HHS Public Access

Author manuscript

J Am Chem Soc. Author manuscript; available in PMC 2022 June 16.

Published in final edited form as:

J Am Chem Soc. 2021 June 16; 143(23): 8590–8596. doi:10.1021/jacs.1c03563.

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

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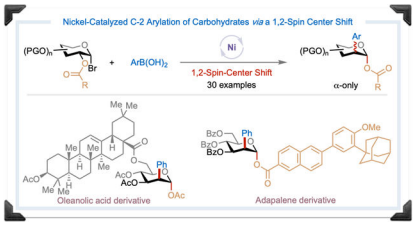
Abstract

Nickel catalysis offers exciting opportunities for addressing 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-deoxy glycosides from readily available 1-bromo sugars and aryl boronic 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 carbohydrates mimics and building blocks, allows for new strategic bond disconnections, and expands the reactivity profile of nickel catalysis.

Graphical Abstract



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Supporting Information

Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

This paper is dedicated to Prof. Shunichi Fukuzumi on the occasion of his 70th birthday. The authors declare no competing financial interests.

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 towards C-1 modification of carbohydrates such as the *O*-glycosylation[3] and *C*-glycosylation.[4] Yet, 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] Given 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* the 2-electron β-hydrogen elimination/migratory insertion sequences (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 formation that leads to otherwise difficult or unobtainable molecular architecture; (ii) expand the reactivity profile of Ni catalysis; (iii) advance fundamental knowledge in radical chemistry; and (iv) promote new reaction design and 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-bromo sugars and aryl boronic acids (Figure 1C).[17]

Noteworthily, 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 carbonyl ene cyclization strategy[19] or epoxide ring-opening of 2,3-epoxy sugars with aryl magnesium iodides or lithium diarylcuprates.[20] These methods, however, require the multi-step 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 proceeding 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 because the replacement of dtbbpy with other classes of (*N,N*)-bidentate ligands such as phenanthroline (**L1**), pyridine-pyrazole (**L2**), and bisoxazoline (**L3**) greatly reduced reaction yields (entries 2–4).[23] Removal of *i*-PrOH, which is known to promote the transmetallation 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 formed hydro-debromination 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).

Next, we explored the scope of aryl and heteroaryl boronic acids (Table 2A). The reaction tolerates a range of aryl boronic acids with different substituents such as methyl, *t*-butyl, phenyl, methoxy, diphenylamino, methyl sulfide, and methyl ester, forming the corresponding products (**3b**-**3i)** in 46–86% yields with moderate axial/equatorial selectivity. 2-Naphthyl boronic acid and heteroaryl boronic acids, including 9-phenyl-9*H*-carbazol-3-yl and 2-benzofuranylboronic acids, were viable substrates and gave the desired products (**3j**-**3l)** with moderate yields. Examination of the generality of 1-bromo sugars 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**, **3p**) with yields of 40–74%. Noteworthily, these substrates gave the product 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 *t*-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**-**3x**) in 38–85% yields.

The synthetic utility of the reaction is further highlighted by its amenability to a late-stage modification of functionally dense natural product- and drug-conjugated sugar derivatives (Table 2C). For instance, a melibiose derivative and the oleanolic acid-derived α-glucosyl bromide reacted under the standard conditions, affording the desired products (**5a**, **5b**) in 52% and 77% yields, respectively. 1-Bromo-glucosyl derivatives of the uricosuric agent Probenecid, the anti-inflammatory drug Zaltoprofen, and the anti-hyperuricemic drug Febuxostat all underwent C-2 arylation giving the corresponding products (**5c**-**5e**) in good yields, demonstrating that the method can be used in the preparation of pharmaceutically relevant compounds. With the anti-acne 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 intellectual 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-tetramethyl-1-piperidinyloxy (TEMPO) completely inhibited the reaction (Figure 2A),[8b, 15b] and when the 1,2-trans- and 1,2-cis 2-iodo-sugars (**6a**, **6b**) were subjected to 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. Cross-over experiments using substrates **1a** and **1u** afforded only the non-cross-over products (**3a**, **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, 8d] and DFT calculations (see SI, 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) transmetallation of [Ni^{II}]Br_2 precatalyst with two equivalents of dihydroxyisopropoxyaryl borate (**2'**), (ii) reductive elimination of the resulting [Ni^{II}]Ar_2 complex to liberate diaryl side products and [Ni^{0}] species, and (iii) comproportionation of [Ni^{0}] with [Ni^{II}]Br_2.[29] [Ni^{I}]Br could undergo transmetallation with an arylboronate, forming a [Ni^{I}]Ar species (**II**). Bromine atom abstraction of α-glycosyl bromide (**1**) by complex **II** generates [Ni^{II}](Br)Ar species and chair 1-glycosyl radical (**III**). This radical intermediate could directly recombine with [Ni^{II}](Br)Ar and then reductive eliminate 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 SI, 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 electron of the endocyclic-*O*, the singly occupied molecular orbital (SOMO), and the $\sigma^*_{C\text{-}O}$ 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 the 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 [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, transmetallation of the resulting [Ni^{II}]Br_2 with aryl borate 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 in SI for details).

In conclusion, we have developed the first nickel-catalyzed 1,2-SCS cross-coupling reaction that enables a direct synthesis of saturated, fully oxygenated 2-aryl-2-deoxy glycosides. The reaction features broad substrate scope, is amenable for 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 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 the C-2 position, alternative transition metal catalysts, and reaction development beyond carbohydrate functionalization. These are the subjects of an ongoing investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

The research reported in this publication was supported by the National Institutes of Health (R35-GM119652 to M.-Y.N and R35-GM128779 to P.L.). DFT calculations were performed at the Center for Research Computing at the University of Pittsburgh, the TACC Frontera supercomputer, and the Extreme Science and Engineering Discovery Environment (XSEDE) supported by the National Science Foundation grant number ACI1548562. The Shimadzu UPLC/MS used for portions of this work were purchased with funds from NIGMS equipment administrative supplement, Shimadzu Scientific Instruments grant, and Office of the Vice President for Research at Stony Brook University. We also thank all the reviewers for their insightful comments and suggestions.

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(27). DFT calculations were performed using a simplified model of glucosyl bromide (**1y**), where the OMe group was used instead of OAc group at C-3, 4, and 6 positions of the sugar backbone, see Figures S4 and S5 in SI for details**1y**.

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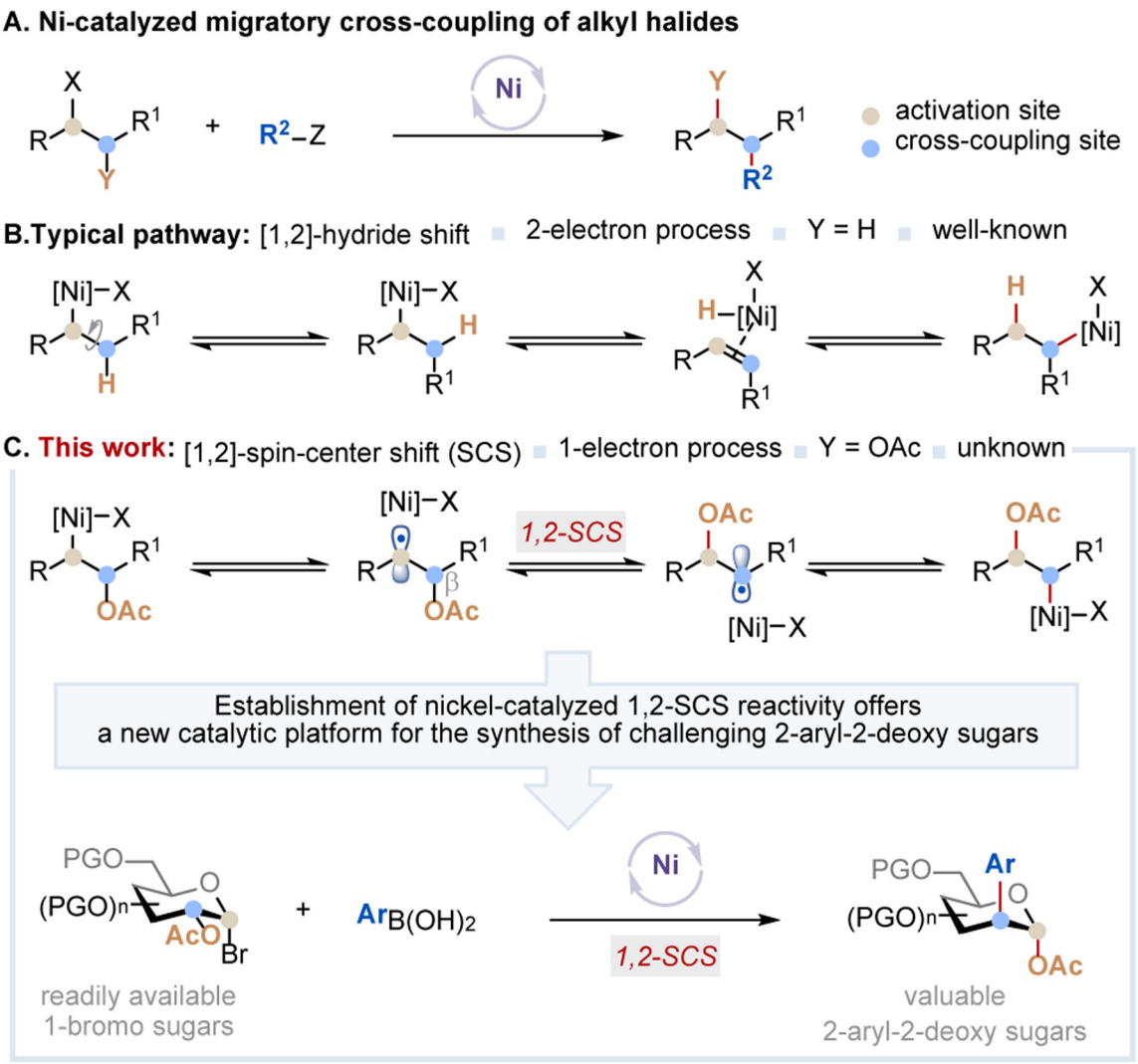


Figure 1.

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

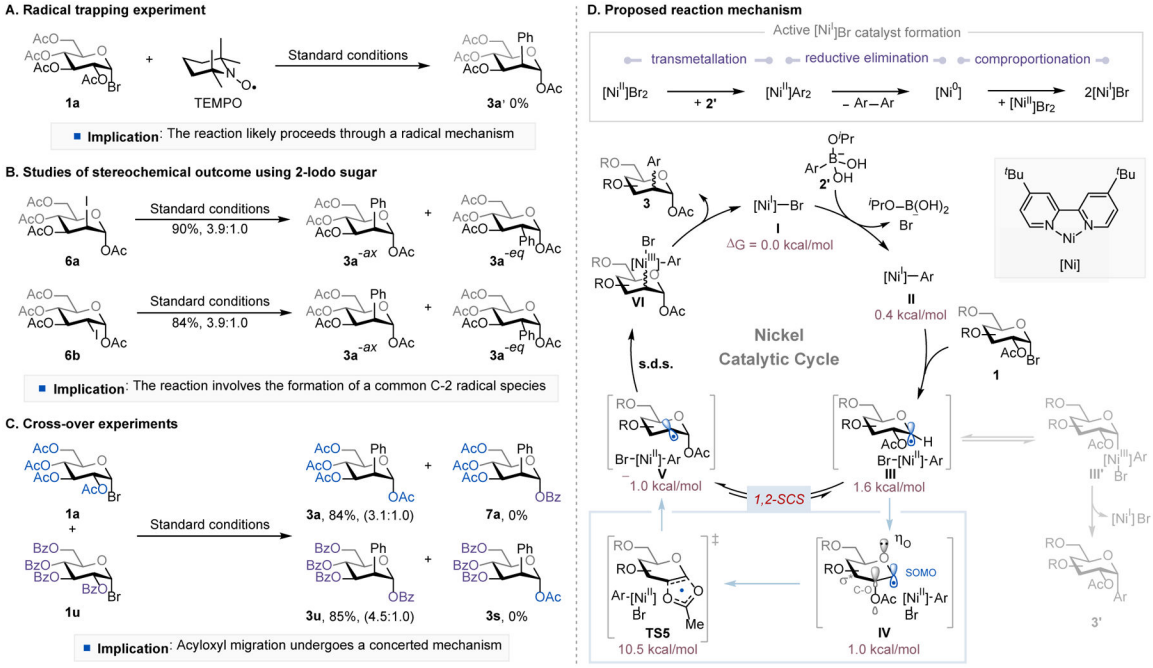
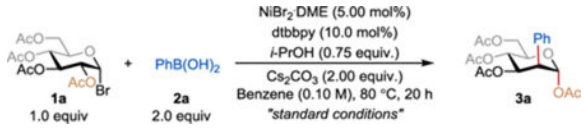


Figure 2.

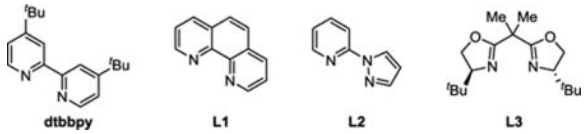
Mechanistic studies and proposed reaction mechanism. See SI for experimental and computational details. s.d.s. = stereoselectivity-determining step.

Table 1.

Selected optimization experiments.[a]



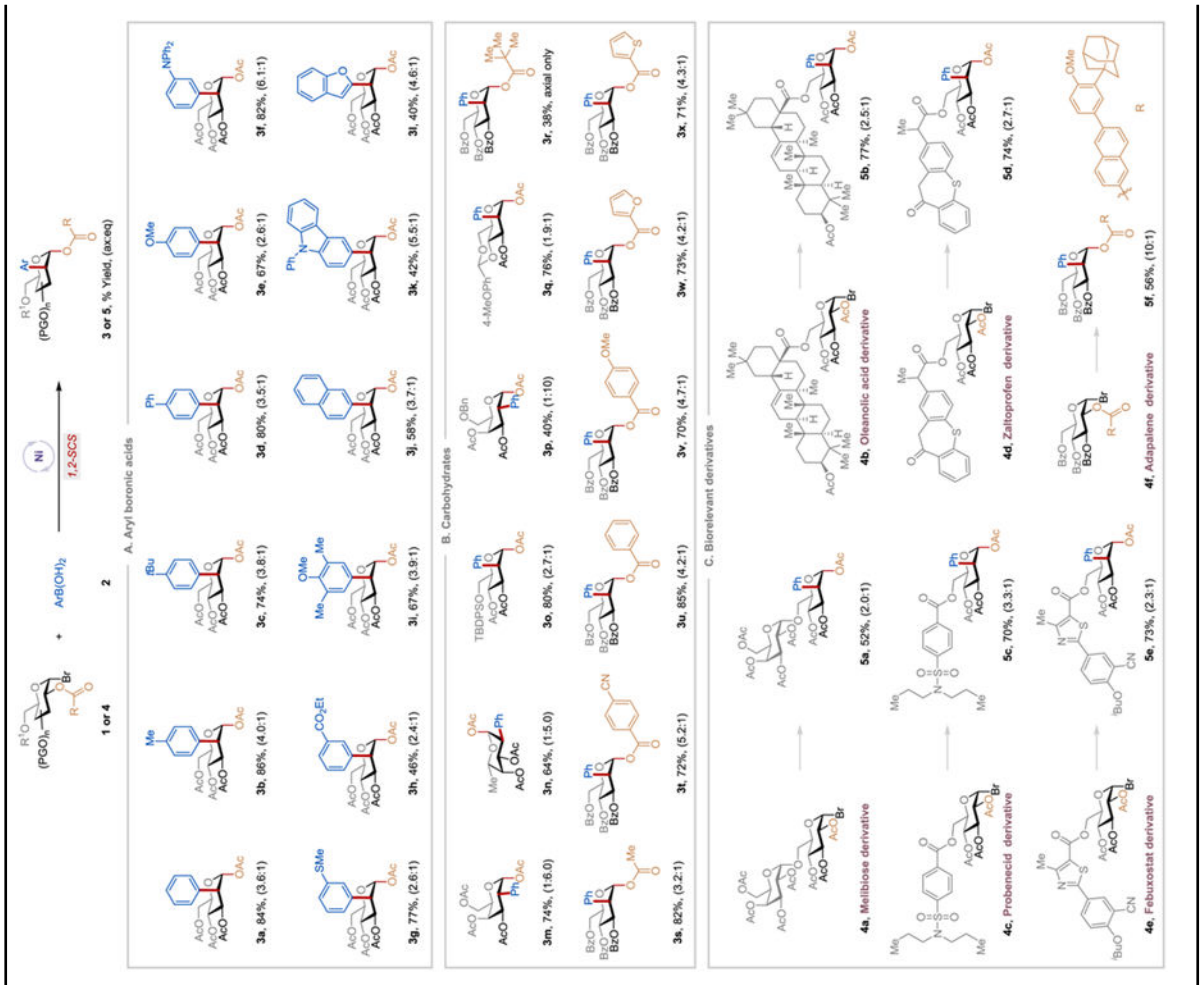
Entry	Deviation from standard conditions	Yield of 3a (%) (ax:eq)
1	-	84 (3.6:1)
2	**L1** instead of dtbbpy	0
3	**L2** instead of dtbbpy	10 (2.9:1)
4	**L3** instead of dtbbpy	<1
5	Without *i*-PrOH	63 (3.5:1)
6	1,4-Dioxane as solvent	40 (3.4:1)
7	$Ni(cod)_2$ instead of $NiBr_2$·DME	35 (3.8:1)
8	DIPEA instead of CS_2CO_3	0
9	Room temp instead of 80 °C	<1
10	With air	0



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

Table 2.

Scope of C-2 arylation of α-glycosyl bromides *via* Ni-catalyzed 1,2-SCS strategy.[a]



[a]See SI for experimental details. Isolated yield and axial:equatorial (ax:eq) ratio are indicated below each entry.