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Communication

Copper-mediated *O*-arylation of lactols with aryl boronic acids

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ABSTRACT

An efficient and novel methodology to access phenolic glycosides has been established by using copper-mediated coupling reaction of aryl boronic acids with hemiacetals. The reaction takes place normally in the presence of $Cu(OAc)_2$ (1.0 equiv.) and pyridine (2.0 equiv.) at 40 °C. This protocol distinguishes itself by wide substrate scope, operational simplicity and giving rise to a myriad of phenolic glycosides in good to excellent yields.

Phenolic glycosides such as vancomycin [1], seenoside A [2] and camellianin B [3] (Scheme 1a), refer to molecules containing a sugar unit bound to a phenol aglycone. These compounds are widely distributed in nature and play numerous important roles in living organisms. Phenolic glycosides have also received special attention owing to their vital pharmaceutical potentials, such as antitumor [4], antidiabetic [5] and anti-inflammatory effects [6]. A major obstacle in the development of pharmacological characterization of phenolic glycosides is their extremely trace content in natural sources.

Chemical synthesis enables facile access to phenolic glycosides in pure and large quantities. There has been a growing emphasis on investigating the synthesis of phenolic glycosides. A great deal of efforts has been devoted to the development of effective methods for the synthesis of phenolic glycosides. *O*-Glycosylation of phenols is the main strategy for the formation of these compounds. A large variety of glycosyl donors such as glycosyl halides [7], glycosyl trichloroacetimidates [8], glycosyl *N*-phenyl trichloroacetimidates [9], glycosyl acetates [10], thioglycosides [11], alkynyl glycosides [12], 1,2-anhydrosugar [13], and hemiacetals [14], have been used for the assembly of phenolic glycosides either through an S_N2 type mechanism under basic conditions or through an S_N1 type mechanism under acidic conditions (Scheme 1b). However, when using these methods, the anomerization, formation of C-glycoside by-products, and low functional-group tolerance usually hamper the versatility and utility of phenolic glycoside synthesis.

O-Arylation of hemiacetals represents another route to afford phenolic glycosides. The Olofsson group developed a novel method for anomeric *O*-arylation using bench-stable iodonium (III) reagents [15]. Xiao group revealed a new coupling reaction of sugar lactols with aryl bromides to form phenolic glycosides *via* dual photoredox/Ni catalysis [16]. As part of our continuous studies on the preparation of carbohydrate derivatives by the coupling reactions with aryl boronic acids [17], we herein report the synthesis of phenolic glycosides via copper-mediated *O*-arylation of lactols with aryl boronic acids (Scheme 1c).

We started our investigations on the coupling reaction of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose (**1a**) with commercially available 4-methoxyphenylboronic acid (**2a**) (Table 1 and Tables S1-S3 in Supporting information). We anticipated that a stoichiometric amount of copper salt would be necessary for the formation of the C–O bond. Indeed, the desired product **3aa** was obtained in 8% isolated yield by the use of $CuCl_2$ (1.0 equiv.) in the presence of pyridine (3.0 equiv.) (entry 1). The reaction appeared completely inert to $Cu(OTf)_2$, $CuSO_4{\cdot}5H_2O$, CuCl and CuBr (entries 2–5). Gratifyingly, the use of $Cu(OAc)_2$ instead of $CuCl_2$ afforded the desired product **3aa** in 62% yield (entry 6). Increasing the reaction temperature to 40 °C improved the reaction efficiency (Table S3). It was observed that pyridine was the proper base and the amount of pyridine also influenced the reaction yield (the best amount was 2.0 equiv.) (entries 7–11 and 14–15, and Tables S1 and S3). Further studies indicated that dichloromethane would be the best solvent (Table S2). The omission of molecular sieves failed to

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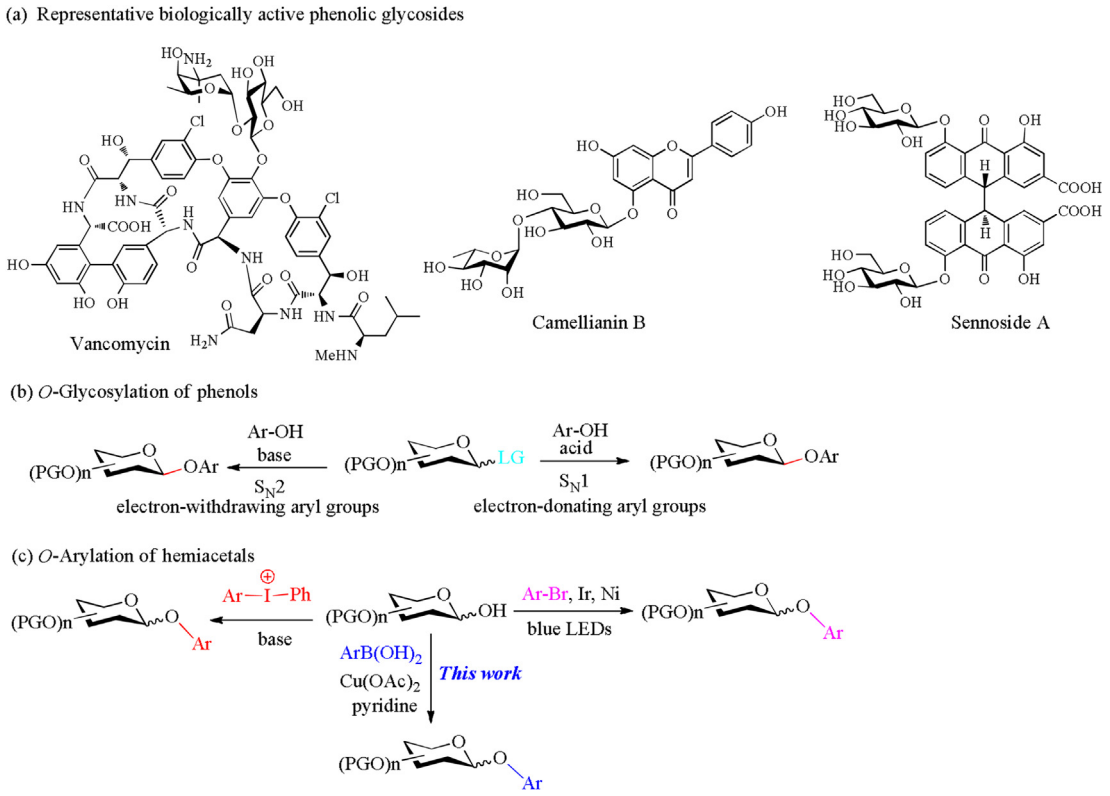
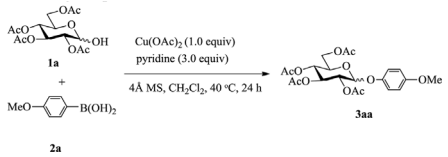


Scheme 1. Phenolic glycosides and their synthetic methods.

Table 1
Screening of optimal conditions.[a]



Entry	Conditions	Yield (%)[b]
1	$CuCl_2$	8
2	$Cu(OTf)_2$	trace
3	$CuSO_4·5H_2O$	N.R.[c]
4	CuCl	N.R.
5	CuBr	N.R.
6	$Cu(OAc)_2$	62
7	$Cu(OAc)_2$, 2,6-lutidine	N.R.
8	$Cu(OAc)_2$, Et_3N	12
9	$Cu(OAc)_2$, DMAP	trace
10	$Cu(OAc)_2$, K_2CO_3	N.R.
11	$Cu(OAc)_2$, Cs_2CO_3	trace
12	$Cu(OAc)_2$, 40 °C	71
13	$Cu(OAc)_2$, 50 °C	68
14	$Cu(OAc)_2$, pyridine (1.0 equiv.), 40 °C	77
15	$Cu(OAc)_2$, pyridine (2.0 equiv.), 40 °C	90
16	$Cu(OAc)_2$, no 4 Å MS	N.R.

[a] Reaction conditions: **1a** (1.0 equiv.), **2a** (3.0 equiv.), Cu salt (1.0 equiv.), pyridine (3.0 equiv.), 4 Å MS (0.10 g), CH_2Cl_2 (1.0 mL), r.t., under air atmosphere for 24 h.
[b] Isolated yield.
[c] N.R.: no reaction.

give the product (entry 16, Table S4 in Supporting information). Therefore, the optimized conditions are as follows: lactol (1.0 equiv.), aryl boronic acid (3.0 equiv.), $Cu(OAc)_2$ (1.0 equiv.), pyridine (2.0 equiv.) and activated 4 Å molecular sieves, in CH_2Cl_2 at 40 °C for 24 h (entry 15).

Under the optimized conditions, the reaction of lactol **1a** with different aryl boronic acids were surveyed, as shown in Table 2. The results showed that aryl boronic acids bearing both electron-donating substituents and electron-withdrawing substituents underwent the reaction smoothly, affording the phenolic glycosides in moderate to excellent yields. The reaction of *ortho*-, *meta*- and *para*-substituted aryl boronic acid substrates gave good yields (entries 8 and 9). Interestingly, the reaction of vinyl-, chloro- and iodo-substituted aryl boronic acids with compound **1a** also proceeded very well, providing the desired coupled products, which could be used for further transformations. The reaction of disubstituted 3,5-dimethoxyphenylboronic acid gave the desired product **3ak** in moderate yield (52%, entry 10).

Next, the scope of lactols was explored under the optimized conditions and the results are summarized in Table 3. The reaction of 2,3,4,6-tetra-*O*-acetyl-D-galactose (**1b**), 2,3,4,6-tetra-*O*-acetyl-D-mannose (**1c**), 2,3,4-tri-*O*-acetyl-L-arabinose (**1d**) and 2,3,4-tri-*O*-acetyl-D-xylose (**1e**) with both electron-rich *p*-methoxybenzeneboronic acid (**2a**) and electron-deficient *p*-nitrobenzeneboronic acid (**2 h**), proceeded in good yields (entries 1–5). 2,3,4-Tri-*O*-benzyl-L-fucose (**1f**) also tolerated in this transformation, generating product **3fa** in 65% isolated yield (entry 6). Similarly, the benzylated/benzoylated counterpart of glucose/galactose/mannose, underwent the reaction smoothly in satisfactory yields (entries 7–16). It is noteworthy that the reaction of the mannose-derived **1c** and **1k** provided an exclusive α-product (entries 3, 15 and 16). In all the reactions, no *C*-glycoside byproducts were detected. Most of the produced phenolic glycosides were lack of

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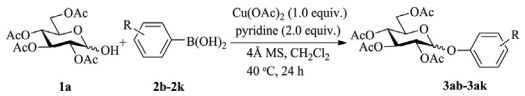
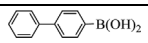
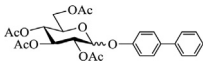
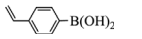
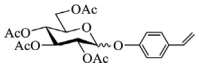
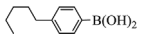
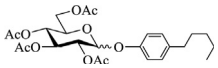
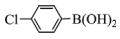
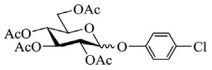
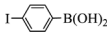
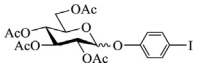
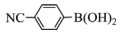
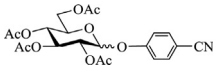
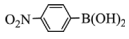
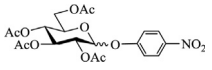
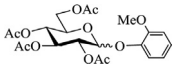
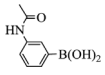
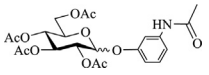
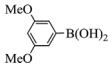
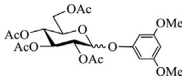
Table 2
The scope of aryl boronic acids.[a]



Entry	Aryl boronic acid		Product		Yield (α/β)[b]
1	**2b**		**3ab**		93%, (1:1.5)
2	**2c**		**3ac**		94%, (1:1)
3	**2d**		**3ad**		91%, (1:1)
4	**2e**		**3ae**		92%, (1:1)
5	**2f**		**3af**		90%, (1:1)
6	**2g**		**3ag**		66%, (1:2)
7	**2 h**		**3ah**		71%, (1:1)
8	**2i**		**3ai**		95%, (1:1)
9	**2j**		**3aj**		94%, (1:1)
10	**2k**		**3ak**		52%, (1:1)

[a] Reaction conditions: **1a** (0.037 mmol), aryl boronic acid (0.111 mmol), $Cu(OAc)_2$ (0.037 mmol), pyridine (0.074 mmol), 4 Å MS (0.15 g), CH_2Cl_2 (1.5 mL), 40 °C, under air atmosphere for 24 h.
[b] Isolated yield.

stereoselectivity, and the anomeric ratio of the obtained glycosides was not identical with that of the corresponding lactols in $CDCl_3$. It might be because that the anomeric ratio of lactols could vary as the change of temperature, basicity, and solvent.

Based on the literature report [18], a plausible reaction mechanism is depicted in Scheme 2. Initially, the aryl boronic acid reacts with $Cu(OAc)_2$ to generate $Cu^{II}(Ar)OAc$, which is oxidized with another $Cu(OAc)_2$ to form $Cu^{III}(Ar)(OAc)_2$. Finally, the ligand exchange and the latter reductive elimination furnishes the phenolic glycosides.

In conclusion, we have developed an efficient and practical copper-mediated coupling reaction of lactols with aryl boronic acids for the preparation of phenolic glycosides. The *O*-arylation of the anomeric oxygen in sugar moiety proceeded in moderate to excellent yields under mild reaction conditions. A broad range of lactols and aryl boronic acids with various functional groups were tolerated. The disclosed approach may find wide applications in the synthesis of many phenolic glycosides with biological importance.

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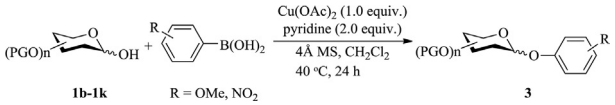
Table 3
The scope of lactols.[a]



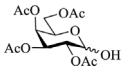
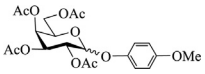
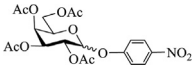
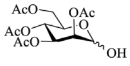
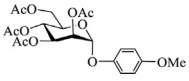
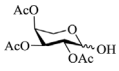
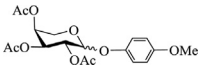
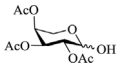
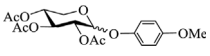
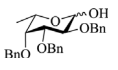
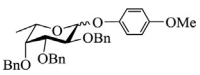
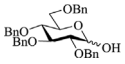
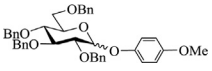
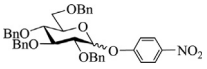
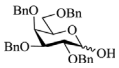
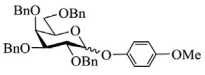
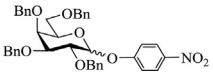
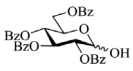
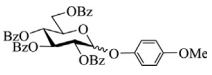
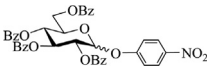
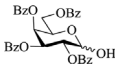
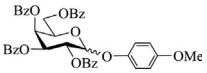
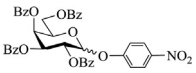
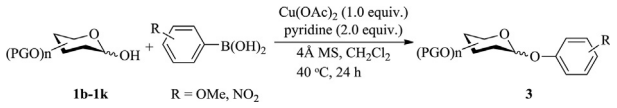
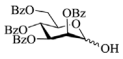
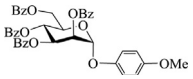
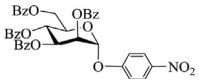
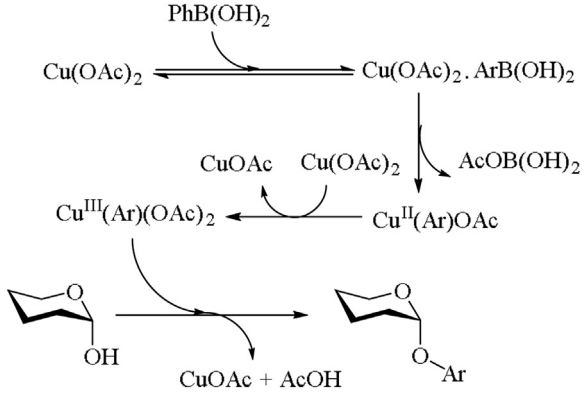
Entry	Lactol		Aryl boronic acid	Product		Yield (α/β)[b]
1	**1b**		**2a**	**3ba**		77%, (1:2)
2			**2 h**	**3bh**		64%, (1:2)
3	**1c**		**2a**	**3ca**		83%, α only
4	**1d**		**2a**	**3da**		74%, (1: 1)
5	**1e**		**2a**	**3ea**		84%, (1:1)
6	**1f**		**2a**	**3fa**		65%, (1:1)
7	**1g**		**2a**	**3ga**		90%, (1.5:1)
8			**2 h**	**3gh**		58%, (1.5:1)
9	**1h**		**2a**	**3ha**		73%, (1:1)
10			**2 h**	**3hh**		69%, (1:1)
11	**1i**		**2a**	**3ia**		82%, (2:1)
12			**2 h**	**3ih**		56%, (1.5:1)
13	**1j**		**2a**	**3ja**		72%, (2: 1)
14			**2 h**	**3jh**		53%, (2: 1)
15	**1k**		**2a**	**3ka**		75%, α only

Table 3 (*Continued*)



Entry	Lactol	Aryl boronic acid	Product	Yield (α/β)[b]
				
16		**2 h**	**3kh** 	56%, α only

[a] Reaction conditions: lactol (0.037 mmol), **2a** or **2 h** (0.111 mmol), $Cu(OAc)_2$ (0.037 mmol), pyridine (0.074 mmol), 4 Å MS (0.15 g), CH_2Cl_2 (1.5 mL), 40 °C, under air atmosphere for 24 h.
[b] Isolated yield.



Scheme 2. The proposed mechanism for the *O*-arylation of lactols.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2019.06.014.

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