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A Bulky Biaryl Phosphine Ligand Allows for Palladium-Catalyzed Amidation of Five-Membered Heterocycles as Electrophiles**

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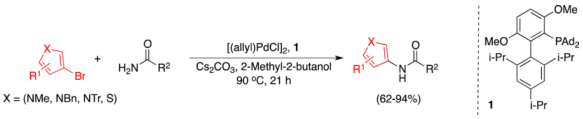
Abstract



Palladium-catalyzed amidation of five-membered heterocyclic bromides that contain multiple heteroatoms was achieved for the first time using the Pd/**1** catalyst system. This system allows for efficient access to *N*-arylated imidazoles, pyrazoles, thiazoles, pyrroles, and thiophenes in moderate to excellent yield. Experimental results and DFT calculations point to the need for electron-rich and especially sterically demanding biaryl phosphine ligand to promote these difficult cross-coupling reactions.

Keywords

C–N coupling; amidation; heterocycles; homogeneous catalysis; palladium

Five-membered heterocyclic compounds are ubiquitous in both industrial and academic settings.[1a–c] The biological properties they confer and their ability to engage in hydrogen-bonding have rendered them exceedingly important, particularly in drug discovery applications.[1d] As a testament to this, five of the top ten best-selling brand name drugs in 2010 contained five-membered heterocycles.[1e]

Despite significant advances made in palladium-catalyzed C–N cross-coupling methodology, especially with respect to the historically difficult palladium-catalyzed amidation reaction, five-membered heterocyclic halide electrophiles are notoriously difficult coupling partners.[2] This is partially due to their altered electronic properties relative to six-membered heteroarenes, which are more easily transformed. While halothiophenes, -furans and -indoles have been utilized as substrates with some success, transformations of analogous heterocycles containing multiple heteroatoms, such as haloimidazoles and halopyrazoles, remain a challenge.[2a,e] One explanation for their reticence to react is based on the presence of a basic heteroatom, which has the potential to ligate the palladium center leading to catalyst inhibition or deactivation.[3] Further, despite interest in heterocycles

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containing a fused imidazole ring, such as imidazo[1,2-a]pyridine,[4a–c] imidazo[1,2-b]pyridazine,[4d] and imidazo[1,2-a]pyrazine,[4e] the use of these types of substrates has not been extensively explored in cross-coupling reactions.

Catalysts based on ligands **L1–L4** have been shown to be uniquely effective in facilitating palladium-catalyzed amidations with aryl and heteroaryl halides.[3,5] In the case of monodentate biarylphosphine ligands (**L2–L4**), mechanistic studies and DFT calculations have indicated that this enhanced reactivity may be due to their conformational rigidity; the Pd(II) center is forced to position itself over the non-phosphine-containing ring, thus preventing catalyst inhibition via formation of a κ^2-amidate complex.[5c,e] It has also been postulated that enhanced rigidity around the Pd(II) center accelerates the rate of reductive elimination. However, despite the efficiency of these biarylphosphine-ligated palladium complexes in facilitating a variety of C–N cross-coupling reactions, a prominent limitation has been their deficiencies in processing five-membered heterocyclic halides that contain multiple heteroatoms with success largely limited to aniline nucleophiles.[2a] Thus, the development of a process for the combination of these difficult electrophiles with challenging nucleophiles, has been a daunting task. Herein, we report an example of such a technique, the first palladium-catalyzed amidation of multi-heteroatom, five-membered heterocyclic bromides facilitated by a novel bulky biarylphosphine ligand bearing adamantyl phosphine substituents (AdBrettPhos, **L6**).

Our initial studies focused on the coupling of 4-bromo-1-methylimidazole and benzamide (Table 1). Among the previously reported ligands **L1–L4**, only the use of **L3** provided a moderate conversion of aryl bromide (entries 1–4), suggesting the importance of the BrettPhos biaryl motif.[6] Considering the lessened steric bulk associated with five-membered heterocycles, we reasoned that ligands bearing even larger substituents on phosphorus might facilitate the product-forming reductive elimination step. Thus, we prepared **L5** and **L6**, which conserve the BrettPhos biaryl backbone framework yet possess one or two extremely bulky adamantyl substituents. Indeed, the use of the larger **L5** resulted in a 43% conversion and an improved yield of 24% (Table 1, entry 5). Notably, the use of the diadamantyl ligand **L6** resulted in full conversion of the bromoimidazole and an isolated yield of 83% of the desired amidation product (Table 1, entry 6).

The substrate scope of the palladium-catalyzed cross-coupling of five-membered heteroaryl bromides and amides was examined and the results are shown in Table 2. The present system was effective for the cross-coupling of a variety of five-membered heterocyclic bromides, including imidazoles, pyrazoles, thiazoles, pyrroles and thiophenes. Notably, this system provides access to the products derived from 4-bromo-1-alkylimidazoles (entries 1–4). In addition, substrates of interest in the medicinal chemistry arena such as 3-bromoimidazo[1,2-a]pyridine, -imidazo[1,2-b]pyridazine, and - imidazo[1,2-a]pyrazine (entries 5–7) were also transformed in good yield. Other heterocyclic halides such as 4-bromothiazole, 4-bromopyrrole and 2-bromothiophene (entries 8–12) were also found to be suitable coupling partners, as well as 4-bromo-1-alkylpyrazoles, though in this case higher temperatures were required (entries 13–16). In addition, amides containing pyridine, thiophene or furan units were well tolerated. However, the reaction of substrates containing free (H)*N*-bromoimidazoles and pyrazoles remain problematic.

We were particularly intrigued by the contrasting performance between reactions that utilized **L3** and **L6**, given that the difference in electronic effects between the *tert*-butyl and adamantyl groups is minimal (e.g., the ^{31}P NMR shift of **L3** and **L6** are nearly identical, 35 ppm and 37 ppm, respectively). This led us to speculate that the altered steric environment of **L6** might be the key in promoting cross-coupling in the case of five-membered heterocyclic aryl bromides. Thus, we decided to examine the structural differences between

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the oxidative addition complexes derived from **L3** and **L6**. Unfortunately, due to insufficient crystallinity, structural information for the five-membered heterocyclic series could not be obtained. However, we were able to prepare the oxidative addition complexes derived from six-membered aryl bromides for a direct comparison of the **L3**- and **L6**-derived intermediates (Figure 1). The X-ray structures of **2a** and **2b** revealed that the P–Pd–C1 angles were respectively, 96.0° and 99.1°.[7] It seems likely that the increased angle observed in **2b** can be attributed to the size of the adamantyl groups. With this information in mind, we turned to computational studies in an effort to gain insight into the ligand effects on the cross-coupling of five-membered heterocycles.

To conduct this study, geometry optimizations on **L**Pd(HetAr)(benzamidate) complexes were performed, where **L** was **L3, L5** and **L6** (Figure 2, **A**, **B**, **C** respectively). It has been previously suggested that the most favored geometry around biaryl phosphine-ligated palladium centers is one in which the amidate is trans to the phosphorus.[5c] While it has also been reported that ligands with methoxy group *ortho* to phosphorus can freely rotate with the palladium moiety being either over or away from the lower biaryl ring,[5e] we believe that in the case of ligands like **L6,** this rotation is restricted due to the presence of the very large adamantyl groups. Thus, based on our experimental results and the X-ray structures described above, we postulated that five-membered heterocycles, require the presence of a more sterically demanding dialkyl phosphino group to facilitate reductive elimination. Indeed, upon examining the P–Pd–C1 angle for complexes **A**, **B** and **C**, we observed that the heteroaryl group is pushed more towards the benzamidate in **C** relative to **A** and **B** (bond angles in A: 97.0°; in B: 97.7°; in C: 98.5°), consistent with our experimental observations; i.e., distorted toward the transition state for reductive elimination.[8]

In summary, the development of a bulky biaryl phosphine ligand **L6** has allowed for palladium-catalyzed amidation of five-membered heterocyclic electrophiles, representing the first such cross-coupling with this class of substrates. Structural and DFT studies suggest the need for the use of an electron-rich and sterically demanding ligand to promote these amidation reactions. Further exploration of these concepts as applied to other cross-coupling reactions involving five-membered heterocyclic halides is under investigation.

Experimental Section

General procedure

An oven-dried test tube was equipped with a magnetic stir bar and charged with $[(allyl)PdCl]_2$, **L6**, Cs_2CO_3 (2 mmol) and amide (2 mmol) (the heteroaryl bromide (1 mmol), if solid, is added at this point). The test tube was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of 3 times). 2-methyl-2-butanol (2 mL) and heteroaryl bromide (1 mmol) were then added via syringe. The reaction mixture was heated at 90°C for 21h. The reaction mixture was cooled to room temperature, diluted with EtOAc, washed with a saturated solution of sodium bicarbonate, dried over Na_2SO_4, concentrated in vacuo and purified by flash chromatography on silica gel to give pure products.

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7. Complexes **2a** and **2b** showed signs of rearrangement in solution (see: Maimone TJ, Milner PJ, Kinzel T, Zhang Y, Takase MK, Buchwald SL. J. Am. Chem. Soc. 2011; 133:18106–18109. [PubMed: 21999801] However, for the reactions reported in this paper, arylated ligands were not detected in the crude reaction mixture at the end of the reaction.
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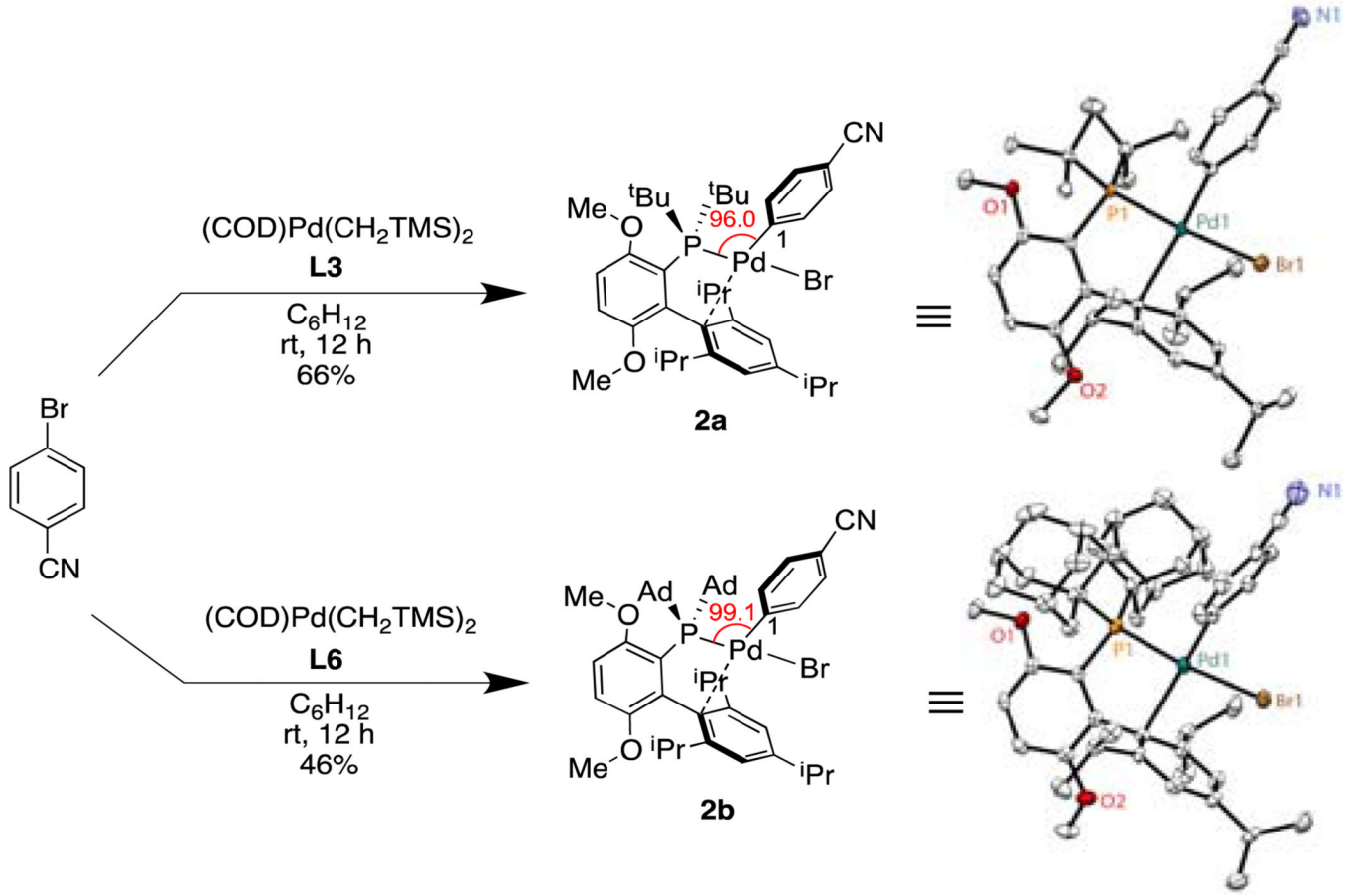

Figure 1.

Synthesis and X-ray structures of oxidative addition complexes (where **L3** = *t*BuBrettPhos and **L6** = AdBrettPhos). Thermal ellipsoid plot at 50% probability; hydrogen atoms omitted for clarity.

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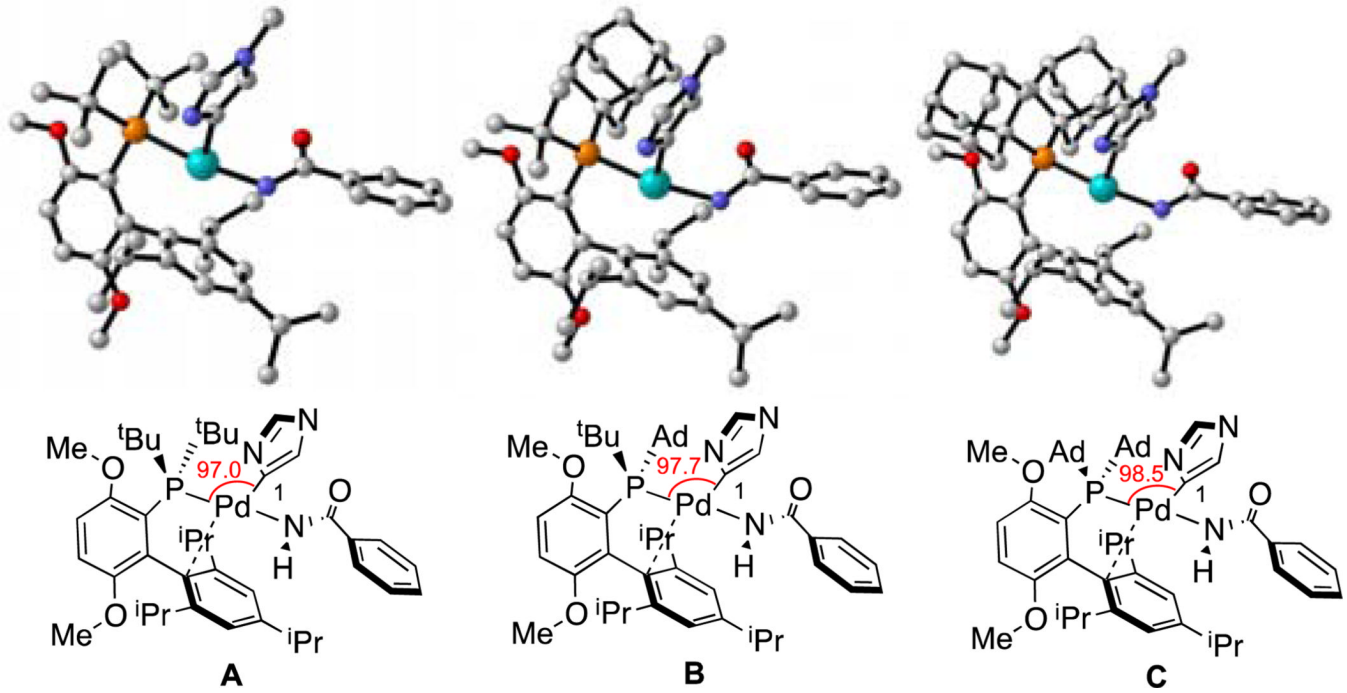

Figure 2.

Optimized ground state structures for monoligated LPd(HetAr)(benzamidate) complexes (phosphorus in orange, palladium in green, nitrogen in blue, oxygen in red). Hydrogen atoms omitted for clarity. Angle P–Pd–C1: (**A**, 97.0°; **B**, 97.7°; **C**, 98.5°)

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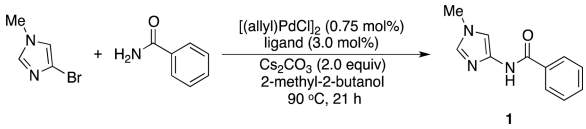
Table 1

Ligand effects in the palladium-catalyzed amidation of 4-bromo-1-methylimidazole.[a]



Entry	Ligand	Conversion [%][b]	Yield [%][c]
1	**L1**	<5	0
2	**L2**	<5	0
3	**L3**	35	15
4	**L4**	<5	0
5	**L5**	43	24
6	**L6**	100	83

[a]Reaction conditions: 4-bromo-1-methylimidazole (0.5 mmol), benzamide (1 mmol), $[(allyl)PdCl]_2$ (0.75 mol%), ligand (3 mol%), Cs_2CO_3 (1 mmol), 2-methyl-2-butanol (1 mL), 90 °C, 21 h.

[b]Determined by GC.

[c]Yield of isolated product.

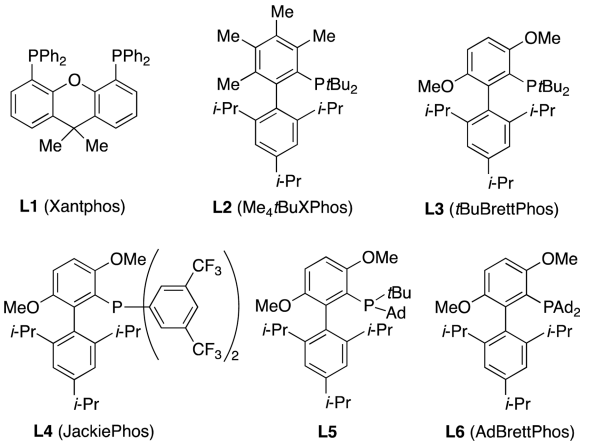


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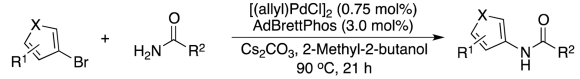
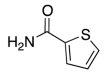
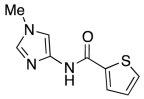
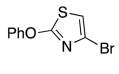
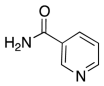
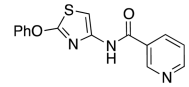
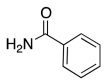
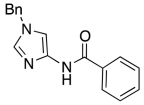
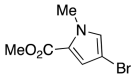
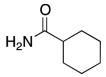
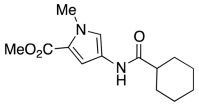
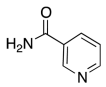
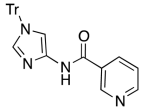
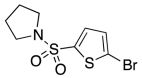
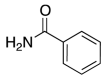
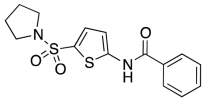
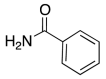
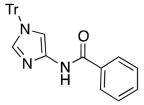
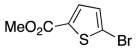
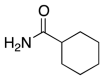
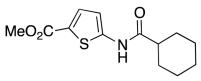
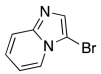
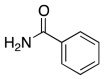
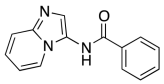
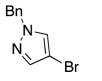
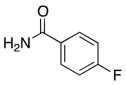
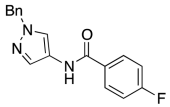
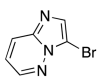
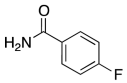
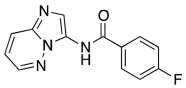
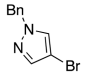
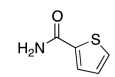
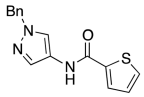
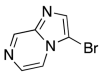
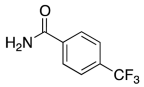
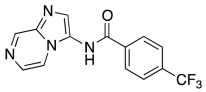
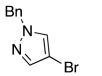
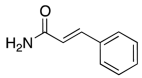
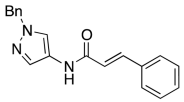
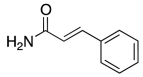
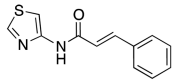
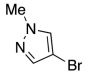
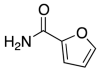
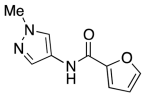
Table 2

Palladium-catalyzed coupling of five-membered heterocyclic bromides with amides.[a]



X = (NMe, NBn, NTr, S)

Entry	HetArBr	Amide	Product	Yield [%][b]	Entry	HetArBr	Amide	Product	Yield [%][b]
1				70	9[c]				74
2				62	10[c]				91
3				90	11[c]				81
4				90	12[c,d]				77
5				84	13[c,e]				87
6[c]				88	14[c,e]				81
7				84	15[c,e]				86
8[c]				94	16[c,e]				89

[a]Reaction conditions: HetArBr (1 mmol), amide (2 mmol), [(allyl)PdCl]$_2$ (0.75 mol%), ligand (3 mol%), Cs_2CO_3 (2 mmol), 2-methyl-2-butanol (2 mL), 90 °C, 21 h.

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[b] Yield of isolated product (average of two runs).

[c] HetArBr (1 mmol), amide (1.2 mmol), $[(allyl)PdCl]_2$ (0.75 mol%), ligand (3 mol%), Cs_2CO_3 (1.4 mmol), 2-methyl-2-butanol (2 mL), 90 °C, 21 h.

[d] $[(allyl)PdCl]_2$ (1.0 mol%), ligand (4 mol%).

[e] 120 °C. Bn = benzyl, Tr = trityl (triphenylmethyl).