*Organic Synthesis*

# Pd-Catalyzed Amination of Nucleoside Arylsulfonates to yield $N^6$-Aryl-2,6-Diaminopurine Nucleosides**

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Palladium-catalyzed amination methods have become significantly important in organic synthesis over recent years, and major developments have been made in both the development of the catalysts as well as insight into mecha-

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nisms.[1] Application of such methods to the modification of biomolecules opens interesting new avenues for investigation, with a plethora of potential applications for the end products. In this context, we have focused our efforts on the understanding and development of Pd-catalyzed reactions of nucleosides because these compounds display some unusual reactivities that are often not comparable to simpler molecules. Our contributions to Pd-catalyzed C–N bond formation reactions, as well as the contributions of others, have led to the synthesis of unusual nucleosides that contain entities appended to the exocyclic amino groups of 2′-deoxyadenosine, 2′-deoxyguanosine, and C-8 aryl aminonucleosides.[2–4] Unnatural nucleosides have long since held interest as novel pharmacophores and as probes of biofunction. These types of applications provide added importance to newer methods that lead to modification of nucleosides. For the synthesis of $N^6$-aryl 2′-deoxyadenosine analogues, the readily available C-6 bromonucleoside **1** has been the substrate of choice, whereas the $O^6$-benzyl-2-bromonucleoside **2** has been used for the synthesis of $N^2$-modified 2′-deoxyguanosine derivatives.[4] Although the $O^6$-arylsulfonate derivatives of purine nucleosides, and particularly those of guanine, are readily available (**3a–c** in Figure 1),[5] the utility of these compounds in Pd-catalyzed transformations has not been explored to date. Purine arylsulfonates, on the other hand, have been used for nucleophilic ($S_NAr$) displacement chemistry.[5–7] By and large, direct displacement of leaving groups at the C-6 position of purines is possible with good nucleophiles, and amination reactions have been conducted with alkyl amines.[7] There are not many examples of direct displacement reactions with aryl amines, and recently a few examples with bromonucleosides were reported.[8] Among simpler aromatic systems, Pd-catalyzed amination reactions of arene arylsulfonates have been reported recently,[9,10] and herein we report the first such studies that involve arylsulfonates of nucleosides.

From our recent studies on the Suzuki–Miyaura reactions of **3a**, it was clear that insertion of Pd into the C–sulfonate bond would occur quite readily.[11] However, experience with amination reactions of **1** suggested that the product turnover could highly depend on the nature of the ligand.[3] Therefore, two lines of investigation were initiated: One investigation was directed towards the determination of conditions that lead to optimal coupling results, whereas the second involved an evaluation of the influence of the sulfonate group on these reactions. For this purpose, sulfonates **3a–c**, which differ in steric factors, were synthesized by known methods.

The supporting ligands chosen for this initial analysis are shown in Figure 2.[12] The choice of these ligands originated from various results that we obtained in previous amination

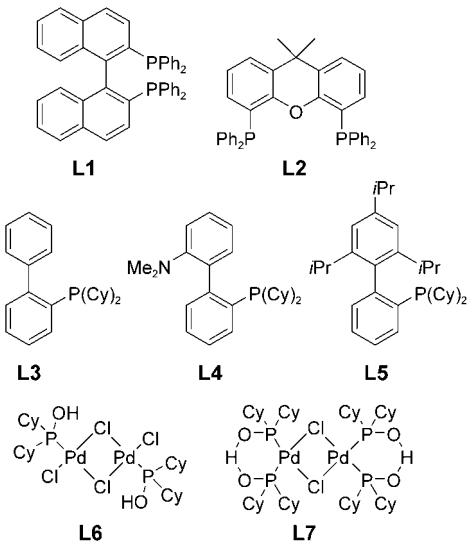



***Figure 2.*** The ligands that were screened for the amination reactions. Cy = cyclohexyl.

reactions of nucleosides. So far, **L1** and **L4** had been successful for aminations, and **L2** was chosen based upon bite-angle considerations relative to **L1** (**L2** has a bite angle of 110° relative to 93° for **L1**).[13] **L3** has been the preferred ligand for C–C bond-forming reactions of nucleosides and bears the core structure of **L4** and **L5**, a factor that may be useful in an analysis of the structural elements of ligands that can be used for these amination reactions. However, **L3** has so far not been very useful for amination reactions of nucleosides. **L6** and **L7** had not been tested for reactions of nucleosides and were chosen because they contain $(Cy)_2P$ moieties bound to the metal, a factor that we have previously found to be important among the biphenyl-based phosphanes (*tert*-butyl groups in place of cyclohexyl (Cy) groups render the ligands ineffective for amination).[2b]

The representative aryl amine chosen for the optimization experiments was 4-toluidine, and a $Pd(OAc)_2$/ligand ratio of 1:3 was employed. Based upon our experience with the C–C cross-coupling reaction, sulfonate **3a** was selected for the initial experiments.[11] Parameters that were varied include the ligand, the solvent, and the base; the results of these experiments are summarized in entries 1–6 of Table 1. Certain interesting observations emerge from the data in Table 1. From entries 1 and 2, it becomes apparent that the

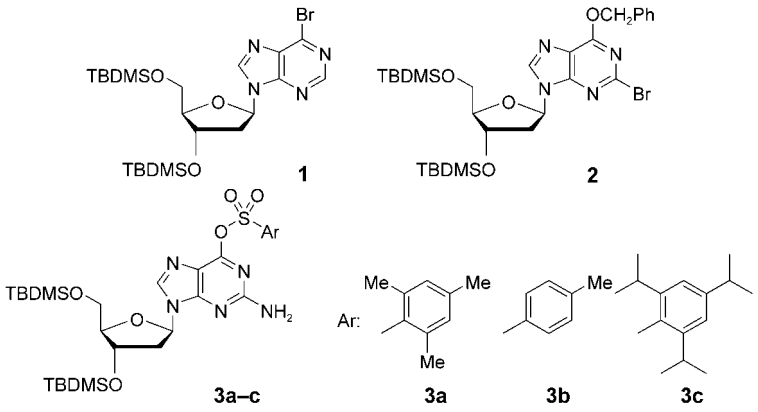
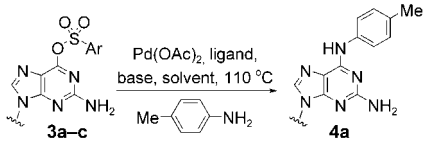



***Figure 1.*** The substrates that were studied in Pd-catalyzed amination reactions. TBDMS = *tert*-butyldimethylsilyl.

***Table 1:*** Coupling of the nucleoside arylsulfonates **3a–c** with 4-toluidine under various conditions.[a]




| Entry | Sulfonate | Ligand | Base | Solvent | Reaction time[b] | Yield [%][c] |
|---|---|---|---|---|---|---|
| 1 | **3a** | **L1** | $Cs_2CO_3$ | PhMe | 45 min | 57 |
| 2 | **3a** | **L1** | $Cs_2CO_3$ | 1,4-Dioxane | 30 min | [d] |
| 3 | **3a** | **L2** | $Cs_2CO_3$ | PhMe | 1 h | 55 |
| 4 | **3a** | **L3** | $Cs_2CO_3$ | PhMe | 11 h | [d] |
| 5 | **3a** | **L4** | $Cs_2CO_3$ | PhMe | 1 h | 63 |
| 6 | **3a** | **L4** | $K_3PO_4$ | 1,4-Dioxane | 30 min | 65 |
| 7 | **3b** | **L4** | $K_3PO_4$ | 1,4-Dioxane | 30 min | 75 |
| 8 | **3b** | **L4** | $K_3PO_4$ | 5:1 1,4-Dioxane/*t*BuOH | 30 min | 77 |
| 9 | **3c** | **L4** | $K_3PO_4$ | 5:1 1,4-Dioxane/*t*BuOH | 30 min | [d] |
| 10 | **3b** | **L5** | $K_3PO_4$ | 5:1 1,4-Dioxane/*t*BuOH | 30 min | 71[e] |
| 11 | **3b** | **L6** | $K_3PO_4$ | 5:1 1,4-Dioxane/*t*BuOH | 5 h | 0 |
| 12 | **3b** | **L7** | $K_3PO_4$ | 5:1 1,4-Dioxane/*t*BuOH | 24 h | [f] |

[a] Reaction conditions: **3** (0.1 M in the respective solvent), aryl amine (2.0 equiv), $Pd(OAc)_2$ (10 mol%), **L** (30 mol%), base (1.5 equiv), 110°C. [b] Disappearance of the sulfonate was monitored by tlc. [c] Yields reported are of isolated and purified **4a**. [d] The sulfonate was consumed, but an insignificant amount of product formed. [e] The product was impure after chromatography. [f] The sulfonate was still present in the reaction mixture, and an insignificant amount of product formed.

solvent has a significant influence on the reaction which involves **L1** as the ligand. However, this does not appear to be the case with **L4** as the difference in the yields in entries 5 and 6 is only marginal, with the combination of **L4**/$K_3PO_4$ in 1,4-dioxane producing a faster reaction. **L1** and **L2** produced comparable results which indicate that a change in the bite angle of the ligand does not seem to significantly alter the coupling. As expected, **L3** was ineffective which is consistent with previous aminations at the C-6 position of purine nucleosides.[2b]

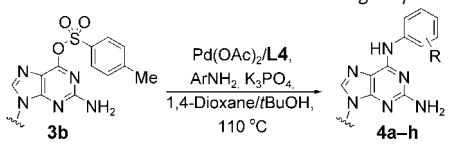
As a reasonable set of reaction parameters had been obtained, the coupling efficiency of the sulfonate **3b** was next studied. Interestingly, this less-hindered sulfonate substrate gave a 10% increase in the yield of **4a** within 30 min (entry 7). Another factor was the importance of *t*BuOH for the aryl amination; this presented a critical deviation from the amination of simpler arene arylsulfonates. It has been reported that *t*BuOH is necessary for the amination reaction and reactions in 1,4-dioxane or toluene were very slow.[9] This was not the case here, and although the addition of *t*BuOH appeared to provide a marginal improvement in yield and product quality, reactions in its presence or absence proceeded rapidly (entries 7 and 8).[14] For this reason, all subsequent reactions were conducted in a mixture of 5:1 1,4-dioxane/*t*BuOH.

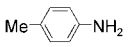
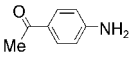
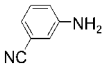
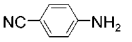
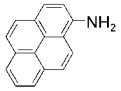
Reaction of the hindered tri(isopropyl)benzenesulfonate **3c** yielded another insight into a plausible steric effect. With this substrate, no product was recovered after 30 min although the sulfonate was consumed (entry 9): This apparently implies that product turnover diminishes with increased alkyl substitution proximal to the sessile C–O bond. With **L5** as the ligand, **4a** was furnished in a yield that was comparable to the yield obtained with **L4**, but the quality of the product was lowered (entry 10). Use of $Pd_2(dba)_3$ (5 mol%) and **L5** (30 mol%) led to a significant amount of unconverted **3b** even after 5 h. The use of ligands **L6** and **L7** did not provide any product from the amination step although **3b** was completely consumed in one case. In two cases (entries 2 and 9) in which consumption of the sulfonate occurred and very little product formation was observed, the $^1$H NMR spectra of the reaction mixtures were analyzed. In both cases, formation of some product (also discernable by tlc) and nucleosidic resonances for another uncharacterized compound were observed. However, no starting material was present as resonances that correspond to the arylsulfonate unit had completely disappeared. No further attempt was made at determining what course these reactions had taken. Finally, to ascertain whether any product formation occurred through a $S_NAr$ displacement mechanism, **3b** was treated with 4-toluidine in the absence of $Pd(OAc)_2$ in the reaction mixture. After 24 h at 110°C, a 12% yield of highly impure **4a** was obtained which clearly indicates that under these conditions, the metal-catalyzed process is the significant contributor to the amination reaction.

These experiments provided a basis for a more detailed analysis of the scope of the amination reaction with respect to the steric and electronic nature of the aryl amine component as well as different catalyst and ligand concentrations. Thus, a series of experiments were conducted using several aryl amines in the presence of different ratios of ligand/Pd. Table 2 provides some interesting insight into these amination reactions. At a catalyst load of 10 mol% $Pd(OAc)_2$ and 30 mol% **L4**, all of the amines that were studied reacted smoothly within 30 min to afford the $N^6$-aryl-2,6-diaminopurine nucleosides **4a–h**. The electron-deficient amines provided high yields, and the yields obtained with 4-toluidine, 1-naphthylamine, and 2-anisidine were also very good. A lower yield in the reaction of the sterically encumbered 2-toluidine (entry 2) was observed relative to that observed for 4-toluidine (entry 1): this is consistent with a steric influence and is reasonable when the yields obtained with 2-anisidine are also considered (entry 3). Upon lowering the catalyst loading to 5 mol% $Pd(OAc)_2$ and 15 mol% **L4**, the unhindered, electron-deficient amines and 4-toluidine again provided good (although slightly lower) yields. However, a dramatic effect was seen with the *ortho*-substituted amines and 1-naphthylamine (entries 2–4). In these cases, the reactions were incomplete which is consistent with a steric influence. The yield with 2-toluidine was significantly lower than that with the sterically less-hindered 2-anisidine. With 5 mol% $Pd(OAc)_2$ and 30 mol% **L4** (1:6 Pd/ligand), some other differences emerged. All of the reactions, with the

***Table 2:*** Results of the amination reaction with various ratios of ligand/Pd.[a]




| Entry | $ArNH_2$ | Conditions[b] | Time[c] | Yield [%][d] | Product |
|---|---|---|---|---|---|
| 1 |  | A | 30 min | 77 | **4a** |
| | | B | 1 h | 73 | **4a** |
| | | C | 30 min | 70 | **4a** |
| 2 |  | A | 30 min | 58 | **4b** |
| | | B | 5 h | 22[e] | **4b** |
| | | C | 30 min | 27 | **4b** |
| 3 |  | A | 30 min | 66 | **4c** |
| | | B | 5 h | 42[e] | **4c** |
| | | C | 30 min | 62 | **4c** |
| 4 |  | A | 30 min | 79 | **4d** |
| | | B | 8 h | 56[e] | **4d** |
| | | C | 30 min | 75 | **4d** |
| 5 |  | A | 30 min | 95 | **4e** |
| | | B | 2.5 h | 78 | **4e** |
| | | C | 30 min | 94 | **4e** |
| 6 |  | A | 30 min | 97 | **4f** |
| | | B | 30 min | 87 | **4f** |
| | | C | 30 min | 96 | **4f** |
| 7 |  | A | 30 min | 91 | **4g** |
| | | B | 45 min | 80 | **4g** |
| | | C | 30 min | 81 | **4g** |
| 8 |  | A | 30 min | 87 | **4h** |
| | | B | 2.5 h | 63 | **4h** |

[a] General reaction conditions: **3b** (0.1 M in 5:1 1,4-dioxane/*t*BuOH), aryl amine (2.0 equiv), $K_3PO_4$ (1.5 equiv), 110°C. [b] Conditions: A: $Pd(OAc)_2$ (10 mol%), **L4** (30 mol%); B: $Pd(OAc)_2$ (5 mol%), **L4** (15 mol%); C: $Pd(OAc)_2$ (5 mol%), **L4** (30 mol%). [c] Disappearance of **3b** was monitored by tlc. [d] Yields reported are of isolated and purified **4a–h**. [e] Incomplete reaction.

exception of 2-toluidine, proceeded to completion with yields that were comparable to those obtained when a higher loading of Pd was used. Therefore, these results suggest that with the exception of highly sterically congested *ortho*-substituted aryl amines, which require 10-mol% $Pd(OAc)_2$, most reactions run successfully at 5-mol% $Pd(OAc)_2$ as long as the ratio of Pd/**L4** ratio is $\approx$1:6. Finally, two reactions of **3b** and 4-toluidine were conducted at 10 and 5 mol% $Pd(PPh_3)_4$ in 1,4-dioxane and 1,4-dioxane/*tert*-BuOH, respectively. Both reactions were complete within 30 min to provide a yield of 78–84% of **4a**. In contrast, even with 10 mol% $Pd(PPh_3)_4$, the amination of bromonucleoside **1** with 4-toluidine was incomplete after 5 h under the reaction conditions described here and those described previously.[2a] Currently, complexes of **L4**/Pd appear to be generally good for amination reactions of nucleosides.

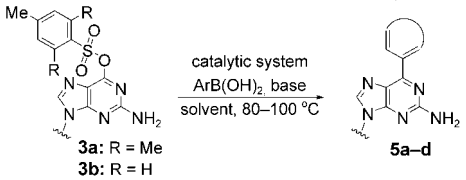
In light of the results of the amination studies, we reanalyzed the C–C cross-coupling reaction of **3a** and **3b**. In our earlier report on the Suzuki–Miyaura cross-coupling reaction using **L3**/Pd, **3a** was extensively studied and proved to be a generally good substrate, but one reaction with **3b** indicated that it might be comparable or superior to **3a**, whereas **3c** had again proven less useful.[11] Therefore, the reactions of **3a** and **3b** with selected arylboronic acids were tested in the presence of $Pd(OAc)_2$/**L3** as well as $Pd(PPh_3)_4$, which has also found utility for such reactions, under conditions that were previously reported.[11,15] The results of these experiments are summarized in Table 3.

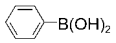
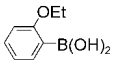
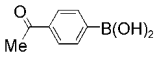
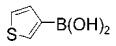
In the presence of 5 mol% $Pd(PPh_3)_4$ and $K_2CO_3$ in toluene,[15] the reaction of phenylboronic acid with **3b** was incomplete after 5 h; upon prolonged treatment (overnight), **5a** was obtained in 48% yield (entry 1). The replacement of $K_2CO_3$ with $K_3PO_4$ gave significantly superior yields with a decreased reaction time (entry 2). Little improvement was observed upon increasing the $Pd(PPh_3)_4$ load to 10 mol% in 1,4-dioxane (entry 3). However, all of the subsequent reactions were performed at the higher load for comparison with our previous reaction conditions.[11] All of the reactions of **3a** and **3b** gave good yields of the product (Table 3, entries 2–6), but **3a** appeared to be a better substrate. A similar trend was seen for reactions with 2-ethoxyphenylboronic acid (entries 7–10). Reaction of the electron-deficient 4-acetylphenylboronic acid with **3b** produced **5c** in 45% yield (entry 11) with a prolonged reaction time. On the other hand, with sulfonate **3a** the reaction was incomplete (entry 13). This is consistent with previous reports in which electron-deficient arylboronic acids gave low yields of the cross-coupled product with the $Pd(PPh_3)_4$ catalytic system.[16] Both **3a** and **3b** gave a comparable yield of the product in the presence of $Pd(OAc)_2$, **L3**, and $K_3PO_4$ (entries 12 and 14).[11] With 3-thienylboronic acid, good recoveries of the product were generally observed (entries 15–18), and $Pd(PPh_3)_4$ was somewhat superior to $Pd(OAc)_2$/**L3** despite the longer reaction times required and incomplete reaction observed with **3a** (entry 17). The results summarized in Table 3 also show that both **3a** and **3b** can be used for C–C bond-formation reactions, and that the $Pd(OAc)_2$/**L3** system is applicable with a variety of arylboronic acids.

Certain details on the nature of the catalytic systems warrant comment. The $Pd(PPh_3)_4$ catalyst shows applicability

***Table 3:*** Reaction of nucleoside sulfonates **3a** and **3b** with various arylboronic acids.




| Entry | $ArB(OH)_2$ | Sulfonate | Conditions[a] | Time[b] | Yield [%][c] | Product |
|---|---|---|---|---|---|---|
| 1 | | **3b** | A | 17 h | 48[d] | **5a** |
| 2 | | **3b** | B | 45 min | 78 | **5a** |
| 3 | | **3b** | C | 30 min | 81 | **5a** |
| 4 |  | **3b** | D | 30 min | 66 | **5a** |
| 5 | | **3a** | C | 30 min | 89 | **5a** |
| 6 | | **3a** | D | 30 min | 76[e] | **5a** |
| 7 | | **3b** | C | 5 h | 72 | **5b** |
| 8 | | **3b** | D | 5 h | 27[f] | **5b** |
| 9 |  | **3a** | C | 5 h | 76 | **5b** |
| 10 | | **3a** | D | 5 h | 65[e] | **5b** |
| 11 | | **3b** | C | 4.5 h | 45 | **5c** |
| 12 | | **3b** | D | 2 h | 64[g] | **5c** |
| 13 |  | **3a** | C | 4.5 h | 27[f] | **5c** |
| 14 | | **3a** | D | 30 min | 64[e] | **5c** |
| 15 | | **3b** | C | 1.5 h | 95 | **5d** |
| 16 |  | **3b** | D | 30 min | 83[g] | **5d** |
| 17 | | **3a** | C | 4 h | 87[f] | **5d** |
| 18 | | **3a** | D | 30 min | 78[e] | **5d** |

[a] Conditions: A: **3** (0.1 M), $Pd(PPh_3)_4$ (5 mol%), $K_2CO_3$ (1.5 equiv), PhMe, 100°C; B: **3** (0.1 M), $Pd(PPh_3)_4$ (5 mol%), $K_3PO_4$ (1.5 equiv), PhMe, 100°C; C: **3** (0.085–0.089 M), $Pd(PPh_3)_4$ (10 mol%), $K_3PO_4$ (2.0 equiv), 1,4-dioxane, 80°C; D: **3** (0.085–0.089 M), $Pd(OAc)_2$ (10 mol%), **L3** (20 mol%), $K_3PO_4$ (2.0 equiv), 1,4-dioxane, 80°C. [b] Disappearance of the sulfonate was monitored by tlc. [c] Yields reported are of isolated and purified **5a-d**. [d] Reaction incomplete after 5 h and was allowed to proceed overnight. [e] Yield reported in ref. [11]. [f] Reaction was incomplete at the time of workup. [g] Reactions were conducted as in ref. [11], but with $K_3PO_4$ (1.5 quiv).

for C–C bond-formation reactions and despite low yields with electron-deficient arylboronic acids, it can provide good to high yields when, in combination with $K_3PO_4$, other boronic acids are used. On the other hand, the biphenylphosphane-based catalysts appear to be more-broadly applicable, but they show some interesting differences. From the results presented in Table 1 and in our previous studies,[2] **L3** appears to be ineffective for the formation of C–N bonds at the C-6 position of purine nucleosides, whereas both **L4** and **L5** produce effective catalysts. However, **L3** is an effective ligand for C–C cross-coupling reactions.[2b,11] This leads us to speculate about the nature of the ligand–Pd interactions that may contribute to these two different reactions with the same substrate. With **L3**, an intramolecular $\eta^1$-arene coordination of the metal has been observed at room temperature.[17] Such interactions or plausible cyclopalladation of the biphenyl entity, as has been reported with the di(*tert*-butyl) analogue,[18] could perhaps provide an active catalyst for the formation of C–C bonds but not for C–N bonds. The prevention of cyclopalladation either through hemilabile heteroatom coordination to the metal in **L4** or the simple blockage of cyclopalladation centers in **L5** could lead to different types of non-cyclopalladated ligand–Pd complexes that display activity for C–N bond-formation reactions.

In summary, we have shown for the first time that an easily prepared arylsulfonate derivative of 2′-deoxyguanosine can be effectively utilized for Pd-catalyzed amination reactions with aryl amines to lead to $N^6$-aryl-2,6-diaminopurine nucleoside analogues. Furthermore, the results from our studies on amination and C–C cross-coupling reactions seem to indicate a delicate interplay between the nature of the ligand, the substituents on the arylsulfonate, as well as the type of reaction that is conducted, all of which contribute to the success of these reactions.

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**Keywords:** amination · C–C coupling · nucleosides · palladium · phosphane ligands

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