JOC Article

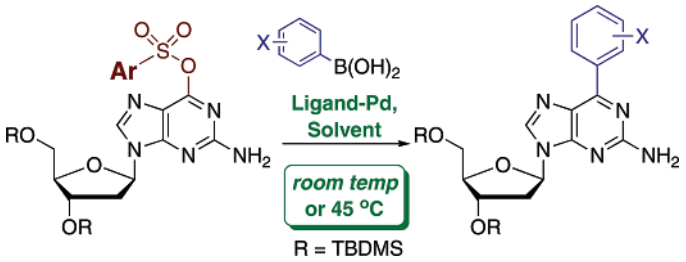
Mild and Room Temperature C−C Bond Forming Reactions of Nucleoside C-6 Arylsulfonates

Mahesh K. Lakshman,* Padmaja Gunda, and Padmanava Pradhan†

Department of Chemistry, The City College and The City University of New York, 138th Street at Convent Avenue, New York, New York 10031-9198

lakshman@sci.ccny.cuny.edu

Received July 3, 2005



Palladium catalyzed cross coupling of nucleoside arylsulfonates and arylboronic acids has been accomplished under mild conditions and at room temperature. Among three structurally similar ligands that differ in their steric and electronic properties, one yielded an effective catalyst in conjunction with $Pd(OAc)_2$. Of the nucleoside arylsulfonates evaluated, the O^6-(2,4,6-trimethylphenyl)sulfonate proved optimal, but other alkyl and alkoxy derivatives were also reasonably reactive. On the other hand, a 2-nitrophenyl and a 2-thienyl derivative were ineffective substrates. PhMe and THP were suitable as solvents, yielding good results in several cases, although reactions of some arylboronic acids were faster in PhMe. In contrast, reactions of arylboronic acids bearing strongly electron-withdrawing groups proceeded more successfully in THP. Interplay between several factors that include substituents on the nucleoside arylsulfonate, ligand substituents, and solvent is responsible for successful cross coupling. Using ^{31}P NMR, an initial investigation has been conducted to study the interaction of $Pd(OAc)_2$ with the ligand. At a 1:1 stoichiometry of ligand and $Pd(OAc)_2$, a predominant species, likely a cyclopalladation product, was obtained. At a 2:1 ratio of ligand and $Pd(OAc)_2$, a different species bearing chemically distinct phosphine ligands was observed. Both complexes display catalytic activity, although the 2:1 species may be superior.

Introduction

The use of aryl triflates for C−C bond formation with boronic acids has become a standard in organic synthesis.[1] On the other hand, aryl arenesulfonates that are generally cheaper to prepare have not been perceived as general substrates for Pd- or Ni-catalyzed Suzuki−Miyaura cross-coupling until recently.[2,3] Among nucleoside derivatives, we[4] and others[5,6] have shown that halopurine nucleosides can be efficiently converted to C-6 aryl nucleosides, wherein the hydrogen-bonding amino group is replaced by hydrophobic aryl moieties and some C-6 aryl nucleosides so derived have shown cytostatic activity against cancer cell lines.[6] Among nonhalo nucleoside substrates, we have demonstrated that the easily prepared O^6-(2,4,6-trimethylphenyl)sulfonyl derivative of 2′-deoxyguanosine could be converted to an assortment of C-6 aryl nucleoside analogues via Pd-catalyzed C−C bond formation at elevated temperatures.[7] In that study,

* Corresponding author. Tel.: (212) 650-7835; fax: (212) 650-6107.
† P. P. NMR Facility Manager, CCNY.

(1) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263−303. (c) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (d) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633−9695.

(2) Pd-catalyzed: Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818−11819.

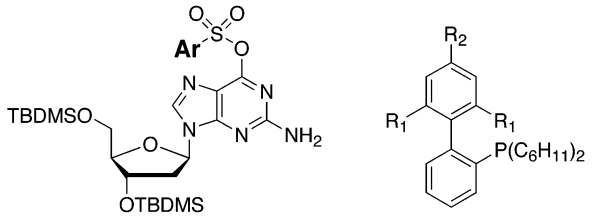
(3) Ni-catalyzed: (a) Zim, D.; Lando, V. R.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2001**, *3*, 3049−3051. (b) Tang. Z.-Y.; Hu, Q.-S. *J. Am. Chem. Soc.* **2004**, *126*, 3058−3059. (c) Percec, V.; Golding, G. M.; Smidrkal, J.; Weichold, O. *J. Org. Chem.* **2004**, *69*, 3447−3452.

(4) Lakshman, M. K.; Hilmer, J. H.; Martin, J. Q.; Keeler, J. C.; Dinh, Y. Q. V.; Ngassa, F. N.; Russon, L. M. *J. Am. Chem. Soc.* **2001**, *123*, 7779−7787.

(5) (a) Havelková, M.; Hocek, M.; Česnek, M.; Dvořák, D. *Synlett* **1999**, 1145−1147. (b) Hocek, M.; Holý, A.; Votruba, I.; Dvořáková, H. *Collect. Czech. Chem. Commun.* **2000**, *65*, 1683−1697. (c) Hocek, M.; Holý, A.; Votruba, I.; Dvořáková, H. *Collect. Czech. Chem. Commun.* **2001**, *66*, 483−499.

(6) (a) Hocek, M.; Holý, A.; Votruba, I.; Dvořáková, H. *J. Med. Chem.* **2000**, *43*, 1817−1825. (b) Hocek, M.; Nauš, P.; Pohl, R.; Votruba, I.; Furman, P. A.; Tharnish, P. M.; Otto, M. J. *J. Med. Chem.* **2005**, *48*, 5869−5873.

10.1021/jo0513764 CCC: $30.25
Published on Web 11/12/2005



1a: Ar = 2,4,6-trimethylphenyl
1b: Ar = 2-nitrophenyl
1c: Ar = 4-methylphenyl
1d: Ar = 2,4,6-triisopropylphenyl
1e: Ar = 4-methoxyphenyl
1f: Ar = 2-thienyl

L-1: $R_1 = R_2 = H$
L-2: $R_1 = R_2 =$ *iso*-Pr
L-3: $R_1 = OCH_3$, $R_2 = H$

FIGURE 1. Structures of the nucleoside arylsulfonates and biphenyl ligands evaluated.

although catalysis was seen to occur at room temperature, conversions were largely incomplete.

Compared with smaller aryl systems, nucleosides are more complex in their reactivities, and data obtained from reactions of simpler aromatics are not always directly applicable to nucleosides. Furthermore, little is known about factors that influence Pd catalyzed reactions of nucleosides in general. For these reasons, we became interested in understanding whether C−C cross coupling of nucleoside arylsulfonates could be accomplished at room temperature and in gaining further insight into these reactions. To our knowledge, room temperature reactions at the C-6 position of nucleosides have not been reported to date. In the broader context, accomplishing such reactions under ambient conditions generally represents a nontrivial undertaking. In addition, we were interested in evaluating the interactions between the ligand and the metal that lead to catalyst activity.

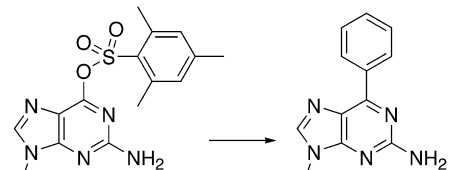
Results and Discussion

In a recent preliminary communication, we had shown that a single O^6-arylsulfonyl derivative of 2′-deoxyguanosine was an effective substrate for C−C cross coupling at elevated temperatures (80 °C in 1,4-dioxane).[7] Although good yields were obtained and the method was generally applicable, a detailed analysis of the cross coupling was not performed in that study. Influence of the arylsulfonate substituents, solvents, and other factors on the course of these reactions had not been analyzed. Since each of these can substantially impact the efficiency of the cross coupling, we were interested in a more detailed evaluation of the reactions. In fact, even among reactions of simpler aryl arenesulfonates, these factors do not seem to have received attention thus far.

For this study, a variety of O^6-arylsulfonyl 2′-deoxyguanosine derivatives (Figure 1) was selected that not only varied in electronic properties but also differed in steric requirements around the reactive center. Additionally, three related ligands were chosen for analysis (Figure 1). We have shown that **L-1** is a good ligand for C−C cross coupling,[4,7] but the commercial availability of newer ligands **L-2** and **L-3**, which differed from **L-1** in their steric and electronic properties, begged a comparison of the relative reactivities of catalytic systems derived from them.

(7) Lakshman, M. K.; Thomson, P. F.; Nuqui, M. A.; Hilmer, J. H.; Sevova, N.; Boggess, B. *Org. Lett.* **2002**, *4*, 1479−1482.

TABLE 1. Influence of Solvent on the Cross Coupling of 1a with $PhB(OH)_2$ at Room Temperature[a]



1a **2a**

entry	solvent	time (h)	% **2a** formed[b]
1	*tert*-BuOH	21	19
2	1,2-DME	21	49
3	1,4-dioxane	21	55
4	THF	21	79
5	THF/H_2O[c]	21	70
6	THF/*iso*-PrOH[d]	21	40
7	tetra-Me-THF	21	5
8	THP	19	100[e]
9	$PhCF_3$	21	46
10	PhMe	15.5	100[e]

[a] Sulfonate concentration 0.084 M. [b] Reactions were monitored by TLC, and the ratio of **1a/2a** was determined by integration of the H-1′ signals in the crude reaction products (H-1′ appears at δ 6.28 ppm in **1a** and δ 6.43 ppm in **2a**). [c] H_2O (10 μL) was added to the reaction mixture. [d] *iso*-PrOH (96 μL) was added to the reaction mixture. [e] H-1′ of **1a** was not observed by NMR.

At the outset of this series of experimentation, influence of the solvent was considered an important factor. The coupling of **1a** and $PhB(OH)_2$ with 10 mol % $Pd(OAc)_2$/20 mol % **L-1**/2 molar equiv of K_3PO_4 was used as a model for analyzing solvent influence. Since we have observed faster reactions with increased concentrations of arylboronic acids in some instances,[4,7] 2 molar equiv of the boronic acids was used in the present study to offset the decrease in reaction rate due to temperature.[8] The data gathered from this initial assessment are summarized in Table 1.

From these initial experiments, both tetrahydropyran (THP) and PhMe emerged as optimal solvents (entries 8 and 10). THF alone (entry 4) was better than combinations with H_2O or *iso*-PrOH (entries 5 and 6). 2,2,5,5-Tetramethyltetrahydrofuran (entry 7) was substantially inferior as compared to THF, as was $PhCF_3$ (entry 9) as compared to PhMe.

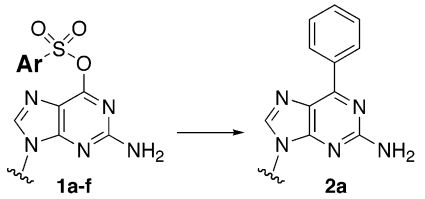
The effectiveness of catalytic systems derived from **L-2** and **L-3** was also analyzed for the cross coupling of **1a** with $PhB(OH)_2$ under the conditions stated previously. In PhMe, the **L-2** derived catalyst was superior to that from **L-3**, with a 72% yield of **2a** obtained from the former and incomplete reaction observed with the latter. Thus, among the three related ligands, **L-1** yielded a catalytic system that was by far the most effective. With $Pd(PPh_3)_4$ (10 mol %) and K_3PO_4 (2 molar equiv), the coupling of $PhB(OH)_2$ (2 molar equiv) with **1a** in PhMe at room temperature showed no progress. In contrast, this catalytic system was effective at 80−100 °C, clearly demonstrating the superior nature of the biphenyl-based ligands.[9]

Next, we reasoned that oxidative addition of the metal to the C−O bond of the nucleoside arylsulfonate could be perhaps manipulated through substituents on the

(8) Ambient air temperature was measured during the entire course of the experimentation and was found to be 23−28 °C.

(9) Gunda, P.; Russon, L. M.; Lakshman, M. K. *Angew. Chem., Int. Ed.* **2004**, *43*, 6372−6377; also see corrigendum: Gunda, P.; Russon, L. M.; Lakshman, M. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1154.

TABLE 2. Cross Coupling of Various O^6-Arylsulfonates of 2′-Deoxyguanosine with $PhB(OH)_2$ at Room Temperature[a]



entry	sulfonate	time (h)	result, yield of **2a**[b]
1	**1a**	15.5	complete, 90%
2	**1b**	15.5	no progress
3	**1c**	15.5	complete, 85%
4	**1d**	15.5	complete, 82%
5	**1e**	15.5	complete, 85%
6	**1f**	15.5	incomplete, 21%[c]

[a] Sulfonate concentration 0.084 M in PhMe. [b] Reactions were monitored by TLC for completion; yield is of isolated, purified product. [c] Assessed by integration of the H-1′ signals in the crude reaction product (H-1′ appears at δ 6.30 ppm in **1f** and at δ 6.43 ppm in **2a**).

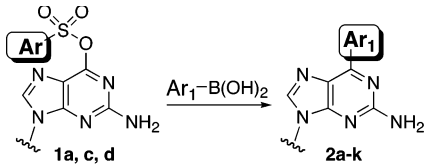
arylsulfonate moiety. Among simpler aryl systems, electron deficient ones are activated toward oxidative addition.[10,11] Attempts were therefore directed toward rendering the nucleoside−sulfonate bond more labile. Thus, 2-nitrophenylsulfonate **1b** (Figure 1) was synthesized via known procedures.[12] Reaction of **1b** with 2 molar equiv of $PhB(OH)_2$ using 10 mol % $Pd(OAc)_2$/20 mol % **L-1**/2 molar equiv of K_3PO_4 in PhMe showed little progress. This therefore prompted the screening of several other arylsulfonates listed in Figure 1, the results of which are tabulated in Table 2.

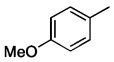
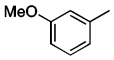
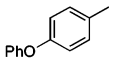
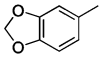
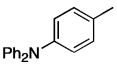
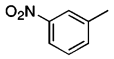
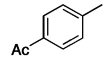
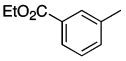
The ineffectiveness of **1b** was somewhat surprising (entry 2). In contrast, all alkyl-substituted phenylsulfonates were reactive. Interestingly, the (2,4,6-triisopropylphenyl)sulfonate **1d**, which had produced diminished C−C coupling yields at 80 °C,[7] provided a significant yield improvement at room temperature. It is therefore plausible that a competing reaction pathway at elevated temperature is a contributing factor to the diminished yield. 4-Methoxyphenylsulfonate **1e** was also effectively activated for the reaction.

At this stage, the generality of the room temperature cross coupling was explored, and arylboronic acids with varying electronic properties were selected for this purpose. A continued comparison of the arylsulfonate substrates as well as PhMe and THP as solvents was considered. The results of these experiments are compiled in Table 3. For comparative purposes, prior results from reactions performed in 1,4-dioxane at 80 °C are also presented in this table.

As evident from Table 3, several arylboronic acids underwent cross coupling at room temperature. A slightly elevated temperature (45 °C) was necessary for effecting complete cross coupling of the electron deficient arylboronic acids (*m*-nitro, *p*-acetyl, and *m*-carboethoxy) and the hindered *o*-ethoxyphenylboronic acid. PhMe was a generally better solvent as compared to THP, in many cases producing shorter reaction times. The solvent effect was most pronounced in the reactions of *p*-phenoxyphenylboronic acid (entry 17 vs 18) and *p*-(diphenylamino)-phenylboronic acid (entry 22 vs 23). When strongly electron-depleting substituents were present (*m*-nitro and *p*-acetyl), THP was superior to PhMe (entry 24 vs 25 and

TABLE 3. Generality of the Cross Coupling, Solvent Effects, and Yields of the C-6 Aryl Nucleoside Derivatives



entry	sulfonate	Ar_1 =	solvent	time, yield
				2a
1	**1a**		THP	19 h, 90%
2	**1a**		PhMe	15 h, 90%
3	**1a**		1,4-Dioxane	0.5 h, 76%[a]
4	**1c**		THP	24 h, inc[c]
				2b
5	**1a**		THP	19 h, 90%
6	**1a**		PhMe	15 h, 88%
7	**1a**		1,4-Dioxane	0.5 h, 73%[a]
8	**1c**		THP	24 h, 86%
				2c
9	**1a**		THP	19 h, 88%
10	**1a**		PhMe	15 h, 91%
11	**1a**		1,4-Dioxane	0.5 h, 81%[a]
12	**1c**		THP	20 h, 91%
				2d
13	**1a**		THP	19 h, 90%
14	**1a**		PhMe	15 h, 91%
15	**1a**		1,4-Dioxane	0.5 h, 78%[a]
16	**1c**		THP	20 h, 93%
				2e
17	**1a**		THP	60 h, 93%
18	**1a**		PhMe	27 h, 92%
				2f
19	**1a**		THP	40 h, 82%
20	**1a**		PhMe	46 h, inc[c]
21	**1a**		1,4-Dioxane	0.5, 78%[a]
				2g
22	**1a**		THP	51 h, inc[c]
23	**1a**		PhMe	15 h, 89%
				2h
24	**1a**		THP	16 h, 82%[b]
25	**1a**		PhMe	16 h, 55%[b]
26	**1a**		1,4-Dioxane	0.5 h, 82%[a]
27	**1d**		THP	16 h, 72%[b]
28	**1d**		PhMe	16 h, 44%[b]
				2i
29	**1a**		THP	19 h, 75%[b]
30	**1a**		PhMe	39 h, 53%[b]
31	**1a**		1,4-Dioxane	0.5, 64%[a]
				2j
32	**1a**		THP	19 h, 87%[b]
33	**1a**		PhMe	18 h, 84%[b]
				2k
34	**1a**		THP	40 h, inc[b,c]
35	**1a**		PhMe	18 h, 60%[b]
36	**1a**		1,4-Dioxane	5 h, 65%[a]

[a] Reported in ref 7 (reactions were conducted in 1,4-dioxane at 80 °C). [b] Conducted at 45 °C. [c] Reaction was incomplete.

(10) Amatore, C.; Pfluger, F. *Organometallics* **1990**, *9*, 2276−2282.
(11) Jutand, A.; Mosleh, A. *Organometallics* **1995**, *14*, 1810−1817.
(12) (a) Hayakawa, Y.; Hirose, M.; Noyori, R. *J. Org. Chem.* **1993**, *58*, 5551−5555. (b) Nagatsugi, F.; Uemura, K.; Nakashima, S.; Maeda, M.; Sasaki, S. *Tetrahedron* **1997**, *53*, 3035−3044.

29 vs 30). This was also the case with 3,4-(methylenedioxy)phenylboronic acid (entries 19 and 20).

Among the arylsulfonates, **1a** appeared to be a more general substrate (entry 1 as compared to 4), although in several cases (entries 8, 12, and 16), **1c** showed good utility. Entries 24 and 25 as well as 27 and 28 provide additionally interesting comparisons. The more hindered sulfonate **1d** is a less effective substrate as compared to **1a**, but the solvent effect was identical in each, with reactions in THP providing better product yields. When comparing the results from the cross coupling reactions performed in 1,4-dioxane at 80 °C to those at room temperature, the latter are significantly superior in most cases. Comparable results were observed with *p*-nitrophenylboronic acid and *o*-ethoxyphenylboronic acid. It is noteworthy, however, that reactions in entries 15 and 36 were conducted with 2.5 and 3 molar equiv of the arylboronic acids, respectively, whereas the room temperature reactions were conducted with 2 molar equiv.

Toward gleaning more insight into the cross coupling, **1a** was allowed to react with phenylboronic acid, and the reaction was stopped when TLC indicated complete consumption of the sulfonate (7.5 h). The yield of chromatographically purified **2a** in this case was 82%. The absence of **1a** in this reaction and a lowered product yield (by ~10%) may indicate that consumption of starting material alone may not signify complete product formation and that conversion of intermediates may require longer periods. Since the reactions of *m*-nitro and *p*-acetylphenylboronic acids with **1a** in PhMe were lower yielding, crude products from these reactions were analyzed by ^{1}H NMR. In these cases TLC had indicated consumption of **1a**. Correspondingly, evaluation of the NMR spectra of the reaction mixtures showed no pseudo-triplet corresponding to the anomeric H-1′ of **1a**. However, in addition to the H-1′ resonance of **2h** and **2i**, other smaller pseudo-triplets were observed in each case. In contrast, reactions performed in THP, which afforded higher product yields (entries 19, 24, 27, and 29 in Table 3), did not show discernible additional pseudo-triplets in the H-1′ region.

Similarly, reactions of **1a** with $PhB(OH)_2$ catalyzed by the Pd/**L-2** and Pd/**L-3** complexes were evaluated. The reaction mixture obtained with the Pd/**L-2** complex showed no H-1′ corresponding to **1a**, but a resonance from **2a** and smaller pseudo-triplets were observed. The reaction with the Pd/**L-3** complex that was incomplete showed H-1′ resonances of **1a** and **2a** as well as additional minor pseudo-triplets. Although these data are not evidence of reaction intermediates, minor H-1′ resonances other than that of product were observed in reactions that were lower yielding. More detailed studies of the mechanistic aspects of the cross coupling are currently being considered.

^{31}P NMR Data of L-1/Pd(OAc)$_2$ Complexes. To obtain some understanding of the interactions of **L-1** with $Pd(OAc)_2$, preliminary $^{31}P\{^1H\}$ NMR studies were undertaken. In toluene-d_8, relative to 85% H_3PO_4 as external standard, the ^{31}P resonance of the free phosphine **L-1** appeared at −13.36 ppm and the corresponding phosphine oxide at 46.14 ppm.

(a) 1:1 Complex of L-1 and Pd(OAc)$_2$. The addition of an equimolar amount of $Pd(OAc)_2$ to **L-1** [1:1 ratio of **L-1**/$Pd(OAc)_2$] in toluene-d_8 at room temperature led to the disappearance of free phosphine within 10 min. An AB_{quart} at 24−32 ppm, a small singlet at 31.71 ppm, two sharp singlets at 42.49 and 42.74 ppm, and a broad signal at 47.27 ppm appeared. After 1.5 h at room temperature (Figure 2A), the singlet at 31.71 diminished, but the AB_{quart}, two sharp singlets, and the broad resonance remained. After 24 h (Figure 2B), the intensity of the broad signal at 47.27 ppm increased slightly, whereas the AB_{quart} and the two sharp singlets decreased. A singlet appeared at 50.21 ppm, and the singlet at 31.71 ppm disappeared. After 3 days, the AB_{quart} completely disappeared.

Preparation of the same 1:1 complex as stated previously and warming to 40 °C resulted in the disappearance of the free phosphine signal within 10 min and the formation of two sharp singlets (42.50 and 42.75 ppm) along with a broad resonance (46.55 ppm) and a trace of an AB_{quart} (24−32 ppm). After 1 h at 40 °C, there was an increase in the broad signal with a concomitant decrease in intensity of the two sharp singlets. A trace of the AB_{quart} remained, and a small sharp singlet appeared at 50.28 ppm. After 24 h at 40 °C, the singlets (42.50 and 42.75 ppm) were significantly smaller, and the broad resonance (46.55 ppm) was predominant (>90%). There was no evidence of the AB_{quart}, the signal at 50.28 ppm increased, and a trace of a signal at 44.09 ppm became evident (see Supporting Information for NMR traces). There was no change after 29 h. In benzene-d_6, these patterns were essentially identical except that progress seemed faster.

(b) 2:1 Complex of L-1 and Pd(OAc)$_2$. When a 2:1 mixture of **L-1**/$Pd(OAc)_2$ in toluene-d_8 was analyzed by $^{31}P\{^1H\}$ NMR, interesting differences emerged. After 2 h at room temperature, ^{31}P NMR showed a broad signal at −13.33 ppm (perhaps free phosphine), and the predominant signal was the AB_{quart} (24−32 ppm). A singlet at 31.71 ppm, a minor broad resonance (47.27 ppm), and a singlet at 50.21 ppm appeared. After 21 h, the broad signal at −13.33 ppm persisted, and the AB_{quart} remained as the major component. The singlet at 31.71 ppm diminished, the broad resonance (46.77 ppm) remained minor, and the singlet at 50.21 ppm increased in intensity slightly.

When the 2:1 system was analyzed at 40 °C, after 10 min, the broadened signal at −13.33 ppm was visible. The AB_{quart} (24−32 ppm) was the predominant signal, and a singlet appeared at 32.15 ppm. Two sharp singlets at 42.50 and 42.75 ppm and a minor broad signal at 46.55 ppm were also evident. After 3 h, the broad signal at −13.33 ppm was still present, but the AB_{quart} remained significant. The singlets at 32.15, 42.50, and 42.75 ppm decreased significantly. The broad signal at 46.55 ppm increased slightly, and a singlet at 50.28 ppm appeared. After 24 h, the broad signal at −13.33 ppm remained, and the AB_{quart} was still the predominant resonance. The singlet at 32.15 ppm completely disappeared, the broad resonance (46.55 ppm) was still present, the singlet at 50.28 ppm increased, and a singlet at 44.33 ppm appeared (see Supporting Information for NMR traces). There were no major changes when this system was reanalyzed after 28 h at room temperature.

There are striking differences in the $^{31}P\{^1H\}$ NMR spectra of the 1:1 and 2:1 complexes, although the overall phenomena appear similar within each type at room

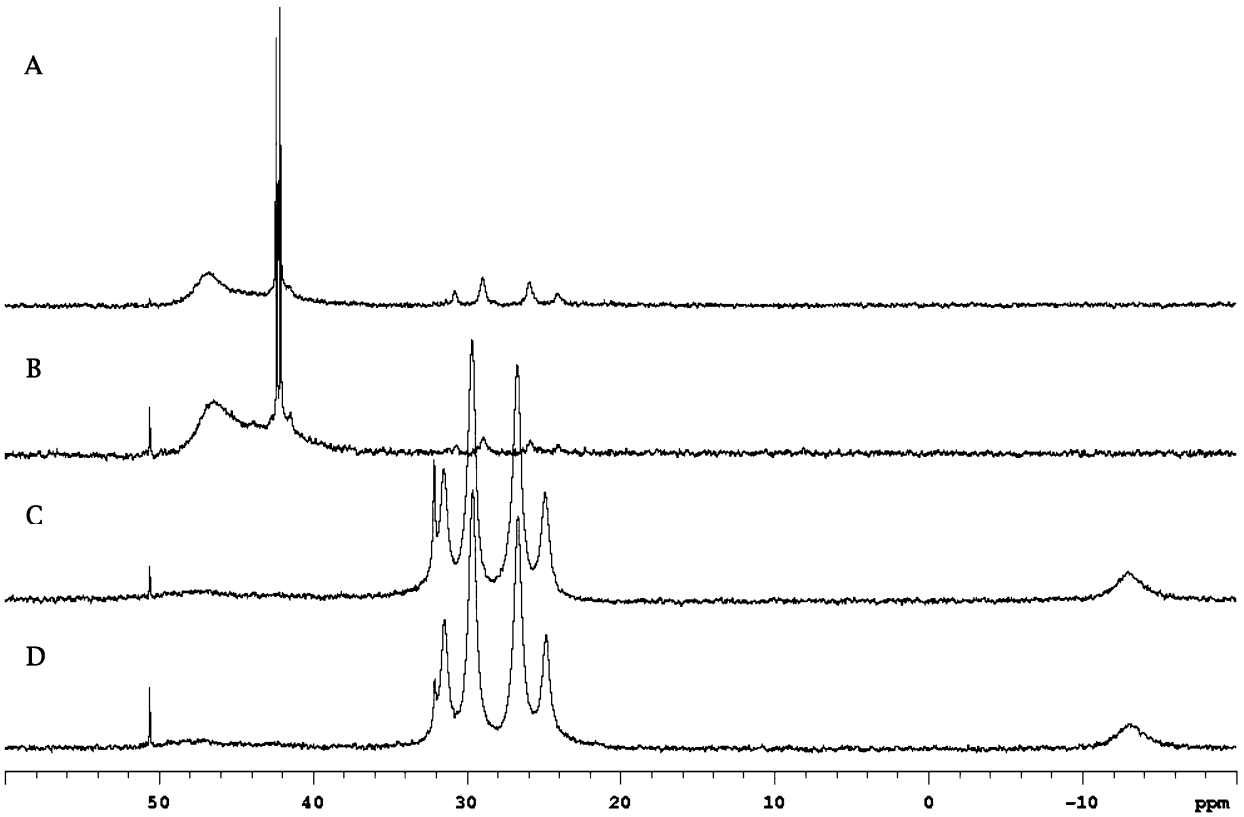
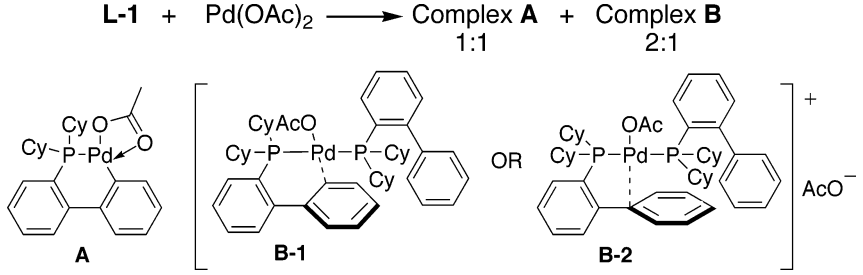


FIGURE 2. $^{31}P\{^{1}H\}$ NMR spectra of 1:1 and 2:1 **L-1**/$Pd(OAc)_2$ complexes in toluene-d_8. (A) The 1:1 complex after 1.5 h at room temperature. (B) The 1:1 complex after 24 h at room temperature. (C) The 2:1 complex after 2 h at room temperature. (D) The 2:1 complex after 21 h at room temperature.

SCHEME 1. Plausible Complexes that Can Be Formed from L-1 and $Pd(OAc)_2$



temperature and at 40 °C. The data indicate that there are discrete entities possible depending upon the **L-1**/$Pd(OAc)_2$ stoichiometry (Scheme 1). Complex **A**, a 1:1 species, produces the broad resonance at 46−47 ppm and is the dominant species formed within 24 h at 40 °C. The ^{1}H NMR spectrum of this complex indicates 8 aromatic and 25 aliphatic protons. This would be consistent with a cyclopalladated species such as that shown in Scheme 1. Although current experiments are not indicative of the oxidation state of Pd in the species, it is most likely Pd(II) with coordinated acetate and this is also consistent with the integration in the aliphatic region of the ^{1}H NMR. Additionally, the signal at ∼50 ppm in the ^{31}P NMR is consistent with the phosphine oxide as determined by a spiking experiment. Since the phosphine oxide was formed slowly and was a minor component, it is possible that phosphine mediated reduction of Pd(II) to Pd(0) is not very rapid, and this is also indicative that **A** is possibly a Pd(II) complex. A similar cyclopalladated Pd(II) species from di(*tert*-butylphosphino)biphenyl is known where acetate is coordinated with the metal.[13]

Complex **B**, on the other hand, is an unsymmetrical 2:1 complex based upon the chemically distinct phosphorus resonances (AB_{quart} $\delta_A = 25.74$ ppm, $\delta_B = 30.60$ ppm, $J_{AB} = 370$ Hz). The magnitude of the coupling constant is suggestive of a trans relationship between the phosphorus atoms. As observed by NMR, during the formation of the 1:1 complex, some 2:1 product is also initially formed (appearance of the AB_{quart} even at 40 °C). This accounts for the absence of free phosphine in this case. Since the AB_{quart} diminishes and disappears, one possible explanation is that the 2:1 complex converts to the 1:1 complex irreversibly, over time. During the formation of the 2:1 complex, some 1:1 product is formed as a minor component accounting for a signal at −13.33 ppm and the broad resonance at 46.55 ppm. However, the 2:1 complex appears quite stable in solution through the

(13) Zim, D.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2413−2415.

continued presence of the AB_{quart} as the major ^{31}P resonance at both room temperature and at 40 °C.

Since reactions were conducted at a 2:1 **L-1**/$Pd(OAc)_2$ ratio, complex **B** is a species of interest. Again, although present results do not provide information on the oxidation state of Pd, slow formation of the phosphine oxide may indicate **B** to be a Pd(II) complex with coordinated acetate. Since Pd(0) species with η^1 as well as ipso carbon coordination are known in the literature,[14,15] entities such as **B-1** and **B-2** could be plausible candidates for the 2:1 complex as these possess chemically distinct, trans coordinated phosphines that could display an AB_{quart} pattern in the ^{31}P NMR as seen in this study.[16]

In additional ^{31}P NMR experiments, the 2:1 complex **B** was exposed to a stoichiometric amount of $PhB(OH)_2$ and K_3PO_4. Upon shaking the NMR tube and data acquisition, changes observed included the formation of several new species as well as a significant entity that produced a broad signal at 31 ppm. A similar broad resonance has been reported for a 2:1 **L-1**/Pd(0) complex.[14]

To determine the catalytic viability of various ligand−palladium complexes that were identified, C−C cross coupling reactions of **1a** were conducted using the 1:1 complex **A** isolated by forming that species at 40 °C. Using this complex, the reaction with phenylboronic acid in PhMe was complete within 15 h, affording **2a** in 86% yield, and that with *m*-nitrophenylboronic acid in THP was complete in 24 h at 45 °C, producing **2h** in 66% yield. Since we have been unable to isolate the 2:1 complex, this was generated as solutions in PhMe and THP for reactions with phenylboronic and *m*-nitrophenylboronic acids, respectively. Use of the preformed 2:1 species for the coupling of **1a** with phenylboronic and *m*-nitrophenylboronic acids, in PhMe and THP, respectively, led to complete reaction in each case with isolated yields of 90% for **2a** (15 h at room temperature) and 78% for **2h** (18 h at 45 °C). These experiments seem to suggest that although the 1:1 complex could have reasonable catalytic activity, a 2:1 **L-1**/$Pd(OAc)_2$ stoichiometry may be important for higher activity. Results of experiments aimed at greater mechanistic understanding of these reactions and detailed structural evaluations of Pd complexes, as well as other applications of the room temperature cross coupling, will be forthcoming.

In recent years, metal mediated C−C and C−N bond forming reactions have generated much interest due to the high biological value of modified nucleosides. Via this approach, our own research[17] as well as those of others[18] has begun to provide facile access to novel structural entities. With the exception of the recently reported aqueous phase C−C cross coupling reactions at the C-8 position of purine nucleosides,[19] there are no other reports of such cross coupling reactions under ambient conditions. In the present case, aqueous conditions are precluded due to the hydrolytic lability of the nucleoside arylsulfonates. The activation of nucleoside arylsulfonates under mild catalysis conditions represents an advantage in that metal catalyzed transformations can be conducted in a relatively simple and facile manner, without the need for more sophisticated precursors.[20]

Experimental Procedures

Thin-layer chromatography was performed on 250 μm silica plates, and column chromatographic purifications were performed on 200−300 mesh silica gel. The ligands, $Pd(OAc)_2$ and all other reagents were obtained from commercial sources and used without further purification. Prior to each reaction, toluene was freshly distilled from sodium. All nucleoside arylsulfonates were prepared based upon reported methods.[12] ^1H NMR spectra (500 MHz) and ^{13}C data (125 MHz) were recorded in deacidified $CDCl_3$ (prepared by percolating the solvent through a bed of solid $NaHCO_3$ and basic alumina). Spectra were referenced to residual protonated solvent. ^{31}P NMR spectra (202.3 MHz) were acquired in toluene-d_8 and were referenced to 85% H_3PO_4 as an external standard. Chemical shifts are reported in δ ppm, and coupling constants are in hertz. Sugar protons are numbered 1′−5′ beginning at the anomeric carbon and proceeding via the carbon chain to the primary carbinol carbon. Where possible, proton assignments have been made based upon analogy to known compounds and $^1H-^1H$ COSY data of representative examples.

3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-*O*^{6}-[(4-methylphenyl)sulfonyl]-2′-deoxyguanosine (1c).[12b] (Typical Procedure for Synthesis of Nucleoside Arylsulfonates). In an oven-dried, round-bottomed flask equipped with a stir bar was placed 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (500 mg, 1.008 mmol). CH_2Cl_2 (16 mL) was added, and the mixture was cooled to 0 °C. Et_3N (0.3 mL, 2 molar equiv), DMAP (30 mg, 24.5 μmol), and *p*-TsCl (400 mg, 2.098 mmol) were added. The mixture was brought to room temperature and left stirring at room temperature under nitrogen. Upon completion, the reaction mixture was diluted with additional CH_2Cl_2 and washed with saturated aq $NaHCO_3$ and brine. Evaporation of the filtrate provided the crude product that was triturated with 1:1 ether−hexanes to yield **1c** as a white powder (72%). Data for this compound have been reported in the literature.[12b] Compounds that were homogeneous by ^1H NMR were routinely obtained by this method.

3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-*O*^{6}-[(2,4,6-trimethylphenyl)sulfonyl]-2′-deoxyguanosine (1a).[12a] White powder (84%), R_f (10% EtOAc in CH_2Cl_2) = 0.65. ^1H NMR: 7.98 (s, 1H, Ar−H), 6.97 (s, 2H, Ar−H), 6.28 (t, 1H, 1′, J = 6.4), 4.82 (br s, 2H, NH_2), 4.57 (m, 1H, 3′), 3.97 (app q, 1H, 4′, $J \sim$ 3.4), 3.79 (dd, 1H, 5′, J = 4.4, 11.2), 3.74 (dd, 1H, 5′, J = 2.9, 11.2), 2.75 (s, 6H, CH_3), 2.53 (app quint, 1H, 2′, J = 6.8, 6.8, 13.2), 2.34 (ddd, 1H, 2′, J = 3.4, 6.4, 13.2), 2.31 (s, 3H, CH_3), 0.91, 0.90 (2s, 18H, $SiC(CH_3)_3$), 0.096, 0.070, 0.061 (3s, 12H, $SiCH_3$). ^{13}C NMR: 159.1, 156.3, 155.6, 144.5, 141.0, 140.7, 133.2, 132.3, 117.3, 88.5, 84.5, 72.6, 63.5, 41.5, 26.6, 26.4, 23.4, 21.8, 19.1, 18.7, −4.0, −4.1, −4.7, −4.8. HRMS calcd for $C_{31}H_{52}N_5O_6SSi_2$ (M^+ + H) 678.3177, found 678.3182.

(14) Reid, S. M.; Boyle, R. C.; Mague, J. T.; Fink, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 7816−7817.

(15) (a) Kočovský, P.; Vyskočil, S.; Císařová, I.; Sejbal, J.; Tišlerová,I.; Smrčina, M.; Lloyd-Jones, G. C.; Stephen, S. C.; Butts, C. P.; Murray, M.; Langer, V. *J. Am. Chem. Soc.* **1999**, *121*, 7714−7715. (b) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871−1876. (c) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685−4696.

(16) The reviewers are thanked for their insightful comments. In particular, one reviewer pointed out details regarding the structures shown in Scheme 1 as well as matters that helped the discussion of the complexes.

(17) Reviewed in: (a) Lakshman, M. K. *J. Organomet. Chem.* **2002**, *653*, 234−251. (b) Lakshman, M. K. *Curr. Org. Synth.* **2005**, *2*, 83−112.

(18) For other reviews, please see: (a) Hocek, M. *Eur. J. Org. Chem.* **2003**, 245−254. (b) Agrofoglio, L. A.; Gillaizeau, I.; Saito, Y. *Chem. Rev.* **2003**, *103*, 1875−1916.

(19) Western, E. C.; Daft, J. R.; Johnson, E. M., II; Gannett, P. M.; Shaughnessy, K. M. *J. Org. Chem.* **2003**, *68*, 6767−6774.

(20) For some examples of cross coupling reactions involving iodo, azolyl, fluoro, alkylsulfanyl, and alkylsufonyl nucleoside derivatives, please see: (a) Liu, J.; Janeba, Z.; Robins, M. J. *Org. Lett.* **2004**, *6*, 2917−2919. (b) Liu, J.; Robins, M. J. *Org. Lett.* **2004**, *6*, 3421−3423. (c) Liu, J.; Robins, M. J. *Org. Lett.* **2005**, *7*, 1149−1151.

3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-*O*^{6}-[(2-nitrophenyl) sulfonyl]-2′-deoxyguanosine (1b). Yellow powder (48%), R_f (10% EtOAc in CH_2Cl_2) = 0.51. ^{1}H NMR: 8.32 (dd, 1H, Ar−H, J = 1.0, 7.8), 8.02 (s, 1H, Ar−H), 7.85−7.75 (m, 3H, Ar−H), 6.29 (t, 1H, 1′, J = 6.6), 5.03 (br s, 2H, NH_2), 4.57 (m, 1H, 3′), 3.98 (app q, 1H, 4′, $J \sim$ 3.5), 3.80 (dd, 1H, 5′, J = 3.9, 11.2), 3.74 (dd, 1H, 5′, J = 3.4, 11.2), 2.54 (app quint, 1H, 2′, J = 5.9, 5.9, 13.2), 2.36 (ddd, 1H, 2′, J = 3.9, 6.4, 13.2), 0.91, 0.90 (2s, 18H, $SiC(CH_3)_3$), 0.098, 0.074, 0.066 (3s, 12H, $SiCH_3$). ^{13}C NMR: 158.4, 156.2, 154.0, 148.7, 140.7, 135.1, 132.1, 132.0, 130.8, 124.8, 116.7, 87.9, 84.0, 71.9, 62.8, 41.0, 26.0, 25.8, 18.4, 18.0, −4.7, −4.8, −5.4, −5.5. HRMS calcd for $C_{28}H_{45}N_6O_8SSi_2$ (M^+ + H) 681.2558, found 681.2537.

3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-*O*^{6}-[(2,4,6-triisopropylphenyl)sulfonyl]-2′-deoxyguanosine (1d). White foam (60%), R_f (10% EtOAc in CH_2Cl_2) = 0.51. ^{1}H NMR: 7.97 (s, 1H, Ar−H), 7.19 (s, 2H, Ar−H), 6.29 (t, 1H, 1′, J = 6.6), 4.85 (br s, 2H, NH_2), 4.57 (m, 1H, 3′), 4.31 (sept, 2H, CH, J = 6.7), 3.98 (app q, 1H, 4′, $J \sim$ 3.3), 3.80 (dd, 1H, 5′, J = 3.9, 11.2), 3.74 (dd, 1H, 5′, J = 2.9, 11.2), 2.91 (sept, 1H, CH, J = 6.8), 2.55 (app quint, 1H, 2′, J = 5.9, 5.9, 13.2), 2.34 (ddd, 1H, 2′, J = 3.4, 5.9, 13.2), 1.28−1.25 (overlapping d, 18H, $(CH_3)_2$), 0.91, 0.89 (2s, 18H, $SiC(CH_3)_3$), 0.096, 0.066, 0.054 (3s, 12H, $SiCH_3$). ^{13}C NMR: 158.4, 155.6, 155.2, 154.2, 150.9, 139.9, 131.5, 123.8, 116.7, 87.9, 83.9, 72.0, 62.8, 40.9, 34.3, 29.8, 25.9, 25.8, 24.6, 23.5, 18.4, 18.0, −4.7, −4.8, −5.4, −5.5. HRMS calcd for $C_{37}H_{64}N_5O_6SSi_2$ (M^+ + H) 762.4116, found 762.4083.

3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-*O*^{6}-[(4-methoxyphenyl)sulfonyl]-2′-deoxyguanosine (1e). White powder (64%), R_f (10% EtOAc in CH_2Cl_2) = 0.32. ^{1}H NMR: 8.08 (d, 2H, Ar−H, J = 9.1), 7.99 (s, 1H, Ar−H), 7.01 (d, 2H, Ar−H, J = 9.1), 6.29 (t, 1H, 1′, J = 6.6), 4.98 (br s, 2H, NH_2), 4.57 (m, 1H, 3′), 3.97 (app q, 1H, 4′, $J \sim$ 3.4), 3.89 (s, 3H, OCH_3), 3.80 (dd, 1H, 5′, J = 4.4, 11.2), 3.74 (dd, 1H, 5′, J = 3.4, 11.2), 2.54 (ddd, 1H, 2′, J = 5.9, 6.8, 13.2), 2.34 (ddd, 1H, 2′, J = 3.4, 5.9, 13.2), 0.91, 0.89 (2s, 18H, $SiC(CH_3)_3$), 0.099, 0.072, 0.064 (3s, 12H, $SiCH_3$). ^{13}C NMR: 164.5, 158.9, 156.0, 154.8, 140.4, 131.6, 128.3, 117.2, 114.4, 88.1, 84.1, 72.2, 63.0, 56.0, 41.1, 26.2, 26.0, 18.7, 18.2, −4.4, −4.6, −5.2, −5.3. HRMS calcd for $C_{29}H_{48}N_5O_7SSi_2$ (M^+ + H) 666.2813, found 666.2821.

3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-*O*^{6}-[(2-thienyl)sulfonyl]-2′-deoxyguanosine (1f). White powder (62%), R_f (10% EtOAc in CH_2Cl_2) = 0.37. ^{1}H NMR: 8.01 (s, 1H, Ar−H), 7.97 (dd, 1H, Ar−H, J = 1.5, 3.9), 7.75 (dd, 1H, Ar−H, J = 1.5, 4.9), 7.14 (dd, 1H, Ar−H, J = 3.9, 4.9), 6.30 (t, 1H, 1′, J = 6.6), 5.03 (br s, 2H, NH_2), 4.57 (m, 1H, 3′), 3.98 (app q, 1H, 4′, $J \sim$ 3.4), 3.80 (dd, 1H, 5′, J = 4.4, 11.2), 3.75 (dd, 1H, 5′, J = 2.9, 11.2), 2.54 (app quint, 1H, 2′, J = 6.4, 6.4, 13.2), 2.36 (ddd, 1H, 2′, J = 3.7, 6.4, 13.2), 0.91, 0.90 (2s, 18H, $SiC(CH_3)_3$), 0.099, 0.076, 0.068 (3s, 12H, $SiCH_3$). ^{13}C NMR: 158.4, 155.9, 154.3, 140.4, 136.3, 136.1, 135.0, 127.3, 116.8, 87.9, 83.9, 71.9, 62.8, 41.0, 25.9, 25.7, 18.4, 18.0, −4.7, −4.8, −5.4, −5.5. HRMS calcd for $C_{26}H_{44}N_5O_6S_2Si_2$ (M^+ + H) 642.2272, found 642.2286.

Typical Procedure for the Cross Coupling of 1a with Arylboronic Acids. In an oven-dried, screw-cap vial equipped with a stir bar were placed $Pd(OAc)_2$ (1.3 mg, 5.8 μmol), **L-1** (4.1 mg, 11.7 μmol), K_3PO_4 (25 mg, 117 μmol), the nucleoside arylsulfonate **1a** (40 mg, 58.9 μmol), and the arylboronic acid (2 molar equiv). THP or PhMe (0.7 mL) was added, the vial was flushed with nitrogen and sealed with a Teflon-lined cap, and the mixture was allowed to stir at room temperature. Upon completion, the reaction mixture was filtered through Celite, and the residue was washed with CH_2Cl_2. Evaporation of the filtrate provided the crude product mixtures that were purified by column chromatography on silica gel using CH_2Cl_2 followed by 3% acetone in CH_2Cl_2.

Characterization data for **2a**−**d**, **2f**, **2h**, **2i**, and **2k** have been described previously,[7,9] and data for new compounds are listed.

2-Amino-6-[4-(phenoxy)phenyl]-9-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuranosyl]purine (2e). Pale cream-colored foam, R_f (4% MeOH/16% CH_2Cl_2/80% hexanes) = 0.29. ^{1}H NMR: 8.67 (d, 2H, Ar−H, J = 8.8), 8.05 (s, 1H, Ar−H), 7.38−7.35 (m, 2H, Ar−H), 7.16−7.07 (m, 5H, Ar−H), 6.40 (t, 1H, 1′, J = 6.6), 4.98 (br s, 2H, NH_2), 4.62 (m, 1H, 3′), 4.01 (app q, 1H, 4′, $J \sim$ 3.6), 3.82 (dd, 1H, 5′, J = 4.4, 11.2), 3.77 (dd, 1H, 5′, J = 3.4, 11.2), 2.65 (ddd, 1H, 2′, J = 5.9, 6.8, 12.7), 2.39 (ddd, 1H, 2′, J = 3.4, 5.9, 12.7), 0.93, 0.91 (2s, 18H, $SiC(CH_3)_3$), 0.12, 0.083, 0.080 (3s, 12H, $SiCH_3$). ^{13}C NMR: 159.6, 159.4, 156.6, 155.2, 153.9, 139.7, 131.4, 130.8, 129.8, 125.8, 123.7, 119.5, 118.3, 87.8, 83.6, 72.1, 62.9, 40.7, 26.0, 25.8, 18.4, 18.0, −4.7, −4.8, −5.3, −5.5. HRMS calcd for $C_{34}H_{50}N_5O_4Si_2$ (M^+ + H) 648.3401, found 648.3404.

2-Amino-6-[4-(diphenylamino)phenyl]-9-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuranosyl]purine (2g). Yellow foam, R_f (5% EtOAc in CH_2Cl_2) = 0.33. ^{1}H NMR: 8.51 (d, 2H, Ar−H, J = 8.8), 8.02 (s, 1H, Ar−H), 7.29−7.28 (m, 4H, Ar−H), 7.17−7.14 (m, 6H, Ar−H), 7.07 (t, 2H, Ar−H, J = 7.5), 6.39 (t, 1H, 1′, J = 6.6), 4.95 (br s, 2H, NH_2), 4.62 (m, 1H, 3′), 4.00 (app q, 1H, 4′, $J \sim$ 3.6), 3.82 (dd, 1H, 5′, J = 4.4, 11.2), 3.77 (dd, 1H, 5′, J = 3.4, 11.2), 2.65 (ddd, 1H, 2′, J = 5.9, 6.8, 13.2), 2.39 (ddd, 1H, 2′, J = 3.4, 5.9, 13.2), 0.93, 0.91 (2s, 18H, $SiC(CH_3)_3$), 0.12, 0.079, 0.076 (3s, 12H, $SiCH_3$). ^{13}C NMR: 159.4, 155.6, 153.8, 150.1, 147.2, 139.4, 130.6, 129.3, 129.1, 125.7, 125.2, 123.6, 122.0, 87.7, 83.6, 72.1, 62.9, 40.6, 26.0, 25.8, 18.4, 18.0, −4.7, −4.8, −5.3, −5.5. HRMS calcd for $C_{40}H_{55}N_6O_3Si_2$ (M^+ + H) 723.3874, found 723.3881.

2-Amino-6-[3-(ethoxycarbonyl)phenyl]-9-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuranosyl]purine (2j). White foam, R_f (4% MeOH/16% CH_2Cl_2/80% hexanes) = 0.24. ^{1}H NMR: 9.25 (t, 1H, Ar−H, J = 1.5), 8.92 (td, 1H, Ar−H, J = 1.5, 6.4), 8.15 (td, 1H, Ar−H, J = 1.5, 7.8), 8.10 (s, 1H, Ar−H), 7.60 (t, 1H, Ar−H, J = 7.8), 6.40 (t, 1H, 1′, J = 6.6), 5.04 (br s, 2H, NH_2), 4.63 (m, 1H, 3′), 4.43 (q, 2H, J = 7.3), 4.01 (app q, 1H, 4′, $J \sim$ 3.7), 3.83 (dd, 1H, 5′, J = 4.4, 11.2), 3.77 (dd, 1H, 5′, J = 3.4, 11.2), 2.65 (ddd, 1H, 2′, J = 5.9, 6.8, 13.2), 2.40 (ddd, 1H, 2′, J = 3.4, 5.9, 13.2), 1.43 (t, 3H, CH_3, J = 7.3), 0.93, 0.92 (2s, 18H, $SiC(CH_3)_3$), 0.12, 0.088, 0.083 (3s, 12H, $SiCH_3$). ^{13}C NMR: 166.5, 159.5, 154.7, 154.1, 140.2, 136.3, 134.2, 131.4, 130.9, 130.3, 128.5, 126.2, 87.8, 83.6, 72.1, 62.9, 61.1, 40.7, 26.0, 25.8, 18.4, 18.0, 14.4, −4.7, −4.8, −5.4, −5.5. HRMS calcd for $C_{31}H_{50}N_5O_5Si_2$ (M^+ + H) 628.3351, found 628.3344.

Acknowledgment. Support for this work by NSF Grant CHE-0314326 and a PSC-CUNY 36 award is gratefully acknowledged. Acquisition of a 500 MHz NMR spectrometer was funded by NSF Grant CHE-0210295. We thank Prof. Kevin Shaughnessy (University of Alabama) for helpful discussions.

Supporting Information Available: Proton NMR spectra of **1a**, **1b**, **1d**, **1e**, **1f**, **2e**, **2g**, and **2j** and ^{31}P{^{1}H} NMR spectra of 1:1 and 2:1 **L-1**/$Pd(OAc)_2$ complexes obtained at 40 °C. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0513764