

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

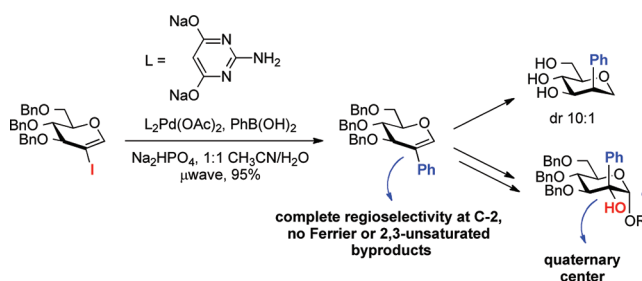
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## ABSTRACT



A general strategy for the synthesis of 2-aryl-glycals and their elaboration to 2-C-aryl- $\alpha$ -glycosides and 1,5-anhydro-2-C-aryl-2-deoxy aldittols are 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-Arylglycosides are members of the C-glycosides<sup>1</sup> family of carbohydrate mimetics, and their synthesis has attracted considerable interest due to the presence of such motifs in several naturally occurring bioactive products.<sup>2</sup> Many methods have been developed for the synthesis of 1-C-arylglycosides where a carbon atom substitutes the

anomeric glycosidic oxygen.<sup>3</sup> The most common method for 1-C-arylglycosides synthesis involves the use of transition-metal-catalyzed reactions, in particular, the addition of organometallic species to the sp<sup>2</sup>-hybridized anomeric center of glycals.<sup>4</sup> Regioselectivity may be efficiently controlled using a directing halogen atom at the anomeric position<sup>5</sup> (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  $\beta$ -elimination processes.<sup>4–7</sup> Although the high demand for functionalized 1-C-arylglycosides has stimulated

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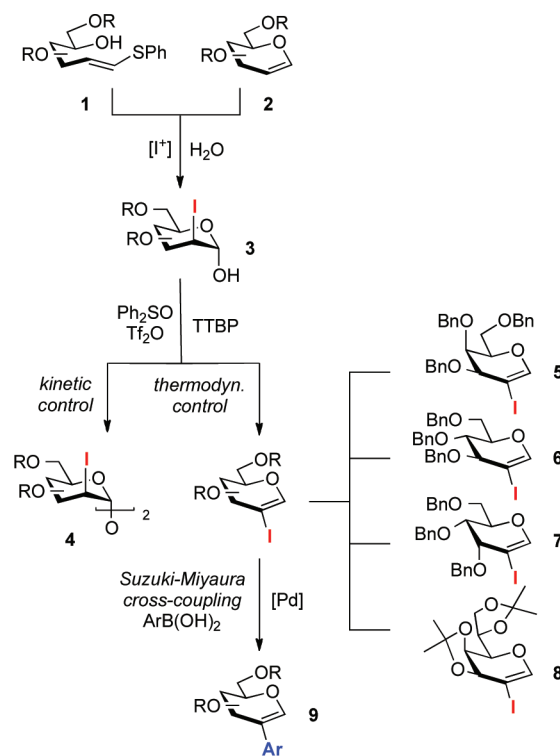
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extensive studies on metal-catalyzed C–C bond-forming reactions,<sup>8</sup> the development of more efficient methods that involve arylation at other positions is highly desirable. C-Functionalizations at other positions of the sugar ring leading to C-branched sugars are by far less explored because they usually require many steps,<sup>9</sup> the use of strongly basic organolithium and Grignard reagents,<sup>10</sup> or the use of toxic reagents such as tin or mercury.<sup>11</sup> Particularly, the synthesis of 2-C-aryl-modified-carbohydrates<sup>12</sup> 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.<sup>13–15</sup> 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 complex<sup>16</sup> (Scheme 1).

Although iodo-derivates are preferable over chlorine or bromine for these reactions<sup>17</sup> they are less used, probably due to the lack of a general method for their preparation.<sup>18</sup> 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

**Scheme 1.** General Strategy towards the Preparation of 2-Arylglycals **9**



provide the corresponding 2-deoxy-2-iodopyranoses **3** which were then eliminated with Ph<sub>2</sub>SO/Tf<sub>2</sub>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 Supporting Information (SI) for details). Under kinetic control, 2-deoxy-2-iodo-trehaloses **4** were principally obtained.<sup>18,19</sup>

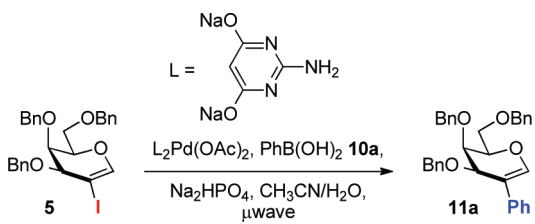
The feasibility of the Suzuki–Miyaura cross-coupling reaction was initially examined by using our recently developed Pd catalyst<sup>16</sup> (Table 1). Treatment of 2-iodogalactalactal **5** and phenylboronic acid **10a** with 2 mol % catalyst and Na<sub>2</sub>HPO<sub>4</sub> in 1:3 CH<sub>3</sub>CN/H<sub>2</sub>O afforded 2-phenylgalactalactal **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 CH<sub>3</sub>CN/H<sub>2</sub>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 was evaluated (entries 4–6), 125 °C being optimal. The best yield for **11a** (95%) was finally obtained with 2 mol % catalyst in 1:1 CH<sub>3</sub>CN/H<sub>2</sub>O 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

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competing elimination reactions<sup>20</sup> and also avoids 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  $\text{PBu}_3$  (see SI for details).

**Table 1.** Optimization of Reaction Conditions for the Suzuki–Miyaura Cross-Coupling of 2-Iodogalactal **5** with Phenylboronic Acid **10a**<sup>a</sup>



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

<sup>a</sup> Reactions were performed in a sealed vessel under single-mode microwave irradiation (65 W) with 2-I-galactal **5** (1 equiv),  $\text{PhB(OH)}_2$  **10a** (1.5 equiv),  $\text{L}_2\text{Pd(OAc)}_2$  (up to 5 mol %), and  $\text{Na}_2\text{HPO}_4$  (5 equiv) in solvent (0.02 M) unless otherwise indicated. <sup>b</sup> Isolated yield. <sup>c</sup> NR = no reaction (>98% starting material was recovered). <sup>d</sup> Microwave power (300 W).

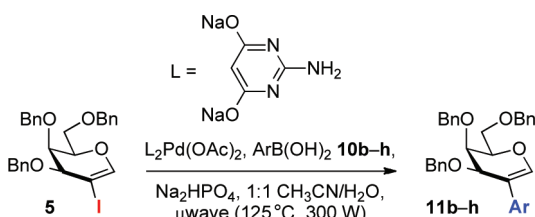
Encouraged by these results, a variety of arylboronic acids **10b–h** containing representative groups with potential in different imaging modalities<sup>21</sup> (e.g., PET, MRI, and fluorescence) were examined to expand the scope of the Suzuki–Miyaura cross-coupling of 2-iodogalactal **5** (Table 2). Phenylboronic acids with electron-withdrawing groups (entries 1, 3, and 7) or electron-donating groups (entry 2) 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).

Having demonstrated the success of the Suzuki–Miyaura cross-coupling reaction with 2-iodoglycals, the potential of the resulting 2-arylglycals as intermediates for the preparation of 2-C-arylglycoconjugates was

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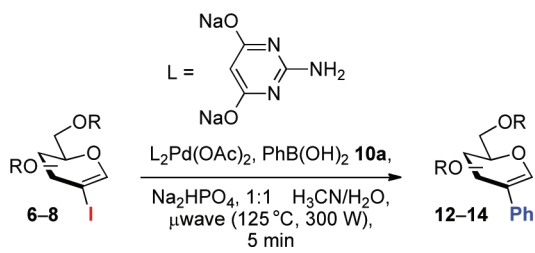
**Table 2.** Scope of Suzuki–Miyaura Cross-Coupling of 2-Iodogalactal **5** with Arylboronic Acids **10b–h**<sup>a</sup>



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

<sup>a</sup> Conditions: a mixture of 2-I-galactal **5** (1 equiv),  $\text{ArB(OH)}_2$  **10b–h** (1.5 equiv),  $\text{L}_2\text{Pd(OAc)}_2$  (2 mol %), and  $\text{Na}_2\text{HPO}_4$  (5 equiv) in 1:1  $\text{CH}_3\text{CN}/\text{H}_2\text{O}$  (0.02 M) was microwave irradiated (125 °C, 300 W) unless otherwise indicated. <sup>b</sup> Isolated yield. <sup>c</sup> 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<sup>a</sup>

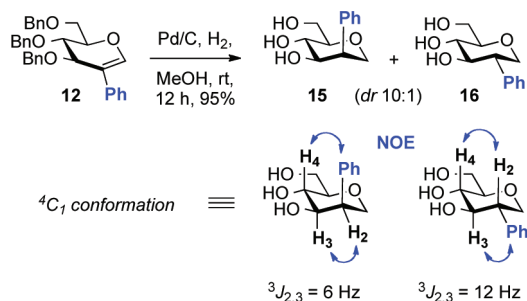


entry	2-I-glycal	product	yield <sup>b</sup> (%)
1	<b>6</b>	<b>12</b>	95 <sup>c</sup>
2	<b>7</b>	<b>13</b>	95
3	<b>8</b>	<b>14</b>	96

<sup>a</sup> Conditions: a mixture of 2-I-glycal **6–8** (1 equiv),  $\text{PhB(OH)}_2$  **10a** (1.5 equiv),  $\text{L}_2\text{Pd(OAc)}_2$  (2 mol %), and  $\text{Na}_2\text{HPO}_4$  (5 equiv) in 1:1  $\text{CH}_3\text{CN}/\text{H}_2\text{O}$  (0.02 M) was microwave irradiated (125 °C, 300 W) for 5 min unless otherwise indicated. <sup>b</sup> Isolated yield. <sup>c</sup> Traces of 3,4,6-tri-*O*-benzyl-D-galactal were also detected (see Supporting Information for full details).

investigated. Thus, 2-phenylglucal **12** was efficiently hydrogenated with Pd/C in methanol to afford 1,5-anhydro-2-*C*-aryl-2-deoxy alditols **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 Alditols **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.<sup>22</sup> Thus, treatment of 2-phenylglucal **12** with Oxone and acetone afforded epoxide **17** in quantitative yield<sup>23,24</sup> (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  $\alpha$ -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  $\alpha$ -configuration.<sup>25</sup> 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.

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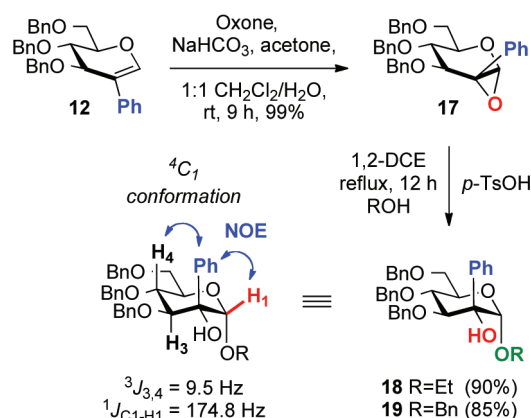
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To the best of our knowledge this transformation represents the first transition-metal-catalyzed 2-*C*-arylation of 2-haloglycals. The simplicity and relative mildness of this method allow the regioselective preparation of various 2-arylglycals with different configurations in excellent yields with no Ferrier or 2,3-unsaturated byproduct 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 alditols and challenging quaternary 2-*C*-aryl- $\alpha$ -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>.

The authors declare no competing financial interest.