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Oxidant-Controlled Heck-Type *C*-Glycosylation of Glycals with Arylboronic Acids: Stereoselective Synthesis of Aryl 2-Deoxy-*C*-glycosides

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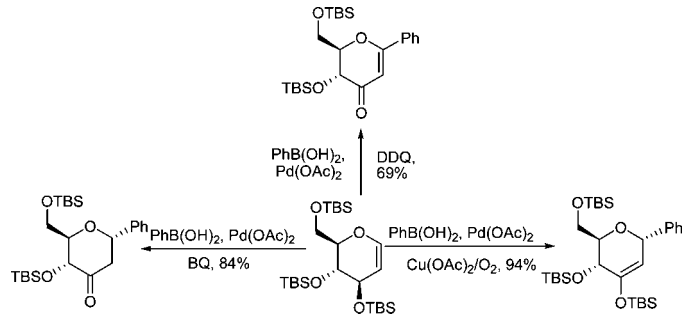
ABSTRACT



Oxidative Heck-type *C*-glycosylations of glycals with various arylboronic acids using $Pd(OAc)_2$ as catalyst in the presence of oxidant were developed. The corresponding ketone, enol ether, and enone types of *C*-glycosides were predictably obtained with benzoquinone (BQ), $Cu(OAc)_2/O_2$, and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as oxidants, respectively. This method provides a simple, mild, and stereoselective synthesis of aryl 2-deoxy-*C*-glycosides.

Carbohydrate analogues possessing a key carbon−carbon (C−C) glycosidic bond between the aglycon and the anomeric carbon of the attached sugar moiety are called *C*-glycosides. Among *C*-glycosides, the importance of aryl *C*-glycosides is evident from their occurrence in natural products, their various biological activities,[1] and their value as chiral synthetic building blocks.[2] In particular, the aryl 2-deoxy-*C*-glycoside structure is embodied in a variety of therapeutically important natural products such as pluramycins, angucyclines, and benzoisochromanequinones.[1] Transition-metal-catalyzed coupling reactions are extremely powerful tools for carbon−carbon bond formation. Although several methods are available for the preparation of aryl-*C*-$\Delta^{2,3}$-glycosides using the transition-metal-catalyzed carbon-Ferrier reaction of glycals,[3] methods for aryl 2-deoxy-*C*-glycosides are quite limited.[4]

We have been particularly interested in investigating an approach that involves palladium(II)-catalyzed oxidative Heck-type reaction of arylboronic acids with glycals to obtain aryl 2-deoxy-*C*-glycosides. The reasons include the follow-

(1) Bililign, T.; Griffith, B. R.; Thorson, J. S. *Nat. Prod. Rep.* **2005**, *22*, 742–760, and references therein.

(2) (a) Qin, H.-L.; Lowe, J. T.; Panek, J. S. *J. Am. Chem. Soc.* **2007**, *129*, 38–39. (b) Reddy, C. R.; Reddy, G. B.; Rao, C. L. *Tetrahedron Lett.* **2008**, *49*, 863–866.

(3) (a) Steihuebel, D. P.; Fleming, J. F.; DuBios, J. *Org. Lett.* **2002**, *4*, 293–295. (b) Price, S.; Edwards, S.; Wu, T.; Minehan, T. *Tetrahedron Lett.* **2004**, *45*, 5197–5201, and references therein. (c) Ramnauth, J.; Poulin, O.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *3*, 2013–2015.

(4) (a) Benhaddou, R.; Czernecki, S.; Ville, G. *J. Org. Chem.* **1992**, *57*, 4612–4616. (b) Ramnauth, J.; Poulin, O.; Bratovanov, S. S.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *3*, 2571–2573.

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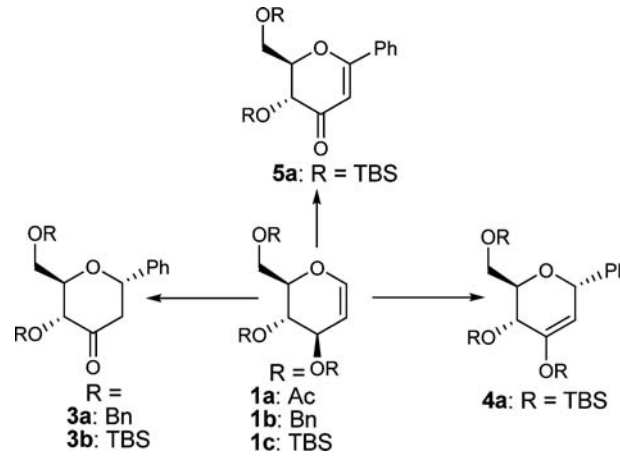
ing: (1) σ-Aryl-Pd complexes can undergo aryl palladation to glycal double bonds to generate the organopalladium σ-adduct with perfect regiospecificity and stereospecificity.[5] (2) According to Daves' work,[6] the organopalladium σ-adducts are versatile chiral intermediates, as σ-adduct decomposition with elimination of palladium and a β-substituent (H, OH, OAc, alkoxy) or protonolysis are likely to furnish various products. (3) The efficiency of the transmetalation from boron to palladium to form the σ-aryl-Pd complex was previously demonstrated in the cross-coupling reaction.[7] (4) Among the various organometallic reagents, organoboronic acids are one of the most popular reagents due to their air and moisture stability, their broad commercial availability, and their low toxicity.[8] Maddaford[3c] and de la Figuera[9] investigated the carbon-Ferrier reaction of glycals with arylboronic acids; they all showed syn addition of the σ-aryl−Pd bond to the α-face of the glycal double bond followed by anti elimination of the heteroatom to yield 2,3-dihydroarylglycopyrans, but the Heck-type β-hydride elimination product was not observed. Herein we report controllable Heck-type *C*-glycosylation of glycals with arylboronic acids.

To begin our study, the reactions of glucals **1a**−**c** and phenylboronic acid (**2a**) were first examined (Table 1, entries 1−3). When **1b**,**c** and **2a** were catalyzed by $Pd(OAc)_2$ in the presence of benzoquinone (BQ), ketone type *C*-glycosides **3a** and **3b** were isolated in moderate to good yield, respectively (entries 2 and 3). The coupling products **3a** and **3b** resulted from β-hydride elimination of the intermediate σ-adducts and cleavage of the benzyl and silyl group. However, when **1a** was used as the starting material, no β-hydride elimination product was obtained. In accord with Daves' conclusion[5b] that conformational rigidity and poor leaving property at the *C*-3-*O*-substituent facilitate syn-β-hydride elimination of the intermediate σ-adduct, we chose TBS (*tert*-butyldimethylsilyl)-protected glycals as our substrates.

Subsequently, we checked the palladium-catalyzed reactions of **1c** and **2a** utilizing various oxidants (Table 1, entries 4−15). When the combination of $Cu(OAc)_2$ and O_2 was used as the oxidant, enol ether type *C*-glycoside **4a** was obtained in high yield (94%) (entry 6). Interestingly, enone-type *C*-glycoside **5a** was generated in moderate yield (69%) when 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was used as the terminal oxidant (entry 8). Strong oxidants were also used to explore a Pd^{II}/Pd^{IV} process,[10] but with no success (entries 9−14). We also failed in the protonolysis process[11] (entry 15). Thus, we found that BQ was the best terminal oxidant to generate ketone **3b**, the combination of $Cu(OAc)_2$/O_2 was the best terminal oxidant to produce enol ether **4a**, and DDQ was the best terminal oxidant to form enone **5a**.

Table 1. Coupling Reactions of **1a**−**c** and **2a** To Form *C*-Glycosides[a]



entry	substrate	oxidant (equiv)	product	yield[b] (%)
1	**1a**	BQ (2.0)		
2	**1b**	BQ (2.0)	**3a**	32
3	**1c**	BQ (2.0)	**3b**	84
4	**1c**	DMSO (6.0)/O_2	**3b/4a**	68/7
5	**1c**	$Cu(OAc)_2$ (2.0)	**4a**	50
6	**1c**	$Cu(OAc)_2$ (2.0)/O_2	**4a**	94
7	**1c**	O_2	**4a**	trace
8	**1c**	DDQ (2.0)	**5a**	69
9	**1c**	IBX (2.0)	**3b**	39
10	**1c**	$PhI(OAc)_2$ (2.0)	**3b/4a**	10/78
11	**1c**	oxone (2.0)	**3b**	11
12	**1c**	H_2O_2 (2.0)	**3b**	10
13	**1c**	TEMPO (2.0)		
14	**1c**	CAN (2.0)	**3b**	trace
15	**1c**	BQ (2.0)/AcOH(2.0)	**3b**	70

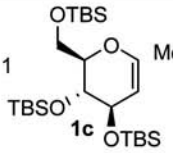
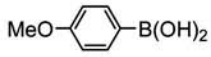
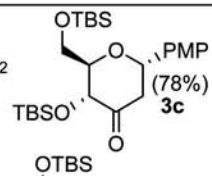
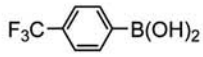
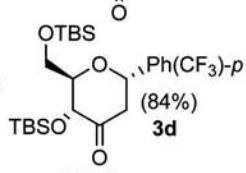
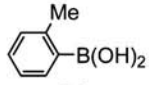
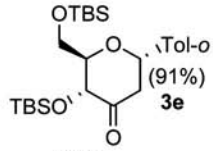
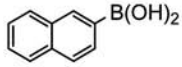
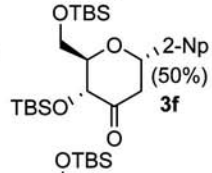
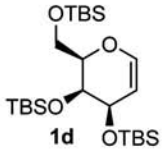
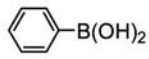
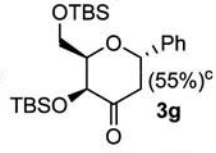
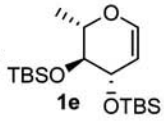
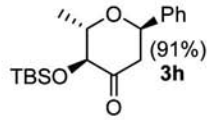
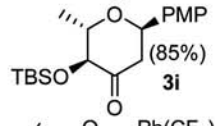
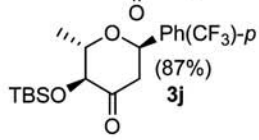
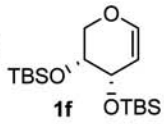
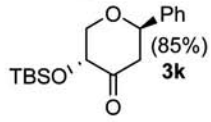
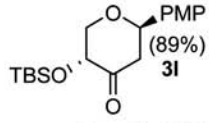
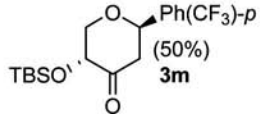
[a] Reaction conditions: $Pd(OAc)_2$ (0.1 equiv), $PhB(OH)_2$ (2.0 equiv), oxidant, CH_3CN, 30−40 °C. [b] Isolated yield.

Encouraged by these results, the scope of the reaction was investigated by varying both the arylboronic acids and the glycals in the presence of BQ (Table 2). A variety of arylboronic acids containing electron-donating, electron-withdrawing, and sterically congested groups were employed, giving ketone-type coupling products in moderate to good isolated yields. A series of glycals were also examined, and all provided the desired products as single anomers. Interestingly, the cross-coupling of galactal **1d** and phenylboronic acid (**2a**) must be carried out under O_2 atmosphere, and enol ether **4e** was also obtained as a side product in 19% yield (entry 5). Mechanistic considerations suggest that the steric configuration of newly introduced aryl group at anomeric position will be on the face opposite the C_3-*O*-substituent of the starting glycals. Indeed, the anomeric configuration of the coupling product was unambiguously identified by its ^1H and ^{13}C NMR analyses as described in the literature.[4]

As shown in Table 3, under the optimized reaction conditions, the palladium-catalyzed coupling reactions of a series of arylboronic acids and glycals were also performed

(5) (a) Czernecki, S.; Dechavanne, V. *Can. J. Chem.* **1983**, *61*, 533–540. (b) Cheng, J. C.-Y.; Daves, G. D., Jr. *J. Org. Chem.* **1987**, *52*, 3083–3090. (c) Daves, G. D., Jr. *Acc. Chem. Res.* **1990**, *23*, 201–206.
(6) Arai, I.; Daves, G. D., Jr. *J. Am. Chem. Soc.* **1981**, *103*, 7683.
(7) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
(8) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695.
(9) de la Figuera, N.; Forns, P.; Fernàndez, J.-C.; Fiol, S.; Fernández-Forner, D.; Albericio, F. *Tetrahedron Lett.* **2005**, *46*, 7271–7274.
(10) Yin, G.; Liu, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5442–5445, and references therein.
(11) Lu, X. *Top. Catal.* **2005**, *35*, 73–86.

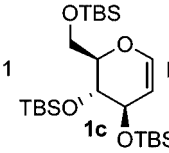
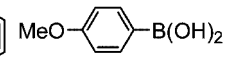
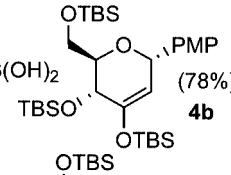
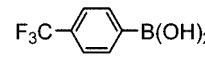
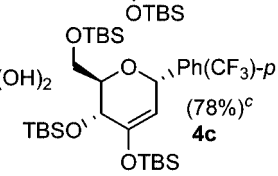
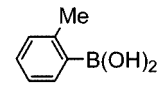
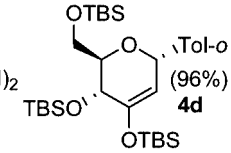
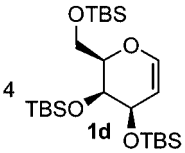
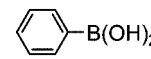
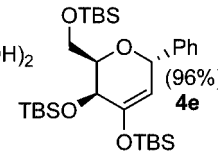
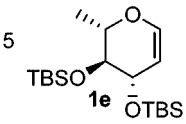
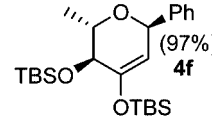
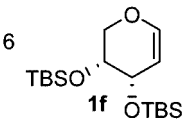
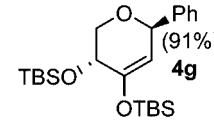
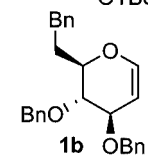
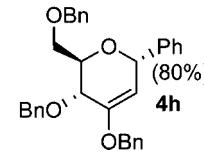
Table 2. The Preparation of Ketone Type *C*-Glycosides **3c**−**m** with BQ as the Oxidant[a]

entry	substrate	arylboronic acid	product (%)[b]
1	 **1c**	 **2b**	 (78%) **3c**
2	**1c**	 **2c**	 (84%) **3d**
3	**1c**	 **2d**	 (91%) **3e**
4	**1c**	 **2e**	 (50%) **3f**
5	 **1d**	 **2a**	 (55%)[c] **3g**
6	 **1e**	**2a**	 (91%) **3h**
7	**1e**	**2b**	 (85%) **3i**
8	**1e**	**2c**	 (87%) **3j**
9	 **1f**	**2a**	 (85%) **3k**
10	**1f**	**2b**	 (89%) **3l**
11	**1f**	**2c**	 (50%) **3m**

[a] Reaction conditions: $Pd(OAc)_2$ (0.1 equiv), BQ (2.0 equiv), $ArB(OH)_2$ (2.0 equiv), CH_3CN, 30−40 °C, 4−48 h. [b] Isolated yield. [c] Conditions a under O_2 atmosphere and enol ether: **4e** was obtained in 19% yield.

in the presence of $Cu(OAc)_2/O_2$. In all cases, the desired enol ether product was obtained in good yield, and only a single

Table 3. Preparation of Enol Ether Type *C*-Glycosides **4b**−**h** with $Cu(OAc)_2/O_2$ as the Oxidant[a]

entry	substrate	arylboronic acid	product (%)[b]
1	 **1c**	 **2b**	 (78%) **4b**
2	**1c**	 **2c**	 (78%)[c] **4c**
3	**1c**	 **2d**	 (96%) **4d**
4	 **1d**	 **2a**	 (96%) **4e**
5	 **1e**	**2a**	 (97%) **4f**
6	 **1f**	**2a**	 (91%) **4g**
7	 **1b**	**2a**	 (80%) **4h**

[a] Reaction conditions: $Pd(OAc)_2$ (0.1 equiv), $Cu(OAc)_2$ (2.0 equiv)/O_2, $ArB(OH)_2$ (2.0 equiv), CH_3CN, 30−40 °C, 12−24 h. [b] Isolated yield. [c] $Cu(OAc)_2$ (0.4 equiv) was used, 48 h.

anomer was detected. However, for the cross-coupling of **1c** with **2c**, a catalytic amount of $Cu(OAc)_2$ had to be used to reduce the formation of homocoupling byproduct of 4-(trifluoromethyl)phenylboronic acid (**2c**) (entry 2, Table 3). The anomeric stereochemistry of the product followed the same rule as that for the above-mentioned ketone product and was confirmed by its ^{13}C NMR and NOESY spectra.[12]

Finally, the coupling reactions of **1c** and other arylboronic acids in the presence of DDQ were examined. Although the

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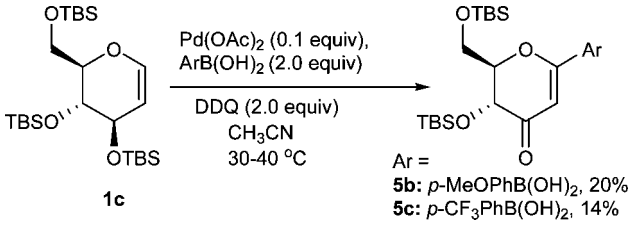
(13) (a) Tanemura, K.; Suzuki, T.; Horaguchi, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2997–2998. (b) Tanemura, K.; Suzuki, T.; Horaguchi, T. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 290–292.

enone-type *C*-glycoside was obtained, the isolated yield was low (Scheme 1). Presumably under the reaction conditions, the TBS group of the reactant is easily cleaved.[13]

Scheme 1. Preparation of Enone-Type *C*-Glycosides **5b**−**c** with DDQ as the Oxidant



Although the details are not yet known, we propose the possible mechanism shown in Figure 1. As delineated in cycle I, a Heck-type *C*-glycosylation first occurs to give enol ether type product under all conditions. When BQ or DDQ is used as the oxidant, like the Saegusa oxidation, the palladium adducts (**A**, **B**) are formed.[14] The subsequent hydrolysis (cycle II) or β-H elimination (cycle III) of the palladium adducts generates the ketone- or enone-type product. Cycle III may be also a radical process.[15]

In conclusion, a simple, mild, and oxidant-controlled Heck-type *C*-glycosylation of glycals with various arylboronic acids has been developed. Different types of *C*-glycosides (ketones, enol ethers, and enones) were predictably obtained by just adjusting the oxidants. The cross-coupling reactions proceeded with high regioselectivity and stereoselectivity. To the best of our knowledge, this is the first Heck-type *C*-glycosylation by using $Pd(OAc)_2$ as catalyst in the presence of oxidant. Given all the advantages associated with arylboronic acids, the disclosed methodology may find wide applications in the preparation of many biologically important *C*-glycosides. Further investigations into protonolysis and the

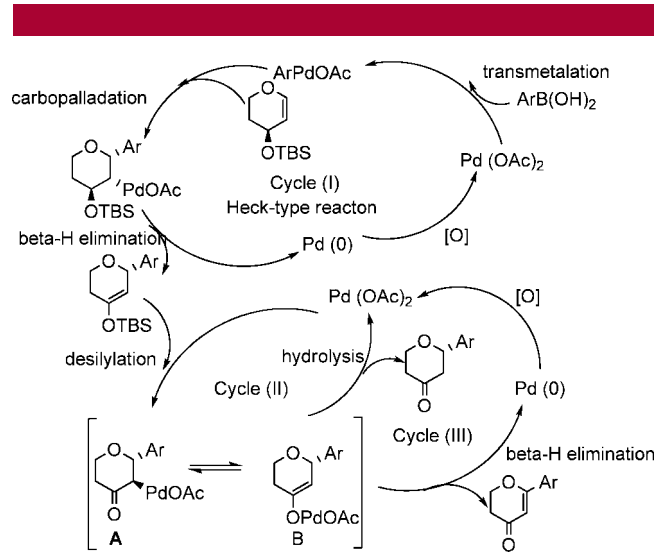


Figure 1. Proposed mechanistic rationale.

Pd^{II}/Pd^{IV} processes of the reaction in the presence of oxidant are in progress.

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Supporting Information Available: Experimental procedures and data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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