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Stereocontrolled Synthesis of 2-Deoxy-C-glycopyranosyl Arenes Using Glycals and Aromatic Amines

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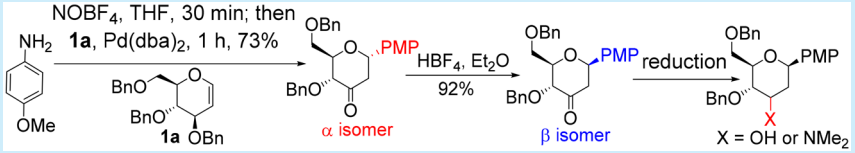
Supporting Information

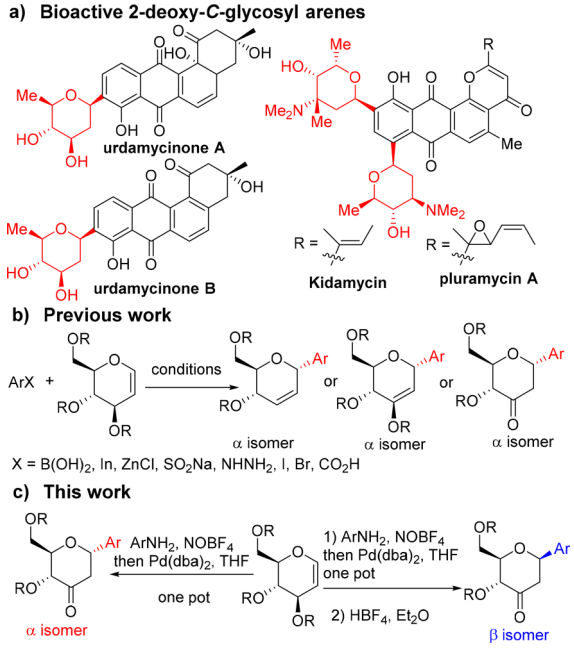


ABSTRACT: An efficient and stereoselective one-pot, two-step tandem α-arylation of glycals from readily available aryl amines via stable diazonium salts has been developed. Moreover, the stereoselective preparation of the challenging β-*C*-glycosyl arenes by the anomerization of α-*C*-glycosides using HBF_4 is also described. This protocol has a broad substrate scope and a wide functional-group tolerance. It can be used for the gram-scale preparation of 3-oxo-*C*-glycosides, which are versatile substrates for the preparation of many biologically important *C*-glycosides.

The *C*-glycopyranosyl motif is present in numerous biologically active compounds and drugs such as angucyclines, marmycin A−B, urdamycinones A−D, kidamycin, pluramycin A, canagliflozin, dapagliflozin, and ipragliflozin (Scheme 1a).[1] A key carbon−carbon glycosidic bond between the aglycon carbon and the anomeric carbon of the attached carbohydrate confers remarkable stability against both enzymatic and/or chemical hydrolysis, thus improving the physiological efficacy of a bioactive compound. Therefore, carbon−carbon glycosidic bond construction is one of the enduring and crucial goals of organic synthesis.[2] Transition-metal-catalyzed coupling reactions are powerful tools for the construction of unique *C*-glycosyl linkages.[3] Especially, Heck-type arylations of glycals[4] with arylboronic acids,[5] triarylindium reagents,[6] arylzinc reagents,[7] arylhydrazines,[8] sodium arylsulphinates,[9] aryl bromides/iodides,[10] aromatic acids,[11] and others have been developed.[12] Indeed, all have now been extensively employed as useful approaches for the synthesis of 2-deoxy-α-*C*-D-glycosyl arenes (Scheme 1b). Nevertheless, these reactions suffer from some limitations such as limited substrate scope, low yield, long reaction time, or byproducts. Moreover, these transformations are unable to generate 2-deoxy-β-D-glycosyl arenes, which are naturally occurring *C*-glycosides. Therefore, the development of more practical and stereoselective protocols for the synthesis of 2-deoxy-*C*-glycosyl arenes from readily accessible starting materials still remains a challenge.

Aryl diazonium salts are ideal electrophilic partners for palladium-catalyzed coupling reactions at room temperature under mild conditions, especially for a Heck reaction of allylic alcohols/esters.[13] Glycals are somewhat similar to allylic

Scheme 1. Some Bioactive 2-Deoxy-*C*-glycosyl Compounds and Their Transition-Metal-Catalyzed Synthetic Methods



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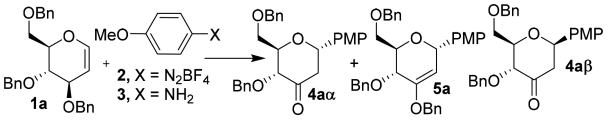
alcohols/esters. However, diazonium salts are absent from *C*-glycoside synthesis. The instability and explosive nature of the salts might be the main restriction on their widespread application. Nevertheless, the *in situ* diazotization of readily available anilines is an alternative safe way to diazonium salts.[14] So, we herein report a stereocontrolled protocol for the synthesis of 2-deoxy-*C*-glycopyranosyl arenes from glycals and aromatic amines (Scheme 1c).

We embarked on our investigation by studying the arylation of glucal **1a** with 4-methoxybenzenediazonium tetrafluoroborate (**2**) in the presence of various Pd catalysts and additives at room temperature for 1 h (Table 1). No arylation occurred utilizing

Table 1. Screening of the Reaction Conditions[a,b]



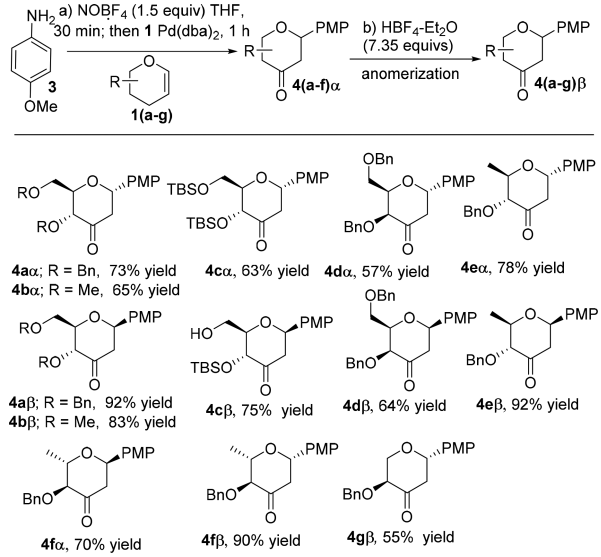
entry	conditions	yield (%) of **4a**	yield (%) of **5a**
1	**2**, $Pd(OAc)_2$	α (0)	0
2	**2**, $Pd(OAc)_2$, PPh_3 (20%)	α (34)	25
3	**2**, $Pd(PPh_3)_4$	α (36)	31
4	**2**, $Pd(PPh_3)_4$, Xanphose (20%)	α (33)	30
5	**2**, $Pd(dba)_2$	α (81)	0
6	**2**, $Pd(dba)_2$, PPh_3 (20%)	α (74)	0
7	**2**, $Pd(dba)_2$, $NaHCO_3$ (10 equiv)	α (53)	26
8	**2**, $Pd(dba)_2$, K_2CO_3 (10 equiv)	α (56)	17
9	**2**, $Pd(dba)_2$, HOAc (10 equiv)	α (76)	0
10[c]	**3**, $Pd(dba)_2$, $NaNO_2$, HBF_4	α (0)	0
11[c,d]	**3**, $Pd(dba)_2$, $NaNO_2$, HBF_4	α (0)	0
12[c]	**3**, $Pd(dba)_2$, ^{t}BuONO, HBF_4	α (0)	0
13[c]	**3**, $Pd(dba)_2$, $NOBF_4$	α (73)	0
14[e]	**4aα**, HBF_4	β (92)	0

[a]Reaction conditions: **1a** (21.0 mg, 0.05 mmol), Pd catalyst (0.0075 mmol), and **2** (22.0 mg, 0.1 mmol) in THF (4 mL) at room temperature for 1 h. [b]Isolated yield. [c]**3** (31.0 mg, 0.25 mmol) and $NaNO_2$/Me_3CNO_2/$NOBF_4$ (0.25 mmol) in THF (4 mL) at −40 °C to room temperature for 30 min; then **1a** (42.0 mg, 0.1 mmol) and $Pa(dba)_2$ (0.015 mmol) at room temperature for 1 h. [d]MeOH as the solvent. [e]**4aα** (10.0 mg) and HBF_4-Et_2O complex (50−75 μL) in Et_2O (1 mL) at room temperature for 1 h. PMP = *p*-methoxyphenyl.

$Pd(OAc)_2$ as the catalyst (entry 1). The desired α-arylation products **4aα** (34% yield) and **5a** (25% yield) were, however, obtained in the presence of PPh_3 (entry 2). The use of $Pd(PPh_3)_4$ as the catalyst, with or without Xanphose as the ligand, led to similar results (entries 3−4). To our delight, only **4aα** (81% yield) was obtained when the reaction was catalyzed by $Pd(dba)_2$ instead of $Pd(PPh_3)_4$ (entry 5). Further optimization studies of other additives did not increase the yield of **4aα** (Table 1, entries 6−9; Table S1, entries 1−19). Next, compound **2**, generated *in situ* by different methods from amine **3**, was applied to the above optimal conditions. After screening different diazotizing reagents (entries 10−13), $NOBF_4$ proved the best. Diazotization of amine **3** with $NOBF_4$ in THF at 0 °C for 30 min, followed by the treatment of glycal **1a** and $Pd(dba)_2$ at room temperature for 1 h, gave 2-deoxy-α-D-glycosyl arene **4aα** in 73% isolated yield (entry 13). By this point, we had established an efficient method to produce α-*C*-glycosides via the arylation of glycals from aryl amines. In addition, the α-*C*-glycosides could be further transformed into β-*C*-glycosides through the action of HBF_4-Et_2O complex (Table 1, entry 14, for more details on condition screening, see Table S2 in the Supporting Information (SI)).

With the optimized reaction conditions in hand, a variety of glycals were subjected to these arylation/anomerization reactions (Scheme 2). The reactions of methylated glucal or

Scheme 2. *C*-Glycosylation of *p*-Anisidine (3) with Glycals and Anomerization[a]



[a]The *C*-glycosylation conditions (see Table 1, entry 13); the anomerization conditions (see Table 1, entry 14); isolated yield.

benzylated galactal/6-deoxy-glucal/rhamnal afforded the corresponding α- or β-linked product in 57−92% yields. The *tert*-butyldimethylsilyl protective group was well tolerated under the arylation conditions (product **4cα**), whereas the anomerization product **4cβ** was partially desilylated. It is noteworthy that the reaction of benzylated L-arabinal with amine **3** could only generate **4gβ**, which is a thermodynamically stable arylation product whose anomerization is forbidden.

Subsequently, we explored the scope of the aryl amines; the results are summarized in Table 2. Aryl amines bearing both electron-withdrawing and electron-donating substituents underwent the reactions smoothly, affording the corresponding α-products in moderate to good yields. The anomerization of 2-deoxy-α-*C*-D-glycosyl arenes with electron-donating substituents could provide the β-products in excellent yields (entries 4, 15). To our delight, β-*C*-glycosides were accessed in moderate yields from the arenes with electron-withdrawing substituents. The ring-opened compound **6** was detected in 25% yield when α-*C*-D-glycosyl *para*-bromobenzene (**4iα**) was converted to its β-counterpart (**4iβ**). Interestingly, compound **6** was inert to the anomerization conditions (Scheme 3A). This is quite a common occurrence as the aryl moiety contains electron-withdrawing substituents. To further demonstrate the practicality of this newly developed method, the reaction of **3** and **1f** was carried out on 6.44 mmol scale (entry 15). Product **4fα** was obtained in 58% isolated yield (1.20 g). Anomerization of **4fα** was performed on 3.68 mmol scale, and **4fβ** was afforded in 98% isolated yield (1.18 g).

The anomeric configurations were mainly confirmed by the values of the $J_{1,2}$ coupling constant. That is, a large $J_{1,2}$ constant was assigned for a $^4C_1$ (D, β, >10 Hz), $^1C_4$ (L, β, >10 Hz), or $^1C_4$ (D, α, ~9.5 Hz) conformer, and a small $J_{1,2}$ constant (<7.0 Hz)

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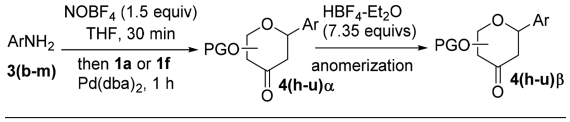
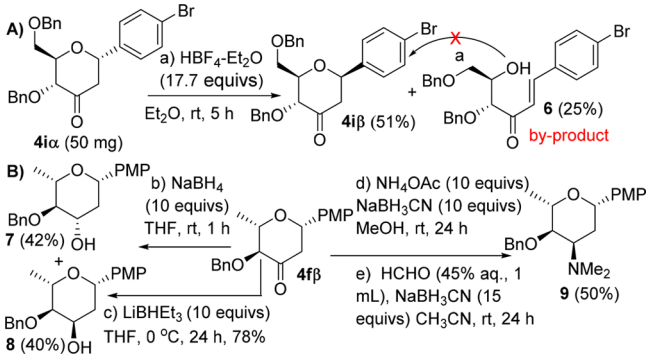
Table 2. *C*-Glycosylation of Glycals with Various Amines and Anomerization[a,b]



entry	amine	yield (%) of **4α**	Yield (%) of **4β**
1	**3b**	**4hα**, 76%	**4hβ**, 61%
2	**3c**	**4iα**, 78%	**4iβ**, 51%
3	**3d**	**4jα**, 73%	**4jβ**, 63%
4	**3e**	**4kα**, 76%	**4kβ**, 90%
5	**3f**	**4lα**, 64%	**4lβ**, 62%
6	**3g**	**4mα**, 69%	**4mβ**, 60%
7	**3b**	**4nα**, 80%	**4nβ**, 45%
8	**3c**	**4oα**, 75%	**4oβ**, 42%
9	**3h**	**4pα**, 78%	**4pβ**, 65%
10	**3i**	**4qα**, 49%	**4qβ**, 52%
11	**4j**	**4rα**, 60%	**4rβ**, 41%
12	**3k**	**4sα**, 63%	**4sβ**, 45%
13	**3l**	**4tα**, 69%	**4tβ**, 36%
14	**3m**	**4uα**, 66%	**4uβ**, 35%
15[c]	**3**	**4fα**, 58[d]	**4fβ**, 98[e]

[a]For the *C*-glycosylation conditions, see Table 1, entry 13; for the anomerization conditions, see Table 1, entry 14. [b]Isolated yield. [c]Gram-scale reaction. [d]Amine **3** (2.0 g, 16.2 mmol, 2.5 equiv), **1f** (2.0 g, 6.44 mmol), and $Pa(dba)_2$ (0.97 mmol) were used at room temperature for 3 h. [e]Substrate **4fα** (1.2 g, 3.68 mmol), HBF_4 (2.5 mL), and Et_2O (100 mL) were used at room temperature for 1.5 h.

Scheme 3. Transformation of 4i*α* and 4f*β*

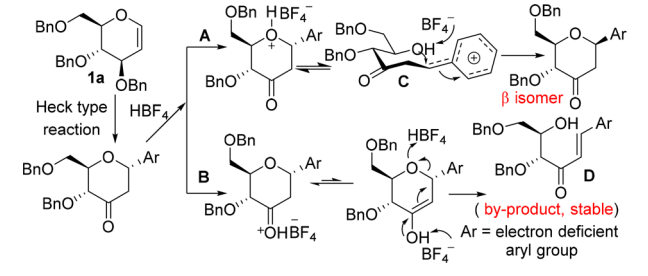


was assigned for a $^4C_1$ (D, *α*, <7.0 Hz) or $^1C_4$ (L, *α*, <7.0 Hz) conformer. Others were assigned on the basis of the NMR spectra of known compounds or the 2D NMR spectra.

Next, the generated 2-deoxy-3-oxo-*C*-glycosides were transformed into 3-hydroxy or 3-dimethylamino 2-deoxy-*C*-glycosides (Scheme 3B), which are valuable *C*-glycosyl motifs in bioactive natural products. Reduction of compound **4f*β*** using $NaBH_4$ afforded 42% yield of the alcohol **7** and 40% yield of the alcohol **8** with no stereoselectivity. When $LiBHEt_3$ was employed, the alcohol **8** was obtained in 78% yield as a single isomer. Treatment of **4f*β*** with NH_4OAc and $NaBH_3CN$ formed 3-amino-*C*-glycoside, which was subsequently converted into the expected 3-dimethylamino-*C*-glycoside **9** (50% yield) in the presence of HCHO and $NaBH_3CN$. The structures of compounds **7**, **8**, and **9** were unambiguously identified by their NMR analyses (Scheme S2 in the SI).

Although the formation mechanism of *α*-*C*-glycosides from glycals and aryl diazonium salts via a Heck-type reaction is clear,[5,15] the details of this anomerization reaction are not yet known. Thus, a plausible mechanism, based on the combination of the previous work of Suzuki, Zou, and our group, through our observations, is proposed (Scheme 4). We propose that HBF_4

Scheme 4. Plausible Mechanism



activates the O5 oxygen, resulting in an endocyclic C1−O5 bond cleavage to generate the acyclic oxocarbenium C (pathway A in Scheme 4),[2,16] which would prefer to produce the *β*-product via a kinetic cyclization. If an electron-deficient aryl group is present, HBF_4 promotes activation of the O3 oxygen to produce the stable byproduct D (pathway B in Schemes 4 and 3A).

In conclusion, for the first time, we have disclosed the one-pot, two-step tandem *α*-arylation of glycals from readily available aryl amines via a stable diazonium salt offering exclusive 3-oxo-*α*-*C*-glycosides. Furthermore, the challenging *β*-*C*-glycosyl arenes can be obtained from anomerization of *α*-*C*-glycosides in the presence of HBF_4. The protocols can be used for the gram-scale preparation of the products and show a broad substrate

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scope and wide functional-group tolerance. The versatile 3-oxo-*C*-glycosides can be easily transformed into other bioactive natural *C*-glycosyl motifs, thereby expanding the usefulness of the methods. Given all of the advantages, our protocols could find wide applications in the preparation of many biologically important *C*-glycosides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01117.

Detailed experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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