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# Organo-zinc Promoted Diastereoselective *C*-Arylation of 1,2-Anhydrosugars from Arylboronic Acids

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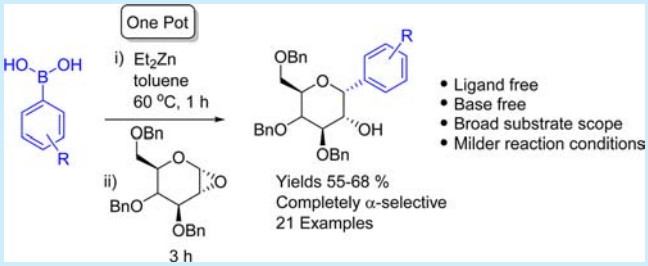
Supporting Information

**ABSTRACT:** α-*C*-arylglycosides can be obtained through the addition of aryl zinc reagents to sugar epoxides. The required aryl zinc nucleophiles can be easily obtained from the corresponding boronic acids by B−Zn exchange and attack sugar 1,2 epoxides in a highly diastereoselective fashion to generate 1,2-*cis*-α-hexapyranosyl aryl glycosides under ligand- and base-free conditions.




*C*-Aryl glycosides are an important class of compounds often possessing significant biological properties.[1] Several of them,

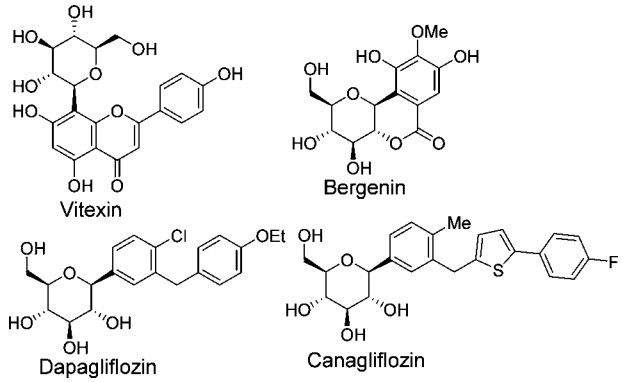
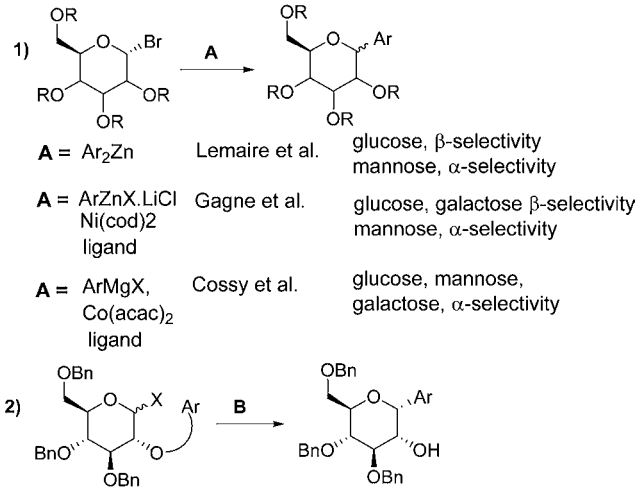



**Figure 1.** Medicinally important *C*-aryl glycosides.

such as Vitexin, Orientin,[2] Bergenin,[3] and Papulacandin D[4] (Figure 1), are naturally occurring with promising medicinal activity. They can also serve as inhibitors of carbohydrate processing enzymes.[5] The importance of aryl *C*-glycosides can be realized from the fact that some of them (Figure 1) are now FDA approved drugs for diabetics,[6] e.g. Dapagliflozin, Canagliflozin, etc.

Although there are several methods for the synthesis of the β-aryl glycosides,[7] only a few methods are available for the α-epimers.[8] One way of achieving this is to perform metal-catalyzed cross-coupling reactions between 1-bromo glycosides and organometallics where stereoselectivity depends strongly on the nature of the sugar unit; e.g., bromo mannoside and galactoside afforded desired α-glycosides whereas bromoglucosides gave a mixture of anomers, all in moderate yield. From a synthetic point of view, the stereoselective generation of 1,2-*cis*-α-hexapyranosyl aryl glycosides is challenging and only one report is available in the literature which deals with the intramolecular delivery of the aryl group from a 2-*O*-aryldialkylsilyl substituent.[8b] However, the above-mentioned method requires multistep generation of a monosaccharide unit with a silicon-tethered electron-rich aryl group at the 2-position and an *O*-pentenyl group at the anomeric center, thus limiting the substrate scope.[8b]

**Literature Reports for α-*C*-Arylation**




It is therefore desirable to have a direct practical strategy for the synthesis of medicinally important 1,2-*cis*-α-hexapyranosyl aryl glycosides with a broad substrate scope and predictable stereoselectivity. In continuation of our efforts in the field of *C*-

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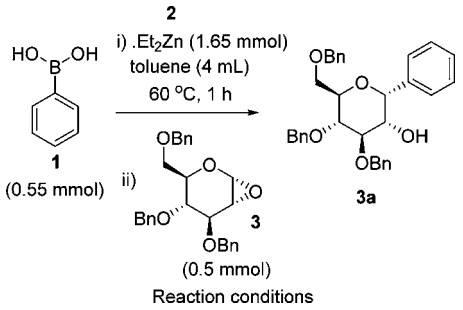
**Table 1. Optimization of Diethylzinc (2) Promoted One-Pot Arylglycosylation Using Phenylboronic Acid (1) and Glucal Epoxide (3)**

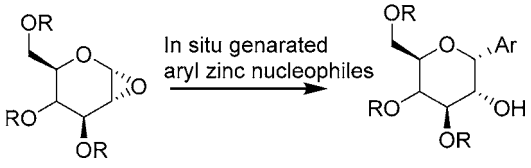



| | reaction conditions | | | | | |
|---|---|---|---|---|---|---|
| entry | solvent | $t$ (°C) | additive[a] | time (h) | yield[b] (%) | $\alpha/\beta$[c] |
| 1 | toluene | rt | – | 6 | 36 | $\alpha$ only |
| **2** | **toluene** | **60** | – | **3** | **68**[d] | **$\alpha$ only** |
| 3 | THF | rt | – | 6 | 25 | 20/1 |
| 4 | DCM | rt | – | 6 | 20 | 20/1 |
| 5 | toluene | rt | $BF_3{\cdot}OEt_2$ | 0.33 | 35 | 20/1 |
| 6 | toluene | rt | $ZnCl_2$ in THF | 0.33 | 42 | $\alpha$ only |
| 7 | toluene | rt | $AlCl_3$ in THF | 0.33 | 40 | 20/1 |
| 8 | toluene | rt | $ZnBr_2$ in toluene | 0.33 | 45 | $\alpha$ only[e] |
| 9 | toluene | rt | $Cu(OTf)_2$ | 0.33 | 20 | 3/1 |

[a]20 mol % of Lewis acid was used. [b]Isolated yields. [c]Diastereomeric ratio determined from $^1$H NMR of crude product. [d]Other minor byproducts were ethyl glycoside (15–20%) and diol from hydrolysis of the epoxide. [e]Under the same reaction conditions, 20% of $\beta$-arylglycoside was obtained when phenylboronic acid was replaced by 4-*tert*-butylphenylboronic acid.

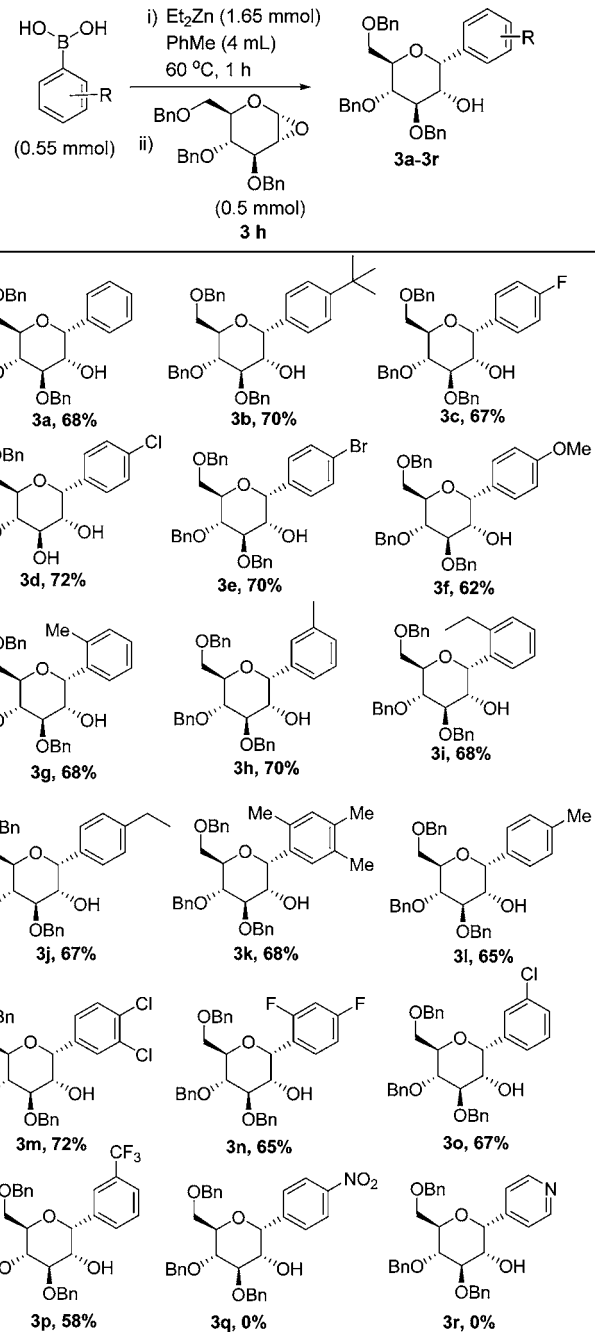
glycosylation,[9] now we would like to disclose a ligand- and base-free general strategy for the diastereoselective synthesis of $\alpha$-*C*-aryl glycosides through regioselective ring opening of 1,2-anhydro sugars with aryl zinc reagents derived by facile B–Zn exchange. There are a few reports available in the literature which describe the opening of 1,2-sugar epoxides by different organometallic nucleophiles such as phenyl-derived aluminum,[11a] titanium,[11b] boron,[11c] zinc,[11d,e] magnesium,[11f,g] copper,[11h] and lithium[11i] reagents. However, it is difficult to predict the stereochemical outcome of such processes, which appears to be substrate and/or nucleophile specific, and sometimes mixtures of $\alpha$- and $\beta$-*C*-glycosides are obtained.[8a] Further, site nonspecific metal–halogen exchange for *dihalo*-substituted aryl compounds can generate undesired side products making them synthetically less practical. Other limitations include the lack of commercial availability of many aryl nucleophiles and requirement for conducting reactions at cryogenic temperatures.[11]

**Current approach**




In order to overcome all these above limitations we thought of an alternative strategy for the opening of glycal epoxides by arylzinc reagents generated from aryl boronic acids and

**Scheme 1. Substrate Scope of Arylboronic Acids for $\alpha$-Arylation with Glucal Epoxide**




diethylzinc.[12] The organozinc species could be easily generated[13] from the corresponding readily available[14] arylboronic acids via a facile B–Zn exchange process thereby greatly expanding the scope of *C*-aryl glycoside formation.

With the above-mentioned background, we initiated our study with phenylboronic acid (**1**), which was converted to requisite phenyl zinc reagent by the reaction with diethyl zinc reagent in toluene. The exchange reaction occurred within 1 h at 60 °C. Subsequent addition of glucal 1,2-epoxide (**3**) resulted in a new product which was characterized as the aryl glycoside from spectroscopic analysis. The stereochemistry of the $\alpha$-*C*-glycosides was assigned from the coupling constant, the $J_{1,2}$ value ranging from 4.2 to 5.9 Hz. This small $J_{1,2}$ value was indicative of their *cis* arrangement ($\alpha$-*C*-aryl glycosides) which



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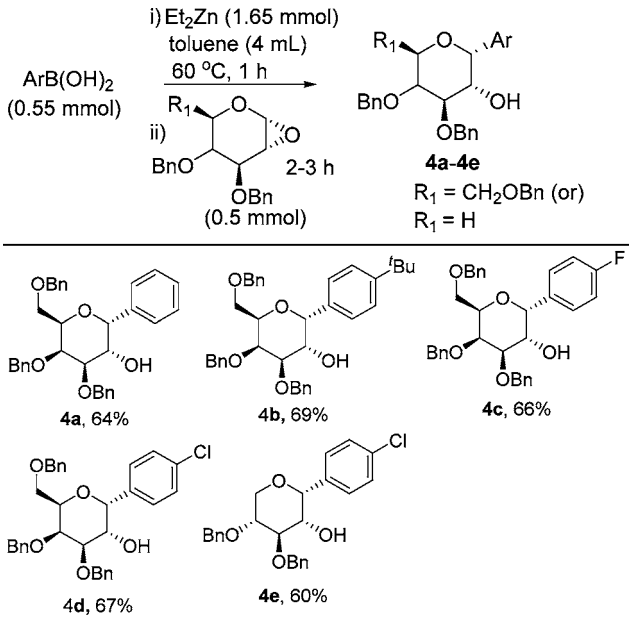
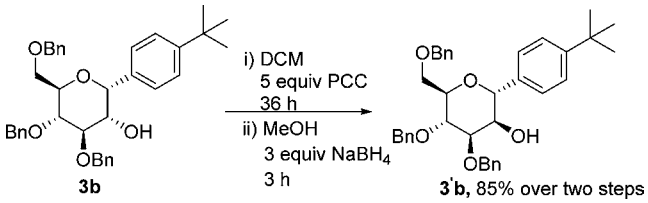
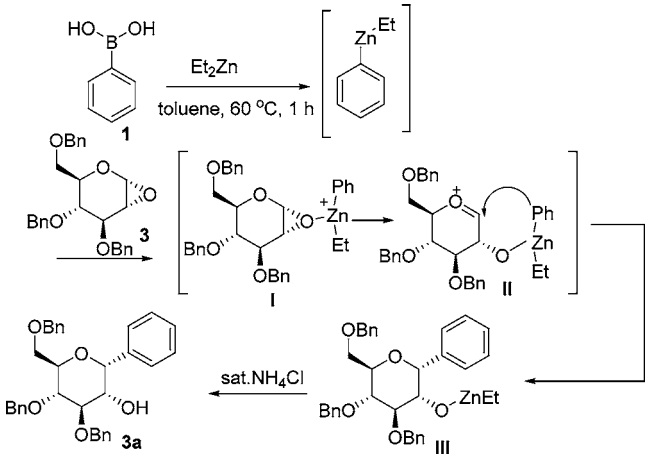
**Scheme 2. Substrate Scope for α-Arylation with D-Galactal and D-Xylal Epoxide**




**Scheme 3. Conversion of α-Arylglucoside to α-Arylmannoside**




**Scheme 4. Plausible Mechanism for the Formation of α-Aryl Glycoside**




was further confirmed by comparing the literature data.[11a] Other aprotic solvents such as $CH_2Cl_2$ and THF failed to give satisfactory yields, thus identifying toluene as the solvent of choice. It is pertinent to mention that addition of external Lewis acids such as $BF_3{\cdot}OEt_2$, $AlCl_3$, $Cu(OTf)_2$, $ZnCl_2$, and $ZnBr_2$ (Table 1, entries 5−9) only accelerated the product formation with decreased yield and selectivity Surprisingly, addition of the external Lewis acid $ZnBr_2$ in toluene led to the formation of the β-aryl glycoside in lower yield when 4-*tert*-butylphenylboronic acid (Table 1, footnote e) was used as the aryl nucleophile.

The substrate scope of this methodology was tested using various phenylboronic acids (**3b**−**3p**) derived from electron-rich and electron-deficient aryl boronic acids, and the results are summarized in Scheme 1. The reaction worked well in the case of aryl nucleophiles derived from electron-rich aryl boronic acids, and the desired products (**3f**, **3k**) were obtained in reasonably good yield.

In the case of *dihalo* substituted phenylboronic acid, chemoselective activation of boron in the presence of a halogen occurred to afford the corresponding products (**3m**, **3n**). Finally in the case of *o*/*m*/*p*-alkyl substituted aryl boronic acids, the expected products (**3b**, **3g**−**3j**, **3l**) were isolated in good yields. Unfortunately 4-nitro phenyl (**3q**) and 4-pyridyl boronic acids (**3r**) failed to react under the optimized reaction conditions.

This methodology was further elaborated to other glycal epoxides such as D-galactal epoxide and D-xylal epoxide, and in those cases the expected products (Scheme 2, **4a**−**4e**) were isolated in good yields. Even though it is not possible to synthesize arylmannosides via this method, it is easy to convert α-*C*-arylglucoside to α-*C*-arylmannosides (Scheme 3) by oxidation−reduction due to the availability of the free *C*-2 hydroxyl group.

The high diastereoselectivity observed for the α-arylation of the sugar epoxides may be explained in the following way (Scheme 4). The Lewis acidic character of *in situ* generated PhZnEt activates the epoxide ring (I, Scheme 4) and thereby assists oxocarbonium ion (II) formation. The intramolecular delivery of the aryl substituent to the anomeric carbon may take place thereafter. In this working model, the *syn* attack of the arylzinc reagent to the anomeric carbon results in diastereomerically pure α-aryl glycoside.

In summary, we have developed an organo-zinc promoted diastereoselective *C*-arylation of 1,2-anhydrosugars from aryl boronic acids. High diastereoselectivity was achieved using these *in situ* generated, ortho/meta/para-substitued arylzinc reagents and sugar epoxides. Our methodology allows transfer of a broad range of aryl groups, since a large number of arylzinc reagents can be efficiently prepared from the corresponding boronic acids. The presence of a free C-2 hydroxyl group in the products makes them a suitable acceptor for 2-branched oligosaccharide or natural product synthesis.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02364.

Experimental procedures; $^1H$, $^{13}C$ spectra of all compounds (PDF)

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### Notes

The authors declare no competing financial interest.
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