

Phosphine-Free Suzuki-Miyaura Cross-Coupling in Aqueous Media Enables Access to 2-C-Aryl-Glycosides

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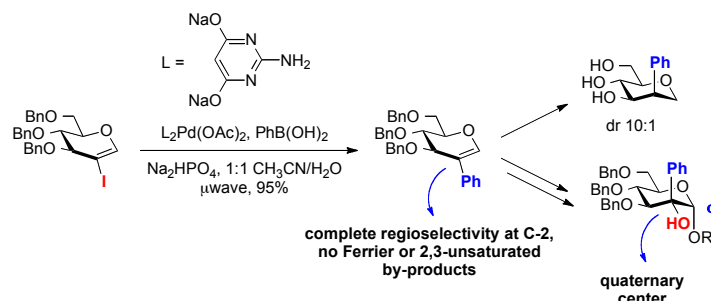
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ABSTRACT



A general strategy for the synthesis of 2-aryl-glycals and their elaboration to 2-C-aryl- α -glycosides and 1,5-anhydro-2-C-aryl-2-deoxy alditols is described. The use of reliable, efficient phosphine-free Suzuki-Miyaura cross-coupling of 2-iodoglycals in aqueous media as a key step proceeds with complete regioselectivity at C-2 and enables access to 2-aryl-glycals with different configurations in excellent yields.

C-Aryl-glycosides are members of the C-glycosides¹ family of carbohydrate mimetics and their synthesis has attracted considerable interest due to the presence of such motifs in several naturally occurring bioactive products.²

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Many methods have been developed for the synthesis of 1-C-aryl glycosides where a carbon atom substitutes the anomeric glycosidic oxygen.³ The most common method for 1-C-aryl glycosides synthesis involves the use of transition metal-catalyzed reactions, in particular, the addition of organometallic species to the sp²-hybridized anomeric center of glycals.⁴ Regioselectivity may be

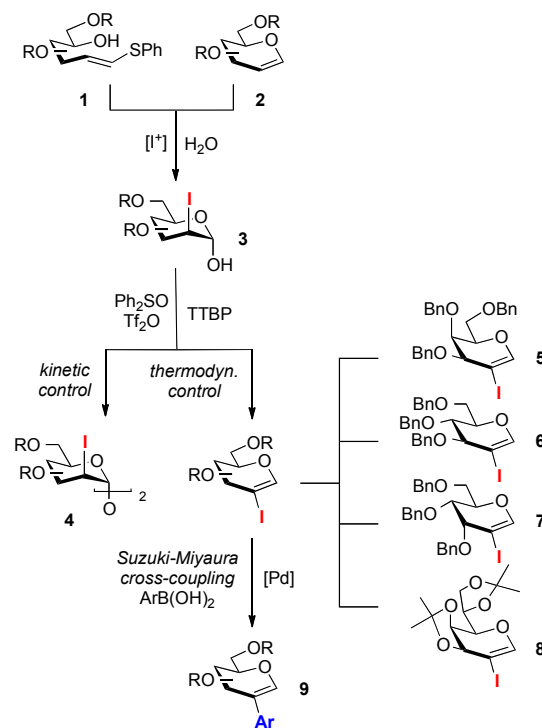
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efficiently controlled using a directing halogen atom at the anomeric position⁵ (e.g. 1-haloglycals). However, and when this regiocontrol element is missing, reactions often lead to the formation of Ferrier and other 2,3-unsaturated products due to β -elimination processes.^{4–7} Although the high demand for functionalized 1-C-arylglycosides has stimulated extensive studies on metal-catalyzed C–C bond-forming reactions,⁸ the development of more efficient methods that involve arylation at other positions is highly desirable. C-Functionalizations at other positions of the sugar ring leading to C-branched sugars are by far less explored because they usually require many steps,⁹ the use of strongly basic organolithium and Grignard reagents,¹⁰ or the use of toxic reagents such as tin or mercury.¹¹ Particularly, the synthesis of 2-C-aryl-modified-carbohydrates¹² is rare, even though they are of potential interest for the development of new biologically active carbohydrate mimetics.

We envisaged a general strategy for accessing 2-arylglycals (Scheme 1) as key intermediates for synthesizing 2-C-arylglycosides. We anticipated that this could be achieved through the use of 2-haloglycals as privileged starting materials for this transformation featuring a regiocontrol element at the desired C-2 position.^{13–15} Herein we report a general and efficient method for the synthesis of 2-arylglycals **9** with different configurations under relatively mild conditions by an aqueous, phosphine-free Suzuki-Miyaura cross-coupling of 2-iodoglycals **5–8** with aryl boronic acids in the presence of an inexpensive Pd complex¹⁶ (Scheme 1).

Scheme 1. General strategy towards the preparation of 2-arylglycals **9**



Although iodo-derivates are preferable over chlorine or bromine for these reactions¹⁷ they are less used, probably due to the lack of a general method for their preparation.¹⁸ Thus, starting 2-iodoglycals **5–8** were prepared by treating alkenyl sulfanyl derivatives **1** or commercially available glycals **2** with iodonium reagents in aqueous media to provide the corresponding 2-deoxy-2-iodopyranoses **3** which were then eliminated with $\text{Ph}_2\text{SO}/\text{Tf}_2\text{O}$ and TTBP. Importantly, the optimization of original reaction conditions by driving the reaction under thermodynamic control allowed the selective preparation of otherwise elusive 2-iodoglycals **5** and **6** (see SI for details). Under kinetic control, 2-deoxy-2-iodo-trehaloses **4** were principally obtained.^{18,19}

The feasibility of the Suzuki-Miyaura cross-coupling reaction was initially examined by using our recently developed Pd catalyst¹⁶ (Table 1). Treatment of 2-iodogalactal **5** and phenylboronic acid **10a** with 2 mol% catalyst and Na_2HPO_4 in 1:3 $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ afforded 2-phenylgalactal **11a** in 82% yield with complete selectivity at C-2 after 300 min at 100 °C (entry 1). Attempts to decrease the catalyst loading proved ineffective (entry 2). Changing the solvent ratio from 1:3 to 1:1 $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ to increase the solubility of **5**, improved the yield of **11a** to 90% after only 30 min at 100 °C (entry 3). Next, the effect of reaction temperature

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was evaluated (entries 4–6), being 125 °C optimal. The best yield for **11a** (95%) was finally obtained with 2 mol% catalyst in 1:1 CH₃CN/H₂O at 125 °C for only 5 min (entry 6). Globally, the use of this cheap and environmentally friendly catalyst provides several advantages; carrying out the reaction under aqueous conditions is key since the use of *nonpolar* solvents accelerates competing elimination reactions²⁰ and also avoiding the use of degassed solvents combined with expensive, easily oxidized phosphines that are particularly detrimental for the success of this reaction. For example, we observed 40% hydrodehalogenation of 2-iodogalactal **5** when reacted with PBu₃ (see SI for details).

Table 1. Optimization of reaction conditions for the Suzuki-Miyaura cross-coupling of 2-iodogalactal **5** with phenylboronic acid **10a**^a

entry	[Pd] (mol %)	CH ₃ CN/H ₂ O (v/v)	temp (°C)	t (min)	yield ^b (%)
1	2	1:3	100	300	82
2	0.1	1:3	100	30	NR ^c
3	2	1:1	100	30	90
4	2	1:1	40	720	NR ^c
5	5	1:1	80	190	84
6 ^d	2	1:1	125	5	95

^a Reactions were performed in a sealed vessel under single-mode microwave irradiation (65 W) with 2-I-galactal **5** (1 equiv), PhB(OH)₂ **10a** (1.5 equiv), L₂Pd(OAc)₂ (up to 5 mol%), and Na₂HPO₄ (5 equiv) in solvent (0.02 M) unless otherwise indicated. ^b Isolated yield. ^c NR = no reaction (>98% starting material was recovered). ^d Microwave power (300 W).

Encouraged by these results, a variety of arylboronic acids **10b–h** containing representative groups with potential in different imaging modalities²¹ (e.g. PET, MRI, and fluorescence) were examined to expand the scope of the Suzuki-Miyaura cross-coupling of 2-iodogalactal **5** (Table 2). Phenylboronic acids with electron-withdrawing groups (entries 1, 3, and 7) or electron-donating groups (entry 2) both afforded excellent results. Similarly, the use of sterically hindered boronic acids (entries 4 and 6), or heterocyclic derivatives (entry 5) also afforded excellent results although longer reaction times were required. Next, 2-iodoglycals **6–8** were reacted with phenylboronic acid **10a** under the optimized reaction conditions (Table 1, entry 6) and 2-phenylglycals **12–14** were efficiently obtained in excellent yields (up to

95%) confirming that different configurations are compatible with this procedure (Table 3).

Table 2. Scope of Suzuki-Miyaura cross-coupling of 2-iodogalactal **5** with arylboronic acids **10b–h**^a

entry	boronic acid	Ar	product	t (min)	yield ^b (%)
1	10b	4-CN	11b	5	95
2	10c	4-OMe	11c	5	95
3	10d	4-F	11d	5	90 ^c
4	10e	2-Me	11e	40	90
5	10f	3-Py	11f	40	89
6	10g	1-Naph	11g	5	94
7	10h	3,5-(CF ₃) ₂	11h	5	95

^a Conditions: a mixture of 2-I-galactal **5** (1 equiv), ArB(OH)₂ **10b–h** (1.5 equiv), L₂Pd(OAc)₂ (2 mol %), and Na₂HPO₄ (5 equiv) in 1:1 CH₃CN/H₂O (0.02 M) was microwave irradiated (125 °C, 300 W) unless otherwise indicated. ^b Isolated yield. ^c Traces of 3,4,6-tri-*O*-benzyl-D-galactal were also detected (see Supporting Information for a mechanistic investigation).

Table 3. Scope of Suzuki-Miyaura cross-coupling of 2-iodoglycals **6–8** with phenylboronic acid^a

entry	2-I-glycal	product	yield ^b (%)
1	6	12	95 ^c
2	7	13	95
3	8	14	96

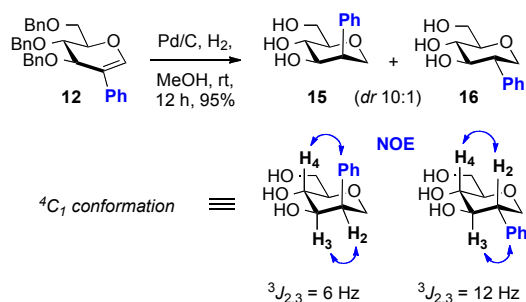
^a Conditions: a mixture of 2-I-glycal **6–8** (1 equiv), PhB(OH)₂ **10a** (1.5 equiv), L₂Pd(OAc)₂ (2 mol %), and Na₂HPO₄ (5 equiv) in 1:1 CH₃CN/H₂O (0.02 M) was microwave irradiated (125 °C, 300 W) for 5 min unless otherwise indicated. ^b Isolated yield. ^c Traces of 3,4,6-tri-*O*-benzyl-D-glucal were also detected (see Supporting Information for full details).

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Having demonstrated the success of the Suzuki-Miyaura cross-coupling reaction with 2-iodoglycals, the potential of resulting 2-arylglycals as intermediates for the preparation of 2-C-arylglycoconjugates was investigated. Thus, 2-phenylglucal **12** was efficiently hydrogenated with Pd/C in methanol to afford 1,5-anhydro-2-C-aryl-2-deoxy alditiols **15** and **16** in 95% yield and *dr* 10:1 as indicated by the analysis of diagnostic coupling constants and key NOE signals in **15** and **16** both present in their 4C_1 conformation (Scheme 2).

Scheme 2. Synthesis and conformational analysis of 1,5-anhydro-2-C-aryl-2-deoxy alditiols **15** and **16**

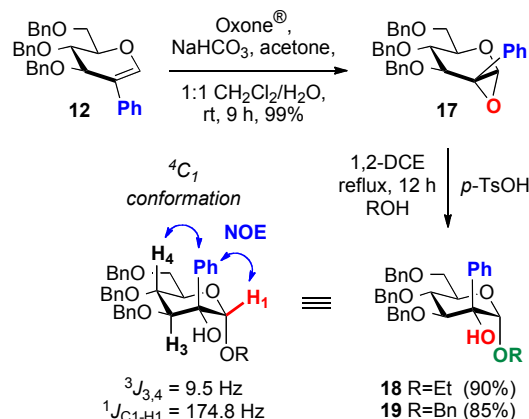


The preparation of challenging quaternary 2-C-aryl moieties was next studied using our two-step approach, which involves the epoxidation of starting 2-arylglycals followed by ring-opening of resulting 2-C-aryl branched 1,2-anhydropyranosides.²² Thus, treatment of 2-phenylglucal **12** with Oxone[®] and acetone afforded epoxide **17** in quantitative yield^{23,24} (Scheme 3). Next, 2-C-phenyloxirane **17** was subjected to an acid-promoted glycosylation with EtOH or BnOH. Under such conditions, 2-C-phenylglycosides **18** and **19** were obtained in good yields (85–90%) with exclusive α -selectivity (Scheme 3). The stereochemistry of compounds **18** and **19** was initially deduced by analysis of diagnostic $^3J_{3,4} = 9.5$ Hz coupling constants that account for a 4C_1 conformation. Moreover, the anomeric $^1J_{C1-H1} = 174.8$ Hz coupling constant is indicative of an α -configuration.²⁵ Finally, selective NOE irradiation of the aromatic Ph protons at C-2 caused an enhancement of signals corresponding to H-1 and H-4, which confirmed the axial disposition of the Ph group at C-2 in both **18** and **19**.

In conclusion, we have developed a general catalytic strategy for the efficient synthesis of 2-arylglycals by phosphine-free Suzuki-Miyaura cross-coupling of 2-iodoglycals in aqueous media using an inexpensive Pd catalyst. To the best of our knowledge this transformation represents the first transition metal catalyzed 2-C-

arylation of 2-haloglycals. The simplicity and relative mildness of this method allows the regioselective preparation of various 2-arylglycals with different configurations in excellent yields with no Ferrier or 2,3-unsaturated by-products detected. Notably, the 2-iodoglycal substrates proved unstable in the presence of phosphines, necessitating systems that avoid their use. The elaboration of the 2-C-arylglycal moiety gives access to both 1,5-anhydro-2-C-aryl-2-deoxy alditiols and challenging quaternary 2-C-aryl- α -glycosides which will broaden the plethora of 2-C-aryl branched glycosides at positions different than C-1. Further application of this methodology to the synthesis of more complex 2-C-aryl branched glycosides is currently under investigation.

Scheme 3. Synthesis and conformational analysis of branched 2-C-phenylglycosides **18** and **19**



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Supporting Information Available: Experimental procedures, additional experiments, characterization data and copies of 1H , ^{13}C and ^{19}F NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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