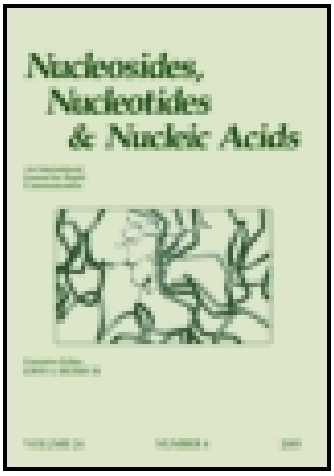

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Palladium Catalysis in the Synthesis of 8-Position modified Adenosine, 2′-Deoxyadenosine and Guanosine

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PALLADIUM CATALYSIS IN THE SYNTHESIS OF 8-POSITION MODIFIED ADENOSINE, 2'-DEOXYADENOSINE AND GUANOSINE

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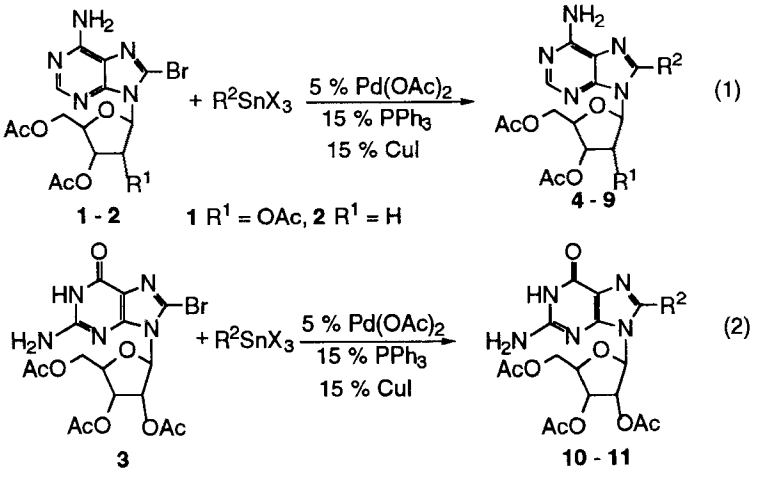
Abstract. Adenosine and guanosine analogs with 8-position vinyl and aryl groups were prepared by palladium catalyzed cross-coupling of organostannanes with 8-bromopurine nucleosides. The reaction conditions and catalyst composition were improved so that both vinyl and aryl modifications could be made by a general procedure.

Systematic evolution of ligands by exponential enrichment (SELEX) is a procedure that generates nucleic acid ligands capable of high-affinity binding to both protein and small molecule targets.[1] Recent examples of RNA ligand binding to proteins include: R17 coat protein,[2] HIV reverse transcriptase,[3] HIV rev protein,[4] basic fibroblast growth factor,[5] vascular endothelial growth factor,[6] thrombin[7] and *Escherichia coli rho* factor.[8] Several examples of RNA ligands binding small molecules have also been reported including ATP,[9] theophylline,[10] tryptophan,[11] arginine[12] and valine.[13] SELEX is remarkably effective at generating highly specific nucleic acid ligands; however, the scope of potential SELEX targets could be expanded if the nucleic acids were altered by chemical modification.

Palladium catalyzed methods have been reported previously for the modification of uridine nucleosides.[14] One of the first methods reported for making new C-C bonds to purine nucleosides involved palladium catalyzed reductive coupling of a terminal acetylenes to 6- or 8-halogenated purine nucleosides.[15] More recently, palladium catalyzed cross coupling of stannanes to halogenated purine nucleosides has been used successfully. These methods are complimentary to the acetylene coupling reactions and are ideal because the attachment of new substituents is accomplished in a single step. For generating new SELEX reagents it was important that the point of attachment to the purine nucleoside be at the 8-position so that the new functionality be presented in the major groove of duplex regions away from the H-bonding groups required for stable Watson-Crick or Hoogsteen hybridization. It had been previously reported that Stille type coupling occurred for 2-, 6-

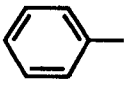
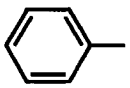
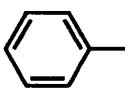
and 8-halogenated adenosine nucleosides with organostannane reagents.[16] Allyl and vinylstannanes have been used previously in palladium catalyzed crosscoupling reactions with 8-iodo-2'-deoxyadenosine and 8-iodo-2',3'-dideoxyadenosine.[17] However, it was unclear whether the 8-bromo derivatives would couple in satisfactory yields using aryltrimethylstannane reagents since pervious reports on the palladium catalyzed synthesis of 8-phenyladenosine used tetraphenylstannane and Ph_3As.[18] In addition, to our knowledge no reports of vinylstannane coupling to guanosine had been reported. The recent publication of palladium catalyzed cross coupling of protected 8-bromoguanosine with 4-tributyltinbenzaldehyde in good yield[19] is consistent with our results disclosed herein.

Previous experience in the carbonylative cross coupling of vinyl and arylstannanes to uridine[20] and 2'-deoxyuridines[14a] suggested that the choice of palladium, solvent, ligands and reaction temperature could be crucial to the success of these reactions. The synthesis of vinyl or aryl substituted adenosine, 2'-deoxyadenosine and guanosine nucleosides may be accomplished by the synthetic methods depicted by equations 1 and 2. The reaction conditions were arrived at by varying palladium,[21] solvent, ligand, reducing agent, reaction temperature and time.



The investigation of the reaction conditions resulted in a procedure involving the use of 1 equivalent of the nucleoside, 1.2 equivalent of the organostannane compound, 5 mol % $Pd(OAc)_2$, 15 mol % CuI, 15 mol % PPh_3 in THF under argon at indicated reaction temperature and time (TABLE 1). Most importantly, the standard catalyst ($Pd[PPh_3]_4$) for Stille type coupling was significantly less effective and for some solvent and stannane

TABLE 1. Palladium-catalyzed coupling reaction of 8-bromopurine nucleosides with phenyl and vinylstannanes

nucleoside	X	temp(°C)/time(h)	R^2	yield(%)	product
1	Me	100 / 24		62	**4**
1	Bu	80 / 24 60 / 24		56 100	**5**
1	Bu	110 / 24 80 / 24 60 / 24		67 81 72	**6**
2	Me	100 / 24		81	**7**
2	Bu	110 / 24 90 / 12		27 95	**8**
2	Bu	90 / 24		72	**9**
3	Me	100 / 48		67	**10**
3	Bu	100 / 36 80 / 48		61 0	**11**

combinations failed to give any product. The yield of these reactions was also dependent upon the reactivity of the organostannane compounds, which is vinyltributylstannane > 2-ethoxyvinyltributylstannane > phenyltrimethylstannane. Phenyltrimethylstannane usually required a higher reaction temperature and longer reaction time. With more reactive organostannane compounds lower temperatures usually provided higher yields of product.

Vinyl- and aryltrialkylstannane reagents reacted with nucleosides **1** and **2** to give good to excellent yields of coupling products **4** - **9**. Different protection groups on the nucleosides were also studied, such as isopropylidene protection of the 2',3'-dihydroxy

and *t*-butyldimethylsilyl protection of the 5'-hydroxyl group. Protection of the 5'-hydroxyl in **1**, **2**, and **3** is essential for the reaction to proceed successfully, while the type of protecting group does not make a significant difference in the yield of the products.

Temperature has a significant effect on the coupling reaction. It was observed that when the reaction temperature is higher than 100 °C, the palladium catalyst is decomposed and the starting material recovered. Therefore, careful control of the reaction temperature is important for the success of the coupling reaction. A similar result was observed by Hauck.[22]

It was previously reported that the ligand tri(2-furyl)phosphine (TFP) led to smooth palladium catalyzed coupling and that other ligands such as *trans,trans*-dibenzylidieneacetone (dba) and PPh_3 caused decomposition of the catalyst. However, our studies with several ligands, such as PPh_3, TFP, $P(o\text{-}CH_3C_6H_4)_3$ and dba, indicated that PPh3 is the preferred ligand. One interpretation of these results is that the most critical reaction variables are temperature and the ratio of palladium to phosphine and that the type of phosphine ligand plays a minor role in determining the activity of the catalyst system used.

In conclusion, we have developed a palladium catalyzed method which allows 8-bromo purine nucleosides to cross-couple with vinyl- or arylorganostannanes. The catalyst used is more active allowing the reaction to proceed at lower temperature, which enables the completion of the coupling with higher yields. Work is underway to study RNA and DNA structures that include these modified purines.

Experimental. NMR spectra were obtained in $CDCl_3$ on a Bruker ARX300 spectrometer using either Me_4Si or the residual ^1H resonances in deuterated solvent as an internal standard. Mass Spectra were obtained from the facilities at the University of California at Berkeley and Washington State University. Fast atom bombardment mass spectra (FAB MS) were obtained with VG 70 SE & ZAB2-EQ/FAB(+). THF was distilled under an argon atmosphere from sodium and benzophenone. Pyridine was distilled from CaH_2. Phenyltrimethylstannane, vinyltributylstannane, ethoxylvinyltributylstannane, **1**, **3** and 2'-deoxyadenosine monohydrate were from Aldrich Chemical Company. The starting nucleosides **1**, **2** and **3** were prepared according to literature procedures.[23]

General procedure for the palladium catalyzed coupling reaction. To a reaction flask with a Teflon vacuum valve was added nucleoside (0.2 mmol), organostannane (0.22 mmol), $Pd(OAc)_2$ (0.01 mmol), CuI (0.03 mmol), PPh_3 (0.03 mmol), and THF. The flask was flushed with argon gas for 5 minutes and then heated at the desired temperature until TLC shown all nucleoside was consumed. THF was removed on a rotary evaporator and the residue was dissolved in CH_2Cl_2 (15 mL) and washed with brine (2 x 10 mL). After drying over $MgSO_4$, the CH_2Cl_2 was removed on a rotary

evaporator and the crude product was purified by flash silica gel chromatography (MeOH:CH_2Cl_2, 2:98).

Analytical Data

8-Phenyl-2',3',5'-triacetyladenosine (4). ^1H NMR ($CDCl_3$) δ 2.02 (s, 3 H), 2.08 (s, 3 H), 2.10 (s, 3 H), 4.35 (m, 2 H), 4.52 (m, 1 H), 5.95 (d, J = 4.3 Hz, 1 H), 6.02 (t, J = 5.9 Hz, 1 H), 6.16 (s, 2 H), 6.50 (dd, J = 5.9, 4.3 Hz, 1 H), 7.56 (m, 3 H), 7.76 (m, 2 H), 8.35 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.4, 20.5, 20.7, 62.9, 70.6, 72.1, 79.9, 87.8, 119.5, 128.9, 129.0, 129.6, 130.6, 150.7, 151.8, 152.6, 155.4, 169.3, 169.5, 170.7; HRMS (EI) m/z 469.1585, calcd 469.1597 for $C_{22}H_{24}N_5O_7$.

8-Vinyl-2',3',5'-triacetyladenosine (5). ^1H NMR ($CDCl_3$) δ 2.06 (s, 3 H), 2.07 (s, 3 H), 2.15 (s, 3 H), 4.37 (m, 2 H), 4.50 (m, 1 H), 5.75 (dd, J = 11.1, 1.2 Hz, 1 H), 5.88 (t, J = 5.4 Hz, 1 H), 5.95 (s, 2 H), 6.13 (d, J = 5.1 Hz, 1 H), 6.25 (t, J = 5.4 Hz, 1 H), 6.47 (dd, J = 17.1, 1.2 Hz, 1 H), 6.87 (dd, J = 17.1, 11.1 Hz, 1 H), 8.32 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.4, 20.6, 20.7, 63.1, 70.4, 72.4, 80.1, 86.2, 123.0, 124.8, 148.5, 150.6, 152.8, 155.1, 169.4, 169.6, 170.5; HRMS (EI) m/z 419.1436, calcd 419.1441 for $C_{18}H_{21}N_5O_7$.

8-2-Ethoxyvinyl-2',3',5'-triacetyladenosine (6). ^1H NMR ($CDCl_3$) δ 1.44 (t, J = 7.0 Hz, 3 H), 2.06 (s, 3 H), 2.09 (s, 3 H), 2.13 (s, 3 H), 4.01 (m, 2 H), 4.34 (m, 2 H), 4.52 (m, 1 H), 4.67 (d, J = 2.9 Hz, 1 H), 5.04 (d, J = 2.9 Hz, 1 H), 5.91 (s, 1 H), 6.05 (t, J = 5.8 Hz, 1 H), 6.38 (dd, J = 5.8, 4.3 Hz, 1 H), 6.43 (d, J = 4.3 Hz, 1 H), 8.34 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 20.4, 20.5, 20.7, 63.2, 64.2, 70.6, 72.5, 79.7, 87.7, 92.0, 119.0, 147.0, 150.5, 151.1, 153.2, 155.4, 169.2, 169.4, 170.6; HRMS (EI) m/z 463.1691, calcd 463.1703 for $C_{20}H_{25}N_5O_8$.

8-Phenyl-2'-deoxy-3',5'-diacetyladenosine (7). ^1H NMR ($CDCl_3$) δ 2.08 (s, 3 H), 2.09 (s, 3 H), 2.06 (m, 1 H), 3.96 (m, 1 H), 4.30 (m, 1 H), 4.42 (dd, J = 11.6, 6.4 Hz, 1 H), 4.59 (dd, J = 11.6, 5.3 Hz, 1 H), 5.65 (m, 1 H), 5.74 (s, 2 H), 6.25 (t, J = 7.1 Hz, 1 H), 7.56 (m, 3 H), 7.77 (m, 2 H), 8.35 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.8, 21.0, 29.7, 34.0, 63.7, 75.2, 82.6, 85.4, 120.2, 128.9, 129.4, 129.6, 130.4, 150.8, 151.9, 152.3, 155.3, 170.3, 170.8; HRMS (EI) m/z 411.1529, calcd 411.1543 for $C_{20}H_{21}N_5O_5$.

8-Vinyl-2'-deoxy-3',5'-diacetyladenosine (8). ^1H NMR ($CDCl_3$) δ 2.10 (s, 3 H), 2.14 (s, 3 H), 2.43 (m, 1 H), 3.57 (m, 1 H), 4.29 (m, 1 H), 4.38 (dd, J = 11.8, 5.2 Hz, 1 H), 4.48 (dd, J = 11.1, 4.3 Hz, 1 H), 5.53 (m, 1 H), 5.70 (dd, J = 11.1, 1.2 Hz, 1 H), 6.28 (s, 2 H), 6.47 (m, 2 H), 6.97 (dd, J = 17.2, 11.1 Hz, 1 H), 8.32 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.7, 20.9, 35.5, 63.6, 74.5, 82.2, 83.8, 119.3, 123.7, 124.1, 148.6, 150.6, 152.5, 155.3, 170.3, 170.5; HRMS (FAB) m/z $(M + 1)^+$ 362.1467, calcd 362.1464 for $C_{16}H_{19}N_5O_5 + H^+$.

8-2-Ethoxyvinyl-2'-deoxy-3',5'-diacetyladenosine (9). ^{1}H NMR ($CDCl_3$) δ 1.40 (t, J = 7.0 Hz, 3 H), 2.03 (s, 3 H), 2.09 (s, 3 H), 2.32 (m, 1 H), 3.71 (m, 1 H), 3.97 (m, 2 H), 4.25 (m, 1 H), 4.40 (dd, J = 17.4, 6.6 Hz, 1 H), 4.55 (dd, J = 17.4, 6.6 Hz, 1 H), 4.64 (d, J = 3.0 Hz, 1 H), 4.95 (d, J = 3.0 Hz, 1 H), 5.60 (m, 1 H), 6.06 (s, 1 H), 6.53 (t, J = 7.1 Hz, 1 H), 8.27 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 20.8, 20.9, 34.8, 63.8, 64.2, 75.0, 82.3, 85.6, 91.9, 119.3, 147.3, 150.5, 151.3, 152.8, 155.6, 170.2, 170.7; HRMS (FAB) m/z $(M + 1)^+$ 406.172659, calcd 406.172580 for $C_{18}H_{23}N_5O_6 + H^+$.

8-Phenyl-2',3',5'-triacetylguanosine (10). ^{1}H NMR ($CDCl_3$) δ 2.00 (s, 3 H), 2.06 (s, 3 H), 2.09 (s, 3 H), 4.33 (m, 2 H), 4.52 (m, 1 H), 5.88 (d, J = 3.3 Hz, 1 H), 6.26 (t, J = 5.6 Hz, 1 H), 6.33 (t, J = 5.3 Hz, 1 H), 6.71 (s, 2 H), 7.55 (m, 3 H), 7.76 (m, 2 H), 12.46 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.5, 20.5, 20.7, 62.5, 70.3, 72.5, 79.1, 87.4, 117.1, 128.9, 129.2, 129.4, 129.9, 148.3, 152.2, 153.4, 159.2, 169.3, 169.4, 170.8; HRMS (EI) m/z 485.1546, calcd 485.1547 for $C_{22}H_{23}N_5O_8$.

8-Vinyl-2',3',5'-triacetylguanosine (11). ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 3 H), 2.09 (s, 3 H), 2.11 (s, 3 H), 4.35 (m, 2 H), 4.46 (m, 1 H), 5.65 (d, J = 11.7 Hz, 1 H), 5.97 (s, 2 H), 6.16 (s, 1 H), 6.25 (d, J = 17.1 Hz, 1 H), 6.61 (s, 2 H), 6.69 (dd, J = 17.1, 5.7 Hz, 1 H), 12.05 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.5, 20.5, 20.6, 62.8, 70.3, 72.4, 79.4, 85.9, 91.9, 116.7, 122.6, 145.5, 152.0, 153.4, 158.9, 169.4, 169.5, 170.7; HRMS (FAB) m/z $(M + 1)^+$ 436.147290, calcd. 436.146838 for $C_{18}H_{21}N_5O_8 + H^+$.

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