

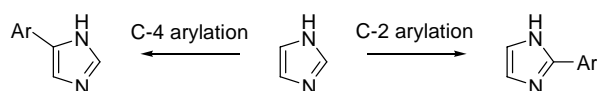
# C-H Bond Functionalization of Nitrogen Heterocycles

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## ABSTRACT



**Transition metal-mediated C-H functionalization is an efficient approach for the direct construction of substituted heterocycles from simple precursors. A brief review of the recent developments in nitrogen heterocycle C-H bond functionalization is presented.**

Metal catalyzed cross-coupling reactions are among the most important C-C bond forming reactions in synthetic chemistry. Direct C-H bond functionalization offers an attractive alternative to traditional approaches that require prior modification of the coupling partners. The use of relatively strong and unreactive C-H bonds as sites of C-C bond formation has been intensely researched and has been the subject of several reviews.<sup>1</sup> The directed insertion of a metal center into a C-H bond is an effective strategy,<sup>2</sup> but the necessity of a coordinating group limits substrate scope. Most other methods have achieved modest regioselectivity in intermolecular settings.

Present in numerous biologically active natural products and pharmaceuticals, nitrogen heterocycles are ideal targets for new synthetic methods. The embedded heteroatoms in such structures contribute electronic polarization and coordinating ability, which can be exploited to achieve regioselective reactivity. Synthetic methods that enable direct and selective heterocycle elaboration are invaluable tools for natural product synthesis and medicinal chemistry. This review will

focus on recent examples of nitrogen heterocycle C-H functionalization directly involving a transition metal in the C-C bond forming step, excluding examples occurring via radical or ionic mechanisms.

In 1989, Jordan disclosed the first catalytic C-H functionalization of pyridines, using a zirconium catalyst to alkylate  $\alpha$  to the pyridine nitrogen.<sup>3</sup> A recent report by Murakami and coworkers<sup>4</sup> described a ruthenium-mediated  $\alpha$ -alkenylation of pyridine (Scheme 1). The reaction of (alkyn-1-yl)trimethylsilanes with a cationic ruthenium source generated the catalytically active ruthenium vinylidene species **2** *in situ*. The authors hypothesized that the C-C bond formation occurs via [2+2] cycloaddition between the ruthenium vinylidene and a coordinated molecule of pyridine. The *E*-alkene selectivity was suggested to be the result of olefin equilibration under the reaction conditions. Phenyl and aliphatic alkynes were employed to achieve pyridine alkenylation in good yield for most substrates. Substitution on pyridine was tolerated in the 3- and 4-positions, but 2-methylpyridine failed due to steric interference. The general utility of this method is limited by the required excess of pyridine (20:1, pyridine:alkyne).

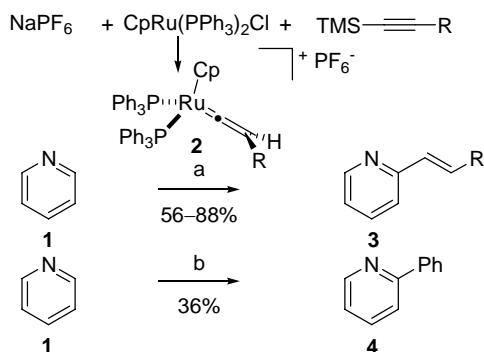
(1) (a) Shilov, A.; Shul'pin, G. *Chem. Rev.* **1997**, *97*, 2879. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (c) Dyker, G. *Angew. Chem. Int. Ed.* **1999**, *38*, 1698. (d) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211.

(2) Desai, L.; Hull, K.; Sanford, M. *J. Am. Chem. Soc.* **2004**, *126*, 9542.

(3) Jordan, R. F.; Taylor, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 778.

(4) Murakami, M.; Hori, S. *J. Am. Chem. Soc.* **2002**, *125*, 4720.

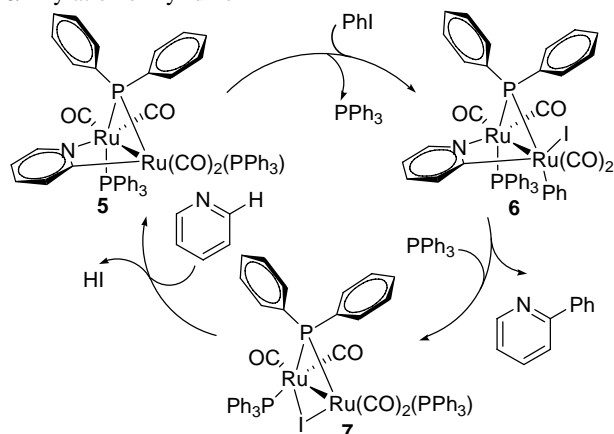
### Scheme 1. $\alpha$ -Alkenylation and Arylation of Pyridine



a)  $\text{CpRu}(\text{PPh}_3)_2$ ,  $\text{NaPF}_6$ , TMS-alkyne,  $150^\circ\text{C}$   
b)  $\text{Ru}_3(\text{CO})_{12}$ ,  $\text{PPh}_3$ ,  $\text{PhI}$ ,  $\text{Cs}_2\text{CO}_3$ ,  $150^\circ\text{C}$

The Sames lab has developed a ruthenium-catalyzed  $\alpha$ -arylation of pyridine<sup>5</sup> (Scheme 1) and conducted detailed mechanistic studies. In the presence of pyridine and triphenylphosphine,  $\text{Ru}_3(\text{CO})_{12}$  undergoes a defined series of transformations to form the bisruthenium catalyst **5** (Scheme 2). Loss of triphenylphosphine generates a coordinatively unsaturated ruthenium species, which oxidatively adds iodobenzene to give **6**. Reductive elimination forms the desired C-C bond and the  $\alpha$ -phenylpyridine product is replaced by triphenylphosphine. A molecule of pyridine coordinates one of the ruthenium atoms, undergoes C-H oxidative addition at the second metal center, then hydrogen iodide is eliminated to complete the catalytic cycle.

### Scheme 2. Proposed Mechanism for the Ruthenium-Catalyzed $\alpha$ -Arylation of Pyridine

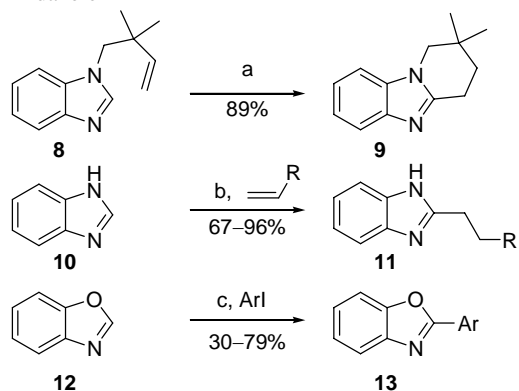


(5) Godula, K.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 3648.

This pyridine arylation mechanism is related to cyclometallation strategies that use a pendant coordinating group to position the metal center for C-H bond insertion. Sames' work instructively takes advantage of functionality embedded in the heterocycle rather than requiring an additional directing group. Although the reaction is currently low yielding, the mechanistic insights are important progress toward future optimization and the design of new reactions using bisruthenium intermediates.

Bergman and Ellman reported a valuable method for the rhodium-catalyzed formal addition of heterocycle C-H bonds to alkenes, known as hydroarylation.<sup>6</sup> Initial reports were limited to the intramolecular hydroarylation of tethered alkenes **8** (Scheme 3). Subsequent studies found that weak Brønsted acids increased reaction rate and facilitated intermolecular hydroarylation to alkylated products **11**.<sup>7</sup> Optimized conditions using lutidinium chloride as the acidic additive provided reliable yields across a broad range of substrates. The mild conditions accommodated isomerizable olefins and diverse functional groups, but coupling was unsuccessful with sterically hindered olefins. Subsequent reports have expanded the utility of this reaction to include other heterocycles and coupling partners.<sup>8</sup> Using similar conditions, benzoxazole was coupled with aryl iodides to afford C-2 arylated products **13**, where electron-rich aryl iodides were observed to couple most effectively.

### Scheme 3. Rhodium-Catalyzed Direct Functionalization of Benzimidazole



a)  $[\text{RhCl}(\text{coe})_2]_2$ ,  $\text{PCy}_3$ ,  $135^\circ\text{C}$ .

b)  $[\text{RhCl}(\text{coe})_2]_2$ ,  $\text{PCy}_3$ , lutidinium chloride,  $150^\circ\text{C}$ .

c)  $[\text{RhCl}(\text{coe})_2]_2$ ,  $\text{PCy}_3$ ,  $\text{Et}_3\text{N}$ ,  $150^\circ\text{C}$ .

During the course of mechanistic investigations, reaction of benzimidazole with the ruthenium catalyst generated the extraordinary *N*-heterocyclic carbene

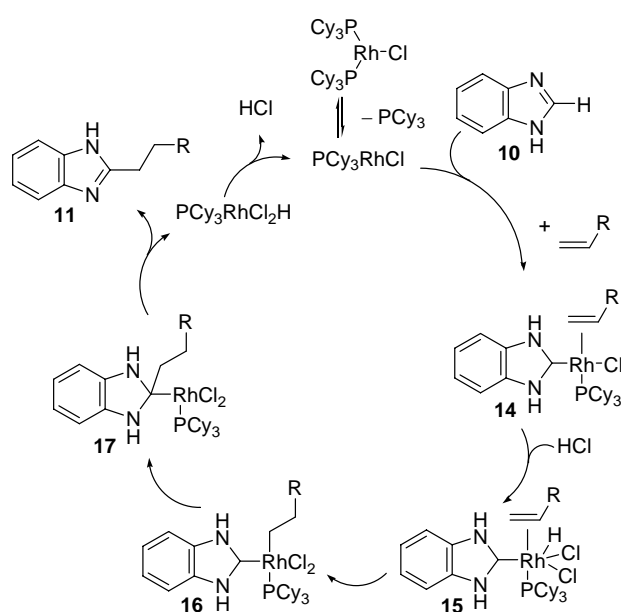
(6) (a) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 3202.

(7) Tan, K. L.; Park, S.; Ellman, J. A.; Bergman, R. G. *J. Org. Chem.* **2004**, *69*, 7329.

(8) Lewis, J. C.; Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 35.

(NHC) **14** (Scheme 4). This unexpected intermediate was structurally characterized by X-ray crystallography and shown to be catalytically active. According to the proposed mechanism, an olefin coordinates the rhodium center then inserts into the metal-hydride bond to form rhodium alkyl complex **16**. The C-C bond formation occurs by alkyl migration onto the substrate and  $\beta$ -hydride elimination releases the alkylated heterocycle **11**. The NHC mechanism restricts the substrate scope to heterocycles that form metal-carbene complexes. Interestingly, this is a rare example of an NHC playing a reactive role in a catalytic cycle rather than acting as a spectator ligand.

**Scheme 4.** Proposed Mechanism for the Rhodium-Catalyzed Hydroarylation of Olefins with Benzimidazole

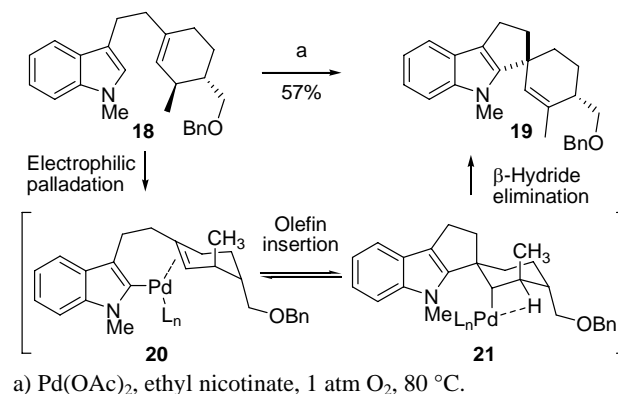


Oxidative indole annulation is an important reaction that has been used as a key step in several natural product syntheses.<sup>9</sup> Previous examples typically required stoichiometric palladium. The Stoltz lab developed a catalytic variant<sup>10</sup> using a pyridine-ligated palladium catalyst and molecular oxygen as the terminal oxidant. The reaction accomplished oxidative cyclization of a tethered alkene onto either C-2 or C-3 of an indole. The electronics of the pyridine ligand were systematically varied, and the highest reactivity was achieved using the electron-poor pyridine derivative ethyl nicotinate. Electron-deficient ligands presumably facilitate the reaction by increasing the electrophilicity of the catalyst.

Chiral indole **18** was subjected to the oxidative arylation conditions to distinguish between two possible

mechanistic pathways: direct palladation of the heterocycle or electrophilic activation of the olefin (Scheme 5). The direct palladation sequence would require *syn* migratory insertion of the pendant olefin, and *syn*  $\beta$ -hydride elimination. The electrophilic activation sequence would be anticipated to give an *anti* addition product via nucleophilic attack of indole on the coordinated olefin. The stereochemistry of the product **19** was consistent with direct palladation of indole.

**Scheme 5.** Mechanism of Palladium-Catalyzed Oxidative Cyclization



Selective palladium-catalyzed C-arylation of unprotected indole and imidazole was achieved by the Sames group (Scheme 6).<sup>11</sup> Deprotonation of the indole NH and formation of a salt having a strong M-N bond can suppress the inherent and undesired nucleophilicity of the nitrogen atom, while enhancing the reactivity of the annular carbons. With this in mind, the choice of MgO as a base was found to be essential in achieving palladium-catalyzed coupling of indole with iodoarenes to afford 2-arylimidole **23**. A variety of electron-rich and electron-deficient aryl iodides were coupled in good yield. *N*-arylation was not observed, and competing C-3 arylation only occurred with sterically hindered aryl iodides. Under identical conditions, imidazole was selectively arylated at C-4. The imidazole regioselectivity was most likely determined by electrophilic palladation at the more nucleophilic site. The indole regioselectivity is not well understood, but palladation at the less nucleophilic C-2 may be favored by an activating effect from the neighboring nitrogen atom.

Having accomplished a remarkably selective, direct route to 4-phenylimidazoles, Sames and coworkers pursued a complimentary route to 2-phenylimidazoles. A complete reversal of regioselectivity was observed when CuI was used as an additive, yielding 2-phenylimidazole as the only isolated product. High yields and complete regioselectivity were maintained for C-4 arylation using

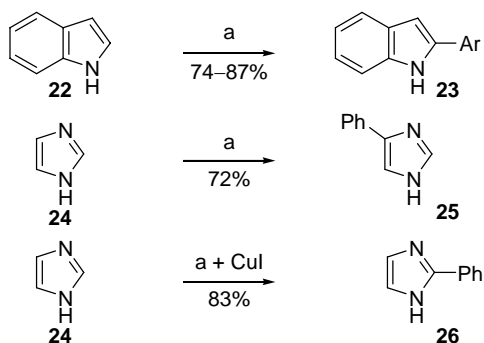
(9) Baran, P. S.; Guerrero, C. A.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5628.

(10) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578.

(11) (a) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 5274. (b) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 10580.

an electronically diverse array of aryl iodides; whereas the C-2 phenylation has currently been described only using iodobenzene. Subsequent efforts extended the scope to include selective phenylation of thiazole and oxazole.<sup>12</sup> Combined with known *N*-arylation procedures, this work enables selective functionalization of any position of unprotected azoles by modification of the reaction conditions, advancing simple and inexpensive heterocycles to complex materials.

**Scheme 6.** Regioselective Arylation of Indole and Imidazole

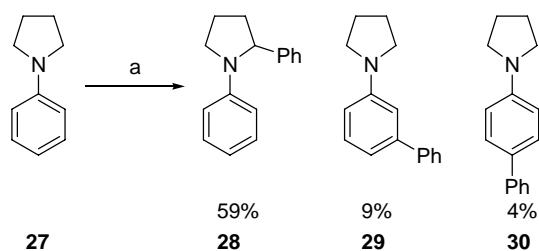


a) PhI, Pd(OAc)<sub>2</sub>, PPh<sub>3</sub>, MgO, 150 °C 12–15 h.

Selective C-H bond functionalization at sp<sup>3</sup> centers is a challenging undertaking, particularly in the presence of more reactive sp<sup>2</sup> C-H bonds. Examples of selective intermolecular sp<sup>3</sup> C-H functionalization are rare, and most often occur by cyclometallation.<sup>13</sup> However, sp<sup>3</sup> C-H bonds adjacent to a nitrogen atom are activated for oxidative addition, which makes the selective arylation of saturated nitrogen heterocycles possible.

Sames and coworkers recently disclosed a selective ruthenium-catalyzed  $\alpha$ -arylation of *N*-phenylpyrrolidine (Scheme 7).<sup>14</sup> Initial attempts using Cp<sup>\*</sup>Rh(H)<sub>2</sub>PMe<sub>3</sub> gave the desired product in only 3% yield in addition to side products **29** and **30** from arylation of more reactive sp<sup>2</sup> sites. Careful screening of ruthenium sources and reaction conditions favored sp<sup>3</sup> arylation in an optimized 59% yield. Electron-donating, sterically hindered phosphine ligands were used to stabilize high oxidation state ruthenium intermediates. The mechanism proceeds by oxidative addition of iodobenzene, followed by a second oxidative addition of the pyrrolidine C-H, then reductive elimination to form the  $\alpha$ -phenylpyrrolidine. Currently, the reaction has only been described using iodobenzene in modest yield, but this is an impressive demonstration of selective intermolecular sp<sup>3</sup> C-H functionalization that will serve as a foundation for future development.

**Scheme 7.** Catalytic Arylation of *N*-Phenylpyrrolidine



a) Ru(H<sub>2</sub>)<sub>2</sub>(H)<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub>, PhI, Cs<sub>2</sub>CO<sub>3</sub>, 150 °C, 18 h.

Transition metal-mediated C-H functionalization is rapidly emerging as an important approach for the formation of C-C bonds. Using innovative methods developed during the past few years, a variety of nitrogen heterocycles can be directly functionalized with high regioselectivity. While encouraging progress has been made, future work is expected to focus on the development of milder reaction conditions and increasing the scope of such processes. Nevertheless, the omnipresence of nitrogen heterocycles in numerous pharmaceuticals and biologically active natural products necessitates the development of novel and versatile methods for their preparation. C-H bond functionalization of nitrogen heterocycles represents a potentially powerful, selective, and direct method to achieve such goals.

(12) Sezen, B.; Sames, D. *Org. Lett.* **2003**, *5*, 3607.

(13) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935.

(14) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 5284.