Efficient Pd-Catalyzed Amination Reactions for Heterocycle Functionalization

Published in final edited form as:
Org Lett. 2010 October 15; 12(20): 4442–4445. doi:10.1021/ol101929v.

Efficient Pd-Catalyzed Amination Reactions for Heterocycle Functionalization

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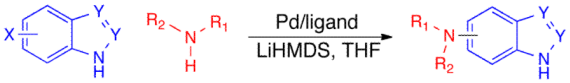
Abstract



The Pd-catalyzed amination of unprotected benzo-fused heterocycles is reported, which allows for greater flexibility and efficiency in the modification of this important class of molecules. The generality of these simple and efficient procedures is demonstrated through the synthesis of a wide variety of structural types.

Indoles, indazoles and benzimidazoles feature prominently in pharmaceuticals, agrochemicals, dyes and novel materials (Figure 1).[1-6] However, despite their utility, they are often overlooked during the development of cross-coupling methods.[7-9] Investigations into their use as nucleophiles in C-N cross-coupling reactions have been conducted, however, there have been few reports employing the heteroaryl halides as the electrophilic component.[10-12] As a result, the majority of cross-coupling processes employing these substrates utilize the *N*-protected heteroaryl halide to avoid complications associated with the reactive *N*–H functional group, such as homocoupling or catalyst deactivation.[13,14] In addition to adding extra synthetic steps, protecting group strategies can be particularly problematic in the case of benzimidazoles and indazoles. Mixtures of *N*–1 and *N*–2/3 protected regioisomers are often formed, which can display different reactivities under cross-coupling conditions.[15-17] A general method for the amination of unprotected haloheterocycles would thus offer a valuable tool for the synthesis of these important molecules.

The development, by our group, of new phosphine ligands, along with Pd-precatalysts for the rapid generation of mono-ligated Pd(0) species, has resulted in robust and general catalyst systems for C-N cross-coupling reactions.[18,19] Such systems should be ideal for addressing the challenges of selectivity and functional group tolerance posed by these benzofused heterocyclic halides.

We recently reported an efficient protocol for the Pd-catalyzed C-N cross-coupling of bromo and chloro 7-azaindoles, using our Pd-precatalyst systems (Figure 2) in combination with LiHMDS.[20] This method would be of even greater appeal if it were applicable to a wider range of heterocyclic halides, allowing the synthesis of a variety of amino-heterocycles.

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

We were pleased to discover that under the same reaction conditions as developed for azaindoles, using a RuPhos based catalyst system (**P1**) and LiHMDS in THF as the base, 4-, 5- and 6-bromo-indazoles underwent efficient C-N cross-couplings with both aromatic and aliphatic secondary amines (Table 1). Moreover, a range of functional groups are well tolerated. In particular, pharmacologically relevant and functionally complex amines, such as the 4-(4-chlorophenyl)-4-hydroxypiperidine from haloperidol[21] (**1i**), underwent this transformation in good yields. Notably, in cases where a bromoheterocycle was combined with an amine containing an aryl chloride, no reaction of the chloride was observed (**1b**, **1f**, **1i**).

We next examined the coupling of 4-, 5- and 6-bromoindazoles with primary amines, using the BrettPhos precatalyst (**P3**, Figure 2), which is often the preferred ligand for cross-coupling reactions of this type.[19] Using this system both aliphatic and heteroaromatic amines could be incorporated in high yields.

While a wide variety of amines could be employed, electron-deficient secondary anilines, such as 4-*N*-methylaminobenzonitrile and *N*-methylaminopyridines, proved to be uniquely challenging coupling partners. Only trace amounts of the desired products were detected after extended reaction times, with increased catalyst loading, or with various bases. We hypothesized that the reductive elimination of these substrates might be slow due to their reduced nucleophilicity, and thus we reasoned that a more bulky phosphine ligand might be more effective in facilitating this step.[22] Indeed, we found that a *t*-BuXPhos-derived catalyst system (**P2**) is effective for these substrates (**1g**, **3c**). However, even using this bulkier phosphine ligand, secondary 2-aminopyridines (*N*–methyl- and *N*–benzyl-2-aminopyridine) remained unreactive. Of the primary amines examined, we also found that 2,2,2,-trifluoroethylamine and cyclopropylamine did not undergo successful cross-coupling reactions using BrettPhos (**P3**).[23] Again, the use of *t*-BuXPhos (**P2**) allowed an efficient coupling in the case of 2,2,2,-trifluoroethylamine (**2c**), although it too was ineffective in the case of cyclopropylamine (**2d**).[24,25]

We next sought to extend the reaction scope to include halo-benzimidazoles. Both chloro- and bromo-benzimidazoles underwent cross-coupling reactions efficiently using the standard procedures, with RuPhos (**P1**) or BrettPhos (**P2**) precatalysts (Scheme 3). Although some base sensitive groups, particularly nitro and ester groups, are not tolerated, the cross-coupling can be applied to amines containing aromatic and aliphatic nitriles (**3b** and **3c**), ketones (**3a**) and protected aldehydes (**3e**). This method was also effective in the cross-coupling of halo-benzotriazoles. Commercially available 5-chlorobenzotriazole, which has not previously been utilized for Pd-catalyzed C-N cross-coupling reactions, reacted effectively (Scheme 4), using a slightly higher temperature.

We have previously published a brief account of the cross-coupling of halo-indoles with simple amines using an XPhos-based catalyst system,[11] and we wished to demonstrate the expanded substrate scope that could be achieved using the procedure reported herein (Scheme 5). Of the commercially available 4-, 5- and 6- halogenated indoles examined, all participated in successful cross-coupling reactions. Reactions of both chloroindoles and bromoindoles proceeded with similar yields, although similarly to chlorobenzotriazole, chloroindoles required an elevated temperature to achieve full conversions. Notably, while reactions of 5-iodoindole were equally efficient when combined with primary amines (**5h**, **5i**), it was considerably less effective when reacted with secondary amines (**5d**), in agreement with our previous findings.[26] Functional group compatibility was demonstrated for both the indole and amine components *via* the successful incorporation of a carboxylic acid (**5c**), a urea (**5b)**, an aryl chloride (**5b**) and a phenolic OH group (**5j**).

The absence of examples of 7-substituted heterocyclic electrophiles in the previous tables is notable. Cross-coupling reactions of these particular substrates, with both primary and secondary amines, were found to be particularly challenging. However, through the use of extended reaction times, reasonable yields could be obtained in a number of cases (Scheme 6).

In conclusion, we have reported selective, efficient and robust general procedures for the functionalization of unprotected benzofused-heterocyclic halides using Pd-catalyzed C-N cross-coupling. These procedures should find application to a wide range of related heterocyclic systems, allowing the synthetic chemist to rapidly obtain interesting and complex molecules.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This activity is supported by an educational donation provided by Amgen and from the National Institutes of Health Grant (GM-58160) to whom we are grateful. We also acknowledge the efforts of Sarah M. McDermott, Department of Chemistry, Massachusetts Institute of Technology.

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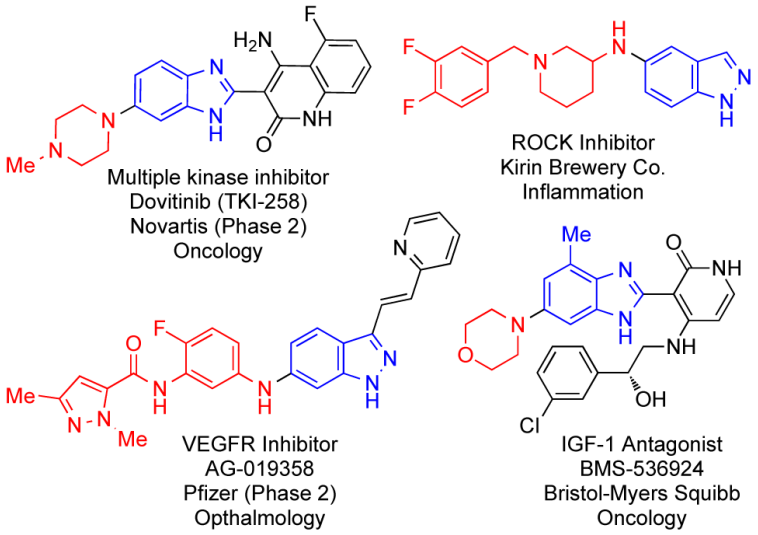


Figure 1.
Pharmacologically active compounds containing amino-1*H*-indazoles and benzimidazoles.

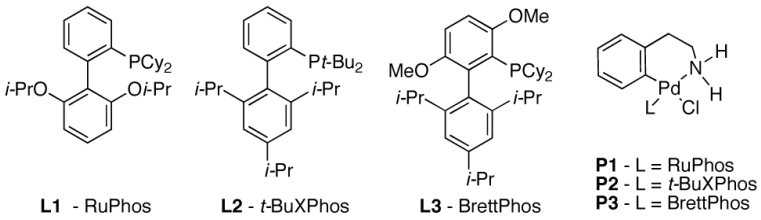
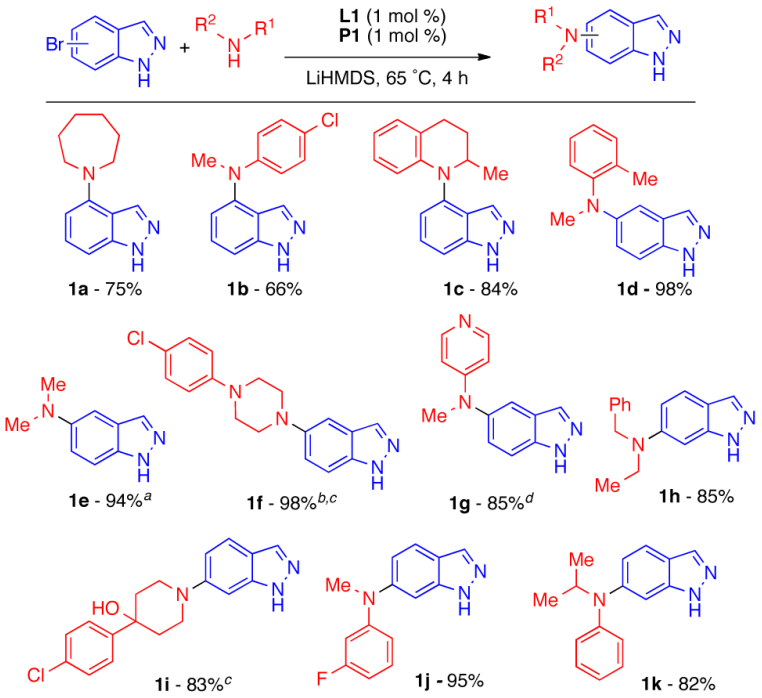


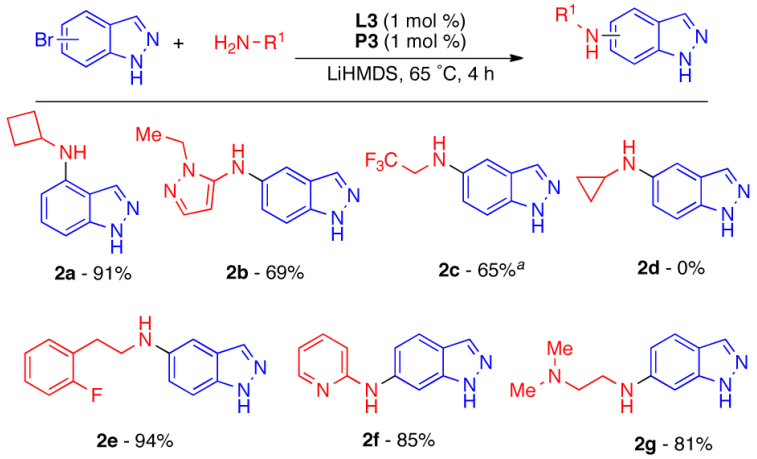
Figure 2.
Ligands and precatalysts used herein



Scheme 1.

Cross-coupling of Bromo-indazoles with Secondary Amines.

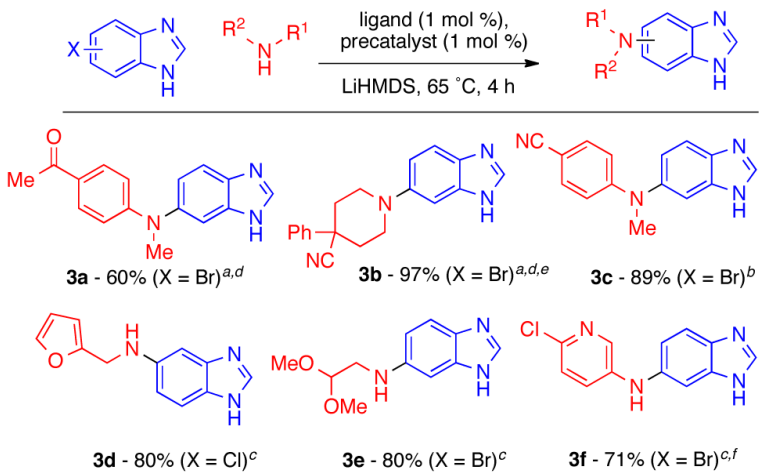
Reaction conditions: Bromoindazole (0.5 mmol), amine (0.6 mmol), **L1** (1 mol %), **P1** (1 mol %), LiHMDS (1.2 mmol, 1 M in THF). Isolated yields are for an average of at least two runs. [a]2 M solution of $HNMe_2$ in THF. [b]HCl salt of amine. [c]3.4 equiv LiHMDS (1.7 mmol). [d]**L2** (1 mol %), **P2** (1 mol %)



Scheme 2.

Cross-coupling of Bromo-indazoles with Primary Amines.

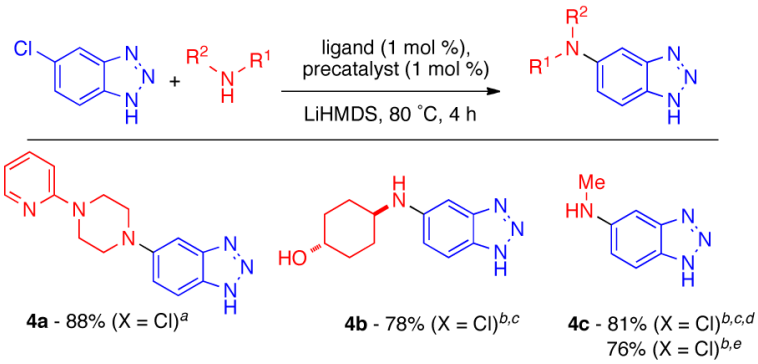
Reaction conditions: ArX (0.5 mmol), amine (0.6 mmol), **L3** (1 mol %), **P3** (1 mol %), LiHMDS (1.2 mmol, 1 M in THF). Isolated yields are for an average of at least two runs. [a]**L2** (1 mol %), **P2** (1 mol %), LiHMDS (1.7 mmol). Amine used as HCl salt.



Scheme 3.

Cross-coupling Reactions of Halo-benzimidazoles

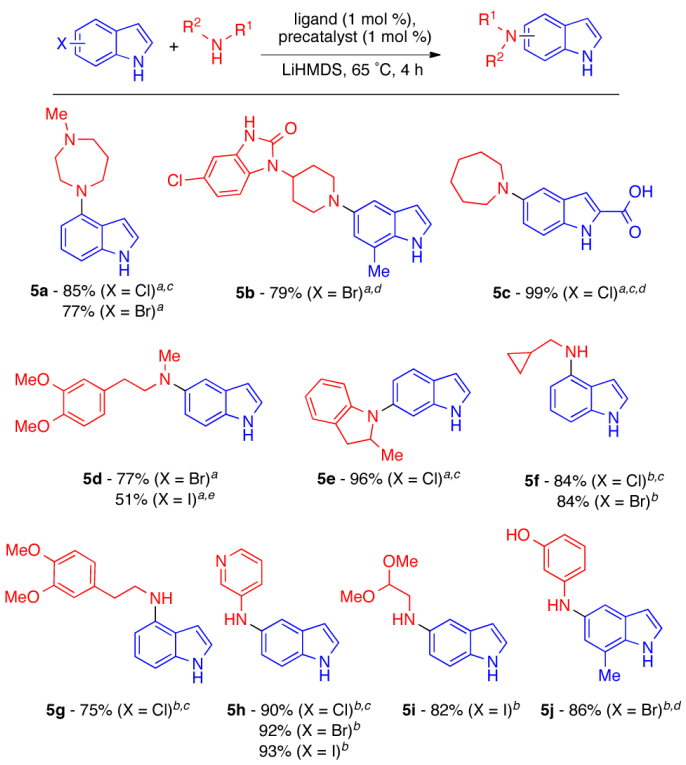
Reaction conditions: ArX (0.5 mmol), amine (0.6 mmol), LiHMDS (1.2 mmol, 1 M in THF). Isolated yields are an average of two runs. [a]**L1** (1 mol %), **P1** (1 mol %), [b]**L2** (1 mol %), **P2** (1 mol %), [c]**L3** (1 mol %), **P3** (1 mol %), [d]3.4 equiv (1.7 mmol) LiHMDS used. [e]Amine used as HCl salt. [f]16 h.



Scheme 4.

Cross-coupling Reactions of 5-Chlorobenzotriazole

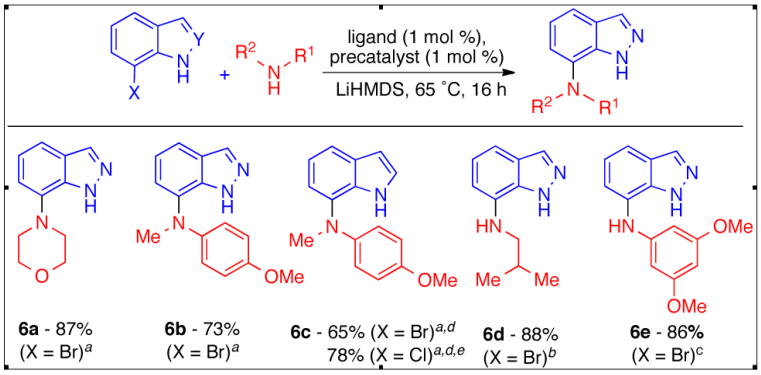
Reaction conditions: ArX (0.5 mmol), amine (0.6 mmol), LiHMDS (1.2 mmol, 1 M in THF). Isolated yields are an average of two runs. [a]**L1** (1 mol %), **P1** (1 mol %), [b]**L3** (1 mol %), **P3** (1 mol %), 65 °C. [c]3.4 equiv (1.7 mmol) LiHMDS used. [d]Amine used as HCl salt. [e]$MeNH_2$ (2 M in THF).



Scheme 5.

Cross-coupling Reactions of Halo-indoles.

Reaction conditions: ArX (0.5 mmol), amine (0.6 mmol), LiHMDS (1.2 mmol, 1 M in THF). Isolated yields are an average of two runs. [a]**L1** (1 mol %), **P1** (1 mol %), [b]**L3** (1 mol %), **P3** (1 mol %), [c]80 °C, [d]3.4 equiv LiHMDS (1.7 mmol). [e]16 h.



Scheme 6.

Cross-coupling of 7-Haloheterocycles with Primary and Secondary Amines. Reaction conditions: ArX (0.5 mmol), amine (0.6 mmol), LiHMDS (1.2 mmol, 1 M in THF). Isolated yields are an average of two runs. [a]**L1** (1 mol %), **P1** (1 mol %), [b]**L3** (1 mol %), **P3** (1 mol %), [c]**L3** (2 mol %), **P3** (2 mol %), [d]LiHMDS (1 M in toluene), [e]80 °C.