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Simple Methodology for Heck Arylation at C-8 of Adenine Nucleosides

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Abstract: A simple method for the arylation of 8-vinyladenine nucleoside derivatives is reported. With a broad set of aryl iodides and bromides, the reaction is catalyzed by the simple combination palladium acetate/tris(*o*-tolyl)phosphine/triethylamine [$Pd(OAc)_2/(o\text{-tol})_3P/Et_3N$]. As expected, aryl chlorides are more difficult coupling partners but some undergo reactions with more exotic catalysts. Although *trans*-olefins are the major products, minor amounts of *cis*-isomers are detected in some cases, and a *post*-arylation mechanism for their formation is proposed. Finally, by subtle catalyst modulation chemoselective *N*-arylation of the nucleoside can be achieved in the presence of the vinyl moiety.

Keywords: Heck reaction; nucleosides; palladium; phosphanes; vinyl group

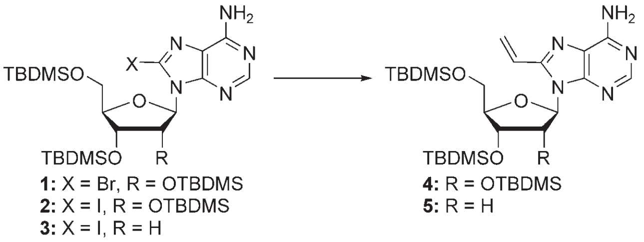
Introduction

The physiological and medicinal importance of nucleosides and their analogues has long been known, and these have, over years, spurred the development of novel methods for their syntheses.[1,2] In this context, palladium-mediated transformations play a prominent role in providing access to hitherto unknown structural motifs.[3] In addition, reactivities of complex molecules such as nucleosides may not necessarily parallel those of simpler compounds and they can often provide novel insights. For these reasons it is important to understand the catalyzed reactions of nucleosides.

To our knowledge, among the various C–C bond forming reactions of nucleosides the Heck arylation has not received significant attention. Although Heck reactions at the C-5 position of pyrimidine nucleosides have been reported,[4] little is known about the chemistry of purine derivatives. In this context, Heck arylation and reductive Heck alkylation at the C-6 position of purines have been accomplished.[5,6] However, reactions of purine nucleosides in general, and specifically those at the C-8 position, are unknown. Modification at C-8 could have important biological consequences. For instance, substitution at this position can influence the *syn-anti* conformational equilibrium around the glycosidic bond or produce structural factors that can influence enzymatic recognition.[7,8] On the basis of these considerations, we set out to explore the Heck reaction at the C-8 position of adenine nucleosides. In this communication we report reactions of iodo-, bromo- as well as chloroaromatics with vinyl nucleosides, and an evaluation of catalytic systems. We also investigate a *trans-cis* isomerization of the Heck products and provide an initial test of our hypothesis that subtly different catalysts can offer the possibility for modification at different sites within a nucleoside.

Results and Discussion

Halonucleosides **1**–**3** were our starting substrates for this investigation. Commercially available 8-bromoadenosine was silylated to provide **1** and the 8-iodo compounds **2** and **3** were easily synthesized by lithiation-iodination of silyl-protected adenosine and 2′-deoxyadenosine, respectively.[9] These compounds were then converted to the 8-vinyladenosine derivatives **4** and **5**. Although routes to **4** and **5** are known,[9,10] we briefly reinvestigated their syntheses. Prior reports utilize $Pd(PPh_3)_4$ and tri-*n*-butylvinylstannane or tetravinylstannane in DMF or NMP as solvent. Although these reactions proceed as reported, we found it more convenient to prepare **4** from **2** and **5** from **3**, *via* the use of $Pd(PPh_3)_4$ (10 mol%), tri-*n*-butylvinylstannane (2 mol equivs.) in anhydrous THF (Scheme 1). These reactions were typically complete within 24 h and provided the 8-vinyl products in >85% yields (see the Supporting Information for details). The 8-halo- as well as the 8-vinyladenine nucleosides formed the set of substrates for initial investigations into the arylation.



Scheme 1. C-8 halo- and vinylnucleosides as substrates for the arylation.

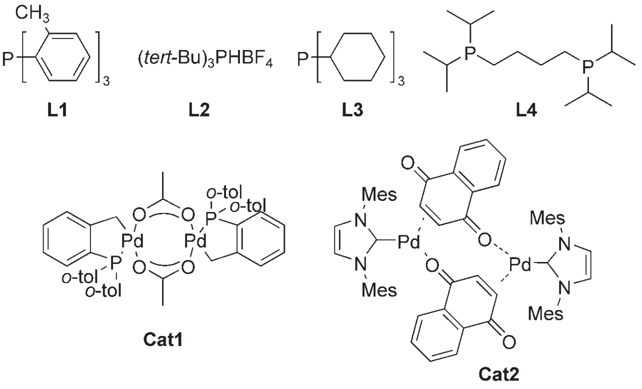
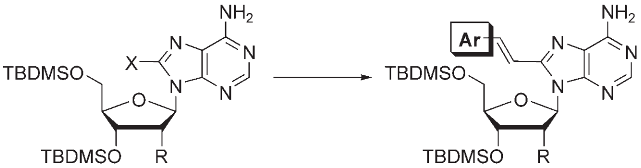


Figure 1. Ligands and preformed catalysts tested for the arylation reactions.

Initial reactions of the halonucleosides with styrene proved to be unsatisfactory (entries 1–3 in Table 1) even with $P(o\text{-tol})_3$ (**L1**, Figure 1) as ligand.[11] On the other hand, **4** and **5** underwent smooth reactions with iodobenzene within short reaction spans with 10 mol% $Pd(OAc)_2$/20 mol% $P(o\text{-tol})_3$/5 mol equivs. Et_3N. The use of **L1** in combination with iodobenzene did not seem problematic,[11] and *N*-arylation was not detected under these conditions. These results indicate that effective Heck arylation of purines and their derivatives can be achieved when the purine serves as the vinyl entity and not as the aryl halide.

With these initial results, we next investigated other catalytic systems for purposes of comparing reactivity. A careful selection of entities was made based upon their reported utility with simpler systems. **Cat1**[12] (Figure 1) constituted an obvious choice since **L1**/$Pd(OAc)_2$ proved effective in the initial studies. **L2**, an air-stable species, has been shown to provide excellent results in Heck reactions of a hindered aryl chloride as well as a deactivated aryl bromide.[13] **L3** has been shown to be effective in the activation of aryl chlorides for Heck reactions with a range of olefins.[14] **L4** has been shown to effectuate oxidative addition of chlorobenzene, and Heck reactions with it produce

Table 1. Initial results on the Heck reactions leading to the C-8 modified adenine nucleosides.



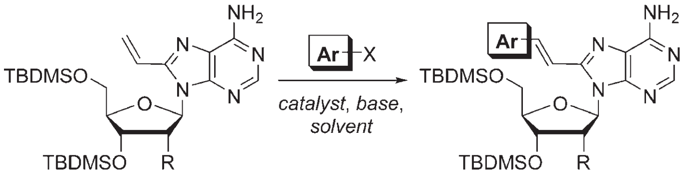
Entry	Substrate	Conditions[a]	Result[b]
1	**1:** X = Br, R = OTBDMS	10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 5 mol equivs. Et_3N, 2 mol equivs. styrene	11% yield in 24 h
2	**3:** X = I, R = H	10 mol% $Pd(OAc)_2$, 20 mol% $P(o\text{-tol})_3$, 5 mol equivs. Et_3N, 2 mol equivs. styrene	Reduction of **3**[c]
3	**3:** X = I, R = H	10 mol% $Pd(PPh_3)_4$, 5 mol equivs. Et_3N, 2 mol equivs. styrene	NR in 4 h[d]
4	**4:** X = -CH=CH2, R = OTBDMS	10 mol% $Pd(PPh_3)_4$, 5 mol equivs. Et_3N, 2 mol equivs. 4-bromotoluene	NR in 24 h[d]
5	**4:** X = -CH=CH2, R = OTBDMS	10 mol% $Pd(OAc)_2$, 20 mol% $P(o\text{-tol})_3$, 5 mol equivs. Et_3N, 2 mol equivs. iodobenzene	3 h, 90%[e]
6	**5:** X = -CH=CH2, R = H	10 mol% $Pd(OAc)_2$, 20 mol% $P(o\text{-tol})_3$, 5 mol equivs. Et_3N, 2 mol equivs. iodobenzene	2 h, 92%[e]

[a] Reactions were conducted in DMF at 100 °C.
[b] Reactions were monitored by TLC.
[c] Determined by the appearance of the H-8 resonance of adenosine in the ^1H NMR of the crude product mixture.
[d] No reaction observed.
[e] Isolated yield of purified product.

largely *trans*-arylated products,[15] and **Cat2** has been utilized for Heck reactions of aryl chlorides.[16]

Table 2 is a listing of the most relevant results from this series of experiments. With iodobenzene, formation of the catalytic species from **L1**/Pd(OAc)$_2$ *in situ* proved to be superior to the use of **Cat1** (entries 1 and 2 in Table 2). Although ^{31}P{^{1}H} NMR experiments have not provided insight into the observed differences in reactivity, it may be possible that the additional equivalent of **L1** is not simply a bystander (see below). With **Cat1** formation of the *cis*-product was observed in the ^{1}H NMR of the crude product mixture (explained later). Catalysts involving **L2** and **L3** were useful but inferior. Other aryl iodides such as 1-

Table 2. Detailed evaluation of the arylation conditions and generality of the arylation of nucleoside substrates **4** and **5**.



4: R = OTBDMS
5: R = H

6a – n: R = OTBDMS
7a – n: R = H

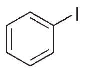
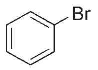
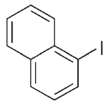
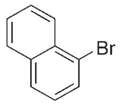
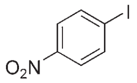
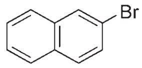
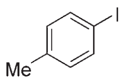
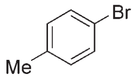
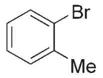
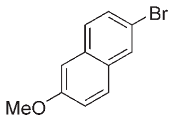
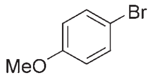
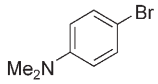
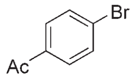
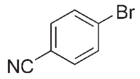
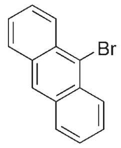
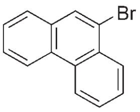
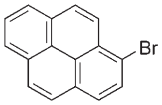
Entry	Aryl halide	Substrate	Conditions[a]	Result[b,c]
1		**4**	*A*	**6a:** 3 h, 90%
2		**4**	*B*	**6a:** 3 h, 70%[d]
3		**4**	*C*	**6a:** 8 h, 68%
4		**4**	*D*	**6a:** 24 h, 61%
5		**5**	*A*	**7a:** 2 h, 92%
6		**4**	*A*	**6a:** 4 h, 67%
7		**4**	*B*	**6a:** 6 h, 60%[d]
8		**4**	*E*	**6a:** 6 h, 62%[d]
9		**4**	*D*	**6a:** 24 h, 66%
10		**4**	*F*	**6a:** 24 h, 48%
11		**4**	*A*	**6b:** 2 h, 86%
12		**4**	*A*	**6b:** 2 h, 81%
13		**5**	*A*	**7b:** 2 h, 80%
14		**4**	*A*	**6c:** 7 h, 80%
15		**5**	*A*	**7c:** 2 h, 87%
16		**4**	*A*	**6d:** 5 h, 78%
17		**5**	*A*	**7d:** 2 h, 81%
18		**5**	*A*	**7e:** 2 h, 79%
19		**4**	*A*	**6e:** 4 h, 71%
20		**5**	*A*	**7e:** 5 h, 67%
21		**4**	*A*	**6f:** 5 h, 57%
22		**5**	*A*	**7f:** 5 h, 61%
23		**5**	*G*	**7f:** 24 h, 59%
24		**4**	*A*	**6g:** 24 h, 87%[d]
25		**5**	*A*	**7g:** 6 h, 82%[d]
26		**4**	*A*	**6h:** 5 h, 71%
27		**5**	*A*	**7h:** 5 h, 73%

Table 2. (Continued)

Entry	Aryl halide	Substrate	Conditions[a]	Result[b,c]
28		**4**	*A*	**6i:** 24 h, 86%[d]
29		**5**	*A*	**7i:** 24 h, 88%[d]
30		**4**	*A*	**6j:** 3 h, 89%
31		**5**	*A*	**7j:** 1 h, 91%
32		**4**	*A*	**6k:** 2 h, 81%
33		**5**	*A*	**7k:** 1 h, 96%
34		**4**	*A*	**6l:** 5 h, 82%
35		**5**	*A*	**7l:** 4 h, 91%
36		**4**	*A*	**6m:** 5 h, 79%
37		**5**	*A*	**7m:** 4 h, 89%
38		**4**	*A*	**6n:** 24 h, 89%
39		**5**	*A*	**7n:** 24 h, 91%

[a] *Conditions A*: 10 mol% $Pd(OAc)_2$, 20 mol% **L1**, 5 mol equivs. Et_3N, DMF, 100 °C; *B*: 10 mol% **Cat1**, 5 mol equivs. Et_3N, DMF, 100 °C; *C*: 30 mol% $PdCl_2$, 90 mol% **L3**, 1 mol equiv Cs_2CO_3, DMF, 130 °C; *D*: 10 mol% $Pd_2(dba)_3$, 20 mol% **L2**, 2 mol equivs. Cs_2CO_3, 1,4-dioxane, 90 °C; *E*: 10 mol% **Cat1**, 10 mol% **L1**, 5 mol equivs. Et_3N, DMF, 100 °C; *F*: 10 mol% $Pd(OAc)_2$, 20 mol% **L4**, 2 mol equivs. NaOAc, DMF, 130 °C; *G*: 10 mol% $Pd(OAc)_2$, 10 mol% **L1**, 5 mol equivs. Et_3N, DMF, 100 °C.

[b] Reactions were monitored by TLC.

[c] Isolated yield of purified product.

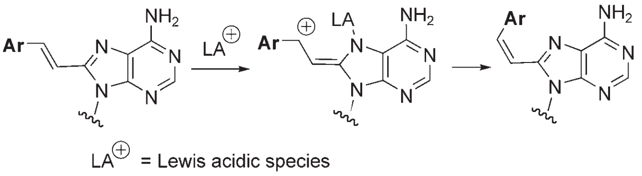
[d] *cis*-Isomer was detected by ^1H NMR.

iodonaphthalene, 4-iodo-1-nitrobenzene and 4-iodotoluene also underwent efficient reaction with 20 mol% **L1**/10 mol% $Pd(OAc)_2$/5 mol equivs. Et_3N in DMF at 100 °C (Conditions *A*).

In order to broaden the scope of the reaction, aryl bromides were tested, and reactions were conducted with both the riboside **4** as well as the 2′-deoxyriboside **5**. These results are also displayed in Table 2. With bromobenzene yields were lower than with iodobenzene (entries 6 and 7). Again, the *in situ* formed catalyst complex from **L1** and $Pd(OAc)_2$ was superior to **Cat1**. In order to assess the influence of **L1** on the course of the reaction, a coupling was performed with 10 mol% **Cat1** and an additional 10 mol% **L1**. The result of this reaction was essentially identical to that obtained with **Cat1** alone (entry 8). On the other hand, the additional equivalent of **L1** seems necessary when used in combination with $Pd(OAc)_2$. For example, as seen from entry 23, equimolar amounts of **L1** and $Pd(OAc)_2$ (10 mol% each) led to a substantially slower reaction compared to entry 22 where 20 mol% of **L1** and 10 mol% of $Pd(OAc)_2$ were employed.

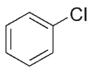
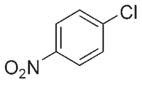
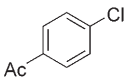
The method is general and the simple combination of **L1**/$Pd(OAc)_2$ is of broad utility for reactions of the vinylnucleosides with aryl iodides and bromides. Notably, deactivated aryl bromides, 6-bromo-2-methoxynaphthalene (entries 24 and 25), 4-bromoanisole (entries 26 and 27) and 4-bromo-*N*,*N*-dimethylaniline (entries 28 and 29), all underwent reaction.

At the initial stages of the investigation, the *cis*-alkene isomer was evident in the ^1H NMR of the crude product mixtures.[17] Subsequently, we discovered that the *cis*-isomer could form by a number of ways. For example, in reactions of 4-bromotoluene and 4-bromoanisole although only *trans*-olefins were detected at the end of the reactions, we found that the products were prone to isomerization on silica gel. However, in the cases of 6-bromo-2-methoxynaphthalene and 4-bromo-*N*,*N*-dimethylaniline the *cis*-olefin isomers were evident in the crude reaction mixtures. Therefore, **6n**, a product that could undergo facile isomerization, was selected for further investigation. Although **6n** was obtained as the pure *trans*-isomer, exposure to $CDCl_3$, silica gel and CH_2Cl_2 or acetone, all led to various levels of isomerization (see the Supporting Information). Thus, it became clear that a variety of factors could influence the *trans-cis* isomerism ranging from photochemical to presence of mildly acidic agents. The isomerization was pronounced when electron-donating groups were present



Scheme 2. A possible mechanism for the *trans-cis* isomerization of some arylation products.

Table 3. Use of aryl chlorides for the arylation.

Entry	Aryl chloride	Substrate	Conditions[a]	Result[b,c]
1		**4**	*C*	**6a:** 48 h, 65%
2		**4**	*F*	**6a:** 5 h, 52%
3		**4**	*F*	**6c:** 24 h, 59%
4		**4**	*H*	**6c:** 3 h, 64%
5		**4**	*F*	**6j:** 24 h, 57%
6		**4**	*H*	**6j:** 4 h, 67%

[a] *Conditions C*: 30 mol% $PdCl_2$, 90 mol% **L3**, 1 mol equiv Cs_2CO_3, DMF, 130°C; *F*: 10 mol% $Pd(OAc)_2$, 20 mol% **L4**, 2 mol equivs. NaOAc, DMF, 130°C; *H*: 10 mol% **Cat2**, 1 mol equiv NaOAc, 6 mol equivs. $(n\text{-Bu})_4N^+Br^-$, DMA, 150°C.

[b] Reactions were monitored by TLC.

[c] Isolated yield of purified product.

on the aryl moieties, as in the cases of 6-bromo-2-methoxynaphthalene as well as 4-bromo-*N*,*N*-dimethylaniline, where both olefin isomers were evident at the end of the reaction. One possible mechanism for the isomerization is shown in Scheme 2.

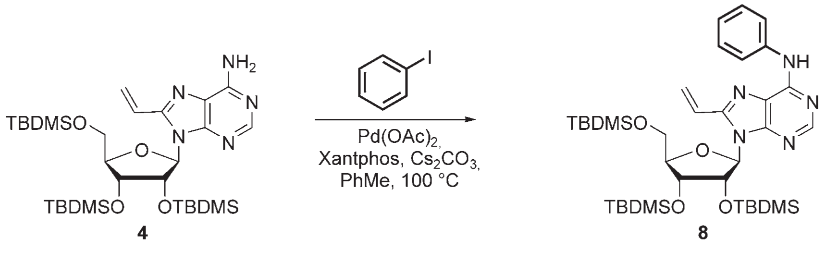
As shown in Scheme 2, any weak electron-acceptor including the metal itself could, through coordination with the N^7, lead to a benzylic cation. Such a species would be stabilized by electron-donor groups on the aromatic moiety. Consistent with this notion, product **6e** from 4-bromotoluene isomerized upon contact with silica gel, but the isomeric **6f** did not to any observable extent. In the case of **6f**, it is plausible that coplanarity necessary for the isomerization is obstructed by the presence of the *o*-methyl group. Similarly, when electron-withdrawing substituents were present on the aryl moiety, no isomerization was detected. Nevertheless, in every case the *trans* olefin was either the exclusive or the major product. When possible, isomerization could be avoided through the use of neutral alumina for chromatography as well as eliminating contact of the product with $CHCl_3$ and CH_2Cl_2. In some cases, chromatography on silica gel was unavoidable and in these cases rapid purification was necessary.

We next focused on the activation of aryl chlorides for the transformation (Table 3). **L2**, **L3**, **L4** and **Cat2** had been selected due to their ability to activate aryl C–Cl bonds. Aryl chlorides containing electron-withdrawing groups could be effectively utilized, with **Cat2** providing the better conversions (entries 4 and 6). As expected the reaction of 4-chloroanisole was inefficient.

Pd catalysis has proven to be incredibly powerful for C–N bond forming reactions,[18] and this has also provided access to a variety of *N*-arylated nucleoside analogues.[3a] Therefore, we tested the hypothesis that catalysts with differing reactivities can be utilized for functionalization at different reactive centers of nucleosides. Using our recently reported method,[19] **4** could be *N*-arylated in 69% yield (Scheme 3) without vinyl arylation. This unoptimized reaction provided clear evidence that catalyst modulation can be utilized for chemoselective functionalization at different sites within the same molecule.

Conclusions

This constitutes the first study on Heck arylation chemistry of nucleosides, particularly at the C-8 position. The purine moiety functions as an electron-withdrawing group leading to selective functionalization at the β-C of the olefin. Aryl iodides and a wide range of the more common aryl bromides can be effectively utilized for these reactions. The combination $(o\text{-tol})_3P$ (**L1**)/$Pd(OAc)_2$/Et_3N (2:1 ligand/Pd stoichiometry) proved to be effective and was superior in reactivity to the well-defined **Cat1**. The role of additional **L1** is currently unclear but the one example in Table 2 where equimolar amounts (10 mol% each) of **L1** and $Pd(OAc)_2$ were used (entry 23) demonstrates that the additional equivalent of **L1** is necessary, the absence of which led to retardation of the reaction.



Scheme 3. N^6-Arylation of the C-8 vinylnucleoside by catalyst modulation.

Although *trans*-alkenes are the predominant products, in some cases isomerization to the *cis*-alkene can occur after the arylation. This may be the reason for the minor *trans*-olefins observed in the catalytic reduction of C-8 alkynyl-2′-deoxyadenosine.[10b] The methodology described here should be applicable to many related heteroaryl compounds and the proposed olefin isomerization mechanism may occur in a variety of other systems that contain basic nitrogen atoms. Aryl chlorides can also be used for the chemistry described, although at the present time efficient conversions were observed only with activated aromatic compounds. As shown with the one preliminary example in Scheme 3 it appears that reactivity of the catalyst can be modulated, leading to C–N reactions in the presence of the vinyl moiety. Finally, in comparison to the single reported Suzuki–Miyaura reaction at the C-8 position using *trans*-β-styreneboronic acid,[20] the present method is superior in terms of product yield, and is of wider scope since it does not depend on the availability of the rare *trans*-β-styreneboronic acid derivatives.

Experimental Section

Thin layer chromatography was performed on 250 μm silica plates and column chromatographic purifications were performed on 200–300 mesh silica gel and neutral alumina as needed. Solvents used for eluting the compounds, as well as TLC conditions and R_f values are provided under individual compound headings (see the Supporting Information). THF was distilled over $LiAlH_4$ and redistilled over sodium and Et_3N was distilled over CaH_2. All other reagents as well as anhydrous DMF were obtained from commercial sources and used without further purification. ^1H NMR spectra were recorded at 500 MHz and were referenced to residual protonated solvent. ^{13}C NMR spectra were recorded at 125 MHz and were referenced to the ^{13}C signals of the solvent. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are in hertz (Hz). The sugar ring is numbered 1′-5′ beginning at the anomeric carbon and proceeding *via* the carbon chain to the primary carbinol carbon. The conventional numbering is used for the purine. Complete characterization data for all compounds is available in the Supporting Information.

Typical Procedure for the Arylation of 8-Ethenyl-2′,3′,5′-tris-*O*-(*tert*-butyldimethylsilyl)adenosine (4)

With aryl iodides (Conditions A): A mixture of $Pd(OAc)_2$ (1.7 mg, 7.6 μmol), $P(o\text{-tol})_3$ (4.7 mg, 15.4 μmol), Et_3N (55 μL, 0.39 mmol), 8-vinylnucleoside **4** (50 mg, 0.08 mmol) and aryl iodide (2 mol equivs.) in DMF (0.8 mL) was prepared in an oven-dried vial, equipped with a stirring bar. The reaction mixture was flushed with N_2 gas, sealed with a Teflon lined cap, and placed in a sand bath that was maintained at 100–105 °C. Although the general procedure described is for reactions on the 50 mg scale of **4**, some reactions were conducted at different scales and in these cases the proportions of reagents and solvents were appropriately adjusted. Reactions were monitored by TLC and upon consumption of the starting material, the reaction mixtures were diluted with EtOAc (10 mL) and washed with brine (5 mL) and then twice with water. The organic layer was separated, dried (Na_2SO_4) and concentrated. The crude reaction products were purified by column chromatography using appropriate solvents (listed under the individual compound headings in the Supporting Information). Fractions containing pure product were combined, evaporated and dried under vacuum.

With aryl bromides (Conditions A): A mixture of $Pd(OAc)_2$ (1.0 mg, 5.0 μmol), $P(o\text{-tol})_3$ (2.8 mg, 9.2 μmol), Et_3N (31 μL, 0.22 mmol), 8-vinylnucleoside **4** (30 mg, 0.047 mmol) and aryl bromide (2 mol equivs.) in DMF (0.5 mL) was prepared in an oven-dried vial, equipped with a stirring bar. The reaction mixture was flushed with N_2 gas, sealed with a Teflon lined cap, and placed in a sand bath that was maintained at 100–105 °C. Although the general procedure described is for reactions on the 30 mg scale of **4**, some reactions were conducted at different scales and in these cases the proportions of reagents and solvents were appropriately adjusted. Reactions were monitored by TLC and upon consumption of the starting material, the reaction mixtures were diluted with EtOAc (10 mL) and washed with brine (5 mL) and then twice with water. The organic layer was separated, dried (Na_2SO_4) and concentrated. The crude reaction products were purified by column chromatography using appropriate solvents (listed under the individual compound headings in the Supporting Information). Fractions containing pure product were combined, evaporated and dried under vacuum.

With aryl chlorides (Conditions F): Within a N_2 gas-filled glove bag, a mixture of $Pd(OAc)_2$ (1.7 mg, 7.6 μmol), diisopropylphospinobutane (4.5 μL, 15.5 μmol), NaOAc (13.0 mg, 0.16 mmol), 8-vinylnucleoside **4** (50 mg, 0.08 mmol) and aryl chloride (2 mol equivs.) in DMF (0.8 mL) was prepared in an oven-dried vial, equipped with a stirring bar. The reaction mixture was sealed with a Teflon lined cap, removed from the glove bag and placed in a sand bath that was maintained at 130–135 °C. Reactions were monitored by TLC and upon consumption of the starting material, the reaction mixtures were diluted with EtOAc (10 mL) and washed with brine (5 mL) and then twice with water. The organic layer was separated, dried (Na_2SO_4) and concentrated. The crude reaction products were purified by column chromatography using appropriate solvents (listed under the individual compound headings in the Supporting Information). Fractions containing pure product were combined, evaporated and dried under vacuum.

With aryl chlorides (Conditions H): A mixture of **Cat2** (8.9 mg, 8 μmol), NaOAc (7.7 mg, 0.09 mmol), $(nBu)_4N^+Br^-$ (160 mg, 0.48 mmol), 8-vinylnucleoside **4** (50 mg, 0.08 mmol) and aryl chloride (2 mol equivs.) in *N*,*N*-dimethylacetamide (0.8 mL) was prepared in an oven-dried vial, equipped with a stirring bar. The reaction mixture was flushed with N_2 gas, sealed with a Teflon lined cap, and placed in a sand bath that was maintained at 150–155 °C. Reactions were monitored by TLC and upon consumption of the starting material, the reaction mixtures were diluted with EtOAc (10 mL) and washed with brine (5 mL) and then twice with water. The organic layer was separated, dried (Na_2SO_4) and concentrated. The crude reaction products were purified by column chromatography using appropriate solvents (listed under the individual compound headings in the Supporting Information). Fractions containing pure product were combined, evaporated and dried under vacuum.

Typical Procedure for the Arylation of 8-Ethenyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (5)

With aryl iodides and bromides (Conditions A): A mixture of $Pd(OAc)_2$ (2.2 mg, 9.8 μmol), $P(o\text{-tol})_3$ (6.0 mg, 19.7 μmol), Et_3N (68 μL, 0.49 mmol), 8-vinylnucleoside **5** (50 mg, 0.10 mmol) and aryl iodide or aryl bromide (2 mol equivs.) in DMF (1.0 mL) was prepared in an oven-dried vial, equipped with a stirring bar. The reaction mixture was flushed with N_2 gas, sealed with a Teflon lined cap, and placed in a sand bath that was maintained at 100–105 °C. Reactions were monitored by TLC and upon consumption of the starting material, the reaction mixtures were diluted with EtOAc (10 mL) and washed with brine (5 mL) and then twice with water. The organic layer was separated, dried (Na_2SO_4) and concentrated. The crude reaction products were purified by column chromatography using appropriate solvents (listed under the individual compound headings in the Supporting Information). Fractions containing pure product were combined, evaporated and dried under vacuum.

Supporting Information

Analysis of methods for the synthesis of **4** and **5**, details of their synthesis and characterization, complete characterization data for **6a**–**n** and **7a**–**n**, synthesis and characterization of **8**. ^{1}H NMR of **6n** showing the *trans* to *cis* isomerization.

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