JOC Featured Article

pubs.acs.org/joc

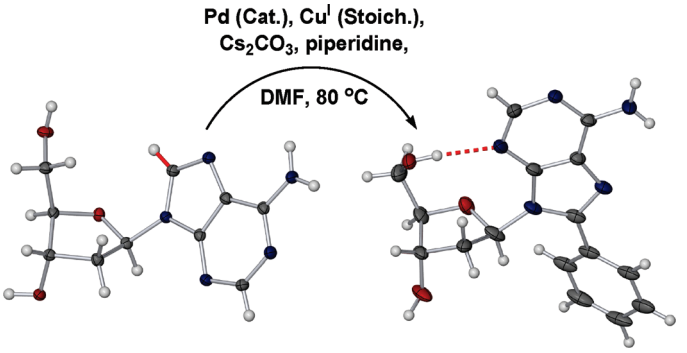
Pd(0)/Cu(I)-Mediated Direct Arylation of 2′-Deoxyadenosines: Mechanistic Role of Cu(I) and Reactivity Comparisons with Related Purine Nucleosides

Thomas E. Storr,[†,‡] Christoph G. Baumann,[‡] Robert J. Thatcher,[†] Sara De Ornellas,[†,‡] Adrian C. Whitwood,[†] and Ian J. S. Fairlamb*,[†]

[†]*Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K., and* [‡]*Department of Biology, Area 10, University of York, Heslington, York YO10 5YW, U.K.*

ijsf1@york.ac.uk

Received June 10, 2009



Pd/Cu-mediated direct arylation of 2′-deoxyadenosine with various aryl iodides provides 8-arylated 2′-deoxyadenosine derivatives in good yields. Following significant reaction optimization, it has been determined that a substoichiometric quantity of piperidine (secondary amine) in combination with cesium carbonate is necessary for effective direct arylation. The general synthetic protocol allows lower temperature direct arylations, which minimizes deglycosylation. The origin of the piperidine effect primarily derives from the in situ generation of $Pd(OAc)_2[(CH_2)_5NH]_2$. Various copper(I) salts have been evaluated; only CuI provides good yields of the 8-arylated-2′-deoxyadenosines. Copper(I) appears to have a high binding affinity for 2′-deoxyadenosine, which explains the mandatory requirement for stoichiometric amounts of this key component. The conditions are compared with more general direct arylation protocols, e.g., catalytic Pd, ligand, acid additives, which do not employ copper(I). In each case, no detectable arylation of 2′-deoxyadenosine was noted. The conformational preferences of the 8-aryl-2′-deoxyadenosine products have been determined by detailed spectroscopic (NMR) and single crystal X-ray diffraction studies. Almost exclusively, the preferred solution-state conformation was determined to be *syn*-C2′-*endo* (ca. 80%). The presence of a 2-pyridyl group at the 8-position further biases the solution-state equilibrium toward this conformer (ca. 88%), due to an additional H-bond between H1′ and the pyridyl nitrogen atom. The Pd/Cu catalyst system has been found to be unique for adenosine type substrates, the reactivity of which has been placed into context with the reported direct arylations of related 1*H*-imidazoles. The reactivity of other purine nucleosides has been assessed, which has revealed that both 2′-deoxyguanosine and guanosine are incompatible with the Pd/Cu-direct arylation conditions. Both substrates appear to hinder catalysis, akin to the established inhibitory effects in Suzuki cross-couplings with arylboronic acids.

Introduction

C-modified non-natural nucleosides are widely employed as fluorescent markers,[1] sensors to detect light,[2] therapeutic agents,[3] novel ligands for metals,[4] and supramolecular building blocks.[5] These analogues allow biomolecular structure and biochemical mechanisms to be probed,[6] which in turn provides the impetus to develop more efficient synthetic routes to structurally distinct nucleosides, particularly purine-based compounds.[7] Indeed, Sonogashira, Suzuki, and Stille cross-coupling processes, catalyzed by Pd(0),[8]

*To whom correspondence should be addressed. Tel: +44 (0)1904 434091. Fax: (0)1904 432516.

Published on Web 07/27/2009 DOI: 10.1021/jo9012282

provide *C*-functionalized purine nucleosides of varying substitution patterns.[9] There is a particular interest in the synthesis of 8-modified purine nucleosides and the following bioapplications: conformational studies to assess DNA/RNA base pairing,[10] cytostatic properties against certain tumor cell lines,[11] antagonist effects at the A3 adenosine receptor,[12] thrombin inhibitory activity,[13] fluorescence applications,[14] components in supramolecular assembly,[15] among other possibilities.[16] In addition to these bioapplications, other structurally diverse 8-aryl-2′-deoxyadenosines act as pH-sensing fluorescent probes,[17] as biomarkers for exposure to chemical carcinogens,[18] and as luminescent and electroactive labels[19] (selected examples given in Figure 1).

Protection of both the sugar hydroxyl groups and the reactive heteroaromatic substituents was considered mandatory until recently developed conditions showed that unprotected

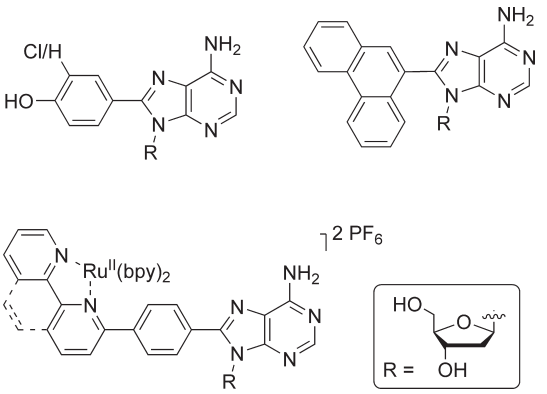


FIGURE 1. Selected 8-aryl-2′-deoxyadenosines.

halogenated nucleosides can be effectively cross-coupled with various nucleophilic components.[20] Quite remarkably, halogenated nucleoside triphosphates are also viable substrates for Suzuki−Miyaura cross-couplings.[21,22]

Significant progress has been made in the synthetic chemistry of prefunctionalized nucleosides. A new challenge has emerged in nucleoside chemical synthesis, which involves the use of nonfunctionalized derivatives, e.g., 2′-deoxyadenosine rather than 8-bromo-2′-deoxyadenosine. This approach would allow one to greatly diversify the portfolio of *C*-functionalized purine nucleosides with the ultimate goal of selectively synthesizing *C*-functionalized nucleotides and oligonucleotides. The emergence of direct arylation (functionalization) strategies for aromatic and heteroaromatic compounds, which is a popular replacement[23] for classical cross-coupling methodologies, allows us to assess the potential for selective C−H functionalization in nucleosides, particularly purines.

Some methods have been described for the Pd-catalyzed intermolecular direct arylation of similar compounds, e.g., (benz)imidazoles derivatives.[24] However, rather curiously there is a requirement for stoichiometric Cu^{I} additives, although not exclusively.[25] Furthermore, some success has been had in arylating suitably protected purine derivatives, e.g., *N*9-benzyl derivatives.[26] In parallel with the Hocek group,[27]

(1) (a) Burgess, K.; Cook, D. *Chem. Rev.* **2000**, *100*, 2047. (b) Asseline, U. *Curr. Org. Chem.* **2006**, *10*, 491. (c) Rist, M. J.; Marino, J. P. *Curr. Org. Chem.* **2002**, *6*, 775. For a fascinating special issue dedicated to this area, see: (d) Tor, Y. *Tetrahedron* **2007**, *63*, 3425.

(2) Gao, J. M.; Watanabe, S.; Kool, E. T. *J. Am. Chem. Soc.* **2004**, *126*, 12748.

(3) Alvarez-Salas, L. M. *Curr. Top. Med. Chem.* **2008**, *8*, 1379.

(4) Ropartz, L.; Meeuwenoord, N. J.; van der Marel, G. A.; van Leeuwen, P. W. N. M.; Slawin, A. M. Z.; Kamer, P. C. J. *Chem. Commun.* **2007**, 1556.

(5) (a) Cowley, M. J.; Lynam, J. M.; Whitwood, A. C. *Dalton Trans.* **2007**, 4427. (b) Lynam, J. M. *Dalton Trans.* **2008**, 4067.

(6) (a) De Clercq, E. *Biochem. Pharmacol.* **1984**, *33*, 2159. (b) Minakawa, N.; Kojima, N.; Sasaki, T.; Matsuda, A. *Nucleosides Nucleotides* **1996**, *15*, 251. (c) De Clercq, E.; Descamps, J.; De Somer, P.; Barr, P. J.; Jones, A. S.; Walker, R. T. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 2947. (d) Manfredini, S.; Baraldi, P. G.; Bazzanini, R.; Marangoni, M.; Simoni, D.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1995**, *38*, 199. (e) Hocek, M.; Holy, A.; Votruba, I.; Dvoráková, H. *J. Med. Chem.* **2000**, *43*, 1817.

(7) For a review covering the recent advances in the synthesis of purine derivatives, see: Legraverend, M. *Tetrahedron* **2008**, *64*, 8585.

(8) Fairlamb, I. J. S. *Tetrahedron* **2005**, *61*, 9661.

(9) (a) Agrofoglio, L. A.; Gillaizeau, I.; Saito, Y. *Chem. Rev.* **2003**, *103*, 1875. (b) Hocek, M. *Eur. J. Org. Chem.* **2003**, 245. (c) Lakshman, M. K. *Curr. Org. Synth.* **2005**, *2*, 83.

(10) (a) Bhardwaj, P. K.; Vasella, A. *Helv. Chim. Acta* **2002**, *85*, 699. (b) Eppacher, S.; Solladié, N.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **2000**, *83*, 1311. (c) Saenger, W. *Principles of Nucleic Acid Structure*; Springer Verlag: Berlin, 1984; pp 69−78. (d) Catalanotti, B.; Galeone, A.; Paloma, L. G.; Mayol, L.; Pepe, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2005.

(11) Manfredini, S.; Baraldi, P. G.; Bazzanini, R.; Marangoni, M.; Simoni, D.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1995**, *38*, 199.

(12) Volpini, R.; Costanzi, S.; Lambertucci, C.; Vittori, S.; Klotz, K.-N.; Lorenzenc, A.; Cristalli, G. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1931.

(13) He, G. -X.; Krawczyk, S. H.; Swaminathan, S.; Shea, R G.; Dougherty, J. P.; Terhorst, T.; Law, V. S.; Griffin, L. C.; Coutré, S.; Bischofberger, N. *J. Med. Chem.* **1998**, *41*, 2234.

(14) (a) Srivatsan, S. G.; Greco, N. J.; Tor, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 6661. (b) Srivatsan, S. G.; Weizman, H.; Tor, Y. *Org. Biomol. Chem.* **2008**, *6*, 1334. (c) Firth, A. G.; Fairlamb, I. J. S.; Darley, K.; Baumann, C. G. *Tetrahedron Lett.* **2006**, *47*, 3529.

(15) (a) Sessler, J. L.; Sathiosatham, M.; Doerr, K.; Lynch, V.; Abboud, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1300. (b) Davis, J. T. *Angew. Chem., Int. Ed.* **2004**, *43*, 668.

(16) (a) Crisp, G. T.; Gore, J. *Tetrahedron* **1997**, *53*, 1523. (b) Gillet, L. C. J.; Scha1rer, O. D. *Org. Lett.* **2002**, *4*, 4205.

(17) (a) Sun, K. M.; McLaughlin, C. K.; Lantero, D. R.; Manderville, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 1894. For a related application for 8-phenol-2′-deoxyguanosines, see: (b) Weishar, J. L.; McLaughlin, C. K.; Baker, M.; Gabryelski, W.; Manderville, R. A. *Org. Lett.* **2008**, *10*, 1839.

(18) (a) Dai, Q.; Xu, D.; Lim, K.; Harvey, R. G. *J. Org. Chem.* **2007**, *72*, 4856. (b) Vrábel, M.; Hocek, M.; Havran, L.; Fojta, M.; Votruba, I.; Klepetářová, B.; Pohl, R.; Rulíšek, L.; Zendlová, L.; Hobza, P.; Shih, I.-h.; Mabery, E.; Mackman, R. *Eur. J. Inorg. Chem.* **2007**, *12*, 1752.

(19) (a) Vrábel, M.; Horáková, P.; Pivoková, H.; Kalachova, L.; Černocká, H.; Cahová, H.; Pohl, R.; Šebest, P.; Havran, L.; Hocek, M.; Fojta, M. *Chem.—Eur. J.* **2009**, *15*, 1144. (b) Vrábel, M.; Pohl, R.; Klepetářová, B.; Votruba, I.; Hocek, M. *Org. Biomol. Chem.* **2007**, *5*, 2849.

(20) (a) Collier, A.; Wagner, G. *Synth. Commun.* **2006**, *36*, 3713. (b) Shaughnessy, K. H. *Eur. J. Org. Chem.* **2006**, 1827. (c) Čapek, P.; Hocek, M. *Synlett* **2005**, 3005. (d) Western, E. C.; Daft, J. R.; Johnson, E. M. II; Gannett, P. M.; Shaughnessy, K. H. *J. Org. Chem.* **2003**, *68*, 6767.

(21) Capek, P.; Pohl, R.; Hocek, M. *Org. Biomol. Chem.* **2006**, *4*, 2278.

(22) (a) Collier, A.; Wagner, G. *Org. Biomol. Chem.* **2006**, *4*, 4526. (b) Collier, A.; Wagner, G. *Chem. Commun.* **2008**, 178.

(23) For specific reviews concerning the direct arylation of heteroaromatics, see: (a) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (b) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. Regioselective aspects in the direct arylation of heteroaromatics are covered in: (c) Fairlamb, I. J. S. *Chem. Soc. Rev.* **2007**, *36*, 1036. For general reviews, see: (d) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (e) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (f) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. For an excellent special issue dedicated to catalytic aromatic C−H activation, see: Bedford, R. B. *Tetrahedron* **2008**, *64*, 5973.

(24) (a) Bellina, F.; Cauteruccio, S.; Mannina, L.; Rossi, R.; Viel, S. *J. Org. Chem.* **2005**, *70*, 3997. (b) Bellina, F.; Cauteruccio, S.; Mannina, L.; Rossi, R.; Viel, S. *Eur. J. Org. Chem.* **2006**, 693. (c) Bellina, F.; Cauteruccio, S.; Rossi, R. *Eur. J. Org. Chem.* **2006**, 1379. (d) Bellina, F.; Cauteruccio, S.; Rossi, R. *J. Org. Chem.* **2007**, *72*, 8543. (e) Bellina, F.; Calandri, C.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 1970. (f) Bellina, F.; Cauteruccio, S.; Di Fiore, A.; Rossi, R. *Eur. J. Org. Chem.* **2008**, *543*, 5445. (g) Bellina, F.; Cauteruccio, S.; Di Fiore, A.; Marchetti, C.; Rossi, R. *Tetrahedron* **2008**, *64*, 6060.

(25) In ref 24a, it was shown that C2-arylation can occur as a *minor* reaction pathway using catalytic $Pd(OAc)_2$ (5 mol %), $AsPh_3$ (10 mol %), and CsF (2 equiv) in DMF at 140 °C. C5-arylation is usually the preferred and major reaction pathway.

(26) Čerňa, I.; Pohl, R.; Klepetářová, B.; Hocek, M. *Org. Lett.* **2006**, *8*, 5389.

(27) Čerňa, I.; Pohl, R.; Hocek, M. *Chem. Commun.* **2007**, 4729.

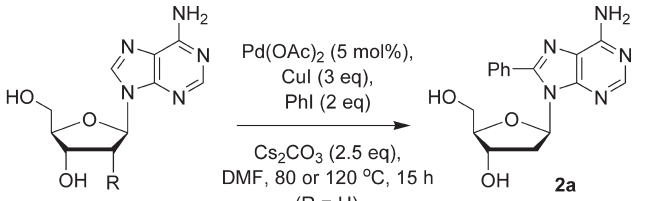
we have investigated[28] the reactivity of adenosine toward selective C8-H arylation mediated by a Pd−Cu catalyst system in the presence of aryl iodides using an appropriate base (in our case, Cs_2CO_3; Hocek employed piperidine only) in DMF at ~120 °C. In a single example, the Hocek group reported the Pd−Cu-mediated arylation of 2′-deoxyadenosine using 4-iodotoluene heating to 125 °C for 5 h, which gave the C8-arylated product in 31% yield (an 8% yield of a N^6/C8-diarylation product was also reported). Indeed, the *N*6-arylation pathway[29] is always a problem for this chemistry, particularly when run at higher temperatures.

Building on these findings, we reported a single result concerning the C8-arylation of unprotected 2′-deoxyadenosine (**1**) under slightly modified conditions to that required for adenosine (a change in temperature from 120 to 80 °C, to avoid extensive deglycosylation in the case of **1**). Subsequent studies in our laboratories have revealed that the efficacy of this specific reaction is dependent on how the DMF solvent is purified. Therefore, we have chosen to comprehensively explore the reactivity of **1** as a substrate for this type of reaction toward iodobenzene initially under a variety of conditions. We have determined that secondary amines are *necessary additives* for reactions employing $Pd(OAc)_2$ when run at 80 °C: either dimethylamine (generated by degradation of DMF → $NHMe_2$ + CO) or intentionally added piperidine (as a dimethylamine mimic). The optimized conditions have been applied against a range of aryl iodides to deliver a series of novel 8-aryl-2′-deoxyadenosine (**2a**−**j**) compounds. A structural analysis of these compounds has been carried out (by single-crystal X-ray diffraction studies and solution-based NMR spectroscopic studies). The reactivity of **1** has been compared with other related purine nucleosides, e.g., guanosine, inosine, and fluorinated adenosines. Defined trends emerge concerning the efficient C8-arylations of these purine nucleosides.

Results and Discussion

2′-Deoxyadenosine **1** can be arylated at the C8-position under the modified reaction conditions determined for adenosine **3** vide infra. The instability of the glycosyl bond at higher temperatures, e.g., > 100 °C, is a significant problem for this type of chemistry (note: **3** is over 2 orders of magnitude more stable toward deglycosylation than **1**).[30] Indeed, the use of high-temperature microwave conditions [$Pd(OH)_2$/C (5 mol %), CuI (2 equiv), Cs_2CO_3 (2 equiv), NMP at 160 °C with MWI] developed by Alami and co-workers[31] for non-ribose-based purine C8-arylation is ultimately precluded due to this key detail.[32] At 120 °C, using our standard conditions

SCHEME 1. Arylation of 2′-Deoxyadenosine 1

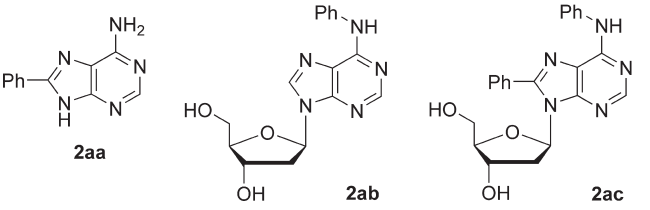


R = H (**1**): $t_{1/2}$ = 10 x10^3 min
R = OH (**3**): $t_{1/2}$ = > 5 x10^5 min

Temp / °C	Yield / %
120	29*
80	84

* yield of **2aa**.

Other products observed in this study by LC-MS



(see Scheme 1), substantial deglycosylation for **1** was observed, giving mainly 8-phenyladenine (**2aa**), which confirms that direct arylation has taken place but that the resulting 8-phenyl-2′-deoxyadenosine product (**2a**) is more susceptible to deglycosylation than **1**. At 80 °C, a higher yield of **2a** was achieved (84%).[28] Therefore, milder conditions facilitate the C8-arylation of the less stable 2′-deoxyribose compound **1**, providing increased yields of the arylation product **2a**.

Curiously, we noted that reaction efficacy was severely affected by the use of a thoroughly dried and degassed batch of DMF. The typical protocol for DMF purification is distillation from $MgSO_4$ under a N_2 atmosphere, which usually provides a sufficiently dry, oxygen-free solvent ready for use. This procedure does not fully remove trace water, but degassing by the freeze/pump/thaw method and storing the distillate over 4 Å molecular sieves essentially provides "water-free" DMF. When using DMF purified in this manner, we noticed that the yields for **2a** were severely affected (ca. 10% ± 5% isolated yields). It was also found that if DMF was used directly from the distillation (without degassing), the reaction yields were much higher (ca. 65% yields). This allowed us to identify that low concentrations of dimethylamine, a well-known degradation product of DMF on prolonged heating, were necessary for efficient direct arylation of **1**. Interestingly, the use of thoroughly dried and degassed DMF did not affect the efficacy of the arylation of adenosine at 120 °C. This is most likely due to the higher temperatures either producing the necessary amine in situ (more likely) or as a result of a change in mechanism. Given the low boiling point of dimethylamine (bp 7 °C)[33] and the practicalities associated with its handling, we chose to assess other amine additives for optimization of this reaction using thoroughly dry and degassed DMF (Table 1).

(28) Storr, T. E.; Firth, A. G.; Wilson, K.; Darley, K.; Baumann, C. G.; Fairlamb, I. J. S. *Tetrahedron* **2008**, *64*, 6125.

(29) One can selectively *N*-arylate protected 2′-deoxyadenosines and 2′-deoxyguanosines with aryl bromides using a Pd−Xantphos catalytic system; see: Ngassa, F. N.; DeKorver, K. A.; Melistas, T. S.; Yeh, E. A.-H.; Lakshman, M. K. *Org. Lett.* **2006**, *8*, 4613.

(30) The $t_{1/2}$ value for deglycosylation is expected to fall dramatically in the presence of a base.

(31) Sahnoun, S.; Messaoudi, S.; Peyrat, J. -F.; Brion, J. -D.; Alami, M. *Tetrahedron Lett.* **2008**, *49*, 7279.

(32) Using the conditions described by Alami and co-workers (ref 31), the arylation of **1** (1 equiv) with iodoanisole (1.5 equiv) resulted in the formation of a trace amount of 8-(*p*-methoxyphenyl)-2′-deoxyadenosine and adenine (the deglycosylation product derived from **1**) in our hands [other conditions: $Pd(OH)_2$/C (5 mol %), CuI (1 equiv), Cs_2CO_3 (2 equiv), NMP, μW, 160 °C, 15 min].

(33) Aston, J. G.; Eidinoff, M. L.; Forster, W. S. *J. Am. Chem. Soc.* **1939**, *6*, 1539.

TABLE 1. Effect of Amine Additives on the Reaction of 1 with Iodobenzene To Give 2a[a]

entry	amine additive	equiv[b]	yield (%)[c]
1			12
2	dimethylamine (Me_2NH)	trace[d]	84,[e] 65,[f] 64[f]
3	diethylamine (Et_2NH)	0.4	50
4	diisopropylamine (i-Pr_2NH)	0.4	14
5	diphenylamine (Ph_2NH)	0.4	7
6	piperidine	0.1	47
7	piperidine	0.2	57
8	piperidine	0.4	65
9	piperidine	0.8	41
10	piperidine	1.2	41
11	piperidine	1.6	28
12	piperidine (without Cs_2CO_3)	2.5	5[g]
13	pyrrolidine	0.4	45
14	triethylamine (Et_3N)	0.4	26
15	N,N,N',N'-tetramethylethylenediamine (TMEDA)	0.2	< 5

[a]Reaction conditions as for Scheme 1 at 80 °C, using thoroughly dry and degassed DMF (entry 2 employed freshly distilled DMF). [b]With respect to **1** (0.37 mmol scale). [c]Isolated yield, following chromatography on silica gel. [d]Due to solvent distillation (not quantified). [e]Previously reported yield[28] obtained using freshly distilled solvent. [f]Repeat runs of this reaction. [g]Product **2a** was contaminated by a significant amount of piperidine·HX (ca. 10 equiv).

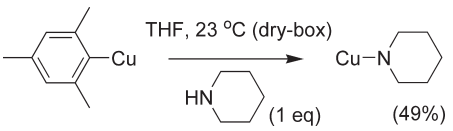
The reaction of **1** with iodobenzene under the standard conditions using thoroughly dry and degassed DMF gave compound **2a** in 12% yield (entry 1, Table 1). In the presence of trace dimethylamine (from freshly distilled, nondegassed DMF), the yields obtained were substantially higher (yields for three runs are shown in entry 2). In the presence of the secondary amines diethylamine, diisopropylamine, and diphenylamine, yields of 50, 14, and 7% were recorded for **2a**, respectively (entries 3−5). Piperidine is a superior secondary amine base for these reactions (entries 6−11). By varying the concentration of this base additive, the most efficient reaction was determined to be that employing a substoichiometric quantity of piperidine (0.4 equiv; entry 8). Higher concentrations of piperidine lead to diminishing yields (entries 9−11). When 2.5 equiv of piperidine in the absence of Cs_2CO_3 was used, **2a** was formed in ca. 5% yield, which was contaminated with piperidine·HX (entry 12). It was also noted that pyrrolidine is an effective secondary base for this reaction (entry 13); however, piperidine is superior at equivalent loadings (compare entries 8 and 13). Tertiary amines (triethylamine and TMEDA) are generally poor base additives for these reactions (entries 14 and 15, respectively). In the case of TMEDA, it is plausible that the chelating bidentate nature of this ligand could interfere with catalysis (at Pd^{II} or Cu^{I}; or facilitate oxidation of Cu^{I} to Cu^{II}).

The use of piperidine as the sole base for the direct arylation reaction of **1** has been employed by Hocek and co-workers (also tested at 80 °C; entry 12, Table 1).[27] However, our studies allow us to conclude that the combination of Cs_2CO_3 (stoichiometric) and piperidine (substoichiometric) is more effective in reactions run at lower temperatures, e.g., 80 °C. At this stage in our study, the origin of the secondary amine effect remained unclear. There were several possibilities; however, generation of a Cu^{I}−amide type complex or slower reduction of "$Pd(OAc)_2L_2$" to give the active "Pd(0)" catalyst seemed like the most plausible explanation.

The $Cu[N(CH_2)_5]$ complex[34] was prepared from mestylcopper(I) and piperidine in 49% yield (Scheme 2) vide infra.

It is established that secondary amines react with $Pd(OAc)_2$ to give $Pd(OAc)_2(R_2NH)_2$ complexes,[35] which can also reduce on heating to give Pd^0 species in situ. We similarly determined that piperidine (2 equiv) reacts with $Pd(OAc)_2$ (1 equiv) in DMF to afford *trans*-$Pd(OAc)_2[(CH_2)_5NH]_2$ at 20 °C in a few seconds (Scheme 3). Pd^0/Pd colloids are slowly formed, following prolonged heating (15 h) of this complex in DMF at 80 °C (with formation of 2,3,4,5-tetrahydropyridine), indicating that this complex is likely a precatalyst. For the actual direct arylation, other components in the reaction mixture may serve to reduce Pd^{II} to Pd^0.[36]

SCHEME 2. Synthesis of $Cu[N(CH_2)_5]$



Direct arylation of **1** proceeds to a certain extent using $Cu[N(CH_2)_5]$ complex (either 1 or 3 equiv; entries 1 and 2, respectively) as a substitute for CuI (Table 2). However, the yields of **2a** do not mirror the identical reaction conducted in the presence of CuI and piperidine.

The direct arylation of **1** with PhI mediated by *trans*-$Pd(OAc)_2[(CH_2)_5NH]_2$ (5 mol %), in the absence of added piperidine, gave **2a** in 64% yield (entry 3). Running an otherwise identical reaction with 0.3 equiv of piperidine gave **2a** in 68% yield (entry 4). A similar reaction using 2.4 equiv of piperidine gave **2a** in 54% yield, which was contaminated by piperidine·HX following chromatography on silica gel (entry 5). In the absence of both CuI and piperidine additive no product formation was observed (entry 6). To summarize, *the enhancing effect of piperidine* (*secondary amine*) *in the direct arylations of* ***1*** *derives from N-ligation to* Pd^{II}, *most likely providing a more effective precatalyst in situ.*

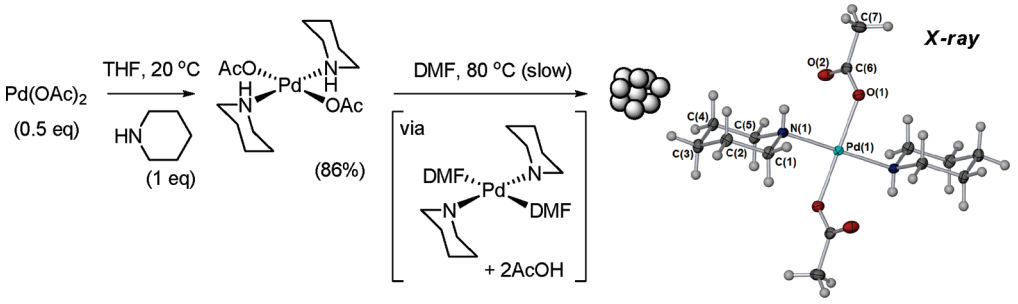
To further determine the role of CuI, other Cu^{I} sources have been evaluated, i.e., Cu^{I}−thiophene carboxylate and CuOTf. These electrophilic Cu^{I} sources were unable to promote the direct arylation of **1**, highlighting the importance of the iodide anion. Of further interest is the finding that tetra-*n*-butylammonium iodide is an ineffective substitute for CuI.

(34) Tsuda, T.; Watanabe, K.; Miyata, K.; Yamamoto, H.; Saegusa, T. *Inorg. Chem.* **1981**, *20*, 2728.

(35) Tao, B.; Boykin, D. W. *J. Org. Chem.* **2004**, *69*, 4330.

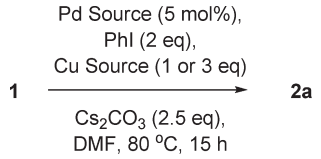
(36) Prolonged incubation of $Pd(OAc)_2[(CH_2)_5NH]_2$ in DMF (at 20 °C) revealed palladium adducts containing 2,3,4,5-tetrahydropyridine (by ESI-MS/MS).

SCHEME 3. Synthesis of *trans*-Pd(OAc)$_2$[(CH$_2$)$_5$NH]$_2$[a]



[a]X-ray: the thermal ellipsoids shown at 50% probability; this and all subsequent X-ray crystal structure images were prepared using X-Seed and POVRay (v. 3.6).

TABLE 2. Effect of Pd and Cu Sources on the Reaction of 1 with Iodobenzene To Give 2a[a]



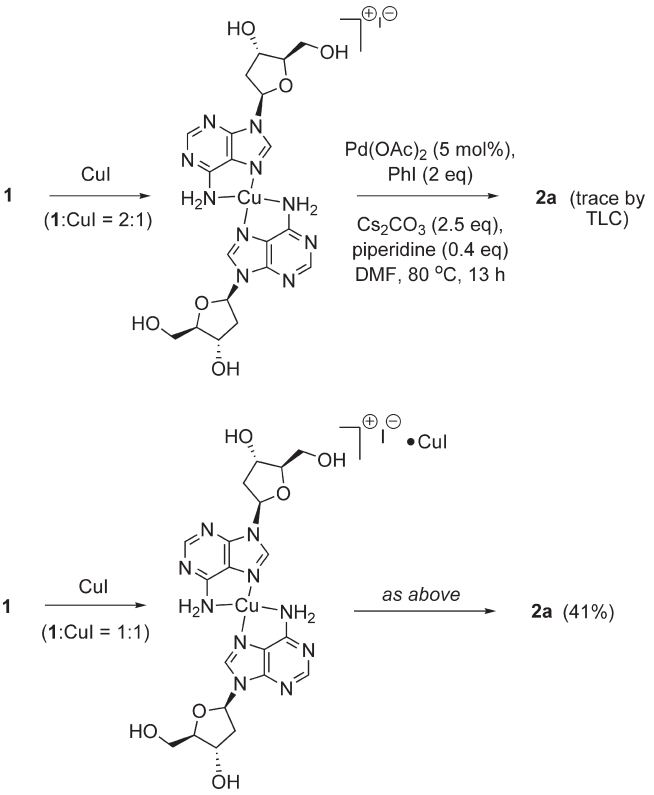
Entry	Pd Source (5 mol%)	Cu Source[b]	Yield (%)[c]
1	Pd(OAc)$_2$	Cu–N (1 eq)	14
2	Pd(OAc)$_2$	Cu–N (3 eq)	24
3	*trans*-Pd(OAc)$_2$ {(CH$_2$)$_5$NH}$_2$	CuI (3 eq)	64
4	*trans*-Pd(OAc)$_2$ {(CH$_2$)$_5$NH}$_2$	CuI (3 eq) + piperidine (0.3 eq)	68
5	*trans*-Pd(OAc)$_2$ {(CH$_2$)$_5$NH}$_2$	CuI (3 eq) + piperidine (2.4 eq)	54[d]
6	*trans*-Pd(OAc)$_2$ {(CH$_2$)$_5$NH}$_2$	-	0[e]

[a]Reaction conditions were otherwise identical to footnote *a* (Table 1). [b]With respect to **1** (0.37 mmol scale). [c]Isolated yield following chromatography on silica gel. [d]Product **2a** was contaminated by piperidine·HX (ca. 1 equiv). [e]Unreacted **1** remaining (by TLC analysis).

As late transition metals are well-known to form stable metal complexes with purines, a Cu^{I} complex containing **1** was synthesized. Reaction of CuI (1 equiv) with **1** (1 or 2 equiv) in DMF at 80 °C for 1 h gave in both cases new Cu^{I} complexes (Scheme 4). ESI-MS/MS analysis of both reaction mixtures revealed the [Cu(*N*^{6},*N*7-**1**)$_2$]$^+$ cation (*m*/*z* 564.9), which upon MS−MS fragmentation gave [Cu(*N*6,*N*7-**1**)]$^+$ (*m*/*z* 313.9) (Figure 2). Where the Cu^{I}:**1** ratio was 1:1 the product has been formulated as [Cu(*N*6,*N*7-**1**)$_2$]CuI$_2$, whereas at a 1:2 ratio it was [Cu(*N*6,*N*7-**1**)$_2$]I.

The ^{1}H NMR spectrum of [Cu(*N*6,*N*7-**1**)$_2$]I in DMSO-d_6 at 298 K (*c* = 0.015 M) exhibits differences with **1** (Figure 3). The purine protons (C2-H and C8-H) both exhibit line broadening and become deshielded on coordination to Cu^{I} [C8-*H* = δ 8.33, s, $\Delta\delta$ = C8-H$_{complex}$ − C8-H$_{ligand(1)}$ = 0.11; $\Delta\nu_{1/2}$ = 25 Hz; C2-*H* = δ 8.25, s, $\Delta\delta$ = C2-H$_{complex}$ − C2-H$_{ligand(1)}$ = 0.12; $\Delta\nu_{1/2}$ = 40 Hz], which confirms that **1** is

SCHEME 4. Synthesis and Evaluation of Cu^{I}−2′-Deoxyadenosyl Complexes



binding in a bidentate coordination mode.[37] A similar chemical shift difference and line broadening is exhibited for the coordinating purine amino group [$NH_2 = \delta$ 7.43, s, $\Delta\delta = NH_{2complex} - NH_{2ligand(\mathbf{1})} = 0.14$; $\Delta\nu_{1/2} = 30$ Hz]. It is interesting to note that the remaining chemical shifts and line widths of the 2′-deoxyribose motif in the complex are nearly identical to those observed for **1**. ^{13}C NMR spectroscopic data revealed the presence of sugar carbons in this complex; however, the apparent exchange process that is occurring results in none of the carbons of the purine ring being observed (see the Supporting Information). At higher concentrations of [Cu(*N*6,*N*7-**1**)$_2$]I in DMSO-d_6 we noted further line broadening and iodine liberation ($c = 0.15$ M).

[Cu(*N*6,*N*7-**1**)$_2$]CuI_2 and [Cu(*N*6,*N*7-**1**)$_2$]I were independently subjected to the general direct arylation conditions (Scheme 4). A 41% yield for **2a** was recorded with the former complex, whereas for the latter complex **2a** only a trace amount of product was detected by TLC analysis. This key experiment confirms that a Cu^{I}:**1** ratio of at least 1:1 is necessary for effective direct arylation.

We have also evaluated three synthetic protocols which utilize a $Pd(OAc)_2$ precatalyst in the presence of pivalic acid (PivOH), specifically *similar conditions* to those recently described as follows: You and co-workers, a method for

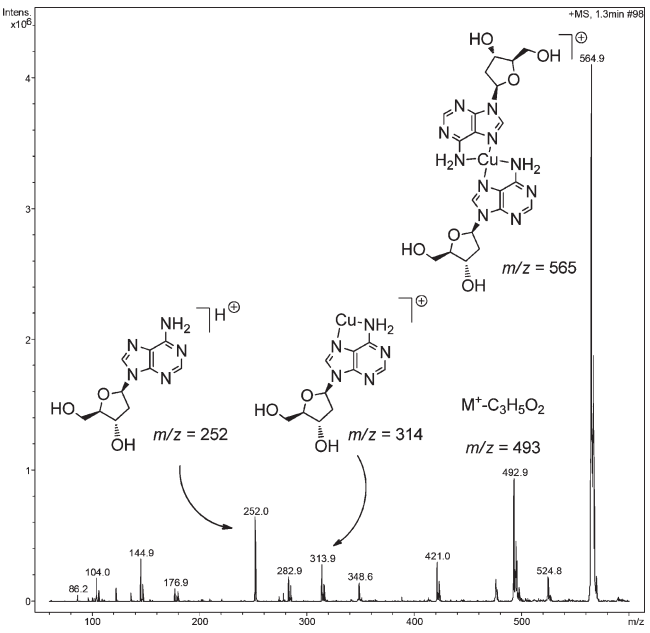


FIGURE 2. ESI-MS spectrum of [Cu(*N*6,N^7-**1**)$_2$]I (MS/MS on m/z = 564.9 gives m/z 313.9 as the major fragment ion).

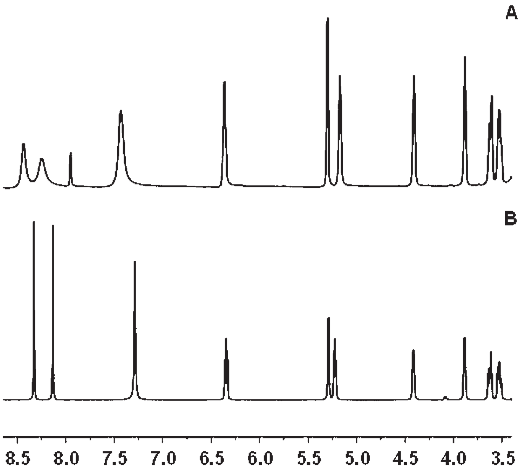


FIGURE 3. ^1H NMR spectra: **A**, [Cu(*N*6,*N*7-**1**)$_2$]I (c = 0.015 M); **B**, compound **1**. Both samples were dissolved in DMSO-d_6 and run at 500 MHz (note: the singlet species at ca. δ 7.85 ppm is trace DMF).

direct arylation of caffeine [**1** (1 equiv), PhI (2 equiv), $Pd(OAc)_2$ (5 mol %), PivOH (10 mol %), Cs_2CO_3 (2.5 equiv), DMF, 80 °C, 15 h] "protocol A"; Larrosa and co-workers[39], a method for room-temperature direct arylation of indoles [**1** (1 equiv), PhI (2 equiv), $Pd(OAc)_2$ (5 mol %), PivOH (1.5 equiv), Ag_2O (0.75 equiv), DMF, 80 °C, 15 h] "protocol B"; and Fagnou and co-workers, a general method for the direct arylation of heteroaromatic compounds [**1** (1 equiv), PhI (1 equiv), $Pd(OAc)_2$ (1 mol %), PCy_3 (2 mol %), PivOH (30 mol %), K_2CO_3 (1.5 equiv), DMF, 80 °C, 15 h] "protocol C".

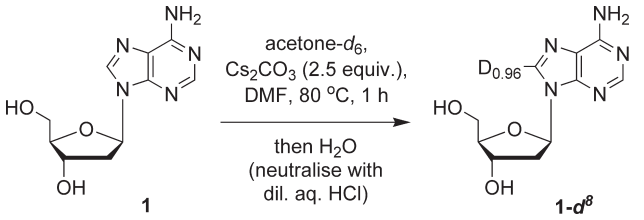
(37) In DMSO-d_6, adenosine acts as a monodentate ligand (*N*7-coordinated) in Pt^{II} complexes. Importantly, only a chemical shift difference is observed at C8-H ($\Delta\delta = 0.21$) on coordination to Pt^{II} (the C2-H chemical shift was unaffected). Similar (small) chemical shift differences are observed for Pd^{II}−adenosine complexes; see: (a) Dehand, J.; Jordanov, J. *J. Chem. Soc., Chem. Commun.* **1976**, 598. (b) Quirtk, M.; Salas, J. M.; Sánchez, M. P.; Beauchamp, A. L.; Solans, X. *Inorg. Chim. Acta* **1993**, *204*, 213.

(38) Zhao, D.; Wang, W.; Lian, S.; Yang, F.; Lan, J.; You, J. *Chem.—Eur. J.* **2009**, *15*, 1337.

(39) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926. The reported reactions in this paper were generally run at lower temperature than our experiment.

(40) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826. Note: this paper generally employed a reaction temperature of 100 °C, $PCy_3 \cdot HBF_4$ and DMA as the solvent. In our experiment, PCy_3 (stored in a drybox, < 1 ppm O_2) and DMF were employed.

SCHEME 5. Deuteration of the C8-Position in 1



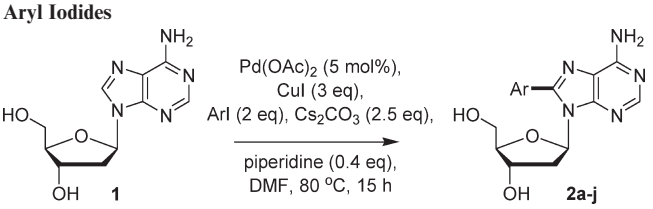
For comparison purposes, and because of the risk of deglycosylation, a temperature of 80 °C was used in this study. We anticipated that protocol A would be most suited to the adenine ring system. The high activity of protocol B encouraged us to test it on our very different heteroaromatic ring system (and at higher temperature). Finally, we anticipated that protocol C would be ineffective because similar substrates, e.g., imidazoles and related ring systems do not effectively couple at the C2-H position (C8-H in purines) under these conditions.[41] In brief, for each set of conditions, **1** was not arylated (note: predominantly recovered starting materials after 15 h); these surprising results are placed into context vide infra.

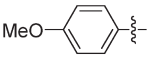
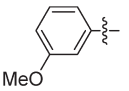
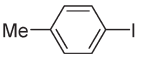
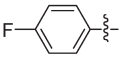
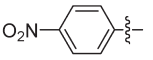
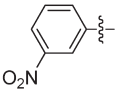
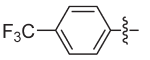
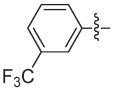
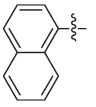
In keeping with the previously reported[28] base deprotonation of adenosine **3**, compound **1** is deprotonated in the absence of metal under "arylation conditions". Acetone-d_6 provides a suitable source of deuterium in the presence of Cs_2CO_3 in DMF at 80 °C for 1 h (Scheme 5). A nearly complete exchange occurred at C8, and there was no evidence for deuterium incorporation at C2. Running this reaction in the presence of Cs_2CO_3 (2.5 equiv) and piperidine (0.4 equiv) resulted in the same outcome (96% deuteration at C8). Under identical conditions, 2′-deoxyguanosine was not deuterated at the C8 position.

Substrate Scope. Having established the optimized reaction conditions for the direct arylation of **1**, further reactions of other aryl iodides have been evaluated (Table 3). In addition to direct arylation working well for iodobenzene, bromobenzene was also found to be compatible with the reaction conditions (entry 1). The direct arylation of **1** using aryl iodides which possessed *p*-OMe and *m*-OMe substituents proceeded well (entries 2 and 3) and compared favorably against iodobenzene (entry 1). The *p*-Me- and *p*-F-substituted aryl iodides gave good yields of the arylated products **2d** and **2e**, respectively (entries 4 and 5). *p*-Nitroiodobenzene reacted with **1** to give compound **2f** in modest yield (46%), which was accompanied by a trace quantity of the *N*6-arylation product (**2f′**). It is perhaps then surprising that the *m*-nitroiodobenzene arylated compound **1** effectively (entry 7).

Both *p*-trifluoromethyliodobenzene and *m*-trifluoromethyliodobenzene provided arylated products **2h** and **2i** in 95 and 99% yields, respectively (entries 8 and 9). 2-Iodonapthalene essentially mirrored the reactivity of iodobenzene, affording the arylated product **2j** in 58% yield (entry 10).

TABLE 3. Substrate Scope in the Direct Arylation of 1 Using Various Aryl Iodides



Entry	Ar =		Yield (%) [a]
1		**2a**	65 (66) [b]
2		**2b**	75
3		**2c**	73
4		**2d**	85 [d]
5		**2e**	71
6		**2f**	46 [c]
7		**2g**	87
8		**2h**	95 [d]
9		**2i**	99
10		**2j**	58

[a]Yield after chromatography on silica gel, reactions performed on a 1.88 mmol scale (with respect to **1**) unless otherwise stated. [b]Using PhBr. [c]*N*-Arylated product (**2f′**) formed (ca. 1%). [d]Performed on a 1.71 mmol scale (with respect to **1**).

Wishing to expand the scope of products formed under the direct arylation conditions, two arbitrarily selected brominated heteroaromatics were evaluated as coupling partners (Scheme 6). 6-Methoxy-2-bromopyridine was found to couple with **1** to give **2k** in 53% yield. 3-Bromothiophene coupled with **1** to give **2l** in a modest 32% yield.

Conformational and Structural Analysis of the Arylation Products. The NMR spectroscopic data of the 8-aryl-2′-deoxyadenosines provided informative details concerning (i) the orientation (conformation) of the purine ring with respect to the glycosyl bond in the 2′-deoxyribose moiety and (ii) the ring conformation of the 2′-deoxyribose moiety (Figure 4).

(41) One can get around the 1*H*-imidazole problem by using *N*-oxide derivatives; see: (a) Campeau, L. -C.; Stuart, D. R.; Leclerc, J. -P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H. -Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291. Note: it would be difficult to selectively prepare a similar *N*-oxide of compound **1**.

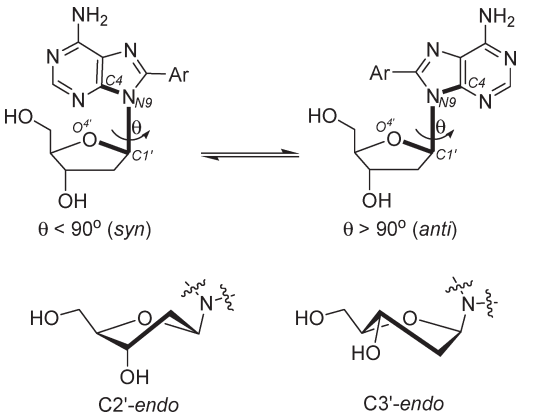
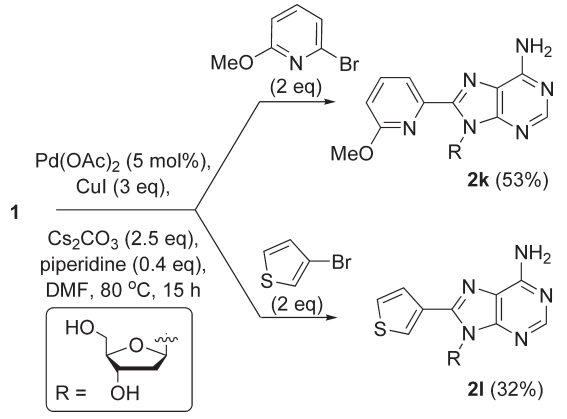


FIGURE 4. Conformational preferences in 8-aryl-2′-deoxyadenosines.

SCHEME 6. Evaluation of Brominated Heteroaromatic Coupling Partners



According to established rules,[42] the 8-aryl-2′-deoxyadenosines (**2a**−**j**) can be found to preferentially adopt the expected *syn*-orientation (by comparison of the chemical shifts of C1′, C2′, C3′, C4′, and H2′; see the Supporting Information for further details). It is well established that the 2′-deoxyribose moiety can adopt various ring conformations.[43] The two low energy conformers are referred to as C2′-*endo* (south type) and C3′-*endo* (north type), for which there is a small barrier to interconversion (ca. 2 kcal mol^{-1}).[44] These conformations exhibit unique spectroscopic properties, and while the different conformations cannot be resolved on the NMR time scale, the ^{1}H NMR spin−spin coupling constants can be used to calculate the relative populations of each conformer in solution at ambient temperature.[45] The relative population of the C2′-*endo* conformer was determined by the eq C2′-*endo* = 100[$J_{1'2'}$/($J_{1'2'}$ + $J_{3'4'}$)] (see the Supporting Information for further details). The C2′-*endo* conformation is adopted preferentially by the new 8-aryl-2′-deoxyadenosines, representing ∼80% of the molecular population in all cases, which is slightly higher than 2′-deoxyadenosine **1** (75% C2′-*endo* and 25% C3′-*endo*; for adenosine **3**, 67% C2′-*endo* and 33% C3′-*endo*). We presume that the addition of the 8-aryl group affects the 2′-deoxyribose conformation, possibly as a result of these compounds preferring a *syn*-orientation (as opposed to the *anti* orientation, which is observed for **1**).[46]

Atomic-level information on the conformational preferences of the 8-aryl-2′-deoxyadenosines has been gained by single-crystal X-ray diffraction studies. Compound **2a** was crystallized from a MeOH solution using the slow evaporation method. The X-ray data[47] revealed two different molecules in the asymmetric unit cell (Figure 5).

The *syn*-conformation in molecule 1 is stabilized by an intramolecular H-bond[48] [O(3A)−H(3A)···N(2) = 2.00(3) Å; 173(3)°], whereas molecule 2 does not possess such a H-bond despite still being in a *syn*-conformation. The torsion angle, e.g., O$^{4'}$−C1′−N9−C4 (Figure 4), is an effective measure for the orientation of the purine relative to the 2′-deoxyribose (∼ < 90° = *syn*; > 90° = *anti*). For molecule 1, markedly different torsion angles are observed [O(1A)−C(6)−N(3)−C(2) = 63.8(3)°, *syn*-C2′-*endo*; O(1B)−C(6)−N(3)−C(2) = 101.1(3)°, *syn*-C3′-*exo*]. The latter can be considered as moving toward an *anti*-orientation. In molecule 2, the torsion angle O(4)−C(22)−N(8)−C(18) is 85.83(19)°, *syn*-C3′-*endo*/C4′-*exo*.

For comparison, 8-phenyladenosine[28] **4** was crystallized from a MeOH/pyridine (1:1, v/v) solution using the slow evaporation method (see the Supporting Information). The X-ray data reveals that the molecule adopts a *syn*-conformation with respect to the purine ring and ribose motif [torsion angle O(1)−C(6)−N(3)−C(2) = 49.76(17)°, *syn*-C2′-*endo*], which is stabilized[49] by an intramolecular H-bond [O(4)−H(4)···N(2) = 1.92(3) Å; 174(2)°].

Compound **2j** was crystallized from MeOH using the slow evaporation method (Figure 6). The X-ray data[50] revealed a fascinating structure exhibiting strong intermolecular π−π stacking interactions between the two naphthyl groups (the centroid[51] distance was found to be ca. 3.865 Å).

(42) (a) Stolarski, R.; Dudycz, L.; Shugar, D. *Eur. J. Biochem.* **1980**, *108*, 111. (b) Uesugi, S.; Ikehara, M. *J. Am. Chem. Soc.* **1977**, *99*, 3250. (c) Gannett, P. M.; Sura, T. P. *Chem. Res. Toxicol.* **1993**, *6*, 690.

(43) Van Roey, P.; Salerno, J. M.; Chu, C. K.; Schinazi, R. F. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 3929.

(44) Brameld, K. A.; Goddard, W. A. III. *J. Am. Chem. Soc.* **1999**, *121*, 985.

(45) (a) Altona, C.; Sundaralingam, M. *J. Am. Chem. Soc.* **1973**, *95*, 2333. (b) Esho, N.; Desaulniers, J. P.; Davies, B.; Chui, H. M. P.; Rao, M. S.; Chow, C. S.; Szafert, S.; Dembinski, R. *Bioorg. Med. Chem.* **2005**, *13*, 1231.

(46) (a) Hocquet, A.; Leulliot, N.; Ghomi, M. *J. Phys. Chem. B* **2000**, *18*, 4560. (b) Stolarski, R.; Dudycz, L.; Shugar, D. *Eur. J. Biochem.* **1980**, *108*, 111. (c) Uesugi, S.; Ikehara, M. *J. Am. Chem. Soc.* **1977**, *10*, 3250. (d) Gannett, P. M.; Sura, T. P. *Chem. Res. Toxicol.* **1993**, *5*, 690.

(47) X-ray data for compound **2a** (CCDC 721575): $C_{32}H_{38}N_{10}O_{8.50}$; M_{w_a} = 698.69; T = 110(2) K; λ = 0.71073 Å; triclinic; $P1$ space group; a = 7.3242(7) Å, b = 10.7071(11) Å, c = 11.3268(12) Å; α = 96.261(2)°, α = 99.177(2)°, γ = 108.178(2)°; V = 821.10(14) Å^3; Z = 1, D = 1.413 Mg/m^3; crystal size = 0.45 × 0.26 × 0.24 mm^3; $R1$ = 0.0467, w$R2$ = 0.0961 (all data)

(48) For solid-state XRD studies illustrating intramolecular H-bonding and a *syn*-conformation in related purine nucleosides, see: (a) Lesyng, B.; Marck, C. H.; Saenger, W. *Z. Naturforsch.* **1984**, *39c*, 720. (b) Koyama, G.; Nakamura, H.; Umezawa, H.; Iitaka, Y. *Acta Crystallogr.* **1976**, *B32*, 813. (c) Koyama, G.; Nakamura, H.; Umezawa, H. *Acta Crystallogr.* **1976**, *B32*, 969. For related solution NMR spectroscopic studies, see: (d) Koole, L. H.; de Boer, H.; de haan, J. W.; Haasnoot, C. A. G.; van dael, P.; Buck, H. M. *J. Chem. Soc., Chem. Commun.* **1986**, 362. (e) Hamm, M. L.; Rajguru, S.; Downs, A. M.; Cholera, R. *J. Am. Chem. Soc.* **2005**, *127*, 12220. (f) Ghosh, A. K.; Lagisetty, P.; Zajc, B. *J. Org. Chem.* **2007**, *72*, 8222.

(49) It is established that the rotation about the C(1′)−N(9) and C(4′)−C(5′) bonds is influenced by the intramolecular H-bond from HO−C(5′) to N(3) in purines; see: (a) Fuji, S.; Fujiwara, T.; Tomita, K. *Nucleic Acids Res.* **1976**, *3*, 1985. (b) Gunji, H.; Vasella, A. *Helv. Chim. Acta* **2000**, *83*, 1.

(50) X-ray data for compound **2j** (CCDC 721576): $C_{41}H_{44}N_{10}O_8$; M_{w_a} = 804.86; T = 120(2) K; λ = 1.5418 Å; triclinic; $P1$ space group; a = 7.8036(3) Å, b = 10.1562(3) Å, c = 12.3581(3) Å; α = 93.768(2)°, β = 94.058(3)°, γ = 101.822(3)°; V = 953.03(5) Å^3; Z = 1; D = 1.402 Mg/m^3; crystal size = 0.75 × 0.17 × 0.13 mm^3; $R1$ = 0.0335, $wR2$ = 0.0929 (all data).

(51) The following centroids were found for **2j** (molecule 1: centroid = C11, C12, C17, C18, C19, and C20; molecule 2: centroid = C31, C32, C37, C38, C39, C40) using Mercury 2.2 (Build RC5), copyright CCDC 2001−2008, http://www.ccdc.cam.ac.uk/mercury/.

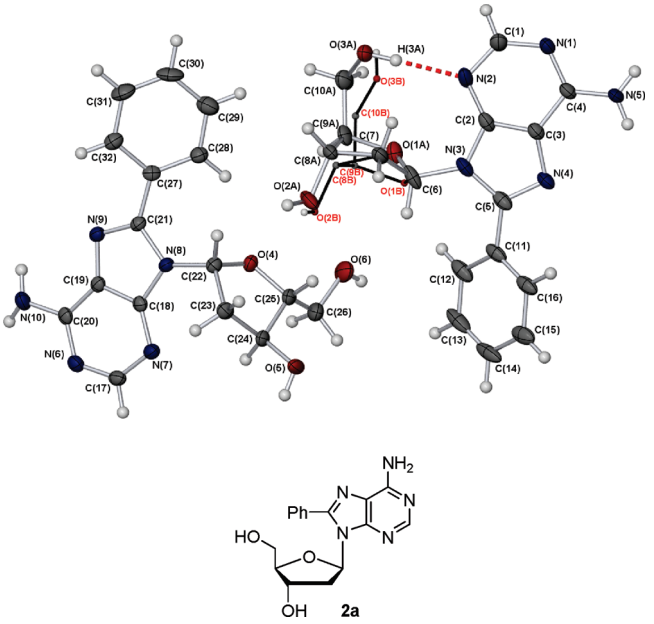


FIGURE 5. X-ray structure of compound **2a** (note: arbitrary numbering used in 3D structure). Thermal ellipsoids are shown at 50% probability. An alterative conformer for the structure on the right is shown in black bonds with the atoms shown as spheres (C-*H* atoms and solvent molecules removed for clarity). The *syn*-conformer in molecule 1 (right) is stabilized by an intramolecular H-bond, while molecule 2 (left) adopts this conformation in the absence of this interaction.

The *syn*-orientation is adopted in both molecules 1 and 2 [molecule 1: torsion angle O(1)−C(6)−N(3)−C(2) = 67.5(2)°, *syn*-C2′-*endo*; molecule 2: torsion angle O(1)−C(6)−N(3)−C(2) = 53.7(2)°, *syn*-C2′-*endo*]. Intramolecular H-bonding is apparent [molecule 1: O(3)−H(3)···N(2) = 1.94(4) Å; 165(3)°; molecule 2: O(6)−H(6A)···N(7) = 1.84(4) Å; 168(3)°], while intermolecular H-bonding interactions with methanol and water molecules for molecule 1 [O(8)−H(8A)···N(4) = 1.96(3) Å; 169(3)°] and 2 [O(5)−H(5)···O(7) = 1.86(4) Å; 168(3)°], respectively, are involved in the crystal packing. X-ray structure determinations of compounds **2b** and **2f′** have also been made (see the Supporting Information).

The ^{1}H and ^{13}C NMR spectroscopic data for **2k** indicate that the molecule shows the highest preference for the *syn*-C2′-*endo* conformation (88%). In addition, there is a marked difference in the chemical shift of C1′-*H* in **2k** (δ 7.34) relative to the other compounds in this series (**2a**−**j**: C1′-*H* δ ∼6.11−6.17; avg = δ 6.15). This difference is attributed to an intramolecular H-bond between the 8-pyridyl nitrogen and H1′. The proposal is supported by the increased C5′O-*H* chemical shift (δ 6.11) which also appears downfield relative to the other compounds in this series (**2a**−**j**: C5′O-*H* δ ∼5.39−5.61; avg = δ 5.52). These intramolecular H-bonds serve to stabilize the *syn*-C2′-*endo* conformation (Figure 7).

Reactivity Comparisons with Other Purines. We compared the reactivity of various purines relative to 2′-deoxyadenosine **1** and adenosine **3** in order to probe the possible "templating" role of the exocyclic amine in adenosine. We envisaged that 2′-deoxyguanosine **5** and guanosine **7** could be problematic substrates because Cu^{I}-coordination can occur at sites distal to the C8 position. Using our optimized conditions, poor yields of the direct arylation products **6** and **8**, respectively, were obtained (entry 1, Table 4). We also note that C8-H deuteration experiments performed on compounds **5** and **7** (using conditions in Scheme 5) did not show any appreciable incorporation of deuterium at C8.

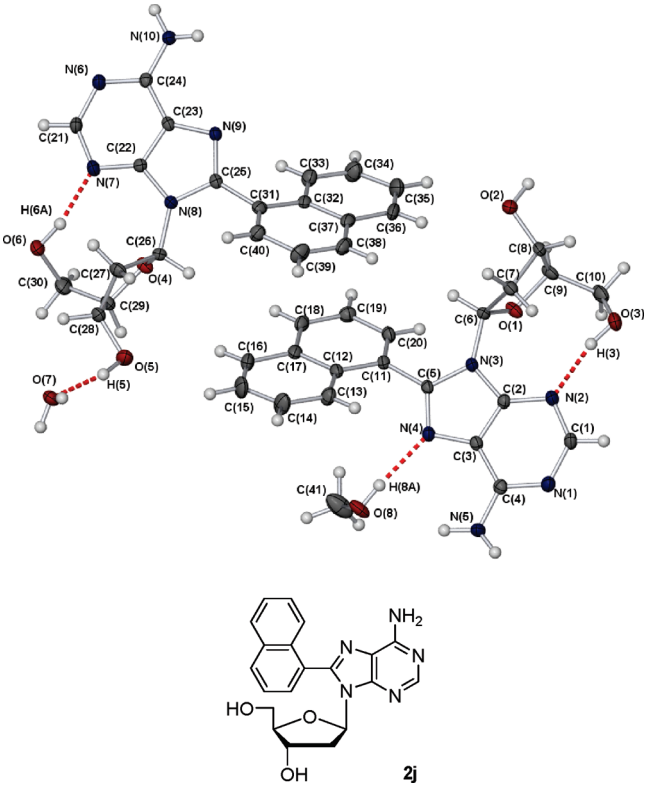
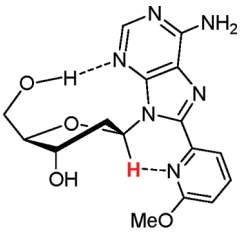


FIGURE 6. X-ray structure of compound **2j** (note: arbitrary numbering used in 3D structure). Thermal ellipsoids are shown at 50% probability.



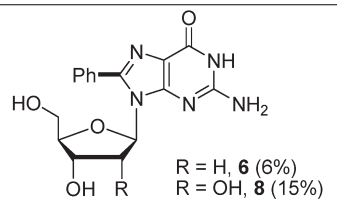
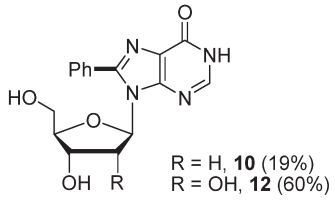
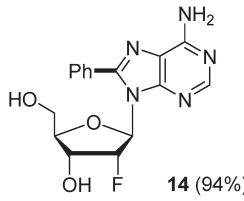
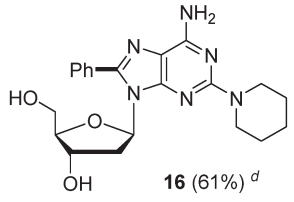
syn-C2′-*endo*

FIGURE 7. Interaction of the 8-pyridyl group with H1′ in **2k**.

The ionizable proton at N2 in guanine-type substrates is an issue in these reactions. Therefore, we chose to also evaluate 2′-deoxyinosine **9** and inosine **11**. While **9** gave the direct arylation product **10** in low yield (19%), the latter gave product **12** in 60% yield (entry 2). An adenosine type substrate, i.e., 2′-fluoro-2′-deoxyadenosine **13**, was arylated most effectively, affording **14** in 94% yield (entry 3). As noted in previous reports[52] the 2′-fluoro-substituent induces a conformational flip to *syn*-C3′-*endo* (ca. 61%). Arylation of 2-fluoro-2′-deoxyadenosine **15** also occurred, although nucleophilic displacement of fluorine by piperidine is a

(52) Uesugi, S.; Miki, H.; Ikehara, M.; Iwahashi, H.; Kyogoku, Y. *Tetrahedron Lett.* **1979**, *20*, 4073.

TABLE 4. Reactivity Comparison for Related Purine Nucleosides: Direct Arylation with Iodobenzene[a,b]

Entry	Product[c]
1	 R = H, **6** (6%) R = OH, **8** (15%)
2	 R = H, **10** (19%) R = OH, **12** (60%)
3	 **14** (94%)
4	 **16** (61%)[d]

[a]Reagents and conditions. [b]Reactions of 2'-deoxypurines run at 80 °C using the optimized conditions (otherwise at 120 °C, as previously reported). [c]Yield following chromatography on silica gel. [d]Yield is based on piperidine.

competing reaction giving **16** in 61% yield (entry 4; yield based on piperidine, the limiting reagent).

The poor reactivity of 2′-deoxyguanosine **5** in these reactions led us to test whether the guanine moiety was inhibiting the catalytic direct arylation process, akin to the insightful observations made by Western and Shaughnessy in aqueous Pd-catalyzed Suzuki cross-coupling of 8-bromo-2′-deoxyguanosine (and other unprotected halonucleosides) with arylboronic acids.[53] The yield of **2a** was diminished slightly in the presence of a substoichiometric quantity of **5** (0.1 equiv), while a stoichiometric quantity of **5** hindered the reaction, diminishing the yield of **2a** (no arylation products of **5** were detected; **2a** was isolated following chromatography on silica gel) (Scheme 7).

Several important observations have been made in this study. "General" direct arylation reaction conditions proved ineffective for the reaction of **1** with iodobenzene to give **2a**. Related 1-aryl-1*H*-imidazoles or 1-benzyl-1*H*-imidazoles

SCHEME 7. Effects of 2′-Deoxyguanosine 5 on the Arylation of 1

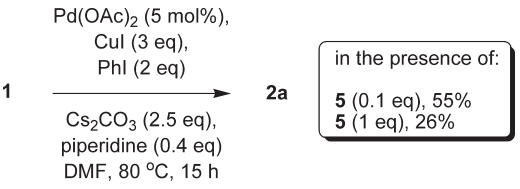


exhibit similar, if not identical reactivity, and would prefer to undergo functionalization at C5 rather than C2.[54] We are able to comment on the mechanistic details of the Pd−Cu catalyst system by comparing our findings herein with previous work showing that imidazole derivatives are generally resistant to C2-H functionalization (in the absence of Cu).[41] Despite the recent mechanistic proposal by You and coworkers[38] for the Pd-catalyzed C8-H functionalization of caffeine, we propose that a concerted metalation−deprotonation (CMD) process[55] is unlikely for the Pd−Cu catalyst system described here and elsewhere[24] for related "imidazole-like" substrates. We have demonstrated that a combination of Cs_2CO_3 and piperidine (secondary amine) is necessary for obtaining good yields of the 8-arylated 2′-deoxyadenosines at 80 °C. Crucially, substoichiometric quantities of piperidine (0.4 equiv) were required for optimal yields. The mechanism whereby piperidine (the secondary amine) acts as a promoter for the reaction primarily derives from the generation of a $Pd(OAc)_2[(CH)_5NH]_2$ in situ. The independent preparation of this complex and evaluation in the direct arylation of **1** with PhI gave **2a** in yields comparable to those reactions mediated by $Pd(OAc)_2$/piperidine. We have shown that $Cu[N(CH_2)_5]$ resulted in lower yields as compared to otherwise identical direct arylation reactions run in the presence of CuI. Other more reactive and "naked" Cu^I sources, e.g., Cu^I−thiophene carboxylate or CuOTf, resulted in negligible reaction. In addition, tetra-*n*-butylammonium iodide was a poor substitute for CuI. To probe the Cu^I role further, the independent preparation of a Cu^I complex containing two 2′-deoxyadenosine ligands (**1**) was undertaken. Altering the Cu^I:*N*6,*N*7-(**1**) stoichiometry to either 1:1 or 1:2 gave a cationic Cu^I species, e.g., $[Cu^I(N6,N7\text{-}\mathbf{1})_2]^+$, which was unambiguously characterized by ESI-MS/MS and ^{1}H NMR spectroscopy. The direct arylation only proceeded satisfactorily in the presence of an additional equivalent of CuI, e.g., in $[Cu^I(N6,N7\text{-}\mathbf{1})_2]CuI_2$, to give **2a** in 41% yield. This outcome confirms that Cu^I has a high binding affinity for **1** under the direct arylation conditions. Crucially, this "templating" indicates that Cu^I assists the C−H functionalization process, and excess CuI is required to disrupt an otherwise stable complex, e.g., **I** → **II** (Scheme 8). It is interesting to note that a similar Pd−Cu catalyst system was found to be broadly ineffective for the direct arylation of 9-benzyl-6-phenyl-7-deazapurine at 160 °C,[56] suggesting

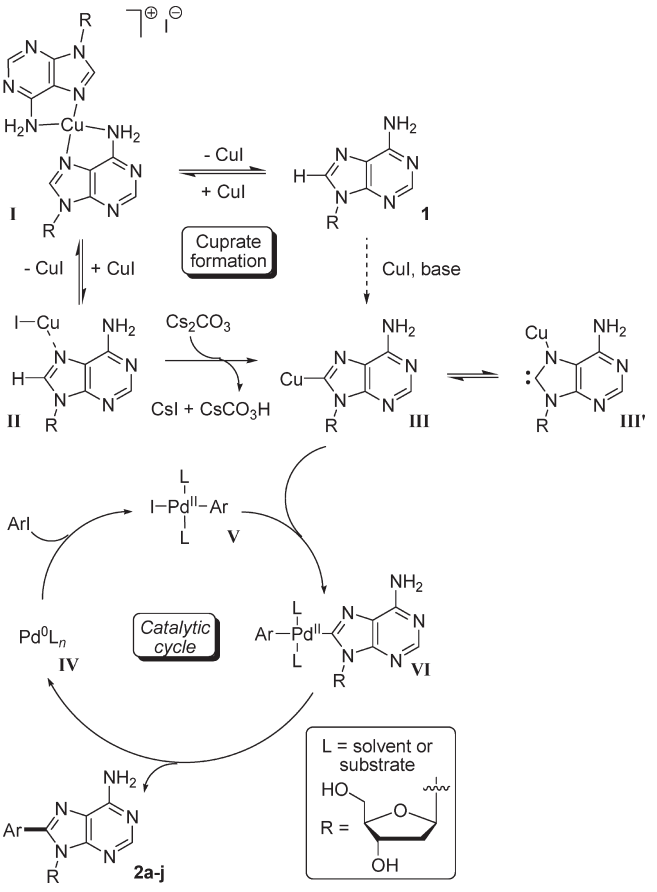
(53) (a) Western, E. C.; Shaughnessy, K. H. *J. Org. Chem.* **2005**, *70*, 6378. For further coordination chemistry studies on guanosine and related purines, see: (b) Dehand, J.; Jordanov, J. *J. Chem. Soc., Dalton Trans.* **1977**, 1588.

(54) The reaction of either 4-bromoanisole or 2-bromonaphthalene with *N*-methylimidazole gave exclusively the C5-arylated products in 34% and 40% yields, respectively (in both cases, following lengthy reaction times, e.g., 25 and 27 h, respectively); see ref 40.

(55) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 16754. (b) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (c) Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880. (d) Pascual, S.; De Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *Tetrahedron* **2008**, *64*, 6021. (e) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299.

(56) Klečka, M.; Pohl, R.; Klepetářvá, B.; Hocek, M. *Org. Biomol. Chem.* **2009**, *7*, 866.

SCHEME 8. Proposed Mechanism for the Pd−Cu-Mediated Direct Arylation of 1



that the "imidazole-like" purine (*N*7) is necessary to aid coordination to either Pd and/or Cu. This coordination hypothesis is supported by our studies and by the comprehensive work of Bellina and Rossi on 1*H*-imidazoles and related compounds.[24] The base-assisted deprotonation step leads to the formation of 8-cuprio-2′-deoxyadenosine **III**,[57] which can then enter a standard Pd(0) catalytic cycle. The process can be related to alkynylcuprate formation in the Sonogashira reaction,[58] and although this proposal suggests that Cu^{I} ought to be catalytic, the high binding affinity of **1**, and presumably product **2a**, for Cu^{I} leads to the requirement for excess CuI in the direct arylation reaction. The $CsCO_3H$ formed during step **II** → **III** can in principle be metered out by piperidine (assuming that the irreversible generation of CsOH and CO_2 does not occur) to give a carbamic acid/carbamate salt derivative, representing a possible secondary role for piperidine. This argument is supported by the established solution behavior[59] of similar DMF soluble carbamic acid salt derivatives. Finally, it is plausible that **III** could be in equilibrium with a nucleophilic C8-carbene **III′** (which can also be described as an imidazolium ylide).[60] We anticipate **III′** would be a strong σ-donating ligand for Pd^{II}. The established reductive elimination[61] of certain organo groups from "R-Pd^{II}−NHC" complexes (R = Me, aryl or acyl; NHC = *N*-heterocyclic carbene) to give Pd^{0} and R-NHC products highlights this as alternative mechanistic path for the reaction.

The optimized direct arylation conditions for **1** are essentially incompatible with 2′-deoxyguanosine **5** (or guanosine **7**). Shaughnessy and Western[53] were able to show that the ionization of the imide group in guanine is a problem for Suzuki cross-couplings, leading to Pd catalyst inhibition. The pH of our direct arylation is comparable to these Suzuki cross-couplings (pH ∼10), and we anticipate similar catalyst inhibition. Our competition experiments confirm that **5** slows down the direct arylation of **1**; separate reactions of **5** or **7** with iodobenzene provide only low yields of the 8-phenylated products (**6** and **8**, respectively).

At a reaction temperature of 80 °C, the direct arylation conditions described herein have been completely optimized for the functionalization of adenine-type ring systems. Small changes in the structure of the purine ring affect the direct arylation yields significantly (see Table 4), and this has to be balanced against the inevitable deglycosylation problem for reactions run at higher temperatures, e.g., > 100 °C, which is an issue for 2′-deoxyribose purine derivatives.

On a general note, the yields of 8-aryl-2′-deoxyriboses obtained from the Pd/Cu-mediated direct arylation of **1** described herein are similar to those reported[53] for Suzuki cross-coupling of 8-bromo-2′-deoxyribose with aryl or heteroaryl boronic acids. However, one needs to consider that C8-bromination of **1** by either (1) NBS, DMF, rt[62] or (2) Br_2, NaOAc, H_2O, rt[63] gives 8-bromo-2′-deoxyadenosine in 40% yield (in both cases). Suzuki cross-couplings are efficient in their own right, but they do require bromination (prefunctionalization) of **1**.

In summary, we have comprehensively studied the reactivity of 2′-deoxyadenosine **1** in Pd−Cu-mediated direct arylations. Following reaction optimization, we have found that secondary amines promote direct arylations, and are necessary additives at 80 °C. The binding affinity of Cu^{I} for 2′-deoxyadenosine dictates that stoichiometric amounts of CuI are necessary to deliver an activated CuI−nucleoside complex (e.g., **II** in Scheme 8). Reactivity comparisons with structurally related purines showed that the guanine moiety is disfavored in the C8 direct arylation reaction, possibly due to Cu^{I} "templating" at nonadjacent sites and a different rate of base-assisted

(57) Similar "cuprated" purines have been recently utilized in oxidative amination processes; see: Boudet, N.; Dubbaka, S. R.; Knochel, P. *Org. Lett.* **2008**, *10*, 1715.

(58) Cai, C.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 2053. Note: we do not rule out the possible involvement of bimetallic "Pd−Cu" species in the reaction mechanism, as suggested in this paper concerning Sonogashira cross-coupling of alkynes or haloalkyne derivatives with aryl halides.

(59) (a) Salvatore, R. N.; Chu, F.; Nagle, A. S.; Kapxhiu, E. A.; Cross, R. M.; Jung, K. W. *Tetrahedron* **2002**, *58*, 3329. (b) Masuda, K.; Ito, Y.; Horiguchi, M.; Fujita, H. *Tetrahedron* **2005**, *61*, 213.

(60) Professor Fabio Bellina (University of Pisa, Italy) commented on this possibility for the related Pd/Cu-mediated direct arylation of imidazoles at the Catalytic C−H Activation of Organic Molecules Conference held in Lyon, France (5−8 April 2009). See also: Chodowska-Palicka, J.; Milsson, M. *Synthesis* **1974**, 128.

(61) Reductive elimination from Me-Pd^{II}−NHC: (a) McGuinness, D. S.; Saendig, N.; Yates, B. F.; Cavell, K. J. *J. Am. Chem. Soc.* **2001**, *123*, 4029 and references cited therein. Ar-Pd^{II}−NHC: (b) McGuinness, D. S.; Cavell, K. J.; Skelton, B. W.; White, A. H. *Organometallics* **1999**, *18*, 1596. (c) Caddick, S.; Cloke, F. G. N.; Hitchcock, P. B.; Leonard, J.; de, K.; Lewis, A. K.; McKerrecher, D.; Titcomb, L. R. *Organometallics* **2002**, *21*, 4318. Acyl-Pd^{II}−NHC: (d) McGuinness, D. S.; Cavell, K. J. *Organometallics* **2000**, *19*, 4918.

(62) Nandanan, E.; Camaioni, E.; Jang, S. -Y.; Kim, Y. -C.; Cristalli, G.; Herdewijn, P.; Secrist, J. A. III; Tiwari, K. N.; Mohanram, A.; Harden, T. K.; Boyer, J. L.; Jacobson, K. A. *J. Med. Chem.* **1999**, *42*, 1625.

(63) Chen, Y.; Shen, L.; Zhang, F.; Lau, S. S.; van Breemen, R. B.; Nikolic, D.; Bolton, J. L. *Chem. Res. Toxicol.* **1998**, *11*, 1105.

deprotonation at the C8-position. Our results provide greater insight into the direct arylation reactivity of not only purines, e.g., the adenine moiety, but also 1*H*-imidazoles in general. We are currently identifying milder reaction conditions for metal-mediated direct functionalization of purines.

Experimental Section

General details can be found in the Supporting Information. All X-ray crystal structures were processed in X-seed (author: Prof. L. J. Barbour, version 2.0; with March 2008 update),[64] then traced using Pov-Ray for Windows (author: C. Cason, version 3.6) and labeled using POV-label (part of the X-seed suite of software).

General Procedure for the Direct Arylation of 1. To a vacuum-dried Schlenk tube were added 2′-deoxyadenosine (473 mg, 1.88 mmol, 1.0 equiv), Cs_2CO_3 (1.53 g, 4.68 mmol, 2.5 equiv), CuI (1.07 g, 5.61 mmol, 3.0 equiv), $Pd(OAc)_2$ (21 mg, 94 μmol, 5 mol %), and the aryl iodide (3.74 mmol, 2.0 equiv). The reaction vessel was evacuated under high vacuum at 25 °C with stirring and then flushed with N_2 (three cycles). Dry distilled and degassed DMF (10 mL) or "extra dry" DMF (Acros) was then added along with degassed piperidine (stored over 3 Å molecular sieves, 74 μL, 0.75 mmol, 0.4 equiv). The vessel was sealed and heated in an oil bath at 80 °C and stirred continuously for 15 h. The mixture was then allowed to cool to 25 °C and 1 M HCl solution (10 mL) added. The pH was then adjusted to 6.5 with 1 M NaOH and the aqueous solution extracted with a ^{i}PrOH/EtOAc (1:9, v/v, 5 × 50 mL) mixture by decanting from the reaction mixture. The organic extracts were combined, dried ($MgSO_4$), filtered, and reduced in vacuo to yield a thick gum, which was dried under high vacuum (ca. 0.8 mmHg). The crude mixture was redissolved/suspended in $MeOH/CH_2Cl_2$ (1:1, 20 mL) and adsorbed onto silica gel (approximately 0.5 g) with reduction in vacuo. A short silica gel column (approximately 10 g) was eluted using $MeOH/CH_2Cl_2$ (2:98 v/v, moving in stepwise increments to 10:90 by gradient elution). The fractions containing the product were combined, the solvents were removed in vacuo, and CH_2Cl_2 (10 mL) was added and then removed. The isolated product was then dried under high vacuum and the purity ascertained by HPLC.

(64) Barbour, L. J. *J. Supramol. Chem.* **2001**, *1*, 189−191. Also see http://x-seed.net/.

Acknowledgment. We thank Professor A. Vasella (ETH, Zurich) for suggesting the possible role of carbamic acid/salts under our direct arylation conditions in the presence of piperidine. We also thank Drs. I. Larrosa (QMUL, London), J. Slattery (York), and J. Lynam (York) for useful discussions. EPSRC and Replizyme Ltd. (T.E.S. studentship), BBSRC (grant award to C.G.B. and S.D.O. studentship), and the Royal Society (University Research Fellowship to I.J.S.F.) are acknowledged for funding this work. AstraZeneca (Dr. David Hollinshead) is thanked for an unrestricted research award (to I.J.S.F.). The EPSRC Service at Durham University (UK) is acknowledged for running ^{13}C solid-state NMR experiments (Dr. D. C. Apperley). Dr. R. G. Sturmey and Professor H. J. Leese are acknowledged for the use of an Agilent 1100 HPLC system.

Supporting Information Available: Experimental details (including characterization data for all compounds) and X-ray data (for **1**, **2a**,**b**,**f′**,**j**, **4**, and *trans*-$Pd(OAc)_2[(CH_2)_5NH]_2$, including CIF files). This material is available free of charge via the Internet at http://pubs.acs.org.