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

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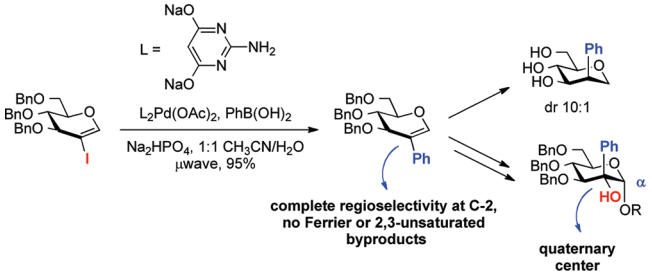
ABSTRACT



A general strategy for the synthesis of 2-aryl-glycals and their elaboration to 2-*C*-aryl-α-glycosides and 1,5-anhydro-2-*C*-aryl-2-deoxy alditols 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[1] 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] Many methods have been developed for the synthesis of 1-*C*-arylglycosides where a carbon atom substitutes the anomeric glycosidic oxygen.[3] 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^2-hybridized anomeric center of glycals.[4] Regioselectivity may be efficiently controlled using a directing halogen atom at the anomeric position[5] (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

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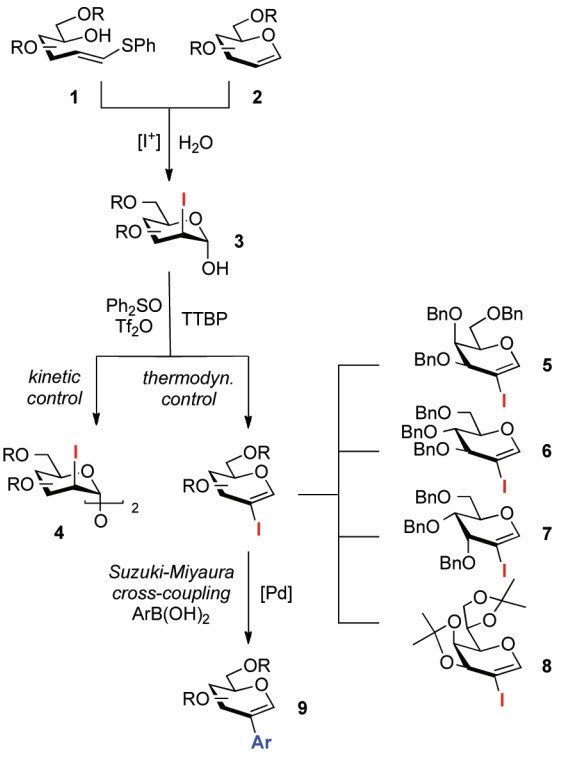
extensive studies on metal-catalyzed C–C bond-forming reactions,[8] the development of more efficient methods that involve arylation at other positions is highly desirable. *C*-Functionalizations at other positions of the sugar ring leading to *C*-branched sugars are by far less explored because they 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-carbohydrates[12] 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 complex[16] (Scheme 1).

Although iodo-derivates are preferable over chlorine or bromine for these reactions[17] 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

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_2SO/Tf_2O 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.[18,19]

The feasibility of the Suzuki–Miyaura cross-coupling reaction was initially examined by using our recently developed Pd catalyst[16] (Table 1). Treatment of 2-iodogalactal **5** and phenylboronic acid **10a** with 2 mol % catalyst and Na_2HPO_4 in 1:3 CH_3CN/H_2O 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 CH_3CN/H_2O 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_3CN/H_2O 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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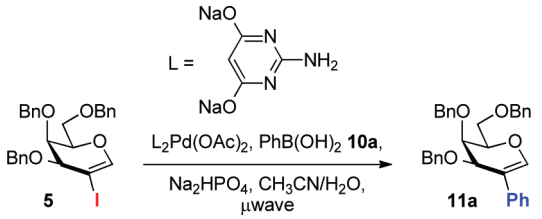
competing elimination reactions[20] and also avoids the use of degassed solvents combined with expensive, easily oxidized phosphines that are particularly detrimental for the success of this reaction. For example, we observed 40% hydrodehalogenation of 2-iodogalactal **5** when reacted with PBu_3 (see SI for details).

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



entry	[Pd] (mol %)	CH_3CN/H_2O (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), $L_2Pd(OAc)_2$ (up to 5 mol %), and Na_2HPO_4 (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 modalities[21] (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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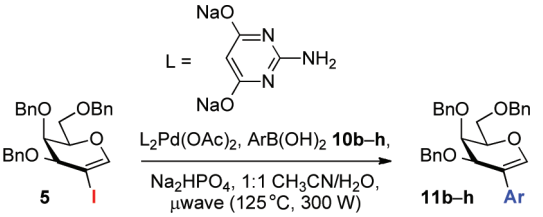
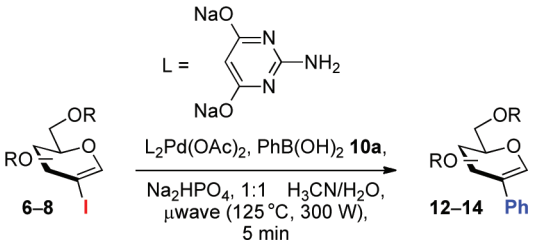
Table 2. Scope of Suzuki–Miyaura Cross-Coupling of 2-Iodogalactal **5** with Arylboronic Acids **10b–h**[a]

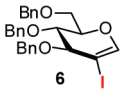
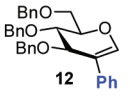
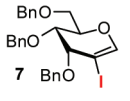
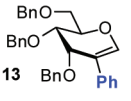
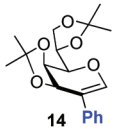


entry	boronic acid	Ar	product	t (min)	yield[b] (%)
1	**10b**	4-CN	**11b**	5	95
2	**10c**	4-OMe	**11c**	5	95
3	**10d**	4-F	**11d**	5	90[c]
4	**10e**	2-Me	**11e**	40	90
5	**10f**	3-Py	**11f**	40	89
6	**10g**	1-Naph	**11g**	5	94
7	**10h**	3,5-$(CF_3)_2$	**11h**	5	95

[a] *Conditions*: a mixture of 2-I-galactal **5** (1 equiv), $ArB(OH)_2$ **10b–h** (1.5 equiv), $L_2Pd(OAc)_2$ (2 mol %), and Na_2HPO_4 (5 equiv) in 1:1 CH_3CN/H_2O (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]

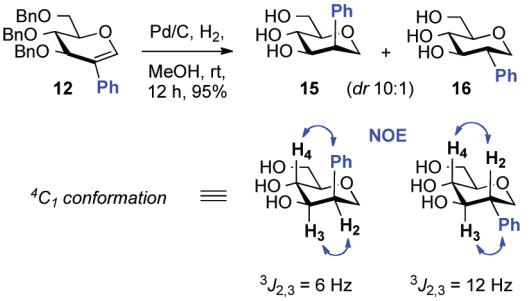


entry	2-I-glycal	product	yield[b] (%)
1			95[c]
2			95
3			96

[a] *Conditions*: a mixture of 2-I-glycal **6–8** (1 equiv), $PhB(OH)_2$ **10a** (1.5 equiv), $L_2Pd(OAc)_2$ (2 mol %), and Na_2HPO_4 (5 equiv) in 1:1 CH_3CN/H_2O (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).

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).

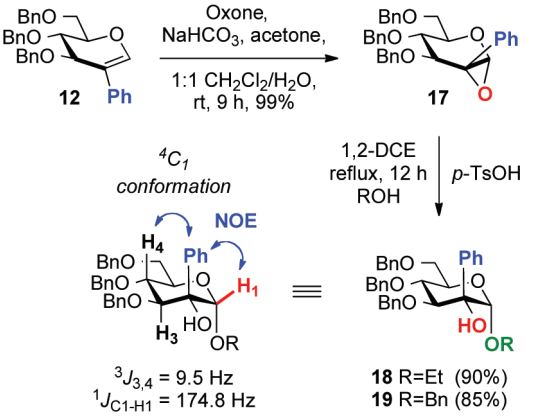
Scheme 2. Synthesis and Conformational Analysis of 1,5-Anhydro-2-*C*-aryl-2-deoxy Alditols **15** and **16**



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.[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 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-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 ^{1}H, ^{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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