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Pd–Xantphos-Catalyzed Direct Arylation of Nucleosides

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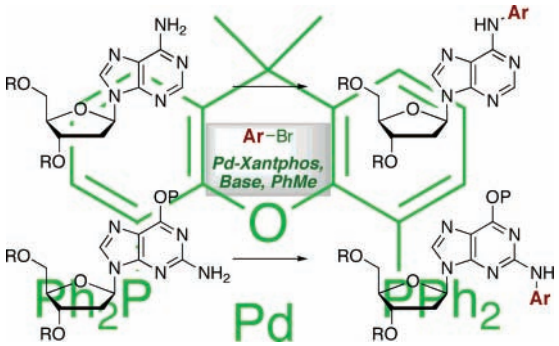
ABSTRACT



Direct arylation of the exocyclic amino groups of nucleosides represents a simple approach to *N*-aryl nucleoside derivatives. To date, one limitation has been that only electron-deficient aryl bromides and triflates possessed adequate reactivity for efficient, direct N-arylation of nucleosides. We demonstrate herein that Pd–Xantphos catalytic systems lead to successful N-arylation of suitably protected 2′-deoxyadenosine and 2′-deoxyguanosine with a wide range of aryl bromides.

Palladium-catalyzed C−N bond formation is emerging as a powerful technique for the synthesis of unusual and biologically important nucleoside derivatives.[1] This method has yielded nucleoside conjugates of carcinogens and mutagens at the C-6, C-2, and C-8 positions that can be used for structural, biochemical, and biological studies.[2−9]

Generally, the most effective method for aryl amination of nucleosides involves the reaction between a halogenated nucleoside and an arylamine, mediated by a suitable Pd−ligand complex.[2−12] Although there are also recent examples of aryl amination by a direct displacement of halides or other leaving groups from the C-6 position of purine nucleosides, the applicability of these reactions to electron-deficient aniline derivatives is presently unknown.[13−15]

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A simple synthesis of *N*-aryl nucleosides is through the use of the nucleoside as the amine donor in Pd-mediated amination reactions. Although this has been tested with protected adenine and guanine nucleosides, typically only activated (electron-deficient) aryl bromides and triflates produced good yields.[9,16,17] In our own work, we have encountered only limited applicability of this method.[8]

Recently, we have been studying the use of Pd−Xantphos complexes for amination reactions of nucleosides with azoles.[18] In this context, we decided to reevaluate the use of protected nucleosides in amination reactions with aryl bromides. Pd−Xantphos combinations have been utilized for the synthesis of aryl amino 2′-deoxyguanosine derivatives,[19] but only limited success has been realized for N^2-arylation.[20] This communication demonstrates a generally good utility of Pd−Xantphos complexes in effecting arylation at the exocyclic C-6 and C-2 amino groups of purine 2′-deoxyribonucleosides.

Initial experimentation began by assessing conditions for the amination of bromobenzene with the easily prepared 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine.[21] Four ligands were selected for this analysis (Figure 1). $Pd(OAc)_2$ and $Pd_2(dba)_3$ were utilized as the metal source, and toluene was chosen as solvent. At 90 °C, the combination of $Pd(OAc)_2$, any one of the ligands **L-1**, **L-2**, or **L-3**, and either Cs_2CO_3 or K_3PO_4 as base led to no discernible product formation over a 24 h period. On the other hand, 10 mol % of $Pd(OAc)_2$/15 mol % of **L-4** with either Cs_2CO_3 or K_3PO_4 (1.4 equiv) led to low yields of the desired product (∼20%), and 10 mol % of $Pd(OAc)_2$/10 mol % of **L-4**/1.4 equiv of Cs_2CO_3 gave a 48% yield. Interestingly, 10 mol % of $Pd_2(dba)_3$/15 mol % of **L-4**/1.4 equiv of Cs_2CO_3 led to some yield improvement (59%), but replacing Cs_2CO_3 with K_3PO_4 lowered the yield (45%).[22] Finally, combinations of $Pd_2(dba)_3$ and ligands **L-1**, **L-2**, and **L-3** with Cs_2CO_3 or K_3PO_4 were tested. In these cases, no product formation to low levels of product formation were observed (see the Supporting Information for a comprehensive table of results). Formation of a N^6,N^6-dimer has previously been observed when stoichiometric amounts of **1** were employed that could be suppressed by use of **1** in excess.[16] Therefore, in the present study, 30% excess **1** was used.

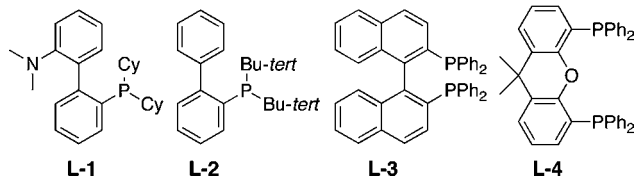

Figure 1. Four ligands selected for analysis.

These initial experiments helped establish the combination of $Pd_2(dba)_3$/**L-4**/Cs_2CO_3 as optimal for successful reaction. The special properties of **L-4** such as the possible trans coordination and the presence of the apical oxygen atom that can enable cis−trans isomerization of oxidative−addition complexes are likely contributions to the effectiveness of this ligand when compared to **L-3**, which like **L-4** is also capable of bis coordination.

Next, the generality of this direct arylation was probed. Aryl bromides of varied electronic nature and substituents were utilized, and the results of these experiments are collected in Table 1. The results in Table 1 clearly show that good to excellent yields of N^6-aryl 2′-deoxyadenosine analogues can be obtained. The reaction works well with ortho-substituted aryl bromides (entries 2, 4, 9, and 12). As expected, electron-deficient aryl bromides undergo amination, but more remarkably, electron-rich aryl halides also react quite well. The naphthalene systems are slower reacting (entries 10−12), and among the three, the least-hindered 2-bromonaphthalene reacts fastest. It is currently not clear why the 4-acetyl and 4-formyl bromobenzenes react slowly compared to the 4-cyano. Nevertheless, good conversions were observed in each case.

Confirmation of the arylation site was obtained via two methods. Because we have synthesized **2c**, **2d**, **2g**, and **2m** via a C−N bond formation between an arylamine and a C-6 bromo nucleoside,[8,10] unequivocally established ^{1}H NMR data could be directly compared in these cases. Second, as representative examples, ^{13}C NMR spectra of **2c** and **2g** were compared to those of the products obtained via C−N bond formation of the C-6 bromo nucleoside with the respective arylamines[10] (see the Supporting Information). These comparisons indicated the arylation reactions to occur at the N^6.

Attention was next focused on 2′-deoxyguanosine. Although unprotected 2′-deoxyguanosine has been utilized for efficient C−C bond-forming reactions in an aqueous medium,[23] it was subsequently demonstrated that O^6-unprotected guanine may retard the rates of C−C bond formation via N^1 and/or O^6 coordination.[24] On the basis of these results, we chose the use of an O^6-protected 2′-deoxyguanosine derivative and decided to conduct initial experimentation on the

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(22) It has been demonstrated that a 2:1 ligand−Pd complex forms even at a 1:l 4,7-di-*tert*-butylXantphos/Pd ratio. This 2:1 complex is a relatively unreactive precatalyst: Klingensmith, L. M.; Strieter, E. R.; Barder, T. E.; Buchwald, S. L. *Organometallics* **2006**, *25*, 85−91. In an attempt to favor a greater proportion of a 1:1 Xantphos−Pd complex, only 15 mol % of ligand was used with 10 mol % of $Pd_2(dba)_3$.
(23) Western, E. C.; Daft, J. R.; Johnson, E. M.; Gannett, P. M.; Shaughnessy, K. H. *J. Org. Chem.* **2003**, *68*, 6767−6774.
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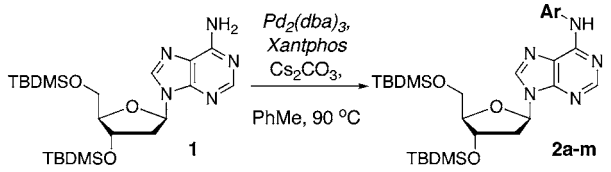
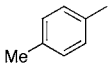
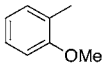
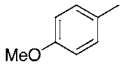
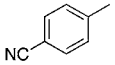
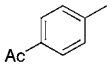
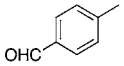
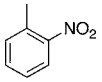
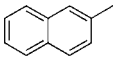
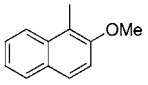
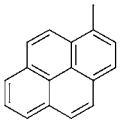
Table 1. Reactions of Various Aryl Bromides with 3′,5′-Bis-*O*-(*tert*-butyldimethyl)-2′-deoxyadenosine[a]



entry	Ar-Br	time (h)[b]	product, yield[c]
1		2	**2a**: 59%
2		4	**2b**: 75%
3		4	**2c**[10]:70%
4		2	**2d**[10]: 88%
5		5	**2e**: 61%
6		5	**2f**: 94%
7		24	**2g**[10]: 84%
8		24	**2h**: 95%
9		1	**2i**: 98%
10		47	**2j**: 98%
11		22	**2k**: 82%
12		48	**2l**: 87%
13		18	**2m**[8]: 53%

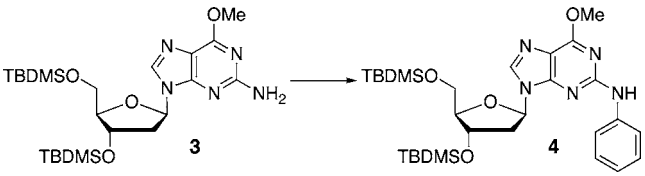
[a] Reaction conditions: 0.42 mmol of nucleoside in 3 mL of PhMe, 10 mol % of $Pd_2(dba)_3$, 15 mol % of **L-4**, 1.4 equiv of Cs_2CO_3, 90 °C. [b] Reactions were monitored for completion by TLC. [c] Yield is of isolated, purified product.

easily prepared 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-O^6-methyl-2′-deoxyguanosine **3**.[25] The results from these experiments are summarized in Table 2.

The initial experimentation made it evident that the Pd(OAc)$_2$/**L-4**/*tert*-BuONa combination was suitable for N^2-arylation of **3**. Although $Pd_2(dba)_3$ was useable in this case,

(25) Lakshman, M. K.; Ngassa, F. N.; Keeler, J. C.; Dinh, Y. Q. V.; Hilmer, J. H.; Russon, L. M. *Org. Lett.* **2000**, *2*, 927−930.

Table 2. N^2-Arylation of 3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-O^6-methyl-2′-deoxyguanosine with Bromobenzene[a]



entry	**3**:Ph−Br	catalytic system, solvent, temp	time,[b] result
1	1:1	10 mol % of Pd(OAc)$_2$, 10 mol % of **L-4**, 1.5 equiv of *tert*-BuONa, PhMe, 85 °C	24 h, 33% yield[c]
2	1:2	10 mol % of Pd(OAc)$_2$, 10 mol % of **L-4**, 1.5 equiv of *tert*-BuONa, PhMe, 85 °C	1 h, 88% yield[c]
3	1:2	10 mol % of Pd(OAc)$_2$, 10 mol % of **L-4**, 1.5 equiv of *tert*-BuONa, DME, 85 °C	24 h, trace[d]
4	1:2	20 mol % of Pd(OAc)$_2$, 20 mol % of **L-4**, 1.5 equiv of *tert*-BuONa, PhMe, 85 °C	1 h, 89% yield[c]
5	1:2	30 mol % of Pd(OAc)$_2$, 30 mol % of **L-4**, 1.5 equiv of *tert*-BuONa, PhMe, 85 °C	1 h, 68% yield[c]
6	1:2	10 mol % of Pd(OAc)$_2$, 15 mol % of **L-4**, 1.5 equiv of *tert*-BuONa, PhMe, 85 °C	24 h, trace[d]
7	1:2	10 mol % of Pd(OAc)$_2$, 20 mol % of **L-4**, 1.5 equiv of *tert*-BuONa, PhMe, 85 °C	24 h, incomplete[d]
8	1:2	10 mol % of Pd(OAc)$_2$, 30 mol % of **L-4**, 1.5 equiv of *tert*-BuONa, PhMe, 85 °C	24 h, incomplete[d]

[a] Reactions conducted with 0.08 mmol of nucleoside in 1 mL of solvent. [b] Reactions were monitored by TLC. [c] Yield is of isolated, purified product. [d] Product formation was observed by TLC but was not isolated.

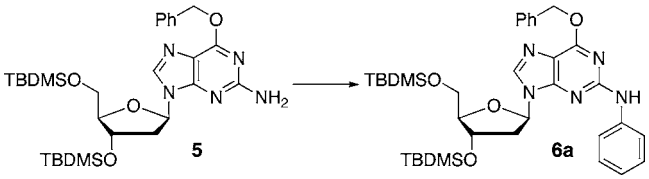
as for the arylation of **1**, the results were inferior in comparison to Pd(OAc)$_2$. Other critical factors also came to light in Table 2: (a) in contrast to the reactions of **1**, a 1:2 ratio of **3** to bromobenzene is necessary for effective conversion (entry 1 vs 2); (b) use of PhMe as solvent is critical (entry 2 vs 3); (c) a 1:1 stoichiometry of Pd/ligand results in reasonably good product yields (entries 2, 4, and 5); and (d) an increase in ligand concentration relative to Pd is detrimental to the reaction (entry 2 vs 6−8).

With these results in hand, we conducted the next series of experiments with O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine **5**,[11] where the O^6 protecting group can be readily removed by catalytic debenzylation. The results from the arylation of **5** with bromobenzene are shown in Table 3.

Results in Table 3 parallel those in Table 2 and lead to some additional understandings. As with **3**, the ratio of nucleoside to bromobenzene is important (entry 1 vs 2), and use of PhMe as solvent continued to be a critical factor (entry 2 vs 3). A 1:1 ratio of Pd/ligand provided satisfactory results, although in this case both 10 mol % of Pd(OAc)$_2$/10 mol % of **L-4** and 30 mol % of Pd(OAc)$_2$/30 mol % of **L-4** produced comparable yields (entries 2 and 4). Use of the weaker bases K_3PO_4 and Cs_2CO_3 was ineffective for the arylation reaction (entries 5 and 6). Interestingly, a good yield of **6a** could be realized even at a catalyst loading of 5 mol % of Pd(OAc)$_2$/5 mol % of **L-4**, although the reaction was a little slower and produced a lowered yield.

Having completed the optimization experiments with two O^6-protected 2′-deoxyguanosine derivatives **3** and **5**, the next set of experiments involved an assessment of the generality

Table 3. N^2-Arylation of O^6-Benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine with Bromobenzene[a]



entry	**5**:Ph−Br	catalytic system, solvent, temp	time,[b] result
1	1:1	10 mol % of $Pd(OAc)_2$, 10 mol % of **L-4**, 1.5 equiv of *tert*-BuONa, PhMe, 85 °C	24 h, 40% yield[c]
2	1:2	10 mol % of $Pd(OAc)_2$, 10 mol % of **L-4**, 1.5 equiv of *tert*-BuONa, PhMe, 85 °C	1 h, 89% yield[c]
3	1:2	10 mol % of $Pd(OAc)_2$, 10 mol % of **L-4**, 1.5 equiv of *tert*-BuONa, DME, 85 °C	24 h, incomplete[d]
4	1:2	30 mol % of $Pd(OAc)_2$, 30 mol % of **L-4**, 1.5 equiv of *tert*-BuONa, PhMe, 85 °C	1 h, 91% yield[c]
5	1:2	30 mol % of $Pd(OAc)_2$, 30 mol % of **L-4**, 1.5 equiv of K_3PO_4, PhMe, 85 °C	24 h, trace[d]
6	1:2	10 mol % of $Pd(OAc)_2$, 10 mol % of **L-4**, 1.5 equiv of Cs_2CO_3, PhMe, 85 °C	24 h, incomplete[d]
7	1:2	5 mol % of $Pd(OAc)_2$, 5 mol % of **L-4**, 1.5 equiv of *tert*-BuONa, PhMe, 85 °C	3.5 h, 78% yield[c]

[a] Reactions conducted with 0.07 mmol of nucleoside in 1 mL of solvent. [b] Reactions were monitored by TLC. [c] Yield is of isolated, purified product. [d] Product formation was observed by TLC but was not isolated.

of this arylation chemistry. The results from these experiments are displayed in Table 4.

As seen from Table 4, **5** not only undergoes reaction with electron-deficient aryl bromides (entries 4, 9, and 10) but also undergoes reaction with unsubstituted, alkyl-substituted, and polyaromatic systems (entries 1, 2, and 5−7) and, more importantly, the electron-rich ones (entries 3 and 8). Notably, reported reactions of **5** with bromobenzene and 4-bromoanisole involving (+)-BINAP as the ligand provided a 57% yield of **6a** and a 0% yield of **6c**.[17] In contrast to the successful reaction of 4-bromoanisole, 2-bromoanisole did not yield product, and electronic factors alone are perhaps not the reason for this. In the case of 4-bromobenzonitrile, a secondary product arising from bisarylation was observed and it is possible that with electron-deficient aryl bromides bisarylation could be a competing reaction. Allowing the reaction of 4-bromobenzonitrile to proceed longer resulted in a lowered yield, possibly due to bisarylation.

In summary, we have demonstrated that Pd catalysts with Xantphos as the supporting ligand are effective for direct N-arylation of 2′-deoxyadenosine as well as 2′-deoxyguanosine and that these are superior to BINAP-based ones. Although there are subtle differences in the reactions of two purine nucleosides, the methods appear to be reasonably general. Further studies on Pd−Xantphos complexes are being conducted in our laboratories.

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Supporting Information Available: Experimental details and ^1H NMR spectra of **2a**−**m**, **4**, and **6a**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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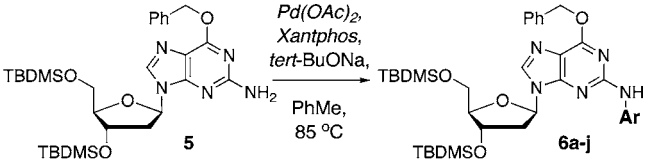
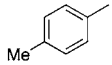
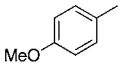
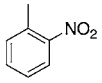
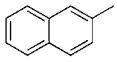
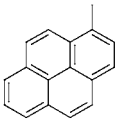
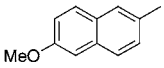
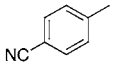
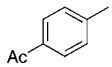
Table 4. Reactions of Various Aryl Bromides with O^6-Benzyl-3′,5′-bis-*O*-(*tert*-butyldimethyl)-2′-deoxyguanosine[a]



entry	Ar-Br	time (h)[b]	product, yield[c]
1		1	**6a**[17]: 89%
2		1.5	**6b**: 75%
3		4	**6c**[17]: 48%
4		1.5	**6d**[16]: 84%
5		2.5	**6e**: 77%
6		1.5	**6f**: 71%
7		1.5	**6g**[8,9]: 69%
8		2.5	**6h**: 54%
9		1 4	**6i**: 78% **6i**: 65%
10		3	**6j**: 68%

[a] Reaction conditions: 0.07 mmol of nucleoside in 1 mL of PhMe, 10 mol % of $Pd(OAc)_2$, 10 mol % of **L-4**, 1.5 equiv of *tert*-BuONa, 85 °C. [b] Reactions were monitored for completion by TLC. [c] Yield is of isolated, purified product.