## Fluoro, Alkylsulfanyl, and Alkylsulfonyl Leaving Groups in Suzuki Cross-Coupling Reactions of Purine 2'-Deoxynucleosides and Nucleosides<sup>†</sup>

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## ABSTRACT



Protected 2'-deoxynucleoside and nucleoside derivatives of 6-fluoropurine, 6-(3-methylbutyl)sulfanylpurine, and 6-(3-methylbutyl)ylsulfonylpurine undergo nickel- or palladium-mediated C-C cross-coupling with arylboronic acids to give good yields of 6-arylpurine products.

Modified purines and purine nucleoside derivatives play a major role in biochemistry and biology and as pharmaceutical agents.<sup>1</sup> Recently, 6-arylpurine ribonucleosides have been shown to exhibit cytostatic activity.<sup>2</sup> Classical methods for synthesis of nucleoside biaryls via Suzuki–Miyaura procedures have employed Pd- or Ni-mediated cross-couplings of aryl halides or sulfonates with arylboronic acids.<sup>3</sup> We recently reported a heteroaromatic Finkelstein process for conversion of 6-chloropurine 2'-deoxynucleoside and nucleoside deriva-

<sup>†</sup> Nucleic Acid Related Compounds. 125. Paper 124 is ref 9.

tives into the corresponding 6-iodopurine analogues and noted the markedly increased reactivity of the iodo compounds in certain classical organometallic cross-coupling reactions.<sup>4</sup> Aryl fluorides have rarely been used in such processes because of their diminished reactivity.

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In 1981, we reported efficient methodology for the synthesis of 2-fluoropurine nucleosides by nonaqueous diazotization fluoro-dediazoniation of the 2-amino group of protected purine nucleosides.<sup>5</sup> Secrist et al. have also applied this protocol for the conversion of 6-amino- to 6-fluoropurine nucleoside derivatives.<sup>6</sup> We now report that this diazotative fluoro-deamination of protected adenosine and 2'-deoxy-adenosine analogues gives the 6-fluoropurine compounds in good yields. We then began an investigation of the utility of 6-fluoropurine nucleoside derivatives as cross-coupling

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partners with arylboronic acids. We report that this opens an effective new avenue for modifications at C6 of purine nucleosides.

Our first challenge was to identify a catalytic complex that would insert readily into the purine C6–F bond. Several methods involving different transition metal centers have been described for activation of aromatic carbon–fluorine bonds.<sup>7</sup> Cross-couplings of phenylmagnesium halides and fluorobenzenes have been performed at ambient temperature with nitrogen-heterocyclic carbene ligands and nickel catalysts.<sup>8</sup>

We first tried  $Ni(COD)_2$  with addition of 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene (IPr) (Figure 1) for



Figure 1. Structure of the imidazolium-carbene ligand IPr.

attempted cross-coupling of 4-methoxyphenylboronic acid and 6-fluoro-9-[2,3,5-tri-O-(2,4,6-trimethylbenzoyl)- $\beta$ -D-ribofuranosyl]purine. At ambient temperature, none of the coupling product was detected. However, we were delighted to find that the desired 6-(4-methoxyphenyl)-9-[2,3,5-tri-O-(2,4,6-trimethylbenzoyl)- $\beta$ -D-ribofuranosyl]purine (**1c**) was produced in high yield (84% isolated) in THF at 60 °C (Scheme 1) (Table 1). Different boronic acids were employed



to evaluate the scope of this coupling reaction. Both electronrich and electron-poor arylboronic acids underwent coupling in good yields with 6-fluoropurine nucleoside derivatives. Application of this coupling protocol with a protected 6-fluoropurine 2'-deoxynucleoside also gave 6-arylpurine products in good isolated yields (Table 1).

Table 1.	Yields of	Coupling	Products	from	Fluoropurines	

entry	R	R′	Y	product (% yield)
1	Mes	OMes	Н	<b>1a</b> (84)
2	Mes	OMes	$CH_3$	<b>1b</b> (82)
3	Mes	OMes	$OCH_3$	<b>1c</b> (84)
4	Mes	OMes	$\mathbf{F}$	1d (73)
5	Tol	Н	$CH_3$	<b>1e</b> (60)
6	Tol	Н	F	1f(67)

It is noteworthy that poor results were obtained upon replacement of  $Ni(COD)_2$  by  $Pd(PPh_3)_4$  as the catalyst. With  $Pd(PPh_3)_4$ , major formation of an oxygen-insertion<sup>9</sup> compound **2** (Figure 2) was observed.



Figure 2. Structure of the oxygen-insertion compound 2.

We next focused our attention on cross-couplings of 6-alkylsulfanylpurine nucleoside derivatives, which are readily accessible by  $S_NAr$  displacements with 6-(imidazol-1-yl)-,<sup>10</sup> 6-(1,2,4-triazol-4-yl)-,<sup>11</sup> and 6-halopurine<sup>12</sup> precursors. They also are easily prepared by alkylation of thioinosine derivatives,<sup>12,13</sup> which can be obtained by deoxygenative thiation of inosine or deaminative sulfhydrolysis of 6-N-substituted adenosine intermediates.<sup>12</sup> Cross-coupling of Grignard reagents and 6-(methylsulfanyl)purine derivatives with a nickel—phosphine complex had been reported.<sup>14</sup>

Our first cross-coupling of 6-[(3-methylbutyl)sulfanyl]-9-(2,3,5-tri-O-acetyl- $\beta$ -D-ribofuranosyl)purine and 4-methoxyphenylboronic acid was incomplete after 8 h with Pd(OAc)<sub>2</sub>/ IPr/K<sub>2</sub>CO<sub>3</sub>/THF at 60 °C. However, when the solvent was changed from THF to toluene and the temperature was



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increased to 90  $^{\circ}$ C, the coupling reaction was complete in 8 h. Electron-rich and electron-poor arylboronic acids were also well tolerated with the alkylsulfanylpurine substrates (Scheme 2; Table 2).

Table 2.	Yields of Coupling Products from Sulfanylpurines						
entry	R	Y	product (% yield)				
1	Tol	$CH_3$	<b>3a</b> (69)				
2	Ac	$OCH_3$	<b>3b</b> (78)				
3	Tol	F	<b>3c</b> (71)				

The oxidation state of the sulfur substituent at C6 was then briefly probed. Oxidation of 6-benzylsulfanylpurine nucleoside derivatives with Oxone in buffered brine had given 6-benzylsulfonyl compounds in high yields.<sup>10</sup> Oxidation of a protected 6-(isopentylsulfanyl)purine nucleoside gave 6-[(3-methylbutyl)sulfonyl]-9-[2,3,5-tri-O-(2,4,6-trimethylbenzoyl)- $\beta$ -D-ribofuranosyl]purine (**4**). The sulfone **4** and 4-methoxyphenylboronic acid underwent coupling at 60 °C in 8 h [Pd(OAc)<sub>2</sub>/IPr/K<sub>3</sub>PO<sub>4</sub>/THF] to give **1c** (81%, isolated yield) (Scheme 3).

This coupling with the sulfone **4** occurred more readily (60 °C, THF) than with the corresponding thioether (90 °C, toluene). It was known that arylsulfonyl chlorides function

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as substrates for Suzuki and Stille couplings,<sup>15</sup> but we did not find prior examples of Suzuki couplings with sulfones.

In summary, we have developed nickel- and palladiumbased systems with imidazolium-carbene ligands that catalyze efficient Suzuki cross-couplings of arylboronic acids and 6-fluoro-, 6-[(3-methylbutyl)sulfanyl]-, and 6-[(3-methylbutyl)sulfonyl]purine nucleoside derivatives to give the corresponding 6-arylpurine products. These reactions enlarge the scope of our complementary Suzuki couplings of arylboronic acids and 6-(azolyl)purine derivatives and expand possibilities for new medicinal applications.

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

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