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Palladium-Catalyzed Aryl Amination Reactions of 6-Bromo- and 6-Chloropurine Nucleosides

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Abstract: Palladium-catalyzed C–N bond forming reactions of 6-bromo- as well as 6-chloropurine ribonucleosides and the 2′-deoxy analogues with arylamines are described. Efficient conversions were observed with palladium(II) acetate/Xantphos/cesium carbonate, in toluene at 100 °C. Reactions of the bromonucleoside derivatives could be conducted at a lowered catalytic loading [5 mol% $Pd(OAc)_2$/7.5 mol% Xantphos], whereas good product yields were obtained with a higher catalyst load [10 mol% $Pd(OAc)_2$/15 mol% Xantphos] when the chloro analogue was employed. Among the examples evaluated, silyl protection for the hydroxy groups appears better as compared to acetyl. The methodology has been evaluated *via* reactions with a variety of arylamines and by synthesis of biologically relevant deoxyadenosine and adenosine dimers. This is the first detailed analysis of aryl amination reactions of 6-chloropurine nucleosides, and comparison of the two halogenated nucleoside substrates.

Keywords: amination; C–N bond formation; ligands; nucleosides; palladium; Xantphos

Introduction

Palladium-catalyzed C–N bond forming reactions have become an important type of transformation in the synthetic repertoire.[1] In this context, we have been gaining an understanding of and exploiting such catalyzed amination reactions of nucleosides.[2] The high biochemical, physiological and medicinal value of compounds that can arise by alteration of the nucleoside scaffold adds significant importance to the development of methods for nucleoside modification.[3,4]

In 1999 we demonstrated, for the first time, that N^6-aryl-2′-deoxyadenosine analogues could be efficiently synthesized *via* C–N bond-formation using a suitable Pd-ligand complex.[5] Subsequently, we analyzed a series of ligands for C–C and C–N bond formation.[6] This led to the identification of specific ligands that were effective for aryl amination. These included 2-(dicyclohexylphosphino)-2′-(*N,N*-dimethylamino)-1,1′-biphenyl and (±)-BINAP. In subsequent aryl amination work the same two ligands also proved to be useful in gaining access to N^6-(6-benzo[*a*]pyrenyl)-2′-deoxyadenosine.[7]

In all these cases, the halopurine nucleoside tested and used was 6-bromo-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine. In comparison, there are fewer analyses of the use of the 6-chloropurine nucleoside analogues in Pd-mediated amination reactions. Among these, reactions of 6-chloro-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine using $Pd_2(dba)_3$/BINAP with either Cs_2CO_3 or *t*-BuOK were evaluated.[8] Although reactions of alkylamines proceeded well, comparable reactions of arylamines were not efficient. Using $Pd(OAc)_2$/(±)-BINAP/Cs_2CO_3 we have studied the amination of silyl-protected 6-chloro-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine with a sterically-demanding alkylamino derivative of a polycyclic aromatic hydrocarbon.[9] Subsequently we have synthesized more elaborate carcinogen-nucleoside adducts using this chloronucleoside.[10] We have also studied C–N(sp^2) bond-forming reactions of 6-bromo- and 6-chloropurine nucleosides with azoles.[11]

Despite these results, there has not been the development of effective Pd-catalyzed aryl amination methods to involve 6-chloropurine nucleosides. Also, no comparative performance evaluation of 6-bromo- and 6-chloropurine nucleosides under Pd-catalyzed aryl amination conditions has been conducted. In this context it should be noted that S_NAr displacement reactions between a 6-bromopurine nucleoside and two arylamines have been accomplished, but reactions of corresponding 6-chloro compound are stated to be ineffective.[12]

Pd catalysis appears to offer a simple, unifying method for involving both 6-bromo- and 6-chloropurine nucleosides in aryl amination reactions. This paper reports our studies on such reactions of these nucleoside derivatives.

Results and Discussion

For the current work, 6-bromo- and 6-chloropurine ribonucleosides as well as the 2′-deoxy analogues were chosen for analysis. We also wanted to assess silyl and acetyl protecting groups for the sugar moieties. Thus, six compounds **1a–2c** (Figure 1) became the choices for the initial experiments. The overall goal was not the determination of the best conditions for reactions of each substrate, but rather to find generally optimal conditions for the aryl amination reactions that can be applied to the synthesis of a broad class of N^6-aryladenosine analogues.

Bromo nucleosides **1a–c** were conveniently synthesized through a diazotization-bromination protocol[11,12] by appropriate modification of a literature route.[13] Chloro nucleoside **2a**[14] was prepared by silylation of 6-chloro-9-(2-deoxy-β-D-ribofuranosyl)purine[15] whereas **2b**[11,16] and **2c** were prepared by silylation and acetylation of commercially available 6-chloro-9-(β-D-ribofuranosyl)purine. Alternatively, **2c** can be prepared by chlorination of inosine triacetate.[17]

With these compounds, we began to evaluate conditions for aryl amination. We selected six ligands, 2-(dicyclohexylphosphino)-2′-*N,N*-(dimethylamino)-1,1′-biphenyl (**L1**), (±)-BINAP (**L2**), Xantphos (**L3**), 2-(dicyclohexylphosphino)biphenyl (**L4**), 2-(di-*tert*-butylphosphino)biphenyl (**L5**) and 4-(diphenylphosphino)-9,9-dimethylxanthene (**L6**) shown in Figure 2. The first three were chosen since these have previously yielded effective amination catalysts for nucleosides,[2,5–11,18–24] whereas **L4** and **L5** were included due to their similarity to **L1**. Monophosphane **L6** was included for comparison to **L3**. $Pd(OAc)_2$ and $Pd_2(dba)_3$ were the metal sources, K_3PO_4 and Cs_2CO_3 were chosen as bases.

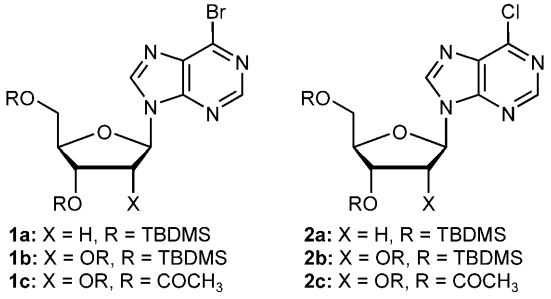


Figure 1. Six nucleoside substrates selected for analysis.

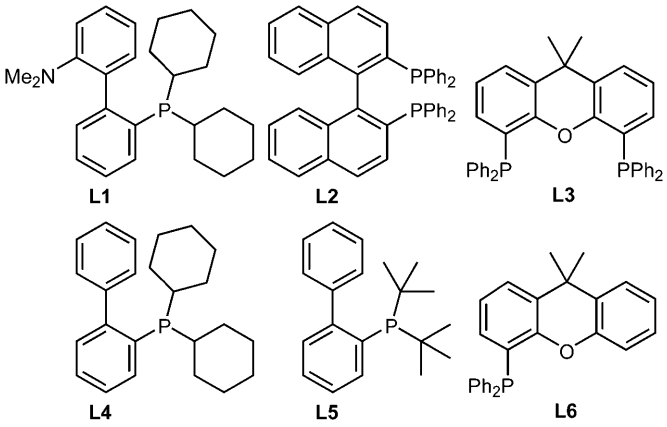


Figure 2. Six ligands selected for analysis.

Our initially reported work on **1a**[5,6] was the starting point upon which the newer results were developed. Using *p*-toluidine as a representative amine in the initial test reactions, the most significant results (product yields >50%) from several experiments are shown in Table 1.

Our first attempt was to further tune conditions in entry 1 using substrate **1a**. Use of 10 mol% $Pd(OAc)_2$/15 mol% **L1**, under otherwise comparable conditions to entry 1, resulted in a poor yield (37%, 9 h). Use of 10 mol% $Pd_2(dba)_3$/30 mol% **L1**/1.5 molar equiv. Cs_2CO_3 in toluene at 100 °C, did not produce an improvement (41% yield in 4 h). This led us to consider **L2** as well as **L3**. Initial reactions were conducted with 10 mol% $Pd(OAc)_2$/15 mol% **L2** or **L3**/1.5 molar equiv. Cs_2CO_3, in toluene at 100 °C. Under these conditions, the reaction utilizing **L2** gave a 64% yield of product, whereas that involving **L3** gave 89% yield (entries 2 and 3). We next considered reducing the Pd/**L3** loading by half, and this modification produced essentially no difference, resulting in an excellent 90% yield of the amination product (entry 4). Under these best conditions, replacing **L3** with **L4** or **L5** resulted in poorer results (entries 5 and 6).

The foregoing results formed the basis for subsequent experiments, and a similar trend was observed with the ribose derivative **1b**, where the lower Pd-$(OAc)_2$/**L3** loading gave excellent product recovery (compare entries 7 and 8). Whether both phosphane

Table 1. Initial results from C–N bond-forming reactions of substrates **1a**–**2c** with *p*-toluidine.

Entry	Substrate	Pd source (mol%)	Ligand (mol%)	Base (1.5 molar equiv)	Solvent	Temp. [°C]	Time [h][a]	Yield [%][b]
*Reactions of bromonucleosides **1a**, **b** with p-toluidine*								
1	**1a**	$Pd_2(dba)_3$ (10)	**L1** (30)	K_3PO_4	DME	80	3	69[c]
2	**1a**	$Pd(OAc)_2$ (10)	**L2** (15)	Cs_2CO_3	PhMe	100	1	64
3	**1a**	$Pd(OAc)_2$ (10)	**L3** (15)	Cs_2CO_3	PhMe	100	1	**89**
4	**1a**	$Pd(OAc)_2$ (5)	**L3** (7.5)	Cs_2CO_3	PhMe	100	1	**90**
5	**1a**	$Pd(OAc)_2$ (5)	**L4** (7.5)	Cs_2CO_3	PhMe	100	6	70
6	**1a**	$Pd(OAc)_2$ (5)	**L5** (7.5)	Cs_2CO_3	PhMe	100	24	56[d]
7	**1b**	$Pd(OAc)_2$ (10)	**L2** (15)	Cs_2CO_3	PhMe	100	2	76
8	**1b**	$Pd(OAc)_2$ (5)	**L3** (7.5)	Cs_2CO_3	PhMe	100	1	**93**
9	**1b**	$Pd(OAc)_2$ (5)	**L6** (7.5)	Cs_2CO_3	PhMe	100	7	66
*Reactions of chloronucleosides **2a**, **b** with p-toluidine*								
10	**2a**	$Pd_2(dba)_3$ (10)	**L1** (30)	K_3PO_4	DME	80	22	49
11	**2a**	$Pd_2(dba)_3$ (10)	**L1** (30)	Cs_2CO_3	DME	80	26	52
12	**2a**	$Pd_2(dba)_3$ (10)	**L1** (30)	Cs_2CO_3	PhMe	100	1	80
13	**2a**	$Pd(OAc)_2$ (10)	**L1** (15)	Cs_2CO_3	PhMe	100	1	59
14	**2a**	$Pd(OAc)_2$ (10)	**L2** (15)	Cs_2CO_3	PhMe	100	1	**88**
15	**2a**	$Pd(OAc)_2$ (5)	**L2** (7.5)	Cs_2CO_3	PhMe	100	1	67
16	**2a**	$Pd(OAc)_2$ (10)	**L3** (15)	Cs_2CO_3	PhMe	100	1	**86**
17	**2a**	$Pd(OAc)_2$ (5)	**L3** (7.5)	Cs_2CO_3	PhMe	100	1	**86**
18	**2b**	$Pd(OAc)_2$ (10)	**L2** (15)	Cs_2CO_3	PhMe	100	2	**88**
19	**2b**	$Pd(OAc)_2$ (5)	**L2** (7.5)	Cs_2CO_3	PhMe	100	2	**88**
20	**2b**	$Pd(OAc)_2$ (10)	**L3** (15)	Cs_2CO_3	PhMe	100	1	**92**
21	**2b**	$Pd(OAc)_2$ (5)	**L3** (7.5)	Cs_2CO_3	PhMe	100	1	74
22	**2b**	$Pd(OAc)_2$ (10)	**L6** (15)	Cs_2CO_3	PhMe	100	5	60
*Reactions of chloronucleoside **2b** with o-toluidine*								
23	**2b**	$Pd(OAc)_2$ (10)	**L2** (15)	Cs_2CO_3	PhMe	100	1	86 (87[e])
24	**2b**	$Pd(OAc)_2$ (5)	**L2** (7.5)	Cs_2CO_3	PhMe	100	1	73 (76[e])
25	**2b**	$Pd(OAc)_2$ (10)	**L3** (15)	Cs_2CO_3	PhMe	100	1	**92**
*Reactions of acetate-protected nucleosides **1c** and **2c** with p-toluidine*								
26	**1c**	$Pd(OAc)_2$ (5)	**L3** (7.5)	Cs_2CO_3	PhMe	100	1.5	82
27	**2c**	$Pd(OAc)_2$ (10)	**L3** (15)	Cs_2CO_3	PhMe	100	1.5	62
*Reactions of **1a** and **2a** with p-toluidine using $Pd(PPh_3)_4$ as catalyst*								
28	**1a**	$Pd(PPh_3)_4$ (5)	none	Cs_2CO_3	PhMe	100	4	56
29	**2a**	$Pd(PPh_3)_4$ (5)	none	Cs_2CO_3	PhMe	100	5	62

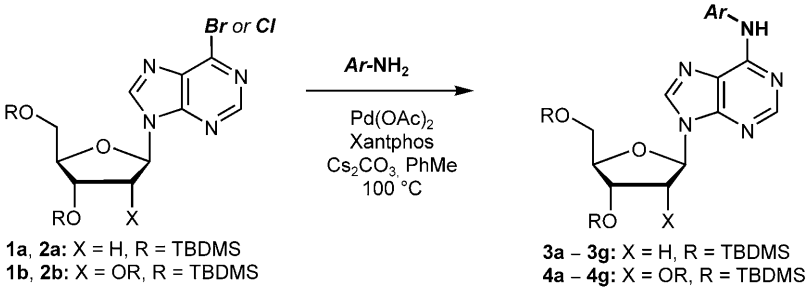
[a] Reactions were monitored by TLC for complete disappearance of the halonucleoside.
[b] Where reported, yield is of isolated and purified products.
[c] Reported in ref.[5]
[d] Reaction was incomplete.
[e] Reaction time was 2 h.

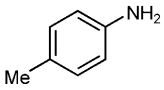
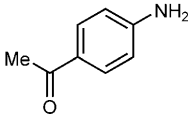
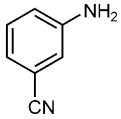
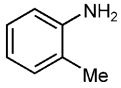
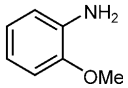
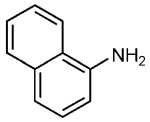
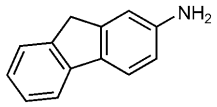
units in **L3** are critical for an effective catalyst was next queried. Use of **L6** in place of **L3** (entry 9) clearly showed that **L3** was superior.

Next, optimization of amination conditions with the chloronucleosides was conducted, starting with **2a**. Use of 10 mol% $Pd_2(dba)_3$/30 mol% **L1** with either K_3PO_4 or Cs_2CO_3 in DME gave *ca.* 50% product yields (entries 10 and 11). In contrast, this catalytic system with Cs_2CO_3 in PhMe gave a high 80% yield (entry 12), but replacing $Pd_2(dba)_3$ with 10 mol% $Pd(OAc)_2$ lowered the yield to 59% (entry 13). We next investigated the use of **L2**. At 10 mol% $Pd(OAc)_2$/15 mol% **L2** an excellent 88% product yield was realized (entry 14), which decreased to 67% when the catalytic load was reduced by half (entry 15). When **L2** was replaced with **L3**, the higher and lower catalyst load produced identical, good results (entries 16 and 17). On the basis of these experiments, substrate **2b** was then investigated. At 10 mol% $Pd(OAc)_2$/15 mol% **L2**, again an excellent 88% yield of aminated product was obtained (entry 18), which remained unaltered when the catalyst load was decreased (entry 19). Upon replacement of **L2** with **L3**, some other differences emerged. Use of the higher 10 mol% $Pd(OAc)_2$/15 mol% **L3** resulted in an excellent 92% yield of product, but reduction of the catalytic load by half produced only a 74% yield (compare entries 20 and 21). Here again presence of 2 phosphane units in **L3** proved essential as shown by the poorer result with **L6** (entry 22)

These results indicated some differences in the reactions of **2a** and **2b**. With **2a**, the higher and lower

Table 2. Amination reactions of the bromo- (**1a** and **1b**) and chloronucleosides (**2a** and **2b**) with several amines.



Entry	Amine	Substrate	Conditions,[a] time[b]	Product: Yield [%][c]
1		**1a**	**A**, 1 h	**3a**: 90
2		**1b**	**A**, 1 h	**4a**: 93
3		**2a**	**B**, 1 h	**3a**: 86
4		**2b**	**B**, 1 h	**4a**: 92
5		**1a**	**A**, 1 h	**3b**: 88
6		**1b**	**A**, 1 h	**4b**: 92
7		**2a**	**B**, 1 h	**3b**: 92
8		**2b**	**B**, 1 h	**4b**: 92
9		**1a**	**A**, 1 h	**3c**: 79
10		**1b**	**A**, 1.5 h	**4c**: 87
11		**2a**	**B**, 1 h	**3c**: 72
12		**2b**	**B**, 1 h	**4c**: 91
13		**1a**	**A**, 1 h	**3d**: 68
14		**1b**	**A**, 1 h	**4d**: 84
15		**2a**	**B**, 1 h	**3d**: 78
16		**2b**	**B**, 1 h	**4d**: 92
17		**1a**	**A**, 1 h	**3e**: 87
18		**1b**	**A**, 1 h	**4e**: 86
19		**2a**	**B**, 1 h	**3e**: 87
20		**2b**	**B**, 1 h	**4e**: 93
21		**1a**	**A**, 1 h	**3f**: 91
22		**1b**	**A**, 1 h	**4f**: 88
23		**2a**	**B**, 1 h	**3f**: 95
24		**2b**	**B**, 1 h	**4f**: 89
25		**1a**	**A**, 1 h	**3g**: 88
26		**1b**	**A**, 1 h	**4g**: 84
27		**2a**	**B**, 1 h	**3g**: 92
28		**2b**	**B**, 1 h	**4g**: 99

[a] Reactions were performed at a nucleoside concentration of 0.1 M in the reaction solvent. *Conditions **A**:* 5 mol% $Pd(OAc)_2$/7.5 mol% **L3**/1.5 molar equiv. Cs_2CO_3, PhMe, 100 °C. *Conditions **B***: 10 mol% $Pd(OAc)_2$/15 mol% **L3**/1.5 molar equiv. Cs_2CO_3, PhMe, 100 °C.

[b] Reactions were monitored by TLC for complete disappearance of the halonucleoside.

[c] Yield of isolated and purified products.

$Pd(OAc)_2$/**L3** loads produced comparable results, whereas this was not the case with $Pd(OAc)_2$/**L2**. The exact opposite trend was observed with **2b**, where the higher and lower loads of $Pd(OAc)_2$/**L2** showed comparable results, but not with $Pd(OAc)_2$/**L3**. In an attempt to gain additional insight, three other reactions were conducted between **2b** and the sterically hindered *o*-toluidine (entries 23–25). Reaction of this amine and **2b** catalyzed by 10 mol% $Pd(OAc)_2$/15 mol% **L2** gave an 86% product yield, versus 73% with 5 mol% $Pd(OAc)_2$/7.5 mol% **L2**, both in 1 h. These yields did not change appreciably when the reaction was conducted over 2 h (entries 23 and 24, yields in parentheses). On the other hand use of 10 mol% $Pd(OAc)_2$/15 mol% **L3** gave an excellent 92% yield (entry 25). A review of the data indicates that 10 mol% $Pd(OAc)_2$/15 mol% **L3** gave consistently good results for reactions of both **2a** and **2b**.

Thus, the combination of $Pd(OAc)_2$/**L3**/Cs_2CO_3 in PhMe, at 100 °C is generally applicable for amination of 6-bromo- and 6-chloropurine nucleosides. However, a lowered catalytic load can be used for the

former. We also compared reactions of acetate-protected derivatives **1c** and **2c** using the best conditions identified for reactions of the bromo- and chloronucleosides (entries 26 and 27). In both cases, although reasonable product yields were attained, the results were not superior to those involving the silyl-protected derivatives. Finally we tested 5 mol% $Pd(PPh_3)_4$ under otherwise identical conditions. This Pd(0) catalyst has been used for Suzuki–Miyaura cross-coupling reactions of nucleosides.[23,25] Both **1a** and **2a** reacted with *p*-toluidine, but these reactions (entries 28 and 29) were inferior to the low catalyst loading experiments with **L2** and **L3**. On the basis of these results, we then evaluated the amination reactions using the silylated nucleoside substrates and several amines with varying electronic and steric properties. These results are displayed in Table 2.

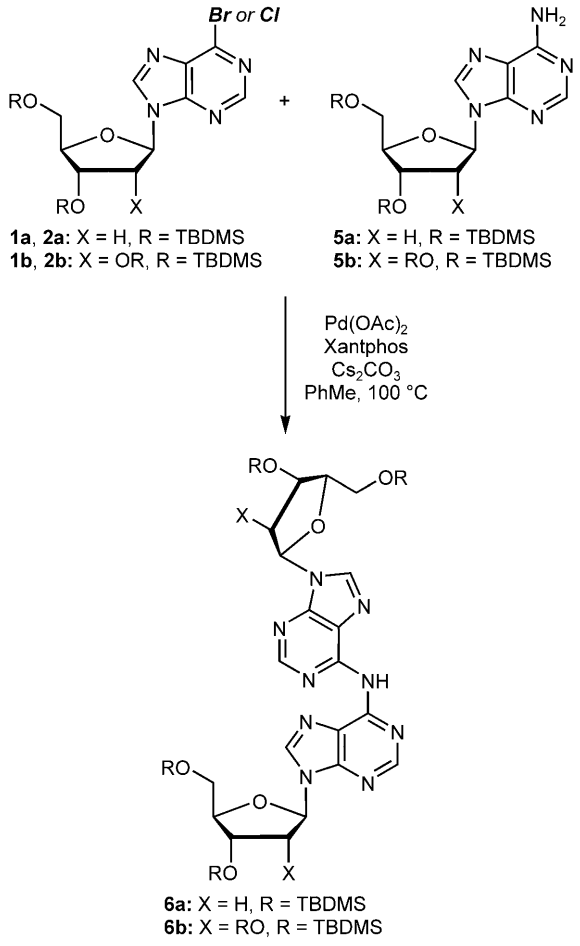
From the results in Table 2, it is evident that both bromo- (**1a**, **b**) and chloronucleosides (**2a**, **b**) are effective substrates for amination with a variety of arylamines. For reactions of the bromonucleosides **1a** and **1b**, conditions **A** [5 mol% $Pd(OAc)_2$/7.5 mol% **L3**] are reasonable for efficient reactions, and good-to-excellent yields were observed. Only the reaction of *o*-toluidine with **1a** gave $<70\%$ yield (entry 13). On the other hand, all reactions with *o*-anisidine gave satisfactory results (entries 17–20). The electron-deficient *p*-acetylaniline reacted very well (entries 5–8), and good results were also obtained with *m*-cyanoaniline (entries 9–12).

Reactions of the chloronucleosides **2a** and **2b** under conditions **B** [10 mol% $Pd(OAc)_2$/15 mol% **L3**] gave good-to-excellent results. These data clearly indicate that such chloronucleosides are excellent coupling partners in Pd-catalyzed C–N bond-forming reactions.

When comparing these catalyzed transformations to the S_NAr chemistry of 6-halopurine nucleosides, the following are notable. The Pd-catalyzed reactions of **1b** produced comparable yields to displacement reactions on **1c**,[12] but require 3 times less arylamine. Also, Pd-catalyzed reactions with the chloronucleosides resulted in amination products, whereas such chloronucleosides were reported to be unreactive under S_NAr conditions.[12]

Arylation of nucleosides by aryl bromides had been challenging until our recent report.[24] Thus, reactivity properties of nucleosides often do not follow known trends of simpler aryl systems. With the reactions of the simple arylamines completed, we next analyzed the use of nucleosides themselves as the arylamine in coupling reactions with the halonucleosides. Nucleoside dimers are of interest since they can be formed *in vitro* by nitrous acid-induced DNA cross-linking. Such a process could have a physiological role due to the presence of nitrite in cured meats.[26,27] Pd-catalyzed approaches have been used for the non-biomimetic synthesis of adducts produced by DNA cross-linking.[28,29] Among the various nucleoside dimers, deoxyguanosine-deoxyguanosine (dG–dG), deoxyadenosine-deoxyguanosine (dA–dG), and deoxyadenosine-deoxyadenosine (dA–dA), the synthesis of dA–dA posed particular challenges. For instance, reaction of **1a** and **5a** using several Pd/**L2** complexes were reported to be low yielding, and thus use of the iodo analogue of **1a** was necessary.[29] On the basis of our results, we wanted to reassess the reaction of **1a** with **5a** and analyze reactivity of the chloro analogue **2a** for synthesis of dA–dA dimer. We also wanted to compare these reactions to those leading to the adenosine-adenosine (A–A, ribose) dimers (Scheme 1). The results of these experiments are shown in Table 3.

From Table 3 it becomes clear that 6-bromonucleosides **1a** and **1b** are good substrates for Pd-catalyzed amination reactions with the more complex amines **5a** and **5b**. Good yields were obtained with 5 mol% $Pd(OAc)_2$/7.5 mol% **L3** (entries 1 and 2), and some improvement was attained with the increased catalyst load of 10 mol% $Pd(OAc)_2$/15 mol% **L3** (entries 3 and 4). More interestingly, chloropurine analogues **2a** and **2b** are also highly effective in these reactions and



Scheme 1. Application of the $Pd(OAc)_2$/Xantphos system for the synthesis of the adenine nucleoside dimers.

Table 3. Results from the reactions leading to the dA–dA, and A–A dimers.

Entry	Partners	Conditions,[a] time[b]	Product: Yield [%][c]
1	**1a**+**5a**	**A**, 1 h	**6a**: 65
2	**1b**+**5b**	**A**, 1 h	**6b**: 70
3	**1a**+**5a**	**B**, 1 h	**6a**: 79
4	**1b**+**5b**	**B**, 1 h	**6b**: 84
3	**2a**+**5a**	**B**, 1 h	**6a**: 77
4	**2b**+**5b**	**B**, 1 h	**6b**: 81

[a] Reactions were performed at a nucleoside concentration of 0.1 M in the reaction solvent. *Conditions* ***A***: 5 mol% $Pd(OAc)_2$/7.5 mol% **L3**/1.5 molar equiv. Cs_2CO_3, PhMe, 100 °C. *Conditions* ***B***: 10 mol% $Pd(OAc)_2$/15 mol% **L3**/1.5 molar equiv. Cs_2CO_3, PhMe, 100 °C.

[b] Reactions were monitored by TLC for complete disappearance of the halonucleoside.

[c] Yield of isolated and purified products.

provide comparable product yields to the bromopurine nucleoside derivatives at the higher catalyst loading of 10 mol% $Pd(OAc)_2$/15 mol% **L3**. Thus, contrary to prior results,[29] our data indicate that it is unnecessary to involve the iodo nucleosides in Pd-catalyzed syntheses of nucleoside dimers.

Since modified nucleosides could possess interesting biological properties, the amination products were desilylated (see the Supporting Information for details, and Table S1). The deprotected compounds from this study as well as those obtained from previously synthesized compounds[11,23,30] were subjected to a wide variety of antiviral assays. Unfortunately, none showed specifically interesting activity at subtoxic concentrations as shown in Tables S2–S5 of the Supporting Information. Instead, several compounds showed a mild cytostatic and/or cytotoxic activity against a variety of cell lines (CC_{50} or MIC in the 10 to 100 $\mu g\,mL^{-1}$ range). Only the desilylated product from **4f** was endowed with a marked cytostatic activity against CRFK cells (CC_{50}: 4.32 μM). This compound should be further explored for its potential antiproliferative activity against a broad variety of tumor cell lines. Pd-catalyzed C–N and C–C bond-forming reactions have led to this diverse set of compounds for antiviral and cytostatic analysis that would otherwise not be available.

Conclusions

In conclusion, Pd-catalyzed C–N bond formation is an effective method for access to N^6-aryl adenosine analogues. Herein we show that 5 mol% $Pd(OAc)_2$/7.5 mol% Xantphos is a generally effective catalyst in combination with Cs_2CO_3 in PhMe at 100 °C for reactions of 6-bromopurine ribonucleosides as well as the 2′-deoxy analogues. Remarkably, the corresponding 6-chloropurine nucleosides are also excellent substrates for such reactions, requiring 10 mol% $Pd(OAc)_2$/15 mol% Xantphos, under otherwise comparable conditions. Finally, the method has been applied to the synthesis of deoxyadenosine-deoxyadenosine and adenosine-adenosine dimers. Bromo- as well as chloropurine ribo- and deoxyribonucleosides are effective substrates for reactions with protected 2′-deoxyadenosine and adenosine. Therefore, the methodology described appears to present broad generality and scope for nucleoside modification with both 6-bromo and 6-chloropurine nucleosides.

Experimental Section

Thin layer chromatography was performed on 250 μm silica plates and column chromatographic purifications were performed on 200–300 mesh silica gel. Ligands **L1–L5** and $Pd(OAc)_2$ were purchased from commercial suppliers. All other reagents were obtained from commercial sources and were used without further purification. Toluene was distilled over Na. Nucleoside substrates were prepared as described previously. Characterization data for all compounds are provided in the Supporting Information. ^{1}H NMR spectra were recorded at 500 MHz in the solvents indicated (when $CDCl_3$ was used, it was deacidified by percolating the solvent through a bed of solid $NaHCO_3$ and basic alumina). All proton spectra are referenced to residual protonated solvent resonance. No attempt has been made to ascertain the position of the arylamino proton (N*H*Ar) in the products. Therefore, this and the aromatic protons are collectively assigned as Ar-H. The sugar protons are numbered 1′–5′ beginning at the anomeric carbon and proceeding *via* the carbon chain to the primary carbinol carbon.

C–N Bond-Formation under Conditions A

$Pd(OAc)_2$ (5 mol%), Xantphos (7.5 mol%) and Cs_2CO_3 (1.5 molar equiv.) were premixed in a small volume of toluene in an oven-dried, screw-cap vial equipped with a stirring bar. Bromonucleoside (1 molar equiv., 0.08 mmol of **1a** or **1b**), arylamine (2 molar equiv.) and toluene were then added to the vial so that the final reaction mixture was 0.1 M in nucleoside. The vial was flushed with nitrogen gas, sealed with a Teflon-lined cap, and placed in a sand bath that was maintained at 101–102 °C. Reactions were monitored by TLC. Upon completion, the mixtures were diluted with Et_2O (7 mL) and washed with brine (5 mL). The organic phase was separated, dried (Na_2SO_4) and concentrated. Products were purified by column chromatography on silica gel using appropriate solvents (listed under individual headings), evaporated and finally dried under high vacuum to remove traces of solvent.

C–N Bond-Formation under Conditions B

$Pd(OAc)_2$ (10 mol%), Xantphos (15 mol%) and Cs_2CO_3 (1.5 molar equiv.) were premixed in a small volume of toluene in an oven-dried, screw-cap vial equipped with a stirring bar. Chloronucleoside (1 molar equiv., 0.08 mmol of **2a** or

0.085 mmol of **2b**), amine (2 molar equiv.) and toluene were then added to the vial so that the final reaction mixture was 0.1 M in nucleoside. The vial was flushed with nitrogen gas, sealed with a Teflon-lined cap, and placed in a sand bath that was maintained at 101–102 °C. Reactions were monitored by TLC. Upon completion, work-up as above and column chromatography on silica gel using appropriate solvents yielded the amination products.

Biological Assays

The antiviral assays, other than the anti-HIV assays, were based on inhibition of virus-induced cytopathicity in HEL [herpes simplex virus type 1 (HSV-1) (KOS), HSV-2 (G), vaccinia virus, vesicular stomatitis virus, cytomegalovirus (HCMV) and varicella-zoster virus (VZV)], Vero (parainfluenza-3, reovirus-1, Sindbis virus and Coxsackie B4), HeLa (vesicular stomatitis virus, Coxsackie virus B4, and respiratory syncytial virus), Crandel–Rees feline kidney (CRFK) [feline coronavirus (FIPV) and feline herpes virus] or MDCK [influenza A (H1N1; H3N2) and influenza B] cell cultures. Confluent cell cultures (or nearly confluent for MDCK cells) in microtiter 96-well plates were inoculated with 100 $CCID_{50}$ of virus (1 $CCID_{50}$ being the virus dose to infect 50% of the cell cultures) in the presence of varying concentrations (100, 20, 4, … $\mu g\,mL^{-1}$) of the test compounds. Viral cytopathicity was recorded as soon as it reached completion in the control virus-infected cell cultures that were not treated with the test compounds. The minimal cytotoxic concentration (MCC) of the compounds was defined as the compound concentration that caused a microscopically visible alteration of cell morphology. The CC_{50} was defined as the compound concentration that resulted in a 50% reduction of the MTT- or MTS-directed (blue) viability staining of the (CRFK and MDCK) cell cultures. The methodology of the anti-HIV assays was as follows: human lymphocyte MT-4 cells (*ca.* 3×10^5 cells/mL) were infected with 100 $CCID_{50}$ of HIV(IIIB) or HIV-2-(ROD)/mL and seeded in 200 μL wells of a microtiter plate containing appropriate dilutions of the test compounds. After 4 days of incubation at 37 °C, virus-induced cytopathicity was recorded with the MTT dye staining method.

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