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Stereoselective Preparation of α-C-Vinyl/Aryl Glycosides via Nickel-Catalyzed Reductive Coupling of Glycosyl Halides with Vinyl and Aryl Halides

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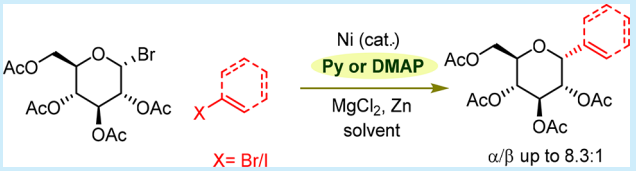
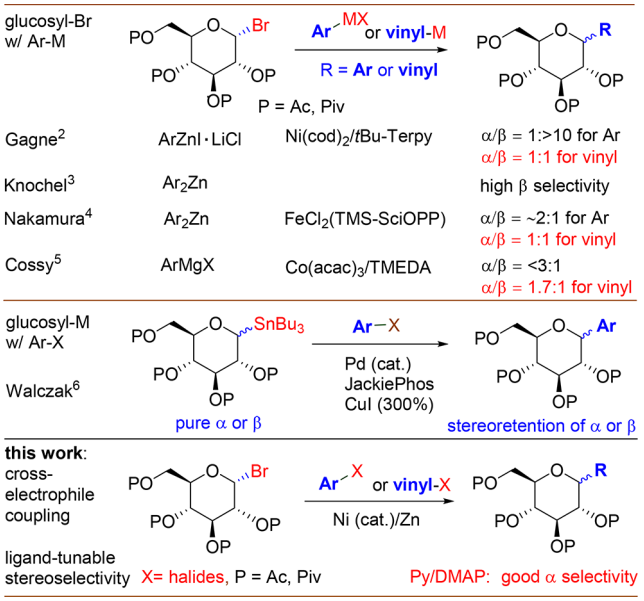
Supporting Information

ABSTRACT: Facile preparation of the α-C-vinyl and -aryl glycosides has been developed via mild Ni-catalyzed reductive vinylation and arylation of C1-glycosyl halides with vinyl/aryl halides. Good to high α-selectivities were achieved for C-glucosides, galactosides, maltoside, and mannosides, which were dictated by the employment of pyridine type ligands. As such, the present work represents unprecedented control for a high level of α-selectivity for C-vinyl-glucosides using cross-coupling approaches and offers hitherto optimal α-selective preparation of C-aryl glucosides via catalyst-controlled coupling strategies.



Stereoselective construction of C-glycosides remains a challenge, in particular for those fully oxygen saturated C-glucosides.[1] This topic has evoked growing interest in the development of transition-metal-catalyzed cross-coupling methods based upon the manipulation of glycosyl C1(sp^3)-nucleophiles or -electrophiles (Scheme 1).[2−6] The coupling of organometallic reagents with readily accessible C1-glycosyl halides has proven to be beneficial for such purposes.[3−6] The seminal work revealed by Gagné highlights the first Ni-catalyzed Negishi method to realize catalytic alkylation and arylation of C1-glycosyl halides.[2] In this context, the Ni-catalysts provide fully saturated C-aryl glucosides with high β-selectivities. Knochel described an additional notable example using Ar_2Zn as the nucleophiles leading to excellent β-selectivity for C-aryl glucosides in the absence of a metal catalyst.[3] By contrast, the achievements of moderate α-selectivities via arylation of glucosyl bromides have recently been disclosed using Fe- and Co-catalyzed Negishi and Kumada conditions (Scheme 1).[4,5] In a different strategy, Walczak demonstrated a Pd-catalyzed Stille coupling protocol to access α- and β-C-aryl glucosides based on the stereoretentive reactions of glycosyl-Sn with aryl electrophiles.[6] Albeit with considerable progress, the concurrent methods do not show effective control of the stereochemistry for C-vinyl glucosides. In addition, arylation of glucosyl halides only offers no to moderate α-selectivities under catalyst-controlled coupling conditions.

Scheme 1. Cross-coupling Methods to C-Aryl- and Vinyl-glucosides[2−6]



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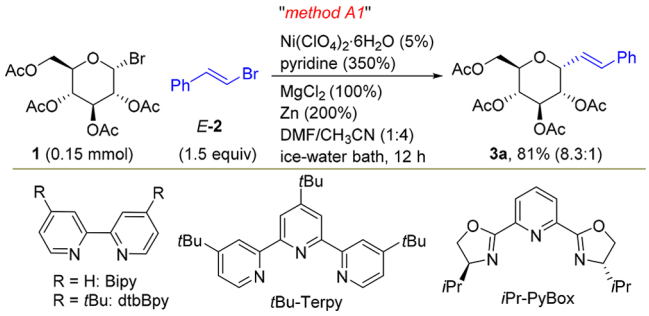
with an α/β ratio of 8.3:1 (*method A1*, Table 1, entry 1).[8] Alternation of the reaction temperatures and solvents did not yield better results (entries 2−4). Without Ni catalyst, pyridine, or $MgCl_2$, only trace amounts of **3a** were generated (entries 5−7).[8] Other ligands and nickel sources did not enhance the coupling efficiency (entries 8−15). No reaction took place when we used $Ni(OTf)_2$; only hydrolysis and elimination of glucosyl halide **1** to glucal were detected. An equimolar mixture of **1** and **2** delivered **3a** in 74% yield without eroding the selectivity (entry 16). Finally, the reaction can be scaled up on a gram scale (entry 17).

Table 1. Optimization for the Formation of 3a[a,b]



entry	variation from the standard conditions	yield % (α/β)
1	none	81% (8.3:1)[c]
2	25 °C instead of 0 °C	76% (6:1)
3	DMF	20% (7.2:1)
4	CH_3CN	trace
5	w/o $MgCl_2$	trace
6	w/o $Ni(ClO_4)\bullet 6H_2O$	N.D.
7	w/o pyridine	N.D.
8	DMAP	trace
9	Bpy (10%)	20% (2.2:1)
10	dtbBpy (10%)	24% (2.8:1)
12	*t*Bu-Terpy (10 mol %)	30% (1.2:1)
13	*i*Pr-Pybox (10 mol %)	20% (1:1)
14	$NiCl_2$	N.D.
15	$Ni(acac)_2$	63% (7:1)
16	**1** (0.15 mmol), **2** (0.15 mmol)	74% (8.1:1)
17	**1** (3 mmol scale)	75% (8.8:1)[c]

[a]Method A1: see entry 1. [b]Yield determined by ^1H NMR spectroscopy using 2,5-dimethylfuran as an internal reference. The ratios in the parentheses refer to α/β ratios. [c]Isolated yields.

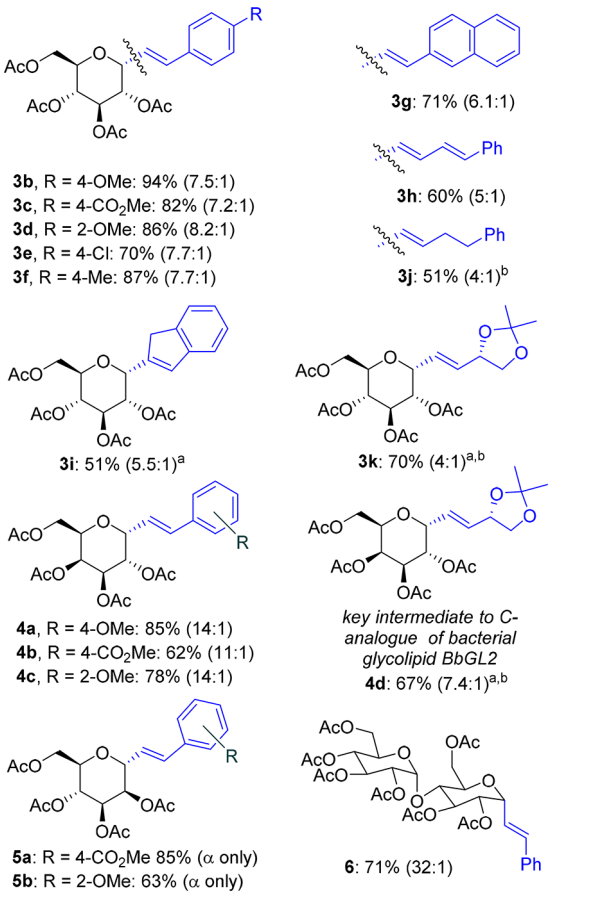


Figure 1. Selective preparation of α-*C*-vinyl-glycosides using *method A1* (as in Table 1, entry 1); yield refers to isolated yield, and ratio in parentheses refers to α/β ratio. (a) 1 equiv of vinyl bromide and 2 equiv of **1** were used. (b) 1 equiv of Bu_4NI and 10% of Ni were used, 25 °C.

Next, a survey of the scope of vinyl bromides was performed (Figure 1). Couplings of **1** with a range of vinyl bromides were subjected to the optimized *method A1*. As shown in Figure 1, the aryl-conjugated vinyl bromides produced **3b**−**3g** in good to excellent yields with good to high α selectivities. In contrast, (*Z*)-1-(2-bromovinyl)-4-methoxybenzene provided a mixture of *E*/*Z* isomers of **3b** (*E*/*Z* = 1:3) in a comparable yield and α/β selectivity (Table S1).[8,9] The dienyl bromide was also effective which furnished **3h** in 60% yield (α/β = 5:1). While coupling of α-vinyl bromides was generally unsuccessful, **3i** derived from 2-bromo-1*H*-indene was obtained in a moderate yield with good α-selectivity. The alkyl-decorated vinyl bromide resulted in **3j** and **3k** in good yields with 4:1 α/β ratios. High α-selectivities were also observed for galactoside (e.g., **4a**−**d**), mannoside **5**, and maltoside **6**. Of note was that facile preparation of α-**4d** was also achieved from the coupling of Ac-protected galactosyl bromide, which can be considered as a key intermediate to the *C*-analogue of bacterial glycolipid BbGL2.[10]

We applied the vinylation conditions to the arylation of **1** with methyl 4-iodobenzoate. Using *method A1*, **7a** was obtained in a low yield with poor reproducibility. This is not surprising, as vinyl halides often display distinctive reactivities from aryl counterparts under reductive coupling conditions.[11] Modification of *method A1* using **1** in excess, 20% of Ni and 80% of DMAP, and DMA/THF as the solvent (*method A2*, Figure 2) showed the yield can be promoted to 85% with a 6:1 α/β ratio. A small amount of HBr was necessary to initiate the reaction, possibly for activation of Zn. The coupling of 4-methyl benzoate with per-*O*-acetyl glucopyranosyl iodides (an iodo analog of **1**) only resulted in a trace amount of **7a**; glucal (~37%) and hydrolysis (~42%) of the iodide were detected as the major products. Unfortunately, when Ac was replaced with Bn, no reaction occurred, due to rapid hydrolysis of the glycosyl bromide. The use of a chloro analog did not provide an appreciable result; most of the chloride remained intact (85%). The generality of this method was also manifested by the examples of **7b**−**d** containing electron-withdrawing groups in the arenes. For iodobenzene and other electron-rich aryl iodides, the yields were poor although the α-selectivities remained unaffected (e.g., for **7e**). With *method A2*, galactoside **8a** was obtained in good yield and high α-selectivity. Whereas

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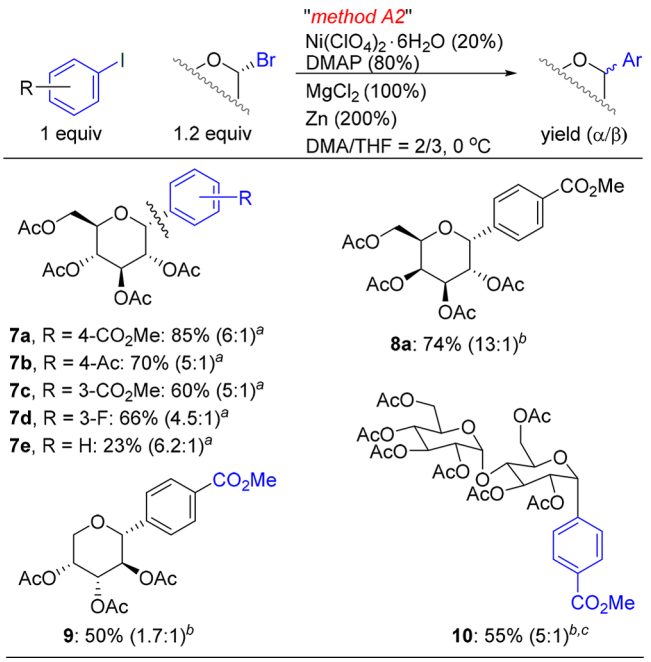


Figure 2. Arylation of *C*-glycosyl bromides with electron-deficient aryl iodides: yield refers to isolated yield, and ratio in parentheses refers to α/β ratio. (a) Ni (20 mol %), DMAP (80 mol %) with trace quantity of HBr/AcOH. (b) Ni (10 mol %), DMAP (40 mol %), w/o HBr/AcOH. (c) 25 °C.

arabinoside **9** did not show good selectivity, maltoside **10** were obtained in 55% yield with a 5.5:1 α/β ratio (Figure 2).

To solve the problem for arylation of electron-rich arenes as in Figure 2, replacement of DMAP with dtbBpiy and use of 1.5 equiv of **1** and DMA as the solvent furnished **7f** in 80% yield with a 2.8:1 α/β ratio (*method A3*, Figure 3).[12,13] It appears that bipyridine can boost the arylation efficiency including those electron-rich arenes, but at the expense of the α selectivities. Likewise, **7g** was obtained in a good yield and moderate α/β ratio, which is the α-anomer of Ac-protected commercial drug Canagliflozin for type-2 diabetes.[14] The

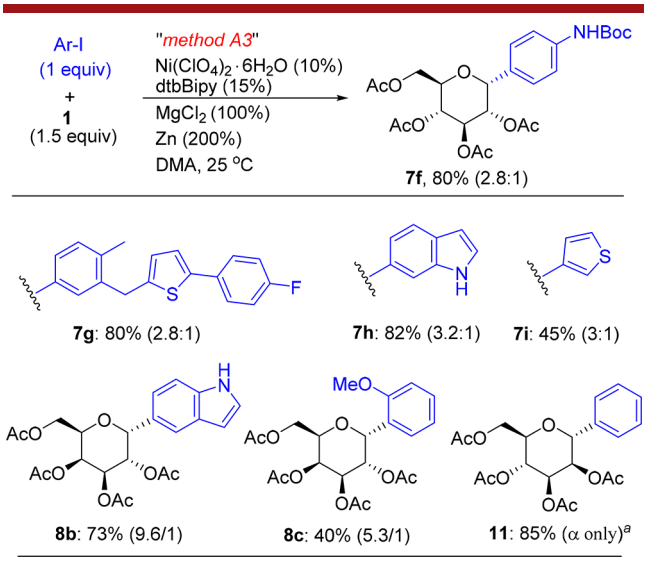
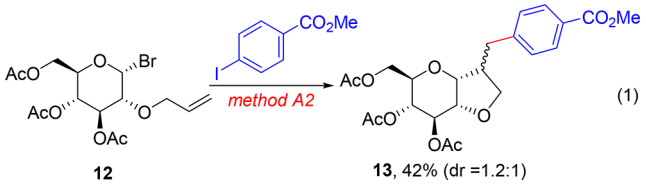


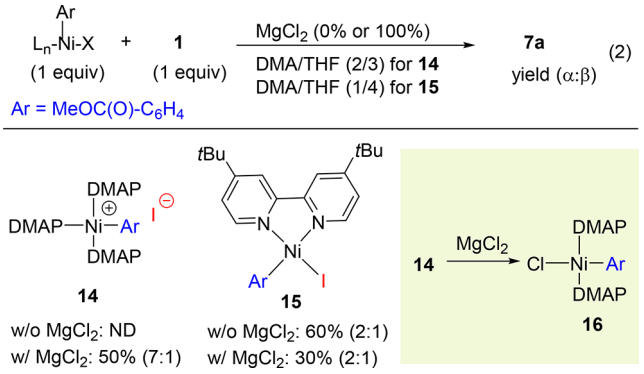
Figure 3. Arylation of *C*-glycosyl bromides with electron-rich aryl iodides: yield refers to isolated yield, and ratio in parentheses refers to α/β ratio. (a) DMA/THF = 1:4 (1 mL).

arylation *method A3* displayed excellent substrate compatibility, allowing effective incorporation of 6-indole and 3-thiophenyl groups into **7h–i**. Good to high α-selectivities were also observed for galactosides and mannosides **8b–c** and **11** using *method A3*.

According to the previous mechanistic studies on the Ni-catalyzed reductive arylation of alkyl halides,[15] we speculate this glycoside forming protocol may comply with a radical-chain mechanism, wherein an aryl–Ni^{II} intermediate intercepts an alkyl radical generated from halide abstraction of a Ni^{I} species.[8,14] The radical nature of glucosyl was confirmed by the coupling of **12** with methyl 4-iodobenzate, which resulted in a cyclization/coupling product **13** in 42% yield (eq 1).



Treatment of methyl 4-iodobenzoate with Ni^0 in the presence of DMAP and dtbBipy led to mono- and bidentated Ni^{II} complexes **14** and **15**, respectively,[8] which are paramagnetic and cationic in polar solvents.[8,16] Stoichiometric reactions of **14–15** with **1** were examined (eq 2). For complex



14, $MgCl_2$ is crucial for the α-selective formation of **7a**.[8] The reaction of **15** with **1** produced **7a** in 60% or 30% yield with a 2:1 α/β ratio in the presence or absence of $MgCl_2$. These results are in agreement with a radical-chain mechanism proposed by Weix, in which an Ar–Ni^{II} species can initiate alkyl radical formation and capture it to yield an Ar–Ni^{III}–alkyl intermediate that releases aryl–alkyl products upon reductive elimination.[8,15]

Our recent studies on the roles of $MgCl_2$ suggest that it may involve Cl^- and I^- exchange to form a more stable Ni^{II}–Cl bond than a Ni^{II}–I bond, as the latter generally dissociates in polar solvents to give cationic Ni species.[17] For instance, a reaction of **14** with excess $MgCl_2$ yields a neutral $(DMAP)_2Ni^{II}$–Ar(Cl) species **16** by releasing a DMAP ligand (eq 2), which may account for the authentic intermediate for intercepting a glycosyl radical.[8]

Steric interactions may play a key role in dictating the α/β selectivities for the glucosides. A boat-like $B_{2,5}$-comfomer was proposed as the more stable glucosyl radical intermediate than the chairlike ones with a free energy difference by 0.57 kcal/mol.[18] The Ar–Ni^{II} intermediate can approach the radical via α or β sides, resulting in an α- or a β-C–Ni bond (eq 3), with the α-intermediate being more stable due to anomeric

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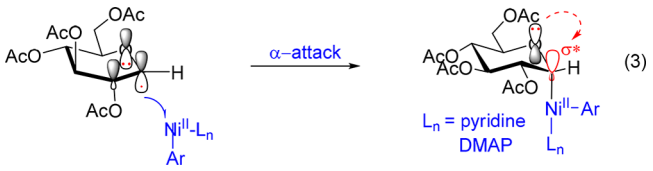

(3)

interaction of the p-lone electron pair of the oxygen atom with the antibonding orbital of the C–Ni bond.[18] Owing to the flexibility of the boat conformer, moderate α-selectivities (α/β < 3:1) are generally observed as evidenced in the previous *C*-glucoside forming methods. Similar results were observed in our studies when bipyridine ligands were used. The labile pyridine/DMAP ligands however deliver good α-selectivities (α/β up to 8:1), likely involving dissociation of a ligand from the Ni center upon formation of the α-Ni–C bond.[19] As such, the repulsive steric interaction via α-attack is reduced, leading to enhanced α-selectivity. The high α-selectivity for C-mannosides can be explained by a chairlike mannosyl radical that leads to preferential formation of α-products due to less steric hindrance of the α-face.[4]

In summary, a facile Ni-catalyzed cross-electrophile coupling method for the construction of *C*-aryl and -vinyl glycosides has been developed. The stereoselective outcomes were determined by both the catalysts and the structures of the substrates. For *C*-glucosides, a unique ligand-controlled diastereoselectivity was observed, wherein good to high α-selectivities were attained using Py/DMAP ligands, respectively. Steric effects induced by the catalysts and the glucosyl radical may explain this profound stereoselective result.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03567.

Detailed experimental procedures, characterization of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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