

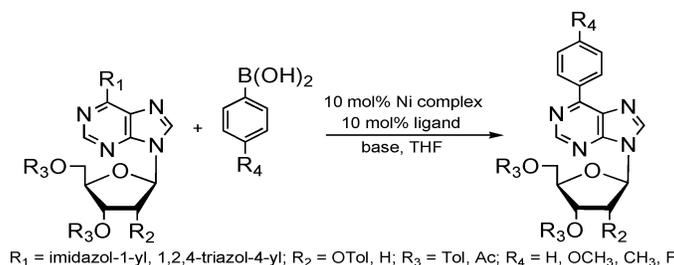
# Azoles as Suzuki Cross-Coupling Leaving Groups: Syntheses of 6-Arylpurine 2'-Deoxynucleosides and Nucleosides from 6-(Imidazol-1-yl)- and 6-(1,2,4-Triazol-4-yl)purine Derivatives<sup>1</sup>

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## ABSTRACT



6-(Imidazol-1-yl)-, 6-(benzimidazol-1-yl)-, and 6-(1,2,4-triazol-4-yl)purine nucleosides undergo a nickel-mediated C–C cross-coupling of azole-substituted purine derivatives with arylboronic acids to give good yields of 6-arylpurine nucleosides.

Modified purines and purine nucleoside derivatives play a major role in biology, biochemistry, and pharmaceuticals.<sup>2</sup> Recently, 6-arylpurine ribonucleosides have been shown to possess cytostatic activity.<sup>3</sup> Classic methodology for the synthesis of biaryls by the Suzuki–Miyaura protocol involves the Pd/Ni-mediated cross-coupling of haloaromatic or aryl-sulfonate derivatives with arylboronic acids.<sup>3,4</sup>

We recently demonstrated that 6-iodopurine nucleoside derivatives are markedly superior to their 6-chloropurine analogues as substrates for the Suzuki–Miyaura and other

cross-coupling procedures.<sup>1</sup> However, syntheses of such 6-halopurine 2'-deoxynucleosides from naturally occurring 2'-deoxy(inosine/adenosine) are problematic, and high yields are obtained only with considerable care and persistence.<sup>1,5</sup> By contrast, 6-(imidazol-1-yl)purine (2'-deoxy)nucleoside derivatives can be prepared readily in excellent yields from (2'-deoxy)inosine.<sup>6</sup> Because of these considerations, we have probed the unexplored utility of 6-(imidazol-1-yl)purine nucleosides as substrates for cross-coupling with arylboronic acids. Such couplings would provide a new avenue for modifications at C6 of purine nucleosides from readily accessible 6-azolyl precursors.

Our initial attempts to couple 4-methoxyphenylboronic acid and 6-(imidazol-1-yl)purine nucleoside derivatives with palladium-based catalyst systems were not successful. Hartwig

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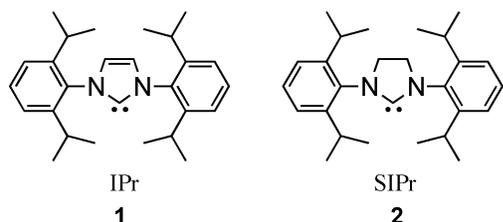
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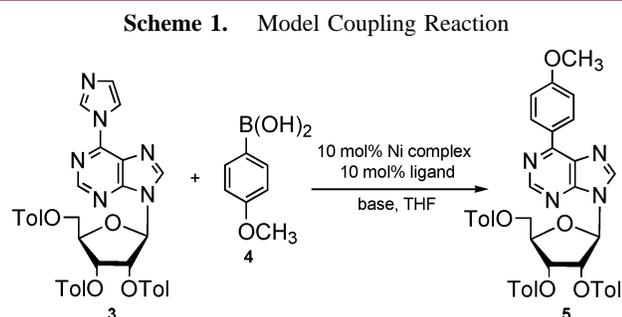
recently prepared three-coordinate arylpalladium amido complexes, which were subjected to reductive elimination to give *N*-coupled arylamines.<sup>7</sup> However, the precursor three-coordinate arylpalladium amido complexes were prepared by treatment of an arylpalladium bromide complex with the potassium salt of a diarylamine. This is drastically different from palladium insertion into the C–N bond of a 6-(imidazol-1-yl)purine. Nickel catalysts have been used successfully in a wide variety of Suzuki reactions, which provide ample precedent for transmetalations with arylboronic acids.<sup>8</sup> Our challenge was to identify a catalytic complex that could insert readily into the purine–imidazole (C6–N) bond.

Imidazolium carbene ligands (Figure 1) have been used successfully in various cross-coupling reactions.<sup>9</sup> On the basis



**Figure 1.** Structures of the imidazolium carbene ligands IPr (**1**) and SIPr (**2**).

of the studies of Blakey and MacMillan,<sup>10</sup> we examined Ni(COD)<sub>2</sub> as a catalyst with addition of IPr·HCl for the cross-coupling of 6-(imidazol-1-yl)-9-[2,3,5-tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl]purine (**3**) and 4-methoxyphenylboronic acid (**4**) (Scheme 1). However, none of the coupling product,



6-(4-methoxyphenyl)-9-[2,3,5-tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl]purine (**5**), was detected (Table 1, entry 9). Next, we investigated the catalyst complex resulting from Ni(COD)<sub>2</sub> and SIPr·HCl in the presence of K<sub>3</sub>PO<sub>4</sub>. We were delighted that the cross-coupled adduct **5** was produced in

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**Table 1.** Cross-Coupling Reaction Conditions and Yields<sup>a</sup>

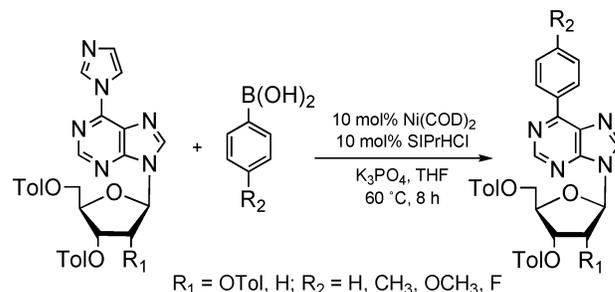
entry	catalyst	ligand	base	<b>5</b> (%)
1	Pd(PPh <sub>3</sub> ) <sub>4</sub>	none	K <sub>2</sub> CO <sub>3</sub>	<5
2	Pd(PPh <sub>3</sub> ) <sub>4</sub>	SIPr	K <sub>3</sub> PO <sub>4</sub>	<5
3	Pd(OAc) <sub>2</sub>	SIPr	K <sub>3</sub> PO <sub>4</sub>	<5
4 <sup>b</sup>	Ni(dppp)Cl <sub>2</sub>	SIPr	K <sub>3</sub> PO <sub>4</sub>	30
5	Ni(COD) <sub>2</sub>	SIPr	KF	<5
6	Ni(COD) <sub>2</sub>	SIPr	CsF	64
7	Ni(COD) <sub>2</sub>	SIPr	K <sub>3</sub> PO <sub>4</sub>	83
8 <sup>c</sup>	Ni(COD) <sub>2</sub>	SIPr	K <sub>3</sub> PO <sub>4</sub>	<5
9	Ni(COD) <sub>2</sub>	IPr	K <sub>3</sub> PO <sub>4</sub>	<5

<sup>a</sup> Reaction conditions: 1.0 equiv of **3**, 2.0 equiv of **4**, 10 mol % of catalyst, 10 mol % of ligand, 3.0 equiv of base, 60 °C, 8 h. <sup>b</sup> BuLi (0.4 equiv) was used to reduce Ni(II) to Ni(0). <sup>c</sup> Ambient temperature instead of 60 °C.

high yield (83% isolated) (entry 7). Heating (60 °C) was required to achieve reasonable reaction rates (entry 8). Replacement of Ni(COD)<sub>2</sub> by palladium catalysts in analogous coupling reaction mixtures did not give coupling products in meaningful yields.

The superior reaction efficiency observed with the Ni(0)·SIPr system and K<sub>3</sub>PO<sub>4</sub> as base prompted additional evaluation with this catalytic combination. Potential electronic effects on the coupling of 6-(imidazol-1-yl)purine nucleosides by the aryl substituent of the boronic acids was then investigated. Both electron-rich and electron-poor arylboronic acids underwent coupling with **3** in good yields (Schemes 1 and 2) (Table 1, entry 7; Table 2, entries 1–3).

**Scheme 2.** Coupling Reactions with Varied Substrates



This methodology is efficient for conversions of inosine into various 6-aryl-purine ribonucleosides, but alternative cross-coupling reactions with 6-halopurine nucleosides provide comparatively convenient approaches. However, syntheses of 6-halopurine 2'-deoxynucleosides are more chal-

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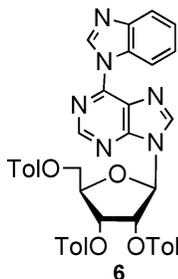
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**Table 2.** Yields of Coupling Products with Varied Substrates

entry	R <sub>1</sub>	R <sub>2</sub>	yield (%)
1	OTol	H	73
2	OTol	CH <sub>3</sub>	81
3	OTol	F	78
4	H	H	68
5	H	CH <sub>3</sub>	61
6	H	OCH <sub>3</sub>	75
7	H	F	65

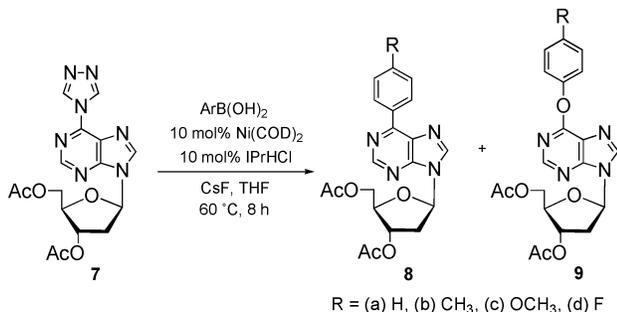
lenging because of the markedly less stable glycosyl linkage of the 2'-deoxy analogues, which can result in cleavage under even mildly acidic conditions.<sup>1,5</sup> Our modified Appel methodology provides convenient conversions of 2'-deoxyinosine derivatives into 6-(imidazol-1-yl)purine 2'-deoxynucleoside analogues in excellent yields (>90%) with virtually no glycosyl bond cleavage.<sup>6</sup> Application of the present coupling protocol to such protected 2'-deoxynucleosides gave the corresponding 6-arylpurine products in good isolated yields (Table 2, entries 4–7).

Sensitivity to the azole substituent was probed with the 6-(benzimidazol-1-yl)purine nucleoside derivative **6** (Figure 2) (also prepared in excellent yield by our modified Appel

**Figure 2.** Nucleoside derivative **6**.

procedure<sup>6</sup>). Coupling of **6** (under the noted conditions) gave **5** (80% isolated yield), which demonstrated that azoles other than imidazole could be used.

Our modified-Appel approach for quantitative conversion of 6-oxapurine (2'-deoxy)nucleoside derivatives into the

**Scheme 3.** Couplings with 6-(1,2,4-Triazol-4-yl)purine **7**

corresponding 6-(azolyl)purine analogues<sup>6</sup> is buttressed by our methodology for elaboration of the amino group of 6-aminopurine (2'-deoxy)nucleosides into their 6-(1,2,4-triazol-4-yl)purine counterparts.<sup>11</sup> Thus, such 6-(azolyl)purine (2'-deoxy)nucleosides are readily available by convenient transformations of the natural products (2'-deoxy)adenosine<sup>11</sup> and (2'-deoxy)inosine,<sup>6</sup> as well as for other naturally occurring and synthetic analogues. A brief investigation of the 6-(1,2,4-triazol-4-yl)purine system was then undertaken (Scheme 3, Table 3).

**Table 3.** Yields of **8** with 6-(1,2,4-Triazol-4-yl)purine **7**

entry	R	<b>8</b> (%)
1	H	80
2	CH <sub>3</sub>	78
3	OCH <sub>3</sub>	85
4	F	75

The noted reaction conditions were applied to a cross-coupling of 9-(3,5-di-*O*-acetyl-2-deoxy- $\beta$ -D-erythro-pentofuranosyl)-6-(1,2,4-triazol-4-yl)purine<sup>11</sup> (**7**) and 4-methoxyphenylboronic acid (**4**). Two products, **8c/9c** (45:55), were obtained. Fortunately, the use of IPr·HCl as ligand and CsF as base gave the desired cross-coupling product **8c** in high yield (85%), with the oxygen-insertion byproduct **9c** detected as a minor impurity (~5%). This coupling also was found to be tolerant with respect to substituents on the arylboronic acid component [with trace oxygen-insertion byproduct formation ( $\leq 5\%$ )].

In summary, we now report nickel-based systems with imidazolium carbene ligands, which catalyze efficient Suzuki cross-coupling of arylboronic acids and 6-(imidazol-1-yl)-, 6-(benzimidazol-1-yl)-, and 6-(1,2,4-triazol-4-yl)purine (2'-deoxy)nucleoside derivatives to provide the corresponding 6-arylpurine (2'-deoxy)nucleosides. Different ligand/base combinations give better results with imidazole versus triazole substrates. Novel 6-(aryloxy)purine 2'-deoxynucleosides, oxygen-insertion byproducts, were observed with the 6-(1,2,4-triazol-1-yl)purine derivatives. Further studies are in progress with different substrates and catalytic systems.

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

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