C-H Activation Hot Paper

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Remote C–H Glycosylation by Ruthenium(II) Catalysis: Modular Assembly of *meta*-*C*-Aryl Glycosides

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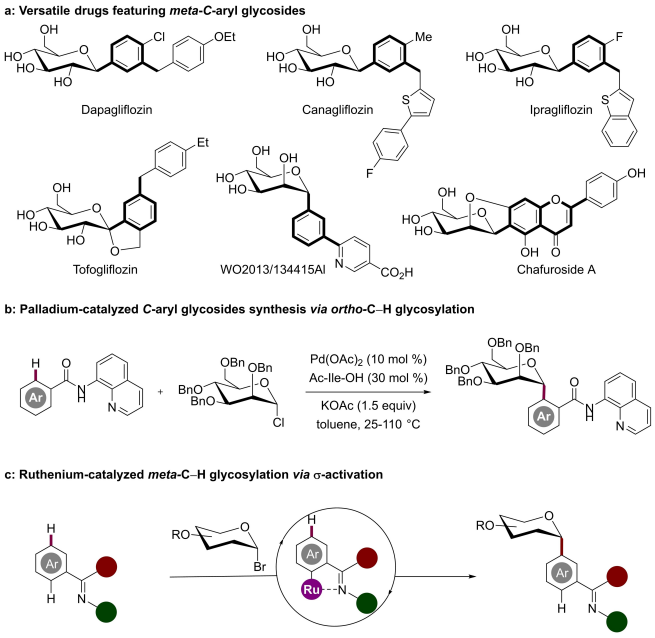
Abstract: The prevalence of *C*-aryl glycosides in biologically active natural products and approved drugs has long motivated the development of efficient strategies for their selective synthesis. Cross-couplings have been frequently used, but largely relied on palladium catalyst with prefunctionalized substrates, while ruthenium-catalyzed *C*-aryl glycoside preparation has thus far proven elusive. Herein, we disclose a versatile ruthenium(II)-catalyzed *meta*-C–H glycosylation to access *meta*-*C*-aryl glycosides from readily available glycosyl halide donors. The robustness of the ruthenium catalysis was reflected by mild reaction conditions, outstanding levels of anomeric selectivity and exclusive *meta*-site-selectivity.



Scheme 1. Selected *C*-aryl glycosides and methods for *C*-aryl glycoside synthesis.

Introduction

C-aryl glycosides represent an important carbohydrate scaffold in which the glycosidic C–C bond confers a remarkable stability to both enzymatic and chemical hydrolysis.[1] As a consequence, *C*-aryl glycosides were widely exploited in a variety of pharmacologically relevant drugs, such as Dapagliflozin, Canagliflozin and Ipragliflozin (Scheme 1a).[2] For the chemical assembly of *C*-aryl glycosides, transition metal-catalyzed cross couplings with two prefunctionalized substrates, such as the Corriu-Kumada,[3] Suzuki–Miyaura,[4] Stille,[5] and Negishi[6] couplings, were developed.[7] In contrast, during the recent years C–H activation has emerged as an increasing viable alternative for the late-stage functionalization, avoiding the synthesis of the two prefunctionalized agents[8] In this context, palladium-catalyzed *ortho*-C–H glycosylation of arenes provided an efficient access to *ortho*-*C*-aryl glycosides (Scheme 1b).[9] Despite of indisputable advances, the selective installation of carbohydrates at a distal position of arenes remains to be in high demand via *meta*-C–H functionalization.[10–13] Unlike the proximal C–H glycosylation of arenes,[14] the distal C–H glycosylation is significantly more challenging and limited methods are available. Combined with the role of a palladium(II) catalyst as Lewis acid promoter for glycosyl chloride donor activation,[15] a Catellani-type reaction was recently designed to achieve *meta*-C–H glycosylation.[16] Given the unique power of ruthenium catalysis for *meta*-C–H functionalization,[17] we wondered whether a ruthenium-catalyzed C–H glycosylation could be amenable for the particularly challenging construction of *meta*-*C*-aryl glycosides (Scheme 1c).[18] As a result, we herein disclose our findings on *meta*-*C*-aryl glycoside synthesis with the salient features comprising (a) unprecedented ruthenium-catalyzed *σ*-activation for *meta*-C–H glycosylation of arenes, (b) high levels of site-, chemo- and stereoselectivities, and (c) exceedingly mild reaction conditions applicable for late-stage functionalization of drug scaffolds.

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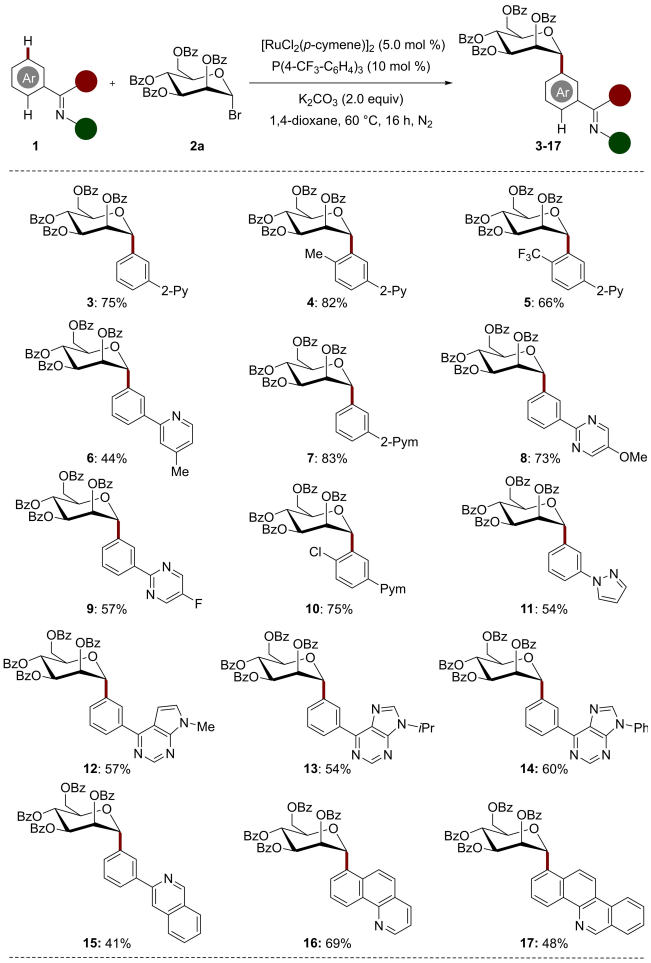
Results and Discussion

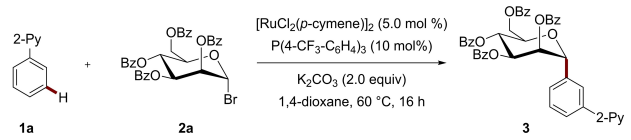
We initiated our studies for the *meta*-C(sp^2)–H glycosylation with mannosyl bromide donor **2a** as the glycosylation reagent (Table 1). The reaction with $[RuCl_2(p\text{-cymene})]_2$ as the catalyst and $MesCO_2H$ as the additive failed to deliver the desired product **3** (entry 2). Instead, P(4-CF_3–C_6H_4)$_3$ used as ligand provided *meta*-glycosylation product **3** in 29 % yield at 100 °C (entry 3).[12g] Decreasing the reaction temperature improved the catalytic efficiency, with 60 °C being the best choice to give the product **3** in 75 % yield with exclusive α-selectivity (entries 1–3). Next, $[RuCl_2(PPh_3)_3]$ as catalyst in the absence of P(4-CF_3–C_6H_4)$_3$ was tested, delivering product in 37 % yield (entry 4).[19] When replacing the P(4-CF_3–C_6H_4)$_3$ with different phosphine ligands, the yield could not be improved (entries 5–7). An optimization of the base demonstrate that K_2CO_3 was the best of choice (entries 8). A set of typical solvents, such as NMP, toluene and THF, was probed, but with limited success (entry 9). Control experiments verified the essential roles of the ruthenium catalyst and the phosphine ligand (entry 10 and 11).

With the optimized reaction conditions for the *meta*-C(sp^2)–H glycosylation in hand, we examined its generality (Scheme 2).[19] Initially, the substitution pattern on the arene moiety was tested, and *para*-decorated arenes **1b** and **1c** were well tolerated (**4** and **5**). Electron-rich pyridine **1d** exhibited a lower efficiency (**6**). When methyl substituent was installed at the *meta*-position, no desired product was observed.[19] Then, pyrimidine derivatives **1e**–**1g** were used in the *meta*-C–H glycosylation and high catalytic efficiencies were observed (**7**–**9**). The electrophilic chloro-group at the *para*-position of phenyl **1h** also proved to be feasible (**10**), without any *ortho*-arylation observed.[20] The *meta*-C–H glycosylation was not restricted to pyridine-guided function-



Scheme 2. Ruthenium-catalyzed *meta*-C–H glycosylation of heteroarenes.

Table 1: Optimization of ruthenium-catalyzed *meta*-C–H glycosylation.[a]



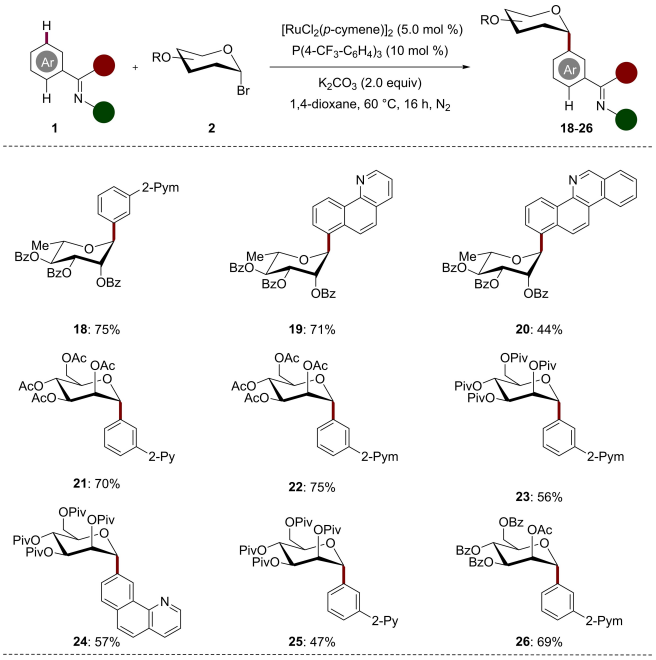
Entry	Deviation from the standard conditions	Yield[%][b]
1	none	75
2	$MesCO_2H$ as ligand	NR
3	At 100 °C, 80 °C, 40 °C	29/57/12
4	$[RuCl_2(PPh_3)_3]$ as catalyst	37[c]
5	P(4-OMe–C_6H_4)$_3$ as ligand	40
6	P(4-F–C_6H_4)$_3$ as ligand	59
7	P(3,5-CF_3–C_6H_3)$_3$ as ligand	NR
8	Na_2CO_3/K_3PO_4/KOAc as bases	28/49/NR
9	NMP/toluene/THF as solvents	NR/NR/27
10	Without $[RuCl_2(p\text{-cymene})]_2$	NR
11	Without P(4-CF_3–C_6H_4)$_3$	NR

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.2 mmol), catalyst (5.0 mol %), ligand (10 mol %), base (2.0 equiv), solvent (1.0 mL). [b] Yield of isolated product. [c] Without P(4-CF_3–C_6H_4)$_3$. NMP: *N*-methyl-2-pyrrolidon.

alization. Indeed, a plethora of heterocycles, such as pyrazole **1i**, purine derivatives **1j**–**1l** and quinoline **1m**, was identified as amenable substrates for the challenging *meta*-*C*-aryl glycosides assembly (**11**–**15**). In addition, fluorescent scaffolds, such as benzo[*h*]quinoline **1n** and benzo[*c*]phenanthridine **1o** afforded products **16** and **17** irrespectively in a remote C–H glycosylation manner.

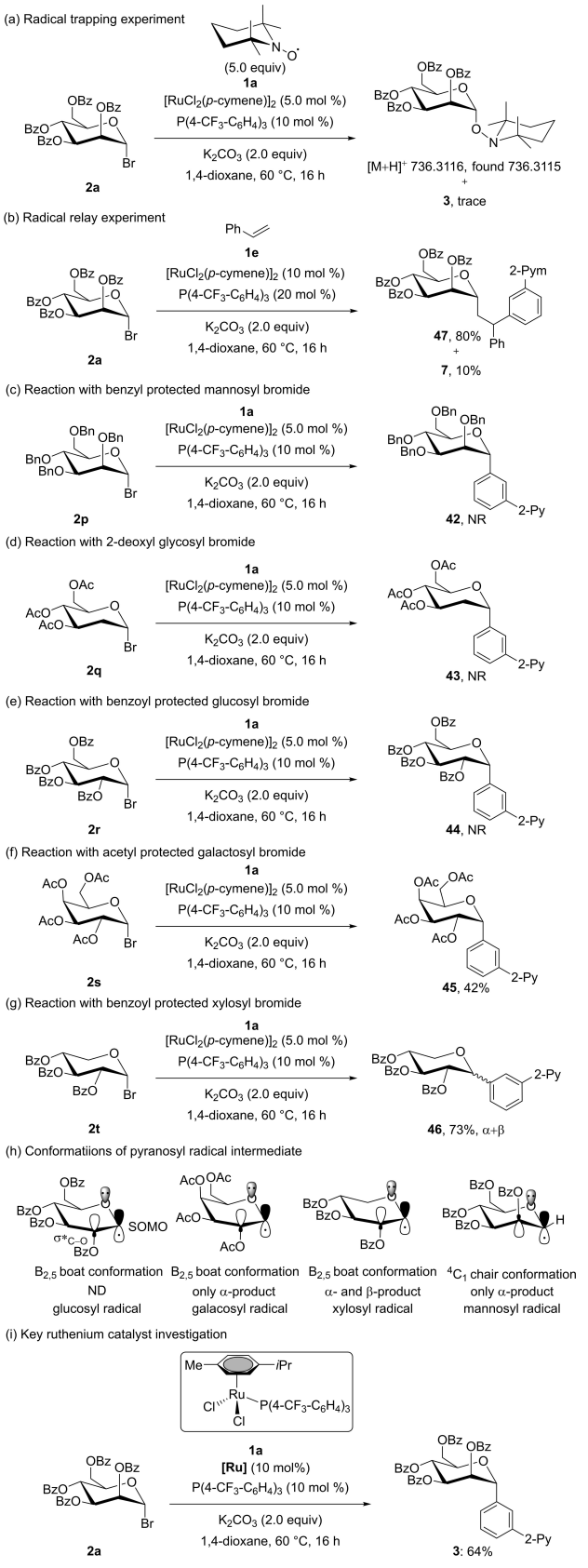
Subsequently, the ruthenium-catalyzed *meta*-C–H glycosylation strategy was probed with different glycosyl bromides **2** (Scheme 3). Rhamnosyl bromide **2b** proved efficient to site- and stereo-selectively stitch rhamnose moiety into the *meta*-position of a series of heteroarenes (**18**–**20**). Diversely protected mannosyl bromides **2c**–**2e**, containing acetyl and pivaloyl group, generated **21**–**26** with exclusive α-anomeric selectivity.

To gain insights into the reaction mechanism, we conducted mechanistic experiments (Scheme 4). The involvement of radical intermediates was supported by the detection of the glycosyl radical-TEMPO adduct via high resolution mass-spectrometry (Scheme 4a). The mannosyl radical was further substantiated by a ruthenium-catalyzed radical relay experiment, with three-component product **47** formed in 80 % yield as well as 10 % of direct *meta*-C–H



Scheme 3. Ruthenium-catalyzed *meta*-C–H glycosylation with different glycosyl bromide donors **2**.

glycosylation product **7** (Scheme 4b). Based on these observations, we attempted our ruthenium catalysis with catalytic amount of phenyl pyridine in the Giese addition, but mannosyl radical conjugate addition products were not detected.[19] Noteworthily, there is no 1,2 acyloxyl migration process[21] observed in the *meta*-C–H glycosylation reaction due to the difficulty to form the rigid 1,3-dioxolanyl radical with mannosyl bromide.[22] To examine whether there is a neighboring effect of the *C*2-benzoyl group, substrate **2p** was utilized under otherwise identical reaction conditions and product **42** was not detected (Scheme 4c). Similarly, 2-deoxyl glycosyl bromide **2q** featuring no substituent at the *C*2-position proved not suitable for the *meta*-C–H glycosylation, suggesting that the *C*2-carboxyl protecting group might be crucial for an efficient transformation (Scheme 4d). Glucosyl bromide **2r** failed to generate the desired *meta*-C–H glycosylation product **44** (Scheme 4e). Compared to the $^4C_1$ and $^1C_4$ conformers, the slightly distorted $B_{2,5}$ boat conformation of glucopyranosyl radical is more stable (Scheme 4h).[19,23] The *C*2-benzoyl group and lone pair electrons of the endocyclic oxygen hence may block the attack of a glucosyl radical to the *para*-position of the cyclometalated C–Ru bond.[12j] In contrast, when acetyl protected galactosyl bromide **2s** was employed, the product **45** was formed with α-anomeric selectivity in 42% yield (Scheme 4f). This α-selectivity may be caused by the *C*4-acetyl group, instead of the α-selectivity control derived from the sterically encumbered catalyst. Interestingly, when conformationally unrestricted benzoyl protected xylosyl bromide **2t** was employed, product **46** was isolated, albeit with poor stereoselectivity (Scheme 4g). We assume that the $B_{2,5}$ boat conformer of xylosyl radical is more flexible than its chair conformers. It features a planar *C*1-carbon center

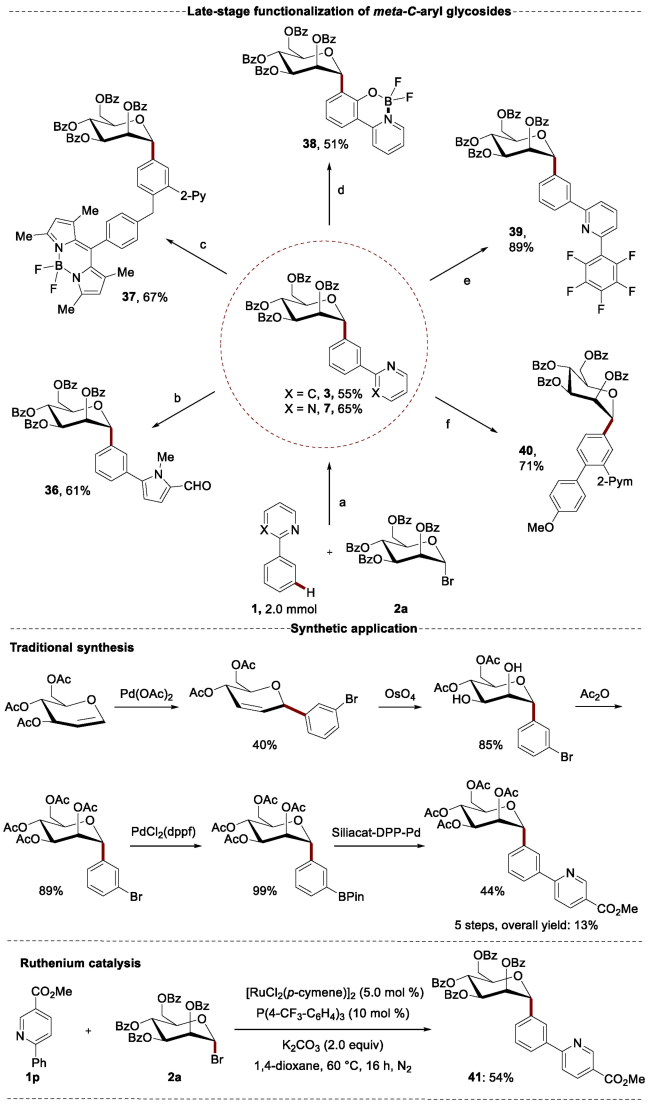


Scheme 4. Summary of key mechanistic studies.

and allows the attack from either the α- or the β-side (Scheme 4h).[19,24] The mannosyl radical possessed stable $^4C_1$-chairlike conformation, which was stabilized by the interaction between the anomeric radical orbital (SOMO), the σ*-orbital of the adjacent C–O bond, and the *p*-orbital of a lone pair of the ring oxygen in their periplanar arrangement.[19] The *C*2 axial benzoyl group and lone pair electrons of ring oxygen force the formation of the *meta*-C–H glycosylation product with complete α-stereoselectivity (Scheme 4h). In addition, the ruthenium catalyst **[Ru]** was employed for the challenging *meta*-C–H transformation (Scheme 4i), the *meta*-glycosylation product **3** was obtained in 64 % yield, which indicates that this catalyst could be catalytically relevant.

Based on our findings, a plausible catalytic cycle (Figure 1) commences with a *ortho*-C–H ruthenation to form intermediate **A**. Subsequently, single electron transfer (SET) from the ruthenium(II) complex to the mannosyl bromide occurs,[19] generating ruthenium(III) intermediate **B** and radical **C**, followed by addition of the radical **C** to the *para*-position of intermediate **B** to give intermediate **D**. The reactive triplet radical **D** is stabilized by singlet metallacycle **E** via ligand to metal charge transfer. Finally, proton abstraction and ligand exchange deliver the desired *meta*-glycosylation product **3** and regenerate ruthenium(II) complex **A**.

The practical utility of the ruthenium-catalyzed *meta*-C–H glycosylation was illustrated by a gram-scale synthesis of *C*-aryl glycosides **3** and **7** (Scheme 5a). Likewise, a two-step sequence enabled the efficient transformation of pyridyl group into useful 2-formylpyrrole **36** (Scheme 5b). Late-stage diversification of product **3** allowed the construction of fluorescent labelled *C*-aryl glycosides **37** and **38** by ruthenium[25] and copper[26] catalysis (Scheme 5c, d). In addition, to enrich the structural diversity of the products, the selective arylations of the arene scaffolds were featured in the synthesis of biaryl **39** and **40** (Scheme 5e, f). In addition, the versatility of the ruthenium catalysis was



Scheme 5. Late-stage transformation of *C*-aryl glycosides and application.[19]

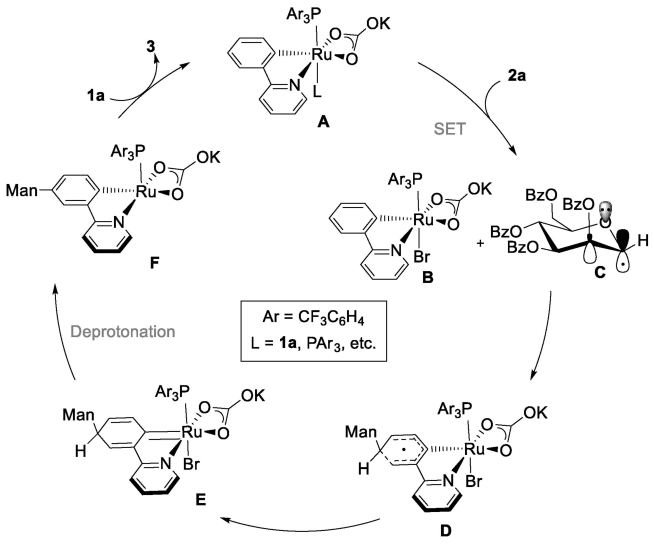
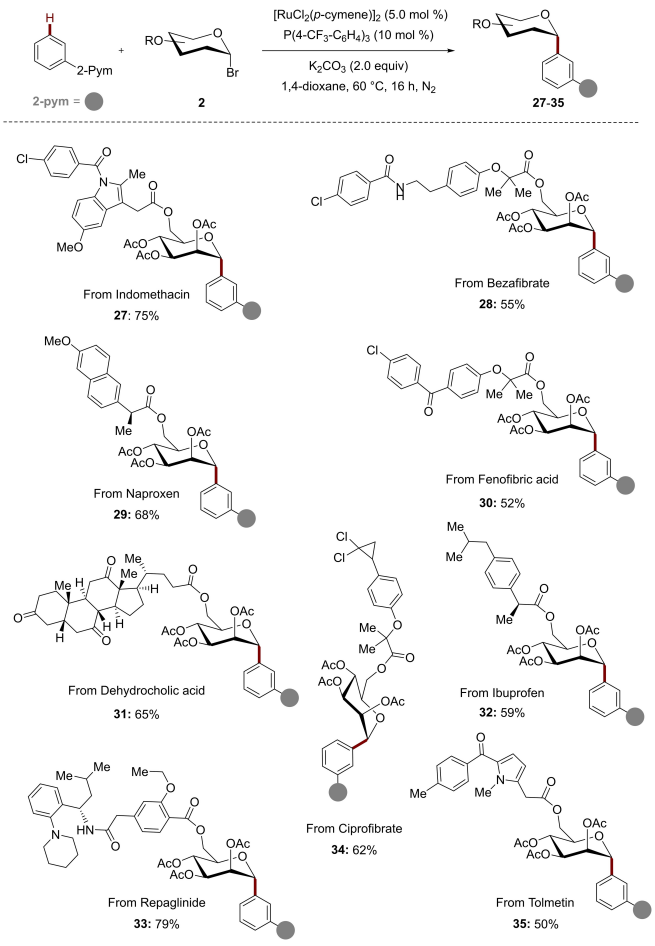


Figure 1. Proposed catalytic cycle.

mirrored by the one-pot synthesis of product **41** in 54 % yield with the commercially available substrate **1p** and easily prepared **2a**. It is noteworthy that the synthesis of product **41** through an established conventional cross-coupling involved multiple synthetic steps and resulted in a much lower overall yield.

Finally, the robustness of the *meta*-*C*-aryl glycoside assembly was exploited for the *meta*-C–H glycosylation with structurally complex glycosyl bromides (Scheme 6). Hybrid glycosyl donors bearing natural products and drug derivatives, such as indomethacin, bezafibrate, naproxen, fenofibric acid, dehydrochloric acid, ibuprofen, repaglinide, ciprofibrate, and tolmetin, were thereby selectively converted to *C*-aryl glycosides **27**–**35**, leading to highly functionalized conjugates with excellent levels of chemo- and stereoselectivities.



Scheme 6. Late-stage *meta*-C–H glycosylation.

Conclusion

In summary, we have developed a ruthenium-catalysed late-stage C–H glycosylation to enable a platform for the assembly of biologically important *meta*-*C*-aryl glycosides. Mild and robust ruthenium catalysis allowed for the expedient *meta*-C–H glycosylation with excellent levels of chemo-, site- and stereoselectivities. Our strategy proved efficient and operationally simple while versatile glycosyl bromides were probed for the elucidation of anomeric selectivity. Overall, this *meta*-C–H glycosylation strategy well complements the current established *ortho*-C–H glycosylation for *C*-aryl glycosides synthesis.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: C–H Activation · Glycosyl Bromide · *meta*-*C*-Aryl Glycoside · *meta*-C–H Glycosylation · Ruthenium Catalysis

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