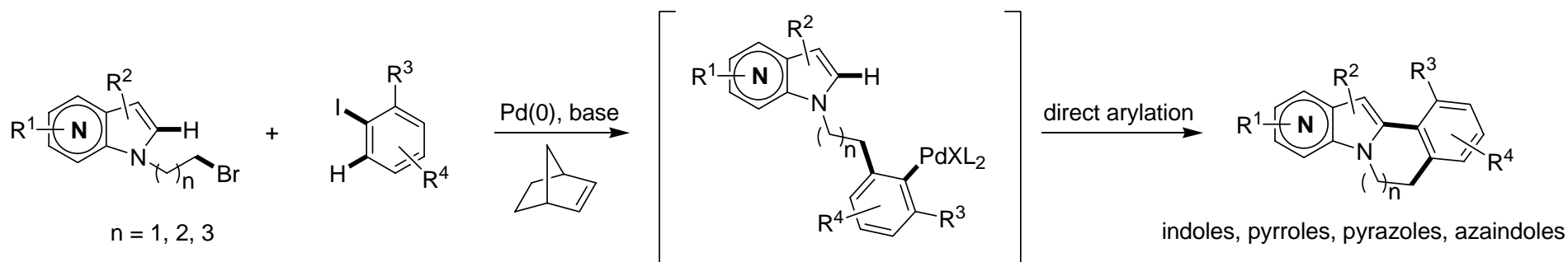


A Palladium-Catalyzed Alkylation/Direct Arylation Synthesis of Nitrogen-Containing Heterocycles

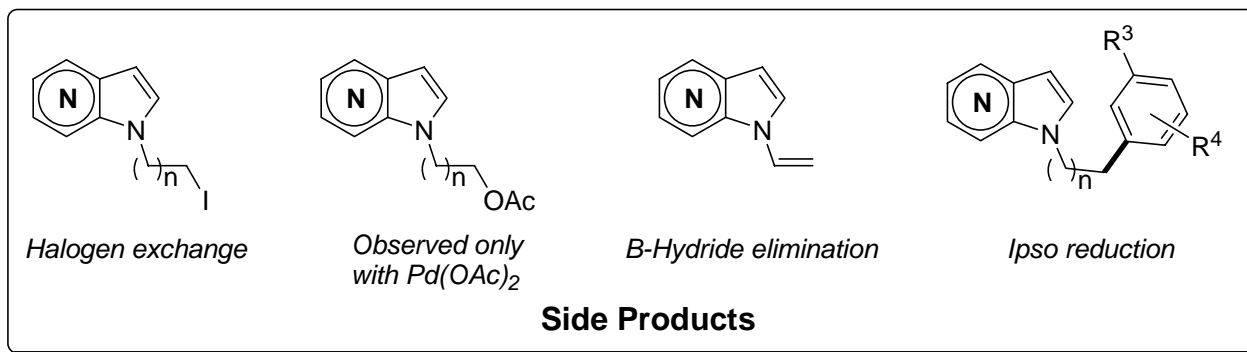
Blaszykowski, C.; Aktoudianakis, E.; Alberico, D.; Bressy, C.; Hulcoop, D. G.; Jafarpour, F.; Joushaghani, A.; Laleu, B.; Lautens, M. *J. Org. Chem.* **2008**, ASAP.

Chad Hopkins
Wipf Group Literature Presentation
2-16-08

Reaction Overview



Typical reaction conditions: Aryl iodide (1 equiv), *N*-bromoalkyl heterocycle (2 equiv), Pd cat. ($\text{Pd}(\text{OAc})_2$ or PdCl_2 , 10 mol%), tri-2-furylphosphine (22 mol%), CsCO_3 (2 equiv), and norbornene (2 equiv). MeCN (0.1M), sealed tube, 90°C, 16-24h

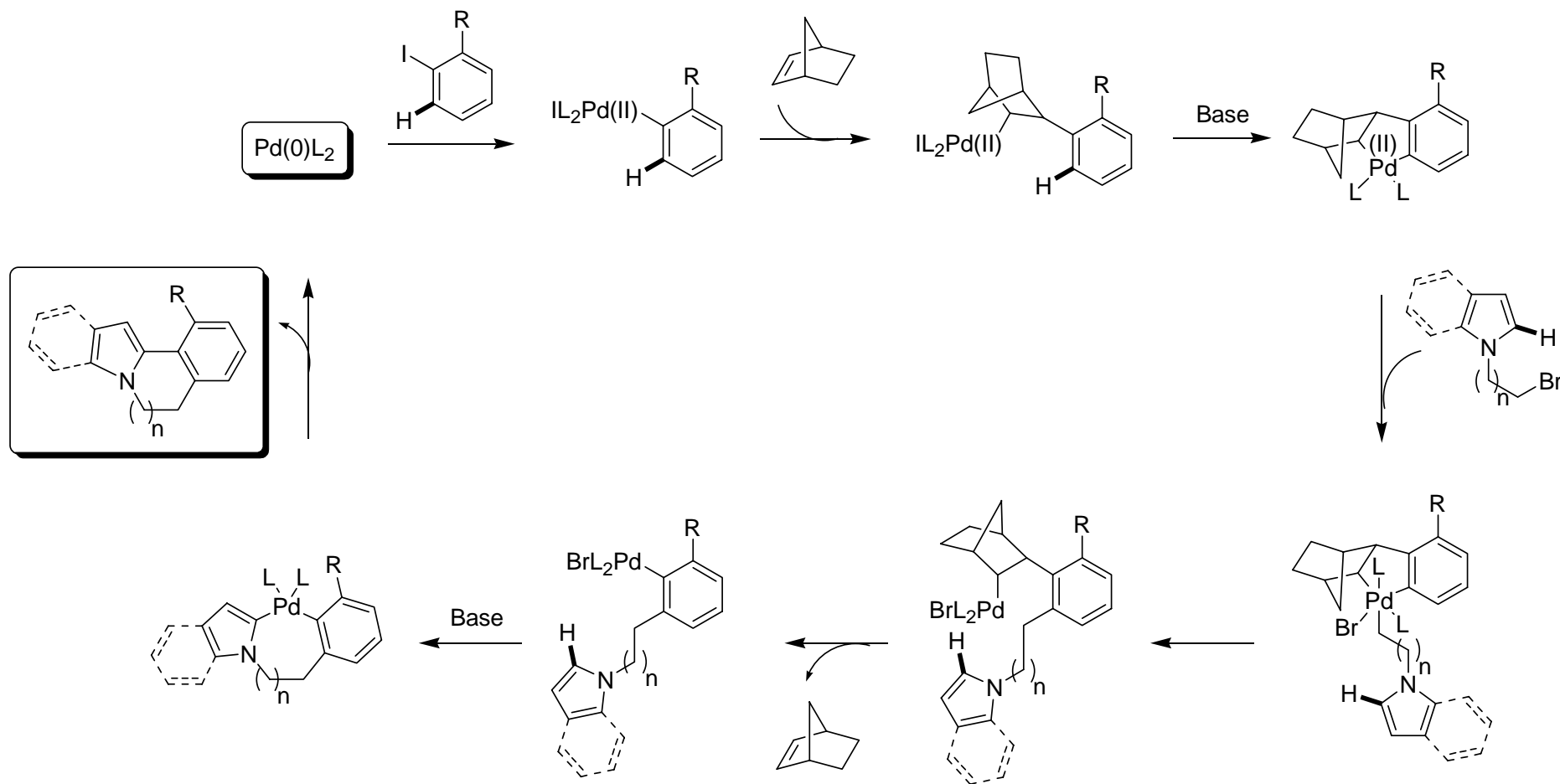


For preliminary studies see:

Lautens, M. et al. *Org. Lett.* **2006**, 8, 2043.

Lautens, M. et al. *J. Am. Chem. Soc.* **2005**, 127, 13148.

Proposed Mechanism

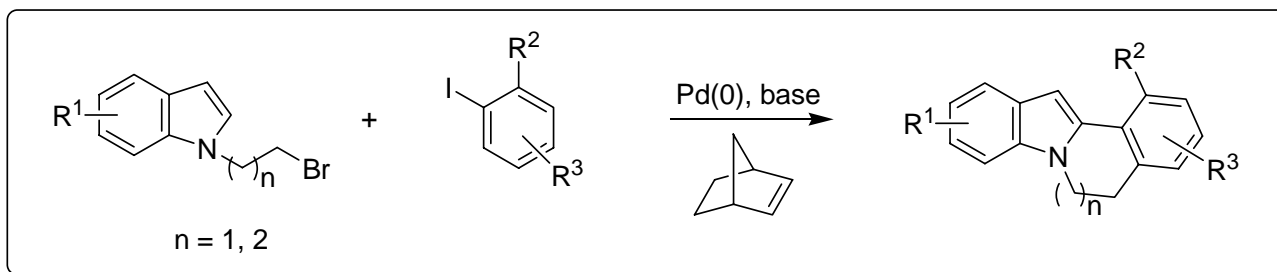


For additional reading see:

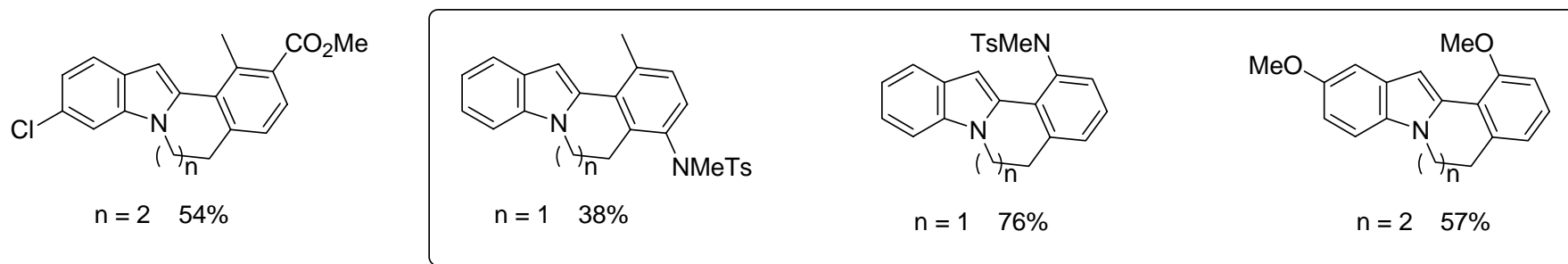
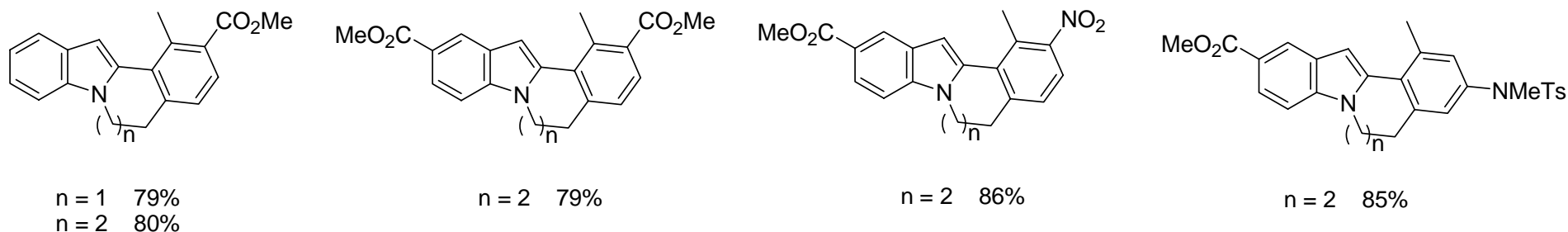
Catellani, M. et al. *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 119.

Catellani, M. et al. *J. Am. Chem. Soc.* **2002**, 124, 4336.

Six- and Seven-Membered Ring Annulated Indoles



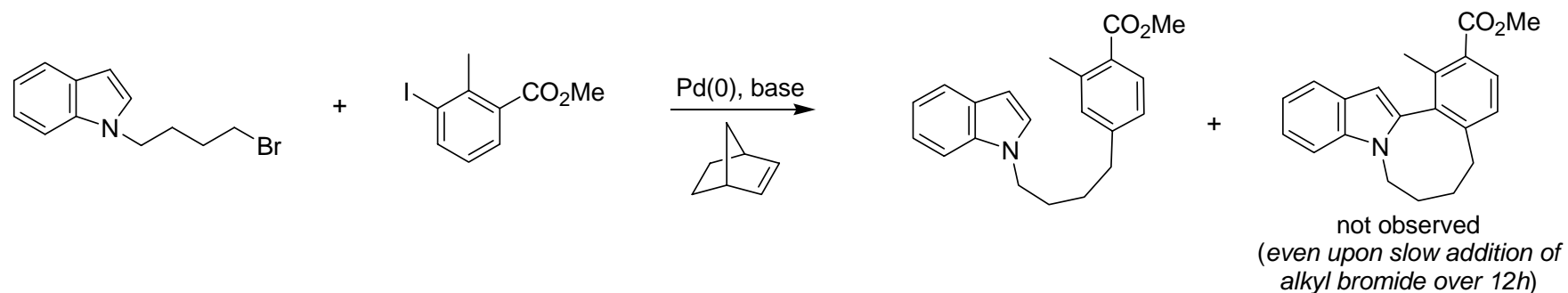
Note: Pyrroles undergo Pd-catalyzed annulation with similar yields (59-91%)
 Lautens, M. et al. *Org. Lett.* **2006**, 8, 2043.



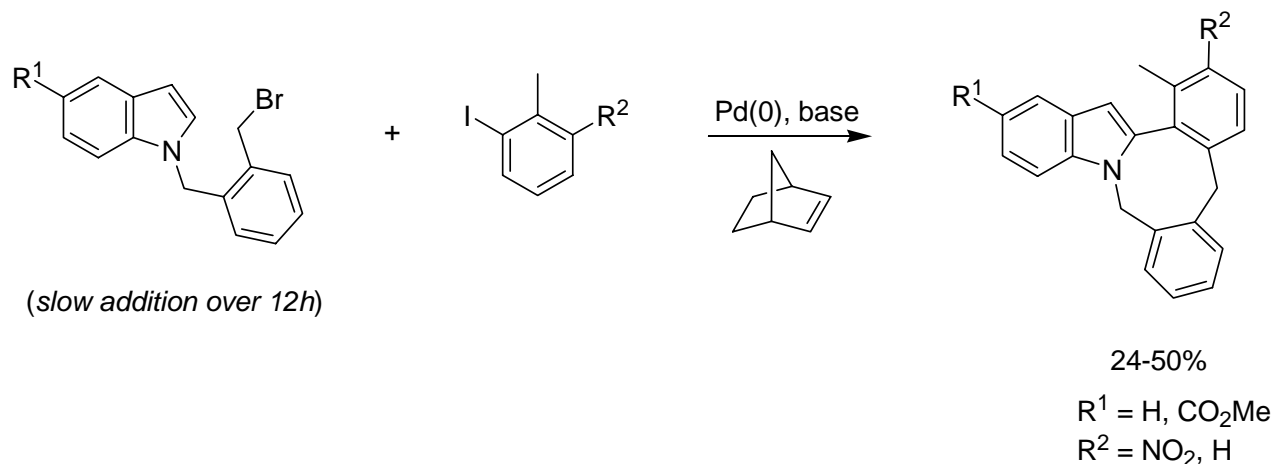
Also see: Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, 127, 13148.

For a similar sequence involving thiophenes and furans, see: Lautens, M. et al. *Org. Lett.* **2006**, 8, 4827.

Eight-Membered Ring-Annulated Indoles

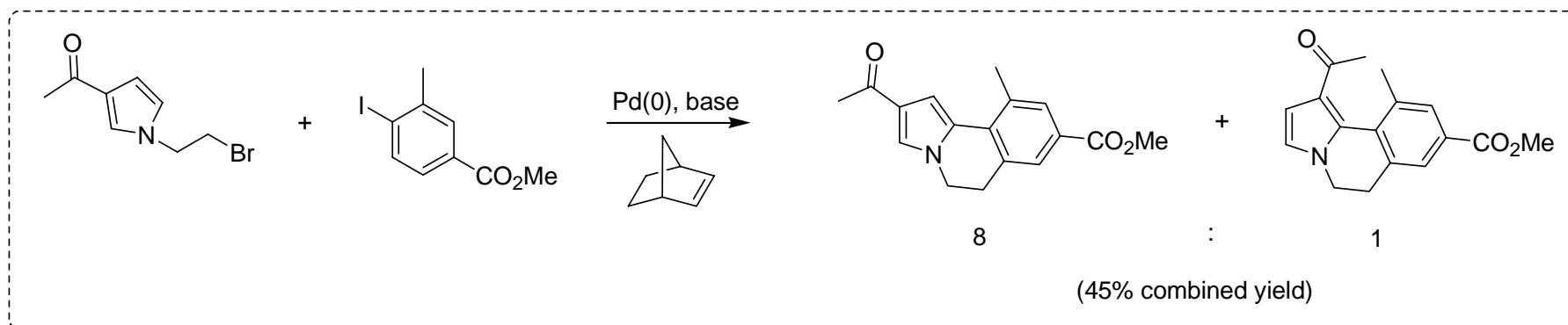
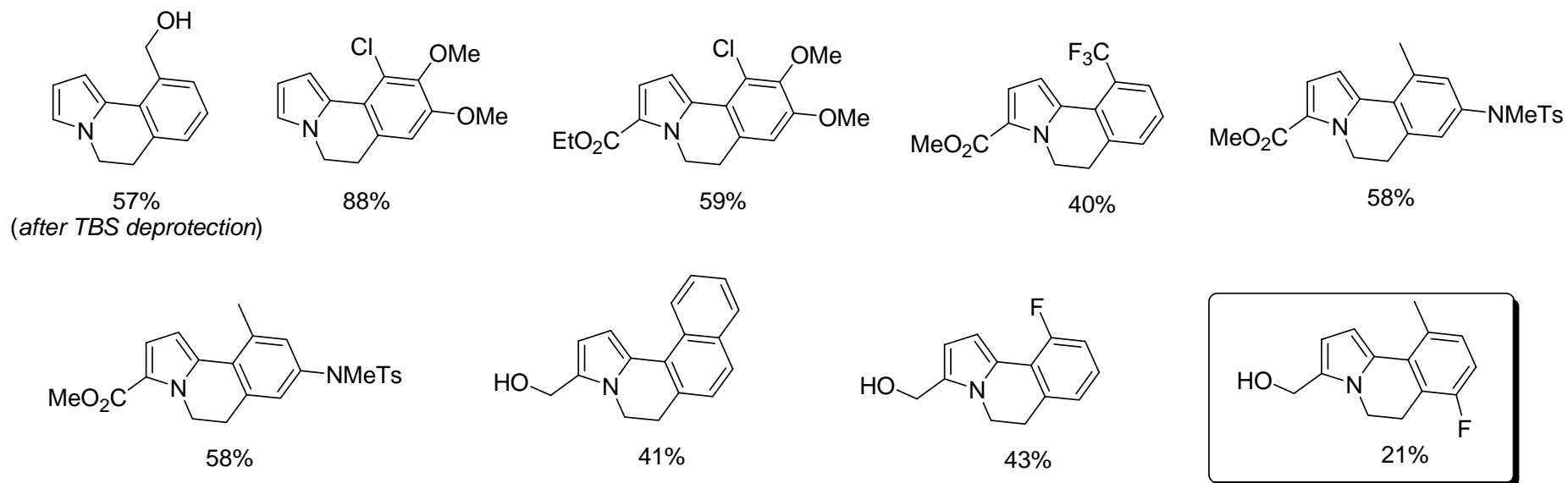
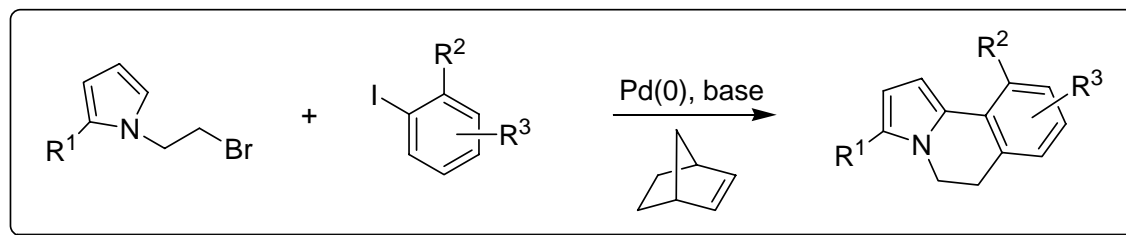


Adapt and Overcome: *Limit the degrees of freedom*

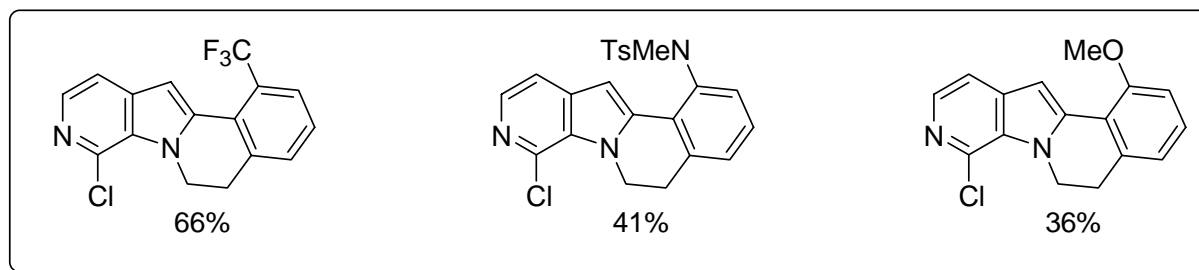
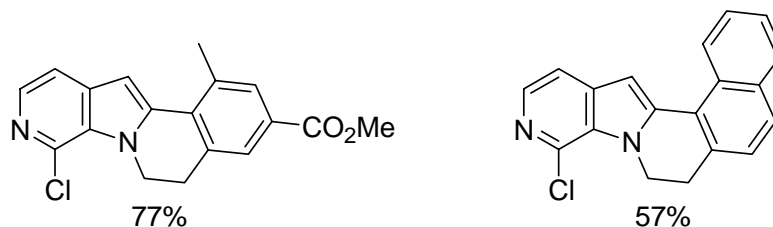
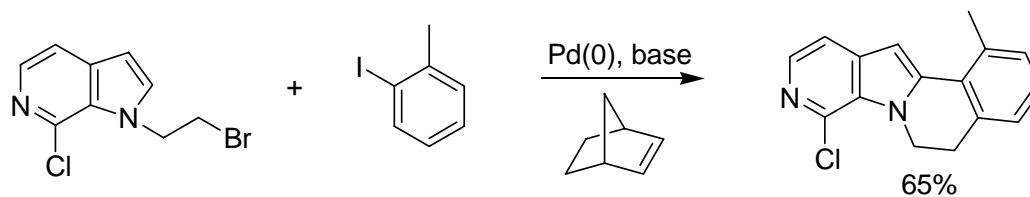
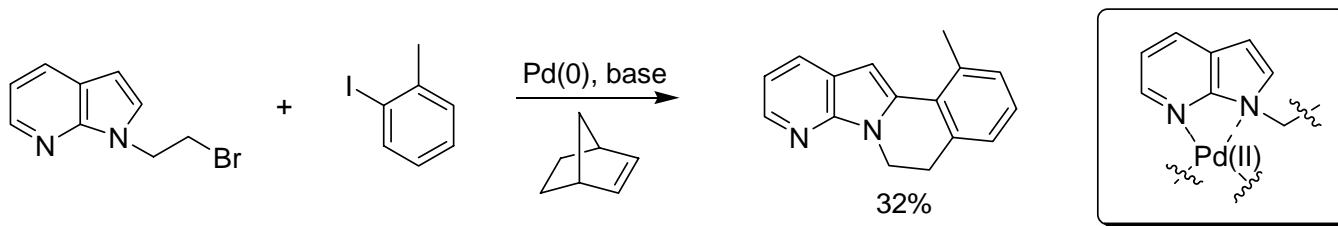


Single example in simple pyrrole series: R² = NO₂, 30%

Functionalized Annulated Pyrroles

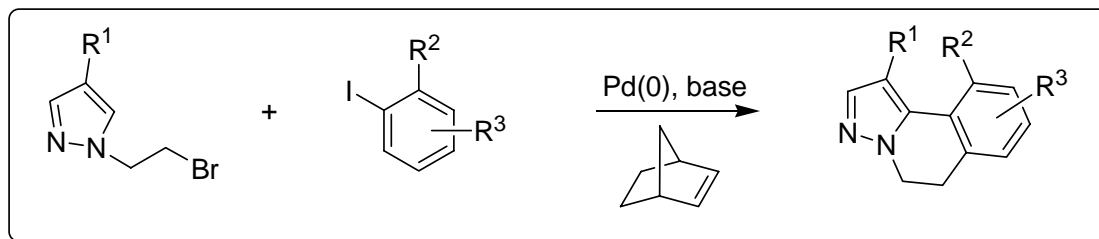


Annulation of Azaindoles

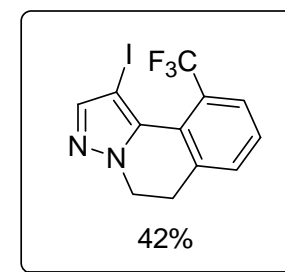
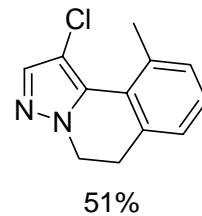
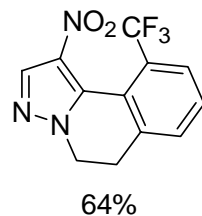
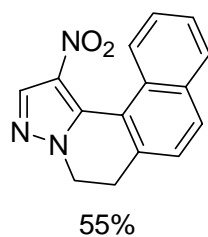
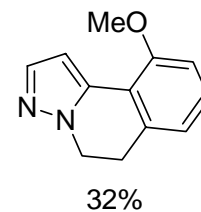
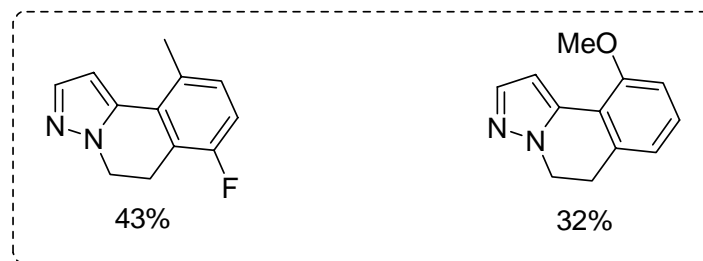
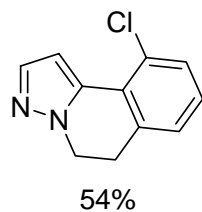
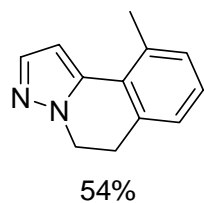


For a review on the synthesis and functionalization of azaindoles, see: Song, J. J. *Chem. Soc. Rev.* **2007**, 36, 1120.

Six-Membered Ring Annulated Pyrazoles



Slow addition of alkyl bromide was performed over 17h

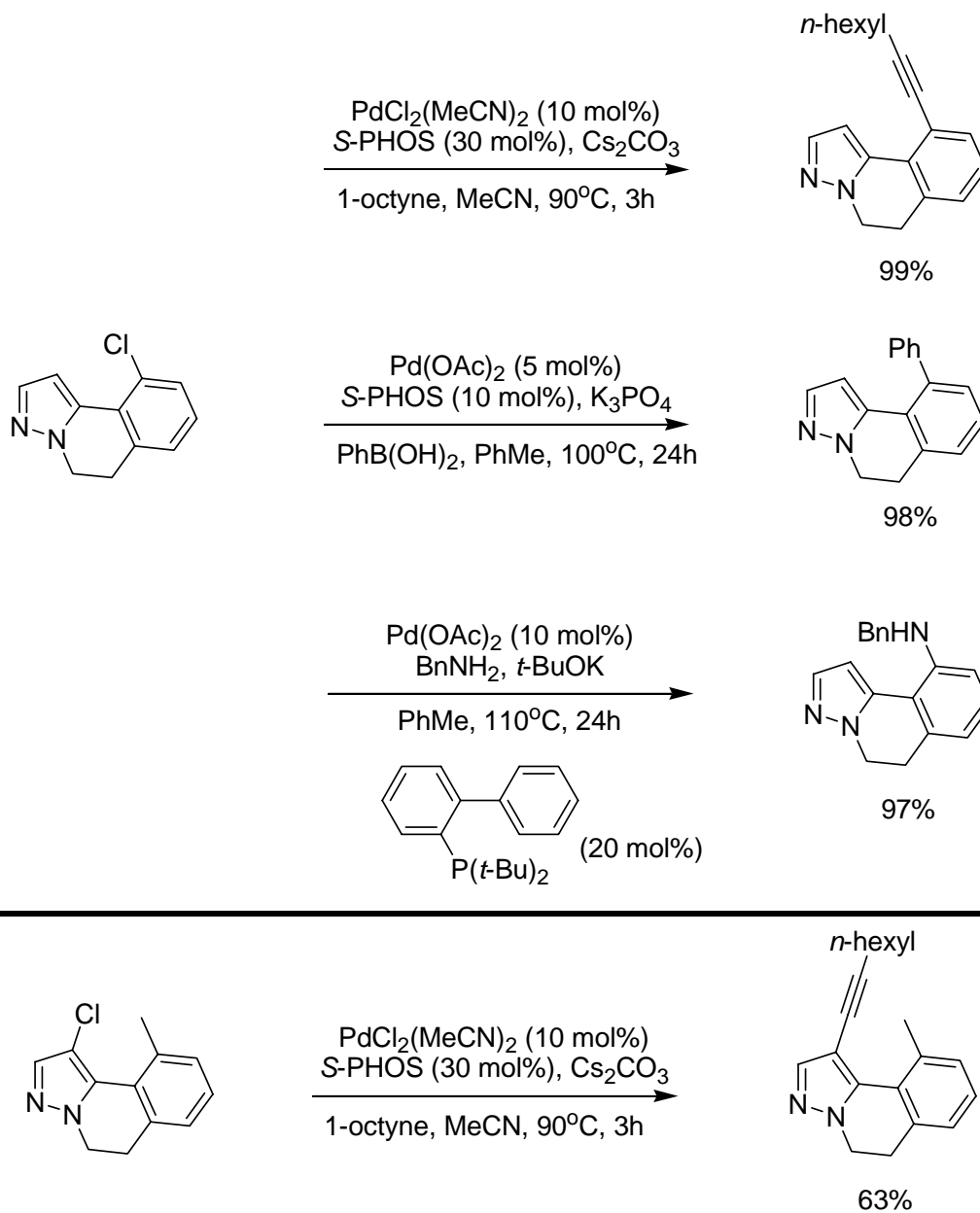


For use of annulated pyrazoles as insecticides and CB₁ inhibitors see:

Lamberth, C. *Heterocycles*, **2007**, 71, 1467.

Kruse, C. G. et al. *Chem. Pharm. Bull.* **2002**, 50, 1109.

Further Functionalization of Annulated Pyrazoles



Summary

- A route to highly functionalized six-, seven-, and eight-membered ring annulated indoles, azaindoles, pyrroles, and pyrazoles has been developed.
- The reaction proceeds through a palladium-catalyzed, norbornene-mediated tandem process involving an intermolecular *ortho*-arylation followed by a subsequent intramolecular aryl-aryl coupling.
- An array of reactive functionalities are tolerated under the reaction conditions, including esters, nitro, amine, methoxy, chloro, and fluoro groups.
- The further elaboration of the annulated products into increasingly more complex structures was demonstrated.