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Microwave-assisted palladium-catalyzed cross-coupling reactions between pyranoid glycals and aryl bromides. Synthesis of 2′-deoxy *C*-aryl-β-glycopyranosides

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ABSTRACT

Under microwave irradiation, perbenzylated pyranoid glycals were coupled with aryl bromides in the presence of 5% mol palladium(II) acetate in dimethylformamide to produce 2′,3′-unsaturated *C*-aryl-α-glycopyranosides in a rapid and stereospecific manner. The synthetic applicability of the method was further demonstrated by converting the resulting *C*-aryl glycosides to 2′-deoxy *C*-aryl-β-glycopyranosides through oxidation mediated by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and stereoselective reduction.

The *C*-aryl glycosides, part of the general *C*-glycoside family, are structurally unique carbohydrates with an aromatic moiety directly bound to the anomeric carbon.[1] These compounds display diverse biological activities, such as antibacterial, antitumor, enzyme inhibitory effects, and inhibition of platelet aggregation, and they are currently attracting significant synthetic interests. In this context, a number of synthetic methodologies for assembly of the *C*-aryl glycosidic linkages have been developed to date,[2] and they can be typically classified as (a) the transition metal-mediated coupling of glycals (1,2-unsaturated sugars) with performed aromatic or heterocyclic aglycons,[3] (b) the electrophilic aromatic substitution of activated glycosyl donors such as glycosyl halides and glycosyl trichloroacetimidates with aromatic species,[4] (c) the Lewis acid-promoted *O*→*C* glycoside rearrangements,[5] and (d) the de novo construction of *C*-aryl glycosidic scaffold from nonsaccharide precursors through cycloaddition[6] or ring-closure methasis[7] reaction.

Of these methods for preparing *C*-aryl glycosides, we thought that the palladium-catalyzed Heck cross-coupling reaction between glycals and halogenated aromatic coupling partners deserved to be tried, because it permits direct introduction of the aryl moiety to the anomeric center of carbohydrate substrate to form the *C*-glycosidic bond and employs readily available glycals and aryl halides as starting materials. Previously, Daves and coworkers reported such Heck-type coupling of furanoid and pyranoid glycals with iodo aglycons for the synthesis of *C*-nucleosides and *C*-glycoside antibiotics.[8] Although the viability of the reaction was demonstrated, the reported protocols suffered from the large excess of glycals (up to 6 equiv), the moderate stereochemical outcome (formation of a mixture of α/β-anomers in some cases), the prolonged reaction time (up to several days), and the limited reaction examples of pyranoid glycals (only four examples). These disadvantages prompted us to find a more practical Heck *C*-aryl glycosylation protocol that can proceed ideally in a fast and highly stereocontrolled manner. In order to tackle this issue, we sought to employ flash-heating by microwave irradiation which proved to be useful for reducing reaction time and in some cases improving regio- and/or chemoselectivity of Heck reactions.[9] Herein, we describe a rapid and stereospecific Heck-type *C*-aryl glycosylation under microwave irradiation. The process was mediated by a high-temperature stable catalytic system consisting of palladium(II) acetate, inorganic base potassium carbonate (K_2CO_3), and quaternary ammonium salt tetra-*n*-butylammonium bromide (TBAB) and effected cross-couplings between a range of pyranoid glycals and aryl bromides with low palladium loadings (0.05 equiv), fast reaction time (ca. 30 min), and complete α-stereoselectivity, producing 2′,3′-unsaturated *C*-aryl-α-glycosides in good yields. Furthermore, extension of the method to the preparation of 2′-deoxy *C*-aryl-β-glycosides is also detailed.

First, the effectiveness of microwave irradiation on the cross-coupling of glycal with aryl halide was tested by conducting the model experiment of 3,4,6-tri-*O*-benzyl-D-glucal **1a** (0.05 mmol) with phenyl bromide (0.15 mmol) in the presence of 10 mol %

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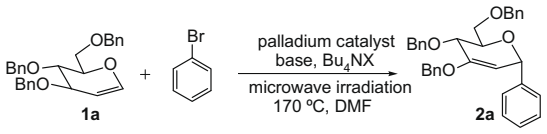
palladium(II) acetate (1.1 mg) in anhydrous dimethylformamide (DMF, 0.2 mL) containing sodium formate (0.15 mmol) as a base. The reaction mixture was subjected to microwave irradiation until **1a** was completely consumed as monitored by TLC analysis. As illustrated in Table 1, the glycosylation proceeded fast in only 60 min and delivered 24% isolated yield of *C*-phenyl gluctopyranoside **2a** as a single α-anomer (entry 1). The double-bond migrated to 2′,3′-position of the pyranoid ring in a fashion similar to the carbon-Ferrier rearrangement.[10]

Following the initial promising result, we then turned our attention to the optimization of the reaction conditions with respect to salt additives, equivalents of glycal, base and catalyst (Table 1). It was found that addition of 1.0 equiv of tetra-*n*-butylammonium bromide (TBAB) to the reaction medium exerted a useful effect on the reaction outcome and consequently improved the yield of **2a** to 40% (Table 1, entry 2). On the other hand, the use of tetra-*n*-butylammonium chloride was detrimental, resulting in the generation of numerous side products and thus giving a reduced yield (entry 3). A similar observation on enhancement of tetrabutylammonium salts for the Pd-catalyzed C_1-arylations of glycals was noted as well by Daves and co-workers.[8e] As for the equivalents of glycal, the decrease in the ratio of phenyl bromide to **1a** lowered the yield of **2a** (entries 4 and 5). We also assessed the role of base in the reaction yield and found that the combined use of 3.0 equiv of sodium hydride or potassium carbonate rather than sodium formate with TBAB led to great improvements in both reaction yields and rate (entries 6 and 7, respectively). In contrast, no coupling was realized with either piperidine or triethylamine as the base, and the starting **1a** was largely recovered. Phenyl iodide was much less reactive than phenyl bromide under these conditions, providing **2a** in only 25% yield (entry 10). As a palladium source, $Pd(OAc)_2$ proved to be the best choice of catalyst, while zerovalent $Pd_2(dba)_3$ afforded a poor yield (entry 11), and none of the desired product was detected when $Pd(PPh_3)_4$ or $PdCl_2$ was used (entries 12 and 13). Furthermore, introduction of 1.0 equiv of PPh_3 as ligand for palladium had no significant impact on the reaction outcome (entry 6 vs 14).

Table 1
Survey of reaction conditions of microwave-assisted Pd-catalyzed coupling of 3,4,6-tri-*O*-benzyl-D-glucal (**1a**) with phenyl bromide[a]



Entry	Amt. of phenyl bromide/**1a** (equiv)	Catalyst	X in Bu_4NX	Base	Reaction time (min)	Yield of **2a**[b] (%)
1[c]	3	$Pd(OAc)_2$	—	HCO_2Na	60	24
2	3	$Pd(OAc)_2$	Br	HCO_2Na	60	40
3	3	$Pd(OAc)_2$	Cl	HCO_2Na	60	20
4	2	$Pd(OAc)_2$	Br	HCO_2Na	60	37
5	1	$Pd(OAc)_2$	Br	HCO_2Na	60	22
6	3	$Pd(OAc)_2$	Br	NaH	30	71
7	3	$Pd(OAc)_2$	Br	K_2CO_3	30	81
8	3	$Pd(OAc)_2$	Br	Piperidine	30	0
9	3	$Pd(OAc)_2$	Br	Et_3N	30	0
10[d]	3	$Pd(OAc)_2$	Br	NaH	60	25
11	3	$Pd_2(dba)_3$	Br	K_2CO_3	30	27
12	3	$Pd(PPh_3)_4$	Br	K_2CO_3	30	0
13	3	$PdCl_2$	Br	K_2CO_3	30	0
14[e]	3	$Pd(OAc)_2$	Br	NaH	30	74

[a] Reactions were performed with palladium (0.05 equiv), tetrabutylammonium salt (1.0 equiv) and base (3.0 equiv) under microwave irradiation (170 °C) in DMF (*C* = 10 M), unless otherwise indicated.
[b] Isolated yields based on **1a** after purification by column chromatography on silica gel.
[c] 0.1 equiv of $Pd(OAc)_2$ was used.
[d] Use of phenyl iodide rather than phenyl bromide as starting material.
[e] In the presence of 1.0 equiv of PPh_3.

Based on these results, we next explored the synthetic generality of this microwave-assisted coupling protocol. Thus, a series of representative perbenzyl-protected glycals, including D-glucal **1a**, D-galactal **1b**, D-rhamnal **1c**, and L-rhamnal **1d**, all of which exist as common glycosidic components in many *C*-aryl glycoside antibiotics, were prepared and used for coupling with aryl bromides.

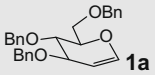
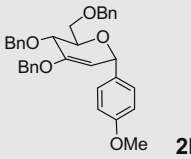
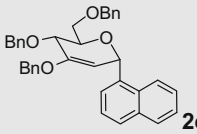
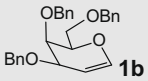
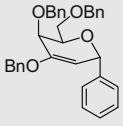
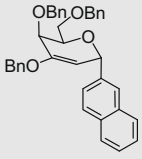
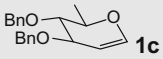
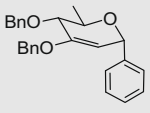
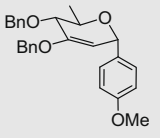
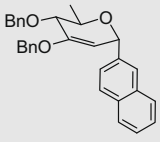
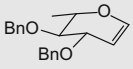
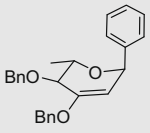
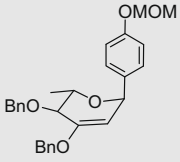
We were pleased to find that under the suitable conditions (1.0 equiv of glycal, 3.0 equiv of aryl bromide, 0.05 equiv of $Pd(OAc)_2$, 1.0 equiv of TBAB, 3.0 equiv of K_2CO_3, and microwave-heating, 30 min, DMF), as recognized in entry 7 (Table 1), *C*-aryl glycosylations of the selected D- and L-series glycals afforded the expected products **2b**–**j** in high yields (73–81%) with exclusive α-stereoselectivity in all cases, which demonstrated that the procedure is generally applicable for a rapid and stereospecific synthesis of various 2′,3′-unsaturated *C*-aryl-α-glycosides (Table 2).[11] The yield of the products appeared to be strongly related to the nature of the starting bromoarenes. For example, reactions with phenyl bromide (Table 2, entries 3, 5 and 8) gave substantially better yields than those with more sterically hindered 1- and 2-naphthyl bromides (entries 2, 4 and 7). Compared with the corresponding unsubstituted analogues (entries 3, 5 and 8), bromoarenes possessing para-substituted electron-donating groups (entries 1, 6 and 9) gave lower yields. That was consistent with the previous observations on the couplings of glycal tin[12] or indium[13] reagents with aryl halides. Moreover, the methoxy group and the acid-labile methoxymethyl group remained stable under the reaction conditions, which expanded the functional-group tolerance (entries 1, 6 and 9).

The configuration of C-1′ in **2a**–**j** was assigned on the basis of NOE correlation between H-1′and H-5′as well as compared with literature reports on similar compounds.[14] For instance, irradiation of the C-5′ methine signal (δ_H 3.89 ppm) in **2a** at 400 MHz ($CDCl_3$) showed no evidence of any NOE enhancement in the C-1′ methine signal (δ_H 5.03 ppm), which indicated an α configuration at the anomeric center.

Having obtained the *C*-aryl-α-glycosides **2a**–**j**, we further investigated their applications in the synthesis of 2′-deoxy *C*-aryl glycosides (Scheme 1). Thus, treatment of **2a**–**j** with 1.2 equiv of oxidizing agent 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in wet dichloromethane (0.1 M for **2a**–**j**) at room temperature for 2–4 h led to, respectively, the formation of the corresponding C_1-arylated enones **3a**–**j** in quantitative yields. Subsequent catalytic hydrogenation of the resulting enones[15] in the presence of 10% palladium on charcoal in basic ethanol stereoselectively generated the desired 2′-deoxy *C*-aryl-β-glycopyranosides **4a**–**j** with free 3′-hydroxyl groups in excellent yields (78–90%) after chromatographic separation. These results are evidence of simultaneous reductions of both C=C and C=O bonds from α-face of the enones.

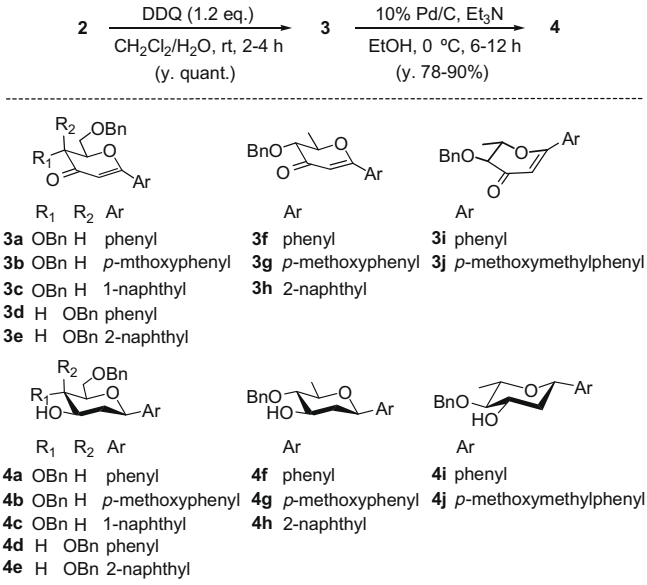
The structures of the obtained 2′-deoxy *C*-aryl glycosides were unambiguously established on the basis of spectroscopic data.[14b] The configurations at C-3′ were determined by the values of $J_{3',4'}$ coupling constants which were, respectively, in the range of 8.8–9.6 Hz for **4a**–**c** and **4f**–**j** (axial–axial relationship), and 2.4–2.8 Hz for **4d**–**e** (axial-equatorial relationship). In the ^1H NMR (400 MHz) spectra, the H-1′ signal was a characteristic doublet of doublets with a large $J_{1',2a'}$ constant (>10 Hz, e.g., 11.6 Hz for **4a**), revealing an axial–axial coupling relationship between H-1′ and H-2a′. These data are consistent with a β anomeric configuration for all the compounds, and a $^4C_1$(D) conformation for **4a**–**h** and a $^1C_4$(L) conformation for **4i**–**j**. NOE experiments were further used to confirm the configuration at the anomeric sites. Take compound **4a**, irradiation of the H-1′ (δ_H 4.49 ppm) showed an enhancement of 10% of the H-5′ signal at δ_H 3.60 ppm, which was in agreement with a cis disposition of these two atoms.

Table 2
$Pd(OAc)_2$-catalyzed glycal-aryl bromide cross-couplings promoted by microwave irradiation[a]

Entry	Glycal	Aryl bromide	Product	Yield (%)
1	 **1a**	*p*-Methoxyphenyl bromide	 **2b**	75
2		1-Naphthyl bromide	 **2c**	78
3	 **1b**	Phenyl bromide	 **2d**	81
4		2-Naphthyl bromide	 **2e**	73
5	 **1c**	Phenyl bromide	 **2f**	79
6		*p*-Methoxyphenyl bromide	 **2g**	76
7		2-Naphthyl bromide	 **2h**	74
8	 **1d**	Phenyl bromide	 **2i**	80
9		*p*-Methoxymethylphenyl bromide	 **2j**	75

[a] General conditions: glycal (1.0 equiv), aryl bromide (3.0 equiv), $Pd(OAc)_2$ (0.05 equiv), TBAB (1.0 equiv), and K_2CO_3 (3.0 equiv) in DMF (C = 10 M), microwave-heating (170 °C).

In summary, we have developed a microwave-assisted cross-coupling reaction of perbenzylated pyranoid glycals with aryl bromides in the presence of catalytic amounts of palladium(II) acetate. Compared with the known techniques, this high-yielding and stereospecific procedure offers a more practical approach to the formation of structurally diverse 2′,3′-unsaturated *C*-aryl-α-glycopyranosides in a rapid and well-applicable way. Through DDQ-mediated oxidation and stereoselective reduction, the obtained *C*-glycosides can be further transformed into 2′-deoxy *C*-aryl-β-glycopyranosides. Thus, this sequence of reactions described con-



Scheme 1. Conversion of *C*-aryl-α-glycosides **2a–j** to 2′-deoxy *C*-aryl-β-glycopyranosides **4a–j**.

stitutes a new synthetic pathway to 2′-deoxy β-*C*-glycosylarenes. Further investigations are underway to apply this methodology to the synthesis of biologically important natural products.

Acknowledgments

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Supplementary data

Supplementary data (the optical rotation, ^{1}H and ^{13}C NMR spectroscopic data as well as results of HR ESI-MS for **4a–j**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.116.

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11. *Typical experimental procedure for microwave-assisted cross-couplings between pyranoid glycals and aryl bromides*. An oven-dried round flask was charged with glycal (1.0 equiv), Pd catalyst (0.05 equiv), TBAB (1.0 equiv), and K_2CO_3 (3.0 equiv). The aryl bromides (3.0 equiv) and anhydrous DMF (0.1 mL/mmol) were successively added via syringe. Then the vessel was equipped with a condensation tube and irradiated by microwave (400 W) without stirring under a nitrogen atmosphere until the starting glycal was completely consumed as judged by TLC analysis. The reaction mixture was cooled to room temperature and then diluted with water and dichloromethane. The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated. The crude material was purified by flash column chromatography on silica gel eluted with petroleum ether/EtOAc to afford the 2′,3′-unsaturated *C*-aryl-α-glycopyranosides **2a–j**.
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