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KO^{t}Bu-mediated aromatic O-glycosylation of 1,2-anhydrosugar and aryl boronic acid

Chen-Fu Liu [a,†], De-Cai Xiong [a,†], Xin-Shan Ye [a,b,*]

[a] State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Xue Yuan Road No. 38, Beijing 100191, China
[b] National Engineering Research Center for Carbohydrate Synthesis, Jiangxi Normal University, Nanchang 330022, Jiangxi, China

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ABSTRACT

A new approach for the synthesis of phenolic glycosides via aromatic O-glycosylation of 1,2-anhydrosugar and aryl boronic acids was disclosed. This method is characterized by the use of aryl boronic acid as the aryl source and produces phenolic glycosides in a stereoselective manner. This reaction provides an alternative approach to the synthesis of phenolic glycosides. It also represents a new application of aryl boronic acids as versatile reagents in organic synthesis.

Phenolic glycoside refers to the compounds containing a sugar unit bound to a phenol aglycone and encompasses a vast number of secondary metabolites such as vancomycin and chromomycin.[1] The synthesis of phenolic glycosides has received considerable attentions from both synthetic chemists and medicinal chemists because of their diverse biological activities and pharmaceutical potentials.[2] During the past years, many efforts have been made in the O-glycosylation of phenols by varying different glycosyl donors and the corresponding activation conditions.[3] However, due to the electron-withdrawing properties of aromatic rings, phenols are usually difficult to be glycosylated. The existing methods suffer from some drawbacks such as anomerization,[4] the formation of *C*-glycoside by-products,[5] or limited substrate scope. Thus, the development of new approaches to the synthesis of phenolic glycosides is still highly desired.

In our search for the development of new methods toward aryl-*C*-glycoside synthesis, phenolic glycoside **3a** was accidentally obtained in 35% yield by the reaction of 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose (**1a**)[6] with phenyl boronic acid (**2a**) catalyzed by $Pd_2(dba)_3$, whereas *C*-glycoside **4a** was not detected (Scheme 1). In fact, aromatic boronic acids enjoy the high prestige in organic synthesis due to their low toxicity, stability to air and moisture, and good functional group tolerance.[7] They might be suitable surrogates of phenols for the synthesis of phenolic glycosides.[8] Herein we report the synthesis of phenolic glycosides by the reaction of 1,2-anhydrosugars[9] with aryl boronic acids.

To begin our study, the reaction of **1a** with **2a** was further examined (Table 1). It was found that the catalyst $Pd_2(dba)_3$ was not essential for the generation of phenolic glycoside **3a** (entry 1). Base was crucial for this reaction and KO^{t}Bu was identified to be the best base (entries 2–13, up to 73% yield). Although the reaction was able to proceed in the solvents such as toluene, acetonitrile, and DME, THF was the most proper solvent (entries 13–19). The yields of **3a** decreased with the decrease of the reaction temperature (entries 20 and 21). It seemed that the use of 2.0 equiv of KO^{t}Bu afforded product **3a** in the best yield (entries 22, 23 and 13). Under either argon atmosphere or air atmosphere, the reaction gave no different results (entries 13 and 24). Therefore, the optimized reaction conditions are as follows: 1,2-anhydrosugar (1.0 equiv), aryl boronic acid (1.2 equiv), KO^{t}Bu (2.0 equiv) in THF at 50 °C.[10]

With the optimized conditions in hand, the scope of aryl boronic acids was examined, and the results are summarized in Table 2. All aryl boronic acids with electron-donating, electron-withdrawing, or sterically congested groups worked well. In the case of *ortho*/*meta*/*para*-methyl substituted aryl boronic acids, the expected coupling products **3b**, **3c**, and **3d** were isolated in 71%, 74%, and 79% yields, respectively (entries 1–3). When the electron-rich aryl boronic acid **2e** was used, the reaction occurred and the desired product **3e** was obtained in 69% yield (entry 4).

* Corresponding author. Tel.: +86 10 8280 5736; fax: +86 10 8280 2724.
E-mail address: xinshan@bjmu.edu.cn (X.-S. Ye).
† These authors contributed equally to this work.

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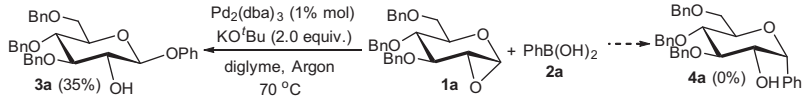
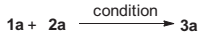
0040-4039/



Scheme 1. Reaction of anhydrosugar **1a** with phenyl boronic acid (**2a**).

Table 1
Optimization of the reaction conditions[a]



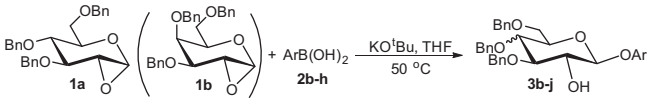
Entry	Conditions	Yield[b] (%)
1	KO^{t}Bu, diglyme, argon, 70 °C	35
2	Diglyme, 70 °C	0
3	$NaHCO_3$, THF, 50 °C	0
4	Na_2CO_3, THF, 50 °C	0
5	K_2CO_3, THF, 50 °C	0
6	Ag_2CO_3, THF, 50 °C	0
7	Cs_2CO_3, THF, 50 °C	0
8	NaOAc, THF, 50 °C	0
9	Et_3N, THF, 50 °C	0
10	DMAP, THF, 50 °C	0
11	NaOH, THF, 50 °C	0
12	NaOMe, THF, 50 °C	31
13	KO^{t}Bu, THF, 50 °C	73
14	KO^{t}Bu, DMF, 50 °C	<30
15	KO^{t}Bu, toluene, 50 °C	33
16	KO^{t}Bu, MeCN, 50 °C	48
17	KO^{t}Bu, DCE, 50 °C	Trace
18	KO^{t}Bu, DMSO, 50 °C	Trace
19	KO^{t}Bu, DME, 50 °C	51
20	KO^{t}Bu, THF, 40 °C	56
21	KO^{t}Bu, THF, 30 °C	39
22	KO^{t}Bu (1.0 equiv), THF, 50 °C	21
23	KO^{t}Bu (3.0 equiv), THF, 50 °C	42
24	KO^{t}Bu, THF, argon, 50 °C	71

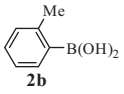
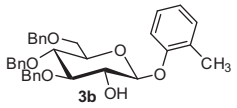
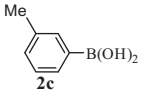
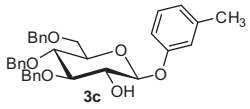
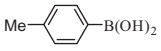
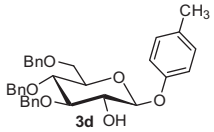
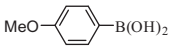
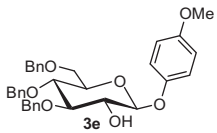
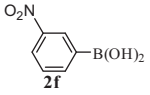
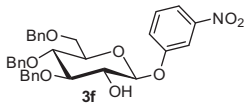
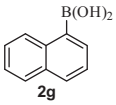
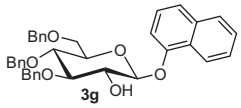
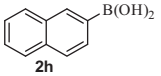
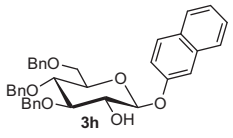
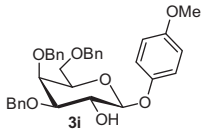
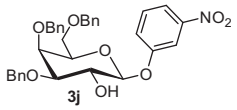
[a] Compound **1a** (0.1 mmol, 1 equiv), compound **2a** (0.12 mmol, 1.2 equiv), base (0.2 mmol, 2.0 equiv), solvent (1.0 mL).
[b] Isolated yield.

Fortunately, the reaction of compound **1a** with the electron-deficient aryl boronic acid **2f** proceeded smoothly (64% yield, entry 5). Moreover, when 1-naphthyl boronic acid (**2g**) and 2-naphthyl boronic acid (**2h**) were used as the reactants, the corresponding products **3g** and **3h** were afforded in 67% and 64% yields, respectively (entries 6 and 7). The desired phenolic glycosides (**3i**, **3j**) were also obtained in moderate yields when using 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-galactopyranose (**1b**)[6] as the glycosyl donor (entries 8 and 9). It is noteworthy that all coupling products were isolated in the β-only configuration. The structures and anomeric configurations of the products were unambiguously identified by its ^{1}H and ^{13}C NMR analyses.

Next, phenol was used instead of phenyl boronic acid (**2a**) to perform this reaction under the same conditions (Scheme 2A). The product **3a** was isolated in 65% yield, which was slightly lower than that of the use of phenyl boronic acid. Acetylation of compound **3a** afforded compound **5** in 96% isolated yield. The ^{1}H NMR data of compound **5** are in accordance with those reported previously,[9a,12] further confirming the structure of phenolic glycoside **3a**. On the other hand, when 4-methoxyphenyl boronic acid (**2e**) was subjected to the standard reaction conditions, 4-methoxyphenol (**6**) was detected (Scheme 2B). In fact, it was reported that phenols were observed as major products or byproducts in many metal-catalyzed coupling reactions of aryl boronic acids.[8,11] Although there are no procedures that deal with hydroxylation of aryl boronic acids only by the use of bases, the formation of phenolic glycosides might be attributed to the

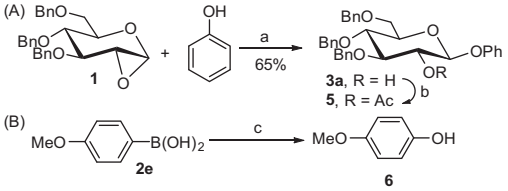
Table 2
Coupling reactions of 1,2-anhydrosugars with various aryl boronic acids[a]



Entry	ArB(OH)$_2$	Product	Yield[b] (%)
1			71
2			74
3			79
4			69
5			64
6			67
7			64
8	**2e**		62
9	**2f**		58

[a] Compound **1** (0.1 mmol, 1 equiv), aryl boronic acid (0.12 mmol, 1.2 equiv), KO^{t}Bu (0.2 mmol, 2.0 equiv), THF (1.0 mL), 50 °C.
[b] Isolated yield.

KO^{t}Bu-mediated formation of phenol intermediates from aryl boronic acids. This could explain the major product is β-configuration.[12] A nucleophilic attack of boronic acid to epoxide in basic conditions and a subsequent rearrangement might be another possible mechanism. However, the underlying mechanism is still unclear.



Scheme 2. Control experiments. (A) The reaction of 1,2-anhydrosugar **1** with phenol. (B) The treatment of boronic acid **2e** with base. Reagents and conditions: (a) Compound **1** (0.1 mmol, 1 equiv), phenol (0.12 mmol, 1.2 equiv), KO^{t}Bu (0.2 mmol, 2.0 equiv), THF (1.0 mL), 50 °C, 65% isolated yield; (b) Ac_2O, pyridine, 96% isolated yield; (c) **2e** (0.12 mmol, 1.2 equiv), KO^{t}Bu (0.2 mmol, 2.0 equiv), THF (1.0 mL), 50 °C.

In summary, we report a useful method for the synthesis of phenolic glycosides by the reaction of 1,2-anhydrosugars with aryl boronic acids. In the presence of KO^{t}Bu, 1,2-anhydrosugars smoothly underwent the aromatic O-glycosylation reaction with aryl boronic acids to generate β-phenolic glycosides in moderate yields. The products with a free hydroxyl group at the C-2 position can be further used as the glycosyl acceptors to synthesize more complex glycosides with biological importance.[9a,12] This method is complementary to the glycosylation of phenols with glycosyl donors and provides an alternative approach to the synthesis of phenolic glycosides. It also offers new examples for the use of aryl boronic acids as versatile substrates in organic synthesis.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, characterization of compounds, and copies of NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.02.059.

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10. General experimental procedure. 1,2-Anhydrosugar **1a** (0.1 mmol, 1.0 equiv), aryl boronic acid (0.1 mmol, 1.2 equiv), and KO^{t}Bu (0.2 mmol, 2.0 equiv) were dissolved in THF (1.0 mL), the mixture was stirred at 50 °C in a sealed tube overnight. After the completion of the reaction, the mixture was filtrated through Celite and then the filtrate was evaporated to dryness. The residue was purified by column chromatography on silica gel (petroleum ether/acetone) to afford the desired product. For compound **3b**: white amorphous solid, R_f = 0.52 (petroleum ether/acetone = 2:1), 38.2 mg, 71% yield; $[\alpha]_D^{25}$ −3.9 (c = 0.28, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.27 (s, 3H), 2.39 (d, 1H, J = 2.4 Hz), 3.60–3.63 (m, 1H), 3.68–3.73 (m, 3H), 3.79 (dd, 1H, J = 1.9, 10.8 Hz), 3.85–3.90 (m, 1H), 4.53 (d, 1H, J = 12.4 Hz), 4.59 (d, 1H, J = 10.8 Hz), 4.60 (d, 1H, J = 12.0 Hz), 4.84 (d, 1H, J = 8.0 Hz), 4.87 (d, 1H, J = 10.8 Hz), 4.88 (d, 1H, J = 11.2 Hz), 4.96 (d, 1H, J = 11.2 Hz), 6.94–6.98 (m, 1H), 7.06–7.15 (m, 3H), 7.20–7.22 (m, 2H), 7.27–7.40 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.4, 68.8, 73.5, 74.5, 75.0, 75.2, 75.3, 77.4, 84.4, 101.5, 115.5, 122.7, 127.0, 127.6, 127.7, 127.8, 127.8, 127.9, 128.0, 128.3, 128.4, 128.5, 130.8, 138.0, 138.1, 138.5, 155.5; HRMS (ESI) calcd for $C_{34}H_{36}O_6Na$ [M+Na]$^+$: 563.2404, Found: 563.2415.
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