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# 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[1]

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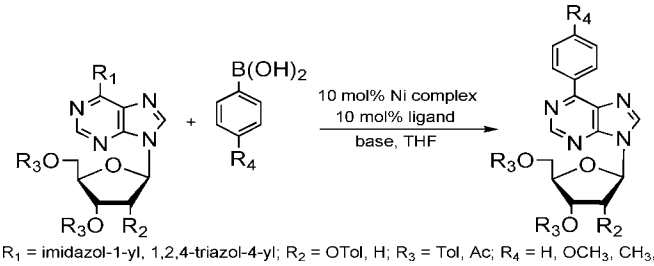
**ABSTRACT**




$R_1$ = imidazol-1-yl, 1,2,4-triazol-4-yl; $R_2$ = OTol, H; $R_3$ = Tol, Ac; $R_4$ = H, $OCH_3$, $CH_3$, F

**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 pharmaceutics.[2] Recently, 6-arylpurine ribonucleosides have been shown to possess cytostatic activity.[3] Classic methodology for the synthesis of biaryls by the Suzuki−Miyaura protocol involves the Pd/Ni-mediated cross-coupling of haloaromatic or arylsulfonate derivatives with arylboronic acids.[3,4]

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.[1] 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.[1,5] By contrast, 6-(imidazol-1-yl)purine (2′-deoxy)nucleoside derivatives can be prepared readily in excellent yields from (2′-deoxy)inosine.[6] 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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recently prepared three-coordinate arylpalladium amido complexes, which were subjected to reductive elimination to give *N*-coupled arylamines.[7] 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.[8] 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.[9] On the basis

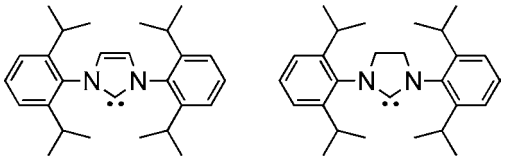
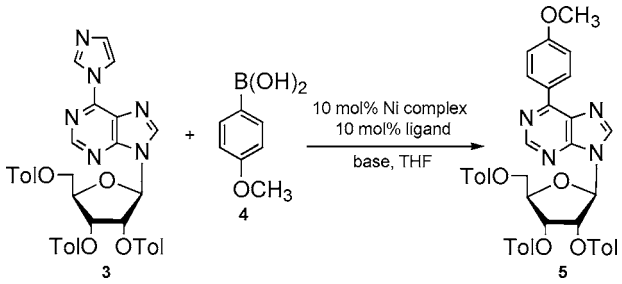



**Figure 1.** Structures of the imidazolium carbene ligands IPr (**1**) and SIPr (**2**).

of the studies of Blakey and MacMillan,[10] we examined Ni(COD)$_2$ 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,

**Scheme 1.** Model Coupling Reaction




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)$_2$ and SIPr·HCl in the presence of $K_3PO_4$. We were delighted that the cross-coupled adduct **5** was produced in

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**Table 1.** Cross-Coupling Reaction Conditions and Yields[a]

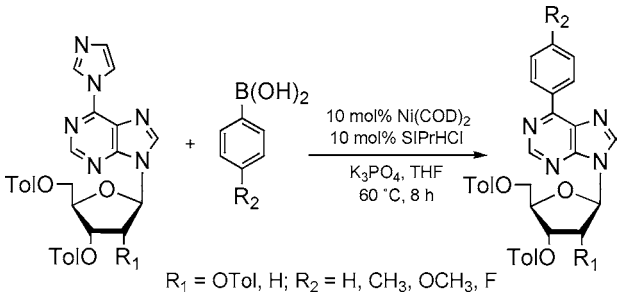
| entry | catalyst | ligand | base | **5** (%) |
|---|---|---|---|---|
| 1 | $Pd(PPh_3)_4$ | none | $K_2CO_3$ | <5 |
| 2 | $Pd(PPh_3)_4$ | SIPr | $K_3PO_4$ | <5 |
| 3 | $Pd(OAc)_2$ | SIPr | $K_3PO_4$ | <5 |
| 4[b] | $Ni(dppp)Cl_2$ | SIPr | $K_3PO_4$ | 30 |
| 5 | $Ni(COD)_2$ | SIPr | KF | <5 |
| 6 | $Ni(COD)_2$ | SIPr | CsF | 64 |
| 7 | $Ni(COD)_2$ | SIPr | $K_3PO_4$ | 83 |
| 8[c] | $Ni(COD)_2$ | SIPr | $K_3PO_4$ | <5 |
| 9 | $Ni(COD)_2$ | IPr | $K_3PO_4$ | <5 |

[a] 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. [b] BuLi (0.4 equiv) was used to reduce Ni(II) to Ni(0). [c] 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)$_2$ 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 $K_3PO_4$ 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-arylpurine 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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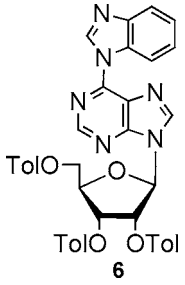
**Table 2.** Yields of Coupling Products with Varied Substrates

| entry | $R_1$ | $R_2$ | yield (%) |
|---|---|---|---|
| 1 | OTol | H | 73 |
| 2 | OTol | $CH_3$ | 81 |
| 3 | OTol | F | 78 |
| 4 | H | H | 68 |
| 5 | H | $CH_3$ | 61 |
| 6 | H | $OCH_3$ | 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.[1,5] 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.[6] 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



**6**

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

procedure[6]). 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-oxopurine (2′-deoxy)nucleoside derivatives into the corresponding 6-(azolyl)purine analogues[6] 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.[11] Thus, such 6-(azolyl)purine (2′-deoxy)nucleosides are readily available by convenient transformations of the natural products (2′-deoxy)adenosine[11] and (2′-deoxy)inosine,[6] 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).

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

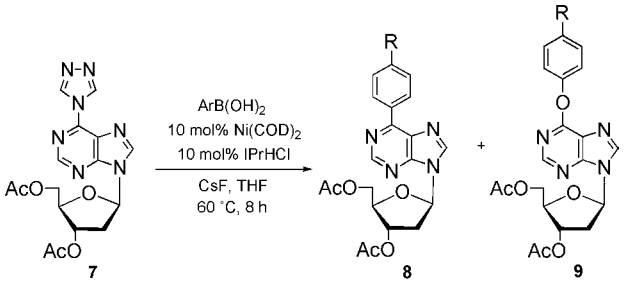



**Table 3.** Yields of **8** with 6-(1,2,4-Triazol-4-yl)purine **7**

| entry | R | **8** (%) |
|---|---|---|
| 1 | H | 80 |
| 2 | $CH_3$ | 78 |
| 3 | $OCH_3$ | 85 |
| 4 | F | 75 |

The noted reaction conditions were applied to a cross-coupling of 9-(3,5-di-*O*-acetyl-2-deoxy-*β*-D-*erythro*-pentofuranosyl)-6-(1,2,4-triazol-4-yl)purine[11] (**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 (≤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 $^1$H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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