C-Glycoside Synthesis Enabled by Nickle Catalysis

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Abstract

C-Glycosides are critical, naturally occurring products and medicinal candidates, and extensive efforts have been made to explore efficient approaches for creating C-glycosidic bonds. Transition-metal-catalysis, particularly nickel-catalyzed C-glycosylation reactions constitute a promising strategy. However, achieving a stereoselective synthesis of α- and β-C-glycosides has been a long-standing challenge. To address this problem, a variety of nickel-mediated strategies have been developed. This review highlights recent developments in the nickel-catalyzed diastereoselective C-glycosylation reactions and briefly summarizes the mechanistic understandings of these methods.

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C-Glycoside Synthesis Enabled by Nickle Catalysis

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Comprehensive Summary

Text. C-Glycosides are critical, naturally occurring products and medicinal candidates, and extensive efforts have been mad

Keywords

C-Glycoside | Nickel catalysis | Glycosylation | Glycosyl radical | Carbohydrate

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1. Introduction

Glycosides play a critical role in diverse biological processes,[1] and studies of these carbohydrates are essential for further advancement in fields such as biology, medicine, and pharmacology. [2] Access to significant quantities of well-defined bioactive carbohydrates is a prerequisite for the investigation of the roles of carbohydrates in these areas.[3] In this context, developing methods to chemically forge glycosidic bonds is critical to meet the above demands. In drug discovery endeavors, C -linked glycosides are usually employed as bioisosteres of O - or N -linked glycosides. The synthesis of C -linked glycosides, however, lagged behind their O - or N -linked counterparts. Stereoselective construction of α- and β-C -glycosides remains an enduring challenge. In recent decades, transition-metal-mediated methods have exhibited remarkable potential in the stereoselective construction of glycosidic bonds, with significant advancements achieved employing gold,[4] copper, [5] iron,[6] palladium, [7] and nickel as catalysts. Among these fields, the Ni-catalyzed reactions displayed tremendous versatility. In this mini-review, we focus on the recent developments in nickel-catalyzed C-glycosylation reactions, given our longstanding interest in Ni-catalyzed glycosylation. This review is divided into two sections based on the type of glycoside products obtained, namely aryl/vinyl C-glycosides, acyl C-glycosides, and alkyl C-glycosides.

2. Ni-catalyzed synthesis of C-glycosides

C-Glycosides are essential, naturally occurring products and medicinal candidates. Being inert to metabolic processing, these compounds have piqued significant interest in areas of medicine and chemical biology. Therefore, many efforts have been made to construct C-glycosides efficiently in a stereoselective manner. This section summarizes recent developments in the nickel-catalyzed synthesis of C-glycosides, including aryl/vinyl, acyl, and alkyl C-glycosides.

2.1. Aryl/vinyl C-glycoside synthesis

In 2008, Gong and Gagné reported a diastereoselective nickel-catalyzed Negishi Cross-Coupling approach to synthesize saturated, fully oxygenated aryl C-glycosides (Scheme 1). [8] To show the generality of the method, various arylzinc reagents and glucosyl bromides were coupled in a β-selective fashion, yielding the corresponding aryl C-glucosides in high yields (**3a**–**3q**). However, aryl cross-coupling partners bearing ortho substituents (**3h**–**3j**) and pyridine-derived zinc reagents (**3p**)were not as effective. The trans-phenyl vinyl zinc reagent worked, albeit with a low d.r. (α/β=1:1) (**3q**). This protocol was also effective with other glycosyl halides (**3r**–**3y**). Whereas the α-D-galactosyl bromides (**3s**) produced the β-

Scheme 1 Synthesis of aryl C-glycosides via Ni-catalyzed Negishi Cross-Coupling

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configured products predominantly, the α-D-mannose-derived bromides (**3r** , **3x**) favored α-products. Unfortunately, 2-deoxyglucose failed to yield products due to the decomposition of glycosyl bromide and chloride. When furanose derivatives were investigated, *D* -ribofuranose-derived chloride produced the desired product in low yield with high β-selectivity (**3u**), although *D* -arabinofuranose-derived bromide resulted in significant hydrolysis products. The authors found that ligand could play a significant role in the stereochemical outcome of the reaction. Take the synthesis of phenyl C-mannoside as an example. They found that by using tBuTerpy, a 2.9:1 ratio of α/β isomers was produced (**3q**). However, good-to-excellent α-selectivities were achieved using Terpy and PyBox in good efficiency (**3q**). These results suggested that different ligand catalysts may function by different mechanisms, with the observed selectivity indicative of a stereochemical mismatch between the ligated nickel catalysis and carbohydrate substrates. Catalyst such as PyBox/Ni$(COD)_2$, which is smaller, provided good α-arylation selectivities likely *via*substrate control. Mechanistically, the authors proposed two variants of the nickel-catalyzed Negishi cross-coupling pathway. As shown in Scheme 1-C, the reaction could occur either by halogen abstraction (inner sphere, top) or by a single electron transfer (outer sphere, bottom) mechanism.[9] Lastly, the authors demonstrated the utility of this protocol with the successful total synthesis of Salmochelin SX (**8** , Scheme 1-B).

Scheme 2 α-Vinyl/Aryl C-glycosides via nickel-catalyzed reductive couplings

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In 2018, Gong and co-workers disclosed a stereoselective method of preparing α-C-vinyl/aryl glycosides via nickel-catalyzed reductive coupling of glycosyl halides with vinyl and aryl halides (Scheme 2).[10] In their report, three different reaction conditions were developed. Method A, which used pyridine as the ligand, enabled the coupling of a variety of *E* -vinyl bromides with various α-glycosyl bromides, yielding vinyl C-glycosides in high yields with moderate-to-good α-selectivities. Styrene-derived vinyl bromides, dienyl bromides, and alkyl-decorated vinyl bromides were all glycosylated successfully under method A (**21a**–**21f**). Notably,*Z* -vinyl bromide is also amenable to the reaction, although affording the corresponding products as a mixture of E/Z isomers (**21a**). Moreover, the reaction displayed high α-selectivities when applied to galactosides (**21d**), mannosides (**21e**), and maltosides (**21f**).

The authors developed method B when they failed to prepare aryl C-glycoside using method A. Method B employed DMAP as a ligand and per-O-acetyl glycosyl bromide as an effective glycosyl partner, with a small amount of HBr necessary to initiate the reaction. They then found aryl iodides bearing electron-withdrawing groups are more effective than iodobenzene and other electron-rich aryl iodides in yielding corresponding aryl C-glucosides (**21g**–**21j**). Good diastereoselectivity was also observed in galactosides (**21k**) and maltoside (**21m**), but not for arabinoside (**21l**). To further improve the glycosylation of electron-rich arenes, method C was developed, which utilized dtbBpiy (4,4‘-di-tert-butyl-2,2‘-bipyridine) as a ligand. Notably, 6-indole (**21q**) and 3-thiophenyl groups (**21p**) were well-tolerated and good-to-high α-selectivities were observed for galactosides (**21q, 21r**) and mannosides (**21s**).

The authors proposed a radical chain mechanism involving an aryl-Ni(II) intermediate, which intercepts a glycosyl radical generated from the corresponding glycosyl halide. [11] The role of $MgCl_2$ was also examined (Scheme 2-B), and the authors suggested that DMAP and Cl^- may exchange to form Ni(II)-Cl bond (**24**) by releasing a DMAP ligand, presumably accounting for the authentic intermediate for intercepting a glycosyl radical. Moderate α-selectivities are generally observed with glucoside products, likely owing to the more stable nature of the boat conformer of the glucopyranosyl radical intermediate (**25** , Scheme 2-C). However, in this study, the use of pyridine/DMAP ligands resulted in a significant enhancement of α-selectivities. The authors suggested that the enhanced α-selectivity could be attributed to the dissociation of the ligand from the nickel center upon formation of the α-Ni-C bond, thus reducing the repulsive steric interaction via α-attack. Additionally, the high α-selectivity for C-mannosides can be explained by the chair-like mannosyl radical, which leads to a preferential formation of α-products due to less steric hindrance of the α-face. Both

catalysts and substrate structure play an important role in determining the stereoselective outcomes of the developed reactions.

In 2019, Gong and co-workers developed a ligand-controlled β-selective glycosylation via a nickel-catalyzed reductive coupling of glycosyl halides with aryl/vinyl halides (Scheme 3). [12]The combination of Ni/*t* Bu-Terpy/Zn was proved to be optimal. The reaction conditions feature a wide scope of aryl iodides, yielding the corresponding aryl C-glycosides in moderate-to-good yields with high β-

Selectivities (**29a**–**29s**). Notably, *meta* -bromo substitutes in aryl iodides were found to be intact in the reaction. (**29i**) Remarkably, the use of $MgCl_2$ improved the yields of reactions with electron-rich and -neutral arenes. The authors reasoned that $MgCl_2$ is essential to activate Zn and reduce Ni(II) to Ni(0), which was validated by the control experiment that showed no reaction in the absence of $MgCl_2$. It was also discovered that the formation of glucal and hydrodehalogenation byproducts accounted for the low-yielding reactions. The utility of the developed methods was further highlighted by the successful synthesis of Salmochelin derivatives **29n** and the precursor of the commercial drug canagliflozin for type-2- diabetes **29o** . Additionally, the developed coupling protocol was also extended to synthesize β-C-vinyl glycosides (**29t**–**29ac**). Preliminary mechanistic studies revealed that the developed glycosylation process involves a radical mechanism. The authors proposed that the stereochemistry of the developed approach is largely dependent on a favorable β-attack of a glycosyl radical to a bulky Terpy-Ni(II)-Ar intermediate, and in the case of mannoside, α-configured product was favored due to substrate control.

Scheme 3 Nickel-catalyzed β-selective preparation of aryl/vinyl C-glycosides

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In 2018, the Molander group reported a protocol for accessing non-anomeric aryl C-glycosides *via* nickel/photoredox dual catalysis (Scheme 4). [13] This method involved the use of mono-saccharide DHPs (1,4-dihydropyridine derivatives) as radical precursors, which gave the best results when used in conjunction with 4-CzIPN photocatalyst, NiBr2*dme, and dMeOby as the ligand. The reaction proved to be tolerant of a range of pentose-derived DHPs and (hetero)aryl bromide partners, resulting in moderate-to-high yields of products (**34a**–**34f, 34l**–**34n, 34q**). Diastereoselectivity was found to be excellent with certain furanosyl units, likely due to the steric interactions with the adjacent substituent; this was evidenced by comparing the effect of the vicinal substituent, where small substituents, such as MeO (**34b**) and F (**34c**), gave low diastereoselectivity, whereas sterically encumbered, TBS-protected moieties gave high diastereoselectivity (**34d**). Additionally, good-to-excellent diastereoselectivities were observed in D-ribofuranose-derived DHPs. The more flexible radicals generated from hexosyl DHPs yielded lower diastereoselectivities (**34g**). Notably, a pinacol boronic ester was well accommodated in the reaction, allowing for late-stage diversification (**34j**). Furthermore, electron-neutral aryl bromides gave diminished yields, likely due to a challenging oxidative addition (**34l**). To showcase the potential of this method, the successful C-glycosylation of functionally dense aryl bromides at a late stage was achieved (**34o-34q**).

Scheme 4 Synthesis of non-anomeric aryl C-Glycosides via nickel/photoredox dual catalysis

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Mechanistically, the reaction pathway was proposed to start from the photoexcitation of 4CzIPN photocatalyst, followed by reductive quenching with the saccharide-derived DHP **35** (Scheme 4-B). This results in the formation of a radical cation **36** , giving rise to a saccharyl radical **38** and an aromatized pyridine derivative from a rapid radical fragmentation. The saccharyl radical **38** then adds to the Ni(0) catalyst **43** , forming a saccharyl-Ni(I) complex **39** . Subsequently, oxidative addition of this complex with an aryl bromide takes

place, leading to the Ni(III) species**41** . This species then undergoes a reductive elimination, yielding a non-anomeric aryl C-glycoside product **34** and a Ni(I) species **42** that is in turn reduced to Ni(0) with the reduced 4CzIPN, thus regenerating the active catalysts. It is worth noting that the diastereomeric ratios (d.r.) of the product can be influenced by both the saccharide backbone and the aromatic partner. Previous mechanistic studies indicated high valence Ni(III) **41**ultimately dictates the observed diastereoselectivity after the irreversible reductive elimination. [14] Thus, to improve the d.r. values, the authors tested the use of bidentate and tridentate ligands with both Ni(0) and Ni(II) species. Modifying the bipyridine backbone by replacing electron-donating methoxy groups with bulkier, less electron-rich tert-butyl substituents proved to be successful in achieving excellent diastereoselectivity (Scheme 4-C). Likewise, phenanthroline yielded >20:1 d.r. for**34l** , whereas dtbbpy (4,4‘-di-tert-butyl-2,2‘-bipyridine) did not show any improvement. A general approach for the coupling of saccharyl radicals with aryl and heteroaryl bromides has not yet been established.

Scheme 5 Synthesis of aryl/heteroaryl-C-glycosides via the nickel-catalyzed cross-coupling of glycosyl ester with aryl bromide

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In 2020, the Diao group showcased a diastereoselective synthesis of aryl/heteroaryl-C-glycosides via the cross-coupling of DHP-derived glycosyl esters with aryl bromides (Scheme 5).[15] This method involves the initial oxidation of DHP-derived glycosyl ester with excited photocatalyst 4CzIPN, followed by deprotonation, to generate radical **49** (Scheme 5-A). Fragmentation of this radical, driven by the formation of Hantzsch pyridine **50** , then enables the formation of glycosycarbonyl radical **51** . The subsequent ejection of CO_2leads to the formation of a glycosyl radical **52** , which was then captured by aryl-Ni(II) species **54** to form an essential Ni(III) intermediate **53** . This is followed by reductive elimination to yield aryl C-glycoside **46** and the concomitant formation of Ni(I) species **47** . The authors suggested that the initial formation of active Ni(0) species from a Ni(II) precatalyst could be accomplished by the reduced photocatalyst. The reaction tolerated a range of aryl bromides when using D-mannofuranosyl esters as coupling partners, but oxidizable substrates such as para-dimethylaminophenyl bromide (**46d**) and 3-bromo furan (**46h**)/pyrrole (**46i**) were ineffective. The furanoses, including D-xylofuranose (**46q**), D-glucofuranose (**46r**), D-galactofuranose (**46s**), and D-arabinofuranose (**46t**), were all suitable substrates, and all of these reactions favored the generation of 1,2-trans products due to the steric hindrance caused by adjacent substituents. This notion was further supported by a moderate 1,2-trans selectivity when 2-deoxyl-D-ribose (**46u**), lacking a C2 substituent. The pyranoses were also competent coupling partners in the developed reaction and the observed diastereoselectivity can be attributed to the counterbalance between the kinetic anomeric effect and steric repulsion generated by adjacent substituents. For example, excellent 1,2-trans selectivity was observed in the case of D-mannopyranose (**46v**–**46x**)due to the presence of these two effects, which both favor α-attack. Poor selectivity was observed in the reactions of D-glucosyl (**46ab, 46ac**) and D-galactosyl esters (**46ad**), as the steric hindrance at C2 favors β-attack, though the transition state for the α-attack could be stabilized by the anomeric effect, thereby neutralizing these two effects. Interestingly, a much better α-selectivity was observed for per-Bn-protected 2-deoxy-D-glucose (**46y**) than per-Bn-protected D-glucose (**46ab**), despite there being no further discussion of this in the report.

In 2019, the Niu group reported a nickel-catalyzed Suzuki-Miyaura cross-coupling of 1-sulfonyl glycals with aryl boronic acids

and their derivatives to prepare aryl C-glycals (Scheme 6).[16] The developed methods proceed under mild conditions and can accommodate a broad spectrum of organoboron nucleophiles and 1-sulfonyl glycals (**50a**–**50r** , Scheme 6). Notably, the synthetic value of the transformation was demonstrated by the successful synthesis of ipragliflozin **51a** , 2-deoxy ipragliflozin **51b** , and glycosyl tryptophan derivative**50t** (Scheme 7-A).

Scheme 6 Nickel-catalyzed Suki-Miyaura cross-coupling

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The authors' preliminary mechanistic studies revealed that the presence of an α-heteroatom such as oxygen in 1-sulfonyl glycal **47** could facilitate the cross-coupling of sulfones [17](Scheme 7-B). This precoordination with the nickel catalyst could explain the high regioselectivity of the oxidative insertion step, where the cleavage of the C–S bond adjacent to the oxygen atom is favored. Moreover, The modified conditions without a boronic acid coupling partner yielded **50a** in high yield, indicating that the oxidative insertion of **47b** by Ni(0) and the desulfination of the resulting phenyl sulfinate are both efficient and straightforward reactions. Based on the above information, the authors proposed a plausible reaction mechanism, as depicted in Scheme 7-C. The regioselective C–S bond insertion of 1-sulfonyl glycal by Ni(0) initiates the reaction pathway, which is hypothesized to be facilitated by a transient formation of a vinyl nickel species **60** . This vinyl nickel species could potentially undergo two distinct pathways: either a desulfination/reductive elimination sequence resulting in**61** or a transmetallation step followed by reductive elimination to produce **63** as the final product. The success of the reaction suggests that. the transmetalation process was favored over the desulfination step.

Scheme 7 Synthetic applications and plausible mechanism

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Recently, the Niu group reported a stereoselective approach for the preparation of aryl C-glycosides through a reductive cross-coupling of glycosyl chlorides and aryl bromides, induced by photoredox/nickel catalyst (Scheme 8). [18] The reaction exhibits a wide scope of glycosyl halides and aryl bromides, producing desired products in moderate yields and with high 1,2-trans-selectivities. The configuration of glycosyl chloride coupling partners appears to have little effect on the stereochemistry of the products. Notably,

Scheme 8 Nickel-catalyzed synthesis of aryl C-glycosides using glycosyl chloride as donors

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1-Cl-2-deoxyglucose, which is known for facile β-H elimination of C2, can afford aryl glycoside product (**66y**) smoothly under the developed conditions, though with 1:1 diastereoselectivity. Acceptable 1,2-trans-selectivities were also observed in glycosyl halides lacking C5-substituents, such as arabinose (**66aa**), xylose (**66ab**), and lyxose (**66ac**). Heteroaryl bromides. Thiophenes (**66q**) and indoles (**66r, 66s**) were also competent coupling partners. Lastly, to demonstrate the synthetic utility of this method, the successful synthesis of canagliflozin**66ad** was realized. A plausible mechanism was showcased in Scheme 8-C. The initial step is the reductive quenching of the excited photocatalyst [Ir(III)*] by a Hantzsch ester (HE), affording the HE radical cation. Subsequent deprotonation of such radical cation produces the HE radical (**HE***). This radical could undergo either a SET process with a photocatalyst or the direct electron transfer to glycosyl chloride to furnish the glycosyl radical**67** . Concurrently, in the nickel catalytic cycle, the oxidative addition of Ni(0) catalyst **69** into an aryl bromide **65**generates aryl-Ni(II) intermediate **70** , which would be rapidly intercepted by the glycosyl radical **67** , forming the glycosyl-Ni(III) complex **71** . The subsequent reductive elimination of this species would produce the desired aryl C-glycoside**66** and Ni(I) species **68** . The resulting Ni(I) species would be reduced by Ir(II) to afford active Ni(0) catalyst, while simultaneously regenerating the ground-state photocatalyst Ir(III).[19]

Scheme 9 Synthesis of unprotected aryl C-glycosides by photoredox/nickel-catalyzed cross-coupling

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The same group reported a direct synthesis of unprotected aryl C-glycosides by photoredox/nickel-catalyzed cross-coupling of bench-stable allyl glycosyl sulfones with aryl halides (Scheme 9).[20] The developed protocol features a wide scope of aryl halides and allyl glycosyl sulfones, delivering desired products in moderate-to-good yields with high 1,2-trans selectivities. A great functional group tolerance was observed in aryl halide coupling partners, though a limitation of scope was observed in the reaction of aryl iodides bearing a bulky, *ortho* -isopropyl group. Notably, protic hydrogen atoms, such as those in free hydroxyls (**75p**) and secondary amides. (**75m**), and potentially chelating alkyl sulfide groups (**75n**) were compatible with the reaction. Moreover, various heterocycles were accommodated. It was found that electron-rich aryl iodides gave slightly higher yields than electron-deficient ones. Aryl chlorides (**75o**) survived in the reaction, though aryl bromides and iodides are reactive in the developed method. Diverse glycosyl donors were examined in the reaction. Remarkably, the selectivity profiles of the developed method appeared quite insensitive to the identity of glycosyl donors and the 1,2-trans aryl C-glycosides were generated preferentially or exclusively in all examined examples. For example, C-pentopyranosides, such as xylopyranoside (**75af**), lyxoside (**75ah**), and arabinoside (**75ak**), were obtained in good yields and with moderate-to-excellent diastereoselectivity. Aryl C-furanosides were also conveniently prepared with acceptable selectivity by the method. Additionally, the method was successfully applied to the synthesis of complex drug-sugar conjugates (**75an, 75ao**) and glycopeptide (**75ap**), affording desired products in good yields and with excellent 1,2-trans selectivity. Finally, the synthetic applicability of the developed protocol was further highlighted by the rapid synthesis of enzyme inhibitors (Scheme 10-B, **75aq**) and active pharmaceutical ingredients of commercial drugs (Scheme 10-B, **75ar**–**75au**). Of note, Niu's approach worked well in the synthesis of dapagliflozin under continuous flow conditions, allowing over 1 gram of dapagliflozin (**75as**) preparation in their reaction setup.

Preliminary mechanistic investigations suggest the following: 1) the glycosyl radical is generated during the reaction; 2) the formation of glycosyl radicals is triggered by the initial generation of a tolyl sulfonyl radical, which subsequently adds to the terminal alkene group of allyl glycosyl sulfones; 3) the aryl-Ni(II) complex is likely generated during the process.

Scheme 10 Plausible mechanism and synthetic application of Niu's method

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Based on the above information, a plausible dual-catalytic mechanism was proposed, as described in Scheme 10-A. First, the tolyl sulfinate is oxidized by $^*Ru(bpy)_3^{2+}[E_{1/2}{}^{*II/I}$ (half-wave potential = +0.77 V versus saturated calomel electrode; τ (lifetime) = 1,100 ns], affording a sulfonyl radical. The resulting tolyl sulfonyl radical then adds to the terminal alkene group of the glycosyl donor**73** , triggering a cascade of bond cleavage and sulfur dioxide (SO_2) loss to produce glycosyl radical **78** , via**76** and **77** . Meanwhile, in the nickel catalytic cycle, oxidative addition of Ni(0) to aryl halide produces Aryl-Ni-X intermediate **79** . Subsequently, capturing **79** by glycosyl radical leads to **80** , followed by reductive elimination to deliver the desired aryl C-glycoside **75** and releases Ni(I). The resulting Ni(I) species is reduced by Ru(I) to regenerate Ru(II) and active Ni(0) catalyst, closing the catalytic cycles. An alternative pathway cannot be ruled out, which involves the addition of glycosyl radical to Ni(0) species. [14] Moreover, DFT calculations were performed to provide a deeper understanding of the origin of the stereochemical outcome.

A key finding was that the radical addition to the aryl nickel complex is reversible, and the reductive elimination step is the rate-limiting step. Within the transition structure of reductive elimination step, the

interaction between the C2-OH group and the ligated metal unit plays a crucial role in determining the stereochemical outcome.

Scheme 11 Photoredox/nickel dual-catalyzed glycosylation

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Zhang, Wang, and co-workers presented a photoredox/nickel dual-catalyzed cross-coupling approach for the stereoselective synthesis of aryl/heteroaryl-C-nucleosides (Scheme 11). [21]This method allowed for the cross-coupling of various anomeric ribosyl/deoxyribosyl carboxylic acids with a wide range of aryl/heteroaryl bromides, resulting in nucleoside products in moderate-to-good yields. Both O-benzyl protected α- and β-ribosyl acids served as competent coupling partners (**83a**), whereas O-benzoyl-protected ribosyl acids (**83b**) suppressed the reaction presumably due to the extra coordination interaction induced by the Bz group at the C2 position with nickel catalysis. Low diastereoselectivity was noted in the reaction of O-benzyl protected β-deoxyribosyl acid (**83g**), indicating that C2-substituents could be essential for controlling the anomeric configuration. Moreover, the position of bromo groups on pyridine coupling partners was observed to dramatically affect diastereoselectivity, with the variation of Br from C3 or C4 to C2 producing utterly opposite diastereoselectivity (**83h, 83i, 83j**), although the exact mechanism underlying this phenomenon remains unclear. Non-anomeric furanosyl acids were also found to be effective coupling partners (**83m**), whereas the pyranosyl ones failed to produce the desired products.

Mechanistically, the authors proposed that initial photoexcitation of 4CzIPN generates a potent excited state (E^{*red} = +1.35 V vs. SCE, CH_3CN) that induces an oxidative fragmentation of ribosyl/deoxyribosyl acids (E^{OX} = +1.15 V vs. SCE, CH_3CN), delivering anomeric radical**84** (Scheme 11-B). Concurrently, the active Ni(0) species**85** undergo oxidative addition with aryl bromides **82a** , producing the electrophilic aryl-Ni(II) intermediate **85** . Subsequently, Ni(II) species **85** intercept the anomeric ribosyl radical intermediates **84** , forming an aryl-Ni(III)-ribosyl complex **86** , which subsequently undergoes reductive elimination to give the desired glycoside product **83n** . Furthermore, the versatility of this method was further highlighted by synthesizing various vinyl-C-nucleosides. Notably, the coupling of a mixture of*trans* - and *cis* -styryl bromides with ribosyl acids furnished exclusive *trans* -products.

Scheme 12 Nickel/photoredox catalytic synthesis of 2-deoxy-α-C-glycosylation using β-glycosyl trifluoroborates

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In 2021, Hirai and co-workers presented a method to synthesize 2-deoxy-α-C-glycosylation using β-glycosyl trifluoroborates as glycosyl radical precursors (Scheme 12). [22] This approach allowed for the successful coupling of three different glycosyltrifluoroborates, such as potassium glucosyltrifluoroborate, 2-deoxy-D-galactosyltrifluoroborate, and 2,6-dideoxy-D-arabinosyltrifluoroborate, with a wide range of aryl bromides, delivering desired products in good efficiencies. Aryl bromides were found to be more reactive than their corresponding aryl chlorides and aryl iodides. Although the free amino group disturbed the formation of the coupling product, the acetamide derivative was obtained in an acceptable yield (**89l**). Moreover, the coupling with heteroaromatic halides, such as 2-bromofuran (**89m**) or 3-bromothiophene (**89n**), also proceeded smoothly. While unprotected 5-indole derivative **89o** was produced in only 18% yield, the reaction with Boc-protected 5-bromoindole afforded the desired product **89p** in 53%. The authors suggested that D-Olivose-type C-glycoside products exhibited a flipped conformation from the standard $^4C_1$ conformation to a $^1C_4$ conformation with an α-aryl group (**89t**). This is likely due to glycosyl radical reactivity and a steric repulsion between the C1-aryl group and C3 and C5 hydrogen atoms. Additionally, the reaction conditions were also examined with*E* -vinyl halides, resulting in a good efficiency of the desired aliphatic

C-glycoside (**89w**–**89y**). Furthermore, the utility of this method was further demonstrated through the successful synthesis of CH2- and CHF-linked 2-deoxydisacharides (**91, 92**). A plausible reaction mechanism was proposed, as shown in Scheme 13. The desired products **89** are generated by the reductive elimination of glycosyl-Ni(II)-aryl species **96** .

Scheme 13 Plausible mechanism

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Scheme 14 Nickel-catalyzed synthesis of aryl C-glycoside using anomeric trifluoroborates as donors

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Scheme 15 Synthesis of vinyl C-glycoside via nickel-catalyzed reductive hydroglycosylation

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After that, Walczak and co-workers reported a light-induced cross-coupling of anomeric trifluoroborates (Scheme 14).[23] A wide range of aryl iodides and 2-deoxyglycosyl trifluoroborates was well-tolerant with the developed method, affording corresponding products as exclusive α-anomers in moderate-to-excellent yields. The authors found that aryl units with electron-withdrawing groups furnish better yields likely because of increasing the rate of reductive elimination and the ability to stabilize the generated aryl radical. Moreover, free hydroxy groups of substrates were compatible with the reaction conditions (**101d, 101f**). Pyridine moiety (**101j, 101k**), aldehyde group (**101e**), and phenylalanine moiety (**101l**) were also tolerated. Notably, diminished α-selectivities were observed when carbohydrate substrates bearing C2-substituents were used as coupling partners (**101s, 101t**).

Yu and co-workers recently developed a method for the preparation of vinyl C-glycosyl amino acids/peptides via nickel-catalyzed reductive hydroglycosylation of alkynes (Scheme 15). [24]Inspired by works of NiH-catalyzed hydrocarbonation of unsaturated bonds, a reaction pathway was proposed by the authors, as shown in Scheme 15-A. Initially, the branch-selective insertion of NiH species to terminal alkyne **103** to furnish the vinyl nickel species**107** . Subsequently, this intermediate is oxidized by glycosyl bromide **102,** leading to the formation of a high-valent Ni(II) complex **108** and a glycosyl radical. The glycosyl radical recombines with the nickel species to give the nickel species**109** which undergoes the process of reductive elimination, furnishing the desired vinyl C-glycoside **104** and nickel catalyst **105** . Lastly, the active NiH species **106** is regenerated through a hydride transfer event.

In this report, two types of optimal conditions were developed for mannose- and glucosamine-type saccharides, and these reactions tolerate a wide scope of terminal alkyne-containing amino acid derivatives and glycosyl bromides, affording corresponding C-glycosides**104a**–**104y** in good efficiencies (Scheme 15-B). Notably, no epimerization of amino acid residue was observed. Additionally, the method could also be extended to internal acetylenic amino acids (**104z, 104aa** , Scheme 15-C). The authors suggested that the observed stereoselectivity could be governed by the predominant conformation of glycosyl radical intermediate, which is stabilized by the anomeric effect. [25] For mannose-type bromides, the anomeric radical is predominantly in the$^4C_1$ conformation, leading to the 1,2-trans (α-selectivity) product. For glucose-type bromides, a shift between α- and β-anomer is observed, owing to a flexible $B_{2,5}$ conformation adopted by glucosyl radical; however, the moderate-to-good β-selective glycosylation can be obtained when the C2-substituent is a bulky substituent, such as NPhth group (**104l**–**104o, 104s, 104t, 104v, 104w**). For xylose-type bromides,

lacking C5 substituent, a moderate 1,2-trans selectivity was observed since xylosyl radical can adopt both $B_{2,5}$ conformation and $^1C_4$ conformation, as suggested by the authors (**104p**). Lastly, the potential utilities of the current method were further demonstrated by convergent C-glycosylation of complex saccharides (**104ab, 104ac** , Scheme 15-D).

Goddard-Borger and co-workers developed a method for the synthesis of C-mannosylated glycopeptide *via* nickel-catalyzed photoreductive cross-coupling reactions (Scheme 16). [26] The reaction using HE as a photoreductant enabled the coupling of per-acetyl protected α-D-mannosyl bromide with a range of halogenated (hetero)arenes, delivering desired products in good yields. Both electron-rich and -deficient systems were effective substrates in the reaction (**112a-112c**), with the only exception of thiazole (**112d**), which decomposed under the reaction. Notably, C-mannosylation of peptides was successfully achieved (**112e**). Interestingly, the authors found that during the process, the typical $^4C_1$ conformation was adopted by simple α-C-mannosylated arene products (**112a-112d**), whereas complex, bulky α-C-mannosylated glycopeptides favored the $^1C_4$ conformation (**112e**). As suggested by the authors, this could be attributable to the role of tryptophan in driving a shift in the pyranose's preferred conformation from $^4C_1$ to$^1C_4$. Furthermore, the synthesis of Fmoc-protected Trp(Man) (**113**), which is an essential building block for SPPS (solid-phase peptide synthesis), was successfully realized on a gram-scale, which facilitated the first automated SPPS of α-C-mannosylated glycopeptides (**116** , Scheme 16-B). Notably, during this process, the authors found Trp(Man) derivatives underwent facile acid-mediated anomerization. The preliminary mechanistic studies suggested that such an anomerization most likely occurred as a result of the protonation of the endocyclic pyranose oxygen and the formation of a stabilized acyclic benzylic cation (**118a** , Scheme. 16-C). Although the developed reaction condition enabled the formation of glycopeptides, the solubility of peptide substrates in organic solvent precluded the further expansion of peptide scope, especially the utility in late-stage mannosylation. To complement the method, the authors also developed a photocatalytic variation of this cross-coupling reaction that operates in polar aprotic solvents and tolerates water (Scheme 17). The reaction provided efficient access to late-stage mannosylation of larger complex peptides. For example, a range of complex peptides bearing a 2-bromo-L-tryptophan residue was successfully C-mannosylated, affording the desired products in synthetically useful yields (**123a-123f**). Lastly, a mechanism was proposed for the nickel-catalyzed cross-coupling of mannosyl bromide **110** and Trp-derived bromide **121a** with Hantzsch ester acting as a photoreductant (Scheme 17).

Scheme 16 Nickel-catalyzed synthesis of C-mannosylated glycopeptide bearing 2-bromo-L-tryptophan residue

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Scheme 17 Nickel-catalyzed mannosylation of peptides in aqueous media and its plausible mechanism

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Later, Liang and co-workers developed a regioselective and stereoselective method for the preparation of aryl C-glycosides through nickel-catalyzed *ortho* -C-H glycosylation of 8-aminoquinoline benzamides (Scheme 18). [27] The reaction exhibits excellent α-selectivity and regioselectivity. Notably, the scope of glycosyl bromide is somewhat limited. For example, the pyranosides, such as Bn-protected L-rhamnose (**133f**)/D-mannose (**133g**), showed poor reactivity under the developed conditions, though exclusive α-selectivity was observed. Additionally, only a trace amount of aryl C-glycosides were formed during the reactions using Me-protected D-mannosyl chloride (**133h**), Bn-protected D-galactosyl chloride (**133i**), and Bn-protected D-glucosyl chloride (**133j**). Preliminary mechanistic experiments indicated that the ortho-C-H activation could be the rate-determining step, and C-H activation was reversible. A plausible mechanism was proposed,

as described in Scheme 18-B. The reaction starts with the coordination of amide and Ni(II) catalyst**,** followed by ligand exchange and reversible cleavage of the ortho C-H bond. The resulting Ni(II) intermediate **134**gets engaged in the oxidative addition of the C-Cl bond in α-glycosyl chloride **131** prior to reductive elimination to afford product**133** after proton-metal exchange. Another possible pathway invoking oxocarbenium ion being attacked by Ni(II) species was not ruled out.

Scheme 18 Nickel-catalyzed ortho-C-H glycosylation of 8-aminoquinoline benzamides

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In 2022, the Li group presented a chemoselective and diastereoselective method that enables the synthesis of aryl C-nucleotides by nickel-catalyzed cross-coupling of furanosyl acetates with aryl iodides (Scheme 19). [28] The method enabled chemoselective coupling of multihalogenated aryl iodide with furanosyl acetate (**139a**), presumably owing to the higher oxidative addition rate of low-valent nickel to aryl iodide than other aryl halides in the examined solvent. The authors found that electron-rich (**139b**), electron-neutral (**139c**), and electron-poor aryl iodides (**139d**) all coupled with equal levels of efficiency. Moreover, medicinally relevant heterocycles were also effective coupling partners in the reaction, affording the corresponding products in synthetically useful yields (**139e**–**139g**). Limitations in scope were observed in reactions using para-dimethylaminophenyl iodide and aryl iodides bearing ketone moieties. Notably, exclusive 1,2-trans selectivity was observed when D-ribofuranosides were used as coupling partners, which could be attributed to the steric hindrance at the α-face of D-ribofuranose produced by substituents in C2 and C3. Moreover, other glycosyl acetates, such as mannofuranosyl acetate and three pyranosyl acetates, were also examined and furnished the desired aryl C-glycosides in moderate yields and with good 1,2-trans selectivities (**139h**–**139j**), with one exception that benzyl-protected D-glucosyl acetate affords product with modest β-selectivity (**139k**). To showcase the synthetic utility of this strategy, a series of late-stage functionalizations with the resulting aryl bromide was successfully realized (**139la**–**139le** , Scheme 19-A, bottom). Furthermore, a concise synthetic route of the IMPDH (inosine 5‘-monophosphate dehydrogenase) inhibitor was developed using the developed method. Remarkably, the reaction was successfully incorporated in the synthesis of BRDP-Hep (**142** , Scheme 19-B), designed analogs of ADP-Hep (ADP-β-D-manno-heptose). BRDP-Hep showed better effects than the naturally occurring ADP-Hep on both the activation of NF-ϰB signaling and the phosphorylation induction of TIFA (TRAF-interacting protein with the forkhead-associated domain).

Scheme 19 Aryl C-nucleoside analog synthesis enabled by nickel-catalyzed cross-coupling of furanosyl acetates with aryl iodides

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Preliminary mechanistic studies revealed the following: 1) the glycosyl radical is generated during the process; 2) a radical chain mechanism may be ruled out; 3) the glycosyl radical could be generated directly from the reduction of furanosyl acetate by zinc in the presence of TMSBr. Based on these results obtained and Doyle's elegant studies,[29] the authors proposed a mechanism shown in Scheme 20. A rapid oxidative addition of Ni(0) catalyst **143** to an aryl iodide produces the aryl-Ni(II) complex **144** , which is captured by a glycosyl radical **146** , affording a Ni(III) adduct**145** . Subsequent reductive elimination of this intermediate can furnish the desired aryl C-glycosides **139** and Ni(I) species**148** . This Ni(I) species is reduced by Zn to regenerate active Ni(0) catalyst. Of note, an alternative reaction pathway for the generation of Ni(III) species **145** cannot be ruled out. The Ni(II) aryl complex **144** was reduced by Zn, and the resulting Ni(I) aryl complex **149** reduces the glycosyl bromide toward a glycosyl radical, companying with the generation of Ni(II) **150** . Further combining these two species would generate the same Ni(III) species **145** .

Scheme 20 Plausible mechanism

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2.2. Acyl C-glycoside synthesis

The first report detailing the nickel-catalyzed synthesis of acyl C-glycosides via reductive coupling of aliphatic carboxylic acids and glycosyl halides featuring α-selectivities emerged from the Gong group (Scheme 21). [30] The initial mechanistic investigation ruled out the double oxidation reaction pathway (Scheme 21-B, left) and suggest instead a radical chain mechanism (Scheme 21-B, right). The critical role of $MgCl_2$ in reducing Ni(II) species was also disclosed. The proposed mechanism for this transformation is shown in Scheme 21-B. The oxidative addition of acid anhydride **153b** formed in situ to Ni(0) **155** affords Ni(II) species **156** . The combination of intermediate**156** with an alkyl radical **159** furnishes intermediate**157** , which undergoes reductive elimination affording the product **154** . It is suggested that the initial generation of intermediate **158** may arise from the halide abstraction of an alkyl halide **152** with complex **156** to afford $R^1C(O)$-Ni(III)[OC(O)R]-X, followed by reductive elimination of acyl-X. This catalytic strategy provides access to several acyl C-glycosides derived from D-glucose (**154a**–**154d**), D-mannose (**154c-154g**), and D-galactose (**154h-154l**), wherein α-anomers are the favored products across all reactions.

In 2015, the Gong group reported an improved nickel-catalyzed method for synthesizing alkyl-aryl ketones via directly coupling unactivated alkyl bromides with an excess of acids (Scheme 22). [31]This method applies to the synthesis of aroyl C-glycosides. The reductive coupling of 1-glucosyl/galactosyl bromides with benzoic acid derivatives delivered desired products in moderate-to-excellent yields with moderate diastereoselectivities (**167a**–**167k**). Notably, α-aroyl C-mannoside was exclusively obtained in the coupling of mannosyl bromide (**167l**), albeit with moderate yield. The authors suggested that the low yield obtained was presumably owing to E-2 elimination during silica column chromatography.

Scheme 21 Nickel-catalyzed synthesis of acyl C-glycosides via reductive coupling of aliphatic carboxylic acids and glycosyl halides

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Scheme 22 Gong's nickel-catalyzed method in the synthesis of glycosyl-aryl ketone

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In 2018, Molander and co-workers described a route to synthesize non-anomeric acyl C-glycosides via a nickel/photoredox dual catalytic system, wherein a range of glycosyl-based radicals generated from 1,4-dihydropyridines efficiently coupled with functionalized carboxylic acids (Scheme 23). [32] Utilizing this protocol, a range of carboxylic acids as cross-coupling partners were coupled with pyranosyl- or furanose-based DHP, which tolerated various functionalities, for example, including free hydroxyl groups (**170f**–**170i**), protected amino groups (**170h, 170k**), and strained rings (**170j, 170l, 170m, 170o, 170p**), furnishing ketone products in high efficiencies with acceptable diastereoselectivities. The utility of this transformation was highlighted by the modification of naturally occurring or medicinally relevant molecules (**170t, 170v**) and difficult-to-synthesize disaccharide alkyl ketones (**170u, 170x**).

Meanwhile, the Molander group reported a nickel-mediated synthesis of non-anomeric acyl C-glycosides from the coupling of two different activated carboxylic acid sources, which is driven by the synergistic interaction of electron donor-acceptor complex and nickel catalysis (Scheme 24). [33] The reaction exhibits a wide scope of various glycosyl acids and alkyl redox-active esters, producing desired products in good efficiencies. Both

pyranose- and furanose carboxylic acid derivatives are competent coupling partners. Remarkably, carboxylic acid derived from uridine nucleoside afforded the desired products in good yield (**173e**). Moreover, primary, secondary, and tertiary alkyl radicals were all efficiently inserted, which establishes the synthetic value of the reaction. A great functional group tolerance was also observed. For example, sulfur-containing moieties (**173g, 173l, 173w, 173x**), bicyclic groups (**173s–173v**), medicinally/biologically relevant motifs (**173j–173m**), and strained small-size rings (**173n, 173o**) were all compatible with the reaction. Notably, photoisomerization of internal alkene moiety in coupling partners was observed (**173k**).

Scheme 23 Nickel/photoredox-catalyzed synthesis of non-anomeric acyl C-glycosides

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Preliminary mechanistic studies provided evidence of the formation of the EDA complex between HE and redox-active ester and the generation of the alkyl radical during the reaction. An EDA complex is proposed to form between HE and redox-active ester (Scheme 24-B). This EDA complex**180** triggers a single electron transfer event upon photoirradiation, which produces a dihydropyridine radical cation and the corresponding alkyl radical **176** . Concurrently, saccharide acid **171** would be activated by DMDC (dimethyl dicarbonate), affording an activated carbonic anhydride **174** in situ. Subsequently, the oxidative addition of this anhydride with Ni(0) species forms an acyl-Ni(II) intermediate **175** , which is trapped with alkyl radical **176** , affording a high valent Ni(III) complex**177** . Subsequent reductive elimination of **177** yields the desired non-anomeric C-acyl glycoside **173** and the corresponding Ni(I) complex **178** . The resulting Ni(I) complex is then reduced by the photoexcited HE [$E_{red}(HE^*/HE^{+\,*}) = -2.28$ V vs SCE] via SET to regenerate the active Ni(0) catalyst. The other plausible reaction pathway is proposed to begin with the initial combination of an alkyl radical **176** with a Ni(0) complex, furnishing an alkyl-Ni(I) species **179** . Subsequent oxidative addition of the resulting alkyl-Ni(I) species **179** to the anhydride **174**generates the high valent Ni(III) species **177** , which continues through the reaction pathway described above.

Scheme 24 Nickel-catalyzed synthesis of non-anomeric acyl C-glycosides via EDA complex photoactivation

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The Diao group later developed a method to synthesize C-acyl furanosides*via* the nickel-catalyzed cross-coupling of glycosyl ester with carboxylic acid (Scheme 25). [34] This method enables the coupling of a wide range of carboxylic acids with various DHP esters derived from furanoses and pyranoses, delivering acyl C-glycosides in useful yields and with good selectivity. Notably, functional groups such as alkene (**183g, 183l, 183r**) and sulfide (**183q**) were intact in the reaction. Moreover, glycosylation of biologically active substrates proceeded smoothly, producing desired acyl C-glycosides in moderate-to-good yields (**183l, 183n, 183o, 183q, 183r**). In all examined reactions of DHP-derived furanosyl esters, the 1,2-trans product was isolated as the predominant product, presumably owing to the approach of an incoming catalyst from the opposite face of the C2-substituent. Not surprisingly, the 2-deoxy-D-ribose substrate, lacking C2-substituent, generated products with a modest α-selectivity (**183af**). With respect to the stereoselectivity observed for pyranosyl coupling partners, the kinetic anomeric effect was suggested to determine the stereoselectivity of acyl C-pyranosides. Of note, low efficiency and diminished anomeric diastereoselectivity were observed in reactions of D-galactopyranose (**183ao**) and D-glucopyranose (**183ap**), which could be attributed to the contradictory preferences of the steric hindrance of C2-substituent and the kinetic anomeric effect. To further demonstrate the generality of this protocol, the successful synthesis of biologically relevant molecules, a thymidine analog, and diplobifuranylones B, was realized (**187** , Scheme 26-A).

Scheme 25 Synthesis of acyl C-glycoside via nickel/photoredox catalyzed coupling of DHP esters with carboxylic acids

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Based on literature precedents and a previous radical trapping experiment, [15] the authors proposed a mechanism shown in Scheme 26-B. The key step involves the subsequent fragmentation of the DHP ester to deliver glycosyl radicals upon the release of Hantzsch pyridine and dioxide. Another important step is the activation of the carboxylic acid by DEDC (diethyl decarbonate). The oxidative addition of the resulting mixed decarbonates **192** by Ni(0) species **191** delivers Ni(II) intermediate **193** , followed by capturing glycosyl radical **189** to form acyl-Ni(III)-glycosyl complex **194** . Subsequently, the reductive elimination of**194** produces the desired acyl C-glycosides **183** and Ni(I)Br **190** . Ni(I)Br is reduced by reduced photocatalyst to regenerate active Ni(0) catalyst **191** .

Scheme 26 Synthetic application and plausible mechanism

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Koh and co-workers disclosed a nickel-catalyzed three-component synthesis of acyl C-glycoside, wherein they realized the consecutive cross-electrophile couplings of three different organohalide substrates, namely, glycosyl halides (**195**), organoiodides (**197**), and isobutyl chloroformate (**196**) (Scheme 27).[35] The reaction features a wide scope of various functionalized organoiodides and glycosyl halides, producing desired products in good yields (Scheme 27-B). Notably, high 1,2-trans selectivity was observed in coupling partners derived from furanose (**198a**–**198n**), D-mannopyranose (**198o**–**198q**), and L-rhamnopyranose (**198v**–**198x**). Glycosyl halide coupling partners derived from D-glucopyranose (**198r**), D-galactopyranose (**198s, 198t**) and L-fucopyranose (**198u**) produced good 1,2-cis selectivities. The synthetic applicability of the developed methods was further underlined by the glycosylation of oligopeptides (**198y**–**198ae** , Scheme 27-C) and the preparation of (1-2)-linked C-disaccharides (**198ag**–**198aj** , Scheme 27-D).

Preliminary mechanistic studies provide evidence supporting that the oxidation of the active ligated Ni(0) species by isobutyl chloroformate occurs preferentially, and cross-electrophile coupling between isobutyl chloroformate with organoiodides likely precedes the subsequent coupling with glycosyl chloride. Based on

Scheme 27 Nickel-catalyzed multicomponent synthesis of acyl C-glycosides

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DFT calculations and experimental observations, a plausible mechanism was proposed, as depicted in Scheme 27-A. The oxidative addition of Ni(0) species **199** to **196** followed by reduction and (net)decarboxylation provides a CO-coordinated Ni(0) complex**200** . Subsequent oxidative addition of organoiodides**197** affords a Ni(II) species **201** , which is then converted to a Ni(II)-acyl complex **202** after carbonyl insertion. Another reduction enables the formation of Ni(I) species**203** , which can undergo a stepwise oxidative addition with**195** to furnish Ni(III) intermediate **204** . During the process, halogen atom transfer (XAT) and radical re-association steps are involved, which provides the rationale for the observed high selectivity towards the formation of the carbonylative cross-coupling product. Finally, the reductive elimination of Ni(III) species**204** produces the desired glycosyl ketone product **198**and Ni(I) species **205** . The reduction of this nickel species forms active Ni(0) **199** . Moreover, an alternative radical relay mechanism can be excluded based on calculated energetics.

2.3. Alkyl C-glycoside synthesis

The facile β-elimination of C1-substituted glycosyl metallics may explain why fully oxygenated and saturated carbohydrate structures are not typically reachable via transition metal-mediated cross-coupling.[36] Elegant studies of pincer-ligated organometallic complexes presented that such ligands can effectively inhibit undesired β-hydrogen elimination by occupying the cis coordination sites essential for the elimination.[37] In this context, the Gagné group developed a Negishi cross-coupling approach to access alkyl C-glycosides, where $NiCl_2$/PyBox was employed to diminish the formation of undesired glucal (Scheme 28). [38]

Scheme 28 Synthesis of alkyl C-glycoside via Negishi cross-coupling

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The authors found that in the nickel-catalyzed coupling of aceto-α-bromo-D-glucose with MeZn–I, nonpolar solvents accelerated competing elimination events, and oligomeric baseline products were produced without adding a nickel catalyst. They also found that the smaller ligand furnished higher yields, presumably due to steric effects in the catalyst. Notably, during the process of ligand screening exclusive β-selectivity was observed when using terpy (terpyridine) as a ligand (**211a**), while the diastereomeric ratio modestly favored the β-anomer in other cases. The results suggest that catalyst-controlled selectivity in the synthesis of C-glycoside might be achievable. The developed conditions were also extended to other alkyl zinc reagents and glycosyl halides. Notably, "fully armed" benzyl-protected sugars were best matched to chloride-leaving groups, and "disarmed" acetyl-protected sugars worked best as the bromide (the chlorides were unreactive). Moreover, glucosides produced a modest β-selectivity (**211a, 211b, 211l, 211m, 211n**), while mannosides uniformly afforded high α-selectivity (**211c, 211e–211k**), presumably owing to anchimeric assistance or additional steric effects exerted by the proximal axial OAc or OBn group.

Later, the same group reported a nickel-catalyzed Giese glycosyl radical addition, which enabled the synthesis of α-alkyl C-glycosides (Scheme 29). [39] The reaction features a low alkene loading and obviates toxic heavy metals. In this protocol, both ligands and nickel catalysts played an essential role in promoting the desired reactivity in favor of background elimination. The reactions of glucosyl bromides with three different acylates proceeded smoothly under the reaction conditions, affording desired alkyl C-glycosides as α-anomers in good yields. Notably, electron-poor styrene derivatives were also amenable to this method, whereas only a trace amount of products were formed from styrene (**214d**) and 4-methoxystyrene (**214e**). Moreover, other glycosyl bromides were also suitable substrates. Not surprisingly, 5-dealkylated C-arabinoside (**214p**) was produced with a diminished stereoselectivity. To increase the diastereoselectivity of coupling glucosyl bromides with methyl methacrylate, the authors examined a range of proton sources where i-Pr_2CHOH afforded 5:1 of d.r. as the best result. The optimal conditions then were applied to various geminally disubstituted alkenes, which afforded the desired products in moderate-to-good diastereoselectivities. (**214s–214n**). Mechanistically, the authors suggested that glycosyl radical could be involved while a mechanism relying on olefin insertion into a nickel-glycosyl intermediate followed by transmetalation to zinc cannot be rigorously ruled out.

Scheme 29 Nickel-mediated Giese glycosyl radical addition toward alkyl C-glycoside

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In 2022, the Koh group described a practical strategy that merges glycosyl halide with redox-active derivatives of ubiquitous carboxylic acids and amines to synthesize alkyl C-glycosides *via*photoinduced nickel-catalyzed C–C coupling (Scheme 30).[40] In the report, two approaches, decarboxylative and deaminative glycosylation, were developed. Alkyl-substituted carboxylic acids and primary amines were activated to obtain stable redox-active electrophiles [N-(acyloxy)phthalimides (NHPI esters)] and pyridium salts, which then served as alkylating agents in cross-coupling reactions. The reactions feature a wide scope of alkylating agents (NHPI

esters and pyridinium salts) and glycosyl halides, delivering desired products in moderate-to-good efficiencies. Notably, the glycosylation of complicated bioactive molecules, such as biotin (**218g**), dehydrocholic acid (**218h**), Lipitorintermediate (**218q**), and (S)-amlodipine (**218r**) preceded smoothly under the developed methods. The late-stage glycosylation of amino acids and oligopeptides further underscored the robustness of the developed strategies. These methods provided efficient access to the glycosylation of a freely exposed carboxylic acid or amine motif on peptides' C-terminus, N-terminus, or side chain, affording corresponding glycopeptide conjugates in moderate-to-good yields (**218s**–**218aa**). In contrast to furanosyl coupling partners, pyranosyl donors gave products in generally lower yields due to the competitive β-alkoxy elimination (**218ah**–**218al**). Notably, in most cases, moderate-to-excellent control of selectivities were achieved.

Scheme 30 Photoinduced, nickel-catalyzed method for the stereoselective assembly of C-linked glycosides and glycopeptides

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Mechanistically, the authors suggested the generation of photoactive electron-donor-acceptor complexes between the redox-active electrophile (NHPI ester or pyridinium salt), Hantzsch ester, and LiI (or Et_3N) are central to the success of the developed approaches, which was supported by spectroscopy experiments. A detailed mechanism was proposed, as described in Scheme 31. The photoinduced single-electron transfer enables the generated EDA complex to undergo decarboxylative or deaminative fragmentation, affording alkyl radical species **222** . In a concurrent nickel-catalyzed cycle, a Ni(0)-mediated halogen atom abstraction enabled the formation of glycosyl radical from a glycosyl halide **215** . The resulting glycosyl radical diastereoselectively re-associates with the nickel center to produce a glycosyl-Ni(II) intermediate **228** , followed by trapping of alkyl radical **222** generated from EDA, furnishing a glycosyl-Ni(III)-alkyl species **229** . Subsequent reductive elimination of this crucial intermediate produces the desired alkyl C-glycoside adduct **218** . The active nickel catalyst **226**is regenerated by a single-electron reduction of **227** .

Scheme 31 Plausible mechanism

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3. Conclusions and Perspectives

In summary, a variety of successful examples have been presented in the development of nickel-catalyzed glycosylation, providing versatile approaches for the construction of C-glycosides. Although significant progress has been achieved, several challenges remain to be solved in the future, as follows:

1. Most of the reported methods of aryl C-glycoside preparation exhibit modest diastereoselectivity and require fully or partially protected glycosyl donors and sensitive reagents. Thus, methods that feature wide scopes, high diastereoselectivities, and mild conditions from stable starting are still desirable.
2. In contrast to the rapid development of aryl C-glycosides, methods accessing vinyl/alkyl/acyl C-glycosides lagged severely behind, although a few elegant works have been reported.
3. In most reported methods, the glycosyl radical precursors are confined to unstable glycosyl halides. Although several novel glycosyl donors have successfully participated in synthesizing C-glycosides, such as glycosyl esters, [15, 28, 34] and allyl glycosyl sulfones. [20] Further efforts are still needed to exploit their potential in glycosylation.

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C-Glycosides are critical, naturally occurring products and medicinal candidates, and extensive efforts have been made to ex

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