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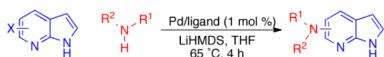
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## Palladium-Catalyzed Amination of Unprotected Halo-7-azaindoles

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### Abstract



Simple and efficient procedures for the Pd-catalyzed cross-coupling of primary and secondary amines with halo-7-azaindoles (pyrrolo[2,3-b]pyridine) are presented. Previously, no general method was available to ensure the highly selective reaction of the heteroaryl halide in the presence of the unprotected azaindole *N*-H. Using palladium precatalysts recently reported by our group, such reactions are easily accomplished under mild conditions that can be applied to cross-coupling reactions with a wide array of aliphatic and aromatic amines.

Azaindoles have been receiving increased attention from the pharmaceutical and agrochemical industries over the last decade, due both to their potential as indole-isosteres and as interesting core structures in their own right.<sup>1,2</sup> The substitution of a carbon by a nitrogen not only confers altered electronic properties but also adds a potential hydrogen bond acceptor, which can form the basis for altering the physicochemical or biological properties of a compound.<sup>3</sup> The close proximity of hydrogen bond donor and acceptor sites also distinguishes azaindoles as important substructures in dyes, ligands for transition metals, and novel materials.<sup>2,4</sup>

Despite their utility, methods for the synthesis and functionalization of azaindole scaffolds remain limited. The majority of methods provide *N*-1, C-2 or C-3 substituted structures, with few offering general solutions to functionalization of the pyridine ring.<sup>2,5-7</sup> A particularly interesting subset of these molecules are amino-substituted azaindoles, which appear in a variety of biologically active molecules (Figure 1)<sup>8-12</sup> and can be particularly challenging or lengthy to prepare *via* reported methods. Amino-7-azaindoles are often accessed from the corresponding halide *via* S<sub>N</sub>Ar displacement reactions, which typically require high temperatures, extended reaction times, and a large excess of the amine partner.<sup>13</sup> Furthermore, 5-haloazaindoles are not suitable substrates for S<sub>N</sub>Ar, nor are some amines. Alternative approaches employ the amino-substituted azaindole as the key intermediate, which can be challenging to prepare.<sup>14</sup>

Our approach to the synthesis of amino-azaindoles is to use Pd-mediated cross-coupling technology<sup>15-18</sup> for the reaction of halo-azaindoles with amines. Although azaindoles have previously been reported to undergo arylation of the heterocyclic *N*-H nitrogen in the presence of copper or palladium catalysts,<sup>19,20</sup> the cross-coupling of halo-azaindoles has received little attention.<sup>21-23</sup> Haloazaindoles present a particular challenge for two reasons:

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Supporting Information Available Experimental procedures and spectral data for all products.

the donor-acceptor system of the two adjacent nitrogens forms an excellent chelating ligand for metals, and there is the potential for homo-coupling between the halide and azaindole *N*-H.

Our recently reported precatalyst systems (Figure 2, **P1** – **P5**),<sup>24,25</sup> which are efficiently converted to an active monoligated Pd(0) complex when exposed to base, provided a potentially attractive solution to the first problem. We speculated that the pre-ligated palladium species would prove more resistant to undesirable azaindole coordination. To address the second issue of azaindole homo-coupling, we hypothesized that the use of a strong base such as LiHMDS, which would fully deprotonate both the amine and azaindole substrates, might reduce the rate of undesired transmetalation to Pd.<sup>26</sup> Previous studies in our group support this hypothesis, having demonstrated that the cross-coupling of unprotected halo-indoles and simple amines could be achieved using LiHMDS as the base, in conjunction with either an XPhos- (**L3**) or DavePhos- (**L6**) based catalyst system.<sup>27</sup>

An examination of Pd precatalysts based on our biaryl phosphine ligands revealed that cross-coupling between 4-chloroazaindole and *N*-methylpiperazine occurred rapidly at catalyst loadings as low as 0.5 mol % (Table 1). A combination of RuPhos (**L1**) and RuPhos precatalyst (**P1**) proved to be the most effective system for this transformation, providing the product in 94% yield after 30 minutes (Table 1, entry 1), although SPhos (**L2**) and XPhos (**L3**) were also effective (Table 1, entries 2 and 3). Interestingly, Pd(OAc)<sub>2</sub> can also be employed in lieu of a Pd precatalyst (Table 1, entry 5). However, the rate of formation of Pd(0) from phosphine and Pd(OAc)<sub>2</sub> is highly amine dependent, thus precatalyst **P1** was chosen for subsequent studies.<sup>28</sup>

Alternative base and solvent combinations were also examined (Table 2), as there have been isolated reports of employing NaOt-Bu or Cs<sub>2</sub>CO<sub>3</sub> as base for the cross-coupling reaction of unprotected halo-azaindoles.<sup>21-23</sup> We found that procedures using these bases were ineffective with our catalyst systems (Table 2, entries 1-5), with LiHMDS in THF proving optimal in terms of reaction time and temperature. Interestingly, the cross-coupling also proceeded at room temperature (Table 2, entry 9) although longer reaction times and higher catalyst loadings were required for complete conversion. Milder temperatures could be more convenient for parallel reactions, or for those involving sensitive substrates.

We next applied this Pd-based cross-coupling process to a range of both aliphatic and aromatic secondary amines with 4-chloroazaindole. High yields and selectivities were observed in all cases examined (Scheme 1).<sup>29</sup> By the addition of an extra equivalent of LiHMDS, amines containing a second protic functional group could be employed, allowing access to products containing phenols (**1b**), aliphatic alcohols (**1e**) or more hindered secondary amines (**1c**). Not unexpectedly, 4-bromoazaindole displayed reactivity similar to its chloro analog (**1b**).

Without any alteration of the reaction conditions, we also found that 5-bromoazaindole (**2a** - **2f**), 6-chloroazaindole (**2f**) and the related 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (**2g**) were effective coupling partners with a similarly wide range of secondary amines (Scheme 2). 5-Bromo-3-chloro-7-azaindole (**2h**) underwent reaction exclusively at the 5-position, with no diamination or coupling of the chloride observed.<sup>30</sup>

Finally, we explored the cross-coupling of haloazaindoles with primary amines (Scheme 3). We have previously reported that catalyst systems based on BrettPhos (**L5**) are superior to other biarylphosphines for the cross-coupling of primary amines, and provide exceptional selectivity for mono-arylation.<sup>25</sup> Using this system (**P5**), haloazaindoles underwent efficient cross-coupling with aliphatic, aromatic, and heteroaromatic amines without any other modification of the reaction parameters. While again, in some cases, Pd(OAc)<sub>2</sub> can be used

as the Pd source, the importance of using the precatalyst (**P5**) is highlighted in example **3a**. In cases where the reacting amine lacks a  $\beta$ -hydrogen atom, Pd(OAc)<sub>2</sub> cannot be reduced, and thus no cross-coupling occurs. We also found that the addition of extra ligand is not always necessary. For example, **3a** was isolated in a yield of 88% in both the presence or absence of an extra equivalent of BrettPhos (**L5**).

In summary, we have developed operationally simple and efficient methods for the cross-coupling of unprotected halo-7-azaindoles with a wide range of primary and secondary amines. Notably this reaction can be performed in the presence of a variety of protic functional groups. The success of these reactions further demonstrates the advantages of conducting Pd-catalyzed cross-coupling reactions using metallacyclic precatalysts such as **P1** and **P5**, as these precatalysts permit rapid Pd activation in the presence of a wide range of substrates.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

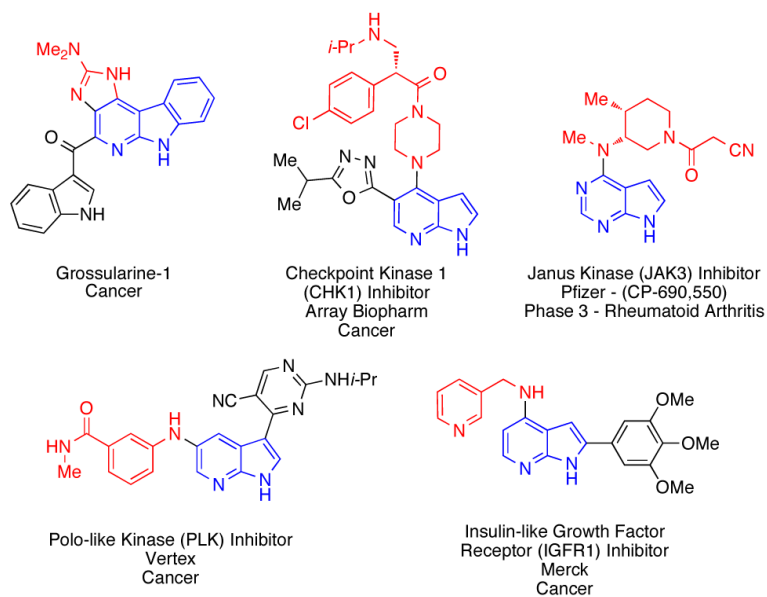
## Acknowledgments

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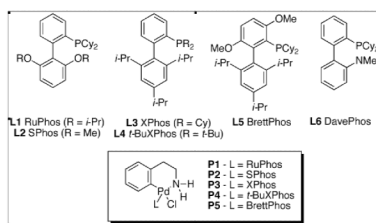
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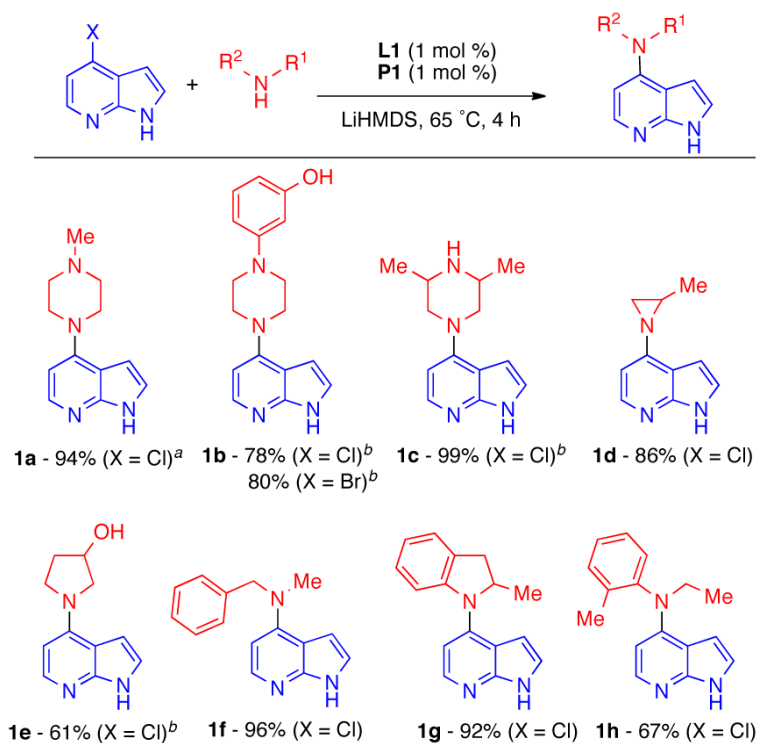
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- (29). In no instance was arylation of the azaindole N-H, nor the formation of amino-azaindoles through reaction with LiHMDS observed.
- (30). In the absence of Pd, the halo-azaindoles do not undergo reaction with *N*-methylpiperazine under the reaction conditions.



**Figure 1.**  
Pharmacologically active compounds containing the amino-azaindole motif.

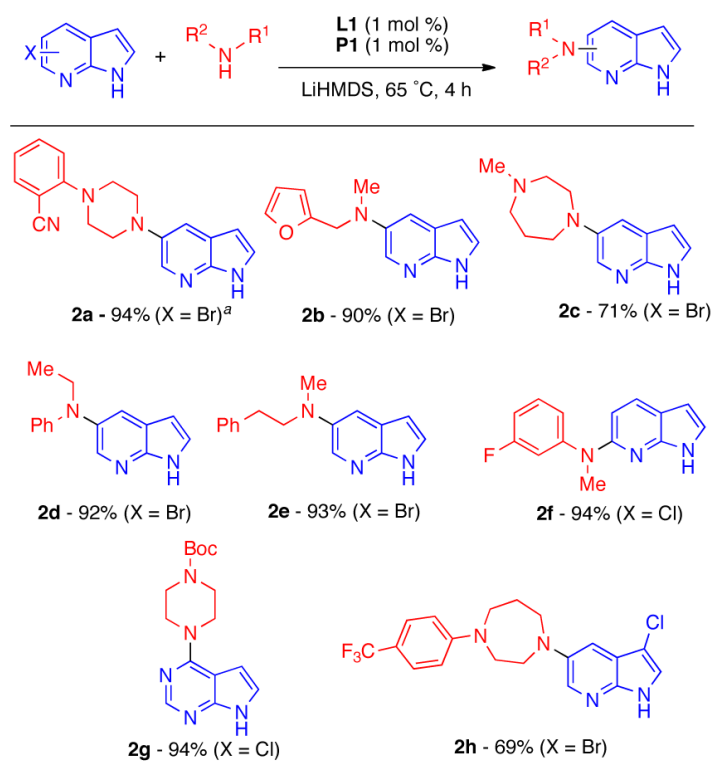


**Figure 2.**  
Biarylphosphine Ligands and Precatalysts

**Scheme 1.**

Cross-Couplings of 4-Azaindole with Secondary Amines.

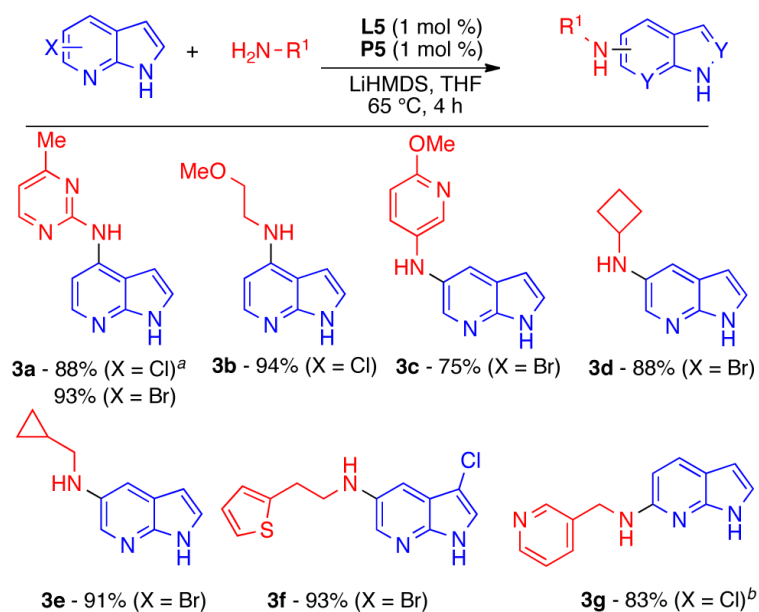
Reaction conditions: ArX (0.5 mmol), amine (0.6 mmol), **L1** (1 mol %), **P1** (1 mol %), LiHMDS (1.2 mmol, 1 M in THF). Isolated yields are an average of at least two runs. <sup>a</sup>**L1** 0.5 mol %, **P1** 0.5 mol %, 30 min <sup>b</sup>3.6 equiv LiHMDS.

**Scheme 2.**

Cross-Coupling of 5- and 6-Haloazaindoles.

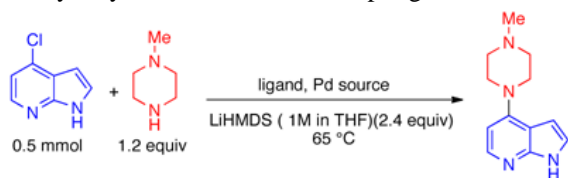
Reaction conditions: ArX (0.5 mmol), amine (0.6 mmol), **L1** (1 mol %), **P1** (1 mol %), LiHMDS (1.2 mmol, 1 M in THF). Isolated yields are an average of at least two runs. <sup>a</sup>3.6 equiv LiHMDS. <sup>b</sup>**L1** (2 mol %), **P1** (2 mol %).



**Scheme 3.**

## Cross-Coupling using Primary Amines

Reaction Conditions: ArX (0.5 mmol), amine (0.6 mmol), **L5** (1 mol %), **P5** (1 mol %), LiHMDS (1.2 mmol, 1 M in THF). Isolated yields are an average of at least two runs.<sup>a</sup>No reaction when Pd(OAc)<sub>2</sub> (1 mol %) used in place of **P5**.<sup>b</sup> Amine purified before use.

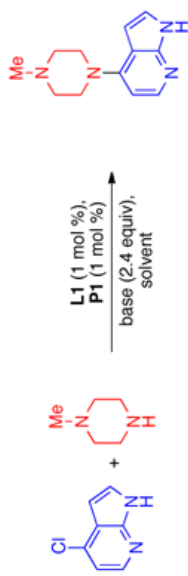
**Table 1**Catalyst Systems used for the Coupling of 4-Chloroazaindole and *N*-Methylpiperazine

entry	Pd source (mol %)	ligand (mol %)	time	yield
1	<b>P1</b> (0.5)	<b>L1</b> RuPhos (0.5)	30 min	94%
2	<b>P2</b> (0.5)	<b>L2</b> SPhos (0.5)	30 min	81%
3	<b>P3</b> (0.5)	<b>L3</b> XPhos (0.5)	30 min	90%
4	<b>P4</b> (0.5)	<b>L4</b> <i>t</i> -BuXPhos (0.5)	30 min	0%
5	Pd(OAc) <sub>2</sub> (0.5)	<b>L1</b> RuPhos (1)	30 min	80%
6	Pd <sub>2</sub> dba <sub>3</sub> (0.25)	<b>L1</b> RuPhos (1)	30 min	33%
7	Pd(OAc) <sub>2</sub> (1)	<i>Rac</i> -BINAP (2)	4 h	0%
8	Pd(OAc) <sub>2</sub> (1)	Xantphos (2)	4 h	0%

Conditions: 4-chloroazaindole (0.5 mmol), *N*-methylpiperazine (0.6 mmol), LiHMDS (1.2 mmol, 1 M in THF).

Table 2

Examination of Base and Solvent Combinations for the Cross-Coupling of 4-Chloroazaindole.



entry	base	solvent	temp (°C)	time	yield
1	Cs <sub>2</sub> CO <sub>3</sub>	Toluene	110	16 h	0%
2	NaOt-Bu	Toluene	110	16 h	7%
3	K <sub>3</sub> PO <sub>4</sub>	Toluene	110	16 h	0%
4	K <sub>2</sub> CO <sub>3</sub>	Toluene	110	16 h	0%
5	K <sub>2</sub> CO <sub>3</sub>	<i>t</i> BuOH	110	16 h	0%
6	LiHMDS	THF	65	30 min	94% <sup>a</sup>
7	LiHMDS	Dioxane	80	4 h	91% <sup>a</sup>
8	LiHMDS	Toluene	80	4 h	68% <sup>a</sup>
9	LiHMDS	THF	rt	16 h	42% <sup>a</sup>

Conditions: 4-chloroazaindole (0.5 mmol), *N*-methylpiperazine (0.6 mmol), **L1** (1 mol %), base (1.2 mmol), solvent (1 mL).

<sup>a</sup>**L1** (0.5 mol %), **P1** (0.5 mol %).