Direct C-Arylation of Free (NH)-Indoles and Pyrroles Catalyzed by Ar–Rh(III) Complexes Assembled In Situ

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Erick B. Iezzi
Current Literature
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Why is this paper significant?

- Heteroaromatics are important structural units found in natural products, pharmaceuticals and numerous functional synthetics

- C–H bond activation represents a chemical process of broad synthetic scope:

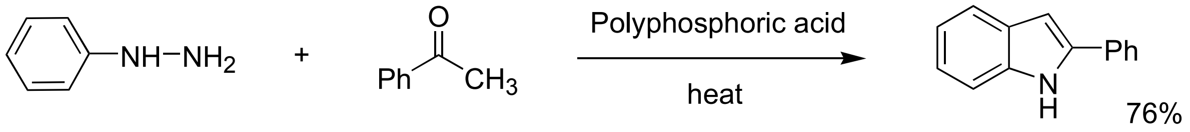
    - ability to selectively and/or systematically functionalize a heteroaromatic molecule
    - selectively functionalize sp^2 and sp^3 carbon atoms

- Direct C-arylation of free (NH)-azoles eliminates the need for introducing protecting groups and reactive functionalities prior to C–C formation (i.e., halogenation or stoichiometric metalation prior to C–C coupling)

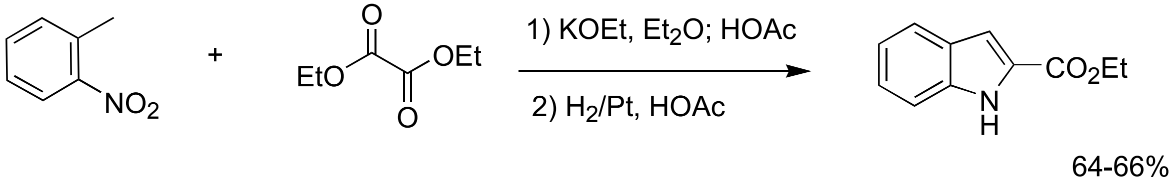
- Free pyrroles, indoles and imidazoles are unreactive under known arylation conditions, yielding little or no C-arylated products

Common Methods for Synthesizing Substituted Indoles

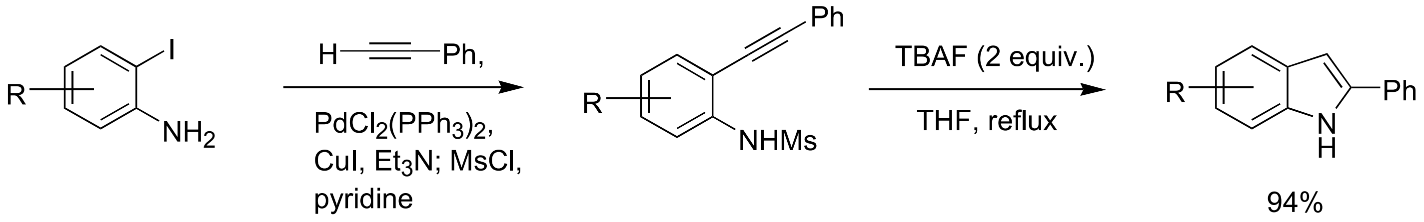
Fisher indole synthesis



Reissert indole synthesis



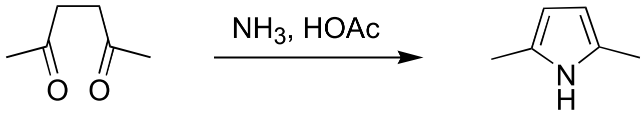
Sonagashira coupling/base-mediated cyclization



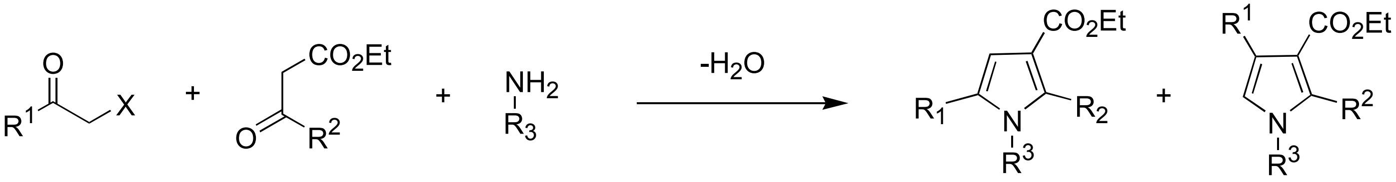
Sakamoto, et al. *J. Chem. Soc., Perkin Trans. 1,* **1999**, 529-534

Classical Methods for Synthesizing Substituted Pyrroles

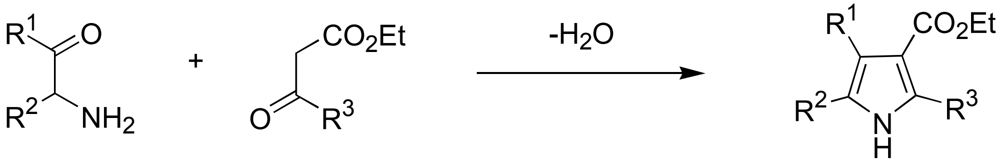
Paal-Knorr Synthesis



Hantzsch Synthesis

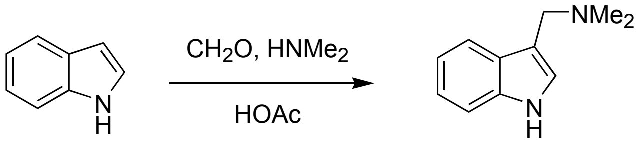


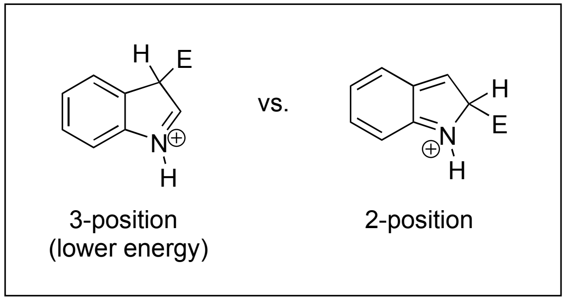
Knorr Synthesis



Electrophilic Aromatic Substitution of Indoles and Pyrroles

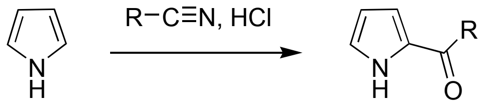
Mannich Reaction

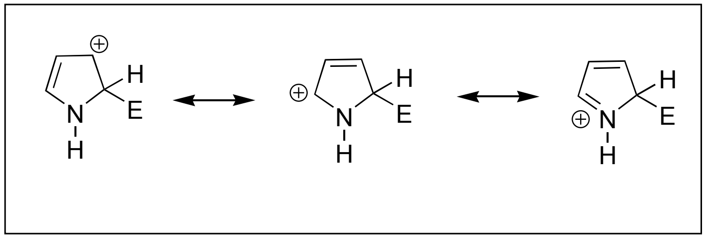




- Indole favors C-3 substitution

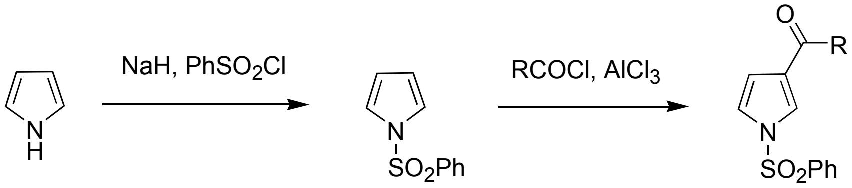
Houben-Hoesh Reaction





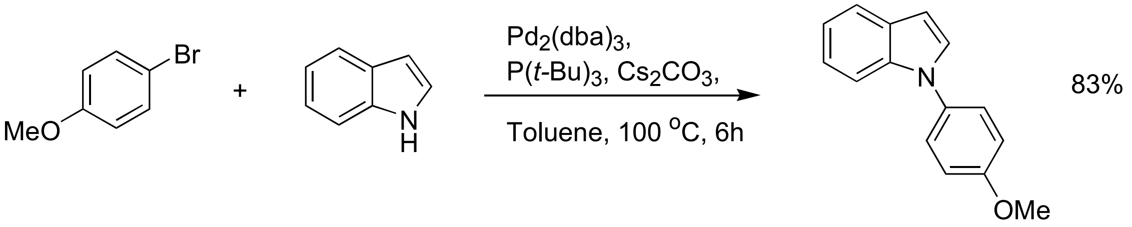
- Pyrrole favors C-2 substitution

Friedel-Crafts Acylation with Protected Pyrrole



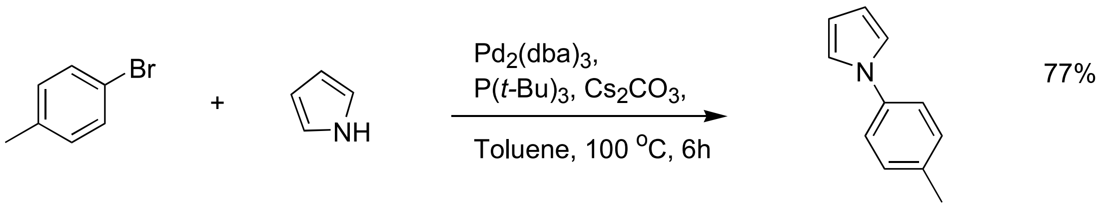
Anderson, et al. *Tetrahedron Lett.* **1981**, *22*, 4899-4900

N-Arylation of Azoles



$Pd_2(dba)_3$, $P(t\text{-}Bu)_3$, Cs_2CO_3, Toluene, 100 °C, 6h

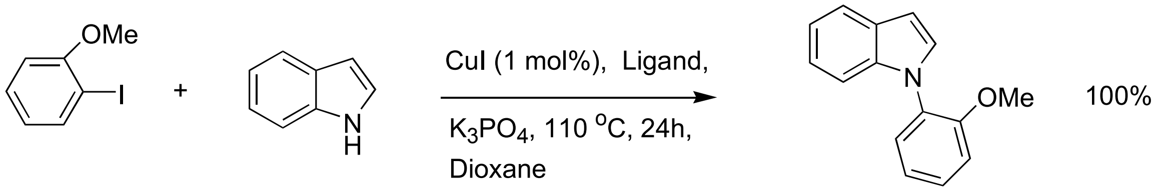
83%



$Pd_2(dba)_3$, $P(t\text{-}Bu)_3$, Cs_2CO_3, Toluene, 100 °C, 6h

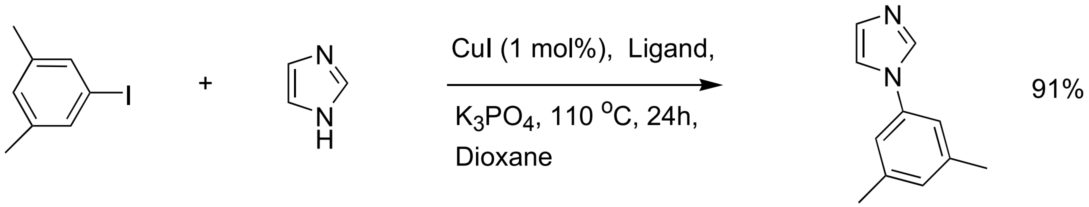
77%

Hartwig, et al. *J. Org. Chem.* **1999**, *64*, 5575-5580.



CuI (1 mol%), Ligand, K_3PO_4, 110 °C, 24h, Dioxane

100%

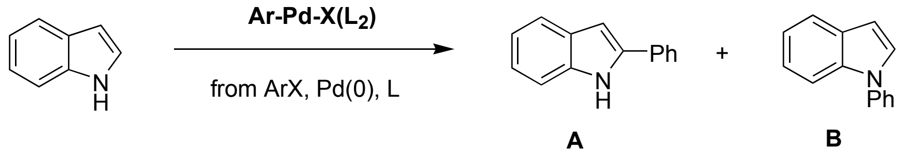


CuI (1 mol%), Ligand, K_3PO_4, 110 °C, 24h, Dioxane

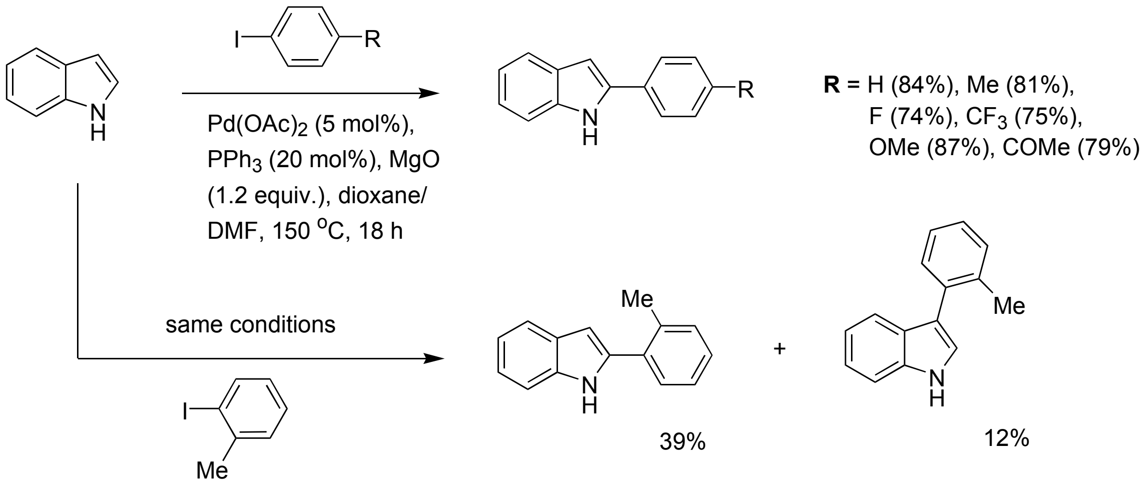
91%

Buchwald, et al. *J. Am. Chem. Soc.* **2001**, *123*, 7727-7729.

Metalation as N-Protection and Activation of Heteroarenes



Base (1.2 equiv.)	Isolated yield (A / B)
LiOH or NaOMe	0 / 0%
K_3PO_4 or KOAc	0 / 0%
Cs_2CO_3	0 / 5%
MgO	**53** / 0%
EtMgBr	**65** / 0%
ZnO	44 / 0%

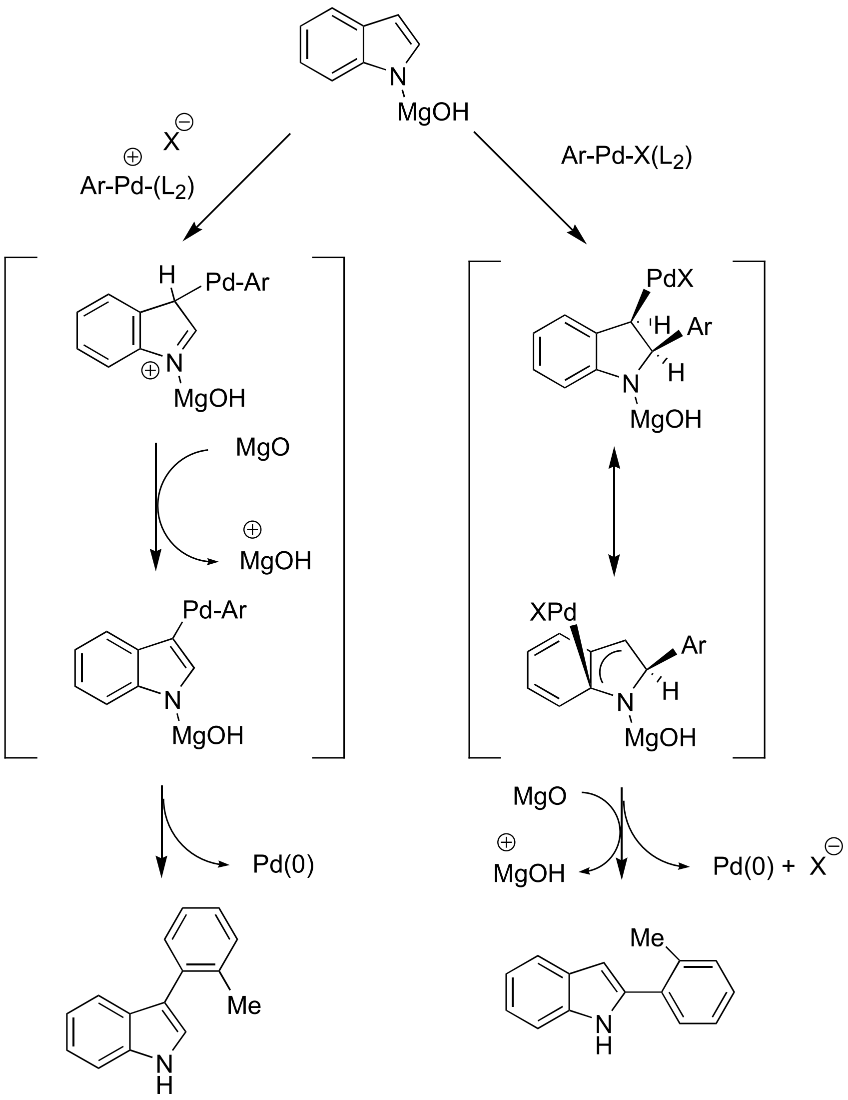


R = H (84%), Me (81%), F (74%), CF_3 (75%), OMe (87%), COMe (79%)

- this process suffers from considerable moisture sensitivity and limited functional group scope

Sames, et al. *J. Am. Chem. Soc.* **2003**, *125*, 5274-5275

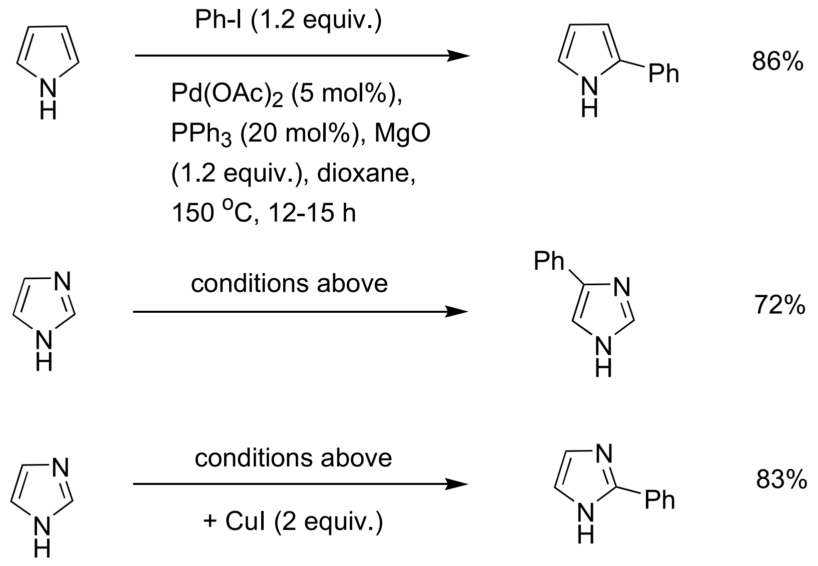
Mechanistic Explanations for C-2 and C-3 Arylation of N-Metalated Indole



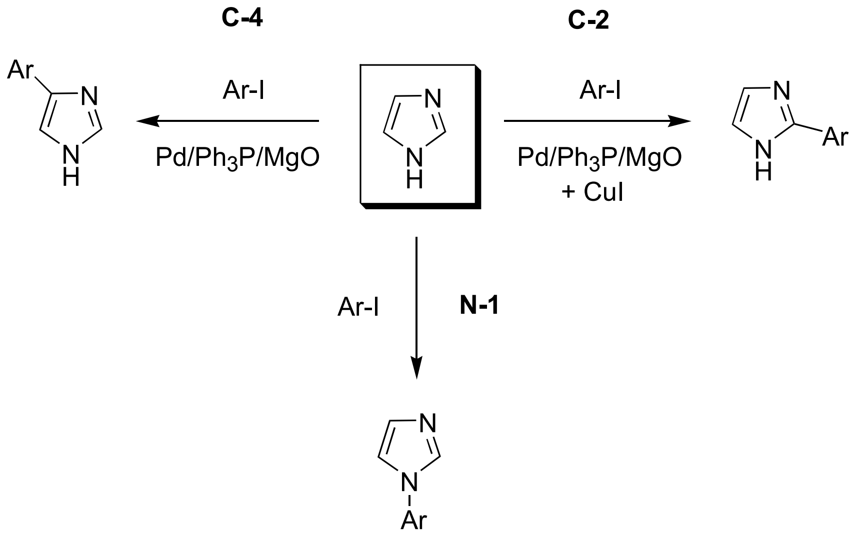
C-3

C-2

Selectivity in C-Arylation of In Situ N-Metalated Azoles

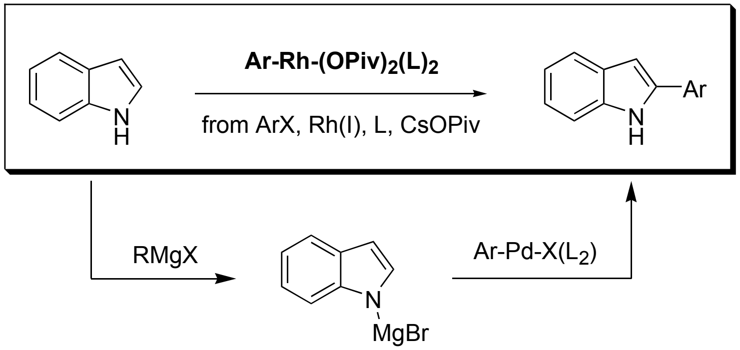


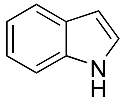
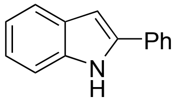
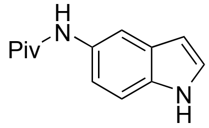
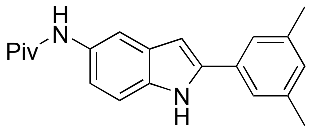
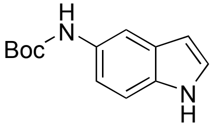
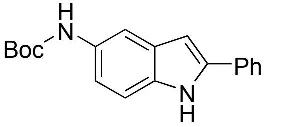
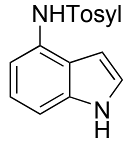
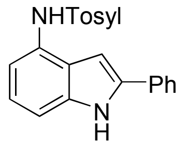
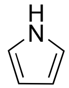
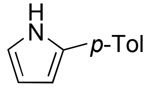
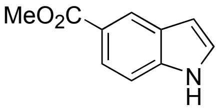
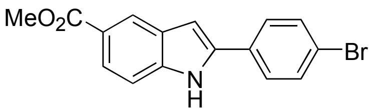
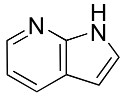
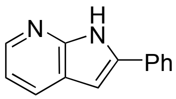
Arylation of Imidazole: Complete Orthogonality



Sames, et al. *J. Am. Chem. Soc.* **2003**, *125*, 5274-5275

Direct C-Arylation of Free (NH)-Azoles by a Rh(III) Catalyst: Evaluation of Substrates and Functional Groups



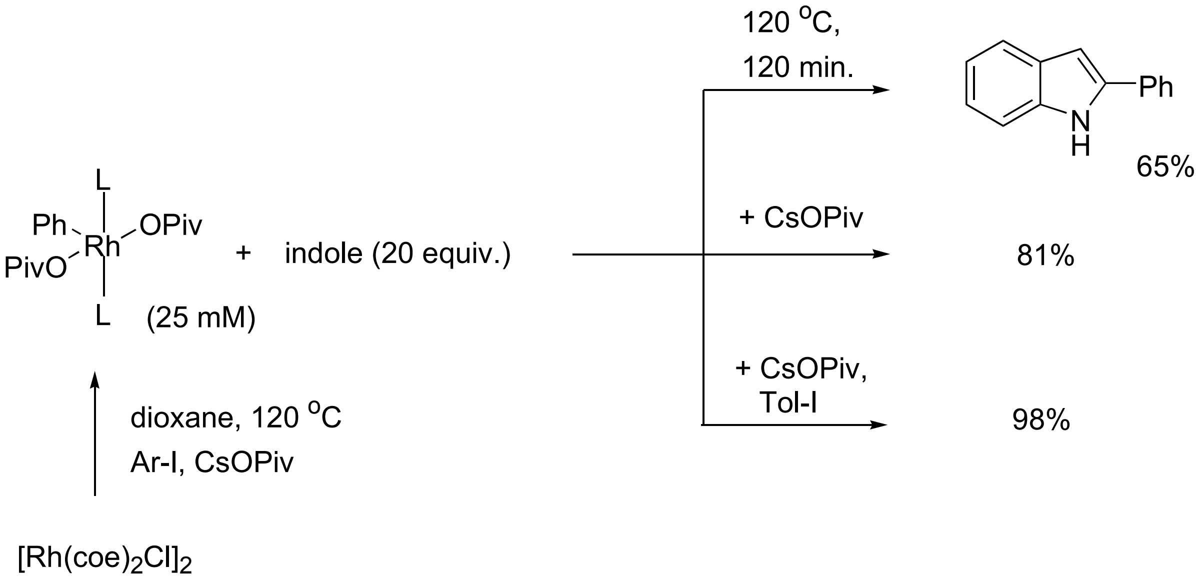
Azole	Product	Isolated yield
		82%
		78%
		59%
		65%
		81%
		59%
		0%

Reaction conditions:

Azole (1 equiv.), ArI (1.2 equiv.),
CsOPiv (1.4 equiv.), $[Rh(coe)_2Cl]_2$ (1 mol%),
$[p\text{-}(CF_3)\text{-}C_6H_4]_3P$ (15 mol%), Dioxane,
120 ^oC, 18-36 h.

Sames, et al. *J. Am. Chem. Soc.* **2005**, ASAP.

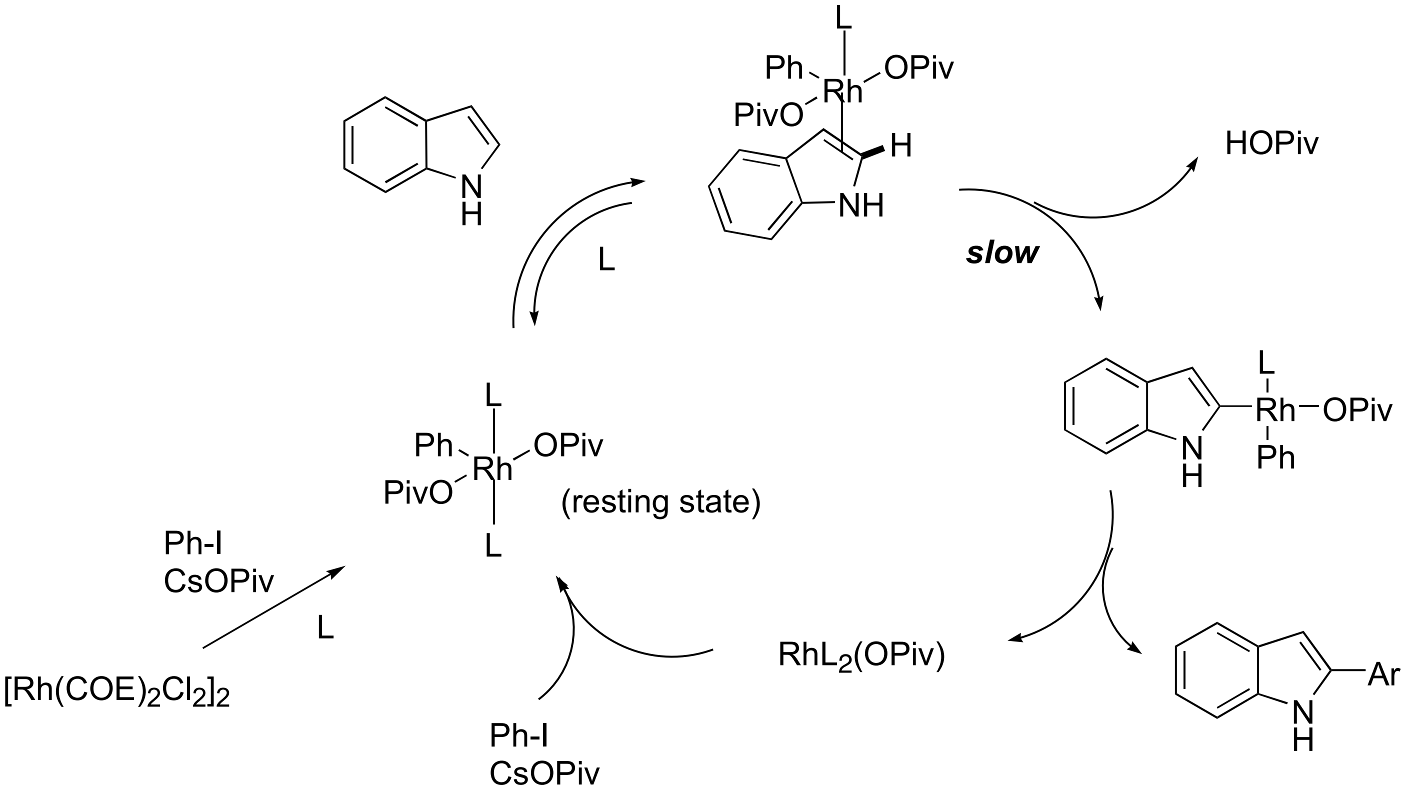
Synthesis and Reactivity of Rh(III) Catalyst



L = [*p*-(CF_3)C_6H_4]$_3$P, Ar = Ph, 4-Tol

- CsOPiv and 4-Tol-I serve as trapping agents to prevent decomposition of Rh(I)
- Carbonates and phosphates of alkali metals as well as amines were ineffective as bases
- CsOAc gave 45% product, versus 82% for CsOPiv

Proposed Catalytic Cycle



$L = [p\text{-}(CF_3)C_6H_4]_3P$

Future Work

- Taylor catalyst to work with basic amine substrates (i.e., 7-azaindole)
- Clearify mechanistic details of C-H metalation via the Rh(III) catalyst