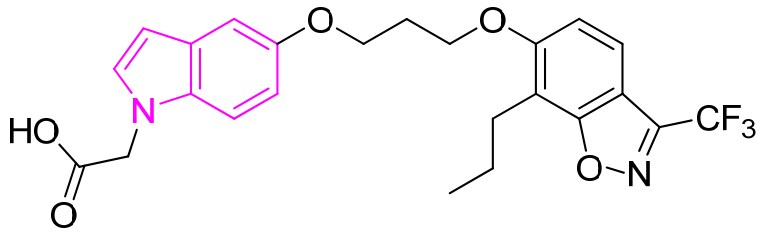
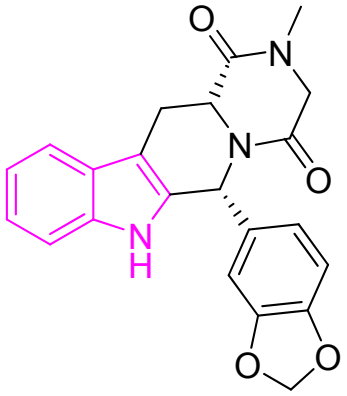


Recent Developments toward Synthesis of the "Privileged" Indole Scaffold



Dimitra Kontokosta

November 11, 2009

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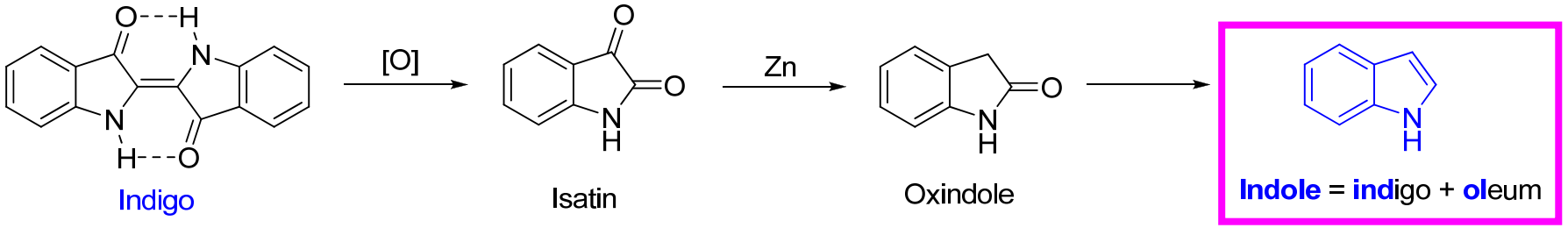
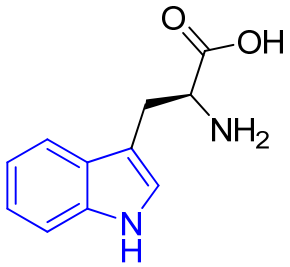
Historical Background

- First synthesis by Adolf von Baeyer in 1866.

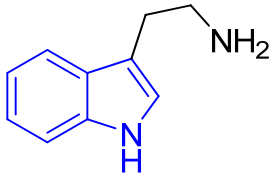


- Indole structure proposed in 1869.
- Used in dyes until the end of the 19th century.
- Special interest gained in 1930's with the discovery of biologically important molecules.

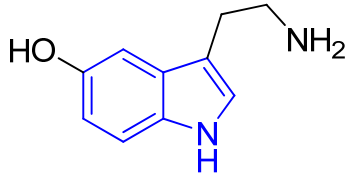
Indoles in Nature



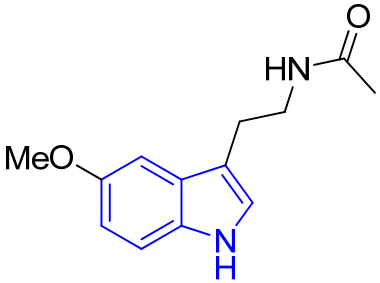
Tryptophan
(amino acid)



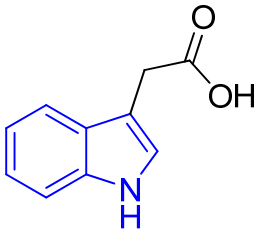
Tryptamine
(alkaloid)



Serotonin
(neurotransmitter)



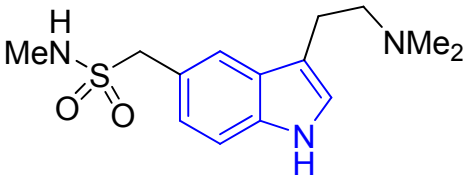
Melatonin
(hormone)



Auxin
(plant hormone)

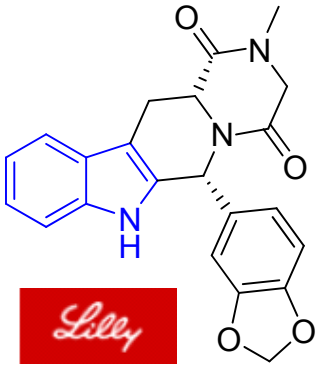
Indoles in Pharmaceuticals

Imitrex (rank # 35)



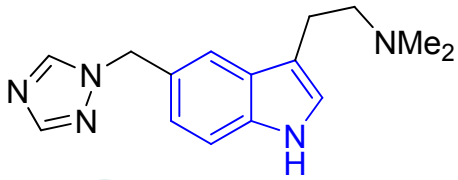
Serotonin receptor agonist;
treatment of migraines

Cialis (rank # 66)



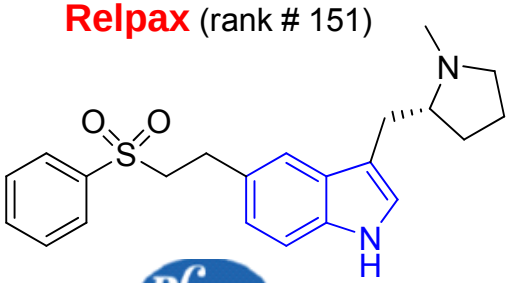
Phosphodiesterase inhibitor;
treatment of erectile dysfuntion

Maxalt (rank # 148)



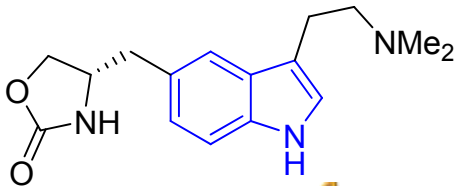
Serotonin receptor agonist;
treatment of migraines

Relpax (rank # 151)



Serotonin receptor agonist;
treatment of migraines

Zomig (rank # 196)

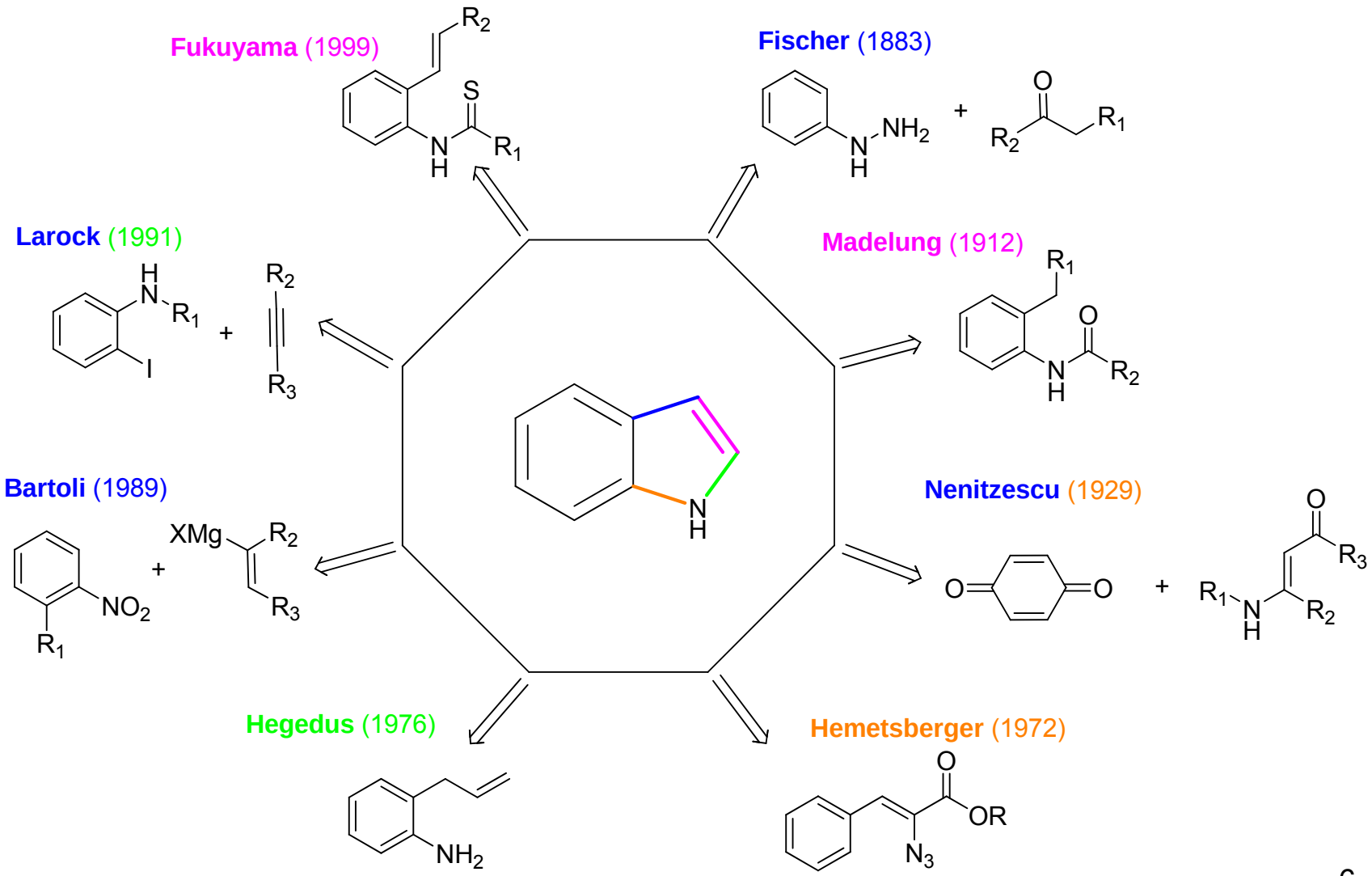


Serotonin receptor agonist;
treatment of migraines

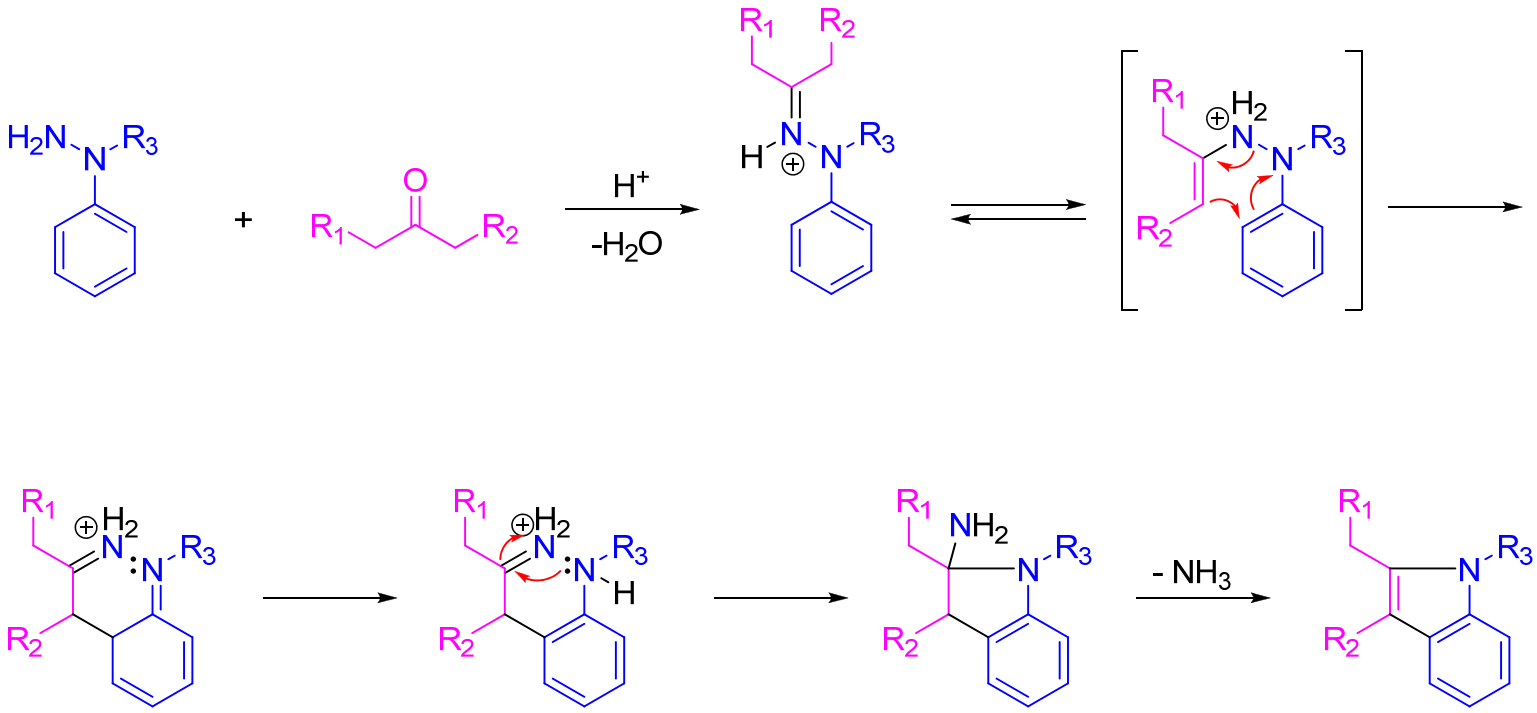
* Rankings among top 200 drugs in 2008

http://www.chem.cornell.edu/jn96/outreach.html

Indole Synthesis: Classical Approaches

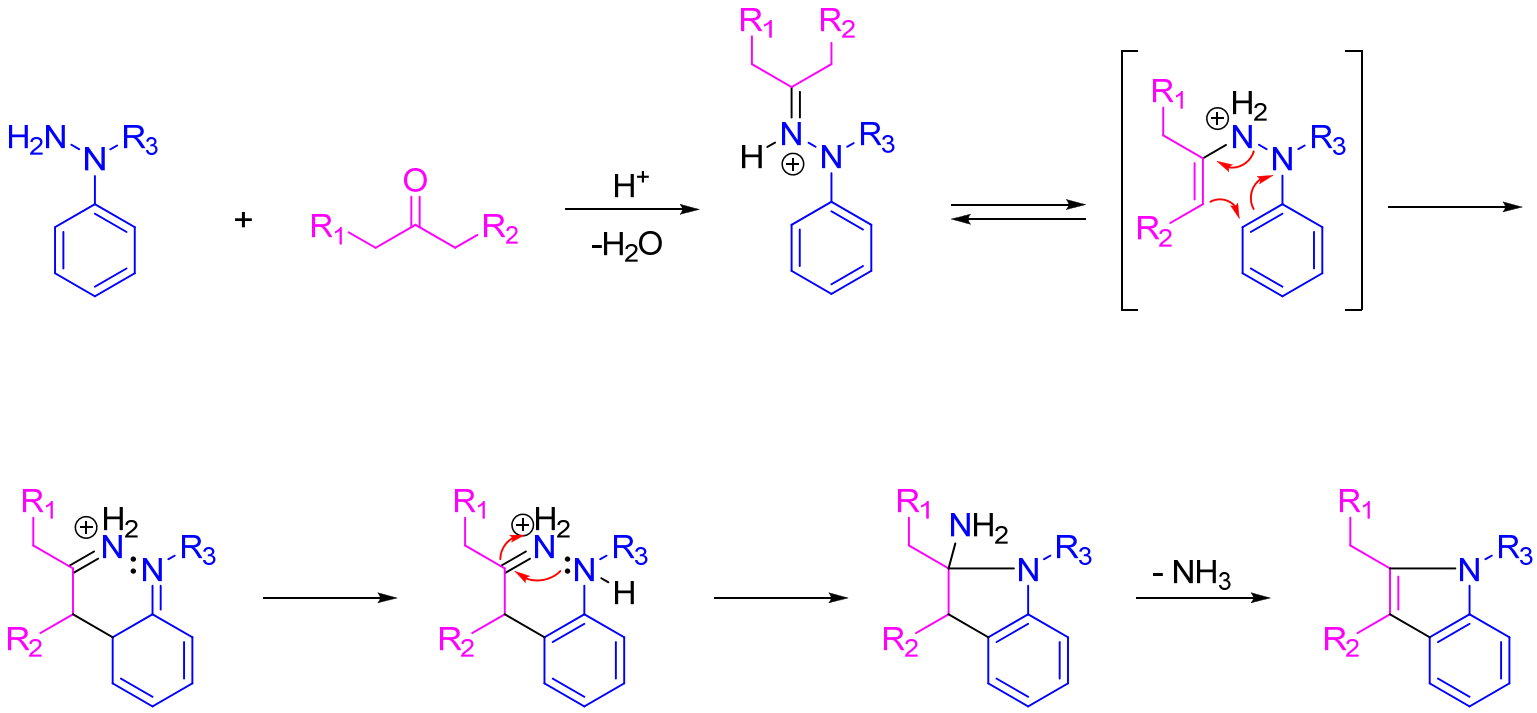


Fischer Indole Synthesis



Fischer, E.; Jourdan, F. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241.

Fischer Indole Synthesis

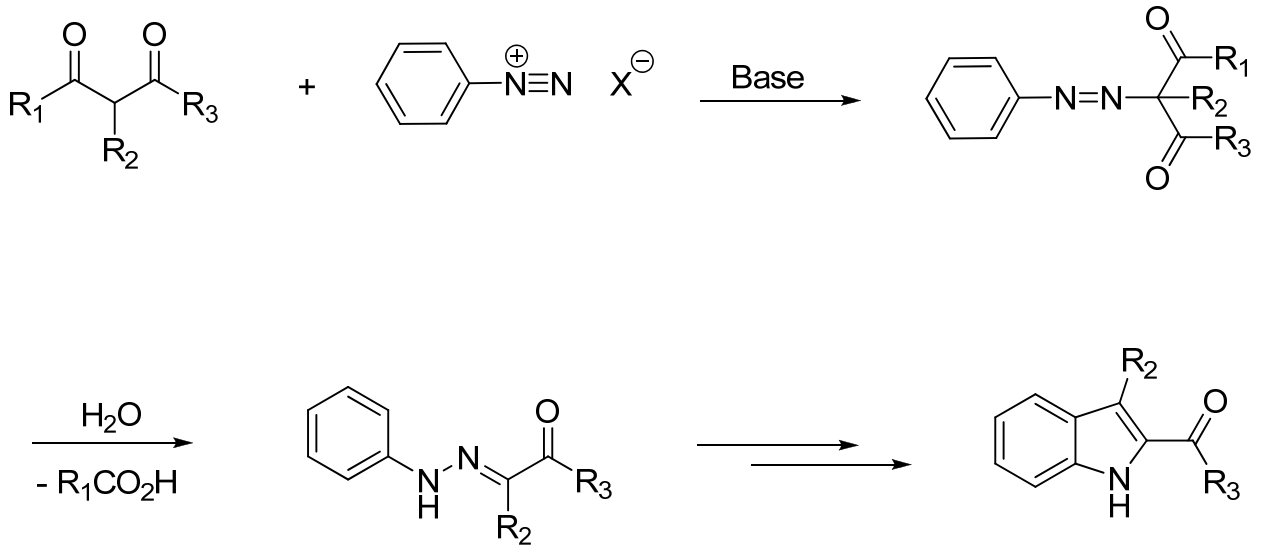


Limitations

- Availability of certain substituted aryl hydrazines.
- Unsymmetrical ketones give a mixture of regioisomers.
- EWG groups on the aromatic ring are not well tolerated.
- Slow reaction times with *ortho*-substituted arylhydrazines.

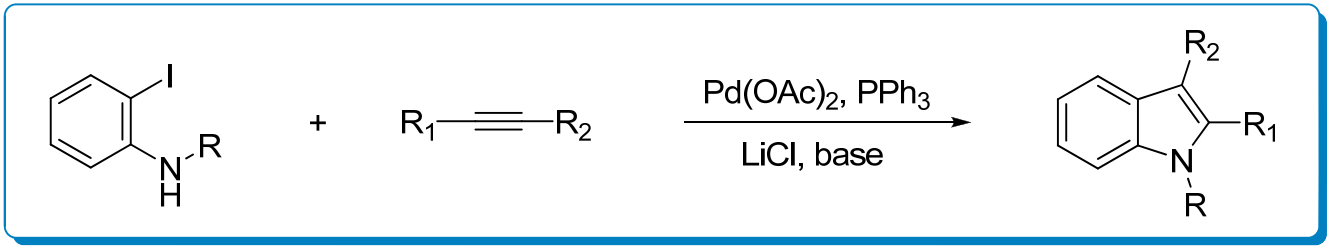
Fischer, E.; Jourdan, F. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241.

Japp-Klingemann Reaction



Japp, F. R.; Klingemann, F. *Ber.* **1887**, *20*, 2942.

Larrock Heteroannulation

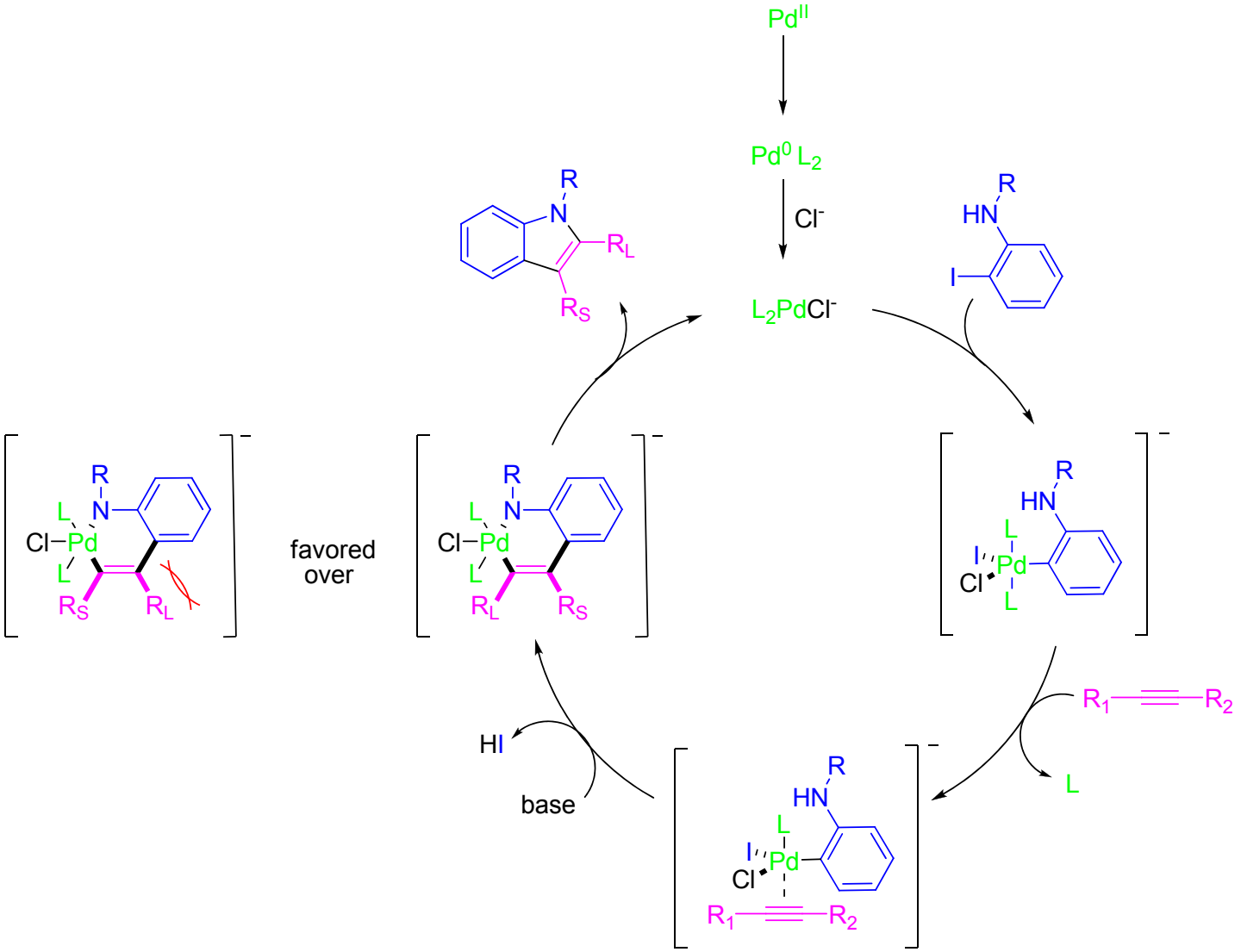


Limitation

- Iodoanilines required; low yields with 2-bromo- or 2-chloroanilines.

Larock, R. C. *J. Am. Chem. Soc.* **1991**, *113*, 6689.

Larrock Heteroannulation



Larock, R. C. *J. Org. Chem.* **1998**, *63*, 7652.

Why New Methodologies?

Continuous interest in the development of synthetic routes that:

- Tolerate a wide variety of functional groups.
- Provide a variety of substitution patterns.
- Utilize readily available starting materials.
- Are economical, efficient, and take place under mild, “green” conditions.

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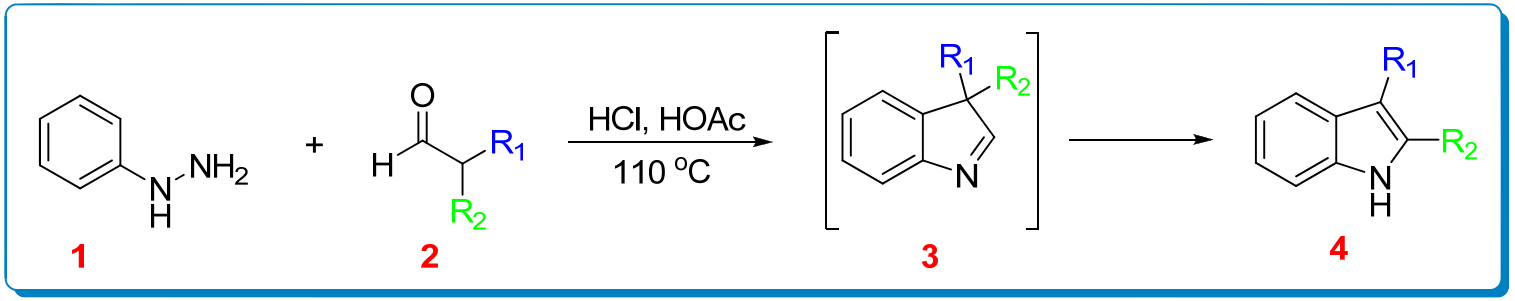
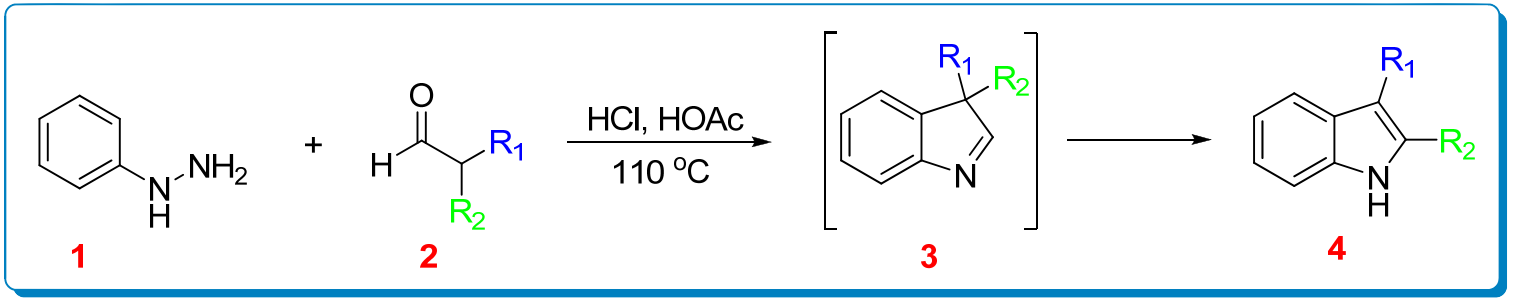
3,3-Disubstituted Indolenine Rearrangement



Liu, K. G. *et al. Organic Letters* **2006**, *8*, 5769.

3,3-Disubstituted Indolenine Rearrangement



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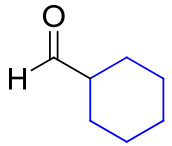
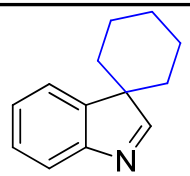
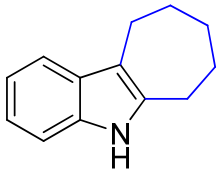
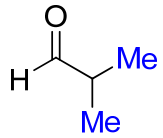
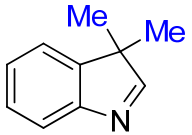
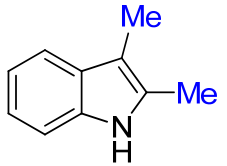
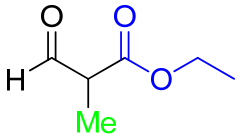
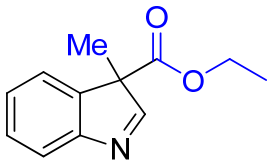
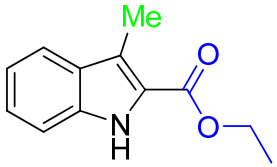
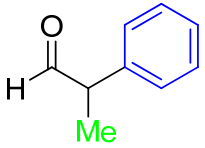
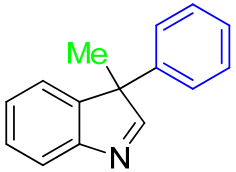
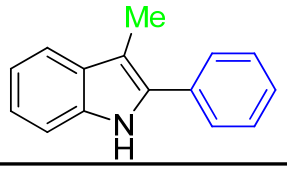
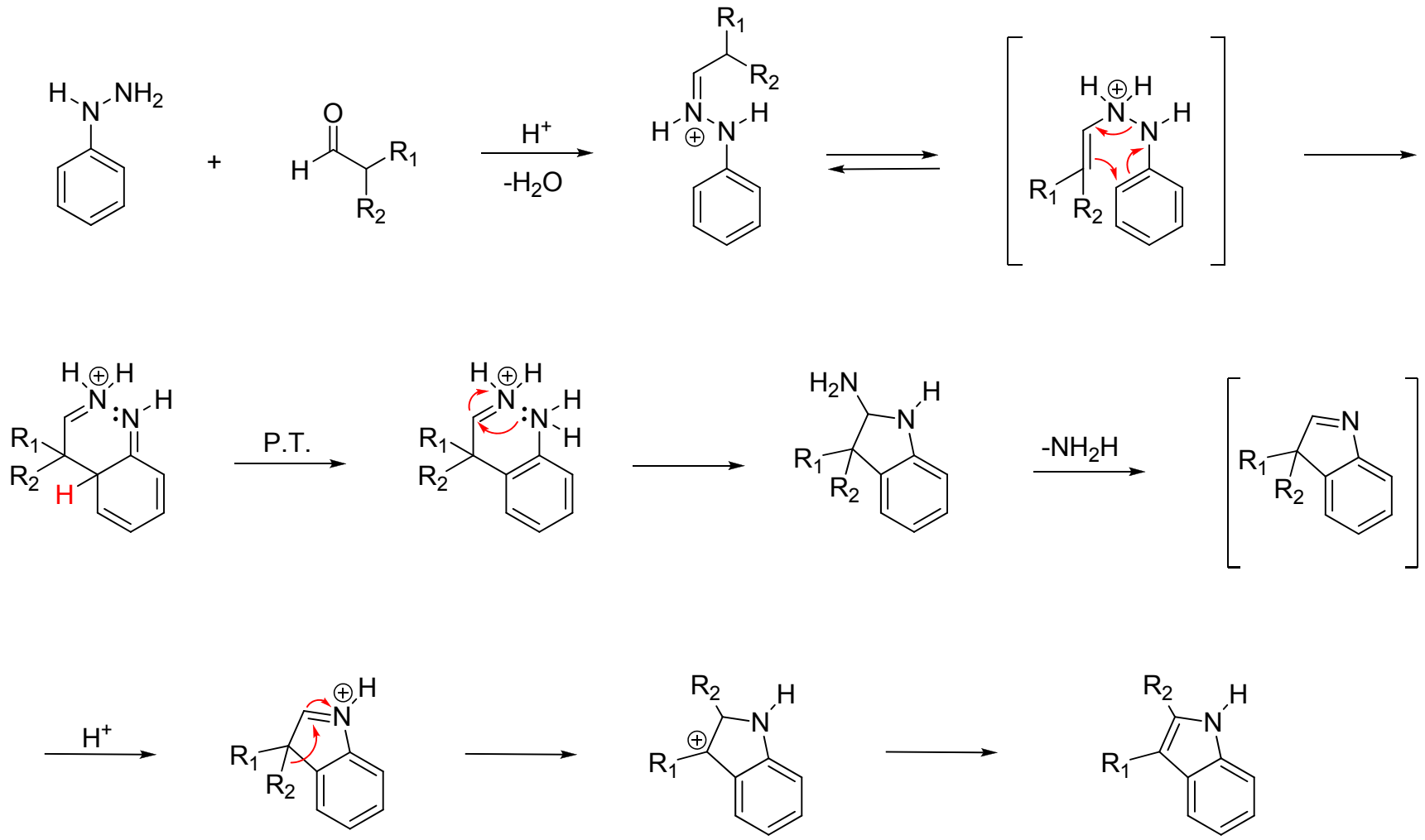
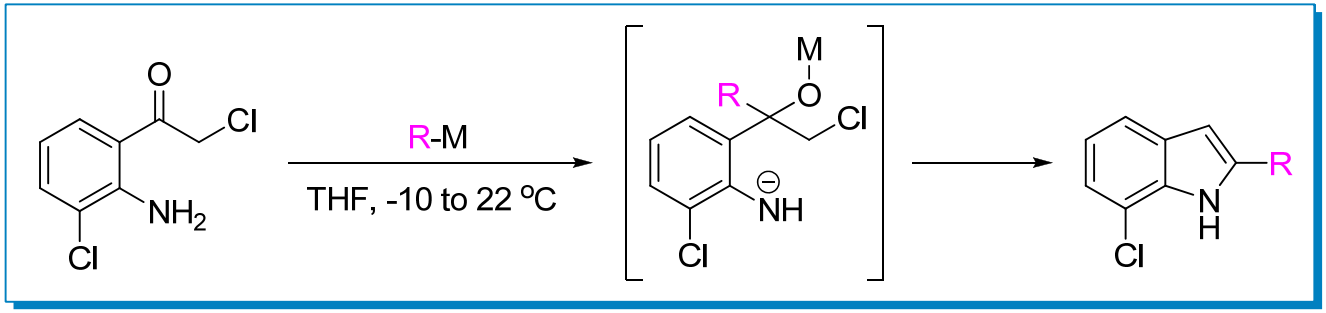
1				55%
2				50%
3				56%
4				60%

Liu, K. G. *et al. Organic Letters* **2006**, *8*, 5769.

Mechanism

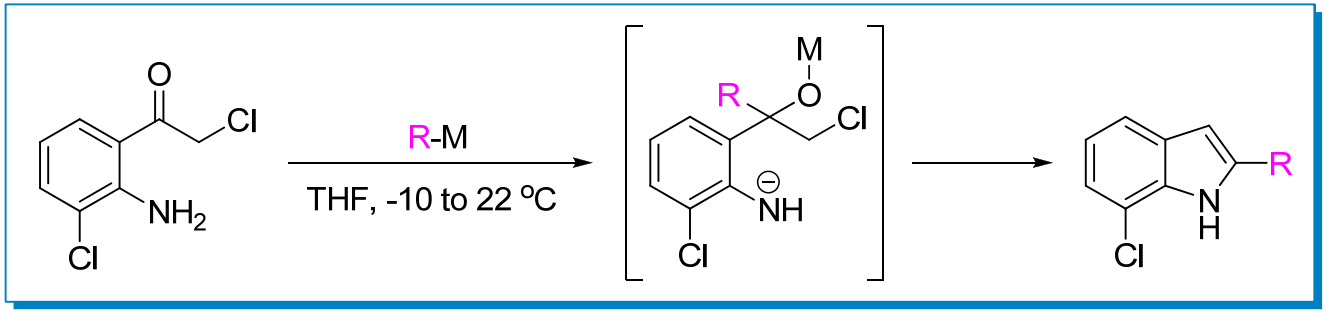


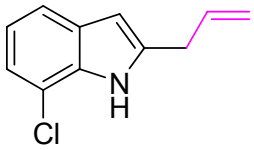
[1,2]-Aryl Rearrangement



Pei, T. *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 4231.

[1,2]-Aryl Rearrangement





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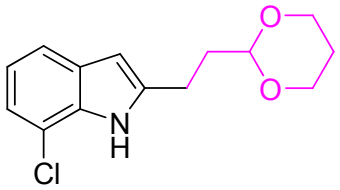

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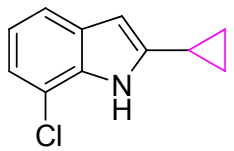

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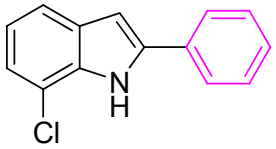

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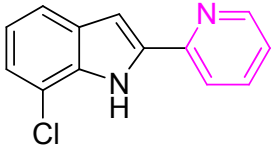

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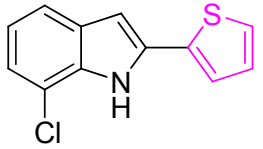

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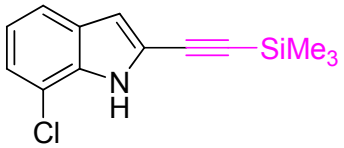

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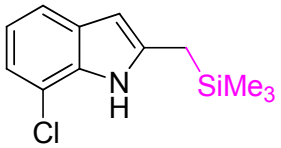

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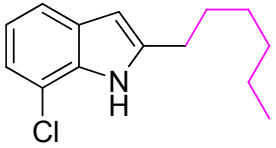

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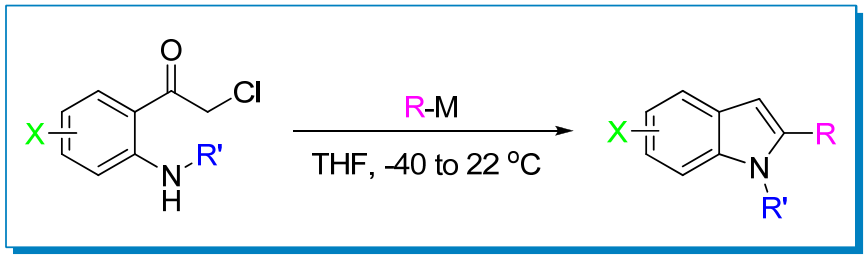
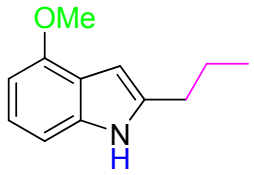
[1,2]-Aryl Rearrangement





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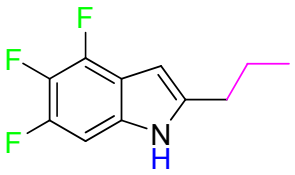

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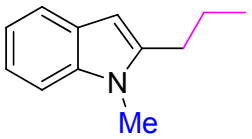

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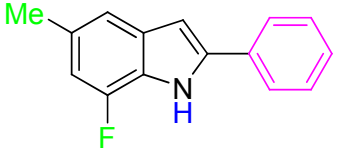

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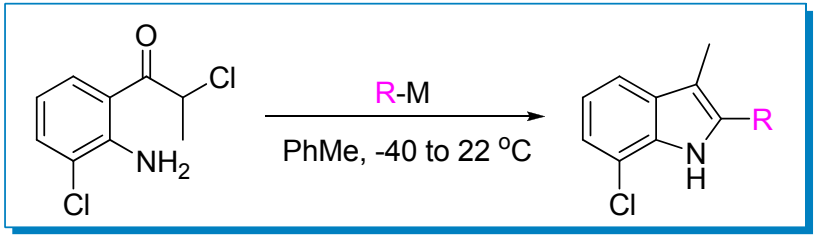

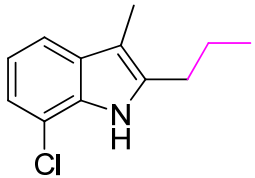

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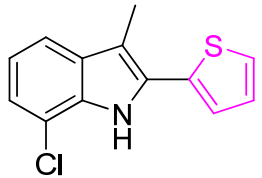

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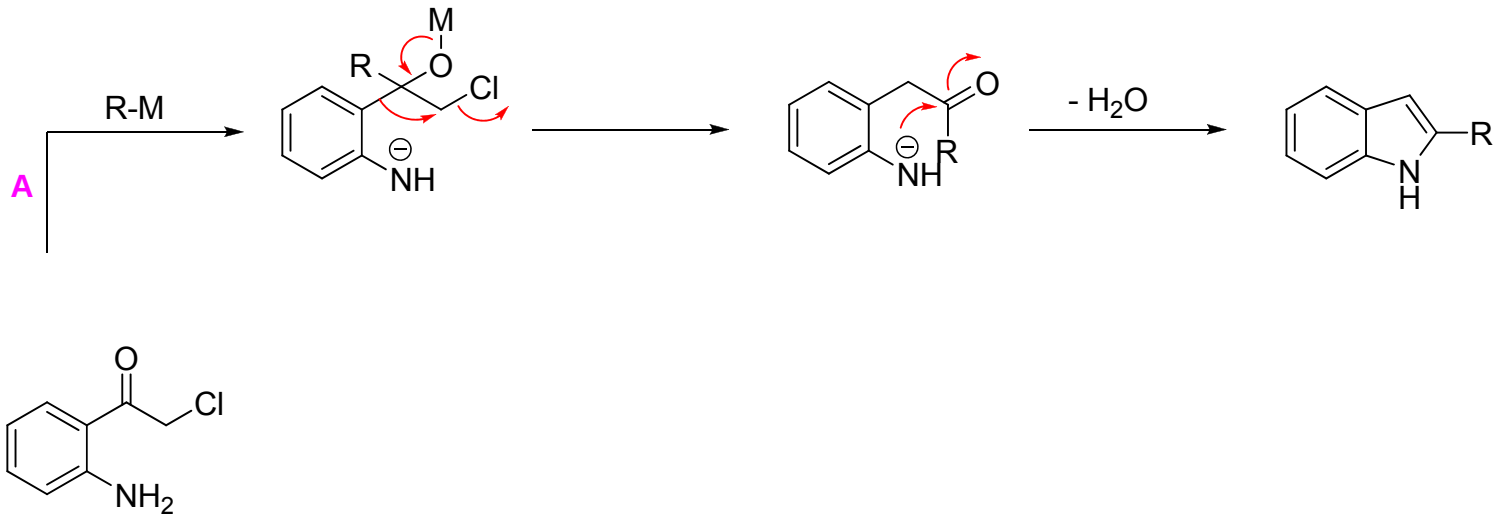
Pei, T. *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 4231.

Proposed Mechanism



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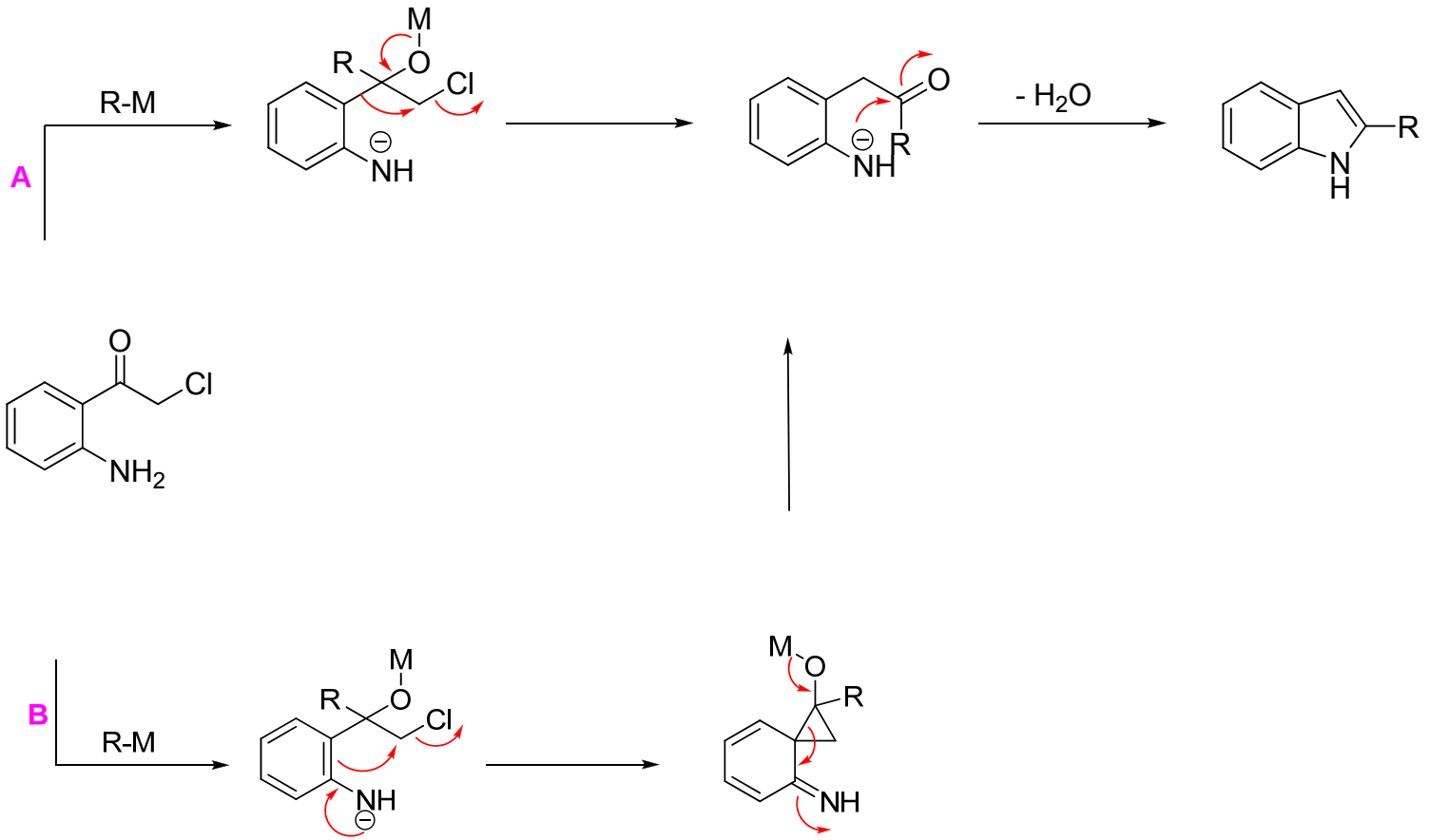
Proposed Mechanism



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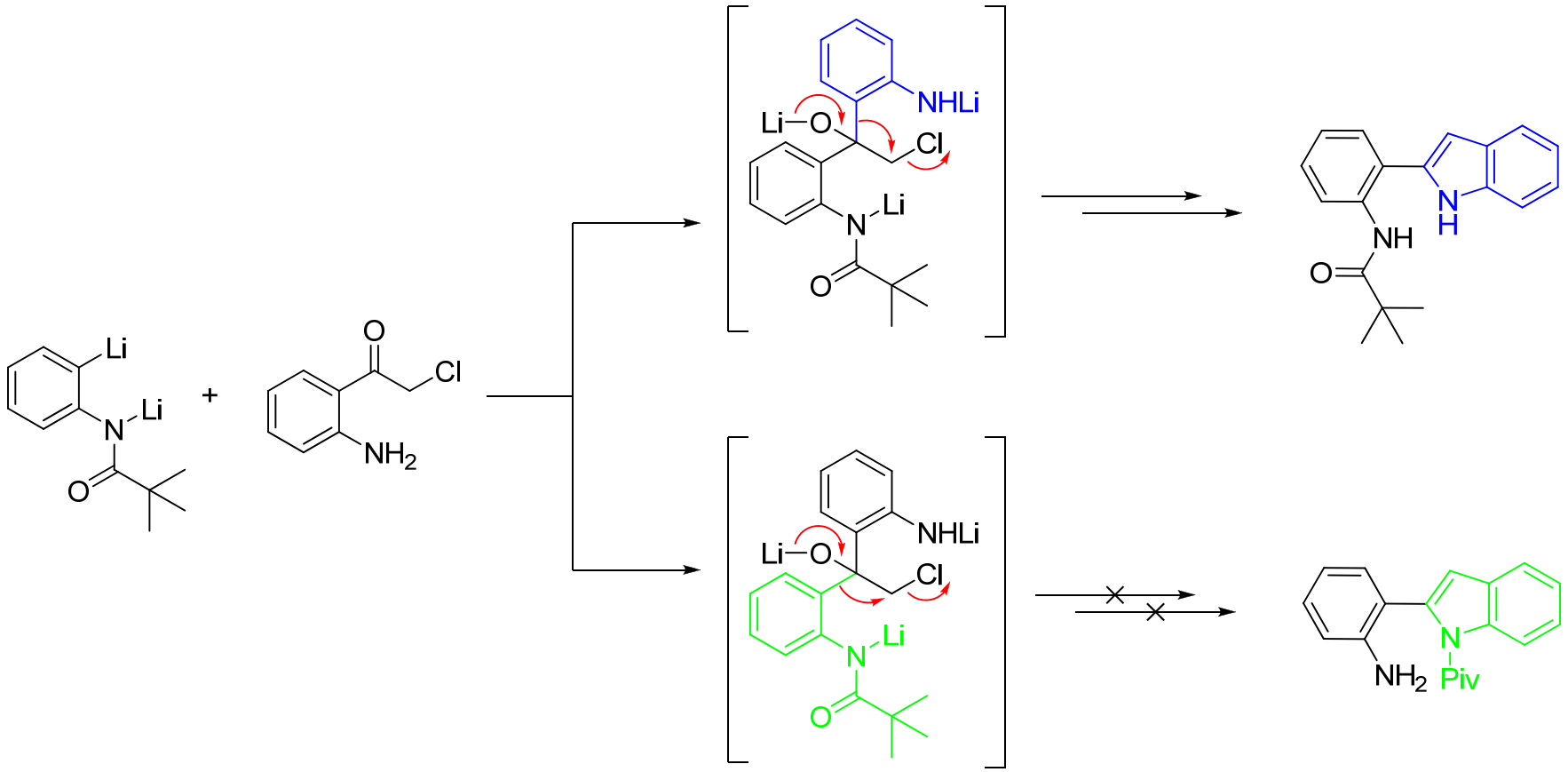
Control Experiment



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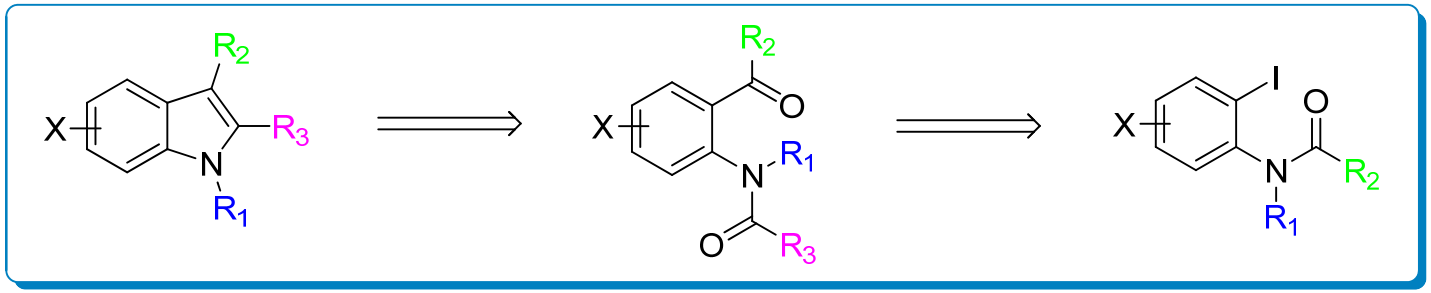
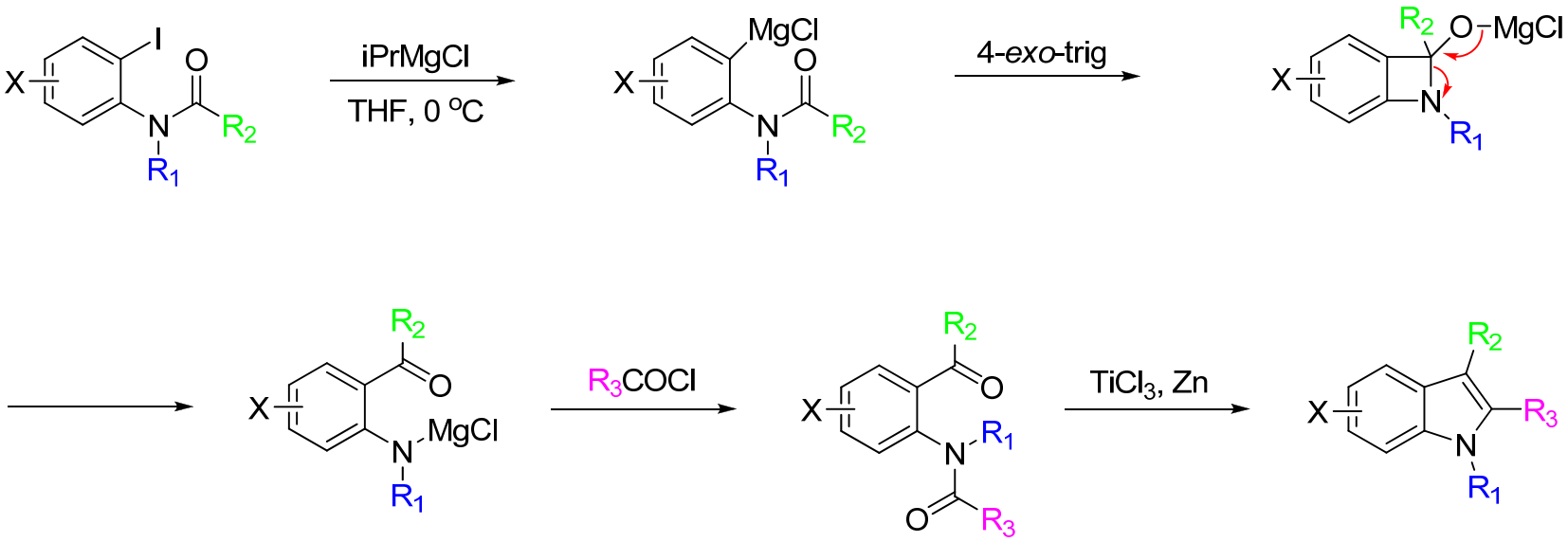
Anionic N-Fries Rearrangement





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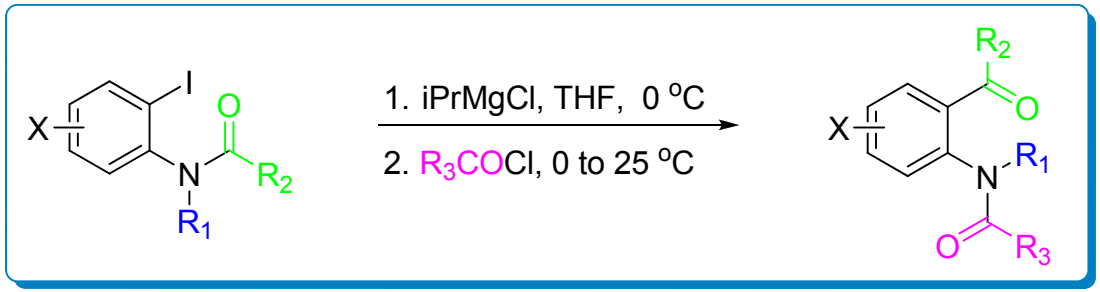
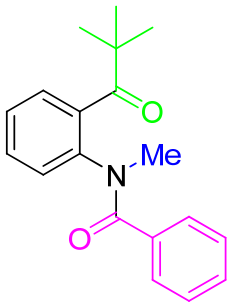
Anionic N-Fries Rearrangement





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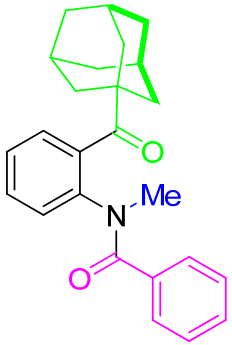

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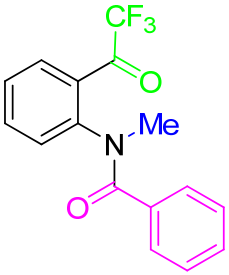

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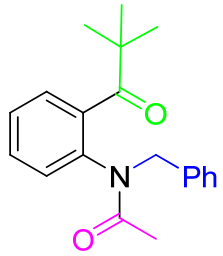

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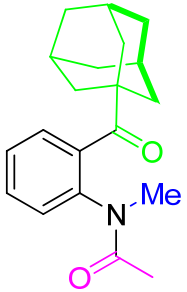

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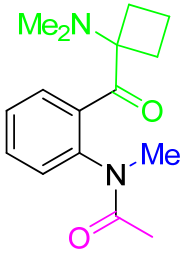

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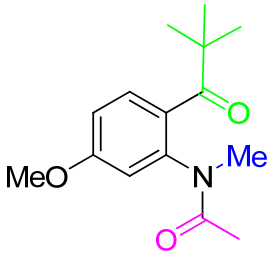

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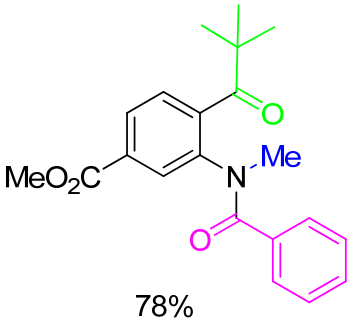

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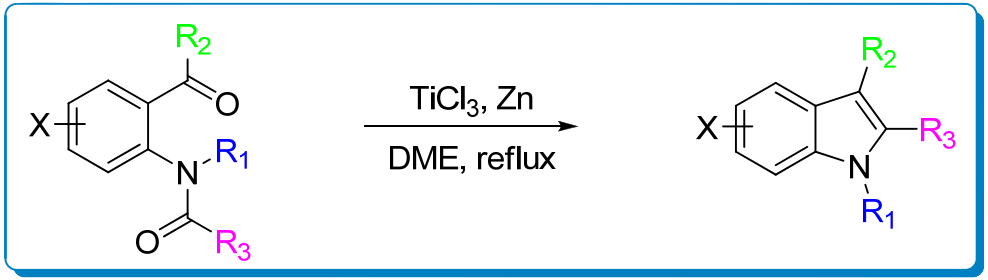
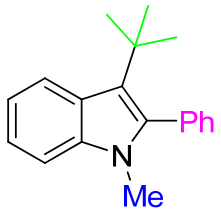
McMurry Cyclization





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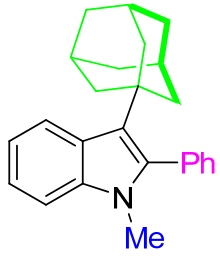

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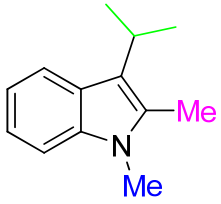

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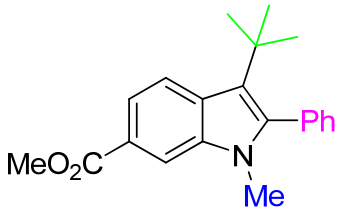

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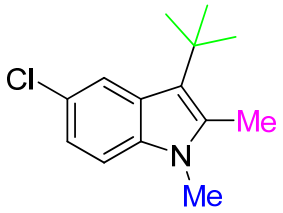

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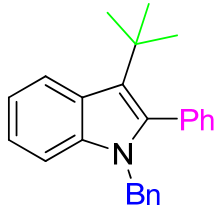

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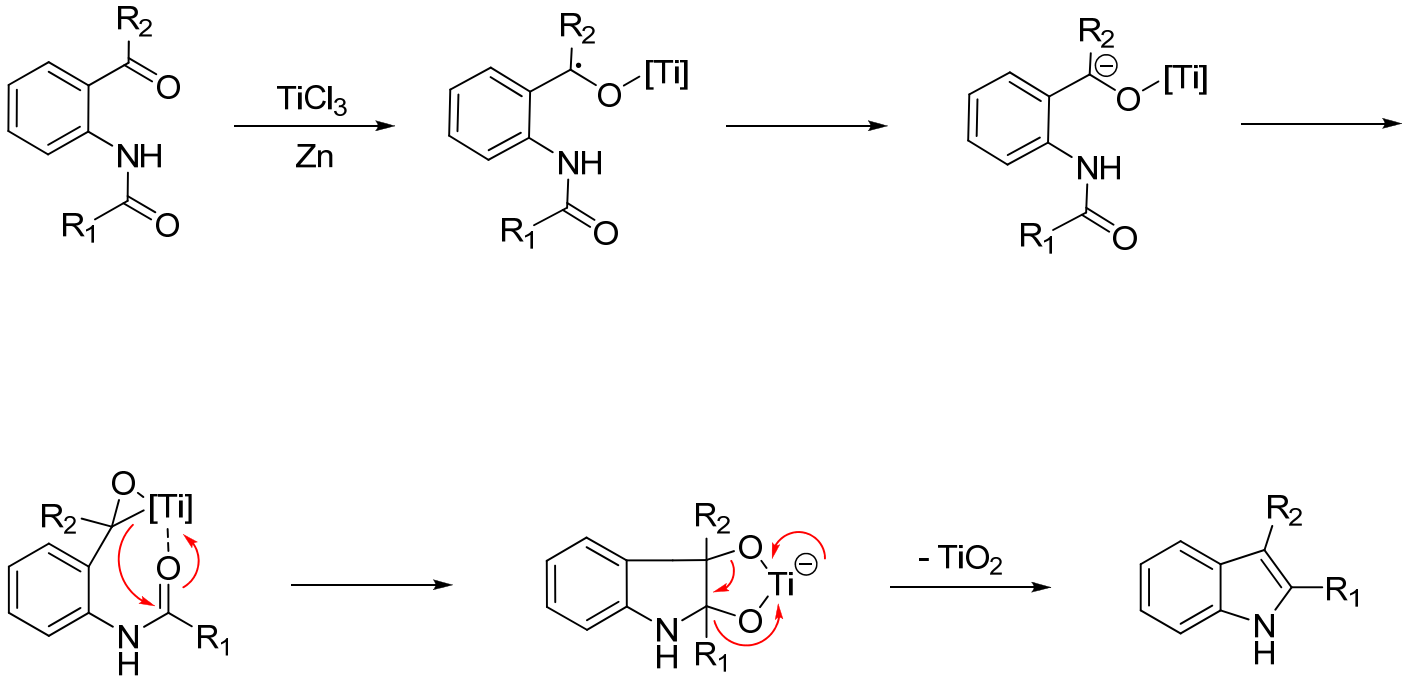
Ding, F. *et al. Organic Letters* **2008**, *10*, 1067.

McMurry Reaction Mechanism



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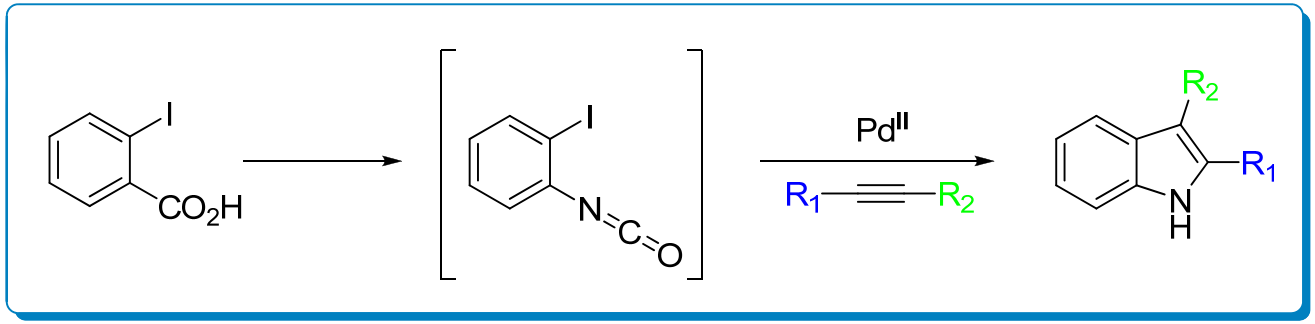
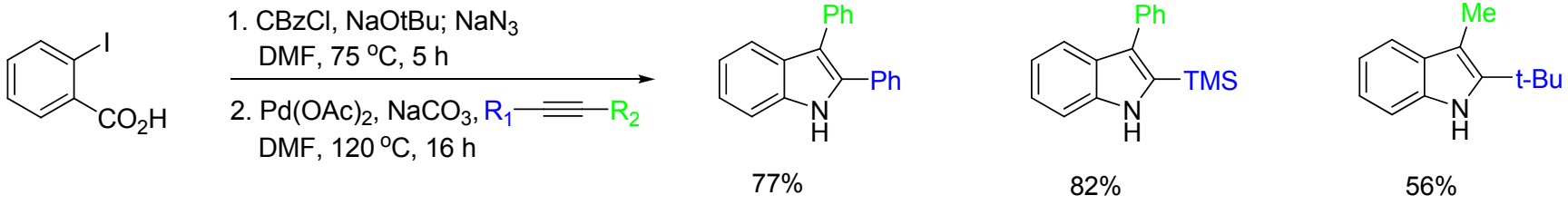
- Pd-Catalyzed C–H Functionalization
- Nb-Promoted C–F Functionalization
- Conclusion

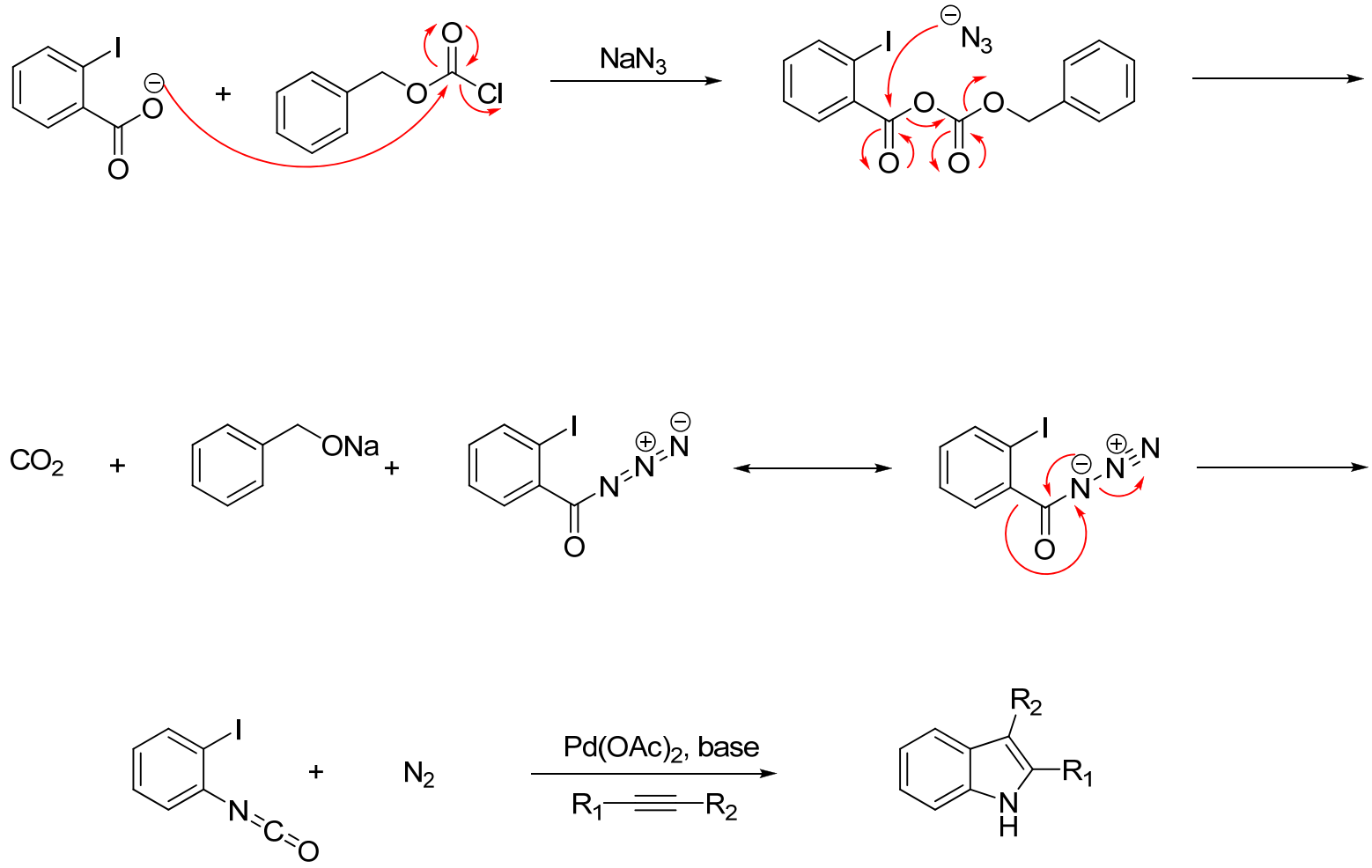
One-pot Curtius Rearrangement/Pd-Cat. Indolization





Lebel, H. *Angew. Chem.* **2008**, *120*, 356.

Curtius Rearrangement Mechanism



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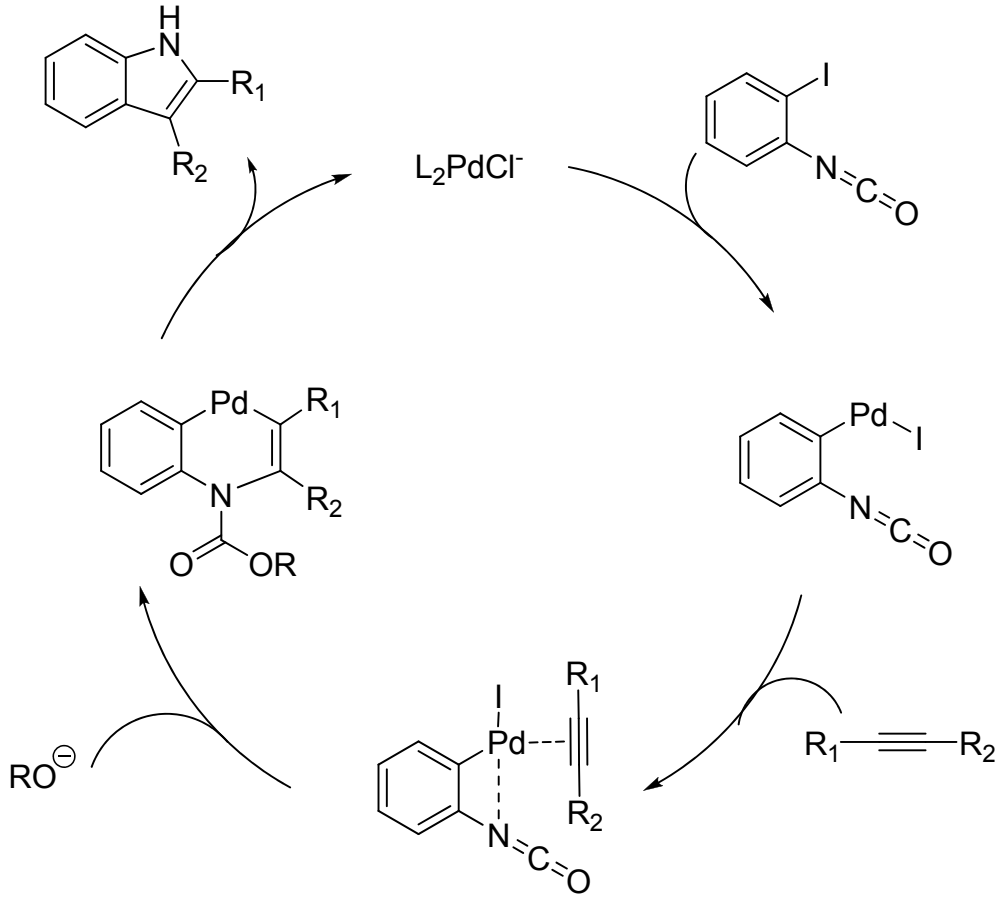

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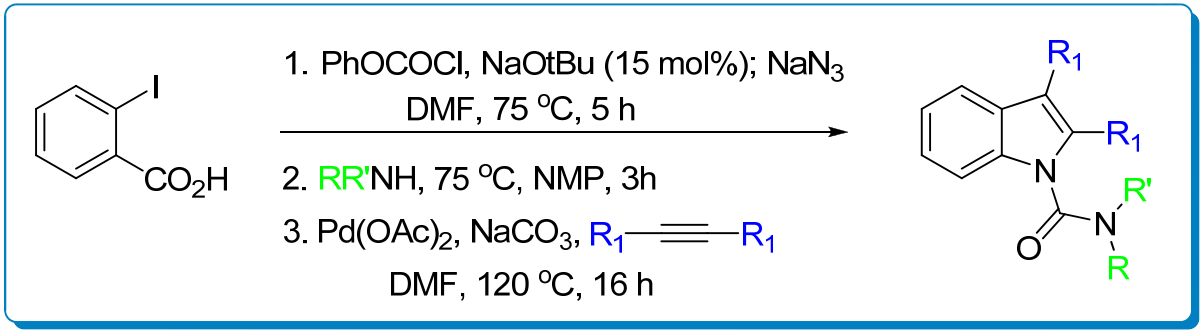
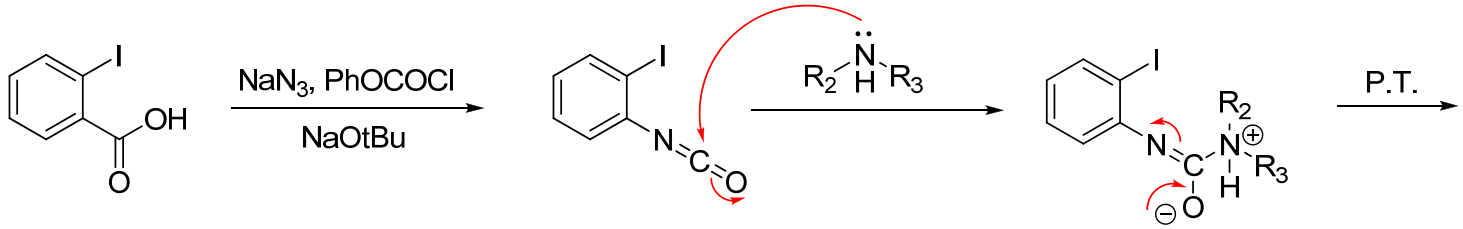
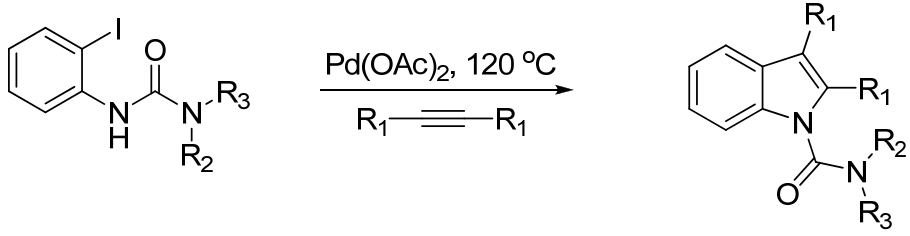
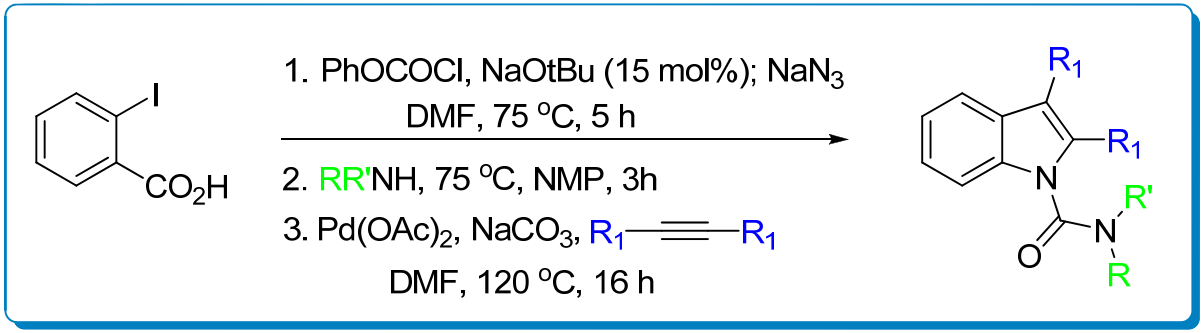


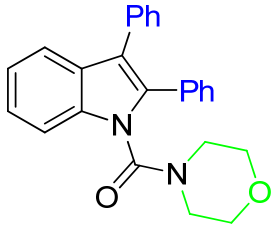




Lebel, H. *Angew. Chem.* **2008**, *120*, 356.

Indole N-carboxamide Derivatives





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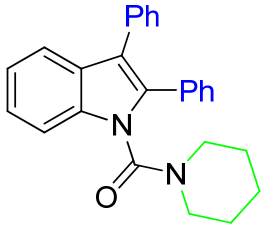

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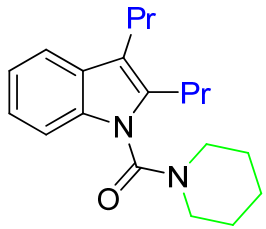

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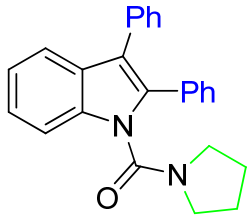

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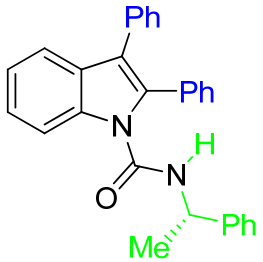

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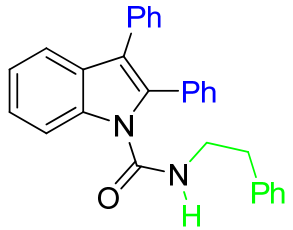

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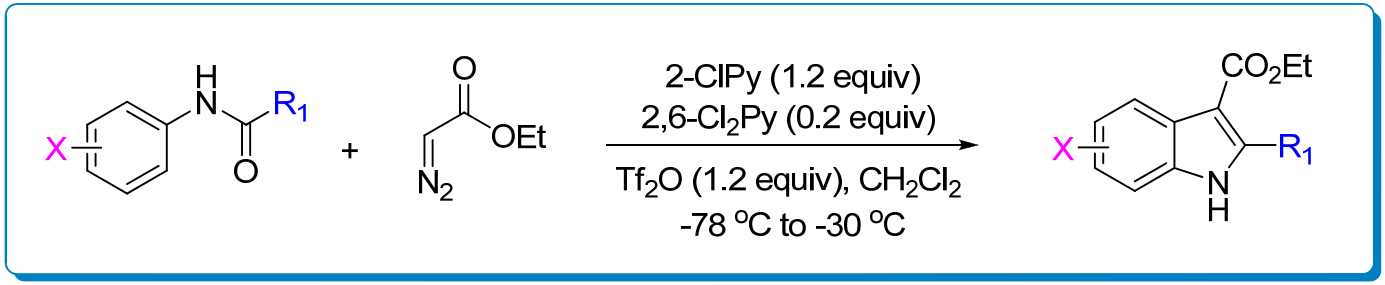
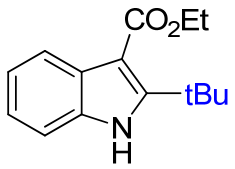
N-Aryl Amides and Ethyl Diazoacetate





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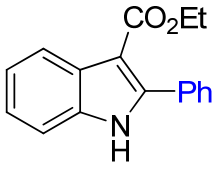

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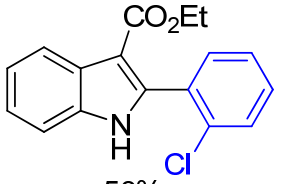

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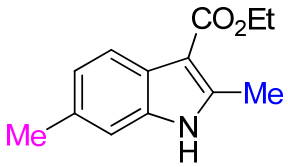

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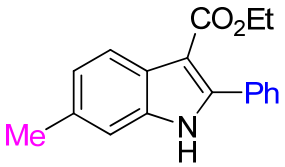

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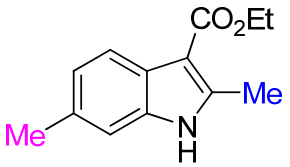

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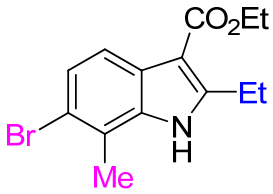

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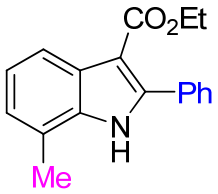

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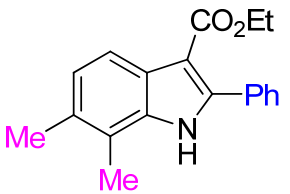

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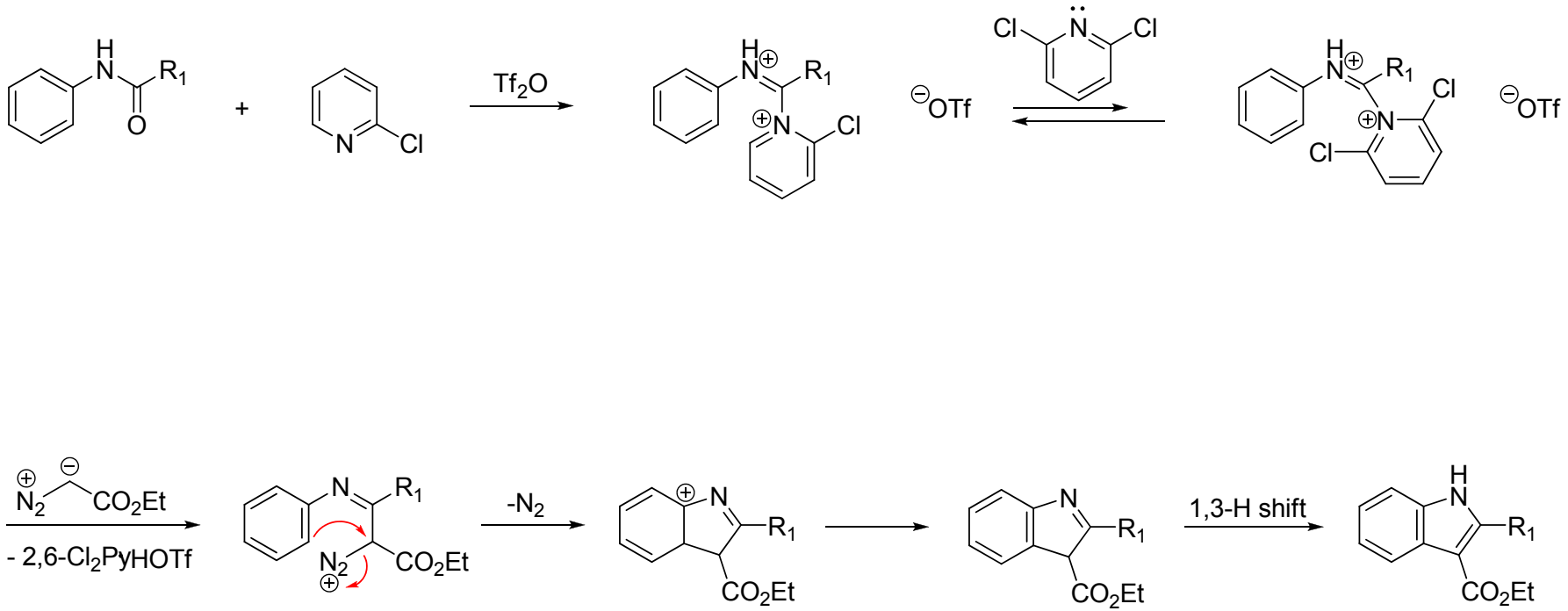
Mechanism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- 2,6-Cl2PyHOTf
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CO2Et
-N2
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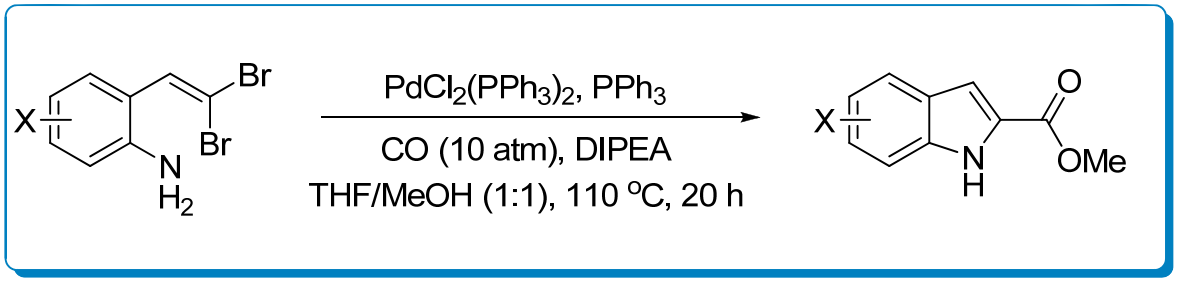
CO2Et

Tandem C–N/Carbonylation/Suzuki



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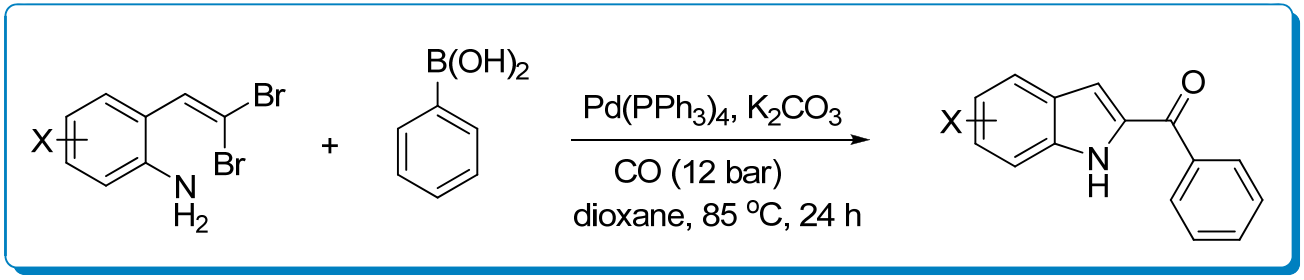

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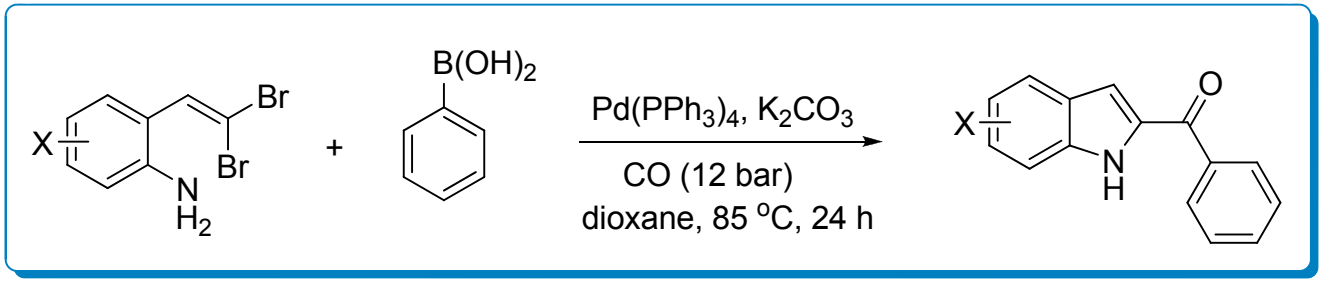
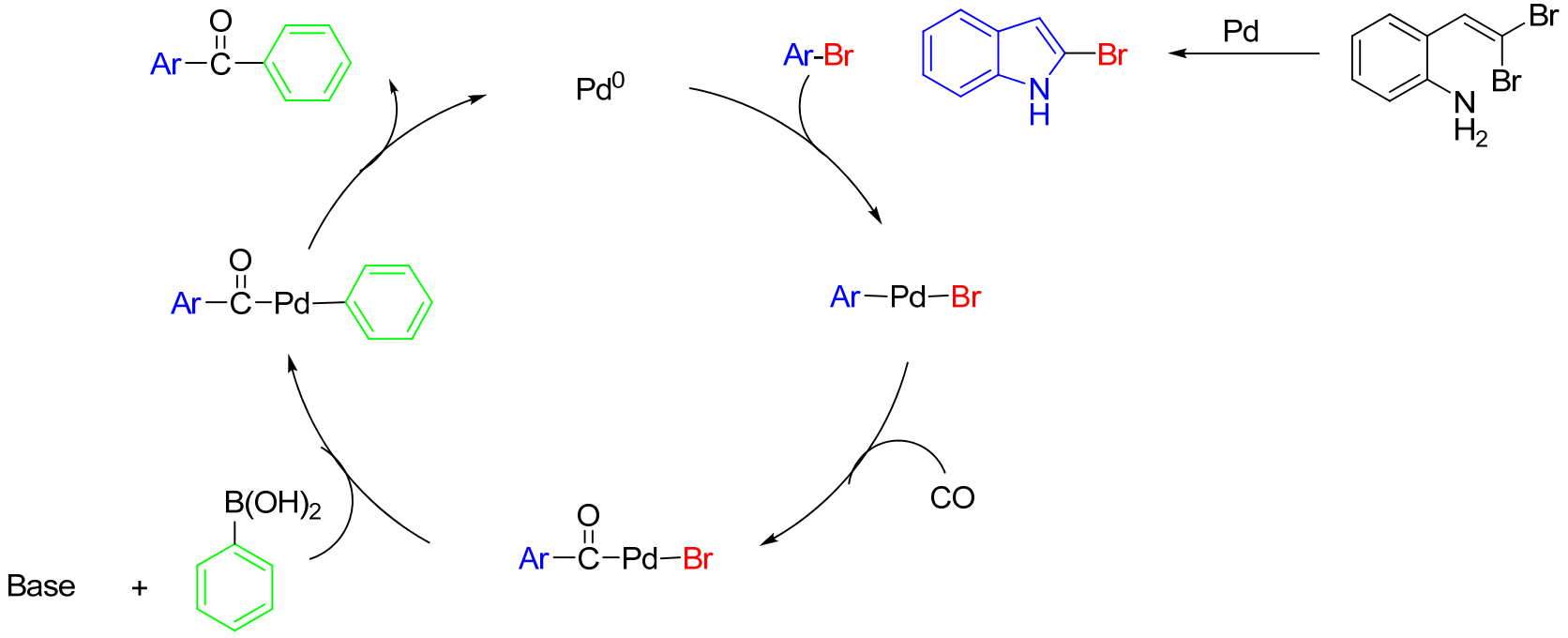
Tandem C–N/Carbonylation/Suzuki





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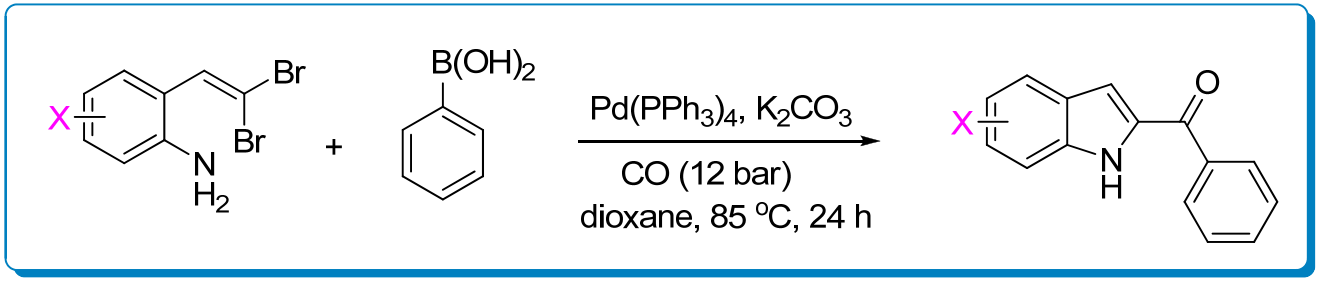
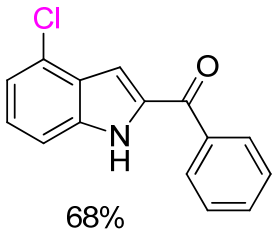
Tandem C–N/Carbonylation/Suzuki





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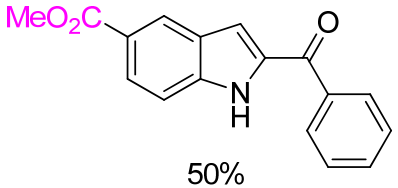

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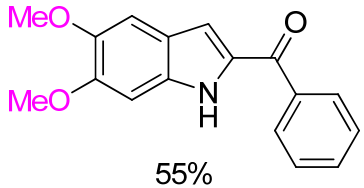

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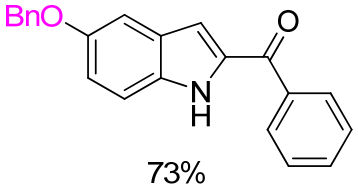

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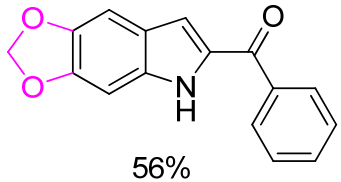

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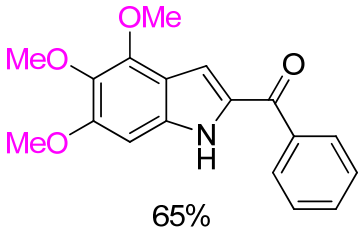

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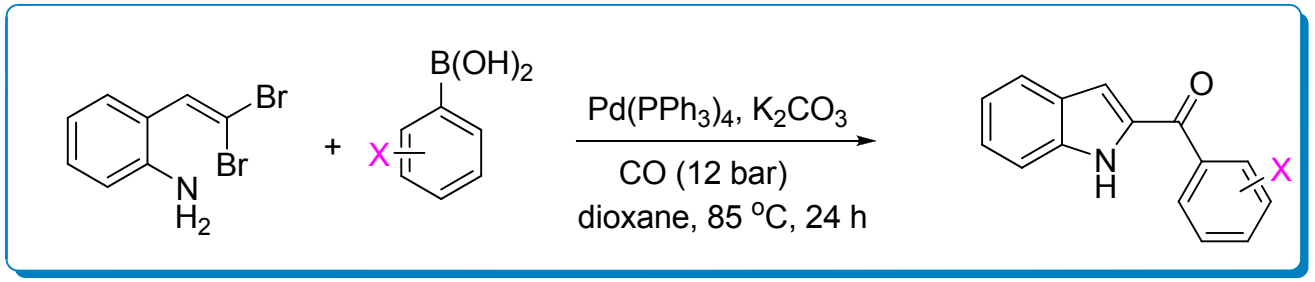
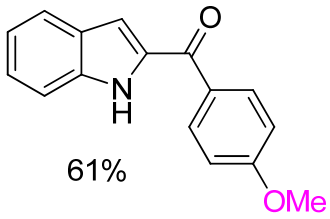
Florent, J. *Org. Lett.* **2009**, *11*, 4608.

Tandem C–N/Carbonylation/Suzuki





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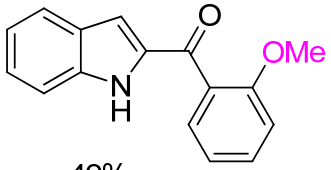

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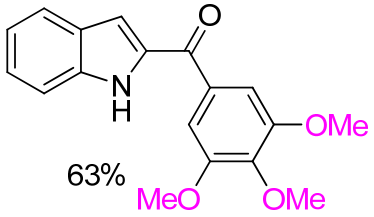

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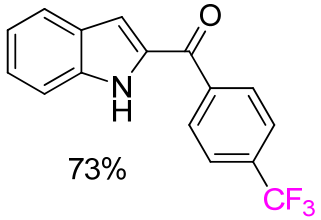

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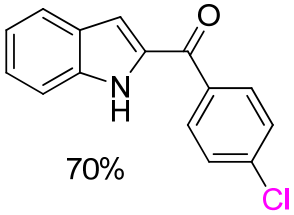

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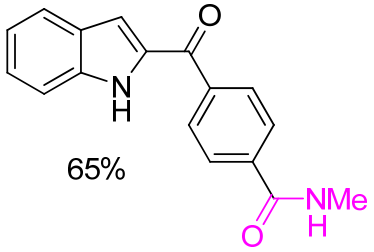

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Florent, J. *Org. Lett.* **2009**, *11*, 4608.

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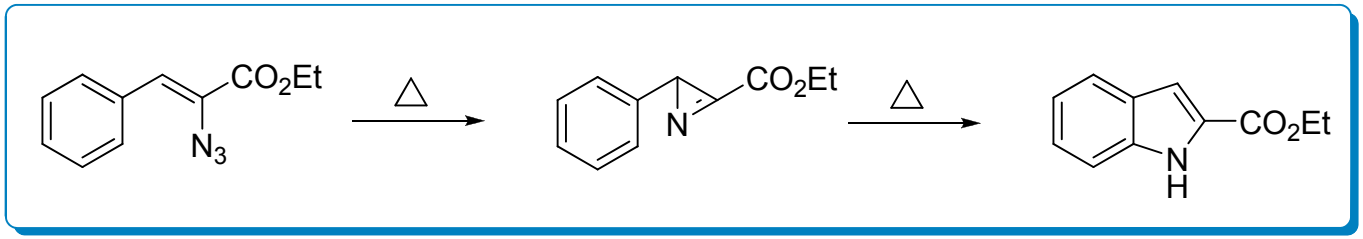

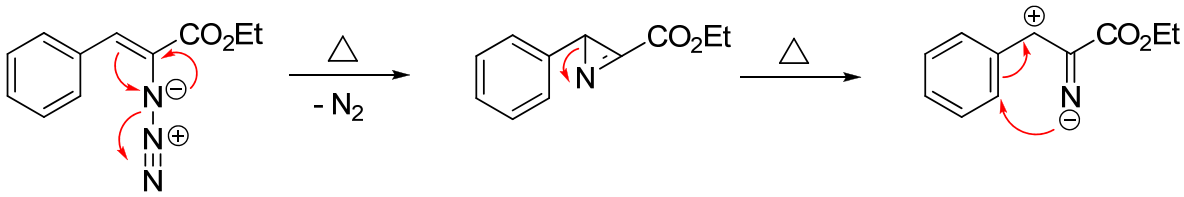

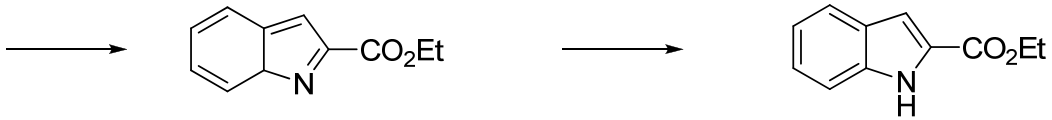

Taniguchi, H. *J. Chem. Soc., Chem. Commun.* **1980**, 1252.

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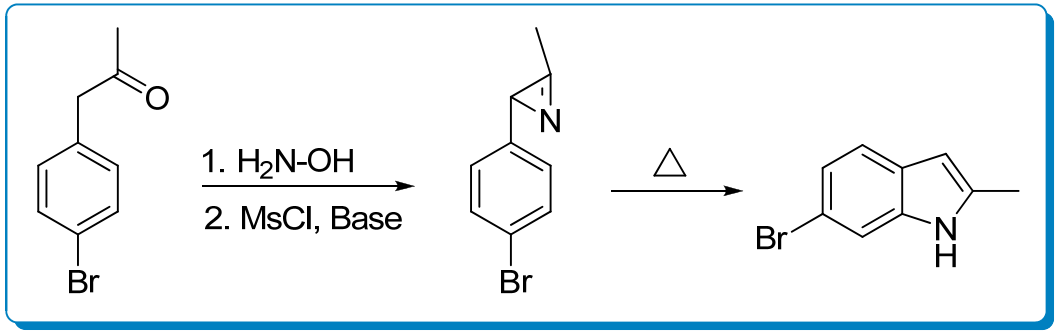

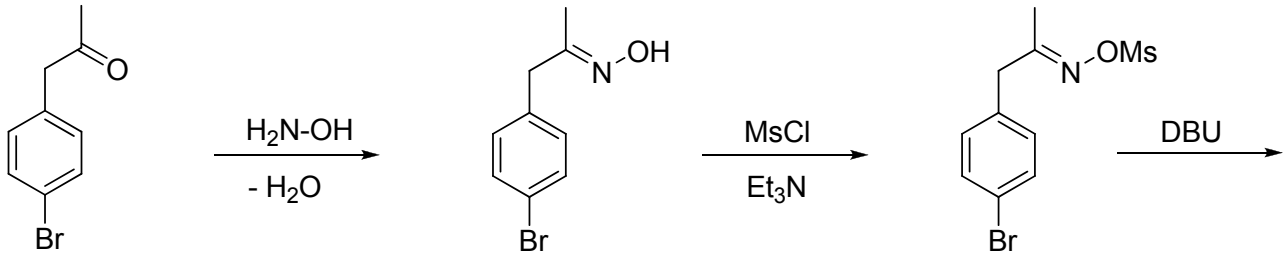

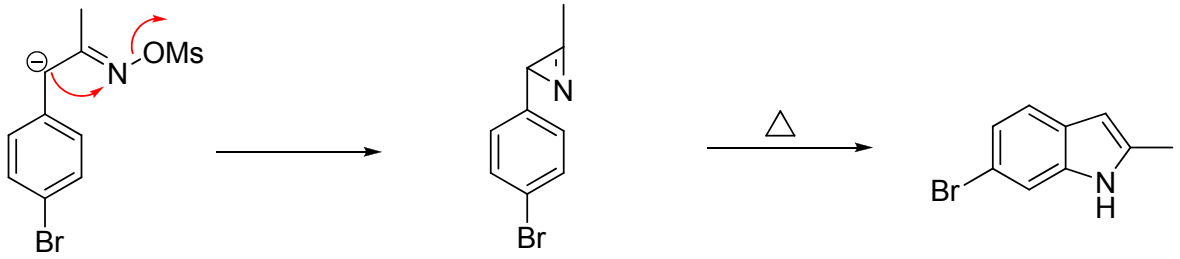

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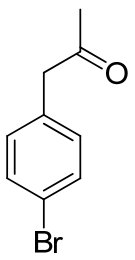
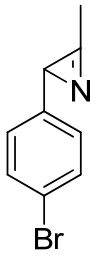
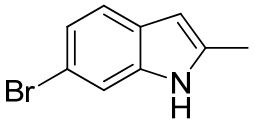
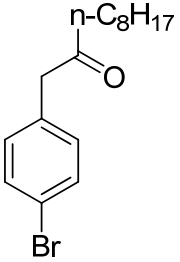
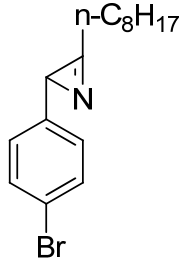
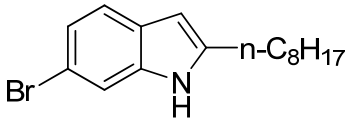
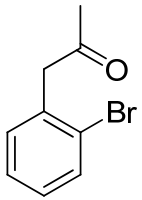
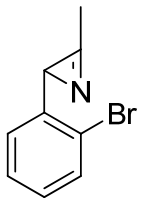
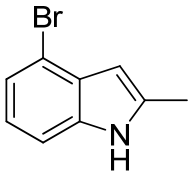
1		 78%		170	88
2		 70%		170	86
3		 78%		170	84

Taber, D. *J. Am. Chem. Soc.* **2006**, *128*, 1058.

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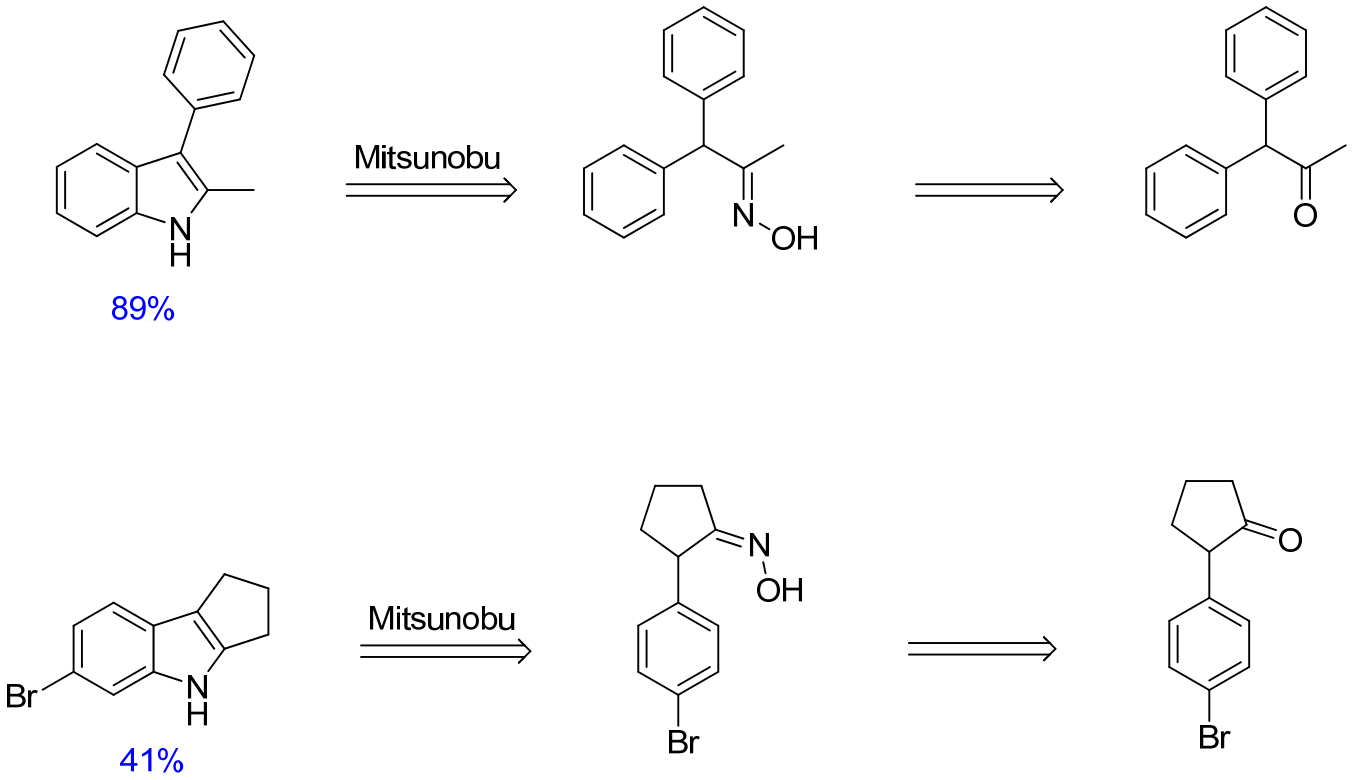

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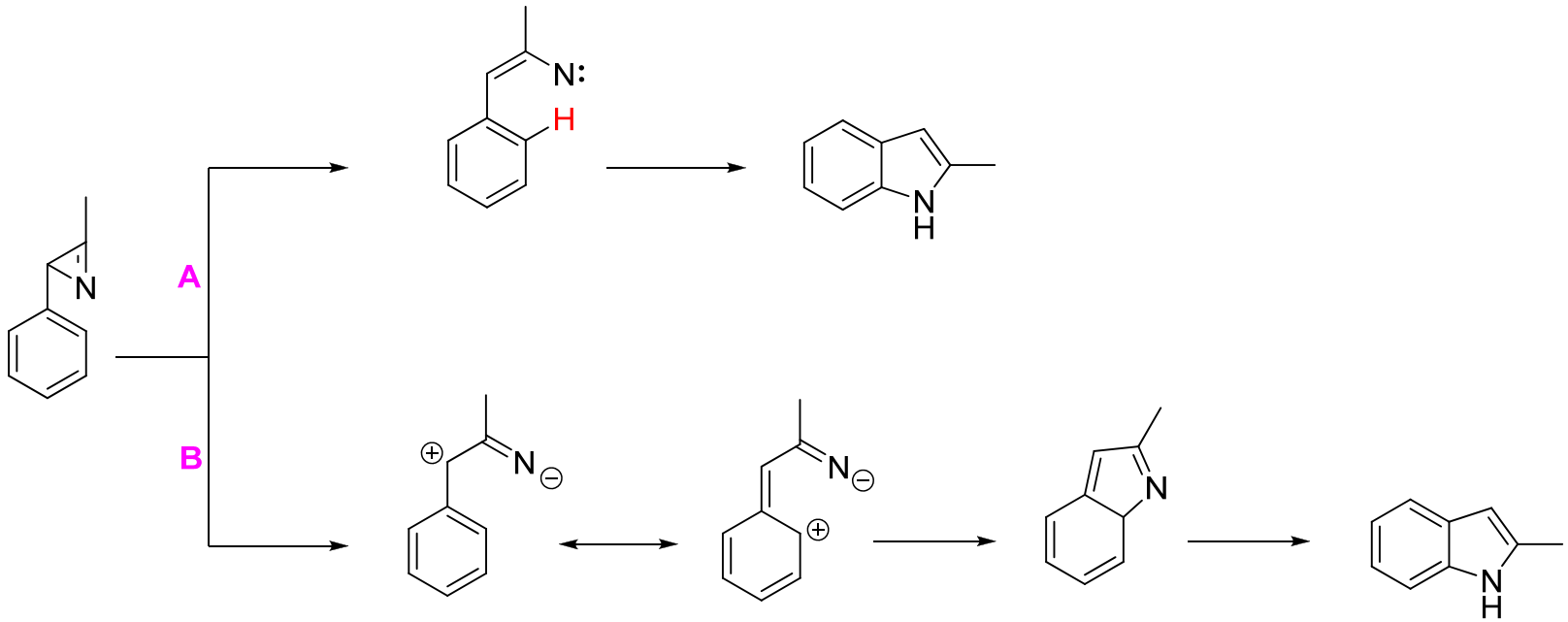
Mechanistic Studies



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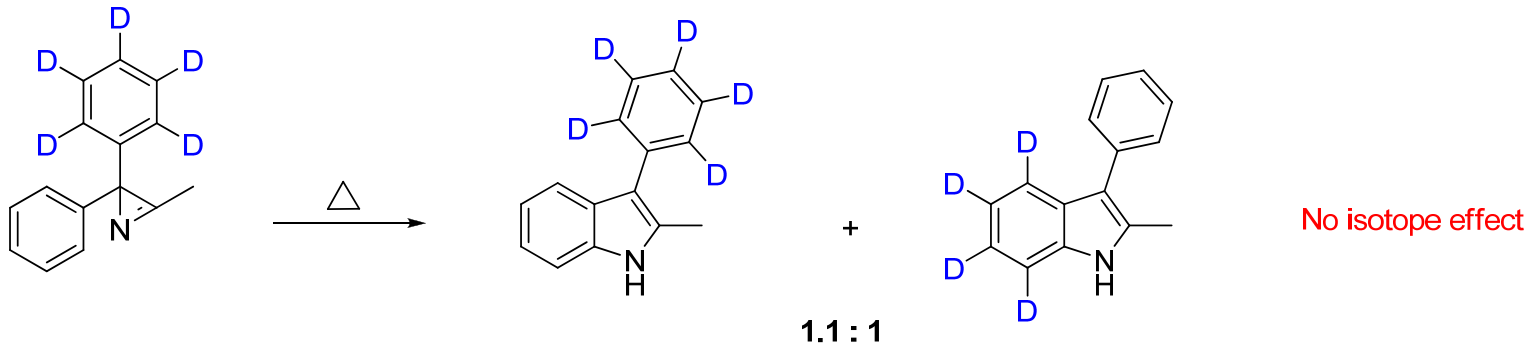

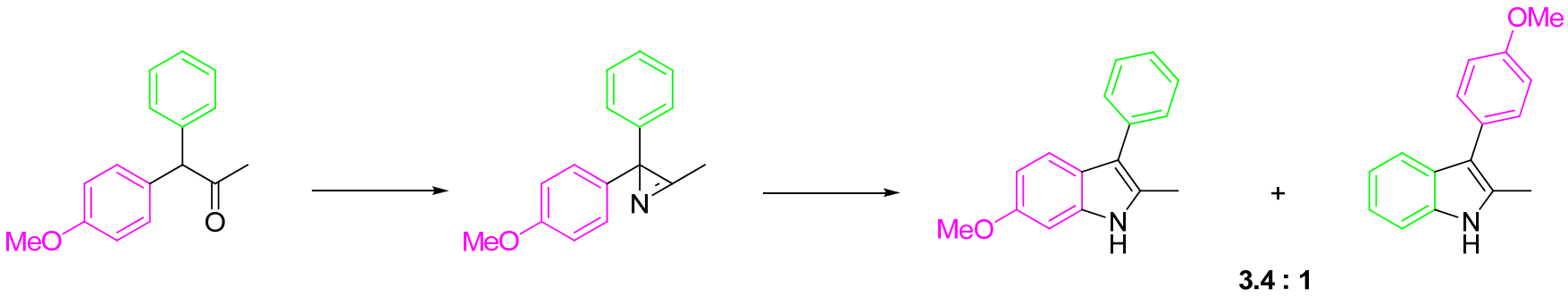

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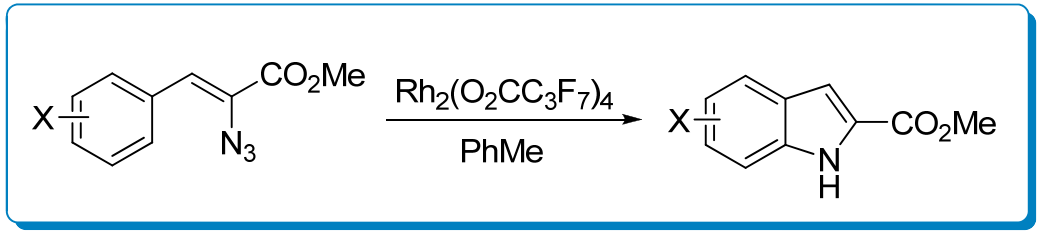
C–H Amination of Vinyl Azides



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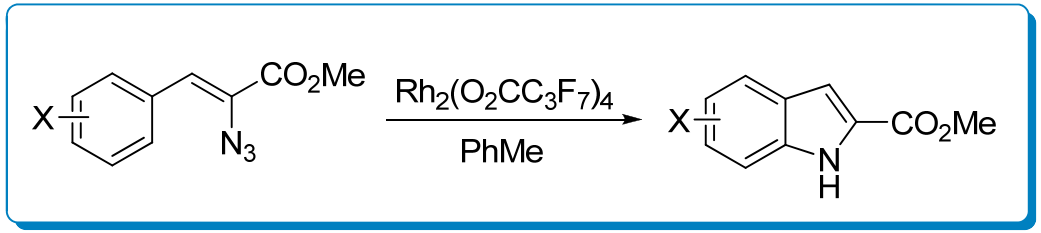

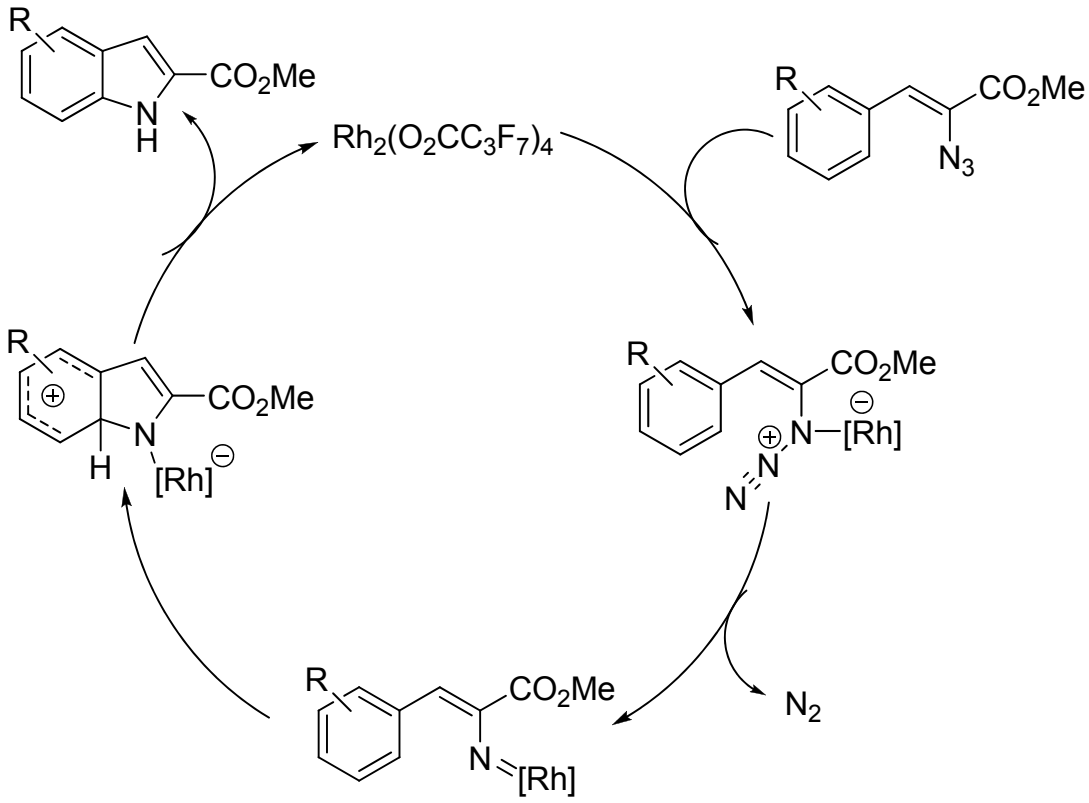

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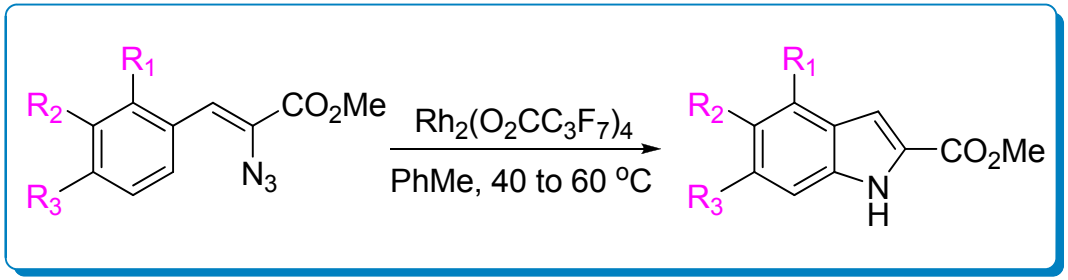

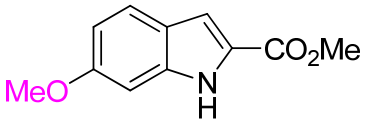

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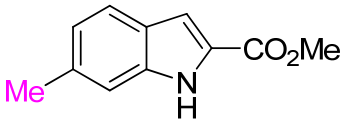

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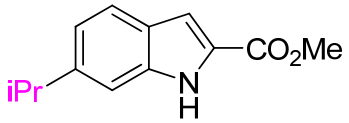

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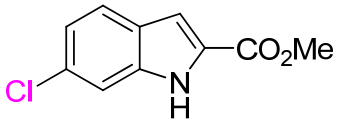

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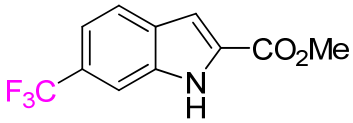

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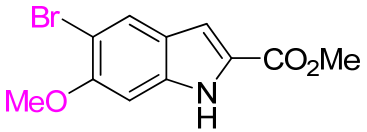

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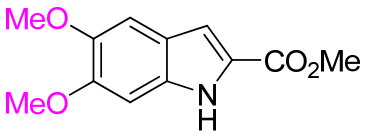

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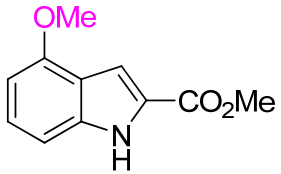

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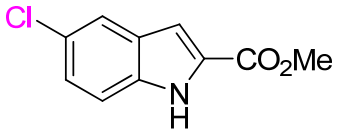

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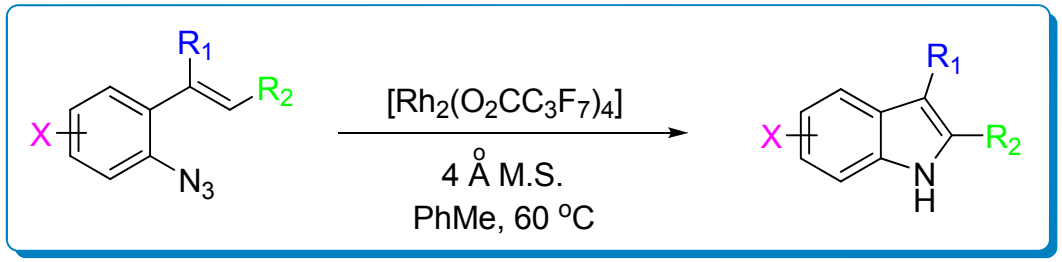
C–H Amination of Aryl Azides



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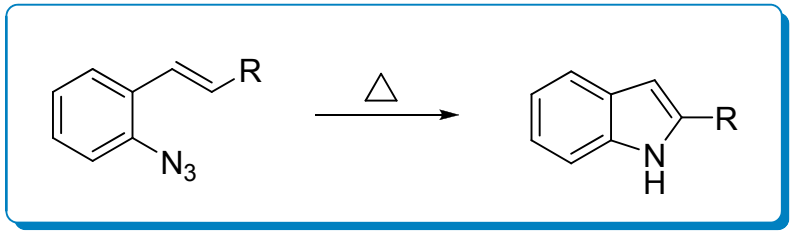

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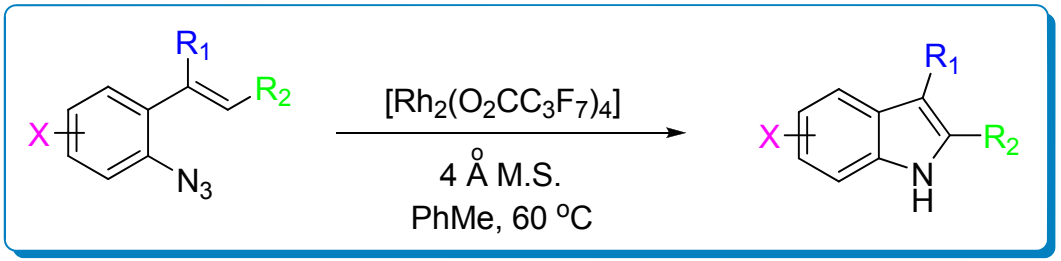

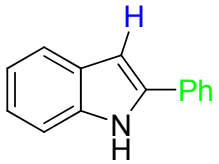

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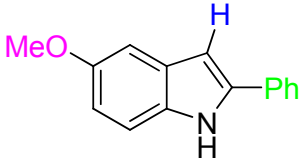

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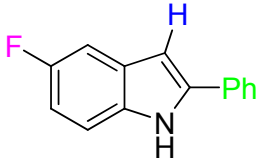

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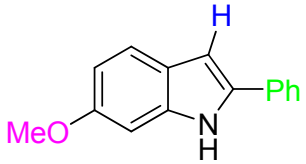

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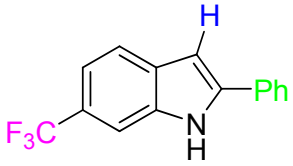

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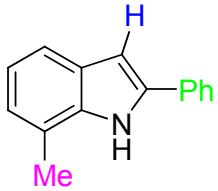

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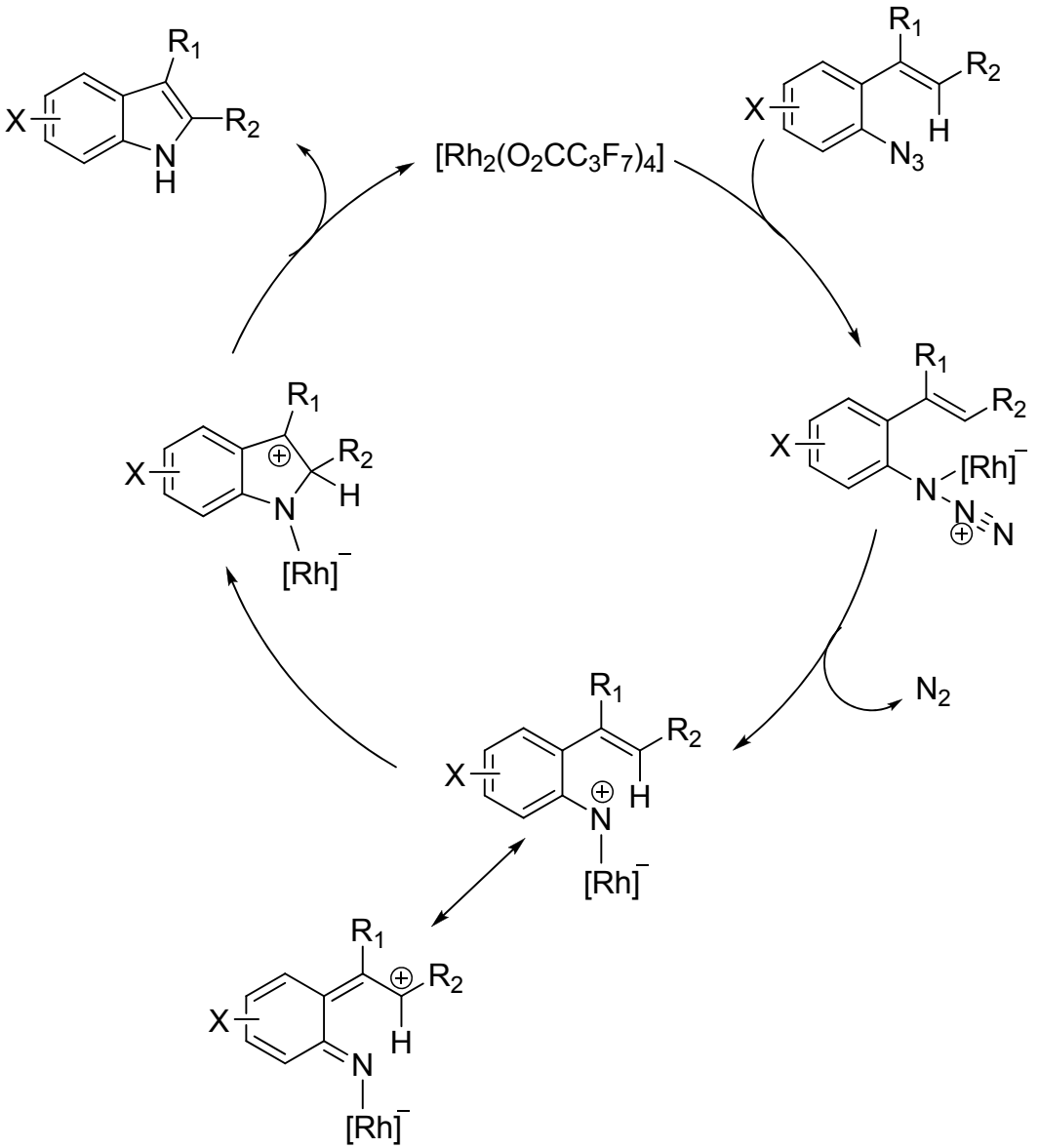

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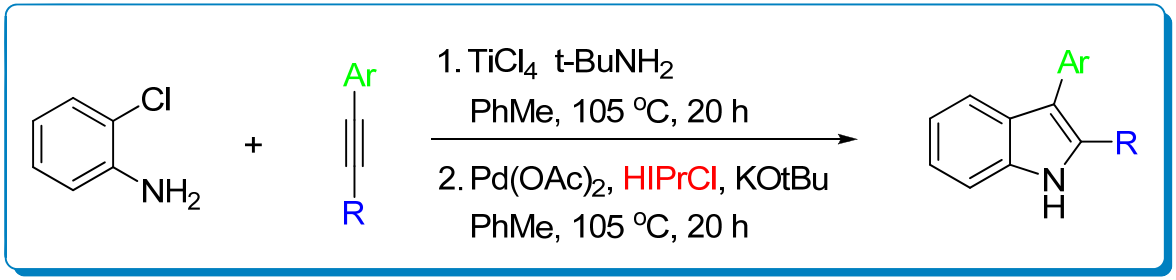
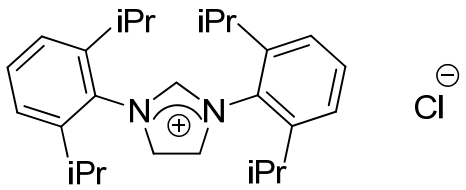
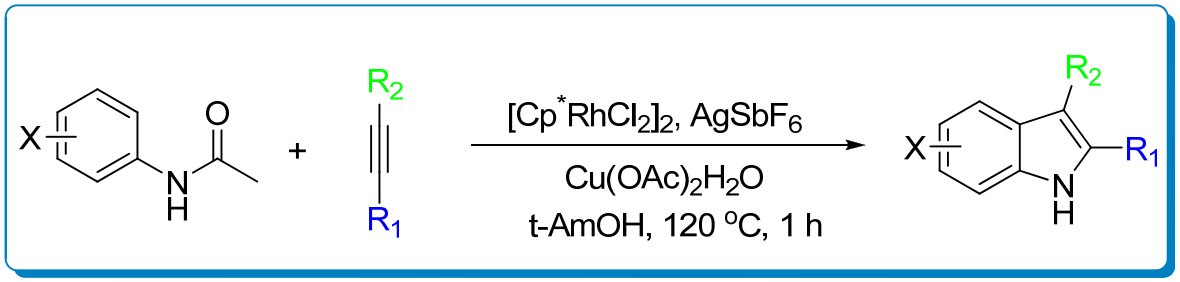




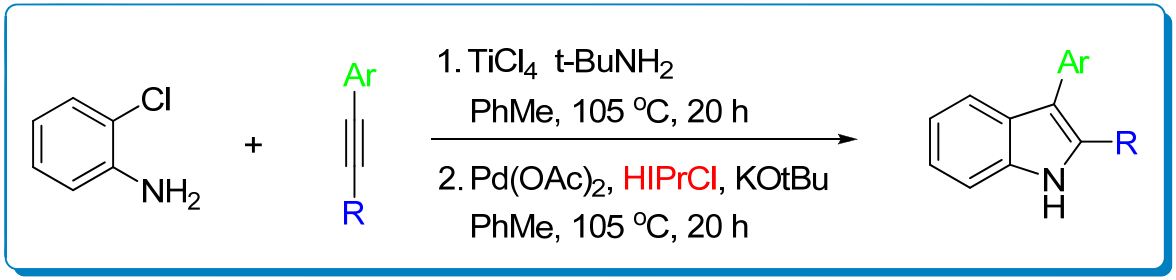
HIPrCl

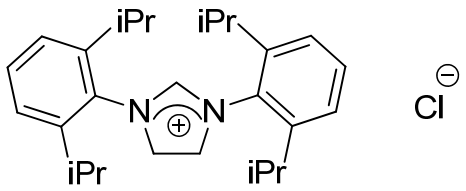
Ackerman, L. *Tetrahedron* **2008**, *64*, 769.



Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474.

Intermolecular Cyclizations with Alkynes

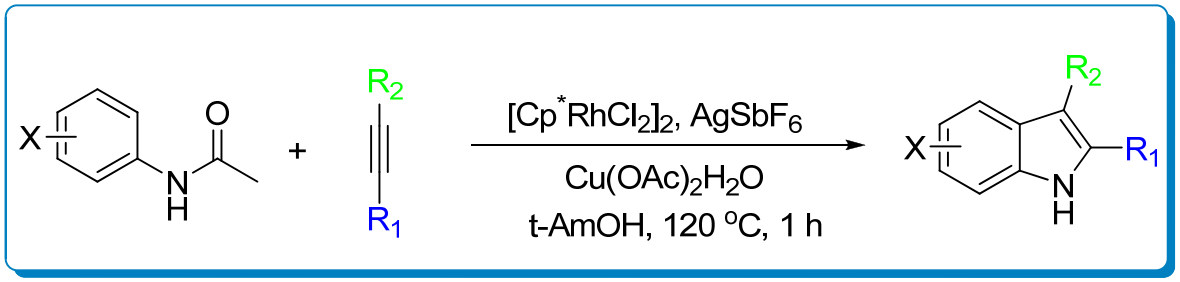




HIPrCl

Ortho-halogenated anilines required

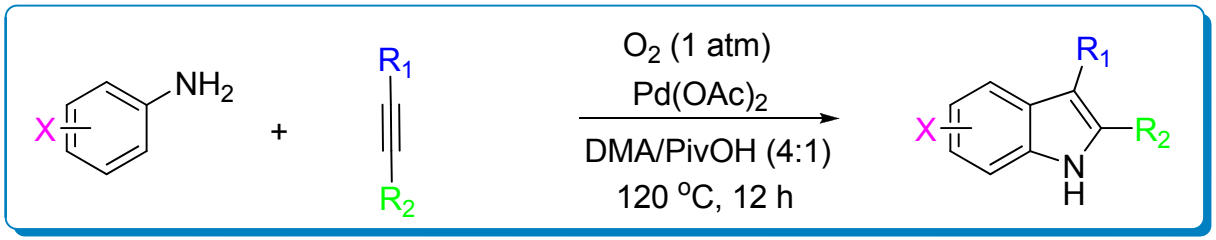
Ackerman, L. *Tetrahedron* **2008**, *64*, 769.

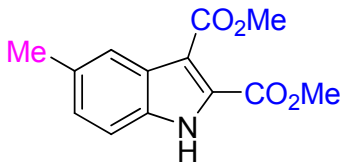


Directing group (OAc) required

Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474.

Pd-Catalyzed C–H Functionalization





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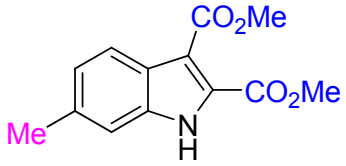

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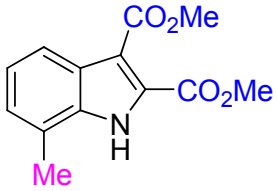

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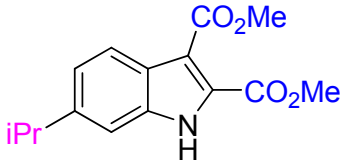

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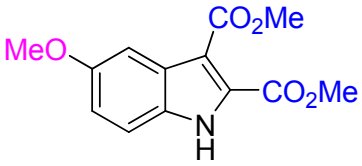

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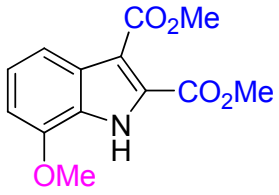

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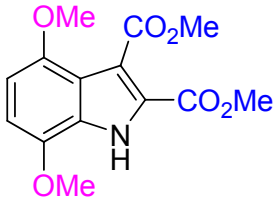

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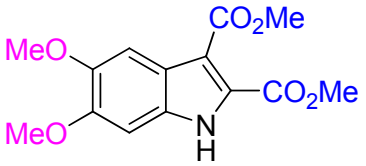

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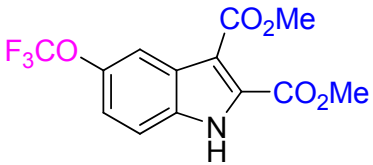

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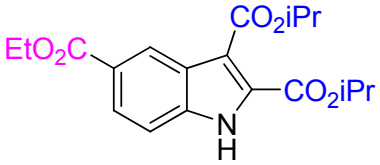

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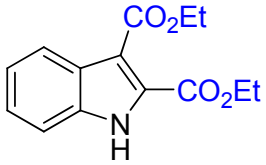

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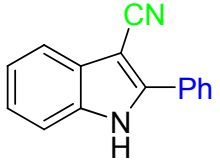

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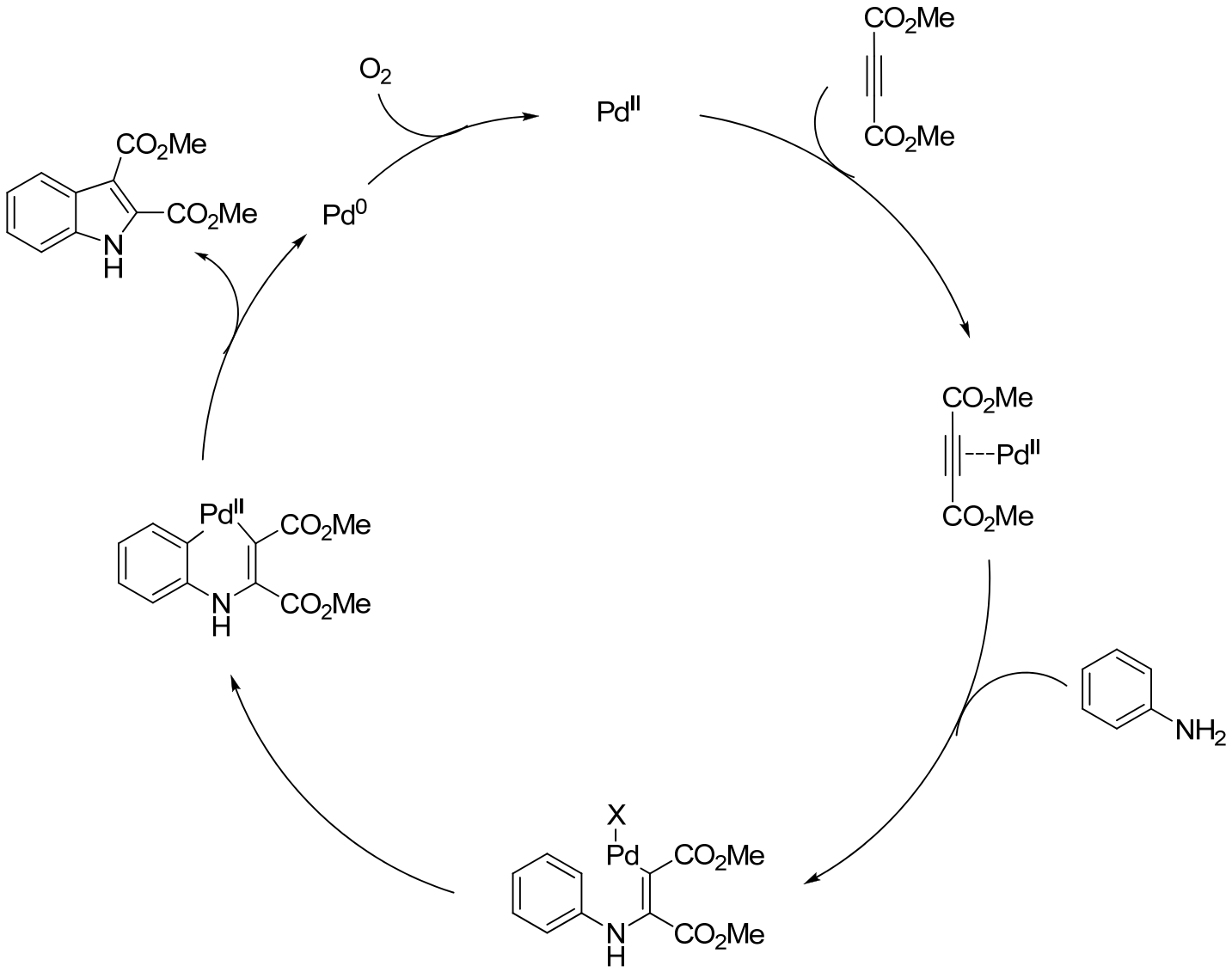
Jiao, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 4572.

Proposed Mechanistic Cycle



Jiao, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 4572.

Contents

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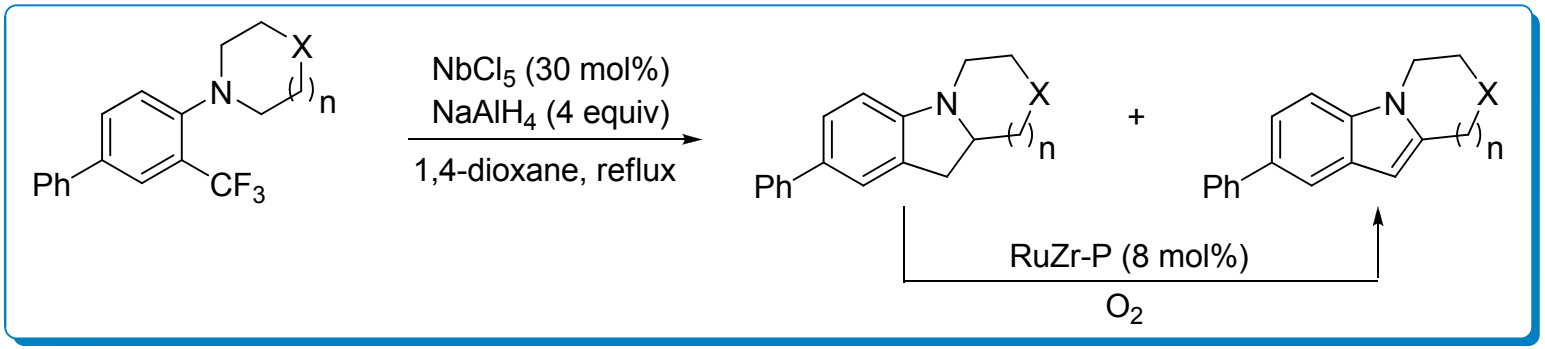
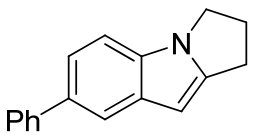
Synthesis of substituted indoles via:

- Rearrangement Reactions
- Multi-component, One-Pot Syntheses
- C–H Amination of Azides
- Pd-Catalyzed C–H Functionalization
- Nb-Promoted C–F Functionalization
- Conclusion

Nb-Promoted C–F Functionalization





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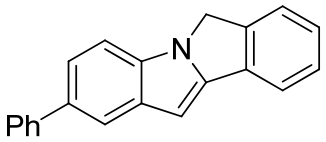

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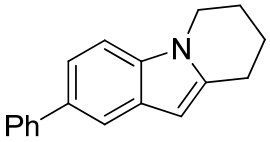

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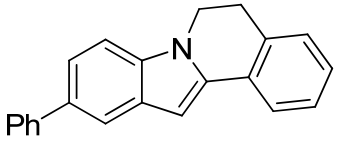

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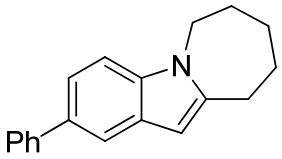

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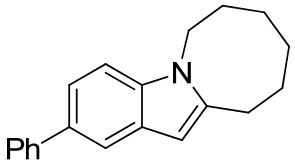

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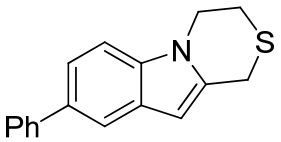

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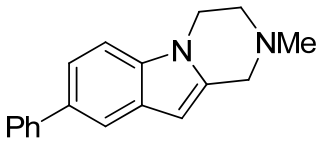

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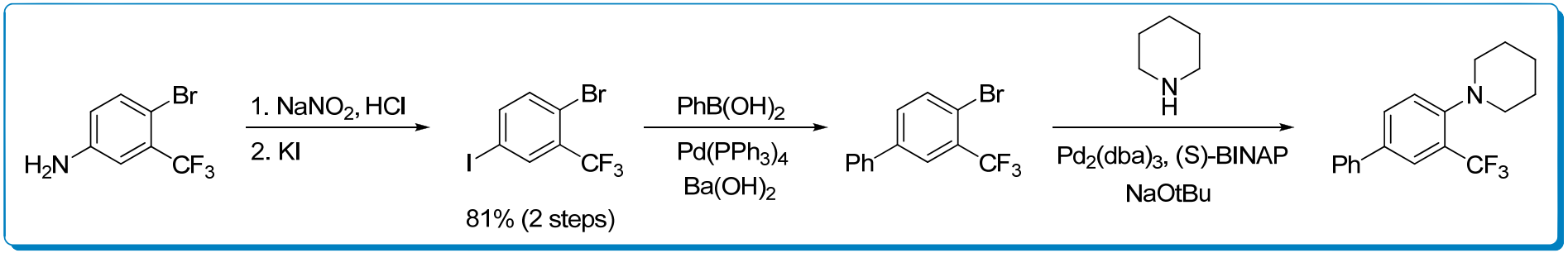
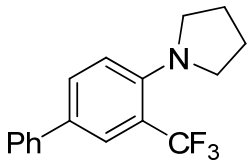
Akiyama, T. *Angew. Chem. Int. Ed.* **2009**, *48*, 8070.

Preparation of Fused Ring Components





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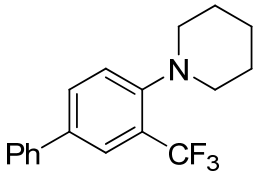

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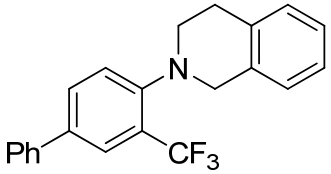

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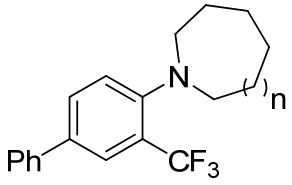
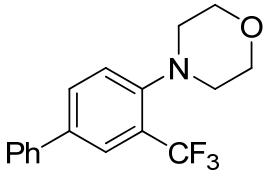


(n=1), 70%
(n=2), 25%



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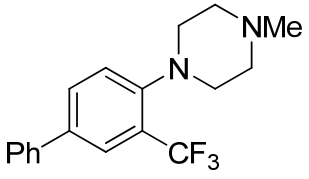

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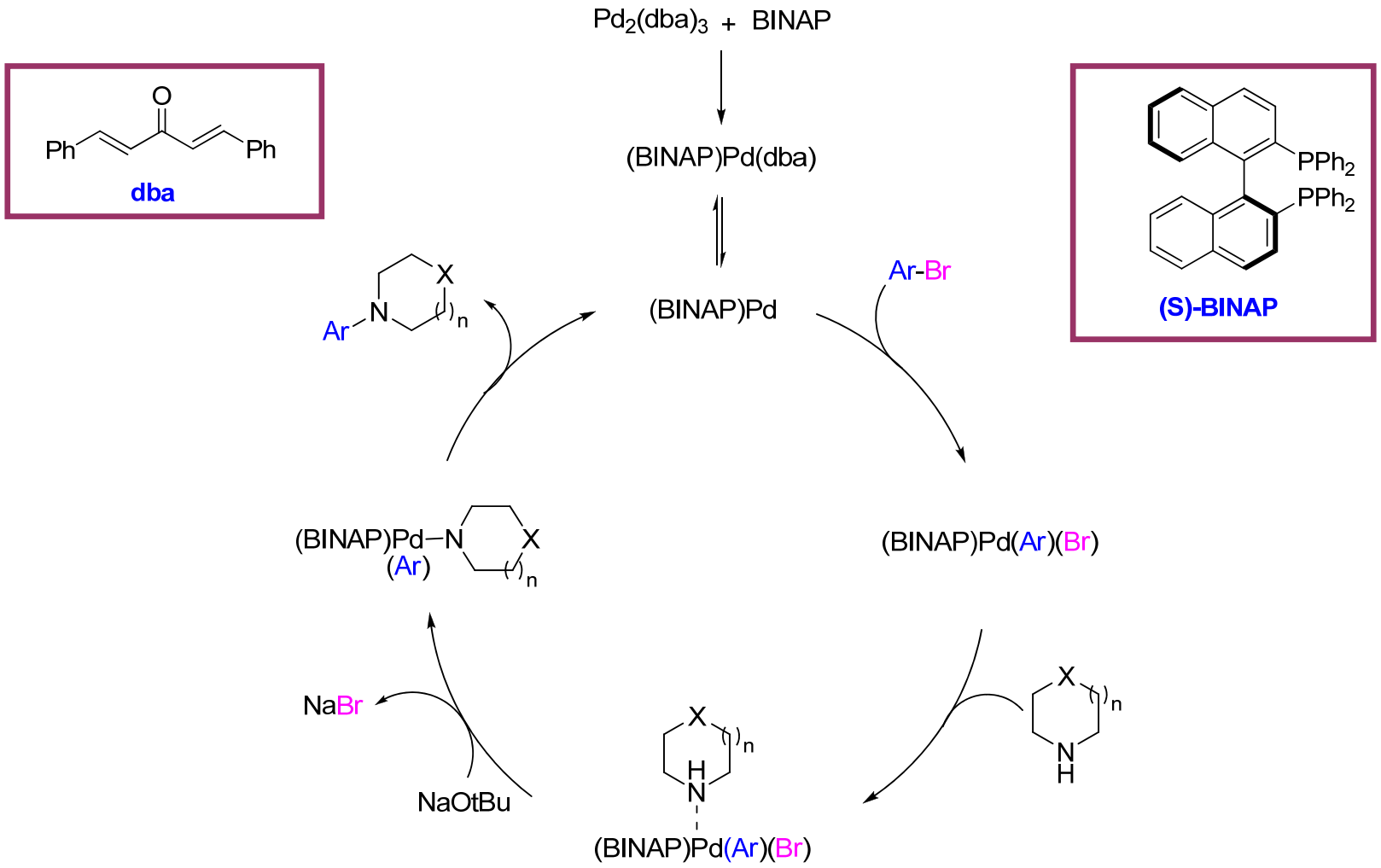
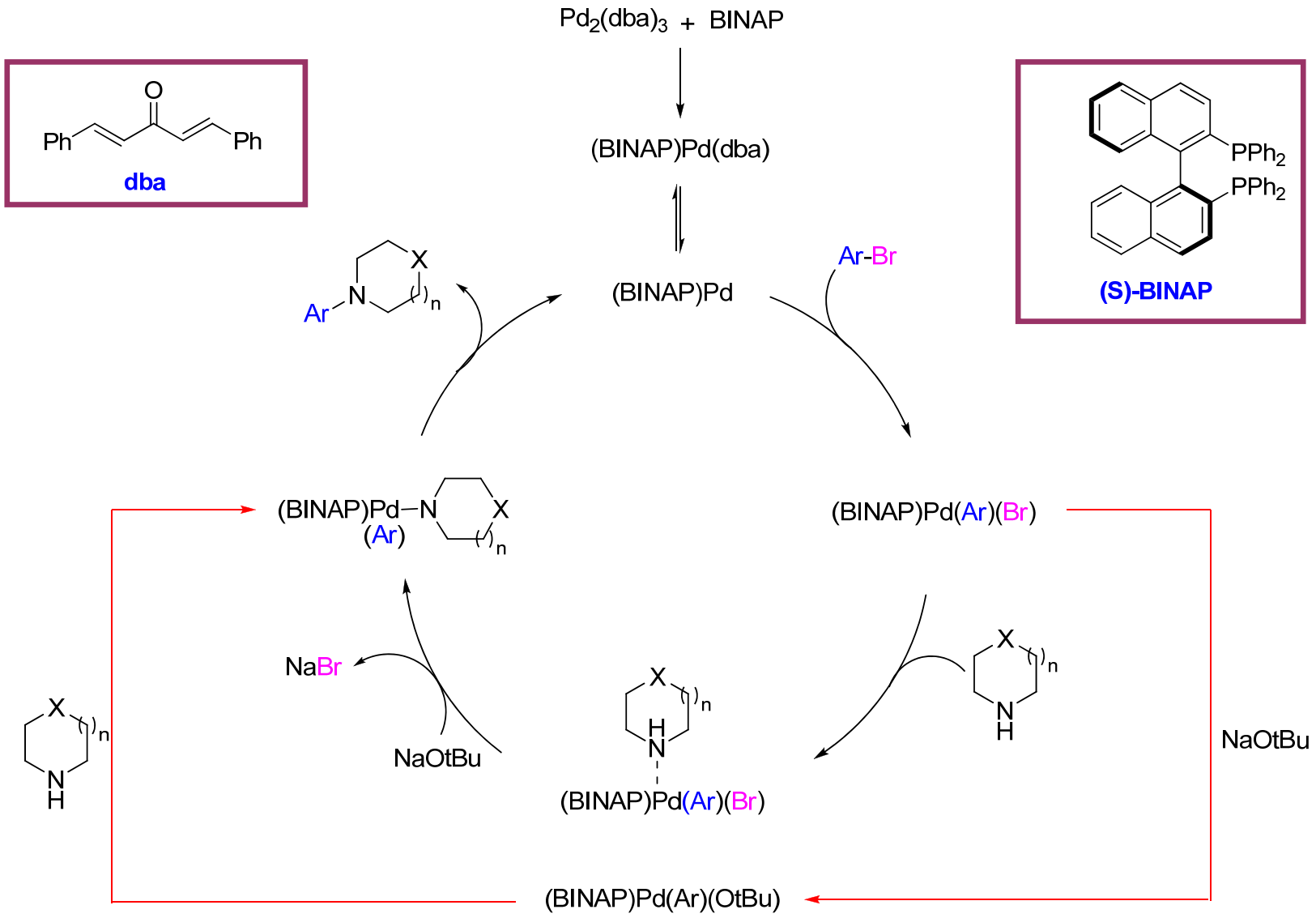
Akiyama, T. *Angew. Chem. Int. Ed.* **2009**, *48*, 8070.

Amination Reaction Pathway



Buchwald, S. *J. Org. Chem.* **2000**, *65*, 1144.

Amination Reaction Pathway



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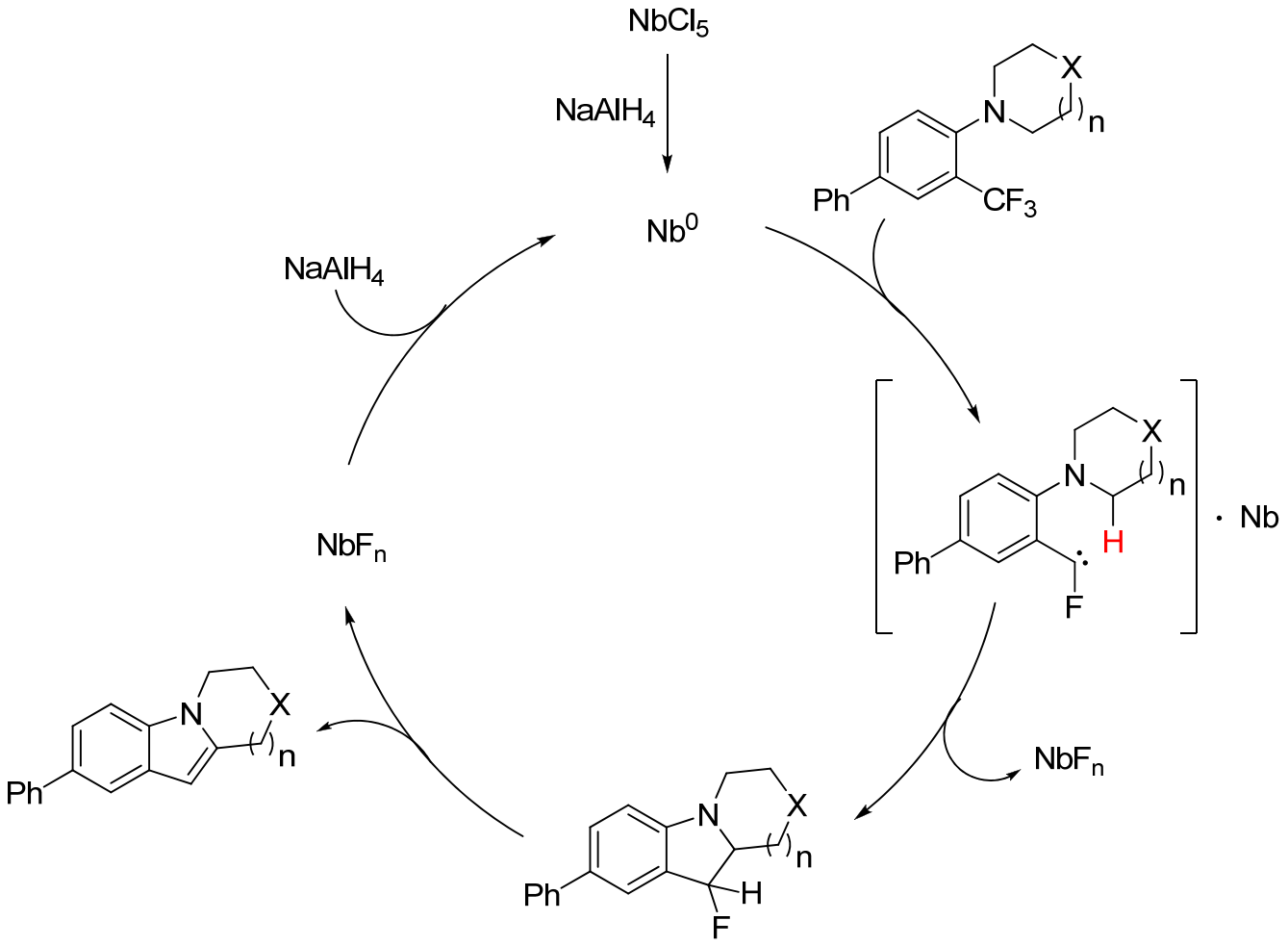
Proposed Catalytic Cycle



Driver, T. G. *Angew. Chem. Int. Ed.* **2009**, *48*, 7974.

Akiyama, T. *Angew. Chem. Int. Ed.* **2009**, *48*, 8070.

Conclusion

- The indole scaffold is of particular importance in nature and medicinal chemistry.
- New synthetic strategies target the efficient preparation of indoles that exhibit multiple substitution patterns.
- Novel developments have been made toward the functionalization of otherwise unreactive bonds.

THANK YOU