Palladium Catalysis for the Synthesis of Hydrophobic C-6 and C-2 Aryl 2′-Deoxynucleosides. Comparison of C−C versus C−N Bond Formation as well as C-6 versus C-2 Reactivity

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Abstract: Suzuki−Miyaura cross-coupling of haloaromatic compounds with arylboronic acids provides a simple entry to biaryl systems. Despite its ease, to date, there are no detailed investigations of this procedure for deoxynucleoside modification. As shown in this study, a wide variety of C-6 arylpurine 2′-deoxyriboside (C-6 aryl 2′-deoxynebularine analogues) and C-2 aryl 2′-deoxyinosine analogues can be conveniently prepared via the Pd-mediated cross-coupling of arylboronic acids with the C-6 halonucleosides, 6-bromo- or 6-chloro-9[2-deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-*erythro*-pentofuranosyl]purine (**1** and **2**), and the C-2 halonucleoside, 2-bromo-O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (**3**). Although bromonucleoside **1** proved to be a good substrate for the Pd-catalyzed Suzuki-Miyaura cross-couplings, we have noted that for several C-6 arylations, the chloronucleoside **2** provides superior coupling yields. Also described in this study is a detailed evaluation of catalytic systems that led to optimal product recoveries. Finally, a comparison of the C−C and C−N bond-forming reactions of deoxynucleosides is also reported. On the basis of this comparison, we provide evidence that C−N bond formation at the C-6 position, leading to *N*-aryl 2′-deoxyadenosine analogues, is more sensitive to the ligand used, whereas C−C bond-forming reactions at the same position are not. In contrast to the ligand dependency exhibited in C−N bond formation at the C-6 position, comparable reactions at the C-2 position of purine deoxynucleosides proceed with less sensitivity to the ligand used.

Introduction

Synthetic access to unusual nucleosides is becoming markedly important for a variety of reasons. For example, unusual deoxyribosides have recently been used to probe enzymatic activities such as recognition by polymerases, base-pairing properties, and repair.[1−4] In addition, unnatural nucleosides have been evaluated for fidelity in replicative processes with a view to expansion of the genetic alphabet.[5,6] Purine deoxynucleosides bearing aryl rings at the C-6 and C-2 positions are interesting for several reasons. Such nucleosides, while maintaining the basic purine skeleton that is potentially recognizable by intracellular systems, also bear hydrophobic aromatic moieties that possess *π*-stacking ability. Thus, DNA containing such nucleosides could exhibit unusual properties. For instance, in unrelated studies, we have seen that covalent modification of the N^6 amino group of 2′-deoxyadenosine with carcinogenic metabolites of the multiple aryl ring-containing benzo[*a*]pyrene leads to an increase in thermal stability of a short *N-ras* duplex in the presence of an apyrimidinic site opposite the adducted adenine.[7] Further, in these cases, the pyrene moiety seemed to undergo intercalative accommodation within the duplex.[7] Similar effects have also been seen with unusual pyrene nucleosides.[8] In addition, aryl nucleosides could have potential pharmacological activity, and they could be used in the development of new molecular assembly motifs. Therefore, we became interested in probing questions on the applications of hydrophobic nucleosides, as well as studies on DNA containing these unusual nucleosides. As a first step in our studies it is therefore necessary to delineate a general chemical method for the preparation of aryl nucleosides.

Although several methods have been described for C−C bond formation among purines and to an extent on nucleosides,[9−13] surprisingly, the application of the Suzuki−Miyaura cross-coupling[14] for purine and nucleoside modification has only recently received attention,[15] with the most recent reports appearing while this work was in progress.[15b−d] This cross-

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coupling method offers distinct advantages over others because of its operational simplicity as well as the broad range of compounds that can be prepared on the basis of the ready availability (or easy synthesis) of a wide assortment of arylboronic acids. Among nucleosides, aryl group introduction at the C-6 position of purine ribosides via the Suzuki−Miyaura reaction has received much more attention in the recent past,[15a,b,d] whereas far fewer examples are available on similar reactions with the more labile 2′-deoxyribosides.[15c] In addition, to our knowledge, arylation at the C-2 position of 2′-deoxynucleosides has not been explored to date. Thus, details of the Suzuki−Miyaura cross-coupling remain largely unstudied for deoxynucleoside modification particularly with respect to understanding the catalytic systems necessary as well as the generality of the approach. On the basis of recent developments in C−C bond-formation methods,[16−21] as well as our own interests in Pd-catalyzed methods for nucleoside and, conceivably, DNA modification, we report herein a facile approach to C-6 aryl 2′-deoxynebularine and C-2 aryl 2′-deoxyinosine analogues via the Suzuki−Miyaura protocol. We also compare, for the first time, the utility of C-6 chloro- and C-6 bromopurine nucleosides in these reactions. With a view to understanding Pd-catalyzed cross-coupling as a general entry to modified nucleosides, we have compared C−C and C−N bond formation at the C-6 position and also C−N bond formation at the C-6 and C-2 positions. Therefore, this study offers the first, relatively extensive investigation of palladium catalysis for nucleoside modification.

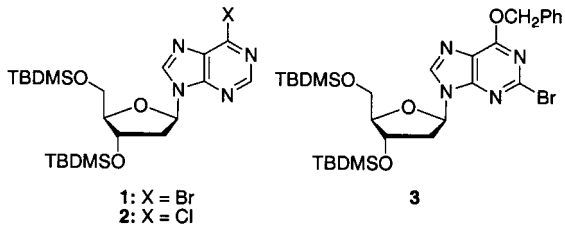

Figure 1. Structures of C-6 and C-2 halo 2′-deoxynucleosides that are suitable substrates for Suzuki−Miyaura cross-coupling reactions.

Results and Discussion

The Suzuki−Miyaura protocol for C−C bond formation, leading to biaryl compounds, is an operationally simple method involving a Pd-catalyzed cross-coupling of haloaromatics with arylboronic acids.[14] This method does not necessitate the use of anhydrous conditions, and a variety of protecting groups are well-tolerated under the reaction conditions. Application of this procedure for the introduction of aryl groups into nucleosides would represent a simple and efficient approach to unusual, hydrophobic nucleosides. Two possible alternatives can be envisioned for the arylation of nucleosides through such an approach: (a) coupling of a halonucleoside with arylboronic acids or (b) coupling of a nucleoside boronic acid with halo aromatic compounds. Between the two, approach (a) is more straightforward for two reasons; syntheses of halonucleosides, such as those shown in Figure 1, are well-established,[22−24] and a wide assortment of arylboronic acids are commercially available.

Suzuki−Miyaura reactions usually involve the use of a base such as aqueous carbonate;[14,15a] however, halonucleosides could potentially face hydrolysis with an aqueous base. Further, on the basis of our recent experience with Pd-mediated C−N bond formation,[22] we anticipated the use of the *tert*-butyldimethylsilyl (TBDMS) protecting group at the 3′,5′-hydroxyls of the nucleoside. The use of this protecting group precludes the use of the commonly employed CsF[25] and KF.[17,19,20,25a] We have found the TBDMS group to be stable under reaction conditions when employing bases such as K_3PO_4 and Cs_2CO_3.[22] Whereas K_3PO_4 has been utilized in Suzuki−Miyaura reactions,[16,17,19] Cs_2CO_3 has been used in Heck couplings[26] as well as Suzuki−Miyaura reactions,[21] and both seemed worthy choices. However, we preferred K_3PO_4 on the basis of its compatibility with the systems we that anticipated investigating.

Synthesis of C-6 Aryl 2′-Deoxynebularine Derivatives. (a) Utility of Bromonucleoside 1 for Suzuki−Miyaura Cross-Coupling. The halonucleoside presursor, 6-bromo-9[2-deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-*erythro*-pentofuranosyl]-

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(23) (a) Synthesis of 6-chloro-9(2-deoxy-*β*-D-*erythro*-pentofuranosyl)-purine: Robins, M. J.; Basom, G. L. *Can. J. Chem.* **1973**, *51*, 3161−3169. (b) Synthesis of the corresponding bis TBDMS ether, 6-chloro-9[2-deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-*erythro*-pentofuranosyl]purine (**2**): Maruenda, H.; Chenna, A.; Liem, L.-K.; Singer, B. *J. Org. Chem.* **1998**, *63*, 4385−4389. Compound **2** has been reported as an oil, but we have isolated this material as a colorless solid.

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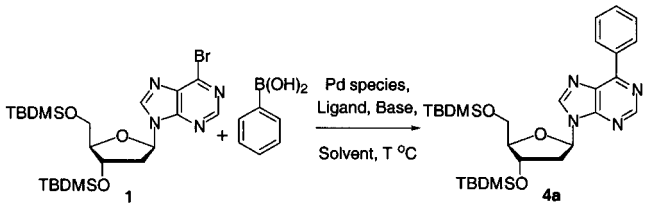
Table 1. Evaluation of Catalytic Systems for the Coupling of Bromonucleoside **1** with Phenylboronic Acid[a,b]



entry	catalyst/ligand	solvent	temp, °C	time, h; result
1	$Pd(OAc)_2$/**L-1**	1,4-dioxane	100	12, 40%
2	$Pd(OAc)_2$/**L-2**	1,4-dioxane	100	1.75, 73%
3	$Pd(OAc)_2$/**L-3**	1,4-dioxane	100	6, 67%
4	$Pd(OAc)_2$/**L-4**	1,4-dioxane	100	1, 91%
5	$Pd(OAc)_2$/**L-5**	1,4-dioxane	100	reaction ~50% complete after ~48 h[c]
6	$Pd(OAc)_2$/**L-6**	1,4-dioxane	100	reaction ~50% complete after ~48 h[c]
7	$Pd(OAc)_2$/**L-3**	1,2-DME	80	after ~12 h, product formation ceased; degradation after ~36 h[d]
8	$Pd_2(dba)_3$/**L-2**	1,4-dioxane	100	0.5, 80%
9	$Pd(PPh_3)_4$	toluene	100	8, 87%[e]

[a] Reaction conditions (entries 1−8): bromonucleoside (**1**) 0.15 M in anhydrous 1,4-dioxane (or 1,2-DME for entry 7), 1.5 molar equiv phenylboronic acid, 2 molar equiv K_3PO_4, 10 mol % $Pd(OAc)_2$, 15 mol % **L**, 100 °C (80 °C for entry 7). [b] % yields refer to isolated and purified products. [c] Product was not isolated, but extent of reaction was estimated by TLC. [d] Heating beyond 12 h seemed to produce byproducts, as visualized on TLC; product not isolated. [e] Reaction conditions: bromonucleoside (**1**) 0.05 M in anhydrous toluene, 1.5 molar equiv phenylboronic acid, 1.25 molar equiv powdered anhydrous K_2CO_3, 25 mol % $Pd(PPh_3)_4$.

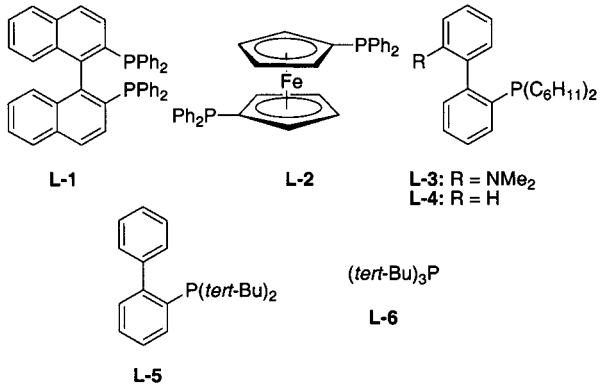


Figure 2. Structures of commercially available or readily synthesized phosphine ligands that are potentially useful for C−C and C−N bond-forming reactions of nucleosides.

purine (**1**), can be conveniently synthesized on the multigram scale by a diazotization-bromination.[22] In the recent literature, two palladium reagents have been successfully used for Suzuki−Miyaura reactions on simple systems; these are $Pd(OAc)_2$ and $Pd_2(dba)_3$. On the basis of the relative costs of the two reagents as well as the results of a recent study[27] that suggested the superiority of $Pd(OAc)_2$ over $Pd_2(dba)_3$, the former was chosen for detailed investigation. In addition, the recently described beneficial influence of the acetate counter-ion in Pd-catalyzed Heck reactions as well as other cross-couplings further justified the choice of $Pd(OAc)_2$.[28] In contrast to the limited number of Pd reagents, a large assortment of ligands is available (Figure 2).[29] Therefore, choice of the catalytic system posed a significant number of possibilities. To simplify the identification of a generally applicable catalytic system, we chose to perform the initial optimization experiments using **1** and phenylboronic acid. Table 1 lists the results of these initial experiments.

From these data, several points are worth specific mention. In every case, the ratio of phosphine:Pd was 1.5:1. Thus, formation of bis-coordinated, 1:1 Pd(0)−ligand complexes would be a significant likelihood only in the case of ligands **L-1**, **L-2**, and **L-3** through intramolecular P,P−Pd or P,N−Pd linkages. In contrast, ligands **L-4**, **L-5**, and **L-6** are mono-coordinating, and any bis-coordinated Pd(0) intermediate would arise as a consequence of two phosphine ligands per Pd. Evident from Table 1 is the fact that the combination of **L-4**/$Pd(OAc)_2$/K_3PO_4 (entry 4) was superior to all others tested, resulting in a 91% isolated yield of **4a**. The $(Ph_3P)_4Pd$/anhydrous K_2CO_3 system (entry 9), which is similar to that recently reported in Suzuki−Miyaura reactions of nucleosides, provided approximately comparable results, but required a longer reaction time.[15a,30] Interestingly, **L-5**, which is similar to but sterically bulkier than **L-4**, was relatively ineffective, with only ~50% product formation after 48 h (entry 5). Similar results (~50% product formation after 48 h) were obtained with (*t*-Bu)$_3$P (**L-6**, entry 6), a ligand that has otherwise found admirable use in simpler systems.[20,26] We have recently shown that ligand **L-3**, which differs from **L-4** by only the dimethylamino moiety, was highly effective for C−N bond formation at the C-6 position of deoxynucleosides.[22] However, in the present case, **L-3** proved to be less effective as compared to **L-4** in both time for the reaction to attain completion and the ensuing product yield (entry 3). In addition, in the case of **L-3**, when the higher-boiling 1,4-dioxane was replaced with 1,2-DME (1,2-dimethoxyethane, the solvent used in C−N bond-forming reactions), the reaction did not progress to completion, and degradation seemed to set in upon prolonged heating. The system **L-2**/$Pd(OAc)_2$/K_3PO_4 was also quite effective, with a relatively short reaction time, but produced a lower product yield (entry 2) than the **L-4**/$Pd(OAc)_2$/K_3PO_4 system. Use of $Pd_2(dba)_3$ in combination with **L-2** and K_3PO_4 provided what appeared to be a fast reaction with a slightly lower isolated yield of **4a** (80%, entry 8).

On the basis of the optimization experiments carried out using unsubstituted phenylboronic acid, the next step was the utiliza-

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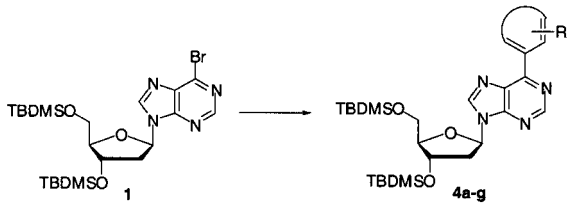
(30) In the studies described in ref 15, anhydrous K_2CO_3 has been used for the cross-coupling of hydrolytically labile compounds. On the other hand, the reactions were observed to be faster with aqueous K_2CO_3 (ref 15a). To avoid complications, such as hydrolysis of the bromonucleoside or protecting group degradation, we employed anhydrous K_2CO_3.

Table 2. Synthesis of C-6 Aryl 2′-Deoxynebularine Derivatives **4a**−**g** Using Bromonucleoside **1**[a]



entry	arylboronic acid	time, h[b]	product	%yield[c]
1	phenylboronic acid	1	**4a**	91
2	4-methoxyphenylboronic acid	1.5	**4b**	69
3	3-methoxyphenylboronic acid	1	**4c**	73
4	2-ethoxyphenylboronic acid[d]	19.5	**4d**	62
5	3-nitrophenylboronic acid	1.5	**4e**	59
6	4-acetylphenylboronic acid	8.5	**4f**	49
7	3-thiopheneboronic acid	6	**4g**	58

[a] Reaction conditions: bromonucleoside (**1**) 0.15 M in anhydrous 1,4-dioxane, 1.5 molar equiv arylboronic acid, 2 molar equiv K_3PO_4, 10 mol %, $Pd(OAc)_2$, 15 mol % **L-4**, 100 °C. [b] Reactions were monitored by TLC for complete disappearance of **1** and are approximate values. [c] Isolated and purified products. [d] In this case, 3 molar equiv of 2-ethoxyphenylboronic acid was used.

tion of the method for the synthesis of an assortment of arylnucleosides having different substituents on the aryl moiety. Thus, a selection of arylboronic acids bearing either electron-withdrawing or electron-donating substituents was made so as to evaluate the overall utility of the process for the generation of the modified nucleosides. Such a detailed investigation, to our knowledge, has not been reported in the literature for nucleosides. Table 2 shows the phenylboronic acids used and the yields of the C-6 arylnucleosides **4a**−**g**.

From the data in Table 2, it is apparent that arylboronic acids with electron-withdrawing groups seem to return lower product yields, as compared to the remaining substituted boronic acids. This type of a trend, though not evident in recent reports of Suzuki−Miyaura cross-couplings in relatively simpler systems,[17,20] has been observed in the arylation at the C-6 position of a chloropurine precursor.[15a,b] As described later in this paper, the low-yield problem can be resolved, and substantial yield improvements can be attained.

The coupling with 2-ethoxyphenylboronic acid presented an interesting case. In the reaction of this arylboronic acid, use of 10 mol % $Pd(OAc)_2$ and 15 mol % **L-4** resulted in incomplete reaction even after 67 h, and the product yield from this reaction was 31%. Replacement of **L-4** with **L-3** under otherwise identical conditions also resulted in incomplete reaction after 77 h. In an attempt to achieve complete conversion in a reasonable period and in better yield, we rationalized increasing the concentration of the catalytic system. When 30 mol % $Pd(OAc)_2$ and 45 mol % **L-4** were employed, the reaction was complete within 20 h; however, the isolated product yield was only 13%. Since this result was somewhat unexpected, a second alternative was attempted. Increasing the molar equivalence of 2-ethoxyphenylboronic acid from 1.5 to 3 resulted in a complete reaction within 20 h with a 62% isolated yield of **4d**. Although we cannot be certain about the reasons for this behavior, it is conceivable that complexes such as those shown in Figure 3 are responsible for the observed results. Such complexes could potentially contribute to degradation of the catalytic system, leading to termination of the catalytic cycle, causing product degradation by processes such as deglycosylation, or both, etc., leading to lowered yields. In the absence of a direct precedent for the formation of these complexes in the Suzuki−Miyaura reaction, some understanding can be garnered from studies on

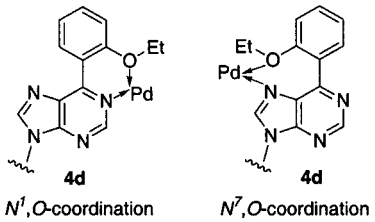


Figure 3. Two possible structures of compound **4d** with coordinated Pd.

nucleoside complexes of Pd(II). Pd(II), a class B or "soft" metal, prefers coordination with nitrogen donor atoms (N^1 and N^7) of the purine nucleobases,[31,32] and purine nucleosides in their basic form have been shown to bind Pd(II) at both sites, with a preference for N^1-binding.[33] Thus, it is plausible that **4d** could compete with the ligand for coordination to Pd utilizing the O on the aryl moiety and either the N^1 or N^7 of the purine (Figure 3). This is similar to the belief that formation of bis indolyl Pd(II) complexes is responsible for low yields in some C−N bond-forming reactions of indoles.[34] Support for our rationale is also obtained from the fact that 2-tolylboronic acid, in contrast to 2-ethoxyphenylboronic acid, couples rather smoothly with a 6-chloropurine ribonucleoside precursor.[15b] On the other hand, synthesis of biphenyls with more than one ortho substituent is generally problematic,[17] and it is conceivable that the prevailing reasons are also the causes of the anomalous reaction with 2-ethoxyphenylboronic acid.

In contrast to **4d**, placement of the alkoxy groups at the para or meta positions on the aryl ring dispenses with the bis coordinating ability of the products, because the alkoxy groups are more remote from the N^7 and N^1 sites. Alternatively, any steric conflicts are also diminished. Correspondingly, reactions leading to the 4- and 3-methoxyphenyl nucleosides (**4b** and **4c**) are rapid (1−1.5 h), and good product yields are obtained with 1.5 molar equiv of the respective boronic acids (Table 2, entries 2 and 3).

(b) Utility of Chloronucleoside 2 for Suzuki−Miyaura Cross-Coupling. With the experiments described above, the generality of Pd catalysis for the synthesis of C-6 arylated purine 2′-deoxyribosides from a bromonucleoside precursor had been established, as well as an understanding of the optimal catalytic system for the process. However, the fact that chloropurine derivatives were efficient substrates in Suzuki−Miyaura reactions was interesting to us.[15] Ni-promoted cross-coupling of boronic acids with aryl chlorides has been quite useful for C−C bond formation in relatively simple systems,[35] and a modestly yielding Ni-catalyzed synthesis of C-6 phenyl nebularine has been reported.[36] On the other hand, highly effective Pd catalysts for Suzuki−Miyaura reactions involving chloroaromatics that provide consistent results have only recently been identified.[16−21,37] On the basis of these reasons, an evaluation of the utility of **2**

(31) Kazakov, S. A. In *Bioorganic Chemistry: Nucleic Acids*; Hecht, S. M., Ed.; Oxford University Press: New York, 1996; Chapter 9, pp 244−287.

(32) Although N^3 could also be a potential coordination site, steric hindrance by the sugar is thought to preclude coordination here.[31]

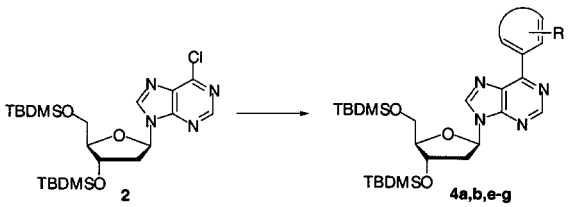
(33) Martin, R. B. In *Metal Ions in Biological Systems*; Sigel, A., Sigel, H., Eds.; Marcel Dekker: New York, 1996; Vol. 32, Chapter 3, pp 61−89.

(34) (a) Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030−3039. (b) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403−1406.

(35) For examples, please see: (a) Saito, S.; Oh-tani, S.; Miyaura, N. *J. Org. Chem.* **1997**, *62*, 8024−8030. (b) Lipshutz, B. H.; Sclafani, J. A.; Blomgren, P. A. *Tetrahedron* **2000**, *56*, 2139−2144. (c) Galland, J.-C.; Savignac, M.; Genêt, J.-P. *Tetrahedron Lett.* **1999**, *40*, 2323−2326.

(36) Bergstrom, D. E.; Reddy, P. A. *Tetrahedron Lett.* **1982**, *23*, 4191−4194.

Table 3. Synthesis of Five C-6 Aryl 2′-Deoxynebularine Derivatives Using Chloronucleoside **2**[a]



entry	arylboronic acid	time, h[b]	product	%yield[c]
1	phenylboronic acid	1.5	**4a**	93
2	4-methoxyphenylboronic acid	1.5	**4b**	83
3	3-nitrophenylboronic acid	1.5	**4e**	84
4	4-acetylphenylboronic acid	1.5	**4f**	84
5	3-thiopheneboronic acid	8	**4g**	74

[a] Reaction conditions: chloronucleoside (**2**) 0.15 M in anhydrous 1,4-dioxane, 1.5 molar equiv arylboronic acid, 2 molar equiv K_3PO_4, 10 mol % $Pd(OAc)_2$, 15 mol % **L-4**, 100 °C. [b] Reactions were monitored by TLC for complete disappearance of **2** and are approximate values. [c] Isolated and purified products.

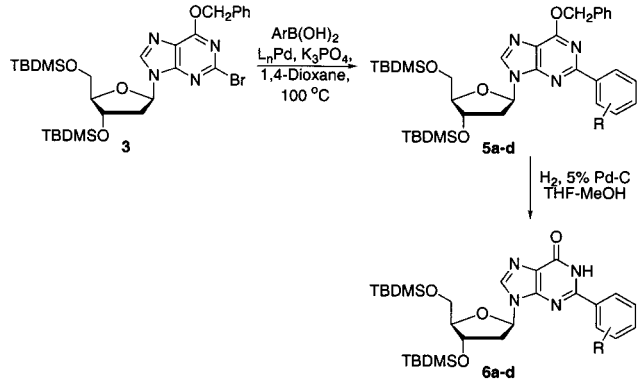
(prepared in three steps from 2′-deoxyinosine[23]) in the Suzuki−Miyaura coupling reactions was warranted.

Again, as an initial test, **2** was subjected to cross-coupling with phenylboronic acid using the optimized catalytic system [$Pd(OAc)_2$, **L-4**, K_3PO_4] under the conditions described above (1,4-dioxane, 100 °C). However, one change was incorporated into the procedure, which was premixing the $Pd(OAc)_2$ and **L-4**. This was done largely because of its reported beneficial effect on C−N bond formation,[27] as well as the possibly lower reactivity of chloroaromatic **2**, as compared to the bromoaromatic **1,** under Pd-catalyzed conditions (it should be noted that **2** possesses higher reactivity under S_NAr displacement conditions). The reaction of **2** with phenylboronic acid proved to be very facile, attaining completion within 1.5 h with a 93% isolated yield of **4a**. On the basis of this result, we decided to investigate the reaction of **2** with other boronic acids, particularly those that provided lower yields in their reaction with **1**. Table 3 shows the results that were obtained in the cross-coupling of four substituted boronic acids with **2**.

Clear from Table 3 is the fact that C-6 aryl nucleosides can be obtained by Suzuki−Miyaura reactions of the chloronucleoside **2** with arylboronic acids. Also indicated by the results, is that in many cases, the product yields from this precursor may, in fact, be superior to those obtained by utilizing the bromonucleoside **1**. To evaluate whether premixing $Pd(OAc)_2$ and **L-4** had any effect on the rate or yield of a reaction involving bromonucleoside **1**, a single cross-coupling reaction of **1** with 3-nitrophenylboronic acid was attempted. With the premixed catalyst, the reaction was complete within ∼1 h but the isolated yield of **4e** was 56% (which is comparable to the 59% obtained without premixing), indicating no particular advantage to premixing the catalyst when **1** was employed for these reactions.

A point that is significant to note is that our results with chloronucleoside **2** contrast with recent observations, which report that arylboronic acids with electron-withdrawing groups do not provide satisfactory yields of the cross-coupled products.[15b] In one study, the yield of 6-(3-nitrophenyl)-9-benzylpurine from a cross-coupling involving 3-nitrophenyboronic acid has been reported as 19% (in 48 h under nonaqueous conditions) and 66% (in 7 h using aqueous K_2CO_3).[15a] In our case, the yield of **4e** was 84% (reaction complete within 1.5 h under nonaqueous conditions). Further, 4-acetylphenylboronic acid provided a gratifying cross-coupling with **2** (84% yield), although a modest 49% yield of **4f** was realized from **1**, as well. Thus, our results demonstrate that arylboronic acids with electron-withdrawing substituents not only couple with both halo precursors **1** and **2**, but they do so rapidly and efficiently when chloronucleoside **2** is utilized.

Scheme 1



From the foregoing experiments, the effectiveness of Pd catalysis for the synthesis of C-6 aryl 2′-deoxynebularines is clear. In addition, both halonucleosides **1** and **2** undergo Suzuki−Miyaura cross-coupling reactions, with the caveat that the chloro precursors may be more suitable in some cases. Introduction of aryl moieties at the C-2 position of nucleosides became our next consideration.

Synthesis of C-2 Aryl 2′-Deoxyinosine Derivatives. Although Pd-catalyzed C−C bond-forming reactions at the 2-position of an O^6-protected inosine (a ribonucleoside) have been carried out using a C-2 iodo precursor, these have been largely Heck and Stille cross-couplings.[38] To our knowledge, there are no studies utilizing the Suzuki−Miyaura reaction, and more importantly, there are no reports of C−C bond formation using Pd catalysis on the more labile 2′-deoxyribonucleosides.

A simple reaction protocol for the synthesis of C-2 aryl 2′-deoxyinosine analogues is shown in Scheme 1. The synthesis of **3** from 2′-deoxyguanosine has been reported in the literature,[24] and it is easily prepared on the multigram scale. As in the case of C-6 modification, initial experimentation involved the Pd-catalyzed cross-coupling of **3** with phenylboronic acid using conditions that had been optimized for the generation of the C-6 aryl 2′-deoxynebularine derivatives. Under the cross-coupling conditions, the C-2 phenyl O^6-benzyl-2′-deoxyinosine derivative **5a** was obtained in 87% yield within 1 h. The cross-coupling of **3** and phenylboronic acid was briefly investigated using another catalytic system; $Pd(OAc)_2$/**L-1**/Cs_2CO_3 (0.1, 0.15, and 2 molar equiv, respectively). Under these conditions, although **5a** was obtained in 84% yield, the reaction time appears to be longer (∼10 h, unoptimized). Given the overall superiority and generality of the $Pd(OAc)_2$/**L-4**/K_3PO_4 system for C−C bond formation at both the C-6 and the C-2 positions, further reactions on **3** were performed with this combination. Because the final step in the synthesis of 2-aryl 2′-deoxyinosine derivatives involves a catalytic hydrogenolysis of the benzyl group, boronic acids in which the substituents would not pose problems in the reduction step were selected. However, reactions with boronic acids bearing electron-donating and electron-withdrawing groups were studied in order to assess the ease and generality of the reaction. Table 4 shows the yields for the

(37) Bei, X.; Turner, H. W.; Weinberg, W. H.; Guram, A. S.; Peterson, J. L. *J. Org. Chem.* **1999**, *64*, 6797−6803.

(38) (a) Nair, V.; Turner, G. A.; Chamberlain, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 7223−7224. (b) Nair, V.; Turner, G. A.; Buenger, G. S.; Chamberlain, S. D. *J. Org. Chem.* **1988**, *53*, 3051−3057.

Table 4. Two-Step Synthesis of C-2 Aryl 2′-Deoxinosine Derivatives **6a**−**d**[a,b,c]

entry	arylboronic acid	time h[d]	step 1: compd, % yield[e]	step 2: compd, % yield[e,f]
1	phenylboronic acid	1	**5a**, 87	**6a**, 84
2	4-methoxyphenylboronic acid	6	**5b**, 67	**6b**, 86
3	3-methoxyphenylboronic acid	4	**5c**, 78	**6c**, 93
4	4-acetylphenylboronic acid	1.25	**5d**, 80	**6d**, 70

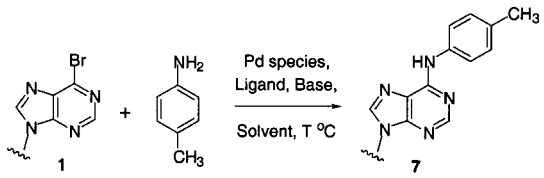
[a] Step 1, cross-coupling. [b] Step 2, removal of the O^6-benzyl group. [c] Reaction conditions for step 1: bromonucleoside (**3**) 0.13 M in anhydrous 1,4-dioxane, 1.5 molar equiv arylboronic acid, 2 molar equiv K_3PO_4, 10 mol % $Pd(OAc)_2$, 15 mol % **L-4**, 100 °C. [d] Step 1 reactions were monitored by TLC for complete disappearance of **3** and are approximate values. [e] Isolated and purified products. [f] Reaction conditions for step 2: products **5a**−**d** were reduced with 5% Pd−C in 1:1 THF-MeOH at room temperature and 1 atm of H_2.

cross-coupling (step 1, leading to **5a**−**d**) as well as for the hydrogenolysis (step 2, leading to **6a**−**d**). In each case, step 1 proceeded smoothly, in good yield, and step 2 yielded the final products uneventfully.

C−C versus C−N Bond Formation at the C-6 Position of Purine Deoxynucleosides. In this report, we have clearly demonstrated the facile manner in which Suzuki−Miyaura reactions can be accomplished at the C-6 and C-2 positions of purine 2′-deoxynucleosides under anhydrous conditions. In contrast to C−C bond formation, C−N bond formation at the C-6 and C-2 positions of purine deoxynucleosides has been investigated to a greater extent in the recent past by us[22] and others.[24,39] It would, therefore, be interesting and instructive to compare the catalytic systems involved in successful C−C and C−N bond formations with a view to understanding the requirements imposed on the catalytic systems in each case. Quite clearly evidenced in this study, a variety of ligand−Pd complexes are effective in the cross-coupling of **1** with phenylboronic acid in yields ranging from 67 to 91%. In contrast to this, efficient C−N bond formation at the C-6 position appears to depend much more on the catalytic system that is used. Significantly, our studies show that reactions involving the bis coordinating ligands **L-1**, **L-2**, and **L-3** generally produce faster reactions, as compared to the mono-coordinating ligands **L-4** and **L-5** (compare, for example, entries 1−3 as well as 6−8 to entries 10 and 12 in Table 5). Whereas the mono-coordinating **L-4** led to a complete reaction in 20 h, use of **L-5**, which has *t*-Bu instead of cyclohexyl residues on the phosphorus, resulted in incomplete conversion within the same duration (entries 10 and 12 in Table 5). Catalytic systems **L-1**/$Pd_2(dba)_3$/Cs_2CO_3, **L-2**/$Pd_2(dba)_3$/Cs_2CO_3, and **L-3**/$Pd_2(dba)_3$/K_3PO_4 provided reasonably good yields (62−69%); however, the use of **L-1** and **L-2** resulted in products that were somewhat more darkly colored than that produced with **L-3**, although the ^{1}H NMR spectra of the products obtained in each case indicated no impurities to account for the coloration. Use of K_3PO_4 in conjunction with **L-1** or **L-2** in 1,2-DME prolonged the reaction time, leading to **7** in only 31−33% yield. Changing the 1:3 ratio of $Pd_2(dba)_3$ to ligand or lowering catalyst loading in reactions involving **L-1** and **L-3** led to complete reaction rapidly, albeit in lower yield. It is noteworthy, however, that 5 mol % $Pd_2(dba)_3$/15 mol % **L-3** resulted in an ∼50% yield of **7**, as compared to the 69% yield obtained with 10 mol % $Pd_2(dba)_3$/30 mol % **L-3**, within 3 h. Thus, in our experience a 10 mol % $Pd_2(dba)_3$/30 mol % **L-3** combination is optimal for the synthesis of N^6-aryl 2′-deoxyadenosine analogues using K_3PO_4 as base.

(39) (a) De Riccardis, F.; Bonala, R. R.; Johnson, F. *J. Am. Chem. Soc.* **1999**, *121*, 10453−10460. (b) De Riccardis, F.; Johnson, F. *Org. Lett.* **2000**, *2*, 293−295. (c) Bonala, R. R.; Shishkina, I. G.; Johnson, F. *Tetrahedron Lett.* **2000**, *41*, 7281−7284.

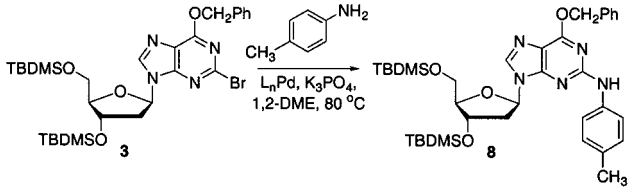
Table 5. Results of C−N Bond Formation at the C-6 Position with Various Catalytic Systems[a]



entry	Pd species (mol %)	ligand (mol %)	base	solvent	T, °C	time, h[b]	% yield[c]
1	$Pd_2(dba)_3$ (10)	**L-1** (30)	Cs_2CO_3	PhMe	100	2	63
2	$Pd_2(dba)_3$ (10)	**L-1** (20)	Cs_2CO_3	PhMe	100	2.5	54
3	$Pd_2(dba)_3$ (5)	**L-1** (10)	Cs_2CO_3	PhMe	100	3	39
4	$Pd_2(dba)_3$ (10)	**L-1** (30)	K_3PO_4	1,2-DME	80	24	31
5	$Pd(OAc)_2$ (5)	**L-1** (10)	Cs_2CO_3	PhMe	70	12	33
6	$Pd_2(dba)_3$ (10)	**L-2** (30)	Cs_2CO_3	PhMe	100	7	62
7	$Pd_2(dba)_3$ (10)	**L-2** (30)	K_3PO_4	1,2-DME	80	9	33
8	$Pd_2(dba)_3$ (10)	**L-3** (30)	K_3PO_4	1,2-DME	80	3	69
9	$Pd_2(dba)_3$ (5)	**L-3** (15)	K_3PO_4	1,2-DME	70	3	49
10	$Pd_2(dba)_3$ (10)	**L-4** (30)	K_3PO_4	1,2-DME	80	19	28
11	$Pd_2(dba)_3$ (10)	**L-4** (12)	K_3PO_4	1,2-DME	80	20	Inc.
12	$Pd_2(dba)_3$ (10)	**L-5** (30)	K_3PO_4	1,2-DME	80	20	Inc.

[a] Reactions were performed essentially as described in ref 22. [b] Reactions were monitored by TLC for complete disappearance of **1** and are approximate values. [c] Isolated and purified products.

Scheme 2



These reactions also indicate that bis-coordinating ligands are generally significantly better in effecting the arylamination of **1**, and this is a striking contrast to the Suzuki−Miyaura cross-coupling reactions involving **1**.

C−C versus C−N Bond Formation at the C-2 Position of Purine Deoxynucleosides. General methods for C−N bond formation at the C-2 position of purine deoxynucleosides utilizing **3** for the cross-couplings have been reported in the literature.[24,39c] The report by Hopkins and co-workers describes the use of $Pd_2(dba)_3$/*t*-BuONa, whereas Johnson and colleagues have utilized the $Pd(OAc)_2$/Cs_2CO_3 combination;[24,39c] however, both reports describe reactions involving either (±)- or (+)-**L-1** as the ligand. Yields for the arylamination in both studies are good, although only one arylamination is reported in ref 39c.

A particularly important question that arose was whether a high ligand dependence would be observed in the arylamination of **3,** as was seen in the case of **1**, and for the reasons explained later, our initial hypothesis was that this would not be the case. Given the known success of the $Pd_2(dba)_3$/*t*-BuONa/**L-1** as well as the $Pd(OAc)_2$/Cs_2CO_3/**L-1** system,[24,39c] we decided to investigate only the efficiency of the bis-coordinating ligand **L-3** to that of the mono-coordinating ligand **L-4**, again using *p*-toluidine as a model amine for this purpose (Scheme 2).

Therefore, two parallel C−N bond-forming reactions were conducted using conditions described for the amination of **1**, where one reaction involved use of **L-3** and the other, **L-4**. Consistent with our expectation, both reactions were complete quite rapidly (within 3 h), and the isolated yields of **8** were also comparable (75% using **L-3** and 65% using **L-4**). Thus, it is quite clear that C−N bond-forming reactions at the C-2

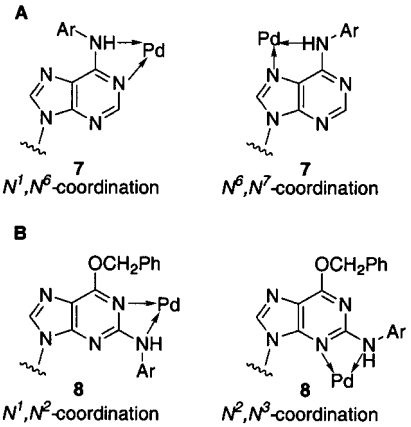


Figure 4. Panel A: two possible structures of C-6 aminoaryl nucleosides with coordinated Pd. Panel B: two possible structures of C-2 aminoaryl nucleosides with coordinated Pd.

position are not quite so dependent on the ability of a ligand to bis-coordinate, although a slightly better yield was obtained with the bis-coordinating **L-3**. The yields in these two reactions also compare favorably with yields obtained for other arylamination reactions on **3** using $Pd_2(dba)_3$/(+)-**L-1**/*t*-BuONa but involve the use of a much milder base.[24] This factor will be significant when the use of either *t*-BuONa or Cs_2CO_3 is precluded. An important point to note is that in contrast to the reported efficient arylaminations of **3** with *t*-BuONa as base,[24] we have observed that arylamination of **1** with *p*-toluidine in the presence of *t*-BuONa proceeds at room temperature, and modest product formation is accompanied by significant amounts of uncharacterized byproducts.

One possible explanation for the differences observed in reactions at the C-6 and the C-2 position has to do with the competition of the product with the ligand for coordination with the palladium, thereby lowering throughput. Structures of possible Pd-chelated nucleosides that could be produced in C−N bond-forming reactions are shown in Figure 4. In each of these structures, there can be N,N bis-coordination of the product with Pd. As alluded to earlier, studies on palladium−nucleoside complexes indicate that the N^1 and N^7 are most probable coordination sites, with N^3 usually being considered a disfavored site.[31−33] On the basis of these reasons, as well as the fact that five-membered palladacycles are preferred over the four-membered ones,[40] the N^6,N^7-coordinated complex is a plausible species that can be produced in C−N bond-forming reactions at the C-6 position of purines. Ligands that more effectively sequester the palladium and prevent Pd coordination with the product are, therefore, more likely to be effective in C−N bond formation at the C-6 position. Thus, the bis-coordinating ligands, such as **L-1**, **L-2**, and **L-3**, provide efficient conversion in the amination reaction at this site. On the basis of the same rationale, C−N bond formation at the C-2 position should be less ligand-dependent. Our observations are, in fact, consistent with this, and both the mono- and the bis-coordinating ligands (**L-3** and **L-4**) provide comparable results.

Conclusions

In this study, the applicability of palladium catalysis to effect arylation at the C-6 and C-2 positions of purine deoxynucleosides via the Suzuki−Miyaura protocol has been demonstrated. Whereas the C-6 bromonucleoside **1** is a convenient starting point in most cases, providing good yields of arylated products, the C-6 chloronucleoside **2** proved to be superior as compared with **1** in certain cross-coupling reactions. Thus, both C-6 halonucleosides can be used in a complementary manner for C−C bond-forming reactions. In reactions involving modification at the C-2 position, four boronic acids were studied, and in each case, good cross-coupling yields were obtained using the O^6-benzyl-2-bromo-2′-deoxyinosine derivative **3**; however, the boronic acids used in the Suzuki−Miyaura reactions with **3** were limited to those in which the substituent would not cause complications during the hydrogenolytic deprotection of the O^6. A remedy to this potential problem with some boronic acids is the use of a different protecting group at the O^6. Examples include the 2-cyanoethyl and the 4-nitrophenylethyl groups, both of which can be readily cleaved under basic conditions.[41]

Comparison of the C−C and C−N bond-forming reactions at C-6 and C-2 of purine deoxynucleosides provides some interesting results. C−C bond formation at the C-6 position is relatively independent of the ligand used, and with the exception of ligands containing *tert*-butyl groups (**L-5** and **L-6**), both mono- and bis-coordinating ligands provide complete reactions with good to high yields. In contrast, C−N reactions at the C-6 position are more ligand-dependent, with bis-coordinating ligands being effective, among which **L-3** is the best in our experience. In comparison to C−N bond formation at the C-6 position, similar reactions at the C-2 position are less sensitive to the ligand used, with both the mono-coordinating **L-4** and the bis-coordinating **L-3** producing complete reactions in good yields. Thus, among nucleosides, modification at C-6 can potentially be more difficult if a coordinating moiety is introduced at C-6. On the other hand, this may not be the case for C-2 modification, and reactions at this site may be simpler to achieve. Remarkably, despite the potential multiple coordination sites in purine deoxynucleosides, Pd-catalyzed reactions with these compounds are quite effective in constructing hitherto unknown and unusual nucleosides for exploring new avenues on modified DNA. The method described in this report complements known reactions of nucleosides and enables the development of products that are not readily attainable otherwise. Further studies on Pd catalysis within the domain of nucleoside and DNA modification are currently being explored in our laboratories.

Experimental Section

The arylboronic acids, palladium(II)acetate [$Pd(OAc)_2$], tris(dibenzylidineacetone)dipalladium [$Pd_2(dba)_3$], ligands **L-1**, **L-2**, **L-4**, **L-5**, **L-6**, Cs_2CO_3, K_3PO_4, and anhydrous 1,2-dimethoxyethane (1,2-DME), as well as 5% Pd on C, were purchased from commercial sources and were used without additional purification. Ligand **L-3** was synthesized as previously reported.[16] The catalysts and ligands were stored under N_2 in a desiccator at 0 °C and the bases were stored under N_2 in a desiccator at room temperature. For each cross-coupling, 1,4-dioxane was distilled from $NaBH_4$ just prior to performing the reaction, whereas THF used for catalytic reduction was distilled from $LiAlH_4$. The halonucleosides **1**, **2**, and **3** were synthesized as described.[22−24] Reactions were monitored by TLC (silica gel, 250 μ), and column chromatographic purifications were performed on 200−300 mesh silica gel. Solvents used for eluting the compounds, as well as TLC conditions and R_f values, are provided under individual compound headings. Proton

(40) (a) Kočovský, P.; Vyskočil, Š.; 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) Newkome, G. R.; Puckett, W. E.; Gupta, V. K.; Kiefer, G. E. *Chem. Rev.* **1986**, *86*, 451−489. (c) Zhang, L.; Zetterberg, K. *Organometallics* **1991**, *10*, 3806−3813.

(41) For removal of the 2-cyanoethyl group, please see: (a) Gaffney, B. L.; Jones, R. A. *Tetrahedron Lett.* **1982**, *23*, 2257−2260. (b) Beaucage, S. L.; Iyer, R. P. *Tetrahedron* **1992**, *48*, 2223−2311. For removal of the 4-nitrophenylethyl group, please see: Trichtinger, T.; Charubala, R.; Pfleiderer, W. *Tetrahedron Lett.* **1983**, *24*, 711−714.

NMR spectra were obtained at 500 MHz; chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hz.

Typical Procedure for the Coupling of Bromonucleoside 1 with Arylboronic Acids. In an oven-dried, screw-cap vial equipped with a stirring bar were placed $Pd(OAc)_2$ (2 mg, 8.9 μmol), **L-4** (4.8 mg, 13.6 μmol), the boronic acid (1.5 molar equiv), and K_3PO_4 (39 mg, 0.18 mmol). Finally, the bromonucleoside (**1**, 50 mg, 0.092 mmol) was added, followed by the addition of freshly distilled, dry 1,4-dioxane (0.6 mL). The vial was flushed with nitrogen, sealed with a Teflon-lined cap, and placed in a sand bath that was maintained at 100−102 °C. The reactions were monitored by TLC, and upon completion, the reaction mixtures were filtered through Celite. In each case, the residue was washed with CH_2Cl_2 and the filtrate was evaporated to dryness. The products were purified by column chromatography on silica gel using appropriate solvents (listed under individual compound headings, vide infra). Fractions that contained the pure products were combined, evaporated and finally dried under high vacuum to remove traces of solvent.

6-Phenyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxynebularine (4a). Chromatography, CH_2Cl_2, followed by 2% acetone in CH_2Cl_2. Colorless oil, R_f (2% acetone in CH_2Cl_2) = 0.31. ^{1}H NMR ($CDCl_3$): 9.02 (s, 1H, purine-*H*), 8.79−8.77 (m, 2H, Ar-*H*), 8.43 (s, 1H, purine-*H*), 7.60−7.52 (m, 3H, Ar-*H*), 6.59 (t, 1H, 1′, J = 6.5), 4.67 (m, 1H, 3′), 4.07 (app q, 1H, 4′, $J \sim 3.6$), 3.90 (dd, 1H, 5′, J = 4.3, 11.2), 3.81 (dd, 1H, 5′, J = 3.2, 11.2), 2.73 (app sept, 1H, 2′, J = 5.9, 6.9, 13.0), 2.51 (ddd, 1H, 2′, J = 3.7, 6.1, 13.1), 0.94, 0.92 (2s, 18H, C(CH_3)$_3$), 0.13, 0.10, 0.098 (3s, 12H, Si−CH_3). HRMS calcd for $C_{28}H_{44}N_4O_3Si_2Na$ (M^+ + Na), 563.2850. Found, 563.2864.

6-(4-Methoxyphenyl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxynebularine (4b). Chromatography, CH_2Cl_2, followed by 2% acetone in CH_2Cl_2. Colorless oil, R_f (2% acetone in CH_2Cl_2) = 0.11. ^{1}H NMR ($CDCl_3$): 8.96 (s, 1H, purine-*H*), 8.81 (d, 2H, Ar-*H*, J = 9.0), 8.40 (s, 1H, purine-*H*), 7.09 (d, 2H, Ar-*H*, J = 9.0), 6.57 (t, 1H, 1′, J = 6.5), 4.66 (m, 1H, 3′), 4.06 (app q, 1H, 4′, $J \sim 3.6$), 3.91 (s, 3H, OCH_3), 3.89 (dd, 1H, 5′, J = 4.3, 11.2), 3.80 (dd, 1H, 5′, J = 3.2, 11.2), 2.72 (app sept, 1H, 2′, J = 6.0, 6.8, 13.0), 2.50 (ddd, 1H, 2′, J = 3.7, 6.1, 13.0), 0.94, 0.92 (2s, 18H, C(CH_3)$_3$), 0.13, 0.10, 0.098 (3s, 12H, Si−CH_3). HRMS calcd for $C_{29}H_{46}N_4O_4Si_2Na$ (M^+ + Na), 593.2955. Found, 593.2960.

6-(3-Methoxyphenyl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxynebularine (4c). Chromatography, CH_2Cl_2. Yellow oil, R_f (CH_2Cl_2) = 0.38. ^{1}H NMR ($CDCl_3$): 9.01 (s, 1H, purine-*H*), 8.44 (s, 1H, purine-*H*) overlaps with (br d, 1H, Ar-*H*, J = 7.0), 8.36 (br s, 1H, Ar-*H*), 7.49 (t, 1H, Ar-*H*, J = 8.0), 7.09 (dd, 1H, Ar-*H*, J = 2.7, 8.2), 6.59 (t, 1H, 1′, J = 6.5), 4.67 (m, 1H, 3′), 4.07 (app q, 1H, 4′, $J \sim$ 3.5), 3.95 (s, 3H, OCH_3), 3.90 (dd, 1H, 5′, J = 4.1, 11.2), 3.81 (dd, 1H, 5′, J = 3.2, 11.2), 2.72 (app quint, 1H, 2′, $J \sim 6.3$), 2.51 (ddd, 1H, 2′, J = 3.8, 5.9, 13.0), 0.94, 0.91 (2s, 18H, C(CH_3)$_3$), 0.13, 0.10 (2s, 12H, Si−CH_3). HRMS calcd for $C_{29}H_{46}N_4O_4Si_2Na$ (M^+ + Na), 593.2955. Found, 593.2957.

6-(2-Ethoxyphenyl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxynebularine (4d). Chromatography, 2% acetone in CH_2Cl_2. Yellow oil, R_f (2% acetone in CH_2Cl_2) = 0.12. ^{1}H NMR ($CDCl_3$): 9.03 (s, 1H, purine-*H*), 8.34 (s, 1H, purine-*H*), 7.64 (dd, 1H, Ar-*H*, J = 1.7, 7.5), 7.45 (dt, 1H, Ar-*H*, J = 1.7, 8.4), 7.10 (t, 1H, Ar-*H*, J = 7.5), 7.07 (d, 1H, Ar-*H*, J = 8.4), 6.58 (t, 1H, 1′, J = 6.6), 4.66 (m, 1H, 3′), 4.12 (q, 2H, OCH_2, J = 7.0), 4.06 (app q, 1H, 4′, $J \sim 3.6$), 3.90 (dd, 1H, 5′, J = 4.3, 11.2), 3.80 (dd, 1H, 5′, J = 3.3, 11.2), 2.76 (app sept, 1H, 2′, J = 5.6, 7.0, 13.0), 2.48 (ddd, 1H, 2′, J = 3.5, 6.0, 13.0), 1.24 (t, 3H, CH_3, J = 7.0), 0.94, 0.91 (2s, 18H, C(CH_3)$_3$), 0.13, 0.09, 0.08 (3s, 12H, Si−CH_3). HRMS calcd for $C_{30}H_{49}N_4O_4Si_2$ (M^+ + H), 585.3292. Found, 585.3286.

6-(3-Nitrophenyl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxynebularine (4e). Chromatography, 1% acetone in CH_2Cl_2. Off-white solid, R_f (1% acetone in CH_2Cl_2) = 0.37. ^{1}H NMR ($CDCl_3$): 9.74 (t, 1H, Ar-*H*, J = 1.9), 9.23 (td, 1H, Ar-*H*, J = 1.3, 7.9), 9.06 (s, 1H, purine-*H*), 8.53 (s, 1H, purine-*H*), 8.38 (ddd, 1H, Ar-*H*, J = 1.0, 2.3, 8.2), 7.75 (t, 1H, Ar-*H*, J = 8.0), 6.60 (t, 1H, 1′, J = 6.4), 4.68 (m, 1H, 3′), 4.08 (app q, 1H, 4′, $J \sim 3.4$), 3.91 (dd, 1H, 5′, J = 4.1, 11.2), 3.82 (dd, 1H, 5′, J = 3.1, 11.2), 2.72 (app quint, 1H, 2′, $J \sim 5.9$), 2.53 (ddd, 1H, 2′, J = 3.9, 6.1, 13.1), 0.94, 0.93 (2s, 18H, C(CH_3)$_3$), 0.13, 0.11 (2s, 12H, Si−CH_3). HRMS calcd for $C_{28}H_{43}N_5O_5Si_2Na$ (M^+ + Na), 608.2700. Found, 608.2704.

6-(4-Acetylphenyl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxynebularine (4f). Chromatography, CH_2Cl_2 followed by 2% acetone in CH_2Cl_2. Colorless oil, R_f (2% acetone in CH_2Cl_2) = 0.17. ^{1}H NMR ($CDCl_3$): 9.06 (s, 1H, purine-*H*), 8.91 (d, 2H, Ar-*H*, J = 8.5), 8.50 (s, 1H, purine-*H*), 8.15 (d, 2H, Ar-*H*, J = 8.5), 6.60 (t, 1H, 1′, J = 6.4), 4.67 (m, 1H, 3′), 4.08 (app q, 1H, 4′, $J \sim 3.5$), 3.91 (dd, 1H, 5′, J = 4.1, 11.2), 3.81 (dd, 1H, 5′, J = 3.1, 11.2), 2.72 (app quint, 1H, 2′, $J \sim 6.1$), 2.69 (s, 3H, COCH_3), 2.52 (ddd, 1H, 2′, J = 3.8, 6.1, 13.1), 0.94, 0.92 (2s, 18H, C(CH_3)$_3$), 0.13, 0.11 (2s, 12H, Si−CH_3). HRMS calcd for $C_{30}H_{47}N_4O_4Si_2$ (M^+ + H), 583.3136. Found, 583.3134.

6-(3-Thiopheno)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxynebularine (4g). Chromatography, CH_2Cl_2, followed by 5% EtOAc in CH_2Cl_2. Colorless oil, R_f (5% EtOAc in CH_2Cl_2) = 0.35. ^{1}H NMR ($CDCl_3$): 8.95 (s, 1H, purine-*H*), 8.93 (dd, 1H, Ar-*H*, J = 1.1, 3.1), 8.43 (s, 1H, purine-*H*), 8.29 (dd, 1H, Ar-*H*, J = 1.1, 5.1), 7.46 (dd, 1H, Ar-*H*, J = 3.1, 5.1), 6.57 (t, 1H, 1′, J = 6.4), 4.66 (m, 1H, 3′), 4.06 (app q, 1H, 4′, $J \sim 3.6$), 3.90 (dd, 1H, 5′, J = 4.2, 11.2), 3.80 (dd, 1H, 5′, J = 3.2, 11.2), 2.71 (app quint, 1H, 2′, $J \sim 6.7$), 2.50 (ddd, 1H, 2′, J = 3.9, 6.1, 13.1), 0.94, 0.93 (2s, 18H, C(CH_3)$_3$), 0.13, 0.11 (2s, 12H, Si−CH_3). HRMS calcd for $C_{26}H_{42}N_4O_3SSi_2Na$ (M^+ + Na), 569.2414. Found, 569.2437.

Typical Procedure for the Coupling of Chloronucleoside 2 with Arylboronic Acids. In an oven-dried, screw-cap vial equipped with a stirring bar were placed $Pd(OAc)_2$ (2 mg, 8.9 μmol) and **L-4** (4.8 mg, 13.6 μmol). Freshly distilled, dry 1,4-dioxane (0.6 mL) was added, the vial was flushed with nitrogen and sealed with a Teflon-lined cap, and the mixture was stirred at room temperature for a few minutes. The boronic acid (1.5 molar equivalents), chloronucleoside (**2**, 46.0 mg, 0.092 mmol) and K_3PO_4 (39 mg, 0.18 mmol) were then added to the vial, the vial was again flushed with nitrogen, sealed with a Teflon-lined cap, and placed in a sand bath that was maintained at 100−102 °C. Reactions were monitored by TLC, and upon completion, the reaction mixtures were filtered through Celite. In each case, the residue was washed with CH_2Cl_2, and the filtrate was evaporated to dryness. The products were purified by column chromatography on silica gel using appropriate solvents (described under the individual compound headings, vide supra). Fractions that contained the pure products were combined, evaporated, and finally dried under high vacuum to remove traces of solvent. The ^{1}H NMR spectra of compounds **4a**, **4b**, and **4e**−**g** were identical to those obtained from the bromonucleoside reactions.

Typical Procedure for the Coupling of Bromonucleoside 3 with Arylboronic Acids. In an oven-dried, screw-cap vial equipped with a stirring bar were placed $Pd(OAc)_2$ (1.7 mg, 7.5 μmol), **L-4** (4.0 mg, 11.4 μmol), the boronic acid (1.5 molar equivalents), and K_3PO_4 (39 mg, 0.15 mmol). Finally, the bromonucleoside (**3**, 50 mg, 0.077 mmol) was added, followed by the addition of freshly distilled, dry 1,4-dioxane (0.6 mL). The vial was flushed with nitrogen, sealed with a Teflon-lined cap, and placed in a sand bath that was maintained at 100−102 °C. The reactions were monitored by TLC, and upon completion, the reaction mixtures were filtered through Celite. In each case, the residue was washed with CH_2Cl_2, and the filtrate was evaporated to dryness. The products were purified by column chromatography on silica gel using appropriate solvents (listed under individual compound headings, vide infra). Fractions that contained the pure products were combined, evaporated, and finally, dried under high vacuum to remove traces of solvent.

2-Phenyl-*O*^{6}-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (5a). Chromatography, 2% EtOAc in CH_2Cl_2. Colorless foam, R_f (2% EtOAc in CH_2Cl_2) = 0.31. ^{1}H NMR ($CDCl_3$): 8.50 (dd, 2H, Ar-*H*, J = 1.9, 8.2), 8.22 (s, 1H, purine-*H*), 7.60 (d, 2H, Ar-*H*, J = 7.2), 7.52−7.29 (m, 6H, Ar-*H*), 6.57 (t, 1H, 1′, J = 6.5), 5.81 (AB quart, 2H, OCH_2, J = 12.1), 4.68 (m, 1H, 3′), 4.05 (app q, 1H, 4′, $J \sim$ 3.8), 3.91 (dd, 1H, 5′, J = 4.7, 11.0), 3.81 (dd, 1H, 5′, J = 3.4, 11.0), 2.79 (app quint, 1H, 2′, $J \sim 6.2$), 2.48 (ddd, 1H, 2′, J = 4.0, 6.3, 13.3), 0.95, 0.92 (2s, 18H, C(CH_3)$_3$), 0.14, 0.09 (2s, 12H, Si−CH_3).

2-(4-Methoxyphenyl)-*O*^{6}-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (5b). Chromatography, 5% EtOAc in CH_2Cl_2. Colorless foam, R_f (5% EtOAc in CH_2Cl_2) = 0.49. ^{1}H NMR ($CDCl_3$): 8.45 (d, 2H, Ar-*H*, J = 9.0), 8.19 (s, 1H, purine-*H*), 7.59 (d, 2H, Ar-

H, $J = 7.2$), 7.39−7.36 (m, 2H, Ar-*H*), 7.33−7.31 (m, 1H, Ar-*H*), 7.01 (d, 2H, Ar-*H*, $J = 9.0$), 6.56 (t, 1H, 1′, $J = 6.5$), 5.78 (AB quart, 2H, OCH_2, $J = 12.3$), 4.67 (m, 1H, 3′), 4.04 (app q, 1H, 4′, $J \sim 3.9$), 3.90 (s, 3H, OCH_3), 3.89 (dd, 1H, 5′, $J = 4.6, 11.0$), 3.81 (dd, 1H, 5′, $J = 3.4, 11.0$), 2.77 (app quint, 1H, 2′, $J \sim 6.2$), 2.46 (ddd, 1H, 2′, $J = 3.8, 6.2, 13.2$), 0.95, 0.92 (2s, 18H, C(CH_3)$_3$), 0.14, 0.094, 0.092 (3s, 12H, Si−CH_3).

2-(3-Methoxyphenyl)-*O*^{6}-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (5c). Chromatography, 1% EtOAc in CH_2Cl_2. Colorless oil, R_f (2% EtOAc in CH_2Cl_2) = 0.28. ^{1}H NMR ($CDCl_3$): 8.25 (s, 1H, purine-*H*), 8.10 (d, 1H, Ar-*H*, $J = 7.8$), 8.05 (dd, 1H, Ar-*H*, $J = 1.7, 2.5$), 7.59 (d, 2H, Ar-*H*, $J = 7.1$), 7.42−7.30 (m, 4H, Ar-*H*), 7.02 (dd, 1H, Ar-*H*, $J = 2.1, 7.6$), 6.59 (t, 1H, 1′, $J = 6.4$), 5.79 (AB quart, 2H, OCH_2, $J = 12.3$), 4.66 (m, 1H, 3′), 4.05 (app q, 1H, 4′, $J \sim 3.7$), 3.92 (s, 3H, OCH_3), 3.90 (dd, 1H, 5′, $J = 4.4, 11.1$), 3.81 (dd, 1H, 5′, $J = 3.3, 11.1$), 2.72 (app quint, 1H, 2′, $J \sim 6.4$), 2.48 (ddd, 1H, 2′, $J = 3.8, 6.1, 13.1$), 0.94, 0.92 (2s, 18H, C(CH_3)$_3$), 0.13, 0.10, 0.09 (3s, 12H, Si−CH_3).

2-(4-Acetylphenyl)-*O*^{6}-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (5d). Chromatography, 10−20% EtOAc in CH_2Cl_2. Pale yellow solid, R_f (20% EtOAc in hexane) 0.19. ^{1}H NMR ($CDCl_3$): 8.58 (d, 2H, Ar-*H*, $J = 8.6$), 8.30 (s, 1H, purine-*H*), 8.08 (d, 2H, Ar-*H*, $J = 8.6$), 7.60 (d, 2H, Ar-*H*, $J = 7.5$), 7.38 (t, 2H, Ar-*H*, $J = 7.5$), 7.32 (t, 1H, Ar-*H*, $J = 7.3$), 6.59 (t, 1H, 1′, $J = 6.3$), 5.81 (AB quart, 2H, OCH_2, $J = 12.3$), 4.67 (m, 1H, 3′), 4.05 (app q, 1H, 4′, $J \sim 3.6$), 3.90 (dd, 1H, 5′, $J = 4.3, 11.2$), 3.82 (dd, 1H, 5′, $J = 3.2, 11.2$), 2.72 (app quint, 1H, 2′, $J \sim 6.2$), 2.66 (s, 3H, COCH_3), 2.51 (ddd, 1H, 2′, $J = 3.8, 5.8, 12.7$), 0.95, 0.92 (2s, 18H, C(CH_3)$_3$), 0.14, 0.10 (2s, 12H, Si−CH_3).

Typical Procedure for the Catalytic Hydrogenolysis of the Benzyl Group in 5a−d. The debenzylation of **5a** is a typical procedure. The C-2 phenyl O^6-benzyl nucleoside **5a** (0.08 mmol) was dissolved in 1:1 THF-MeOH (2 mL), and 5% Pd−C (0.01 g) was added to the mixture. The flask was evacuated and refilled with hydrogen gas. The mixture was stirred under a H_2 balloon at room temperature until TLC indicated complete consumption of the starting material. The mixture was filtered through Celite, and the residue was washed with THF. The filtrate was evaporated under reduced pressure, and the crude product was chromatographed on a silica column using an appropriate solvent (listed under individual compound headings, vide infra). Fractions that contained the pure product were combined, evaporated, and finally, dried under high vacuum to remove traces of solvent.

2-Phenyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (6a). Chromatography, 3% MeOH in CH_2Cl_2. Colorless foam, R_f (3% MeOH in CH_2Cl_2) = 0.28. ^{1}H NMR (acetone-d_6): 11.15 (br s, 1H, *NH*), 8.23−8.21 (m, 2H, Ar-*H*), 8.15 (s, 1H, purine-*H*), 7.62−7.57 (m, 3H, Ar-*H*), 6.51 (t, 1H, 1′, $J = 6.6$), 4.80 (m, 1H, 3′), 4.00 (app q, 1H, 4′, $J \sim 3.5$), 3.92 (dd, 1H, 5′, $J = 5.2, 11.0$), 3.84 (dd, 1H, 5′, $J = 4.0, 11.0$), 2.97 (app quint, 1H, 2′, $J \sim 6.7$), 2.51 (ddd, 1H, 2′, $J = 3.9, 6.5, 13.3$), 0.95, 0.90 (2s, 18H, C(CH_3)$_3$), 0.18 0.17, 0.07, 0.06 (4s, 12H, Si−CH_3). HRMS calcd for $C_{28}H_{44}N_4O_4Si_2$Na ($M^+ + Na$), 579.2799. Found, 579.2768.

2-(4-Methoxyphenyl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (6b). Chromatography, 5% MeOH in CH_2Cl_2. Colorless powder, R_f (5% MeOH in CH_2Cl_2) = 0.31. ^{1}H NMR (acetone-d_6): 11.10 (br s, 1H, N*H*), 8.22 (d, 2H, Ar-*H*, $J = 8.9$), 8.11 (s, 1H, purine-*H*), 7.12 (d, 2H, Ar-*H*, $J = 8.9$), 6.50 (t, 1H, 1′, $J = 6.7$), 4.79 (m, 1H, 3′), 4.00 (m, 1H, 4′), 3.93 (s superimposed on a dd, 4H, OCH_3, H5′), 3.84 (dd, 1H, 5′, $J = 4.0, 11.0$), 2.93 (app quint, 1H, 2′, $J \sim 6.4$), 2.50 (ddd, 1H, 2′, $J = 3.8, 6.3, 13.2$), 0.96, 0.91 (2s, 18H, C(CH_3)$_3$), 0.184, 0.178, 0.081, 0.071 (4s, 12H, Si−CH_3). HRMS calcd for $C_{29}H_{47}N_4O_5Si_2$ ($M^+ + H$), 587.3085. Found, 587.3075.

2-(3-Methoxyphenyl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (6c). Chromatography, 5% MeOH in CH_2Cl_2. Colorless foam, R_f (5% MeOH in CH_2Cl_2) = 0.44. ^{1}H NMR ($CDCl_3$): 10.72 (br s, 1H, N*H*), 8.03 (s, 1H, purine-*H*), 7.60 (br s, 1H, Ar-*H*), 7.56 (d, 1H, Ar-*H*, $J = 7.9$), 7.37 (t, 1H, Ar-*H*, $J = 8.1$), 7.02 (dd, 1H, Ar-*H*, $J = 2.5, 8.3$), 6.41 (t, 1H, 1′, $J = 6.4$), 4.54 (m, 1H, 3′), 3.93 (app q, 1H, 4′, $J \sim 3.6$), 3.88 (s, 3H, OCH_3), 3.76 (dd, 1H, 5′, $J = 4.2, 11.1$), 3.70 (dd, 1H, 5′, $J = 3.2, 11.1$), 2.50 (app quint, 1H, 2′, $J \sim 6.5$), 2.38 (ddd, 1H, 2′, $J = 3.8, 5.9, 13.0$), 0.84, 0.83 (2s, 18H, C(CH_3)$_3$), 0.03, 0.00 (2s, 12H, Si−CH_3). HRMS calcd for $C_{29}H_{47}N_4O_5Si_2$ ($M^+ + H$), 587.3085. Found, 587.3066.

2-(4-Acetylphenyl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (6d). Chromatography, 20% EtOAc in CH_2Cl_2, then 50% EtOAc in CH_2Cl_2. Colorless powder, R_f (EtOAc) = 0.12. ^{1}H NMR (acetone-d_6): 11.56 (br s, 1H, N*H*), 8.20 (d, 2H, Ar-*H*, $J = 8.5$), 8.04 (s, 1H, purine-*H*), 7.98 (d, 2H, Ar-*H*, $J = 8.5$), 6.36 (t, 1H, 1′, $J = 6.6$), 4.62 (m, 1H, 3′), 3.84 (app q, 1H, 4′, $J \sim 3.7$), 3.74 (dd, 1H, 5′, $J = 5.2, 11.0$), 3.67 (dd, 1H, 5′, $J = 3.9, 11.0$), 2.78 (app quint, 1H, 2′, $J \sim 6.5$), 2.49 (s, 3H, COCH_3), 2.36 (ddd, 1H, 2′, $J = 4.0, 6.2, 13.1$), 0.82, 0.72 (2s, 18H, C(CH_3)$_3$), −0.10, −0.11 (2s, 12H, Si−CH_3). HRMS calcd for $C_{30}H_{47}N_4O_5Si_2$ ($M^+ + H$), 599.3085. Found, 599.3074.

Synthesis of 2-(4-Methylphenyl)-*O*^{6}-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-guanosine (8) Using K_3PO_4 as Base. In an oven-dried, screw-cap vial equipped with a stirring bar were placed $Pd_2(dba)_3$ (5.6 mg, 6.1 μmol), K_3PO_4 (19.6 mg, 0.09 mmol), *p*-toluidine (13.2 mg, 0.12 mmol) and either **L-3** (6.5 mg, 18.5 μmol) or **L-4** (7.3 mg, 18.5 μmol). The bromonucleoside **3** (40 mg, 0.06 mmol) dissolved in anhydrous 1,2-DME (0.6 mL) was added, and the vial was flushed with nitrogen, sealed with a Teflon-lined cap, and placed in a sand bath that was maintained at 80−82 °C. The reaction was monitored by TLC. Upon completion (3 h), the mixture was cooled and diluted with Et_2O. The mixture was washed with water and the organic layer was separated and dried over Na_2SO_4. Evaporation under reduced pressure provided the crude product, which was loaded onto a silica column packed in CH_2Cl_2. Sequential elution with CH_2Cl_2, followed by 2% EtOAc in CH_2Cl_2, afforded the requisite compound as a white foam, which was finally dried under high vacuum to remove traces of solvent. Use of **L-3** yielded 31.0 mg (75%) of **8**, whereas **L-4** yielded 26.9 mg (65%). ^{1}H NMR ($CDCl_3$): 7.98 (s, 1H, purine-*H*), 7.49 (m, 4H, Ar-*H*), 7.38−7.30 (m, 3H, Ar-*H*), 7.13 (d, 2H, Ar-*H*, $J = 8.3$), 6.92 (s, 1H, N*H*), 6.40 (t, 1H, 1′, $J = 6.4$), 5.61 (AB quart, 2H, OCH_2, $J = 12.4$), 4.59 (m, 1H, 3′), 4.01 (app q, 1H, 4′, $J \sim 3.4$), 3.82 (dd, 1H, 5′, $J = 4.3, 11.2$), 3.78 (dd, 1H, 5′, $J = 3.3, 11.2$), 2.56 (app quint, 1H, 2′, $J \sim 6.4$), 2.41 (ddd, 1H, 2′, $J = 3.5, 5.9, 13.0$), 2.34 (s, 3H, CH_3), 0.94, 0.92 (2s, 18H, C(CH_3)$_3$), 0.12, 0.09 (2s, 12H, Si−CH_3). HRMS calcd for $C_{36}H_{54}N_5O_4Si_2$ ($M^+ + H$), 676.3714. Found, 676.3714.

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Supporting Information Available: ^{1}H NMR spectra (16 pages, print/PDF) of **4a−g**, **5a−d**, **6a−d** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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