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Stereoselective *C*-Glycoside Formation by a Rhodium(I)-Catalyzed 1,4-Addition of Arylboronic Acids to Acetylated Enones Derived from Glycals

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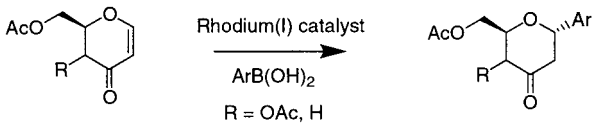
ABSTRACT



A new method for the formation of *C*-glycosides has been developed employing a cationic rhodium(I)-catalyzed 1,4-addition of arylboronic acids to enones derived from glycals. The reaction is stereoselective for the α-anomer and is highly dependent on the nature of the rhodium catalyst.

C-Glycosides and *C*-nucleosides are interesting carbohydrate congeners of *O*-glycosides and *N*-nucleosides that are resistant to enzymatic cleavage.[1] Several *C*-nucleosides and *C*-glycosides possess potent antibacterial, antiviral, and antitumor activity.[2] For example, several halogenated benzimidazole *C*-nucleosides are known to be active against human cytomegalovirus.[3]

While the importance of *C*-glycosides is evident from their range of biological activities, methods for their preparation are quite limited. Typically they have been synthesized by the addition of an appropriate organometallic reagent to a carbohydrate lactone to form a hemiketal that could be subsequently reduced to the cyclic ether.[4] Alternatively they have been made by the addition of organometallics such as Grignards, stannanes, and organomecurials to 1-halo sugars, alkyl and acylsilanes to glucals, or 1,2-anhydro-sugars and electron-rich aromatics to glycosyl donors.[4] Cross-coupling reactions of a suitable 1-vinylstannane or boronic acid have also been reported.[4] An interesting example of a palladium-catalyzed *C*-glycosidation of *tert*-butylphenyl-α-*O*-Δ^2-glycopyranoside with various arylmagnesium bromides has been reported by Sinou and co-workers.[5] An approach that we were particularly interested in investigating involved the palladium(II)-mediated arylation of acetylated enones derived from glycals.[6] This reaction proceeded by the addition of the *σ*-arylpalladium complex to the enone double bond but was limited to simple phenyl substitution. We therefore sought a more general methodology allowing for the addition of various substituted aryl groups. To this end, we felt that the rhodium(I)-catalyzed addition of arylboronic acids to acyclic and cyclic enones reported by Miyaura[7] would provide a suitable means for introducing a *C*1-aryl group into the pyranose ring.

(1) (a) Jarmillo, C.; Knapp, S. *Synthesis* **1994**, 1. (b) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545.
(2) Hacksell, C. V.; Daves, G. D., Jr. *J. Med. Chem.* **1985**, *22*, 1.
(3) (a) Townsend, L. B.; Devivar, R. V.; Turk, S. R.; Nassiri, M. R.; Drach, J. C. *J. Med. Chem.* **1995**, *38*, 4098. (b) Gudmunsson, K. S.; Drach, J. C.; Townsend. L. B. *J. Org. Chem.* **1997**, *62*, 3453.
(4) Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913 and references therein.
(5) Moineau, C.; Bolitt, V.; Sinou, D. *J. Chem. Soc., Chem. Commun.* **1995**, 1103.
(6) Benhaddou, R.; Czernecki, S.; Ville, G. *J. Org. Chem.* **1992**, *57*, 4612.
(7) (a) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **1998**, *120*, 5579. (c) Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 5951.

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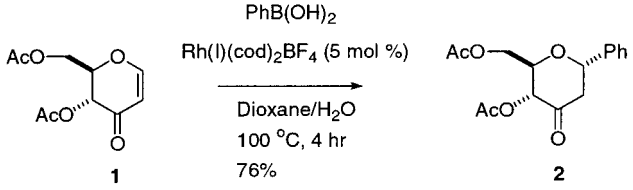
The enone **1** was synthesized by direct oxidation of tri-*O*-acetyl-D-glucal with [hydroxy(tosyloxy)-iodo]benzene.[8] Using the conditions reported by Miyaura, we attempted a rhodium-catalyzed 1,4-addition of phenylboronic acid. Unfortunately, reaction of **1** with $Rh(acac)(C_2H_4)_2$ in the presence of phosphine ligands such as R- and S-BINAP, dppf, and others did not lead to 1,4-addition products. A series of other rhodium(I) catalysts were tried, including $Rh(PPh_3)_3Cl$, Rh(bicyclo[2.2.1]heptadiene-dppb BF_4, and Rh_2Cl_2(bicyclo[2.2.1]heptadiene)$_2$, but were unsuccessful. Also, conventional Lewis acid catalysts such as BF_3OEt_2, $SnCl_4$, and TMSOTf failed to give any 1,4-addition product. However, this problem could be overcome by the use of the cationic rhodium complex $Rh(cod)_2BF_4$. To our delight, when enone **1** was heated with phenylboronic acid in the presence of $Rh(cod)_2$ BF_4 in dioxane/water at 100 °C, a 76% yield of the 1,4-addition product **2** was obtained (Scheme 1).

Scheme 1. Rhodium(I)-Catalyzed 1,4-Addition of Phenylboronic Acid to Enone **1**

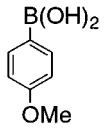
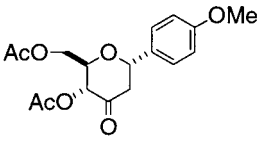
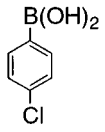
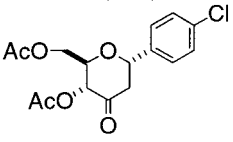
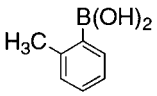
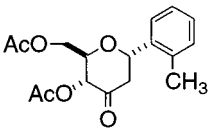
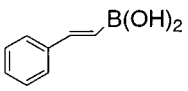
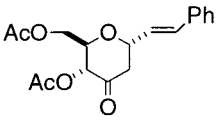


The ^1H and ^{13}C NMR revealed the presence of a single anomer that was assigned the α-configuration at the anomeric center. This assignment was based on the ^1H NMR data of **2** that was reported in the literature.[6] It was shown that **2** adopts a $^4C_1$(D) conformation bearing two bulky groups in equatorial positions and the phenyl group in an axial position at the anomeric center. On the basis of this conformation, the coupling constant for the anomeric proton (5.52 ppm) is small ($J_{1,2'}$ = 5.2 Hz) as the result of an axial−equatorial coupling, consistent with an axial aryl group. In addition, the ^{13}C NMR revealed an upfield shift of the C-5 carbon (<75 ppm) that is indicative of a 1,5-*trans* relationship of substituents.[9] The lack of epimerization at C-4 and the axial−axial relationship of H4 and H5 in compound **2** was confirmed by the doublet at 5.28 ppm with a large coupling constant ($J_{4,5}$ = 10.1 Hz).

A variety of boronic acid derivatives can be used, including electron-donating, vinyl, electron-withdrawing, and sterically conjested groups, with isolated yields ranging from modest to good (Table 1).[10]

In all cases, the ^1H and ^{13}C NMR indicated that only one anomer is present (see Supporting Information). Based on similar arguments for the phenyl derivative **2**, the configuration at the anomeric center in each case is α.

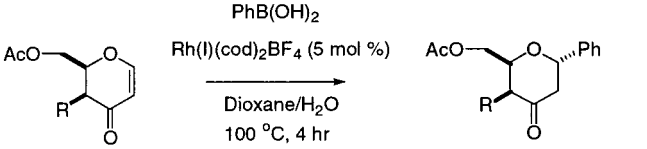
Table 1. Rhodium(I)-Catalyzed 1,4-Addition of Boronic Acid Derivatives to Enone **1**

entry	boronic acid	*C*-glycoside (yield)[a]
1		 **3** (81%)
2		 **4** (50%)
3		 **5** (74%)
4		 **6** (56%)

[a] Isolated yields after chromatography.

The 1,4-addition reaction could be applied to other enones that are derived from glycals. The acetylated enones **7** and **8** were synthesized by the oxidation of 2,4,6-tri-*O*-acetyl-D-galactal and 3,6-di-*O*-acetyl-4-deoxy-D-glucal,[11] respectively, with [hydroxy(tosyloxy)-iodo]benzene. Addition of phenylboronic acid using the general procedure gave the 1,4-addition products **9** and **10** in yields of 70% and 75%, respectively (Scheme 2).

Scheme 2. Rhodium(I)-Catalyzed 1,4-Addition of Phenylboronic Acid to Enones **7** and **8**



In both cases, the ^1H and ^{13}C NMR indicated that a single anomer is present. The stereochemistry of **9** was assigned

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(10) **General Procedure.** A mixture of the enone (0.2 mmol), boronic acid (0.4 mmol), $Rh(I)(cod)_2BF_4$ (0.01 mmol), 0.05 mL of H_2O, and 1.0 mL of dioxane was heated at reflux for 4 h. After this time, the reaction mixture was diluted with ethyl acetate (10 mL) and filterd through a pad of silica gel. The filtrate was concentrated and subjected to silica gel flash column chromatography using 80% hexanes/20% ethyl actetate as eluant.

(11) Greico, P. A.; Speake, J. D. *Tetrahedron Lett.* **1998**, *39*, 1275.

the α configuration at the anomeric center on the basis of the ^{1}H NMR data reported in the literature.[6] It was reported that **9** adopts a $^1C_4$(D) conformation, in which one bulky group out of the three is in the axial position. This results in a $J_{1,2'}$ larger than that of the corresponding glucal derivative **2** suggesting an axial position for H1. The ^{13}C NMR spectra for compounds **9** and **10** indicated an upfield shift of the C-5 carbon (<75 ppm) that is indicative of a 1,5-*trans* relationship of substituents. Also, the ^{1}H NMR data for **10** is consistent with the α-anomer since the $J_{1,2'}$ value is similar to that of **2**. If it were the *β*-anomer, the substituents would be in equatorial positions, placing the anomeric proton in an axial position and thus resulting in a larger coupling constant for $J_{1,2'}$. It is interesting that the reaction is stereoselective for the α-anomer. This had been observed for the addition of organopalladium reagents to carbohydrate enones.[6]

Similar to the catalytic cycle proposed by Miyaura, the mechanism for the rhodium(I)-catalyzed 1,4-addition of arylboronic acid derivatives to the carbohydrate enones is shown in Figure 1.[7] Initial transmetalation of the aryl group from boron to rhodium occurs, which is probably facilitated by fluoride anion.[12] The organometallic species then adds stereoselectively to the α-face of the enone double bond with subsequent hydrolysis of the Rh−O bond. Under anhydrous conditions, a low yield (<5%) of the 1,4-addition product **2** was obtained, suggesting a need for H_2O. Presumably, water serves to protonate the Rh−O bond. It is noteworthy that the use of rhodium(I)$(cod)_2$OTf as a catalyst did not give any product. However, when a catalytic amount of KOH is added to the reaction mixture (1:1 catalyst/KOH), the reaction is complete after 15 min of heating at 100 °C. The role of hydroxide could be to facilitate the transmetalation,[13] or it could react with the rhodium triflate precatalyst to give HORh$(cod)_2$ or a combination of both. Fürstner and Krause observed a similar effect of the base on the rhodium-catalyzed addition of arylboronic acids to aldehydes.[14] Using our new system, the molar ratio of the catalyst can be reduced to 1% with a similar yield of the 1,4-addition product **2**.

Unlike the 1,4-addition to cyclic and acyclic enones, the present reaction is inhibited by the addition of phosphine ligands. It seems that the pyranose oxygen may reduce the reactivity of the double bond and the addition of phosphine ligands might reduce the cationic nature of the rhodium catalyst. Oi has reported a similar inhibition with the addition of phosphine ligand for the cationic rhodium-catalyzed addition of trimethylstannane to benzaldehydes.[15]

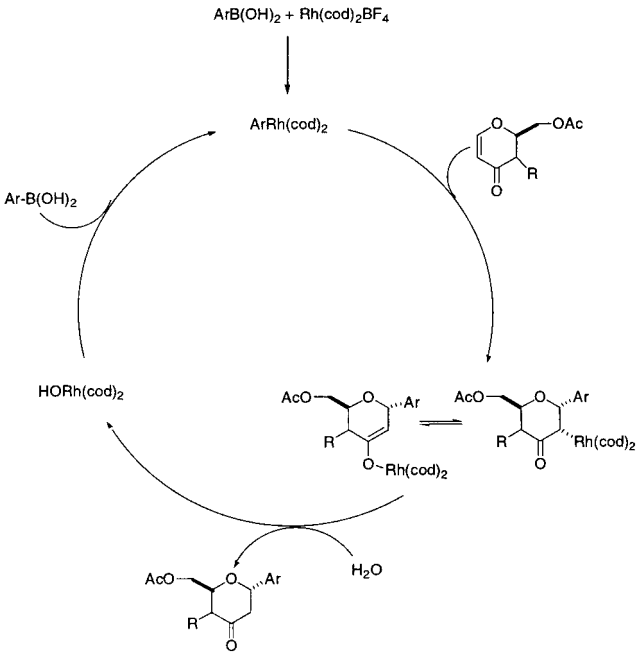

Figure 1. Proposed catalytic cycle.

In summary, we have reported the first rhodium-catalyzed 1,4-addition reaction for the stereoselective synthesis of *C*-glycosides. With the availability of a number of boronic acid derivatives, 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**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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