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Palladium catalyzed stereocontrolled synthesis of *C*-aryl glycosides using glycals and arenediazonium salts at room temperature

Adesh Kumar Singh and Jeyakumar Kandasamy*

Department of Chemistry, Indian Institute of Technology (BHU), Varanasi, Uttar Pradesh-221005

ABSTRACT: A stereocontrolled synthesis of aryl-*C*-glycosides was achieved using glycals and aryldiazonium salts in the presence of palladium acetate. A wide range of glycals including D-glucal, D-galactal, L-rhamanal, D-xylal and D-ribal underwent *C*-arylation at the anomeric carbon in the presence of different aryldiazonium tetrafluoroborates and gave synthetically useful 2,3-deoxy 3-keto α-aryl-*C*-glycosides in good to excellent yields. Broad substrate scope, simple operation and room temperature reactions make this protocol very attractive in organic synthesis.

Carbohydrates play an important role in biological system, which are used not only as source of energy, but also drugs, diagnostic tools, vaccines, drug targets, etc.[1] Aryl *C*-glycoside is one of the distinct motifs found in various bio-active molecules and natural products, thus attracted tremendous interest in synthetic organic chemistry (Figure 1).[2] Aryl glycosides are typically achieved by Friedel-Crafts alkylation of electron-rich arenes with glycosyl donors[3] or by the reaction of protected aldonolactones with organometallic reagents such as aryllithium or Grignard reagents.[4] Alternatively, coupling reaction between glycosyl bromides and arylzinc reagent has been reported to provide β-arylated glycosides.[5] On the other hand, palladium catalysed coupling reaction of glycals with various aryl donors such as arylboronic acids,[6] arylhydrazines,[7] arylzinc reagents,[8] aryl halides,[9] etc.[2, 10] have been recently demonstrated for the preparation of various aryl *C*-glycosides.

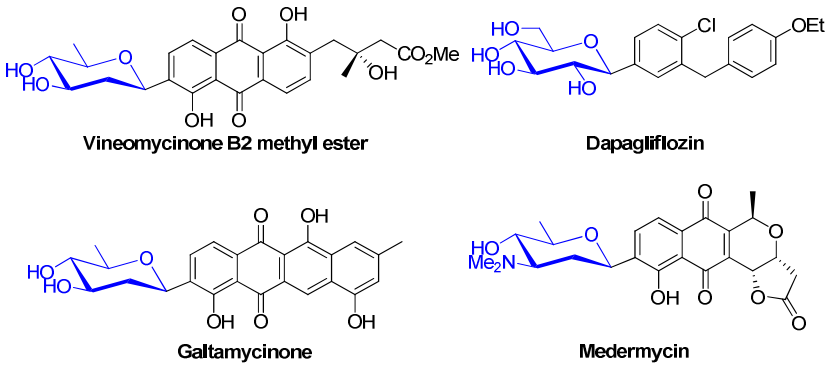

Figure 1. Structures of some bioactive aryl *C*-glycosides.

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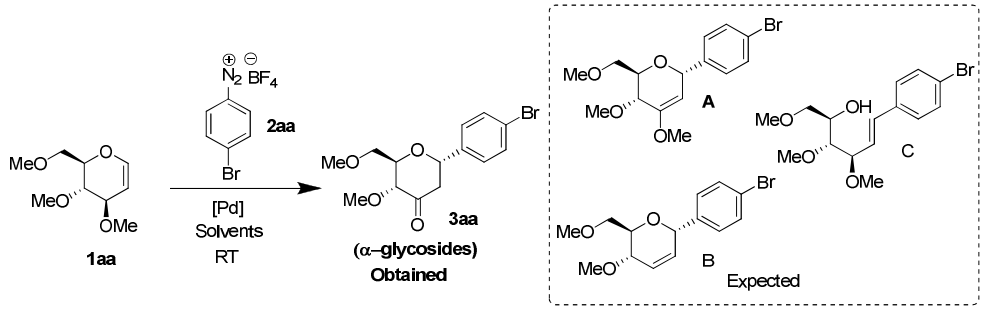
Arenediazonium salts are highly useful aryl donors which can be easily obtained from corresponding anilines.[11] Aryl diazonium salts have been identified as an efficient alternative to arylhalides and arylboronic acids in Pd-catalyzed cross-coupling reactions.[11a] Recently, palladium mediated Heck-type cross coupling between glycal and arylboronic acid was explored by Ye *et al.*[6a, 6c] and Mukherjee *et al.*[6b] In this context, we have envisioned that arenediazonium salts can be used as an efficient alternative to arylboronic acids to prepare aryl-*C*-glycosides,[12] because, the inherent electrophilicity of diazonium salts might allow the coupling reaction under mild reaction conditions in the absence of ligand or base.[11a,11b]As part of our ongoing research on glycosylation reactions,[13] here we report an efficient preparation of synthetically useful 2,3-deoxy 3-keto α-aryl-*C*-glycosides from the corresponding glycals and aryldiazonium salts in the presence of palladium catalyst.

At the outset, the glycosylation of *O*-permethylated glucal (**1aa**) was investigated with 4-bromobenzenediazonium tetrafluoroborate (**2aa**) in various solvents in the presence of different palladium salts (Table 1). Initially, the reaction was performed with 5 mol% of palladium acetate in methanol at room temperature without any base or ligand. The reaction underwent smoothly resulting in a new product within 60 mins (Table 1, entry 1). Going by the previously reported literature pertaining to boronic acid and the glycal,[6a, 6c, 6e] one of the Ferrier rearrangement products (**A**-**C**) was only expected as shown in Table 1. Surprisingly, unlike boronic acid, the reaction provided 2,3-deoxy 3-keto α-aryl-*C*-glycoside (**3aa**) exclusively with 91% yield. In fact, formation of similar ketone product was previously reported with arylboronic acids, however, in the presence of external oxidants such as benzoquinone (BQ) or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[6c] Encouraged, we further tested the reaction in other solvents including DCM, dioxane, THF, acetonitrile, toluene and acetic acid (Table 1, entries 2-7). Among them, THF provides **3aa** in ~ 10% yield (Table 1, entry 4), while other solvents failed to provide the desired product. Further, the reaction was tested with water mixed DCM, methanol and acetonitrile in the presence of 5 mol% of $Pd(OAc)_2$ at room temperature (Table 1, entries 8-10). Interestingly, acetonitrile-water (3:1) was found to be equally good as of methanol and gave the desired product **3aa** in 90% yield within 1.5 h (Table 1, entry 10). Further, the optimal conditions were investigated with other typically used Pd(0) and Pd(II) catalysts such as $Pd(dba)_2$, $Pd(PPh_3)_4$, $Pd(TFA)_2$, $PdCl_2$ and $PdCl_2(CH_3CN)_2$ (Table 1, entry 11-15). Among them, $Pd(dba)_2$ and $Pd(TFA)_2$ showed equal efficiency to that of palladium acetate (Table 1, entry 11 & 13), while other catalysts gave the desired product **3aa** in a low yield (i.e. <30%).

Table 1. Optimization of the reaction condition with 4-bromobenzenediazonium tetrafluoroborate.[a]

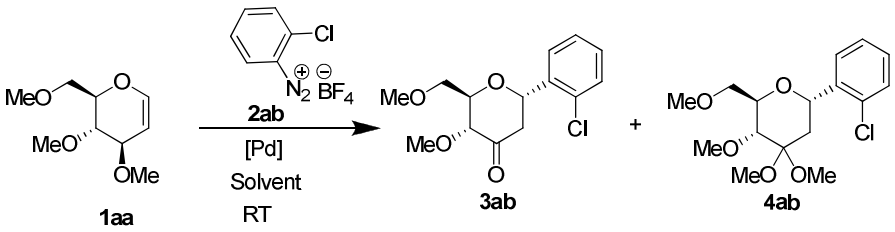


Entry	Catalyst (5 mol%)	Solvent	Time (h)	Yield (%)[b] (3aa)
1	$Pd(OAc)_2$	Methanol	1	91
2	$Pd(OAc)_2$	DCM	1	nd
3	$Pd(OAc)_2$	Dioxane	1	nd
4	$Pd(OAc)_2$	THF	1	~10
5	$Pd(OAc)_2$	CH_3CN	1	nd
6	$Pd(OAc)_2$	Toluene	1	nd
7	$Pd(OAc)_2$	CH_3COOH	1	nd
8	$Pd(OAc)_2$	DCM:H_2O (3:1)	2.5	70
9	$Pd(OAc)_2$	MeOH:H_2O (3:1)	1.5	87
10	$Pd(OAc)_2$	CH_3CN:H_2O (3:1)	1.5	90
11	$Pd(dba)_2$	Methanol	1	89
12	$Pd(PPh_3)_4$	Methanol	1	30
13	$Pd(TFA)_2$	Methanol	1	86
14	$PdCl_2$	Methanol	1	10
15	$Pd(CH_3CN)_2Cl_2$	Methanol	1	10

[a]Reaction condition: Glucal **1aa** (95 mg, 0.5 mmol) and diazonium salt **2aa** (152 mg, 0.56 mmol, 1.1 equiv.) were stirred in a solvent (4 mL) following which the catalyst (0.025 mmol) was added. [b]Isolated yield.

Although, methanol was seen to be an efficient medium, it provides dimethyl acetal **4ab** as the product during the reaction of glucal **1aa** with 2-chlorobenzenediazonium tetrafluoroborate (**2ab**) (Table 2, entry 1). In fact, other active catalysts such as $Pd(dba)_2$ and $P(TFA)_2$ also gave **4ab** as the only product in similar yields (Table 2, entries 2 & 3). Nevertheless, the desired product **3ab** was successfully obtained in 89% yield when the reaction was performed in acetonitrile-water medium (Table 2, entry 4). Under this condition, palladium acetate was found to be slightly better than $Pd(dba)_2$ and $P(TFA)_2$ (Table 2, entries 5 & 6).

Table 2. Optimization of reaction condition with 2-chlorobenzenediazonium tetrafluoroborate.[a]



Entry	Metal salt	Solvent	Time (h)	Yield (%)[b]	
				3ab	**4ab**
1	$Pd(OAc)_2$	Methanol	1 h	nd	94
2	$Pd(dpa)_2$	Methanol	1 h	nd	90
3	$Pd(TFA)_2$	Methanol	1 h	nd	89
4	$Pd(OAc)_2$	CH_3CN:H_2O (3:1)	1.5 h	89	nd
5	$Pd(dba)_2$	CH_3CN:H_2O (3:1)	1.5 h	84	nd
6	$Pd(TFA)_2$	CH_3CN:H_2O (3:1)	1.5 h	82	nd

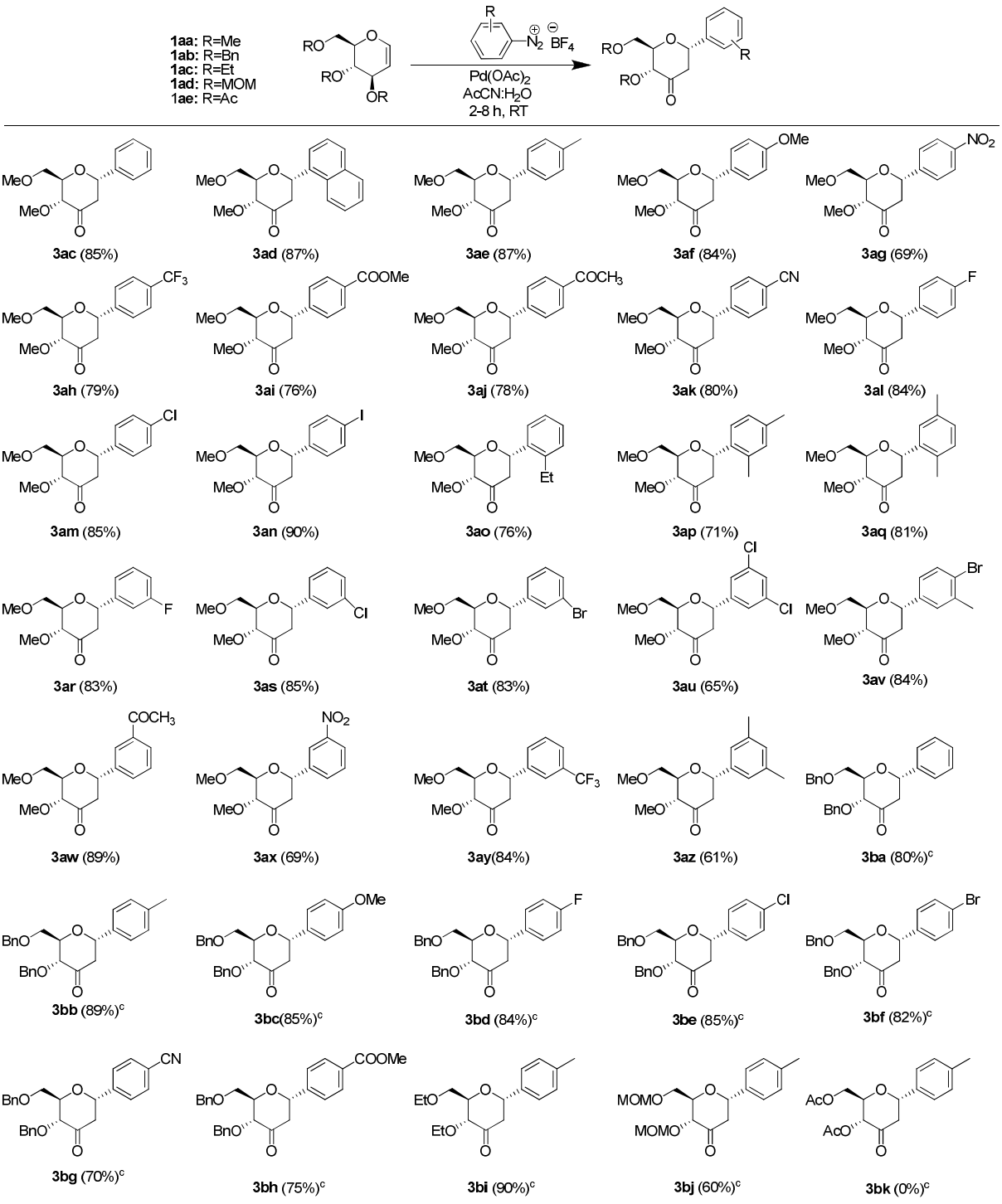
[a]Reaction condition: Glucal **1aa** (95 mg, 0.5 mmol) and diazonium salt **2ab** (125 mg, 0.55 mmol, 1.1 equiv.) were stirred in a solvent (4 mL) following which the catalyst (0.025 mmol) was added. [b]Isolated yield.

Having established the optimized condition, the reaction of permethylated glucal (**1aa**) with different aryldiazonium tetrafluoroborates was investigated and the results are summarized in Table 3. The unsubstituted phenyl and naphthyldizaonium salts as well as aryldizaonium salts bearing electron donating and withdrawing groups at the *para*- position underwent coupling reaction with glucal and gave the desired products **3ac-3an** in 69-90% yields. It was observed that strongly electron withdrawing groups (e.g. NO_2, CF_3, CO_2Me, $COCH_3$ and CN) functionalized phenyldiazonium salts gave the desired products (*i.e.* **3ag-3ak)** in slightly lower yields (i.e. 69-80%). Further, the *C*-arylation of glucal **1aa** was investigated with sterically hindered, *i.e. ortho*-functionalized phenyldiazonium salts. To our delight, the reactions were preceded with efficiency similar to that of *para*-substituted diazonium salts and gave the desired products **3ao-3aq** in 71-81% yields. Likewise, *C*-arylation of glucal (**1aa**) with *meta*-substituted diazonium salts was successfully accomplished to obtain the desired products **3ar-3az** in 61-89% yields.

Having studied the reaction with permethylated glycal (**1aa)** with different diazonium tetrafluoroborate salts, we further investigated the coupling of benzyl, ethyl and MOM-protected glucals (**1ab-1ad**) with different diazonium salts. All these reactions were preceded smoothly and gave the 3-keto *C*-aryl glucals **3ba-3bj** in 60-90% yields, which demonstrates the broad scope of the methodology. However, glycosylation was unsuccessful with tri-*O*-

acetyl-D-glucal (**1ae**) in the presence of 4-methylbenzenediazonium tetrafluoroborate under optimized conditions (Table 3, **3bk**).

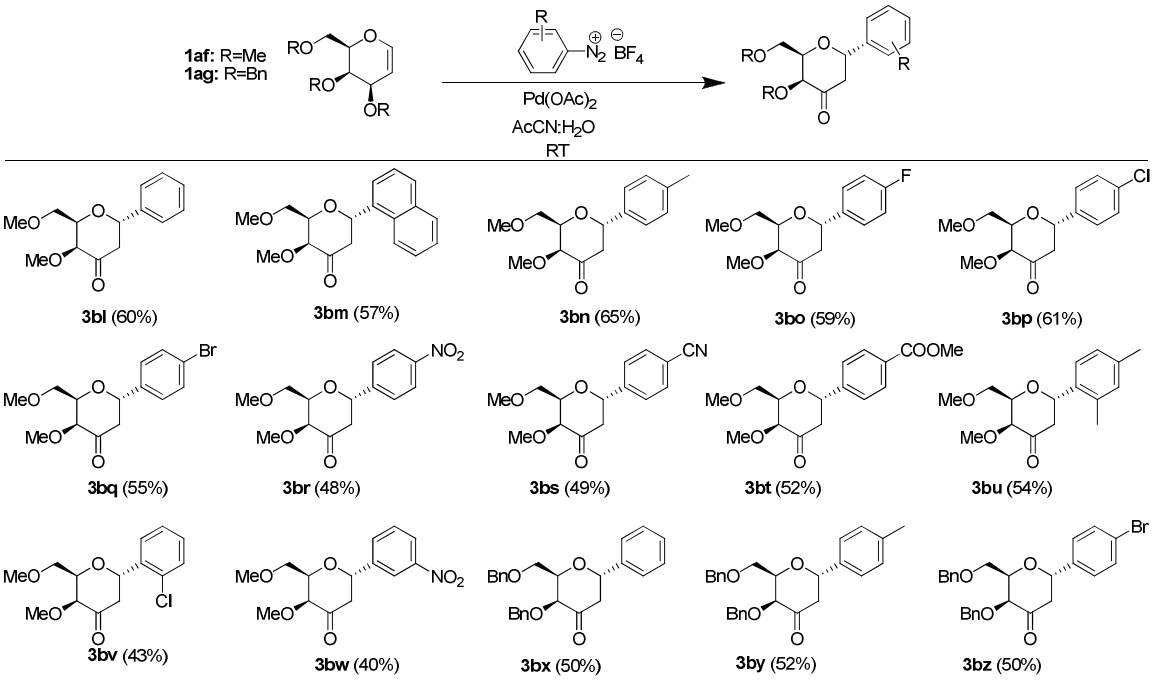
Table 3. Reaction of protected glucal with different aryldiazonium salts.[a,b]



[a]Reaction condition: Glucal (0.5 mmol) and diazonium salt (1.1 equiv.) were stirred in AcCN:H_2O (4 mL, 3:1) following which the catalyst $Pd(OAc)_2$ (5.5 mg, 0.025 mmol) was added. [b]Isolated yield.[c] $Pd(OAc)_2$ (11 mg, 0.05 mmol) was used.

Encouraged by the results obtained with differently protected glucals and diazonium salts, the reaction of protected galactal was studied under optimized conditions (Table 4). Initially, *C*-arylation of permethylated galactal (**1af**) was investigated with aryldiazonium tetrafluoroborates bearing electron donating and withdrawing groups. To our delight, *C*-aryl glycosylation proceeded smoothly at room temperature and resulted in the desired products **3bl**-**3bt** in 52-65% yields. Similarly, sterically hindered *ortho*-substituted diazonium salts as well as *meta*-substituted diazonium salts also underwent glycosylation with galactal (**1ae**) and provided **3bu-3bw** in 40-55% yields. To increase scope of the methodology, perbenzylated galactal (**1ag**) was subjected for glycosylation with different diazonium salts, which provided the desired ketones **3bx-3bz** in >50% yields. Over all, it was observed that the reaction of galactals (**1af** and **1ag**) with aryldiazonium salts provided lower yields to that of glucals (**1aa**-**1ad**).

Table 4. Reaction of protected galactal with different aryl diazonium salts.[a,b]



[a]Reaction condition: Galactal (0.5 mmol) and diazonium salt (1.1 equiv.) were stirred in AcCN:H_2O (4 mL, 3:1) following which the catalyst $Pd(OAc)_2$ (11 mg, 0.05 mmol) was added. [b]Isolated yield.

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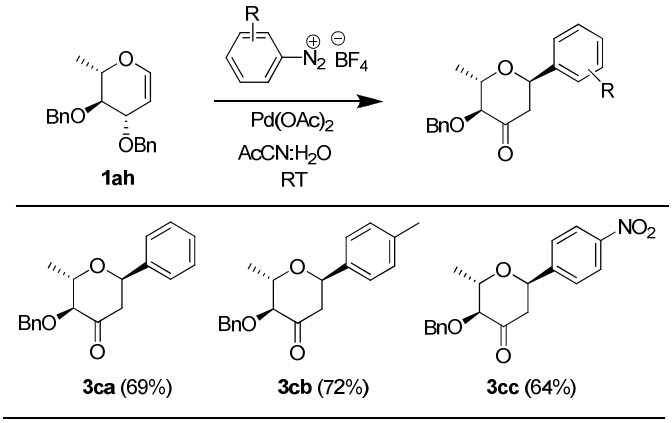
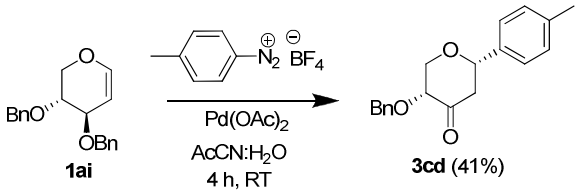
Table 5. Reaction of benzyl protected L-rhamnal **1ah** with diazonium salts.[a,b]



[a]Reaction condition: Rhamnal (0.5 mmol) and diazonium salt (1.1 equiv.) were stirred in AcCN:H_2O (4 mL, 3:1) following which the catalyst $Pd(OAc)_2$ (11 mg, 0.05 mmol) was added. [b]Isolated yield.

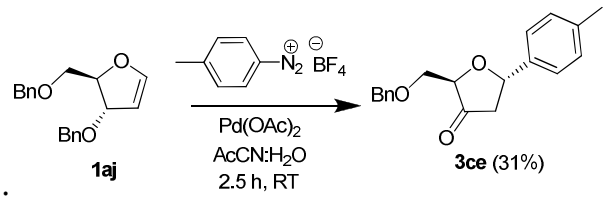
In order to study the versatility of this protocol, *C*-glycosylation of other hexose such as perbenzylated L-rhamnal and D-xylal (**1ah** and **1ai,** respectively) was investigated with different diazonim salts (Table 5 and Scheme 1). Similar to glucal, the reaction of L-rhamnal (**1ah**) with different diazonim salts proceeded smoothly under optimized conditions and gave the α-*C*-arylated products **3ca**-**3cc** in good to excellent yields (64-72%). Likewise, benzyl protected D-xylal (**1ai**) underwent *C*-arylation with 4-methylphenyldiazonium tetrafluoroborate successfully and gave the desired product **3cd** in 41% yield (Scheme 1).



Scheme 1. Reaction of benzyl protected D-xylal **1ai** with 4-methylbenzenediazonium tetrafluoroborate.

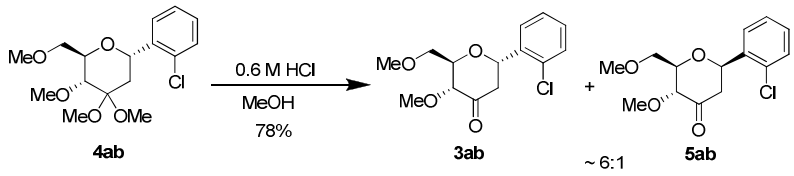
Considering the biological significance of 2-deoxypentose sugars, 4-methylphenyldiazonium tetrafluoroborate was subjected for glycosylation with benzyl protected D-ribal (**1aj**). To our delight, similar to pyranose glycals, the desired 2,3-deoxy 3-keto α-*C*-glycosylated product

3ce was obtained in 31% yield under optimized condition (Scheme 2). Overall, this protocol shows excellent substrate scope in *C*-aryl glycosylation reactions.



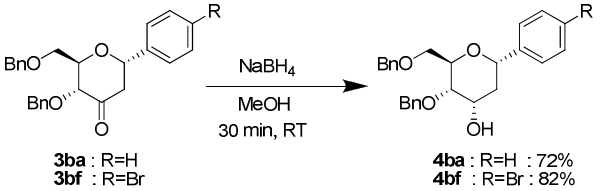
Scheme 2. Reaction of benzyl protected D-ribal **1aj** with 4-methylbenzenediazonium tetrafluoroborate tetrafluoroborate.

Of the two anomers of aryl-*C*-glycosides (i.e. α/β), β-isomers were most commonly found in natural products.[2] While attempting hydrolysis of dimethyl acetal **4ab**, we observed a mixture of anomeric products **3ab** (α-isomer) and **5ab** (β-isomer) in 6:1 ratio (Scheme 3). We propose that this acid catalyzed anomerization might be useful for the preparation of β-aryl-*C*-glycosides from corresponding α-glycosides.



Scheme 3. Acid catalyzed hydrolysis of dimethyl acetal **4ab**.

The resulted ketone compounds (*i.e.* **3aa**-**3ce**) are expected to have wide applications in carbohydrate synthesis. For instance, these compounds can serve as the starting materials for the preparation of 2-deoxy *C*-aryl glycosides. Thus, we have attempted the reduction of the ketones **3ba** and **3bf** using sodium borohydride in methanol. To our delight, the reaction proceeded smoothly at room temperature and gave 2-deoxy-α-aryl D-allose derivatives **4ba** and **4bf** in >70%, as a single isomer (Scheme 4).[14]



Scheme 4. Reduction of **3ba** and **3bf** using sodium borohydride.

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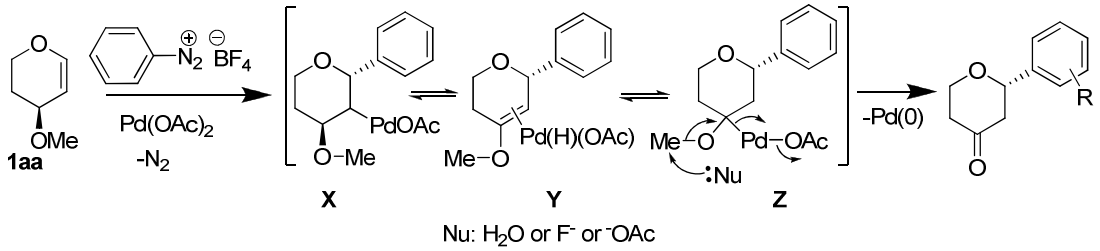
A plausible mechanism of the palladium catalyzed *C*-arylation of glycal is shown in Scheme 5.[11] At first, the oxidative addition of the palladium to the aryldiazonium salt in the presence of glycal provides the intermediate **X** which undergoes β-elimination to form palladium enol ether **Y**.[11c] Palladium-hydride reinsertion provides the intermediate **Z** which undergoes reductive elimination to provide the desired ketone and palladium (0).



Scheme 5. Plausible mechanism for palladium catalyzed *C*-arylation of glycals

In summary, we have demonstrated a new reaction of diazonium salts with glycals in the presence of palladium catalysts. A wide range of glycals including protected D-glucals, D-galactals, L-rhamanal, D-xylal and D-ribal underwent stereocontrolled *C*-glycosylation with different aryldiazonium tetrafluoroborates in the presence of 5-10 mol% of palladium acetate at room temperature. All the reactions provide 2,3-deoxy-3-keto α-aryl *C*-glycosides in good to excellent yields in a stereo-controlled manner under optimized condition. This simple method does not require base or ligand or additives, and thus providing scope for wide applications in organic synthesis.

ASSOCIATED CONTENT

Supporting Information

Experiment procedures and Copies of ^{1}H NMR and ^{13}C NMR of **1aa-1aj**, **3aa-3ce, 4ab, mixture of 3ab+5ab, 4ba, 4bf**, and **5ba**.

AUTHOR INFORMATION

Corresponding Author

Email: jeyakumar.chy@iitbhu.ac.in

DEDICATION

Dedicated to Professor Peter H. Seeberger on the occasion of his 50th birthday

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NOTES

The authors declare no competing financial interest

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14. The stereochemistry of C-3 carbon in **4ba** was assigned in a relative manner. The compound **4ba** was subjected for *O*-benzylation to obtain **5ba.** The NMR of the **5ba** is compared with previously reported 2-deoxy 3,4,6-*O*-tribenzyl α-phenyl *C*-glucopyranoside (see the ref. 6a). The NMR data does not match with glucose derivative thus we have assigned as allose derivate.