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Synthesis of Non-Classical, Arylated *C*-Saccharides *via* Nickel/Photoredox Dual Catalysis

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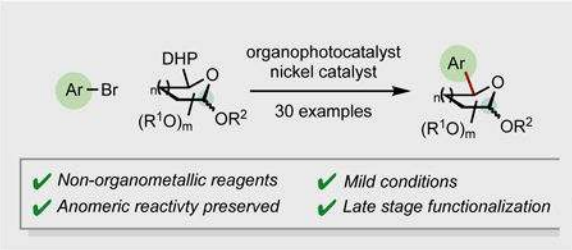
Abstract

The development of synthetic tools to introduce saccharide derivatives into functionally complex molecules is of great interest, particularly in the field of drug discovery. Herein, we report a new route toward highly functionalized, arylated saccharides, involving a nickel-catalyzed cross-coupling of photoredox-generated saccharyl radicals with a range of aryl- and heteroaryl bromides, triggered by an organic photocatalyst. In contrast with existing methods, the mild reaction conditions achieve arylation of saccharide motifs while leaving available the anomeric carbon, thus providing access to a class of arylated glycosides underexplored until now. To demonstrate the potential of this strategy in late-stage functionalization, a variety of structurally complex molecules incorporating saccharide moieties were synthesized.

Graphical Abstract



Keep the anomeric! The development of synthetic tools to introduce saccharide derivatives into functionally complex molecules is of great interest, particularly in the field of drug discovery. Herein, we report a new route toward highly functionalized, arylated saccharides, involving a nickel-catalyzed cross-coupling of photoredox-generated saccharyl radicals with a range of aryl- and heteroaryl bromides, triggered by an organic photocatalyst. In contrast with existing methods, the mild reaction conditions achieve arylation of saccharide motifs while leaving available the anomeric carbon, thus providing access to a class of arylated glycosides underexplored until now. To demonstrate the potential of this strategy in late-stage functionalization, a variety of structurally complex molecules incorporating saccharide moieties were synthesized.

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Conflict of interest

The author declare no conflict of interest.

Keywords

Photoredox; Nickel Catalysis; 1,4-Dihydropyridines; Glycosylation

The incorporation of saccharide derivatives into lead compounds represents an attractive way to diversify drug candidate scaffolds by modulating crucial parameters related to the *in vivo* efficacy of a therapeutic drug (e.g., solubility, membrane transport, pharmacodynamics or pharmacokinetics).[1] Notably, "reverse aryl *C*-glycosides"[2] comprise a class of saccharides that have proven to be efficient antibiotics,[3] antitumor agents[4] or inhibitors for diabetes.[2d, 5] These glycosides have the particularity of bearing an aromatic moiety directly attached to the carbohydrate through a C-C bond, differentiating them from the usual *O*-glycosides, thus leading to better stability to both enzymatic and acidic hydrolysis, while preserving excellent biological efficacy.

Several routes toward anomeric, arylated saccharides have been reported,[2] such as Friedel-Crafts reactions or nucleophilic additions of organometallic reagents (e.g., organolithium or Grignard reagents) to suitable electrophiles. However, such methods suffer from serious drawbacks, including harsh acidic or basic conditions, low functional group tolerance, and undesired side-products arising from elimination or epimerization processes.

Recently, the transition metal-catalyzed cross-coupling of *in situ* generated glycosyl radicals[6] (from the corresponding glycosyl chloride or bromide) with organometallic reagents (aryl- or alkenylzinc and magnesium reagents) has emerged as one of the most efficient ways to access aryl *C*-saccharides (Scheme 1). This transformation has been achieved in the presence of nickel,[7] cobalt[8] or iron[9] catalysts, affording the desired saccharide derivatives in moderate to good yields. Alternatively, pyranosylstannanes could be coupled with aryl halides in the presence of a palladium catalyst.[10] Despite these improvements, such reaction conditions remain limited in terms of functional group tolerance and operational simplicity as they involve highly reactive organometallic species that need to be freshly prepared and suffer from β-elimination.[8a] Furthermore, stoichiometric amounts of metal waste are generated. Finally, these processes rely on substitution reactions at the anomeric center, thus preventing the substrate from being further functionalized by traditional chemistry at the anomeric carbon.

In this context, the development of straightforward, modular, and operationally simple conditions to access *C*-arylated saccharides remains an unsolved challenge and, specifically, methods that would preserve the anomeric carbon to afford non-classical "reverse aryl *C*-glycosides" are particularly scarce. Indeed, despite their attractive biological properties,[11] few synthetic efforts have been carried out in this regard.[12] Other approaches toward the synthesis of "reverse aryl *C*-glycosides" have been reported, such as the [4+2] cycloaddition between Danishefsky's dienes and aromatic aldehydes, yielding glycal derivatives,[13] or the addition of organozinc reagents to 4α-epoxypyranosides (Scheme 2).[14] However, these strategies are restricted to pyranoses, lack modularity, and require several extra steps to obtain the desired "reverse aryl *C*-glycoside."

In recent years, photoredox/nickel cross-coupling reactions have drawn extensive attention from the chemistry community.[15] Such processes allow the cross-coupling of Csp^3 nucleophiles under mild conditions by invoking a single-electron transmetalation pathway. Taking advantage of these modular and operationally simple conditions would allow access to virtually unexplored, non-classical, arylated saccharides. This approach would be a chemoselective strategy wherein arylation is directed to one of the two potential anomeric positions, one being masked by the DHP.[12]

With the goal of accessing glycosyl radicals that could be engaged in such dual catalytic processes, we turned our attention to 4-alkyl-1,4-dihydropyridine derivatives (DHPs).[16] These species have proven to afford Csp^3-centered alkyl radicals efficiently upon SET oxidation. In addition to being bench stable and easy to handle, these compounds tolerate high functionalization levels owing to the mild reaction conditions required for their preparation from the corresponding aldehyde. A wide range of 4-glycosyl-1,4-DHPs was accessed from commercially available pentose and hexose derivatives *via* deprotection and oxidation chemistry to form the aldehyde. Using Tripathi and coworker's procedure, the monosaccharide DHPs were accessed *via* the reported acid-catalyzed condensation reaction.[17] It is worth mentioning that this synthetic pathway accommodated a broad range of carbohydrate derivatives (e.g., ribonucleoside **1g**, furanoses and pyranoses).

Next, the feasibility of the photoredox/nickel cross-coupling reaction between DHPs and 2-bromonaphthalene was studied by means of microscale high-throughput experimentation.[18] Results from the screening revealed that the organic photocatalyst 4CzIPN (excited state E_{red} = +1.35 V vs SCE)[19] was extremely efficient in oxidatively cleaving the DHP [E_{red} (**1a**) = +1.20 V vs SCE],[18] delivering the desired glycosyl radical. Among the advantages of 4CzIPN compared to traditional iridium-based photocatalyst are its lower cost ($4.7/mmol vs $140.0/mmol),[19] which provides significant benefit when it comes to industrial application. After further screening, the best yields were obtained in the presence of 2 mol % of 4-CzIPN photocatalyst, 5 mol % of $NiBr_2$•dme and 7 mol % of dMeObpy as a ligand in acetone at room temperature for 24 h. As expected, control experiments showed that all parameters were essential for the transformation to proceed.

Next, the generality of the reaction with respect to the DHP derivative was explored. As illustrated in Figure 1, the reaction was remarkably tolerant of substitution in the saccharide scaffold, providing the desired products in moderate to high yields. Noteworthy, good to excellent diastereoselectivity was observed for certain furanosyl units (**2a**, **2d**, and **2e**), likely because of steric interactions with the adjacent substituent, an effect observed by Nakamura and coworkers in their recent iron-catalyzed arylation of halosugars.[9] Excellent *dr* has also been observed in the field of photoredox/Ni catalysis when 2-methylcyclopentyltrifluoroborate was coupled with aryl bromide, affording exclusively the *trans* product.[20]

The steric control on the L-arabinofuranose and D-xylofuranose derivatives was made evident when comparing the effect of the vicinal substituent, where small substituents (e.g., MeO and F, **2b** and **2c**, respectively) afforded poor *dr*s, whereas sterically encumbered, TBS-protected moieties afforded excellent steric control (9:1 *dr*). D-Ribofuranosyl DHP

afforded excellent *dr*. X-Ray crystallography confirmed the retention of configuration (**2f**). Likewise, uridine-derived DHP afforded excellent diastereoselectivity, although in low yields; again, this highlights the prevalent role of steric interactions. Additionally, aryl pyranose **2h** generated excellent *dr* with the aryl group *cis* to the dimethyl acetal protecting group (confirmed by X-ray crystallography). Not suprisingly, the more flexible radical leading to **2i** afforded lower diastereoselectivity.[6, 21, 22] Finally, the TBS protecting group choice allowed the formation of unprotected derivative **2e** upon TBAF addition to the crude reaction mixture of **2d**.

The next step was to explore the limitations with respect to the (hetero)aryl bromide partner (Figure 2). Aryl bromides bearing electron-withdrawing groups exhibited excellent reactivity, affording the corresponding product in good yields and high diastereoselectivities (**2j**-**2k**, **2m**-**2p**). In addition, electron-neutral and electron-rich aryl bromides were tolerated (**2q**- **2t**). Notably, a pinacol boronic ester (**2r**) was well accommodated, providing a handle for further functionalization.[23] Although excellent functional group tolerance was observed, we hypothesize that the diminished yields with electron-neutral aryl bromides (**2s** and **2t**) result from a challenging oxidative addition. To access more complex structures, (hetero)aryl bromides, such as pyridine moieties (**2u** and **2v**), oxadiazoles (**2w** and **2y**) and thiophene derivatives (**2x** and **2z**), were successfully employed. Interestingly, carbonyl groups, which could react in the presence of organometallic reagents, pose no problem (**2n**, **2o** and **2x**).

To explore further the chemical diversity accessible through this method, several structurally complex molecules were engaged under the developed reaction conditions (Figure 3). Coupling with a steroid derivative (**3a**) proved successful, thus offering a privileged substructure of use in medicinal chemistry.[24] Recognizing the potential for late-stage functionalization, we introduced functional group-dense aryl bromides from Merck's chemistry informer library containing drug-like motifs.[25] A quinoxalinedione derivative, which is encountered in ionotropic glutamate receptor antagonists,[26]

exhibited good reactivity under optimized conditions to furnish pyranose product **3b** with excellent diastereocontrol. Even the more complex 3-bromothiophene derivative bearing a guanidine motif, belonging to the family of aspartic protease inhibitors,[27]

afforded the desired products in high yield (**3c**). In addition, a furanosyl residue could be introduced into the loratadine scaffold (**3d**) under the standard reaction conditions.

Based on previous reports on the reactivity of DHPs under Ni/photoredox dual catalytic conditions,[16c,d] a plausible mechanism is outlined in Scheme 3. This pathway involves the initial photoexcitation of the 4CzIPN photocatalyst (E_{red} = +1.35 V vs SCE),[18] which undergoes reductive quenching with the DHP derivative [E_{red} (**1a**) = + 1.20 V vs SCE]. The resulting radical cation **A** rapidly fragments to generate an aromatized pyridine derivative along with the corresponding saccharyl radical **B**. This latter species would first add to the active Ni(0) catalyst, thus producing a Ni(I)-saccharyl complex **C** that would undergo oxidative addition with the aryl bromide to afford the corresponding Ni(III) complex **D**.[28] Subsequent reductive elimination would take place to yield the cross-coupling product **2** and a Ni(I) species **E**. This latter complex would then be reduced to Ni(0) **F** with the reduced

form of the 4CzIPN photocatalyst (E_{red} = + 1.21 V vs SCE),[18] thus regenerating both active catalysts for subsequent catalytic cycles.

It is worth noting that although the saccharide backbone plays a key role in the observed diastereomeric ratios, leading in certain cases to substrate control products (e.g., **2f**–**2h**), it is evident when looking at other examples that the aryl bromide is playing a role as well (e.g., **2k** and **2s**), where different substitution patterns in the aromatic backbone lead to different *drs* in the presence of the same saccharyl radical. Previous mechanistic studies suggest the high-valent Ni(III) species **D** ultimately dictates the observed diastereoselectivity after the irreversible reduction elimination;[29] therefore, we sought to improve the lower *drs* by identifying suitable ligands.[7] Bidentate and tridentate ligands were screened with both Ni(0) and Ni(II) species.[18] Modifying the bipyridine backbone by replacing electron-donating methoxy groups with bulkier, less electron-rich, *tert*-butyl substituents afforded excellent diastereoselectivities, improving **2w** from 3.3:1 *dr* to >20:1, for example. Alternatively, the use of phenanthroline resulted in a >20:1 *dr* for hexose 1,4-dihydropyridine **1i**, whereas the previously successful dtbbpy showed no improvement. Although the subtleties dictating the diastereoselectivity remain elusive, it is clear that diastereoselectivities can be improved on a case-by-case basis, if needed, through effective screening efforts. Further mechanistic studies are ongoing to shed light on these ligand effects.

In summary, we disclosed the first general synthesis of non-classical, "reverse" aryl *C*-glycosides *via* Ni/photoredox dual catalysis using dihydropyridyl saccharide motifs as radical precursors. The optimized conditions provide straightforward access to a wide variety of highly functionalized, arylated saccharides. Further studies were conducted to improve observed diastereoselectivities by targeting the diastereo-determining step, reductive elimination from the high-valent Ni(III) complex. This new strategy could find broad applications in the field of medicinal chemistry research, affording structurally novel materials that have been largely underexplored.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Abbreviations

DHP	1,4-dihydropyridine
SET	Single Electron Transfer
4CzIPN	2,4,5,6-tetra(9H-carbazol-9-yl)isophthalonitrile

dMeObpy 4–4′-dimethoxy-2–2′-bipyridine

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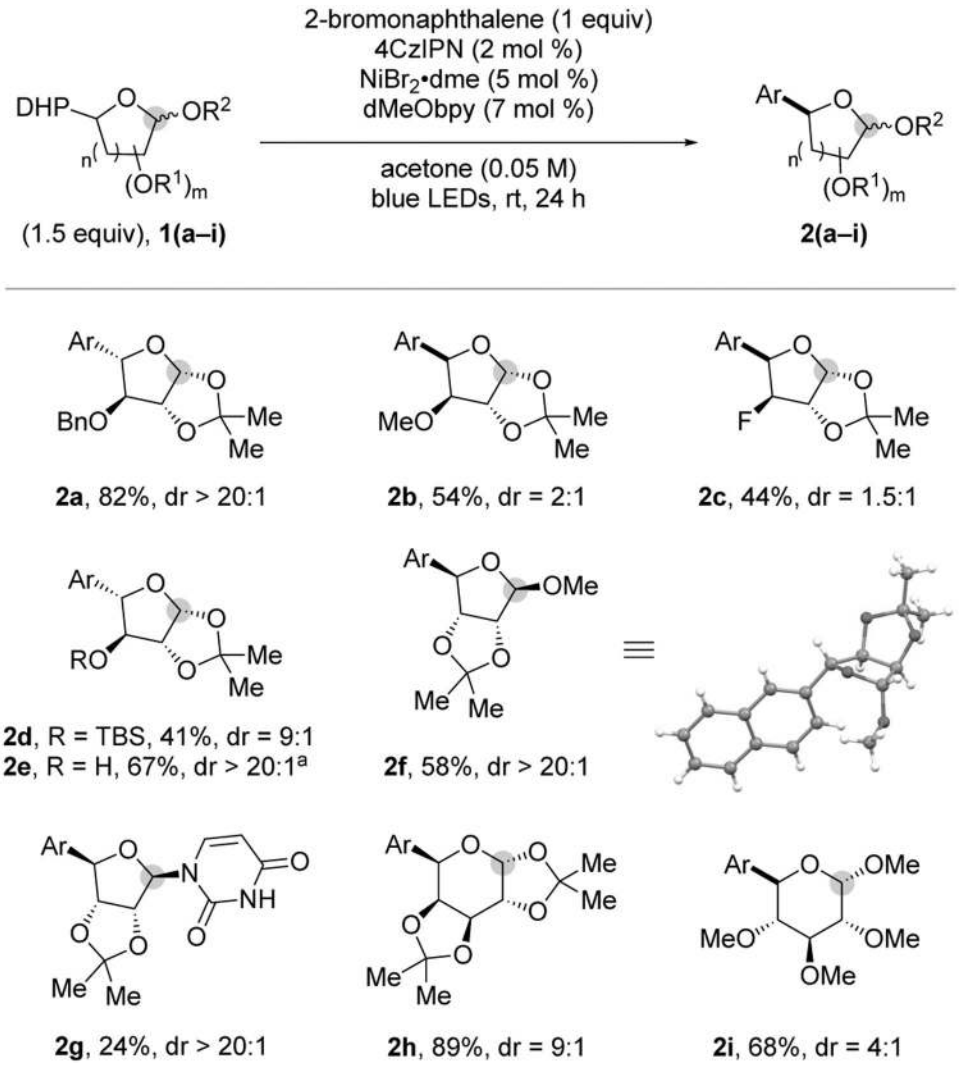


Figure 1.

Carbohydrate scope under optimized conditions: 2-bromonaphthalene (1.0 equiv), **1** (1.5 equiv), 4CzIPN (2 mol %), NiBr2•dme (10 mol %), dMeObpy (14 mol %), acetone, blue LEDs, rt, 24 h. [a]Standard conditions followed by TBAF addition (1 M in THF, 6 equiv). Ar = 2-naphthyl.

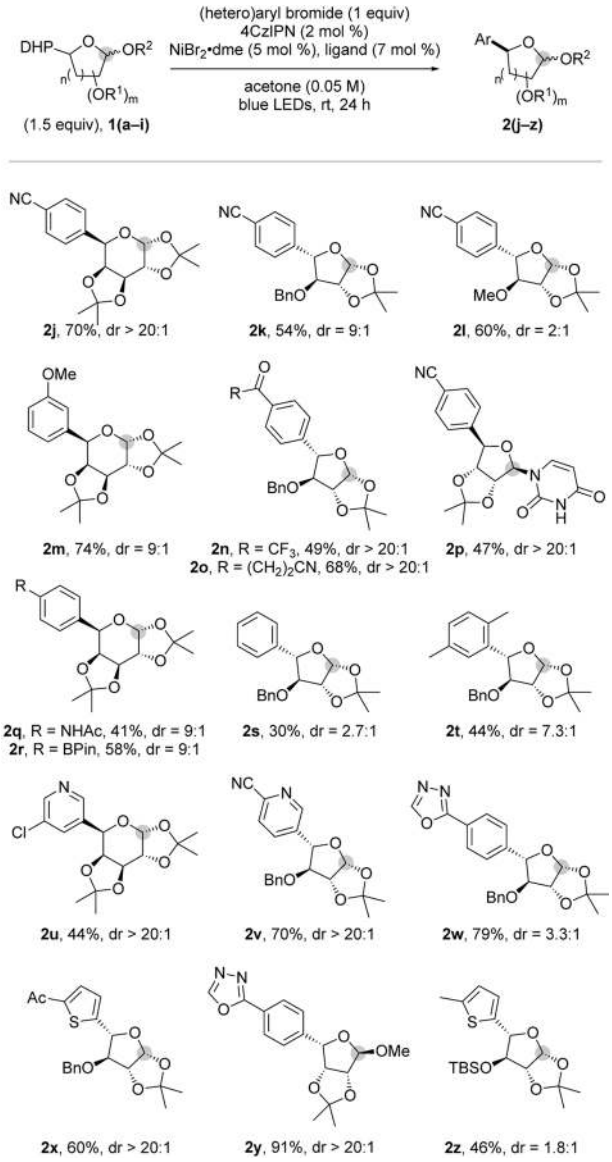


Figure 2.
Exploration of the aryl and heteroaryl bromide scope.

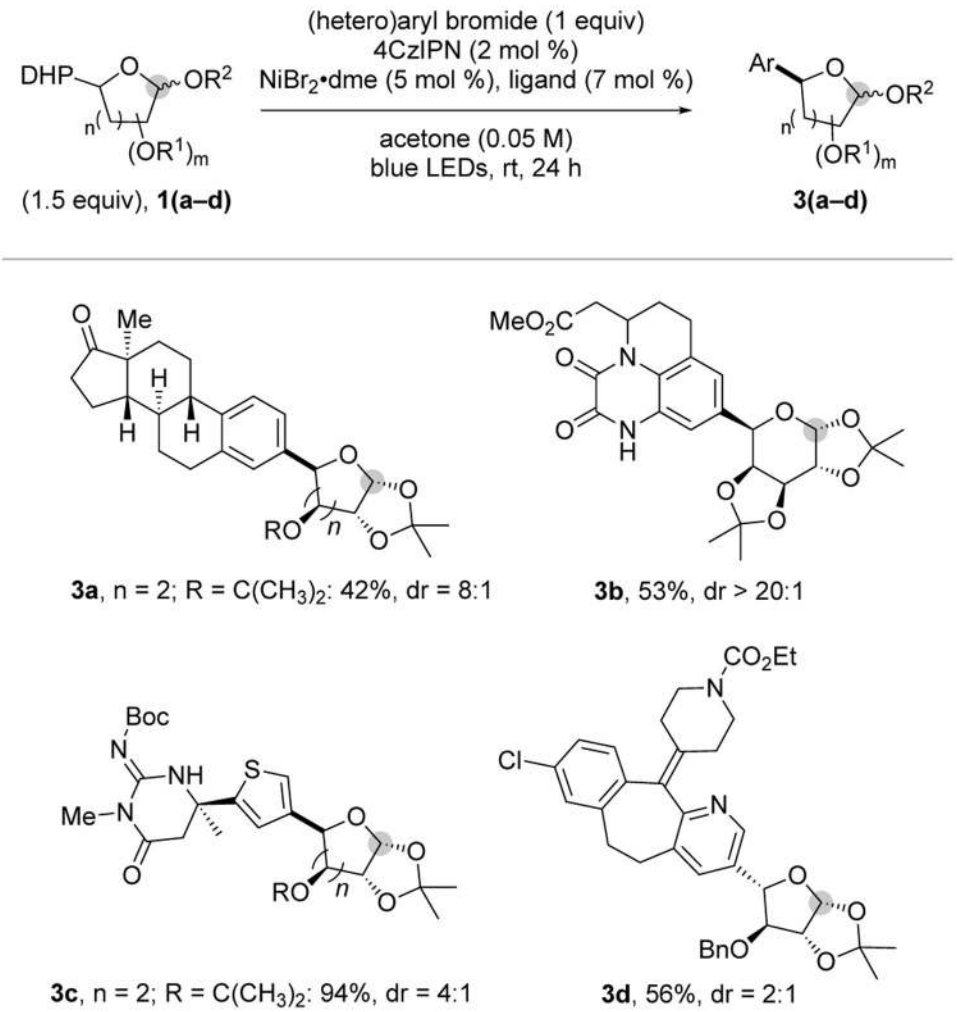


Figure 3.

Late-stage C-glycosylation of functionally dense aryl bromides (see Supporting Information for experimental details).

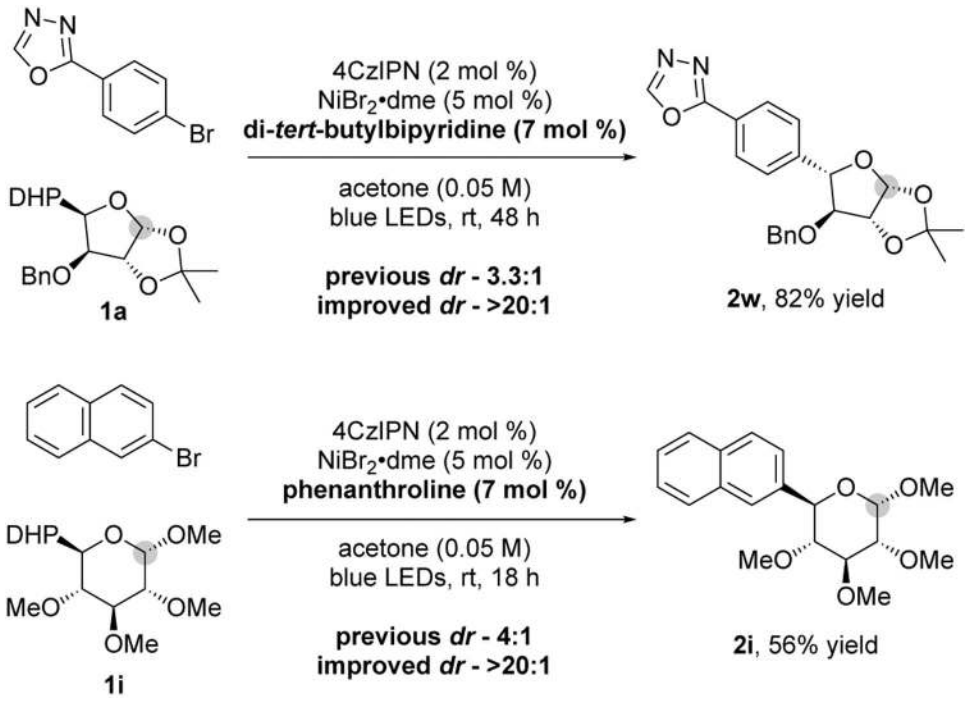
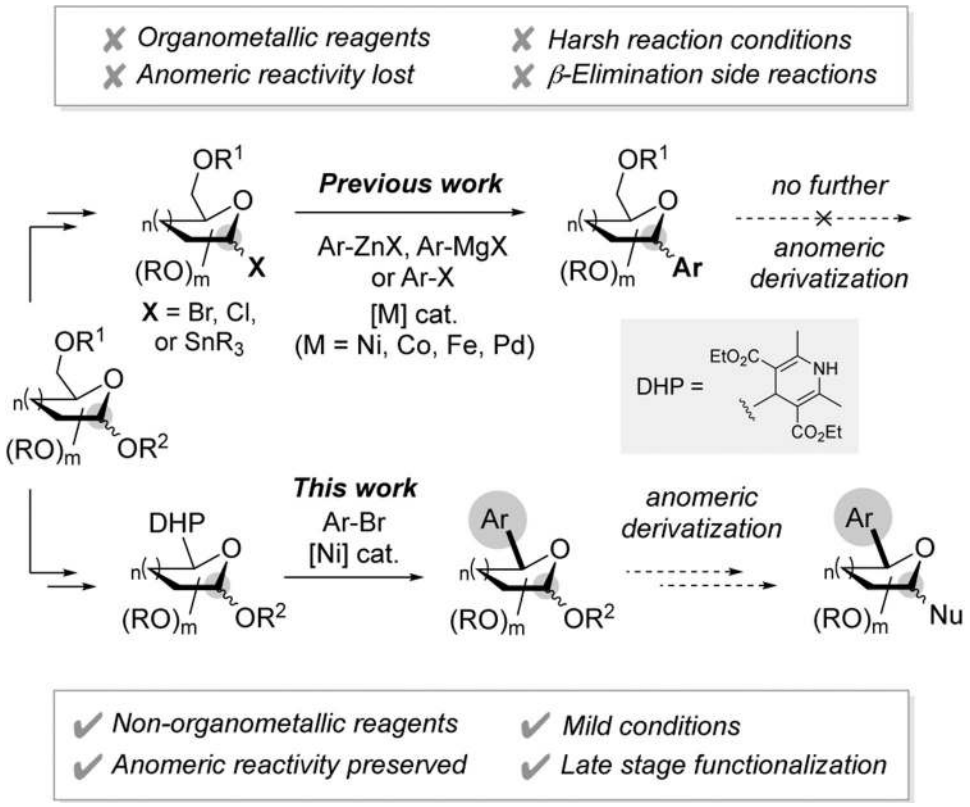


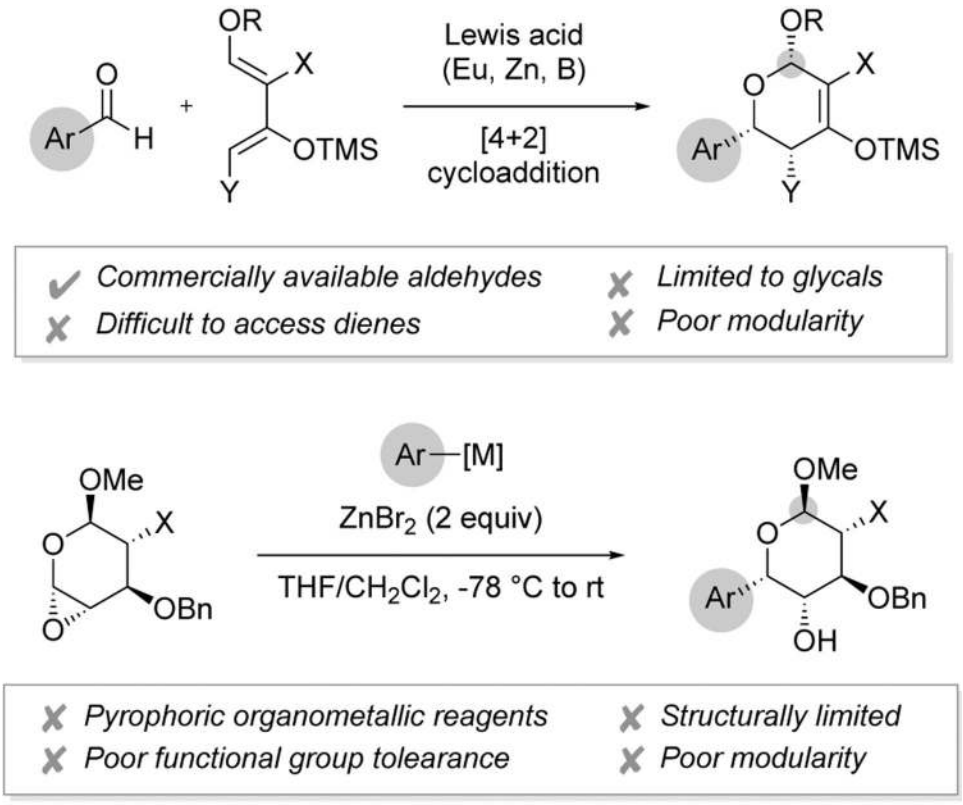
Figure 4.

Exploring the ligand effect on the diastereoselectivity. Improving the catalyst-control.



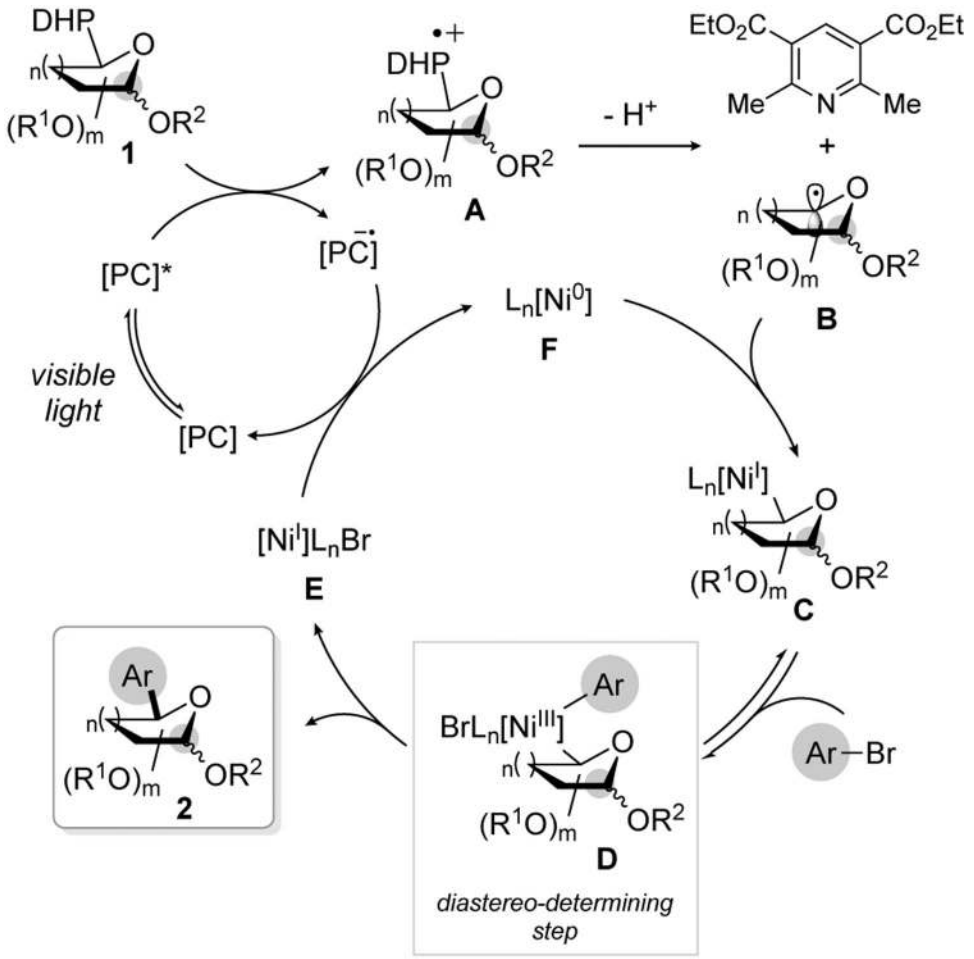
Scheme 1.

Transition metal-catalyzed synthesis of aryl *C*-glycosides: classical vs. non-classical anomeric arylation.



Scheme 2.

Previous reports forming reverse *C*-aryl glycals and glycosides *via* cycloadditions and organozinc addition to epoxides.



Scheme 3.

Putative mechanism for Ni/photoredox dual catalysis for the synthesis of arylated *C*-saccharides.