Supporting Information

Pd-Xantphos Catalyzed Direct Arylation of Nucleosides

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General Methods.

Reactions were carried out in freshly distilled and dried solvents, in oven-dried glassware. The ligands, Pd(OAc)₂, Pd₂(dba)₃, and all other reagents were obtained from commercial sources and were used without further purification. Thin layer chromatographic analyses were carried out on 250 μ m silica gel plates containing a fluorescent indicator and if needed with I₂. Column chromatographic purifications were performed using 200-300 mesh silica gel. ¹H NMR spectra were obtained in deacidified CDCl₃ (prepared by percolating the solvent through a bed of NaHCO₃ and basic alumina) and were referenced to residual CHCl₃. ¹H NMR data for the 2'-deoxyadenosine derivatives were recorded at 300 MHz and at 500 MHz for the 2'-deoxyguanosine derivatives. Chemical shifts are reported in parts per million and coupling constants are in hertz (Hz). ¹H NMR splitting patterns are designated as singlet (s), doublet (d), double doublet (dd), triplet (t), quartet (q), quintet (quint) or multiplet (m). The protons on the sugar unit are numbered 1'–5' beginning at the anomeric carbon and proceeding via the carbon chain to the primary carbinol carbon.

Table 1. Optimization experiments for the synthesis of *N*⁶-phenyl-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyadenosine^a

Ligands used:

Entry	Catalytic System	Result
1	10 mol % Pd(OAc) ₂ /15 mol % L-1 /1.4 equiv Cs ₂ CO ₃	No product
2	10 mol % Pd(OAc) ₂ /15 mol % L-1 /1.4 equiv K ₃ PO ₄	No product
3	10 mol % Pd ₂ (dba) ₃ /15 mol % L-1 /1.4 equiv Cs ₂ CO ₃	5% yield, impure
4	10 mol % Pd ₂ (dba) ₃ /15 mol % L-1 /1.4 equiv K ₃ PO ₄	8% yield
5	10 mol % Pd(OAc) ₂ /15 mol % L-2 /1.4 equiv Cs ₂ CO ₃	No product
6	10 mol % Pd(OAc) ₂ /15 mol % L-2 /1.4 equiv K ₃ PO ₄	No product
7	10 mol % Pd ₂ (dba) ₃ /15 mol % L-2 /1.4 equiv Cs ₂ CO ₃	No product
8	10 mol % Pd ₂ (dba) ₃ /15 mol % L-2 /1.4 equiv K ₃ PO ₄	14% yield, impure
9	10 mol % Pd(OAc) ₂ /15 mol % L-3 /1.4 equiv Cs ₂ CO ₃	No product
10	10 mol % Pd(OAc) ₂ /15 mol % L-3 /1.4 equiv K ₃ PO ₄	No product
11	10 mol % Pd ₂ (dba) ₃ /15 mol % L-3 /1.4 equiv Cs ₂ CO ₃	4% yield
12	10 mol % Pd ₂ (dba) ₃ /15 mol % L-3 /1.4 equiv K ₃ PO ₄	7% yield, impure
13	10 mol % Pd(OAc) ₂ /15 mol % L-4 /1.4 equiv Cs ₂ CO ₃	21% yield
14	10 mol % Pd(OAc) ₂ /15 mol % L-4 /1.4 equiv K ₃ PO ₄	20% yield
15	10 mol % Pd ₂ (dba) ₃ /15 mol % L-4 /1.4 equiv Cs ₂ CO ₃	59% yield
16	10 mol % Pd ₂ (dba) ₃ /15 mol % L-4 /1.4 equiv K ₃ PO ₄	45% yield
17	10 mol % Pd(OAc) ₂ /10 mol % L-4 /1.4 equiv Cs ₂ CO ₃	48% yield

^a Reactions were conducted in PhMe at 90 °C, nucleoside concentration was 0.42 mmol in 3 mL PhMe.

General Coupling Procedure for *N*⁶-Arylation of 2'-Deoxyadenosine:

Preparation of *N*⁶-(phenyl)-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyadenosine (**2a**).

Into an oven-dried screw-cap vial equipped with a stirring bar were placed Pd₂(dba)₃ (0.04 g, 0.044 mmol) and Xantphos (0.04 g, 0.069 mmol). Toluene (3.0 mL) was added, the vial was flushed with N₂ gas, and the mixture was stirred at room temperature for 10 minutes. To the resulting mixture were added the protected nucleoside (0.2 g, 0.42 mmol) and bromobenzene (0.05 g, 0.32 mmol) followed by Cs₂CO₃ (0.19 g, 0.6 mmol). The reaction mixture was again flushed with N₂ gas, sealed with a Teflon-lined cap, and heated in an oil bath that was maintained at 90 °C. The reaction was monitored by TLC and judged to be complete within 1 h at which time the mixture was cooled, diluted with EtOAc, and extracted twice with water. The aqueous layer was back extracted with EtOAc and the combined organic layer dried in anhydrous Na₂SO₄ and concentrated on a rotary evaporator. The crude product was purified by silica gel column chromatography, eluting first with CH₂Cl₂ and then with 5% acetone in CH₂Cl₂ to afford **2a** as a yellowish oil (0.104 g, 59% yield). R_f (silica/5% acetone-CH₂Cl₂) = 0.57. ¹H NMR: δ 8.51 (s, 1H), 8.22 (s, 1H, Ar-H), 8.01 (s, 1H, NH), 7.89, 7.78 (d, 2H, Ar-H, *J* = 8.5), 7.36 (t, 1H, Ar-H, *J* = 7.4), 7.10 (t, 2H, Ar-H, *J* = 7.4), 6.47 (t, 1H, H-1', *J* = 6.3), 4.60 (m, 1H, H-3'), 4.01 (q, 1H, H-4', *J*_{app} = 3.3), 3.88 (dd, 2H, H-5'a, *J* = 11.3, 3.9), 3.76 (dd, 1H, H-5'b, *J* = 11.3, 3.1), 2.61 (quint, 1H, H-2'a, *J*_{app} = 6.0), 2.47 (ddd, 2H, H-2'b, *J* = 12.9, 6.0, 3.6), 0.893, 0.855 (2s, 18H, *tert*-Bu), 0.0585, 0.0475 (2s, 12H, SiCH₃). HRMS exact mass calculated for C₂₈H₄₅N₅O₃Si₂ (M⁺+H) 556.3061, found, 556.3062.

*N*⁶-(2-Methylphenyl)-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyadenosine (**2b**).

Yellow oil (0.125 g, 75% yield). R_f (silica/5% acetone-CH₂Cl₂) = 0.66. ¹H NMR: δ 8.43 (s, 1H, Ar-H), 8.08 (s, 1H, Ar-H), 7.91 (d, 1H, Ar-H, J = 6.0), 7.66 (s, 1H, NH), 7.23 (m, 2H, Ar-H), 7.11 (m, 1H, Ar-H), 6.44 (t, 1H, H-1', J = 6.3), 4.61 (m, 1H, H-3'), 4.00 (m, 1H, H-4'), 3.83 (dd, 1H, H-5'a, J = 11.0, 4.4), 3.76 (dd, 1H, H-5'b, J = 11.0, 3.6), 2.66 (quint, 1H, H-2'a, J_{app} = 6.0), 2.43 (ddd, 1H, H-2'b, J = 13.0, 6.9, 3.6), 2.33 (s, 3H, CH₃), 0.89 (s, 18H, *tert*-Bu) 0.08 (2s, 12H, SiCH₃). HRMS exact mass calculated for C₂₉H₄₇N₅O₃Si₂ (M⁺+H) 570.3217, found, 570.3308.

***N*⁶-(4-Methylphenyl)-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyadenosine (2c).¹⁰**

Yellow oil (0.119 g, 70% yield). R_f (silica/3% acetone-CH₂Cl₂) = 0.25. The ¹H NMR spectrum of this material is provided in the Supporting Information.

***N*⁶-(2-Methoxyphenyl)-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyadenosine (2d).¹⁰**

Yellowish-brown oil (0.151 g, 88% yield). R_f (silica/5% acetone-CH₂Cl₂) = 0.64. The ¹H NMR spectrum of this material is provided in the Supporting Information.

***N*⁶-(4-Methoxyphenyl)-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyadenosine (2e).**

Yellow oil (0.105 g, 61% yield). R_f (silica/5% acetone-CH₂Cl₂) = 0.43. ¹H NMR: δ 8.44 (s, 1H, Ar-H), 8.11 (s, 1H, Ar-H), 7.85 (s, 1H, NH), 7.59 (d, 2H, Ar-H, J = 9.1), 6.88 (d, 2H, Ar-H, J = 8.8), 6.44 (t, 1H, H-1', J = 6.3), 4.59 (m, 1H, H-3'), 3.99 (q, 1H, H-4', J_{app} = 3.3), 3.85 (dd, 1H, H-5'a, J = 11.0, 4.4), 3.76 (s, 3H, OCH₃), 3.74 (dd, 1H, H-5'b, J = 11.0, 3.3), 2.64 (quint, 1H, H-2'a, J_{app} = 6.3), 2.42 (ddd, 1H, H-2'b, J = 12.9, 6.1, 3.9), 0.89 (s, 18H, *tert*-Bu), 0.06 (s, 12H, SiCH₃). HRMS exact mass calculated for C₂₉H₄₇N₅O₄Si₂ (M⁺+H) 586.3167, found 586.3267.

***N*⁶-(4-Cyanophenyl)-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyadenosine (2f).**

Yellow foam (0.164 g, 94% yield). R_f (silica/5% acetone-CH₂Cl₂) = 0.21. ¹H NMR: δ 8.56 (s, 1H, Ar-H), 8.29 (s, 1H, NH), 8.25 (s, 1H, Ar-H), 8.00 (d, 2H, Ar-H, J = 8.8), 7.61 (d, 2H, Ar-H, J = 8.8), 6.48 (t, 1H, H-1', J = 6.3Hz), 4.60 (m, 1H, H-3'), 4.02 (q, 1H, H-4', J_{app} = 3.3 Hz), 3.88 (dd, 1H, H-5'a, J = 11.3, 3.3), 3.76 (dd, 1H, H-5'b, J = 11.3, 3.0), 2.63 (quint, 1H, H-2'a, J_{app} = 6.1), 2.46 (ddd, 1H, H-2'b, J = 13.0, 6.3, 4.1), 0.89 (s, 18H, *tert*-Bu), 0.08 (s, 12H, SiCH₃). HRMS exact mass calculated for C₂₉H₄₄N₆O₃Si₂ (M⁺+H) 581.3013, found 581.3098.

***N*⁶-(4-Acetylphenyl)-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyadenosine (2g).¹⁰**

Yellow foam (0.146 g, 84% yield). R_f (silica/2% acetone-CH₂Cl₂) = 0.13. The ¹H NMR spectrum of this material is provided in the Supporting Information.

***N*⁶-(4-Formylphenyl)-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyadenosine (2h).**

Yellow oil (0.162 g, 95% yield). R_f (silica/5% acetone-CH₂Cl₂) = 0.41. ¹H NMR: δ 9.91 (s, 1H, CHO), 8.59 (s, 1H, Ar-H), 8.24 (s, 1H, Ar-H), 8.10 (s, 1H, NH), 8.03 (d, 2H, Ar-H, J = 8.5), 7.88

(d, 2H, Ar-H, $J = 8.5$), 6.49 (t, 1H, H-1', $J = 6.3$), 4.61 (m, 1H, H-3'), 4.02 (q, 1H, H-4', $J_{app} = 3.3$), 3.88 (dd, 1H, H-5'a, $J = 11.0, 4.1$), 3.77 (dd, 1H, H-5'b, $J = 11.0, 3.0$), 2.64 (quint, 1H, H-2'a, $J_{app} = 5.8$), 2.46 (ddd, 1H, H-2'b, $J = 12.9, 6.0, 3.8$), 0.90 (s, 18H, *tert*-Bu), 0.08 (s, 12H, SiCH₃). HRMS exact mass calculated for C₂₉H₄₅N₅O₄Si₂ (M⁺+H) 584.3010, found, 584.3090.

N⁶-(2-Nitrophenyl)-3',5'-bis-O-(*tert*-butyldimethylsilyl)-2'-deoxyadenosine (2i).

Greenish-yellow solid (0.175 g, 98% yield). R_f (silica/5% acetone-CH₂Cl₂) = 0.66. M.p.: 138-141 °C. ¹H NMR: δ 11.1 (s, 1H, NH), 9.10-9.14 (m, 1H, Ar-H) 8.60 (s, 1H, Ar-H), 8.34 (1s, 1H, Ar-H), 8.26-8.29 (m, 1H, Ar-H), 7.67-7.72 (m, 1H, Ar-H), 7.14-7.19 (m, 1H, Ar-H), 6.50 (t, 1H, H-1', $J = 6.0$), 4.63-4.65 (m, 1H, H-3'), 4.04 (q, 1H, H-4', $J_{app} = 3.6$), 3.88 (dd, 1H, H-5'a, $J = 11.2, 4.1$), 3.78 (dd, 1H, H-5'b, $J = 11.2, 3.0$), 2.67 (quint, 1H, H-2'a, $J_{app} = 6.3$), 2.48 (ddd, 1H, H-2'b, $J_{app} = 12.9, 6.0, 3.8$), 0.91, 0.92 (2s, 18H, *tert*-Bu), 0.09, 0.10 (2s, 12H, SiCH₃). HRMS exact mass calculated for C₂₈H₄₄N₆O₅Si₂ (M⁺+H) 601.2912, found 601.2913.

N⁶-(1-Naphthyl)-3',5'-bis-O-(*tert*-butyldimethylsilyl)-2'-deoxyadenosine (2j).

Yellow foam (0.177 g, 98% yield). R_f (silica/2% acetone-CH₂Cl₂) = 0.37. ¹H NMR: δ 8.31 (s, 1H, Ar-H), 8.10 (s, 1H, Ar-H), 7.86 (s, 1H, NH), 7.76-7.83 (m, 3H, Ar-H), 7.31-7.42 (m, 4H, Ar-H), 6.45 (t, 1H, H-1', $J = 6.8$), 4.59-4.64 (m, 1H, H-3'), 4.02 (q, 1H, H-4', $J_{app} = 4.1$), 3.86 (dd, 1H, H-5'a, $J = 11.3, 4.4$), 3.76 (dd, 1H, H-5'b, $J = 11.3, 3.6$), 2.65 (quint, 1H, H-2'a, $J_{app} = 6.0$), 2.40 (ddd, 1H, H-2'b, $J_{app} = 13.2, 6.1, 3.9$), 0.93, 0.92 (2s, 18H, *tert*-Bu), 0.11, 0.10 (2s, 12H, SiCH₃). HRMS exact mass calculated for C₃₂H₄₇N₅O₃Si₂ (M⁺+H) 606.3217, found 606.3217.

N⁶-(2-Naphthyl)-3',5'-bis-O-(*tert*-butyldimethylsilyl)-2'-deoxyadenosine (2k).

Yellow foam (0.144 g, 82% yield). R_f (silica/5% acetone-CH₂Cl₂) = 0.55. ¹H NMR: δ 8.60 (s, 1H, Ar-H), 8.22 (s, 1H, Ar-H), 8.14 (s, 1H, NH), 7.37-7.86 (m, 7H, Ar-H), 6.51 (t, 1H, H-1', $J = 6.5$), 4.61-4.65 (m, 1H, H-3'), 4.03 (q, 1H, H-4', $J_{app} = 3.8$), 3.91 (dd, 1H, H-5'a, $J = 11.0, 3.8$), 3.79 (dd, 1H, H-5'b, $J = 11.0, 3.0$), 2.67 (quint, 1H, H-2'a, $J_{app} = 6.0$), 2.47 (ddd, 1H, H-2'b, $J_{app} = 12.9, 6.1, 3.9$), 0.91, 0.92 (2s, 18H, *tert*-Bu), 0.10, 0.11 (2s, 12H, SiCH₃). HRMS exact mass calculated for C₃₂H₄₇N₅O₃Si₂ (M⁺+H) 606.3217, found 606.3267.

N⁶-(2-Methoxynaphthyl)-3',5'-bis-O-(*tert*-butyldimethylsilyl)-2'-deoxyadenosine (2l).

Yellow foam (0.161 g, 87% yield). R_f (silica/5% acetone-CH₂Cl₂) = 0.32. ¹H NMR: δ 8.31 (s, 1H, Ar-H), 8.10 (s, 1H, Ar-H), 7.86 (s, 1H, NH), 7.76-7.83 (m, 3H, Ar-H), 7.31-7.42 (m, 3H, Ar-H), 6.45 (t, 1H, H-1', $J = 6.8$), 4.59-4.64 (m, 1H, H-3'), 4.02 (q, 1H, H-4', $J_{app} = 4.1$), 3.87 (s, 3H, OCH₃), 3.86 (dd, 1H, H-5'a, $J = 11.3, 4.4$), 3.76 (dd, 1H, H-5'b, $J = 11.3, 3.6$), 2.65 (quint, 1H, H-2'a, $J_{app} = 6.0$), 2.40 (ddd, 1H, H-2'b, $J = 13.2, 6.1, 3.9$), 0.93, 0.92 (2s, 18H, *tert*-Bu), 0.11, 0.10

(2s, 12H, SiCH₃). HRMS exact mass calculated for C₃₃H₄₉N₅O₄Si₂ (M⁺+H) 636.3323, found 636.3423.

***N*⁶-(2-Pyrenyl)-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyadenosine (2m).⁸**

Golden-yellow powder (0.103 g, 53% yield, this reaction was not complete at 18 h). R_f (silica/5% acetone-CH₂Cl₂) = 0.67. When this reaction was conducted on 0.21 mmol of **1** under the conditions in ref. 16, a 59% yield of **2m** was obtained (20 h, completed reaction). The ¹H NMR spectrum of this material is provided in the Supporting Information.

General Procedure for the *N*²-Arylation of Protected 2'-Deoxyguanosine:

In a clean, dry reaction vial equipped with a stir bar were placed *O*⁶-benzyl-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyguanosine (40 mg, 68.3 μmol), the aryl bromide (2 mol equiv), *tert*-BuONa (10.1 mg, 0.105 mmol, 1.5 equiv), Pd(OAc)₂ (1.5 mg, 6.8 μmol, 0.1 equiv) and Xantphos (4.1 mg, 7 μmol, 0.1 equiv). Toluene (1 mL) was added, the reaction vial was purged with N₂ and the mixture was allowed to stir at 85 °C. TLC was used to monitor the progress of the reaction and the reactions were completed within 1-4 h. Upon completion, the reaction mixture was partitioned between Et₂O and brine, and the organic layer was collected. The aqueous layer was then extracted with of Et₂O (2 x 2 mL). The combined organic layer was dried over Na₂SO₄ and evaporated. Purification was performed by column chromatography on silica gel using 20% EtOAc-hexanes as eluting solvent (deviations from this procedure are noted under the individual compound heading). For the guanosine compounds any *NH* proton detected has been listed as Ar-H.

3',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-*O*⁶-Methyl-*N*²-phenyl-2'-deoxyguanosine (4).

Light-yellow solid (41.8 mg, 88% yield). R_f (silica/20% EtOAc-hexanes) = 0.22. ¹H NMR: δ 8.00 (s, 1H, Ar-H), 7.69 (d, 2H, Ar-H, *J* = 8.3), 7.33 (t, 2H, Ar-H, *J* = 7.3), 7.06 (s, 1H, N-H), 7.02 (t, 1H, Ar-H, *J* = 7.2), 6.41 (t, 1H, H1', *J* = 6.4), 4.59-4.57 (m, 1H, H3'), 4.12 (s, 3H, OCH₃), 4.01-4.00 (narrow m, 1H, H4'), 3.81 (dd, 1H, H5'a, *J* = 11.2, 3.9), 3.77 (dd, 1H, H5'b, *J* = 11.2, 3.4), 2.54 (app. quint, 1H, H2'a, *J* ~ 6.5), 2.42 (ddd, 1H, H2'b, *J* = 12.7, 5.9, 3.4), 0.93, 0.91 (2s, 18H, *tert*-Bu), 0.11, 0.08 (2s, 12H, SiCH₃).

***O*⁶-Benzyl-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-*N*²-phenyl-2'-deoxyguanosine (6a).¹⁷**

Light yellow solid (40.3 mg, 89% yield). R_f (silica/20% EtOAc-hexanes) = 0.25. The ¹H NMR spectrum of this material is provided in the Supporting Information.

***O*⁶-Benzyl-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-*N*²-(4-methylphenyl)-2'-deoxyguanosine (6b).**

Clear oil (75.4 mg, 75% yield). R_f (silica/20% EtOAc-hexanes) = 0.18. ^1H NMR: δ 7.97 (s, 1H, Ar-H), 7.51-7.49 (m, 4H, Ar-H), 7.37-7.30 (m, 2H, Ar-H), 7.12 (d, 2H, Ar-H, J = 8.3), 6.95 (s, 1H, Ar-H), 6.40 (t, 1H, H1', J = 6.4), 5.60 (AB_q, 2H, OCH₂, J = 12.2), 4.59-4.57 (narrow m, 1H, H3'), 4.02-4.00 (narrow m, 1H, H4'), 3.82 (dd, 1H, H5'a, J = 11.2, 4.4), 3.77 (dd, 1H, H5'b, J = 11.2, 2.9), 2.56 (app. quint, 1H, H2'a, J ~ 6.7), 2.40 (ddd, 1H, H2'b, J = 13.2, 5.9, 3.4), 2.33 (s, 3H, CH₃) 0.94, 0.91 (2s, 18H, *tert*-Bu), 0.12, 0.09 (2s, 12H, SiCH₃). HRMS calcd for C₃₆H₅₄N₅O₄Si₂ (M^+ +H) 676.3714, found 676.3710.

O⁶-Benzyl-3',5'-bis-O-(*tert*-butyldimethylsilyl)-N²-(4-methoxyphenyl)-2'-deoxyguanosine (6c).¹⁷

Yellow oil (23.0 mg, 48% yield). R_f (silica/20% EtOAc-hexanes) = 0.27. The ^1H NMR spectrum of this material is provided in the Supporting Information.

O⁶-Benzyl-3',5'-bis-O-(*tert*-butyldimethylsilyl)-N²-(2-nitrophenyl)-2'-deoxyguanosine (6d).¹⁶

Bright-orange solid (40.5 mg, 84% yield). R_f (silica/20% EtOAc-hexanes) = 0.23. The ^1H NMR spectrum of this material is provided in the Supporting Information.

O⁶-Benzyl-3',5'-bis-O-(*tert*-butyldimethylsilyl)-N²-(1-naphthyl)-2'-deoxyguanosine (6e).

Light-brown oil (37.7 mg, 77% yield). R_f (silica/20% EtOAc-hexanes) = 0.25. ^1H NMR: δ 8.08-8.04 (m, 2H, Ar-H), 7.98 (s, 1H, Ar-H), 7.90-7.89 (m, 1H, Ar-H), 7.66 (d, 1H, Ar-H, J = 7.8), 7.53-7.47 (m, 3H, Ar-H), 7.37-7.26 (m, 5H, Ar-H), 6.39 (t, 1H, H1', J = 6.4), 5.50 (AB_q, 2H, OCH₂, J = 12.2), 4.57-4.55 (narrow m, 1H, H3'), 4.00-3.98 (narrow m, 1H, H4'), 3.79 (dd, 1H, H5'a, J = 11.2, 3.9), 3.75 (dd, 1H, H5'b, J = 11.2, 2.9), 2.57 (app. quint, 1H, H2'a, J ~ 6.4), 2.38 (ddd, 1H, H2'b, J = 13.2, 5.9, 3.9), 0.93, 0.91 (2s, 18H, *tert*-Bu), 0.11, 0.08 (2s, 12H, SiCH₃). HRMS calcd for C₃₉H₅₄N₅O₄Si₂ (M^+ +H) 712.3714, found 712.3697.

O⁶-Benzyl-3',5'-bis-O-(*tert*-butyldimethylsilyl)-N²-(2-naphthyl)-2'-deoxyguanosine (6f).

Pure compound was purified by preparative TLC using 20% EtOAc-hexanes. Yellow oil (34.9 mg, 71% yield). R_f (silica/20% EtOAc-hexanes) = 0.28. ^1H NMR: δ 8.39 (s, 1H, Ar-H), 8.03 (s, 1H, Ar-H), 7.79-7.72 (m, 3H, Ar-H), 7.55-7.52 (m, 3H, Ar-H), 7.43 (t, 1H, Ar-H, J = 7.3), 7.38-7.30 (m, 4H, Ar-H), 7.21 (s, 1H, Ar-H), 6.48 (t, 1H, H1', J = 6.8), 5.67 (AB_q, 2H, OCH₂, J = 12.2), 4.63-4.62 (narrow m, 1H, H3'), 4.07-4.06 (narrow m, 1H, H4'), 3.83 (dd, 1H, H5'a, J = 11.2, 4.4), 3.78 (dd, 1H, H5'b, J = 11.2, 2.9), 2.63 (app. quint, 1H, H2'a, J ~ 5.9), 2.47 (ddd, 1H, H2'b, J = 12.7, 5.9, 2.9), 0.95, 0.91 (2s, 18H, *tert*-Bu), 0.13, 0.08, 0.068 (3s, 12H, J = 3.9, SiCH₃). HRMS calcd for C₃₉H₅₄N₅O₄Si₂ (M^+ +H) 712.3714, found 712.3711.

O⁶-Benzyl-3',5'-bis-O-(*tert*-butyldimethylsilyl)-N²-(1-pyrenyl)-2'-deoxyguanosine (6g).^{8,9}

Brownish powder (37.4 mg, 69% yield). R_f (silica/20% EtOAc-hexanes) = 0.20. The ^1H NMR spectrum of this material is provided in the Supporting Information.

O^6 -Benzyl-3',5'-bis- O -(*tert*-butyldimethylsilyl)- N^2 -(6-methoxy-2-naphthyl)-2'-deoxyguanosine (6h).

Yellow oil (27.7 mg, 54% yield). R_f (silica/20% EtOAc-hexanes) = 0.27. ^1H NMR: δ 8.29 (s, 1H, Ar-H), 8.00 (s, 1H, Ar-H), 7.67 (d, 1H, Ar-H, J = 8.8), 7.64 (d, 1H, Ar-H, J = 8.8 Hz), 7.51 (d, 3H, Ar-H, J = 6.8), 7.36-7.31 (m, 3H, Ar-H), 7.15-7.11 (m, 3H, Ar-H), 6.47 (t, 1H, H1', J = 6.3), 5.64 (AB_q, 2H, OCH₂, J = 12.2), 4.61-4.59 (narrow m, 1H, H3'), 4.05-4.03 (narrow m, 1H, H4'), 3.92 (s, 3H, OCH₃), 3.82 (dd, 1H, H5'a, J = 11.2, 4.4), 3.78 (dd, 1H, H5'b, J = 11.2, 4.4), 2.62 (app. quintet, 1H, H2'a, J ~ 5.9), 2.45 (ddd, 1H, H2'b, J = 12.7, 5.9, 3.4), 0.95, 0.91 (2s, 18H, *tert*-Bu), 0.13, 0.08, 0.07 (3s, 12H, SiCH₃). HRMS calcd for C₄₀H₅₅N₅O₅Si₂ (M^+ +H) 741.3742, found 741.3763.

O^6 -Benzyl-3',5'-bis- O -(*tert*-butyldimethylsilyl)- N^2 -(4-cyanophenyl)-2'-deoxyguanosine (6i).

White solid (36.6 mg, 78% yield). R_f (silica/20% EtOAc-hexanes) = 0.29. ^1H NMR: δ 8.09 (s, 1H, Ar-H), 7.73 (d, 2H, Ar-H, J = 8.8), 7.56 (d, 2H, Ar-H, J = 8.3), 7.49 (d, 2H, Ar-H, J = 7.3), 7.38-7.32 (m, 3H, Ar-H), 6.43 (t, 1H, H1', J = 6.3), 5.62 (AB_q, 2H, OCH₂, J = 12.7), 4.60-4.57 (narrow m, 1H, H3'), 4.04-4.03 (narrow m, 1H, H4'), 3.83 (dd, 1H, H5'a, J = 11.2, 4.3), 3.78 (dd, 1H, H5'b, J = 11.2, 3.9), 2.51 (app. quint, 1H, H2'a, J ~ 6.4), 2.43 (ddd, 1H, H2'b, J = 13.2, 5.9, 3.9), 0.94, 0.91 (2s, 18H, *tert*-Bu), 0.12, 0.09 (2s, 12H, SiCH₃). HRMS calcd for C₃₆H₅₁N₆O₄Si₂ (M^+ +H) 687.3510, found 687.3527. This yield decreased to 65% (30.5 mg) when the reaction was allowed to proceed for 17 h.

The by product obtained in this reaction was O^6 -benzyl-3',5'-bis- O -(*tert*-butyldimethylsilyl)- N^2,N^2 -bis-(4-cyanophenyl)-2'-deoxyguanosine

Clear oil (10-20% yield). R_f (silica/20% EtOAc-hexanes) = 0.18. ^1H NMR: δ 8.11 (s, 1H, Ar-H), 7.58 (d, 4H, Ar-H, J = 8.8), 7.29-7.25 (m, 7H, Ar-H), 7.16-7.14 (s, 2H, Ar-H), 6.16 (t, 1H, H1', J = 6.4), 5.29 (AB_q, 2H, OCH₂, J = 12.5), 4.46-4.45 (narrow m, 1H, H3'), 3.94-3.93 (narrow m, 1H, H4'), 3.71 (narrow m, 2H, H5'a,b), 2.36 (app. quintet, 1H, H2'a, J ~ 6.3), 2.25 (ddd, 1H, H2'b, J = 13.2, 5.8, 3.9), 0.90, 0.88 (2s, 18H, *tert*-Bu), 0.08, 0.07, 0.05 (3s, 12H, SiCH₃). HRMS calcd for C₄₃H₅₃N₇O₄Si₂ (M^+ +H) 788.3698, found 788.3796.

N^2 -(4-Acetylphenyl)- O^6 -Benzyl-3',5'-bis- O -(*tert*-butyldimethylsilyl)-2'-deoxyguanosine (6j).

White solid (33.0 mg, 68% yield). R_f (silica/20% EtOAc-hexanes) = 0.18. ^1H NMR: δ 8.06 (s, 1H, Ar-H), 7.95 (d, 2H, Ar-H, J = 8.9), 7.73 (d, 2H, Ar-H, J = 8.9), 7.51 (d, 2H, Ar-H, J = 7.5), 7.39-7.32 (m, 2H, Ar-H), 7.27 (s, 1H, Ar-H), 6.44 (t, 1H, H1', J = 6.5), 5.64 (AB_q, 2H, OCH₂, J =

12.7), 4.60-4.58 (m, 1H, H3'), 4.04-4.02 (narrow m, 1H, H4'), 3.83 (dd, 1H, H5'a, $J = 11.0, 3.5$), 3.78 (dd, 1H, H5'b, $J = 11.0, 3.5$), 2.52 (app. quint, 1H, H2'a, $J \sim 6.5$), 2.43 (ddd, 1H, H2'b, $J = 13.5, 5.8, 3.9$), 1.61 (s, 3H, CH₃), 0.95, 0.91 (2s, 18H, *tert*-Bu), 0.12, 0.09 (2s, 12H, SiCH₃). HRMS calcd for C₃₇H₅₄N₅O₅Si₂ (M⁺+H) 704.3663, found 704.3640.

Confirmation of the site of arylation in 2'-deoxyadenosine

In order to confirm that the exocyclic amino group of 2'-deoxyadenosine is the site of arylation and not any of the ring nitrogens, the ¹³C NMR spectra of products from the reactions in the Scheme below were compared. We have previously reported amination of the bromo nucleoside with aryl amines via Pd catalysis (ref. 10). In the products derived from this reaction the aryl moiety is unambiguously located at the exocyclic amino group. The ¹³C NMR spectra of two of these products (obtained by reactions of the bromo nucleoside with 4-toluidine and 4-acetylaniline) were compared to the ¹³C NMR spectra of compounds **2c** and **2g** obtained in this study. The following 2 pages show the spectra of the products obtained via the two methods. From this comparison it becomes clear that the products obtained via the direct arylation described here are identical to those obtained by aryl amination of the bromo nucleoside, indicating that the arylation occurs at the exocyclic amino group of 2'-deoxyadenosine.

For reference, the ¹³C chemical shifts for 4-bromotoluene, 4-toluidine, 4-bromoacetophenone and 4-acetylaniline are given below (source: <http://www.aist.go.jp/RIODB/SDBS/> National Institute of Advanced Industrial Science and Technology)

136.70	143.98	196.90	196.65
131.23	129.76	135.86	151.68
130.78	127.61	131.89	130.82
119.08	115.28	129.83	127.45
20.90	20.42	128.28	113.67
		26.50	26.00

IP-1203-05-31

Pulse sequence: a2pul

Solvent: CDCl3

Temp. 25.0 C / 298.1 K

File: IP-1203-05-31

NOVA-500 "capella500"

Pulse 45.0 degrees

Acq. time 1.892 sec

Width 8000.0 Kz

16 repetitions

OBSERVE H1, 499.7707222 MHz

DATA PROCESSING

Gauss apodization 0.900 sec

FT size 32768

Total time 0 min, 30 sec

EY-1203-01-10-column

Pulse sequence: a2pul

Solvent: CDCl3

Ambient temperature

File: EY-1203-01-10-column

INOVA-500 "casella500"

Pulse 45.0 degrees

Acq. time 1.892 sec

Width 8000.0 Hz

24 repetitions

OBSERVE KL, 499.7707217 MHz

DATA PROCESSING

FT size 32768

Total time 1 hr, 4 min, 52 sec

EY-1203-01-16-column
 Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 File: EY-1203-01-16-column
 INOVA-S00 "cpella500"
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 44 repetitions
 OBSERVE H1, 499.7707217 MHz
 DATA PROCESSING
 FT size 32763
 Total time 1 hr, 4 min, 52 sec

TBDMSO
 6a

8 7 6 5 4 3 2 1 0 ppm

EY-1203-01-16-column
 Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 File: EY-1203-01-16-column
 INOVA-S00 "cpella500"
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 44 repetitions
 OBSERVE H1, 499.7707217 MHz
 DATA PROCESSING
 FT size 32763
 Total time 1 hr, 4 min, 52 sec

TBDMSO
 6a

EY-1203-01-16-column
 Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 File: EY-1203-01-16-column
 INOVA-S00 "cpella500"
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 44 repetitions
 OBSERVE H1, 499.7707217 MHz
 DATA PROCESSING
 FT size 32763
 Total time 1 hr, 4 min, 52 sec

Cc1ccc(NC2=NC3=C(N=CN3C2C4C(C(C(C4)OC(C)C)OC(C)C)OC(C)C)C5=CC=CC=C5)N=CN=C5C=CC=CC=C5)N=CN=C5C=CC=CC=C5
6a

EY-1203-01-16-column
 Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 File: EY-1203-01-16-column
 INOVA-S00 "cpella500"
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 44 repetitions
 OBSERVE H1, 499.7707217 MHz
 DATA PROCESSING
 FT size 32763
 Total time 1 hr, 4 min, 52 sec

Cc1ccc(NC2=NC3=C(N=CN3C2C4C(C(C(C4)OC(C)C)OC(C)C)OC(C)C)C5=CC=CC=C5)N=CN=C5C=CC=CC=C5)N=CN=C5C=CC=CC=C5
6a

EY-1203-01-16-column
 Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 File: EY-1203-01-16-column
 INOVA-S00 "cpella500"
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 44 repetitions
 OBSERVE H1, 499.7707217 MHz
 DATA PROCESSING
 FT size 32763
 Total time 1 hr, 4 min, 52 sec

Cc1ccc(NC2=NC3=C(N=CN3C2C4C(C(C(C4)OC(C)C)OC(C)C)OC(C)C)C5=CC=CC=C5)N=CN=C5C=CC=CC=C5)N=CN=C5C=CC=CC=C5
6a

EY-1203-01-16-column
 Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 File: EY-1203-01-16-column
 INOVA-S00 "cpella500"
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 44 repetitions
 OBSERVE H1, 499.7707217 MHz
 DATA PROCESSING
 FT size 32763
 Total time 1 hr, 4 min, 52 sec

Cc1ccc(NC2=NC3=C(N=CN3C2C4C(C(C(C4)OC(C)C)OC(C)C)OC(C)C)C5=CC=CC=C5)N=CN=C5C=CC=CC=C5)N=CN=C5C=CC=CC=C5
6a

EY-1203-01-16-column
 Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 File: EY-1203-01-16-column
 INOVA-S00 "cpella500"
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 44 repetitions
 OBSERVE H1, 499.7707217 MHz
 DATA PROCESSING
 FT size 32763
 Total time 1 hr, 4 min, 52 sec

TBDMSO
 6a

8 7 6 5 4 3 2 1 0 ppm

EY-1203-01-16-column
 Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 File: EY-1203-01-16-column
 INOVA-S00 "cpella500"
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 44 repetitions
 OBSERVE H1, 499.7707217 MHz
 DATA PROCESSING
 FT size 32763
 Total time 1 hr, 4 min, 52 sec

TBDMSO
 6a

8 7 6 5 4 3 2 1 0 ppm

EY-1203-01-16-column
 Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 File: EY-1203-01-16-column
 INOVA-S00 "cpella500"
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 44 repetitions
 OBSERVE H1, 499.7707217 MHz
 DATA PROCESSING
 FT size 32763
 Total time 1 hr, 4 min, 52 sec

Cc1ccc(NC2=NC3=C(N=CN3C2C4C(C(C(C4)OC(C)C)OC(C)C)OC(C)C)C5=CC=CC=C5)N=CN=C5C=CC=CC=C5)N=CN=C5C=CC=CC=C5
6a

EY-1203-01-16-column
 Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 File: EY-1203-01-16-column
 INOVA-S00 "cpella500"
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 44 repetitions
 OBSERVE H1, 499.7707217 MHz
 DATA PROCESSING
 FT size 32763
 Total time 1 hr, 4 min, 52 sec

TBDMSO
 6a

8 7 6 5 4 3 2 1 0 ppm

EY-1203-01-16-column
 Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 File: EY-1203-01-16-column
 INOVA-S00 "cpella500"
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 44 repetitions
 OBSERVE H1, 499.7707217 MHz
 DATA PROCESSING
 FT size 32763
 Total time 1 hr, 4 min, 52 sec

TBDMSO
 6a

8 7 6 5 4 3 2 1 0 ppm

EY-1203-01-16-column
 Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 File: EY-1203-01-16-column
 INOVA-S00 "cpella500"
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 44 repetitions
 OBSERVE H1, 499.7707217 MHz
 DATA PROCESSING
 FT size 32763
 Total time 1 hr, 4 min, 52 sec

TBDMSO
 6a

8 7 6 5 4 3 2 1 0 ppm

EY-1203-01-16-column
 Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 File: EY-1203-01-16-column
 INOVA-S00 "cpella500"
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 8000.0 Hz
 44 repetitions
 OBSERVE H1, 499.7707217 MHz
 DATA PROCESSING
 FT size 32763
 Total time 1 hr, 4 min, 52 sec

TBDMSO
 6a

8 7 6 5 4 3 2 1 0 ppm

EX-1203-01-37

Pulse Sequence: szpul

Solvent: CDCl3

Ambient temperature

File: EX-1203-01-37

NOVA-500 "capella500"

Pulse 45.0 degrees

Acq. time 1.892 sec

Width 3000.0 Hz

32 repetitions

OBSERVE H1, 499.7707212 MHz

DATA PROCESSING

FT size 32768

Total time 1 hr, 4 min, 52 sec

EX-1203-01-30

Pulse Sequence: s2pul

Solvent: CDCl3

Ambient temperature

File: EX-1203-01-30

NOVA-500 "casella500"

Pulse 45.0 degrees

Acq. time 1.892 sec

Width 8000.0 Hz

24 repetitions

OBSERVE H1, 499.7707207 MHz

DATA PROCESSING

FT size 32768

Total time 1 hr, 4 min, 52 sec