C-glycosides with noticeable biological activities.

Pro-xylane™ is a rare example of C-alkylglycoside, synthesized from renewable feedstock, which is used in skin anti-aging applications in cosmetic.¹⁹ Synthetic α -galactosylceramide (α -GalCer also named KRN7000) has shown interesting anti-cancer activities among others.²⁰ The corresponding C-glycoside (α -C-GalCer) was shown to remain active in a mouse malaria model for a longer period of time than its O-glycosyl counterpart, one reasonable explanation being the highest stability of the former toward degradation by endogenous α -galactosidases. α -C-GalCer was also found to be 100 times more effective than α -GalCer against B16 melanoma cells in C57BL/6 mice. However, none of these compounds were developed as drugs up to date.



Scheme 1. Previous organometallic catalyzed methods for the synthesis of C-glycosides.

Owing to the interesting pharmacological properties of numerous C-glycosides, their synthesis^{21,22} and the synthesis of their analogues are a field of intense studies. Besides organic synthetic methods, the development of organometallic catalyzed processes under *sub*-stoichiometric conditions has emerged in the eighties. The Tsuji-Trost approach, firstly reported in 1985,²³ allowed a stereospecific access to Csp³- or Csp²-glycosides (Scheme 1) where the outcome of the reaction is controlled by the nature of the nucleophile: stabilized nucleophiles favor the formation of products with retention of configuration whereas non-stabilized nucleophiles led to an inversion of configuration. Nevertheless, loss of stereoselectivity may be observed *via* an inversion of configuration of the π -allyl intermediate. Due to the electron-rich vinyl ether motif, the process is totally regioselective, the attack of the nucleophile proceeds at the C1 position of the π -allyl glucal and needs the presence of a good leaving group.^{24,25} Heck²⁶ or Heck type²⁷ reactions were also applied to C-aryl-glycosides syntheses.²⁸ The reaction is fully regioselective at the C1 position and stereospecific, an *anti*-chirality transfer from the initial stereocenter C3 of the reactant governing the anomeric configuration in the products.²⁹ Recently, 2,3-pseudoglycal building blocks were also used for the synthesis of C2-aryl glycosides through transfer chirality approach.³⁰ Stille, Suzuki-Miyaura, Hiyama, Denmark and Negishi cross-couplings were useful tools to deliver vinyl- or aryl-Csp²-glycosides since the seminal work of Friesen and Sturino.³¹ These methods were both successfully applied to glycal- or glycoside-type substrates^{32,33,34,35,36,37,38} (Scheme 1) in mild conditions. In the former case, a major disadvantage lies in the preparation of C1 functionalized glycals which generally require the use of a strong base excess, not compatible with a wide range of functional groups. In an inverted strategy, 2-

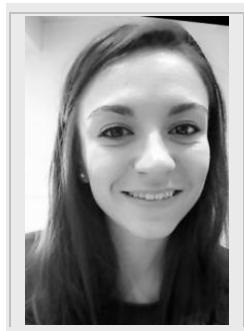
iodoglycals were widely used as electrophilic partners for the synthesis of 2-C-branched glycosides (Scheme 1). Various Pd-catalyzed reactions such as Suzuki-Miyaura,³⁹ Heck,⁴⁰ Sonogashira,⁴¹ and carbonylative cross couplings⁴² have been applied successfully in this context.

These last few years, organometallic catalysis evolved toward C–H functionalization^{43,44,45} and dual photoredox^{46,47} processes with the concern of limiting as much as possible number of steps in a synthetic route. In view of these different advantages, this review will deal with the synthetic successes of these two approaches.

Juba Ghouilem received his M.Sc. in *BioOrganic Chemistry* at Lille University in 2018, France. The same year, he joined the CosMIT team at Paris Saclay University as a Ph.D student under the supervision of Dr. Samir Messaoudi. His ANR research project "SelfSuCHI" is focused on the synthesis of C-aryl glycosides through C(sp³)–H functionalization.



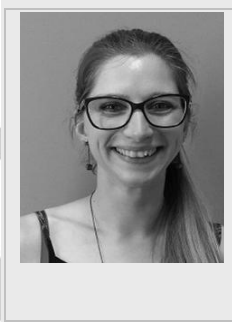
Morgane de Robichon was born in Maisons-Laffitte (78 - France) in 1995. She obtained a Master degree in Molecular and Macromolecular Chemistry at CY Cergy-Paris University. She is currently a second year PhD student at the School of CY Cergy-Paris University under the supervision of Dr. Jacques Uziel and Dr. Angélique Ferry. She studied carbonylative metallo-catalyzed cross-coupling reactions on iodoglycals and is currently working on metallo-catalyzed directed C–H functionalisation of glycoside substrates.



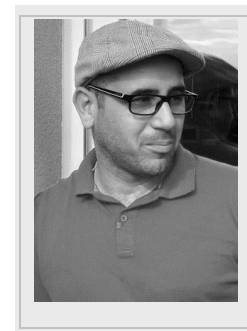
Franck Le Bideau graduated with a Ph.D in 1995 at the Université Pierre et Marie Curie (Paris, France), under the supervision of Professor Max Malacria, working on palladium-catalyzed rearrangement of silicon substituted vinyloxiranes. In 1996, he joined the group of Professor Léon Ghosez in Belgium at Université Catholique de Louvain (Louvain-la-Neuve) as a post-doctoral researcher and worked on [2+2] cycloaddition reactions. In 1997, he joined the CNRS as a researcher at the Ecole Nationale Supérieure de Chimie de Paris (France) where his research mainly focused on the synthesis of organometallic species of potential biological interest. In 2011, he moved to the Université Paris Sud (Châtenay-Malabry, France) where he is currently working on organocatalysis and subsequent total synthesis of natural products.



Angélique Ferry was born in Mulhouse (France) in 1987. She obtained her Master degree in 2010. She then started her PhD on the synthesis of phostone and hydroxylamine-type glycomimetics (Prof. Crich, Dr. Guinchard, ICSN) and received, in 2014, the Dina Surdin PhD Award of the French Chemical Society. Then, she joined Prof. Glorius team (Germany) to work on heterogeneous C–H functionalization and on N-heterocyclic carbenes-stabilized metallic nanoparticles. In 2015, she became associate professor at the CY Cergy-Paris University, where she develops metal-catalyzed functionalization on glycosides. She received, in 2018, the "women and science" award of the CY Cergy-Paris University and a "Young Researchers" ANR funding as project coordinator. In 2020, she obtained the Marc Julia Award of the French Chemical Society and the GFG Award of the French Group of Glycosciences.



Samir Messaoudi completed his PhD in 2004 at Blaise Pascal University, Clermont Ferrand, France. After two years as postdoctoral fellow, he joined the group of "Therapeutic Chemistry" in 2007 as a junior CNRS-researcher at BioCIS UMR 8076, university of Paris Saclay. In 2017, he was promoted as Director of Research DR-CNRS. His main research concern deals with glycochemistry (functionalization of carbohydrates under transition-metal catalysis), as well as with the preparation of molecules and molecular scaffolds of biological and therapeutic interest.



2. New emerging methods

2.1. C–H functionalization methodologies

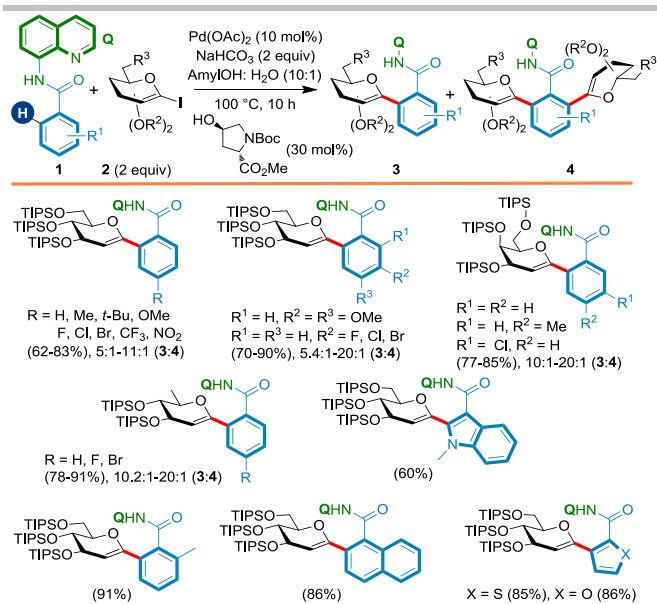
2.1.1. Where the sugar is the electrophilic partner

2.1.1.1. Directed C–H functionalization of aromatic and aliphatic substrates

One of the established strategies for the synthesis of C-branched glycosides through C–H functionalization is based on the use of aryl or alkyl substrates bearing a designed directing group (DG). In this case, the link between the sugar and the aglycone was performed via a C–H functionalization using sugar halides as electrophilic partners.

2.1.1.1.1. Csp²–H functionalization

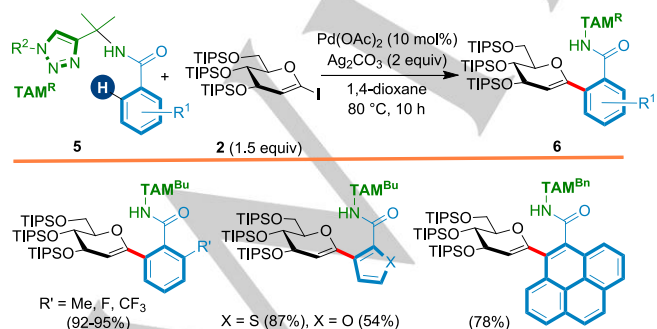
In 2016, Ye *et al.* published⁴⁸ the synthesis of aryl-C-Δ^{1,2} glycosides from 1-iodoglycals **2** based on a palladium-catalyzed C–H activation of benzamides **1** (Scheme 2) directed by an *ortho* N-quinolyl (*N*-Q) motif, leading to mono- and di-arylated products **3** and **4**.



Scheme 2. Pd(II) catalyzed synthesis of aryl-C- $\Delta^{1,2}$ glycosides according to Ye *et al.*

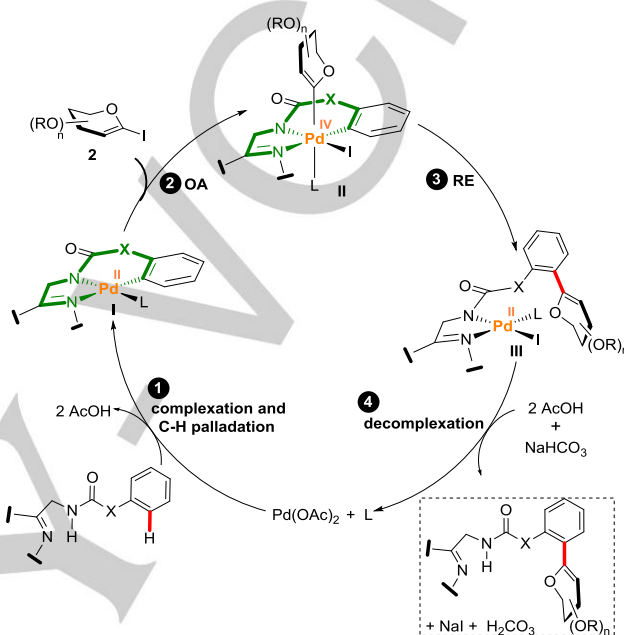
A thorough screening of the reaction conditions allowed a reversal in the proportion of the two possible products in favor of the monoglycosylated adduct **3**. Thus, the use of NaHCO₃ as an inorganic base, *t*-amylOH/H₂O (10:1) as a solvent mixture and a L-proline derivative as an external ligand led preferentially to the formation of a wide array of monoglycosylated products **3**, bearing electron-donor or electron-withdrawing groups in different positions of the aryl moieties in yields ranging from 60 to 91%. However, when the second *ortho* position is not substituted, up to 16% of di-arylated compounds **4** were observed despite the use of two equivalents of expensive glycals for one equivalent of the aryls **1**. Removal of the DG was accomplished using two equivalents of the expensive Schwartz's reagent (bis(cyclopentadienyl)-zirconium(IV) chloride hydride) followed by transformation *in situ* of the unstable resulting aldehydes into alkenes or alcohols in good yields (68-70%).

Recently, Ackermann *et al.* reported⁴⁹ on the same type of transformation involving a *N*-triazolyldimethylmethyl (*N*-TAM) DG (**5**, Scheme 3). Milder reaction conditions (80 °C) were used to afford, without the need of an additional ligand, monoglycosylated derivatives **6** in excellent yields (78-95%), except in the case of the furan adduct (54%).



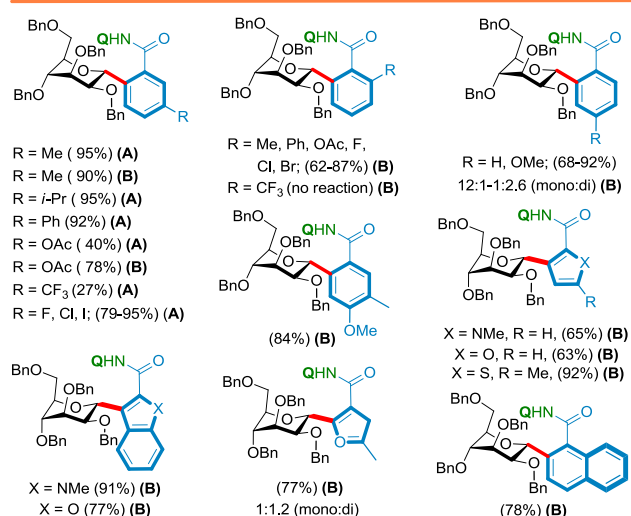
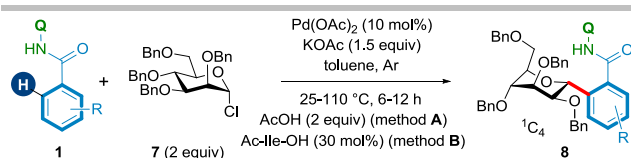
Scheme 3. Pd(II) catalyzed synthesis of aryl-C- $\Delta^{1,2}$ glycosides according to Ackermann *et al.*

A reasonable catalytic cycle (Scheme 4) starts with the complexation and the C-H palladation of the benzamide, delivering the Pd(II) palladacycle **I**. Oxidative addition of the latter in the C-I bond of the glucal then leads to Pd(IV) intermediate **II**, which undergoes a reductive elimination to release the aryl-C- $\Delta^{1,2}$ glycoside moiety in the Pd(II) complex **III**. The strong electron donor effect of the *N,N*-bidentate *N*-Q ligand in **I** facilitates the oxidative addition step. Eventually, decomplexation in the presence of AcOH and a base regenerates Pd(OAc)₂ concomitantly with the formation of the product of the reaction.

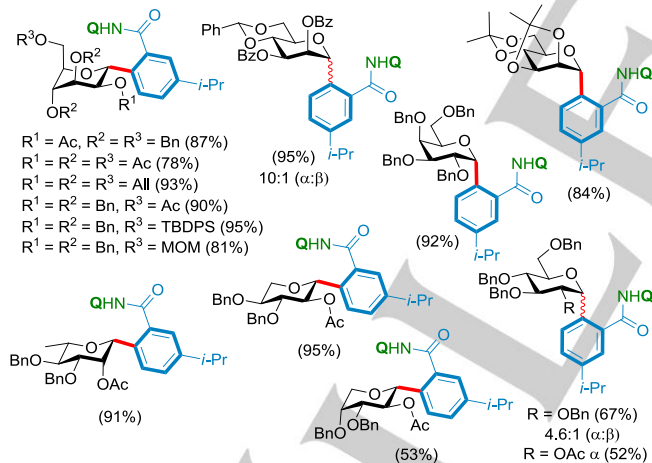
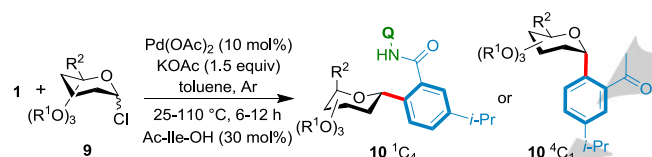


Scheme 4. A possible mechanism for the Pd(II) catalyzed synthesis of aryl-C- $\Delta^{1,2}$ glycosides ($X = \text{no atom}$) according to Ye and Ackermann reports. Except for the oxidative addition step, this mechanism is also reasonable for the synthesis of *C*-aryl pyranosides ($X = \text{no atom, CH}_2 \text{ or O}$) relatively to Chen's work (*vide infra*).

In 2019, Chen *et al.* disclosed⁵⁰ the synthesis of *C*-aryl glycosides (Scheme 5) in reaction conditions close to Ye's work, using KOAc as base and toluene as the solvent. Despite excellent results (90-95% yield, except in one case ($R = \text{OAc}$, 40%)) obtained with the inexpensive co-ligand, the more expensive *N*-acetyl protected isoleucine (Ac-Ile-OH) was used in most cases. The exact role of this co-ligand is not clear, but appears to be essential to obtain excellent yields (90%) at low temperatures (up to 45 °C).



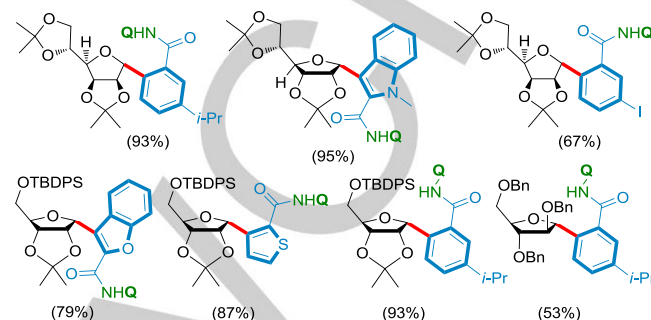
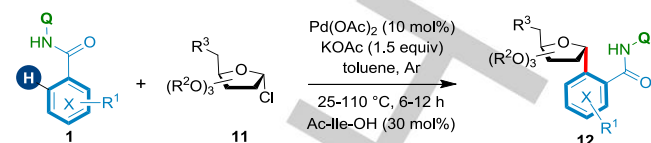
Scheme 5. Pd(II) catalyzed synthesis of C-aryl pyranosides varying the aryl moiety. All compounds have an α configuration and adopt a 1C_4 conformation. Di-arylation products are observed only when mentioned.



Scheme 6. Pd(II) catalyzed synthesis of C-aryl pyranosides varying the sugar and the aryl moieties.

A wide range of products was synthesized in good to excellent yields (62-95%) varying the nature of the benzamide **1** (Scheme 5 and 6) or the nature of the pyranose/furanose (Scheme 6 and 7). The presence of a strong electron withdrawing group (CF_3) on the aryl ring of **1** led to a low 27% yield of the desired product. A moderate yield (53%) was also obtained in the case of *L*-xylose with no particular explanation. Heteroarenes such as furans, pyrroles, thiophenes and indoles were used successfully in this reaction. Formation of di-arylated

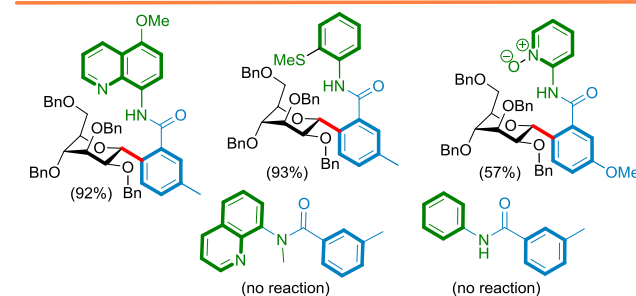
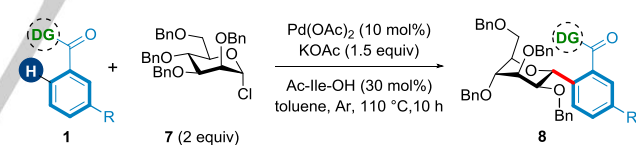
substrates was prevented by steric hindrance found in 1,3-substituted benzamides. Functional groups such as *tert*-butyldiphenylsilyl (TBDPS), methoxymethyl (MOM), acetate, 4,6-benzylidene, isopropylidene and allyl were tolerated.



Scheme 7. Pd(II) catalyzed synthesis of C-aryl furanosides varying the sugar and the aryl moieties.

This reaction was also applied to more complex substrates such as tri- and tetra-saccharides and to the mannosylation of repaglinide, an antidiabetic drug. Removal of the NHQ DG was studied on a few examples, using Schwartz's reagent or saponification conditions.

A few other DG were tested in the C-H activating process (Scheme 8) showing that the presence of a bidentate moiety as well as a non-substituted *N*-amide atom were essential, leading to the coupled products in moderate to excellent yields (57-93%).



Scheme 8. Other DG tested in the Pd(II) catalyzed synthesis of C-aryl pyranosides.

The nature of the different amidoquinolyl-type DG were also studied as shown in Figure 3. In the case of aryl acetamide ($X = CH_2$ in scheme 4) and phenol derivatives ($X = O$ in scheme 4). The corresponding aryl and heteroaryl substrates were obtained in moderate to excellent yields (42-95%).

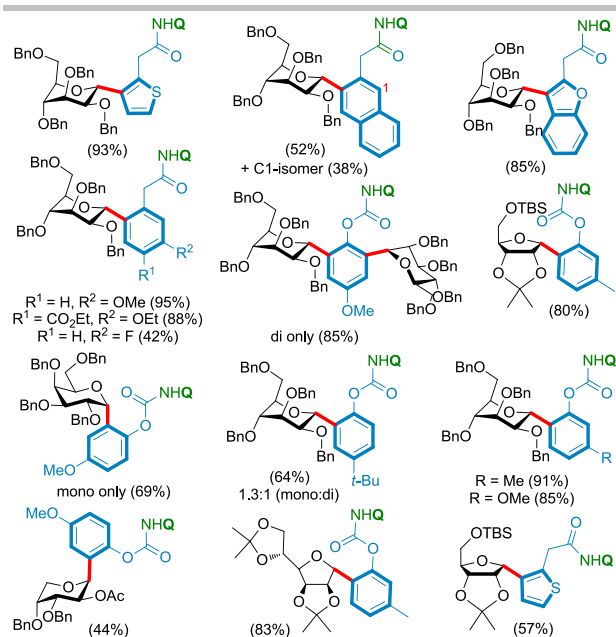
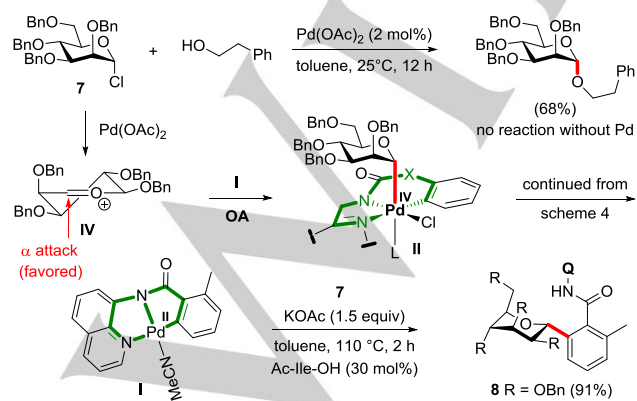


Figure 3. Pd(II) catalyzed synthesis of C-aryl pyranosides and furanosides bearing an amidoquinolyl-DG. Reaction conditions are the same as reported in Scheme 5 using Ac-Ile-OH (30%) as the additional ligand.

Removal of the DG and recovery of the phenolic group was quantitatively realized on one derivative in the presence of ethylamine in methanol at room temperature, opening the route to further modification of such compounds.

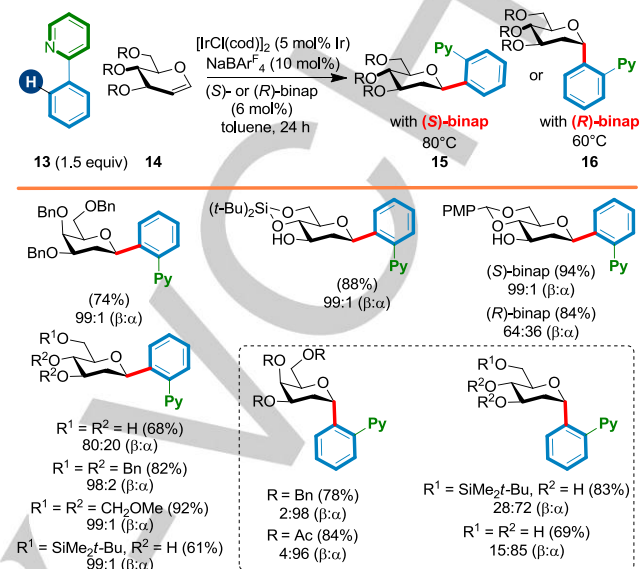
Using methyl iodide (MeI) as electrophilic partner in the presence of **1** (Scheme 5, R = 3-methyl) under the standard reaction conditions, resulted in an absence of reactivity, suggesting that a more reactive species than starting glycosides **7** could be involved in the process. Moreover, the stereoretention in favor of the α configuration observed in most cases, as well as the exclusive formation of this α product starting from a 2:1 α/β mixture of glycosyl chloride led the authors to propose the existence of an oxocarbenium ion **IV** (Scheme 9) prior to oxidative addition. Such an intermediate, which could be formed from **7** in the presence of Pd(OAc)₂, which acts as a Lewis acid, would be preferentially attacked through its less hindered side, explaining the large observed α selectivity. This suggestion was also supported by the example involving 2-phenylethanol and mannose (Scheme 9).

Complex **I** includes a 5,5- or 5,6- bicyclic structure (in green in scheme 4 and 9; 5,5: X = no atom, 5,6: X = CH₂ or O) incorporating the metal, which could explain a C-H activation in favor of the *ortho* position of the aryl ring.



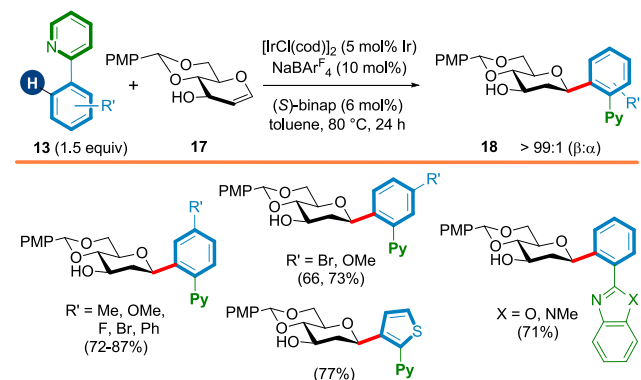
Scheme 9. Mechanism of the Pd(II) catalyzed synthesis of C-aryl pyranosides and furanosides: modification of the general catalytic cycle proposed in scheme 7.

To demonstrate its role in the catalytic cycle, Palladacycle **1** (Scheme 9) was prepared by reacting Pd(OAc)₂ with 2-methylbenzamide in acetonitrile and submitted to standard conditions in the presence of **7** to furnish the C-aryl glycoside **8** in excellent yield (91%) Kinetic isotope effect experiments showed that the formation of **1** is not the rate-limiting step.



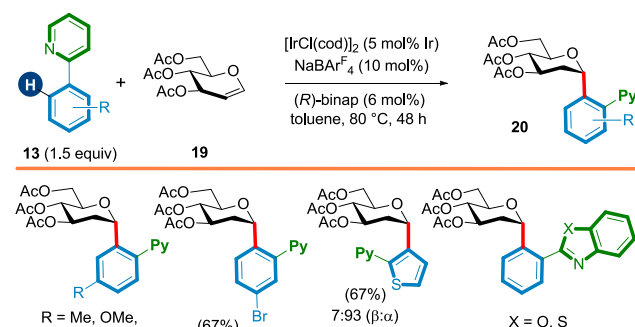
Scheme 10. Ir(I) catalyzed hydroarylation of glycols via C-H functionalisation: influence of the absolute configuration of the additional ligand binap on the diastereoselectivity of the reaction.

Iridium complexes were also used in hydroarylation of glycols *via* a C-H functionalization process as recently reported by Nishimura *et al.* (Scheme 10).⁵¹ Thus, compounds **13** and **14** were reacted in the presence of [IrCl(cod)]₂ (5 mol% Ir), NaBARF₄ (10 mol%) and (S)-binap (6 mol%) to afford mostly, after 24 hours in toluene, the β adducts **15**. By the same way, (R)-binap led to the α adducts **16**. The high β -selectivity was observed at higher temperature (80°C) than the α -selectivity, and several C-aryl glycosides **15** and **16** were obtained in good to excellent yields (61-92%) and excellent diastereoselectivities (up to 98% *de*) except in four cases (28%-70% *de*) from diversely protected or non-protected glycols **14**. This method shortens the access to the desired products, when compared to Pd(II) catalyzed coupling (*vide supra*), since glucals **14** are precursors of the corresponding halogenated compounds **2** (Scheme 2). Moreover, it allows an access to both α and β configurations starting from the same precursor, just by changing the configuration of the additional catalytic ligand ((S)- or (R)-binap) and no di-arylated products were observed.



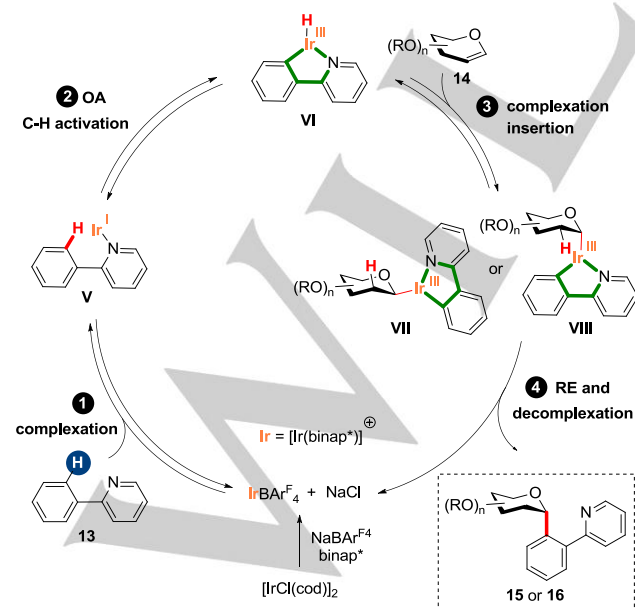
Scheme 11. Ir(I) catalyzed hydroarylation of glycal **17** in the presence of (*S*)-binap, varying the nature of the aryl: access to compounds **18**, predominantly under their β configuration.

The present catalytic system was applied to β - and α -selective hydroarylation of several aromatic compounds with glycal **17** (Scheme 11) and **19** (Scheme 12), in moderate to excellent yields (53-97%) and with excellent diastereoselectivities for the former (98% *de*) while the latter gave lower values (87-98% *de*)



Scheme 12. Ir(I) catalyzed hydroarylation of glycal **19** in the presence of (*R*)-binap, varying the nature of the aryl: access to compounds **20**, predominantly under their α configuration.

Other aromatic compounds, such as acetophenone, acetophenone *O*-methyl oxime, and *N*-(4-methoxyphenyl)-1-phenylethen-1-imine, previously used in other Ir-catalyzed *ortho*-C-H alkylations, were inactive in this coupling reaction. Based on previous studies by the same team,⁵² a plausible mechanism for this transformation is depicted in scheme 13. The Ir(I) complex ($[\text{Ir}(\text{binap})]^+[\text{BARF}_4]^-$), generated by reaction of $[\text{IrCl}(\text{cod})]_2$ and NaBARF_4 in the presence of the appropriate binap ligand, is transformed into **V** via complexation of the aryl **13**. The favored *ortho* C-H functionalization of 2-phenylpyridine moiety then affords the aryl(hydrido)iridium(III) **VI**.

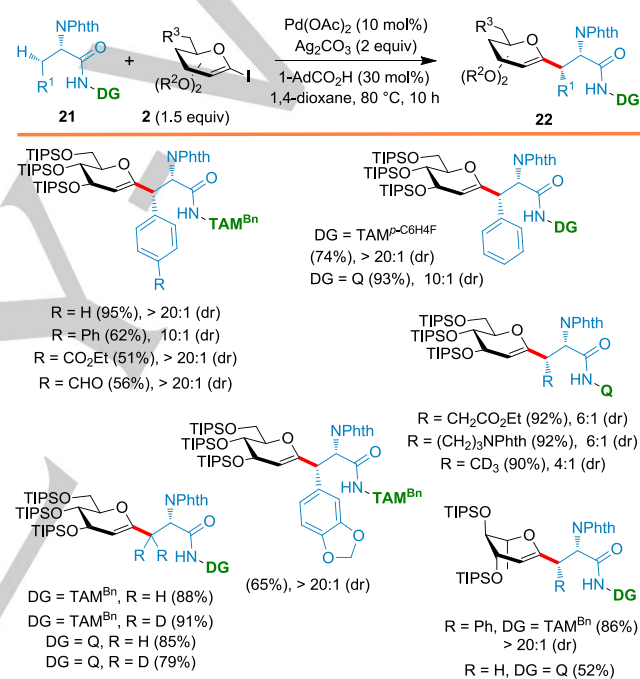


Scheme 13. A reasonable mechanism for the Ir(I) catalyzed hydroarylation of glycals.

Alkene insertion of glycal **14** into Ir-H bond affords preferentially **VII** or **VIII** according to the absolute configuration of the chosen (*S*)- or (*R*)-binap. Intermediate **VII** eventually delivers the β -aryl glycoside **15** (**VIII** led respectively to α -aryl glycoside **16**) through an irreversible reductive elimination, whose rate might determine the observed diastereoselectivity. An alternative pathway was proposed in which the alkene insertion occurs through the irreversible carbometalation of the aryl(hydrido)iridium complex to glycal to form an alkyliridium intermediate.

2.1.1.1.2. Csp³-H functionalization

Csp³-H functionalization is far less common in the synthesis of C-glycosides.



Scheme 14. Pd(II) catalyzed Csp³-H activation process according to Ackermann *et al.*

Ackermann *et al.* recently reported⁴⁹ the pallado-catalyzed C-H activation of α -phthalimide substituted amides **21** and subsequent coupling with iodoglycals **2**, which delivered products **22** in moderate to excellent yields and good diastereoselectivities (Scheme 14). TAM^R and Q assisting groups gave similar results and rhamnose derived glycals were found effective in the process.

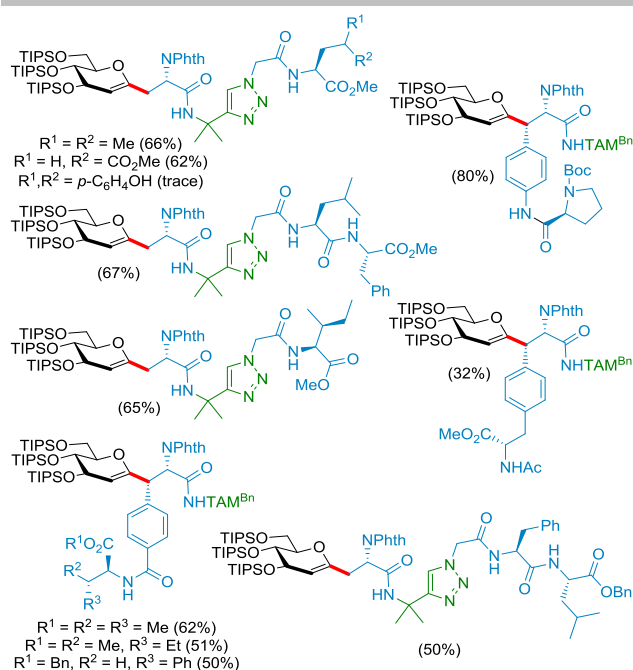


Figure 4. Synthesis of small peptides following Ackermann's methodology.

Based on a DFT study, a mechanistic pathway was proposed but no explanation was furnished about 1-adamantane carboxyl acid additive (AdCO_2H), which is used in *sub*-stoichiometric amount (30 mol%) in the reaction. As previously mentioned (Scheme 4), the catalytic cycle should imply a favored 5,5-bicyclic structure around the metal, and a Pd(II)-Pd(IV)-Pd(II) pathway.

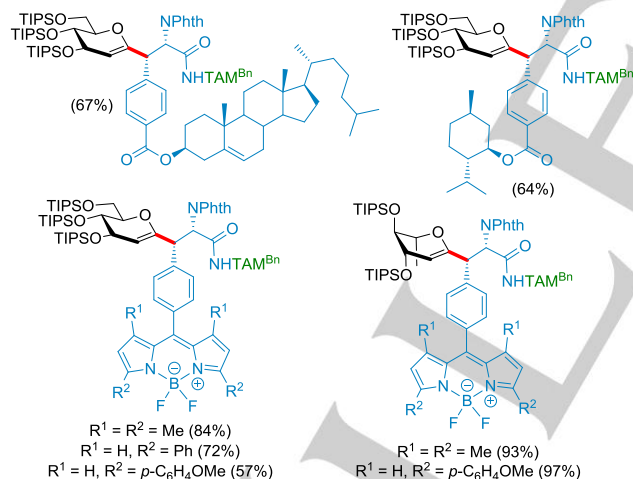
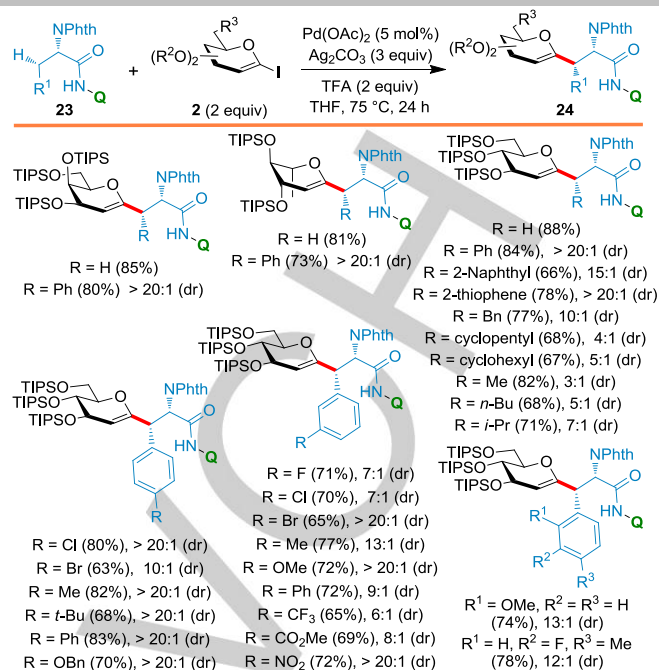


Figure 5. Synthesis of BODIPY labeled glycoamides and other bio-ligands following Ackermann's methodology.

This methodology was applied with success to the synthesis of small peptides as illustrated in figure 4, replacing Pd(OAc)₂ by Pd(TFA)₂ on a longer reaction time (16 h). Only traces of unprotected peptide Phth-Ala-Tzl-Tyr-OMe were obtained while the reaction allowed the access to other congested glycopeptides.

Other biomolecules and BODIPY labeled glycoamides were also synthesized following this methodology in moderate to excellent yields (Figure 5).

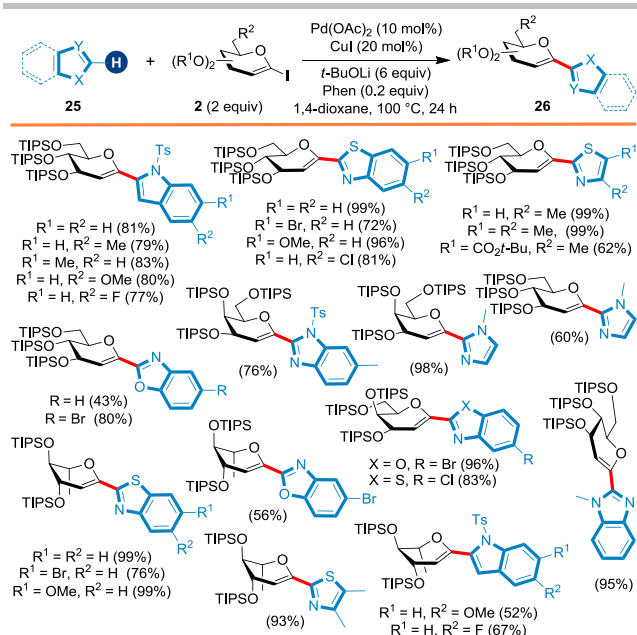


Scheme 15. Pd(II) catalyzed Csp³-H activation process according to Liu *et al.*

Concomitantly to Ackermann's report, Liu *et al.* published⁵³ a similar protocol (Scheme 15) to synthesize close compounds **24**, replacing AdCO_2H by trifluoroacetic acid (TFA) in good yields (63-83%) and moderate to excellent diastereoselectivities (3:1 to >20:1 (*dr*)). Both teams showed through deuterium kinetic studies that the Csp³-H bond cleavage was not the rate-limiting step of the catalytic cycle and the mechanism depicted in scheme 4 seems to be reasonable in that case too.

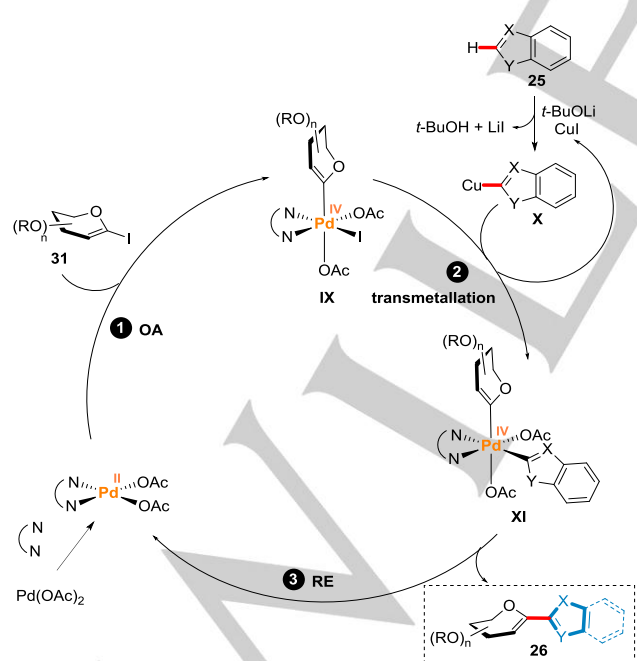
2.1.1.2. Non-directed C-H functionalization of (hetero)aromatics substrates

In 2017, Ye *et al.* described⁵⁴ an access to five-membered nitrogen-containing heteroaryl C-glycosides based on a Pd(II)/Cu(I) co-catalyzed methodology (Scheme 16). Heteroaryl-C- $\Delta^{1,2}$ -glycosides, incorporating indole, thiazole, benzothiazole, imidazole, benzimidazole, and benzoxazole moieties as aglycones were obtained in 43–99% yields starting from 1-iodoglycals in the presence of *t*-BuOLi (4 equiv.) and 1,10-phenanthroline (0.2 equiv.) in 24 hours at 100°C in 1,4-dioxane.



Scheme 16. Synthesis of *N*-heteroaryl C-glycosides following Ye's methodology.

The tosyl-protecting group on the indole ring was chosen to decrease the nucleophilicity of its C3 position owing to its electron-withdrawing ability. The reaction is effective with electron-withdrawing and donating groups except in the case of an indole ring bearing a nitro substituent. 1-iodoglycals derived from *D*-galactose and *L*-rhamnose were successfully coupled in these conditions. The main limitation of the method is the use of 6 equivalents of *t*-BuOLi, which is not compatible with base sensitive compounds.

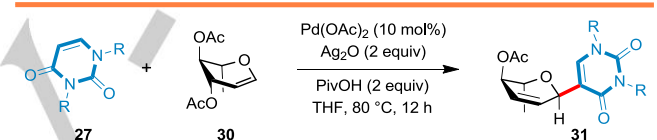
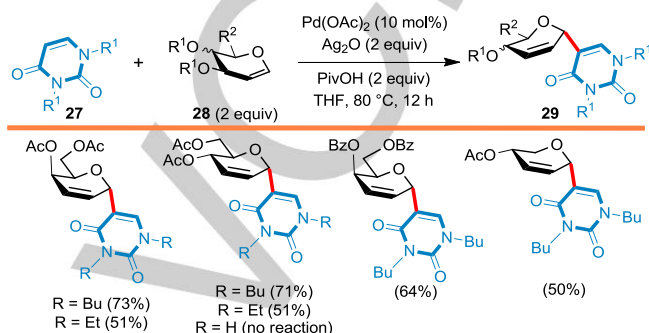


Scheme 17. A reasonable mechanism for the synthesis of *N*-heteroaryl C-glycosides following Ye's methodology.

The most reasonable catalytic cycle for this transformation depicted in scheme 17 begins with the complexation of the 1,10-

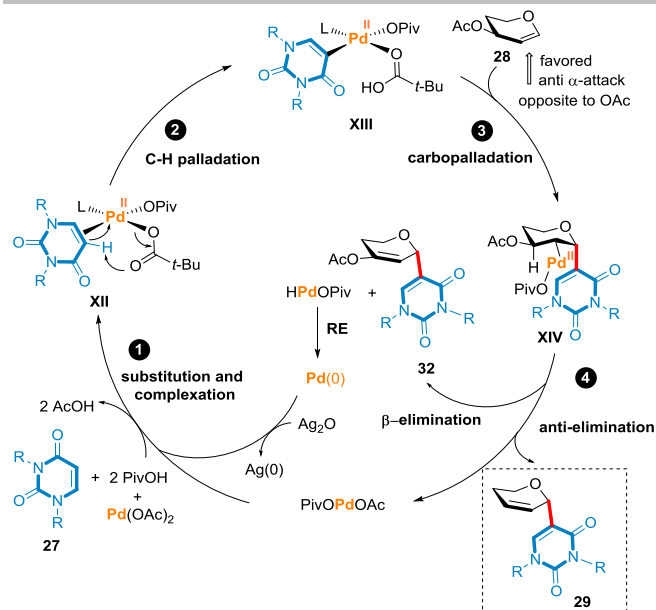
phenanthroline to $\text{Pd}(\text{OAc})_2$ follows by oxidative addition of the latter in the C-1 bond of the 1-iodoglycal **2** delivering the Pd(IV) intermediate **IX**. Copper assisted deprotonation of the *N*-heteroaryl reactant by *t*-BuOLi and subsequent lithium-copper exchange then furnishes the organo-copper species **X** whose transmetalation with **IX** provides the Pd(IV) species **XI**. Desired products **26** are finally obtained by reductive elimination of **XI** with concomitant regeneration of Pd(II). 1,10-Phenanthroline could favor the oxidative step through Pd(II) electronic enrichment.

A second example of a C-glycoside synthesis *via* a non-directed C-H activation was reported in 2017 by Rasool and Mukherjee (Scheme 18).⁵⁵



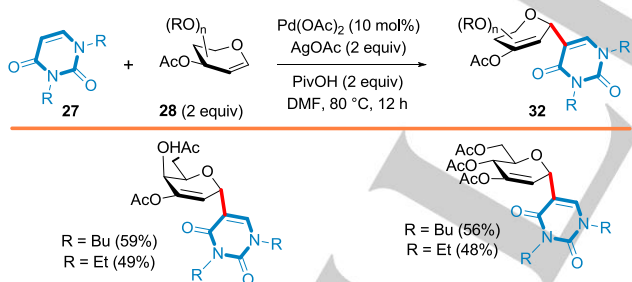
Scheme 18. Synthesis of uracil C-glycosides following Mukherjee's methodology.

Several uracil-substituted pseudo glycals were synthesized reacting compounds **27** and pyranoid glycals **28** catalyzed by $\text{Pd}(\text{OAc})_2$ in the presence of Ag_2O and PivOH (2 equiv.) in moderate to good yields. Unprotected uracil failed to react due to poor solubility and uracil bearing longer protective alkyl chains gave better yields. Contrary to C3- β -substituted glycals, which delivered the corresponding C1- α -products, glycal **30** derived from rhamnose was converted into the C1- β -pseudo glycal **31**, thus showing that the stereoselectivity of the process is governed by the orientation of the C3 substituent in the starting material, possibly explained by the mechanism depicted in scheme 19 (*vide infra*).



Scheme 19. A reasonable mechanism for Mukherjee's methodology

The first step of the process is the substitution of an -OAc ligand by an -OPiv and complexation of the uracil to the resulting Pd(II) species **XII**. C-H palladation next occurs to generate the intermediate **XIII** which undergoes a regioselective *syn* addition by the less hindered (in *anti* of the C3-OAc group) α -side of the glycol double bond to form **XIV**. The desired product **29** is then generated by *anti*-elimination of palladium(II) acetate delivering PivOPdOAc. Compound **32**, arising from β -hydride elimination from **XIV** with concomitant formation of HPdOPiv, was also observed as a minor product. In this pathway, reductive elimination of HPdOPiv leads to Pd(0), justifying the use of an oxidant (Ag_2O) in order to regenerate the starting Pd(II) species.



Scheme 20. Synthesis of products **32** via β -hydride elimination following Mukherjee's methodology.

A screening of the reaction conditions allowed the exclusive formation of products **32** in moderate yields (Scheme 20) using AgOAc in polar DMF solvent.

2.1.2. Where the sugar is the C-H activated partner

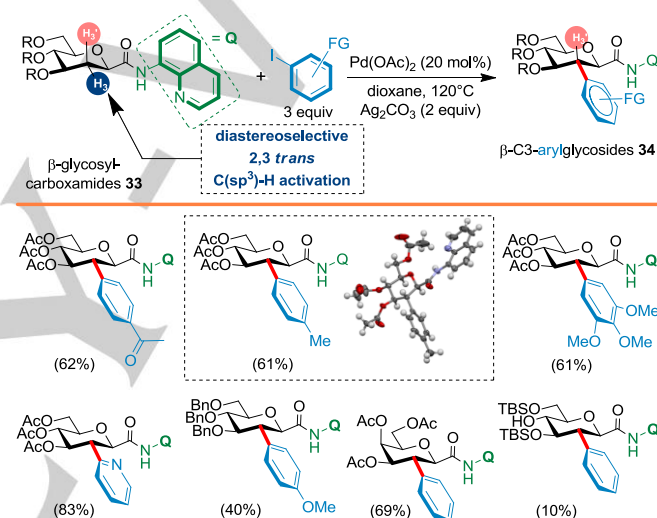
2.1.2.1. Directed C-H functionalization of sugar substrates

2.1.2.1.1. $\text{C}(\text{sp}^3)\text{-H}$ functionalization

One another approach for the synthesis of C-glycosides is based on directed C-H functionalization of a C-H sugar bond

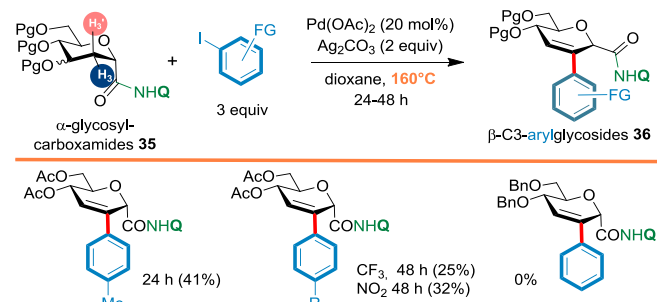
where the DG was placed on the sugar core. The C-H functionalization process in this case may occur in a convergent way with aryl halides. The main advantage of this approach compared to the previous one is the commercial availability of one of the reaction partners (aryl halides)..

In this context, Messaoudi and co-workers⁵⁶ reported for the first time the use of this approach to the diastereoselective $\text{C}(\text{sp}^3)\text{-H}$ arylation of glycosides. As a proof of concept, the authors designed at first the β -amidosugar substrate **33** bearing a 8-aminoquinoline DG and showed that the use of $\text{Pd}(\text{OAc})_2$ (20 mol%) and Ag_2CO_3 (2 equiv.) in dioxane at 120 °C led to the C3-aryl-glycosides **34** in good to excellent yields (Scheme 21). Interestingly, the authors reported that the $\text{C}(\text{sp}^3)\text{-H}$ arylation occurs in an exclusive 2,3-*trans* diastereoselectivity, which contrasts with the reported *cis* one in the case of unsubstituted cyclic substrates.⁵⁷ Different functional groups on the (hetero)aromatic ring are tolerated such as methoxy, nitro, methyl ester, ketone, cyano, fluoride and chloride. Although the acetyl and benzyl protecting groups were used successfully in this study, silyl groups led to low yield (~ 10%).



Scheme 21. Pd(II)-catalyzed diastereoselective 2,3-*trans* $\text{C}(\text{sp}^3)\text{-H}$ arylation of β -amidoglycosides **33** according to Messaoudi *et al.*

The authors examined the influence of the anomeric configuration in this C-H activation process, and showed that α -amidoglycosides **35** (Scheme 22) necessitates higher reaction temperature (up to 160 °C) to observe the arylation process. In this case, C-aryl pseudoglucals **36** arising from $\text{C}(\text{sp}^3)\text{-H}$ arylation followed by AcOH elimination were obtained in moderate yields ranging from 23% to 41%. Corresponding benzylated glycoside failed to yield an arylated product.



Scheme 22. Pd(II)-catalyzed arylation of α -amidoglycosides **35** according to Messaoudi's procedure.

In the aim to get further insights into this exclusive equatorial C_{sp^3} -H activation, the authors performed DFT calculations. They thus showed that the lowest transition state found corresponds to a *trans*-CMD with a +13.1 kcal.mol⁻¹ activation barrier (Figure 6), where the C4 acetate is equatorial, yielding the *trans* palladacycle min-tri-β2a with a release of 6.9 kcal/mol of free energy. To achieve the *cis* palladacycle, the conformational shape of a pyranose switches from the ⁴C₁ conformation to ¹C₄ one in which the C4 acetate substituent occupies an axial position by demanding higher value of the free energy of activation of +15.7 kcal.mol⁻¹.

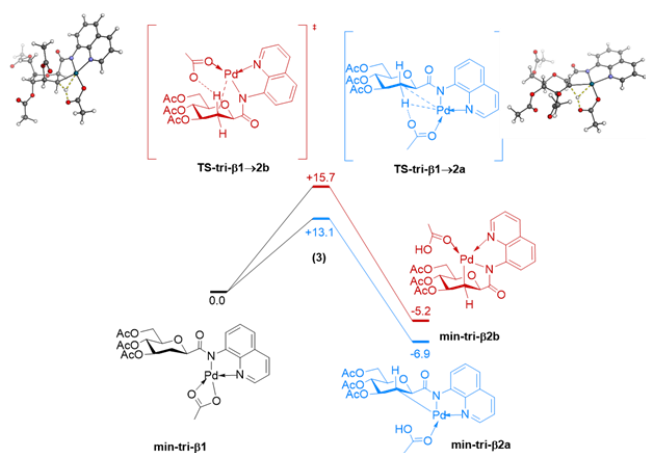
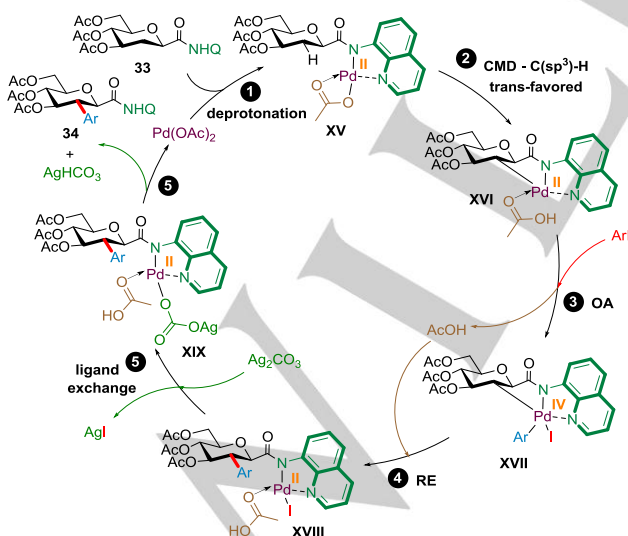


Figure 6. Free energy profiles of the *cis* and *trans* CMDs.

Based on these calculations, the authors proposed the mechanism depicted in scheme 23. Initial deprotonation of the quinolyl amide leads to the formation of complex **XV**, which undergoes C–H metalation through a concerted metalation deprotonation (CMD) mechanism, to give σ -organopalladium complex **XVI**. Oxidative addition of the aryl iodide generates palladium(IV) complex **XVII** followed by C–C bond formation by reductive elimination to **XVIII**.



Scheme 23. Proposed Mechanism for *trans*-arylation reaction reported by Messaoudi *et al.*

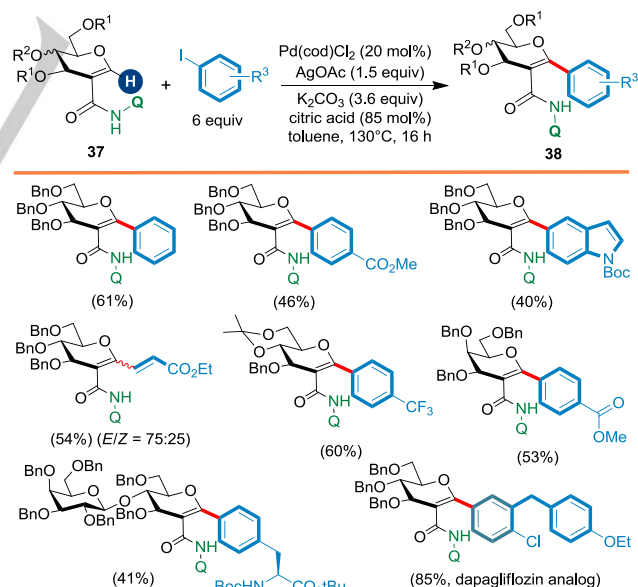
After ligand exchange, the arylated product **34** is formed and the active palladium species **XV** is regenerated.

One important point to solve in this approach is the ability to remove the DG at the end of the process. The authors demonstrated in their study that the aminoquinoline DG could be removed from the final C3-aryl-glycoside under Maulide's conditions (oxidative cleavage with O₃ followed by ammoniac aminolysis) to deliver the free amide C3-aryl-glycoside.⁵⁸

2.1.2.1.2. Csp²-H functionalization

By using the same approach, Ferry and co-workers⁵⁹ reported recently a novel route to C-aryl/alkenyl-glycosides **38** through a directed palladium-catalyzed Csp²-H functionalisation of C2-amido glycals **37** onto the anomeric position (Scheme 24). The 8-aminoquinoline DG was used to successfully introduce diverse (hetero)aryl and alkenyl groups at the C1 position of various protected glycals. The reaction conditions involve the use of Pd(cod)Cl₂ (20 mol%) as the catalyst, 6 equivalents of the aryl-iodide in the presence of a mixture of K₂CO₃ (3.6 equiv.), AgOAc (1.5 equiv.) and citric acid (0.85 equiv.) in toluene at 130 °C. The exact role of citric acid is not clear but it probably intervenes in the CMD step of the catalytic cycle.

Different functional groups on the aromatic ring are tolerated such as methoxy, trifluoromethyl, nitro, methyl ester, cyano and chloride with moderate to good yields (38 to 78%). Moreover, this methodology tolerates *N*-Boc-indole and protected iodo phenylalanine. Interestingly, alkenylation also occurred under these conditions when activated alkene iodide was used. In addition, the synthesis of a disaccharide amino acid could be performed between the D-lactal and the phenylalanine iodide (41%). This method was applied successfully to the synthesis of an analogue of the dapagliflozin drug (FORXIGAs), commercialized to treat type 2 diabetes. In addition to benzyl-protecting groups, the sensitive isopropylidene-protecting group is tolerated in this process, however, ester-type protecting groups on glycal such as -OAc inhibit completely the reactivity due a possible "disarming-like effect".



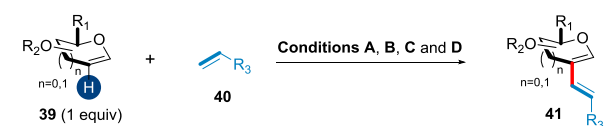
Scheme 24. Pd(II)-catalyzed arylation of glycal **37** reported by Ferry *et al.*

2.1.2.2. Non-directed C–H functionalization of sugar substrates

2.1.2.2.1. Csp²-H functionalization

Metal-catalyzed C–H functionalization processes are well-known methods for the construction of C–C bonds on glycal type

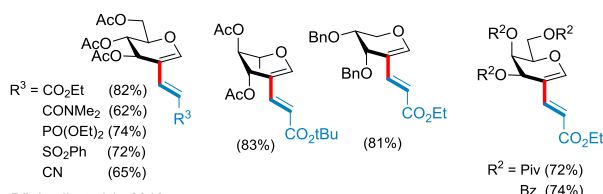
substrates. Besides, without any DG, the addition of electrophilic partners occurs exclusively at the nucleophilic position 2 of the glycal. The first example of this type of reactivity was reported by Liu *et al.* in 2011 and deals with the coupling of glycals with substituted alkenes.⁶⁰ The best conditions require the use of catalytic quantities of Pd(OAc)₂, the presence of Cu(OTf)₂, in a mixture of solvents (DMA/AcOH = 1:1) under an atmosphere of O₂ (Scheme 25, A). They thus described 18 examples in moderate to good yields (43-87%).



Liu *et al.* in 2011 and Yu *et al.* in 2015

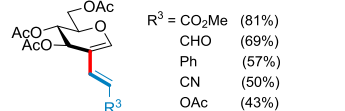
Conditions A : **40** (2 equiv.), Pd(OAc)₂ (10 mol%), Cu(OTf)₂ ou Cu(OAc)₂ (1 equiv), DMA/AcOH (1:1), O₂ (1 atm), 65-70 °C, 24 h.

Selected examples :



Bäckvall *et al.* in 2013

Conditions B : **40** (2 equiv.), Pd(OAc)₂ (2.5-5 mol%), BQ (5-10 mol%), Fe(pc) (1-2.5 mol%), O₂ (balloon), AcOH/DMA (1:1), 70 °C, 24 h.



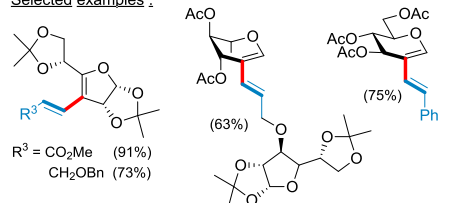
Mukherjee *et al.* in 2018

Conditions C : **40** (1.2 equiv.), Pd(OAc)₂ (0.1 equiv),

Cu(OAc)₂·H₂O (3 equiv), Pyridine (2 equiv), Dioxane, 80 °C, 24 h.

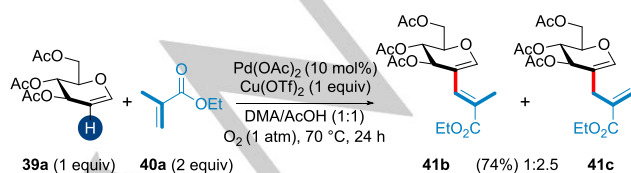
Conditions D : **40** (1.2 equiv.), Pd(OAc)₂ (0.1 equiv), AgOAc (2.5 equiv), DMF/DMSO (20:1), 80 °C, 20 h.

Selected examples :



Scheme 25. Pd(II) catalyzed C2-vinyl glycosides according to Liu *et al.*

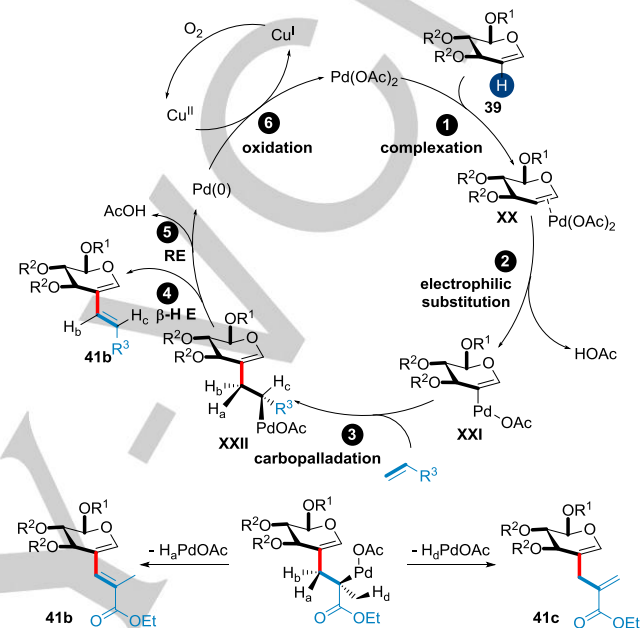
Furthermore, they investigated the use of a disubstituted alkene (ethyl methacrylate), which gave a mixture of compounds **41b** and **41c** with a ratio of 1:2.5 in 74% total yield (Scheme 26). A plausible mechanism was proposed for this reaction (Scheme 27): the Pd complex **XXI** is formed after steps 1 and 2 through complexation and subsequent electrophilic substitution on the glycal at the C2 position.



Scheme 26. Liu *et al.* C-H functionalization with a disubstituted alkene.

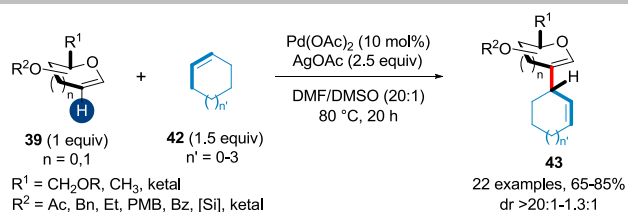
A carbopalladation of the acrylate occurs delivering the more stable conformation **XXII** with the two bulky groups

situated in *anti* (Scheme 27, step 3). The formation of the *anti*-product justifies the observation of the *E* configuration **3** for all the synthesized compounds. Then the final compound **3** is formed via a β -hydride elimination during the step 4. Finally, the Pd(0) complex obtained through reductive elimination (step 5) is oxidized by Cu(II) to regenerate the active Pd(II) catalyst species (Scheme 27, step 6). Concerning products **41b** and **41c**, the conformation is explained regarding the β -hydride elimination step, which could occur on the two possible carbons in β of the Pd.

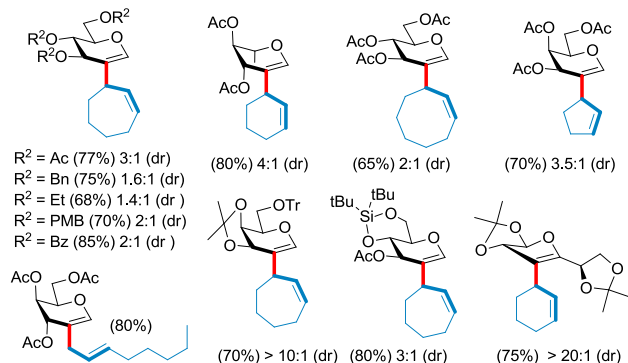


Scheme 27. Liu *et al.* plausible mechanism for C-H functionalisation with alkenes on glycal type substrates.

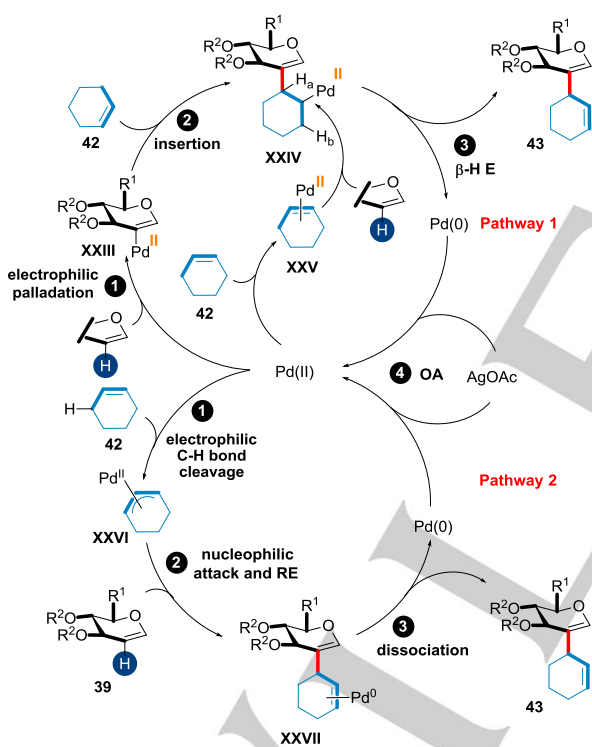
Inspired by this work, Yu *et al.* used these C-H functionalization conditions in 2015 in a total synthesis of a monosaccharide, the bradyrhizose.⁶¹ This process was achieved from the tri-O-acetyl-D-glucal in 26 steps with a global yield of 9%. The pallado-catalyzed Csp²-H activation was applied at the first step of this synthesis, which permits to combine glucal with a methyl acrylate moiety (Scheme 25, A). They optimized the previous conditions to increase the yield to 76%. Another example of alkenylation on glycals was reported in 2013 by Bäckvall *et al.*⁶² Their conditions were close to those described by Liu *et al.* but they aimed to develop a biomimetic aerobic oxidative coupling between two C_{vinyl}-H bonds for the synthesis of conjugated dienes. Indeed, they engaged smaller quantities of Pd(OAc)₂ in combination with iron phthalocyanine and *p*-benzoquinone in catalytic amounts as electron-transfer mediators, and O₂ as an oxidant to regenerate the catalyst in its active form (Scheme 25, B). In this case, they established that the key step is the reoxidation of Pd(0) to Pd(II) by this biomimetic approach. Thereby, five C2-substituted glycals with yield ranging from 43% to 81% were synthesized. Additionally, a scale up was done with the methyl acrylate as the electrophilic partner on the tri-O-acetyl-D-glucal and 2.1g of the corresponding product was obtained in a good 81% yield. Afterward, Mukherjee's group developed in 2016 a C-H allylation reaction between glycals **39** and inactivated cycloalkenes **42** (Scheme 28).⁶³ Pd(OAc)₂ was used as a catalyst and AgOAc as an oxidant in the process. They thus obtained 22 compounds **43** in yields ranging between 65 and 85%. The same group implemented two years after a coupling between glycals and alkenes using the same previous conditions with some modifications (Scheme 25, C and D).⁶⁴



Selected examples :



Scheme 28. Mukherjee's group C-H functionalization on glycals with cycloalkenes substrates.



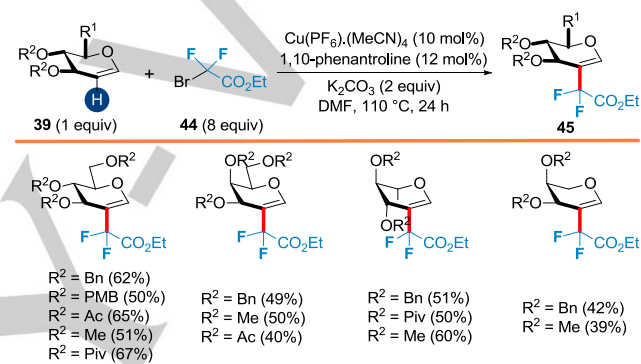
Scheme 29. Mukherjee's group proposed mechanism for C-H functionalization with cycloalkenes on glycal type substrates by two pathways.

They also developed other conditions for the same reaction, giving similar results. In view of the equal efficiency for both conditions, they used principally conditions B for economic reasons, and they could obtain 22 examples in 59 to 91% yield. On top of that, a mechanism was proposed for this coupling implying two pathways (Scheme 29).

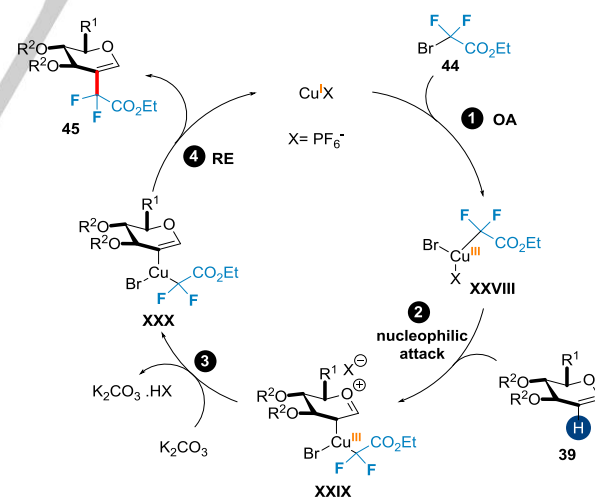
The first one begins with an electrophilic palladation at the C2 position of the glycal to give a vinyl Pd(II) complex **XXIII**, followed by a cycloalkene insertion leading to the species **XXIV**. Additionally, a Wacker type nucleopalladation reaction could

take place, where the cycloalkene-Pd(II) π -complex **XXV** formed previously, is attacked by the sugar enol ether which acts as a nucleophile, forming the intermediate **XXIV**. The latter then undergoes a β -H elimination delivering the desired product **5** and a Pd(0) complex. The second pathway involves the formation of a π -allyl-Pd(II) complex **XXVI** in the first step, reacting Pd(II) with cycloalkane *via* an electrophilic allylic C-H bond cleavage. Then, **XXVI** is attacked by the glycal *via* its nucleophilic C2 position leading to the formation of species **XXVII** after reductive elimination which undergoes dissociation of Pd(0) to generates the desired product **43**. Eventually, silver acetate is supposed to help the oxidative addition of Pd(0) to Pd(II) in both pathways.

Finally, Pannecoucke *et al.* developed a copper-catalyzed C-H process to introduce fluorinated ester moieties on the C2 position of glycal-type substrates (Scheme 30).⁶⁵ First of all, the optimal conditions were developed on simple 1,2-dihydropyrans and were then extended to glycals. Thanks to the addition of ethyl bromo(difluoro)acetate as electrophilic partner, 13 examples were reported in modest to good yields (39 and 67%).



Scheme 30. Pannecoucke *et al.* C-H functionalization on glycals with fluorinated compounds.



Scheme 31. Pannecoucke *et al.* proposed mechanism for the fluorination of glycals.

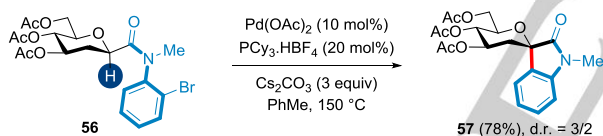
Moreover, a mechanism was proposed based on experimental studies (Scheme 31). Firstly, a radical pathway was excluded thanks to the addition of radical inhibitors and radical scavengers on the reaction mixture, which led to the same yields. Secondly, the standard conditions were applied on enol ether, which allowed to show an isomerization of the double

compound led only to mixtures where low amount of **55** was accompanied to dimers and 1,4-C-H insertion product. They explain this trend by the possibility that anomeric effect in the α compound could deactivate the C5-H bond.

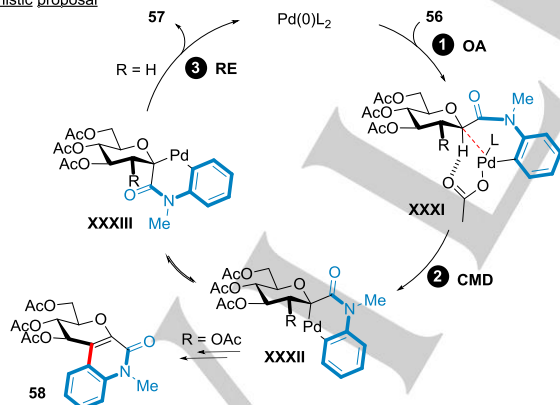


Scheme 34. Lecourt *et al.* non-directed Csp³-H quaternization of the position 5 on glycopyranosides.

In 2017, Messaoudi *et al.* investigated the intramolecular arylation of 2-bromophenyl glycosylcarboxamide substrates (Scheme 35) in the presence of palladium catalysts.⁷⁰ In the case of a peracetylated 2-deoxy glucoanalogue **56**, they described an intramolecular Pd-catalyzed selective anomeric C-H activation leading to glucosylspirooxindole **57** in very good yield as a mixture of two diastereoisomers α and β (d.r. = 3:2). Acetyl protecting groups appear to be crucial in the success of the process since a perbenzylated- or a protecting group-free analogue failed to furnish the corresponding spirocompound in the same conditions. Supported by DFT calculations, the authors proposed that the process starts by an oxidative addition of Pd(0) into the C-Br bond of the carboxamide moiety, followed by ligand exchange leading to intermediate **XXXI** (Scheme 35) where the palladium atom is spatially close to the anomeric C-H bond. *Via* a concerted metalation deprotonation (CMD) mechanism, a palladium C-enolate is then formed (equilibrium between the two diastereoisomers **XXXII** and **XXXIII**).



Mechanistic proposal



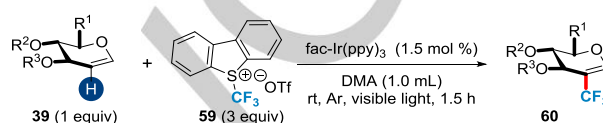
Scheme 35. Messaoudi's intramolecular arylation of 2-deoxy-glycosylcarboxamide **56**.

From these species, a reductive elimination process furnishes **57** in the case of a 2-deoxy starting substrate (R = H). Indeed, when R = OAc, **XXXII** evolved to glucal **58** through a three-step process involving a 1,2 Pd-migration, followed by a reductive elimination, and finally an anti-HOAc elimination (Scheme 35).

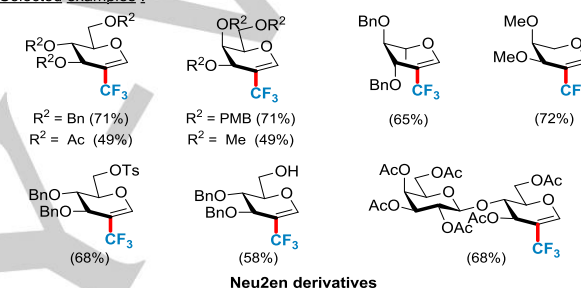
2.2. Dual photoredox

2.2.1. Csp²-H functionalization

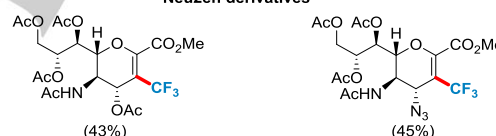
Photoredox catalysis became very attractive these last decades and is described as a mild, efficient and practical transformation. In 2015, a photoredox process was used by Ye *et al.* for the direct C-H trifluoromethylation of glycals (Scheme 36).⁷¹ This photocatalytic reaction needs the presence of $\text{fac-Ir}^{3+}(\text{ppy})_3$ as photocatalyst, Umemoto's reagent (CF_3 source) and a visible light source. This trifluoromethylation was applied on a wide range of glycals, with both electron-withdrawing and -donating protecting groups, and allows the formation of 17 products in moderate to good yields (49-78%). On top of that, two glycal derived drugs, namely NeuZen derivatives, were synthesized in 43 and 45% yields.



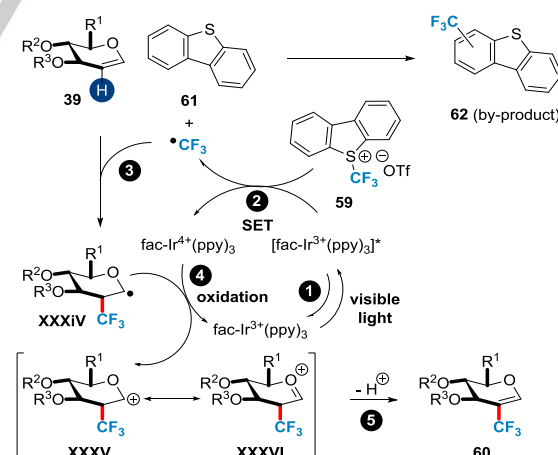
Selected examples :



NeuZen derivatives



Scheme 36. Ye *et al.* C-H functionalization on glycals *via* Photoredox trifluoromethylation.



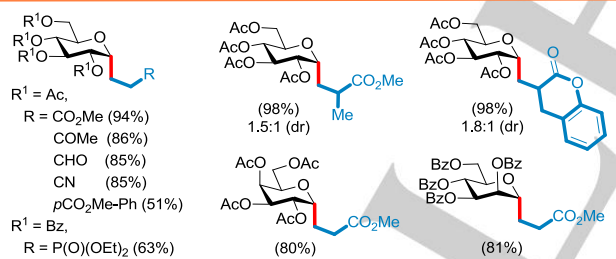
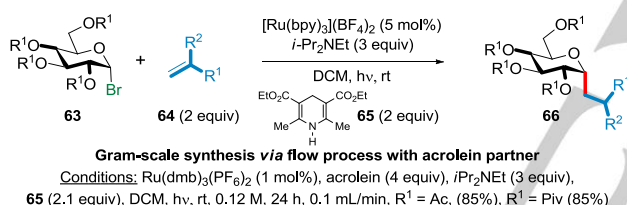
Scheme 37. Ye *et al.* plausible mechanism for C-H functionalization *via* photoredox trifluoromethylation.

Furthermore, they investigated the reaction mechanism with a series of experiments. In this respect, a possible mechanism illustrated in Scheme 37 was proposed. Firstly, the emission of a photon from the light source, accepted by $\text{fac-Ir}^{3+}(\text{ppy})_3$, induces the excited state $[\text{fac-Ir}^{3+}(\text{ppy})_3]^*$. Then a single electron from latter is transferred to the CF_3 reagent and

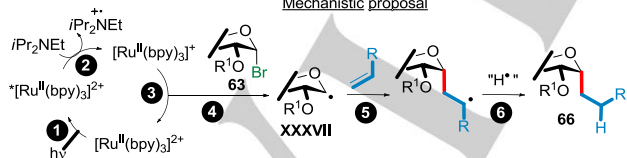
generates the electron deficient intermediate $\text{fac-Ir}^{4+}(\text{ppy})_3$, CF_3 radical and **61**. A small amount of trifluoromethylated dibenzothiophene **62** was observed, resulting from the free-radical aromatic substitution reaction of dibenzothiophene with the CF_3 radical. The addition of CF_3 radical to the double bond of the glycal leads to the glycal **XXXIV**, which undergoes an oxidation by $\text{fac-Ir}^{4+}(\text{ppy})_3$, regenerating $\text{fac-Ir}^{3+}(\text{ppy})_3$ in the catalytic cycle, and forming the glycosyl oxocarbenium ion **XXXV**. Finally, the intermediate **XXXV** or **XXXVI** furnishes the desired compound **60** by deprotonation.

2.2.2. $\text{Csp}^3\text{-H}$ functionalization

In the 2010s, Gagné *et al.* used the well-known capacity to form anomeric radical species from glycosyl bromides **63** to perform intermolecular additions with electron-deficient alkenes mediated by visible light.⁷² Indeed, $[\text{Ru}(\text{bpy})_3](\text{BF}_4)$ as photocatalyst in combination with visible light led to the formation of C1 sugar radicals which can react with alkenes **64** and furnish exclusively α -C-glycosides **66** in modest to excellent yields (Scheme 38). A key parameter to suppress side reactivities (oligomerization, hydrolysis) was to use Hantzsch ester **65** as a proton donor in highly concentrated dichloromethane solution. *N,N*-diisopropylethylamine was chosen as the best reductant to effectively run the photocatalyst cycle. Diverse acetate or benzoate protected glucosyl-, mannosyl- or galactosyl-type bromides were successfully used in this process. In terms of alkene partners, several mono- or 1,1-disubstituted compounds were involved but over-conjugate addition was more competitive in the case of highly electron deficient alkenes.



Mechanistic proposal



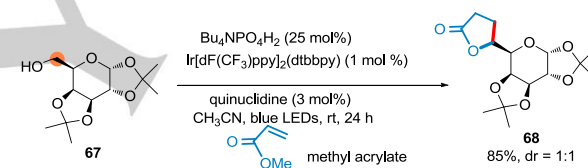
Scheme 38. Gagné's photoredox synthesis of C-glycosides.

Moreover, this method was scaled up to 1.2 mmol. Several control experiments were performed to understand mechanistic aspects of the reaction. Based on control experiments and EPR measurements, the authors thus proposed the following mechanism: the reaction starts by the irradiation of the photocatalyst which enters in an excited state ($^*\text{Ru}(\text{bpy})_3$). This species is then reduced by the amine to generate the reactive strongly reductant ruthenium complex ($\text{Ru}(\text{bpy})_3^+$) capable to form the C1 radical in the presence of **63**. Addition of this radical **XXXVII** to the alkene and reduction by Hantzsch ester provide

C-glycosides **66** (Scheme 38). Via several experiments, the authors investigated the key parameters of the reaction.⁷³ Indeed, the conditions described in Scheme 38 need long reaction time, witnessing a possible inefficient photoredox cycle. They demonstrated that, at low concentrations, the reductant (amine) and the catalyst concentration influence the reaction rate, whereas a saturation effect is observed at high concentrations. Moreover, they observed that the presence of water and the use of a hydrophobic catalyst ($\text{Ru}(\text{dmb})_3$) are beneficial to obtain an efficient conversion.

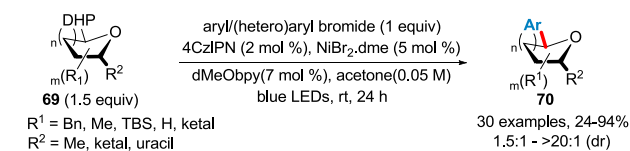
In 2012, Gagné *et al.* developed a continuous flow photoredox equipment which led to an improvement of the TOF value of the process.⁷⁴ They observed that a thin diameter of the reaction vessel increases the flux of photons, inducing an increase of the concentration of active catalyst. Their optimized reactor using a 1.6 mm inner diameter tubing and a concentration of 1 mM. By this way, they synthesized two C-glycosides on almost 5 g scale using acrolein as alkene partner in 85% yield in the presence of only 1 mol% of ruthenium photocatalyst (Scheme 38). These gram-scale aldehydes were proved to be versatile building blocks for the synthesis of a series of C-linked glycoconjugates such as C-glycopeptides and C-glycolipids.

MacMillan and coworkers reported in 2015 a photoredox α -alkylation/lactonization of alcohols with methyl acrylate via a hydrogen atom transfer mechanism.⁷⁵ The study was not focused in the reactivity of glycosides but the authors reported in their scope one example with protected sugar **67**. Under the optimized reaction conditions, the lactone alkyl C-glycoside **68** was isolated in 85% yield and 1:1 diastereoselectivity (Scheme 39).

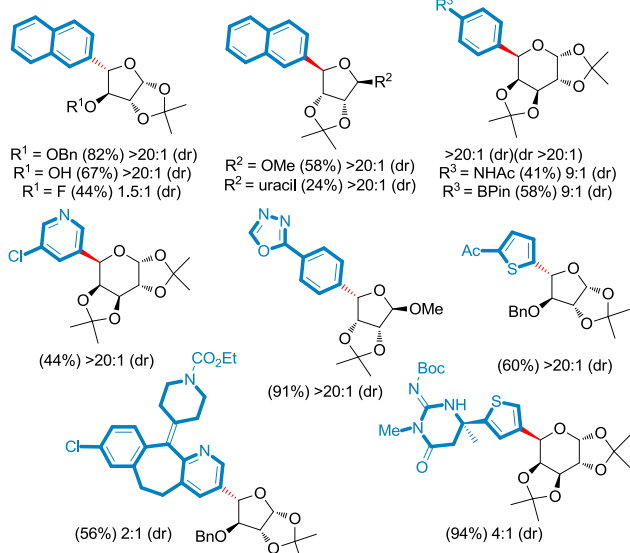


Scheme 39. MacMillan *et al.* synthesis of lactone C-glycosides via Ir/Photoredox Dual Catalysis.

More recently, Dumoulin *et al.* developed a new route for the construction of C-aryl/(hetero)arylglycosides via a nickel-catalyzed photoredox cross-coupling using aryl/heteroaryl bromides and an organic photocatalyst (Scheme 40).⁷⁶ They synthesized 30 products **70** in mild conditions in yields ranging between 24 and 94% and diastereoisomeric ratios between 1.5:1 and >20:1.

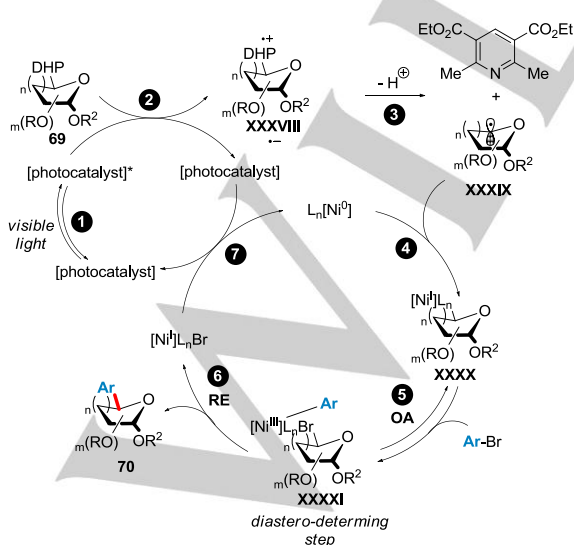


Selected examples :

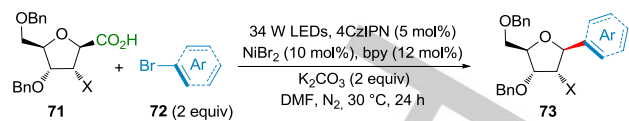


Scheme 40. Dumoulin *et al.* synthesis of C-aryl/(hetero)aryl glycosides via Nickel/Photoredox Dual Catalysis.

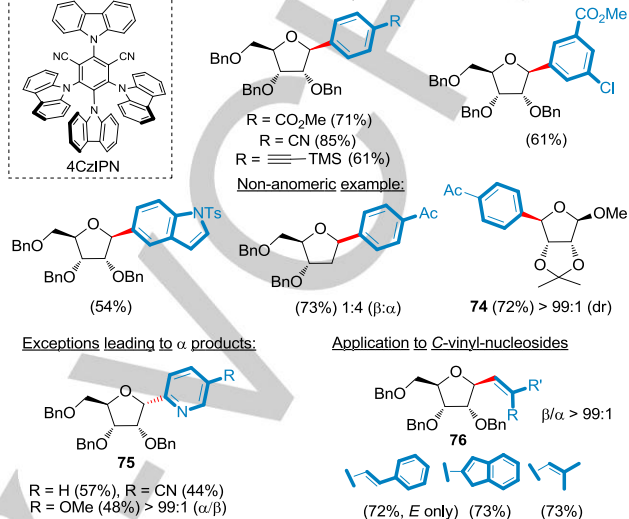
They used dihydropyridyl saccharides as radical precursors initiated by the organic photocatalyst in its excited form. Besides, a plausible mechanism was proposed where the photoexcitation of the photocatalyst by blue LEDs initiates the reaction (Scheme 41). Then the resulting radical cation **XXXVIII** generates by fragmentation an aromatized pyridine derivative and the corresponding radical **XXXIX**. The active Ni(0) catalyst is complexed to this last species forming a Ni(I)-saccharyl complex **XXXX** and the aryl bromide is added by oxidative addition yielding the Ni(III) complex **XXXXI**. Finally, reductive elimination gives both the desired compound **70** but also generates a Ni(I) species which is then reduced to Ni(0) thanks to the reduced form of the photocatalyst allowing in this case generation of both active catalysts.



Scheme 41. Dumoulin *et al.* proposed mechanism for synthesis of C-aryl/(hetero)aryl glycosides via Nickel/Photoredox Dual Catalysis.



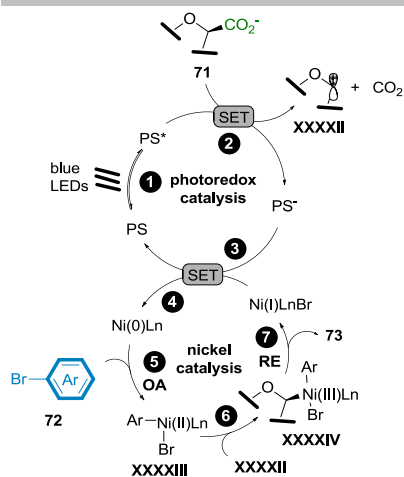
Selected examples: $\beta:\alpha = >99:1$



Scheme 42. Wang and Zhang photoredox/nickel dual catalyzed synthesis of C-aryl/vinyl-nucleosides.

Very recently, Wang and Zhang proposed a combination of photoredox and nickel catalysis capable to promote arylation of the anomeric position of ribosyl/deoxyribosyl acids *via* a decarboxylative cross-coupling reaction with aryl/heteroaryl bromides.⁷⁷ They developed mild reaction conditions using visible-light irradiation in the presence of an organic photocatalyst (4CzIPN), which led to the synthesis of diverse C-aryl/heteroaryl-nucleosides in a highly stereoselective manner in moderate to high yields (Scheme 42).

Their conditions were compatible with both electron-rich and electron-poor aryl-heteroaryl bromide partners and benzyl protected starting substrates, but did not tolerate benzoyl protected ribosides. A *para*-strongly electron-donating group on the bromide decreases the reactivity, as well as a substituent in *ortho*-position. In term of stereoselectivity, both α and β starting materials led to almost exclusively the β products (>99:1) in high yields, except for β -deoxyribosyl acid which led to low β diastereoselectivity and 2-bromopyridine partners which furnished the completely opposite diastereoselectivity α (**75**, Scheme 41). Moreover, a non-anomeric furanosyl acid was also successfully converted to **74** in the same conditions (Scheme 41). Finally, the authors applied this reactivity to the synthesis of various C-vinyl-nucleosides **76**. They could observe the formation of the *trans*-product exclusively and independently of the conformation of the starting bromide.



Scheme 43. Proposed mechanism for the formation of C-aryl-nucleosides **18**.

From a mechanistic point of view, based on control experiments, the authors suggested a photocatalytic cycle starting from the generation of an excited state of the photocatalyst (PS*), which promotes a photo-oxidative decarboxylation reaction of **69**, leading to the formation of a key anomeric radical **XXXXII**. Concomitantly, nickel (0) species, generated by a photoredox process, undergoes an oxidative addition into the bromide partner to form **XXXXIII**, which reacts with radical **XXXXII** to furnish intermediate **XXXXIV**. Finally, reductive elimination process produces product **71** and regenerates the active Ni(0) species and the ground state of the photocatalyst after photoredox reduction (Scheme 43).

3. Conclusion

This review has highlighted the recent progresses achieved on complex sugar substrates using C–H functionalisation and photoredox approaches as two useful methods for the synthesis of C-branched glycosides. These new and sustainable processes have emerged as powerful methodologies, in comparison with former organometallic catalytic routes, offering the advantage of reducing the generation of wastes from the time-consuming preparation of often unstable prefunctionalized substrates. In the span of approximately two years, these processes have become a workhorse for the construction of an array of C–C bonds on the sugar nucleus.

The illustrated methodologies showed the considerable interest that these two emerging tools took in the past years and proved their success for the construction of complex C-branched glycosides. The protocols presented in this review show high efficiency as well as stereo- and regioselectivity, good functional group tolerance and good scalabilities. Future development in this field include the development of additional photoredox reactivity involving, for example, more visible-light catalyzed process, electrochemical methodologies, general protocols for C–H activation on tertiary centers, and alkyl-alkyl couplings. The continuation of efforts in these areas will serve to increase further the impact of this rapidly growing field of research and to reach complex glycosides of biological interest.

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Keywords: C-glycosides • C–H functionalization • Photoredox dual catalysis • glycols • glycosylation

Lit of abbreviation

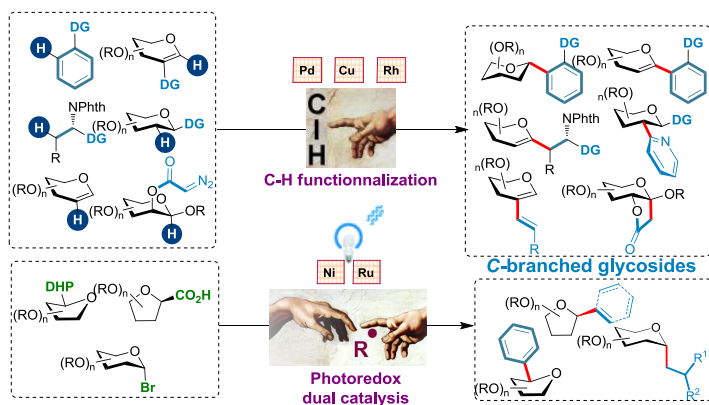
AD	Alzheimer's disease
DNA	Deoxyribonucleic acid
α -Gal-Cer	α -Galactosylceramide
C57BL/6 mice	Common inbred strain of laboratory mouse
B16 melanoma cells	Murine tumor cell line
Nu	Nucleophile
Ar	Aryl
FG	Functional group
DG	Directing group
LG	Leaving group
C- $\Delta^{1,2}$ glycosides	Glycosides possessing an intracyclic double bond between the carbon 1 and 2 of the sugar
N-Q	N-quinolyl
TAM	Triazolylidimethylmethyl
Schwartz's reagent	Bis(cyclopentadienyl)-zirconium(IV) chloride hydride
OA	Oxidative addition
RE	Reductive elimination
1C_4	Chair conformation where carbon 1 is located above the reference plane of the chair, made up by C–2, C–3, C–5 and the ring oxygen and carbon 4 below.
4C_1	Chair conformation where carbon 4 is located above the reference plane of the chair, made up by C–2, C–3, C–5 and the ring oxygen and carbon 1 below.
Py	Pyridinyl
cod	1,5-Cyclooctadiene
Binap	Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
de	Diastereoisomeric excess
Phth	Phthalimidyl
Ad	Adamantyl
DFT	Density Functional Theory
BODIPY	Boron-dipyrromethene
Ala	Alanine
Tzl	Triazolyl
Tyr	Tyrosine
dr	Diastereoisomeric ratio
Phen	1,10-Phenanthroline
CMD	Concerted metalation deprotonation
BQ	<i>p</i> -Benzoquinone
Pc	Phthalocyanine
β -H E	β -H elimination
L	Ligand
Cy	Cyclohexyl
ppy	2-Phenylpyridine
Umemoto's reagent	5-(Trifluoromethyl)dibenzothiophenium trifluoromethanesulfonate
Neu2en	2,3-Unsaturated <i>N</i> -acetylneuraminic acid
SET	Single Electron Transfer
Bpy	2,2'-Bipyridine
Hantzsch ester	Diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate
Dmb	4,4'-dimethyl-2,2'-bipyridine
EPR	Electron paramagnetic resonance
TOF	Turnover Frequency
4CzIPN	1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-

LED	dicyanobenzene
PS	Light-emitting diode
PS*	Photocatalyst
	Excited state of the photocatalyst

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Entry for the Table of Contents



This review highlights the major progresses on C–H functionalization and dual photoredox catalysis as two powerful approaches for the synthesis of C-branched glycosides.

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