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Facile Pd-Catalyzed Cross-Coupling of 2′-Deoxyguanosine O^6-Arylsulfonates with Arylboronic Acids

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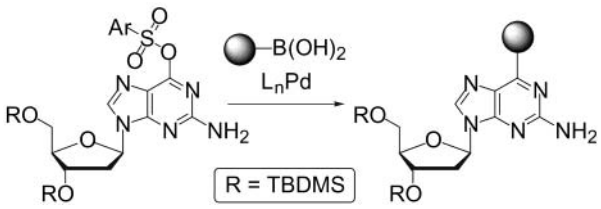
ABSTRACT



The O^6-(2-mesitylenesulfonyl) derivative of 2′-deoxyguanosine undergoes a facile palladium-mediated C–C cross-coupling with arylboronic acids. Demonstrating the general applicability of this method, the synthesis of a previously undescribed class of 2-amino-6-arylpurine 2′-deoxynucleosides has been accomplished. The study also describes an evaluation of the O^6-(2,4,6-triisopropylphenylsulfonyl) and the O^6-(4-toluenesulfonyl) derivatives for the cross-coupling.

Modified purines and purine nucleoside derivatives play a prominent role in biology, biochemistry, and pharmaceutics. For example, several are modulators of adenosine receptors, some stimulate plant cell growth and cell division, some are known to inhibit DNA polymerases with inhibitory properties toward normal as well as cancer cells, and others have antiviral properties.[1−5] Recently, a class of C-6 aryl purine ribonucleosides has been shown to possess cytostatic activity toward T-lymphoblastoid, He-La, and L1210 cells, as well as L929 cell lines.[6] Also, unusual hydrophobic nucleosides have been utilized for studies on aryl stacking in DNA and for their base-pairing properties.[7,8]

Whereas palladium-catalyzed C−C bond formation is not new to the class of nucleosides,[9] the Suzuki−Miyaura cross-coupling for nucleoside modification has received attention only recently.[6,10,11] This method has since led to the development of several nucleoside analogues.[12]

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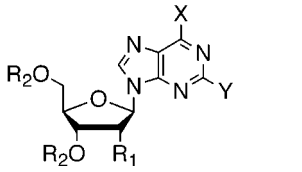
The classic method for the synthesis of biaryls by the Suzuki−Miyaura protocol involves the Pd-mediated cross-coupling of a haloaromatic or aryltriflate with an arylboronic acid.[13,14] Such a method has been the basis of recent work by us[11] and others[6,10] on nucleoside modification. For example, the 6-halo 2′-deoxy nucleosides (**1** and **2**, Figure 1) and the 6-chloro ribonucleosides (**3** and **4**, Figure 1) have



1: X = Br, Y = R_1 = H
2: X = Cl, Y = R_1 = H
3: X = Cl, Y = H, R_1 = OR_2
4: X = Cl, Y = NH_2, R_1 = OR_2

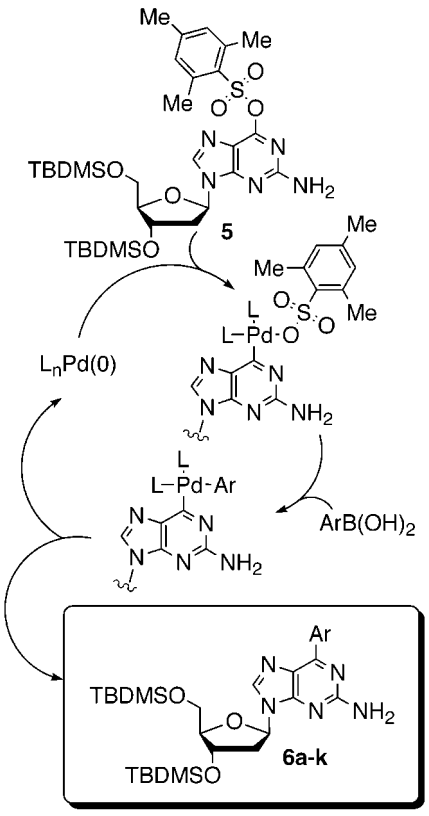
Figure 1. C-6 halonucleosides that have been used in Suzuki−Miyaura cross-coupling reactions (R_2 = TBDMS or acyl).

been used for the synthesis of the corresponding 6-arylpurine nucleosides. Among the four substrates studied to date, **4** bears an additional 2-amino functionality. This chloro derivative is readily prepared from guanosine[15] and is also commercially available. In contrast to the convenient availability of **4**, synthesis of the corresponding 2′-deoxy analogue (X = Cl, Y = NH_2, and R_1 = H in Figure 1) via chlorination of 2′-deoxyguanosine proceeds in only 15% yield.[16] Therefore, this is an immediate limitation for the synthesis of 2-amino-6-arylpurine 2′-deoxynucleosides.

As a result of our interest in studying Pd-mediated C−N and C−C bond formation on nucleic acid components we became involved in addressing this problem. In their studies on DNA cross-linking, Sasaki and co-workers have demonstrated that the O^6-sulfonate (triflate and tosylate) derivatives of guanosine and 2′-deoxyguanosine can be efficiently coupled with vinylstannanes under catalysis by Pd.[17] Whereas cross-coupling of the nucleoside triflate was not very surprising, based on the known reactivity of triflates, the reaction of the tosylate was interesting to us. In simpler aromatic systems, arylsulfonates have not received general applicability as substrates for cross-coupling, and only recently has the utility of aryltosylates been studied for Ni-catalyzed Suzuki reactions.[18]

On the basis of these considerations we became interested in probing the utility of O^6-arylsulfonates of purine nucleosides for cross-coupling with arylboronic acids, an aspect that has not been explored to date. This would also open a novel avenue to nucleoside modification from the readily prepared O^6-arylsulfonates.[19] For our studies we focused on the O^6-arylsulfonates of 2′-deoxyguanosine since Suzuki−Miyaura reactions at the C-6 position of this nucleoside have not been reported. Although a variety of O^6-arylsulfonates can be prepared from guanosine and 2′-deoxyguanosine, we chose the 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl) O^6-(2-mesitylenesulfonyl) derivative of the latter[20] (**5** in Scheme 1) because

Scheme 1



of the following considerations: (a) the easily removed silyl protection on the carbohydrate moiety is robust under Pd-catalyzed cross-coupling conditions, and (b) we were familiar with its reactivity and stability as a result of our previous

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experience with this derivative for C−O as well as C−N bond formation under S_NAr conditions.[21]

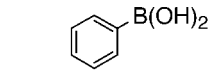
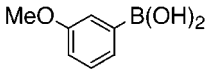
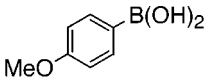
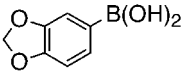
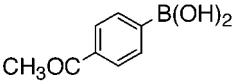
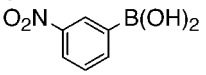
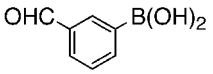
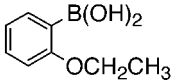
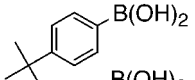
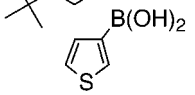
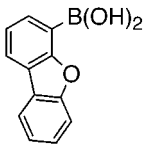
As an initial test the reaction of **5** with phenylboronic acid was considered. However, an optimal catalytic system needed determination. On the basis of our recent report, the combination of $Pd(OAc)_2$/2-(dicyclohexylphosphino)biphenyl/K_3PO_4 was initially chosen.[11] Use of this catalytic system in anhydrous 1,4-dioxane led to a smooth cross-coupling of **5** with phenylboronic acid within 1 h at 100 °C, with a 59% yield of the C-6 phenyl derivative **6a**. Several other ligands were tested in combination with $Pd(OAc)_2$ and K_3PO_4, keeping all other conditions the same, but these proved to be inferior. The yields of the C-6 phenyl product **6a** obtained in these cases were (a) 45% with 1,1′-bis(diphenylphosphino)ferrocene, (b) 15% with 2-(di-*tert*-butylphosphino)biphenyl, (c) 0% with (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (consumption of **5** occurred, but no product formation was observed by TLC), and (d) 22% with 2-(dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino)-1,1′-biphenyl.

Initial experimentation also led to an interesting observation. Reactions of **5** with phenylboronic acid involving catalytic systems composed of $Pd(OAc)_2$/2-(dicyclohexylphosphino)biphenyl/K_3PO_4 and $Pd(OAc)_2$/2-(dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino)-1,1′-biphenyl/K_3PO_4 showed progress at room temperature but were incomplete at this temperature after 24 h. This led to evaluation of reaction temperatures below 100 °C but higher than room temperature. At 80 °C extremely fast reactions were observed and the cross-coupling of **5** with phenylboronic acid was complete within *30 min*, providing the C-6 phenyl product **6a** in 76% yield. To our knowledge this reaction, if not the fastest Suzuki−Miyaura reaction, is the fastest such reaction among nucleosides.

With the initial experimentation completed and the optimal conditions ascertained, the next stage was an evaluation of the generality of the methodology with a variety of boronic acids. Table 1 shows the structures of the boronic acids used, the cross-coupling times, and the isolated yields of the products from these reactions.

From Table 1 it is clear that a wide assortment of arylboronic acids undergoes cross-coupling under the reaction conditions. Particularly noteworthy are reactions with the electron-deficient arylboronic acids containing 4-acetyl, 3-nitro, and 3-formyl moieties, all of which react smoothly. Interestingly, in contrast to the 4-acetyl and 3-formylphenylboronic acids, 3-acetylphenylboronic acid did not yield any product, and we are currently unaware of the reasons for this. Compounds **6a**−**g** were produced in an extremely short reaction period of 30 min, with 1.5 molar equiv of the arylboronic acids. In our previous study we have reported that 2-ethoxyphenylboronic acid undergoes relatively slow cross-coupling.[11] Along similar lines, in the present work, reaction of **5** with 1.5 molar equiv of this arylboronic acid resulted in a slow reaction (incomplete in 24 h). Increasing the boronic acid to 3.0 molar equiv resulted in a significantly faster reaction (5 h). Analogous to the reaction with 2-ethoxyphenylboronic acid, use of 1.5 molar equiv of dibenzofuran-4-boronic acid resulted in a slow reaction (46 h). In this case increasing the boronic acid to 2.5 molar equiv yielded a significantly faster reaction, reaching completion in just 30 min. The faster reaction rate with dibenzofuran-4-boronic acid compared to 2-ethoxyphenylboronic acid is perhaps attributable to a more tied-back ortho substituent compared to the 2-ethoxy derivative. Alternatively, the oxygen atom in **6k** being less electron-rich could render it less effective in enabling any potential Pd sequestration

Table 1. Arylboronic Acids Used for the C−C Cross-Coupling, Reaction Times, and Yields[a]

Ar-$B(OH)_2$	rxn. time	product, % yield
	0.5 h	**6a**, 76
	0.5 h	**6b**, 81
	0.5 h	**6c**, 73
	0.5 h	**6d**, 78
	0.5 h	**6e**, 64
	0.5 h	**6f**, 82
	0.5 h	**6g**, 82
	5.0 h	**6h**, 65*
	2.0 h	**6i**, 90*
	0.5 h	**6j**, 78*
	0.5 h	**6k**, 71*

[a] For yields marked by asterisk, see discussion in the text.

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compared to that in **6h**. The cross-coupling of **5** with 1.5 molar equiv of 3-thiopheneboronic acid was also slow (70 h), consistent with our previous observations.[11] Use of 2.5 molar equiv of this boronic acid led to complete reaction within 30 min in this case as well. Perhaps a more surprising result stemmed from the use of 4-*tert*-butylphenylboronic acid, where incomplete reaction (48 h) was observed with 1.5 molar equiv of the boronic acid. Again, in this case increasing the boronic acid to 3.0 molar equiv resulted in a complete reaction within 2 h.

Reactions leading to products **6h**−**k** provide an interesting insight into the reaction course. Since use of higher amounts of the arylboronic acid yielded faster reactions, it is conceivable that at least in these cases if not others, the transmetalation step involving the arylboronic acid may be rate-limiting. This is similar to what has been recently suggested for Ni-catalyzed C−C cross-coupling of simpler aryltosylates.[18]

Although we had conclusively demonstrated the utility of **5** for C−C cross-coupling, we were interested in performing an initial evaluation of other arylsulfonates for the transformation. Thus, the O^6-(2,4,6-triisopropylphenylsulfonyl) (O^6-TIPS) and the O^6-(4-toluenesulfonyl) (O^6-Ts) derivatives (**7** and **8** in Figure 2) were prepared as described.[17] Reactions

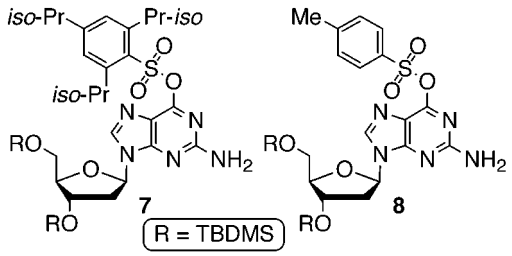

Figure 2. The O^6-TIPS (**7**) and O^6-Ts (**8**) derivatives of 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine.

of **7** and **8** with phenylboronic acid under the optimized cross-coupling conditions were complete within 30 min in each case. The isolated yield of **6a** from **7** was 50%, whereas a 90% yield of the product was obtained from **8**. These results seem to suggest that any O^6-arylsulfonate of 2′-deoxyguanosine is potentially a substrate for Pd-mediated C−C cross-coupling. However, there appear to be currently unknown factors that lead to the different product yields in the reactions of **5**, **7**, and **8** with phenylboronic acid.

Although nucleoside dimers have been synthesized by Pd-catalyzed C−N cross-coupling involving the exocyclic amino groups of nucleosides, it is noteworthy that in the present cases no competing C−N bond-formation was observed.[22] Finally, regarding the hydroxyl protection, our results[11,23] and those of others[6,10] suggest that either the TBDMS or acyl groups are effective in Pd-catalyzed transformations of nucleosides. The TBDMS groups can be readily cleaved without degradation of the nucleoside,[24] and removal of the acyl group has already been described.[6,10]

In conclusion, we have demonstrated that the O^6-arylsulfonate derivatives of 2′-deoxyguanosine can be used as surrogates for the halo analogues in Suzuki−Miyaura reactions. This has also led to the identification of some of the fastest C−C cross-coupling reactions reported to date on nucleosidic substrates. Further, the use of anhydrous reaction conditions allows for C−C bond formation to be conducted with nucleoside arylsulfonate substrates that can potentially hydrolyze under the more conventional aqueous conditions. Detailed investigations on the exact utility of various arylsulfonates, as well as other types of metal-mediated transformations on these derivatives, are currently being investigated in our laboratories.

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Supporting Information Available: Experimental procedures and NMR and HRMS data for compounds **6a**−**k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Cleavage of the TBDMS groups in 6-phenyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxynebularine (ref 11) was achieved within 0.5 h with n-$Bu_4N^+F^-$ in THF at 0 °C (see Supporting Information).