

Efficient One-Step Suzuki Arylation of Unprotected Halonucleosides, Using Water-Soluble Palladium Catalysts

Elizabeth C. Western,[§] Jonathan R. Daft,[‡] Edward M. Johnson, II,[‡] Peter M. Gannett,[‡] and Kevin H. Shaughnessy*,[§]

Department of Chemistry and the Center for Green Manufacturing, The University of Alabama, Box 870336, Tuscaloosa, Alabama 35487-0336, and Department of Basic Pharmaceutical Science, West Virginia University, Morgantown, West Virginia 26506-9530

kshaughn@bama.ua.edu

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Modification of nucleosides to give pharmaceutically active compounds, mutagenesis models, and oligonucleotide structural probes continues to be of great interest. The aqueous-phase modification of unprotected halonucleosides is reported herein. Using a catalyst derived from tris(3-sulfonatophenyl)phosphine (TPPTS) and palladium acetate, 8-bromo-2'-deoxyguanosine (8-BrdG) is coupled with arylboronic acids to give 8-aryl-2'-deoxyguanosine adducts (8-ArdG) in excellent yield in a 2:1 water: acetonitrile solvent mixture. The TPPTS ligand was found to be superior to water-soluble alkylphosphines for this coupling reaction. The coupling chemistry has been extended to 8-bromo-2'-deoxyadenosine (8-BrdA) and 5-iodo-2'-deoxyuridine (5-IdU), as well as the ribonucleosides 8-bromoguanosine and 8-bromoadenosine. Good to excellent yields of arylated adducts are obtained in all cases. With use of tri(4,6-dimethyl-3-sulfonatophenyl)phosphine (TXPTS), the Suzuki coupling of 8-BrdA and 5-IdU can be accomplished in less than 1 h at room temperature. This methodology represents an efficient and general method for halonucleoside arylation that does not require prior protection of the nucleoside.

Introduction

Synthesis of nonnatural nucleosides has attracted significant interest over the past 25 years due to the central role that oligonucleotides play in biochemical systems. *C*-Modified nucleosides have shown significant antiviral^{1–7} and anticancer^{1,8–10} activity, and have been studied as model compounds for DNA modification by carcinogenic compounds.^{11–18} 5-Substituted uracil deriva-

tives have been prepared containing protein recognition elements,^{19–21} fluorophores,^{21–24} and spin labels.^{25–27} Modified nucleosides have also been incorporated into oligonucleotides to induce site-specific cross-linking of nucleic acid structures.^{28–33} Because of the importance

* Corresponding author. Phone: (205) 348-4435. Fax: (205) 348-9104.

[§] The University of Alabama.

[‡] West Virginia University.

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of *C*-modified nucleosides, there is a continuing need to develop efficient syntheses of these compounds.

8-Aryl-2'-deoxyguanosine (8-ArdG) adducts have been shown to form in DNA in the presence of carcinogenic arylhydrazines.^{13,14,17,34} Arylhydrazines are metabolized to arenediazonium ions^{35,36} and then to aryl radicals¹⁵ that lead to 8-ArdG and 8-aryl-2'-deoxyadenosine (8-ArdA) adducts.^{13,14,17,37} Although formation of 8-arylpurine nucleosides under biological conditions is well precedented, the role of these modifications in mutagenesis is less clear. To study the mutagenic role of 8-arylpurine nucleosides, it is necessary to prepare authentic samples and incorporate them into oligonucleotides. Therefore, we have sought to develop an efficient and general method to prepare 8-arylpurine nucleoside adducts.

Palladium-catalyzed cross-coupling reactions are powerful methods for the *C*-modification of nucleosides.^{38,39} Although Pd-catalyzed modification of halonucleosides has been widely used, there are few examples of palladium-catalyzed syntheses of 8-arylpurine nucleosides.^{40–42} A Suzuki coupling of the readily available 8-halopurine nucleosides and arylboronic acids was expected to be an efficient method to prepare the desired arylated adducts. Typically, the Suzuki coupling would be carried out under anhydrous conditions in nonpolar solvents with a nucleoside that has been protected to make it more lipophilic. The necessary protection/deprotection sequence adds two steps to the synthetic scheme, which typically are achieved in 50–80% overall yield, and results in increased production of waste.

Given our experience with aqueous-phase Suzuki couplings,⁴³ we felt that arylated nucleosides could be prepared more efficiently in an aqueous solvent from unprotected halonucleosides. Water-soluble palladium catalysts have received much interest due to the potential environmental and economic benefits of doing catalysis in water–organic biphasic systems.^{44,45} The use of water-soluble catalysts to carry out *homogeneous* cross-coupling reactions with hydrophilic biomolecules has received much less attention, however.^{46–48} Casalnuovo⁴⁸ initially

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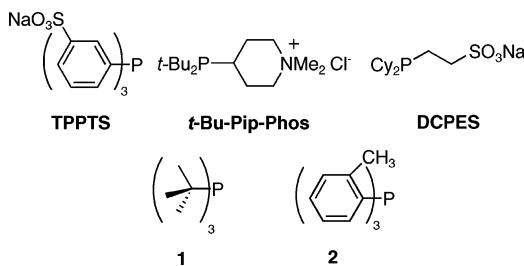
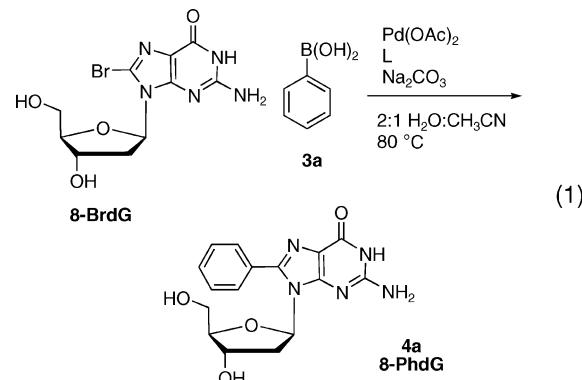


FIGURE 1. Phosphines screened for coupling of 8-BrdG.

reported the Suzuki and Sonogashira couplings of 5-iodopyrimidine nucleosides in 1990, but the yields were generally modest. To our knowledge, there have been no subsequent studies of the usefulness of this methodology. In this paper we report the development of a successful aqueous-phase method for the Suzuki coupling of 8-bromo-2'-deoxyguanosine (8-BrdG) using commercially available, or easily prepared, water-soluble phosphine ligands and the application of this methodology to other halogenated nucleosides.

Results

Nucleoside Arylation with TPPTS/Pd(OAc)₂. A series of water-soluble phosphines were screened for their ability to provide active palladium catalysts for the model coupling of 8-BrdG⁴⁹ and phenylboronic acid (eq 1). The



ligands screened were water-soluble phosphines TPPTS, *t*-Bu-Pip-phos, and DCPES,⁵⁰ and hydrophobic phosphines tri-*tert*-butylphosphine (**1**) and tri-*o*-tolylphosphine (**2**, Figure 1). On the basis of our experience with aqueous-phase Suzuki couplings, we felt that the bulky, water-soluble alkylphosphine *t*-Bu-Pip-phos⁴³ would prove more effective than DCPES and the commonly used TPPTS for the arylation of 8-BrdG.

Screening reactions were carried out with standard conditions of Pd(OAc)₂ (5 mol %), the ligand (5–12.5 mol %), sodium carbonate, and a 2:1 water:acetonitrile mixture as solvent (Table 1). In contrast to typical aryl bromides, Suzuki coupling of 8-BrdG with *t*-Bu-Pip-phos/Pd(OAc)₂ gave less than 10% conversion at room temperature after 18 h. At 80 °C, the *t*-Bu-Pip-phos/Pd(OAc)₂ catalyst system gave approximately 50% conversion after 2 h, with complete conversion occurring after 18 h as

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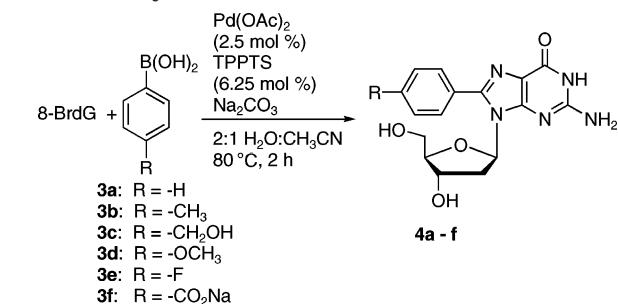
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TABLE 1. Ligand Effects on the Arylation of 8-BrdG^a

entry	ligand	time, h	T, °C	8-BrdG:8-PhdG ^b
1	none	18	80	75:18
2	TPPTS	2	80	<1:97 ^c
3	TPPTS	7	50	11:89
4	t-Bu-Pip-phos ^d	18	80	13:79
5	DCPES ^d	2	80	<1:89 ^c
6	DCPES ^d	7	50	55:34
7	(t-Bu) ₃ P (1) ^d	18	80	81:5
8	(o-tol) ₃ P (2)	18	80	90:3

^a 5 mol % of catalyst (2.5:1 L:Pd), 0.1 mmol of 8-BrdG, 0.12 mmol of PhB(OH)₂, 0.2 mmol of Na₂CO₃ in 1 mL of 2:1 water:CH₃CN.

^b Relative HPLC peak area observed at 263 nm. Remainder of area represents side products. ^c No 8-BrdG was detected. ^d L:Pd = 1:1.

TABLE 2. Synthesis of 8-ArdG Adducts^a

entry	ArB(OH) ₂	8-ArdG	yield, ^b %
1	3a	4a	82
2	3b	4b	95
3	3c	4c	73
4	3d	4d	85
5	3e	4e	82
6	3f	4f	77

^a Reactions were run with 2.5 mol % of TPPTS/Pd(OAc)₂, (L:Pd = 2.5:1) at 80 °C for 2–4 h. ^b Average isolated yield from two or more trials.

determined by RP-HPLC. Surprisingly, the catalyst derived from TPPTS/Pd(OAc)₂ gave complete conversion to 8-PhdG in less than 2 h at 80 °C. DCPES, which gave less active catalysts than t-Bu-Pip-phos for aryl halides,⁵¹ also gave complete conversion to 8-PhdG after 2 h at 80 °C. Hydrophobic phosphines such as tri-*tert*-butylphosphine (**1**)⁵² and tri-*o*-tolylphosphine (**2**) gave inactive catalysts for the arylation of 8-BrdG (entries 7 and 8). Palladium acetate alone was also ineffective for this reaction. At 50 °C, TPPTS gave a more active catalyst than DCPES (entries 3 and 6). In all cases, HPLC traces of the crude reaction mixture showed that 8-BrdG and 8-PhdG comprised >90% of the material with absorbance at 263 nm.⁵³ Traces of guanine or 8-phenylguanine from deglycosylation and biphenyl from phenylboronic acid homocoupling were also observed.

Although surprised by the low activity of catalysts derived from t-Bu-Pip-phos compared to TPPTS, we were gratified that the desired coupling of the unprotected nucleoside could be carried out efficiently. The TPPTS/Pd(OAc)₂ catalyst system was applied to the preparative scale synthesis of 8-PhdG (**4a**, Table 2). For these reactions, the catalyst loading was lowered to 2.5 mol %

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TABLE 3. Arylation of Halonucleosides with TPPTS/Pd(OAc)₂^a

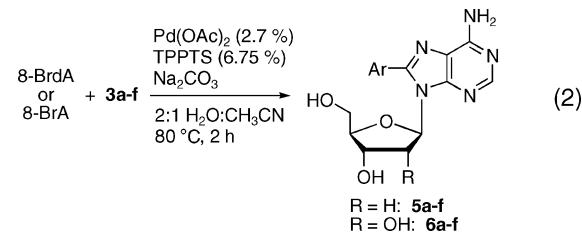
entry	nucleoside	ArB(OH) ₂	product	yield, ^b %
1	8-BrdA	3a	5a	87
2	8-BrdA	3b	5b	90
3	8-BrdA	3c	5c	91
4	8-BrdA	3d	5d	77
5	8-BrdA	3g	5g	68
6	8-BrA	3a	6a	88
7	8-BrA	3d	6d	85
8	8-BrA	3e	6e	99
9	5-IdU	3a	7a	83
10	5-IdU	3d	7d	82
11	5-IdU	3e	7e	92
12	8-BrG	3a	8a	64
13	8-BrG	3d	8d	65
14	8-BrG	3e	8e	73

^a Reactions were run with 2.7 mol % of TPPTS/Pd(OAc)₂ (L:Pd = 2.5:1) at 80 °C for 2–4 h. ^b Average isolated yield from two or more trials.

with no apparent decrease in the reaction rate. While all of the reactants dissolve readily in the 2:1 water:acetonitrile solvent under the reaction conditions, 8-PhdG is only sparingly soluble in water (pH 7). Thus, 8-PhdG was easily recovered by diluting the reaction mixture with water and adjusting the pH to 6–7. The 8-PhdG adduct precipitated as a pure solid as determined by ¹H and ¹³C NMR spectroscopy. Over a series of trials, the average yield of 8-PhdG was 82%.

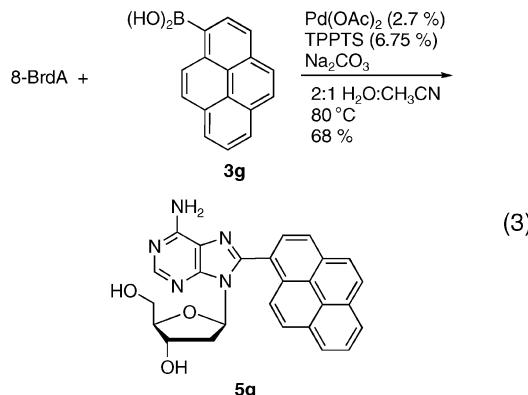
Aqueous-phase coupling of 8-BrdG and a series of arylboronic acids was carried out to determine the scope and utility of the reaction (Table 2). Targets were chosen both to probe the electronic effects of the boronic acid on the reaction and to provide 8-ArdG adducts of interest for conformational studies of DNA containing these adducts. 8-ArdG adducts **4b** and **4c** are formed under biologically relevant conditions.^{12–14,34} These adducts were prepared in good to excellent yield with TPPTS/Pd(OAc)₂ (entries 2 and 3). High yields were also obtained by using arylboronic acids with electron-donating (4-methoxy, **4d**) and electron-withdrawing (4-fluoro, **4e**) substituents (entries 4 and 5). Spectroscopically pure samples of the 8-ArdG products **4a–e** were conveniently recovered by recrystallization directly from the crude reaction mixture. Coupling of 8-BrdG with 4-carboxyphenylboronic acid gave the desired product as a sodium salt (**4f**), which was isolated in 77% yield by reverse-phase chromatography (entry 6).

With an efficient methodology in hand, its application to other halonucleosides was explored. Purine nucleoside 8-bromo-2'-deoxyadenosine (8-BrdA) also gave excellent yields of 8-ArdA adducts in the presence of TPPTS/Pd(OAc)₂ (eq 2, entries 1–4, Table 3). The 8-ArdA adducts

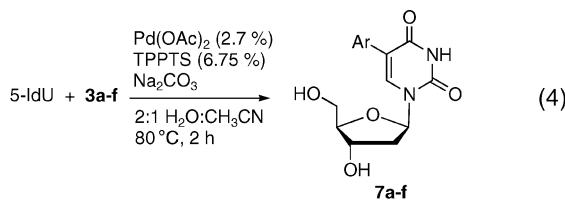


were more water-soluble than the 8-ArdG adducts, so they could not be recovered by precipitation/recrystallization.

zation. After dilution and pH adjustment, these compounds were purified by passing the reaction mixture through a 10-g column of C-18 RP-silica gel eluting with a water/methanol gradient. More hydrophobic boronic acids can also be accommodated. Pyren-1-ylboronic acid was coupled with 8-BrdA to give 8-(pyren-1-yl)-2'-deoxyadenosine (**5g**) in 68% yield (eq 3). Pyrene-substituted

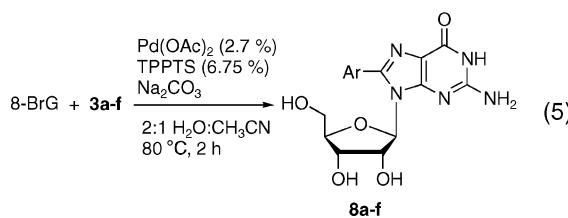


nucleosides are of interest for electron injection into DNA^{54,55} and as fluorescence probes.²¹ Coupling of 5-iodo-2'-deoxyuridine (**5-IdU**) and phenylboronic acid in the presence of TPPTS/Pd(OAc)₂ gave the desired 5-PhdU adduct (**7a**) in 83% yield (eq 4). The 4-methoxyphenyl (**7d**)



and 4-fluorophenyl (**7e**) adducts were also isolated in excellent yields (82 and 92% respectively, entries 10 and 11).

Ribonucleosides could also be efficiently coupled by using the TPPTS/Pd(OAc)₂ catalyst system (Table 3). Coupling of 8-bromo-2'-deoxyadenosine (**8-BrdA**) and arylboronic acids gave excellent yields (85–99%) of 8-aryla adducts (**6a–c**) (eq 2, entries 6–8). Coupling of 8-bromo-2'-deoxyguanosine (**8-BrG**) with phenylboronic acid under the standard conditions gave 8-PhdG (**8a**) in somewhat lower yield



than was obtained with 8-PhdG (64% compared to 82%). As in the 8-PhdG case, the products could be recovered by simple recrystallization from the reaction mixture. HPLC analysis of the crude reaction mixture showed that the reaction had gone cleanly to completion at ap-

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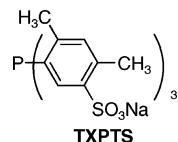


FIGURE 2. Tri(4,6-dimethyl-3-sulfonatophenyl)phosphine trisodium salt (TXPTS).

TABLE 4. Ligand Screening in the Arylation of 8-BrdA^a

entry	ligand	time, h	T, °C	8-BrdA:8-PhdA ^b
1	TPPTS	1	80	<1:97 ^c
2	TPPTS	3	50	<1:89 ^c
3	TPPTS	24	23	13:74
4	TXPTS	1	80	<1:98 ^c
5	TXPTS	1	50	<1:98 ^c
6	TXPTS	0.5	23	<1:96 ^c
7	t-Bu-Pip-phos	1	80	<1:89 ^c
8	t-Bu-Pip-phos	3	50	55:30
9	t-Bu-Pip-phos	24	23	43:38
10	t-Bu-Pip-phos	24	23	16:62 ^d
11	DCPES	1	80	<1:92 ^c
12	DCPES	3	50	<1:97 ^c
13	DCPES	24	23	45:48
14	none	1	80	89:6

^a 10 mol % of catalyst (2.5:1 L:Pd), 0.1 mmol of 8-BrdA, 0.12 mmol of PhB(OH)₂, 0.2 mmol of Na₂CO₃ in 1 mL of 2:1 water: CH₃CN. ^b Relative HPLC peak area observed at 263 nm. Remainder of area represents side products. ^c No 8-BrdG was detected. ^d L:Pd = 1:1.

proximately the same rate observed for 8-PhdG. Isolated yields were consistently lower than were obtained with dG, however. Coupling of 8-BrG with 4-methoxyphenylboronic acid and 4-fluorophenylboronic acid gave good yields of adducts **8d** and **8e** (entries 13 and 14, Table 3).

Comparison of the reactivity of 8-BrdG, 8-BrdA, and 5-IdU. Although a very efficient methodology for the Suzuki coupling of unprotected halonucleosides had been developed, we were intrigued by the unexpected ligand dependence on catalyst activity observed with 8-BrG. To determine how the nucleoside structure affected the rate of the cross-coupling reaction, small-scale (0.1 mmol) model couplings of 8-BrdA and 5-IdU with phenylboronic acid were followed by HPLC. The activity of catalysts derived from the ligands initially screened with 8-BrG, TPPTS, t-Bu-Pip-phos, and DCPES was determined as a function of nucleoside and temperature. A fourth ligand, tri(4,6-dimethyl-3-sulfonatophenyl)phosphine trisodium salt (TXPTS),⁵⁶ was also included in this round of screening (Figure 2). TXPTS was prepared as a more electron-rich, sterically demanding analogue of TPPTS.

The coupling of 8-BrdA and phenylboronic acid at 80 °C gave very different results than were obtained with 8-BrG. In this case, t-Bu-Pip-phos gave comparable conversion rates to TPPTS and DCPES. For each ligand, the 8-PhdA adduct accounted for between 90% and 98% of the area in HPLC traces taken after 1 h with no residual 8-BrdA observed (Table 4, entries 1, 4, 7, and 11). Essentially no conversion is observed in the absence of phosphine (entry 14). At 50 °C, the activity of the t-Bu-Pip-phos/Pd(OAc)₂ begins to drop off relative to the other ligands tested. TPPTS- and DCPES-derived catalysts each gave complete conversion in 3 h at 50 °C. TXPTS

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TABLE 5. Ligand Screening in the Arylation of 5-IdU^a

entry	ligand	time, h	T, °C	5-IdU:5-PhdU ^b
1	TPPTS	0.5	80	<1:97 ^c
2	TPPTS	0.5	50	32:48
3	TPPTS	1	50	<1:91 ^c
4	TPPTS	1	23	81:<1
5	TPPTS	17	23	<1:99 ^d
6	TXPTS	0.2	80	<1:99 ^d
7	TXPTS	0.5	50	<1:99 ^d
8	TXPTS	1	23	<1:99 ^d
9	t-Bu-Pip-phos	0.5	50	<1:99 ^{d,e}
10	t-Bu-Pip-phos	1	23	85:15 ^e
11	t-Bu-Pip-phos	5	23	<1:99 ^d

^a 10 mol % of catalyst (2.5:1 L:Pd), 0.1 mmol of 5-IdU, 0.12 mmol of PhB(OH)₂, 0.7 mmol of Na₂CO₃ in 1 mL of 2:1 water:CH₃CN.

^b Relative HPLC peak area observed at 300 nm. Remainder of area represents side products. ^c No 5-IdU was detected. ^d 5-PhdU was the only peak observed. ^e L:Pd = 1:1.

gave the most active catalyst under these conditions, giving complete conversion in less than 1 h. At room temperature, the TPPTS/Pd(OAc)₂ system gave 74 area % product after 17 h, DCPES gave only 50% conversion to product after 17 h, and t-Bu-Pip-phos gave approximately 40% product. A second run was carried out with the t-Bu-Pip-phos/Pd(OAc)₂ system with use of a 1:1 ratio of ligand:Pd, since this ratio was known to give more active catalysts at room temperature than the 2:1 ratio used in entry 9.⁴³ Under these conditions, the t-Bu-Pip-phos system gave comparable activity to the TPPTS system (entry 10). The TXPTS/Pd(OAc)₂ gave 100% conversion and >95% product in less than 30 min at room temperature (Table 4, entry 6).

The same set of four ligands was screened in the coupling of 5-IdU and phenylboronic acid (Table 5). At 80 °C, 5-IdU was completely converted to 5-PhdU in 30 and 10 min in reactions catalyzed by TPPTS/Pd(OAc)₂ and TXPTS/Pd(OAc)₂ respectively (entries 1 and 6). At 50 °C, the TXPTS system gave complete conversion to 5-PhdU after 30 min (entry 7). The t-Bu-Pip-phos system (1:1 ligand:Pd) also gave complete conversion in this time frame (entry 9). The TPPTS system, however, gave only a 32:48 ratio of 5-IdU:5-PhdU as determined by HPLC after 30 min at 50 °C, but went to completion after 1 h (entries 2 and 3). At room temperature, the TXPTS system gave complete conversion to product in less than 1 h. In contrast, the TPPTS system gave only traces of product after 1 h, although complete conversion to 5-PhdU is accomplished after 17 h (entries 4 and 5). The t-Bu-pip-phos/Pd(OAc)₂ system gave only 15% product after 1 h with a 1:1 ligand:Pd ratio. Increasing the amount of phosphine to a 2.5:1 ligand:Pd ratio gave complete conversion after 5 h (entry 11).

A comparison of the coupling rate for 8-BrdA, 8-BrdG, and 5-IdU at room temperature with TPPTS and TXPTS shows the significant differences in reactivity of the nucleosides (Figure 3). In the presence of TXPTS/Pd(OAc)₂ (10 mol %) the coupling rate followed the trend 8-BrdA ≈ 5-IdU ≫ 8-BrdG. The catalyst derived from TXPTS gave significantly higher rates of conversion for all nucleosides than TPPTS/Pd(OAc)₂. With TXPTS, 8-BrdA is completely converted to 8-PhdA in less than 30 min (96 area % 8-PhdA), while a TPPTS derived catalyst gave only a 13:74 ratio of 8-BrdA and 8-PhdA after 30 min. Coupling of 5-IdU and phenylboronic acid

goes to completion in less than 30 min in the presence of TXPTS/Pd(OAc), while the TPPTS/Pd(OAc)₂ catalyst system requires 17 h to reach completion. A similar, but more dramatic effect is seen with 8-BrdG. With TXPTS, a 1:1 ratio of 8-PhdG:8-BrdG is seen after 18 h, while TPPTS gave less than 10 area % product after 24 h. After 76 h, only a small amount of product (8-PhdG:8-BrdG = 16:70) had formed with the TPPTS/Pd(OAc)₂ system.

Solvent Effects. Although a 2:1 water:acetonitrile mixture proved to be effective for the arylation of halonucleosides, we have explored the use of other solvent systems with the goal of increasing the water content of the solvent. The coupling of 8-BrdA and phenylboronic acid in the presence of TPPTS/Pd(OAc)₂ at 50 °C in a variety of solvent mixtures was monitored by HPLC (Table 6). Increasing the water:acetonitrile ratio from 2:1 to 4:1 gave nearly identical results (entry 1 and 2), while a further increase to 10:1 water:acetonitrile caused an appreciable inhibition of the coupling reaction and an increase in the formation of deglycosylated adenine derivatives and boronic acid homocoupling products (entry 3). Use of methanol as the organic cosolvent in a 2:1 water:methanol ratio gave similar results to those seen with 2:1 water:acetonitrile (entry 5), while increasing the amount of methanol to give a 1:1 ratio resulted in a significant increase in byproduct formation (entry 4). Similar to the water/acetonitrile system, an increase in the water concentration also resulted in a decrease in the rate of product formation and an increase in side product formation. Acetone was shown to be a poor cosolvent, as the reactions gave lower conversion and an increase in side product formation (entries 7 and 8).

Palladium Precursor Screening. We reasoned that the lower conversions observed at higher water concentration might have been due in part to the poor solubility of Pd(OAc)₂ in water. To test this hypothesis, the activity of water-soluble palladium(II) sources for the coupling of 8-BrdA and phenylboronic acid in water were screened (Table 7). 8-BrdA was completely consumed after 20 min at 80 °C in neat water in the presence of the TPPTS/Pd(OAc)₂ system (10 mol %), but 8-PhdA was formed in low yield (entry 1). At room temperature with TXPTS as the ligand, slow, but clean, conversion to 8-PhdA was observed (entry 2). Palladium nitrate, palladium sulfate, and sodium tetrachloropalladate in combination with TPPTS, in contrast, gave complete conversion and good yields of 8-PhdA in less than 30 min at 80 °C, using water as the only solvent (entries 3, 5, and 7). Catalysts derived from Pd(NO₃)₂, Pd(SO₄), or Na₂PdCl₄ and TXPTS gave very efficient coupling to 8-PhdA at room temperature in water (entries 4, 6, and 8). Complete conversion was obtained in less than 30 min as determined by HPLC analysis. In these reactions, 8-PhdA accounted for ≥94% of the HPLC area.

Application of TXPTS/Pd Catalyst System. Several preparatory scale reactions were carried out with use of the TXPTS/Pd(OAc)₂ catalyst system (Table 8). Excellent yields were obtained for the coupling of 8-BrdA and arylboronic acids with this system, using 2.7 mol % of Pd. 8-PhdA (**7a**) and 8-(4-methoxyphenyl)da (**7d**) were obtained in 94% and 99% isolated yield, respectively (entries 1 and 2). Preparative scale coupling of 8-BrdA and phenylboronic acid in water with Pd(NO₃)₂ as the catalyst precursor gave 8-PhdA in 71% yield at room

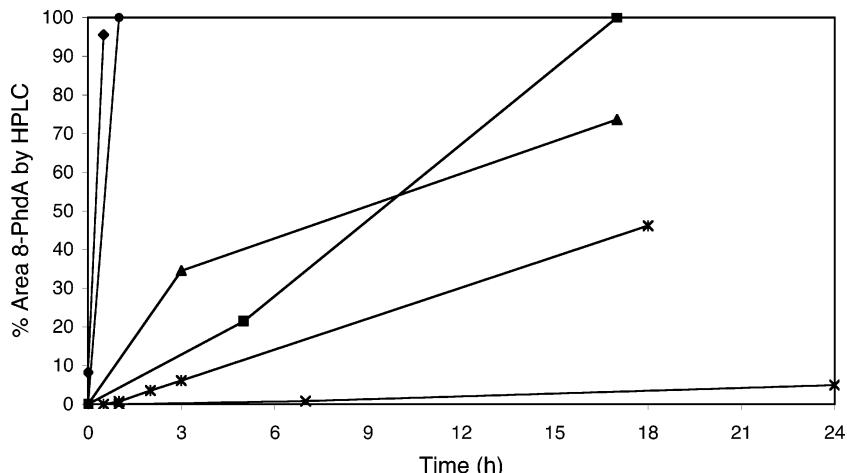


FIGURE 3. Room-temperature cross-coupling of halonucleosides and phenylboronic acids with TPPTS or TXPTS: \blacklozenge , 8-BrdA, TXPTS; \bullet , 5-IdU, TXPTS; \blacktriangle , 8-BrdA, TPPTS; \blacksquare , 5-IdU, TPPTS; $*$, 8-BrdG, TXPTS; \times , 8-BrdG, TPPTS.

TABLE 6. Solvent Screening^a

entry	cosolvent	ratio ^b	8-BrdA:8-PhdA ^c
1	CH ₃ CN	2:1	<1:89 ^d
2	CH ₃ CN	4:1	<1:90 ^d
3	CH ₃ CN	10:1	18:57
4	CH ₃ OH	1:1	2:73
5	CH ₃ OH	2:1	<1:93 ^e
6	CH ₃ OH	5:1	22:57
7	acetone	1:1	34:35
8	acetone	2:1	10:57

^a Reactions were run with 10 mol % of TPPTS/Pd(OAc)₂ at 50 °C for 30 min. ^b Water:cosolvent ratio. ^c Relative HPLC peak area observed at 263 nm. Remainder of area represents side products. ^d No 8-BrdG was detected. ^e No 8-BrdA was observed.

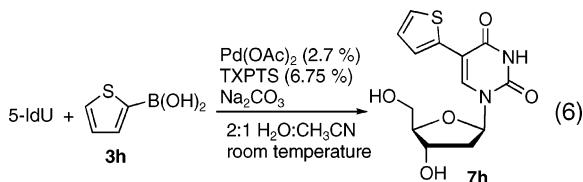
No 8-BrG was detected. No 8-BrdA was observed.

TABLE 7. Pd Precursor Screening for Coupling in Water^a

entry	Pd precursor	ligand	8-BrdA:8-PhdA ^b
1	Pd(OAc) ₂	TPPTS	<1:34 ^c
2	Pd(OAc) ₂	TXPTS	82:18
3	PdSO ₄	TPPTS	2:75
4	PdSO ₄	TXPTS	<1:94 ^c
5	Pd(NO ₃) ₂	TPPTS	<1:87 ^c
6	Pd(NO ₃) ₂	TXPTS	<1:>99 ^d
7	Na ₂ PdCl ₄	TPPTS	<1:89 ^c
8	Na ₂ PdCl ₄	TXPTS	<1:96 ^c

^a All reactions were run with 10 mol % of Pd for 30 min. Reactions with TPPTS were run at 80 °C, while reactions with TXPTS were run at 23 °C. ^b Relative HPLC peak area observed at 263 nm. Remainder of area represents side products. ^c No 8-BrdA observed. ^d 8-PhdA was the only peak observed by HPLC.

temperature (entry 3). Coupling of 5-IdU with thien-2-ylboronic acid (**3h**) gave a modest yield (45%) of 5-(thien-2-yl)-2'-deoxyuridine **7h** (eq 6), which has been shown to



be an active antiviral agent against the herpes simplex virus.^{3,6,57} Attempted coupling of 8-BrdG and phenylboronic acid gave a modest yield of 8-PhdG (49%) after 19 h at 50 °C (entry 6).

TABLE 8. Room-Temperature Arylation of Halonucleosides with TXPTS^a

entry	nucleoside	ArB(OH) ₂	product	yield, ^b %
1	8-BrdA	3a	5a	94
2	8-BrdA	3d	5d	99
3	8-BrdA	3a	5a	71 ^c
4	5-IdU	3h	7h	45
5	8-BrdG	3a	4a	50

^a Reactions were run with 2.7 mol % of TXPTS/Pd(OAc)₂ (L:Pd = 2.5:1) in 2:1 water:CH₃CN at room temperature. ^b Average isolated yield from two or more trials. ^c 2.7 mol % of TXPTS/Pd(NO₃)₂ in water at room temperature.

Discussion

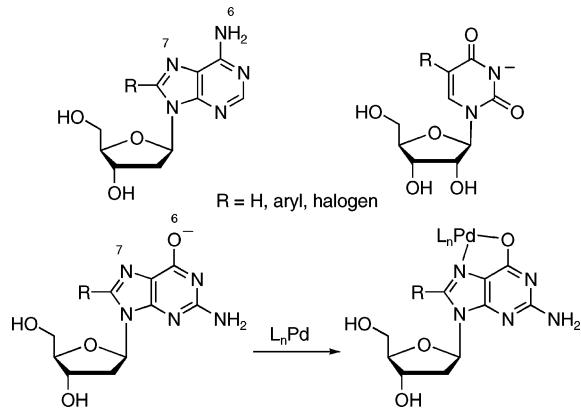
The methodology reported herein has proven to be a general and convenient method to prepare arylated nucleoside adducts. The components of the TPPTS/Pd(OAc)₂ catalyst are commercially available and air stable. Although the reactions should be run under a nitrogen atmosphere, reactions assembled in air and bubbled with nitrogen prior to heating gave similar yields to those assembled in a glovebox. The TPPTS/Pd(OAc)₂ system has been applied to the synthesis of 500-mg lots of 8-ToldG (**4b**) and 8-PhdA (**5a**). Yields of these larger scale reactions were as good or better than the 100-mg-scale reactions in Tables 2 and 3. 8-PhdG prepared by this methodology has been incorporated into an oligonucleotide to study the conformational effects of guanine arylation.⁵⁸ By using the easily prepared ligand TXPTS, the coupling chemistry can be accomplished efficiently at room temperature for 8-BrdA and 5-IdU, while 8-BrdG requires higher temperatures. Water-soluble palladium salts, such as palladium nitrate or tetrachloropalladate, in combination with TXPTS allow the coupling reaction to be carried out at room temperature in water without the need for an organic cosolvent.

Although the methodology reported herein should prove more efficient than the traditional organic solvent-based methods in many cases, a limitation of the aque-

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SCHEME 1. Pd Coordination to Nucleosides



ous-phase methodology should be noted. Aqueous-base labile functional groups will not be tolerated under aqueous-phase Suzuki conditions. In contrast many base-labile groups are tolerated when the arylation is carried out under anhydrous conditions. Therefore, for certain functional groups, coupling under anhydrous conditions will be the preferred method.

Nucleoside Effects on Reactivity. Dramatic differences in the activity of nucleosides for aqueous-phase coupling were observed particularly at room temperature. Guanosine nucleosides were found to be significantly less reactive than adenosine or uridine nucleosides. We believe that the decreased activity of 8-BrdG may be due to competitive coordination of palladium by the guanine base that occurs less efficiently with the adenine or uracil bases. Guanine and uracil have acidic protons and exist as their conjugate base under the reaction conditions (pH ca. 11, Scheme 1). Adenine does not have any appreciably acidic protons and remains as the neutral purine base. It is well-documented that guanine can coordinate to palladium and platinum through N7. Under basic conditions, guanine can form a stable chelate by coordination of N7 and O6 to the metal center.^{59–61} The ability of guanine to coordinate as an anionic chelating ligand appears to result in the observed inhibition. Uracil contains an acidic imide functionality, but cannot act as a chelating ligand. Adenine could act as a neutral chelating ligand (N7 and N6), but does not exist as an anion under these conditions. Both 8-BrdA and 5-IdU undergo facile Suzuki coupling at room temperature with the TXPTS/Pd(OAc)₂ catalyst system, while 8-BrdG is much less reactive.

Catalysts derived from *t*-Bu-Pip-phos were found to be less active than those derived from TPPTS for the coupling of 8-BrdG. These results are reversed from the relative catalytic activity observed for aqueous-phase Suzuki coupling of aryl bromides under similar conditions.⁴³ The higher activity of catalysts derived from TPPTS and TXPTS compared to *t*-Bu-Pip-phos, even at room temperature, is surprising, since it has been established that sterically demanding alkylphosphines, such as *t*-Bu₃P,^{52,62–65} give much more active catalysts than triarylphosphines for palladium-catalyzed cross-

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couplings under mild conditions. Although the reason for this reversal of activity remains unclear at this time, it does appear to be related to the nucleoside structure as well. Catalysts derived from *t*-Bu-Pip-phos gave similar or better activity to those derived from TPPTS for the coupling of 8-BrdA and 5-IdU (Tables 4 and 5), while they were much less active than TPPTS/Pd(OAc)₂ for the coupling of 8-BrdG (Table 1). Lakshman⁶⁶ has observed a similar lack of activity for *tert*-butyl-substituted phosphines in the Suzuki coupling of a protected 6-bromopurine nucleoside in organic solvents. Lakshman's results and our own show that there are significant differences in catalytic activity in the coupling of simple aryl halides and of halogenated nucleosides.

Conclusion

Water-soluble phosphines TPPTS and TXPTS in combination with Pd(OAc)₂ are efficient and general catalysts for the synthesis of 8-arylpurine nucleosides. This chemistry has also been extended to the synthesis of 5-aryl-2'-deoxyuridine adducts. The desired aryl-modified nucleosides can be obtained in a single step from the halogenated nucleoside, which are commercially available or can be prepared in one step from the parent nucleoside, through known procedures. In comparison, traditional methods would require protection of the halonucleoside, arylation, and deprotection, thus adding two steps to the synthetic scheme that are typically achieved in less than 80% overall yield. TPPTS is commercially available, while TXPTS is easily made in two steps via a published procedure.⁵⁶ With proper choice of palladium precursor it is possible to carry out the cross-coupling chemistry with water as the only solvent, which may prove advantageous with more hydrophilic substrates. The ligands and the palladium sources used are air-stable and require no special handling. Therefore, the methodology described herein should be accessible to anyone interested in preparing arylated nucleosides. We feel this methodology will prove to be a general and efficient extension of prior palladium-catalyzed modification of halonucleosides.

Experimental Section

General Method for Arylation of 8-BrdG and 8-BrG: Synthesis of 8-(4-Methoxyphenyl)-2'-deoxyguanosine (4d). Palladium acetate (2.2 mg, 0.01 mmol), TPPTS (14.8 mg, 0.025 mmol), sodium carbonate (80 mg, 0.75 mmol), 8-BrdG (128.6 mg, 0.371 mmol), and 4-methoxyphenylboronic acid (68.3 mg, 0.449 mmol) were placed in a round-bottomed flask under nitrogen. Degassed 2:1 water:acetonitrile was added (3.5 mL) and the reaction was heated in an oil bath at 80 °C until RP-TLC (1:1 water:methanol) showed complete conversion (2–4 h). The reaction was diluted with ca. 20 mL of water and the pH adjusted to 6–7 with use of 10% aqueous HCl. The

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mixture was heated to dissolve precipitated solids and then allowed to cool to 0 °C and stand for several hours. The product was recovered as a fine powder (123.5 mg, 89% yield). ¹H NMR (360 MHz, DMSO-*d*₆): δ 10.70 (br s, 1H), 7.58 (d, *J* = 8.63 Hz, 2H), 7.09 (d, *J* = 8.63 Hz, 2H), 6.35 (br s, 2H), 6.04 (dd, *J* = 6.78, 8.02 Hz, 1H), 5.11 (d, *J* = 4.31 Hz, 1H), 4.96 (dd, *J* = 5.55, 6.16 Hz, 1H), 4.33 (m, 1H), 3.83 (s, 3H), 3.79–3.77 (m, 1H), 3.67–3.61 (m, 1H), 3.57–3.52 (m, 1H), 3.27–3.14 (m, 1H), 2.03–1.97 (m, 1H). ¹³C NMR (90.6 MHz, DMSO-*d*₆): δ 161.3, 159.9, 156.0, 152.0, 146.0, 130.5, 123.0, 117.3, 114.0, 88.1, 85.1, 71.6, 62.5, 55.3, 37.0. High-resolution FAB-MS: calcd for C₁₇H₁₉N₅O₅·Na⁺ 396.1284, found 396.1285. Anal. Calcd for C₁₇H₁₉N₅O₅·H₂O: C, 52.19; H, 5.41; N, 17.89. Found: C, 52.79; H, 5.38; N, 17.89.

General Method for Arylation of 8-BrdA, 8-BrA, and 5-IdU: Preparation of 8-Phenyl-2'-deoxyadenosine (5a). Palladium acetate (2.2 mg, 0.01 mmol), TPPTS (11.5 mg, 0.02 mmol), sodium carbonate (80 mg, 0.75 mmol), 8-BrdA (122.3 mg, 0.371 mmol), and phenylboronic acid (51.9 mg, 0.428 mmol) were placed in a round-bottomed flask under nitrogen. Degassed 2:1 water:acetonitrile was added (3.5 mL) and the reaction was heated in an oil bath at 80 °C until RP-TLC (1:1 water:methanol) or HPLC showed completed conversion (2–4 h). The reaction was diluted with ca. 20 mL of water and the pH adjusted to 7 with use of 10% aqueous HCl. The solution was purified by loading onto a column of reverse phase silica, eluted with a gradient ranging from 100% water to 100% methanol. 8-PhdA (105.8 mg, 87%) was recovered as a white, microcrystalline solid. ¹H NMR (360 MHz, DMSO-*d*₆): δ 8.15 (s, 1H), 7.71 (t, *J* = 3.08 Hz, 2H), 7.61 (d, *J* = 3.70 Hz, 3H),

7.45 (s, 2H), 6.15 (t, *J* = 7.40 Hz, 1H), 5.57 (dd, *J* = 3.70, 8.63 Hz, 1H), 5.24 (d, *J* = 4.32 Hz, 1H), 4.46 (s, 1H), 3.90–3.85 (br m, 1H), 3.73–3.66 (m, 1H), 3.57–3.49 (m, 1H), 2.15 (dd, *J* = 6.16, 13.56 Hz, 1H), one proton masked by residual water in sample. ¹³C NMR (90.6 MHz, DMSO-*d*₆): δ 156.2, 152.0, 150.5, 149.9, 130.1, 129.7, 129.5, 128.8, 119.2, 88.4, 85.7, 71.5, 62.3, 59.8, 37.2. High-resolution FAB-MS: calcd for C₁₆H₁₈N₄O₃⁺ 328.1410, found 328.1410.

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Supporting Information Available: Experimental details, characterization data, and ¹H and ¹³C NMR spectra of newly reported compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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