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Communication

Nickel-Catalyzed Radical Migratory Coupling Enables C-2 Arylation of Carbohydrates

Gaoyuan Zhao, Wang Yao, Ilia Kevlishvili, Jaclyn N. Mauro, Peng Liu,* and Ming-Yu Ngai*

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ABSTRACT: Nickel catalysis offers exciting opportunities to address unmet challenges in organic synthesis. Herein we report the first nickel-catalyzed radical migratory cross-coupling reaction for the direct preparation of 2-aryl-2-deoxyglycosides from readily available 1-bromosugars and arylboronic acids. The reaction features a broad substrate scope and tolerates a wide range of functional groups and complex molecular architectures. Preliminary experimental and computational studies suggest a concerted 1,2-acyloxy rearrangement via a cyclic five-membered-ring transition state followed by nickel-catalyzed carbon−carbon bond formation. The novel reactivity provides an efficient route to valuable C-2-arylated carbohydrate mimics and building blocks, allows for new strategic bond disconnections, and expands the reactivity profile of nickel catalysis.

Carbohydrates, the most abundant biomolecules, play vital roles in a wide array of biological processes, including cell−cell recognition, protein folding, neurobiology, inflammation, and infection.[1] The modification of carbohydrate structure(s) to enhance or alter the physiological properties of the parent molecule is therefore an attractive strategy for the development of novel pharmaceuticals. Indeed, carbohydrates and their mimics are present in a range of commercially available therapeutics and vaccines, and the evolving methods for carbohydrate synthesis and modification continue to influence the drug discovery landscape.[2] Over the past few decades, tremendous progress has been made toward C-1 modification of carbohydrates, such as O-glycosylation[3] and C-glycosylation.[4] Nevertheless, a general catalytic strategy for the preparation of diverse and valuable C-2-functionalized 2-deoxy sugars from readily available sugar precursors remains elusive.[5,6] In view of the fact that C-2-functionalized 2-deoxy sugars are ubiquitous in nature and are found in medicine, molecular imaging, cell engineering, and catalysis,[7] the establishment of a versatile catalytic approach for the preparation of this class of sugars is highly attractive.

Nickel catalysis has advanced as a general technology for chemical synthesis.[8] Recently, significant progress has been made in nickel-catalyzed migratory cross-coupling (MCC) reactions[9] that enable a range of remote functionalization reactions of alkyl halides (Figure 1A). These include hydroarylation,[10] hydroalkylation,[11] alkenylation,[10d] acylation,[12] and carboxylation.[13] In such reactions, the nickel catalyst typically migrates from the activation site to the cross-coupling site via a two-electron β-hydrogen elimination/migratory insertion sequence (Figure 1B).[9] In contrast, Ni-catalyzed MCC reactions that proceed through a radical migratory pathway such as a 1,2-spin-center shift (SCS)[14] are rare.[15] Inspired by the seminal work of Surzur and Tanner, who showed that β-(acyloxy)alkyl radical could undergo a 1,2-SCS with concomitant acyloxy migration,[16] we hypothesized that such a reactivity could serve as the basis of a nickel-catalyzed radical MCC reaction via a 1,2-SCS pathway (Figure 1C). The success of such a reaction could (i) provide new strategic bond formations that lead to otherwise difficult or unobtainable molecular architectures; (ii) expand the reactivity profile of Ni catalysis; (iii) advance fundamental knowledge in radical chemistry; and (iv) promote new reaction design and

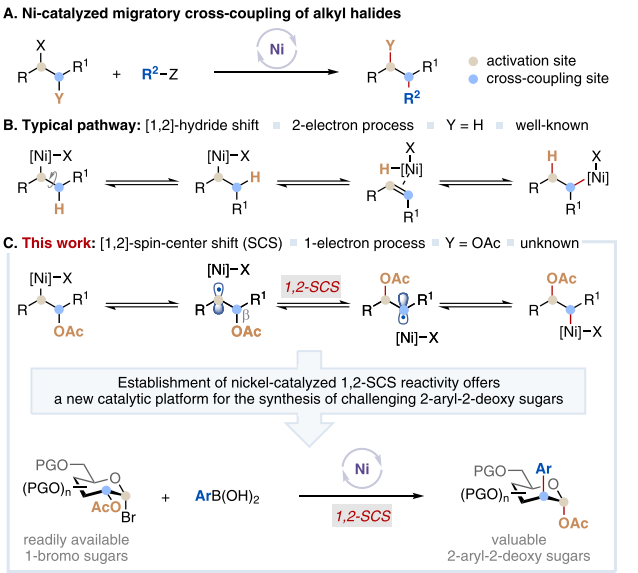

Figure 1. Ni-catalyzed migratory cross-coupling enables the catalytic synthesis of challenging 2-aryl-2-deoxy sugars.

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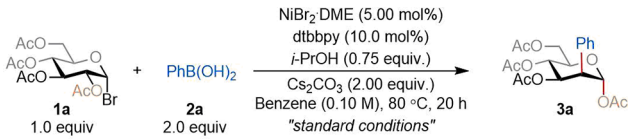
development. Herein we report the establishment and application of such a reaction platform for the preparation of synthetically challenging C-2-arylated carbohydrates from readily available 1-bromosugars and arylboronic acids (Figure 1C).[17]

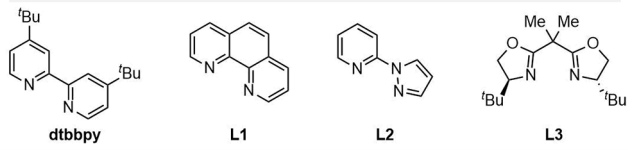
It is noteworthy that catalytic C-2 arylation of readily available sugar precursors for the preparation of saturated, fully oxygenated 2-aryl-2-deoxy sugars has not been reported.[18] The existing approaches to this class of sugar derivatives involve either the construction of carbon skeletons by homologation of chiral aldehydes using the carbonyl ene cyclization strategy[19] or epoxide ring opening of 2,3-epoxy sugars with arylmagnesium iodides or lithium diarylcuprates.[20] However, these methods require the multistep synthesis of advanced intermediates, involve harsh reaction conditions, and have limited substrate and reaction scopes. Thus, the work described here offers rapid access to novel 2-aryl-2-deoxy sugars and serves as the first example of a nickel-catalyzed radical MCC reaction that proceeds through a 1,2-SCS pathway.

We commenced our investigation by examining the reaction of α-glucosyl bromide **1a** and phenylboronic acid (**2a**) in the presence of Ni catalysts and found that when a mixture of **1a** (1.00 equiv), **2a** (2.00 equiv), $NiBr_2$·DME (5.00 mol %), 4,4′-di-*tert*-butyl-2,2′-dipyridyl (dtbbpy) (10.0 mol %), isopropanol (*i*-PrOH) (0.75 equiv), and Cs_2CO_3 (2.00 equiv) in benzene (0.100 M) was heated at 80 °C for 20 h, the desired C-2-arylated 2-deoxyglucoside **3a** was produced in 84% yield with 3.6:1 axial to equatorial selectivity together with a small amount of the C-1-arylated byproduct (Table 1, entry 1).[21,22] The nature of the ligand is critical for the success of the reaction, as replacing dtbbpy with other classes of N,N-bidentate ligands such as phenanthroline (**L1**), pyridine−pyrazole (**L2**), and bisoxazoline (**L3**) greatly reduced the reaction yield (entries 2−4).[23] Removal of *i*-PrOH, which is known to promote transmetalation in the nickel-catalyzed Suzuki−Miyaura cross-coupling reaction,[24] also diminished the efficiency of the reaction (entry 5). The use of 1,4-dioxane as a solvent resulted in the formation of hydrodebromination side products, lowering the product yield (entry 6). Finally, control experiments showed that $NiBr_2$·DME, Cs_2CO_3, elevated reaction temperature, and an oxygen-free environment were critical for the success of the reaction (entries 7−10).

Table 1. Selected Optimization Experiments[a]



entry	deviation from standard conditions	yield of **3a** (%) (ax:eq)
1	–	84 (3.6:1)
2	**L1** instead of dtbbpy	0
3	**L2** instead of dtbbpy	10 (2.9:1)
4	**L3** instead of dtbbpy	<1
5	Without *i*-PrOH	63 (3.5:1)
6	1,4-Dioxane as solvent	40 (3.4:1)
7	$Ni(cod)_2$ instead of $NiBr_2$·DME	35 (3.8:1)
8	DIPEA instead of Cs_2CO_3	0
9	Room temp instead of 80 °C	<1
10	With air	0



[a]See the Supporting Information for experimental details. Yields of **3a** and axial:equatorial (ax:eq) ratios were determined by ^{1}H NMR analysis using dibromomethane as the internal standard.

Next, we explored the scope of aryl- and heteroarylboronic acids (Table 2A). The reaction tolerates a range of arylboronic acids with different substituents such as methyl, *tert*-butyl, phenyl, methoxy, diphenylamino, methyl sulfide, and methyl ester, forming the corresponding products **3b−i** in 46−86% yield with moderate axial/equatorial selectivity. 2-Naphthylboronic acid and heteroarylboronic acids, including 9-phenyl-9*H*-carbazol-3-yl- and 2-benzofuranylboronic acids, were viable substrates and gave the desired products **3j−l** in moderate yields. Examination of the generality of 1-bromosugars revealed that an array of sugar derivatives bearing different protecting and migratory groups were competent under this protocol (Table 2B).[25] D-Galactoside and L-fucoside derivatives reacted smoothly and formed the corresponding products **3m**, **3n**, and **3p** in yields of 40−74%. It is noteworthy that these substrates gave the products with the opposite stereoselectivity. Steric interaction between the nickel catalyst and the axial C-4 OAc appears to favor the formation of the equatorial product. Protecting groups such as *tert*-butyldimethylsilyl, benzyl, acetyl, pivaloyl, and benzoyl are well-tolerated. A substrate with a fused ring structure was compatible, producing **3q**. We also investigated the effect of structural modification of the migratory ester group on the reaction efficiency and found that C-2 esters substituted with alkyl, aryl, or heteroaryl groups successfully migrated, delivering the corresponding products **3r−x** in 38−85% yield.

The synthetic utility of the reaction is further highlighted by its amenability to the late-stage modification of functionally dense natural-product- and drug-conjugated sugar derivatives (Table 2C). For instance, a melibiose derivative and an oleanolic acid-derived α-glucosyl bromide reacted under the standard conditions, affording the desired products **5a** and **5b** in 52% and 77% yield, respectively. 1-Bromoglucosyl derivatives of the uricosuric agent probenecid, the anti-inflammatory drug zaltoprofen, and the antihyperuricemic drug febuxostat all underwent C-2 arylation to give the corresponding products **5c−e** in good yields, demonstrating that the method can be used in the preparation of pharmaceutically relevant compounds. With the antiacne agent adapalene (**4f**) as a migratory group, the desired product **5f** was obtained in 56% yield with 10:1 axial/equatorial selectivity. This and earlier results, such as the formation of **3r**, indicated that increasing the size of the migratory group enhances the axial selectivity. It is worth noting that our protocol (i) affords the α-2-aryl-2-deoxy glycosides exclusively, with none of the corresponding β isomers; (ii) enables access to previously inaccessible C-2-arylated carbohydrate derivatives and building blocks; and (iii) expands chemical and patent spaces for drug discovery.

While a detailed understanding of the reaction mechanism awaits further investigation, preliminary mechanistic studies suggested a radical process. The addition of a radical scavenger such as 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) completely inhibited the reaction (Figure 2A),[8b,15b] and when the 1,2-*trans*- and 1,2-*cis*-2-iodosugars **6a** and **6b** were subjected to

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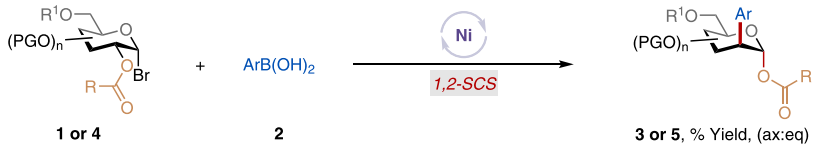
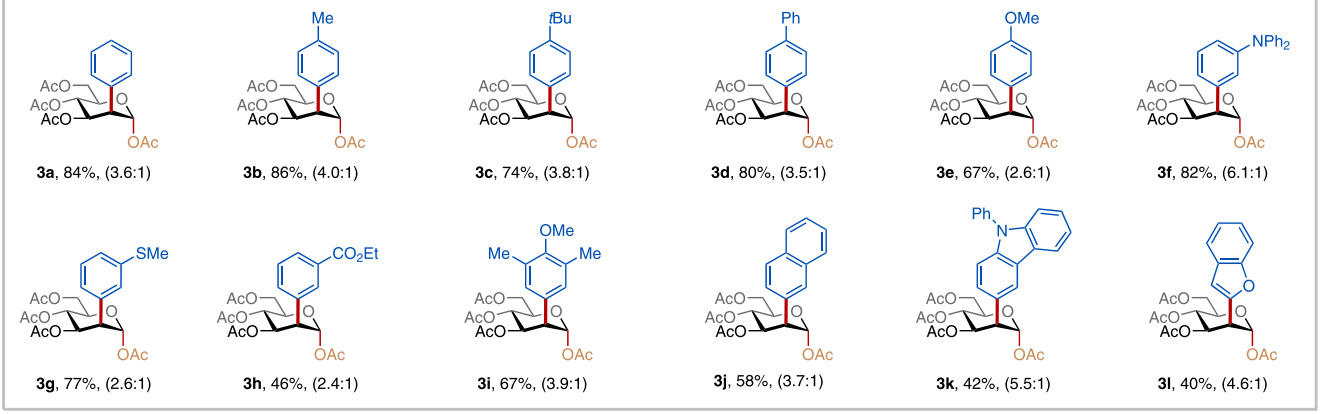
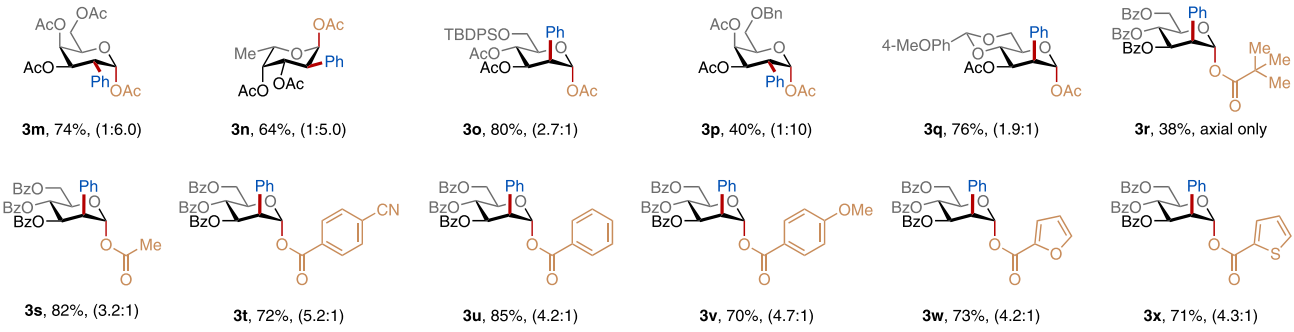
Table 2. Scope of C-2 Arylation of α-Glycosyl Bromides via Ni-Catalyzed 1,2-SCS Strategy[a]



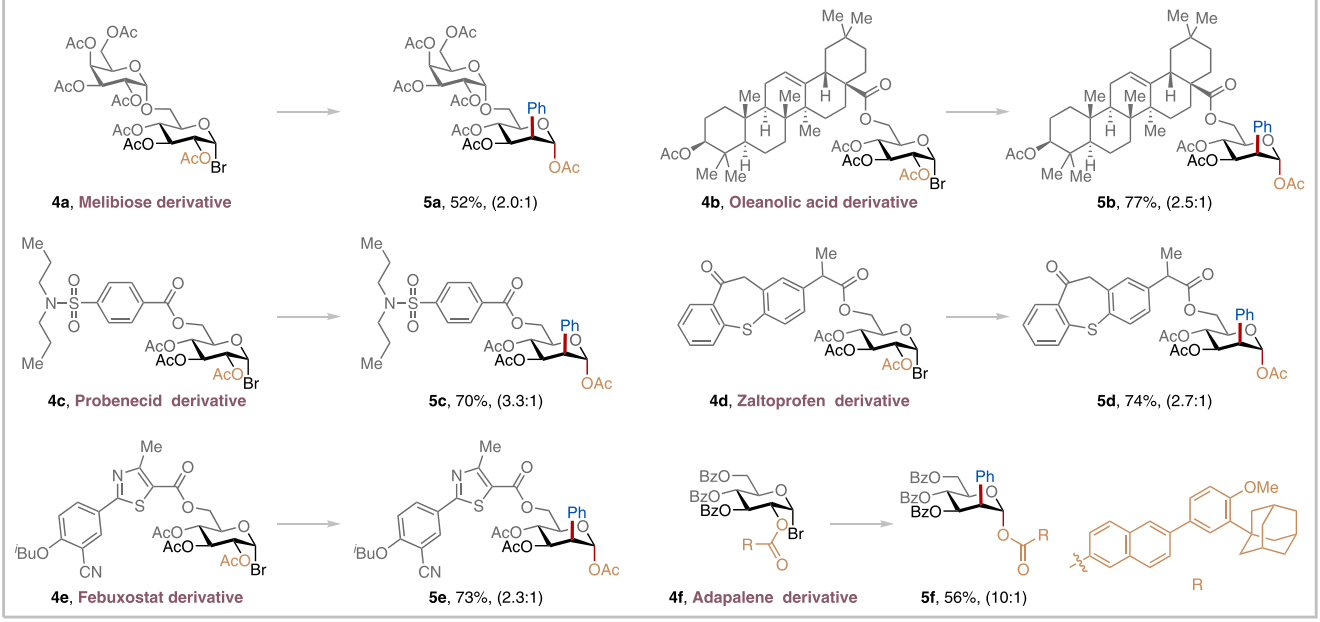
A. Aryl boronic acids



B. Carbohydrates



C. Biorelevant derivatives



[a]See the Supporting Information for experimental details. The isolated yield and axial:equatorial (ax:eq) ratio are indicated below each entry.

the reaction conditions, they both formed the desired product **3a** in excellent yields with the same level of stereoselectivity (Figure 2B). This stereoselectivity was similar to that observed in the standard reaction using α-glucosyl bromide **1a** as the substrate, suggesting that these reactions proceed through a common C-2 radical intermediate. Crossover experiments using substrates **1a** and **1u** afforded only the non-crossover

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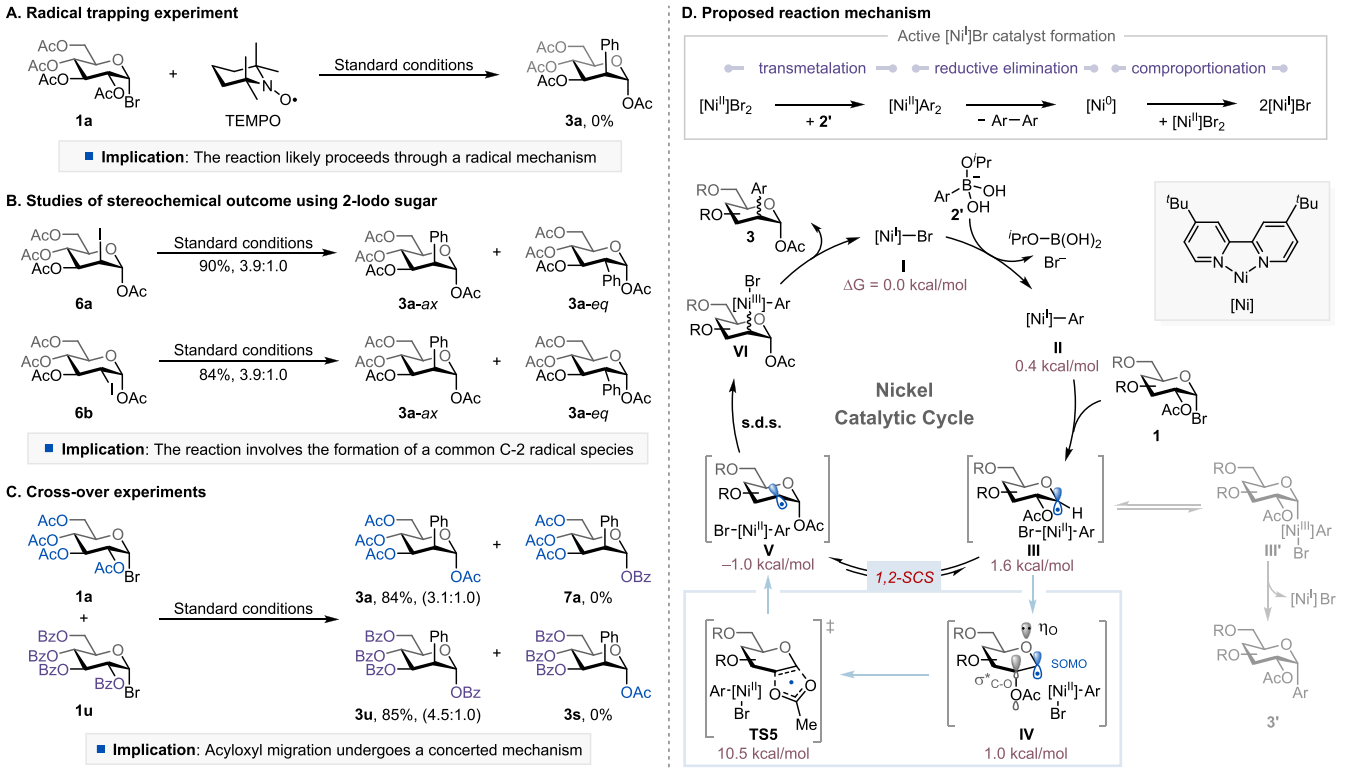

Figure 2. Mechanistic studies and proposed reaction mechanism. See the Supporting Information for experimental and computational details. s.d.s. = stereoselectivity-determining step.

products **3a** and **3u**, indicating that the acyloxy migration likely takes place through a concerted mechanism (Figure 2C).

On the basis of these results, the known acyloxy migration,[17,26] the nickel-catalyzed Suzuki–Miyaura coupling,[8b,d] and DFT calculations (see Figure S4 for the computed reaction energy profiles),[27] a plausible catalytic cycle is shown in Figure 2D. The active catalyst [Ni^{I}]Br (**I**)[28] is presumably generated under the standard conditions through (i) transmetalation of the [Ni^{II}]Br$_2$ precatalyst with 2 equiv of dihydroxyisopropoxyarylborate **2′**, (ii) reductive elimination of the resulting [Ni^{II}]Ar$_2$ complex to liberate diaryl side products and a [Ni^{0}] species, and (iii) comproportionation of [Ni^{0}] with [Ni^{II}]Br$_2$.[29] [Ni^{I}]Br could undergo transmetalation with an arylborate to form [Ni^{I}]Ar species **II**. Bromine atom abstraction of α-glycosyl bromide **1** by complex **II** generates the [Ni^{II}](Br)Ar species and chair 1-glycosyl radical (**III**). This radical intermediate could directly recombine with [Ni^{II}](Br)Ar and then undergo reductive elimination to form C-1-arylated side products (**3′**).[22] However, DFT calculations showed that the conversion of **III** to its $B_{2,5}$ boat conformation **IV** followed by a concerted 1,2-acyloxy rearrangement is more favorable under our reaction conditions (see Figures S6 and S7). The 1-glucosyl radical prefers the $B_{2,5}$ boat conformation **IV** by 0.6 kcal/mol, which stems from the extended anomeric interaction between the lone-pair electrons of the endocyclic O, the singly occupied molecular orbital (SOMO), and the σ^{*}_{C-O} orbital of the C-2 OAc group.[30] This interaction weakens the C-2 OAc bond and promotes the 1,2-SCS through a concerted 1,2-acyloxy rearrangement via a cyclic five-membered-ring transition state (**TS5**),[26c,30] affording deoxypyranosan-2-yl radical **V**.[31] Although a typical secondary alkyl radical would be less stable than an anomeric radical, in this case the molecular stability gained from the formation of an anomeric C–O bond in **V** drives the desired 1,2-SCS[32] and makes this step (**IV** → **V**) exergonic by 2.0 kcal/mol. DFT calculations suggested that the stereoselectivity-determining step (s.d.s.) is the addition of the [Ni^{II}](Br)Ar species to deoxypyranosan-2-yl radical, where the axial addition is more favorable than the equatorial addition because the equatorial addition to square-planar Ni complex is hindered by unfavorable steric interactions with the cis C-1 acetoxy group (Figures S4 and S5). These results agree with the experimentally observed preference for the 1,2-trans product. Once intermediate **VI** is formed, it undergoes reductive elimination, liberating the desired C-2-arylated product **3** and regenerating the [Ni^{I}]Br catalyst **I**. At this stage, we cannot rule out an alternative mechanism involving bromine atom abstraction of α-glycosyl bromide by [Ni^{I}]Br, transmetalation of the resulting [Ni^{II}]Br$_2$ with arylborate to form [Ni^{II}]Br(Ar), and then recombination of [Ni^{II}]Br(Ar) with 2-glycosyl radical followed by reductive elimination to give 2-arylated carbohydrates and regenerate [Ni^{I}]Br (see Figure S8 for details).

In conclusion, we have developed the first nickel-catalyzed 1,2-SCS cross-coupling reaction that enables the direct synthesis of saturated, fully oxygenated 2-aryl-2-deoxy glycosides. The reaction features a broad substrate scope, is amenable to late-stage functionalization of natural-product- and drug-conjugated sugar derivatives, and allows for the formation of C-2-arylated glycosides that cannot otherwise be easily accessed. Preliminary mechanistic studies suggest a radical reaction pathway with a concerted acyloxy migration. It is anticipated that this reaction will serve as the basis for the development of Ni-catalyzed radical migratory coupling reactions and a broadly useful C-2 functionalization of carbohydrates. This approach will eventually allow for the preparation of a wide array of novel carbohydrate mimics and

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building blocks for synthesis, medicinal chemistry, and materials science. A myriad of exciting studies and extensions of this chemistry can be envisaged, including detailed mechanistic studies, the identification of factors that govern the regio- and diastereoselectivities, the introduction of different functional groups at C-2, alternative transition metal catalysts, and reaction development beyond carbohydrate functionalization. These are the subjects of an ongoing investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c03563.

Experimental details and characterization data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Peng Liu − *Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States; Department of Chemical and Petroleum Engineering, University of Pittsburgh, Pittsburgh, Pennsylvania 15261, United States;* orcid.org/0000-0002-8188-632X; Email: pengliu@pitt.edu

Ming-Yu Ngai − *Department of Chemistry and Institute of Chemical Biology and Drug Discovery, State University of New York, Stony Brook, New York 11794, United States;* orcid.org/0000-0002-3055-6662; Email: ming-yu.ngai@stonybrook.edu

Authors

Gaoyuan Zhao − *Department of Chemistry, State University of New York, Stony Brook, New York 11794, United States*

Wang Yao − *Department of Chemistry, State University of New York, Stony Brook, New York 11794, United States*

Ilia Kevlishvili − *Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States*

Jaclyn N. Mauro − *Department of Chemistry, State University of New York, Stony Brook, New York 11794, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.1c03563

Notes

The authors declare no competing financial interest.

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