Palladium-Catalyzed C−N Bond Formation: Facile and General Synthesis of N^6-Aryl 2′-Deoxyadenosine Analogues

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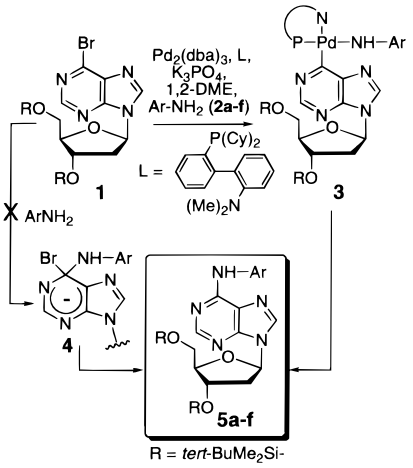
Palladium catalysis has been emerging as a versatile technique for C−N bond formation through cross-coupling reactions of aryl halides with amines.[1,2] Besides the synthesis of small molecules, this method has also provided facile entry to larger dendrimers and to oligoanilines.[3,4] On the basis of these studies, we became interested in determining whether this type of cross coupling would be applicable to labile biomolecules, such as nucleosides. Carcinogenic aromatic amines, for example 2-aminofluorene and 2-amino-1-methyl-6-phenylimidazolo[4,5-*b*]pyridine (which is present in cooked meat), are metabolically converted to *N*-hydroxy derivatives which bind to DNA bases through solvolytic pathways.[5] In the ensuing adducts, the nucleobase and arylamine are linked through a C−N bond. Thus, we reasoned that Pd-mediated C−N bond formation, if applicable, would allow easy access to biologically important systems such as aminoaryl nucleosides. The exocyclic N^6-amino group of 2′-deoxyadenosine offers a convenient target for modification, and we believe that the chemical methods developed for accomplishing this could become the basis for the synthesis of second generation or other more complex nucleosides. In this paper we report our preliminary results on the synthesis of N^6-aryl 2′-deoxyadenosine derivatives through Pd catalysis. This also represents the first facile and general approach for introduction of aryl groups at the exocyclic amine functionalities of nucleosides.

Although S_NAr displacement of halogens from the C-6 position of purines is known, this is limited to relatively strong nucleophiles such as aliphatic amines.[6] Even with the highly reactive 6-fluoro-9-[2-deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-*erythro*-pentofuranosyl]purine[7] (which requires a six-step synthesis from 2′-deoxyadenosine), reaction with relatively unreactive aliphatic amines is difficult.[8] Also, in our experience the C-6 chloro analogue (which can be prepared in three steps from 2′-deoxyadenosine[6,9]) does not react with arylamines. Thus, 6-bromo-9-[2-deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-*erythro*-pentofuranosyl]purine (**1**) should be even less reactive toward arylamines through the S_NAr mechanism. Therefore, **1** is a suitable substrate for Pd-mediated arylaminations. Synthetically, **1** can be prepared in just two steps from 2′-deoxyadenosine (silylation of the 3′,5′-hydroxyls,[10] 94%, and diazotization−bromination,[11] 60%). Bromonucleoside **1** shares structural features with both 1- and 4-bromopyridine, compounds that have been successfully aminated using Pd catalysis.[12] Although it has been demonstrated that pyridines do not cause ligand exchange with the Pd catalysts when bis(phosphine) ligands are employed,[12] we could not determine a priori whether the multiple chelation sites in **1** could pose problems of this nature.

Scheme 1



At the outset, we decided to evaluate the amination of **1** with *p*-toluidine as a representative amine. For this, the $Pd_2(dba)_3$/(±)-BINAP combination and the more commonly employed sodium *tert*-butoxide were chosen as catalyst and base, in toluene as solvent at 100 °C. Disappointingly, we learned that *tert*-butoxide was detrimental to the nucleoside and was replaced with the milder Cs_2CO_3. With this catalyst−base combination, complete consumption of **1** was observed within 2 h. However, the N^6-(4-methylphenyl)-2′-deoxyadenosine derivative (**5a**), which was obtained in ∼60% yield, was contaminated with a minor inseparable impurity that caused product coloration. Buchwald and co-workers recently reported the synthesis and use of 2-(dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino)-1,1′-biphenyl (**L**, Scheme 1).[13] This electron-rich ligand, which is thought to accelerate the initial oxidative-addition step, seemed particularly attractive to us for such a reason.[13,14] Replacement of (±)-BINAP with **L**, while maintaining Cs_2CO_3 as base in toluene, resulted in

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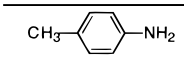
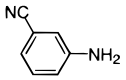
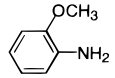
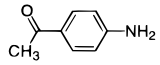
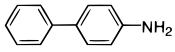
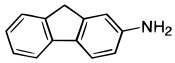
Table 1. Amines Used and Yields of the N^6-Aryl Nucleosides[a]

Amine		Yield[b]
	**2a**	**5a:** 69
	**2b**	**5b:** 61
	**2c**	**5c:** 72
	**2d**	**5d:** 52
	**2e**	**5e:** 64
	**2f**	**5f:** 68

[a] Reaction conditions: 1.0 equiv **1**, 2.0 equiv amine, 1.5 equiv K_3PO_4, 10 mol % $Pd_2(dba)_3$, 30 mol % ligand, 1,2-DME, 80 °C. [b] Refers to isolated, purified products.

a dramatic decrease in reaction rate even at 100 °C (complete in 36 h). While progress of the reaction at room temperature was observed with sodium *tert*-butoxide as base, formation of significant amounts of byproducts was also seen. On the other hand, the combination $Pd_2(dba)_3$/**L** and sodium 2,4,6-tri-*tert*-butylphenoxide[15] in toluene proved ineffective.

Buchwald and co-workers have reported the use of K_3PO_4 as a mild base in cross-coupling reactions involving two sensitive substrates.[13] On the basis of solubility considerations of the base, toluene was replaced with 1,2-dimethoxyethane (1,2-DME), but this results in lower reaction temperatures. However, despite this, we were delighted to find that the combination of $Pd_2(dba)_3$ (10 mol %)/**L** (30 mol %)/K_3PO_4 (1.5 equiv) in 1,2-DME at 80 °C proved to be the best for effecting arylamination of **1**. Reducing the catalyst and ligand (5 mol % and 15 mol %, respectively) resulted in extremely slow conversion and lower product yield (reaction complete in 97 h at 80 °C, 49% yield), as did lower temperatures.

Mechanistically, we believe this arylamination proceeds through the nucleoside−palladium intermediate **3** and that the S_NAr mechanism which should proceed through **4** is not competitive. This is supported by the fact that in the absence of the Pd−ligand complex no product formation was observed even after 24 h at 80 °C. Table 1 shows the amines used in the evaluation of the generality of this coupling procedure. In every case the amination was complete within 3.5−4 h regardless of the substituent on the arylamine, and separation of the products from excess amine was readily achieved by column chromatography. Excess amines can potentially be recovered, and this may be significant when synthetically precious amines are used. The product yields are good, and only in the case of the sensitive *p*-aminoacetophenone is a <60% yield obtained. It is particularly noteworthy that the method provides high yields with the biologically significant, carcinogenic amines: 4-aminobiphenyl (**2e**) and 2-aminofluorene (**2f**). Interestingly, reversal of the bromo species and the amine donor led only to the recovery of starting compounds. For example, an attempt at coupling *p*-bromotoluene with 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine, in toluene with **L** and *tert*-butoxide as base, was unsuccessful.

In conclusion, we have developed a convenient approach for the introduction of aryl moieties at the exocyclic amino group of 2′-deoxyadenosine.[16] We have also shown that the potential multiple coordination sites in such nucleosides do not cause termination of the catalytic cycle through ligand exchange. This method, we believe, can be easily extended to the guanine nucleosides as well as the less labile ribonucleosides. Also, due to the facile C-8 halogenation of purine nucleosides,[17] Pd-mediated C−N bond formation should be applicable to the synthesis of C-8 adducts from carcinogenic arylamines. Conceivably, problems associated with difficult S_NAr reactions utilizing less reactive aliphatic amines can be alleviated through this protocol as well. Examples of this are the axially constrained, sterically hindered aliphatic amines derived from diol epoxide metabolites of carcinogenic hydrocarbons.[18] Since this method provides facile access to biologically significant *N*-modified nucleosides, which are important for site-specific DNA modification,[19] synthetic efforts addressing these issues are currently underway in our laboratory.

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Supporting Information Available: Experimental procedures and characterization data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) **General procedure.** Into an oven-dried screwcap vial were placed $Pd_2(dba)_3$ (0.018 mmol), ligand **L** (0.055 mmol), and K_3PO_4 (0.28 mmol). Anhydrous 1,2-DME (1.8 mL) was added, followed by bromonucleoside **1** (0.18 mmol) and 4-aminobiphenyl (**2e**, 0.36 mmol). The vial was flushed with N_2, capped, and heated in a sandbath which was maintained at 80−81 °C. The reaction was monitored by TLC and was complete in 3 h. The mixture was subsequently cooled and diluted with Et_2O. A small volume of H_2O was added to solubilize K_3PO_4, and then an equal volume of brine was added. The layers were shaken, the aqueous layer was removed, and the organic layer was washed once with brine. The aqueous layers were back-extracted once with Et_2O, and the combined organic layer was dried over Na_2SO_4 and evaporated. The crude product was chromatographed on a silica gel column packed in CH_2Cl_2 which was eluted sequentially with CH_2Cl_2 and 5% acetone in CH_2Cl_2. N^6-(4-Phenylphenyl)-9-[2-deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-*erythro*-pentofuranosyl]purine (**5e**) was obtained as a yellow foam in 64% yield.

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