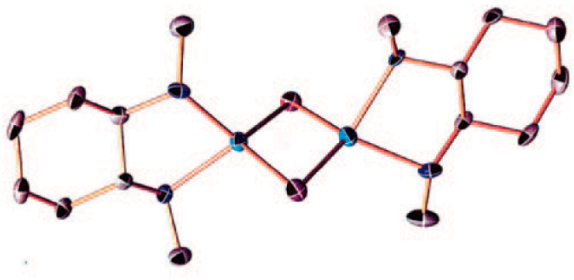
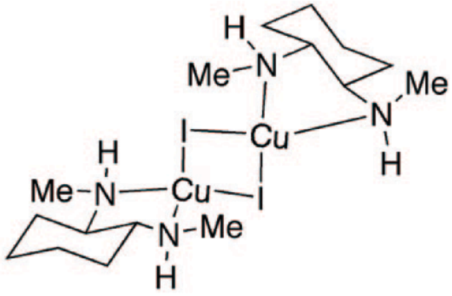
Mechanistic Studies on the Copper-Catalyzed *N*-Arylation of Amides





Strieter, E. R.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.*, **ASAP**

A brief discussion on how ligands effect the kinetics of copper catalysis

John Maciejewski

Current Literature - December 20th, 2008

Molecular Assembly Using Copper

Uses of copper in organic synthesis:

- stoichiometric and catalytic formation of C-C, C-O and C-N bonds
- organocuprate additions, Sonogashira, Glaser, Ullmann, heteroaryl Heck, Sandmeyer and *Goldberg*
- may be used in conjunction with other metals (transmetallation) or in red/ox processes

Advantages of copper over palladium catalysis:

- higher functional group compatibility (free amines, alcohols, amides and heterocycles)
- Cu^0 powder 99.999% purity - 25 g/\$169.00 ~\$7/1 g (Strem Chemicals)
- Pd^0 powder 99.999% purity - 5 g/\$440.00 ~\$88/1 g (Strem Chemicals)

Disadvantages of copper over palladium catalysis:

- Pd catalysis has received more attention than Cu catalysis
- Oxidation states of Pd (Pd^0 - Pd^{IV}) have been identified and studied
- Cu suffers from lower turnover numbers for the catalysts used
- Organometallic complexes existing in oxidation states higher than Cu^+ have not been studied extensively

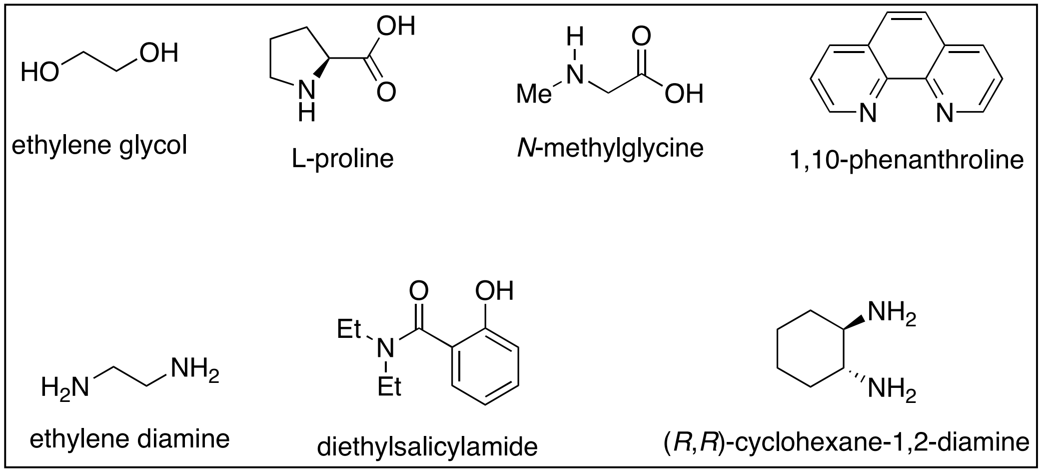
Strieter, E. R.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.*, **ASAP**
Huffman, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196

Advancements in Catalysis *via* Ligand Choice

Ligand choice for Cu(I) salts will greatly effect catalyst solubility, reactivity and reaction efficiency

Advantages include lower reaction temperatures, shorter reaction times and broad solvent compatibility

Common ligands used in copper catalysis



Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453.
Kwong , F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581.
Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657.

Success Through a Common Oxidation State

Studies have been done to see which oxidation state is most efficient in copper couplings

- experiments show Cu(I) is the most likely the common active species

Various copper sources provided nearly the same reactivity when dealing with Cu^0, Cu(I) and Cu(II)

Cu^0 in catalysis:

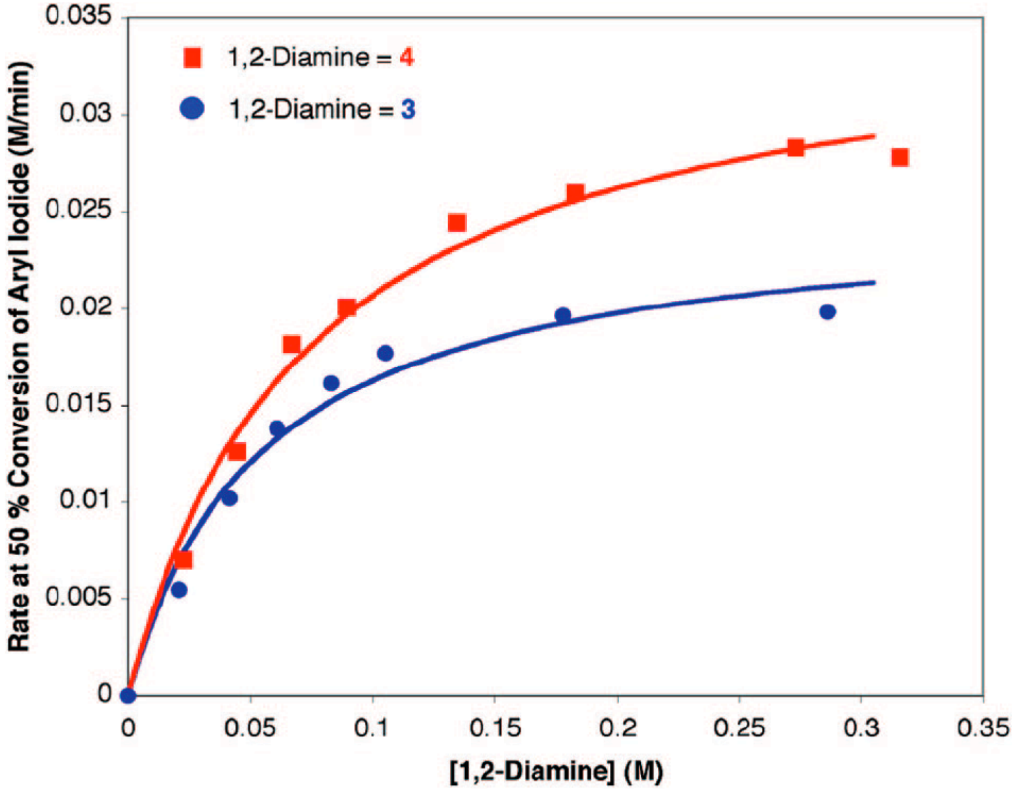
- Paine used SEM to identify a layer of Cu_2O on the surface of Cu^0
- trace Cu(I) is then dissolved after coordination with amine present

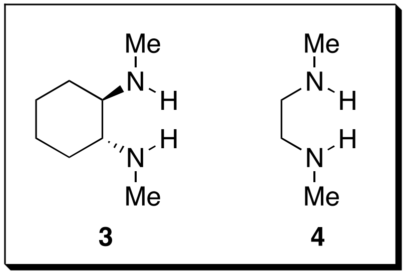
Cu(II) salts in catalysis:

- $CuBr_2$ becomes reduced by ligand(s) to form Cu(I) *in situ*

Paine, A. J. *J. Am. Chem. Soc.* **1987**, *109*, 1496.
Kondratov, S. A. *Zh. Org. Khim.* **1979**, *15*, 2160.
Weingarten, J. *J. Org. Chem.*, **1964**, *29*, 3624.
Weston, P. W.; Adkins, H. *J. Am. Chem. Soc.* **1928**, *50*, 859.

Nonlinear Rate Dependence on [Amine]

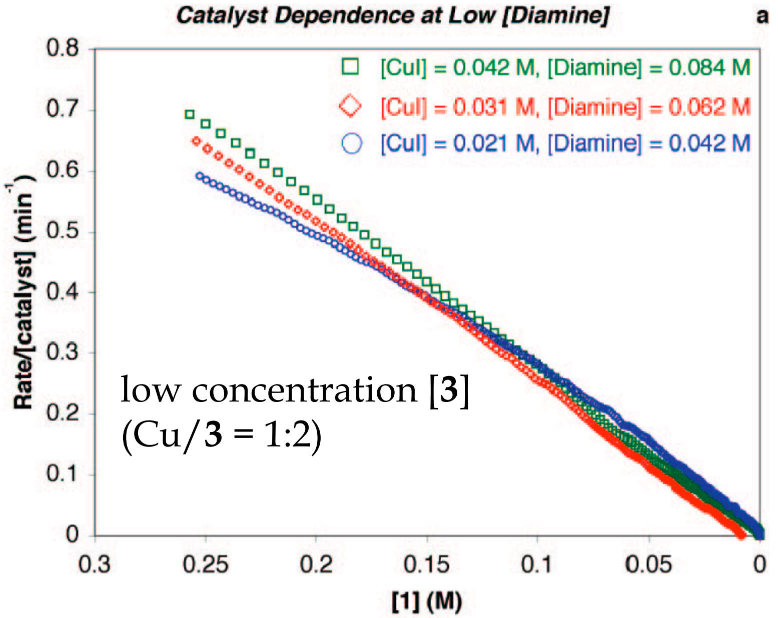




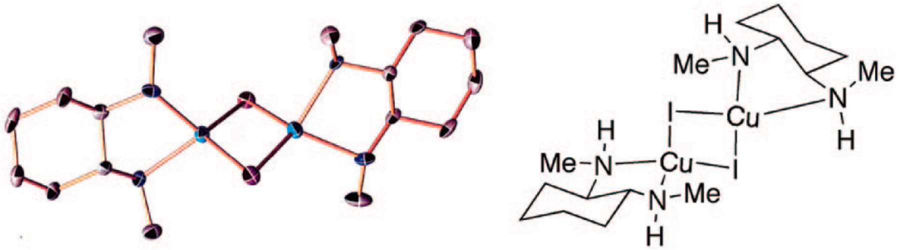
Graph shows reaction rate at 50% conversion of aryl iodide (determined by GC analysis)

Nonlinear dependence raises concerns with both catalyst solubility and that high concentration of amine may inhibit or disrupt active catalyst complex (to be addressed).

The Effect of Ligand Concentration



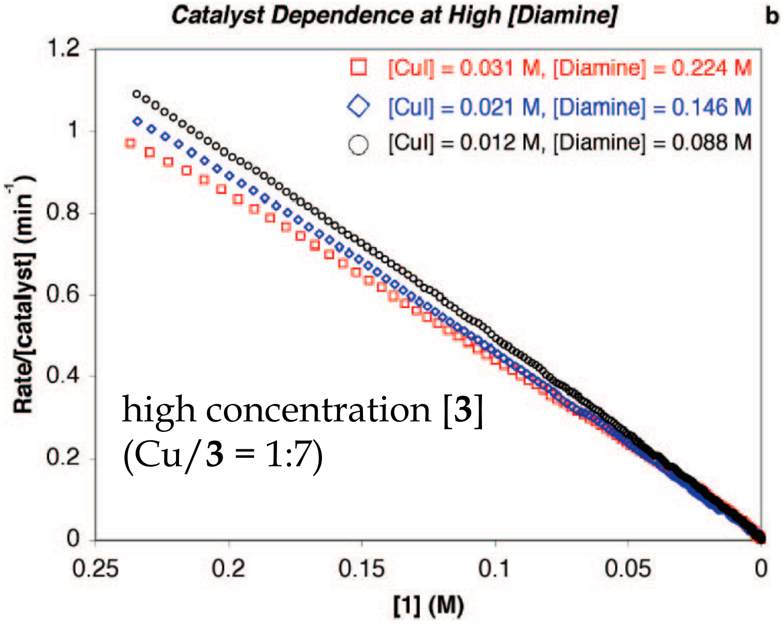
low concentration [**3**]
(Cu/**3** = 1:2)



(proposed active catalyst in solution)

Cu(I)/**3** (1:1) mixture is completely soluble in toluene

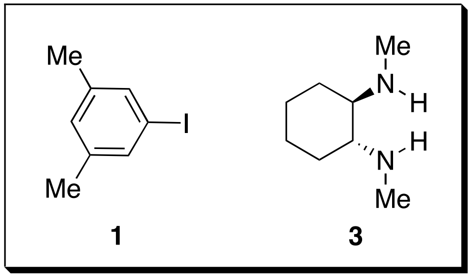
- precipitation of Cu-**3** complex (*shown above*)
- solubility of active copper species is ruled out



high concentration [**3**]
(Cu/**3** = 1:7)

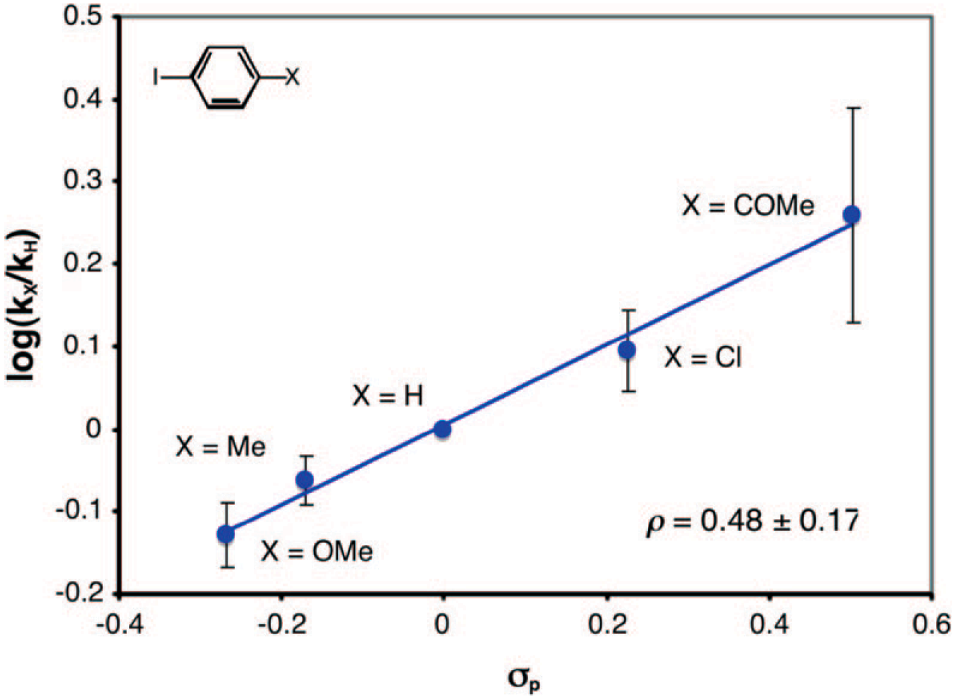
Reaction rate shows first-order dependence with [Cu]

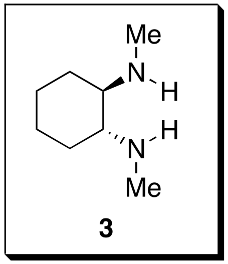
Other factors (such as other intermediates along the reaction pathway) may cause this observed phenomenon



1 **3**

Electronic Effects of Aryl Iodide





3

Hammett plot shows electron-deficient substrates exhibit higher turnover rates than electron rich

- each point is the average of six experiments (three at high [**3**] and three at low [**3**])
- small ρ value shows small electron demand in transition state

Properties of Copper(I) Amidates In Solution

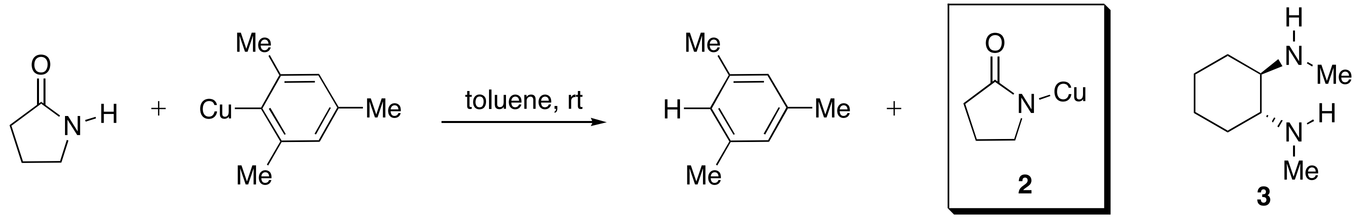
Copper(I) amidate **2** was prepared by reacting 2-pyrrolidinone with halide free mesitylcopper

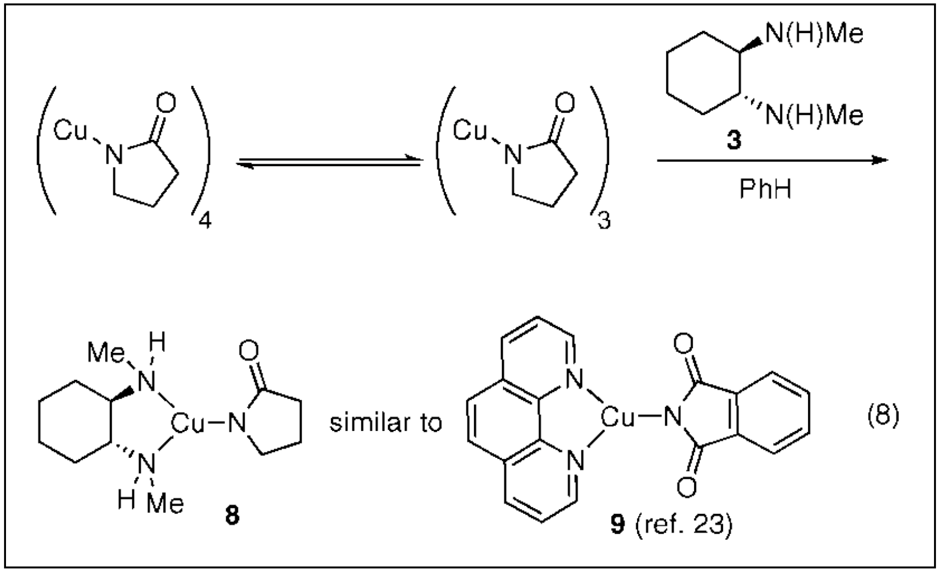
In toluene, amidate **2** exists as rapidly exchanging oligomeric species

- observation supported by broad pyrrolidinoate resonances in ^{1}H NMR at room temperature

Copper(I) amidate:1,2-diamine complex (**2**:**3**) sharpens ^{1}H NMR spectrum

- supports amine:copper complexation to form a single species in solution



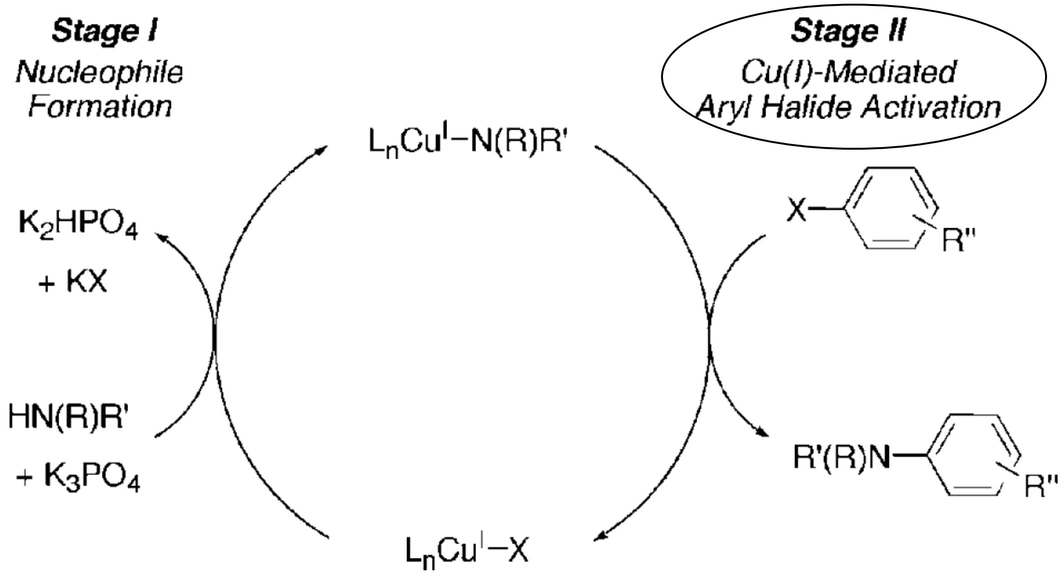


Singer method used to determine molecular weights of pyrrolidinoate species in solution

Intermediates similar to those isolated and characterized by Hartwig

Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2008**, *130*, 9971

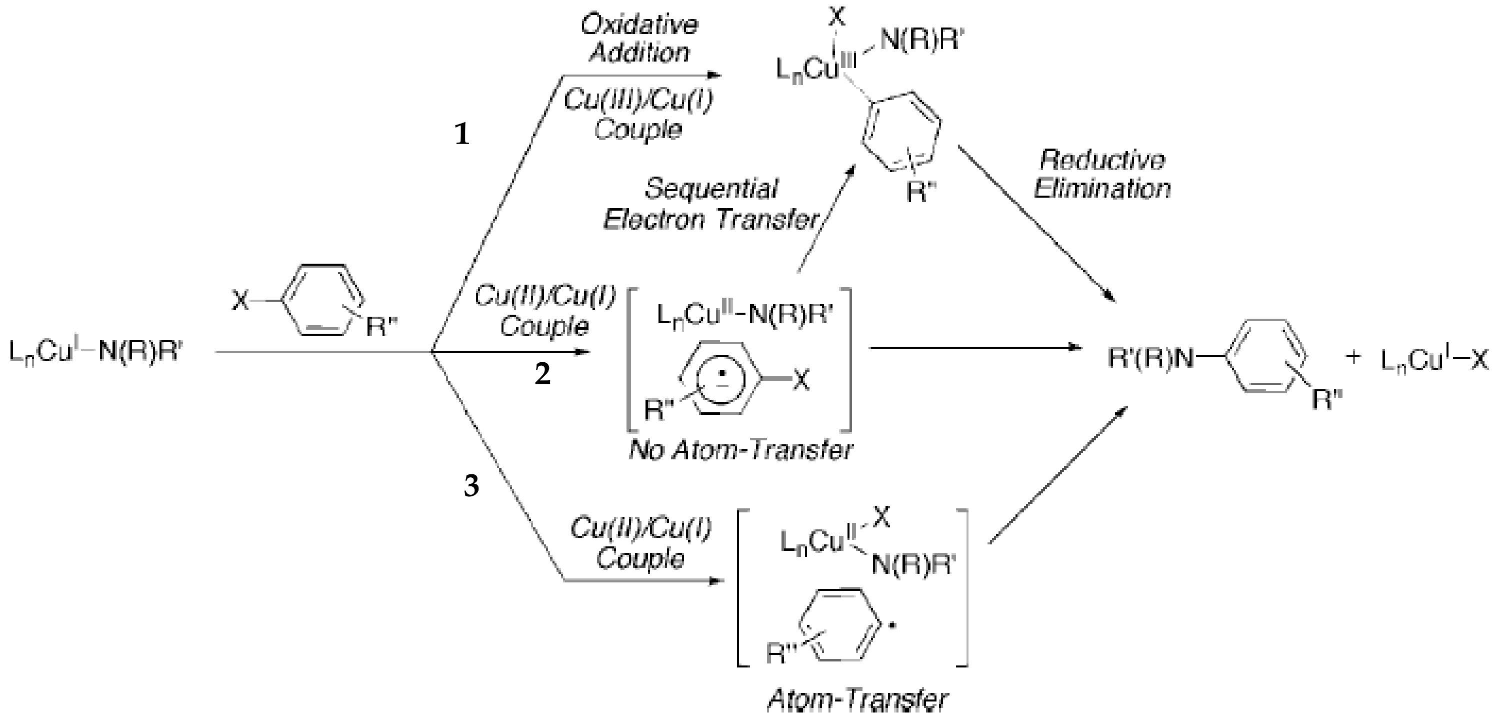
Summary of Mechanistic Studies



Studies show that two independent stages comprise the Cu(I)-catalyzed coupling

- stage I involves formation of the copper(I) amidate nucleophile
- stage II involves the activation of the aryl halide (primary focus of this work)

Mechanisms for Aryl Halide Activation

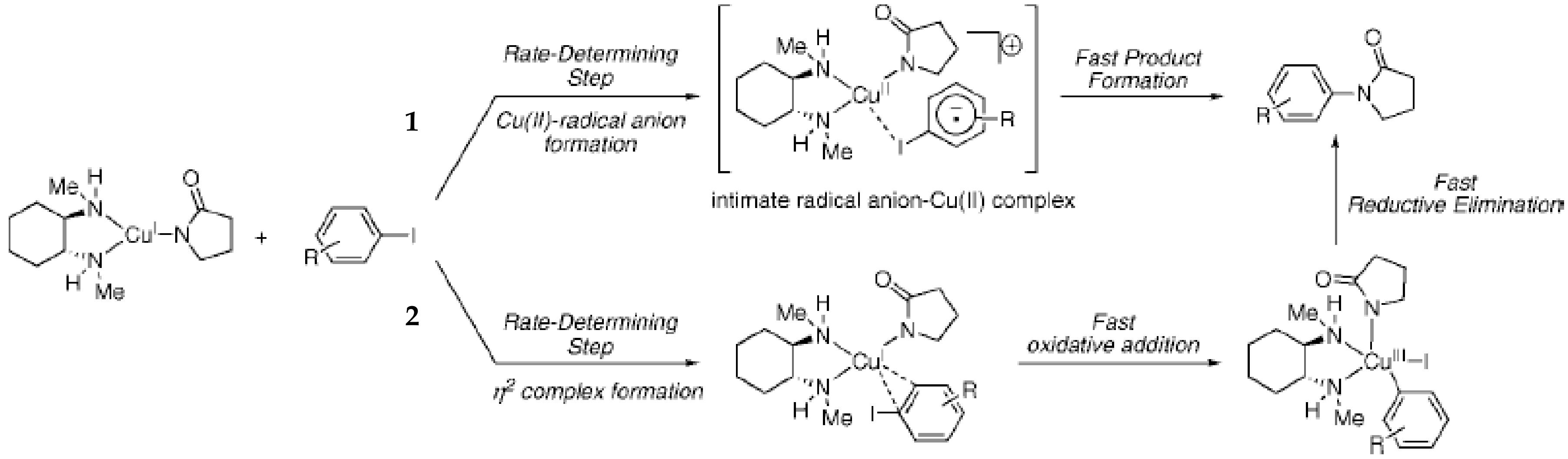


Path **1** - Oxidative addition into aryl halide followed by reductive elimination

Path **2** - SET to aryl halide along $S_{RN}1$ reaction pathway followed by propagation

Path **3** - Oxidation of Cu(I) followed by atom transfer and then C-N bond formation

Aryl Iodide Activation *via* Cu(I) Amidate



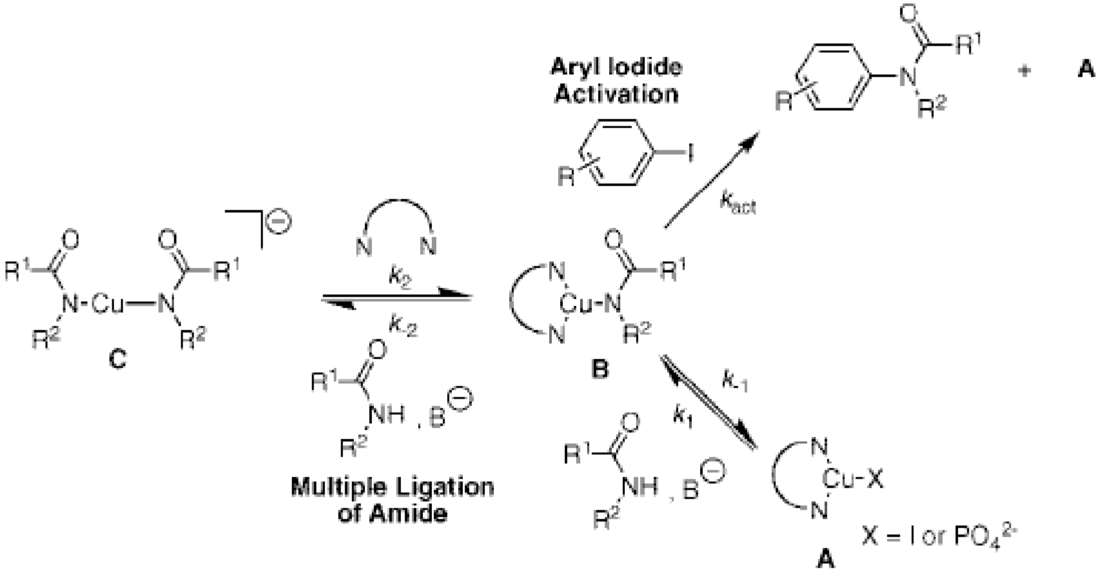
Hypotheses from this work:

Path **1**: aryl iodide/Cu(I) amidate coordination, SET, halide transfer then reductive elimination

Path **2**: aryl iodide coordination to Cu(I) amidate *via* an η^2 complex, oxidative addition to form Cu(III) amidate intermediate and finally reductive elimination

Huffman, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196 - (Cu(III) chemistry)
Zhang, S.-L.; Liu, L.; Fu, Y.; Guo, Q.-X. *Organometallics* **2007**, *26*, 4546 - (η^2 complex of Cu intermediate)

Key Observations in the Kinetics Study



Cu(I) amidate **B** exists in equilibrium with inactive intermediates **A** and **C**

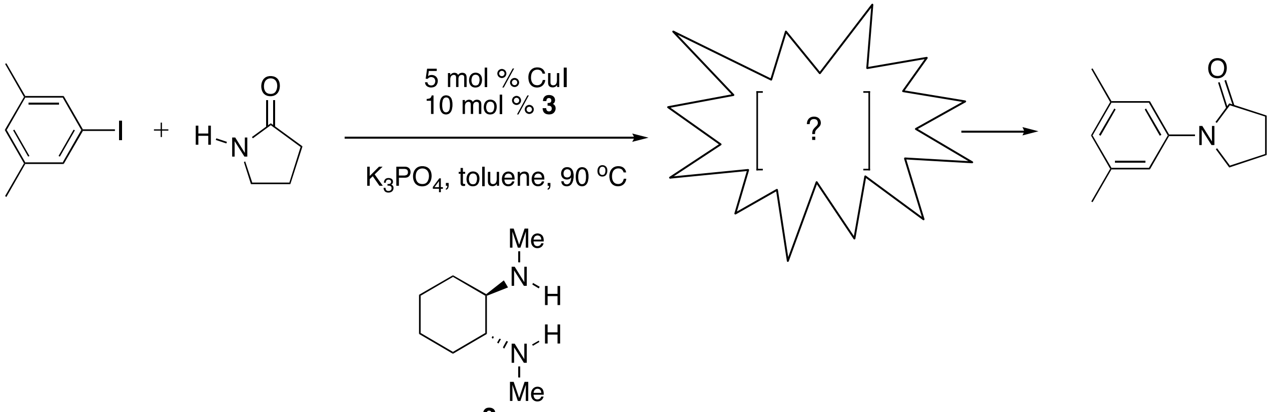
Equilibrium between **B** and **C** dominates over the equilibrium over **A** and **B** if [amine] is low

Increasing [amine] drives reaction to **B** in equilibrium with **A**

Intermediate such as **C** has been shown to be inactive towards aryl iodides (see also Hartwig *et al.*)

Strieter, E. R.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.*, **ASAP**
Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2008**, *130*, 9971

Conclusions: Why Is This Work Significant?



3

- In-depth study of the kinetics of copper-catalyzed aryl amidation
- Revealed key factors that control catalyst activity and reaction rates
- Results will greatly improve our understanding of key intermediates in copper catalysis
- Supports the formation of Cu(III) intermediates in catalytic cycle
- Experimentally, this work supports the predicted reaction intermediates (which is important)