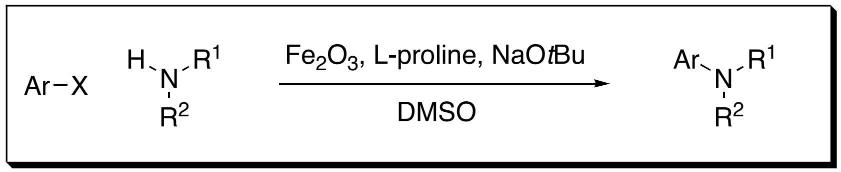
Efficient Iron-Catalyzed *N*-Arylation of Aryl Halides with Amines



Guo, D.; Huang, H.; Xu, J.; Jiang, H.; Liu, H *Org. Lett.* ASAP

Recent advances in aromatic carbon-nitrogen bond formation

John Maciejewski

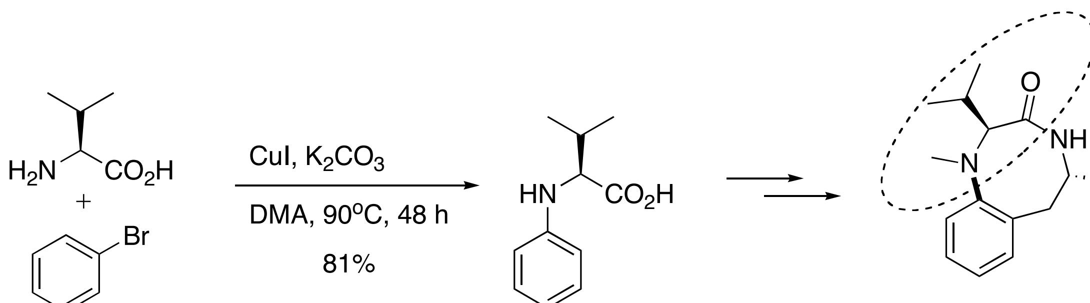
Current Literature - 9/27/08

1

Ullmann Reaction

- Coupling between aromatic halides with either aliphatic and aromatic amines using copper salts and base
- Drawbacks: high reaction temperatures (>150 ^{o}C) and stoichiometric copper usage
- Using ligands that include phosphines, amines, and amino alcohols improve yields and applications
- Current methods use readily available ligands, catalytic copper salts at temperatures as low as 40 ^{o}C

Ma, D.; Cai, Q. *Acc. Chem. Res*. ASAP.
Yang, M.; Liu, F. *J. Org. Chem.* **2007**, *72*, 8969.
Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453.
Ullmann, F. *Ber*. *Dtsch*. *Chem*. *Ges*. **1903**, *36*, 2382.



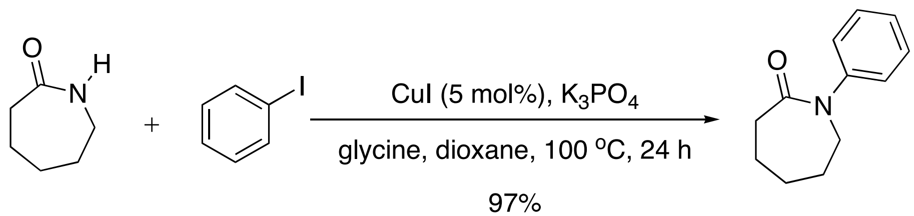
benzolactam-V8

protien kinase C activator

Ma, D.-W.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem.Soc*. **1998**, *120*, 12459.

Goldberg Reaction

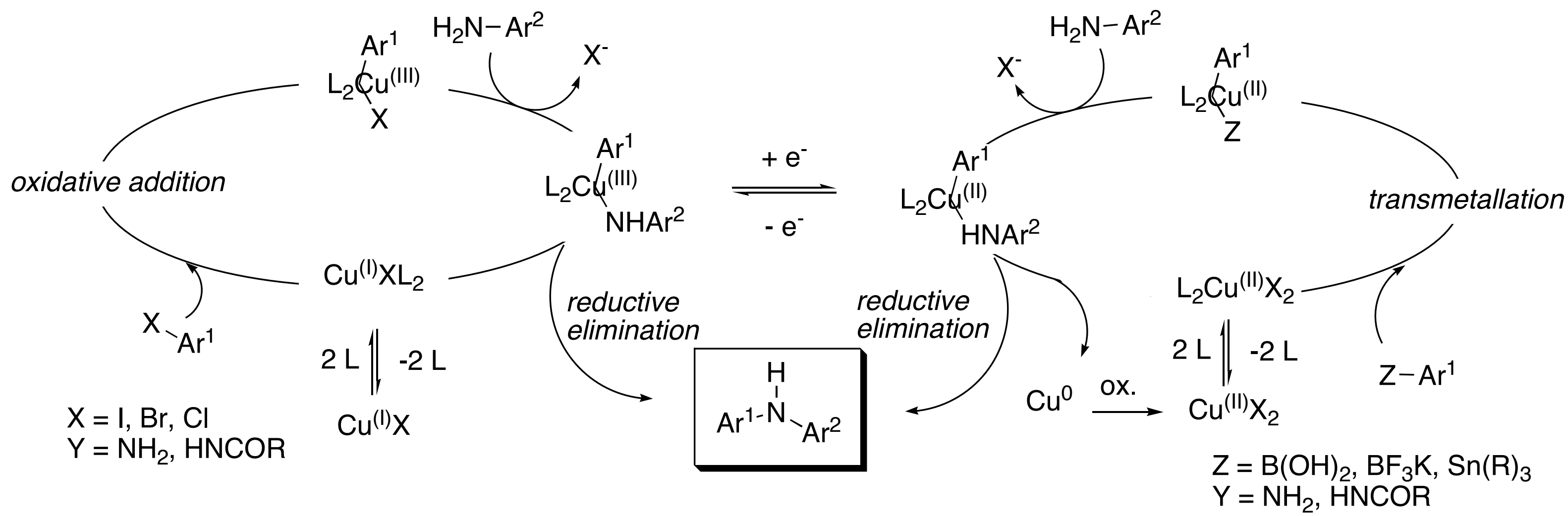
- Amidation of aryl halides using primary and secondary amides (cyclic or acyclic)
- Drawbacks similar to Ullmann reaction (high temp., strong base and stoichiometric copper salts)
- Efficiency of reaction depends on choice of ligand, temperature and base (similar to Ullmann reaction)
- Aryl amidation using copper salts is less expensive on industrial scale compared to palladium catalysis



representative example

Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120 (kinetic study)
Deng, W.; Wang, Y.-F.; Zou, Y.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett*. **2004**, *45*, 2311 (ligand studies).
Goldberg, I. *Ber*. *Dtsch*. *Chem*. *Ges*. **1906**, *39*, 16911.

Mechanism for Ullmann & Goldberg Couplings



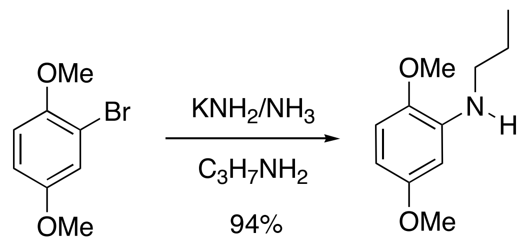
- Two possible mechanisms, but oxidation state of copper intermediates are not known
- Radical mechanisms have been ruled out
- Ligand choice is critical for reaction efficiency

Kurti, Laszlo, Barbara Czako. Strategic Applications of Named Reactions in Organic Synthesis. San Diego: Elsevier, 2005.

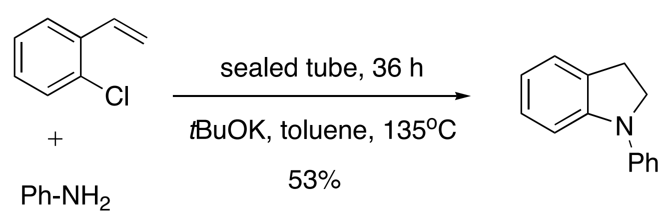
4

Transition-Metal Free Aryl Amination

via a benzyne intermediate



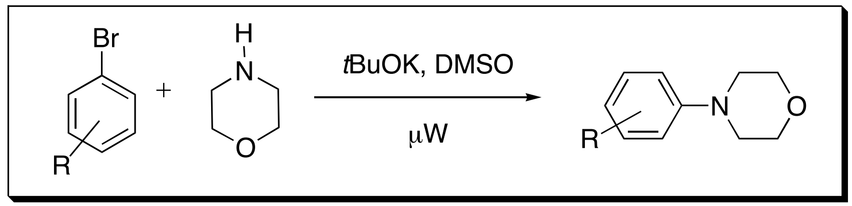
Han, Y. X.; Jovanovic, M. V.; Biehl, E. R.*J. Org. Chem.* **1985**, *50*, 1334
Biehl, E. R.;Razzuk, A.; Jovanovic, M. V.; Khanapure, S. P.*J. Org. Chem.* **1986**, *51*, 5157. (addition of amines, nitriles and mercaptans)

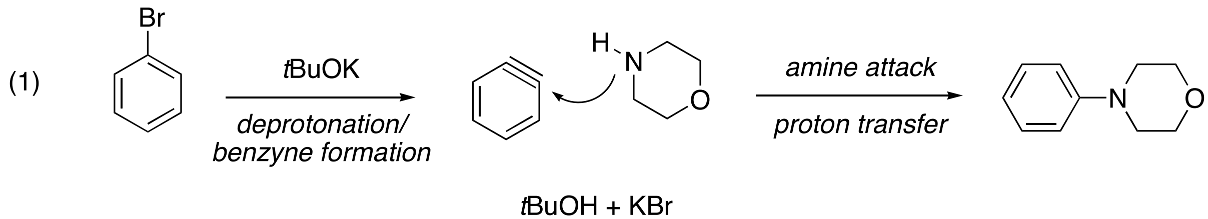


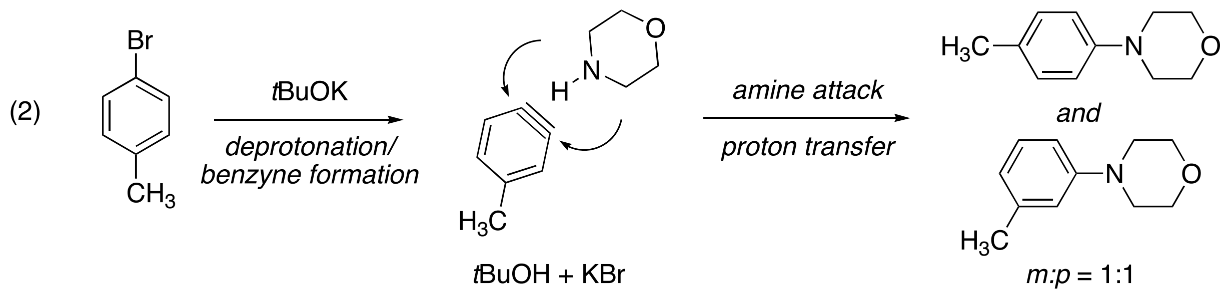
Beller, M.; Breindl, C.; Riermeier, T. H.; Eichberger, M.; Trauthwein, H *Angew. Chem. Int. Ed.*,**1998**, *37*, 3389.
Beller, M.; Breindl, C.; Riermeier, T. H.; Tillack, A. *J. Org. Chem.* **2001,** *66,* 1403 (hydroamination/cyclization studies)

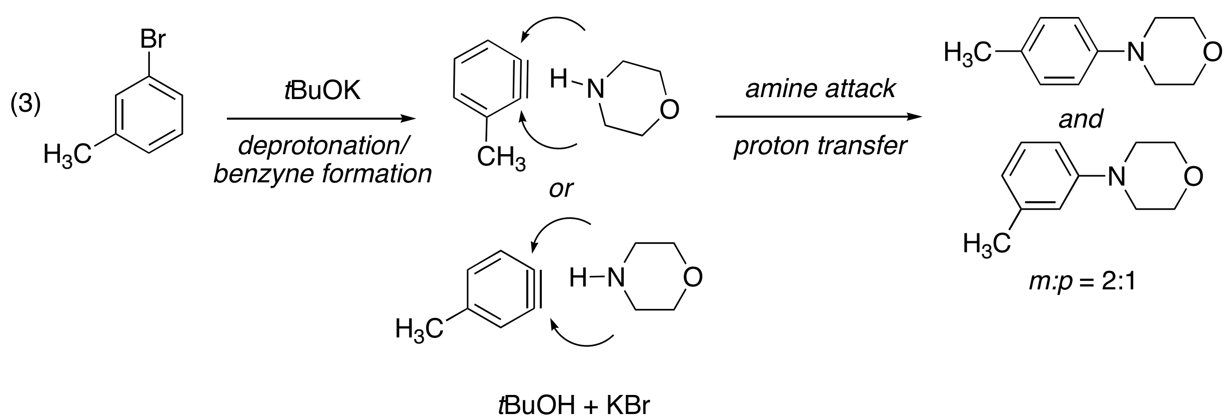
5

Mechanism for Benzyne Addition





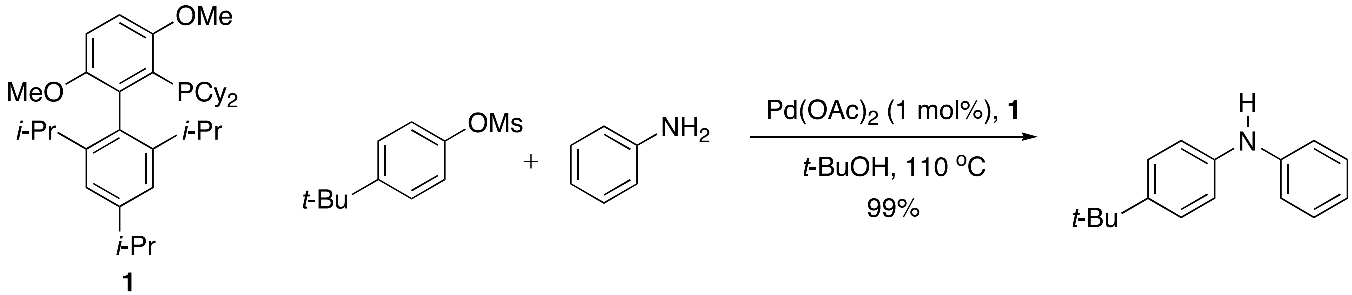




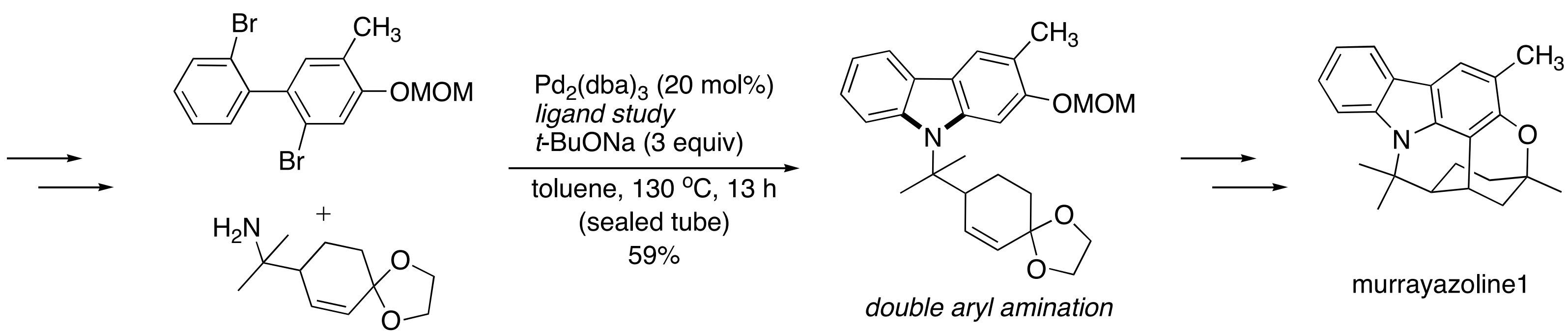
Shi, L.; Wang, M.; Fan, C.-A.; Zhang, F.-M.; Tu, Y.-Q. *Org. Lett.* **2003**, *5*, 3515 (and references therein).

Buchwald-Hartwig Coupling

- Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927 (Stille-type coupling with amino stannanes)
- Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1995**, *34*, 1348.
- Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.



Fors, B. P.; Watson, D. A.; Briscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* ASAP

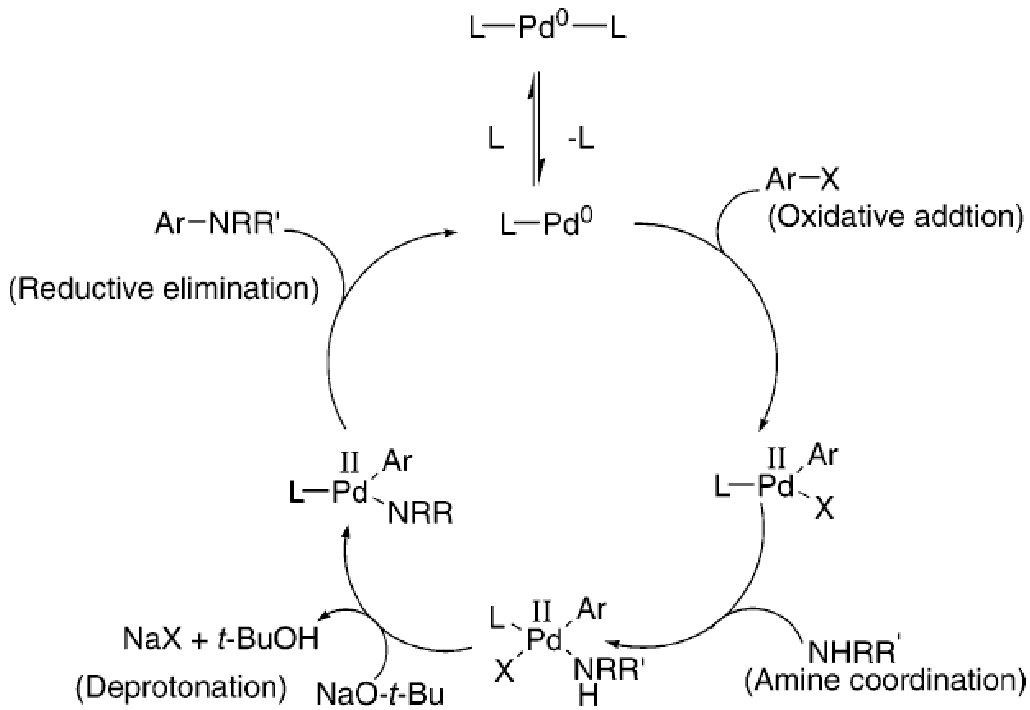


Ueno, A.; Kitawaki, T.; Chida, N. *Org. Lett.* **2008**, *10*, 1999.

Buchwald-Hartwig Coupling

- Advantage over Ullmann and Goldberg reactions due to the mild reaction conditions
- Ligand choice is *critical* for the stabilization of the active Pd^0 species in catalytic cycle
- Broadening reaction scope and new ligand design remains a popular research area

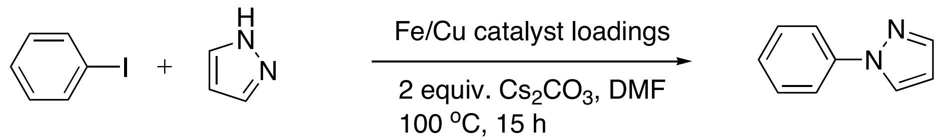
Reddy, C. V.; Kingston, J. V.; Verkade, J. G. *J. Org. Chem*. **2008**, *73*, 3047 (aryl chloride coupling)
Christensen, H.; Kiil, S.; Dam-Johansen, K. *Org. Proc. Res. Dev.* **2006**, *10*, 762.



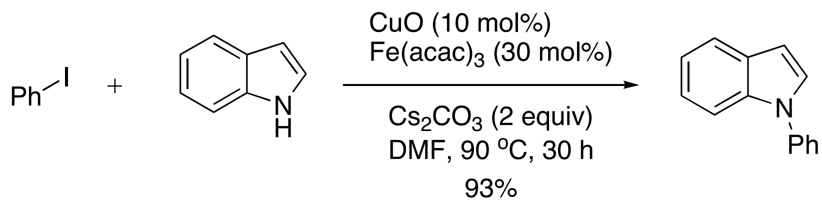
Urgaonkar, S.; Xu, J.-H.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8416.

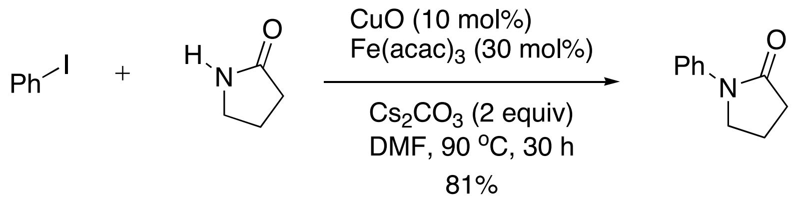
8

Iron/Copper-catalyzed Aryl Amination



Entry	Iron (mol%)	Copper (mol%)	Yield (%)
1	$Fe(acac)_3$ (30)	Cu^0 (10)	100
2	—	Cu^0 (10)	0
3	$Fe(acac)_3$ (30)	—	0

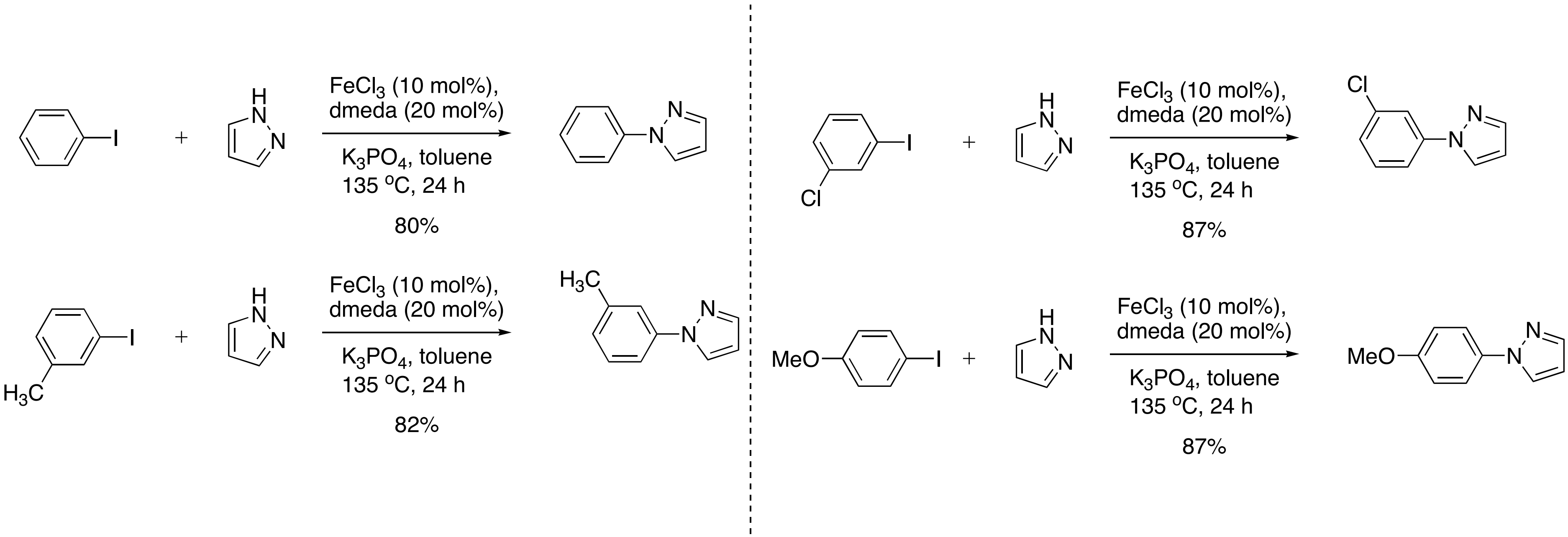




- Various iron catylsts were studied, but $Fe(acac)_3$ worked most efficiently with copper metal
- First bimetallic catalysis (Fe/Cu) for N-arylation (works for aryl iodides and bromides)
- Efficient for heterocyclic amines and 2-pyrrolidinone but not for aliphatic amines

Taillefer, M.; Xia, N.; Ouali, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 934.

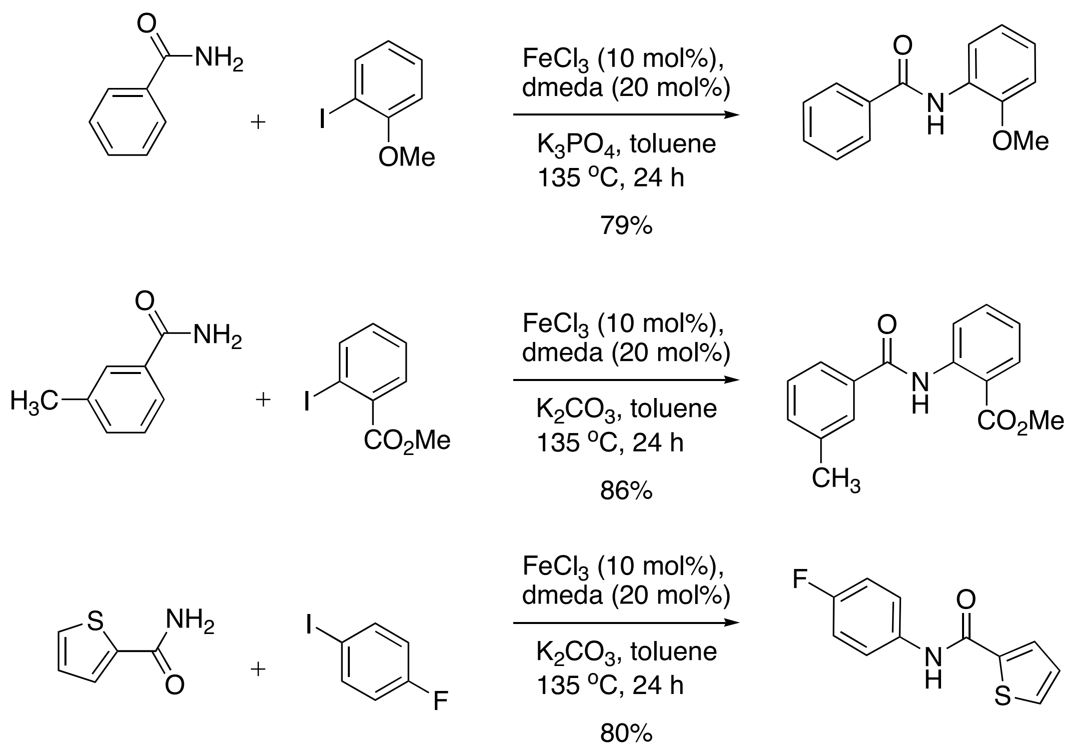
First Iron *only* Aryl Amination



- First ligand-assisted iron (only) catalyzed aryl amination process
- Scope included pyrazoles, indoles and 2-pyrrolidinone
- Aliphatic and aromatic amines failed (gave low yields)
- Ligand study showed that catalytic system will work for both electron rich and deficient substrates
- No mention of regioselectivity problem using unsymmetrical substrates

Correa, A.; Bolm, C. *Angew. Chem. Int. Ed.* **2007**, *46*, 8862.

Iron-catalyzed Aryl Amidation

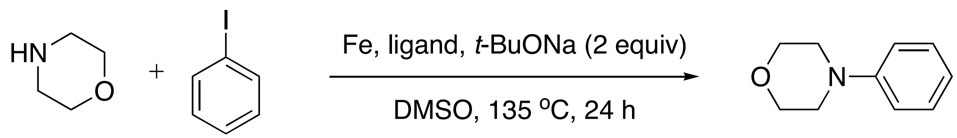


- First ligand-assisted iron catalyzed aryl *amidation*
- Yields complement those of palladium-catalyzed processes

Correa, A.; Elmore, S.; Bolm, C. *Chem. Eur. J.* **2008**, *14*, 3527

11

Efficient Iron-Catalyzed *N*-Arylation of Aryl Halides with Amines

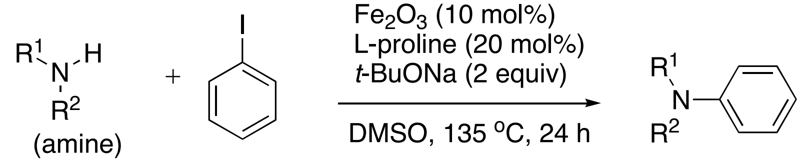


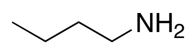
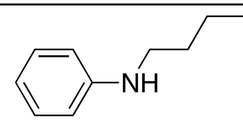
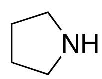
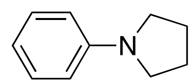
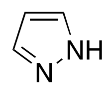
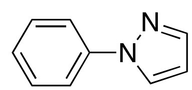
Entry	catalyst (10 mol%)	ligand (20 mol%)	Yield (%)
1	—	—	53
2	—	L-proline	52
3	$FeCl_3$	L-proline	77
4	Fe_2O_3	L-proline	85

- Coupling observed when using no catalyst or ligand
- Entry 3 shows slightly improved yield of product
- Entry 4 shows different iron catalyst improves yield
- DMSO is superior solvent compared to dioxane, toluene or DMF

Guo, D.; Huang, H.; Xu, J.; Jiang, H.; Liu, H *Org. Lett.* ASAP

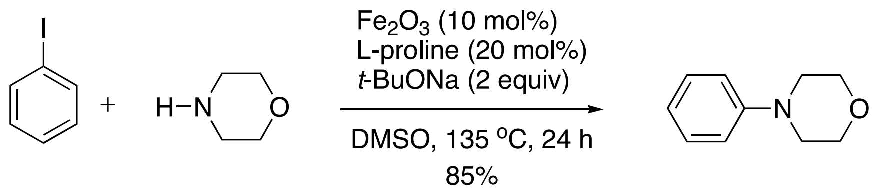
Efficient Iron-Catalyzed *N*-Arylation of Aryl Halides with Amines

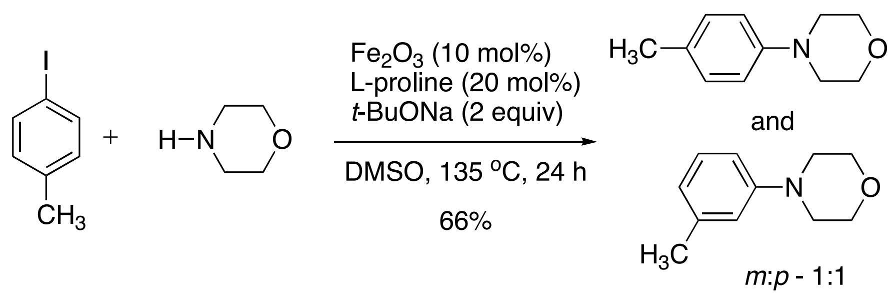


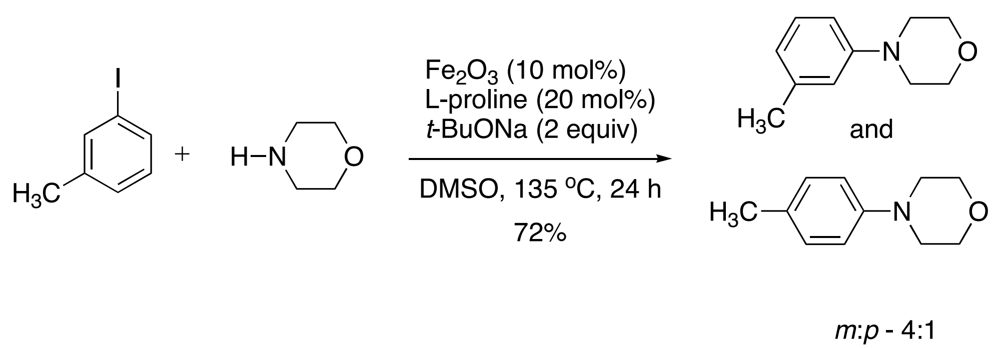
Entry	amine	product	Yield (%)
1			72
2			90
3			67

- System works well with aromatic and aliphatic amines
- Reaction not as efficient with pyrazole (entry 3 - Bolm observed 80% yield)
- *What role does iron play in this reaction?*

Efficient Iron-Catalyzed *N*-Arylation of Aryl Halides with Amines

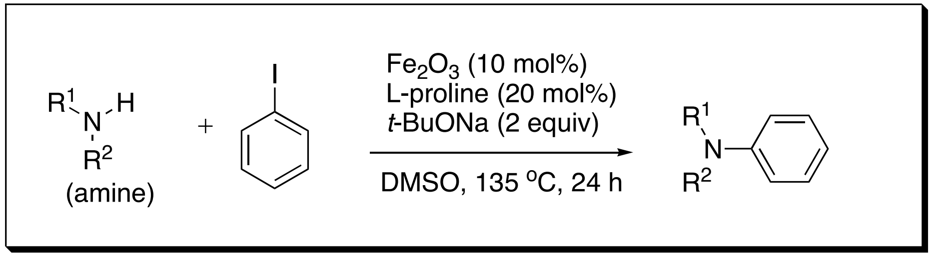






- Unsymmetrical aryl iodides affords regioisomeric mixtures - reminiscent of TM free benzyne mechanism(?)
- What type of reaction mechanism does this transformation fall under?
- Bolm and co-workers do not note any selectivity issues in previous papers using iron catalysis

Conclusions



- Aryl amination and amidation using iron catalysis is an emerging field with environmental benefits
- Scope of process will need to be improved to compete with palladium-based Buchwald-Hartwig systems
- Some results in title paper do not agree with those of Bolm and co-workers
- Is iron really being used catalytically, or is regioselectivity issue a result of a benzyne intermediate