ORGANIC LETTERS

2001
Vol. 3, No. 13
2013−2015

Palladium(II) Acetate Catalyzed Stereoselective *C*-Glycosidation of Peracetylated Glycals with Arylboronic Acids

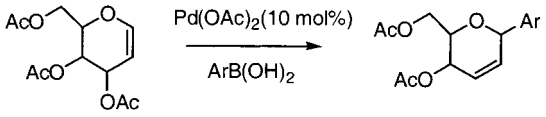
Jailall Ramnauth, Odile Poulin, Suman Rakhit, and Shawn P. Maddaford*

MCR Research Inc., York University, 4700 Keele Street, Toronto, Ontario, Canada M3J 1P3

shawnm@mcr.chem.yorku.ca

Received April 16, 2001

ABSTRACT



Addition of a variety of arylboronic acids to peracetylated glycals takes place in the presence of a catalytic amount of $Pd(OAc)_2$. The reaction involves the *syn* addition of a σ-aryl-Pd complex to the glycal double bond followed by *anti* elimination of $Pd(OAc)_2$ to provide a carbon-Ferrier type product. This method provides a practical and convenient stereoselective synthesis of *C*-arylglycosides.

There is a great deal of interest in *C*-aryl glycosides due to a number of factors that include their occurrence in natural products with important pharmacological properties[1] and their potential use as inhibitors of carbohydrate-processing enzymes[2]. These compounds are also valuable as chiral building blocks[3]. In particular, *C*-arylglycopyranosides with a double bond in the 2,3-position are useful synthetic intermediates, since this unsaturation can be further functionalized. A number of synthetic methods are available for such unsaturated compounds. Some of these include palladium(II)-mediated arylation of glycals[4], palladium- and nickel-catalyzed addition of Grignard reagents to an unsaturated glycopyranoside[5], and palladium(0)-catalyzed addition of arylzinc derivatives to hex-2-enopyranosides[6]. Although the yields of these reactions are good, in most cases they involve organometallic reagents that are air- and moisture-sensitive, toxic, pyrophoric, and not easy to handle. Also, the aryl groups are limited as a result of the incompatibility of different functional groups with the reaction conditions. As an alternative, we are interested in using arylboronic acids as carbo- based nucleophiles for the construction of *C*-arylglycosides. These reagents would be attractive because of their air and moisture stability, availability, and low toxicity.

The Lewis acid mediated carbon-Ferrier reaction of glycals with carbon nucleophiles including mildly nucleophilic organozinc reagents has been reported.[7] However, our initial attempts using a Lewis acid promoted carbon-Ferrier reaction with phenylboronic acid and 3,4,6-tri-*O*-acetyl-D-glucal **1** were unsuccessful. Lewis acids that were tried included $BF_3{\cdot}OEt_2$, $SnCl_4$, and TMSOTf. We next focused our attention to Czernecki's work, which showed that σ-aryl-Pd complexes undergo aryl palladation to glycal double bonds.[4] While this work provides a route to *C*-aryl glycosides, it lacks regioselectivity and generality in that it is limited by the substituents on the aromatic ring. We thought that we could generate a wide variety of σ-aryl-Pd complexes by a transmetalation reaction of boronic acid derivatives with a palladium(II) salt under very mild conditions. This method for generating σ-aryl-Pd complexes would be very valuable

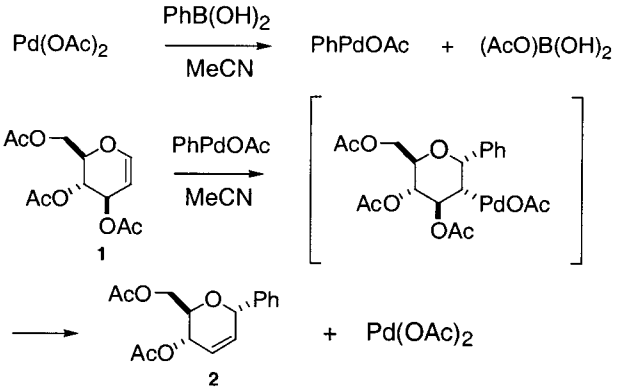
(1) Subadolnik, R. J. *Nucleoside Antibiotics*; Wiley-Interscience: New York, 1970.
(2) Nicotra, F. *Topics Curr. Chem.* **1997**, *187*, 55.
(3) (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. (b) Paterson, L.; Kewon, L. E. *Tetrahedron Lett.* **1997**, *38*, 5727. (c) Horika, K.; Sakkurai, Y.; Nagasawa, M.; Hachiya, S.; Yonemitsu, O. *Synlett* **1994**, 43.
(4) (a) Kwok, D.-I.; Farr, R. N.; Daves, G. D., Jr. *J. Org. Chem.* **1991**, *56*, 3711. (b) Czernecki, S.; Dechavanne, V. *Can. J. Chem.* **1983**, *61*, 533. (c) Daves, G. D., Jr. *Acc. Chem. Res.* **1990**, *23*, 201.

10.1021/ol010070q CCC: $20.00
Published on Web 05/26/2001

because of the regioselective control at the aromatic nucleus. The efficiency of the transmetalation from boron to palladium was previously demonstrated in the cross-coupling reaction of organoboron compounds with organic electrophiles.[8]

When commercially available 3,4,6-tri-*O*-acetyl-D-glucal **1** was treated with 1 equiv of palladium(II) acetate and 2 equiv of phenylboronic acid in acetonitrile at room temperature for 16 h, to our delight only product **2** was obtained in an isolated yield of 82% (Scheme 1). The ^{1}H and ^{13}C NMR

Scheme 1. Palladium(II) Acetate Mediated *C*-Glycosidation of Tri-*O*-acetyl-D-glucal **1**



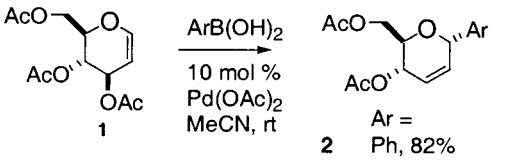
revealed the presence of a single anomer (**2**). Furthermore, the spectral data of **2** is identical to that reported in the literature,[4b] which had previously been assigned the α-configuration at the anomeric center. The mechanism of the reaction is believed to involve transmetalation of the phenylboronic acid to Pd(II)$(OAc)_2$ to give PhPdOAc,[9] which then undergoes *syn* addition to the α-face of the glycal double bond followed by *anti* elimination of palladium(II) acetate to give **2** (Scheme 1).[4]

Given the success of stoichiometric palladium in forming **2**, we were obligated to examine the possibility of using palladium(II) acetate in catalytic amounts. The yield of the *C*-phenylglycoside was similar with as little as 10% catalyst. Interestingly, in the reaction mixture we detected the presence of a black precipitate, which indicated that Pd(0) had formed. Upon examination of the nonpolar fraction we observed the formation of biphenyl. It had been shown previously that PhPdOAc can undergo a second transmetalation to give $PdPh_2$, which can undergo reductive elimination to give Pd(0) and biphenyl.[9] Although the formation of $PdPh_2$ would lead to the consumption of the catalyst, it could also add to the glycal double bond and generate **2** and PhPdOAc after *anti* elimination.

It should be noted that the use of $PdCl_2$ as catalyst lead to **2** in a poor yield of 8% with mostly unreacted starting material **1** after 3 days. It had been observed by others that the organic groups on the boron atom readily displace AcO-Pd(II)-X under neutral conditions, whereas the halogen−metal complexes are quite inert to such transmetalation with boronic acids.[10] Also, the use of $Pd(PPh_3)_4$ as a catalyst did not lead to any product.

The reaction is amenable to a variety of arylboronic acids; both electron-withdrawing, electron-donating, and sterically congested groups can be present on the phenyl ring (Scheme 2).[11] Electron-withdrawing groups on the phenyl ring seem

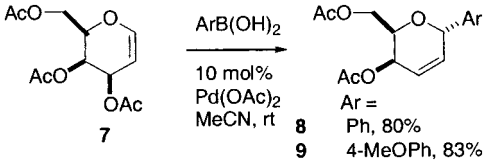
Scheme 2. Palladium(II) Acetate Catalyzed *C*-Glycosidation of Tri-*O*-acetyl-D-glucal **1** with Arylboronic Acids



to lower the yields of the *C*-glycoside product. However, the reaction does not seem to be affected by moderate steric congestion on the phenyl group (example **4**).

Similar results were obtained with the *C*-4 epimer of **1**. The galactal derivative **7** underwent addition with a variety of arylboronic acids to furnish the carbon-Ferrier type products (Scheme 3).

Scheme 3. Palladium(II) Acetate Catalyzed *C*-Glycosidation of Tri-*O*-acetyl-D-galactal **7** with Arylboronic Acids



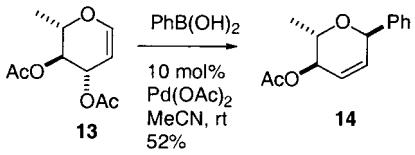
In all cases, only the α-anomer was obtained. This assignment is based on the mechanism and was confirmed by ^{13}C NMR (see Supplementary Information). The chemical shift of *C*-5 is diagnostic of the stereochemistry at the anomeric position. Upfield chemical shifts with values of

(5) Moineau, C.; Bolitt, V.; Sinou, D. *J. Org. Chem.* **1998**, *63*, 582.
(6) (a) Dunkerton, L. V.; Serino, A. J. *J. Org. Chem.* **1982**, *47*, 2812. (b) Dunkerton, L. V.; Euske, J. M.; Serino, A. J. *Carbohydr. Res.* **1987**, *171*, 89.
(7) Thorn, S. N.; Gallagher, T. *Synlett* **1996**, 185.
(8) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 247.
(9) Moreno-Manas, M.; Perez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346.
(10) (10) Cho, C. S.; Motofusa, S.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1995**, *60*, 883.
(11) **General Procedure.** To a mixture of the glycal (0.2 mmol) and arylboronic acid (0.4 mmol) in 1 mL of acetonitrile was added $Pd(OAc)_2$ (0.02 mmol). The resulting suspension was stirred at room temperature for 24 h. After this time, the mixture was diluted with 10 mL of CH_2Cl_2 and filtered through a pad of silica gel. The filtrate was concentrated and subjected to silica gel column chromatography using 80% hexanes/20% ethyl acetate as eluant. The reaction with phenylboronic acid was scaled up to a 5 g (**1**) scale with similar yield of the *C*-phenylglycoside product.

less than 75 ppm are characteristic of the *trans* relationship between substituents at the *C*-1 and *C*-5 positions (α-anomer) in unsaturated *C*-glycopyranosyl compounds.[2]

We also applied this methodology to a glycal derivative with the opposite stereochemistry at the *C*-3 position (Scheme 4). The reaction of phenylboronic acid with

Scheme 4. Palladium(II) Acetate Catalyzed *C*-Glycosidation of Di-*O*-acetyl-L-rhamnal **13** with Phenylboronic Acids



L-rhamnal diacetate furnished a single product in 52% yield whose spectral data is consistent with **14**. We assigned the product **14** as having a 1,5-*trans* stereochemistry on the basis of the reaction mechanism and the ^{13}C NMR data.

Mechanistically, it is possible that the intermediates that are generated under these reaction conditions could undergo a Heck-type β-hydride elimination to give the corresponding enol acetates. In fact, Czernecki and Daves, who used different conditions to generate the σ-aryl-Pd complexes, observed the Heck-type products.[4] Czernecki's method involved high temperature, whereas Daves' involved basic conditions. When we raised the temperature of our reaction, we did not observe any enol acetate, only unreacted starting material and a low yield of the carbon-Ferrier type products. Similar results were obtained under basic conditions using aqueous KOH in the reaction mixture. In both cases, under basic conditions and higher temperature, the reductive elimination to give biphenyl and Pd(0) predominated. We also tried conditions reported by Uemura and Cho, who showed that the Heck reaction of aliphatic alkenes with boronic acid derivatives occurred in the presence of catalytic $Pd(OAc)_2$ and sodium acetate in acetic acid.[13]

Surprisingly, under these conditions with the galactal derivative **7** only the product **8** was obtained in a yield of 15% along with recovered starting material. It seems that under the mild transmetalation conditions employed, *anti* elimination to give the *C*-Ferrier products is preferred over the Heck-type β-hydride elimination. It may be that the β-hydride elimination is reversible under these conditions.[14]

To conclude, we have disclosed preliminary results on a simple and convenient method for the stereoselective preparation of *C*-arylglycosides using arylboronic acids and $Pd(OAc)_2$ as catalyst. With the wide variety of boronic acid derivatives available and their stability toward moisture and air, this method could have many useful applications.

Acknowledgment. We wish to thank the Natural Sciences and Engineering Research Council of Canada for providing a fellowship to J.R.

Supporting Information Available: Spectroscopic data for compounds **2**−**6**, **8**−**12**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL010070Q

(12) Brakta, M.; Farr, R. N.; Chaguir, B.; Massiot, G.; Lavaud, C.; Anderson, W. R., Jr.; Sinou, D.; Daves, G. D., Jr. *J. Org. Chem.* **1993**, *58*, 2992.
(13) Cho, C. S.; Uemura, S. *J. Organomet. Chem.* **1994**, *465*, 85.
(14) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.