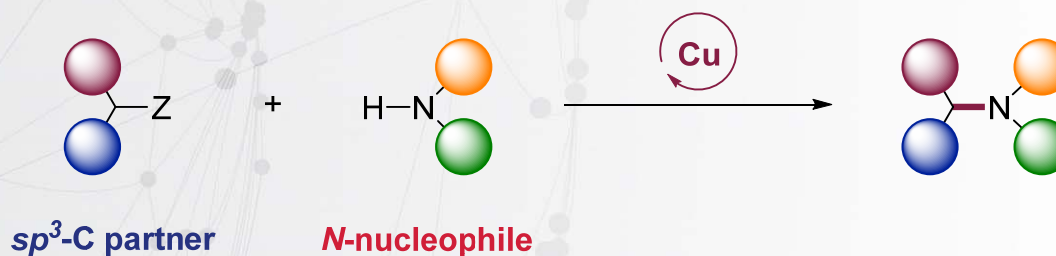


Copper-catalyzed Intermolecular Coupling of *N*-nucleophiles and C(*sp*³) Partners



Reporter: Qian Zhang
Supervisor: Prof. Shengming Ma
December 04, 2020



CONTENT

01 /

Background

02 /

$C(sp^3)$ -N Bond Formation

- alkyl halide
- C-H nucleophile
- Others

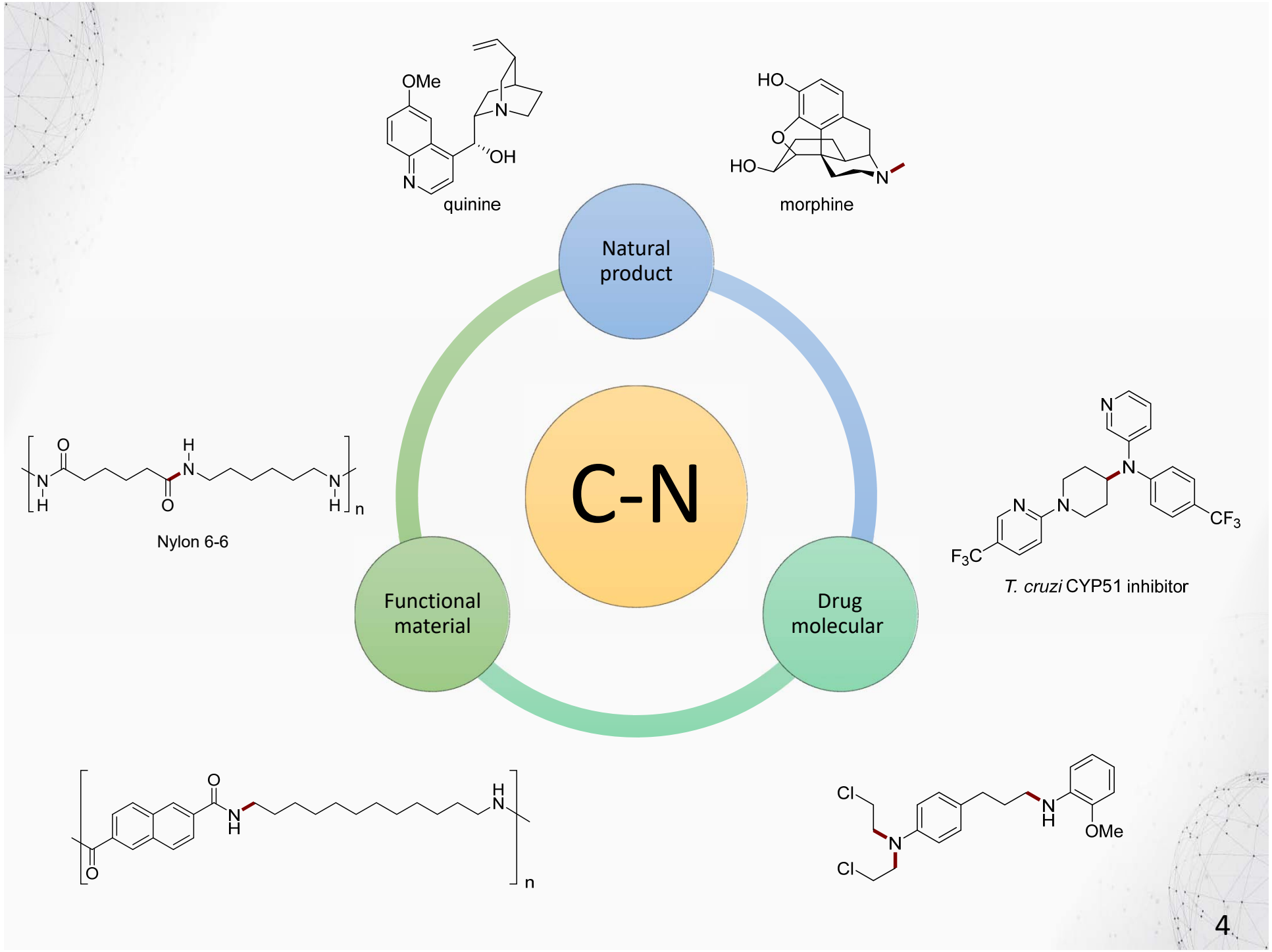
03 /

Summary and Prospect

The background features two large, semi-transparent circular logos of Fudan University, one on the left and one on the right. The logos contain the university's name in Chinese and English. A network of grey lines and dots is overlaid on the background, creating a digital or scientific aesthetic.

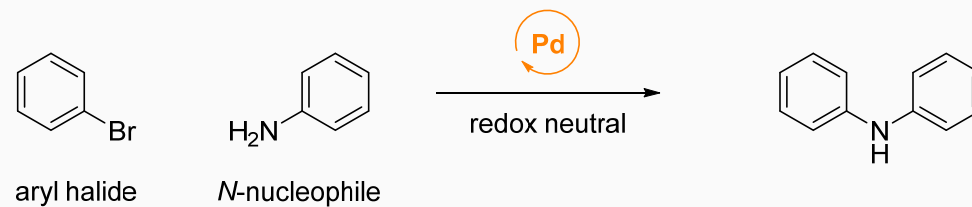
01

Background

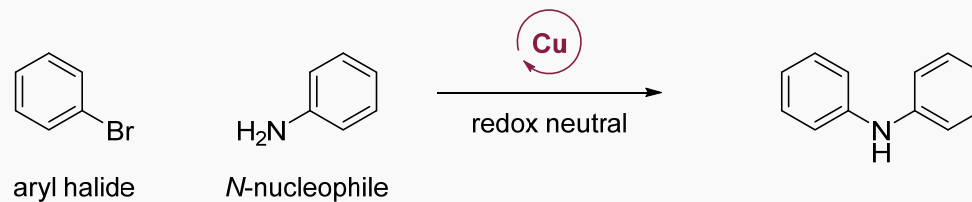


C(sp²)-N Bond Formation

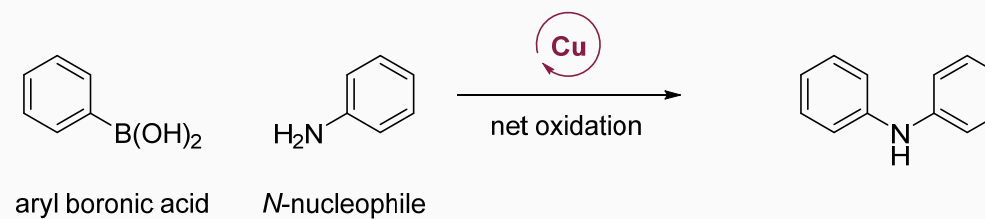
Buchwald-Hartwig reaction



Ullmann coupling



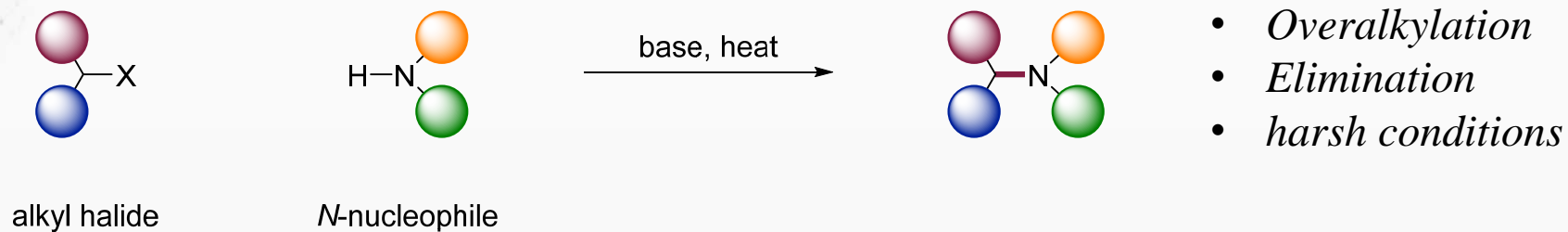
Chan-Evans-Lam coupling



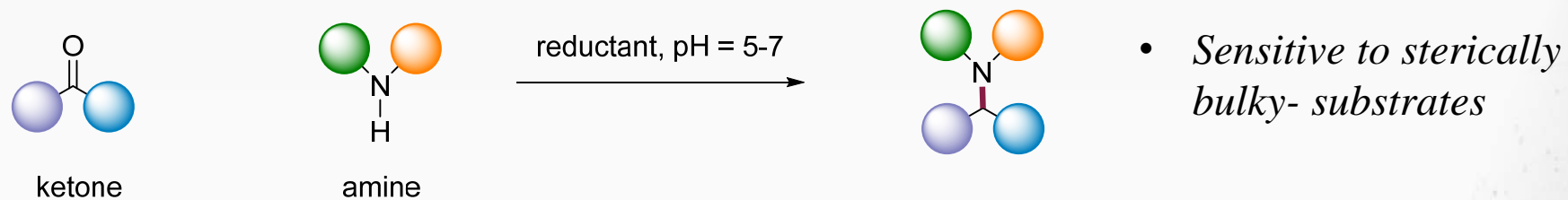
Buchwald, S. L. et al., *Chem. Rev.* **2016**, *116*, 12564.
Beletskaya, I. P. et al., *Organometallics* **2012**, *31*, 7753.

C(sp³)-N Bond Formation: Other Classic Methods

Classic S_N1 or S_N2 nucleophilic substitution



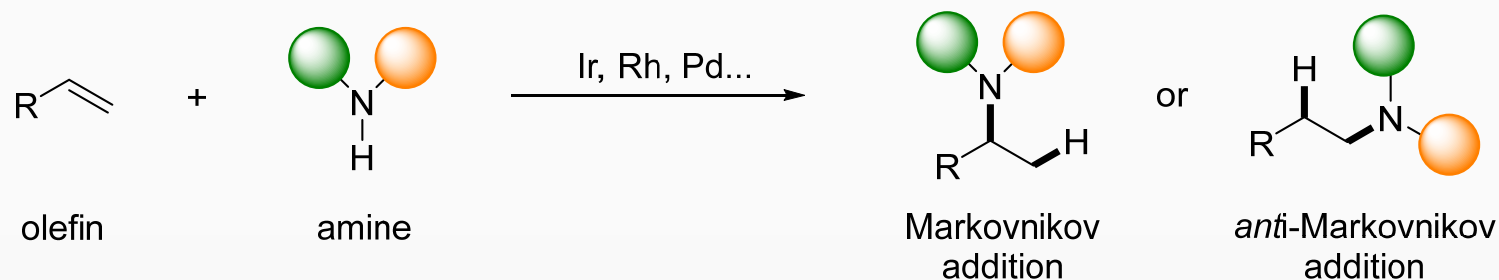
Reductive amination



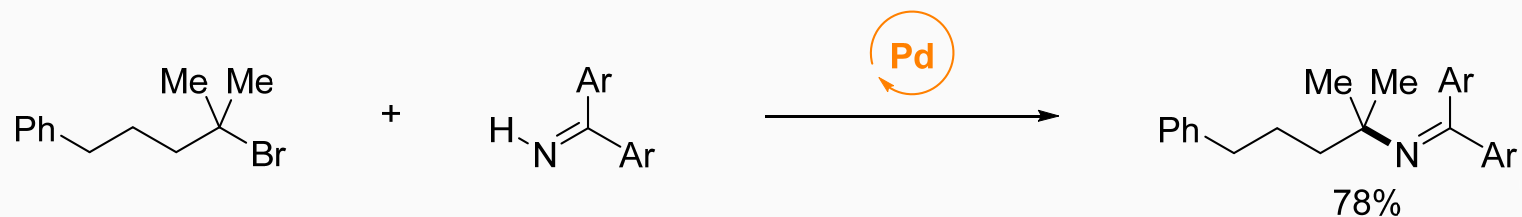
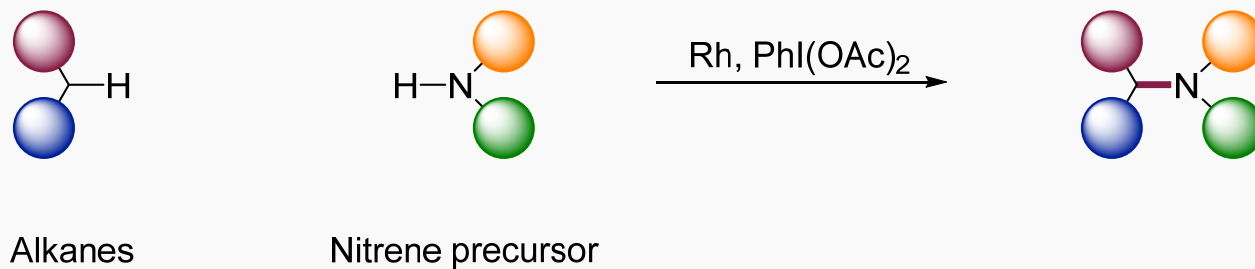
MacMillan, D. W. C. et al., *J. Am. Chem. Soc.* **2006**, *128*, 84
Chiba, S. et al., *ACS Catal.* **2017**, *7*, 4697.

C(sp³)-N Bond Formation: Other Transition Metal

Hydroamination of olefins



Nitrene insertion of C-H bond



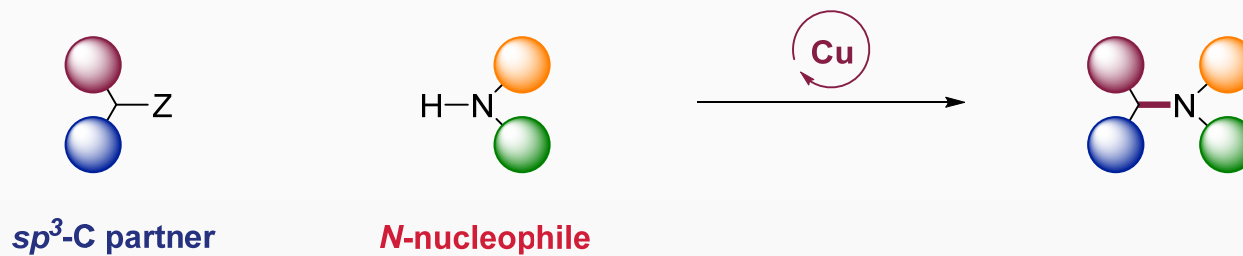
Hartwig, J. F. et al., *J. Am. Chem. Soc.* **2014**, *136*, 3200.

Hull, K. L. et al., *J. Am. Chem. Soc.* **2015**, *137*, 13748.

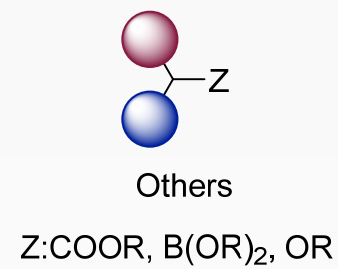
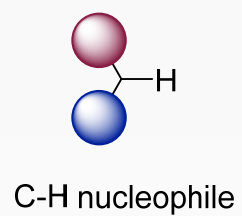
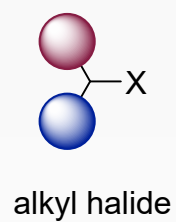
Gaunt, M. J. et al., *Chem. Rev.* **2020**, *120*, 2613.

Hartwig, J. F. et al., *ACS Cent. Sci.* **2016**, *2*, 647.

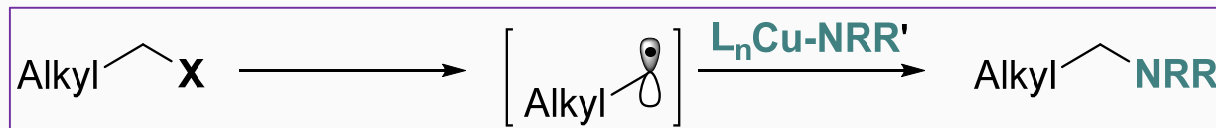
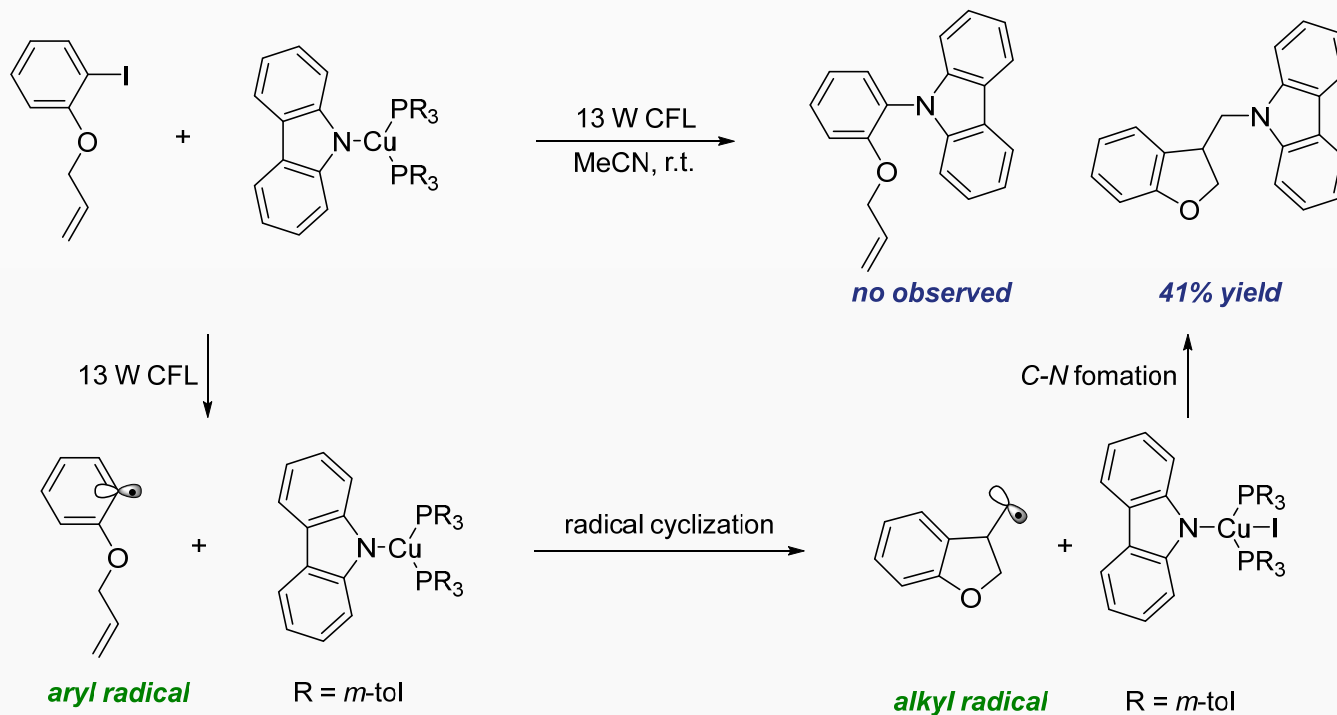
Copper-catalyzed Intermolecular Coupling of *N*-nucleophiles and $C(sp^3)$ Partners



Coupling partners

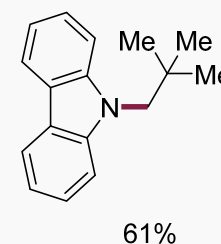
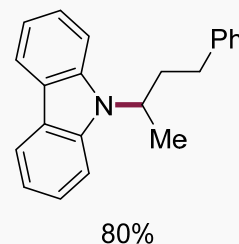
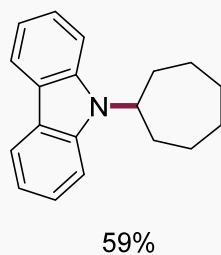
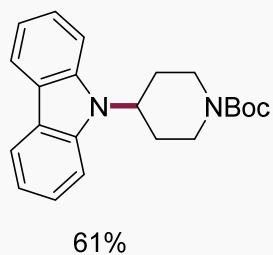
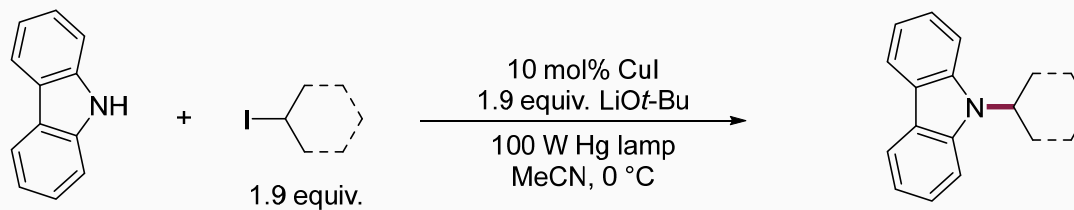


Inspiration of Copper-Catalyzed C(sp³)-N Bond Formation using Alkyl Halides

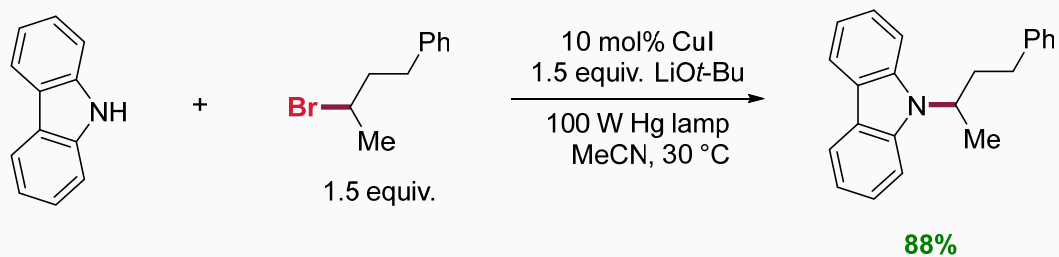


Copper-Catalyzed C(sp³)-N Bond Formation using Alkyl Halides

N-alkylation of carbazoles

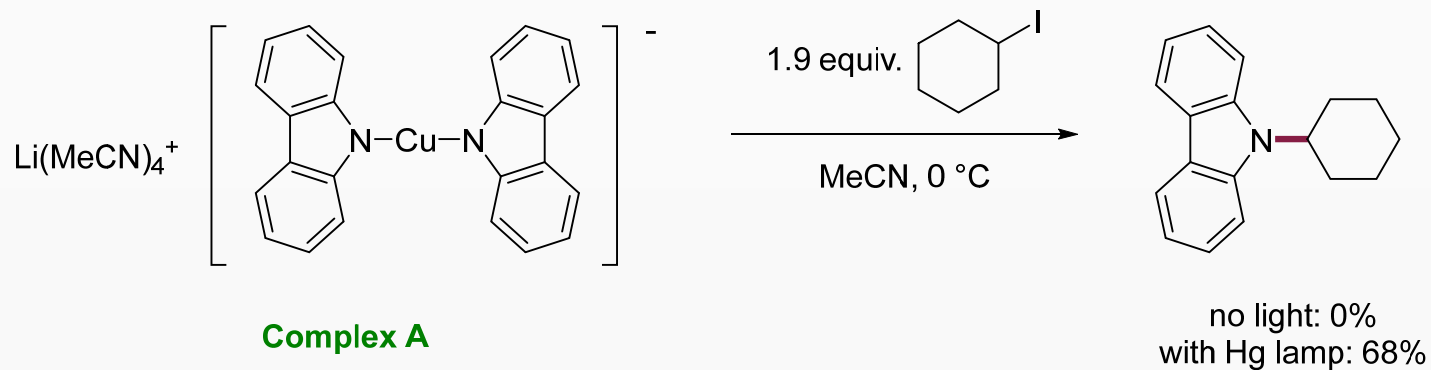


Alkyl bromide as electrophile



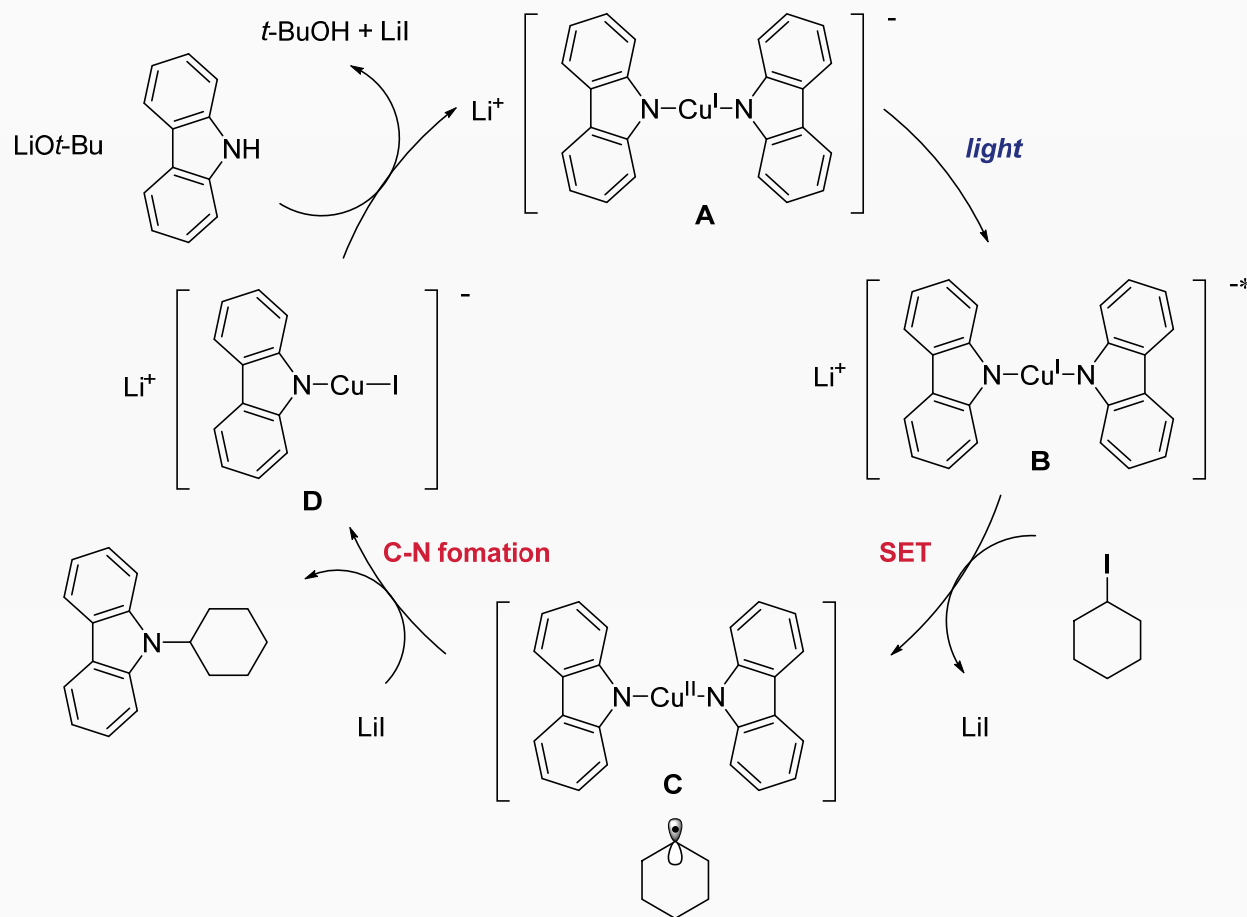
Copper-Catalyzed C(sp³)-N Bond Formation using Alkyl Halides

Mechanistic studies



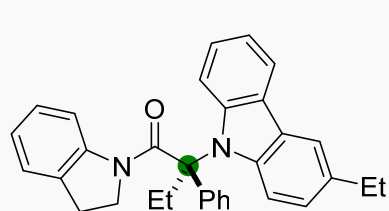
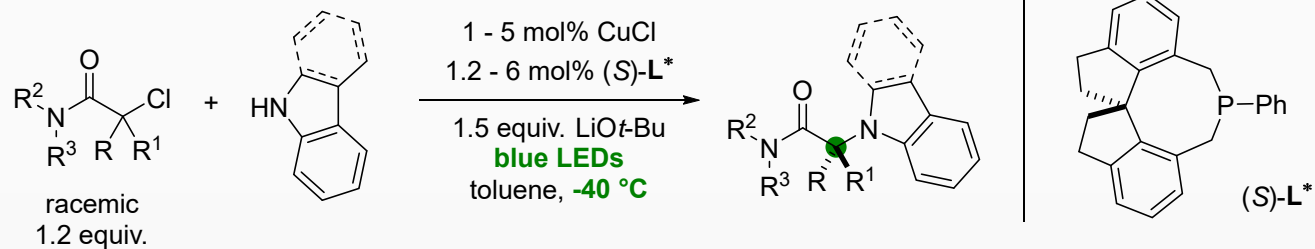
Copper-Catalyzed C(sp³)-N Bond Formation using Alkyl Halides

One possible catalytic cycle

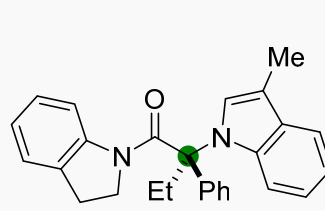


Copper-Catalyzed C(sp³)-N Bond Formation using Alkyl Halides

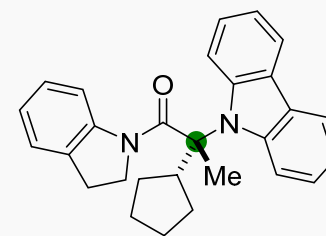
Enantioselective alkylation with tertiary alkyl chlorides



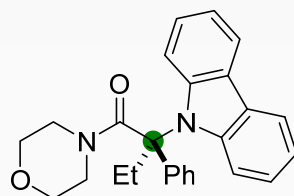
95%, **92%ee**



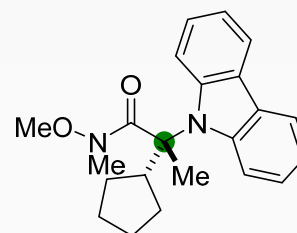
79%, **92%ee**



84%, **98%ee**



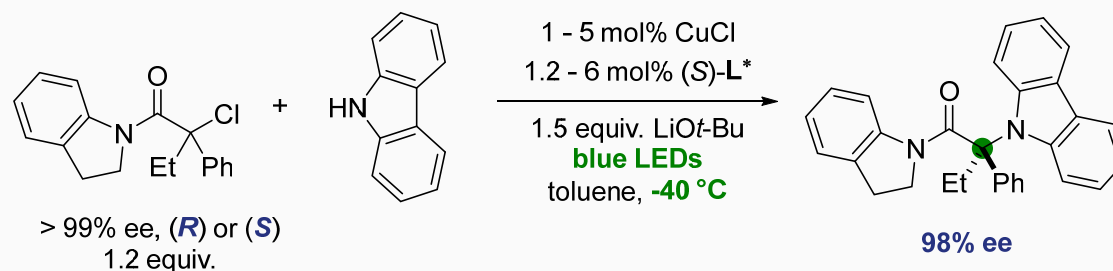
74%, **90%ee**



73%, **95%ee**

Copper-Catalyzed C(sp³)-N Bond Formation using Alkyl Halides

Mechanistic studies



unreacted electrophile

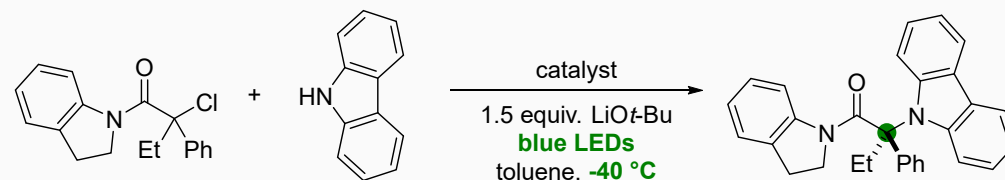
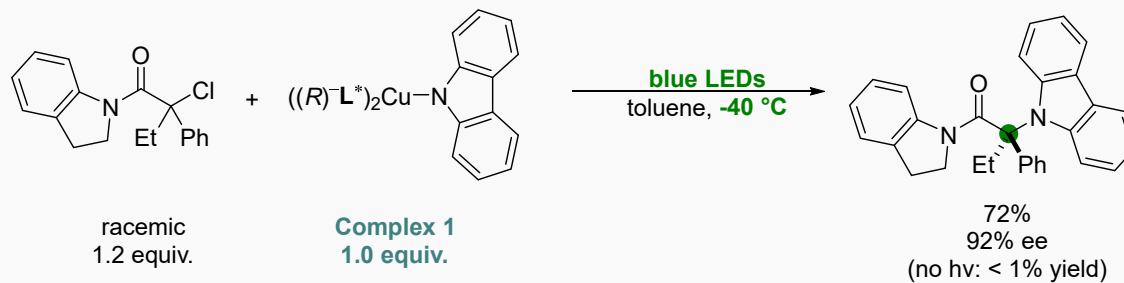
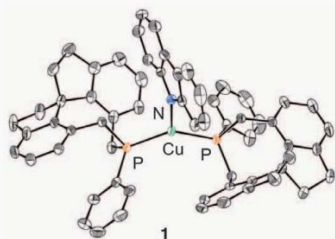
product

98% ee (*S*)

95%, 98% ee

98% ee (*R*)

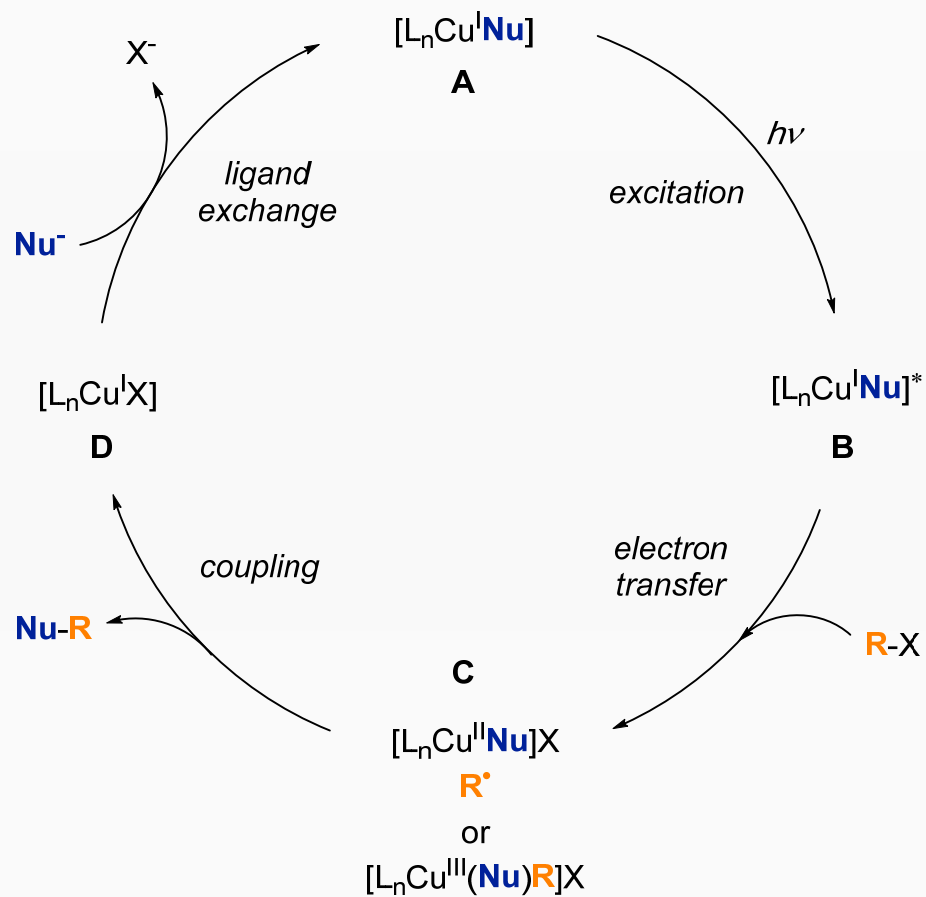
96%, 98% ee



1 mol% CuCl	95%, ee 95%
1.2 mol% L*:	
1 mol% Complex 1 :	92%, ee 94%

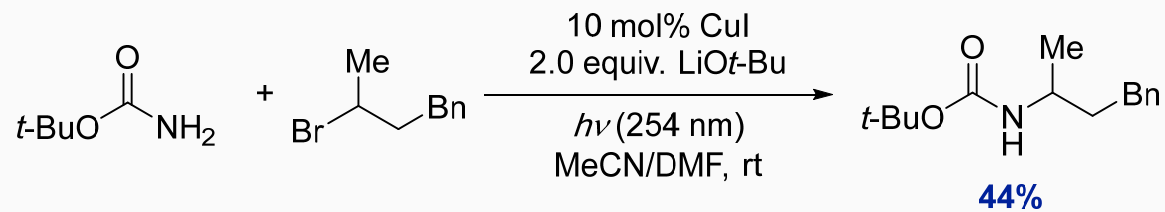
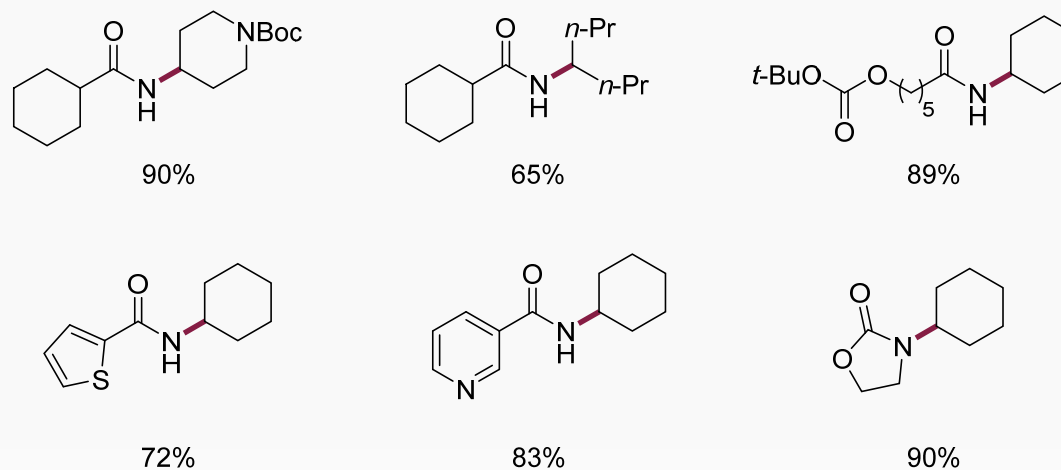
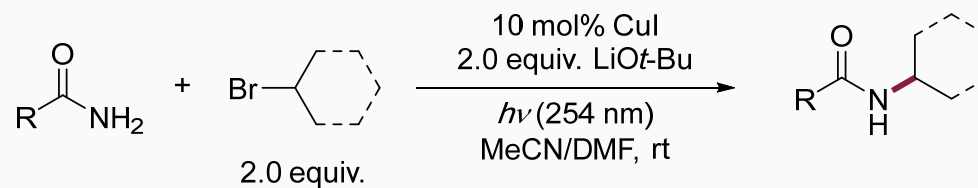
Copper-Catalyzed C(sp³)-N Bond Formation using Alkyl Halides

A possible pathway



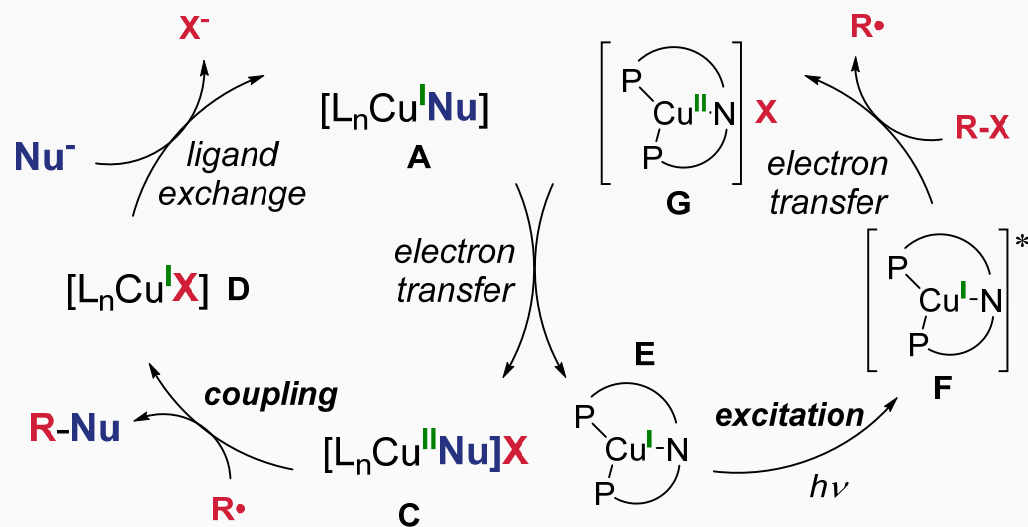
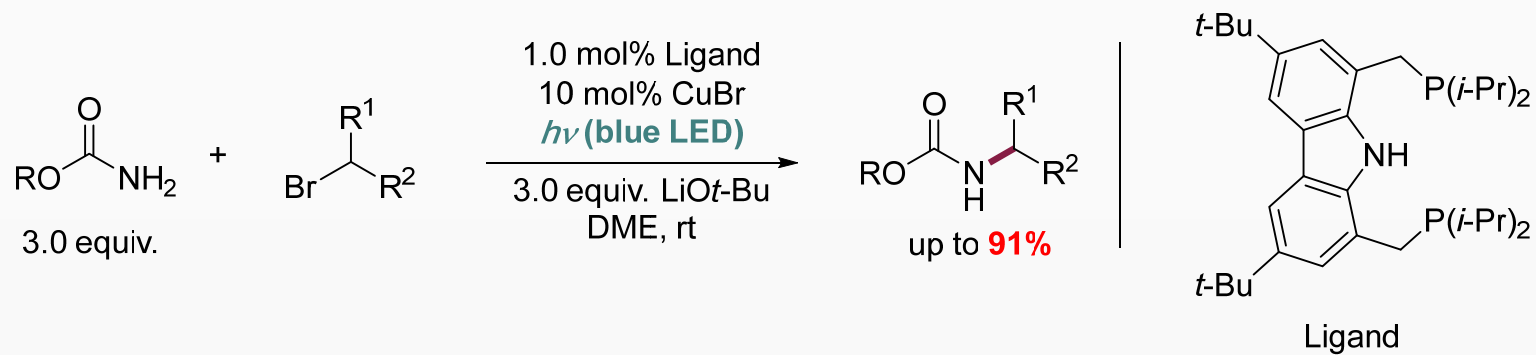
Copper-Catalyzed C(sp³)-N Bond Formation using Alkyl Halides

N-alkylation of amides



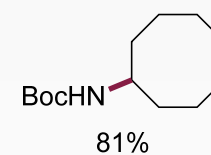
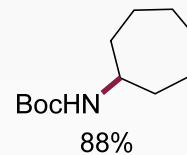
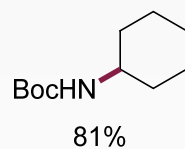
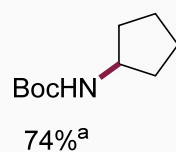
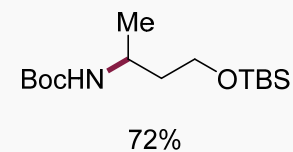
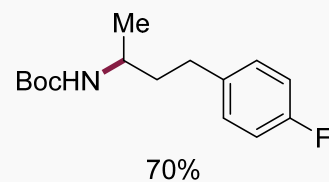
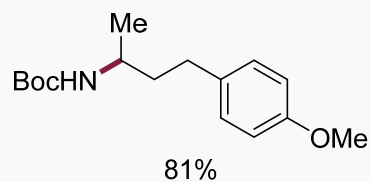
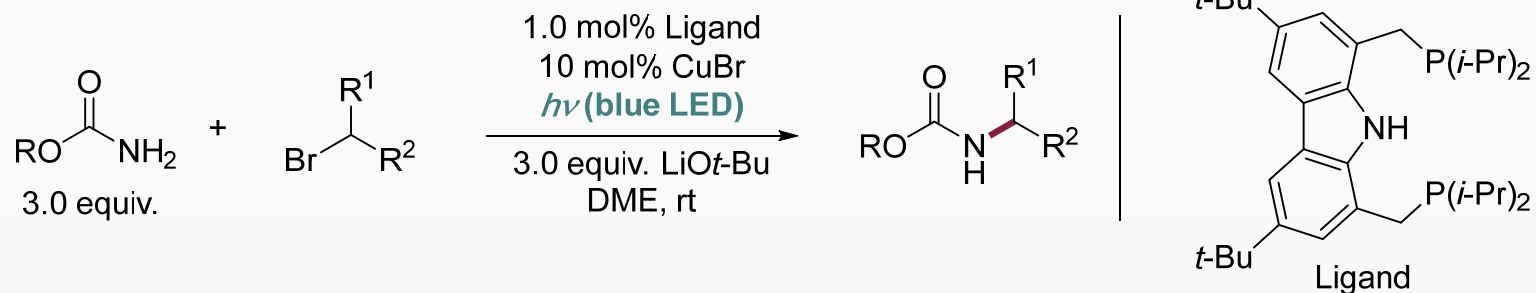
Copper-Catalyzed C(sp³)-N Bond Formation using Alkyl Halides

N-alkylation of carbamates



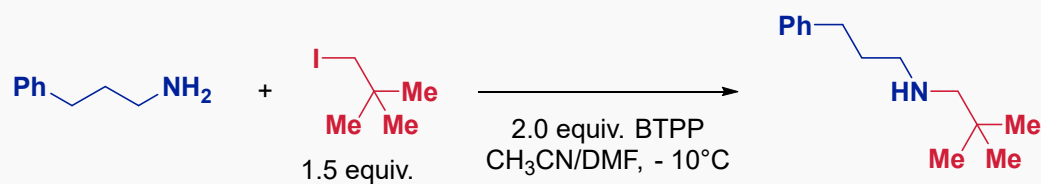
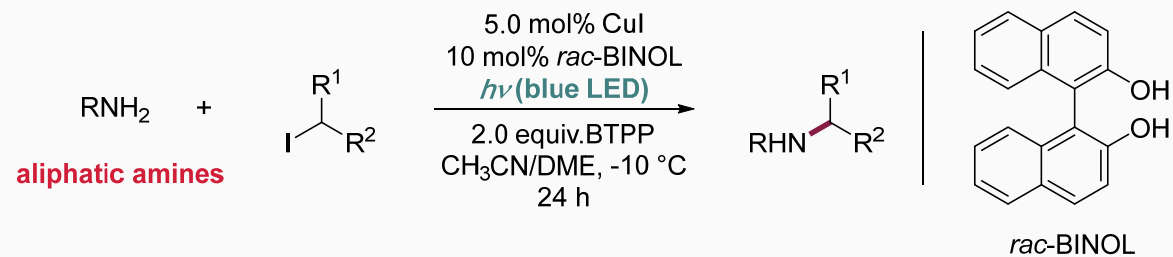
Copper-Catalyzed C(sp³)-N Bond Formation using Alkyl Halides

N-alkylation of carbamates



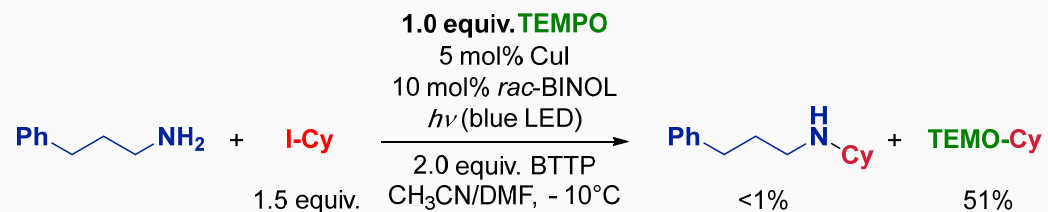
a: Hg lamp irradiated.

Copper-Catalyzed C(sp³)-N Bond Formation using Alkyl Halides

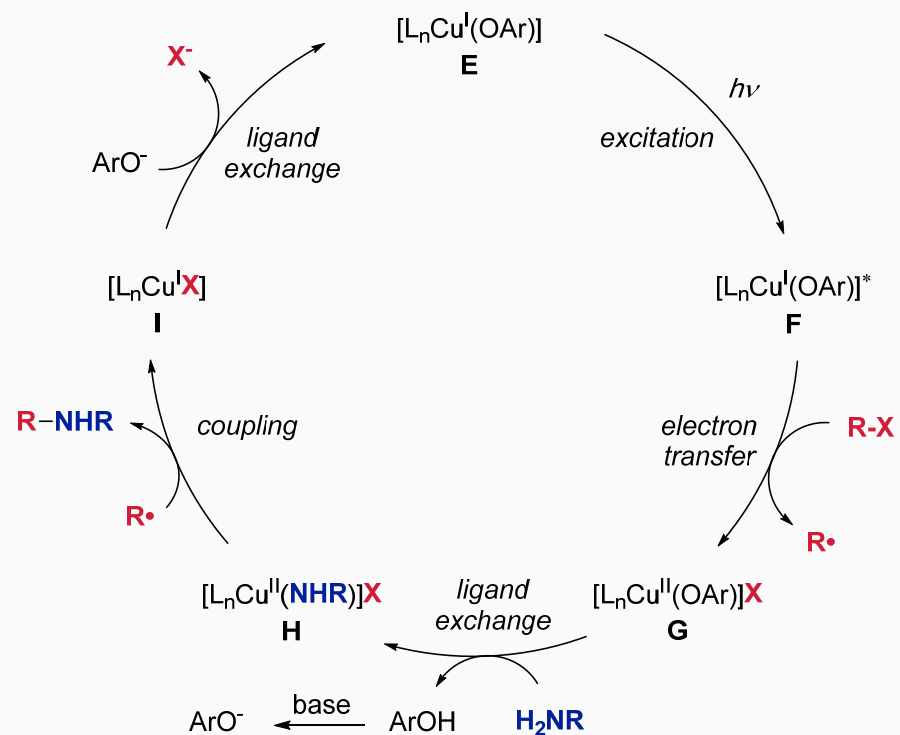


conditions	yield
-10 °C	<1%
100 °C	4%
10 mol% CuI, 20 mol% <i>rac</i> -BINOL $h\nu$ (blue LED), -10 °C	70%
10 mol% CuI, 20 mol% <i>rac</i> -BINOL, 100 °C	4%

Copper-Catalyzed C(sp³)-N Bond Formation using Alkyl Halides

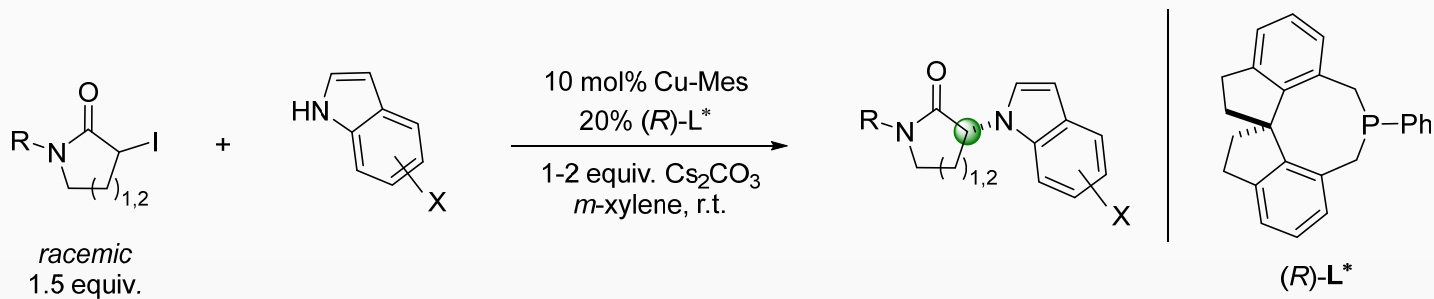


A possible pathway

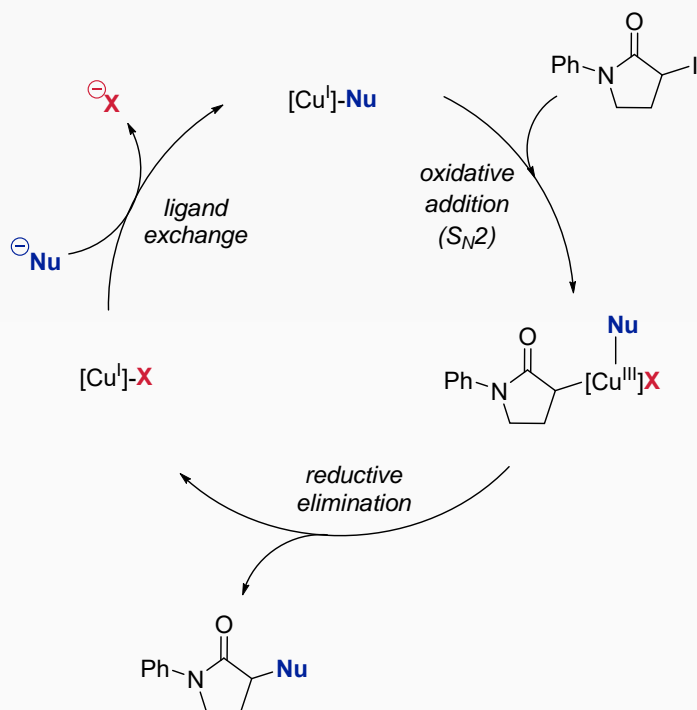


Copper-Catalyzed C(sp³)-N Bond Formation using Alkyl Halides

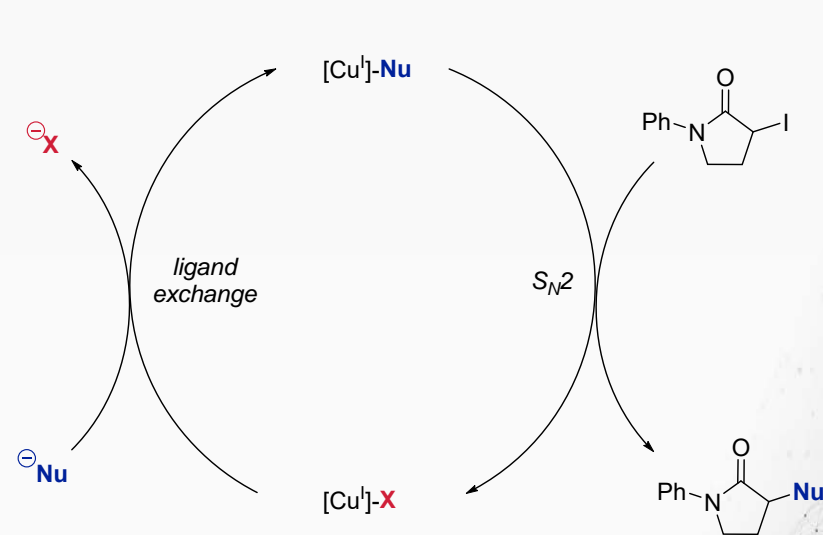
Alkylation by secondary alkyl iodides in the *absence of light*



Nucleophilic substitution by **copper**

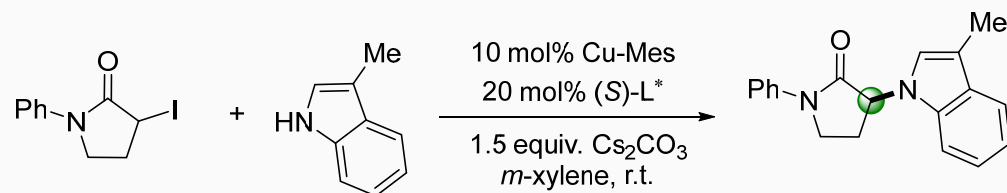


Nucleophilic substitution by **nitrogen**

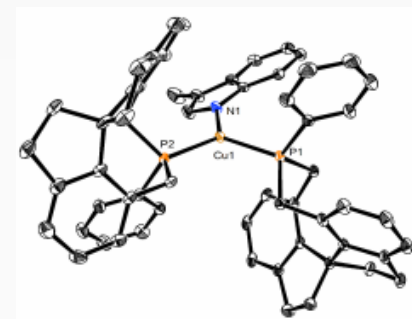
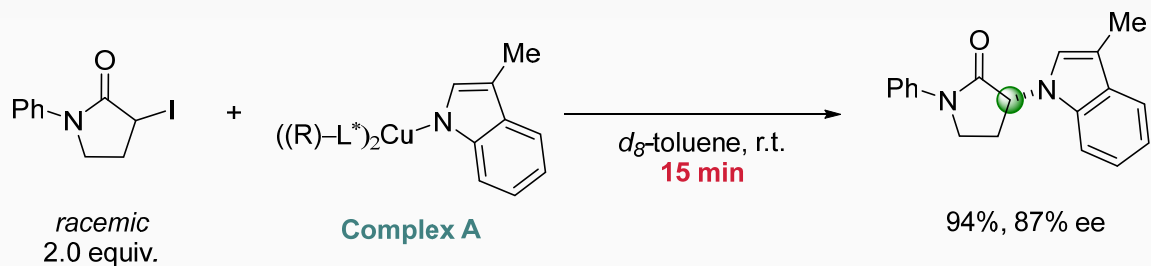
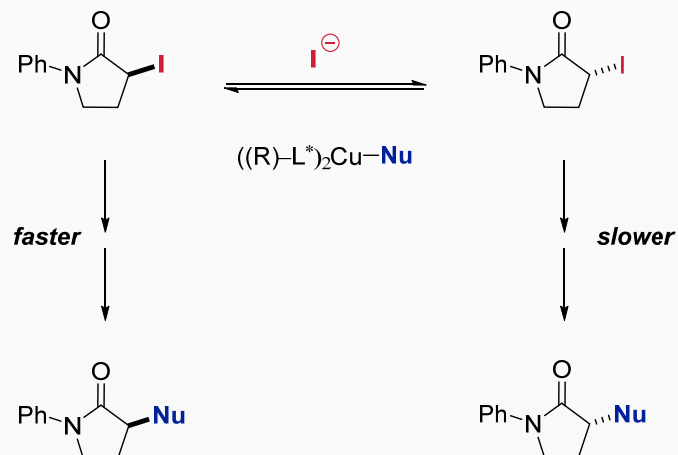
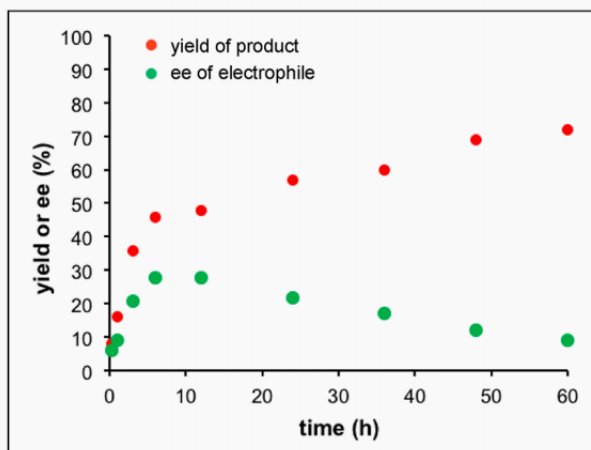


Fu, G. C. et al., *J. Am. Chem. Soc.* **2019**, *141*, 14864.

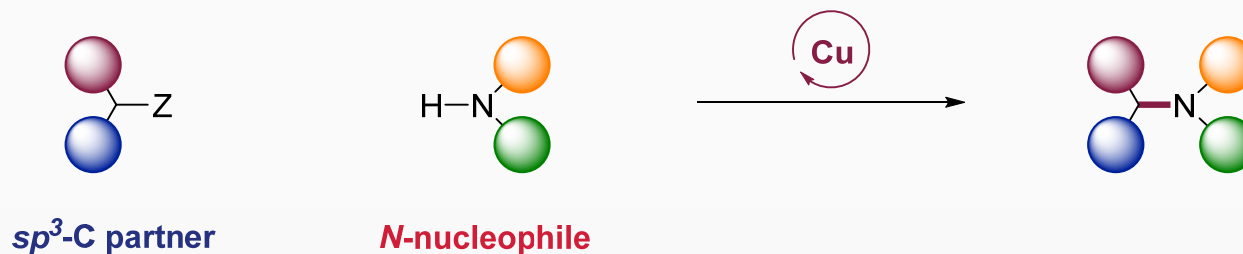
Copper-Catalyzed C(sp³)-N Bond Formation using Alkyl Halides



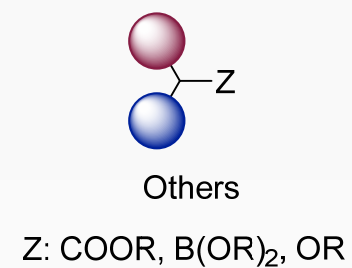
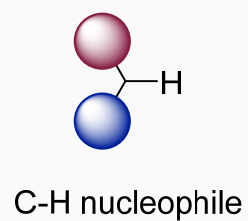
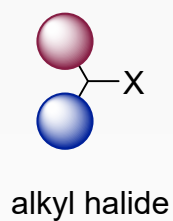
racemic
1.5 equiv.



Copper-catalyzed Intermolecular Coupling of *N*-nucleophiles and $C(sp^3)$ Partners

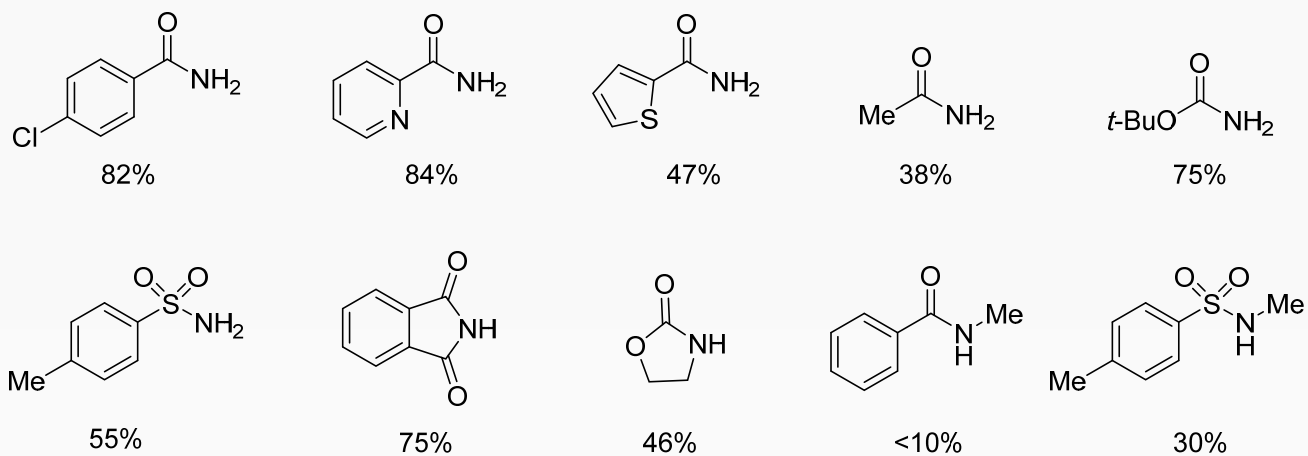
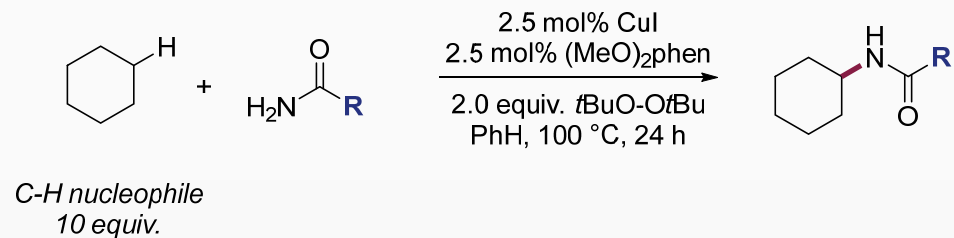


Coupling partners



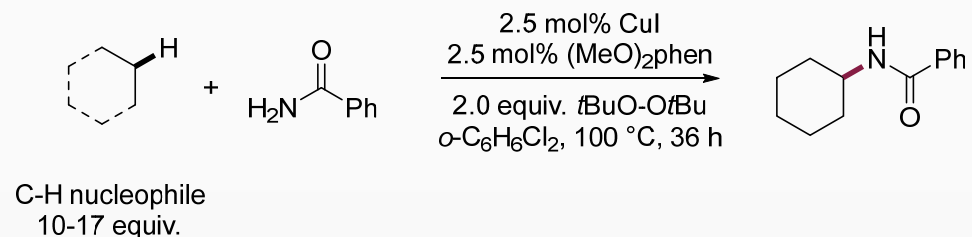
Copper-Catalyzed C(sp³)-N Bond Formation using C-H Nucleophiles

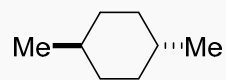
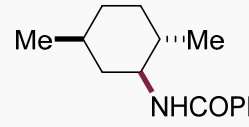
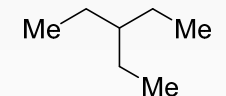
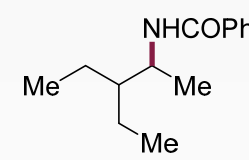
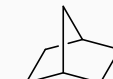

Seminal report from Prof. John Hartwig



Copper-Catalyzed C(*sp*³)-N Bond Formation using C-H Nucleophiles

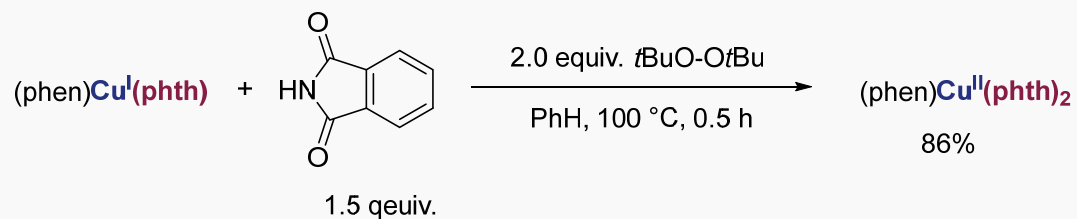
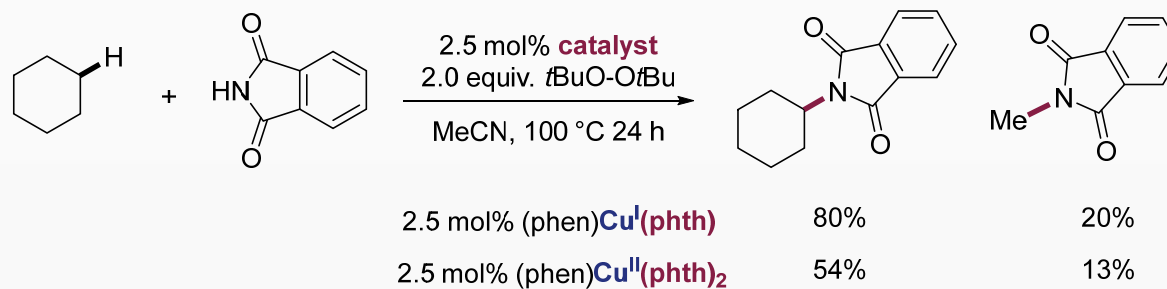
C-H nucleophile scope



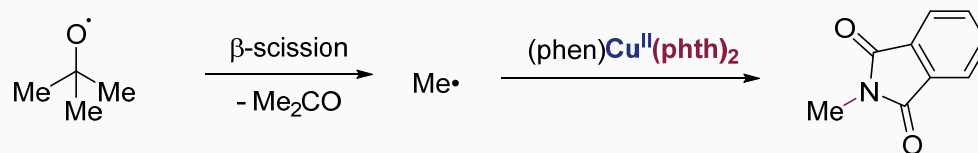
substrate	product	isolated yield
		69% > 10:1 r.r.
		54% 2:1 r.r.
		81% > 10:1 d.r.

Copper-Catalyzed C(sp³)-N Bond Formation using C-H Nucleophiles

Mechanistic studies: using preformed copper(I) and copper(II) complexes

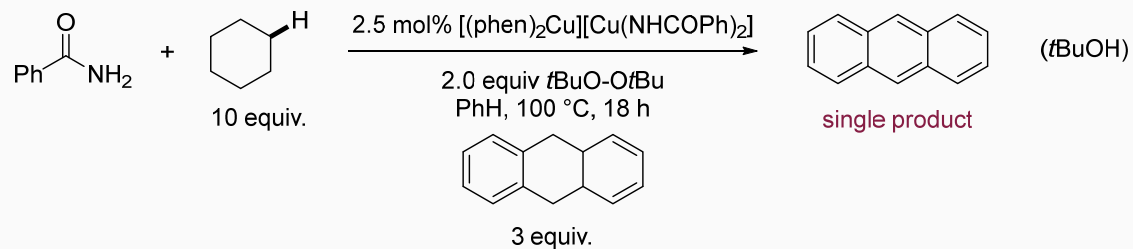


Formation of the N-Me side product: β -scission of tBuO[•] radical

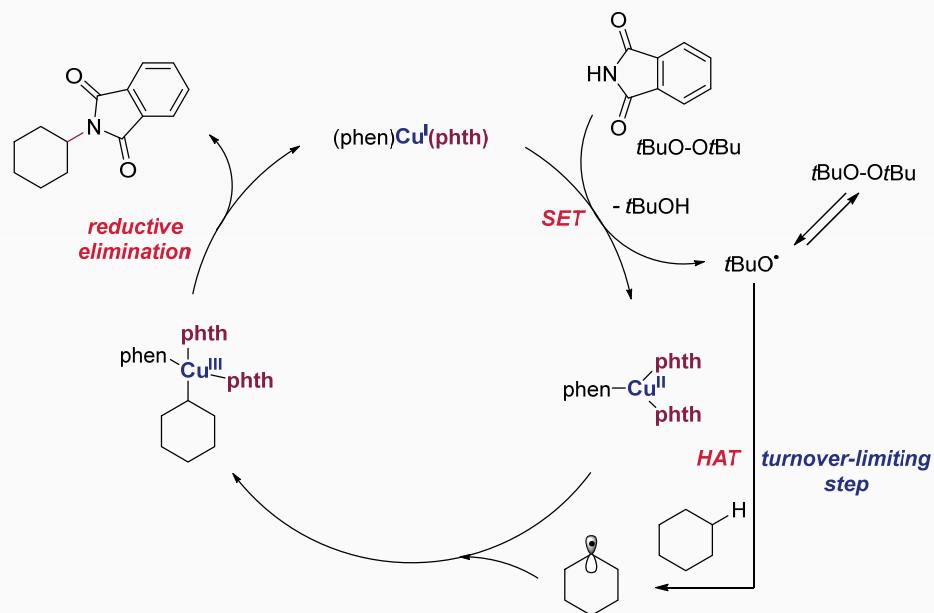


Copper-Catalyzed C(sp³)-N Bond Formation using C-H Nucleophiles

Radical trapping experiments:

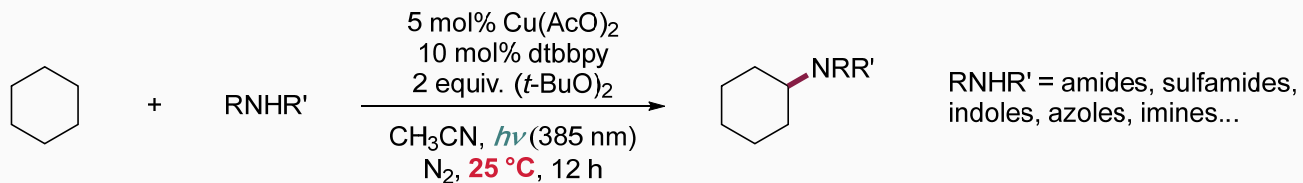


Proposed mechanism

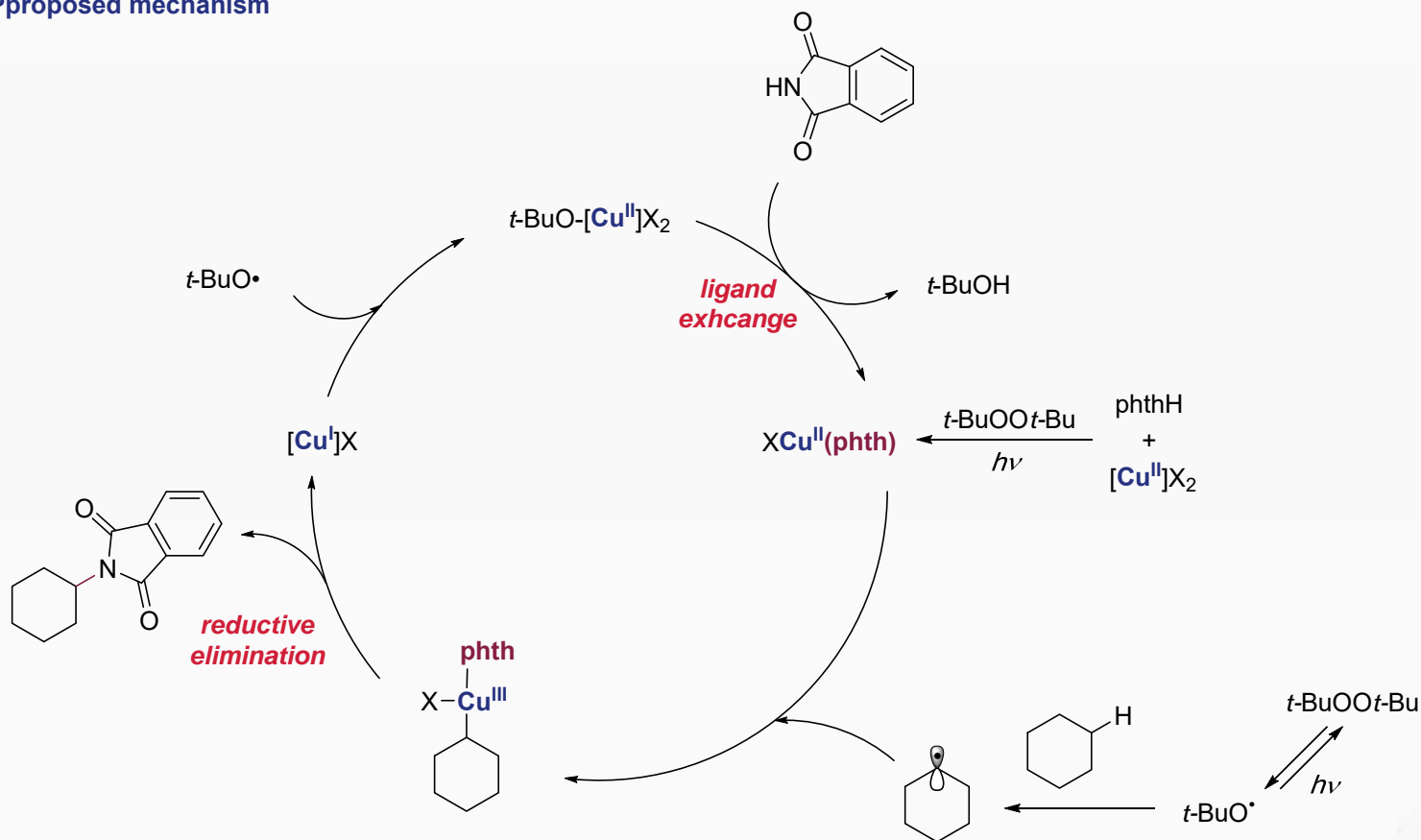


Hartwig, J. F. et al., *J. Am. Chem. Soc.* **2014**, *136*, 2555.

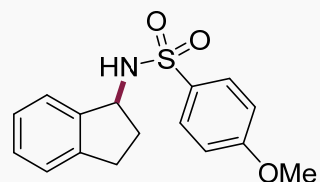
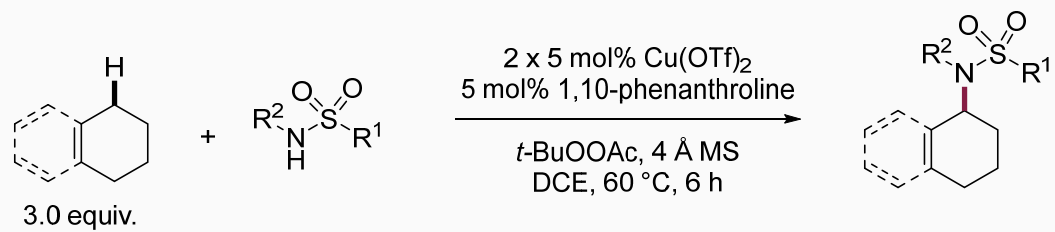
Copper-Catalyzed C(sp³)-N Bond Formation using C-H Nucleophiles



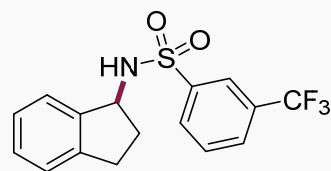
Proposed mechanism



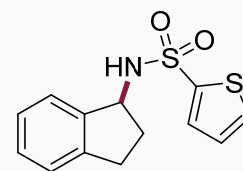
Copper-Catalyzed C(sp³)-N Bond Formation using C-H Nucleophiles



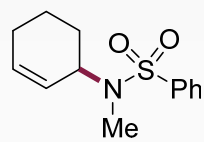
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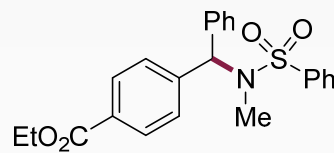
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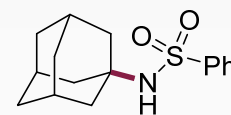
67%



61%



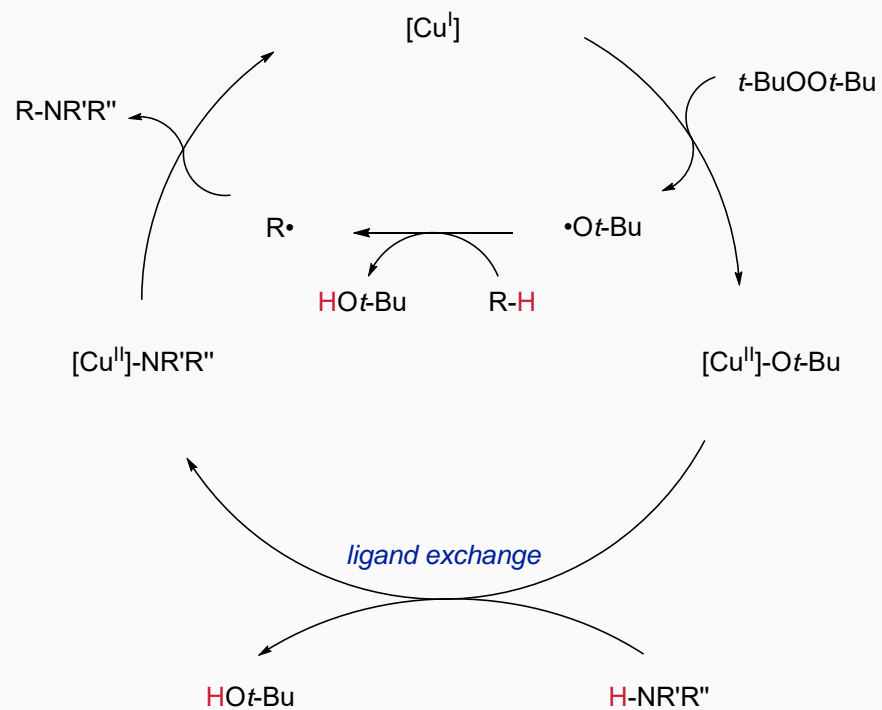
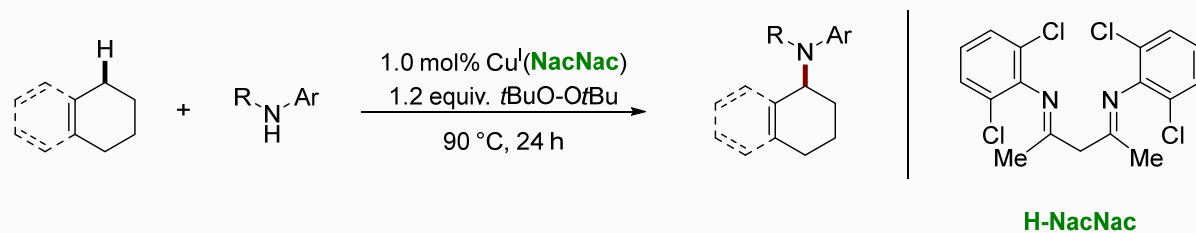
50%



56%
>95% r.r.

Copper-Catalyzed C(sp³)-N Bond Formation using C-H Nucleophiles

Benzylic and allylic C-H amination



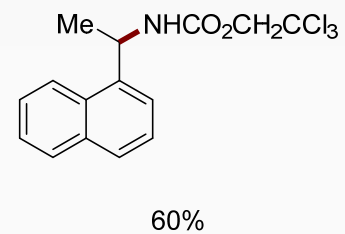
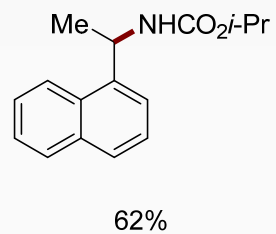
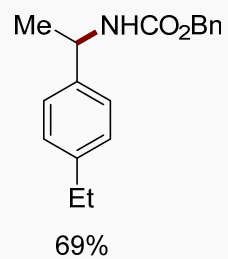
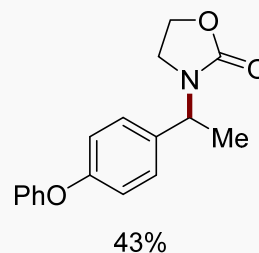
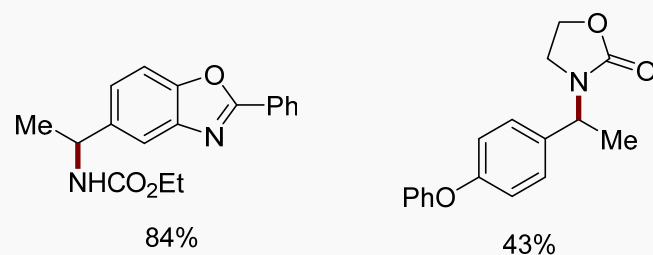
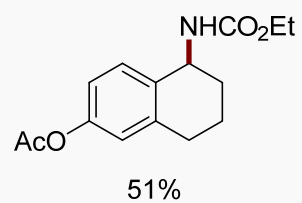
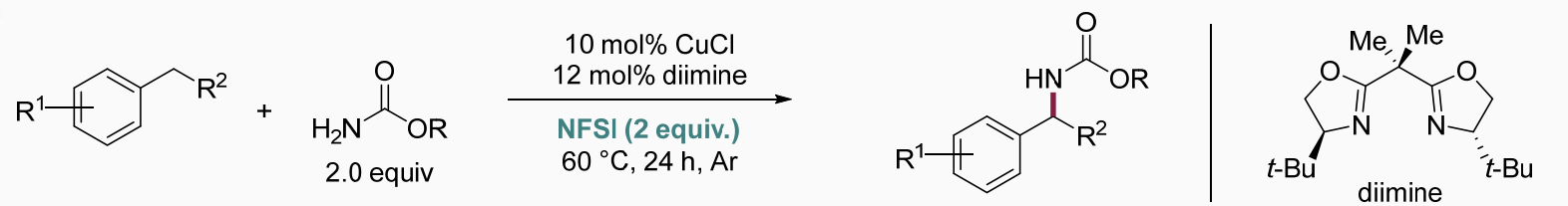
Warren, T. H. et al., *Angew. Chem. Int. Ed.* **2010**, *49*, 8850.

Warren, T. H. et al., *Angew. Chem. Int. Ed.* **2012**, *51*, 6488.

Warren, T. H. et al., *J. Am. Chem. Soc.* **2014**, *136*, 10930.

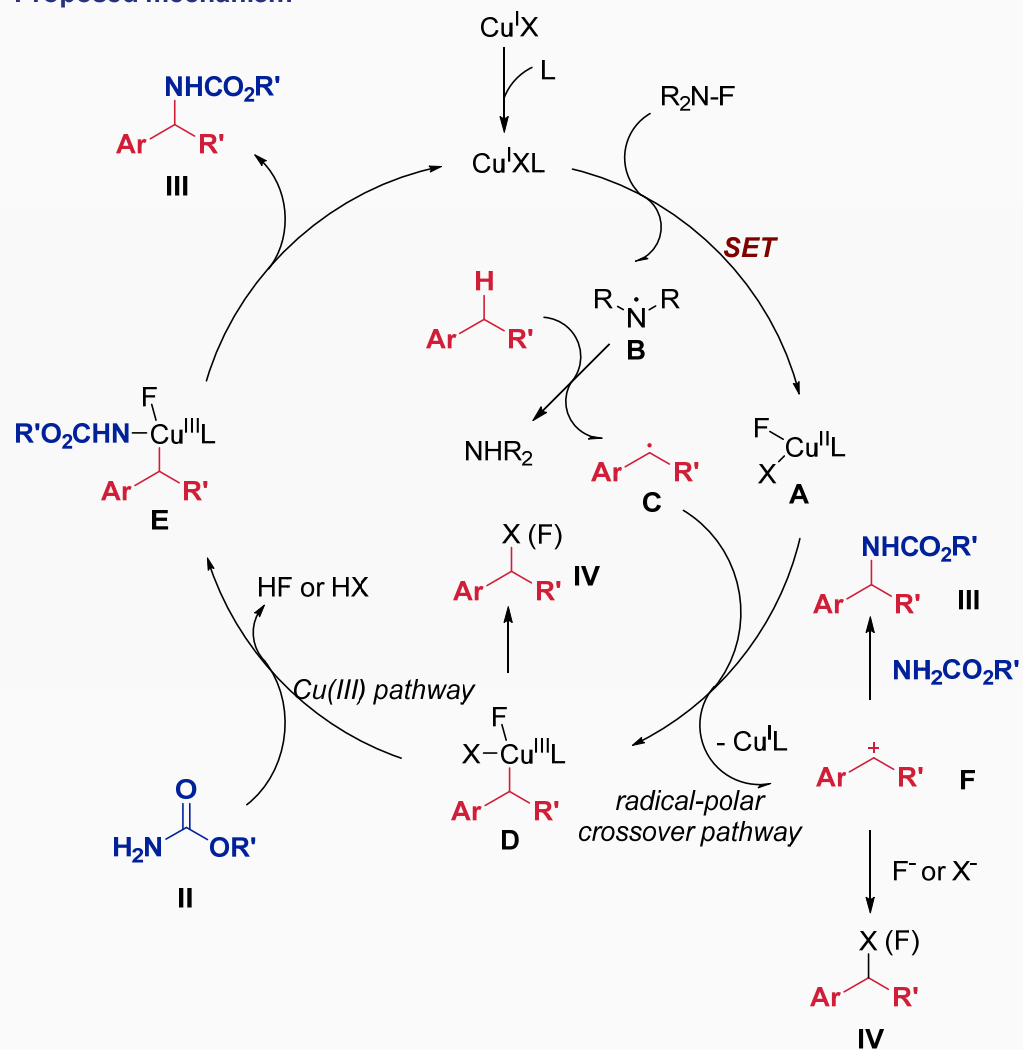
Copper-Catalyzed C(*sp*³)-N Bond Formation using C-H Nucleophiles

Benzylic C-H amination



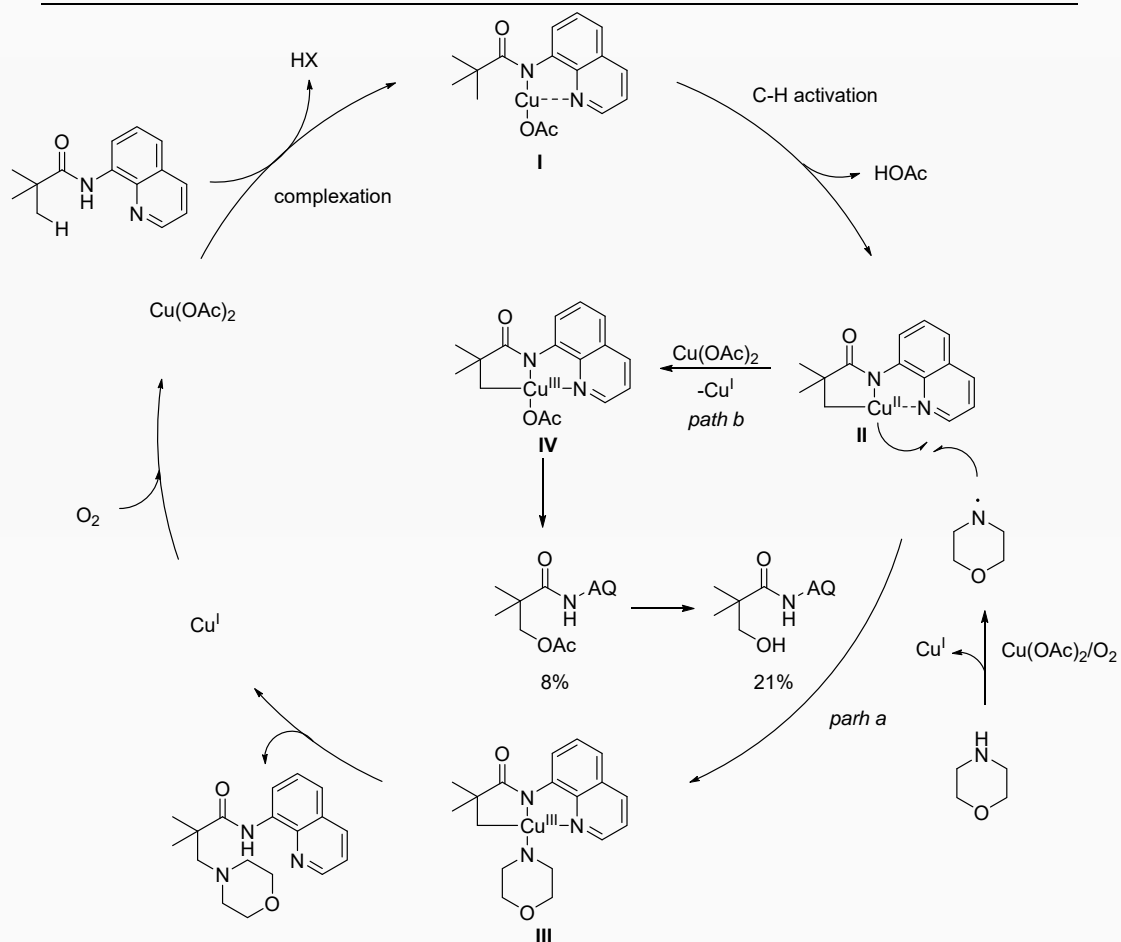
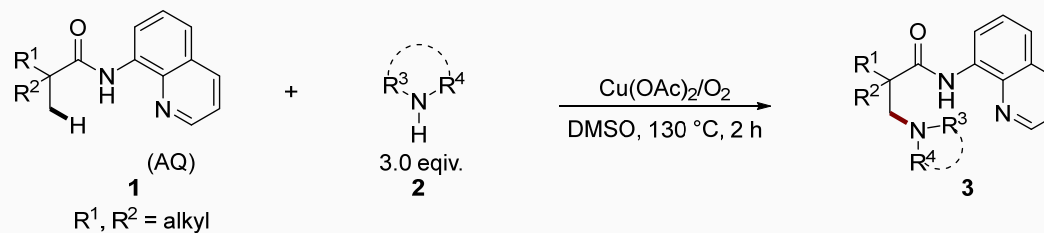
Copper-Catalyzed C(sp³)-N Bond Formation using C-H Nucleophiles

Proposed mechanism



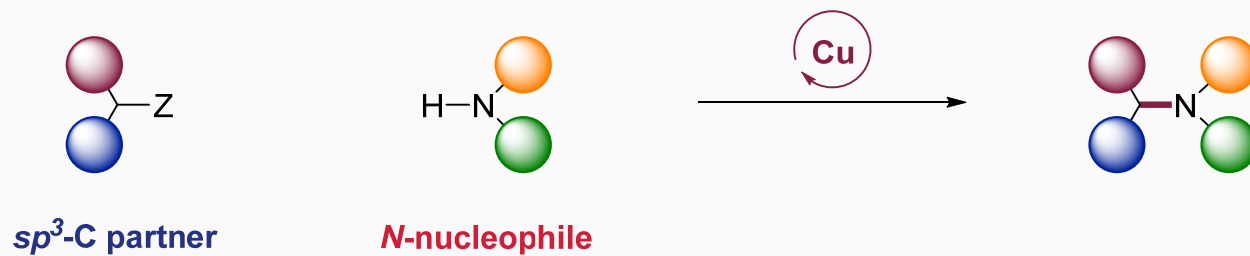
Copper-Catalyzed C(sp³)-N Bond Formation using C-H Nucleophiles

C(sp³)-H Bonds with Cyclic Alkylamines

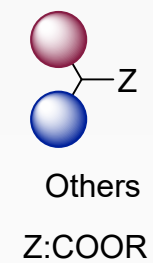
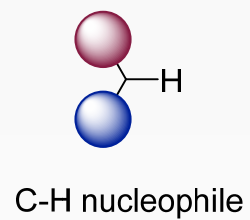
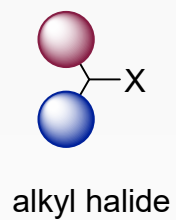


Qin, J. et al., *Chem. Eur. J.* **2016**, *22*, 16057.

Copper-catalyzed Intermolecular Coupling of *N*-nucleophiles and $C(sp^3)$ Partners

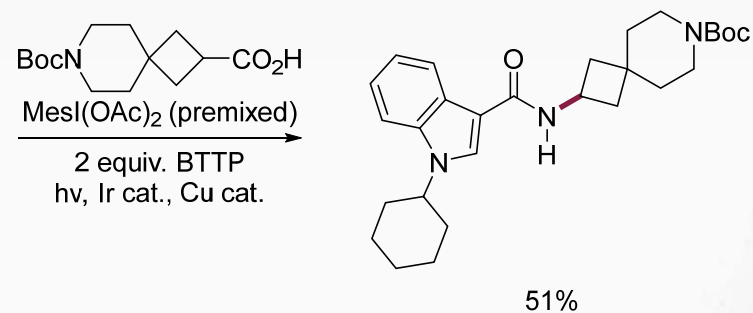
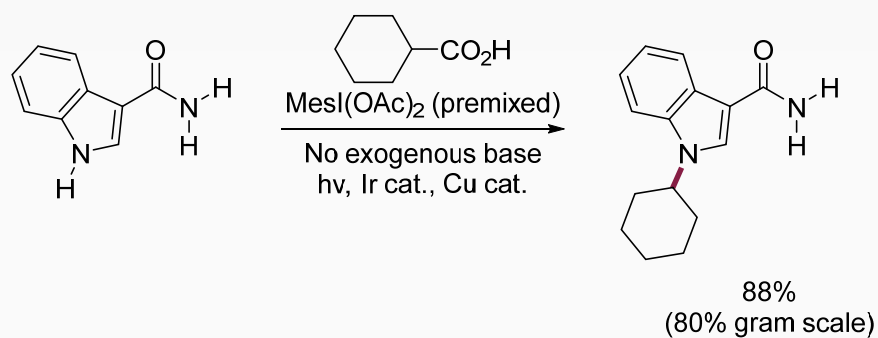
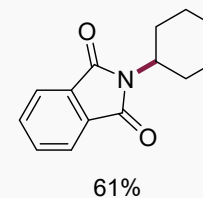
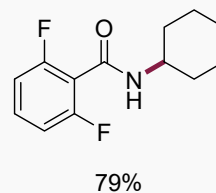
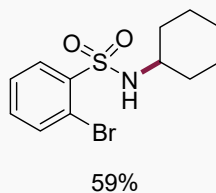
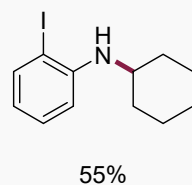
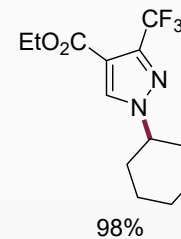
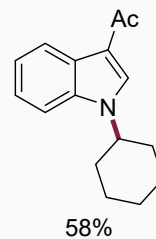
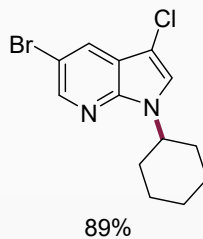
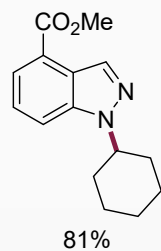


Coupling partners



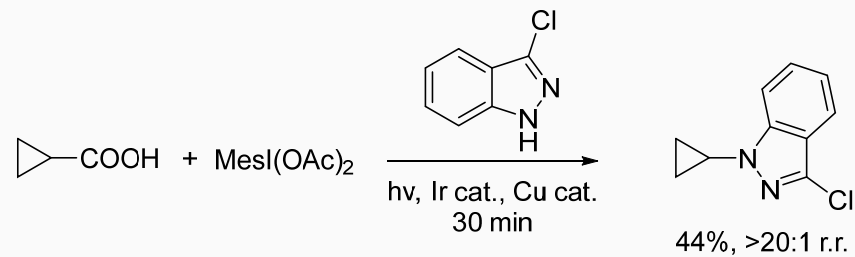
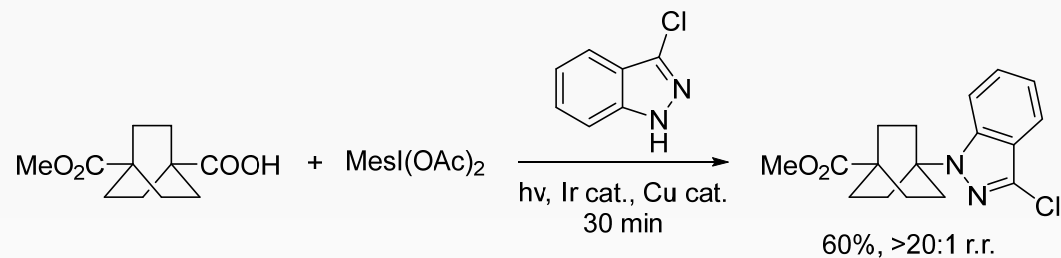
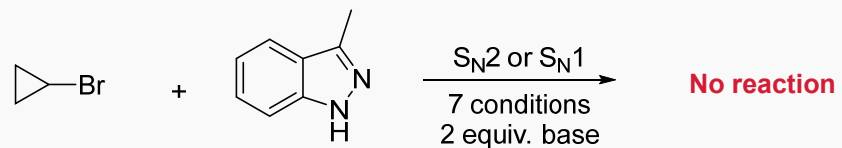
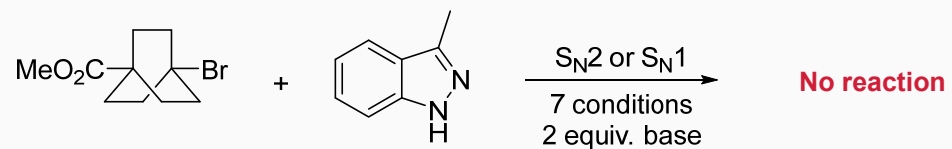
Copper-Catalyzed C(sp³)-N Bond Formation using Carboxylic Acids

Scope of nitrogen nucleophiles:



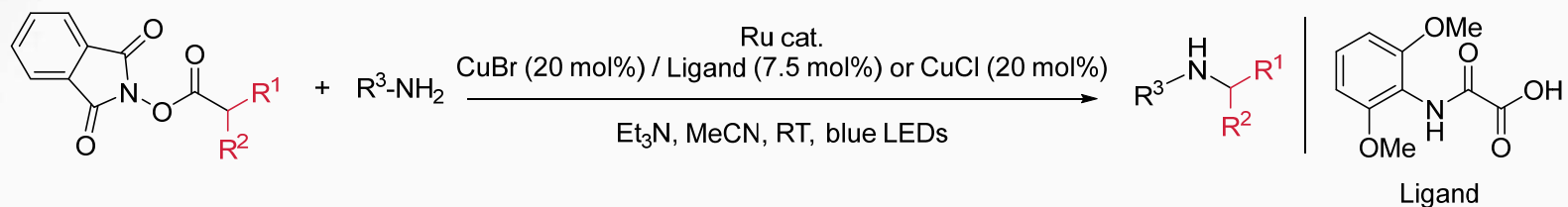
Copper-Catalyzed C(sp³)-N Bond Formation using Carboxylic Acids

Compare classic S_N2 and S_N1 reaction with this protocol

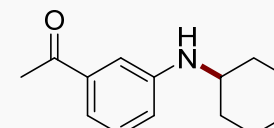
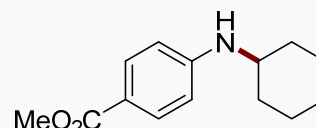
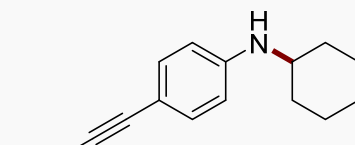
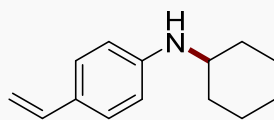
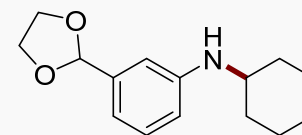
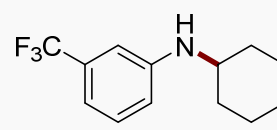
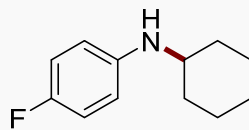
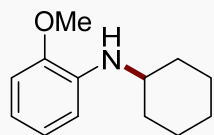


Copper-Catalyzed C(sp³)-N Bond Formation using Carboxylic Acids

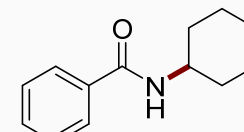
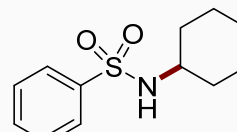
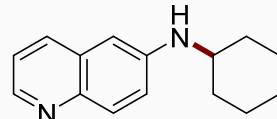
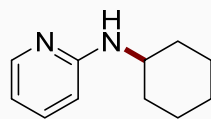
Decarboxylative C(sp³)-N cross-coupling



Anilines:

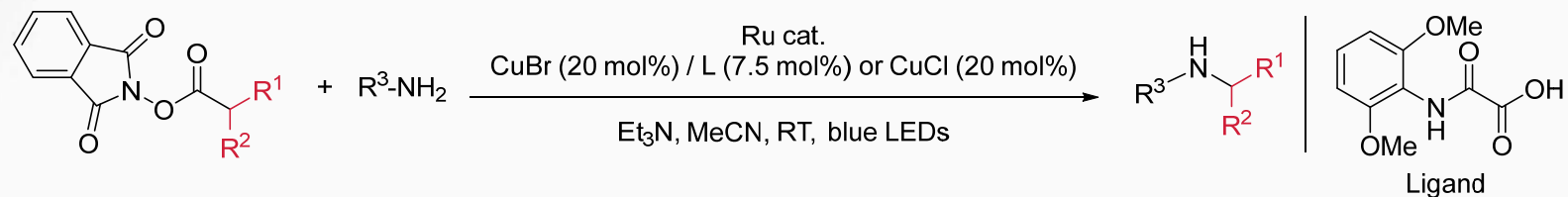


Other nitrogen nucleophiles:

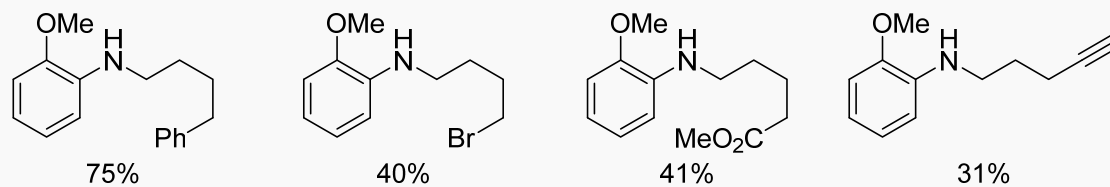


Copper-Catalyzed C(sp³)-N Bond Formation using Carboxylic Acids

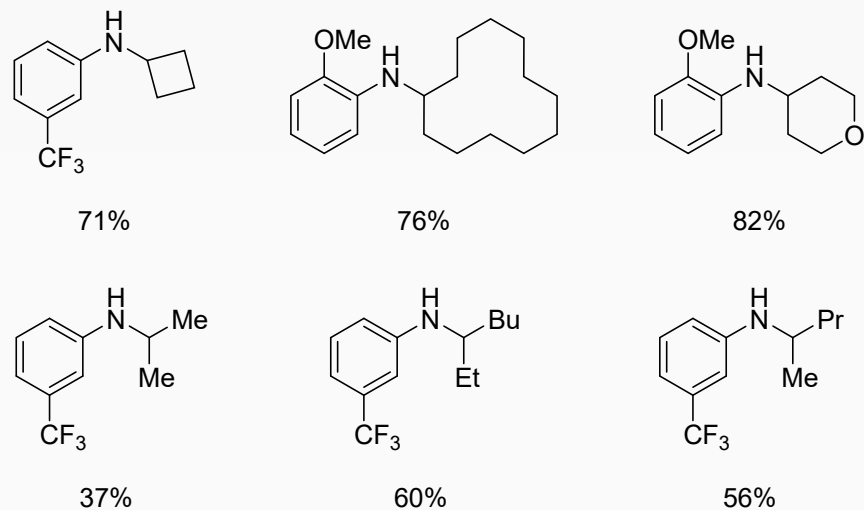
Decarboxylative C(sp³)-N cross-coupling



Primary acids:

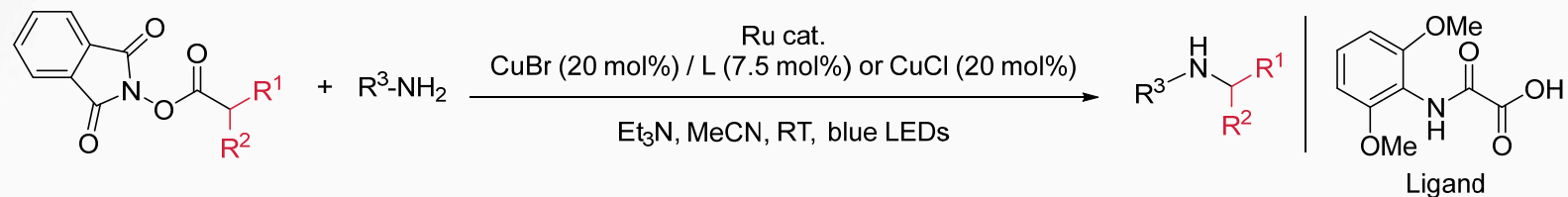


Secondary acids:

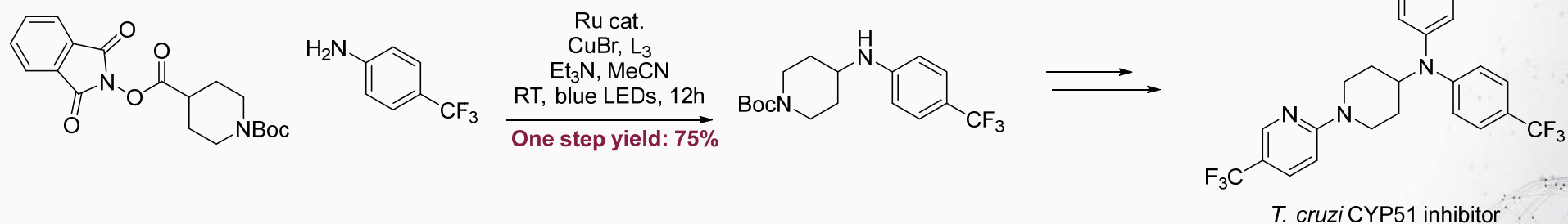
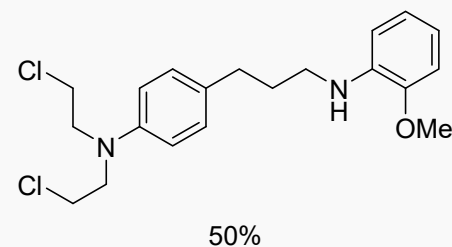
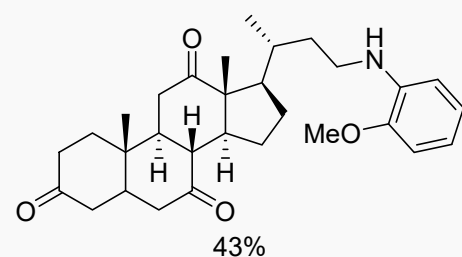


Copper-Catalyzed C(sp³)-N Bond Formation using Carboxylic Acids

Decarboxylative C(sp³)-N cross-coupling

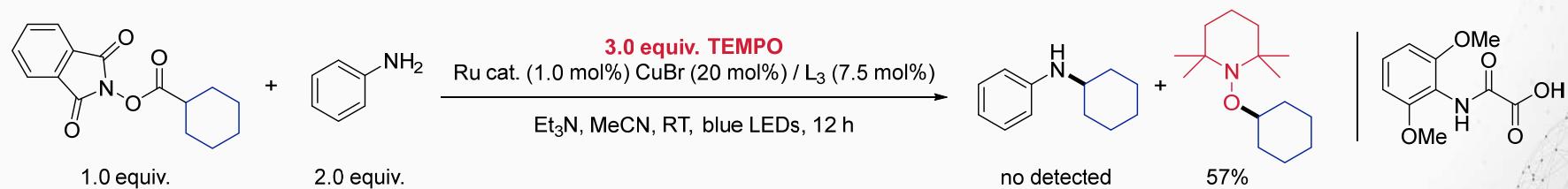
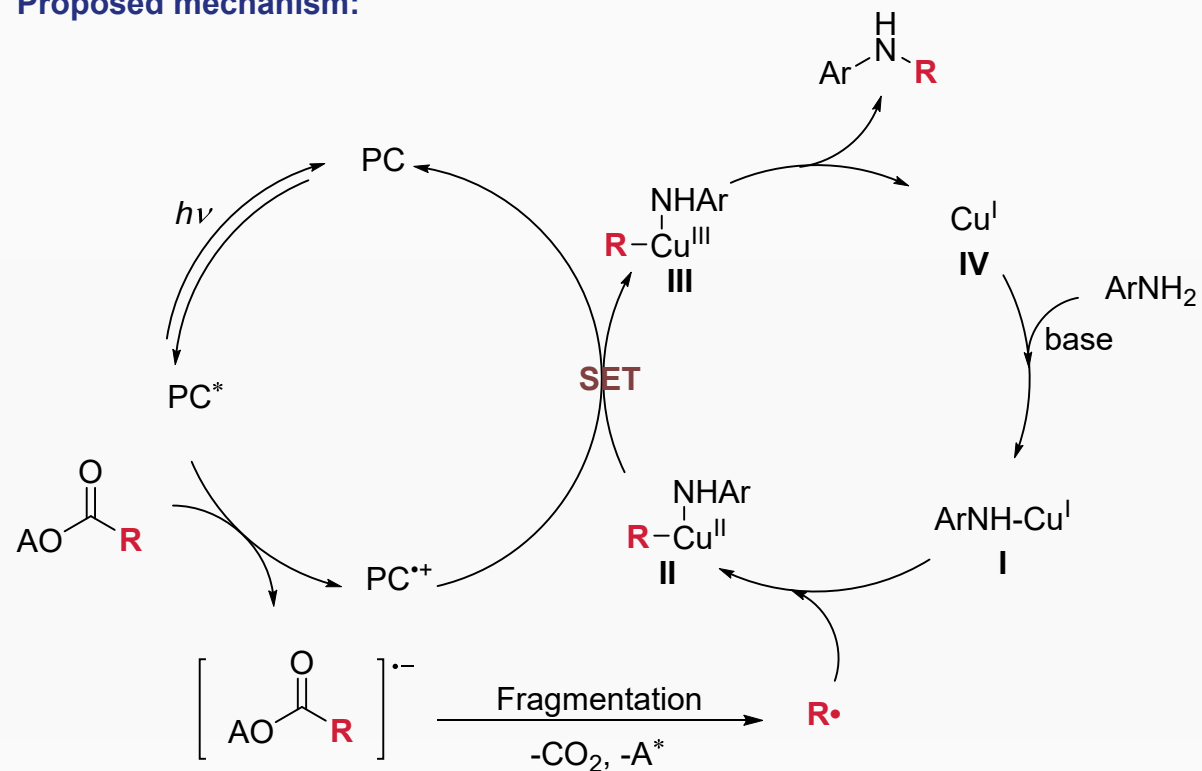


Natural products and drugs:



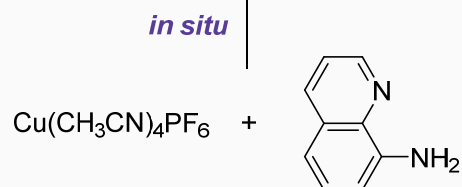
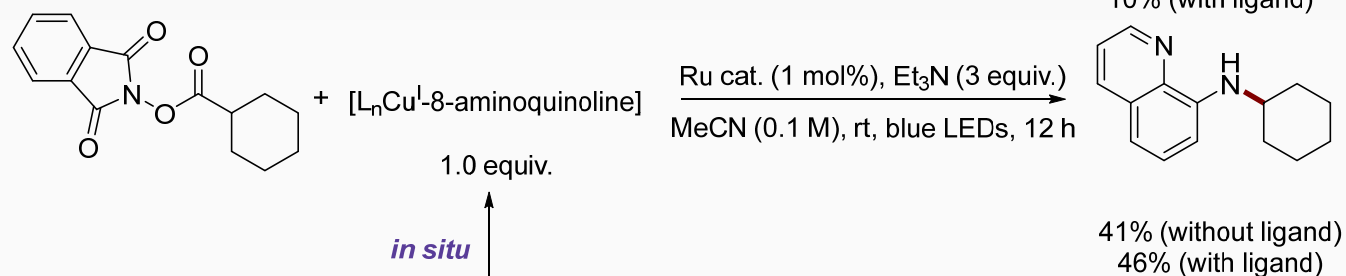
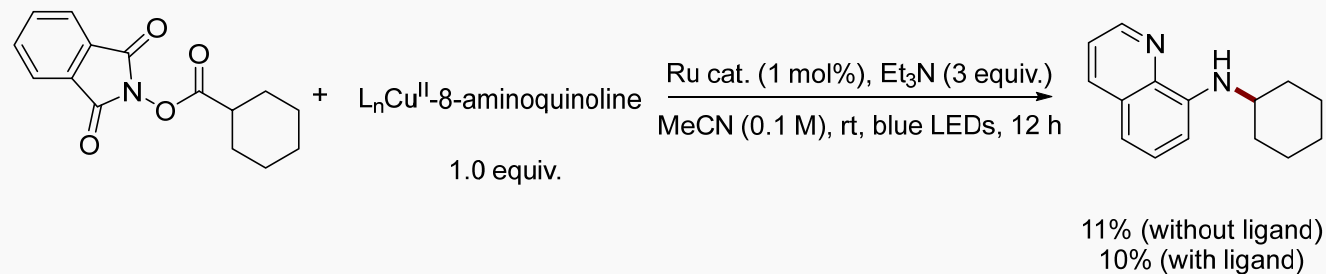
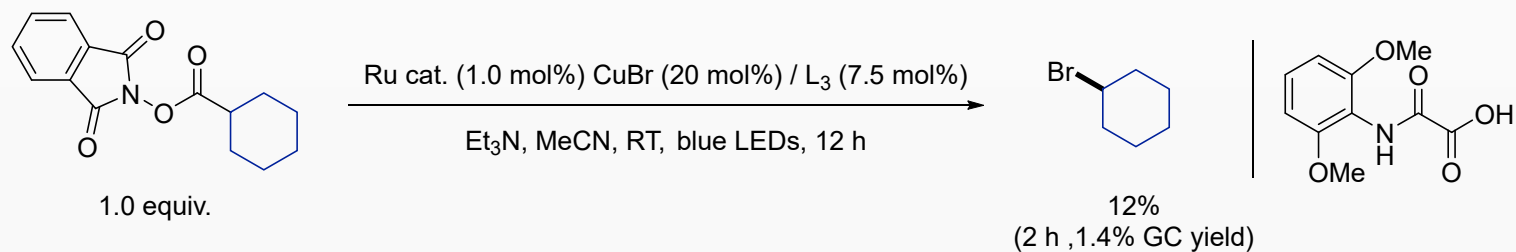
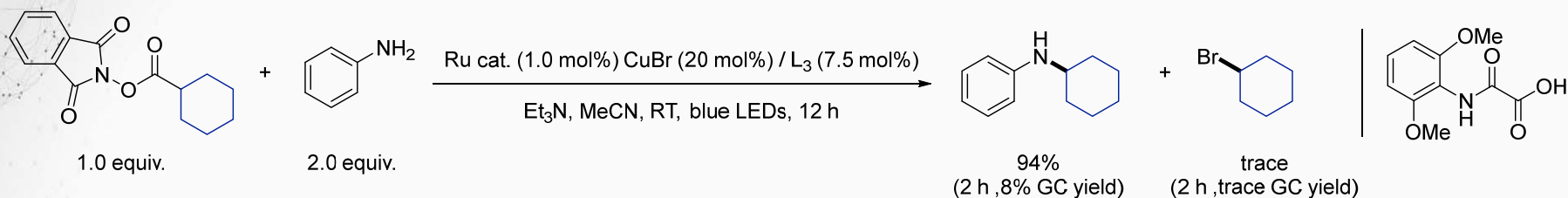
Copper-Catalyzed C(sp³)-N Bond Formation using Carboxylic Acids

Proposed mechanism:



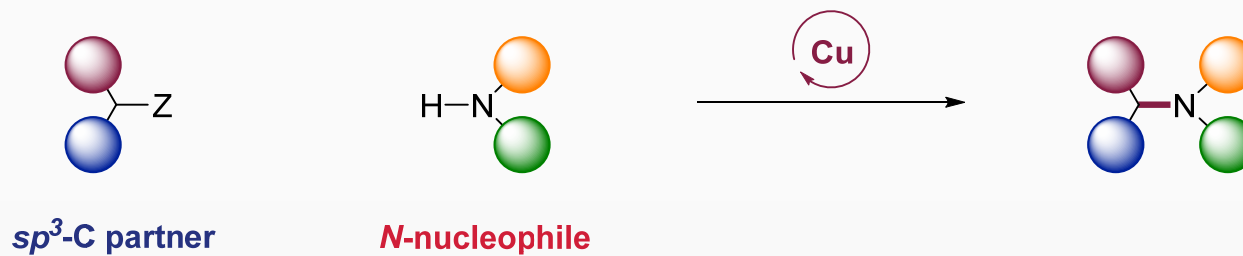
Hu, X. et al., *Nat Catal.* **2018**, *1*, 120 .

Copper-Catalyzed C(sp³)-N Bond Formation using Carboxylic Acids

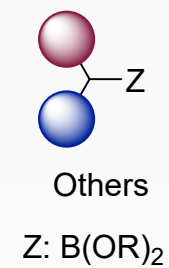
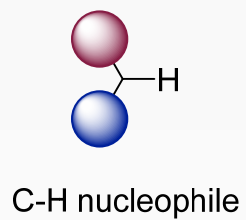
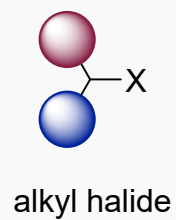


Hu, X. et al., *Nat Catal.* **2018**, *1*, 120 .

Copper-catalyzed Intermolecular Coupling of *N*-nucleophiles and $C(sp^3)$ Partners

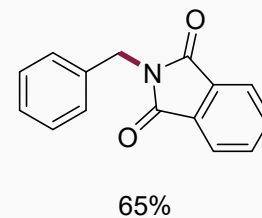
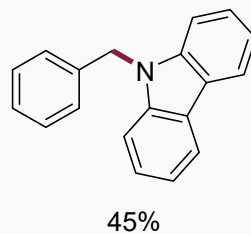
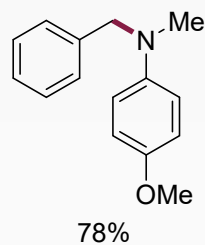
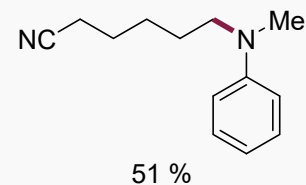
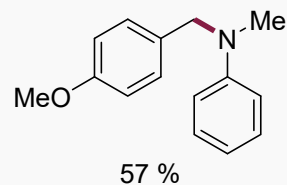
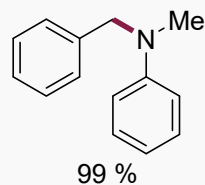
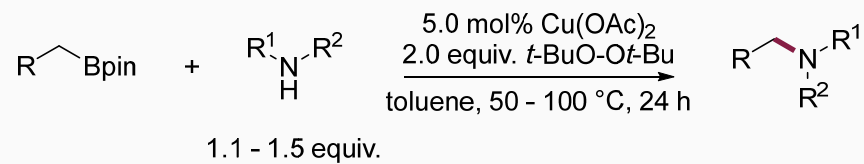


Coupling partners



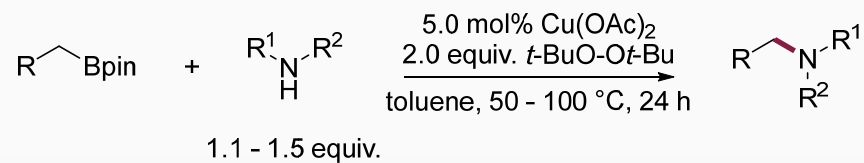
Copper-Catalyzed C(sp³)-N Bond Formation using Alkyl Boronic Acid Derivatives

Amine alkylations with primary alkyl boronic acid derivatives

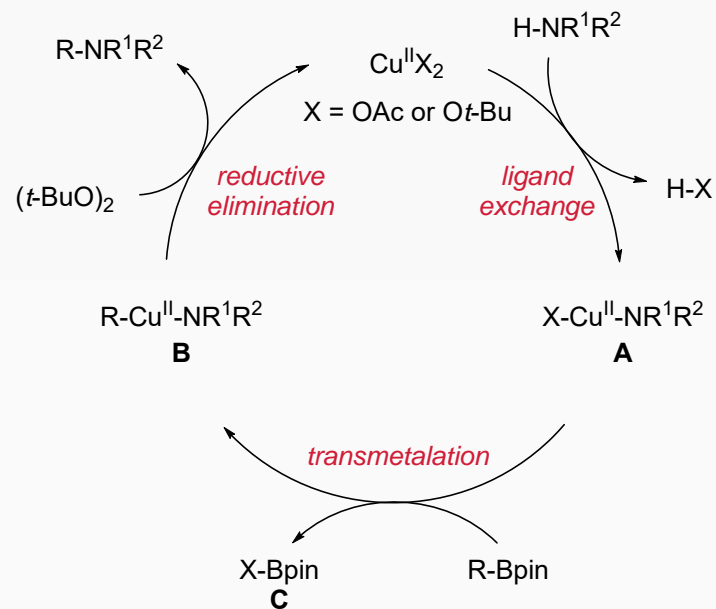


Copper-Catalyzed C(sp³)-N Bond Formation using Alkyl Boronic Acid Derivatives

Amine alkylations with primary alkyl boronic acid derivatives

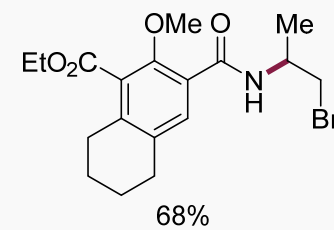
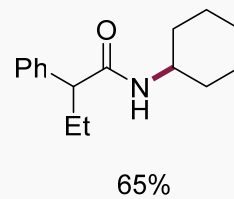
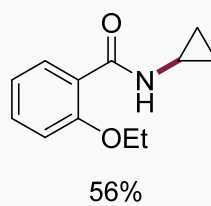
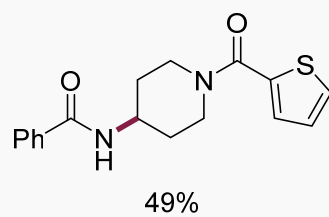
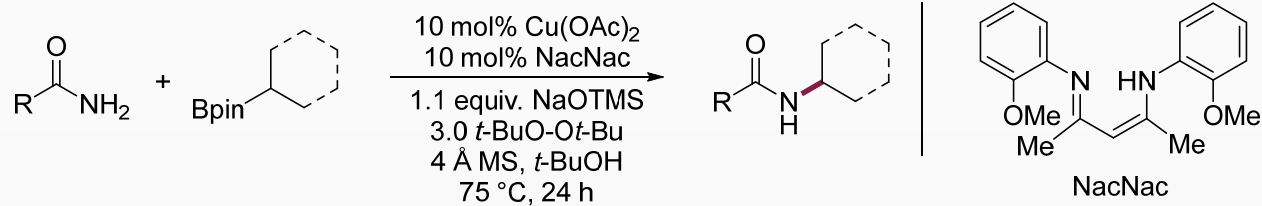


Proposed mechanism

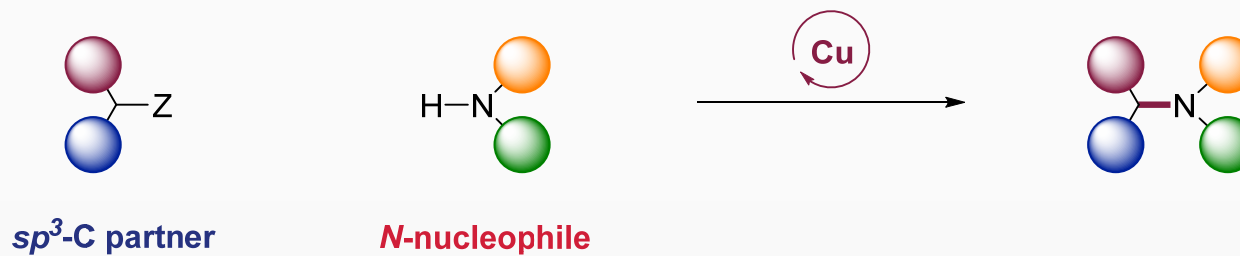


Copper-Catalyzed C(sp³)-N Bond Formation using Alkyl Boronic Acid Derivatives

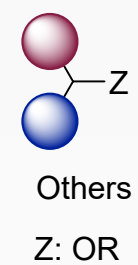
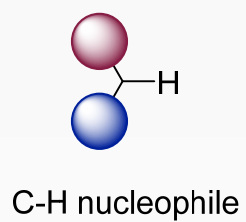
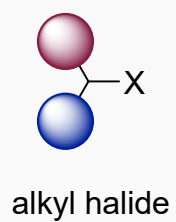
Amide alkylations with secondary alkyl boronic acid derivatives



Copper-catalyzed Intermolecular Coupling of *N*-nucleophiles and $C(sp^3)$ Partners

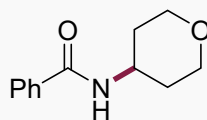
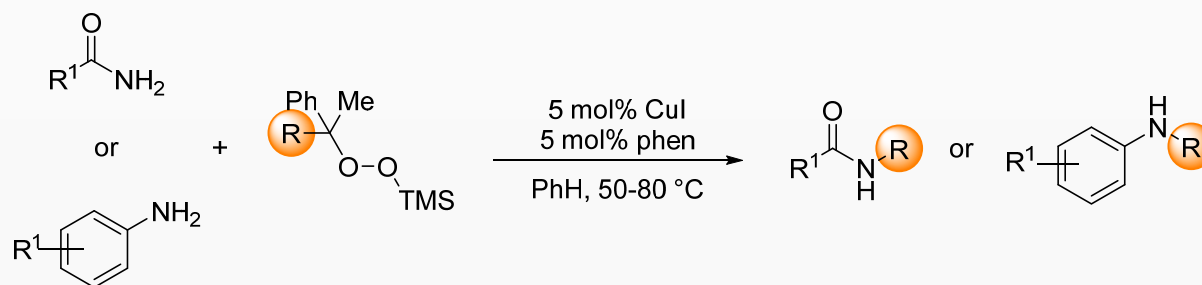


Coupling partners

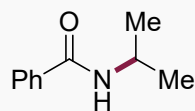


Copper-Catalyzed C(sp³)-N Bond Formation using Alcohol Derivatives

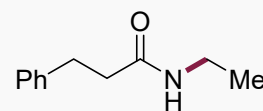
Alkylation with alkylsilyl peroxides



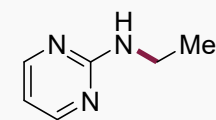
98%



94%



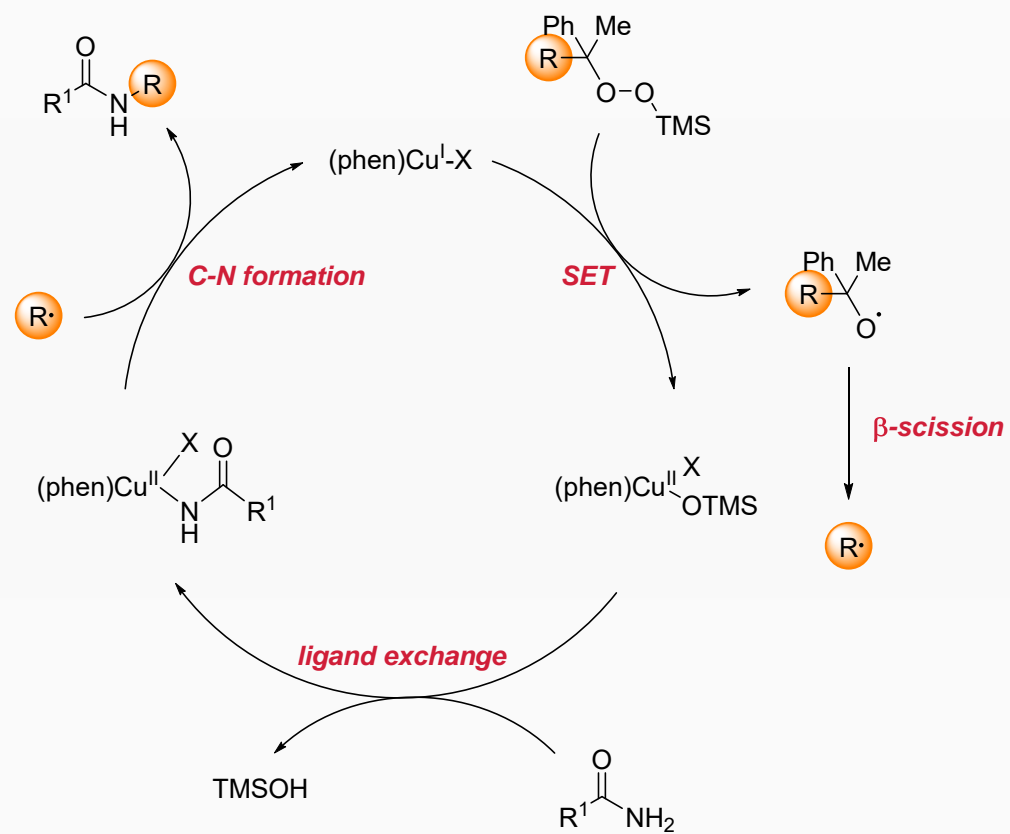
97%



68%

Copper-Catalyzed C(sp³)-N Bond Formation using Alcohol Derivatives

Proposed mechanism



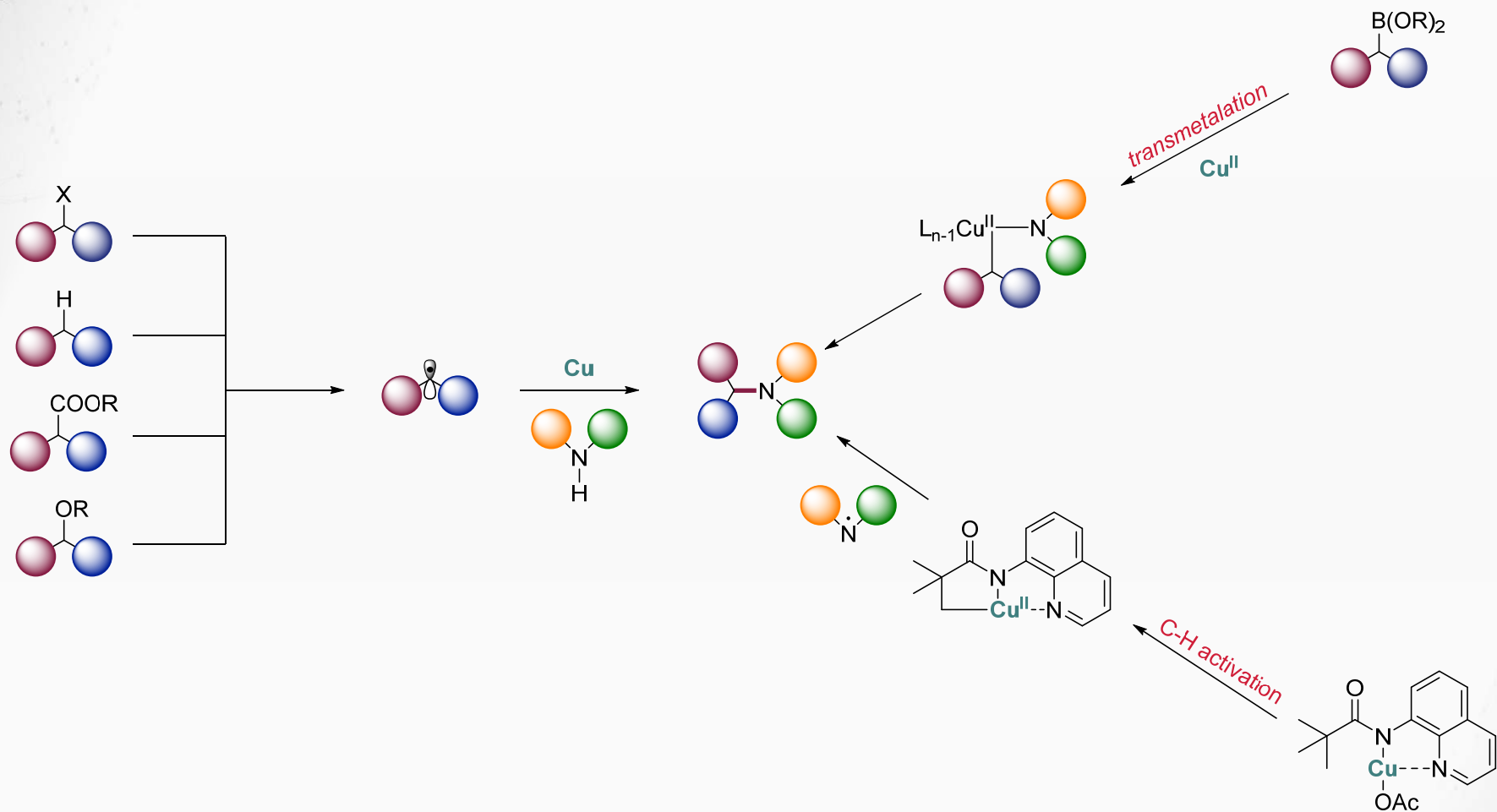


03

Summary and Prospect

Copper-catalyzed Intermolecular Coupling of *N*-nucleophiles and $C(sp^3)$ Partners

Summary





Copper-catalyzed Intermolecular Coupling of *N*-nucleophiles and C(*sp*³) Partners Prospect

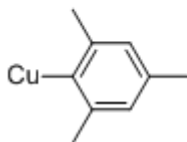
- ✓ Asymmetric C-N bond synthesis
- ✓ Mechanism study



THANK YOU

Welcome suggestions and criticisms

appendix



PreView

CBNumber: CB71181110

英文名称: **Mesitylcopper(I)**

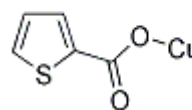
中文名称: **甲基异丁烯铜**

MF: C9H11Cu

MW:

CAS: 75732-01-3

MOL: [Mol file](#)



PreView

CBNumber: CB4323572

英文名称: **CUTC**

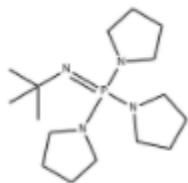
中文名称: **噻吩-2-甲酸铜(I)**

MF: C5H3CuO2S

MW: 190.69

CAS: 1292766-17-6

MOL: [Mol file](#)



PreView

CBNumber: CB4469999

英文名称: **BTTP**

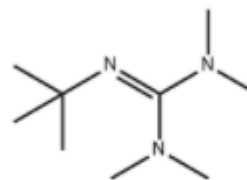
中文名称: **(叔丁基氨基)三(吡咯烷)膦**

MF: C16H33N4P

MW: 312.43

CAS: 161118-67-8

MOL: [Mol file](#)



PreView

CBNumber: CB5464951

英文名称: **BTMG**

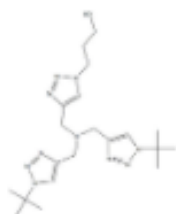
中文名称: **2-叔丁基-1,1,3,3-四甲基胍**

MF: C9H21N3

MW: 171.28

CAS: 29166-72-1

MOL: [Mol file](#)



PreView

CBNumber: CB83340444

英文名称: **BTTP**

中文名称: **BTTP**

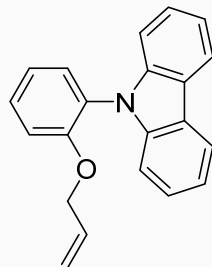
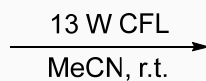
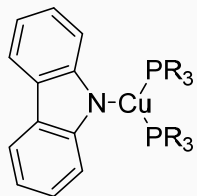
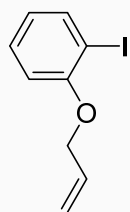
MF: C20H34N10O

MW: 430.55036

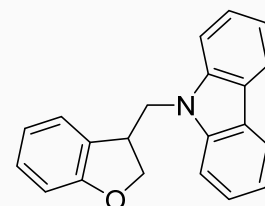
CAS: 1341215-17-5

MOL: [Mol file](#)

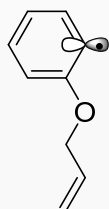
appendix



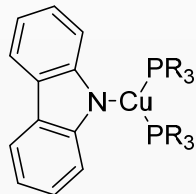
no observed



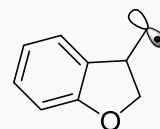
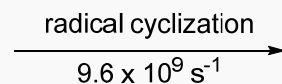
41% yield



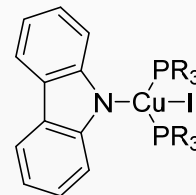
aryl radical



R = *m*-tol

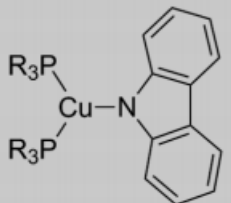
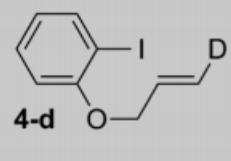


alkyl radical

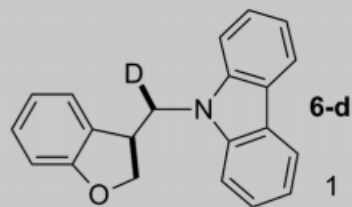
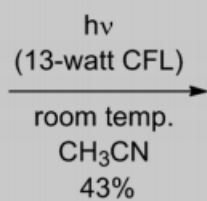


R = *m*-tol

C



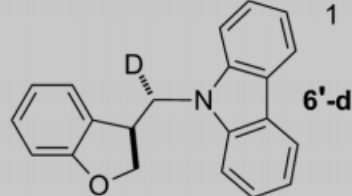
1 (R = *m*-tol)



6-d

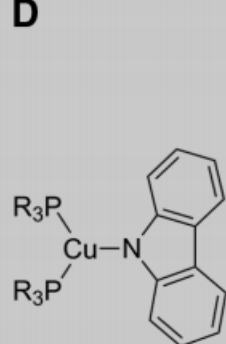
1

1

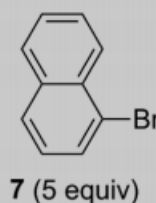


6'-d

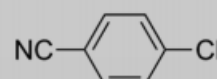
D



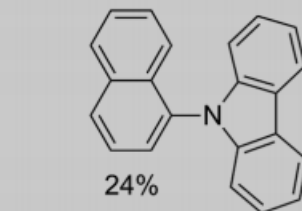
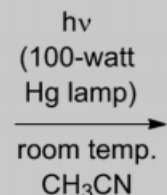
1 (R = *m*-tol)



7 (5 equiv)



8 (5 equiv)

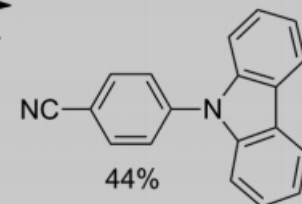


24%

9

1

2

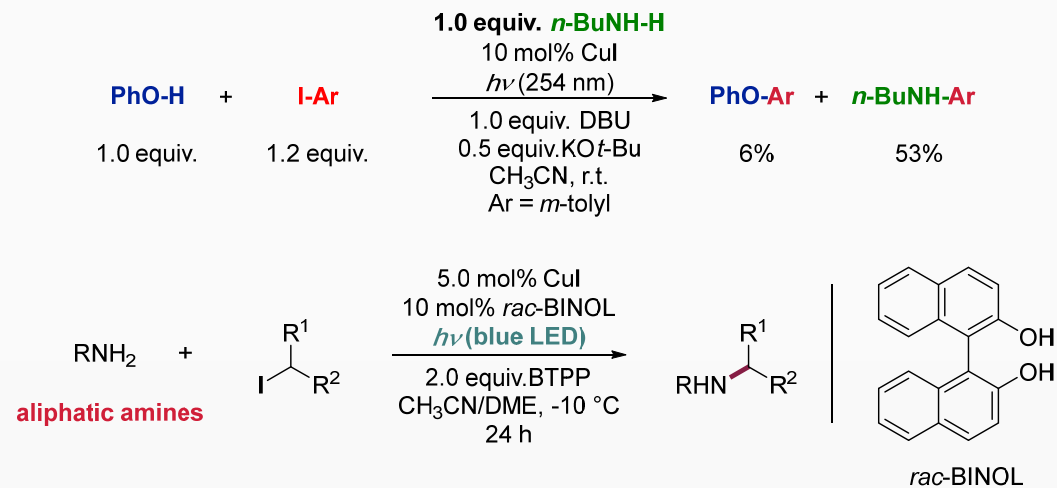


44%

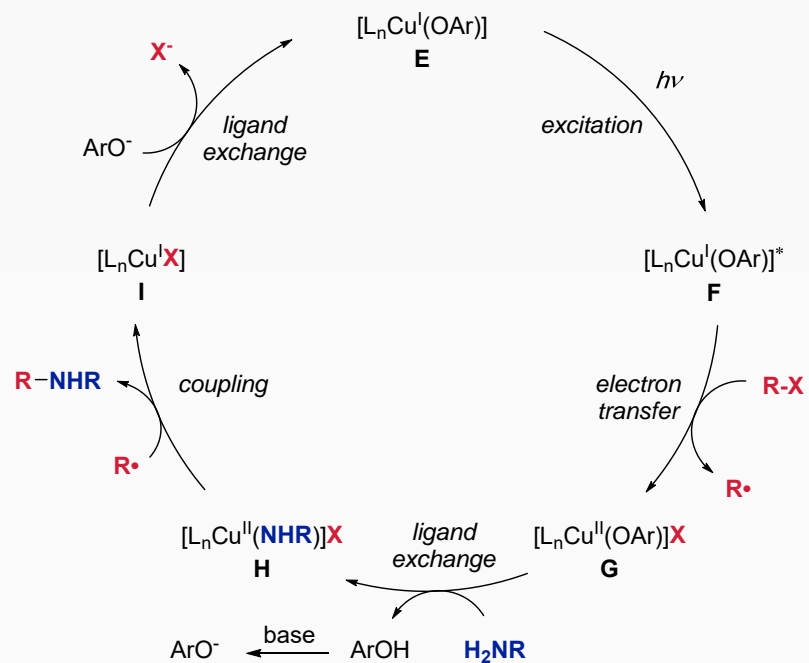
10

(−2.03 V for 8; −2.17 V for 7 versus SCE in DMF)

appendix



A possible pathway

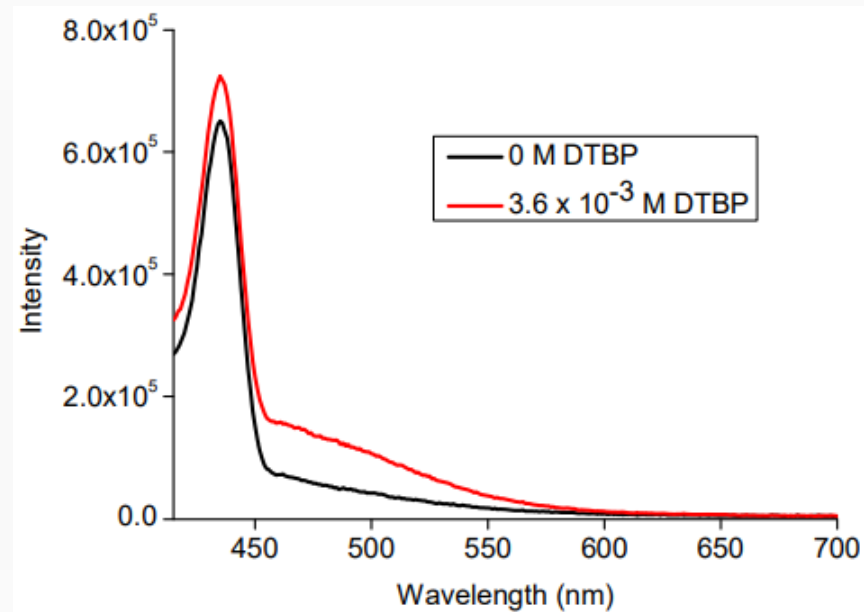
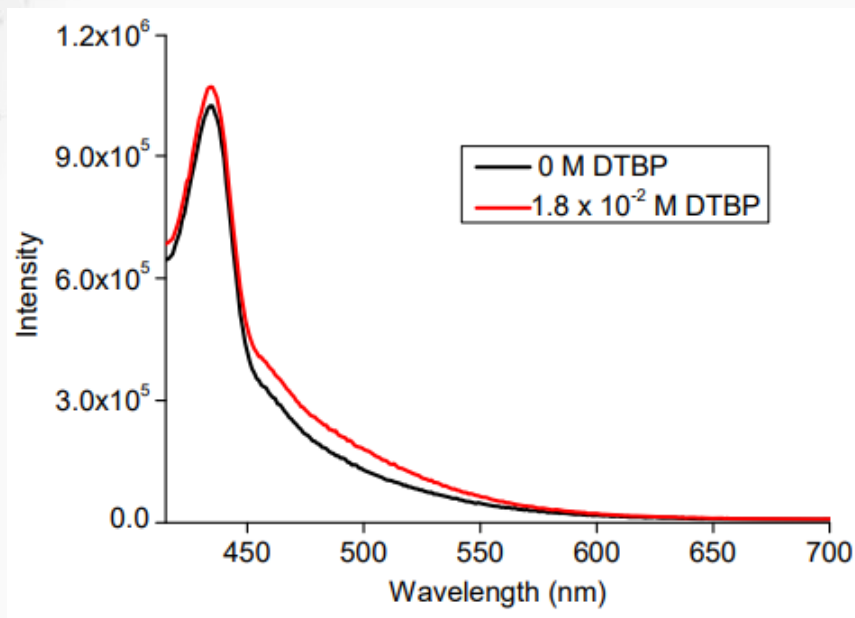


Fu, G. C.; Peters, J. C. et al., *J. Am. Chem. Soc.* **2017**, *139*, 17707.

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Quenching experiments

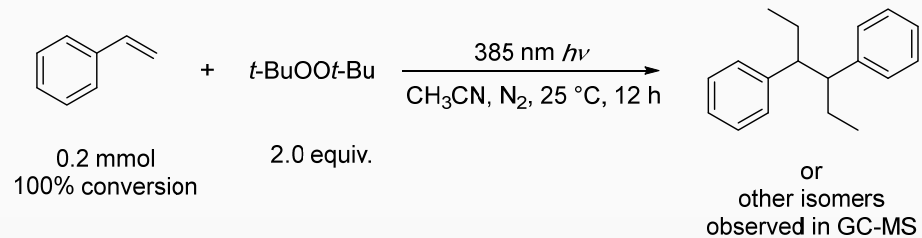
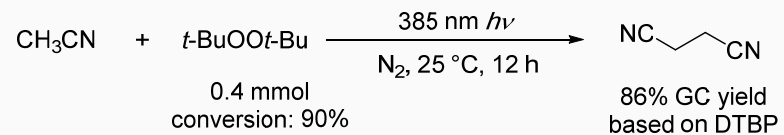
Excitation wavelength: 385 nm, entrance slit: 10 nm, exit slit: 10 nm.



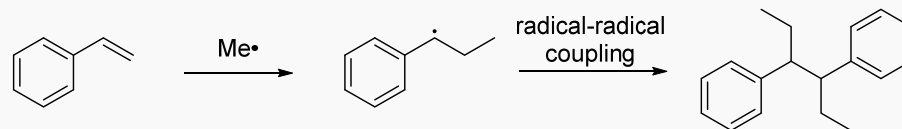
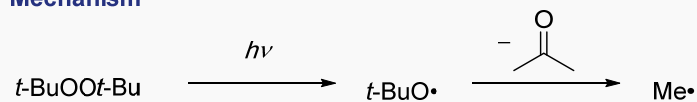
Fluorescence spectra of $\text{Cu}(\text{AcO})_2$ ($1 \times 10^{-3} \text{ M}$) and dtbbpy ($2 \times 10^{-3} \text{ M}$) in CH_3CN with different amount of DTBP.

Fluorescence spectra of CuI ($1.65 \times 10^{-4} \text{ M}$) and dtbbpy ($3.3 \times 10^{-4} \text{ M}$) in CH_3CN with different amount of DTBP.

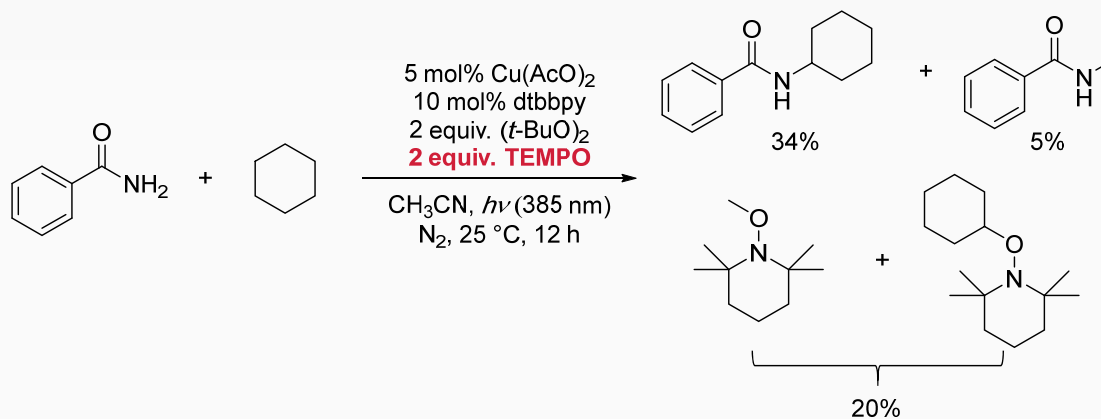
appendix



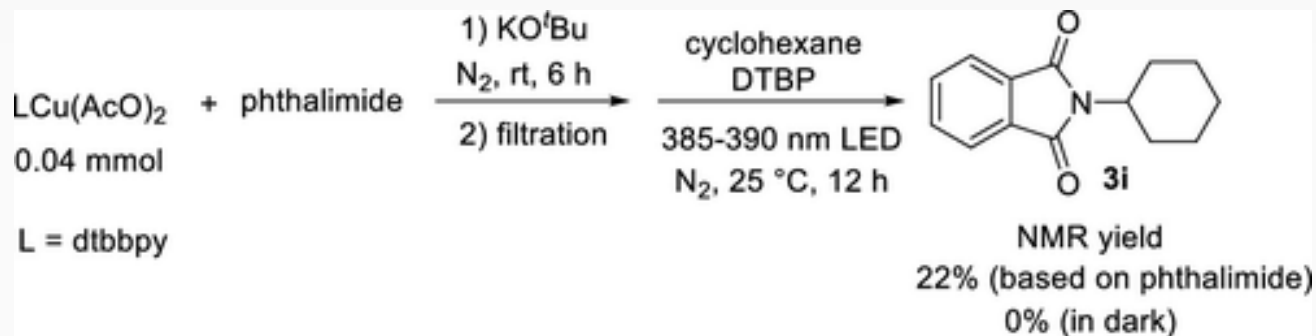
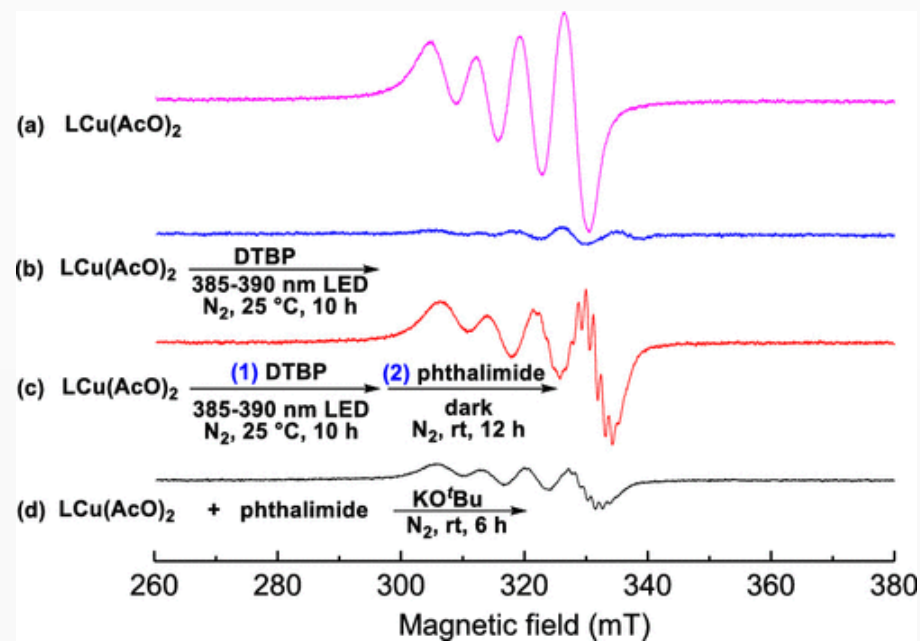
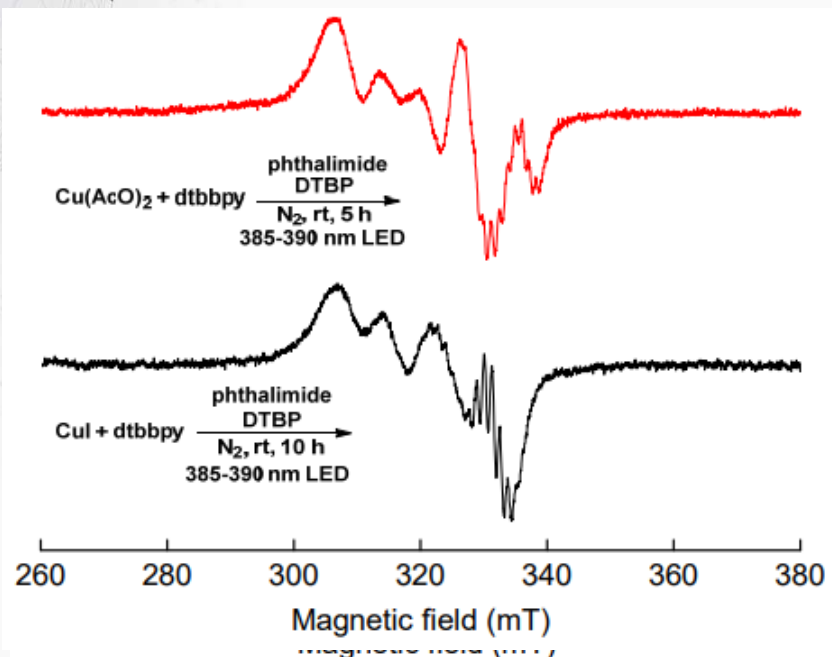
Mechanism



Radical trapping with TEMPO



appendix



appendix

