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Nickel-catalyzed reductive coupling of glucosyl halides with aryl/vinyl halides enabling β-selective preparation of *C*-aryl/vinyl glucosides

Jiandong Liu, Chuanhu Lei* & Hegui Gong*

School of Materials Science and Engineering, Center for Supramolecular Chemistry and Catalysis, Department of Chemistry, Shanghai University, Shanghai 200444, China

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This work describes stereoselective preparation of β-*C*-aryl/vinyl glucosides via mild Ni-catalyzed reductive arylation and vinylation of *C*1-glucosyl halides with aryl and vinyl halides. A broad range of aryl halides and vinyl halides were employed to yield *C*-aryl/vinyl glucosides in 42%–93% yields. Good to excellent β-selectivities were obtained for *C*-glucosides by using tridentate ligand.

nickel-catalyzed, reductive coupling, β-selective preparation, *C*-aryl/vinyl glucosides

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C-glycosides embody an important class of bioactive compounds found in nature and commercial drugs [1]. The prestigious examples of natural products include (+)-varitriol (anticancer activities) [2], Aspalathin (antimutagenic and antioxidant properties) [3] and Salmochelins (e.g., Salmochelin S1 as a metabolite of the ferric-binding siderophores) (Figure 1) [4]. *C*-glycosides are inert towards the metabolic processes as compared to their *O*-counterparts, where a plethora of *C*-glycosides were synthesized as potent therapeutic agents [5]. Among them, canagliflozin (Invokana), empagliflozin (Jardiance) and dapagliflozin (Farxiga) have been widely used for the treatment of type-2 diabetes (Figure 1) [6].

The cross-coupling methods to access fully oxygen saturated β-*C*-glycosides, in particular β-*C*-glucosides, often require transition-metal-catalysis (Scheme 1) [7–16]. Gagné first utilized Ni-catalyzed Negishi strategy for the coupling of C1-glycosyl halides with alkyl- and aryl-Zn reagents, which delivered high β-selectivities for *C*-aryl glucosides (Reaction (1)) [7,8]. Knochel *et al*. [9] employed Ar_2Zn as the organometallic nucleophiles under catalyst-free conditions to react with glucosyl bromide (Reaction (1)). The reaction generates *C*-aryl glucosides with excellent β-selectivities. By contrast, Walczak *et al*. [12,13] disclosed that *C*1-glycosyl stannanes underwent an excellent stereoretentive cross-coupling reaction with aryl halides (Reaction (2)). Recently, our group [14] developed a method employing pyridine/DMAP as ligand to prepare α-*C*-vinyl/aryl glycosides via nickel-catalyzed reductive coupling of glycosyl halides with vinyl and aryl halides in mild conditions. Such a method adds a new entry to α-selective preparation of *C*-glycosides as compared to the concurrent protocols that generally produce moderate α-selectivities for arylation of *C*1-glucosyl bromide [10,11].

Herein, we report efficient preparation of β-*C*-aryl and -vinyl glucosides and galactosides using Ni-catalyzed cross-electrophile coupling strategy (Reaction (3), Scheme 1) [17]. This work features a ligand-controlled β-selective construc-

*Corresponding authors (email: chlei@shu.edu.cn; hegui_gong@shu.edu.cn)

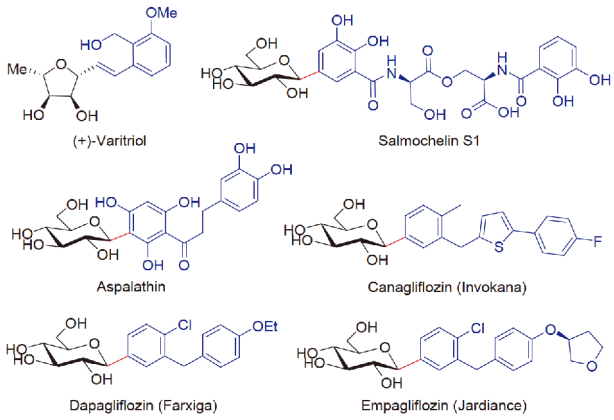
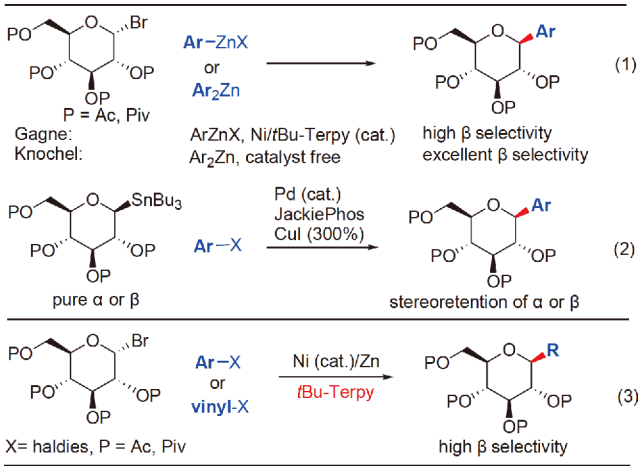


Figure 1 The representative examples of natural-occurring *C*-glycosides and drugs for type II diabetes (color online).

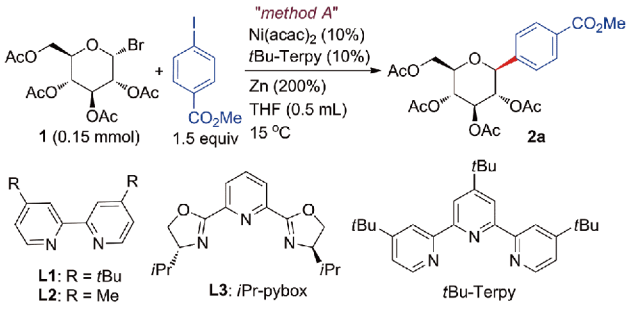


Scheme 1 β-Selective preparation of *C*-aryl/vinyl-glucosides (color online).

tion of *C*-glucosides and represents a rare example for transition metal-catalyzed stereoselective preparation of *C*-vinyl glucosides/galactosides. The application of this method was manifested by expeditious access to the intermediates of Salmochelin derivatives and a commercial anti-diabetes drug canagliflozin [4,6].

We commenced our work with the reaction of Ac-protected glucosyl bromide **1** and methyl 4-iodobenzoate. Extensive examination revealed a combination of Ni/*t*Bu-Terpy/Zn in tetrahydrofuran (THF) at 15 °C to be optimal, with which *C*-aryl glucoside **2a** was obtained in 85% yield with an α/β ratio of 1:12 (Table 1, entry 1) [18]. Other nickel sources and ligands, as well as solvents did not give a better result (entries 2–7). Without nickel catalyst and ligand, or without the ligand only no desired product was detected (entries 8 and 9). When one equivalent of $MgCl_2$ was used, similar yield but lower β-selectivity was observed, indicating $MgCl_2$ can interfere β-selectivity, likely due to halide exchange within the aryl-Ni intermediates (entry 10) [14]. Keeping the temperature at 15 °C appeared to be crucial to

Table 1 Optimization for the formation of **2a** [a), b)]



Entry [a)]	Variation from the standard method A	Yield [b)]
1	None	85% (1:12) [c)]
2	$Ni(ClO_4)_2$•$6H_2O$ instead of $Ni(acac)_2$	32% (1:11)
3	**L1** instead of *t*Bu-Terpy	trace
4	**L2** instead of *t*Bu-Terpy	N.D.
5	**L3** instead of *t*Bu-Terpy	trace
6	DMAinstead of THF	trace
7	DMFinstead of THF	N.D.
8	w/o $Ni(acac)_2$, w/o *t*Bu-Terpy	N.D.
9	Without *t*Bu-Terpy	N.D.
10	$MgCl_2$ (100 mol%)	80% (1:3)
11	0 °C	N.D.
12	21 °C	74% (1:12)
13	25 °C	66% (1:12)

a) Method A as in entry 1; b) yield determined by ^{1}H NMR spectroscopy using 2,5-dimethylfuran as an internal reference, and ratio in parenthesis refers to α/β ratio; c) isolated yields.

high yields (entries 11–13).

To further probe the applicability of the present method, coupling of a range of substituted aryl iodides with Ac-protected glucosyl bromide **1** was carried out using method A. As shown in Figure 2, compounds **2b**–**2e** were obtained in good to excellent yields with high β-selectivities. Compound **2f** bearing less electron deficient substituents was obtained in a good yield and high β-selectivity, which is the Ac-protected commercial drug empagliflozin for type-2 diabetes [6]. Use of 3-iodothiophene as coupling partner gave **2g** in a moderate yield and excellent β selectivity. Aryl iodides decorated with *meta*-bomo furnished **2h** with good yield and selectivity, which is useful for further functionalization. For electron-rich and -neutral arenes, method A also yielded moderate to good yields and high β-selectivities by employing 15 mol% $MgCl_2$, as exemplified by **2i**–**2m**. For the low-yielding reactions, we observed that the formation of glucal accounted for the mass balance for glucosyl bromides, whereas hydrodehalogenation by-products did for aryl halides. We reason that $MgCl_2$ is required to activate Zn and reduce Ni(II) to Ni(0), particularly in the cases of electron-rich aryl halides (Figure 2). We performed an experiment using $Ni(COD)_2$ as the precatalyst without addition of $MgCl_2$

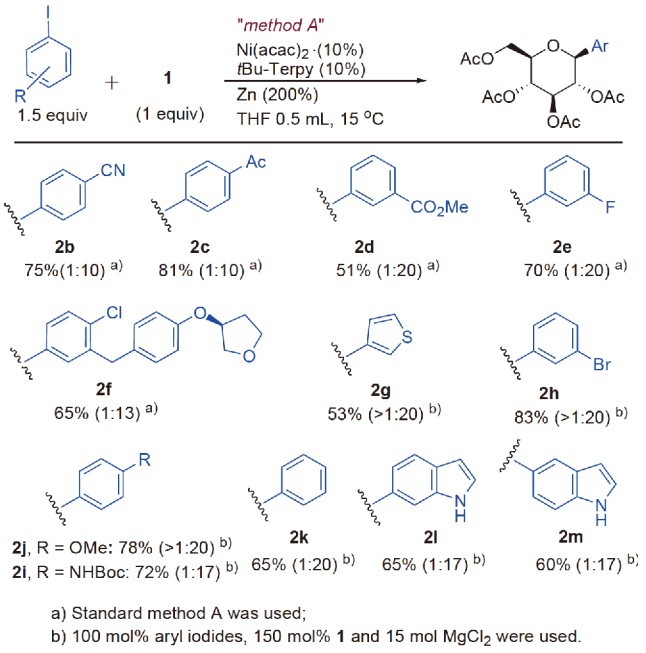


Figure 2 Scope of the aryl iodides. Yield refers to as isolated yield, and ratio in parenthesis refers to α/β ratio (color online).

(Scheme S3, Supporting Information online), and similar results for **2j** were obtained. Without $MgCl_2$, a control experiment showed that no reaction occurred for **2j** using method A.

The utility of this work was further showcased by the synthesis of β-**2n** and β-**2o** (Figure 3), which served as key intermediates of Salmochelin derivatives (Fe^{3+}-siderophores) and the precursor of a commercial drug canagliflozin for type-2 diabetes, respectively (Figure 4) [4,6,19]. Saponification of the latter provided canagliflozin in 90% yield. Finally, a brief investigation of the scope of other glycosyl halides for the coupling with 4-iodoanisole and 4-iodobenzoate was explored. Arylation of benzyl-protected glucosyl chloride with 4-iodoanisole in the presence of 15 mol% $MgCl_2$ delivered **3** in 60% yield with a 1:5 of α/β ratio. Galactosyl bromide displayed similar selectivities to the glucosyl analogs (e.g., **4**); high β selectivities were also observed in 2-phthalimido glucosyl bromide (α/β=1:19) and 2,3,5-tri-*O*-aceto-D-ribofuranosyl chloride (e.g., **5** and **6**).

We also investigate the preparation of β-*C*-vinyl glycosides using the same coupling protocol. It was noted that vinyl halides are generally more prone to dimerization as compared to aryl counterparts [20]. Thus, coupling of Piv-protected glucosyl bromide 7 with *E*-8 under Ni(acac)$_2$/*t*Bu-Terpy/Zn/$MgCl_2$/THF conditions provided **9a** in an optimal 65% yield with an α/β ratio of 1:8 (Figure 4, method B). By contrast, the acetyl-protected glucosyl bromide **1** gave 78% yield with an α/β ratio of 1:3 (Table S2, Supporting Information online) [18]. The aryl moiety bearing 4-CO_2Me within the styrene resulted in an enhanced yield, whereas a MeO-group was slightly inferior without eroding the ste-

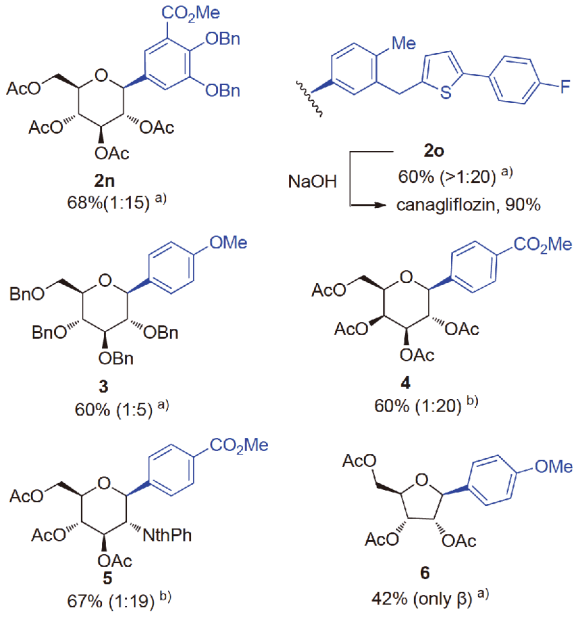


Figure 3 Selective preparation of β-*C*-aryl-glycosides. Yield refers to as isolated yield, and ratio in parenthesis refers to α/β ratio (color online).

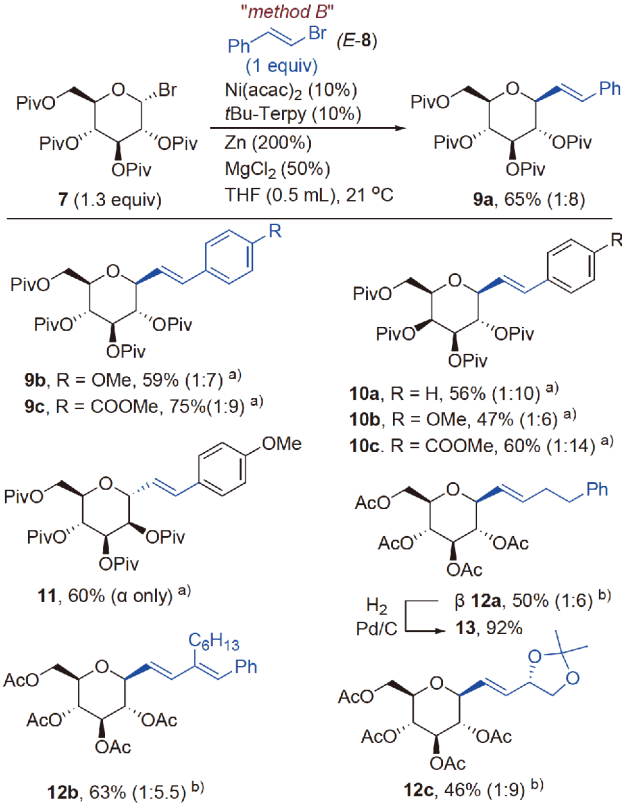
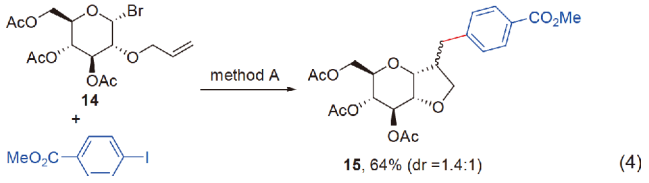


Figure 4 Selective preparation of β-*C*-vinyl-glycosides. Yield refers to as isolated yield, and ratio in parenthesis refers to α/β ratio (color online).

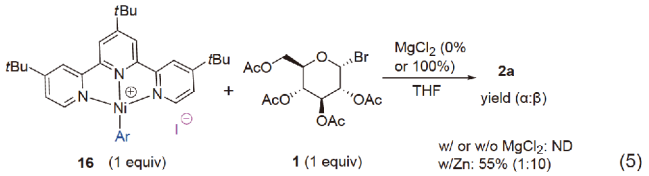
reoselectivity, as evidenced by **9b** and **9c** (Figure 4). Method B was also effective for the construction of Piv-protected β-*C*-galactosides (e.g., **10a**–**10c**), but not for β-mannoside **11**. Only the α-anomer was isolated, suggesting that substrate-controlled stereochemistry dictates in this case. With slight modifications, method B was suited for alkyl-substituted vinyl and dienyl bromides furnishing β-selective preparation of **12a**–**12c** (Figure 4). In these cases, **1** was more effective than **7**, possibly due to enhanced reactivity of the former arising from less steric hindrance. A quick application of the vinyl product β-**12a** was conducted by hydrogenation to afford the reduction product **13**. It was noted that the preparation of *C*-alkyl glucosides with good control of α- and β-selectivities remains a challenge [7].

According to previously reported Ni-catalyzed reductive cyclization/coupling of alkyl halides [11,14], coupling of **14** and methyl 4-iodobenzoate using method A produced **15** in 64% yield (Reaction (4)). Thus, we proposed this glycoside forming protocol involves a radical mechanism, wherein an aryl-Ni^{II} intermediate may intercept a glucosyl radical generated from halide abstraction by a Ni^{I} intermediate [8,17].



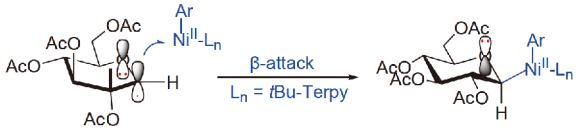
(4)

To further understand the reaction mechanism, a tridentate Ni^{II} complex **16** was obtained by reaction of methyl 4-iodobenzoate with Ni^{0} in the presence of *t*Bu-Terpy [18]. ^{1}H NMR studies indicated it was paramagnetic and cationic in polar solvents (Scheme S2) [18,21,22]. No appreciable **2a** was detected for the reactions of **16** with **1** (Reaction (5)), regardless of the presence of $MgCl_2$. With Zn, **2a** was obtained in 55% yield with high β-selectivity. We reason that it is likely that complex **16** was reduced by Zn to *t*Bu-Terpy-Ni^{I}-Ar, to which oxidative addition of **1** leads to Ar-Ni^{III}-alkyl prior to the reductive elimination giving **2a** (Scheme S1), similar to Vicic's proposal for Ni-catalyzed Negishi mechasim [23,24].



(5)

The origin of β selectivity in this *C*-glucoside forming approach is explained by a favourable β-attack of the Ac-protected glucosyl radical to a Terpy-Ni(II)-Ar intermediate (e.g., **17**). It was known that Ac-protected glucosyl radical adopts a boat-like $B_{2,5}$-comfomer which is more stable than the chair-like one with a free energy (ΔG) difference by 0.57 kcal/mol (Reaction (6)) [10,25]. Thus, radical attack using the boat conformer is possible, and it favors β site due to the bulkiness of Terpy-Ni(II) intermediate (Reaction (6)). In contrast to our previous report, the use of labile pyridine and DMAP resulted in good α selectivities under similar reaction conditions [14]. In those cases, α-attack is favoured possibly due to reduced steric interactions between Ni-Py complex and the α-site of the glucosyl scaffold, in addition to the anomeric stabilization of σ^{*}(α-Ni–C) by p-lone electron pair of the oxygen atom [25].



(6)

In summary, we have described an efficient Ni-catalyzed cross-electrophile coupling method for stereoselective preparation of β-*C*-aryl/vinyl glucosides. A unique *t*Bu-Terpy ligand-controlled diastereoselectivity was observed. We envisage that this method is synthetically practical for accessing the relevant bioactive compounds containing β-glucosides and -galactosides by using readily available glycosyl and aryl/vinyl halides, and by avoiding the preparation of organometallic reagents.

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Conflict of interest The authors declare that they have no conflict of interest.

Supporting information The supporting information is available online at http://chem.scichina.com and http://link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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